IDSA
Infectious Diseases Society of America

hivma
hiv medicine association

OXFORD

Concomitant Treatment of Tuberculosis and Hepatitis C Virus in Coinfected Patients Using Serum Drug Concentration Monitoring

Alex Ashkin,[1] Afe Alexis,[2] Megan Ninneman,[3] Rene Rico Tresgallo,[4] David Ashkin,[5] and Charles A. Peloquin[6]

[1]Internal Medicine Resident, NCH Healthcare System, Naples, Florida, USA, [2]Jackson Memorial Hospital, University of Miami, Miami, Florida, USA, [3]Jackson Memorial Hospital, Respiratory Care Unit, Miami, Florida, USA, [4]Jackson Memorial Hospital, University of Miami, Pulmonary and Critical Care Division, Miami, Florida, USA, [5]Bureau of Communicable Disease, Florida Department of Health, University of Florida, Gainesville, Florida, USA, and [6]College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, Florida, USA

Background. Concern for drug-drug interactions leading to treatment failure and drug-resistant strains have discouraged clinicians from attempting concomitant treatment of hepatitis C virus (HCV) and tuberculosis (TB). Increased metabolism of direct-acting antivirals (DAAs) by rifamycins has hindered concurrent use. Development of an assay for ledipasvir and sofosbuvir (LDV/SOF) serum concentrations for therapeutic drug monitoring (TDM) can ensure adequate therapy. We present the first cases of concomitant therapy of active TB and HCV with rifamycin-containing regimens and DAAs using TDM.

Methods. Using TDM, we aim to determine whether concomitant therapy with rifamycin-containing regimens and DAAs is safe and effective for patients coinfected with TB and HCV. Five individuals with TB and HCV who experienced transaminitis before or during TB therapy were concomitantly treated with rifamycin-containing regimens and LDV/SOF. Therapeutic drug monitoring was performed for LDV, SOF, and rifabutin during therapy. Baseline laboratory tests and serial liver enzymes were performed. Hepatitis C virus viral load and mycobacterial sputum cultures were obtained upon completion of therapy to determine efficacy of therapy.

Results. All patients were found to have nondetectable HCV viral loads and negative mycobacterial sputum cultures upon completion of therapy. No clinically significant adverse effects were reported.

Conclusions. These cases illustrate concomitant use of LDV/SOF and rifabutin in patients with HCV/TB coinfection. Utilizing serum drug concentration monitoring to guide dosing, correction of transaminitis were achieved, which allowed the use rifamycin-containing TB therapy. These findings suggest that concomitant therapy of TB/HCV is possible, safe, and effective.

Keywords. drug monitoring; hepatitis C; tuberculosis.

Tuberculosis (TB) remains one of the leading causes of death from a single infectious agent in the world, with 1.5 million recorded deaths in 2020. Globally, 2 billion people are infected with latent TB, and the incidence of those progressing to active TB is in excess of 8.8 million adults [1]. There is a significant disease burden in the United States, with 13 million adults infected by latent TB with an estimated 13 billion dollars spent annually by the United States for prevention, diagnosis, and treatment [1, 2].

Hepatitis C virus (HCV) causes acute and chronic illness, ranging from asymptomatic infection to chronic infection with complications such as liver cirrhosis and hepatocellular

carcinoma. Globally, the prevalence of chronic HCV infection is approximately 58 million, with over 100 000 new cases diagnosed in the United States in 2020 [3, 4]. Although they are distinct disease entities, TB and HCV share commonalities from a public health perspective. Both infections have increased disease burden in middle- and low-income countries along with a disproportionate incidence among injection drug users and the incarcerated, resulting in coinfection rates of TB and HCV to be reported to range from 2% to 27% [5]. Therapies utilizing direct-acting antivirals (DAAs) are currently available, which cure close to 95% of patients infected with HCV, potentially reducing the development of its associated morbidities [6, 7].

Rifamycins are considered to be the most effective medications used to treat patients with drug susceptible TB, allowing for short-course, 6- to 9-month, TB therapies. Success rates utilizing these regimens are shown to reach 90%–95% [8]. One of the leading adverse effects associated with rifamycins is drug-induced liver injury (DILI). Drug-induced liver injury associated with TB therapy is one of the most common and concerning adverse effects of TB treatment, occurring in 2% to 28% of patients treated for TB [9]. The development of DILI often causes interruptions of TB therapy leading to prolonged illness

courses and prolonged periods of infectiousness. Drug-induced liver injury can also lead to significant morbidity including death from fulminant hepatic injury. Drug-induced liver injury is known to occur with an even higher frequency in patients coinfected with HCV. Ungo et al [10] showed that patients coinfected with TB and HCV have an increased risk (5-fold increase if HCV (+), human immunodeficiency virus (HIV) (−) and 14-fold increase if HCV (+), HIV (+)) of DILI secondary to the hepatotoxicity of the first-line anti-TB agents such as isoniazid, rifampin, and pyrazinamide. Furthermore, treatment of underlying HCV, previously performed with alpha interferon, demonstrated efficacy in their case series to reduce the incidence of DILI in coinfected patients. Hepatitis C virus therapy also allowed the reintroduction of rifamycin therapy due to alpha interferon's ability to ameliorate the HCV-induced transaminase elevation. This resulted in sustained mycobacterial response and subsequent cure of TB in these patients [11]. However, effective cure of the HCV was unable to be achieved with the therapeutic agents available at the time.

Clinicians treating patients with TB and HCV are often faced with the dilemma of how to manage patients who are found to have transaminase elevations either before initiating therapy or who develop such elevations during therapy. In clinically stable patients, common practice often entails adjusting the antituberculous regimen with less hepatotoxic ("liver-sparing regimen") effects albeit being suboptimal in efficacy requiring prolonged durations. Another option is treating the patient's underlying HCV with 8–12 weeks of antivirals before initiating TB therapy to avoid drug-to-drug interactions (DDIs). Because active TB is contagious, delay in therapy by up to 12 weeks would not only place the patient's health at risk but also pose a risk to public safety. Patients are often recommended to isolate during the 8–12 weeks of HCV therapy, which can lead to substantial socioeconomic and emotional distress. Patients can be admitted to the inpatient setting for isolation, which leads to increased hospital length of stay and significant medical expense. On occasion, patients with active TB experience rapid clinical deterioration requiring urgent antituberculous therapy preferably with the most effective medications, such as rifamycins, but are precluded from being able to utilize these medications due to elevated transaminases.

As previously demonstrated by Ungo et al [10], the concomitant treatment of TB and HCV offers the ability to both reduce the incidence of DILI in these patients as well as improve the transaminitis. Melikyan et al [12] demonstrated concomitant treatment of HCV and multidrug-resistant TB using DAAs and second-line, nonrifamycin-containing regimens with a 95.8%, 12-week sustained viral response (SVR) rate and 1 treatment failure. Prolonged TB duration (18–24 months) of therapy was required due to resistance to rifamycins in these patients with multidrug-resistant TB resulting in the subsequent inability to use this class of medications. Concerns regarding adverse effects of rifamycins in patients with HCV have previously led to the avoidance of the concurrent treatment of HCV and active TB. The interactions of concern include hepatotoxicity and increased metabolism of the DAAs. This metabolism is proposed to lead to subtherapeutic levels of the DAAs, resulting in potential treatment failure as well as the possibility of developing drug-resistant strains [13]. Case reports to date have only demonstrated sequential treatment of TB using rifamycin-based regimens followed by HCV treatment or vice versa [14, 15, 16].

Current recommended therapies for HCV and TB are well tolerated, safe, and very effective. Expected serum concentrations of DAAs and rifamycins required to achieve successful outcomes in HCV and TB patients have been established when used separately. It stands to reason that if the serum concentrations of rifamycins as well as DAAs, when used concomitantly, could be maintained within the expected "therapeutic" serum concentration range, treatment of HCV and TB could be achieved effectively, efficiently, and in a safe manner.

The concerns of rifamycins inducing a subtherapeutic level of DAAs pertains most significantly for rifampin, which is known to be a significant CYP3A microsomal enzyme as well as a P-glycoprotein (Pgp) inducer. Rifabutin, another member of the rifamycin class of drugs, has similar effectiveness against TB but is known to cause less induction of these hepatic and intestinal pathways. Rifabutin has been shown to have a decreased effects on the expected serum concentrations (eg, HIV medications) of drugs that are involved in these pathways [13]. Lutz et al [17] found rifabutin to have only weak effects on the serum area under the curve (AUC) concentration of sofosbuvir (SOF) (24% reduction) compared with the 72% serum AUC concentration reduction caused by rifampin. Kempker et al [13] have suggested that of the DAA combinations currently available, the least DDIs may occur between rifabutin and ledipasvir (LDV)/SOF and recommend this as the treatment of choice.

Although the effects of rifamycins on the metabolism of different drugs is generally known for a population of patients, the interpatient variability is significant. This makes predicting the dosage adjustment required to achieve therapeutic concentrations of the DAAs and rifamycins unreliable. Incorrectly achieving therapeutic serum concentrations, either too high or too low, could result in adverse effects, treatment failure, and/or development of resistance. Thus, to use these classes of drugs concomitantly, serum drug monitoring of the particular drugs would need to be performed to assure the known required therapeutic concentrations of the individual drugs are achieved. Although serum concentration measurement has previously only been possible in select research settings, the availability of clinical serum drug monitoring has been limited. The University of Florida's Pharmacokinetics Laboratory developed a clinically available assay in 2020 to measure LDV/SOF serum concentrations in addition to rifabutin serum concentrations. We report 5 cases of concomitant treatment of

pulmonary TB and HCV utilizing serum therapeutic drug monitoring (TDM). To date, these are the first cases of simultaneous therapy of active TB and HCV using DAAs and a rifamycin in the literature.

METHODS

Patient Consent Statement
All patients included in this case series were hospitalized at the Florida Department of Health inpatient Tuberculosis Unit. As part of hospitalization, all patients signed written consent for hospitalization and treatment. In addition, risk and benefits of concomitant HCV/TB therapy was explained and consent to treat was obtained. This study was considered to be a public health programmatic exemption by Institution Review Board.

Patients
The State of Florida contracts with the Jackson Memorial Hospital in Miami, Florida to operate a 20-bed, inpatient, TB unit. The inpatient TB unit admits patients who are determined by the Florida TB program to be too medically complex to be treated as an outpatient and/or those that have failed outpatient therapy. All patients admitted to the Florida Department of Health's inpatient TB unit from September 2020 to May 2022 had their medical records reviewed. Those patients who were admitted to the TB unit and were subsequently concomitantly treated for HCV and TB, whereas inpatients were retrospectively identified. Deidentified data included demographics, diagnosis, prior therapies, microbiologic parameters, dates of therapy, microbiologic response, serum drug concentrations, and adverse events. All patients diagnosed with active TB (microbiological findings, clinical findings and/or both) who were HCV positive via blood polymerase chain reaction (PCR) testing and received concomitant rifamycin and LDV/SOF therapy were included.

Procedures
All patients admitted to the TB unit underwent an initial assessment including the following: medical history, clinical evaluation, testing for hepatitis A, B, and C serologies (via enzyme-linked immunosorbent [ELISA] assay testing), sputum PCR for TB, sputum culture for TB, acid-fast bacilli (AFB) smear, TB susceptibilities (molecular and conventional), HIV antibody testing (via ELISA testing), CD4 count and HIV viral load, if applicable, CBC, liver enzymes, total bilirubin, creatinine, glucose, and appropriate imaging. Patients with a positive hepatitis C antibody had a serum HCV viral load measured as well as genotypic classification. Weekly monitoring of liver enzymes, total bilirubin, complete blood count (CBC), and basic metabolic panel were performed throughout therapy.

The decision to treat for HCV and TB concomitantly was made by the treating clinician when a coinfected patient either had previously presented with or developed increased transaminases and she/he deemed that concomitant HCV and TB therapy including a rifamycin would be clinically warranted to decrease risks of liver injury. All patients who were to be started on DAA therapy had their rifampin switched to rifabutin (initial dose 300 mg per day) to decrease potential interactions with the DAAs. Patients with HCV genotypes 1, 4, 5, or 6 were treated with LDV/SOF at an initial dose of 90 mg/400 mg per day, respectively. Ledipasvir/SOF therapy was given for 12 weeks duration, due to the evidence for liver injury in the patients treated. Ledipasvir/SOF therapy was provided by the inpatient TB unit as part of the supporting contract with the Florida Department of Health.

Hepatitis C virus viral load was measured at baseline and repeated at 4 and 12 weeks of LDV/SOF therapy. Favorable response to HCV therapy was defined as nondetectable viral load upon completion of therapy. Repeat viral load was measured 4 weeks after treatment to monitor for sustained response. Sustained virologic response 4 weeks after treatment completion was defined as a viral load concentration below 12I U/mL [18]. Sustained mycobacterial response was defined as a sustained negative sputum culture occurring after the initiation of therapy. Adverse events were identified and reported by the treating physicians based on clinical and laboratory results. Adverse events included the following: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels greater than 5 times the upper limit of normal (ULN), any adverse event that resulted in interruption or discontinuation of therapy, significant disability, and death.

Therapeutic drug monitoring was performed for all TB medications before DAA, and doses were adjusted to achieve expected values. In particular, rifabutin peak concentrations of 0.30–0.90 mcg/mL at 3 hours or 7 hours postdose were expected, and peaks of ≥0.45 mcg/mL were targeted. Therapeutic drug monitoring was performed approximately 2 weeks after starting DAAs and repeated as needed at approximately 2 weeks after any dose adjustments were made.

Therapeutic drug monitoring was performed using validated liquid chromatography-tandem mass spectrometry assays in a Clinical Laboratory Improvement Amendments (CLIA)-licensed, College of American Pathologists certified laboratory. Ledipasvir/SOF validation calibrator precision values ranged from 0.6% to 6.5% and from 1.3% to 7.4%, respectively. Sofosbuvir peak concentrations of 0.63–0.77 mcg/mL occur at approximately 1 hour postdose, followed by rapid conversion to active and inactive metabolites [19]. Ledipasvir peak concentrations of 0.36–0.37 mcg/mL occured at approximately 4 hours postdose [20]. We also collected 8-hour and trough concentrations.

RESULTS

Five patients were found to have concomitant TB and HCV disease (see Tables 1–3) and were determined by their treating clinician to warrant therapy for both HCV and TB concomitantly.

Table 1. Demographics

Subject	Age	Race	Sex	BMI/kg on Admission	BMI/kg Start LDV/SOF	BMI/kg End LDV/SOF	Hx ETOH	Hx IVDA	HIV Status	CD4	HIV 1 RNA Quant, Copies/mL Before and After DAA Therapy
Patient 1	54	White	M	22.3/76.7	24.0/82.6	25.6/87.9	Y	N	Neg	N/A	N/A
Patient 2	29	White	F	22.9/55.65	21.3/51.9	23.6/57.4	Y	N	Neg	N/A	N/A
Patient 3	68	Black	M	23.5/68.0	26.0/75.0	25.6/74.1	N	Y	Pos	877	ND/ND
Patient 4	60	White	M	13.6/43.0	16.0/50.6	17.2/54.45	Y	Y	Neg	N/A	N/A
Patient 5	54	Black	F	17.1/46.0	18.5/49.7	27.3/73.5	Y	Y	Pos	155	8256/179

Abbreviations: BMI, body mass index; DAA, direct-acting antivirals; HIV, human immunodeficiency virus; Hx ETOH, history of alcohol abuse; Hx IVDA, history of intravenous drug abuse; LDV, ledipasvir; N, no; N/A, not applicable; ND, not done; Neg, negative; Pos, positive; Quant, quantitative; RNA, ribonucleic acid; SOF, sofosbuvir; Y, yes.

Table 2. Initial HCV Viral Load Prior to and on Completion of LDV/SOF, Genotype, Duration of LDV/SOF, and Duration of TB Therapy Before Initiation of LDV/SOF

Subject	HCV RNA Quant RT-PCR, IU/mL Before LDV/SOF	HCV Genotype	MELD-Na	Abdominal Imaging Findings	Duration of TB Therapy Before Initiation of HCV Therapy (in days)	Duration of HCV Therapy (Weeks)	6 Weeks HCV RNA Quant RT-PCR, IU/mL	12 Weeks HCV RNA Quant RT-PCR, IU/mL	4 Weeks After Treatment HCV RNA Quant RT-PCR, IU/mL
Patient 1	499 681	1a	8	CT: cirrhosis with portal HTN; no ascites	144	12	ND	ND	ND
Patient 2	19 397	1a	7	None	131	12	ND	ND	ND
Patient 3	11 738 373	1a	26	CT: Normal liver size and attenuation.	53	12	ND	ND	Not performed
Patient 4	10 064 177	1a	13	MRI: Normal liver contour and homogenous signal intensity.	135	12	ND	ND	ND
Patient 5	9 737 882	1a	15	CT: unremarkable noncontrast study	70	12	ND	ND	ND

Abbreviations: CT, computed tomography; HCV, hepatitis C virus; HTN, hypertension; LDV, ledipasvir; MELD, Model for End-Stage Liver Disease score; MRI, magnetic resonance imaging; ND, not done; Quant, quantitative; RNA, ribonucleic acid; RT-PCR, reverse-transcription polymerase chain reaction; SOF, sofosbuvir; TB, tuberculosis.

Table 3. Table Showing Location of TB Infection and Initial MTB PCR, Smear and Culture Results, Time to Culture Conversion, and Duration of TB Therapy

Subject	Location of TB	Initial MTB PCR	Initial Culture	Time to Culture Conversion (Days)	Duration of Therapy (Months)
Patient 1	Pulm	Pos	Pos	99	9
Patient 2	Pulm	Pos	Pos	93	7
Patient 3	Pulm	Neg	Neg	N/A	5
Patient 4	Pulm	Pos	Pos	38	7
Patient 5	Pulm	Neg	Pos	41	7

Abbreviations: MTB, *Mycobacterium tuberculosis*; N/A, not applicable; Neg, negative; PCR, polymerase chain reaction; Pos, positive; Pulm, pulmonary; TB, tuberculosis.

All 5 required hospitalization, and they had experienced an elevation of their transaminases before or during TB therapy. The patients were treated with first-line antituberculosis regimens containing a rifamycin derivative, rifabutin, along with LDV/SOF. All 5 patients were treated for both TB and HCV (see Table 4). Treatment was defined as a nondetectable viral load at the completion of LDV/SOF therapy along with MTB culture negative after TB therapy. Of note, 1 patient was culture negative for TB at baseline with the diagnosis based on positive interferon gamma release assay, clinical and radiographic findings consistent with TB, 3 negative sputum cultures, and improvement with antituberculosis therapy [21]. The average duration of therapy for TB was 7 months. All 5 patients were treated for 12 weeks with LDV/SOF for HCV. The average HCV ribonucleic acid viral load on admission was 4.6 million. Four patients were found to have nondetectable SVR at 4 weeks post-LDV/SOF therapy, and a follow-up viral load at 4 weeks was unable to be obtained for 1 patient. The average time to *Mycobacterium tuberculosis* (MTB) culture conversion was 68 days from the time of the original initiation of TB therapy. There were no clinically significant elevations in liver enzymes (greater than 5× the ULN without symptoms or 3× ULN with symptoms of hepatitis) (see Figures 1–3) once concomitant HCV and TB therapy were initiated. No interruptions in therapy were required in any of the patients during the 12-week interval of cotreatment. The starting dose of LDV/SOF was 90

Table 4. Tuberculosis/HIV Regimen at Initiation of LDV/SOF (mg Daily Unless Otherwise Specified)

Subject	RBN (mg)	INH (mg)	EMB (mg)	PZA (mg)	LEVO (mg)	DOL (mg)	Truvada (mg)	3TC (mg)
Patient 1	300	300	N/A	1250	N/A	N/A	N/A	N/A
Patient 2	300	300	1600	N/A	N/A	N/A	N/A	N/A
Patient 3	N/A	N/A	N/A	N/A	N/A	50 BID	200/300	N/A
Patient 4	300	600	800	1000	N/A	N/A	N/A	N/A
Patient 5	300	300	800	1000	N/A	100 BID	N/A	300

Abbreviations: 3TC, lamivudine; DOL, dolutegravir; EMB, ethambutol; INH, isoniazid; LDV, ledipasvir; LEVO, levofloxacin; N/A, not applicable; PZA, pyrazinamide; RBN, rifabutin; SOF, sofosbuvir.

Table 5. Therapeutic Drug Monitoring Results for Rifabutin Before and After LDV/SOF and LDV/SOF

Subject	RBN Initial Dose (mg)	RBN 3 hr mcg/mL	RBN 7 hr mcg/mL	RBN With LDV/SOF (mg)	Trough mcg/mL	Conc. No. 1 mcg/mL	Conc. No. 2 mcg/mL	Dose Adjustment (mg)
Patient 1	300	0.39	0.21	RBN 300	N/A	3 hr: 0.47	7 hr: 0.35	None
			…	LDV 90	0.06	4 hr: 0.07	8 hr: 0.07	↑ 180
			…	SOF 400	0.00	4 hr: 0.82	8 hr: 0.01	↑ 800
Patient 2	300	0.30	0.41	RBN 300	N/A	3 hr: 0.68	7 hr: 0.27	none
			…	LDV 90	0.30	3 hr: 0.60	7 hr: 0.48	None
			…	SOF 400	0.00	3 hr: 0.31	7 hr: trace	none
Patient 3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			…	LDV 90	0.13	2 hr: 0.20	6 hr: 0.02	↑ 180
			…	SOF 400	0.00	2 hr: 0.58	6 hr: 0.25	↑ 800
Patient 4	300	0.23	0.28	RBN 300	N/A	3 hr: 0.42	7 hr: 0.41	none
			…	LDV 90	0.06	3 hr: 0.07	6 hr: 0.11	↑ 180
			…	SOF 400	0.00	3 hr: 0.7	6 hr: 0.09	↑ 800
Patient 5	300	0.38	0.24	RBN 300	N/A	3 hr: 0.30	7 hr: 0.25	none
			…	LDV 90	0.09	4 hr: 0.08	8 hr: 0.16	↑ 180
			…	SOF 400	0.00	4 hr: 0.98	8 hr: 0.07	↑ 800

Abbreviations: Conc., concentration; hr, hour; LDV, ledipasvir; N/A, not applicable; RBN, rifabutin; SOF, sofosbuvir.
NOTE: Expected ranges in mcg/mL: RBN 0.3–0.9, LDV 0.63–0.77, SOF 0.63–0.77.

and 400 mg, respectively, for all 5 patients. Four patients required increased dosages of LDV/SOF to 180 and 800 mg, respectively, with 1 of the 4 patients requiring the dose to be later decreased to 90 and 400 mg secondary to supratherapeutic concentrations on TDM. Four patients had a starting dose of 300 mg of rifabutin and continued 300 mg for the duration of their treatment. Further information regarding each patient's medication dosages are shown in Table 5. One patient's TB medications were held due to DILI before starting DAAs. Ledipasvir/SOF was started while the patient was off TB medications. Once the liver enzymes improved on LDV/SOF, TB therapy was reinitiated. This patient was started on rifabutin 300 mg and ultimately required a 600-mg dose based on subtherapeutic concentrations. Two of the five patients also were concomitantly treated for HIV with regimens listed in Table 4. None of the patients were lost to follow up during TB and HCV therapy. No deaths or major adverse events were reported. Unfortunately, due to difficulty with patient adherence with follow-up care after treatment completion, long-term follow-up to confirm sustained HCV response at 12 weeks was not possible.

DISCUSSION

First-line therapy for active tuberculosis includes a rifamycin, isoniazid, pyrazinamide, and ethambutol (RIPE), for 2 months, followed by rifamycin and isoniazid for ≥4 months [22]. Rifamycins are the cornerstone for the treatment of TB, allowing for high rates of cure in 6–9 months. Rifampin is one of the most potent inducers of membrane transport proteins and microsomal enzymes, which play a prominent role in the absorption and metabolism of many medications. Use of rifampin with medications that are metabolized or transported by these systems may cause subtherapeutic concentrations, as well as increasing the risk of acquired drug resistance and treatment failure. Rifabutin is a rifamycin that seems to be as effective against TB as rifampin, with less inductive effects on transporters and microsomal enzymes [23]. Standard of care for the treatment of HCV involves the use of DAAs, including LDV/SOF, for 8 to
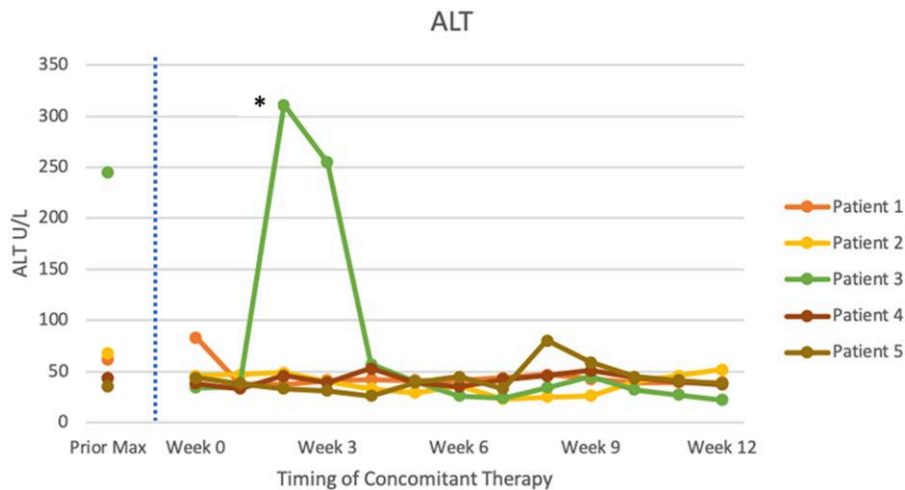
Figure 1. Demonstrates the trend of alanine aminotransferase (ALT) levels during concomitant TB/HCV therapy. "Peak Max" represents the highest level documented before initiation of ledipasvir (LDV)/sofosbuvir (SOF). Week 0 represents the level at the start of LDV/SOF therapy. *Patient asymptomatic, medications continued.
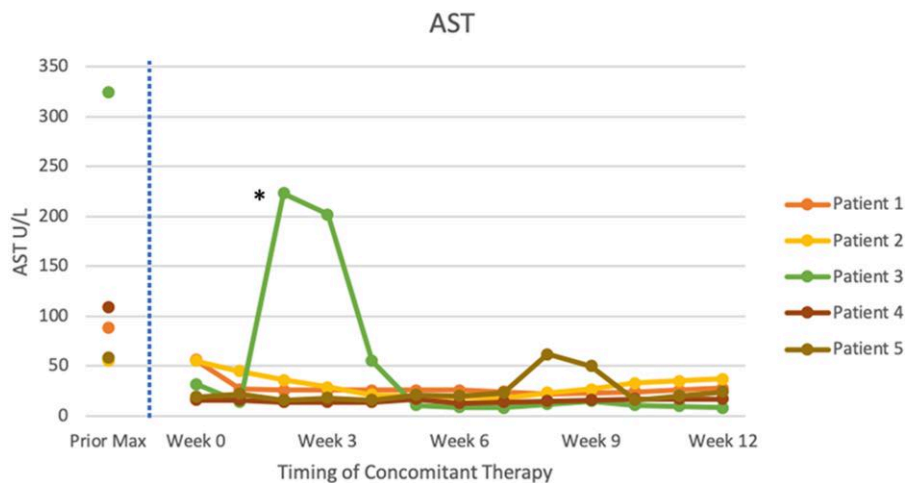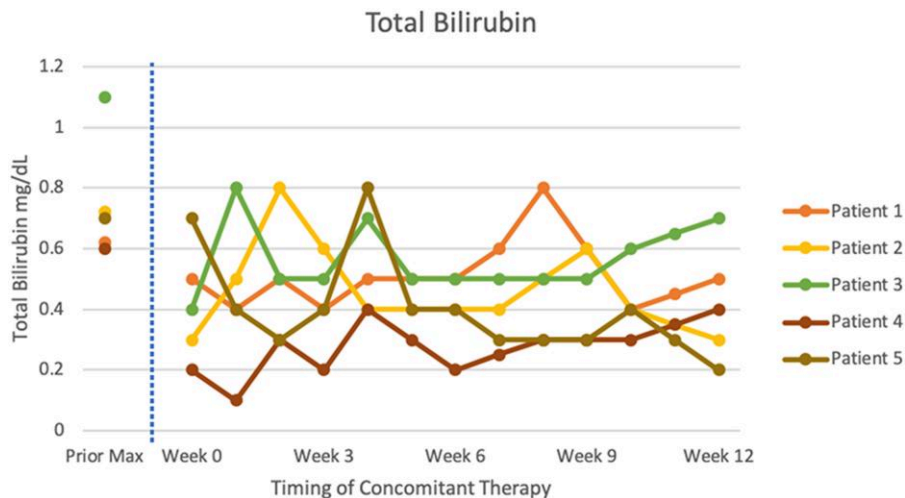

Figure 2. Demonstrates the trend of aspartate aminotransferase (AST) levels during concomitant tuberculosis/hepatitis C virus therapy. "Peak Max" represents the highest level documented before initiation of ledipasvir (LDV)/sofosbuvir (SOF). Week 0 represents the level at the start of LDV/SOF therapy. *Patient asymptomatic, medications continued.

12 weeks [24]. Given the prolonged treatment courses, sequential TB and HCV therapy substantially increases overall duration of therapy. In addition, untreated HCV is believed to increase the risk of DILI in patients receiving first-line anti-TB agents, often leading to a delay, interruption, and/or prolongation of the treatment of active TB infection by up to 24 weeks beyond the standard 4 months of therapy. This leaves the question, why not treat both diseases at the same time?

Previously, simultaneous treatment of TB and HCV was contraindicated because of the DDIs [13]. In our patients, first-line, rifamycin-containing regimens were used to treat TB, whereas LDV/SOF was used to treat HCV. Ledipasvir/SOF is a common anti-HCV combination regimen, approved for genotypes 1, 4, 5, and 6. Both drugs are Pgp substrates, making them susceptible to interactions with Pgp inhibitors or inducers. In the presence of rifampin, a potent Pgp inducer, the peak plasma drug concentrations were decreased by approximately 35% for ledipasvir and 70% for sofosbuvir. Given these significant effects on serum concentrations, concomitant treatment with LDV/SOF plus rifampin was designated as "contraindicated" [13, 19]. It should be noted that similar "formal" pharmacokinetic studies were not performed with rifabutin, a less potent inducer [13, 25]. However, while examining models to predict microsomal enzyme and Pgp induction by drugs, Lutz et al [17] showed rifabutin to be a weak metabolic inducer of sofosbuvir, with a 24% reduction of the AUC of sofosbuvir

Figure 3. Demonstrates the trend of total bilirubin levels during concomitant tuberculosis/hepatitis C virus therapy. "Peak Max" represents the highest level documented before initiation of ledipasvir (LDV)/sofosbuvir (SOF). Week 0 represents the level at the start of LDV/SOF therapy.

compared with a 72% reduction induced by rifampin. Furthermore, initial dose-finding studies found minimal additional antiviral activity with LDV doses greater than 30 mg [13]. Therefore, the typical LDV dose of 90 mg should retain significant antiviral activity, even when coadministered with rifabutin. When compared with other DAA combinations, LDV/SOF has fewer DDIs when used in combination with rifabutin, isoniazid, pyrazinamide, and ethambutol, suggesting that this might be the regimen of choice in those coinfected with TB and HCV [13].

We have presented 5 cases of concomitant treatment of both HCV and TB using first-line regimens for both diseases. The patients required an average of 7 months of anti-TB therapy with an overlapping 12 weeks of anti-HCV therapy. All patients had a favorable treatment response for both TB and HCV at the end of their regimens. Successful treatment of TB was demonstrated by negative AFB smear and culture upon completion of therapy. Favorable treatment response of HCV was demonstrated with a SVR and undetectable viral load upon completion of therapy. The SVR at 4 weeks posttherapy has been shown to have a 98% concordance with SVR at 12 weeks, which has a 99.7% concordance with SVR at 24 weeks [18]. All patients received LDV/SOF with dosages ranging from 90 to 180 mg of LDV and 400 to 800 mg of SOF. Four of the five patients were treated with rifabutin, isoniazid, pyrazinamide, and ethambutol, whereas 1 received rifabutin and levofloxacin secondary to transaminitis before administration of DAAs. Of note, 2 of the patients were also being treated with HIV antiretroviral agents before initiating DAAs with subsequent continued acceptable HIV therapeutic response as measured by continued viral suppression as well as acceptable serum HIV drug concentrations. Weekly liver function tests were performed, which did not reveal any clinically significant elevations in AST, ALT, or total

bilirubin during therapy in any of the 5 cases. All 5 patients received therapy to completion, with no indications for early termination of treatment, and none of the patients were lost to follow up while on HCV and/or TB therapy.

With consistent drug monitoring, we were able to achieve therapeutic concentrations of LDV/SOF, as well as adequate concentrations of TB medications in all 5 of our patients. Dosage increases were common for LDV/SOF, and these were well tolerated. There has been no evidence of LDV/SOF altering anti-TB drug concentrations, which was supported in our findings [26].

Another factor contributing to prior avoidance of concomitant treatment of TB and HCV is the increased risk of DILI secondary to RIPE therapy. Previous studies had demonstrated an approximately 5-fold increase in the incidence of hepatoxicity in patients treated for TB who also were coinfected with untreated HCV [27]. Our expectation was that concomitant treatment of the underlying HCV would decrease the risk of DILI. Weekly liver function tests were performed on all 5 patients with no clinically significant elevations noted in AST, ALT, or total bilirubin. One patient was noted to have drug-induced transaminitis from RIPE before DAA administration requiring treatment alteration to rifabutin and levofloxacin. The DAA was initiated along with the alternative regimen with subsequent resolution of the transaminitis.

Potential limitations of the study findings include the small sample size of 5 patients, which limits the generalizability for the findings. Larger studies are necessary for further validation. All patients in the current study were found to have HCV genotype 1a. Similar results are expected for individuals diagnosed with genotypes 1, 4, 5, and 6, although further studies are necessary to support this claim. Due to difficulty with patient adherence with follow-up care after hospitalization, long-

term follow up to confirm sustained HCV response was not possible. Therapeutic drug monitoring has been recommended as a method to limit adverse effects from DDIs [28]. Unfortunately, access to serum drug monitoring may currently not be universally available and/or affordable. Another potential limitation to future application of these regimens is the cost of these medications, especially if the dosages need to be increased. It is hoped with increased evidence of efficacy and safety, insurance companies will be provided the evidence that may support the approval of covering the cost of these regimens. In addition, as the medications become available in generic forms, the expenses should be reduced. The possibility of preventing liver failure and the need for transplant may also be an incentive for governing bodies and insurance companies to support these interventions. Nonetheless, to ensure completion of therapy and to reduce obstacles to treatment, clinicians considering utilizing this regimen should assure that potential additional doses are approved and available before initiation.

CONCLUSIONS

We report the first 5 cases of intentional, concomitant treatment of both TB and HCV with first-line agents using TDM. With the use of TDM, appropriate dosage adjustments were assured for both the TB and HCV medications to attain expected serum concentrations throughout the duration of treatment. Patients required an average of 7 months of anti-TB therapy with an overlapping 12 weeks of anti-HCV therapy. All 5 patients showed favorable treatment response for both TB and HCV upon the completion of therapy. Serial liver function tests were performed during the duration of treatment with no clinically significant elevations in AST, ALT, or total bilirubin. It is hoped that the findings presented will guide further investigation into the safety and efficacy of concomitant treatment of TB and HCV, 2 very significant public health diseases.

References

1. World Health Organization. Tuberculosis (TB). Available at: https://www.who.int/news-room/fact-sheets/detail/tuberculosis. Accessed 9 March 2023.
2. Centers for Disease Control and Prevention. 2021 WTBD. Available at: https://www.cdc.gov/tb/features/wtbd/2021WTBD_Feature.html. Accessed 1 March 2023.
3. World Health Organization. Hepatitis C. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed 1 March 2023.
4. Centers for Disease Control and Prevention. "2020 Hepatitis C | Viral Hepatitis Surveillance Report. Available at: https://www.cdc.gov/hepatitis/statistics/2020surveillance/hepatitisc.htm#:~:text=During%202020%2C%2041%20states%20reported,3.33%20deaths%20per%20100%2C000%20people.
5. Behzadifar M, Heydarvand S, Behzadifar M, Luigi Bragazzi N. Prevalence of hepatitis C virus in tuberculosis patients: a systematic review and meta-analysis. Ethiop J Health Sci **2019**; 29:945–56.
6. Basyte-Bacevice V, Kupcinskas J. Evolution and revolution of hepatitis C management: from non-A, non-B hepatitis toward global elimination. Dig Dis **2020**; 38: 137–42.
7. Cárdaba-García ME, Abad-Lecha E, Calleja-Hernández MÁ. Effectiveness of direct-acting antiviral drugs against hepatitis C virus: predictive factors of response to the treatment. LJM **2021**; 16:1949797.
8. MMWR. "Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America." Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm. Accessed 9 March 2023.
9. Zhao H, et al. Drug-Induced liver injury from anti-tuberculosis treatment: a retrospective cohort study. Med Sci Monit **2020**; 26:e920350.
10. Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med. **1998**; 157(6 Pt 1):1871–6. http://doi.org/10.1164/ajrccm.157.6.9711039
11. Jaimer U, Denis J, David A, et al. Antituberculosis drug–induced hepatotoxicity. Am J Respir Crit Care Med **1998**; 157:1871–6.
12. Melikyan N, Huerga H, Atshemyan H, et al. Concomitant treatment of chronic hepatitis C with direct-acting antivirals and multidrug-resistant tuberculosis is effective and safe. Open Forum Infect Dis **2021**; 8:ofaa653.
13. Kempker RR, Alghamdi WA, Al-Shaer MH, Burch G, Peloquin CA. A pharmacology perspective on simultaneous tuberculosis and hepatitis C treatment. Antimicrob Agents Chemother **2019**; 63:e01215–19.
14. Tsai M-C, Lin M-C, Hung C-H. Successful antiviral and antituberculosis treatment with pegylated interferon-alfa and ribavirin in a chronic hepatitis C patient with pulmonary tuberculosis. J Formos Med Assoc **2009**; 108:746–50.
15. Musso M, Mosti S, Gualano G, et al. Hepatitis C virus infection: a challenge in the complex management of two cases of multidrug-resistant tuberculosis. BMC Infect Dis **2019**; 19:882.
16. Wahid B, Saleem K, Waqar M, Wasim M, Idrees M. Successful treatment of HCV/TB co-infected patient with sofosbuvir and daclatasvir: a case report. Future Virol **2018**; 13:317–21.
17. Lutz JD, et al. Cytochrome P450 3A induction predicts P-glycoprotein induction; part 2: prediction of decreased substrate exposure after rifabutin or carbamazepine. Clin Pharmacol Ther **2018**; 104:1191–8.
18. Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology **2014**; 61:41–5.
19. Kirby BJ, Symonds WT, Kearney BP, Mathias AA. Pharmacokinetic, pharmacodynamic, and drug interaction profile of the hepatitis C virus NS5B polymerase inhibitor sofosbuvir. Clin Pharmacokinet **2015**; 54:677–90.
20. German P, Mathias A, Brainard D, Kearney BP. Clinical pharmacokinetics and pharmacodynamics of ledipasvir/sofosbuvir, a fixed-dose combination tablet for the treatment of hepatitis C. Clin Pharmacokinet **2016**; 55:1337–51.
21. Nguyen M-VH, Levy NS, Ahuja SD, Trieu L, Proops DC, Achkar JM. Factors associated with sputum culture-negative vs culture-positive diagnosis of pulmonary tuberculosis. JAMA Network Open **2019**; 2:e187617.
22. Centers for Disease Control and Prevention. Treatment for TB disease. Available at: https://www.cdc.gov/tb/topic/treatment/tbdisease.htm. Accessed 23 February 2023.
23. Horne DJ, Spitters C, Narita M; U.S. National Library of Medicine. Experience with Rifabutin replacing rifampin in the treatment of tuberculosis. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3290133/#:~:text=Rifabutin%20has%20a%20much%20longer,with%20a%20rifabutin%2Dcontaining%20regimen. Accessed 23 February 2023.
24. World Health Organization. Hepatitis C. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c#:~:text=DAAs%20can%20cure%20most%20persons,absence%20or%20presence%20of%20cirrhosis. Accessed 1 March 2023.
25. Skinner MH, Blaschke TF. Clinical pharmacokinetics of rifabutin. Clin Pharmacokinet **1995**; 28:115–25.
26. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs **2014**; 74:839–54.
27. Lomtadze N, Kupreishvili L, Salakaia A, et al. Hepatitis C virus co-infection increases the risk of anti-tuberculosis drug-induced hepatotoxicity among patients with pulmonary tuberculosis. PLoS One **2013**; 8:e83892.
28. Nahid P, Dorman S, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis **2016**; 63:e147–95.