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## Treatment of drug-susceptible tuberculosis among people living with human immunodeficiency virus infection: an update

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### Abstract

**Purpose of review**—The present review describes recent advances in the treatment of drug-susceptible tuberculosis (DS-TB) among people living with human immunodeficiency virus (PLWH).

**Recent findings**—Higher than standard rifampicin doses (>10 mg/kg/day) are well tolerated and have improved sterilizing activity. Standard pyrazinamide doses may result in low drug exposures; modeling reveals that higher doses (>25 mg/kg/day) may be required to reach target levels, although safety is unknown. Four-month fluoroquinolone-containing regimens are not recommended in the 2017 World Health Organization DS-TB treatment guidelines. These guidelines also recommend fixed-dose combination (FDC) therapy over single drug formulations based on patient preference, though FDC is not associated with improved outcomes. Treatment for 6 months is recommended, with an emphasis on expanded antiretroviral therapy (ART) coverage and monitoring for relapse among those not started on ART within 8 weeks of tuberculosis treatment. Directly observed therapy (DOT) is recommended over self-administered therapy, as is daily therapy over intermittent therapy – both are associated with better tuberculosis outcomes.

**Summary**—Current WHO tuberculosis treatment guidelines recommend 6 months of daily tuberculosis treatment for PLWH who have DS-TB, and timely ART initiation. Higher rifampin and pyrazinamide doses may enhance treatment effectiveness, but safety data are needed. DOT and FDC therapy are recommended.

### Keywords

drug-susceptible; human immunodeficiency virus infection; treatment; tuberculosis

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## INTRODUCTION

The antituberculosis drugs used to treat drug-susceptible tuberculosis (DS-TB) have remained largely unchanged since the human immunodeficiency virus (HIV) epidemic began in the 1980s. The current preferred regimen includes a 2-month intensive phase of isoniazid (H), a rifamycin (rifampin [R] or rifabutin), pyrazinamide (Z), and ethambutol (E), followed by a 4-month continuation phase of H plus R or rifabutin [1,2]. Here, we review recent advances (through May 2018) in the treatment of DS-TB among people living with HIV (PLWH).

### Optimization of anti-tuberculosis drugs currently in use

One approach to advancing anti-tuberculosis therapy (ATT) includes dose-optimization of drugs in the current preferred regimen.

### High-dose rifampin

Rifampin dosing (10 mg/kg/day) was determined in the 1960s based on cost and efficacy, although the highest tolerable dose was not identified [3]. Higher rifampin doses may increase effectiveness but worsen tolerability and drug– drug interactions (DDI) with ART. Currently, efavirenz (600 mg) plus two nucleoside reverse transcriptase inhibitors (NRTIs) is the recommended ART regimen during rifamycin-based therapy for DS-TB. The preferred NRTI backbone is zidovudine (AZT) or tenofovir (TDF) with either lamivudine (3TC) or emtricitabine (FTC) [2,4,5]. Rifampin, a potent cytochrome P450 inducer, can lower serum efavirenz levels. A trial evaluating the co-administration of standard dose rifampin (10 mg/kg/day) and efavirenz (600 mg/ day) revealed a trend toward higher (not lower) efavirenz concentrations, although study participants also received isoniazid, which increases efavirenz levels [6]. Studies of the co-administration of efavirenz and higher-dose rifampin are lacking.

The RAFA trial was an open-label randomized controlled trial (RCT) among ~750 PLWH comparing early ART initiation (week 2)/standard tuberculosis treatment, delayed ART initiation (week 8)/ standard tuberculosis treatment, and delayed ART initiation (week 8)/ high-dose rifampin (15 mg/kg/ day) during the intensive phase followed by standard rifampin dosing in the continuation phase. The high-dose rifampin arm was associated with decreased 12-month mortality compared to standard rifampin dosing; there were no differences in hepatotoxicity [7].

The RIFAVIRENZ phase II RCT among ~100 PLWH compared rifampin 20 mg/kg/day with efavirenz 600 mg/day, rifampin 20 mg/kg/day with efavirenz 800 mg/day, and rifampin 10 mg/kg/day with efavirenz 600 mg/day (control). All participants also received H+Z+E and tenofovir (TDF) + lamivudine (3TC) during the 8-week study followed by standard-dose tuberculosis and HIV treatment for 16 weeks ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01986543) Identifier: NCT01986543). There was no difference in adverse events [8]. There was a trend toward lower efavirenz concentrations when co-administered with the higher rifampin dose. However, the efavirenz concentration remained therapeutic and there was no association of efavirenz concentrations

with viral load results. Higher dose rifampin was associated with an increase in week 8 culture conversion in liquid media [9<sup>■</sup>].

An additional randomized study, HIRIF, found both a dose-exposure and exposure-response of rifampin on sputum culture conversion with higher rifampin doses (10 vs. 15 vs. 20 mg/kg/day) leading to lower sputum culture counts on solid media during the first 8 weeks of therapy. However, among 180 enrolled participants, only 5 (2.8%) were HIV-positive. ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01408914) Identifier: NCT01408914) [10<sup>■</sup>].

The MAMS-TB Trial was a randomized, multiarm, and multistage adaptive trial with four experimental arms: rifampin 35 mg/kg/day, HZE; rifampin 10 mg/kg/day, HZ, SQ109; rifampin 20 mg/kg/day, HZ, SQ109 and; rifampin 10 mg/kg/day, HZ, moxifloxacin. The primary endpoint was time to culture conversion in liquid media after 12 weeks. PLWH were excluded if they were receiving ART and/or likely to require ART during study treatment. Enrollment into both SQ109-containing arms was stopped early based on preplanned interim efficacy analyses. Time to culture conversion in liquid media was shorter in the 35 mg/kg/day rifampin group compared to standard ATT, but not in the other experimental arm; there were no differences in adverse events [11<sup>■</sup>]. Together, these studies suggest that higher doses of rifampin among PLWH on efavirenzbased ART regimens may be well tolerated, and support evaluation beyond the intensive phase.

### High-dose pyrazinamide

The currently recommended weight-based pyrazinamide dose ranges from 1000 to 2000 mg/day (18 to 26 mg/kg/day) [1<sup>■</sup>,2,4,12]. Recent modeling studies utilizing clinical pharmacokinetic data support higher pyrazinamide doses. The first used data collected during pharmacokinetic substudies of Tuberculosis Trials Consortium (TBTC) Studies 27 and 28; both were phase II RCTs in which moxifloxacin was substituted for ethambutol (Study 27) or isoniazid (Study 28) during the intensive phase. PLWH were included if they were not taking or planning to start ART during the intensive phase; HIV-negative persons were also included. Simulations revealed that pyrazinamide doses of 30–80 mg/kg/day are needed to achieve therapeutic targets [13<sup>■</sup>]. The second study used data from an intensive pharmacokinetic sampling study among 61 PLWH from South Africa co-infected with tuberculosis. All patients received weight-based, fixed-dose ATT per WHO guidelines. Over half of patients weighing less than 55 kg did not achieve target pyrazinamide exposures, although the addition of 400 mg of pyrazinamide improved simulated drug exposure predictions [14<sup>■</sup>]. These modeling data support evaluating higher doses of PZA, although the safety of these higher PZA doses is unclear.

### Rifapentine

Rifapentine (P) is a rifamycin with a lower minimum inhibitory concentration and longer half-life than rifampin, allowing for higher rifamycin drug exposures, particularly when given daily. It is included in an alternative ATT regimen in the ATS/CDC/IDSA guidelines in which isoniazid and rifapentine are given weekly during the continuation phase. However, this regimen is recommended only among HIV-negative persons without cavitory disease, who are unable to receive more than once weekly DOT because of an increased risk of

acquired rifamycin resistance with the once-weekly regimen [2,15]. Daily rifapentine was well tolerated and effective during the intensive phase in TBTC Studies 29 and 29X [16,17]. PLWH were included if they were not taking or not planning to start taking ART during the intensive phase. Among 657 adults included in a pharmacokinetic/PD modeling study using data from these two studies (including 69 [11%] PLWH), rifapentine exposures were lower among PLWH although HIV-infection was not associated with time to culture conversion in liquid media. Optimal treatment efficacy and safety signals were achieved with a dose of 1200 mg daily [18]. The TBTC and ACTG are now conducting a phase III study, (TBTC Study 31/ACTG 5349), in which rifapentine (1200 mg daily) is substituted for rifampin throughout a shorter 4-month regimen. PLWH are eligible if their CD4+ count is more than 100 cells/ ml<sup>3</sup> and their current or planned ART regimen is efavirenz-based ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02410772).

### **Study of novel anti-tuberculosis regimens**

An alternative approach to advancing ATT is the study of regimens substituting traditional anti-tuberculosis drugs with novel anti-tuberculosis drugs.

### **Fluoroquinolone-containing regimens**

Fluoroquinolones have been evaluated among PLWH in clinical trials of short-course ATT [19–21]. In all trials, PLWH were eligible although the CD4+ count and ART criteria differed (Table 1). In a meta-analysis, the pooled rate of unfavorable outcomes was 5% higher (95% CI, –3 to 13) in patients with noncavitary disease treated with fluoroquinolone-containing regimens of any duration; rates of adverse events were similar [22]. The updated 2017 WHO DS-TB guidelines explicitly state that 4-month fluoroquinolone-containing regimens are not recommended, regardless of HIV status [1].

It is possible that the standard moxifloxacin dose of 400 mg daily studied was suboptimal, particularly among PLWH. This is supported by a pharmacokinetic substudy within the ongoing Improving Retreatment Success (IMPRESS) RCT being conducted among PLWH in South Africa ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02114684). The IMPRESS trial is evaluating the substitution of ethambutol with moxifloxacin throughout a 6-month regimen. In this study, moxifloxacin exposures were decreased by co-administration of efavirenz and to a lesser degree by rifampin. The ongoing TBTC Study 31/ACTG 5349 will evaluate the effect of rifapentine on moxifloxacin exposures when co-administered with efavirenz ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02410772).

### **Novel tuberculosis regimens**

There is interest in evaluating anti-tuberculosis regimens including novel drugs to which there is little or no drug resistance in the treatment of DS-TB. There are currently several novel tuberculosis regimens currently in or about to enter phase II or III clinical trials including PLWH (Table 2).

### **Other WHO DS-TB treatment guidelines updates**

The 2017 WHO guidelines for the treatment of DS-TB included additional important new guidelines as summarized below [1].

### Fixed-dose combinations

The use of fixed-dose combinations (FDC) is recommended by the WHO over separate drug formulations as a conditional recommendation with low certainty in the evidence [1■■■]. This recommendation comes despite the fact that most evidence favors separate drug formulations. A Cochrane review found no differences in tuberculosis treatment failure, death, smear, or culture conversion at the end of tuberculosis treatment, serious adverse events, or adverse events resulting in drug discontinuation between FDC and single-drug formulations, although it did find a trend toward increased tuberculosis relapse with FDC (RR 1.28; 95% CI, 1.00–1.64) [23]. A separate meta-analysis found a trend toward a higher tuberculosis treatment failure or relapse with FDC (RR 1.28; 95% CI, 0.99–1.7) [24]. The WHO Guideline Development Group noted that it considered patient satisfaction to be the most important factor in their recommendation, although only one of two trials that assessed patient satisfaction and no trials that assessed patient adherence favored the use of FDC [24]. The WHO noted that the reduced pill burden may particularly benefit populations with a high prevalence of comorbidities, such as PLWH. However, attention was drawn to the lack of data on bioavailability of FDC compared to single-drug formulations [1■■■].

### Intermittency of dosing

WHO recommends daily dosing of ATT in both the intensive and continuation phases as a conditional recommendation with very low certainty in the evidence [1■■■]. An updated systematic review and meta-analysis revealed that the risk of relapse, acquired drug resistance (ADR), and tuberculosis treatment failure were higher with the use of thrice-weekly dosing throughout therapy when compared with daily therapy throughout [25■]. Thrice-weekly dosing during the intensive phase was associated with treatment failure and relapse, but not with ADR when compared with daily therapy throughout. During the continuation phase, twice-weekly dosing was associated with increased relapse, ADR, and tuberculosis treatment failure when compared to thrice-weekly dosing. Therefore, twice-weekly therapy is never recommended and thrice-weekly therapy can only be used during the continuation phase in the setting of DOT [25■]. The Guideline Development Group specifically recognized that PLWH may be at a higher risk of poor outcomes because of decreased absorption of tuberculosis medications, making intermittent dosing even less favorable for PLWH [1■■■].

Following publication of the WHO DS-TB guideline update, the results of a RCT comparing the efficacy and safety of daily, part-daily, and intermittent ATT among PLWH, provided even stronger evidence supporting this recommendation [26■■■]. The study was conducted in India and enrolled 331 participants with a median CD4+ count of 138 cells/ml<sup>3</sup>. All participants not already on ART were initiated on ART per national guidelines. The primary outcome was completion of treatment with all available sputum cultures negative during the final 2 months of ATT. The study was stopped early because the daily regimen was superior to the intermittent regimen, and all cases of acquired rifampin resistance ( $n=4$ ) were in the intermittent therapy group.

## 6 versus 8 months treatment duration

A 6-month tuberculosis treatment duration is recommended over a longer course in the updated WHO guidelines as a conditional recommendation with very low certainty in the evidence [1■■■]. This recommendation places emphasis on expanding ART coverage and starting ART soon after tuberculosis treatment initiation. Results of a systematic review and meta-analysis demonstrated that an extended duration of rifamycin therapy was associated with a decreased risk of relapse [27]. However, this association did not remain after accounting for treatment with ART. There was no association of the duration of rifamycin therapy with tuberculosis treatment failure or death regardless of treatment with ART. The WHO guidelines caution that consideration be given to monitoring for relapse among PLWH not started on ART within 8 weeks of ATT initiation [1■■■]. Increased toxicity and stigma were acknowledged as potential adverse consequences of extended therapy among PLWH, although further study is needed on this topic [1■■■].

ATS/CDC/IDSA guidelines recommend extension of the continuation phase to 7 months (9 months total) among people with cavitory disease and positive sputum cultures after 8 weeks of ATT, regardless of HIV-status. They also recommend extended treatment duration among people with cavitory disease or positive sputum cultures after 8 weeks of ATT if they are HIV-positive. Moreover, they recommend extended treatment for PLWH who do not receive ART during ATT [2]. The evidence on which this recommendation is based includes both clinical trial and cohort studies conducted mainly prior to the wide availability of ART [27]. These recommendations are not endorsed by the WHO [1■■■,4].

## Patient care and support

Overall, the WHO guidelines committee concluded that the evidence to provide a recommendation for DOT versus self-administered ATT was lacking. However, PLWH were considered as a specific subgroup that could benefit from treatment adherence support [1■■■]. The recommendation was based largely on data from observational cohort studies, not clinical trials, conducted either in the pre-ART or early-ART eras. The definition of DOT in these studies with respect to the person providing the DOT and the setting in which the DOT was given varied. In these studies, PLWH who received self-administered therapy (SAT) had lower rates of treatment success (completion and cure) and a higher risk of mortality, tuberculosis treatment failure, and loss to follow-up [28–43]. As a result, SAT alone is not recommended among PLWH. This subgroup difference may be related to differences in DDI and severity of disease among HIV-positive compared to HIV-negative tuberculosis patients. Overall, WHO prefers provision of DOT by trained lay providers and healthcare workers (compared to family members) in community or home settings (compared to health facilities) regardless of HIV status [1■■■].

## THERAPEUTIC DRUG MONITORING

Patients tuberculosis with HIV may have low plasma anti-tuberculosis drug concentrations; however, data on the association of plasma anti-tuberculosis drug concentrations and tuberculosis treatment outcomes are conflicting [44–51]. In a prospective cohort study among PLWH and tuberculosis co-infection in Uganda (the SOUTH study), among 227

participants with ATT drug levels available, 190 (84%) were low for isoniazid and 176 (78%) were low for rifampicin. Low plasma isoniazid and rifampicin concentrations were independently associated with lower sputum culture conversion rates. Additionally, low isoniazid and rifampicin plasma concentrations were associated with unfavorable treatment outcomes (death, failure, loss to follow-up, default) [52]. The WHO does not currently recommend TDM during ATT although the ATS/ CDC/IDSA guidelines suggest that TDM may be helpful among PLWH. Future randomized trials evaluating the impact of adjusting anti-tuberculosis drug dosages using TDM results on tuberculosis treatment outcomes are needed.

### Empiric tuberculosis treatment

The diagnosis of tuberculosis among PLWH, particularly those with severe immunosuppression, is difficult. Currently available diagnostic tools are either poorly sensitive, do not provide results in a timely manner, or are not available in resource-limited settings [53]. There is high morbidity and mortality associated with TB among PLWH, particularly after ART initiation, when subclinical tuberculosis may be unmasked by immune reconstitution [54]. One strategy to improve outcomes includes empiric TB treatment either without testing for tuberculosis or while awaiting TB test results. A recent randomized controlled trial (STATIS) conducted in Cote d'Ivoire, Uganda, Cambodia, and Vietnam compared rates of death or invasive bacterial disease at 24 weeks between extensive tuberculosis screening (sputum Xpert MTB/RIF, urine lipoarabinomannan, and chest radiography; arm 1) versus systematic empiric TB treatment (arm 2) among 1047 ART naïve adults with CD4+ counts less than 100 cells/μl. ART was started immediately among those who did not start tuberculosis treatment at baseline (patients in the extensive TB screening arm with negative tests) and within 2 weeks of TB treatment initiation (patients in the extensive tuberculosis screening arm with positive tests and all patients in the systematic empiric tuberculosis treatment arm). There was no difference between the arms with respect to the primary combined endpoint of death and invasive bacterial diseases (HR 0.93; 95% CI, 0.61–1.42), death alone (HR 0.92; 95% CI, 0.57–1.48) or invasive bacterial diseases alone (HR 1.14; 95% CI, 0.54–2.4). However, there was a higher risk of grade 3–4 toxicity in the systematic treatment arm compared to the extensive tuberculosis screening arm (HR 2.70; 95% CI, 1.80–4.04) [55].

Another study, the tuberculosis Fast Track study, was an open, pragmatic, cluster randomized trial in South Africa to evaluate the use of an empiric algorithm to determine treatment versus standard of care [56]. Participants in the sites randomized to the intervention arm were classified as at high, medium, or low probability of having tuberculosis. Participants classified as high probability started tuberculosis treatment immediately, followed by ART within 2 weeks; participants classified as medium probability were treated according to national guidelines for test-negative tuberculosis and re-classified within 1 week. Participants classified as low probability started ART as soon as possible. Among 3030 participants, the adjusted 6-month mortality rate ratio for the intervention arm was 0.87 (95% CI, 0.61–1.24) compared to standard of care [56,57]. Although these studies did not demonstrate significantly improved mortality with empiric tuberculosis treatment among PLWH with advanced immunosuppression, the STATIS trial results

suggest that empiric tuberculosis treatment may be considered if extensive tuberculosis screening is not available.

## CONCLUSION

Recently updated guidelines on the treatment of DS-TB from the WHO recommend the use of fixed-dose combinations, daily therapy throughout the entire duration of ATT, 6-month duration of therapy in the setting of timely ART initiation, and DOT using the currently recommended DS-TB regimen. However, higher-quality evidence on which to base these recommendations is needed. Short-course therapy with fluoroquinolones is not recommended based on strong, high-quality evidence. Several studies are either ongoing or in planning phases to evaluate optimization of the doses and duration of drugs in the currently preferred anti-TB regimen and novel shorter course DS-TB regimens.

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**KEY POINTS**

- Early phase trials of pulmonary tuberculosis have revealed that doses of rifampicin and pyrazinamide higher than currently recommended may lead to improved tuberculosis treatment outcomes. Further study on the efficacy and safety of higher doses is needed.
- Updated WHO DS-TB treatment guidelines recommend the use of fixed-dose combinations of ATT over single-drug formulations, daily therapy throughout both the intensive and continuation phases of therapy, 6-month ATT duration over longer treatment durations, and DOT over self-administered therapy alone among PLWH. These recommendations are conditional and based on low-quality evidence, although evidence behind the recommendation for daily therapy was strengthened by results from a recent clinical trial in India.
- Four-month fluoroquinolone-containing regimens are not recommended for treatment of DS-TB regardless of HIV-status based on the evidence from high-quality clinical trials. There are several studies either ongoing or in planning phases to evaluate additional 4-month anti-TB regimens with optimized doses of currently used drugs and novel anti-TB drugs.
- Further studies evaluating the impact of adjusting anti-TB drug dosages using therapeutic drug monitoring results and the strategy of empiric tuberculosis treatment on tuberculosis treatment outcomes are needed.

**Table 1.** Studies of fluoroquinolone-containing regimens used as basis for 2017 WHO DS-TB treatment guidelines update

	REMoxTB	RIFAQUIN	OFOLOTUB
Control arm	HRZE × 8 weeks followed by HR × 18 weeks	HRZE × 8 weeks followed by HR × 16 weeks	HRZE × 8 weeks followed by HR × 16 weeks
Experimental arms	Arm 1: HRZE × 8 weeks followed by HRM × 9 weeks Arm 2: MRZE × 8 weeks followed by RM × 9 weeks	Arm 1: MRZE × 8 weeks followed by MPZE twice weekly × 8 weeks Arm 2: MRZE x weeks followed by MPZE once weekly × 16 weeks	HRZG × 8 weeks followed by HRG × 8 weeks
HIV eligibility criteria	PLWH already on ART and with CD4 < 250 cells/ml <sup>3</sup> were ineligible N=110 PLWH (7%) enrolled; median CD4 not reported	PLWH who required ART were initially ineligible; as the trial progressed, PLWH were eligible CD4 count < 200 cells/ml <sup>3</sup> were initially ineligible, but this was subsequently amended to 150 cells/ml <sup>3</sup> N=158 PLWH (27%) enrolled; median CD4 314 cells/ml (IQR 253–441 cells/ml <sup>3</sup> )	PLWH with WHO stage 3 infection (except those presenting with only the loss of weight criterion) and all PLWH with WHO stage 4 infection were ineligible N=110 PLWH (7%) enrolled; median CD4 not reported
Primary outcome	Unfavorable outcomes: Treatment failure or relapse within 18 months of randomization	Unfavorable outcomes: Treatment failure, relapse or death within 12–18 months of randomization	Unfavorable outcomes: Treatment failure, recurrence, study withdrawal or death within 24 months after end of treatment
Secondary outcome	Grade 3 or 4 adverse events	Grade 3 or 4 adverse events	Serious adverse events
Results	Unfavorable outcomes were more frequent in both experimental arms compared to the control arm. No significant difference in grade 3 or 4 adverse events between arms. No significant difference in 8 week culture conversion although both experimental arms had shorter time to culture conversion on solid and liquid media.	The 6-month experimental arm was as effective as the control arm and the 4-month arm was not noninferior to the control arm with respect to unfavorable outcomes No significant difference in grade 3 or 4 adverse events between arms.	The experimental arm was not noninferior to the control arm with respect to unfavorable outcomes No significant difference in serious adverse events between arms
HIV subgroup analyses	No difference in unfavorable outcomes according to HIV status	No difference in unfavorable outcomes according to HIV status	Fewer unfavorable outcomes in the experimental group compared to the control group

E, ethambutol; G, gatifloxacin; H, isoniazid; M, moxifloxacin; P, rifapentine; PLWH, people living with HIV; R, rifampin; Z, pyrazinamide.

**Table 2.**

Currently planned or on-going novel TB regimen trials including PLWH

ClinicalTrials.gov Identifier	Phase	HIV exclusion criteria	Study Arms
APT NCT02256696C	2	CD4 <350 cells/ml <sup>3</sup> or; currently taking or planning to take ART during the study	Experimental arm 1: 2 months HRZPa followed by 1 month HRPa Experimental arm 2: 2 months HRbZPa followed by 1 month HRbPa Experimental arm 3: 2 months HRZE followed by 1 month HR
TRUNCATE-TB NCT03474198	2/3	HIV-positive participants are excluded although it is noted that this eligibility criteria may be modified in later stages of the trial	Experimental arm 1: 2 months HRZE + linezolid Experimental arm 2: 2 months HRZE + clofazimine Experimental arm 3: 2 months HPZE + linezolid Experimental arm 4: 2 months HBZE Control arm: 2HRZE followed by 4HR
STAND NCT02342886 Accrual halted and not resumed in May 2017; focus was moved toward SimpliCtB trial.	3	CD4+ count <100 cells/ml <sup>3</sup> ; Karnofsky score <60%; WHO Clinical Stage 4 or; intravenous antifungal medication in the previous 90 days; participants started on ART in the past 30 days or expected start ART within 30 days after randomization (ART regimens not specified)	Experimental arm 1: 4 months Pa (200 mg) MZ Experimental arm 2: 6 months Pa (200 mg) MZ Experimental arm 3: 4 months Pa (100 mg) MZ Control arm: 2HRZE followed by 4HR
SimpliCtB NCT03338621	2/3	CD4+ count <100 cells/ml <sup>3</sup> ; Karnofsky score <60%; WHO Clinical Stage 4 or; intravenous antifungal medication in the previous 90 days; participants started on ART in the past 30 days or expected start ART within 30 days after randomization <sup>a</sup>	Experimental arm 1: 4 months BPaMZ Control arm: 2HRZE followed by 4HR
TBTC Study 31/ ACTG 5349 NCT02410772	3	CD4+ count <100 cells/ml <sup>3</sup> ; current or planned use of ART, which is not efavirenz based	Experimental arm 1: 2 months HPZE followed by 2 months HP Experimental arm 2: 2 months HPZM followed by 2 months HPM Control arm: 2 months HRZE followed by 4 months HR

ART, antiretroviral therapy; B, Bedaquiline; E, ethambutol; H, isoniazid; M, moxifloxacin; P, rifampin; Pa, Pretomanid; R, rifampin; Rb, Rifabutin; Z, pyrazinamide.

<sup>a</sup>Only the following ART regimens are allowed in the SimpliCtB trial: Nevirapine (NVP), lopinavir/ritonavir, or an integrase inhibitor in combination with two nucleoside reverse transcriptase inhibitors (NRTIs)—either tenofovir (TDF) or abacavir (ABC) with either emtricitabine (FTC) or lamivudine (3TC). Among participants who are virally suppressed on efavirenz at the time of screening, efavirenz can be changed to rilpivirine. Among participants randomized to rifampin – EFV can be used, lopinavir dose should be doubled, and rilpivirine cannot be used.