Preventive therapy for HIV-associated tuberculosis

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Purpose of review
Tuberculosis (TB) remains the leading cause of death in people living with HIV (PLHIV) despite the achievements in antiretroviral therapy coverage. TB preventive therapy (TPT) has proved efficacy but has been neglected and poorly implemented. We reviewed recent publications and guidelines about TPT in PLHIV.

Recent findings
High-quality studies showed that TPT has a durable effect, over 5 years, preventing TB and all-cause mortality. There is new evidence showing the noninferiority of shorter, rifamycin-based regimens of TPT increasing the options for treatment. Recent studies describing robust implementation in different settings showed promising results for feasibility, tolerance, retention, and cost-effectiveness. New WHO recommendations, unifying previous versions, have been released to guide countries implementation.

Summary
New evidence support the scale up of TPT for PLHIV globally, further studies are needed to bring more evidence for specific populations, like pregnant women and for drug–drug interactions with antiretroviral agents.

Keywords
HIV, latent tuberculosis infection, tuberculosis preventive therapy

INTRODUCTION

Tuberculosis (TB) is the leading cause of death for people living with HIV (PLHIV) globally and has remained so despite the increasing uptake of antiretroviral therapy (ART) in resource-limited settings. A significant amount of evidence shows that TB preventive therapy (TPT) is efficacious, reducing TB morbidity, and mortality among PLHIV in multiple settings. In addition, there is substantial and recent data documenting the safety, feasibility, and cost-effectiveness of TPT.

Preventing TB in PLHIV has been a challenging undertaking for many years. The most recent estimate from the WHO, for 2016, is that 42% of patients newly enrolled in HIV care started TPT [1,2]. Uptake of TPT has been limited by lack of commitment, concerns about toxicity, fear of selecting for drug resistance, and prioritization of ART delivery. Mathematical modeling shows that global TB control will not be possible without a massive increase in use of TPT, both in those with and without HIV infection [3]. It is clear that the achievement of the Sustainable Development Goals and the End TB strategy to reduce TB incidence by 90% by 2030 and 95% by 2035 will not happen if TPT is not escalated [4,5].

WHY USE TUBERCULOSIS PREVENTIVE THERAPY?

TPT has been shown to be effective for PLHIV and has an additive or synergistic effect with ART for reducing TB incidence, as well as a durable effect in reducing overall mortality independently of ART [6,7].

The long-term evaluation of the Temprano study, a randomized, factorial design trial of PLHIV with CD4 counts above thresholds for treatment according to WHO guidelines assigned to deferred or immediately initiation of isoniazid (INH) preventive therapy (IPT) for 6 months and/or ART or neither showed a reduction of all-cause mortality for PLHIV who started TPT earlier. The effect was independent of ART, but additional benefit was observed among those receiving both TPT and antiretroviral

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KEY POINTS

- TPT is effective and has a durable effect in preventing TB and reducing mortality in PLHIV.
- There are now more options and shorter regimens recommended to treat latent TB.
- There is new and robust evidence that TPT can be implemented in large scale with good tolerance and adherence.

(ARV). PLHIV who received TPT early in the course of HIV infection had a 37% reduction in all-cause mortality over 5 years from randomization. This is the first randomized controlled trial to show a durable survival effect of TPT in long-term follow-up. These results add to the robust evidence of the benefits of TPT and make it difficult to understand why such an important therapy is not widely used [8▪▪].

WHOM TO TREAT?

Recently updated WHO guidelines recommend that all PLHIV should receive TPT after active TB has been excluded regardless of tuberculin skin test (TST) or IFNγ release assay (IGRA) status or whether they are receiving ART. TPT is also recommended for other individuals at high risk of progressing to active TB, including household contacts of pulmonary TB, patients initiating antitumor necrosis factor treatment, receiving dialysis, preparing for an organ or hematological transplant and with silicosis.

Infants aged less than 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of IPT if the investigation shows no TB disease. Children aged at least 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting with a high prevalence of TB [9▪▪].

Preventive treatment is recommended for PLHIV living in high TB incidence areas and successfully treated for TB, regardless of age. The efficacy of secondary preventive therapy in HIV-infected individuals is unknown; however, a recent systematic review including four studies showed that secondary preventive therapy, compared with nontreatment or placebo, significantly decreased the incidence of recurrent TB in this population, but this needs further confirmation [10].

TPT has been recommended for pregnant women living with HIV considering the risk for TB and its consequences for the mother and the fetus. However, sound clinical judgment is required to determine the best time to provide it [9▪▪]. A phase IV randomized, placebo-controlled trial in TB endemic areas evaluated the safety and efficacy of IPT during or after pregnancy. The trial compared initiation of IPT in antepartum (immediate) versus at 12 weeks postpartum (deferred) in pregnant HIV-positive women. There was no difference in maternal or infant TB by study arm, but adverse pregnancy outcomes were significantly higher in the immediate IPT group [11▪].

RULING OUT ACTIVE TUBERCULOSIS

Prior to beginning TPT, it is important to exclude active TB. The use of clinical algorithms with high sensitivity and high negative predictive values to rule out TB is a valuable approach. The WHO four-symptoms clinical screening performs well for PLHIV not on ART; although this algorithm has lower sensitivity for individuals on ART, its use is also recommended in this setting. The addition of chest radiography increases the sensitivity for patients on ART and may be added to the algorithm, but the unavailability of chest radiography should not be an impediment to providing TPT [9▪▪,12].

Asymptomatic or subclinical TB is not unusual in people with HIV infection and can be detected by using sensitive liquid culture techniques. Pregnant women with HIV infection may be especially likely to be asymptomatic, as pregnancy may mask typical TB symptoms. One study reported a 10-fold increase in the yield of TB screening in HIV-infected women when liquid culture was performed regardless of symptoms rather than only for those with symptoms [13].

TESTING FOR LATENT TUBERCULOSIS INFECTION

Both TST and IGRAs can be used in settings where they are available, but testing should not be an obstacle to implementing TPT. Previous studies have shown that PLHIV with a positive TST benefit more from the TPT than those with a negative result, but more recent data showed similar benefits regardless of the TST or IGRA results [14].

There is renewed interest in identifying host biomarkers for better predicting latent and active TB. Yoon *et al.* recently showed the potential of C-reactive protein (CRP) as a point-of-care test for ruling out TB before initiating TPT. CRP is a non-specific protein the concentration of which rises in the presence of an ongoing inflammatory process. In ART naïve patients with CD4 cell counts 350 cells/μl or less, a point-of-care CRP test yielded a

high negative predictive value (98%) and had a specificity higher than the current standard symptom-based screening [15]. The use of plasma RNA transcripts as markers of TB risk is another promising approach [16].

WHAT TO TREAT WITH AND FOR HOW LONG?

INH has been the keystone of latent tuberculosis infection (LTBI) treatment since the 1950s, but in the last decade shorter, safer, and more acceptable regimens have been developed, leading to a number of alternative treatment options to prevent TB. Currently, 3–4 months of daily rifampicin and INH, 3 months of once-weekly rifapentine and INH, or 3–4 months of rifampicin may be used as an alternative to INH monotherapy to prevent TB [9▪▪].

The BOTUSA study, performed in Botswana where the prevalence of TB is high, found that rates of TB were lower among TST-positive individuals, most of whom were not receiving ART, if they received 36 months as opposed to 6 months of INH [17]. However, another study in South Africa found no additional benefit to prolonged courses of INH compared with only 6 months of treatment [18].

In addition, long-term protection from 6 months of IPT was observed in the THRio study in Brazil; and in the long-term observation phase of the Temprano study, in Côte d'Ivoire, showing that given early in the HIV course, 6 months of IPT, has a durable survival benefit over an average of 4.9 years [8▪▪,19].

Rifamycin-based, shorter regimens may be an option for PLHIV but their use has to be cautious because of potential drug–drug interactions. Rifapentine and INH weekly for 3 months can be coadministered with efavirenz-based ART, as can daily rifampicin-based regimens, but other nonnucleoside reverse transcriptase inhibitors should not be used with these regimens. The use of rifampicin-based regimens also is not recommended with protease inhibitors or with cobicistat-boosted ART. Coadministration of rifampicin-based TPT with integrase strand inhibitors has not been well studied. A small trial of dolutegravir and weekly rifapentine and INH in healthy volunteers was halted early after two of four participants developed hypersensitivity reactions characterized by high levels of proinflammatory cytokines [20]. An additional study of dolutegravir and weekly rifapentine and INH in PLHIV is currently underway. There was no significant difference in the TB incidence comparing the rifapentine regimen to INH for 6 or 9 months. The risk of hepatotoxicity was lower and the completion rates were higher with the rifapentine regimen for adults with HIV [9▪▪,18,21].

Recent results of a randomized, controlled trial comparing 1 month of daily INH and rifapentine (1HP) to 9 months of INH (9H) demonstrated that the ultra-short 1HP regimen was noninferior to and safer than 9H for PLHIV. The study enrolled 3000 people older than 13 years of age living with HIV whom either lived in areas with high TB incidence or had a skin or blood test indicating LTBI. Fewer adverse events occurred and treatment adherence was significantly better for the shorter regimen [22▪].

A frequent concern related to LTBI treatment is the potential increase of resistance to the drug used. Among studies on IPT efficacy, none demonstrated increase in INH resistance [17,18,23]. Available data on the impact of the new, shorter-duration rifamycin containing regimens on emerging drug resistance showed no significant increased risk of rifamycin resistance after LTBI treatment [24].

The current recommendation for TPT for persons with a suspected multidrug-resistant latent TB infection (MDR-LTBI) is an individualized management using a regimen based on drug resistance profile of the source case. The data available results from few observational studies. A recent systematic review and meta-analysis, which did not included people PLHIV, suggests that MDR-LTBI treatment is associated with reduction in MDR-TB incidence but the best regimen to these patients is still a big challenge [9▪▪,25].

IMPLEMENTATION AND ADHERENCE

Among the recurrent excuses for not implementing TPT are poor adherence and tolerability. As more treatment options become available and countries make efforts to scale up TPT new data show that even with long-course therapy (36 months of INH), adherence can be obtained, and tolerability is good. In Swaziland, one of the countries with the highest TB incidences globally, Mueller included 288 PLHIV eligible for IPT in a prospective observational cohort. The study, conducted in two clinics under routine circumstances, showed that 253 (87.8%), 234 (81.3%), and 228 (79.2%) individuals were still on IPT after 48, 96, and 144 weeks, respectively. Overall the tolerability was good with 5.6% (15/286) side effects reported in the first year, 2.0% (5/253) in the second year, and 0.9% (1/234) in the third year. There were two cases of severe hepatotoxicity leading to hospitalization with full recover [26▪].

An implementation study in Thailand, including seven hospitals in multiple provinces, obtained good retention with 85% patients completing 9 months of INH, interestingly 14% of the screened patients were diagnosed with TB. The study underlines the feasibility of large-scale implementations and highlights importance of the TPT cascade, not only to prevent TB but also to early identify TB cases among PLHIV [27].

In Malawi, an implementation study showed a lower retention rate of 75% and found that there is an increased risk of missed follow-up and initiation of IPT soon after HIV diagnosis. The authors emphasized the importance of early diagnosis of HIV and immediate onset of ARV and IPT as patients with advanced disease, low CD4 counts and those who suffer side effects are those at highest risk of abandoning the IPT [28].

A cost-effectiveness study of PLHIV was done in six urban-based clinics in Tanzania. In this, prospective cohort study, patients screened using a symptom-based tool were started on INH for 6 months. Effectiveness was assessed using TB cases prevented and deaths averted, they found that 420 TB cases per 100 000 were prevented and 979 deaths per 100 000 were avoided in the IPT group. The authors concluded that TST with INH for 6 months, after using the symptom-based screening tool was cost-effective and should be implemented pending on financial affordability and prioritization from the national governments [29].

CONCLUSION

There is an auspicious moment for TB control with high level political commitments and aspiring target for the world. TPT is crucial to accelerate the decreasing trends in TB incidence and HIV-related TB deaths. Important new evidence is now available to help overcome the usual barriers to implementing TPT for PLHIV. Still, there is need for new and affordable diagnostic tests and treatments to accelerate large-scale implementation and redraw the curve to meet the ambitious targets.

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Conflicts of interest

The authors report no potential conflicts of interest related to this work.

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