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The Pharmacokinetics and Pharmacogenomics of Efavirenz and Lopinavir/Ritonavir in HIV-Infected Persons Requiring Hemodialysis

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Abstract

Objective—To evaluate the pharmacokinetics and pharmacogenomics of efavirenz (EFV) and lopinavir/ritonavir (LPV/RTV) in HIV-infected persons requiring hemodialysis.

Design—Prospective, observational study of HIV-infected hemodialysis subjects receiving one 600mg tablet daily of EFV (N=13) or three 133.3/33.3mg capsules twice daily of LPV/RTV (N=13).

Methods—24-hour EFV and 12-hour LPV/RTV pharmacokinetics were assessed. Geometric mean ratios were calculated using historical controls with normal renal function. The effects of several candidate gene polymorphisms were also explored.

Results—The geometric mean (95% CI, %CV) C_{min}, C_{max}, and AUC for the EFV group were 1.81μg/mL (0.93, 3.53; 103%), 5.04μg/mL (3.48, 7.29; 72%), and 71.5μg·h/mL (43.2, 118.3; 93%), respectively. These parameters were 2.76μg/mL (1.86, 4.11; 53%), 8.45μg/mL (6.41, 11.15; 52%), and 69.6μg·h/mL (55.6, 87.2; 37%) for LPV and 0.08μg/mL (0.05, 0.14; 63%), 0.58μg/mL (0.44, 0.76; 41%), and 3.74μg·h/mL (2.91, 4.80; 37%) for RTV. The AUC geometric mean ratios (90% CI) for EFV, LPV, and RTV were 132% (89, 197), 81% (67, 97), and 92% (76, 111), respectively. LPV C_{min} was lower than expected in the hemodialysis group. Higher EFV concentrations were associated with the CYP2B6 516G>T polymorphism.

Conclusions—The pharmacokinetics of EFV and LPV/RTV in hemodialysis suggest that no dosing adjustments are necessary in treatment-naïve patients. As HIV-infected hemodialysis patients are disproportionately black, the increased frequency of the CYP2B6 516G>T polymorphism may lead to higher EFV levels. The potentially lower LPV trough levels in this population suggest that LPV/RTV should be used with caution in protease inhibitor-experienced patients.

Keywords

Pharmacokinetics; Pharmacogenomics; Renal Failure; Dialysis; HIV; Efavirenz; Lopinavir; Ritonavir

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INTRODUCTION

It has been assumed that non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) classes of antiretrovirals do not require dose adjustments in patients with ESRD due to insignificant renal elimination [1]. However, the dispositions of several other medications which primarily undergo hepatic metabolism are affected by renal impairment [2–7] as a result of reduced hepatic or intestinal metabolism, reduced hepatic uptake, or reduced plasma protein binding during renal failure [5–7].

Therefore, we evaluated the steady-state pharmacokinetics of the NNRTI efavirenz (EFV) and the PI lopinavir/ritonavir (LPV/RTV), in HIV-infected patients requiring hemodialysis. We then compared these PK profiles to HIV-infected historical controls without renal insufficiency. We did not find that the levels of these drugs were substantially altered by ESRD. However, there was an unexpectedly high variability in EFV PK parameters and the trough levels for LPV were somewhat lower than those found in patients without ESRD. We then explored the possible impact of several polymorphisms in genes encoding proteins potentially involved in the disposition of these drugs to explain these findings.

METHODS

Study Participants

HIV-infected persons requiring hemodialysis and between the ages of 18 and 65 were enrolled into this observational study if they had received as part of their antiretroviral regimen either a single 600mg tablet of EFV daily or three 133.3/33.3mg capsules of LPV/RTV twice daily for at least 30 days immediately prior to entry and if the following laboratory criteria were met: alanine aminotransferase and aspartate aminotransferase levels $\leq 5 \times$ upper limit of normal (ULN), total bilirubin $\leq 1.5 \times$ ULN, hemoglobin ≥ 8.0 g/dL, and serum lipase $\leq 3.0 \times$ ULN. Participants were not enrolled if they had a serious illness, besides ESRD, requiring systemic treatment and/or hospitalization within 30 days prior to entry; if they had known liver cirrhosis; if they had a Division of AIDS Toxicity Grade [http://rcc.tech-res.com/tox_tables.htm] ≥ 2 nausea, vomiting, diarrhea, or abdominal pain within 7 days prior to entry; if they had significant change in tobacco use within 6 weeks prior to study entry (which may acutely alter CYP450 enzyme regulation); or if they had used any medications or herbal products known to induce or inhibit CYP 450 enzymes, cancer chemotherapeutic agents, investigational agents, systemic steroids ≥ 100 mg/day of prednisone, or an NNRTI or PI besides EFV or LPV/RTV or a combination of these two within 30 days of entry. Women of reproductive potential were enrolled only if a serum pregnancy test obtained on the study day was negative.

Study Design

The objectives of this study were met by conducting a prospective, multicenter, observational pharmacokinetic study. Participants in the EFV arm and LPV/RTV arms underwent 24-hour and 12-hour PK evaluations, respectively, in the General Clinical Research Centers of their home institutions. The acute effects of dialysis on PK and drug clearance were not studied as we had presumed that dialysis clearance would be too small to measure, even if the extremely high protein-binding of these drugs were altered. This protocol was approved by the local institutional review boards of the participating institutions. Written, informed consent was provided by all participants.

Participants recorded the timings of their antiretroviral intake for three days prior to study entry; if doses were missed or not taken approximately 24 hours (EFV arm) or 12 hours (LPV/RTV arm) prior to the scheduled observed dosing time on the study visit day, the study visit was

rescheduled. Standardized moderate-fat meals, comparable to those used in the control studies, were provided for all participants during their study visits.

To better mimic typical clinical practice, observed doses of EFV were administered in the evening at 7pm and at least 4 hours after dialysis completion with blood samples taken at -0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the observed dose. Observed doses of LPV/RTV were given at 8am and blood samples taken at -0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours. A blood sample was obtained for measurement of unbound lopinavir at the 2 hour time point. Hematologies, chemistries, CD4 cell counts, and HIV-1 RNA levels were also obtained at the study visit. Hepatitis B and C serologies were abstracted from the participants' records, if these were obtained within six months of enrollment, or were obtained at screening; active hepatitis B was defined as having a positive surface antigen and hepatitis C as having a positive antibody. Symptoms and signs, including rash, gastrointestinal symptoms (nausea, vomiting, diarrhea), and central nervous system disturbances (sleep disturbances, confusion, difficulty concentrating), that occurred within 30 days prior to entry were also graded and recorded.

Because the PK analyses suggested high EFV PK variability and lower than expected concentrations of LPV, we performed post-hoc pharmacogenomic analyses to explore potential host-related factors that would explain these findings. DNA samples were obtained from participants who were co-enrolled in ACTG A5128. This protocol archives genetic samples of consenting enrollees across various ACTG studies. Four single nucleotide polymorphisms, chosen for their potential effects on NNRTI and PI metabolism, were assessed for each drug. These polymorphisms were at positions CYP2B6 516, CYP3A5 6986, MDR1 2677, and MDR1 3435 [8–11].

Laboratory Analyses

Drug plasma concentrations were measured at the University of California at San Francisco (LPV and RTV) and the University of North Carolina (EFV) ACTG Pharmacology Support Laboratories. These laboratories participated in the ACTG Pharmacology Laboratory Proficiency Testing Program for antiretroviral drug quantitation. EFV concentrations were measured using ultraviolet high performance liquid chromatography in a Diode array with a lower limit of quantification of 25ng/mL. LPV and RTV concentrations were measured using liquid chromatography-tandem-mass spectrometry with lower limits of detection of 50ng/mL and 25ng/mL, respectively. Measurement of unbound drug concentration was performed using equilibrium dialysis at 37°C using a semi-permeable membrane; high (CV 6.47%, SD 0.0323) and low (CV 8.73%, SD 0.0896) concentration control samples were analyzed with each run.

DNA was isolated from whole blood, obtained under ACTG protocol A5128 (PUREGENE® (Gentra Systems Inc., Minneapolis, MN) [12]. Genetic polymorphisms were identified by real-time PCR (ABI PRISM® 7900HT Sequence Detection System, Applied Biosystems Inc., Foster City, CA) using 5' nuclease allelic discrimination *Taqman* assays at the Vanderbilt Center for Human Genetics Research (Nashville, TN). Genotypic data were analyzed using ABI Sequence Detection System version 2.1.2 software and confirmed by visual inspection of the plots. Assay results were confirmed in replicate on a separate plate. The assays used to genotype *CYP2B6* 516G>T (rs3745274), *ABCB1* 3435C>T (rs1045642) and *CYP3A5* 6986A>G (rs776746) were Applied Biosystems C_7817765_60, C_7586657_1, and C_26201809_30, respectively. For *ABCB1* 2677G>T/A (rs2032582), custom primer and probe sequences were used. Forward and reverse primer sequences were GGACAAGCACTGAAAGATAAGAAAGA and GTAGGGAGTAACAAAATAACACTGATTAGAA, respectively. Probe sequences were VICCTAGAAGGTGCTGGGAAMGBNFQ, 6FAMCTAGAAGGTTCTGGGAAGMGBNFQ, and

NEDCTAGAAGGTACTGGGAAGMGBNFQ for G, T, and A alleles, respectively. The PCR conditions for all assays involved 10 minutes at 95°C, then 50 cycles (15 seconds at 92°C, 1 minute at 60°C). No other genes or polymorphisms were analyzed.

Statistical Analyses

Area under the plasma concentration versus time curves (AUCs) were calculated using the linear trapezoidal rule over the steady-state dosing interval [13]. Cmin and Cmax were defined as the minimum and maximum observed plasma concentrations, respectively. Tmax was time at which the Cmax was observed. Clearance was calculated as dose divided by AUC, and elimination rate constant as the subject-specific slope of the log-linear terminal decline in the plasma concentration versus time relationship (chosen by visual inspection). Half-life was calculated as 0.693 divided by the elimination rate constant.

Assuming a log-normal distribution of PK parameters, summary statistics were calculated on the natural log scale, then converted back to the original scale (geometric mean, associated 95% CI and CV). For assessment of bioequivalence, geometric mean ratios of PK parameters (study subjects relative to historical controls) and associated 90% CIs were calculated, using a method developed for the current case where, for the EFV historical control group, only summary data on the raw scale is available. These 90% CIs were compared to no-effect boundaries (NEBs) of 80%–125%, 67%–150%, and 50%–200%. Bioequivalence was said to be demonstrated if the 90% confidence interval (CI) around the geometric mean ratio (GMR) lay entirely within pre-specified no-effect boundaries (NEBs). When the CI lies entirely below or above the NEB, inequivalence is demonstrated. When the CI straddles one or both NEB, the result is considered inconclusive [14]. The FDA NEB standard of 80%–125% is based on the assumption that the groups being compared would be identical except for the variable of interest. In our study, the primary variable of interest was the presence or absence of end stage renal disease requiring hemodialysis. However, we recognized that the hemodialysis study group would likely differ from the historical controls for race, sex, age, and PK study methodologies. Because we considered any potential recommendation for dose adjustment based on the relatively narrow NEB of 80%–125% too strict given these likely group differences, we chose *a priori* the wider NEB of 50%–200% for AUC on which to base dose adjustment recommendations.

Two-sided exact nonparametric tests with type I error rate set to 5% were used to compare PK parameters between genotypes (more than 2 groups, Kruskal-Wallis) and between presence/absence of Hepatitis B surface antigen, Hepatitis C antibody, and signs/symptoms (2 groups, Wilcoxon rank sum). Associations between PK and laboratory parameters (plasma HIV-1 RNA, CD4+ T-cell count and liver function tests) were assessed using Spearman correlation coefficients and associated p-values.

RESULTS

The baseline characteristics of the 26 participants enrolled in this study (13 in each arm) are presented in Table 1. The study subjects were predominantly Black men. Dialysis experience ranged from 1 to 25 years. Overall, 76% had CD4 cell counts $\geq 200/\mu\text{L}$ and 46% had HIV-1 RNA levels ≤ 50 copies/mL. 58% were active smokers. The plasma concentration versus time profiles for each of the three study drugs are shown in Figure 1. The summary PK data and comparisons with historical controls for each drug are listed in Table 2.

Efavirenz (EFV)

The GMR for EFV AUC is 132% and the associated 90% CI ranges from 89% to 197% (Figure 2). Bioequivalence would only be declared using NEBs of 50%–200%. The wide CI in the

present study reflects the highly variable EFV AUCs in A5177 subjects with hemodialysis. The coefficient of variation (CV) in the present study was 93% whereas it was 40% in the controls. Similar to AUC, the point estimate for C_{min} is about 18% higher in subjects requiring dialysis. For C_{min}, even using NEBs of 50%–200%, the bioequivalence procedure is inconclusive.

DNA was analyzed from 11 of 13 subjects who provided consent (all were Black, non-Hispanics). As shown in Table 3, for CYP2B6 516, the median EFV C_{min}, C_{max}, and AUC were significantly greater for those with the GT and TT genotypes compared to the GG genotype (all $P < 0.05$). The elimination half-lives for EFV was also significantly greater ($P = 0.009$), whereas EFV clearances were significantly lower ($P = 0.04$), with the GT and TT genotypes compared to the GG genotype. No statistically significant differences in EFV PK were noted for polymorphisms in MDR1 2677, MDR1 3435, and CYP3A5 6986.

Lopinavir (LPV)

The GMR for LPV AUC is 81%, and the associated 90% CI ranges from 67% to 97% (Figure 2). This 90% CI for LPV would be considered bioequivalent for NEBs of 67%–150% and wider. However, the LPV 90% CI excludes 100%, suggesting that the systemic exposure in the subjects requiring hemodialysis is somewhat lower than those without renal insufficiency. The results for LPV C_{max} are similar to those for LPV AUC. However, C_{min} was lower and inequivalent using the standard NEB of 80%–125% compared to the historical controls.

In the hemodialysis-requiring subjects in this study, the mean percent free LPV was 0.89% and ranged from 0.42 to 1.86%. These results are similar to those obtained in those without chronic kidney disease measured using equilibrium dialysis [(n=20; mean (SD), 1.32% (0.44%)] [15].

Ten subjects in the LPV/RTV arm provided consent for provision of DNA samples. Of the four polymorphisms assessed, the only statistically significant difference found was for C_{min} due to the CYP3A5 6986 polymorphism (Table 3). The median C_{min} for genotype AA, AG, and GG were 4.07, 1.49, and 0.86 µg/mL, respectively ($P = 0.048$). Similarly significant associations were found between free LPV C_{min} concentrations and these polymorphisms at position 6986 of the CYP3A5 gene. However, there were no significant associations between these SNPs and percent free LPV. In addition, no associations were found with these polymorphisms and LPV C_{max} or AUC.

Ritonavir (RTV)

Bioequivalence was shown for RTV AUC using NEBs of 67%–150% and wider (Figure 2). Similar results held for C_{max}. The bioequivalence procedure for RTV C_{min} was inconclusive at any NEB, although evidence pointed to it being lower in hemodialysis. As shown in Table 3, no significant associations were found between RTV PK parameters and the four genetic polymorphisms assessed in this study.

Associations with viral hepatitis, HIV-1 RNA, CD4 cell count, and toxicities

No significant associations were found between the PK for each of the three drugs and the presence of either hepatitis B surface Ag or hepatitis C Ab. There were no significant relationships between PK and HIV-1 RNA level, CD4 cell count, graded symptoms or signs, or laboratory parameters typically associated with EFV, LPV, or RTV. The only exception was for RTV AUC and AST levels for which there was a significant positive correlation ($r = 0.72$; $p = 0.01$).

DISCUSSION

Previous evaluations of the pharmacokinetics of EFV and LPV/RTV in hemodialysis have relied on single case studies or small series. For instance, Izzedine et al. suggested that EFV dosing may need to be increased in the hemodialysis population as the drug levels in a single subject were lower than those reported for normal subjects [16]. However, the HIV-1 viral load was <200 copies/mL after 6 months of therapy in this subject suggesting that virologic efficacy at the usual dose was not compromised. In a case series of two subjects, Das reported that the projected 10-hour trough levels were in the therapeutic range in one subject but was below this target in another [17]. However, the HIV-1 RNA levels were below 50 copies/mL, which suggested good virologic control at standard dosing.

Our data do not suggest lower concentrations of EFV in HIV-infected subjects receiving hemodialysis. Rather, bioequivalence using no-effect boundaries of 50–200% was observed for C_{max} and AUC, but not for C_{min}, when compared to historical controls. There was a trend toward increased C_{min}, C_{max}, and AUC in the hemodialysis group with higher than expected coefficients of variation. This result is likely due to known effects of polymorphisms of the CYP2B6 gene on the disposition of EFV. Similar to other studies [8,18], higher EFV AUC, C_{min}, and C_{max} were observed in the two subjects with the TT polymorphism of the CYP2B6 516 codon compared to the four subjects with the GG genotype. Because HIV-infected African-Americans are more likely to require hemodialysis [19] and are also more likely to carry the TT genotype compared to European-Americans and Hispanics [8], increases in EFV drug concentrations are not unexpected in the HIV-infected hemodialysis population. The frequency rate of the TT genotype in our study (18%) is similar to that found in the general Black population (17%) [8], so it is unlikely that a selection bias for this genotype occurred in our study. Although others have reported an association between higher EFV concentrations with more severe side effects [20,21], we did not find any relationships between EFV levels and adverse signs, symptoms, or laboratory parameters. However, as only medically stable subjects without severe symptoms were enrolled, our ability to correlate pharmacokinetic parameters with adverse events was limited. We also did not find any correlations between EFV levels and either CD4 cell count or HIV-1 RNA level, which is in agreement with most [8,22,23], but not all [24,25], studies in subjects without renal failure.

Overall, the PK parameters for LPV in the hemodialysis subjects in this study suggest a potentially lower systemic exposure in this group. Even though the confidence intervals for the LPV AUC and C_{max} geometric mean ratios were within the no-effect boundaries of 50%–200%, the confidence interval for the LPV AUC ratio did not include 100%. Using NEB of 80%–125%, C_{min} in the hemodialysis group was definitely lower compared to historical controls. To our knowledge, the only other published report of LPV pharmacokinetics in hemodialysis involved a single subject [26]. C_{min}, C_{max}, and AUC were all substantially higher in this subject compared to the values found in the current study [26], perhaps due to differences in methodologies in measurement of LPV concentrations. Interestingly, a study performed by the manufacturer of the PI atazanavir also found an unexpected reduction in pharmacokinetic parameters in hemodialysis subjects, which prompted a change in the labeling for this drug to avoid its use in treatment-experienced patients requiring hemodialysis (<http://www.fda.gov/cder/foi/label/2007/021567s014lbl.pdf>).

On average, we found less than 1% free LPV, suggesting that protein-binding in this group is similar to that found in HIV-infected subjects with normal renal function [15]. Thus, a reduction in protein-binding of LPV in subjects requiring hemodialysis, with subsequently greater metabolism and clearance of this drug, likely does not explain the possibly lower trough concentrations and suggests that LPV clearance by hemodialysis itself likely would not occur. It is possible that altered gastrointestinal absorption, volume of distribution, or function or

regulation of hepatic metabolic enzymes for LPV may occur in severe chronic kidney disease, thereby resulting in lower trough concentrations of LPV/RTV. We did find a marginal association between lower C_{min} concentrations and A→G polymorphisms at the CYP3A5 6986 position. The homozygous GG genotype results in very low expression of CYP3A5 protein. Therefore, we would have expected to see increased concentrations of LPV with the GG genotype. Although the allelic frequency ranges for the CYP3A5 AA, AG, and GG genotypes in Blacks are estimated, respectively, to be 36–54%, 25–50%, and 3–35% [27], which are roughly comparable to those found in this study, our findings should be interpreted with caution as only one of ten subjects was homozygous for the GG genotype. Further research is clearly needed to investigate the associations between LPV and CYP3A5 polymorphisms.

To maximize virologic efficacy and prevent resistance development, LPV concentrations considerably higher than the protein-binding corrected IC₅₀ against HIV should be maintained throughout the dosing interval. For this reason, once daily LPV dosing, which typically results in lower C_{min} values compared to twice daily dosing [28], is not recommended for PI-experienced patients. The LPV C_{min} values in the current study of hemodialysis patients are similar to those found in those receiving 800mg of LPV in those with normal renal function. Therefore, this suggests that twice daily dosing of LPV 400mg in hemodialysis would be expected to be adequate therapy in those not previously receiving PI-based therapy but perhaps not in PI-experienced patients. However, once daily dosing of LPV in a hemodialysis population may result in further decreases in C_{min}, thereby possibly jeopardizing virologic efficacy even in PI-naïve patients with end stage renal disease. We studied subjects who had been receiving the capsular form of LPV/RTV, which is no longer available. It is unknown if kidney disease and the use of hemodialysis would affect the disposition of LPV or RTV when given as the tablet co-formulation.

The primary limitation to this study was the use of historical controls as opposed to concurrently enrolled subjects with normal renal function. However, the results of this study suggest that tight matching by genotype would have been required to determine the effects of renal disease alone on the pharmacokinetics of these drugs. Screening by genotype would have been overly cumbersome to perform as part of this study. We limited any systematic biases by designing protocols that were closely matched to those used in the studies chosen for comparison. These studies also included HIV-infected patients receiving the identical dose and formulation of EFV and LPV/RTV. Our studies also rigorously assessed pharmacokinetic parameters over the full dosing interval, which is especially important for EFV, in a large number of patients, which should have minimized variability. Therefore, the differences found in PK values between hemodialysis patients and those with normal renal function are likely to be accurate. Because screening logs were not kept, we cannot assess the generalizability of these results to those patients who did not meet the strict eligibility criteria of this protocol. As such, extension of our conclusions to the general HIV-infected population requiring hemodialysis may not be warranted.

In summary, these results suggest that the effects of CYP2B6 polymorphisms at position 516 on EFV pharmacokinetics may be especially important in HIV-infected hemodialysis patients as this group is disproportionately black. However, dosing of EFV in this population does not appear to require adjustment based on our results. LPV/RTV dosing also does not require adjustment if being used in PI-naïve patients, but caution should be exercised with the 400mg/100mg twice daily regimen in those who are PI-experienced. Once daily dosing of LPV/RTV may also be inadequate, even in PI-naïve patients. Further study of the LPV/RTV tablet formulation at various doses in the HIV-infected hemodialysis population is warranted.

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REFERENCES

1. Izzedine H, Launay-Vacher V, Baumelou A, Deray G. An appraisal of antiretroviral drugs in hemodialysis. *Kidney Int* 2001;60:821–830. [PubMed: 11532078]
2. Elston AC, Bayliss MK, Park GR. Effect of renal failure on drug metabolism by the liver. *Br J Anaesth* 1993;71:282–290. [PubMed: 8123408]
3. Kanfer A, Stamatakis G, Torlotin JC, Fredj G, Kenouch S, Mery JP. Changes in erythromycin pharmacokinetics induced by renal failure. *Clin Nephrol* 1987;27:147–150. [PubMed: 3494560]
4. Ahmed JH, Grant AC, Rodger RS, Murray GR, Elliott HL. Inhibitory effect of uraemia on the hepatic clearance and metabolism of nicardipine. *Br J Clin Pharmacol* 1991;32:57–62. [PubMed: 1888642]
5. Leblond FA, Giroux L, Villeneuve JP, Pichette V. Decreased in vivo metabolism of drugs in chronic renal failure. *Drug Metab Dispos* 2000;28:1317–1320. [PubMed: 11038159]
6. Veau C, Leroy C, Banide H, Auchere D, Tardivel S, Farinotti R, et al. Effect of chronic renal failure on the expression and function of rat intestinal P-glycoprotein in drug excretion. *Nephrol Dial Transplant* 2001;16:1607–1614. [PubMed: 11477162]
7. Boobis SW. Alteration of plasma albumin in relation to decreased drug binding in uremia. *Clin Pharmacol Ther* 1977;22:147–153. [PubMed: 407044]

8. Haas DW, Ribaud HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004;18:2391–2400. [PubMed: 15622315]
9. Winzer R, Langmann P, Zilly M, Tollmann F, Schubert J, Klinker H, et al. No influence of the P-glycoprotein genotype (MDR1 C3435T) on plasma levels of lopinavir and efavirenz during antiretroviral treatment. *Eur J Med Res* 2003;8:531–534. [PubMed: 14711599]
10. Frohlich M, Hoffmann MM, Burhenne J, Mikus G, Weiss J, Haefeli WE. Association of the CYP3A5 A6986G (CYP3A5*3) polymorphism with saquinavir pharmacokinetics. *Br J Clin Pharmacol* 2004;58:443–444. [PubMed: 15373940]
11. Ernest CS 2nd, Hall SD, Jones DR. Mechanism-based inactivation of CYP3A by HIV protease inhibitors. *J Pharmacol Exp Ther* 2005;312:583–591. [PubMed: 15523003]
12. Haas DW, Wilkinson GR, Kuritzkes DR, Richman DD, Nicotera J, Mahon LF, et al. A multi-investigator/institutional DNA bank for AIDS-related human genetic studies: AACTG Protocol A5128. *HIV Clinical Trials* 2003;4:287–300. [PubMed: 14583845]
13. Yeh KC, Kwan KC. A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximation. *J Pharmacokinet Biopharm* 1978;6:79–98. [PubMed: 650423]
14. FDA Guidance for Industry. In vivo drug metabolism/drug interaction studies - Study design, data analysis, and recommendations for dosing and labeling. Edited by U.S. Health and Human Services FDA, CDER, CBER; 1999 Nov.
15. Boffito M, Hoggard PG, Lindup WE, Bonora S, Sinicco A, Khoo SH, et al. Lopinavir protein binding in vivo through the 12-hour dosing interval. *Ther Drug Monit* 2004;26:35–39. [PubMed: 14749547]
16. Izzedine H, Aymard G, Launay-Vacher V, Hamani A, Deray G. Pharmacokinetics of efavirenz in a patient on maintenance haemodialysis. *AIDS* 2000;14:618–619. [PubMed: 10780727]
17. Das S, Ghanem M, Huengsborg M. Experience with efavirenz in end-stage renal disease. *Int J STD AIDS* 2004;15:143. [PubMed: 15006080]
18. Rodriguez-Novoa S, Barreiro P, Rendon A, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. *Clin Infect Dis* 2005;40:1358–1361. [PubMed: 15825040]
19. U.S. Renal Data System, USRDS 2005 Annual Data Report. Atlas of End-Stage Renal Disease in the United States [package insert]. Bethesda, MD: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases; 2007.
20. Nunez M, Gonzalez de Requena D, Gallego L, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. Higher efavirenz plasma levels correlate with development of insomnia. *Journal of Acquired Immune Deficiency Syndromes: JAIDS* 2001;28:399–400.
21. Clifford DB, Evans S, Yang Y, Acosta EP, Goodkin K, Tashima K, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005;143:714–721. [PubMed: 16287792]
22. Nasi M, Borghi V, Pinti M, Bellodi C, Lugli E, Maffei S, et al. MDR1 C3435T genetic polymorphism does not influence the response to antiretroviral therapy in drug-naïve HIV-positive patients. *AIDS* 2003;17:1696–1698. [PubMed: 12853754]
23. Haas DW, Wu H, Li H, Bosch RJ, Lederman MM, Kuritzkes D, et al. MDR1 gene polymorphisms and phase 1 viral decay during HIV-1 infection: an adult AIDS Clinical Trials Group study. *Journal of Acquired Immune Deficiency Syndromes: JAIDS* 2003;34:295–298.
24. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001;15:71–75. [PubMed: 11192870]
25. Fellay J, Marzolini C, Meaden ER, Back DJ, Buclin T, Chave JP, et al. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *Lancet* 2002;359:30–36. [PubMed: 11809184]
26. Izzedine H, Launay-Vacher V, Legrand M, Lieberherr D, Caumes E, Deray G. ABT 378/r: a novel inhibitor of HIV-1 protease in haemodialysis. *AIDS* 2001;15:662–664. [PubMed: 11317012]
27. Xie HG, Wood AJ, Kim RB, Stein CM, Wilkinson GR. Genetic variability in CYP3A5 and its possible consequences. *Pharmacogenomics* 2004;5:243–272. [PubMed: 15102541]

28. Eron JJ, Feinberg J, Kessler HA, Horowitz HW, Witt MD, Carpio FF, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naïve HIV-positive patients: a 48-week randomized clinical trial. *J Infect Dis* 2004;189:265–272. [PubMed: 14722892]

Figure 1. Geometric mean concentrations ($\mu\text{g/mL}$) of efavirenz (top panel), lopinavir (middle panel), and ritonavir (bottom panel) at each scheduled sample time. Ninety-five percent confidence intervals around the geometric means are also shown. The dosing intervals were 24 hours for efavirenz and 12 hours for lopinavir and ritonavir.

Figure 2.

90% confidence intervals around geometric mean ratios, hemodialysis subjects relative to historical controls, for efavirenz, lopinavir, and ritonavir areas under the curve (AUC), minimum concentrations (Cmin), and maximum concentrations (Cmax).

Table 1

Baseline characteristics of the study groups.

Characteristic	Efavirenz (N=13)	Lopinavir/ritonavir (N=13)
Median age, years (range)	47 (35, 57)	47 (41, 62)
Male sex, n (%)	12 (92)	12 (92)
Black race, n (%)	13 (100)	12 (92)
Injection drug use, n (%)		
Never	6 (46)	12 (92)
Previously	7 (54)	1 (8)
Duration of hemodialysis, years (range)	3.8 (1.3, 8.7)	3.6 (1.2, 25.4)
Median body weight, kg (range)	74 (55, 112)	70 (60, 101)
Current smoker, n (%)	8 (62)	7 (54)
Diabetes, n (%)	2 (15)	0 (0)
Hypertension, n (%)	12 (92)	11 (85)
Hepatitis BsAg positive, n (%)	1 (8%)	4 (31%)
Hepatitis C Ab positive, n (%)	8 (62%)	2 (15%)
Median CD4 cell count, cells/ μ L (range)	360 (87, 723)	271 (137, 956) ^a
HIV-1 RNA level $\leq$ 50 copies/mL, n (%)	8 (62)	4 (31)
Median Hemoglobin, g/dL (range)	11.8 (9.8, 14.0)	12.9 (7.6, 14.8)

^a N=12; CD4 cell count missing for one subject on the LPV/RTV arm

Table 2

Comparisons of efavirenz, lopinavir, and ritonavir pharmacokinetics between HIV-infected hemodialysis recipients (present study) and those with normal renal function (historical controls [28, 32]).

Parameter	HD	Controls ^a	GMR ^b (%)
Efavirenz (n=13)			
AUC (µg·h/mL)	^c 71.5 (43.2, 118.3; 93%)	58.1 (23.0; 40%)	132 (89, 197)
Cmin (µg/mL)	^c 1.81 (0.93, 3.53; 103%)	1.8 (1.0; 57%)	118 (70, 200)
Cmax, (µg/mL)	^c 5.04 (3.48, 7.29; 72%)	4.1 (1.2; 29%)	129 (96, 172)
Tmax (hrs), mean (SD)	7.1 (6.5)		
Clearance (L/h)	^c 8.39 (5.07, 13.89; 71%)		
Half-life ^d (h), mean (SD)	26.0 (18.5)		
Lopinavir (n=13)			
AUC (µg·h/mL)	^c 69.6 (55.6, 87.2; 37%)	92.6 (36.7; 40%)	81 (67, 97)
Cmin (µg/mL)	^c 2.76 (1.86, 4.11; 53%)	5.5 (2.7; 49%)	56 (41, 77)
Cmax, (µg/mL)	^c 8.45 (6.41, 11.15; 52%)	9.8 (3.7; 37%)	92 (74, 115)
Tmax (hrs), mean (SD)	3.3 (1.8)		
Clearance (L/h)	^c 5.75 (4.59, 7.20; 35%)		
Half-life ^e (h), mean (SD)	9.1 (6.9)		
Protein binding (% free), mean (SD)	0.89 (.41)		
Ritonavir (n=13)			
AUC (µg·h/mL)	^c 3.74 (2.91, 4.80; 37%)	4.6 (2.4; 52%)	92.(76,111)
Cmin (µg/mL)	^c 0.08 (0.05, 0.14; 63%)	0.17 (0.08; 47%)	55(36,82)
Cmax, (µg/mL)	^c 0.58 (0.44, 0.76; 41%)	0.68 (0.50; 74%)	105 (81,137)
Tmax (hrs), mean (SD)	3.4 (1.2)		
Clearance (L/h)	^c 26.8 (20.8, 34.4; 41%)		
Half-life ^f (h), mean (SD)	4.4 (1.4)		

HD=hemodialysis; Cmin=minimum concentration; Cmax=maximum concentration; AUC=Area Under the Curve; Tmax=time to maximum concentration

NOTE: The EFV historical controls (N=35) were HIV-infected and received 600mg of EFV once daily as a single tablet in combination with stavudine and lamivudine; PK was measured at 'steady-state' with no further information available on sampling times or subject demographics (personal communication, March 2008, Tejal Gandhi, Bristol-Myers Squibb). The LPV/RTV historical controls (N=19; 13 men, 6 women; mean age 35 years; 5 Caucasian, 9 Black, 5 Hispanic) were HIV-infected and received 3 capsules of LPV/RTV (133.3mg/33.3mg) twice daily with food in combination with stavudine and lamivudine for 3 weeks prior to PK assessment; samples were obtained pre-dose and at 0.5, 2, 4, 6, 8, and 12 hours post-dose and analyzed using an LC/MS/MS assay and analyzed using non-compartmental methods.

^aMean (standard deviation; coefficient of variation)

^bGeometric mean ratio (90% confidence interval) between hemodialysis PK and control PK

^cGeometric mean (95% confidence interval; coefficient of variation)

^dData available on 9 subjects

^eData available on 11 subjects

^fData available on 12 subjects

Table 3

The effects of selected single nucleotide polymorphisms on the pharmacokinetics of efavirenz (EFV), lopinavir (LPV), and ritonavir (RTV) in HIV-infected patients requiring hemodialysis.

Drug	Gene Codon	SNP	N	AUC (µg·h/mL) Median (range)	Cmin (µg/mL) Median (range)	Cmax (µg/mL) Median (range)
EFV	CYP2B6 516	GG	4	30.69 (22.71, 61.41)	0.71 (0.39, 1.59)	3.33 (2.14, 4.23)
		GT	5	83.17 (62.01, 167.81)	2.61 (1.57, 4.86)	5.26 (4.45, 9.51)
		TT	2	125.19 (85.48, 164.90)	4.13 (2.19, 6.08)	6.51 (4.78, 8.23)
		p(KW)		0.009	0.023	0.012
	MDR1 2677	GG	8	73.45 (22.71, 167.81)	1.89 (0.39, 6.08)	4.51 (2.14, 9.51)
		GT	2	64.77 (62.01, 67.52)	1.90 (1.57, 2.23)	4.86 (4.45, 5.26)
		TT	1	83.17 (83.17, 83.17)	2.61 (2.61, 2.61)	4.71 (4.71, 4.71)
	MDR1 3435	p(KW)		0.958	0.869	0.990
		CC	7	62.01 (28.93, 167.81)	1.59 (0.70, 6.08)	5.26 (3.02, 9.51)
		CT	4	75.34 (22.71, 85.48)	2.21 (0.39, 2.61)	4.58 (2.14, 4.78)
LPV	CYP3A5 6986	p(WRS)		0.788	0.788	0.412
		AA	5	62.01 (28.93, 167.81)	1.57 (0.70, 4.86)	5.26 (3.02, 9.51)
		AG	4	75.34 (22.71, 85.48)	2.21 (0.39, 2.61)	4.58 (2.14, 4.78)
		GG	2	113.16 (61.41, 164.90)	3.83 (1.59, 6.08)	6.23 (4.23, 8.23)
	CYP2B6 516	p(KW)		0.891	0.691	0.674
		GG	3	50.71 (39.01, 71.85)	2.07 (1.05, 2.18)	5.64 (4.41, 9.27)
		GT	6	69.88 (45.37, 112.04)	3.81 (0.86, 5.83)	7.80 (6.44, 18.60)
		TT	1	135.00 (135.00, 135.00)	5.08 (5.08, 5.08)	20.10 (20.10, 20.10)
	MDR1 2677	p(KW)		0.119	0.357	0.119
		GG	9	71.85 (39.01, 135.00)	3.75 (1.05, 5.83)	8.30 (4.41, 20.10)
		GT	1	45.37 (45.37, 45.37)	0.86 (0.86, 0.86)	6.44 (6.44, 6.44)
	MDR1 3435	p(WRS)		0.400	0.200	0.600
		CC	6	77.56 (39.01, 135.00)	3.81 (2.07, 5.83)	8.56 (4.41, 20.10)
		CT	4	63.61 (45.37, 71.85)	1.27 (0.86, 4.27)	7.54 (6.44, 9.27)
	CYP3A5 6986	p(WRS)		0.352	0.114	0.762
		AA	6	69.88 (39.01, 135.00)	4.07 (2.07, 5.83)	7.04 (4.41, 20.10)
		AG	3	71.85 (60.89, 81.68)	1.49 (1.05, 3.75)	9.27 (8.30, 9.82)
		GG	1	45.37 (45.37, 45.37)	0.86 (0.86, 0.86)	6.44 (6.44, 6.44)

Drug	Gene Codon	SNP	N	AUC (µg·h/mL) Median (range)	Cmin (µg/mL) Median (range)	Cmax (µg/mL) Median (range)
Free LPV	CYP2B6 516	p(KW)		0.612	0.048	0.612
		GG	3	0.35 (0.34, 0.95)	0.02 (0.01, 0.02)	0.04 (0.04, 0.12)
		GT	6	0.47 (0.35, 1.23)	0.02 (0.01, 0.08)	0.07 (0.04, 0.13)
	MDR1 2677	TT	1	0.90 (0.90, 0.90)	0.03 (0.03, 0.03)	0.13 (0.13, 0.13)
		p(KW)		0.674	0.674	0.164
		GG	9	0.50 (0.34, 1.23)	0.02 (0.01, 0.08)	0.07 (0.04, 0.13)
	MDR1 3435	GT	1	0.38 (0.38, 0.38)	0.01 (0.01, 0.01)	0.05 (0.05, 0.05)
		p(WRS)		0.800	0.200	0.800
		CC	6	0.43 (0.34, 0.90)	0.02 (0.02, 0.04)	0.06 (0.04, 0.13)
	CYP3A5 6986	CT	4	0.70 (0.38, 1.23)	0.01 (0.01, 0.08)	0.09 (0.05, 0.13)
		p(WRS)		0.257	0.257	0.476
		AA	6	0.60 (0.34, 1.23)	0.03 (0.02, 0.08)	0.08 (0.04, 0.13)
RTV	CYP2B6 516	AG	3	0.45 (0.35, 0.95)	0.01 (0.01, 0.02)	0.06 (0.04, 0.12)
		GG	1	0.38 (0.38, 0.38)	0.01 (0.01, 0.01)	0.05 (0.05, 0.05)
		p(KW)		0.921	0.021	0.921
	MDR1 2677	GG	3	2.57 (2.45, 5.42)	0.04 (0.01, 0.08)	0.48 (0.34, 0.93)
		GT	6	4.27 (1.85, 5.85)	0.12 (0.03, 0.24)	0.60 (0.27, 0.80)
		TT	1	6.03 (6.03, 6.03)	0.17 (0.17, 0.17)	1.08 (1.08, 1.08)
	MDR1 3435	p(KW)		0.298	0.357	0.381
		GG	9	5.06 (2.45, 6.03)	0.08 (0.01, 0.24)	0.68 (0.34, 1.08)
		GT	1	1.85 (1.85, 1.85)	0.06 (0.06, 0.06)	0.27 (0.27, 0.27)
	CYP3A5 6986	p(WRS)		0.200	0.800	0.200
		CC	6	3.94 (2.45, 6.03)	0.12 (0.04, 0.19)	0.62 (0.34, 1.08)
		CT	4	4.46 (1.85, 5.85)	0.05 (0.01, 0.24)	0.60 (0.27, 0.93)
	CYP3A5 6986	p(WRS)		0.914	0.352	0.914
		AA	6	4.05 (2.45, 6.03)	0.12 (0.04, 0.24)	0.58 (0.34, 1.08)
		AG	3	5.06 (3.49, 5.42)	0.03 (0.01, 0.19)	0.80 (0.53, 0.93)
		GG	1	1.85 (1.85, 1.85)	0.06 (0.06, 0.06)	0.27 (0.27, 0.27)
		p(KW)		0.357	0.538	0.164

Cmin=minimum concentration; Cmax=maximum concentration; AUC=Area Under the Curve; SNP=single nucleotide polymorphism; p(KW)=p-value using Kruskal-Wallis for comparisons of more than 2 groups; p(WRS)=p-value using Wilcoxon Rank Sum for comparisons between only 2 groups