INT J TUBERC LUNG DIS 23(2):241–251

http://dx.doi.org/10.5588/ijtld.18.0207

STATE OF THE ART

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

A. D. Harries,*† V. Schwoebel,* I. Monedero-Recuero,* T. K. Aung,*‡ S. Chadha,*§ C-Y. Chiang,*¶ F. Conradie,#** J-P. Dongo,*†† E. Heldal,* P. Jensen,* J. P. K. Nyengele,*‡‡ K. G. Koura,*§§ A. M. V. Kumar,*§ Y. Lin,*¶¶ N. Mlilo,*## A. Nakanwagi-Mukwaya,*†† R. T. Ncube,*## R. Nyinoburyo,*†† N. L. Oo,*‡ L. N. Patel,** A. Piubello,*,*** I. D. Rusen,*,** T. Sanda,*‡‡ S. Satyanarayana,*§ I. Syed,* A. S. Thu,*‡ J. Tonsing,*§ A. Trébucq,* V. Zamora,*††† C. Zishiri,*## S. G. Hinderaker,*‡‡‡ N. Aït-Khaled,* A. Roggi,* J. Caminero Luna,*§§§ S. M. Graham,*¶¶¶ R. A. Dlodlo,*## P. I. Fujiwara*

*International Union Against Tuberculosis and Lung Disease (The Union), Paris, France; †London School of Hygiene & Tropical Medicine, London, UK; ‡The Union, Myanmar Office, Mandalay, Myanmar; §The Union, South-East Asia Office, New Delhi, India; ¶Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; #Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; **Vital Strategies, New York, New York, USA; ††The Union, Uganda Office, Kampala, Uganda; ‡‡The Union, DRC Office, Kinshasa, Democratic Republic of Congo; §§Mère et enfant face aux infections tropicales Institut de recherche pour le développement, Université Paris 5, Sorbonne Paris Cité, Paris, France; ¶¶The Union, China Office, Beijing, China; ##The Union, Zimbabwe Office, Harare, Zimbabwe; ***Damien Foundation, Brussels, Belgium; †††The Union, Peru Office, Lima, Peru; ‡‡‡University of Bergen, Bergen, Norway; §§§Pneumology Department, Dr Negrin General Hospital of Gran Canaria, Las Palmas, Spain; ¶¶¶Centre for International Child Health, University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Victoria, Australia

SUMMARY

People living with the human immunodeficiency virus (HIV) (PLHIV) are at high risk for tuberculosis (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 World Health Organization recommendations that all PLHIV initiate ART regardless of clinical stage or CD4 cell count could provide a considerable TB preventive benefit at the population level in high HIV prevalence settings. Preventive therapy can treat tuberculous infection and prevent new infections during the course of treatment. It is now established that isoniazid preventive therapy (IPT) combined with ART among PLHIV significantly reduces the risk of TB and mortality compared with ART alone, and therefore has huge potential benefits for millions of sufferers. 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, appropriate screening procedures for excluding active TB, reliable drug supplies, patient-centred support to ensure adherence and well-organised follow-up and monitoring that includes drug safety are needed for successful implementation of IPT, and these features 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 the detection and treatment of active TB, particularly among contacts of PLHIV, and control measures for tuberculous infection in health facilities, the homes of index patients and congregate settings.

KEY WORDS: human immunodeficiency virus/acquired immune-deficiency syndrome; TB; antiretroviral therapy; isoniazid preventive treatment; infection control

SINCE THE EMERGENCE of the human immunodeficiency virus (HIV)/acquired immune-deficiency syndrome (AIDS) epidemic in the 1980s, infection with the 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*.[1] The resulting immunosuppression increases the risk of reactivation of tuberculous infection,[2] as well as the risk of rapid progression of a recently acquired tuberculous infection.[3] Without treatment, people living with HIV (PLHIV) and with *M. tuberculosis* infection have an annual risk of developing TB of approximately 10% per year compared with an estimated 10%

Correspondence to: Professor A D Harries, Old Inn Cottage, Vears Lane, Colden Common, Winchester SO21 1TQ, UK. e-mail: adharries@theunion.org
Article submitted 12 March 2018. Final version accepted 21 August 2018.

Table 1 Key ART intervention studies with direct implications for TB prevention

First author, study name, year of publication	Type of study and country	Key findings
Suthar, 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, HPTN 052, 2014[18]	RCT; multiple countries	Early ART (started at median CD4 count of 442 cells/μl) was associated with a 51% reduction of TB compared with deferred ART (started at median CD4 count of 230 cells/μl)
Collins, CIPRA HT-001, 2015[19]	RCT; Haiti	Deferred ART (started at CD4 count <200 cells/μl) was associated with higher TB risk (hazard ratio 2.41) compared with early ART (started between 200 and 350 cells/μl) during 5 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/μl or the development of AIDS)
TEMPRANO ANRS 12136 Study Group, 2015[21]	RCT; Cote d'Ivoire	Early ART (CD4 count <800 cells/μl 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

ART = antiretroviral therapy; TB = tuberculosis; PLHIV = people living with HIV; HPTN = HIV Prevention Trials Network; CIPRA HT-001 = Comprehensive International Program for Research on AIDS Haiti-001; RCT = randomised controlled trial; HIV = human immunodeficiency virus; INSIGHT = Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection; AIDS = acquired immunodeficiency syndrome; WHO = World Health Organization; IPT = isoniazid preventive therapy; ANRS = Agence Nationale de Researches sur les SIDA et les Hepatites Virales.

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 *M. tuberculosis* transmission in the community.

A third of PLHIV with TB die annually.[6] The reasons include 1) failure to suspect or diagnose TB,[7] 2) delays and challenges in diagnosing TB due to immunodeficiency-related presentations with smear-negative pulmonary disease or extra-pulmonary/disseminated disease,[8,9] 3) non-provision or delayed treatment with antiretroviral therapy (ART) and cotrimoxazole preventive therapy in co-infected TB patients, and 4) 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 have developed 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 et al. discussed the important challenges and concerns regarding isoniazid (INH) preventive therapy (IPT).[11] A recent review of barriers to IPT scale-up concluded that none should prove unsurmountable.[12] However, despite the strong 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 (LICs) based on their field experience.

Here, we review the most important therapeutic interventions—ART (now recommended for all PLHIV regardless of 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.

ROLE OF ANTIRETROVIRAL THERAPY IN TUBERCULOSIS PREVENTION

Does antiretroviral therapy reduce the individual risk of tuberculosis in people living with the human immunodeficiency virus?

ART is associated with rapid recovery of mycobacteria-specific immune responses, and results 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 (Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection [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 was conducted in Cote d'Ivoire and 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 6-month IPT; early ART (starting ART immediately); and early ART plus 6-month 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 antiretroviral therapy reduce tuberculosis incidence at the programmatic level?

At the programmatic level, despite PLHIV routinely initiating ART at low CD4 counts, particularly 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 *M. tuberculosis* 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] 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 to immediate initiation of treatment 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 reduced 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]

Can antiretroviral therapy alone optimally prevent tuberculosis?

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

Role of treatment for tuberculous infection

Until recently, IPT has been the most widely used treatment for the prevention of TB. It is an intervention which is immediately appealing for controlling an infectious disease such as TB. It can eliminate *M. tuberculosis* from the body by treating latent tuberculous infection (LTBI) and may additionally prevent new infections during the course of treatment.

Did isoniazid preventive therapy reduce the individual risk of tuberculosis in the pre-antiretroviral therapy era?

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

Table 2 Key studies showing impact of IPT interventions in pre-ART and ART eras

First author, study name, year of publication	Type of study and country	Key findings
IPT in the pre ART era		
Akolo, 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 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, THRio, 2007[37]	Prospective cohort; Brazil	Concurrent use of ART and IPT (for 6 months) showed 76% reduction in TB risk compared with no treatment
Golub, 2009[38]	Prospective cohort; South Africa	Concurrent use of ART and IPT (for 6 months) showed 89% reduction in TB risk compared with no treatment
Samandari, 2011[39]	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, 2014[40]	Retrospective cohort; Ethiopia	Concurrent use of ART and IPT (for 6 months either simultaneously or with IPT after ART) showed 65% and 78% reduction in TB risk compared with no treatment
Rangaka, 2014[41]	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, 2010[42]	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, THRio, 2013[43]	Stepped wedge, cluster-randomised trial; Brazil	IPT for 6 months showed 31% reduction in risk of TB or death after adjusting for key characteristics and use of ART
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, regardless of CD4 count at ART initiation. Reduction in TB incidence in IPT-treated vs. non-IPT-treated patients was only significant among those with a positive IGRA test
Badjé, TEMPRANO ANRS 12136, 2017[44]	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

IPT = isoniazid preventive therapy; ART = antiretroviral therapy; TB = tuberculosis; TST = tuberculin skin test; THRio = TB/HIV in Rio; RCT = randomised controlled trial; IGRA = interferon-gamma release assay; HIV = human immunodeficiency virus; ANRS = Agence Nationale de Researches sur les SIDA et les Hepatites Virales.

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 were 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]

What are the expected benefits of isoniazid preventive therapy in the antiretroviral therapy era?

In the current situation, where ART is recommended for all PLHIV regardless of the level of immunity,[14] the important question is whether IPT provides additional benefits to ART. Several recent studies (highlighted in Table 2) confirm an affirmative response, further strengthened by observational data from Botswana,[39,45] Brazil,[37] South Africa[38] and Ethiopia,[40] showing lower incidence rates of TB in those on ART plus IPT compared with those on ART alone (Table 3).

Two major RCTs have provided 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.[41] The effect of IPT was not significantly different according to whether patients had a positive or a negative TST or interferon-gamma

Table 3 TB incidence rates/100 py for people living with HIV on ART alone or on ART + IPT

First author, study name, year of publication	Type of study and country	Key findings: ART alone TB incidence rate/100 py (95%CI)	Key findings: ART + IPT TB incidence rate/100 py (95%CI)
Golub, THRio, 2007[37]	Prospective cohort; Brazil	1.9 (1.7–2.2)	0.8 (0.4–1.5)
Golub, 2009[38]	Prospective cohort; South Africa	4.6 (3.4–6.2)	1.1 (0.02–7.6)
Yirdaw, 2014[40]	Retrospective cohort; Ethiopia	0.74*	0.36*
Rangaka, 2014[41]	RCT; South Africa	3.6 (2.8–4.7)	2.3 (1.6–3.1)

* 95%CIs not provided.
TB = tuberculosis; py = person-years; HIV = human immunodeficiency virus; ART = antiretroviral therapy; IPT = isoniazid preventive therapy; THRio = TB/HIV in Rio; CI = confidence interval; RCT = randomised controlled trial.

release assay (IGRA) result. The second (the 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, regardless of CD4 count at ART initiation.[21]

Long-term follow-up of patients enrolled in the TEMPRANO study 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.[44] This evidence from Cote d'Ivoire on reduced mortality with IPT was also confirmed in two previous studies—an observational design study in South Africa and a stepped wedge, cluster-randomised design study in Brazil.[42,43]

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

Which PLHIV benefit more from isoniazid preventive therapy in the antiretroviral therapy 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.[41,44] Because of this demonstrated benefit and given the difficulties and obstacles that TST poses for IPT scale-up, the WHO revised its guidelines in 2011 and again in 2018, recommending that IPT 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 previous 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 a moderate-to-low risk of tuberculous infection because the number of PLHIV with previous tuberculous infection will be fewer. The WHO recommends that PLHIV be screened for LTBI if resources permit, as those with a positive TST benefit more from preventive treatment,[15] and this is the standard approach in most high-income countries.[46]

What is the role of isoniazid preventive therapy in children?

The evidence of benefit of preventive treatment in all children living with HIV is not as clear as that 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 INH was given to children on ART.[48,49] As the prevalence of tuberculous 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] In contrast, young children who are not TB contacts have a low probability of being infected by *M. tuberculosis*, for example, this is $<5\%$ in children aged <5 years where the annual risk of tuberculous infection is $<1\%$, a situation observed in several LICs.[51]

While the WHO recommends that all adults and adolescents living with HIV receive preventive treatment, 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 $\geqslant 12$ months only if living in settings with a high TB prevalence, and for infants (<12 months) only if they are in contact with a TB case.[15]

For how long should isoniazid preventive therapy be given?

The WHO recommends that the duration of IPT be at least 6 months; 36 months (as a surrogate for lifelong treatment) is conditionally recommended in areas with high TB incidence and transmission.[15] The question of how long to give IPT is thus 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 of IPT + ART has a durable effect on mortality for almost 5 years, presumably by combining the two complementary mechanisms of IPT (curing LTBI and preventing new infections during the treatment course) and ART (leading to immune recovery that decreases the risk of both new tuberculous infection and reactivation).[21,44]

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] 6 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.[39] However, after cessation of IPT, TB incidence rebounded even in the presence of ART.[45] These findings suggest 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] The choice of regimen duration should thus 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.

What are the conditions to consider for the programmatic implementation of isoniazid preventive therapy in the context of antiretroviral therapy?

As with any public health strategy, programmatic implementation of IPT must 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 previous testing for tuberculous 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 should 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 because 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 presented in Table 4.

How should programmes organise the initiation of isoniazid preventive therapy?

A crucial principle is that IPT should not be given to PLHIV who may have active TB, and IPT should be discontinued in any PLHIV who develops symptoms and signs of active TB. If active TB is unrecognised, there is not only a risk of delayed diagnosis and death for the patient, but also a risk of promoting INH-resistant disease which may be more difficult to treat, is associated with worse treatment outcomes,[55] and may be transmitted to others. A systematic review in the pre-ART era assessing the effect of IPT on the risk for INH-resistant TB reported a summary relative risk of 1.45 (95% confidence interval [CI] 0.85–2.47).[56] While this result did not reach statistical significance, an increased risk for INH-resistant TB after use of IPT could not be excluded. In a more recent study, the prevalence of INH resistance in patients diagnosed with TB during or after IPT was 16%.[57] In Botswana, after IPT implementation at the national level, the overall prevalence of INH resistance increased from 1.7% in 1995 to 7.6% in 2007–2008.[58] Based on these observations, it is critical that 1) active TB be excluded before starting IPT, and 2) TB be 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.[59] Simple and clear diagnostic procedures accompanied by adequate training and supervision are needed, particularly as staff at HIV clinics are usually not fully trained to diagnose TB. Use of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) should be encouraged due to its increased sensitivity compared with sputum smear microscopy.[60] This is particularly the case for immunosuppressed patients who present with non-specific symptoms of disseminated disease in whom sputum smears can be negative and chest radiography (CXR) normal. However, it is essential that there is a stable and regular electricity supply, adequate maintenance, uninterrupted supplies of cartridges and close monitoring of the screening activities by the TB programme to ensure the effectiveness and added value of this tool.[61]

The costs and organisational problems associated with CXR led to the abandonment of this diagnostic modality in providing IPT in Botswana,[62] and the systematic use of CXR is currently not considered mandatory in resource-limited settings with high HIV prevalence.[15] However, if resources permit, it is worth considering. Indeed, the WHO states that a combination of absence of any CXR abnormality and absence of symptoms suggestive of TB offers the highest sensitivity and negative predictive value for ruling out TB.[63]

Given these screening and diagnostic challenges, a prudent course of action is to initiate ART and wait for patients to stabilise and gain weight before starting IPT so that patients with undiagnosed prevalent TB are not mistakenly placed on INH monotherapy. In the TEMPRANO study during a 1-month waiting period before initiating IPT, 1.6% of participants were diagnosed with active TB,[64] and in another operational study among PLHIV starting ART in Malawi, TB was diagnosed 20–50 days after enrolment in ~10% of those with TB.[65] 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 standardisation across programmes and would allow for the early 'unmasking' of TB from immune reconstitution inflammatory disease during the first few months of ART.[66,67] Starting PLHIV on IPT who are stable and asymptom-

Table 4 Issues to be considered by countries before introducing IPT alongside ART as a national intervention policy

Question	Answer	Considerations, prerequisites and challenges
1 What benefits for PLHIV are expected?	Benefits for PLHIV 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 >150 and very high if >300/100 000[6] In settings with high TB transmission, applying IPT to treat LTBI in PLHIV without previous screening is required.[15] Screening with TST or IGRA* should be considered in lower TB transmission settings, but will necessitate considerable resources and organisation Provision of IPT to PLHIV who are contacts of patients with active TB and are not considered to have active TB is recommended without previous screening for LTBI whatever the level of TB transmission, particularly for HIV-infected child contacts of any age[15,54] 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?	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/100 000.† It may be considered high if >30 and very high if >100/100 000 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 following two indicators: • TB notification rate/100 000 (high if >80/100 000); • HIV prevalence among TB patients (high if >20%)
3 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 the implementation of nationwide IPT requires a good level of preparation to maximise effectiveness and minimise 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 programmes, social mobilisation 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-centred care and follow-up • Adequately supervised 5) Monitoring and evaluation of the intervention • Simple standardised tools (registers and information system) • Real-time data analysis activities • Technical assistance

* Supply and storage of tuberculin along with performance and interpretation of TST in PLHIV are challenging, particularly 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 decentralised.
† Estimates of TB incidence rate/100 000 PLHIV are provided annually in the WHO Global TB report.
‡ A waiting period of 3 months after ART initiation will allow TB to be distinguished from immune reconstitution inflammatory disease during the first few months of ART. Close clinical surveillance of PLHIV should be conducted during this period to conduct all necessary examinations to eliminate active TB and to ensure that they are stable and asymptomatic for the initiation of IPT.
IPT = isoniazid preventive therapy; ART = antiretroviral therapy; PLHIV = people living with HIV; TB = tuberculosis; LTBI = latent tuberculous infection; TST = tuberculin skin test; IGRA = interferon-gamma release assay; HIV = human immunodeficiency virus; WHO = World Health Organization.

atic allows for easier monitoring during ART follow-up. Any individual who develops new symptoms or signs or starts to lose weight should be suspected as having TB. IPT should be stopped and the patient investigated for TB and other HIV-related disease.

How should programmes ensure safety and adherence?

The most serious adverse event is INH-induced hepatitis which, if unrecognised and unattended, can lead to acute liver failure and death. The estimated rate of symptomatic INH-related hepatitis is 1–3 per 1000 persons, with established risk factors being increasing age, pre-existing liver disease, chronic hepatitis C infection, concomitant use of other hepatotoxic medications, such as non-nucleoside reverse transcriptase inhibitors and regular alcohol consumption.[68] In the Botswana studies, INH-induced hepatitis was the main adverse effect, occurring in ~1% of patients and usually during the first 9 months of treatment.[39,45]

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 should 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. INH 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 INH be ensured: drug shortages were the most common reason for discontinuing IPT in an Ethiopian community-based study.[69] Adherence to medication is critical for ensuring the effectiveness of IPT, and it is well recognised that adherence to preventive treatment is more difficult to achieve than adherence to curative treatment. Several 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),[70,71] and completion rates under programmatic rather than study conditions are likely to be even lower. PLHIV already receive many pills. It is therefore crucial to deliver appropriate 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 in patient education, treatment follow-up and the monitoring and management of adverse events, as well as treatment completion or discontinuation. This strategy will require strong collaboration between HIV and TB programmes.

Should other treatment regimens to prevent tuberculosis be considered?

The WHO has recently recommended alternative options to IPT for TB preventive treatment in high TB incidence countries: 1) daily rifampicin (R) and INH for 3 months (3HR) in those aged <15 years, and 2) rifapentine (RPT) and INH weekly for 3 months (3HP) in 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 correct drug dose.[72] Much attention has been paid to weekly 3HP, which appears to be effective in low and high TB incidence settings and is associated with less hepatotoxicity and higher treatment completion rates than daily IPT given for at least 6 months.[73–78] In addition, a recently completed trial showed non-inferiority of 1 month of daily INH and RPT (1HP) compared with 9 months of IPT.[79]

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, rifamycin 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 treatment.[80] Nonetheless, these shorter regimens of 1–3 months make these potentially useful TB preventive therapy options for PLHIV in resource-limited settings in the future, provided the costs of RPT can be reduced. Shorter regimens could also encourage countries to pursue the necessary TB preventive approaches. Despite their inherent advantages for patients, physicians and programmes, however, shorter regimens will not completely offset the challenges facing programmatic implementation, and a coordinated network and strengthening of programmes will continue to 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 tuberculosis in people living with the human immunodeficiency virus

Other interventions can contribute significantly to TB prevention in PLHIV. Early detection and treatment of active TB among contacts of PLHIV is important.[54] PLHIV should thus be informed about the necessity to report on the 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 unrecognised 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 the 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 has been demon-

strated clearly,[88] LICs should 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 1) the choice of treatment duration, 2) a clear and applicable procedure to exclude active TB before starting IPT using the best diagnostic tools available and including a 3-month waiting period before IPT initiation, 3) a robust drug supply to prevent drug interruptions, 4) adequate patient support and well-organised patient follow-up to ensure safety and adherence, and 5) appropriate monitoring of this activity. Shorter regimens are promising and may replace IPT in the future, although these will require the same organisational 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 benefits, the challenges of implementation should be addressed. As countries with the highest prevalence of both HIV and tuberculous infection are also those with the most under-funded programmes, additional resources will be needed.

Conflicts of interest: none declared.

References

1 Lawn S D, Butera S T, Shinnick T M. Tuberculosis unleashed: the impact of human immunodeficiency virus infection on the host granulomatous response to *Mycobacterium tuberculosis*. Microbes Infect 2002; 4: 635–646.
2 Selwyn P A, Hartel D, Lewis V A, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989; 320: 545–550.
3 Daley C L, Small P M, Schecter G F, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. N Engl J Med 1992; 326: 231–235.
4 Lawn S D, Harries A D, Williams B G, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? Int J Tuberc Lung Dis 2011; 15: 571–581.
5 Corbett E L, Watt C J, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 2003; 163: 1009–1021.
6 World Health Organization. Global tuberculosis report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: WHO, 2017.
7 Gupta R K, Lucas S B, Fielding K L, Lawn S D. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015; 29: 1987–2002.
8 Chamie D, Abizaid A, Costa J R, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. Int J Tuberc Lung Dis 2010; 14: 1295–1302.
9 Guirado E, Schlesinger L S. Modeling the *Mycobacterium tuberculosis* granuloma—the critical battlefield in host immunity and disease. Front Immunol 2013; 4: 98.
10 World Health Organization. The End TB Strategy. Geneva, Switzerland: WHO, 2015. http://www.who.int/tb/post2015_TBstrategy.pdf Accessed October 2018.
11 Aït-Khaled N, Alarcon E, Bissell K, et al. Isoniazid preventive therapy for people living with HIV: public health challenges and implementation issues. Int J Tuberc Lung Dis 2009; 13: 927–935.
12 Pathmanathan I, Ahmedov S, Pevzner E, et al. TB preventive therapy for people living with HIV: key considerations for scale-up in resource-limited settings. Int J Tuberc Lung Dis 2018; 22: 596–605.
13 Gupta S, Granich R, Date A, et al. Review of policy and status of implementation of collaborative HIV-TB activities in 23 high-burden countries. Int J Tuberc Lung Dis 2014; 18: 1149–1158.
14 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva, Switzerland: WHO, 2016.
15 World Health Organization. Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. WHO/CDS/TB/2018.4. Geneva, Switzerland: WHO, 2018.
16 Lawn S D, Bekker L G, Wood R. How effectively does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control. AIDS 2005; 19: 1113–1124.
17 Suthar A B, Lawn S D, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLOS Med 2012; 9: e1001270.
18 Grinsztejn B, Hosseinipour M C, Ribaudo H J, et al., and the NPTN 052-ACTG Study Team. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis 2014; 14: 281–290.
19 Collins S E, Jean Juste M A, Koenig S P, et al. CD4 deficit and tuberculosis risk persist with delayed antiretroviral therapy: 5-year data from CIPRA HT-001. Int J Tuberc Lung Dis 2015; 19: 50–57.
20 The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015; 373: 795–807.
21 The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med 2015; 373: 808–822.
22 Siedner M J, Ng C K, Bassett I V, Katz I T, Bangsberg D R, Tsai A C. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013: a meta-analysis. Clin Infect Dis 2015; 60: 1120–1127.
23 Yuen C M, Weyenga H O, Kim A A, et al. Comparison of trends in tuberculosis incidence among adults living with HIV and adults without HIV–Kenya, 1998–2012. PLOS ONE 2014; 9: e99880.
24 Haumba S, Dlamini T, Calnan M, et al. Declining tuberculosis notification trend associated with strengthened and expanded HIV care in Swaziland. Public Health Action 2015; 5: 103–105.
25 Kanyerere H, Harries A D, Tayler-Smith K, et al. The rise and fall of tuberculosis in Malawi: associations with HIV infection and antiretroviral therapy. Trop Med Int Health 2016; 21: 101–107.
26 Takarinda K C, Harries A D, Sandy C, Mutasa-Apolo T, Zishiri C. Declining tuberculosis case notification rates with the scale-up of antiretroviral therapy in Zimbabwe. Public Health Action 2016; 6: 164–168.
27 Kanyerere H, Girma B, Mpunga J, et al. Scale-up of ART in Malawi has reduced case notification rates in HIV-positive and HIV-negative tuberculosis. Public Health Action 2016; 6: 247–251.
28 Williams B G, Granich R, De Cock K M, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine

African countries. Proc Nat Acad Sci USA 2010; 107: 19485–19489.
29 Ford N, Migone C, Calmy A, et al. Benefits and risks of rapid initiation of antiretroviral therapy. AIDS 2018; 32: 17–23.
30 Cohen M S, Chen Y Q, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011; 365: 493–505.
31 Iwuji C C, Orne-Gliemann J, Larmarange J, et al. Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomized trial. Lancet HIV 2018; 5: e116–e125.
32 Gupta A, Wood R, Kaplan R, Bekker L-G, Lawn S D. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. PLOS ONE 2012; 7: e34156.
33 Wilkinson D, Squire S B, Garner P. Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo-controlled trials. BMJ 1998; 317: 625–629.
34 Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev 2004; (1): CD000171.
35 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV-infected persons. Cochrane Database Syst Rev 2010; (1): CD000171.
36 World Health Organization & UNAIDS. Policy statement on preventive therapy against tuberculosis in people living with HIV. WHO/TB/98.255. UNAIDS/98.34. Geneva, Switzerland: WHO, 1998.
37 Golub J E, Saraceni V, Cavalcante S C, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS 2007; 21: 1441–1448.
38 Golub J E, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS 2009; 23: 631–636.
39 Samandari T, Agizew T B, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 377: 1588–1598.
40 Yirdaw K D, Jerene D, Gashu Z, et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. PLOS ONE 2014; 9: e104557.
41 Rangaka M X, Wilkinson R J, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet 2014; 384: 682–690.
42 Charalambous S, Grant A D, Innes C, et al. Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme. AIDS 2010; 24 (Suppl 5): S5–S13.
43 Durovni B, Saraceni V, Moulton L H, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janiero, Brazil: a stepped wedge, cluster-randomised trial. Lancet Infect Dis 2013; 13: 852–858.
44 Badjé A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the TEMPRANO ANRS 12136 trial. Lancet Glob Health 2017; 5: e1080–1089.
45 Samandari T, Agizew T, Nyirenda S, et al. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. AIDS 2015; 29: 351–359.
46 US Department of Health and Human Services. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. *Mycobacterium tuberculosis* infection and disease. Washington DC, USA: US Department of Health and Human Services, 2017. https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb Accessed October 2018.
47 Zar H J, Cotton M F, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ 2007; 334: 136–139.
48 Charan J, Goyal J P, Reljic T, Emmanuel P, Patel A, Kumar A. Isoniazid for the prevention of tuberculosis in HIV-infected children: a systematic review and meta-analysis. Pediatr Infect Dis 2017; 37: 773–780.
49 Zunza M, Gray D M, Young T, Cotton M, Zar H J. Isoniazid for preventing tuberculosis in HIV-infected children. Cochrane Database Syst Rev 2017; 8: CD006418.
50 World Health Organization. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. 2nd ed. WHO/HTM/TB/2014.03. Geneva, Switzerland: WHO, 2014.
51 Houben R M, Dodd P J. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLOS Med 2016; 13: e1002152.
52 Ferebee S H. Controlled chemoprophylaxis trials in tuberculosis. A general review. Adv Tuberc Res 1970; 17: 28–106.
53 Den Boon S, Matteelli A, Ford N, Getahun H. Continuous isoniazid for the treatment of latent tuberculosis infection in people living with HIV: a systematic review and meta-analysis. AIDS 2016; 30: 797–801.
54 World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. WHO/HTM/TB/2012.9. Geneva, Switzerland: WHO, 2012.
55 Van der Hiejden Y F, Karim F, Mufamadi G, et al. Isoniazid-monoresistant tuberculosis is associated with poorer treatment outcomes in Durban, South Africa. Int J Tuberc Lung Dis 2017; 21: 670–676.
56 Balcells M E, Thomas S L, Godfrey-Faussett P, Grant A D. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis 2006; 12: 744–751.
57 Sibanda T, Tedla Z, Nyirenda S, et al. Anti-tuberculosis treatment outcomes in HIV-infected adults exposed to isoniazid preventive therapy in Botswana. Int J Tuberc Lung Dis 2013; 17: 178–185.
58 Menzies H J, Moalosi G, Anisimova V, et al. Increase in anti-tuberculosis drug resistance in Botswana: results from the fourth National Drug Resistance Survey. Int J Tuberc Lung Dis 2014; 18: 1026–1033.
59 Harries A D, Zachariah R, Corbett E L, et al. The HIV-associated tuberculosis epidemic—when will we act? Lancet 2010; 375: 1906–1919.
60 World Health Organization. Xpert MTB/RIF assay for diagnosis of pulmonary and extra-pulmonary TB in adults and children. Policy update. WHO/HTM/TB/2013.16. Geneva, Switzerland: WHO, 2013.
61 Trébucq A, Enarson D A, Chiang C Y, et al. Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? Int J Tuberc Lung Dis 2011; 15: 1567–1072.
62 Samandari T, Bishai D, Lutejin M, et al. Costs and consequences of additional chest X-ray in a tuberculosis prevention program in Botswana. Am J Respir Crit Care Med 2011; 183: 1103–1111.
63 World Health Organization. Chest radiography in tuberculosis detection. WHO/HTM/TB/2016.20. Geneva, Switzerland: WHO, 2016.
64 Moh R, Badjé A, N'takpé J-B, et al. Screening for active tuberculosis before isoniazid preventive therapy among HIV-

infected West African adults. Int J Tuberc Lung Dis 2017; 21: 1237–1244.
65 Van Lettow M, Akesson A, Martiniuk A L C, et al. Six-month mortality among HIV-infected adults presenting for antiretroviral therapy with unexplained weight loss, chronic fever or chronic diarrhea in Malawi. PLOS ONE 2012; 7: e48856.
66 Lawn S D, Wilkinson R J, Lipman M C, Wood R. Immune reconstitution and 'unmasking' of tuberculosis during antiretroviral therapy. Am J Respir Crit Care Med 2008; 177: 680–685.
67 Manabe Y C, Breen R A, Perti T, Girardi E, Sterling T R. Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after highly active antiretroviral therapy initiation. J Infect Dis 2009; 199: 437–444.
68 Landry J, Menzies D. Preventive chemotherapy. Where has it got us? Where to go next? Int J Tuberc Lung Dis 2008; 12: 1352–1364.
69 Datiko D G, Yassin M A, Theobald S J, Cuevas L E. A community-based isoniazid preventive therapy for the prevention of childhood tuberculosis in Ethiopia. Int J Tuberc Lung Dis 2017; 21: 1002–1007.
70 Aisu T, Raviglione M C, van Praag E, et al. Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. AIDS 1995; 9: 267–273.
71 Ayele H T, van Mourik M S M, Bonten M J M, et al. Predictors of adherence to isoniazid preventive therapy in people living with HIV in Ethiopia. Int J Tuberc Lung Dis 2016; 20: 1342–1347.
72 Graham S M. *Mycobacterium tuberculosis* in young children post-2015: an opportunity to close the policy-practice gap. Exp Rev Resp Med 2017; 11: 41–49.
73 Bliven-Sizemore E E, Sterling T R, Shang N, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. Int J Tuberc Lung Dis 2015; 19: 1039–1044.
74 Sterling T R, Scott N A, Miro J M, et al. Three months of weekly rifapentine plus isoniazid for treatment of *M. tuberculosis* infection in HIV co-infected persons. AIDS 2016; 30: 1607–1615.
75 McClintock A H, Eastment M, McKinney C M, et al. Treatment completion for latent tuberculosis infection: a retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. BMC Infect Dis 2017; 17: 146.
76 Sandul A L, Nwana N, Holcombe J M, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and rifapentine (3HP) for latent *Myobacterium tuberculosis* infection. Clin Infect Dis 2017; 65: 1085–1093.
77 Belknap R, Holland D, Feng P J, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. Ann Intern Med 2017; 167: 689–697.
78 Johnson K T, Churchyard G J, Sohn H, Dowdy D W. Cost-effectiveness of preventive therapy for tuberculosis with isoniazid and rifapentine versus isoniazid alone in high-burden settings. Clin Infect Dis 2018; 67: 1072–1078.
79 Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279. Conference on Retroviruses and Opportunistic Infections, 4–7 March 2018, Boston, MA, USA. [Abstract number 37LB].
80 World Health Organization. HIV treatment. Transition to new antiretrovirals in HIV programmes. Policy brief. WHO/HIV/2017.20. Geneva, Switzerland: WHO, 2017.
81 Bock N N, Jensen P A, Miller B, Nardell E. Tuberculous infection control in resource-limited settings in the era of expanding HIV care and treatment. J Infect Dis 2007; 196 (Suppl 1): S108–S113.
82 Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med 2017; 5: 291–360.
83 Shah N S, Auld S C, Brust J C M, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. N Eng J Med 2017; 376: 243–253.
84 Isaakidis P I, Casas E C, Das M, Tseretopoulou X, Ntzani E E, Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. Int J Tuberc Lung Dis 2015; 19: 969–978.
85 Isaakidis P I, Das M, Kumar A M V, et al. Alarming levels of drug-resistant tuberculosis is HIV-infected patients in metropolitan Mumbai, India. PLOS ONE 2014; 9: e110461.
86 World Health Organization. WHO policy on TB infection control in health facilities, congregate settings and households. WHO/HTM/TB/2009.419. Geneva, Switzerland: WHO, 2009.
87 Duarte R, Lönnroth K, Carvalho C, et al. Tuberculosis, social determinants and comorbidities (including HIV). Pulmonol 2018; 24: 115–119.
88 Chaisson R E, Golub J E. Preventing tuberculosis in people living with HIV—no more excuses. Lancet Global Health 2017; 5: e1048–1049.

RÉSUMÉ

Les personnes vivant avec le virus de l'immunodéficience humaine (VIH) (PVVIH) ont un risque élevé de TB et la TB est une cause majeure de décès parmi elles. La prévention de la TB chez les PVVIH est donc une priorité majeure. Une mise en route précoce du traitement antirétroviral (ART) chez les PVVIH asymptomatiques a un puissant effet préventif de la TB, et le bénéfice est encore plus grand chez ceux qui ont un déficit immunitaire avancé. L'application des plus récentes recommandations de l'Organisation Mondiale de la Santé selon laquelle tous les PVVIH devraient mettre en route l'ART, quel que soit le stade clinique ou le nombre des CD4, aurait un important bénéfice en termes de prévention de la TB dans la population des zones de prévalence élevée du VIH. Le traitement préventif peut traiter l'infection tuberculeuse et prévenir de nouvelles infections pendant la durée du traitement. Il est maintenant établi que le traitement préventif par isoniazide (IPT) combiné à l'ART parmi les PVVIH réduit significativement le risque de TB et diminue la mortalité comparé à l'ART seul, et a donc des bénéfices potentiels énormes pour des millions de personnes. En dépit de ces évidences cependant, cette intervention n'est pas mise en œuvre dans la majorité des pays à faible revenu très touchés par la TB associée au VIH. L'engagement du programme VIH et TB, l'intégration des services, des procédures de dépistage appropriées pour exclure une TB active, une fourniture fiable de médicaments, un soutien centré sur le patient afin d'assurer son adhérence et un suivi bien organisé incluant la sécurité des médicaments, sont nécessaires pour la réussite de la mise en route du IPT, et ces éléments seraient également requis pour les protocoles préventifs raccourcis du futur. Une approche holistique de la prévention de la TB parmi les PLHIV devrait également inclure d'autres mesures de prévention importantes comme la détection et le traitement de la TB active, particulièrement parmi les contacts des PLHIV ainsi que des mesures de lutte contre la TB dans les structures de santé, les domiciles des patients index et les lieux surpeuplés.

RESUMEN

Las personas que viven con el virus de la inmunodeficiencia humana (VIH) (PVVIH) presentan un alto riesgo de contraer la tuberculosis (TB), que es una de las principales causas de muerte en esta población. Por consiguiente, prevenir la TB en las PVVIH constituye una gran prioridad. El inicio temprano del tratamiento antirretrovírico (ART) en las PVVIH asintomáticas ejerce un potente efecto de prevención de la TB y su utilidad es aún mayor en las personas con inmunodeficiencia avanzada. La aplicación de la recomendación más reciente de la Organización Mundial de la Salud, que preconiza el inicio del ART en todas las PVVIH, con independencia del estadio clínico y de la cifra de linfocitos CD4, aportaría un considerable efecto preventivo de la TB a escala poblacional, en los entornos con alta prevalencia de infección por el VIH. El tratamiento preventivo con isoniazida (IPT) trata la infección tuberculosa latente y puede prevenir nuevas infecciones durante el ciclo de tratamiento. Se acepta que el IPT combinado con el ART en las PVVIH reduce notablemente el riesgo de sufrir la TB y disminuye la mortalidad en comparación con la administración exclusiva del ART y por lo tanto ofrece beneficios muy grandes a millones de personas. Sin embargo, pese a la evidencia, esta intervención no se aplica en la mayoría de los países con ingresos bajos y alta carga de morbilidad por TB asociada con el VIH. Una aplicación eficaz del IPT exige el compromiso de los programas contra el VIH y la TB, la integración de los servicios, procedimientos adecuados de detección para excluir la TB activa, suministros fiables de medicamentos, una atención centrada en el paciente que favorezca la adhesión al tratamiento y una organización eficaz del seguimiento y la supervisión que incluya la seguridad de los medicamentos; estas condiciones son también necesarias para el desarrollo de esquemas preventivos más cortos en el futuro. Un enfoque holístico de la prevención de la TB en las PVVIH debería comportar importantes medidas preventivas como la detección y el tratamiento de la TB activa, sobre todo en los contactos de las PVVIH y el cumplimiento de medidas de control de la infección tuberculosa en los establecimientos de atención de salud, los hogares de los pacientes nuevos y los entornos colectivos.