Global Health Council

ISSUE NO. 1
MARCH 2004

Research Brief

Preventing tuberculosis in HIV-infected persons

A systematic review of randomized controlled trials

Background

One-third of the world's population is believed to be infected with the bacterium that causes tuberculosis (TB). While most infected people will never have symptoms (latent TB infection), every year eight million of these individuals become ill with active TB and two million die (Corbett 2003). The vast majority of those affected by TB today live in low- and middle-income countries.

The HIV pandemic has changed the historic pattern of active TB progression. While only 5–10% of HIV-negative persons infected with TB will develop the disease (Enarson 1994), those with HIV and latent TB co-infection have a 30% lifetime risk of developing active TB (Selwyn 1989). Reactivation of latent tuberculosis infection due to a weakened immune system appears to be the main mechanism for the development of HIV-related tuberculosis. HIV-positive individuals may also be at greater risk of acquiring TB. The World Health Organization (WHO) estimates that nearly a third of the 40 million people living with HIV/AIDS today are co-infected with tuberculosis. In this group, TB is the single biggest killer.

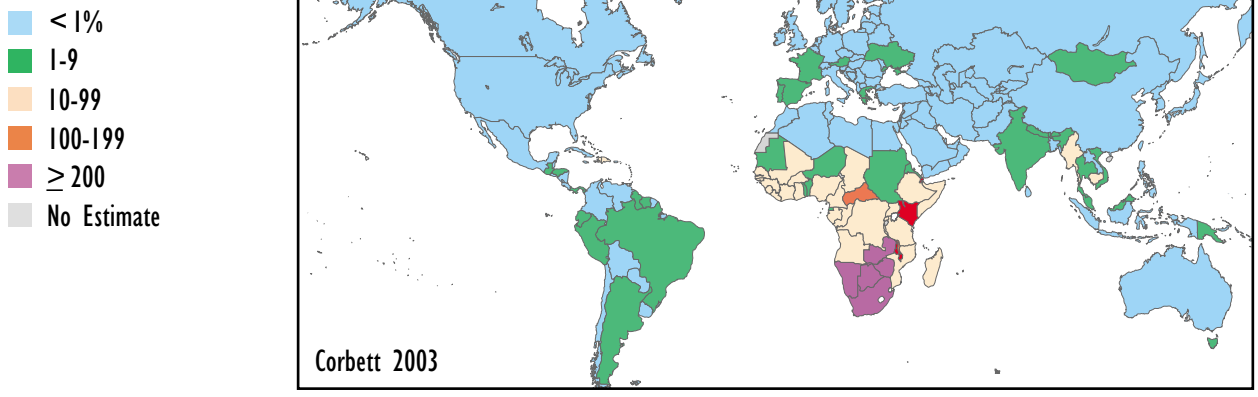
Preventive therapy (PT) aims to eradicate latent infection before it develops into active disease. It is known that anti-tuberculosis drugs substantially reduce the risk of active TB in HIV-negative populations (Smieja 2003).

When HIV and TB Collide

- TB is the leading cause of mortality and morbidity in persons with HIV.
- HIV-positive persons who are also infected with TB have a 30% lifetime risk of developing active TB.

However, in the context of HIV infection, a variety of factors including adverse drug reactions, poorer treatment adherence, and treatment interactions with antiretroviral drugs may lessen the effectiveness of TB preventive therapy in HIV-positive individuals. For this reason, a systematic review of all relevant trials was conducted to evaluate TB preventive therapy in persons with HIV.

HIV-positive tuberculosis cases per 100,000 population (all ages), 2000 estimates



Systematic Review Objectives

To determine the effectiveness of tuberculosis preventive therapy (PT) in reducing the risk of active tuberculosis and death in persons infected with HIV.

Key Points

- **This systematic review found that TB preventive therapies reduced the risk of active TB in those with HIV by 36%**
- **Different drug regimens were similarly effective; however, short-course multi-drug regimens had more adverse events that led to discontinuation of therapy**
- **There were limited data suggesting that preventive therapy may reduce the risk of AIDS and increase the time to full-blown AIDS among PPD+ individuals**

Main Findings

- 11 trials with more than 8,000 randomized participants evaluated 4 different drug regimes: isoniazid (INH); INH + rifampicin[1] (RIF); RIF + pyrazinamide (PZA); and INH + RIF + PZA
- The overall analysis showed that preventive therapy reduced the risk of active TB in HIV positive persons by 36%; however, a sub-group analysis showed that this effect was much stronger (62%) and only significant among those with a positive PPD[2] test
- Different drug regimens were similarly effective, but short-course, multi-drug treatments were more likely to be discontinued due to adverse events
- Overall, there was no evidence that PT reduced all-cause mortality but there was a trend toward a lower mortality in PPD+ persons
- There was no evidence that PT reduced incidence of AIDS. However, there were limited data to suggest a lower risk of AIDS and an increase in the mean time of progression to AIDS in PPD+ individuals receiving PT

Practice Implications

Current CDC and WHO guidelines recommending preventive therapy for HIV-infected individuals who have a positive tuberculin skin test are supported by the results of this review. However, in resource-poor settings where the rates of both TB and HIV are high, logistical and financial constraints to providing wide-scale preventive treatment may be substantial. Policy-makers should take all factors into consideration when designing broad public health interventions.

Research Implications

Randomized controlled trials that are large enough to assess the long-term effects of anti-tuberculosis preventive therapies, their impact on progression of HIV disease, and overall mortality are still needed. It may also be beneficial to compare the cost-effectiveness of anti-tuberculosis drugs with that of highly active antiretroviral therapy (HAART) for preventing tuberculosis. Future trials should collect data on drug resistance, adherence to treatment and cost in order to provide decision-makers with sufficient information for choosing a particular drug regimen.

A systematic review is a review of all relevant research literature on a particular topic. It differs from a traditional review in its attempt to reduce bias by applying comprehensive search strategies and explicitly stating methods to systematically find, appraise and summarize relevant studies.

Key Review Components

Search Strategy for Studies[3]

- The Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE, AIDSLINE, AIDSTRIALS, AIDSDRUGS
- Reference lists
- Study authors and other researchers in the field

Selection Criteria for Studies

- Randomized trials comparing an anti-TB drug with placebo/no drug or another drug regimen
- HIV-infected adults who did not have active TB currently or in the past
- Outcomes assessed: incidence of active TB, interval to active TB, incidence of death and interval to death, progression of HIV disease, incidence of adverse drug reactions leading to discontinuation of treatment

[1] *Also known as Rifampin.*

[2] *PPD (purified protein derivative): this tuberculin skin test is the primary screening test for tuberculosis infection where material derived from the tuberculosis bacterium is introduced into the skin. People infected with the bacterium typically have a strong reaction to this skin test, and are termed positive for the tuberculin skin test (PPD-positive, PPD+).*

[3] *Databases were searched through July 2002.*

Studies Reviewed

- 11 trials, ranging in size from 118 to 2,018 randomized participants for a total of 8,130, were included
- Trials were conducted in eight countries: Haiti, Kenya, Spain, Uganda, United States and Zambia; one multi-national study was conducted in Brazil, Haiti, Mexico and United States
- All 11 trials evaluated isoniazid (INH) compared either with placebo (8 trials) or with INH plus rifampicin (RIF) (3 trials), RIF plus pyrazinamide (PZA) (4 trials) or INH plus RIF plus PZA (1 trial)

Study Participants

- 13 years of age or older (mean age 32)
- 52% female
- 55% PPD+, 24% PPD- and 21% unknown PPD

Results

Development of Active Tuberculosis

Overall, preventive therapies reduced the risk of active TB. Different regimens had similar effectiveness, but a sub-group analysis showed that treatment efficacy was greater in PPD+ individuals.

Preventive therapies vs. no treatment (placebo)

Comparison	Relative Risk	95% CI [4]	No. Trials	No. Participants
Any anti-TB drug	0.64	0.51-0.81	13	5,664
INH	0.67	0.51-0.87	13	4,136
INH + RIF	0.41	0.21-0.81	2	1,179
RIF + PZA	0.54	0.34-0.86	4	855
INH + RIF + PZA	0.48	0.23-1.00	1	926

Comparison of different preventive therapies

Comparison	Relative Risk	95% CI	No. Trials	No. Participants
INH vs. RIF + PZA	1.00	0.73-1.38	6	3,196
INH vs. INH + RIF	1.05	0.51-2.17	4	1,390
INH + RIF vs. RIF + P ZA	2.82	0.30-26.51	1	159
INH vs. INH + RIF + PZA	0.60	0.23-1.57	1	998
INH + RIF vs. INH + RIF + PZA	0.75	0.31-1.82	1	1,018

Sub-group analysis of preventive therapies vs. placebo in persons testing PPD+ or PPD-

Sub-Group	Relative Risk	95% CI	No. Trials	No. Participants
All	0.64	0.51-0.81	13	5,664
PPD+	0.38	0.25-0.57	4	2,378
PPD-	0.83	0.58-1.18	7	2,822

(Results continued)

Death from All Causes

Overall, preventive therapies, with the exception of INH + RIF, did not reduce all-cause mortality.[5]
Preventive therapies vs. no treatment (placebo)

Comparison	Relative Risk	95% CI	No. Trials	No. Participants
Any anti-TB drug	0.95	0.85-1.06	13	5,664
INH	0.95	0.85-1.06	13	4,136
INH + RIF	0.69	0.50-0.95	2	1,179
RIF + PZA	1.04	0.77-1.41	4	855
INH + RIF + PZA	0.91	0.65-1.27	1	926

Sub-group analysis of preventive therapies vs. placebo in persons testing PPD+ or PPD-

Sub-Group	Relative Risk	95% CI	No. Trials	No. Participants
All	0.95	0.85-1.06	13	5,664
PPD+	0.80	0.63-1.02	4	2,378
PPD-	1.02	0.89-1.15	7	2,822

Incidence of AIDS

Data from one small trial suggests a reduction in the risk of AIDS in PPD+ individuals.
Sub-group analysis of preventive therapies vs. placebo in persons testing PPD+ or PPD-

Sub-Group	Relative Risk	95% CI	No. Trials	No. Participants
All	0.88	0.60-1.25	2	355
PPD+	0.36	0.15-0.85	1	63
PPD-	1.10	0.72-1.69	2	292

Mean Time to AIDS

One trial found that preventive therapies increased the mean time to AIDS significantly.

Sub-Group	Weighted Mean Difference	95% CI	No. Trials	No. Participants
All	7.8 months	1.71-13.89 months	1	118

Adverse Events Leading to Stopping Treatment

The likelihood of stopping treatment due to adverse effects was lower with INH monotherapy than with combination therapies.
Indirect comparison: monotherapy (INH) or combination therapy vs. placebo

Sub-Group	Relative Risk	95% CI	No. Trials	No. Participants
INH vs. placebo	1.66	1.09-2.51	7	3,899
INH + RIF vs. placebo	16.72	3.29-84.90	2	1,179
RIF + PZA vs. placebo	7.84	2.60-23.67	2	855
INH + RIF + PZA vs. placebo	26.11	3.56-191.64	1	926

(Results continued)

Adverse Events Leading to Stopping Treatment

Direct comparison: monotherapy (INH) vs. combination therapy.

Sub-Group	Relative Risk	95% CI	No. Trials	No. Participants
INH vs. RIF + PZA	0.64	0.48-0.86	4	3,196
INH vs. INH + RIF	0.75	0.46-1.24	3	1,390
INH vs. INH + RIF + PZA	0.10	0.03-0.33	1	998

Adherence to Preventive Therapy

- There were insufficient data to definitively assess whether adherence modified the effect. Only 5 studies reported on adherence and definitions varied across the studies.
- Two studies (Halsey 1998; Martinez 2001) reported better adherence with short-course multi-drug treatments as compared to longer term INH monotherapy. One study (Whalen 1997) reported no difference.

Source

Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons (Cochrane Review). This systematic review is maintained and updated in: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

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