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CO-INFECTIONS AND COMORBIDITY (D BHATTACHARYA, SECTION EDITOR)

Evidence for Implementation: Management of TB in HIV and Pregnancy

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Abstract

Purpose of Review Pregnant people living with HIV (PLWH) are at especially high risk for progression from latent tuberculosis infection (LTBI) to active tuberculosis (TB) disease. Among pregnant PLWH, concurrent TB increases the risk of complications such as preeclampsia, intrauterine fetal-growth restriction, low birth weight, preterm-delivery, perinatal transmission of HIV, and admission to the neonatal intensive care unit. The grave impact of superimposed TB disease on maternal morbidity and mortality among PLWH necessitates clear guidelines for concomitant therapy and an understanding of the pharmacokinetics (PK) and potential drug-drug interactions (DDIs) between antitubercular (anti-TB) agents and antiretroviral therapy (ART) in pregnancy.

Recent Findings This review discusses the currently available evidence on the use of anti-TB agents in pregnant PLWH on ART. Pharmacokinetic and safety studies of anti-TB agents during pregnancy and postpartum are limited, and available data on second-line and newer anti-TB agents used in pregnancy suggest that several research gaps exist. DDIs between ART and anti-TB agents can decrease plasma concentration of ART, with the potential for perinatal transmission of HIV. Current recommendations for the treatment of LTBI, drug-susceptible TB, and multidrug-resistant TB (MDR-TB) are derived from observational studies and case reports in pregnant PLWH.

Summary While the use of isoniazid, rifamycins, and ethambutol in pregnancy and their DDIs with various ARTs are well-characterized, there is limited data on the use of pyrazinamide and several new and second-line antitubercular drugs in pregnant PLWH. Further research into treatment outcomes, PK, and safety data for anti-TB agent use during pregnancy and postpartum is urgently needed.

Keywords Pregnancy · Tuberculosis · HIV AIDS · Antiretroviral therapy · Antitubercular drugs · Pharmacokinetics

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Introduction

Despite being preventable and curable, tuberculosis (TB), an infectious disease caused by the bacterium *Mycobacterium tuberculosis*, overtook HIV as the leading cause of death from infectious disease globally in 2014, with an estimated 1.5 million people dying from TB in 2020 [1]. In context, the reported global deaths due to COVID-19 in 2020 totaled 1.8 million [2]. TB is the leading cause of morbidity and mortality among people living with HIV (PLWH) worldwide; in 2021, 787,000 people living with HIV were reported to have TB, and approximately 214,000 global deaths were attributed to TB in PLWH [1]. Ninety-five percent of TB cases and 98% of TB deaths occur in resource-limited countries; in several high TB burden countries, HIV rates are also high [3]. In resource-limited countries, the greatest burden of both HIV and TB in women

occurs during reproductive years (15–49 years of age) [4]. Moreover, fertility rates in the highest-burden countries are high; 12 of the 30 countries with the highest fertility rates in the world are also within the 30 countries with the highest TB/HIV burden [1]. Women in these high-burden countries therefore spend a considerable portion of time either pregnant, postpartum, or in a lactating state.

TB disease can occur at any CD4 cell count, though the risk increases with progressive immunodeficiency [5], and TB infection in PLWH synergistically amplifies the burden of both disease processes. The development of TB disease has been found to increase HIV replication 5- to 160-fold in PLWH [6], and conversely, the immunodeficiency induced by HIV has also been shown to increase TB prevalence, decrease interval between exposure and disease, and lead to greater risk of progression of latent TB infection (LTBI) to active TB disease [7–10]. The development of TB disease has been shown to be associated with a fourfold increase in HIV-related mortality [11], and HIV infection is associated with a ≥ 30-fold increased risk of reactivation of latent TB [7–9].

Pregnant women living with HIV are at especially high risk of progression of LTBI to TB disease, with immunologic suppression related to pregnancy enhancing the risk associated with HIV alone [12, 13]. Estimates from 2011 suggest > 200,000 active tuberculosis cases existed in pregnant women globally at the time, with the greatest burdens in the World Health Organization (WHO) African region and the WHO South East Asian region [14]. In South Africa, the rate of TB disease among pregnant women living with HIV was found to be 10.6 times higher than that among pregnant women without HIV [15]. Similarly, a study of maternal mortality reported a 3.1-fold increase in the relative risk of death in mothers living with HIV with TB infection, compared with mothers without HIV with TB infection; 54% of maternal deaths caused by TB disease in the study population were attributable to HIV [16]. In a study in India, postpartum women with HIV with incident TB had a 2.2-fold increased risk of death compared with postpartum women with HIV without active TB [17]. Among pregnant women living with HIV, concurrent TB infection has also been shown to increase the risk of complications such as preeclampsia, low birth weight, preterm delivery, hospitalization, and perinatal transmission of HIV [18–21]. Despite the grave impact of TB on maternal morbidity and mortality in PLWH, there is a paucity of literature regarding the global epidemiology of TB in pregnant women living with HIV [12].

Pregnant and postpartum women experience an undue burden of HIV-associated TB [12] and require complex management with close monitoring. In addition, the significant potential for drug-drug interactions (DDIs) between antiretroviral therapy (ART) and antitubercular regimens underscores the need for safe and effective concomitant treatment guidelines for TB and HIV. The objective of this paper is to review the clinical and pharmacological considerations of HIV-associated TB treatment in the context of pregnancy.

Considerations for Treatment with Antiretroviral and Antitubercular Therapy in Pregnancy

Physiologic changes during pregnancy are known to cause alterations in the pharmacokinetics (PK) of many drugs [22], generally resulting in reduced drug concentrations (especially during late pregnancy). This, in turn, leads to the need for increased loading and maintenance medication doses to mitigate the potential for subtherapeutic drug exposures during pregnancy, or for avoiding certain drugs altogether, which is particularly relevant for anti-TB and ART agents.

ARTs, other than nucleoside reverse transcriptase inhibitors (NRTIs), have lipophilic characteristics [23]; this is significant because the increased maternal plasma volume and body mass during pregnancy result in an increased volume of distribution of lipophilic drugs (and a decreased volume of distribution of hydrophilic drugs) [24], and thus may affect ART drug disposition during pregnancy. The relative dilution of maternal plasma proteins (albumin or alpha-1-acid glycoprotein) leads to variations in free-drug concentrations and unbound fractions of drugs, with decreased clearance of extensively protein-bound ART and anti-TB agents such as rifamycins, and increased clearance of drugs that are not highly protein-bound [22].

Reduced gastrointestinal motility and altered stomach pH in pregnancy can also alter the absorption and bioavailability of anti-TB drugs and ART. The increase in maternal renal blood flow and glomerular filtration rate (GFR) during pregnancy increases renal drug clearance. Similarly, changes in tubular transmembrane receptor function, expression, and regulation alter PK on a drug-specific level. Progesterone-mediated inhibition of smooth muscle motility delays the absorption and onset of action of orally administered medications [25]. The activity of most phase I cytochrome P450 and phase 2 drug metabolic enzymes increases during pregnancy, leading to an increase in the hepatic elimination of many antibiotic and antiviral agents during pregnancy [26]. The impacts of physiologic changes of pregnancy on the PK of the first-line anti-TB drugs, as well as associated reproductive toxicology, are outlined in Table 1 and will be discussed in detail in subsequent sections of this review. The PK and reproductive toxicology of the new and WHO group A drugs for MDR-TB are outlined in Table 2 and will be discussed in detail in subsequent sections of this review.

Table 1 First-line anti-TB drugs used during pregnancy—mechanism of action, effect of pregnancy on pharmacokinetics of drug, major adverse effects, and potential reproductive toxicology

Antitubercular drug	Mechanism of action	Pharmacokinetics of drug and effect of pregnancy	Major adverse effects	Potential reproductive toxicology
Isoniazid (INH)	Inhibits mycolic acid synthesis, preventing formation of mycobacterial cell wall	• Renal elimination after hepatic metabolism • Variation in clearance rate with N-acetyltransferase 2 (NAT2) acetylator status • No statistically significant difference in drug plasma concentrations in pregnancy [24]	• Hepatotoxicity • Drug-induced lupus erythematosus • Vitamin B_6 deficiency • Anion gap metabolic acidosis	INH therapy or associated vitamin B6 deficiency might have adverse effects on embryo development [27]. Treatment of TB during pregnancy is nonetheless considered to be justified when indicated
Rifamycins				
Rifampin	Inhibits bacterial DNA-dependent RNA polymerase	• Biliary elimination • Pregnancy reportedly reduces rifampin clearance by 14% [28]	• Cytochrome P450 induction (CYP3A4, CYP2C9) • Harmless red–orange discoloration of bodily fluids • Flu-like symptoms • Minor hepatotoxicity	Rifampin has been found to interfere with embryo development in animals but not in humans [29, 30]. Drug transfer to milk during lactation has not been associated with adverse effects in exposed neonates [31]
Rifabutin	Inhibits bacterial DNA-dependent RNA polymerase	• Biliary elimination • No PK studies in pregnancy at this time	• Rifabutin has lower CYP induction potential than rifampin • Harmless red–orange discoloration of bodily fluids • Flu-like symptoms • Minor hepatotoxicity	Rifabutin has not been found to increase incidence of congenital anomalies in animal or human studies [32]
Pyrazinamide	Not completely understood	• Renal elimination after hepatic metabolism • No statistically significant difference in drug plasma concentrations in pregnancy [33]	• Hyperuricemia • Hepatotoxicity	Pyrazinamide has not been found to increase incidence of congenital anomalies in animal studies [34]. No well-controlled studies have been performed in human pregnancy
Ethambutol	Inhibits arabinosyl-transferase, preventing mycobacterial cell wall synthesis	• Renal elimination • No statistically significant difference in drug plasma concentrations in pregnancy [33]	• Optic neuritis (decreased red-green color discrimination)	Ethambutol has not been found to increase incidence of congenital anomalies in animal or human studies [35]

Table 2 New and WHO group A drugs for MDR-TB—mechanism of action, effect of pregnancy on pharmacokinetics of drug, major adverse effects, and potential reproductive toxicology

Antitubercular drug	Mechanism of action	Pharmacokinetics of drug and effect of pregnancy	Major adverse effects	Potential reproductive toxicology
Bedaquiline	Inhibits proton pump of mycobacterial ATP synthase	• Hepatic metabolism • No PK studies in pregnancy at this time	• QT prolongation • Hepatotoxicity • Pancreatitis • Phospholipidosis • Musculopathy	Studies in animals have not demonstrated reproductive toxicity [36]. No well-controlled studies have been performed in human pregnancy
Fluoroquinolones	Inhibits activity of bacterial DNA topoisomerases, preventing DNA synthesis	• Predominantly renal elimination • Pregnancy reportedly reduces moxifloxacin exposure [37, 38]	• Arthropathy • Cartilage and tendon abnormalities • QT prolongation	Fluoroquinolones are avoided during pregnancy due to cartilage toxicity in experimental animals [39, 40]. These adverse effects have not been demonstrated in human pregnancy
Linezolid	Binds to 70S initiation complex of bacterial ribosomes, disrupting protein synthesis	• Renal elimination • Pregnancy reportedly reduces linezolid exposure [27, 41]	• Serotonin syndrome • Thrombocytopenia • Peripheral neuropathy • Optic neuropathy • Lactic acidosis	Linezolid has not been found to increase incidence of congenital anomalies in animal studies [42]. No well-controlled studies have been performed in human pregnancy
Delamanid	Inhibits mycobacterial cell wall synthesis	• Stool excretion • No PK studies in pregnancy at this time	• QT prolongation • Palpitations • Drowsiness and impairment in operating machinery	Studies in animals have demonstrated reproductive toxicity [43]. No well-controlled studies have been performed in human pregnancy
Pretomanid	Inhibits mycobacterial cell wall synthesis	• Renal elimination after hepatic metabolism • No PK studies in pregnancy at this time	• Peripheral neuropathy • Increased transaminases • Hemoptysis	Reduced fertility and/or testicular toxicity have been observed in male rats and mice after oral administration [44]. No well-controlled studies have been performed in human pregnancy

Drug-drug interactions (DDIs) between ART and anti-TB drugs, as described in detail in Table 3, are also a concern in the treatment of TB disease in PLWH. The DDI of each antitubercular drug will be discussed in detail in subsequent sections of this review.

Management of Tuberculosis in Pregnant Women Living with HIV

Latent TB Infection in Pregnant Women Living with HIV

Per joint guidelines from the Center for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and HIV Medicine Association of the Infectious Diseases Society of America (HIVMA), all patients living with HIV should be screened for LTBI at the time of their HIV diagnosis, regardless of their TB risk category [59]. The tuberculin skin test is considered positive in patients living with HIV if induration of ≥ 5 mm is demonstrated 48–72 h after the intradermal placement of 0.1 mL purified protein derivative (PPD) [60], and in vitro assays that detect IFN-γ release in response to *M. tuberculosis*–specific peptides, known as interferon-gamma release assays (IGRAs), diagnose LTBI by blood test [61]. Patients with negative diagnostic tests for LTBI at the time of diagnosis and CD4 count < 200 cells/μL should be re-tested for LTBI once they start ART and attain a CD4 count > 200 cells/μL. Pregnant women living with HIV infection without documentation of a prior negative latent TB screening test result, or who are at high risk for repeated or ongoing exposure to individuals with active TB disease (e.g., patients living in high-burden countries, or who are or have been incarcerated, live in congregate settings, are active substance users, or have other sociodemographic risk factors for TB), should be screened for latent TB during pregnancy [59]. Following screening, all pregnant PLWH with a positive diagnostic test for LTBI should then undergo chest radiography (with abdominal shielding to minimize fetal radiation exposure) and clinical evaluation for active TB.

The WHO recommends that PLWH with a positive or unknown LTBI test in settings with high TB transmission be treated with isoniazid (INH) for at least 3–6 months [62]. The US Department of Health and Human Services (DHHS) Opportunistic Infection guidelines were updated in

Table 3 Drug-drug interactions between antitubercular and antiretroviral therapy during pregnancy

Antiretroviral class	Drug-drug interactions	Studies
NRTIs	No known drug interactions with antitubercular drugs	
NNRTIs		
Efavirenz	Isoniazid decreases efavirenz clearance and increases serum concentrations, reportedly by 7% in *CYP2B6* normal metabolizers and 13% in slow and intermediate metabolizers [45]	Gausi et al. (2021) Atwine et al. (2020) Dooley et al. (2012)
	Rifampin causes a small well-tolerated decrease in efavirenz serum concentration [46]	Svennson et al. (2013)
	Efavirenz increases bedaquiline metabolism via CYP3A4 induction, increasing exposure to its metabolites; this effect is unlikely to be clinically significant [47, 48]	
Nevirapine	Rifampin reduces serum concentrations of nevirapine by 20–55% via strong CYP3A4 induction [33, 49–51]	Ribera et al. (2001) Ramachandran et al. (2006) Manosuthi et al. (2007) Autar et al. (2005)
Rilpivirine	Rifampin reduces serum concentrations of rilpirivine by up to 82% via strong CYP3A4 induction [52]	Rajoli et al. (2019)
Protease inhibitors		
Lopinavir/ritonavir	Rifampin decreases lopinavir/ritonavir plasma concentrations via strong CYP3A4 induction [53]	la Porte et al. (2004) Sekar et al. (2010)
	Lopinavir/ritonavir increases exposure and serum concentrations of rifabutin via strong CYP3A4 inactivation [54]	
Indinavir	Indinavir increases risk of rifabutin toxicity; rifampin and rifabutin reduce indinavir plasma concentrations via strong CYP3A4 induction [55]	Hamzeh et al. (2003)
Integrase inhibitors		
Dolutegravir	Rifampin decreases dolutegravir exposure via strong CYP3A4 induction and may lead to loss of efficacy [56]	Dooley et al. (2013)
Raltegravir	Rifampin may decrease plasma concentrations of raltegravir [57]	Burger et al. (2009)
CCR5-receptor antagonists	Rifampin decreases serum concentrations of maraviroc via strong CYP3A4 induction [58]	Yost et al. (2009)

February 2022 to recommend rifamycin-based LTBI treatments 3HP (3 months of once-weekly doses of INH plus rifapentine) or 3HR (3 months of daily doses of INH plus rifampin) as preferred, with isoniazid preventive therapy (IPT) or 9H (9 months of daily INH), 4R (4 months of daily rifampin), or the new regimen 1HP (28 days of daily INH and rifapentine) as alternatives. However, among pregnant patients with LTBI, antitubercular therapy is now deferred per CDC guidelines until 3 months after delivery [63], an approach based on a 2019 double-blind, placebo-controlled, non-inferiority randomized clinical trial of patients in TB-endemic countries (the IMPAACT P1078 APPRISE Study) published by Gupta et al. in 2019, with 956 PLWH (CD4 count 351–670 cells/μL on ART) randomly assigned to initiate LTBI treatment with isoniazid immediately (immediate group) or defer treatment (deferred group) [64•]. The trial demonstrated more frequent adverse pregnancy outcomes (stillbirth or spontaneous abortion, low birth weight, preterm delivery, or congenital anomalies) among patients treated with isoniazid during pregnancy than among patients treated 3 months after delivery (23.6% vs. 17.0%, difference 6.7%; 95% CI 0.8–11.9), and the incidence of TB was low and comparable between the groups (0.60 versus 0.59 per 100 person-years). Of note, only 30% of participants had positive IGRA results at enrollment. However, treatment of PLWH with unknown LTBI testing in settings with high TB transmission is consistent with WHO guidance [62]. Patients in the first trimester and those with recent TB exposure within the 12 weeks prior to study entry were excluded from the trial. Tiendrebeogo et al. reported in 2020 their findings from a randomized controlled clinical trial in a high TB-endemic area (TEMPRANO ANRS 12,136) suggesting that the risk of adverse pregnancy outcomes might also increase even when IPT is administered during the first trimester [65]. Based on these results, the United States DHHS guidelines recommend delaying LTBI treatment until 3 months after delivery in the absence of a recent TB exposure, but they do not specify a CD4 threshold [66]. A general recommendation is for patients with CD4 counts > 350 cells/μL to not be treated for LTBI during pregnancy; that is, in pregnant PLWH with LTBI, timing of antitubercular therapy is determined by CD4 count and recent TB exposure status.

In contrast to the IMPAACT P1078 findings, in a study of pregnant women who were exposed to study medications in two latent tuberculosis infection trials (PREVENT TB or iAdhere) evaluating 3HP and 9 months of daily isoniazid (H, 300 mg) (9H), Moro et al. reported in 2018 no unexpected fetal loss or congenital anomalies [67]. In a secondary analysis of the Tshepiso study, Salazar-Austin et al. reported in 2020 that IPT exposure during pregnancy was not negatively associated with pregnancy outcomes, after controlling for demographic, clinical, and HIV-related factors [68]. These results provide some reassurance that isoniazid preventative therapy may be safely used in the second or third trimester of pregnancy. The status of this debate is ongoing.

For patients with CD4 count ≤ 350 cells/μL, LTBI treatment is usually initiated during pregnancy, given the increased risk of progression to active TB [69]. For patients with a recent exposure to untreated active respiratory TB, LTBI treatment is also initiated during pregnancy. For patients with LTBI and a CD4 count > 350 cells/μL in the absence of a recent TB exposure, antitubercular therapy may be deferred until 3 months after delivery, as described above [66]. Notably, many studies have shown that women with HIV and CD4 count > 350 cells/μL are still at high risk of developing active TB in the early postpartum period [70, 71]. Among pregnant women living with HIV with LTBI not on ART, ART should be initiated promptly, as the risk of progression to active TB disease is known to be significantly decreased in individuals on ART [17, 72, 73]. There is no current expert consensus on timing for initiation of antitubercular management for pregnant patients living with HIV with LTBI not on ART; additional research is needed to evaluate the optimal management of these patients, which may include initiation of LTBI treatment during pregnancy for all patients living with HIV not on ART, versus initiation of LTBI treatment during pregnancy only for those with CD4 count ≤ 350 cells/μL or ≤ 200 cells/μL [69], with deferral of treatment until 3 months after delivery otherwise.

Active TB Infection in Pregnant Women Living with HIV

Pregnant patients with active TB disease overall may have similar clinical manifestations as nonpregnant patients, including fever, cough, night sweats, and malaise. However, women are known to be less likely than men to present with symptoms of hemoptysis, fever, and night sweats [74], and pregnancy further masks these symptoms. In South Africa, only < 30% of pregnant women diagnosed with tuberculosis had fevers or night sweats, but 60% reported cough of ≥ 2 weeks [75]; in Tanzania, the most common tuberculosis symptoms in pregnant women were malaise and anorexia [76]. Because malaise and fatigue as well as atypical symptoms such as nausea may be attributed to pregnancy rather than disease, and because TB symptoms may be attenuated in pregnancy, TB in pregnant patients can present insidiously [77, 78]. For pregnant women diagnosed with active TB disease, antitubercular treatment must be initiated immediately, as treatment with anti-TB drugs during pregnancy decreases maternal and fetal morbidity from TB [79].

While some first-line medications used for TB treatment may be teratogenic in animal models, this has not been observed in humans. For example, ethambutol is teratogenic in rodents and rabbits at doses that are much higher than those used in humans, but no evidence of ethambutol

teratogenicity has been observed in humans. Rifampin and isoniazid have not been demonstrated to be teratogenic in humans and, therefore, are therapies which may be used during pregnancy. Isoniazid-associated hepatotoxicity might occur more frequently during pregnancy and the postpartum period; therefore, monthly monitoring of liver transaminases is strong encouraged [59, 80]; however, unavailability of liver function tests should not be a barrier to treatment unless a patient has other risk factors for liver toxicity [81]. Although pyrazinamide has not been demonstrated to be teratogenic in animals, its use during pregnancy in the USA is limited because its effect on the fetus is unknown, and TB can be cured without its use. While the WHO and the International Union Against Tuberculosis and Lung Diseases have made recommendations for the routine use of pyrazinamide in pregnant women, pyrazinamide has not been recommended for general use during pregnancy by the U.S. CDC [63, 82, 83]. However, if pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy is nine months.

Thus, the preferred first-line regimen for drug-susceptible TB in pregnant patients in the US is isoniazid, rifampin, and ethambutol for a duration of nine months [84], while elsewhere in the world, pyrazinamide is added and a 6-month treatment is given. The use of fixed-dose combinations in most global settings precludes use of ethambutol without pyrazinamide. Treatment for HIV-associated TB is similar to TB alone, except that drug substitutions or adjustments to drug doses may be needed in consideration of DDIs, as discussed in the subsequent sections of this review and outlined in Table 2. When multidrug-resistant TB (MDR-TB) occurs in pregnancy, selection of second-line drugs requires consideration of the risks and benefits that are unique to pregnant women, as is discussed in subsequent sections of this review.

Conventional/Standard Antitubercular Drugs

First-line regimens for active TB include a combination of isoniazid, a rifamycin, ethambutol, and pyrazinamide. These drugs are used in combination to promote rapid clearance of bacilli and to prevent the emergence of drug resistance.

Isoniazid (INH)

Isoniazid, also known as isonicotinic acid hydrazide (INH), is the cornerstone of modern tuberculosis treatment and was introduced into medicine in 1952 [85]. It is inexpensive, well-tolerated, and safe, and isoniazid was thus quickly introduced to antitubercular regimens in combination with para-aminosalicylic acid as a replacement for streptomycin. Isoniazid acts via inhibition of mycolic acid synthesis, preventing formation of the mycobacterial cell wall, and is renally eliminated following hepatic metabolism. Genetic variations in phenotype of N-acetyltransferase 2 (NAT-2), a phase-II conjugating liver enzyme, lead to differential rates of clearance [86]. The autosomal recessive slow acetylator phenotype may experience toxicity from isoniazid, whereas the rapid acetylator phenotype may require increased doses of isoniazid. Studies have shown large variations in the rate of the slow acetylator phenotype among ethnic populations: roughly 70% of white Americans and Black Americans, 30% of East Asians, and more than 80% of Egyptians, for example, exhibit the slow acetylator phenotype [87].

The PK of INH has been extensively studied during pregnancy. Isoniazid crosses the placenta and is substantially distributed in the fetal compartment, with mean fetal/maternal cord-blood concentration ratios of 0.73 1 h following a single administration of a 100 mg oral dose of isoniazid [88]. Isoniazid and its metabolite, acetyl-isoniazid, have also been detected in breast milk of lactating women, with peak concentrations of 16.6 mcg/mL (isoniazid) and 3.76 mcg/mL (acetyl-isoniazid) observed in breastmilk within 3–5 h post-administration of a single oral dose of 300 mg of isoniazid [89]; the therapeutic reference range is 3–5 mcg/mL after 2 h. Vorherr et al. reported the milk-plasma ratio of isoniazid as 1.0 [90]. While there is potential for isoniazid-induced hepatotoxicity, no reports of such effects in neonates or infants have been described. Based upon these isoniazid PK and safety data, women with TB living with HIV on isoniazid may safely breastfeed their neonates. Notably, infants of breastfeeding patients being treated for drug-sensitive TB would still require 3–6 months isoniazid prophylaxis, as the levels acquired in the breast milk alone are not sufficient; the American Academy of Pediatrics (AAP) recommends isoniazid prophylaxis to all neonates of mothers diagnosed with tuberculosis in the postpartum period and/or after the commencement of breastfeeding has started [45].

A study assessing the PK of isoniazid and efavirenz and the drug-drug interactions between both medications, among 847 pregnant women who received isoniazid and efavirenz from 28 weeks gestation to 12 weeks postpartum, demonstrated that pregnancy increased isoniazid and efavirenz clearance by 26% and 15%, respectively. Isoniazid decreased clearance of efavirenz and increased serum concentrations, reportedly by 7% in *CYP2B6* normal metabolizers and 13% in slow and intermediate metabolizers [91]. This effect appears to be counterbalanced by the inducing effect of rifampin on efavirenz clearance, and thus efavirenz dosages do not need to be adjusted in patients on rifampin and isoniazid therapy [92]. A two-compartment first-order population PK model with data from a sub-study of the Tshepiso trial, involving 29 pregnant women with TB and living with HIV on 4–6 mg/kg daily dosing of isoniazid, demonstrated no significant differences in drug clearance,

volume of distribution, or bioavailability of isoniazid during pregnancy (in 21 pregnant persons) compared to postpartum (8 persons), with the conclusion that pregnancy did not appear to alter isoniazid dosage and disposition [93•]. The volume of distribution of isoniazid was also increased (approximately 130 L) in pregnant women.

In 1980, Snider et al. published a review of the literature and reported that among 1302 pregnant women who received isoniazid in 1480 pregnancies—some in combination with other anti-TB drugs for the treatment of TB disease, and others who received isoniazid alone for LTBI; 400 of whom were treated within the first 4 months of their pregnancy—there were 5 miscarriages, 9 perinatal deaths and 16 abnormal fetuses, all at a lower frequency than found in the normal population at that time [94]. Adverse effects of isoniazid therapy may include hepatitis, dizziness, headache, and peripheral neuropathy in the setting of vitamin B_6 (pyridoxine) deficiency. Isoniazid induces a state of functional pyridoxine deficiency by directly binding and inactivating pyridoxine species, as well as by inhibiting its activation by pyridoxine phosphokinase. Pregnancy and HIV infection are both risk factors for isoniazid-induced pyridoxine deficiency and neuropathy [95]; thus, pregnant women living with HIV receiving isoniazid therapy should receive pyridoxine supplementation to minimize risk of peripheral nerve damage. The CDC recommends 25–50 mg pyridoxine daily or 50–100 mg pyridoxine twice weekly be administered to all PLWH undergoing TB treatment with isoniazid [96]. In pregnancy there may be also an increased risk of isoniazid-associated hepatotoxicity; thus, pregnant women on isoniazid therapy require frequent monitoring of transaminase levels [97].

Isoniazid may be used alone or in combination with rifampin or rifapentine for treatment of latent tuberculosis, or as part of a three- or four-drug regimen for treatment of active tuberculosis. The US CDC favors the following regimens for treatment of LTBI in pregnancy: isoniazid daily therapy for 9 or 7 months; rifampin daily therapy for 4 months; or combined isoniazid and rifampin daily therapy for 3 months [63]. In non-pregnant patients, the WHO recommends that PLWH with a positive or unknown LTBI test in settings with high TB transmission be treated with isoniazid for at least 36 months [62].

Rifampin

Rifampin acts via inhibition of bacterial DNA-dependent RNA polymerase. In the 1970s, rifampin was introduced as an antitubercular therapeutic; the use of rifampin enabled the course of treatment to be reduced to nine months. Rifampin is rapidly absorbed and is about 80% protein-bound. It is deacetylated in the liver and excreted in the bile and urine [28]. Rifamycins, most notably rifampin, are strong inducers of drugs undergoing cytochrome P450 enzyme metabolism (notably CYP3A4), which can lead to reduced bioavailability and increased clearance of co-administered medications. In a one-compartment model with first-order elimination, transit compartment absorption, and an allometric scaling population PK model using data from the Tshepiso trial, pregnancy reportedly reduced rifampin clearance by 14% during the third trimester compared to postpartum. However, the resultant increased rifampin exposures were modest, so dosage adjustments are not required during pregnancy. The volume of distribution was similar to non-pregnant controls [98]. The PK of rifampin in the first trimester of pregnancy appears to be comparable to non-pregnant rifampin PK concentrations [99]. Rifampin is deacetylated in the liver and excreted in the bile and urine. Thus, it is not uncommon for pregnant patients on rifampin to present with estrogen-induced intrahepatic cholestasis. The magnitude of the risk is unclear, but it is known that the average half-life of rifampin in non-pregnant patients with obstructive jaundice may be twice that of patients without biliary obstruction [100]. Notably, HIV infection has also been associated with reduced rifampin concentrations, independent of ART DDI; that is, in studies in which patients on ART were excluded, HIV infection was still significantly associated with reduced rifampin concentrations [101, 102]. However, women living with HIV do not appear to experience a significantly further decrease in bioavailability of rifampin during pregnancy [98].

Rifampin is known to cross the placenta but is poorly distributed in the fetal compartment, with mean fetal/maternal cord-blood concentration ratios of 0.23 demonstrated within 2 h following a single administration of a 300 mg oral dose of rifampin [99]. Despite its ability to cross the placenta in relatively small amounts, rifampin has been generally found to be safe in pregnancy without adverse effect of exposure on the fetus and neonate. In 1980, Snider et al. reviewed reports of 442 women taking rifampin during 446 pregnancies, including 109 exposed during the first trimester, and found no excess risk of birth defects associated with this exposure [94]. One of the reviewed studies reported a malformation rate of 4.4% in 204 pregnancies, including hydrocephalus, anencephaly, and limb defects at rates significantly higher than the general rate of 1.8% [31], but this study was counterbalanced by the other studies in which malformations were rarer than expected [94]. The more significant effect rifampin may exert on a developing fetus is that of its property as a strong inducer of CYP enzymes, which may theoretically indirectly affect fetal exposures to levels of other drugs which the mother may be receiving. Rifampin has been measured in very low concentration in breastmilk, with an average milk-plasma ratio of 0.2 [46]. Rifampin is known to cause orange discoloration of bodily fluids, including breastmilk; breastfeeding patients should be counseled regarding that this effect is expected and

harmless. No adverse effects of rifampin or its metabolites have been reported in neonates. These data suggest that it is reasonable to breastfeed while on rifampin.

Rifampin's property as a strong inducer of P450 enzymes can lead to enhanced clearance of co-administered medications, including a number of ARTs. This drug-drug interaction with rifampin includes non-nucleoside reverse-transcriptase inhibitors (nevirapine and rilpivirine) [33, 49–53], protease inhibitors (lopinavir with or without cobicistat or ritonavir, indinavir) [56], integrase inhibitors (dolutegravir, raltegravir) [57, 58], and CCR5-receptor antagonists (maraviroc) [103]. In some settings, rifabutin, a rifamycin with weaker CYP induction properties, is substituted for rifampin to avoid DDIs with ART. In most settings, dolutegravir is used (but dosing increased from 50 mg once daily to 50 mg twice daily) or efavirenz is used (may be used with rifampin without dose adjustment) [57].

Other Rifamycins—Rifabutin and Rifapentine

Rifabutin, a semi-synthetic ansamycin antibiotic derivative of rifamycin-S, was developed to overcome the problem of DDIs caused by rifampin, and is well tolerated by patients who develop rifampin-related adverse effects [104]. Rifabutin has low oral bioavailability, is 72–85% protein-bound, and has a long elimination half-life of approximately 45 h. Rifabutin has five major metabolites, with one of them causing a unique adverse effect—uveitis. Approximately 95% of rifabutin is eliminated by metabolism, with minimal renal excretion of the unchanged drug [54]. Relative to rifampin, rifabutin is more lipid-soluble; is more extensively distributed in tissues; has a larger volume of distribution, longer half-life, and lower maximum serum concentration (C_{max}); and is a weaker inducer of cytochrome P450 metabolism and thus has reduced potential for DDIs [54]. Therefore, rifabutin is preferred in place of rifampin in PLWH who are being treatment with protease inhibitors. Because rifabutin is also itself a substrate of CYP3A4, its concentrations may be affected by concomitant ART use. Protease inhibitors such as ritonavir, a potent CYP-3A4 inhibitor, are known to significantly increase rifabutin concentrations and so dose reduction of rifabutin is needed [55, 105]. Conversely, efavirenz, a NNRTI and potent CYP-3A4 inducer, decreases rifabutin serum concentrations by one-third [106], making rifampin the rifamycin of choice for patients taking efavirenz-based ART.

There are limited PK and safety studies for rifapentine and none for rifabutin in pregnant women at this time. In an analysis of the PREVENT TB or iAdhere study evaluating exposure to 3HP (3 months of once weekly INH and rifapentine) in pregnancy, Moro et al. reported no unexpected fetal loss or congenital anomalies [67]. While it is unknown if rifabutin or rifapentine or their active metabolites traverse the feto-placental unit, their PK characteristics suggest that transplacental transfer will potentially occur, given their high lipid solubility, extensive tissue distribution, larger volume of distribution, and long half-life. Among pregnant women, clearance of rifapentine in the setting of HIV infection is known to be more rapid than among those without HIV infection [107], and Mathad et al. found no serious adverse events and few adverse effects in women or infants following rifapentine use during pregnancy.

Ethambutol

Ethambutol, another first-line antitubercular agent, acts via inhibition of arabinosyl-transferase and thus prevents mycobacterial cell wall synthesis, and is renally eliminated. Isoniazid was first used in regimens in combination with para-aminosalicylic acid until the introduction of ethambutol in 1960 replaced para-aminosalicylic acid.

A two-compartment first-order population PK model with data from a sub-study of the Tshepiso trial involving 18 pregnant PLWH with TB on a standard daily dosing of ethambutol (15–25 mg/dL) demonstrated no significant differences in drug clearance, volume of distribution, or bioavailability of ethambutol during pregnancy (in 15 pregnant persons) compared to postpartum (4 persons). In this small dataset, pregnancy did not appear to impact ethambutol's dosage and disposition. These data are consistent with ethambutol's PK properties, including its low intrinsic clearance and low protein-binding, which indicates a low free fraction and reduced clearance of ethambutol during pregnancy [93•].

Ethambutol is generally considered safe during pregnancy. In 1980 Snider et al. reviewed reports of 650 women taking ethambutol with 655 pregnancies, of whom 320 received the drug in the first trimester, and found no increase in birth defects associated with this exposure [94]. Ethambutol has been found to be teratogenic in rodents and rabbits at doses that are much higher than those used in humans; no evidence of teratogenicity has been observed in humans. Optic neuropathy, most often manifesting as a change in visual acuity or red-green color blindness, has been reported in adults taking ethambutol [108], but changes in visual acuity have not been detected in children exposed to ethambutol in-utero. Baseline visual acuity and red-green color perception testing before initiation of therapy and periodic follow-up ocular examinations are indicated for patients on ethambutol therapy. Ocular toxicity due to ethambutol is generally reversible [109].

Ethambutol crosses the placenta and is substantially distributed in the fetal compartment, with mean cord blood/maternal ethambutol plasma concentration ratios of 0.75 reported 30 h following a single administration of 800 mg oral dose of ethambutol [110]. Ethambutol has also been

demonstrated in breastmilk. Snider et al. reported the milk-plasma ratio of ethambutol as approximately 1.1 [46].

Pyrazinamide

The antitubercular function of pyrazinamide, a synthetic agent derived from niacinamide, was discovered in 1952, but it did not become part of standard TB treatment until 1972. Incorporation of pyrazinamide into the first-line regimen enabled a reduction of treatment duration to 6 months. Despite over 60 years of research, the mechanism of action of pyrazinamide remains unclear [111].

Pyrazinamide is renally eliminated after hepatic metabolism. A two-compartment first-order population PK model with data from a sub-study of the Tshepiso trial involving 18 PLWH with TB on a standard daily dosing of pyrazinamide (20–30 mg/kg) demonstrated no significant differences in drug clearance, volume of distribution, or bioavailability of pyrazinamide during pregnancy (in 15 pregnant persons) compared to postpartum (4 persons), with the conclusion that pregnancy did not appear to impact pyrazinamide's dosage and disposition. These data are consistent with pyrazinamide's PK properties, including its low protein-binding which implies a low free fraction and reduced clearance of pyrazinamide during pregnancy [93•]. Pyrazinamide crosses the placenta and has been demonstrated in low concentrations in breastmilk. Keskin and Yilmaz reported the milk-plasma ratio of pyrazinamide as approximately 0.04, suggesting that the concentration of pyrazinamide is low in breastmilk [112]. Thus, it would be reasonable to breastfeed while on pyrazinamide. The most clinically significant adverse event associated with pyrazinamide administration is hepatotoxicity [113]. As such, neonates may develop rare clinical symptoms and signs of toxicities suggestive of pyrazinamide hepatotoxicity like jaundice, rash and thrombocytopenia [114].

At this time, the CDC does not recommend pyrazinamide use in pregnancy because its effect on the fetus is unknown; however, the CDC acknowledges that the benefits of a TB treatment regimen that includes pyrazinamide for pregnant women living with HIV may outweigh the potential risks to the fetus [115]. The WHO recommends standard four-drug therapy, including pyrazinamide, for pregnant women, regardless of HIV status. Further clinical studies evaluating these benefits and risks are needed.

New and Second-Line Antitubercular Drugs

Data regarding the majority of second-line drugs for TB during pregnancy is limited to observational case studies [116–127]. Multidrug-resistant TB (MDR-TB), described as *M. tuberculosis* infection that is resistant to rifampicin and isoniazid with or without resistance to other drugs, represents approximately 3% of new TB cases worldwide [128]. When nosocomial transmission of MDR-TB has been documented, most cases developed in individuals living with HIV, with high reported mortality [47, 48, 129]. When MDR-TB is diagnosed, the WHO group A TB drugs are typically used, including bedaquiline, fluoroquinolones (levofloxacin/moxifloxacin), and linezolid. MDR-TB treatment during pregnancy involves discussion of the risks and benefits of these drugs during pregnancy, and requires consideration of second-line TB medications (WHO MDR-TB Groups B, C and D).

Bedaquiline, approved by the U.S. Food and Drug Administration (FDA) approval in 2012, acts via inhibition of the proton pump of mycobacterial ATP synthase. It has a clear mortality benefit and is recommended for all patients with MDR-TB as a group A drug. In a study comparing outcomes in pregnant women receiving bedaquiline vs. those not receiving the drug, MDR-cure rates were higher with bedaquiline (71% vs. 62%), and birth weights were similar (2690 vs. 2900 g, respectively) [130]. With regard to use of bedaquiline in PLWH, several model-based studies by Svensson et al. have investigated the compatibility of bedaquiline with concomitant ART. Due to bedaquiline's metabolism via cytochrome P450 3A4, the NNRTI efavirenz was predicted to increase bedaquiline metabolism via CYP3A4 induction, increasing exposure to its metabolites. However, this effect does not appear to be clinically significant [43, 131]. No significant DDIs of nevirapine on bedaquiline PK were identified in modeling, suggesting that bedaquiline may be co-administered with nevirapine without dose adjustments. However, the predicted elevation of bedaquiline (nearly threefold) and its metabolites (twofold) with lopinavir/ritonavir co-administration on modeling are a safety concern [44]. Further evaluation in clinical trials of bedaquiline-ART combination regimens is needed. Per the CDC, bedaquiline may be considered for pregnant women living with HIV with MDR-TB, in combination with at least three other anti-TB drugs to which the patient's MDR-TB isolate has been found to be susceptible [39, 40]. In this setting, an INSTI like dolutegravir is likely optimal.

Delamanid, another new second-line antitubercular agent with acts via inhibition of cell wall synthesis, received FDA approval in 2017 for the treatment of adult pulmonary MDR-TB when an effective treatment regimen cannot otherwise be devised. While there are very limited PK and safety data on the use of delamanid in pregnant women, studies in animals have demonstrated reproductive toxicity: in rabbits, embryo-fetal toxicity was observed at maternally toxic dosages, and in lactating rats, the maximum concentration of delamanid in breast milk was fourfold higher than in the blood [132].

In 2019, the FDA approved pretomanid, which acts via inhibition of cell wall biosynthesis, for treatment of pulmonary MDR-TB when administered in combination with bedaquiline and linezolid. There is currently very limited data available on use of pretomanid in pregnancy; animal studies have failed to demonstrate evidence of fetal toxicity but have revealed evidence of increased spontaneous miscarriages at maternally toxic doses. Increased spontaneous miscarriage was observed in rats with maternal toxicity (including reduced body weight and feed consumption) at doses around four times the human exposure for a 200 mg dose; no adverse fetal effects have been observed in rats or rabbits at doses up to 2 times the human exposure. There are no controlled data yet available in human pregnancy. Reduced fertility and/or testicular toxicity have been observed in male rats and mice after oral administration; reduced fertility and testicular toxicity could not be definitively ruled out in male humans at this time and is now being assessed in humans [133].

Fluoroquinolones have become critically important in the treatment of MDR-TB, and are typically used with bedaquiline and linezolid. Although arthropathy is a known adverse effect of immature animals exposed to fluoroquinolones, and thus fluoroquinolones are typically not recommended for pregnant women or children aged < 18 years, studies evaluating fluoroquinolone use in pregnant women have not found an increased risk of birth defects or congenital musculoskeletal abnormalities [42, 134]. Thus, fluoroquinolones may be used in pregnancy for MDR-TB if they are required [135]. Linezolid, which binds to the 70S initiation complex of bacterial ribosomes and disrupts protein synthesis, has effective antimycobacterial activity but has significant potential for worsening of HIV-related neuropathy and bone marrow dysfunction, particularly when co-administered with isoniazid, zidovudine, and stavudine [136]. With careful monitoring, linezolid can be used for MDR-TB treatment in PLWH. No well-controlled studies of linezolid have been performed in human pregnancy, but animal studies in mice, rats, and rabbits have not shown teratogenic effects [137].

Cycloserine, a WHO group B drug for MDR-TB, is an antimycobacterial agent for which rigorous studies do not exist regarding use in humans during pregnancy; however, anecdotal evidence is reassuring [138]. The WHO group C drugs for MDR-TB include amikacin, ethionamide, p-aminosalicylic acid, and delamanid. Amikacin is the only aminoglycoside currently recommended for treatment of MDR-TB, and aminoglycosides should be avoided in pregnant women unless there are no other options [139]. Streptomycin in utero drug exposure has been associated with a 15% rate of vestibulocochlear nerve toxicity in human studies [140]; hearing loss has also been detected in approximately 2% of infants exposed to long-term kanamycin therapy in utero. Ethionamide has been associated with an increased risk for several anomalies in animal studies after high-dose exposure, and case reports have documented CNS defects in humans; thus, ethionamide should be avoided in pregnancy [141]. Para-aminosalicylic acid, another salvage agent for highly resistant TB, is not teratogenic in rats or rabbits [142]; however, one study reported a possible increase in limb and ear anomalies among 143 infants exposed to p-aminosalicylic acid during the first trimester of pregnancy [143]. No specific pattern of defects has been detected in other human studies, however, indicating that this agent can be used in pregnancy with caution when required. Clofazimine, another antimycobacterial agent, is known to cross the placenta but has not been associated with teratogenic effects in animal studies [144]. Case reports regarding the use of clofazimine in pregnancy for the treatment of describe two patients who were successfully treated without harm to the fetus [145].

Discussion

The role of antitubercular therapy for women living with HIV during pregnancy varies depending on stage of TB disease (LTBI, active TB, MDR-TB), recent exposure to a patient with untreated active respiratory TB, and CD4 cell count. Among patients with active TB disease, multidrug treatment should be started immediately. Among patients with recent TB exposure or evidence of LTBI who have a CD4 count ≤ 350 cells/μL, we currently recommend initiating TB preventative therapy (TPT) during pregnancy given increased risk of progression to active TB, and among pregnant patients with LTBI and a CD4 count > 350 cells/μL in the absence of a recent TB exposure, we recommend tuberculosis treatment be deferred until 3 months after delivery based on the findings of the IMPAACT P1078 trial reported in 2019 [64•]. This recommendation is not yet reflected in formal guidelines: the U.S. DHHS guidelines recommend delaying LTBI treatment until 3 months after delivery in the absence of a recent TB exposure, but they do not specify a CD4 threshold, and the WHO guidelines from 2018 have not been updated since the publication of the IMPAACT P1078 trial findings in 2019 [62, 66]. In patients for whom antitubercular treatment is indicated during pregnancy, maintaining therapeutic levels of antitubercular medications is necessary to prevent active disease (in latent TB), to treat active TB disease, and to prevent maternal complications of HIV and TB.

Among pregnant women living with HIV with latent TB infection or TB disease not on ART, ART should be initiated promptly. Beyond the benefits of viral load reduction and reduced risk of vertical transmission, the risk of progression from latent TB infection to active TB disease in PLWH is significantly decreased by ART [146–149]. Because ART and antitubercular therapy are prone to significant DDIs,

dose adjustments and careful monitoring (e.g., monthly) of patient liver enzymes are essential components of management of this population.

The U.S. CDC and other professional organizations state that breastfeeding should not be discouraged in women taking first-line antitubercular drugs, as the concentrations of these drugs in breast milk are too small to produce toxicity in the newborn [63]. Pertinently for pregnant women with TB who are weighing postpartum contraceptive options, rifampin, along with other rifamycins, increases clearance of oral contraceptives and thus can lead to unplanned pregnancy [150, 151]. Rifabutin has also been demonstrated to reduce systemic exposure to oral contraceptives. Thus, back-up, nonhormonal methods of contraception are recommended for women on rifabutin who using oral contraceptives [35].

Pregnant women living with HIV are at especially high risk of progression of LTBI to active TB disease. Among pregnant women living with HIV, concurrent tuberculosis disease has also been shown to increase the risk of complications such as preeclampsia, low birth weight, preterm delivery, hospitalization, and perinatal transmission of HIV [18–21]. The grave impact of superimposed TB disease in individuals living with HIV on maternal morbidity and mortality necessitates clear guidelines for concomitant therapy and an understanding of the PK and potential DDIs of antitubercular and ART in pregnancy. While the use of isoniazid, rifamycins, and ethambutol in pregnancy and their DDIs with various ARTs are well-characterized, further study is needed into the use of pyrazinamide and of several newly developed second-line antitubercular drugs in pregnant women living with HIV. Among new antitubercular agents under development, bedaquiline has shown promise in pregnant women and in co-administration with some ARTs; delamanid is less promising due to concerns for reproductive toxicity; and pretomanid completely lacks data in pregnant women at this time.

Conclusions

Concerns about including pregnant women in research have led to a scarcity of evidence to guide safe and effective treatment of TB-HIV coinfection in pregnancy [34]. Limited safety data on these therapeutics in pregnancy inspires concern about unknown potential fetal exposure risks. This leads to reluctance to study pregnant women, thus further propagating the lack of safety data that could inform next steps for TB research in pregnant women. As may be seen in the case of the IMPAACT 1078 findings regarding isoniazid use for LTBI treatment in pregnancy, the absence of this research in pregnant women led to the medical field potentially exposing women and their infants to potential risk of these medications until this data changed management protocols. The absence of research in pregnant women can potentially increase harm, and studying safety data in pregnancy should not be neglected. Including pregnant women in clinical trials of any medication likely to be used in pregnancy has been recommended by the FDA since 1993 [152]. Given the epidemiology of the increasing risk of HIV/TB co-infection during pregnancy, further data, ideally in the form of randomized controlled trials, are warranted to determine optimal antitubercular and ART regimens for use during pregnancy.

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Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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