Pharmacokinetic evaluation of the interaction between etravirine and rifabutin or clarithromycin in HIV-negative, healthy volunteers: results from two Phase 1 studies

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Objectives: Drug–drug interactions between etravirine and rifabutin or clarithromycin were examined in two separate open-label, randomized, two-period, crossover trials in HIV-negative, healthy volunteers.

Methods: Rifabutin study: 16 participants received 300 mg of rifabutin once daily (14 days) and then 800 mg of etravirine twice daily (Phase 2 formulation; 21 days) plus 300 mg of rifabutin once daily (days 8–21). Clarithromycin study: 16 participants received 200 mg of etravirine twice daily (commercial formulation; 8 days) and then 500 mg of clarithromycin twice daily (13 days) plus 200 mg of etravirine twice daily (days 6–13). A 14 day washout period between treatments was mandatory in both studies. Full pharmacokinetic profiles of each drug and safety/tolerability were assessed.

Results: Rifabutin decreased etravirine exposure by 37%; etravirine decreased rifabutin and 25-O-desacetyl rifabutin exposure by 17%. Clarithromycin increased etravirine exposure by 42%, whereas etravirine decreased clarithromycin exposure by 39% and increased 14-OH clarithromycin exposure by 21%. No serious adverse events were reported in either trial.

Conclusions: Short-term etravirine coadministration with rifabutin or clarithromycin was well tolerated. Etravirine can be coadministered with 300 mg of rifabutin once daily in the absence of an additional potent cytochrome P450 inducer. No dose adjustments are required upon etravirine/clarithromycin coadministration, but alternatives to clarithromycin are recommended when used for Mycobacterium avium complex prophylaxis or treatment.

Keywords: anti-infectives, pharmacokinetics, non-nucleoside reverse transcriptase inhibitors

Introduction

The increased use of highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS has reduced the incidence of opportunistic infections dramatically in industrialized countries.1−3 Yet, there remains the risk of acquiring a severe opportunistic infection, particularly among the following groups: patients who are unaware they have HIV infection and present for emergency care with an opportunistic infection as the initial indicator of late-stage disease; patients who are aware of their HIV status, but lack access to HAART due to psychosocial or economic factors, or choose not to take HAART; and patients who have inadequate immunological response to HAART due to resistance to treatment, or who are not given timely opportunistic infection prophylaxis based on their CD4+ cell counts.1,4−6

Mycobacterium avium complex (MAC) and tuberculosis are both common opportunistic infections that afflicting HIV-infected patients. The antimycobacterial rifabutin and the macrolide clarithromycin are both used to prevent and treat MAC, with clarithromycin being among the preferred first-line agents.3,7,8 Rifabutin can also be combined with other medications to treat tuberculosis in HIV-infected patients.3

Rifabutin is a cytochrome P450 (CYP) inducer and, as such, may be expected to reduce plasma concentrations of agents that are primarily hepatically metabolized.5,10 In addition, the metabolism of rifabutin to 25-O-desacetyl rifabutin, the primary active metabolite of rifabutin, is mediated by CYP3A.11 Therefore, coadministration of rifabutin with drugs that induce CYP3A could decrease rifabutin plasma concentrations. The activity of 25-O-desacetyl rifabutin is known to be as potent as rifabutin in vitro against MAC and it is further metabolized prior to its elimination.9

Rifabutin is associated with drug–drug interactions when combined with most antiretroviral agents.12 Underdosing of antiretrovirals or rifabutin can result in selection of HIV drug-resistant
Interactions between etravirine and rifabutin or clarithromycin

Mutants or acquired rifabutin resistance, respectively, whereas rifabutin overdose could result in dose-related toxicities such as neutropenia and uveitis.3

Clarithromycin is an inhibitor of CYP3A and is converted by CYP3A to its major active metabolite, 14-OH clarithromycin.13 Both clarithromycin (parent) and 14-OH clarithromycin have activity against most bacterial infections; however, for MAC isolates, 14-OH clarithromycin is ≥4-fold less active than its parent drug.14

The non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine is indicated for use, in combination with other antiretrovirals, in treatment-experienced, HIV-1-infected paediatric (≥6 years old) and adult patients. Etravirine is a weak inducer of CYP3A and a weak inhibitor of CYP2C9, 2C19 and P-glycoprotein.15,16 Although etravirine is metabolized by the CYP enzyme system, the extent of clinically relevant interactions with other antiretrovirals is limited. During the clinical development programme, several formulations of etravirine were developed and used. In Phase 2 trials, etravirine was administered at 800 mg twice daily, which was subsequently replaced with a formulation based on spray-drying that allowed etravirine to be dosed at 200 mg twice daily. The mean (±SD) Cmax and AUC when etravirine was administered at 800 mg twice daily (Phase 2 formulation) at steady-state were 318.8 (245.8) ng/mL and 2607 (2135) ng·h/mL, respectively; when etravirine was administered at 200 mg twice daily (commercial formulation), these values were 451.3 (232.3) ng/mL and 3713 (2069) ng·h/mL, respectively.17

As rifabutin and clarithromycin could be used to prevent or treat opportunistic infections in HIV-infected patients, and the potential for drug–drug interactions, it is important to understand how rifabutin or clarithromycin interact with etravirine and vice versa. We present the findings of two Phase 2, open-label, randomized, two-period, crossover trials that assessed the pharmacokinetics and short-term safety profile of the concomitant administration of etravirine with each drug (separately) in HIV-negative, healthy volunteers.

Methods

Ethics approval

Ethics approval (Institutional Review Board: rifabutin study: IntegReview, 3001 S. Lamar Blvd, Suite 210, Austin, TX 78704, USA; clarithromycin study: Hôpital Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne Billancourt, Paris, France; and Independent Ethics Committee: clarithromycin study: Hôpital Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne Billancourt, Paris, France) was obtained. All volunteers gave written and informed consent prior to any study-related procedure. The trials were carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, in line with the European Union Clinical Trials Directive.

Participants

Both studies recruited healthy, non-smoking volunteers (or those who smoked ≤10 cigarettes/two cigars/two pipes daily for ≤3 months prior to selection) aged 18–55 years and who had no clinically relevant abnormalities on physical and laboratory examination. Participants were required to have a normal body mass index.

Volunteers were not permitted to enter the trial if they tested positive for HIV-1 or HIV-2 at screening; had a history of alcohol, barbiturate, amphetamine, recreational or narcotic drug use; were female, except if post-menopausal for >2 years, post-hysterectomy or post-tubal ligation (without reversal operation); had hepatitis A, B or C infection at screening; had a positive urinary drug test for amphetamines, benzodiazepines, cocaine, cannabinoids or opioids at screening; or had a history of significant skin disease or hypersensitivity to the therapies used or their excipients.

Volunteers were withdrawn from the trials if any serious/grade 3–4 adverse event (AE), grade ≥2 rash, persistent grade ≥2 nausea or clinical hepatitis occurred; any rifabutin-related renal complication developed in the rifabutin study; they withdrew consent; or if the investigator considered this was in the participant’s best interest.

Study design and treatment

In both trials, two treatment periods (A and B) were scheduled, separated by a washout period of ≥14 days. The crossover design was employed in consideration of the previously observed wide interpatient variability in the pharmacokinetic profile of etravirine.17 Eight volunteers were assigned to each treatment group. In the rifabutin study, participants received 300 mg of rifabutin once daily for 14 days (Treatment A rif), followed by 800 mg of etravirine twice daily (Phase 2 formulation) for 21 days plus 300 mg of rifabutin once daily on days 8–21 (Treatment B rif). In the clarithromycin study, participants received 200 mg of etravirine twice daily for 8 days (Treatment A clar, commercial formulation), followed by 500 mg of clarithromycin twice daily for 13 days with concomitant etravirine administration on days 6–13 (Treatment B clar). The etravirine tablets used in the rifabutin study were the 200 mg Phase 2 formulation, whereas those used in the clarithromycin study were the 100 mg Phase 3 (commercial) formulation. The steady-state pharmacokinetics of etravirine administered at 800 mg twice daily of the Phase 2 formulation are comparable to those of 200 mg twice daily of the commercial formulation.17 The study designs are shown in Figure S1 (available as Supplementary data at JAC Online).

All treatments were taken with food. On the day of pharmacokinetic evaluation, study medications were taken within 10 min after a standardized breakfast. Etravirine and rifabutin were administered simultaneously, while etravirine was taken 5 min before clarithromycin. Treatment adherence was monitored by the investigators at the testing facility in the rifabutin study, and with patient diaries and inspection of unused medication and packaging in the clarithromycin study.

Pharmacokinetic measurements

In the rifabutin study, plasma concentrations of etravirine were determined over 12 h on days 7 and 21 of Treatment B rif; plasma concentrations of rifabutin and 25-O-desacetyl rifabutin were determined over 24 h on day 14 of Treatment A rif and day 21 of Treatment B rif. Plasma concentrations of etravirine, rifabutin and 25-O-desacetyl rifabutin were determined using previously validated liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) methods. Details of the assays are described elsewhere.18,19

The lower limit of quantification (LLOQ) was 2.00 ng/mL for all compounds. In the clarithromycin study, plasma concentrations of etravirine were determined over 12 h on day 8 of Treatment A clar and day 13 of Treatment B clar; plasma concentrations of clarithromycin and 14-OH clarithromycin were determined over 12 h on days 5 and 13 of Treatment B clar. Plasma concentrations of etravirine, clarithromycin and 14-OH clarithromycin were determined using previously validated LC-MS/MS methods with LLOQs of 2.00, 50.00 and 50.00 ng/mL, respectively. Details of the assays are described elsewhere.18,20

Safety evaluations

Safety and tolerability data were collected throughout both trials until ≥30 days after the last dose of study medication. AEs, laboratory measurements, electrocardiographs, vital signs and physical examinations were evaluated. The severity and drug relationship of AEs to etravirine, rifabutin or clarithromycin were recorded.
Pharmacokinetic and statistical analyses

A non-compartmental model with extravascular input (WinNonlin Professional™ version 4.1; Pharsight Corporation, Mountain View, CA, USA) was used for the pharmacokinetic analyses. The minimum plasma concentration ($C_{\text{min}}$), $C_{\text{max}}$ and $T_{\text{max}}$ were obtained by inspection of the plasma concentration–time profiles. AUC from 0 to 12 h ($\text{AUC}_{0-12}$) or $\text{AUC}_{0-\infty}$ was estimated using the linear–linear trapezoidal rule. Descriptive statistics were calculated for the pharmacokinetic parameters of etravirine, rifabutin, 25-O-desacetyl rifabutin, clarithromycin and 14-OH clarithromycin.

All statistical analyses were carried out with the intent-to-treat population (i.e. those volunteers who received at least one dose of study medication). Demographic data were tabulated and analysed descriptively. Analyses were carried out with SAS System for Windows® version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

In the rifabutin study, statistical comparisons were made between day 21 of Treatment $B_{\text{rif}}$ (test) versus day 7 of Treatment $A_{\text{rif}}$ (reference) for etravirine, and between day 21 of Treatment $B_{\text{rif}}$ (test) versus day 14 of Treatment $A_{\text{rif}}$ (reference) for rifabutin and 25-O-desacetyl rifabutin. In the clarithromycin study, statistical comparisons were made between day 13 of Treatment $B_{\text{clar}}$ (test) versus day 8 of Treatment $A_{\text{clar}}$ (reference) for etravirine, and between day 13 of Treatment $B_{\text{clar}}$ (test) versus day 5 of Treatment $A_{\text{clar}}$ (reference) for clarithromycin and 14-OH clarithromycin.

The primary pharmacokinetic parameters were $C_{\text{max}}$, $C_{\text{min}}$ and $\text{AUC}_{0-12}$ or $\text{AUC}_{0-\infty}$. The least squares means (LSM) of the primary parameters for each treatment group were estimated; 90% CIs were constructed around differences between the LSM of test and reference values. Treatment and period effects were considered significant at the 5% level and sequence effects at the 10% level. A statistically significant interaction was declared if the 90% CIs were outside the pre-specified limits of 80.00%–125.00%. Safety parameters were evaluated by descriptive statistics and tabulation of frequency.

Results

Baseline characteristics were well balanced between the treatment groups and also between the two trials. Volunteers had a median age of 34 years (range 22–55) and 29 years (range 18–45) in the rifabutin and clarithromycin studies, respectively. In the rifabutin study, 15 of 16 volunteers (94%) were male; all volunteers in the clarithromycin study were male. In the rifabutin and clarithromycin studies, respectively, 50% and 69% of participants were Caucasian/white.

Four volunteers in the rifabutin study and one in the clarithromycin study withdrew consent. Two volunteers were withdrawn from the rifabutin study due to AEs; there were no discontinuations from the clarithromycin study due to AEs.

Etravirine pharmacokinetics

Mean etravirine concentrations were lower across the dosing interval in the presence of rifabutin and higher in the presence of clarithromycin compared with etravirine alone (Figure 1). Based on the LSM ratios, etravirine $C_{\text{min}}$, $C_{\text{max}}$ and $\text{AUC}_{0-12}$ were decreased

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Table 1. Pharmacokinetics of etravirine when coadministered with rifabutin or clarithromycin

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Rifabutin study</th>
<th>Clarithromycin study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>etravirine alone (reference; $n=12$), mean±SD</td>
<td>etravirine + rifabutin (test; $n=11$), mean±SD</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/mL)</td>
<td>257±118</td>
<td>178±129</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>547±234</td>
<td>371±259</td>
</tr>
<tr>
<td>AUC$_{0-12}$ (ng·h/mL)</td>
<td>4122±1949</td>
<td>3220±2196</td>
</tr>
</tbody>
</table>

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Figure 1. Mean plasma concentration–time curves for etravirine with and without coadministration of (a) rifabutin or (b) clarithromycin.
by 35%, 37% and 37%, respectively, in the presence of rifabutin versus etravirine alone (Table 1). Conversely, based on the LSM ratios, etravirine $C_{min}$, $C_{max}$ and AUC$_{0–12}$ were increased by 46%, 46% and 42%, respectively, when coadministered with clarithromycin versus etravirine alone (Table 1).

**Rifabutin and 25-O-desacetyl rifabutin pharmacokinetics**

Mean plasma concentrations of rifabutin and 25-O-desacetyl rifabutin were slightly lower across the dosing interval in the presence of etravirine compared with rifabutin alone (Figure 2). Rifabutin and 25-O-desacetyl rifabutin $C_{min}$, $C_{max}$ and AUC$_{0–24}$ were all slightly decreased in the presence of etravirine (Table 2). Based on the LSM ratios, the $C_{min}$, $C_{max}$ and AUC$_{0–24}$ for rifabutin were decreased by 24%, 10% and 17%, respectively, while the same parameters for 25-O-desacetyl rifabutin were reduced by 22%, 15% and 17%, respectively (Table 2).

**Clarithromycin and 14-OH clarithromycin pharmacokinetics**

Mean plasma concentrations of clarithromycin were lower across the dosing interval in the presence of etravirine compared with clarithromycin alone (Figure 3a). In contrast, mean plasma concentrations of 14-OH clarithromycin were increased across the dosing interval in the presence of etravirine compared with clarithromycin alone (Figure 3b). Based on the LSM ratios, clarithromycin $C_{min}$, $C_{max}$ and AUC$_{0–12}$ were decreased by 53%, 34% and 39%, respectively; 14-OH clarithromycin $C_{min}$ was unchanged, while $C_{max}$ and AUC$_{0–12}$ were increased by 33% and 21%, respectively, in the presence of etravirine versus clarithromycin alone (Table 3).

**Safety**

No serious AEs were reported in either trial. One volunteer in the rifabutin study discontinued after developing grade 1 atrial flutter during the rifabutin-only phase of treatment. No volunteers discontinued the clarithromycin study due to AEs.

AEs in both studies were mild to moderate in severity, except for one case of a grade 3 increase in serum amylase during the rifabutin-only phase of treatment in the rifabutin study, which led to discontinuation. No grade 3–4 AEs were reported in the clarithromycin study.

The most frequent AEs in the rifabutin study were treatment-related chromaturia (a known side effect of rifabutin use), which was reported by seven volunteers, and headache reported by five volunteers; all events were grade 1 in severity. The most frequent AEs in the clarithromycin study were grade 2 abdominal pain.

### Table 2. Pharmacokinetics of rifabutin and 25-O-desacetyl rifabutin when coadministered with etravirine in the rifabutin study

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Rifabutin alone (reference; $n=12$), mean ± SD</th>
<th>Etravirine + rifabutin (test; $n=11$), mean ± SD</th>
<th>LSM ratio (90% CI) test versus reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{min}$ (ng/mL)</td>
<td>79 ± 27</td>
<td>59 ± 20</td>
<td>0.76 (0.66 – 0.87)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>500 ± 148</td>
<td>448 ± 141</td>
<td>0.90 (0.78 – 1.03)</td>
</tr>
<tr>
<td>AUC$_{0–24}$ (ng·h/mL)</td>
<td>4815 ± 1374</td>
<td>4012 ± 1123</td>
<td>0.83 (0.75 – 0.94)</td>
</tr>
<tr>
<td><strong>25-O-desacetyl rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{min}$ (ng/mL)</td>
<td>4.07 ± 2.38</td>
<td>3.22 ± 1.88</td>
<td>0.78 (0.70 – 0.87)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>28.7 ± 8.98</td>
<td>24.4 ± 7.55</td>
<td>0.85 (0.72 – 1.00)</td>
</tr>
<tr>
<td>AUC$_{0–24}$ (ng·h/mL)</td>
<td>272 ± 103</td>
<td>230 ± 92.7</td>
<td>0.83 (0.74 – 0.92)</td>
</tr>
</tbody>
</table>
(one case, which was considered unrelated to study medication) and grade 1 pruritus, which was considered probably related to both etravirine and clarithromycin use. No cases of rash were reported in either study. No consistent or clinically relevant changes were observed in laboratory or cardiovascular safety parameters or physical examinations in either study.

**Discussion**

Rifabutin is an inducer of CYP3A12 and, consistent with this, decreased the exposure of etravirine (a CYP3A substrate). Systemic exposure (AUC0–12) of etravirine was reduced by 37% when etravirine was coadministered with rifabutin, which is similar to the 33%–37% decrease in etravirine exposure observed when etravirine is combined with boosted HIV protease inhibitors (e.g. darunavir/ritonavir,18 lopinavir/ritonavir21 and saquinavir/ritonavir).16 The efficacy of etravirine when combined with darunavir/ritonavir, and therefore at reduced pharmacokinetic exposure, has been demonstrated in the Phase 3 DUET trials.22–25

Based on the results of the rifabutin interaction study, in the absence of a boosted protease inhibitor or other drugs that may decrease etravirine exposure, etravirine can be coadministered with rifabutin without any dose adjustment for either drug. However, etravirine is often used in combination with a boosted protease inhibitor, such as darunavir/ritonavir, lopinavir/ritonavir or saquinavir-ritonavir. As these boosted protease inhibitors are known to reduce the mean systemic exposure of etravirine, coadministration of any of these protease inhibitors with etravirine and rifabutin could potentially further lower the mean plasma concentrations of etravirine to subtherapeutic levels. Caution is, therefore, recommended if rifabutin is coadministered with etravirine in the presence of a boosted protease inhibitor; the recommended dose of rifabutin is determined by the prescribing information for the boosted protease inhibitor component of the regimen.

The mean systemic exposures of rifabutin and 25-O-desacetyl rifabutin were lower in the presence of etravirine, most likely as a result of CYP3A induction by both compounds. The 17% decrease in the AUC of rifabutin is not considered to be clinically relevant. Blood concentrations of rifabutin do not necessarily translate to clinical effectiveness and >10-fold differences in rifabutin exposure have been reported. Further, rifabutin is >70% bound to plasma proteins at concentrations <100 ng/mL and this binding does not necessarily reflect distribution of free drug into infected tissues.26 Nevertheless, one study has shown that 6 HIV patients with tuberculosis failure or relapse had a numerically lower rifabutin AUC than

**Table 3. Pharmacokinetics of clarithromycin and 14-OH clarithromycin when coadministered with etravirine in the clarithromycin study**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Clarithromycin alone (reference; n = 12), mean ± SD</th>
<th>Etravirine + clarithromycin (test; n = 11), mean ± SD</th>
<th>LSM ratio (90% CI) test versus reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clarithromycin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>735 ± 363</td>
<td>371 ± 288</td>
<td>0.47 (0.38–0.57)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>3144 ± 917</td>
<td>2088 ± 572</td>
<td>0.66 (0.57–0.77)</td>
</tr>
<tr>
<td>AUC0–12 (ng·h/mL)</td>
<td>20240 ± 6208</td>
<td>12430 ± 6208</td>
<td>0.61 (0.53–0.69)</td>
</tr>
<tr>
<td><strong>14-OH clarithromycin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>382 ± 134</td>
<td>394 ± 109</td>
<td>1.05 (0.90–1.22)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>766 ± 205</td>
<td>1030 ± 318</td>
<td>1.33 (1.13–1.56)</td>
</tr>
<tr>
<td>AUC0–12 (ng·h/mL)</td>
<td>6761 ± 1893</td>
<td>8183 ± 2100</td>
<td>1.21 (1.05–1.39)</td>
</tr>
</tbody>
</table>
Interactions between etravirine and rifabutin or clarithromycin

those (n=96) without failure [3.3 μg·h/mL (IQR 1.95–4.28) versus 2.5 μg·h/mL (IQR 3.97–7.39); P=0.06]. Therefore, etravirine and rifabutin can be coadministered without dose adjustment. However, if etravirine is used in conjunction with a protease inhibitor, alternative agents to rifabutin should be considered, if at all possible.

Systemic exposure to etravirine was increased by 42% in the presence of clarithromycin, most likely due to clarithromycin inhibition of CYP3A. This increase in exposure is not believed to be clinically significant, given the known safety profile of etravirine and the lack of any observed relationship between etravirine pharmacokinetics and safety in clinical trials to date. A post hoc analysis of high etravirine exposure (AUC0–12 >11 000 ng·h/mL, n=43) did not reveal any association with either AE incidence or changes in laboratory parameters. When coadministered with etravirine, clarithromycin exposure was decreased by 39% and its metabolite 14-OH clarithromycin was increased by 21%, probably due to the induction of CYP3A by etravirine. Adjustments to the dose of clarithromycin are unnecessary for the treatment of most bacterial infections, since 14-OH clarithromycin has similar activity to clarithromycin. However, based on the pharmacokinetic results observed here, an alternative antimycobacterial such as azithromycin should replace clarithromycin to treat or prevent MAC in HIV-infected patients who use etravirine. Clarithromycin, but not its 14-OH metabolite, demonstrates significant activity against MAC; therefore, as clarithromycin exposure is reduced upon coadministration with etravirine and that of its 14-OH metabolite is increased, the overall activity of clarithromycin against MAC may be altered when coadministered with etravirine. Azithromycin is not extensively metabolized and it can be used in the presence of protease inhibitors or NNRTIs without concerns for drug interactions.

Short-term coadministration of etravirine with rifabutin or clarithromycin in HIV-negative volunteers was generally well tolerated. The majority of AEs in both studies were mild to moderate in severity. The most common AE was grade 1 chromaturia in the rifabutin study. There were no incidences of chromaturia reported during treatment with etravirine only. In the clarithromycin study, the only notable AE was one case of grade 1 pruritus considered probably related to etravirine and clarithromycin use. There were no new safety concerns in either study.

In summary, these data illustrate that etravirine can be coadministered with rifabutin without adjusting the dose of either drug, provided that the HAART regimen does not include a ritonavir-boosted protease inhibitor. Our findings also demonstrate that coadministration of etravirine and clarithromycin does not require any dose adjustment for either drug. However, it should be noted that guidelines for the treatment or prophylaxis of MAC recommend the use of an alternative antimycobacterial in lieu of clarithromycin as, overall, its activity against this pathogen may be diminished when coadministered with etravirine. It should be noted that recommendations on the concomitant use of etravirine with rifabutin or clarithromycin vary according to local prescribing information and all drugs in a given antiretroviral regimen should be considered before initiating treatment.

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Transparency declarations

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Supplementary data

Figure S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References