Amprenavir and efavirenz pharmacokinetics before and after the addition of nelfinavir, indinavir, ritonavir, or saquinavir in seronegative individuals

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Antimicrobial Agents and Chemotherapy

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Amprenavir and Efavirenz Pharmacokinetics before and after the Addition of Nelfinavir, Indinavir, Ritonavir, or Saquinavir in Seronegative Individuals

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Adult AIDS Clinical Trials Group 5043 examined pharmacokinetic (PK) interactions between amprenavir (APV) and efavirenz (EFV) both by themselves and when nelfinavir (NFV), indinavir (IDV), ritonavir (RTV), or saquinavir (SQV) is added. A PK study was conducted after the administration of single doses of APV (day 0). Subjects (n = 56) received 600 mg of EFV every 24 h (q24h) for 10 days and restarted APV with EFV for days 11 to 13 with a PK study on day 14. A second protease inhibitor (PI) (NFV, 1,250 mg, q12h; IDV, 1,200 mg, q12h; RTV, 100 mg, q12h; or SQV, 1,600 mg, q12h) was added to APV and EFV on day 15, and a PK study was conducted on day 21. Controls continued APV and EFV without a second PI. Among subjects, the APV areas under the curve (AUCs) on days 0, 14, and 21 were compared using the Wilcoxon signed-rank test. Ninety-percent confidence intervals around the geometric mean ratios (GMR) were calculated. APV AUCs were 46% to 61% lower (median percentage of AUC) with EFV (day 14 versus day 0; P values of <0.05). In the NFV, IDV, and RTV groups, day 21 APV AUCs with EFV were higher than AUCs for EFV alone. Ninety-percent confidence intervals around the GMR were 3.5 to 5.3 for NFV (P < 0.001), 2.8 to 4.5 for IDV (P < 0.001), and 7.8 to 11.5 for RTV (P = 0.004). Saquinavir modestly increased the APV AUCs (GMR, 1.0 to 1.4; P = 0.106). Control group AUCs were lower on day 21 compared to those on day 14 (GMR, 0.7 to 1.0; P = 0.042). African-American non-Hispanics had higher day 14 efavirenz AUCs than white non-Hispanics. We conclude that EFV lowered APV AUCs, but nelfinavir, indinavir, or ritonavir compensated for EFV induction.

The clinical use of antiretroviral regimens containing combinations of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI) has become the accepted approach to therapy for human immunodeficiency virus (HIV) infection, especially for patients with multiple prior antiretroviral regimens (1, 29). This has led to the development of new antiretroviral treatments and clinical studies of three- and four-drug combinations as salvage regimens for antiviral-experienced patients. While these combination regimens are often guided by HIV-1 resistance assays, there are often incomplete pharmacokinetic (PK) data available to guide optimal dosing of dual protease inhibitors in an NNRTI-containing regimen.

Due to the complex nature of drug interactions (metabolic induction versus inhibition, efflux transporter interactions) and the desire to understand mechanisms underlying these drug interactions, Adult AIDS Clinical Trials Group (ACTG) protocol A5043 was developed to examine these interactions. At the time A5043 was developed, the routine use of low-dose ritonavir (RTV) was not considered to be the standard of care, and the optimal approach to combining two PIs with efavirenz (EFV) was under investigation in ACTG 398. ACTG 398 utilized NNRTI-PI combinations similar to those of ACTG 5043 along with nucleoside analogs and reported ∼30% antiviral responses in a group of PI-experienced patients (10). Another clinical study was conducted in a small group of patients with HIV-1 infection, examining two dosage regimens of reduced-dose ritonavir in combination with amprenavir (APV), efavirenz, and NRTIs, indicating that efavirenz induction could be offset by ritonavir (6). The pharmacologic objective of ACTG 5043 was to extend these studies and obtain additional data on indinavir (IDV)-, nelfinavir (NFV)-, and saquinavir (SQV)-containing regimens and their dosage requirements when combined with amprenavir and efavirenz in HIV-seronegative subjects. In addition, the inclusion of a control group that did not have a second PI added allowed for comparison against results obtained by continued efavirenz and amprenavir dosing.

The rationale for conducting ACTG 5043 in HIV-seronegative volunteer subjects was that stepwise introduction of a second PI to the combination of amprenavir plus efavirenz could be accomplished without the concern of drug concentrations being less than therapeutic, which might put HIV-in-
fected individuals at risk for the development of drug resistance.

MATERIALS AND METHODS
ACTG 5043 was an open-label, pharmacokinetic study of orally administered amprenavir 600 mg alone, followed by efavirenz 600 mg alone, followed in turn by the combination of amprenavir added to efavirenz, which was then continued with or without the administration of a second PI. The second PI was nelfinavir 1,250 mg every 12 h (q12h) (arm B), indinavir 1,200 mg q12h (arm C), ritonavir 100 mg q12h (arm D), or saquinavir soft gelatin capsules 1,600 mg q12h (arm E). The following pharmacokinetic studies were conducted on three days: a 24-hour study after the first dose of amprenavir, a 12-hour study after the attainment of steady state on efavirenz and amprenavir (day 14), and a 12-hour study after the attainment of steady state on the three-drug regimen (amprenavir plus efavirenz plus a second PI) on day 21. On each study day, intravenous catheters were placed to facilitate blood sampling. Study medications were ingested and blood samples were collected prior to and 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after dosing (and 24 h after dosing on day 0).

Approximately 90 subjects were targeted to be enrolled in order to obtain 70 evaluable subjects with 14 per arm. Inclusion criteria were an age greater than or equal to 18 but less than or equal to 65 years, a body weight within 20 percent of ideal, a body weight of at least 50 kg, and HIV-1 seronegative status. Laboratory parameters were white blood cell counts ≥4,000 and ≤11.7 and ≤12.5 × 10^9/L for men, and ≥100,000 and ≤450,000 platelet/μL. The following parameters also applied: total cholesterol and triglyceride levels, <200 mg/dL; blood urea nitrogen level, <1.25 × ULN; creatinine level, less than ULN or corresponding to a calculated creatinine clearance of ≥80 mL/min; an albumin level within the normal limits for the testing laboratory; amylase level, less than ULN; and, if elevated, a lipase level of less than the ULN and a pancreatic amylase level of less than the ULN. Total bilirubin, aspartate aminotransferase (serum glutamic oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), and alkaline phosphatase levels were <1.25 × ULN. Subjects had the ability and willingness to sign consent forms. Exclusion criteria included the following: reproductive potential (for women); ongoing cardiovascular, renal, hematologic, neurologic, gastrointestinal, pulmonary, psychiatric, endocrine, or immunologic disease or chronic ongoing gastrointestinal condition that might interfere with drug absorption; and any other medical condition which, in the opinion of the investigator, would interfere with the subject's ability to participate in this protocol. Subjects were not enrolled if they received protease inhibitors, NNRTIs, or investigational agents within 60 days prior to study entry or any acute therapy for an infection or other medical illness within 14 days prior to study entry. Healthy HIV-1 seronegative adult subjects who met the eligibility criteria signed a consent form. Subjects received their randomized study drug assignment (arms A through E) at the first pharmacokinetic study visit.

Antiretroviral assays. Efavirenz, nelfinavir, M(8) (a primary metabolite of nelfinavir), amprenavir, indinavir, ritonavir, and saquinavir were measured using liquid chromatography with tandem mass spectrometry in the University at Buffalo ACTG Pharmacology Support Laboratory with a validated assay method (7, 12). The study medications were generally well tolerated; however, concern about the possible occurrence of moderately severe rashes prompted the inclusion of the safety criterion that any subject developing a rash (not clearly attributable to a cause other than a study drug) was to be immediately discontinued from the study.

Predose fasting biochemistry and endocrine evaluations were performed at all three pharmacokinetic study visits and at the final safety visit. These included measurements of insulin, glucose, cholesterol, triglyceride, total cholesterol, and high-density lipoprotein cholesterol. At all three PK visits, glucose and insulin were also measured 2 h after the ingestion of the study medications and the protocol-specified breakfast. The lipid and endocrine data will be the subject of a separate report.

Statistical and pharmacokinetic analysis. Sample size calculations were based on a two-sided paired t test, with the type I error rate set to 5%, assuming a within-subject coefficient of variation (CV) in AUC of 20% for amprenavir. A sample size of 12 eligible subjects per arm provided 80% power to detect a 25% difference in AUCs (e.g., the percent change in the amprenavir AUCs without versus with the coadministration of a second PI). Accrual targets were set to 14 subjects per arm; the additional 2 subjects per arm were a buffer against adherence, sample, or assay problems not detected until after study closure. Only subjects who were able to provide pharmacokinetic data on all three study days were included in the statistical analysis of pharmacokinetic parameters. Throughout most of the study, subjects who discontinued early were replaced; due to slow accrual, however, a compromise between full accrual and provision of timely results was accepted, and accrual was closed before all targets were met. The final counts of subjects eligible for PK analysis on arms A through E were 11, 12, 13, 9, and 10, respectively, yielding detectable changes in APV AUCs ranging from 24% (arm C) to 29% (arm D).

A model-independent method was used to determine pharmacokinetic parameters using standard noncompartmental techniques (WinNonlin) based on individual subject concentration time profiles. In each arm, differences between APV and efavirenz (EFV) AUCs on days 21 and 14 were of primary interest and were evaluated using the nonparametric Wilcoxon signed-rank test. PK interactions were also evaluated using the Food and Drug Administration-recommended method for testing bioequivalence (3, 4). For each agent and pair of study days, the geometric mean of within-subject ratios was calculated along with the associated 90% confidence interval (CI). To compare AUCs across groups of subjects (those who did versus did not experience certain categories of toxicities or belong to certain racial/ethnic groups), the Wilcoxon rank sum and Kruskal-Wallis tests were used. Two-sided P values were considered throughout. As each arm was considered a separate experiment, no adjustments were made for multiple comparisons.

RESULTS

Subjects and tolerance of study medications. Eighty-five individuals were enrolled, of whom 82 received some study drug. Fifty-nine of these completed all three pharmacokinetic assessments; however, due to dosing errors, only 56 were included in pharmacokinetic analyses. Distributions by age, sex, and race were similar for the 56 subjects who were included in the pharmacokinetic analyses and for the 26 who were not. All but one were between 18 and 49 years old, and 54 of 56 were male.

The study medications were generally well tolerated; however, a wide variety of adverse events was reported, including a notable number of central nervous system effects, causing many subjects to be discontinued. Table 1 summarizes the toxicity data. Rash was not a major problem, with only nine subjects (11% of 82 receiving any medication) reporting the onset of rashes, all of which were of grade 1. Four rashes occurred during dosing with EFV alone (before a second dose of amprenavir was given), one occurred on day 5, and three occurred on day 9 or 10. However, median day 0 amprenavir AUCs were not significantly different between subjects with rashes and those without rashes. The remaining five rashes occurred 1 day into APV-plus-EFV dosing (two subjects), 1 day into APV-plus-EFV-plus-IDV dosing (one subject), 10 days into APV-plus-EFV-plus-SQV dosing (one subject), and 3 days after discontinuation of APV plus EFV plus IDV. Median day 14 efavirenz AUCs were significantly different between subjects with rashes and those without rashes (81.3 μg·h/mL).

Subjects who discontinued early were replaced; due to slow accrual, however, a compromise between full accrual and provision of timely results was accepted, and accrual was closed before all targets were met. The final counts of subjects eligible for PK analysis on arms A through E were 11, 12, 13, 9, and 10, respectively, yielding detectable changes in APV AUCs ranging from 24% (arm C) to 29% (arm D).

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h/ml \( n = 4 \); range, 37.7 to 160.6) and 37.5 \( \mu g \cdot h/ml \) \( n = 59 \); range, 20.5 to 169.0, respectively; exact Wilcoxon rank sum \( P \) value = 0.035). Medications in subjects with rash (except for one case of topical irritation attributable to a cause other than a study drug) were promptly discontinued and the rashes resolved. Other side effects were uncommon, with two subjects experiencing clinical chemistry abnormalities. No hematologic abnormalities were observed. Of subjects who took any study drug, 23 of 79 males (29%) and 0 of 3 females (0%) experienced clinical chemistry abnormalities. No hematologic abnormalities were observed. Of subjects who took any study drug, 61 were white non-Hispanic and 16 were African-American non-Hispanic. The remaining five subjects, of whom two were Hispanic and three were Asian/Pacific Islander, were not considered in the following analyses. There was no statistically significant association between race/ethnicity and or discontinued early.

Among the 63 subjects for whom day 14 efavirenz AUCs were available, 12 subjects (19%) experienced no central nervous system (CNS) toxicities, 47 subjects (75%) experienced one or more CNS toxicities of grade 1, and 4 subjects (6%) experienced one or more CNS toxicities with maximums of one or more CNS toxicities of grade 2. Median efavirenz AUCs in these three groups were available, 12 subjects (19%) experienced no central nervous system (CNS) toxicities, 47 subjects (75%) experienced one or more CNS toxicities and/or discontinued early.

**Pharmacokinetics. (i) Amprenavir.** The pharmacokinetics of amprenavir, as illustrated by changes in AUC, are summarized in Tables 2 and 3. Figure 1 provides the median (25th to 75th percentile) amprenavir plasma concentrations on days 14 and 21 for each arm. After 13 days of efavirenz dosing, the median amprenavir AUC decreased an average of 52% across arms, ranging from 46% (arm A) to 61% (arm D). After 20 days of efavirenz coadministration, the median amprenavir AUC decreased 62% relative to that of amprenavir alone (no second PI; day 0). Compared with amprenavir AUCs on day 0, nelfinavir (arm B) led to a 107% median increase, indinavir (arm C) led to a 60% median increase, ritonavir (arm D) led to a 288% increase, and saquinavir (arm E) resulted in no significant change. Amprenavir AUCs were higher on day 21 than on day 0 in 100%, 85%, and 100% of subjects in the nelfinavir, indinavir, and ritonavir arms, respectively. Relative to the amprenavir AUC after 14 days of efavirenz coadministration, the second protease inhibitor was associated with percentage changes in the amprenavir AUCs of −20.04, +315.74, +291.83, +888.40, and +17.56% for no second PI, nelfinavir, indinavir, ritonavir, and saquinavir, respectively. Ninety-percent CI around geometric mean ratios were as follows: 3.5 to 5.3 for nelfinavir \( (P = 0.001) \), 2.8 to 4.5 for indinavir \( (P < 0.001) \), and 7.8 to 11.5 for ritonavir \( (P = 0.004) \). The addition of saquinavir resulted in a change in the amprenavir AUC that was at the margin of statistical significance \( (GMR, 1.0 to 1.4; P = 0.106) \). AUCs in the control group were slightly lower on day 21 than on day 14 (Table 3).

(ii) **Efavirenz.** Ninety-percent CIs around the EFV geometric mean ratios (days 21 and 14) for arms A through E were as follows: 0.78 to 1.05, 0.91 to 1.06, 0.78 to 0.97, 0.82 to 1.08, and 0.80 to 0.97, respectively (Fig. 2).

(iii) **Pharmacokinetics of second PI.** The pharmacokinetics of the second PIs are summarized in Table 4. The median AUCs for nelfinavir, indinavir, ritonavir, and saquinavir were 26.46, 18.79, 3.21, and 2.81 \( \mu g \cdot h/ml \) respectively. Median \( C_{max} \) values were 3.80, 5.95, 0.59, and 0.99 \( \mu g/ml \) respectively. Median \( C_{12} \) values were 0.89, 0.04, 0.09, and 0.04 \( \mu g/ml \) respectively. The ratio of the AUC of M8 to that of nelfinavir is described in Table 4.

**Race/ethnicity relationships.** Among 82 subjects who took any study drug, 61 were white non-Hispanic and 16 were African-American non-Hispanic. The remaining five subjects, of whom two were Hispanic and three were Asian/Pacific Islander, were not considered in the following analyses. There was no statistically significant association between race/ethnicity and day 0 amprenavir AUCs or between racial group and day 14 amprenavir AUCs. However, African-American non-Hispanics had significantly higher day 14 efavirenz AUCs than...
white non-Hispanics: the median efavirenz AUCs were 49.0 and 37.6 μg · h/ml, respectively (exact two-sided Wilcoxon rank sum P value = 0.025), as shown in Fig. 3.

**DISCUSSION**

At the time ACTG 5043 was conducted, the routine use of low-dose ritonavir was uncommon, but the desire to optimize individual protease inhibitor pharmacokinetics was under active investigation. The use of efavirenz combined with PIs was also under investigation in clinical trials for patients failing PI therapy (6, 9, 10). In addition, the need for salvage therapy protocols often preceded the availability of intensive three-way drug interaction studies, and it was common to include pharmacokinetic substudies as means of determining complex interactions. In contrast, conducting pharmacokinetic studies in seronegative subjects may provide an opportunity to examine three-way drug interactions without the potential for the development of resistance. On the other hand, the data from this type of study design may not be directly applicable to HIV-infected patients who have coinfective hepatitis B and/or C due to altered metabolic capacities.

**Safety and tolerability.** Pharmacokinetic studies of antiretroviral agents in HIV-seronegative subjects have merit because short durations and sequential additions of antiretroviral medications can be evaluated without concern for the development of drug-resistant virus in HIV-infected individuals. Further,
the influence of concurrent viral infection on toxicity assessment is eliminated. However, previous studies of amprenavir pharmacokinetics in HIV-seronegative subjects showed frequent rashes, including grade 3 rashes (27). In contrast, other studies in healthy volunteers and clinical studies with amprenavir in HIV-infected patients indicate that the drug is well tolerated when administered for long periods of time, although cutaneous reactions were the most common adverse experiences reported by clinical investigators as possibly due to amprenavir. There was an overall incidence of rash in 19% of subjects enrolled in phase II/III trials (20, 21, 23, 24, 26). We found an overall rash rate of 11% in A5043, and none of the rashes were greater than grade 1. We noted no relationship between rash occurrence and amprenavir plasma concentrations, but we noted higher EFV concentrations in subjects exhibiting rash.

In our study, efavirenz concentrations did not correlate with CNS symptoms, possibly because subjects with more-severe CNS toxicities dropped out before the efavirenz AUCs were obtained on day 14. This conjecture is supported by the fact that efavirenz AUCs were available for 93% (13/14) of those without CNS toxicities, 85% (47/55) of those with CNS toxicities, but we noted higher EFV concentrations in subjects that efavirenz AUCs were available for 93% (13/14) of those without CNS toxicities; 85% (47/55) of those with CNS toxicities; however, with the other three PIs, amprenavir concentrations were increased markedly over those seen with amprenavir alone. Consistent with the elevated levels of amprenavir seen in the A5043 subjects with indinavir and nelfinavir added to their amprenavir and efavirenz, prior pharmacokinetic studies at weeks 2 and 24 noted that intrinsic clearance of amprenavir was reduced by 41% and 54% by nelfinavir and indinavir, respectively (13). In a prior study of dual PIs with efavirenz in salvage regimens (ACTG 398), saquinavir had a minimal effect on amprenavir clearance, similar to the results of the present study. Amprenavir clearance was noted to increase by more than 30% from week 2 to week 24. The mechanism for this long-term change in exposure remains unclear but may be partially due to additional enzyme induction after the antiviral activity of a regimen has been maximized. This may also explain why the APV concentrations were lower on day 21 than on day 14 in the absence of a second PI. We have recently reported a similar finding for the effect of efavirenz on nelfinavir over a 32-week period (25).

In a prior study of salvage regimens containing efavirenz, amprenavir, and a second PI (indinavir, nelfinavir, or saquinavir), a ~30% success rate was reported (10). It is possible that the use of higher initial doses, optimal drug combinations that enhance PI levels, or therapeutic drug monitoring allowing higher doses in some patients would have resulted in improved clinical responses.

The effect of ritonavir in countering efavirenz induction has been previously described (2, 14, 15), and the A5043 data are consistent with these findings. In addition, Wire et al. reported an interaction among fosamprenavir, ritonavir, and efavirenz. Amprenavir exposure was not reduced when efavirenz was added to fosamprenavir (700 mg twice a day [BID]) with ritonavir (100 mg BID). However, amprenavir exposure was reduced when efavirenz was added to fosamprenavir (1,400 mg once a day) with ritonavir (100 mg once a day). Because lower plasma amprenavir trough concentrations are observed with the regimen of one daily dose, these results suggest that plasma ritonavir concentrations must be maintained at levels necessary to counteract the induction effects of efavirenz. Given the rapid and nearly complete conversion of fosamprenavir to am-

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prenavir in vivo and the similarity of metabolic drug interaction data, drug interaction data from amprenavir may be reasonably applied to fosamprenavir (28).

In a prior study (ACTG 398), nelfinavir and indinavir increased plasma amprenavir exposure to similar extents, whereas saquinavir was associated with an increase of marginal significance. The “pharmacokinetic-enhancing” effects of nelfinavir and indinavir on plasma amprenavir exposure (in combination with efavirenz) also appeared to be greater in the present study (~200% versus 300%). Several factors associated with A5043 may account for the apparent greater magnitude of boosting, such as the shorter duration of amprenavir dosing in combination with the second PI (7 days versus 14 days), the lower amprenavir dose (600 mg BID versus 1,200 mg BID), the use of uninfected subjects, and the use of intrasubject comparisons. It is interesting that an increased amprenavir exposure in A5043 was also observed in combination with nelfinavir and indinavir (both in combination with efavirenz) as in a prior report (ACTG 398). With regard to the plasma pharmacokinetic parameters for the second PI in A5043, values appeared to be within the range reported in other studies. Similar to what has been seen in other reports, none of the

FIG. 1. Arm-specific amprenavir concentrations by sample time when amprenavir is coadministered with EFV and with EFV plus a second PI. For each arm separately, median amprenavir concentrations are plotted against (offset) scheduled sample times when subjects had taken APV plus EFV only (day 14) and when subjects had taken APV plus EFV and (on all but arm A) a second protease inhibitor (day 21). Error bars indicate the 25th and 75th percentiles of amprenavir concentrations. So that the day 14 and 21 points can be distinguished, they are offset slightly to the left and right, respectively.
various A5043 study arms appeared to have significant effects on plasma efavirenz exposure; however, efavirenz concentrations were higher in African-Americans. Higher plasma concentrations and increased CNS toxicity from efavirenz have been observed in African-Americans in recent clinical studies (22). These increased concentrations are thought to result from altered efavirenz metabolism. Polymorphisms in CYP 2B6, more common in African-Americans, result in reduced metabolism of efavirenz with consequent higher plasma concentrations (2, 8). This should be considered when EFV is prescribed for African-Americans.

In considering the possible mechanisms that may be underly- ing these three-way interactions, it is likely that efavirenz induces CYP4503A induction in hepatocytes (and possibly intestinal endothelial cells), which accounts for the lower plasma concentrations of amprenavir following coadministration with efavirenz. If this is the case, then the addition of a 3A4 inhibitor would be expected to counter, to some degree, the greater metabolic capacity induced by efavirenz. This was the case for each of the protease inhibitors (except saquinavir) as follows: for indinavir to a lesser extent than for nelfinavir, and for nelfinavir to a lesser extent than for ritonavir. Although nelfinavir and indinavir provide increases in plasma amprenavir exposure, they are not as potent as low-dose ritonavir. However, full doses of these agents would be expected to provide additional virologic activity, whereas low-dose ritonavir does not.

In summary, there still exists some uncertainty as to whether the incidence of amprenavir-associated rash among HIV-sero- negative volunteers is a significant barrier to conducting mechanistic studies. Observations from some studies suggest that prior exposure to ritonavir or lopinavir-ritonavir seems to reduce the occurrence of amprenavir-associated rash (27). A similar finding when investigating delavirdine with ritonavir

![FIG. 2. Efavirenz bioequivalence results for each arm showing the geometric mean of within-subject ratios (EFV AUC with APV + a second PI/EFV AUC with APV only; days 21 and 14) and the associated 90% confidence intervals. Lower and upper dashed lines represent the no-effect boundaries of 80% to 125%. Reference lines for 62.5% and 160.0% are also shown.]

![FIG. 3. Box plot of day 14 efavirenz AUCs in white non-Hispanic and black non-Hispanic subjects. The height of each box represents the interquartile range (the distance between the 25th and the 75th percentiles), the horizontal lines in the box interiors represent the medians, and the vertical lines issuing from the boxes extend to the most extreme data points that are within 1.5 times the interquartile ranges of the boxes. The circles represent points outside these ranges.]

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>CV (%)</th>
<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>NFV</td>
<td>AUC</td>
<td>12</td>
<td>31.13</td>
<td>12.83</td>
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<td>26.46</td>
<td>18.40–65.46</td>
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<td>12</td>
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<td>1.45</td>
<td>33.4</td>
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<td>12</td>
<td>1.11</td>
<td>0.81</td>
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<td>0.89</td>
<td>0.37–3.33</td>
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<tr>
<td>M8</td>
<td>AUC</td>
<td>12</td>
<td>5.72</td>
<td>2.95</td>
<td>51.7</td>
<td>5.86</td>
<td>1.10–11.02</td>
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<tr>
<td>M8:NFV</td>
<td>AUC</td>
<td>12</td>
<td>0.19</td>
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<td>46.7</td>
<td>0.17</td>
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<tr>
<td>IDV</td>
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<td>19.57</td>
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<td>0.05</td>
<td>0.03</td>
<td>55.5</td>
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<td>0.02–0.11</td>
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<tr>
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<td>AUC</td>
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<td>3.22</td>
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<td>3.21</td>
<td>1.46–5.37</td>
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<td>62.8</td>
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<tr>
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<td>1.60</td>
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<td>1.23–7.23</td>
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<tr>
<td></td>
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<td>10</td>
<td>1.01</td>
<td>0.46</td>
<td>45.7</td>
<td>0.99</td>
<td>0.44–2.09</td>
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<td>0.04</td>
<td>0.03</td>
<td>69.2</td>
<td>0.04</td>
<td>0.02–0.12</td>
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* AUCs in µg · h/ml; C<sub>max</sub> and C<sub>12</sub> values in µg/ml.
was observed (25), suggesting that an intermediate metabolite may mediate the hypersensitivity. This remains an important area of clinical investigation, since new interactions with fosamprenavir will require in-depth drug interaction studies, especially in dual-PPI regimens with ritonavir pharmacokinetic enhancement. Conducting this three-way interaction study in seronegative volunteers was a safe and ethical alternative to studying HIV-infected patients and allowed a more robust study methodology to investigate these complex interactions by a crossover (within-subject) design. These data indicate that PI dosing may not be readily predicted from in vitro inhibition data and that clinical pharmacokinetic studies are required when dual PIs are combined with an inducing NNRTI, such as efavirenz.

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