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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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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 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 amprenavir (APV), efavirenz, and NRTIs, indicating that efavirenz induction could be accomplished without the concern of drug concentrations being less than therapeutic, which might put HIV-in-
ected 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 1.25 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 <1.5 times the upper limit of normal (ULN), absolute neutrophil counts >1,500 cells/mm³ and <1.5 ULN, hemoglobin counts >11.7 and <16 g/dl for women and >12.7 and <18 g/dl for men, and >100,000 and <450,000 platelets/mm³. The following parameters also approached normal limits for the testing laboratory: triglyceride levels, <200 mg/dl; blood urea nitrogen level, <1.25 × ULN; creatinine level, less than or equal to the calculated creatinine clearance of >80 ml/min; an albumin level within the normal limits for the testing laboratory; amylase level, less than the 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 partici-pate 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, M8 (a primary metabolite of nelfi-navir), 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 following pharmacokinetic analyses and for the 26 who were not. All but one were between 18 to 49 years old, and 54 of 56 were male. The study medications were generally well tolerated; how-ever, 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 5 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 vs. 45.6 μg·h/ml).
TABLE 1. Proportions of subjects evidencing toxicities among those who had treatment dispensed and those with three evaluable pharmacokinetics studies

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Control arm: APV + EFV</th>
<th>Arm B: APV + EFV + NFV</th>
<th>Arm C: APV + EFV + IDV</th>
<th>Arm D: APV + EFV + RTV</th>
<th>Arm E: APV + EFV + SQV</th>
<th>All arms combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥2 chemistry in: Subjects receiving treatment PK completers</td>
<td>0/16 (0)</td>
<td>1/18 (6)</td>
<td>0/18 (0)</td>
<td>1/15 (7)</td>
<td>0/15 (0)</td>
<td>2/82 (2)</td>
</tr>
<tr>
<td>Grade ≥1 rash in: Subjects receiving treatment PK completers</td>
<td>0/11 (0)</td>
<td>0/12 (0)</td>
<td>0/13 (0)</td>
<td>1/10 (10)</td>
<td>0/10 (0)</td>
<td>1/56 (2)</td>
</tr>
<tr>
<td>Grade ≥2 CNS in: Subjects receiving treatment PK completers</td>
<td>2/16 (13)</td>
<td>1/18 (6)</td>
<td>3/18 (17)</td>
<td>1/15 (7)</td>
<td>2/15 (13)</td>
<td>9/82 (11)</td>
</tr>
<tr>
<td>Grade ≥2 signs/symptoms in: Subjects receiving treatment PK completers</td>
<td>0/11 (0)</td>
<td>2/18 (12)</td>
<td>0/13 (0)</td>
<td>2/10 (20)</td>
<td>0/10 (0)</td>
<td>2/56 (4)</td>
</tr>
</tbody>
</table>

a There were no ≥grade 2 hematologic adverse events.
b One subject experienced a grade 3 CNS toxicity (excessive rage) after a single dose of amprenavir, at which time the site ascertained that the subject had prior depression that would interfere with his study participation. This subject was discontinued from study drug, was followed up for safety on day 25, and is excluded from the analysis presented here.
c Excluding rash and CNS events.

h/ml [n = 4; range, 37.7 to 160.6] and 37.5 µg · 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 toxicities 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 maximum of grade 2. Median efavirenz AUCs in these three groups were 42.6, 37.7, and 36.7 µg · h/ml, respectively. According to the Kruskal-Wallis (three groups) and exact two-sided Wilcoxon rank sum (no versus some toxicity) tests, there were no statistically significant differences in efavirenz AUCs between these groups (P = 0.778 and 0.883, respectively.

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, +888.4, and +17.56% for no second PI, nelfinavir, indinavir, ritonavir, and saquinavir, respectively. Ninety-percent CIs 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 µg · h/ml, respectively. Median Cmax values were 3.80, 5.95, 0.59, and 0.99 µg/ml, respectively. Median C12 values were 0.89, 0.04, 0.09, and 0.04 µg/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-Hisricanes had significantly higher day 14 efavirenz AUCs than Hispanic and white non-Hispanic subjects. Additionally, there was no statistically significant association between race/ethnicity and 14-day day 14.
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 ACTG 5043, 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 with more severe CNS toxicities, possibly because subjects with more-severe CNS symptoms, possibly due to amprenavir (5, 6, 14). Prior studies indicate that induction and inhibition are mediated by cytochrome P4503A4 effects (16–19). Consistent with previous reports, A5043 found that a low dose of ritonavir could overcome the efavirenz induction effects (14). Interestingly, the additions of other PIs had variable effects on the amprenavir AUC in the presence of efavirenz. When saquinavir was the second PI, this increase was not sufficient to compensate for induction by efavirenz; 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-

### Table 3. Comparison of amprenavir AUCs in each arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>Comparison of</th>
<th>Median percent change</th>
<th>90% CI around GMR</th>
<th>Wilcoxon signed-rank P value</th>
<th>Paired t test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Day 14 to day 0</td>
<td>−46.21</td>
<td>0.34, 0.65</td>
<td>0.0020</td>
<td>0.0016</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 14</td>
<td>−20.04</td>
<td>0.69, 0.97</td>
<td>0.0420</td>
<td>0.0690</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 0</td>
<td>−61.75</td>
<td>0.27, 0.53</td>
<td>0.0010</td>
<td>0.0004</td>
</tr>
<tr>
<td>B</td>
<td>Day 14 to day 0</td>
<td>−48.42</td>
<td>0.44, 0.63</td>
<td>0.0005</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 14</td>
<td>315.74</td>
<td>3.52, 5.27</td>
<td>0.0005</td>
<td>≤0.0001</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 0</td>
<td>107.17</td>
<td>1.66, 3.12</td>
<td>0.0005</td>
<td>0.0014</td>
</tr>
<tr>
<td>C</td>
<td>Day 14 to day 0</td>
<td>−53.11</td>
<td>0.35, 0.66</td>
<td>0.0017</td>
<td>0.0034</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 14</td>
<td>291.83</td>
<td>2.83, 4.47</td>
<td>0.0002</td>
<td>≤0.0001</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 0</td>
<td>59.65</td>
<td>1.24, 2.36</td>
<td>0.0017</td>
<td>0.0037</td>
</tr>
<tr>
<td>D</td>
<td>Day 14 to day 0</td>
<td>−61.34</td>
<td>0.31, 0.50</td>
<td>0.0039</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 14</td>
<td>888.40</td>
<td>7.83, 11.47</td>
<td>0.0039</td>
<td>≤0.0001</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 0</td>
<td>287.78</td>
<td>2.73, 5.07</td>
<td>0.0039</td>
<td>0.0001</td>
</tr>
<tr>
<td>E</td>
<td>Day 14 to day 0</td>
<td>−51.05</td>
<td>0.32, 0.71</td>
<td>0.0059</td>
<td>0.0059</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 14</td>
<td>17.56</td>
<td>1.00, 1.45</td>
<td>0.1055</td>
<td>0.1509</td>
</tr>
<tr>
<td></td>
<td>Day 21 to day 0</td>
<td>−42.09</td>
<td>0.37, 0.89</td>
<td>0.0645</td>
<td>0.0540</td>
</tr>
</tbody>
</table>
amprenavir 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 CYP2B6, 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 underlying 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-seronegative 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.
was observed (25), suggesting that an intermediate metabolite may mediate the hypersensitivity. This remains an important area of clinical investigation, since new interactions with fos-amprenavir will require in-depth drug interaction studies, especially in dual-PI 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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