Antiretroviral drugs and the prevention of mother-to-child transmission of HIV infection in resource-constrained settings

Recommendations for use

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
d4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
HIV	Human Immunodeficiency Virus
MTCT	Mother-to-Child-transmission
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PEP	Post Exposure Prophylaxis
PI	Protease Inhibitor
3TC	Lamivudine
UNGASS	UN General Assembly Special Session on HIV/AIDS
VTR	Vertical Transmission Rate
WHO	World Health Organization
ZDV	Zidovudine

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Executive Summary and Preface

[*to be written after final recommendations from consultation*]

1. Background to Mother-to-Child Transmission of HIV

In 2003 an estimated 700,000 children became infected with HIV (1) (http://www.who.int/hiv/). The overwhelming majority of infected children acquire the infection through mother-to-child transmission (MTCT), which can occur during pregnancy, delivery and, postnatally, during breastfeeding. In the absence of any intervention, rates of MTCT of HIV can vary from 15% to 30%, without breastfeeding, and can reach as high as 30% to 45% with prolonged breastfeeding (2). Transmission during the peripartum period[1] accounts for one- to two-thirds of the overall transmission rate, depending on whether breastfeeding occurs or not, and the peripartum and breastfeeding period has thus become the focus for efforts to prevent MTCT.

The transmission of HIV from an infected mother to her child can be reduced to 2 % or less by intensive interventions that include combination potent antiretrovirals, obstetrical interventions including elective caesarean section at 38 weeks and complete avoidance of breastfeeding (3-6).ARV prophylaxis alone, administered in the period around a vaginal delivery, reduces by between 30% and 50% the rate of peripartum transmission. In resource-constrained settings, elective cæsarean section is seldom available and safe, and refraining from breastfeeding is often not feasible or acceptable. Also, even where peripartum ARV prophylaxis is used, infants remain at substantial risk of acquiring infection in the breastfeeding period. Research is ongoing to address approaches to prevent postnatal transmission of HIV (7). Furthermore, preventive ARV interventions have not yet been implemented on the scale required (8).

At the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS in June 2001, governments from 189 countries committed themselves to a comprehensive programme of international and national action to fight the HIV/AIDS pandemic by adopting the Declaration of Commitment on HIV/AIDS. The Declaration established specific goals,

[1] Peripartum period includes the last month of pregnancy, labour and the first week after delivery

including the reduction of the proportion of infants infected with HIV by 20 per cent by 2005 and by 50 percent by 2010. The follow up to the 2001 UNGASS Progress Report presented in 2003 indicated that by the end of December 2002, 88% of countries had national MTCT prevention policies in place. However, many countries with severe HIV/AIDS epidemics had experienced difficulty in increasing access to MTCT prevention services, including ARV prophylaxis.[2]

A large proportion of HIV-infected women do not yet have access to comprehensive prenatal, obstetrical and postnatal care and require specific and innovative strategies for MTCT prevention. To accomplish the UNGASS goal, it will be necessary to take the following actions:

a) ensuring that 80% of pregnant women accessing antenatal care have information, counseling and other HIV prevention services available ;

b) increasing the availability and access of effective ARV prophylaxis to reduce MTCT of HIV for HIV infected women and their infants;

c) ensuring access to treatment, including ARV treatment, for HIV-infected women and provision of follow up and a continuum of care to themselves, their partners and children; and

d) provision of breast milk substitutes where appropriate.

A comprehensive and integrated approach to prevent HIV infection in women, infants and young children is urgently required. Interventions focusing on HIV-infected pregnant women need to be complemented by interventions that address primary prevention of HIV infection, particularly in women of child-bearing age and their partners, and prevention of unintended pregnancies among HIV-infected women.[3]

[2] http://www.unaids.org/ungass/en/global/ungass00_en.htm

[3] http://www.who.int/hiv/topics/mtct/en

2. Review of use of prophylactic ARV drug regimens for the prevention of MTCT

ARV drugs, including nucleoside reverse transcriptase inhibitors (NRTIs), such as zidovudine (ZDV) and lamivudine (3TC), and non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine (NVP), (either alone or in combinations of two or three drugs), have been shown to be effective in reducing the transmission of HIV from mothers to infants (Table 1). These regimens reduce the risk of MTCT by decreasing viral replication during pregnancy and delivery and through prophylaxis of the neonate during and after exposure to the virus.

Randomised clinical trials, open-label trials and cohort studies have provided evidence of the efficacy of ARV prophylaxis. Research to evaluate ARV prophylaxis in the USA, Europe and Thailand have focused on longer ARV regimens and have been set against a background of high rates of elective cæsarean section and/or avoidance of breastfeeding, early initiation of antenatal care, and high rates of antenatal service coverage. In Africa the research has focused on short regimens of peri-partum ARV drugs and has been conducted in settings where elective cæsarean section deliveries are rarely carried out, where antenatal service coverage is sometimes inadequate, and where breastfeeding is the norm, often for prolonged periods.

The design and efficacy of the various short course ARV drug regimens evaluated to date for the prevention of peripartum MTCT are presented in Table 1. Short term efficacy, as determined by infant infection status at 6-8 weeks of life, has been demonstrated for short course prophylactic ARV drug regimens comprising:

- ZDV alone (9-11)
- ZDV together with 3TC (12-14)
- NVP alone in two single-dose regimens to the mother and the infant (14-16)
- ZDV boosted by single-dose NVP (17-18)
- ZDV+3TC boosted by single-dose NVP (19).

MTCT rates at 6-8 weeks have been reported as low as 2.8% with ZDV+3TC in the absence of breastfeeding (13) and 4.6% with ZDV+3TC boosted by single-dose NVP in women, half of whom breastfed (19). Long term efficacy as determined by the child's infection status at 18-24 months of age (which accounts for continued risk of acquisition of infection through the breastfeeding period) has been confirmed for short-course ZDV (20), and for the two single-dose NVP alone regimens for the mother and the infant (16), in breastfeeding populations. Long-term efficacy is less than short-term efficacy due to the post-natal acquisition of infection during breastfeeding.

The only combination drug prophylaxis that has been assessed to date for long-term efficacy at 18 months is ZDV+3TC in three different regimens (12). The antepartum + intrapartum + postpartum ZDV+3TC regimen was the only one to show a sustained, although reduced, effect at 18 months. Triple ARV combinations prescribed for treating HIV disease in adults have also shown a very substantial efficacy in reducing peri-partum MTCT in observational studies in industrialized countries (3-6), where MTCT rates are now below 2% in the absence of breastfeeding. However there is as yet no evidence from resource-constrained settings where breastfeeding is common.

In a recent trial from Malawi (21) evaluating post-exposure prophylaxis (PEP), of either single-dose NVP or single-dose NVP plus 1 week ZDV given to infants born to mothers who had not received antenatal or peripartum ARV prophylaxis, showed that the combination of NVP+ZDV was significantly more effective, as PEP, than NVP alone. With the exception of this trial, all other regimens evaluated to date include an intrapartum component, and varying durations of antepartum and/or neonatal (and sometimes maternal) postpartum prophylaxis. Although available data from these trials individually would suggest that short-course regimens using a combination of ARVs may be more effective than single drug regimens in reducing peripartum transmission, it is difficult to compare results from individual trials (22). The rate of transmission is associated with maternal, delivery and infant characteristics which differ by site and population and furthermore methodology to assess the efficacy of an intervention varies between studies, which can greatly affect the results (23).

An individual meta-analysis of data from the African ARV trials is underway to allow a direct comparison of the efficacy of ARV regimens starting antenatally or intrapartum and using ZDV alone, NVP alone, and ZDV+3TC, in terms of MTCT rates at 6-8 weeks. Other

relevant studies performed in industrialized countries and in Thailand are reported in Table 1 (24-26). In one trial, in a South African non- breastfeeding population (14), there has been a formal comparison of peripartum ZDV+3TC and NVP alone showing similar rates of transmission at eight weeks. An ongoing trial in Thailand, also in a non breastfeeding population, is comparing two regimens of ZDV boosted by single-dose NVP to ZDV alone and has prematurely stopped the enrolment to the ZDV-alone arm, because of lower efficacy at the first scheduled interim analysis (18).

The prophylactic ARV drug regimens with one drug have been shown to prevent half of infections that occur in the peripartum period, while combination ARV regimens, (e.g. AZT+3TC boosted by single-dose NVP), potentially prevent four-fifths of peripartum infections, from 25% to less than 5%, as assessed at 6-8 weeks of age. However, in both cases the impact on overall MTCT rates is less due to the continued transmission risk in the post-natal period during breastfeeding (12, 16, 20, 27). Recently, preliminary results were presented from a trial carried out in Kampala and Kigali. Infants, born to HIV-infected women, who were HIV negative at birth were given NVP or 3TC for six months to reduce the risk of acquisition of infection through breastfeeding, with a median duration of exposure of 3.5 months (28). The rate of postnatal transmission between birth and six months was about 1%, which is comparable to a natural (without ARV) rate of postnatal transmission between four weeks and six months of 3 to 4% (29). It is difficult to tell which of the interventions (ARV in mother and neonate, exclusive breastfeeding or early weaning) affected most the postnatal transmission rates. Further research is required to develop more effective ARV prophylactic drug regimens that can be applied in resource-constrained settings, and clinical trials are planned or have started to address the prevention of postnatal transmission during the breastfeeding period (8).

Table 1. Prophylactic ARV regimens for MTCT prevention (Summary of the evidence)

Study	Principle	Antenatal/Intrapartum	Post-partum infant	Median maternal CD4+ count by arm at enrolment	Mode of infant feeding	Vertical transmission rate (VTR) and efficacy
PACTG 076 / ANRS 024 trial USA, France (24)	ZDV vs placebo	Long (from 14 wks), intravenous intrapartum	Long (6 weeks)	538, 560	Formula Feeding	VTR 7.6% in intervention arm versus 22.6% in placebo arm at 18m (68% efficacy) [363 infants]
Bangkok CDC short-course ZDV trial Thailand (11)	ZDV vs placebo	Short (from 36 weeks), oral intrapartum	None	411, 427	Formula Feeding	VTR 9.4% in intervention arm versus 18.9% in placebo at 6m (50.1% efficacy) [392 infants]
Thai Perinatal HIV Prevention trial Thailand (25)	ZDV different regimens, no placebo	Long (from 28w), short (from 36 w)	Long (for 6w), short (for 3 days)	350, 380	Formula Feeding	Short-Short arm was stopped. VTR 6.5% in long-long arm versus 4.7% in long-short arm and 8.6% in the short-long arm at 6m (statistical equivalence) [1079 infants]
Ivory Coast CDC short-course ZDV trial Côte D'Ivoire (10, 20)	ZDV vs placebo	Short (from 36 weeks)	None	528, 548	Breastfeeding	VTR 15.7% in intervention arm versus 24.9% in placebo at 3m (37% efficacy) [230 infants]
DITRAME / ANRS 049a trial Côte D'Ivoire, Burkina Faso (9, 20)	ZDV vs placebo	Short (from 36 weeks)	Short (1 week) (mother only)	535, 568	Breastfeeding	VTR 18.0% in ZDV arm, 27.5% in placebo at 6m (38% efficacy); 21.5% versus 30.6% (30% efficacy) at 15m; 22.5% versus 30.2% (26% efficacy) in pooled analysis with other Ivory Coast trial at 24 m [276 infants]

Study	Principle	Antenatal/Intrapartum	Post-partum infant	Median maternal CD4+ count by arm at enrolment	Mode of infant feeding	Vertical transmission rate (VTR) and efficacy
PETRA trial South Africa, Tanzania and Uganda (12)	ZDV+3TC in 3 regimens vs placebo	Short (from 36w)	Short (7 days) Mother and Infant	435, 475	Breastfeeding	VTR 14.9% at 18m for antenatal/ intrapartum/ neonatal ZDV+3TC, 18.1% for intrapartum/neonatal ZDV+3TC, 20.0% for intrapartum ZDV+3TC only and 22.2% for placebo [1413 infants]
French AZT+3TC / ANRS 075 trial France (26)	Open label, non-randomised ZDV+3TC	From 32 weeks	3TC and ZDV for 6 weeks	426	Formula feeding	VTR 1.6% [437 infants]; 5-fold lower than in controls receiving ZDV only
Thai ZDV+3TC trial Thailand (13)	Open label, non randomised ZDV+3TC	Short (from 34w)	Long (ZDV 4 weeks)	274	Formula feeding	VTR 2.8% at 18m [106 infants]
PACTG 316 trial (USA, Europe, Brazil, Bahamas) (6)	NVP vs placebo in women already receiving ZDV or ZDV plus other ART	Non-study ART antenatal. Intrapartum: single NVP dose 200mg plus ZDV intravenously	Single dose 2mg/kg within 72 hr of birth plus non-study ART including ZDV	423, 441	Formula feeding	Trial stopped early due to very low VTR in both arms. VTR 1.4% in intervention arm versus 1.6% in placebo arm [1248 infants]
HIVNET 012 trial Uganda (15, 16)	NVP vs ZDV	No antenatal ART Intrapartum: single dose NVP 200mg versus oral ZDV	Single dose NVP 2mg/kg within 72 hr of birth versus short ZDV (7 days)	426, 461	Breastfeeding	Placebo arm was stopped. VTR 15.7% in NVP arm versus 25.8% in ZDV arm (41% efficacy) at 18 m [451 infants]

Study	Principle	Antenatal/Intrapartum	Post-partum infant	Median maternal CD4+ count by arm at enrolment	Mode of infant feeding	Vertical transmission rate (VTR) and efficacy
SAINT trial South Africa (14)	NVP versus ZDV+3TC	No antenatal ART Intrapartum: single dose NVP 200mg versus ZDV+3TC	Single NVP dose within 48 hrs of birth versus short ZDV+3TC (7 days) (mother and infant)	384, 404	Breastfeeding and formula feeding	VTR 12.3% in NVP arm versus 9.3% in ZDV+3TC arm at 8 weeks [1301 infants]
DITRAME Plus / ANRS 1201.0 trial Abidjan, Côte D'Ivoire (17)	Open label, ZDV boosted by single dose NVP	ZDV from 36 weeks, NVP one dose at onset of labour	Infant single dose NVP, plus one week ZDV	370	Breastfeeding and formula feeding	VTR at 6 weeks 6.4% [331 infants]
DITRAME Plus / ANRS 1201.1 trial Abidjan, Côte D'Ivoire (19)	Open label, ZDV+3TC boosted by single dose NVP	ZDV+3TC from 32 weeks (stopped at day 3 postpartum), NVP one dose at onset of labour	Infant single dose NVP, plus one week ZDV	439	Breastfeeding and formula feeding	VTR at 6 weeks 4.6% [99 infants]
SIMBA trial Rwanda, Uganda (28)	NVP vs 3TC postnatally in nenonates exposed antenatally to ZDV+ddI	ZDV+ ddI from 36 weeks to 1 week Postpartum	NVP once then twice daily versus 3TC twice daily while breastfeeding	423, 432	Breastfeeding for 3-5 months	VTR at 6 months 7.8% (no difference between the two arms) Postnatal (6 weeks - 6 months) transmission rate 0.9% [397 infants]
NVAZ trial Malawi (21)	Neonatal NVP vs NVP+ZDV	None (late comers)	Single dose NVP right after birth; ZDV twice daily for one week	Not reported	Breastfeeding	Overall VTR at 6-8 weeks 15.3% in NVP+ZDV arm and 20.9% with ZDV only. VTR at 6-8 weeks in infants who were negative at birth 7.7% and 12.1%, respectively (36% efficacy) [952 infants]

3. ARV drug treatment in adult women

Women who are identified as being infected in the antenatal period, and who have clinical indications to be treated with ARV treatment combinations for their own disease, should be given the appropriate treatment based on the current WHO recommendations.[4] In addition, with ARVs for treatment becoming more widely available in resource-poor settings, the use of ARVs to prevent MTCT needs to be re-assessed. Moreover, infected women under treatment with ARV may become pregnant and the impact of ARVs on pregnancy outcome needs to be considered.

WHO recommends[5], that in ARV treatment programmes in resource-constrained settings, HIV infected adolescents and adults should start ARV treatment in one of the following conditions:

1. If CD4 testing available:

- WHO Stage IV disease irrespective of CD4 cell count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary tuberculosis, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis) with consideration of using CD4 cell counts < 350/mm^3 to assist decision making
- WHO Stages I or II disease with a CD4 cell count < 200/mm^3

2. If CD4 testing not available:

- WHO Stage IV disease irrespective of total lymphocyte count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary

[4] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

[5] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

tuberculosis, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis) irrespective of lymphocyte count

- WHO Stage II disease with a total lymphocyte count = 1200/mm^3

The WHO preferred first-line ARV regimens in adults and adolescents consist of a triple combination of ZDV+3TC+NVP, d4T+3TC+NVP, ZDV+3TC+Efavirenz (EFV) or d4T+3TC+EFV. EFV may be considered to be the NNRTI of choice in patients with tuberculosis. These basic regimens have been chosen on the basis of clinical experience with the efficacy and toxicity of the NRTI and NNRTI components, the lack of requirement of a cold chain, drug availability and cost.

The guiding principle for treatment of women of childbearing potential or who are pregnant is that therapeutic decisions should be based primarily on their need and eligibility for ARV treatment. However, the choice of therapy in women with the potential to become pregnant must consider that the ARV drugs may be received in the first trimester during the period of fetal organ development.

EFV should not be given to women of childbearing age, unless effective contraception can be assured, or women who are pregnant because of its teratogenic potential. In those women for whom effective contraception can be assured, EFV remains a viable option for the NNRTI component of the regimen. However EFV may interact with estrogen metabolism in combined oral contraceptive pills. Women who are receiving ART and become pregnant should continue their treatment with the exception that EFV should be discontinued and replaced by NVP if the woman is in the first or second trimester of pregnancy.

WHO recommends that ZDV+3TC+NVP, d4T+3TC+NVP should be utilized in pregnant women who are eligible based on the same criteria as for non-pregnant women. For pregnant women it may be desirable to initiate ARV treatment after the first trimester of pregnancy, this is after the period of major organ development in the fetus, although for pregnant women who require treatment or who are severely ill, the benefit of early therapy would likely outweigh any potential fetal risks and therapy should be initiated in such cases. Where initiation of ARV treatment is too complex or not practical before the end of pregnancy, this decision needs to be reconsidered as soon as possible after delivery.

4. Safety

4.1 Safety of short courses of ARV drugs in pregnant women and their infants

For women and infants who are offered ARV prophylaxis for MTCT prevention, the risk associated with exposure to one or more drugs for a limited period of time must be weighed against the benefit of reducing the risk of transmission to infants of a fatal infection. ARV drugs should be used only when there is a clear clinical indication (e.g., for preventing peripartum transmission from a pregnant woman who is known to be HIV positive, or treatment of the mother as required). The risk of adverse events when ARVs are used for a limited period of time in pregnancy for the prevention of peripartum MTCT is considerably less than when these drugs are used to delay disease progression. The potential short-term toxicity in exposed infants, if any, is expected to be very small (8, 30). Short-term safety and tolerance of the ARV prophylactic regimens has been demonstrated in all the controlled clinical trials on MTCT prevention (9-14,16).

Toxicities of drugs widely used for MTCT and also used for ARV treatment are summarized below.

When used for treatment in adults for prolonged periods, the contraindications to ZDV and 3TC are similar and include known allergy to these drugs, severe haematological disorders (hæmoglobin < 7 g/dl or severe neutropenia with neutrophils < $750x10^6$ cells/l), and liver or kidney deficiency. The hæmatoxicity associated with the use of these drugs is usually moderate and reversible after treatment interruption. Other potential toxic effects are lactic acidosis, pancreatitis and, more rarely, mitochondrial diseases. The most frequent side effects are nausea, headache, myalgia and insomnia. Their incidence usually decreases with time.

The major adverse effect of using NVP is idiosyncratic allergic reaction, even at low level (known allergy to NVP or other benzodiazepine derivatives). The most frequent adverse effects are hepatotoxicity and cutaneous rash, the incidence of which are higher in women with CD4 counts >250/mm^3. Few cases of fatal hepatotoxicity (fulminant hepatitis) and rashes (Stevens-Johnson and Lyell syndromes) have been reported. When used as treatment in adults, NVP should be started at half dose during the first two weeks in order to minimize the risk of rash.

The safety of ARVs used for a limited period of time in pregnancy for the prevention of peri-partum MTCT has been demonstrated. However, the risk of serious rash or hepatic toxicity following NVP exposure is more frequent in women than men. It is not known whether pregnancy further predisposes women to such toxicities. For the infants, although relatively short, the intrapartum exposure to ZDV, with or without 3TC, may lead to adverse events such as haematotoxicity, sometimes lactic acidosis or, more rarely, mitochondrial dysfunction. NVP is associated with infant haematologic toxicity including neutropenia (HPTN 023 data, JAIDS). ZDV, 3TC and NVP are detected in human breast milk at concentrations that would achieve doses 10 to 20 times lower than the paediatric therapeutic doses.

In infants anaemia (usually mild and reversible) is the major toxicity associated with exposure to prophylactic ZDV to reduce MTCT (9-12, 32, 37). ZDV administered during the perinatal period may in fact result in a small but significant and durable effect on haematopoiesis for all exposed infants, infected or not, up to the age of 18 months but the clinical significance of this biological observation is unknown (37bis). Severe neonatal anaemia and neutropenia has been reported to be associated with the use of the ZDV+3TC combination for MTCT prophylaxis (26). Although theoretically ZDV may have mutagenic and carcinogenic effects (38-40), no adverse effects have been reported from any of the trials or studies on ZDV-exposed children (32, 41, 42). There have been reports of a small number of serious adverse effects possibly associated with exposure to ART in the form of mitochondrial dysfunction (43-45), but an increased rate of serious clinical manifestations has not been confirmed by other studies (46-48).

Despite the above mentioned evidence there is still lack of information on the effects of short-courses of ARVs to prevent MTCT on the long-term health of the infected mother (and that of her infected infant) or on future treatment options, but research is ongoing. The issue of resistance is discussed below.

4.2 Special considerations concerning the safety of long-term use of ARV drugs during pregnancy

The increasing use of complex and potent ARV combinations in pregnancy in some settings, particularly in the early weeks of pregnancy, has raised questions relating to pregnancy outcome. In an analysis of European data on nearly 4000 mother-child pairs, use of antenatal

combination therapy with a protease inhibitor (PI) was associated with a two and a half time increased risk of premature delivery compared with no treatment (31, 32). Risk of premature delivery was predominantly associated with the use of PIs in early pregnancy. However, studies from the USA have not identified prematurity as an adverse effect of combination ART in pregnancy (33), which may be because of differences in underlying population characteristics.

Clinical trials (PACTG 076 and 185) and observational data have shown no evidence of an increased risk of congenital malformations associated with exposure to ZDV prophylaxis (30, 32). Lactic acidosis is a well-known toxicity related to nucleoside analogue drugs, possibly associated with mitochondrial toxicity. There have been several case reports of lactic acidosis in pregnant women receiving ARV combinations including ddI and d4T, some resulting in maternal death; all women had received this combination prior to conception and all presented with lactic acidosis late in pregnancy (34, 35). It is recommended that the ddI-d4T combination is avoided in pregnancy (30, 36).

The most frequent adverse effects of NVP are hepatotoxicity and cutaneous rash within 2 weeks of initiating, the incidence of which is higher in women with CD4 counts >250/mm^3. Few cases of fatal hepatotoxicity (fulminant hepatitis) and rashes (Stevens-Johnson and Lyell syndromes) have been reported. However, if well tolerated, NVP is one of the drugs recommended during pregnancy. No evidence of 3TC intolerance or toxicity during pregnancy has been reported. Some of the most important adverse effects of EFV include Central Nervous System toxicity and potential teratogenicity. Therefore EFV should be avoided in pregnancy, especially in the first trimester.

PIs are not among the first line regimens for adults recommended by WHO in resource-limited settings. Nevertheless, if a woman is under treatment with PIs and she is tolerating them well, it is not recommended to change regimen. However the risks and the benefits need to be evaluated on a case-by-case basis.

5. ARV resistance following short-course ARV regimens

Emergence of viral resistance is frequent during ARV treatment especially with mono or dual drug regimens. Emergence of viral resistance is a risk for infants infected with HIV despite exposure to ARV prophylaxis, and for women after short-term exposure to ARV to

prevent MTCT (26, 36, 40, 49). Such resistance may interfere with future treatment options but there is lack of data to quantify this risk.

Selection for pre-existing resistant viral populations or development of new mutations may occur with any ARV drug or drug regimen that does not fully suppress viral replication. NVP and 3TC are drugs where a single mutation leads to high level of resistance, while for ZDV several mutations are needed to confer resistance. Virus containing ARV-resistant mutations usually decreases in number quite rapidly once the drug is discontinued, and wild type becomes the dominant virus type again.

Resistance to ZDV is usually only observed after several months of partially suppressive therapy. Studies to date show low prevalence of ZDV resistance after short-course ZDV to reduce the risk of MTCT (50-52). It is unlikely that exposure to short-course ZDV in MTCT-prevention programmes will impact on future ARV treatment options.

Resistance to 3TC can develop more rapidly, even when given in combination with ZDV, with reversion to wild type virus after discontinuation of 3TC. The PETRA study reported 12% resistance to 3TC in women who received the regimen prepartum, intrapartum and one week postpartum (49). In a cohort study in France an overall resistance rate of 39% was observed 6 weeks after delivery (26). The risk of 3TC resistance increases substantially when ZDV+3TC is used for one to two months during pregnancy and reaches 50% with more than two months of prophylaxis and 20 % with one to two months prophylaxis. No resistance was reported with prophylaxis with 3TC when used for less than 1 month (26). However, resistance was not associated with an increased risk of MTCT in either study. To date, 3TC has not been used extensively in MTCT-prevention programmes and thus any impact of resistance to 3TC on future MTCT-prevention and treatment options remains limited. However, this may change as ARV regimens containing ZDV, 3TC and NVP become more widely used as a first-line treatment options for adults and for prevention of MTCT.

Resistance to NVP develops rapidly, and in the HIVNET 012 trial 20% of NVP-exposed women had evidence of NVP resistance at 6 week post-partum, as did 46% of the infants who became infected (53). Patterns of resistance differed between mothers and infants. Nevertheless that resistance was no longer detectable after 1 year in women, and earlier, in most infants. The clinical consequences for future MTCT prevention or ARV treatment of

transient selection of NVP-resistant virus with single-dose prophylaxis remain uncertain, but research is ongoing to clarify this issue.

Infants who are infected despite ARV use to reduce the risk of MTCT or ARV use in pregnancy for management of the mother's HIV related disease, could be infected with drug-resistant virus. It is unknown whether ARV choices should be modified for infants who have been exposed to ARVs in utero, during delivery or breastfeeding. Studies are in progress in children to understand whether single-dose NVP prophylaxis compromises their response to subsequent ARV treatment with NNRTI. However, until these data are available children should be considered eligible for NNRTI-based regimens as in the revised recommendations of WHO for resource-limited settings, 2003.[6]

6. General principles of prevention of MTCT through the use of ARV interventions

Prophylactic use of an ARV regimen is just one component of an MTCT-prevention programme. While the focus on the use of such regimens increases public awareness that transmission of HIV to infants can be prevented and provides a catalyst for action, the other components should not be neglected. MTCT-prevention programmes are often limited to these ARV interventions delivered to HIV-infected women during pregnancy and around the time of delivery. A significant and sustainable impact will only be achieved when all components of the comprehensive programme are in place and functioning. Furthermore, many of these other components are themselves key strategies in the broader HIV prevention effort, constituting the four-pronged UN strategy of primary HIV prevention in young adults, prevention of unwanted pregnancy in HIV-infected women, MTCT prevention, and care and treatment.[7] ARV prophylaxis for MTCT prevention must be integrated into a comprehensive strategy that includes other specific interventions to prevent HIV transmission from an infected mother to her child, such as safer delivery practices, and infant feeding counselling and support. Follow up needs to be further strengthened as well the involvement of men and the sensitization of the community.

[6] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

[7] http://www.who.int/hiv/topics/mtct/en

MTCT prevention is part of continuum of care for HIV-infected women and their children and should be linked with other relevant elements (including health care for adults and children living with HIV/AIDS, early diagnosis of infant HIV infection, clinical and immune monitoring, prevention of opportunistic infections, ARV treatment, education and counselling, adherence support, social and psychological support, outreach and community linkages, retention in long-term care, prevention of transmission to others), the so-called MTCT Plus concept (http://www.mtctplus.org). Some African countries, India and Thailand have specifically given priority access to treatment for mothers who have participated on MTCT-prevention programs. Such a family-centred approach is expected to improve uptake and adherence to MTCT prevention and treatment programmes.

ARV prophylaxis to reduce the risk of MTCT should be available for all HIV-infected pregnant women before, during and after delivery, regardless of their stage of HIV disease. ARV prophylaxis should be available to their newborns as well, according to a schedule that seeks to ensure maximum efficacy, while remaining feasible, and with minimal toxicity. Counselling and initiation of ARV prophylaxis in HIV-infected pregnant women should include information on risks and benefits.

ARV treatment recommendations for HIV-infected pregnant women are based on the principle that therapies of known benefit to women should not be withheld during pregnancy unless the risk of adverse effects in the mother, fetus or infant outweighs the expected benefit to the woman concerned. The limited data relating to ARV drug safety in pregnancy highlight the need for close clinical and biochemical monitoring in the early stages of introduction of ARV combination regimens in pregnancy as recommended in the WHO ARV adult guidelines.

Early diagnosis of HIV infection in newborns (between four and eight weeks of age) where available should be considered in order to provide maximum clinical benefit for the infants who have acquired infection despite the exposure to ARV interventions to reduce the risk of MTCT, and international guidelines for resource-constrained settings are being developed. Early pædiatric HIV diagnosis may also help inform feeding decisions.

Adherence to ARV drugs for prevention of MTCT or treatment is of critical importance, and should be promoted from the time ARV is started, and reinforced throughout prophylaxis and/or treatment, ideally at the family and community level. Guidance should include

discussion with women about the known potential adverse effects of the ARV regimen they have been prescribed and importance of adherence, so they can anticipate and know how to manage minor and/or transient side effects and do not inappropriately stop therapy. After starting ARV treatment or prophylaxis, women should be seen frequently to reinforce the need for adherence to the regimen and to assess and manage any side effects of the drug. WHO recommends that innovative approaches to enhance adherence to ARV treatment be developed, due to the lifelong nature of this treatment. When ARVs are used as prophylaxis to prevent MTCT, side effects such as ARV-associated nausea, which may compound the pregnancy-associated sickness, or fears that ARV drugs might harm the fetus, should not be considered to be a contra-indication or a reason for stopping ARV treatment.

6.1 Choice of MTCT prophylactic antiretroviral regimen(s)

The choice of regimen(s) to be included in a national MTCT-prevention programme should be determined by assessment of feasibility, efficacy, acceptability, safety and cost and in relation to the national HIV care strategy. It should be noted that the drug cost may represent only a fraction of the costs of the services that are required in an effective MTCT-prevention programme**.** Currently, all MTCT-prevention programmes depend on the timely identification of HIV-infected women in pregnancy. Additionally, early paediatric HIV diagnostic services should be included as well as the need for adequate postnatal interventions to reduce the risk of postnatal transmission.

Practical considerations in choosing ARV regimens for the prevention of peripartum MTCT include:

- Availability of voluntary testing and counselling services
- Proportion of HIV-infected women who are aware of their serostatus at different stages of pregnancy
- Proportion of women seeking antenatal care
- Timing of first antenatal visit
- Frequency of antenatal visits
- Quality of antenatal care
- Proportion of births occurring in health-care facilities

- Access to early postnatal care
- Acceptability and ease of dosage schedules
- Efficacy and safety of different ARV drug regimens, including their potential to compromise future treatment options
- Access to and cost of drugs.

ZDV, 3TC and NVP are the drugs of first choice to be used to prevent peripartum MTCT. They are the only three ARV drugs that have been formally assessed for safety and efficacy in MTCT-prevention clinical trials. Their administration is relatively simple. All three drugs can be taken twice daily, and appropriate infant formulations are available. To further simplify the treatment, ZDV and 3TC are available in a co-formulation, thus reducing the number of pills to be taken. Finally, NVP can be used in a single dose formulation for intra-partum use only. It is expected that NVP will soon be available in a single dose formulation for infant use.

There are limitations with using alternative ARV drugs. EFV, an alternative NNRTI, is teratogenic, and is not recommended in pregnancy. If EFV has to be used then it should be only taken after the first trimester of pregnancy. The dual NRTI combination d4T+ddI should be avoided in pregnancy, due to the potential increased risk of lactic acidosis with this combination in pregnant women. PIs remain expensive and they may not be affordable in resource-constrained settings.

7. Recommendations for the use of ARV interventions to prevent MTCT in resource-constrained settings

Recommendations depend on when in pregnancy the HIV-infected woman is first identified and on the need for ARV treatment to delay disease progression. All efforts should be provided to ensure that all pregnant women who need ARV treatment following the WHO guidelines can have access to it. For pregnant women who do not yet need, or have access to, ARV treatment for their own disease, the use of ARV prophylaxis for prevention of HIV transmission to their infants is recommended. The choice of ARV drug regimens is based on evidence of safety and efficacy in reducing the transmission of HIV from mothers to infants (Table 1). Furthermore, the choice of ARV drug regimen should be made locally, taking into account issues of feasibility, efficacy and cost. The lack of availability of ARV treatment

should not stop the development of MTCT-prevention programmes based on NVP only. The following sections provide specific recommendations for the most frequently encountered situations (Table 2).

(a) Newly diagnosed HIV-infected pregnant women without indications for ARV treatment

If a woman does not require ARV treatment for her HIV-related disease, one of the antiretroviral prophylaxis regimens known to be effective should be used for MTCT-prevention. Where available a highly potent ARV prophylactic regimen for these women would be the triple combination of ZDV+3TC+NVP from 32 weeks of gestation through delivery and for three days post-partum. In some countries it is recommended to continue with three days ZDV+3TC after stopping NVP because of the long half-life of NVP (see for example the British guidelines[8]). When the triple combination is not used for treatment of the mother's disease but only to prevent MTCT, then its theoretical efficacy for MTCT prevention must be balanced against its potential toxicity.

An alternative regimen would be ZDV prophylaxis from 34-36 weeks of pregnancy boosted by single-dose NVP during labour and delivery (ZDV+3TC during pregnancy boosted by single-dose NVP during delivery is less attractive because of the high risk of resistance with 3TC in a double NRTI regimen). In both scenarios, infants should receive one dose NVP within 72 hours of delivery and one week ZDV (21). In settings where neither of these more potent ARV combination regimens are feasible or available, HIV-infected women should receive one dose NVP given at the onset of labour, with at least one dose of NVP (within 72 hours) to the infant. When delivery occurs less than two hours after the maternal labour dose of NVP, the neonate should receive an additional dose of NVP at birth as well as the standard dose on day 2 or 3 (54, 55).

Following the delivery, ARVs given to non-breastfeeding women can be stopped (see above), unless there are clinical indications warranting ARV treatment to delay maternal disease progression. However, in women deciding to initiate breastfeeding, it may be helpful to give post-exposure prophylaxis to the infant for two (rather than one) weeks to counteract the

[8] http://www.bhiva.org/guidelines

possibility of a transient viral rebound in the mother when stopping combination ARV. Thus in these particular circumstances, the neonate would receive two weeks of ZDV, plus one dose of NVP within 72 hours of birth and a second dose five to seven days later.

(b) Newly diagnosed HIV-infected women with indications for ARV treatment who might become pregnant

Recommendations for initiation of ARV treatment should follow the WHO guidelines for non-pregnant women in resource-limited settings.[9] The first line regimens recommended by WHO for adult women who may become pregnant are d4T+3TC+NVP or ZDV+3TC+NVP. EFV may be considered to be the NNRTI of choice in patients with tuberculosis. However, EFV should not be given to women of childbearing age, unless effective contraception can be assured, or who are pregnant, because of its potential for teratogenicity.

(c) Newly diagnosed HIV-infected pregnant women with indications for ARV treatment

Recommendations for initiation of ARV treatment should follow the WHO guidelines for non-pregnant women in resource-limited settings.[10] The first line regimens recommended by WHO for adult women who may become pregnant are d4T+3TC+NVP or ZDV+3TC+NVP. Because of the greater experience and better documented safety profile with the use of the ZDV, 3TC and NVP combination in pregnancy, the latter regimen is preferred in pregnancy.

The period when the fetus is most susceptible to potential teratogenic effects of drugs is during the first 10 weeks of gestation. The risks of ARV treatment to the fetus during this period are not yet quantified for all individual drugs or their combinations. Consequently, women in the first trimester of pregnancy may wish to consider delaying the initiation of ARV treatment until after 10-12 weeks of gestation. The decision to delay the initiation of treatment hinges in part on a consideration of the severity of maternal HIV disease and the potential benefits and risks of delaying initiation for several weeks until completion of the first trimester. ARV treatment is rarely initiated because of a medical emergency. However, as mentioned above, for women who are severely ill, the benefit of early initiation may

[9] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

[10] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

outweigh the theoretical risk to the fetus. Similarly, the conditions to initiate ARV treatment may not be met if an HIV-infected pregnant woman with clinical indications is seen late in pregnancy, e.g. beyond 36-38 weeks of gestation. In this case, women will be treated as in the next scenario while planning to initiate ARV treatment as soon as possible after delivery (paragraph d).

(d) Newly diagnosed HIV-infected pregnant women with indications for ARV treatment who did not initiate therapy during pregnancy

If an HIV-infected pregnant woman with clinical indications for ARV treatment is seen late in pregnancy, e.g. beyond 36-38 weeks of gestation, it may not be possible to initiate ARV treatment immediately. Such women may or may not have received any ARV for MTCT prophylaxis. ARV treatment should be initiated as soon as possible. Women will be treated in the same way as non-pregnant adults with one of the recommended first line regimens.[11] There is currently no information regarding the risk of postnatal transmission in these circumstances. Studies on preventing HIV transmission during breastfeeding are ongoing.

(e) HIV-infected pregnant women newly diagnosed at the time of delivery

If women come to a health care facility for the first time while they are in labour, it may not be appropriate to test for HIV at this time. In these cases a rapid test should carried on as soon as it is feasible to obtain informed consent for HIV testing, at labour/delivery or right after delivery (21). If the test is positive, single-dose NVP + ZDV twice-daily for one week should be started in the infant immediately and no later than 72 hours. There is no evidence currently available to recommend adding 3TC for one week to this regimen. If the woman requires ARV treatment for her own disease, refer to the case above.

(f) HIV-infected women on ARV treatment for their own disease

Ensure that ARV treatment combinations are being properly administered and the choice of drug regimens follows WHO recommendations for HIV-infected adults.[12] It is recommended to exclude a pregnancy before starting ARV treatment with ARV drugs. The first line

[11] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

[12] http://www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf

regimens recommended by WHO for adult women who may become pregnant are d4T+3TC+NVP or ZDV+3TC+NVP. EFV may be considered to be the NNRTI of choice in patients with tuberculosis. However given its teratogenic potential, EFV should not be given to women of childbearing age, unless effective contraception can be assured, or who are pregnant.

Women who are receiving ARV therapy and become pregnant should continue their treatment with the exception that EFV should be discontinued and replaced by NVP if the woman is in the first or second trimester of pregnancy. To suspend treatment temporarily during the first trimester is not generally recommended. The issues to be considered in making a decision include the stage of gestation, the severity of maternal disease, the tolerance of the regimen in pregnancy and the potential for adverse effects on the fetus. In some circumstances, clinicians or women may decide to temporarily discontinue ARV treatment during the first trimester.

To fully address the issue of MTCT prevention in this group of ARV-treated women, maternal ARV drugs should continue to be given during labour, because all regimens of proven prophylactic effectiveness have included intrapartum drug administration.

8. Prevention of transmission during breastfeeding

Women with clinical indications for ARV treatment and who are breastfeeding should continue their ARV therapeutic regimen to delay disease progression. However, the efficacy of potent ARV treatment in preventing postnatal transmission of HIV during breastfeeding is not yet known.

The way ARV maternal and infant prophylaxis could be discontinued in women who do not need ARV treatment for themselves has been described in section 7c) according to the infant feeding choice. A number of international clinical trials are evaluating the effect of ARV prophylaxis on the risk of early and late postnatal breast-milk HIV transmission in women who do not require therapy for their own health. In these studies, ARVs are provided to the infected woman solely for reducing breast-milk transmission and are stopped after breastfeeding has stopped. As yet, there are no data on the safety and efficacy of this approach.

An alternative approach to prevention of transmission through breastfeeding may be prophylaxis given to the breastfed uninfected infant, and this is being explored in a number of trials. The timing of the postpartum interventions explored in these trials includes ultra-short regimens given in the first week of life to prevent transmission by colostrum or early breast-milk. They also include interventions covering the first 6-12 weeks of breastfeeding and interventions that provide ARV prophylaxis to the infant through the first six months of life accompanied by early weaning.

9. Resistance patterns and maternal treatment after receiving MTCT prophylaxis

Short-course ARV drug regimens that are used to prevent MTCT of HIV do not fully suppresses viral replication and may be associated with the development of ARV drug resistance. This is most likely to occur with prophylaxis regimens using ARV drugs for which resistance can occur rapidly, such as NVP or 3TC. It is unknown whether the presence of transient drug resistance to NVP induced by a single dose of NVP or to 3TC with short-course ZDV+3TC prophylaxis might be associated with diminished virological response to subsequent NNRTI- or 3TC-based therapy in women who subsequently initiate treatment. Alternative drug regimens not specified in WHO ARV treatment guidelines, such as a triple NRTI or a PI-based regimen should be substituted for an NNRTI-based regimen for initial therapy in women who have received single-dose NVP prophylaxis during the period that NVP resistance is likely to be detectable. The dynamics of NVP resistance following single-dose prophylaxis have not been defined.

In the absence of data to indicate an adverse effect, denying use of WHO-recommended first-line ARV treatment regimen to any woman who has received single-dose NVP could significantly limit her treatment options. Further research is urgently needed to examine the impact of specific drug mutations on future maternal treatment outcomes. Nevertheless, based on current information, prior administration of short-course ZDV+3TC or single-dose NVP for MTCT-prevention should not preclude use of these agents as part of a combination ARV drug regimen initiated for treatment of HIV disease in women.

Table 2 Recommendations for use of antiretroviral (ARV) drugs in pregnant women in different clinical scenarios in resource-constrained settings

Clinical Situation	Recommendation
Newly diagnosed HIV-infected pregnant women without indication for ARV treatment	Mother • ZDV+3TC+NVP from 32 weeks gestation, through delivery (1), (2),(3); stop NVP and continue ZDV+3TC for 3 days after delivery • alternatively: ZDV+ 3TC from 34-36 weeks boosted with single-dose NVP at onset of labour • alternatively: ZDV from 34-36 weeks boosted with single-dose NVP at onset of labour • Single-dose NVP in settings where none of the more potent ARV combinations are feasible or available • Infant • Single-dose NVP within 72 hours of delivery and one week daily ZDV (extend ZDV for a second week with a second dose of NVP 5-7 days after the first one if ZDV+3TC+NVP was the maternal regimen and breastfeeding has been initiated) • If delivery occurred within two hours of maternal single dose of NVP, infant should receive an additional dose of NVP immediately after birth as well as the routine dose within 72 hours
Newly diagnosed HIV-infected women with indications for ARV treatment who may become pregnant	Exclude pregnancy before starting treatment. Avoid EFZ. Prefer ZDV+3TC+NVP regimen.
Newly diagnosed HIV-infected pregnant women with indications for ARV treatment	Delay start of treatment until after the first trimester of pregnancy Proceed as for non-pregnant adults (1), (2), (3) except EFV
Newly diagnosed HIV-infected pregnant women with indications for ARV treatment who did not initiate therapy during pregnancy - received short-course MTCT prophylaxis - did not receive any MTCT prophylaxis	In both cases proceed as for non-pregnant adults (WHO guidelines) with first line regimen recommended Initiate ARV treatment as soon as possible, including in post partum period.
HIV-infected pregnant women newly diagnosed at the time of delivery	If there is time, offer rapid test; if no time, rapid test as soon as possible (and acceptable) after delivery If test positive, initiate post-exposure prophylaxis in infant: single-dose NVP within 72 hours of delivery plus one week ZDV
HIV infected women on ARV treatment for their own disease	Exclude pregnancy before starting treatment. EFV should be avoided in women who can potentially become pregnant Discontinue drugs with teratogenic potential (EFV) or with known adverse potential for the pregnant mother (d4T/ddI) Consider switching to regimens which include ZDV, 3TC or NVP

	Continue therapeutic regimen during intrapartum period

Notes:

(1) Start NVP with half-dose for the first two weeks as recommended for adults in WHO guidelines

(2) Monitor closely clinical and biochemical tolerance in the first month of ARV use

(3) Stop NVP in case of NVP-associated toxicity, continue ZDV only until labour

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See also:

the US guidelines at http://www.aidsinfo.nih.gov/guidelines

the French guidelines at http://www.ladocumentationfrancaise.fr/brp/notices/03000460.shtml

the British guidelines at http://www.bhiva.org/guidelines

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