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Multidrug Resistant Tuberculosis in Patients with HIV: Management Considerations within High-Resourced Settings

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Abstract

The management of multidrug-resistant tuberculosis (MDR TB) is notably complex among patients with HIV. TB treatment recommendations typically include very little information specific to HIV and MDR TB, which often is derived from clinical trials conducted in low-resource settings. Mortality rates among patients with HIV and MDR TB remain high. We reviewed the published literature and recommendations to synthesize possible patient management approaches demonstrated to improve treatment outcomes in high-resourced countries for patients with MDR TB and HIV. Approaches to diagnostic testing, impact and timing of antiretroviral therapy (ART) on mortality, anti-MDR TB and antiretroviral drug interactions and the potential role for short-course MDR TB therapy are examined. The combination of ART with expanded TB drug therapy, along with the management of immunologic reconstitution inflammatory syndrome (IRIS), other potential HIV-associated opportunistic diseases and drug toxicities, necessitate an integrated multidisciplinary patient care approach utilizing public health case management and provider expertise in drug-resistant TB and HIV management.

Keywords

HIV; Tuberculosis; MDR TB

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Introduction

Despite a relatively low incidence of tuberculosis (TB) diagnosed among patients with HIV living within the U.S., TB is associated with significant increased risk for both all-cause and AIDS-related death(1–6). The negative immunologic impact on T-cell function conferred by HIV heightens the risk of TB disease progression. The presence of HIV significantly influences TB pathogenesis, clinical presentation and management. Rifampin mono-resistance has been identified more often in people living with HIV compared to those without HIV(7–9). A recent systemic review and meta-analysis of predominately non-US patients found a marginal but consistent increased risk of multidrug-resistant TB (resistance to at least isoniazid and rifampin; MDR TB) occurring among patients with HIV, and more notably for primary MDR TB acquisition(10). Primary extensively drug resistant TB (XDR-TB) acquisition among patients with HIV has been described in both community and healthcare settings in South Africa(11, 12). Persons with untreated HIV, because of immunosuppression, may be particularly susceptible to acquiring *Mycobacterium tuberculosis* (*Mtb*) infection (including MDR *Mtb*) upon exposure in settings of poor infection control and have been shown to rapidly progress to TB disease(13).

From 2013 through 2017 in the United States, 498 cases (1% of total reported TB cases) had MDR TB, of which 24 (5% of MDR TB cases) also had HIV(14). Despite the low percentage of patients in the U.S. with both MDR TB and HIV, this comorbidity remains an important public health concern. Higher rates of unsuccessful treatment outcomes, including death, occur among patients with HIV and MDR TB(15, 16). Low CD4 cell counts (e.g., 50 cells/uL or less) in patients with HIV and MDR TB correlate with higher mortality(17, 18). Current published guidelines provide only limited guidance specifically addressing the management of MDR TB in persons with HIV(19–22).

We discuss the treatment approaches for MDR TB in the context of HIV co-infection and ART therapy in high-resourced settings. Treatment recommendations for MDR- TB have been recently updated by the World Health Organization (WHO) and supported through a large-scale meta-analysis of individualized patient data for the preferential inclusion of a later generation fluoroquinolone, bedaquiline and linezolid(19, 23). Available medical resources vary significantly among countries endemic with TB with HIV, and providers must appropriately utilize available diagnostic tools and local drug formularies to optimize treatment outcomes. Anticipated in 2019–2020 are guidelines for the treatment of drug-resistant TB in well-resourced settings, from the American Thoracic Society (ATS), in collaboration with the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of American (IDSA) and European Respiratory Society (ESR).

HIV and Rapid TB Testing

Globally, only 60% of the human population with HIV is aware of their infection, and many patients learn they have HIV when diagnosed with TB. Because of the serious consequences of TB in this highly susceptible population combined with the mortality of untreated HIV, the CDC, the European Union Standards for Tuberculosis Care (ESTC) and the WHO jointly recommend HIV testing of people with suspected or confirmed TB(24–27). The

WHO's End TB Strategy further recommends universal HIV testing to reduce TB incidence and mortality(28).

Confirming a bacteriologic diagnosis of TB in patients with advanced HIV can be challenging, as the lack of sufficient immunologic response hinders pulmonary cavity formation and promotes extrapulmonary dissemination. The higher prevalence of drug-resistant TB among patients with HIV, especially among those who have lived within endemic TB regions, coupled with the increased risk of death if effective MDR TB treatment is delayed, further support the CDC recommendation for the routine adjunctive use of nucleic acid amplification tests (NAAT) to expedite a diagnosis of TB and molecular diagnostic drug susceptibility testing for rifampin (with or without isoniazid) as part of the initial diagnostic evaluation for patients with HIV and TB(29, 30). NAATs amplify specific target *Mtb* RNA or DNA sequences and significantly shorten the time to diagnosis compared to culture-based identification methods.

The lateral flow lipoarabinomannan (LF-LAM) assay (Alere DetermineTM TB LAM Ag, Alere Inc, Waltham, MA, USA) is a point of care urine test to rapidly detect mycobacterial cell wall LAM antigens in persons with TB disease. The WHO has endorsed its use in persons with CD4 cell counts under 100 cells/uL suspected of having TB and in those with severe TB disease at any stage of HIV(31); but the test has decreased sensitivity if CD4 counts are above 100 cells/uL, has cross-reactivity with other mycobacteria, and requires confirmatory testing by NAAT or culture(32). Also, it has not yet been approved by the US Food and Drug Administration (FDA) for use in the U.S.

The use of molecular diagnostic assays such as the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA), for both the rapid detection of *Mtb* and gene mutations conferring resistance to rifampin (a key drug used to treat TB) have reduced time to diagnosis, thereby enabling an earlier start of effective MDR TB therapy(33, 34). The Xpert® MTB/RIF assay utilizes real-time PCR directly on sputum samples in an automated cartridge- based testing platform and has demonstrated a sensitivity of identifying *Mtb* in 98% of AFB smear positive sputum samples and 73% in smear-negative samples, as well as, identifying 98% of rifampin-resistant strains(35). Among patients with HIV and pulmonary TB, the sensitivity of the Xpert® MTB/RIF assay is slightly lower compared to those without HIV (93.9% vs. 98.4%, P=0.02)(35). To improve upon the low sensitivity of Xpert in the detection of more paucibacillary, smear-negative pulmonary TB (which is more commonly seen in patient with HIV), the Xpert® MTB/RIF Ultra was developed. A recent comparison of Cepheid's Xpert® MTB/RIF Ultra to Xpert® MTB/RIF in eight high-TB-incident (including MDR TB) countries and in a Western European country revealed a higher overall sensitivity for *Mtb* detection using the Ultra assay, especially in patients with smear-negative disease or with HIV (36, 37). However, Xpert® MTB/RIF Ultra has not yet been FDA-approved for use in the U.S.

Line probe assays incorporate reverse hybridization of microbial DNA on a paper strip and detect both the presence of *Mtb* DNA as well as gene mutations conferring resistance to select drugs. The INNO-LiPA RIF TB (Innogenetics, Ghent, Belgium) identifies resistance to rifampin, the GenoType MTBDR*plus* (Hain Life-Science, Nehren, Germany) identifies

resistance to both isoniazid and rifampin, and the GenoType MTBDR*s* (Hain Life-Science, Nehren, Germany) identifies resistance to the fluoroquinolones and injectable agents. The sensitivity of the GenoType MTBDR*plus* for *Mtb* detection and rifampin resistance is comparable to that of the Xpert® MTB/RIF(38). In settings where whole genome sequencing is utilized, the role of line probe assays for rapid detection of drug resistance and determination of effective treatment medications is still useful.

The CDC's Division of Tuberculosis Elimination offers a service for Molecular Detection of Drug Resistance (MDDR) that identifies resistance to isoniazid, rifampin, pyrazinamide, ethambutol, the fluoroquinolones and injectable agents directly through targeted DNA sequencing(39). Other select U.S. state and regional public health laboratories have started utilizing sequencing-based drug resistance detection platforms for more rapid and accurate diagnosis of drug resistant TB(40–42).

Impact of HIV and antiretroviral therapy (ART) in patients with MDR TB

ART is a vital component towards successful MDR TB management in patients with HIV. A systematic review of 10 observational studies, including individual patient data from 217 patients with both HIV and drug-resistant TB (92% of which was MDR TB) showed that patients taking ART had higher survival and TB cure rates compared to those not taking ART(43). Although the relationship between the time of starting ART and TB mortality was not specifically evaluated, the benefit of ART was most prominently identified among patients with CD4 counts less than 50 cells/uL. An individual patient data meta-analysis that included 1,833 patients with MDR TB and HIV, of whom 906 were receiving antiretroviral therapy, documented treatment success for 55% (95% CI: 43%−66%) of those receiving ART, compared with 34% (24%−46%) of those not receiving ART; mortality was also marginally lower (26% vs. 29%), with authors stating a need to treat HIV as well as drug-resistant TB(23). A sub-cohort of HIV patients with XDR TB in South Africa were prospectively followed for up to 60 months after starting TB therapy(44). Although outcomes among patients with XDR TB were generally poor, ART was a significant predictor of survival in patients with HIV and comparable to those without HIV.

Other retrospective and case-control studies within South Africa among patients with drug resistant TB and HIV have also shown a strong favorable relationship between starting ART and decreasing patient mortality. A review of XDR TB patients from four provincial treatment centers by Dheda et al revealed 41% decreased mortality at 12 months among HIV patients receiving ART (25% mortality) compared to those not on ART (66%)(45). In a region within rural KwuaZulu-Natal province where over 80% of all patients with TB also have HIV, Ghandi et al. evaluated patients with HIV and MDR or XDR TB and found that a CD4 cell count under 50 cells/uL was a strong risk factor for mortality while use of ART was correspondingly protective(17). In Eastern Cape Province, Kvasnovsky et al found that patients with XDR TB and HIV who were not taking ART had a significantly lower 12-month survival compared to patients taking ART(46). Within Lesotho, Satti et al. found that among patients with MDR TB and HIV who died, those not taking ART had a shorter median time to death(47). Despite the more limited treatment options, these studies within

South Africa collectively support the assertion that patients with HIV and drug resistant TB have better outcomes when taking ART.

Timing of ART in patients with MDR TB

Among patients with HIV and predominantly drug-susceptible TB evaluated in the SAPiT, CAMELIA and A5221 STRIDE trials, starting effective ART during TB therapy has been shown to increase patient survival, with an emphasis on starting ART earlier in patients with lower CD4 cell counts(48–51). The SAPiT trial demonstrated 56% reduction in relative risk of death among patients starting ART within 12 weeks after starting TB therapy compared to those starting ART after completion of TB therapy; the survival benefit was restricted to patients with CD4 cell counts under 50 cells/uL(49, 51). Among a subgroup of patients in the SAPiT study in South Africa with HIV and MDR TB, a 86% reduction in mortality was seen among patients who started ART within 12 weeks of starting TB therapy compared with those who deferred ART until after completion of TB therapy(52). Interestingly, the survival advantage was seen even among patients receiving inappropriate TB treatment, further illustrating the importance of concurrent effective HIV care. The CAMELIA trial found significantly increased survival with ART initiation 2 weeks after the start of TB treatment among adults with CD4 cell counts of less than or equal to 200 cells/uL, compared with starting ART eight or more weeks after commencing TB treatment(48). Similar reduced mortality benefits of early ART in patients with CD4 counts under 50 cells/uL were demonstrated in the STRIDE A5221 trial(50). These trials, however, did not correlate outcomes based on TB drug resistance.

Results from these studies were influential in the updated joint CDC/ATS/IDSA and WHO TB management guidelines that recommend starting ART as soon as possible in all patients with drug susceptible TB and HIV; ideally within 2 weeks of starting TB therapy for patients with CD4 counts under 50 cells/uL and by 8–12 weeks for patients with CD4 counts of 50 cells/uL or higher(53, 54). At this time, however, no controlled studies have been performed outlining the optimal time to start ART in patients with HIV and drug-resistant TB, and such trials would most likely require a multicenter collaborative across a number of countries. Regardless of ART timing, persons with HIV on ART and with MDR TB demonstrated similar culture-conversion rates and time-to-negative cultures compared to those without HIV in several studies(55–57). However, longer time to culture conversion was found in two large cohort studies in nine countries (Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea, Taiwan, and Thailand), where only half of the HIV-infected patients received ART(58). The decreased mortality associated with starting ART in patients with drug-resistant TB, especially those with MDR and XDR TB and in patients with CD4 cell count below 50 cells/uL, collectively suggests that a similar ART approach for persons with drug-resistant TB to that for drug susceptible TB may be beneficial.

Clinical monitoring for immune reconstitution inflammatory syndrome (IRIS) is encouraged as the SAPiT, CAMELIA and A5221 STRIDE trials all showed a higher incidence of IRIS among patients starting ART earlier compared to those starting later(48–51). Diagnosing IRIS is predicated on excluding alternative etiologies, including other opportunistic infections and TB treatment failure, which can be challenging in patients with more

extensive drug-resistant TB. IRIS usually does not require changes in TB drug therapy and can often be controlled with NSAIDS or corticosteroids(59). Treatment of patients with confirmed TB-IRIS with corticosteroids (e.g., oral prednisone) for one or more months might lower incidence of IRIS complications, but is not recommended for those with Kaposi's sarcoma. More information can be found in the Department of Health and Human Services Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb. A recent randomized clinical trial in South Africa that treated patients at increased risk of IRIS, including those with low CD4 cell counts, with prednisone during the first 4 weeks after initiation of ART demonstrated a lower incidence of IRIS compared to placebo but was not sufficiently powered to address mortality or associated malignancies(60). Further characterization of patient mortality and associated malignancy risk by CD4 count requires further study in other settings.

Starting ART in patients with central nervous system (CNS) MDR TB

Resistance to isoniazid and/or rifampin in HIV patients with TB meningitis is associated with increased mortality(61, 62), and the early identification of drug resistance is important towards achieving a successful outcome. Although not specifically evaluating drug-resistant TB, a randomized controlled trial in Vietnam among patients with HIV and TB meningitis found a higher frequency of severe (grade 4) adverse events and a non-statistically significant increase in death among patients starting ART within seven days of starting TB therapy compared to those starting ART after receiving 2 months of TB treatment(63). Out of concern that early ART initiation may be detrimental in patients with TB meningitis, it has been recommended to delay starting ART in patients with drug-susceptible CNS TB and HIV by 2 months after starting TB therapy(54).

The optimal timing to start ART in patients with CNS MDR TB and HIV remains unclear as there is little published data to provide further guidance. Until more outcome data are available in patients with CNS MDR TB, a similar approach with ART used in patients with drug susceptible CNS TB and HIV seems reasonable. Patients who develop new adverse neurologic symptoms or worsening neuroimaging findings during treatment of MDR CNS TB, should be evaluated for IRIS, other opportunistic infections, select malignancies and the potential for TB treatment failure(64). Therapeutic drug monitoring of second-line anti-TB medications may help optimize dosing and CNS penetration(65).

ART-TB drug interactions

Drug interactions between antiretroviral and anti-tuberculosis agents are common in the management of patients with HIV and TB. While the rifamycins are not typically used in patients with MDR and XDR TB, rifabutin occasionally is included by some authorities in select cases of discordant rifampin drug resistance and/or the presence of disputed *rpoB* gene mutations. Rifampin (and to a lesser degree rifapentine and rifabutin) increases the metabolic activity of the hepatic cytochrome P450 (CYP) enzymes (including CYP subfamilies 3A and 2C), P-glycoprotein, as well as uridine diphosphate glucuronosyltransferase. The specific rifamycin impact on the protease inhibitors,

nonnucleoside reverse transcriptase inhibitors, integrase strand transfer inhibitors (INSTI) and chemokine receptor inhibitors along with corresponding dosing recommendations has been described in detail elsewhere(66, 67). Non-rifamycin first line TB drugs (isoniazid, pyrazinamide and ethambutol), the fluoroquinolones, the injectables (amikacin, kanamycin, streptomycin and capreomycin), as well as other second- and third-line drugs (including ethionamide, cycloserine, para-aminosalicylic acid (PAS), linezolid and meropenem) pose fewer pharmacokinetic interactions with most antiretroviral drugs. Select adverse non-rifamycin drug interactions and overlapping toxicities with ART are listed in Table 1.

Antiretroviral drugs such as efavirenz, etravirine and nevirapine have the potential to accelerate the metabolism and consequently decrease the exposure of rifabutin, bedaquiline and delamanid by inducing the hepatic CYP 3A4 enzyme system. Protease inhibitors and pharmacokinetic boosting agents such as cobicistat and ritonavir impede drug metabolism through this this same pathway, resulting in corresponding increased serum drug concentrations of CYP3A4 substrates. A more detailed review of specific drug-drug interactions can be reviewed in Tables 17–20 of the National Institutes of Health HIV treatment guidelines which can be found at https://aidsinfo.nih.gov.

Prolongation of the QTc interval may occur with select antiretroviral and TB drugs, and the effect can be enhanced when administered together. Bedaquiline, delamanid, clofazimine, the fluoroquinolones, as well as, efavirenz and some protease inhibitors can all contribute towards QTc interval prolongation and potential ventricular dysrhythmia. Electrolyte abnormalities including hypokalemia, hypocalcemia and hypomagnesemia from aminoglycoside or capreomycin use may augment this effect. In addition, commonly used supportive care medications including methadone, high-dose trimethoprim/sulfamethoxazole (e.g., treatment of pneumocystis pneumonia) and triazoles may also collectively contribute to QTc prolongation(68, 69). For patients receiving multiple medications with QTc prolonging potential and for patients with other risks for cardiac dysrhythmia, baseline and follow up electrocardiogram monitoring should be considered. There currently are no formal recommendations regarding the timing and frequency of QTc monitoring in patients with TB. Prolonged QTc intervals over 500 msec or an increase in over 60 msec should raise consideration for alternative drug selection(70).

Providers should also have heightened awareness for other possible overlapping drug toxicities including nephrotoxicity in patient receiving an injectable agent and tenofovir disoproxil, adverse changes in mental health among patients taking efavirenz with cycloserine, and additive gastric intolerance among patients taking select protease inhibitors with ethionamide and/or PAS. Cation-containing drugs (e.g. antacids or supplements containing aluminum, calcium, magnesium and iron) can bind to INSTIs and the fluoroquinolones, resulting in reduced enteric absorption. Antacids, H2 antagonists and proton pump inhibitors can reduce the enteric absorption of medications that require gastric acidity such as atazanavir, rilpivirine and PAS. A full review of all medications should be performed with each patient in order to identify potential drug interactions and toxicities before starting MDR TB and HIV therapies.

Case Management

Employing appropriate case management that includes directly observed therapy (DOT) helps ensure patient adherence with a complex treatment program, identify onset of drug toxicity, and helps prevent treatment lapses that might pose challenges to infection control. Composing an effective, non-antagonistic combination ART and anti-TB regimen, managing drug toxicities and assessing longitudinal patient responses require a closely integrated multidisciplinary healthcare team with expertise in drug resistant TB, HIV and public health. Most health providers have limited clinical experience managing patients with combined MDR TB and HIV, and available expert medical consultation can help ensure timely patient care decisions including the identification of referral laboratories for expanded rapid molecular drug susceptibility testing and appropriate public health interventions. Expert medical consultation, education and training can be obtained from U.S. public health programs (https://www.cdc.gov/tb/links/tboffices.htm), the CDC-funded Centers of Excellence (https://www.cdc.gov/tb/education/tb_coe/default.htm) and international organizations including the ERS-WHO Electronic Consilium and Global TB Network(71, 72).

Short course MDR TB therapy

Shorter courses of MDR TB drug therapy ranging from 9 to 12 months have been recommended by the WHO for select patients(20). While patients with HIV are not excluded by the WHO from these shorter regimens, treatment outcome data supporting the use of shorter regimens specifically in patients with HIV is minimal and mainly from study sites in Africa where laboratory capacity for drug susceptibility testing was low. A clinical observational study using a 9-month MDR TB regimen conducted in Bangladesh did not specifically evaluate treatment outcome in patients with HIV(73, 74). In Cameroon, 20% of patients evaluated with a 12-month MDR TB regimen had HIV infection with no measurable effect on treatment outcome; however the study was not powered to determine the impact of HIV infection on outcome(75). In another observational study using a 12-month MDR TB regimen in Niger, there were not enough patients with both HIV and MDR TB to make any conclusions(76). The drug regimens in these studies included a 4 month induction period of kanamycin, isoniazid, prothionamide, gatifloxacin, clofazimine, ethambutol and pyrazinamide, followed by another 5–8 months with the latter 5 drugs. They predominantly included patients who had both confirmed or suspected pulmonary MDR TB that was susceptible to the injectable and fluoroquinolone drugs used and who had not received prior therapy with non-first line TB drugs for greater than one month prior to enrollment.

A subsequent randomized clinical trial involving patients from nine countries in West and Central Africa used a standardized 9-month regimen of moxifloxacin, clofazimine, ethambutol, and pyrazinamide that was supplemented during the first 4–6 months with kanamycin, protionamide and isoniazid(77). Among the 20% of enrolled patients who were HIV positive, there was a higher proportion of deaths, but no difference in rates of successful outcome or bacteriologic failure based on HIV status. Fluoroquinolone drug resistance was the strongest identified risk factor for unsuccessful treatment and failure. Preliminary data from the STREAM-1 trial enrolling patients with MDR TB in Mongolia,

Ethiopia, South Africa and Vietnam also found a higher but non-statistically significant number of deaths among patients with HIV randomized to receive the same short course treatment regimen(78).

The best utilization of the short course regimens in patients with MDR TB and HIV has not yet been well defined. Until more outcome data with the shorter course MDR TB regimens in patients with HIV is available, these shorter course MDR TB regimens for patients with HIV should be used with caution and considered within a clinical trial setting. Given that drug susceptibility testing is more widely available within the U.S., it is preferable to use drugs confirmed susceptible in vitro for such regimens.

Limitations

Well-designed clinical trials involving patients with MDR TB and HIV are lacking. Many of the studies citing the impact of ART in patients with HIV and MDR TB, including short course MDR-TB therapies, were observational and non-randomized. There is possible risk of biased data in studies from countries with differing MDR TB and HIV endemicity rates and medical resources. The CAMELIA, SAPiT and STRIDE trials took place in low resource settings, and diagnostic testing and treatment outcomes might be improved in higher-resourced locations. Because of the relative low numbers of patients with TB and HIV in high-resource settings(14, 18) large trials focusing on the timing of ART in such settings have not been conducted. Available data from high-resource locations, however, do show benefit of starting ART early during the course of TB therapy to prevent TB incidence(79).

Summary

HIV has a profound effect on TB, including faster rates of disease progression, higher rates of drug resistance and increased mortality among patients with MDR TB. While HIV testing should be performed on all people with suspected or confirmed TB, rapid molecular assays such as the Xpert® MTB/RIF assay for detection of both TB and drug resistance should be considered in patients with HIV suspected of having TB. Patients with HIV and MDR TB have a lower mortality when taking ART, and the benefits seen with starting ART in patients with MDR TB, especially those with CD4 cell counts below 50 cells/uL, support the management approach as recommended for patients with drug-susceptible tuberculosis. The composition of an effective, non-antagonistic combination ART and anti-TB medication program, along with managing medication intolerances and monitoring patient responses will require a closely integrated multidisciplinary health care team.

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Table 1:

Overlapping Adverse Reactions Among Select Antiretroviral and Non-rifamycin anti-TB drugs

Potential overlapping toxicities and drug-drug interactions	Antiretroviral drugs[a]	Non-Rifamycin TB drugs	Comments
Dysglycemia	Lopinavir/ritonavir (Kaletra), ritonavir, zidovudine	Ethionamide, PAS, fluoroquinolones[b], linezolid	Recommend close serum glucose monitoring in patient with glucose intolerance or diabetes
Hepatic cytochrome P450 enzyme system metabolism	Induce CYP P450 metabolism: efavirenz, etravirine and nevirapine Impede CYP P450 metabolism: Protease inhibitors, cobicistat	Bedaquiline, delamanid	Other medications including over the counter drugs should be thoroughly reviewed for CYP P450 metabolic interactions
Hepatoxicity	Lactic acidosis with hepatic steatosis higher risk with zidovudine; protease inhibitors; Nevirapine (higher risk in patients with elevated CD4 cell counts); less common with efavirenz, etravirine & rilpivirine; maraviroc Indirect hyperbilirubinemia[c]: atazanavir	Isoniazid, pyrazinamide, ethionamide, para-aminosalicylic acid (PAS), clofazimine	Serum LFT monitoring recommended in patients with HIV and TB; consider more frequent monitoring in those with underlying chronic liver disease
Lactic acidosis	Zidovudine (see hepatoxicity above)	Linezolid	
Mental health changes (depression, psychosis, dizziness, etc)	Efavirenz, rilpivirine; dolutegravir, elvitegravir, raltegravir	Cycloserine, isoniazid, ethionamide, fluoroquinolones[b]	Use with caution in patients with mental health conditions Risk of evoking serotonin syndrome when combining linezolid with either SSRI[d] or SNRI agents
Myelosuppression / cytopenias	Zidovudine	Linezolid	Recommend CBC monitoring with linezolid usage
Nephrotoxicity	Tenofovir[e], atazanavir	Aminoglycosides, capreomycin	Recommend monitoring serum creatinine when an injectable agent is used. Isolated creatinine elevation[f]: cobicistat, dolutegravir
Peripheral neuropathy	Zidovudine	Aminoglycosides, capreomycin, linezolid, isoniazid, ethionamide, cycloserine, fluoroquinolones[b]	Consider vitamin B6 supplementation with cycloserine, ethionamide, high-dose isoniazid, linezolid
QTc interval prolongation; cardiac dysrhythmia	Lopinavir/ritonavir (Kaletra), efavirenz Note PR interval prolongation[g] with atazanavir, lopinavir/ritonavir	Fluoroquinolones[b], bedaquiline, delamanid, clofazimine	Consider baseline and follow-up ECG monitoring in patients taking combination medications with QTc prolongation potential
Skin rash	Nevirapine (higher risk in patients with elevated CD4 cell counts), efavirenz, etravirine, rilpivirine; Any protease inhibitor (esp. those containing sulfonamide moiety: e.g. darunavir); abacavir (hypersensitive reaction a risk in patient who are HLA-B5701 positive); raltegravir	All TB drugs Note skin pigmentation with clofazimine use Thiacetazone[h] is contraindicated in patients with HIV	Review patients other medications that commonly may cause skin rash (e.g. trimethoprim / sulfamethoxazole)

[a] Saquinavir, indinavir, fosamprenavir, tipranavir, stavudine, zidovudine, nevirapine, lopinavir and didanosine are older antiretroviral drugs that are rarely used in the United States. They can, however, have many of the potential adverse interactions listed above with select antituberculosis drugs, and clinicians considering the use of these agents should therefore consult with an expert.

[b] Fluoroquinolones include ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin

[c] Indirect hyperbilirubinemia expected with atazanavir and indinavir; not a toxicity

[d] SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor

[e] Tenofovir alafenamide (TAF) – a prodrug of tenofovir and FDA approved in 2015; associated with decreased incidence of osteoporosis and nephrotoxicity compared to tenofovir disoproxil fumarate (TDF) via achieving higher intracellular drug concentrations with a lower dose administered

[f] Increases in serum creatinine via decrease renal tubular creatinine excretion are commonly seen with cobicistat and dolutegravir usage; not a toxicity

[g] Use with caution in patients with underlying cardiac dysrhythmia

[h] Thiacetazone is not available in the U.S.