*Invited Review*

# Update on Tuberculosis/HIV Coinfections: Across the Spectrum From Latent Infection Through Drug-Susceptible and Drug-Resistant Disease

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*Tuberculosis (TB) remains the leading cause of death among people with HIV, and annual risk of progression from latent TB infection to active disease in this population is 10%. Diagnostic tests for latent and active TB remain suboptimal for people with HIV who have a CD4+ count below 200 cells/µL, and there is an urgent need for assays that predict progression from latent to active disease, monitor treatment response, and test for cure after latent and active TB treatment. Traditional treatment duration for latent infection and active TB disease has been onerous for patients; however, shorter-course regimens are increasingly available across the spectrum of TB, including for drug-resistant TB. Simultaneous treatment of HIV and TB is complicated by drug-drug interactions, although trials are ongoing to better understand the magnitude of these interactions and guide clinicians in how to use short-course regimens, particularly for people with HIV.*

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## Background

Tuberculosis (TB) remains a global threat to public health, with 10 million new cases and 1.2 million deaths attributed to TB in 2019. Despite the

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dramatic improvement in global access to antiretroviral therapy (ART), TB is still the leading cause of death among people with HIV.[1] Additionally, 1 in 4 people in the world have latent TB infection (LTBI).[2]

TB is spread from person to person via airborne droplet nuclei; recent data also suggest that aerosolization via passive breaths may contribute to onward spread of TB, including in individuals with asymptomatic infection.[3] As with other respiratory infections, the risk of TB transmission is determined by the infectiousness of the index case, host susceptibility, and duration as well as proximity of exposure. Although TB is largely a pulmonary disease, it can infect any area of the body; TB meningitis, one form of extra-pulmonary disease, is the most lethal manifestation of TB.

Despite the massive global burden of TB and the morbidity and mortality risks it confers, resources to diagnose, treat, cure, and prevent TB are still inadequate. In 2019, global funding for research and development of TB therapeutics reached an all-time high of US $906.4 million, a triumph that still falls far short of the US $2 billion recommended by the 2018 United Nations General Assembly High-Level Meeting on Tuberculosis,[4] and of the US $10 billion over 2 years recommended by the Stop TB Partnership.[5] Prevention efforts have also been hampered by the lack of an effective vaccine. Currently, the bacille Calmette-Guérin (BCG) vaccine is the only available tool to prevent infection and, at best, reduces TB infection by 50%.[6] Because of its variable efficacy as well as injection-site reactions and risk of local or systemic infection, BCG vaccine is now only used in high–TB-burden countries where the benefits outweigh the potential risks. Finally,

TB remains a heavily stigmatized disease and is inextricably linked to poverty and poor living conditions. Stigmatization is a major barrier to seeking care among persons with TB, and this has worsened during the SARS-CoV-2 pandemic. The Global Fund estimates that about 1 million fewer patients were treated for TB in 2020; the COVID-19 pandemic is likely to adversely affect TB control worldwide for decades to come.

Although HIV was only identified in the last 40 years, patients and clinicians have access to a variety of fully active, well-tolerated regimens, many of which are available in 1-pill-per-day combinations or in long-acting injectable formulations. In contrast, the TB bacterium was identified more than 140 years ago, and there is only one regimen considered the standard of care for drug-susceptible (DS) TB. There has been little incentive for pharmaceutical companies to participate in the TB drug development process, given the limitations of existing animal models for preclinical drug testing, the challenges posed by the pharmacokinetic (PK)–pharmacodynamic relationship between mycobacterial agents and TB, and the low expected financial returns. Thankfully, after decades of limited options, the TB pipeline is now increasingly accumulating promising candidates in preclinical and clinical testing (Table 1).

## Spectrum of TB Disease

TB has historically been categorized as latent or active, but infection and disease exist on a spectrum. On one end of that spectrum, exposed individuals may immediately eliminate the bacteria from the body via an innate or an acquired immune response without memory T-cell response. These individuals would not develop symptoms or evidence of TB infection based on tuberculin skin test (TST) or interferon gamma release assay (IGRA). There are others who eliminate TB after exposure but do have a memory T-cell response, and therefore would have positive TST and IGRA test results. A third group acquires TB, but the bacteria remain in a quiescent (or latent) form, conferring future risk of activation to TB disease. For the 23% of the world population that is infected with TB, their lifetime risk of

developing active disease is 10%. However, among those with HIV who are latently infected, the risk of developing TB disease is 10% per year. Subclinical TB disease is a more recently described condition in which individuals do not develop symptoms but nonetheless have low-level active disease with intermittently positive mycobacterial cultures. Among people who develop symptomatic TB disease, there is a range of severity from minimally ill to severely and critically ill; some of the latter cases are further complicated by the development of pulmonary cavitation and dissemination of disease outside of the lungs.

## Diagnosis of Latent TB

Among those individuals who are exposed to TB and develop a memory immune response but who do not immediately progress to active disease, testing for latent disease with TST or IGRA is likely to yield positive results. A TB skin test is performed by injecting tuberculin purified protein derivative (PPD) intradermally in the forearm. If a patient is infected with TB, this injection will induce an immune response and induration at the injection site. What constitutes a positive result on TST depends on the pretest probability for TB, as well as the likelihood of a robust immune response. For patients with HIV, other immunosuppressed individuals, and those who are close contacts of people with TB, a lower threshold of 5 mm induration at the injection site is considered positive. A diameter of 10 mm is considered positive for people born in countries where TB is common, those with certain medical conditions that increase risk of TB, and those who work or reside in settings where TB exposure would be likely. A higher threshold of 15 mm is used for those with no known risk factors for TB infection. IGRA testing measures the immune response to TB in whole blood. Sensitivity of all LTBI testing is about 80% in the general population and 64% to 70% among those with HIV. Anergy, or lack of response, on TST or an indeterminate result on an IGRA test is more likely among people with HIV who have a low CD4+ count, generally defined as less than 200 cells/µL. Positive testing using any of these assays is likely to persist; therefore, there is rarely any value

**Table 1.** 2021 Global New Tuberculosis Drug Pipeline by Stage and Development.[a]

| Discovery | Preclinical development | | | Clinical development | | | Regulatory market approval |
|---|---|---|---|---|---|---|---|
| Lead optimization | Early-stage development | Good manufacturing practice / good laboratory practice toxicology | Phase I | Phase II | Phase III | | |
| PanD inhibitors | JSF-3285[b] | FNDR-20081[b] | BVL-GSK098[b] | Delpazolid | Pretomanid[b]/moxifloxacin/bedaquiline[b]/ pyrazinamide (4-month regimen) | | Bedaquiline[b] |
| Indazole sulfonamides | MPL-446, 447[b] | TB-47[b] | GSK-286[b] | BTZ-043[b] | Truncate TB (2-month regimens) | | Delamanid[b] |
| Diarylthiazoles | CPZEN-45[b] | GSK-839[b] | TBAJ-587 | | Rifapentine/moxifloxacin/isoniazid/ pyrazinamide (4-month regimen) | | Pretomanid[b] |
| DprE1 inhibitors | NTB-3119[b] | OTB-658 | TBAJ-876 | TBA-7371[b] | | | |
| Direct InhA inhibitors | TZY-5-84 | Sanfetrinem | TBI-223 | OPC-167832[b] | | | |
| Mtb energy metabolism | MBX-4888A (1810)[b] | | Macozinone[b] (PBTZ-169) | GSK-656[b] (070) | | | |
| Macrolides | FNDR-10045[b] | | Pyrifazimine (TBI-166) | SQ-109[b] | | | |
| Mycobacterial gyrase inhibitors | FNDR-20364[b] | | | Telacebec[b] | | | |
| Arylsulfonamides | | | | SPR720[b] | | | |
| Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase, Oxazolidinones | | | | | | | |

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[a]New molecular entities are not yet approved, are being developed for tuberculosis, or are only conditionally approved for tuberculosis. This table lists the most advanced stage reported for each drug as as of October 2021, except for highlighted drug names, which are current as of March 2021.

[b]New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, and beta-lactam.

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in repeat testing once a positive result is observed. These are also indirect tests, as it is not possible to grow the TB bacterium from an infected person or to test for drug susceptibility of the infecting strain.

## Diagnosis of Active TB

For over a century, the mainstay of diagnosis for active TB disease has been smear microscopy and culture on solid media. In the last decade, rapid molecular diagnostic tests have entered clinical practice and have considerably shortened the time to TB diagnosis. The Xpert mycobacterium tuberculosis/rifampicin (Mtb/RIF) platform generates results in 2 hours, is more sensitive than smear microscopy for acid-fast bacilli (AFB), and can identify rifampicin resistance.[7] Xpert Ultra has further increased sensitivity and reduced time to result.[8] Genotype Mtb drug resistant (MtbDR) plus gives results in 5 hours and is able to identify isoniazid (INH) and rifampicin resistance. Numerous other platforms using line-probe assays, liquid culture, nucleic acid amplification testing (NAAT), and next-generation sequencing (NGS) are in various stages of development and may hold promise for future diagnostic speed, accuracy, and access. Despite these innovations, smear microscopy and culture conversion are still the only standard tests used to monitor treatment response. There remain crucial needs in the TB diagnostic landscape, including a highly accurate test for TB infection, a test of cure after TB preventative therapy (TPT) of latent infection, biomarkers to predict progression from latent to active disease and monitor treatment response over time, nonsputum-based diagnostics, and proof of cure from active disease.

## TB Preventive Therapy

Treatment of latent TB infection can be effective in preventing progression to active disease. A Cochrane review of 11 randomized trials examining 8130 participants with HIV found that the overall reduction in TB disease was 36%, with an even greater reduction of 62% among those participants with positive TST at study entry.[9] Although TPT was effective, uptake was poor. A meta-analysis of 58 studies of TPT found that each step in the care cascade resulted in a considerable drop in the proportion of patients receiving that recommended intervention. These points of attrition included initial testing (71.9% completion), receiving a positive test result (66.7%), referral for positive test (56.0%), completion of medical evaluation (43.7%), recommendation for treatment (35.0%), acceptance and commencement of treatment (30.7%), and treatment completion (18.8%).[10] The main barriers to TPT uptake included length of treatment, concern about adverse effects, unfounded fear of selection for resistance, and for those with HIV, prioritization of ART over TPT.

In response to concerns about the burden of TPT duration, there are now numerous short-course options from which practitioners and patients may choose. The first regimen to treat LTBI was 9 months of INH (9H); this is still included in World Health Organization (WHO) recommendations, as is 6 months of INH (6H). However, the Centers for Disease Control and Prevention (CDC) currently recommends only the shorter course regimens, which include 3 months of daily INH plus rifampicin (3HR), 4 months of daily rifampicin (4R), or 3 months of once-weekly INH plus rifapentine (3HP). Rifapentine (RPT) is a rifamycin, like rifampicin and rifabutin, and has the benefits of a longer half-life and increased potency against TB.[11] Rifapentine has a similar adverse-effect profile to other rifamycins but has potentially more drug-drug interactions, including with nevirapine.[12] Given its potency, it was recently tested in an ultra-short course regimen of 1 month (4 weeks) of daily rifapentine plus INH (1HP) and was found to be noninferior to 9H for preventing TB disease and TB-associated death, or death from unknown cause among adults and adolescents with HIV. Completion rates were also higher (97%) than for 9H (89.5%) (*P*<.01).[13] This regimen can be coadministered with efavirenz-based ART,[14] and a recent study has demonstrated acceptable dolutegravir exposures when dosed twice daily with daily rifapentine plus INH for TPT.[15]

Given that exposure to drug-resistant TB can result in latent infection (rather than active disease), some of the traditional TPT regimens may not

provide sufficient treatment for LTBI caused by a drug-resistant strain of TB. The optimal treatment for drug-resistant latent TB is currently unknown. For high-risk contacts of persons with drug-resistant TB, a fluoroquinolone is often recommended. Various studies are ongoing to better guide the clinical approach to drug-resistant latent TB (TB-CHAMP, VQUIN MDR, PHOENIx MDR-TB).

## Treatment of Drug-Susceptible TB

Although treatment-shortening regimens have been a scientific priority for years,[16] there was until recently only a single recommended regimen for the treatment of drug-susceptible TB: 2 months of INH, rifampicin, pyrazinamide, and ethambutol (HRZE) followed by 4 months of INH and rifampicin (2HRZE/4HR). With this one-size-fits-all approach to the treatment of TB, adverse effects are common and treatment completion rates are suboptimal. For people with HIV, treatment for TB limits or alters ART (Table 1) and can increase monitoring requirements. Treatment duration for drug-susceptible TB was initially 24 months in the 1950s, then shortened to 18 months in the 1960s, 9 months in the 1970s, and finally 6 months in the 1980s. Duration remained stuck at 6 months for the next 40 years, until preclinical data began to emerge that rifapentine could shorten time to culture conversion in a murine model of TB. The TBTC (Tuberculosis Trials Consortium) study 29X demonstrated the treatment-shortening potential of rifapentine, and Study 31/A5349 (S31/A5349) has now demonstrated that a 4-month regimen containing rifapentine and moxifloxacin (2 months of INH, rifapentine, pyrazinamide, and moxifloxacin [2HPZM]/2 months of INH, rifapentine, and moxifloxacin [2HPM]) is noninferior to standard 2HRZE/4HR. The third regimen used in the study without moxifloxacin (2 months of INH, rifapentine, pyrazinamide, and ethambutol [2HPZE]/2 months of INH and rifapentine [2HP]) did not meet noninferiority criteria for efficacy. All-cause mortality during treatment was slightly lower in participants in both of the RPT-containing arms than those in the control arm. Safety was similar between the arms.

**Table 2.** Antiretroviral Drugs That Are Compatible With Tuberculosis Medications

| Tuberculosis drug(s) | Compatible antiretroviral drug(s) |
|---|---|
| Isoniazid, pyrazinamide, ethambutol | Any antiretroviral drugs |
| Rifampicin | Any nRTI<br>Efavirenz 600 mg daily<br>Efavirenz 400 mg daily<br>Dolutegravir 50 mg twice daily<br>Raltegravir 800 mg twice daily |
| Rifapentine 900 mg weekly | Any nRTI<br>Efavirenz 600 mg daily<br>Lopinavir/ritonavir 400 mg/ 100 mg twice daily<br>Dolutegravir 50 mg daily<br>Raltegravir 400 mg twice daily |
| Rifapentine 450 mg or 600 mg daily | Efavirenz 600 mg daily<br>Dolutegravir 50 mg twice daily |
| Rifapentine 1200 mg daily | Efavirenz 600 mg daily |
| Bedaquiline | Any nRTI<br>Doravirine 100 mg daily<br>Nevirapine 200 mg daily followed by twice daily<br>Efavirenz 600 mg daily<br>Bictegravir/emtricitabine /tenofovir alafenamide<br>Cabotegravir 30 mg oral, cabotegravir 400 mg/rilpivirine 600 mg injection monthly<br>Dolutegravir 50 mg daily<br>Raltegravir 400 mg twice daily |
| Pretomanid 200 mg daily | Efavirenz 600 mg daily<br>Lopinavir/ritonavir 400 mg/ 100 mg twice daily |
| Moxifloxacin 400 mg daily | Any nRTI<br>Doravirine 100 mg daily<br>Nevirapine 200 mg daily followed by twice daily<br>Rilpivirine 25 mg daily<br>Darunavir/cobicistat 800 mg/ 150 mg daily<br>Any integrase strand transfer inhibitor |
| Delamanid 100 mg twice daily | Any antiretroviral drug(s) |

For additional details, please see the Liverpool Anti-tuberculosis Treatment Selector. Adapted from Liverpool Drug Interactions Group and Imperial et al.[15,30]

In the rifapentine-moxifloxacin arm, there was 1 instance of QT corrected (QTc) prolongation to 460 milliseconds and 1 instance of knee tendonitis. The WHO now supports the use of this regimen as an acceptable alternative to the current standard 6-month regimen,[17] without reference to people with HIV. The CDC recommends the 4-month rifapentine-moxifloxacin regimen, including for use in people with HIV who have CD4+ counts of 100 cells/μL or more and who are receiving or planning to initiate efavirenz as part of their ART.[18] There are ongoing studies to better understand how to prospectively stratify patients based on severity risk factors in order to shorten TB treatment duration for certain low-risk groups.

## Treatment of Drug-Susceptible TB Among People With HIV

There was also uncertainty for many years about the optimal timing of ART initiation and TB treatment. Numerous studies across different countries have now demonstrated that earlier commencement of ART is associated with improved outcomes.[19-21] Though earlier start does increase the risk of immune reconstitution inflammatory syndrome (IRIS), there is still a clear benefit; therefore, ART should not be delayed in persons with pulmonary TB. Major guidelines groups, including the American Thoracic Society (ATS), the Department of Health and Human Services (DHHS), and the International Antiviral Society–USA (IAS–USA),[22] currently recommend early initiation of ART, defined as within 2 weeks for CD4+ count less than 50 cells/μL, and within 8 weeks for CD4+ count greater than 50 cells/μL. The exception to this recommendation is for people with TB meningitis, given that early ART initiation has been associated with increased adverse events and death.[23]

Though there were relatively few participants with HIV enrolled in S31/A5349, efficacy data are so far encouraging for 2HPZM/2HPM. Results were similar among the 194 (8.3%) participants with HIV, with the rifapentine-moxifloxacin arm showing more favorable outcomes than the control arm. An embedded PK substudy within S31/A5349 also demonstrated that efavirenz (EFV) concentrations were not significantly affected by rifapentine and can be coadministered without dose adjustment.[24,25] An upcoming ACTG (AIDS Clinical Trial Group) study will evaluate the effect of this rifapentine-moxifloxacin–containing regimen on dolutegravir PK (A5406).

## Antiretroviral Drug-Drug Interactions With TB Medications

As mentioned, potent drug-drug interactions between rifamycins and components of ART complicate TB/HIV cotreatment. Current ART regimens that are compatible with concurrent TB treatment are summarized in Table 2. To varying degrees, all rifamycins are potent inducers of numerous metabolizing enzymes via pregnane X receptor (PXR)–mediated pathways. Rifamycins bind PXR, thereby increasing gene expression of cytochrome P450 enzymes and drug transporters such as P-glycoprotein and multidrug-resistance protein 1, among others.[26] The elucidation of rifamycin drug-drug interactions is particularly crucial for the many millions of people coinfected with HIV and TB who require simultaneous treatment of both diseases.

## Immune Reconstitution Inflammatory Syndrome

IRIS occurs as the immune system rebounds with successful virologic control of HIV. TB-related IRIS is more commonly seen with early ART initiation and with a low (ie, <100 cells/μL) baseline CD4+ count. Rarely is TB IRIS severe or fatal, but it can be in certain extrapulmonary manifestations of TB, such as TB meningitis. Management of IRIS requires establishing the diagnosis (often a diagnosis of exclusion after other opportunistic infections are ruled out), performing surgical drainage if necessary, and at times prescribing steroids such as prednisone.[27] There is evidence from a randomized clinical trial that prescribing prophylactic prednisone at 40 mg per day for 2 weeks, followed by 20 mg per day for 2 weeks, may reduce the risk of IRIS in patients with CD4+ count below 100 cells/μL.[28]

## Drug-Resistant TB

Drug-resistant TB is a widely observed occurence, with 465,000 incident cases in 2019. Multidrug-resistant (MDR) TB is resistant to rifampicin and INH; pre-extensively drug-resistant (pre-XDR) TB is resistant to rifampicin, INH, and any fluoroquinolone; and XDR TB is resistant to INH, rifampicin, any fluoroquinolone, and either bedaquiline or linezolid. Historically, treatment for any degree of drug-resistant TB substantially increased the duration, complexity, and toxicity of the regimen. A common regimen would contain at least 5 drugs for 18 to 24 months, although these regimens and durations were largely based on observational data and few of the recommended drugs were ever tested in a randomized controlled trial for MDR TB. In 2017, the WHO endorsed a 9-month short course regimen for select patients; the regimen consisted of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, INH, and ethambutol. Expert consultation was still recommended for these drug-resistant cases. Data from the Nix-TB (Bedaquiline, Pretomanid, and Linezolid for Treatment of Extensively Drug Resistant, Intolerant or Non-responsive Multidrug Resistant Pulmonary Tuberculosis) study have demonstrated that a combination regimen of pretomanid, bedaquiline, and linezolid results in high cure rates for patients with treatment-refractory MDR and XDR TB. Although the efficacy results were impressive, myelosuppression and neuropathy were seen in the majority of participants; therefore, the ZeNIX (Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB) trial and others are ongoing to determine the optimal linezolid dose to mitigate these toxicities. Additionally, recent data from TB-PRACTECAL has demonstrated that three different 24-week regimens for rifampicin-resistant TB were safe, well tolerated, and efficacious: bedaquiline, pretomanid, linezolid, with or without either clofazimine or moxifloxacin.[29]

## Conclusion

Although progress in the treatment of HIV-associated TB has been slow, achievements are steadily being made, including an ultra-short course for TB preventive therapy, a comparably effective 4-month treatment regimen, and monumental improvements in the treatment regimens for MDR and XDR TB. Remaining urgent challenges include finding an effective vaccine, better diagnostics that can be used longitudinally to monitor treatment response, additional short-course regimens for treatment of TB disease, and more studies in children and pregnant women.

All relevant financial relationships with ineligible companies have been mitigated.

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