

Isoniazid to prevent first and recurrent episodes of TB

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TB is a significant re-emerging infectious disease in many parts of the world. The World Health Organization (WHO) global TB control report found that, in Africa, TB incidence rates have tripled since 1990, especially in those countries with high HIV prevalence, and are still rising at a rate of 3–4% annually,¹ despite an overall stabilization of incidence rates in many other regions. The major reason for this increase in rates is the co-existing HIV epidemic that is affecting much of sub-Saharan Africa.

HIV infection is the strongest known risk factor for TB. HIV-positive individuals have a 5–10% annual risk, and a 30% lifetime risk, of developing active TB; while in HIV-negative populations, the lifetime risk is only 5–10%. Because of the overlapping epidemics, it is estimated that 11 million adults living with HIV are co-infected with TB. Of the 1.7 million deaths globally attributable to TB, 229,000 are estimated to be in part due to the co-infection with HIV.¹

Primary preventive therapy (or treatment of latent TB infection) for TB is the treatment of asymptomatic persons infected with *Mycobacterium tuberculosis* to prevent the development of active TB. The rationale for the use of one or more anti-TB drugs as preventive therapy is that it reduces the small population of dormant bacilli in the body to such levels that the chance of re-activation of this latent infection is significantly reduced.² Secondary prevention of TB involves the use of one anti-TB drug, usually isoniazid, following completion of a full

course of treatment of active TB. The intention of this strategy is to reduce the incidence of relapse disease. This review will examine the evidence for and use of isoniazid as both primary and secondary prevention of TB, specifically as they apply to the HIV-positive population.

Efficacy of isoniazid as primary prophylaxis

Prior to the HIV epidemic, many studies demonstrated the efficacy of isoniazid preventive therapy (IPT) in both adults and children infected with TB, as demonstrated by a positive tuberculin skin test (TST).³ A Cochrane review of 11 trials involving 73,375 HIV negative, but at risk, individuals concluded that either 6- or 12-month regimens reduced the development of TB disease (relative risk of 0.40 (95% confidence interval [CI] 0.31–0.52), and that the interventions could also reduce deaths from TB disease but not all-cause mortality.⁴

In HIV-positive individuals, a number of randomized controlled trials have also shown a benefit of IPT, as well as other combinations of anti-TB drugs, in reducing the incidence of active TB disease (Table 1). A recent Cochrane review of 11 trials, involving 8130 randomized participants, showed that, overall, IPT reduced the risk of active TB by 33% (relative risk [RR] 0.67, 95% CI 0.51–0.87).⁵ Among individuals who were TST positive, preventive therapy (any regimen) reduced the risk of active TB by 62% (RR 0.38, 95% CI 0.25–0.57). There was, however, no significant effect of isoniazid, either on the all-cause mortality or on progression to AIDS in these trials.

The durability of the effectiveness of IPT in HIV-positive individuals is not known, but appears to be more limited than in the studies of HIV-negative individuals. Two studies that have attempted to look at this issue have shown slightly differing results. In Zambia, the effect of isoniazid wore off over 3 years,⁶ whereas in Uganda, the effect of a rifampicin-containing regimen appeared to be maintained at 3 years but the isoniazid-alone regimen also appeared to wane.⁷ Both studies were based on follow-up data from the original efficacy trials and significant numbers of losses to follow-up occurred, which means that a definitive answer cannot be deduced. In these high burden areas, it may well be that re-infection significantly occurs often to nullify the effect of a one-off course of prevention⁸ and further studies are

Table 1 Randomized trials of primary TB preventive therapy in developing countries

Study	No. of participants	% Tuberculin skin test positive	Regimen (months)	Rate of TB/100 per year	Relative risk (95% confidence interval)
Haiti (Ref. 31)	58	66	H+B6 (12)	2.2	1.29 (0.09–0.91)
	60	42	B6 (12)	7.5	1
Kenya (Ref. 32)	342	22	H (6)	4.29	0.92 (0.49–1.71)
	342	23.5	Placebo (6)	3.86	1
Uganda (Ref. 33)	536	100	H (6)	1.1	0.33 (0.14–0.77)
	556	100	H/R (3)	1.3	0.40 (0.18–0.86)
	463	100	H/R/Z (3)	1.7	0.51 (0.24–1.08)
	464	100	Placebo (6)	3.4	1
	395	Anergic	H (6)	2.53	0.83 (0.34–2.04)
Zambia (Ref. 34)	323	Anergic	Placebo (6)	3.06	1
	350	23	H (6)*	2.74	0.56 (0.3–1.05)
	351	22	R/Z (3)*	3.16	0.65 (0.35–1.19)
	352	27	Placebo (6)*	4.94	1
Haiti (Ref. 35)	370	100	H (6)	1.7	N/A
	370	100	R/Z (2)	1.8	N/A
Haiti, Brazil, Mexico, USA (Ref. 36)	792	100	H (12)	1.1	1
	791	100	R/Z (2)	0.8	0.72 (0.40–1.31)

*Given twice weekly, all others are daily therapy

H, isoniazid; R, rifampicin; Z, pyrazinamide; B6, pyridoxine

ongoing to attempt to identify the optimal duration of therapy.

Policy and guidelines

IPT for the prevention of TB in HIV-positive individuals is a policy both internationally and nationally for many developed countries.⁹⁻¹² WHO and UNAIDS issued a joint policy statement on preventive therapy in 1998 that recommended to governments that:

- 1 preventive therapy should be part of a package of care for people living with HIV/AIDS
- 2 preventive therapy should only be used in settings where it is possible to exclude active TB cases and ensure adequate monitoring and follow-up
- 3 information about TB including preventive therapy should be made available to people living with HIV
- 4 preventive therapy should be provided within settings that include established voluntary counselling and testing (VCT) services for HIV
- 5 the priority for TB control programmes continues to be the detection and cure of infectious TB cases
- 6 the procurement and supply of TB drugs must be regulated by national authorities in order to prevent the development of drug resistance.¹³

The use of IPT has since been emphasized in the WHO Interim policy on TB/HIV¹⁴ and in the Second Global Plan to Control TB [www.stoptb.org/globalplan/]. Despite these policies, few of the countries most affected by the dual TB/HIV epidemics have adopted the widespread use of IPT, concerned mainly by the feasibility of implementation, especially in excluding active TB, the fear of isoniazid resistance and concerns of adverse effects, especially hepatotoxicity.

Feasibility

Exclusion of active TB

Active TB must be excluded prior to commencing primary IPT, but this is challenging in HIV-positive individuals. Guidance on appropriate screening is still lacking. The WHO policy states that screening should initially be symptom-based, as most individuals with active TB will be symptomatic, but that a chest X-ray is recommended until the validity of different screening tools or algorithms is established. Debate on the usefulness of chest X-rays in the screening algorithm started during the original efficacy trials,¹⁵ although early evidence from one of the only countries in Africa to embark on a widespread implementation of isoniazid preventive therapy, Botswana, shows that it may not be necessary.¹⁶

One significant benefit of introducing preventive therapy for TB is the additional cases of active TB that are diagnosed during the screening process. Several studies at VCT centres, PMTCT (prevention of mother-to-child transmission) service providers and HIV-care clinics have demonstrated an undiagnosed population of HIV-positive TB patients.¹⁷⁻¹⁹ This benefit should not be underestimated and may, in fact, be as beneficial for public health as the isoniazid alone.

Tuberculin skin testing

Meta-analysis has demonstrated that IPT is most effective in individuals with a positive TST. This test may,

however, be extremely unreliable in HIV, with many false-negatives.^{20,21} Feasibility studies where tuberculin tests have been used for the screening of HIV-positive individuals have demonstrated that this test presents an additional barrier to the provision of preventive therapy, and may actually reduce the gains of providing preventive therapy to those most highly at risk.²²

Adherence to therapy

Adherence to preventive therapy is challenging, but if active TB has been excluded, then poor adherence probably does not influence drug resistance.²³ Different studies in both developing and developed country settings demonstrate that adherence is poor unless clients are motivated and barriers to treatment are minimized.²⁴⁻²⁶

Monitoring of adverse drug reactions

The major adverse drug reaction of isoniazid is hepatotoxicity. This ranges from asymptomatic hepatocellular injury to fatal hepatitis. Other potential hepatotoxins such as alcohol and drugs, especially antiretroviral drugs, should be identified and the risks and benefits weighed. Routine measurement of liver function tests is not automatically recommended in the international policy, but may be considered if availability is not a problem, and for higher risk cases. Hepatitis has not been identified as a significant problem in the studies on HIV-infected persons reported to date.²⁷

Development of isoniazid resistance

The use of IPT has not led to any documented rise in isoniazid resistance—examples of widespread use are few. The main route through which resistance would develop is if isoniazid is used alone in cases where active TB has not been excluded. For this reason, exclusion of TB is of utmost importance. Regimens that combine two or more anti-TB drugs may be safer in this regard, and have the additional attraction of shorter regimens. However, they have not demonstrated increased efficacy as compared with isoniazid alone. They also have the additional risk of increased adverse effects, especially in HIV-negative individuals, such that rifampicin/pyrazinamide in combination has been discontinued as preventive therapy in HIV-negative populations.²⁸

Secondary preventive therapy

HIV infection increases the risk of re-infection and relapse of TB following re-exposure to TB.⁸ Fewer studies have been conducted to assess the value of secondary IPT in this context. In Haiti, a study of using isoniazid for 12 months after completion of a 6-month rifampicin-containing regimen for active TB randomized 142 HIV-positive individuals to isoniazid or placebo. There was a significant reduction in the risk of recurrent TB in those receiving isoniazid (RR 0.18, 95% CI 0.04-0.83).²⁹ An observational cohort study among gold miners in South Africa with a history of TB found a 55% reduction in recurrent TB among individuals who had received secondary IPT, given under operational conditions (incidence rate ratio 0.45; 95% CI 0.26-0.78).³⁰

To date, no policy exists to recommend the use of secondary IPT.

Recommendations for practice

With all of the evidence presented above, what are the recommendations for practice, especially in high burden, poor countries?

- Primary IPT should be offered to HIV-positive individuals, following screening for active TB
- In early HIV disease (e.g. individuals diagnosed through VCT or PMTCT programme), a symptomatic screen is probably sufficient to exclude TB
- For late-stage HIV disease, exclusion of active TB is much harder. In these situations, symptom screen, chest X-ray and sputum examination may be necessary, and if any doubt exists, IPT should be withheld
- Tuberculin skin testing can be done if it is practical but in high TB prevalence areas it is not necessary, and its non-availability should not exclude individuals from receiving IPT
- The duration of treatment may be 6–12 months, but the optimal length is unknown
- The role of IPT in individuals taking antiretroviral therapy (ART) is unknown and further research is necessary.

The use of secondary IPT is less clear. Certainly individuals who have had TB previously and who are HIV positive should not be excluded from receiving IPT. Since their TB has already been treated, the risk of isoniazid resistance developing due to poor exclusion of active disease is less; therefore this may be more acceptable from a public health perspective.

Conclusion

While the priority for TB control programmes remains the detection and treatment of active cases, the introduction of a preventive therapy service may lead to more TB screening in highly-at-risk populations and the additional benefit of prevention of disease in HIV-positive individuals and their close contacts. Primary IPT has an undisputed role in the care of individuals living with HIV, although further research is needed to determine the optimal duration of therapy and the role of IPT with ART. Secondary preventive therapy appears to have an important role and is potentially easier to implement. Its application should be considered.

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