Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers


1Medical Service, Department of Veterans Affairs Medical Center; 2Department of Medicine, University of Texas Health Science Center, San Antonio, TX, USA; 3College of Pharmacy, University of Florida, Gainesville, FL, USA; 4Bioanalytical Systems, Inc., McMinville, OR, USA; 5Department of Pathology, University of Texas Health Science Center, San Antonio, TX, USA; 6Department of Epidemiology and Biostatistics, University of Texas Health Science Center, San Antonio, TX, USA; 7Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA, USA

*Corresponding author. Medical Service/Infectious Diseases (111), Department of Veterans Affairs Medical Center, San Antonio, TX 78229-4404, USA. Tel: +1-210-617-5300, ext. 16060; Fax: +1-210-617-5297; E-mail: weiner@uthscsa.edu

Received 4 September 2013; returned 2 October 2013; revised 28 October 2013; accepted 14 November 2013

Objectives: Latent tuberculosis infection and tuberculosis disease are prevalent worldwide. However, antimycobacterial rifamycins have drug interactions with many antiretroviral drugs. We evaluated the effect of rifapentine on the pharmacokinetic properties of raltegravir.

Methods: In this open-label, fixed-sequence, three-period study, 21 healthy volunteers were given: raltegravir alone (400 mg every 12 h for 4 days) on days 1–4 of Period 1; rifapentine (900 mg once weekly for 3 weeks) on days 1, 8 and 15 of Period 2 and raltegravir (400 mg every 12 h for 4 days) on days 12–15 of Period 2; and rifapentine (600 mg once daily for 10 scheduled doses) on days 1, 4–8 and 11–14 of Period 3 and raltegravir (400 mg every 12 h for 4 days) on days 11–14 of Period 3. Plasma raltegravir concentrations were measured. ClinicalTrials.gov database: NCT00809718.

Results: In 16 subjects who completed the study, coadministration of raltegravir with rifapentine (900 mg once weekly; Period 2) compared with raltegravir alone resulted in the geometric mean of the raltegravir AUC from 0 to 12 h (AUC0–12) being increased by 71%; the peak concentration increased by 89% and the trough concentration decreased by 12%. Coadministration of raltegravir with rifapentine in Period 3 did not change the geometric mean of the raltegravir AUC0–12 or the peak concentration, but it decreased the trough concentration by 41%. Raltegravir coadministered with rifapentine was generally well tolerated.

Conclusions: The increased raltegravir exposure observed with once-weekly rifapentine was safe and tolerable. Once-weekly rifapentine can be used with raltegravir to treat latent tuberculosis infection in patients who are infected with HIV.

Keywords: rifamycin, latent tuberculosis infection, antiretroviral therapy, integrase strand transfer inhibitor, HIV

Introduction

The WHO estimates that one-third of the world’s population has latent tuberculosis infection (LTBI).1–3 Rifapentine, a potent antimycobacterial rifamycin antibiotic, may be 2–4 times as active as rifampicin against Mycobacterium tuberculosis in vitro and in animal models.4–7 The US CDC has recommended a short-course alternative treatment for LTBI in adults who are at high risk of developing active tuberculosis.5–8 In the PREVENT TB Phase 3, randomized treatment trial of 8053 patients who had LTBI, a 12-dose, once-weekly regimen of rifapentine and isoniazid had similar efficacy and tolerability compared with daily isoniazid for 9 months.6 Clinical dose-ranging studies of daily rifapentine in intensive-phase therapy have been performed in patients with tuberculosis because in vivo models of active tuberculosis have shown that the bactericidal and sterilizing activity of rifapentine is concentration dependent, increasing at higher mg/kg doses.4,5,9

Raltegravir10 is an integrase inhibitor and potent antiretroviral agent, and clinical trials have established the clinical efficacy, safety and tolerability of raltegravir. In a Phase 3, double-blind, non-inferiority study, regimens containing raltegravir or efavirenz were similar in reducing the viral load of HIV-1 to undetectable
levels (<50 copies/mL) at 240 weeks.\textsuperscript{11} The immunological response was greater in the regimen containing raltegravir (CD4 cell count 295 cells/mm\textsuperscript{3}) than efavirenz (CD4 cell count 236 cells/mm\textsuperscript{3}).\textsuperscript{11} Raltegravir, combined with emtricitabine and tenofovir, is currently recommended as one of four preferred regimens for patients who have not had previous treatment for HIV. Furthermore, raltegravir may be substituted for efavirenz in pregnant women, and there are fewer drug interactions with raltegravir than with the other preferred regimens. Therefore, it is important to understand the interactions of raltegravir with each of the rifamycins.\textsuperscript{12}

Rifamycins may decrease plasma concentrations of antiretroviral integrase inhibitors, protease inhibitors and non-nucleoside reverse transcriptase inhibitors.\textsuperscript{13} The primary metabolic pathway for the inactivation of raltegravir is through the cytosol enzyme uridine diphosphate glucuronosyltransferase 1A1, and the activity of glucuronosyltransferase is up-regulated by rifampicin.\textsuperscript{14–17} Compared with raltegravir alone, the coadministration of rifampicin (600 mg once daily) with raltegravir (a 400 mg single oral dose) caused a decrease in the geometric mean raltegravir trough concentration 12 h after administration (C\textsubscript{min}) by 61%, the AUC from 0 to 12 h (AUC\textsubscript{0–12}) by 40% and the peak concentration (C\textsubscript{max}) by 38%.\textsuperscript{15} Compared with raltegravir alone, coadministration of rifabutin (300 mg once daily) with raltegravir (a 400 mg single oral dose) caused a decrease in the geometric mean raltegravir C\textsubscript{min} by 20%, but the AUC\textsubscript{0–12} increased by 19% and the C\textsubscript{max} increased by 39%.\textsuperscript{16} The effect of a third rifamycin, rifapentine, on raltegravir or other antiretroviral agents has not been evaluated.

Pharmacokinetic drug interactions between rifapentine and raltegravir may determine the potential utility of once-weekly rifapentine in treating LTBI and daily rifapentine for active tuberculosis in patients who are infected with HIV. The purpose of the present study was to evaluate the effect of rifapentine, at doses that are used to treat LTBI and tuberculosis, on the pharmacokinetic properties of raltegravir.

**Methods**

**Subjects**

This was a single-centre, open-label, fixed-sequence, three-period pharmacokinetic study (Figure 1) (ClinicalTrials.gov database: NCT00809718). There were 21 healthy adults [age >18 years; median age 30 years (IQR 25–39 years)] (12 men and 9 women) who were recruited for the study from the University of Texas Health Science Center, the South Texas Veterans Administration Medical Center and ClinicalTrials.gov. Inclusion criteria were normal haematological, renal and liver function tests and a Karnofsky score ≥90. Subjects were excluded because of HIV infection, illicit drug use, prior gastrointestinal surgery, known intolerance to rifamycin drugs or raltegravir, prior use of these drugs in the previous 30 days, regular use of other drugs or current pregnancy or breastfeeding. Women of childbearing potential agreed to practise birth control by a barrier method or abstinence during the study.

If the subject needed to take non-study drugs such as non-narcotic pain relievers, investigators determined whether the drug was anticipated to alter concentrations of raltegravir or rifapentine. Non-study drugs taken during study periods included ibuprofen (200 mg once after a minor toe injury in one subject during Period 2); acetaminophen (one or two doses for upper respiratory symptoms in one subject during Period 2 and one subject during Period 3); aciclovir (400 mg, three times daily for 5 days for a localized herpetic rash in one subject 1 day after completion of Period 2); topical ophthalmic drops (to one eye after traumatic corneal abrasion in one subject during Period 3); and ondansetron (4 mg tablet, three tablets, for nausea in one subject during a washout interval after Period 2 of the study).

The Institutional Review Boards of the US CDC and University of Texas Health Science Center at San Antonio approved the study. Written informed consent was obtained from all participants. Adverse events were classified for severity using a graded toxicity scale adapted from the National Cancer Institute (Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life-threatening).\textsuperscript{18}

**Drug dosage and pharmacokinetic sampling**

Subjects were given: raltegravir alone (400 mg every 12 h for 4 days) on days 1–4 of Period 1; rifapentine (900 mg once weekly for 3 weeks) on days 1, 8 and 15 of Period 2 and raltegravir (400 mg every 12 h for 4 days) on days 12–15 of Period 2; and rifapentine (600 mg once daily for 10 scheduled doses) on days 1, 4–8 and 11–14 of Period 3 and raltegravir (400 mg every 12 h for 4 days) on days 11–14 of Period 3. The timing of pharmacokinetic sampling for each period is shown in Figure 1. The dosing periods were separated by 10 day washout intervals with no study drugs. Drug administration diaries were kept by the subjects. On the morning of pharmacokinetic sampling in each period, the subjects were not allowed any food (from 8 h before to 2 h after the administration of the study drugs), and raltegravir (with or without rifapentine) was administered with direct observation. All other doses of raltegravir and rifapentine were taken without regard to food. Blood samples for the pharmacokinetic measurements of raltegravir in each study period and for rifapentine in Periods 2 and 3 were collected just before the morning study drugs were given and at 1, 2, 3, 4, 5, 6, 8 and 12 h after the study drugs had been given. Additional blood samples in Periods 2 and 3 to measure raltegravir concentration were obtained 12 h after the eighth dose of raltegravir (24 h after the seventh raltegravir dose).

Raltegravir concentrations were below the level of quantification in one subject at baseline pharmacokinetic sampling (before the administration of the study drugs) in Periods 2 and 3. These two baseline samples were not included in the pharmacokinetic analyses.

**Drug determinations**

The measurement of raltegravir concentration in human plasma was performed at a commercial laboratory (Bioanalytical Systems, Inc., McMinnville, OR, USA) using an automated sample preparation process followed by reverse-phase HPLC and tandem mass spectrometry modified from a procedure previously described.\textsuperscript{19} Internal standard solution ([\textsuperscript{13}C\textsubscript{6}-raltegravir, 1000 ng/mL, 20 μL] was added to plasma (200 μL) and acidified with ammonium acetate (200 mM, 150 μL, pH 4). The samples were transferred to 96-well plates and extracted into hexane and methylene chloride (50:50 solution, 1.2 mL). The organic layer was transferred to a clean plate, evaporated to dryness and reconstituted in methanol and 0.1 mM EDTA with 0.1% formic acid (55:45 solution, 350 μL). Samples (5 μL) were injected onto an analytic column (3.0×50 mm, 3 μm, Ace C18 column, Part number ACE-111-0503; Mac-Mod Analytical, Chadds Ford, PA, USA) with titanium frits at ambient temperature. Mobile phase A was 0.1% formic acid in 0.1 mM EDTA and mobile phase B was methanol. The flow rate was 0.5 mL/min with an isocratic run at 57.5% mobile phase B. Detection by tandem mass spectrometry incorporated an atmospheric pressure chemical ionization interface in positive ion mode. The range of the validated assay for raltegravir was 0.002–1.000 μg/mL. The accuracy of undiluted control samples between days was 101.5%–102.9% and the coefficient of variation was 2.1%–3.6%. Plasma concentrations of rifapentine were determined with a validated HPLC assay.\textsuperscript{20}

**Statistical and pharmacokinetic analysis**

Pharmacokinetic parameters were calculated with non-compartmental analyses (WinNonlin, Version 5.3; Pharsight Corporation, Mountain View,
CA, USA). Statistical analysis of pharmacokinetic parameters transformed to natural logarithm was performed using mixed model analysis of variance with repeated measures, a general variance–covariance matrix and adjustments for period and subject (SAS, version 9.2; SAS Institute Inc., Cary, NC, USA), and the data were transformed back to the original linear scale. Pharmacokinetic values were reported as the geometric mean adjusted for period and subject, the ratios of geometric means between different study periods, 90% CIs and coefficients of variation (%).

Drug concentrations were examined for outlier status by the Extreme Studentized Deviate test. All raltegravir concentrations were used in the primary analyses with one exception: an outlier value of $C_{12}$ in one sample from Period 1 was 52-fold greater than the median, 3.7 SD away from the mean and identified as an outlier by statistical testing (Extreme Studentized Deviate test; $P \leq 0.05$). When the outlier was included in the analysis of variance, a similar result was obtained.

Results

Effects of rifapentine on raltegravir

Of the 21 subjects who enrolled and started the study, 16 subjects (76%) completed the 10 week study; five subjects did not complete the study during Period 2 or soon thereafter (two subjects had mild or moderate Grade 2 constitutional or gastrointestinal symptoms, one subject relocated to another city, one withdrew due to the duration of the study and one subject was withdrawn due to a rash to a non-study drug, ondansetron, during the washout after Period 2). Subjects self-reported race/ethnicity as non-Hispanic white in 11 subjects, Hispanic white in 7 subjects, African-American in 2 subjects and Asian in 1 subject. The median body weight of all the subjects was 75 kg (IQR 64–80 kg). The median dosage of raltegravir (all periods) was 5.3 mg/kg (IQR 5.0–6.2 mg/kg) every 12 h. The median dosage of rifapentine in Period 2 was 12.0 mg/kg (IQR 11.3–14.0 mg/kg) once weekly and in Period 3 was 8.0 mg/kg (IQR 7.5–9.3 mg/kg) once daily on 5 of 7 days per week.

In all three study periods, the time of peak concentration of raltegravir was 2 h (Figure 2). Coadministration of raltegravir with rifapentine (900 mg once weekly; Period 2) compared with raltegravir alone resulted in the geometric mean of the raltegravir AUC$_{0–12}$ being increased by 71%; $C_{\text{max}}$ increased by 89% and $C_{12}$ decreased by 12% (Table 1). Coadministration of raltegravir with rifapentine (600 mg once daily for 5 of 7 days per week; Period 3) did not change the geometric mean of the raltegravir AUC$_{0–12}$ or $C_{\text{max}}$, but the geometric mean of raltegravir $C_{12}$ decreased by 41% (Table 1). The raltegravir dose (not fasting and not observed) $\approx 12$ prior to the baseline plasma raltegravir concentration was taken without concomitant rifapentine. The baseline, pre-dose raltegravir concentrations [geometric mean (90% CI)] in sequential periods were 0.221 (0.123–0.396), 0.212 (0.113–0.399) and 0.233 (0.141–0.385) µg/mL. These baseline, pre-dose concentrations were significantly different from the first $C_{12}$ raltegravir concentrations (all comparisons $P<0.005$) but not significantly different from the second $C_{12}$ raltegravir concentrations (Period 1, $P=1.00$; Period 2, $P=0.92$; Period 3, $P=0.14$) (Table 1).

The coefficients of variation showed that there was marked variation of the raltegravir pharmacokinetic parameters AUC$_{0–12}$, $C_{\text{max}}$ and $C_{12}$ in each study period (Table 1). In Periods 2 and 3, the second raltegravir $C_{12}$ (obtained non-fasting and without administration of rifapentine) was $\geq 4$-fold greater than the first raltegravir $C_{12}$ (fasting and with coadministration of rifapentine) (Table 1).

Rifapentine exposure (geometric mean AUC$_{0–24}$) in Period 2 was 323 µg·h/mL (90% CI 277–377 µg·h/mL) and in Period 3 was 346 µg·h/mL (90% CI 292–411 µg·h/mL).
Tolerability of drugs

The administration of raltegravir with and without rifapentine was well tolerated, and no Grade 3 or 4 adverse events occurred. During the 10-week study, 16 of the 21 subjects (76%) who took the study drugs had symptoms or signs of mild or moderate adverse events (Grade 1 or 2). The Grade 1 or 2 adverse events that occurred in 1 subject were constitutional, respiratory, neurological, gastrointestinal, endocrine and dermatological (Table 2).

In the five subjects who did not complete the study, three subjects had adverse events: two subjects had mild or moderate constitutional or gastrointestinal symptoms and one subject had a rash. The latter subject, who had the highest raltegravir AUC0–1 and Cmax of all subjects in Period 2, discontinued the study 9 days after taking raltegravir and rifapentine. In Period 2, raltegravir was given once weekly, and rifapentine was given with raltegravir (Table 2).

Table 1. Pharmacokinetic parameters of raltegravir in healthy subjects in three study periods.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Ratio of geometric means for Periods 2:1</th>
<th>Ratio of geometric means for Periods 3:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Raltegravir 400 mg every 12 h</td>
<td>400 mg every 12 h</td>
<td>—</td>
<td>400 mg every 12 h</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Rifapentine none</td>
<td>900 mg once weekly</td>
<td>—</td>
<td>600 mg daily (5 of 7 days a week)</td>
<td>—</td>
</tr>
<tr>
<td>AUC0–1 (µg·h/mL)</td>
<td>5.32 (3.71, 7.62) [79]</td>
<td>9.07 (6.21, 13.24) [61]</td>
<td>1.71 (1.07, 2.71) [86]</td>
<td>5.04 (3.24, 7.84) [72]</td>
<td>0.95 (0.59, 1.53) [101]</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>1.59 (1.00, 2.52) [105]</td>
<td>3.00 (1.90, 4.75) [72]</td>
<td>1.89 (1.06, 3.44) [120]</td>
<td>1.62 (1.00, 2.62) [77]</td>
<td>1.02 (0.60, 1.72) [103]</td>
</tr>
<tr>
<td>C12 (first) (µg/mL)</td>
<td>0.057 (0.037, 0.089) [d] [136]</td>
<td>0.050 (0.038, 0.066) [105]</td>
<td>0.88 (0.62, 1.25) [d] [46]</td>
<td>0.033 (0.254, 0.044) [62]</td>
<td>0.59 (0.34, 1.02) [d] [100]</td>
</tr>
<tr>
<td>C12 (second) (µg/mL)</td>
<td>0.222 (0.127, 0.386) [e] [96]</td>
<td>—</td>
<td>0.137 (0.074, 0.251) [e] [118]</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

AUC0–1, Cmax, and C12 are all for raltegravir.

n = 16 subjects. Data are reported as the geometric mean (90% CI) [coefficient of variation, %].

The first value of C12 was determined 12 h after the seventh dose (fasting) of raltegravir, which was taken with rifapentine.

Period 2: comparison of morning and evening raltegravir C12 values: P ≤ 0.001.

n = 15 subjects.

Period 3: comparison of morning and evening raltegravir C12 values: P ≤ 0.001.

The second value of C12 was determined 12 h after the eighth dose (non-fasting) of raltegravir (24 h after the seventh dose of raltegravir) in Periods 2 and 3. Data for a baseline C12 obtained just prior to the administration of the seventh dose of raltegravir are described in the text.

Table 2. Pharamacokinetic parameters of rifapentine in healthy subjects in three study periods.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Ratio of geometric means for Periods 2:1</th>
<th>Ratio of geometric means for Periods 3:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Rifapentine 900 mg once weekly</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AUC0–1 (µg·h/mL)</td>
<td>11.30 (7.39, 18.13) [79]</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>3.15 (2.08, 4.93) [79]</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C12 (µg/mL)</td>
<td>0.125 (0.078, 0.200) [d] [136]</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

The second value of C12 was determined 12 h after the seventh dose (fasting) of rifapentine, which was taken with raltegravir.

n = 15 subjects.

Period 3: comparison of morning and evening rifapentine C12 values: P ≤ 0.001.

The second value of C12 was determined 12 h after the eighth dose (non-fasting) of rifapentine (24 h after the seventh dose of rifapentine) in Periods 2 and 3. Data for a baseline C12 obtained just prior to the administration of the seventh dose of rifapentine are described in the text.
with once-weekly or daily rifapentine in the present study are similar to those of atorvastatin with single-dose and daily rifampicin, which lead to increased and decreased atorvastatin AUCs, respectively.22–28

Although the clinical efficacy, safety and tolerability of rifapentine were established in previous clinical trials, the pharmacodynamic properties of raltegravir were not well characterized. The mean concentration of raltegravir necessary to in vitro inhibit wild-type HIV-1 (IC_{50}) in the presence of 50% normal human serum is 3 nM, but no in vivo threshold has been established.10,14,16,29 In the present study, the C_{12} of raltegravir with fasting drug administration was substantially lower than the non-fasting C_{12}, consistent with other reports of increased C_{12} of raltegravir after administration with food.30 Of note, two raltegravir C_{12} concentrations (baseline pre-dose C_{12}, and the second C_{12}) resulting from raltegravir doses taken under similar conditions (a non-fasting state in the evening and without concomitant rifapentine administration) were not significantly different. Diurnal variation also may affect C_{12}, with morning concentrations >5-fold higher than the C_{12} in the evening.31

Although a fixed-sequence of periods was used in this pharmacokinetic study, it was not a design limitation. Rifapentine exposures in Period 3 were not affected by prior rifapentine use because rifapentine autoinduction with the regimen in Period 2 was not demonstrated in another pharmacokinetic study of 157 adults and children treated for LTBI who had weekly rifapentine exposures similar to those found in Period 2 of this study.32 Rifapentine has not been evaluated in the setting of daily rifapentine exposure. Therefore, in this study, no effect on raltegravir pharmacokinetics in Period 3 sampling would be anticipated 24 days after Period 2 (because of a 10 day washout period and 10 daily doses of rifapentine given over 14 days).

Table 2. Adverse events in healthy subjects who received raltegravir and rifapentine

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse event</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>fatigue</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>fever</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>diaphoresis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>generalized weakness</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>rhinorrhea</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>sneezing</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>sore throat</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>cough</td>
<td>4</td>
</tr>
<tr>
<td>Neurological</td>
<td>headache (mild)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>drowsiness</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>vivid dreams</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>insomnia</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>diarrhoea</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>nausea</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>loss of appetite</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>vomiting</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>dyspepsia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>abdominal cramps</td>
<td>2</td>
</tr>
<tr>
<td>Endocrine</td>
<td>hot flashes</td>
<td>3</td>
</tr>
<tr>
<td>Dermatological</td>
<td>pruritus</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>rashb</td>
<td>2</td>
</tr>
</tbody>
</table>

α=16 study subjects who had Grade 1 (mild) to Grade 2 (moderate) adverse events. There were no Grade 3 (severe) or Grade 4 (life-threatening) adverse events. Adverse events listed were those that occurred in >1 subject.

bIn one subject, the rash appeared herpetic.

Discussion

The present study showed a substantial drug interaction between rifapentine and raltegravir. Rifapentine given once weekly, as currently recommended for the treatment of LTBI, did not affect the C_{12} of raltegravir but increased the AUC_{0–12} and C_{\text{max}} (Table 1). Therefore, when administered with once-weekly rifapentine, raltegravir reached adequate concentrations, and the moderate increase in concentrations appeared to be safe and well tolerated. Rifapentine exposure was similar to that of those patients treated for LTBI. These pharmacokinetic findings suggest that once-weekly rifapentine can be used with raltegravir without dose adjustment for the treatment of LTBI in patients who are infected with HIV.

Rifapentine given for 5 of 7 days per week as treatment for active tuberculosis disease resulted in a 41% geometric mean decrease in the C_{12} of raltegravir without a significant change in the AUC_{0–12} or C_{\text{max}} (Table 1). The proper dosing strategy of daily rifapentine for the treatment of active tuberculosis is still under clinical investigation.

The enzyme uridine diphosphate glucuronosyltransferase 1A1, which metabolizes raltegravir, is likely to be up-regulated by rifapentine, analogous to its up-regulation by rifampicin.14,15 The different effects observed with the coadministration of raltegravir and rifapentine...
also be used in HIV-infected patients taking raltegravir-based antiretroviral therapy. The rifapentine once-weekly doses in Period 2 were the same as recommended for LTBI in adults. Isoniazid is not reported to have an effect on the enzyme that metabolizes raltegravir. Finally, the 12 dose, once-weekly rifapentine and isoniazid regimen in 393 HIV-infected patients not receiving antiretroviral therapy was better tolerated and had a higher frequency of treatment completion than 9 months of isoniazid for treatment of LTBI. In summary, the present study showed a drug interaction between rifapentine and raltegravir that varied with the frequency of rifapentine dosing. Once-weekly rifapentine administration did not substantially affect the mean C\text{\textsubscript{max}} of raltegravir but increased the AUC\text{\textsubscript{0-12}} and C\text{\textsubscript{max}} of raltegravir. The increased raltegravir exposure observed with once-weekly rifapentine was safe and tolerable. Therefore, further clinical investigation is warranted to characterize the virological response to raltegravir-based antiretroviral therapy that includes rifapentine once weekly to treat patients infected with HIV and LTBI.

Acknowledgements
We are grateful to Drs Andrew Vernon, Susan Dorman and Philip LoBue for reviewing the manuscript prior to submission and Dr Elly Trepanier for medical editing.

Funding
This study was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck & Co., Inc. Support was also provided by the Veterans Administration, United States Centers for Disease Control and Prevention (Tuberculosis Trials Consortium), and National Center for Advancing Translational Sciences, through Grant 8UL1TR000149.

Transparency declarations
None to declare.

Disclaimer
The opinions expressed in this manuscript are those of the authors and do not reflect the official view of any of the supporting agencies.

References

Lam JL, Shugarts SB, Okochi H, Benet LZ. Elucidating the effect of final day dosing of rifampin in induction studies on hepatic drug disposition and metabolism. *J Pharmacol Exp Ther* 2006; 319: 864–70.


