

Three-way Pharmacokinetic Interaction Among Amprenavir, Efavirenz and a Second Protease Inhibitor

GD Morse, Pharm.D., S Rosenkranz, Ph.D., MF Para, M.D., E Adams, M.D., KE Yarasheski, M.D., RC Reichman, M.D. and the AACTG 5043 Protocol Team

University at Buffalo, SUNY; Harvard University, Boston MA; Ohio State University, Columbus, Ohio; Division of AIDS, Bethesda, MD; Washington University, St Louis, MO; University of Rochester, Rochester, NY; Adult AIDS Clinical Trials Group (ACTG); NIAID, National Institutes of Health, Bethesda, MD.

ABSTRACT

Background: Drug interaction studies of HIV-1 protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) are often based on predictions from pre-clinical cytochrome P450 inhibition studies. ACTG protocol 5043 was conducted to examine the two-way pharmacokinetic interactions among amprenavir and efavirenz, and the three-way interaction among amprenavir, efavirenz and a second PI (ritonavir (RTV), indinavir (IDV), nelfinavir (NFV) or saquinavir (SQV)) based on anticipated mild inhibitive and inhibitory effects.

Methods: Healthy subjects (n=85) were enrolled of which 59 completed three pharmacokinetic study days. An amprenavir PK study was conducted after a single dose of APV (Day 0). Subjects then received only EFV 600 mg q24h or 12h, then retained APV with EFV for days 11-13 with APV PK study on day 14. A second PI (NFV 1250 mg q12h, IDV 1200 mg q12h, RTV 100 mg q12h or SQV 600 mg q12h) was added to APV and EFV on day 14 with a repeat PK on day 21. A control group continued APV and EFV without a second PI. APV AUCs were compared, within-subject, between days 11 (with EFV and second PI) and 14 (with EFV only) using the nonparametric signed rank test. Ninety-percent confidence intervals (CI) around the geometric mean ratios (GMR; Day 21:Day 14) were calculated.

Results: In the five arms, APV AUCs were 38% to 55% lower (median percent change in AUC) with the addition of EFV (Day 14 compared to Day 0, all *p*-values < 0.05). In the groups receiving NFV, IDV and RTV, APV AUCs with EFV+PI were significantly higher than those with EFV alone. 90% CI around GMR were: 3.7 to 5.2 for NFV (*p*=0.0001), 3.0 to 5.1 for IDV (*p*=0.0001) and 8.3 to 9.3 for RTV (*p*=0.0020). The addition of SQV resulted in modest increases in AUC. GMRs = 1.10 to 1.5 (*p*=0.0273). AUCs in the control group did not differ significantly from Day 14 to 21.

Conclusions: These observations indicate that EFV induces lower AUC. The addition of NFV, IDV or RTV countered this induction and increased APV AUCs significantly after one week of triple drug administration. The addition of SQV resulted in a modestly increased AUC. Interestingly, NFV and IDV increased the APV AUC in the presence of EFV in a manner not predicted from prior in vitro and two-way clinical interaction studies. Additional EFV PK analyses are underway.

OBJECTIVES

Primary:
To compare the PK of APV when taken under six conditions: (1) alone, (2) with EFV, (3) with EFV plus NFV, (4) with EFV plus IDV, (5) with EFV plus RTV, and (6) with EFV plus SQV.

To compare the PK of EFV when taken under five conditions: (1) with APV, (2) with APV plus NFV, (3) with APV plus IDV, (4) with APV plus RTV, and (5) with APV plus SQV(s).

Secondary:
To examine the safety and tolerance of APV combined with EFV before and after the addition of a second PI (NFV, IDV, RTV, or SQV(s)).
To examine the effects of APV combined with EFV and the effects of APV combined with EFV plus a second PI (NFV, IDV, RTV, or SQV(s)) on blood glucose and lipid measurements.

To estimate the PK parameters of NFV, IDV, RTV, and SQV(s) when co-administered with EFV and APV.

BACKGROUND & RATIONALE

- The clinical use of antiretroviral regimens containing various combinations of NRTIs, NNRTIs, and PIs has been the accepted approach to therapy for HIV infection, especially for patients with previous antiretroviral therapy. This has led to the design of more potent antiretroviral compounds, requiring clinical studies of new 3- and 4-drug combinations, and the evolution of "salvage regimens" for PI-resistant patients.
- Earlier Adult AIDS Clinical Trials Group (ACTG) trials utilized a study design to address the issue of virologic failure in patients previously treated with a PI-containing regimen by comparing multiple arms with different combinations. This approach utilized antiviral regimens that included dual NRTIs, dual PIs (one of which was APV) and EFV (NNRTI). While these combinations were logical with respect to viral genotypes expected in the patients with limited failures, there were limitations: pharmacokinetic data available to guide the design selection of APV in combination with EFV and a second PI (IDV, SQV, NFV, or RTV). This comparing protocol regimens is often combined with a substudy approach to obtaining pharmacokinetic data during multiple drug administration.
- Due to the complex nature of these interactions (hepatic induction versus inhibition) and the need to understand mechanisms underlying these drug interactions, an alternative study design was developed for A5043 to enroll a population of HIV-seronegative individuals in whom 3-way drug interactions would be examined.
- A trial of similar design to A5043, but in HIV-infected subjects, has been conducted by the intramural program at NIH. In this study of a small group of patients with HIV-1 infection, two drug regimens of RTV were examined in combination with APV, EFV, and NNRTIs. A5043 was designed to complement the intramural study. We obtain additional data on EFV and SQV-containing regimens and their dosage requirements as well as with RTV 100 mg q12h and NFV 1250 mg q12h combined with APV and EFV.
- The rationale for conducting A5043 in HIV-seronegative volunteers is that the seropositive individual of a second PI in the combination of APV plus EFV would be accomplished in HIV-infected individuals and would put them at risk for the development of HIV drug resistance. In addition, the use of a control arm for the combination of APV plus EFV will enhance the interpretation of the PK data obtained. Two-way regimens would not be used in HIV-infected subjects.

METHODS

Design:
An open-label, pharmacokinetic (PK) trial of orally administered amprenavir (APV) alone, followed by APV plus efavirenz (EFV), which were then continued with or without the administration of a second protease inhibitor (PI).

Sample Size:
Approximately 90 subjects were targeted to be enrolled in order to obtain 10 evaluable subjects per treatment arm.

Population:
Healthy HIV-1 seronegative subjects ≥ 18 and < 65 years of age who will not be eligible for other research.

Regimen:
Subjects received their randomized study drug assignment (Arms A through E) at the first PK visit.

PK Studies were done at three time points: after the single dose of APV (Day 0), after reaching steady-state for both EFV and APV, and after reaching steady-state for the three-drug (APV + EFV + second PI) regimen.

Arm	Dose and Regimen
A	APV 600 mg q12h + EFV 600 mg q24h
B	APV 600 mg q12h + EFV 600 mg q24h + NFV 1250 mg q12h
C	APV 600 mg q12h + EFV 600 mg q24h + IDV 1200 mg q12h
D	APV 600 mg q12h + EFV 600 mg q24h + RTV 100 mg q12h
E	APV 600 mg q12h + EFV 600 mg q24h + SQV(s) 600 mg q12h

Schedule	
First PK Visit (day 0)	Subjects took EFV 600 mg q24h at bedtime
Days 1-7	Subjects continued EFV 600 mg q24h, but switched to morning dosing until the end of the study
Days 11-13	Subjects added APV 600 mg q12h to the EFV 600 mg q24h
Second PK Visit	3 or more days after taking the APV + EFV regimen
Third PK Visit	2 or more days after beginning the second PI

INCLUSION CRITERIA

- Age ≥ 18 to < 65 years.
- Within 10 percent (*v/v*) of ideal body weight and weight at least 50 kg.
- HIV-1 seronegative.
- The following laboratory parameters: WBC > 4000 cells/cu mm; Hb > 10.5 g/dL; serum total bilirubin (total, AUC) < 1.50 mg/dL; and < 1.5 U/L; HbA1c > 117 and < 16 mg/dL for men, > 100.00 and < 65.00 mg/dL for women.
- Fasting total cholesterol and triglycerides, blood urea nitrogen (BUN), creatinine, albumin, and serum amylase (WHL). Fasting total cholesterol and triglycerides < 200 mg/dL. BUN < 12.8 U/L, Creatinine < 1.5 U/L or Creatinine clearance > 30 mL/min, albumin within the normal limits for the testing laboratory. Amylase < 1000 U/L or gamma-glutamyl transferase < 100 U/L. Serum amylase tests: total bilirubin, AST, SGPT, ALP, (SGPT), and alkaline phosphatase (WNL). LFTs must be < 1.25 U/L.
- Ability and willingness to give informed consent.

EXCLUSION CRITERIA

- Women of reproductive potential.
- Ongoing cardiovascular, renal, hematologic, gastrointestinal, pulmonary, psychiatric, diabetes, cardiac, or immunodeficiency disease, but not limited to, including, asymptomatic coronary artery disease, dyslipidemia, or other conditions that may affect the study.
- Chronic, ongoing, gastrointestinal condition that might interfere with drug absorption. Any other medical condition which, in the opinion of the investigator, would interfere with the subject's ability to participate in this protocol.
- Receipt of PI, NNRTI, or investigational agents within 60 days prior to study entry.
- Receipt of acute therapy for an infection or other medical illness within 14 days prior to study entry.

ENDPOINTS

Primary Endpoints
The AUCs of APV and EFV are the primary PK endpoints. Other PK parameters may be examined such as C_{max} and C_{trough} .

Risk Monitoring
Adverse reactions were monitored with a severity of Grade 1 or above, as defined by the DAIDS Toxicity Tables, which cannot be directly attributed to another cause besides study treatment after consultations involving the protocol team. For each regimen within each treatment arm, the number of Grade ≥ 1 rashes and the number of Grade 2 reactions of other kinds was counted, as well as the proportion of subjects experiencing such reactions.

Metabolic Testing
Pre-dose fasting metabolic evaluations will be made at all three PK visits, and fasting metabolic evaluations will be made at the final study visit. The metabolic measures are glucose, insulin, C-peptide, triglycerides, total cholesterol, and HDL-cholesterol. At all three PK visits, glucose and insulin will also be measured 2 hours after ingestion of study drug and the protocol-specified breakfast.

SAMPLE SIZE AND ACCRUAL

Sample size calculations were based on a two-sided paired *t*-test, with the type I error rate set to 5 percent and the power set to 80 percent. A sample size of 12 per arm was calculated using the minimum detectable percent difference in AUC (i.e., percent change in mean APV AUC without versus with co-administration of a second PI) for the various within-subject comparisons of variation (CV) in AUC.

PHARMACOKINETIC & STATISTICAL ANALYSIS

- A model-independent method was used to determine PK using standard noncompartmental techniques (WinNonlin®) based on individual subject concentration-time profiles.
- Statistical analysis of APV AUCs employed repeated-measures ANOVA. The differences between the day 14 and day 21 AUCs on each arm were of primary interest. The robustness of conclusions to distributional assumptions were evaluated using the nonparametric Wilcoxon signed rank test. Statistical analysis of EFV used the paired *t*-test to compare the second and third PK EFV AUCs (without versus with second PI). Its robustness was evaluated using the Wilcoxon nonparametric analogue.

RESULTS

Table 1. Enrollment and Demographics

	Treatment Arm					
	All Arms	A	B	C	D	E
Median	21	18	20	19	20	21
Age at Baseline (yr)						
18 to 24	14 (26%)	2 (10%)	7 (35%)	3 (16%)	3 (15%)	4 (20%)
25 to 30	14 (26%)	2 (10%)	6 (30%)	2 (10%)	2 (10%)	2 (10%)
31 to 35	10 (19%)	3 (15%)	1 (5%)	3 (15%)	3 (15%)	2 (10%)
36 to 40	2 (4%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gender						
Female	7 (13%)	1 (5%)	1 (5%)	1 (5%)	1 (5%)	2 (10%)
Male	45 (76%)	9 (45%)	11 (55%)	9 (45%)	7 (35%)	7 (35%)
Race/Ethnicity						
Black	16 (30%)	2 (10%)	3 (15%)	4 (20%)	3 (15%)	2 (10%)
Hispanic/Latino	1 (2%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Asian	1 (2%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Other	28 (53%)	5 (25%)	7 (35%)	3 (15%)	3 (15%)	3 (15%)
Sex (by race)						
Female	7 (13%)	1 (5%)	1 (5%)	1 (5%)	1 (5%)	2 (10%)
Male	45 (76%)	9 (45%)	11 (55%)	10 (50%)	7 (35%)	7 (35%)

Table 2. Toxicity and Rash Occurrence

	Treatment Arm					
	Total n=59	APV-EFV n=11	APV-EFV-NFV n=14	APV-EFV-IDV n=14	APV-EFV-RTV n=10	APV-EFV-SQV n=10
Any Rash (Grade ≥ 1)	11 (19%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)
Severe Rash (Grade ≥ 2)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache (Grade ≥ 2)	15 (26%)	1 (5%)	1 (5%)	1 (5%)	2 (20%)	1 (10%)
Stomach Symptoms/evaluating rash (Grade ≥ 2)	15 (26%)	1 (5%)	1 (5%)	1 (5%)	3 (30%)	0 (0%)
Rash (Grade ≥ 1)	15 (26%)	1 (5%)	0 (0%)	2 (14%)	0 (0%)	0 (0%)
No Rash (Grade ≥ 1)	44 (74%)	11 (100%)	14 (100%)	12 (86%)	10 (100%)	10 (100%)

Table 3. Amprenavir GMR of AUCs for Day 14 and Day 21

Treatment Arm	Median percent change Day 14 to Day 21 (Day 21:Day 14)	90% CI ¹ (around the GMR) ²	Wilcoxon signed rank p-value
A (no 2 nd PI)	-21.99	(-6.64 to 69.4)	0.0771*
B (2 nd PI = NFV)	352.76	(1.566 to 118)	0.0001*
C (2 nd PI = IDV)	272.109	(2.298 to 14.81)	0.0001*
D (2 nd PI = RTV)	1,067.53	(8.47 to 14.56)	0.0020*
E (2 nd PI = SQV)	19.92	(1.06 to 1.44)	0.0771*

¹CI = confidence interval
²GMR = geometric mean ratio; \log_2 (APV AUC_{Day 21}/APV AUC_{Day 14})

Fig 1. Amprenavir Pharmacokinetics: Median (25-75 Interguarile Range) Day 14 vs 21

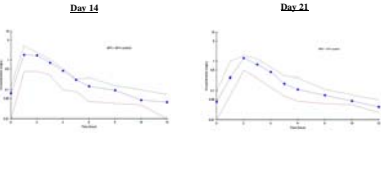
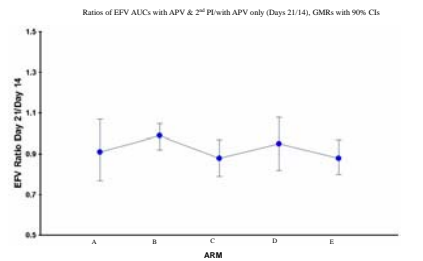


Figure 2. Efavirenz Pharmacokinetics



SUMMARY

- Rash did not seem to be as much of a problem in this seronegative volunteer pharmacokinetics study as in some prior seropositive studies.
- Amprenavir clearance was increased during the 10-day period of combined efavirenz administration.
- The impact of adding a second PI had variable effects on amprenavir disposition:
 - Indicated increased Amprenavir AUC
 - Ritonavir increased Amprenavir AUC
 - Indicated increased Amprenavir AUC
 - Saquinavir had minimal effect on Amprenavir AUC.
- The addition of a second PI had minimal effect on EFV disposition.

Metabolic tests, EFV and PI PK pharmacokinetic analysis and toxicity analysis are ongoing.

CONCLUSIONS

- Conducting seronegative pharmacokinetic studies provides the opportunity to examine three-way drug interactions that would be difficult to examine in HIV-infected patients.
- The addition of amprenavir and indinavir to an amprenavir and efavirenz containing regimen increased amprenavir AUCs and could be considered as alternatives to ritonavir in patients with ritonavir intolerance.
- The positive effect of adding nelfinavir, and the minimal effect of saquinavir, suggest that the mechanisms of these three-way interactions are complex and likely include contributions from both efflux transporter and biotransformation.

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