

HIV/AIDS Care and Treatment

A Clinical Course for People Caring for Persons Living with HIV/AIDS



Participant Manual



Part A

HIV/AIDS Care and Treatment



Part B

Antiretroviral Therapy



PART B
Antiretroviral Therapy



Part C

Appendices



Module A1

HIV/AIDS Programming and HIV Disease: An Introduction



Module A2

Managing Patients with HIV-Related Diseases

MODULE A2



Module A3

Special Issues in Managing Women and Children with HIV Disease



MODULE A3



Module A4

Antiretroviral Therapy: A Brief Introduction



MODULE A4



Module A5

Supporting People with HIV/AIDS: Palliative Care, Home-Based Care and Nutrition



Module B1

Managing Patients on Antiretroviral Therapy



Module B2

Special Issues: TB, Women, Children and Post-Exposure Prophylaxis

MODULE B2



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Cover Photos:

Lead photo: The late Kabanda and Brigitte Syamalevwe. Brigitte Syamalevwe passed away in February 2003 and was buried on her farm in Luanshya Ibenga, Zambia, near her late husband, Kabanda, who died in 2002. Brigitte and Kabanda were married for 30 years. Brigitte worked as a schoolteacher and Kabanda as a senior clinical officer for the public health service in northern Zambia. Together, Brigitte and Kabanda shared their experience of HIV/AIDS with courage and dynamism. Photo by Mary Lyn Field-Nguer/FHI.

First row, left to right:

Children in Chennai, India. Photo by Mary Lyn Field-Nguer/FHI.
Doctor at HIV clinical care center in Peddapuram, India. Video still by Robert Ritzenthaler/FHI.
Counselor Theresa Tetteh talks with a client at St. Martin's Catholic Hospital, Ghana. Photo by Mary Lyn Field-Nguer/FHI.
Lab technologist, Rwanda. Photo by Brian Pederson/FHI.

Second row, left to right:

Queen Mothers of the Start/Ghana program. Photo by Mary Lyn Field-Nguer/FHI.
Child in the Cedico school project in Guatemala. Photo by Jon Warren/World Vision.
HIV-positive couple in Maesai, Thailand. Photo by World Vision.

Back cover, far left:

Post-test club, Western Province, Kenya. Video still by Robert Ritzenthaler/FHI.

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PREFACE

Only about five percent of the 30 million people in poor countries who need treatment for HIV infection are receiving it. As the need for treatment grows, so does the demand. The June 2001 Declaration of Commitment by the United Nations General Assembly states that “Prevention, care, support and treatment for those infected and affected by HIV/AIDS are mutually reinforcing elements of an effective response and must be integrated in a comprehensive approach to combat the epidemic.” Encouraged by global support for expanding access to treatment and by a decrease in the price of antiretroviral drugs, programs are increasingly seeking ways to add a treatment component to their prevention, care, and support services.

A major aspect of preparing to implement these programs is human and infrastructure capacity building. In resource-constrained settings, planning for human capacity development must take place in the challenging context of health care systems that are struggling to cope with HIV as well as deal with continuing high maternal, infant and overall disease mortalities. It is critical that efforts to prepare and support health care workers, nurses, doctors, clinical officers and others who care for people living with HIV/AIDS be tailored to the setting in which they are implemented. Capacity building must also motivate health care staff so that they are able to provide the care and support needed for safe and effective use of lifelong treatment.

This participant manual presents new knowledge and skills for delivering and organizing clinical care and treatment services for people living with HIV/AIDS. It is shaped by FHI’s longstanding work in HIV-related prevention, care and support activities in more than 60 countries. Recently, FHI began supporting public and NGO efforts to deliver strengthened HIV care and support, including antiretroviral treatment (ART), in three countries at the district level.

We hope this manual will help clinical care providers develop the skills to ensure that their health care system provides high-quality HIV disease management, including the safe and effective use of ART.

INTRODUCTION

As FHI has embarked on strengthening HIV care, including the use of ART, it has become clear that one of the important prerequisites to a care and treatment program is staff who are adequately prepared to provide clinical care services at the facility and community level. Clinical services include the prophylaxis and management of HIV-related illnesses, including opportunistic infections, and provision of antiretroviral therapy for those who need it. FHI decided to develop this facilitator's guide because training is an important first step in preparing health care teams to provide care and treatment. However, workshop training alone is not sufficient. Supervision, monitoring and refresher training—as well as a supportive health system and prepared communities—must follow.

Clinical HIV care is a complex area, in part because there are psychological and social issues that compound the physical effects of HIV infection. The implications for service delivery are many, including the need for a cadre of providers. A team of professionals from health care and other fields, as well as community groups—often from various institutions and programs—must work together to provide and share quality care, treatment, and support. Collaboration between clinical care facilities and other services is critical if individuals and families are to receive a continuum of care through timely and functional referral. Training from this perspective can help programs achieve these goals.

It is important to bear in mind that diagnosis, management, follow-up and referral resources vary from country to country and, within countries, from one site or level to another (for example, primary/health center; secondary/district hospital; tertiary/referral hospital). Each level will need to adapt recommendations from a course such as this. Facilitators offering the course should be aware of the needs of different levels in a country; they should use every opportunity to discuss all aspects of clinical management in the context of the various settings in which course participants operate day to day. While the course draws much upon experience in Africa, most of the content is relevant and appropriate for settings in all regions. Moreover, content can be adapted easily. (Facilitators working in Thailand or Asia, for example, should add opportunistic infections particular to that locale.)

COURSE DESCRIPTION

For whom is this course designed?

The course is designed for those who treat and care for people living with HIV/AIDS in resource-constrained settings. Those responsible for delivering HIV-related services and who anticipate the addition of treatment and support services may also find it useful.

What does the guide include?

The course focuses primarily on clinical content for those who prescribe drugs and treat patients, with complementary sessions on programmatic issues. Sessions present treatment in the context of comprehensive care and support. The approach covers the provision of care and treatment services across a continuum of care, including HIV clinical management at a facility, as well as clinical and psychosocial community services. The guide has sections on epidemiology, transmission and prevention of HIV, the organization of HIV care services, and nutrition and palliation. However, it focuses mainly on preventing and managing opportunistic infections and HIV-related illnesses and using antiretroviral therapy.

HIV/AIDS Care and Treatment

A Clinical Course for People Caring for Persons Living with HIV/AIDS



Part A: HIV/AIDS Care and Treatment

Module A1: HIV/AIDS Programming and HIV Disease: An Introduction

- Session 1: Program Overview
- Session 2: General Background on HIV/AIDS: Epidemiology
- Session 3: HIV/AIDS Prevention
- Session 4: Comprehensive Care for People Living with HIV/AIDS
- Session 5: Immunology and Natural History of HIV/AIDS
- Session 6: Diagnosis of HIV
- Session 7: Patient Clinical Presentation, Differential Diagnosis and Follow-up

Module A2: Managing Patients with HIV-Related Diseases

- Session 1: Diagnosis of HIV-Related Illnesses: A Brief Overview
- Session 2: Conditions of the Respiratory System
- Session 3: Tuberculosis: HIV-TB Interaction
- Session 4: Conditions of the Neurological System
- Session 5: Conditions of the Gastrointestinal System
- Session 6: Conditions of the Lymph System
- Session 7: Conditions of the Mouth and Throat
- Session 8: Skin Conditions
- Session 9: Fever
- Session 10: Prophylaxis of Opportunistic Infections
- Session 11: Diagnosis and Management of HIV-Related Cancers

Module A3: Special Issues in Managing Women and Children with HIV Disease

- Session 1: HIV and Pregnancy: Prevention of Mother-to-Child Transmission
- Session 2: Management of HIV Disease in Women
- Session 3: Management of HIV Disease in Children

Module A4: Antiretroviral Therapy: A Brief Introduction

- Session 1: Setting up the Antiretroviral Therapy (ART) Component
- Session 2: Brief Introduction to ART
- Session 3: Management of Drug Side Effects
- Session 4: Case Studies: Managing Patients with Multiple Issues

Module A5: Supporting People Living with HIV/AIDS: Palliative Care, Home-Based Care and Nutrition

- Session 1: Palliative Care
- Session 2: Community Home-Based Care
- Session 3: Nutrition

Module B1: Managing Patients on Antiretroviral Therapy

- Session 1: The Goal and Basic Principles of ART
- Session 2: When to Start ART in Adults
- Session 3: Antiretroviral Drug Mechanisms
- Session 4: Drug Interactions and Adverse Drug Reactions: Side Effects and Toxicities
- Session 5: Recommended First-Line Regimens in Adults
- Session 6: Patient Follow-up and Monitoring ART
- Session 7: Drug Adherence and Strategies for Compliance
- Session 8: Why and When to Change Therapy

Module B2: Special Issues: TB, Women, Children and PEP

- Session 1: Management of Tuberculosis and Other HIV-Related Infections and Conditions in Relation to ART
- Session 2: ART in Women: During Pregnancy and for Preventing Mother-to-Child Transmission
- Session 3: ART in Infants and Children
- Session 4: Post-Exposure Prophylaxis (PEP)

ESTIMATED DURATION OF SESSIONS AND TOTAL MODULE AND COURSE TIMES**Part A: HIV/AIDS Care and Treatment****Module A1: HIV/AIDS Programming and HIV Disease: An Introduction**

Session 1	Program Overview	50 minutes
Session 2	General Background on HIV/AIDS: Epidemiology	30 minutes
Session 3	HIV/AIDS Prevention	50 minutes
Session 4	Comprehensive Care for People Living with HIV/AIDS	120 minutes
Session 5	Immunology and Natural History of HIV/AIDS	60 minutes
Session 6	Diagnosis of HIV	150 minutes
Session 7	Patient Clinical Presentation, Differential Diagnosis and Follow-up	110 minutes

Total time: 570 minutes or 9.5 hours

Module A2: Managing Patients with HIV-Related Diseases

Session 1	Diagnosis of HIV-Related Illnesses: A Brief Overview	10 minutes
Session 2	Conditions of the Respiratory System	80-105 minutes
Session 3	Tuberculosis: HIV-TB Interaction	75 minutes
Session 4	Conditions of the Neurological System	120 minutes
Session 5	Conditions of the Gastrointestinal System	120 minutes
Session 6	Conditions of the Lymph System	80 minutes
Session 7	Conditions of the Mouth and Throat	70 minutes
Session 8	Skin Conditions	120 minutes
Session 9	Fever	60 minutes
Session 10	Prophylaxis of Opportunistic Infections	90 minutes
Session 11	Diagnosis and Management of HIV-Related Cancers	45 minutes

Total time: 895 minutes or 15 hours

Module A3: Special Issues in Managing Women and Children with HIV Disease

Session 1	HIV and Pregnancy: The Prevention of Mother-to-Child Transmission	60 minutes
Session 2	Management of HIV Disease in Women	50 minutes
Session 3	Management of HIV Disease in Children	165 minutes
		210 minutes with case studies

Total time: 275 – 320 minutes or 4.6 - 5.3 hours

Module A4: Antiretroviral Therapy: A Brief Introduction

Session 1	Setting up an Antiretroviral Therapy ART Program	90 minutes
Session 2	Brief Introduction to ART	90 minutes
Session 3	Management of Drug Side Effects	45 minutes
Session 4	Case Studies: Managing Patients with Multiple Issues	120 minutes

Total time: 390 minutes or 6.5 hours

Module A5: Supporting People Living with HIV/AIDS: Palliative Care, Home-Based Care and Nutrition

Session 1	Palliative Care	120 minutes
Session 2	Community Home-Based Care	60 minutes
Session 3	Nutrition	180 minutes

Total time: 360 minutes or 5.5 hours

Total time for Part A: 41.8 hours or five 8-hour days, not including breaks and lunch times

Part B: Antiretroviral Therapy

Module B1: Managing Patients on Antiretroviral Therapy

Session 1	The Goal and Basic Principles of ART	30 minutes
Session 2	When to Start ART in Adults	45 minutes
Session 3	Antiretroviral Drug Mechanisms	60 minutes
Session 4	Drug Interactions and Adverse Drug Reactions: Side Effects and Toxicities	120 minutes
Session 5	Recommended First-Line Regimens in Adults	45 minutes
Session 6	Patient Follow-up and Monitoring ART	60 minutes
Session 7	Drug Adherence and Strategies for Compliance	100 minutes
Session 8	Why and When to Change Therapy	90 minutes

Total time: 550 minutes or 19 hours

Module B2: Special Issues: TB, Women, Children and Post-Exposure Prophylaxis

Session 1	Management of Tuberculosis and Other HIV-Related Infections and Conditions Related to ART	40-60 minutes
Session 2	ART in Women: During Pregnancy and for Preventing Mother-to-Child Transmission	60-90 minutes
Session 3	ART in Infants and Children	75 minutes
Session 4	Post Exposure Prophylaxis (PEP)	90 minutes

Total time: 270-330 minutes or 4.5-5.5 hours

Total time for Part B: 24.5 hours or three 8-hour days, not including breaks or lunch

Total time for Course, Parts A and B, all modules: 57 hours or 8 days

Based on 7 hours of sessions per day, not including time for lunch and at least one 15-minute break each morning and afternoon

ABBREVIATIONS

Antiretroviral Drug Abbreviations

ARV	Antiretroviral
NNRTI	Nonnucleoside reverse transcriptase inhibitor
DLV	Delavirdine
EFZ	Efavirenz
NVP	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitor
TDF	Tenofovir
NsRTI	Nucleoside reverse transcriptase inhibitor
3TC	Lamivudine
ABC	Abacavir
AZT	Zidovudine
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
ZDV	Zidovudine
PI	Protease inhibitor
APV	Amprenavir
IDV	Indinavir
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
NFV	Nelfinavir
RTV	Ritonavir
SQV	Saquinavir
SQV/r	Saquinavir/ritonavir

TB Treatment Regimens

EMB	Ethambutol
INH	Isoniazid
PZA	Pyrazinamide
RIF	Rifampin
SMX	Sulfamethoxazole
TMP	Trimethoprim
TMP-SMX	Trimethoprim-sulfamethoxazole or Cotrimoxazole
EHRZ	Ethambutol (E), Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)
HE	Isoniazid (H) and Ethambutol (E)
HR	Isoniazid (H), Rifampicin (R)
HRE	Isoniazid (H), Rifampicin (R), Ethambutol (E)
HRZ	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)
HRZE	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)
SHRZ	Streptomycin (S), Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)
SHRZE	Streptomycin (S), Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)

Drug Administration Abbreviations

/ml	Microliter
bid	Twice a day
cm	Centimeter
d/c	Discontinue
G, gr or gm	Gram
gr/dl	Grams per deciliter
H	Hour
IM	Intramuscular
IV	Intravenous
kg	Kilogram
mg	Milligram
mg/L	Milligrams/liter
mm³	Cubic millimeter
mmHg	Millimeters of mercury
mmol/mL	Millimole per milliliter
nocte	At nighttime
OD	Once daily
PO	By mouth
PRN	As needed
q	Every
qd	Every day
qid	Four times a day
tid	Three times a day

General Abbreviations

ml	Microliter
3TC	Lamivudine
ABC	Abacavir
ACTG	AIDS clinical trial group
ADC	AIDS dementia complex
ADR	Adverse drug reaction
AFB	Acid-fast bacteria - Ziehl-Neelsen stain
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANC	Antenatal care
APV	Amprenavir
ARC	AIDS-related complex
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the (plasma time) curve
AZT	Zidovudine
B1	Thiamine
B12	Cobalamine
B2	Riboflavin
B6	Niacin pyrodoxine

BA	Bacillary angiomatosis
BCC	Behavior change communication
BCG	Bacille Calmette-Guérin
bid	Twice a day
BMI	Body mass index
BMS	Bristol Myers Squibb
BRAT	Diet of bananas, rice, applesauce, toast, and tea
BUN	Blood urea nitrogen
C&S	Culture & sensitivity
C&T	Counseling and testing
CBC	Complete blood count
CBO	Community-based organization
CDC	Centers for Disease Control and Prevention
CHBC	Community home-based care
CIN	Cervical intraepithelial neoplasia
cm	Centimeter
CMV	Cytomegalovirus
CNS	Central nervous system
CPK	Creatinine phosphokinase
CSF	Cerebrospinal fluid
CSF-CRAG	Cerebrospinal fluid-cryptococcal antigen test
CT	Computerized tomography
CXR	Chest x-ray
d/c	Discontinue
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DFID	Department for International Development
DLV	Delavirdine
DMO	District medical officer
DNA	Deoxyribonucleic acid
DOT	Directly observed treatment
DOTS	Directly observed treatment strategy
DPT	Diphtheria, pertussis, and tetanus
DRESS	Drug rash, eosinophilia, and systemic symptoms
DS	Double strength
DTR	Deep tendon reflex
EBV	Epstein-Barr virus
EFZ	Efavirenz
EHRZ	ethambutol (E), isoniazid (H), rifampicin (R), pyrazinamide (Z)
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EMB	Ethambutol
ENT	Ear, nose and throat

EPI	Expanded Program for Immunization	IMCI	Integrated Management of Childhood Illnesses
ESN	Nutrition Programmes Service of the FAO Food and Nutrition Division	IMPACT	Implementing AIDS Prevention and Care Project
ESR	Erythrocyte sedimentation rate	INH	Isoniazid
ETEC	Enterotoxogenic E.coli	ITP	Idiopathic thrombocytopenia
ETOH	Alcohol	IU	International units
FBC	Full blood count	IV	Intravenous
FDA	Food and Drug Administration	JCV	JC virus
FHI	Family Health International	kg	Kilogram
FTT	Failure to thrive	KOH	Potassium hydroxide
FUO	Fever of unknown origin	KS	Kaposi's sarcoma
G, gr or gm	Gram	LDH	Lactate dehydrogenase
GI	Gastrointestinal	LDL	Low-density lipoprotein
gr/dl	Grains per deciliter	LFT	Liver function tests
GYN	Gynecological	LGV	Lymphogranuloma venereum
H	Hour	LIP	Lymphoid interstitial pneumonia
HAART	Highly active antiretroviral therapy	LPV	Lopinavir
HAD	HIV-associated dementia	LPV/r	Lopinavir/ritonavir
HAV	Hepatitis A virus	MAC	Mycobacterium avium complex or M. avium complex
HbC	Hemoglobin C	MEMS	Medication Event Monitoring Systems
HBC	Home-based care	mg	Milligram
HbcAb or AHBC	Hepatitis B core antibody	mg/L	Milligrams/liter
HBcAG	Hepatitis B core antigen	mm3	Cubic millimeter
HBs	Hepatitis B surface	mmHg	Millimeters of mercury
HBsAG	Hepatitis B surface antigen	mmol/mL	Millimole per milliliter
HBV	Hepatitis B virus	MRI	Magnetic resonance imaging
HCO3	Bicarbonate	MSF	Médecins Sans Frontières
HCV	Hepatitis C virus	MTCT	Mother-to-child transmission
HCW	Health care worker	NAM	Nucleoside analogue mutation
HDV	Hepatitis D virus	NCHS	National Center for Health Statistics
HE	isoniazid (H) and ethambutol (E)	NFV	Nelfinavir
HEV	Hepatitis E virus	NGO	Nongovernmental organization
Hgb	Hemoglobin	NHD	WHO Department of Nutrition for Health and Development
HHV	Human herpes virus	NHL	NonHodgkin's lymphoma
HIV	Human immunodeficiency virus	NNRTI	Nonnucleoside reverse transcriptase inhibitor
HPV	Human papilloma virus	nocte	At nighttime
HR	Isoniazid (H), Rifampicin (R)	NRTI	Nucleoside reverse transcriptase inhibitor
HRE	Isoniazid (H), Rifampicin (R), Ethambutol (E)	NSAID	Nonsteroidal anti-inflammatory drug
HRZ	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)	NsRTI	Nucleoside reverse transcriptase inhibitor
HRZE	Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)	NVP	Nevirapine
HSR	Hypersensitivity reaction	O&P	Ova and parasites
HSV	Herpes simplex virus	OI	Opportunistic infection
IDU	Intravenous drug use	ORS	Oral rehydration solution
IDV	Indinavir	OVC	Orphans and vulnerable children
IgG	Immunoglobulin G		
IgM	Immunoglobulin M		
IM	Intramuscular		

PCP	Pneumocystis carinii pneumonia	TMP	Trimethoprim
PCR	Polymerase chain reaction	TMP-SMX	Trimethoprim-sulfamethoxazole or cotrimoxazole
PEP	Post-exposure prophylaxis	TSH	Thyroid stimulating hormone
PGL	Persistent generalized lymphadenopathy	UGI	Upper gastrointestinal
PI	Protease inhibitor	UNAIDS	Joint United Nations Program on AIDS
PID	Pelvic inflammatory disease	UNICEF	United Nation's Children's Fund
PLHA	People living with HIV/AIDS	URTI	Upper respiratory tract infection
PML	Progressive multifocal leukoencephalopathy	USAID	United States Agency for International Development
PMN	Polymorphonuclear	UTI	Urinary tract infection
PMTCT	Prevention of mother-to-child transmission	UV	Ultraviolet
PO	By mouth	VCT	Voluntary counseling and testing
PO2 and pO2	Partial pressure of oxygen	VDRL	Venereal disease research laboratory
PP	PowerPoint	VZIG	Varicella-zoster immune globulin
PPD	Purified protein derivative of tuberculin	VZV	Varicella-zoster virus
PRN	As needed	WB	Western blot
PT	Preventive therapy	WBC	White blood count
PTB	Pulmonary TB	WHO	World Health Organization
PZA	Pyrazinamide	ZDV	Zidovudine
q	Every	ZN	Ziehl-Neelsen stain
qd	Every day		
qid	Four times a day		
RBC	Red blood cells		
RFTs	Renal function tests		
RIBA	Recombinant immunoblot assay		
RIF	Rifampin		
RNA	Ribonucleic acid		
RPR	Rapid plasma reagin		
RTV	Ritonavir		
SGOT	Serum glutamic oxaloacetic transaminase		
SGPT	Serum glutamic pyruvic transaminase		
SHRZ	Streptomycin (S), Isoniazid (H), Rifampicin (R), Pyrazinamide (Z)		
SHRZE	Streptomycin (S), Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)		
SIT	Structured intermittent therapy		
SMX	Sulfamethoxazole		
SQV	Saquinavir		
SQV/r	Saquinavir/ritonavir		
STAT	Immediately		
STD	Sexually transmitted disease		
STI	Sexually transmitted infection		
STI	Structured treatment interruption		
Stool R/E	Stool routine examination		
TB	Tuberculosis		
TDF	Tenofovir		
TDM	Therapeutic drug monitoring		
tid	Three times a day		
TLC	Total lymphocyte count		

Part A:
HIV/AIDS Care and Treatment



Module A1

HIV/AIDS Programming and HIV Disease: An Introduction



Session 1: Program Overview

This session introduces the participants to the course on HIV/AIDS care and provides an overview of the program.

Session 2: General Background on HIV/AIDS: Epidemiology

Participants learn about the HIV/AIDS epidemic and its impact worldwide, including in sub-Saharan Africa. The session addresses the epidemiology of HIV/AIDS, mechanisms of transmission and disease progression.

Session 3: HIV/AIDS Prevention

Participants learn about the components of comprehensive HIV/AIDS programming. The session covers risk reduction, behavior change communication, voluntary counseling and testing, care and treatment and the relationships among these different components.

Session 4: Comprehensive Care for People Living with HIV/AIDS

This session provides an opportunity for participants to explore issues and strategies involved in providing comprehensive care and treatment services.

Session 5: Immunology and Natural History of HIV/AIDS

Participants learn about the normal immune system, how the HIV virus damages and destroys the immune system, and how the disease progresses.

Session 6 : Diagnosis of HIV

Participants learn how to make an initial assessment, what questions to ask when taking a history, and what to look for in a physical exam. Participants practice taking a sexual history and learn when and how to advise patients to consider HIV testing. They learn about serologic and laboratory tests to diagnose HIV infection and AIDS.

Session 7: Patient Clinical Presentation, Differential Diagnosis, and Follow-up

Participants learn about oral lesions, dysphagia and odynophagia, including common etiological agents, recommended diagnostics, common findings, management and treatment.

SESSION 1 Program Overview

PURPOSE

This session introduces participants to the course on HIV/AIDS care and provides an overview of the program.

The goal of this course is to train doctors and others involved in patient care (nurses, pharmacists, lab technicians) in resource-limited countries to diagnose and manage HIV/AIDS and HIV-related diseases, including opportunistic infections. Improving care for opportunistic infections and HIV-related conditions is a critical component of HIV/AIDS programs.

The course presents the biomedical facts of care for people with HIV/AIDS in the context of a comprehensive public health approach, taking into account the physical and psychosocial needs of clients, patients, and their households. It approaches the specific recommendations for diagnostic measures and patient treatment from a global perspective and directs the facilitator and participants to refer to and discuss local guidelines.

The course uses participatory approaches and methodologies, such as clinical management algorithms and case studies.

A preliminary pretest and self-assessment of knowledge and skills in the major areas of the workshop opens the course; a post-workshop assessment uses the same tools.

OBJECTIVES:

By the end of this session, participants will be able to

1. Identify the goals, objectives and areas to be addressed.
2. Assess and discuss their own level of knowledge and sense of competency in those areas.

TIME:

50 minutes

SESSION 2 General Background on HIV/AIDS: Epidemiology**PURPOSE**

In this session, participants will learn about the HIV/AIDS epidemic and its impact worldwide, including in sub-Saharan Africa. The session will address the epidemiology of HIV/AIDS, mechanisms of transmission and disease progression. Different regions should incorporate locally relevant facts about epidemiology and other aspects of HIV/AIDS.

OBJECTIVES

By the end of this session, the participants will be able to:

1. Discuss the impact of the HIV/AIDS epidemic globally and in Africa.
2. Describe the various types and subtypes of HIV.
3. Discuss how HIV is transmitted and the biological and socioeconomic factors that facilitate transmission.

TIME

30 minutes

1. Epidemic Update

- Global picture:
 - Fourth biggest killer worldwide
 - Estimated 42 million now living with HIV
 - About one-third are aged 15-24
 - Most people do not know they are infected
 - Young women are especially vulnerable, for reasons discussed later
- Sub-Saharan Africa:
 - The region most affected by the epidemic
 - HIV is now the leading cause of death in that region
 - Estimated 3.5 million new HIV infections in 2002
 - 29 million Africans now live with the virus
 - 11 million children have lost their mother or both parents, and this figure is expected to double over the next decade
- National and local data
 - Country of workshop: Estimated national prevalence _____
 - Areas of country that have an especially high prevalence

2. Types and Subtypes of HIV

Two types of HIV are currently recognized: HIV-1 and HIV-2. Worldwide, the predominant virus is HIV-1. Transmission of both types of virus is by sexual contact, through blood, and from mother to child, and they appear to cause clinically indistinguishable AIDS. However, HIV-2 is transmitted less easily, and the period between initial infection and illness is longer in the case of HIV-2

a. HIV-1

Because of its high rate of replication, HIV-1 mutates rapidly into subtypes.

We currently know of at least 10 genetically distinct subtypes of HIV-1 within the major group (group M), containing subtypes A to J.

In addition, group O (Outliers) contains a distinct group of very heterogeneous viruses.

These subtypes are unevenly distributed throughout the world.

For instance:

- Subtype B is found mostly in the Americas, Japan, Australia, the Caribbean and Europe.
 - Subtypes A and D predominate in sub-Saharan Africa.
 - Subtype C predominates in South Africa and India.
 - Subtype E predominates in Central African Republic, Thailand and other countries of southeast Asia.
- Subtypes F (Brazil and Romania), G, and H (Russia and Central Africa), I (Cyprus) and O (Cameroon) are of very low prevalence.
- In Africa, one finds most subtypes, though subtype B is less prevalent.

What are the major differences among these subtypes?

The major difference is their genetic composition; biological differences observed in vitro and/or in vivo may reflect this. It may be that certain subtypes are associated predominantly with specific modes of transmission, for example: subtype B with homosexual contact and intravenous drug use (essentially via blood) and subtypes E and C with heterosexual transmission (via a mucosal route).

- Many countries report a variety of subtypes.
- A person can be coinfecting with different subtypes.
- Subtype C currently accounts for more than half of all new HIV infections worldwide.

b. HIV-2

- This is another human retrovirus, causing a similar immune deficiency because of depletion of CD4 cells.
- Confined primarily to West Africa
- Compared to HIV-1, is less transmissible, is associated with a lower viral burden and a slower rate of both cell decline and clinical progression.
- Note local HIV-2 prevalence: _____.

3. HIV Transmission

Geographic and socioeconomic factors influence which modes of transmission predominate. In some countries more than one of the modes of HIV transmission below is responsible for the HIV/AIDS epidemic.

a. Modes of transmission

- **Sexual contact:** male-to-female, female-to-male, male-to-male, and female-to-female
- **Parenteral:** blood transfusion, intravenous drug use (IDU) through needle-sharing, needle stick accidents
- **Perinatal:** in utero, during labor and delivery, postpartum through breastfeeding

Worldwide, sexual transmission is the predominant mode.

HIV cannot be transmitted by casual contact (for example, hugging or shaking hands), surface contact (for example, toilet seats) or from insect bites (for example, from mosquitoes).

b. Biological factors affecting transmission

- Factors that increase risk of transmission

Infectiousness of host

High viral load: initial stage of infection and more advanced stages

Presence in semen and genital secretions

Exposure to blood, for example, genital ulcers, trauma during sexual contact, menstruation during sexual contact

Breastfeeding by HIV-positive mother

Susceptibility of recipient

Inflammation or disruption of genital or rectal mucosa

Lack of circumcision in heterosexual men

Sex during menstruation, increasing a woman's risk

Presence of an ulcerative or non-ulcerative STD

Viral properties

Virus may be resistant to antiviral drugs

- Factors that decrease risk

Correct and consistent use of latex condoms

Antiretroviral therapy (ART) may decrease, but not eliminate, the risk of HIV transmission. Therefore, patients on ART need intensive counseling on continued risk reduction behaviors.

ART has been shown to reduce vertical transmission from a mother to a fetus by more than 50% when administered late in pregnancy or during labor.

c. Socioeconomic factors facilitating transmission

- Social mobility

Global economy: more people traveling and working away from home

HIV/AIDS follows the routes of trade and commerce

Men have sex with prostitutes, contract HIV and return home to their wives, who contract HIV and pass it along to their infants in utero or through breast milk.

- Stigma and denial

Denial and silence regarding HIV are the norm.

People with HIV are stigmatized for many reasons:

HIV is a slow, incurable disease, resulting in illness and death.

HIV is considered a death sentence.

People often do not understand how HIV is spread and are irrationally afraid of acquiring it from those infected with it.

HIV transmission is often associated with moral violations of social mores concerning sexual relations, so people with HIV are tainted with the notion of their having done something “bad.”

People do not want to admit that a fatal disease spread by behavior branded as “immoral” could be rampaging through their community or country.

People tend to stigmatize or blame certain groups for spreading HIV, for example, sexually promiscuous people or drug users.

Stigma prevents people from speaking about or acknowledging HIV as a major cause of illness and death.

Stigma prevents HIV-infected people from seeking care and from taking preventive measures.

Even when counseling and testing are offered, people may not want to know if they are infected for fear of being stigmatized; this fuels the spread of the disease.

- People in conflict

AIDS is spread at times of instability, war, and violent struggles for power.

Members of the military engage in commercial sex.

They use rape as a way to humiliate and control civilians or to weaken an enemy by destroying the bonds of family and society.

- Cultural factors

Cultural traditions, beliefs and practices affect people’s understanding of health and disease and their acceptance of conventional medical treatment.

Culture describes learned behavior affected by gender, home, religion, ethnic group, language, community and age group.

Culture can create barriers that prevent people, especially women, from taking precautions.

For example, in many cultures, domestic violence is viewed as a man’s right, which reduces a woman’s control over her environment. This means she cannot question her husband’s extramarital affairs, cannot negotiate condom use and cannot refuse to have sex.

Give country-specific examples.

- **Gender**
Gender roles have a powerful influence on HIV transmission. In many cultures, men are expected to have many sexual relationships. There is social pressure for them to do so. This increases their risk of becoming infected. Because women often suffer economic inequities, as described elsewhere, they often need to use sexual exchange as a means of survival. This exposes them to unacceptable risks when they try to negotiate safe sex (for example, rejection, loss of support and violence).
- **Poverty**
Poor people lack access to information needed to understand and prevent HIV/AIDS. Ignorance of the basic facts makes millions of people worldwide vulnerable to HIV infection. A study in Carleton, South Africa showed that one-third of people were convinced that HIV-positive people always show symptoms.
- **Drug use and alcohol consumption**
These lower a person's inhibitions and impair judgment, which may result in risky behavior. Injecting illicit drugs frequently involves the sharing of needles and injection equipment, increasing the risk of HIV transmission.

SESSION 3 HIV/AIDS Prevention

PURPOSE

In this session, participants will learn about the components of comprehensive HIV/AIDS programming. The session covers risk reduction, behavior change communication, voluntary counseling and testing, and care and treatment. It also explores the relationships among the different components.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the major components of HIV/AIDS programs and the factors that make programs effective.
2. Discuss interventions targeted at risk reduction and causative factors.
3. Identify approaches to STI management, VCT, and the synergy among prevention, care and treatment.

TIME:

50 minutes

A. Prevention Interventions

1. Mainstays of a successful prevention program
 - a. To be successful, prevention interventions must address the modes of HIV transmission.
 - b. Heterosexual intercourse is the most common mode of HIV transmission in resource-poor countries. Interventions must take into account variables that fuel heterosexual transmission and ways of reducing this transmission.
 - c. The key factors in heterosexual transmission of HIV are:
 - Frequent change of sexual partners
 - Unprotected sexual intercourse
 - Presence of STIs and poor access to STI treatment
 - Lack of male circumcision
 - Social vulnerability of women and young people
 - Economic and political instability of the community
 - Lack of knowledge of serostatus
 - d. Ways to reduce heterosexual transmission of HIV:
 - Better recognition of the symptoms of STIs and improved behavior in seeking treatment
 - Better management of STIs
 - Sexual abstinence or delayed onset of sex, especially for adolescents
 - Fewer sexual partners
 - Safer sex practices, including consistent, correct use of condoms
 - Supportive social environment to sustain behavioral change
 - Reduced stigma and discrimination against people with HIV
 - Promotion of male circumcision
 - Abstinence
 - e. Despite the explosive spread of HIV/AIDS, several intervention programs have been successful. The mainstays of these programs are:
 - Improved access to VCT
 - Behavior change communication that includes messages about abstinence, fidelity and condom use
 - Improved access to condoms to reduce the risk of infection and to decrease vulnerability to HIV
 - Effective management of STIs
 - Change in social norms to support behavior change
 - Safe blood transfusions through widespread testing of donors
 - Rigorous application of universal precautions and PEP in health care settings
2. **Interventions aimed at decreasing the risk of infection include:**
 - Interventions to reduce high-risk sexual behaviors such as frequent changes in sexual partners, unprotected sexual intercourse and early sexual debut.
 - Interventions aimed at changing situations that support high risk sexual behavior, such as poverty among young women, truck stop situations in communities where these women live, heavy alcohol use associated with sexual behavior. High-risk groups are typically sex workers and their clients; people who are highly mobile, such as long distance truck drivers and migrant workers; the military; and police.
 - Behavior change interventions and behavior change communications can be targeted at the general population or at high-risk groups, and must be tailored accordingly. Examples include:

- Community drama to increase a community's awareness of risks for HIV transmission
- Peer education sessions to teach skills in condom use and condom negotiation
- Group discussions with youth about delaying sexual debut
- Social marketing of condoms
- Social norm changes to support risk reduction through drama, peer education and community meetings

3. Interventions must address causative factors, including vulnerability

Vulnerability results from individual and societal factors that increase the risk of HIV infection. These factors—which include poverty, unemployment, illiteracy, gender inequities, cultural practices, lack of information and services, and human rights abuses—greatly increase the vulnerability of some groups, most typically adolescent girls, women, sex workers, illegal immigrants, orphans and displaced persons. Young people are often more vulnerable because they lack financial independence and are in a stage of life where experimentation is common.

The following are examples of how vulnerability can be an issue for some of these groups:

- Illiterate women with limited skills, few job opportunities and limited access to health information and services are more likely than other women, and the population as a whole, to engage in unprotected sex for money.
- Child prostitution and financial enticement of young girls by adult men increase girls' vulnerability to HIV/AIDS in many countries.
- Orphaned girls often have to curry favors from their teachers or other adult men in order to stay in school or support their siblings.

Interventions to decrease vulnerability include those that aim to:

- Change adverse policies, social norms and harmful cultural practices.
- Create income-generation schemes and programs for orphans and other vulnerable children.

Behavior change interventions need to take into account the factors that increase vulnerability

4. Effective management of STIs can reduce the risk of HIV infection.

This is because STIs increase the transmission and acquisition of HIV. Worldwide, more than 300 million new cases of STIs occur each year, mostly in poor countries, and the global distribution of HIV is similar to that of STIs. Note that STIs are an important cause of ill health, especially in women and children.

B. Voluntary Counseling and Testing (VCT)—An Essential First Step

There is a synergistic relationship between VCT and HIV care and treatment.

Counseling and testing is not only an effective prevention, care and support intervention aimed at the public in general, it is an essential first step in the diagnostic process for people with suspected HIV-related illness. Counseling is an important component of testing. Counseling has a place at both pre- and post-test points, and testing can be both an entry point to care and an opportunity to reinforce prevention messages. This applies to those who test positive and to those who test negative. For those who are positive, this is an important opportunity to promote affirmative living.

- A randomized control trial in Kenya, Tanzania and Trinidad showed that VCT significantly reduced high-risk sexual behavior among individuals and couples.

C. Care and Treatment: Enhancing the Efficacy of Prevention

Providing care and treatment enhances the efficacy of prevention in several ways. Access to care and treatment:

- Helps provide hope to those living with HIV/AIDS and their families
- Helps restore dignity to PLHA and thereby reduce the stigma associated with HIV infection
(Providing hope and restoring dignity help to decrease stigma, thereby increasing the likelihood that there will be community dialogue about HIV, which is a prerequisite to prevention.)
- Helps reduce the risk of sexual transmission through effective ART
- Helps encourages people to seek VCT and PMTCT services
- May promote behavior change
- Provides additional opportunities for prevention education and counseling

Note: Studies in industrialized countries have shown that access to ARV drugs may lead to more high-risk behavior. Counseling on prevention while on ART is critical.

SESSION 4 Comprehensive Care for People Living with HIV/AIDS (PLHA)

PURPOSE

To provide an opportunity for participants to explore issues and strategies involved in providing comprehensive care and treatment services

OBJECTIVES:

By the end of the session participants will be better prepared to:

1. Describe the purpose and components of a comprehensive care and treatment program in primary, secondary and tertiary health care settings.
2. Discuss the HIV/AIDS continuum of care.
3. Discuss the management of HIV/AIDS as a chronic disease.
4. Describe the importance of and elements of standards of care.
5. Discuss the opportunities within care and treatment programs to promote prevention.
6. Discuss HIV/AIDS programmatic issues in their local situation.

TIME:

2 hours

1. Background

Care, treatment and support programs should be designed to respond to the needs and demands of people living with HIV/AIDS and their families or households. This often requires considering a context of stigma, fear, neglect and impoverishment that complicates the clinical picture. Access to antiretroviral treatment can help mitigate the effect of this context.

The purpose of HIV/AIDS care, treatment and support programs is to:

- Assure equitable access to diagnosis, medical care, pharmaceuticals and supportive services.
- Reduce morbidity and mortality from HIV/AIDS and related complications.
- Promote prevention opportunities within care, treatment and support clinical encounters.
- Improve the quality of life for adults and children living with HIV/AIDS and their families.

2. Components of comprehensive care, treatment and support

Providing HIV/AIDS care to people living with HIV and AIDS, and to their families requires a broad range of services that includes not only medical care and pharmaceuticals, but also supportive services to assure adequate nutrition; psychological, social, and daily living support; and prevention messages wherever the opportunity arises.

Comprehensive HIV care includes the following components:

- Medical and nursing care
 - Counseling and testing for screening and diagnostic purposes
 - Prophylaxis of opportunistic infections
 - Management of HIV-related illnesses, including opportunistic infections
 - TB control
 - STI management
 - Management of HIV disease with HAART
 - Palliative care
 - Access to HIV-related drugs, including drugs for opportunistic infections, antiretrovirals and traditional therapies
 - Interventions to reduce parent-to-child transmission of HIV
 - Clinical HIV/AIDS care for mothers and infants
 - Support systems such as functional laboratories and drug management systems
 - Nutritional support
 - Health education
 - Adequate universal precautions in clinical settings and post-exposure prophylaxis (PEP)
- Psychological support
 - Community services to meet the emotional and spiritual needs of positive individuals and their families, including support through post-test clubs and peers
- Socioeconomic support
 - Material and social support within communities to ensure that nutritional and daily living needs are met
 - Support for orphans and vulnerable children (OVC)
- Involvement of HIV-positive individuals and their families in service planning and delivery to ensure that HIV care, treatment and support programs intended for them address their needs and include human rights
- Respect for human rights and legal needs
 - Services that address stigma and discrimination issues in health facilities, in communities and in the workplace as well as promote equal access to care

Figure A1, 4.1, below illustrates the main domains and elements of HIV comprehensive care.

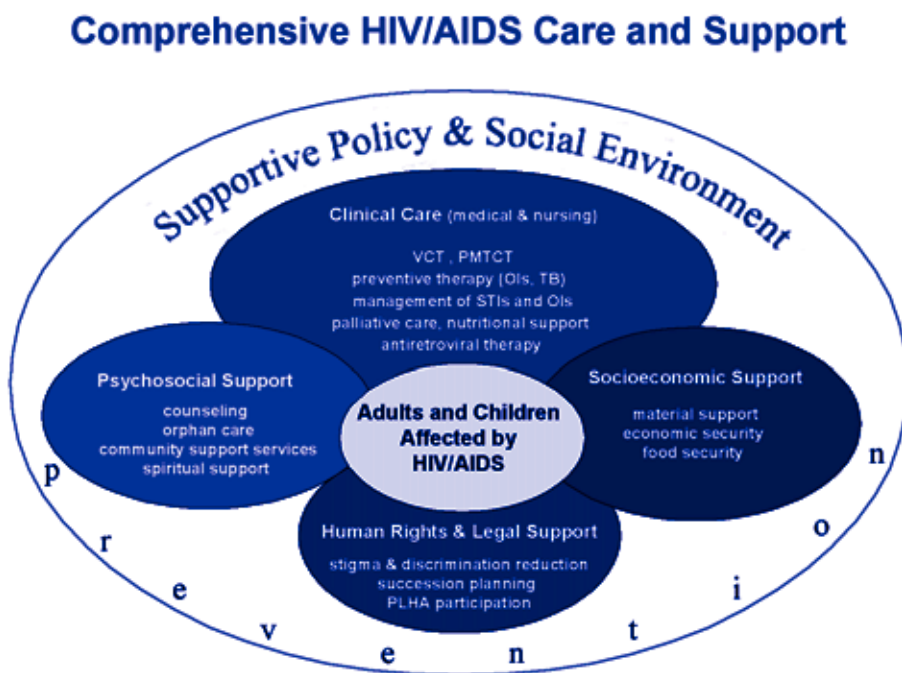


Figure A1, 4.1: Comprehensive HIV/AIDS Care, Treatment and Support

In this comprehensive approach, each service is linked to and reinforces other services.

3. Continuum of HIV/AIDS care, treatment and support

Multiple providers or programs may offer the range of care, treatment and support services in different locations. However, partnership and collaboration are essential to make timely patient access to the appropriate services possible. The HIV Care Continuum (Figure A1, 4.2, below) illustrates how these linkages should function in a referral system. Care providers at any service point should know who provides other services within comprehensive care, where the services are located, and when and how to make a referral.

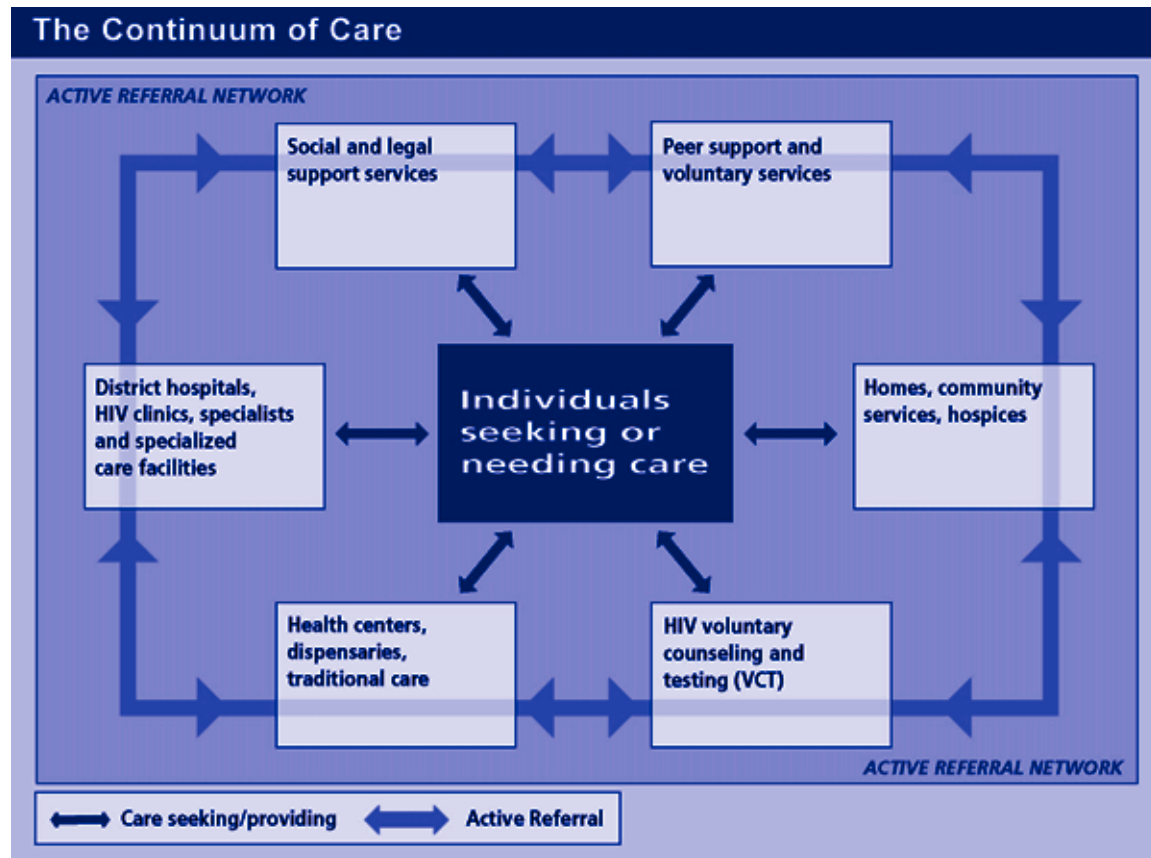


Figure A1, 4.2: The HIV Care Continuum

In the medical and nursing domain, referrals need to be made to higher echelons and discharge planning to lower echelons, for example, home care. Home care providers should be able to assess risk situations for referrals to both medical and support services. Referrals at all levels must be explicit to ensure that social, legal, human rights, and peer support needs are being met. Peers from PLHA support groups play a major role and should be involved in shaping the delivery of care in communities.

4. HIV/AIDS care requires a chronic disease management approach

In resource-poor settings, chronic disease management has been relegated to the background. Priority has been given to acute illnesses, for example, respiratory illnesses and malaria. But chronic disease management is essential, especially once life-prolonging treatment for HIV/AIDS is available, creating a demand for long-term care.

Principles of chronic disease management that are pertinent to HIV/AIDS care follow.

- a. The patient and health providers work as a team to foster the patient's self-management skills, the health care provider's application of technical knowledge and skills, and assistance from social services. This demands a steady relationship between patient and health care team members. At a minimum, the team includes a clinician authorized to prescribe medications, a nurse and a pharmacist. Supporting this is collaboration with community service organizations providing services to meet the patient's many nonmedical needs. There should be regular interdisciplinary care team meetings to discuss care issues, review treatment protocols, express concerns, and support colleagues.
- b. Continuing care involves regularly scheduled visits with clinical and support staff, on a predetermined schedule, to (1) monitor disease status and treatment effect, including labs; (2) provide ready response to emerging health and socioeconomic issues; while at the same time (3) maintaining up-to-date, easily retrievable documentation. The corollary is that continuing care always tries to avoid or reduce disease-related exacerbations that require acute management.
- c. Support for care team members is essential to provide quality of care and avoid frustration and burnout.
- d. Currently, available treatment is life-long. It is to be expected that motivation to maintain wellness and adhere to treatment will fluctuate during the course of the disease.

5. Standards of care

- a. Setting standards of care for HIV-infected persons is intended to promote delivery of the highest possible quality of care and establish measures to evaluate and improve client services. This requires deciding how to achieve the standards, applying them in clinical practice and then evaluating whether they have been achieved (what is needed/process issues/desired outcomes).
- b. There will be different standards for a comprehensive care package at each level of the health care system—that is, referral hospital, district or peripheral hospital, health center and dispensary/community. Developing practice standards and then monitoring the quality of their implementation are both important to delivering appropriate HIV care.
- c. Clinical services include affordable and standardized practices based on international and national guidelines: preventive therapies, management of HIV-related conditions and opportunistic infections, laboratory services, secure supply of prescribed medications, highly active antiretroviral therapy (HAART), post-exposure prophylaxis (PEP) for occupational injuries and rape, STI management and palliative care.

6. Prevention as a part of care and treatment

Prevention must not be neglected as PLHA receive care and treatment. In developed countries, there has been a tendency to relax prevention behaviors, such as condom use, once many with HIV/AIDS are treated. This can be a tragic consequence of what is perceived as an enhanced program for PLHA.

At each point in the process of providing care and treatment, opportunities exist to introduce or reinforce prevention messages.

Targets of opportunity for integrating prevention into care and treatment follow:

Clinic waiting room	<ul style="list-style-type: none"> • Posters about preventing HIV transmission (partner reduction, abstinence, condom use) • General HIV/AIDS videos • Simple visually oriented brochures about transmission
Provider-patient interaction	The provider should remind clients about preventing HIV transmission at each visit (through simple messages, such as “Remember the ABCs,” and checking to see that the client understands, as well as by providing condoms or at least having them visibly available in the provider’s office).
Home care	Visitors to the homes of PLHA can also carry condoms and talk to the family about proper precautions in caring for patients, as well as reminding them of general and specific risk reduction behaviors for themselves.

SESSION 5 Immunology and Natural History of HIV/AIDS

PURPOSE:

In this session, participants will learn about the normal immune system, how the HIV virus damages and destroys the immune system, and how the disease progresses.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss how the normal immune system works.
2. Describe the HIV lifecycle and its effect on the immune system.
3. Describe the stages of disease progression, including symptoms, laboratory findings and management of primary infection and seroconversion.

TIME:

60 minutes

A. The Normal Immune System

1. The Normal Immune System

- a. Protects the body by recognizing antigens on invading bacteria and viruses and reacting to them.
- b. Consists of lymphoid organs and tissues, including the bone marrow, thymus gland, lymph nodes, spleen, tonsils, adenoids, appendix, blood and lymphatic vessels.
- c. All components are vital in the production and development of lymphocytes or white blood cells.
- d. B-cells and T-lymphocytes (T-cells) are produced from stem cells in the bone marrow. B-cells mature in the marrow, but T-cells travel to and mature in the thymus gland.
- e. B-cells recognize specific antigen targets and secrete specific antibodies that coat the antigens by making them more vulnerable to phagocytosis or by triggering the complement system.
- f. T-cells regulate the immune system and kill cells that bear specific target antigens. Each T-cell has a surface marker such as CD4, CD8 and CD3 that distinguishes it from other cells.
- g. CD4 cells are helper cells that activate B-cells, killer cells (CD8) and macrophages when a specific antigen is present.
- h. Phagocytes include monocytes and macrophages—large white blood cells that engulf and digest cells carrying antigenic particles.
- i. The complement system consists of 25 proteins and is capable of inducing an inflammatory response when it functions with antibodies to facilitate phagocytosis or to weaken the bacterial cell membrane.
- j. When the immune system is weakened or destroyed by a virus such as HIV, the body is vulnerable to opportunistic infections.

2. The Human Immunodeficiency Virus

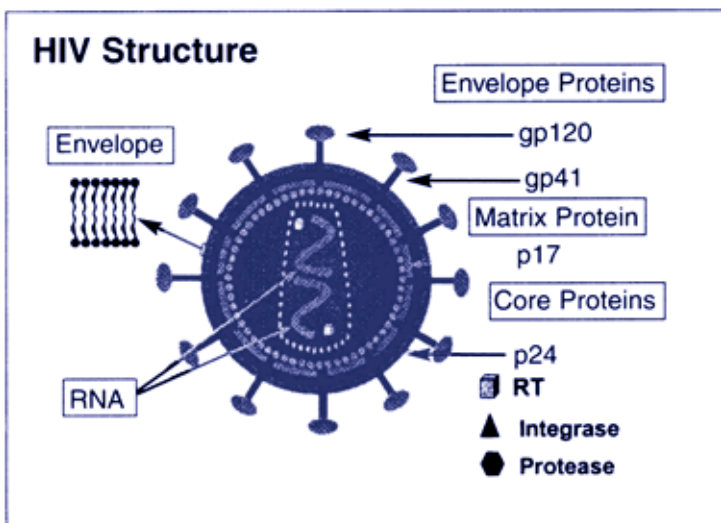


Figure A1, 5.1: The Human Immunodeficiency Virus

- a. It is a retrovirus, which uses its RNA and the host's DNA to make viral DNA. It has a long incubation period (clinical latency).
- b. It consists of a cylindrical center surrounded by a sphere-shaped lipid envelope. The center consists of two single strands of ribonucleic acid (RNA).
- c. It causes severe damage to and eventually destroys the immune system by utilizing the DNA of CD4 lymphocytes to replicate itself. In the process, the virus destroys the CD4 lymphocyte.
- d. HIV lifecycle
 - Host cells infected with HIV have a very short lifespan.
 - Therefore, HIV is continuously using new host cells to replicate itself.
 - Up to 10 million individual viruses are produced daily.
 - In the first 24 hours after exposure, the virus attacks or is captured by dendritic cells (type of phagocyte) in the mucous membranes and skin.
 - Within five days of exposure, infected cells make their way to lymph nodes and eventually to the peripheral blood, where viral replication becomes very rapid.
 - The five phases are: binding and entry, reverse transcription, replication, budding, and maturation (see Figure A1, 5.2, below).

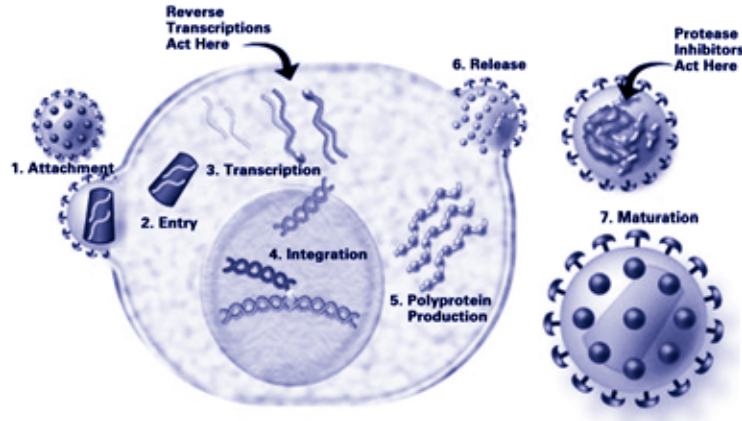


Figure A1, 5.2: The Five Phases of the HIV Lifecycle

B. Natural History: The Chronology of HIV-Induced Disease

1. Primary HIV Infection and Seroconversion

a. Clinical features

- On first exposure, there is a 2-4 week period of intense viral replication before onset of an immune response and clinical illness.
- Acute illness lasts from 1-2 weeks and occurs in 53% to 93% of cases.
- Clinical manifestations resolve as antibodies to virus become detectable in patient serum.
- Patients then enter a stage of asymptomatic infection lasting months to years.

b. Seroconversion illness

- Manifests as a flu-like syndrome. General symptoms may include:
 - Acute onset of fever with or without night sweats
 - Myalgia is common, may be associated with muscle weakness
 - Lethargy and malaise are frequent and often severe, may persist for several months
 - Depressed mood
 - Pharyngitis/sore throat
 - Lymphadenopathy
 - Arthralgia
 - Anorexia/weight loss
- Neurological symptoms
 - HIV readily isolated from the cerebrospinal fluid during primary infection
 - Early infection of central nervous system frequently results in aseptic meningoencephalitis with symptoms of headache, photophobia and retro-orbital pain.
 - Other more unusual features include:
 - Myelopathy
 - Peripheral neuropathy
 - Brachial neuritis
 - Facial palsy
 - Guillain-Barre syndrome

- Gastrointestinal symptoms
 - Mucocutaneous ulceration is a distinctive feature. Ulcers are generally small, round or oval. Surrounding mucosa looks normal.
 - Pharyngeal edema is common.
 - Oral/oropharyngeal candidiasis
 - Nausea/vomiting
 - Diarrhea

- Dermatological symptoms
 - Erythematous, non-pruritic, maculopapular rash is common.
 - Roseola-like rash
 - Diffuse urticarias
 - Desquamation of palms and soles
 - Alopecia

- Laboratory findings

First 1-2 weeks:

- Profound reduction in CD4 and CD8 lymphocyte counts with inversion of the CD4:CD8 (The normal ratio is 2:1—2 CD4 cells to 1 CD8 cell.)
- Followed by a peripheral lymphocytosis consisting of predominantly CD8 cells.
- Mild thrombocytopenia is common.
- C-reactive protein level and erythrocyte sedimentation rate are frequently elevated.
- Hemoglobin level usually remains stable.
- Elevated serum alkaline phosphatase and transaminase levels are common.

First 2-6 weeks:

- Antibodies to HIV are detectable.
- HIV antigen (p24) may be detected in serum before detecting antibodies; therefore, antigen testing is important in diagnosing seroconversion.
- The *window period*: Period in which HIV-positive patients may not test positive for anti-HIV antibodies. Generally limited to first 2-6 weeks, but up to 3 months is given to be sure. In rare cases, the window period may last as long as 6-12 months.

Note: In high prevalence, high incidence settings such as STD or sex worker clinics, as many as 5% of those testing HIV antibody negative will actually be in the window phase and are really infected with HIV. People in these settings who test HIV negative should be counseled strongly to return in three months for repeat testing.

- Management

Clinical management is primarily symptomatic.

The goal at this stage is to give appropriate counseling and education to prevent further spread.

Issues to consider:

- The physical distress of the illness
- Tentative nature of the diagnosis before serodiagnosis is made
- Patient's self-reproach
- Implications for the patient's lifestyle
- Contact tracing should be attempted to identify the source.
(Contact person may be unaware of their infection; may be seroconverting themselves; may be unaware of safe sex or safe injecting practices.)
- Study of using antiretroviral agents during this stage is underway

2. Stages of Disease Progression

a. Early immune depletion (CD4 cell count >500/ μ L)

- During this stage, level of virus in blood is very low.
- HIV replication taking place mostly within lymph nodes
- Generally lasts for five years or more
- Persistent Generalized Lymphadenopathy (PGL) without other symptoms may be noted.
- Usually symptom-free, but several autoimmune disorders may appear, such as:
Idiopathic thrombocytopenia (ITP)
Guillain-Barre syndrome

b. Intermediate immune depletion (CD4 cell count between 500 and 200/ μ L)

- Immune deficiency increases.
- Infections start and persist or increase as the CD4 cell count drops.
- Consider beginning first-line antiretroviral therapy (if indicated by the guidelines).

Consider preventive treatment for TB and Cotrimoxazole PT

- Less severe infections appear, particularly of skin and mucosal surfaces:

Tinea	Molluscum contagiosum
Seborrheic dermatitis	Bacterial folliculitis
Warts	Gingivitis

- Other infections begin to manifest
 - Oral candidiasis appears late in this phase.
 - Reactivation of herpes zoster and herpes simplex may occur.
 - Infection with Mycobacterium tuberculosis occurs relatively early in this phase.
 - Chronic sinusitis

[Refer to chart depicting chronology of HIV induced diseases.]

c. Advanced immune depletion (CD4 cell count <200/ μ L)

- Case definition of AIDS is having a CD4 cell count of less than 200/ μ L.

SESSION 6 | Diagnosis of HIV**PURPOSE:**

Clinicians or health care providers all too often miss the diagnosis of HIV. They need to know the many presentations of HIV disease and use a systematic framework to ensure a proper diagnosis.

In this session, participants will learn how to make an initial assessment, what questions to ask when taking a history and what to look for in a physical exam. They will practice taking a sexual history and learn when and how to advise patients to consider HIV testing. They will learn about the various serologic and laboratory tests available for diagnosing HIV infection and AIDS, as well as how they work and how they are used, and will discuss the various options available in their local situation, including availability and costs.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe why establishing trust between the caregiver and the patient is essential.
2. Identify the questions to ask in taking a patient's history and what to look for on a physical exam.
3. Discuss why it is important to take a proper sexual history.
4. Take a sexual history using open-ended questions and listening skills.
5. Identify clinical and lifestyle clues using an algorithmic approach to HIV testing, and describe when and how to advise patients to consider HIV testing.
6. Describe the various serologic tests and how they work.
7. Interpret the results of the tests and make a diagnosis.
8. Establish the stage of the disease and exposure to other infectious diseases through a baseline laboratory evaluation of CD4 cell count.
9. Discuss guidelines for testing in their local situation based on availability and cost.

TIME:

2 hours and 40 minutes

A. Overview

1. Clinicians and health care providers all too often miss the diagnosis of HIV infection. They need to know the many presentations of HIV disease.
2. Knowing when and how to advise patients to consider HIV testing is a challenge.
3. The chronology of HIV disease provides a useful framework.
4. Using clinical decision-making algorithms helps decide whether or not to advise HIV testing.

B. Patient Assessment

1. Initial Assessment

- a. Establishing trust is essential
 - Providers should remember that most patients are anxious and frightened by the mention of HIV; it is a life-threatening disease with stigma attached to it.
 - The ability to empathize, share knowledge without being patronizing, provide reassurance and remain non-judgmental helps gain a patient's trust.
 - Trust between caregiver and patient is essential in order to obtain accurate information and care for the patient.

- b. The patient interview

The interview is a way to establish trust between the patient and the doctor or nurse (or health care worker of any discipline). Interviews have three main functions: to gather information, to handle emotions, and to manage behavior. You need to develop the specific skills for each of these functions. Doing so takes time. This workshop does not deal with this particular set of skills, but all professionals caring for people with HIV/AIDS should get special training addressing them.

Here is a brief overview of the three functions of the interview and the skills associated with them, with examples:

- **Information gathering**

Skills

- Open-ended questions (cannot be answered with a simple “yes” or “no”)

“Tell me about how things have been going since your last visit.”
- Facilitation

“Go on...I am listening.” (nonverbal: nodding)
- Direction

“I understand that many things are bothering you...could we focus on the diarrhea for just a minute?”
- Summarizing

“So, from what I understand, you have had a lot of nausea and some cramping, you have taken all of the pills each day this week and you want some help with these symptoms...do I have it all right?”

- **Emotion handling**

This is especially important in caring for PLHA and their families.

Skills

- Empathy

“I can see that you are very discouraged.”
- Reassurance

(Understandability) “It is understandable that you are sad...look at what has happened in the last month: you lost your best friend, you are feeling weak and your son is not doing well in school...anyone would

be sad facing all of that.”

(Time limitedness) “It might help to keep remembering that these symptoms last for no more than one month in most people, and you’ve been through this for three weeks now.”

- Education about illness
- Support /partnership
“I want you to know that I will be here to help you through this.”

- **Behavior management**

This is used to achieve both medication adherence and lifestyle change (such as risk reduction). You can accomplish this best through education and motivational skills.

Skills

- Authority/modeling
“I have seen this drug work in many patients.”
- Conditioning
“You really did well this week....you remembered most of your pills.”
- Trait and choice attribution
Trait “You do a good job of keeping track of things at work and caring for your children, so you probably can keep track of these medicines.”
Choice “It is up to you to decide what method you want to use to remind yourself of when to take which pills.”
- Rehearsal and affirmation of intent.
Through rehearsal, you help the patient think through a typical day, review what they will be doing about their medication and say what they intend to do (Affirmation of intent).

History specific to HIV/AIDS:

In addition to the usual aspects of history taking, you should address the following areas:

- Previous tests for HIV? If yes, why tested and what were results?
- Presence of HIV-associated signs and symptoms
- History of sexually transmitted diseases and other infectious diseases
- Other medical diagnoses, for example, malignant or premalignant conditions
- Mental health history (look for signs of depression)
- Family history: age and health of children, HIV in other family members
- Medications taken regularly
- Social history
- Sources of support (family, friends, community, health care providers)
- Sexual history (see 2 and 3 below)
- If appropriate, ask if he/she remembers ever being treated for HIV. (If yes, then *ideally* you would find out about the pretherapy CD4 cell count, HIV viral load and treatment, including duration/adherence.)

c. The physical exam: looking for signs of HIV

- General: look for evidence of wasting, marked fat loss in extremities, face and buttocks
- Skin: rash, papular, macular, vesicular or ulcerative lesions
- Eyes: examine conjunctiva and fundus for changes (retinal opacification, cotton wool spots)
- Oropharynx: (often yields earliest evidence of HIV) examine for thrush, etc.
- Lymph nodes: nontender or minimally tender lymphadenopathy, regional adenopathy, extremely tender lymph nodes
- Lungs: rales
- Gastrointestinal: hepatosplenomegaly
- Neurology: dementia, headache, seizures, focal neuropathies
- Pelvic exam: discharge, ulcers, abscesses

2. Taking a sexual history

a. Why it is important

- Taking an effective and comprehensive sexual practice and lifestyle history is an integral part of medical management.
- Taking a sexual history helps to determine the possibility of past exposure. Emphasize eliciting information about behavior that might have placed the person at risk.
- You will decide to recommend testing on the basis of clinical and lifestyle information obtained from a patient's history and from physical exam.

b. Try to begin with the least sensitive issues.

c. Put patient at ease by asking other relevant details, such as any history of symptoms or signs of concern to the patient and details of past illnesses, including STDs, etc.

d. Explain that taking a sexual history is important in order to assess the person's overall health and determine what tests to do.

e. If possible, ask questions in the context of a general medical history.

f. The interview should move from open-ended to close-ended questions.

In the examples below, most are closed-ended questions on the assumption that the interview has progressed from the initial, more open-ended stage. For example: "Please tell me about how you see your risk for HIV?" to "When was the last time you engaged in sexual intercourse without a condom?"

g. Listen carefully to the responses and ask clarifying questions.

h. Make sure that the patient understands the terms you are using. If possible, use the patient's vocabulary, and be culturally sensitive.

i. Modify your questions to suit the situation and the responses.

j. Be sure all questions about sexual practices are free of any assumptions regarding sexual orientation or monogamy.

k. Be sure to establish whether the patient has had unprotected sex at any time, and especially during the last three months, or has at any time had problems using condoms (for example, breakage).

l. Elicit a history of sexual contacts, taking the most recent first and working back from there.

3. Questions for sexual history

The following questions are mostly close-ended, to be asked only after there has been time for more open-ended discussion and the development of rapport:

- a. To initiate a more detailed discussion of sexual history in relation to potential exposure:
 - Tell me what part sexual activity plays in your life right now? (If necessary, ask “Are you sexually active?”)
 - Can you describe for me what you think about your risk for HIV infection? Why do you think you may/may not be at risk?
 - Have you ever had a sexually transmitted infection? (It helps to give examples.) Do you know if any of your sexual partners have developed a sexually transmitted disease or AIDS?

- b. To elicit more details about the number and sex of partners and the use of condoms:
 - Have you ever had, or do you currently have, sex with men, with women or both?
 - How many sexual partners have you had? (If possible, determine the number of partners in the patient’s lifetime, during the past year and in the past three months.)
 - Do you use condoms?
 - If so, how often?
 - When did you begin using condoms?
 - If not, what was your reason for not using condoms?

- c. To identify sexual practices:
 - What form of sex do you usually have with your partner?
 - Do you have vaginal intercourse?
 - Do you have anal sex? (This may require additional explanation or description.)
 - Do you have oral sex? (This may require additional explanation or description.)

- d. To elicit (nonsexual) lifestyle clues to the risk of HIV infection:
 - Injecting drug use
 - Do you smoke cigarettes, drink alcohol or use other drugs?
 - If the patient currently injects drugs:
 - Do you share needles or other drug equipment?
 - If the patient is a former injecting drug user:
 - When did you stop injecting drugs?
 - Did you share needles or other drug equipment? If so, until when?
 - Blood products
 - Have you ever had a blood transfusion?
 - Have you ever had surgery or a major accident?
 - Did you receive any blood as a result of this surgery/accident?

Role-Play #1

ROLE PLAYER INSTRUCTIONS: PROVIDER

You are a primary care doctor in rural Ghana. This is your 35th patient of the day. She is a 20-year-old woman who looks very worried. This makes you worry about how long this will take and how much trouble it will be to find out what is really going on. You think she is the niece of your neighbor.

CUT OR SEPARATE SHEET HERE

ROLE PLAYER INSTRUCTIONS: PATIENT

You are a 20-year-old woman who has just learned that your boyfriend is HIV positive. You also have been having some headaches, but otherwise you feel well. You are upset about your boyfriend and decided to come to the hospital so the doctor could treat your headaches. The headaches feel like a grabbing sensation around your head and have been there for two weeks. They last all day. They do not wake you up or cause nausea, vomiting or other problems. Aspirin helps.

For your sexual history: You began having sex at the age of 15. But it was not a good experience. Your teacher in high school seduced you after class one day, and you felt you couldn't refuse. You liked him but didn't think sex with him was in the picture. You have not told anyone about this except for one girlfriend, whom you suspected he had also had sex with.

You and your current boyfriend have been together for one year. You have vaginal intercourse (no anal intercourse or oral sex) about every other week when you are able to be alone. He travels a lot for his work as a truck driver and you suspect he has been with other women, but the two of you have never talked about this.

You and your boyfriend have used condoms occasionally, but usually you don't.

Your boyfriend is your fourth partner in the last four years. The others were all men you knew well; you were with each for about one year. You always used condoms with them and had sex about every other week, as well. None of them ever reported an STD or other problem, and you have had no STDs until this boyfriend. He told you three months ago that you should get checked because he had had an ulcer for a few weeks while he was away.

You have never had a blood transfusion and use no IV drugs.

You are nervous because the doctor looks a little familiar to you and you don't want anyone in your family to know about your situation.

Role-Play #2

ROLE PLAYER INSTRUCTIONS: PROVIDER

You are a primary care doctor in Ghana. This is your 35th patient of the day. He is a 45-year-old doctor from a district about four hours away. You have met him at medical meetings. He looks worried, and you wonder what is going on.

CUT OR SEPARATE SHEET HERE

ROLE PLAYER INSTRUCTIONS: PATIENT

You are a 45-year-old physician in a rural district in northern Ghana, where you have worked for six months after returning from postgraduate studies in rural health in the UK.

You began experiencing a cough a few weeks ago and also got a rash and a fever. You spent last summer in Zambia where you saw many AIDS patients. You have been careful but wanted to leave your district to get checked and maybe discuss your fear of being HIV infected, even though you feel you are at low risk. You cannot get it out of your mind.

You have been happily married for 13 years to a woman who is your age. You have four children, now between 5 and 12 years old.

You and your wife have vaginal intercourse about twice a week, no anal intercourse, but oral sex fairly frequently. You were with one other woman twice during your time in London. You engaged in vaginal intercourse using a condom with no breaks or problems with the condom. You have had no STI symptoms, and you do not know if your partner in London has or has not had an STI. To your knowledge, your wife has been faithful and has not had any STIs. For the last 13 years, your wife and the one other woman have been your only partners.

You do not use drugs or alcohol and have not had a blood transfusion.

C. Laboratory Testing

1. Introduction

- a. HIV antibody tests detect antibodies that the immune system forms against HIV. These tests do not look for the virus itself, but search for antibodies produced against a number of viral capsules and core antigens.
- b. *Sensitivity* means the ability of the test to detect antibodies in general.
- c. *Specificity* is the ability of the test to detect antibodies to specific HIV viral proteins.
- d. *Predictive values* measure whether or not an individual actually has the disease, given the result of the screening test. (Accuracy of HIV serology is excellent.)

2. Serologic tests

- a. ELISA (enzyme-linked immunosorbent assay)/EIA (enzyme immunoassay)
 - Tests for a number of antibody proteins in combination
 - A very *sensitive* test, but not entirely *specific*—can detect antibodies to antigens other than HIV, making it possible to give a false positive
 - A positive (or indeterminate) ELISA result means that the sample needs to be tested further by western blot or a different ELISA test.
- b. Western Immunoblot test
 - Used as a confirmatory test
 - Detects antibodies to a number of specific HIV proteins and is considered to be very specific for HIV
 - Samples yielding a negative result are reported as negative.
 - Antibodies to only a selection of viral proteins may yield an indeterminate western blot; you need to collect a further sample to confirm diagnosis.
 - Bands corresponding to p24 and p55 typically are detected early in seroconversion, followed by glycoprotein bands (gp120; gp41) of the viral envelope [refer to diagram of HIV structure shown in section B.2 above].
- c. DNA PCR (polymerase chain reaction)
 - A qualitative test used to detect intracellular virus
 - Can detect 1-10 copies of HIV proviral DNA
 - Used primarily for viral detection with neonatal infection and with indeterminate serology
- d. Rapid Tests
 - There are various tests available that provide results in about 10 minutes. SUDS, Recombigen and Genie are three examples.
 - *Sensitivity* approaches 100 percent; *specificity* is >99 percent—analogous to EIA screening tests.
 - You can report negative tests as definitely negative; you should confirm positive results with standard serology.
 - Useful in situations where immediate results are important to management decisions, such as:
 - Cases of occupational exposure, where the use of post-exposure prophylaxis (PEP) may be possible
 - STD clinics and emergency rooms, where seroprevalence rates are high, but follow-up may be impractical or compliance with follow-up poor

3. WHO testing strategy

a. Overview

- HIV infection is diagnosed by a positive HIV test. Many low-income countries cannot afford expensive Western tests.
- WHO has recommended testing strategies based on a combination of screening tests that do not require expensive Western Blot (WB) confirmation assays.
- HIV testing has become much more widely available than initially predicted, and the diagnosis of HIV purely on clinical features has become less frequent.
- Confirmatory assays (WB) should be used only to resolve indeterminate results for diagnostic purposes.
- A note about tests results:
 - *Positive test results:* Criteria for a positive test are: (1) a positive ELISA followed by a different positive HIV test or (2) a positive WB. (Depending on the criteria, two different rapid tests reporting positive results can also be considered a positive result.)

Tests that that can predict antigens other than HIV can give a false positive result (for example, ELISA).

- *Negative test results:* A negative test result means the patient has not been infected with HIV or that the infection is so recent that detectable antibodies to the virus have not yet appeared in the blood.

False negative test results may occur because of time delay following infection (the “window”), the HIV strain type (for example, HIV-2), and the reagents used.

- *Indeterminate results:* Most often indeterminate results come from a positive ELISA and an indeterminate Western blot, for example, one showing a single band, usually p24.

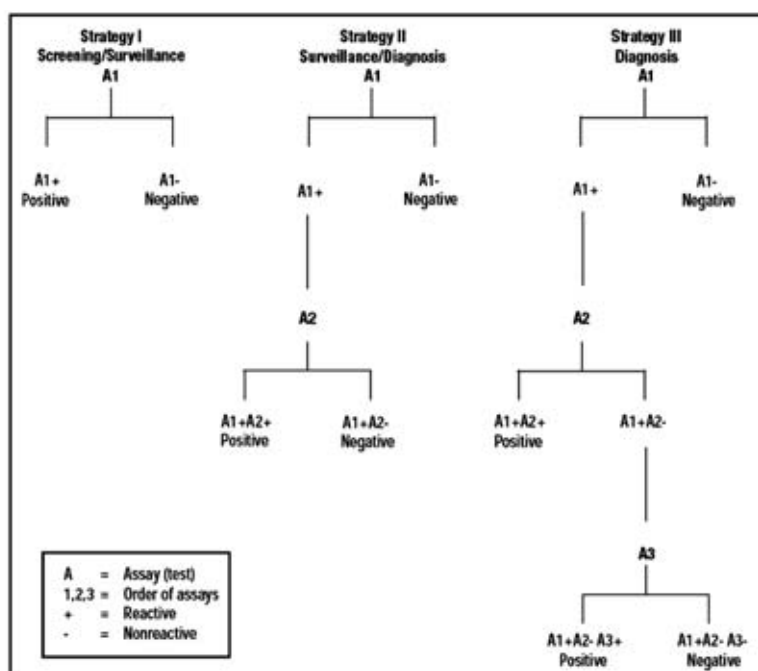
b. Objectives of the test:

- Transfusion and transplant safety
- Surveillance
- Diagnostic

c. Prevalence of infection in the sample population

- UNAIDS and WHO recommendations for HIV testing strategies according to test objectives and prevalence of infection in the sample population:

Objective of the testing	Prevalence of infection	Testing Strategy
Transfusion and transplant safety	All prevalences	I
Surveillance	>10%	I
	< or =10%	II
Diagnostic	>30%	I
	≤30%	II
Asymptomatic	>10%	II
	≤10%	III



WHO/CDC/UNAIDS/USAID Guidelines for Using HIV Testing Technologies in Surveillance: Selection, Evaluation, and Implementation. 2001. WHO/CDS/CRS/EDC/2001.16, UNAIDS/01.22E

Order of use: The order of use is determined by the specificity and sensitivity of the tests.

- The *sensitivity* of a test is the probability of a positive result if infection or disease is truly present. As the sensitivity of a test increases, the proportion of false-negatives decreases.
- The *specificity* of a test is the probability of a negative result if infection or disease is truly absent. As the specificity of a test increases, the proportion of false-positives decreases.
- The first test should have a higher sensitivity (greater than 99 percent), resulting in fewer false negatives. The second and third tests should have a higher specificity (greater than 99 percent), resulting in fewer false positives.
- In most situations where you are involved in the clinical care of AIDS patients, the prevalence of HIV infection in the population is high, and you encounter patients who meet clinical stage III or IV of HIV infection.

In this situation, one **simple** positive screening test is sufficient to diagnose AIDS. (**testing strategy I**)

- For safe transfusion, testing **strategy I** (1 test) is also sufficient to reject blood if it is positive.
- In all other situations, you will need at least two tests to diagnose AIDS. (**testing strategy II and III**)

4. Voluntary Counseling and Testing (VCT)

a. Perform HIV testing for individual diagnosis according to the rules of voluntary counseling and testing (VCT) services:

a. Testing is done **voluntarily**, with **informed consent**. You should exercise no coercion. Mandatory testing is out of the question. Everyone has the right to know (or not know) his or her HIV status.

- Pre- and post-test **counseling** services are in place
- **Confidentiality** must be guaranteed in order to prevent discrimination
- The test must be **technically sound**, and there must be access to a confirmation test.
- The tests are financially (and culturally) **accessible**
- **Minimum care** is available for the patient

- The rationale behind VCT is that it may reinforce preventive behavior in seronegative people.
- If people know they are seropositive, they can take measures to prevent the development of some OIs, to prevent further HIV transmission, and to prepare themselves and their families for the future.
- *Note:* In high prevalence, high incidence settings such as STD or sex worker clinics, as many as five percent of those testing HIV antibody negative will be in the window phase and will in fact be infected with HIV. People in these settings who test HIV negative should be counseled strongly to return in three months for repeat testing.

5. Baseline laboratory tests

- a. After diagnosis is confirmed, a baseline laboratory evaluation is needed to establish the stage of the disease and exposure to other infectious diseases as quantified by the CD4 count.
- b. Other recommended baseline tests include:
 - CBC
 - Serum chemistry panel
 - Syphilis serology
 - Chest x-ray
 - PPD skin testing
 - PAP smears
 - Serology for hepatitis B (HBV)
- c. CD4 lymphocyte count
 - Normal laboratory ranges are usually 500-1400/mm.
 - A CD4 count is the most useful test for assessing immune function.
 - Depletion of CD cells is the most consistent and notable laboratory abnormality observed in persons with HIV.
 - Knowing the baseline CD4 count is vitally important in assessing the patient.
 - Staging of HIV infection, recommendations for antiretroviral treatment, and prophylaxis against OIs are based on the degree of immunosuppression.

6. Syndromic approach to diagnosis

- a. Where diagnostic facilities are severely limited, management decisions must be based on clinical features and simple laboratory findings. It is always preferable to use HIV testing to make a diagnosis.
- b. Flowchart algorithms are useful tools in the assessment and clinical management of HIV infection in adults in resource-limited settings.
- c. The algorithms in this manual are based on MSF/WHO guidelines and cover the following clinical syndromes:
 - Respiratory problems
 - Neurological disorders
 - Chronic diarrhea and gastrointestinal problems
 - Lymphadenopathy
 - Oral lesions and odynophagia and dysphagia
 - Skin lesions
 - Fever

SESSION 7 Patient Clinical Presentation, Differential Diagnosis and Follow-up**PURPOSE:**

There are several different ways to define HIV infection and AIDS. In this session, participants will learn about the clinical presentation of HIV/AIDS and common disorders associated with HIV infection, including the WHO laboratory and clinical classification systems.

Since initial diagnosis of HIV infection may be difficult because the more general signs and symptoms are common to many other infections, participants will also learn about diseases with a similar presentation to HIV and how to make a differential diagnosis.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Identify common disorders associated with HIV infection.
2. Diagnose HIV infection based on major and minor signs and symptoms when CD4 lymphocyte counts are not available.
3. Diagnose HIV infection based on the WHO laboratory and clinical classification systems.
4. List diseases that have a similar presentation to HIV infection.
5. Describe the importance of testing for HIV when testing for these other diseases.
6. Give examples of factors that help in making a diagnosis.
7. Discuss follow-up procedures in their local situation.

TIME:

110 minutes or 1 hour and 50 minutes

A. Patient Clinical Presentation

1. Introduction:

- a. Diagnosing and staging of HIV disease in a person living in a resource-limited country is not as easy and quick as one might think.
- b. You need to do a good clinical examination and thorough interview; this can easily take 20 minutes per patient. Common findings to look for on a physical examination include:
 - Oral thrush
 - Macular rash on palate as a sign of Kaposi's sarcoma
 - Herpes zoster scar
Example: In Zambia, in patients under 40 years old, 9 out of 10 with herpes zoster have HIV.
 - Florid nature of skin manifestations, a hallmark of HIV
 - Condition of the pectoralis, temporalis, biceps, gluteus and shin cover muscles as a clue to wasting. Ask yourself if hair is standing up straight. HIV is a wasting *disease* like cancer and TB.
 - Lymphadenopathy usually not >2.5 cm.
- c. In resource-limited countries, health care workers use the WHO AIDS case definitions and staging system adapted for countries with limited clinical and laboratory diagnostic facilities.
- d. Where laboratory monitoring is available, one should use a further refinement of the WHO staging system.

2. WHO case definitions for HIV/AIDS surveillance in countries with limited clinical and laboratory diagnostic facilities

- a. Where HIV testing is *not* available, diagnose patients clinically based on major and minor signs and symptoms.
- b. The presence of at least two major signs and at least one minor sign fulfill the case definition for HIV/AIDS.
 - Major signs:
 - Weight loss >10 percent of body weight
 - Chronic diarrhea (>1 month)
 - Prolonged fever (>1 month)
 - Minor signs:
 - Persistent cough for more than one month (in case of TB, do not use this criterion)
 - Generalized pruritic dermatitis
 - History of herpes zoster
 - Oropharyngeal candidiasis
 - Chronic progressive or disseminated herpes simplex infection
 - Generalized lymphadenopathy
 - The presence of either generalized Kaposi's sarcoma or cryptococcal meningitis suffices for the case definition of AIDS

This method has the problem of low sensitivity and specificity.

c. Where HIV testing is available

- A positive HIV test together with the presence of one or more of the conditions below fulfills the case definition for HIV/AIDS.
- Weight loss >10 percent of body weight, or cachexia—with diarrhea or fever, or both—for at least one month and not known to be the result of a condition unrelated to HIV infection
- Cryptococcal meningitis
- Tuberculosis (pulmonary or extrapulmonary)
- Kaposi's sarcoma
- HIV encephalopathy: neurological impairment that prevents independent daily activities and not known to be the result of a condition unrelated to HIV infection
- Esophageal candidiasis
- Life-threatening or recurrent episodes of pneumonia
- Invasive cervical cancer

d. The WHO Clinical Staging System

- WHO has also developed a staging system that includes a clinical classification system and a laboratory classification to categorize the immunosuppression of adults by their total lymphocyte counts.
- This staging system has been proven reliable for predicting morbidity and mortality in infected adults.
- Clinical markers believed to fall into four stages of prognostic significance form the basis of the WHO Clinical Staging System. The system incorporates a patient performance scale.

Clinical Stage I

1. Asymptomatic infection
2. Persistent generalized lymphadenopathy (PGL)
3. Acute retroviral infection

Performance scale 1: asymptomatic, normal activity

Clinical Stage II

4. Unintentional weight loss, <10 percent of body weight
5. Minor mucocutaneous manifestations (e.g., seborrheic dermatitis, prurigo, fungal nail infections, oropharyngeal ulcerations or angular cheilitis)
6. Herpes zoster within previous five years
7. Recurrent upper respiratory tract infections (for example, bacterial sinusitis)

Performance scale II: symptoms, but nearly fully ambulatory

Clinical Stage III

8. Unintentional weight loss, >10 percent of body weight
9. Chronic diarrhea, > one month
10. Prolonged fever (intermittent or constant) > one month
11. Oral candidiasis (erythematous or pseudomembranous)
12. Oral hairy leukoplakia
13. Pulmonary tuberculosis (typical or atypical) within the previous year
14. Severe bacterial infections (for example, pneumonia or pyomyositis)
15. Vulvovaginal candidiasis, chronic (> one month) or poorly responsive to therapy

Performance scale III: in bed < 50 percent of normal daytime, but more than normally during previous month

Clinical Stage IV

16. HIV wasting syndrome

17. Pneumocystis carinii pneumonia (PCP)
18. Toxoplasma of the brain
19. Cryptosporidiosis with diarrhea, > one month
20. Isosporiasis with diarrhea, > one month
21. Extrapulmonary cryptococcosis
22. Cytomegaloviral disease of an organ other than the liver, spleen or lymph node
23. Herpes simplex virus infection, mucocutaneous (> one month) or visceral (any duration)
24. Progressive multifocal leukoencephalopathy (PML)
25. Any disseminated endemic mycosis (for example, histoplasmosis or coccidioidomycosis)
26. Candidiasis of the esophagus, trachea, bronchi and lungs
27. Atypical mycobacteriosis, disseminated
28. Non-typhoid Salmonella septicemia
29. Extrapulmonary tuberculosis
30. Lymphoma
31. Kaposi's sarcoma (KS)
32. HIV encephalopathy

Performance scale IV: in bed for longer than 50 percent of the day over the previous month

- WHO Improved Clinical Staging System

A further refinement of the WHO clinical staging system includes a laboratory axis. The laboratory axis subdivides each category into three strata (A, B, C) depending on the number of CD4 cells. If this is not available, use total lymphocytes as an alternative marker.

Laboratory Axis		Clinical Axis			
Lymphocytes*	CD4**	Stage I Asymptomatic PGL	Stage II Early HIV	Stage III Intermediate (ARC)***	Stage IV Late AIDS
A >2000	>500	1A	2A	3A	4A
B 1000-2000	200-500	1B	2B	3B	4B
C <1000	<200	1C	2C	3C	4C

* Reference range total lymphocytes: 1500-4000/mm₃

** Reference range CD4 count: 450-1400/mm₃

*** ARC: AIDS-related complex

Grey area refers to progression to AIDS

Note: Data from the developed world are the basis for the reference values used for lymphocytes and CD4 count. There are indications that Africans may have a physiologically higher lymphocyte count. If possible, projects with laboratory equipment to conduct lymphocyte counts in HIV patients should collect data about lymphocyte counts and CD4 counts and correlate them with the disease stage.

B. Differential Diagnosis and Follow-up

1. Differential diagnosis

- a. Initial diagnosis of HIV may be difficult
 - The more general signs and symptoms of HIV are common to many infections.
 - Patients may have acquired both HIV and other sexually transmitted or blood-borne diseases at the same time.
 - Be sure to consider HIV testing when testing for other infections that have a similar presentation.

- b. The following diseases have a similar presentation, and you should consider them when making a differential diagnosis:
 - Epstein-Barr virus mononucleosis
 - Cytomegalovirus mononucleosis
 - Toxoplasmosis
 - Rubella
 - Syphilis
 - Viral hepatitis
 - Primary herpes simplex virus infection
 - Disseminated gonococcal infection
 - Other viral infections

- c. Examples of differentiating factors:
 - Epstein-Barr virus mononucleosis

Factor	EBV infection	HIV infection
Onset	Insidious	Acute
Tonsillar hypertrophy	Common	Mild enlargement
Exudative pharyngitis	Common	Rare
Skin rash	Rare	Common
Mucocutaneous ulcers	Rare	Common
Jaundice	Occurs in 8 percent	Rare
Diarrhea	Unknown	Occurs
Atypical lymphocytes	Occurs in 80-90 percent	Occurs < 50 percent

- Ulcers

HIV infections	Other infections
Mucocutaneous ulceration is a distinctive feature and has been reported on the buccal mucosa, gingiva, palate, esophagus, anus and penis.	Such ulceration is uncommon in most conditions that constitute the differential diagnosis.
Ulcers are generally small, round or oval, and surrounding mucosa usually look normal.	Only primary herpes may present with similar ulcers.

- Rash

HIV infections	Other infections
An erythematous, non-pruritic, maculopapular rash is common during primary HIV infection.	Skin rashes are not a feature of infectious mononucleosis, toxoplasmosis or cytomegalovirus infection.
It is generally symmetrical and may become generalized, with lesions 5-10 mm in diameter.	
The face or trunk is usually affected, but extremities, including the palms and soles, can also be involved.	Rashes involving the palms and soles are rare in most viral infections.

d. You can use laboratory tests to make the diagnosis. See session 7.

2. Follow-up visits

- a. After being informed about their test results, patients may need closer follow-up (weekly or monthly).
- b. An accessible system of referrals is important, and the clinician following the patient should not fall into three common errors of thinking:
 - That they must provide for all of the patient's needs
 - That the only needs the patient has are those that a physician can provide, that is, that nutrition, emotional support, and the like are not the concern of the clinician
 - That "follow-up" means care for acute problems and not continuous contact
- c. Once the relationship has been established, and the patient understands his or her situation and is in stable condition, you may extend the interval to every three months.
- d. The subsequent visits should include:
 - Blood tests:
 - Complete blood count every three months
 - CD4 cell count or total lymphocyte count (TLC) every six months (some use every three months for TLC)
 - Other examinations according to symptoms

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PART A: MODULE A1

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Module A2

Managing Patients with HIV-Related Diseases



Session 1: Diagnosis of HIV-Related Illnesses: A Brief Overview

This session gives a brief overview of HIV-related opportunistic infections and explains why people living with HIV/AIDS are susceptible to them.

Session 2: Conditions of the Respiratory System

Participants learn about respiratory problems, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment. Part One, Module 2, Session 10 discusses prophylaxis of opportunistic infections affecting the respiratory system.

Session 3: Tuberculosis: HIV-TB Interaction

Participants will learn about HIV and TB coinfection, including clinical presentation, recommended diagnostic laboratory and radiologic tests and common findings, management and treatment. Part One, Module 2, Session 10 discusses prophylaxis of TB.

Session 4: Conditions of the Neurological System

Participants learn about neurological disorders related to HIV, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment. This session will also cover the clinical features, management and treatment of AIDS dementia complex, painful sensory and motor neuropathies, PML, primary CNS lymphoma and neurosyphilis.

Session 5: Conditions of the Gastrointestinal System

Participants learn about chronic diarrhea and conditions of the gastrointestinal system, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment. This session also discusses hepatitis.

Session 6: Conditions of the Lymph System

Participants learn about lymphadenopathy, including common etiological agents, the clinical presentation and diagnostic criteria of persistent generalized lymphadenopathy (PGL) and features of lymph nodes that indicate further evaluation.

Session 7: Conditions of the Mouth and Throat

Participants learn about oral lesions, dysphagia and odynophagia, including common etiological agents, recommended diagnostics, common findings, management and treatment.

Session 8: Skin Conditions

Participants learn about skin lesions and infections, including common etiological agents, clinical presentation, management and treatment.

Session 9: Fever

Participants learn about fever, including common etiological agents, recommended diagnostics, common findings and management and treatment of bacteremia/septicemia.

Session 10: Prophylaxis of Opportunistic Illnesses

Participants will learn about prophylaxis for selected opportunistic infections.

Session 11: Diagnosis and Management of HIV-Related Cancers

Participants learn about the pathology, clinical features, management and treatment of Kaposi's sarcoma (KS) and the clinical features, treatment, and management of nonHodgkin's lymphoma (NHL) and central nervous system (CNS) lymphoma.

SESSION 1 Diagnosis and Management of HIV-Related Illnesses: A Brief Overview**PURPOSE**

This session gives a brief overview of HIV-related opportunistic infections (OIs) and explains why people living with HIV/AIDS (PLHA) are susceptible to them.

OBJECTIVES:

By the end of this session, the participants will be able to:

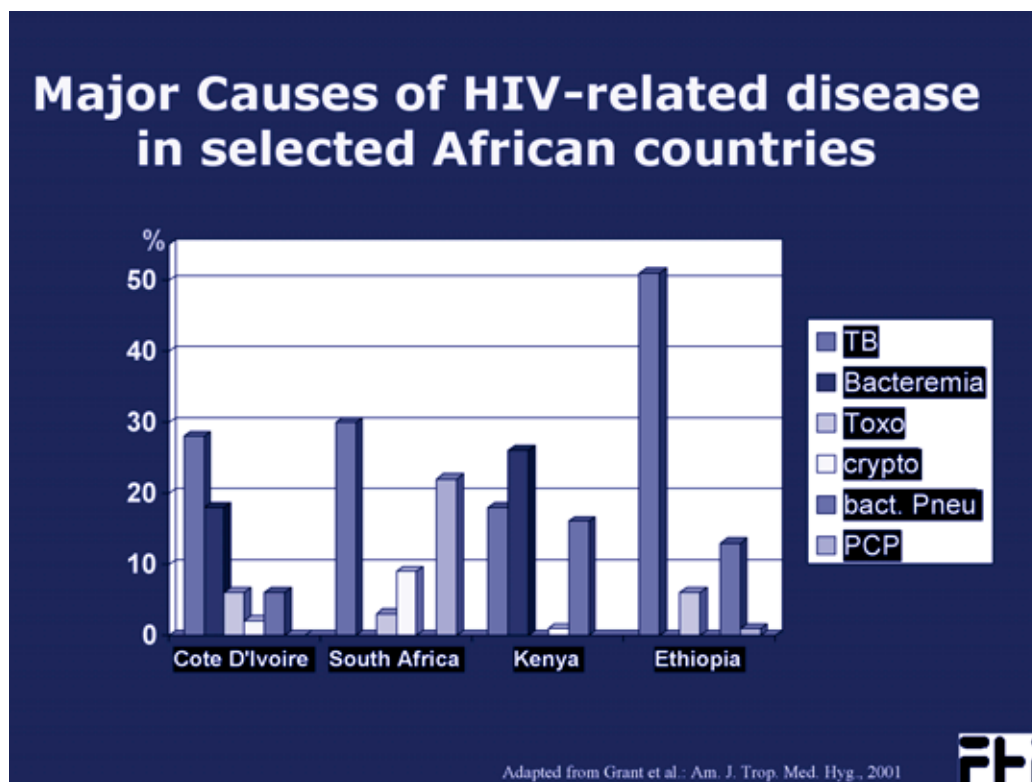
1. Define the term opportunistic infection.
2. Describe why PLHA are susceptible to OIs.
3. Discuss the impact on disease progression of seeking care promptly.
4. Describe the correlation between CD4 cell count levels and opportunistic infections.
5. Name the general pathogens causing OIs.

TIME:

10 minutes

A. Brief overview

1. Definition of OI: infections caused by organisms that would not cause a disease in a person with a well-functioning immune system.
2. People with HIV/AIDS are especially susceptible to OIs. This is the result of:
 - a. Suppression of the immune system
 - b. Psychological stress, which can influence the immune system
 - c. Depletion of nutritional status
3. Coinfections with pathogens such as TB and malaria increase the HIV viral burden and thus accelerate the disease progression. Therefore, preventing other infections such as STDs, malaria and TB can be of HIV-clinical benefit.
4. Uganda is an example of a country where high-quality HIV care services were offered early in the epidemic, prior to the availability of ART. Providers in Uganda report that HIV-infected patients seek care promptly when symptoms appear. As a result, many HIV-positive persons seem to be living well, despite a lack of access to ART.
5. Many first learn they have AIDS through diagnosis with an OI.
6. The natural history of HIV involves a progressive loss of CD4 lymphocytes.
7. As the CD4 level declines, the risk of contracting OIs increases.
8. OIs may be bacterial, viral, fungal or protozoal.
9. Figure A2, 1.1, below shows major causes of HIV-related diseases in selected African countries.



SESSION 2 Conditions of the Respiratory System**PURPOSE**

In this session, participants will learn about respiratory problems, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment. Part A, Module A2, Session 10 discusses prophylaxis.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the various etiological agents that cause respiratory infections.
2. Describe the clinical presentation of each infection.
3. List the recommended diagnostics and common findings for each infection.
4. Discuss the treatment and management of respiratory infections.
5. Make a differential diagnosis using the case study.

TIME:

80-105 minutes. Duration depends on which approach the presenter selects. Using the detailed chart, the session will last 105 minutes. Using the text that is less detailed and includes fewer etiologies, the session will last about 80 minutes.

1. Introduction

a. Overview

- Pulmonary involvement is among the most common complaints in AIDS patients. At least one-third of patients have a cough lasting over one month at some time during the progression of the disease.
- Bacterial pneumonia and tuberculosis can occur early in the course of HIV infection at CD4>500.
- *Pneumocystis carinii* pneumonia (PCP) almost always occurs when the CD4<200.
- Toxoplasmosis, CMV and *Mycobacterium avium* complex (MAC) usually occur at CD4<100.
- In the advanced stages of the disease, there is often more than one pathogen.

b. The differential diagnosis includes the following pathogens:

- **Mycobacterial infection:** *M. tuberculosis*, *M. avium* complex
- **Protozoal infection:** *Toxoplasmosis gondii*
- **Bacterial infection:** *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*
- **Fungal infection:** *Pneumocystis carinii**, *Penicillium marneffe*, *Cryptococcus neoformans*, *Histoplasmosis*, *Coccidioidomycosis*, *Aspergillosis*
- **Helminthic infection:** *Strongyloides stercoralis*, *Paragonimus westermanii*

* *Pneumocystis carinii* is now referred to by some as *pneumocystis jiroveci*. PCP is still used.

Table A2, 2.1: Conditions of the Respiratory: Respiratory Infections

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Mycobacterial				
M. tuberculosis	<ul style="list-style-type: none"> • Cough of > 3 wks, not responding to antibiotic treatment • Purulent or blood-stained sputum • Night sweats • Weight loss • Evening fevers 	<p>Chest x-ray:</p> <ul style="list-style-type: none"> • Miliary pattern • Hililar adenopathy • Pleural effusions • Focal infiltrates upper & hilar regions • Multilobar infiltrates • Interstitial infiltrates • Cavitation • With severe immunosuppression, x-ray might appear normal <p>Sputum in adults:</p> <ul style="list-style-type: none"> • Sputum in adults: WHO recommends 3 samples: one on the spot, one early morning (day 2), and another on the spot (day 2) 	<p>The management and treatment of TB is presented in Part A, Module 2, Session 3.</p>	<p>More common with HIV and worsens HIV</p> <p>Atypical presentation if there is severe immuno-suppression</p> <p>Pulmonary TB at any CD4 level; disseminated TB usually at CD4 <250</p> <p>For details, see Part A, Module 2, Session 3.</p>
Bacterial				
Streptococcus pneumoniae	<ul style="list-style-type: none"> • Abrupt onset • High fever • Productive cough • Pleuritic chest pain • Purulent sputum • Dyspnea 	<ul style="list-style-type: none"> • Localized infiltrates limited to one lobe • Often with pleural effusion • Sputum Gram stain with gram positive cocci • Sputum for culture and sensitivity (C&S) • Leukocytosis • Blood cultures may be positive 	<ul style="list-style-type: none"> • Cefotaxime 2 gm IV q6h • Ceftriaxone 2 gm/day IV • Amoxicillin 750 mg PO tid • Fluoroquinolone: <ul style="list-style-type: none"> Levofloxacin 500 mg PO/IV qd; gatifloxacin 400 mg PO/IV qd; moxifloxacin 400 mg PO/day <p>Where S. pneumoniae is not resistant to penicillin, give 4 to 6 million units of procaine penicillin G in 2 to 4 IM injections.</p> <p>Alternative treatment:</p> <ul style="list-style-type: none"> • Macrolide (azithromycin clarithromycin, erythromycin) • Vancomycin 	<p>Pneumonia in HIV-positive patients is more frequently associated with bloodstream infections and is a not uncommon cause of early death in HIV patients in developing countries. Treat an acute respiratory illness accompanied by fever and chills in an HIV-infected person an emergency.</p> <p>Preventive measures: See Part A, Module 2, Session 10.</p>

Table A2, 2.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Bacterial</p> <p>Haemophilus Influenzae</p>	<ul style="list-style-type: none"> • Fever • Cough • Purulent sputum • Dyspnea 	<ul style="list-style-type: none"> • Infiltrates more diffuse • Reticular or granular pattern • Leukocytosis • Blood cultures may be positive • Sputum for culture and sensitivity (C&S) 	<ul style="list-style-type: none"> • Cefuroxime <p>Alternative regimens:</p> <ul style="list-style-type: none"> • TMP-SMX, cephalosporins (2nd and 3rd generation) or fluoroquinolones 	<p>Preventive measures: See Part A, Module 2, Session 10.</p>
<p>Staphylococcus aureus</p>	<ul style="list-style-type: none"> • Similar to streptococcus pneumoniae 	<ul style="list-style-type: none"> • Bilateral patchy consolidation in critically ill patient • Sputum Gram stain • Sputum for culture and sensitivity (C&S) 		<p>Often see other signs of staphylococcal infection, including pyomyositis, abscess</p>
<p>Protozoal</p> <p>Toxoplasmosis gondii</p>	<ul style="list-style-type: none"> • Fever • Nonproductive cough • Dyspnea 	<ul style="list-style-type: none"> • Diffuse interstitial pattern or reticulonodular infiltrates confirmed by Giemsa staining of broncho-alveolar washings 		<p>Consider toxoplasma pneumonitis where induced sputum fails to demonstrate PCP.</p>
<p>Fungal</p> <p>Pneumocystis carinii (PCP) or pneumocystis jiroveci*</p> <p>NB: PCP is no longer classified as protozoal; current classification is fungal</p>	<ul style="list-style-type: none"> • Dry cough • Progressive shortness of breath • Fever • Few chest pains • Pt becomes increasingly ill with fever, severe dyspnea/hypoxia, confusion/delirium. • Presentation is nonspecific and insidious 	<ul style="list-style-type: none"> • Bilateral diffuse lace-like interstitial infiltrates extending from perihilar region • Chest x-ray may be normal • Signs of pneumonitis on CXR develop as disease slowly progresses • Definitive dx rests in finding cysts in induced sputum, broncho-alveolar lavage or biopsy specimens 	<ul style="list-style-type: none"> • TMP-SMX 15 mg/kg/day (trimethoprim) PO or IV x 21 days + PO2 < 70 mm Hg or A-a gradient > 35 mm Hg; prednisone 40 mg bid x 5 days, then 40 mg/day x 5 days; then 20 mg/day to completion of treatment. <p>Alternative Treatments:</p> <ul style="list-style-type: none"> • TMP 15 mg/kg/day PO + dapsone 100 mg/day x 21 days • Pentamidine 4 mg/kg/day IV x 21 days • Clindamycin 600 mg IV q8h or 300-400 mg PO q6h + primaquine 15-30 mg base/day x 21 days • Atovaquone 750 mg PO bid with meal x 21 days 	<p>PCP is the most frequently identified serious OI in HIV disease. Treatment is effective, but early recognition and treatment are important because of acute morbidity and mortality.</p> <p>More common in western countries CD4 < 200; cases have been reported CD4 < 300 where PLHA has experienced another OI</p> <p>Preventive measures: see Part A, Module 2, Session 10.</p>

*Pneumocystis carinii is now referred to by some as pneumocystis jiroveci. PCP is still used.

Table A2, 2.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Fungal Penicillium marneffei	<ul style="list-style-type: none"> • Abrupt onset of fever • Anemia • Skin lesions • Weight loss • Cough, shortness of breath • Local or generalized lymphadenopathy, hepatomegaly or splenomegaly may occur (less common) 	<ul style="list-style-type: none"> • Diffuse nodular pulmonary infiltrates or cavity disease 		<p>Skin involvement occurs in patients with disseminated disease. The typical appearance is one of multiple, popular lesions, often with central umbilication or ulceration, resembling molluscum contagiosum. The lesions are typically on the face, scalp and upper trunk. The differential diagnosis with TB and disseminated cryptococcal disease must be made. If there are no skin lesions, the diagnosis is difficult.</p> <p>CD4<50</p>
Cryptococcus neoformans		<ul style="list-style-type: none"> • Dx confirmed by sputum sample 		<p>Pneumonia is sometimes an early manifestation of cryptococcosis. In PLHA, dissemination to extrapulmonary sites occurs frequently. Cryptococcosis has a tendency to spread to the CNS. However, most patients with cryptococcal meningitis do not have a clinically evident pneumonia.</p>

2. Respiratory problems

a. Bacterial pneumonia

- Common etiological agents: *Streptococcus pneumoniae*
- Clinical presentation: Abrupt onset with fever, cough, production of purulent sputum, dyspnea and pleuritic chest pain (exacerbated by breathing)
- Recommended diagnostics: Chest x-ray, blood culture, FBC, Gram stain of sputum, sputum culture and sensitivity (C&S)
- Common findings: X-ray may show pneumonic consolidation, infiltrates or pleural effusions. Leukocytosis blood cultures may be positive.
- Management and treatment:
 - Cefotaxime 2 gm IV q6h
 - Ceftriaxone 2 gm/day IV
 - Amoxicillin 750 mg PO tid
 - Fluoroquinolone:
 - Levofloxacin 500 mg PO/IV qd;
 - gatifloxacin 400 mg PO/IV qd;
 - moxifloxacin 400 mg PO/day

Where *S. pneumoniae* is not resistant to penicillin, give 4 to 6 million units of procaine penicillin G in 2 to 4 IM injections.

Alternative treatment:

 - Macrolide (azithromycin clarithromycin, erythromycin)
 - Vancomycin
- Comments: Amoxicillin is the drug most likely to be used in resource-constrained countries. Rates of resistance are increasing. Strains highly resistant to penicillin should be treated with vancomycin or newer quinolones. If pneumonia fails to respond to standard antibiotics, consider other diseases, like tuberculosis.

b. Pneumonia: *Haemophilus influenzae*

- Common etiological agents: *H. influenzae*
- Clinical presentation: Fever, cough, purulent sputum, dyspnea, bronchopneumonia
- Recommended diagnostics: Chest x-ray, FBC, Gram stain of sputum
- Common findings: X-ray may show pneumonic consolidation, infiltrates or pleural effusions
Leukocytosis
Blood cultures may be positive
- Management and treatment: Cefuroxime
Alternative regimens: TMP-SMX, Cephalosporins (2nd and 3rd generation) or fluoroquinolones
- Comments: *H. influenzae* vaccine not indicated in adults—most *H. flu* in patients with HIV is atypical

c. *Pneumocystis carinii* pneumonia (PCP) or *pneumocystis jiroveci*

- Common etiological agent: *Pneumocystis carinii*
- Clinical presentation: Dry cough, progressive shortness of breath, fever and few chest signs. The patient becomes increasingly ill as disease slowly progresses, with fever, severe dyspnea, hypoxia and maybe confusion and delirium. Signs of pneumonitis develop on chest x-ray.
Presentation is nonspecific and insidious.
- Recommended diagnostics: Induced sputum, broncho-alveolar lavage or biopsy
When these investigations are unavailable, diagnosis depends on the clinical and chest x-ray findings
- Common findings: Definitive diagnosis rests in finding cysts in induced sputum, broncho-alveolar lavage or biopsy specimens. Whenever possible, make attempts to identify the organisms.
Chest x-ray shows bilateral diffuse lace-like interstitial infiltrates extending from the perihilar region. In some cases, the x-ray may be completely normal.
- Management and treatment:
 - Treatment: TMP-SMX 15 mg/kg/day (trimethoprim) PO or IV x 21 days + PO₂ < 70 mm Hg or A-a gradient > 35 mm Hg: prednisone 40 mg bid x 5 days, then 40 mg/day x 5 days, then 20 mg/day to completion of treatment.
 - Alternative Treatments:
 - TMP 15 mg/kg/day PO + dapsone 100 mg/day x 21 days
 - Pentamidine 4 mg/kg/day IV x 21 days
 - Clindamycin 600 mg IV q8h or 300-400 mg PO q6h + primaquine 15-30 mg base/day x 21 days
 - Atovaquone 750 mg PO bid with meal x 21 days
- Comments: PCP is the most frequently identified serious OI in HIV disease
Treatment is effective, but early recognition and treatment are important because of acute morbidity and mortality. More common in western countries.

Case study: patient with respiratory symptoms

A 40-year-old businessman is complaining of fever, dry cough and shortness of breath since ten days. He was diagnosed with HIV infection eight years ago. He is married and has three children. His wife and children are healthy. The wife was tested for HIV infection three years ago and found to be HIV negative. He was successfully treated for pulmonary tuberculosis four years ago. One year ago he had a medical checkup in Europe. His CD4 lymphocyte count was found to be 80 x10⁹/l and his viral load 100,000 copies/ml plasma. Cotrimoxazole and a triple combination therapy was prescribed: zidovudine + lamivudine + efavirenz. He started this treatment but stopped taking drugs three months later because of financial difficulties. His doctor gave him amoxicillin and erythromycin because of his cough, with no improvement. Because of severe shortness of breath, he is hospitalized. His temperature is 37.8 °C. Lung auscultation is normal. A chest x-ray shows a bilateral interstitial shadowing (slide).

- What is the most likely diagnosis?
- What further investigations would you perform?
- What are this patient's needs?
- What to offer?

Case study (patient with respiratory symptoms)—Answers*Most likely diagnosis*

This patient has a very low CD4 lymphocyte count and is therefore at risk for serious opportunistic infections. The symptoms and signs, his x-ray findings, and the fact that he stopped taking cotrimoxazole all indicate PCP. A reactivation of his TB or a reinfection with TB is possible, but less likely.

Investigations to perform

If a bronchoscopy can be performed, you should perform a broncho-alveolar lavage to confirm the diagnosis of PCP. You could also try to obtain expectorations by an induced sputum method. You should certainly also examine broncho-alveolar lavage fluid or sputum for acid fast bacilli.

*Patient's needs – What to offer?**Medical care*

This patient should be started on high doses of cotrimoxazole (trimethoprim 15 mg/kg/day + sulfamethoxazole 75 mg/kg/day IV initially); later po for three weeks (in 3-4 divided doses), initially with corticosteroids and oxygen, if available. After disappearance of the pulmonary symptoms, consider antiretroviral treatment. He certainly has to continue cotrimoxazole as maintenance treatment to avoid recurrent PCP.

Psychosocial support

This patient may panic because of his severe shortness of breath. He may be afraid of dying. You should explain that with adequate treatment his pulmonary infection can be cured and that he will be able to return home. You should tell his wife and children that his pulmonary infection is not contagious.

Socioeconomic support

This patient's family budget is probably too small to afford ART. You can, however, advise this family to use the family budget in an optimal way. For example, the medical checkup in Europe one year earlier was probably unnecessary and very expensive. Buying antiretrovirals in Europe is very expensive. Maybe there is an organization in Africa that provides triple therapy at a much lower price. His wife is not currently working. Maybe she can try to find a job or some other family members could help to provide money for treatment.

SESSION 3 Tuberculosis: HIV-TB Interaction**PURPOSE**

In this session, participants will learn about HIV and TB coinfection, including clinical presentation; recommended diagnostic tests and radiology; and common findings, management and treatment.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the interaction between HIV and TB and how it is manifested.
2. Describe the clinical presentation of TB and the most important signs and symptoms to look for.
3. List the recommended diagnostics and common findings.
4. Describe the treatment and management of HIV-positive patients with TB, including drug regimens and how to monitor during treatment.
5. Discuss treatment approaches and strategies, including directly observed treatment strategies (DOTS).
6. Discuss ART for individuals with TB coinfection.

TIME:

1 hour and 15 minutes

1. Tuberculosis: HIV-TB interaction and coinfection

a. Overview:

- Most common cause of death in people with HIV worldwide
- HIV infection increases the likelihood that new infection with *M. tuberculosis* (due to immune suppression) will progress rapidly to TB disease.
- HIV is the most potent factor known to increase risk of progression from *M. tuberculosis* infection to disease.
- Among HIV-infected individuals, lifetime risk of developing active TB is 50 percent, compared to 5-10 percent in persons who are not HIV-infected.
- In a person infected with HIV, the presence of other infections, including TB, allows HIV to multiply more quickly. This may result in more rapid progression of HIV infection.
- HIV-related TB can present typical or atypical clinical and/or radiological features. Atypical features are usually found in HIV-infected individuals with severe immunosuppression.
- Initial signs of TB disease may become apparent at any time during the evolution of HIV-infection.
- Can come well before other manifestations of HIV infection or after patient has become symptomatic
- May be pulmonary or extra-pulmonary
 - Pulmonary TB is most common form—presentation depends on degree of immunosuppression:
 - With mild immunosuppression:
 - Chest x-ray (CXR) typically shows upper lobe and or bilateral infiltrates, cavitation, pulmonary fibrosis, and shrinkage.
 - Clinical picture often resembles post-primary pulmonary TB (PTB), and sputum smear is usually positive.
 - In severely immunosuppressed patient, the features are atypical, resembling that of primary PTB:
 - Sputum smear often negative
 - CXR shows interstitial infiltrates, especially in lower zones, with no features of cavitation and fibrosis.
 - CXR may look exactly like that in bacterial pneumonia.
 - In the setting of an HIV epidemic, it is not possible to look at a CXR and say this is or is not TB.
- Disseminated and extrapulmonary TB is more common in advanced HIV infection because the immune system is less able to prevent growth and local spread of *M. tuberculosis*.
 - Unilateral or bilateral infiltrates in the lower lobes are seen more often than upper lesions and cavities.
 - Most common forms are lymphadenitis, pleural effusion, pericarditis, miliary disease and meningitis.

2. Clinical presentation

a. Signs and symptoms

The most important symptoms are:

- Cough lasting more than three weeks and not responding to usual antibiotic treatment
- Production of purulent, sometimes blood stained sputum
- Evening fevers
- Night sweats
- Weight loss

b. What to ask in taking a history:

- Always ask about history of contact with a chronically coughing person
- Always ask a “new” patient if he or she has ever been treated for TB

3. Diagnostic tests

- a. Microscopic examination of specimen of sputum that has been stained by the Ziehl-Neelsen (ZN) method
 - A PTB suspect should submit three sputum samples for microscopy:
 - Sample 1:** On first visit, the patient should provide an on-the-spot sputum sample.
 - Sample 2:** Give the patient a sputum container to take home for an early morning sample on the following day (that is, on day two).
 - Sample 3:** On day two, when the patient brings in sample two, he or she provides another on-the-spot sample.
 - An inpatient can provide three early morning sputum samples.
 - False negative reports: A PTB suspect with three negative ZN sputum smears may not have TB at all, because the sample may be inadequate or there may have been faulty smear preparation or interpretation.

- b. Radiology
 - If TB is still suspected despite negative smears, you should do a chest x-ray. The classical pattern is upper lobe infiltrates with cavitation.
 - However, no chest x-ray is very typical of PTB patients with HIV infection. In severe immunosuppression, the appearance is often atypical, as described above.

4. Treatment

- a. HIV-infected patients should be treated according to national guidelines and in cooperation with local authorities such as the District Medical Officer (DMO) and the District TB supervisor. Register patients so that there can be correct follow-up.
- b. Aims of treatment are to:
 - Cure the patient of TB
 - Prevent death from active TB or its late effects
 - Prevent TB relapse
 - Decrease TB transmission to others
- c. Drug regimens
 - Initial phase—first two-three months
 During the initial phase, there is rapid killing of TB bacilli.
 Three or more drugs are used in combination
 Infectious patients become noninfectious within about two weeks, and symptoms usually improve.
 - Continuation phase—additional four-six months
 Fewer drugs are necessary (usually two), but for a longer time.
 These drugs eliminate the remaining bacilli.
- d. Monitoring during treatment
 - Bacterial monitoring is possible only for patients with smear positive PTB
 - Do sputum smear exam as follows:
 - At the time of diagnosis
 - At the end of initial phase
 - During the continuation phase—at the end of month five
 - On completion of treatment—month six or eight
 - Using chest x-rays as a monitoring tool is unnecessary and wasteful.
- e. Treatment approaches and strategies
 - Directly observed treatment, short course (DOT)
 It is hard to adhere to anti-TB treatment for 6-8 months or more.
 It is also hard to predict which patient will adhere to self-administered treatment.
 One certain way to ensure patient adherence is through DOT, where a trained supervisor watches the patient

swallow the drugs.

Basic principles of DOT:

- For patients who need admission, start DOT right away and have nursing staff supervise.
- For patients requiring no admission or for discharged patients, DOT may be supervised by staff of a nearby health facility, a trained community health worker or a trained family member.
- Directly Observed Treatment Strategy (DOTS)

DOTS is a strategy for TB control that aims to detect 70 percent of active TB cases and to successfully treat 85 percent of them. The essential features of DOTS include:

- Government commitment to sustained TB control activities
- Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services
- Directly observed, standardized treatment regimen of six to eight months
- Efficient information systems for monitoring and reporting treatment outcomes
- A regular, uninterrupted supply of all essential anti-TB drugs

Table A2, 3.1: WHO-Recommended TB Treatment Regimen for Each Treatment Category

Alternative TB Treatment Regimens			
Treatment Category	Patients	Initial Phase (Daily or 3 times/wk)	Continuation Phase
I	New smear-positive PTB; new smear-negative PTB with extensive parenchymal involvement; new cases of severe forms of extra-pulmonary TB	2 EHRZ (SHRZ) ^a 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE 4 HR 4 H ₃ R ₃ ^b
II	Previously treated smear-positive PTB: relapse treatment failure treatment after interruption	2 SHRZE/1 HRZE 2 SHRZE/1 HRZE	5 H ₃ R ₃ E ₃ 5 HRE
III	New smear-negative PTB (other than category I); new, less-severe forms of extra-pulmonary TB	2 HRZ 2 HRZ 2 HRZ	6 HE 4 HR 4 H ₃ R ₃
IV	Chronic case (still sputum positive after supervised re-treatment)	NOT APPLICABLE: refer to WHO guidelines for use of second-line drugs in specialized centers	

Note: Some authorities recommend seven-month continuation phase with daily isoniazid and rifampicin (7HR) for Category 1 patients with various forms of disease: TB meningitis, military TB and spinal TB with neurological signs.

Examples:

a. **2 HRZE / 6 HE**: This is a common regimen. The initial phase is **2 HRZE**. The duration of the phase is two months. Drug treatment is daily (no subscript number, e.g., 3, after the letters), with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). Alternatively, streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z).

The continuation phase is **6 HE**. The duration of the phase is six months. Drug treatment is daily, with isoniazid (H) and ethambutol (E).

b. **4 H₃R₃**: In some countries, resources are available to provide rifampicin in the continuation phase as well as in the initial phase.

The initial phase is **2 H₃R₃Z₃E₃**. The duration of the phase is two months. Drug treatment is three times per week (subscript number 3 after the letters). The continuation phase is **4 H₃R₃**. The duration is four months, with isoniazid and rifampicin three times per week (subscript number 3 after the letters).

WHO 1997.

5. Antiretroviral therapy for individuals with tuberculosis coinfection

a. WHO recommendations for ARV therapy

- WHO recommends that people with TB/HIV complete their TB therapy before beginning ARV treatment, unless there is high risk of HIV disease progression and death during the period of TB treatment (for example, a CD4 count $<200/\text{mm}^3$ or the presence of disseminated TB).
- In cases where a person needs TB and HIV treatment concurrently, first line treatment options include ZDV/3TC or d4T/3TC plus either an NNRTI or ABC.
- If an NNRTI-based regimen is used, EFZ would be the preferred drug, as its potential to aggravate hepatotoxicity of TB treatment appears less than with NVP. However, you need to increase to 800mg/day.
- Except for SQV/r, PIs are not recommended during TB treatment with rifampicin because of interactions with the latter drug.

Table A2, 3.2: Antiretroviral Therapy for Individuals with Tuberculosis Coinfection

Antiretroviral Therapy for Individuals with Tuberculosis Coinfection	
Situation	Recommendations
Pulmonary TB and CD4 count $<50/\text{mm}^3$ or extrapulmonary TB	Start TB therapy. Start one of the non-PI regimens listed below concurrently with TB therapy. <ul style="list-style-type: none"> • ZDV/3TC/ABC^a • ZDV/3TC/EFZ • ZDV/3TC/SQV/r^b • ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/ mm^3 or total lymphocyte count $<1200/\text{mm}^3$	Start TB therapy with one of these regimens after two months of TB therapy: <ul style="list-style-type: none"> • ZDV/3TC/ABC^a • ZDV/3TC/EFZ • ZDV/3TC/SQV/r^b • ZDV/3TC/NVP
Pulmonary TB and CD4 $>200/\text{mm}^3$ or total lymphocyte count $>1200/\text{mm}^3$	Treat TB. Monitor CD4 counts if available. Start ART as indicated in Table A4, 2.1 in Part A, Module 4, Session 2 (Brief Introduction to Antiretroviral Therapy) .

a Note: Subsequent research does not support this regimen.

b Note: According to current research, the option of 2 NRTIs and a ritonavir-enhanced PI or nelfinavir should not be used as a first choice. Such a regimen should only be used if a NNRTI regimen is not indicated, for example, in the case of an HIV-2 infection or if a patient presents with side effects to EFZ or NVP.

WHO 1997

6. TB Prevention

- a. Evidence shows that TB preventive therapy among HIV-infected people is effective.
- b. Can be given to those people with HIV who have been screened to exclude active TB, who are PPD positive (Mantoux test ≥ 5 mm), who have not been BCG vaccinated and who have a high TB risk
- c. In a setting where doing a PPD skin test is not practical, consider TB prophylaxis for the following individuals, if they are HIV-infected:
 - Individuals living in population with high prevalence for TB infection (>30 percent)
 - Health care workers
 - Household contacts of TB patients
 - Prisoners
 - Miners
 - Other selected groups at high risk for acquisition or transmission of TB

7. Prophylaxis: See Part A, Module 2, Session 10.

SESSION 4 Conditions of the Neurological System**PURPOSE**

In this session, participants will learn about neurological disorders related to HIV, including common etiological agents, clinical presentation, recommended diagnostics and common findings, management and treatment. This session will also cover the clinical features, management, and treatment of AIDS dementia complex, painful sensory and motor neuropathies, PML, primary CNS lymphoma and neurosyphilis.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the various etiological agents that cause neurological disorders.
2. Give key points when taking a history.
3. Describe the clinical presentation of each disorder.
4. List the recommended diagnostics and common findings for each disorder.
5. Discuss the treatment and management of neurological disorders.
6. Discuss preventive measures.
7. Make a differential diagnosis using a case study approach.

TIME:

2 hours

1. Introduction

a. Overview

- Reported incidence of neurological abnormalities on clinical examination varies greatly, from 16 percent to 72 percent among hospitalized patients.
- A wide range of neurological manifestations is reported: cognitive defects, focal deficits such as hemiplegia and acute peripheral facial palsy, painful feet syndrome, encephalopathy and so on
- Some of these manifestations are caused directly by HIV itself; others result from OIs caused by different pathogens or drugs.

b. The differential diagnosis of OIs involving the brain includes the following pathogens:

- **Protozoal infection:** *Toxoplasmosis gondii*
- **Mycobacterial infection:** *M. tuberculosis*
- **Fungal infection:** *Cryptococcus neoformans*, *Candida* species (rare)
- **Viral infection:** Cytomegalovirus, Herpes simplex virus, Varicella zoster virus, JC virus (PML)

You will find a case study included at the end of this session. We recommend that participants use algorithms from Appendix A as they work on it.

Table A2, 4.1: Conditions of the Neurological System

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Protozoal infection</p> <p><i>Toxoplasma Gondii</i> (toxoplasmosis)</p>	<p>Clinical symptoms may evolve in under 2 weeks.</p> <ul style="list-style-type: none"> • Headache (severe, localized) • Fever • Confusion • Myalgia • Arthralgia • Focal neurological defects such as seizures, hemiparesis, hemiplegia, cerebellar tremor, cranial nerve palsies, hemisensory loss, visual problems or blindness, personality changes and cognitive disorders. 	<p>Where available:</p> <ul style="list-style-type: none"> • CT scan or MRI • Toxoplasma IgG titer • In a resource-constrained setting: diagnosis based on clinical symptoms • CT scan or MRI findings: multiple ring lesions in the cerebral hemispheres <p>**Put an HIV-infected individual presenting with typical symptoms and normal cerebrospinal fluid findings on treatment for toxoplasmosis.</p> <p>CSF values</p> <ul style="list-style-type: none"> • Normal: 20-30 percent • Protein: 10-150/ml • WBC: 0-40 (monos) • Blood: FBC 	<p>Start anti-convulsant treatment:</p> <ul style="list-style-type: none"> • Epanutin 50-100 mg bid or tid or tegretol 100-200 mg bid or tid (to be started only if the patient has convulsion) <p>Treatment for acute phase:</p> <ul style="list-style-type: none"> • Pyrimethamine 100-200 mg loading dose, then 50-100 mg/day po + folinic (or folic acid) 10 mg/day po + sulfadiazine 1-2 g qid for at least 6 weeks <p>OR</p> <ul style="list-style-type: none"> • Trimetoprim/sulfamethoxazole 10/50mg/kg daily for 4 weeks <p>OR</p> <ul style="list-style-type: none"> • Clindamycin (600mg tid) + pyrimethamine 100mg daily loading dose followed by 50 mg daily + folinic acid 10 mg daily <p>Preferred regimen for suppressive therapy required after a patient has had Toxo:</p> <ul style="list-style-type: none"> • Pyrimethamine 25-75 mg po qd + folinic acid 10 mg qd + sulfadiazide 0.5-1.0 gm po qid if allergic to sulfa • Give dapsone po 100 mg po once daily or clindamycin IV (or oral) 600 mg qid or atovaquone 750 mg po qid <p>Provide physiotherapy as necessary</p>	<p>Cerebral toxoplasmosis is one of the most common HIV-related neurological complications. If patient does not receive maintenance therapy, cerebral toxoplasmosis will recur. Usually occurs when CD4<100. Check blood picture regularly as the relatively high doses of drugs can lead to toxicities. Leukopenia, thrombocytopenia and rash are common. Folic acid reduces the risk of myelosuppression. During treatment, advise patients to maintain a high fluid intake and urine output.</p> <p>Prophylaxis: See Part A, Module 2, Session 10.</p>
<p><i>Mycobacterial infection</i> <i>M. tuberculosis</i> (TB meningitis)</p>	<p>Gradual onset of headache and decreased consciousness</p> <ul style="list-style-type: none"> • Low grade evening fevers • Night sweats • Weight loss • Neck stiffness and positive Kernig's sign • Cranial nerve palsies result from exudate around base of the brain 	<p>Lumbar puncture/CSF microscopy: CSF may be cloudy</p> <ul style="list-style-type: none"> • Normal: 5-10 percent • Protein: High (40 -100 mg/dl) • WBC: 5-2000 (average is 60-70 percent monos) • Glucose: low (<20 mg/dl) • AFB smear pos: 20 percent <p>X-ray not indicated as skull x-ray will be normal</p>		<p>CD4<350</p> <p>Up to 10 percent of AIDS patients who present with TB will show involvement of the meninges. This results from rupture of a cerebral tuberculoma or is blood-borne.</p> <p>Always exclude cryptococcal meningitis by CSF microscopy (Indian ink stain).</p>

Table A2, 4.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Bacterial</p> <p><i>Strep pneumoniae</i>, <i>Neisseria meningitis</i> (Bacterial meningitis)</p>	<ul style="list-style-type: none"> • Fever • Headache • Stiff neck • Photophobia • Vomiting • Malaise • Irritability • Drowsiness • Coma <p>Symptoms tend to present within one week of infection. May be preceded by a prodromal respiratory illness or sore throat.</p>	<ul style="list-style-type: none"> • Cerebrospinal fluid (CSF) examination • Full blood count <p>Common findings:</p> <ul style="list-style-type: none"> • Leukocytosis; cerebrospinal fluid shows increased pressure, cell count (100 – 10,000/mm³), and protein (> 100 mg/dl) and decreased glucose (<40 mg/dl or <50% of the simultaneous glucose blood level) • Gram-stained smear of the spun sediment of the CSF can reveal the etiologic agent <p>X-ray not indicated, as skull x-ray will be normal.</p>	<ul style="list-style-type: none"> • Penicillin (24 million units daily in divided doses every 2-3 hours) or ampicillin (12 gr daily in divided doses every 2-3 hours) or chloramphenicol (4 to 6 grams IV/day). Treatment should be continued for 10 to 14 days. <p>Crystalline penicillin 2-3 mega units and chloramphenicol 500-750 mg 6 hourly for 10-14 days</p>	<p>Often encountered during late stages of HIV disease. Prompt diagnosis and aggressive management and treatment ensure a quick recovery.</p>
<p>Fungal</p> <p><i>Cryptococcus neoformans</i> (cryptococcal meningitis)</p>	<p>Presentation usually nonspecific at onset, which may be true for > one month.</p> <ul style="list-style-type: none"> • Protracted headache and fever may be the only signs. • Nausea, vomiting and stiff neck may be absent, and focal neurological signs uncommon. • Extraneural symptoms include skin lesions, pneumonitis, pleural effusions and retinitis. • Fever, malaise and nuchal pain signify a worse prognosis, and nausea and vomiting and altered mental status in terminal stages. 	<p>CSF values:</p> <ul style="list-style-type: none"> • Normal 20 percent • Protein 30-150/dl • WBC: 0-100 (monos) • Glucose decreased: 50-70 mg/dl • Culture pos: 95-100 percent • India ink pos: 60-80 percent • Crypt Ag nearly 100 percent sensitive and specific • India ink staining of spinal fluid; test spinal fluid and/or serum for cryptococcal antigen. 	<p>Preferred regimen:</p> <ul style="list-style-type: none"> • Amphotericin B 0.7 mg/kg/day IV + flucytosine 100 mg/kg/day po x 14 days, followed by fluconazole 400 mg/day x 8-10 weeks • Finally, maintenance therapy with fluconazole 200mg/day for life <p>Alternate regimen:</p> <ul style="list-style-type: none"> • Amphotericin B 0.7 mg/kg/day IV + flucytosine 100mg/kg/day po x 14 days followed by itraconazole 200mg bid for 8 weeks • Fluconazole 400 mg/day po x 8 weeks, followed by 200 mg once daily • Itraconazole 200 mg po tid x 3 days, then 200 mg po bid x 8 weeks after initial treatment with amphotericin • Fluconazole 400 mg/day po + flucytosine 100 mg/kg/day po 	<p>If untreated, it is slowly progressive and ultimately fatal.</p> <p><i>Cryptococcus neoformans</i> is the most common life-threatening fungal infection in patients with HIV/AIDS. It is the most common cause of meningitis in HIV/AIDS patients in Africa and Asia. It occurs most often in patients with CD4<50.</p> <p>It is better prevented than treated.</p> <p>Headache is secondary to fungal accumulation, so the headache increases gradually over time, goes away and then comes back and is harder to get rid of. Then it becomes continuous, and this is what the patient reports.</p> <p>Requires lifelong suppressive treatment unless immune reconstitution occurs.</p>

Table A2, 4.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Viral</p> <p>Cytomegalovirus (CMV)</p>	<ul style="list-style-type: none"> Fever ± delirium, lethargy, disorientation, malaise. Headache most common Stiff neck, photophobia, cranial nerve deficits less common No focal neurological deficits Gastrointestinal symptoms: diarrhea, colitis, esophageal ulceration appear in 12-15 percent of patients Respiratory symptoms, i.e., pneumonitis, present ~1 percent 	<ul style="list-style-type: none"> Retinal exam to check for changes. Consult an ophthalmologist. CMV retinitis, characterized by creamy yellow white, hemorrhagic, full thickness retinal opacification, which can cause visual loss and lead to blindness if untreated; patient may be asymptomatic or complain of floaters, diminished acuity or visual field defects. Retinal detachment if disease is extensive. UGI endoscopy when indicated 	<ul style="list-style-type: none"> Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h x 14-21 days; ganciclovir 5mg/kg IV bid x 14-21 days. Patients without immune recovery will need to be on maintenance therapy lifelong for retinitis. Extra-ocular: ganciclovir and/or foscarnet. 	<p>Evolution <2 weeks CD4<100</p> <p>Although any part of the retina may be involved, there is a predilection for the posterior pole; involvement of the optic nerve head and macular region is common. Characteristically involves the retinal vessels, which are always abnormal in areas affected by retinitis. There is minimal or no accompanying uveitis.</p> <p>Rare but devastating illness in resource-poor settings. Treatment is very expensive and usually not available. CMV management needs special care. Therefore, early referral is essential.</p>
<p>Progressive multifocal leukoencephalopathy (PML)</p>	<ul style="list-style-type: none"> Afebrile, alert, no headache Progressively impaired speech, vision, motor function Cranial nerve deficit and cortical blindness Cognition affected relatively late 	<ul style="list-style-type: none"> CT brain scan may be normal or remarkable for areas of diminished density or demyelination (deterioration of the covering of the nerve). PCR of CSF for detection of JC virus JC virus PCR + in about 60 percent of the cases Differential diagnosis: Toxoplasmosis Primary CNS lymphoma Definitive diagnosis is by brain biopsy (if available). 	<ul style="list-style-type: none"> There is no treatment for this illness. ART can improve symptoms and prolong life. 	<p>An end-stage complication of HIV, caused by the JC virus</p> <p>PML is rare in the general community, but relatively common in HIV infection (affecting 4 percent of all AIDS patients). Routine testing for HIV should be considered for any patient with PML.</p> <p>Evolution: weeks to months Usually occurs when CD4<100</p>

Table A2, 4.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Other</p> <p>Primary CNS lymphoma</p>	<ul style="list-style-type: none"> • Disease progresses slowly over a few weeks • Afebrile; headache • Focal and multifocal neuro deficits (confusion, hemiplegia, seizures) • Mental status change (60 percent, personality or behavioral) • Seizures (15 percent) 	<ul style="list-style-type: none"> • CT Scan/MRI • Location: pre-ventricular in one or more sites • Prominent edema, irregular and solid on enhancement. <p>CSF:</p> <ul style="list-style-type: none"> • Normal—30-50 percent • Protein—10-150/ml • WBC—0-100 (monos) • Cytology + in <5 percent • Suspect when there is a negative toxo IgG or failure to respond to empiric toxo treatment 	<ul style="list-style-type: none"> • There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative. • Corticosteroids can also help some patients. 	<p>Primary CNS Lymphoma is RARE in the general community, but affects about 2 percent of AIDS patients.</p> <p>Survival after diagnosis is usually limited (a few months only).</p> <p>Typical end-stage complication of HIV disease</p> <p>Evolution: 2-8 weeks Usually occurs when CD4<100</p>
<p>AIDS Dementia Complex (ADC)</p> <p>(HIV-associated dementia [HAD])</p>	<p>In up to 10 percent of patients, it is the first manifestation of HIV disease.</p> <ul style="list-style-type: none"> • Afebrile; general lethargy • Triad of cognitive, motor and behavioral dysfunction • Early concentration and memory deficits, inattention, motor-incoordination, ataxia, depression, emotional lability • Late: global dementia, paraplegia, mutism <p>The frequency in all patients is 10-15 percent.</p>	<ul style="list-style-type: none"> • Neuropsychological tests show subcortical dementia • Mini-mental exams not very sensitive 	<ul style="list-style-type: none"> • Possible benefit from antiretroviral regimens with agents that penetrate the CNS (AZT, d4T, ABC, nevirapine) • Benefit of AZT at higher dose for mild or moderately severe cases is established; monitor therapy with neurocognitive tests • Anecdotal experience indicates response to ART, if started early • Sedation for those who are agitated and aggressive—use smaller doses initially to avoid over-sedation • Close monitoring: <ul style="list-style-type: none"> • to prevent self-harm • to ensure adequate nutrition • to diagnose and treat OIs early • Psychological support for caregivers—looking after demented patients is exhausting; caregivers need regular breaks and may need counseling 	<ul style="list-style-type: none"> • Prevalence increases with improvement of general management of various OIs because patients live long enough to develop severe immune suppression. • Patients present with a demeanor similar to Parkinson's disease and may even be misdiagnosed as such.

Table A2, 4.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Viral</p> <p>Painful sensory and motor peripheral neuropathies</p>	<ul style="list-style-type: none"> Burning pain and numbness in toes and feet, ankles, calves and fingers in more advanced cases Paraplegia Autonomic dysfunction Poor bowel/bladder control Dizziness secondary to postural hypotension Contact hypersensitivity in some cases Mild/moderate muscle tenderness Muscle weakness Later: Reduced pinprick/vibratory sensation; reduced or absent ankle/knee jerks Sweating 	<ul style="list-style-type: none"> Electromyography/nerve conduction velocities show predominantly axonal neuropathy CPK usually elevated CSF: look for cytomegalovirus or herpes simplex virus infections—lymphomatous infiltration Spinal fluid to determine etiology Serum B12 and TSH Quantitative sensory testing or thermal thresholds may be helpful 	<ul style="list-style-type: none"> Exclude other causes such as neurotoxic drugs, alcoholism, diabetes, B12 deficiency and thyroid problems, and treat underlying causes if known. Discontinue presumed neurotoxic medication. Provide proper nutrition and vitamin supplements. Pain control: <ul style="list-style-type: none"> Ibuprofen 600-800 mg po tid or codeine for modest symptoms Amitriptyline 25-50 mg at night Phenytoin 50-100 mg bid or carbamazepine 100-200 mg tid—especially for episodic shooting pain. May have to combine anti-depressants with anti-convulsants Methadone or morphine for severe symptoms Lidocaine 10-30 percent ointment for topical use Physical therapy may help, but may be hampered by pain. Nutrition counseling and psychological support 	<p>Differential: Toxoplasmosis, primary CNS lymphoma</p> <p>Management and treatment is difficult.</p> <p>Consider physical therapy combined with pain management.</p>

Table A2, 4.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Other</p> <p>Neurosyphilis</p>	<ul style="list-style-type: none"> • Can be asymptomatic • Headache, fever, photophobia, meningismus ± seizures, focal findings, cranial nerve palsies • Tabes dorsalis—sharp pains, paresthesias, decreased DTRs, loss of pupil response • General paresis—memory loss, dementia, personality changes, loss of pupil response • Meningovascular strokes, myelitis • Ocular syphilis—iritis, uveitis, optic neuritis 	<ul style="list-style-type: none"> • CT scan/MRI: Aseptic meningitis—may show meningeal enhancement. General paresis—cortical atrophy, sometimes with infarcts. Meningovascular syphilis—deep strokes. May present like dementia. • CSF: Protein—45-200/ml • WBCs—5-100 (monos) • VDRL positive—sensitivity 65 percent; specificity 100 percent positive • Serum VDRL and FTA-ABS are clue in >90 percent false neg serum VDRL in 5-10 percent with tabes dorsalis or general paresis • Definitive diagnosis: positive CSF, VDRL (found in 60-70 percent) 	<ul style="list-style-type: none"> • Give Aq penicillin G, 18-24 mil units/day x 10-14 days • Follow-up VDRL q 6 months until negative • Indications to re-treat: <ul style="list-style-type: none"> • CSF WBC fails to decrease at 6 mos or, CSF still abnormal at two yrs • Persisting signs and symptoms of inflammatory response at three mos • Four-fold increase in CSF VDRL > 6 mos • Failure of CSF VDRL of > 1:16 to decrease by two-fold by two months or four-fold by twelve months 	<p>Most common forms in HIV-infected persons are ocular, meningeal and meningovascular</p> <p>There is some evidence that syphilis progresses more rapidly in the context of HIV infection, so complications such as meningovascular syphilis may occur at an unusually early phase.</p> <p>RARE: Affects 0.5 percent of all AIDS patients</p> <p>Recommended that syphilis testing be offered to all clients presenting for VCT in high prevalence areas because it is treatable in early stages, and has an accelerated course in HIV.</p> <p>Usually occurs at CD4<350</p>

2. Neurological conditions

a. Cerebral Toxoplasmosis

- Common etiological agent: *Toxoplasma gondii*
- Clinical presentation: Headache, fever, confusion, focal neurological signs (e.g., hemiplegia, seizures)
- Recommended diagnostics: Where available, a CT scan or MRI Toxoplasma IgG titers
In a resource-constrained setting, you can make diagnosis on the basis of clinical symptoms. (An HIV-infected individual presenting with headache, fever, focal neurological signs and normal CSF finding may be put on treatment for toxoplasmosis.)
- Common findings: CT scan or MRI will show lesions in the cerebral hemispheres
- Management and treatment:
 - Start anti-convulsant treatment: Epanutin 50-100 mg bid or tid or tegretol 100-200 mg bid or tid (to be started only if the patient has convulsion)
 - Treatment for acute phase: Pyrimethamine 100-200 mg loading dose, then 50-100 mg/day po + folic (or folic) acid 10 mg/day po + sulfadiazine 1-2 g qid for at least six weeks
OR trimethoprim/sulfamethoxazole (10/50mg/kg daily) for four weeks

OR clindamycin (600mg tid) + pyrimethamine 100mg daily loading dose followed by 50 mg daily + folic acid 10 mg daily
 - Preferred regimen for suppressive therapy required after a patient has had toxo: Pyrimethamine 25-75 mg po qd + folic acid 10 mg qd + sulfadiazide 0.5-1.0 gm po qid
 - If allergic to sulfa: Give dapsone po 100 mg po once daily or clindamycin IV (or oral) 600 mg qid or atovaquone 750 mg po qid
 - Provide physiotherapy, as necessary
- Preventive measures: Avoid eating raw meat and exposure to cats, if possible.

Diminish risk of transmission by cooking meat adequately and washing vegetables and fruit carefully before eating.
- Comments: Cerebral toxoplasmosis is one of the most common HIV-related neurological complications. If patient does not receive maintenance therapy, cerebral toxoplasmosis will recur.

b. Cryptococcal meningitis

- Common etiological agent: *Cryptococcus neoformans*
- Clinical presentation: Presentation is nonspecific at the beginning and possibly for more than one month in 87-90 percent of cases.
Headache is secondary to fungal accumulation and has periods of exacerbation and remission until it becomes continuous. Fever, malaise and nuchal pain signify a worse prognosis; nausea, vomiting and altered mental status occur in terminal stage. Extranatural symptoms include skin lesions, pneumonitis, pleural effusions and retinitis.
- Diagnostic tests: India ink staining of spinal fluid; test spinal fluid and/or serum for cryptococcal antigen.
CSF-CRAG is positive in over 90 percent of cases.
- Management and treatment:
 - Preferred regimen: Amphotericin B 0.7 mg/kg/day IV, + flucytosine 100 mg/kg/day po for 14 days, followed by fluconazole 400 mg/day for 8-10 weeks. Finally, maintenance therapy with Fluconazole 200mg/day for life, or after immune system recovery.
 - Alternate regimen: Amphotericin B 0.7 mg/kg/day IV + flucytosine 100mg/kg/day po x 14 days, followed by itraconazole 200mg bid for 8 weeks

Fluconazole 400 mg/day po for 8 weeks, followed by 200 mg once daily

Itraconazole 200 mg po tid for 3days, then 200 mg po bid for 8 weeks, after initial treatment with amphotericin

Fluconazole 400 mg/day po + flucytosine 100 mg/kg/day po
- Comments: Cryptococcal meningitis is the most common life-threatening AIDS-related fungal infection (after PCP). Untreated, the disease runs a slowly progressive and ultimately fatal course.
Patients who have completed initial therapy for cryptococcosis should receive lifelong suppressive treatment (that is, secondary prophylaxis or chronic maintenance therapy, preferably fluconazole 200mg/day) unless immune reconstitution occurs as a consequence of ART.

c. Bacterial meningitis

- Common etiological agents: *Strep pneumoniae*, *Neisseria meningitidis*
- Clinical presentation: Fever, headache, stiff neck, vomiting, malaise, irritability, drowsiness, coma
May be preceded by a prodromal respiratory illness or sore throat
- Recommended diagnostics: Cerebrospinal fluid (CSF) examination
Full blood count, blood C&S
- Common findings: Leukocytosis; cerebrospinal fluid shows increased pressure, cell count (100–10,000/mm³), and protein (>100 mg/dl) and decreased glucose (<40 mg/dl or <50% of the simultaneous glucose blood level) Gram-stained smear of the spun sediment of the CSF can reveal the etiologic agent.
- Management and treatment: Penicillin (24 million units daily in divided doses every 2-3 hours) or ampicillin (12 gr daily in divided doses every 2-3 hours) or Chloramphenicol (4 to 6 grams IV/day). Continue treatment for 10 to 14 days.
Crystalline penicillin (2-3 mega units) and chloramphenicol (500-750 mg, 6 hourly for 10-14 days).
- Prevention: Cotrimoxazole (trimethoprim [TMP] 160mg), sulfamethoxazole (SMX) 800mg once daily, (equivalent to one double strength or two single strength tablets a day)
If CD4 count less than 200/mm³ or, where CD4 cell counts are not available, symptomatic HIV infection meeting criteria for WHO Stage II, III or IV disease
- Comments: Often encountered during late stages of HIV disease. Prompt diagnosis and aggressive management and treatment ensure a quick recovery.

d. Cytomegalovirus (CMV)

- Common etiological agent: *Cytomegalovirus*
- Clinical presentation: Retinitis, characterized by creamy yellow white, hemorrhagic, full-thickness retinal opacification, which can cause visual loss and lead to blindness if untreated; patient may be asymptomatic or complain of floaters, diminished acuity or visual field defects. Retinal detachment, if disease is extensive.

Gastrointestinal symptoms: diarrhea, colitis, esophageal ulceration appear in 12-15 percent of patients.

Neurological symptoms, for example, encephalitis, respiratory symptoms and pneumonitis present ~1 percent.

- Recommended diagnostics: Fundoscopic exam to check for changes. Consult an ophthalmologist. Upper GI (UGI) endoscopy, when indicated.
- Common findings: Although any part of the retina may be involved, there is a predilection for the posterior pole; involvement of the optic nerve head and macula region is common. Characteristically, this involves the retinal vessels, which are always abnormal in areas affected by retinitis. There is minimal or no accompanying uveitis.
- Management and treatment: Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14-21 days; ganciclovir 5mg/kg IV bid for 14-21 days
Patients without immune recovery will need to be on maintenance therapy life-long for retinitis.
Extraocular: ganciclovir and/or foscarnet
- Comments: Rare but devastating illness in resource-poor settings. Treatment is very expensive and usually not available. CMV management needs special care. Therefore, early referral is essential.

e. AIDS dementia complex (ADC) (HIV-associated dementia [HAD])

- Presentation
 - Feature distinguishing ADC from other dementias is its subcortical cluster of symptoms
 - Patient may complain of slowed mental processing, with diminished concentration and memory, and general lethargy.
- Key history points:
 - Carry out a detailed mental assessment
 - Be sure to begin by using open-ended questions in making a mental assessment
 - Start by explaining why you are asking these questions:
 - Say something like “In order to assess your medical condition, we need to see how you are doing in terms of memory and problem solving, since memory is sometimes affected in people with certain diseases.”
 - Ask the patient such questions as:
 - “Please tell me how your memory has been...how you’ve been doing at remembering things day to day.”
 - “What has changed in the recent past about how you manage to remember things—are you using different strategies, methods, etc.?”
 - Depending on responses to the previous questions, ask all or some of the following questions:
 - “Do difficult tasks take you longer to complete?”
 - “Do you lose track of the conversation?”
 - “Do you have trouble keeping your balance?”
 - “Do you have tremors when you try writing?”
- Listen to accounts of relatives and associates. (This is especially important in early cases.)

- Clinical features: Patient is afebrile; presents with a triad of cognitive, behavioral and motor dysfunction
 - Cognitive dysfunction: Forgetfulness
Loss of concentration
Mental slowing down
Reduced performance of complex mental activities
 - Behavioral symptoms: Apathy
Reduced spontaneity and emotional responsivity
Social withdrawal
Depression, irritability or emotional lability
 - Motor dysfunction: Loss of balance and coordination
Clumsiness and leg weakness
Paraplegia
 - In late stages: Speech deterioration—possible progression to mutism
Bedridden, with indifference to their illness or surroundings
Bladder and bowel incontinence
Consciousness usually preserved, with occasional excessive sleep
Unpredictable course, with many fluctuations
Death usually results from aspiration pneumonia or an opportunistic infection
- Diagnostic workup: Diagnosis is based primarily on clinical presentation.
- CT scan/MRI: Location—diffuse, deep white matter hyperintensities
Sites—variable
Enhancement—negative
Atrophy—prominent
No mass effect
- CSF:* Normal—30-50 percent of patients
Protein—increased in 60 percent of patients
WBC—increased in 5-10 percent (monos) of patients
Beta-2 microglobulin elevated (>3 mg/L)
- Other diagnostic tests: Neuropsychological tests show subcortical dementia
Mini-mental exam is insensitive

*CSF Normal Values

1. Normal values:

Protein: 14-45 mg/dl; traumatic tap: 1 mg/1000 RBCs

Glucose: 40-80 mg percent or CSF/blood glucose ratio >0.6

Leukocyte counts: <5 mononuclear cells/mL; 5-10 is suspect; I PNM

Bloody tap – 1 WBC/700 RBC

Opening pressure: 80-200 mm H₂O

2. CSF analysis in asymptomatic HIV-infected persons shows that 40-50 percent have elevated protein and/or pleocytosis (>5 mononuclear cell/mL); the frequency of pleocytosis decreases with progressive disease.

- Management and treatment:
 - Possible benefit from antiretroviral regimens with agents that penetrate the CNS (AZT, d4T, ABC, nevirapine)
Benefit of AZT at higher dose for mild or moderately severe cases is established; monitor therapy with neurocognitive tests
Anecdotal experience indicates response to ART, if started early
 - Sedation for those who are agitated and aggressive—use smaller doses initially, to avoid oversedation
 - Close monitoring:
 - To prevent self-harm
 - To ensure adequate nutrition
 - To diagnose and treat OIs early
 - Psychological support for caregivers—looking after demented patients is exhausting; caregivers need regular breaks and may need counseling.

- Comments:
 - In up to 10 percent of cases, ADC will be the first manifestation of HIV-induced disease. The frequency in all patients is 10-15 percent.
 - Prevalence increases with improvement of general management of various OIs because patients live long enough to develop severe immune suppression.
 - Patients present with a demeanor similar to Parkinson's disease and may even be misdiagnosed as such.

f. Painful sensory and motor peripheral neuropathies

- Key history points
 - When taking a history, keep in mind that the peripheral nerves may be:
 1. Directly damaged by HIV itself or other infections as a result of progressive immunosuppression
 2. Affected by other conditions that are commonly associated with chronic ill health, including:
 - Poor nutrition
 - Multiple drug therapy and herbal remedies, with their toxic and other side effects (toxic neuropathy), for example, INH, d4T, ddI
 - Renal failure, with uremia and other electrolyte disorders
 - OIs and cancers
 - Look for and ask about the following symptoms:
 - Pain and numbness in toes and feet; ankles, calves and fingers are involved in more advanced cases
 - Recurrent episodes of *pins and needles* in upper and lower limbs
 - Severe burning pain in distal lower extremities—aggravated by extremes of temperatures, touch or dryness; sometimes shooting pains
 - Pain and aching in muscles, usually thighs and shoulders—weakness, with difficulty rising from a chair or reaching above shoulders
 - Rapidly evolving weakness and numbness of legs
 - Poor bowel and bladder control (incontinence)
 - Uncontrollable sweating
 - Dizziness from postural hypotension

- Clinical features: Depending on the syndrome, any of the following may be present:
 - Burning pain and numbness
 - Mild/moderate muscle tenderness
 - Muscle weakness
 - Contact sensitivity, in some cases
 - Reduced pinprick/vibratory sensation (later)
 - Reduced or absent ankle/knee jerks (later)
 - Dizziness secondary to postural hypotension
 - Autonomic dysfunction (later)
 - Poor bowel and bladder control (later)

- Diagnostic tests:
 - Electromyography/nerve conduction velocities (if available)—show predominantly axonal neuropathy
 - Quantitative sensory testing or thermal thresholds may be helpful.
 - CPK—usually elevated
 - Spinal fluid to determine etiology (cytomegalovirus or herpes simplex virus infections—lymphomatous infiltration)
 - Serum B12 and TSH

- Management and Treatment:
 - Exclude other causes, such as neurotoxic drugs, alcoholism, diabetes, B12 deficiency and thyroid problems
 - Discontinue presumed neurotoxic medication
 - Provide proper nutrition and vitamin supplements
 - Administer pain control:
 - Ibuprofen 600-800 mg po tid or codeine for modest symptoms
 - Amitriptyline 25-50 mg at night
 - Phenytoin 50-100 mg bid or carbamazepine 100-200 mg tid, especially for episodic shooting pain; may have to combine antidepressants with anti-convulsants
 - Methadone or morphine for severe symptoms
 - Lidocaine 10-30 percent ointment for topical use
 - Physical therapy may help, but may be hampered by pain
 - Counseling and psychological support

g. Progressive multifocal leukoencephalopathy (PML)

- Presentation: An end-stage complication of HIV, caused by the JC virus
- Clinical features:
 - Multifocal neurological symptoms:
 - Weakness: Typically hemiparesis, but could also be monoparesis, hemiplegia
 - Visual deficits: Homonymous hemianopsia or quadrantanopsia
Cognitive abnormalities
 - More rapidly advancing and occur in conjunction with focal neurological deficits:
 - Personality and behavioral changes
 - Motor impersistence
 - Memory impairment
- Diagnostic tests:
 - Definitive diagnosis is by brain biopsy (if available).
 - CT brain scan may be normal or remarkable for areas of diminished density or demyelination (deterioration of the covering of the nerve).
 - PCR of CSF for detection of JC virus
- Differential diagnosis:
 - Toxoplasmosis
 - Primary CNS lymphoma
- Management and treatment
 - There is no treatment for this illness.
 - Highly active antiretroviral therapy (HAART) can improve symptoms and prolong life.
- Comments: PML is rare in the general community and relatively common in HIV infection (affecting 4 percent of all AIDS patients). Consider routine testing for HIV for any patient with PML.

h. Primary central nervous lymphoma

- Presentation: Typical end-stage complication of HIV disease
- Clinical features: Focal and multifocal neurological deficits are similar to toxoplasmosis (headache, confusion, hemiplegia, seizures), but the tempo of disease evolution is usually slower, with symptoms worsening over few weeks.
 - Afebrile
 - Mental status change (60 percent)—personality or behavioral
 - Seizures (15 percent)
 - CD4<100

- Diagnostic tests:
 - CT scan/MRI:
 - Location—periventricular, anywhere from 2-6 cm
 - Sites—one or many
 - Enhancement—prominent, usually solid, irregular
 - Edema/mass effect—prominent
 - CSF:
 - Normal—30-50 percent
 - Protein—10-150/ml
 - WBC—0-100 (monos)
 - Experimental—EBV PCR or in situ hybridization
 - Cytology + in <5 percent
 - Suspect with negative toxo IgG or failure to respond to empiric toxo treatment
 - Other diagnostic tests: EBV DNA in CSF
- Management and treatment
 - There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative.
 - Corticosteroids can also help some patients.
- Comments:
 - Primary CNS lymphoma is rare in the general community, but it affects about 2 percent of AIDS patients.
 - Survival after diagnosis is usually limited (a few months only).

i. Neurosyphilis

- Presentation:
 - Past history of STDs and/or treatment for syphilis
- Clinical features
 - Can be asymptomatic
 - Meningeal—headache, fever, photophobia, meningismus± seizures, focal findings, cranial nerve palsies
 - Tabes dorsalis—sharp pains, paresthesias, decreased DTRs, loss of pupil response
 - General paresis—memory loss, dementia, personality changes, loss of pupil response
 - Meningovascular strokes, myelitis
 - Ocular syphilis—iritis, uveitis, optic neuritis

- Diagnostic tests:
 - CT scan/MRI: with aseptic meningitis, may show:
 - Meningeal enhancement
 - General paresis—cortical atrophy, sometimes with infarcts
 - Meningovascular syphilis—deep strokes
 - CSF: protein—45-200/ml
 - WBCs—5-100 (monos)
 - VDRL positive—sensitivity 65 percent; specificity 100 percent positive
 - Serum VDRL and FTA-ABS are clue in >90 percent
 - A false neg serum VDRL occurs in 5-10 percent with tabes dorsalis or general paresis
 - Definitive diagnosis: positive CSF VDRL (found in 60-70 percent)
- Management and treatment
 - Give Aq penicillin G, 18-24 mil units/day for 10-14 days
 - Follow-up VDRL q 6 months until negative
 - Indications to re-treat:
 - CSF WBC fails to decrease at six months or CSF still abnormal at 2 years
 - Persisting signs and symptoms of inflammatory response at ≥ 3 mos
 - Four-fold increase in CSF VDRL ≥ 6 mos
 - Failure of CSF VDRL of $\geq 1:16$ to decrease by two-fold by 2 mos or four-fold by 12 mos

Comments: Most common forms in HIV-infected persons are ocular, meningeal and meningovascular
 Some evidence that syphilis progresses more rapidly in the context of HIV infection, so that complications such as meningovascular syphilis may occur at an unusually early phase
 Affects 0.5 percent of all AIDS patients
 Recommended that you offer syphilis testing to all clients presenting for VCT in high prevalence areas because it is treatable in early stages and has an accelerated course in HIV

j. Differential diagnosis neuropsychiatric diseases

- The following table provides valuable information on clinical features and diagnostics that will help the provider make a differential diagnosis.

Table A2, 4.2: Central Nervous System Conditions in Patients with HIV Infection

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT SCAN/MRI	CSF*	Other Diagnostic Tests
Toxoplasmosis (2 percent to 4 percent)	<ul style="list-style-type: none"> Fever, reduced alertness, headache, focal neurological deficits (80 percent), seizures (30 percent) Evolution: < 2 weeks CD4count<100cells/mm³ 	<ul style="list-style-type: none"> Location: Basal ganglia, gray-white junction Sites: Usually multiple Enhancement: prominent; usually ring lesions (1 to 2 cm) Edema/mass effect: Usually not as great as lymphoma 	<ul style="list-style-type: none"> Normal 20 percent to 30 percent Protein: 10 to 150/mg/dL WBC: 0 to 40 (monos) Experimental: toxo ag (ELISA) or PCR 	<ul style="list-style-type: none"> Toxoplasmosis serology (IgG) false-negative in < 5 percent Response to empiric therapy: >85 percent; most respond by day 7 (N Engl J Med 1993;329:995) MRI: Repeat at 2 weeks Definitive diagnosis: brain biopsy
Primary CNS Lymphoma (2 percent)	<ul style="list-style-type: none"> Afebrile, headache, focal neurological findings, mental status change (60 percent), personality or behavioral; seizures (15 percent) Evolution: 2 to 8 weeks CD4 count <100 cells/mm³ 	<ul style="list-style-type: none"> Location: periventricular, anywhere, 2 to 6 cm Sites: one or many Enhancement: prominent; usually solid, irregular Edema/mass effect: prominent 	<ul style="list-style-type: none"> Normal 30 percent to 50 percent Protein: 10 to 150/mg/dL WBC: 0 to 100 (monos) EBV PCR in 50 percent EBV DNA in CSF (Lancet 1992; 342:398) 	<ul style="list-style-type: none"> Suspect with negative toxo, IgG, single lesion or failure to respond to empiric toxoplasmosis treatment (MRI and clinical evaluation at 2 weeks) Thallium 201 SPECT scan (90 percent sensitive and specific)
Cryptococcal meningitis (8 percent to 10 percent)	<ul style="list-style-type: none"> Fever, headache, alert (75 percent); less common are visual changes, stiff neck, cranial nerve deficits, seizures (10 percent); no focal neurological deficits Evolution: < 2 weeks CD4 count <100 cells/mm³ 	<ul style="list-style-type: none"> Usually normal or shows increased intracranial pressure Enhancement: negative or meningeal enhancement Edema mass effect: ventricular enlargement/ obstructive hydrocephalus 	<ul style="list-style-type: none"> Protein: 30 to 150/mg/dL WBC: 0 to 100 (monos) Culture positive: 95 percent to 100 percent India ink pos: 60 percent to 80 percent Crypt Ag: >95 percent sensitive and specific 	<ul style="list-style-type: none"> Cryptococcal antigen in serum – 95 percent Definitive diagnosis: CSF antigen and/or positive culture
CMV (cytomegalovirus) (>0.5 percent)	<ul style="list-style-type: none"> Fever + delirium, lethargy, disorientation; headache; stiff neck, photophobia, cranial nerve deficits; no focal neurologic deficits Evolution: < 2 weeks CD4 count <100 cells/mm³ 	<ul style="list-style-type: none"> Location: periventricular, brainstem Site: confluent Enhancement: variable, prominent to none 	<ul style="list-style-type: none"> CSF may be normal Protein: 100 to 1000/mg/dL WBC: 10 to 1000 (polys)/mL Glucose usually decreased CMV PCR positive CSF cultures usually negative for CMV 	<ul style="list-style-type: none"> Definitive diagnosis: brain biopsy with histopath and/or positive culture Hyponatremia (reflects CMV adrenalitis) Retinal exam for CMV retinitis
HIV Dementia (7 percent)	<ul style="list-style-type: none"> Afebrile; triad of cognitive, motor and behavioral dysfunction Early: Decreased memory, concentration, attention, coordination; ataxia Late: Global dementia, paraplegia, mutism Evolution: Weeks to months CD4 count<200cells/mm³ 	<ul style="list-style-type: none"> Location: Diffuse, deep white matter hyperintensities Site: Diffuse, ill-defined Enhancement: Negative Atrophy: Prominent No mass effect 	<ul style="list-style-type: none"> Normal 30 percent to 50 percent Protein: increased in 60 percent WBC: increased in 5 percent to 10 percent (monos) Beta-2-micro-globulin elevated (>3mg/L) 	<ul style="list-style-type: none"> Neuropsychological tests show subcortical dementia HIV dementia scale for screening

Source: Bartlett 2003

Table A2, 4.2 (cont.)

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT SCAN/MRI	CSF*	Other Diagnostic Tests
	<ul style="list-style-type: none"> Asymptomatic meningeal: headache, fever, photophobia, meningismus + seizures, focal findings, cranial nerve palsies Tabes dorsalis: Sharp pains, paresthesias, decreased DTRs, loss of pupil response General paresis: memory loss, dementia, personality changes, loss of pupil response Meningovascular: strokes, myelitis Ocular: iritis, uveitis, optic neuritis Any CD4 cell count 	<ul style="list-style-type: none"> Aseptic meningitis: may show meningeal enhancement General paresis: cortical atrophy, sometimes with infarcts Meningovascular syphilis: deep strokes 	<ul style="list-style-type: none"> Protein: 45 to 200/mg/dL WBC: 5 to 100 (monos) VDRL positive: sensitivity = 65 percent specificity = 100 percent positive Experimental: PCR for T. pallidum 	<ul style="list-style-type: none"> Serum VDRL and FTA-ABS are clue in >90 percent; false negative serum VDRL in 5 percent to 10 percent with tabes dorsalis or general paresis Definitive diagnosis: Positive CSF VDRL (found in 60 percent to 70 percent) Note: most common forms in HIV-infected persons are ocular, meningeal and meningovascular
PML (1 percent to 2 percent)	<ul style="list-style-type: none"> No fever; no headache; impaired speech, vision, motor function, cranial nerves Late: cognition Evolution: weeks to months CD4 count <100 cells/mm³, some >200 cells/mm³ 	<ul style="list-style-type: none"> Location: white matter, subcortical, multifocal Sites: variable Enhancement: negative No mass effect 	<ul style="list-style-type: none"> Normal CSF PCR for JC virus: 80 percent 	<ul style="list-style-type: none"> Brain biopsy: positive DFA stain for JC virus
Tuberculosis (0.5 percent to 1 percent)	<ul style="list-style-type: none"> Fever, reduced alertness, headache, meningismus, focal deficits (20 percent) CD4 count <350 cells/mm³ 	<ul style="list-style-type: none"> Intracerebral lesions in 50 percent to 70 percent (N Engl J Med 1992;326:668; Am J Med 1992; 93:524) 	<ul style="list-style-type: none"> Normal: 5 percent to 10 percent Protein: Normal (40 percent)-500ml WBC: 5 to 2000 (average is 60 percent to 70 percent monos) Glucose: 4 to 0/mL AFB smear positive: 20 percent 	<ul style="list-style-type: none"> Chest x-ray: active TB in 50 percent; PPD positive: 20 percent to 30 percent Definitive diagnosis: positive culture CSF

*CSF: cerebrospinal fluid

Normal Values: Protein: 15 to 45 mg/dL; traumatic tap: 1 mg/1000 RBCs; glucose: 40 to 80 mg percent or CSF/blood glucose ratio >0.6; leukocyte counts: <5 mononuclear cells/mL, 5 to 10 is suspect, 1PMN is suspect; bloody tap: 1 WBC/700 RBC; opening pressure: 80 to 200 mm H2O

CSF analysis in asymptomatic HIV infected persons shows 40 percent to 50 percent have elevated protein and/or pleocytosis (>5 mononuclear cell/mL); the frequency of pleocytosis decreases with progressive disease.

Case Study: Patient with neurological symptoms

A 25-year-old truck driver was diagnosed with HIV infection two years ago during a visit to a health center because of urethritis. He did not believe the test result and never went back for medical follow-up.

He is married and the father of four children. On weekends, he is a heavy alcohol drinker and also visits prostitutes.

He is admitted at the district hospital because of an epileptic insult. Diazepam is administered intrarectally.

A few days earlier, before the insult, he had complained of weakness in his left arm and leg. For four months he has been complaining of generalized papular pruritic eruption. For one month he has had a painful ulcerative lesion on his penis. This lesion persisted even though he received several antibiotics.

After recovery from the epileptic insult, a left hemiparesis is noted. Lymph nodes are slightly enlarged in the cervical, axillary and inguinal region. His blood pressure is 130/70 mmHg.

Laboratory tests show a hemoglobin of 9 g/dl, a white blood cell count: $3.200 \times 10^9/l$ with 20% lymphocytes. Creatinine, glucose and electrolyte levels are normal. His transaminases are slightly elevated. A thick smear does not show parasites. A CT scan is not available.

- What can be the reason for this patient's epileptic insult?
- What does this patient need?
- What should you offer?

Case study (patient with neurological symptoms)—Answers*Cause of the epileptic insult*

This patient probably has AIDS. Arguments for this are the chronic painful ulceration on his penis, probably caused by a herpes simplex infection, and his very low lymphocyte count of $300 \times 10^9/l$, suggesting a CD4+ lymphocyte count below $200 \times 10^9/l$.

The most likely diagnosis in this patient is a cerebral toxoplasmosis or abscess; the second most likely diagnosis is a tuberculoma or a tuberculous abscess of the brain.

Less likely diagnoses are: a cerebral lymphoma, neurosyphilis, progressive multifocal leukoencephalopathy, a fungal brain abscess, herpes or cytomegalo encephalitis, or a cerebro-vascular accident.

*Patient's needs – What can you offer?**Medical care*

You should start this patient on pyrimethamine 100 mg po loading dose, then 50 mg po daily + 10 mg po folinic acid daily, and sulfadiazine 4 g po daily for at least six weeks. Thereafter, you should give antitoxo maintenance because of a possible toxoplasmosis brain abscess. You should perform a serological test for syphilis to exclude neurosyphilis and do a checkup for tuberculosis. Treat the herpes ulceration with acyclovir 400 mg po tid, if available. Start antiepileptic medication, if available. If possible, do a funduscopy to look for retinal abnormalities and papilledema. Clinical improvement is expected within one week. If cerebral edema is suspected (nausea, headache) corticosteroids may be indicated. If the patient is not improving during anti-toxoplasmosis treatment and if there are no signs of papilledema, consider a lumbar puncture.

Nursing care

Because of his left hemiparesis, this man probably has difficulty caring for himself. Exercises with his left arm and leg may help him to recover. Once the patient is improving clinically, start safe sex counseling and discuss his relationship with his wife. You could propose HIV testing for his wife.

Psychosocial support

This man clearly has difficulty accepting his HIV seropositive status. If he cannot receive antiretroviral drugs, he will probably develop other HIV-related complications. This will cause extra stress for him and his family.

Socioeconomic support

This man and his family will probably have to face serious financial problems. The history of an epileptic insult will make it hard for him to continue as a truck driver. Because he will have many medical costs, he should reduce expenses for nonessential needs as much as possible and decrease his use of alcohol. These issues mean that it is likely that it will be necessary to involve social services in his case management.

SESSION 5 Conditions of the Gastrointestinal System**PURPOSE**

In this session, participants will learn about chronic diarrhea and conditions of the gastrointestinal system, including common etiological agents; clinical presentation; recommended diagnostics; and common findings, management, and treatment. This session will also discuss hepatitis.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the various infectious agents that cause chronic diarrhea.
2. Describe the clinical presentation of each infection.
3. List the recommended diagnostics and common findings for each infection.
4. Discuss the treatment and management of chronic diarrhea.
5. Discuss hepatitis, including management, treatment and prevention.
6. Make a differential diagnosis using a case study approach.

TIME:

2 hours

1. Introduction

a. Overview

- Chronic diarrhea is a very frequent and frustrating problem in PLHAs; at least 50 percent experience it some-time during the evolution of the disease
- Often accompanied by nausea, weight loss, abdominal cramps and dehydration
- Often an intermittent watery diarrhea, without blood or mucus
- In one-third to two-thirds of cases, no cause is identified.
- In areas of high prevalence of HIV infection, chronic diarrhea is invariably the result of symptomatic HIV infection.
- Wherever possible, establish the cause and give specific treatment. Failing this, management is symptomatic: give antidiarrheals such as codeine phosphate.
- The key to good management is rehydration without much sugar and including potassium.
- High energy and protein intake reduces the degree of muscle wasting.
- Prevention consists of attention to personal hygiene hand washing, drinking boiled water and eating only thoroughly cooked meat and vegetables.

b. An infectious agent can be identified in about 50 percent of patients with AIDS-associated diarrhea. Differential diagnosis includes the following pathogens:

- **Bacterial infection:** *Campylobacter, shigella and salmonella*
- **Protozoal infection:** *Cryptosporidium species, giardia lamblia, isospora belli, entamoeba histolitica, microsporidium species*
- **Toxin induced:** *E. coli and clostridium difficile*
- **Mycobacterial infection:** *M. tuberculosis, M. avium complex*
- **Helminthic infection:** *Strongyloides stercoralis*
- **Fungal infection:** *Candida species (seldom a cause of diarrhea)*

These conditions should be differentiated from:

- AIDS enteropathy:** Direct cytopathic effect of HIV
- Noninfectious disorders:** Kaposi's sarcoma, lymphoma

Table A2, 5.1: Conditions of the Gastrointestinal System: Chronic Diarrhea

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p><i>Campylobacter</i></p>	<ul style="list-style-type: none"> Fever and general malaise, sometimes without GI symptoms GI symptoms would be bloody diarrhea, abdominal pain and weight loss. 	<p><i>Campylobacter</i> bacilli found in stool culture</p>	<ul style="list-style-type: none"> Erythromycin 500 mg bid x 5 days (1st choice) Fluoroquinolones are also effective, but resistance rates of 30-50 percent have been reported in some developing countries. 	<p>It is clinically impossible to distinguish the different etiological agents of bacterial gastroenteritis without a stool culture. Therefore, if empiric therapy with TMP/SMX is not effective in patients with bacillary dysentery, you can try fluoroquinolones, followed by a trial of erythromycin, if symptoms of bloody diarrhea persist.</p>
<p><i>Salmonella</i></p>	<ul style="list-style-type: none"> Fever; general malaise Sometimes no GI symptoms, but if so, will see: bloody diarrhea, abdominal pain and weight loss 	<p>Stool culture</p> <p><i>Salmonella</i> bacilli may be found in stool/blood cultures.</p> <p>Serology: positive Widal test with increased titres</p>	<ul style="list-style-type: none"> TMP/SMX 960 mg bid or chloramphenicol 250 mg qid for 3 weeks In case of signs of sepsis, IV therapy is necessary. <p>Shorter regimens are:</p> <ul style="list-style-type: none"> Ciprofloxacin 500 mg bid or ofloxacin 400 mg bid or ceftriaxone 2 g IV for 7-10 days <p>Many patients often relapse after treatment, and chronic maintenance therapy (TMP/SMX 1 DD daily) is sometimes necessary.</p>	<p>Salmonellosis is a frequent cause of bacteremia in PLHA.</p>
<p><i>Shigella</i></p>	<ul style="list-style-type: none"> High fever Abdominal pain Bloody diarrhea 	<p>Stool microscopy— fresh examination and after concentration. Multiple stool samples may be necessary. <i>Shigella</i> bacillus found in stool.</p>	<ul style="list-style-type: none"> TMP/SMX 960 mg bid x 5 days or amoxicillin 500 mg tid x 5 days <p>If resistant to the above, give ciprofloxacin 500 mg bid, or norfloxacin 400 mg bid x 5 days or nalidixic acid 1 g qid x 10 days.</p>	<p>In many developing countries, resistance of <i>Shigella</i> (and <i>Salmonella</i>) to TMP/SMX has increased.</p>

Table A2, 5.1 (cont.)

Etiology Protozoal	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<i>Clostridium difficile</i>	<ul style="list-style-type: none"> • Diarrhea • Fever 	Stool microscopy and culture		<p>May be underestimated as a cause of diarrhea in AIDS patients in the tropics because of the difficulty in making the diagnosis. Frequent hospitalization and exposure to antibiotics puts patients at high risk of infection.</p> <p>As in HIV-negative patients, 5-30 percent of patients with <i>C. difficile</i>-associated diarrhea experience relapse.</p>
<i>Cryptosporidium</i>	<ul style="list-style-type: none"> • Recent and prolonged history of severe diarrhea—usually large volume, watery stools with a lot of abdominal pain, bowel noise, and activity • Severe weight loss/wasting in those with longer history 	<p>Stool samples x 3 for staining/AFB smear</p> <p>Oocysts present in stool exam</p> <p>No fecal WBCs</p>	<ul style="list-style-type: none"> • Rehydration (IV and/or ORS) • Paromomycin 500 mg qid for 2-3 weeks; maintenance with 500 mg bid often required • Codeine phosphate 30-60 mg tid until under control (or other anti-diarrheal agents such as loperamide 2-4 mg tid or qid—maximum of 32 mg in 24 hours) • ARV is protective against cryptosporidiosis. 	<p>Cryptosporidia are highly infectious and transmitted through water, food, animal-to-human and human-to-human contact. Special precautions should be taken to prevent exposure. People with HIV and a CD4<200 should boil tap water for at least one minute to reduce risk of ingestion of oocysts in potentially contaminated drinking water.</p> <p>May be the AIDS-defining presentation in patients who previously had few symptoms of HIV infection</p>
Toxin induced: <i>E. coli</i>	<ul style="list-style-type: none"> • Diarrhea • Fever 	Stool microscopy and culture		
<i>Entamoeba histolytica</i>	<ul style="list-style-type: none"> • Colitis • Bloody stools • Cramps • Can be asymptomatic 	<p>Stool for ova and parasite exam</p> <p>O&P present in stool exam</p> <p>No fecal WBCs</p>	<p>Metronidazole 500-700 mg po or IV tid x 5-10 days or paromomycin 500 mg po qid x 7 days</p>	<p><i>E. histolytica</i> may be common in the general population in developing countries, but may be recurrent or more severe in HIV patients.</p>
<i>Giardia lamblia</i>	<ul style="list-style-type: none"> • Enteritis • Watery diarrhea ± malabsorption • Bloating • Flatulence 	<p>Stool for ova and parasites</p> <p>O&P in stool exam</p>	<p>Metronidazole 250 mg po tid x 10 days</p>	<p>Common cause of diarrhea in general population, but may be recurrent or more severe in HIV patients</p>

Table A2, 5.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Protozoal <i>Isospora belli</i>	<ul style="list-style-type: none"> • Enteritis, watery diarrhea • No fever • Wasting, malabsorption (Similar symptoms as <i>Cryptosporidium</i>)	Stool x 3: unstained wet preparation <i>Isospora belli</i> oocysts are relatively big (2030 µm) and can be easily identified in unstained wet stool preparation No fecal WBCs	<ul style="list-style-type: none"> • Most cases are readily treated with sulfamethoxazole/ trimethoprim (960 mg qid for 10 days) followed by 1 double strength tablet (960 mg bid for 3 weeks) then chronic suppression with sulfamethoxazole/ trimethoprim (960mg) daily. • High dose of pyrimethamine with calcium folinate to prevent myelosuppression. • Long-term maintenance therapy may be necessary to prevent relapse. 	
<i>Microsporidium</i>	<ul style="list-style-type: none"> • Profuse watery, non-bloody diarrhea • Abdominal pain and cramping • Nausea • Vomiting • Weight loss 	Fresh stool microscopy with modified trichrome stain Spores present in stool exam		Species of microsporidia have been linked to disseminated disease, for example, cholangitis, keratoconjunctivitis, hepatitis, peritonitis and infections of the lungs, muscles and brain. However, the presence of microsporidia does not always correlate with symptomatic disease. Most microsporidial infections are not treatable.
Helminthic <i>Strongyloides stercoralis</i>	<ul style="list-style-type: none"> • Serpiginous erythematous skin lesions (larva currens) • Diarrhea • Abdominal pain • Cough • Full-blown hyper-infection syndrome has the characteristics of a Gram-negative sepsis, with acute respiratory distress syndrome, disseminated intravascular coagulation, secondary peritonitis and cough. 	<ul style="list-style-type: none"> • Chest x-ray: the chest x-ray may reveal diffuse pulmonary infiltrates • Stool microscopy, (multiple stool samples may be necessary) • Sputum sample In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, bronchoalveolar lavage fluid pleural fluid, peritoneal fluid and surgical drainage fluid.	Ivermectin 12 mg daily for 3 days This is also the drug of choice for the treatment of systemic strongyloidiasis. An alternative treatment is albendazole 400 mg bid x 5 days. A maintenance therapy once a month is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once monthly).	In immuno-compromised patients, strongyloides can cause overwhelming infection. This serious complication is called strongyloides hyper-infection syndrome and has a high case-fatality rate. Disseminated strongyloidiasis and heavy worm loads can occur in patients with HIV, but the full-blown hyper-infection syndrome is less common. The likelihood of developing the hyper-infection syndrome is also higher in patients taking high-dose steroids.

See below (3.a) for all content regarding hepatitis.

2. Gastrointestinal conditions

a. Salmonellosis

- Common etiological agent: **Salmonella**
- Clinical presentation: Fever and general malaise, sometimes without GI symptoms
- Recommended diagnostics: Stool microscopy—fresh examination and after concentration. Multiple stool samples may be necessary
Stool and blood cultures
Serology: Widal test
- Common findings: Salmonella bacilli may be found in stool/blood cultures
Positive Widal test with increased titers
- Management and treatment: TMP/SMX 960 mg bid or
Chloramphenicol 250 mg qid for 3 weeks
In case of signs of sepsis, IV therapy is necessary.
Shorter regimens are: ciprofloxacin 500 mg bid or ofloxacin 400 mg bid or ceftriaxone
2 g IV for 7-10 days
Many patients often relapse after treatment, and chronic maintenance therapy (TMP/SMX DS daily) is sometimes necessary.
- Comments: Salmonellosis is a frequent cause of bacteremia in PLHAs.

b. Shigella infection

- Common etiological agent: *Shigella*
- Clinical presentation: High fever, abdominal pain and bloody diarrhea
- Recommended diagnostics: Stool microscopy—fresh examination and after concentration. Multiple stool samples may be necessary.
- Common findings: Shigella bacillus found in stool
- Management and treatment: TMP/SMX 960 mg bid x 5 days or
Amoxicillin 500 mg tid x 5 days
If resistant to the above, give ciprofloxacin 500 mg bid or norfloxacin 400 mg bid x 5 days or nalidixic acid 1 g qid x 10 days
- Comments: In many developing countries, resistance of *Shigella* (and *Salmonella*) to TMP/SMX has increased.

c. **Campylobacter enteritis**

- Common etiological agent: *Campylobacter*
- Clinical presentation: Fever, bloody diarrhea, abdominal pain and weight loss
- Recommended diagnostics: Stool culture
- Common findings: *Campylobacter* bacilli found in stool culture
- Management and treatment: Erythromycin 500 mg bid x 5 days (1st choice)
Fluoroquinolones are also effective, but resistance rates of 30-50 percent have been reported in some developing countries.
- Comments: It is clinically impossible to distinguish the different etiological agents of bacterial gastroenteritis without a stool culture. Therefore, if empiric therapy with TMP/SMX is not effective in patients with bacillary dysentery, you can try fluoroquinolones, followed by a trial of erythromycin, if symptoms of bloody diarrhea persist.

d. **Cryptosporidium**

- Common etiological agent: *Cryptosporidium*
- Clinical presentation: Recent and prolonged history of severe diarrhea—usually large volume, watery stools with a lot of abdominal pain, bowel noise and activity; no fecal WBCs. Severe weight loss/wasting in those with longer history.
- Recommended diagnostics: Stool samples x 3 for staining/AFB smear
- Common findings: Oocysts present in stool exam
- Management and treatment: Rehydration (IV and/or ORS)
Paromomycin 500 mg qid for 2-3 weeks; maintenance with 500 mg. bid often required
Codeine phosphate 30-60 mg tid until under control (or other anti-diarrheal agents such as loperamide 2-4 mg tid or qid—maximum of 32 mg in 24 hours)
The use of ARV is protective against cryptosporidiosis.
- Preventive measures: Cryptosporidia are highly infectious and can be transmitted through water, food and animal-to-human and human-to-human contact. Special precautions should be taken to prevent exposure: people with HIV and a CD4<200 should boil tap water for at least one minute to reduce risk of ingestion of oocysts in potentially contaminated drinking water.
- Comments: This may be the AIDS-defining presentation in patients who previously had few symptoms of HIV infection.

e. **Isospora belli**

- Common etiological agent: *Isospora belli*
- Clinical presentation: Enteritis, watery diarrhea, no fecal WBCs, no fever, wasting, malabsorption (same presentation/symptoms as cryptosporidium)
- Recommended diagnostics: Stool x 3: unstained wet preparation
- Common findings: *Isospora belli* oocysts are relatively big (2030 mm) and can be easily identified in unstained wet stool preparations.
- Management and treatment: Most cases are readily treated with sulfamethoxazole/trimethoprim (960 mg qid for 10 days) followed by sulfamethoxazole/trimethoprim 1 double strength tablet (960 mg bid for 3 weeks), then chronic suppression with sulfamethoxazole/ trimethoprim (960mg) daily.
High dose of pyrimethamine with calcium folinate to prevent myelosuppression
Long-term maintenance therapy may be necessary to prevent relapse.

f. **Entamoeba histolytica**

- Common etiological agent: *E. histolytica*
- Clinical presentation: Colitis; bloody stools; cramps; no fecal WBCs
Can be asymptomatic
- Recommended diagnostics: Stool for ova and parasite exam
- Common findings: O&P present in stool exam
- Management and treatment: Metronidazole 500-700 mg po or IV tid x 5-10 days or paromomycin 500 mg po qid x 7 days
- Comments: *E. histolytica* may be common in the general population in developing countries, but may be recurrent or more severe in HIV patients.

g. **Giardia lamblia**

- Common etiological agent: *G. lamblia*
- Clinical presentation: Enteritis, watery diarrhea ± malabsorption, bloating, flatulence
- Recommended diagnostics: Stool for ova and parasites
- Common findings: O&P in stool exam
- Management and treatment: Metronidazole 250 mg po tid x 10 days
- Comments: *G. lamblia* is a common cause in the general population, but may be recurrent or more severe in HIV patients.

h. **Strongyloides**

- Common etiological agent: *S. stercoralis*
- Clinical presentation: Serpiginous erythematous skin lesions (larva currens), diarrhea, abdominal pain and cough
Full-blown hyper-infection syndrome has the characteristics of a Gram-negative sepsis, with acute respiratory distress syndrome, disseminated intravascular coagulation and secondary peritonitis
- Recommended diagnostics: Stool microscopy, (multiple stool samples may be necessary) sputum sample, chest x-ray
- Common findings: In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, broncho-alveolar lavage fluid, pleural fluid, peritoneal fluid and surgical drainage fluid.
The chest x-ray reveals diffuse pulmonary infiltrates
- Management and treatment: Ivermectin 12 mg daily for 3 days
This is also the drug of choice for the treatment of systemic strongyloidiasis. An alternative treatment is albendazole 400 mg bid x 5 days.
A maintenance therapy once a month is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once monthly).
- Comments: In immunocompromised patients, strongyloides can cause overwhelming infection, especially when cell-mediated immunity is impaired. This serious complication is called strongyloides hyper-infection syndrome and has a high case-fatality rate. Hyper-infection strongyloidiasis is generally associated with other conditions of depressed host cellular immunity. Disseminated strongyloidiasis and heavy worm loads can occur in patients with HIV, but the full-blown hyper-infection syndrome is less common. The likelihood of developing the hyper-infection syndrome is also higher in patients taking high-dose steroids.

3. Other conditions

a. Hepatitis

- Etiological agents: *Hepatitis A, B, C, D and E*
- Clinical presentation: Flu-like symptoms of lassitude, weakness, drowsiness, anorexia, nausea, abdominal discomfort, fever, headache, jaundice (including dark urine, gray stools, and mild pruritis), hepatomegaly
- Recommended diagnostics: Serology for hepatitis A (anti-HAV IgM, anti-HAV IgG), B (HBsAg, anti-HBc, anti-HBs), and C (anti-HCV IgG [ELISA], anti-HCV IgG [RIBA], HCV RNA)
Liver function tests (SGPT, SGOT, alkaline phosphatase)
- Common findings: Markers for both past hepatitis B infection: test result showing negative hepatitis B surface antigen (HBsAG) and positive hepatitis B core antibody (HBcAb) and chronic carriage (positive HBsAG and positive HBcAb) are common in the HIV- infected patients and in people in certain risk groups
- Management and treatment: Symptomatic and supportive care. Where available, interferon for treatment of hepatitis B and C and havrix as a preventive measure for patients at risk for hepatitis A. Epivir-HBV for hepatitis B
Discourage alcohol consumption during convalescence.
- Prevention: Frequent hand washing and good hygiene are important as hepatitis A is spread by oral-fecal route and often by food contamination.
Hepatitis B and C are transmitted through contact with blood or through sexual contact. Condoms can reduce risk of transmission. Discourage needle sharing.
- Comments: Vaccines are very expensive and may not be available.
Confection with HIV and hepatitis C signifies probable acceleration of HIV disease and hepatitis C disease.
The hepatotoxic effect of some ARVs (for example, nevirapine) and other drugs (for example, ketoconazole) is significant.

Table A2, 5.2: The ABCs of Hepatitis

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
What is it?	HAV is a virus that causes inflammation of the liver. It does not lead to chronic disease.	HBV is a virus that causes inflammation of the liver. It can cause liver cell damage leading to cirrhosis and cancer.	HCV is a virus that causes inflammation of the liver. It can cause liver cell damage, leading to cirrhosis and cancer.	HDV is a virus that causes inflammation of the liver. It only infects those persons with HBV.	HEV is a virus that causes inflammation of the liver. It is rare in the US. There is no chronic state.
Incubation Period	2 to 7 weeks Average 4 weeks	6 to 23 weeks Average 17 weeks	2 to 25 weeks Average 7 to 9 weeks	2 to 8 weeks	2 to 9 weeks Average 40 days
How is it spread?	Transmitted by fecal/oral (anal/oral sex) route, through close person-to-person contact or ingestion of contaminated food and water. Hand to mouth after contact with feces, such as changing diapers.	Contact with infected blood, seminal fluid, vaginal secretions or contaminated needles, including tattoo and body piercing tools. Infected mother to newborn. Human bite. Sexual contact.	Contact with infected blood, contaminated IV needles, razors and tattoo or body piercing tools. Infected mother to newborn. NOT easily spread through sex.	Contact with infected blood, contaminated needles. Sexual contact with HDV infected person.	Transmitted through fecal/oral route. Outbreaks associated with contaminated water supply in other countries.
Symptoms	May have none. Others may have light stools, dark urine, fatigue, fever, nausea, vomiting, abdominal pain and jaundice.	May have none. Some persons have mild flu-like symptoms, dark urine, light stools, jaundice, fatigue and fever.	Same as HBV	Same as HBV	Same as HBV
Treatment of Chronic Disease	Not applicable.	Interferon and Lamivudine with varying success.	Interferon and combination therapies with varying success.	Interferon with varying success.	Not applicable.
Vaccine	Two does of vaccine to anyone over 2 yrs of age.	Three doses may be given to persons of any age.	None	HBV vaccine prevents HDV infection.	None
Who is at risk?	Household or sexual contact with an infected person or living in an area with HAV outbreak. Travelers to developing countries, persons engaging in anal/oral sex and injection drug users.	Infants born to infected mother, having sex with an infected person or multiple partners, injection drug users, emergency responders, healthcare workers, persons engaging in anal/oral sex and hemodialysis patients.	Blood transfusion recipients before 1992, healthcare workers, injection drug users, hemodialysis patients, infants born to infected mother and multiple sex partners.	Injection drug users, persons engaging in anal/oral sex and those having sex with an HDV infected person.	Travelers to developing countries, especially pregnant women.
Prevention	Immune Globulin within 2 weeks of exposure. Vaccination. Washing hands with soap and water after going to the toilet. Use household bleach (10 parts water to 1 part bleach) to clean surfaces contaminated with feces, such as changing tables. Safe sex.	Immune Globulin within 2 weeks of exposure. Vaccination provides protection for 18 years or more. Clean up infected blood with household bleach and wear protection gloves. Do not share razors, toothbrushes or needles. Safe sex.	Clean up spilled blood with household bleach. Wear gloves when touching blood. Do not share razors, toothbrushes or needles with anyone. Safe sex.	Hepatitis B vaccine to prevent HBV infections. Safe sex.	Avoid drinking or using potentially contaminated water.

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Case Study: Patient with chronic diarrhea

A 35-year-old farmer is hospitalized in a district hospital with chronic diarrhea, severe weight loss and dysphagia. His wife died two years ago with similar symptoms. The man is the father of six children and lives in a village 30 km from the hospital. Six years ago he developed a thoracic herpes zoster infection. Since the death of his wife, he has not felt well and is now complaining of weakness, loss of appetite and episodes of diarrhea. His mother is still alive and has been taking care of the children. The nurse at the district health center gave him several antibiotics and antiparasitic drugs, but they have had no effect on the diarrhea. The traditional healer in the village has also been unable to improve the patient's condition. Because of his illness over the last six months, he has been unable to work. His younger brother brought him to the hospital in a last effort to find a cure.

He is presenting with liquid diarrhea without blood or mucus up to 10 times a day.

On clinical examination, he is very weak, cachectic, anemic, dehydrated and presents with white patches in his mouth. He has never been tested for HIV.

- What can be causing this patient's diarrhea?
- Identify this patient's needs.
- What can you offer?

Case Study (patient with chronic diarrhea)—Answers*Cause of the diarrhea*

This patient probably has chronic diarrhea caused either by the HIV infection itself or by a parasite for which there is no etiological treatment (such as a cryptosporidia infection).

*Patient's needs - What to offer ?**Medical care*

You could treat the diarrhea symptomatically. You could rehydrate the patient, using oral rehydration solution or an infusion. With loperamide, he may be without diarrhea for at least a few hours of the day. He has oral candidiasis and probably candida esophagitis, for which you could give him fluconazole or ketoconazole. This certainly will decrease his dysphagia and improve his nutritional status. You could propose an HIV test to the patient, but based on clinical symptoms and signs, and the fact that his wife died two years earlier with similar symptoms, it is likely that this person will be HIV seropositive. If you have no antiretrovirals to offer to this patient, he will probably die in the near future. Therefore, proposing an HIV test to him may do more harm than good. If or when the patient improves, you could ask him whether he is still sexually active.

Nursing care

This man has important nursing needs. He is unable to wash himself. Planning for home care will probably be the best solution for this patient. Providing families with soap is not very costly; this may keep the patient clean and decrease the fears that family members have of becoming infected. Nutritional advice can decrease the diarrhea and improve his nutritional state.

Psychosocial support

The patient probably feels he may die in the following weeks. Since he has been hospitalized, he probably has seen several other patients with similar complaints die. He must be afraid that he will never be able to return to his village. He may have great concerns about the future of his children. He may suspect he has AIDS, but may be afraid of talking about it with the health care staff and his younger brother. He may be afraid of talking openly about the possibility of dying. Discussing more openly the patient's future may help him and his brother make decisions that reflect his wishes and help him return to the village as soon as his clinical condition has slightly improved.

Socioeconomic support

This family has serious financial problems. They have to pay for the patient's transportation back to his village and they may have problems paying for food for him and the six children. It is therefore important that they return to the village while this is still possible, otherwise they will spend their entire family budget on hospital costs, without any benefit. Maybe some financial support for transportation and nutritional support is available through an NGO or a religious organization.

SESSION 6 Conditions of the Lymph System**PURPOSE**

In this session, participants will learn about lymphadenopathy, including common etiological agents, the clinical presentation and diagnostic criteria of persistent generalized lymphadenopathy (PGL), and features of lymph nodes that indicate the need for further evaluation.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the various etiologies that cause lymphadenopathy.
2. Describe the clinical presentation of persistent generalized lymphadenopathy (PGL).
3. List the diagnostic criteria for PGL.
4. Describe features of lymph nodes that indicate further evaluation.
5. Make a differential diagnosis using a case study approach.

TIME:

1 hour and 20 minutes

1. Introduction

a. Overview

- Swelling of lymph nodes is a symptom often encountered.
- You should carry out a careful history and physical exam.
- The cause often becomes obvious, but in more complicated cases, laboratory tests and lymph node biopsy may be necessary to establish a definitive diagnosis.

b. Differential diagnosis includes the following pathogens:

- HIV-related: Persistent generalized lymphadenopathy (PGL)
- Opportunistic infections: Tuberculous lymphadenitis, CMV, toxoplasmosis, infections with nocardia species, fungal infections (histoplasmosis, penicilliosis, cryptococcus, etc.)
- Reactive lymphadenopathy: Pyomyositis, pyogenic skin infections, ear, nose, and throat (ENT) infections
- STI: Syphilis, inguinal lymphadenopathy resulting from donovanosis, chancroid or lymphogranuloma venereum (LGV). See WHO or MSF guidelines.
- Malignancies: Lymphoma, Kaposi's sarcoma

You should differentiate these etiologies from other causes of lymphadenopathies: carcinomatous metastases, brucellosis, visceral leishmaniasis (kala azar), sarcoidosis, trypanosomiasis, rickettsial disease, infectious mononucleosis and drug reactions (for example, phenytoin hypersensitivity).

2. Features of lymph nodes that indicate further evaluation:

- Large (>4cm diameter) or rapidly growing lymph nodes
- Asymmetrical lymphadenopathy
- Tender/painful lymph nodes not associated with a local infection
- Matted/fluctuant lymph nodes
- Obvious constitutional symptoms (fever, night sweats, weight loss)
- Hilar or mediastinal lymphadenopathy on chest x-ray
- Suspicion of pulmonary TB
- Evidence of abscesses (cutaneous, pulmonary and the like)

Table A2, 6.1: Conditions of the Lymph System: Lymphadenopathy

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Persistent generalized lymphadenopathy (PGL)	<ul style="list-style-type: none"> Lymph nodes larger than 1.5 cm in diameter in 2 or more extraxillary sites of 3 or more months duration Nodes are non-tender, symmetrical and often involve the posterior cervical, axillary, occipital and epitrochlear nodes <p>Lymph nodes that require further evaluation:</p> <ul style="list-style-type: none"> Large (>4cm diameter) Rapidly growing nodes Tender/painful nodes not associated with a local infection Matted/fluctuant lymph nodes Obvious constitutional symptoms (fever, night sweats, weight loss) Suspicion of pulmonary TB Evidence of abscesses 	<p>Where possible, CBC and chest x-ray before making a diagnosis of PGL</p> <p>Hilar or mediastinal lymphadenopathy on CXR</p>	<p>There is no specific treatment for PGL.</p>	<p>Develops in up to 50 percent of HIV-infected individuals. Up to one-third do not have any other symptom on presentation (WHO clinical stage I).</p> <p>In HIV-positive patients, PGL is a clinical diagnosis. No further examinations are necessary, unless there are features of another disease.</p> <p>PGL may slowly regress during the course of HIV infection and may disappear before the onset of AIDS.</p>
Tuberculosis lymphadenopathy	<ul style="list-style-type: none"> Cervical nodes most commonly involved Usual course of lymph node disease is as follows: <ul style="list-style-type: none"> Firm, discrete nodes ↓ fluctuant nodes matted together ↓ skin breakdown, abscesses, chronic sinuses ↓ healing and scarring 	<p>Fine-needle aspiration of the involved lymph node</p> <p>Extra-thoracic lymph node aspiration</p> <p>Positive smears for acid-fast bacilli on fine-needle aspirates of the involved lymph nodes (high rate in HIV patients)</p> <p>In smear-negative pulmonary TB, it is worthwhile aspirating extra-thoracic lymph nodes to confirm diagnosis of TB (80 percent positive)</p>	<p>Treatment should be started following the national TB guidelines. For further details, see Part A, Module 2, Session 3.</p>	<p>One of the most common forms of extra-pulmonary TB in HIV patients.</p> <p>Fluctuant cervical nodes that develop over weeks to months without significant inflammation or tenderness suggest infection with <i>M. tuberculosis</i>, atypical mycobacteria or scratch disease (<i>Bartonella henselae</i>).</p> <p>In severe immunocompromised patients, tuberculosis lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis.</p> <p>Miliary TB is an important consideration in patients with generalized lymphadenopathy.</p>

Table A2, 6.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Nocardiosis	<ul style="list-style-type: none"> Chronic lymphadenopathy Abscesses (skin, pulmonary, etc.) 	<ul style="list-style-type: none"> Fine-needle aspiration of the involved lymph node Organism may stain weakly on acid-fast staining. The organisms are different from the Koch bacilli because of their thread-like filaments. Nocardia organisms are easily recognized on Gram stain. 	<ul style="list-style-type: none"> TMP/SMX 10/50 mg/kg bid or minocycline 100 mg bid combined with amikacin 15-25 mg/kg daily, or ceftriaxone 2 gm daily combined with amikacin. Limit use of aminoglycosides to 2 weeks. 	<p>While nocardiosis is a rare cause of lymphadenitis in immune-competent patients, consider the diagnosis in HIV-infected patients with chronic lymphadenopathy and abscesses (skin, pulmonary, etc.).</p>
Fungal infections (histoplasmosis, penicilliosis, cryptococcosis)	<ul style="list-style-type: none"> Fever Lymphadenopathy Often skin lesions or lung lesions 	<p>Biopsy for histology and culture of skin lesions or lymph nodes often reveals the diagnosis.</p>	<p>Initial treatment for <i>histoplasmosis</i> and <i>penicilliosis</i>:</p> <ul style="list-style-type: none"> Amphotericin B for moderate-to-severe cases. Itraconazole 200 mg daily is the preferred lifelong maintenance therapy. If itraconazole is not available, use ketoconazole 400 mg daily. <p>For cryptococcosis give:</p> <ul style="list-style-type: none"> Amphotericin B (IV) 0.7 mg/kg daily for 14 days, followed by fluconazole 400 mg daily for 8-10 week After that, maintenance therapy consists of fluconazole 200 mg once a day. 	

Table A2, 6.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Secondary syphilis	<ul style="list-style-type: none"> • Generalized painless lymphadenopathy • Maculo-papular, papular or pustular rash on entire body, especially on palms and soles • Highly infectious lesions on mucous membranes (lips, mouth, pharynx, vulva, glans penis) that are silvery grey superficial erosions with a red halo and not painful, unless there is a secondary infection. • 40 percent of these patients will have CNS involvement with headache and meningismus • 1-2 percent will develop acute aseptic meningitis 	CSF exam CSF shows increased protein and lymphocytic pleocytosis	<p>Although there is some doubt about treatment efficacy in HIV patients, the CDC recommends the same treatment for primary and secondary syphilis as in HIV-negative individuals:</p> <ul style="list-style-type: none"> • Benzathine penicillin 2.4 million units IM single dose <p>In case of penicillin allergy, give:</p> <ul style="list-style-type: none"> • Doxycycline 100 mg PO bid for 21 days OR • Ceftriaxone 1 gm IM/IV daily for 14 days 	
Lymphoma and Kaposi's Sarcoma	<ul style="list-style-type: none"> • Lymphadenopathy • Characteristic skin lesions in oral cavity, GI tract and respiratory tract 	Diagnosis confirmed by histopathology	For treatment and management, see Part A, Module 2, Session 11.	

Case Study: Patient presenting with lymphadenopathy

A 28-year-old teacher, unmarried, was diagnosed with HIV infection two years ago when he went for voluntary testing with his girlfriend. When he found out that his girlfriend was HIV negative and he was HIV seropositive he interrupted the relationship. Since then, he has been feeling depressed. For a few weeks he has been experiencing night sweats and fatigue.

Physical examination reveals several large cervical lymph nodes. His temperature is 37.9°C. A smear obtained by puncture aspiration of one of the cervical lymph nodes does not reveal acid fast bacilli. Personnel then perform a lymph node biopsy. This lymph node is full of caseum.

- What is the most likely diagnosis?
- How would you manage this patient?
- What other problems does this patient have?
- What can you offer?

Case Study (patient with lymphadenopathy)—Answers*Diagnosis*

A lymph node full of caseum is pathognomonic for lymph node tuberculosis.

*Patient's needs – What to offer ?**Medical care*

You should give the patient a short course of antituberculous treatment. Because he presents with extrapulmonary tuberculosis and is not severely ill, beginning with only three antituberculous drugs (isoniazid, rifampicin and pyrazinamide) in the initial phase is enough.

Psychosocial support

We should know why this man is depressed. Is it because he is afraid about his future? Is it because he lost his girlfriend? Is it because he fears he will never find a new girlfriend and that he will not be able to have children? This man clearly needs a lot of counseling. It is possible that once he feels physically better, he will also become less depressed. On the other hand, his depression may put him at risk of not adhering to his antituberculous treatment.

SESSION 7: Conditions of the Mouth and Throat

PURPOSE

In this session, participants will learn about oral lesions, dysphagia and odynophagia, including common etiological agents, recommended diagnostics, common findings, management and treatment.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the various etiologies that cause oral lesions, dysphagia and odynophagia.
2. Describe the clinical presentation of these infections.
3. Explain the recommended diagnostics for each and describe the common findings for these tests.
4. Provide management and treatment for these illnesses.
5. Make a differential diagnosis using a case study approach.

TIME:

72 minutes

1. Introduction

a. Overview

- Patients with AIDS have many different conditions involving the oral cavity.
- An examination of the mouth needs to be part of the physical exam of every patient suspected of HIV infection; even in the absence of complaints, oral lesions and difficulty swallowing can develop rapidly.
- Patients often present with another complaint, and it is the presence of oral thrush that raises the suspicion of HIV infection.
- Oral lesions may be debilitating because they interfere with correct feeding and increase the risk of weight loss. (Painful eating and swallowing and decreased appetite are signs.) These decrease quality of life considerably.
- Misdiagnosis of peptic ulcer is common.
- Esophageal complaints are common and present in about one-third of patients.
- Incidence is higher in patients with $CD4 < 200$

b. Differential diagnosis includes the following pathogens:

- Bacterial infection: Aerobic infections causing gingivitis
- Fungal infections: Candida albicans
- Viral infections: Epstein-Barr virus (hairy leukoplakia), herpes simplex virus (HSV),
 Cytomegalovirus (CMV)
- Oncologic conditions: Kaposi's sarcoma

Table A2, 7.1: Conditions of the Mouth and Throat

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Oral hairy leukoplakia</p>	<p>Non-removable whitish plaques with vertical folds, mostly on the lateral surface of the tongue</p>			<p>This condition is caused by the Epstein-Barr Virus (EBV). It is neither dangerous nor painful and does not require any treatment. It is a sign of immune suppression and heralds a poor prognosis.</p>
<p><i>Candida albicans</i></p>	<p>Oral (thrush):</p> <ul style="list-style-type: none"> • Pseudomembranous white/yellow colonies or clusters appearing anywhere in the oral cavity. May be quite discrete or extensive, and can be easily removed by wiping. • Erythematous: appears as red patches on mucosal areas; if tongue is involved it may lose its usual surface texture • Hyperplastic similar to pseudomembranous, but usually adheres to the tissue • Angular cheilitis: fissuring at corners of mouth with or without visual colonization. <p>Esophageal:</p> <p>Pseudomembranous lesions extend into lower pharynx and esophagus, causing difficulty swallowing, nausea and retrosternal and epigastric pain.</p>	<ul style="list-style-type: none"> • Microscopic exam of scrapings from lesions • Microscopic exam of scrapings will be KOH-positive • Endoscopic biopsy • Tissue invasive mycelia on endoscopic exam 	<p>Step 1: Use topical antifungals:</p> <ul style="list-style-type: none"> • Nystatin (1 tablet of 500,000 IU qid) may be sucked or chewed. • Gentian violet: local application of gentian violet 1 percent aqueous solution twice daily for one week • Miconazole gel (60 mg qid) • Miconazole gum patch (once daily for 7 days) • Amphotericin B (10 mg lozenges qid) if available (suck or chew to maintain contact with oral mucosa.) <p>Step 2: Systemic therapy (recommended when no improvement is seen after 7 days with topical treatment and for all cases of esophageal candidiasis)</p> <ul style="list-style-type: none"> • 1st choice — Fluconazole (200 mg loading dose, then 100 mg/day) until symptoms have resolved. If fluconazole is not available (affordable), then use Ketoconazole (200-400 mg /day). • 2nd choice — Itraconazole (100 mg bid, doses can be increased to a maximum of 400 mg a day for 10 to 14 days) • 3rd choice — Amphotericin B (IV) (0.5-1.5 mg/kg per day) <p>Use intermittent therapy for as long as possible to delay the emergence of resistant candidiasis.</p>	<p>Oral candidiasis is a rare condition in a healthy person, but is frequently the first indication of immune impairment in HIV-infected patients. It is often used as an indicator disease for starting TMP-SMX prophylaxis.</p> <p>Recurrent episodes of oral candidiasis usually occur in patients with CD4<300.</p> <p>Over 60 percent of patients with CD4<100 will develop oropharyngeal candidiasis each year.</p> <p>Esophageal candidiasis will develop in 10-20 percent of AIDS patients and is the most common cause of dysphagia (inability or difficulty in swallowing). The absence of oral thrush does not completely exclude the diagnosis.</p> <p>Avoid continuous use of antifungals, except in patients that were treated for systemic fungal infections and patients with severe and recurrent oropharyngeal and esophageal candidiasis.</p>

Table A2, 7.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
CMV esophagitis	<ul style="list-style-type: none"> Pain on swallowing 	<ul style="list-style-type: none"> Endoscopic exam Esophageal ulcers are usually single or few in number, large, and deep and are located in the lower third of the esophagus 		<p>The most frequent clinical manifestation of CMV disease is retinitis, followed by gastrointestinal symptoms. Clinically, if it cannot be distinguished from candida esophagitis, consider CMV infection in patients with esophageal symptoms that do not respond to empiric antifungal therapy.</p> <p>Most esophageal ulcers result from CMV infection (45 percent), the other main cause being aphthous ulcers (40 percent). In the presence of fever, CMV infection is more likely than aphthous lesions.</p>
Necrotising gingivitis	Inflammation of the gums that can become very extensive and necrotic and lead to tooth loss.			Caused by bacteria of the oral flora
Herpes simplex (HSV) (stomatitis and esophagitis)	<ul style="list-style-type: none"> Painful mucocutaneous lesions Small painful crops of vesicles in the mouth that evolve into destructive gingivostomatitis Retrosternal pain and pain on swallowing 	Biopsy and tissue culture		<p>HSV 1 and 2 are common in HIV-positive patients, often appearing among the earlier infections associated with HIV infection. For some, HSV remains asymptomatic or causes only occasional outbreaks. For others, in the presence of severe immunodeficiency, HSV mucocutaneous lesions may persist or continue to enlarge, exposing the patient to extreme pain and the risk of secondary infection.</p> <p>HSV esophagitis is a more rare cause of viral esophagitis in AIDS patients. Without biopsy and tissue cultures, it is difficult to make the differential diagnosis between HSV and CMV ulcerative esophagitis. Often there are bacterial and fungal secondary infections. An empiric antifungal treatment may improve symptoms slightly.</p>

Table A2, 7.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Epstein-Barr virus infection (EBV)	<ul style="list-style-type: none"> Fever of unknown origin. Other minor symptoms similar to the common cold: malaise, pharyngitis, pharyngeal hyperplasia, lymphadenopathy 	<ul style="list-style-type: none"> CBC Total white blood count can be normal or low; patient can be lymphopenic and/or have evidence of reactive lymphocytes on blood smear. Endoscopic exam Ulcers are located in the mid-esophagus 	Primarily symptomatic	Often patient has oral hairy leukoplakia.
Kaposi's sarcoma	Lesions appear as red or purple maculae or nodules. Sometimes they are painful and interfere with food intake and speech.		See Part A, Module 2, Session 11 for management and treatment.	When Kaposi's sarcoma (KS) involves the oral cavity, it is considered to be an aggressive form of KS. Lesions can be stable for a long time, however.
Aphthous ulcers & aphthous esophagitis	<ul style="list-style-type: none"> Oral ulcers that can lead to painful giant lesions Esophageal ulcers 			Of unknown origin. Herpes simplex and CMV should be excluded. After CMV infection, most esophageal ulcers are due to aphthous ulcers (40 percent). May be very debilitating. CMV is more likely in the presence of fever.

2. Oral and esophageal candidiasis

a. Management and treatment:

Step 1: Use topical antifungals:

- Nystatin (1 tablet of 500,000 IU qid). May be sucked or chewed.
- Gentian violet: Local application of Gentian violet 1 percent aqueous solution twice daily for one week
- Miconazole gel (60 mg qid)
- Miconazole gum patch (once daily for 7 days)
- Amphotericin B (10 mg lozenges qid) if available

* Tablets or troches: suck or chew to maintain contact with oral mucosa

Step 2: Systemic therapy (recommended when no improvement is seen after seven days with topical treatment and for all cases of esophageal candidiasis)

- 1st choice — fluconazole (200 mg loading dose, then 100 mg/day until symptoms have resolved). If fluconazole is not available (affordable), then use ketoconazole (200-400 mg /day).
- 2nd choice — itraconazole (100 mg bid, doses can be increased to a maximum of 400 mg a day for 10 to 14 days)
- 3rd choice — amphotericin B (IV) (0.5-1.5 mg/kg per day)

Use intermittent therapy for as long as possible to delay the emergence of resistant candida.

- b. Comments: Oral candidiasis is a rare condition in a young healthy person, but is frequently the first indication of immune impairment in HIV-infected patients.

3. Epstein-Barr virus infection (EBV)

a. Management and treatment: Primarily symptomatic

- b. Comments: You need to consider EBV when making a differential diagnosis for HIV. Infection of the HIV-infected child with EBV can be associated with lymphoid interstitial pneumonia (LIP). EBV is also associated with Burkitt's lymphoma.

Case Study: Patient with oral lesions and other problems

A 26-year-old soldier has been complaining of headache since a few weeks and nausea since a few days. He gradually lost 10 kg of body weight during the last two months. For a few days he has complained of double vision.

On physical examination, his temperature is 38°C. There is no neck stiffness. There is paralysis of the nervus abducens of the right eye. There are several slightly swollen, dark, painless, nonpruritic lesions, relatively symmetrically distributed over his body on his chest and arms. These lesions appeared four months ago and are gradually increasing. There are white patches in his mouth.

He is living alone in Accra, but his family is from a village 200 kms from the capital. He is unmarried, but his family has already chosen a future wife for him.

A CT-scan is not available.

- What are the possible explanations for this patient's oral lesions and other problems?
- How would you manage this patient?

Case Study (patient with oral lesions and other problems)—Answers*Diagnosis*

The slightly swollen, dark, painless, nonpruritic lesions are probably Kaposi's sarcoma lesions. Moreover, he has oral candidiasis. Both of these conditions indicate that the patient has a severe form of immune deficiency. Therefore, the headache, the temperature and the nervous abducens paralysis are probably caused by an opportunistic infection. The two most likely diagnoses are tuberculous and cryptococcal meningitis. In both conditions, neck stiffness may be absent. The diagnosis of cryptococcal meningitis can be made by a cerebrospinal tap showing the cryptococci in an Indian ink preparation. An Indian ink preparation of the cerebrospinal fluid (CSF) will show cryptococci in 60 – 80 percent of the patients. You can perform a test for cryptococcal antigen on CSF and on serum, and it will be positive in nearly 95 percent of patients with cryptococcal meningitis. However, such a test is expensive. Certain patients with cryptococcal meningitis present with papular or small ulcerative skin lesions caused by the cryptococcal infection.

In the absence of cryptococci in the cerebrospinal fluid, increased protein levels, decreased glycochorrhachia (glucose in the CSF) and an increased number of white blood cells with 60 – 70 percent lymphocytes, suspect the diagnosis of tuberculous meningitis. In 50 percent of patients with tuberculous meningitis, there are also chest x-ray findings suggesting active TB. In only 20 percent of patients with tuberculous meningitis, a Ziehl smear shows acid fast bacilli. The diagnosis of cryptococcal meningitis was confirmed in this patient.

*Patient's needs – what to offer?**Medical care*

Amphotericin B 0.7-1.0 mg/kg/day intravenously. The headache, the nausea and the nervous abducens paralysis may suggest that this patient has intracranial hypertension. He may feel relief from a cerebrospinal tap. You can repeat such a tap if his complaints do not disappear. Continue the amphotericin for 14 days, and then you can switch to fluconazole 400 mg/daily for 8 to 10 weeks, followed by maintenance fluconazole treatment 200 mg/day. The amphotericin will also cure his oral candidiasis. This patient is certainly also a candidate for antiretroviral treatment once his cryptococcal meningitis is under control, but it is unlikely that he will be able to afford such treatment and that adequate follow-up will be possible in his village.

Psychosocial support

If we are not able to obtain antiretroviral treatment for this patient, his life expectancy will be short. He may even have difficulty paying for the fluconazole. He probably has a very high viral load, and therefore may be highly infectious if he is not using condoms. Counseling is in order to deal with issues such as the proposed marriage.

SESSION 8 Skin Conditions

PURPOSE

In this session, participants will learn about skin lesions and infections, including common etiologies, clinical presentation, management and treatment.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the various etiological agents that cause skin lesions and infections.
2. Classify skin lesions and infections by presenting signs and symptoms.
3. Describe the clinical presentation of each lesion or infection.
4. Discuss the treatment and management of skin conditions.
5. Make a differential diagnosis using a case study approach.

TIME:

2 hours

(Be sure to include at least one break for this long session.)

1. Introduction

a. Overview

- Many patients with HIV infection (80-100 percent) develop dermatological conditions at some point in the course of the disease
- Skin conditions may be very disabling, disfiguring and even life-threatening.

b. Differential diagnosis includes the following etiologies:

- Bacterial infection: *Streptococcus aureus*, *streptococcus* species, *treponema pallidum*, *bartonella* species
- Mycobacterial infection: *M. tuberculosis*, *M. avium* complex
- Viral infection: Herpes simplex and zoster virus, molluscum contagiosum, condylomata acuminata
- Infestations: Scabies
- Fungal infection: Seborrheic dermatitis, tinea corporis, pityriasis versicolor, *penicillin marneffeii*, *cryptococcus neoformans*, *histoplasma capsulatum*, *candida* species

Table A2, 8.1: Skin Conditions

Etiology Bacterial	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Skin abscess or pyomyositis	<ul style="list-style-type: none"> Abscess or affected area is fluctuant and warm 		<p>Surgical drainage and care of the lesion</p> <p>Antibiotics: Vancomycin, cephalixin or dicloxacillin 500 mg po qid x 7 to 21 days</p> <p>(Flu)cloxacillin 500 mg po qid for 10 days or (flu)cloxacillin 1-2g IV qid for 10 days</p> <p>In case of treatment failure, use cloxacillin or erythromycin 250-500 mg po qid x five days.</p> <p>Where facilities are available to determine the antibiotic sensitivity of the microorganisms responsible for abscesses, the treatment should be in accordance with the findings.</p>	<p>Pyomyositis, caused most commonly by <i>Staphylococcus aureus</i>, has emerged as an unusual complication of HIV in Africa. In Tanzania, for example, 62 percent of a series of patients with pyomyositis were HIV-infected. In the northern hemisphere, individual cases have been reported, but the condition is rare.</p>
Furunculosis or folliculitis	<ul style="list-style-type: none"> Skin sepsis around hair follicles Carbuncles (clusters of furuncles) with multiple openings form as a result of invasion and necrosis of subcutis. 		<p>Local lesion care</p> <p>Antibiotics: Vancomycin, cephalixin or dicloxacillin 500 mg po qid x 7 to 21 days</p> <p>(Flu)cloxacillin 500 mg po qid for 10 days or (flu)cloxacillin 1-2g IV qid for 10 days.</p> <p>In case of treatment failure, use cloxacillin or erythromycin 250-500 mg po qid x five days.</p> <p>Where facilities are available to determine the antibiotic sensitivity of the microorganisms responsible for abscesses, the treatment should be in accordance with the findings.</p>	<p>Usually caused by staphylococci. Need careful management in HIV patients because life-threatening disseminated infections may occur.</p>

Table A2, 8.1 (cont.)

Etiology Bacterial	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Cellulitis and Erysipelas	<ul style="list-style-type: none"> Fever, chills, nausea, vomiting, painful and warm skin Face and head lesions that are hot and red usually appear within 24 hours 			<p>Cellulitis: inflammation of cellular or connective tissue caused by a deep abscess</p> <p>Etiology: <i>Streptococcus</i> species</p> <p>Erysipelas: acute, febrile disease with localized inflammation and swelling of skin and subcutaneous tissue caused by <i>Streptococcus pyogenes</i></p>
Syphilis	<p>Primary:</p> <ul style="list-style-type: none"> A painless, indurated genital ulcer (chancere) Inguinal lymphadenopathy <p>Secondary:</p> <ul style="list-style-type: none"> Rash, usually involves the palms and soles and is maculopapular. Condyloma lata Oral lesions 	<p>Diagnostics:</p> <ul style="list-style-type: none"> VDRL or RPR 	<ul style="list-style-type: none"> Give Aq penicillin G, 18-24 mil units/day x 10-14 days Follow-up VDRL q 6 months until negative <p>For further information on management and treatment, see Part A, Module 2, Session 4: Conditions of the Neurological System.</p>	<p>About 25 percent of untreated patients develop a systemic illness (weeks to months later) with fever, rash, condyloma lata, lymphadenopathy and oral lesions (mucous patch).</p> <p>VDRL or RPR is not positive until 7-10 days after appearance of chancre.</p> <p>It is recommended that syphilis testing be offered to all clients presenting for VCT in high prevalence areas because it is treatable in early stages, and has an accelerated course in HIV.</p> <p>For more details, see Part A, Module 2, Session 4: Conditions of the Neurological System.</p>
Bacillary angiomatosis (BA)	<ul style="list-style-type: none"> Angioproliferative lesions that look like Kaposi's sarcoma Cutaneous lesions start with small red papules that gradually expand into large papular, nodular, pedunculated forms. Lesions have vascular appearance and surface is friable and easy to bleed. Symptoms include fever, malaise, headache, hepatomegaly and skin lesions. 			<p>Bacillary angiomatosis (BA) and bacillary peliosis are newly recognized OIs in PLHA. They are caused by tiny Gram-negative bacilli, <i>bartonella henselae</i> and <i>bartonella quintana</i>, which are difficult to cultivate in the laboratory.</p> <p>BA is epidemiologically linked to exposure to cats, especially young cats infested with fleas.</p> <p>Differential diagnosis with Kaposi's sarcoma is not always easy.</p>

Table A2, 8.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Bacterial Hydradenitis suppurative	<ul style="list-style-type: none"> Recurrent multiple sores and boils in the armpit or other wet areas 		<ul style="list-style-type: none"> Local lesion care and/or surgical drainage Antibiotics: <ul style="list-style-type: none"> Tetracycline 500 mg po bid x 6 weeks In case of treatment failure, use cloxacillin or erythromycin 250-500 mg po qid x five days. Amoxicillin 250-500 mg qid is also effective and can be given if none of the above-mentioned drugs are available. Where facilities are available to determine the antibiotic sensitivity of the microorganisms responsible for abscesses, treat in accordance with the findings. 	
Impetigo	<ul style="list-style-type: none"> Multiple superficial skin sores 		<ul style="list-style-type: none"> Gently keep the lesions clean with soap and water. As impetigo is highly contagious, maintain good hygiene and hand washing techniques to prevent spread to others. In severe cases, give cloxacillin or erythromycin 50 mg/kg/day qid for 5 days. 	
Mycobacterial diseases	<ul style="list-style-type: none"> Suspect if patient presents with papulopustular eruption on trunk and extremities and is extremely ill 	Diagnostics <ul style="list-style-type: none"> Aspiration and/or biopsy of lymph nodes Skin biopsy Microscopic examination of skin biopsy reveals numerous acid-fast bacilli Aspiration and/or biopsy of lymph nodes has a higher diagnostic yield than skin biopsy in extra pulmonary TB. 		Disseminated miliary tuberculosis of the skin is a rare form of tuberculosis.

Table A2, 8.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Fungal Skin infections Dermatophytosis	<ul style="list-style-type: none"> Hyper- or hypopigmented patches that are itchy, with or without a ring pattern and with scaling 	Direct microscopy of KOH preparation	<ul style="list-style-type: none"> Use topically a broad-spectrum antifungal treatment, such as clotrimazole cream 1 percent daily up to 3 weeks. Explain to the patient that local treatment may take a long time. Widespread dermatophytosis may necessitate systemic treatment with griseofulvin 500 mg once daily or ketoconazole 200 mg daily for 3 weeks for skin lesions and up to 6 months for lesions of the nails. 	<p>Tinea corporis, tinea pedis, tinea cruris and onychomycosis all occur more frequently in HIV-infected patients. The most frequent is tinea pedis.</p> <p>Onychomycosis requires long-term therapy, and not all patients with dystrophic nails have a fungal infection. Therefore, it is necessary to make the correct diagnosis. Direct microscopy of KOH preparation is sufficient to confirm diagnosis.</p> <p>Tinea cruris follows tinea pedis and onychomycosis in frequency. KOH preparation of skin scraping can distinguish it from seborrheic dermatitis.</p> <p>Recurrence is frequent and maintenance therapy may be necessary.</p>
Seborrheic dermatitis or generalized erythroderma	<ul style="list-style-type: none"> Generalized greasy scaling with excessive dandruff on the scalp, face and chest 			A very common complaint and one of the earliest clinical markers of HIV infection.
Skin Candidiasis	<ul style="list-style-type: none"> Itchy, wet lesions prominent in armpits, groin and under breast 	Diagnostics <ul style="list-style-type: none"> KOH preparation of affected areas KOH preparation may show pseudohyphae and budding yeasts	<ul style="list-style-type: none"> Local application of 1 percent aqueous solution of gentian violet or nystatin ointment twice daily until lesions are cleared. Might need to be a prolonged course of treatment. If there is no response to therapy, try other topical antifungals drugs, such as clotrimazole 1 percent cream. In severe cases, or if there still is no response to therapy, ketoconazole 200 mg po bid x 10 days may be required. 	Candida intertrigo is uncommon in PLHA, but severely immunocompromised patients may have balanitis, distal urethritis or paronychia (nail infection).

Table A2, 8.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
<p>Fungal Skin Infections</p>				
<p>Deep mycosis</p>	<ul style="list-style-type: none"> 70 percent of patients with disseminated <i>Penicillium marneffei</i> infection will have skin lesions. Histoplasmosis and cryptococcosis can also present with pustules, nodules, ulcers and papules. Patients with cryptococcosis and penicilliosis may have molluscum contagiosum-like, centrally umbilicated lesions typically located on face and trunk. 	<p>Diagnostics</p> <ul style="list-style-type: none"> Organisms can be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright's stain or Cotton blue stain. Diagnosis is confirmed by culturing the fungus from clinical specimens. 		<p>Diagnostic techniques are not readily available in developing countries. Diagnosis is suggested by clinical picture: high fever, severe anemia, cough, lymphadenopathy, hepatomegaly and meningeal signs.</p>
<p>Viral</p>				
<p>Chronic muco-cutaneous herpes simplex (HSV)</p>	<ul style="list-style-type: none"> Painful clusters of vesicles, ulcers or lesions on the mouth or ano-genital area 		<ul style="list-style-type: none"> Herpes simplex in HIV disease runs a chronic ulcerative course. If available, acyclovir 200mg five times daily for 7 days (14 days if disseminated mucocutaneous herpes simplex infection) If acyclovir is not available, treat local lesion by using local antiseptics such as gentian violet or cleaning the ulcerative vesicles with salt water and keeping them dry. Where available, administer chemosuppression with oral acyclovir 200-400 mg bid. 	<p>One of the most annoying skin conditions in AIDS patients. Chronic ulcers (>3 weeks) are seen only with advanced immune suppression. If untreated, they can last for months and finally involve most of the genital and peri-anal skin and mucous membranes. Recurrences occur frequently (more than 6/year) in some patients.</p>
<p>Shingles (<i>Herpes zoster</i>)</p>	<ul style="list-style-type: none"> Painful cluster of vesicles on an erythematous patch of skin in a localized neurodermatomal distribution Lesions can become necrotic and extensive, taking a long time to heal 		<ul style="list-style-type: none"> Lesions may be self-limiting and may not need more than pain relief— aspirin or paracetamol 500 mg qid—and local lesion care with gentian violet or antiseptics. Local application of lidocaine gel 2 percent may help improve pain relief in some patients. Calamine lotion is cheap, soothes the skin, reduces intense pruritus and accelerates drying up process. 	<p>Herpes zoster in a young person is highly predictive for HIV infection. Almost 25 percent of PLHA experience recurrences.</p> <p>If they involve the ophthalmic branch of the trigeminal nerve, they can involve the cornea and cause corneal scarring with loss of vision in that eye.</p>

Table A2, 8.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Fungal Skin infections <i>Shingles</i> (cont.)			<ul style="list-style-type: none"> Stronger analgesics are sometimes needed, such as paracetamol 1g plus codeine 60 mg q 4 hours. Acyclovir 800 mg qid x 7 days is indicated in patients with ophthalmic lesions or disseminated zoster. Antibiotics for secondary infection – recommendations as for impetigo Post-herpetic neuralgia is uncommon, but if present, should be treated with pain modifying agents: phenytoin 100 mg slowly increasing to 250-300 mg daily or carbamazepine 100 mg daily, increasing to 400 mg daily in 10 days 	
<i>Molluscum contagiosum</i>	<ul style="list-style-type: none"> Centrally umbilicated non-pruritic papules on the face, neck and anogenital areas. Lesions on the face tend to proliferate, especially if injured during shaving. 		<ul style="list-style-type: none"> Prick each lesion with a needle dipped in phenol; follow by expressing the central core. Alternatively, where available, cryotherapy with liquid nitrogen is recommended or curettage. The recurrence rate is high. 	<p>Differential diagnosis with disseminated cryptococcosis, histoplasmosis and penicilliosis. Those systemic mycoses are usually associated with fever, pulmonary or meningeal involvement.</p> <p>Remission with ARVs</p>
<i>Condylomata acuminata</i> (genital warts)	<ul style="list-style-type: none"> Finger-like projections on surface with cauliflower appearance Can be very extensive, involving both the genital and perianal region 		<ul style="list-style-type: none"> Treat with podophyllin 20 percent solution twice weekly until cleared. Podophyllin 20 percent can be corrosive to the surrounding unaffected skin. It should only be applied to the tips of the warts and washed away no later than 6 hours after application. For warts on the genital mucosa and mouth, a lower concentration of podophyllin (10 percent) may be applied. Alternatively, glacial trichloroacetic acid may be applied 1-2 times a week until the lesion has cleared. Where available, cryotherapy with liquid nitrogen is recommended. 	<p>The lesions are caused by the human papillomavirus, which can give rise to cervical and anal cancer. Patients with small number of warts may be asymptomatic. Other patients may have pruritis, bleeding or pain.</p> <p>Recurrence rate is high.</p>

Table A2, 8.1 (cont.)

Etiology	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Fungal Skin Infections <i>Condylomata acuminata</i> (cont.)			<ul style="list-style-type: none"> Other alternative treatments include electro-cauterization and surgical removal. If the number of lesions is small, treatment is best done by the patient with daily podophyllotoxin 0.5 percent solution strictly on the lesions. Instruct patient in taking measures to prevent transmission. 	
CMV	<ul style="list-style-type: none"> Ulcerations of oral mucosa and anogenital area 			For more details, see Part A: Module 2, Session 4: Conditions of the Neurological System and Module 2, Session 7: Conditions of the Mouth and Throat.
Prurigo and/or other skin conditions				
Drug eruptions	<ul style="list-style-type: none"> Generalized skin eruption and/or inflamed mucous membranes 		<ul style="list-style-type: none"> Withdraw drug(s) Local lesion care Give oral antihistamines 	Systemic corticosteroids are immune depressing and should only be given in life-threatening situations Co-trimoxazole, sulfadiazine, pentamidine, acyclovir and anti-TB drugs are often associated with drug eruptions. Thioacetazone has also been incriminated, as well as ARVs including Nevirapine, Efavirenz, AZT and d4T.
HIV-associated skin rash	<ul style="list-style-type: none"> Itchy generalized maculo-papular skin rash; erythroderma 		<ul style="list-style-type: none"> Topical calamine lotion or antihistamines, such as diphenhydramine 50 mg po q 6 hours, chlorpheniramine 4 mg po q 8 hours, or promethazine 10 mg bid Ultraviolet light and topical steroids may be helpful 	A generalized pruritic maculopapular skin rash due to eosinophilic folliculitis is typical of HIV. No specific opportunistic infection has been identified as the cause. Treatment is mainly symptomatic.

Table A2, 8.1 (cont.)

Etiology Prurigo and/or other skin	Presenting Signs and Symptoms	Diagnostics (laboratory, x-ray and other)	Management & Treatment	Unique Features, Caveats
Psoriasis	<ul style="list-style-type: none"> Extensive plaques that have well-demarcated borders and are covered with thick silvery white scales. It is often mistaken for a fungal skin infection. Lesions are often bilateral and favor the scalp, elbow, knees, hairline and intertriginous areas. 		<ul style="list-style-type: none"> Coal tar in salicylate ointment applied twice daily Severe cases may respond to topical corticosteroids. 	
Scabies	<ul style="list-style-type: none"> Parasitic skin infection: superficial burrows, intense pruritus (most intense at night) and secondary inflammation 	KOH preparation of skin scales. Mites can be seen by microscope.	<ul style="list-style-type: none"> Topical benzyl benzoate lotion 25 percent—left on the skin to dry and then repeated the next day. Avoid contact with the eyes. 	Scabies can lead to extensive disease in AIDS patients with hypertrophic, hyperkeratotic lesions that become secondarily infected with bacteria. It can be life-threatening when secondary infection is severe.
Xerosis	<ul style="list-style-type: none"> Diffuse, pruritic, scaly rash, involving mainly the limbs and neck 			Frequently encountered in PLHA. Etiology is unknown.
Kaposi's Sarcoma	<ul style="list-style-type: none"> Dark, patchy, painless swelling or nodules that are not itchy and no ring pattern, with or without similar oral lesions 		<ul style="list-style-type: none"> Discrete solitary or few lesions are best left alone. Lesions of the face or exposed parts of the body may be treated locally with cryotherapy (topical liquid nitrogen), intra-lesional therapy with either vinblastine (0.2–0.4 mg at two-week intervals) or alpha interferon, and surgical excision. In single lesions, the results with any of the treatment choices mentioned are promising. If lesions are disseminated or extensive and if treatment is envisaged, do a biopsy. Radiotherapy: for localized intraoral or pharyngeal KS painful cutaneous KS, and lymphedema of the face and extremities. 	Remission reported with ARVs Association with HHV type 8 Visceral with lung involvement may mimic TB For further information on KS, see Part A, Module 2, Session 11.

a. Classification by presenting signs and symptoms:

- Warm, inflamed, painful and/or fluctuating → a bacterial infection
- Discolored skin patches → a fungal infection or Kaposi's sarcoma
- Localized eruptions or localized pimple-like swellings → a viral infection
- Prurigo/urticaria, macular, maculopapular or scaly lesions → classified as other skin conditions, including drug eruptions, seborrhea, psoriasis and scabies

Bacterial infections:a. **Skin abscess or pyomyositis**

- Clinical presentation: abscess or affected area is fluctuant and warm
- Management and treatment:

Surgical drainage and care of the lesion

Antibiotics:

Vancomycin, cephalexin or dicloxacillin 500 mg PO qid x 7 to 21 days

(Flu)cloxacillin 500 mg P) qid for 10 days or (flu)cloxacillin 1-2g IV qid for 10 days

In case of treatment failure, use cloxacillin or erythromycin 250-500 mg po qid x five days.

Where facilities are available to determine the antibiotic sensitivity of the micro-organisms responsible for abscesses, treat in accordance with the findings.

- Comments: Although surgical drainage is all that is usually required in abscesses or pyomyositis, immunosuppressed patients receive antibiotics to prevent possible development of bacteremia or septicemia during the procedure and also to speed up recovery.
In severe cases, the patient may require IV treatment with penicillinase-resistant penicillin or cephalosporins because of the risk of systemic spread. Pyomyositis, caused most commonly by staphylococcus aureus, has emerged as an unusual complication of HIV in Africa. In Tanzania, for example, 62 percent of a series of patients with pyomyositis were HIV-infected. In the northern hemisphere, individual cases have been reported, but the condition is rare.

b. **Furunculosis or folliculitis**

- Clinical presentation: Skin sepsis around hair follicles
- Management and treatment:

Local lesion care

Antibiotics:

Vancomycin, cephalexin or dicloxacillin 500 mg PO qid x 7 to 21 days

(Flu)cloxacillin 500 mg P) qid for 10 days or (flu)cloxacillin 1-2g IV qid for 10 days

In case of treatment failure, use cloxacillin or erythromycin 250-500 mg po qid x five days.

Where facilities are available to determine the antibiotic sensitivity of the micro-organisms responsible for abscesses, the treatment should be in accordance with the findings.

c. **Hydradenitis suppurative**

- Clinical presentation: Recurrent multiple sores and boils in the armpit or other wet areas
- Management and treatment:

Local lesion care and/or surgical drainage

Antibiotics:

Tetracycline 500 mg po bid x 6 weeks

In case of treatment failure, use cloxacillin or erythromycin 250-500 mg po qid x five days.

Amoxicillin 250-500 mg qid is also effective, and you can give it if none of the above-mentioned

drugs are available.

Where facilities are available to determine the antibiotic sensitivity of the micro-organisms responsible for abscesses, treat in accordance with the findings.

d. Impetigo

- Clinical presentation: Multiple superficial skin sores
- Management and treatment:
 - Gently keep the lesions clean with soap and water.
 - As impetigo is highly contagious, maintain good hygiene and hand washing techniques to prevent spreading to others.
 - In severe cases, give cloxacillin or erythromycin 50 mg/kg/day qid for 5 days.

Kaposi's sarcoma

- a. Clinical presentation: Dark patchy, painless swelling or nodules that are not itchy and no ring pattern, with or without similar oral lesions
- b. Management and treatment:
 - Discrete solitary or few lesions are best left alone.
 - You may treat lesions of the face or exposed parts of the body locally with cryotherapy (topical liquid nitrogen), intra-lesional therapy with either vinblastine (0.2 –0.4 mg at two-week intervals), or alpha interferon, and surgical excision.
 - In single lesions, results with any of the treatment choices mentioned are promising.
 - If lesions are disseminated or extensive, and if treatment is envisaged, do a biopsy.
 - Use radiotherapy for localized intraoral or pharyngeal KS, painful cutaneous KS and lymphedema of the face and extremities.
 - For further management/treatment of systemic KS, see Part A, Module 2, Session 11
 - Comments:
 - Remission reported with ARVs
 - Association with HHV type 8
 - Visceral with lung involvement may mimic TB (describe x ray findings)

Fungal skin infections

a. Tinea (dermatophytosis)

- Clinical presentation: Hyper- or hypopigmented patches that are itchy, with or without a ring pattern and with scaling
- Management and treatment:
 - Use topically a broad-spectrum antifungal treatment, such as clotrimazole cream 1 percent, daily up to three weeks. Explain to the patient that local treatment may take a long time.
 - Widespread dermatophytosis may necessitate systemic treatment with griseofulvin 500 mg once daily or ketoconazole 200 mg daily for three weeks for skin lesions and up to six months for lesions of the nails.

b. Skin candidiasis

- Clinical presentation: Itchy, wet lesions, prominent in armpits, groin and under breast
- Management and treatment:
 - Local application of 1 percent aqueous solution of gentian violet or nystatin ointment twice daily, until lesions are cleared. Might need a prolonged course of treatment.
 - If there is no response to therapy, try other topical antifungals drugs, such as clotrimazole 1 percent cream.
 - In severe cases, or if there still is no response to therapy, ketoconazole 200 mg po bid x 10 days may be required.

- c. Cutaneous lesions of systemic cryptococcus or disseminated histoplasmosis are rare, but respond well to antifungal chemotherapy.

Viral infections

a. Herpes simplex (HSV)

- Clinical presentation: Painful clusters of vesicles, ulcers or lesions on the mouth or anogenital area
- Management and treatment:
 - Herpes simplex in HIV disease runs a chronic ulcerative course
 - If available, acyclovir 200mg five times daily for 7 days (14 days if disseminated mucocutaneous herpes simplex infection)
 - If acyclovir is not available, treat local lesion by using local antiseptics such as gentian violet or cleaning the ulcerative vesicles with salt water and keeping them dry.
 - Where available, administer chemosuppression with oral acyclovir 200-400 mg bid.
- Comments: For severe cases, the Namibia guidelines recommend acyclovir 400 mg tid for five days; may give great relief if administered within 24 hours.

b. Herpes zoster (varicella zoster virus)

- Clinical presentation: Painful cluster of vesicles on an erythematous patch of skin in a localized neurodermatomal distribution
- Management and treatment:
 - Lesions may be self-limiting and may not need more than pain relief— aspirin or paracetamol 500 mg qid—and local lesion care with gentian violet or antiseptics.
 - Local application of lidocaine gel 2 percent may help improve pain relief in some patients.
 - Calamine lotion is cheap, soothes the skin, reduces intense pruritus and accelerates drying up process.
 - Stronger analgesics are sometimes needed, such as paracetamol 1g plus codeine 60 mg q 4 hours.
 - Acyclovir 800 mg qid x 7 days is indicated in patients with ophthalmic lesions or disseminated zoster.
 - Antibiotics for secondary infection – recommendations as for impetigo
 - Post-herpetic neuralgia is uncommon, but if present, should be treated with pain modifying agents: phenytoin 100 mg slowly increasing to 250-300 mg daily or carbamazepine 100 mg daily increasing to 400 mg daily in 10 days.

c. Molluscum contagiosum

- Clinical presentation: Small non-pruritic papule with a central dimple. There can be very extensive multiple lesions, especially when on the face.
- Management and treatment:
 - Prick each lesion with a needle dipped in phenol then express the central core.
 - Alternatively, where available, use cryotherapy with liquid nitrogen or curettage. The recurrence rate is high.
- Comments: Differential diagnosis with disseminated cryptococcosis, histoplasmosis and penicilliosis. Those systemic mycoses are usually associated with fever, pulmonary or meningeal involvement. Remission with ARVs

d. Condylomata acuminata (genital warts)

- Clinical presentation: Finger-like projections on surface, with cauliflower appearance
- Management and treatment:
 - Treat with podophyllin 20 percent solution twice weekly until cleared.
 - Podophyllin 20 percent can be corrosive to the surrounding unaffected skin. You should apply it only to the tips of the warts and wash it away no later than six hours after application. For warts on the genital mucosa and mouth, you may apply a lower concentration of podophyllin (10 percent).

Alternatively, glacial trichloroacetic acid may be applied 1-2 times a week until the lesion has cleared.

Where available, cryotherapy with liquid nitrogen is recommended.

Other alternative treatments include electro-cauterization and surgical removal.

If the number of lesions is small, treatment is best done by the patient with daily podophyllotoxin 0.5 percent solution, strictly on the lesions.

Instruct the patient to take measures to prevent transmission.

- Comments: Recurrence rate is high

Prurigo and/or other skin conditions

a. Drug eruptions

- Clinical presentation: Generalized skin eruption and/or inflamed mucous membranes
- Management and treatment: Withdraw drug(s)
Local lesion care
Give oral antihistamines
- Comments: Systemic corticosteroids are immune depressing and should be given only in life-threatening situations

Co-trimoxazole, sulfadiazine, pentamidine, acyclovir and anti-TB drugs are often associated with drug eruptions. Thioacetazone has also been incriminated.

Drug eruptions are associated with certain ARVs: nevirapine, efavirenz, AZT and d4T.

b. HIV-associated skin rash

- Clinical presentation: Itchy generalized maculopapular skin rash; erythroderma
- Management and treatment: Topical calamine lotion or antihistamines, such as diphenhydramine 50 mg po q 6 hours, chlorpheniramine 4 mg po q 8 hours, or promethazine 10 mg bid
Ultraviolet light and topical application of steroids may be helpful.
- Comments: A generalized pruritic maculopapular skin rash resulting from eosinophilic folliculitis is typical of HIV. No specific opportunistic infection has been identified as the cause. Treatment is mainly symptomatic.

c. Seborrheic dermatitis or generalized erythroderma

- Clinical presentation: Generalized greasy scaling with excessive dandruff on the scalp, face and chest
- Management and treatment: Usually responds well to topical steroids (1 percent hydrocortisone), coal tar and soothing cream
If response to therapy is poor, suspect secondary infection, which would require local antiseptics (povidone iodine or chlorhexidine) and may need systemic antibiotics (cloxacillin or ampicillin 250-500 mg tid).
May also be complicated by cutaneous fungal infection. In this case, combine topical steroids with clotrimazole cream 1 percent.
With coexistent candidiasis, topical ketoconazole is beneficial.
In severe cases, oral ketoconazole 200 mg daily may be indicated.
- Comments: Recurrence is frequent, and maintenance therapy may be necessary.

d. Psoriasis

- Clinical presentation: Extensive plaques which have well demarcated borders and are covered with thick silvery white scales. It is often mistaken for a fungal skin infection. Lesions are often bilateral and favor the scalp, elbow, knees, hairline and intertriginous areas.
- Management and treatment: Coal tar in salicylate ointment applied twice daily
Severe cases may respond to topical corticosteroids.

e. Scabies

- Clinical presentation: Parasitic skin infection characterized by superficial burrows, intense pruritis (most intense at night) and secondary inflammation
- Management and treatment: Topical benzyl benzoate lotion 25 percent—left on the skin to dry and then repeated the next day. Avoid contact with the eyes.

f. **Other dermatoses:** Not all HIV associated skin diseases can be easily identified or diagnosed. You may often have to make a decision to give only symptomatic relief.

g. General recommendations for symptomatic relief:

- Avoid exposure to dry wind.
- Dry scaly lesions need a soothing lotion, such as calamine lotion, emulsifying ointment or vaseline.
- Use bath oil; dry skin after bath by patting with a soft towel.
- Oil skin after bathing with cream, body oil or lanolin.
- A cucumber, cut and rubbed over itchy areas, is a good home remedy for dry itchy skin.
- Local corticosteroids (hydrocortisone cream 1 percent) may be useful if inflammation is present, in the absence of any bacterial, fungal or viral infection.
- Oral antihistamines, such as chlorpheniramine 4 mg po q 8 hours and/or promethazine 10 mg at bedtime, may be useful.
- Hydroxyzine 25 mg at bedtime may be useful for severe itching.

Case Study: Patient with a skin condition

A 33-year-old French-speaking woman from Ivory Coast living in Accra complains of left thoracic pain. She was diagnosed with HIV infection two years ago. She was tested because her husband, a businessman, had been found to be HIV infected a few months earlier. Her husband often travels abroad and does not want any discussion about HIV in the household. He also never wanted to use condoms. There are two children, one is five years old and the other is three years old. Both were found to be HIV negative. So far the woman has never experienced any complication, but she is complaining of fatigue since a few months. Physical examination reveals a few vesicular lesions on the thorax wall, where she is feeling the pain. She is very afraid that she is developing AIDS and that she may infect their children.

She would like to start an antiretroviral treatment.

- What is the most likely diagnosis of the patient's thoracic pain?
- What are her needs?
- What can you offer?

Case Study (patient with a skin condition): Answers*Diagnosis:*

A herpes zoster infection is causing the patient's thoracic pain.

*Patient's needs and what to offer**Medical care*

Acyclovir treatment (800 mg po 5 x/day), if available, but such treatment is not absolutely needed. The herpes zoster lesions will also disappear spontaneously without complications. Provide treatment for pain and instruct patient on good hand washing. The patient wants to get antiretroviral treatment, but is this really needed? Certainly in this nearly asymptomatic person we would like to get a CD4 lymphocyte count before starting therapy. Her fatigue could be related to the HIV infection or to an infectious complication, but as there are no other symptoms, such as fever or weight loss, the fatigue could just be the consequence of the many problems this woman is facing. You could offer prophylaxis with isoniazid po 300 mg/day, after active tuberculosis is excluded. If her CD4 lymphocyte count drops below 200 or if she develops symptomatic HIV infection, you could add cotrimoxazole prophylaxis.

Psychosocial support

This woman may be afraid that she will develop a serious illness in the near future. A herpes zoster infection often occurs early during HIV infection and certainly does not mean that she needs antiretroviral therapy. During counseling, you should explain to her that because she has two healthy children and has never had any serious infectious complication, her immune status is probably relatively good and that it is unlikely she would develop life threatening health problems in the near future. Explain the modes of HIV transmission and stress that there is no risk that she will transmit the virus to her children. An important problem for this woman may be her feeling of isolation, since she cannot discuss her infection with her husband, family members or friends. Try to have a discussion with her and her husband. Maybe you can give a referral to a nongovernmental organization (NGO) that is supporting persons with HIV infection. Because of the language barrier, and because of the stigma associated with the infection, the woman may be reluctant to contact such an organization. She may, however, be willing to meet or contact another HIV seropositive woman who is also French speaking.

Socio-economic support

For the time being, this family has no financial problems; but if they have to buy antiretrovirals, such problems may rapidly develop. It is therefore important to discuss how to use the family budget optimally, to save money for later—for the education of the children and to buy antiretrovirals at a time when they may be life saving, but also when there will be more effective drugs at a lower price. If the family budget is limited, it is best to start with antiretrovirals only when the patient develops clinical signs of immune deficiency, such as oral candidiasis, or if the CD4 lymphocyte count drops below 200.

SESSION 9 Fever

PURPOSE

In this session, participants will learn about fever, including common etiologies, recommended diagnostics, common findings, management and treatment of bacteremia/septicemia.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the various etiologies of fever.
2. Describe the clinical presentation of bacteremia/septicemia.
3. Explain the recommended diagnostics and describe the common findings for these tests.
4. Provide management and treatment for bacteremia/septicemia.
5. Make a differential diagnosis using a case study approach.

TIME:

1 hour

a. Overview

- Defined as a recurrent or persistent fever (temperature >37.5 °C) with a duration of more than two weeks as the only clinical presentation in a patient with HIV infection

b. Differential diagnosis includes the following etiologies:

- Protozoal infection: Malaria
- Bacterial infection: Pyogenic infections of the chest, the CNS, the urinary tract, etc.
Bacteremia due to borreliosis, salmonella, Streptococcus pneumonia, H. influenzae and the like
- Mycobacterial infection: Mycobacterium tuberculosis, atypical mycobacteria
- Viral infection: Upper respiratory tract infections, cytomegalovirus, EBV, HIV infection itself
- Malignancies: Lymphomas

c. Bacteremia/Septicemia

- Common etiological agents: *Pneumococcal, meningococcal*
- Clinical presentation: Fever (intermittent), chills at onset, pulse weak and rapid, skin eruptions (petechial or purpuric most common), headache, anorexia, vomiting, diarrhea, delirium, shock, hypotension, vascular collapse, renal failure, death
- Recommended diagnostics: Urinalysis for albumin, erythrocytes, leukocytes. Blood cultures for aerobic and anaerobic organisms
Blood counts for anemia
- Common findings: Urine may be positive for albumin, etc.
Blood cultures may be positive
Patient may be anemic
- Management and treatment: Amoxicillin and gentamycin or ciprofloxacin. Supportive measures: adequate nutrition and fluid intake maintain electrolyte balance with IV fluids
- Comments: Requires vigorous treatment, including hospitalization

Case Study: Patient with a fever

A 17-year-old girl is complaining of high fever, headache and a sore throat. One of her teachers raped her two years ago. Three months after the rape, she was found to be HIV seropositive. She is still studying and wants to become a secretary.

Physical examination reveals enlarged cervical lymph nodes and exudates over both amygdala (tonsils).

She is living with her parents. The family has four children. The father has a small shop in the city. She has a boyfriend and would like to marry next year.

- What is the most likely diagnosis?
- What are this patient's needs?
- What can you offer?

Case study (patient with fever): Answers*Diagnosis*

This girl may have been infected only two years ago. Therefore, her immunological status is probably good. There is no reason to suspect a serious HIV-related complication. Her symptoms could be explained by a streptococcal angina or a mononucleosis infection.

*Patient's needs – What to offer?**Medical care*

You could give penicillin for the angina.

Psychosocial support

This patient may have problems coping with her HIV seropositivity and the way she acquired the HIV infection. She may have problems with disclosing her seropositivity to her boyfriend. She probably would like to have children with her future husband. Counseling should address all these issues.

SESSION 10 Prophylaxis of Opportunistic Infections

PURPOSE

In this session, participants will learn about prophylaxis for selected opportunistic infections.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the prophylactic use of TMP/SMX and INH.
2. Describe the WHO recommendations for TMP/SMX and INH.
3. Discuss when to prescribe prophylactic treatment, to whom, and which regimen to use.
4. Describe other preventive measures, such as 23-valent pneumococcal vaccine, antifungals and hepatitis vaccine.
5. Discuss the purpose of secondary prevention and describe the different regimens.
6. Discuss local and national guidelines regarding the prophylaxis of opportunistic infections.

TIME:

1 hour 30 minutes

Prophylaxis for Selected OIs: Indications and Treatment Guidelines

1. Overview

- a. Prevention of opportunistic infections in developing countries is quite different from that in the Western world. For example:
 - Many AIDS patients in Africa do not survive long enough to develop CMV or MAC .
 - With limited resources, CD4 counts are not available in most sites. This limits the ability of providers to follow disease progression.
 - HIV infection is often diagnosed only at an advanced stage of disease in developing countries.

- b. Important opportunistic infections for HIV-infected individuals in the developing world are:
 - Tuberculosis: widespread
 - Pneumococcal disease: widespread
 - Nontyphoid salmonellosis: particularly East and West Africa, Thailand and Cambodia
 - Cryptococcosis: particularly East and South Africa, Thailand and Cambodia
 - Pneumocystis carinii or p. jiroveci pneumonia (PCP): South Africa and Asia
 - Penicilliosis: Thailand
 - Bacterial infections

- c. Some of the prevention measures recommended in the U.S. (see: “Prophylactic Treatment as Recommended in the U. S.” below) are not too expensive and may provide opportunities to prevent OIs in developing countries. These include:
 - TMP/SMX for PCP, cerebral toxoplasmosis and various bacterial infections
 - INH for tuberculosis

- d. Indications for prophylaxis in developing countries include use of the WHO clinical stage, CD4 count and, in some situations, viral load.

- e. General prevention measures:
 - Avoid unpasteurized dairy products, raw or undercooked eggs, meat, poultry or fish as sources of salmonella infection.
 - Avoid undercooked or raw meat as a source of toxoplasmosis. Risk of transmission can be reduced if meat is adequately cooked and vegetables and fruit are carefully washed before eating. Also avoid exposure to cats to the degree that this is possible.
 - If no safe water supply is available, advise patients and family to boil drinking water to avoid diarrheal diseases such as cryptosporidiosis.
 - Moldy sugar cane or bamboo are possible sources of penicillium marneffeii infection (in Thailand).

2. Prophylaxis/preventive measures

- a. **Cotrimoxazole (TMP/SMX)**
 - An effective prophylaxis against:
 - Various bacterial infections: Streptococcus pneumoniae, salmonella species and nocardia
 - Pneumocystis carinii or p. jiroveci (PCP)
 - Toxoplasmosis
 - Isospora belli
 - Cyclospora
 - According to UNAIDS, cotrimoxazole should be used for prophylaxis in adults and children living with HIV/AIDS in Africa as part of a minimum package of care.
 - UNAIDS/WHO recommendations: see page 162.

UNAIDS/WHO Recommendations for OI Prophylaxis

<p>Overview:</p>	<ul style="list-style-type: none"> • Recruit candidates for cotrimoxazole prophylaxis from all levels of health care facilities, AIDS service organizations and nongovernmental organizations. • Trained health care personnel should make initial prescription of prophylaxis. • Provide counseling.
<p>Cotrimoxazole prophylaxis should be offered to:</p>	<ol style="list-style-type: none"> 1. HIV-positive adults (defined as over the age of 13 years), including: <ul style="list-style-type: none"> • All persons with symptomatic HIV (Stage II, III, IV) • Asymptomatic individuals who have a CD4 count of 500 or less, or a total lymphocyte count equivalent • Pregnant women after the first trimester 2. HIV-exposed infants from six weeks of age, including: <ul style="list-style-type: none"> • Any child born to an HIV-infected woman, regardless of whether the woman received ARV therapy during pregnancy • Any child who is identified as being HIV-infected within the first year of life, either by PCR, HIV serology or by a clinical diagnosis of HIV infection (according to WHO/ national guidelines) • Children older than 15 months who have had a PCP event, have symptomatic HIV disease, an AIDS defining illness or have CD4 percentage less than 15 <p>Use PCR or other special diagnostic tests, if available, to confirm the diagnosis in children.</p> <p>Do not use CD4 count/total lymphocyte counts (TLC) to decide whether to initiate therapy in this period because they do not predict the risk of acquiring PCP in infants less than one year of age.</p>
<p>The recommended drug regimens are:</p>	<p>Adults:</p> <ul style="list-style-type: none"> • 1 double strength (DS) tablet daily or 2 single strength (SS) tablets daily: <ul style="list-style-type: none"> 1 DS = SMX 800 mg + TMP 160 mg 1 SS = SMX 400 mg + TMP 80 mg <p>Children:</p> <ul style="list-style-type: none"> • Administer cotrimoxazole syrup once a day on a daily basis. • If syrup is unavailable, use crushed tablets. • The health professional may switch from syrup to tablet to ensure continuing access to medication. • The recommended dose is TMP 10 mg/kg, SMX 50 mg/kg.
<p>Duration of treatment:</p>	<ul style="list-style-type: none"> • Give prophylaxis lifelong both for adults and children over the age of 15 months. • For infants up to 15 months, prophylaxis should continue until HIV infection has been reasonably ruled out and the risk of exposure has ceased. • For children older than 15 months, administer prophylaxis if they have had a PCP event, have symptomatic HIV disease, an AIDS-defining illness or have CD4 percentage less than 15.

Criteria for stopping treatment:	<p>In both adults and children, stop prophylaxis:</p> <ul style="list-style-type: none"> • in the event of severe cutaneous reactions, such as fixed drug reaction and Stevens Johnson syndrome, renal and/or hepatic failure, and severe hematological toxicity. • if antiretroviral agents become available and when CD4 is greater than 500.
Adverse reactions:	<p>Adverse reactions are common, especially in Western countries, and tolerance is said to be better if you use one SS a day or one DS three times a week.</p> <p>Make every effort to continue prophylaxis with cotrimoxazole because it is more active against PCP than alternative regimens, and it is also protective against toxoplasmosis, bacterial respiratory infections and some enteric pathogens.</p> <p>Lower doses of cotrimoxazole, although better tolerated, are less effective than the recommended daily DS tablet. Moreover, the efficacy of lower doses of TMP/SMX on other opportunistic infections, in particular toxoplasmosis, is not given.</p>
Alternative regimens:	<p>Dapsone 50 mg 2 x daily or 100 mg once daily as the first alternative, if a patient does not tolerate TMP/SMX</p> <p>In patients with CD4<100 and positive toxoplasma antibodies, add pyrimethamine 50 mg weekly + folinic acid 25 mg weekly to this regimen. This regimen is much more expensive and complex than the cotrimoxazole preventive therapy.</p> <p>Pentamidine aerosols 300 mg/ month are more difficult to implement, are less effective in preventing PCP, and their effect on toxoplasmosis is not entirely understood</p> <p>In cases of nonlife -threatening adverse reactions, stop treatment for two weeks; then re-challenge the patient with TMP/SMX in a gradually increasing dose. For example:</p> <p>TMP/SMX suspension (40 mg TMP + 200 mg SMX/5 ml): 1 ml daily for 3 days, 2 ml daily for 3 days, then 5 ml daily for 3 days, then 10 ml daily for 3 days, then 20 ml daily for 3 days, then 1 DS tab daily or 1 SS tab daily (if DS is not supported)</p> <p>After desensitization under surveillance, up to 70 percent of patients may again tolerate TMP/SMX.</p> <p>Fansidar® (sulphadoxine/pyrimethamine), 1 or 2 tablets weekly, is likely to have a preventive activity against PCP and toxoplasmosis.</p>

<p>Follow-up:</p>	<ul style="list-style-type: none"> • Use cotrimoxazole prophylaxis where regular follow-up of patients is possible. • In adults, initially follow-up should be every month and then every three months, if the medication is well tolerated. • Evaluate children on a monthly basis. • In adults and children, monitor for toxicity, clinical events and compliance. • Monitoring of adults should also include measuring of hemoglobin and white blood counts every six months where facilities are available or when clinically indicated.
<p>Monitoring:</p>	<ul style="list-style-type: none"> • Interventions to help PLHA in Africa are urgently needed. • Each country should develop an implementation and monitoring plan for cotrimoxazole prophylaxis. • Concurrent monitoring for clinical effectiveness is important, especially in areas where there is widespread resistance to cotrimoxazole. In addition to cotrimoxazole prophylaxis, investigation into new interventions is needed.
<p>Evaluation</p>	<p>A task force led by UNAIDS will develop program evaluation and clinical effectiveness indicators. These could include surveillance for:</p> <ul style="list-style-type: none"> • Background rates of opportunistic infections and antimicrobial resistance • Changes in antimicrobial resistance to cotrimoxazole (including impact on the treatment of malaria) • Acute and cumulative toxicities
<p>Research</p>	<p>Research activities could cover:</p> <ul style="list-style-type: none"> • Comparative studies to identify affordable alternative therapies • Further studies on dose and time of initiation • Willingness and ability to pay at the household level for cotrimoxazole prophylaxis • Impact on household income, savings and expenditures
<p>Cost</p>	<p>TMP/SMX in the recommended dose of 1DS daily costs \$US60 per year.</p>
<p>Distribution:</p>	<p>Cotrimoxazole can be:</p> <ul style="list-style-type: none"> • Given through community clinics and home-care projects • Integrated into counseling activities, with renewal of the cotrimoxazole prescription at the same time as the counselor does regular follow-up of the PLHA

b. Isoniazid (INH)

- HIV infection is the strongest known risk factor for the progression of latent TB infection to active TB.
- In countries with high TB prevalence, between 2.4 percent and 7.5 percent of HIV-infected adults may develop active TB each year. In those with a positive PPD test, the rate rises to between 3.4 percent and 10 percent per year, with a lifetime risk of 50 percent.
- The mechanisms of this include reactivation of latent infection and/or a re-infection with mycobacterium tuberculosis, characterized by a rapid progression towards active disease and a rapid progression of primary-infection.
- Before the AIDS epidemic, preventive therapy for tuberculosis was never recommended in developing countries (poor cost-effectiveness, high rate of reinfection) except for breast-feeding infants of mothers with PTB or for children <5 years old living with infectious persons.
- Preventive therapy is now being reconsidered as a public health strategy because of the high incidence of TB in HIV-positive patients in developing countries. Active TB might accelerate the clinical course of HIV infection.
- In the pre-AIDS era, several placebo-controlled trials in the USA and Europe demonstrated the efficacy of INH prevention in PPD-positive persons, which is believed to be at least 60 percent.
- The cost of this drug is about \$US60 per year.
- WHO recommendations: Preventive therapy (PT) against tuberculosis in people living with HIV
Several large randomized controlled trials have now demonstrated that PT is effective in preventing TB in individuals dually infected with HIV and *M. tuberculosis*. However, studies of the feasibility of PT demonstrate that the process required to target appropriate individuals, to exclude active tuberculosis, to deliver PT, and to achieve compliance is complex and inefficient.

WHO Recommendations for Preventative Therapy for TB

<p>Prerequisites:</p>	<p>The following should be in place before considering a PT service:</p> <ul style="list-style-type: none"> • Adequate capacity for HIV counseling • Adequately trained health care staff • Linkage between HIV care and TB control services • TB treatment services that have a high probability of curing cases of TB identified through the PT service (defaulter and failure rate <10 percent)
<p>Recommendations to governments:</p>	<p>In settings that meet the above standards:</p> <ol style="list-style-type: none"> 1. PT against tuberculosis should be part of a package of care for people living with HIV/AIDS. 2. PT should be used only in settings where one can exclude active TB cases and ensure appropriate monitoring and follow-up. 3. Information about tuberculosis, including preventive therapy, should be provided to people with HIV. 4. PT should be provided from within settings that include established voluntary counseling and testing (VCT) services for HIV. 5. Detection and cure of infectious tuberculosis cases continues to be the priority for TB control programs. 6. National authorities must regulate the procurement and supply of tuberculosis drugs to prevent the development of drug resistance.
<p>Those who have a positive HIV test should receive:</p>	<ol style="list-style-type: none"> 1) Counseling on tuberculosis People living with HIV risk developing TB. They should receive health education and be encouraged to seek early diagnosis and treatment of cough and other symptoms suggestive of TB. 2) Screening for active tuberculosis PT is inadequate treatment for active TB and could lead to the development of drug resistance, if taken in such cases. Therefore, exclude active TB before starting PT. Do a chest x-ray for every individual before considering PT.
<p>Target those most likely to benefit from PT:</p>	<p>PT is recommended for PPD-positive HIV-infected individuals who do not have active tuberculosis</p> <p>In some settings, PPD testing may not be feasible. Under these circumstances, the following individuals may still be considered for PT if they are infected with HIV:</p> <ul style="list-style-type: none"> • Those living in populations with a high prevalence of tuberculous infection (estimated to be >30 percent) • Health care workers • Household contacts of TB patients • Prisoners • Miners • Other selected groups at high risk of acquisition or transmission of TB

Drug regimens:	<p>Providing preventive therapy to those without active tuberculosis:</p> <p>The strongest evidence is for using INH alone. Trials using combination treatment report higher rates of adverse drug reaction.</p> <p>Isoniazid is the regimen recommended in developing countries.</p> <p>Isoniazid may be given as a daily, self-administered therapy for six months at a dose of 5 mg/kg to a maximum of 300 mg. See these individuals monthly and give them a one-month supply of medication at each visit.</p> <p>Compliance may be improved by giving an additional two-week emergency buffer supply for use if the individual has to defer his or her monthly review.</p> <p>To eliminate the risk of promoting rifampicin resistance through inadequate screening procedures or misuse of the tablets, rifampicin-containing regimens are not recommended.</p>
Contraindications for PT:	<p>Preventive therapy is contraindicated in patients with active tuberculosis and in patients with active (chronic or acute) hepatitis.</p> <p>Active tuberculosis must be excluded before beginning preventive therapy.</p> <p>For individuals who consume alcohol daily, give isoniazid with caution.</p>

- Conclusions

Preferably, there will already be programs with cotrimoxazole prevention for PLHA that show proof of good patient adherence and have strategies in place to follow up on defaulters.

INH prophylaxis is recommended for all known HIV-infected persons without performing a PPD skin test.

It is important to exclude active TB before starting the PT.

In practice, this means that PT is only for asymptomatic PLHA who are in WHO clinical stage I and II and who have a negative chest x-ray.

Patients who have a clinical stage III disease, such as oral candidiasis or oral hairy leukoplakia, with no other symptoms, might also be candidates for starting preventive therapy (no prolonged fever, no chronic diarrhea, no recurrent severe bacterial infections).

Dose of INH: 5 mg/kg, with a maximum of 300 mg daily, for a duration of six months (WHO guidelines)

All projects facing difficulties in the control of tuberculosis (high defaulter rates, unregulated drug supply leading to incomplete TB treatment by private providers and national TB programs, high treatment failure rate, and so on) should not start INH preventive therapy on a routine basis.

Projects wanting to implement PT should have a close working relationship between HIV and TB services. The programs should have qualified counseling staff, a high cure rate for TB and a low defaulter rate (less than 10 percent).

All projects, except pilot projects in HIV/AIDS care, should follow the national guidelines.

Attachment 3 in Part A, Module 4, Session 2, presents *Prophylactic Treatment as Recommended in the U. S.*

c. Other preventive measures

- 23-valent pneumococcal vaccine

HIV-infected people are at increased risk of invasive pneumococcal disease caused by streptococcus pneumoniae.

The frequency of recurrent *S. pneumoniae* infection in patients with prior pneumococcal disease is quite high (26 percent in a group of Kenyan sex workers). It might therefore be appropriate to give pneumococcal vaccine to this group of people.

The 23-valent-pneumococcal vaccine is immunogenic in HIV-infected people. However, it remains to be determined whether these antibody responses translate into clinical efficacy.

One study in Uganda did not show any benefit. Pneumococcal disease was even more frequent in the vaccinated group than in the control group. The 23-valent vaccine may be inadequate for the prevailing pneumococcal serotypes in that region. Ongoing trials in Gambia, Malawi and South Africa using newer-generation conjugate pneumococcal vaccines may show better results.

- Antifungals

You might consider primary prophylaxis with fluconazole or itraconazole in some regions with an unusually high incidence of cryptococcal meningitis or *P. marneffei*.

However, primary prophylaxis of fungal infections is expensive, and therefore not feasible in developing countries. As the price of fluconazole continues to go down, it might be appropriate for regions with a high incidence of cryptococcosis.

In the Thai ARV project, all PLWH/A receive fluconazole prophylaxis 200 mg 3 x weekly when the CD4 count is below 50.

Other preventive doses used are fluconazole 400 mg weekly, 100 mg daily or 200 mg daily.

There have been no randomized trials in high prevalence countries. However, even in the industrialized world, most clinicians are reluctant to use azoles for primary prophylaxis because of the potential promotion of azole-resistant candida species.

- Hepatitis B vaccination

HIV-infected patients have a higher risk of hepatitis B because of common risk factors. Patients who are HIV-positive are more likely to develop chronic hepatitis.

In the industrialized world, hepatitis B vaccination is recommended for certain risk groups, such as IV drug users, homosexuals, household contacts of hepatitis B carriers, health-care workers and sex workers. In developing countries, although EPI programs include vaccination against hepatitis B, it is not routinely recommended in adult HIV patients because very few countries are able to purchase the vaccine.

3. Secondary prevention

a. Lifelong secondary prophylaxis has been advocated for most OIs because of the high rate of recurrence.

b. Tuberculosis

- Until now, secondary prevention for TB has not been advocated.
- Extended therapy (beyond 6-9 months of treatment) has been shown to reduce the incidence of relapse, but has shown no benefit in terms of survival.
- Although no firm recommendation can be made, the results of a study done in Haiti favor the use of secondary INH prophylaxis in patients who had symptomatic HIV disease before the initial diagnosis and treatment of TB.

- c. PCP
 - TMP/SMX: The recommended dose is one DS daily. Tolerance is improved with lower doses (see notes on primary prophylaxis, above).

- d. Fungal infections
 - *P. marneffeii*: Itraconazole 200 mg daily is effective in reducing the relapse of *P. marneffeii* in HIV patients who were successfully treated with amphotericin B.
 - *Cryptococcus neoformans*: Fluconazole 200 mg daily is the first choice, or amphotericin B, IV, once a week, or fluconazole 200 mg 3 x weekly
 Another possible regimen to explore is fluconazole 400 mg once a week. Once-weekly fluconazole 400 mg was shown to be as effective as daily fluconazole 200 mg in primary prevention of deep fungal infection (candidal esophagitis, candidaemia, cryptococcosis, coccidioidomycosis, blastomycosis and histoplasmosis). The weekly dose was only half as effective as the daily dose in preventing oral thrush.
 - Oral thrush/
esophageal candidiasis: Fluconazole 100-200 mg daily— only if recurrences are severe and frequent:
TMP/SMX1DS daily
 - Toxoplasmosis:
 - Mucocutaneous
herpes simplex: If frequent and severe recurrences: acyclovir 200 mg 3 x daily or acyclovir 400 mg 2 x daily

4. Necessary drugs and diagnostics: A summary

Drugs	Diagnostics
<p><i>First line:</i></p> <ul style="list-style-type: none"> • Fluconazole • Isoniazid • Itraconazole • TMP-SMX 	Chest x-ray Complete blood count Liver function tests
<p><i>Second line:</i></p> <ul style="list-style-type: none"> • Dapsone • Fansidar • Folinic acid • Pyrimethamine 	

SESSION 11 | Diagnosis and Management of HIV-Related Cancers**PURPOSE**

In this session, participants will learn about the pathology, clinical features, management and treatment of Kaposi's sarcoma (KS). They will also learn about the clinical features, treatment and management for nonHodgkin's lymphoma (NHL) and central nervous system (CNS) lymphoma.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the pathology, clinical features, management and treatment for KS.
2. Describe the clinical features, management and treatment of NHL and CNS lymphoma.
3. Discuss the diagnosis, management and treatment of HIV-related cancers in local settings.

TIME:

45 minutes

1. Kaposi sarcoma (KS)

a. Introduction and pathology

- KS is a spindle-shaped cell tumor thought to be caused by the human herpes virus-8 (HHV-8).
- May occur at any time, regardless of the CD4 cell count, but becomes more common and aggressive as CD4 count drops.
- Occurs almost equally among men and women.
- Peak age is from 15-45 years, like that of HIV infection
- Is often disseminated and involves many organs of the body—skin, lymph nodes, mouth, lungs, brain, gastrointestinal system, liver and spleen
- Usually responds poorly to anticancer treatments because of underlying immunosuppression

b. Clinical features:

- Painless, nonitching skin lesions which may be macular, papular, nodular or plaque-like.
- Oral lesions that may occur first and are usually present when KS lesions are elsewhere.
- Generalized or localized swelling of the face, genital area or one or more of the lower and upper limbs, resulting from lymphatic infiltration causing lymphedema.
- Generalized lymphadenopathy resulting from adenopathic KS.
- Localized lesions (for example, eye, foot or hand).
- Occasionally a patient may present with abdominal pain, GI bleeding and distension from visceral KS; this may lead to abdominal obstruction.
- Cerebral KS may present as a space-occupying lesion that is difficult to differentiate from other possible causes.
- Disseminated pulmonary KS presents with progressive shortness of breath and persistent cough with frothy or blood-stained sputum. In some patients, nodular lesions may be present on chest x-ray. Bloody or blood-stained pleural effusion is another manifestation of KS in the chest.
- Diagnosis is confirmed by punch biopsy of a cutaneous lesion.
- Excessive bleeding may complicate biopsy of oral lesions, which should be done by an oral surgeon, if necessary.

c. Management and treatment

- Standard treatment is either chemotherapy or radiotherapy
 - For treatment of systemic KS, alpha interferon alone (or in combination with zidovudine) has been used in patients with severe immunodepression. The treatment may benefit up to half of the patients, but only temporarily.
 - For rapidly progressive and/or disseminated mucocutaneous disease, or when the tumor compromises the function of vital organs, chemotherapy may effect rapid tumor regression and be lifesaving.
 - Among the drugs reported to be effective: liposomal daunorubicin; adriamycin; bleomycin + either vincristine or vinblastine; vincristine/vinblastine; bleomycin/vinca alkaloids
 - The main threat to life is not usually the cancer itself, but the underlying immunodeficiency and associated opportunistic infections or neoplasms other than KS. Initially KS lesions may be few, small and asymptomatic. Radiotherapy or chemotherapy treatment given at this stage may further damage the immune system, making the patient more prone to OIs. The patient may then be worse off than before treatment was started. Before considering referral of a patient with KS, weigh the benefits and disadvantages, and, if necessary, discuss with the patient and caring family.
- Indications for treatment:
 - Numerous, unattractive, painful or ulcerating lesions
 - Bulky lesions of the mouth or tongue that interfere with feeding
 - Large eye lesions that interfere with vision
 - Life threatening complications like disseminated pulmonary KS associated with severe shortness of breath, massive oral lesions that interfere with feeding and GI visceral lesions that obstruct internal functions (if a diagnosis can be made)
 - Severe swelling from lymphatic obstruction affecting the face, genital organs and limbs
 - Occasionally patients may request treatment for cosmetic reasons. They should receive proper counseling on the available treatment options and their advantages and disadvantages.
 - Treatment of Kaposi's and other cancers with chemotherapy affects the immune system. If the patient has only one or two KS lesions, it may be better to postpone chemotherapy.
- Treatment options
 - Surgical excision: for isolated lesions or nodules; recurrence may be a problem
 - Radiation:
 - Effective for localized lesions
 - Most effective for relief of bleeding (80 percent) and least effective for relief of edema (<30 percent)
 - Side effects range from mild erythema to moist desquamation of the skin and blistering, painful mucosal reactions in oral lesions
 - Response is usually progressive over a few weeks
 - Complete remission in 70 percent of cases, but is usually temporary
 - If recurring, give further treatment.
 - Chemotherapy:
 - Use intralesional cytotoxic chemotherapy for some lesions. However, systemic chemotherapy is more often used for widespread KS.
 - Combination therapy, even in reduced doses, yields good results.
 - Drugs tend to depress bone marrow and cause pancytopenia so they are best given with a near normal white cell count. Unfortunately, neutropenia is a common complication of HIV disease, so many patients are unable to tolerate chemotherapy.
 - Visceral KS responds poorly to chemotherapy.

2. NonHodgkin's lymphoma (NHL)

a. Clinical features

- Systemic symptoms include fever, night sweats and unexplained weight loss.
- Clinical features include lymphadenopathy, splenomegaly, pancytopenia, bowel obstruction, ascites, cranial nerve lesions, spinal cord suppression, and nerve root lesions, plus cutaneous, testicular and lung mass lesions.

b. Management and treatment

- Various chemotherapy protocols (as used in seronegative patients) given in several courses over a number of months
- Prognosis is often poor, particularly with CD4 cell count <100/ml.

3. Central nervous system lymphoma

a. Clinical features:

- Occurs at total CD4 counts well under 100 cells and is a typical end-stage complication
- Definitive diagnosis is made by brain biopsy or CSF cytology in the presence of (a) space-occupying lesion(s) on CT or MRI scan.
- Because brain biopsy may be difficult to obtain, patients who fail a trial therapy for toxoplasmosis are often assumed to have CNS lymphoma.

b. Management and treatment

- There is no effective cytotoxic chemotherapy, and irradiation is considered palliative.
- Survival after diagnosis is usually limited to a few months.

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PART A: MODULE A2

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Module A3

Special Issues in Managing Women and Children with HIV Disease



Session 1: HIV and Pregnancy: Prevention of Mother-to-Child Transmission

This session gives a brief overview of HIV infection and discusses mother-to-child transmission (MTCT), including the factors that may increase transmission, measures that reduce MTCT and the use and limitations of ARV therapy as a preventive measure.

Session 2: Management of HIV Disease in Women

Participants learn about the common manifestations of gynecological problems in HIV-infected women, including common etiological agents, clinical features, management and treatment.

Session 3: Management of HIV Disease in Children

Participants learn about the diagnosis of HIV in children and the management and treatment of HIV-related conditions, including persistent diarrhea, oral thrush, respiratory conditions, persistent or recurring fever, failure to thrive, lymphadenopathy and skin conditions.

SESSION 1 HIV and Pregnancy: Prevention of Mother-to-Child Transmission

PURPOSE

This session gives a brief overview of HIV infection and discusses mother-to-child transmission (MTCT), including the factors that may increase transmission, measures that reduce MTCT and the use and limitations of ARV therapy as a preventive measure.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the effects of HIV on pregnancy.
2. Discuss MTCT, factors that may increase transmission and measures that reduce transmission.
3. Describe how ART is used for the prevention of MTCT.
4. Describe the various regimens used during pregnancy, intrapartum and postpartum, including short course ART.
5. Discuss the relationship between ART and breast feeding and WHO recommendations.
6. Discuss national guidelines with regard to HIV and infant feeding.

TIME:

1 hour

A. HIV Infection and Pregnancy

1. Introduction:

Each year, worldwide, two million women infected with HIV become pregnant, most of them in poor countries. Between one-quarter and one-third transmit the disease to their newborns, either during labor, during delivery, or while breast-feeding. That translates into about 2,000 new HIV-infected infants each day. Children born to HIV-infected mothers who die are left orphaned and are harder to care for than the HIV-negative infant.

- a. _____percent of women are HIV positive (give country-specific numbers) and prevalence is higher in _____areas.
- b. HIV presentation is the same in both sexes, but the disease has greater implications on a woman's reproductive health—her ability to cope with pregnancy and the possibility of transmission of the virus to her unborn and newborn child.
- c. During the asymptomatic phase of HIV, most women are unaware of their infection until the disease is diagnosed in their infants. This may cause conflict within the family; relatives think she brought in the infection. (PMTCT programs are working to increase women's awareness.)

2. Effects of HIV on pregnancy

- a. Some studies in Africa suggest that HIV may have an adverse affect on fertility in both symptomatic and asymptomatic women. Pregnancy rates are lower and pregnancy loss more common in those who are HIV infected. Others state that fertility is affected only in late HIV disease.
- b. When comparing changes in CD4 count/percentage over time, there is no difference between HIV-positive pregnant and non-pregnant women.
- c. HIV does not seem to be a significant cause of congenital abnormalities or spontaneous abortion.
- d. Pregnancy does not accelerate disease progression in early HIV infection.
- e. Late HIV disease may affect the outcome of pregnancy, that is, poor fetal growth, preterm delivery, low birth weight and prenatal and neonatal death.
- f. Common HIV-related problems are no different in pregnant and non-pregnant women, and both groups should receive the same management (except for drugs that are contraindicated or used with caution, like streptomycin and efavirenz).

B. Mother-to-Child Transmission (MTCT) of HIV

1. Transmission

- a. HIV may be transmitted to the infant during pregnancy, at the time of delivery, and through breast feeding; most transmission is thought to take place during delivery.

For a mother known to be HIV-infected prenatally, the additional risk of transmitting HIV to her infant through breast feeding has been estimated at 14 percent. For mothers who acquire HIV postnatally, the risk is as high as 29 percent. Many studies indicate that the risk of breast milk transmission is higher in the first few months of life, with a subsequent tapering off of risk. However, the risk persists as long as the infant is breast fed. HIV transmission is also higher if the mother has mastitis.

- b. Factors that may increase the risk of transmission:

- High maternal viral load: >5-10,000 copies/ml (at time of seroconversion), and, during late HIV disease, CD4 cell counts <100 cells/mm
- Recurrent STDs
- Malaria interferes with placental functions and eases viral transmission across the placenta
- Vitamin A deficiency
- Preterm delivery
- Firstborn twin
- Infected amniotic fluid (chorioamnionitis) (Limited data; recent studies do not suggest increased risk)
- Vaginal delivery
- Duration of rupture of membranes is longer than four hours
- Placental disruption
- Invasive procedures during delivery (for example, vacuum extraction, episiotomy, use of forceps, fetal scalp monitoring)
- Mechanical nasal suction after delivery
- Breast feeding, and especially mixed feeding

One study suggests that mixed feeding may be a greater risk because the infant has a higher risk of contracting a viral or bacterial GI infection, which then compromises the integrity of the intestinal wall and makes it easier for the HIV virus to pass into the infant's bloodstream.

- c. Measures to reduce MTCT:

- During pregnancy
 - Provide voluntary counseling and HIV testing, plus psychosocial support.
 - Diagnose and provide aggressive treatment of malaria, STDs and other infections as early as possible.
 - Provide basic antenatal care including:
 - Iron supplementation
 - Discussion of MTCT and infant feeding options
 - Starting ART for MTCT (see recommendations below)
 - Information on practicing safer sex
- During labor and delivery
 - Delay rupturing of membranes
 - Do only minimal digital examinations after rupture of membranes
 - Cleanse the vagina with hibitane or other virucides, if available (this procedure is more likely to reduce puerperal sepsis than HIV transmission)
 - Reduce use of assisted delivery with forceps and the like and episiotomies
 - Elective caesarean section has been demonstrated to have a more protective effect against MTCT than vaginal delivery. However, caesarean section has limited applications in resource-constrained settings

where the procedure is associated with increased rates of maternal morbidity and mortality and transmission to health care workers can be an additional risk.

- If not already on ART, give NVP.
- After delivery
 - Avoid mechanical nasal suction.
 - Cleanse the newborn immediately of all maternal secretions and blood.
 - Support safer infant feeding (according to national guidelines about mother's choice to put the infant to breast within 30 minutes of birth).
 - If mother chooses breast feeding, encourage exclusive breast feeding, and advise early cessation (up to six months) or BMS.
 - Advise giving milk substitutes where conditions are suitable, and no breast feeding after six months.
- Current WHO/UNAIDS/UNICEF guidelines recommend that women with HIV infection be fully informed of both risks and benefits of breast feeding and be supported in their decision about feeding practices.
- Safe alternatives may not exist in some resource-limited settings; for example, there may be only unsafe or inadequate water available for mixing formulas. In that case, recommend exclusive breast feeding for the first six months of life.
- Comparative risks and benefits of breast feeding and replacement feeding
- Risks to the infant
 - HIV infection
 - Infection risk persists for as long as the infant is breast feeding
 - Children who receive mixed feeding seem to be at higher risk of HIV infection during the first months of life than children who receive exclusive breast feeding or exclusive replacement feeding.
 - Shortening the period of breast feeding may reduce the risk of HIV transmission; discourage mixed feeding.
 - The alternative of exclusive replacement feeding also has considerable risks.
Studies in Africa indicate that children without HIV infection who receive replacement feeding have 2.5 to 5 times more risk of dying from any cause before the age of 12 months than breast fed children.
- Benefits to the infant
 - The immunological, nutritional, psychosocial and child-spacing benefits are well recognized.
 - Breast milk plays an important role in preventing infections that could accelerate progression of HIV-related diseases in already infected children.

2. ARV therapy and MTCT

a. Prevention of prenatal transmission

- The use of ARV therapy can reduce MTCT significantly

Studies conducted in industrialized countries in 1994 showed that administering AZT to women from the 14th week of pregnancy and to the newborn during labor decreased the risk of MTCT by nearly 70 percent in the absence of breast feeding.

A shorter regimen of AZT alone, starting from the 36th week of pregnancy, was shown to reduce the risk of transmission of HIV at six months by 50 percent in the nonbreastfeeding population and by 37 percent in those breastfeeding.

A short course of NVP (HIVNET 012 study) has been shown to reduce the risk of transmission and is the protocol most commonly used because clinical trials have demonstrated its efficacy in reducing MTCT, it has a low cost and it is easy to use in MTCT programs. The regimen is:

Intrapartum short course: 200 mg at start of labor or at hospital intrapartum

Postpartum infant: 2mg/kg stat within 48-72 hours

Other trials of short course ARV regimens using a combination of AZT and lamivudine also substantially decrease the risk of transmission (PETRA study).

- Women on treatment with ARVs for HIV infection have very low transmission if viral load is <1000 copies/ml.

b. Women first diagnosed with HIV infection during pregnancy

- Women in the first trimester may consider delaying initiation of ART.
- Consider severity of maternal HIV disease and potential benefits and risks of delaying ART until after first trimester.
- For women who are severely ill, the benefit of early initiation may outweigh theoretical risk to fetus; in these cases, recommend initiating with drugs such as AZT, 3TC and NVP or NFV.

c. HIV-infected women on ART who become pregnant

- Options are:

Suspend therapy temporarily during first trimester

Continue same therapy

Change to a different regimen

- Issues to consider:

Gestational stage of the pregnancy

Severity of maternal disease

Tolerance of regimen in pregnancy

Potential for adverse fetal effects

Fetus is most susceptible to potential teratogenic effects of drugs during the first 10 weeks of gestation; risks of ART to fetus during this period are unknown.

d. ART and breast feeding

- Women who require ART and who are breast feeding should continue their current ART regimen.
- Efficacy of potent ART taken by the mother solely to prevent postnatal transmission of HIV through breast milk is unknown, but is currently under study.

- e. HIV-infected women who receive short-course ARV prophylaxis to reduce MTCT and require treatment postpartum
- Short-course ARV regimens, which do not fully suppress viral replication, may be associated with development of ARV drug resistance
- The Ugandan HIVNET 012 study of single dose intrapartum/newborn NVP for prevention of MTCT found that 19 percent of the women developed resistance to the drug. This was associated with delivery, HIV viral load and CD4 cell count.
- Based on current information (until further research is done), prior administration of short-course AZT/3TC or single dose NVP for prevention of MTCT should not preclude use of these agents as part of a combination ARV drug regimen initiated for treatment of these women.
- f. Adherence to therapy in pregnancy and postpartum
- Adherence may be more difficult in pregnant and postpartum women than nonpregnant women.
 - Obstacles to adherence may include:
 - Morning sickness and GI upset, which can be further compounded by ARV-associated nausea
 - Fears that ARV drugs might harm fetus
 - If for any reason there is a need to discontinue therapy temporarily during pregnancy, stop and restart all drugs together to reduce the potential for the emergence of resistance.
 - Physical changes of postpartum period, coupled with stresses and demands of caring for a newborn infant, may make adherence to treatment especially difficult after birth.
- Providing additional support for maintaining adherence to therapy during ante- and postpartum periods is important.
- g. Recommendations:
- Taking all factors into account, it is important to promote and support exclusive breast feeding for the first six months of life because the serostatus of most mothers is unknown and the benefits to infants outweigh the risks, regardless of the mother's HIV status.
 - The mother should make the final choice about the method of feeding. Whatever her choice may be, health staff should provide support to ensure the optimal nutrition of mother and child. [Refer to national HIV and infant feeding guidelines.]

SESSION 2 Management of HIV Disease in Women

PURPOSE

Participants will learn about the common manifestations of these problems including common etiologies, clinical features, management and treatment.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe common manifestations of GYN problems and the various etiological agents that cause them.
2. Describe the clinical features of each infection.
4. Describe the treatment and management of GYN problems.
5. Discuss prevention of OIs in pregnancy.
6. Discuss management and treatment protocols in-country.

TIME:

45 minutes

A. Gynecological Problems and STDs

Introduction:

Gynecological problems are common among women living with HIV/AIDS and may be the presenting sign of immunosuppression in women. HIV/AIDS contributes to the frequency and severity of many gynecological infections, including vaginal candidiasis, herpes simplex, pelvic inflammatory disease and genital warts. Treatment for many of these infections is relatively inexpensive, but women living with HIV/AIDS often require higher doses and longer courses of therapy; they may also suffer from more frequent recurrences.

1. Vaginal discharge

a. Etiology:

- Gonococcal infection
- Chlamydia trachomatis
- Trichomonas vaginalis
- Bacterial vaginosis
- Candidiasis

b. Management and treatment

- General: Follow the national STD management guidelines. Ensure treatment of partners.
- Candidiasis: Patients often get recurrent attacks (even after treatment), and these may become persistent as the HIV disease worsens. If recurrence is very frequent, you may consider regular intermittent treatment.

Treatment includes:

Intravaginal:	Miconazole 200 mg suppository/day x 3days; clotrimazole 100 mg tab vaginal bid x 3days or qd x 7 days; clotrimazole 1 percent cream, miconazole 2 percent cream qd x 7days, or nystatin pessary qd or bid
Oral:	Fluconazole 150 mg po x 1 Ketaconazole 200 mg po/day x 7 days or bid x 3 days

Note: Avoid fluconazole, ketaconazole and itraconazole during pregnancy because of teratogenicity.

Table A3, 2.1: Vaginal Infections

	Bacterial Vaginosis	Vulvovaginal Candidiasis	Trichomoniasis	Gonorrhea	Chlamydia
Causes	Replacement of normal lactobacillus with mixed flora, e.g. gardnerella vaginalis, mycoplasma hominis	Candida albicans	Trichomonas vaginalis	Neisseria gonorrhoea	Chlamydia trachomatis
Clinical Features and Diagnosis	<ul style="list-style-type: none"> • Homogeneous grayish or yellowish discharge • Clue cells on microscopy • Vaginal PH >4.5 • Positive whiff test (i.e. fishy odor of discharge before or after addition of 10 percent KOH) • Diagnosis requires at least three of the above clinical features 	Thick, white discharge with pruritis Vulvar burning, vaginal soreness, dyspareunia, dysuria Diagnosis: clinical symptoms + identification of budding yeast on a wet mount or KOH prep or Gram stain of vaginal discharge	Profuse, malodorous, often frothy, yellow-green discharge and vulvar irritation. May have urinary symptoms and/or dyspareunia Diagnosis: Saline wet mount will show motile trichomonads in positive culture	Commonly asymptomatic	Commonly asymptomatic

2. Lower abdominal pain and fever (PID)

a. Etiology:

- Gonococcal infection
- Chlamydia trachomatis
- Mixed bacterial infections (including anaerobes)
- TB

b. Management and treatment

- Counsel women to report these symptoms right away to ensure prompt diagnosis and treatment.
- Treat bacterial infections aggressively with strong broad spectrum antibiotics, for example, ciprofloxacin 500 bid x one week.
- If STD is the cause, follow the national STD management guidelines; ensure treatment of partners.
- Exclude acute conditions (for example, appendicitis, ectopic pregnancy, and the like)

If patient does not respond to treatment, refer for pregnancy test on blood to exclude ectopic pregnancy with a negative urine pregnancy test and to exclude pelvic abscess or TB.

You may find huge pelvic abscesses in immunosuppressed patients following pelvic infection or surgical procedures.

Drainage and appropriate antibiotic therapy to cover aerobic and anaerobic organisms is necessary.

3. Genital sores (ulcers or blisters)

a. Etiology

- Syphilis
- Chancroid
- Lymphogranuloma venereum (LGV)
- Herpes simplex

b. Management and treatment

- If an STD is the cause, follow the national STD management guidelines; ensure treatment of partners.
- Herpes simplex:

Recurrent genital herpes ulcers are very common in patients with HIV; they tend to be more severe and may spread to buttocks and abdomen.

In late HIV disease, lesions become persistent, extensive and extremely painful.

Give supportive treatment: pain relief and gentian violet.

Oral acyclovir 200 mg qid x 5 days reduces pain and promotes healing; in severe cases, you may need to extend treatment for 2-3 weeks.

Note: Oral acyclovir is usually not used to prevent prenatal HSV transmission.

In case of secondary infection, give antibiotics: co-trimoxazole 2 tabs bid or cloxacillin 250 mg qid x 5 days.

4. Genital warts

a. Etiology

- Condylomata acuminata. This should be distinguished from:
- Condylomata lata (from secondary syphilis)

b. Management and treatment

- Tend to be more common and severe in persons with HIV
- Treat with topical podophyllin 20 percent twice a week, or remove by surgery or electro cauterization.
- If caused by secondary syphilis, follow the national STD management guidelines; ensure treatment of partners.
- Counsel on prevention of transmission to partner.

5. Malignancies

a. Etiology

- Cervical cancer, CIN
- Kaposi's sarcoma

b. Management and treatment

- Do not undertake extensive surgical intervention if you can give equally effective treatments, such as radiotherapy.
- If HIV seropositive patients have a severely compromised immunological status, they often do not respond well to cancer surgery, radiotherapy and chemotherapy.

6. Amenorrhea and intermenstrual bleeding

a. Etiology

- Menstrual disturbances are often associated with chronic ill health and are frequent in women with HIV.
- May be linked to general deterioration and weight loss due to HIV disease

b. Management and treatment

- Exclude other causes such as pregnancy, perimenopause, uterine fibrosis, genital tract infections, cervicitis, PID, TB and cancer.
- Menses may return after treatment of other infections and weight gain.
- Best management is to provide counseling and reassurance.
- If the woman is sexually active and not using an effective method of contraception consistently, do a pregnancy test.

Table A3, 2.2: Prevention of OIs in Pregnancy

OI	Prevention Regimen
PCP	<ul style="list-style-type: none"> Use TMP-SMX, with dapsone as the alternative. Because of theoretical concerns for teratogenicity, providers may choose to withhold prophylaxis in the 1st trimester or use aerosolized pentamidine.
Toxoplasmosis	<ul style="list-style-type: none"> Primary prophylaxis: TMP-SMX, with theoretical concerns for teratogenicity in 1st trimester. Avoid pyrimethamine regimens. Secondary prophylaxis: This is a risk/benefit issue with concerns for teratogenicity of pyrimethamine vs. recurrent toxoplasmosis; most clinicians favor continued treatment. A specialist should manage primary toxoplasmosis during pregnancy.
TB	<ul style="list-style-type: none"> INH + pyridoxine regimens are preferred for prophylaxis; some providers avoid INH in first trimester because of theoretical concerns for teratogenicity. Be sure to perform chest x-ray to R/O active TB using lead apron shields for the patient. RIF and RBT appear safe during pregnancy, but experience is limited. Avoid PZA, especially during first trimester.
MAC	<ul style="list-style-type: none"> Primary prophylaxis: azithromycin is preferred, but some providers withhold prophylaxis in 1st trimester; experience with RBT is limited. Clarithromycin is teratogenic in animals; use with caution.
<i>S. pneumoniae</i>	<ul style="list-style-type: none"> May give pneumovax. Because of <i>HIV viral burst</i>, some delay vaccination until after ART.
Fungal infections	<ul style="list-style-type: none"> General: avoid azoles (fluconazole, ketaconazole and itraconazole) because of teratogenicity. Cryptococcosis, histoplasmosis and coccidioidomycosis: for secondary prophylaxis, amphotericin B is preferred instead of azoles, especially during first trimester
CMV	<ul style="list-style-type: none"> Standard recommendations apply
HSV	<ul style="list-style-type: none"> Oral acyclovir during late pregnancy to prevent prenatal HSV transmission is controversial, but usually not used; acyclovir prophylaxis to prevent severe recurrences may be indicated
VZV exposure; Non-immune host	<ul style="list-style-type: none"> VZIG within 96 hrs. of exposure is recommended
Human papilloma virus (HPV)	<ul style="list-style-type: none"> Avoid intravaginal 5 fluorouracil.

SESSION 2 Management of HIV Disease in Children

PURPOSE

In this session, participants will learn about the diagnosis of HIV in children and the management and treatment of HIV-related conditions, including persistent diarrhea, oral thrush, respiratory conditions, persistent or recurring fever, failure to thrive, lymphadenopathy and skin conditions.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the HIV-related conditions in children and the various etiological agents that cause these conditions.
2. Describe the assessment and management of each condition following the IMCI approach.
3. Discuss preventive measures.
4. Counsel the mother about HIV testing and provide follow-up care.

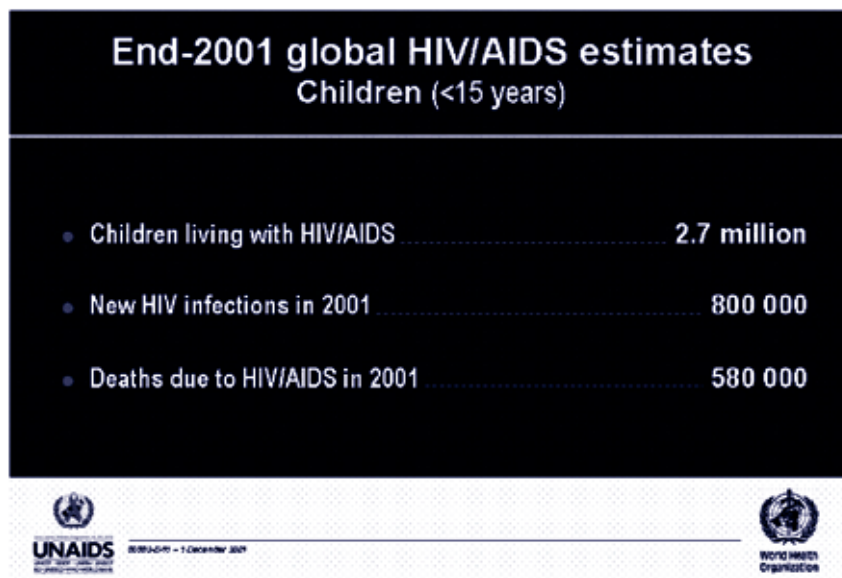
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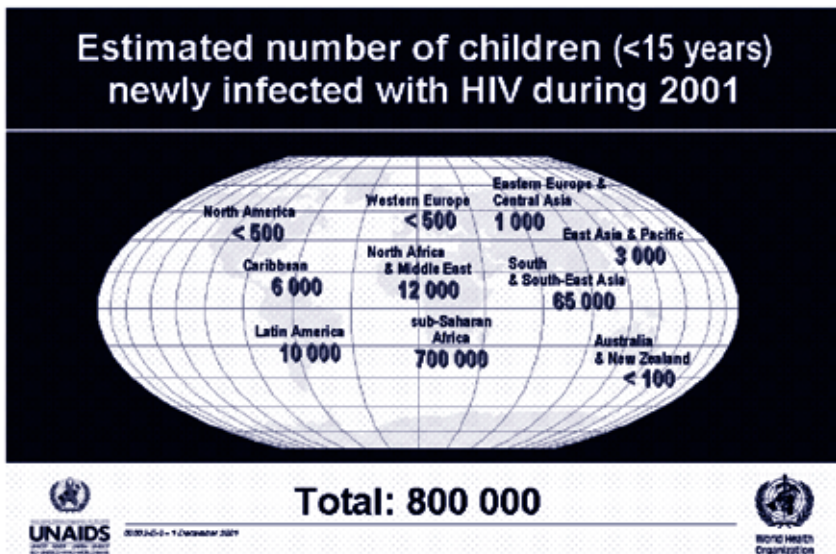
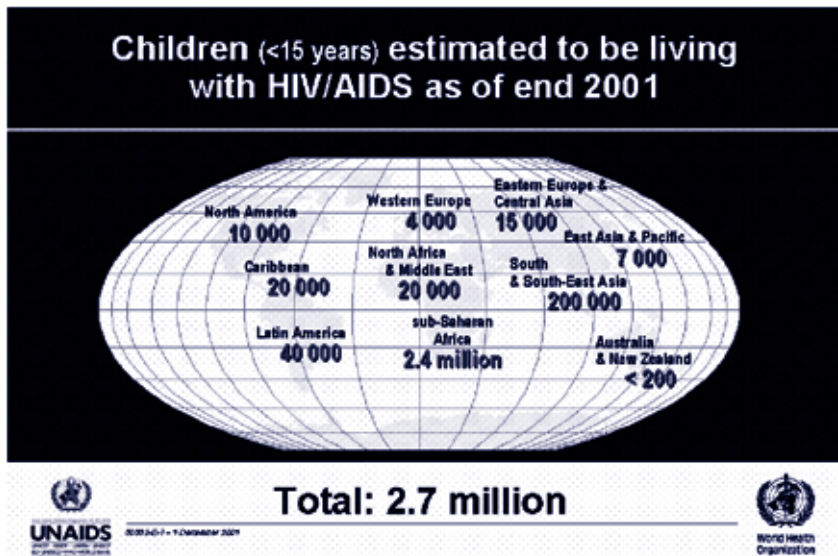
3 hours using case studies; 2 hours and 15 minutes without

A. Overview

1. Dimensions of the problem

The following slides from WHO depict the situation of children and HIV/AIDS in the world.





Global summary of the HIV/AIDS epidemic, December 2001

Number of people living with HIV/AIDS	Total	40 million
	Adults	37.2 million
	<i>Women</i>	17.6 million
	Children under 15 years	2.7 million
People newly infected with HIV in 2001	Total	5 million
	Adults	4.3 million
	<i>Women</i>	1.8 million
	Children under 15 years	800,000
AIDS deaths in 2001	Total	3 million
	Adults	2.4 million
	<i>Women</i>	1.1 million
	Children under 15 years	580,000

About 14 000 new HIV infections a day in 2001

- More than 95% are in developing countries
- 2000 are in children under 15 years of age
- About 12 000 are in persons aged 15 to 49 years, of whom:
 - almost 50% are women
 - about 50% are 15–24 year olds

2. Consequences:

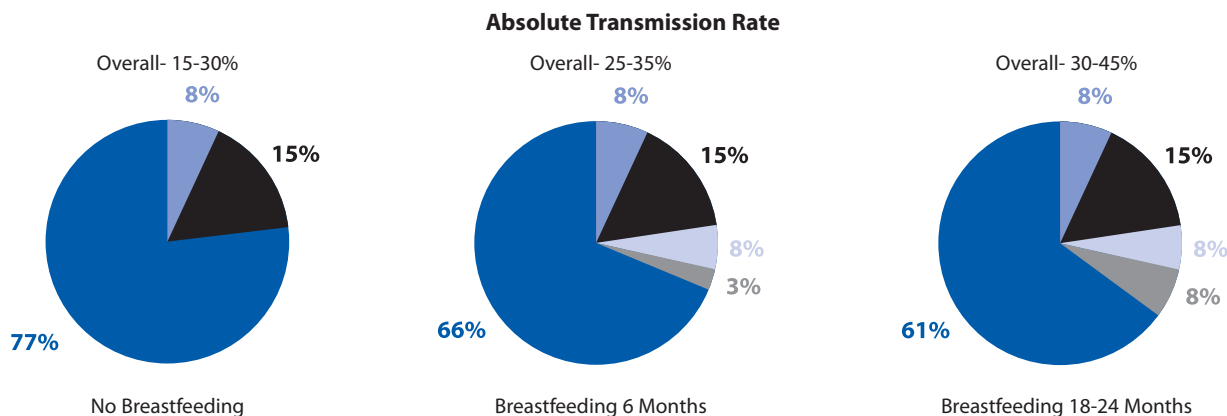
- a. One of the biggest challenges we face with HIV-infected children is identifying them early and giving proper care and support to them and their families.
 - 75 percent of children living with HIV/AIDS present with symptoms in the first or second year of life (most often at the primary level clinic).
 - 40-80 percent of HIV-infected children die before two years of age.
 - Most children living with HIV/AIDS die of common childhood illnesses rather than AIDS.
 - 80 percent of infant deaths occur in the home.

B. How children become infected with HIV and the course of the disease

1. Modes of infection

- a. The vast majority of HIV-positive children are infected vertically, that is, the virus is transmitted from the mother during pregnancy, labor or delivery.
- b. The HIV antibodies to HIV of infected mothers pass through the placenta during pregnancy. Therefore, all children born to HIV-positive mothers have a positive reaction to any test that relies on HIV antibodies.
- c. However, only about one-third of these infants will actually be HIV infected.
- d. Because maternal antibodies can be detected in an infant’s blood up to 18 months after birth, the ELISA and Western blot serum tests will be positive, whether the infant is infected or not.
- e. Published estimates of MTCT rates of HIV-1 range from 15-45 percent, depending on whether or not the child is breast fed and the length of breast feeding (see chart below). Most infections seem to occur during labor and delivery. The transmission rate from breast feeding is estimated at 3.2 percent per year of breast feeding after four months of age; 5 percent of breast milk transmission occurs in the first months of life. The following Table A3, 3.1 is a simplified representation of rates and timing of MTCT:

Table A3, 3.1: Timing of HIV-1 Perinatal Transmission in Untreated Mothers & Infants (de Cock, JAMA 2000; 283:1175)



2. The natural course of HIV disease in children

- a. HIV RNA levels in perinatally-infected infants are generally low at birth (<10,000 copies/ml), increase to high values by age two months and then decrease slowly after the first year.
- b. CD4 cell count and percentage values in healthy infants who are not infected are considerably higher than those observed in uninfected adults and slowly decline to adult values by age six years.
- c. Although the CD4 absolute number that identifies a specific level of immune suppression changes with age, the CD4 percentage that defines each immunologic category does not. Thus, a change in CD4 percentage, not the number, may be a better marker of identifying disease progression in children.
- d. CD4 cell values can be associated with considerable variation because of minor infections and are therefore best measured when patients are clinically stable.

Table A3, 3.2: HIV Pediatric Classification System Immune Categories Based on Age-specific CD4 Cell Count and Percentage

Immune category	Child's Age					
	<12 months		1-5 years		6-12 years	
	No./ml	(%)	No./ml	(%)	No./ml	(%)
Category 1: No suppression	>1,500	(>25%)	>1,000	(>25%)	>500	(>25%)
Category 2: Moderate suppression	750-1,499	(15-24%)	500-999	(15-24%)	200-499	(15-24%)
Category 3: Severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

Source: CDC 1994

- e. A small proportion of infants who are infected early in pregnancy progress more rapidly to advanced HIV disease because of a disruption of the thymus, where CD4 and CD8 cells are produced. These children have low CD4 and CD8 cell counts. As a result, their immune system cannot respond to HIV infection. This means that infants under six months who present with symptoms of HIV disease usually have a shorter survival period than older children.

C. Clinical presentation: when to suspect HIV

1. Introduction

The clinical expression of HIV infection in children is highly variable. Some HIV-positive children develop severe HIV-related signs and symptoms in the first year of life; these are associated with a high mortality. Other HIV-positive children may remain asymptomatic or mildly symptomatic for more than a year and may survive for several years.

2. Suspect HIV if any of the following signs are present:

- a. Signs that are uncommon in HIV-negative children
 - Recurrent infection: three or more severe episodes of a bacterial and/or viral infection (such as pneumonia, meningitis, sepsis, cellulitis) in the past 12 months
 - Oral thrush: punctate or diffuse erythema and white-beige pseudomembranous plaques on the oral mucosa. After the neonatal period, the presence of oral thrush—without antibiotic treatment, or lasting over 30 days despite treatment, or recurring—is highly suggestive of HIV infection.
 - Chronic parotitis: the presence of unilateral or bilateral parotid swelling (just in front of the ear) for >14 days, with or without associated pain or fever
 - Generalized lymphadenopathy: the presence of enlarged lymph nodes in two or more extra-inguinal regions without any apparent underlying cause
 - Hepatosplenomegaly in the absence of concurrent viral infections such as cytomegalovirus (CMV)
 - Persistent and/or recurrent fever: fever (>38°C) lasting seven days or occurring more than once over a period of seven days
 - Neurological dysfunction: progressive neurological impairment, microcephaly, delay in achieving developmental milestones, hypertonia or mental confusion
 - Herpes zoster (shingles): painful rash with blisters confined to one dermatome on one side
 - HIV dermatitis: erythematous papular rash
- b. Signs common in HIV-infected children, but also common in ill non-HIV-infected children
 - Chronic otitis media: ear discharge lasting 14 days or longer
 - Persistent diarrhea: diarrhea lasting 14 days or longer
 - Failure to thrive: weight loss or a gradual but steady deterioration in weight gain from the expected growth, as indicated in the child's growth card. Suspect HIV particularly in breast fed infants <6 months old who fail to thrive.
- c. Signs or conditions very specific to HIV-infected children
 - Strongly suspect HIV infection if any of the following are present:
 - Pneumocystis pneumonia (PCP)
 - Esophageal candidiasis
 - Lymphoid interstitial pneumonia (LIP)
 - Shingles across several dermatomes
 - Kaposi's sarcoma

These conditions are very specific to HIV-infected children. However, the diagnosis is often very difficult where diagnostic facilities are limited.

3. Classification of signs and symptoms according to the WHO Staging System for HIV Infection and Disease in Children

Clinical Stage I

1. Asymptomatic
2. Generalized lymphadenopathy

Clinical Stage II

3. Unexplained chronic diarrhea
4. Severe persistent or recurrent candidiasis outside the neonatal period
5. Weight loss or failure to thrive
6. Persistent fever
7. Recurrent severe bacterial infections

Clinical Stage III

8. AIDS-defining OI
9. Severe failure to thrive
10. Progressive encephalopathy
11. Malignancy
12. Recurrent septicemia or meningitis

D. Diagnosis and management

Many HIV-positive children die from common childhood illnesses rather than from HIV/AIDS. Most of these deaths are preventable by early diagnosis and correct management. Effective management of these conditions can make an important contribution to the quality of life of HIV-positive children. In particular, these children have a greater risk of pneumococcal infections and pulmonary tuberculosis, as well as unusual opportunistic infections, which respond poorly to therapy.

One approach to early diagnosis and management is through the integration of HIV into the WHO Integrated Management of Childhood Diseases (IMCI) model. IMCI is an integrated approach to child health that focuses on the well-being of the whole child. A mother or other caretaker may bring a sick child to the clinic for a particular problem or symptom. If the child is assessed only for that particular problem or symptom, other signs of disease may be overlooked. The child might have pneumonia, diarrhea, malaria, measles or malnutrition, as well as HIV. These diseases can cause death or disability in young children if they are not diagnosed and treated.

1. Respiratory conditions

- a. Definition: Child with symptomatic HIV infection and respiratory symptoms of difficulty breathing and/or persistent or worsening cough
- b. Etiology:
 - Infections: Bacteria
Viral
Parasitic
Pneumocystis carinii pneumonia (PCP)
 - Mycobacteria: M. Tuberculosis
Atypical mycobacteria
 - Fungi: Candidiasis
 - Malignancies: Kaposi’s sarcoma
Lymphoma
 - Other: Lymphocytic interstitial pneumonitis (LIP), bronchiectasis and chronic lung disease
- c. IMCI—assess and classify (suggested entry points for HIV are in boldface)

Assess	Classify
Ask: does the child have cough or difficulty breathing?	
<i>If yes, ask:</i> <ul style="list-style-type: none"> • For how long? • More than one episode in the last three months? <i>If yes, check for possible symptomatic infection.</i>	Cough or difficulty breathing Persistent or worsening cough

Assess the severity of respiratory distress based on age and clinical examination, as follows:

Clinical Assessment of Respiratory Distress	
All children under 2 months of age: refer if respiratory rate is >60 or chest in drawing (with or without cyanosis)	
Children older than 2 months of age:	
Clinical Signs	Classify as
No chest in drawing and no fast breathing	Upper respiratory tract infection or bronchitis (no pneumonia)
Fast breathing, but no chest indrawing: <1 year: Respiratory rate: 50 or more 1-2 yrs: Respiratory rate: 40 or more	Pneumonia Pneumonia
Fast breathing and chest indrawing, with or without central cyanosis	Severe pneumonia

d. Management and treatment (level 1)

- If child has mild dyspnea, is not undernourished and is more than 2 months old, treat with antibiotics: amoxicillin 50 mg/kg/day in 4 doses x 5 days

Advise mother to:

- Continue breast feeding the child
- Give extra fluids
- Prevent child from chilling
- Return immediately if child's condition worsens

Reassess child after three days:

- If improved, complete treatment and follow-up, as needed
- If not improved, refer to level 2

- Refer the child for further assessment and management and evaluation if:

Child has chronic cough (lasting longer than 15 days) or pneumonia that does not respond to treatment quickly (within three days)

Child is in severe respiratory distress (see chart above)

In infants below two months of age, pneumonia is always a severe condition and requires admission.

If child has severe dyspnea, oxygen therapy is crucial. Start on antibiotics immediately, if transport may be delayed, give ampicillin 50 mg/kg IV stat.

Child is severely undernourished (treat as severe pneumonia)

e. Management and treatment (level 2)

- If in respiratory distress upon admission, start supportive treatment including oxygen, sufficient fluids, clear airway and so on.
- Perform chest x-rays and other tests:
 - Sputum: microscopy, culture, AFB stain, ESR, WBC
 - Blood culture, if fever is present

- Start treatment based on presumptive diagnosis from chest x-rays and substantiated by ZN stain of gastric aspirate, microscopy of pleural effusion and so on.
If child has severe dyspnea, severe malnutrition and is under two months old, admit to hospital; give supportive care and treat with antibiotics.

Antibiotic treatment by age:

0-3 months	Ampicillin 50-100 mg/kg/day IV in 4 doses PLUS gentamycin 4 mg/kg/day IV as single dose
4 months-5 years	Ampicillin 50-100 mg/kg/day IV in 4 doses OR cefuroxime 50 mg/kg/day IV in 3 doses
>5 years	Penicillin 50,000-100,000 IU/kg/day IV in 4 doses OR cloxacillin 50-100 mg/day in 4 doses, if x-ray is suggestive of staphylococcus

- f. In making a presumptive diagnosis, consider the information presented in Table A3, 3.3, below:
- If improved after seven days, follow up as needed.
 - If not improved after seven days, reevaluate.
Repeat earlier performed tests.
 - If further evaluation does not result in a final diagnosis and/or cough persists for longer than 30 days, consider a therapeutic trial of TB treatment.
- g. Comments: Many HIV-infected children have recurrent respiratory problems. Give supportive treatment with adequate feeding, sufficient fluids and management of nasal secretions. Follow up with child, as needed.

Table A3, 3.3: Disease Features, Diagnosis and Treatment in Children with HIV

Disease	Distinctive Features	Clinical Presentation	Diagnosis	Treatment
<i>Pneumocystis carinii pneumonia (PCP)</i>	<p>One of the common OIs occurring in children with HIV</p> <p>Occurs frequently in children under 1 yr of age and has a very poor prognosis</p>	Characterized by sudden onset of fever and tachypnea	Diffuse interstitial infiltrate on x-ray	<p>Treat with co-trimoxazole 20 mg/kg per day of trimethoprim component divided in 4 doses for 14-21 days.</p> <p>WHO recommends that all infants born to HIV-infected mothers receive cotrimoxazole prophylaxis from 4-6 weeks, for at least the first 6 months (and ideally for the first 12 months) of life to prevent PCP.</p>
<i>Lymphoid interstitial pneumonia (LIP)</i>	<p>A slowly progressive interstitial lung disease of unknown etiology occurring commonly in HIV-infected children above the age of 1 yr</p> <p>Usually has a good prognosis</p>	Characterized by mild tachypnea and clubbing, wheezing, lymphadenopathy and parotid enlargement.	Bilateral reticular nodular infiltrates and mediastinal lymphadenopathy on x-ray, which can be confused with military TB or PCP	<p>No specific therapy is available, but steroids may be helpful; prednisone 2mg/kg/day for 10-14 days.</p> <p>Bronchodilators given as metered dose inhalers (or through spacer devices for younger children) may also be helpful.</p>
Tuberculosis	Close contact with a TB-infected adult	<p>Failure to thrive</p> <p>Fever for more than one month</p>	<p>Repeated abnormal chest x-ray shows no improvement after 2 weeks despite antibiotic therapy</p> <p>Tine test (grade II or Mantoux >5mm) is considered positive in HIV infected children*</p>	<p>Same as in adults</p> <p>See Module A2, Session 3, Table on TB treatment according to WHO guidelines.</p>

* A negative Mantoux does not exclude TB and may be negative in the presence of TB because of underlying immunosuppression (HIV), overwhelming TB disease, malnutrition, incorrectly done test or recent measles infection. When in doubt about the diagnosis of TB, give a trial of anti-TB therapy and document response to treatment by weight gain and resolution of symptoms.

2. Persistent diarrhea

- a. Definition: Persistent liquid stools for more than 14 days
- b. Etiology: A pathogen will be identified in only 15-50 percent of the cases

Protozoal	Giardia lamblia E. histolytica Cryptosporidium Isospora belli
Bacterial	Salmonella (non-typhoid) Campylobacter jejuni Enterotoxogenic E.coli (ETEC) Mycobacterium (atypical TB) Yersinia enterocolitica
Viral	Rotavirus Cytomegalovirus HIV/AIDS enteropathy
Helminthic	Strongyloides
Fungal	Candida infection

When a child also has a fever, look for other causes of diarrhea such as malaria, pneumonia and otitis; treat as indicated.

- c. IMCI—assess and classify (suggested entry points for HIV are in boldface)

Assess	Classify
Ask: Does the child have diarrhea?	
If yes, ask: <ul style="list-style-type: none"> • For how long? Number of days? • Is there blood in the stools? • Had diarrhea for more than 14 days in the last three months? <i>If yes, check for possible symptomatic infection</i>	Diarrhea Persistent diarrhea in last three months

d. Management and treatment (level 1=at home/local clinic)

- Prevent dehydration and maintain hydration: give ORS even if child is not dehydrated
- Maintain nutrition:
 - Advise the mother to breast feed more frequently, and continue feeding the child.
 - Maintain caloric intake.
 - You may give multivitamins to ensure sufficient vitamin intake (and to increase the appetite of the child).
- If the child has diarrhea with blood and fever, treat with nalidixic acid (50 mg/kg/per day divided into 4 doses). If child has had antimicrobial treatment within the previous 3 months, do not give nalidixic acid, but consider referral.
- Improvement is defined as:
 - Child is clearly better with no signs of dehydration AND
 - Fewer stools than before AND
 - No fever and less blood in stool (if present)
- If no improvement after five days, stop all antimicrobial treatment. In areas where strongyloides is prevalent, consider giving albendazole (200 mg x 3 days; repeat after three weeks). If the child is not improving, maintain hydration and nutrition and consider referral.
- If the child is not severely ill, that is, has no bloody stool, no fever, is not dehydrated and not malnourished, observe the child for 10 days and maintain hydration and nutrition.

e. Management and treatment (level 2=referred to hospital)

- Maintain hydration (oral or IV) as indicated.
- Test or check:
 - Stool cultures for ova and parasites
 - Fecal smears for blood and neutrophils, which would indicate a bacterial infection, E. histolytic, ulcerative colitis or clostridium difficile.
 - Fever: fever and/or bloody stools are more indicative of bacterial infections. Exclude pneumonia, otitis and so on, and if found, treat appropriately. If living in an endemic area, treat for malaria during malaria season.
 - Malnutrition: malnutrition puts an HIV-infected child at risk of dying from persistent diarrhea
- Treatment
- Further evaluations: exclude lactose intolerance, TB, typhoid, urinary tract infections and so on.

E. histolytica	Metronidazole 10 mg/kg tid x 10 days
G. Lamblia	Metronidazole 10 mg/kg tid x 5 days
Isospora belli	Co-trimoxazole for 3 weeks: children 1-5 yrs: 5 ml of syrup bid children 6-12: 1 tab bid
Cryptosporidium	No proven effective treatment; give supportive care
Helminth infections	Albendazole single dose: 200 mg for children under 2 years 400 mg for children 2 years and older

3. Persistent or recurrent fever

- a. Definition: Fever as the only obvious clinical presentation in an HIV-infected child and is defined as a body temperature of >37.5° C for more than one episode during a five-day period.
- b. Etiology:
 - Fever is common among HIV-infected pediatric patients.
 - May be a consequence of common childhood illnesses, endemic diseases, serious bacterial or opportunistic infections, carcinomas and/or HIV itself.
 - May be a fever of unknown origin (FUO) and should be investigated in the same fashion as the child without HIV and FUO
- c. IMCI—assess and classify (suggested entry points for HIV are in boldface)

Assess	Classify
Ask: Does the child have a fever?	
If yes, ask: <ul style="list-style-type: none"> • For how long? Number of days? • More than one episode in the last 5 days? <i>If yes, check for possible symptomatic infection</i> 	Fever of unknown origin (If no other obvious cause i.e., malaria, measles)

- d. Management and treatment (level 1)
 - If the child is acutely or seriously ill and has a temperature of 39° C or higher:
 - Treat with antimalarials (in endemic areas) according to national guidelines.
 - For possible septicemia, start treatment with antibiotics:
 - Give ampicillin 50 mg/kg IV STAT.
 - Refer immediately to nearest health facility with greater diagnostic capacity (level 2).
 - If not acutely or seriously ill:
 - Thoroughly examine child for possible localized infections, such as skin infections, abscesses and the like, and give specific treatment.
 - Consider malaria as a possibility, if in an endemic area, and treat according to national guidelines.
 - If no cause of fever is identified, treat empirically with ampicillin 50 mg/kg/qid for 5 days for possible occult infections, such as UTIs, otitis media and so on.
 - If the child still has fever, but is clinically stable (is attentive, eats and drinks satisfactorily), then presume HIV itself is the cause. Consider treatment with antipyretics and maintain hydration and nutrition. Follow up as needed.
 - If not clinically stable or you suspect a serious infection (for example, osteomyelitis or endocarditis) requiring prolonged course of antibiotics, refer to level 2.

e. Management and treatment (level 2)

- If child is acutely or seriously ill with a temperature of 39° C or higher:
 - Admit to hospital
 - Investigate for possible cause:
 - Blood slides for malaria parasites
 - Examine CSF
 - Blood culture to diagnose meningitis and sepsis
 - Treat with broad spectrum antibiotics for presumed sepsis or meningitis: give ampicillin 200 mg/kg/day 6 hourly for 10 days PLUS chloramphenicol 100 mg/kg/day 6 hourly.
 - Treat for malaria, even if blood slides are negative, according to national guidelines.
- If not acutely or seriously ill, investigate to identify possible cause of fever. Tests include:
 - Malaria slides White blood cell count Stool microscopy
 - Blood culture Urinalysis Widal
 - Chest x-ray CSF Ultrasound
- For many HIV-infected children with fever and no local findings, HIV may be the cause. However, you should consider other conditions:
 - Occult bacterial infections: chronic sinusitis, otitis media, UTIs, osteomyelitis, abscess, salmonella, syphilis, liver abscess and endocarditis
 - Mycobacterial infection: *M. tuberculosis*, *M. avium*
 - Fungal infections: *Candida*
 - Chronic viral infections: MCV, EBV
 - Parasitic infections: malaria, toxoplasma
 - Neoplasms: lymphoma, Kaposi's sarcoma, smooth muscle tumors
- If you find no source of fever, treat empirically with amoxicillin 50 mg/kg qid x 5 days.
- If fever resolves, follow up as needed.
- If fever persists, but child is clinically stable, presume HIV-associated fever; treat with antipyretics, and maintain hydration.
- If not clinically stable, repeat investigations. If no yield, most likely cause is HIV-associated fever.

4. Ear Problems

- IMCI (suggested entry points for HIV are in boldface)
- Management and treatment is the same as for any child presenting with an ear problem.

Assess	Classify
Ask: Does the child have a ear problem?	
If yes, ask: <ul style="list-style-type: none"> • Is there ear pain? • Is there ear discharge? • If yes, for how long? Number of days? • Discharge any time in the past? <i>If yes, check for possible symptomatic infection</i>	Ear infection in the past

5. Failure to thrive (FTT)

- a. Definition: FTT should be suspected when a child deviates from his/her own apparent path of growth or from the normal growth patterns for his/her age. Severe forms of malnutrition, such as kwashiorkor and marasmus, may occur as a result of FTT.
- b. Etiology: May be a result of imbalance in food intake, food losses and body requirements. Contributing causes may be vomiting, diarrhea, oral thrush, pneumonia, mouth ulcers or neurological diseases.
- c. IMCI (Suggested entry points for HIV are in boldface.)

THEN CHECK FOR MALNUTRITION AND ANEMIA	
Ask: • Has the infant lost weight?	<ul style="list-style-type: none"> • Look for visible, severe wasting • Look for pallor • Look for edema of both feet • Determine weight for age <ul style="list-style-type: none"> Very low Not very low • Growth faltering below yellow row

- d. Management and treatment (level 1)
 - Important to take a detailed feeding and social history to assess caloric intake and social conditions (especially to determine if the mother is the caretaker of the child).
 - Determine the degree of FTT and possible contributing illnesses
 - Weigh the child and chart the weight; do a complete physical examination.
 - If prior weights are available, define points on a growth curve to assess severity.
 - If not available, FTT is defined as:
 - Mild to moderate: Weight is 60-80 percent of normal weight for age
 - Severe: Weight is lower than 60 percent of expected weight for age, OR weight is 60-80 percent of weight for age if edema is present.
 - To assess as precisely as possible, ask the mother to describe exactly what food the child is taking, how much and how often.
 - Give feeding advice to the mother about breast feeding, weaning and other foods. It is important to increase the caloric intake through a balanced diet.
 - If possible, have the mother record exactly what the child eats and any problems she may encounter.
 - Do a home visit to assess availability of dietary resources at home and in the community.
 - Consider supplementing the diet with:
 - Vitamin A according to national guidelines (at nine months of age and every six months thereafter)
 - Iodine, which is adequately contained in iodized salt
 - Iron, if evidence of anemia
 - Multivitamins that include zinc
 - Evaluate dietary trial after seven days
 - If improved, continue treatment until resolved, and follow up as needed.
 - Improvement is defined as weight gain and increased alertness of child and/or loss of edema (if present).
 - If no improvement, refer to level 2.
 - If poor diet does not seem to be the cause, determine contributing causes and treat appropriately.
 - If cause cannot be determined or if treatment fails, refer to level 2.

- d. Management and treatment (level 2)
- Assess eating habits as above, and do appropriate tests to determine contributing causes; treat accordingly.
 - If child does not improve, consider admission for trial nasogastric feeding, especially if home dietary trial failed.
 - If child shows no improvement and no underlying cause can be determined, investigate for endocrine disorders, renal failure CNS disease and chronic infections.
- e. Comments: Many HIV-infected children show FTT without identifiable cause (including poor diet) and despite adequate caloric intake. This is thought to be the result of HIV itself.

6. Oral thrush

- a. Definition:
- Presumptive: Presence of characteristic white plaques on oral mucus, usually located on palate, which often bleed when removed. In some cases, it may present only as a red mucosal surface.
 - Definitive: Candida spores or pseudohyphae in mouth scrapings
- b. Etiology: Candida infection
- c. Management and treatment (level 1)
- In HIV-infected patients, oral thrush may extend into the esophagus. Look for signs and symptoms of esophageal candidiasis:
 - Pain on swallowing, reluctance to take food, salivation, crying during feeding, weight loss. If untreated, the condition may alter eating habits and add to poor nutrition of child.
 - Severe oral thrush (plaques on tongue, soft and hard palates, extending to pharynx) is highly indicative of esophageal thrush, even in the absence of pain on swallowing.
 - For presumed oral thrush only, treat with nystatin suspension 500,000 IU tid x 5 days or tablets if suspension is not available.
 - Follow up as needed; patient may need prolonged or prophylactic treatment with nystatin once or twice daily.
 - If no improvement, and for presumed esophageal candidiasis, refer for further investigation and treatment.
- d. Management and treatment for severe oral thrush (level 2)
- Treat with ketoconazole 3-6 mg/kg daily x 5 days.
 - Avoid use in presence of active liver disease and for patients receiving rifampicin.
 - If child is breast feeding, the nipples of the mother are often infected; instruct to apply gentian violet on nipples before breast feeding.
 - Exclude candidiasis of the perineal area. If available, apply clotrimazole 1 percent; if not available, give nystatin po, as above.
- e. Comments: Recurrence of oral thrush and esophageal candidiasis is very common. Recent use of antibiotics is an important predisposing factor. Esophageal lesions heal slowly, although symptomatic response is usually prompt. Prolonged treatment is often required.

7. Lymphadenopathy

a. Definition:

- Localized lymphadenopathy: usually affects only one or two regions of the body and is caused by a local infection
- Persistent generalized lymphadenopathy (PGL): a nonspecific finding that is very common in children with HIV infection, defined as:
 - Lymph nodes measuring at least 0.5 cm
 - Present in two or more sites, with bilateral nodes counting as one site
 - Duration of more than one month
 - No local infection that might explain presence of enlarged nodes

b. Etiology: possible causes include:

- HIV infection itself
- Other infections:

Bacterial:	Tuberculosis
Fungal:	Cryptococcus
	Histoplasmosis
Protozoal:	Toxoplasmosis

HIV-associated cancers: Lymphomas

Dermatological conditions: Serborrheic dermatitis
Chronic pyoderma

c. Management and treatment

- Identify and treat any local or regional infection that might explain lymphadenopathy.
- If no infection is identified, evaluate for fever, weight loss, unilateral nodes increasing in size, matted nodes, fluctuant nodes and/or nodes showing signs of inflammation (hot and tender).
If any of these signs and symptoms is present, refer to level 2.
- If none of the above is present, child can be diagnosed as having HIV-related PGL. Follow up as needed.

d. Management and treatment (level 2)

- Do a lymph node biopsy and treat accordingly.
- If TB is diagnosed, start TB treatment.

e. Comments:

PGL in HIV-infected children is mostly the result of normal immune reaction to HIV infection.
If no other problems are identified, no additional investigation or treatment is required.
Lymph nodes usually disappear as immunosuppression advances and OIs appear.

8. Skin problems

a. Definition:

Any kind of skin condition or infection similar in manifestation to that of an adult or child who is not HIV-infected

b. Etiology:

- Prurigo and nonspecific dermatitis
- Drug reactions to sulfas, TB drugs and other medications
- Bacterial: furunculosis, impetigo, pyoderma, folliculitis and abscesses
- Viral: chicken pox, herpes zoster, herpes simplex (usually the result of HIV-1 affecting mouth and lips) and molluscum contagiosum
- Fungal: candida and dermatophytosis
- Other: scabies, atopic dermatitis, seborrheic dermatitis and Kaposi's sarcoma

c. Management and treatment is the same as for adults.

E. HIV infection and immunization

1. Check that all children are fully immunized according to their age.

- a. Children who have, or are suspected of having, HIV infection but are not yet symptomatic should receive all appropriate vaccines (according to the national EPI program schedule), including BCG and, where relevant, yellow fever vaccine. Because most HIV-positive children have an effective immune response in the first year of life, give immunization as early as possible after the recommended age of vaccination.
- b. Children with symptomatic HIV infection (including AIDS) should receive measles and oral poliomyelitis vaccines as well as nonlive vaccines (DPT and, if locally relevant, hepatitis B). Do **not** give BCG and yellow fever vaccines to children with symptomatic HIV infection.
- c. Give all children with HIV infection (regardless of whether or not they are symptomatic) a dose of measles vaccine at the age of six months, as well as the standard dose at nine months.

2. General guidelines for immunizing HIV-infected children and adults:

	Vaccine	Asymptomatic HIV Infection	Symptomatic HIV Infection
Infants	BCG	Yes	No
	DPT	Yes	Yes
	Polio	Yes	Yes
	Measles	Yes	Yes
	Yellow Fever	Yes	No
Women of childbearing age	Tetanus toxoid	Yes	Yes

F. Counseling the mother

a. HIV testing and counseling

- If there are reasons to suspect HIV infection (based on clinical signs or diagnoses in the family), and the child's HIV status is unknown, test the child for HIV, where possible.
- Transplacental maternal antibodies interfere with conventional serological testing in children aged <15 months. If the child is suspected of having HIV infection on clinical grounds, offer the mother counseling, followed by HIV testing of both mother and child. This also provides an opportunity for clinical assessment to rule out other HIV-associated and potentially treatable clinical problems, such as tuberculosis. In the very uncommon event that you know that the mother became infected after delivery, the presence of antibodies in the first year of life is indicative of HIV infection in the infant.
- Both pretest and post-test counseling should accompany any HIV testing. Pretest counseling should include securing informed consent before any tests proceed. Even in high prevalence countries, HIV remains an extremely stigmatizing condition and the mother (or both partners) may feel reluctant to undergo testing
- HIV counseling should take account of the child as part of a family. This should include the psychological implications of HIV for the child, mother, father and other family members. Counseling should stress that, although cure is currently not possible, there is much that can be done to improve the quality and duration of the child's life and the mother's relationship with the child. Counseling should make it clear that the staff want to help, and that the mother should not be frightened of going to a health center or hospital early in an illness, if only to ask questions.
- Counseling requires time and has to be done by trained staff. All health workers at the first referral level should be trained in the principles of HIV counseling and be able to carry it out. However, if staff at the first referral level have not been trained, seek assistance from other sources, such as local community AIDS support organizations.
- Stress confidentiality of HIV testing and counseling. However, you could encourage mothers to find at least one other person, preferably within the family, with whom they can talk about this problem.

b. Indications for counseling

- 1) For a child with unknown HIV status presenting with clinical signs of HIV infection and/or risk factors (such as a mother or sibling with HIV/AIDS), follow these steps:
 - (a) Decide if you will do the counseling or if you will refer the child.
 - (b) If you are doing the counseling, make time for the counseling session. Take advice from local people experienced in counseling so that any advice given is consistent with what the mother will receive from professional counselors at a later stage.
 - (c) Where available, arrange for an HIV test to confirm the clinical diagnosis, alert the mother to HIV-related problems and discuss prevention of future mother-to-child transmissions (including, where possible, prevention using antiretrovirals).
Note: If HIV testing is not available, discuss the presumptive diagnosis of HIV infection in the light of the existing signs, symptoms and risk factors.
 - (d) If counseling is not being carried out at the hospital, explain to the parent why you are referring them elsewhere for counseling.

- 2) For a child known to be HIV-positive and responding poorly to treatment or needing further investigations, discuss the following in the counseling sessions:
 - (a) Parents' understanding of HIV infection
 - (b) Management of current problems
 - (c) Need to refer to a higher level, if necessary
 - (d) Support from community-based groups, if available

- 3) For a child known to be HIV-positive who has responded well to treatment and is to be discharged (or referred to a community-based care program for psychosocial support), discuss the following in the counseling sessions:
 - (a) Reason for referral to a community-based care program, if appropriate
 - (b) Follow-up care
 - (c) Risk factors for future illness
 - (d) Immunization and HIV

G. Follow-up

a. Discharge from hospital

Manage serious illnesses in HIV-positive children as for any other children. However, HIV-infected children may respond slowly or incompletely to the usual treatment. They may have persistent fever, persistent diarrhea and chronic cough. If the general condition of these children is good, they do not need to stay in the hospital, but can be seen regularly as outpatients.

b. Referral

If your hospital does not have available facilities, consider referring a child suspected to have HIV infection:

- For HIV testing with pre- and post-test counseling
- To another center or hospital for further investigations or second-line treatment, if there has been little or no response to treatment
- To a trained counselor for HIV and infant feeding counseling, if the local health worker cannot do this
- To a community home-based care program, a community institution-based voluntary counseling and testing center or a community-based social support program for further counseling and continuing psychosocial support

Discuss with the mother or caregiver the reason for referring the child, as well as the services available at the referral site. The referral note should be comprehensive, concise and clear, while maintaining confidentiality, with a request for written feedback on the child's condition.

c. Clinical follow-up

Children who are known or suspected to be HIV-positive should, when not ill, attend well-baby clinics like any other children. It is important that they receive prompt treatment of common childhood infections. In addition, they need regular clinical follow-up at first-level facilities at least twice a year, to monitor:

- Their clinical condition
- Growth
- Nutritional intake
- Immunization status
- Psychosocial support (where possible, give this through community-based programs)

In a child with repeated serious infections, consider antibiotic prophylaxis. Research on the benefits of prophylaxis with cotrimoxazole (trimethoprim 5 mg/kg, sulfamethoxazole 25 mg/kg, twice a day for three days per week) conducted mainly in industrially developed countries has shown that it reduces the incidence of PCP and bacterial infection in HIV-positive children. The decision to start prophylaxis should take into account national guidelines (which consider the cost of prophylaxis and the possible impact on development of cotrimoxazole resistance) and the availability of an adequate supply of the drug over a long period of treatment.

H. Summary

A 10-Point Approach for the Management of Children Infected with HIV

1. Early diagnosis: the two common approaches include clinical methods (based on WHO staging I-III and CDC classification A, B, C) and laboratory methods (based on antibody tests for over those 18 and DNA/RNA tests for younger children). There are advantages and shortcomings to each approach.
2. PCP prophylaxis
3. Growth monitoring
4. Nutritional supplementation
5. Treatment of acute illnesses
6. Treatment of opportunistic infections: bacterial, TB, oral and esophageal candida, and dermatophytes
7. The need and importance of psychosocial support and adolescent care, including the issue of timely disclosure to HIV-infected adolescents
8. Immunizations
9. Antiretroviral therapy, becoming increasingly accessible to the poor (currently the cheapest cost using generic drugs is about \$30/month in Uganda)
10. Care for HIV/AIDS-infected mothers

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PART A: MODULE A3

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Module A4

Antiretroviral Therapy: A Brief Introduction



Session 1: Setting up the Antiretroviral (ART) Component

In this session, participants learn about setting up a care program with ART including the essential elements of the ART component, the steps involved in developing these essential elements and the critical areas for organization and program development. They also learn about integrating the principles of chronic disease management so that care and treatment are sustainable.

Session 2: Brief Introduction to ART

Participants learn about ART, including the goal and basic principles of therapy and the WHO recommendations on: what therapy to begin with and when to change therapy, the types of therapies and their modes of action, WHO-recommended first-line ARV regimens, adherence issues, monitoring ART and drug interactions. The session also covers treatment options for patients who fail therapy, including WHO-recommended second-line regimens, barriers to treatment and research treatment approaches.

Session 3: Management of Drug Side Effects

Participants review the major side effects of antiretroviral drugs and of some of the drugs given to prevent and treat OIs; they learn how to advise patients in managing these symptoms.

Session 4: Case Studies: Managing Patients with Multiple Issues

Participants will work on two case studies of patients with multiple issues to apply what they have learned in Module 2 about managing patients with HIV-related diseases.

SESSION 1 Setting up the Antiretroviral (ART) Component**PURPOSE**

In this session, participants will learn about setting up a care program with ART, including the essential elements of the ART component, the steps involved in developing these essential elements and the critical areas for organization and program development as well as chronic disease management, so that care and treatment are sustainable.

This session builds on session 4 of Module 1 *Programming Comprehensive Care for People living with HIV/AIDS* (the components of comprehensive care, service delivery across a continuum from facility to community and back and the principles of chronic disease management) by outlining the practical aspects of setting up the ART component of care. A case study of FHI's experience in this area complements this session.

OBJECTIVES:

By the end of this session, participants will be better prepared to:

1. Describe the process of setting up the ART component of an HIV care program, including assuring HIV counseling and testing (C&T) services; reorganized service delivery and referrals; trained clinicians; a basic medical records system; access to laboratory services and a secure, consistent supply of affordable antiretroviral drugs.
2. Plan the necessary steps for developing the essential elements of the ART component.
3. Discuss critical areas for program development to ensure sustainability and implement additional components of care and support.
4. Discuss how they might introduce or strengthen an antiretroviral therapy program in the context of comprehensive HIV/AIDS prevention, care and support in their local situations.

TIME:

1 hour and 30 minutes

Family Health International, Management Sciences for Health (RPM Plus), John Snow, Inc. (Deliver Project) and others have several tools available, or in development, for assessing a site with respect to the essential elements of an ART program and determining what is needed to prepare the site to deliver ART. Below is a brief outline of what is needed for setting up the ART component of comprehensive care.

A. Setting up the ART component

1. What are the essential elements of an ART program?

- a. **Access to HIV counseling and testing (C&T)** services, either as a voluntary counseling and testing unit within a health facility, as a stand-alone center or integrated into clinical care provision is essential. HIV C&T identifies HIV-infected individuals and provides support in accessing health care services, coping and living positively, and preventing transmission and reinfection.
- b. **Trained clinicians** who can diagnose and treat common HIV-related illnesses and manage ART, observing the principles of chronic disease management and in accordance with national or international guidelines and standards are also required. Health care services include doctors, clinical officers and nurses who diagnose, treat and manage opportunistic infections (OIs) and drug side effects to resolve illness and promote quality of life. They determine the appropriateness of ARVs in terms of the individual's HIV disease status, counsel on treatment adherence, prescribe the regimen, provide continual monitoring of effectiveness and manage secondary effects of the drugs.
- c. **A basic medical records system** that includes access to clinical data, facilitating management of HIV over time (lifetime patient monitoring), as well as access to disease surveillance data
- d. An ART program must have access to **laboratory services** capable of doing routine laboratory tests, such as complete blood count, liver function tests, renal function tests and, if possible, CD4 count or as alternative, total lymphocyte count (TLC). In some situations, the ability to measure viral load will be important. Laboratory tests are used for baseline patient assessment, monitoring the patient's response to ARVs, including treatment effectiveness and adverse drug effects, as well as diagnosis of HIV-related illnesses and treatment response
- e. **A secure, consistent supply of affordable antiretroviral drugs**, as well as drugs to treat HIV-related illnesses, palliation and prophylaxis for certain opportunistic infections is required. ARVs must be taken for life and come as a combination of drugs. Assured drug availability and affordability is necessary for a continuous and ready supply of the prescribed regimens.

2. What are the necessary planning steps to start ART?

The following questions raise issues to consider. They are not necessarily sequential and can occur simultaneously.

- a. Is there a referral system between HIV counseling and testing services and clinical care provision?
 - If accessible C&T services do not exist, identify, or, if necessary, create the capacity to diagnose HIV.
 - Create linkages to refer HIV-infected individuals needing care and support to appropriate services.

- b. Does the health care staff have the capacity (knowledge, skills and attitude) to provide HIV care that includes managing opportunistic infections and the safe and effective use of ARVs?
 - Provide training to staff, including physicians, nurses, counselors, pharmacists, laboratory technicians and nutritionists on ART, management of HIV disease and adherence counseling.
 - Provide follow-up supervision.

- c. Does a functional medical records system exist?
 - Provide technical assistance for developing a data-management system for long-term patient monitoring according to the principles of chronic disease management.
 - Is it easy for the clinician to retrieve the patient's record at the time of the patient's visit?

- d. What facility has laboratory services with the capacity to perform the essential tests for ART management?
 - Finalize an agreement for lab services with this facility, including a mechanism for the safe and timely transport of lab specimens and specifications for timely reporting of lab results.

- e. Is there a drug management system in place that includes a mechanism for ordering, storing, securing and distributing ARVs?
 - If yes, finalize an agreement to procure ARVs, including procedures for ordering, securing storage, assuring consistent supply, monitoring of supply and dispensing drugs to patients.
 - If not, investigate preferential pricing for ARVs and establish a system for reliable procurement, storage and dispensing of drugs.

- f. Is the clinic site set up to accommodate patient appointments and continuity of care?
 - Is there a system that allows for following a patient by the same team over time, or at a minimum, by the same physician?
 - Are there regular clinic days and a consistent location for HIV care? Is there a place that ensures privacy for the patient-physician interaction?

3. As a health care site develops the essential elements of ART, what other elements are critical for comprehensive HIV care?

As health care facilities develop the essential elements outlined to provide ART, initiate plans to assure sustainability and to implement additional components of care and support. Critical areas for program development are:

- a. Involve PLHA and community groups throughout the process: have advisory committees and stakeholder groups participate in developing community treatment preparedness and care services.
- b. Develop national standards and guidelines for clinical HIV management, including C&T, prevention and management of OIs (including tuberculosis) and use of ART, if guidelines do not exist.
- c. Establish policies on charges for laboratory tests, clinic visits, OI drugs and ART.
- d. Develop standard operating procedures for HIV testing and counseling, universal precautions, post-exposure prophylaxis, ART eligibility, patient follow-up and referrals within and across services.
- e. Create or expand a functional referral system between clinical care and community support services to link clients and PLHA. The objective is to achieve a continuum of care and address a variety of needs, including nutrition, mental health, legal and economic support, palliative care and psychosocial and spiritual support.
- f. Strengthen capacity of health care system based on initial assessments; for example, improve data management and health commodity management, upgrade infrastructure and expand HIV services.
- g. Develop and implement a monitoring and evaluation plan.
- h. Maintain continual capacity building and support of staff through training, monitoring and supervision.

PROGRAM EXAMPLE

Introducing antiretroviral therapy programs in the context of comprehensive HIV/AIDS prevention, care and support: an example of what is being done in three African countries

1. Family Health International (FHI) has set out to introduce antiretroviral therapy (ART) in resource-poor settings within the context of comprehensive HIV/AIDS prevention, care and support.
 - a. The first ART learning sites are in Ghana, Kenya and Rwanda.

Each program is geographic in focus, allowing multiple entry points to care and treatment. Each fosters a close collaboration between national, district and private sector entities and coordinates activities among clinical care facilities, community support systems and NGOs in the selected communities. The U.S. Agency for International Development (USAID) is the primary funder; additional support comes from FHI and the U.K. Department for International Development (DFID).

- b. The guiding principles in each program include:
 - Making a commitment to community preparedness
 - Facilitating communication among the government, NGOs, PLHA and clinical care sectors
 - Ensuring comprehensive care that addresses client needs along a continuum of care
- c. The programs involve various levels of the health care system
 - In Kenya, the program is in an urban and a semiurban area and involves a provincial tertiary care referral hospital, a government referral hospital, and two semiprivate and government primary care clinics.
 - In Rwanda, the program is at a mission hospital, an urban mission health clinic and will reach eight rural health centers.
 - In Ghana, the program is at a district government hospital and a mission hospital, both in a semirural area near the capital city; it will soon expand to teaching hospitals in Accra and Kumasi.

VCT was operational in the Kenya and Rwanda settings when the treatment program was introduced, whereas in Ghana, part of the program's task was to set up VCT services in the district. Prevention of mother-to-child transmission (PMTCT) services are operational in all three sites.

- d. In all three sites, national guidelines on opportunistic infections (OIs) and ART have only recently been developed. Standard operating procedures for each site are consistent with the national guidelines; in Kenya and Ghana the programs played a collaborating role in developing the guidelines.

The following tables summarize the program details in Kenya, Ghana and Rwanda.

Table A4, 1.1: Summary of FHI's Antiretroviral Therapy Programs

	Ghana	Kenya	Rwanda
Location	Manya Krobo and Yilo Krobo Districts (semirural districts in the eastern region)	Mombasa (coastal city)	<ul style="list-style-type: none"> Kabgayi District (rural) Kigali (capital city)
Facilities	<ul style="list-style-type: none"> Atua Government Hospital: district hospital Semiurban: 123 beds, 162 staff St. Martin's Catholic Hospital: mission hospital Semiurban: 84 beds, 100 staff Korle-Bu Teaching Hospital: major university/teaching hospital in Accra Komfo Anokye Teaching Hospital: major university/teaching hospital in Kumasi 	<ul style="list-style-type: none"> Coast Provincial General Hospital: provincial tertiary referral hospital Urban: 700-bed, 395 HCWs on staff Port Reitz District Hospital: government referral hospital Mkomani-Bomu Clinic: semiprivate primary health care clinic Semiurban: outpatient clinic, 11 HCWs on staff Magongo Health Center: local government primary health care clinic Semiurban: ambulatory care, 6 HCWs on staff 	<ul style="list-style-type: none"> Kabgayi District Hospital: mission hospital Urban: 400-bed Health centers (8) in the rural district of Kabgayi Biryogo Medical and Social Center Mission health clinic serving the poorest in Kigali
HIV Prevalence	National: 4 percent (UNAIDS, 2002) Site Prevalence: 8-14 percent	National: 15 percent (UNAIDS, 2002)	National: 8.9 percent (UNAIDS, 2002)
Initial Sources of Drugs (# of patients)	<ul style="list-style-type: none"> FHI: 100 USAID: 200 Global Fund: 1,700 planned 	<ul style="list-style-type: none"> FHI: 120 USAID: 300 Global Fund: expected 	<ul style="list-style-type: none"> FHI: 60 USAID: 300 Global Fund: expected Clinton Foundation: expected
ARV Start Date	May 30, 2003	May 30, 2003	February 27, 2003
Existing Services (at time of start-up)	<ul style="list-style-type: none"> National pilot PMTCT program supported by UNICEF at Atua and St. Martin's hospitals Home-based care: limited HBC program through St. Martins hospital 	<ul style="list-style-type: none"> PMTCT Services: Port Reitz VCT: Port Reitz, Mkomani-Bomu and Magongo Clinics (established through IMPACT subagreement) Clinical Care: preventive therapy for TB and OIs at Mkomani-Bomu and Magongo Clinics; HIV clinic at CGPH Home-based care (Pathfinder/COPHIA) 	<ul style="list-style-type: none"> Treatment & Research AIDS Center (TRAC, formerly NACP) supports ART at 3 hospitals. Currently 500 are receiving ART. Clinical care: TB and OI preventive therapy offered at Kabgayi District Hospital. PMTCT: June 2002, Kabgayi launched PMTCT program with Kabgayi Health Center (ANC offered here). IMPACT-supported PMTCT services at Biryogo. VCT: Kabgayi District Hospital and IMPACT-supported VCT at Biryogo PLHA Groups: Duteraninkunga at Kabgayi and Ihumure at Biryogo

Table A4, 1.1 (cont.)

	Ghana	Kenya	Rwanda
Guidelines	<ul style="list-style-type: none"> National Guidelines on ART, 2002 National Guidelines on OIs, 2002 National Guidelines on VCT being finalized (2003) 	<ul style="list-style-type: none"> National Guidelines on ART, 2002 National Guidelines on OI, 2002 National Guidelines on VCT, 2001 	<ul style="list-style-type: none"> National Guidelines on ART, 2002 (2nd edition) National Guidelines on OIs, 2002 National Guidelines on VCT, 2002
FHI's Role	<ul style="list-style-type: none"> Provide technical assistance in developing national guidelines on HIV clinical management and ART. Collaborate with Ministry of Health, District Health Services and health facilities to develop and/or expand VCT, clinical care and PMTCT services. Leverage resources and secure additional funds to support existing program as well as expansion (USAID, DFID, Global Fund). Organize trainings for NGO staff and HCWs on VCT, PMTCT, clinical care, clinical management of OIs and TB, antiretroviral therapy and adherence. Facilitate development of a BCC strategy for care. Support refurbishment and upgrading of laboratory and expansion of clinical facilities. Fund, design and co-teach workshops on OI and ART for national audience of providers. Develop client referral systems. Strengthen data management system and analysis. 	<ul style="list-style-type: none"> Provide technical assistance on development of national guidelines on HIV clinical management and ART. Develop site assessment tools to assess accessibility, capacity and quality of the 4 sites (including laboratory) identified to provide ART and determine the needs for training, equipment and other support. Train health care providers on clinical management of OIs and TB, antiretroviral therapy and adherence. Develop client referral systems. Strengthen the capacity of the laboratory services to provide quality ART services, including training of laboratory technicians in procedures for clinical management of HIV patients, including ARV monitoring. Develop health literacy campaign on adherence, early-treatment seeking and patient education materials on ART and OI treatment. Strengthen data management system and analysis at the 4 sites, including staff training in data collection methods, analysis and reporting related to ARV management. Provide ART to eligible patients over a five-year period, and develop a client monitoring system and surveillance for drug resistance. Sensitize and strengthen communities and PLHA support groups in HIV/AIDS comprehensive care, including ART. 	<ul style="list-style-type: none"> Provide technical assistance on development of national guidelines on HIV clinical management and ART. Conduct an assessment of the two facilities to determine availability of human resources, training needs, infrastructure (including laboratory), inventory of HIV-related drugs and commodities, capacity and functionality of drug management systems, referral networks and capacity of potential local CBO partners. Organize trainings for health care providers on clinical management of OIs and TB, antiretroviral therapy and adherence. Develop counseling training program in collaboration with TRAC. Establish a mechanism for the follow up and monitoring of patients receiving ART. Implement community-based prevention programs and home-based care programs and develop BCC materials.

Table A4, 1.1 (cont.)

	Ghana	Kenya	Rwanda
Program Development	<ul style="list-style-type: none"> January 2002: Program Development Workshop January 2002: BCC, VCT, PMTCT, clinical care and laboratory support subagreements finalized with 6 NGOs, 2 hospitals, 2 labs February 2002: program launch Formative research and community preparedness activities July 2002: VCT services begin April–November 2002: Clinic, laboratory and pharmacy upgrading August 2002: OI Workshop November 2002: ARV Workshop February 2003: Grant to Ghana Health Services to procure ARVs for 100 patients for six months May 2003: ART begins 	<ul style="list-style-type: none"> February 2002: Task Force on ART (under NAACC) begins meetings to monitor use of ART in Kenya (FHI is secretariat and provides TA) April 2002: Stakeholders workshop organized September 2002: Clearance to proceed with implementation obtained September 2002: Health system capacity assessment April 2003: Health care provider training on HIV clinical management, including ART May 2003: ART begins 	<ul style="list-style-type: none"> November 2002: Assessment to determine existing health system capacity and needs completed November–February 2003: Capacity building process including: upgrading of services, improving drug management systems and personnel training (based on findings of assessment phase) February 2003: Health care provider training on HIV clinical management, including ART February 2003: ART began
Implementing Partners (in addition to intervention facilities)	<ul style="list-style-type: none"> Centre for Integrated Rural Environmental Development (CEFRIEND) Klo Drivers Alliance Manya Krobo Youth Club PHLAB Foundation Noguchi Memorial Institute for Medical Research Public Health Reference Laboratory Queenmothers Association Youngsters Peer Education Project 	<ul style="list-style-type: none"> Management Sciences for Health/RPM-Plus Population Council/HORIZONS COPHIA Aga Khan Local PLHA Group International Centre for Reproductive Health (ICRH) 	<ul style="list-style-type: none"> PLHA Groups: Duteraninkunga and Ihumure

Table A4, 1.2: Summary of Technical Approaches to Treatment at the Three Learning Sites

	Ghana	Kenya	Rwanda
Treatment Criteria	<p>Adults</p> <ul style="list-style-type: none"> • WHO Clinical Stage III or IV • CD4 <250. • Resident of Manga or Yib Krobo • Disclosure to at least one person <p>Children</p> <p>The child must meet any one of the following:</p> <ul style="list-style-type: none"> • Symptomatic children in Pediatric Stage II and III whose mothers are HIV positive • CD4 <20 percent in child less than 18 months • CD4 <15 percent in child more than 18 months 	<p>Adults</p> <ul style="list-style-type: none"> • WHO Clinical Stage III or IV • CD4 <200 <p>Children</p> <ul style="list-style-type: none"> • CD4 <15 percent in child more than 18 months <p>Social criteria:</p> <ul style="list-style-type: none"> • Resident of Mombasa District • Willingness to visit CPGH regularly and be contacted anytime at home or elsewhere • Staff of health facilities and their spouses who meet the medical criteria and is willing to start treatment • Tuberculosis patient who meets the medical criteria and has completed the intensive phase of treatment 	<p>Adults</p> <ul style="list-style-type: none"> • WHO Clinical Stage III or IV • CD4 <200 <p>Children</p> <ul style="list-style-type: none"> • CD4 <15 percent in child more than 18 months
Drug Regimen	<p>First line</p> <ul style="list-style-type: none"> • AZT 300mg + 3TC 150mg: one tablet two times a day • NVP 200mg: one tablet daily for two weeks. If there are no adverse reactions at this dosage, the dosage will be increased to one tablet two times a day. <p>Second line</p> <ul style="list-style-type: none"> • For patients who develop severe adverse side effects to AZT, d4T will be used in its place. These patients will therefore receive d4T, 3TC and NVP. • For patients who react to NVP or experience severe adverse drug reactions, EFZ will be used in its place. 	<p>First line (adults & adolescents)</p> <ul style="list-style-type: none"> • d4T + 3TC + efavirenz <p>For pregnant women or women likely to become pregnant:</p> <ul style="list-style-type: none"> • d4T + 3TC + NVP <p>Second Line</p> <ul style="list-style-type: none"> • AZT + ddl + LVP/r <p>OR</p> <ul style="list-style-type: none"> • AZT (retrovir) + ddl + NVP 	<p>First line</p> <ul style="list-style-type: none"> • d4T + 3TC + EFV or • AZT + 3TC + EFV <p>Second line</p> <ul style="list-style-type: none"> • AZT + ddl + IDV for patients who fail the first line combination of D4T + 3TC + EFV • d4T + ddl + IDV for patients who fail the first line combination of AZT + 3TC + EFV <p>*For women of reproductive age, EFV will be systematically replaced with NVP.</p>

Table A4, 1.2 (cont.)

<p>Laboratory Baseline</p>	<p>Baseline</p> <ul style="list-style-type: none"> • Full blood count • Total lymphocyte count • CD4 count • Urinalysis • Stool R/E • BUN and creatinine • Liver function Tests • CXR and sputum for AFBs if indicated • Viral load • First 200 ART patients • Treatment failure <p>Baseline</p> <ul style="list-style-type: none"> • HIV serology • Complete blood count (includes TLC) • CD4 count
<p>Laboratory Monitoring</p>	<p>For patients on Nevirapine, liver function tests will be performed at:</p> <ul style="list-style-type: none"> • Baseline • One month after initiating therapy • At three 3 months <p>For patients on all regimens, including those taking Nevirapine, monitoring should be done as follows:</p> <p>At 3 months:</p> <ul style="list-style-type: none"> • Full blood count • Total lymphocyte count • Liver function tests • Other tests only as needed <p>At 6 months:</p> <ul style="list-style-type: none"> • CD4 • Full blood count • Total lymphocyte count • Liver function tests • Other tests only as needed <p>First year</p> <p>Second patient visit</p> <ul style="list-style-type: none"> • Baseline viral load • LFTs • Renal function tests • Complete urinalysis • Chest x-ray <p>Month 1</p> <ul style="list-style-type: none"> • Total lymphocyte count (TLC) • LFTs <p>Month 3 and 12</p> <ul style="list-style-type: none"> • Full blood count (includes TLC) • CD4+ count • LFTs • Other tests as needed

Table A4, 1.2 (cont.)

<p>Laboratory Monitoring</p>	<p>At 12 months:</p> <ul style="list-style-type: none"> • CD4 • Full blood count • Total lymphocyte count • Other tests only as needed <p>After the first year:</p> <ul style="list-style-type: none"> • CD4 every 6 months • Total lymphocyte count every 6 months • Full blood count every 6 months • Liver function test every 6 months • Other tests only as needed <p>Month 6</p> <ul style="list-style-type: none"> • Full blood count (includes TLC) • CD4+ count • LFTs <p>Month 9</p> <ul style="list-style-type: none"> • Total lymphocyte count • Subsequent years • Quarter • Full blood count (includes TLC) <p>Every 6 months</p> <ul style="list-style-type: none"> • CD4 count • LFTs • Other tests as needed <p>For a patient not responding to treatment, the viral load test and resistance testing will be requested.</p>
<p>Follow-up Visits</p>	<p>For the first three months, patients receiving ARVs will be seen as follows:</p> <ul style="list-style-type: none"> • A visit two weeks after initiation of ARVs • A visit once a month for the first 3 months, unless physician and patient see the need for this to be more frequent • Followed by a bimonthly schedule <p>Physicians in dialogue with the patient will determine the frequency of visits, based on patient condition, adherence needs, etc. Patients can also walk-in as needed.</p> <p>Clinical and Adherence Monitoring Visits</p> <ul style="list-style-type: none"> • First two months: every 2 weeks • Thereafter: every month • Three pre-ARV counseling sessions with ART nurse • 48-72 hours after starting ART, the patient will meet with the ART nurse for assessment of adverse drug effects and medication adherence (discuss experience, difficulties, strategies to manage difficulties, input from family member/friend, review medication and encouragement) <p>Follow-up visits every 2 weeks with a doctor.</p>
<p>Adherence Plan</p>	<ul style="list-style-type: none"> • At least one session of adherence counseling prior to starting medication • Adherence counselors must verify the location of residence during the process • If possible, a supporting relative or friend will participate in the adherence sessions and assist the patient in taking the drugs for the first two weeks. • If the patient is unable, for whatever reason, to involve a relative or friend, they will receive support to do this eventually through follow-up counseling. <ul style="list-style-type: none"> • Five adherence counseling sessions with a “buddy” prior to starting treatment • Mini-DOT for 6 weeks; patients will attend health facility in the morning to take their pill supervised by a nurse. Evening dosage will be on their own.

SESSION 2 Brief Introduction to ART**PURPOSE**

In this session, participants will learn about antiretroviral therapy (ART), including the goal and basic principles of therapy and the WHO recommendations on: what therapy to begin with, when to change therapy, the types of therapies and their modes of action, WHO-recommended first-line ARV regimens, adherence issues, monitoring ART and drug interactions. The session also covers treatment options for patients who fail therapy, including WHO-recommended second-line regimens, barriers to treatment and research treatment approaches.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the goals and basic principles of ART.
2. List the criteria for when to start therapy, which regimen to use and when to change therapies.
3. Describe the different types of therapy, their mode of action and WHO- recommended first-line and second-line regimens.
4. Discuss adherence issues and discuss country-specific solutions.
5. Discuss the importance of and how to monitor patients on ART.
6. Describe drug interactions.
7. Discuss treatment options for patients who fail therapy, the barriers to treatment and how to address these in their local situation.
8. Discuss research treatment approaches.
9. Discuss in-country options and national guidelines for ART.

TIME:

1.5 hours

1. The goal of antiretroviral therapy (ART) is to:

- a. Prolong and improve the quality of life
- b. Reduce the viral load as much as possible, for as long as possible, to halt disease progression and prevent or reduce resistant variants
- c. Achieve immune reconstitution that is quantitative (CD4 count in normal range) and qualitative (pathogen-specific immune response)
- d. Provide an antiretroviral regimen that not only achieves reduced viral loads, but also preserves future therapeutic options, is relatively free of side effects and is tailored to individual needs for adherence

2. The basic principles of therapy

- a. When to start therapy
 - WHO recommends that HIV-infected adolescents and adults start ART when they have:
 - WHO stage IV disease (clinical AIDS), irrespective of CD4 cell count
 - 2003 WHO guidelines: for stage III use $<350\text{mm}^3$ in situation of rapid clinical decline
 - WHO stages I and II disease, with CD4 cell count below $200/\text{mm}^3$
 - WHO stages II or III HIV disease, with a total lymphocyte count below $1200/\text{mm}^3$
 - In cases where you cannot assess CD4 counts, use the presence of a total lymphocyte count of $1200/\text{mm}^3$ or below as a substitute indication for treatment in the presence of symptomatic HIV disease.
 - An assessment of viral load is not considered essential for starting therapy.

Table A4, 2.1:
Recommendations for Initiating Antiretroviral Therapy in Adults and Adolescents with Documented HIV Infection

If CD4 testing is available:	
<ul style="list-style-type: none"> • WHO stage IV, irrespective of CD4 cell count^a • WHO stage I, II, or IIIa with CD4 cell count less than 200/mm^{3b} 	
If CD4 testing is not available:	
<ul style="list-style-type: none"> • WHO stage IV, irrespective of TLC • WHO stage II or III^c, with less than 1200/mm^{3c} 	
<p>a Treatment is also recommended for patients with advanced WHO stage III disease, including recurrent or persistent oral thrush and recurrent bacterial infections, irrespective of the CD4 cell count or total lymphocyte count.</p> <p>b The precise CD4 level above 200/mm³ at which to start ARV treatment has not been established, but factor the presence of symptoms and the rate of CD4 cell decline (if measurement is available) into decision making. A CD4 level of 200/mm³ corresponds to a CD4 percentage of approximately 15 percent.</p>	<p>c A total lymphocyte count below 1200/mm³ can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, do not treat asymptomatic HIV-infected patients (WHO stage I), because there is currently no other reliable marker available in severely resource-constrained settings.</p>

b. What therapy to begin with

- The only regimens potent enough to drastically reduce viral replication as well as prevent the emergence of resistance and treatment failure for a significant amount of time involve a combination of at least three antiretrovirals.
- There are currently 16 approved ART agents for the treatment of HIV-1 infection (in the U.S.), encompassing six nucleoside reverse transcriptase inhibitors (NtRTI), three nonnucleoside reverse transcriptase inhibitors (NNRTIs) and six protease inhibitors (PIs). The WHO guidelines incorporate thirteen of them.

Table A4, 2.2: Approved Antiretroviral Agents Included in WHO's ARV Guidelines^a

Nucleoside reverse transcriptase inhibitors (NsRTIs)	Nucleotide reverse transcriptase inhibitor (NtRTI)	Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
zidovudine (ZDV, AZT) ^b didanosine (ddl) ^b stavudine (d4T) ^b lamiduvine (3TC) ^b abacavir (ABC) ^b	tenofovir disoproxil fumarate (TDF)	nevirapine (NVP) ^b efavirenz (EFZ) ^b	saquinavir (SQV) ^b ritonavir (RTV) (as pharmacoenhancer) ^b indinavir (IDV) ^b nelfinavir (NFV) ^b lopinavir/ritonavir (LPV/r) ^b
a Approved and generally available in industrialized countries as of January 2002.		b Approved for inclusion in WHO's Essential Drug List as of April 2002.	

- WHO recommends that ARV treatment programs in resource-constrained settings choose one potent first-line ART regimen with which to start treatment in the majority of patients.

Table A4, 2.3:
Recommended First-Line Antiretroviral Regimens in Adults and Adolescents with Documented HIV Infection

Regimen ^a	Pregnancy considerations	Major toxicities
ZDV/3TC/EFZ or ZDV/3TC/NVP	Substitute NVP for EFZ in pregnant women or in women for whom effective contraception cannot be assured.	ZDV-related anemia EFZ-associated CNS symptoms Possible teratogenicity of EFZ NVP-associated hepatotoxicity and severe rash NsRTI-related metabolic side effects
ZDV/3TC/ABC ^{a,c}	ABC safety data limited	ZDV-related anemia ABC hypersensitivity NsRTI-related metabolic side effects
ZDV/3TC/RTV-PI ^{b,d} or ZDV/3TC/NVP	LPV/r safety data limited NFV: most supportive safety data	ZDV-related anemia NFV-associated diarrhea IDV-related nephrolithiasis PI- and NsRTI-related metabolic side effects
<p>a ZDV/3TC is listed as initial recommendation for dual NsRTI component based on efficacy, toxicity, clinical experience and availability of fixed-dose formulation. It is acceptable to substitute other dual NsRTI components, including d4T/3TC, d4T/ddl and ZDV/ddl, depending on country-specific preference. (See source, p. 28.)</p> <p>Never use ZDV and d4T together because of proven antagonism. Fixed-dose formulations are preferred whenever possible, as they promote enhanced drug adherence.</p> <p>b RTV-PI includes IDV/r, LPV/r or SQV/r.</p>		
<p>c NOTE: Subsequent research does not support this regimen, and WHO is currently revising its guidelines.</p> <p>d NOTE: According to current research, the option of two NRTIs and a ritonavir-enhanced PI or nelfinavir should not be used as a first choice. Such a regimen should be used only if a NNRTI regimen is not indicated, e.g., in the case of an HIV-2 infection or if a patient presents with side effects to EFZ or NVP.</p>		

c. When to change therapy

- Because of failure, defined in terms of:

Clinical failure:	Clinical disease progression with development of an OI or malignancy after when the drugs have been given sufficient time to induce a protective degree of immune restoration
Immunologic failure:	A fall in the CD4 counts higher than 30 percent from the peak value or a return to a level at or below the pretherapy baseline
Virologic failure:	Refers to an incomplete virologic response, that is, not achieving HIV RNA <400 copies/mL by 24 weeks or <50 copies/mL by 48 weeks, in a treatment-naïve patient
- Because of toxicity:

Clearly defined toxicity to a single drug permits drug substitution without compromising the overall regimen. For example: you can substitute d4T for ZDV when ZDV-related symptoms or anemia appear, or NVP for EFZ when EFZ-related central nervous system symptoms are unremitting.

When you cannot identify the drug causing the toxicity and/or low-grade, intolerable side effects compromise adherence, we recommend a complete regimen switch.

If an interruption in therapy is indicated to permit resolution of toxicity, suspend the entire regimen temporarily to prevent the emergence of drug resistance.

3. Antiretroviral therapies

- Medication groups: (See Tables A4, 2.2 and A4, 2.3 above for a listing of drugs.)
 - Mode of action: antiretroviral drugs (ARVs) act on the HIV by interfering with its reproductive cycle. They act to inhibit replication of the virus at these main stages of the cycle:
 - Inhibit reverse transcriptase enzyme to interrupt the production of proviral DNA.* ARVs prevent formation of proviral DNA. NRTI and NNRTI act here.
 - Inhibit maturation of virion by interrupting the protein processing and virus assembly.* Protease enzymes are required during this stage and protease inhibitors act here.
 - Nucleoside reverse transcriptase inhibitors (NRTIs):
 - Lead to premature termination of the production of the HIV DNA chain
 - Are active against both HIV-1 and HIV-2
 - Resistance develops rapidly if given as single drugs alone (monotherapy)
 - Side effects include:
 - Nausea and vomiting
 - Anemia (AZT), neutropenia
 - Peripheral neuropathy (d4T, ddl, ddC)
 - Pancreatitis (ddl, ddC, d4T, 3TC)
 - AZT and d4T are structurally similar; do not use them together.
 - Nonnucleoside reverse transcriptase inhibitors (NNRTIs):
 - Are active only against HIV-1
 - Delavirdine and nevirapine are antagonistic in action on the HIV reverse transcriptase activity; therefore, do not use them together.
 - Interaction with some drugs occurs because of induction and/or inhibition of cytochrome P450 enzymes.
 - Adverse effects include diffuse maculopapular rash, hepatitis, headache and nausea.
 - Protease inhibitors (PIs):
 - HIV protease enzyme is responsible for cleaving various polyproteins in the process of producing mature infectious virions. Interference with this enzyme by PIs leads to significant reduction of the virus in the body to undetectable levels.

Rapid resistance will develop if PIs are used as single agents.

PIs are associated with multiple drug interactions because they inhibit cytochrome P450 enzymes.

For example: PIs increase the metabolism of rifampicin and decrease its effectiveness in treating TB

Side effects include GI problems, that is, nausea and vomiting.

Indinavir should be taken with plenty of water to prevent kidney stones.

b. Adherence

- Drug adherence is one of the key determinants of therapy success.
- Poor adherence can lead to virologic failure, evolution of drug resistance and subsequent immunologic and clinical failure.
- Adherence is promoted by simplified, well-tolerated regimens involving as few pills as possible and administered no more than two times per day.
- Counseling patients carefully before initiating therapy and involving physicians, nurses and other health care providers in the process are important.
- Do *not* start ART at the first clinic visit—a period of education and preparation to try to maximize future adherence is important.
- Once treatment has begun, continued monitoring of adherence is essential.
- Physician assessment has repeatedly been shown to be the least reliable approach; pill counts are subject to error and manipulation.
- Validated patient questionnaires have been shown to be one of the more reliable and easy-to-institute tools for monitoring adherence in the outpatient setting.
- Each country and/or health center should develop its own brief, culturally appropriate questionnaire since one standardized tool may not be applicable to all regions and cultures.

c. Monitoring of ART

- Baseline clinical assessment and preparation of the patient
 - Baseline medical and psychosocial history:
 - Essential demographic characteristics
 - Past medical history, including major illnesses (for example, tuberculosis), hospitalizations and surgeries
 - Length of time since diagnosis of HIV infection, current medications and symptoms
 - For women, current or planned pregnancy and access to contraceptive services
 - Family economic status
 - Family coping
 - Review of systems (respiratory, cardiac, neurological, genitourinary, etc.)
 - Baseline physical exam:
 - Vital signs, weight, and detailing of any abnormalities (including fundi, if possible), oropharynx, lymph nodes, lungs, heart, abdomen, extremities, nervous system and genital tract
 - Preparation of the patient:
 - Review expected benefits and potential side effects of the regimen chosen, possible drug interactions, concept of partnership between patient and caregiver, probable lifelong commitment to treatment, critical need to maintain safe sexual practices to prevent HIV transmission, the importance of drug adherence and the need to report perceived side effects.
- Establish a reasonable schedule for clinical monitoring.
 - First follow-up visit one month (preferably one or two weeks) after initiation to ensure tolerance
 - A minimum of one visit every 3-4 months thereafter (preferably monthly at first, to assess drug reaction, response and encourage adherence)
 - Monthly visits, combined with drug dispensing, are ideal to reinforce adherence.
 - At each visit, ask about any new symptoms that may be related to drug side effects, HIV progression or intercurrent processes.

- Clinical monitoring of toxicities and effectiveness of antiretroviral drugs and regimens

Whether CD4 cell monitoring is available or not, clinical effectiveness of ART is important and can be monitored by:

 - Patient’s perception of how he or she is doing on treatment—sense of well-being
 - Changes in body weight over the course of therapy
 - Changes in frequency and/or severity of HIV-associated symptoms (fevers, diarrhea, skin rashes and the like) and findings (oropharyngeal or vulvovaginal candidiasis)
 - Signs of immune reconstitution syndromes or HIV-related disease progression

Tell the patient about symptoms of ARV toxicities and the need to seek care

See Table A4, 2.4, below.

Table A4, 2.4: Clinical Signs and Symptoms and the Monitoring and Management of Symptoms of Serious Adverse Effects of Antiretroviral Drugs That Require Drug Discontinuation

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms	Management
Acute hepatitis	Nevirapine (NVP); efavirenz (EFZ) less common; more uncommon with zidovudine (ZDV), didanosine (ddl), stavudine (d4T) (<1 percent); and protease inhibitors, most frequently with ritonavir (RTV)	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia).	If possible, monitor serum transaminases and bilirubin. All ART should be stopped until symptoms resolve. NVP should be permanently discontinued.
Acute pancreatitis	ddl, d4T; lamivudine (3TC) (infrequent)	Nausea, vomiting and abdominal pain	If possible, monitor serum pancreatic amylase and lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NsRTI, preferably one without pancreatic toxicity (e.g. ZDV or ABC).
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NsRTIs)	Initial symptoms are variable. A clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea) or neurological symptoms (including motor weakness).	Discontinue all ART; symptoms may continue or worsen after discontinuation of ART. Supportive therapy. Regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either ABC or TDF.

Table A4, 2.4 (cont.)

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms	Management
Hyper-sensitivity reaction	Abacavir (ABC), nevirapine (NVP)	<p>ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhea, abdominal pain, pharyngitis, cough and dyspnea (with or without rash). While these symptoms overlap those of common infectious illnesses, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hyper-sensitivity reaction.</p> <p>NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.</p>	<p>Discontinue all ART until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with a change to different NsRTI if ABC-associated or to PI- or NsRTI-based regimen if NVP-associated.</p>
Severe rash / Stevens-Johnson syndrome	Non nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP), efavirenz (EFV)	<p>Rash usually occurs during the first two to four weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis has been reported in ~0.3 percent of infected individuals receiving NVP.</p>	<p>Discontinue all ARVs until symptoms resolve. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or Stevens-Johnson syndrome or toxic epidermal necrolysis; once resolves, switch ART regimen to different ARV class (e.g. three NsRTIs or two NsRTIs and PI). If rash is moderate (not severe) and without mucosal or systemic symptoms, change in NNRTI (e.g. NVP to EFV) could be considered after rash resolves.</p>
Severe peripheral neuropathy	ddl, d4T, 3TC	<p>Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness and areflexia can occur.</p>	<p>Stop suspect NsRTI and switch to different NsRTI that does not have neurotoxicity (e.g. ZDV, ABC). Symptoms usually resolve in two to three weeks.</p>

- Laboratory monitoring
 - Basic laboratory monitoring for toxicity and effectiveness of ART
 - Baseline tests before the initiation of ART:
 - HIV antibody test
 - Hemoglobin or hematocrit level
 - Additional basic testing should include:
 - White blood cell count and differential (to assess neutropenic side effects and total lymphocyte cell count)
 - Serum alanine or aspartate aminotransferase level (to assess the possibility of hepatitis coinfection and to monitor for hepatotoxicity)
 - Serum creatinine and/or blood urea nitrogen (to assess baseline renal function)
 - Serum glucose (given the propensity of PIs to induce insulin resistance)
 - Pregnancy test for women
 - Resources permitting, serum bilirubin, amylase and lipids (triglycerides and cholesterol)
 - CD4 lymphocyte counts
 - Useful in deciding whether a patient should start ART
 - Important for assessing effectiveness of ART with rises of >100 CD4 cells/mm³ in the first 6-12 months of therapy or immunologic failure
 - Plasma HIV-RNA levels (viral load)
 - A useful indicator of the activity of the ARV regimen in individual patients, but not currently recommended because of its high cost and unavailability in resource-constrained settings. Treatment failure will need to be assessed immunologically and clinically rather than virologically until inexpensive methods for viral quantitation are established.
- d. Drug interactions (For details, see appendices below)
- Drugs of NNRTI and PI classes interact with the cytochrome P450 enzyme system, resulting in either inhibition or induction of these enzymes.
 - When coadministered with other drugs metabolized by the cytochrome P450 enzyme system, increases or decreases in the given NNRTI or PI and/or concomitant medication may occur
 - This can result in increased toxicity because of elevated drug concentrations (or increased efficacy, such as in RTV-boosted PI regimens) or drug failure due to subtherapeutic drug concentrations
 - The only recommended PI-containing combination for patients receiving rifampin is SQV/r/ZDV (or d4T) 3TC. Use of other PIs (NFV, IDV/r, LDV/r) is contraindicated because rifampicin induces hepatic enzymes that reduce exposure to protease inhibitors to subtherapeutic levels.
 - Review handout of concomitant medications and requirements for dose modification.

See Table A4, 2.5.

Table A4, 2.5: Relevant Drug Interactions for Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors for Resource-Poor Countries

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antifungal						
Ketoconazole	NVP increased 15-30 percent Ketoconazole decreased 63 percent Recommendation: Do not coadminister	No data	IDV increased 68 percent Recommendation: Change IDV to 600 mg three times daily	LPV decreased 13 percent Ketoconazole increased threefold Recommendation: None	No dose adjustment	SQV increased threefold Recommendation: Standard dosing
Antimycobacterials						
Rifampin	NVP decreased 37 percent Recommendation: Use with caution only if no alternatives available	EFZ decreased 25-33 percent Recommendation: Consider EFZ 800 mg daily	IDV decreased 89 percent Recommendation: Do not coadminister	LPV AUC decreased 75 percent Recommendation: Do not coadminister	NFV decreased 82 percent Recommendation: Do not coadminister	SQV decreased 84 percent when given without RTV Recommendation: If using SQV/RTV, rifampin can be used at 600 mg/day or two or three times weekly
Rifabutin	NVP decreased 16 percent Recommendation: Standard dosing	EFZ unchanged Rifabutin decreased 35 percent Recommendation: Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFZ no change	IDV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); IDV dose change to 1000 mg three times daily	Rifabutin AUC increased threefold Recommendation: Decrease rifabutin dose to 150 mg daily; LPV/r no change	NFV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); NFV dose: increase to 1000 mg three times daily	SQV decreased 40 percent (RTV increases rifabutin levels fourfold) Recommendation: If using SQV/RTV, use rifabutin 150 mg two or three times weekly
Clarithromycin	NVP increased 26 percent Clarithromycin decreased 30 percent Recommendation: Standard dosing	EFZ unchanged Clarithromycin decreased 39 percent Recommendation: Do not coadminister	Clarithromycin increased 53 percent Recommendation: Standard dosing	No data	No data	Clarithromycin increased 45 percent SQV increased 177 percent Recommendation: Standard dosing

Table A4, 2.5 (cont.)

Anticonvulsant	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Additional drugs that should NOT be coadministered	Herbs: St. John's wort, garlic supplements	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements When IDV is used with low-dose RTV: Cardiac: flecainide, propafenone Neuroleptic: pimozide	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements Cardiac: flecainide, propafenone Neuroleptic: pimozide	Antihistamine: Astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements When SQV is used with low-dose RTV: Cardiac: flecainide, propafenone Neuroleptic: pimozide
Miscellaneous	Can induce glucocorticoid metabolism, resulting in lower serum steroid levels	Monitor warfarin if used concomitantly.	Grapefruit juice decreases IDV by 26 percent			Grapefruit juice increases SQV levels. Dexamethasone decreases SQV levels.

Source: *Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach*. Geneva: WHO, 2002, pp. 114-119.

4. Treatment options for patients who fail therapy

- a. As previously stated, reasons for altering an initial ART regimen include:
 - intolerance, leading to poor adherence
 - drug toxicity
 - the occurrence of active tuberculosis or pregnancy
 - treatment failure

- b. The Table A4, 2.6 below outlines alternative treatment regimens.

Table A4, 2.6: Recommended Second-Line Regimens in Adults and Adolescents

First-line regimens	Second-line regimens for treatment failure	Alternative second-line regimens for treatment failure
ZDV/3TC/EFZ or ZDV/3TC/NVP	d4T/ddI/RTV-PI ^{a,b,c}	RTV-PI ^a / ABC/ddI ^{c,d} NFV + ABC/ddI ^{c,d} or d4T/ddI ^{b,c} /NFV
ZDV/3TC/ABC	d4T/ddI ^{b,c} /NNRTI ^e	d4T/ddI ^{b,c} /RTV-PI ^a
ZDV/3TC/RTV-PI or ZDV/3TC/NFV	d4T/ddI ^{b,c} /NNRTI ^e	ABC/ddI ^{c,d} /NNRTI ^e

- a RTV-enhanced PI = IDV/r, LPV/r, SQV/r. An RTV-enhanced PI regimen is preferred because of the potency of these regimens. NFV can be considered as an alternative for the PI component of second-line therapy if RTV-enhanced PI is not available or if there is a clinical contraindication to its use.
- b Nucleoside cross-resistance may compromise the potency of d4T/ddI at the time of switching for treatment failure as it is assumed that virological failure will have been prolonged at that point and several nucleoside analogue mutations (NAMs) are likely to be present. However, choices are limited in the setting of treatment failure. See also footnote c.
- c Tenofovir is a once-daily nucleotide NtRTI with activity against some nucleoside-resistant strains. If available, TDF can either be added to d4T/ddI or ABC/ddI or substituted for either d4T or ABC in these combinations. Its currently restricted availability in resource-limited settings is recognized.
- d High-level ZDV/3TC coresistance confers diminished susceptibility to ABC. If d4T/3TC is used as the first-line dual nucleoside backbone, AZT/ddI can be used as the second-line nucleoside component and vice versa.
- e NNRTI can be either EFZ or NVP.

c. Limitations to selecting alternative therapy

- Drug resistance: If viral load and resistance monitoring are not defining treatment failure, virological failure will probably have been present for an extended period by the time treatment failure is detected. Viral replication over time leads to the evolution of more drug resistance mutations; without drug resistance testing, it will be hard to know which drugs have been compromised.

5. Barriers to treatment

Barriers to treatment need to be assessed according to each country's resources and limitations.

a. Cost: How much does ART cost in-country?

b. Drug-specific issues

- Availability:
 - Which drugs are available in-country?
 - Where (at what locations) are they available?
 - Is refrigeration needed? Available?
 - Are there any issues around toxicity? resistance?

c. Laboratory: which tests can be done in-country and where?

d. Culture-specific issues affecting adherence?

6. Research treatment approaches

a. Structured treatment interruption (STI)

All forms of STI are considered experimental because there are no data providing guidance and indications of when to stop, when to restart and what agents to use.

- Virologic failure

Discontinuation of ART usually results in rapid CD4 decline beginning at 2-4 weeks and is attributed to the return to wild type HIV, which is more "fit" than resistant strains. The wild type HIV strain is usually sensitive to those drugs to which there was previous resistance and responds to reintroduction of ART. However, resistant strains presumably remain as minority species and will eventually return with selective pressure.

- Structured intermittent therapy (SIT)

This is an experimental protocol in which patients who have achieved good virologic control with ART receive the successful ART regimen every other week in an attempt to decrease toxicity and cost. The experience to date shows preservation of CD4 level and viral suppression.

- Pulse therapy

The goal of this therapy is to keep the CD4 cell count above a predetermined threshold using cycles of therapy followed by prolonged interruptions. A subset of patients—presumably those with relatively low viral load set points and good CD4 cell count responses to HAART—may be able to discontinue therapy safely for prolonged periods of time. Randomized, controlled clinical trials are in progress to evaluate this approach, although results may not be available for several years. If the CD4 cell count is truly the most important predictor of time-off therapy, and the most important indicator of the need to resume therapy, this raises the question of whether we might combine a pulse-therapy strategy with immune-based therapies, such as interleukin-2, to increase the CD4 cell count and prolong the treatment interruption. (Medscape General Medicine 4(3), 2002)

b. Directly observed therapy (DOT): WHO recommendations

- There is a need to try and evaluate innovative models such as DOT for an initial training period for patients.
- Try introducing DOT with the assistance of caregivers or family members, to assist in adherence.
- Sites with tuberculosis treatment programs may consider DOT (although the open-ended nature of ART, as opposed to the limited course of treatment for TB, raises questions about sustainability of such an approach).

Table A4, 2.7: Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Nevirapine		No effect on NVP EFZ AUC decreased 22 percent Recommendation: Standard dosing	NVP increased twofold IDV decreased 28 percent Recommendation: Change IDV dose to 1000 mg three times daily No change NVP	No effect on NVP LPV trough decreased 55 percent Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change NVP	No effect on NVP NFV levels increased 10 percent Recommendation: Standard dosing	No effect on NVP SQV decreased 25 percent Recommendation: Standard dosing
Efavirenz			No effect on EFZ IDV decreased 31 percent Recommendation: Change IDV dose to 1000 mg three times daily No change EFZ	No effect on EFZ LVP AUC decreased 40 percent Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change EFZ	No effect on EFZ NFV increased 20 percent Recommendation: Standard dosing	EFZ decreased 12 percent SQV decreased 62 percent Recommendation: Do not coadminister (SQV/r boosting may be possible)
Indinavir				No effect on LPV IDV AUC and trough increased Recommendation: Change IDV dose to 600 mg twice daily No change LPV	NFV increased 80 percent IDV increased 50 percent Recommendation: Limited data for IDV 1200 mg twice daily with NFV 1250 mg twice daily	SQV increased fourfold to sevenfold No effect on IDV Recommendation: Insufficient data to provide recommendation
Lopinavir					No data	SQV AUC/trough increased Recommendation: SQV 800 mg twice daily No change LPV/r
Nelfinavir						SQV increased twofold to fivefold NFV increased 20 percent Recommendation: Fortovase 1200 mg twice daily No change NFV

Source: Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach. Geneva: WHO, 2002, pp. 112-113.

Table A4, 2.7 (cont.)

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antifungal						
Ketoconazole	NVP increased 15-30 percent Ketoconazole decreased 63 percent Recommendation: Do not coadminister	No data	IDV increased 68 percent Recommendation: Change IDV to 600 mg three times daily	LPV decreased 13 percent Ketoconazole increased threefold Recommendation: None	No dose adjustment	SQV increased threefold Recommendation: Standard dosing
Antimycobacterials						
Rifampin	NVP decreased 37 percent Recommendation: Use with caution only if no alternatives available	EFZ decreased 25-33 percent Recommendation: Consider EFZ 800 mg daily	IDV decreased 89 percent Recommendation: Do not coadminister	LPV AUC decreased 75 percent Recommendation: Do not coadminister	NFV decreased 82 percent Recommendation: Do not coadminister	SQV decreased 84 percent when given without RTV Recommendation: If using SQV/RTV, rifampin can be used at 600 mg/day or two or three times weekly.
Rifabutin	NVP decreased 16 percent Recommendation: Standard dosing	EFZ unchanged Rifabutin decreased 35 percent Recommendation: Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFZ no change	IDV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); IDV dose change to 1000 mg three times daily	Rifabutin AUC increased threefold Recommendation: Decrease rifabutin dose to 150 mg daily; LPV/r no change	NFV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); NFV dose increase to 1000 mg three times daily	SQV decreased 40 percent (RTV increases rifabutin levels fourfold) Recommendation: If using SQV/RTV, use rifabutin 150 mg two or three times weekly.
Clarithromycin	NVP increased 26 percent Clarithromycin decreased 30 percent Recommendation: Standard dosing	EFZ unchanged Clarithromycin decreased 39 percent Recommendation: Do not coadminister	Clarithromycin increased 53 percent Recommendation: Standard dosing	No data	No data	Clarithromycin increased 45 percent SQV increased 177 percent Recommendation: Standard dosing

Table A4, 2.7 (cont.)

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antimycobacterials						
Oral contraceptives	Estradiol decreased 20 percent Recommendation: Use alternative or additional methods.	Estradiol increased 37 percent; no data on other components Recommendation: Use alternative or additional methods.	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods.	Estradiol decreased 42 percent Recommendation: Use alternative or additional methods.	Estradiol decreased 47 percent; norethindrone decreased 18 percent Recommendation: Use alternative or additional methods.	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods.
Methadone	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	No change, but there may be a decrease if given with low-dose RTV Recommendation: When IDV is given with low-dose RTV, opioid withdrawal is possible; may require increase in methadone dose	Methadone AUC decreased 53 percent Recommendation: Opioid withdrawal possible; may require increase in methadone dose	May decrease methadone levels Recommendation: Opioid withdrawal possible; may require increase in methadone dose	No data, but may decrease if given with low-dose RTV Recommendation: When given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose
Anticonvulsant						
Phenobarbital	Unknown	Unknown		Unknown, but may decrease LPV levels substantially Recommendation: Monitor anticonvulsant levels	Unknown, but may decrease NFV levels substantially Recommendation: Monitor anticonvulsant levels	Unknown, but may decrease SQV levels substantially Recommendation: Monitor anticonvulsant levels
Lipid-lowering agents: Simvastatin Lovastatin Atorastatin	No data	No data	Potential for large increase in statin levels (except pravastatin) Recommendation: Do not coadminister except pravastatin; no dose adjustment	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister

Prophylactic Treatment as Recommended in the U. S.

Prevention and the use of chemoprophylaxis are an important part of clinical management of individuals infected with HIV.

The following guidelines and recommendations are for the use of prophylaxis; they are grouped into measures that are strongly recommended, generally recommended and not recommended.

1. Strongly recommended as standard of care

a. *Pneumocystis carinii* or *p. jiroveci* pneumonia (PCP)

- Risk: CD4 count < 200/mm³, prior PCP, or HIV-associated thrush or FUO x 2 weeks
- Preferred: TMP-SMX (co-trimoxazole) 1DS/day or 1 SS/day
- Alternatives: dapsone 100 mg qd or 50 mg po bid
 - Dapsone 50 mg qd plus pyrimethamine 50 mg/wk plus leucovorin 25 mg/wk
 - Dapsone 200 mg/wk plus pyrimethamine 75 mg/wk plus leucovorin 25 mg/wk
 - Atovaquone 750 mg po bid with meals
- Comments: test patients given dapsone for G6PD deficiency
CP is the major AIDS-defining diagnosis and the major identifiable cause of death in patients with AIDS.
Risk of PCP for patients with prior PCP is 60-70 percent; with CD4 < 100/ mm³ is 40-50 percent/year.
Risk increases with progressive declines of CD4 count.

b. *M. Tuberculosis*

- Risk: positive PPD (≥5mm induration) with prior treatment, recent TB contact or history of inadequately treated TB that healed
- Preferred: INH 300mg/day + pyridoxine 50 mg/day ≥270 doses, 9 months or up to 12 months with interruptions
INH 900 mg + pyridoxine 100 mg twice weekly with directly observed therapy, ≥76 doses, 9 months or up to 12 months with interruptions
- Alternatives: rifampin 600 mg qd x 4 months
- Contact with INH resistant strain: rifampin plus pyrazinamide x 2 months (above doses)
- Contact with strain resistant to INH and rifamycin: use 2 agents with anticipated activity—ethambutol + pyrazinamide or levofloxacin + pyrazinamide
- Pregnancy: INH regimens

c. *Toxoplasmosis gondii*

- Risk: CD4 count < 100/mm³ plus positive IgG serology for *T. gondii*
- Preferred: TMP-SMX 1 DS/day
- Alternatives: TMP-SMX 1 SS/day
 - Dapsone 50 mg qd plus pyrimethamine 50 mg/wk plus leucovorin 25 mg/wk
 - Dapsone 200 mg/wk plus pyrimethamine 75 mg/wk plus leucovorin 25 mg/wk

d. *M. avium* complex

- Risk: CD4 count < 50 mm³ Preferred measure: Clarithromycin 500 mg po bid or azithromycin 1200 mg po weekly
- Alternatives: rifabutin 300 mg po qd or azithromycin 1200 mg/wk plus rifabutin 300 mg po qd
- Immune reconstitution: It appears safe to discontinue primary MAC prophylaxis when CD4 count has increased to >100mm³ for 3-6 months. Continue preventive therapy for patients with prior MAC bacteremia.

e. *Varicella*

- Risk: significant exposure to chicken pox or shingles and no history of either, or negative serology
- Preferred: VZIG 5 vials IM within 96 hours of exposure, preferably within 48 hours
- Alternatives: acyclovir 800 mg po 5x/day x 3 weeks

f. *S. pneumoniae*

- Risk: All patients (standard of care for patients with CD4 count >200/mm³)
- Preferred: pneumovax 0.5 ml IM x 1
- Revaccinate: when CD4 count increases to >200 mm³ if initial immunization was done with CD4 count <200 mm³

2. Generally recommended

a. Hepatitis B

- Risk: negative anti-HBc screening test
- Preferred: recombivax HB 10 ug IM x 3 or energix-B 20 ug IM x 3

b. Influenza

- Risk: all patients annually
- Preferred: influenza vaccine 0.5 ml IM each year preferably October-November
- Alternative: amantadine 100 mg po bid or rimantadine 100 mg po bid

c. Hepatitis A

- Risk: gay men, hepatitis C infection, injection drug users, community outbreak and travel to endemic area
- Preferred: Havrix 0.5 ml IM x 2 separated by 6 months

3. Not recommended for most patients—consider for selected patients

a. Cryptococcosis

- Risk: CD4 count <50/mm³
- Preferred: fluconazole 100-200 mg po qd
- Alternatives: itraconazole 200 mg po qd

b. Histoplasmosis

- Risk: CD4 count <100/mm³ plus residence in endemic area
- Preferred: itraconazole 200 mg po qd

c. CMV

- Risk: CD4 count <50/mm³ plus positive CMV serology
- Preferred: oral ganciclovir 1 gm po tid

d. Bacterial infection

- Risk: neutropenia
- Preferred: G-CSF 5-10 µg/kg sc qd x 2-4 wks

SESSION 3 Management of Drug Side Effects**PURPOSE**

In this session, participants will review the major side effects of antiretroviral drugs and of some of the drugs given to prevent and treat OIs. They will learn how to advise patients in managing these symptoms.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. List the common side effects of these drugs and the rough percentage of people reporting each side effect for each drug.
2. Advise the patient on how to manage some of the major side effects, such as fatigue, anemia, headaches, nausea and vomiting, diarrhea, weight loss, dry mouth, rash, peripheral neuropathy, menstrual problems and hair loss.

TIME:

45 minutes

1. Introduction

- a. All antiretroviral drugs, as well as drugs used to treat and prevent OIs, have some side effects. These side effects may vary from person to person. Some may experience few or no side effects, while others have mild to severe side effects.
- b. Side effects often occur after starting a new drug or therapy; they may decrease or disappear entirely after several weeks or may persist throughout the therapy.
- c. Some of the more common side effects include: fatigue, anemia, headaches, nausea and vomiting, diarrhea, weight loss, dry mouth, rash, peripheral neuropathy, menstrual problems and hair loss. There is information in Part B, Module 1, Session 4 on the drugs most commonly used in HIV disease and the side effects most commonly reported with these drugs.

2. Advice a caregiver can give to the patient on some of the more common side effects associated with antiretroviral drugs and drugs used for prevention and treatment of OIs. Local practices and remedies should be assessed and integrated as appropriate.

- a. Fatigue
 - Symptoms of fatigue can be physical (it may be hard to get out of bed or to walk upstairs) or psychological (patient may find it hard to concentrate; suffer depression, anxiety, and/or stress).
 - Fatigue may result from sleep problems (having trouble falling asleep, staying asleep, suffering sleep disturbances).
 - Fatigue can also be a symptom of anemia.
 - Advise the patient to:
 - Try going to sleep at night and waking in the morning at the same time every day; changes in sleep patterns can make a person feel more tired.
 - Avoid caffeine, alcohol, or nicotine for 4-6 hours before going to bed. A light snack, chamomile tea, warm milk and relaxation techniques before bedtime are often helpful.
 - Try to get a little exercise. Exercise eases stress and makes a person feel stronger and more alive.
 - Have someone help with day-to-day chores such as cooking. Keep easy-to-prepare foods on hand for times when cooking is too tiring.
 - Eat snack foods throughout the day and fresh fruits that don't require preparation.
 - Drink high-energy, high-protein liquids.
- b. Anemia
 - Anemia may be caused by HIV itself or be a side effect of drugs.
 - Give intramuscular injections of vitamin B12 every 1-2 weeks, if necessary or feasible.
 - Advise the patient to:
 - Return to the clinic to check hemoglobin count regularly
 - Eat a diet of locally available foods that are high in folic acid, including spinach and other green leafy vegetables, and high in iron and vitamin B12, such as fish, meat and poultry, if available
 - Take multivitamins and/or supplements of folic acid or iron
- c. Headache
 - Headaches are generally treatable with nonprescription drugs and by stress reduction.
 - Advise the patient:
 - For on-the-spot relief, try resting in a quiet, dark room with your eyes closed; place cold washcloths over your eyes; massage the base of your skull with your thumbs and massage both temples gently; take hot baths or showers.

To prevent headaches from recurring, try to anticipate when the pain will strike. Avoid or limit those foods known to trigger headaches, especially caffeine (in coffee, tea, soft drinks), chocolate, alcohol, citrus fruit (if more than half a cup a day), food additives (monosodium glutamate), nuts, onions, hard cheese and vinegar.

d. Nausea and vomiting

- Persistent vomiting can lead to serious medical problems, such as dehydration, chemical imbalances or even tearing of the esophagus. Advise the patient to come to the clinic if nausea or vomiting persists and/or interferes with his/her taking the medications.
- Give anti-nausea medications, as needed.
- Nausea often improves if antiretrovirals are taken with food, and most ART drugs can be taken with a meal or snack. Ritonavir or saquinavir should be taken with foods that are high in fat. Indinavir can be taken with a light, fat-free, low-protein meal or snack. Only ddI must absolutely be taken on an empty stomach.
- Advise the patient to:
 - Eat a diet of bananas, rice, applesauce, toast and tea, if possible (known as the BRAT diet).
 - Eat small amounts of bland, odorless foods such as toast, crackers, clear soup or broth, which are easier to keep down. Eat simple boiled foods such as porridge, potatoes and beans.
 - Avoid hot, spicy, strong-smelling and greasy food.
 - Keep some dry crackers at your bedside. Before getting out of bed in the morning, eat a few dry crackers and sit in bed for a few moments.
 - Eat small snacks throughout the day, and avoid large meals.
 - Try peppermint, chamomile or ginger tea (or the equivalent in the local situation).
 - Sip cold carbonated drinks like 7-Up.

e. Diarrhea

- Watch for signs of dehydration and weight loss. If patient is dehydrated, teach him or her how to make an oral rehydration solution.
- A small study found that taking 500 mg of calcium twice a day greatly reduced nelfinavir-related diarrhea.
- Advise the patient to:
 - Eat a diet high in soluble fiber (which slows the diarrhea by absorbing liquid). These include the BRAT diet (see d. above) and soft white rice, oatmeal (or oat bran), cream of wheat or other locally available porridge and soft bread (not whole grain). Psyllium husk fiber is another source of soluble fiber, if available locally.
 - Avoid foods high in insoluble fiber, such as corn, popcorn, fruits (dried and raw), vegetables, nuts, seeds and most grains. These can make diarrhea worse.
 - Decrease high fat foods.
 - Avoid milk products and greasy, high fiber or very sweet foods. These tend to aggravate diarrhea.
 - Prevent dehydration by drinking lots of fluids. If dehydrated, drink rehydration solution.
 - Drink rice or barley water made by boiling a half cup of rice or barley in one liter of water. Once the rice or barley is cooked, pour off the water and drink it in small sips.

f. Weight loss

- Weight loss is a serious problem and may result from some of the other drug side effects such as vomiting, diarrhea, dry mouth, anemia or fatigue. Monitor the patient's weight regularly and determine the cause of weight loss: is it stress related? accompanied by nausea and vomiting? has it occurred after starting a new medication? and so on.
- Advise the patient to:
 - Take a diet high in protein (and low in sugar), and/or take high protein supplement drinks, if available
 - Take multivitamins

g. Dry mouth

- Dry mouth can make chewing, swallowing and talking difficult; it can affect one's sense of taste and can promote mouth problems, like tooth decay and oral yeast infections (thrush).
 - * If necessary, prescribe a synthetic saliva or anti-dry mouth medication, such as pilocarpine.
- Advise the patient to:
 - Drink plenty of liquids during or between meals.
 - Rinse the mouth throughout the day with salted warm water.
 - Avoid sugary or sticky foods or caffeinated drinks; these can make the mouth even drier.
 - Chew sugarless gum; it can stimulate saliva flow. Suck on sugarless candies, lozenges, or crushed ice (if available), to cool the mouth and give it moisture.
 - Try slippery elm or licorice tea (or the local equivalent). This will lubricate the mouth.

h. Rash

- Many people get a rash when starting antiretrovirals, but most of the time it is mild and goes away after a couple of weeks.
- Rash seems to be a slightly more common side effect among women taking certain antiretroviral medications than among men. Nevirapine appears to be the main culprit, along with abacavir, efavirenz and amprenavir, as well as cotrimoxazole, isoniazid and many antibiotics. Women also seem more prone to severe rash.
- Sometimes the rash can be a sign of hypersensitivity that can include fever and flu-like symptoms, such as aches, pains, fatigue, headache, difficulty breathing, sore throat and cough.
- Be sure to monitor a patient's skin for discoloration and changes in its surface, as well as for signs of hypersensitivity, especially after starting a new medication; teach the patient to monitor for such signs.
- Advise the patient to:
 - Use creams, moisturizers or a topical ointment such as Benadryl to soothe and comfort the skin, if a rash should develop.
 - Use unscented, nonsoap cleansers or oatmeal soaps.
 - Avoid taking very hot showers or baths; they tend to irritate the skin.
 - If a rash should develop, protect skin from sun exposure; the ultraviolet (UV) rays of the sun may exacerbate a rash.

i. Peripheral neuropathy

- Peripheral neuropathy results from damage to the nerves, which may be caused by HIV itself or be a side effect of certain drugs. Signs of peripheral neuropathy include a sensation of burning, stinging, stiffness, tickling or numbness in the feet, toes or hands.
- Look for these signs during a patient's follow-up visits and advise the patient to watch out for these signs and report them to his or her caregiver.
- Treatment of peripheral neuropathy includes stopping or decreasing the offending drug. Once there is damage to the nerves, it cannot be reversed, therefore be sure to monitor for signs of peripheral neuropathy from the start of therapy.
- Because vitamin B deficiency can contribute to peripheral neuropathy, prescribe a B-complex supplement containing thiamine (B1), riboflavin (B2), niacin, pyridoxine (B6) and cobalamin (B12). Consider giving the patient a weekly B12 injection.
- Advise the patient to:
 - Wear loose-fitting shoes, roomy cotton socks and padded slippers around the house. Good air circulation around the feet helps.
 - Keep feet uncovered in bed. Bedding that presses down on the toes can add to the problem.
 - Walk around, but not too much. Walking helps blood to circulate in the feet, but too much walking or standing can make the problem worse.

Soak feet in ice water (or the coldest water available) to reduce foot pain.

Massage the feet; this reduces foot pain temporarily.

Try ibuprofen (or the equivalent) to reduce pain and swelling.

Take vitamin B complex supplements.

If available, use L-acetyl carnitine to prevent the peripheral neuropathy related to ddI, d4T and/or hydroxyurea.

j. Menstrual problems

- Women with weakened immune systems tend to have more problems with their periods, including irregular, heavier, lighter and/or painful periods, or no menstrual bleeding at all. These problems can also be a side effect of some medications: recently, excessive bleeding has been noted with the use of ritonavir.
- Monitor for these symptoms and advise the woman to note any changes in her periods, especially when starting a new antiretroviral drug.
- Oral contraceptives may be used to regulate abnormal periods, but before prescribing them to the patient, check to see if there are any drug interactions with the antiretroviral drugs she may be taking.
- Advise the patient to:
 - Consider what else is happening in her life. For example, weight loss or stress may affect the periods as well, and addressing these issues may alleviate the menstrual problem.
 - For menstrual cramps, hold a hot water bottle or heating pad over the lower stomach or back, or take a hot bath. This will also reduce stress.
 - Do mild exercise, like walking or stretching. Exercise may increase blood flow and decrease period pain.

k. Hair loss

- Sudden or abnormal hair loss may result from taking certain medications.
- Advise the patient to:
 - Protect the hair from further damage or loss: avoid or decrease damaging hair practices or use them infrequently. These include dyeing, perming, straightening, braiding, using hair dryers and so on.
 - Stress can make hair loss worse, so taking steps to reduce stress and anxiety often helps.

SESSION 4 Case Studies: Managing Patients with Multiple Issues

PURPOSE

In this session, participants will receive two case studies of patients with multiple issues in order to apply what they have learned in Module 2 about managing patients with HIV-related diseases.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Identify the needs of the patient and give the probable cause of the patient's symptom.
2. Discuss the management and treatment for the presumptive diagnosis and any follow-up that may be indicated.
3. Discuss whether ART is appropriate for this patient, which ART regimen would be best and how the medicines can be managed to ensure adherence.
4. Discuss other clinical interventions that may be indicated.
5. Discuss the psychosocial and economic needs of the patient and any other issues that may need attention.

TIME:

2 hours

PREPARATION:

Make copies of the participant handouts for each case study.

PARTICIPANT HANDOUT: CASE STUDY 1

CASE STUDY 1: MULTIPLE ISSUES

Mrs. N is a 45-year-old widow who is a known HIV-positive patient (diagnosed in 1999). She has been coming to your health center for many years. She has three adult daughters, one of whom accompanies her today. Mrs. N complains of a chronic dry cough and intermittent headaches that are not severe. Today, Mrs. N's daughter tells us that the family wants her mother to start ART.

Medical history:

Herpes zoster in 1999

Diagnosed with TB in 2000, recurrence of active TB in December, 2002

Positive HIV test: 1999

Physical exam:

Weight: 54 kg; 12/02 59 kg

General: Fatigued

Orientation: Alert, oriented X 3

Eyes: Pale conjunctivae

Throat: White clusters on pharynx, light white coat on tongue (patient denies difficulty swallowing or pain on swallowing)

Lungs: Clear

Abdomen: Soft, no tenderness, without hepatosplenomegaly

Current medications:

Rifampicin, INH, pyrazinamide, ethambutol, cotrimoxazole. Laboratory tests ordered

Adherence: Good

Plan:

Laboratory: Complete blood count, LFTs, renal function tests, CD4

Return appointment in one week for the lab results

Question:

What other needs does this patient have that might require referral or immediate attention?

1. Is the prescribed treatment appropriate for the presumptive diagnosis?

Why?

Why not?

Continuing Case Situation

It is four days later.

Mrs. N returns to the health center with her three children, unable to talk or walk. Her daughter reports that the patient complained of worsening headaches. During the past two days, her speech and ability to ambulate have progressively decreased. She also had two episodes of vomiting. There has been no seizure activity.

Physical exam:

Clouded mentation

Aphasia

Afebrile

Left hemiparesis

Normal babinski

Laboratory findings:

RBC 3.090/mm³, Hg 9.1 gr/dl, Hct 28.6%, WBC 2.600/mm³

Liver function tests normal

Renal function tests normal

CD4 24/mm³; CD8 360/mm³.

2. What is the probable cause of the patient's symptoms?

3. What course of treatment do you recommend?

4. Is the prescribed treatment appropriate for the presumptive diagnosis?

Why?

Why not?

Continuing Case Situation

After three weeks, the patient and her children return for follow-up.

The patient is alert and oriented X 3, her speech is normal, the paresis has diminished, but she is unable to walk without assistance.

Her weight is 52 kg; Hg 9.7 gr/dl.

Her daughter reported that it was difficult to find the medications prescribed at the last visit. Folic acid was available at a nearby pharmacy, but the family had to go to a neighboring country to purchase the two other drugs. Covering the cost for a six-week supply of the three drugs (\$367.04) was also difficult, and they purchased a four-week supply with assistance from a family friend.

5. What steps can be taken to assure that the patient will obtain the needed supply of drugs and complete the initial treatment?

What about drugs for maintenance treatment?

6. Are the psychosocial and economic needs of this patient being addressed?

The patient wishes to start ART. To monitor medication adherence of patients starting on ARVs, the health center has a modified DOTS policy: during the first six weeks of treatment, the patient must take the morning dose in the presence of the facility's ART nurse. This patient, however, does not want to come to the health center each day.

7. Is starting ART appropriate for this patient at this time? Why? Why not?

8. When ARTs are started, what ARV regime would you prescribe?

9. What should be done to assure adherence?

10. What other clinical interventions are indicated for this patient at this time?

CASE STUDY 2: MULTIPLE ISSUES

A 32-year-old woman is hospitalized in a district hospital with diffuse lesions on her face, all extremities and her back. This is her second hospitalization in the past three months.

Family members, including her mother, several sisters and brothers, visit regularly. They report that the patient's husband left home two years ago and that her three-year old son died six months ago from a respiratory infection. The patient currently lives with a sister and the sister's family. The sister indicates that the patient has been getting weaker and spending more time in bed. Her appetite is poor.

Medical history:

Latent TB (1997) followed by a course of INH (adherence unknown)

Oral candidiasis (1997)

Herpes zoster (1998)

Chronic diarrhea

Lymphadenopathy

Physical exam and symptoms:

Weight: 41 kg

Previous hospitalization: 44 kg

Dysphagia

Pale conjunctivae and nail beds

Dry skin and oral mucosa

Dry cough

Diminished lung sound bilaterally

Mild hepatomegaly, no pain on palpation

Current medications:

ART (started last hospitalization): combivir and nevirapine

Cotrimoxazole

Laboratory findings:

Red blood cell count: 2.802/mm³; hemoglobin: 8.7 gr/dl; hematocrit: 26.1 percent

White blood cells: 2.300/mm³

Liver function tests: mildly elevated

Renal function tests: normal

CD4 (3 months ago): 21/mm³; current: 22/mm³

1. How would you manage this patient?

2. What referrals can you make to assist the patient and her family when she is discharged home?

Continuing Case Situation

One month after the patient's discharge home, she returns to the hospital with additional lesions, including two lesions in her mouth: one on the upper rear palate and the second on the posterior wall of the oropharynx. She reports dysphagia and odynophagia. The patient also complains of intermittent pain in the right upper abdominal area. She has lost an additional 2 kg.

She continues to take combivir, nevirapine and cotrimoxazole, but says that even when the pills are crushed, it is hard for her to swallow these drugs.

On examination, you note increased hepatomegaly, with pain on palpation of the liver. There is bilateral lower extremity 3+ pedal to midcalf edema. Laboratory test results are comparable to those of the previous hospitalization, with the exception of increased elevation of liver function tests.

You initiate chemotherapy, including: vinblastine 3.7 mg/m² IV single dose, with plans to increase weekly by 1.8 mg/m² to maximum of 5.5 mg/m² weekly.

3. Discuss the current management of this patient. What else would you offer?

Continuing Case Situation

One month has passed, and the patient remains in the district hospital. She is very weak, is unable to get out of bed and needs assistance to walk. Her family members no longer visit. They say they cannot care for her at home and that it is too difficult to see her in this condition.

The patient responds to questions appropriately but is minimally interactive. She continues to have difficulty swallowing and often refuses to eat. The nurses crush her medications and mix them with soft foods, but the patient frequently gags and is unable to swallow the mixture. The patient's abdomen is now grossly distended. She complains of increased pain in the upper right quadrant, radiating to her back.

The attending staff is considering additional diagnostic workup of the distended abdomen. Discontinuation of the ARVs and the chemotherapy is also being considered. Treatment options have not been discussed with the patient.

4. Identify the needs of this patient.

5. How would you manage this patient at this point?

6. Discuss the proposed discontinuation of ARVs and chemotherapy. What issues are involved?

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PART A: MODULE A4

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Module A5

Supporting People Living with HIV/AIDS: Palliative Care, Home-Based Care and Nutrition



Session 1: Palliative Care

In this session, participants learn about the goal and management of palliative care, including management of symptoms such as pain, fatigue, shortness of breath, nausea and vomiting, and persistent diarrhea.

Session 2: Community Home-Based Care

Participants learn about community home-based care, including the essential elements of home-based care, patient assessment in the home, care plan and setting realistic goals, adherence monitoring and follow-up.

Session 3: Nutrition

Participants learn about nutrition, including the interaction between HIV and nutrition, the clinical context of how infections influence nutritional status, the processes that lead to weight loss and wasting, the role of micronutrients, nutrition assessment, options for nutrition support programs and nutrition care and support for adults and children with HIV/AIDS.

SESSION 1 Palliative Care

PURPOSE

In this session, participants will learn about the goal and management of palliative care, including management of symptoms such as pain, fatigue, shortness of breath, nausea and vomiting and persistent diarrhea.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Discuss the meaning and goal of palliative care.
2. Discuss the management of palliative care interdisciplinary teams and identify the team composition.
3. Describe the management of the following symptoms: pain, fatigue, shortness of breath, nausea and vomiting, and persistent diarrhea.
4. Discuss the causes and assessment of pain, the barriers to its management and the WHO three-step treatment model.
5. Describe the assessment and management of other symptoms.
6. Discuss the needs for palliative care and pain management for children with HIV/AIDS.

TIME:

2 hours

A. Definition and Goals of Palliative Care

1. Introduction

In spite of recent advances in the treatment of HIV/AIDS, there is no known cure; the final outcome for every HIV-infected patient is death. Unlike other terminal diseases, it is not easy to predict when death is imminent. A patient may die as a consequence of his or her first HIV manifestation or may develop a life-threatening OI and recover if appropriate, timely treatment is given.

Most patients, however, will experience an increasing frequency of health problems and finally reach a stage of severe immunosuppression over a period of several years. As the disease progresses, the need for symptomatic relief will become more important than curative treatment.

2. Definition

- a. Palliative care is the active total care of patients and their families and friends when a patient's disease is no longer responsive to curative treatment and life expectancy is relatively short.

3. Goals of palliative care

- a. To provide support and care that makes life comfortable for patients throughout all phases of the disease so they can live as fully and comfortably as possible.
- b. The underlying principles include:
 - Management of symptoms
 - Psychosocial support
 - Teamwork and partnership
 - Appropriate ethical considerations
 - Sustaining hope with realistic goals

4. Initiating and managing palliative care

- a. The decision to stop causal treatment should be based on two criteria:
 - The patient has had a long course of progressively worsening illness (is in an advanced stage of immunodeficiency).
 - Everything possible has been done to investigate and manage the specific conditions from which the patient is suffering and, despite adequate management, the patient continues to deteriorate.
- b. Managing palliative care
 - It is essential to establish interdisciplinary teams to deal with all the problems, for no single health or social worker can adequately address HIV-related problems in all their complexity, and it is emotionally draining on staff to support persons and families affected by HIV.
 - The core of this team are the medical, nursing, counseling, social and other services working in collaboration with NGOs, the private sector, volunteers and community-based support groups.
 - Transition from active care to palliative care does not happen at a single point in time. Palliative care is most successful when initiated early in the disease process since it takes time to develop the necessary supportive relationships between the patient and the interdisciplinary team.

Continuum of Care in the Management of HIV Disease and AIDS

	Medical	Management Palliative	Care	
Stages of HIV disease	Early HIV disease (stage II)	Intermediate HIV disease (stage III)	Advanced HIV disease or AIDS (stage IV)	D
Clinical problems	Frequent infections with common pathogens	Infections with common and opportunistic pathogens	Combination of health problems (e.g., chronic diarrhea, weight loss, fever, anemia)	E
General condition	Mobile and active. Rapid response to treatment	Mostly mobile with increasing periods of illness	Patients often at home or in bed	A
Medical treatment	Curative anti-infectious treatment	Curative or causal treatment. Consider prophylaxis or maintenance treatment. Supportive treatment (skin lesions, anemia, nutrition, vitamins).	Supportive treatment (skin lesions, anemia, diarrhea, etc.). Maintain nutrition. Discontinue causative treatment and prophylaxis?	T
Palliative care	Analgesics, antipyretics. Pre- and post-test counseling. Involve family member(s) or other persons of confidence.	Analgesics, antipyretics. Follow-up counseling with family members. Address social issues. Nursing care during periods of illness.	Narcotic analgesics when needed. Continuous (home) nursing care. Terminal counseling and support.	H

B. Management of Symptoms

1. Introduction

- a. The most common symptoms are:
 - Pain
 - Fatigue/weakness
 - Shortness of breath/dyspnea
 - Persistent diarrhea
 - Difficulty sleeping/insomnia
 - Nausea and vomiting

- b. Providers may overlook these symptoms because they do not know how to manage them or feel inadequate to address them.

- c. Patients may avoid acknowledging them to providers because they believe they must “put up with them” or “it is God’s punishment.”

- d. Effective symptom management is based on a thorough understanding of the symptom and education of patient and family.
 - It requires a multidisciplinary approach
 - Goal is to help the patient move from a feeling of helplessness to a feeling of supremacy over the symptom and develop or retain as much control as possible over his or her life and illness.
 - Medication and/or nonpharmacologic interventions can manage symptoms.

- e. You can identify all symptoms by reviewing each of them: ask about its character (what it feels like), the location, what makes it worse, what makes it better, are other symptoms associated with it and how does it limit or affect the patient’s daily life.
 - Asking these questions conveys your interest in the patient.
 - Just the *act* of asking and being aware how important a symptom is to the patient provides some relief from it; a symptom often worsens when a patient has to deal with it alone and has growing fear about what is causing it.
 - A review of symptoms will also alert the provider to the appearance of new symptoms that might herald progression of disease.

2. Pain

- a. Definition:

Persistent or recurrent pain lasting more than 48 hours and not alleviated by simple comfort measures. It can be burning; tingling; flashes of pain or unremitting pain that is sharp, aching or dull.

b. Assessment of pain

- First principle in managing pain is an adequate and full assessment of the cause, bearing in mind that most patients have more than one pain and different pains have different causes.
- Take a detailed history of the pain
 - Site and radiation (where it is localized or radiating)
 - Nature (sharp, pulsating, dull, burning, stabbing, aching, squeezing)
 - Duration (continuous or intermittent, how long and how frequent)
 - Factors: Aggravating (what brings it on; what makes it worse), relieving (what reduces the pain: drugs and dosages, resting position, and the like)
 - Effect on patient’s mobility, activities of daily living and sleep
 - Intensity and severity (mild, moderate or severe)
 - Assess the intensity using a numeric pain scale (or a faces pain scale for children)

<u>0</u>	<u>5</u>	<u>10</u>
No pain	Moderate	Worst pain

Associated symptoms (nausea, difficulty swallowing, diarrhea or constipation, vomiting, fever, neck stiffness, seizures, neurological symptoms, fatigue, skin problems, anorexia, dyspnea, cognitive problems)

- Do a psychosocial assessment
 - Assess patient’s mood (depressed, anxious, angry, guilty), which will affect his or her perception of pain.
 - Take a detailed social history. Social factors (family problems, lack of care) can affect pain.
- Do a full physical and neurological examination.
- Carry out investigations and follow-up: start with simple, available, affordable tests. Monitor control of pain and adjust treatment, if necessary.

c. Types and common causes of pain

Headache	Cryptococcal meningitis TB meningitis Viral meningitis (HIV, CMV) Malaria Muscle tension headache Neurosyphilis Side effect of some medications Toxoplasmosis Dehydration Lymphoma of the brain Herpes zoster
Peripheral neuropathy	HIV Cytomegalovirus From medication Diabetes Avitaminosis Postherpetic neuralgia
Abdominal pain	Peptic ulcer Gastroenteritis Retroperitoneal adenopathy Abdominal tumors (lymphomas and Kaposi’s sarcoma) Pelvic inflammatory disease

	Abdominal abscesses Worm infestations Acute abdomen
Oropharyngeal and esophageal pain	Reflux esophagitis Candidiasis Herpes simplex Kaposi's sarcoma Tonsillitis/Pharyngitis Aphthous ulcers
Skin pain	Herpes zoster (either acute initial pain or postherpetic pain) Skin sepsis
Chest pain	Lung infections Mediastinal lesions (retrosternal adenopathy, Kaposi's sarcoma, etc.) Esophageal candidiasis
Generalized pain	Fever Bedridden status Rheumatism Nonspecific etiology

d. Barriers to pain management

- Problems related to health care providers
 - Inadequate knowledge of pain management
 - Poor assessment of pain
 - Concern about regulation of controlled substances
 - Fear of patient addiction
 - Concern about side effects of analgesics
 - Concern about patients becoming tolerant of analgesics
- Problems related to patients
 - Reluctance to report pain
 - Concern about distracting physicians from treatment of underlying disease
 - Fear that pain means disease is worse
 - Concern about not being a "good" patient

- Reluctance to take pain medications
- Fear of addiction
- Worries about unmanageable side effects
- Concern about becoming tolerant to pain medications
- Problems related to health care system
 - Low priority given to AIDS pain treatment
 - Most appropriate treatment may be too costly
 - Restrictive regulation of controlled substances
 - Problems of availability or access to it
- e. Therapeutic approaches
 - Principles of pain management:
 - For most patients, physical pain is only one of several symptoms. You should view relief of pain as part of a comprehensive pattern of care.
 - While the cause of pain is often susceptible to specific treatment, you should not delay symptomatic treatment. We recommend oral medication to encourage a patient's autonomy.
 - The later stages and terminal phase of illness require aggressive treatment of pain.
 - Regular medication is preferred over PRN medication. The goal is to prevent pain round-the-clock; addiction should not be a consideration.
 - Anticipate and prevent side effects of nausea and/or vomiting with an antiemetic.
 - Opiates can cause constipation; this may actually be a positive effect in patients who have chronic diarrhea. If they do not, give laxatives or appropriate dietary advice.
 - Inform the patient that sedation usually decreases after 3-5 days.
 - Initially, pain relief may simply allow the exhausted patient to sleep.

The WHO Three-Step Treatment Model for Pain

Drug	Dosage
Step 1: Mild pain—give nonopioids	
<ul style="list-style-type: none"> • Aspirin • Paracetamol • NSAIDs <ul style="list-style-type: none"> Ibuprofen Naproxen 	600mg q 4-6 hrs 1gm q 6-8 hrs 200-400 mg qid 250-500 mg qid
Step 2: Moderate pain—when the above drugs fail, give a weak opioid in addition to the nonopioid	
<ul style="list-style-type: none"> • Codeine 	32-65mg po q 4 hrs
Step 3: Severe pain—when the above combination is no longer effective, give a strong opioid, preferably with a nonopioid	
<ul style="list-style-type: none"> • Morphine (oral or injectable) 	Minimum 5-30 mg q 4 hrs. In severe pain, the patient might need a much larger dose, as high as 60 mg q 4 hrs, depending on the severity of the pain. Dosage should be modified according to the the patient's response , but not limited unnecessarily.
Adjuvant therapies may be used at each step for specific pain treatment.	
<ul style="list-style-type: none"> • Anticonvulsants: For pain of a nervous origin such as herpes zoster • Antidepressants For tingling or burning pains of peripheral neuropathy and nerve compression • NSAIDs For pain of inflammatory origin such as rheumatic conditions and hepatomegaly or bone pain • Anxiolitics, hypnotics • Antihistamines • Neuroleptics To reduce side effects of morphine (that is, nausea and agitation) 	Carbamazepine 200 mg tid Amitriptyline 10-25 mg at bedtime Ibuprofen 200-400 mg tid Indomethacin 25 mg tid Lorazepam 1mg at bedtime Hydroxyzine (Atarax) 25 mg tid Promethazine 10 mg at bedtime Haloperidol 1.5 mg at bedtime or 10 mg tid qid Chlorpromazine 10 mg tid qid Hydroxyzine 50-100 mg tid qid

- The use of steroids
 - You can use steroids, provided you treat any concurrent infection at the same time and give nystatin or ketaconazole to prevent/treat thrush.
 - Side effects are seen with prolonged use; use lowest effective dose.
 - If you see no benefit, withdraw steroids after 1-2 weeks.

Indication	Recommended Steroid
<ul style="list-style-type: none"> • Raised intracranial pressure • Spinal cord compression 	Dexamethasone 24 mg daily in divided doses. Reduce by 2 mg on alternative days for maintenance dose.
<ul style="list-style-type: none"> • Nerve compression 	Dexamethasone 8-16 mg qd, then reduce as above to 2 mg bid
<ul style="list-style-type: none"> • Anorexia • Severe itching • Stevens Johnson syndrome 	Dexamethasone 4-6 mg qd, then reduce to 2 mg qd

3. Fatigue or weakness

a. Definition:

Lack of energy, stamina or endurance. Chronic fatigue is present when symptoms of disproportionate tiredness, unrelated to activity or exertion, lasts for one month or more.

b. Assessment:

- Identify and define the problem: do a review of symptoms (see above).
- Take a complete history to rule out correctible causes.

c. Treatable causes of fatigue

- | | |
|---|--|
| <ul style="list-style-type: none"> • Adrenal/hormonal insufficiency • Anemia • Depression • Disease progression • End-stage organ disease • Fear of the unknown • Hypothyroidism | <ul style="list-style-type: none"> • Insomnia • Lack of exercise • Malignancy • Malnutrition • Medications • Metabolic (low kg/mg) • Occult infection (abscess/MAC) |
|---|--|

d. Management

- Treat etiological causes.
- Provide emotional support.
 - Discuss what helps the patient minimize the symptom.
 - As each possible etiological cause is addressed, remind patient to have realistic expectations and avoid having false hopes.
 - Use a positive, encouraging tone, and help patient set small goals.
- Provide spiritual and/or supportive counseling (through the interdisciplinary team).
- Provide physiotherapy of simple exercises to build strength and self-esteem.
- Palliative care could include pharmacologic treatments, using steroids in very advanced cases.

4. Shortness of breath/dyspnea

a. Definition:

Dyspnea is the uncomfortable feeling of not being able to breathe even though oxygen saturation may be normal.

b. Assessment

- Take a full history and do a full physical exam to rule out cardiovascular or pulmonary causes.
- Assess the pattern of the problem.

c. Possible causes

- Cardiovascular or pulmonary problems:
 - Infections (PCP bacterial chest infections)
 - Asthma
 - Heart failure
 - COPD
 - Pneumothorax
 - Tumor (primary, secondary, KS)
 - Superior venacaval obstruction
 - Pleural effusion
 - Anemia
- Studies have shown that dyspnea is one of the five symptoms correlated with a shortened life expectancy, even when the patient has had no demonstrable cardiovascular or pulmonary disease.

d. Management

- Do chest x-ray, PO₂ (using pulse oximeter), FBC
- Treat any underlying cause.
- Provide oxygen therapy, where available.
- Give supportive treatment as appropriate, that is, fluid replacement, temperature management, propping up the patient and fresh air.
- Give symptomatic relief using bronchodilators, diuretics, oral or nebulized morphine, as necessary.

5. Persistent diarrhea

a. Definition

Liquid stools three or more times a day, continuously or intermittently, for more than two weeks. Usually occurs at some point in the clinical course of HIV infections, and incidence/duration increases during the course of the disease.

b. Assessment

- Take a full history and do a physical exam.
- Assess level of dehydration.

Clinical Features	Moderate	Severe
General appearance/condition	Restless/irritable	Usually conscious; cold, apprehensive, sweaty, cyanotic extremities
Pulse	Rapid	Rapid, feeble, sometimes impalpable
Respiration	Deep, may be rapid	Deep and rapid
Skin elasticity	Pinch retracts slowly	Pinch retracts very slowly (>2 seconds)
Eyes	Sunken	Deeply sunken
Mucous membranes	Dry	Very dry
Urine flow	Reduced amount and dark	None passed for 6 or more hours; bladder empty

- Investigate underlying causes and carry out appropriate laboratory tests.

c. Causes of diarrhea

- Infections: parasites, bacteria, viruses, protozoa
- Malignancies such as KS or lymphoma
- Idiopathic (possibly HIV infection)

d. Management

- The first priority is fluid replacement and maintaining adequate hydration, preferably by means of oral fluids.
- Provide electrolyte supplements:
 - Oral rehydration salt solution (ORS)
 - Potassium found in oranges, bananas and other local fruits
- Treat underlying causes of diarrhea with appropriate medication.
- Give supportive treatment with antidiarrheal drugs.

6. Difficulty sleeping/insomnia

a. Definition

Insomnia and excessive daytime sleepiness are primary complaints regardless of the stage of disease. Insomnia includes difficulty falling asleep, difficulty staying asleep and early morning awakening.

b. Assessment

- Determine the pattern of the sleep problem (frequency, associated events, how long it takes to go to sleep and how long the patient can stay asleep).

- Include a full history of alcohol and caffeine intake and other factors that might affect sleep (for example, environment).
- Review current medications that patient is taking to eliminate these as possible causes.
- Take a history to rule out physical cause and/or psychosocial cause.

c. Possible causes of insomnia:

- Headache
- Bad or vivid dreams
- Problems breathing
- Chest pain/heartburn
- Abdominal pains
- Need to pass urine or move bowels
- Fever/night sweats
- Leg cramps
- Fear/anxiety
- Depression

d. Management

- Treat underlying causes, whenever possible.
- Advise patient to avoid exercise, heavy meals, alcohol or arguing just before bed.
- Plain aspirin or paracetamol in low doses may be helpful, or give short-acting hypnotics or a sedative.
- Treat underlying depression.

7. Nausea and vomiting

a. Assessment

- Take a full history including:
 - Gastrointestinal problems
 - Use of medications
- Assess pattern of the problem

b. Possible causes:

- Gastrointestinal problems, such as esophagitis, diarrhea, severe dehydration
- Must also consider medications as a cause

c. Management

- Treat underlying causes; provide rehydration if necessary.
- Adjust medications, as necessary.
- Give antiemetics such as chlorpromazine 25 mg tid or metoclopramide 10 mg tid.

C. Palliative care and pain management in children

1. Selected palliative care issues in children

- For children, as for adults, palliative care is an integral part of the spectrum of care and is not limited to the terminal stages of the illness.
- Children are often unconsciously aware of the seriousness of their condition, even if no one has discussed it with them. Many children with HIV/AIDS will not have been told their diagnosis. Families may need support in order to address the children's emotional needs.
- Several factors determine and affect the decision and experience of caring for a very ill child at home. These include:
 - Going home might look like a loss of hope.
 - No one outside the family knows the diagnosis.

- The parents themselves may be ill.
 - The family might not have access to community resources and support.
 - A reduction in the child's appetite is often very stressful to families, and they need reassurance and support in dealing with this issue.
- d. Bereavement follow-up is important for families, especially when the caregiver may be the only one aware of the child's diagnosis.

2. Selected pain management issues in children

- a. There is no evidence that the sensitivity to pain of infants and children is different from that of adults. Despite this, children are often undermedicated. We recommend using an analgesic ladder that sequences pain medications for mild to severe pain, using drugs ranging from acetaminophen, to a combination of a nonsteroidal anti-inflammatory medication plus codeine, to morphine.
- b. Principles of pain management in children (adapted from Health Canada. *A Comprehensive Guide for the Care of Persons with HIV Disease*, Module 2):
1. Prevent pain whenever possible, and treat underlying etiology.
 2. Use nonpharmacological interventions as adjunct to pain medications.
 3. Use pain assessment tools tailored to the child's communicative abilities.
 4. Be sure to administer pain medications at regular intervals, rather than on an "as needed" basis, unless the pain is truly very intermittent. Individualize doses and assess frequently to determine the need for adjustments.
 5. The goal is a dose of medication that provides pain relief with few or no side effects, with a plan for doses to treat breakthrough pain.
 6. You must achieve a balance of toxicity and analgesic effectiveness. Intramuscular administration is less desirable than oral, intravenous or rectal routes. Intramuscular injections cause pain, and drug absorption is unpredictable.
 7. You must monitor closely the variables of level of consciousness and respiratory status.
 8. If dependence has developed, we recommend tapering dosages of medicines given for more than two weeks to avoid withdrawal symptoms. Addiction in children is rare, but dependence can occur.
 9. Morphine remains an effective drug for many children with pain when given in appropriate doses.

You need to consider emotional and psychological factors in assessing the experience of disease-related pain. Factors that influence the response to pain include fear, anxiety, anger and frustration. Fostering coping mechanisms and using cognitive and behavioral techniques (for example, relaxation training, structured play and the like) are critical.

SESSION 2 Community Home-Based Care**PURPOSE**

In this session, participants will learn about community home-based care, including the essential elements of home-based care, patient assessment in the home, making the care plan and setting realistic goals, adherence monitoring and follow-up.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss the definition, objectives and types of home-based care.
2. Discuss the essential elements and principles that should be in home-based care programs.
3. Describe major factors to address when assessing potential home-based care clients and families.
4. Discuss issues of home-based care that are specific to their local situation.

TIME:

1 hour

1. Definition of community home-based care (CHBC)

CHBC provides comprehensive services in the home, including health and social services, by formal and informal caregivers. Services are aimed at promoting, restoring and maintaining a person's maximal level of comfort, function and health, and at helping with a dignified death.

CHBC includes physical, psychosocial, palliative and spiritual activities. It is a very important component of the continuum of care, which extends from the hospital, through different levels of the health and social welfare facilities, to the home.

2. Goal of CHBC

The goal of CHBC is to provide hope through good care, helping patients and families maintain their independence and have the best quality of life.

3. Models of home-based care

There are different types or models of home-based care, depending on national policy or local community situations. In determining which model is best for a given situation, you need to take into account such factors as cost, stigma, community resources, sustainability and adequacy of systems available to support CHBC.

a. Facility-based or outreach

- Usually a hospital outreach program that sends health care workers or teams out periodically to visit the homes and families of PLHA
- Often focus on addressing the nursing and medical needs, but have increasingly integrated psychosocial support

b. Community-based model

- Community-driven and owned; typically relies on volunteers who reside in the communities covered by the program
- Volunteers are trained to provide basic nursing care as well as emotional and spiritual support to the patient and family members.
- Volunteers instruct family members in caring for the patient and provide back-up support through regular visits.
- Transportation costs are minimal since volunteers live close to families.
- The challenge is to maintain and support the volunteers.

c. Integrated model

- Combination of a. and b. above. A community-based program that relies on local health facility for training, supervision and supplies for home-care kits and ensures referrals for patients back to the facility, when needed.
- Evolution into this model is a natural one in response to needs of communities, families and patients. It can yield a continuum of care through synergistic working relations and referrals (for example, communities should explore linking pharmacies with HBC services).

d. Community day care model

- Patients come to a site for a few hours during the day and get services such as symptom monitoring, drugs, recreation and counseling. This gives caregivers a respite.

4. Essential elements of home-based care

- Preventative
- Instructive
- Therapeutic
- ARV adherence support
- Rehabilitative
- Long-term maintenance
- Palliative care & pain relief

Examples of services HBC can include:

a. Provision of care

- Basic physical care
 - Recognition of symptoms
 - Treatment and symptom management

Examples: reduce fever; relieve pain; treat diarrhea and vomiting; treat skin, mouth, throat and genital problems; address general tiredness and weakness and neurophysiological symptoms
- Referral and follow-up
- Prevention for patient and caregivers, including provision of supplies such as condoms, household bleach
- Basic nursing care
 - Positioning and mobility
 - Bathing
 - Wound cleansing
 - Skin care
 - Oral hygiene
 - Adequate ventilation
 - Guidance and support for adequate nutrition

b. Palliative care—see Part A, Module 5, Session 1 on palliative care

c. Psychosocial support and counseling

Effective psychosocial support and counseling is known to improve quality of life. Caregivers, including both the family and the CHBC team, must themselves receive support if they are to support patients. Burnout is a major risk for families and HBC team members.

d. Care of affected and infected children

- In addition to the more immediate issues addressed below, this also involves advance or succession planning for surviving children and dependents.
- HIV/AIDS and other terminal illnesses have a profound effect on children's lives. Economic hardships lead to malnutrition, prostitution, the life of a street child and early marriage. Their education is often interrupted. They feel the pressure of caring for sick family members or orphaned siblings. Emotional suffering can lead to other problems, such as depression, aggression, drug abuse, insomnia and failure to thrive. Children suffering multiple losses can experience profound grief, stigma and poverty. Psychosocial support is critical and involves a continuing process of meeting their physical, emotional, social and spiritual needs.

- CHBC programs can become involved in orphan care. They can promote an environment that enables psychosocial support for vulnerable children and can help create an expanded response by families, communities, governments and faith-based and other organizations. Programs should include:
 - Information and education for patients and families
 - Training for family caregivers
 - Immediate practical support for children and families in distress (material, nutritional, financial, funeral arrangements)
 - Linkages and referral mechanisms for services such as legal support

5. Assessing the patient in the home and developing a care plan

- a. Using a holistic approach, begin with a thorough assessment that addresses, among other elements:
 - Patient and family needs and current capacity for:
 - Maintaining basic hygiene
 - Maintaining good nutrition
 - Taking comfort measures
 - Preventing transmission of infection
 - Managing symptoms
 - Taking drugs and medical measures that require physician input
 - Maintaining food and income security
 - Reaching sources of psychosocial and spiritual support
 - Getting legal support
- b. Set realistic goals
 - With the patient, family members and interdisciplinary team, establish a care plan based on the assessment above.
 - Set realistic goals based on the patient's condition, disease stage, care plan and available resources.
- c. Establish linkages between CHBC and other care and prevention programs.
 - CHBC volunteers can participate as DOTs monitors in programs that manage HIV-infected patients with TB.
 - Volunteers can also participate as monitors for ARV DOT patients.
 - CHBC programs can provide mechanisms for support in PMTCT programs, including documentation of any inadvertent negative outcomes.
 - CHBC plays a role in ART adherence for PMTCT programs or chronic ART management.

6. Selected basic principles to guide home-based care programs

- a. It is good practice to include all sectors of society, that is, communities, public and private institutions, and traditional groups.
- b. CHBC does not aim to shift the burden solely onto the community, but there should be active efforts to empower families and communities to take responsibility for their health, with the community sharing responsibility for care within that community.
- c. People living with HIV/AIDS should be integral to the planning, design, monitoring and evaluation of programs.
- d. Provide services along a continuum of care that responds to needs of the infected and affected across different stages of illness and in a variety of settings. HBC should reduce unnecessary visits and admissions to health facilities.
- e. Ideally, home-based care workers are part of a multidisciplinary team that provides access to the diverse service needs of patients and families. Where this is a luxury, as is often the case, training must help CHBC workers meet and assess their own needs, so they understand their own limitations and know where they can make needed referrals.
- f. There must be care for the caregivers: family members, community volunteers and health care workers.
- g. Raise awareness and build skills to support confidentiality about disclosing patients' HIV status to families and caregivers. Patients have a right to privacy.
- h. HBC should be an entry point to other services such as legal aid, household aid and facility-based care for patients and families. A home-based care program should ensure that children and families have access to social welfare services within their communities.
- i. Programs must address the special needs of orphans and vulnerable children.

SESSION 3 Nutrition**PURPOSE**

In this session, participants will learn about nutrition, including the interaction between HIV and nutrition, the clinical context of how infections influence nutritional status, and the processes that lead to weight loss and wasting. They will learn about the role of micronutrients, nutrition assessment, options for nutrition support programs, and nutrition care and support for adults and children with HIV/AIDS.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the interaction between HIV and nutrition.
2. Discuss the clinical context of how infectious diseases influence nutritional status, including the vicious cycle of micronutrient deficiencies and HIV pathogenesis, and the symptoms and causes of poor nutrition.
3. Describe the processes that lead to weight loss and wasting.
4. Discuss the role of vitamins and minerals in the body and list locally available sources of these nutrients.
5. Carry out a nutritional assessment for children and adults.
6. Discuss options for nutritional support programs.
7. Make recommendations for nutrition care and support for adults and children with HIV/AIDS and adapt these to their local situation.

TIME:

2 hours and 30 minutes +

A. HIV and Nutrition—the Interaction

1. Introduction

Malnutrition is a serious danger for people living with HIV/AIDS. Even at the early stages of HIV infection, when no symptoms are apparent, HIV makes demands on the body's nutritional status. The risk of malnutrition increases significantly during the course of the infection.

Good nutrition cannot cure AIDS or prevent HIV infection, but it can help to maintain and improve the nutritional status of a person with HIV/AIDS and delay progression of HIV disease, thereby improving the quality of life of PLHA. Nutritional care and support are important from the early stages of the infection to prevent the development of nutritional deficiencies. A healthy and balanced diet will help to maintain body weight and fitness. Eating well helps to maintain and improve the performance of the immune system—the body's protection against infection—and thereby helps a person to stay healthy.

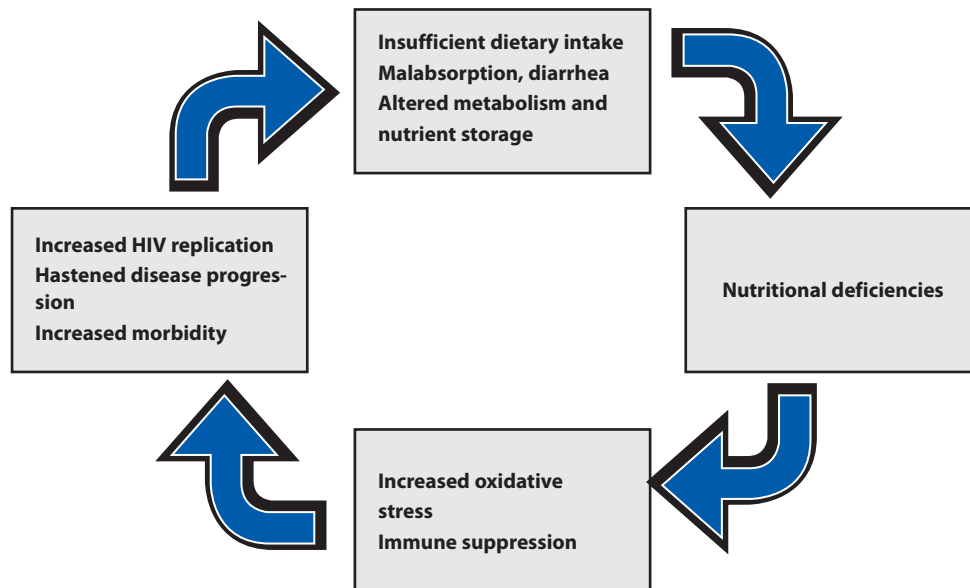
Many of the conditions associated with HIV/AIDS affect food intake, digestion and absorption, while others influence the functions of the body. Many of the symptoms of these conditions (for example, diarrhea, weight loss, sore mouth and throat, nausea or vomiting) are manageable with appropriate nutrition. Good nutrition will complement and reinforce the effect of any medication taken.

2. Malnutrition takes many forms

- a. Protein-energy malnutrition—usually measured in terms of body size
 - Common indicators in children are:
 - Low height-for-age (stunting)
 - Low weight-for-age (underweight)
 - Low weight-for-height (wasting or acute malnutrition)
 - Indicators in adults include:
 - Low body mass index (BMI)
- b. Micronutrient malnutrition—not always recognized in its mild and moderate forms; often referred to as hidden hunger
 - The most commonly reported micronutrient deficiencies in both adults and children are iron, vitamin A and iodine deficiency.
 - Deficiencies in other vitamins and minerals that are vital for the body's normal functions and for the work of the immune system are not commonly measured, but they occur frequently in populations with high infectious disease burdens and monotonous, poor-quality diets characterized by limited consumption of animal products and seasonal or periodic food insecurity.

3. The clinical context

- a. Infectious diseases, no matter how mild, influence nutritional status and almost any nutrient deficiency, if sufficiently severe, will impair resistance to disease.
- b. Infections affect nutritional status by reducing dietary intake and nutrient absorption and by increasing the utilization and excretion of protein and micronutrients as the body responds to invading pathogens.
- c. Anorexia, fever and catabolism of muscle tissue frequently accompany the acute phase response.
- d. Infections also result in the release of prooxidant cytokines and other reactive oxygen species. This leads to the increased utilization of antioxidant vitamins (vitamin E, vitamin C, beta-carotene), as well as the sequestration of several minerals (iron, zinc, selenium, manganese, copper) that are used to form antioxidant enzymes. *Oxidative stress* occurs when there is an imbalance between prooxidants and antioxidants, causing further damage to cells, proteins, and enzymes.
- e. The relationship between HIV and nutrition is complicated by the fact that the virus directly attacks and destroys the cells of the immune system.
- f. The vicious cycle of micronutrient deficiencies and HIV pathogenesis:
 - Nutritional deficiencies affect immune functions that may influence viral expression and replication, further affecting HIV disease. Oxidative stress, for example, may indirectly hasten HIV replication.
 - HIV affects the production of hormones, such as glucagons, insulin, epinephrine and cortisol, which are involved in the metabolism of carbohydrates, proteins and fats. Elevated levels of these hormones contribute to weight loss and the wasting syndrome seen in most adult AIDS patients.

Table A5, 3.1: The Vicious Cycle of Micronutrient Deficiencies and HIV Pathogenesis

g. Symptoms of malnutrition in PLHA include:

- Weight loss
- Loss of muscle tissue and subcutaneous fat
- Vitamin and mineral deficiencies
- Reduced immune competence
- Increased susceptibility to infection

h. Poor nutritional status may have multiple causes:

- Depressed appetite, poor nutrient intake and limited food availability
- Chronic infection, malabsorption, metabolic disturbances and muscle and tissue catabolism
- Fever, nausea, vomiting and diarrhea
- Depression
- Side effects from drugs used to treat HIV-related infections

4. Weight loss and wasting in HIV/AIDS

- a. To understand the relationship between nutrition and HIV/AIDS, one must consider the effect of the disease on body size and composition (weight, lean body mass, body cell mass), as well as on the functioning of the immune system. Nutrition plays a role in each area. Keep in mind that malnutrition may contribute to HIV disease progression and be a consequence of the disease.
- b. The wasting syndrome typically found in adult AIDS patients is a severe nutritional manifestation of the disease. Wasting is usually preceded by:
 - Decrease in appetite
 - Repeated infections
 - Weight fluctuations
 - Subtler changes in body composition, for example, changes in lean body mass and body cell mass, both more difficult to measure than changes in weight alone
- c. Weight loss typically follows two patterns in PLHA:
 - Slow and progressive weight loss from anorexia and gastrointestinal disturbances
 - Rapid, episodic weight loss from secondary infection
 - Even relatively small losses in weight (five percent) have been associated with decreased survival and are therefore important to monitor.
- d. Weight loss and wasting in PLHA develop as a result of three overlapping processes:
 - Reductions in food intake
 - Because of:
 - Painful sores in the mouth, pharynx and/or esophagus
 - Fatigue, depression, changes in mental state and other psychosocial factors
 - Economic factors affecting food availability and nutritional quality
 - Side effects from medications, including nausea, vomiting, metallic taste, diarrhea, abdominal cramps and anorexia
 - Nutrient malabsorption
 - Malabsorption accompanies frequent bouts of diarrhea due to *Giardia*, *cryptosporidium* and other pathogens that affect persons with compromised immune systems.
 - Some HIV-infected individuals have increased intestinal permeability and other intestinal defects, even when asymptomatic.
 - HIV infection itself may cause epithelial damage to the intestinal walls and malabsorption.
 - Malabsorption of fats and carbohydrates is common at all stages of HIV infection in adults and children.
 - Fat malabsorption, in turn, affects the absorption and utilization of fat-soluble vitamins (vitamins A, E), further compromising nutrition and immune status.
 - Metabolic alterations
 - Infection results in increased energy and protein requirements, as well as inefficient utilization and loss of nutrients.
 - During HIV infection, changes in metabolism occur from severe reductions in food intake as well as from the immune system's response to the infection. When food is restricted, the body responds by altering insulin and glucagon production, which regulate the flow of sugar and other nutrients to the intestine, blood, liver and other body tissues. Over time, the body uses up carbohydrate stores from muscle and liver tissue, and it begins to break down body protein to produce glucose. This process causes body loss and muscle wasting.

- Wasting also results from a process called cachexia. This is characterized by a significant loss of lean body mass resulting from metabolic changes during the acute phase response to infection. During this phase, the liver produces large amounts of specific proteins to bind and clear infectious agents. These proteins come, in large part, from skeletal muscle. If the response, induced by immune-system cytokines, is prolonged, muscle wasting may become severe. Cachexia also affects appetite, sleep-wake cycles and other body processes. As a result of these processes, HIV infection increases the body's protein and energy requirements to maintain weight and body composition.

Table A5, 3.2: Metabolic Alterations that Accompany Acute Infections

Protein
<ul style="list-style-type: none"> Increased urinary nitrogen loss Increased protein turnover Decreased skeletal muscle protein synthesis Increased skeletal muscle breakdown Increased hepatic protein synthesis
Lipid (fat)
<ul style="list-style-type: none"> Hypertriglyceridemia Increased hepatic de novo fatty acid synthesis Increased hepatic triglyceride esterification Increased very low-density lipoprotein production Decreased peripheral lipoprotein lipase activity Increased adipocyte triglyceride lipase
Carbohydrate
<ul style="list-style-type: none"> Hyperglycemia Insulin resistance Increased peripheral glucose utilization Increased gluconeogenesis

Source: Babameto and Kotler (1997)

5. Micronutrients: Vitamins and Minerals in HIV/AIDS

- a. Many vitamins and minerals are important to the HIV/nutrition relationship because of their critical roles in cellular differentiation, enzymatic processes, immune system reactions and other body functions.
- b. The following table summarizes the roles of different vitamins and minerals in supporting body functions and lists some of the foods that contain them.

Table A5, 3.3: The Role of Some Vitamins and Minerals in the Body and Sources of Nutrients

Nutrient	Its Role	Sources
Vitamin A	Required for maintenance of epithelial cells, mucous membranes and skin. Needed for immune system function and resistance to infections. Ensures good vision. Needed for bone growth.	Full-cream milk (when fortified), cheese, butter, red palm oil, fish oil, eggs, liver, carrots, mangoes, papaya, pumpkin, green leafy vegetables and yellow sweet potatoes
Vitamin B ₁ /Thiamine	Used in energy metabolism supports appetite and central nervous system functions.	Whole grain cereals, meat, poultry, fish, liver, milk, eggs, oil, seeds and legumes
Vitamin B ₂ /Riboflavin	Used in energy metabolism; supports normal vision, health and integrity of skin.	Milk, eggs, liver, fish, yogurt, green leaves, whole-grained cereals and legumes
Vitamin B ₃ /Niacin	Essential for energy metabolism; supports health and integrity of skin, nervous and digestive system.	Milk, eggs, meat, poultry, fish, peanuts, whole-grained cereals and unpolished rice
Vitamin B ₆	Facilitates metabolism and absorption of fats and proteins; converts tryptophan to niacin; helps make red blood cells. Some TB drugs cause B6 deficiency.	Legumes (white beans), potatoes, meats, fish, poultry, shellfish, watermelon, oil seeds, maize, avocado, broccoli and green leafy vegetables. Alcohol destroys vitamin B ₆ .
Folate (folic acid)	Required for synthesis of new cells, especially red blood cells and gastrointestinal cells.	Liver, green leafy vegetables, fish, legumes, groundnuts and oil seeds
Vitamin B ₁₂	Required for synthesis of new cells; helps to maintain nerve cells. Works together with folate.	Meat, fish, poultry, shellfish, cheese, eggs and milk
Vitamin C	Helps the body to use calcium and other nutrients to build bones and blood vessel walls. Increases non-heme iron absorption. Increases resistance to infection and acts as an antioxidant. Important for protein metabolism.	Citrus fruits such as baobab, guava, oranges and lemons; cabbage, green leaves, tomatoes, peppers, potatoes and yams. Cooking plantains and fresh milk. Vitamin C is lost when food is cut up, heated or left standing after cooking
Vitamin D	Required for mineralization of bones and teeth.	Produced by skin on exposure to sunshine; milk, butter, cheese, fatty fish, eggs and liver

Nutrient	Its Role	Sources
Vitamin E	Acts as an antioxidant. Protects cell membranes and metabolism, especially red and white blood cells. Protects vitamin A and other fats from oxidation. Facilitates resistance against diseases, particularly in lungs.	Green leafy vegetables, vegetable oils, wheat germ, whole-grain products, butter, liver, egg yolk, peanuts, milk fat, nuts and seeds
Calcium	Required for building strong bones and teeth. Important for normal heart and muscle functions, blood clotting and pressure, and immune defenses.	Milk, yogurt, cheese, green leafy vegetables, broccoli, dried fish with bones that are eaten, legumes and peas
Zinc	Important for function of many enzymes. Acts as an antioxidant. Involved with making genetic material and proteins, immune reactions, transport of vitamin A, taste perception, wound healing and sperm production.	Meats, fish, poultry, shellfish, whole grain cereals, legumes, peanuts, milk, cheese, yogurt and vegetables
Selenium	Acts as an antioxidant together with vitamin E. Prevents the impairing of heart muscles.	Meat, eggs, seafood, whole grains and plants grown in selenium-rich soil
Magnesium	Important for building strong bones and teeth, protein synthesis, muscle contraction and transmission of nerve impulses.	Nuts, legumes, whole grain cereals, dark green vegetables and seafood
Iodine	Ensures the development and proper functioning of the brain and of the nervous system. Important for growth, development and metabolism.	Seafood, iodized salt and plants grown in iodine-rich soil

Source: Piwoz & Preble, pp. 15-16

B. Nutrition Assessment

1. Elements of a nutritional assessment:

- a. Identify risk factors (see above)
- b. Determine weight gain or loss, linear growth, growth failure or body mass index (BMI)
 - Weight loss may be so gradual that it is not obvious. There are two basic ways to discover whether weight is being lost:
 - (1) Weigh the person on the same day, once a week, and keep a record of the weight and date. For an average adult, serious weight loss is indicated by a 10 percent loss of body weight or 6-7 kg in one month. If a person does not have a scale at home, it may be possible to take the weight by making an arrangement with a pharmacist, clinic or local health unit having a scale.
 - (2) When clothes become loose and no longer fit properly

- c. Do nutrition laboratory values (if available)
 - CBC
 - ESR
 - Total protein
 - Albumin (dehydration can lead to falsely elevated serum levels)
 - Prealbumin (Albumin and prealbumin assess protein status)
 - Take a dietary intake and feeding history:
 - Actual food intake by 24-hour recall or written record of three-day food intake
 - Types of foods, formulas, fluids, breast milk consumed and amounts
 - Other helpful information:
 - Length of time it takes the patient to eat
 - Appetite
 - Any chewing, sucking or swallowing problems
 - Nausea, vomiting or diarrhea
 - Abdominal pain
 - Any feeding refusal, food intolerance, allergies and/or fatigue

2. Nutrition assessment for children

- a. Assess weight gain and linear growth. WHO recommends using the National Center for Health Statistics (NCHS) growth chart.
- b. For children under the age of three, measurement of the frontal occipital head circumference is a valuable tool for assessing growth.
- c. Weight alone is a valuable tool when no other measurements are available.
- d. Growth failure is defined as:
 - Crossing two major percentile lines on the NCHS growth chart over time
 - For a child <5th percentile weight/age, failing to follow his or her own upward growth curve on the growth chart
 - Loss of five percent or more of body weight

3. Nutrition assessment for adults

- a. Formula for determining ideal body weight:
 - Male: $48 \text{ kg} + 1.07 \text{ kg/cm}$, if over 152 cm
 - Female: $45.5 \text{ kg} + 0.9 \text{ kg/cm}$, if over 152 cm
- b. BMI
Weight kg/height (meters squared)
- c. Malnutrition in an adult is defined as involuntary weight loss greater than 10 percent, weight less than 90 percent estimated ideal weight or BMI less than 20.

C. Nutritional Support [Program Options]

1. Goals of a program to provide nutrition support to PLHA may vary from prevention of nutrition depletion to the provision of palliative nutrition care and support for people with AIDS and the family members who care for them.

The overall program objectives should be to:

- a. Improve or develop better eating habits and diet
- b. Build or replenish body stores of micronutrients
- c. Prevent or stabilize weight loss
- d. Preserve (and gain) muscle mass
- e. Prevent food-borne illness
- f. Prepare for and manage AIDS-related symptoms that affect food consumption and dietary intake
- g. Provide nutritious food for AIDS-affected families living in conditions of food insecurity

2. Nutritional support should be provided in a holistic manner.

- a. When locally available, a nutritionist should be part of the HIV care team, not only to provide education and counseling, but also to assist with referrals for food support.
- b. Components of care should include:
 - Appropriate treatment of opportunistic infections
 - Stress management
 - Physical exercise
 - Emotional, psychological and spiritual counseling and support
- c. Programs that provide nutritional care and support may include:
 - Nutrition education and counseling in health facilities, in community settings or at home (to change dietary habits, to increase consumption of key foods and nutrients or to manage anorexia and other conditions that affect eating patterns)
 - Water, hygiene and food safety interventions to prevent diarrhea
 - Food-for-work programs for healthy family members affected by HIV/AIDS, including orphan caregivers
 - Food baskets for home preparation
 - Home-delivered, ready-to-eat foods for homebound patients who are unable to prepare their own meals

D. Recommendations for nutrition care and support for adults with HIV/AIDS

1. Recommendations for nutritional support of HIV-positive, asymptomatic individuals:

- a. *Promote a healthy diet that is adequate in energy, protein, fat and other essential nutrients.* This is a key component of positive living for people with HIV. Good nutrition and a healthy diet may prolong the period of time between HIV infection and the onset of opportunistic infections commonly attributed to progression of the disease. This is because of the relationship between nutritional status and immune system function/integrity, as described above in section A.3.

You should recognize that people with HIV, even if asymptomatic, may have increased body metabolism; this increases their daily energy, protein and micronutrient requirements (see section A.4). Therefore, a person with HIV requires 10-15 percent more energy and 50-100 percent more protein a day.

- HIV-positive adults (men and women) should increase their energy intakes to an additional 300 to 400 kcal per day. They should take in an additional 25-30 grams per day of protein. This can be accomplished by consuming high energy snacks 2-3 times a day, such as a cup of yogurt, dried fish or peanut butter on bread, with milk (fermented or fresh).
- They should take care to select foods that are rich in micronutrients containing antioxidants and B-vitamins. The PLHA may need to consume 2-5 times the recommended daily allowance for healthy adults in order to delay HIV progression.

They may need daily multiple vitamin-mineral supplements of these micronutrients to reverse underlying nutrition deficiencies and build nutrient stores. Caution is advised with respect to zinc and iron supplements:

- The HIV virus requires zinc for gene expression, replication and integration. PLHA may have low plasma zinc levels but higher zinc intakes may be associated with faster HIV replication and disease progression.
- Although anemia is common in PLHA, advanced HIV disease may also be characterized by increases in iron stores in bone marrow, muscle, liver and other cells. This accumulation of iron likely results from the body's attempts to withhold iron from the plasma, although other factors (like ZDV use, cigarette smoking and blood transfusions) may play a role. Increased iron stores can predispose to microbial infection and also cause oxidative stress, with implications for HIV progression.
- In summary, a healthy diet should contain a balance of:
 - Carbohydrates and fats, to produce energy and growth: rice, maize/millet porridge, barley, oats, wheat, bread, cassava, plantain, bananas, yams, potatoes and the like
 - Proteins to build and repair tissue: meat, chicken, liver, fish, eggs, milk, beans, soybeans, groundnuts and the like
 - Vitamins and minerals (found in fruits and vegetables) to protect against opportunistic infections by ensuring that the lining of skin, lungs and gut remain healthy and that the immune system functions properly

- b. *Provide nutrition counseling and support.* Develop algorithms for the nutritional management of PLHA and identify appropriate locally available foods.

- All health and support personnel who counsel and/or provide medical care for PLHA should be familiar with these algorithms and foods.
- Home-based care providers should be familiar with basic nutritional advice and practices for the patients they care for.
- These providers should also access existing local sources of social support to help address problems of household food security for families affected by HIV/AIDS.
- Nutrition counseling should include information on locally available foods and diets that will meet estimated requirements, given the individual's age, sex and physiologic state (for example, pregnancy, lactation, engaged in laborious physical activity).

- c. *Encourage people living with HIV to maintain their levels of physical activity and to exercise.* Exercise is important for preventing weight loss and wasting; it stimulates the appetite, reduces nausea, improves functioning of the digestive system, strengthens muscles, helps to relieve stress and makes the person feel more alert. Weight-bearing exercise may be helpful in building lean body mass.
- Exercise is the only way to strengthen and build up muscles. The body uses muscles to store energy and protein that the immune system can draw upon when required. Exercise is therefore especially important for maintaining the health of people with HIV/AIDS.
 - It may be that everyday activities such as cleaning, working in the field and collecting firewood and water provide enough exercise. If a person's work does not involve much exercise, PLHA should find an enjoyable exercise program that can be part of their daily life. Exercise should not be tiring or stressful; gentle muscle-building exercise is recommended. Walking, running, riding a bicycle or dancing are all suitable. People living with HIV/AIDS need to make an effort to find the exercise that they enjoy and that suits their situation.
- d. *Provide counseling on hygiene and safe food handling and preparation.* PLHA have an increased susceptibility to bacterial infections. Failure to prevent contamination can result in diarrhea, which could have spiraling nutrition and health consequences.
- Hygiene and food safety messages should include these practices:
- Always wash hands before preparing food and eating and after defecating.
 - Keep all food preparation surfaces clean, and use clean utensils to prepare and serve foods.
 - Cook food thoroughly.
 - Avoid contact between raw foodstuffs and cooked foods.
 - Serve food immediately after preparation, and avoid storing cooked foods unless they can be kept in a refrigerator or a cool place. Do not store them for more than one or two days, and always reheat them at a high temperature.
 - Wash fruits and vegetables before serving.
 - Use safe water that is boiled or filtered.
 - Use clean cups and bowls, and use cups rather than bottles for feeding babies.
 - Protect foods from insects, rodents and other animals.
 - Store nonperishable foodstuffs in a safe place (separate from pesticides, disinfecting agents and other toxic chemicals).
- e. *Encourage PLHA to seek immediate attention for any digestive and health-related problems to prevent further nutritional and physical deterioration.*

2. Recommendations for nutritional support for HIV-positive individuals experiencing weight loss:

- a. *Ascertain circumstances that may have led to weight loss.* Most early weight loss associated with HIV/AIDS occurs episodically and results from depressed appetite during secondary infections.
- b. *Identify and treat any underlying infections early.* This includes any secondary infections, such as mouth sores, skin infections, cough, fever, diarrhea, tuberculosis and oral KS.
- c. *Provide specific advice on how to maintain intake during these periods.* For example, advise the person to take more frequent meals and snacks and to eat well-liked foods.
- d. *Increase intake to promote nutritional recovery following periods of appetite loss, fever or acute diarrhea.* Follow the recommendations in section D. 1, above.
- e. *Minimize the nutritional impact of infection.* See the table below for advice on managing common conditions.
- f. *Advise all PLHA to avoid unhealthy lifestyles.* This includes:
 - Alcohol consumption, tobacco and drug use, which may affect many nutritional processes.
 - Unsafe sexual practices, which increase risk of reinfection or coinfection with HIV and other STDs.

Table A5, 3.4: Practical Suggestions: How to Maximize Food Intake During and Following Common HIV/AIDS-Related Infections

Symptom	Suggested strategy
Fever and Loss of Appetite	Drink high-energy, high-protein liquids and fruit juice. Eat small portions of soft, preferred foods with a pleasing aroma and texture throughout the day. Eat nutritious snacks, whenever possible. Drink liquids often.
Sore Mouth and Throat	Avoid citrus fruits, tomatoes and spicy foods. Avoid sweet foods. Drink high-energy, high-protein liquids with a straw. Eat foods at room temperature or cooler. Eat thick, smooth foods, such as pudding, porridge, mashed potato, mashed carrots or other non-acidic vegetables and fruits.

Table A5, 3.4 (cont.)

Symptom	Suggested strategy
Nausea and Vomiting	<p>Eat small snacks throughout the day, and avoid large meals.</p> <p>Eat crackers, toast and other plain, dry foods.</p> <p>Avoid foods that have a strong aroma.</p> <p>Drink diluted fruit juices, other liquids and soup.</p> <p>Eat simple boiled foods, such as porridge, potato and beans.</p>
Loose Bowels	<p>Eat bananas, mashed fruits, soft rice and porridge.</p> <p>Eat smaller meals more often.</p> <p>Eliminate dairy products to see if they are the cause.</p> <p>Decrease high-fat foods.</p> <p>Don't eat foods with insoluble fiber (roughage).</p> <p>Drink liquids often.</p>
Fat Malabsorption	<p>Eliminate oils, butter, margarine and foods that contain or were prepared with them.</p> <p>Eat only lean meats.</p> <p>Eat fruits and vegetables and other low-fat foods.</p>
Severe Diarrhea	<p>Drink liquids frequently.</p> <p>Drink oral rehydration solution.</p> <p>Drink diluted juices.</p> <p>Eat bananas, mashed fruits, soft and rice porridge.</p>
Fatigue, Lethargy	<p>Have someone precook foods to avoid energy and time spent in preparation (care with reheating).</p> <p>Eat fresh fruits that don't require preparation.</p> <p>Eat snack foods throughout the day.</p> <p>Drink high-energy, high-protein liquids.</p> <p>Set aside time each day for eating.</p>

Adapted from Woods (1999)

1. Recommendations for nutritional support for people with AIDS

- a. *Mitigate the nutritional consequences of the disease at this stage and preserve functional independence, whenever possible.* Give consideration to the nutritional consequences of various drugs that AIDS patients may be taking.
- b. *Take the following points into consideration:*
 - Preservation of lean body mass remains important at this stage; maintain earlier recommendations about energy and protein consumption as long and as often as possible.
 - During periods of nausea and vomiting, people with AIDS should try to eat small snacks throughout the day and avoid foods with strong or unpleasant aromas. They should maintain fluid intake to avoid dehydration.
 - To minimize gastrointestinal discomfort, gas and bloating, consume foods that are low in insoluble fiber and low in fat. If there is lactose intolerance, avoid milk and dairy products. Caregivers should try to identify fermented foods (for example, sour milk, porridge or yogurt) or nondairy, high-protein foods that are easy to prepare and consume. Avoid spicy foods.
 - During diarrhea, ensure that fluid intake is maintained (30 ml/kg body weight per day for adults and somewhat more for children). Patients should continue eating and drinking, whenever possible. Give oral rehydration solutions to avoid life-threatening dehydration.
 - People with mouth and throat sores should avoid hot and spicy or very sweet foods, as well as caffeine and alcohol. Encourage patients to eat preferred foods that are softened, mashed or liquefied, if necessary.
 - For patients with depressed appetites or lack of interest in eating, caregivers should try to increase dietary intake by offering small portions of food several times a day. Set specific eating times; try to find ways to make eating times pleasant and supportive.
 - Treat all infections that affect appetite, ability to eat and nutrient retention immediately.
 - Avoid tobacco products.
 - Follow the guidelines above (section D.1.d) for hygiene and food safety.
- c. *Be sure to address the nutritional consequences of any medications given.* Several medications for treating opportunistic infections may have drug-nutrient interactions or side effects like nausea and vomiting. For example:
 - Administer Vitamin B6 with isoniazid therapy for TB to avoid Vitamin B6 deficiency.
 - Do not give iron and zinc-containing supplements with ciprofloxacin (take at least two hours apart). Many antiretroviral drugs have dietary requirements (for example, to be taken on an empty or full stomach), and most have side effects such as nausea, vomiting, abdominal pain and diarrhea, which must be managed nutritionally. Some drugs, such as ZDV, affect red blood cell production and increase the risk of anemia.

Table A5, 3.5: HIV Medication and Food Interactions

Antiretroviral Medication and Usual Adult Daily Dosage	Food Effect	Dietary Recommendations	Dosage Form
NRTI			
Zidovudine (Retrovir-AZT-ZDV), Glaxo Wellcome, 300 mg bid	Administration of zidovudine capsules with food decreased peak plasma concentration by >50 percent; however, AUC may not be affected; or AUC decreased by 25 percent after meal. Avoid alcohol.	Take on empty stomach, if possible. If this is not possible because of GI side effects, recommend taking with low-fat meal.	300 mg tablet; 100 mg capsule; 50 mg/5 mL syrup
Lamivudine (epivir-3TC), Glaxo Wellcome, 150 mg bid or 300 mg q.d.	Food has little effect on the extent of absorption. Avoid alcohol.	Can be taken without regard to meals. If taken with meals, may decrease GI side effects.	150 mg tablet; 10 mg/ml oral solution
Zidovudine- lamivudine (Combivir, AZT-3TC), Glaxo Wellcome, 1 tablet bid	Administration of zidovudine capsules with food decreased peak plasma concentration by >50 percent; however, AUC may not be affected; or AUC decreased by 25 percent after meal. Avoid alcohol.	Take on empty stomach, if possible. If this is not possible because of GI side effects, recommend taking with low-fat meal.	300 mg AZT and 150 mg 3TC per tablet
Abacavir (Ziagen-ABC), Glaxo Wellcome, 300 mg bid	There was no significant difference in systemic exposure (AUC) in the fed and fasted states. Alcohol increased AUC by 41 percent. Avoid alcohol.	Can be taken without regard to meals.	300 mg tablet; 20 mg/ml oral solution
Zidovudine-lamivudine-abacavir (Trizivir,AZT-3TC-ABC), Glaxo Wellcome, 1 tablet bid	Administration of zidovudine capsules with food decreased peak plasma concentration by >50 percent; however, AUC may not be affected; or AUC decreased by 25 percent after meal. Alcohol increased AUC of ABC by 41 percent.	Take on empty stomach, if possible. If this is not possible because of GI side effects, recommend taking with low-fat meal. Avoid alcohol.	300 mg AZT and 150 mg 3TC and 300 mg ABC per tablet
Didanosine (Videx EC-ddI), Bristol Myers Squibb, 400 mg tablets qd for >60 kg and 250 mg tablets qd for <60 kg	Food decreases absorption. Administration with food results in approximately 55 percent decrease in AUC. Avoid alcohol as it exacerbates toxicity. Avoid antacids containing magnesium and aluminum.	Take on empty stomach, at least 30 min before or 2 h after a meal. Take only with water.	25, 50, 100, 150, 200 mg chewable/buffered tablets; 100,167, 250 mg/packet buffered powder for oral solution; 2 or 4 g/bottle of pediatric powder or oral solution; 125, 200, 250, 400 mg enteric-coated ddl
Stavudine (zerit-d4T), Bristol Myers Squibb, 40 mg bid for >60 kg 30 mg bid for <60 kg	Food has little effect on absorption. Avoid alcohol.	Can be taken without regard to meals.	15, 20, 30, 40 mg capsule, 1 mg/ml oral solution
Tenofovir (Viread), Gilead Sciences, 300 mg qd	Administration with high-fat meal increased AUC by 40 percent. If taking didanosine, must take tenofovir 2 h before or 1 h after didanosine.	Take with food.	300 mg tablets
Zalcitabine (Hivid-ddC), Roche Laboratories, 0.75 mg q8h	Administration with food decreases AUC by 14 percent (not clinically significant). Do not take antacids containing magnesium and aluminum at the same time as medication. Avoid alcohol. Do not take with metoclopramide (decreases AUC by 10 percent).	Can be taken without regard to meals.	0.375, 0.750 mg tablets

Table A5, 3.5 (cont.)

Antiretroviral Medication and Usual Adult Daily Dosage	Food Effect	Dietary Recommendations	Dosage Form
NNRTI			
Delavirdine (Rescriptor-DLV), Pharmacia and Upjohn, 400 mg tid	Concentrations similar in fasting and fed states in steady-state dosing. Medications such as antacids containing aluminum and magnesium and didanosine should be taken at least 1 h after; they can decrease absorption. Avoid St. John's wort (<i>Hypericum perforatum</i>), alcohol.	Can be taken without regard to meals.	100, 200 mg tablets
Efavirenz (Sustiva-EFV), Dupont Merck, 600 mg/d	Low-fat meal improves tolerability. High-fat meal increased bioavailability by 50 percent. Take in the evening or bedtime to minimize side effects. Alcohol may increase side effects. Avoid St. John's wort.	Can be taken without regard to meals; however, avoid high-fat meal.	50, 100, 200 mg capsules; 600 mg tablets
Nevirapine (Viramune-NVP), Roxane, 200 mg/d for 14 d, then 200 mg bid	Absorption not affected by food, antacids or didanosine. Avoid St. John's wort, alcohol.	Can be taken without regard to meals.	200 mg tablet, 50 mg/teaspoon oral suspension
PROTEASE INHIBITOR			
Amprenavir (Agenerase-APV), Glaxo Wellcome, 1200 mg bid	Take with or without food. If taken with food, avoid high-fat meal (>67 g fat), as high-fat decreases absorption (decreases C _{max} and AUC). Avoid grapefruit juice. Increase fluid intake. Avoid extra vitamin E supplements (872 IU vitamin E /1200 mg amprenavir). Avoid St. John's wort. Do not take antacids within 1 h of this medicine.	Can be taken without regard to meals; however, avoid high-fat meal.	50, 150 mg soft-gel capsules (109 IU vitamin E/150 mg capsule) a 15 mg/ml oral solution (14 percent less bioavailable than capsules, thus doses not equivalent to capsules)
Indinavir (Crixivan-IDV), Merck, 800 mg q8h	Administration with high-fat, high-protein meal decreased serum concentrations by 84 percent and decreased AUC by 77 percent. It can be taken with a nonfat snack. Avoid grapefruit juice. Drink an additional 48 ounces of liquid daily to avoid kidney problems. Avoid St. John's wort. Ritonavir-indinavir combination (400 mg q12h each) significantly increases the drug level of indinavir and eliminates the need to fast.	Take on empty stomach at least 1 h before or 2 h after a meal or with a low/non-fat meal (juice, skim milk, etc.). Take 1 h before or after ddl as buffer impairs IDV absorption.	200, 333, 400 mg capsules
Saquinavir (soft-gel capsule) (Fortovase-SQVsgc), Roche Laboratories, 1200 mg tid	Administration with food (i.e., fatty meal) increases AUC 670 percent. Store capsules in refrigerator. Avoid alcohol, St. John's wort.	Take with meal or up to 2 h after a full meal.	200 mg soft-gel capsule

Table A5, 3.5 (cont.)

Antiretroviral Medication and Usual Adult Daily Dosage	Food Effect	Dietary Recommendations	Dosage Form
PROTEASE INHIBITOR			
Saquinavir (hard-gel capsule) (Invirase-SQV), Roche Laboratories, 600 mg tid	Administration with food (i.e., fatty meal) increases AUC 200 percent. Taking with grapefruit juice will also increase absorption by 40 percent - 100 percent because of inhibition of gut CYP3A4. Avoid alcohol, St. John's wort.	Take with meal or up to 2 h after a full meal with high calories and high-fat foods for better absorption.	200 mg hard-gel capsules
Lopinavir-ritonavir(Kaletra, LPV-RTV), Abbott, 3 capsules bid	Take with high-fat food for better absorption. Store the capsules in the refrigerator. Avoid St. John's wort.	Take with meals, especially with high fat content.	133.3 mg LPV and 33.3 mg RTV per soft-gel capsule, 80 mg LPV and 20 mg RTV per mL oral solution
Ritonavir (Norvir-RTV), Abbott, 600 mg bid	Extent of absorption of ritonavir from the soft-gel capsule formulation was 13 percent - 15 percent higher when administered with a meal. Store capsules in refrigerator. Avoid St. John's	Take with meals, if possible. Mix oral solution with chocolate milk or oral supplements to improve taste.	100 mg soft-gel capsules, 80 mg/ml oral solution
Nelfinavir (Viracept-NLF), Agouron, 750 mg tid or 1250 mg bid	Plasma concentrations and AUC were 23-fold higher under fed versus fasting conditions. Increase fluid intake. Lactose-free dairy products or lactase may be needed to minimize diarrhea. Avoid acidic food or liquid. Avoid St. John's wort.	Take with a meal or light snack that includes a high-protein food to increase absorption and to decrease GI side effects.	250 mg tablet, 50 mg/g (1 level scoop) oral powder (or 200 mg per teaspoon of powder. Note: Oral powder contains aspartame, not for children with phenylketonuria.

Source: Nerad et al. (2003). General Nutrition Management in HIV. *Clin Infect Dis* 36:S52-S62.

NOTE: AUC, area under the concentration-time curve (the total amount of drug absorbed is reduced when the AUC is decreased); GI, gastrointestinal; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor. Dosages for protease inhibitors are listed at nonboosted amounts. Ritonavir is often given in combination with other protease inhibitors, and the dosages are different. Refer to a physician with HIV expertise. Recommended daily intake for adults for vitamin E is 30 IU.

- d. *Consider overall nutrition support for PLHA in situations of food insecurity and secure basic foods for families where possible.* However, use caution in giving food donations. If you give food aid, take care to:
- Ensure that these foods complement rather than replace foods normally consumed by the patient.
 - Be aware of the food and nutritional situation of the patient's family. A food ration is likely to be shared or handed over completely to other family members, including children.
 - Provide food supplements of sufficient size to meet the needs of the HIV/AIDS patient and his or her dependents, if resources permit.
 - Counsel the patient and caregivers on how to prepare and offer the supplement to maximize food safety and appropriate consumption by the person with HIV/AIDS.

E. Recommendations for nutrition care and support for children with HIV/AIDS

1. *Provide well-baby care and monitor growth of all children born to HIV-infected mothers.* This is especially important for babies who are not being breast fed and for those who have been weaned early. Failure to gain weight may be a sign of HIV-infection or could reflect inadequate feeding practices.
2. *Follow the same nutritional recommendations as for all young children.* But remember to take into consideration the increased nutritional requirements that accompany an HIV-infection and the increased likelihood of fat and other nutrient malabsorption.
3. *Feed young children patiently and persistently, with supervision and love.* This is especially true of HIV-infected children; they may be frequently ill and suffering from fever, mouth and throat sores, and depressed appetite.
4. *Introduce solid foods gradually to match the age and developmental characteristics of the child.* First foods should be soft and enriched with energy sources (for example, oil, peanut butter, sugar and the like). Give small portions (200-250 ml) frequently (at least three times a day) because the child's stomach is small. Increase the portions as the child gets older. Most children can eat all the foods of an adult diet by the time they are one year old (except very spicy foods) as long as the food is cut up, mashed or ground to prevent choking.
5. *Ensure that the young child's diet contains as much variety as possible to increase the intake of essential vitamins and minerals.* Caregivers should feed children a variety of locally available fruits and vegetables, animal products and fortified foods, if they are available. Provide nutritious snacks between meals to increase consumption. Give daily multivitamin supplements, if available, to help prevent nutritional deficiencies.
6. *Follow the same recommendations offered to adults for safe and hygienic practices and for feeding during and following acute infections* (see section D.1.d). Follow the nutritional management of specific symptoms and conditions as adults. (See Table in section D.2.)
7. *Take the following guidelines into consideration:*
 - a. Monitor body weight, height, arm circumference and triceps skin fold regularly.
 - b. Review the child's diet at every well-child and sick-child health visit. Discuss conditions affecting appetite and food intake and treat, as appropriate. Give advice on how to improve the child's diet, taking into consideration the child's age, local resources and the family's circumstances.
 - c. Provide immunizations and give prophylactic vitamin A supplements, according to local guidelines.
 - d. Promptly treat all secondary infections, such as tuberculosis, oral thrush, persistent diarrhea and pneumonia. Minimize the impact of these infections by maintaining food and fluid intake to the degree possible and by increasing intake after the acute symptoms have subsided.
 - e. Many HIV-infected children are likely to become severely malnourished. Follow the local guidelines for managing severe malnutrition. Consider enteral or parenteral nutrition, when available, if the child is unable to eat.

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PART A: MODULE A5

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Part B:

Antiretroviral Therapy

Module B1

Managing Patients on Antiretroviral Therapy



Session 1: The Goal and Basic Principles of ART

In this brief introductory session, participants learn about the goal of antiretroviral therapy (ART), management considerations and WHO guidance on scaling up ARV therapies in resource-constrained settings.

Session 2: When to Start ART

Participants learn about the current thinking on why, how and when to start antiretroviral therapy. They discuss the clinical evaluation, lab tests for initiation and monitoring purposes and WHO's recommendations for initiating ART in adults using the WHO Clinical Staging System.

Session 3: Antiretroviral Drug Mechanisms

Participants learn about the drug mechanisms of the major antiretrovirals, including how and when to take them, their form and dosage and how to store them.

Session 4: Drug Interactions and Adverse Drug Reactions: Side Effects and Toxicities

Participants learn about drug interactions and adverse drug reactions (ADRs), as well as side effects, dosing schedules, formulations, toxicity risks and monitoring guidelines for the major antiretrovirals.

Session 5: Recommended First-Line Regimens in Adults

Participants learn about approved antiretroviral agents and WHO-recommended first-line antiretroviral regimens.

Session 6: Patient Follow-up and Monitoring ART

Participants learn about clinical and laboratory monitoring of patients on ART. This session addresses clinical, laboratory and efficacy monitoring; schedules for monitoring; and measures of toxicity and effectiveness.

Session 7: Drug Adherence and Strategies for Compliance

Participants learn about the issues involved in promoting antiretroviral drug adherence.

Session 8: Why and When to Change Therapy

Participants learn about drug resistance, reasons for changing an ART regimen and which second-line regimens to use.

SESSION 1 | The Goal and Basic Principles of ART

PURPOSE

In this brief introductory session, participants will learn about the goal of antiretroviral therapy (ART), management considerations and WHO guidance on scaling up antiretroviral (ARV) therapies in resource-constrained settings.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the goal of ART.
2. List key considerations in the management of chronic HIV illnesses in resource-constrained settings.
3. Briefly describe the overall effects of HIV/AIDS and the effect of ART on the incidence of tuberculosis (TB) in South Africa.
4. Discuss the vast collateral benefits of ART, the obstacles for ART programs in resource-poor countries and the prerequisites for scaling up.
5. Discuss the prerequisites for scaling up, the pros and cons of antiretroviral therapy and what comprises optimal antiretroviral therapy.

TIME:

30 minutes

RESOURCES:

Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach. Geneva: WHO. June 2002.

Planning the incorporation of antiretroviral therapy into comprehensive care programs, pp. 52-60 in: *Improving Access to Care in Developing Countries: Lessons from Practice, Research, Resources and Partnerships.* France: UNAIDS/WHO/Ministry of Foreign Affairs. July 2002.

Module 3. ARV Treatments: Planning and Integration into Health Services, in: *Guidance Modules of Antiretroviral Treatments.* WHO/ASD/98.7. Geneva: WHO/UNAIDS. 1987.

1. The goal of highly active antiretroviral therapy (HAART) is to:

- a. Prolong and improve the quality of life for PLHA
- b. Reduce the viral load as much as possible, for as long as possible, in order to halt disease progression and prevent or reduce resistant variants
- c. Achieve immune reconstitution that is quantitative (CD4 count in normal range) and qualitative (pathogen-specific immune response)
- d. Reduce mother-to-child transmission

2. Management of chronic HIV illnesses in resource-constrained settings: key considerations and WHO guidance

- a. The pros and cons of standardized versus individualized diagnosis, treatment and follow-up
- b. Factors determining readiness of patient and clinician to start and continue a long-term relationship for managing HIV with ART
- c. Guidance by WHO and national policies and strategies: what it is and what it is not
- d. Provide an antiretroviral regimen that not only achieves reduction in viral loads, but also:
 - Maintains alternative options in the event of treatment failure AND
 - Is relatively free of side effects AND
 - Is tailored to individual needs for adherence

3. The effect of HIV/AIDS

- a. On life expectancy in Africa
- b. New AIDS cases in Western Europe

4. Effect of ART on the incidence of TB in South Africa

- a. ART reduced the incidence of HIV-associated TB by more than 80 percent

5. Vast collateral benefits of ART

- a. Increases voluntary testing and counseling uptake
- b. Increases awareness of HIV
- c. Increases motivation of health care workers
- d. Increases access to health facilities
- e. Decreases expenses for palliative and OI care
- f. Decreases number of orphans
- g. Keeps households and businesses intact
- h. Has potential to enhance prevention
 - Behavioral: access to prevention education during care encounters
 - Biological: decreased transmission because of lowered viral load

6. Obstacles for ART programs in resource-poor countries

- a. Lack of resources
- b. Procurement of affordable drugs
- c. Available drug supply
- d. Lack of infrastructure
- e. Complicated laboratory monitoring
- f. Lack of trained doctors and nurses
- g. Rapid staff turnover
- h. Stigma

7. Prerequisites for scaling up

- a. Adequate infrastructure
- b. Minimal lab support
- c. Access to OI/symptomatic treatment
- d. Continuous supply of a minimum of ARVs
- e. Patient ready and trained
- f. Physicians and team ready and trained
- g. ARV treatment guidelines in place
- h. Political will to sustain program

8. WHO ARV guidelines

- a. To support and facilitate better management of PLHA using ARV therapy
- b. To standardize and simplify ARV regimens
- c. To scale up ARV treatment programs
- d. To provide scientific evidence for ARV treatment programs

9. Antiretroviral treatment

- a. Advantages: efficacy
- b. Disadvantages:
 - Durability
 - Toxicity
 - Adverse effects
 - Drug interactions
 - Cost

10. Optimal antiretroviral therapy

- a. Prolongs and improves quality of life
- b. Reduces viral load, little risk for resistance
- c. Achieves immune reconstitution
- d. Preserves future therapeutic options
- e. Free of side effects
- f. Tailored to individual needs for adherence
- g. Inexpensive

SESSION 2 When to Start ART in Adults**PURPOSE**

Participants will learn about the current thinking on why, how and when to start antiretroviral therapy. They will discuss the clinical evaluation, lab tests for initiation and monitoring purposes and WHO's recommendations for initiating ART in adults using the WHO Clinical Staging System.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss the rationale and timing for ART initiation, including the pros and cons of different approaches to this issue.
2. Describe the objectives of the clinical evaluation for ART.
3. Discuss the WHO clinical classification system and its use in deciding when to initiate ART.

TIME:

45 minutes

1. Rationale and timing of ARV initiation

- a. Typical course of HIV infection and progression of AIDS to death, with and without ART
Refer to PowerPoint slide “Average Progression Without Treatment”
Refer to PowerPoint slide “Impact of Treatment on Viral Load and CD4”
- b. When and how to start ARV therapy
 - A patient needs ART only when he or she is symptomatic and/or there is evidence of significant immune system damage
 - Do *not* start ART if:
 - The patient is not motivated
 - You have not provided intensive counseling
 - Treatment cannot be continued
 - Patient is asymptomatic and there is no information about CD4 count
 - No biological monitoring is possible
 - There is no access to diagnosis and treatment of OIs
 - *It is a time of acute opportunistic infection (including TB)*
 - There is poor renal/hepatic function
 - Patient has terminal incurable disease, for example, cerebral lymphoma
 - How to start:
 - Use the simplest, cheapest and most effective three-drug combination as the first-line therapy
 - Then select the next one or two combinations as the second-line therapy

2. Objectives of clinical evaluation before the start of ART

- a. Conduct a clinical evaluation to:
 - Establish presence of HIV infection by means of:
 - History and physical exam
 - Voluntary counseling and testing (results from patient seeking a test while not hospitalized or seeking clinical care)
 - Counseling and testing for diagnostic purposes
 - Establish status of the HIV disease, for example, whether OIs are present
 - Discuss and decide the need for ARV therapy
 - Determine when to start and what to use
 - Discuss adherence and other issues
- b. Obtain basic laboratory support and establish baseline laboratory test results
 - Absolute minimum tests: HIV test, hemoglobin or hematocrit level
 - Basic tests: WBC count, liver function tests (LFTs) and renal function tests (RFTs), blood sugar, lymphocyte count
 - Desirable tests: CD4, amylase, bilirubin, lipids
 - Optional: viral load

- c. Do a baseline clinical assessment and prepare the patient
- Baseline medical history
 - Psychosocial history:
 - Essential demographic characteristics
 - Family economic status
 - Family coping
 - Length of time since diagnosis of HIV infection, current medications and symptoms
 - Past medical history including major illnesses (for example, TB), hospitalizations, surgeries, past medications and allergies
 - For women, pregnancy history (gravida), current or planned pregnancy and access to contraceptive services
 - Review of systems (respiratory, cardiac, neurological, genitourinary and so on)
 - Baseline physical exam:
 - Vital signs
 - Weight
 - Physical exam, documenting abnormalities
 - Eyes: fundoscopic exam, if possible
 - Oropharynx
 - Lymph nodes
 - Lungs
 - Heart
 - Abdomen
 - Extremities
 - Nervous system
 - Genital tract

3. WHO clinical classification system and its use in deciding to start ART

a. Overview of the WHO clinical classification system

Stage I:	Asymptomatic, persistent generalized lymphadenopathy
Stage II:	Weight loss <10 percent, prurigo, fungal nail infection, herpes zoster, recurrent URTIs
Stage III:	Weight loss > 10 percent, chronic diarrhea or fever, oral candidiasis, pulmonary TB, severe bacterial infections
Stage IV:	AIDS defining illnesses: for example, HIV wasting syndrome, PCP, brain toxoplasmosis, candida esophagitis, extrapulmonary TB, CMV retinitis, Kaposi's sarcoma, nonHodgkins lymphoma, and/or performance score 4: bedridden >50 percent of the day during the last month

b. Adults: When to start ART

- WHO stage IV disease (clinical AIDS) irrespective of CD4 cell count (CD4 cell count irrelevant)
- WHO stages I, II, or stage III HIV disease with a CD4 cell count <200/mm³
- WHO stages II or stage III HIV disease + lymphocyte count <1200/mm³

See Table 1 below, Recommendations for Initiating ART in Adults and Adolescents with Documented HIV Infection.

Recommendations for Initiating Antiretroviral Therapy in Adults and Adolescents with Documented HIV Infection

Laboratory Axis
<p>If CD4 testing is available:</p> <ul style="list-style-type: none"> • WHO stage IV irrespective of CD4 cell count • WHO stage I, II or III³ with CD4 cell counts ≤ 200/mm³⁻¹
<p>If CD4 testing is not available:</p> <ul style="list-style-type: none"> • WHO stage IV irrespective of TLC • WHO stage II or III^c with TLC ≤ 1000-1200/mm³⁻²

1. The precise CD4 level above 200/mm³ at which to start ARV treatment has not been established, but the presence of symptoms and the rate of CD4 cell decline (if measurement is available) should be factored into decision-making. A CD4 level of 200/mm³ corresponds to a CD4 percentage of approximately 15 percent.
2. A total lymphocyte count below 1200/mm³ can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, asymptomatic HIV-infected patients (WHO stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.
3. Treatment is also recommended for patients with advanced WHO stage III disease, including recurrent or persistent oral thrush and recurrent invasive bacterial infections, irrespective of the CD4 cell count or the total lymphocyte count.

c. Children: When to start ART (See Module 2, Session 3 for more details)

is not considered essential to start therapy.

- <18 months: Stage III or stages I & II disease + CD4 <20 percent
- For children >18 months: Stage III or stages I & II disease + CD4 <15 percent. An assessment of viral load is not considered essential to start therapy.

4. The WHO Clinical Staging System

- a. The WHO Staging System includes a clinical classification system and a laboratory classification to categorize the immunosuppression of adults by their *total* lymphocyte counts.
- b. This staging system has been proven reliable for predicting morbidity and mortality in infected adults.
- c. The WHO Clinical Staging System is based on clinical markers believed to have prognostic significance resulting in four categories. It helps to incorporate a patient performance scale into the system.

Clinical Stage I

1. Asymptomatic infection
2. Persistent generalized lymphadenopathy (PGL)

Performance scale I: asymptomatic, normal activity

Clinical Stage II

3. Weight loss, <10 percent of body weight
4. Minor mucocutaneous manifestations (for example, seborrheic dermatitis, prurigo, fungal nail infections, oropharyngeal ulcerations, angular cheilitis)
5. Herpes zoster, within the last five years
6. Recurrent upper respiratory tract infections (for example, bacterial sinusitis)

Performance scale II: symptomatic, normal activity

Clinical Stage III

7. Weight loss, >10 percent of body weight
8. Unexplained chronic diarrhea, > 1 month
9. Unexplained prolonged fever (intermittent or constant) >1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis within the past year
13. Severe bacterial infections (for example, pneumonia, pyomyositis)

Performance scale III: bedridden <50 percent of the day during the last month

Clinical Stage IV

14. HIV wasting syndrome, as defined by the Centers for Disease Control
15. *Pneumocystis carinii* pneumonia (PCP)
16. *Toxoplasma* of the brain
17. Cryptosporidiosis with diarrhea >1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegaloviral disease of an organ other than the liver, spleen or lymph node
20. Herpes simplex virus infection, mucocutaneous (>1 month) or visceral (any duration)
21. Progressive multifocal leukoencephalopathy (PML)

- 22. Any disseminated endemic mycosis (for example, histoplasmosis, coccidioidomycosis)
- 23. Candidiasis of the esophagus, trachea, bronchi and lungs
- 24. Atypical mycobacteriosis, disseminated
- 25. Nontyphoid Salmonella septicemia
- 26. Extrapulmonary tuberculosis
- 27. Lymphoma
- 28. Kaposi’s sarcoma (KS)
- 29. HIV encephalopathy, as defined by the Centers for Disease Control

Performance scale IV: bedridden >50 percent of the day during the last month

d. WHO Improved Clinical Staging System

A further refinement of the WHO clinical staging system includes a laboratory axis. The laboratory axis subdivides each category into three strata (A, B, C) depending on the number of CD4 cells. If this is not available, you can use total lymphocytes as an alternative marker.

Laboratory Axis		Clinical Axis			
Lymphocytes*	CD4**	Stage I Asymptomatic PGL	Stage II Early HIV	Stage III Intermediate (ARC)***	Stage IV Late AIDS
A >2000	>500	1A	2A	3A	4A
B 1000-2000	200-500	1B	2B	3B	4B
C <1000	<200	1C	2C	3C	4C

* Reference range total lymphocytes: 1500-4000/mm³

** Reference range CD4 count: 450-1400/mm³

*** ARC: AIDS-related complex

Grey area refers to progression to AIDS

Note: The reference values used for lymphocytes and CD4 count are based on data available from the developed world. There are indications that Africans may have a physiologically higher lymphocyte count. Projects with laboratory equipment to conduct lymphocyte counts in HIV patients should, if possible, collect data about lymphocyte counts and CD4 counts and correlate them with the disease stage.

SESSION 3 Antiretroviral Drug Mechanisms**PURPOSE**

Participants learn about the drug mechanisms of the major antiretrovirals, including how and when to take them, their form and dosage and how to store them.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe how the different classes of ARVs work.
2. Describe dosages and administration of ARVs.
3. Discuss storage and availability in country.
4. Discuss pros and cons and availability of generic drugs in country.

TIME:

1 hour

PREPARATION:

Visual aid for Step 3: Obtain samples of the ARV drugs available locally to show to participants.

1. Antiretroviral therapies: Mode of action

- a. Antiretroviral drugs (ARVs) act on HIV by interfering with its reproductive cycle. The main stages of the cycle where these drugs act to inhibit replication of the virus are:
- Inhibit reverse transcriptase enzyme to interrupt the production of proviral DNA. ARVs prevent formation of proviral DNA. NRTI and NNRTI act here.
 - Inhibit maturation of virion by interrupting the protein processing and virus assembly. During this stage protease enzymes are required, and protease inhibitors act here.
- b. Nucleoside reverse transcriptase inhibitors (NsRTIs):
- Lead to premature termination of the production of the HIV DNA chain
 - Are active against both HIV 1 and 2
 - Resistance develops rapidly if given as single drugs alone (monotherapy)
 - Do not use the following drugs together:

AZT	+	d4T
ddI	+	ddC
d4T	+	ddC
ddC	+	3TC

Also, the combination of ddI and Indinavir is difficult for patients.

Nucleoside reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
AZT (ZDV)	Zidovudine	Retrovir®	300 mg	2 x 1/d
ddl	Didanosine	Videx® Videx® EC	100 mg 250/400 mg	4 /d 1 /d
ddC	Zalcitabine	Hivid®	0.75 mg	3 x 1 /d
d4T	Stavudine	Zerit®	30/40 mg	2 x 1 /d
3TC	Lamivudine	Epivir®	150 mg	2 x 1 /d
AZT + 3TC	Zidovudine + Lamivudine	Combivir®		2 x 1 /d
ABC	Abacavir	Ziagen®	300 mg	2 x 1 /d
AZT+3TC+ABC	Zidovudine + Lamivudine + Abacavir	Trizivir®		2 x 1 /d

Note: Adapt ARV dose for the following according to body weight:

- Didanosine (Videx®)
 - > 60 kg 400 mg once daily
 - < 60 kg 250 mg once daily
 - Stavudine (Zerit®)
 - > 60 kg 40 mg bid
 - < 60 kg 30 mg bid
- c. Nonnucleoside reverse transcriptase inhibitors (NNRTIs):
- NNRTIs do not work in HIV-2 and HIV-1 group O infection.
 - Delavirdine and nevirapine are antagonistic in action on the HIV reverse transcriptase activity. Do not, therefore, use them together.
 - Interaction with some drugs occurs because of induction and/or inhibition of cytochrome P450 enzymes.

Nucleoside reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
NVP	Nevirapine	Viramune®	200 mg	1/d x 14d then 2/d
EFZ	Efavirenz	Stocrin® Sustiva®	200 mg	3 /d
DLV	Delavirdine	Rescriptor®	200 mg	Two tabs 3x a day

d. Protease inhibitors (PIs)

- HIV protease enzyme is responsible for cleaving various polyproteins in the process of producing mature infectious virions. PIs interfere with the production of HIV protease enzyme; this leads to a reduction of the virus in the body that is sometimes sufficient to lead to undetectable levels of virus.
- Rapid resistance will develop if PIs are used as single agents.
- PIs are associated with multiple drug interactions because of their inhibition of cytochrome P450 enzymes. For example, PIs increase the metabolism of rifampicin and decrease its effectiveness in treating TB.
- Take indinavir with plenty of water to prevent kidney stones.
- If a patient develops diabetes during PI treatment, it is best to stop the PIs if there is another alternative.

Nucleoside reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
IDV	Indinavir	Crixivan®	200/400 mg	3 x 2/d
RTV	Ritonavir	Norvir®	100 mg	2 x 6/d
NFV	Nelfinavir	Viracept®	250 mg	3 x 3/d or 2 x 5/d
SQV	Saquinavir HG	Invirase®	200 mg	3 x 6/d
	Saquinavir SG	Fortovase®	200 mg	2 x 8/d
APV	Amprenavir	Agenerase®	150 mg	2 x 3/d
LPV/RTV	Lopinavir/Ritonavir	Kaletra®	400/100 mg	1 x 2/d

e. Nucleotide Reverse Transcriptase Inhibitor (NRTI)

- Tenofovir disoproxil fumarate (TDF)
 - First nucleotide RTI with durable activity against some nucleoside-resistant strains of HIV with significant HIV RNA reductions
 - Favorable safety profile
 - If available, add TDF either to d4T/ddI or to ABC/ddI or substitute for either d4T or ABC in these combinations.
 - When ddI is given with TDF, reduce the dosage of ddI and give the ddI with food.
 - A possible side effect is Fanconi syndrome.
 - You may use tenofovir and/or nevirapine cases of high cholesterol and triglyceride levels.
 - Currently restricted availability in resource-limited settings

Nucleoside reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
TDF	Tenofovir	Viread®	300 mg	Once daily

2. Administration and storage of ARVs:

- a. Take on an empty stomach—1h before or 2h after a meal
 - Didanosine
 - Indinavir (except if given with ritonavir)
- b. Take with food
 - Nelfinavir, ritonavir, lopinavir, saquinavir
 - Tenofovir
 - ddI, when given with tenofovir
- c. Take with or without food
 - ZDV, D4T
 - Nevirapine
 - Efavirenz, but avoid high fat food
- d. Administer crixivan with liquids, with or without a light meal, one hour before or two hours after a regular meal.
- e. Storage of ARVs in the refrigerator
 - Ritonavir
 - ddI suspension
 - d4T solution
 - Lopinavir/ritonavir capsules and solution
- f. Storage of ARVs in glass jars
 - ZDV syrup
 - d4T syrup

3. Discussion on the use of generic antiretrovirals

- a. Overview: Generic antiretrovirals are now being produced in India, Brazil, Argentina and Thailand using ingredients produced largely by Indian companies. These companies often provide ingredients to the pharmaceutical companies that make branded antiretrovirals.

Thailand and Brazil have promised to assist several African countries in making generic versions of ARVs.

China, Vietnam and Indonesia also have pharmaceutical companies that have announced their intention to produce and supply these drugs.

In theory, generic antiretrovirals are attractive because their price is often much lower than the lowest price offered by the manufacturer of the branded equivalent. While there continue to be arguments about how much of an obstacle patents pose to treatment access, there is substantial evidence that countries that make their own generic versions of drugs are also able to secure better prices for branded versions.

Some have argued that patents are not a serious barrier to treatment access because relatively few drugs are patented in the countries with the most PLHA and the least access to drugs. Thus, the major factor limiting access would be political will and commitment on the part of national governments and international funders.

Médecins Sans Frontières has compared the effectiveness of three strategies for reducing prices across six countries (Senegal, Honduras, Cameroon, Uganda, Brazil and Thailand). The organization found that countries that allowed generic competition, and especially those with local generic manufacture, had substantially lower prices for affected drugs than countries that got drugs exclusively from proprietary drug companies.

In Brazil, generic drugs have been a key factor in controlling the cost of ARV treatment. There was a 43 percent reduction in the cost of triple drug combinations (including a PI or NNRTI) from 1997 to 2000, and a 34 percent reduction of quadruple drug combinations (using ritonavir-boosted PIs). Through the period, the number of patients on treatment in Brazil has increased in a linear fashion by 1,400 per month; the average individual cost was US\$13.3 per day in 2002.

b. Concerns

Quality control: Generic producers must carry out biological equivalence studies in healthy volunteers to show that their product has a pharmacokinetic profile equivalent to the branded product. So far, little information is available about the bioequivalence studies that Indian manufacturers have conducted, although it is reported that Cipla has carried out studies on eight antiretrovirals: Ranbaxy on seven and Hetero on five drugs or combinations of drugs. Any license application will include a review of this bioequivalence data as a requirement for use of the drugs outside India.

Before the World Health Organization lists antiretrovirals, WHO officials must inspect the manufacturing processes. Generic producers should also receive a certificate of Good Manufacturing Practice to show that their equipment and procedures meet minimum industry standards.

The International Dispensary Association, the world's largest nonprofit supplier of essential medicines to resource-limited countries, is inspecting Indian antiretroviral manufacturing during 2002.

Manufacturing issues: Generic producers must take a finished product and try to trace back how it was made. Each step, or chemical reaction, could lead to impurities or loss of efficacy. With some drugs, notably the nucleoside analogues AZT (zidovudine) and d4T (stavudine), the process of reverse engineering is relatively simple; but for others, such as 3TC (lamivudine), nevirapine and efavirenz, the process is tricky. Protease inhibitors take more time to make because they involve many more stages than nucleoside analogues. So far, Indian manufacturers have been unable to bring the cost of their generic protease inhibitors down below the cost price of the manufacturer of the branded product.

SESSION 4 Drug Interactions and Adverse Drug Reactions: Side Effects and Toxicities**PURPOSE**

In this session, the participants will learn about drug interactions and adverse drug reactions (ADRs), as well as side effects, dosing schedules, formulations, toxicity risks and monitoring guidelines for the major ARVs.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the important drug interactions among various ARVs and discuss the significance of these interactions.
2. List various toxicities and common side effects of each drug.
3. Discuss monitoring and management of toxicities and side effects.
4. Describe class adverse drug reactions, including class-specific and ARV-specific adverse effects of ART.

TIME:

2 hours

REFERENCE:

For further information and details on drug interactions and adverse drug reactions: side effects and toxicities, refer to: WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*. Annexes 11A & B, pp. 128-141.

1. Antiretroviral drug interactions

a. Introduction

Pharmacokinetic interactions occur when one drug alters the serum or tissue concentration of another by changing its absorption, distribution, metabolism or elimination. Such interactions can result in clinically significant changes in drug concentration; this may require modifying the dose of one or more drugs or may necessitate the use of an alternative drug or drugs.

b. Changes in drug absorption

- Alterations of gastric pH

If a drug changes the gastric pH, it can affect the absorption and hence the concentration of other drugs that have specific pH requirements for absorption.

For example, ddI requires a higher gastric pH for optimal absorption and is administered with an antacid buffer that raises the gastric pH. Thus, ddI decreases the absorption of drugs whose absorption requires low gastric pH, such as ketoconazole, itraconazole, tetracycline, quinolone antibiotics, IDV and LPV/r. If coadministration occurs, give these drugs two hours apart from ddI.

- Presence or absence of food

Food can enhance or decrease the bioavailability of a drug, often because of its effect on gastric acidity. Therefore, you should administer some drugs, such as ddI and IDV, one hour before or two hours after eating.

Additionally, the bioavailability of lipid-soluble drugs, such as efavirenz, may be enhanced when administered with a high-fat meal.

- Chelation

The binding of two drugs or compounds to form insoluble complexes that cannot be absorbed can change the absorption of a drug.

For example, chelation, with calcium in milk products, or with cations such as those of aluminum, magnesium, iron or zinc found in antacids or multivitamins significantly decrease the absorption of the fluoroquinolone drugs.

c. Changes in distribution

- Protein-binding

Things that alter the protein-binding of a drug affect the amount of free drug that is available to produce the necessary therapeutic effect.

For example, warfarin is 99 percent protein-bound and, if given with other protein-bound drugs such as EFZ, can be displaced from its protein sites. This places the patient at risk for bleeding and requires monitoring of the prothrombin time.

- Hypoalbuminemia

Patients with low albumin levels can experience an increased therapeutic effect and/or risk for toxicity of drugs that are highly protein-bound, such as warfarin or phenytoin.

2. Changes in metabolism

- Metabolism in the liver cytochrome P450 system

The induction or inhibition of various P450 enzymes by one drug can significantly alter the serum concentration of another drug that is metabolized by the same P450 enzyme.

The PIs and NNRTIs are primarily metabolized by the same P450 CYP3A4 isoenzyme and can inhibit or induce this isoenzyme, resulting in increases or decreases in concentration of concomitantly administered drugs. Moreover, other drugs that inhibit or induce this isoenzyme can bring about increases and decreases in the concentration of concomitantly administered PIs and/or NNRTIs. Each PI and NNRTI has a different drug interaction profile, depending primarily on its potency as an inducer or inhibitor of CYP3A4 and/or other P450 enzymes.

- Ritonavir is the most potent CYP3A4 inhibitor and consequently has the largest amount of drug interactions and contraindications.
- NVP is a CYP3A4 inducer.
- EFZ is both an inducer and inhibitor of CYP3A4.
- Rifampicin is a potent inducer of hepatic metabolism and significantly decreases the concentration of PIs to subtherapeutic levels.

NFV, RTV and the NNRTIs can significantly decrease the estrogen levels in contraceptives. Consequently, women taking these drugs cannot rely on oral contraceptives and should use another or an additional method of contraception.

PIs and EFZ can raise the serum concentration of cisapride and of nonsedating antihistamines (astemizole, terfenadine), which can lead to cardiotoxicity. They can also increase the serum concentration benzodiazepines, and this can result in prolonged sedation. Therefore, do not administer PIs and these other drugs concomitantly.

e. Changes in elimination

- Kidney function

The inhibition of the tubular secretion of one drug by another that is eliminated by the kidney can result in changes in drug concentration.

For example, probenecid can increase levels of ZDV.

3. Summary

- Do not combine indinavir (crixivan[®]) and nelfinavir (viracept[®]) with:
Rifampin (rifadin[®])
Terfenadine (triludan[®])
Astemizole (hismanal[®])
Cisapride (cyprid[®], prepulsid[®])
- Interactions with ritonavir

Do not use ritonavir with:		Possible Alternatives	
Generic Name	Brand Name	Generic Name	Brand Name
Piroxican	Feldene [®]	Aspirin	
Auriodarone	Cordarone [®]		
Artemizole	Hismanal [®]	Loratidine	Claritin [®]
Terfenadine	Triludan [®]		
Cisapride	Prepulsid [®]		
Alprazolam	Xanax [®]	Temazepam	Euhypnos [®]
Chlorazepate	Tranxene [®]	Lorazepam	Temesta [®]
Diazepam	Valium [®]		
Midazolam	Dormicum [®]		
Triazolam	Halcion [®]		

- Protease inhibitors and antituberculous treatment

	Rifampicin	Rifabutin
Saquinavir	Mixed Case (NO)*	NO
Indinavir	NO	1/2 dose
Ritonavir	NO	NO
Nelfinavir	NO	1/2 dose

*can be given when boosted with ritonavir

- Adapt ARV dose because of drug interactions. (See tables below for further information.)

Nevirapine 400 mg/d (no change)
 Indinavir 3 x 1000 mg/q 8h

Efavirenz 600 mg/d (no change)
 Indinavir 3 x 1000 mg/q 8h

Nevirapine 400 mg/d (no change)
 Lopinavir/ritonavir 2 x 500/100 mg/bid

- The tables below summarize drug interactions between NNRTIs and PIs and relevant drug interactions involving NNRTIs and PIs.

Table B1, 4.1: Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Nevirapine	No effect on NVP EFZ AUC decreased 22 percent Recommendation: Standard dosing	NVP increased twofold IDV decreased 28 percent Recommendation: Change IDV dose to 1000 mg three times daily No change NVP	No effect on NVP LPV trough decreased 55 percent Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change NVP	No effect on NVP NFV levels increased 10 percent Recommendation: Standard dosing	No effect on NVP SQV decreased 25 percent Recommendation: Standard dosing	
Efavirenz		No effect on EFZ IDV decreased 31 percent Recommendation: Change IDV dose to 1000 mg three times daily No change EFZ	No effect on EFZ LVP AUC decreased 40 percent Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change EFZ	No effect on EFZ NFV increased 20 percent Recommendation: Standard dosing	EFZ decreased 12 percent SQV decreased 62 percent Recommendation: Do not coadminister (SQV/r boosting may be possible)	
Indinavir			No effect on LPV IDV AUC and trough increased Recommendation: Change IDV dose to 600 mg twice daily No change LPV	NFV increased 80 percent IDV increased 50 percent Recommendation: Limited data for IDV 1200 mg twice daily with NFV 1250 mg twice daily	SQV increased fourfold to sevenfold No effect on IDV Recommendation: Insufficient data to provide recommendation	
Lopinavir				No data	SQV AUC/trough increased Recommendation: SQV 800 mg twice daily No change LPV/r	
Nelfinavir					SQV increased twofold to fivefold NFV increased 20 percent Recommendation: Fortovase 1200 mg twice daily No change NFV	

Source: *Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach*. Geneva: WHO, 2002, pp. 112-113.

B1, 4.1 (cont.)

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antifungal						
Ketoconazole	NVP increased 15-30 percent Ketoconazole decreased 63 percent Recommendation: Do not coadminister	No data	IDV increased 68 percent Recommendation: Change IDV to 600 mg three times daily	LPV decreased 13 percent Ketoconazole increased threefold Recommendation: None	No dose adjustment	SQV increased threefold Recommendation: Standard dosing
Antimycobacterials						
Rifampin	NVP decreased 37 percent Recommendation: Use with caution only if no alternatives available	EFZ decreased 25-33 percent Recommendation: Consider EFZ 800 mg daily	IDV decreased 89 percent Recommendation: Do not coadminister	LPV AUC decreased 75 percent Recommendation: Do not coadminister	NFV decreased 82 percent Recommendation: Do not coadminister	SQV decreased 84 percent when given without RTV Recommendation: If using SQV/RTV rifampin can be used at 600 mg/day or two or three times weekly
Rifabutin	NVP decreased 16 percent Recommendation: Standard dosing	EFZ unchanged Rifabutin decreased 35 percent Recommendation: Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFZ no change	IDV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); IDV dose change to 1000 mg three times daily	Rifabutin AUC increased threefold Recommendation: Decrease rifabutin dose to 150 mg daily; LPV/r no change	NFV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); NFV dose increase to 1000 mg three times daily	SQV decreased 40 percent (RTV increases rifabutin levels fourfold) Recommendation: If using SQV/RTV, use rifabutin 150 mg two or three times weekly
Clarithromycin	NVP increased 26 percent Clarithromycin decreased 30 percent Recommendation: Standard dosing	EFZ unchanged Clarithromycin decreased 39 percent Recommendation: Do not coadminister	Clarithromycin increased 53 percent Recommendation: Standard dosing	No data	No data	Clarithromycin increased 45 percent SQV increased 177 percent Recommendation: Standard dosing

B1, 4.1 (cont.)

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (L.PV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antimycobacterials						
Oral contraceptives	Estradiol decreased 20 percent Recommendation: Use alternative or additional methods	Estradiol increased 37 percent; no data on other components Recommendation: Use alternative or additional methods	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods	Estradiol decreased 42 percent Recommendation: Use alternative or additional methods	Estradiol decreased 47 percent; norethindrone decreased 18 percent Recommendation: Use alternative or additional methods	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods
Methadone	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	No change, but there may be a decrease if given with low-dose RTV Recommendation: When IDV is given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose	Methadone AUC decreased 53 percent Recommendation: Opioid withdrawal possible; may require increase in methadone dose	May decrease methadone levels Recommendation: Opioid withdrawal possible; may require increase in methadone dose	No data but may decrease if given with low-dose RTV Recommendation: When given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose
Anticonvulsant						
Phenobarbital	Unknown	Unknown		Unknown, but may decrease LPV levels substantially Recommendation: Monitor anticonvulsant levels	Unknown, but may decrease NFV levels substantially Recommendation: Monitor anticonvulsant levels	Unknown, but may decrease SQV levels substantially Recommendation: Monitor anticonvulsant levels
Lipid-lowering agents: Simvastatin Lovastatin Atorastatin	No data	No data	Potential for large increase in statin levels (except pravastatin) Recommendation: Do not coadminister except pravastatin; no dose adjustment	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister

Drug Name	Side Effects and Toxicity (toxins are italicized)	How to Monitor
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Nucleotide reverse transcriptase inhibitors (NtRTIs)		
Protease inhibitors (PIs)		

4. Common side effects and toxicities, and how to monitor

Drug Name	Side Effects and Toxicity (toxicities are italicized)	How to Monitor
Nucleoside reverse transcriptase inhibitors (NsRTIs)		
ZDV, AZT	• GI intolerance, asthenia, headache, <i>anemia, leukopenia</i>	• Full blood count
ddI	• GI intolerance: <i>pancreatitis, peripheral neuropathy, lactic acidosis</i>	• Foot pain, paresthesias, deep tendon reflexes, abdominal pain
d4T	• <i>Peripheral neuropathy, pancreatitis, lactic acidosis</i>	• Foot pain, paresthesias, deep tendon reflexes
3TC	• Generally well tolerated: <i>lactic acidosis</i>	
ABC	• Hypersensitivity reaction (HSR)— symptoms of fever, rash, GI, respiratory problems, <i>lactic acidosis</i>	• Educate patient on signs and symptoms of HSR and what to do; check history for prior reaction.
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)		
TDF		• Liver function tests (LFTs)
Nonnucleotide Reverse Transcriptase Inhibitors (NNtRTIs)		
NVP	• <i>Extensive rash, fulminant hepatitis</i>	• Liver function tests q 2 wks x 2, then q mo x 12, then q 3 mo.
EFX	• CNS— <i>dissociated state x 2 to 3 weeks</i> ; rash Avoid pregnancy	• Liver function tests
Protease Inhibitors (PIs)		
SQV • Fortovase (FTV) • Invirase (INV)	• <i>GI intolerance, lipodystrophy</i>	• Liver function tests • Lipid profile
RTV	• <i>GI intolerance, paresthesias, hepatitis, lipodystrophy</i>	• Liver function tests • Lipid profile
IDV	• GI intolerance, <i>nephrolithiasis</i> , benign increase in bilirubin, lipodystrophy	• Lipid profile • Liver function tests • UA
NFV	• <i>Diarrhea, lipodystrophy</i>	• Liver function tests • Lipid profile
LPV/r	• <i>GI intolerance (esp. diarrhea), asthenia, lipodystrophy</i>	• Liver function tests • Lipid profile

5. Class adverse drug reactions (ADRs)

- a. Lipodystrophy: fat distribution
 - Diagnosis
 - Fat accumulation: abdomen, dorsal neck, (*buffalo hump*), breasts
 - Fat atrophy: Extremities, buccal fat, buttocks
 - Measurement
 - Waist-hip ratio >0.85 (women) or >0.95 (men)
 - Patient perception
 - Intervention
 - Results with changing therapy, including use of different classes, are inconclusive

- b. Hyperlipidemia
 - Evaluation
 - Baseline for patient at risk for cardiovascular disease and prior to ART
 - Triglycerides
 - Normal levels: <150 mg/dl
 - Elevated levels: 200-499 mg/dl
 - Very high levels requiring immediate intervention to prevent pancreatitis and reduce risk of cardiovascular disease: >500 mg/dl
 - Drug selection
 - ACTG expert panel recommendations for statins with concurrent PI or NNRTI: Atorvastatin or Pravastatin
 - Therapeutic switch
 - PIs, and possibly NNRTI agents, appear to be associated with increases in blood lipids, including cholesterol, LDL cholesterol, and triglycerides. Use of nonPI-containing regimens may reverse these changes. Changing from PI-based regimens to an NRTI/NNRTI regimen may improve lipid profile.

- c. Diabetes
 - Risk is associated with the use of all drugs classified as PIs
 - Frequency: 3-17 percent of diabetic patients on PIs have a reaction that occurs at median of 60 days
 - Cause: Peripheral insulin resistance
 - Monitoring: Fasting blood glucose at pre-ART baseline; some recommend fasting blood sugar at 3 to 4 month intervals for the first year of PI therapy; subsequent measurements based on baseline measurements and risks
 - Treatment: Insulin sensitizers (metformin or glitazones) preferred over insulin or sulfonylureas, based on mechanism of diabetes; most do not recommend changes in ART unless there is severe diabetes

- d. Mitochondrial toxicity: lactic acidosis ± steatosis
 - Rate: 1.3 per 1,000 patient years
 - Risk: Prolonged NRTI use, obesity, female sex, pregnancy, d4T > AZT, ddI > ABC, 3TC

- Symptoms: Fatigue, nausea, vomiting, wasting, abdominal pain, dyspnea, diarrhea, anorexia, weakness, myalgias, paresthesias, hepatomegaly. May cause respiratory failure requiring ventilator therapy.

	2DV	3TC	d4T	ddC	ddl
Neuropathy			++	++	++
Myopathy	++				
Cardiomyopathy	+			+	+
Pancreatitis		++	+		++
Hepatitis	+	+	+		
Lactic acidosis	+	+/-	+		+
Bone marrow depression	++	+/-		+	+

- Lab: Lactic acid—obtain without tourniquet, fist-clenching or stasis; use prechilled fluoride-oxalate tubes
Transport on ice for processing within four hours.
<2 mmol/mL: normal
2-5 mmol/mL: d/c NRTI, if symptomatic (after ruling out other cause of symptoms; at this low level may be something else)
>5 mmol/mL: d/c NRTI
>10 mmol/mL: potentially lethal
 - Other lab: Variable ↑ CPK, LDH, lipase, amylase, ALT4 anion gap, ↓ HCO₃, CT scan or echo—fatty liver; liver biopsy—steatosis
 - Management: Discontinue NRTI, or switch to NRTI with reduced frequency of lactic acidosis (ABC, AZT, tenofovir). NRTI-sparing regimens with established efficacy: LPV/RTV, EFV/IDV ± RTV, SQV/RTV, APV/RTV/EFV
 - Recovery: Mean time to normal lactic acid levels after stopping NRTIs is 50 days
- e. Hepatotoxicity
- Definition: ALT or AST elevation to 3-4 x the upper limits of normal that is not otherwise explained
 - Frequency with ART: 2 percent to 18 percent
 - Mechanism: NRTI—mitochondrial toxicity; PI and NRTI—unclear; liver biopsy usually not helpful
 - Agents: All retroviral agents, especially RTV and NVP.
Note: NVP-associated hepatitis usually occurs in the first 12 weeks of therapy; may be asymptomatic and in rare cases may progress to hepatic necrosis and death. Monitor ALT levels.
With PIs the hepatotoxicity may occur at any time during treatment; stop the implicated drug when the ALT is 5 x the upper limits of normal.
 - Risk: chronic hepatitis (HCV, HBV), d4T use, alcoholism and increased baseline transaminase levels. With HCV or HBV coinfection, the increased ALT may result from immune reconstitution rather than drug toxicity.
 - Dose modification (decrease dose) with hepatic failure (any cause): AZT, all PIs, all NRTIs
- f. Osteoporosis
- Risk: Osteopenia in 25-50 percent of ART recipients; osteoporosis in 5-10 percent
 - Routine screening: Not indicated
 - Treatment: Increase intake of calcium and vitamin D, plus weight bearing exercises
- g. Avascular necrosis
- Rate: 0.3 percent to 1.3 percent
 - Risks: ETOH abuse, hyperlipidemia, steroid use, hypercoagulability, hemoglobinopathy; relationship with ART is unclear

- Diagnosis: MRI or CT scan
- Most frequent sites: femoral head, shoulder

h. Rash

- Most common with NNRTIs: NVP, DLV, EFV; frequency—10 percent to 20 percent
Most are cutaneous and can be treated with antihistamines.
Severe or life threatening reactions include Stevens-Johnson syndrome and DRESS (drug rash, eosinophilia and systemic symptoms with fever, and multiple organ involvement).
- Indications to D/C NNRTI: Symptoms of DRESS or rash with fever, desquamation, mucous membrane involvement, blistering or arthritis (1 percent to 2 percent)
- Safety of alternative NNRTIs: Unknown; chemical structures of NNRTIs are very different and limited experience shows that a switch from NVP to EFV for rash is safe
- PI most likely to cause rash: APV—22 percent (sulfonamide)
- NRTI most likely to cause rash: ABC

i. Summary

- ARVs : Potential problems in tropical countries
AZT (retrovir®): Be careful if anemia, for example, caused by HIV, malaria, ankylostomiasis, malnutrition, cotrimoxazole, hydroxyurea
ddI (videx®) d4T (zerit®): Be careful if polyneuritis, caused by HIV, isoniazid, dapson, vitamin deficiency, ethylism, diabetes
- NRTIs: Adverse effects

AZT (zidovudine)	Retrovir®	Anemia Neutropenia Nausea Myopathy Headache
3TC (lamivudine)	Epivir®	Neutropenia Polyneuritis
ddl (didanosine)	Videx®	Pancreatitis, polyneuritis
ddC (zalcitabine)	Hivid®	Pancreatitis Polyneuritis Oral ulcerations
d4T (stavudine)	Zerit®	Pancreatitis Polyneuritis
ABACAVIR	Ziagen®	Rash, fever Shock Nausea

- NNRTIs: adverse effects

Nevirapine	Viramune®	Rash Hepatotoxicity
Efavirenz	Sustiva® Stocrin®	Neuropsychiatric disorders Sleep abnormalities Dizziness Rash

- Protease inhibitors: adverse effects

Indinavir	Crixivan®	Nephrolithiasis Arthralgias, paronychia, Dry skin, hair loss ↑ bilirubin
Ritonavir	Norvir®	Diarrhea Nausea Oral paresthesia
Saquinavir	Invirase® Fortovase®	Diarrhea
Nelfinavir	Viracept®	Diarrhea

- Long-term adverse effects of protease inhibitors
 - Hepatitis
 - ↑ Cholesterol
 - ↑ Triglycerides
 - Diabetes
 - Lipodystrophy (60-65 percent of patients)
 - Sexual dysfunction?
 - Atherosclerosis? Coronary insufficiency?

- ART adverse effects

	Class specific	ARV specific
NRTI	Mitochondrial toxicity (lactate acidosis, lipoatrophy?)	Nail pigmentation (ZDV) Hypersensitivity (abacavir)
NNRTI	Rash	CNS dysfunction (efavirenz) Severe hepatitis (nevirapine)
PI	Metabolic abnormalities Lipodystrophy Bleeding in hemophiliacs	Nephrolithiasis (indinavir) Diarrhea (nelfinavir, ritonavir, lopinavir) Rash (amprenavir)

4. Management of side effects: See PowerPoint slides for algorithms on management of:

- ZDV-associated anaemia
- Didanosine-associated pancreatitis
- Nevirapine-associated rash
- Stavudine-associated polyneuropathy
- Efavirenz-associated rash
- Indinavir-associated nephrotoxicity
- Efavirenz-associated CNS effects
- Nelfinavir/ritonavir associated diarrhea:
 - Loperamide, calcium carbonate (500mg bid), psilium
 - Dietary advice: good fluid intake; food that may worsen diarrhea: coffee, alcohol, spicy food, high fat food, lactose rich food
 - Take into account patients' experience.
- Adequate hydration is essential to healthy body function.
Patients taking crivivan™ should drink at least 1.5 L (approximately 48 oz) of water or other liquids every day.

CASE STUDIES

Case 1

A 45-year-old man with a previous history of seizure disorder is seen at the clinic. For the past two years he has been on combivir (lamivudine and zidovudine), one tablet two times a day, nevirapine 200mg bid and phenobarb 30mg in the morning and 60mg at night.

Recently the lab results show a fall in the CD4 count and a rise in the viral load. You decide to change therapy to stavudine 40mg bid, didanosine 400mg daily, nelfinavir 1.25mg bid and phenobarb as before. Two weeks later on review, the patient's wife complains to the doctor that the man is sleeping all the time and unable to work.

- a. *What might be the cause of patient's problem?*
- b. *What would you do?*

Case 2

A 35-year-old patient on 20 units of humulin (insulin) is started on zidovudine, lamivudine and indinavir. Three months later, on review, you observe the fasting blood sugar has gone up from 3.8mmol/l to 10mmol/l.

- a. *What do you think is happening?*
- b. *What would you do?*
- c. *Did the patient receive optimal treatment?*

ANSWERS

Case 1

- a. Nelfinavir(PI) is an inhibitor of cytochrome P-450 system, unlike nevirapine, which is an inducer. The high blood levels of phenobarb are a result of reduced activity of cytochrome system.
- b. Reduce dose of phenobarb and review.

Case 2

- a. Insulin resistance from the indinavir
- b. NNRTI; adapt insulin needed
- c. No, patient did not. Generate discussion on putting diabetics on PIs.

SESSION 5 Recommended First-Line Regimens in Adults

PURPOSE

In this session, participants will learn about approved antiretroviral agents and WHO-recommended first-line antiretroviral regimens.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Identify the drugs to be included in several first-line ARV regimens.
2. Discuss use of these regimens in reference to in-country guidelines and availability.

TIME:

45 minutes

1. What therapy to begin with:

- a. The only regimens potent enough to reduce viral replication drastically and to prevent the emergence of resistance and treatment failure for a significant amount of time involve a *combination of at least three antiretrovirals*.
- b. There are currently 16 approved ART agents for the treatment of HIV-1 infection (in the U.S.). These include six nucleoside reverse transcriptase inhibitors (NtRTI), three nonnucleoside reverse transcriptase inhibitors (NNRTIs) and six protease inhibitors (PIs). Thirteen of the drugs have been incorporated into WHO's guidelines: See Table B1, 5.1 below.

Table B1, 5.1: Approved Antiretroviral Agents Included in WHO's ARV Guidelines^a

Nucleoside reverse transcriptase inhibitors (NsRTIs)	Nucleotide reverse transcriptase inhibitor (NtRTI)	Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
Zidovudine (ZDV, AZT) ^b	Tenofovir disoproxil fumarate (TDF)	Nevirapine (NVP) ^b	Saquinavir (SQV) ^b
Didanosine (ddI) ^b		Efavirenz (EFZ) ^b	Ritonavir (RTV) (as pharmacoenhancer) ^b
Stavudine (d4T) ^b			Indinavir (IDV) ^b
Lamivudine (3TC) ^b			Nelfinavir (NFV) ^b
Abacavir (ABC) ^b			Lopinavir/ritonavir (LPV/r) ^b
a Approved and generally available in industrialized countries as of January 2002		b Approved for inclusion in WHO's Essential Drug List as of April 2002	

1. How to start therapy

- Use the simplest (that is, few pills a few times a day) cheapest and most effective (that is, potent enough to make a difference with the least number of side effects) three-drug combination as the first line therapy.
- Then select the next one or two combinations on the list as the second-line therapy to be used if or when the first line drugs fail.
- WHO's recommended first line therapies are as follows:

Table B1, 5.2: Recommended First-Line Antiretroviral Regimens in Adults and Adolescents with Documented HIV Infection

Regimen ^a	Pregnancy Considerations	Major Toxicities
ZDV/3TC/EFZ or ZDV/3TC/NVP	Substitute NVP for EFZ in women for whom effective contraception cannot be assured.	ZDV-related anemia EFZ-associated CNS symptoms Possible teratogenicity of EFZ NVP-associated hepatotoxicity and severe rash NsRTI-related metabolic side effects
ZDV/3TC/ABC ^{a,c}	ABC safety data limited	ZDV-related anemia ABC hypersensitivity NsRTI-related metabolic side effects
ZDV/3TC/RTV-PI ^{b,d} or ZDV/3TC/NVP	LPV/r safety data limited NFV: most supportive safety data	ZDV-related anemia NFV-associated diarrhea IDV-related nephrolithiasis PI- and NsRTI-related metabolic side effects
<p>a ZDV/3TC is listed as initial recommendation for dual NsRTI component based on efficacy, toxicity, clinical experience and availability of fixed-dose formulation. You can substitute other dual NsRTI components, including d4T/3TC. D4T/ddl and ZDV/ddl, depending on country-specific preference.</p>		<p>Never use ZDV and d4T together because of proven antagonism. Fixed-dose formulations are preferred whenever possible as they promote enhanced drug adherence.</p> <p>b RTV-PI includes IDV/r, LPV/r, or SQV/r.</p>
<p>c NOTE: Subsequent research does not support this regimen, and WHO is currently revising its guidelines.</p>		
<p>d NOTE: According to current research, the option of two NRTIs and a ritonavir-enhanced PI or nelfinavir should not be used as a first choice. Such a regimen should only be used if an NNRTI regimen is not indicated, for example, in the case of an HIV-2 infection or if a patient presents with side effects to EFZ or NVP.</p>		

CASE STUDIES

Case 1

A 35-year-old truck driver comes to the clinic complaining of persistent diarrhea that started five months ago. You conduct a lab test and stool exam and find that his lymphocyte count is $1200/\text{mm}^3$; cryptosporidium is found in the stool exam.

- a) How would you classify this patient?
- b) Would you start this patient on ARV therapy? Why or why not?
- c) If so, which regimen would you put him on?

Case 2

A 24-year-old student presents for anonymous HIV testing. She was raped three months ago. Two months ago, she was seen in the clinic for fever, malaise, fatigue and swollen lymph nodes. At that time, she was diagnosed with influenza. Presently she has no complaints or symptoms. Her HIV test is positive. Her CD4 count is 550.

- a) How would you classify this patient?
- b) Was the diagnosis she received two months ago correct? If not, what would you assume the diagnosis to have been?
- c) Would you start this patient on ARV therapy? Why or why not?
- d) If yes, which regimen would you put her on?

Case 3

A young woman who is three months pregnant comes to the clinic complaining of fever for over a month. From her previous record, you see that six months ago she weighed 54 kg. She now weighs 46 kg. She has a history of herpes zoster. You have no facilities to test the woman for HIV or do a CD4 count or lymphocyte count.

- a) How would you classify this patient and why?
- b) Would you start this patient on ARV therapy? Why or why not?
- c) If so, which regimen would you start her on?

SESSION 6 Patient Follow-up and Monitoring ART

PURPOSE

In this session, participants will learn about clinical and laboratory monitoring of patients on ART. This session addresses clinical, laboratory and efficacy monitoring; schedules for monitoring; and measures of toxicity and effectiveness.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss clinical monitoring, including clinical and laboratory parameters to follow, barriers, specimen transport and personnel capacity.
2. Describe how to monitor for tolerability, efficacy, toxicity and resistance to ARV therapy.
3. Discuss recommended protocols for clinical monitoring.

TIME:

1 hour

1. Monitoring ARV therapy

Gather the following information:

- Clinical symptoms
- Detailed past and present history
 - Other medical problems
 - Other drugs, including herbs
- Thorough and regular physical examination

b. Laboratory

- Absolute minimum tests: HIV test, hemoglobin or hematocrit level
- Basic tests: WBC count, liver function tests (LFTs) and renal function tests (RFTs), blood sugar, lymphocyte count
- Desirable tests: CD4, amylase, bilirubin, lipids
- Optional: viral load
- Efficacy

Look for:

- Decrease or disappearance of symptoms
- Gain in body weight
- Decrease in frequency or severity of OIs
- Decrease of Kaposi's lesions
- Increase in total lymphocyte count
- Increase in CD4 count
- Sustained suppression of VL

2. How to monitor

- a. For clinical and efficacy monitoring, it is very important to examine the patient at every visit. The monitoring schedule should be as follows:
- First follow-up after one week, or earlier if there are side effects
 - Monthly visits thereafter, or more, if needed
 - At each visit, ask about symptoms, adherence, HIV and nonHIV-related problems, quality of life
 - Physical examination, body weight
- b. Laboratory monitoring for tolerance and toxicities of ART

Laboratory Tests	Antiretroviral Drug Class		
	NRTI	NNRTI	Protease Inhibitor
Essential at baseline and follow-up:			
Complete blood count	✓		
Urine (glucose, protein, microscopy)	✓		✓
Indicated by clinical features:			✓
Serum transaminases	✓	✓	
Serum amylase	✓		✓
Serum creatinine/Urea	✓		✓
Creatinine phosphokinase	✓		✓
Serum triglycerides			✓
Blood glucose			✓

- Frequency of blood chemistries
 - ALT after two weeks and one month, if NVP treatment or if abnormal ALT at baseline, or if the patient develops symptoms; in other cases, every three months
 - Hb every three months, or more frequently, if clinically indicated
 - Creatinine, glucose, amylases and lipids, when clinically indicated
- Desired CD4 and viral load changes during ART
 - Viral load decline of 1.5-2.0 logs in first month
 - Viral load decline to <50 copies/ml in 80-90 percent of patients at 24 weeks

Some clinicians use the following rates of CD4 increase to assess success of therapy, but these are only suggestive, and there is much individual variation. In patients with severe immune deficiency, it is likely that the rate of increase will be slower than that indicated.

 - Median CD4 increase 100-200 in first year
 - Median CD4 increase 100 in next years
- Total lymphocyte/CD4 count
 - Total lymphocytes: baseline and then every three months
 - CD4 count: at baseline and then every six months (this might vary according to national/site protocols)
- Viral load
 - Only when suspicion of treatment failure unrelated to nonadherence

3. HIV drug resistance

- a. Refers to a reduction in the ability of a drug, or a combination of drugs, to block HIV reproduction in the body
 This reduction occurs because of the changes (or mutations) in the genetic structure of HIV resulting from the rapid and often inaccurate reproduction of new viral copies.
 The best way to avoid the development of drug resistance is to keep HIV under control. The less virus there is in the body, the less likely it is that the virus will reproduce and mutate.
- b. Factors that can prevent HIV medications from controlling the virus are poor treatment adherence, poor drug absorption and varying pharmacokinetics (the individualized absorption, distribution, metabolizing and removal of drugs from the body).
- c. Testing for resistance
 - There are two ways to test for HIV drug resistance:
 - Genotypic testing: identifies mutations that are linked to the reverse transcriptase and protease genes of a person's HIV
 - Phenotypic testing: measures the growth of HIV in the presence of HIV drugs
 - Weaknesses and drawbacks
 - The tests measure only the dominant HIV strains that exist at the time of testing, not *minority* strains or strains that may be hiding in, for example, resting cells.
 - The tests should be performed when the patient is taking ARVs and no later than three weeks from stopping treatment (otherwise, the virus will likely have reverted to *wild type*).
 - The tests are difficult to interpret and often present conflicting results, particularly in patients who have had multiple regime failures.
 - The tests are costly.

4. Drug level monitoring

- a. At present, therapeutic drug monitoring (TDM) is infrequently performed outside research settings. Since this is a new and investigational area of HIV management, it seems unlikely to become widely available very quickly. Currently, British treatment guidelines recommend TDM in circumstances where providers are using doses other than those recommended by the manufacturer. You should also use TDM in cases of severe liver impairment and to manage toxicity. In patients with high peak levels, but no current evidence of toxicity, dosage reduction may be a strategy to prevent toxicity from developing.

- b. High peak levels or high drug exposure with the following drugs are associated with toxicities:
 - Ritonavir and triglyceride elevations, circumoral paraesthesia, diarrhea
 - Indinavir and kidney stones, colic and other urinary tract or kidney problems associated with indinavir crystals
 - Efavirenz and central nervous system toxicities such as vivid dreams, anxiety, feeling *stoned*High drug levels have not been clearly linked to other adverse effects of therapy.

- c. Summary: testing drug levels
 - Poor treatment adherence is a major cause of poor drug levels.
 - Interactions between drugs can influence drug levels.
 - Some people's bodies get rid of drugs faster than others.
 - Low drug levels in the blood may cause treatment to fail.
 - A small number of treatment centers are testing drug levels in people taking protease inhibitors.
 - Higher drug levels may mean greater anti-HIV activity but more severe and more frequent side effects.

SESSION 7 Drug Adherence and Strategies for Compliance**PURPOSE**

In this session, participants will learn about the issues involved in promoting ARV drug adherence.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the importance of good adherence and the consequences of poor adherence.
2. Describe effective strategies to promote adherence and discuss how to help patients cope with nontoxic side effects of ARVs.
3. Demonstrate ways to counsel patients about adherence.
4. Develop a tool or questionnaire to measure adherence in their local context.

TIME:

1 hour and 40 minutes

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1. Definitions of adherence and compliance

- a. Adherence is the term used to describe the patient's taking drugs correctly in terms of dose, frequency and time.
- b. In adherence, the patient is involved in deciding whether or not to take the drugs.
- c. Compliance means the patient does what he or she has been told to do by the doctor/pharmacist.

2. Measuring adherence

- a. Directly Observed Therapy (DOT): theoretically associated with 100 percent adherence; labor intensive and impractical outside institutional setting
- b. Electronic pill bottle monitoring, for example, Medication Event Monitoring Systems (MEMS) is expensive. A patient can remove doses but then not take them. It cannot be used on blister packs.
- d. Patient self-report: convenient and inexpensive
- e. Pill count: labor intensive
- f. Plasma drug levels: objective measure
- g. Pharmacy records/prescription refill monitoring
- h. Viral load assay: not a primary measure of adherence; surrogate marker; can be helpful when used with patient self-reports

3. Adherence: General comments

- a. One of the key determinants of success
- b. Poor adherence leads to virologic failure, evolution of drug resistance, and subsequent immunologic and clinical failure.
- c. Important to counsel patients carefully before initiating ART; involves clinicians, nurses, pharmacist, family, and others
- d. Do not start ART on first clinic visit. You need to counsel patient in treatment adherence to maximize the adherence.
- e. Once treatment has started, you need to monitor and provide support continuously.

4. Factors affecting adherence

- a. Patient-related factors
 - Patient readiness and commitment
 - Forgetfulness
 - Being away from home
 - Lifestyle
 - Depression
 - Cultural elements
 - Socioeconomic elements
- b. Provider-related factors
 - Provider readiness (knowledge, skills)
 - Counseling
 - Patient education
 - Medication alerts, for example, charts and diaries
 - Adherence team
 - Provider support
- c. Regimen and drug-related factors
 - Pill burden
 - Frequency
 - Side effects
 - Food restrictions
 - Drug interactions
 - Storage
- d. Other factors
 - Cost

5. Adherence intervention strategies

Educate and motivate, provide basic drug information, and discuss importance of adherence, timing of medications, drug interactions and the like

- Simplify regimen
- Tailor treatment to patient's lifestyle
- Prepare for and manage side effects
- Use an adherence team
- Address patient-related issues
- Recruit an adherence monitor
- Provide adherence promoting devices
- Use home-based care staff to promote adherence
- Use adaptation of directly observed therapy for a time to be determined

Role Play: Setting the Stage for Adherence

CLIENT

You are a 43-year-old schoolteacher. You were diagnosed as HIV positive three years ago. You have not wanted to think about it, so you have not returned to the clinic for checkups as advised, and you have been well—until last week. Today you want to see a doctor because for the past week, you have been having difficulty swallowing and you noticed that there are sores in your mouth.

You are feeling anxious, but you want help. You fear you will have to take many pills, something you have never liked to do and something that might mean you will have to tell your wife you are HIV positive.

CLINICIAN

The patient is a 43-year-old schoolteacher who was diagnosed with HIV three years ago. He has not been to see a doctor in three years. He says he has been feeling healthy. On examination, he has oral thrush and his history revealed he has had difficulty swallowing.

You prescribe fluconazole for the oral/esophageal candidiasis. You also think he should start on zidovudine, lamivudine and efavirenz. You plan to order the lab work and to have him come back next week.

Before you begin, think about the following:

1. How should you begin the discussion about the drugs and issues that would affect adherence?
2. What do you say to start the discussion?
3. What issues do you bring up during the discussion?
4. What follow-up do you recommend?

OBSERVER

1. What are the verbal and nonverbal skills demonstrated by the clinician?
2. What might the clinician use that he or she did not?
3. What is the client's reaction to the clinician's approach?
4. What major points are addressed that are important to compliance? (See points under "Strategies" in # 5, above.)
5. What major points are missed?
6. Develop a locally appropriate adherence measure instrument.

Validated patient questionnaires have proven to be one of the more reliable, easily instituted tools for monitoring adherence in the outpatient setting. The questionnaire should record information about tolerance, side effects and toxicity.

Each country and/or health center may develop its own brief, culturally appropriate questionnaire; one standardized tool may not be applicable to all regions and cultures.

SESSION 8 Why and When to Change Therapy**PURPOSE**

In this session, participants will learn about drug resistance, reasons for changing an ART regimen and which second-line regimens to use.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss the reasons for changing therapies.
2. Identify choices for second-line ARV regimens.
3. Describe what limitations there may be to selecting alternative therapy.

TIME:

1 hour and 30 minutes

1. Situations in which regimen or individual drug should be changed

a. Treatment failure

- Defined as:
 - **Clinical failure:** clinical disease progression signaled by the development of new symptoms, symptoms that do not disappear, or an OI or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration
 - **Immunologic failure:** a fall in the CD4 counts > 30 percent from the peak value or a decline equivalent to or less than the pretherapy baseline
 - **Virologic failure:** failure to achieve undetectable viral load levels after 3-6 months; repeated, continual, detectable viremia indicative of incomplete viral suppression; the reappearance of a detectable viral load
- Reasons for treatment failure:
 - ARV potency is insufficient
 - Drug levels are insufficient (including cellular mechanisms)
 - Poor adherence
 - Preexisting viral drug resistance
 - Poor prescribing

Reasons for no improvement or clinical deterioration, despite ARV treatment:

Treatment failure	Other reasons
<ul style="list-style-type: none"> • No optimal treatment regimen • Nonadherence • Bad absorption, drug interactions • Resistance 	<ul style="list-style-type: none"> • Side effects of ARVs or other drugs • Immune reconstitution phenomenon • OI or other HIV-related problems. • Non-HIV-related problems

Viral loads when no improvement or clinical deterioration occurs:

Treatment failure	Other reasons
Viral load ↑ or insufficient decrease	Viral load ↓↓ or undetectable

- What to do in the case of treatment failure:
 - Check treatment regimen
 - Check adherence with ARVs
 - Perform resistance testing, if available
 - Monitor therapeutic drug, if possible

Adherence	Undetectable viral load after 3 months
> 95 percent	100 percent
90-95 percent	64 percent
80-90 percent	50 percent
70-80 percent	25 percent
<70 percent	6 percent

b. Toxicity:

Plasma drug levels: objective measure

- Drug causing the toxicity cannot be identified, and/or low-grade, intolerable side effects compromise adherence. (See session 4 on drug interactions and ADRS: side effects and toxicities, for details.)
- Clearly-defined toxicity to a single drug
This permits drug substitution without compromising the overall regimen. For example, you can substitute d4T for ZDV when ZDV-related symptoms or anemia appear or NVP for EFZ when EFZ-related central nervous system symptoms are unremitting.
If an interruption in therapy is indicated to permit resolution of toxicity, suspend the entire regimen temporarily to prevent the emergence of drug resistance.

2. Recommended second-line regimens in adults and adolescents

a. Reasons for altering an initial ART regimen include:

- Side effects interfering with activities of daily living and leading to poor adherence
- Drug toxicity
- Occurrence of active tuberculosis or pregnancy
- Treatment failure
- WHO-recommended second-line regimens (See Table B1, 8.1 below.)

Table B1, 8.1: Recommended Second-Line Regimens in Adults and Adolescents

First-line regimens	Second-line regimens for treatment failure	Alternative second-line regimens for treatment failure
ZDV/3TC/EFZ or ZDV/3TC/NVP	d4T/ddI/RTV-PI ^{a,b,c}	RTV-PI ^a / ABC/ddI ^{c,d} NFV + ABC/ddI ^{c,d} or d4T/ddI ^{b,c} /NFV
ZDV/3TC/ABC	d4T/ddI ^{b,c} /NNRTI ^e	d4T/ddI ^{b,c} /RTV-PI ^a
ZDV/3TC/RTV-PI or ZDV/3TC/NFV	d4T/ddI ^{b,c} /NNRTI ^e	ABC/ddI ^{c,d} /NNRTI ^e

a RTV-enhanced PI = IDV/r, LPV/r, SQV/r. An RTV-enhanced PI regimen is preferred because of the potency of these regimens. NFV can be considered as an alternative for the PI component of second-line therapy if RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

b Nucleoside cross-resistance may compromise the potency of d4T/ddI at the time of switching for treatment failure as it is assumed that virological failure will have been prolonged at that point and several nucleoside analogue mutations (NAMs) are likely to be present. However, choices are limited in the setting of treatment failure. See also footnote c.

c Tenofovir is a once-daily nucleotide (NtRTI) with activity against some nucleoside-resistant strains. If available, TDF can either be added to d4T/ddI or ABC/ddI or substituted for either d4T or ABC in these combinations. Its currently restricted availability in resource-limited settings is recognized.

d High-level ZDV/3TC coresistance confers diminished susceptibility to ABC. If d4T/3TC is used as the first-line dual nucleoside backbone, AZT/ddI can be used as the second-line nucleoside component and vice versa.

e NNRTI can be either EFZ or NVP.

c. Limitations to selecting alternative therapy

- Drug resistance:
 - If you do not use viral load and resistance monitoring to define treatment failure, virological failure is likely to have been present for an extended period by the time you detect it.
 - Viral replication over time leads to the evolution of more drug resistant mutations, and it will be difficult to know which drugs have been compromised without drug resistance testing.
- How to avoid drug resistance:
 - Triple therapy
 - Optimal adherence
 - Monitoring for treatment failure
 - Switch all ARVs in the case of treatment failure
- Stop ARVs in the presence of:
 - Serious adverse effects
 - Inefficient treatment, for example, monotherapy
 - Nonadherence
- Remember:

When ARVs are stopped, viral load will increase, leading to an increased risk of HIV transmission.

CASE STUDIES

Case 1

A 34-year-old man has been on stavudine, lamivudine and nevirapine for the past four years. On his last visit, the CD4 count had fallen from 300 cell/mm³ to 200 cells/mm³ and the viral load had risen from undetectable levels to 50,000 copies/ml.

- a. What do you think is happening to the patient?
- b. What possible regimen can you give to the patient, based on your local situation?

Case 2

A 30-year-old teacher comes to you; he was recently diagnosed with HIV infection. He complains of difficulty in swallowing and loss of weight. He has no other complaints and no fever.

Medical History

Herpes zoster, six years ago

Findings on physical exam

Weight loss < 10 percent of body weight

Dysphagia from oral candidiasis

Lab test results

No CD4 lymphocyte count available

Hemoglobin 9mg/dl

Leukocytes 5200 10⁹/l

Lymphocytes 15 percent

Total lymphocytes 780 10⁹/l

ALT 200 U/l

Plan

You give him fluconazole 200mg x 14 days to treat the oral candidiasis.

Start him on a regimen of efavirenz/stavudine/epivir (EFZ/d4T/3TC).

- a. Is this an appropriate regimen to begin with?
- b. Why or why not?

Continuing case situation

After one month, he is experiencing nausea and has no appetite. His lab results show:

Hemoglobin 9.2 mg/dl

AST 450 U/l

ALT 465 U/l

- a. What do you think is happening to this patient?
- b. What would you do next?

Continuing case situation

You decided to stop efavirenz and continue stavudine epivir for three days.

You do a control liver test after one month, with the following test results:

ALT: 120 U/l

AST: 130 U/l

a. What do these lab results tell you?

b. What do you do next?

Continuing case situation

You start the patient on indinavir and continue with stavudine/epivir. After one month, you repeat the lab tests, with the following results:

ALT: 125 U/l

AST: 140 U/l

a. What is your conclusion?

ANSWERS

Case 1

What do you think is happening to the patient?

There may be a problem with adherence. If patient is adherent, then it comes from treatment failure.

What possible regimen can you give to the patient based on your local situation?

PI-containing regimen with completely new NRTIs

Case 2

What do you think is happening to this patient?

This may be a toxic effect from NNRTI or an immune reconstitution syndrome.

What is your conclusion?

The abnormal liver tests were probably a toxic effect of the NNRTI and not an immune reconstitution syndrome in a patient with HIV/hepatitis coinfection.

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PART B: MODULE B1

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<http://www.aidsmap.com> (updated Dec 11, 2000)

Module B2

Special Issues: TB, Women, Children and Post-Exposure Prophylaxis



Session 1: Management of Tuberculosis and Other HIV-Related Infections and Conditions in Relation to ART

In this session, participants learn about the management of tuberculosis and other HIV-related infections and conditions, such as opportunistic infections, hepatitis and the immune reconstitution syndrome, in relation to ART.

Session 2: ART in Women and Pregnancy

Participants learn about the choice of ART drugs in women of childbearing age and ART during pregnancy. The session also addresses how to manage drugs in preventing mother-to-child transmission (PMTCT) and the use and limitations of ART as a preventive measure.

Session 3: ART in Infants and Children

Participants learn about the natural course of HIV disease in children, how it differs from adults, how to make a diagnosis, the WHO clinical classification system for diagnosis and classification, and ART for children.

Session 4: Post-Exposure Prophylaxis (PEP)

Participants learn about occupational exposure to HIV, how to manage it, HIV post-exposure prophylaxis (PEP) and drug selection for PEP.

SESSION 1 Management of Tuberculosis and other HIV-Related Infections and Conditions in Relation to ART

PURPOSE

In this session, participants will learn about the management of tuberculosis and other HIV-related infections and conditions, such as opportunistic infections, hepatitis, and the immune reconstitution syndrome, in relation to ART.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the relationship between TB and HIV coinfection.
2. Discuss how to manage and treat people with TB and HIV coinfection in their local situation, and discuss national guidelines for the treatment and management of TB and HIV coinfection.
3. Describe the problems and management of ART in patients with other HIV-related infections and conditions, such as OIs and hepatitis.
4. Describe the immune reconstitution syndrome and how to manage it.

TIME:

40-60 minutes

1. People with TB and HIV coinfection

- a. WHO recommends that people with both TB and HIV complete their TB therapy before beginning ARV treatment, unless there is high risk of HIV disease progression and death during the period of TB treatment (that is, a CD4 count $<200/\text{mm}^3$ or the presence of disseminated TB).
- b. In cases where a person needs concurrent TB and HIV treatment, first-line treatment options include ZDV/3TC or d4T/3TC, plus either an NNRTI or ABC.
 - If an NNRTI-based regimen is used, EFZ would be the preferred drug since its potential to aggravate hepatotoxicity of TB treatment appears less than with NVP. However, you need to increase the dosage to 800mg/day.
 - Except for SQV/r, PIs are not recommended during TB treatment with rifampicin because of its interactions with the latter drug.

Table B2, 1.1: Antiretroviral Therapy for Individuals with Tuberculosis Coinfection

Situation	Recommendations
Pulmonary TB and CD4 count $< 50/\text{mm}^3$ or extrapulmonary TB. Start TB therapy.	Start one of these regimens as soon as TB therapy is tolerated: <ul style="list-style-type: none"> • ZDV/3TC/ABC • ZDV/3TC/EFZ • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/ mm^3 or total lymphocyte count 1000-1200/ mm^3	Start TB therapy. Start one of these regimens after two months of TB therapy: <ul style="list-style-type: none"> • ZDV/3TC/ABC • ZDV/3TC/EFZ • ZDV/3TC/SQV/r • ZDV/3TC/NVP
Pulmonary TB and CD4 $>200/\text{mm}^3$ or total lymphocyte count $>1000-1200/\text{mm}^3$	Treat TB. Monitor CD4 counts if available. Start ART according to ART Guidelines presented in Day 3: Section D.2.a Table 1.

2. Other opportunistic infections and hepatitis

- a. Patients who develop other OIs should be treated with ARVs.
- b. In contrast to the situation with TB, drug interactions with standard ARV regimens do not pose a significant problem.
- c. Consider prompt initiation of ART when OIs occur for which treatment is not available or for which it is sub-optimal because improvement of the immune system may enhance recovery.
- d. Patients coinfecting with hepatitis B or C can be treated safely with several ARV regimens.
 - Avoid regimens with ddI/d4T in patients known to have active hepatitis because of the possibility of additive hepatotoxicity.
 - 3TC and TDF (see comment below) are both active against hepatitis B and may even protect against new infections. Patients receiving 3TC or TDF who are known to have hepatitis B and experience ARV regimen failure may wish to continue these medications when the ARV regimen is switched.

Comment: Tenofovir (TDF), a relatively new NRTI (approved for use in the U.S. by the FDA in October 2001), is active against most NRTI resistant strains.

3. Immune reconstitution syndrome

- a. Mechanism: For many OIs, including TB, there can be a transient worsening of infection 2-3 weeks after initiating ART. This is called the *immune reconstitution syndrome*. Initiation of ART can unmask previously undiagnosed infections by augmenting the inflammatory response.
- b. Clinical presentation: Fevers, lymphadenopathy, worsening pulmonary lesions and expanding lesions of the central nervous system
- c. Management: Reactions are self-limiting, although the patient may require a brief course of corticosteroids to reduce inflammation of CNS or severe respiratory symptoms

Do not interrupt ART if immune reconstitution syndrome occurs.

4. ART and antimicrobial prophylaxis

ART is the most effective approach to reducing incidence of OIs, but you should complement it with antimicrobial prophylaxis.

On the basis of observations made in developing countries, patients responding to ART with sustained elevation in CD4 cell counts above 200 cells/mm for 3-6 months may be able to discontinue prophylaxis for some OIs.

SESSION 2 ART in Women: During Pregnancy and for Preventing Mother-to-Child Transmission**PURPOSE**

In this session, participants will learn about the choice of ARV drugs in women of childbearing age and ARV therapy during pregnancy. The session also addresses how to manage drugs in preventing mother-to-child transmission (PMTCT) and the use and limitations of ARV therapy as a preventive measure.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss specific considerations affecting the use of ARVs in women.
2. Describe how ART is used for PMTCT.
3. Describe the various regimens used during pregnancy, intrapartum and postpartum, including short course ART.
4. Discuss the relationship between ART and breast feeding, and WHO recommendations.
5. Discuss national guidelines for HIV and infant feeding as they relate to ARV therapy.

TIME:

60-90 minutes

- a. Choice of ARV drugs in nonpregnant women of childbearing age
- b. Women who are receiving ART should have access to effective contraceptive methods to reduce the likelihood of unintended pregnancy.
- c. Avoid drugs with potential toxicity to the developing fetus, such as EFZ, in women who may become pregnant.
- d. ARV therapy and MTCT

Preventing prenatal transmission

 - You can achieve significant reduction of MTCT by using ARV therapy.

Studies conducted in 1994 in industrialized countries showed that administering AZT to women from the 14th week of pregnancy, and to the newborn during labor, decreased the risk of MTCT by nearly 70 percent in the absence of breast feeding.

A shorter AZT alone regimen, starting from the 36th week of pregnancy, was shown to reduce the risk of transmission of HIV at six months by 50 percent in a nonbreast feeding population and by 37 percent in those breast feeding.

A short course of NVP (HVNET 012) has been shown to reduce the risk of transmission; it is the most commonly used protocol because of its demonstrated efficacy in clinical trials in reducing MTCT by 47 percent, its low cost and its ease of use in MTCT programs. The regimen is:

Intrapartum short course: 200 mg at start of labor or at hospital intrapartum

Postpartum mother who did not receive intrapartum dose: 200 mg stat

Postpartum infant: 2mg/kg syrup within 48-72 hours

Other trials of short course ARV regimens using a combination of AZT and lamivudine also substantially decrease the risk of transmission (PETRA).
 - Women on treatment with ARVs for HIV infection have very low transmission if viral load is <1000 copies/ml.
- e. Women first diagnosed with HIV infection during pregnancy
 - Women in the first trimester may consider delaying initiation of ART.
 - Consider severity of maternal HIV disease and potential benefits and risks of delaying ART until after the first trimester
 - For women who are severely ill, the benefit of early initiation may outweigh the theoretical risk to the fetus; in these cases, we recommend initiating with drugs such as AZT, 3TC, NVP or NFV.
- f. HIV-infected women on ART who become pregnant
 - Options are:
 - Suspend therapy temporarily during first trimester
 - Continue same therapy
 - Change to a different regimen
 - Issues to consider:
 - Gestation of the pregnancy
 - Severity of maternal disease
 - Tolerance of regimen in pregnancy
 - Potential for adverse fetal effects

The fetus is most susceptible to potential teratogenic effects of drugs during the first 10 weeks of gestation, and the risks of ART to the fetus during this period are unknown.

g. ART and breast feeding

- Current WHO/UNAIDS/UNICEF guidelines recommend that you fully inform women with HIV infection about both the risks and benefits of breast feeding and support them in their decision about feeding practices.
- Safe alternatives may not be available in some resource-limited settings (for example, an unsafe or inadequate water supply may be the only source available for mixing formulas), in which case, exclusive breast feeding for the first six months of life is recommended.
- Women who require ART and are breast feeding should continue their ART regimen.
- The efficacy of potent ART for mothers used solely to prevent postnatal transmission of HIV through breast milk is unknown, but studies are under way.

h. Approaches to HIV-infected women who received short-course ARV prophylaxis to reduce MTCT and require treatment postpartum:

- Short-course ARV regimens do not fully suppress viral replication and may be associated with development of ARV drug resistance.
The Ugandan HIVNET 012 study of single dose intrapartum/newborn NVP for prevention of MTCT found that 19 percent of the women developed resistance to the drug. This was associated with delivery, HIV viral load and CD4 cell count.
- Based on current information and pending further research, prior administration of short-course AZT/3TC or single dose NVP for preventing MTCT should not preclude using these agents as part of a combination ARV drug regimen initiated for treating these women.

i. Adherence to therapy in pregnancy and postpartum

- Adherence may be more difficult in pregnant and postpartum women than in nonpregnant women.
- Obstacles to adherence may include:
 - Morning sickness and GI upset, which can be compounded by ARV-associated nausea
 - Fears that ARV drugs might harm the fetus
- To reduce the potential for resistance to emerge, if for any reason, you need to discontinue therapy during pregnancy, stop and restart all drugs together.
- Physical changes of the postpartum period, coupled with the stresses and demands of caring for a newborn infant, may make adherence to treatment especially difficult after birth.
You need to provide additional support for maintaining adherence to therapy during the ante- and postpartum periods.

CASE STUDY

A young woman has been newly diagnosed with both HIV and TB (identified in the antenatal clinic). She is 14 weeks pregnant. Her lab results show a CD4 count of 150 and a VL of 62,000.

- 1) *What antiretroviral therapy (if any) would you prescribe?*
- 2) *What TB therapy (if any) would you prescribe?*
- 3) *What would you do if this pregnant woman has a CD4 count of 5?*

Give your reasons.

ANSWERS

Examining interaction between TB, ARVs and pregnancy.

1. Examine possible regimen for teratogenicity and significant drug interaction.
2. This is a difficult question. If you have to use ARVs with TB treatment in pregnancy, use nevirapine or ritonavir boosted saquinavir with ZDV and 3TC .

SESSION 3 ART in Infants and Children

PURPOSE

In this session, participants will learn about the natural course of HIV disease in children, how it differs from adults, how to make a diagnosis, the WHO clinical classification system for diagnosis and classification and ART therapy for children.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the natural course of HIV disease in children.
2. Discuss the WHO clinical classification system and how to make a diagnosis of HIV in children.
3. Describe when and how to provide ART.
4. Discuss national guidelines for ARV therapy in children.

TIME:

1 hour and 15 minutes

Note: If participants are mostly pediatricians, you may need to go into greater depth about the challenges of adherence in children and available drug formulations.

1. The natural course of HIV disease in children

- a. HIV RNA levels in perinatally-infected infants are generally low at birth (<10,000 copies/ml), increase to high values by age two months and then decrease slowly after the first two years.
- b. CD4 cell count and percentage values in healthy infants who are not infected are considerably higher than those observed in uninfected adults and decline slowly to adult values by the age of six years.
- c. Although the CD4 absolute number that identifies a specific level of immune suppression changes with age, the CD4 percentage that defines each immunologic category does not. Thus, a change in CD4 *percentage, not the number*, may be a better marker for identifying disease progression in children.
- d. CD4 cell values can be associated with considerable variation because of minor infections and are therefore best measured when patients are clinically stable.

Table B2, 3.1: HIV Pediatric Classification System Immune Categories Based on Age-Specific CD/Cell Count and Percentage

Immune category	Child's Age					
	<12 months		1-5 years		6-12 years	
	No./ml	percent	No./ml	percent	No./ml	percent
Category 1: No suppression	>1,500	>25 percent	>1,000	>25 percent	>500	>25 percent
Category 2: Moderate suppression	750-1,499	15-24 percent	500-999	15-24 percent	200-499	15-24 percent
Category 3: Severe suppression	<750	<15 percent	<500	<15 percent	<200	<15 percent

Source: CDC 1994

- e. A small proportion of children who are infected early in pregnancy will progress to advanced HIV disease more rapidly because of a disruption of the thymus, where CD4 and CD8 cells are produced. These children have low CD4 and CD8 cell counts; their immune system cannot respond to HIV infection. Thus, infants under six months who present with symptoms of HIV disease usually have a shorter survival period than older children.

2. Diagnosis of HIV disease

- a. Most infants are diagnosed on the basis of symptoms and a positive test of the mother or child.
- Passively transferred maternal HIV antibody may persist for up to 18 months.
 - To establish a definitive serologic diagnosis, repeat the test at 18 months.
 - You can use viral diagnostic assays—PCR—to detect HIV in children younger than 18 months, but because of their complexity and cost, these tests are not readily available everywhere.
- b. Pattern of disease and management often differs for children of various age groups
- Some HIV-related conditions are less frequent in children; for example, TB, cryptococcal meningitis, Kaposi's sarcoma
 - Other conditions, such as lymphocytic interstitial pneumonitis (LIP), are usually found only in children or will express themselves differently, as, for example, the condition of HIV encephalopathy
 - You need to adapt drug dosages to the child's weight or surface area (in the case of ARVs)
 - Management of some diseases, such as oral and skin manifestations, is similar for children and adults.
- c. WHO systems for diagnosis and classification
- WHO staging system for HIV infection and disease in children

Clinical Stage I

1. Asymptomatic
2. Generalized lymphadenopathy

Clinical Stage II

3. Unexplained chronic diarrhea
4. Severe persistent or recurrent lymphadenopathy
5. Weight loss or failure to thrive
6. Persistent fever
7. Recurrent severe bacterial infections

Clinical Stage III

8. AIDS-defining opportunistic infections
 9. Severe failure to thrive
 10. Progressive encephalopathy
 11. Malignancy
 12. Recurrent septicemia or meningitis
- You should suspect children presenting with any three of the following signs or conditions of having HIV infection:
 - Two or more chest infections requiring antibiotics (pneumonia) in the past two months
 - One or more episode of persistent diarrhea OR two or more episodes of acute diarrhea in the past two months
 - A parent with tuberculosis
 - Oral candidiasis (thrush)

- Enlarged lymph nodes in two or more sites
- Growth faltering (weight curve flat or falling for two consecutive months)
- Weight-for-age below the third percentile (using international growth reference standards)

CDC classification system for HIV infection in children less than 13 years of age

CDC definition of HIV infection in children: Any child over the age of 18 months who was born to an HIV-infected mother, or who has been exposed to infected blood or blood products, or other known methods of transmission and who is HIV positive by ELISA and a confirmatory test

3. ART therapy for children

a. WHO recommendations for initiating ART in children

Table B2, 3.2: WHO Recommendations for Initiating ART in Children

CD4 Testing	Age	HIV Diagnostic Testing	Recommendations for Initiating Treatment
If CD 4 testing is available	<18 months	Positive HIV virologic test ¹	<ul style="list-style-type: none"> • WHO Pediatric Stage III (AIDS irrespective of CD4 cell percentages²) • WHO Pediatric Stage I disease (asymptomatic) or Stage II disease with CD4 percentage <20 percent
		HIV virologic testing not available, but infant is HIV seropositive or born to HIV-infected mother <i>Note: You must repeat HIV antibody test at age 18 months to obtain definitive diagnosis of HIV infection.</i>	<ul style="list-style-type: none"> • WHO Pediatric Stage III disease (AIDS) with CD4 cell percentage <20 percent
	≥18 months	HIV antibody seropositive	<ul style="list-style-type: none"> • WHO Pediatric Stage III disease (AIDS) irrespective of CD4 cell percentage² • WHO Pediatric Stage I disease (asymptomatic) or Stage II disease with CD4 percentage <15 percent³
If CD 4 testing is not available	<18 months	Positive HIV virologic test	•WHO Pediatric Stage III ²
		HIV virologic test not available, but infant is HIV seropositive or born to known HIV-infected mother	•Treatment not recommended ⁴
	≥18 months	HIV antibody seropositive	• WHO Pediatric Stage II ²

- 1 HIV DNA PCR or HIV RNA or immune complex p24 antigen assays
- 2 You can also consider initiation of ARV for children who have advanced WHO Pediatric Stage II disease, including severe recurrent or persistent oral candidiasis outside the neonatal period, weight loss, fevers or recurrent severe bacterial infections irrespective of CD4 count.
- 3 Factor the rate of decline in CD4 percentage (if measurement available) into the decision making.
- 4 Many of the clinical symptoms in the WHO Pediatric Stage II and III disease classification are not specific for HIV infection and significantly overlap those seen in children without HIV infection in resource-limited settings. Generally, in the absence of virologic testing and CD4 cell assay availability, do not consider HIV-exposed infants <18 months of age for ART, regardless of symptoms.

b. WHO recommended ART regimens in children

Table B2, 3.3: WHO Recommended First-Line Regimens for Children

First-Line Regimen ¹	Comments
ZDV/3TC ² plus ABC	Preferred, if concomitant anti-TB therapy being received
ZDV/3TC ² plus NNRTI	NNRTI choice: <ul style="list-style-type: none"> • If <3 years or <10 kg give NVP • If ≥3 years or ≥10 kg give NVP or EFV
<p>1 Country-specific considerations and preferences should determine which regimen or regimens to make available.</p> <p>2 ZDV/3TC is the first-choice dual NRTI regimen for children, as there has been the most clinical experience with this regimen. You can substitute other dual NRTI components, including ZDV/ddl, d4T/3TC, d4T/ddl, and ddl/3TC. Never use ZDV/d4T together because of proven antagonism.</p>	

Table B2, 3.4: WHO Recommended Second-Line Regimens for Children

Second-Line Regimens (in relation to first-line regimens)		
First-line	Second-line	Alternative Second-line
ZDV/3TC ² plus ABC	d4T/ddl plus LPV/r ¹ or NFV or an NNRTI	D4T/ddl plus an NNRTI ² plus either LPV/r or NFV
ZDV/3TC ² plus NNRTI	d4T/ddl plus LPV/r ¹ or NFV	
<p>1 For children who can swallow capsules and for whom the current capsule formulations allow appropriate weight- or body-surface-area-calculated dosing, additional options include SQV/r and IDV/r.</p> <p>2 NNRTI choice: If <3 years or <10 kg: NVP; if ≥3 years or ≥10 kg: NVP or EFV</p>		

- c. Monitoring drug levels in young children, especially below the age of two years, may be useful because of the wide variability in the metabolism of protease inhibitors and NNRTIs in this age group.

- d. ARV liquid formulations
 - ZDV 10 mg/ml (syrup, large volume)
 - 3TC 10 mg/ml (syrup)
 - ddI 10 mg/ml (powder, suspension)
 - D4T 1 mg/ml (syrup, large volume)
 - ABC 20 mg/ml (syrup)
 - EFV 30 mg/ml (open capsules)
 - NVP 10 mg/ml (suspension)
 - NFV (suspension; powder, but best to crush tablets)

- e. Storing ARVs in the refrigerator
 - Ritonavir
 - ddI suspension
 - d4T solution
 - Lopinavir/ritonavir capsules and solution

- f. Storing ARVs in glass jars
 - ZDV syrup
 - d4T syrup

CASE STUDY

Case 1

A child age 3 comes into your clinic. Her lab results show CD4 percentage below 10 percent. You decide to prescribe ARVs for her.

- a. *List three possible regimens for this child.*
- b. *What are the challenges in delivering ART to children?*

Case 2

What ARV combination would you give to a 7-year-old who had previously failed stavudine, didanosine, and nevirapine?

ANSWERS

Answers: See section 3. ART Therapy for Children in the trainer's notes.

Issues for discussion: Adherence is a major issue in giving ART to children. Some suggestions are:

Use available syrup formulations.

Investigate the use of lower doses of tablet formulation as a child grows.

For example:

- AZT – Syrup. Large volumes 10mg/ml
- 3TC – Syrup. Use within one month 10mg/ml
- Stavudine – Syrup. Large volume 1mg/ml; keep refrigerated
- Didanosine – Suspension 10mg/ml. Must shake well; keep refrigerated
- Lower strength Tabs 25mg, 50mg
- Abacavir – Syrup 20mg/ml
- Nevirapine – Suspension 10mg/ml
- Efavirenz 30mg/ml or low strength Capsule 50mg, 100mg
- Lopinavir/ritonavir (kaletra) Suspension, refrigerated. Can be stored for two months; has a bitter taste

SESSION 4 Post-Exposure Prophylaxis (PEP)**PURPOSE**

In this session, participants will learn about occupational exposure to HIV, how to manage it, HIV post exposure prophylaxis (PEP), and drug selection for PEP.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Discuss issues and concerns that health care workers might have about working with HIV-infected persons.
2. Describe how to manage occupational exposure to HIV effectively.
3. Discuss the various PEP regimens and when to use which.
4. Describe ways of helping health care workers overcome their fears and biases about working with HIV infected persons.
5. Discuss national guidelines with regard to PEP.
6. Discuss post-sexual-exposure prophylaxis.

TIME:

1 hour and 30 minutes

1. Occupational exposures

a. Relative risk of viral transmission with sharps injury from infected source

- | | |
|---|--------------------------|
| • Hepatitis B virus (HbsAG positive + unvaccinated HCW) | 37 percent to 62 percent |
| Source HbsAG positive | 23 percent to 37 percent |
| Source HbsAG negative | 1.8 percent |
| • HIV | 0.3 percent |

b. Management of occupational blood exposure

- Immediate care: wash wounds with soap and water; flush mucous membranes with water
- Risk assessment: type of fluid and type of exposure
- Evaluate source: test source for HIV serology (rapid test, if available)
- Exposed person: initiate PEP as quickly as possible (see below)
- Follow-up: HIV exposure (source positive HIV serology or acute HIV with positive HIV RNA)
 - HIV serology at baseline, 1.5, 3 and 6 months
 - Reevaluate and adjust regimen at 72 hours, if taking PEP
 - Monitor for drug toxicity

c. Nonoccupational HIV exposure

You need to learn the relative risk of HIV infection as depicted on the table on the next page.

Table B2, 4.1: Risks Related to HIV Exposure

Exposure	Risk/10,000 Exposures
Needle sharing	67
Percutaneous (occupational exposure)	30
Receptive anal intercourse	10 to 30
Receptive vaginal intercourse	8 to 20
Insertive vaginal sex	3 to 9
Insertive anal sex	3

Am J Med 1999; 106:324; Ann Intern Med 1996;125:497; J Acquir Immune Defic Syndr 1992;5:1116; N Engl J Med 1997;336:1072.

- Some states in the U.S. have policies for PEP after sexual exposure (Massachusetts, New York and California); policies also exist in France, Italy, Spain, Switzerland, Australia and at the UN, including WHO. The U.S. Public Health Service does not recommend for or against prophylaxis after nonoccupational exposure because of lack of data.
- It is biologically possible for PEP medications, taken soon after exposure, to prevent HIV infection.
- There is limited evidence available to suggest that prophylactic use of antiretroviral medications is efficacious.
- In particular, one study of PEP following occupational exposure to HIV showed an 81 percent reduction in risk of seroconversion when medications were started, on average, four hours after exposure. Here is one example of a policy guideline (from the San Francisco Department of Health, the state of California, in the U.S.). It recommends:
In cases where PEP is appropriate, offer it to the survivor as soon as possible. In no case offer it after 72 hours following the assault. When deciding whether to offer PEP, consider if any of the following factors were present during the assault: presence of blood; survivor or assailant with a sexually transmitted disease, with inflammation such as gonorrhea, chlamydia, herpes, syphilis, bacterial vaginosis, trichomoniasis, and the like; significant trauma to survivor; ejaculation by assailant; multiple assailants or multiple penetrations by assailant(s).
- When deciding whether to offer PEP, categorize the act of assault into one of the following three categories:
 1. Acts with measurable risk of HIV transmission, including anal penetration, vaginal penetration and injection with a contaminated needle
 2. Acts with possible risk of HIV transmission, including oral penetration with ejaculation, unknown act, contact with other mucous membrane, victim biting assailant and assailant with bloody mouth biting victim
 3. Acts with no risk of HIV transmission, including kissing; digital or object penetration of vagina, mouth or anus; and ejaculation on intact skin
- The simplest regimen that meets the goals of providing two nucleoside analog antiretrovirals (one of which is zidovudine) is zidovudine (300mg) together with lamivudine (150mg) in a combination pill (combivir) to be taken twice a day for 28 days. Dosing of combivir is twice a day rather than every 12 hours; it can be taken with or without food, although taking with food can reduce some of the gastrointestinal side effects. Alternative combinations include lamivudine plus stavudine (40 mg stavudine twice a day for a person weighing \geq 60 kg; 30 mg twice a day for a person weighing $<$ 60 kg; 150 mg lamivudine twice a day for body weight \geq 50 kg; 2mg/kg of body weight twice a day for $<$ 50 kg). Then we recommend treatment for four weeks with combivir (AZT 300 mg bid /3TC 150 mg bid) or d4T (40 mg bid) + ddI (400 mg qd).

- If a protease inhibitor is to be added, consider adding nelfinavir (1250 mg bid with meals) or IDV (800 mg tid on empty stomach) or IDV + RTV or LPV/r (400/100 mg bid) if source has viral load >50,000 c/ml, advanced HIV disease or source has been treated with one or both NRTIs. Be sure to consider PEP medications as one important part of the larger post-assault treatment program. Specialized counseling is another critical aspect of the post-assault treatment.

2. HIV PEP

- a. Through June 2000, there were 56 confirmed transmissions (in the U.S.) from an infected source to a HCW. All involved blood, bloody body fluids or high titer viral cultures; 48 of the 56 exposures were sharps injuries; 5 were mucous membranes/nonintact skin exposures; and 2 had both types of exposure.
- b. Potential sources of transmission (no confirmed cases with occupational exposures): semen, vaginal secretions, tissue or cerebrospinal, peritoneal, pericardial, synovial or amniotic fluid.
- c. Start PEP as soon as possible; if delay exceeds 36 hours, we suggest expert consultation.
- d. Continue prophylaxis for four weeks, if tolerated.
- e. Reevaluate exposed person within 72 hours, as additional information about the source becomes available—serologic status, VL, current treatment, any resistance test results or other factors that would modify recommendations.
- f. Use HIV EIA to monitor for seroconversion; perform this test at baseline and at 6 weeks, 3 months, and 6 months post exposure. We do not recommend VL tests for screening in the HCW unless there is an illness compatible with acute retroviral syndrome.
- g. If you give PEP, monitor the HCW for drug toxicity at baseline and at 2 weeks with CBC, renal function tests and hepatic function tests. For those receiving IDV, also do urinalysis.
- h. Ask HCWs to commit to behavioral measures, for example, sexual abstinence or condom use, for several weeks to 2 months. The greatest risk is during the first 6 to 12 weeks following exposure.
- i. Treat female HCWs with known or possible pregnancy as you would anyone else, except for selection of drugs. The care provider should discuss the drug benefits and risks with the HCW. Avoid EFV and the combination d4T and ddI.

3. Drug selection for PEP

a. Recommended regimens for PEP

- Base decisions in part on information about the source of exposure (that is, the HIV-infected patient). Is the patient on ART? What has been his or her response to therapy (including VL at the time of exposure and history of HIV resistance testing)? Health care workers often resist serology, but it is important because of the inadequacy of the PEP regimen for an HIV-positive HCW.
- Do not let decisions delay initiation of PEP; you can make modifications after obtaining the information.
- **Two drug combinations**
 - AZT + 3TC
 - 3TC + d4T
 - d4T + ddI
- **Three drug combinations**
 - Two nucleosides (above list) + IDV, NFV, EFV, ABC, RTV, FTV, APV, DLV or LPV/RTV
Preferred: NFV, EFV, ABC + LPV/RTV

b. Specific recommendations based on type of injury or exposure

- HIV PEP for percutaneous injuries (see table below)

Table B2, 4.2: PEP for Percutaneous Injuries

Exposure	Status of Source		
	Low risk ¹	High risk ¹	Unknown
Not severe: solid needle, superficial	2 drug PEP ²	3 drug PEP ²	Usually none; consider 2 drug PEP ³
Severe: large bore needle, deep injury, visible blood on device, needle in patient artery/vein	3 drug PEP ²	3 drug PEP ²	Usually none; consider 2 drug PEP ³

1 Low risk: asymptomatic HIV or VL <1500c/mL. High risk: symptomatic HIV, AIDS, acute seroconversion, high VL or WHO Stage IV, if viral load not available

2 Concern for drug resistance: initiate prophylaxis without delay and consult an expert

3 Consider two-drug PEP if source is high risk for HIV exposure from unknown source, when HIV-infected source is likely

- HIV PEP for mucous membranes and nonintact skin exposures, for example, dermatitis, abrasion, wound (see table below)

Table B2, 4.3: PEP for Mucous Membrane and Nonintact Skin Exposures

Exposure	Status of Source		
	Low risk ¹	High risk ¹	Unknown
Small volume (drops)	Consider two-drug PEP	Two-drug PEP	Usually no PEP; consider two-drug PEP ²
Large volume (major blood splash)	Two-drug PEP	Three-drug PEP	Usually no PEP; consider two-drug PEP ²

1 Low risk: asymptomatic HIV or VL <1500c/mL. High risk: symptomatic HIV/AIDS, acute seroconversion, high VL.

2 Consider if source has high risk factors or exposures from unknown source where HIV-infected source is likely.

CASE STUDIES

In the following cases, assess if the risk is low, moderate or high.

Case 1

A nurse is setting an IV line in a patient and accidentally pricks herself. The patient is a known injecting-drug user, but his HIV status is unknown.

Case 2

A nurse suffers a deep wound when someone passes her a bloodstained instrument during orthopedic surgery on an HIV-positive hemophiliac.

ANSWERS

Case 1

You need to take a history from the nurse and examine the patient who is an IV drug user. You can assess what needs to be done, depending on the risk assessment and the HIV test result.

Case 2

The risk is high.

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PART B: MODULE B2

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Appendices

Appendix A

Algorithms



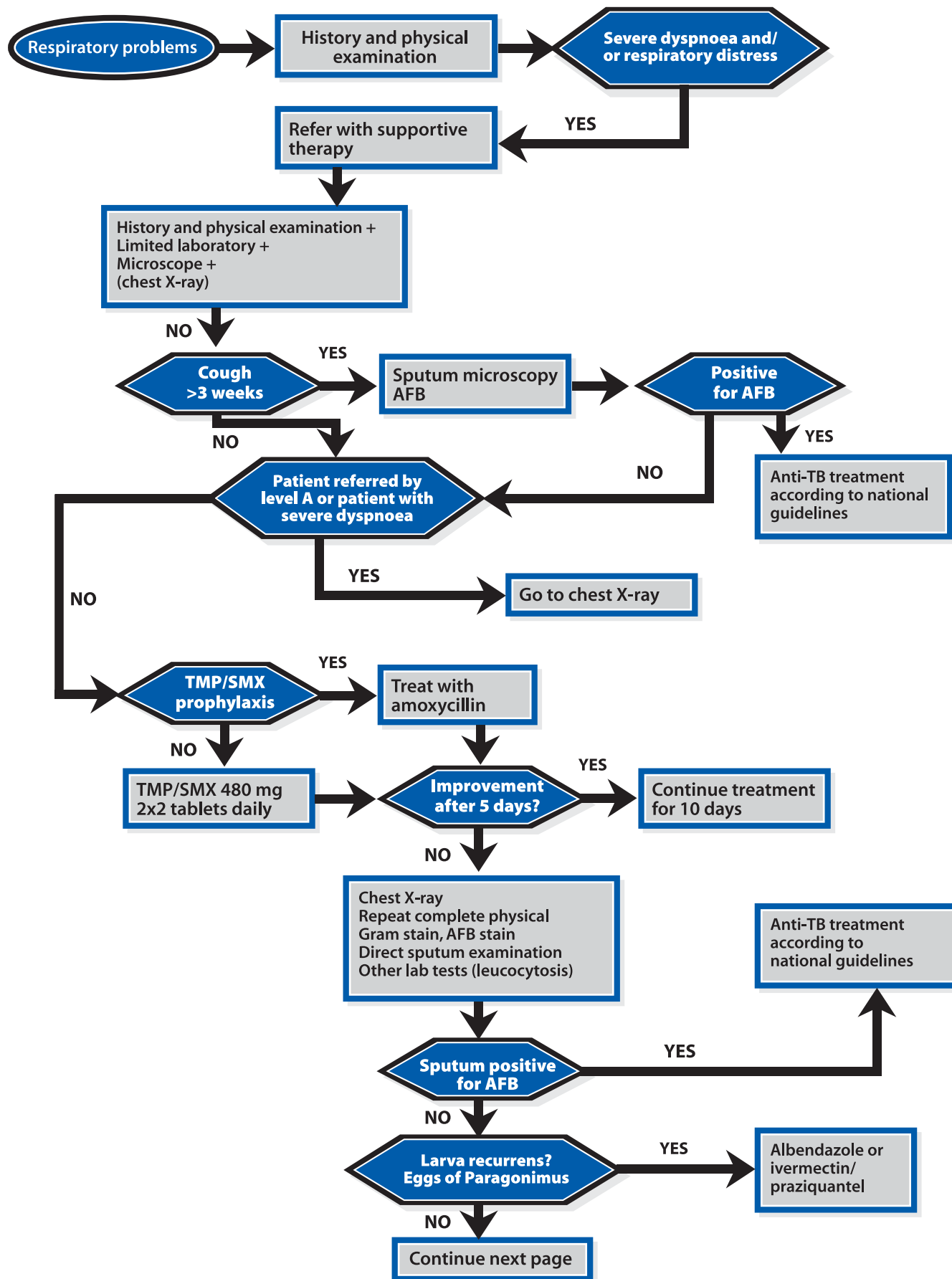
Trainers and course facilitators should use these algorithms as needed during case study discussions and in teaching clinical decision making and case management. They are also useful as a reference in the clinical setting. You can adapt them for different levels of care and settings, depending on laboratory, radiological and other resources.

The algorithms are adapted from the publication Lynen, L. and M. Biot. (eds.) 2000. *Clinical Aids Care Guidelines for Resource-Poor Settings*. Brussels, Belgium: Médecins Sans Frontières.

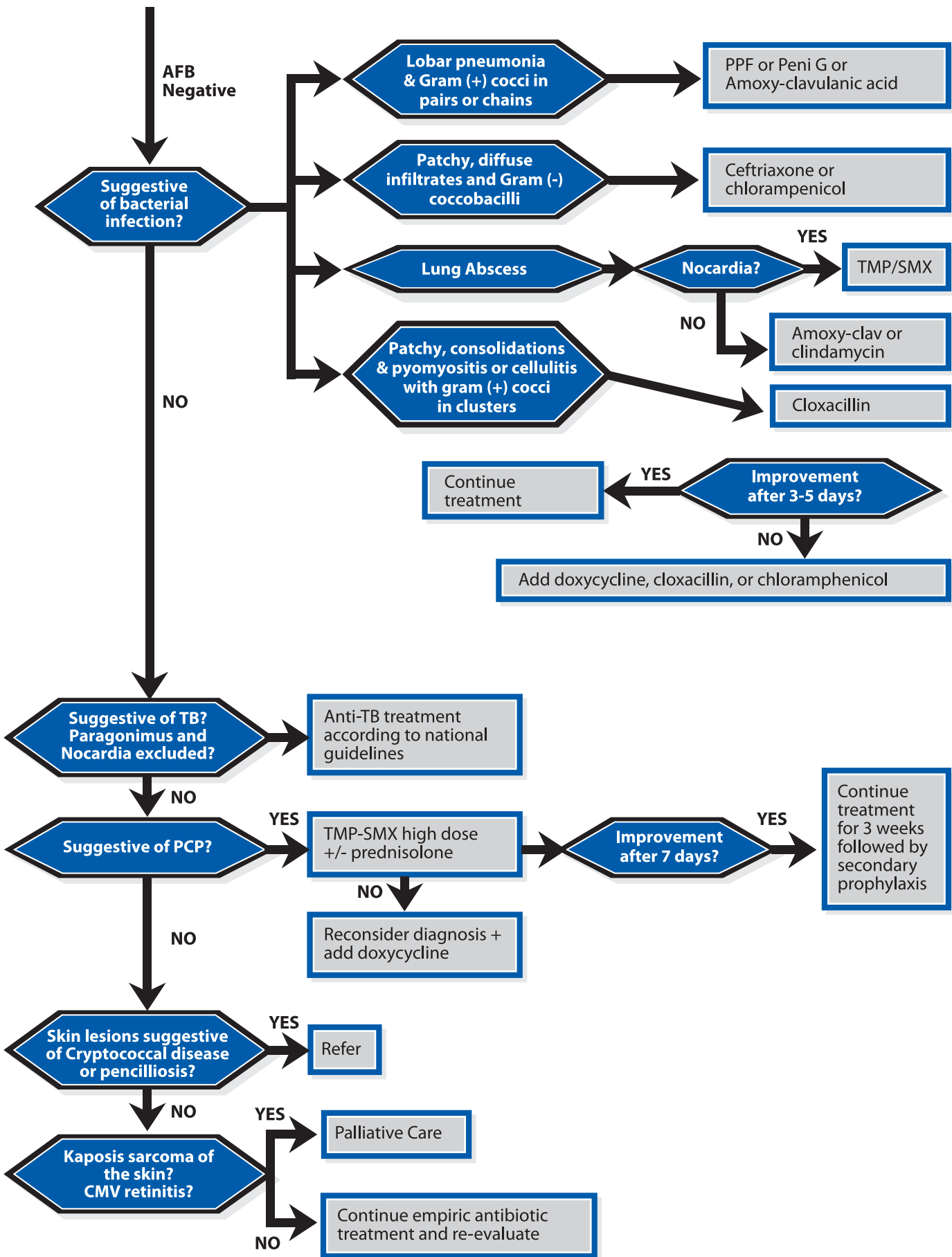
You will find algorithms for the following clinical presentations:

- Respiratory problems
- Lymphadenopathy
- Skin lesions
- Headache
- Diarrhea
- Oral lesions
- Dysphagia/Odynophagia

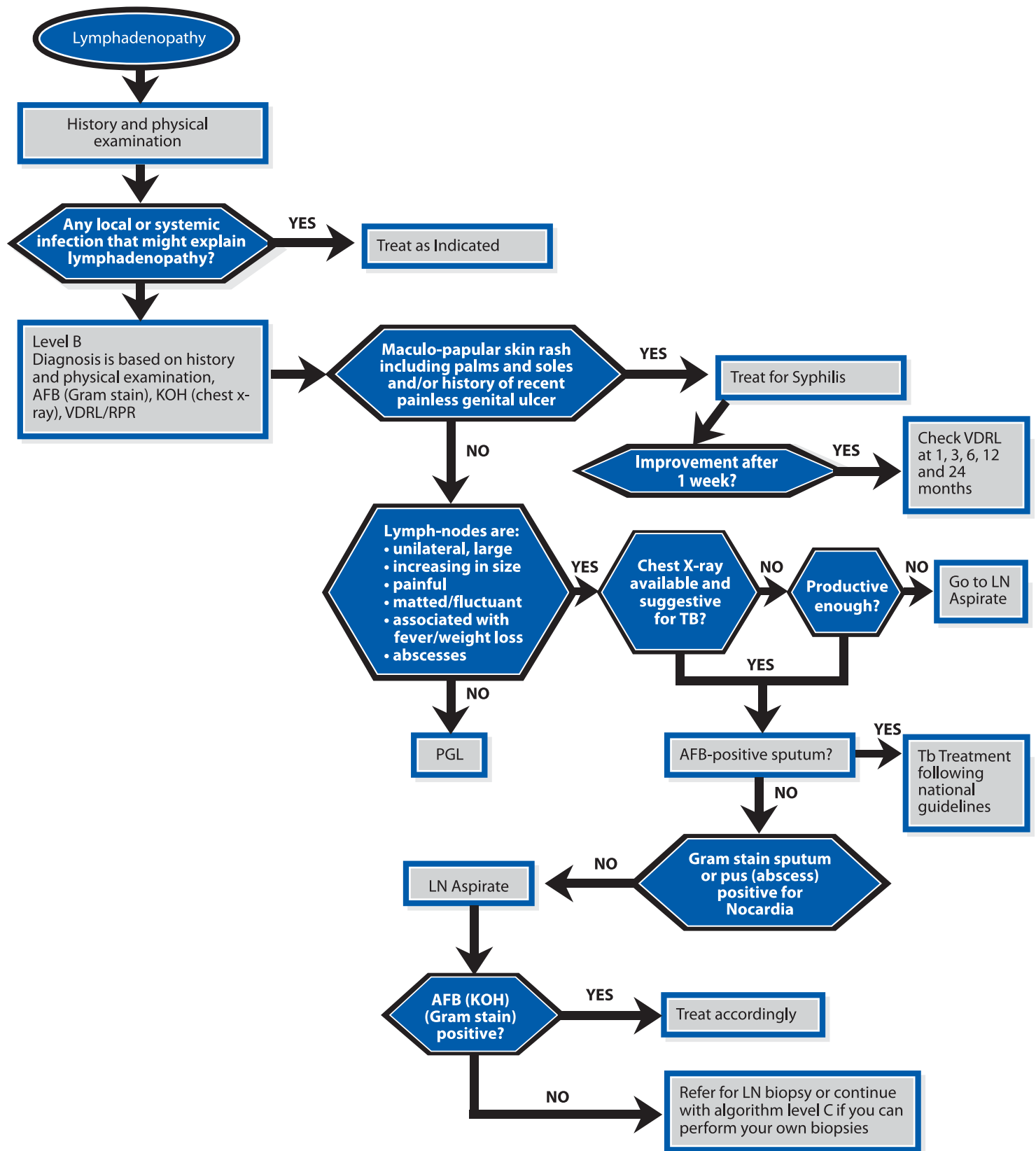
Clinical Management of Respiratory Problems



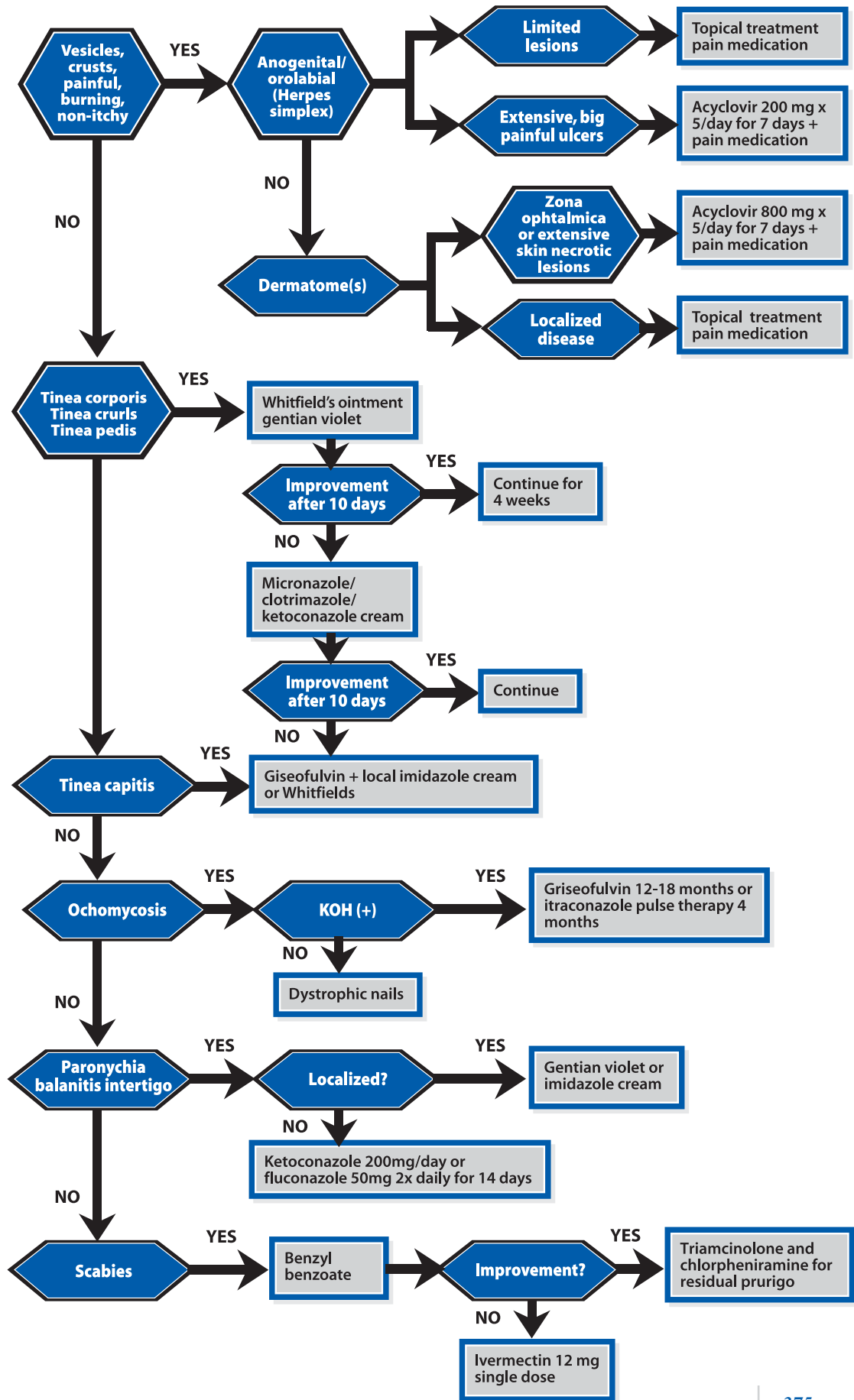
Clinical Management of Respiratory Problems (continued)



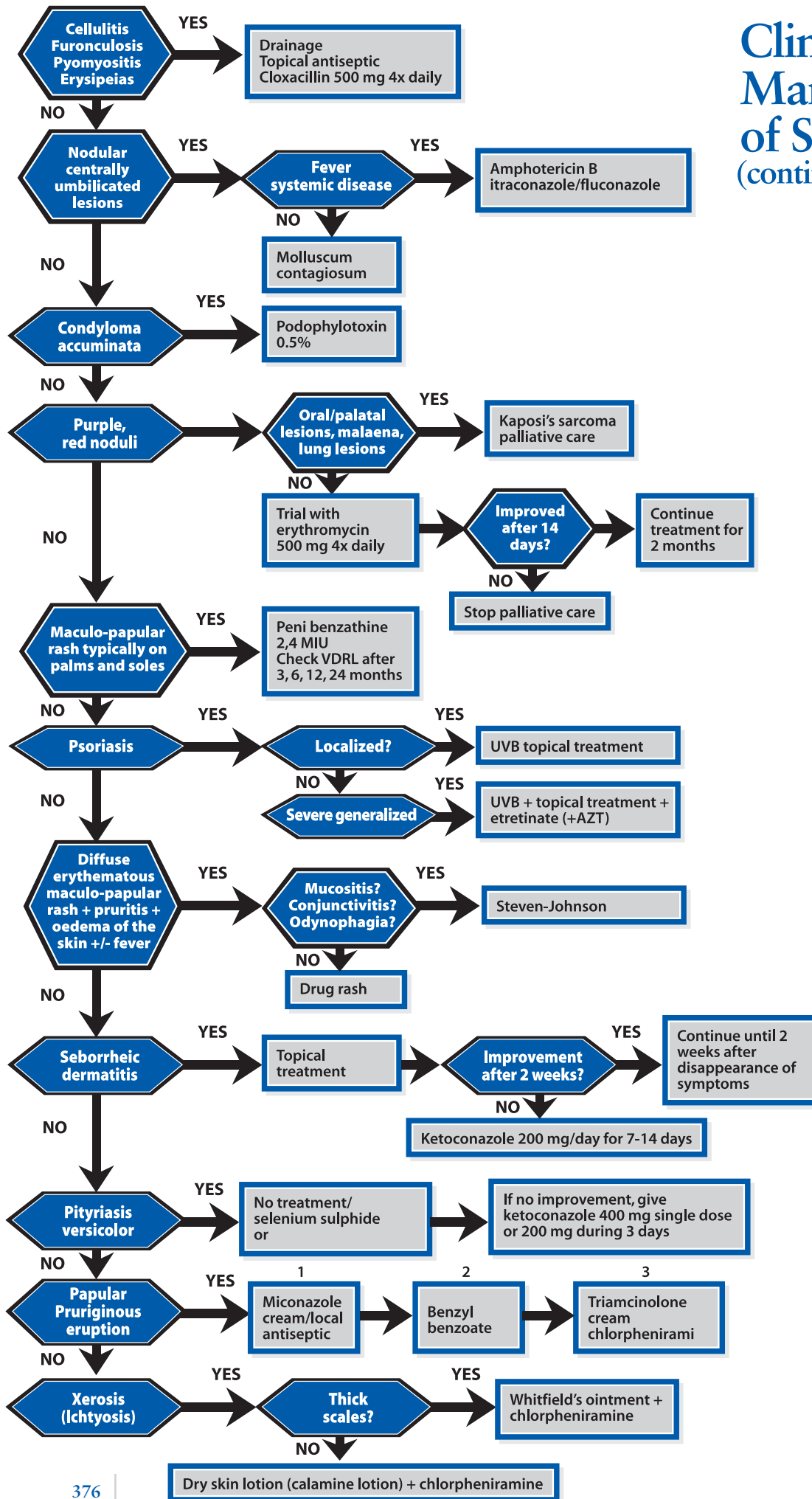
Clinical Management of Lymphadenopathy



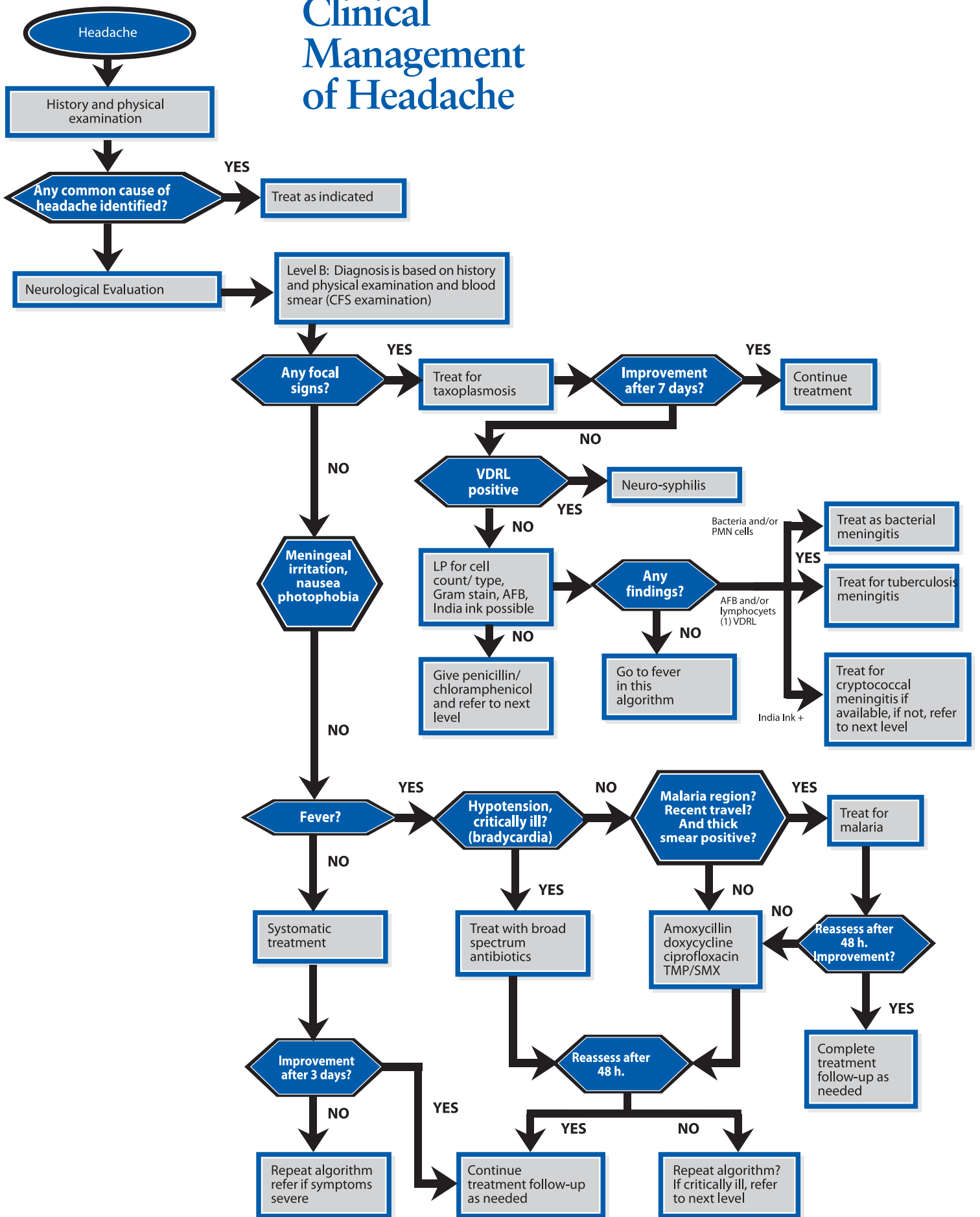
Clinical Management of Skin Lesions



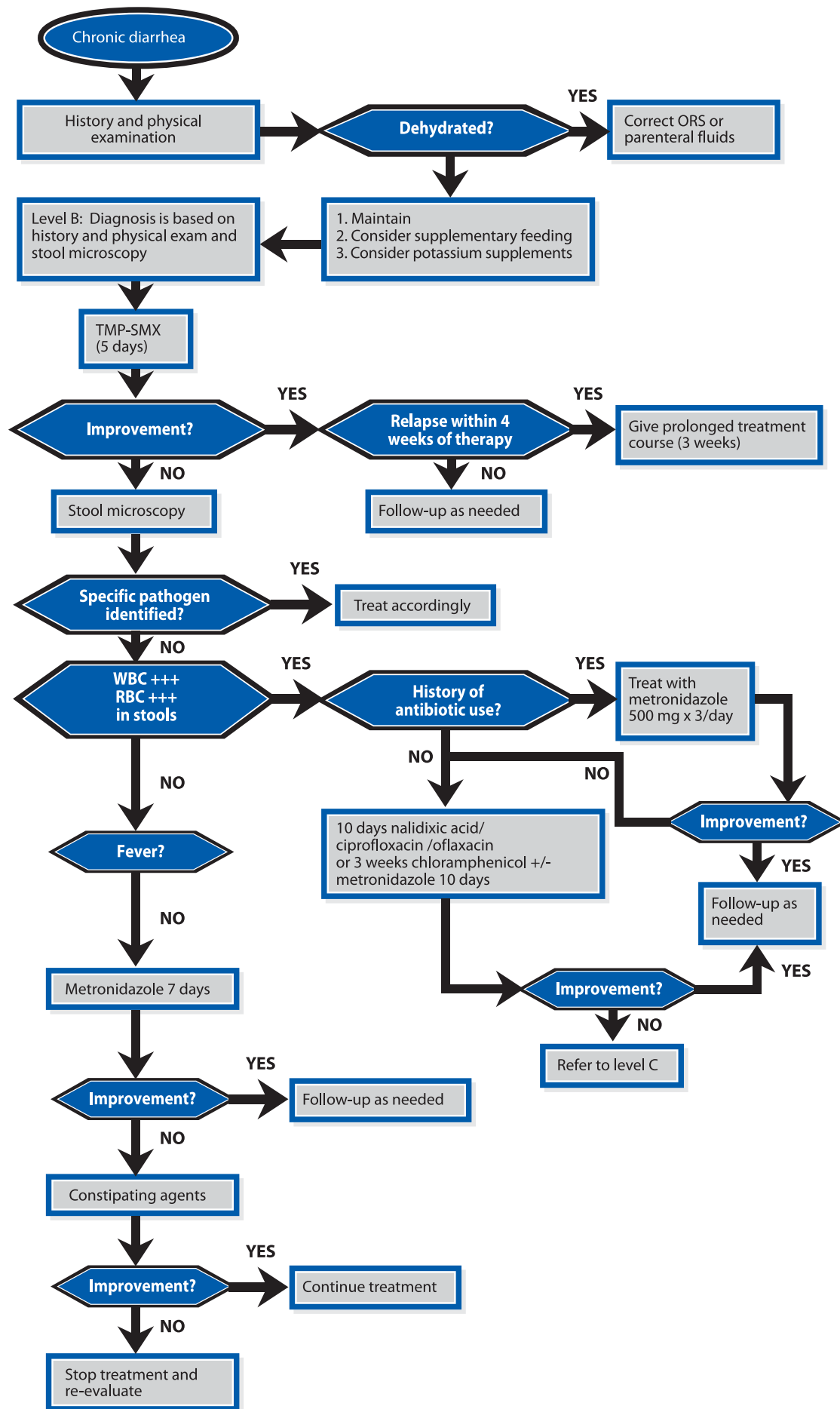
Clinical Management of Skin Lesions (continued)



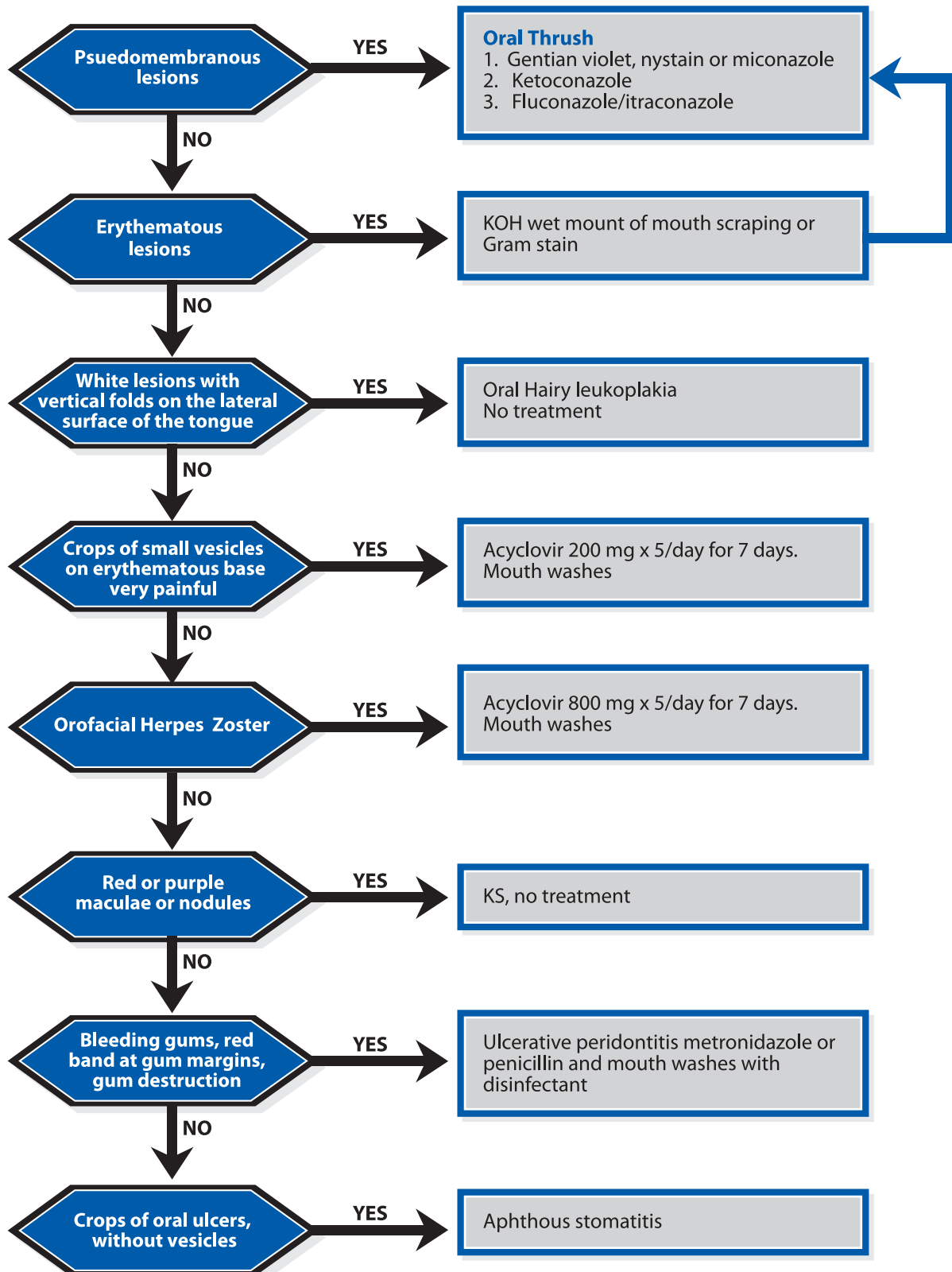
Clinical Management of Headache



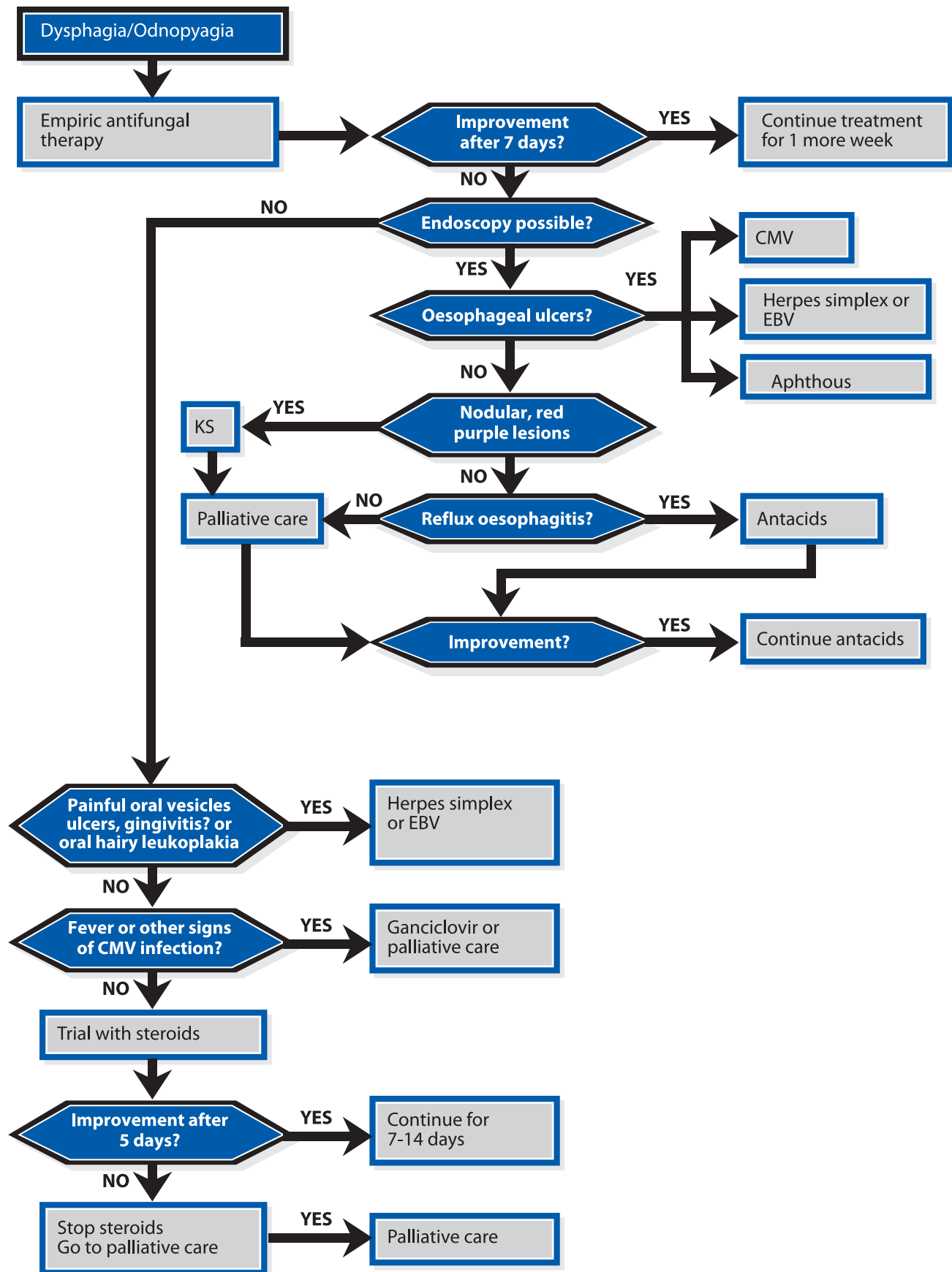
Clinical Management of Diarrhea



Clinical Management of Oral Lesions



Clinical Management of Dysphagia/Odynophagia



Appendix B

Resources on Clinical Management of HIV/AIDS and Antiretroviral Therapy in Resource-Constrained Settings, July 2003



1. AIDSMap website. *HIV & AIDS Treatment in Practice*. <http://www.aidsmap.com/main/hatip.asp>
HIV & AIDS Treatment in Practice is an e-mail newsletter for doctors, nurses, health care workers and community treatment advocates working in limited-resource settings.
2. AIDSmeds.com website. <http://www.aidsmeds.com>
AIDSmeds.com is dedicated to providing people living with HIV the information they need to make empowered treatment decisions. The founder and writers of this website are all living with HIV and know firsthand the challenges of learning how to fight this virus. By offering complete, uncomplicated, up-to-date information, AIDSmeds.com seeks to help those that are both new and old to this challenge and to remain a powerful resource for years to come.
3. Anderson, Jean R., 2001. *A Guide to the Clinical Care with Women with HIV/AIDS*. English, 510 pages.
<http://hab.hrsa.gov/publications/womencare.htm>
This guide provides information on gynecologic problems associated with HIV, as well as psychosocial, psychiatric and pharmacological considerations associated with the disease. It also contains information pertaining to adolescents and HIV, HIV and reproduction, and palliative and end-of-life care.
4. Bartlett, John G., 2002. *The 2002 Abbreviated Guide to Medical Management of HIV Infection*. English, 160 pages. <http://hopkins-aids.edu/publications/abbrevgd/abbrevgd.html>
This book is a resource for physicians and other health care professionals who provide care and treatment to patients with HIV/AIDS. This *Abbreviated Guide* is intended for bedside clinical management decisions.
5. Bartlett, John G. and Joel E. Gallant, 2001. *2003 Medical Management of HIV Infection*. English.
<http://hopkins-aids.edu/mmhiv2003/order.html>
The 2003 edition of *Medical Management of HIV Infection* serves as the standard of care for the Johns Hopkins AIDS Service. Maryland Medicaid has accepted it as the standard of care for quality assurance. You can order the full text of the book online.
6. Baylor College of Medicine, 2003. *HIV Curriculum for the Health Professional*.
<http://bayloraids.org/africa/nursingdownload.shtml>
This second edition *HIV Curriculum for the Health Professional* was developed by the Baylor International Pediatric AIDS Initiative and sponsored by the Bristol-Myers Squibb Secure the Future Program. The guidelines and study results in the curriculum are current through January 2003. The entire text can be downloaded.

7. Hoffmann, Christian and B.S. Kamps, 2003. *HIV Medicine 2003*. English, 350 pages.
<http://www.hivmedicine.com/>
HIV Medicine is a medical textbook that provides a comprehensive and up-to-date overview of the treatment of HIV infection. Its mission is to be a source for comprehensive and in-depth HIV/AIDS information. Access to the online version is free.

8. The FANTA Project, 2003. *Handbook: Developing and Applying National Guidelines on Nutrition and HIV/AIDS*. English, 72 pages. <http://www.fantaproject.org/>
 The handbook provides guidance for country teams and national AIDS control programs on developing and applying national guidelines on nutritional care and support of people living with HIV/AIDS. The handbook provides information on building a multisectoral team, adapting generic and country-specific materials to write national guidelines, integrating HIV/AIDS nutritional care and support into programs and services, and monitoring and evaluating the process and outcomes.

9. Food and Agriculture Organization, 2002. *Living Well with HIV/AIDS: A Manual on Nutritional Care and Support for People Living with HIV/AIDS*. English. <http://www.fao.org/DOCREP/005/Y4168E/Y4168E00.HTM>
 The manual was developed following an extensive review of existing guides from both developed and developing countries. Though it is applicable to many real life situations, users may find that they can further improve its usefulness if they adapt sections to local circumstances. The manual was prepared by the Nutrition Programs Service of the FAO Food and Nutrition Division (ESN) in collaboration with the WHO Department of Nutrition for Health and Development (NHD), Geneva, and is jointly published by FAO and WHO.

10. Forum for Collaborative HIV Research, 2002. *Proceedings of Workshop: Transfer of Diagnostic & Monitoring Technologies into Resource-Poor Settings, Washington DC, 22 April 2002*. English, 46 pages. Summary report in English/French. <http://www.hivforum.org/publications/publications.htm>
 The Forum for Collaborative HIV Research organized a meeting of key international researchers, industry representatives and others working on efficient and economical diagnostic and monitoring assays for people with HIV infection. Held on April 22, 2002, the meeting reviewed the development status of CD4 T-cell and HIV quantitative assays and considered steps for further study, with the ultimate goal of transferring validated technologies to resource-limited settings.

11. International Association of Physicians in AIDS Care, 2002. *Global AIDS Learning & Evaluation Network Curriculum (GALEN). Module 8: Introduction to Antiretroviral Therapies; Module 9: Antiretroviral Therapy in Resource-Limited Settings*. English. <http://www.iapac.org/>
 The *GALEN Curriculum* is divided into Basic and Advanced HIV Medicine components to accommodate the particular needs of various local and national settings. It may be adapted easily to further reflect these needs and situational realities and to complement existing HIV medical education programs where they exist. Each component of the curriculum has an individual learning/training manual that includes a program overview, clinical descriptions, reference charts, case studies and evaluation questions.

12. International HIV/AIDS Alliance, 2002. *Voices from the Community: Report from a Community Consultation on Antiretroviral Treatment in Zambia*. Email: info@alliancezambia.org.zm or mail@aidsalliance.org.
 This report describes a community consultation by the International HIV/AIDS Alliance, the Network of Zambian People Living with HIV/AIDS, Catholic Diocese of Ndola, and Churches Health Association of Zambia in November 2002. The consultation aimed to develop an understanding of community perceptions, knowledge and experience of ARV treatments and to encourage the involvement of PLHA and communities in planning, developing and implementing ARV treatment programs.

13. International HIV/AIDS Alliance, 2002. *Mobilising NGOs, CBOs and PLHA Groups for Improving Access to HIV/AIDS-Related Treatment. A Handbook of Information, Tools and Other Resources*. English, 135 pages. http://www.aidsalliance.org/_docs/index_eng.htm; <http://www.unaids.org/publications/documents/health/access/NGOtoolkit/>
A collection of information, tools, and other resources to help NGOs, CBOs and PLHA groups to think through issues around access to HIV/AIDS-related treatment. This handbook is a product of a collaborative project including the International HIV/AIDS Alliance, WHO and UNAIDS. The project aims to develop a practical toolkit for NGOs, CBOs and groups of people living with HIV/AIDS on access to HIV/AIDS-related treatment in developing countries.

14. John Snow, Inc., 2003. *The Tool to Assess Site Programme Readiness for Initiating Antiretroviral Therapy (ART)*. English. 20 pages. http://deliver.jsi.com/2002/archives/hiv aids/SofR_tool/index.cfm
Developed under the USAID-funded DELIVER project, the tool provides sites, program managers and others conducting assessments with some measure of a site's capacity to initiate ART. It has been field-tested in a number of countries and undergone multiple revisions based on feedback from the users. The tool seeks to establish a set of criteria to help in assessing a site's readiness to implement antiretroviral therapy and to select ART sites based not on site type, but on capacity, vision and activities needed for rational introduction and expansion of ART into HIV care. The tool is also useful for site self-assessment, for helping sites and donors identify areas needing technical assistance, and for helping programs to determine sites for ART introduction and scale-up. Finally, the tool can identify areas where site programs can serve as resources for other programs.

15. Katabira E., M.R. Kanya, F.X. Mubiru, and N.N. Bakuyaita, 2000. *HIV Infection: Diagnostic and Treatment Strategies for Healthcare Workers*. English, 132 pages. Email: makprint@infocom.co.ug
Published by Makerere University in Uganda, this book provides health workers with a simple, practical management approach for HIV/AIDS.

16. Médecins sans Frontières, 2001. *Clinical AIDS Care Guidelines for Resource-Poor Settings*. English. Email: zoom@brussels.msf.org or office-lu@msf.org
These guidelines aim to develop and describe strategies for managing the health problems of AIDS patients at the different levels of care provision to ensure a continuum of care. For each level of care, they propose a strategy, as well as the necessary equipment and drugs, for responding to the health needs of PLHA.

17. Médecins sans Frontières, 2003. *Untangling the Web of Price Reductions: A Pricing Guide for the Purchase of ARVs for Developing Countries*. English, French, 31 pages.
<http://www.accessmed-msf.org/prod/publications.asp?scntid=9520031050482&contenttype=PARA&>
The data in this guide on ARV prices offered by originator companies and some generic companies in low- and middle-income countries are meant to provide potential buyers with clear, verified information. The guide is intended for use by government and nonprofit procurement agencies, as well as other bulk purchasers of ARVs, including health facilities and NGOs. This document includes both adult and pediatric formulations and is meant to be used in tandem with the report on "Pilot Procurement, Quality, and Sourcing Project: Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality," a project initiated by WHO and developed in collaboration with other UN Organizations (UNAIDS, UNICEF, UNFPA).

18. Pan American Health Organization, 2002. *Building Blocks: Guidelines for Antiretroviral Treatment in Adults for Latin American and Caribbean Countries*. Spanish, 60 pages.
http://www.paho.org/English/HCP/HCA/arv_adultos.htm
These guidelines, part of the series of documents for the building blocks strategy, are a response to numerous requests by health authorities of the region of the Americas for information on how to ensure improved care and especially greater access to antiretroviral treatment for people who live with HIV/AIDS in Latin America and the

Caribbean. The guidelines are based on recommendations of a PAHO Advisory Group (August, 2001) and on the WHO document *Expansion of Antiretroviral Treatment in Low-Resource Settings* (2002).

19. Pan American Health Organization, 2000. *Building Blocks: Proceedings of the Consultations on Standards of Care for Persons Living with HIV/AIDS in the Americas*. English, 48 pages. <http://www.paho.org/English/HCP/HCA/PoceedingsBldingBlcks.pdf>
This document is a narrative of the process of developing the building blocks framework. The summary report explaining the framework is under *Comprehensive Care Guidelines for Persons Living with HIV/AIDS in the Americas*.

20. Pan American Health Organization, 2000. *Building Blocks: Comprehensive Care Guidelines for Persons Living with HIV/AIDS in the Americas*. Spanish, English, 15 pages.
<http://www.paho.org/English/HCP/HCA/BuildingBlocks.pdf> and http://www.paho.org/Spanish/HCP/HCA/BB_Summary_span.pdf
This summary report provides an operational definition of HIV/AIDS comprehensive care and outlines its core components. It presents a care model that is meant to provide guidance for developing policies and strategies and to promote discussion about the full spectrum of care required to meet the needs of PLHAs, their families and caregivers.

21. Pan American Health Organization, 1999. *Building Blocks: Women and HIV/AIDS Prevention and Care Strategies*. English, Spanish, 35 pages. http://www.paho.org/English/HCP/HCA/Women_HIV.pdf and <http://www.paho.org/Spanish/HCP/HCA/MujeryVIH.pdf>
This manual, part of the *Building Blocks* series for HIV/AIDS comprehensive care, aims to provide information for use in developing training programs and workshops that enable health care workers to respond competently and compassionately to HIV-affected women, their partners and their families. Among the topics highlighted are: clinical diagnosis of HIV in women; mother-to child transmission interventions; confidential VCT; sexual health, including safe sex; family planning; emotional support and counseling; personal and environmental hygiene; universal precautions and food safety.

22. Piwoz, E. & E. Preble, 2000. *HIV/AIDS and Nutrition: A Review of the Literature and Recommendations for Nutritional Care and Support in sub-Saharan Africa*. English, 54 pages. http://sara.aed.org/publications/cross_cutting/hiv_nutrition/HIV%20and%20Nutrition.pdf

23. Population Council/Horizons Program, 2001. *Access to Treatment for HIV/AIDS: Report of a Meeting of International Experts 12-13 June 2001, Washington, DC*. English, 42 pages.
<http://www.popcouncil.org/pdfs/horizons/accesstotreatment.pdf>
Operations research questions for access to treatment for HIV/AIDS

24. Princeton, Douglas C., 2003. *Manual of HIV/AIDS Therapy, 2003 Edition*. English, 91 pages.
www.ccsypublishing.com
This reference contains new information on the treatment of HIV-infected patients, and it outlines current management of all opportunistic infections. It includes new therapeutic regimens not yet available in any other book; it is the most up-to-date reference on AIDS available.

25. Project Inform website. <http://www.projinf.org/>
Project Inform is a national nonprofit CBO working to end the AIDS epidemic. Their mission is to: provide vital information on the diagnosis and treatment of HIV disease; advocate for enlightened regulatory, research and funding policies; and to inspire people to make informed choices and to choose hope over despair.

26. UNAIDS and WHO, 2002. *Improving Access to Care in Developing Countries: Lessons from Practice, Research, Resources and Partnerships*.
http://www.unaids.org/publications/documents/care/acc_access/JC809-Access-to-Care-E.pdf
 A report from the meeting *Advocating for Access to Care and Sharing Experiences*, this publication reflects the mobilization of a group of experts in the fields of medicine, science, economics, social services and care in sharing their experiences and advocating for accelerating access to care for people living with HIV/AIDS in developing countries. It includes papers from 2001 by members of this group, collating lessons learned and analyzing key issues in implementing the care agenda, as well as a Declaration for a Framework for Action adopted at this Paris meeting.
27. UNICEF, UNAIDS, WHO and MSF, 2003. *Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS*.” English, 92 pages. <http://www.who.int/medicines/organization/par/ipc/sources-prices.pdf>
 This report includes 59 active ingredients in 100 dosage forms, is issued annually, and is available in printed documents and on the websites of all partners (UNICEF, UNAIDS, and MSF). This joint project on sources and indicative prices started in 1999 was first published in 2000, and will be closely linked with the Expressions of Interest launched as part of the *Accelerated Access*. The June 2003 report includes updated prices of pharmaceutical products and diagnostic tests. In addition to antiretroviral medicines, it includes medicines for treating a range of OIs, for pain relief, for use in palliative care, for the treatment of HIV/AIDS-related cancers and for managing drug dependence. It also provides information on a range of HIV/AIDS test kits for initial diagnosis of the infection and ongoing monitoring of antiretroviral treatment. The report also includes a section on registration status of products included in the survey and the updated publication of MSF’s *Untangling the Web of Price Reductions: a Pricing Guide for the Purchase of ARVs for Developing Countries*.
28. World Health Organization, 2003. *Pilot Procurement, Quality and Sourcing Project: Access to HIV/AIDS Drugs of Acceptable Quality*. English. <http://www.who.int/medicines/organization/qsm/activities/pilotproc/pilotproc.shtml>
 This pilot project website evaluates pharmaceutical products according to WHO-recommended standards of quality and compliance with Good Manufacturing Practices. It is part of an ongoing process that will expand as more suppliers participate. Note that this list of *pre-qualified drugs* is not exhaustive, and exclusion from the list does not mean that a drug has not been approved by one or more national drug regulatory authorities. In fact, all generic drugs included in this pricing guide are at least cleared for marketing in their countries of origin.
29. World Health Organization, 2003. *Adherence to Long-Term Therapies: Evidence for Action*. English, 209 pages. http://www.who.int/chronic_conditions/adherencereport/en/
 This report, intended for policy makers, health managers and clinical practitioners, is based on an exhaustive review of the published literature on the definitions, measurements, epidemiology, economics and interventions applied to nine chronic conditions and risk factors. The report provides a concise summary of the consequences of poor adherence for health and economics. It also discusses the options available for improving adherence and demonstrates the potential impact on desired health outcomes and health care budgets. Chapter XII addresses HIV/AIDS.
30. World Health Organization, Regional Office for South East Asia, 2002. *Fact Sheets on Antiretroviral Drugs*. English, 58 pages. http://w3.whoasia.org/hivaids/antiretro_content.htm
 These fact sheets and accompanying notes are designed for use in the daily activities of physicians responsible for the management of HIV-infected patients at any level. The set consists of fact sheets of all currently approved antiretroviral drugs. The fact sheet for each drug includes information about the class of the drug, available formulations, storage, dosage, known interactions with other drugs (including other antiretrovirals) and main side effects. The information is updated until April 2002.

31. World Health Organization, Regional Office for South East Asia, 2002. *The Use of Antiretroviral Therapy: A Simplified Approach for Resource-Constrained Countries*. English, 54 pages.
http://w3.whosea.org/hiv/aids/therapy_cont.htm
The WHO Southeast Asia Regional Office developed these practical guidelines as a model to assist countries in the region in formulating national antiretroviral treatment guidelines according to their own needs and resources.
32. World Health Organization, June 2002. *Scaling up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*. English, 97 pages. Executive summary available in English, French and Spanish. <http://www.who.int/hiv/topics/arv/en/>; <http://www.who.int/docstore/hiv/scaling/>
These guidelines are part of WHO's commitment to the global scale-up of antiretroviral therapy. The recommendations come largely from a review of evidence and reflect the best current practices. The document guides the development and setting of standards for regimens as well as eligibility and monitoring criteria for patient management.
33. World Health Organization and UNAIDS, 1998. *Nine Guidance Modules on Antiretroviral Treatments*. (Note: Only modules 3, 7, 8 and 9 are still recommended.) English, 175 pages.
<http://www.paho.org/english/hcp/hca/ModulosARV.htm>
Nine modules form a complete set and together address the major issues relating to the use and provision of ARVs, including treatments; regulations; distribution; control; ethical issues; safe, effective use and more. The following modules are recommended: Module 3 Antiretroviral Treatments: Planning and Integration into Health Services; Module 7 Treatments Following Exposure to HIV; Module 8 Antiretrovirals: Regulation, Distribution, and Control; and Module 9 Ethical and Societal Issues Relating to Antiretroviral Treatments.

Appendix C

Sample Assessments and Tests



For Part A: HIV/AIDS Care and Treatment

Pre- and Post-tests and Participant Self-Assessments

Part A: HIV/AIDS Care and Treatment

Pretest

These questions are intended to provide information on what you know and what you need to learn in the areas the workshop will cover. This pretest also serves as a baseline against which to measure learning from the workshop through a post-test at the end of the workshop. Your completing the pretest will help the trainer.

Please answer each question as instructed.

1. Factors that facilitate transmission of HIV include (*circle all that apply*):
 - a. Multiple-partner sex
 - b. Needle-sharing
 - c. Poverty
 - d. Lack of religious commitment
 - e. Education of women

2. Clinical features of primary seroconversion illness include (*circle all that apply*):
 - a. On first exposure, there is a 32-week period of intense viral replication before onset of an immune response and clinical illness. Acute illness lasts from one to two weeks and occurs in 53 percent to 93 percent of cases.
 - b. Clinical manifestations resolve as antibodies to the virus become detectable in patient serum.
 - c. Patients then enter a stage of asymptomatic infection lasting from months to years.

3. The case definition of AIDS includes having a CD4 of less than (*fill in the blank*):_____.

4. Infections characteristic of severe immune depletion phase include (*circle all that apply*):
 - a. Pneumonia resulting from Pneumocystis Carinii (PCP)
 - b. Tinea versicolor
 - c. Bell's palsy
 - d. Cytomegalovirus retinitis
 - e. Mycobacterium avium

5. *True or False*
____When taking a patient history, the health care worker should begin with closed-ended questions.

6. What major elements should you address when taking a sexual history to assess HIV risk? (*circle all that apply*.)
 - a. Route of penetration
 - b. Partner(s): gender, monogamous or polygamous
 - c. History or presence of STIs
 - d. Frequency of orgasm
 - e. Use of condoms

7. Which of the four WHO clinical stages is characterized by: in bed <50 percent of normal daytime, but more than normally during the previous month? (*Fill in the blank*.) Stage ____.

8. *True or False*
____Negative test results mean the patient has not been infected with the AIDS virus or that the infection is so recent that detectable antibodies to the virus have not yet appeared in the blood.

9. *True or False*
____Voluntary counseling and testing is best used only with persons who are fairly sure they are not infected and need reassurance.

10. In situations other than transfusion screening and testing, for a person in clinical stage III or IV in a high prevalence area, you should use (*fill in the blank*) _____ tests to determine a client's HIV status.

11. *True or False*

____ Breaking bad news to patients is difficult. It is best to tell them all the details at once.

12. Common mycobacterial organisms responsible for respiratory infections in HIV-infected persons include (*circle all that apply*):

- a. M. tuberculosis
- b. M. Avium complex
- c. Streptococcus pneumoniae
- d. Aspergillosis

13. *True or False*

____ The most common form of TB is pulmonary.

14. Factors that increase the risk of transmission of HIV from a mother to a newborn include all but one of the following (*circle the one that does not fit*):

- a. Vaginal delivery
- b. Duration of rupture of membranes for longer than four hours
- c. Vitamin C deficiency
- d. High maternal viral load
- e. Invasive procedures during delivery

15. Therapy with nevirapine and AZT can reduce mother-to-infant transmission. You should administer nevirapine (*check the one that applies*):

- a. ____ To the mother during labor
- b. ____ To the mother just after delivery
- c. ____ To the mother starting at 34 weeks of pregnancy

16. When using CD4 counts to monitor disease progression and drug efficacy in children, it is best to look at the (*check one*) ____ percentage of CD4 or ____ absolute number of CD4 cells.

17. *True or False*

____ An HIV-positive child with a fever of 39° or higher should be treated with antimalarials in endemic areas.

18. *True or False*

____ If an HIV-positive mother chooses to breast feed, it is best for her to breast feed exclusively.

19. Choose the type of care described by the phrase "to provide support and care for patients throughout all phases of the disease so they can live as fully and comfortably as possible."

(*Check one.*)

- ____ Symptomatic
- ____ Curative
- ____ Palliative
- ____ Psychiatric

20. *True or False*

Dyspnea may be a cause of insomnia.

21. Persistent diarrhea is defined as (*check one*):

Diarrhea more than 10 times a day for more than three days

Loose stools more than three times in one day

Liquid stools three or more times a day, continuously or intermittently, for more than two weeks

22. *True or False*

Growth failure in a child is defined as loss of five percent or more of body weight.

Part A: HIV/AIDS Care and Treatment

Pre-Workshop Participant Self-Assessment

As part of the workshop evaluation, we would like to see how you assess yourself before and after participating in the workshop. There are areas in which you already have experience or skills, and therefore feel comfortable, and other areas that you find less familiar or more difficult, and in which you may feel less comfortable. We are asking you to complete this self-assessment at the beginning and again at the end of the workshop. We will then compare the results to see if this training has helped you become more confident in managing patients with HIV and AIDS.

Thank you for filling out this instrument.

Please circle the rating that best matches your level of comfort with the stated behavior or skill.

A. Answering questions from a patient who has a positive HIV test as a result of a medical visit (not as part of the local VCT program)

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

B. Describing the epidemiology of HIV/AIDS in my country to a district health council

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

C. Listing the common neurological symptoms of a patient with HIV/AIDS

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

D. Describing interpretation of CD4 counts in children with HIV

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

E. Recommending MTCT prevention interventions for a community setting

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

F. Prescribing treatment for PCP

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

G. Describing the life cycle of the HIV virus

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

H. Identifying biological risk factors for HIV transmission and acquisition

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

I. Diagnosing and treating neuropsychiatric manifestations of HIV/AIDS

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

J. Diagnosing and managing HIV-related cancers

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

K. Diagnosing and managing opportunistic infections (OIs) affecting the gastrointestinal system

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

L. Diagnosing and managing OIs affecting the respiratory system

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

M. Diagnosing and managing a child with OIs

1. Very Comfortable

2. Comfortable

3. Not Comfortable

4. Very Uncomfortable

N. Telling a pregnant woman and her husband that the woman is HIV positive

1. Very Comfortable

2. Comfortable

3. Not Comfortable

4. Very Uncomfortable

Part A: HIV/AIDS Care and Treatment

Post-Test

These questions are intended to provide some information about what you have learned in the workshop sessions. The results of this test can be compared to the pretest you took at the beginning of the workshop to gauge progress and identify areas where more study might be needed.

Please answer each question as instructed.

1. Factors that facilitate transmission of HIV include (*circle all that apply*):
 - a. Multiple partner sex
 - b. Needle-sharing
 - c. Poverty
 - d. Lack of religious commitment
 - e. Education of women

2. Clinical features of primary seroconversion illness include (*circle all that apply*):
 - a. On first exposure, there is a 32-week period of intense viral replication before onset of an immune response and clinical illness. Acute illness lasts from one to two weeks and occurs in 53 percent to 93 percent of cases.
 - a. Clinical manifestations resolve as antibodies to the virus become detectable in patient serum.
 - b. Patients then enter a stage of asymptomatic infection lasting from months to years.

3. The case definition of AIDS includes having a CD4 of less than (*fill in the blank*)_____.

4. Infections characteristic of severe immune depletion phase include (*circle all that apply*)
 - a. Pneumonia resulting from Pneumocystis Carinii (PCP)
 - b. Tinea versicolor
 - c. Bell's palsy
 - d. Cytomegalovirus retinitis
 - e. Mycobacterium avium

5. *True or False*
____When taking a patient history, the health care worker should begin with closed-ended questions.

6. What major elements should you address when taking a sexual history to assess HIV risk? (*circle all that apply.*)
 - a. Route of penetration
 - b. Partner(s): gender, monogamous or polygamous
 - c. History or presence of STIs
 - d. Frequency of orgasm
 - e. Use of condoms

7. Which of the four WHO clinical stages is characterized by: in bed <50 percent of normal daytime, but more than normally during the previous month? (*Fill in the blank*) Stage ____.

8. *True or False*
____Negative test results mean the patient has not been infected with the AIDS virus or that the infection is so recent that detectable antibodies to the virus have not yet appeared in the blood.

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____ The most common form of TB is pulmonary.

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18. *True or False*

____ If an HIV-positive mother chooses to breast feed, it is best for her to breast feed exclusively.

19. Choose the type of care described by the phrase "to provide support and care for patients throughout all phases of the disease so they can live as fully and comfortably as possible." (*Check one*)

- ____ Symptomatic
- ____ Curative
- ____ Palliative
- ____ Psychiatric

20. *True or False*

____ Dyspnea may be a cause of insomnia.

21. Persistent diarrhea is defined as (*check one*):

Diarrhea more than 10 times a day for more than three days

Loose stools more than three times in one day

Liquid stools three or more times a day, continuously or intermittently, for more than two weeks

22. *True or False*

Growth failure in a child is defined as loss of five percent or more of body weight.

Part A: HIV/AIDS Care and Treatment

Post-Workshop Participant Self-Assessment

As part of the workshop evaluation, we would like to see how you assess yourself before and after participating in the workshop. There are areas in which you already have experience or skills, and therefore feel comfortable, and other areas that you find less familiar or more difficult, and in which you may feel less comfortable. We are asking you to complete this self-assessment at the beginning and again at the end of the workshop. We will then compare the results to see if this training has helped you become more confident in managing patients with HIV and AIDS.

Thank you for filling out this instrument.

Please circle the rating that best matches your level of comfort with the stated behavior or skill.

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B. Describing the epidemiology of HIV/AIDS in my country to a district health council

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E. Recommending MTCT prevention interventions for a community setting

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1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

M. Diagnosing and managing a child with OIs

1. Very Comfortable

2. Comfortable

3. Not Comfortable

4. Very Uncomfortable

N. Telling a pregnant woman and her husband that the woman is HIV positive

1. Very Comfortable

2. Comfortable

3. Not Comfortable

4. Very Uncomfortable

Appendix C

Sample Assessments and Tests



For Part B: Antiretroviral Therapy

Pre- and Post-Tests and Participant Self-Assessments

Part B: Antiretroviral Therapy

Pretest

1. The goal of Antiretroviral Therapy (ART) is to (*circle the one that DOES NOT apply*):
 - a. Prolong and improve the quality of life of people living with HIV and AIDS
 - b. Reduce the viral load as much as possible, for as long as possible, to halt disease progression and prevent or reduce resistant variants
 - c. Achieve immune reconstitution that is quantitative and qualitative
 - d. Decrease the need for condom use

2. *True or False*
 A person needs ART only when the CD4 count is below 100 or when he or she is unable to engage in activities of daily living for at least 10 percent of the day.

3. The absolute minimum tests to use as clinical evaluation for ART include (*name two*):
_____ and _____.

4. *True or False*
 Measuring CD4 is preferable to measuring viral load when assessing both the need for and the response to ART.

5. *True or False*
 No matter what the CD4 count, WHO stage IV disease is a sound basis for starting ART.

6. *True or False*
 In a child, WHO stage III disease or stage I and II + CD4 < 20 percent, is a sound basis for starting ART.

7. *True or False*
 An assessment of viral load is not essential for starting therapy.

8. The WHO Clinical Staging System (*circle all that apply*):
 - a. Includes a clinical classification system and a laboratory classification to categorize the immunosuppression of adults by their total lymphocyte counts
 - b. Is based on clinical markers believed to have prognostic significance resulting in four categories; it is helpful to incorporate a patient performance scale into the system
 - c. Should be used only by junior providers
 - d. Has been proven reliable for predicting morbidity and mortality in infected adults

9. *True or False*
 Pneumocystis carinii pneumonia or p. jiroveci (PCP) is characteristic of clinical stage IV.

10. The main stages of the HIV life cycle where ARVs act include (*circle all that apply*):
 - a. The production of proviral DNA
 - b. Maturation of virion

11. Place “NNRTI” in front of the characteristics of nonnucleoside reverse transcriptase inhibitors (NNRTIs) and place “NsRTI” in front of the characteristics of nucleoside reverse transcriptase inhibitors (NsRTI).

- a. Lead to premature termination of the production of the HIV DNA chain
- b. Active only against HIV-1
- c. Interacts with some drugs because of the induction and/or inhibition of cytochrome P450 enzymes
- d. Typical side effects include maculopapular rash, hepatitis and headache.
- e. Typical side effects include nausea and vomiting, anemia, peripheral neuropathy and pancreatitis.
- f. Active against both HIV 1 and HIV 2

12. Circle the statements below that accurately describe protease inhibitors:

- a. Interfere with the production of mature infectious virions
- b. Can lead to decreases in viral load to the level of undetectable virus
- c. If used alone, resistance develops rapidly.
- d. Produce few, if any, side effects
- e. Inhibit cytochrome P450 enzymes, leading to multiple drug interactions

13. Name three protease inhibitors

1. _____ 2. _____ 3. _____

14. How many antiretrovirals should be together to be effective for preventing the emergence of resistance and treatment failure for a significant amount of time? (*Fill in the blank.*) _____

15. What is the first line regimen recommended by WHO for adults and adolescents not at risk of pregnancy? (*Drug names only*) _____

16. Check the conditions that are possible adverse drug reactions to ARVs:

- hypothyroidism
- lipodystrophy
- diabetes
- hyperlipidemia
- lactic acidosis
- osteoporosis

17. Variables you should monitor as measures of the clinical effectiveness of ARVs include (check all that apply):

- Patient’s perception of how he or she is doing on treatment
- Changes in body weight
- Changes in frequency and/or severity of HIV-associated symptoms
- Signs of immune reconstitution syndromes

18. *True or False*

- CD4 counts are useful ONLY in deciding whether a patient should start ART.

19. Check all that are true:

Treatment failure

- a. Is signaled by an OI or malignancy, when the drugs have been given long enough to induce a protective degree of immune restoration
- b. A fall in the CD4 counts greater than 10 percent from the peak value
- c. Failure to achieve undetectable viral load levels after 6-12 weeks.

20. As an approach to treatment failure, change only one drug in a three-drug regimen when (*Complete the sentence.*) _____.

21. *True or False*

People with tuberculosis and HIV coinfection should complete their TB therapy before beginning ARV treatment unless there is a high risk of HIV-disease progression and death during the period of TB treatment.

22. Immune reconstitution is a transient (*circle the correct word*)

- a. worsening
 - b. improvement
- of an infection that occurs 2-3 weeks after initiation of ART.

23. What other symptoms might occur in immune reconstitution syndrome, in addition to fever, lymphadenopathy and expanding lesions of the central nervous system? (*Fill in the blank.*) _____

24. Check all that apply:

There are three main options for women on ART who become pregnant:

- a. Suspend therapy temporarily during the first trimester
- b. Continue the same therapy
- c. Change to a different regimen
- d. Increase doses of all ARVs to prevent transmission to the infant more effectively

25. *True or False*

Women who require ART and are breast feeding should continue their ART regimen.

26. HIV RNA levels in perinatally-infected infants are generally _____ at birth (<10,000 copies/ml), increase to high values by age _____, and then _____ slowly after the first year. (*Fill in the blanks*)

27. Which of the following are NOT among the steps in providing care for an occupational blood exposure? (*Check the ones that DO NOT apply.*)

- Immediate washing of the wound with soap and water
- Flush mucous membranes
- Send for viral load test immediately
- Provide OI prophylaxis
- Initiate PEP as quickly as possible
- Test source for HIV (rapid test if available)

Part B: Antiretroviral Therapy

Post-Test

1. The goal of Antiretroviral Therapy (ART) is to (*Circle the one that DOES NOT apply*):
 - a. Prolong and improve the quality of life of people living with HIV and AIDS
 - b. Reduce the viral load as much as possible, for as long as possible, to halt disease progression and prevent or reduce resistant variants
 - c. Achieve immune reconstitution that is quantitative and qualitative
 - d. Decrease the need for condom use
2. *True or False*
 A person needs ART only when the CD4 count is below 100 or when he or she is unable to engage in activities of daily living for at least 10 percent of the day.
3. The absolute minimum tests to use as clinical evaluation for ART include (*name two*):
_____ and _____.
4. *True or False*
 Measuring CD4 is preferable to measuring viral load when assessing both the need for and the response to ART.
5. *True or False*
 No matter what the CD4 count, WHO stage IV disease is a sound basis for starting ART
6. *True or False*
 In a child, WHO stage III disease, or stage I and II + CD4 < 20 percent, is a sound basis for starting ART.
7. *True or False*
 An assessment of viral load is not essential for starting therapy
8. The WHO Clinical Staging System (*circle all that apply*):
 - a. Includes a clinical classification system and a laboratory classification to categorize the immunosuppression of adults by their total lymphocyte counts
 - b. Is based on clinical markers believed to have prognostic significance resulting in four categories; it is helpful to incorporate a patient performance scale into the system
 - c. Should be used only by junior providers
 - d. Has been proven reliable for predicting morbidity and mortality in infected adults
9. *True or False*
 Pneumocystis carinii pneumonia or p. jiroveci (PCP) is characteristic of clinical stage IV.
10. The main stages of the HIV life cycle where ARVs act include (*circle all that apply*):
 - a. The production of proviral DNA
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11. Place “NNRTI” in front of the characteristics of nonnucleoside reverse transcriptase inhibitors (NNRTIs) and place “NsRTI” in front of the characteristics of nucleoside reverse transcriptase inhibitors (NsRTI).
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- d. Typical side effects include maculopapular rash, hepatitis and headache.
- e. Typical side effects include nausea and vomiting, anemia, peripheral neuropathy and pancreatitis
- f. Active against both HIV 1 and HIV 2

12. Circle the statements below that accurately describe protease inhibitors:

- a. Interfere with the production of mature infectious virions
- b. Can lead to decreases in viral load to the level of undetectable virus
- c. If used alone, resistance develops rapidly
- d. Produce few, if any, side effects
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13. Name three protease inhibitors

1. _____ 2. _____ 3. _____

14. How many antiretrovirals should be together to be effective for preventing the emergence of resistance and treatment failure for a significant amount of time?

(Fill in the blank.) _____

15. What is the first line regimen recommended by WHO for adults and adolescents not at risk of pregnancy?

(Drug names only)

16. Check the conditions that are possible adverse drug reactions to ARVs:

- hypothyroidism
- lipodystrophy
- diabetes
- hyperlipidemia
- lactic acidosis
- osteoporosis

17. Variables you should monitor as measures of the clinical effectiveness of ARVs include (circle all that apply):

- Patient's perception of how he or she is doing on treatment
- Changes in body weight
- Changes in frequency and/or severity of HIV-associated symptoms
- Signs of immune reconstitution syndromes

18. True or False

- CD4 counts are useful ONLY in deciding whether a patient should start ART.

19. Check all that are true:

Treatment failure

- a. Is signaled by an OI or malignancy, when the drugs have been given long enough to induce a protective degree of immune restoration
- b. A fall in the CD4 counts greater than 10 percent from the peak value
- c. Failure to achieve undetectable viral load levels after 6-12 weeks.

20. As an approach to treatment failure, change only one drug in a three-drug regimen when (Complete the sentence.)

_____.

Part B: Antiretroviral Therapy

Post-Workshop Participant Self-Assessment

As part of the workshop evaluation, we would like to see how you assess yourself before and after participating in the workshop. There are areas in which you already have experience or skills, and therefore feel comfortable, and other areas that you find less familiar or more difficult, and in which you may feel less comfortable. We are asking you to complete this self-assessment at the beginning and again at the end of the workshop. We will then compare the results to see if this training has helped you become more confident in managing patients with HIV and AIDS.

Thank you for filling out this instrument.

Please circle the rating that best matches your level of comfort with the stated behavior.

A. Describe the indications for starting a patient on ART

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

B. Identify the minimum, basic and desirable tests for monitoring a patient on ART

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

C. Describe the four clinical stages of HIV infection as defined by WHO

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

D. Explain the mode of action of the different classes of ARVs

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

E. List the major side effects for each class of drugs

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

F. Discuss the national guidelines for ARVs and the rationale for selecting drugs as first-line and second-line regimens

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

G. Identify the major drug interactions to watch for when prescribing ARVs

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

H. Describe the major adverse drug reactions

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

I. Use strategies to promote adherence

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

J. Refer clients for supportive services

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

K. Recognize and manage treatment failure

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

L. Identify the steps in managing occupational HIV exposure

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

M. Discuss options for pregnant women who need ART

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

N. Address continued risk reduction measures while following a patient on ART

1. Very Comfortable 2. Comfortable 3. Not Comfortable 4. Very Uncomfortable

Appendix D

Sample Session and Workshop Evaluation Forms



Session Evaluation Module: _____

Session: _____

Please complete this form to give us your evaluation of this workshop session. The focus is on the content of the session and the methods used to present it.

Please check one. Feel free to comment on your response.

1. Sequence: The session was at a logical time in relation to the other topics of the day.

___Agree ___Disagree

Comment:

2. Length: The session lasted the right amount of time.

___Agree ___Disagree

Comment:

3. Level: The session was taught at a level appropriate for participants.

___Agree ___Disagree

Comment:

4. Content Relevance: The content of the session was relevant to the local situation.

___Agree ___Disagree

Comment:

5. Methodology (participatory exercises): The training methods were useful.

___Agree ___Disagree

Comment:

The training methods were well suited to the content.

___Agree ___Disagree

Comment:

6. Other comments: Please tell us what you think would have made the session more useful, clear or relevant.

Workshop Evaluation

Thank you in advance for completing your evaluation of this workshop thoughtfully and honestly. Feel free to comment. Please rate each of the statements below from 1-4.

1-Strongly agree 2-Agree 3-Disagree 4-Strongly disagree

___1. The workshop covered material that is relevant to my clinical practice.

Comment:

___2. The workshop content was at a level suitable for the majority of the participants.

Comment:

___3. The trainers used methods that actively engaged participants in learning the material.

Comment:

___4. The workshop covered the content in sufficient detail.

Comment:

5. Please note areas where you would like to see greater emphasis.

-
-
-

___6. The workshop achieved its stated objectives.

Comment:

___7. The trainers facilitated the understanding of the participants.

Comment:

___8. The cases studies helped me learn.

Comment:

___9. Trainers could have made greater use of these other methodologies:

-
-
-

Comment:

10. If any content were to be eliminated, I would suggest it be the following session(s). [Please use exact session titles from the workshop program. Please indicate why would you eliminate these sessions.]

11. Sessions that should be added are: