

COMMENTARY

New opportunities in tuberculosis prevention: implications for people living with HIV

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Abstract

Introduction: Tuberculosis (TB) is a leading cause of mortality among people living with HIV (PLHIV). An invigorated global END TB Strategy seeks to increase efforts in scaling up TB preventive therapy (TPT) as a central intervention for HIV programmes in an effort to contribute to a 90% reduction in TB incidence and 95% reduction in mortality by 2035. TPT in PLHIV should be part of a comprehensive approach to reduce TB transmission, illness and death that also includes TB active case-finding and prompt, effective and timely initiation of anti-TB therapy among PLHIV. However, the use and implementation of preventive strategies has remained deplorably inadequate and today TB prevention among PLHIV has become an urgent priority globally.

Discussion: We present a summary of the current and novel TPT regimens, including current evidence of use with antiretroviral regimens (ART). We review challenges and opportunities to scale-up TB prevention within HIV programmes, including the use of differentiated care approaches and demand creation for effective TB/HIV services delivery. TB preventive vaccines and diagnostics, including optimal algorithms, while important topics, are outside of the focus of this commentary.

Conclusions: A number of new tools and strategies to make TPT a standard of care in HIV programmes have become available. The new TPT regimens are safe and effective and can be used with current ART, with attention being paid to potential drug-drug interactions between rifamycins and some classes of antiretrovirals. More research and development is needed to optimize TPT for small children, pregnant women and drug-resistant TB (DR-TB). Effective programmatic scale-up can be supported through context-adapted demand creation strategies and the inclusion of TPT in client-centred services, such as differentiated service delivery (DSD) models. Robust collaboration between the HIV and TB programmes represents a unique opportunity to ensure that TB, a preventable and curable condition, is no longer the number one cause of death in PLHIV.

Keywords: TB; HIV care continuum; differentiated care; public health; co-infection; treatment

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1 | INTRODUCTION

Tuberculosis (TB) is a leading cause of mortality among people living with HIV (PLHIV). This population contributes substantially to the global TB burden, with a higher risk of progressing from TB infection to disease than HIV-negative people [1–3]. In 2015, WHO launched the “End TB” strategy, setting ambitious targets of a 90% reduction in TB incidence and 95% reduction in mortality by 2035. These aspirations were included in the Sustainable Development Goals [4,5]. In 2018, the UN High-Level Meeting (UNHLM) on Tuberculosis galvanized the global efforts to prevent TB by setting renewed targets to provide TB preventive therapy (TPT) to 30 million people by 2020 including six million PLHIV [6,7]. Following the UNHLM, a Lancet Commission on TB: “Building a tuberculosis-free world” underscored the rollout of TPT among PLHIV as a cornerstone for achieving success in the global TB control efforts, complemented with active TB case-

finding and initiation of prompt and effective TB treatment [4,8]. Evidence shows that TPT reduces TB incidence, and also mortality in PLHIV up to 37% independent of ART and is a cost-effective intervention, even using shorter regimens [9–11]. Moreover modelling studies underpin expanded use of TPT as an essential intervention to reduce the global TB burden, with great effect in high HIV prevalence settings [12–14]. Despite these facts, TPT scale-up within HIV programmes has been appallingly low and insufficient to effectively decrease the TB burden in PLHIV [8,10,15–20]. With an estimated 920,000 new TB infections among PLHIV and 300,000 deaths (a third of HIV-related deaths globally in 2017), the UN target to reduce TB deaths among PLHIV by 75% by 2020 will remain unmet [21]. Barriers preventing TPT rollout are related to access to patient-friendly formulations, including for children, difficulties of ruling out active TB, unfounded fear of development of drug resistance, perceived provider beliefs that drug toxicity outweighs the

benefit, or competing priorities to deliver antiretroviral treatment (ART) [22,23].

We present a summary of the current TPT options and innovations in this field. We discuss challenges and opportunities to scale-up TPT within HIV programmes. Finally, we call for action to stakeholders in HIV high-burden settings to improve access to new TPT, exploring innovative ways to deliver TPT using differentiated services and demand creation approaches.

2 | DISCUSSION

2.1 | Research and innovation in TB prevention: implications for PLHIV

The understanding of the dynamics of TB infection and activation keeps improving and has evolved to describe a continuum between “latent” and “active” states that cover different scenarios between latent subclinical infection to clinically active disease [3,24–26]. While much remains to be done in the quest for diagnostic technologies to provide a public health solution that can effectively find cases of TB infection at high risk of progression, the field of treatment has advanced significantly [26]. Antiretroviral therapy alone prevents TB at individual and programmatic levels, and is now recommended for all people with HIV infection, including during additional preventive therapy for TB [23,27,28].

TPT in PLHIV aims to prevent progression to clinical disease, reducing TB-related mortality, morbidity, including hospitalizations and ultimately decrease TB transmission [11,17,18,29–32]. In this context, TPT should be integrated as a standard package of care including routine TB screening, early diagnosis and treatment of TB disease, effective ART, and education and access to harm reductions programmes such as use and abuse of alcohol and drugs, including tobacco [26,33].

Much progress has been made to make new, shorter and better tolerated TPT regimens available by including rifapentine [27,34,35]. A 3-month course of weekly rifapentine and isoniazid (3HP) has proved as effective as nine months of isoniazid (INH), was better tolerated, had higher completion rates and is safe and effective in PLHIV [27,34]. This regimen can be co-administered with dolutegravir (DTG) without dose adjustment and it is included in the 2018 WHO recommendations for the treatment of latent TB infection [27,36]. The most recent, and not yet included in international recommendations, uses 1-month daily rifapentine plus isoniazid (1HP) and has shown non-inferiority to nine months of isoniazid alone for preventing TB in HIV co-infected patients, with lower incidence of adverse events and better adherence to treatment completion [35].

However today, the most commonly used TPT regimen contains classically one drug, isoniazid, administered for six to twelve months and can be co-administered with any ART regimen. The INH-CoTrim-VitB6 combination may offer benefits with respect to pill burden [32,37]. The length of the course and repetition of courses remain as important questions, for which current evidence goes as far as 36 months as a proxy for life-long treatment [27,38]. Current WHO recommendations support the use of isoniazid preventive treatment (IPT) for six months, while thirty-six months remains a recommendation for high incidence areas [38]. Another TPT regimen using 4-months

of rifampin (RIF) was non-inferior to the 9-month regimen of isoniazid for the prevention of active tuberculosis in adults and was associated with higher rates of treatment completion and better safety. This study was done in a large cohort of adults, however, it contained relatively few PLHIV [39].

TPT-related adverse events vary depending on the regimen used but they are considered manageable from a public health perspective. In the case of INH, despite occurring quite commonly, the considerable majority are low grade, transient and do not influence treatment adherence and completion [40]. A recent meta-analysis demonstrated that the three-month isoniazid-rifapentine regimen was associated with similar risk of adverse events and treatment discontinuation than other latent tuberculosis infection regimens [41]. Regarding drug-drug interactions (DDI) between TPT regimens and the existing ART, there are still some knowledge gaps to cover, such as co-administration of TAF with any rifamycin, or use of 1HP with DTG. Rifampicin is a potent inducer of cytochrome P450 oxidase system, which reduces concentrations of many non-nucleoside reverse transcriptase inhibitors (NNRTI), such as nevirapine, all protease inhibitors (PIs), and integrase inhibitors. Co-administration with tenofovir alafenamide (TAF) decreases plasma exposure of TAF, but a healthy volunteer study with 23 participants demonstrated that intracellular levels are actually higher with TAF plus rifampicin compared to tenofovir disoproxil fumarate without rifampicin [42]. Further study of TAF with rifampicin in patients with HIV infection is planned. In adults, doubling the dose of dolutegravir (50 mg twice daily rather than 50 mg once daily) with rifampicin containing TB treatment achieves adequate drug concentrations and it is likely that the same is true in older children, in whom drug disposition is similar to adults (Table 1).

Children and pregnant women living with HIV must get dedicated efforts to increase access to TPT anchored to HIV programmes and maternal and child services [27,49,50]. While most evidence is based on a 6-month INH course; in children, the use of 3-months daily isoniazid and rifampicin (3HR) regimen with the new paediatric TB formulations offers equal effectiveness, better adherence and fewer adverse events than standard IPT [27].

HIV positive pregnant women are at especially high risk of progression from TB infection to disease [51]. TB is a significant cause of infant and maternal morbidity and mortality, especially in high-burden settings, and has been associated with increased risk of mother-to-child transmission of HIV [52,53]. Treatment guidelines generally recommend use of the same regimens and dosages for pregnant women and non-pregnant adults. However, the safety, efficacy, and appropriate timing of TPT in pregnant women living with HIV remain uncertain [54]. One of the few PK studies conducted in pregnant women showed only modest changes with rifampin, so dose adjustment is not needed [55]. A randomized trial of IPT during or after pregnancy in 956 HIV-infected women on ART showed higher than expected rates of treatment-related adverse events, and excess adverse pregnancy outcomes in the immediate IPT arm [54]. However, in a post-hoc analysis of 3HP in 112 pregnant women, the rates of spontaneous abortion and birth defects were similar to those in the general US population [56].

The knowledge gap persists in children under the age of three years: with the use of LPV/r in first line regimens (efavirenz cannot be given), options are very limited for rifamycin-

Table 1. Tuberculosis preventive therapy and antiretroviral therapy co-administration

TPT regimen	WHO Recommendation		Compatible ART	Supporting evidence and ongoing DDI trials	Knowledge gaps
	for the TPT regimen	Recommended for children			
IPT	Strong recommendation	Any age	Any		Ideal length of treatment Use in pregnancy
3HR	Strong recommendation	Any age	Any NRTI, possibly including TAF EFV 600 mg QD EFV 400 mg QD with HR DTG 50 mg BID (Adults only) RAL 800 BID	RIFT (TAF + RIF in HV) study [42] STRIDE study [43] Cerrone et al. [37] INSPIRING trial ongoing [44] Taburet et al.[45]	TAF/FTC + RIF in patients with HIV – study in progress in South Africa
3HP	Conditional recommendation	>2 years old only	EFV 600 mg QD DTG 50 mg QD RAL 400 mg BID	Farenc et al. [46] DOLPHIN study [36] Weiner et al. [47]	3HP dosing for children <2 years old 3HP with TAF – healthy volunteer study in progress at US NIH NCT03510468
1HP	Under review	>13 years old only	EFV 600 mg QD	BRIEF-TB PK study [48]	1HP dosing for children <13 years old 1HP with TAF 1HP with dolutegravir – ACTG trial in development (A5372)

1HP, one month daily isoniazid and rifapentine; 3HP, 3 months weekly isoniazid and rifapentine; 3HR, 3 months isoniazid and rifampin; ART, antiretroviral therapy; DDI, drug-drug interaction; DTG, dolutegravir; EFV, efavirenz; HV, healthy volunteer; IPT, isoniazid preventive therapy; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetics; RAL, raltegravir; TAF, tenofovir alafenamide; TPT, tuberculosis preventive therapy; WHO, World Health Organization.

based TPT [57]. A dosing recommendation for dolutegravir with rifampicin cannot yet be made.

The question of the need for repeated courses of TPT in PLHIV is not yet answered, but investigation is going in a randomized, controlled trial of two annual courses of 3HP compared to a single course, or to six months of INH in more than 4000 participants [58]. There is likewise limited evidence on the best TPT regimens for drug-resistant TB (DR-TB), WHO provides a conditional recommendation and studies are underway [27,59–61]. Recent modelling has estimated that three in every 1000 people globally carry latent multidrug-resistant tuberculosis infection, prevalence is around ten times higher among those younger than 15 years and there is inadequate understanding of DR-TB infection in the context of HIV. Treatment options for multidrug-resistant latent tuberculosis infection will be central to contribute to TB elimination [62].

Future TPT options include long-acting drug formulations, with the potential benefit of extended duration for drug delivery that could lead to improved adherence and outcomes [63]. Precedents come from the HIV therapy field and the development of an injectable combination of rilpivirine/cabotegravir that can be administered every one to two months, and ongoing studies of other injectable formulations such as cabotegravir for pre-exposure prophylaxis [63–67]. Since 2015, a working group on long acting/extended release

formulations for TB prevention and treatment was established under the umbrella of the Long-Acting/Extended Release Antiretroviral Resource Programme (LEAP) [68]. The group has developed the target product profile for TPT formulations and is contributing to the efforts of building the pipeline for long-acting formulations using new and existing TB drugs.

2.2 | Programmatic opportunities to scale-up TPT in HIV programmes

Successful TB/HIV control strategies in high-burden settings pivot around strong collaborations and ownership between HIV and TB stakeholders [23,69].

Programme managers, clinicians and community workers in integrated TB/HIV programmes have to be equipped and supported to become the real foundation for a robust TPT programmatic rollout [23]. While increasing training and on-the-job mentorship, programmes could use routine data, triggering quality cycles, to gather in-depth understanding of the successes and gaps along the cascades of care. Tailoring support to recipients of TPT will assure better adherence and management of events arising during the course of the treatment. Tracking and reporting TPT outcomes is critical, not only at individual level, but also programmatically. The quality of TPT programmes should be evaluated by their capacity to attain

Table 2. Differentiated service delivery applied to the integration of TPT in HIV programmes

	What	Where	When	Who	Target population
TB screening	<ul style="list-style-type: none"> Clinical screening package 	<ul style="list-style-type: none"> At facilities Active case finding in the communities In differentiated care models of ART delivery 	<ul style="list-style-type: none"> At every consultation with a clinician At every encounter with a community health worker 	<ul style="list-style-type: none"> Community-based or facility-based health workers Peers Expert clients 	<ul style="list-style-type: none"> PLHIV
Initiation TPT	<ul style="list-style-type: none"> Identify preventive regimen 	<ul style="list-style-type: none"> Health facilities and community settings 	<ul style="list-style-type: none"> After negative TB screening 	<ul style="list-style-type: none"> Nurses, clinicians 	<ul style="list-style-type: none"> PLHIV with negative TB screening and no contraindications
Follow-up	<ul style="list-style-type: none"> Clinical monitoring Reporting/management of side effects Reporting of treatment completion Programmatic quality improvement 	<ul style="list-style-type: none"> Clinical consultation, peer support Task shifted and simplified models of care 	<ul style="list-style-type: none"> During TPT course as per agreed protocol 	<ul style="list-style-type: none"> Nurses Expert clients Peers Community health workers 	<ul style="list-style-type: none"> PLHIV on TPT

the highest completion rates, provide adequate clinical and programmatic monitoring and decrease causes of non-completion, such as death, development of active TB, adverse effects or loss to care. From a global perspective, countries with high TB/HIV burden must include a minimum set of indicators for TPT programmes to their routine reports to WHO and UNAIDS, as a strategy to assure progress and accountability to the UNHLM targets.

The use of optimized, simplified and integrated diagnostic algorithms identify two pathways: PLHIV who screen TB positive will need to complete TB disease diagnostic confirmation steps, and, if positive, be initiated anti-TB therapy. The majority of PLHIV living in high burden areas, where TB screening is negative, should be offered a TPT course. Improvements must assure sustainability and efficient use of diagnostic platforms such as Xpert and urine TB-LAM [70] or adaptation of clinical protocols to minimize concerns about unmasked TB after ART initiation [70–72].

TPT regimens can be optimized to decrease pill burden, become shorter, patient-friendly and decrease side effects as means to maximize treatment completion rates [22]. New TPT options will be a game changer, facilitating programmatic rollout and improving engagement in care until completion. Despite the existing operational challenges related to availability of rifapentine, global stakeholders and Ministries of Health are committing to scale-up shorter TPT regimens, making generic formulations available and reducing prices [8]. National supply chains should ensure that diagnostics and treatment options for TB and HIV are available without interruption.

2.3 | Field perspectives to scale-up TPT in HIV programmes: differentiating care and demand creation

HIV programmes can enable environments that enhance TB integrated services at every possible opportunity as PLHIV engage or re-engage in chronic care. Traditional models of care are expanding approaches that include DSD, creating

client-centred approaches that simplify and adapt services across the cascade of care in ways that both serve the needs of PLHIV, reduce burden on the health system and enable reallocation of resources to reach even more people [73,74]. These models vary the location of the service (e.g. facility-based, community), reduce the frequency of encounter (e.g. 2-monthly to 6-monthly), and distributes tasks among doctors, nurses, pharmacists, lay healthcare workers and peers [75]. Differentiation of HIV testing or ART delivery is being widely used today to improve services and to respond to the needs of specific populations for thousands of stable PLHIV in countries such as Mozambique, South Africa, Malawi or Ghana [74,76–81]. In the era of differentiated care, programmatic scale up of TPT can be supported with the creation of integrated care models that incorporate TB screening and provision of TPT without increasing the frequency of clinic attendance, reflecting the balance for public health approaches and people’s needs that are contextual and change over time [82]. Applying differentiated frameworks in HIV programmes to rollout TPT can promote the creation of context-adapted solutions to the “how” TPT is delivered within chronic ART care, “who” does TB screening and delivers TPT, “when” is TB screening done and TPT delivered and “what” package of interventions is included to achieve best TPT completion rates (Table 2).

Increasing the demand for TPT in PLHIV will also support the path to achieve the very ambitious global TPT targets through a robust programmatic scale-up; in many settings this will include setting up strong collaborations with the private sector or other providers of care [83]. Experience with other prevention programmes such as population-wide tobacco control or preventive voluntary male circumcision shows that social and behaviour change can be modulated with the use of ambitious communications strategies that identify and address the demand-side barriers, increasing awareness and aligning demand with service delivery [83–85].

The lower rifapentine price recently established by the agreement between Sanofi, Unitaid, and the Global Fund,

combined with initiatives such as IMPAACT4TB will contribute to catalyse change and improve uptake by facilitating access and generating evidence for programmatic use [86,87]. Advocacy (e.g. with community leaders, TB champions, healthcare workers), communications through different channels (e.g. television, radio, print media, interpersonal communication, road shows, social media, SMS reminders, household visits), and community engagement and mobilization will also be essential tools [85]. Moreover health workers are in a unique position to refer and initiate TPT in PLHIV [84]. Once mobilized, extensive existing networks of community-based and health facility-based professionals in each setting can contribute to increase awareness, remove major health system barriers and support PLHIV to start and complete TPT. As there is no “one size fits all,” qualitative research and baseline situational analyses can assist identifying context-tailored strategies and unveil breakthroughs in different settings.

3 | CONCLUSIONS

Revitalized approaches to TB prevention that significantly expand the range of TPT options, combined with the integration in people-centred models of care and a solid engagement with communities, will contribute to decrease morbidity and mortality in HIV-associated TB. HIV programmes are at an important crossroad to continue improving HIV quality of care while adding a meaningful contribution to the global TB elimination efforts.

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COMPETING INTERESTS

LGF, EC, VS, GB, EG, WV, SA, SS1, APL, BG, have no competing interests. GJ participated in the WHIP3TB trial evaluating 3HP given once or annually and the DOLPHIN trial that evaluated the safety and PK of 3HP given with dolutegravir in people with HIV. Sanofi donated isoniazid and rifampentine for these trials. GJ also attended a Sanofi Advisory Board on rifampentine without any compensation. AK currently manages grants from Sanofi. SS2 reports research grants to her institution from Viiv Healthcare.

AUTHORS' CONTRIBUTIONS

LGF and EC drafted the first draft of the manuscript, developed the concepts with input from co-authors and managed revisions. VS, GJ, GB, EG, WV, SA, SS1, AK, APL, BG and SS2 discussed key ideas and concepts forming the basis of this commentary. SS2 developed Table 1. All co-authors reviewed and gave input on the final draft, and cleared it for submission.

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REFERENCES

1. Zumla A, Malon P, Henderson J, Grangeet J. Impact of HIV infection on tuberculosis. *Postgrad Med J*. 2000;76(895):259–68.
2. Pawlowski A, Jansson M, Skö M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. *PLoS Pathog*. 2012;8(2):e1002464. <https://doi.org/10.1371/journal.ppat.1002464>.
3. Peters JS, Andrews JR, Hatherill M, Hermans S, Martinez L, Schurr E, et al. Advances in the understanding of *Mycobacterium tuberculosis* transmission in HIV-endemic settings. *Lancet Infect Dis*. 2019;19:e65–e76.
4. World Health Organization (WHO). The END TB strategy. 2015. [cited 2019 Apr 25]. Available from: https://www.who.int/tb/post2015_strategy/en/
5. United Nations. Sustainable Development Goals. 2015. [cited 2018 Jun 10]. Available from: <https://www.un.org/sustainabledevelopment/>
6. USAID, TB DIAH DIA and CH. TB Data Hub – Enhance data. Expand data analysis. End tuberculosis. [cited 2019 Apr 8]. Available from: <https://www.tbdiagnostics.org/>
7. World Health Organization (WHO). United Nations High-level meeting on the fight against Tuberculosis. 2018. [cited 2019 May 15]. Available from: https://www.who.int/tb/features_archive/UNGA_HLM_ending_TB/en/
8. Reid MJA, Arinaminpathy N, Bloom A, Bloom BR, Boehme C, Chaisson R, et al. The lancet commissions building a tuberculosis-free world: the lancet commission on tuberculosis. *Lancet*. 2019;393(10178):1331–84.
9. Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of preventive therapy for tuberculosis with isoniazid and rifampentine versus isoniazid alone in high-burden settings. *Clin Infect Dis*. 2018;67:1072–8.
10. TEMPRANO ANRS 12136 Study Group, 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;373:808–22.
11. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé 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 Heal*. 2017;5:e1080–9.
12. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. *Int J Inf Dis*. 2017;56:68–76.
13. Mills HL, Cohen T, Colijn C. Community-wide isoniazid preventive therapy drives drug-resistant tuberculosis: a model-based analysis. *Sci Transl Med*. 2013;5(180):180ra49. <https://doi.org/10.1126/scitranslmed.3005260>.
14. Rhines AS, Feldman MW, Bendavid E. Modeling the implementation of population-level isoniazid preventive therapy for tuberculosis control in a high HIV-prevalence setting. *AIDS*. 2018;32:2129–40.
15. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010; CD000171.
16. Briggs MA, Emerson C, Modi S, Taylor NK, Date A. Use of isoniazid preventive therapy for tuberculosis prophylaxis among people living with HIV/AIDS: a review of the literature. *J Acquir Immune Defic Syndr*. 2015;68 Suppl 3:S297–305.
17. Golub JE, Cohn S, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRIO) study. *Clin Infect Dis*. 2015;60:639–45.
18. Rangaka MX, Wilkinson RJ, Boule 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;384:682–90.
19. Hausler HP, Sinanovic E, Kumaranayake L, Naidoo P, Schoeman H, Karpakis B, et al. Costs of measures to control tuberculosis/HIV in public primary care facilities in Cape Town, South Africa. *Bull World Health Organ*. 2006;84:528–36.
20. Shrestha RK, Mugisha B, Bunnell R, Mermin J, Odeke R, Madra P, et al. Cost-utility of tuberculosis prevention among HIV-infected adults in Kampala, Uganda. *Int J Tuberc Lung Dis*. 2007;11:747–54.
21. World Health Organization (WHO). Global Tuberculosis Report 2018. 2018. [cited 2019 May 18]. Available from: <http://apps.who.int/medicinedocs/en/m/abstract/Js23553en/>
22. Pathmanathan I, Ahmedov S, Pevzner E, Anyalechi G, Modi S, Kirking H, 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.

23. Harries AD, Schwoebel V, Monedero-Recuero I, Aung TK, Chadha S, Chiang C-Y, et al. Challenges and opportunities to prevent tuberculosis in people living with HIV in low-income countries. *Int J Tuberc Lung Dis.* **2019**;23:241–51.
24. Barry CE, Boshoff HI, Dartois V, Dick T, Ehrst S, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nat Rev Microbiol.* **2009**;7:845–55.
25. Ernst JD. The immunological life cycle of tuberculosis. *Nat Rev Immunol.* **2012**;12:581–91.
26. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med.* **2015**;372:2127–35.
27. World Health Organisation (WHO). Latent tuberculosis infection: 2018 Updated and consolidated guidelines for programmatic management. [cited 2019 May 15]. Available from: <https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf;sequence=1>
28. 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. World Health Organization; **2016**. [cited 2019 May 14]. Available from: <https://www.who.int/hiv/pub/arv/arv-2016/en/>
29. Golub JE, Pronyk P, Mohapi L, Tshabangu N, Moshabela M, Struthers H, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS.* **2009**;23:631–6.
30. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Mosimaneotsile B, et al. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana. *AIDS.* **2015**;29:351–9.
31. Yirdaw KD, Jerene D, Gashu Z, Edgington ME, Kumar AMV, Letamo Y, 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.
32. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. *N Engl J Med.* **2017**;377:233–45.
33. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS Medicine.* **2012**;9:e1001270. <https://doi.org/10.1371/journal.pmed.1001270>.
34. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifampine plus isoniazid for treatment of m. tuberculosis infection in HIV co-infected persons HHS public access. *AIDS.* **2016**;30:1607–15.
35. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One month of rifampine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med.* **2019**;380:1001–11.
36. Dooley KE, Gavin C, Savic RM, Gupte A, Markzinke MA, Zhang N. Safety & PK of weekly Rifampine/Isoniazid (3HP) in adults with HIV on Dolutegravir. [cited 2019 Jun 10]. **2019**. Available from: <https://www.croiconference.org/sessions/safety-pk-weekly-rifampine-isoniazid-3hp-adults-hiv-dolutegravir>
37. Harries AD, Lawn SD, Suthar AB, Granich R. Benefits of combined preventive therapy with co-trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet coformulation. *Lancet Infect Dis.* **2015**;15:1492–6.
38. 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**;30:797–801.
39. 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**;379:440–53.
40. Denholm JT, McBryde ES, Eisen DP, Chen C, Penington J, Street A. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. *Drug Healthc Patient Saf.* **2014**;6:145–9.
41. Nijie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-rifampine for latent tuberculosis infection: a systematic review and meta-analysis. *Am J Prev Med.* **2018**;55:244–52.
42. Cerrone M, Alfarisi O, Neary M, Marzinger MA, Parsons TL, Owen A, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *J Antimicrob Chemother.* **2019**;74:1670–8.
43. Luetkemeyer AF, Rosenkranz SL, Lu D, Marzan F, Ives 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**;57:586–93.
44. 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.* **2019**. <https://doi.org/10.1093/cid/ciz256>
45. Taburet A-M, 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**;61:1328–35.
46. Farenc C, Doroumian S, Cantalloube C, et al. Rifampentine once-weekly dosing effect on efavirenz, emtricitabine and tenofovir pharmacokinetics. Poster CROI 2014. **2014**. [cited 2019 Apr 14]. Available from: <http://www.croiconference.org/sessions/rifampentine-once-weekly-dosing-effect-efavirenz-emtricitabine-and-tenofovir-pks>
47. Weiner M, Egelund EF, Engle M, Kiser M, Prihoda TJ, Gelfond JAL, et al. Pharmacokinetic interaction of rifampentine and raltegravir in healthy volunteers. *J Antimicrob Chemother.* **2014**;69:1079–85.
48. Podany AT, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving rifampentine and isoniazid for tuberculosis prevention. *Clin Infect Dis.* **2015**;61:1322–7.
49. Charan J, Goyal JP, Reljic T, Emmanuel P, Patel A, Kumar A. Isoniazid for the prevention of tuberculosis in HIV-infected children. *Pediatr Infect Dis J.* **2018**;37:773–780.
50. Zunza M, Gray DM, Young T, Cotton M, Zar HJ. Isoniazid for preventing tuberculosis in HIV-infected children. *Cochrane Database Syst. Rev.* **2017**;8:CD006418.
51. Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clin Infect Dis.* **2012**;55:1532–49.
52. Pillay T, Sturm AW, Khan M, Adhikari M, Moodley J, Connolly C, et al. Vertical transmission of *Mycobacterium tuberculosis* in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis.* **2004**;8:59–69.
53. Gupta A, Bhosale R, Kinikar A, Gupte N, Bharadwaj R, Kagal A, et al. Maternal tuberculosis: a risk factor for mother-to-child transmission of human immunodeficiency virus. *J Infect Dis.* **2011**;203:358–62.
54. 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**;381:1333–46.
55. Denti P, Martinson N, Cohn S, Mashabela F, Hoffmann J, Msandwa R, et al. Population pharmacokinetics of rifampin in pregnant women with tuberculosis and HIV coinfection in Soweto, South Africa. *Antimicrob Agents Chemother.* **2016**;60:1234–41.
56. Moro RN, Scott NA, Vernon A, Goldberg SV, Schwartzman K, Narita M, et al. Pregnancy safety assessment of 3 months of once-weekly rifampentine and isoniazid and 9 months of daily isoniazid: a post-hoc analysis of the PREVENT TB and the iAdhere Trials. In: B107. Tuberculosis: Issues during treatment. American Thoracic Society, **2016**, p. A7859.
57. Weld ED, Dooley KE. State-of-the-art review of HIV-TB coinfection in special populations. *Clin Pharmacol Ther.* **2018**;104:1098–109.
58. Evaluation of the effect of 3HP vs periodic 3HP vs 6H in HIV-positive individuals - full text view - ClinicalTrials.gov. [cited 2019 Nov 12]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02980016>
59. Protecting households on exposure to newly diagnosed index multidrug-resistant tuberculosis patients - full text view - ClinicalTrials.gov. [cited 2019 Jun 10]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03568383?term=Phoenix+MDR+TB&rank=1>
60. ISRCTN - ISRCTN92634082: Tuberculosis child multidrug-resistant preventive therapy: TB CHAMP trial. [2019 Jun 10]. Available from: <http://www.isrctn.com/ISRCTN92634082>
61. ANZCTR - Registration. [2019 Jun 10]. Available from: <https://anzctr.org.au/Trial/Registration/TrialReview.aspx?xmlid=369817>
62. Knight GM, McQuaid CF, Dodd PJ, Houben RMG. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. *Lancet Infect Dis.* **2019**; 19(8):903–912. [https://doi.org/10.1016/S1473-3099\(19\)30307-X](https://doi.org/10.1016/S1473-3099(19)30307-X)
63. Swindells S, Siccardi M, Barrett SE, Olsen DB, Grobler JA, Podany AT, et al. Long-acting formulations for the treatment of latent tuberculosis infection: opportunities and challenges. *Int J Tuberc Lung Dis.* **2018**;22:125–32.
64. Swindells S, Andrade-Villanueva F, Richmond GJ. Long-acting Cabotegravir + Rilpivirine as maintenance therapy: atlas week 48 results. CROI Conference. [2019 Apr 6]. **2019**. Available from: <http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-maintenance-therapy-atlas-week-48-results>
65. HPTN 083. Safety and efficacy study of injectable cabotegravir compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis in HIV-uninfected cisgender men and transgender women who have sex with men. [cited 2019 Jun 10]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02720094?term=HPTN+083&rank=2>

66. HPTN 084. Long-acting biomedical HIV prevention in transgender women - full text view - ClinicalTrials.gov. [cited 2019 Jun 10]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03856580?term=HPTN+084&rank=2>
67. Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M, et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. *PLoS Medicine*. 2018;15:e1002690.
68. TB Working Group.LEAP. [cited 2019 Jun 10]. Available from: <https://longactinghiv.org/content/tb-working-group>
69. World Health Organization. WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. *World Health Organ Doc*. 2012; WHO/HTM/TB: 1–34.
70. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. 2017. [cited 2019 May 14]. Available from: <https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/>
71. Manabe YC, Breen R, Perti T, Girardi E, Sterling TR. Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. *J Infect Dis*. 2009;199:437–44.
72. Lapadula G, Soria A, Bandera A, Squillace N, Sabbatini F, Franzetti F, et al. Unmasking tuberculosis in the era of antiretroviral treatment. *Eur Respir J*. 2012;39:1064–75.
73. Grimsrud A, Barnabas RV, Ehrenkrantz P, Ford N. Evidence for scale up: The differentiated care research agenda. *J Int AIDS Soc*. 2017;20:1–6.
74. Society IA. Differentiated care for HIV. A decision framework for antiretroviral therapy delivery. 2016. [cited 2019 Jul 23]. Available from: https://www.differentiatedcare.org/Portals/0/adam/Content/yS6M-GKB5EWs_uTBHk1C1Q/File/Decision%20Framework.pdf
75. Grimsrud A, Bygrave H, Doherty M, Ehrenkrantz P, Ellman T, Ferris R, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. *J Int AIDS Soc*. 2016;19:21484.
76. International Aids Society. Key consideration for differentiated antiretroviral therapy delivery for specific populations: children, adolescents, pregnant and breastfeeding women and key populations. 2017. [cited 2019 Jul 15]. Available from: <https://tz.usembassy.gov/wp-content/uploads/sites/258/2017/08/WHO-HIV-2017.34-eng.pdf>
77. UNAIDS. Miles to go. 2018. [cited 2019 Jun 14]. Available from: <https://www.unaids.org/en/resources/documents/2018/2018-global-aids-update-slides-part1>
78. Decroo T, Koole O, Remartinez D, dos Santos N, Dezebros S, Jofrisse M, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. *Trop Med Int Heal*. 2014;19:514–21.
79. Wilkinson L, Harley B, Sharp J, Solomon S, Jacobs S, Cragg C, et al. Expansion of the adherence club model for stable antiretroviral therapy patients in the Cape Metro, South Africa 2011–2015. *Trop Med Int Health*. 2016;21:743–749.
80. Cawley C, Nicholas S, Szumilin E. Six-monthly appointments as a strategy for stable antiretroviral therapy patients: evidence of its effectiveness from seven years of experience in a Medecins Sans Frontieres supported programme in Chiradzulu district. 2016. [cited 2019 May 15]. Available from: <http://programme.aids2016.org/Abstract/Abstract/3104>
81. Adjetei V, Obiri-Yeboah D, Dornoo B. Differentiated service delivery: a qualitative study of people living with HIV and accessing care in a tertiary facility in Ghana. *BMC Health Serv Res*. 2019;19:95.
82. Pathmanathan I, Pasipamire M, Pals S, Dokubo EK, Preko P, Ao T, et al. High uptake of antiretroviral therapy among HIV-positive TB patients receiving co-located services in Swaziland. *PLoS ONE*. 2018;13:1–11.
83. World Health Organization (WHO). Creating a demand for service. In: Developing and improving national toll-free tobacco quit-lines services. 2011. [cited 2019 May 7]. Available from: https://www.who.int/tobacco/publications/smoking_cessation/quit_lines_services/en/
84. Gold E. Creating demand for VMMC: a training for community mobilizers. [cited 2019 May 7]. Available from: https://www.malecircumcision.org/sites/default/files/document_library/VMMC-FacilitatorsGuide_commun_mobilisation.pdf
85. PEPFAR. Voluntary medical male circumcision demand creation toolkit | Clearinghouse on male circumcision. [cited 2019 Apr 8]. Available from: <https://www.malecircumcision.org/resource/voluntary-medical-male-circumcision-demand-creation-toolkit>
86. Landmark deal secures significant discount on price of medicine to prevent TB – the global fund to fight AIDS, tuberculosis and malaria. [cited 2019 Nov 12]. Available from: <https://www.theglobalfund.org/en/news/2019-10-31-landmark-deal-secures-significant-discount-on-price-of-medicine-to-prevent-tb/>
87. IMPAAct4TB - IMPAAct4TB. [cited 2019 Jun 10]. Available from: <https://www.impaact4tb.org/>