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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Are We There Yet? Short-Course Regimens in TB and HIV: From Prevention to Treatment of Latent to XDR TB

Elisa H. Ignatius[1] · Susan Swindells[2]

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Abstract

Purpose of Review Despite broad uptake of antiretroviral therapy (ART), tuberculosis (TB) incidence and mortality among people with HIV remain unacceptably high. Short-course regimens for TB, incorporating both novel and established drugs, offer the potential to enhance adherence and completion rates, thereby reducing the global TB burden. This review will outline short-course regimens for TB among patients with HIV.

Recent Findings After many years without new agents, there is now active testing of many novel drugs to treat TB, both for latent infection and active disease. Though not all studies have included patients with HIV, many have, and there are ongoing trials to address key implementation challenges such as potent drug-drug interactions with ART.

Summary The goal of short-course regimens for TB is to enhance treatment completion without compromising efficacy. Particularly among patients with HIV, studying these shortened regimens and integrating them into clinical care are of urgent importance. There are now multiple short-course regimens for latent infection and active disease that are safe and effective among patients with HIV.

Keywords HIV infection · Tuberculosis · Drug-susceptible tuberculosis · Drug-resistant tuberculosis · Tuberculosis preventive therapy · Drug-drug interactions

Introduction

Despite global access to and uptake of antiretroviral therapy (ART), the proportion of patients with HIV infection and tuberculosis (TB) who die while on treatment is approximately three times that among patients with TB but without HIV (11% versus 4%) [1•]. In 2018, 251,000 people with HIV infection died from TB, the leading infectious killer globally, accounting for one in every three HIV-related deaths [1•]. Given the known risk that these two conditions jointly pose, it is imperative to diagnose TB and HIV early in the course and maximize the likelihood of successful completion of TB treatment, be that for latent TB infection (LTBI), drug-susceptible (DS), or drug-resistant (DR) disease. Though some data suggest that adherence to TB treatment is slightly higher among patients with HIV [2], the lengthy duration of therapy remains a major barrier to completion and cure. Additionally, patients with both TB and HIV have additional challenges of potent drug-drug interactions, overlapping toxicities, and risk of immune reconstitution inflammatory syndrome (IRIS) in the weeks to months after treatment begins. After a long drought, the pipeline for new TB drugs is now flowing [3]. There is unprecedented movement towards integrating new drugs into the TB treatment continuum and refining older regimens in order to shorten the overall duration of therapy. New, shorter regimens for prevention of TB offer great promise. Though not all such efforts have explicitly included patients with HIV, we will outline those that have, and any resulting knowledge gaps.

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✉ Susan Swindells
sswindells@unmc.edu

Elisa H. Ignatius
eignati1@jhmi.edu

[1] Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

[2] University of Nebraska Medical Center, Omaha, NE 68198-8106, USA

Latent Tuberculosis Infection

Twenty-three percent of the world's population is infected with TB, and 10% of the infected people, on average, will develop

active TB in their lifetime [4]. Among patients with HIV, the lifetime risk of progressing from LTBI to active TB disease is between 5 and 10% [5]. TB is both treatable and preventable, but the global uptake of TB preventive therapy (TPT) remains low [6••]. The first trial of treatment for LTBI was conducted using isoniazid preventative therapy (IPT) in the 1950s–1960s and showed a 70% decrease in TB incidence [7]. Since then, multiple studies have confirmed the efficacy of TPT, including in people infected with HIV [8]. More recently, a large trial of early antiretroviral therapy and isoniazid preventive therapy (IPT) in Africa among 2056 patients with HIV found that TB was the most common endpoint; not only was risk of TB reduced but risk of death was also 37% lower among those who received IPT compared with those who did not (adjusted hazard ratio 0.65, 95% CI 0.48 to 0.88) [9, 10]. In TB endemic countries, the WHO recommends that all patients with HIV be treated for LTBI, regardless of whether they have a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) [11]. HHS/CDC recommends LTBI testing and only initiating treatment after negative results if there is known contact with an infectious case [12]. Despite its well-documented benefit, multiple prior studies have shown that uptake [13] and treatment completion rates for LTBI in the general population are poor, ranging from 46 to 76% [14–17]. Rates are generally higher when patients have both TB and HIV, rather than TB alone, however still fall well short of recommended targets [18]. The length is known to impact likelihood of completion; in trials of shorter duration regimens, such as 2 months of RIF/PZA, treatment completion rates improved substantially (80% vs 69%, $p < 0.001$) [19]. Currently, recommended TB preventive therapy regimens are reviewed below and in Table 1.

Six or Nine Months of Isoniazid (6H–9H)

The IUAT trial demonstrated that 6 months of isoniazid preventative therapy (IPT) was superior to 3 and that 12 months was most effective in preventing TB disease over 5 years follow-up [37]. Six to nine months duration are generally recommended, with the 9-month duration preferred by the US guideline panels [18, 38] and 6 months by the WHO [11]. A network meta-analysis found no difference in efficacy between 6 and 9 months [39]. IPT has also been shown to be effective in HIV positive participants as well and works synergistically with ART to reduce future risk of TB disease [9, 40]. Implementation of IPT for patients with HIV has been partially successful [41], but uptake by clinicians and patients alike has stalled due to real or perceived challenges with adherence to the lengthy course, concerns about the potential for development of drug-resistant TB and adverse effects, and competing demands with rollout of ART [42].

Given mounting evidence that the peripartum period is one of heightened vulnerability to reactivation of latent TB and progression to TB disease, the IMPAACT network conducted a phase IV trial comparing immediate (during pregnancy) versus delayed (postpartum) isoniazid preventative therapy among women with HIV and found equivalent protection against TB disease but increased adverse events in the immediate (during pregnancy) group including liver enzyme elevation among those on efavirenz-based antiretroviral treatment (ART) [43].

Four or Six Months of Rifampicin (4R, 6R)

Though many guidance groups list 4 months of rifampicin as a first-line regimen for TPT, there are no trials to date specifically studying the efficacy or safety of 4 months of rifampicin for the treatment of LTBI among individuals with HIV [44]. A recent study compared completion rates, safety, and effectiveness of 4 months rifampicin versus 9 months isoniazid but included only 242 (4%) participants with HIV. It found that 4R was non-inferior to 9H for the prevention of tuberculosis disease and that safety and completion rates were superior for 4R [28]. When rifampicin is used for LTBI (or active TB) treatment among patients with HIV, care must be taken because of the common drug-drug interactions between ART and rifampicin [45, 46] (Table 2). Helpful resources for clinicians can be found at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/ and https://www.hiv-druginteractions.org/.

2 Months Rifampicin with Pyrazinamide (RIF-PZA)

In what has now become a classical example of the potential for differential tolerance of TB drugs in people with and without HIV infection, a 2-month regimen of RIF-PZA initially appeared quite promising in a study of HIV positive patients. In this group, it was demonstrated to have comparable safety and efficacy to 12 months of isoniazid and could be dosed either daily or twice weekly [19, 20, 64]. However, subsequent study of this regimen given to HIV negative patients resulted in significant increase in hepatotoxicity, compared with 6 months of INH [65, 66]; therefore, this regimen is now little used.

Three Months of Isoniazid with Rifapentine (3HP)

Based on the superior potency of rifapentine compared with rifampicin in murine TB models, as well as the advantageous pharmacokinetics of rifapentine including longer half-life, an earlier trial investigated a regimen of 3 months of weekly isoniazid plus rifapentine for the treatment of LTBI given by directly observed therapy. Very few patients with HIV were included (2.7% in control and 2.6% in intervention arms, respectively). This was largely because of concern about drug-drug interactions and lack of suitable ART to use with rifamycins at the time the study was conducted. Results showed equal effectiveness, enhanced treatment completion,

Table 1 Treatment shortening trials that included patients with HIV[8]

	Study name	Location	Intervention	% HIV positive	Results
LTBI	CPCRA 004 + ACTG 177	USA, Brazil, Mexico, Haiti	RIF 600 mg/d + PZA 20 mg/kg/d (2 months) versus INH 300 mg/day	100%	Completion 80% (intervention) vs 69%; efficacy 2.4% TB disease (intervention) vs 3.3% [19]
		Haiti	INH 600 mg twice weekly (6 months) versus RIF 450 mg plus PZA 1500 mg twice weekly (2 months)	100%%	No difference in effectiveness [20]
		Spain	INH 300 mg daily (12 months) versus RIF 600 mg plus INH 300 mg daily (3 months)	100%	Equivalent TB prevention, fewer safety events for 3HR [21]
		Spain	INH 5 mg/kg daily (6 months) versus RIF 10 mg/kg plus INH 5 mg/kg (3 months) versus RIF 10 mg/kg plus PZA 2000 mg daily (2 months)	100%	No benefit among TST negative patients in TB prevention [22]
		Spain	INH 5 mg/kg daily (6 months) versus RIF 10 mg/kg plus INH 5 mg/kg (3 months) versus RIF 10 mg/kg plus PZA 1500 mg or 2500 mg mg daily (2 months)	100%	Similar safety of 2RZ versus 6H and 3RH regimens [23]
		Uganda	INH 30 mg (6 months) versus INH 300 mg pus RIF 600 mg daily (3 months) versus INH 300 mg plus RIF 600 mg plus PZA 2000 mg daily (3 months)	100%	Reduced TB incidence, no change in HIV progression [24]
		Zambia	INH twice weekly (6 months), RIF/PZA twice weekly (3 months), placebo	100%	Either regimen effective (RR 0.60, CI 0.36–1.01), protective duration limited < 18 months[31]
	PREVENT TB/ NCT00023452; NCT00023452, TBTC Study 26	USA, Brazil, Spain, Peru, Canada, Hong Kong	Weekly rifapentine + INH (3 months) vs INH (9 months)	2.60%, then 100%	In both studies: 3HP equally effective, higher treatment completion [25, 26]
	TEMPRANO	Ivory Coast	2 × 2 factorial design for delayed versus immediate ART and 6 months IPT or no IPT	100%	Immediate ART and 6 months IPT had lower rates of death and severe disease than delayed ART and no IPT [9]
	NCT00057122	South Africa	Weekly 3HP, twice weekly 3RH, daily INH (6 years), daily INH (6 months)	100%	All effective, no regimens superior to daily INH for 6 mo[37]
	BRIEF TB/A5279, NCT01404312	Haiti, Botswana, Peru, Thailand, South Africa, Brazil, Malawi, Zimbabwe, Kenya, USA	1HP versus 9H	100%	1HP non-inferior in TB prevention with equivalent safety and higher treatment completion [27•]
	NCT00931736	Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, South Korea	RIF (4 months) versus INH (9 months)	4%	4R non-inferior to 9H for prevention; safety and completion superior for 4R [28]

Table 1 (continued)

	Study name	Location	Intervention	% HIV positive	Results
	NCT02980016	South Africa, Ethiopia, Mozambique	Annual 3HP (2 years) versus 3HP (once) versus 6H (once)	100%	Higher treatment completion (3HP arms), similar TB incidence, and mortality [29]
DSTB	TBTC Study 28 NCT00144417	USA, Canada, Brazil, South Africa, Spain, Uganda	Moxifloxacin 400 mg OR isoniazid plus RZE	11%	similar culture conversion at 8 weeks [30]
	RIFAQUIN, ISRCTN44153044	South Africa, Zimbabwe, Botswana, Zambia	Moxi plus RZE (2 months) followed by either 2 months twice weekly moxi-rifapentine or 4 months once weekly moxi-rifapentine versus RHZE	28%	Failed to meet non-inferiority for shortened duration arms [31]
	OFLOTUB NCT00216385	Benin, Guinea, Kenya, Senegal, South Africa	4 months RHZ-gatifloxacin versus RHZE	18%	Failed to meet non-inferiority for shortened duration arm [32]
	REMoxTB NCT00864383	South Africa, India, Tanzania, Kenya, Thailand, Malaysia, Zambia, China, Mexico	4 months RHZ-moxifloxacin, 4 months RZE-moxifloxacin, or RHZE	7%	Failed to meet non-inferiority for shortened duration arms [33]
	NC005	South Africa, Tanzania, Uganda	BPaZ for 8 weeks followed by RHZE	15.60%	Enhanced bactericidal activity at 8 weeks in BPaZ arm [34]
DR TB	STREAM	Ethiopia, Mongolia, South Africa, Vietnam	9–11 months moxifloxacin, clofazimine, ethambutol, pyrazinamide plus kanamycin, isoniazid, prothionamide for first 16 weeks versus 20 months per WHO guidelines	32.60%	Short-course efficacy non-inferior to long course [35]
	Nix TB	South Africa	BPaL (6 months) versus historical	51%	Improved efficacy compared with historical controls [36•]

Table 2 Tuberculosis drugs and compatibility with antiretroviral therapy [6, 47]

	Compatible ART	Supporting evidence
Isoniazid, pyrazinamide, ethambutol	Any	
Rifampicin (daily 10 mg/kg) (e.g., 4R, 3HR, RHZE)	Any NRTI (FTC, likely TAF)	RIFT—No effect of RIF on emtricitabine; TAF exposure reduced but intracellular tenofovir-DP concentrations remained over × 4 higher than with TDF [48]
	EFV 600 mg daily (plus TDF/FTC)	STRIDE—Slightly higher EFV exposures with RIF, therefore no weight-based EFV adjustment needed [49]
	EFV 400 mg daily (with HR)	Among patients with HIV administered 12 weeks of HR, EFV exposures were not significantly affected [50]
	DTG 50 mg twice daily	INSPIRING—Among patients with HIV receiving HRZE, twice daily DTG safe and effective [51]
	RAL 800 mg twice daily	Reflate TB—Standard RAL dosing (400 mg twice daily) saw only small reduction in exposures (31%) but given concern about narrow RAL therapeutic window concluded that 800 mg twice daily dosing likely preferred [52]
Rifapentine (weekly 900 mg) (e.g., 3HP)	EFV 600 mg daily (plus FTC, TDF)	Rpt for 3 weeks in patients with HIV on Atripla showed no significant effect on any ART component [53]
	DTG 50 mg daily	Though serious hypersensitivity reaction seen in health volunteer study of DTG plus once weekly INH-Rpt [54], this was not seen in patients with HIV (DOLPHIN). 3HP increased DTG clearance but not enough to require dose adjustment [55]
	RAL 400 mg twice daily	Among healthy volunteers, receiving RAL plus Rpt 900 mg once weekly for 3 weeks, RAL exposures significantly increased but were well-tolerated [56]
Rifapentine (daily 450 or 600 mg) (e.g., 1HP)	EFV 600 mg daily	BRIEF-TB—No meaningful reduction in EFV concentrations or virologic suppression [57]
Rifapentine high dose (1200 mg daily) (e.g., Rpt-HZE)	EFV 600 mg daily	Per recent presentation from TBTC 31/ACTG 5349, only slight reduction in EFV clearance, no effect on virologic suppression, no need for dose adjustment [58]
Bedaquiline (e.g., BPaL)	Nevirapine	Healthy volunteer study of BDQ plus nevirapine or LPV/r showed no significant effect of or on NVP PK, but LPV/r decreased clearance of BDQ and M2 metabolite by 3% and 58%, raising concerns about co-administration [59] Confirmed in patients with HIV and drug-resistant TB, suggesting dose reduction of BDQ may be necessary with LPV/r [60]
	(EFV 600 mg daily)	Healthy volunteers received daily EFV followed by single dose BDQ 400 without significant impact on BDQ exposures [61], however subsequent modeling suggested 50% reduction in BDQ exposures with EFV [62]
Pretomanid (e.g., BPaL)	EFV	Pretomanid AUC minimally reduced (35%) [63]
	LPV/r	Pretomanid AUC minimally reduced (17%) [63]

reduced hepatotoxicity, but more frequent drug discontinuation due to adverse events [25]. After an extension of this trial to recruit more participants with HIV, similar results were observed, but 3HP was better tolerated [26•]. Subsequent studies of this regimen for patients with HIV compared with either 3RH, 6H, or continuous isoniazid showed a similar preventative efficacy [67]. A phase 1/2 trial also evaluated co-administration of 3HP with dolutegravir-based ART and concluded that these regimens could be given together without dose adjustment [55]. Preliminary results from IMPAACT 2001 (NCT02651259), a phase I/II trial to study 3HP in pregnancy in which 40% of participants had HIV demonstrated that though rifapentine clearance was 30% higher among pregnant women with HIV on efavirenz, concentrations remained in the therapeutic range, and, therefore, no dose adjustment of rifapentine would be required [68]. While 3HP appears effective and safe, its cost-effectiveness has remained contingent upon steep price reduction [69].

One Month of Isoniazid with Rifapentine (1HP)

Murine models of LTBI demonstrated comparable effectiveness between 1 month of rifapentine plus isoniazid and either 3HP or 6H [70, 71]. The BRIEF-TB trial assessed the ultra-short 1HP regimen among patients with HIV, compared with 9H, and found a comparable efficacy and higher treatment completion rates for 1HP. Between 50 and 90% of trial participants were on ART during the study, mostly with efavirenz-based regimens (43%) [27•]. A drug-drug interaction study with dolutegravir and 1HP is ongoing (NCT04272242). An additional trial, TBTC Study 37/ASTEROid, is recruiting to study the non-inferiority of

6 weeks of daily rifapentine compared with 3–4 months of rifampicin (NCT03474029). The NIH-funded IMPAACT network is also planning studies of the safety and pharmacokinetics of 1HP in pregnant women and in children using a child-friendly dispersible formulation.

Though the recent publications on 3HP and 1HP have been encouraging that a short duration LTBI regimen is safe and effective in people with HIV, there remains some concern about the durability of prevention. Particularly in TB endemic countries, re-exposure after successful treatment remains a risk. The recently completed WHIP3TB trial compared periodic 3HP (p3HP) administration for 2 years to 3HP and 6H among people with HIV and found that treatment completion was higher for both p3HP and 3HP and there was no additional prevention benefit of p3HP over 3HP [29].

TPT in Drug-Resistant TB

Recent modeling has estimated that three in every 1000 people globally are infected with latent drug-resistant tuberculosis (DR-TB) infection and the prevalence is approximately ten times higher in those younger than 15 years [72]. The optimal preventive therapy regimen for people exposed to DR-TB is not known, and evidence-based guidelines are urgently needed. Based on low-grade evidence, for patients with HIV known to have close contact with a case of drug-resistant TB, a fluoroquinolone is recommended for 6–12 months [73]. There are multiple studies now ongoing to better understand the effectiveness of various agents including levofloxacin for 3 months in children (TB-CHAMP) (ISRCTN92634082), levofloxacin for 6 months (VQUIN MDR) (ACTRN12616000215426), and delamanid for 6 months (PHOENIx MDR-TB) (NCT03568383).

Treatment of Drug-Susceptible Pulmonary TB

As Jindani et al. wrote in their seminal 1980 paper describing the first early bactericidal (EBA) study, "the most important innovation in the chemotherapy of tuberculosis during the past decade has been the development of regimens of short-course chemotherapy." [74] At the time of this writing, they were referring to treatment shortening from 1 to 2 years down to only 6–9 months. This did indeed represent a monumental shift in TB treatment, and yet, since that short course was first described by Fox and Mitchison in 1975 [75], we have not progressed much further in the duration of treatment for drug-susceptible (DS) TB. Currently, the recommended standard combination therapy for DS TB is rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) given for 2 months followed by rifampicin plus isoniazid (RH) given for an additional 4 months [76, 77]. Several trials attempting to shorten TB treatment with both conventional and new TB drugs are reviewed below.

Three trials evaluated shorter courses of TB treatment with 4-month regimens containing various fluoroquinolones, and all three failed to meet non-inferiority for the shortened duration arms. The RIFAQUIN trial compared one 4-month and one 6-month regimen with the standard 6-month RHZE. The two intervention arms consisted of moxifloxacin, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by either 2 months of moxifloxacin plus rifapentine twice weekly or 4 months of moxifloxacin plus rifapentine once weekly. The results showed that the 6-month experimental arm was comparable with RHZE, but the 4-month regimen failed to meet non-inferiority. The trial enrolled 28% participants with HIV, and there was no mention of differing subgroup treatment effects [31]. Similarly, OFLOTUB compared 6 months RHZE with 4 months of RHZ-gatifloxacin and failed to demonstrate non-inferiority of the new, shorter regimen. The trial enrolled 18% participants with HIV, and treatment effects were similar in this subgroup [32]. REMoxTB compared 6 months RHZE with 4 months of either RHZ-moxifloxacin or RZE-moxifloxacin. Both moxifloxacin-containing arms resulted in faster bacterial decline but did not meet non-inferiority margin compared with standard of care. The trial enrolled few patients with HIV (7% in each arm), and there was no evidence of differences in outcomes or toxicity based on HIV diagnosis in these small subsets [33].

The Indian National Institute for Research in TB (NIRT) group studied 4 months of thrice weekly dosing of RHZE versus RHZ-gatifloxacin or RHZ-moxifloxacin, but the study was terminated early due to higher recurrence rates in the 4-month groups and only included HIV negative participants [78]. NIRT recently published data from a trial comparing 3 versus 4 months of daily dosing of RHZE-moxifloxacin versus 6 months RHZE. The 3-month regimen was stopped early due to recurrence rates. With the addition of moxifloxacin to standard RHZE, the 4-month regimen was observed to be equally safe and effective as 6 months of RHZE [79].

The TB Trials Consortium (TBTC) of the US CDC conducted a phase 2 trial of TB treatment shortening, Study 28. Participants with DS TB were randomized to receive either moxifloxacin 400 mg or isoniazid plus rifampicin, pyrazinamide, and ethambutol for 8 weeks, followed by standard of care. Culture conversion at 8 weeks was similar between the arms [30]. A subsequent phase 3 study, TBTC Study 31/ACTG A5349, is comparing 6 months RHZE to one of two 4-month regimens: either 2 months of isoniazid, pyrazinamide, ethambutol, and high-dose rifapentine followed by 2 months of isoniazid and rifapentine or ethambutol switched for moxifloxacin. This trial was open to participants with HIV infection, but pharmacokinetic analyses of high-dose rifapentine with efavirenz were required first, liming the number of participants enrolled [80]. This will likely be

the definitive trial of the potential for TB treatment shortening using conventional TB drugs, and results are anticipated in October 2020.

The SHINE trial will be conducted among pediatric patients with TB and will compare 2 months of RHZE followed by either 2 or 4 months of RH. Per published study protocol, it will recruit children with TB, regardless of HIV status [81]. None of the TB treatment shortening trials completed or in progress has included pregnant women.

From the TB Alliance, NC-005 was a phase 2B trial investigating novel agents (bedaquiline and pretomanid) in combination with pyrazinamide for the treatment of drug-susceptible TB. The trial enrolled 180 patients with DS TB, 28 (15.6%) of whom also had HIV. Though patients received study drug for 8 weeks and then were discharged to community treatment programs to receive standard of care, the two arms that received BPaZ did show enhanced bactericidal activity [34]. These promising results are being further evaluated by TB Alliance in the SimpliciTB trial, a phase 2 and 3 design comparing a regimen of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide to RHZE in people with drug-sensitive as well as those with drug-resistant pulmonary TB. This represents an ambitious attempt to develop a universal TB treatment regimen.

Treatment of Drug-Resistant Pulmonary TB

For many years, treatment of multidrug-resistant TB (resistant to both isoniazid and rifampicin) took 18 months to more than 2 years to complete, with some patients often having to take as many as seven medications, including a daily injection. Challenging for both patients and providers, these regimens had common adverse events with almost half the affected patients having moderate to severe side effects [35]. There were even less attractive prospects for those with extensively drug-resistant TB (XDR TB, defined as resistant to isoniazid, rifampicin, any fluoroquinolone, and at least one injectable drug). Treatment success was only achieved in 14% of patients, on average [82–84]. With much room for improvement, treatment of drug-resistant TB has received more attention in the last few years, and significant progress has been made.

In 2010, Van Deun et al. published the encouraging findings of the 6th short-course drug combination for the treatment of MDR TB that had been trialed in Bangladesh, the so-called Bangladesh regimen. [85•] This treatment was given for a minimum of 9 months and consisted of gatifloxacin, clofazimine, ethambutol, and pyrazinamide, plus also prothionamide, kanamycin, and high-dose isoniazid during the intensive phase. Of note, this trial had only one patient with HIV [85•]. Given that these data were collected in an observational manner, as well as the fact that the trial offered no conclusions for patients with HIV, the STREAM trial was proposed. The STREAM was a phase 3 non-inferiority trial of either a short-course regimen (9–11 months of moxifloxacin, clofazimine, ethambutol, pyrazinamide plus kanamycin, isoniazid, and prothionamide added for the first 16 weeks) or long regimen (20 months per WHO guidelines). The short-course regimen efficacy was found to be non-inferior to long course, though there were more reports of QTc prolongation, death, and acquired drug resistance to fluoroquinolones and aminoglycosides. Unlike the Bangladesh regimen cohort, there were more patients with HIV included (32.6%). Interestingly, in this subgroup of participants with HIV, mortality was numerically greater in the short-course arm (17.5%) than the long-course arm (8.0%), but this did not reach statistical significance (HR 2.23, 95% CI 0.76–6.60) [35]. The WHO now recommends that short-course therapy be considered for select patients with DR-TB [86], though ATS/CDC neither recommends for or against the shorter-course regimen [73].

Based on the results from the Nix TB trial, the FDA in 2019 approved the combination of bedaquiline, pretomanid, and linezolid as a 6-month treatment for extensively drug-resistant (XDR) or treatment intolerant MDR TB. The BPaL regimen used in this study demonstrated impressive efficacy when administered for a fraction of the time as a standard treatment. In Nix TB, there were 56 (51%) patients with HIV, and there were no observed differences in a subgroup analysis of these patients examining efficacy and adverse event rates [36•]. Given the theoretical risk that patients with HIV may be predisposed to peripheral neuropathy, it is recommended that these patients receive pyridoxine when prescribed linezolid. Bedaquiline has been shown to be safe and effective among patients with HIV including in the Nix TB trial as well as in other case series [87, 88]. There are limited data on pretomanid use among patients with HIV, though published series and trial data so far suggest no heightened risk of adverse events among those with HIV. There are, however, some potentially complicated drug-drug interactions with efavirenz [63].

Delamanid is currently listed as a Group C drug (to complete the regimen) by the WHO treatment guidelines for drug-resistant TB [86], though a recent trial of delamanid as an add-on to optimized background regimen failed to improve outcomes [89]. The use of delamanid in patients with HIV has not been well-studied, but one theoretical concern is hypoalbuminemia, which is common among patients with HIV, since albumin is required for excretion of delamanid's toxic metabolite, DM-6705. Hypoalbuminemia is a contraindication to receipt of delamanid, which may limit its use for some patients with HIV [90]. Though there are still limited data to guide these practices, the global shift towards dolutegravir as first-line ART will likely be more permissive to co-administration with some of the newer TB drugs, such as bedaquiline, delamanid, and pretomanid [90].

Conclusions and Future Directions

So, for short-course regimens in TB and HIV, are we there yet? The short answer is no, but despite the fact that TB is often neglected and chronically underfunded from the research perspective, great progress in understanding and implementing new regimens has been made over the last 5 years. Inclusion of patients with HIV infection has been fairly robust in most major trials, although the drug-drug interactions with ART and rifamycins often complicate dosing. Short courses of TB preventive therapy have proved effective and safe in patients with HIV infection, with much higher treatment completion rates than prior regimens [25, 27]. The ultra-short 1HP regimen had the highest completion rates recorded to date and is now endorsed by the WHO [91]. Treatment shortening for drug-susceptible TB disease has not been achieved, but several large studies are ongoing to realize this goal. The results of TBTC Study 28 are eagerly awaited to answer the question as to whether treatment can be shortened using conventional TB drugs. If this study fails, using newer drugs will be the only way forward, and several trials to investigate various combinations are ongoing or in development.

Treatment for drug-resistant TB has been shortened significantly, and most patients can now be treated with all oral regimens as opposed to inconvenient and often toxic daily intramuscular injections. The most dramatic progress has been made in treatment for XDR TB where chronically ill patients have been cured of this previously fatal form of TB.

In parallel with testing novel drugs and combinations, modern trial designs are being increasingly employed to accelerate the development pathway for both TPT and treatment. Such trials invariably take years to complete, and newer methods such as the Bayesian adaptive randomization trial design [92] and the Phase IIC Selection Trial with Extended Post-treatment follow-up (STEP) [93] offer greater efficacy and higher likelihood of success than traditional designs.

Going forward, research priorities for the field include development of a safe and effective TB vaccine. Several candidates are in clinical trials, but no clear winner has emerged thus far [94]. Failing the discovery of an effective and affordable vaccine, TPT is effective but uptake must be increased enormously [13]. Part of the problem with TB prevention is the number needed to treat to prevent a case of TB [95], so a biomarker to target those at highest risk would be a major step forward [96, 97]. Community advocacy has helped to lower the price of rifapentine, so these short-course regimens should be widely adopted in HIV treatment programs. Knowledge gaps remain about the best preventive for contacts of drug-resistant TB and TPT in children and in pregnant women.

Long-acting drug formulations have proved successful in diverse areas of medicine, including HIV disease [98, 99]. Application of this technology to TB could have a substantial impact. For example, monthly injections could improve patient adherence and treatment outcomes, especially for TPT, with new, shorter-course regimens available [100]. The physicochemical properties of some TB drugs make them unsuitable for long-acting formulation, but promising candidates have been identified through modeling and simulation, and other formulations are in preclinical testing [101, 102].

For TB treatment, the holy grail is a universal short course of chemotherapy that would treat both drug-susceptible and drug-resistant TB, as drug susceptibility testing is still not widely enough available. At the same time, such a regimen should be compatible with ART, and robust pharmacology DDI analyses should be conducted in tandem with efficacy trials. Though TB remains a challenge globally, particularly for people with HIV, we are poised, armed with new drugs, and more rapidly emerging clinical data. Given the political will and necessary economic investment, tremendous leaps in TB control are possible.

Compliance with Ethical Standards

Conflict of Interest Elisa Ignatius is supported by T32 GM066691-17. Susan Swindells reports research grants to her institution from ViiV Healthcare and the National Institutes of Health.

Human and Animal Rights and Informed Consent This article references studies with human subjects performed by Susan Swindells. The studies were approved by the relevant Institutional Review Boards/Ethics Committees, and all subjects gave written informed consent.

References

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

1.• World Health Organization (WHO). Global Tuberculosis Report 2019. World Health Organization; 2019. **Current data on the state of the global TB epidemic.**
2. Séraphin MN, Hsu H, Chapman HJ, de Andrade Bezerra JL, Johnston L, Yang Y, et al. Timing of treatment interruption among latently infected tuberculosis cases treated with a nine-month course of daily isoniazid: findings from a time to event analysis. BMC Public Health. 2019;19(1):1214. https://doi.org/10.1186/s12889-019-7524-4.
3. Clinical Pipeline. Working Group on New TB Drugs. https://www.newtbdrugs.org/pipeline/clinical. .
4. Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med. 2016;13(10):e1002152. https://doi.org/10.1371/journal.pmed.1002152.
5. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med. 1999;340(5):367–73. https://doi.org/10.1056/NEJM199902043400507.

6.•• González Fernández L, Casas EC, Singh S, et al. New opportunities in tuberculosis prevention: implications for people living with HIV. *J Int AIDS Soc*. 2020;23(1):e25438. https://doi.org/10.1002/jia2.25438. **This paper offers a comprehnsive review of TB prevention in HIV**.
7. Comstock, Ferebee GW, Shirley H, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Respir Dis. 1967;95(6):935–43. https://doi.org/10.1164/arrd.1967.95.6.935.
8. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010;9(1):CD000171. https://doi.org/10.1002/14651858.CD000171.pub3.
9. Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 2015;373(9):808–22. https://doi.org/10.1056/NEJMoa1507198.
10.• Badje A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health*. 2017;5(11):e1080–9. https://doi.org/10.1016/S2214-109X(17)30372-8. **A report of the first clinical trial showing a mortality benfit for people with HIV from TB preventive therapy.**
11. World Health Organization (WHO). *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management*. Geneva; 2018.
12. Centers for Disease Control and Prevention (CDC). Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. *MMWR Recomm Rep*. 2019:424. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
13. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269–78. https://doi.org/10.1016/S1473-3099(16)30216-X.
14. Stockbridge EL, Miller TL, Carlson EK, Ho C. Predictors of latent tuberculosis infection treatment completion in the US private sector: an analysis of administrative claims data. BMC Public Health. 2018;18(1):662. https://doi.org/10.1186/s12889-018-5578-3.
15. Horsburgh CR, Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest. 2010;137(2):401–9. https://doi.org/10.1378/chest.09-0394.
16. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med. 2003;168(4):443–7. https://doi.org/10.1164/rccm.200303-390OC.
17. Robert M, Todd J, Ngowi BJ, et al. Determinants of isoniazid preventive therapy completion among people living with HIV attending care and treatment clinics from 2013 to 2017 in Dar es Salaam Region, Tanzania. A cross-sectional analytical study. *BMC Infect Dis*. 2020;20(1):276. https://doi.org/10.1186/s12879-020-04997-6.
18. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161(4 Pt 2):S221–47. https://doi.org/10.1164/ajrccm.161.supplement_3.ats600.
19. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. J Am Med Assoc. 2000;283(11):1445–50. https://doi.org/10.1001/jama.283.11.1445.
20. Halsey NA, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet. 1998;351(9105):786–92. https://doi.org/10.1016/S0140-6736(97)06532-X.
21. Martínez Alfaro E, Cuadra F, Solera J, Ángel Maciá M, Geijo P, Antonio Sánchez Martínez P, et al. Evaluación de dos pautas de quimioprofilaxis tuberculosa en pacientes infectados por el virus de la inmunodeficiencia humana. Med Clin (Barc). 2000;115(5):161–5. https://doi.org/10.1016/S0025-7753(00)71496-5.
22. Rivero A, López-Cortés L, Castillo R, Lozano F, Ángel García M, Díez F, et al. Ensayo clínico aleatorizado de tres pautas de quimioprofilaxis para prevenir la tuberculosis en pacientes infectados por el VIH con anergia cutánea. Enferm Infecc Microbiol Clin. 2003;21(6):287–92. https://doi.org/10.1016/S0213-005X(03)72942-5.
23. Rivero A, López-Cortés L, Castillo R, Verdejo J, Ángel García M, Javier Martínez-Marcos F, et al. Ensayo clínico aleatorizado para evaluar tres pautas cortas de tratamiento de la infección latente tuberculosa en pacientes infectados por el VIH. Enferm Infecc Microbiol Clin. 2007;25(5):305–10. https://doi.org/10.1157/13102265.
24. Lim HJ, Okwera A, Mayanja-Kizza H, Ellner JJ, Mugerwa RD, Whalen CC. Effect of tuberculosis preventive therapy on HIV disease progression and survival in HIV-infected adults. HIV Clin Trials. 2006;7(4):172–83. https://doi.org/10.1310/hct0704-172.
25. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365(23):2155–66. https://doi.org/10.1056/NEJMoa1104875.
26.• Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons. *AIDS*. 2016;30(10):1607–15. https://doi.org/10.1097/QAD.0000000000001098. **This study documented efficacy of 3HP regimen in patients with HIV**.
27.• Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380(11):1001–11. https://doi.org/10.1056/NEJMoa1806808. **Report of a large, phase 3 trial in patients with HIV showing effiacy of 1HP**.
28. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med. 2018;379(5):440–53. https://doi.org/10.1056/NEJMoa1714283.
29. Churchyard G, Cardenas V, Chihota V, et al. Effectiveness of 3HP annually vs once for HIV-positive people: the WHIP3TB trial. In: *Conference on Retrovirus and Opportunistic Infections (CROI)*. ; 2020.
30. Dorman SE, Johnson JL, Goldberg S, Muzanye G, Padayatchi N, Bozeman L, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. Am J Respir Crit Care Med. 2009;180(3):273–80. https://doi.org/10.1164/rccm.200901-0078OC.
31. Jindani A, Harrison TS, Nunn AJ, Phillips PPJ, Churchyard GJ, Charalambous S, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med. 2014;371(17):1599–608. https://doi.org/10.1056/NEJMoa1314210.
32. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588–98. https://doi.org/10.1056/NEJMoa1315817.
33. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month Moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371(17):1577–87. https://doi.org/10.1056/NEJMoa1407426.
34. Tweed CD, Dawson R, Burger DA, Conradie A, Crook AM, Mendel CM, et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a

multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med. 2019;7:1048–58. https://doi.org/10.1016/S2213-2600(19)30366-2.

35. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1201–13. https://doi.org/10.1056/NEJMoa1811867.

36.• Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020;382(10):893–902. https://doi.org/10.1056/NEJMoa1901814. **Similar report of successful shoter course therapy for XDR TB**.

37. IUAT International Union Against Tb. Efficacy of various durations of isoniazid preventive therapy for tuberculosis : five years of follow-up in the IUAT trial. Bull WHO. 1982;60(4):555–64.

38. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm reports Morb Mortal Wkly report Recomm reports*. 2020;69(1):1–11. https://doi.org/10.15585/mmwr.rr6901a1

39. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med. 2014;161(6):419–28. https://doi.org/10.7326/M14-1019.

40. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. N Engl J Med. 1997;337(12):801–8. https://doi.org/10.1056/NEJM199709183371201.

41. Durovni B, Saraceni V, Moulton LH, Pacheco AG, Cavalcante SC, King BS, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. Lancet Infect Dis. 2013;13(10):852–8. https://doi.org/10.1016/S1473-3099(13)70187-7.

42. Chaisson RE, Golub JE. Preventing tuberculosis in people with HIV-no more excuses. Lancet Glob Health. 2017;5(11):e1048–9. https://doi.org/10.1016/S2214-109X(17)30390-X.

43. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. N Engl J Med. 2019;381(14):1333–46. https://doi.org/10.1056/NEJMoa1813060.

44. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. Am J Transplant. 2020;20(4):1196–206. https://doi.org/10.1111/ajt.15841.

45. Maartens G, Boffito M, Flexner CW. Compatibility of next-generation first-line antiretrovirals with rifampicin-based antituberculosis therapy in resource limited settings. Curr Opin HIV AIDS. 2017;12(4):355–8. https://doi.org/10.1097/COH.0000000000000376.

46. Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed May 5, 2020.

47. Dooley KE. Short-course rifamycin-based regimens for TB infection (LTBI): why countries should scale up this silver bullet for TB prevention among PLHIV. Boston: TB/HIV Research Meeting Organized by WHO; 2018.

48. Cerrone M, Alfarisi O, Neary M, Marzinke MA, Parsons TL, Owen A, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. J Antimicrob Chemother. 2019;74(6):1670–8. https://doi.org/10.1093/jac/dkz068.

49. Luetkemeyer AF, Rosenkranz SL, Lu D, Marzan F, Ive P, Hogg E, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS clinical trials group A5221 STRIDE study. Clin Infect Dis. 2013;57(4):586–93. https://doi.org/10.1093/cid/cit246.

50. Cerrone M, Wang X, Neary M, Weaver C, Fedele S, Day-Weber I, et al. Pharmacokinetics of efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus–infected individuals. Clin Infect Dis. 2019;68(3):446–52. https://doi.org/10.1093/cid/ciy491.

51. 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;70(4):549–56. https://doi.org/10.1093/cid/ciz256.

52. 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(8):1328–35. https://doi.org/10.1093/cid/civ477.

53. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine once-weekly dosing effect on efavirenz emtricitabine and tenofovir PKs. In: *Conference on Retrovirus and Opportunistic Infections (CROI)*. Boston; 2014. https://2jg4quetidw2blbbq2ixwziw-wpengine.netdna-ssl.com/wp-content/uploads/sites/2/posters/2014/493.pdf.

54. Brooks KM, George JM, Pau AK, Rupert A, Mehaffy C, de P, et al. Cytokine-mediated systemic adverse drug reactions in a drug–drug interaction study of dolutegravir with once-weekly isoniazid and rifapentine. Clin Infect Dis. 2018;67(2):193–201. https://doi.org/10.1093/cid/ciy082.

55. Dooley KE, Savic R, Gupte A, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. *Lancet HIV*. 2020;3018(20). https://doi.org/10.1016/S2352-3018(20)30032-1

56. Weiner M, Egelund EF, Engle M, Kiser M, Prihoda TJ, Gelfond JAL, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. J Antimicrob Chemother. 2014;69(4):1079–85. https://doi.org/10.1093/jac/dkt483.

57. Podany AT, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving Rifapentine and isoniazid for tuberculosis prevention. Clin Infect Dis. 2015;61(8):1322–7. https://doi.org/10.1093/cid/civ464.

58. Podany A. Efavirenz pharmacokinetics in HIV/TB coinfected persons initiating ART while receiving high dose rifapentine. In. 2019; http://regist2.virology-education.com/presentations/2019/20AntiviralPK/07_Podany.pdf.

59. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. Antimicrob Agents Chemother. 2014;58(11):6406–12. https://doi.org/10.1128/AAC.03246-14.

60. Brill MJE, Svensson EM, Pandie M, Maartens G, Karlsson MO. Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug-resistant tuberculosis. Int J Antimicrob Agents. 2017;49(2):212–7. https://doi.org/10.1016/j.ijantimicag.2016.10.020.

61. Dooley KE, Park J, Swindells S, Allen R, Haas DW, Cramer Y, et al. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group study A5267. J

Acquir Immune Defic Syndr. 2012;59(5):455–62. https://doi.org/10.1097/QAI.0b013e3182410503.

62. Svensson EM, Aweeka F, Park JG, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. Antimicrob Agents Chemother. 2013;57(6):2780–7. https://doi.org/10.1128/AAC.00191-13.
63. Dooley KE, Luetkemeyer AF, Park JG, Allen R, Cramer Y, Murray S, et al. Phase I safety, pharmacokinetics, and pharmacogenetics study of the antituberculosis drug PA-824 with concomitant lopinavir-ritonavir, efavirenz, or rifampin. Antimicrob Agents Chemother. 2014;58(9):5245–52. https://doi.org/10.1128/AAC.03332-14.
64. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. Aids. 1998;12(18):2447–57. https://doi.org/10.1097/00002030-199818000-00014.
65. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med. 2002;137(8):640–7. https://doi.org/10.7326/0003-4819-137-8-200210150-00007.
66. Tortajada C, Martínez-Lacasa J, Sánchez F, et al. Is the combination of pyrazinamide plus rifampicin safe for treating latent tuberculosis infection in persons not infected by the human immunodeficiency virus? Int J Tuberc Lung Dis. 2005;9(3):276–81.
67. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11–20. https://doi.org/10.1056/NEJMoa1005136.
68. Mathad JS. Rifapentine pharmacokinetics and safety in pregnant women with and without HIV on 3HP. In: *Conference on Retrovirus and Opportunistic Infections (CROI)*. ; 2020. https://impaactnetwork.org/DocFiles/CROI2020/Mathad_IMPAACT2001.presentation_CROI2020_final.pdf.
69. Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of preventive therapy for tuberculosis with isoniazid and rifapentine versus isoniazid alone in high-burden settings. Clin Infect Dis. 2018;67(7):1072–8. https://doi.org/10.1093/cid/ciy230.
70. Zhang T, Zhang M, Rosenthal IM, Grosset JH, Nuermberger EL. Short-course therapy with daily rifapentine in a murine model of latent tuberculosis infection. Am J Respir Crit Care Med. 2009;180(11):1151–7. https://doi.org/10.1164/rccm.200905-0795OC.
71. Zhang T, Li SY, Williams KN, Andries K, Nuermberger EL. Short-course chemotherapy with TMC207 and rifapentine in a murine model of latent tuberculosis infection. Am J Respir Crit Care Med. 2011;184(6):732–7. https://doi.org/10.1164/rccm.201103-0397OC.
72. Knight GM, McQuaid CF, Dodd PJ, Houben RMGJ. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. Lancet Infect Dis. 2019;19(8):903–12. https://doi.org/10.1016/S1473-3099(19)30307-X.
73. Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2019;200(10):e93–e142. https://doi.org/10.1164/rccm.201909-1874ST.
74. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis. 1980;121(6):939–49. https://doi.org/10.1164/arrd.1980.121.6.939.
75. Fox W, Mitchison DA. Short course chemotherapy for pulmonary tuberculosis. AMERREVRESPDIS. 1975;111(6):845–8. https://doi.org/10.1164/arrd.1975.111.3.325.
76. World Health Organization (WHO). *Guidelines for treatment of drug-susceptible tuberculosis and patient care*. Geneva; 2017. https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf.
77. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):e147–95. https://doi.org/10.1093/cid/ciw376.
78. Jawahar MS, Banurekha VV, Paramasivan CN, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. Doherty TM, ed. *PLoS One*. 2013;8(7):e67030. https://doi.org/10.1371/journal.pone.0067030.
79. Velayutham B, Jawahar MS, Nair D, Navaneethapandian P, Ponnuraja C, Chandrasekaran K, et al. 4-month moxifloxacin containing regimens in the treatment of patients with sputum-positive pulmonary tuberculosis in South India – a randomised clinical trial. Tropical Med Int Health. 2020;25(4):483–95. https://doi.org/10.1111/tmi.13371.
80. Dorman SE, Nahid P, Kurbatova EV, Goldberg SV, Bozeman L, Burman WJ, et al. High-dose rifapentine with or without moxifloxacin for shortening treatment of pulmonary tuberculosis: study protocol for TBTC study 31/ACTG A5349 phase 3 clinical trial. Contemp Clin Trials. 2020;90(January):105938. https://doi.org/10.1016/j.cct.2020.105938.
81. Chabala C, Turkova A, Thomason MJ, et al. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials. 2018;19(1):237. https://doi.org/10.1186/s13063-018-2608-5.
82. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383(9924):1230–9. https://doi.org/10.1016/S0140-6736(13)62675-6.
83. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368(9547):1575–80. https://doi.org/10.1016/S0140-6736(06)69573-1.
84. O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, Horsburgh CR. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. Emerg Infect Dis. 2013;19(3):416–24. https://doi.org/10.3201/eid1903.120998.
85.• Van Deun A, Maug AKJ, Salim MAH, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182(5):684–92. https://doi.org/10.1164/rccm.201001-0077OC. **The first report of successful treatment shorteing for MDR TB**.
86. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. In: *WHO Consol Guidel drug-resistant Tuberc Treat*; 2019. p. 99. http://apps.who.int/bookorders.
87. Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis. 2015;19(8):979–85. https://doi.org/10.5588/ijtld.14.0944.
88. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and

XDR-TB: a multicentre study. *Eur Respir J*. 2017;49(5). https://doi.org/10.1183/13993003.00387-2017.

89. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med. 2019;2600(18):1–12. https://doi.org/10.1016/S2213-2600(18)30426-0.
90. Esmail A, Sabur NF, Okpechi I, Dheda K. Management of drug-resistant tuberculosis in special subpopulations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill. *J Thorac Dis*. 2018;10(5):3102–18. https://doi.org/10.21037/jtd.2018.05.11.
91. *WHO operational handbook on tuberculosis (module 1 - preventino): tuberculosis preventive treatment*. Geneva; 2020. https://apps.who.int/iris/bitstream/handle/10665/331525/9789240002906-eng.pdf.
92. Cellamare M, Ventz S, Baudin E, Mitnick CD, Trippa L. A Bayesian response-adaptive trial in tuberculosis: the endTB trial. Clin Trials. 2017;14(1):17–28. https://doi.org/10.1177/1740774516665090.
93. Phillips PPJ, Dooley KE, Gillespie SH, Heinrich N, Stout JE, Nahid P, et al. A new trial design to accelerate tuberculosis drug development: the phase IIC selection trial with extended posttreatment follow-up (STEP). BMC Med. 2016;14(1):1–11. https://doi.org/10.1186/s12916-016-0597-3.
94. Hatherill M, White RG, Hawn TR. Clinical development of new TB vaccines: recent advances and next steps. Front Microbiol. 2020;10(January):1–12. https://doi.org/10.3389/fmicb.2019.03154.
95. Sester M, van Crevel R, van Leth F, Lange C. Numbers needed to treat to prevent tuberculosis. Eur Respir J. 2015;46(6):1836–8. https://doi.org/10.1183/13993003.01047-2015.
96. Chen RY, Via LE, Dodd LE, et al. Using biomarkers to predict TB treatment duration (Predict TB): a prospective, randomized, noninferiority, treatment shortening clinical trial. *Gates Open Res*. 2017;1:9. https://doi.org/10.12688/gatesopenres.12750.1.
97. Walzl G, McNerney R, du Plessis N, Bates M, McHugh TD, Chegou NN, et al. Tuberculosis: advances and challenges in development of new diagnostics and biomarkers. Lancet Infect Dis. 2018;18(7):e199–210. https://doi.org/10.1016/S1473-3099(18)30111-7.
98. Swindells S, Andrade-Villanueva J-F, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med. 2020;382(12):1112–23. https://doi.org/10.1056/NEJMoa1904398.
99. Orkin C, Arasteh K, Górgolas Hernández-Mora M, Pokrovsky V, Overton ET, Girard PM, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med. 2020;382(12):1124–35. https://doi.org/10.1056/NEJMoa1909512.
100. Swindells S, Siccardi M, Barrett SE, Olsen DB, Grobler JA, Podany AT, et al. Long-acting formulations for the treatment of latent tuberculous infection: opportunities and challenges. Int J Tuberc Lung Dis. 2018;22(2):125–32. https://doi.org/10.5588/ijtld.17.0486.
101. Rajoli RKR, Podany AT, Moss DM, Swindells S, Flexner C, Owen A, et al. Modelling the long-acting administration of anti-tuberculosis agents using PBPK: a proof of concept study. Int J Tuberc Lung Dis. 2018;22(8):937–44. https://doi.org/10.5588/ijtld.17.0515.
102. Kaushik A, Ammerman NC, Tyagi S, Saini V, Vervoort I, Lachau-Durand S, et al. Activity of a long-acting injectable bedaquiline formulation in a paucibacillary mouse model of latent tuberculosis infection. Antimicrob Agents Chemother. 2019;63(4):1–10. https://doi.org/10.1128/AAC.00007-19.