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A Pharmacology Perspective on Simultaneous Tuberculosis and Hepatitis C Treatment

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ABSTRACT Tuberculosis (TB) and hepatitis C virus (HCV) infections are both major public health problems. Despite high rates of coinfection, there is scarce literature addressing the convergence of the two diseases. One particularly unexplored area is the potential for simultaneous treatment of TB and HCV which would allow for leveraging an extensive global TB treatment infrastructure to help scale up HCV treatment. We review the drug metabolism of anti-TB and HCV drugs and the known and potential drug-drug interactions between recommended HCV regimens and individual anti-TB drugs. Rifampin is the only anti-TB drug to have been formally studied for potential drug interactions with anti-HCV direct-acting antivirals (DAAs), and existing data preclude these combinations. However, based on known pathways of drug metabolism and enzyme effects, the combination of HCV DAA regimens with all other anti-TB drugs may be feasible. Pharmacokinetic studies are needed next to help move cotreatment regimens forward for clinical use among patients coinfected with TB and HCV.

KEYWORDS pharmacology, tuberculosis, hepatitis C, drug interactions, cotreatment

Tuberculosis (TB) and chronic hepatitis C virus (HCV) infections are both major public health problems responsible for significant morbidity and mortality worldwide. There are an estimated 10 million incidence cases of TB globally and approximately 1.6 million TB-related deaths per year, making it the leading cause of infectious disease-related mortality worldwide (1). Infection with HCV leads to chronic hepatitis in the majority of cases, and in addition to >70 million prevalent cases, there are an estimated 3 to 4 million new cases and 400,000 deaths annually (2). Disease burden for both TB and HCV are high and disproportionately affect persons in low- and middle-income countries (LMICs) (1, 2). While data are limited, the prevalence of HCV has been found to be high (>5%) among patients with active TB, especially in Eastern Europe and Central Asia (>15%), where high rates of incarceration and injection drug use fuel both epidemics (3, 4). Beyond studies focusing on the coprevalence of TB and HCV (5) or rates of hepatotoxicity (6–8), there has been scarce discussion on the potential synergies of integrating TB and HCV treatment.

The development and rollout of new all oral direct-acting antivirals (DAAs) for the treatment of HCV infection have occurred at breakneck speed and have revolutionized HCV treatment, leading to extremely high cure rates and improved quality of life among those treated (9, 10). However, there are many challenges to expanding HCV treatment with DAAs, including improving case finding for chronic HCV infection (~20% of people with chronic HCV infection know their status), high drug costs, and the development of a health care workforce and infrastructure to provide treatment (2). In 2015, it was estimated that only 7% of people diagnosed with chronic HCV infection were started on treatment and access to DAAs, especially in most LMICs, remains

limited (2). Given the lack of capacity to treat HCV infection in many settings, including in both high-income countries and LMICs, there have been efforts and discussion to leverage existing primary care, HIV, and injection drug use (IDU) treatment programs to administer HCV treatment (11). An additional unexplored area is the use of TB treatment facilities to provide HCV treatment for TB/HCV coinfected patients. National TB programs exist in most countries, and their experienced and skilled health care workforce consisting of physicians and nurses along with extensive associated laboratory networks could offer a vital resource for HCV management in areas with insufficient capacity to meet increasing HCV treatment demand. Treating TB/HCV coinfected patients at a TB facility would also take advantage of the existing therapeutic relationship between TB health care workers and their patients, which develops throughout the long duration of TB treatment and would be in line with the goal of providing patient-centered care to all patients with TB.

To consider the cotreatment of patients with active TB and chronic HCV infection, it is imperative to understand the pharmacology of anti-TB and HCV drugs and consider possible drug-drug interactions (DDIs) that may allow or preclude the use of certain drug combinations. To our knowledge, there has been only one report in the literature of a patient simultaneously treated for active TB and HCV (12) and one published study on anti-TB and anti-HCV DDIs in healthy subjects (13). To evaluate the pharmacology of simultaneous TB and HCV treatment, we first briefly review the metabolism of anti-TB drugs and oral DAAs for HCV and then discuss potential DDIs; lastly, we discuss other issues related to the pharmacology of TB and HCV cotreatment, including liver disease and drug use. Our goal is to drive the field of TB and HCV comanagement ahead and ultimately improve treatment outcomes by providing data to help guide a research agenda for TB and HCV pharmacokinetic and clinical treatment studies.

TB AND HCV DRUG METABOLISM

For anti-TB drugs, we review the metabolism of drugs recommended for drug-susceptible (DS) and multidrug-resistant (MDR) TB (14–16). With regard to HCV drugs, we cover the metabolism of drugs that are currently recommended as either first-line or alternative treatment regimens by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (17). For a more exhaustive review, we direct the reader to recent in depth reviews (18–20). An overview of key routes of metabolism for anti-TB and HCV drugs are displayed in Tables 1 and 2, respectively.

Anti-TB drugs. The rifamycins are a cornerstone of first-line anti-TB treatment, and they also present the most challenging drug class in regard to DDIs, given their various and potent effects on human drug metabolism systems (21). To a great extent, rifamycins are eliminated by intestinal and hepatic metabolism to mostly desacetylated and hydroxylated metabolites (22). The three rifamycins used to treat mycobacterial infections include rifampin, rifapentine, and rifabutin, and all are metabolized to a partially active 25-O-desacetyl metabolite. Rifampin and rifapentine are cleared largely by an esterase, whereas rifabutin and especially 25-O-desacetyl-rifabutin depend on cytochrome P450 (CYP) 3A (CYP3A) for enzymatic clearance. Both the rifamycins and their metabolites are excreted primarily in the bile and eliminated in the feces (22). Approximately 10% of rifabutin, 17% of rifapentine, and 13% to 24% of rifampin are excreted unchanged in the urine (23–25).

Rifampin has an elimination half-life ($t_{1/2}$) of approximately 2 to 4 h (24). Rifampin notably induces its own metabolism or intestinal efflux (autoinduction), with the result that area under the concentration-time curve (AUC) and plasma $t_{1/2}$ are both reduced by 20% to 40% after 7 to 10 days of daily dosing (26). This autoinduction process is different from rifampin's well-known effects on CYP enzymes, since rifampin is not a substrate for CYP enzymes (24, 27). Rifampin causes increased metabolism of many drugs, but it rarely is affected by other drugs. Some genetic variations in carboxylesterase 2 enzyme may alter rifampin metabolism by affecting the gene expression (28).

TABLE 1 Elimination of antituberculosis drugs and their effects on enzyme and transporter activity[a]

Drug	Reference(s)	Route of Elimination	Transporter substrate	Enzyme/transporter inhibition	Enzyme/transporter induction
First-line drugs					
Rifampin	22, 24	Deacetylation	OATP1B1/SLCO1B1, P-gp/ABCB1	Transporters: OATP1B1/SLCO1B1	Enzymes: CYP1A2, -2B6, -2C19, -2C8, -2C9, -3A4, UGT1A1. Transporters: P-gp/ABCB1
Rifabutin	22, 34	CYP3A, hydroxylation, deacetylation	—	—	CYP3A4
Rifapentine	22, 35, 39, 41	Deacetylation, hydrolysis	—	—	CYP3A4, -2C8/9
Isoniazid	43, 45	Acetylation, dehydrazination	—	Enzymes: CYP2C19, -3A, -2A6, -2E1	CYP2E1
Pyrazinamide	46	Hydrolysis	—	—	—
Ethambutol	47	20% oxidation, 80% excreted unchanged in urine	—	—	—
Second-line drugs					
Levofloxacin	49	87% excreted unchanged in urine	—	—	—
Moxifloxacin	55, 56	Glucuronide and sulfate conjugation	P-gp	—	—
Amikacin	47	>90% excreted unchanged in urine	—	—	—
Kanamycin	47	>90% excreted unchanged in urine	—	—	—
Capreomycin	47	50–60% excreted renally	—	—	—
Ethionamide	51	Oxidation to sulphoxide metabolite	—	Enzyme: CYP2C8	—
Cycloserine	47	50–70% excreted unchanged in urine	—	—	—
Linezolid	50	Metabolized by oxidation (independent of CYP enzymes); renal and non-renal excretion	P-gp	—	—
Clofazimine	57, 93	Hydrolysis and glucuronidation	—	Enzymes: CYP3A, P-gp, BCRP, MRP1	—
Bedaquiline	58	CYP3A4 (mainly), CYP2C8, CYP2C19	—	—	—
Delamanid	59, 60	Albumin; metabolites are further metabolized by CYP enzymes (mainly by CYP3A4)	—	—	—
PAS	53	Acetylation	—	—	—

[a]—, either unknown or no well-established effect. ABC, ATP-binding cassette transporters; CYP, cytochrome 450; OATP, organic-anion-transporting polypeptide; BCRP, breast cancer resistance protein; MRP1, multidrug resistance-associated protein 1; P-gp, P-glycoprotein; PAS, *p*-aminosalicylic acid; SLC, solute carrier family; UGT, uridine 5′-diphospho-glucuronosyltransferase.

Rifabutin undergoes extensive intestinal and hepatic metabolism, resulting in more than 20 metabolites (22, 29). The primary metabolites are 25-*O*-desacetyl-rifabutin and 31-hydroxyl-rifabutin (22, 23, 29, 30). Rifabutin elimination $t_{1/2}$ is in the range of 25 to 67 h, depending on whether the data are obtained using a single dose (longer) or at steady state (shorter) (22, 23, 31). Similarly to rifampin, rifabutin undergoes autoinduction with 37% and 13% decreases in AUC and maximum concentration (C_{max}), respectively, after 10 daily doses (22, 29, 32, 33). CYP3A is the major isozyme that transforms rifabutin to its oxidative metabolites in human enterocytes and liver microsomes, and it also catalyzes oxidation of 25-*O*-desacetyl-rifabutin (22, 29). Rifabutin excretion occurs through the biliary tract and, to a small degree, renally (30). After a 150-mg dose, biliary concentrations reach up to 3 to 5 times the plasma concentration (34). Although not free of enzyme induction, rifabutin typically is approximately 40% as potent as rifampin and has been the preferred rifamycin when DDIs are unavoidable (34).

The elimination $t_{1/2}$ of rifapentine ranges from 14 to 18 h in healthy young adults to ~20 h in men >65 years (35) and is reduced with repeated dosing, suggesting autoinduction (36, 37). Rifapentine is metabolized by arylacetamide deacetylase (38), with nearly all radiolabeled drug in plasma being accounted for by rifapentine and its 25-desacetyl metabolite (39, 40). Approximately 87% of radiolabeled rifapentine is recovered in either feces (70%) or urine (17%) (41).

With regard to the remaining first-line drugs, isoniazid is extensively metabolized, mainly in the liver, to a number of inactive compounds by acetylation and dehydrazination. *N*-Acetyltransferase 2 forms acetyl-isoniazid, which is further metabolized to mono- and diacetylhydrazine (42–44). Isoniazid is an inhibitor of CYP2A6, -3A, -2C19, and -2E1, which may interact with other drugs with a narrow therapeutic index (45). Pyrazinamide undergoes hydrolysis (46), and the majority of ethambutol is excreted unchanged in the urine (47).

TABLE 2 Elimination of DAAs for hepatitis C and their effects on enzymes and transporters activity[a]

Drug	Reference(s)	Route of Elimination	Transporter substrate	Enzyme/transporter inhibition	Enzyme/transporter induction
Elbasvir	69	CYP3A4	P-gp	Transporters: BCRP, P-gp	None
Daclatasvir	68	CYP3A	P-gp	Enzymes: CYP3A4. Transporters: P-gp, BCRP, OATP1B1/3	CYP3A4 (weak)
Glecaprevir	70	CYP3A4 (secondary)	P-gp, BCRP, OATP1B1/3	Enzymes: CYP3A, CYP1A2, UGT1A1. Transporters: P-gp, BCRP, OATP1B1/3	—
Grazoprevir	69	CYP3A4	P-gp, OATP1B1	Enzymes: CYP3A4, UGT1A1. Transporter: BCRP	—
Ledipasvir	65, 66	Oxidative metabolism via unknown route	P-gp, BCRP	Enzymes: intestinal CYP3A4, UGT. Transporters: P-gp, BCRP	CYP3A4 (weak), CYP2C (weak), UGT1A1 (weak)
Pibrentasvir	70	None; eliminated via biliary-fecal route	P-gp, BCRP	Enzymes: CYP3A, -1A2, UGT1A1. Transporters: P-gp, BCRP, OATP1B1/3	—
Sofosbuvir	62, 66	Phosphorylated, renal excretion	P-gp, BCRP	—	—
Velpatasvir	72	CYP2B6, CYP2C8, CYP3A4	P-gp, BCRP	Transporters: P-gp, BCRP, OATP1B1/3, OATP2B1	—
Voxilaprevir	71	Extensive via CYP3A4	P-gp, BCRP, OAT1B1/3	Transporters: P-gp, BCRP, OATP1B1/3	—
Paritaprevir	67	CYP3A4, CYP3A5 (minor)	P-gp, BCRP, OAT1B1/3	Enzyme: UGT1A1. Transporters: BCRP, OATP1B1/3	—
Ombitasvir	67	Amide hydrolysis and oxidative metabolism	P-gp, BCRP	Enzyme: UGT1A1	—
Dasabuvir	67	CYP2C8, CYP3A4 (minor)	P-gp, BCRP	Enzyme: UGT1A1. Transporter: BCRP	—
Simeprevir	64	CYP3A4, possibly CYP2C8, CYP2C19	P-gp, OATP1B1/3, OATP2B1	Enzymes: intestinal CYP3A4 (mild), CYPA1A2 (mild). Transporters: P-gp, OATP1B1/3	—

[a]—, either unknown or no well-established effect. BCRP, breast cancer resistance protein; CYP, cytochrome 450; DAAs, direct-acting antiviral; OATP, organic-anion-transporting polypeptide; P-gp, P-glycoprotein; UGT, uridine 5'-diphospho-glucuronosyltransferase.

Many of the second-line anti-TB drugs appear to be metabolized by other non-CYP routes and thus are not affected by CYP inducers or inhibitors; hence, fewer DDIs are expected overall. Aminoglycosides, capreomycin, levofloxacin, and cycloserine are mostly excreted unchanged in the urine (47–49). Ethionamide and linezolid are mainly metabolized by oxidation (50, 51), and *p*-aminosalicylic acid undergoes acetylation (52, 53). Finally, moxifloxacin and clofazimine are metabolized mainly by conjugation (54, 55). Moxifloxacin is a P-glycoprotein (P-gp) substrate (56), while clofazimine is a P-gp inhibitor (57).

Bedaquiline and delamanid are the first new drugs to be approved for TB in >40 years, and they have brought much hope and promise to improve the management of MDR-TB. Bedaquiline is eliminated hepatically, being metabolized predominantly by CYP3A4 to its *N*-desmethyl metabolite. CYP2C8 and -2C19 have also been found to contribute to its metabolism (58). Delamanid, on the other hand, has a unique metabolic pathway. The parent drug is metabolized by plasma albumin to DM-6705 (M1), which is further metabolized by CYP enzymes through multiple metabolic pathways to form several metabolites (M2 to M8) (59, 60). The predominant pathway is mediated by CYP3A4 to form its oxide (M2).

Anti-HCV drugs. The route and extent of metabolism is varied among the oral DAAs (Table 2). Boceprevir and telaprevir were the first DAAs to be introduced and are metabolized by CYP3A4 and are P-gp substrates; consequently, they are prone to many DDIs (61). Given decreasing demand and availability of improved HCV treatments, both boceprevir and telaprevir have been pulled from the market. More recently introduced DAAs, sofosbuvir and simeprevir, are extensively metabolized by the liver. Sofosbuvir is a phosphoramidate prodrug that is hydrolyzed by intracellular cathepsin A and/or carboxylesterase 1 to the inactive metabolite GS-331007 (monophosphate), which is sequentially phosphorylated to the active metabolite GS-461203 (triphosphate) (62, 63). Simeprevir is known to be primarily metabolized by CYP3A4, with possible additional involvement of CYP2C8 and CYP2C19 (64).

The agents formulated in the multiple combination regimens approved between the years 2014 and 2017 also exhibit variable metabolism. Ledipasvir undergoes minimal oxidative metabolism through an unknown route and also requires an acidic pH for absorption (65, 66). Ombitasvir undergoes amide hydrolysis followed by oxidative metabolism in various locations (67). Paritaprevir is predominantly metabolized by CYP3A4 and secondarily through CYP3A5. Daclatasvir, elbasvir, and grazoprevir are also metabolized by CYP3A4 (68, 69). In contrast, dasabuvir is mainly metabolized by CYP2C8, while CYP3A4 is a minor pathway of metabolism. Velpatasvir undergoes extensive liver metabolism and has the potential to be implicated in DDIs due to the fact that it requires an acidic gastric environment for absorption and is metabolized by multiple CYP enzymes, including CYP2B6, -3A4, and -2C8 (65). Glecaprevir is secondarily metabolized by CYP3A4, but pibrentasvir does not undergo any metabolism. Both are primarily eliminated through the biliary-fecal route (70). The most recent agent approved in combination, voxilaprevir, is extensively metabolized in the liver by CYP3A4 (71).

DDIs BETWEEN ANTI-TB AND HCV DRUGS

As there are currently limited published DDI studies of anti-TB drugs and HCV DAAs, we used data from drug package inserts and knowledge of drug metabolism to determine known and potential DDIs, respectively. With regard to available DDI studies contained in drug inserts, the only anti-TB drug studied was rifampin; thus, we extrapolated potential DDIs for the remainder of anti-TB and HCV DAA drug combinations. To further evaluate and confirm potential DDIs, we also utilized the University of Liverpool HEP drug interaction online tool (https://www.hep-druginteractions.org), with the exception of the following anti-TB drugs, which were not include in this database: kanamycin, cycloserine, clofazimine, ethionamide, and *para*-aminosalicylic acid. We evaluated potential DDIs from the perspective of different HCV regimens and

TABLE 3 Drug-drug interactions between drug-susceptible tuberculosis and hepatitis C drugs[a]

Hepatitis C Treatment Regimens* (genotypes covered)	Anti-Tuberculosis Drugs for Drug-Susceptible Disease[#]					
	INH	RIF	RFP	RFB	PZA	ETH
First-line						
Glecaprevir, pibrentasvir (1-6)	yellow	red	red	orange	green	green
Sofosbuvir, velpatasvir (1-6)	yellow	red	red	orange	green	green
Elbasvir, grazoprevir (1,4)	yellow	red	red	orange	green	green
Ledipasvir, sofosbuvir (1,4-6)	green	red	orange	orange	green	green
Alternative						
Paritaprevir, ritonavir, ombitasvir, dasabuvir, ribavirin (1)	yellow	red	red	orange	green	green
Paritaprevir, ritonavir, ombitasvir, ribavirin (4)	yellow	red	red	orange	green	green
Simeprevir, sofosbuvir (1)	yellow	red	red	orange	green	green
Daclatasvir, sofosbuvir (1-3)	yellow	red	red	orange	green	green
Elbasvir, grazoprevir, ribavirin (1)	yellow	red	red	orange	green	green

[a]*, as recommended in the AALSD/IDSA hepatitis C treatment guidelines; #, drugs put into drug-susceptible and drug-resistant categories based on where they are commonly utilized (overlap does exist); INH, isoniazid; RIF, rifampin; RFP, rifapentine; RFB, rifabutin; PZA, pyrazinamide; ETH, ethambutol; red, drugs that should not be coadminstered; orange, potential clinically significant interaction; yellow, potential weak interaction unlikely to be clinically significant; green, no clinically significant interaction expected.

their predicted interaction with individualized anti-TB drugs used for DS- and MDR-TB as shown in Tables 3 and 4.

First-line HCV regimens. Currently, there are two first-line pangenotypic drug regimens for the treatment of HCV infection, including glecaprevir-pibrentasvir and

TABLE 4 Drug-drug interactions between drug-resistant tuberculosis and hepatitis C drugs[a]

Hepatitis C Treatment Regimens* (genotypes covered)	Anti-Tuberculosis Drugs for Drug-Resistant Disease[#]						
	LEV MOX	AMK KAN CAP	LZD	CFZ	PAS CS ETN	BDQ	DEL
First-line							
Glecaprevir, pibrentasvir (1-6)	green	green	green	yellow	green	orange	yellow
Sofosbuvir, velpatasvir (1-6)	green	green	green	yellow	green	green	green
Elbasvir, grazoprevir (1,4)(118)	green	green	green	yellow	green	orange	yellow
Ledipasvir, sofosbuvir (1,4-6)	green	green	green	yellow	green	yellow	yellow
Alternative							
Paritaprevir, ritonavir, ombitasvir, dasabuvir, ribavirin (1)	yellow	green	green	green	green	orange	orange
Paritaprevir, ritonavir, ombitasvir, ribavirin (4)	yellow	green	green	green	green	orange	orange
Simeprevir, sofosbuvir (1)	green	green	green	yellow	green	orange	yellow
Daclatasvir, sofosbuvir (1-3)	green	green	green	yellow	green	green	yellow
Elbasvir, grazoprevir, ribavirin (1)	green	green	yellow	yellow	yellow	orange	yellow

[a]*, as recommended in the AALSD/IDSA hepatitis C treatment guidelines; #, drugs put into drug-susceptible and drug-resistant categories based on where they are commonly utilized (overlap does exist); LEVO, levofloxacin; MOXI, moxifloxacin; AMK, amikacin; KAN, kanamycin; CAP, capreomycin; LZD, linezolid; CFZ, clofazimine; PAS, para-aminosalicylic acid; CS, cycloserine; ETN, ethionamide; BDQ, bedaquiline; DEL, delamanid; orange, potential clinically significant interaction; yellow, potential weak interaction unlikely to be clinically significant; green, no clinically significant interaction expected. Genotypes for first-line treatment with elbasvir and grazoprevir, see reference 94.

sofosbuvir-velpatasvir, and two additional regimens available for specific HCV genotypes, including elbasvir-grazoprevir and sofosbuvir-ledipasvir. Potential DDIs are reviewed below.

Glecaprevir and pibrentasvir are substrates and inhibitors of P-gp and breast cancer resistance protein (BCRP), with glecaprevir also being a substrate and inhibitor of organic-anion-transporting polypeptide (OATP) 1B1/3 (70). Additionally, both drugs are weak inhibitors of CYP3A, CYP1A2, and uridine 5′-diphospho-glucuronosyltransferase (UGT) 1A1. When given with 600 mg rifampin once daily, the C_{max} and AUC of both glecaprevir and pibrentasvir were decreased >80%; hence, rifampin is not recommended to be given with glecaprevir-pibrentasvir (70). Rifabutin has been used successfully with anti-HIV drugs and should be tested with anti-HCV drugs. Based on existing knowledge of drug metabolism, other potentially clinically significant DDIs include bedaquiline, which is metabolized by CYP3A4; thus, its concentrations may be increased with glecaprevir-pibrentasvir. Weaker potential DDIs are possible with isoniazid or clofazimine given their inhibitory effect on CYP3A enzymes which are responsible in part for the metabolism of glecaprevir. Clofazimine also inhibits two of the transporters (BCRP and P-gp) that glecaprevir and pibrentasvir are substrates for (57).

With regard to sofosbuvir and velpatasvir, both are substrates of P-gp and BCRP transporters. Additionally, velpatasvir is slowly metabolized by various CYP enzymes and is an inhibitor of BCRP and OATP transporters. The C_{max} and AUC of both sofosbuvir and velpatasvir were significantly decreased (>70%) in the presence of continuous daily use of rifampin 600 mg; thus, combination use with rifampin and other rifamycins currently is contraindicated (72). Additional potential DDIs exist between isoniazid and clofazimine and velpatasvir given their weak inhibition of CYP3A enzymes. There are no other predicted significant interactions with additional anti-TB drugs given the lack of any induction or inhibition of CYP enzymes by sofosbuvir or velpatasvir. Of note, the DDIs with the salvage regimen of sofosbuvir-velpatasvir-voxilaprevir and anti-TB medications would be expected to be similar to those described above, given both velpatasvir and voxilaprevir are eliminated by CYP enzymes (71).

The combination of elbasvir and grazoprevir is approved for HCV genotypes 1 to 4; both drugs are metabolized by CYP3A4 and are substrates of P-gp. Grazoprevir is also a substrate of OATP1B1. Both drugs can inhibit BCRP. Elbasvir is a weak inhibitor of P-gp while grazoprevir is a weak inhibitor of CYP3A4 and UGT1A1. While elbasvir-grazoprevir is not recommended to be given with rifampin, DDI data demonstrate mixed effects, with single-dose 600 mg rifampin increasing the AUC and C_{max} of elbasvir and grazoprevir, and continuous 600-mg-daily rifampin having minimal effect on grazoprevir AUC and C_{max} and decreasing 24-h postdrug concentrations by 90% (69). The inhibition of CYP3A4 by grazoprevir may increase the concentrations of bedaquiline, and given the uncertainties of the therapeutic index of bedaquiline, this is a potentially clinically significant interaction. Isoniazid and clofazimine may increase concentrations of both elbasvir and grazoprevir given their weak inhibition of CYP3A enzymes. Other anti-TB drugs are expected to have no major DDIs with elbasvir-grazoprevir.

The combination of sofosbuvir and ledipasvir has been the most commonly used DAA combination to date and is approved for genotypes 1 and 4 to 6. Similar to sofosbuvir, ledipasvir is also a substrate of P-gp, but in contrast, is also an inhibitor of P-gp and BCRP. A single dose of 600 mg rifampin decreased the C_{max} and AUC of ledipasvir by 35% and 59%, respectively. With regard to the clinical impact of this decrease, initial dose-finding studies found little additional antiviral activity with ledipasvir >30 mg; however, viral breakthrough with use of 30 mg compared to the standard 90-mg dose in one study was almost double (20% versus 11%) (73, 74). While the exposure-response relationships of sofosbuvir and ledipasvir need to be better defined, the pharmacokinetic impact of rifampin on ledipasvir along with effects on sofosbuvir mentioned above currently precludes the use of sofosbuvir-ledipasvir with rifampin or other rifamycins in clinical practice (66). Given low to no effect on the CYP enzyme system, there is no other clinically significant interaction with additional anti-TB drugs.

Alternative recommended HCV regimens. There are an additional five combination regimens recommended as alternative treatment regimens for HCV genotypes 1 to 4 as outlined in Table 3. With regard to the elbasvir-grazoprevir plus ribavirin combination for genotype 1, the expected DDIs are similar to the elbasvir-grazoprevir mentioned in the above section given no likely DDIs between ribavirin and anti-TB medications. The DDIs for the remaining 4 regimens are discussed below.

For the two regimens containing sofosbuvir, including simeprevir-sofosbuvir and daclatasvir-sofosbuvir, there are potential DDIs due to the metabolism of simeprevir and daclatasvir by CYP3A4 and the inhibition of CYP3A4 by daclatasvir and transporters by both drugs. Daily 600-mg rifampin decreased the C_{max} and AUC of daclatasvir by 79% and 56% (68), respectively, while it increased the C_{max} of simeprevir by 31% but decreased its AUC by 48% and C_{min} by 92% (64). Hence, rifampin and all rifamycins currently are not recommended to be coadministered with either of these regimens. Given a mild inhibition of CYP3A4 by simeprevir, there is a potential increase in bedaquiline concentrations which warrants caution. Conversely, there is no expected interaction between daclatasvir and bedaquiline.

The two regimens based on a backbone of paritaprevir, ritonavir, ombitasvir, and ribavirin plus/minus dasabuvir have no available data including rifampin but have a high potential for DDIs (67). Both paritaprevir and dasabuvir are metabolized by CYP enzymes, which likely prohibit their use with the CYP-inducing rifamycins. Additionally, ritonavir is a strong CYP3A4, which raises the possibility of DDIs with anti-TB drugs, particularly bedaquiline and delamanid. When administered with lopinavir-ritonavir, the AUC of delamanid and its metabolite (DM-6705) was found to be increased by 25% (13), and the clearance of bedaquiline was decreased by 35%, leading to an estimated 3-fold increase in exposure during chronic treatment (75). The inhibition of UGT1A1 by paritaprevir, ombitasvir, and dasabuvir may also cause increased drug concentrations of drugs that undergo glucuronidation, including moxifloxacin.

Overview. We conclude with a few key points from our review of the literature. The use of rifampin with recommended HCV DAA regimens is contraindicated given the strong induction of numerous drug-metabolizing systems and given available data provided through pharmaceutical studies conducted. This would preclude the cotreatment of HCV infection with DAAs and drug-susceptible TB with current first-line rifampin-based regimens. Further pharmacokinetic study of elbasvir-grazoprevir with rifampin and DDI studies of DAAs with rifamycins that have less drug-metabolizing induction effects, specifically, rifabutin, are possible areas of further study. Rifabutin is a potentially attractive rifamycin to use with ant-HCV drugs given its lower potency of CYP enzyme induction than with rifampin; given that it may be feasible to use rifabutin with DAAs from a pharmacokinetic perspective, we labeled rifabutin orange in Table 3, indicating a potentially significant clinically interaction (34). This would provide insight into whether compatible regimens for cotreatment of HCV infection and drug-susceptible TB treatment are available. Additional DDIs with a potential for clinical significance include (i) the use of bedaquiline with DAAs that inhibit CYP enzymes and hence may increase bedaquiline concentrations and alter the concentrations of its metabolites and (ii) the use of isoniazid and/or clofazimine with DAAs that are in part eliminated by CYP3A enzymes given their weak inhibition of this enzyme system. However, given the high tolerability of oral DAAs and no clear correlation of toxicity with concentrations, it is unclear if combination treatment with either isoniazid or clofazimine would lead to higher rates of clinically significant adverse events (20). With regard to use of bedaquiline with DAAs, the potential clinical significance is predicated in large part on the concern for a narrow therapeutic window of bedaquiline, including an early study which showed a higher risk of death in patients receiving bedaquiline and known effects on QT prolongation (76). However, the relationship between bedaquiline concentrations and adverse events is unclear, and recent clinical data show bedaquiline is well tolerated (77). The lack of clinically significant DDIs between other anti-TB drugs used for MDR-TB and DAAs opens up the potential for cotreatment of

patients with MDR/extensively drug-resistant (XDR)-TB and HCV coinfection and highlights the need for pharmacokinetic studies evaluating DDIs. The recent WHO guidelines for MDR-TB list linezolid, fluoroquinolones, and bedaquiline as the key drugs (class A) for treatment, and given few predicted DDIs between DAAs and both linezolid and fluoroquinolones, DDI studies with DAA and bedaquiline should be an initial priority (16). If found that bedaquiline and some or all DAAs have limited or no clinically significant DDIs, this would pave the way for clinical cotreatment studies. In contrast to the Liverpool HEP online drug interaction tool, we listed the combination of delamanid (metabolites eliminated by CYP3A4) with any HCV drug which has inhibition of CYP enzymes as a potentially weak interaction unlikely to be clinically significant (Table 4).

Another important point to bring up with regard to potential DDIs between anti-TB and HCV infection treatment is the therapeutic window of oral DAAs. As detailed in the recent, comprehensive pharmacokinetics-pharmacodynamics (PK-PD) review of DAAs by Smolders et al. (20), the standard dose of most oral DAAs is at the higher end of doses tested given their high tolerability; however, with the exception of sofosbuvir (78), the antiviral effect was similar at lower doses. Thus, the clinical impact of anti-TB drugs which may decrease the concentrations of anti-HCV treatment such as the rifamycins is uncertain given DAA concentrations may still remain in an effective range.

In an effort to provide interim guidance to clinicians who decide to treat TB and HCV infection simultaneously, we provide the following recommendations. If treating a patient with drug-susceptible TB and HCV (genotypes 1 and 4 to 6) infection, we would favor the combination of isoniazid, rifabutin, pyrazinamide, and ethambutol with ledipasvir and sofosbuvir. The rationale being that there are fewer potential DDIs with ledipasvir and sofosbuvir than with other first-line HCV treatment regimens (Table 3). With regard to patients with drug-susceptible TB and infections with HCV genotypes 2 and 3, we would recommend the same anti-TB regimen as described above including rifabutin, given less potential for DDIs versus the other rifamycins and either glecaprevir-pibrentasvir or sofosbuvir-velpatasvir. Among patients with drug-resistant TB, we would recommend the newly recommended regimen (16) of three class A drugs (fluoroquinolone, bedaquiline, and linezolid) along with at least one class B drug (clofazimine or cycloserine) assuming susceptibility along with an HCV regimen of sofosbuvir and velpatasvir. This combination has the least theoretical DDIs (Table 4).

LIVER DISEASE AND SUBSTANCE USE DISORDER

Although no TB drugs are recommended to be dose adjusted in patients with preexisting hepatic disease (Table 5), close and careful monitoring of liver function is needed, especially for unstable or advanced hepatic disease, as some studies have found such patients to be at higher risk of drug-related hepatotoxicity (79). Many TB drugs are metabolized in the liver; hence, the potential impact of liver disease severity on anti-TB drug pharmacokinetics should be addressed. While some data indicate that patients with chronic hepatitis, without cirrhosis, have comparable hepatic enzymatic activity to that of healthy individuals (80), there is also research finding moderate decreases in CYP enzyme activity in treatment-naive HCV patients without significant liver disease (81). In patients with liver cirrhosis, significant impairment in hepatic clearance can occur, including decreases in the expression of some CYP enzymes (e.g., CYP3A4 and -1A2) and transporters (82). Wang et al. have shown that cirrhosis due to HCV infection has different effects on the protein expression of various transporters (83): increased protein expression in MATE-1 (multidrug and toxin extrusion protein 1) and decreased expression of OCT1 (organic cation transporter 1) and P-gp. This could have an impact on anti-TB and HCV drugs that are substrates to those transporters (Tables 1 and 2). In addition, if hypoalbuminemia related to liver disease is present, this could affect drugs metabolized by albumin such as delamanid, which is a highly protein-bound drug (84, 85); in fact, administering delamanid to patients with hypoalbuminemia has been associated with increased risk of QT prolongation, most likely due to high drug concentration. In cases where ascites is present, this would create an additional space for hydrophilic drugs to distribute, resulting in lower plasma drug

TABLE 5 Characteristics of anti-tuberculosis drugs related to liver disease

Drug	Reference(s)	Protein binding (%)	Dosing adjustments for hepatic disease (14)	Associated with hepatotoxicity
First-line drugs				
Rifampin	79, 95–97	72–94	None; use with careful clinical and laboratory monitoring	Yes
Rifapentine	41, 79, 97, 98	97–99	None; use with careful clinical and laboratory monitoring	Yes
Isoniazid	79, 95, 97	0–34	None; use with caution in stable liver disease	Yes
Pyrazinamide	46, 79, 95, 97	0–7	None; use with careful clinical and laboratory monitoring. Contraindicated in severe hepatic impairment	Yes
Ethambutol	79, 95	4–24	None	No
Second-line drugs				
Levofloxacin	99, 100	24–38	None	No[a]
Moxifloxacin	100–102	26–50	None; use with caution secondary to risk of QT prolongation	No[a]
Amikacin	103, 104	0–11	None	No
Kanamycin	103, 104	0	None	No
Capreomycin	104		None	No
Ethionamide	51, 101, 104	30	None; use with caution	Yes
Cycloserine	47, 104		None; use with caution in alcohol-related hepatitis	No
Linezolid	105, 106	31	None; not evaluated in severe hepatic impairment	No; a single case has been reported
Clofazimine	107		Not studied, use with caution, dose reduction may be warranted	No
Bedaquiline	108, 109	>99.9	None; use with caution in severe hepatic impairment (not studied)	Yes
Delamanid	60, 110	99.5	None; not recommended in moderate and severe liver impairments	No
p-Aminosalicylic acid	53, 104, 111	58–73	None; use with close laboratory and clinical monitoring	Yes

[a]Although levofloxacin and moxifloxacin were associated with increased risk of acute liver injury compared to clarithromycin (100), they are generally not considered hepatotoxic drugs.

concentrations (86). The effect of liver disease can also go beyond distribution and metabolism. For instance, drug absorption can be affected due to reduced first-pass metabolism, resulting in higher bioavailability in patients with cirrhosis, as has been observed with carvedilol and midazolam (86). Given all these variables, predicting the changes in drug kinetics in patients with liver disease is challenging and necessitates the need for specific studies in patients with TB and HCV infection to better understand the effect of the coinfection and cotreatment on drug concentrations, with the ultimate goal of optimizing therapy. It also is important to keep in mind the drug selection and dosing adjustment could be extended to drugs that are renally cleared, given that patients with HCV infection are at a higher risk of developing and accelerating the progression of kidney disease (87). The routes of elimination of each drug, including those with renal excretion, are summarized in Tables 1 and 2. Additionally, dosing recommendations for anti-TB drugs are included in recently released TB treatment guidelines (14). With regard to HCV treatment regimens, for patients with chronic kidney disease stages 1 to 3, there are no dosage adjustment recommendations for first-line regimens, whereas for chronic kidney disease stage 4 or 5, the AASLD/IDSA treatment guidelines recommend using either regular dose elbasvir-grazoprevir or glecaprevir-pibrentasvir, given sofosbuvir is renally excreted (17).

Metabolism of FDA-approved medication-assisted treatment (MAT) drugs used to treat substance use opiate disorder can be impacted by TB and HCV medications (88). Both methadone and buprenorphine are metabolized by CYP3A4 among other CYP enzymes. As a potent CYP3A4 inducer, rifampin has the potential to precipitate opiate withdrawal symptoms in patients receiving concomitant TB and opioid replacement therapy (89, 90). Rifabutin is also a CYP3A4 inducer but does not appear to cause a significant interaction with methadone, while studies with buprenorphine are lacking (91). Conversely, anti-TB and HCV drugs which have some inhibitory effect on CYP enzymes (Tables 1 and 2) may increase concentrations of methadone and buprenorphine, thus necessitating MAT dose adjustments. There are also few clinical data on DDIs between opiate replacement therapies and current HCV drugs. Simeprevir, paritaprevir, ombitasvir, ritonavir, and dasabuvir may have clinically significant drug interactions with buprenorphine and should be monitored closely (92). Given that the coepidemic of TB and HCV infection is linked in most cases by injection drug use, it will

be crucial to address substance use disorder and implement MAT and hence to understand the pharmacokinetic implications of combining TB, HCV, and medication-assisted treatments.

CONCLUSION

Our review of available data on the potential DDIs between anti-TB and HCV treatment reveals a large gap in research addressing this topic. While knowledge of drug metabolism and existing data dim the prospects of combining any rifampin-based TB treatment with DAAs, our interpretation of drug metabolism highlights the potential compatibility of many anti-TB and HCV treatment regimens. Given the magnitude of the TB and HCV epidemics and their overlap, cotreatment could have a huge public health impact in many parts of the world, especially countries with well-developed national TB programs and limited existing capacity to scale up HCV treatment. Our review highlights possible anti-TB and HCV drug combinations to test in DDI studies and other pertinent PK issues to consider among patients with TB and HCV disease. Lastly, we hope this work helps to move the conversation and research agenda on addressing simultaneous TB and HCV infection forward.

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Correction for Kempker et al., "A Pharmacology Perspective on Simultaneous Tuberculosis and Hepatitis C Treatment"

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Volume 63, no. 12, e01215-19, 2019, https://doi.org/10.1128/AAC.01215-19. Page 7 of the PDF, 3rd full paragraph, 1st sentence: "The combination of elbasvir and grazoprevir is approved for HCV genotypes 1 to 4" should read "The combination of elbasvir and grazoprevir is approved for HCV genotypes 1 and 4."

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