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ID LEARNING UNITS FOR NON-ID SPECIALISTS

Infectious Diseases Learning Unit: Understanding Advances in the Treatment of Latent Tuberculosis Infection Among People With Human Immunodeficiency Virus

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Tuberculosis (TB) remains the leading cause of death among people with human immunodeficiency virus (PWH). The diagnosis of latent TB infection (LTBI) and treatment with TB preventative therapy (TPT) can reduce morbidity and mortality in this population. Historically, isoniazid has been recommended for TPT in PWH due to the absence of drug-drug interactions with most antiretroviral therapy (ART). However, newer rifamycin-based regimens are safer, shorter in duration, associated with improved adherence, and may be as or more effective than isoniazid TPT. Current guidelines have significant heterogeneity in their recommendations for TPT regimens and acceptability of drug interactions with modern ART. In this Infectious Diseases learning unit, we review common questions on diagnosis, treatment, and drug interactions related to the management of LTBI among PWH.

Keywords. HIV; latent tuberculosis infection; rifamycin.

CLINICAL CASE

A 48-year-old woman with schizophrenia and a 12-year history of human immunodeficiency virus (HIV) had been staying at a homeless shelter in San Francisco where an acquaintance was diagnosed with active pulmonary tuberculosis (TB). Her most recent CD4 cell count was 90 cells/mm and HIV ribonucleic acid (RNA) viral load was 525 000 copies/mL. Although she had difficulty adhering to antiretroviral treatment (ART) while experiencing homelessness, she recently acquired permanent supportive housing and reinitiated ART with the single-tablet regimen of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) 1 month ago. She had been started on a long-acting injectable antipsychotic medication at the same time, which significantly improved symptoms of schizophrenia. She subsequently reported taking ART with near-perfect adherence, in part due to observed doses by a case manager at least once weekly. In light of the recent TB outbreak in her former shelter residence, a QuantiFERON-TB Gold Plus was obtained through routine contact tracing investigations, and her test returned positive. She had no cough, fever, weight loss, or night sweats and a chest x-ray was unremarkable.

WHAT IS LATENT TUBERCULOSIS INFECTION AND WHY SHOULD IT BE EVALUATED IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS?

The transmission of *Mycobacterium tuberculosis* initially leads to latent tuberculosis infection (LTBI) in most individuals, defined "as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB" [1]. Practically, LTBI is defined as tuberculin skin test (TST) or interferon-gamma release assay (IGRA) reactivity in the absence of clinical and radiographic findings of active TB [2]. Replication and metabolism of the bacilli during this time are thought to be limited [3], and individuals are neither ill nor infectious at this stage. However, they are at risk for progressing to active TB disease, which carries a significant risk of morbidity and mortality [4, 5]. The "lifetime risk" of developing active TB is approximately 5%–10% for immune-competent persons after initial infection [6]. However, for people with HIV (PWH), the "annual risk" is ~10% without ART [7] and increases as the CD4 cell count declines [8–12].

HOW FREQUENTLY SHOULD PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION?

Guidelines from the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA)/Centers for Disease Control and Prevention (CDC), the US Department of Health and Human Services (DHHS), and the European AIDS Clinical Society (EACS) recommend that all PWH be tested for TB infection at the time of HIVdiagnosis, regardless of epidemiologic risk of TB exposure [13–15]. Because the accuracy of both TST and IGRA are limited by a host patient's immune function, people with advanced HIV infection (CD4 <200 cells/mm^3) who have a negative diagnostic test and no TB exposure history should be retested for LTBI once they are started

Received 25 March 2021; editorial decision 6 June 2021; accepted 15 June 2021.

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Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab319

on ART and attain a CD4 count ≥200 cells/mm^3 [16, 17]. The DHHS and EACS guidelines note that annual testing for LTBI is recommended for PWH living in low-incidence settings only if they are at high risk of repeated or ongoing exposure to active TB [14, 15]—a change from prior guidelines, which had suggested that all PWH be tested annually. High risk of exposure can be interpreted broadly, however, and should consider incarceration, housing instability, substance use, travel to TB-endemic areas, and known or suspected exposures to people with pulmonary TB.

As was done for the patient in the case presentation above, additional LTBI evaluation should be undertaken after known exposures as part of contact investigations. Identifying recent transmission in the setting of known exposures could allow for more rapid and targeted management of LTBI, aiding attainment of the World Health Organization (WHO) END TB Strategy goals to reduce the mortality and incidence of TB by 95% and 90%, respectively, by 2035 [18]. Moreover, timely identification of a recent transmission event could allow for targeted case-finding of persons with infectious active TB disease among contacts of newly infected individuals.

HOW SHOULD LATENT TUBERCULOSIS INFECTION BE DIAGNOSED IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS?

Diagnosing LTBI in PWH begins with appropriate screening. There are currently 2 main types of assays to assess for tuberculosis infection: TST and IGRAs. Both are indirect tests that assess the immunologic reaction to mycobacterial antigens. Tuberculin skin test is less expensive and has over a century of data supporting its efficacy but requires 2 visits, one for PPD placement and another for PPD reading, and can result in false-positive results among people who have received the Bacillus Calmette-Guérin (BCG) vaccine. Interferon-gamma release assays require 1 visit, are more specific for TB, and are theoretically unaffected by prior BCG vaccination status. In the United States, IGRAs are now preferred under most circumstances in the ATS/IDSA/CDC guidelines (irrespective of HIV status), although TST is considered an acceptable alternative when an IGRA is not available, too costly, or too burdensome [13]. Guidelines from the National Tuberculosis Controller's Association (NTCA)/CDC [19], DHHS [14, 20], and EACS [15] do not indicate a preference of which test to use among PWH, noting that "there have been no published definitive comparisons of the TST and IGRAs for screening persons with HIV in low-burden settings" [14].

More importantly, neither TST nor IGRAs distinguish latent TB from active TB, and a negative test does not rule out the presence of active TB. After a positive IGRA or TST result, a diagnosis of LTBI must ultimately be determined by excluding a diagnosis of active TB through clinical assessment, including symptom screening, performance of chest radiography, and, if either is abnormal, further microbiological testing [13].

WHAT IS THE BENEFIT OF TREATING LATENT TUBERCULOSIS INFECTION AMONG PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS? WHO SHOULD BE TREATED?

In low TB-incidence settings such as the United States, data regarding the treatment of LTBI specifically among PWH is limited. However, there are longstanding data on the benefits of TPT in the general population in the United States [21], and data from higher incidence settings have convincingly demonstrated that treating LTBI reduces mortality in PWH [22–24]. Although ART has led to a decrease in the incidence of TB disease among PWH [22], the risk continues to be greater among PWH than in the general population [23]. Even when ART is initiated immediately after a new HIV diagnosis, TB has remained among the most common opportunistic infections (OIs), underscoring the importance of LTBI treatment [23, 24]. Furthermore, the TEMPRANO study, in which PWH were randomized in a factorial design to early versus delayed ART either with or without isoniazid (INH) preventive therapy (IPT), demonstrated that IPT decreased the risk of death by 37% at 78 months after enrollment, independent of ART status [25].

The DHHS OI guidelines recommend that, once active TB disease has been excluded, PWH with a positive test for TB infection should be treated for LTBI unless there is documentation of prior treatment for active TB or LTBI [14]. In addition, recognizing the suboptimal sensitivity of available assays, some individuals who have had recent close contact with a person with infectious TB and high risk of infection should be considered for LTBI treatment (ie, "window prophylaxis") regardless of their initial TB screening test to prevent early progression under the presumption of possible latent TB infection [14, 15]. Alternatively, testing for LTBI can be repeated several weeks after the "window period," particularly if there are notable drug-drug interactions that make empiric treatment challenging.

WHAT ARE THE CURRENT OPTIONS FOR TREATING LATENT TUBERCULOSIS INFECTION IN THE GENERAL POPULATION?

Recently, most clinical practice guidelines have been updated to prioritize emerging new LTBI treatment regimens. In the general population, medications used to treat LTBI include isoniazid (INH or H), rifapentine (RPT or P), and rifampin (RIF or R)—which can be used individually or in combination (Supplemental Table 1). Specific treatment options included in all guidelines include 4 months of daily RIF (4R), 3 months of daily INH + RIF (3HR), 3 months of weekly INH + RPT (3HP), or 6 or 9 months of daily INH (6H or 9H). The relative preference of these regimens differs between updated NTCA/CDC Guidelines for the treatment of LTBI (2020) [19] and WHO TB prevention guidelines [1] (Table 1).

Table 1. Summary of Latent Tuberculosis Infection Treatment Guidelines in the General Population

Guidelines (Publication Date)	3HP	1HP	4R	3HR	9H	6H
NTCA/CDC (February 2020) [19]	Preferred	No specific recommendation made	Preferred	Preferred	Alternative	Alternative
WHO TB Preventative Therapy (2020) [1]	Preferred	Alternative	Alternative	Preferred	Preferred	Preferred

Abbreviations: CDC, Centers for Disease Control and Prevention; NTCA, National Tuberculosis Controller's Association; TB, tuberculosis; WHO, World Health Organization; 6H, 6 months of daily isoniazid (INH); 9H, 9 months of daily INH; 1HP, 1 month of daily INH + rifapentine (RPT); 3HP, 3 months of weekly INH + RPT; 3HR, 3 months of daily INH + rifampin (RIF); 4R, 4 months of daily RIF.

In the WHO guidelines, 1 month of daily INH + RPT (1HP) is also recommended as an alternative under some circumstances [1]. Drug-drug interactions between the various TPT regimens, especially those containing rifamycins (RIF or RPT), and ART make regimen selection in PWH substantially more complex (Table 2, Figures 1 and 2).

WHAT MEDICATION OPTIONS HAVE BEEN STUDIED FOR LATENT TUBERCULOSIS INFECTION TREATMENT AMONG PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS?

Six or Nine Months of Daily Isoniazid

Historically, INH monotherapy regimens for LTBI have been the most widely used for PWH. This is attributable to INH's status as an efficacious, generally well tolerated drug with minimal interactions with modern ART regimens. A systematic review including 10 trials comparing INH to placebo among PWH demonstrated a 35% risk reduction of active TB in all patients, with pooled relative risk reduction of 52% among patients who were TST positive [26]. More recently, follow-up data from the TEMPRANO study demonstrated an independent mortality benefit of INH in preventing death among PWH taking ART [25]. However, the efficacy of INH monotherapy regimens is significantly diminished by high noncompletion rates—reported to range between 47% and 53% for 9-month [27–29] and 45% and 63% for 6-month INH regimens [27, 30] in US TB programs. Completion rates in non-US settings have also varied considerably, ranging from between 63% and 90% for 9H in large, multinational clinical trials [31, 35, 41].

Four Months of Daily Rifampin

In 2018, results were published from a multinational randomized control trial (RCT) of 6063 patients comparing 4R with 9H for the treatment of LTBI [31]. The authors demonstrated 4R to have improved completion rates (78.8% vs 63.2%), decreased adverse events within 146 days of follow up (1.5% vs 2.6%), and noninferior efficacy (0.10 vs 0.11 TB cases per 100 person-years) compared with 9H [31]. Patients were followed for 28 months postrandomization. Although only 255 patients included in the study were PWH [31], most guidelines have included 4R as a treatment option among PWH. As discussed further below, some guidelines further suggest that rifabutin

Table 2. Summary of Latent Tuberculosis Infection Treatment Guidelines for People With HIV

Guidelines (Publication Date)	3HP	1HP	4R[a]	3HR[a]	9H	6H
NTCA/CDC (February 2020) [19]	Preferred ("as drug interactions allow")	No specific recommendation made	"No evidence is available" in PWH	Preferred ("as drug interactions allow")	Alternative	Alternative
DHHS HIV Adult ART (December 2019) [20]	Preferred (only for patients on RAL- or EFV-based regimens)	No specific recommendation made	Preferred ("pay careful attention to potential DDIs with specific ARV drugs")	No specific recommendation made	Preferred	Preferred
DHHS OI (September 2019) [14]	Alternative (only for patients on RAL- or EFV-based regimens)	No specific recommendation made	Alternative	No specific recommendation made	Preferred	No specific recommendation made
WHO TB Preventative Therapy (2020) [1]	Preferred	Alternative	Alternative	Preferred	Preferred	Preferred
EACS (2020) [15]	Listed option, but RPT not yet approved by EMA	Listed option, but RPT not yet approved by EMA	Preferred ("check interactions with ARVs")	Preferred ("check interactions with ARVs")	Preferred ("consider in high-prevalent TB countries")	Preferred

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; CDC, Centers for Disease Control and Prevention; DHHS, US Department of Health and Human Services; EACS, European AIDS Clinical Society; EMA, European Medicines Agency; EFV, efavirenz; HIV, human immunodeficiency virus; NTCA, National Tuberculosis Controller's Association; OI, opportunist infection; PWH, people with HIV; RAL, raltegravir; TB, tuberculosis; WHO, World Health Organization; 6H, 6 months of daily isoniazid (INH); 9H, 9 months of daily INH; 1HP, 1 month of daily INH + rifapentine (RPT); 3HP, 3 months of weekly INH + RPT; 3HR, 3 months of daily INH + rifampin (RIF); 4R, 4 months of daily RIF.

[a]The NTCA/CDC, DHHS HIV Adult ART, and EACS guidelines note that RIF may be replaced by rifabutin to accommodate potential drug-drug interactions, and pharmacokinetic studies suggest that this may be reasonable. However, there are no formal guideline-based recommendations for the 4Rbt or 3HRbt regimens due to a lack of data on clinical efficacy.

Key: All DDIs Acceptable | Minor interaction or dose adjustment | Guideline discordance; See footnotes | Contraindicated due to one or more DDI

ARV Regimen	4R	3HR	3HP	1HP	*4RBT*[B]	*3HRBT*[B]
TAF/FTC/BIC	• RIF may ↓ TAF[C] • RIF decreases BIC AUC ↓ 75% and should not be co-administered		• RIF may ↓ TAF[D] • RPT may significantly ↓ BIC and should not be co-administered		• RBT may ↓ TAF[D] • RBT decreases BIC AUC ↓ 38% and C_{min} ↓ 56%, and should not be co-administered	
TAF/FTC+DTG	• RIF may ↓ TAF[C] but intracellular TFV-DP are still higher than achieved with TDF • DTG BID with RIF has ↓ AUC than DTG BID without RIF. **Alternative should be used if DTG associated resistant mutations are present** • DTG BID AUC ↑ 33% and C_{min} ↑ 22%, compared to DTG QD (without RIF). **Use DTG 50 mg BID**		• Weekly RPT may ↓ TAF, but magnitude may be less than that of daily RIF[D] • Weekly RPT ↓ DTG AUC by 26%, but may be considered in adherent, suppressed patients[E]	• Daily RPT may ↓ TAF likely to similar degree as RIF[D] • DTG AUC and C_{min} decrease by 46% and 74%, respectively. Do not co-administer.	• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • RBT: ↔ DTG AUC and C_{min} ↓ 30%. No dose adjustment recommended	
TDF/FTC+DTG **ABC/3TC/DTG** **DTG+3TC**	• DTG BID with RIF has ↓ AUC than DTG BID without RIF. **Alternative should be used if DTG-associated resistant mutations are present** • DTG BID AUC 33% and C_{min} ↑ 22% with RIF compared to DTG QD (without RIF). Geometric means similar with BID DTG and RIF, compared to DTG QD. **Use DTG 50 mg BID**		• Weekly RPT ↓ DTG AUC by 26%, but some evidence for use in adherent, suppressed patients[E]	• Limited data with daily RPT & DTG[F] • DTG AUC and C_{min} decreased by 46% and 74%, respectively. Do not co-administer	RBT: ↔ DTG AUC and C_{min} ↓ 30%. No dose adjustment recommended	

Figure 1. Summary of data and guidelines regarding short-course latent tuberculosis infection treatments and preferred initial antiretroviral (ARV) regimens for most patients. ([A]) Isoniazid regimens are not shown. There are no drug-interactions with ARVs that preclude usage of isoniazid, although additive liver toxicity should be assessed with some ARVs. ([B]) The National Tuberculosis Controller's Association (NTCA)/Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services (DHHS) HIV Adult ART, and European AIDS Clinical Society (EACS) guidelines suggest that rifabutin (RBT) can be used in place of rifampin (RIF) [15, 19, 20], but there are no efficacy data to support this, and the use of RBT should be limited to scenarios in which there are no alternatives. ([C]) No interaction is expected between tenofovir disoproxil fumarate (TDF) and RIF, and TDF can be considered as a replacement for tenofovir alafenamide (TAF). Rifampin decreased plasma TAF area under the curve (AUC) by 55% and intracellular tenofovir-diphosphate (TFV-DP) concentrations by 36%; however, intracellular TFV-DP concentrations during RIF/TAF coadministration were more than 4 times greater than those achieved by TDF alone [51]. The DHHS guidelines indicate "do not coadminister, unless benefits outweigh risks" [14]. The EACS guidelines suggest "administer TAF BID" [15]. The World Health Organization (WHO) TB preventive treatment guidelines indicate "contraindicated" [1]. The University of Liverpool drug interaction checker suggests "coadministration is not recommended. If coadministration required, use TAF 25 mg twice daily" [61]. ([D]) Data on the coadministration of weekly RPT (in 3HP), daily RPT (in 1HP), and RBT with TAF are limited, but emerging data suggest these combinations may be considered. Based on the RIF drug-drug interaction study, intracellular TFV-DP is still adequate with RIF/TAF coadministration [51]; and the interaction with TAF is greatest for RIF and daily RPT compared with other rifamycins (RIF~daily RPT > weekly RPT > RBT). The DHHS OI guidelines indicate "do not coadminister" for TAF with RBT or RPT [14]. The EACS guidelines indicate, "consider administration of TAF BID" for RBT and do not comment on RPT [15]. The WHO indicates all rifamycins with TAF are "contraindicated" [1]. The University of Liverpool drug interaction checker suggests "coadministration is not recommended. If coadministration required, use TAF 25 mg twice daily" for all rifamycins [61]. ([E]) In the DOLPHIN study, DTG AUC decreased by 26% and C_{min} by 47% with weekly RPT coadministration, but all patients maintained an undetectable viral load with 59 of 60 of patients with troughs above the 90% MIC [56]. The WHO guidelines suggest DTG may be used with 3HP based on this study [1]. DHHS HIV Adult ART guidelines indicate, "do not coadminister" with RPT [20]. The EACS guidelines do not comment on RPT regimens [15]. The University of Liverpool interaction checker suggests that "coadministration may decrease DTG… magnitude is predicted to be lower than with rifampicin" [61]. ([F]) TheWHO guidelines suggest DTG may be used with 1HP [1], but there are no clinical trial data to support this. ([G]) Daily RPT is expected to reduce RAL C_{min} 41% [40]. Whether this interaction can be overcome by increased dosing is uncertain and the optimal dosing strategy with daily RPT is unknown [61]. The WHO guidelines suggest RAL may be used with 1HP [1], but DHHS guidelines advise against daily RPT with RAL [14].

Key: All DDIs Acceptable | Minor interaction or dose adjustment | Guideline discordance; See footnotes | Contraindicated due to one or more DDI

ART Regimen	4R	3HR	3HP	1HP	*4RBT*[B]	*3HRBT*[B]
TAF[1]/FTC+RAL	• RIF may ↓ TAF, but intracellular TFV-DP are still higher than achieved with TDF[C] • RIF/RAL 400 mg BID, AUC ↓ 40%; RAL 800 mg BID w RIF AUC ↑ 27% and C_{min} ↓ 53%. **Use RAL 800 mg BID; do not use RAL 1200 mg QD**		• Weekly RPT may ↓ TAF, but magnitude may be less than that of daily RIF[D] • RPT once weekly: RAL AUC ↑ 71% and C_{min} ↓ 2%. No dose adjustment	• RPT may ↓ TAF • RPT daily: RAL C_{min} ↓ 41%; do not coadminister[G]	• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • RBT: RAL AUC ↑ 19% and C_{min} ↓ 20%. No dose adjustment needed	
TDF/FTC+RAL			• RPT once weekly: RAL AUC ↑ 71%; **USE RAL 400 mg BID**	• RPT once daily: RAL C_{min} ↓ 41%; do not coadminister[G]	• RBT: RAL AUC ↑ 19% and C_{min} ↓ 20%. No dose adjustment needed	
TAF[1]/FTC/EVG/c **TDF/FTC/EVG/c**	• RIF may ↓ TAF, but intracellular TFV-DP are still higher than achieved with TDF[C] • RIF may significantly ↓ EVG and cobi contra-indicated		• Weekly RPT may ↓ TAF, but magnitude may be less than that of daily RIF[D] • RPT may significantly ↓ EVG; contraindicated		• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • RBT metabolite ↑ 625%, EVG C_{min} 67%. Do not coadminister	
TDF/FTC/EFV	• EFV AUC ↓ 26%. **Do not use EFV 400 mg qd with RIF.** Use EFV 600 mg qd monitor virologic response.		• No impact on EFV. No dose adjustment needed.		• RBT AUC ↓ 38%. The recommended dosing range is RBT 450–600 mg per day	
TAF[1]/FTC/RPV	• RIF may ↓ TAF, but intracellular TFV-DP are still higher than achieved with TDF[C]		• Weekly RPT may ↓ TAF, but magnitude may be less than that of daily RIF[D] • Significant ↓ in DOR and RPV concentration expected; contra-indicated		• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • **Increase RPV to 50 mg once daily**	
TDF/FTC/RPV	• RPV AUC ↓ 80%; contra-indicated				• **Increase RPV to 50 mg once daily**	
TAF[1]/FTC+DOR	• **DOR AUC** ↓ 88%; contra-indicated				• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • DOR AUC ↓ 50%. **Increase DOR to 100 mg BID**	
TDF/FTC+DOR					• DOR AUC ↓ 50%. **Increase DOR to 100 mg BID**	
TDF[1]/FTC+DRV/c **TDF/FTC+DRV/c**	• RIF may ↓ TAF, but intracellular TFV-DP are still higher than achieved with TDF[C] • PI concentration ↓ >75%. Do not coadminister		• Weekly RPT may ↓ TAF, but magnitude may be less than that of daily RIF[D] • PI concentration decreased. Do not coadminister		• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • RBT concentration ↑ and cobi concentration ↓ Do not coadminister	
TDF[1]/FTC+DRV/r					• RBT may ↓ TAF but magnitude expected to be less than that of daily RIF[D] • RBT concentration ↑. Change to 150 mg qd and check drug levels. Higher RBT toxicity possible	
TDF/FTC+DRV/r					• RBT concentration ↑. Change to 150 mg qd and check drug levels. Higher RBT toxicity possible	
DTG/RPV	• RPV AUC ↓ 80%; contra-indicated • DTG BID with RIF has ↓ AUC than DTG BID without RIF		• ↓ RPV expected; contra-indicated • Weekly RPT ↓ DTG AUC by 26%, but may be considered if adherent and suppressed[E]	• ↓ RPV expected; contraindicated • Daily RPT may ↓ DTG significantly; do not coadminister	• **Increase RPV to 50 mg once daily** • RBT: ↔ DTG AUC and C_{min} ↓ 30%. No dose adjustment recommended	
CAB/RPV	• RPV AUC ↓ 80%; contra-indicated • RIF decreases CAB AUC 59%; contra-indicated		• ↓ RPV expected; contra-indicated • Significant ↓ CAB expected. Do not coadminister	• ↓ RPV expected; contra-indicated • Significant ↓ CAB expected. Do not coadminister	• **Increase RPV to 50 mg once daily** • RBT decreases CAB AUC 21%, but inability to adjust IM CAB fixed dose. At this time coadministration not recommended	

Figure 2. Summary of data and guidelines regarding short-course latent tuberculosis infection treatment and alternative antiretroviral (ARV) regimens. ([A]) Isoniazid regimens are not shown. There are no drug-interactions with ARVs that preclude usage of isoniazid, although additive liver toxicity should be assessed with some ARVs. ([B]) The National Tuberculosis Controller's Association (NTCA)/Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services (DHHS) HIV Adult ART, and European AIDS Clinical Society (EACS) guidelines suggest that rifabutin (RBT) can be used in place of rifampin (RIF) [15, 19, 20], but there are no efficacy data to support this, and the use of RBT should be limited to scenarios in which there are no alternatives. ([C]) No interaction is expected between tenofovir disoproxil fumarate (TDF) and RIF, and TDF can be considered as a replacement for tenofovir alafenamide (TAF). Rifampin decreased plasma TAF area under the curve (AUC) by 55% and intracellular tenofovir-diphosphate (TFV-DP) concentrations by 36%; however, intracellular TFV-DP concentrations during RIF/TAF coadministration were more than 4 times greater than

(RBT) can be used in place of rifampin due to drug-drug interactions [15, 19, 20]. However, the effectiveness of rifabutin in preventing TB disease has not been studied in PWH or the general population; therefore, our practice has been to consider 4 months of RBT only in circumstances when no other latent TB treatment regimen is possible due to drug interactions or toxicity concerns.

Three Months of Daily Isoniazid and Rifampin

A meta-analysis of 5 RCTs in adults found that 3HR and standard therapy of 6–12 months of daily INH monotherapy were equivalent in regard to efficacy, severe side effects, and mortality [32], and this regimen is included as preferred for the general population in some guidelines (Table 1). Among PWH, data are more limited. However, in an RCT of 2736 PWH not on ART that compared 3HR with 6H, no difference was found in the incidence of TB disease among people who were TST positive after a mean of 15 months of follow-up posttreatment initiation [33, 34]. In this study, although 6H conferred short-term protection against TB disease, the benefit was lost within the first year of treatment, whereas 3HR provided sustained protection for up to 3 years [34]. Whether RBT substituted for RIF as part of a 3-month regimen with INH is effective for the treatment of LTBI is unknown; therefore, as with 4 months of RBT monotherapy, we would consider 3 months of INH plus RBT only if other options are not feasible or available.

Three Months of Weekly Isoniazid and Rifapentine

In the PREVENT-TB trial, in which 3HP was compared with 9H for the treatment of LTBI, 3HP was found to be better tolerated and as safe as INH monotherapy [35]. Over the course of 33 months of follow-up postenrollment, cumulative rates of TB disease were 0.19% vs 0.43% in the 3HP and 9H arms, respectively, establishing the noninferiority of 3HP, and treatment completion was significantly greater with 3HP than 9H (82.1% vs 69.0%) [35]. Although 3HP was given as directly observed therapy (DOT) in PREVENT-TB [35], self-administered therapy (SAT) has been found to be noninferior to DOT among study participants in the United States [36]. Consequently, current DHHS guidelines suggest that the decision of whether to give 3HP by DOT or SAT should be based on local practice and individual patient attributes [19].

A subgroup analysis of PREVENT-TB that focused specifically on PWH [37], in addition to a second large RCT among PWH [38], have further suggested that 3HP is as effective as and is better tolerated than INH monotherapy for LTBI treatment in patients with CD4 counts >350 (as per study enrollment criteria). In the PREVENT-TB subgroup analysis, the incidence of active TB disease among PWH was 0.39 per 100 person-years in the 3HP arm and 1.25 per 100 person-years in the 9H arm [37]. In a separate RCT comparing 3HP with 6H among PWH, incidence of active TB or death was similar in both groups (3.1 per 100 person-years vs 3.6 per 100 person-years, $P > .05$) after a median of 4 years of follow up [38]. Although these studies were conducted among PWH not on ART, subsequent pharmacokinetic (PK) studies of weekly RPT with efavirenz (EFV) and raltegravir (RAL) have demonstrated favorable results [39, 40].

One Month of Daily Isoniazid and Rifapentine

The BRIEF-TB trial (ACTG 5279) compared 1HP with 9H in PWH on EFV- or nevirapine (NVP)-based regimens living in high-TB burden settings [41]. A total of 3000 patients were enrolled and, at a median of 3.3 years follow up, 1HP was found to be safe and noninferior to 9H in regard to efficacy, in addition to having a higher completion rate (97% vs 90%, $P < .001$) [41]. However, only 21% of the study population in BRIEF-TB were tested for LTBI by TST or IGRA and had a positive result, and the 1HP regimen has not been evaluated in low-TB prevalence settings [41]. Consequently, there is heterogeneity across clinical practice guidelines in recommendations of whether 1HP is an acceptable regimen for treatment of LTBI (Tables 1 and 2).

WHAT DO CURRENT GUIDELINES RECOMMEND FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION AMONG PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS?

Among PWH, guideline-recommended options for LTBI treatment are more limited than in the general population and, in some cases, discrepant (Table 2). This is in part due to a lack

those achieved by TDF alone [51]. The DHHS guidelines indicate "do not coadminister, unless benefits outweigh risks" [14]. The EACS guidelines suggest "administer TAF BID" [15]. The World Health Organization (WHO) TB preventive treatment guidelines indicate "contraindicated" [1]. The University of Liverpool drug interaction checker suggests "coadministration is not recommended. If coadministration required, use TAF 25 mg twice daily" [61]. ([D]) Data on the coadministration of weekly RPT (in 3HP), daily RPT (in 1HP), and RBT with TAF are limited, but emerging data suggest these combinations may be considered. Based on the RIF drug-drug interaction study, intracellular TFV-DP is still adequate with RIF/TAF coadministration [51]; and the interaction with TAF is greatest for RIF and daily RPT compared with other rifamycins (RIF~daily RPT > weekly RPT > RBT). The DHHS OI guidelines indicate "do not coadminister" for TAF with RBT or RPT [14]. The EACS guidelines indicate, "consider administration of TAF BID" for RBT and do not comment on RPT [15]. The WHO indicates all rifamycins with TAF are "contraindicated" [1]. The University of Liverpool drug interaction checker suggests "coadministration is not recommended. If coadministration required, use TAF 25 mg twice daily" for all rifamycins [61]. ([E]) In the DOLPHIN study, DTG AUC decreased by 26% and C_{min} by 47% with weekly RPT coadministration, but all patients maintained an undetectable viral load with 59 of 60 of patients with troughs above the 90% MIC [56]. The WHO guidelines suggest DTG may be used with 3HP based on this study [1]. DHHS HIV Adult ART guidelines indicate, "do not coadminister" with RPT [20]. The EACS guidelines do not comment on RPT regimens [15]. The University of Liverpool interaction checker suggests that "coadministration may decrease DTG… magnitude is predicted to be lower than with rifampicin" [61]. ([F]) TheWHO guidelines suggest DTG may be used with 1HP [1], but there are no clinical trial data to support this. ([G]) Daily RPT is expected to reduce RAL C_{min} 41% [40]. Whether this interaction can be overcome by increased dosing is uncertain and the optimal dosing strategy with daily RPT is unknown [61]. The WHO guidelines suggest RAL may be used with 1HP [1], but DHHS guidelines advise against daily RPT with RAL [14].

of substantial data regarding the use of rifamycin-containing TPT regimens among PWH and differences in the assessment by guideline groups of the significance of ART-TPT drug interactions.

Overall, 9H has subsisted as a preferred or alternative regimen in all official guidelines, and 6H in all with the exception of one (Table 2). In the DHHS OI guidelines, 9H is the preferred treatment option for PWH given the abundance of evidence demonstrating its efficacy in PWH, with 3HP recommended as a favored alternative, acknowledging that "the majority of patients do not complete all 9 months of therapy" [14, 28] and that "patients are more likely to complete shorter regimens" [42–44].

By contrast, the NTCA/CDC and WHO guidelines give preference to the short-course, rifamycin-based regimens in the general population "on the basis of effectiveness, safety, and high treatment completion rates" [19] (Table 1). This preference is largely maintained for PWH (Table 2); however, the guidelines acknowledge many drug interactions between ART and rifamycins [45, 46].

Each set of guidelines also maintains some unique recommendations (Table 2). For example, the NTCA/CDC guidelines do not recommend 4R for PWH, citing minimal data available for the use of 4R in this patient population [19]; the DHHS guidelines do not mention 3HR as an option [14, 20]; in addition, although the EACS guidelines list 3HP as an option, they note that RPT is not yet approved by the European Medicines Agency and thus not available [15]. The NTCA/CDC, DHHS, and EACS guidelines additionally suggest that RBT can be used in place of RIF in the setting of drug interactions [14, 15, 19, 20], although this is not indicated by the WHO guidelines [1], which may be in part due to lack of RBT availability in higher incidence TB settings.

An area in which the existing guidelines diverge significantly is regarding the utility of 1HP in treating LTBI among PWH (Table 2). One month of daily INH + RPT is not explicitly discussed in the most recent NTCA/CDC guidelines nor the DHHS HIV Adult ART guidelines [19, 20]. Moreover, although discussed, no specific recommendations on 1HP were provided by the 2020 DHHS OI guidelines [14]. However, based on results from BRIEF-TB [41], 1HP is included as an alternative regimen by the WHO guidelines among patients with acceptable drug-drug interactions [1].

WHAT ARE THE CONSIDERATIONS FOR ANTIRETROVIRAL SELECTION AND DRUG-DRUG INTERACTIONS WITH LATENT TUBERCULOSIS INFECTION TREATMENT?

Given the dynamic landscape of LTBI treatment guidelines as well as limited data for the use of certain regimens among PWH, determining optimal LTBI treatment regimens can be complex, particularly among patients taking some of the most commonly prescribed ART regimens in the United States. We summarize the guidelines and data available to support specific combinations of LTBI treatment with preferred initial ART regimens for most patients (Figure 1) and alternative initial ART regimens (Figure 2). Specific issues to take into consideration include the following: use of RBT in Place of RIF (ie, 4Rbt or 3HRbt). Although not explicitly recommended, current NTCA/CDC, DHHS, and EACS guidelines note that RBT has fewer or less pronounced drug interactions than RIF, particularly when combined with protease inhibitors (PIs) [14, 15, 19, 20]. Coadministration of RIF dramatically reduces serum concentrations of most PIs, and data have demonstrated that twice-daily dosing of darunavir/ritonavir with RIF carries an unacceptable risk of hepatotoxicity [47]. (Doubling the dose of lopinavir/ritonavir with RIF has been somewhat more acceptable, although this also carries significant risk [48, 49].) Most global guideline bodies thus advise against the use of RIF with PIs [1, 14, 20]. The RPT-based LTBI regimens should also be avoided with PIs, because the magnitude of the effect is expected to be similar or more pronounced as that with RIF.

Given these limitations, some providers regard RBT as a reasonable substitute to RIF in the 4R regimen in such settings, when RIF is contraindicated due to drug-drug interactions and INH cannot be used, because the effects of RBT on ritonavir-boosted PI concentrations are only minimal to moderate [45, 46]. A regimen consisting of daily INH + RBT for 3 months (3HRbt) is discussed only in the EACS guidelines, which specifically note that the use of RBT is "not a WHO recommended regimen" [15]. However, it is important to note that RBT-containing treatment regimens have not been studied (in clinical trials or otherwise) and their efficacy for the treatment of LTBI is speculative. In addition, all PIs markedly increase serum concentrations of RBT, requiring special attention to RBT dosing in these settings to avoid dose-related toxicities, such as hepatitis, uveitis, and neutropenia [50]. Nonetheless, one could consider using RBT in place of RIF as preferable to no LTBI treatment in cases where LTBI treatment is urgent and there are no alternative LTBI treatment options owing to drug interactions with companion drugs or other barriers.

Interaction Between Rifamycins and Nucleotide Reverse-Transcriptase Inhibitors

Tenofovir disoproxil fumarate (TDF), 3TC, emtricitabine (FTC), ABC, and coformulations of these nucleotide reverse-transcriptase inhibitor (NRTI) agents can be used with RIF, RPT (daily and weekly), and RBT without dose adjustments. However, most modern single-tablet regimens now contain tenofovir alafenamide (TAF), which has not yet been extensively studied in combination with rifamycins, resulting in variation in clinical guidelines (Figures 1 and 2). Emerging PK data (summarized below) suggest that daily RIF, weekly RPT, and daily RBT may each be acceptable with TAF. Nonetheless, transitioning from daily TAF to daily TDF temporarily during LTBI

treatment with rifamycins may be considered a better studied alternative approach when there are no TDF contraindications.

Rifampin (4R) and Tenofovir Alafenamide

The DHHS treatment guidelines currently recommend "weighing risks and benefits" when considering combining TAF with RIF [20]. However, PK data have led some providers to believe that this combination may be safe. Specifically, studies have demonstrated that when RIF is coadministered with TAF, the TAF area under the curve (AUC) is reduced by 55%, and the level of active drug at the site of disease, namely, intracellular tenofovir-diphosphate (TFV-DP), is reduced by 36% [51]. However, these intracellular TFV-DP levels with TAF are still 4.2 times higher than those achieved by TDF administration alone without a rifamycin [51], suggesting that usage of RIF with daily TAF is acceptable.

In a separate PK study of healthy volunteers, RIF administered with twice-daily TAF (given as twice-daily BIC/TAF/FTC) resulted in similar plasma TAF and intracellular TFV-DP exposures as that after daily TAF without RIF [52]. This suggests that administering TAF twice daily with daily RIF could also be considered, and this dosing strategy is recommended in the EACS guidelines [15]. However, twice-daily TAF may be challenging to implement given limited availability of standalone TAF in some countries.

Rifapentine Weekly (3HP) and Tenofovir Alafenamide

Based on human hepatocyte studies and a trial using midazolam as a CYP3A probe drug, daily RPT has comparable or slightly stronger CYP3A4 induction properties compared with daily RIF [46, 53]; in addition, the magnitude of the interaction between TAF and rifamycins is expected to be greater for RIF and daily RPT compared with weekly RPT [45]. A recent study of bictegravir (BIC) plus TAF and FTC also showed that once-weekly RPT (without INH) did not meaningfully reduce plasma TAF concentrations or intracellular TFV-DP [54]. In light of the likelihood that, compared with daily RIF, weekly RPT is expected to cause a lower magnitude drug interaction with TAF, these preliminary PK data provide some reassurance that TAF can be given safely with 3HP without dose adjustment. Consequently, some providers are comfortable with this combination, although RPT is listed as "do not coadminister" with TAF in most guidelines (Figures 1 and 2).

Rifabutin [4Rbt, 3HRbt] and Tenofovir Alafenamide

As noted above, the use of RBT in place of RIF is speculative with regards to treatment efficacy. However, from the perspective of drug-interactions, data suggest that the CYP3A4 induction, which causes decreased TAF concentrations, is expected to be less for RBT than occurs with RIF and RPT [46]. Therefore, in clinical scenarios in which alternative regimens are not considered feasible, some providers may feel comfortable extrapolating the above data on RIF and RPT with TAF to RBT-based regimens.

Interaction Between Rifamycins and Integrase Strand Transfer Inhibitors

Historically, rifamycin-based regimens had not been used in combination with integrase strand transfer inhibitors (INSTIs) due to limited data, but guidelines have evolved over the past several years in response to studies supporting the use of several specific combinations and refuting the use of others (Figures 1 and 2). These data are summarized below.

Rifampin (4R) and Integrase Strand Transfer Inhibitors

Current guidelines suggest dosing RAL 800 mg twice daily when coadministered with RIF based on PK studies that demonstrate AUC is reduced 40% with RAL 400 mg [55]. Once-daily RAL 1200 mg with RIF has not been studied and thus not recommended. There are also data to support usage of 4R with DTG, which stem from the INSPIRING study, in which DTG was dosed twice daily to overcome potential reductions in plasma levels with daily RIF [56]. By comparison, the use of BIC with RIF is not currently advised, because BIC AUC was found to be reduced by 61% and trough by 80% in a small healthy volunteer study, even when BIC was given twice daily [57]. The use of elvitegravir/cobicistat (EVG/c) is also contraindicated because the concentrations of both of these drugs are expected to be significantly reduced with RIF, as is the case with cabotegravir (CAB).

Rifapentine (Daily [1HP] or Weekly [3HP]) and Integrase Strand Transfer Inhibitors

The DHHS OI recommendations suggest that using weekly RPT (ie, 3HP) is an acceptable regimen for LTBI treatment when given with RAL in combination with ABC/3TC or TDF/FTC [14]. This is based on PK studies demonstrating that weekly RPT did not reduce RAL concentrations [40]. In contrast, daily RPT (ie, 1HP) is expected to reduce RAL C_{min} 41% [40]. Whether this interaction can be overcome by increased dosing is uncertain, and the optimal dosing strategy of RAL with daily RPT is unknown. Although WHO guidance suggests RAL may be used with 1HP [1], DHHS guidelines advise that daily RPT should not be coadministered with RAL [14].

The DHHS treatment guidelines also list BIC, DTG, and EVC/c as "do not coadminister" with RPT [20]. However, there are emerging data on the use of DTG with weekly RPT, leading some providers to feel comfortable using 3HP with DTG under some circumstances.

In the DOLPHIN study, in which 3HP was coadministered with once daily DTG, weekly RPT decreased DTG AUC by 29% and C_{min} by 47% [58]. Weekly RPT was noted to have a time-dependent inducing effect on the DTG C_{min}, which had decreased by 23%, 64%, and 56% 1, 2, and 5–6 days after RPT-INH

dosing, respectively [58]. However, all but 1 patient had trough values that were over 90% of the minimum inhibitory concentration for DTG [56, 58]. Given that data from trials among PWH have demonstrated that 10 mg, 25 mg, and 50 mg had similar efficacy over 48 and 96 weeks in terms of virologic suppression [58] and 50 mg is the licensed dose, this PK data from DOLPHIN led the study authors to conclude that one could use 3HP without dose adjustment of DTG [58]. The WHO TPT guidelines now describe these findings [1]. Clinicians choosing to coadminister weekly RPT and DTG should consider adherence and clinical context to assess whether DOLPHIN results can be generalized to their population; participants in the DOLPHIN study were virologically suppressed before enrollment, and in this context almost all maintained suppression despite reduced DTG levels [58]. One individual did have a detectable viral load at 24 weeks, which was suppressed again with adherence counseling [58]. Thus, such PK data should only be extrapolated with caution in settings where strict adherence to the recommended regimens is expected, a benchmark upon which it is challenging to speculate in clinical practice. A follow-up study, DOLPHIN-TOO, in which ART-naive patients will start 3HP and DTG concurrently, is currently in progress [59]. There is currently no published clinical trial data examining the combination of daily rifapentine (1HP) with DTG.

At present, RPT-based regimens in combination with BIC are not considered acceptable with or without dosage adjustments. A recent study of once-weekly RPT with BIC/TAF/FTC demonstrated that BIC concentrations were reduced an average of 40%–57% depending on time of dosing [54]. A second PK study evaluating BIC/TAF/FTC use in combination with daily RPT (ie, 1HP) also demonstrated significant reductions in BIC concentrations, resulting in low-level HIV viremia during LTBI treatment [60]. However, all patients returned to full HIV viral suppression after cotreatment was completed [60]. The implications of these preliminary findings are yet to be determined and more research is needed.

CONCLUSIONS

Tuberculosis preventative therapy is a critical component of reducing TB-related morbidity and mortality among PWH. In addition to INH, several newer options for shorter course therapy for TPT are available. "Short course" regimens include a rifamycin and have been shown to be well tolerated and at least as effective as longer INH-based regimens, with improved adherence and treatment completion. Among the challenges to implementing short-course, rifamycin-based TPT in PWH are the complex drug-drug interactions, particularly with TAF and INSTIs. The availability of multiple treatment guidelines with different recommendations may further impede uptake of emerging TPT regimens. In this ID Learning Unit, we have summarized available data on effectiveness of TPT regimens, key differences in guidelines, and offer clinicians a tabular summary of acceptable ART regimens when using short-course rifamycin therapy.

Returning to the introductory clinical vignette, due to the patient's report of near-perfect adherence to a DTG-containing ART regimen, 3HP was initially considered as a potential LTBI treatment option based on results from the DOLPHIN study [58]. Three months of weekly INH + RPT was an attractive option given that the patient was already picking up medications once weekly from a case manager, who would be able to directly observe all 12 of her required doses of INH and RPT over the course of 3 months. However, after weighing the pros and cons of this approach, a decision was ultimately made to pursue a regimen of 9H. Although her recent ART adherence had been excellent, unlike patients in the DOLPHIN study, this patient did not have a suppressed viral load before LTBI treatment initiation, because treatment had only recently been restarted. Moreover, in light of a prior history of difficulty with medication adherence, there was concern that future life stressors might also thwart her ability to take ART regularly, in which case the compounded decline in her DTG blood levels while taking weekly RPT might increase her likelihood of developing INSTI resistance, a risk not believed to be worth taking under these circumstances. The patient had voiced interest in maintaining a once-daily medication regimen. This made twice-daily dosing of DTG to accommodate a RIF-containing LTBI regimen, which would have been supported by results from the INSPIRING study [56], an unacceptable option for the patient. Furthermore, although some guidelines suggest a potential role for using RBT in place of RIF in the setting of drug interactions, given the speculative nature of this practice and the availability of alternatives, consideration of RBT-based regimens was deferred.

The patient's treatment course was not without challenges, reflecting the need for close monitoring and support in the management of LTBI among PWH and other comorbidities. Her symptoms of schizophrenia, including auditory hallucinations and disorganized thought process, resurfaced 1 month into LTBI treatment due discontinuation of her long-acting antipsychotic medication, which led to brief LTBI treatment interruption. She subsequently agreed to a home-based DOT program to restart ART, INH, and a new antipsychotic medication. She subsequently had excellent medication adherence, sustained undetectable HIV RNA viral load, and is on track to complete the 9-month LTBI treatment within an acceptable and recommended duration without further treatment interruptions. The case highlights the nuanced interpretation of data and guidelines required to promote patient-centered care.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader,

the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. N. J. M. contributed to topic development and manuscript writing. S. P., P. P., and K. E. D. contributed to manuscript writing and editing. M. S. conceptualized the manuscript and oversaw writing and editing.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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