Published in final edited form as:

J Acquir Immune Defic Syndr. 2008 August 15; 48(5): 561–566. doi:10.1097/QAI.0b013e31817bebeb.

Influence of Antiretroviral Drugs on the Pharmacokinetics of Prednisolone in HIV-Infected Individuals

Kristin H. Busse, PharmD^{*}, Elizabeth Formentini, RNC, MSN, FNP-C[†], Raul M. Alfaro, MS^{*}, Joseph A. Kovacs, MD[†], and Scott R. Penzak, PharmD, FCP^{*}

^{*}Pharmacy Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD.

[†]Department of Critical Care Medicine, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD.

Abstract

Background—Corticosteroids are cytochrome P450 3A4 substrates, which have been associated with toxicities in patients receiving cytochrome P450 3A4 inhibitors such as human immunodeficiency virus protease inhibitors. In a study in healthy volunteers, ritonavir significantly increased prednisolone exposure.

Methods—We investigated the influence of antiretroviral (ARV) medications on prednisolone pharmacokinetics in 3 groups of 10 human immunodeficiency virus–infected subjects. One group received lopinavir/ritonavir, and another efavirenz, as part of their ARV regimen; a third group did not receive ARV medications. Each subject received a single 20-mg prednisone dose followed by serial blood sampling for prednisolone. Prednisolone pharmacokinetics were compared among the groups.

Results—Area under the concentration–time curve was significantly lower in efavirenz recipients versus subjects receiving lopinavir/ritonavir (geometric mean ratio = 0.60, $P = 0.01$). Average prednisolone area under the concentration–time curve was higher in subjects taking lopinavir/ritonavir versus subjects not on ARVs; however, this difference was not significant ($P > 0.05$).

Conclusions—These data indicate that prednisolone concentrations may fluctuate widely when human immunodeficiency virus–positive individuals established on efavirenz therapy change to lopinavir/ritonavir or vice versa.

Keywords

drug interaction; cytochrome P450; nonnucleoside reverse transcriptase inhibitor; protease inhibitor; corticosteroid

INTRODUCTION

Potent combination antiretroviral (ARV) therapy has been shown to reduce morbidity and mortality in patients with human immunodeficiency virus (HIV) infection.^{1,2} However, drug interactions and toxicities remain an important concern in HIV-infected patients who often receive multiple medications for treatment of HIV and treatment and prophylaxis of opportunistic infections, immunomodulation, and comorbidities. Systemic corticosteroids, such as prednisone, are commonly administered to HIV-infected patients as part of treatment

regimens for *Pneumocystis* pneumonia or toxoplasmic encephalitis and for allergic reactions, neoplastic diseases, inflammatory arthritis, asthma, and renal or liver transplantation. However, corticosteroid, primarily inhaled fluticasone, use has been associated with substantial toxicities in this population, including osteonecrosis and Cushing syndrome.^{3–6} Although few studies demonstrate prednisone toxicities in HIV-positive individuals,⁷ osteonecrosis and other toxicities have been well documented in other patient populations.^{8–11}

At least 14 case reports and case series describe 24 HIV-infected patients with iatrogenic Cushing syndrome secondary to inhaled fluticasone therapy^{6,12–24}; all these individuals (100%) were receiving concurrent protease inhibitor (PI) treatment that included ritonavir. Further, in a study in HIV-infected patients, where systemic corticosteroid use was identified as a potential risk factor in the development of osteonecrosis, 14 of the 15 patients (93%) who developed osteonecrosis received PI therapy in combination with corticosteroid treatment.²⁵ The exact frequency with which PI use accompanies corticosteroid-related toxicities in HIV-infected patients is unclear; however, these data furthered speculation that PIs may reduce the metabolism of corticosteroids via cytochrome P450 (CYP) 3A4 inhibition, possibly leading to excess corticosteroid exposure and toxicities.

To determine whether HIV PIs increase the systemic exposure to corticosteroids, we recently studied the influence of ritonavir on the pharmacokinetics of prednisolone, the active (non-CYP-mediated) metabolite of prednisone primarily metabolized via CYP3A4.²⁶ Ritonavir coadministration (200 mg twice daily for 2 weeks) resulted in a statistically significant increase (28%) in prednisolone exposure when healthy volunteers were administered a single 20-mg prednisone dose in crossover fashion.²⁷ Results from this study were similar to those observed when other CYP3A4 inhibitors, such as diltiazem and itraconazole, were coadministered with prednisone.^{28–30}

In addition to PIs, the nonnucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz and nevirapine, also modulate CYP 450 activity and may interact with corticosteroids^{31–33}; however, drug interaction studies between NNRTIs and corticosteroids have not been conducted. The purpose of the current study was to determine whether prednisolone exposure is altered in the presence of efavirenz or lopinavir/ritonavir-based ARV therapy in HIV-infected patients.

METHODS

Study Subjects

This study was conducted as an open-label, single-phase, parallel study in an outpatient HIV clinic. The study population consisted of HIV-positive patients receiving the following drugs as a component of their ARV treatment regimen: lopinavir/ritonavir (group 1), efavirenz (group 2), and no ARV therapy (group 3). Each group contained 10 unique individuals (total N = 30). To be included in the current study, subjects were required to be 18–50 years of age and free of concurrent illnesses including persistent diarrhea, malabsorption, active substance abuse, and endocrine abnormalities. Subjects also had to have been on a stabilized ARV drug regimen for at least 30 days before study participation. In addition, subjects were required to have adequately controlled HIV disease defined as HIV RNA <50,000 copies/mL, CD4+ count >200 cells/mm³, and no evidence of active opportunistic infections. Other laboratory values such as serum electrolytes, liver function tests, and serum creatinine could not exceed 1.5 times the upper limit of normal. Additional exclusion criteria included ingestion of grapefruit or grapefruit juice within 3 days of pharmacokinetic sampling, pregnancy or breastfeeding, and routine use of prescription, or over the counter, or herbal medications known or suspected to modulate CYP3A4 activity. All participants gave informed consent, and clinical research was conducted according to guidelines for human experimentation as specified by the US

Department of Health and Human Services. This study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board.

Study Design and Treatments

After an overnight fast, subjects arrived at the clinic on the morning of study day 1 and had an intravenous catheter inserted into a forearm vein. After catheter insertion, subjects received a standard light breakfast, which consisted of a bagel with cream cheese, 4 oz of applesauce, 4 oz of orange juice, and 8 oz of 2% milk; subjects refrained from eating additional food for the next 4.5 hours. Within 30 minutes of eating breakfast, subjects took a single 20-mg prednisone tablet (Roxanne Laboratories, Columbus, OH) with 240 mL of water. Because prednisone is rapidly metabolized to prednisolone in vivo (through a non-CYP-mediated pathway), venous blood samples were collected for the determination of prednisolone concentrations at time 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after the prednisone dose. The 24-hour sample was collected by venipuncture. All samples were collected into sodium heparin (6 mL, green top) tubes and centrifuged at 3200 rpm for 10 minutes after which plasma was harvested and stored at -80°C until analysis.

Prednisolone Analysis

Prednisolone concentrations in human plasma were determined using a previously described high-performance liquid chromatography liquid-liquid extraction method developed and validated, in our laboratory.²⁷ Percent errors, as a measure of accuracy, were found to be $<15\%$. As a measure of precision, inter- and intra-assay coefficients of variation (%CVs) were found to be 3.50% – 7.39% and 2.74% – 5.92% , respectively, at 4 different drug concentrations. The limits of quantitation and detection for the assay were $0.020\text{ }\mu\text{g/mL}$ and $0.010\text{ }\mu\text{g/mL}$, respectively.

Pharmacokinetic Analysis

Prednisolone pharmacokinetic parameters were determined using noncompartmental methods with WinNonlin Professional computer program (version 5.0; Pharsight Corporation, Mountain View, CA). Maximum plasma concentrations (C_{max}) and time to reach C_{max} (T_{max}) were determined by visual inspection of the concentration–time profiles. The elimination rate constant (λ_z) was estimated as the absolute value of the slope of a linear regression of a natural logarithm of concentration versus time. Half-life ($T_{1/2}$) was calculated as $\ln 2/\lambda_z$. Area under the concentration versus time curve (AUC) from 0 hours to the last quantifiable concentration ($\text{AUC}_{0\text{--last}}$) was determined using the linear trapezoidal rule. AUC from time 0 to infinity ($\text{AUC}_{0\text{--}\infty}$) was determined by dividing the last measured concentration by the elimination rate constant (λ_z) and adding this value to $\text{AUC}_{0\text{--last}}$. Apparent oral clearance (CL/F) was estimated as dose divided by $\text{AUC}_{0\text{--}\infty}$.

Statistical Analysis

Sample size was calculated using the reported variability in prednisolone AUC in 2 different pharmacokinetic studies in healthy volunteers (%CV $\sim 20\%$).^{27,28} With $\alpha = 0.05$, a sample size of 30 (10 subjects per group) was calculated to provide $<90\%$ power to determine a significant difference of 25% in prednisolone AUC between the study groups. Prednisolone pharmacokinetic parameter values were compared between the 3 groups using analysis of variance with Tukey post hoc comparisons. In accordance with guidelines provided by the US Food and Drug Administration, pharmacokinetic data are presented as geometric means with 90% confidence intervals (CIs) and geometric mean ratios (GMRs) between the groups. Statistical significance was accepted as a P value <0.05 . Statistical comparisons were performed using SYSTAT Statistical System for Windows Program, version 11, 2004

(SYSTAT Software Inc, Richmond, CA). Descriptive statistics were generated using Microsoft Excel 2002 (Microsoft Corporation, Redmond, WA).

RESULTS

Thirty HIV-positive subjects (23 males) were enrolled and completed the study. Baseline characteristics were similar between the groups and displayed in Table 1. Subjects were questioned regarding any missed doses before enrollment into the study to determine compliance with ARVs. When questioned, no subjects reported missing any of their ARV doses within 14 days of study participation. Each prednisone dose was well tolerated by the study subjects after directly observed administration.

Figure 1 displays the mean prednisolone concentration–time profiles for the respective study groups. Geometric means with 90% CIs for prednisolone pharmacokinetic parameter values are shown in Table 2, and between-group comparisons are reported in Table 3.

Subjects in the efavirenz group (group 2) had a significantly lower mean $AUC_{0-\infty}$ (GMR = 0.60) for prednisolone compared with subjects in the lopinavir/ritonavir group (group 1, $P = 0.006$). In accordance with these findings, prednisolone CL/F was significantly higher in the efavirenz group compared with the lopinavir/ritonavir group (GMR = 1.66). Prednisolone $T_{1/2}$ was significantly shorter in subjects receiving efavirenz compared with the HIV-infected subjects receiving no ARV therapy (GMR = 0.60; $P = 0.04$). Lastly, the average prednisolone C_{max} was significantly lower ($P < 0.05$) in the efavirenz group versus the lopinavir/ritonavir group (GMR = 0.75).

DISCUSSION

HIV-infected patients frequently receive multiple medications that require close monitoring for drug–drug interactions. Indeed, PIs and NNRTIs have been shown to modulate (ie, inhibit or induce) CYP3A activity and alter the systemic exposure of many coadministered medications.³¹ To ensure that corticosteroids are administered safely in patients with HIV infection, drug–drug interactions between ARVs and corticosteroids must be considered before coadministering medications from these classes.

Efavirenz and lopinavir/ritonavir were chosen for this drug interaction study due to their widespread use and the fact that both are recommended as first-line ARV therapy for HIV-infected patients naive to ARV treatment.³⁴ Moreover, both medications are known to modulate CYP3A activity and potentially interact with prednisolone.

The influence of lopinavir/ritonavir on prednisolone pharmacokinetics was generally consistent with its ability to inhibit CYP3A4 activity and elevate plasma concentrations of drugs metabolized through this pathway. However, the higher prednisolone exposure observed in lopinavir/ritonavir recipients was not significantly different ($P > 0.05$) from that observed in HIV-positive subjects not receiving ARV medications (GMR = 1.31). In contrast, ritonavir 200 mg administered twice daily for 14 days did produce a statistically significant increase in prednisolone AUC (GMR = 1.28; $P = 0.001$) in a crossover study of healthy volunteers.²⁷ These results are likely due to increased variability in prednisolone exposure observed in HIV-infected subjects (%CV = 38%) versus -uninfected volunteers (%CV = 27%).

Greater variability in prednisolone exposure in HIV-positive patients versus healthy volunteers may be due to factors such as CYP-modulating cytokines and/or concurrent medications potentially altering prednisolone disposition via non–CYP-mediated mechanisms (ie, modulation of transport proteins). Due to the greater variability in prednisolone pharmacokinetics among HIV-infected subjects (versus healthy volunteers), a larger change

in prednisolone AUC would have been necessary, or a larger sample size needed, to identify a significant difference in prednisolone AUC with lopinavir/ritonavir. Of note, the sample size for this investigation was calculated using previously collected healthy volunteer data, as there were no pharmacokinetic data for prednisolone in HIV-infected subjects. As a result, the study was slightly underpowered with regard to influence of lopinavir/ritonavir on prednisolone exposure.

The largest difference in prednisolone exposure between study groups was between the lopinavir/ritonavir and efavirenz groups; efavirenz recipients had 40% lower prednisolone plasma concentrations compared with those in the lopinavir/ritonavir cohort. As such, particular consideration should be given to patients switching from an ARV regimen that contains efavirenz to one containing lopinavir/ritonavir or vice versa. In the setting of virologic failure, it would not be unusual to encounter patients switching from one of these ARVs to the other, in which case patients receiving concurrent prednisolone therapy should be monitored closely for signs and symptoms of corticosteroid toxicity or inadequate pharmacologic response.

In addition to lopinavir, low-dose ritonavir (100–200 mg once or twice daily) is coadministered with a number of PIs. Because the ritonavir component of the lopinavir/ritonavir combination is presumably responsible for the observed interaction with prednisolone, it is possible that other low-dose ritonavir-containing ARV regimens could produce similar effects on prednisolone metabolism. Indeed, a previous study in healthy volunteers observed a 28% increase in prednisolone AUC after 2 weeks of ritonavir 200 mg twice daily dosing ($P = 0.001$); the magnitude of this increase was similar to the difference in prednisolone AUC observed between lopinavir–ritonavir recipients and HIV+ patients void of ARV therapy in the data reported herein (+31% in the lopinavir–ritonavir group).

In contrast to the time required for efavirenz to produce maximal CYP3A4 induction, one would expect CYP3A4 inhibition by ritonavir (ie, all ritonavir-containing ARV regimens) to occur immediately or shortly after initiation.³⁵ Indeed, in our previously conducted healthy volunteer study, prednisolone plasma concentrations were elevated 37% after 4 days of ritonavir administration; this increase in prednisolone exposure was comparable to the 28% increase in prednisolone exposure observed after an additional 10 days of ritonavir dosing in the same study.²⁷ In the current study, prednisolone metabolism was still impaired (albeit not significantly) in subjects receiving lopinavir/ritonavir for a minimum of 1 month, which indicates that although drug interactions with ritonavir may diminish somewhat over time, a potentially relevant interaction may be present after ≥ 4 weeks of lopinavir/ritonavir therapy.

Drug interactions continue to be an important consideration in HIV-infected patients receiving PIs or NNRTIs. We recently showed that prednisolone exposure was elevated by ritonavir 200 mg twice daily in healthy volunteers; in the current study, we observed similar results in HIV-positive patients stabilized on a lopinavir/ritonavir-containing regimen. Moreover, in the current study, we observed significantly lower prednisolone AUC and CL/F values in patients stabilized on an efavirenz-containing regimen versus those receiving lopinavir/ritonavir. The largest difference in prednisolone AUC was between efavirenz and lopinavir/ritonavir recipients, suggesting that switching from one of these drugs to the other will not be an effective means of avoiding interactions with prednisone.

Switching prednisone/prednisolone to another corticosteroid that is not significantly metabolized by CYP3A4 would be a logical means of avoiding the interaction observed in this study. However, other corticosteroids including, but not limited to, hydrocortisone, dexamethasone, budesonide, and methyl-prednisolone are also primarily metabolized via CYP3A.^{36–39} In summary, current data indicate ritonavir- and efavirenz-containing ARV

regimens that can alter prednisolone pharmacokinetics. Clinicians should be aware of these potential interactions to ensure that prednisone/prednisolone is administered to HIV-positive patients in the safest and most effective manner possible.

Acknowledgements

Supported by the National Institutes of Health Clinical Center Pharmacy Department and the National Institute of Allergy and Infectious Diseases.

REFERENCES

1. Hogg RS, O-Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. *Lancet* 1997;349:1294. [PubMed: 9251649]
2. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853–860. [PubMed: 9516219]
3. Glesby MJ, Hoover DR, Vaamonde CM. Osteonecrosis in patients infected with human immunodeficiency virus: a case-control study. *J Infect Dis* 2001;184:519–523. [PubMed: 11471113]
4. Allison GT, Bostrom MP, Glesby MJ. Osteonecrosis in HIV disease: epidemiology, etiologies, and clinical management. *AIDS* 2003;17:1–9. [PubMed: 12478064]
5. Scribner AN, Troia-Cancio P, Cox BA, et al. Osteonecrosis in HIV: a case-control study. *J Acquir Immune Defic Syndr* 2000;25:19–25. [PubMed: 11064500]
6. Samaras K, Pett S, Gowers A, et al. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005;90:4394–4398. [PubMed: 15755851]
7. Wallis RS, Kalayjian R, Jacobson JM, et al. A study of the immunology, virology, and safety of prednisone in HIV-1-infected subjects with CD4 cell counts of 200 to 700 mm³. *J Acquir Immune Defic Syndr* 2003;32:281–286. [PubMed: 12626887]
8. Cruess RL. Cortisone-induced avascular necrosis of the femoral head. *J Bone Joint Surg Br* 1977;59:309–317.
9. Felson DT, Anderson J. A cross-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. *Lancet* 1987;1:902–906. [PubMed: 2882300]
10. Schimmer, BP.; Parker, KL. Adrenocorticotrophic hormones; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman, JL.; Limbird, LE.; Molinoff, PB., et al., editors. *The Pharmacological Basis of Therapeutics*. Vol. 9th ed.. New York: McGraw Hill Companies Inc; 1996. p. 1459-1485.
11. Kelly, HW.; Sorkness, CA.; Asthma. *Pharmacotherapy: A Pathophysiologic Approach*. Vol. 5th ed.. Dipro, JT.; Talbert, RL.; Yee, GC., et al., editors. New York: McGraw Hill Companies Inc; 2002. p. 475-510.
12. Clevenbergh P, Corcostegui M, Gerard D, et al. Iatrogenic Cushing's syndrome in an HIV-infected patient treated with inhaled corticosteroids (fluticasone propionate) and low dose ritonavir enhanced PI containing regimen. *J Infect* 2002;44:194–195. [PubMed: 12099750]
13. Mastroianni A, Sabbatini AMT, Portolani M, et al. Ritonavir-induced Cushing's syndrome in a patient treated with nasal fluticasone. *AIDS* 1999;13:1803–1806. [PubMed: 10509596]
14. Gupta SK, Dube M. Exogenous Cushing syndrome mimicking human immunodeficiency virus lipodystrophy. *Clin Infect Dis* 2002;35:e69–e71. [PubMed: 12203188]
15. Pessanha TM, Campos JM, Barros AC, et al. Iatrogenic Cushing's syndrome in an adolescent with AIDS on ritonavir and inhaled fluticasone: case report and literature review. *AIDS* 2007;21:529–538. [PubMed: 17301576]
16. Johnson SR, Marion AA, Vrchoticky T, et al. Cushing's syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006;388:386–388. [PubMed: 16615973]

17. Arrington-Sanders R, Hutton N, Siberry GK. Ritonavir-fluticasone interaction causing Cushing syndrome in HIV-infected children and adolescents. *Pediatr Infect Dis J* 2006;25:1044–1048. [PubMed: 17072128]
18. St Germain RM, Yigit S, Wells L, et al. Cushing syndrome and severe adrenal suppression caused by fluticasone and protease inhibitor combination in an HIV-infected adolescent. *AIDS Patient Care STDS* 2007;21:373–377. [PubMed: 17594245]
19. Bhumbra NA, Sahloff EG, Oehrman SJ, et al. Exogenous Cushing syndrome with inhaled fluticasone in a child receiving lopinavir/ritonavir. *Ann Pharmacother* 2007;41:1306–1309. [PubMed: 17535841]
20. Rouanet I, Peyrière H, Mauboussin JM, et al. Cushing's syndrome in a patient treated by ritonavir/lopinavir and inhaled fluticasone. *HIV Med* 2003;4:149–150. [PubMed: 12702137]
21. Hillebrand-Haverkot ME, Ten Veen JH, Prummel MF. Ritonavir-induced Cushing's syndrome in a patient treated with nasal fluticasone. *AIDS* 1999;13:1803. [PubMed: 10509596]
22. Chen F, Kearney T, Robinson S, et al. Cushing's syndrome and severe adrenal suppression in patients treated with ritonavir and inhaled nasal fluticasone. *Sex Transm Infect* 1999;75:274. [PubMed: 10615321]
23. Soldatos G, Sztal-Mazer S, Woolley I, et al. Exogenous glucocorticoid excess as a result of ritonavir-fluticasone interaction. *Intern Med J* 2005;35:67–68. [PubMed: 15667475]
24. Gillet MJ, Cameron PU, Nguyen HV, et al. Iatrogenic Cushing syndrome in a HIV-infected patient treated with ritonavir and inhaled fluticasone. *AIDS* 2005;19:740–741. [PubMed: 15821405]
25. Miller KD, Masur H, Jones EC, et al. High prevalence of osteonecrosis of the femoral head in HIV-infected adults. *Ann Intern Med* 2002;137:17–24. [PubMed: 12093241]
26. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990;19:126–146. [PubMed: 2199128]
27. Penzak SR, Formentini E, Alfaro RM, et al. Prednisolone pharmacokinetics in the presence and absence of ritonavir after oral prednisone administration to healthy volunteers. *J Acquir Immune Defic Syndr* 2005;40:573–580. [PubMed: 16284534]
28. Imani S, Jusko WJ, Steiner R. Diltiazem retards the metabolism of oral prednisone with effects on T-cell markers. *Pediatr Transplant* 1999;3:126–130. [PubMed: 10389134]
29. Varis T, Kivisto KT, Neuvonen PJ. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. *Eur J Clin Pharmacol* 2000;56:57–60. [PubMed: 10853878]
30. Zurcher RM, Frey BM, Frey FJ. Impact of ketoconazole on the metabolism of prednisolone. *Clin Pharmacol Ther* 1989;47:366–372. [PubMed: 2639662]
31. Struble, KA.; Piscitelli, SC. Drug interactions with antiretrovirals for HIV infection. In: Piscitelli, SC.; Rodvold, KA., editors. *Drug Interactions in Infectious Diseases*. Vol. 2nd ed.. Totowa, NJ: Humana Press; 2005. p. 101-136.
32. Gerber JG, Rosenkranz SL, Fichtenbaum CJ, et al. Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005;39:307–312. [PubMed: 15980690]
33. Sriwiriyan S, Mahatthanatrakul W, Ridditid W, et al. Effect of efavirenz on the pharmacokinetics of ketoconazole in HIV-infected patients. *Eur J Clin Pharmacol* 2007;63:479. [PubMed: 17345073]
34. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Department of Health and Human Services; [Accessed February 3, 2008]. p. 1-113. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
35. Kashuba, AD.; Bertino, JS. Mechanisms of drug interactions I: absorption, metabolism, and excretion. In: Piscitelli, SC.; Rodvold, KA., editors. *Drug Interactions in Infectious Diseases*. Vol. 2nd ed.. Totowa, NJ: Humana Press; 2005. p. 13-39.
36. Tang C, Kassahun K, McIntosh I, et al. Simultaneous determination of urinary free cortisol and 6 β -hydroxycortisol by liquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry and its application for estimating hepatic CYP3A induction. *J Chromatogr B Biomed Sci Appl* 2000;742:303–313. [PubMed: 10901135]
37. Tomlinson ES, Maggs JL, Park BK, et al. Dexamethasone metabolism in vitro: species difference. *J Steroid Biochem Mol Biol* 1997;62:345–352. [PubMed: 9408089]

38. Jonsson G, Astrom A, Andersson P. Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver. *Drug Metab Dispos* 1995;23:137–142. [PubMed: 7720517]
39. Kotlyar M, Brewer ER, Golding M, et al. Nefazodone inhibits methylprednisolone disposition and enhances its adrenal-suppressant effect. *J Clin Psychopharmacol* 2003;23:652–656.

FIGURE 1.

Median interquartile ranges of prednisolone concentration versus time profiles for 3 HIV-positive groups when administered concurrently with (1) lopinavir/ritonavir, (2) efavirenz, or (3) a control group receiving no ARVs. Bars represent range of data for each group. Solid dots represent outliers from the range of data. LPV/r, lopinavir/ritonavir; EFV, efavirenz; No ARVs, no antiretrovirals.

TABLE 1

Study Subject Demographics

	Lopinavir/Ritonavir n = 10	Efavirenz n = 10	No ARVs n = 10
Age, mean yrs $\pm$ SD	43 $\pm$ 4.7	42 $\pm$ 6.3	37 $\pm$ 8.7
Weight, mean kg $\pm$ SD	81 $\pm$ 16	78 $\pm$ 7	84 $\pm$ 24
Race, n			
African American	4	1	8
White	3	2	0
Hispanic	3	7	2
Sex, n			
Female	3	1	3
Male	7	9	7
CD4+, median cells/mm ³ (range)	445 (271–1807)	534 (260–1016)	498 (278–1012)
HIV RNA			
<50 copies/mL, n	7	10	2
>50 copies/mL, n (median copies/mL; range)	3 (77; 61–9952)	0	8 (8042; 1420–13862)

TABLE 2

Prednisolone Pharmacokinetic Parameter Values After a Single 20-mg Oral Dose of Prednisone in 3 Different Groups of HIV-Infected Individuals

Pharmacokinetic Parameter	Study Group		
	1 Lopinavir–ritonavir *	2 Efavirenz *	3 No ARV therapy
$AUC_{0-\infty}(\text{ng h/mL})^{\ddagger}$	2443 (2065 to 2821)	1475 (1176 to 1774)	1858 (1542 to 2174)
$C_{\max}(\text{ng/mL})^{\ddagger}$	341 (297 to 385)	257 (231 to 283)	300 (277 to 323)
$T_{\max}(\text{h})^{\ddagger}$	1.0 (0.5, 6.0)	2.0 (0.5, 8.0)	1.5 (0.5, 4.0)
$T_{1/2}(\text{h})^{\ddagger}$	2.27 (1.78 to 2.76)	1.42 (1.17 to 1.67)	2.39 (1.70 to 3.08)
$CL/F (\text{L/h})^{\ddagger}$	8.19 (7.30 to 9.08)	13.56 (11.57 to 15.55)	10.76 (8.82 to 12.7)

* Subjects were receiving the indicated medication (lopinavir–ritonavir or efavirenz, for groups 1 and 2, respectively) for at least 30 days before pharmacokinetic sampling.

[†] Geometric mean value (90% CI).

[‡] Median value (minimum, maximum).

TABLE 3

Prednisolone Pharmacokinetic Parameter Values After a Single 20-mg Oral Dose of Prednisone in 30 HIV-Positive Volunteers Compared by GMRs

Parameter*	GMRs (90% CI)		
	Groups 1–3	Group 2 Versus 1	Group 2 Versus 3
AUC _{0–∞} (ng h/mL)	1.31 (<i>P</i> = 0.18)	0.60 (<i>P</i> = 0.006)	0.80 (<i>P</i> = 0.48)
C _{max} (ng/mL)	1.14 (<i>P</i> = 0.42)	0.75 (<i>P</i> = 0.03)	0.85 (<i>P</i> = 0.52)
T _{max} (h)	—	—	—
T _{1/2} (h)	0.95 (<i>P</i> = 0.95)	0.62 (<i>P</i> = 0.14)	0.60 (<i>P</i> = 0.04)
CL/F (L/h)	0.76 (<i>P</i> = 0.16)	1.66 (<i>P</i> = 0.001)	1.26 (<i>P</i> = 0.18)

GMR values with *P* < 0.05 are in bold.

* Group 1 = lopinavir/ritonavir; group 2 = efavirenz; group 3 = HIV+ receiving no ARVs.