

# Prevention of Tuberculosis in People Living with HIV

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**Human immunodeficiency virus (HIV) infection drives tuberculosis (TB) incidence, and in some African countries, 80% of persons with TB have HIV infection. By the end of 2008, an estimated 33.2 million persons were infected with HIV, and in 2007, there were 2.7 million new HIV infections and 2 million HIV infection-related deaths. During the same year, there were 1.37 million (15%) cases of TB and HIV coinfection, resulting in 456,000 deaths. Prevention of TB requires prevention interventions for both HIV infection and TB, including HIV counseling and testing, disclosure and partner testing, behavior modification, earlier antiretroviral therapy, and the “Three I’s for HIV/TB”: isoniazid preventive treatment, intensified case finding, and infection control for TB. Managers of HIV programs should work with their colleagues in the TB field and the community to ensure that persons infected with HIV have access to the “Three I’s for HIV/TB” as part of universal access to high-quality comprehensive prevention, care, and treatment of HIV infection and TB.**

Globally, an estimated 33 million persons are infected with human immunodeficiency virus (HIV) and 2.2 billion persons are infected with *Mycobacterium tuberculosis* [1–4]. Tuberculosis (TB) remains an important cause of morbidity, mortality, and suffering among persons with HIV infection and TB and their families [1–4]. In heavily impacted communities in sub-Saharan Africa, there is very high annual risk of infection, and up to 90% of older adults may be infected with *M. tuberculosis* [2, 5]. HIV infection is the strongest risk factor for TB among those with latent or new infection with *M. tuberculosis* [1, 4, 6–8]. The increased risk of active TB occurs soon after HIV seroconversion and doubles by the end of the first year of HIV infection [9]. The risk for TB is 20–37 times greater among per-

sons infected with HIV, and in some countries in sub-Saharan Africa, up to 80% of patients with TB have HIV infection [1, 4].

Globally, TB remains among the leading causes of death from an infectious agent. In 2008, of the estimated 9.4 million incident cases of TB, 1.4 million were in people living with HIV and TB accounted for 23% of AIDS-related deaths [1, 4, 10]. TB is a leading cause of death among people living with HIV, and without preventive treatment, >30% of people living with HIV will develop TB [11].

The World Health Organization (WHO) recommends 12 collaborative HIV/TB activities, including the “Three I’s for HIV/TB” (isoniazid preventive treatment [IPT], intensified case finding, and infection control for TB), which should be seen as core prevention, care, and treatment services for HIV infection. Of the 12 activities, there has been progress in implementing testing for HIV infection, providing trimethoprim-sulfamethoxazole preventive therapy, and antiretroviral therapy (ART) [1, 4]. Globally, the WHO estimated that, in 2008, only 20% of people living with HIV knew their status [12]. In 2008, a total of 5.7 million incident TB cases were notified by national TB-control programs

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globally; 22% of patients with TB were tested for HIV infection [10]. In Africa, 500,000 (37%) notified patients with TB were tested for HIV in 2007 [1, 4]. Progress is far slower in delivering trimethoprim-sulfamethoxazole preventative therapy, ART, IPT, and prevention interventions for HIV infection to clients of TB services [1, 4, 13, 14].

## HIV PREVENTION IS PREVENTION OF TB

The Stop TB Strategy of directly observed therapy short-course (DOTS)-based TB programs help prevention of TB by reducing transmission through prompt identification, diagnosis, and successful treatment of TB (Table 1) [1, 15, 16]. Although strong DOTS-based TB programs are essential, prevention of HIV infection is necessary to control TB in areas impacted by HIV. Prevention of HIV infection is beyond the scope of this article but is best achieved with a carefully tailored, combined approach that considers the community and incorporates evi-

dence-based behavioral, biomedical, and structural interventions [17–20]. ART offers considerable hope for prevention of HIV infection and TB, because risk of TB approaches 10%–20% per annum among persons with a CD4 cell count <200 cells/ $\mu$ L [21–25]. Perhaps most importantly for TB control, persons receiving ART are less likely to transmit HIV [26]. Combined approaches to prevention of HIV infection can be very effective. For example, providing couples HIV counseling and testing and ART for HIV status-discordant couples in Africa has been associated with an ~98% reduction in HIV transmission [27, 28]. Prevention of HIV infection in TB care settings has received some attention [29]; however, the provision of services for prevention of HIV infection in these settings is not well documented. In addition, services often do not incorporate proven interventions, such as couples counseling [17, 30] or other efforts to diagnose HIV infection or prevent HIV transmission among patients, partners, and family members

**Table 1. Interventions to Prevent Tuberculosis (TB) in People Living with HIV**

Intervention	Individual benefit	Community benefit
Antiretroviral therapy	Decreased risk of <i>Mycobacterium tuberculosis</i> infection and active TB; decreased risk of XDR-TB and MDR-TB	Prevention of HIV transmission to partners and children; decreased incidence and prevalence of HIV infection; decreased incidence and prevalence of TB, including XDR-TB and MDR-TB
Intensified case finding for TB	Earlier TB diagnosis and treatment; reduced morbidity and mortality; earlier use of isoniazid preventative therapy for persons found not to have TB	Diminished transmission of <i>M. tuberculosis</i> to health care workers, clients, partners, families, and the community; decreased incidence and prevalence of TB, including XDR-TB and MDR-TB
Infection control for TB	Decreased risk of infection with <i>M. tuberculosis</i> and development of active TB; decreased risk of reinfection with <i>M. tuberculosis</i> , including XDR-TB and MDR-TB	Diminished transmission of <i>M. tuberculosis</i> to health care workers, clients, partners, families, and communities; decreased incidence and prevalence of TB, including XDR-TB and MDR-TB
Isoniazid preventative treatment	Reduction in the risk of active TB; prevention of <i>M. tuberculosis</i> infection	Decreased incidence and prevalence of TB; decreased transmission of <i>M. tuberculosis</i> , including XDR-TB and MDR-TB
Combined HIV prevention <sup>a</sup>	Decreased risk of HIV infection; earlier diagnosis and treatment of HIV infection; decreased HIV/AIDS-related illnesses; decreased risk of <i>M. tuberculosis</i> infection and active TB; decreased risk of XDR-TB and MDR-TB	Diminished incidence, prevalence, and transmission of HIV infection; diminished transmission of <i>M. tuberculosis</i> infection, diminished incidence and prevalence of TB; decreased incidence and prevalence of XDR-TB and MDR-TB

**NOTE.** ART, antiretroviral therapy; MDR, multidrug-resistant; XDR, extensively drug-resistant.

<sup>a</sup> Partial list includes behavior modification; couples counseling and testing for HIV with improved access to testing for clients to TB services, partners, and family members; early access to ART, including for patients with TB, partners, and family members with HIV infection; and structural interventions (eg, socioeconomic and legal).





**Figure 2.** Reported implementation of isoniazid preventive treatment services, 2005–2007 (*dark shading*), showing an increase from 26,000 persons in 10 countries in 2005 to 29,000 persons in 42 countries in 2007.

involving people living with HIV revealed that 6–12 months of isoniazid therapy substantially reduces the risk of active TB [3, 14]. Rifampicin and pyrazinamide-containing regimens are as effective as isoniazid alone [3] and have prolonged benefit [14]; however, persons receiving these regimens have more serious adverse effects [3]. IPT, compared with placebo, in people living with HIV in high-burden areas had an overall efficacy of a 33% reduction in the risk of active TB; in TST-positive individuals, this reduction increased to 64% [3]. Although a cohort study showed a survival advantage [47], clinical trials involving adults have not shown a survival benefit for those who received IPT [3, 48, 49]. In all studies, isoniazid was generally safe and well tolerated, and discontinuation was most often associated with default rather than adverse reactions [3]. The recommended dosage of IPT in adolescents and adults infected with HIV is 300 mg daily for 6–9 months [13, 39, 43]. Although no study has examined 9 months of IPT in people living with HIV, randomized trials of treatment up to 12 months in HIV-uninfected persons suggest that optimal benefit is achieved by 9 months [50]. In areas where treatment supervision is feasible, 800–900 mg of isoniazid given twice weekly is an effective and well-tolerated alternative regimen [51].

***IPT and children.*** In 2007, ~2.5 million children were infected with HIV, resulting in ~330,000 HIV infection-related deaths [52]. Children are at increased risk of infection with *M. tuberculosis*, and TB is a common cause of respiratory disease and death in children infected with HIV [53, 54]. The outcomes in children with HIV infection and TB are poorer than those in adults, with mortality increased by 6 fold [55–57]. Few studies on TB preventive therapy focus on children, and IPT is rarely provided to children to prevent TB [55]. A recent South African placebo-controlled clinical trial of IPT in children showed a 72% reduction in development of definite or probable TB [58]. Mortality was reduced 54% with IPT, compared with placebo [58]. This effect was evident for both daily or 3-times weekly regimens of 10 mg/kg of isoniazid. Although this study

found a substantial protective effect in the absence of ART, there is no available research regarding IPT for children receiving ART [55]. The duration of protection, long-term effects of prophylaxis, and impact of prophylaxis in areas with a low prevalence of TB also remain open questions. In the absence of additional data, isoniazid should be considered to prevent and treat latent infection in children infected with HIV who live in areas with a high TB prevalence [42, 43, 55]. The WHO recommends 10 mg/kg (range, 10–15 mg/kg) of isoniazid per day for children  $\geq 3$  months of age for treatment or prophylaxis (there was not enough evidence for a recommendation for children  $< 3$  months of age, but it was noted that the same dose is often used). The maximum daily dose should not exceed the recommended adult daily dose [59].

***Duration of protection.*** Protection in people living with HIV may depend on a number of factors, including the duration of the regimen, adherence, the potency of the regimen, the degree of immunosuppression, and the risk of reinfection in the community [3, 60]. In studies performed before the availability of ART in settings with a high TB prevalence, optimal IPT protection was maintained for 18 months [49, 51], and some studies suggest that the durability of effect can last at least 2.5 years [48, 49]. TB reinfection may occur, particularly in persons who are immunocompromised, and can lead to rapid progression to TB disease despite previous treatment for latent or active TB [61]. Studies demonstrate a possible benefit for secondary preventive therapy in persons who have already been treated for active TB [3, 62–64]. The threat of reinfection suggests a role for either prolonged IPT or repeated courses of IPT. Experts at the 2008 WHO Three I's Meeting suggested the potential benefit of a coformulation of isoniazid and trimethoprim-sulfamethoxazole as long-term preventive therapy [32]. Information on the impact of prolonging treatment should be forthcoming from at least 2 ongoing studies of long-term IPT in South Africa and Botswana.

## IPT AND ART

ART in some studies provides up to 80% reduction in the risk of TB [23]; however, the incidence of TB still remains higher among people living with HIV receiving ART than among HIV-uninfected persons [22, 23, 65]. Even among persons with a good response to ART, other interventions (such as IPT) may be needed to prevent TB in people living with HIV. Observational cohort studies in Brazil and South Africa showed a 76%–89% reduction in TB risk among patients receiving both ART and IPT [66, 67]. Although more evidence is needed, IPT with ART are likely to yield important health benefits for individuals and communities and should be a priority intervention as part of global efforts to expand prevention, care, and treatment of HIV infection.

**Screening for TB.** IPT raises the possibility of inadvertent treatment of active TB with monotherapy and the potential development of isoniazid and (more rarely) polydrug resistance [14]. Difficulty in excluding active TB disease is frequently cited as a reason not to provide IPT. Ironically, although it may be difficult to exclude TB, persons suspected to have TB often do not receive IPT or treatment and die of their undiagnosed and untreated TB [68]. Because of the high risk and serious consequences, screening for TB should be one of the first services to be periodically offered to all people living with HIV [29, 32, 69]. Although subclinical TB can be an issue [70, 71], reports from a number of settings, such as Botswana and Zambia, suggest that the rate of TB is very low among asymptomatic people living with HIV [46, 72]. In this population, it is possible to use simple algorithms to exclude most active TB, although a small proportion of patients may have subclinical TB disease with no symptoms and signs of TB [71–74]. Although the 1998 WHO/UNAIDS IPT guidelines recommend that a chest radiograph be performed for all patients before IPT [13, 42], radiography is notoriously unreliable for the diagnosis of TB in the context of HIV infection [75, 76]. The use of chest radiographs in IPT programs is still not clear; a study from Botswana [46] clearly noted that chest radiography was not necessary to screen for active TB in the IPT program, whereas research among mine workers, an arguably special population, support its use [77]. Other diagnostic methods, such as TST and “in-tube” interferon- $\gamma$  release assay–based approaches, although potentially attractive, are unlikely to reach the large numbers of people living with HIV who could benefit from IPT. The WHO is developing guidelines for the optimal screening algorithm for diagnosis of TB and determination of the eligibility for IPT for people living with HIV. In the interim, individuals infected with HIV who do not have symptoms suggestive of TB should be administered IPT; however, persons with symptoms should have further examination for TB and, if eligible, should be offered TB treatment. Although often over-

looked, infection control for TB also relies on the prompt identification, diagnosis, and treatment of TB and should be a part of TB screening efforts [32].

**Drug resistance.** Fear of drug-resistant TB may be the major barrier to access to IPT. A recent systematic review of data published since 1952 reported that the risk of drug-resistant TB in those given IPT among viral strains infecting persons given IPT was not statistically different from that among strains infecting persons who received placebo [78]. Patients with isoniazid-resistant TB respond just as well as patients without isoniazid-resistant TB to standard short-course anti-TB therapy [79], although those with isoniazid-resistant TB experience a slightly increased risk of relapse [80, 81]. Therefore, although there is a possibility of development of isoniazid-resistant TB after use of IPT in people living with HIV, the benefits in terms of its effectiveness and efficacy must be balanced against these small risks [82].

**Toxicity.** In clinical trials involving people living with HIV, isoniazid was more likely than placebo to be discontinued as a result of adverse effects [3]. However, the likelihood of stopping treatment because of adverse effects was rare and was higher for combination therapies than for isoniazid monotherapy [3]. Isoniazid has potential adverse effects, including nausea, vomiting, rash, fever, hepatitis, and peripheral neuropathy. Hepatotoxicity, sometimes severe and even fatal, has been found in a very small proportion of individuals receiving isoniazid treatment [3, 83]. The risk of hepatitis has been found to increase with alcohol use, although in most studies, alcohol use has been poorly quantified, if at all [14]. Vitamin B6 can reduce the risk of peripheral neuropathy. Among patients receiving both ART and IPT, the risk of peripheral neuropathy is potentiated if stavudine or didanosine is used [84]. Careful counseling, clinical monitoring, and good patient education regarding when to stop treatment and seek advice can help in reducing the risk of toxicity [83]. In a large study in Seattle (which has a low prevalence of HIV infection), without laboratory monitoring, only 11 cases of hepatitis were reported after ~7 years in >11,000 patients receiving isoniazid (only 1 patient required hospitalization) [83]. Although information for people living with HIV is more limited, the rate of isoniazid hepatotoxicity during clinically monitored IPT is very low [83, 85, 86]

**IPT in settings with drug-resistant TB.** Although the vast majority of TB is curable, drug resistance (specifically, MDR) has emerged as a growing threat to TB control and public health in general. Data regarding drug resistance in sub-Saharan Africa and in populations with a high prevalence of HIV infection are relatively sparse [87]. However, South Africa, which has the largest number of people living with HIV, ranks fourth worldwide, with an estimated incidence of 16,000 MDR-TB cases per

year [1]. Primary prevention for HIV infection and active TB through use of early diagnosis of HIV infection and ART, infection control, improved DOTS implementation, and IPT may play a significant role in preventing the potential acquisition and transmission of extensively drug-resistant TB or MDR-TB. In most settings, isoniazid resistance is relatively low, which suggests that IPT would be effective for the majority of patients [87]. The role of IPT in persons suspected of MDR *M. tuberculosis* infection is not clear; some recommendations take a wait and see attitude, whereas others advocate preventive treatment with a drug that is likely to be effective [88, 89].

## BROADER PREVENTION ISSUES

Prevention of TB will require more than just medical and health facility-based interventions. Evidence of the historical burden of the disease confirms this; diminishing rates of TB were evident in the Northern Hemisphere long before the advent of chemotherapeutic agents, with decreasing rates consequent to the general effects of development, such as improved sanitation, housing, and nutrition. Addressing disparities in the social determinants of health is of significant importance in preventing TB and must be considered by policy makers concerned with improving public health. Finally, although an oft-neglected facet of TB prevention, successful engagement of a program with people living with HIV, persons with TB, and the community in both the planning and implementation of any TB prevention activity is essential.

## CONCLUSIONS

In summary, TB prevention in the context of HIV infection demands a comprehensive approach that effectively marshals evidence-based interventions for prevention of HIV infection and TB, including earlier diagnosis of HIV infection and ART [13, 28, 29, 32]. The “Three I’s for HIV/TB”—intensified case finding, infection control for TB, and IPT—should be seen as core services for prevention, care, and treatment of HIV infection. IPT is safe and effective in people living with HIV, reducing the risk of TB by 33%–64% for up to 2.5 years [3,13]. Although the number of studies involving children is limited, data also suggest a significant potential reduction in incidence and mortality [55]. Ongoing research studies are evaluating the optimal duration of therapy for IPT and alternate regimens. In the meantime, managers of HIV and TB programs should work with their communities to ensure that people living with HIV have access to the “Three I’s for HIV/TB” as part of high-quality, comprehensive services for prevention, care, and treatment of HIV infection and TB.

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