Nevirapine (NVP) Pharmacokinetics (PK) and Risk of Rash and Hepatitis among HIV-Infected Sub-Saharan African Women

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Abstract

Objectives—To estimate nevirapine pharmacokinetics and examine its association with rash and/or hepatotoxicity in women starting antiretroviral treatment in the ACTG A5208/OCTANE study in Africa.

Design—In HIV-infected, non-pregnant women with screening CD4<200 cells/mm^3 randomized to nevirapine (twice daily, after 14-day once-daily lead-in period) plus tenofovir/emtricitabine, single nevirapine blood samples were collected 14 and 28 days following randomization. Rash and hepatotoxicity that occurred during therapy, or within 7 days after the last dose of nevirapine, were defined as toxicity.

Methods—Nevirapine pharmacokinetics were modeled by population pharmacokinetic analysis. Individual Bayesian pharmacokinetic estimates were used to calculate clearance, 24-hour area under the curve, and predicted plasma concentrations.

Results—Median week 4 nevirapine clearance was 2.0 L/hr. Among the 359 women, 194 (54%) developed a rash of any grade; 82 (23%) had grade 2+ and 9 (3%) had grade 3+ rash. Median clearance was 1.7L/hr for subjects exhibiting 3+ rash versus 2.0 L/hr in women without 3+ rash (p=0.046). The odds of developing 3+ rash was 50% higher for every 20% decrease in clearance (p=0.046). Nevirapine discontinuation due to rash/liver toxicity was significantly more common among women with pretreatment CD4 count > 250 cells/mm^3 (p=0.003).

Conclusions—In this study, HIV-infected African women starting a nevirapine-based antiretroviral regimen had a lower nevirapine clearance compared to previous reports. Severe rash, but not hepatotoxicity, was associated with higher NVP exposure. Albeit observed in a small number of women, baseline CD4 ≥250 cells/mm^3 was significantly associated with NVP toxicity.

Keywords

nevirapine; pharmacokinetics; rash; hepatotoxicity; drug toxicity

Introduction

Nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, is widely prescribed in resource limited settings as part of initial antiretroviral therapy (ART). As the CD4 cell count threshold for initiating ART rises globally[1], it is important to understand the risks of NVP, particularly in women, and among patients with higher CD4 counts (>250 cells/mm^3 in women and > 400 cells/mm^3 in men).[2-7] NVP can be associated with serious and sometimes life threatening rash and and/or hepatotoxicity during the first 6 to 18 weeks of therapy.

The exact etiology of NVP toxicity remains unclear. A potential relationship between NVP pharmacokinetic (PK) exposure and increased risk of toxicity has been proposed but no definitive association has been established. [8-14] Studies linking NVP PK and toxicity have enrolled predominantly male subjects, whereas for women, similar investigations have not been formally conducted. Moreover, women appear to exhibit higher NVP drug exposure compared to men as a result of lower drug clearance.[15] Additionally, the PK disposition of NVP may be influenced by several factors, including body weight, ethnicity, pre-existing liver disease, and pharmacogenetics.[14, 16-18] Therefore, this study was conducted to clarify the association of NVP PK and the risk of rash and/or liver toxicity in non-pregnant women residing in seven sub-Saharan African countries who started NVP-based antiretroviral treatment in the ACTG A5208/OCTANE clinical trial.

Primary study objectives were to: 1) determine NVP PK based on sparse PK sampling from a large cohort of women and 2) examine the association between NVP PK and rash and liver toxicity. A secondary objective was to evaluate the association between NVP toxicity and pre-treatment CD4 count and weight.

Methods

The demographics of 745 HIV+ women from 10 African sites enrolled in ACTG 5208/OCTANE, a phase III, open label trial, have been described in detail by Lockman et al. [19]. In brief, women were antiretroviral-naïve, apart from use of zidovudine or single dose NVP for reducing the risk of mother-to-child HIV transmission (MTCT) (in a subset of participants), and had a CD4 count at screening of less than 200 cells/mm^3. Women were randomized 1:1 to 400 mg lopinavir/100mg ritonavir BID or NVP 200mg daily for 14 days then 200mg BID, each in combination with tenofovir (TDF) 300 mg + emtricitabine (FTC) 200 mg, administered once daily as the fixed co-formulation, *Truvada*®. All 370 women who were randomized to receive NVP (including 121 with prior single-dose NVP exposure for prevention of MTCT and 249 without prior single-dose NVP exposure) were eligible to participate in the NVP PK portion of the study. For the PK study, single random NVP blood samples were collected at 14 (±7) days following randomization (i.e. before NVP BID dose escalation), and again at 28 (±7) days if no NVP doses were missed during the previous three days. All women received treatment and were followed until the last woman randomized had completed 48 weeks of follow-up.

NVP plasma concentrations were quantified by liquid chromatography mass spectrometry (LC-tandem-MS) using a method developed and validated within the Drug Research Unit (DRU) of the Department of Clinical Pharmacy, UCSF. The method was approved through the Clinical Pharmacology Quality Assurance (CPQA) Program funded by the Division of AIDS and utilizes reverse phase HPLC separation coupled with tandem-MS detection. NVP and the internal standard were extracted from EDTA plasma using percholoric acid precipitation of plasma proteins followed by centrifugation. The supernatant was neutralized with ammonium hydroxide and injected onto a Zorbax-Eclipse XDB- C8 reverse phase column and separated using a gradient elution. Ion pairs 267.4/226.8 for NVP and 628.6/421.2 for internal standard were selected for tandem mass detection in multiple reaction monitoring mode. The calibration curve concentration range was 50 to 5000 ng/mL and lower limit of quantification (LLOQ) was 50 ng/mL. Inter-assay precision (CV%) ranged from 2.14 to 4.43. Intra-assay CV% ranged from 2.34 to 13.03%.

Population Pharmacokinetic Analysis

NVP concentration time data were analyzed using the nonlinear mixed-effects modeling program NONMEM® Version 7 (Icon Development Solutions, Ellicott City, MD). Variables incorporated in NONMEM® included measured NVP plasma concentration, dosage, administration time of the last three doses of NVP before sample collection, age, weight, and study site. The first order conditional estimation method with interaction between inter-individual variability (IIV) and residual variability was used throughout the model building and evaluation process. Model selection was based on change in the NONMEM objective function value (ΔOFV), precision of the parameter estimates, and improvements in standard diagnostic plots. Models were compared statistically with a significance set at $P < 0.05$ (ΔOFV = -3.84). To evaluate the accuracy and stability of the final PK model, a non-parametric bootstrap re-sampling method was performed using the NONMEM® interface PLT Tools (Version 3.2, PLTsoft, San Francisco, CA). A total of 1000 bootstrap datasets were generated from the original data set by repeated sampling with replacement. The median parameter estimates obtained from the bootstrap data set were compared with those obtained by the population PK model.

A one-compartment PK structural model with first-order absorption and elimination was selected. IIV of pharmacokinetic parameters was incorporated using an exponential (log normal) model and residual (intra-subject) variability was assumed to be a proportional error model. Since only a single NVP blood sample was obtained at week 2 and week 4 for each subject, a simple additive clearance (CL) model was used to capture any induction of CL after week 2 ($CL_{week4} = CL_{week2} + CL_{additional}$)

The influence of age and bodyweight on PK parameters was investigated assuming an exponential relationship: $\theta_j = \theta \times \left(\frac{weight_j}{median_{weight}}\right)^{\alpha}$ where θ_j and $weight_j$ are the value of the parameter and weight, respectively, for the j-th individual, θ the typical parameter value in the population standardized to an individual with the median weight at enrollment, and θ is the exponent describing the relationship between the parameter and weight .

Definitions of Toxicity

All liver or rash events occurring while receiving NVP, or within 7 days after the last dose of NVP and before starting another ART regimen, and deemed to be potentially related to NVP, were designated as toxicity endpoints. Liver toxicity was defined as any grade 2+ transaminase elevation or grade 3+ total bilirubin or alkaline phosphatase elevation according to the DAIDS Adverse Events Grading Tables (Division of AIDS table for grading the severity of adult and pediatric adverse events. December 2004). Laboratory and safety assessments occurred on six separate occasions during the first 24 weeks, every 12

weeks thereafter, and additionally if clinically indicated. NVP was discontinued if subjects experienced a grade 3 or 4 rash (or rash of any grade accompanied by other signs/symptoms or laboratory abnormalities suggestive of hypersensitivity reaction), grade 2 or higher transaminase elevations, or increases in liver enzymes by one grade or more (or rash) along with concomitant signs or symptoms of hepatitis.

Statistical analysis

Wilcoxon rank sum test, Wilcoxon signed rank test, and Fisher's exact test were used in the univariate comparisons, and logistic regression was used to fit the multivariable models. In the multivariable models for toxicity endpoints, pre-treatment CD4 count was categorized as ≥250 cells/mm^3 versus <250 cells/mm^3 and PK parameters (log transformed) were analyzed as continuous variables. In the model for efficacy outcomes, a variable indicating pre-treatment single dose NVP exposure was also included since women with such exposure had a higher rate of virologic failure/death than non-exposed women. For grade 3+ rash, due to the small number of events (n=9), the univariate exact logistic regression including only PK parameter was performed. The following sensitivity analyses were conducted: only including events determined by site investigators as definitely, probably, or possibly NVP related; only including events occurring 6 weeks after treatment initiation; and only including events occurring 18 weeks after treatment initiation. All p-values were two-sided and not adjusted for multiple comparisons.

Results

Baseline Demographics

Among the 370 women randomized to a NVP-based regimen, eleven (6 with no PK data and 5 with zero concentrations at both PK time points) were excluded, leaving 359 subjects included in the final analysis. Baseline median characteristics of the 359 women were: age 33 years (IQR 28, 38); weight 57 kg (IQR 52, 67), CD4 128 cells/mm^3 (IQR 80,176) and HIV-1 RNA 158,489 copies/mL (IQR 50,119, 316,228). Although the screening CD4 count had to be ≤200 cells/mm^3 (within 90 days of enrollment), there was no restriction on the baseline CD4 count (obtained from a sample drawn at the time of treatment initiation); and a total of 47 women with CD4>200 cells/mm^3 were enrolled. Of these 47 women, 15 had CD4 >250 cells/mm^3 (median CD4 262 cells/mm^3, range 250-386 cells/mm^3). Women weighing < 50 kg vs ≥50 kg were significantly younger (median 30 vs. 34 years, p=0.012), had higher HIV-1 RNA levels (median 199,526 vs.125,893 copies/mL, p=0.010) and more advanced WHO Stage (44% vs. 28% at stage III/IV, p=0.013). No significant differences in demographics were evident for the 11 women excluded from PK analysis.

Adherence was considered excellent: 83% of women had an adherence index (number of pills actually consumed/number of pills expected to consume) ≥0.95, and 87% reported not missing any dose of medication during the past month.

NVP Plasma Concentrations

Of the 359 women with available NVP concentrations, 330 women (92%) had valid NVP measurements at both study weeks 2 and 4; 18 women had week 2 measurements only; and 11 had week 4 measurements only. The majority of the samples were obtained within 6 hours of NVP administration (87% at week 2 and 93% at week 4) and all except two (at 19 and 25 hours) were obtained within 12 hours. The mean ± standard deviation time of sample collection following the daily 2 week dose was 4.06 hr ± 4.18; CV=103%; following the 4 week dose was 3.02± 2.18; CV 72%.

NVP Pharmacokinetics

NVP concentrations were adequately described by a one-compartment model with first order absorption and elimination. The IIV for volume and oral absorption (ka) could not be reliably estimated and removal of these random effects did not change the OFV or goodness of fit plots. Therefore, only IIV for CL was incorporated into the final model. Neither age nor body weight was found to be associated with PK parameters. The final population PK parameters estimates and their confidence intervals are presented in Table 1. The parameter estimates as found by bootstrap were in agreement with those obtained by the final population PK model (Table 1).

From the final population PK model, individual Bayesian estimates of oral clearance (CL/F), volume (Vd/F), and k_a were used to calculate steady state 24 hr area under the plasma concentration versus time curve (AUC_{24}), maximum (C_{max}) and minimum (C_{min}) plasma concentrations for each subject at 200 mg daily (week 2) and 200 mg bid (week 4) (Table 2). As anticipated, a significant difference between weeks 2 and 4 estimated PK parameters (p< 0.001 by signed rank test), including an increase in CL/F, was observed which coincided with dose escalation from 200 mg daily to 200 mg BID at week 2 (to compensate for cytochrome P450 enzyme induction). No significant differences in PK parameters were noted by CD4 count, weight, virologic response, or study site (p> 0.12). Therapeutic estimated NVP C_{min} levels > 3 mcg/mL were achieved in 86% of subjects at week 2 and in all subjects at week 4. Median NVP C_{min} was 7.2 mcg/mL (IQR 6.1, 8.3) with 200 mg bid (Table 2).

NVP Toxicity Outcomes

We classified NVP toxicity into two major categories: 1) rash of any grade and 2) hepatotoxicity of grade ≥2+ with or without rash (Table 3). Forty-six (13%) subjects discontinued NVP due to liver/rash toxicity (Table 3). Kaplan-Meier plots show time to first rash and liver toxicity, respectively. (Figures 1a and 1b). The majority of NVP related rash of any grade (n=164, 84.5%) and hepatotoxicity (n=39, 73.6%) developed within the first 18 weeks of therapy (Figure 1). However, grade 3+ rash occurred earlier by week 5 (7/9 subjects).

Among the 359 women, 194 (54%) developed rash of any grade possibly related to NVP as determined by site investigators; 82 (23%) had grade 2+ and 9 (3%) had grade 3+ rashes (one of which also had 3+ liver toxicity). An association between week 4 (but not week 2) NVP PK exposures (i.e. lower week 4 CL/F, higher C_{min}, AUC_{24hr}, and C_{max}) and a significantly increased odds of grade 3+ rash was observed (Table 4). Median CL/F was 1.7 L/hr for subjects exhibiting grade 3+ rash compared to 2.0 L/hr in women without 3+ rash (p=0.046). The odds of developing grade 3+ rash were estimated to be approximately 50% greater for every 20% decrease in NVP CL/F (p=0.046) which corresponds to a 20% increase in NVP AUC_{24hr}, C_{max}, and C_{min} concentrations (Table 4).

All patients with hepatotoxicity exhibited transaminase elevations except for two women: one with grade 3 alkaline phosphatase and one with grade 3 total bilirubin elevations. Grade ≥2+ hepatotoxicity developed in 53 women (15%); of whom 32 (9%) also had grade 3+ hepatotoxicity (Table 3; Figure 1b). In 23 women with grade 2+ hepatotoxicity, various grades of rash also occurred. However, only 1 participant with grade 3+ rash also experienced hepatotoxicity. No significant association was demonstrated between any NVP PK parameters and liver toxicity (data not shown).

Although the number of women with higher pretreatment CD4 count was small, these women exhibited an increased risk of hepatotoxicity. Specifically, within the first 18 weeks of treatment and following adjustment for body weight and week 4 CL/F, women with

screening CD4 ≥250 versus <250 cells/mm^3 had higher odds of experiencing combined grade 3+ liver/rash toxicity, any liver toxicity, and NVP discontinuation due to liver or rash toxicities (Table 3). In addition, a greater odds of developing any rash/grade 2+ liver toxicity (OR 3.20, p=0.038) and a trend toward greater odds of grade 2+ rash (p=0.046) were observed within six weeks but did not persist at 18 weeks. No significant association was observed between pretreatment CD4 ≥250 versus <250 cells/mm^3 with rash of any grade. Due to the small number of women with grade 3+ rash, multivariate analysis was not undertaken.

Consistent results were observed across our sensitivity analyses, except that in the models including only NVP-related events as determined by site investigators, the women with pretreatment CD4 count ≥250 cells/mm^3 had higher odds for rash of any grade or liver toxicity/rash of any grade.

Discussion

NVP PK is well characterized in men, but its disposition in women -- especially those of sub-Saharan African descent -- is less well defined. In this large cohort of sub-Saharan African women, we observed a week 4 median NVP CL/F of 2.0 L/hr, that is approximately 40% lower than CL/F reported among women from the US and Europe.[16, 18, 20] This lower-than-expected CL/F in sub-Saharan African women receiving standard NVP dosing led to higher NVP exposures and an increased risk of grade 3+ rash but not other grades of rash or hepatotoxicity. The odds of developing grade 3+ rash were estimated to be approximately 50% greater for every 20% reduction in week 4 NVP CL/F and 20% increase in NVP exposures (AUC_{24}, C_{min}, and C_{max}). NVP rash has been reported to be sex specific, being higher in women than men after adjusting for CD4 count.[6, 7, 11, 21, 22] In our study, 54% of subjects developed rash compared to previous reports of 6.5-32%. [7, 11, 13, 21-23] The overall lower NVP clearance in African women along with the greater occurrence of grade 3+ rash associated with higher NVP exposures in our study suggests that lower NVP doses might be appropriate in this population. However, further trials incorporating NVP pharmacogenetic testing in conjunction with PK studies are warranted before dose reductions can be recommended.

Studies comprising >80% men report NVP CL/F to be approximately 3.5 L/hr. [17, 20, 23-30] Overall, women have lower CL/F than men although the reasons are not clear; differences in body weight and liver metabolizing capacity have been suggested.[17, 18, 25, 26] Changes in bioavailability are not likely since NVP absorption is high. In ACTG 241, sex significantly affected NVP CL/F, averaging 3.97 L/hr for men compared to 3.02 L/hr for women, but women only comprised 10 out of 82 subjects.[20] In the 2NN study (n=1091) with 36% female and 36% of subjects from South Africa, steady state median NVP CL/F among all subjects was 2.8 L/hr but was 13.8% lower in women.[24,25] Lower NVP clearances and higher NVP exposures have also been reported in Asians and African Americans.[16, 17, 23, 31] Additionally, NVP CL/F may be influenced by geographical region and concomitant hepatitis B and C infection [16, 25] although no such relationship was observed in our study. However, our cohort included no women with HCV and small numbers of HBV infected women (n=25). Median week 2 and week 4 CL/F were similar (data not shown) between hepatitis B infected and non-infected women (p=0.6). In an intensive NVP PK study of US HIV infected women, NVP exposure was increased by renal insufficiency and hepatic inflammation and reduced by crack cocaine, high fat diets, and amenorrhea > 12 months but not age or exogenous administered hormone. [16] Lower clearance rates of ritonavir and saquinavir have also been reported in women compared to men in other studies conducted by the ACTG. [32, 33]

Our results relating NVP exposure and grade 3+ rash in women have not been previously reported. Although a relationship between higher NVP PK exposure and rash and hepatic events has been proposed, no association had been established in either men or women. [11, 13, 34, 35] Moreover, no specific drug concentration predicting NVP toxicity has been identified.[10, 13, 30, 36] The risk of rash was previously found to be more than two-fold higher in subjects with NVP concentrations greater than 5.3 mg/L, however, only 10% were female. [11] A higher C_{max} has also been associated with liver enzyme elevations.[37] Other studies have not shown such a consistent relationship.[11, 13] Additionally, pharmacogenetics may play an important role in NVP PK and toxicity and may be responsible for the lower CL/F observed in this study. Significantly higher NVP PK exposure and greater risk of skin toxicity were observed in African patients expressing the CYP2B6526TT genotype.[14, 38-41] In Cambodian HIV-infected patients with the CYP2B6526TT genotype, a lower CL/F of 1.86 L/hr was found, similar to our results. Preliminary findings also suggest the contribution of the ABCB1 c.3435C>T SNP in NVP hepatotoxicity.[42, 43]

An increased risk of hepatotoxicity was observed in a few women (n=15) with higher pretreatment CD4 >250 cells/mm^3 but screening CD4<200 cells/mm^3. Some prior studies have reported increased risks of hepatotoxicity and rash for women with CD4 >250 cells/mm^3 [44, 45], while others have not. [4, 46-50] Of note, for participants with pretreatment CD4>200 cells/mm^3 but entry CD4<200 cells/mm^3; we believe these CD4 counts are accurate despite the intra-patient variability, since CD4 testing was performed in monitored labs that successfully met the requirements of the DAIDS Immunology Quality Assurance program. Furthermore, considerable intra-subject CD4 count variability (as much as 200 cells/mm^3 obtained a few weeks apart) has been reported previously. [51-54]

World Health Organization antiretroviral treatment guidelines recommend NVP as one possible component of initial antiretroviral treatment regimens among persons (including women) with CD4 < 350 cells/mm^3 [1]. Our results add to previous data suggesting that vigilance and close monitoring for NVP toxicity are required for all African women starting NVP at any CD4 count, but toxicity is more likely in those with CD4 ≥250 cells/mm^3.

Some study limitations should be noted. Oral NVP CL/F was estimated by NONMEM® using two or fewer collected samples after self-reported dosing rather than an intensive PK study. However, the population model appeared to adequately characterize the drug levels. An important limitation is the lack of pharmacogenetic data to correlate with our PK results since patient consent was not initially obtained. Since only sub-Saharan African women were studied, our findings may not be generalizable to other ethnicities. In addition our findings based on differences between screening and pretreatment CD4 counts deserve cautious interpretation due to the small number of women and the CD4 count within-subject fluctuations that might occur between the two measurements.

Conclusions

In our cohort of HIV+ African women, NVP CL/F was substantially lower than previous reports, resulting in higher NVP plasma levels and drug exposure. Grade 3+ rash but not liver toxicity was significantly associated with a lower week 4 NVP CL/F. Further PK studies with incorporation of pharmacogenetic testing are recommended, particularly in resource limited settings, to determine optimal NVP dosages in African women that will maintain efficacy while minimizing toxicity. Consistent with previous findings, baseline CD4 ≥250 in a small number of women was significantly associated with NVP liver toxicity and drug discontinuation.

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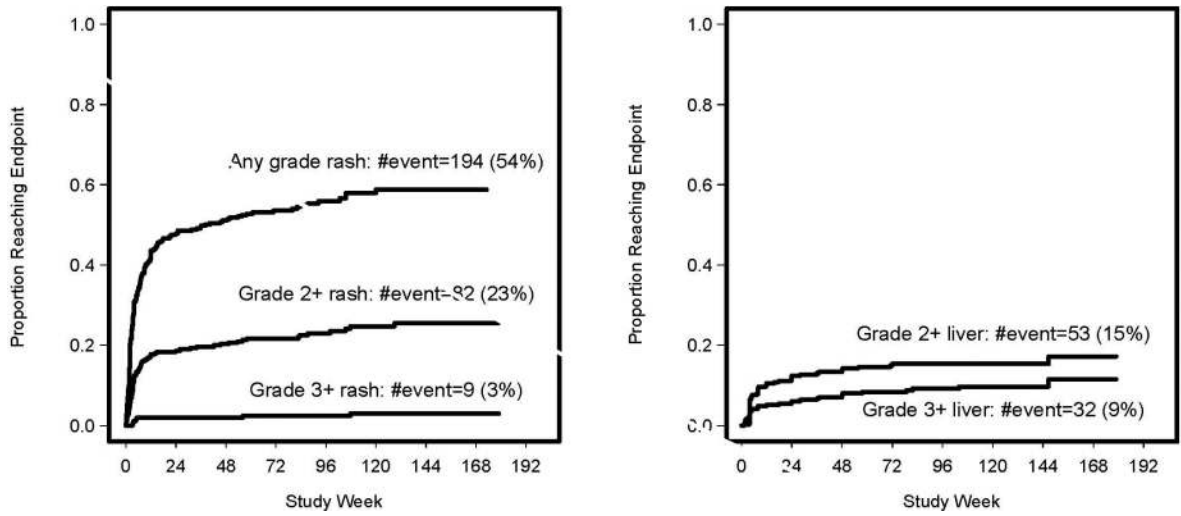
Figure 1a and 1b.
Kaplan–Meier plot for proportion of women experiencing rash and liver related events over time from starting NVP-based therapy.

Table 1

Final population PK model parameter estimates and bootstrap results

Population PK	Final Model		Bootstrap Runs (n=1000)	
	Estimate	95% CI[*]	Median	95% CI[**]
Parameters k_a, (h^{-1})	1.32	0.77-1.87	1.29	0.82-2.03
Week 2 CL/F (L/hr)	1.57	1.50-1.64	1.57	1.49-1.65
Additional CL/F at week 4 (L/hr)[#]	0.4	0.33-0.47	0.4	0.33-0.47
Vd/F (L)	72.8	58.8-86.8	70.1	59.0-87.2
IIV[+] for CL	29.6	22.4-35.4	29.7	25.7-33.3
RES[§]	22.3	20.1-24.2	22.2	20.4-24.2

[*]CI = confidence intervals

[**]95% Confidence intervals corresponding to parameter estimates at the 2.5th and 97.5th percentiles of bootstrap runs.

[#]CL/F$_{Wk4}$ (total CL) = 2 wk CL + additional CL=1.57 + 0.40 = 1.97 L/hr Vd/F = volume

[+]Inter-individual variability

[§]Residual unexplained variability

Table 2

Individual Predicted Median NVP Pharmacokinetic Parameters from the Final Model (n=359)

NVP PK	Week 2 (IQR)[*]	Week 4 (IQR)[*]	p-value[**]
$CL/F_{(L/hr)}$	1.6 (1.4, 1.8)	2.0 (1.8, 2.3)	<0.001
$AUC_{24\ hr}$ (mcg [*] hr/mL)	124.2 (109.0, 144.7)	200.9 (174.4, 227.5)	<0.001
C_{min} (mcg/mL)	4.0 (3.4, 4.8)	7.2 (6.1, 8.3)	<0.001
C_{max} (mcg/mL)	6.3 (5.7, 7.2)	9.3 (8.2, 10.4)	<0.001

CL/F = oral clearance

AUC_{24} = steady state 24 hr area under the curve

C_{min} = minimum plasma concentrations

C_{max}= maxiumum plasma concentrations

[*] IQR= Interquartile range

[**] Wilcoxon signed rank test

Table 3

Overall Rates of Rash and Liver Toxicities by Pretreatment CD4 Count

Toxicity Events	Subjects (n=359)	CD4 <250 (n=344)	CD4 ≥250[*] (n=15)	Fisher's Exact Test p-value
Any grade rash	194 (54.0%)	186 (54.1%)	8 (53.3%)	1.00
Grade 2+ rash	82 (22.8%)	77 (22.4%)	5 (33.3%)	0.35
Grade 3+ rash	9 (2.5%)	8 (2.3%)	1 (6.7%)	0.32
Any liver/rash	224(62.4%)	213(61.9%)	11(73.3%)	0.43
Grade 3+ liver/rash	40 (11.1%)	35 (10.2%)	5(33.3%)	0.02
Grade 3+ liver	32 (8.9%)	28 (8.1%)	4(26.7%)	0.04
Grade 2+ liver	53 (14.8%)	47(13.7%)	6(40.0%)	0.01
NVP Stopped due to liver/rash toxicity	46(12.8%)	41(11.9%)	5(33.3%)	0.03

[*]Range 250-386 cells/mm^3

Table 4

Association of Grade 3+ Rash with Week 4 NVP PK[**]

Week 4 Median PK (IQR)+	3+ Rash (n=9)	No 3+ Rash (n=350)	Odds Ratio[#] (95% CI)	p-value
$CL/F_{(L/hr)}$	1.7 (1.3, 2.0)	2.0 (1.8, 2.3)	1.51 (1.01, 2.21)	0.046
$AUC_{24\,hr}$ (mcg*hr/mL)	235 (203, 298)	200 (174, 223)	1.51 (1.01, 2.21)	0.047
C_{min} (mcg/mL)	8.7(7.3, 11.3)	7.2 (6.1, 8.2)	1.45 (1.01, 2.04)	0.046
C_{max} (mcg/mL)	10.7 (9.4, 13.3)	9.3 (8.2, 10.2)	1.56 (1.01, 2.35)	0.047

+ IQR = interquartile range

[**] no significant association observed between 3+ rash, week 2 PK, or baseline CD4

[#] per 20% increase in AUC, C_{max}, C_{min} or 20% decrease in CL/F