Pharmacokinetics of Raltegravir in HIV-Infected Patients on Rifampicin-Based Antitubercular Therapy

Anne-Marie Taburet, Hélène Sauvageon, Beatriz Grinsztejn, Alex Assuied, Valdilea Veloso, José Henrique Pilotto, Nathalie De Castro, Carine Grondin, Catherine Fagard, and Jean-Michel Molina

1Hospital Bicêtre, Assistance Publique-Hôpitaux de Paris, DHU Hepatinov, INSERM U1184, Center for Immunology of Viral Infections and Autoimmune Diseases, Université Paris-Sud, Kremlin Bicêtre, and 2Hospital Saint-Louis, Assistance Publique-Hôpitaux de Paris, France; 3Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; 4Centre INSERM U897-Epidémiologie-Biostatistiques, Université de Bordeaux, Bordeaux, France; 5Hospital General de Nova Iguaçu and Laboratório de AIDS e Imunologia Molecular, Rio de Janeiro, Brazil; and 6University Paris Diderot, and 7INSERM U941, Paris, France

Background. Rifampicin (RIF) induces UGT1A1, an enzyme involved in raltegravir (RAL) elimination, thereby potentially lowering RAL exposure. We examined the pharmacokinetics of RAL in human immunodeficiency virus (HIV)–infected patients on RIF-based antitubercular therapy in the French National Agency for HIV/AIDS and Viral Hepatitis Research 12 180 Reflate Tuberculosis trial.

Methods. Patients started RAL in combination with tenofovir disoproxil fumarate and lamivudine after initiation of RIF (10 mg/kg/day). In arm 1 (n = 21), they received 400 mg RAL twice daily; in arm 2 (n = 16), they received RAL 800 mg twice daily initially then 400 mg twice daily 4 weeks after RIF discontinuation. Pharmacokinetic sampling was performed over 12-hour periods, 4 weeks after initiation of RAL together with RIF (period 1), 4 weeks after RIF discontinuation (period 2), and after the RAL dose reduction in arm 2 (period 3).

Results. In arm 1, the geometric mean ratio (GMR) between period 1 and period 2 was 0.94 (90% confidence interval [CI], .64–1.37) for the 12-hour area under the time-concentration curve (AUC0–12), and 0.69 (90% CI, .42–1.13) for the concentration at 12 hours (C12). In arm 2, the corresponding GMRs were 0.75 (90% CI, .48–1.17) and 1.10 (90% CI, .61–2.00) for period 1 vs period 2, and 1.10 (90% CI, .78–1.55) and 1.68 (90% CI, .88–3.23) for period 1 vs period 3.

Conclusions. The double dose of RAL overcompensated for RIF induction, but the standard dose was associated with only small decreases in AUC0–12 and C12 during RIF coadministration, warranting further evaluation in patients with HIV/tuberculosis coinfection.

Clinical Trials Registration. NCT0082231.

Keywords. raltegravir; rifampicin; tuberculosis; HIV; pharmacokinetics.

Tuberculosis remains the leading cause of mortality among human immunodeficiency virus (HIV)–infected individuals and is especially common in resource-limited countries with a high burden of HIV infection.

Coadministration of antitubercular drugs with antiretroviral therapy has been shown to reduce mortality among HIV/tuberculosis-coinfected patients and is strongly recommended [1–4]. The World Health Organization (WHO) recommends at least 6 months of rifampicin (RIF)–based antitubercular treatment, plus antiretroviral therapy combining efavirenz (EFV) with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine, started within the first 8 weeks of antitubercular treatment [4]. However, alternatives to EFV are needed, as its adverse effects sometimes lead to treatment discontinuation and its efficacy can be compromised by primary mutations associated with resistance to nonnucleoside reverse transcriptase
inhibitors (NNRTIs) [5, 6]. Because RIF induces hepatic cytochrome P450 (CYP) isoenzyme 3A4, a number of antiretroviral agents, including boosted protease inhibitors and other NNRTIs, may be less clinically effective.

Raltegravir (RAL), a strand-transfer HIV integrase inhibitor, is a potential alternative to EFV for patients receiving RIF-based tuberculosis treatment, as it is not metabolized through the CYP pathway and has potent antiviral activity and good tolerability in first-line antiretroviral therapy [7]. Raltegravir is metabolized by uridine 5’-diphospho (UDP)-glucuronosyltransferase 1A1 and thus carries a low risk of drug–drug interactions; unfortunately, this enzyme is also induced by RIF [8, 9]. A pharmacokinetic study of healthy volunteers showed that when RAL was coadministered with RIF at the standard dose of 400 mg twice a day, the plasma RAL area under the concentration-time curve (AUC) fell by 40% and the plasma RAL trough concentration fell by 61%. Doubling the RAL dose to 800 mg twice a day restored the AUC but the trough concentration remained 53% lower than expected [10]. Therefore, the drug regulatory agencies in the United States and the European Union recommend RAL 800 mg twice daily for patients also taking RIF. The aim of the French National Agency for HIV/AIDS and Viral Hepatitis Research (ANRS) 12 180 Retflate Tuberculosis trial was to determine the efficacy and safety of high-dose RAL coadministered with RIF [11]. This phase 2, noncomparative, open-label, randomized trial assessed the efficacy and safety of 2 doses of RAL (400 mg and 800 mg twice daily) or EFV, plus TDF and 3TC, in antiretroviral-naive HIV/tuberculosis -coinfected adults receiving RIF-based treatment. The standard dose of RAL 400 mg twice daily was found to provide potent antiviral activity, similar to that of the higher dose and EFV, with a good safety profile [11]. Here we report the pharmacokinetic results of this trial for RAL 400 mg or 800 mg twice daily, with and without RIF-based tuberculosis treatment. The aim of this pharmacokinetic substudy was to guide the choice of the RAL dose for use in a follow-up phase 3 trial.

**MATERIALS AND METHODS**

**Patients**

Patients enrolled in the ANRS 12 180 Retflate Tuberculosis trial at 3 sites in Paris or Rio de Janeiro were invited to participate in this pharmacokinetic substudy. All patients gave their written informed consent, and the study was approved by national and local ethics committees in Brazil (Comissão Nacional de Ética em Pesquisa and Comitê de Ética em Pesquisa at Instituto de Pesquisa Clinica Evandro Chagas/Fundação Oswaldo Cruz (IPEC/FIOCRUZ) and Hospital General de Nova Iguacu) and France (Comité de Protection des Personnes de Paris Ile de France I). The ANRS 12 180 Retflate Tuberculosis study design and inclusion criteria have been reported elsewhere [11]. In brief, antiretroviral-naive adult patients (aged ≥18 years) with a plasma HIV type 1 (HIV-1) RNA level >1000 copies/mL, who had been receiving standard RIF-based treatment for pulmonary or extrapulmonary tuberculosis for 2–8 weeks, were eligible provided they had acceptable laboratory parameters, including alanine aminotransferase level <2.5 times the upper limit of normal and creatinine clearance >60 mL/minute (Cockcroft-Gault formula). Patients were not eligible if they were on concomitant treatments known to induce drug-metabolizing enzymes, such as phenytoin and phenobarbital, or to interact with UDP-glucuronosyltransferase 1A1. Patients included in the pharmacokinetic substudy were instructed not to take proton pump inhibitors.

**Study Design**

After a median of 6 weeks of tuberculosis treatment, patients were randomized to receive open-label RAL 400 mg twice daily, RAL 800 mg twice daily, or EFV 600 mg daily, plus TDF 300 mg daily and 3TC 300 mg daily. Only those randomized to RAL (arm 1: standard dose of RAL 400 mg twice daily; arm 2: double dose of RAL 800 mg twice daily) were included in this pharmacokinetic study. Patients enrolled in arm 2 were required to switch to RAL 400 mg twice daily 4 weeks after RIF discontinuation, to allow completion of the pharmacokinetic comparison of high-dose RAL plus RIF vs RAL alone at 800 mg twice daily initially then 400 mg twice daily. Blood sampling was scheduled as follows: first visit 4 weeks after initiation of RAL combined with tuberculosis treatment (period 1); second visit 4 weeks after RIF discontinuation (period 2); and third visit following the RAL dose reduction in arm 2 (period 3).

At each visit, antitubercular therapy was administered first, with water, after an overnight fast, followed 2 hours later by the RAL dose, with a moderate-fat continental breakfast. The antitubercular regimens complied with national guidelines in Brazil and France and included a minimum of RIF (10 mg/kg/day) and isoniazid. Patients were instructed to take RAL with moderate- or high-fat meals to increase its bioavailability [12]. At each visit, blood samples were drawn over a 12-hour dosing interval, before antiretroviral drug intake (time 0) and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after intake.

**Safety and Virologic Monitoring**

Safety evaluations were conducted, with clinical examination and laboratory analyses (including plasma HIV-1 RNA levels) at the screening and baseline visits and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. Adverse signs and symptoms and laboratory events were graded according to the ANRS scale for adverse events in adults [11]. Only grade 3 or 4 adverse events, serious adverse events, and adverse events leading to treatment discontinuation were recorded. Viral suppression was defined by a plasma HIV-1 RNA level <50 copies/mL at week 24 and confirmed at week 48.
Plasma Raltegravir Assay
Blood samples were centrifuged (800g for 20 minutes) at room temperature within 30 minutes of collection. All plasma samples were kept at −80°C at the study sites until shipment in batch for centralized analysis in the pharmacology laboratory of Saint Louis Hospital (Paris, France), which participated in an external quality control program (Asqualab, Paris, France).

Plasma concentrations of RAL were measured by liquid chromatography–tandem mass spectrometry (LC/MS-MS) as previously described [13]. The lower limit of quantification (LLOQ) was 5 ng/mL. Within- and between-day variability of quality control samples included in each analytical run were <15%. The standard curve was linear from 5 ng/mL to 8000 ng/mL.

Pharmacokinetic Analysis
Raltegravir pharmacokinetic parameters were estimated with the noncompartmental method (Phoenix WinNonlin 1.3 software, Pharsight-Certara). The AUC during a 12-hour dosing interval at steady state (AUCC0→∞) was calculated with the linear up–log down trapezoidal method. The maximal plasma concentration (Cmax), the predose concentration (C0) before the morning drug intake, the concentration at the end of the dosing interval (C12), and the time to Cmax (Tmax) were obtained from the plasma concentration-time curve.

Statistical Analysis
This was an observational pilot pharmacokinetic study in which all participants from the ANRS 12 180 Rifampicin Tuberculosis trial were invited to participate, and no formal calculation of the required number of patients was done. We planned to enroll 20 patients per arm to have at least 15 patients assessable to determine whether the planned number was done. We planned to enroll 20 patients per arm to have at least 15 patients assessable to determine whether the planned number was done. We planned to enroll 20 patients per arm to have at least 15 patients assessable to determine whether the planned number was done.

RESULTS

Patient Characteristics
Among the 155 patients randomized in the ANRS 12 180 REFLATE Tuberculosis trial, 46 patients were enrolled in the RAL pharmacokinetic substudy, but only 37 completed all 3 pharmacokinetic visits (21 in arm 1 and 16 in arm 2) and were followed up to week 48. Patient characteristics at the time of the first pharmacokinetic visit (Table 1) were generally similar across the arms and similar to those of the whole trial population. Of note, fewer male and more white patients were enrolled in arm 1, and body weight was also lower in this arm. All the patients had normal hepatic and renal function test results.

Pharmacokinetic visits took place a median of 4 weeks (interquartile range [IQR], 4–5 weeks) (period 1, with RIF), 25 weeks (IQR, 24–29 weeks) (period 2, off RIF), and 30 weeks (IQR, 28–42 weeks) (period 3, off RIF). Patient characteristics at the time of the first pharmacokinetic visit (Table 1) were generally similar across the arms and similar to those of the whole trial population. Of note, fewer male and more white patients were enrolled in arm 1, and body weight was also lower in this arm. All the patients had normal hepatic and renal function test results.

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Table 1. Characteristics of Patients Enrolled in the Pharmacokinetic Study at the First Pharmacokinetic Period (on Rifampicin; 4 Weeks After Initiation of Raltegravir-Based Antiretroviral Therapy)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm 1: Raltegravir 400 BID (n = 21)</th>
<th>Arm 2: Raltegravir 800 BID (n = 16)</th>
<th>Total (N = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, No. (%)</td>
<td>12 (57)</td>
<td>13 (81)</td>
<td>25 (68)</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>37 (32–44)</td>
<td>40 (36–44)</td>
<td>39 (33–44)</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>7 (33)</td>
<td>7 (44)</td>
<td>14 (38)</td>
</tr>
<tr>
<td>Mixed</td>
<td>8 (38)</td>
<td>8 (50)</td>
<td>16 (43)</td>
</tr>
<tr>
<td>White non-Hispanic white</td>
<td>6 (29)</td>
<td>1 (6)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Weight, kg, median (IQR)</td>
<td>58 (53–65)</td>
<td>62 (55–72)</td>
<td>59 (54–70)</td>
</tr>
<tr>
<td>Body mass index, kg/m², median (IQR)</td>
<td>21 (19–24)</td>
<td>20 (19–24)</td>
<td>21 (19–24)</td>
</tr>
<tr>
<td>HIV-1 RNA, log10 copies/mL, median (IQR)</td>
<td>1.7 (1.7–1.9)</td>
<td>1.7 (1.7–1.7)</td>
<td>1.7 (1.7–1.7)</td>
</tr>
<tr>
<td>CD4 count, cells/µL, median (IQR)</td>
<td>290 (191–465)</td>
<td>432 (229–489)</td>
<td>355 (222–467)</td>
</tr>
<tr>
<td>ALT level, IU/L, median (IQR)</td>
<td>37 (28–40)</td>
<td>39 (30–45)</td>
<td>37 (28–42)</td>
</tr>
<tr>
<td>CrCl, mL/min (Cockroft-Gault), median (IQR)</td>
<td>60 (54–67)</td>
<td>69 (62–80)</td>
<td>65 (57–75)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; BID, twice daily; CrCl, creatinine clearance; HIV-1, human immunodeficiency virus type 1; IQR, interquartile range.
29–35 weeks) (period 3 in arm 2 following the switch to the standard dose of RAL) after day 0. The median duration of tuberculosis treatment at the period 1 visit was 11 weeks (IQR, 9–12 weeks). In addition to RIF, 35 patients (95%) received isoniazid, 1 received ofloxacin, and another received streptomycin. During period 1, 11 patients (30%) received ethambutol and 11 (30%) received pyrazinamide. Fourteen patients (38%) also received cotrimoxazole to prevent opportunistic infections.

**Effect of Rifampicin on Raltegravir Concentrations**

As expected, we observed large inter- and intraindividual variability (Figure 1), but all concentrations remained above the LLOQ. Figure 2 shows the mean plasma concentration-time curves of RAL 400 mg twice daily, with RIF (period 1) and without RIF (period 2). Raltegravir C12 values were lower during RIF coadministration, with a GMR of 0.69 (90% CI, 0.42–1.13), but the GMRs for AUC0–12 and Cmax were close to 1 (Table 2). Interestingly, all but 1 of the RAL C12 values during RIF coadministration were >14 ng/L, which is the mean 95% inhibitory concentration (IC95) of RAL in vitro for wild-type HIV-1 in the presence of 50% human serum (data not shown). Figure 3 shows the mean plasma concentration-time curves for RAL 800 mg twice daily, with RIF (period 1) and without RIF (period 2), and Figure 4 shows the mean plasma concentration-time curves for RAL 800 mg twice daily with RIF (period 1), and for RAL 400 mg twice daily without RIF (period 3). Overall, RAL concentrations

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**Figure 1.** Box plots of raltegravir plasma concentration at 12 hours after drug intake (C12) by arm and pharmacokinetic (PK) visit. Box plots represent median and interquartile range, the lines 1.5 times the interquartile range, and open circles the outliers. The first column represents participants on antituberculosis treatment (TB treatment) (period 1), the second column represents participants without tuberculosis treatment (period 2), and the third column shows participants of arm 2 after the switch to a raltegravir 400-mg dose (period 3). One participant in the raltegravir 400 mg group had a C12 raltegravir concentration of 5732 ng/mL at the second PK visit (outlier not shown on the graph).

**Figure 2.** Raltegravir median (interquartile range) steady-state plasma concentration (with log-scale) vs time curves in arm 1. Raltegravir was given at a dose of 400 mg twice daily together with rifampicin (solid line, period 1) or without rifampicin (dotted line, period 2).
were lower with RIF than without RIF (period 1 vs period 2; Table 3). However, the higher dose of RAL (800 mg twice daily) fully compensated for RIF induction (period 1 vs period 3), with a GMR of 1.68 (90% CI, 0.88–3.23) for the RAL C12 and 1.10 (90% CI, 0.78–1.55) for the RAL AUC0–12.

### Safety and Tolerability
Coadministration of RAL with antitubercular therapy comprising RIF and isoniazid was generally well tolerated. The number of patients with at least 1 grade 3 or 4 drug-related adverse event was 4 (19%) in arm 1 (2 neutropenia and 2 immune reconstitution inflammatory syndrome [IRIS]), and 2 (12.5%) in arm 2 (1 IRIS and 1 deep vein thrombosis). None of these patients discontinued their assigned RAL dose.

### Virologic and Antitubercular Outcomes
Tuberculosis was successfully treated in all the participants, and 16 of 21 (76%) patients in arm 1 and 14 of 16 (88%) patients in arm 2 had a plasma HIV-1 RNA level <50 copies/mL at week 24. The respective numbers at week 48 were 18 of 21 (86%) and 11 of 16 (69%). No clear relationship was found between virologic outcome and trough RAL concentrations, although the patient with a RAL C12 level of 10 ng/mL later experienced virologic failure.

### Table 2. Comparison of Plasma Raltegravir Pharmacokinetics Following Administration of Raltegravir 400 mg Twice Daily (Arm 1), With and Without Rifampicin

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Period 1 (on RIF)</th>
<th>Geometric Mean, Median (Range)</th>
<th>Period 2 (off RIF)</th>
<th>Geometric Mean, Median (Range)</th>
<th>Period 1/Period 2</th>
<th>GMR (90% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>2929</td>
<td>3322 (228–7920)</td>
<td>2966</td>
<td>3572 (184–11 632)</td>
<td>0.99 (.67–1.45)</td>
<td>.18</td>
<td></td>
</tr>
<tr>
<td>Tmax, h</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
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</tr>
<tr>
<td>C0, ng/mL</td>
<td>165</td>
<td>205 (5–4395)</td>
<td>368</td>
<td>414 (10–2065)</td>
<td>0.46 (.28–.77)</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td>C12, ng/mL</td>
<td>138</td>
<td>142 (10–1642)</td>
<td>199</td>
<td>260 (24–5732)</td>
<td>0.69 (.42–1.13)</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>AUC0–12, ng × h/mL</td>
<td>9278</td>
<td>10 300 (740–21 835)</td>
<td>9910</td>
<td>14 814 (672–34 437)</td>
<td>0.94 (.64–1.37)</td>
<td>.24</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC0–12, area under the plasma concentration-time curve during a 12-hour dosing interval; C0, concentration before drug intake; C12, concentration at the end of the 12-hour interval; CI, confidence interval; Cmax, maximum concentration; GMR, geometric mean ratio; RIF, rifampicin; Tmax, time to achieve maximum concentration.

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**Figure 3.** Raltegravir median (interquartile range) steady-state plasma concentration (with log-scale) vs time curves in arm 2. Raltegravir was given at a dose of 800 mg twice daily together with rifampicin (solid line, period 1) or without rifampicin (dotted line, period 2).

**Figure 4.** Raltegravir median (interquartile range) steady-state plasma concentration (with log-scale) vs time curves in arm 2. Raltegravir was given at a dose of 800 mg twice daily together with rifampicin (solid line, period 1) and was given at a dose of 400 mg twice daily without rifampicin (dotted line, period 3).
We determined pharmacokinetic parameters of RAL at the standard dose of 400 mg twice daily and at the double dose of 800 mg twice daily during coadministration with rifampicin-based antitubercular therapy, to add to the body of evidence about the choices of the RAL doses to be used in future phase 3 studies in patients with HIV/tuberculosis coinfection.

The main finding of this study is that the impact of rifampicin on RAL pharmacokinetics in HIV/tuberculosis-coinfected patients was not as marked as that reported in healthy volunteers [10, 14]. We observed a huge degree of inter and intraindividual variability of RAL exposure. Such variability has previously been reported in HIV-infected patients but is poorly understood [15–18]. Raltegravir solubility and absorption are influenced by divalent metals, environmental pH, and meals [12, 19]. Meals taken with the evening dose the day before pharmacokinetic sampling could explain the difference between C₀ and C₁₂ concentrations observed in some patients. Allelic variants of the UGT1A1 gene can also affect RAL pharmacokinetics [20]. Indeed, individuals with the UGT1A1*28 genotype, associated with decreased enzyme activity, show a 40% increase in the AUC and Cₘₐₓ and a 91% increase in C₁₂h [20]. UGT1A1 loss-of-function variants are reported to be more prevalent in African American than in white individuals (42%–56% vs 26%–31%, respectively) [21]. However, the RAL pharmacokinetic parameters observed here were compatible with those reported in previous studies of HIV-infected patients [15–17].

We demonstrated that increasing the dose of RAL to 800 mg twice daily compensated for the enzyme-inducing effect of rifampicin. We also found that patients receiving this double dose of RAL plus rifampicin had lower RAL concentrations than those not receiving rifampicin, but had higher concentrations than when receiving the standard 400 mg twice-daily dose, although again variability was large. Whether these higher concentrations could impact tolerance is presently unknown.

Interestingly, the effect of rifampicin on RAL concentrations in patients receiving the standard dose of RAL 400 mg twice daily was not as potent as expected. Indeed, the Cₘₐₓ and AUC₀–₁₂ were only moderately affected and C₁₂ was reduced by only 31%, compared with 61% in healthy volunteers receiving both rifampicin and RAL [10]. Although the pharmacokinetic parameters associated with RAL efficacy are not yet clearly defined, the pharmacokinetic/pharmacodynamic study performed in the QDMRK trial suggested that low trough concentrations were associated with poorer virological outcomes, implying that even a 31% reduction in the trough concentration might be clinically relevant [15]. Indeed, trough concentrations were reported to be 4- to 6-fold lower in the once-daily RAL arm than in the twice-daily arm, and 42.4% of patients in the once-daily arm had trough concentrations below the mean in the in vitro IC₉₅ of RAL (14 ng/mL), vs only 13.8% of those in the twice-daily arm [15]. However, the geometric mean C₁₂ of RAL 400 mg twice daily coadministered with rifampicin was 138 ng/mL in our study, a concentration higher than reported in healthy volunteers, but is poorly understood [15–18]. Raltegravir solubility and absorption are influenced by divalent metals, environmental pH, and meals [12, 19]. Meals taken with the evening dose the day before pharmacokinetic sampling could explain the difference between C₀ and C₁₂ concentrations observed in some patients. Allelic variants of the UGT1A1 gene can also affect RAL pharmacokinetics [20]. Indeed, individuals with the UGT1A1*28 genotype, associated with decreased enzyme activity, show a 40% increase in the AUC and Cₘₐₓ and a 91% increase in C₁₂h [20]. UGT1A1 loss-of-function variants are reported to be more prevalent in African American than in white individuals (42%–56% vs 26%–31%, respectively) [21]. However, the RAL pharmacokinetic parameters observed here were compatible with those reported in previous studies of HIV-infected patients [15–17].

We demonstrated that increasing the dose of RAL to 800 mg twice daily compensated for the enzyme-inducing effect of rifampicin.
There are several possible reasons why our results differ from those reported in healthy volunteers [10]. First, our study was performed at steady state after 4 weeks of RAL treatment and 11 weeks of RIF-based therapy, whereas the study in healthy volunteers involved a single-dose study of RAL administered at RIF steady state. Second, given the potential increase in RAL bioavailability with food, we instructed our patients to take RAL with a moderate- or high-fat meal, whereas the healthy volunteers were fasted. In addition, the patients in our study were severely immunosuppressed, and high gastric pH reported in patients with AIDS may also increase RAL absorption [22]. Also, the low median body weight of our HIV/tuberculosis-coinfected patients receiving RAL 400 mg twice daily (59 kg), compared with that of the healthy volunteers (79 kg), might have contributed to the higher RAL concentrations in our study, as previously reported with EFV [23]. Last, another difference between these 2 pharmacokinetic studies is that the healthy volunteers only received RAL and RIF, whereas our patients received a full antiretroviral regimen combining RAL and TDF + 3TC, together with a tuberculosis regimen comprising RIF and isoniazid at time of sampling for the RAL assay. Isoniazid, TDF, and 3TC are not known to interact with UGT1A1, but any such interaction could not explain the limited enzyme induction observed with RIF in our study, as previously demonstrated for other enzymes as CYP2B6 [24, 25].

Owing to the high intra- and interindividual variability of RAL pharmacokinetics and the small number of patients enrolled in this study, we are unable to draw definitive conclusions regarding the clinical relevance of the pharmacokinetic interaction between RIF and RAL.

In conclusion, we found that the decrease in RAL pharmacokinetic parameters induced by RIF in HIV/tuberculosis-coinfected patients receiving RAL at the standard dose of 400 mg twice daily was smaller than expected and therefore might not adversely affect RAL antiviral activity. These findings, together with those of the entire ANRS 12 180 Relfate Tuberculosis trial, suggest that the standard dose of RAL 400 mg twice daily might be sufficient for the treatment of patients with HIV/tuberculosis coinfection. This standard dose of RAL has been selected for a phase 3 trial comparing RAL to EFV in patients with HIV/tuberculosis coinfection, to confirm that RAL at the regular dose of 400 mg twice daily is a possible alternative to EFV in this setting.

Notes

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Potential conflicts of interest. J.-M. T. has acted as a consultant, participated in advisory boards, has received speaker fees, and has been an investigator for clinical trials for Janssen, ViV Healthcare, Gilead Sciences, Bristol-Myers Squibb (BMS), Abbott Laboratories, Boehringer Ingelheim, and Merck Sharp & Dohme, and has also received research grants from Merck and Gilead. C. F. has received a consulting fee from Merck Sharp & Dohme-Chibret and has had scientific responsibilities in projects receiving specific grant supports that are managed through her institution. A.-M. T. has received travel fees from Janssen, Gilead, and BMS. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


