The International Journal of Tuberculosis and Lung Disease

Challenges and opportunities to prevent tuberculosis in people living with HIV in low income countries

Journal:	*The International Journal of Tuberculosis and Lung Disease*
Manuscript ID	IJTLD-03-18-0207.R2
Manuscript Type:	State of the Art - standalone
Date Submitted by the Author:	18-Aug-2018
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Key Words:	HIV/AIDS, tuberculosis, antiretroviral therapy, isoniazid preventive treatment, infection control

Challenges and opportunities to prevent tuberculosis in people living with HIV in low income countries

An invited "State of the Art" paper for IJTLD – R2

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Paper Content:

Abstract word count = 250

Narrative word count = 4500

References = 88

Tables = 4

Short running title:

Preventing TB in people living with HIV

Key words:

HIV/AIDS; tuberculosis; antiretroviral therapy; isoniazid preventive treatment; infection control

ABSTRACT

People living with HIV (PLHIV) are at high risk for TB, and TB is a major cause of death in PLHIV. Preventing TB in PLHIV is therefore a key priority. Early initiation of antiretroviral therapy (ART) in asymptomatic PLHIV has a potent TB preventive effect, with even more benefits in those with advanced immunodeficiency. Applying the most recent WHO recommendations that all PLHIV initiate ART regardless of clinical stage or CD4 cell count could provide a large TB preventive benefit at the population level in high HIV-prevalence settings. Preventive therapy can treat TB infection and prevent new infections during the course of treatment. It is now established that isoniazid preventive therapy (IPT) combined with ART amongst PLHIV significantly reduces the risk of TB and decreases mortality compared with ART alone, and therefore has huge potential benefits for millions. However, despite the evidence, this intervention is not implemented in most low-income countries with high burdens of HIV-associated TB. HIV and TB programme commitment, integration of services, proper screening procedures for excluding active TB, reliable drug supplies, patient-centred support to ensure adherence and well-organized follow-up and monitoring that includes drug safety are needed for successful implementation of IPT, and these would also be needed for future shorter preventive regimens. A holistic approach to TB prevention in PLHIV should also include other important preventive measures such as detection and treatment of active TB particularly among contacts of PLHIV and TB infection control measures in health facilities, homes of index patients and congregate settings.

Introduction

Since the emergence of the HIV/AIDS epidemic in the 1980s, infection with the human immunodeficiency virus (HIV) has remained the most important risk factor for the development of tuberculosis (TB). HIV targets the host cell-mediated immune response to *Mycobacterium tuberculosis (MTB)*.[1] The resulting immunosuppression increases the risk of reactivation of TB infection,[2] as well as the risk of rapid progression of a recently acquired TB infection.[3] Without treatment, people living with HIV (PLHIV) and with *MTB* infection have an annual risk of developing TB of approximately 10% per year compared to an estimated 10% lifelong risk in non HIV-infected individuals.[4,5] Both mechanisms (reactivation and new infection) lead to an increase in TB incidence among PLHIV as well as increased *MTB* transmission in the community.

One third of PLHIV with TB die annually.[6] The reasons include: i) failure to suspect or diagnose TB,[7] ii) delays and challenges in diagnosing TB due to immunodeficiency-related presentations with smear-negative pulmonary disease or extra-pulmonary /disseminated disease,[8,9] iii) non-provision or delayed treatment with antiretroviral therapy (ART) and cotrimoxazole preventive therapy in co-infected TB patients, and iv) missed opportunities to prevent TB in PLHIV.

The epidemiological impact of this deadly association remains high. In 2016 alone, over 1.0 million PLHIV worldwide were estimated to develop TB (10% of the total burden of incident TB), among whom 74% lived in Africa, and 374,000 PLHIV were estimated to have died from TB (22% of total TB deaths).[6] The overall high mortality in HIV-associated TB and the generally inadequate medical and programmatic responses mean that it is far better to prevent TB than wait for it to

occur. TB prevention is now a vital component of the technical pillar of the World Health Organization (WHO) End TB Strategy.[6,10]

In 2009, Aït-Khaled and colleagues discussed the important challenges and concerns regarding isoniazid preventive therapy (IPT).[11] A recent review of barriers to IPT scale-up concluded that none should prove unsurmountable.[12] Yet, despite the large consensus on the importance of TB prevention in PLHIV, worldwide implementation appears heterogeneous and mainly restricted to countries with better resources.[13]

After the Union World Lung Health Conference in Mexico in 2018, a group of TB-HIV consultants at the International Union Against Tuberculosis and Lung Disease (The Union) discussed key interventions that can be implemented by national programmes to prevent TB among PLHIV in low income countries (LIC), based on their field experience. This paper offers a review of the most important therapeutic interventions: namely, ART (now recommended for all PLHIV regardless of their CD4 cell count or WHO clinical stage of disease[14]) and IPT (with updated WHO guidelines recently published[15]), focusing on the programmatic challenges and opportunities around their implementation and putting them in the context of other preventive interventions.

The role of ART in TB prevention

Does ART reduce the individual risk of TB in people living with HIV?

ART is associated with rapid recovery of mycobacteria-specific immune responses resulting in increased capacity to limit mycobacterial growth.[16] At the clinical level, this translates into a potent TB preventive effect and a reduction in individual risk of TB (**Table 1**).

A systematic review and meta-analysis from 2002 to 2011 showed that ART was associated with a 65% reduction in TB incidence across all baseline CD4 counts in PLHIV.[17] Subsequent studies confirmed the preventive benefit of early ART initiated at higher CD4 cell counts, and also showed that delays in ART initiation can result in long-term immune dysfunction and persistent increased risk for TB.[18,19] Two randomised controlled trials (RCTs) published in 2015 (INSIGHT START and TEMPRANO) further strengthened the evidence.[20,21] The INSIGHT START trial showed that early ART initiation in asymptomatic HIV-positive patients with CD4 counts > 500 cells/μL was associated with an almost 60% reduction in risk of death, serious AIDS-related events or serious non-AIDS-related events, including disseminated TB, compared with deferred initiation until the CD4 count had decreased to 350 cells/μL.[20] The 2-by-2 factorial design TEMPRANO trial, conducted in Cote d'Ivoire, enrolled PLHIV with CD4 cell counts < 800 cells/μL and not meeting criteria for starting ART according to the WHO guidelines available at the time.[21] Patients were randomised to one of four groups: deferred ART (starting ART according to the most recent WHO guideline criteria); deferred ART plus six-months isoniazid preventive therapy (IPT); early ART – (starting ART immediately); and early ART plus six-months IPT. Early ART was associated with a 44% lower risk of death or severe HIV-related illness, including TB, compared with deferred ART, with IPT adding significantly to the individual benefit.[21]

Can ART reduce TB incidence at the programmatic level?

At the programme level, despite PLHIV routinely initiating ART at low CD4 counts especially in sub-Saharan Africa,[22] decreases in TB notification rates have been observed in countries such as Malawi, Swaziland, Zimbabwe and Kenya where

ART coverage in the HIV-infected populations has reached a high level.[23 – 27] Significant declines in TB cases in Malawi and Swaziland were observed in patients with smear-negative pulmonary TB and in patients with recurrent TB, both of which are strongly associated with HIV. In Kenya and Malawi, declines in case notifications were also seen in HIV-negative TB, which might be due to overall decreases in HIV-associated TB leading to reduced transmission of *MTB* in the community.[23,27] It is plausible that part of the decrease in TB incidence observed since 2008 in countries mostly affected by the HIV epidemic could be attributable to the increase in ART coverage, as evidenced by the parallel decrease in HIV prevalence in notified TB cases in these countries.[6]

This positive news from the programmatic front is supported by mathematical models predicting the enormous impact that immediate start of ART might have on TB prevention at the population level.[28] The application of the 2016 WHO Consolidated Guidelines on the use of ART recommending that ART be offered to all PLHIV regardless of clinical stage or CD4 cell count[14] opens the way for immediate initiation of therapy for all those infected. It is crucial then to diagnose HIV early and there are various initiatives now being implemented that facilitate this, including community-based HIV testing, self-testing and partner notification services. Randomised trials also point to better retention in care and decreased mortality in those initiating ART on the same day that HIV infection is diagnosed.[29] These innovative approaches are likely to provide large public health benefits by reducing the incidence of TB and other HIV-related diseases as well as reducing HIV transmission from infected to non-infected individuals.[20, 21,30] Comprehensive and timely linkage of newly diagnosed PLHIV to HIV care and treatment is an essential pre-requisite, however, if these benefits are to be realised.[31]

196

197 **Can ART alone optimally prevent TB?**

198 While these data on ART in preventing TB are encouraging, ART alone does not
199 do the job adequately. Long-term recovery of TB-specific immune function is
200 incomplete on ART.[16] In the clinic, the TB preventive effects of ART increase with
201 length of time on therapy and with ART-induced immune recovery, but the risk of TB
202 never decreases to levels seen in patients without HIV infection in the same
203 community.[32] Optimization of TB prevention therefore requires additional
204 interventions.

205

206 **The role of treatment for TB infection**

207 Until recently, IPT has been the most widely used treatment for the prevention of
208 TB. It is an intervention which is immediately appealing for controlling an infectious
209 disease such as TB. It is capable of eliminating *MTB* from the body by treating latent
210 TB infection (LTBI) and may additionally prevent new infections during the course of
211 treatment.

212

213 **1. Did IPT reduce the individual risk of TB in the pre-ART era?**

214 There have been three systematic reviews of the benefit of IPT in preventing TB
215 in PLHIV, largely of studies from the pre-ART era.[33-35] The last review, published in
216 2010 (**Table 2**), suggested that IPT at a daily dose of 300 mg for 6 months reduced
217 the overall risk of TB by 33%, with the protective effect increased to 64% when
218 targeted at individuals with a positive tuberculin skin test (TST).[35] Because of no
219 demonstrable reduction in TB incidence or mortality when IPT was given to PLHIV

whose TST was negative, TST before IPT was considered an essential component of this policy.

However, the challenge of obtaining and storing tuberculin, then performing, reading and interpreting the skin tests which may be falsely negative in anergic PLHIV and finally implementing this screening in the context of busy HIV clinics was one of the important limiting factors responsible for poor implementation of IPT as recommended by the WHO and the joint United Nations Programme on HIV and AIDS (UNAIDS) in 1998.[36]

2. What is the expected benefit of IPT in the ART era?

In the current situation where ART is recommended for all PLHIV regardless of the level of immunity,[14] the important question is whether or not IPT provides additional benefit to ART. Several recent studies highlighted in **Table 2** confirm an affirmative response, further strengthened by observational data from Botswana,[37, 38] Brazil,[39] South Africa,[40] and Ethiopia [41] showing lower incidence rates of TB in those on ART plus IPT compared with those on ART alone (**Table 3)**.

Two major RCTs provide strong evidence for the additional benefit of IPT. The first, conducted in South Africa, showed that IPT given for 12 months to PLHIV on ART significantly reduced the risk of active TB by 37%, with the greatest benefit being observed in the first year.[42] The effect of IPT was not significantly different according to whether patients had a positive or a negative TST or interferon-gamma release assay (IGRA). The second (TEMPRANO study) showed that 6 months of IPT given in addition to ART resulted in a 35% reduction in HIV-related death or severe illness, of which 42% was due to TB, at whatever CD4 cell count ART was initiated.[21]

Long-term follow-up of patients enrolled in TEMPRANO showed that 6 months of IPT resulted in a 37% reduction in death that was independent of ART over an average of 4.9 years of follow-up.[43] This evidence from Cote d'Ivoire on reduced mortality with IPT was also confirmed in two previous studies –an observational design in South Africa and a stepped wedge, cluster-randomised design in Brazil.[44,45]

In summary, ART plus IPT is more effective than ART alone in reducing mortality as the addition of IPT to ART further reduces the risk of TB in high TB endemic settings. Therefore, WHO now recommends that IPT should be given in combination with ART at the time HIV is diagnosed.[14]

3. Which PLHIV benefit more from IPT in the ART era?

The South African and TEMPRANO long-term follow-up studies showed that the benefits of IPT in reducing TB risk and mortality also occurred in patients with negative TST or IGRA results, but to a lesser extent.[42,43] Because of this demonstrated benefit and given the difficulties and obstacles that TST poses for IPT scale-up, WHO revised guidelines in 2011 and again in 2018 recommending that IPT should be given to PLHIV with an unknown or positive TST who are unlikely to have active TB in resource-constrained settings.[15]

However, giving IPT to all PLHIV without prior TST or IGRA will result in an impact at the population level that will differ according to the level of TB transmission in the country. The impact is likely to be greater in high TB transmission settings, but lower in settings with moderate to low risk of TB infection because the number of PLHIV with prior TB infection will be fewer. WHO recommends that PLHIV be screened for LTBI, if resources permit, since those with a positive TST

benefit more from preventive therapy,[15] and this is the standard approach in most high-income countries.[46]

4. What is the role of IPT in children?

The evidence of benefit of preventive therapy for all children living with HIV is not as clear as with adults. While an early study in a high TB endemic setting in the pre-ART era found that IPT improved early survival and reduced TB incidence in children,[47] recent systematic reviews found no benefit of IPT in reducing TB incidence and no additional benefit when isoniazid was given to children on ART.[48,49]. As the prevalence of TB infection among children in close contact with a TB case is high and as children living with HIV are at high risk of developing TB disease following infection, IPT is always recommended for children living with HIV of any age who are TB contacts provided they do not have active TB.[15,50] By contrast, young children who are not TB contacts have a low probability of being infected by *MTB* – for example, this is less than 5% in children under 5 years of age where the annual risk of TB infection is <1%, a situation observed in several LIC.[51]

While WHO recommends that all adults and adolescents living with HIV receive preventive therapy, in children living with HIV who are considered unlikely to have TB disease, there is a strong recommendation for 6 months of IPT for those aged ≥12 months only if living in settings with a high TB prevalence and for infants (<12 months) only if they are in contact with a case of TB.[15]

5. For how long should IPT be given?

The WHO recommends that the duration of IPT be at least 6 months with 36 months (as a surrogate for life-long treatment) conditionally recommended in areas with high TB incidence and transmission.[15] The question of how long to give IPT is context-specific. The TEMPRANO study in Cote d'Ivoire, West Africa, where TB incidence rates are estimated at about 160 per 100,000 people,[6] suggested that 6-months IPT + ART has a durable effect on mortality for almost five years, presumably by combining the two complementary mechanisms of IPT (curing LTBI and preventing new infections during the course of the treatment) and ART (leading to immune recovery that decreases the risk of both new TB infection and reactivation).[21, 43]

In high TB exposure environments, such as Botswana and South Africa where incidence rates are estimated to be about 350 and 830 per 100,000 respectively,[6] six months of IPT may be insufficient. In Botswana, 36 months of IPT given to PLHIV, who were mostly on ART, reduced TB incidence by 43% compared with 6 months of IPT.[37] However, after cessation of IPT, TB incidence rebounded even in the presence of ART.[38] This suggests that in settings with a high TB burden and transmission, continuous IPT probably acts not only to cure LTBI but also to prevent new infections.[52] In high transmission settings, continuous IPT may therefore be necessary. A systematic review and meta-analysis suggests that in high TB and HIV prevalence settings, continuous IPT in PLHIV for at least 36 months is beneficial and probably outweighs the risk of increased adverse effects as compared with IPT for 6 months.[53] Based on the available evidence, this recommendation is now endorsed by the WHO in the 2018 guidelines.[15] Thus, the choice of regimen duration should be based on the epidemiological situation, with long duration of IPT to be considered for countries with high TB transmission, such as in Southern and Eastern Africa, while

the 6-month regimen could be considered for other low and medium prevalence countries.

6. What are the conditions to consider for the programmatic implementation of IPT in the context of ART?

As with any public health strategy, programmatic implementation of IPT needs to meet acceptable conditions to guarantee effectiveness while limiting potential risks and simultaneously considering resource constraints. First, the level of TB transmission in the country should be assessed to determine the required duration of IPT, the expected benefit to PLHIV if given without prior testing for TB infection, and the respective benefits if given to adults and to children. Second, the expected impact at a population level may be estimated by considering the prevalence of HIV infection together with the level of TB transmission in the community. Third, activities that are necessary to adequately apply the strategy must be considered and resources required to conduct them should be evaluated. All these steps involve both national HIV-AIDS and TB programmes: HIV programmes will be the implementers, as management of PLHIV is mainly conducted in HIV clinics, and TB programmes will play a crucial role in supporting the activity. Guidance for this evaluation is proposed and presented in **Table 4.**

7. How should programmes organize the initiation of IPT?

A crucial principle is that IPT must not be given to PLHIV who may have active TB, and IPT must be discontinued in any PLHIV who develops symptoms and signs of active TB. If active TB is unrecognized, there is not only a risk of delayed diagnosis and death for the patient, but also a risk of promoting isoniazid-resistant

disease which may be more difficult to treat, is associated with worse treatment outcomes,[54] and may be transmitted to others. A systematic review in the pre-ART era assessing the effect of IPT on the risk for isoniazid-resistant TB reported a summary relative risk of 1.45 (95% confidence interval 0.85 – 2.47).[55] While this result did not reach statistical significance, an increased risk for isoniazid-resistant TB after use of IPT could not be excluded. In a more recent study, the prevalence of isoniazid-resistance in patients diagnosed with TB during or after IPT was 16%.[56] In Botswana, after IPT implementation at the national level the overall prevalence of isoniazid-resistance increased from 1.7% in 1995 to 7.6% in 2007-2008.[57] Based on these observations, it is critical that i) active TB is excluded before starting IPT and ii) TB is diagnosed during IPT.

Symptomatic PLHIV who initiate ART may present with a constellation of weight loss, fever, night sweats and respiratory symptoms, due either to HIV-related disease or HIV-associated TB. Making the correct diagnosis is both difficult and prone to error.[58] Simple and clear diagnostic procedures accompanied by adequate training and supervision are needed, particularly since staff at HIV clinics are usually not fully trained to diagnose TB. The use of Xpert® MTB/RIF should be encouraged because of its increased sensitivity compared with sputum smear microscopy.[59] This is especially the case for immunosuppressed patients who present with non-specific symptoms of disseminated disease in whom the sputum smears can be negative and chest radiography normal. However, it is essential that there is stable and regular electricity, adequate maintenance, uninterrupted supplies of cartridges and close monitoring of the screening activities by the TB programme in order to ensure the effectiveness and added value of this tool.[60]

The costs and organizational problems associated with chest x-ray led to the abandonment of this diagnostic modality in providing IPT in Botswana,[61] and the systematic use of chest x-ray is currently not considered mandatory in resource-limited settings with high HIV prevalence.[15] However, if resources permit it is worth considering. Indeed, WHO states that the combination of absence of any chest x-ray abnormality and absence of symptoms suggestive of TB offers the highest sensitivity and negative predictive value for ruling out TB.[62]

Given these screening and diagnostic challenges, a prudent course of action is to initiate ART and wait for the patient to stabilise and gain weight before starting IPT so that patients with undiagnosed prevalent TB are not mistakenly placed on isoniazid monotherapy. In the TEMPRANO study during a one-month waiting period before initiating IPT, 1.6% of participants were diagnosed with active TB,[63] and in another operational study amongst PLHIV starting ART in Malawi, TB was diagnosed between 20-50 days after enrolment in about 10% of those with TB.[64] An intermediate waiting period of up to 3 months after ART initiation, during which PLHIV are under close surveillance would thus be sensible in the routine setting.

While in theory, asymptomatic PLHIV could be safely started on IPT much earlier, a fixed waiting period would enable standardization across programmes and would allow for the early "unmasking" of TB from immune reconstitution inflammatory disease during the first few months of ART.[65,66] Starting PLHIV on IPT who are stable and asymptomatic allows for easier monitoring during ART follow-up. Any individual who develops new symptoms or signs or starts to lose weight must be suspected as having TB. IPT must be stopped and the patient investigated for TB and other HIV-related disease.

8. How should Programmes ensure safety and adherence?

The most serious adverse event is isoniazid-induced hepatitis, which if unrecognised and unattended can lead to acute liver failure and death. The estimated rate of symptomatic isoniazid-related hepatitis can range from one to three per 1,000 persons, with established risk factors being increasing age, pre-existing liver disease, chronic hepatitis C infection, concomitant use of other hepatotoxic medications such as ART non-nucleoside reverse transcriptase inhibitors and regular alcohol consumption.[67] In the Botswana studies, isoniazid-induced hepatitis was the main adverse effect, occurring in about 1% of patients and usually during the first nine months of treatment.[37,38]

Given the absence of laboratory monitoring in most decentralised ART programmes, the approach should be to exclude anyone at higher risk of hepatitis (older people and those with a known history of liver disease or alcohol abuse). Patients and health care workers must all be educated about the importance of stopping IPT in the event of nausea, vomiting, confusion or jaundice with immediate reporting to a health facility for assessment. Isoniazid may also cause peripheral neuropathy although the addition of vitamin B 6 (pyridoxine) may provide some protection.[15]

An important prerequisite, frequently overlooked, is that a safe, secure and robust supply of isoniazid is ensured: drug shortages were the commonest reason for discontinuing IPT in an Ethiopian community-based study.[68] Adherence to medication is then critical for ensuring effectiveness of IPT, and it is well recognized that adherence to preventive treatment is more difficult to achieve than adherence to curative therapy. Many studies on IPT among PLHIV have reported low rates of treatment completion (e.g., 53% in Uganda in the pre-ART era and 64% in Ethiopia

more recently),[69,70] and completion rates under programmatic rather than study conditions are likely to be even lower. PLHIV already receive a high number of pills. Thus, it is crucial to deliver proper information about the action of the drug, potential side effects and the benefits of taking the full course of treatment. Programmes implementing IPT should therefore ensure that health care workers are adequately trained on how to educate patients, to follow-up the treatment, and to monitor and manage any adverse events as well as completion or discontinuation of therapy. This will require strong collaboration between HIV and TB programmes.

9. Should other treatment regimens to prevent TB be considered?

WHO has recently recommended alternative options to IPT for TB preventive therapy in high TB incidence countries that include i) rifampicin and isoniazid daily for 3 months (3HR) in children and adolescents aged<15 years and ii) rifapentine and isoniazid weekly for 3 months (3HP) for both adults and children.[15]

The 3HR regimen has demonstrated at least equivalent effectiveness, better adherence and fewer side effects than IPT (or 6H) among children, and its application is facilitated by the availability of dispersible paediatric fixed-dose formulations offering the right drug dosage.[71] Much attention has been paid to weekly 3HP, which appears to be effective in low- and high-incidence TB settings and is associated with less hepatotoxicity and higher treatment completion rates than daily IPT given for at least 6 months.[72-77] In addition, a recently completed trial showed non-inferiority of one month of daily isoniazid and rifapentine (1HP) compared with 9 months of IPT.[78]

The problem with using rifamycin-containing regimens such as RH or HP in PLHIV is the potential for drug-drug interactions with ART. Based on recent evidence, rifamycins can be used effectively with efavirenz at 600 mg daily, but may

be problematic for PLHIV on ART regimens that include efavirenz 400 mg daily, protease inhibitors or dolutegravir (an integrase inhibitor) for first-line therapy.[79] Nonetheless, these shorter regimens of one to three months make these potentially useful TB preventive therapy options for PLHIV in resource-limited settings in the future, provided the costs of rifapentine can be reduced. Shorter regimens could also encourage countries to pursue the necessary TB preventive approaches. Despite their inherent advantages for patients, physicians and programs, however, shorter regimens will not completely offset the challenges for programmatic implementation, and a coordinated network and strengthening of programmes will still be needed. In the near foreseeable future, both IPT and shorter regimens will probably co-exist in national policies of preventive therapy.

Other measures for preventing TB in PLHIV

Other interventions are capable of contributing significantly to TB prevention in PLHIV. Early detection and treatment of active TB among contacts of PLHIV is important.[80] PLHIV should thus be informed about the necessity to report on signs/symptoms of TB in their close contacts, and HIV clinic staff should be trained to regularly monitor and link such persons to TB diagnosis, treatment and contact investigation.

Infection control is likely to play an important role, particularly in high HIV prevalence areas where PLHIV comprise a large proportion of hospital admissions and out-patient consultations and where the presence of patients with unrecognized TB can result in intense TB transmission.[81-83] Given the global rise in drug-resistant TB and the greater mortality observed in those co-infected with HIV,[84,85] preventive interventions assume even greater importance. They should be given high priority in

health facilities, as well as in other high TB transmission settings such as homes of index patients, prisons or refugee camps.[86]

The TB and HIV-associated TB epidemic, however, will only be ended if the other important social and behavioural determinants of the disease, such as poverty, overcrowding, undernutrition, migration, tobacco and alcohol abuse,[87] are addressed in parallel with these clinical and programmatic interventions.

Conclusion

TB can be significantly reduced in PLHIV by ensuring that all persons at risk know their HIV status and those diagnosed with HIV infection are immediately initiated and sustained on effective ART. Because the effectiveness of IPT combined with early ART to prevent TB and reduce mortality is now well demonstrated,[88] LIC must give serious thought to implementation and scale up.

Strong collaboration between HIV and TB programmes will be necessary. Elements to consider for IPT implementation include i) the choice of treatment duration, ii) a clear and applicable procedure to exclude active TB before starting IPT using the best diagnostic tools that are available and including a three month waiting period before IPT initiation, iii) a robust drug supply so that there are no drug interruptions, iv) adequate patient support and well-organized patient follow-up to ensure safety and adherence, and v) proper monitoring of this activity. Shorter regimens are promising and may replace IPT in the future, although these will require the same organizational elements for effective implementation. Other practical interventions such as TB detection among close contacts and infection control should also be seriously addressed.

TB prevention in PLHIV has been a neglected part of TB control, and while it has huge potential benefit the challenges of implementation must be addressed. Yet, since countries with the highest prevalence of both HIV and TB infection are also those with the most under-funded programmes, additional resources will be needed.

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Table 1: Key ART intervention studies with direct implications for preventing TB

First Author / Study Name / Year of Publication	Type of study and country	Key findings
Suthar AB (2012) [17]	Systematic review and meta-analysis Multiple countries	ART was associated with a 65% reduction in TB incidence across all baseline CD4 counts in PLHIV.
Grinsztejn B HPTN 052 (2014) [18]	RCT Multiple countries	Early ART (started at median CD4 count of 442 cells per uL) was associated with a 51% reduction of TB compared with deferred ART (started at median CD4 count of 230 cells per uL).
Collins SE CIPRA HT-001 (2015) [19]	RCT Haiti	Deferred ART (started at CD4 count < 200 cells /uL) was associated with higher TB risk (hazard ratio 2.41) compared with early ART (started between 200-350 cells per uL) during five years of follow-up.
The INSIGHT START Study Group (2015) [20]	RCT Multiple countries	Early ART start in asymptomatic HIV-positive patients with a CD4 count > 500 cells/μL was associated with a 57% reduction in any serious AIDS-related event (including TB), serious non-AIDS-related event or death from any cause compared with deferred ART (CD4 count < 350 cells per uL or the development of AIDS)
TEMPRANO ANRS 12136 Study Group (2015) [21]	RCT Cote d'Ivoire	Early ART (CD4 count <800 cells per uL and no WHO criteria for starting ART) was associated with a 44% lower risk of death or severe HIV-related illness, including TB, compared with deferred ART (ART started according to WHO criteria), with IPT adding significantly to the individual benefit

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; IPT: isoniazid preventive therapy; RCT: randomized controlled trial; PLHIV: people living with HIV; WHO: World Health Organization

782 **Table 2:** Key studies showing impact of IPT interventions in the pre-ART and ART era

First Author / Study Name / Year of Publication	Type of study and country	Key findings
IPT in the pre ART era		
Akolo C et al. / Cochrane Database Systematic Review (2010) [35]	Systematic review and meta-analysis Multiple countries	IPT given at a daily dose of 300 mg for 6 months reduced the overall risk of TB by 32%. Protective effect increased to 62% when targeted at those with a positive tuberculin skin test (TST), and was only 11% and not significant among those with a negative TST
IPT in the ART era (using both IPT and ART interventions)		
Golub JE / THRio (2007) [39]	Prospective cohort Brazil	Concurrent use of ART and IPT (for 6 months) showed 76% reduction in TB risk compared with no treatment
Golub JE (2009) [40]	Prospective cohort South Africa	Concurrent use of ART and IPT (for 6 months) showed 89% reduction in TB risk compared with no treatment
Samandari T (2011) [37]	RCT Botswana	Concurrent use of ART and IPT (for 6 months or 36 months) resulted in additive effects in reducing the risk of active TB
Yirdaw K. (2014) [41]	Retrospective cohort Ethiopia	Concurrent use of ART and IPT (for 6 month either simultaneously or with IPT after ART) showed 65% and 78% reduction in TB risk compared with no treatment
Rangaka MX (2014) [42]	RCT South Africa	Concurrent use of ART and IPT (for 12 months) showed 37% reduction in risk of TB, irrespective of TST or IGRA
Charalambous S (2010) [44]	Prospective cohort South Africa	Concurrent use of ART and IPT (for 6 months) showed 49% reduction in risk of death after adjusting for key characteristics
Durovni B / THRio (2013) [45]	Stepped wedge, cluster-randomized trial Brazil	IPT for 6 months showed 31% reduction in risk of TB or death after adjusting for key characteristics and use of ART
The TEMPRANO ANRS 12136 Study Group (2015) [21]	RCT Cote d'Ivoire	6-month IPT given in addition to ART resulted in a 35% reduction in HIV-related death or severe illness, of which 42% was due to TB, at whatever CD4 cell count the ART was started. Reduction in TB incidence in IPT-treated vs non IPT-treated patients was only significant among those with a positive IGRA test.
Badje A / TEMPRANO ANRS 12136 (2017) [43]	RCT long-term follow up Cote d'Ivoire	Concurrent use of ART and IPT (for 6 months) showed 37% reduction in risk of death after adjusting for early or deferred ART and other key characteristics

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784 *ART: antiretroviral therapy; IGRA: interferon gamma release assay; IPT: isoniazid preventive*
785 *therapy; RCT: randomized controlled trial; TST: tuberculin skin test*

Table 3: TB incidence rates per 100 person years for people living with HIV on ART alone or on ART plus isoniazid preventive therapy (IPT)

First Author / Study Name / Year of Publication	Type of Study and Country	Key Findings: TB incidence rate per 100 person-years (95% CI)	
		ART alone	ART plus IPT
Golub JE / THRio (2007) [39]	Prospective cohort Brazil	1.9 (1.7-2.2)	0.8 (0.4-1.5)
Golub JE (2009) [40]	Prospective cohort South Africa	4.6 (3.4-6.2)	1.1 (0.02-7.6)
Yirdaw K. (2014) [41]	Retrospective cohort Ethiopia	0.74 [a]	0.36 [a]
Rangaka MX (2014) [42]	RCT South Africa	3.6 (2.8 – 4.7)	2.3 (1.6-3.1)

[a] *95% Confidence intervals not provided*

TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral therapy; IPT = isoniazid preventive therapy; 95% CI = 95% confidence intervals

820 **Table 4:** Issues to be considered by countries prior to the introduction of isoniazid preventive
821 therapy alongside antiretroviral therapy as a national intervention policy

	Question	Answer	Considerations, prerequisites and challenges
1	What benefit for PLHIV will be expected?	The benefit for PLHIV is expected to be highest in countries with the highest levels of TB transmission.	Estimates of TB incidence rates can be used to evaluate TB transmission levels. Level is considered to be high if TB incidence rate is greater than 150 and very high if greater than 300 per 100 000.[6] In settings with high TB transmission, applying IPT to treat LTBI in PLHIV without prior screening is warranted.[15] Screening with TST or IGRA* should be considered in lower TB transmission settings, but will necessitate considerable resources and organization. Provision of IPT to PLHIV who are contacts of patients with active TB and are not considered to have active TB is recommended without prior screening for LTBI whatever the level of TB transmission, particularly for HIV-infected child contacts of any age. [15,80] Duration of IPT should be 36 months or lifelong in settings with very high TB transmission.
2	What impact will be expected at the community level?	The impact of a nationwide implementation of this preventive intervention is expected to be the highest in countries with highest TB burden associated with HIV. High impact may be expected only if intervention is of high quality	The burden of HIV-associated TB in the general population will depend on both TB incidence and HIV prevalence. It can be evaluated with the estimated HIV-positive TB incidence rate per 100,000.** It may be considered high if >30 and very high if >100 per 100,000. Because estimates of HIV-positive TB incidence rates are provided with a considerable uncertainty, the burden of HIV-associated TB can also be evaluated through the combination of the two following indicators: • TB notification rate per 100,000 (high if > 80 per 100 000); • HIV prevalence among TB patients (high if > 20%).
2	Are countries prepared?	Very few countries are currently implementing IPT to scale under field conditions. Countries with a high burden of HIV-associated TB are often low- and middle-income countries, not always prepared for IPT implementation. Engaging in implementation of nationwide IPT requires a good level of preparation to maximize the effectiveness and minimize the risks. Stepwise introduction may be considered. Additional resources will be needed. By no means should IPT implementation divert resources and staff from the priority activity of detection and treatment of TB patients.	High quality implementation requires: 1. *Political commitment :* national policy, effective collaboration between HIV and TB programs, social mobilization 2. *Capacity to screen for and rule out active TB disease* • Symptoms: clinical algorithm • Chest x-ray wherever possible • Sputum smear microscopy • Xpert MTB/RIF wherever possible • Waiting period (3 months on ART) before IPT initiation *** 3. *Robust and uninterrupted supply of isoniazid* 4. *Human resources* • In sufficient number (the capacity to carry out other clinical or public health tasks should not be decreased) • Trained to provide **patient-centered care** and follow-up • Adequately supervised 5. *Monitoring and evaluation of the intervention* • Simple standardized tools (registers and information system) • Real time data analysis activities • Consider technical assistance

ART: antiretroviral therapy; IGRA: interferon gamma release assay; IPT: isoniazid preventive therapy; LTBI: latent tuberculosis infection; TST: tuberculin skin test

** Supply and storage of tuberculin along with performance and interpretation of TST in PLHIV are challenging, especially in the context of busy HIV clinics. The high price of IGRA and the need for laboratory performance limit the capacity for it to be decentralized*

*** Estimates of TB incidence rate per 100,000 PLHIV are provided annually in the WHO Global TB report.*

****A waiting period of 3 months after ART initiation will allow the unmasking of TB from immune reconstitution inflammatory disease during the first few months of ART. Close clinical surveillance of the PLHIV should be conducted during this period in order to conduct all necessary examinations to eliminate active TB and to ensure that they are stable and asymptomatic for the initiation of IPT.*

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Harries, AD; Schwoebel, V; Monedero-Recuero, I; Aung, TK; Chadha, S; Chiang, C-Y; Conradie, F; Dongo, J-P; Heldal, E; Jensen, P; Nyengele, JPK; Koura, KG; Kumar, AMV; Lin, Y; Mlilo, N; Nakanwagi-Mukwaya, A; Ncube, RT; Nyinoburyo, R; Oo, NL; Patel, LN; Piubello, A; Rusen, ID; Sanda, T; Satyanarayana, S; Syed, I; Thu, AS; Tonsing, J; Trebucq, A; Zamora, V; Zishiri, C; Hinderaker, SG; Ait-Khaled, N; Roggi, A; Luna, JC; Graham, SM; Dlodlo, RA; Fujiwara, PI

Title:
Challenges and opportunities to prevent tuberculosis in people living with HIV in low-income countries

Date:
2019-02-01

Citation:
Harries, A. D., Schwoebel, V., Monedero-Recuero, I., Aung, T. K., Chadha, S., Chiang, C. -Y., Conradie, F., Dongo, J. -P., Heldal, E., Jensen, P., Nyengele, J. P. K., Koura, K. G., Kumar, A. M. V., Lin, Y., Mlilo, N., Nakanwagi-Mukwaya, A., Ncube, R. T., Nyinoburyo, R., Oo, N. L. ,... Fujiwara, P. I. (2019). Challenges and opportunities to prevent tuberculosis in people living with HIV in low-income countries. INTERNATIONAL JOURNAL OF TUBERCULOSIS AND LUNG DISEASE, 23 (2), pp.241-+. https://doi.org/10.5588/ijtld.18.0207.