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The Steady-State Pharmacokinetics of Efavirenz and Nevirapine When Used in Combination in Human Immunodeficiency Virus Type 1–Infected Persons

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The steady-state pharmacokinetics of efavirenz and nevirapine, when used in combination to treat human immunodeficiency virus type 1 (HIV-1)–infected subjects, were investigated. HIV-1–infected persons who had used efavirenz (600 mg once daily) for ⩾2 weeks were eligible for study inclusion. The plasma pharmacokinetics of efavirenz were determined over 24 h. Subsequently, nevirapine (400 mg once daily) was added to the regimen. After 4 weeks, the pharmacokinetics of efavirenz and nevirapine were assessed over 24 h. The differences between the pharmacokinetic parameters of efavirenz with and without nevirapine were analyzed, and the pharmacokinetics of nevirapine were compared with those in historical control patients. The exposure to efavirenz when combined with nevirapine was significantly decreased by 22% (area under the plasma concentration vs. time curve), 36% (minimum plasma concentration), and 17% (maximum plasma concentration). Nevirapine pharmacokinetics appear to be unaffected by coadministration of efavirenz, compared with data from historical control patients.

The currently recommended regimen for initiation of therapy for human immunodeficiency virus type 1 (HIV-1) infection consists of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 or 2 protease inhibitors (PIs), 2 NRTIs, and 1 nonnucleoside reverse-transcriptase inhibitor (NNRTI), or 3 NRTIs [1]. During the last several years, a number of alternative regimens have been tested in clinical trials, such as triple NRTI regimens [2, 3]. Other possible combinations are a single PI and 1 NNRTI or 2 PIs [4–6].

Another strategy, not yet evaluated, consists of administering 2 NNRTIs (e.g., nevirapine and efavirenz), with a backbone of 2 NRTIs. When these 2 agents are combined, the possibility exists that compartments or sanctuaries of the body may be more effectively reached. For example, if nevirapine penetrates a designated compartment (e.g., the brain, testes, or specific cell types) better than does efavirenz, efavirenz could penetrate another specific compartment better than does nevirapine. A further potential benefit is that the total NNRTI exposure is increased and more pressure is put on viral replication, while efavirenz and nevirapine have different toxicity profiles.

In a large clinical trial (designated "2NN" for double nonnucleoside) and in a smaller cohort study, the concomitant use of efavirenz and nevirapine is being explored, but no formal pharmacokinetic study is available to describe the combined use of these 2 NNRTIs [7]. A pharmacokinetic study is necessary, since both efavirenz and nevirapine are metabolized by, and influence, the activity of cytochrome (CYP) P450 isoenzymes, and changes in expected exposure to these NNRTIs might occur. The major isoenzymes that are responsible for the biotransformation of efavirenz are CYP3A4 and 2B6. In vivo, efavirenz causes induction of the CYP3A4 isoenzyme and increases the biotransformation of several drugs that are metabolized by CYP3A4. In vitro studies also have shown that efavirenz inhibits the CYP isoenzymes 2C9, 2C19, and 3A4 at concentrations in the range of those achieved clinically [8]. In vitro studies of nevirapine biotransformation have demonstrated that the isoenzymes CYP3A4 and CYP2B6 are responsible for the metabolism of nevirapine and, to a lesser extent, CYP2D6 [9]. The metabolism of both efavirenz and nevirapine is an autoinducible enzymatic process [8, 9]. From the available data, it is not possible to predict whether the steady-state pharmacokinetic parameters of efavirenz and/or nevirapine would

be altered when the drugs are coadministered. This study investigated whether the steady-state plasma pharmacokinetics of efavirenz or nevirapine in HIV-1–infected patients are affected by the coadministration of nevirapine and efavirenz.

Patients and Methods

Patients. HIV-1–infected persons were recruited during June through August 1999 from the outpatient clinics of the St. Paul's Hospital, Vancouver; the Chelsea and Westminster Hospital and the Royal Free Hospital, London; and the South Florida Bioavailability Clinic, Miami. Patients ⩾18 years old with confirmed HIV-1 infection were eligible if they had taken efavirenz as part of their antiretroviral regimen in a dose of 600 mg once daily for ⩾2 weeks and if they had plasma HIV-1 RNA concentrations <400 copies/mL. However, a physician could include a patient with >400 copies/mL in plasma who had no other treatment options available.

Exclusion criteria included the concomitant use of a PI or malabsorption, nausea, emesis, abdominal discomfort, chronic diarrhea, documented active clinically relevant hepatitis, any ongoing opportunistic infection, or the expectation that a patient's drug regimen or dosage would be changed during the study. Women of reproductive potential who were unwilling to use an effective method of contraception during the study period or who were pregnant or breast-feeding were not eligible.

Laboratory exclusion criteria were a hemoglobin concentration <7.0 mmol/L (men) or <6.5 mmol/L (women), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations >5 times the upper limit of normal, and a serum creatinine concentration >1.5 times the upper limit of normal.

The target sample number *(n)* was determined on the basis of an a priori selection of $\alpha = .05$ and $\beta = .1$, an estimated coefficient of variation in pharmacokinetic parameters of efavirenz of 20%, and a minimum detectable difference in efavirenz pharmacokinetic parameters of ~20%. These criteria resulted in a minimum of 13 patients. Continuation of concurrent medication at the time of enrollment was allowed. Plasma HIV-1 RNA concentrations were locally determined at screening and on days 29 and 43.

Study design. At the screening visit, patients were instructed to continue the ingestion of efavirenz capsules (600 mg; 200-mg capsules of Sustiva, DuPont Pharmaceutical) in the morning (~9 A.M.) for the complete study period (until day 43 of the study). After 2 weeks (i.e., day 15 of the study), the pharmacokinetic profile of orally administered efavirenz was assessed over 24 h. The next day, nevirapine (200-mg tablets of Viramune; Boehringer Ingelheim) was added to the regimen in a dosage of 200 mg once daily in the morning. Participants were instructed to ingest efavirenz and nevirapine simultaneously in the morning of each study day at about the same time. After 2 weeks (i.e., study day 29), the dosage of nevirapine was increased to 400 mg once a day in the morning. On day 43, the pharmacokinetic profiles of orally administered efavirenz and nevirapine during 24 h were assessed. Use of nevirapine was stopped after study day 43, and the patients continued their prestudy antiretroviral regimen. Blood was drawn to determine hemoglobin, ALT, AST, bilirubin, alkaline phosphatase, and serum creatinine levels at the screening visit and at study days 15 and 43.

Drug administration and sampling. On days 15 and 43 of the study, participants came to the hospital between 8 and 9 A.M. after an overnight fast. No drugs had been ingested at that time. Efavirenz (study day 15) or efavirenz simultaneously with nevirapine (study day 43) was ingested with a glass of water (observed intake). Other prescribed drugs were administered 90 min after intake of the NNRTIs during a standard breakfast. Blood samples were drawn at designated time intervals associated with the ingestion of the study medication. Venous blood (5 mL) was drawn just before ingestion of the study drugs and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h after ingestion. Blood samples were collected in heparinized tubes, and, within 1 h after the samples were drawn, plasma was separated by centrifugation at 900 *g* for 10 min. Plasma was subsequently stored at −70°C until analysis.

Bioanalysis of nevirapine and efavirenz. Concentrations of nevirapine in plasma were quantitatively determined at the Laboratory of the Department of Pharmacy and Pharmacology of Slotervaart Hospital, Amsterdam, with sensitive and validated reversed-phase high-performance liquid chromatographic (HPLC) assays with UV detection [10, 11]. For both assays, sample pretreatment consisted of protein precipitation with acetonitrile. Subsequently, both compounds were separated from endogenous compounds by isocratic reversed-phase HPLC.

Pharmacokinetic analysis. Plasma concentration data, $C - T,$ where $C =$ plasma concentration and $T =$ time, were analyzed by noncompartmental methods [12]. The highest observed plasma concentration was defined as the C_{max}, with the corresponding sampling time as T_{max}. The area under the plasma concentration versus time curve from 0 to 24 h ($AUC_{[0-24 \, h]}$) was obtained by using the trapezoidal rule. The concentration 24 h after ingestion of the drugs was defined as the trough concentration (C_{min}). The terminal log-linear period (log C vs. T) was defined by the last data points ($n \geqslant 3$) by visual inspection. The absolute value of this slope ($\beta/1n10$) was calculated by least squares regression analysis. The elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 1n2/\beta$. The apparent oral clearance (Cl/F, where F represents the oral bioavailability of efavirenz or nevirapine) was calculated by dividing the dose by the $AUC_{[0-24 \, h]}$. The apparent volume of distribution *(V/F)* was calculated by dividing Cl/F by β.

Statistical analysis. Statistical calculations were done with SPSS for Windows software (version 6.1; SPSS). To detect a difference in the pharmacokinetic parameters of efavirenz on days 15 and 43, we used the Wilcoxon matched pairs signed-rank test. The Mann-Whitney *U* test was used to compare the pharmacokinetic parameters of nevirapine when administered in combination with efavirenz with those of nevirapine when administered as a single NNRTI (historical controls). These historical controls were obtained from a pharmacokinetic study of 20 HIV-1–infected subjects [13]. That study investigated and compared the steady-state plasma pharmacokinetics of nevirapine in a dosing regimen of 400 mg once daily versus 200 mg twice daily. The study participants had been taking nevirapine as part of their antiretroviral regimen and were randomized to continue the current regimen (200 mg twice daily) or to switch to the alternate regimen (400 mg once daily). The steady-state plasma pharmacokinetics of nevirapine were assessed after 2 weeks over 24 h. Subsequently, patients were switched to the alternate regimen, and the pharmacokinetics of nevirapine were assessed again after 2 weeks. The nevirapine plasma concentrations in the samples were analyzed by using the same analytical method

and in the same laboratory [13]. The pharmacokinetic data from the once daily regimen were used for comparison with the present study. $P \leq .05$ was considered statistically significant.

Results

Patients

Nineteen male patients were included in this study. Two patients were excluded from data analysis because they underwent pharmacokinetic sampling only on study day 15. The first patient ceased participation because of family circumstances and the second because of nausea and feeling unwell when nevirapine was introduced on study day 16. Three other patients were excluded from analysis because they ingested nevirapine only at the pharmacokinetic study day 43 and were not at steady state. The predose concentrations of efavirenz in 2 of the 3 subjects were 0.72 and 0.62 mg/L; that of the third subject was below the lower limit of quantitation (0.01 mg/L). All predose nevirapine plasma concentrations were below the lower limit of quantitation (0.02 mg/L). The 24-h postdose concentrations of efavirenz and nevirapine were 0.89, 0.82, and 0.65 and 1.69, 2.76, and 2.90 mg/L, respectively. On the basis of these data, these 3 patients were omitted from the analyses.

The baseline characteristics of the remaining 14 evaluable patients are shown in table 1. Concomitantly administered drugs (including their doses) were not changed during the study period. All patients used efavirenz in combination with a backbone of 2 or more NRTIs. One patient also took fluconazole. Baseline characteristics of the historical controls with respect to age, HIV-1 RNA plasma concentration, and clinical chemical parameters were comparable with those of the study population. Five historical controls were women, and relevant co-medications included indinavir (3 patients), nelfinavir (2), ritonavir (5), saquinavir (2), and fluconazole (1) [13].

HIV-1 RNA Plasma Concentration

The HIV-1 RNA plasma concentrations remained stable in all 14 evaluable patients during the study period. Twelve of 14

Table 1. Characteristics of 14 human immunodeficiency virus type 1 (HIV-1)–infected persons at baseline and at study end (day 43).

Characteristic	Baseline Median	Baseline IQR	Study day 43 Median	Study day 43 IQR
Age, years	40	34–44	NA	NA
Plasma HIV-1 RNA, copies/mL	<50	<50 to <50	<50	<50 to <50
Alanine aminotransferase, U/L	36	26–64	33	21–57
Aspartate aminotransferase, U/L	36	24–53	34	21–41
Total bilirubin, μmol/L	9	7–14	10	9–13
Alkaline phosphatase, U/L	70	59–78	74	61–83
Serum creatinine, μmol/L	80	70–89	80	71–92
CD4:CD8 cell ratio	0.47	0.30–0.60	0.48	0.31–0.62
CD4 cell count, 10^6 cells/L	441	329–486	421	325–519
CD8 cell count, 10^6 cells/L	955	753–1328	905	760–1019

NOTE. IQR, interquartile range; NA, not applicable.

patients had an undetectable HIV-1 RNA plasma concentration at baseline (<50 copies/mL) and had an undetectable HIV-1 RNA plasma concentration at study day 43. The remaining 2 patients had baseline HIV-1 RNA plasma concentrations of 1157 and 2296 copies/mL, respectively. HIV-1 RNA plasma concentrations at study day 43 were 1032 and 16,479 copies/mL, respectively.

Safety

The combination of efavirenz and nevirapine was well tolerated in all but 2 patients. One patient experienced nausea and felt unwell when nevirapine was introduced and withdrew from the study. A second patient reported peripheral neuropathy after nevirapine was added to his regimen. He did not drop out of the study. In all evaluable patients, no changes were seen in ALT, AST, bilirubin, alkaline phosphatase, serum creatinine, or hemoglobin levels.

Pharmacokinetic Analysis

Efavirenz 600 mg once daily. The median plasma concentration of efavirenz versus time curves determined on the pharmacokinetic study days are shown in figure 1. Table 2 lists median values (and interquartile ranges [IQRs]) of the plasma pharmacokinetic parameters of efavirenz alone and in combination with nevirapine. Exposure to efavirenz, as measured by the $AUC_{[0-24\ h]}$, was significantly decreased when nevirapine was added ($P = .001$). The median decrease in $AUC_{[0-24\ h]}$ was 22% (IQR, 13%-41%). The C_{max} and C_{min} were also significantly decreased ($P = .048$ and $P = .001$, respectively). The median decrease in the C_{max} was 17% (IQR, 0%–33%), and the median decrease in the plasma trough concentration was 36% (IQR, 21%–52%).

Nevirapine 400 mg once daily. The median nevirapine plasma concentration versus time curves of patients participating in this study and of the historical controls are shown in figure 2. Median values (and IQRs) of the steady-state plasma pharmacokinetics of nevirapine in a dosage of 400 mg once daily alone (historical controls) and in combination with efavirenz, are shown in table 3. The exposure to nevirapine, as measured by the $AUC_{[0-24\ h]}$, was not significantly different in the 2 groups ($P = .62$). Furthermore, the values for the C_{max}, C_{min}, T_{max}, $t_{1/2}$, Cl/F, and V/F were not significantly different ($P \geq .07$).

Discussion

This study was performed to investigate the steady-state pharmacokinetics of efavirenz and nevirapine when used in combination in HIV-1–infected persons. The results demonstrate that exposure to efavirenz is significantly decreased in combination with nevirapine (median decrease in $AUC_{[0-24\ h]}$ and in C_{min}, 22% and 36%, respectively). The difference between
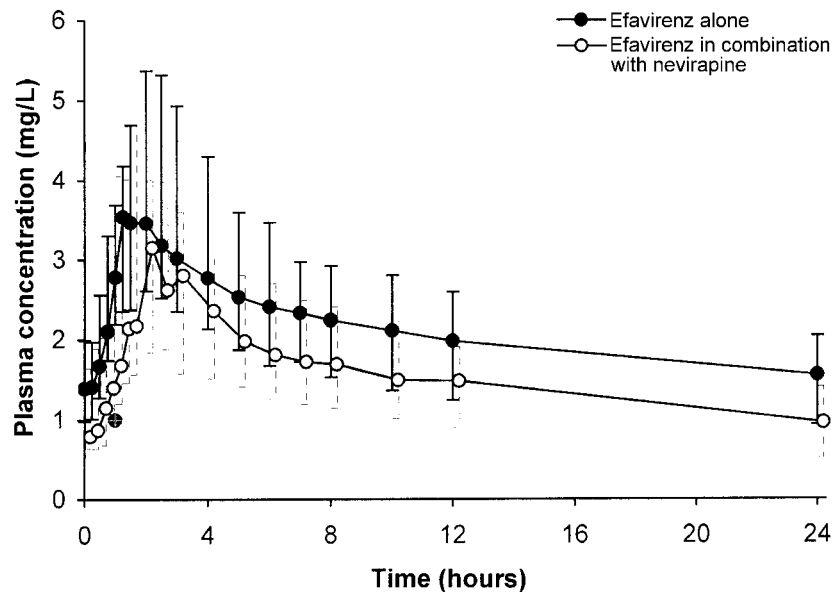
Figure 1. Median efavirenz plasma concentration (mg/L) vs. time curve: day 15, efavirenz alone ($n = 14$); and day 43, efavirenz with nevirapine ($n = 14$). Vertical bars indicate interquartile ranges.

the elimination half-lives of efavirenz on study days 29 and 43 seemed substantial, but these values should be interpreted with care, since the sampling time was only 24 h.

There were a few differences between the study population and the historical controls. Five historical controls were women (compared with all men in the study population), and some used ≥1 PI in combination with nevirapine. In a phase 1 study in 30 healthy volunteers (15 women and 15 men), the apparent volume of distribution of nevirapine was higher in the female subjects than in the male subjects. However, the difference was offset by a slightly shorter terminal phase half-life in the women, resulting in no significant sex-related difference in nevirapine plasma concentrations [14]. The influence of nevirapine

on the pharmacokinetics of concomitantly administered PIs is substantial, but the effect of PIs on the pharmacokinetics of nevirapine is negligible [15]. However, due to these differences between the study population and the historical controls, we can conclude from this study only that the exposure to nevirapine appears to be unaffected by coadministration of efavirenz, when compared with historical control data.

The metabolism of both efavirenz and nevirapine is an autoinducible enzymatic process. When nevirapine is added to efavirenz, the exposure to efavirenz is decreased, most likely due to increased metabolism. The clinical relevance of a decrease in the exposure to efavirenz is not known. However, since efavirenz and other NNRTIs have intrinsic pharmacologic activity, correlations between the plasma drug concentration and virologic response are anticipated. For PIs, strong indications exist that the virologic effects are associated with the pharmacologic exposure [16–19]. For NNRTIs, 1 study reported a correlation between efavirenz trough concentrations and virologic response [20]. In this study, treatment failure was 3 times as frequent in patients with a trough concentration <3.5 μM (<1.1 mg/L) as in patients with higher trough concentrations. Until now, 2 studies have reported relationships between nevirapine plasma concentrations and virologic effect [21, 22]. The first study (51 patients) described relationships between nevirapine exposure and initial virus clearance, the duration of virologic response, and the achievement of an undetectable HIV-1 RNA concentration after 52 weeks of treatment. The second (with 7 patients) reported a correlation between nevirapine trough concentrations and a decrease in immune complex–dissociated serum HIV p24 antigen levels. No data are yet

Table 2. Steady-state plasma pharmacokinetic parameters (median and interquartile range [IQR]) of efavirenz alone (study day 15) and in combination with nevirapine (study day 43) in 14 human immunodeficiency virus type 1 (HIV-1)–infected subjects.

Parameter	Study day 15		Study day 43		
	Median	IQR	Median	IQR	P^a
$AUC_{[0-24\,h]}$, h*mg/L	54.8	33.3–66.6	38.8	23.9–54.3	.001
C_{max}, mg/L	3.63	2.61–5.37	3.36	1.93–4.24	.048
C_{min}, mg/L	1.55	0.93–2.04	0.96	0.51–1.40	.001
T_{max}, h	2.0	1.5–3.0	2.2	1.5–2.5	.84
$t_{1/2}$, h	35.8	18.11–50.6	18.9	14.8–34.0	.06
Cl/F, L/h	11.1	9.1–18.1	15.7	11.1–36.2	.001
V/F, L	506.6	307.5–851.7	416.8	334.9–929.7	.88

NOTE. AUC, area under plasma concentration vs. time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; T_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; Cl/F, apparent oral clearance; V/F, apparent volume of distribution.

[a] For differences between pharmacokinetic parameters of efavirenz with and without coadministration of nevirapine (Wilcoxon matched pairs signed-rank test).
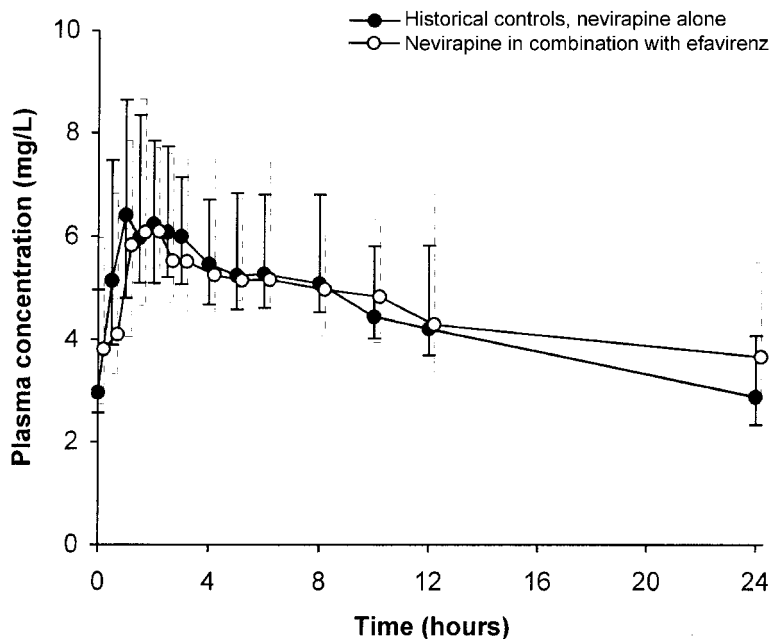
Figure 2. Median nevirapine plasma concentration (mg/L) vs. time curve: nevirapine alone (historical controls; $n = 20$) and nevirapine in combination with efavirenz ($n = 14$). Vertical bars indicate interquartile ranges.

available regarding the minimum exposure or plasma concentration of efavirenz or nevirapine that should be reached to provide adequate suppression of viral replication—or even to establish whether this is clinically relevant.

During this study, the combined use of efavirenz and nevirapine for 4 weeks appeared to be safe. No rash or other serious adverse events were reported when nevirapine was added to the efavirenz-containing regimen. Only 1 patient discontinued study participation when nevirapine was added to the efavirenz-containing regimen. Another patient reported peripheral neuropathy when nevirapine was added but remained in the study.

Table 3. Steady-state plasma pharmacokinetic parameters (median and interquartile range [IQR]) of nevirapine alone (historical controls) and in combination with efavirenz (study day 43) in human immunodeficiency virus type 1 (HIV-1)–infected subjects.

Parameter	Historical controls[a]		Study day 43		
	Median	IQR	Median	IQR	P[b]
$AUC_{[0-24\ h]}$, h*mg/L	101.8	92.6–145.3	112.1	93.6–166.2	.62
C_{max}, mg/L	6.69	5.95–8.64	6.19	5.12–8.79	.51
C_{min}, mg/L	2.88	2.33–4.09	3.66	2.86–5.51	.25
T_{max}, h	1.5	1.0–2.4	2.0	1.5–3.4	.38
$t_{1/2}$, h	21.5	15.0–32.8	27.0	16.4–35.2	.34
Cl/F, L/h	3.9	2.8–4.3	3.6	2.4–4.3	.61
V/F, L	116.5	88.5–161.8	143.8	117.9–199.4	.07

NOTE. AUC, area under plasma concentration vs. time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; T_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; Cl/F, apparent oral clearance; V/F, apparent volume of distribution.

[a] See [13].
[b] For differences between pharmacokinetic parameters of nevirapine with and without coadministration of efavirenz (Mann-Whitney U test).

No significant changes in ALT, AST, bilirubin, alkaline phosphatase, serum creatinine, or hemoglobin levels were observed. One patient had a substantial increase in HIV-1 RNA plasma concentration (from 2296 at baseline to 16,479 HIV-1 RNA copies/mL at the end of the study). Neither the exposure (measured as AUC) to efavirenz on both study days (60.23 and 51.32 h*mg/L, respectively) nor the exposure to nevirapine on study day 43 (101.43 h*mg/L) was decreased, in comparison with the median values observed in the study population. Thus, the exposure to either of the NNRTIs explains the increase in HIV-1 RNA plasma concentration.

In conclusion, our results show a decreased exposure to efavirenz, when used in combination with nevirapine. More pharmacokinetic studies are needed to assess which efavirenz dose will result in the same efavirenz exposure achieved when efavirenz is used without nevirapine. These results also suggest that the nevirapine dose may not need modification when used with efavirenz, but again, well-controlled pharmacokinetic studies are needed before such a recommendation can be made.

Acknowledgments

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References

1. Carpenter CC, Cooper DA, Fischl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society–USA Panel. JAMA **2000**;283:381–90.
2. Gatell J, Murphy R, Katlama C, et al. The ATLANTIC study: a randomized, open-label trial comparing two protease inhibitor (PI)–sparing antiretroviral strategies versus a standard PI-containing regimen, 48 week data [abstract 1243]. In: Program and abstracts of the Seventh European Conference on Clinical Aspects and Treatment of HIV-Infection (Lisbon). Belgium: European AIDS Clinical Society (EACS), **1999**:14.
3. Staszewski S, Keiser P, Gatje J, et al. Ziagen/combivir is equivalent to indinavir/combivir in antiretroviral therapy (ART) naive adults at 24 weeks (CNA3005) [abstract 20]. In: Program and abstracts of the Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, 31 January–4 February 1999 (http://www.retroconference.org).
4. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 team. N Engl J Med **1999**;341:1865–73.
5. Moyle G, Pozniak A, Opravil M, et al. The SPICE study: 48-week activity of combinations of saquinavir soft gelatin and nelfinavir with and without nucleoside analogues. J Acquir Immune Defic Syndr **2000**;23:128–37.
6. Gisolf EH, Jurriaans S, Pelgrom J, et al. The effect of treatment intensification in HIV-infection: a study comparing treatment with ritonavir/saquinavir and ritonavir/saquinavir/stavudine. Prometheus Study Group. AIDS **2000**;14:405–13.
7. Jordan W, Jefferson R, Yemofio F, et al. Nevirapine (NVP) + efavirenz (EFV) + didanosine (ddI): a very simple, safe, and effective once-daily regimen [abstract TuPeB3207]. In: Program and abstracts of the XIII International AIDS Conference, Durban, Republic of South Africa, 2000. Durban: Ince (Pty) Ltd., **2000**:358.
8. Adkins JC, Noble S. Efavirenz. Drugs **1998**;56:1055–64.
9. Murphy RL, Montaner J. Nevirapine: a review of its development, pharmacological profile and potential for clinical use. Exp Opin Invest Drugs **1996**;5:1183–99.
10. Van Heeswijk RPG, Hoetelmans RMW, Meenhorst PL, Mulder JW, Beijnen JH. Rapid determination of nevirapine in human plasma by ion-pair reversed-phase high-performance liquid chromatography with ultraviolet detection. J Chromatogr B Biomed Appl **1998**;713:395–99.
11. Veldkamp AI, Van Heeswijk RPG, Meenhorst PL, et al. Quantitative determination of efavirenz (DMP 266), a novel non-nucleoside reverse transcriptase inhibitor, in human plasma using isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection. J Chromatogr B Biomed Appl **1999**;734:55–61.
12. Gibaldi M. Biopharmaceutics and clinical pharmacokinetics. 4th ed. Philadelphia: Lea & Febiger, **1991**:14–23.
13. Van Heeswijk RPG, Veldkamp AI, Wit FWNM, et al. The steady-state pharmacokinetics of nevirapine during once daily and twice daily dosing in HIV-1 infected individuals. AIDS **2000**;14:F77–82.
14. Lamson MJ, Cort S, Sabo JP, et al. Effects of gender on the single and multiple dose pharmacokinetics of nevirapine 200 mg/day [abstract 3004]. In: Program and abstracts of the XI International Conference on AIDS (Vancouver, Canada). Vancouver: XI International Conference on AIDS Society, **1996**.
15. Barry M, Mulcahy F, Merry C, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. Clin Pharmacokinet **1999**;36:289–304.
16. Hoetelmans RMW, Van Heeswijk RPG, Meenhorst PL, et al. Plasma concentrations of saquinavir (SQV) determine HIV-1 RNA response over a 48-week period [abstract 42261]. In: Program and abstracts of the 12th World AIDS Conference (Geneva, Switzerland). Stockholm: International AIDS Society, **1998**:825.
17. Hoetelmans RMW, Reijers MHE, Weverling GJ, et al. The effect of plasma drug concentrations on HIV-1 clearance rate during quadruple therapy. AIDS **1998**;12:F111–5.
18. Harris M, Durakovic C, Rae S, et al. A pilot study of nevirapine, indinavir, and lamivudine among patients with advanced human immunodeficiency virus disease who have had failure of combination nucleoside therapy. J Infect Dis **1998**;177:1514–20.
19. Murphy RL, Sommadossi JP, Lamson M, Hall DB, Myers M, Dusek A. Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1. J Infect Dis **1999**;179:1116–23.
20. Joshi AS, Barrett JS, Fiske WD, et al. Population pharmacokinetics of efavirenz in phase II studies and relationships with efficacy [abstract A113]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1999**. Available at http://www.euro-aids99.com.
21. Veldkamp AI, Hoetelmans RMW, Beijnen JH, et al. High exposure to nevirapine is associated with a higher initial HIV-1 clearance rate, a higher likelihood to reach undetectability and prolonged suppression of HIV-1 replication [abstract 239]. In: Program and abstracts of the Seventh European Conference on Clinical Aspects and Treatment of HIV-Infection (Lisbon). Belgium: European AIDS Clinical Society (EACS), **1999**.
22. Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. J Infect Dis **1995**;171:537–45.