SUPPLEMENT ARTICLE

Tuberculosis Preventive Therapy in the Era of HIV Infection: Overview and Research Priorities

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The recognition of tuberculosis (TB) as a major cause of morbidity and mortality among human immunodeficiency virus (HIV)–infected persons has led to renewed interest in TB preventive therapy and its incorporation into the essential package of health care for these individuals. Despite convincing data regarding its efficacy, TB preventive therapy has not been widely implemented. Further work is needed to determine how to overcome the barriers to the implementation of such therapy, including how best to exclude the presence of active TB before providing preventive therapy. Such issues as the optimal duration of preventive therapy for and the role of TB preventive therapy in the treatment of individuals receiving antiretroviral therapy remain to be defined. Ongoing research will help to determine how best to use this intervention in the care of HIV-infected persons and in the control of TB on a wider basis.

BURDEN OF LATENT TUBERCULOSIS (TB) INFECTION

The World Health Organization (WHO) estimates that one-third of the world's population is latently infected with *Mycobacterium tuberculosis*. Latent tuberculosis (TB) infection results when individuals infected with *M. tuberculosis* carry the organism in a latent state, which is characterized by slowed or intermittent metabolism and replication below the level necessary to produce clinical illness [1]. The risk of reactivation of latent infection is low in healthy individuals but is greatly increased in individuals with immunosuppression, most notably that due to HIV infection [2]. The greatest burden of latent TB infection is found in Southeast Asia (prevalence, 46%), the Western Pacific region (32%), Africa (31%), and the Eastern Mediterranean region (27%) [2]. This finding contrasts with the much lower prevalence of latent TB infection noted in the Americas (15%) and Europe (14%). In sub-Saharan Africa, 5%–35% of the adult population is infected with HIV, and one-third to one-half of HIV-infected individuals are coinfected with *M. tuberculosis*. Between 1990 and 2005, the incidence of TB increased at an average rate of 7.0% per year in countries where there was a high prevalence of HIV infection among adults (⩾5%), but it increased at an average rate of only 1.3% per year in countries where the prevalence of HIV infection among adults was low (<5%) [3]. Because HIV infection is the major risk factor contributing to the growing burden of TB globally, particularly in countries in sub-Saharan African [4], the present article focuses on the role of TB preventive therapy in resource-poor countries where there is a high burden of HIV infection.

RISK OF TB AMONG HIV-INFECTED INDIVIDUALS

HIV infection leads to an increased risk of active TB, which may result from reactivation of latent infection

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or rapid progression to disease after recent infection [2]. HIV-infected individuals with a positive tuberculin skin test (TST) result have a significantly higher risk of TB than do HIV-infected individuals with a negative TST result [5, 6]. HIV-infected individuals with evidence of anergy have a risk of TB that varies depending on geographic locale. Anergic individuals who progress to disease are more likely to do so from recently acquired TB infection than from reactivating latent TB infection in the setting of a falsely negative TST result [5].

DIAGNOSIS OF LATENT TB INFECTION

The TST is the standard tool used to diagnose latent TB infection, although it has a number of limitations that are not discussed in the present article. Research on TB preventive therapy has used the TST to define latent TB infection, because it is a good predictor of the risk of TB. The role of new interferon-γ assays in the detection of latent TB infection is discussed elsewhere in this supplement [7].

TB PREVENTIVE THERAPY FOR HIV-INFECTED ADULTS WITH NO PREVIOUS HISTORY OF TB

To date, 4 meta-analyses have been published on the efficacy of treatment of latent TB infection in the prevention of a first episode of active TB among HIV-infected adults [8–11]. A recent analysis [11] included 10 placebo-controlled trials involving 8130 participants in Haiti [6, 12, 13], Uganda [5], Kenya [14], Zambia [15], Spain [16, 17], and the United States [18], as well as 1 multinational study involving the United States, Brazil, Haiti, and Mexico [19]. The results of long-term follow-up were subsequently reported for trials conducted in Uganda [20] and Zambia [21]. Although this meta-analysis includes efficacy trials performed in resource-rich countries, the results that are presented represent what is, to our knowledge, the greatest body of evidence of the efficacy of TB preventive therapy in HIV-infected individuals.

Efficacy. The combined efficacy of all TB preventive therapy regimens, regardless of TST status, was a 36% reduction in the TB incidence (relative risk [RR], 0.64 [95% confidence interval {CI}], 0.51–0.81), compared with that noted with placebo (figure 1) [11]. The greatest reduction in the TB incidence (62%) was observed among individuals with a positive TST result (RR, 0.38 [95% CI, 0.25–0.57]). Although the TB incidence was reduced among individuals who had negative TST results (17%) or were anergic (33%), the combined results were not significant (figure 1). It is clear, therefore, that preventive therapy is highly effective in individuals with positive TST results and that it is probably of little value in individuals with negative TST results. Isoniazid (INH) alone, given for 6–12 months, reduced the TB incidence by 33% overall (RR, 0.67 [95% CI, 0.51–0.87]) and by 64% among individuals with positive TST results (table 1). Among individuals with negative TST results and among anergic individuals, a nonsignificant reduction in TB incidence was noted with the use of INH alone (table 1). Multiple-drug regimens given for 2–3 months (rifampin [RIF] with INH and/or pyrazinamide [PZA]) were as efficacious as INH alone.

Durability of preventive therapy. The durability of preventive therapy remains unclear. In the Zambian trial [15, 21], which included individuals with positive TST results as well as those with negative TST results, the risk of TB developing in individuals in the INH and RIF/PZA arms increased over time but remained significantly lower than that for individuals in the placebo arm during the first 2.5 years but not subsequently. In contrast, follow-up of individuals with positive TST results in Uganda over 3 years [5, 20] showed a continued benefit of regimens containing RIF (INH/RIF and RIF/PZA) but not of regimens containing INH alone. These data are consistent with a more durable benefit of regimens containing RIF, but they also suggest that reinfection is an important problem in African settings.

Mortality. Overall, TB preventive therapy is not associated with a reduction in mortality (RR, 0.95 [95% CI, 0.85–1.06]); however, among individuals with positive TST results, there is a 20% reduction in mortality (RR, 0.8 [95% CI, 0.63–1.02]) (figure 1) [11]. Of note, TB preventive therapy using INH/RIF was associated with a significant 31% reduction in mortality in 2 trials (RR, 0.69 [95% CI, 0.5–0.95]). Mortality was reduced by 26% with the use of INH alone among individuals with positive TST results (RR, 0.74 [95% CI, 0.55–1.0]) but not among individuals with negative TST results or anergic indi-

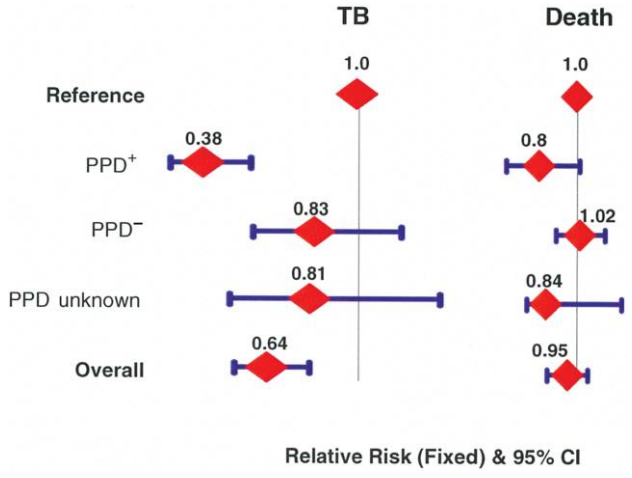

Figure 1. Efficacy of tuberculosis (TB [includes confirmed, probable, and possible active cases of TB]) preventive therapy (with any drug), compared with placebo, in reducing the incidence of active TB. "Death" denotes death due to all causes. CI, confidence interval; PPD, purified protein derivative; PPD unknown, unknown PPD status; +, positive; −, negative. A relative risk of <1 favors treatment. Copyright Cochrane Collaboration; adapted with permission from [11].

Table 1. Efficacy of isoniazid (INH) preventive therapy, compared with placebo.

PPD status, author [reference], year	TB[a] incidence: Among subjects given INH, *n/N*[b]	TB[a] incidence: Among control subjects, *n/N*[b]	TB[a] incidence: RR (95% CI)[c]	Death: Among subjects given INH, *n/N*[b]	Death: Among control subjects, *n/N*[b]	Death: RR (95% CI)[c]
Positive						
Hawken [14], 1997	5/67	8/69	0.64 (0.22–1.87)	3/67	9/69	0.34 (0.10–1.21)
Mwinga [15], 1998	4/52	11/60	0.42 (0.14–1.24)	7/52	4/60	2.02 (0.63–6.51)
Pape [6], 1993	2/38	6/25	0.22 (0.05–1.00)	3/38	7/25	0.28 (0.08–0.99)
Whalen [5], 1997	7/536	21/464	0.29 (0.12–0.67)	58/536	64/464	0.78 (0.56–1.09)
All	18/693	46/618	0.36 (0.22–0.61)	71/693	84/618	0.74 (0.55–1.00)
Negative						
Fitzgerald [12], 2001	6/126	4/111	1.32 (0.38–4.56)	19/126	15/111	1.12 (0.60–2.09)
Gordin [18], 1997	4/260	6/257	0.66 (0.19–2.31)	129/260	126/257	1.02 (0.85–1.21)
Hawken [14], 1997	11/235	8/224	1.31 (0.54–3.20)	50/235	37/224	1.29 (0.88–1.89)
Mwinga [15], 1998	14/178	17/166	0.77 (0.39–1.51)	33/178	28/166	1.10 (0.70–1.74)
Pape [6], 1993	2/20	5/35	0.70 (0.15–3.28)	2/20	5/35	0.70 (0.15–3.28)
Rivero [16], 2003	3/83	4/77	0.70 (0.16–3.01)	9/83	11/77	0.76 (0.33–1.73)
Whalen [5], 1997	9/395	10/323	0.74 (0.30–1.79)	86/395	76/323	0.93 (0.71–1.21)
All	49/1297	54/1193	0.86 (0.59–1.26)	328/1297	298/1193	1.02 (0.90–1.16)
Unknown						
Hawken [14], 1997	9/40	7/49	1.57 (0.64–3.85)	9/40	11/49	1.0 (0.46–2.18)
Mwinga [15], 1998	9/122	16/124	0.57 (0.26–1.24)	19/122	26/124	0.74 (0.43–1.27)
All	18/162	23/173	0.86 (0.48–1.52)	28/162	37/173	0.81 (0.52–1.27)
Total	85/2152	123/1984	0.67 (0.1–0.87)	427/2152	419/1984	0.95 (0.85–1.06)

NOTE. Copyright Cochrane Collaboration; adapted with permission from [11]. CI, confidence interval; PPD, purified protein derivative; RR, relative risk; TB, tuberculosis.

[a] Confirmed, probable, or possible active TB.

[b] *n/N* denotes the no. of TB cases or deaths/no. of subjects randomized.

[c] Fixed RR. The "weighted" RR and 95% CIs reported in the meta-analysis are used. The weight assigned to each study is not shown.

viduals (table 1). From a public health perspective, for approximately every 30 HIV-infected individuals who are found to be positive for purified protein derivative and who are treated with INH, 1 death will be prevented. In an observational study conducted in Brazil, HIV-infected adults with positive TST results who were receiving preventive therapy had a significantly longer survival time than did those who were not receiving preventive therapy [22].

Progression to AIDS. Two randomized controlled trials [6, 12] of INH preventive therapy (IPT) showed no overall effect of IPT on progression to AIDS. However, a small Haitian study [6] showed a lower risk of progression to AIDS in individuals with positive TST results who were given INH than in those who were given placebo. It is likely that preventive therapy reduces the risk of TB that meets the criteria for being an AIDS-defining illness, but it probably does not influence the development of other AIDS-defining illnesses. Early studies, which included small numbers of patients, have suggested that the development of TB was associated with increases in the HIV load, which could then further compromise cellular immunity and result in additional complications [23, 24]. More recent studies conducted in Africa confirm that active TB is associated with high viral loads that do not decline after TB treatment [25], and that high viral loads may precede the development of active TB and are more of a risk factor for than a consequence of TB [26].

Safety. In clinical trials involving HIV-infected patients, INH was more likely than placebo to be discontinued as a result of adverse effects (RR, 1.66 [95% CI, 1.09–2.51]) [11]. Transient asymptomatic elevation of liver transaminase levels commonly occurs after initiation of treatment with INH [27]. Hepatotoxicity is a serious adverse effect that may result in death if INH is not withdrawn soon after symptoms of hepatitis develop [28]. However, with clinical monitoring and with educating patients to discontinue INH immediately if symptoms suggestive of hepatitis develop, the risks of hepatitis and death are very small (range, 0.001%–0.004%) [28–31]. The risk of hepatitis increases with age, and previous recommendations suggested that individuals >35 years of age should not receive TB preventive therapy. Current guidelines of the American Thoracic Society and the Centers for Disease Control and Prevention do not exclude individuals >35 years of age who have a

high risk of developing TB [28]. Similarly, individuals >35 years of age should not be excluded from receiving TB preventive therapy in areas where the burden of TB is high and the benefit-to-risk ratio may be greater. The risk of hepatitis also increases with alcohol use, although, in most studies, alcohol use was poorly quantified, if at all. Better data are required to understand the association between alcohol intake and the risk of INH-induced hepatitis, to weigh the risks and benefits for individuals in different settings.

During clinical trials, regimens containing RIF were more likely to be discontinued because of adverse effects than were regimens containing INH [11]. Increased rates of hepatotoxicity and death among HIV-uninfected individuals have been reported for RIF/PZA, which led the Centers for Disease Control and Prevention and the American Thoracic Society to withdraw the recommendation for the use of RIF/PZA as preventive therapy in the United Sates [32–34]. However, the risk appears to be limited to HIV-uninfected individuals, because a rigorous reanalysis of a large trial of RIF/PZA involving HIV-infected patients confirmed a lack of serious toxicity [35].

Adherence. Only 5 of the clinical trials reported information on adherence. Adherence to shorter RIF-based regimens was better than adherence to 6- or 12-month regimens of INH [13, 17] in some trials and was similar in others [5, 14]. Among a cohort of Southeast Asian refugees and migrants, individuals receiving a multiple-drug regimen were more likely to be nonadherent and to discontinue therapy than were those receiving INH only [36].

The ProTEST initiative, which was established by the WHO in 1997 and which links HIV counseling and testing to a package of prevention, care, and support, is now recommended policy under the Global Plan to Stop TB [37]. Rates of adherence to INH were low at ProTEST pilot sites in South Africa, Zambia, and Malawi and ranged from 24% to 59%. Adherence was better when TST was included in the workup, but it resulted in a greater proportion of patients dropping out of the study before they completed the screening process. Poor adherence was associated with a lack of money for transport and food, perceived and real adverse effects of INH, nondisclosure of HIV infection status, and the perception that INH was not effective [38]. By contrast, good adherence was associated with support from health service staff, clinic groups, and family; easy access to health care facilities; and acceptance of HIV infection status. Modified directly observed therapy has also been associated with higher rates of adherence. In a study of injection drug users in the United States who had adherence measured by urine INH testing and the use of electronic bottle caps, directly observed twice-weekly INH preventive therapy resulted in significantly higher rates of compliance than did self-administered therapy [39].

Cost-effectiveness. Modeling suggests that, for HIV-infected individuals, a 6-month regimen of INH is cost-effective in resource-poor countries, particularly if the savings resulting from averting the costs of medical care and treatment of secondary cases of TB are included [40–43]. The cost-effectiveness of IPT is limited by the low coverage of HIV testing and the low uptake and completion of IPT [43]. In the United States, all TB preventive therapy regimens, other than one 3-month regimen of INH, RIF, and PZA, were found to be cost-effective when modeled for HIV-infected individuals who had positive TST results and a CD4 cell count of <200 cells/mm^3 [44].

The total and incremental costs of providing IPT as part of the ProTEST pilot projects were low, and IPT was thought to be cost-effective despite findings of poor uptake and [43] adherence [45]. A recent study among South African gold miners demonstrated the effectiveness of a 6-month regimen of IPT in a clinic providing routine HIV care [46]. Despite the use of an intensive screening process used to exclude individuals with active TB, one in which 2 sputum samples were obtained for microscopic examination and culture, IPT was found to be cost effective (US $353 per TB case averted vs. US $1736 [the average cost of TB case treated]) [47]. Additional cost-effectiveness data collected during routine implementation are required to rank IPT among the priorities for the treatment and care of HIV infection and to persuade policy makers to implement or expand IPT programs where they can be shown to be cost-effective.

FEASIBILITY

The experience of the ProTEST pilot projects has demonstrated that it is feasible to implement IPT within the context of a TB/HIV collaborative framework. In Northern Thailand, it was feasible to integrate IPT into routine health care as part of a comprehensive package of HIV/AIDS care. The feasibility and acceptability of integrating IPT into a workplace HIV prevention and care program have also been demonstrated [48]. Before the availability of antiretroviral therapy (ART), the potential gains were insufficient to attract the required investment in health care systems, human resources, and supply chains needed for wide-scale implementation of IPT and cotrimoxazole prophylaxis alone. Implementation of wide-scale IPT has become much more feasible now that the rapid ART scale-up under the "3 by 5" initiative has led to greatly increased capacity for the diagnosis of HIV infection and the delivery of care for chronic HIV infection.

Despite the proven feasibility and cost-effectiveness of IPT in resource-poor countries, the Joint United Nations Programme on HIV/AIDS (UNAIDS)/WHO guidelines for IPT for people living with HIV/AIDS [49], and the endorsement of these guidelines by the Interim Policy on Collaborative TB/HIV activities [50], few resource-poor countries with a high burden of HIV infection and TB have an IPT policy for people living with HIV/AIDS. There has been progress, however, with 12 of

41 countries with the highest burden of HIV-associated TB having a national policy of using IPT for HIV-infected individuals in 2004 [3], although there has been limited implementation of IPT in these countries, apart from Botswana, which has a national IPT program [51]. Factors that may contribute to low coverage include poor uptake of voluntary counseling and testing among individuals with presymptomatic HIV disease, the need to screen for active TB, the use of TSTs where this is policy, weak health care systems, lack of treatment literacy, the reluctance of a national TB control program to use a first-line TB drug as preventive therapy, and the stigma associated with such use, as is alluded to below. Further research is required to identify the factors associated with poor uptake of IPT at all levels (governmental, community, and individual) and to evaluate interventions to improve coverage of IPT.

SECONDARY PREVENTIVE THERAPY

The concept of TB preventive therapy was developed in the pre-HIV era. Treatment of latent or recently acquired TB infection was assumed to reduce the lifetime risk of developing active TB disease, which was true in areas where TB transmission was rapidly decreasing as a consequence not only of TB preventive therapy but also of active case finding. Hence, it was also assumed that there was no need for further intervention after successful treatment of active disease. The preventive therapy trials involving HIV-infected individuals were based on the same principle, and, therefore, they included only individuals with no previous history of TB. However, molecular "fingerprinting" techniques have revealed that recurrent TB may occur either as a result of recrudescence of disease from the original infecting organism (relapse) or as a result of reinfection with a new strain of *M. tuberculosis,* particularly in areas where there is a high rate of TB transmission [52, 53]. Reinfection, with rapid progression to disease, has been shown to be an important cause of recurrence among HIV-infected individuals in areas with high rates of TB transmission [53]. In settings where the rate of TB transmission is high, there is growing evidence that preventive therapy for HIV-infected individuals previously treated for TB is effective in reducing TB recurrence (figure 2) [54–57], although current international guidelines do not recommend the use of preventive therapy.

ART

ART is becoming increasingly available in resource-poor countries. In cohorts of clinic attendees, ART reduced the incidence of TB by ⩾80% [59–62], with the greatest effect noted among individuals with the lowest CD4 cell counts [60]. Despite these findings, the rate of TB among individuals receiving ART in countries where the rate of TB is high remains unacceptably high (2%–10% per year) [60, 61, 63]. The benefit of adding IPT to ART to reduce the risk of TB is unknown. Because there is no evidence that IPT is contraindicated with ART, the WHO's interim policy on collaborative TB/HIV activities recommends that the use of ART should not preclude the use of IPT [50]. This position is supported by some investigators [64]. There is evidence from observational cohort studies that IPT significantly reduces the risks of TB [65] and death during early ART [66], and that the combination of IPT and ART results in a significantly greater reduction in TB risk than does either treatment alone.

SCREENING FOR TB: THE ROLE OF CHEST RADIOGRAPHY

Screening for active TB disease before initiation of preventive therapy is required to minimize the risk of drug resistance developing as a result of inadvertent treatment of active TB with an inadequate regimen. The role of chest radiography in the screening process remains unclear. The WHO policy statement on the use of preventive therapy for TB in people living with HIV/AIDS recommends a review of TB symptoms for all patients and examination of a chest radiograph, if available [49]. The evidence for recommending the addition of chest radiography to symptom screening before initiation of preventive therapy for HIV-infected individuals is conflicting. Among 560 asymptomatic HIV-infected Batswana who underwent screening for TB, only 1 case of TB (0.2%) was diagnosed on the basis of the chest radiographic findings. However, the fact that no mycobacterial cultures were performed may have underestimated the prevalence of active TB and the usefulness of chest radiographic screening. Symptom screening alone was also found to be adequate to exclude a diagnosis of TB for 129 patients with WHO stage 3 or 4 HIV infection in Cape Town. In contrast, for Kenyan and South African miners, chest radiographs were found to be of value when combined with symptom screening [67]. If chest radiography is part of the screening process, it adds to the costs, and it may be a barrier to starting preventive therapy, particularly if there are no radiographic facilities on site.

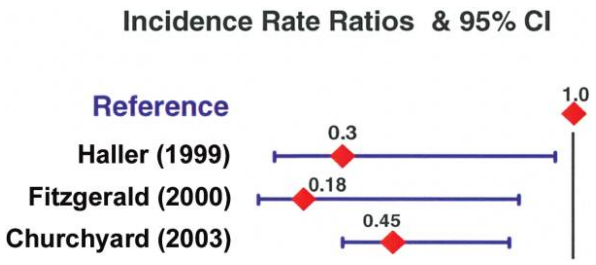

Figure 2. Efficacy of secondary isoniazid tuberculosis (TB) preventive therapy. CI, confidence interval. An incidence rate ratio of <1 favors treatment [54, 55, 57]. Reproduced with permission from [58].

PREVENTIVE THERAPY REGIMENS

Further research is required to determine the optimal regimen, which should be safe, cost-effective, short, intermittent, compatible with ART, and durable and should have a high threshold for generating resistance. The role of new drugs for TB preventive therapy, such as rifapentine, moxifloxacin, and other TB drugs in development, should be evaluated.

DRUG RESISTANCE

Theoretically, if active TB is missed and the bacterial load is large enough, treatment with monotherapy or an inadequate regimen may generate drug resistance. The impact of widespread uptake of preventive therapy on generating drug resistance is unknown. Extensive use of preventive therapy in a resource-rich country where there is a low prevalence of TB, such as the United States, has not led to drug resistance, and the intervention has not been widely implemented in resource-poor countries where the prevalence of TB is high. A systematic review of studies of IPT conducted since 1952 concluded that data were sparse, and interpretation was hindered by incomplete testing of isolates and changes in the definition of resistance. In a recent systematic review, the summary relative risk of INH resistance among individuals who had received IPT, compared with that among control subjects, was 1.45 (95% CI, 0.85–2.47) [68]. Thus, an effect to promote INH resistance cannot be excluded, but any such effect is likely to be small. In addition, in individuals who receive it, IPT could cause a shift in the TB strains causing disease toward initially INH-resistant strains, similar to the shift seen in pneumococcal isolates causing disease in recipients of pneumococcal vaccine [69, 70]. Because the main cause of INH resistance is inadequate treatment of active disease, any effect of IPT to promote resistance must be balanced against its proven efficacy and effectiveness in reducing the risk of active TB.

The effectiveness of IPT in countries with high rates of drug-resistant TB is unknown; it may be less effective among individuals who have latent infection with an INH-resistant organism, but it is unlikely to do harm. Although individuals known to be infected with INH-resistant TB could be treated with RIF alone or with RIF and PZA, this is not recommend by the WHO, to avoid emergence of resistance to RIF [49].

Children. There are clear guidelines for preventive therapy for infants and children <5 years of age who are exposed to adults with smear-positive pulmonary TB [71]. These recommendations are based on studies conducted in the pre-HIV era. Children living in countries where there is a high burden of TB may be exposed to TB within the household or in the community. HIV-infected children are at high risk of having rapid progression from infection to active TB disease, particularly to severe forms of TB, and would benefit from receiving treatment for latent TB infection. However, there has been concern that, because of the difficulty associated with diagnosing TB in children, active TB may be missed and treated inappropriately. Preliminary results from a placebo-controlled trial from Cape Town, South Africa, showed that, among HIV-infected children treated with IPT, the incidence and mortality rate associated with TB were halved [72], although further results from the study have not been presented or published. A large, randomized controlled trial of IPT given to infants born to HIV-infected mothers is under way in Soweto, South Africa.

Pregnancy. HIV-associated TB is the cause of 10% of maternal deaths in some countries in sub-Saharan Africa [73–75]. The TB-associated mortality rate among HIV-infected pregnant women may be 3-fold greater than that among HIV-uninfected pregnant women [75]. Little is known about the impact of maternal HIV infection on the perinatal outcome of pregnancies complicated by active TB. Whereas the need for treatment of active TB during pregnancy is unquestioned, for both mother and fetus, the risk of drug toxicity related to TB preventive therapy must be carefully weighed against the risk and consequences to mother, fetus, and newborn infant should active TB develop. Currently, the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend delaying preventive therapy until the postpartum period because of reports of INH-associated hepatotoxicity developing during pregnancy and the postpartum period [76]. Because of the high prevalence of HIV-associated TB and the high TB-associated mortality rate among pregnant women in resource-poor countries, the safety and efficacy of IPT need to be evaluated in such countries.

THE ROLE OF PREVENTIVE THERAPY IN TB CONTROL

In the United States, TB-control strategies have included evaluation of contacts of individuals with TB and treatment of latent TB infection among high-risk individuals. The widespread use of targeted IPT may have contributed to the decrease in TB incidence in the United States.

Community-wide IPT was first investigated in a household randomized trial conducted in the Bethel district of Alaska [77]. Individuals who received IPT had a 69% reduction in TB incidence during the first year of the trial, and, over the next 5 years, they had a 60% lower incidence of TB. Because this study essentially included the entire population, the community-wide benefit of IPT was an overall reduction in TB incidence of 30%. After these results were obtained, all residents in the Bethel district were offered IPT, which, in addition to an ongoing TB control program of passive case finding and treatment, resulted in the sustained reduction in TB incidence. This study was replicated in Greenland with less effect, largely because of the low dose of INH used [78]. A nationwide targeted IPT program

Table 2. Summary of current or planned trials of tuberculosis (TB) preventive therapy.

Trial type, study name (trial number)	Sponsor(s)	Country/sample size	Inclusion criteria	Trial phase	Study arm		Duration and/or primary outcome
					Intervention	Control	
Individually randomized controlled							
TBTC Study 26: Effectiveness and Tolerability of Weekly Rifapentine/Isoniazid for Three Months Versus Daily Isoniazid for Nine Months for the Treatment of Latent Tuberculosis (NCT00023452)	CDC; Department of Veterans Affairs	United States, Brazil, Canada, and Spain; N = ~8000 (enrolling)	Age ⩾2 years; not pregnant; positive TST result and at high risk of developing TB; HIV-infected close contacts of patients with culture-positive TB	3	RPT/INH once weekly for 3 months	INH for 9 months	Subjects ⩾18 years of age: culture-positive TB; subjects <18 years of age, culture-positive or probable (clinical) TB
Tuberculosis Prevention for HIV-Infected Adults (NCT00057122)	Johns Hopkins University; NIAID	South Africa; N = ~1148 (enrollment closed)	Age ⩾18 years; HIV infected; TST result ⩾5 mm; CXR negative for TB	3	RPT/INH for 3 months and observed weekly; RIF/INH for 3 months and observed twice weekly; continuous INH, self-supervised	INH self-supervised for 6 months	Follow-up, 1–4 years; active TB
A Randomized, Placebo-Controlled Study of Limited vs. Continuous Isoniazid Tuberculosis Preventive Therapy for HIV-Infected Persons in Botswana (NCT00164281)	CDC; Botswana MOH; USAID	Botswana; N = ~1800 (enrolling)	Age ⩾18 years; HIV infected; positive or negative TST result; not pregnant	4	Continuous INH	INH for 6 months	Accrual, 1 year; follow-up, 24–36 months; active PTB or ETB
A Randomized, Double Blind, Placebo Controlled Trial to Determine the Efficacy of Isoniazid (INH) in Preventing Tuberculosis Disease and Latent Tuberculosis Infection Among South Africans with Perinatal Exposure to HIV (NCT00080119)	NIAID; Secure the Future Foundation	South Africa; N = ~1300 (enrolling)	Age 91–120 days; HIV-infected mother; received BCG; normal findings of neuro exam; no TB contact	2	INH daily	Placebo	Follow-up, 192 weeks; TB disease; latent TB infection
Randomized Controlled Trial of 4 Months Rifampin Versus 9 Months of INH for the Treatment of Latent TB (NCT00170209)	McGill University	Canada; no. of subjects not specified	Age ⩾15 years; positive TST result; not pregnant; HIV infected or has other immunosuppression	4	RIF for 4 months	INH for 9 months	April 2004 to July 2007

An Efficacy Study of 2 Preventive Therapy Studies in HIV-Infected Persons in India (NCT00351702)	Tuberculosis Research Centre; USAID	India; $N = 650$ (enrollment closed)	Age ⩾15 years; HIV positive	3	ETH/INH for 6 months	INH for 36 months	Follow-up, 5 years; active TB; death
Community level[a]							
ZAMSTAR[b] (ISRCTN36729271)	CREATE; Bill and Melinda Gates Foundation	Zambia and South Africa	…	Community randomized, factorial design	Improved TB case finding; integrated TB/HIV care delivered through the household, including TB preventive therapy (INH for 6 months)	Standard TB control	Prevalence of culture-positive TB, measured after 3 years of the interventions
Thibela TB Study[c] (ISRCTN63327174)	CREATE; Bill and Melinda Gates Foundation	South Africa	Employees at intervention clusters; age ⩾18 years; no active TB	Cluster-randomized, nonblinded, controlled trial	Standard TB control + INH for 9 months for all eligible employees (n = ~38,000), regardless of HIV infection and silicosis status	Standard TB control (n = ~30000)	Start date: June 2006; end date: June 2010; each arm was followed for 2 years; TB incidence in the second year of follow-up
Impact of TB Preventive Therapy for HIV/TB Co-Infected Patients with Access to Highly Active Antiretroviral Therapy in Rio De Janeiro, Brazil (NCT00107887)	CREATE; Bill and Melinda Gates Foundation	Brazil; N = ~15,000 (enrolling)	Age ⩾16 years; HIV infected; attending a participating HIV clinic	Phased implementation trial	ART drugs and implementation of IPT policy	ART drugs alone	Duration, 4 years; incidence of active TB before and after implementation of IPT policy
Nationwide TB preventive therapy program	Botswana Government; CDC	Botswana; $N > 30,000$	HIV infected; no active TB	Routine implementation	INH for 6 months	NA	TB incidence

NOTE. ART, antiretroviral therapy; BCG, bacille Calmette-Guérin; CDC, Centers for Disease Control and Prevention; CREATE, Consortium to Respond Effectively to the AIDS/TB Epidemic; CXR, chest radiography; ETB, extrapulmonary TB; ETH, ethambutol; INH, isoniazid; IPT, INH preventive therapy; MOH, Ministry of Health; NA, not applicable; neuro exam, neurological examination; NIAID, National Institute of Allergy and Infectious Diseases; PTB, pulmonary TB; RIF, rifampin; RPT, rifapentine; TST, tuberculin skin test; USAID, United States Agency for International Development.

[a] Trials in settings with a high prevalence of HIV infection.

[b] The Zambia, South Africa, Tuberculosis and Acquired Immune Deficiency Syndrome-Reduction Trial.

[c] Effect of Community-Wide Isoniazid Preventive Therapy on Tuberculosis among South African Gold Miners.

has recently been implemented in Botswana, and its impact on TB control has not yet been determined. Mathematical modeling of community-wide preventive therapy in countries where there is a high burden of HIV infection and TB suggests that this strategy may result in a rapid and dramatic reduction in TB incidence [79]. This strategy is currently being tested among South African gold miners (table 2). Modeling studies should also inform the potential role of preventive therapy in meeting The Global Plan to Stop TB targets for reducing the prevalence, incidence, and mortality associated with TB by 2015 and for eliminating TB by 2050 [37].

PREVENTIVE THERAPY RESEARCH

Several areas requiring further research have been highlighted in the present article and in previous reviews [80]. Table 2 summarizes current or planned trials of TB preventive therapy either among or including HIV-infected individuals, as well as cluster-randomized studies of interventions (including IPT) that aim to reduce the burden of TB in communities where there is a high prevalence of HIV infection.

In 2005, the WHO hosted a meeting to establish TB/HIV research priorities in resource-limited countries that would inform policy and lead to improved implementation of joint TB/HIV activities in the context of ART [81]. The priority areas of research that were identified for TB preventive therapy are discussed below.

Despite convincing data on its efficacy, and despite WHO recommendations that it be included as part of the minimum package of care, TB preventive therapy has not been widely implemented. Ministries of health have expressed concern about the emergence of resistance and the limited durability associated with such therapy. There are limited data of the impact of the widespread use of TB preventive therapy on the emergence of drug resistance. Evaluation of individual- and program-level outcomes of the Botswana national TB preventive therapy program will provide important data that could address these concerns and further inform policy and implementation. More effective ways of promoting the implementation of preventive therapy programs need to be identified. Additional work is needed to determine (1) how to overcome the barriers to implementation, such as how best to exclude active TB among adults, infants, and children before preventive therapy is used, and (2) whether extending preventive therapy to those with advanced HIV disease who are at greatest risk of developing active TB is feasible and efficacious and would achieve a public health benefit. The role of TB preventive therapy among HIV-infected infants, children, and individuals receiving antiretroviral therapy also needs to be defined. Research priorities for TB preventive therapy that were recommended by the meeting, at the individual and population levels, are summarized in the Appendix.

CONCLUSIONS

TB preventive therapy among HIV-infected individuals, particularly therapy involving INH, reduces TB incidence and is cost-effective and safe. Strategies to overcome barriers to implementation and poor adherence need to be determined. In response to the resurgence of TB, new drugs are on the horizon that may make treatment of latent infection shorter and more durable, and new diagnostics may enable more accurate diagnosis of latent TB infection. Ongoing and future research will play a vital role in shaping the policy for and implementation of TB preventive therapy.

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APPENDIX

SUMMARY OF INDIVIDUAL- AND POPULATION-LEVEL RESEARCH PRIORITIES FOR TUBERCULOSIS (TB) PREVENTIVE THERAPY

Individual level

- What is the optimal algorithm to exclude TB disease?
- What is the added benefit of isoniazid preventive therapy (IPT) among people receiving antiretroviral therapy?
- Should IPT be rationalized by targeting individuals with advanced HIV disease?
- What is the effectiveness of IPT among infants and children?

Population level

- What are the macroeconomic barriers to implementing IPT and what are the mechanisms for overcoming them?
- What are the lessons learned from Botswana's national IPT program?
- What is the effectiveness of IPT in regions with elevated isoniazid resistance?

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