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HIV/AIDS (C YOON, SECTION EDITOR)

Latent Tuberculosis and HIV Infection

Sara H. Bares[1] · Susan Swindells[1]

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Abstract

Purpose of Review Tuberculosis is the number one infectious killer of people with HIV worldwide, but it can be both prevented and treated. Prevention of tuberculosis by screening for and treating latent tuberculosis infection (LTBI), along with the initiation of antiretroviral therapy (ART), is the key component of HIV care.

Recent Findings While access to ART has increased worldwide, uptake and completion of LTBI treatment regimens among people living with HIV (PWH) are very poor. Concomitant TB-preventive therapy and ART are complex because of drug–drug interactions, but these can be managed. Recent clinical trials of shorter preventive regimens have demonstrated safety and efficacy in PWH with higher completion rates. More research is needed to guide TB-preventive therapy in children and in pregnant women, and for drug-resistant TB (DR-TB).

Summary Antiretroviral therapy and tuberculosis-preventive treatment regimens can be optimized to avoid drug–drug interactions, decrease pill burden and duration, and minimize side effects in order to increase adherence and treatment completion rates among PWH and LTBI.

Keywords Latent tuberculosis infection · HIV · Tuberculosis · Prevention

Introduction

Almost a quarter of the world's population is infected with *Mycobacterium tuberculosis*, including approximately 13 million people in the USA [1, 2]. Most are asymptomatic and are classified as having latent TB infection (LTBI); however, understanding of the dynamics of tuberculosis (TB) infection has evolved to describe a continuum between "latent" and "active" states that includes a broad range of clinical scenarios [3–6].

People living with HIV (PWH) are 15–22 times more likely to develop active TB than people without HIV, and worldwide, TB is the leading cause of death among PWH [7]. Active TB disease can develop after recent exposure to *Mycobacterium tuberculosis* organisms (primary disease) or with reactivation of latent infection. The annual risk of TB disease due to reactivation of latent infection for persons with untreated HIV is approximately 3–16% per year, nearly the lifetime risk of TB (5–10%) among persons without HIV [8]. The increased risk of active TB begins in the first year after HIV infection and rises with progressive immunodeficiency [9, 10].

Furthermore, despite widespread availability of antiretroviral therapy (ART), the risk of mortality among PWH who develop tuberculosis is higher than among those with tuberculosis alone [11]. Globally, approximately 300,000 people with HIV infection died from TB in 2018 [12], even though TB is both preventable and treatable. The End TB strategy of the World Health Organization (WHO) calls for an 80% reduction in TB incidence and 90% reduction in mortality by 2030, both of which will require a dramatic increase in the number of people offered preventive therapy, and universal access to TB diagnosis and treatment for those with active disease [13].

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✉ Sara H. Bares
sara.bares@unmc.edu

✉ Susan Swindells
sswindells@unmc.edu

[1] Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, 988106 Nebraska Medical Center, Omaha, NE 68198-8106, USA

Prevention of Tuberculosis in Persons with HIV

Antiretroviral therapy and TB-preventive therapy (TPT) are both effective interventions to prevent active TB disease in PWH. Antiretroviral therapy has been shown to reduce the risk of active tuberculosis in PWH by 67% across a wide spectrum of disease stages and CD4 cell counts [14]. TPT involves the use of one or more antituberculous drug to treat persons with LTBI who are at high risk of progression to active disease. The efficacy of TPT was first demonstrated over 60 years ago when isoniazid-preventive therapy (IPT) was used to reduce the risk of TB among Alaskan villages, household contacts, and persons living in mental health facilities [15]. Among PWH, 6 to 9 months of IPT reduces not only TB incidence but also mortality by up to 37%, regardless of CD4 cell count or treatment with antiretroviral therapy [16•, 17]. In combination with ART, TPT reduces the risk of TB disease among PWH by 76% [18].

Despite this large body of evidence, uptake of TPT for people with HIV infection is abysmally low. The often cited reasons for not providing TPT include concerns about first excluding active TB disease, poor patient adherence to long courses of therapy, drug toxicity, and unfounded fears about the emergence of drug resistance [19]. Prevention of TB disease by screening for and treating LTBI, along with ART initiation, are key components of HIV care [20•, 21•]. While access to ART has increased worldwide, screening and treatment of LTBI fall short with less than 20% of patients intended for LTBI screening completing treatment as illustrated in Fig. 1 [22]. In recent years, new shorter and better-tolerated regimens have been developed and are now recommended by the WHO, the Centers for Disease Control and Prevention (CDC), and the US Department of Health and Human Services (DHHS) [20•, 21•, 23•]. Herein, we present a summary of the current options for treating LTBI among PWH along with innovations in the field of TB-preventive therapy.

Screening for LTBI in Persons with HIV

The WHO and the US DHHS recommend screening all PWH for LTBI at the time of HIV diagnosis, regardless of their epidemiologic risk factors or TB exposure history [20•, 21•]. In addition to symptom screening, the two currently available methods for the diagnosis of LTBI are the tuberculin skin test (TST) and the interferon gamma release assay (IGRA). IGRA testing is expensive and not widely available in low- and middle-income countries, and reagents for TST are often in short supply; therefore, the WHO guidelines do not require LTBI testing before initiating TPT for PWH [21•]. Moreover, PWH have been shown to benefit from TPT even with negative LTBI testing [16•, 24•, 25].

All individuals with HIV who have a new positive test for LTBI should be offered LTBI treatment after active TB disease is ruled out [20•, 21•]. Additionally, the US DHHS recommends treatment of LTBI for PWH who report close contact with anyone with infectious TB, regardless of their TB screening test results [20•]. PWH in the USA who have negative screening tests for LTBI and no recent contact with anyone with infectious TB are unlikely to benefit from treatment of LTBI [26–29].

While both the TST and IGRA help differentiate those with LTBI from those without LTBI, the diagnostic accuracy of both tests is limited. It is important to note that these tests do not distinguish between LTBI and active disease. Additionally, negative LTBI testing does not definitively rule out underlying disease.

Although the TST has been utilized for years, it has several disadvantages: patients must return for follow-up to have the test read by a provider, false-positive results can occur following exposure to other non-tuberculous mycobacteria and immunization with bacilli Calmette-Guerin (BCG), and false-negative results can occur among persons with advanced

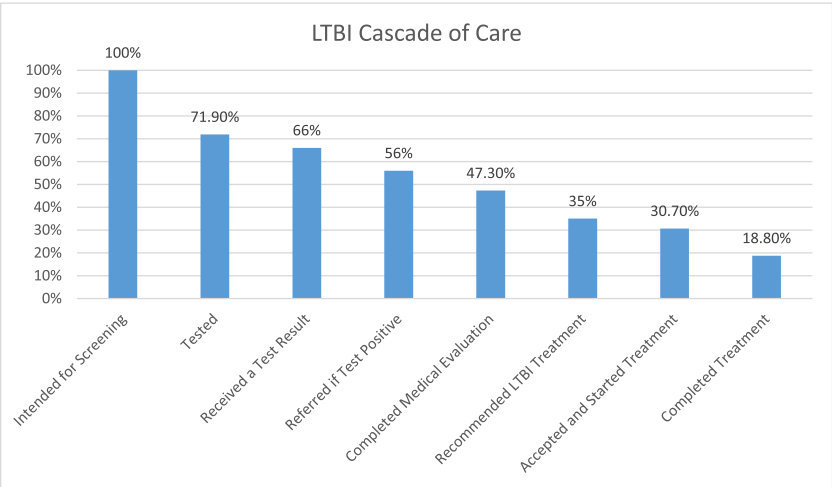

Fig. 1 LTBI cascade of care (Adapted from Alsdurf et al. [22] with permission from Elsevier)

immunodeficiency and active TB disease [30, 31]. While the TST is still a recommended screening test, these limitations have led to increased use of IGRAs as a screening tool for LTBI in recent years.

Two IGRAs have been approved by the Food and Drug Administration (FDA) and are currently available in the USA: the QuantiFERON-TB Gold Plus and the T-SPOT.TB assay. The IGRAs offer some advantages over the TST including higher specificity, higher correlation with surrogate measures of exposure to TB disease, and less cross-reactivity with non-tuberculous mycobacteria and the BCG vaccine [32–34]. However, as with the TST, sensitivity is lower in the setting of advanced immunodeficiency and active TB disease.

Treatment Options for LTBI in PWH

There are several treatment options for PWH with LTBI; underlying comorbidities, drug–drug interactions, toxicities, and adherence should be considered when selecting a regimen.

For many years, isoniazid-preventive therapy (IPT) has been the most widely utilized and recommended regimen for the treatment of LTBI in people with HIV infection. Recent guidelines from the US National TB Controllers Association and CDC now recommend short-course rifamycin-based treatment over INH, but these recommendations do not account for the issues affecting PWH [23]. INH is effective and well tolerated, and severe toxicity is rare. Furthermore, isoniazid can be safely co-administered with any antiretroviral regimen without added risk of toxicity or drug–drug interactions. Peripheral neuropathy, hepatitis, and rash are the most common toxicities, and peripheral neuropathy can largely be prevented via supplementation with pyridoxine at a dose of 25 to 50 mg/day. Recommendations regarding the duration of therapy vary from 6 to 9 months [20•, 21•, 35]. The most significant disadvantage of the 9-month isoniazid regimen is that the majority of patients do not complete therapy [36]. Studies have shown higher completion rates with shorter regimens [36–39], and such regimens are now available (see Table 1).

A 4-month course of daily rifampin is recommended by the CDC and considered an alternative to IPT by the WHO and the US DHHS. A large, open-label, randomized trial comparing 4 months of rifampin (4R) with 9 months of isoniazid (9H) was recently completed, and the 4R regimen was non-inferior to 9H for the prevention of active TB despite low rates of incident active TB in both arms [50]. Treatment completion rates were significantly higher, and adverse events were less common in the 4R arm than in the 9H arm. Despite the large number of participants (> 6000 from 9 countries), only 255 had HIV, and this limits the generalizability of the findings to PWH. Furthermore, rifampin is a potent inducer of the cytochrome P450 (CYP 450) hepatic enzyme system, so ART regimens may need to be adjusted if 4R is utilized for treatment of LTBI. The US DHHS guidelines caution against starting rifampin monotherapy before ruling out active TB disease, possibly with a sputum culture or chest radiograph in addition to symptom screening, given the theoretical risk of drug resistance if rifampin monotherapy is administered in undiagnosed early stage TB disease [20•].

A 3-month course of daily isoniazid and rifampin (3HR) is also recommended by the CDC and considered an alternative regimen for the treatment of LTBI among both adults and children by the WHO [21•, 23•]. A recent systematic review showed similar efficacy rates for the 3HR regimen as compared with 6 months of IPT with comparable rates of adverse events and higher completion rates [51]. As with the 4R regimen, ART regimens may need to be adjusted because of rifampin's potent induction of the CYP 450 enzyme system.

Rifapentine is a rifamycin with a longer half-life than rifampin and has been utilized in combination with isoniazid for the treatment of LTBI with shorter regimens that can be dosed less frequently. Rifapentine plus isoniazid once weekly for 12 weeks (3HP) has been studied in several randomized controlled trials (RCTs) and is recommended for the treatment of LTBI by the CDC and WHO and considered an alternative by the US DHHS. In two RCTs, 3HP was as effective and well tolerated as 6 to 9 months of daily IPT, including in ART-naïve PWH [52•, 53•]. Furthermore, the risk of hepatotoxicity was lower and completion rates were higher in the 3HP regimen. Although 3HP was administered via directly observed therapy (DOT) in these trials, a recently published study demonstrated non-inferior treatment completion and safety of 3HP via self-administered therapy (SAT) as compared with 3HP via DOT in persons living in the USA [54]. Although rifapentine is also a potent inducer of the CYP450 enzyme system, pharmacokinetic (PK) studies suggest that 3HP can be co-administered with efavirenz (EFV), raltegravir (RAL), and dolutegravir (DTG)-based ART regimens without dose adjustment [46–48].

The most recently studied regimen of an ultrashort course of therapy, 1 month of daily rifapentine plus isoniazid (1HP), is under consideration as a recommended regimen in national and international guidelines. The BRIEF-TB study (ACTG 5279) compared 1HP to 9 months of daily isoniazid in PWH and found that 1HP was non-inferior for the primary endpoint of prevention of active TB disease [24•]. Additionally, treatment completion rates were the highest ever reported in a preventive therapy trial (97%), and there was a lower incidence of adverse events in the 1HP arm. This regimen has not yet been evaluated in HIV-uninfected people, or in low TB prevalence settings. Only 23% of participants had a positive test for LTBI in the study; however, this was the largest trial of rifapentine in PWH and had the largest numbers of individuals with confirmed LTBI by TST or IGRA. Furthermore, the number of endpoints in BRIEF-TB was

Table 1 Tuberculosis-preventive therapy and compatible antiretroviral regimens

TPT regimen	Compatible ART	Supporting evidence and ongoing trials for compatible ART
Isoniazid daily × 6–9 months (IPT)	Any	
Rifampin daily × 4 months (4R)	Any NRTI, possibly including TAF	RIFT (TAF + RIF in HIV) study [40]
	EFV 600 mg QD	STRIDE study [41]
	EFV 400 mg QD	Cerrone et al. [42]
	DTG 50 mg BID (adults only)	INSPRING study [43]
	RAL 800 mg BID	Taburet et al. [44]
Isoniazid + rifampin daily × 3 months (3HR)	Any NRTI, possibly including TAF	RIFT (TAF + RIF in HIV) study [40]
	EFV 600 mg QD	STRIDE study [41]
	EFV 400 mg QD	Cerrone et al. [42]
	DTG 50 mg BID (adults only)	INSPRING study [43]
	RAL 800 mg BID	Taburet et al. [44]
Isoniazid + rifapentine weekly × 3 months (3HP)	EFV 600 mg QD	Farenc et al. [45]
	DTG 50 mg QD	DOLPHIN study [46]
	RAL 400 mg BID	Weiner et al. [47]
Isoniazid + rifapentine daily × 1 month (1HP)	EFV 600 mg QD	BRIEF-TB PK study [48]
		DTG + 1HP study ongoing (NCT04272242)

Table adapted from Gonazelez Fernandez et al. [49•].

significant and demonstrates that the population enrolled was indeed at risk for active TB disease.

Drug Interactions

Pharmacokinetic drug–drug interactions between medications used for TPT and antiretroviral medications are common and can lead to either increased or decreased drug exposure. Isoniazid results in few drug–drug interactions with most antiretrovirals, and no dose adjustment is needed, but rifampin and rifapentine are both potent inducers of the CYP450 enzyme system and the uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme, and thus result in numerous drug–drug interactions. The CYP450 system is responsible for the metabolism of many commonly prescribed antiretrovirals including nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), elvitegravir, and maraviroc [20•]. Raltegravir is primarily metabolized via UGT1A1, and bictegravir and dolutegravir are metabolized by both CYP3A4 and UGT1A1. The ART regimens that are compatible with each TPT regimen are outlined in Table 1 along with the evidence to support their use. Importantly, bictegravir is not recommended in combination with either rifampin or rifapentine due to significantly reduced exposure [55].

Although most NRTIs are compatible with rifampin-containing LTBI regimens, the effect of co-administration of tenofovir alafenamide (TAF) and rifamycins is unclear. Although co-administration of TAF and rifampin results in decreased plasma exposure of TAF, a study of 23 healthy volunteers results in higher intracellular levels of tenofovir when TAF was administered with rifampin as compared with tenofovir disoproxil fumarate [40].

Special Circumstances

Children

Although the majority of the evidence regarding TPT in children is based on a 6-month course of IPT, 3HR has been shown to be as effective as 6 months of IPT and was associated with a lower risk of adverse events and a higher adherence rate [56]. 3HP is recommended for children over the age of 2, and 1HP has been studied in children over the age of 13 years. A child-friendly dispersible formulation of rifapentine is under study (TBTC Study 35, NCT03730181), and the safety and pharmacokinetics of 1HP in children will be studied by the NIH-funded IMPAACT network (C5019).

Pregnancy

Pregnant women living with HIV and LTBI are at high risk of progression to active TB disease, but the safety, efficacy, and optimal timing of TPT in pregnant women with HIV remain unclear. An RCT of IPT during pregnancy (immediate) or after delivery (deferred) in 956 women with HIV on ART revealed higher than expected rates of treatment-related adverse events as well as higher adverse pregnancy outcomes in the immediate IPT arm [57]. Post hoc analysis of 126 pregnancies among women who received either 3HP or IPT in the PREVENT TB and iADhere trials did not reveal worse pregnancy outcomes, but only 1 participant in this analysis had HIV [58]. The US DHHS Guidelines for Opportunistic Infections recommend against the use of rifapentine in pregnancy because of fetal loss and malformations in animal studies [20•]. A study of the safety and pharmacokinetics of 1HP

versus 3HP in early versus late pregnancy is in development by the IMPAACT network (CS5021).

Drug-Resistant TB

Recent modeling data estimates that, globally, three in every 1000 people carry latent multidrug-resistant (MDR) tuberculosis infection, and the ideal treatment strategy for MDR LTBI is unknown [59]. The WHO recommends selecting a regimen based on the drug resistance profile of the source case, but additional data are needed [21•]. Three large randomized clinical trials are underway to answer this important question, as effective treatment of MDR LTBI is a critical component of efforts to eliminate TB disease (NCT03568383, ISRCTN92634082, and ACTRN12616000215426).

Research Gaps/Future Directions

Although effective treatment and prevention for TB are available, the impact of these on the global epidemic has been limited and progress is very slow. Recent studies in TB vaccines show some promise, although the number of people with HIV infection included in any of the trials is very limited [60, 61]. In the absence of an effective vaccine, we must rely on provision of preventive therapy to all PWH at risk and prompt diagnosis and treatment of those with active disease.

While significant progress has been made in the development of TPT regimens that are shorter and more easily tolerated, novel strategies are needed to improve LTBI treatment completion rates. Access to rifapentine is limited globally, and the drug is much more expensive than either INH or rifampin [62]. Child-friendly drug formulations are needed, as well as more investigation of TPT in pregnancy. Even shorter courses of TB-preventive therapy that include some newer TB drugs are effective in a mouse model and could be evaluated in human trials [63]. Long-acting drug formulations have proven to be successful in the treatment of HIV, and the application of this technology to the field of TB prevention could have a substantial impact [64, 65]. A long-acting/extended release tuberculosis working group was established in 2015 under the umbrella of the Long-Acting/Extended Release Antiretroviral Assistance Resource Program (LEAP) and recently received funding from Unitaid to develop long-acting drugs for the prevention of TB [66, 67].

National guidelines recommend screening for LTBI in all PWH, but current testing rates are well below target [22, 68]. Although transition from the TST to IGRA-based screening has improved adherence to screening guidelines in many areas where IGRA testing is available, further work is needed to address this first step off in the LTBI treatment cascade.

Additionally, better diagnostic tools are needed as the current tools have limited sensitivity and specificity and do not distinguish between those with subclinical progressing infection and those with nonprogressing latent infection. Without a better biomarker to identify those at high risk of disease progression, the number needed to treat in order to prevent TB is very large, especially in low-prevalence settings [69]. Although many tools ranging from ^{18}F-fluorodexoyglucose positron emission tomography imaging [70] to quantitative blood plasma-based cytokine and chemokine studies [71] to gene expression markers [72] have been explored, results are inconsistent and further research is needed.

An important knowledge gap that remains is the utility of repeat courses of TPT in PWH. Continuous isoniazid has been shown to provide more durable protection in high-burden settings, but uptake of such a regimen is negligible and not recommended outside of a few high-burden countries [73]. Repeat administration of shorter regimens such as 3HP may be associated with a more durable protection with higher completion rates, and one study of periodic 3HP versus a single course of 3HP is currently under way [74].

Conclusions

Improvements must be made in the cascade of LTBI treatment if we are to make progress in reducing the global burden of TB disease. ART and TPT are an essential component of LTBI treatment, and both ART and TPT regimens can be optimized to avoid drug–drug interactions, decrease pill burden and frequency, shorten the duration of therapy, and minimize side effects in order to increase adherence and treatment completion rates.

Compliance with Ethical Standards

Conflict of Interest Dr. Bares reports grant funding to her institution from Gilead Sciences. Dr. Swindells reports research funding to her institution from ViiV healthcare.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med. 2016;13(10):e1002152. https://doi.org/10.1371/journal.pmed.1002152.
2. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. PLoS One. 2015;10(11):e0140881. https://doi.org/10.1371/journal.pone.0140881.
3. Ernst JD. The immunological life cycle of tuberculosis. Nat Rev Immunol. 2012;12(8):581–91. https://doi.org/10.1038/nri3259.
4. Getahun H, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. N Engl J Med. 2015;373(12):1179–80. https://doi.org/10.1056/NEJMc1508223.
5. Barry CE 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. 2009;7(12):845–55. https://doi.org/10.1038/nrmicro2236.
6. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016;2:16076. https://doi.org/10.1038/nrdp.2016.76.
7. World Health Organization. Tuberculosis. https://www.who.int/tb/areas-of-work/tb-hiv/en/ Accessed Feb 3, 2020.
8. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, 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(9):545–50. https://doi.org/10.1056/NEJM198903023200901.
9. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis. 2005;191(2):150–8. https://doi.org/10.1086/426827.
10. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. J Acquir Immune Defic Syndr. 2000;23(1):75–80. https://doi.org/10.1097/00126334-200001010-00010.
11. Metcalfe JZ, Porco TC, Westenhouse J, Damesyn M, Facer M, Hill J, et al. Tuberculosis and HIV co-infection, California, USA, 1993-2008. Emerg Infect Dis. 2013;19(3):400–6. https://doi.org/10.3201/eid1903.121521.
12. World Health Organization (WHO). Global Tuberculosis Report 2019. Available from: https://www.who.int/tb/publications/global_report/en/. Accessed Feb 10, 2019.
13. World Health Organization (WHO). The End TB Strategy. Available from: https://www.who.int/tb/strategy/en/. Accessed Feb 10, 2019.
14. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis. 2010;10(7):489–98. https://doi.org/10.1016/S1473-3099(10)70078-5.
15. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibl Tuberc. 1970;26:28–106.
16.• Badje A, Moh R, Gabillard D, Guehi C, Kabran M, Ntakpe JB, 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(11)):e1080–e9. https://doi.org/10.1016/S2214-109X(17)30372-8 **Landmark trial testing the impact of isoniazid preventive therapy and/or early antiretroviral therapy for individuals with HIV and CD4 cell counts less then 800 cells per uL but above the threshold for initiating treatment during the trial.**
17. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015;373(9):808–22. https://doi.org/10.1056/NEJMoa1507198.
18. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, 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(11):1441–8. https://doi.org/10.1097/QAD.0b013e328216f441.
19. Eldred LJ, Churchyard G, Durovni B, Godfrey-Faussett P, Grant AD, Getahun H, et al. Isoniazid preventive therapy for HIV-infected people: evidence to support implementation. AIDS. 2010;24(Suppl 5):S1–3. https://doi.org/10.1097/01.aids.0000391009.95149.ec.
20.• Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in hiv-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed Feb 3, 2020. **Expert guidelines on the diagnosis and management of latent tuberculosis in patients with HIV.**
21.• Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. **Expert global guidelines on the diagnosis and management of latent tuberculosis.**
22. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269–78. https://doi.org/10.1016/S1473-3099(16)30216-X.
23.• Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69(RR-1):1–11. https://doi.org/10.15585/mmwr.rr6901a1external **Expert national guidelines on the management of latent tuberculosis.**
24.• Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One month of rifapentine plus isoniazid to prevent hiv-related tuberculosis. N Engl J Med. 2019;380(11):1001–11. https://doi.org/10.1056/NEJMoa1806808 **Landmark trial comparing 1 month of daily isoniazid and rifapentine to 9 months of daily isoniazid for the prevention of tuberculosis dsease in patients with HIV.**
25. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384(9944):682–90. https://doi.org/10.1016/S0140-6736(14)60162-8.
26. Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med. 1997;337(5):315–20. https://doi.org/10.1056/NEJM199707313370505.

27. Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. Int J Tuberc Lung Dis. 2007;11(10):1114–20.
28. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. AIDS. 1998;12(18):2447–57. https://doi.org/10.1097/00002030-199818000-00014.
29. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. N Engl J Med. 1997;337(12):801–8. https://doi.org/10.1056/NEJM199709183371201.
30. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis. 2006;10(11):1192–204.
31. Markowitz N, Hansen NI, Wilcosky TC, Hopewell PC, Glassroth J, Kvale PA, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. Ann Intern Med. 1993;119(3):185–93. https://doi.org/10.7326/0003-4819-119-3-199308010-00002.
32. Ewer K, Deeks J, Alvarez L, Bryant G, Waller S, Andersen P, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet. 2003;361(9364):1168–73. https://doi.org/10.1016/S0140-6736(03)12950-9.
33. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med. 2007;146(5):340–54. https://doi.org/10.7326/0003-4819-146-5-200703060-00006.
34. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. Proc Am Thorac Soc. 2006;3(1):103–10. https://doi.org/10.1513/pats.200511-119JH.
35. Centers for Disease Control and Prevention. Treatment Regimens for Latent TB Infection. https://www.cdc.gov/tb/topic/treatment/ltbi.htm Accessed on Feb 3, 2020.
36. Horsburgh CR Jr, Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest. 2010;137(2):401–9. https://doi.org/10.1378/chest.09-0394.
37. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes GM, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. JAMA. 2000;283(11):1445–50. https://doi.org/10.1001/jama.283.11.1445.
38. Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. Int J Infect Dis. 2010;14(4):e292–7. https://doi.org/10.1016/j.ijid.2009.05.007.
39. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med. 2008;149(10):689–97. https://doi.org/10.7326/0003-4819-149-10-200811180-00003.
40. Cerrone M, Alfarisi O, Neary M, Marzinke MA, Parsons TL, Owen A, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. J Antimicrob Chemother. 2019;74(6):1670–8. https://doi.org/10.1093/jac/dkz068.
41. Luetkemeyer AF, Rosenkranz SL, Lu D, Marzan F, Ive P, Hogg E, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. Clin Infect Dis. 2013;57(4):586–93. https://doi.org/10.1093/cid/cit246.
42. Cerrone M, Wang X, Neary M, Weaver C, Fedele S, Day-Weber I, et al. Pharmacokinetics of efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus-infected individuals. Clin Infect Dis. 2019;68(3):446–52. https://doi.org/10.1093/cid/ciy491.
43. Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al. Dolutegravir-based antiretroviral therapy for patients coinfected with tuberculosis and human immunodeficiency virus: a multicenter, noncomparative, open-label. Randomized Trial Clin Infect Dis. 2020;70(4):549–56. https://doi.org/10.1093/cid/ciz256.
44. Taburet AM, Sauvageon H, Grinsztejn B, Assuied A, Veloso V, Pilotto JH, et al. Pharmacokinetics of raltegravir in HIV-infected patients on rifampicin-based antitubercular therapy. Clin Infect Dis. 2015;61(8):1328–35. https://doi.org/10.1093/cid/civ477.
45. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine once-weekly dosing effect on efavirenz, emtricitabine and tenofovir pharmacokinetics. CROI. 2014; Available from: http://www.croiconference.org/sessions/rifapentine-once-weekly-dosing-effect-efavirenz-emtricitabine-and-tenofovir-pks.
46. Dooley KE, Gavin C, Savic RM, Gupte A, Markzinke MA, Zhang N. Safety & PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. CROI. 2019; Available from: https://www.croiconference.org/sessions/safety-pk-weekly-rifapentineisoniazid-3hp-adults-hiv-dolutegravir.
47. Weiner M, Savic RM, Kenzie WR, Wing D, Peloquin CA, Engle M, et al. Rifapentine pharmacokinetics and tolerability in children and adults treated once weekly with rifapentine and isoniazid for latent tuberculosis infection. J Pediatric Infect Dis Soc. 2014;3(2):132–45. https://doi.org/10.1093/jpids/pit077.
48. Podany AT, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving rifapentine and isoniazid for tuberculosis prevention. Clin Infect Dis. 2015;61(8):1322–7. https://doi.org/10.1093/cid/civ464.
49.• Gonzalez Fernandez L, Casas EC, Singh S, Churchyard GJ, Brigden G, Gotuzzo E, et al. New opportunities in tuberculosis prevention: implications for people living with HIV. J Int AIDS Soc. 2020;23(1):e25438. https://doi.org/10.1002/jia2.25438 **An excellent contemporary review of tuberculosis prevention for people living with HIV.**
50. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med. 2018;379(5):440–53. https://doi.org/10.1056/NEJMoa1714283.
51. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. Ann Intern Med. 2017;167(4):248–55. https://doi.org/10.7326/M17-0609.
52.• Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11–20. https://doi.org/10.1056/NEJMoa1005136 **Landmark trial comparing 12 weeks of weekly rifapentine and isoniazid, 12 weeks of twice weekly rifampin plus isoniazid, continuous daily isoniazid and 6 months of daily isoniazid for the prevention of tuberculosis in adults with HIV not receiving antiretroviral therapy.**
53.• Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons. AIDS. 2016;30(10):1607–15. https://doi.org/10.1097/QAD.0000000000001098 **Landmark trial comparing 3 months of weekly isoniazid and rifapentine to 6 to 9 months of daily**

isoniazid for the prevention of tuberculosis dsease in patients with HIV.

54. Belknap R, Holland D, Feng PJ, Millet JP, Cayla JA, Martinson NA, 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(10):689–97. https://doi.org/10.7326/M17-1150.
55. Pham HT, Mesplede T. Bictegravir in a fixed-dose tablet with emtricitabine and tenofovir alafenamide for the treatment of HIV infection: pharmacology and clinical implications. Expert Opin Pharmacother. 2019;20(4):385–97. https://doi.org/10.1080/14656566.2018.1560423.
56. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007;45(6):715–22. https://doi.org/10.1086/520983.
57. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. N Engl J Med. 2019;381(14):1333–46. https://doi.org/10.1056/NEJMoa1813060.
58. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, et al. Exposure to latent tuberculosis treatment during pregnancy. The PREVENT TB and the iAdhere Trials. Ann Am Thorac Soc. 2018;15(5):570–80. https://doi.org/10.1513/AnnalsATS.201704-326OC.
59. Knight GM, McQuaid CF, Dodd PJ, Houben R. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. Lancet Infect Dis. 2019;19(8):903–12. https://doi.org/10.1016/S1473-3099(19)30307-X.
60. Nemes E, Geldenhuys H, Rozot V, Rutkowski KT, Ratangee F, Bilek N, et al. Prevention of M. tuberculosis infection with H4: IC31 vaccine or BCG revaccination. N Engl J Med. 2018;379(2):138–49. https://doi.org/10.1056/NEJMoa1714021.
61. Tait DR, Hatherill M, Van Der Meeren O, Ginsberg AM, Van Brakel E, Salaun B, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. N Engl J Med. 2019;381(25):2429–39. https://doi.org/10.1056/NEJMoa1909953.
62. An Activist's Guide to Rifapentine. Available from: https://www.treatmentactiongroup.org/wp-content/uploads/2019/04/rifapentine_guide_2019_web_final2.pdf. Accessed on Feb 10, 2019.
63. Zhang T, Li SY, Williams KN, Andries K, Nuermberger EL. Short-course chemotherapy with TMC207 and rifapentine in a murine model of latent tuberculosis infection. Am J Respir Crit Care Med. 2011;184(6):732–7. https://doi.org/10.1164/rccm.201103-0397OC.
64. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: ATLAS week 48 results. CROI. 2019; Available from: http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-maintenance-therapy-atlas-week-48-results.
65. Orkin C, Arasteh K, Hernandez-Mora M, et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: FLAIR week 48 results. CROI. 2019; Available from: http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-hiv-maintenance-flair-week-48-results.
66. TB Working Group. Long-Acting/Extended Release Antiretroviral Resource Program. Available from: https://longactinghiv.org/content/tb-working-group. Accessed Feb 8, 2020.
67. Long-acting medicines for malaria, tuberculosis and hepatitis c. Available from: https://unitaid.org/project/long-acting-medicines-for-malaria-tuberculosis-and-hepatitis-c/#en. Accessed Feb 8, 2020.
68. Adams JW, Howe CJ, Andrews AC, Allen SL, Vinnard C. Tuberculosis screening among HIV-infected patients: tuberculin skin test vs. interferon-gamma release assay. AIDS Care. 2017;29(12):1504–9. https://doi.org/10.1080/09540121.2017.1325438.
69. Keshavjee S, Amanullah F, Cattamanchi A, Chaisson R, Dobos KM, Fox GJ, et al. Moving toward tuberculosis elimination. Critical issues for research in diagnostics and therapeutics for tuberculosis infection. Am J Respir Crit Care Med. 2019;199(5):564–71. https://doi.org/10.1164/rccm.201806-1053PP.
70. Yu WY, Lu PX, Assadi M, Huang XL, Skrahin A, Rosenthal A, et al. Updates on (18)F-FDG-PET/CT as a clinical tool for tuberculosis evaluation and therapeutic monitoring. Quant Imaging Med Surg. 2019;9(6):1132–46. https://doi.org/10.21037/qims.2019.05.24.
71. Teklu T, Kwon K, Wondale B, Haile Mariam M, Zewude A, Medhin G, et al. Potential immunological biomarkers for detection of *Mycobacterium tuberculosis* infection in a setting where M. tuberculosis is endemic, Ethiopia. Infect Immun. 2018;86(4). https://doi.org/10.1128/IAI.00759-17.
72. Lee SW, Wu LS, Huang GM, Huang KY, Lee TY, Weng JT. Gene expression profiling identifies candidate biomarkers for active and latent tuberculosis. BMC Bioinformatics. 2016;17(Suppl 1):3. https://doi.org/10.1186/s12859-015-0848-x.
73. Den Boon S, Matteelli A, Ford N, Getahun H. Continuous isoniazid for the treatment of latent tuberculosis infection in people living with HIV. AIDS. 2016;30(5):797–801. https://doi.org/10.1097/QAD.0000000000000985.
74. Evaluation fo the effect of 3hP vs periodic 3HP vs 6H in HIV-positive individuals (WHIP3TB). Available from: https://clinicaltrials.gov/ct2/show/NCT02980016.