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# NNRTI pharmacokinetics in a large unselected cohort of HIV-infected women

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## Abstract

**Background—**Small intensive pharmacokinetic (PK) studies of medications in early-phase trials cannot identify the range of factors that influence drug exposure in heterogeneous populations. We performed PK studies in large numbers of HIV-infected women on nonnucleoside-reverse-transcriptase-inhibitors (NNRTIs) under conditions of actual use to assess patient characteristics that influence exposure and evaluated the relationship between exposure and response.

**Methods—**225 women on NNRTI-based antiretroviral regimens from the Women's Interagency HIV Study (WIHS) were enrolled into 12 or 24-hour PK studies. Extensive demographic, laboratory and medication covariate data was collected before and during the visit to be used in multivariate models. Total NNRTI drug exposure was estimated by area-under-the-concentration-time curves (AUC).

**Results—**Hepatic inflammation and renal insufficiency were independently associated with increased nevirapine (NVP) exposure in multivariate analyses; crack cocaine, high fat diets, and amenorrhea were associated with decreased levels (n=106). Higher efavirenz (EFV) exposure was seen with increased transaminase, albumin levels, and orange juice consumption; tenofovir use, increased weight, being African-American and amenorrhea were associated with decreased exposure (n=119). With every 10-fold increase in NVP or EFV exposure, participants were 3.3 and 3.6 times as likely to exhibit virologic suppression, respectively. Patients with higher drug exposure were also more likely to report side effects on therapy.

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**DISCLOSURES**

None of the authors have commercial or other associations that might pose a conflict of interest

**Conclusions—**Our study identifies and quantitates previously unrecognized factors modifying NNRTI exposure in the "real-world" setting. Comprehensive PK studies in representative populations are feasible and may ultimatley lead to dose optimization strategies in patients at risk for failure or adverse events.

### Keywords

HIV; antiretrovirals; nevirapine; efavirenz; pharmacokinetics; drug exposure; women

## INTRODUCTION

Despite the continuing successes of highly active antiretroviral therapy (HAART) in treated populations, these therapies have limitations. As many as 50% of patients fail to achieve sustained virologic responses on HAART, even in the era of more potent combination regimens[1], and viral resistance is increasingly problematic[1, 2]. ARVs have a range of adverse effects, resulting in high rates of regimen switching or discontinuation[3]. Treatment failures and adverse events are reported more frequently in cohort or clinic-based settings than in clinical trials for many drugs (including ARVs), which may reflect systematic differences in trial participants from "real world" populations. Clinical trial enrollees may be healthier[4], and, in the HIV setting, be less likely to be women and minorities[5], than treated populations.

Pharmacokinetic (PK) studies are often embedded within clinical trials investigating drug safety and efficacy to inform formulation and dosing of new medications. Typically, twelve to 24 hour intensive PK studies are performed in small subsets of patients to determine blood concentrations of drug after dosing at steady state. These focused intensive PK studies in relatively homogenous patient populations or non-HIV-infected volunteers are very important to determine ideal dosing and typical PK curves for new drugs. Conscribed sample sizes and restricted eligibility[6, 7] however, limit the generalizability of these PK findings to heterogeneous patient populations. The typical PK component of clinical trials does not thoroughly investigate the range of individual characteristics (e.g. concurrent medical conditions, dietary patterns, weight differences, ethnicity and gender, use of concomitant medications or recreational drugs) common among patients who will eventually receive drug prescriptions. The end result can be the revelation of unanticipated adverse effects and treatment failures after drug approval and dissemination[8].

We present here the largest intensive PK study performed to date to assess modifiers of exposure for two commonly used nonnucleoside-reverse-transcriptase-inhibitor (NNRTIs) in a diverse cohort of HIV-infected women. In addition to its size and representation of actual HIV-infected populations, the study was performed under conditions of actual use, where participants took their regular concomitant medications, consumed a typical diet, smoked cigarettes as usual, etc., during PK sampling. We also report on the association between drug exposure and virologic response and self-reported side effects in this unselected cohort.

## METHODS

### Study population

The Women's Interagency HIV Study (WIHS) is a large multicenter, prospective cohort study of HIV-infected (and at-risk uninfected) women established in 1994[9]. The cohort is highly representative of HIV-infected women in the United States in terms of age, race, ethnicity, socioeconomic status, rates of substance use, degree of infirmity, and coinfections. All WIHS participants are seen biannually for structured interviews, physical examinations, and specimen collection. For those on HAART, antiretroviral therapy is prescribed by participants' primary providers and not by the observational study. The participating WIHS sites are located in

Washington DC, Bronx, Brooklyn, Chicago, and Northern California. Simulation methods were used to evaluate sample size for identifying a large number of predictors of drug exposure, as estimated by area-under-the-plasma-concentration-time-curve (AUC) from intensively studied subjects, and we found that approximately 110 patients per drug should be sufficient to identify a range of important factors in PK variability[10].

## Intensive PK protocol methods

Enrollment for the "WIHS Intensive PK Study" was initiated in April 2003 and all participants on efavirenz (EFV) or nevirapine (NVP)-based HAART regimens were offered enrollment. The only eligibility criteria for participation in the intensive PK protocol were use of a target ARV for at least six months and participant informed consent. Committees on Human Research at all participating institutions approved the study.

Participants were brought into clinical research centers associated with each of the WIHS sites for 12 or 24-hour sampling of the ARV under conditions of routine use. Participants were seen for the PK visit within six weeks of their core WIHS visit since data collected at both the preceding core visit and substudy visit were used in subsequent exposure models. NVP is usually dosed at 200mg twice a day and drug concentrations were obtained over 12 hours; EFV is typically dosed at 600mg daily and drug levels were measured over a 24 hour period. During the intensive PK visit, a series of plasma samples were collected at various time points relative to the dosing of the target ARV (0, 0.5, 1, 2, 4, 6, 8, and 12 hours after witnessed dosing for NVP; 0, 4, 8, 15, 18, and 24 hours after witnessed dosing of EFV). Actual times of plasma collection were recorded. The participant's usual diet was ascertained by phone prior to the PK visit and simulation of her typical diet was undertaken during the visit. Concomitant medications were administered as usual during PK sampling. While recreational drugs were not permitted during the visit, their use prior to initiation of the protocol, if routine for the subject, did not preclude participation and was recorded as data. If routine for the participant, cigarette smoking was allowed during the visit between blood draws.

On the day of the study visit, participants were administered a series of questionnaires, including details on their current ARV regimen and degree of adherence, use of concomitant medications, recent or current symptoms and illnesses, current menstrual, contraceptive, and obstetric events, substance use patterns, and diet. Weights and urine pregnancy tests were performed during the visit. The longitudinal WIHS core data set included measures of height, fat free mass as measured by bioelectrical impedance analysis, renal, hepatic and other laboratory measurements over time, further menstrual history, and hepatitis B and C coinfection status.

## Laboratory procedures

Procedures for measuring ARV blood levels have been described previously[11]. Plasma samples (0.1 mL) were prepared for injection by adding A-86093 (Abbott Laboratories, Abbott Park, IL) as an internal standard, adding acetonitrile (0.4 mL) to precipitate the protein, mixing, centrifuging, transferring the supernatant to an autosampler vial, and diluting if necessary. Plasma was analyzed for nevirapine and efavirenz by standard techniques of liquid chromatography/tandem mass spectrometry[12]. Nevirapine was analyzed with a ZORBAX Eclipse XDB-C8 (4.6 × 50 mm, 3.5 μm particle size) analytical column and an XDB-C8 (4.6 × 12.5 mm) guard column (Agilent Technologies; Palo Alto, CA). Efavirenz was analyzed with a BDS Hypersil C18 (4.6 × 50 mm, 5 μm) analytical column and a 3 mm × 2 mm ODS guard column (Thermo Electron Corp.; Waltham, MA). Data analysis was performed with MassLynx 3.5 software (Micromass, Manchester, UK). The absolute recovery of NNRTIs from plasma was 94.2% for nevirapine and 99.8% for efavirenz. Intra- and interday precision was

<11.7% for both NNRTIs and accuracies ranged from −2.9% to 0.7% for NVP and −6.0% to 14.8% for EFV[11].

## Study measurements

**Outcome variables—**The outcome variable for the intensive PK study pharmacokinetic analyses is total drug exposure. The dose-adjusted parameter used to define exposure was "AUC/dose", where AUC is the area-under-the-plasma concentration-time curve and dose is the target ARV dose witnessed at the start of the PK sampling. Since our study was observational in nature, each participant brought in her usual dose of the target ARV for witnessed consumption during the study. Four of the women on EFV and 10 of the women on NVP were prescribed or used doses disparate than the standard unit-doses for each of these agents. AUCs were calculated using the trapezoidal rule and the other exposure metrics were calculated using traditional equations programmed in *Stata/SE version 9.2.* If a missing datapoint occurred before the first or after the last observation, it did not contribute to the calculations; if the missing time or concentration occurred between two observed datapoints, it was extrapolated from a straight line between those points. The outcome variable of AUC/dose was log transformed to reduce skewness in the data. The outcome variables for the pharmacodynamic analyses were HIV viral load measurements at the time of the intensive PK study visit and self report of the drug leading to "any" side effects.

**Statistical analyses—**The drug exposure outcome was analyzed in relation to a number of factors that may influence NNRTI PK measurements. Categorical variables and continuous variables that were categorized included race (African American compared to other, including Caucasian, Hispanic, Native American, Asian); age (categorized by decade); hepatitis C infection status; chronic hepatitis B infection (as defined by positive hepatitis B surface antigen); platelet count (<150/mL versus ≥150) as a marker of liver dysfunction; stage in menstrual cycle or menopausal status; pregnancy status; renal dysfunction (creatinine clearance (CrCl) calculated by either the Cockcroft-Gault[13] or Modification of Diet in Renal Disease (MDRD) equation[14] and dichotomized by <60ml/min versus ≥60 and <80ml/min/1.73 $m^2$ versus ≥80, respectively); smoking (yes/no) or alcohol use (categorized into mild, moderate, severe); percentage of fat in the usual diet as ascertained by a validated dietary questionnaire[15] (<30%, 30–35%, 36–40% fat or >40% usual fat intake in the preceding 30 days); persistent diarrhea in the past 30 days; concurrent symptoms or infections; use of medications known to increase or decrease target ARV exposure by inhibition or induction of cytochrome P450 or P-glycoprotein levels (including concomitant protease inhibitors); and self-reported adherence measurements. Continuous variables included hepatitis C RNA levels in hepatitis C-infected patients, creatinine clearance as measured using the two methods above, body mass index and fat free mass measurements, as well as serum hepatic transaminase levels (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl-transferase (GGT)) as markers of liver inflammation. Since measures of lean body mass are typically used to predict drug dosages[16], ideal body weight, lean body weight, adjusted body weight, and predicted normal weight were estimated from height and weight parameters using standard equations[17] and assessed for their independent relationships to the outcome.

Univariate analyses were performed by linear regression between the log-transformed outcomes and the categorical or continuous variables of interest. Multivariable models were constructed by manual forward stepwise selection, starting with the predictor that had the smallest p-value on univariate analysis. At each step, each remaining predictor was examined as a possible addition to the model, and the one with the smallest p-value was added, until no remaining predictor had a p-value of less than 0.10. Each candidate model was run separately to avoid excessive casewise deletion of observations that had missing values on other unselected candidate predictors. Covariates with obvious collinearity were not included in the

same models. Age, race, and ideal body weight were included as variables in all multivariate models.

The pharmacodynamic analyses used NNRTI exposure as the predictor and assessed its relationship to important outcomes, including HIV viral load suppression at the time of sampling and self-reported side effects on the medication. All analyses were performed using the *Stata/SE 9.2* statistical package.

## RESULTS

### Data collection

Enrollment and data collection was completed for 106 WIHS participants on NVP-containing regimens and 119 WIHS participants on EFV-containing regimens. Time versus concentration curves for all of the intensive PK study participants on NVP are depicted in Figure 1a with a median PK curve superimposed on top of the spaghetti plot. Figure 1b shows the time-concentration curves for the 119 participants on EFV with the median curve. Both plots illustrate the marked interindividual variability in the PK curves for this “real world” study population. Table 1 shows the summary of the PK parameters or exposure metrics for NVP and EFV.

### Distribution of covariates in the population under study

Table 2 shows the prevalence of each of the possible variables investigated in this study. The sample is racially diverse (62% and 73% African Americans in the NVP and EFV groups, respectively) and factors that could potentially influence ARV exposure based on previous literature or plausibility were well represented: high BMI (mean of 29 $kg/m^2$ in both groups); active smoking (61% in the group on EFV); renal insufficiency (10% in the NVP group with calculated CrCl < 60ml/min); liver function abnormalities (21.4% in the NVP group had transaminases above reference values); persistent diarrhea over preceding 30 days (22% in the EFV group); concurrent hepatitis C infection (41% in the EFV group); and high fat diets (56% of participants on NVP had greater than 30% fat in their diets).

### Univariate analysis between the exposure outcome and various predictors

Tables 3a and 3b show the univariate relationships between the specified variables and exposure (AUC/dose) for NVP and EFV, respectively. The variables associated with a statistically significant increase in nevirapine AUC were hepatitis C coinfection, renal insufficiency, orange or orange juice consumption in the preceding 5 days, and increases in serum AST, ALT, and GGT levels (Table 3a). Increases in lean body mass, higher CrCl, and a greater percentage of recent dietary fat consumption were associated with lower NVP AUC levels.

Statistically significant associations with a higher EFV AUC in univariate analyses were seen with greater self reported ARV adherence, thrombocytopenia, consumption of orange juice, and increases in hepatic transaminases **(**Table 3b). A decreased EFV AUC was statistically significantly associated with concomitant use of the nucleoside reverse transcriptase inhibitor (NRTI), tenofovir, and marginally associated with larger ideal body weights.

### Multivariate models

The results of the multivariate models for prediction of NVP and EFV exposure are shown in Tables 4a and 4b, respectively. Increases in ALT level remained statistically significantly associated with an increase in NVP AUC/dose (Table 4a), as did increases in AST level and GGT level in independent models. Lower creatinine clearance was also associated with increases in NVP exposure. Routine high fat diets, regular crack cocaine use (at least once a

week) and self-reported amenorrhea for at least 12 months were independently associated with decreases in NVP exposure in multivariate modeling.

Higher EFV exposure was seen with increased serum ALT and serum albumin levels, or consumption of oranges or orange juice in the preceding 5 days (Table 4b) in multivariate models. Factors associated with decreased EFV exposure were self-reported amenorrhea for at least 12 months, being African-American, the concomitant use of tenofovir, and larger ideal body weights.

### Association of exposure with virologic suppression and side effects

In order to assess the relationship between drug exposure and virologic response in the cohort, logistic regression models examined the odds of virologic suppression. Among the patients on EFV, 39 (33%) had detectable HIV viral loads at the time of intensive PK sampling despite being on the drug for more than 6 months. The higher the EFV exposure, the greater the likelihood of having an undetectable viral load at the time of sampling. With every 10-fold increase in EFV AUC, the odds ratio for virologic suppression was 3.58 (95% CI 1.28–14.07) when controlled for self-reported adherence, age, race and ideal body weight. For the patients on NVP, 51 (43%) had detectable HIV viral loads at the time of sampling and the likelihood of exhibiting virologic suppression increased with higher NVP exposure. With every 10-fold increase in NVP AUC, the odds ratio for virologic suppression was 3.34 (95% CI 1.49–17.54) when controlled for adherence, age, race and ideal body weight.

In terms of self-reported side effects, patients with higher AUCs were more likely to report that they felt that their drug “gave any side effects” or was “toxic or harmful”. Those with EFV exposure in the top median were 2.6 (95% CI 1.5–4.9) times as likely to report side effects than those with an EFV AUC in the lower half for the group. Similarly, those with NVP exposure in the top median were 1.9 (95% CI 1.4–2.9) times as likely to report toxicities than those in the lower median. Of note, patients with side effects had markedly reduced odds of adhering to their therapies on a routine basis than who reported no side effects: the odds of ≥95% adherence was 0.05 (95% CI 0.02–0.16) for those reporting side effects on EFV and 0.25 (0.09–0.71) for those on NVP.

## DISCUSSION

### Study significance

In this study, we identify factors that may influence NNRTI exposure in a diverse population of HIV-infected women and show that exposure is associated with virologic suppression and self report of adverse effects on therapy. NNRTIs are increasingly used in first-line treatment regimens in the developed and developing world, especially with their global roll-out, the use of NVP to prevent perinatal transmission[18], and the co-formulation of EFV into a once daily combination regimen (Atripla®). Adequate exposure to these medications is paramount in preventing drug resistance[19]. Although PK studies in selected cohorts are valuable in defining the typical exposure metrics of a medication, intensive PK studies in large unselected cohorts such as ours may identify covariates that influence exposure in “real world” populations. Table 5 lists the characteristics of our study design that distinguish it from smaller intensive PK studies performed to date for these NNRTIs, including our large sample size and the racial and ethnic diversity of the cohort.

Our work demonstrates that detailed studies of representative and diverse patient groups are feasible. Most population PK studies of ARVs to date have employed sparse sampling, extrapolation and simulation methods[20] justified by citing feasibility issues on performing intensive PK measurements on large samples of HIV-infected patients. Full 12 or 24 hour PK

studies for antiretrovirals have been reported in relatively small numbers of patients (40–50 participants in the largest published studies)[21–27]. Because many of these intensive PK studies restrict eligibility, the resultant PK models are limited in the number of covariates examined. We chose to employ a unique study design for intensive PK sampling in a large unselected observational cohort of HIV-infected patients in order to assess the influence of a more comprehensive set of factors on drug exposure. Although the mean exposure metrics for our intensive PK studies are similar to those reported in the literature for both drugs[28, 29], the wider coefficients of variation for our calculated parameters (Table 1 and Figure 1) reflect the variability in an unrestricted study population,

## Factors that contribute to NVP exposure

In this unselected population, hepatic inflammation and renal insufficiency were independently associated with increased NVP exposure in multivariate analyses, whereas crack cocaine, high fat diets, and amenorrhea were associated with decreased levels. Although NVP is cleared hepatically, the effects of uremic toxins on relevant hepatic transporters or metabolizing enzymes[30] may explain the influence of renal insufficiency on NVP clearance. While consumption of a single fatty meal did not influence NVP exposure among 24 adult volunteers studied prior to drug licensure[31], the effects of chronic fat consumption have not been studied. Dietary fat can inhibit the hepatic p-glycoprotein efflux transporter over time[32], and thus lead to increased hepatocyte NVP concentrations[33] with increased metabolism by the cytochrome p450 3A4 (CYP3A4) and 2B6 (CYP2B6) systems[34]. The fact that decreased NVP levels are not seen with the administration of a single high fat meal[31] may reflect the fact that CYP2B6 is found in the liver, but not in the intestine[35]; chronic exposure to high fat may lead to transporter effects and changes in hepatic, but not enteric, metabolism.

Use of crack cocaine and amenorrhea are examples of factors not likely to be examined in more focused intensive PK studies. The decreased exposure to NVP found among participants who reported recent recreational use of crack in our study could be explained by induction of the CYP3A4 metabolic system by cocaine[36]. Crack cocaine use in HIV-infected populations is not infrequent[37] and its effects on exposure may contribute to treatment failure apart from the crack's effect on adherence[38]. Neither age (which should be related to postmenopausal status) nor use of exogenously administered hormones (which can be related to prolonged amenorrhea) was independently associated with decreased NNRTI exposure. Previous reports have shown higher NVP[39] and EFV concentrations[40] in pre-menopausal women than men, but a comparison of NNRTI exposure between postmenopausal women and either premenopausal women or age-matched men has not been performed. Since a systemic analysis of the effects of menstrual status on the disposition of ARVs is lacking in the literature to date, intensive PK studies in unselected cohorts of women are important.

## Factors that contribute to EFV exposure

Hepatic transaminase levels, albumin levels, recent consumption of oranges or orange juice, prolonged amenorrhea, concomitant use of tenofovir, ideal body weight, and race contributed to EFV exposure in multivariate models. The association of increased albumin levels with increased EFV levels is likely explained by the fact that EFV is primarily protein-bound (in contradistinction to NVP)[41]. Inhibition of intestinal p-glycoprotein transport or down-regulation of enteric CYP3A4 by citrus components in oranges or orange juice[42] could lead to enhanced bioavailability and increased exposure to efavirenz[33]. Concomitant use of tenofovir was associated with decreased levels of efavirenz in our multivariate model; an unrelated study failed to demonstrate this relationship in univariate analysis[43]. This drug-drug interaction may be important given the availability of a fixed dose combination containing tenofovir and efavirenz and may be modified by competing factors in the model.

The association of efavirenz exposure with ideal body weight probably reflects increased hepatic clearance in individuals with larger lean and hepatic mass[16]. In previous studies, higher EFV concentration in patients of African descent have been linked to an increased frequency of specific polymorphisms in the multidrug resistance transporter (MDR) and CYP2B6 genes[44]. The association between African-American race and decreased EFV exposure in our multivariate models, however, may reflect the importance of assessing a host of variables in predictions of drug exposure for an individual patient.

### Limitations

The observational nature of our study is not a limitation, but a strength, since modeling the pharmacokinetics of chronically administered medications under conditions of actual use allows for the identification of "real-world" factors that contribute to drug exposure and efficacy. Although we could have included more precise measures of dietary intake, gastrointestinal absorption, metabolic activity or renal function in our models, we chose to focus only on factors readily measured in routine clinical care. However, although our models explain a much larger proportion of NNRTI exposure variability than more limited models in the literature, a large amount of unexplained variation still exists. One major limitation of our current PK models is the lack of data on genetic polymorphisms in the host. In view of the increasing awareness that variability in transporter and metabolic enzymes may have a large contribution to plasma drug levels[44], host pharmacogenomic parameters will be incorporated into the PK models in upcoming analyses.

The ultimate aim of identifying factors that contribute to medication exposure in representative populations with chronic diseases is to provide quantitative data for dose optimization within an individual after data on the exposure-response relationship is assessed longitudinally. Although we explored some pharmacodynamic relationships between AUCs and virologic suppression and self-reported side effects cross-sectionally at the time of intensive PK sampling, longitudinal analyses using population PK models can explore the exposure-response relationship over time. Population PK methods[45–47] employ sparse PK data from an individual and the characteristics identified by intensive PK sampling in a representative population to produce more robust measures of exposure (using techniques of nonlinear mixed effects modeling) for predicting treatment responses. The next step is to model estimates of exposure using sparse level data and these intensive datasets in order to measure the relationship of exposure and response over time and, ultimately, aid in dose individualization parameters.

### Conclusions

By performing intensive PK analyses of NNRTIs in a large, diverse unrestricted sample of HIV-infected women, we were able to identify key previously unidentified factors that contribute to drug exposure in multivariate models. As ARVS are increasingly being provided to diverse populations (in terms of age, sex, ethnicity, coinfections, and other factors), assessing the influence of individual patient characteristics to drug exposure may help optimize responses and diminish adverse effects for these chronically administered therapies in the "real world' setting.

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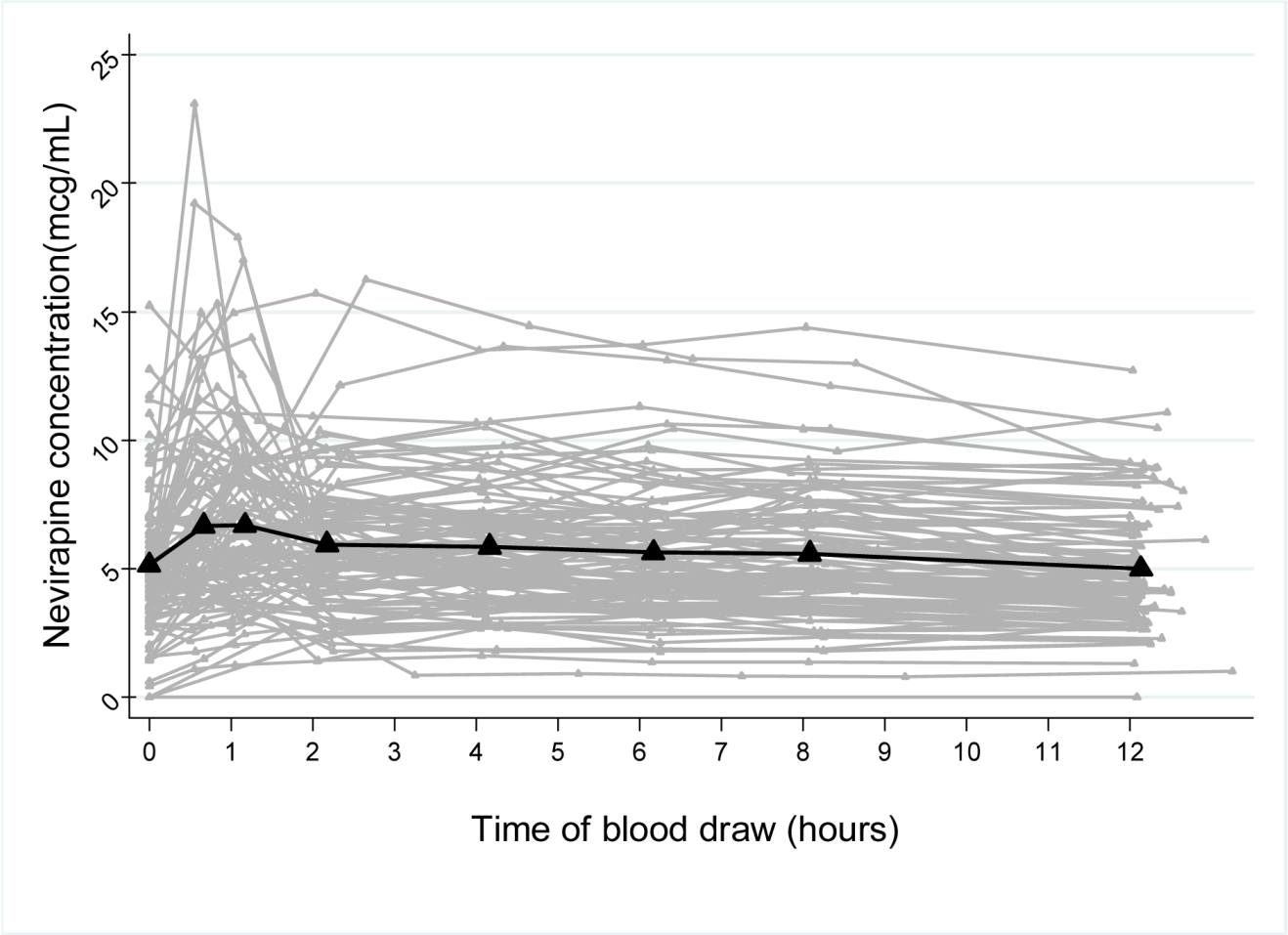

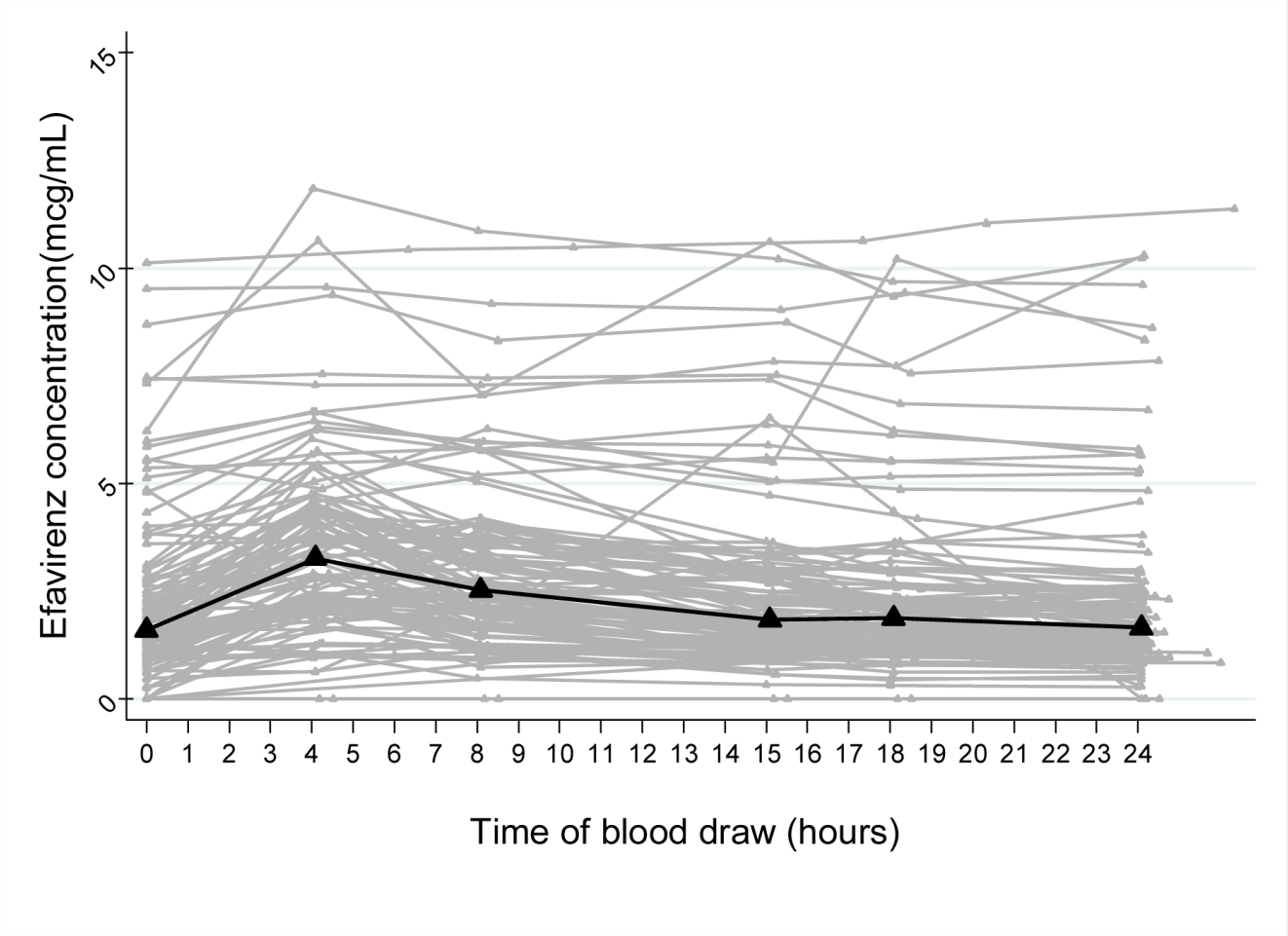


**Figure 1.**

Figure 1a: Time-concentration curves for 106 participants on NVP with superimposed median PK curve (bold line)

Figure 1b: Time-concentration curves for 119 participants on EFV with superimposed median PK curve (bold line)

**TABLE 1**

Summary exposure metrics in the WIHS Intensive PK study

| Drug | AUC (mcg[1] × h/mL) | $C_{min}$ (mcg/mL) | $C_{max}$ (mcg/mL) | $t_{max}$ (hours) | CL/F (ml/h) |
|---|---|---|---|---|---|
| *Nevirapine (n=106)* | | | | | |
| Median | 63.4 | 4.15 | 7.57 | 1.2 | 3.16 |
| Range | (14.2 – 212.0) | (0 – 14.3) | (2.77 – 23.1) | (0–12.6) | (0.94 – 16.5) |
| CV (%) | 47 | 53 | 47 | 110 | 62 |
| *Efavirenz (n=119)* | | | | | |
| Median | 55.6 | 1.46 | 3.79 | 4.2 | 10.8 |
| Range | (11.4 – 639.8) | (0 – 25.2) | (1.9 – 27.5) | (0–24.1) | (0.94 – 52.6) |
| CV (%) | 108 | 133 | 85 | 70 | 62 |

[1] mcg = micrograms; h = hours; mL = milliliter

**TABLE 2**

Distributions of covariates in the WIHS Intensive PK Study for participants on NVP and EFV-containing HAART regimens

| ARV under study (Sample size) | Nevirapine (106) | Efavirenz (119) |
|---|---|---|
| Race distribution | Caucasian (22%); Hispanic (10%); African-American (62%); Other (6%) | Caucasian (8%); Hispanic (18%); African-American (73%); Other (1%) |
| Age distribution | 20–29 years (12%); 30–39 years (31%); 40–49 years (38%); 50–59 years (15%); ≥60 years (4%) | 20–29 years (8%); 30–39 years (29%); 40–49 years (45%); 50–59 years (17%); ≥60 years (1%) |
| Adherence to ARVs (self-report) in past month | ≤35% adherence (1%); 36–65% adherence (4%); 66–80% adherence (6%); 81–94% adherence (36%); ≥95% adherence (53%) | ≤35% adherence (4%); 36–65% adherence (3%); 66–80% adherence (10%); 81–94% adherence (19%); ≥95% adherence (64%) |
| Hepatitis C positive | 33% | 41% |
| Chronic Hepatitis B | 4% | 3% |
| Thrombocytopenia (platelets<150/mL) | 17% | 15% |
| Menstruating at time of PK sampling | 18% | 13% |
| Amenorrhea for ≥ 12 months (self-report) | 19% | 26% |
| Pregnancy | 2% | 0% |
| Renal insufficiency[1] (CrCl <60ml/min, calc. using Cockcroft-Gault equation) | 10% | 7% |
| Renal insufficiency[2] (GFR <80ml/min, calculated using MDRD equation) | 40% | 21% |
| Smoker | 53% | 61% |
| Crack cocaine use more than 1–2 times per month | 7% | 8% |
| Percent fat consumption in diet in past month | <30% fat (44%); 30–35% fat (9%); 36–40% fat (35%); >40% fat (12%) | <30% fat (47%); 30–35% fat (9%); 36–40% fat (25%); >40% fat (18%) |
| Active diarrhea (3 or more soft stools a day within last 30 days) | 13% | 22% |
| Concomitant meds known to increase target ARV levels (e.g. CYP3A4 inhibitors) | 5% | 10% |
| Concomitant meds known to decrease target ARV levels (CYP3A4 inducers) | 0% | 4% |
| Use of tenofovir | 16% | 23% |
| Oranges or orange juice consumption in the preceding 5 days | 63% | 67% |
| Mean AST level (range) IU/L | 35 (11–125) | 33(10–209) |
| Mean ALT level (range) IU/L | 29 (4–95) | 27(8–117) |
| Mean GGT level (range) IU/L | 125 (8–1032) | 119(13–1371) |
| Mean BMI (range) kg/m$^2$ | 29.8 (17.3–55.4) | 28.9 (14.0–57.8) |
| Fat free mass (range) kg as measured by impedance | 45.7 (33.5–64.8) | 45.6 (33.8–111.5) |
| Mean ideal body weight[3] (range) kg | 54.6 (29.6–70.3) | 54.1 (38.6–70.3) |
| Mean creatinine clearance (ml/min) (range)[1] | 105 (39–234) | 110 (11–273) |

[1] Crockfeld-Gault equation: (0.85 if female) × (140-age)(weight/'kg)/(serum creatinine × 72)

[2] MDRD equation: GFR = 186 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if black)

[3] IBW(kg) = 45.4 + 0.89 × (height(cm) − 152.4)[17]

## TABLE 3

**TABLE 3a: Univariate analyses between covariates and nevirapine exposure, as measured by AUC/dose, for 106 HIV-infected women on NVP-containing HAART**

| Variable | Estimated effect on AUC (↑ or ↓) | 95% lower C.I. | 95% upper C.I. | P value |
|---|---|---|---|---|
| ***Categorical variables*** | | | | |
| Race (African American vs. other) | ↑ 1.04 fold | 0.96 | 1.25 | 0.69 |
| Adherence to ARVs (≥95% vs. <95%) in past month | ↑ 1.03 fold | 0.86 | 1.23 | 0.74 |
| Hepatitis C positive | ↑ 1.26 fold | 1.04 | 1.53 | **0.017** |
| Chronic Hepatitis B | ↑ 1.14 fold | 0.70 | 1.87 | 0.59 |
| Low platelet count | ↑ 1.16 fold | 0.88 | 1.55 | 0.27 |
| Menstruating at time of PK sampling | ↓ 0.80 fold | 0.64 | 1.02 | 0.069 |
| Pregnancy | ↓ 0.83 fold | 0.43 | 1.61 | 0.59 |
| Amenorrhea for 12 months | ↓ 0.92 fold | 0.73 | 1.16 | 0.49 |
| Renal insufficiency(CrCl, calculated <60ml/min vs. ≥60; Cockcroft-Gault) | ↑ 1.47 fold | 1.10 | 1.95 | **0.009** |
| Renal insufficiency (GFR, calculated <80ml/min vs ≥80ml/min; MDRD equation) | ↑ 1.23 fold | 1.03 | 1.48 | **0.023** |
| Smoker | ↑ 1.09 fold | 0.91 | 1.30 | 0.37 |
| Percent fat in diet (>40% fat versus ≤40% fat) in past 30 days | ↓ 0.75 fold | 0.57 | 0.98 | **0.03** |
| Diarrhea | ↓ 0.85 fold | 0.66 | 1.11 | 0.24 |
| Drugs known to increase NVP levels (CYP3A4 inhibitors) | ↑ 1.34 fold | 0.88 | 2.04 | 0.17 |
| Oranges or orange juice in past 5 days | ↑ 1.23 fold | 1.02 | 1.48 | **0.027** |
| Crack cocaine use | ↓ 0.80 fold | 0.56 | 1.14 | 0.213 |
| ***Continuous variables*** | | | | |
| Age (in decades) | ↑ 1.0 fold | 0.96 | 1.14 | 0.29 |
| Per doubling of AST level | ↑ 1.21 fold | 1.09 | 1.35 | <**0.0005** |
| Per doubling of ALT level | ↑ 1.24 fold | 1.12 | 1.36 | <**0.0005** |
| Per doubling of GGT level | ↑ 1.14 fold | 1.08 | 1.21 | <**0.0005** |
| Per doubling of body mass index (BMI), which includes fat mass | ↓ 0.79 fold | 0.62 | 1.00 | 0.053 |
| Per doubling of fat free mass | ↓ 0.54 fold | 0.34 | 0.85 | **0.009** |
| Per doubling of creatinine clearance | ↓ 0.78 | 0.67 | 0.92 | **0.003** |

**TABLE 3b: Univariate analyses between covariates and efavirenz exposure, as measured by AUC/dose, for 119 HIV-infected women on EFV-containing HAART**

| Variable | Estimated effect on AUC (↑ or ↓) | 95% lower C.I. | 95% upper C.I. | P value |
|---|---|---|---|---|
| ***Categorical variables*** | | | | |
| Race (African American vs. other) | ↑ 1.05 fold | 0.79 | 1.39 | 0.75 |

**TABLE 3b: Univariate analyses between covariates and efavirenz exposure, as measured by AUC/dose, for 119 HIV-infected women on EFV-containing HAART**

| Variable | Estimated effect on AUC (↑ or ↓) | 95% lower C.I. | 95% upper C.I. | P value |
|---|---|---|---|---|
| Adherence to ARVs (≥95% vs. <95%) in past month | ↑ 1.32 fold | 1.02 | 1.71 | **0.033** |
| Hepatitis C positive | ↑ 1.15 fold | 0.89 | 1.45 | 0.29 |
| Chronic Hepatitis B | ↓ 0.60 fold | 0.27 | 1.34 | 0.21 |
| Low platelet count | ↑ 1.42 fold | 1.00 | 2.01 | **0.05** |
| Menstruating at time of PK sampling | ↓ 0.84 fold | 0.58 | 1.22 | 0.36 |
| Amenorrhea for >12 months | ↑ 1.27 fold | 0.96 | 1.69 | 0.09 |
| Renal insufficiency (Calculated creatinine clearance <60ml/min vs. ≥60ml/min) | ↑ 1.26 fold | 0.77 | 2.06 | 0.36 |
| Smoker | ↓ 0.97 fold | 0.75 | 1.26 | 0.84 |
| Use of tenofovir | ↓ 0.71 fold | 0.53 | 0.95 | **0.022** |
| Diarrhea | ↑ 1.05 fold | 0.78 | 1.43 | 0.74 |
| Concomitant use of LPV or RTV, which can increase EFV levels | ↑ 1.19 fold | 0.79 | 1.80 | 0.40 |
| Concomitant use of meds which can decrease EFV levels | ↓ 0.68 fold | 0.37 | 1.26 | 0.22 |
| Oranges or orange juice in the past 5 days | ↑ 1.31 fold | 1.01 | 1.71 | **0.044** |
| ***Continuous variables*** | | | | |
| Age (in decades) | ↑ 1.08 fold | 0.92 | 1.26 | 0.34 |
| Per doubling of AST level | ↑ 1.29 fold | 1.11 | 1.49 | **0.001** |
| Per doubling of ALT level | ↑ 1.21 fold | 1.05 | 1.41 | **0.012** |
| Per doubling of GGT level | ↑ 1.12 fold | 1.03 | 1.23 | **0.013** |
| Per doubling of bilirubin level | ↑ 1.10 fold | 0.97 | 1.25 | 0.13 |
| Per doubling of albumin level | ↑ 1.88 fold | 0.88 | 4.02 | 0.10 |
| Per doubling of body mass index (BMI), which includes fat mass | ↓ 0.75 fold | 0.54 | 1.03 | 0.073 |
| Per doubling of ideal body weight | ↓ 0.47 fold | 0.21 | 1.07 | 0.072 |
| Per doubling of creatinine clearance | ↓ 0.93 fold | 0.75 | 1.15 | 0.49 |

## Table 4

**Table 4a: Multivariate model depicting effects of various predictors on the outcome of NVP exposure when controlled for other factors in the model[1]**

| Predictor | Estimated effect on AUC (↑ or ↓) | 95% lower C.I. | 95% upper C.I. | P value |
|---|---|---|---|---|
| Per 2-fold increase in ALT | ↑ 1.25 fold | 1.14 | 1.38 | <**0.001** |
| Per 2-fold decrease in creatinine clearance | ↑ 1.22 fold | 1.01 | 1.47 | **0.036** |
| Percent fat in diet (>40% vs ≤40% fat) in past 30 days | ↓ 0.69 fold | 0.54 | 0.87 | **0.002** |
| Crack cocaine use | ↓ 0.70 fold | 0.51 | 0.96 | **0.028** |
| Amenorrhea for > 12 months | ↓ 0.77 fold | 0.61 | 0.97 | **0.026** |

**Table 4b: Multivariate model depicting effects of various predictors on the outcome of EFV exposure when controlled for other factors in the model[1]**

| Predictor | Estimated effect on AUC (↑ or ↓) | 95% lower C.I. | 95% upper C.I. | P value |
|---|---|---|---|---|
| Per 2-fold increase in ALT | ↑ 1.22 fold | 1.05 | 1.41 | **0.009** |
| Per 2-fold increase in albumin level | ↑ 2.47 fold | 1.19 | 5.10 | **0.015** |
| Oranges or orange juice in the past 5 days | ↑ 1.39 fold | 1.09 | 1.78 | **0.009** |
| Amenorrhea for >12 months | ↓ 0.73 fold | 0.55 | 0.97 | **0.030** |
| Use of tenofovir | ↓ 0.75 fold | 0.57 | 0.99 | **0.045** |
| Per 2-fold increase in ideal body weight (IBW) | ↓ 0.38 fold | 0.18 | 0.83 | **0.015** |
| African-American vs. other | ↓ 0.75 fold | 0.56 | 1.00 | **0.05** |

[1] Controlled for age, race, ideal body weight

[1] Controlled for age

**TABLE 5**

Unique attributes of the study method for assessing contributors to antiretroviral exposure

- Sampling performed in diverse population where drug actually used, not a restricted population with exclusions designed to reduce PK variability
- Large sample size for intensive PK sampling to enable modeling of a number of factors
- Racial and ethnic diversity in cohort to allow analyses of these factors
- Sample is representative of HIV-infected populations in terms of risk factors for ARV exposure variability, such as smoking, alcohol, and recreational drug use, degree of baseline renal insufficiency, concurrent HCV infection, BMI range, transaminase elevations, etc.
- Inclusion of women in adequate numbers to assess exposure in this group
- WIHS is an observational study, so components of antiretroviral regimen and dosing are as prescribed by providers (simulates varibility of "real life")
- No exclusions on use of concurrent medications
- Participants' usual diet simulated during the intensive PK sampling
- No exclusions on recreational drug use or alcohol consumption prior to the visit and smoking permitted during the visit
- Concomitant measurement of a large number of potential covariates that could contribute to ARV exposure
- Given longitudinal nature of study, data available for participants on covariates prior to starting the ARV under study to assess directionality