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The Global Landscape of Tuberculosis Therapeutics

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Abstract

Tuberculosis (TB) is one of the oldest infections afflicting humans yet remains the number one infectious disease killer worldwide. Despite decades of experience treating this disease, TB regimens require months of multidrug therapy, even for latent infections. There have been important recent advances in treatment options across the spectrum of TB, from latent infection to extensively drug-resistant (XDR) TB disease. In addition, new, potent drugs are emerging out of the development pipeline and are being tested in novel regimens in multiple currently enrolling trials. Shorter, safer regimens for many forms of TB are now available or are in our near-term vision. We review recent advances in TB therapeutics and provide an overview of the upcoming clinical trials landscape that will help define the future of worldwide TB treatment.

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FIGHTING AN AGE-OLD FOE

Tuberculosis (TB) is one of the oldest diseases affecting humans, and with 10.4 million cases per year, it is the primary infectious disease killer worldwide (1). TB is caused by an airborne bacterium, *Mycobacterium tuberculosis* (*Mtb*). Most people who inhale *Mtb* develop an immune response that walls off the bacterium and prevents disease, so the primary determinants of illness are exposure risk—that is, the extent of "shared air" between infected and noninfected persons—and the immune system's ability to control early infection and prevent reactivation. As a result, the burden is primarily borne by people in heavily populated urban areas or crowded living conditions; those with impaired immunity due to HIV, medications, diabetes, smoking, alcohol use, or malnutrition; and those affected by poverty, which contributes to all other risk factors (2–5).

Treatment of people who are infected with *Mtb* but do not have TB disease, i.e., those with latent tuberculosis infection (LTBI), is an important prevention strategy. LTBI treatment with isoniazid preventive therapy (IPT), given for 6–9 months, reduces incidence of active TB by 65–75% (6), but uptake is poor, with low treatment completion rates (7). In addition, each person with untreated pulmonary TB generates 8–14 new secondary cases per year, underscoring the importance of prompt recognition and treatment (8). Standard short-course therapy with isoniazid, rifampin, pyrazinamide, and ethambutol given for the first two months in the intensive phase, followed by four months of isoniazid and rifampin administered in the continuation phase, can rapidly decrease the bacteria in a person's lungs to reduce transmission and cures most people. The ability of a drug to rapidly reduce the number of viable *Mtb* colonies in the sputum following treatment initiation is known as its early bactericidal activity. Because *Mtb* survives in both metabolically active and inactive semidormant states, effective treatments must combine drugs that have potent bactericidal activity to reduce the bacterial burden quickly (e.g., isoniazid) with those that have sterilizing activity to eradicate the semidormant bacteria that lead to later treatment failure or relapse (e.g., rifampin and pyrazinamide) and those that prevent development of resistance (e.g., ethambutol). Successful population-level TB control requires LTBI treatment, active case finding, and rapid evaluation and treatment of active TB with effective medicines (9).

Although first-line TB treatment is highly effective against drug-susceptible TB (DS-TB), many challenges remain. Substantial resources (for both the patient and the healthcare system) are needed to support the six months of treatment, especially given that drugs are provided, at least in part, by directly observed therapy. In addition, even standard TB treatment is associated with risk of liver toxicity, hypersensitivity reactions, and peripheral neuropathy, and it is complicated by drug-drug interactions (e.g., interactions with antiretroviral agents to treat HIV). Finally, the emergence of multidrug-resistant TB (MDR-TB), in which *Mtb* is resistant to both isoniazid and rifampin, is a global health threat. MDR-TB treatment requires prolonged medical care (12–24 months) with less effective, toxic medications, and there is a critical need for safer, shorter MDR-TB regimens. In this article, we review recent therapeutic advances, including treatment of LTBI, treatment-shortening trials for DS-TB, treatment of drug-resistant TB, new and repurposed TB drugs, and trials evaluating so-called universal regimens that would treat both DS-TB and MDR-TB.

LATENT TUBERCULOSIS

It is estimated that one in four people worldwide are infected with *Mtb*, and in low-burden countries, reactivated LTBI represents the bulk of active TB (10, 11). Standard LTBI treatment, with 6–9 months of daily isoniazid, prevents progression to active TB; in persons with HIV infection, IPT prevents both TB disease and death (6, 12–14). Even in high-burden settings with incident infection rates as high as 8% per year, IPT substantially reduces progression to active TB (15, 16). Despite these benefits, uptake has been stymied by the prolonged treatment duration and

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concerns about side effects or acquired resistance if active disease is not satisfactorily excluded. In addition, there is no guidance for prophylaxis after exposure to MDR-TB.

The World Health Organization (WHO) has issued two sets of recommendations for LTBI management (17, 18). The 2018 update reaffirmed the recommendations to test people at high risk, including close contacts of patients with active TB, health workers, prisoners, homeless persons, immigrants from high-burden to low-burden settings, users of injection drugs, and those with risk factors (such as HIV infection, anti–tumor necrosis factor therapy, dialysis, organ transplantation, or silicosis). This includes a screening algorithm for active TB that includes cough, fever, weight loss, and night sweats, plus chest radiography for people with HIV (in children, one substitutes poor weight gain and a known TB contact for weight loss). This approach accurately rules out active TB, with a negative predictive value of 98%, and performs well (18, 19). As a result, the strategy of "screen, test, and treat" for LTBI is now recommended for those groups at highest risk of progression from latent to active disease, especially children and HIV patients. To substantially impact the epidemic, though, large prophylactic treatment campaigns are needed. These are most feasible and cost-effective if they can target those with LTBI, who are most likely to progress quickly to TB disease (incipient TB). Even among individuals with a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA), over 95% of HIV-uninfected and 70% of HIV-infected persons do not develop active TB (12, 20). Newly identified blood mRNA expression signatures have demonstrated high specificity and sensitivity for incipient TB and may help identify high-risk individuals who can benefit most from preventive therapy (21, 22).

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Treatment Shortening

Completion rates for LTBI treatment range widely (6–94%) and are inversely proportional to treatment duration (17). To improve uptake and adherence, it is important to reduce treatment duration. In the 1990s, in trials employing two sterilizing drugs, rifampin and pyrazinamide, for two months (2RZ), the combination was effective in HIV-infected patients but was associated with three times the adverse event rate as isoniazid monotherapy (0.9 deaths and 2.8 hospitalizations per 1,000 patients) in HIV-uninfected individuals (23–26). After 2RZ was shelved, a regimen of four months of rifampin (4R) was tested and demonstrated noninferior to nine months of isoniazid (9H), with better completion rates and safety (27). A longer-acting rifamycin, rifapentine, given once weekly together with rifapentine for three months (3HP), was subsequently shown to be noninferior to 9H in a large randomized phase III trial (28, 29) and can be given without directly observed therapy as a WHO-endorsed treatment option for LTBI (30). More recently, results were presented from a phase III randomized trial comparing an ultrashort LTBI treatment—one month of daily rifapentine and isoniazid (1HP)—to 9H in HIV-positive adults and adolescents (TST or IGRA evidence of LTBI not required) (31). 1HP was noninferior to isoniazid for the prevention of active TB, death from TB, or death from unknown cause (0.69 versus 0.72 per 100 person-years). This regimen was also associated with improved treatment completion (97% versus 90%) and fewer serious adverse events than 9H (3.3 versus 5.1 per 100 person-years). Although not yet recommended for clinical use, this regimen may represent a new standard for LTBI treatment for some populations in the future.

Latent Tuberculosis Infection After Exposure to Multidrug-Resistant Tuberculosis

Worldwide, 4.1% of new TB cases and 19% of previously treated TB cases are rifampin- or multidrug-resistant, and 8.5% are isoniazid-monoresistant (1). In this context, LTBI treatment

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regimens are needed for people exposed to drug-resistant strains. Only two large studies have investigated prophylactic regimens in this context. In one, ethionamide plus standard DS-TB drugs substantially reduced the odds of active TB compared to no treatment in children (5% versus 20%) (32). In the other, 20% of untreated contacts developed TB after MDR-TB exposure, compared to none of those treated with a fluoroquinolone (given alone or with ethambutol or ethionamide) (33). Three current trials are evaluating prophylaxis for close contacts of persons with MDR-TB. These include placebo-controlled trials of six months of levofloxacin for adults (V-QUIN MDR) and for children under five years of age (TB CHAMP) and a randomized trial of a new oral nitroimidazole anti-TB prodrug, delamanid, versus isoniazid for six months (PHOENIx) in adults and children (34–36). Until these studies are completed, there is no clear guidance for management of close contacts of patients with MDR-TB.

SHORTER TREATMENT REGIMENS FOR DRUG-SUSCEPTIBLE TUBERCULOSIS

Recent trials aimed at shortening treatment duration for DS-TB have been largely unsuccessful. In three phase III trials featuring fluoroquinolone-containing experimental regimens, the treatments did not successfully reduce treatment duration to four months, despite relatively promising phase II clinical data (37–40). In the RIFAQUIN trial, participants were randomized to either standard treatment or one of two experimental arms: (*a*) a six-month arm substituting moxifloxacin for isoniazid during the intensive phase and using once-weekly moxifloxacin and rifapentine during the continuation phase, or (*b*) a four-month arm with similar moxifloxacin substitution but a shorter, twice-weekly moxifloxacin and rifapentine continuation phase (38). In that study, adherence and early culture conversion rates were higher in the moxifloxacin arms than in the standard therapy arms. However, while the six-month arm was noninferior to standard therapy, the four-month arm was not (26.9% versus 14.4% unfavorable outcome), largely owing to more relapses. The REMoxTB trial compared standard treatment with two four-month regimens: moxifloxacin substituted for isoniazid or moxifloxacin substituted for ethambutol and given for four months (39). Favorable outcomes were more frequent with standard treatment than with either the ethambutol-containing or the isoniazid-containing regimens (92%, 80%, and 85%, respectively). Finally, the OFLOTUB trial compared standard therapy to a four-month regimen that included gatifloxacin instead of ethambutol (40). Unfavorable outcomes were more common with the shorter regimen than with standard treatment (21.0 versus 17.2%), with higher associated recurrence rates (14.6% versus 7.1%). Taken together, the studies to date have shown that four-month fluoroquinolone-based regimens performed worse than standard therapy. In addition, they highlighted the weakness of two-month culture conversion and time to culture conversion in phase II studies as stand-alone predictors of the treatment-shortening potential of a regimen. In response, novel trial designs have been developed that combine early microbiologic data and relevant clinical outcomes (failure, relapse, death) to inform regimen selection for definitive trials (41).

Rifapentine, which is a rifamycin like rifampin but has a longer half-life and lower minimum inhibitory concentration (MIC) against *Mtb*, is now being evaluated in a phase III treatment-shortening trial, after pharmacokinetic-pharmacodynamic analyses of phase II data demonstrated a clear exposure–response relationship and provided evidence for selection of a 1,200 mg dose (42, 43). Two four-month regimens are being compared to a standard six-month regimen with results expected in 2020 (44).

It is also possible that the one-size-fits-all approach for treatment duration could be modified in certain populations, such as children with paucibacillary disease, who may be overtreated with the six-month regimen. The multinational SHINE trial is evaluating a four-month regimen for

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children with limited (not cavitary, nonsevere) disease (45). Stratified medicine (e.g., determining treatment duration on the basis of baseline and on-treatment characteristics) should also be explored in adults because many are over- or undertreated with the current six-month regimen.

OPTIMIZING DOSES OF FIRST- AND SECOND-LINE DRUGS

In the absence of effective treatment-shortening regimens, more attention has been placed on rifamycin dosing to maximize the effect of our most potent sterilizing drug class. The selection of the standard rifampin dose of 10 mg/kg (or 600 mg) stemmed from manufacturing cost considerations and the desire to treat as many people as possible with the lowest effective dose when the drug was introduced in the 1960s (46). Since that time, dose-escalation trials have demonstrated that doses up to 35 mg/kg are safe and well tolerated with better microbiological activity (47). One multiarm, multistage trial tested various rifampin doses (along with substitution of moxifloxacin and a novel anti-TB drug currently in development, SQ109) and found that 12-week culture conversion was better in the arms with higher rifampin dosing (70.1%, 78.7%, and 79.9% for 10, 20, and 35 mg/kg, respectively) (48). Time to culture conversion was also shortened from 62 days with 10 mg/kg to 48 days with 35 mg/kg. Whether regimens including high-dose rifampin can shorten TB treatment duration to four months or less remains to be studied.

Optimizing rifamycin dosing, particularly for disease sites with poor drug penetration, is also important. Weight-based dosing is typically required with drugs for which weight has a substantial impact on clearance. This is not true for rifampin: Low-weight adults and malnourished children consistently have lower drug exposures than other patients and should receive higher dosing (49). In TB meningitis (TBM), for example, cerebrospinal fluid concentrations of rifampin barely surpass its MIC against *Mtb* with the standard oral dose of 10 mg/kg. An observational study of high-dose intravenous rifampin (13 mg/kg, equivalent to 30 mg/kg given orally) reduced TBM-associated mortality by 53% in a small group of Indonesian patients (50). A more modest dose increase of 15 mg/kg of oral rifampin, coupled with the addition of levofloxacin to standard treatment, did not improve outcomes in a large trial in Vietnam, except in those patients later found to have isoniazid-resistant (INH-R) TBM (50, 51). Put together, these data demonstrate the importance of dosage, evidence-based weight banding, route of administration, and site of disease in treatment recommendations.

This interest in dose optimization extends to other first-line and second-line drugs as well. The phase II Opti-Q trial is an ongoing levofloxacin dose-ranging study among patients with MDR-TB (52). The AIDS Clinical Trials Group trial A5312 is testing different doses of isoniazid for patients with MDR-TB to see when and to what extent isoniazid resistance can be overcome with dose increases (53).

EMERGING DRUG RESISTANCE AND RESISTANCE-SPECIFIC THERAPY

Shortly after the introduction of effective multidrug TB therapy, resistance to those drugs appeared. On a population level, the emergence of resistance largely follows a predictable pattern: First comes resistance to isoniazid and then resistance to companion drugs rifampin, pyrazinamide, and ethambutol (54). Resistant strains can infect new hosts, and in South Africa, 70% of resistant TB represents transmitted rather than acquired resistance (55). To respond to the threat of drug-resistant TB, including MDR-TB and XDR TB (resistant to isoniazid, rifampin, fluoroquinolones, and injectable agents), recent treatment guidelines have been updated in tandem with the expansion of rapid molecular tests for resistance to the MDR- and XDR-TB defining drugs (56, 57).

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Isoniazid Monoresistance

Isoniazid-monoresistant TB (resistant to isoniazid but sensitive to rifampin) represents ~8.5% of *Mtb* worldwide and is associated with higher rates of treatment failure, relapse, and acquired resistance to other drugs than DS-TB (1, 58). In 2018, WHO issued its first guidelines for management of INH-R-TB. In a commissioned meta-analysis of individual patient-level data from cohort studies, fluoroquinolone use was associated with improved odds of treatment success and lower odds of mortality and acquired resistance (adjusted odds ratio of 2.8, 0.4, and 0.1, respectively) (56). The recommended treatment includes rifampin, ethambutol, pyrazinamide, and levofloxacin, all for six full months. This is a conditional recommendation based on low-quality evidence, highlighting the need for controlled trials in this area. Levofloxacin is prioritized over moxifloxacin due to interactions between moxifloxacin and rifampin. Pyrazinamide is continued for the entire duration—rather than only the first two months—owing to an association between shorter pyrazinamide treatment and worse treatment outcomes (adjusted odds ratio for success of 0.4). Liver function testing is recommended given the prolonged therapy with rifampin and pyrazinamide (26). It is not clear whether some forms of isoniazid resistance (e.g., resistance mediated by *inhA* gene mutations resulting in partial enzyme function and only mild increases in MIC) could be overcome with higher isoniazid dosing. An ongoing phase II dose-finding study is exploring this question (53).

Rifampin-Resistant and Multidrug-Resistant Tuberculosis

Rifampin is unique in its ability to kill semidormant and nonmetabolically active bacilli. Its sterilizing activity allows a substantially shorter duration of treatment. Without it, treatment regimens are long (18–24 months) and poorly efficacious; furthermore, they are quite toxic (59). In India, 88% of patients with DS-TB who receive standard first-line therapy including isoniazid and rifampin have a favorable outcome compared to 46% of MDR-TB patients treated with a standardized regimen that does not include rifampin (60). Until recently, drug-resistance testing was not provided in many settings due to limited global lab capacity. Gene Xpert MTB/RIF, a closed polymerase chain reaction system that identifies *Mtb* and rifampin resistance within hours, is now recommended by WHO (61). Newer versions of this test and others identify resistance to the MDR-TB and XDR-TB-defining drugs (i.e., isoniazid, rifampin, fluoroquinolones, and second-line injectables) with results available much faster than culture, even in paucibacillary sites like cerebrospinal fluid (62, 63). As a result, treatment guidelines have followed the diagnostics, lumping together rifampin-resistant TB and MDR-TB, to facilitate treatment decisions based on available clinical data. Treatment includes at least five drugs: a fluoroquinolone, an injectable drug (amikacin, kanamycin, or capreomycin), two other core drugs (ethionamide/prothionamide, cycloserine/terizidone, linezolid, or clofazimine), and add-on agents that may be active (pyrazinamide, ethambutol, bedaquiline, delamanid, high-dose isoniazid, para-aminosalicylic acid, imipenem-cilastatin, meropenem, and amoxicillin-clavulanate) (57). The drugs are given for eight months, and then oral medications are continued to complete 20 months of treatment (64). Common side effects include deafness or vertigo with injectable drugs, altered mental status with cycloserine, nausea and vomiting with ethionamide, peripheral neuropathy with linezolid, and skin discoloration with clofazimine, to name a few.

Treatment Shortening for Multidrug-Resistant Tuberculosis

Standard MDR-TB treatment is simply too long and too toxic. To address this problem, researchers in Bangladesh developed sequentially shorter and more effective regimens, achieving

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relapse-free cure for 87.9% of MDR-TB patients with the use of 4–6 months of gatifloxacin, clofazimine, pyrazinamide, ethambutol, kanamycin, prothionamide, and high-dose isoniazid, followed by – five months of gatifloxacin, clofazimine, prothionamide, pyrazinamide, and ethambutol (65, 66). The efficacy of the Bangladesh regimen has been replicated in sub-Saharan Africa (with moxifloxacin substituted for gatifloxacin and prothionamide removed from the continuation phase) and confirmed in a multicountry analysis by WHO showing 89.9% success compared to 78.3% with the standard regimen (57, 67–69). As a result, this 9- to 12-month short-course MRD-TB regimen has been recommended by WHO for patients who harbor strains that are not (or are unlikely to be) resistant to fluoroquinolones or pyrazinamide and who have not received second-line treatment before. This regimen should, however, be used with caution in areas with high background rates of drug resistance to the component drugs (70–74).

Because the data supporting this regimen come from observational studies, this regimen is being tested in randomized trials (75, 76). In preliminary analyses of the STREAM Stage 1 trial, in which participants were randomized to standard versus Bangladesh short-course treatment regimens, treatment was successful in 78.1% of participants receiving the short-course regimen and, surprisingly, 80.6% of patients in the standard therapy arm (77). Although this study did not demonstrate superiority, noninferiority is likely sufficient for a regimen that can substantially shorten MDR-TB treatment. This regimen has been adopted in many countries.

NEW AND REPURPOSED DRUGS FOR TUBERCULOSIS

Unfortunately, the story does not stop with MDR-TB. XDR-TB represents 6.2% of MDR-TB cases, and totally drug-resistant TB is now circulating in several countries. There is a dire need not only for new regimens but also for new drugs (1).

Bedaquiline

The first such drug, bedaquiline, was approved to treat MDR-TB in the United States in 2012 and in Europe in 2014 (78). Bedaquiline targets a specific mycobacterial ATP synthase, killing *Mtb* by stopping ATP production and uncoupling ATP synthesis in nonreplicating bacteria. It has demonstrated potent bactericidal and sterilizing activity (79).

Bedaquiline's impressive activity was first shown in a phase IIb trial in patients with MDR-TB on multidrug background treatment (MBT). Sputum culture conversion by eight weeks of treatment occurred in 48% of patients on bedaquiline versus 9% of patients on placebo (80). The same patients had higher six-month culture conversion rates with bedaquiline (81.0% versus 65.2%) (81). A subsequent placebo-controlled phase IIb trial of 160 MDR-TB patients confirmed that the addition of six months of bedaquiline to standard therapy improved culture conversion rates (79% versus 58% at 24 weeks, 62% versus 44% at 120 weeks) and improved cure rates (58% versus 32%) (82). Based on these data, bedaquiline was approved as an orphan drug at a dose of 400 mg daily for two weeks followed by 200 mg three times weekly for 22 weeks, but this approval came with a black box warning of both QT prolongation and an unexplained "mortality imbalance" (10/79 in the bedaquiline arm and an unexpectedly low 2/81 in the control arm). Despite the black box warning, bedaquiline has now been used in >70 countries and is associated with reduced—rather than increased—mortality. Trial data from 233 patients in 11 countries confirmed sputum conversion among 79.5% bedaquiline-treated patients at 24 weeks, cure among 61.0%, and only 6.8% mortality (83). Pending further review, WHO recommends bedaquiline be used as an add-on drug to the standard-duration MDR-TB treatment regimen, with close treatment monitoring and active pharmacovigilance (84).

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Delamanid and Pretomanid

In addition to bedaquiline, two bicyclic nitroimidazole prodrugs are being developed for MDR-TB: delamanid (trade name Deltyba) and pretomanid. These prodrugs are activated by a mycobacterial cofactor F_{420}-dependent nitroreductase enzyme. Once active, they inhibit mycolic acid synthesis in replicating *Mtb* and generate toxic nitrogen radicals in nonreplicating *Mtb*, similar to the toxic effect of cyanide (85).

Delamanid's efficacy has been demonstrated in phase II studies. In one study of patients with pulmonary MDR-TB taking MBT, those randomized to placebo, 100 mg delamanid twice daily, or 200 mg delamanid twice daily had two-month culture conversion rates of 29.6%, 45.4%, and 41.9%, respectively (86). Patients recommended by site investigators for a second randomization could then receive either 100 mg or 200 mg of delamanid twice daily for six months; prolonged treatment of $\geq$6 months seemed to be associated with longer-term treatment success (74.5% versus 55%) (87). As a result of these trials, delamanid was approved in Europe in 2013 and in Japan in 2014, and it was incorporated into WHO guidelines. In compassionate-use programs now active in multiple countries, the recommended dose is 100 mg twice daily for two months followed by 200 mg daily for the next four months. In a subsequent phase III trial in which patients on MBT were randomized to the addition of delamanid versus placebo, delamanid showed a modestly shorter time to culture conversion, but there was no difference in treatment success at 30 months (77.1% versus 77.6%), mortality (5.3% versus 4.7%), or six-month culture conversion (87.6% versus 86.1%) (88). The role of delamanid in multidrug therapy is still being established as data from this trial and others become public.

Pretomanid remains investigational. In one phase IIa study evaluating the early bactericidal activity of multiple combination therapies [bedaquiline alone, bedaquiline with pretomanid, bedaquiline with pyrazinamide, pretomanid with pyrazinamide, and pretomanid with moxifloxacin and pyrazinamide over two weeks. The combination of pretomanid, moxifloxacin, and pyrazinamide (PaMZ) was highly potent, exceeding the activity of standard first-line four-drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol (89). PaMZ was also effective in an eight-week phase IIb trial. PaMZ was subsequently tested in a phase III trial called STAND, which was placed on temporary hold by the US Food and Drug Administration while the agency reviewed hepatotoxicity events among study participants. In the meantime, a different trial, NC-005, demonstrated the exquisite activity of PaMZ plus bedaquiline, prompting this regimen to be studied in the soon-to-open SimpliciTB trial (90). Because this regimen does not include isoniazid or rifampin, some refer to it as a universal regimen that, if effective, could treat patients with either DS-TB or MDR-TB. To help those patients with the greatest unmet medical need, NixTB was designed as a single-arm phase III trial of six months of therapy with bedaquiline, pretomanid, and linezolid for patients with XDR-TB. This regimen has shown >80% six-month culture conversion rates, with longer-term data not yet available, and may form the basis for a new drug application in the United States (91).

Linezolid and Sutezolid

In the search for better MDR-TB treatments, interest has also turned to repurposing existing antibiotics toward *Mtb*. Chief among these is linezolid, an oxazolidinone that has primarily been used against gram-positive cocci. Linezolid first demonstrated efficacy against *Mtb* in a small trial in which linezolid was added to a failing regimen in patients with XDR-TB, either at study entry or two months later (92). Overall, 87% of patients receiving linezolid achieved sputum culture conversion within six months of treatment. Unfortunately, the majority had treatment-limiting adverse events requiring dose reduction (92, 93). The dose of linezolid that optimizes activity while

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minimizing toxicity is still being worked out. In addition to evaluating linezolid, other oxazolidinones are being considered for TB. Sutezolid, like linezolid, inhibits protein synthesis, but it has a higher inhibitory concentration than linezolid, suggesting a more favorable therapeutic margin (94). Its development for TB stopped after early phase II work but may be revived soon (95, 96).

CURRENT LANDSCAPE

In addition to the trials described above, multiple currently enrolling trials are evaluating the safety and efficacy of combinations of these new drugs (97, 98) (**Table 1**). One primary focus is on shorter,

Table 1 Ongoing clinical trials in tuberculosis

Study (Reference)	Problem or goal	Phase	Treatment strategy
V-QUIN MDR (34)	LTBI after MDR-TB exposure	Phase III	Levofloxacin versus placebo for LTBI
TB CHAMP (35)	LTBI after MDR-TB exposure	Phase III	Levofloxacin versus placebo for LTBI in children
PHOENIx (36)	LTBI after MDR-TB exposure	Phase III	Delamanid versus isoniazid for LTBI in adults and children
TBTC Study 31 (44)	Treatment shortening for DS-TB	Phase III	Rifapentine and moxifloxacin for DS-TB
SHINE (45)	Treatment shortening for limited pediatric DS-TB	Phase III	4 versus 6 months of standard treatment
ACTG A5312 (53)	Dose optimization	Phase II	Isoniazid dose ranging for TB with *inhA* mutations
Opti-Q (52)	Dose optimization	Phase II	Levofloxacin dose ranging
LINEZOLIDE (102)	Dose optimization	Phase II	Linezolid dose ranging
NCT01856634 (103)	Safety, tolerability, and pharmacokinetics	Phase I	Pediatric delamanid dose finding
NCT01859923 (104)	Safety, tolerability, and pharmacokinetics	Phase II	Pediatric delamanid dose finding
NCT02354014 (105)	Safety, tolerability, and pharmacokinetics	Phase II	Pediatric bedaquiline dose finding
ACTG A5343 (106)	Safety, tolerability, and pharmacokinetics	Phase II	MBT + bedaquiline, delamanid, or both for MDR-TB
TB-PRACTECAL (98)	Treatment shortening for MDR-TB	Phase II–III	Bedaquiline, pretomanid, linezolid, clofazimine, and moxifloxacin-based regimens versus MBT for MDR-TB
endTB (99)	Injection-sparing MDR-TB treatment	Phase III	Multiarm injection-free trial including bedaquiline, delamanid, clofazimine, levofloxacin, moxifloxacin, linezolid, and pyrazinamide for MDR-TB
MDR-END (101)	Injection-sparing MDR-TB treatment	Phase II	Injection-free regimen including delamanid, linzeolid, levofloxacin, and pyrazinamide versus MBT for MDR-TB
NEXT (100)	Injection-sparing MDR-TB treatment	Phase II–III	Injection-free regimen including bedaquiline, levofloxacin, linezolid, pyrazinamide and ethionamide/high-dose isoniazid (INH) versus MBT for MDR-TB
NixTB (91)	Injection-sparing XDR-TB treatment	Phase III	Bedaquiline, pretomanid, and linezolid for XDR-TB

(*Continued*)

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Table 1 (*Continued*)

Study (Reference)	Problem or goal	Phase	Treatment strategy
STREAM (75)	Treatment shortening for MDR-TB	Phase III	Bangladesh regimen versus standard treatment for MDR-TB
STREAM Stage 2 (107)	Injection-sparing MDR-TB treatment	Phase III	9 months versus 6 months of injection-free MDR-TB treatment
ZeNix (108)	Injection-sparing XDR-TB treatment	Phase III	Dose-ranging injection-free regimen of bedaquiline, pretomanid, and linezolid for MDR- and XDR-TB
SimpliciTB (90)	Universal regimen	Phase III	Treatment-shortening trial of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide for MDR-TB and DS-TB
InDEX (109)	Personalized treatment for MDR-TB	Phase IV	Personalized whole genome sequencing-based treatment for MDR-TB

Abbreviations: ACTG, AIDS Clinical Trials Group; DS-TB, drug-susceptible tuberculosis; INH, high-dose isoniazid; LTBI, latent tuberculosis infection; MDR-TB, multidrug-resistant tuberculosis; MBT, multidrug background treatment; XDR-TB, extensively drug-resistant tuberculosis.

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injection-free treatment regimens for MDR-TB (99–101), with the goal that such regimens could reduce the toxicities common to many new or second-line drugs, such as QT prolongation. In addition to the drugs described above, all of which are in middle to late development, there is a modestly robust pipeline of drugs entering the clinical arena for testing in phase I and early phase II studies, including newer versions of the recently developed new and repurposed drugs that are optimized to increase efficacy or reduce toxicity (e.g., oxazolidinones, nitroimidazoles, ATP synthase inhibitors), as well as compounds with novel mechanisms of action [inhibition of the cell wall synthesis enzyme decaprenyl-phosphoryl-β-D-ribofuranose oxidoreductase (DprE1), inhibition of protein synthesis via leucyl-tRNA synthetase (LeuRS), and alternative inhibitors of energy metabolism]. It is a very exciting time in TB drug development.

CONCLUSIONS

In recent years, two new TB drugs have entered the market, and multiple compounds are in the development pipeline. Short, highly effective, safe regimens for LTBI have been identified in phase III trials and are ripe for broad-scale implementation to bring the burden of disease down. Shorter-duration treatments effective for even the hardest-to-treat patients with DS-TB, though more elusive, are in our sights. There is now a recommended regimen for isoniazid-monoresistant TB (though trial data to support it are lacking), and WHO has recently sanctioned a significantly shorter (9–12 months, as opposed to 18–24 months) regimen for MDR-TB. Yet the short-course seven-drug MDR-TB regimen remains complex and poorly tolerated, and it includes months of intramuscular injections. Safer, shorter, all-oral regimens for MDR-TB are being tested in multiple well-controlled clinical trials, so there is hope for better treatments in this area as well. Even XDR-TB, previously thought untreatable, has been effectively treated with a six-month, three-drug regimen, albeit with notable (largely reversible) toxicities.

DISCLOSURE STATEMENT

K.D. is an investigator on trials sponsored by the National Institutes of Health, Centers for Disease Control and Prevention, US Food and Drug Administration, or Unitaid involving tuberculosis drugs, to include high-dose isoniazid, rifapentine, delamanid, pretomanid, bedaquiline, high-dose

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rifampicin, levofloxacin, meropenem, and amoxicillin-clavulanate, but receives no salary support or other funding from drug companies for these projects.

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Annu. Rev. Med. 2019.70. Downloaded from www.annualreviews.org
Access provided by INSEAD on 12/25/18. For personal use only.

LITERATURE CITED

1. World Health Organ. 2017. *Global Tuberculosis Report 2017*. Geneva: World Health Organ.
2. Chaisson RE, Martinson NA. 2008. Tuberculosis in Africa–combating an HIV-driven crisis. *N. Engl. J. Med.* 358:1089–92
3. Dye C, Bourdin Trunz B, Lonnroth K, et al. 2011. Nutrition, diabetes and tuberculosis in the epidemiological transition. *PLOS ONE* 6:e21161
4. Lawn SD, Zumla AI. 2011. Tuberculosis. *Lancet* 378:57–72
5. Lonnroth K, Castro KG, Chakaya JM, et al. 2010. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet* 375:1814–29
6. Comstock GW. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int. J. Tuberc. Lung Dis.* 3:847–50
7. Stockbridge EL, Miller TL, Carlson EK, et al. 2017. Tuberculosis prevention in the private sector: using claims-based methods to identify and evaluate latent tuberculosis infection treatment with isoniazid among the commercially insured. *J. Public Health Manag. Pract.* 24:E25–33
8. Kendall EA, Fofana MO, Dowdy DW. 2015. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. *Lancet Respir. Med.* 3:963–72
9. Dowdy DW, Grant AD, Dheda K, et al. 2017. Designing and evaluating interventions to halt the transmission of tuberculosis. *J. Infect. Dis.* 216:S654–61
10. Houben RM, Dodd PJ. 2016. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLOS Med.* 13:e1002152
11. Yuen CM, Kammerer JS, Marks K, et al. 2016. Recent transmission of tuberculosis—United States, 2011–2014. *PLOS ONE* 11:e0153728
12. Akolo C, Adetifa I, Shepperd S, et al. 2010. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst. Rev.* 20:CD000171
13. Golub JE, Cohn S, Saraceni V, et al. 2015. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin. Infect. Dis.* 60:639–45
14. Badje A, Moh R, Gabillard D, et al. 2017. 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* 5:e1080–89
15. Christopher DJ, James P, Daley P, et al. 2011. High annual risk of tuberculosis infection among nursing students in South India: a cohort study. *PLOS ONE* 6:e26199
16. Raj R, Prasad H, Arya BK, et al. 2011. Isoniazid preventive therapy programmes for healthcare workers in India: translating evidence into policy. *Natl. Med. J. India* 24:201–7

Review in Advance first posted on November 7, 2018. (Changes may still occur before final publication.)

Annu. Rev. Med. 2019.70. Downloaded from www.annualreviews.org
Access provided by INSEAD on 12/25/18. For personal use only.

17. World Health Organ. 2015. *Guidelines on the Management of Latent Tuberculosis Infection*. Geneva: World Health Organ.
18. World Health Organ. 2018. *Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management*. Geneva: World Health Organ.
19. Getahun H, Kittikraisak W, Heilig CM, et al. 2011. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLOS Med.* 8:e1000391
20. Smieja MJ, Marchetti CA, Cook DJ, et al. 2000. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst. Rev.* 2000:CD001363
21. Zak DE, Penn-Nicholson A, Scriba TJ, et al. 2016. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet* 387:2312–22
22. Suliman S, Thompson E, Sutherland J, et al. 2018. Four-gene pan-African blood signature predicts progression to tuberculosis. *Am. J. Respir. Crit. Care Med.* In press
23. Halsey NA, Coberly JS, Desormeaux J, et al. 1998. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet* 351:786–92
24. Gordin F, Chaisson RE, Matts JP, et al. 2000. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. *JAMA* 283:1445–50
25. Gao XF, Wang L, Liu GJ, et al. 2006. Rifampicin plus pyrazinamide versus isoniazid for treating latent tuberculosis infection: a meta-analysis. *Int. J. Tuberc. Lung Dis.* 10:1080–90
26. McElroy PD, Ijaz K, Lambert LA, et al. 2005. National survey to measure rates of liver injury, hospitalization, and death associated with rifampin and pyrazinamide for latent tuberculosis infection. *Clin. Infect. Dis.* 41:1125–33
27. Aspler A, Long R, Trajman A, et al. 2010. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. *Thorax* 65:582–87
28. Zenner D, Beer N, Harris RJ, et al. 2017. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann. Intern. Med.* 167:248–55
29. Sterling TR, Villarino ME, Borisov AS, et al. 2011. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N. Engl. J. Med.* 365:2155–66
30. Belknap R, Holland D, Feng PJ, et al. 2017. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. *Ann. Intern. Med.* 167:689–97
31. Swindells SRR, Gupta R, Gupta A, et al. 2018. *One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279*. Paper presented at Conf. Retrovir. Opportunistic Infect., Mar. 4–7, Boston, MA. **http://www.croiconference.org/sessions/one-month-rifapentineisoniazid-prevent-tb-people-hiv-brief-tba5279**
32. Schaaf HS, Gie RP, Kennedy M, et al. 2002. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics* 109:765–71
33. Bamrah S, Brostrom R, Dorina F, et al. 2014. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. *Int. J. Tuberc. Lung Dis.* 18:912–18
34. ANZCTR. 2017. The V-QUIN MDR TRIAL: A randomized controlled trial of six months of daily levofloxacin for the prevention of tuberculosis among household contacts of patients with multi-drug resistant tuberculosis. *Australian New Zealand Clinical Trials Registry*. **https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817**
35. ISRCTN Regist. 2017. Tuberculosis child multidrug-resistant preventive therapy: TB CHAMP trial. *ISRCTN registry*. **http://www.isrctn.com/ISRCTN92634082**
36. IMPAACT Netw. 2014. IMPAACT 2003B: (PHOENIx) (DAIDS ID 12041): Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant TB Patients. *International Maternal Pediatric Adolescent AIDS Clinical Trials Netw*. **http://impaactnetwork.org/studies/IMPAACT2003B.asp**
37. Chennai TRCICoMR. 2002. Shortening short course chemotherapy: a randomised clinical trial for treatment of smear positive pulmonary tuberculosis with regimens using ofloxacin in the intensive phase. *Indian J. Tuberc.* 49:27–38

Review in Advance first posted on November 7, 2018. (Changes may still occur before final publication.)

Annu. Rev. Med. 2019.70. Downloaded from www.annualreviews.org
Access provided by INSEAD on 12/25/18. For personal use only.

38. Jindani A, Harrison TS, Nunn AJ, et al. 2014. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N. Engl. J. Med.* 371:1599–608
39. Gillespie SH, Crook AM, McHugh TD, et al. 2014. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N. Engl. J. Med.* 371:1577–87
40. Merle CS, Fielding K, Sow OB, et al. 2014. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N. Engl. J. Med.* 371:1588–98
41. Phillips PP, Dooley KE, Gillespie SH, et al. 2016. A new trial design to accelerate tuberculosis drug development: the Phase IIC Selection Trial with Extended Post-treatment follow-up (STEP). *BMC Med*. 14:51
42. Dorman SE, Savic RM, Goldberg S, et al. 2015. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial. *Am. J. Respir. Crit. Care Med.* 191:333–43
43. Savic RM, Weiner M, MacKenzie WR, et al. 2017. Defining the optimal dose of rifapentine for pulmonary tuberculosis: exposure-response relations from two phase II clinical trials. *Clin. Pharmacol. Ther.* 102:321–31
44. ClinicalTrials.gov. 2016. TBTC Study 31: rifapentine-containing tuberculosis treatment shortening regimens (S31/A5349). *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT02410772**
45. MRC Clin. Trials. 2014. A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/fixed-dose-combination drugs in African and Indian HIV+ and HIV− children. *Medical Research Council Clinical Trials Unit at UCL*. **http://www.ctu.mrc.ac.uk/our_research/research_areas/tuberculosis/studies/shine/**
46. van Ingen J, Aarnoutse RE, Donald PR, et al. 2011. Why do we use 600 mg of rifampicin in tuberculosis treatment? *Clin. Infect. Dis.* 52:e194–99
47. Boeree MJ, Diacon AH, Dawson R, et al. 2015. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am. J. Respir. Crit. Care Med.* 191:1058–65
48. Boeree MJ, Heinrich N, Aarnoutse R, et al. 2017. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect. Dis.* 17:39–49
49. Court R, Chirehwa MT, Wiesner L, et al. 2018. Quality assurance of rifampicin-containing fixed-drug combinations in South Africa: dosing implications. *Int. J. Tuberc. Lung Dis.* 22:537–43
50. Ruslami R, Ganiem AR, Dian S, et al. 2013. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect. Dis.* 13:27–35
51. Heemskerk AD, Bang ND, Mai NT, et al. 2016. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N. Engl. J. Med.* 374:124–34
52. ClinicalTrials.gov. 2018. Efficacy and safety of levofloxacin for the treatment of MDR-TB (Opti-Q). *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT01918397**
53. ClinicalTrials.gov. 2018. High-dose isoniazid among adult patients with different genetic variants of INH-resistant tuberculosis (TB). *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT01936831**
54. Manson AL, Cohen KA, Abeel T, et al. 2017. Genomic analysis of globally diverse *Mycobacterium tuberculosis* strains provides insights into the emergence and spread of multidrug resistance. *Nat. Genet.* 49:395–402
55. Shah NS, Auld SC, Brust JC, et al. 2017. Transmission of extensively drug-resistant tuberculosis in South Africa. *N. Engl. J. Med.* 376:243–53
56. World Health Organ. 2018. *WHO Treatment Guidelines for Isoniazid-Resistant Tuberculosis: Supplement to the WHO Treatment Guidelines for Drug-Resistant Tuberculosis*. Geneva: World Health Organ.
57. World Health Organ. 2016. *WHO Treatment Guidelines for Drug-Resistant Tuberculosis 2016 Update*. Geneva: World Health Organ.
58. Gegia M, Winters N, Benedetti A, et al. 2017. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect. Dis.* 17:223–34
59. Isaakidis P, Rangan S, Pradhan A, et al. 2013. 'I cry every day': experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. *Trop. Med. Int. Health* 18:1128–33
60. Revis. Natl. Tuberc. Control Program. 2017. *Revised National Tuberculosis Control Programme: Annual Status Report: Unite to End TB*. Cent. TB Div., Minist. Health Fam. Welf.: New Delhi

Review in Advance first posted on November 7, 2018. (Changes may still occur before final publication.)

Annu. Rev. Med. 2019.70. Downloaded from www.annualreviews.org
Access provided by INSEAD on 12/25/18. For personal use only.

61. Boehme CC, Nabeta P, Hillemann D, et al. 2010. Rapid molecular detection of tuberculosis and rifampin resistance. *N. Engl. J. Med.* 363:1005–15
62. Dorman SE, Schumacher SG, Alland D, et al. 2018. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect. Dis.* 18:76–84
63. Ajbani K, Nikam C, Kazi M, et al. 2012. Evaluation of genotype MTBDRsl assay to detect drug resistance associated with fluoroquinolones, aminoglycosides and ethambutol on clinical sediments. *PLOS ONE* 7:e49433
64. World Health Organ. 2011. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: 2011 Update*. Geneva: World Health Organ.
65. Van Deun A, Salim MA, Das AP, et al. 2004. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. *Int. J. Tuberc. Lung Dis.* 8:560–67
66. Van Deun A, Maug AK, Salim MA, et al. 2010. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am. J. Respir. Crit. Care Med.* 182:684–92
67. Aung KJ, Van Deun A, Declercq E, et al. 2014. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int. J. Tuberc. Lung Dis.* 18:1180–87
68. Kuaban C, Noeske J, Rieder HL, et al. 2015. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int. J. Tuberc. Lung Dis.* 19:517–24
69. Piubello A, Harouna SH, Souleymane MB, et al. 2014. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int. J. Tuberc. Lung Dis.* 18:1188–94
70. Dalcolmo M, Gayoso R, Sotgiu G, et al. 2017. Resistance profile of drugs composing the "shorter" regimen for multidrug-resistant tuberculosis in Brazil, 2000–2015. *Eur. Respir. J.* 49:pii1602309
71. Javaid A, Ahmad N, Khan AH, et al. 2017. Applicability of the World Health Organization recommended new shorter regimen in a multidrug-resistant tuberculosis high burden country. *Eur. Respir. J.* 49:pii1601967
72. Chee CBE, KhinMar KW, Sng LH, et al. 2017. The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: Are patients from South-East Asia eligible? *Eur. Respir. J.* 50:pii1700753
73. Lange C, Duarte R, Frechet-Jachym M, et al. 2016. Limited benefit of the new shorter multidrug-resistant tuberculosis regimen in Europe. *Am. J. Respir. Crit. Care Med.* 194:1029–31
74. van der Werf MJ, Hollo V, Ködmön C, et al. 2017. Eligibility for shorter treatment of multidrug-resistant tuberculosis in the European Union. *Eur. Respir. J.* 49:pii1601992
75. Nunn AJ, Rusen ID, Van Deun A, et al. 2014. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials* 15:353
76. MRC Clin. Trials. 2016. The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with MDR-TB. *Medical Research Council Clinical Trials Unit at UCL*. **http://www.ctu.mrc.ac.uk/our_research/research_areas/tuberculosis/studies/stream_stage1/**
77. Union. 2017. STREAM clinical trial results provide vital insight into nine-month treatment regimen for multidrug-resistant tuberculosis. *International Union Against Tuberculosis and Lung Disease*. **http://guadalajara.worldlunghealth.org/media/conference-news/updates/stream-clinical-trial-results-provide-vital-insight-into-nine-month-treatment-regimen-for-multidrug-resistant-tuberculosis**
78. Andries K, Verhasselt P, Guillemont J, et al. 2005. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis. Science* 307:223–27
79. Preiss L, Langer JD, Yildiz O, et al. 2015. Structure of the mycobacterial ATP synthase F_o rotor ring in complex with the anti-TB drug bedaquiline. *Sci. Adv.* 1:e1500106
80. Diacon AH, Pym A, Grobusch M, et al. 2009. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N. Engl. J. Med.* 360:2397–405
81. Diacon AH, Donald PR, Pym A, et al. 2012. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob. Agents Chemother.* 56:3271–76
82. Diacon AH, Pym A, Grobusch MP, et al. 2014. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N. Engl. J. Med.* 371:723–32

Review in Advance first posted on November 7, 2018. (Changes may still occur before final publication.)

Annu. Rev. Med. 2019.70. Downloaded from www.annualreviews.org
Access provided by INSEAD on 12/25/18. For personal use only.

83. Pym AS, Diacon AH, Tang SJ, et al. 2015. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur. Respirat. J.* 47:564–74
84. World Health Organ. 2017. *Report of the Guideline Development Group Meeting on the Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis: a Review of Available Evidence (2016)*. Geneva: World Health Organ.
85. Manjunatha U, Boshoff HI, Barry CE. 2009. The mechanism of action of PA-824: novel insights from transcriptional profiling. *Commun. Integr. Biol.* 2:215–18
86. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. 2012. Delamanid for multidrug-resistant pulmonary tuberculosis. *N. Engl. J. Med.* 366:2151–60
87. Skripconoka V, Danilovits M, Pehme L, et al. 2013. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur. Respir. J.* 41:1393–400
88. World Health Organ. 2018. *WHO Position Statement on the Use of Delamanid for MDR-TB*. Geneva: World Health Organ.
89. Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 2012. 14-Day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 380:986–93
90. ClinicalTrials.gov. 2018. Trial to evaluate the efficacy, safety, and tolerability of BPaMZ in drug-sensitive (DS-TB) adult patients and drug-resistant (DR-TB) adult patients. *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT03338621**
91. ClinicalTrials.gov. 2018. A Phase 3 study assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in subjects with drug resistant pulmonary tuberculosis. *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT02333799**
92. Lee M, Lee J, Carroll MW, et al. 2012. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N. Engl. J. Med.* 367:1508–18
93. Lee M, Cho SN, Barry CE 3rd, et al. 2015. Linezolid for XDR-TB–final study outcomes. *N. Engl. J. Med.* 373:290–91
94. Alffenaar JW, van der Laan T, Simons S, et al. 2011. Susceptibility of clinical *Mycobacterium tuberculosis* isolates to a potentially less toxic derivate of linezolid, PNU-100480. *Antimicrob. Agents Chemother.* 55:1287–89
95. Wallis RS, Jakubiec W, Mitton-Fry M, et al. 2012. Rapid evaluation in whole blood culture of regimens for XDR-TB containing PNU-100480 (sutezolid), TMC207, PA-824, SQ109, and pyrazinamide. *PLOS ONE* 7:e30479
96. Wallis RS, Dawson R, Friedrich SO, et al. 2014. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. *PLOS ONE* 9:e94462
97. ClinicalTrials.gov. 2018. Evaluating the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination, for drug-resistant pulmonary tuberculosis. *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT02583048**
98. ClinicalTrials.gov. 2018. Pragmatic clinical trial for a more effective concise and less toxic MDR-TB treatment regimen(s) (TB-PRACTECAL). *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT02589782**
99. ClinicalTrials.gov. 2018. Evaluating newly approved drugs for multidrug-resistant TB (endTB). *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/record/NCT02754765**
100. ClinicalTrials.gov. 2016. An open-label RCT to evaluate a new treatment regimen for patients with multi-drug resistant tuberculosis (NEXT). *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT02454205**
101. ClinicalTrials.gov. 2016. Treatment shortening of MDR-TB using existing and new drugs (MDR-END). *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT02619994**
102. ClinicalTrials.gov. 2018. Pharmacokinetic and therapeutic adaptation of linezolid in the treatment of multi-resistant tuberculosis (LINEZOLIDE). *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT02778828**
103. ClinicalTrials.gov. 2018. Pharmacokinetic and safety trial to determine the appropriate dose for pediatric patients with multidrug resistant tuberculosis. *U.S. National Library of Medicine*. **https://clinicaltrials.gov/ct2/show/NCT01856634**

Review in Advance first posted on November 7, 2018. (Changes may still occur before final publication.)

104. ClinicalTrials.gov. 2018. A 6-month safety, efficacy, and PK trial of delamanid in pediatric patients with multidrug resistant tuberculosis. *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT01859923**
105. ClinicalTrials.gov. 2018. Pharmacokinetic study to evaluate anti-mycobacterial activity of TMC207 in combination with background regimen (BR) of multidrug resistant tuberculosis (MDR-TB medications for treatment of children/adolescents pulmonary MDR-TB. *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT02354014**
106. ClinicalTrials.gov. 2018. Evaluating the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination, for drug-resistant pulmonary tuberculosis. *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT02583048**
107. MRC Clin. Trials. 2016. The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with MDR-TB. *Medical Research Council Clinical Trials Unit at UCL.* **http://www.ctu.mrc.ac.uk/our_research/research_areas/tuberculosis/studies/stream_stage2**
108. ClinicalTrials.gov. 2018. Safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary TB, XDR-TB, Pre- XDR-TB or non-responsive/intolerant MDR-TB (ZeNix). *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT03086486**
109. ClinicalTrials.gov. 2018. The individualized M(X) drug-resistant TB treatment strategy study (InDEX). *U.S. National Library of Medicine.* **https://clinicaltrials.gov/ct2/show/NCT03237182**

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