REVIEW

ASCPT

A literature review of liver function test elevations in rifampin drug–drug interaction studies

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Abstract

Although rifampin drug–drug interaction (DDI) studies are routinely conducted, there have been instances of liver function test (LFT) elevations, warranting further evaluation. A literature review was conducted to identify studies in which combination with rifampin resulted in hepatic events and evaluate any similarities. Over 600 abstracts and manuscripts describing rifampin DDI studies were first evaluated, of which 30 clinical studies reported LFT elevations. Out of these, 11 studies included ritonavir in combination with other drug(s) in the rifampin DDI study. The number of subjects that were discontinued from treatment on these studies ranged from 0 to 71 (0–100% of subjects in each study). The number of subjects hospitalized for adverse events in these studies ranged from 0 to 41 (0–83.67% of subjects in each study). LFT elevations in greater than 50% of subjects were noted during the concomitant administration of rifampin with ritonavir-boosted protease inhibitors and with lorlatinib; with labeled contraindication due to observed hepatotoxicity related safety findings only for saquinavir/ritonavir and lorlatinib. In the lorlatinib and ritonavir DDI studies, considerable LFT elevations were observed rapidly, typically within 24–72 h following co-administration. A possible sequence effect has been speculated, where rifampin induction prior to administration of the combination may be associated with increased severity of the LFT elevations. The potential role of rifampin in the metabolic activation of certain drugs into metabolites with hepatic effects needs to be taken into consideration when conducting rifampin DDI studies, particularly those for which the metabolic profiles are not fully elucidated.

INTRODUCTION

Rifampin is a commonly used antibiotic for treating mycobacterial diseases including all forms of tuberculosis (TB). It works by inhibiting RNA elongation via inhibition of bacterial DNA-dependent RNA polymerase.[1]

Cytochrome P450 (CYP) enzymes play a key role in drug and xenobiotic metabolism and detoxification;

CYP3A is the CYP isozyme most commonly involved in the metabolism of drugs. The CYP isozymes are most abundantly found in the liver, where they enzymatically convert lipid-soluble compounds to water soluble metabolites so they can be easily excreted[2]; however, CYP3A is also abundant in the gut.

Rifampin is one of the strongest known metabolic enzyme inducers.[3] It is a strong activator of the pregnane X

receptor (PXR), a nuclear hormone receptor, which leads to substantial increases in the amounts of the majority of synthesized drug metabolizing enzymes, including CYP3A. Rifampin is also known to induce the synthesis of various drug transporters including P-gp. By virtue of its potent induction capability, rifampin is often used in drug–drug interaction (DDI) studies as an index inducer to assess exposures of investigational drugs that are metabolized by CYP and/or other drug metabolizing enzymes, under conditions of maximal enzyme induction.

At higher than approved doses of rifampin (>600 mg q.d.), liver toxicity has been noted in clinical studies. There have been fatalities associated with jaundice in patients with liver disease who were taking rifampin, as well as in patients without liver disease receiving rifampin concomitantly with other hepatotoxic agents.[1] Hepatitis is infrequently associated with rifampin use but is more common among patients taking rifampin who also have predisposing factors, including administration of concomitant hepatotoxins, HIV co-infection, history of liver disease, regular alcohol consumption, pregnancy, or patients with postpartum depression.[4]

Although DDI studies with rifampin are routinely conducted to assess the effect of maximal induction of CYP3A and other isozymes, instances of hepatoxicity, most commonly noted by way of elevations in liver function test (LFT) results, have been noted in some rifampin DDI studies, typically conducted using rifampin doses at or below 600 mg q.d. These studies are the basis for the current report.

This report describes a literature review of rifampin DDI studies in which LFT elevations have been noted while rifampin was administered in combination with another drug(s). In this review, published LFT elevations have been scrutinized for magnitude of the elevation, time of onset, and recovery time for the LFT elevations.

METHODS

Study search

A literature review was conducted using The University of Washington DDI database, Ovid, PubMed, Pfizer elibrary, Oxford University, and Google Scholar; these were queried for studies that included rifampin DDIs resulting in LFT elevation. Search terms used included "rifampin," "rifampicin," "ritonavir," "rifampin and ritonavir," "rifampin hepatotoxicity," "rifampicin hepatotoxicity," "rifampicin drug interactions," and "rifampin drug interactions." Additionally, abstracts from the American Society for Clinical Pharmacology and Therapeutics (ASCPT), American College of Physicians (ACP), American Society of Clinical Oncology (ASCO), and American Association

for Cancer Research (AACR) annual conferences were screened to search for additional instances of LFT elevations noted in rifampin DDI studies. Abstracts from conferences during 2013 to 2020 were considered.

The current analysis did not require ethical approval or study participant/patient consent. Furthermore, it should be noted that this analysis was strictly a literature review, and was not a systematic review or meta-analysis.

Inclusion and exclusion criteria

Initially, published abstracts were screened for any mention of LFT elevations in rifampin DDI studies, followed by a critical analysis of full-text reviews to examine when the elevations occurred. A study was considered eligible for inclusion in this analysis if it met the following criteria: (i) it was a clinical study (no preclinical/in vitro studies included), and (ii) resulted in LFT elevation when rifampin was administered concomitantly with another drug.

A study was excluded from the analysis if: (i) it did not mention liver-related safety signals (e.g., LFT elevations, jaundice, etc.), (ii) did not confirm that the LFT elevation occurred specifically during period of concomitant administration of rifampin with another drug, and (iii) did not report safety findings.

For publications in which specific details were not readily discernible, the authors were contacted in order to obtain further details to justify inclusion of the study in this analysis.

Data extraction and quality assessment

Data extracted from each publication included study design, subject demographics (health, gender, and age), treatment regimen including duration, changes in pharmacokinetic (PK) end points for the drug co-administered with rifampin (specifically, changes in area under the curve and maximum serum concentration), specifics for the LFT elevation (specific enzyme and adverse event [AE] grade of elevation, where available), onset and recovery times for the LFT change, magnitude of LFT increase, any clinical sequelae, and details regarding any hospitalizations or treatment/study discontinuation (Table 2).

RESULTS

Literature search

Based on the prespecified search criteria as described above, over 600 abstracts and manuscripts were first

selected and evaluated. Based on preliminary findings of LFT elevations in many studies that included ritonavir with rifampin, we also included ritonavir as a search term.

Sixty-four annual conference abstracts mentioned "rifampin," of which 36 were initially excluded because they either only included PK results (without safety results) or the abstracts did not mention instances of LFT increases.

Authors from seven clinical studies were contacted to acquire further information regarding LFT changes. Further details were obtained from responses from four clinical studies; two studies were included in the analysis because it was confirmed that the LFT elevations occurred during the period of coadministration with rifampin.

Of the over 600 abstracts and manuscripts initially identified, after applying the inclusion/exclusion criteria for this analysis, 30 clinical studies were retained.

Study characteristics

Thirty studies were retained in the final analysis; the characteristics of which are summarized in Table 1. Many of these studies include subjects with HIV who were receiving antiretroviral therapy along with rifampin. The number of subjects in the included studies ranged from three to 792. Of 30 studies, 11 rifampin DDI studies included ritonavir combined with other drugs. The number of subjects that were discontinued from treatment on these studies ranged from 0 to 71 (0–100% of subjects in each study). The number of hospitalized subjects in these studies ranged from 0 to 41 (0–83.67% of subjects in each study). Across all studies, LFT elevations which reported for alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and/or bilirubin.

Main analysis

The specific definitions for the criteria used for the grading of AEs were not always provided in all papers. In general, ALT, AST, and ALP elevations are defined per Division of AIDS (DAIDS) criteria[5]: grade 1 defined as greater than 1.25–2.5×upper limit of the normal range (ULN), grade 2 as 2.5 to less than 5.0×ULN, grade 3 as 5.0 to less than 10.0×ULN, and grade 4 as greater than or equal to 10.0×ULN. The LFT elevation noted in these studies ranged from grade 1 to 4. The 30 studies retained in the final analysis described rifampin co-administration with 15 different drugs that resulted in LFT elevation during concomitant treatment.

The drugs that were assessed in the rifampin DDI studies included in this analysis were categorized into three groups: anti-infectives, anti-cancer drugs, or the remainder noted as "other." In addition, the drugs' potential to inhibit and/or induce CYP enzymes and other transporters, were described (Table 1). The use of ritonavir-based regimens in combination with rifampin had a frequent association with LFT increases seen with five ritonavir-based regimens. These five ritonavir-based regimens include atazanavir, indinavir, saquinavir, lopinavir, and darunavir and were described in 11 publications. Hepatic AEs were reported in more than half the study subjects enrolled in rifampin DDI studies with these five ritonavir-based regimens in addition to a rifampin DDI study with lorlatinib, an anti-cancer drug. In three of the studies (lopinavir/ritonavir, atazanavir/ritonavir, and lorlatinib), all subjects experienced LFT elevations in the presence of rifampin (Table 1).[6–8]

In both the lorlatinib and ritonavir DDI studies, considerable LFT elevations were observed rapidly, typically within the first 24–72 h following co-administration.

DISCUSSION

To the best of our knowledge, this is the first reported literature review summarizing LFT elevations in rifampin DDI studies. It is important to know that routinely conducted rifampin drug interaction studies are generally safe. However, the purpose of this literature review is to identify the rare cases in which drug interaction studies with rifampin have resulted in hepatic-related AEs.

A total of 15 drugs were found to result in LFT increases when given in combination with rifampin. The magnitude of LFT elevations ranged from grade 1 to grade 4 for AST, ALT, ALP, GGT, and bilirubin.

Although the exact mechanisms of the observed LFT elevations in rifampin DDI studies are not explicitly known, many authors have provided speculations.

From this literature review, it is apparent that across studies, reporting of actual liver chemistry results, AE grades, and clinical sequelae due to LFT elevations have not been consistent. Thorough reporting of data from future rifampin drug interaction studies could help alleviate this shortcoming.

Importance of ritonavir involvement

The concomitant administration of rifampin with ritonavir-boosted protease inhibitors (atazanavir, indinavir, darunavir, lopinavir, and saquinavir) and lorlatinib were associated with LFT elevations that were noted in

TABLE 1 Drugs with published LFT increases when combined with rifampin

Category	Drug name + RIF[a]	# of Publications	First author	# of subjects with LFT increase	LFT elevation Magnitude (AST/ALT grade)[c]	Inducer/inhibitor[b]
Anti-infective	Lopinavir/ritonavir	6	Decloedt	10/21 (47.6%)	1–4	*Lopinavir* • Clinical moderate CYP3A inducer (400 mg b.i.d. for 4 weeks; Taburet et al.)[71] • In vitro P-gp inducer (Vishnuvardhan et al.)[74] *Ritonavir* • Clinical strong CYP3A inhibitor (100 mg t.i.d. for 3 doses; Greenblatt et al.)[51] • Clinical moderate CYP2B6 inducer (300–600 mg b.i.d. for 23 days; Park et al.)[67] • Possible clinical CYP2C19 strong inducer (400 mg b.i.d. for 20 days; Liu et al.)[58] • Clinical moderate CYP1A2 inducer (escalating doses up to 400 mg b.i.d. for 15 days; Kirby et al.)[55] • Clinical moderate CYP2C9 inducer (escalating doses up to 400 mg b.i.d. for 15 days; Kirby et al.)[55] • Clinical P-gp inducer (100 mg q.d. for 22 days; Kumar et al.)[56] • Clinical P-gp inhibitor (200 mg t.i.d. for 1 day, 300 mg b.i.d. for 7 days, then 400 mg b.i.d. for 13 days; Kharasch et al.)[53] • Clinical weak CYP3A inducer (100 mg q.d. for 10 days; Kasserra et al.)[52]
			la Porte	10/32 (31.3%)	2–3	
			Ren	2/30 (6.7%)	<1.5 × ULN[c]	
			Murphy	5/29 (17.2%)	1–3	
			Nijland	11/11 (100%)	1–4	
			Boulanger	2/11 (18.2%)	2–3	
	Saquinavir/ritonavir	1	Schmitt	14/17 (64.7%)	Arm 1 max ALT: 1.05–8 × ULN[c] Arm 2 max ALT: 11–70 × ULN[c]	*Saquinavir* • Clinical strong CYP3A inhibitor (1200 mg t.i.d. for 5 days; Palkama et al.)[66] *Ritonavir* See above

TABLE 1 (Continued)

Category	Drug name + RIF[a]	# of Publications	First author	# of subjects with LFT increase	LFT elevation Magnitude (AST/ALT grade)	Inducer/inhibitor[b]
	Indinavir/ritonavir	1	Avihingsanon	10/18 (55.6%)	3–4	*Indinavir* • Clinical strong CYP3A inhibitor (800 mg the evening of day 1, and then starting in the morning every 6h for two doses; Tian et al.)[78] • Clinical P-gp inhibitor (800 mg t.i.d. for 21days; Kharasch et al.)[54] *Ritonavir* See above
	Darunavir/ritonavir	1	Ebrahim	12/17 (70.6%)	1–4	*Darunavir* • In vitro inhibitor of CYP3A (Darunavir FDA NDA 21976 Clinical Pharmacology Review)[77] • In vitro slight inducer of CYP3A, at concentrations 4–5 times the in vivo C_{max} (Darunavir FDA NDA 21976 Clinical Pharmacology Review)[77] • In vitro inhibitor of P-gp (Darunavir FDA NDA 21976 Clinical Pharmacology Review)[77] *Ritonavir* See above
	Atazanavir/ritonavir	2	Hass Burger	3/3 (100%) 27/48 (56.3%)[d]	2–4 1–4	*Atazanavir* • In vitro metabolism-dependent inhibitor of CYP3A, and direct inhibitor of CYP2C8 and UGT1A1 (Reyataz USPI)[14] • Clinical moderate CYP3A inhibitor (400 mg q.d. given on days 1–7; Abel et al.)[79] *Ritonavir* See above
	Nevirapine	1	Cohen	3/16 (18.8%) 4/16 (25%)	Moderate[c]	*Nevirapine* • Clinical weak CYP3A inducer (200 mg q.d. from days 8–22, then 200 mg b.i.d.; Murphy et al.)[61] • Clinical weak CYP2B6 inducer (200 mg daily starting after 2weeks on study for 2weeks, then 400 mg daily; Veldkamp et al.)[72]

(Continues)

TABLE 1 (Continued)

Category	Drug name + RIF[a]	# of Publications	First author	# of subjects with LFT increase	LFT elevation Magnitude (AST/ALT grade)	Inducer/inhibitor[b]
	Efavirenz	3	Kwara Atwine Pedral-Sampaio	2/30 (6.7%) 6/98 (6.1%) 6/49 (12.2%)	2 ≥3 Toxic hepatitis[c]	*Efavirenz* • In vitro inhibitor of 2C9, 2C19, and 3A4 (Sustiva USPI)[70] • Clinical moderate CYP3A inducer (600 mg q.d. for 20 days; Kharasch et al.)[54] • Possible clinical moderate CYP2C19 inhibitor (400 mg q.d. for 11 days; Soyinka et al.)[69] • Clinical moderate CYP2B6 inducer (600 mg q.d. for 15 days; Robertson et al.)[68] • Clinical weak CYP2C19 inducer (600 mg q.d. for 17 days; Michaud et al.)[60] • Clinical P-gp inducer (600 mg q.d. for 20 days; Kharasch et al.)[54] • Clinical weak CYP1A2 inhibitor (600 mg q.d. for 17 days; Metzger et al.)[59]
	Tenofovir disoproxil fumarate	1	Droste	1/24 (4.2%)	3	*Tenofovir Disoproxil Fumarate* • Neither inducer nor inhibitor (Viread USPI)[73]
	Isoniazid + RIF (HR) or Pyrazinamide + RIF (RZ) or Pyrazinamide + isoniazid + RIF (HRZ)	2	van Hest Garcia-Rodrigues	RZ: 24/166 (14.5%) HRZ: 47/410 (11.5%) HR: 5/99 (5.1%) HRZ: 11/101 (10.9%)	Mild–severe[c,e] Mild–severe[c,e] Severe[c,e] Severe[c,e]	*Isoniazid* • Clinical moderate CYP2E1 inhibitor (300 mg q.d. for 7 days; Leclercq et al.)[57] • Clinical weak CYP2E1 inducer (300 mg daily for 14 days; O'Shea et al.)[63] • Clinical weak CYP2C19 inhibitor (90 mg b.i.d. for 10 days; Ochs et al.)[64] • Clinical weak CYP3A inhibitor (90 mg b.i.d. for 4 days; Ochs et al.)[65] *Pyrazinamide* • Neither inducer nor inhibitor (Nishimura et al.)[62]
	Pyrazinamide	4	Gordin Leung Priest Jasmer	28/721 (3.8%) 19/40 29/415 (7%) 54/207 (26.1%)	3 >1.5×ULN[c] >3×ULN[c] 1–4	*Pyrazinamide* See above
	Isoniazid Pyrazinamide	1	Noor	Isoniazid + RIF = 7/10 (70%) Pyrazinamide + RIF = 7/10 (70%)	>59 U/L (male)[c] >36 U/L (female)[c]	*Isoniazid* See above *Pyrazinamide* See above

TABLE 1 (Continued)

Category	Drug name + RIF[a]	# of Publications	First author	# of subjects with LFT increase	LFT elevation Magnitude (AST/ALT grade)	Inducer/inhibitor[b]
	Isoniazid	1	Ohno	14/77 (18.2%)	Not Reported	*Isoniazid* See above
	Isoniazid + ethambutol + pyrazinamide	1	Padmpriyadarsini	2/104 (1.92%)	3	*Isoniazid* See above *Ethambutol* • In vitro strong inhibitor of CYP1A2 and CYP2E1, moderate against CYP2C19 and CYP2D6 and weak against CYP2A6, CYP2C9 and CYP3A4 (Lee et al. 2014[40])*Pyrazinamide* See above
	Isoniazid + pyrazinamide + ethambutol + [NAC (in group 2)]	1	Baniasadi	Group 1 = 9/32 (28.1%) Group 2 = 0/28	5 × ULN[c]	*Isoniazid* See above *Ethambutol* See above *Pyrazinamide* See above
Oncology	Lorlatinib	1	Chen	12/12 (100%)	2–4	*Lorlatinib* • In vitro time-dependent inhibitor and inducer (via PXR) of CYP3A (Lorbrena USPI)[10] • In vitro inducer of CYP2B6 via human constitutive androstane receptor activation (Lorbrena USPI)[10] • In vitro inhibitor of P-gp and inducer of P-gp (via PXR) (Lorbrena USPI)[10] • In vitro inhibitor of OCT1, OAT3, MATE1, and intestinal BCRP (Lorbrena USPI)[10] • Clinical moderate CYP3A inducer (150 mg q.d.; Lorbrena USPI)[10] • Clinical moderate P-gp inducer (100 mg q.d.; Lorbrena USPI)[10] • Clinical weak CYP2B6, CYP2C9, and UGT inducer (100 mg q.d.; Lorbrena USPI)[10]

(Continues)

TABLE 1 (Continued)

Category	Drug name + RIF[a]	# of Publications	First author	# of subjects with LFT increase	LFT elevation Magnitude (AST/ALT grade)	Inducer/inhibitor[b]
	Idelalisib	1	Jin	3/12 (25%)	3	*Idelalisib* • In vitro inhibitor of CYP2C8, CYP2C19, CYP3A, and UGT1A1 (Zydelig USPI)[76] • Idelalisib metabolite (GS-563117) inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A, and UGT1A1 in vitro (Zydelig USPI)[76] • In vitro inducer of CYP2B6 and CYP3A4 (Zydelig USPI)[76] • In vitro inhibitor of P-gp, OATP1B1, and OATP1B3 (Zydelig USPI)[76] • GS-563117 inhibits OATP1B1, OATP1B3 in vitro (Zydelig USPI 2014)[76] • Clinical strong CYP3A inhibitor (150 mg b.i.d. for 8 days; Jin et al.)[37]
Other	Sirolimus	1	Tortorici	2/16 (12.5%)	Not reported	*Sirolimus* • No published information found, but not likely to be an inducer or inhibitor • Sirolimus did not affect the exposure of the following drugs: diltiazem, cyclosporine, ketoconazole, rifampin, acyclovir, atorvastatin, digoxin, ethinyl estradiol, norgestrel, glyburide, nifedipine, and tacrolimus. However, sirolimus increased the total exposure of erythromycin and verapamil (Zimmerman)[75]
	Apixaban	1	Vakkaalagadda	1/20 (5.0%)	AST (55) and ALT (85 U/L)[c]	*Apixaban* • Neither inducer nor inhibitor (Eliquis USPI)[50]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; FDA, US Food and Drug Administration; LFT, liver function test; MATE1, multidrug and toxin extrusion 1; NAC, N-acetylcysteine; NDA, new drug application; NR, Not Reported; OCT1, organic cation transporter 1; OAT3, organic anion transporter 3; PXR, pregnane X receptor; RIF, rifampin; ULN, upper limit of normal.

[a]Rifampin doses varied.

[b]Not a comprehensive list of potential inducer and inhibitor drug interactions. Search based on the information provided by the University of Washington Drug Interaction Database: DDI Marker Studies Knowledgebase version January 2022, information available in the US drug label as well as the NDA clinical pharmacology review, and available published human liver microsome studies.

[c]Grade of LFT elevation not reported.

[d]Subjects may have had concurrent AST/ALT elevation.

[e]Mild hepatotoxicity was defined as AST/ALT normal to 5×ULN. Severe hepatotoxicity is defined as ALT/AST >5×ULN.

more than 50% of subjects in many studies. However, it should be noted that a labeled contraindication to observed hepatotoxicity-related safety findings is only listed for saquinavir/ritonavir[9] and lorlatinib.[10] According to the saquinavir (Invirase) US drug labels, the co-administration of saquinavir/ritonavir with rifampin as part of an anti-retroviral therapy regimen is contraindicated due to severe hepatocellular toxicity.[9] Furthermore, the current US label for rifampin only includes warnings and precautions regarding concomitant administration of rifampin with saquinavir/ritonavir.[1] Similarly, in the lorlatinib drug label, there are contraindications regarding the concomitant use of lorlatinib with strong CYP3A inducers, which includes rifampin.[10] All other protease inhibitors' US Food and Drug Administration (FDA) drug labels include precautions/contraindications/warnings with concomitantly administered rifampin, due to the decrease of therapeutic effects, development of drug resistance, or loss of virologic response.[11–14]

Ritonavir, once used to treat HIV, is now administered at low doses as a PK booster for protease inhibitor-based regimens in antiretroviral therapy for patients with HIV/AIDS. Ritonavir itself has been associated with dose-dependent hepatotoxicity, particularly at higher ritonavir doses.[15] It should be noted that on the ritonavir US drug label, it has been noted to cause hepatic transaminase elevations greater than $5 \times ULN$, hepatitis, and jaundice in patients who receive ritonavir alone or with other antiretroviral medications.[16] A study by Shehu et al., hypothesized that PXR modulates ritonavir hepatotoxicity through CYP3A4-dependent pathways involved in ritonavir bioactivation, oxidative stress, and endoplasmic reticulum stress.[15] Therefore, when rifampin and ritonavir are co-administered, the combination may result in hepatotoxicity because rifampin results in increased CYP3A4 expression via PXR activation. In this publication by Shehu et al., two mice models were utilized to test the correlation between hepatotoxicity and the co-administration of rifampin and ritonavir using liver damage biomarkers. They first generated double-transgenic mice that expressed human PXR and CYP3A4 (hPXR/CYP3A4). These mice were treated with rifampin for 7 days followed by ritonavir. Considerable increase in liver damage markers was noted in these mice studies. Specifically, binding immunoglobulin protein, C/EBP homologous protein, and cyclin AMP-dependent transcription factor 3 were used to assess endoplasmic reticulum stress within the hepatocyte. A second mouse model involved use of animals with humanized PXR and deficient in CYP3A4 (hPXR/CYP3A-null). A CYP3A4 deficient mouse mode was utilized as CYP3A4 plays a critical role in ritonavir metabolism and bioactivation. The mice were treated with rifampin for 7 days followed by ritonavir, which resulted in no liver injuries. The authors concluded that PXR and CYP3A4 play essential roles in ritonavir hepatotoxicity.[15]

In a study by Acosta et al., no hepatotoxicity was observed with the administration of atazanavir with and without rifampin.[17] However, in a study by Haas et al., transaminase levels were elevated in all study subjects receiving atazanavir/ritonavir and rifampin.[7] Based on the results from these two studies, it can be inferred that ritonavir in combination with rifampin is likely an important component which results in hepatotoxicity. These results corroborate the conclusions from Shehu et al., because LFT elevations occurred only when atazanavir/ritonavir were administered concomitantly with rifampin in the study described by Haas et al. This is in contrast with no LFT increases noted for atazanavir + rifampin or atazanavir alone by Acosta et al.

Possible sequence effect

Several authors have posited that there may be a possible sequence effect associated with increased LFTs in these rifampin DDI studies with ritonavir boosted protease inhibitors.[7,8] The sequence effect asserts that the LFT changes are most pronounced when multiple dose rifampin administration precedes co-administration of ritonavir-boosted treatment regimens. This sequence effect was demonstrated in the saquinavir/ritonavir and rifampin combination study described by Schmitt et al.[18] A two-arm study was conducted which evaluated the effect of administering multiple dose rifampin prior versus post saquinavir/ritonavir. In the first arm, only two of 14 healthy subjects who were administered 2 weeks of saquinavir/ritonavir alone prior to multiple-dose rifampin plus saquinavir/ritonavir for 2 weeks experienced transaminase elevation. However, in the second arm, nine of 14 healthy subjects who were administered multiple-dose rifampin for 2 weeks alone prior to multiple dose rifampin-saquinavir/ritonavir co-administration experienced transaminase elevation (grade 4 ALT elevation of between $11 \times$ and $70 \times ULN$).[18] Similarly, in the Decloedt et al. study, it was noted that lower rates of hepatoxicity were observed due to subjects being pretreated with lopinavir/ritonavir, prior to combination of lopinavir/ritonavir with multiple-dose rifampin.[19] The outcomes of both the Schmitt et al. and Docloedt et al. studies support a possible sequence effect and are consistent with the hypothesis by Shehu et al. that the pre-induction of rifampin results in PXR-mediated up-regulation of CYP3A4, which metabolizes ritonavir and produces hepatotoxic ritonavir metabolites.[15]

Further regarding the sequence effect, it may be hypothesized that perhaps the net impact of induction is

TABLE 2 Rifampin drug interaction studies with published LFT increases

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/Discontinuation/Death	References
Apixaban (5 mg i.v. and 10 mg oral) + RIF (600 mg)	Open-label, randomized, sequential crossover study. (20 HV)	AUC ↓by 39% (i.v.) ↓by 54% (oral) C_{max} ↓by 42% (oral)	1 subject with elevated AST and ALT: ALT 85 U/L on day 16 (baseline 25 U/L; normal range 0–47U/L) AST 55 U/L on day 16 (baseline 30 U/L; normal range 0–37U/L)	Onset: day 16 Recovery: At follow-up 24days later	One discontinuation due to non-transaminase related AEs, and one subject discontinued due to ALT/AST elevations on discharge day (subject did not take the last RIF dose)	Vakkaalagadda et al.[49]
ATT: Isoniazid (600 mg) + ethambutol (1200 mg) + pyrazinamide (1500 mg). After 2months, randomize to additional ART regimen: either nevirapine (400 mg, after 200 mg q.d. lead-in) or efavirenz (600 mg/day), along with didanosine (250/400 mg for body weight < 60 or 60 kg) + lamivudine (300 mg) + RIF (450/600 mg based on body weight <60kg or ≥60 kg)	Prospective randomized controlled clinical trial (168 TB-HIV patients)	AUC NR C_{max} NR	Patients on ATT+ART (EFV arm): grade 3 ALT/AST = 2/104 (1.9%)	Onset: 1 month after initiating ART (3rd month of ATT)	0 discontinuations	Padmpriyadarsini et al.[45]
ATV/RTV (300/100 mg) + RIF (600 mg)	Open-label, one-arm study (3 HIV-seronegative volunteers)	AUC NR C_{max} NR	Transaminase elevated – 2days after initiating ATV/RTV (3/3 patients who started the study on the same day). Highest documented ALT values: 792 IU/L (grade 4) 173 and 1541 IU/L (grade 2) Only 1/3 had transaminase elevations greater than 5 times the ULN	Onset: 24 h of adding drug during period 2 (nausea and vomiting). (3/3) 2days after drug was added, liver enzymes were elevated (3) Recovery: Nausea resolved within several days after stopping study drugs and transaminase values returned to normal	3/3 discontinued study drugs after no more than 7 doses of ATV/RTV therefore the study was terminated	Hass et al.[7]
ATV/RTV (300/100 mg, 300/200 mg, 400/200 mg) + RIF (600 mg)	Open-label, multiple-dose, randomized, drug interaction study (71 HIV)	AUC ATV/RTV 300/100 mg + RIF (n = 16): ↓by 72% ATV/RTV 300/200 mg (n = 17): ↓by 55% ATV/RTV 400/200 mg + RIF (n = 14): ↓by 28% C_{max} ATV/RTV 300/100 mg + RIF (n = 16): ↓by 53% ATV/RTV 400/100 mg + RIF (n = 17): ↓by 37% ATV/RTV 400/200 mg + RIF (n = 16): ↓by 14%	Of the subjects that received combination ATV/RTV and RIF: 2 subjects experienced ALT/AST grade 2 (2.6–5×ULN); 2 subjects experienced ALT/AST grade 3/4 (3×ULN); 27 experienced total bilirubin > grade 2 (>5×ULN)	NR	4 subjects discontinued - unrelated to hepatotoxicity	Burger et al.[29]

TABLE 2 (Continued)

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/ Discontinuation/Death	References
DRV/RTV (800/100 mg q.d./b.i.d. or 800/200 mg q.d. or 1600/200 mg q.d.) + Dolutegravir (50 mg) + RIF (600 mg q.d. or 750 mg for body weight ≥70 kg)	Open-label, single-center, PK study (17)	*AUC* DRV/RTV 1600/200 mg q.d. + RIF (n = 4): ˅ by 56.8% DRV/RTV 800/100 mg Q12 h + RIF (n = 4): ˅ by 40.2% *C₂₄* DRV/RTV 1600/200 mg q.d. + RIF (n = 4): ˅ by 90.3% DRV/RTV 800/100 mg Q12 h + RIF (n = 4) = ˅ by 45.3%	*Cohort 1 (n = 5):* 1/5 – symptomatic grade 4 ALT elevation 3/5 subjects – asymptomatic ALT elevation (< grade 2) *Cohort 2 (n = 12):* 5/12 symptomatic hepatitis with grade 3/4 ALT elevation 3/12 – asymptomatic grade 1/ 2 ALT elevation None of the 6 with severe ALT elevation and symptomatic hepatitis developed hyperbilirubinemia Three sequential cohorts were planned to be enrolled, based on the safety of the preceding cohort. Enrollment was stopped after cohort 2. Cohorts 1 and 2 had the same dosing and drug regimen.	*Cohort 1 (n = 5):* 1/5 developed on the 9th day of RIF, 2 days after doubling the RTV dose but before the DRV dose was doubled 3/5 subjects: after 18–28 days *Cohort 2 (n = 12):* 5/12: 9–11 days after the introduction of RIF and 2–4 days after 100 mg RTV was added to DRV/RTV 800/100 mg q.d.	6 subjects were withdrawn due to symptomatic hepatitis and grade or 4 ALT elevations without jaundice. That resulted in the premature termination of the study	Ebrahim et al.[32]
Efavirenz (600 mg or 800 mg) + RIF (10 or 20 mg/kg/day)	Phase II, open-label, DDI, parallel, randomized clinical trial. 3 treatment arms: R10EFV600, R20EFV600, and R20EFV800 (98 patients – 1 tested HIV negative)	*AUC* R10EFV600: ˅ by 4.0% R20EFV600: ^ by 13.0% R20EFV800: ^ by 12.0% *Cₘᵢₙ* R10EFV600: ˅ by 8% R20EFV600: ˅ by 17% R20EFV800: ^ by 16%	Hyperbilirubinemia: (3/33, 2/32, 0/33) ALT increase: (1/33, 2/32, 1/33) AST increase: (3/33, 2/32, 2/33) 6 patients in TOTAL (2/arm) had grade ≥3 transaminase elevation	Transaminase elevation within the 1st 8 weeks	1 death in each group (3 total) – one from disseminated TB and the other two due to severe sepsis of digestive origin 3 were withdrawn by study investigators	Atwine et al.[27]
Efavirenz (600 mg q.d.) + Isoniazid (400 mg q.d.) + Pyrazinamide (2 g q.d.) + RIF (600 mg)	Open-label protocol. Patients received efavirenz and RIF as part of standard TB therapy that included isoniazid and pyrazinamide. (49 AFB or TB positive patients)	*AUC* NR *Cₘₐₓ* NR	4/13 (31%) toxic hepatitis (this group initiated simultaneous therapies) 2/36 toxic hepatitis (this group started ARV later)	NR	41 patients in total were hospitalized 4 patients died	Pedral-Sampaio et al.[46]
Efavirenz (600 mg q.d.) + Isoniazid (5 mg/kg – max, 300 mg) + Pyrazinamide (25 mg/kg – 2 g daily) + Ethambutol (15 mg/ kg – max 2 g) + RIF (10 mg/kg - max 600 mg q.d.)	Patients were co-administered efavirenz and a standard TB regimen of RIF, isoniazid, pyrazinamide, and ethambutol 30 TB/HIV co-infected patients	*AUC* Efavirenz in combination with RIF: 31.4 μg h/ml *Cₘₐₓ* Efavirenz in combination with RIF: 1.6 μg/ml	2 patients developed grade 2 AST and ALT abnormalities	NR	1 death was attributed to extensive pulmonary TB in a patient who had already received 2 months of TB treatment before initiation of HAART	Kwara et al.[38]

(continues)

TABLE 2 (Continued)

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/Discontinuation/Death	References
Group 1: Isoniazid (5 mg/kg)+pyrazinamide (25 mg/kg)+ethambutol (15 mg/kg) + RIF (10 mg/kg) Group 2: Group 1 regimen+NAC (600 mg b.i.d.) + RIF (10 mg/kg)	Open label clinical trial (60 TB patients)	*AUC* NR C_{max} NR	*Group 1:* Hepatotoxicity in 12/32 (37.5%) patients. Of 12 patients that experienced hepatotoxicity 6 had AST/ALT elevations 5 ×ULN Elevated total bilirubin in 3/32 (>1.5 mg/dl) *Group 2:* No hepatotoxicity	*Group 1:* Onset: after 1 and 2 weeks of treatment (mean of 4.67±4.58 days) Recovery: 8.17±3.76 days after treatment termination	NR	Baniasadi et al.[24]
Idelalisib (150 mg b.i.d.) + RIF (600 mg)	Phase I, open-label, parallel-group, multiple-dose (24 HV)	AUC_{inf} ˅by 75% C_{max} ˅by 58%	Cohort 2: Grade 3 increased transaminase (n = 1) Grade 3 – ALT and/or AST increase (n = 2)	Cohort 2: Onset: The grade 3 ALT elevation -between 2 and 3 weeks after initiation of Idelalisib Recovery: Transaminase elevation was resolved within 1–4 weeks from grade 3 ALT elevation	1 subject discontinued cohort 2 due to AEs	Jin et al.[37]
IDV/RTV (600/100 mg b.i.d.) + RIF (450 for body weight <50 kg and 600 mg for body weight ≥50 kg)	Prospective, open-label study (18 HIV-1/TB co-infected patients)	*AUC* Indinavir AUC_{0-12}: 8.11 mg h/L RTV: 2.43 mg h/L C_{max} Indinavir: 2.75 mg/L RTV: 0.63 mg/L	44% (8/18) developed asymptomatic ALT ≥100U/L with 2/18 developing grade 3 and 4 ALT elevations	Onset: ALT tended to peak at days 3 & 5. 2 patients with hepatitis C elevation rises were seen later at week 20 – discontinued Recovery: Declined spontaneously by week 1	2 hepatitis C patients discontinued the use of IDV/RTV after the elevation of ALT (grade 3/4). Recovery: ALT declined spontaneously by week 1	Avihingsanon et al.[26]
Isoniazid (300 mg q.d. or 225 mg q.d. or 150mg q.d.) Or Pyrazinamide (1600 mg q.d. or 1200 mg q.d. or 500 mg t.i.d.) + RIF (600 mg q.d. or 450 mg q.d. or 300 mg q.d.)	Retrospective cohort study (20 malaria patients)	*AUC* NR C_{max} NR	*Isoniazid±RIF* 300 mg q.d.+600 mg q.d. = 1/6 elevated ALT, 2/6 elevated ALP 225 mg q.d.+450 mg q.d. = 1/2 elevated ALP 150 mg q.d.+300 mg q.d. = 1/2 elevated ALT, 2/2 elevated ALP *Pyrazinamide±RIF:* 1600 mg q.d.+600 mg q.d. = 1/6 elevated ALT, 2/6 elevated ALP 1200 mg q.d.+450 mg q.d. = 1/2 elevated ALP 500 mg q.d.+450 mg q.d. = 1/2 elevated ALT, 2/2 elevated ALP	NR	NR	Noor et al.[43]

TABLE 2 (Continued)

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/ Discontinuation/Death	References
Isoniazid (400 mg/day; 8.2 ± 2.0 mg/kg/day) RIF (450 mg/day; 9.2 ± 2.2 mg/kg/day)	Prospective study (77 TB patients)	*AUC* NR C_{max} NR	Elevated aminotransferase = 14/77 (18.2%)	Onset: within the 1st month	6 patients discontinued anti-TB drugs for 2–4 weeks after experiencing elevated AST (2–7 × ULN), then restarted. 1 of these subsequently permanently discontinued 3 discontinued isoniazid to avoid greater elevation of aminotransferases	Ohno et al.[44]
Lorlatinib (100 mg) + RIF (600 mg)	Phase I, 2-period, fixed-seq, crossover study in healthy subjects (12 HV)	*AUC* ˅by 85% C_{max} ˅by 76%	During 1st 7 days of period 2, RIF alone – LFT levels were normal except for 1 subject AST/ALT increases (n = 12) Grade 4 elevations AST/ALT (n = 6) Grade 3 elevations (n = 4) Grade 2 elevations (n = 1)	Onset: Period 2 day 8 – 1st day of RIF + lorlatinib. Occurred within 3 days of co-admin. of lorlatinib and RIF Recovery: Dosing halted on day 10 of period 2. Transaminase levels decreased to within normal range after median of 15 days for all subjects. For the subjects with grade 2 elevations – recovered within 7 days. For the subjects with grade 3 and 4 – median recovery time was 18 days	All subjects discontinued treatment due to elevated ALT and AST 5 subjects hospitalized due to elevated ALT and AST 1 withdrew consent and discontinued during period 2 because of AE (nausea and vomiting)	Chen et al.[6]
LPV (230 mg/m² + RTV (57.5 mg/m² and additional 172.5 mg/m² for TB patients) + RIF (dose not specified)	2 parallel group study (total = 30) 15 TB-HIV co-infected children 15 HIV-infected children	*AUC* ˅by 31% C_{max} ˅by 26%	2 children receiving RIF and 1 child not receiving RIF had slightly higher than normal ALT concentrations (35 and 40 and 42 U/L, respectively). All of the elevations were <1.5 times ULN of the ALT normal range	NR	Not reported	Ren et al.[47]
LPV/RTV (400/100 mg, 600/100 mg, 800/200 mg) + RIF (600 mg)	Open-label, sequential, four-period, multiple-dose trial. Patients received LPV/RTV + RIF starting on day 8 and continued at different doses at day 15 and day 22 (21 HIV infected volunteers)	LPV: *AUC* day 8: ˅ by 68% day 15: ˅ by 37% day 22: ˄ by 2% C_{max} day 8: ˅ by 54% day 15: ˅ by 28% day 22: ˄ by 13%	2 subjects withdrew due to grade 3/4 asymptomatic transaminitis 6 subjects had grade 1/ 2 transaminitis 2 subjects developed grade 1 hyperbilirubinemia	All AEs resolved; onset/recovery times not reported	2 discontinuations; due to grade 3/4 transaminitis	Decloedt et al.[19]

(continues)

TABLE 2 (Continued)

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/ Discontinuation/Death	References
LPV/RTV (400/100/ b.i.d., 800/200 mg b.i.d., 400/400 mg b.i.d.) + RIF (600 mg)	Random., phase I, open-label, 2-arm, within-subject controlled study (32 HV)	*AUC* *Arm 1* (LPV/RTV, 533/133 mg b.i.d.; RIF, 600 mg q.d. on day 16 with increasing doses on subsequent days) ˅ by 16%. *Arm 2* (LPV/RTV 400/200 mg b.i.d.; RIF, 600 mg q.d. on day 16 with increasing doses on subsequent days) ˅ by 2% *LPV:* C$_{max}$ *Arm 1* ^ by 2% *Arm 2* ˅ by 7%	One subject prematurely discontinued from the study because of: grade 2 total bilirubin level (>31 μmol/L) – mostly consisted of indirect bilirubin. 9 patients had AST and/or ALT elevations ranging from grade 2 to grade 3	Onset: The onset of all grade 2 or 3 elevations in ALT and AST levels were after the initiation of RIF treatment Maximum changes in AST and ALT occurred between study days 11 and 24. LPV/RTV and RIF co-administration started on study day 11 Recovery: All grade 2 and 3 ALT and AST elevations declined below grade 2, with only 2 subjects remaining about ULN at final study evaluation	12 total study discontinuations with 1 discontinuation due to elevations in bilirubin	la Porte et al.[39]
LPV/RTV (400/100 mg/400/400mg) + RIF (dose not specified)	Retrospective review of HIV-infected patients who receiving 2nd-line ART with LPV/RTV-containing regimen who required concomitant TB treatment, (n = 29)	*AUC* NR C$_{max}$ NR	LPV/RTV (400 mg/100 mg) b.i.d. + RIF q.d. = 5/29 (17%) subjects had grade 1–3 ALT elevations, there were no grade 4 elevations/deaths. LPV/RTV (400 mg/400 mg) b.i.d. + RIF q.d. = experienced a trend toward a higher overall rate of symptomatic transaminitis (27% vs. 7%)	NR	LPV/RTV (400/400 mg) = 7/15 subjects; 3 subjects died or lost to follow-up. LPV/RTV (400/100 mg) = 1/14 subjects; 1 subject died or last to follow-up	Murphy et al.[42]
LPV/RTV (800/200 mg or 600/150mg) + RIF (600 mg)	Open-label, sequential, 2-period, phase IV multiple dose trial in HVs. (40 subjects enrolled, only 11 subjects were dosed with LPV/RTV and RIF)	*AUC* NR C$_{max}$ NR	*Day 6–11 (LPV/RTV±RIF)* *ALT* grade 2 (n = 2), grade 3 (n = 1), grade 4 (n = 8) *AST* grade 2 (n = 2), grade 3 (n = 1), grade 4 (n = 8) *GGT* grade 1 (n = 4), grade 2 (n = 2), grade 3 (n = 1) *Bilirubin* grade 2 (n = 3), grade 3 (n = 5)	Onset: ALT/AST peaked on days 9–10. GGT peaked on days 10–12 Recovery: All clinical parameters returned to normal within 6 weeks after study termination	29 volunteers were withdrawn from the study after receiving only 1 dose of RIF (n = 10) or no study medication at all (n = 19) Study medication stopped on day 7 for 8 subjects/on day 8 for 3 subjects	Nijland et al.[8]
LPV/RTV (800/200 mg or 400/400mg) + RIF (dose not specified)	Open-label, non-randomized PK study. (11 HIV patients)	*LPV:* AUC$_{0-12}$ LPV: 155.8 μg·h/ml C$_{max}$ LPV: 16.8 μg/ml	2 elevated liver transaminases: grade 2 (n = 1), grade 3 (n = 1)	NR	2 discontinuations due to non-compliance	Boulanger et al.[28]

TABLE 2 (Continued)

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/ Discontinuation/Death	References
Nevirapine (200 mg b.i.d.) + RIF (600 mg for body weight ≥55 kg and 450 mg for body weight <55 kg)	Prospective study (16 HIV patients)	AUC Nevirapine AUC$_{0-12}$: ⌄by 36% C$_{max}$ ⌄by 39%	At the first admission: 3/16 had moderately elevated ALT (<4×ULN) At the second administration: 4/16 had moderately elevated ALT (<4×ULN)	NR	0 discontinuations	Cohen et al.[30]
Pyrazinamide (≤19.9 mg/kg, 20.0–29.9 mg/kg, ≥30.0 mg/kg) + Isoniazid (≤3.99 mg/kg, 4.0–4.99 mg/kg, ≥5.0 mg/kg) + RIF (≤7.99 mg/kg, 8.0–9.99 mg/kg, ≥10.0 mg/kg)	Partly prospective and partly retrospective cohort study	AUC NR C$_{max}$ NR	Severe hepatotoxicity 2RZ = 14/166 2HRZ = 14/410 Mild hepatotoxicity 2RZ = 10/166 2HRZ = 33/410	NR	14 patients in the RZ group and 16 patients in the 2HRZ+ group who had severe hepatotoxicity discontinued	van Hest et al.[35]
Pyrazinamide (1000 mg for subjects <50 kg or 1500 mg for subjects ≥50 kg) + RIF (450 mg for subjects <50 kg or 600 mg for subjects ≥50 kg)	Randomized two arm study (40 healthy subjects)	AUC NR C$_{max}$ NR	ALT >1.5×ULN = 19/40 (47.5%) >3×ULN = 16/40 (40%) >5×ULN = 14/40 (35%)	Onset: 0–2 months Recovery: 19–60 days	0 discontinuations	Leung et al.[41]
Pyrazinamide (20 mg/kg) + RIF (600 mg or 450 mg if body weight <50 kg)	Multinational 2 arm study (792 TB-HIV patients)	AUC NR C$_{max}$ NR	Grade 3 bilirubin (>2.5 mg/dl) = 13/718 (1.8%) grade 3 AST (>250 U/L) 15/721 (2.1%). Of these, 4 patients reached a max AST of >500 U/L	Onset: Bilirubin increased slightly at month 1 and 2. There was a mean 8 U/L increase in AST levels from baseline to month 2	0 discontinuations	Gordin et al.[34]
Pyrazinamide (20 mg/kg) + RIF (600 mg)	Multicenter, prospective, open-label trial (307 TB patients)	AUC NR C$_{max}$ NR	ALT (only in 207 patients who had available LFTs) grade 1 (1.25–2.5×ULN) = 29/207 (14%) grade 2 (2.6–5.0×ULN) = 9/207 (4.3%) grade 3 (5.1–10.0×ULN) = 7/207 (3.4%) grade 4 (>10×ULN) = 9/207 (4.3%)	NR	12/207 (5.8%) discontinuations due to hepatotoxicity. 20/274 (9.7%) withdrew 0 hospitalizations 13/274 (6.2%) lost to follow-up	Jasmer et al.[36]
Pyrazinamide (30 mg/kg) + Isoniazid (5 mg/kg) + RIF (10 mg/kg)	Case control study	AUC NR C$_{max}$ NR	Severe hepatotoxicity 6HR = 5/99 6HRZ =11/101	NR	4 deaths due to causes other than TB in the 6HR2Z group	Garcia-Rodrigues et al.[33]

TABLE 2 (Continued)

Drugs	Study design; Subjects (n = #)	Exposure change	Elevation and severity	Onset/Recovery	Hospitalization/ Discontinuation/Death	References
Pyrazinamide (50 mg/kg with max of 4000 mg) + RIF (600 mg or 300 mg if body weight <50 kg)	Retrospective review of public health records (423 TB patients)	AUC NR C_{max} NR	*ALT* Up to 2×ULN (0–79 U/L) = 358/415 (86.3%) 2–3×ULN (80–119 U/L) = 19/415 (4.6%) 3–5×ULN (120–199 U/L) = 10/415 (2.4%) 5–10×ULN (200–400 U/L) = 10/415 (2.4%) >10×ULN (>400 U/L) = 18/415 (4.3%)	Onset: Time from first dose to peak ALT median days (range): 42 (21–105) Recovery: For the two hospitalized patients, the recovery time was 6 months and 35 days after stopping treatment	71 discontinuations, of these 2 hospitalizations	Priest et al.[20]
SAQ/RTV Arm 1: 1000/100 mg b.i.d. for 14 days, then SAQ/RTV 1000/100 mg b.i.d. + RIF 600 mg for an additional 14 days Arm 2: RIF 600 mg for 14 days followed by SAQ/RTV 1000/100 mg b.i.d. + RIF 600 mg for an additional 14 days	Single-center, open-label, randomizer, 1-sequence, 2-arm crossover study (28 HV; of these 17 were given SAQ/RTV + RIF)	AUC NR C_{max} NR	*Arm 1 (n = 8):* 2/8 subjects Moderate elevation in ALT of 5× and 8 × ULN (after 4–5 doses of RIF) – at time of study discontinuation 3/8 – mild ALT elevations (grade 1 or less) of 1.05–1.8×ULN *Arm 2 (n = 9):* All 9 – grade 4 ALT elevations between 11× and 70×ULN	Onset: typically, within 1–3 days Recovery: Clinical symptoms abated, and transaminases normalized following drug discontinuation	All 17 subjects who received SAQ/RTV + RIF discontinued. The study was prematurely discontinued to unexpected hepatic events. Hospitalization: 1 – subjects from arm 2 who had grade 1 ALT elevation while taking RIF alone during phase 1 – due to 70×ULN increase in ALT after 3 doses of SAQ/RTV	Schmitt et al.[18]
Sirolimus (20 mg) + RIF (600 mg)	Open-label, Non-random (16 HV)	AUC ∨by 71% C_{max} ∨by 82%	Liver enzyme (n = 1) GGT (n = 1)	Combination treatment with RIF for 9 days caused expected RIF-related AEs including the LFT elevations	2 discontinuations (1 with elevated liver enzymes and 1 with eosinophilia)	Tortorici et al.[48]
Tenofovir (300 mg q.d.) + RIF (600 mg)	Multiple-dose, open-label, single-group, 2-period study (24 HV)	AUC ∨by 12% C_{max} ∨by 16%	Elevated liver enzyme levels – grade 3 AE (n = 1); 5 days after cessation of combination of tenofovir dosing on day 15	Onset: The onset of symptoms in this subject was in period 2 at follow-up visit, 5 days after combination dosing was stopped on day 15. Recovery: The one subject recovered after 9 days from the follow-up visit	1 discontinuation due to grade 3 elevation in hepatic enzyme levels	Droste et al.[31]

Abbreviations: AEs, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ART, antiretroviral therapy; ARV, antiretroviral; AST, aspartate aminotransferase; ATT, antitubercular treatment; ATV, atazanavir; AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; DDI, drug–drug interaction; DRV, darunavir; EFV, efavirenz; GGT, gamma-glutamyl transferase; HAART, highly active antiretroviral therapy; HR, isoniazid/rifampin; HR2Z, isoniazid/rifampin/HV, healthy volunteer; LFT, liver function test; LPV, lopinavir; NR, not reported; PK, pharmacokinetic; RIF, rifampin; RTV, ritonavir; RZ, rifampin/pyrazinamide; SAQ, saquinavir; TB, tuberculosis; ULN, upper limit of normal.

greater over the first few days of rifampin-ritonavir co-administration when pretreated with rifampin as compared to ritonavir pretreatment. Ritonavir is a net strong time-dependent inhibitor (TDI) of CYP3A4 thus potentially blunting the formation of hepatotoxic metabolites observed when ritonavir-boosted protease inhibitors are initiated in an induced state (rifampin pretreatment). Previously stated, for both the lorlatinib and ritonavir DDI studies, considerable LFT elevations were observed within the first 24–72 h following co-administration.[6] Thus, this sequence effect may only be observed with drugs, like ritonavir, where net mixed induction/TDI results in considerable CYP3A inhibition.

Other potential mechanisms

It has been hypothesized that immune cells have a critical role in drug hepatotoxicity.[8,19,20] The roles of lymphocytes, neutrophils, and macrophages have been noted in some cases of drug-induced liver injury (DILI), and it has been suggested that biomarkers should be used to monitor their function to detect DILI during drug development in in vivo models. The extent of injury is determined by the direct effect of the drug on the hepatocytes which is believed to initiate the immune response that results in drug hepatotoxicity.[21] Patients with TB-HIV have been noted to tolerate concomitant administration of rifampin with protease inhibitors, whereas healthy subjects experience hepatotoxicity. Furthermore, in some cases, the ritonavir-boosted protease inhibitor doses were higher when co-administered with rifampin in patients with TB-HIV, as compared with healthy volunteer studies, to compensate for lower exposures observed in the presence of rifampin.[19,22] A possible explanation for patients with HIV having lower risk of hepatotoxicity is due to their attenuated immune response which results in decreased idiosyncratic drug-induced hepatocellular reactions. Although healthy subjects' intact immunity contributes to higher rates of liver injury.[8,19,20]

It has been acknowledged in the rifampin drug label that the co-administration of rifampin with isoniazid has the potential to increase hepatotoxicity.[1] One possible mechanism is that the co-administration of isoniazid with rifampin has been associated with considerably low levels of glutathione (GSH) that results in oxidative stress and induces hepatic injury. N-acetylcysteine (NAC), a GSH precursor, is used as a hepatoprotective agent to replenish the decreasing GSH levels, scavenge isoniazid electrophiles, and act as an antioxidant. In a study by Attri et al., Wistar rats were co-administered isoniazid and rifampin (both 50 mg/kg

q.d.); the experimental group was given NAC (100 mg/kg q.d.) whereas the control group was not.[23] Both groups were found to have no transaminase elevations (defined as $>3 \times$ ULN), whereas the histopathological findings varied between the two groups. The control group was found to have mild to moderate hepatic lesions of portal triaditis, lobular inflammation, and patch necrosis. Although, in the experimental group, NAC had a hepatoprotective effect on the liver which prevented histopathological injuries except in one rat which showed portal triaditis.[23] These results present the possibility for the involvement of GSH conjugation in the elimination of a hepatotoxic isoniazid metabolite, which is formed at meaningful levels with concomitant rifampin induction.

A similar study was conducted by Baniasadi et al. on newly diagnosed patients with pulmonary TB, that tested whether the addition of NAC to anti-TB regimen (rifampin + isoniazid + pyrazinamide + ethambutol) would decrease the risk of drug-induced hepatotoxicity.[24] Hepatotoxicity occurred in 37.5% of patients who were not administered NAC (group 1) whereas the administration of NAC (group 2) resulted in no hepatotoxicity (Table 2).[24] These results again support that perhaps GSH conjugation is involved in the elimination of hepatotoxic metabolites formed with the combination of rifampin, isoniazid, pyrazinamide, and ethambutol.

CONCLUSIONS

Hepatotoxicity seen with ritonavir or isoniazid when co-administered with rifampin is hypothesized as potentially resulting from increased accumulation of hepatotoxic metabolites as a consequence of rifampin induction.[15,25] Therefore, it has been argued by Askagaard et al. that rifampin itself is not likely responsible for the hepatoxicity noted in clinical studies, and that it is the induction-mediated accumulation of a drug's hepatotoxic metabolite when co-administered with rifampin.[25] Overall, as seen with the 15 drugs that have demonstrated LFT increases when combined with rifampin, there is a possibility that metabolic activation of certain drugs could cause downstream liver damage. Rifampin's role in metabolic activation in drug-induced hepatotoxicity needs to be taken into consideration when conducting rifampin DDI studies with investigational agents, particularly those for which the metabolic profiles are not fully elucidated.

CONFLICT OF INTEREST

J.C., Y.K.P., and M.V. are employees of Pfizer Inc. and may own Pfizer stock. S.I. was an unpaid intern to Pfizer; the internship program with University of

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