



No Effect of Prior Nevirapine Use on 6-Month Virologic and CD4 Responses after Commencement of Efavirenz-based Combination ART in a Cohort of South African HIV+ Females

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BACKGROUND

Single dose nevirapine (sd-NVP) has been used effectively for prevention of mother-to-child transmission (PMTCT) of HIV infection in resource-limited settings. It can, however, lead to selection of NVP-associated resistance mutations. These mutations may confer cross-resistance among most non-nucleoside reverse transcriptase inhibitors (NNRTIs), which form part of most first-line combination antiretroviral therapy (cART) regimens. Consequently, prior sd-NVP exposure could compromise treatment outcomes in patients initiated on NNRTI-based cART. Several studies have shown less robust virologic outcomes at 6 and 12 months of NNRTI-based cART in women with a history of sd NVP, particularly if it had been received within 6 months of cART initiation.

Phidisa II is a completed, randomised, open-label, 2x2 factorial clinical trial conducted in South Africa that compared the safety and efficacy of efavirenz (EFV) vs. LPV/r containing cART regimens in patients who were ARV naive, or had less than 7 days prior ARV exposure (Abstract K-104). The study was designed in 2003, before the recognition of the potential for selection of resistance mutations after sd-NVP, thus women who had previously received sd-NVP were eligible for enrolment into the randomized trial. Even after the reports of NNRTI-resistance after sd-NVP, the significance of this finding on eventual virologic outcome when women are started on an NNRTI-based regimen has not been fully elucidated. Therefore, the study team felt that the study should continue as originally designed with the hope that the results from this trial will help to further delineate the role of an EFV-based regimen in women with history of < 7 days of NVP exposure.

This analysis aims to evaluate the effect of prior NVP (<7 days) on virologic and immunologic outcomes at 6 months of cART initiation in those patients who were randomized to either an EFV or a LPV/r based regimen.

STUDY HYPOTHESIS

Females who received prior (< 7 days) NVP (for PMTCT):

1. May have less virologic suppression at Month 6 when compared to those who did not receive prior-NVP
2. May have less virologic suppression at Month 6 if randomized to receive EFV instead of LPV/r

METHODS

The primary study for this analysis, Phidisa II, is a randomised, open-label 2x2 factorial study that compared the safety and efficacy of different combined antiretroviral therapy regimens in treatment-naïve patients with advanced HIV disease and/or CD4+ cell counts < 200 cells/mm³ (please visit Abs. K-104 for details of study design and results). The primary protocol was approved by the PHIDISA and NIAD Institutional Review Boards. All subjects signed written informed consent.

The aim of Phidisa II was to compare the following in a 2x2 factorial design:

- EFV vs. LPV/r
- Zidovudine (ZDV) plus didanosine (ddI) vs. stavudine (d4T) plus lamivudine (3TC)

Key Eligibility Criteria Included:

- CD4+ cell count < 200 cells/mm³ or history of AIDS-defining condition
- Less than 7 days cumulative exposure to any antiretroviral drug

Sub Study Population:

- At Phidisa II baseline visit, participants had to indicate whether or not they had prior exposure to ART, and specify the drugs.
- Female participants who reported prior use of NVP were identified and this group was compared to female participants who reported no previous use of NVP.

Sub Study Data Collection/Analysis Including:

- Baseline demographic information including age, CD4+ cell count, HIV-RNA, BMI, WHO stage, Hepatitis B co-infection (defined as positive Hepatitis B surface antigen), haemoglobin, education, and % of subjects from rural sites.
- Proportion of patients with viral suppression (defined as viral load <400 copies/mL) at 1, 2, 3 and 6 months
- Change in absolute CD4 count (observed CD4 count minus baseline CD4 count) at 1, 2, 3 and 6 months for both groups.

Statistical Analysis:

- Between the NVP-naïve patients and the patients with prior NVP use, demographic and baseline variables were compared by two sample t-test for continuous variables and Fisher's exact test for binary variables.
- Fisher's exact test was used for the comparison of virologic suppression rate, between the NVP-naïve patients and the prior NVP users, and between the EFV regimen and the LPV/r regimen. As secondary analysis, logistic regression was used to compare the prior NVP users with the NVP-naïve patients accounting for baseline imbalance.
- Two sample t-test was used for the comparison in CD4 change, between the NVP-naïve patients and the prior NVP users, and between the EFV and the LPV/r arm. To account for baseline imbalances, linear regression was used as a secondary analysis. To compare the prior NVP users with the NVP-naïve patients.

Figure 1 Subject Distribution & Treatment Arms

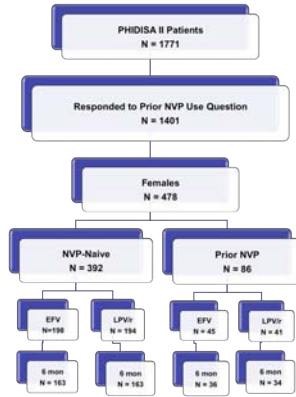


Table 1 Baseline Demographic Characteristics

	NVP-Naïve (N=392)	Prior NVP (N=86)	P-Value
Age (yrs, mean)	34.7	32.0	<0.001*
CD4+ cell count (cells/mm ³ , mean)	109.6	117.7	0.363
Log ₁₀ HIV-RNA (copies/mL, mean)	4.54	4.96	0.787
Hgb (g/dL, mean)	11.47	11.88	0.031*
BMI (kg/m ² , mean)	25.6	27.6	0.008*
WHO Stage 3 or 4	45.9%	39.5%	0.284
% from rural area	61.2%	58.1%	0.627

Table 2 Disposition of Subjects at 6-Month

	NVP-Naïve (N=392)	Prior NVP (N=86)
Observed at 6-month visit*	326 (83.2%)	70 (81.4%)
Censored by 6-month visit	18 (4.6%)	8 (9.3%)
Missing 6-month visit	18 (4.6%)	1 (1.2%)
Withdrawn from study by 6-month	14 (3.6%)	3 (3.5%)
Death	16 (4.1%)	4 (4.7%)

* Subjects included in data analysis

Table 3 Subjects Maintained on Assigned EFV or LPV/r at 6 Months

	Randomized Treatment	
	EFV	LPV/r
NVP-Naïve (N=326)	153/163 (93.9%)	148/163 (90.8%)
Prior NVP (N=70)	35/36 (97.2%)	29/34 (85.3%)

RESULTS

Figure 2 Proportion of Subjects with Viral Suppression (<400 copies/mL) at 6 months, NVP-Naïve vs. Prior Subjects

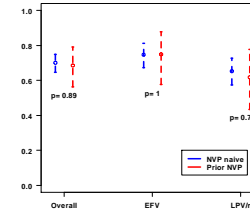


Figure 3 Proportion of Subjects with Viral Suppression (<400 copies/mL) at 6 months, EFV vs. LPV/r-treated Subjects

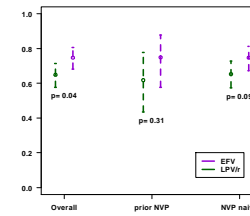
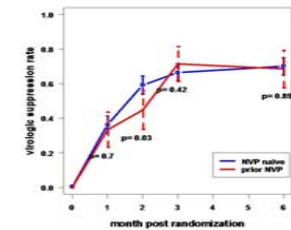


Figure 4 Proportion of Subjects with Viral Suppression at Months 0, 1, 2, 3, and 6 – NVP-Naïve vs. Prior NVP Subjects



Virologic Responses at 6 Months: Because the comparisons between the prior NVP and NVP-naïve subgroups are not a randomized comparison, multivariate logistic regression was used to correct for any baseline imbalances and improve efficiency. The effect of prior NVP was not significant overall, and not significant within each of the EFV and LPV/r arms. (all p>0.30)

Table 4 Absolute CD4+ T Cell Changes (cells/mm³) at 6 Months Among Subjects with Prior NVP and NVP-Naïve Subjects

	NVP-Naïve		Prior NVP		P-value for difference
	N	Mean	N	Mean	
EFV-treated	163	+108.5	70	+127.9	0.22
LPV/r-treated	163	+122.6	36	+112.3	0.55
All Subjects	326	+115.5	34	+120.4	0.67

Table 5 Absolute CD4+ T Cell Changes (cells/mm³) at 6 Months Among Subjects Randomized to EFV vs. LPV/r

	Mean CD4+ T cell Changes (cells/mm ³)		P-value for difference
	EFV	LPV/r	
NVP Naïve (N=326)	+108.5	+122.6	0.19
Prior NVP (N=70)	+127.9	+112.3	0.45
All Subjects (N=396)	+112.0	+120.8	0.35

CD4+ T-cell Changes at 6 Months: Analyses analogous to those conducted for VL were conducted using the 6-month change in CD4 as the outcome. Using t-tests, the average improvement in CD4 counts over 6 months showed no significant difference between the NVP-naïve and prior NVP groups both overall and within each of the EFV and LPV/r arm (all p > 0.20). Additionally, there was no significant difference with EFV and LPV/r within the prior NVP subgroup (p = 0.45) and with the NVP-naïve subgroup (p = 0.1). Multivariate linear regression analyses showed similar results.

STUDY LIMITATIONS

- The primary trial, PHIDISA II, was not designed to answer the questions addressed in this analysis.
- Thus, the number of women with prior NVP was not fixed by design and is relatively small.
- History of prior NVP use in this cohort was based on patient self-reports without documentation.
- Time lapse between NVP and enrolment into PHIDISA II protocol is unknown, it is very likely that most subjects received NVP > 6 months prior to enrolment.
- Baseline and time-of-failure resistance testing were not done in this analysis.

CONCLUSIONS

In this subgroup analysis of a large randomized trial comparing the virologic efficacy of an NNRTI- vs. PI-based regimen in antiretroviral-naïve patients (defined by < 7 days of prior ART):

- Prior NVP use (<7days) had no significant effect on virologic suppression nor CD4 gain at 6 months, both over all arms and within treatment arms (NNRTI-based and PI-based).
- In the prior-NVP group, viral suppression rates and CD4 gain were non-inferior in those randomized to EFV compared to those randomized to LPV/r.
- This analysis suggests that in some resource-limited settings where sd NVP is still the mainstay of PMTCT programmes, good maternal virologic and immunologic outcomes may be achieved with subsequent NNRTI-based first-line cART.
- Results from prospective, randomized controlled trials designed to specifically address this question, such as the ACTG A5208 and other ongoing trials will help to further address this issue.