Published in final edited form as:

Pharmacotherapy. 2011 February ; 31(2): 158–163. doi:10.1592/phco.31.2.158.

Lack of Effect from a Previous Single Dose of Nevirapine on Virologic and Immunologic Responses After 6 Months of Antiretroviral Regimens Containing Efavirenz or Lopinavir-ritonavir

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Abstract

Study Objective—To evaluate the effect of prior single dose nevirapine (sd-NVP) use on HIV RNA and CD4+ T-cell responses after 6 months of efavirenz - or lopinavir/ritonavir -based antiretroviral regimens.

Design—This is a retrospective analysis of a subset of participants in the Phidisa II trial, a randomized controlled trial enrolled HIV+ participants 14 years or older with no or < 7 day history of antiretroviral use. At screening, subjects were asked about prior nevirapine use, a positive response in a woman was used as a surrogate for prior sd-NVP. Virologic and CD4 responses at 6-month were compared between women with or without prior nevirapine exposure, and amongst women who received efavirenz vs. lopinavir/ritonavir.

Setting—Six South African Medical Health Services' Phidisa research clinics.

Subjects—478 women responded to the question regarding prior nevirapine use.

Measurements and Main Results—392 women were nevirapine-naïve (NVP-), 86 had prior nevirapine (NVP+). At 6-month, 396 women (324 NVP-, 70 NVP+) had follow-up HIV-RNA

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Presented at the 16th Conference on Retroviruses and Opportunistic Infections, Montreal, Canada, February 2009

results. 69.9% of NVP- and 68.6% of NVP+ subjects achieved HIV-RNA <400 copies/mL ($p=0.35$), with CD4 changes of +115.5 and +120.4 cells/mm³ respectively ($p=0.67$). Among the NVP+ women, 75% efavirenz-treated and 61.8% lopinavir/ritonavir-treated subjects had HIV-RNA < 400 copies/mL at 6 months ($p=0.31$).

Conclusion—In this retrospective analysis, 75% of participants with self-reported prior sd-NVP use achieved HIV RNA <400 copies/mL with efavirenz-based regimen at 6-month follow-up. Prior exposure to sd-NVP per self report did not affect virologic outcome at 6-month in this small cohort.

Keywords

single-dose nevirapine; South Africa; efavirenz; HIV; response; antiretroviral; women

Introduction

Single dose nevirapine (sd-NVP) given to HIV-1 infected pregnant women at the time of labor followed by sd-NVP to the neonate has been widely used for the Prevention of Mother-to-Child Transmission (PMTCT) of HIV-1 infection in resource-limited settings due to its relatively good efficacy, ease of administration, and low cost.¹ However, the long half-life of nevirapine allows for selection of major non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations including K103N, Y181C and G190A that may confer cross-resistance to nevirapine or efavirenz, the NNRTIs most commonly used in resource-limited countries. Presence of pre-existing drug resistance mutations may limit treatment effectiveness when NNRTI-based combination antiretroviral therapy (cART) is needed for treatment of the mother's HIV infection.²⁻⁴

In sub-Saharan Africa, NNRTI-based cART regimen remains as first line therapy as it is less expensive than protease inhibitor (PI)-based regimens, available as generic formulations and fixed dose combinations, and can be used in patients co-infected with tuberculosis requiring rifamycin-based regimens⁵. PIs are reserved for second line treatment in patients who fail or cannot tolerate NNRTIs⁶. Several studies, including the Thai Perinatal HIV Prevention Trial 27 and the Botswana Mashi Trial 8, have shown less robust virologic outcomes of nevirapine-based cART at 6 and 12 months in women with a history of sd-NVP, particularly if it was received within 6 months of cART initiation. Recently, Trial 1 of the ACTG 5208 (OCTANE) Study was halted for futility, after showing that women previously exposed to sd-NVP had better virologic outcomes when initiated on lopinavir/ritonavir-based cART compared to nevirapine-based cART.⁹ However, this harmful effect waned with increased interval between receiving sd-NVP, and nevirapine-containing cART initiation. Furthermore, a recent study from South Africa suggests that exposure to sd-NVP 18-36 months prior to commencing NNRTI-based therapy is not associated with failure to achieve and sustain viral suppression. In this study, the presence of the K103N mutation pre-cART is a strong predictor of inadequate treatment response.¹⁰

Phidisa II is a randomised, open-label, 2×2 factorial trial conducted in six sites within South Africa, which compared the safety and efficacy of efavirenz vs. lopinavir-ritonavir containing cART regimens in patients with advanced HIV disease who were antiretroviral-naïve or had less than 7 days prior antiretroviral drug exposure.¹¹ This study provides an opportunity to answer some of the questions related to maternal virologic responses to cART following sd-NVP in a resource-limited setting. We undertook a secondary subgroup analysis with the objective to evaluate the effect of prior sd-NVP on virologic and immunologic outcomes after 6 months of cART in women who were randomized to receiving either efavirenz- or lopinavir/ritonavir-based regimens.

Methods

The Phidisa II protocol was conducted in accord with the South African National Defence Force (SANDF)'s and the US National Institutes of Health (NIH)'s, and Declaration of Helsinki's ethical standards on human experimentation. The protocol was approved by the SANDF and the NIH-National Institute of Allergy and Infectious Diseases (NIAID) Institutional Review Boards. All subjects signed written informed consents prior to enrollment. Key eligibility criteria for Phidisa II included: uniformed SANDF personnel and/or family members; age 14 years or older; current or previous history of AIDS-defining illness and/or < 200 CD4⁺ cells/mm³; treatment naïve or ≤ 7 days use of antiretroviral drugs. At baseline visits, demographic information including age, CD4⁺ T-cell count, HIV RNA level, body mass index (BMI), WHO stage, and haemoglobin were collected. Eligible subjects were randomized to receive either efavirenz or lopinavir/ritonavir with either stavudine + lamivudine or didanosine + zidovudine as the NRTI backbone. Prior antiretroviral history per patient interview was recorded at the Phidisa II baseline visit. Females who reported prior nevirapine exposure (NVP+) without other exposure to other antiretroviral drugs were thus identified, and assumed to have received sd-NVP for PMTCT, and were then compared to female subjects who reported no previous use (NVP-).

We compared the proportion of subjects with viral suppression (defined as HIV RNA < 400 copies/mL) and CD4 count changes at 6 months post cART initiation, between NVP+ and NVP- subjects, and between those randomized to lopinavir/ritonavir or efavirenz. Demographics and baseline variables were compared between NVP+ and NVP- subjects using 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 NVP+ and NVP- groups, and between efavirenz and lopinavir/ritonavir regimen in the NVP+ group. As a secondary analysis, logistic regression was also used to compare the NVP+ with the NVP- in virologic suppression rate to account for any baseline imbalances. Two-sample t-test was used for the comparison of CD4 change between the groups. Linear regression was used to compare the NVP+ with the NVP- in CD4 change to account for any baseline imbalances.

Results

Among the 1,771 subjects enrolled into PHIDISA II, 1,401 subjects responded to the question of whether or not they had received nevirapine prior to enrollment. Four hundred and seventy-eight of these were women, 86 of whom (18.0%) responded 'yes' to prior nevirapine use. The baseline demographic characteristics for the two groups are shown in Table 1. The NVP+ women were significantly younger (32.0 vs. 34.7 years, $p<0.001$), had higher baseline haemoglobin (11.88 vs. 11.41 gm/dL, $p=0.031$), and higher BMI (27.6 vs. 25.6 kg/m², $p=0.008$).

Three hundred and ninety-six women attended a 6-month follow-up clinic visit. Seventy were NVP+ (36 randomized to efavirenz, 34 to lopinavir/ritonavir) and 326 were NVP- (163 each randomized to efavirenz or lopinavir/ritonavir). At month 6, 92.2% of the women remained on their assigned efavirenz or lopinavir/ritonavir therapy. A similar proportion of women achieved HIV RNA < 400 copies/mL in the NVP+ and the NVP- groups overall (68.6% vs. 69.9%, $p=0.89$, Table 2), among those under an efavirenz-based regimen (75.0% vs. 74.7%, $p=1.0$), and among those under a lopinavir/ritonavir-based regimen (65.4% vs. 61.8%, $p=0.70$). CD4⁺ T-cell increases were also similar between the NVP+ and the NVP- groups ($+120.4$ cells/mm³ vs. $+115.5$ cells/mm³, $p=0.67$, Table 2). As Phidisa II was not a randomized trial for the comparison between the two subgroups, multivariate regressions were additionally performed to adjust for baseline imbalance in age, hemoglobin, and BMI

between the two subgroups: multivariate logistic regressions indicated no significant effect of prior nevirapine use on virologic suppression overall [odds ratio 0.782 with 95% confidence interval (0.433, 1.415)] or within either the efavirenz- or lopinavir/ritonavir-treated patients, and no significant effect of prior nevirapine use on CD4+T-cell increase was observed from multivariate linear regressions.

Overall, as was seen in the primary Phidisa II study¹¹, significantly more subjects randomized to efavirenz achieved HIV RNA < 400 copies/mL than those randomized to lopinavir/ritonavir (74.7% vs. 64.8% respectively, $p=0.04$) at 6-month. A similar pattern was observed within NVP+ (75% vs. 61.8%) and NVP- (74.7% vs. 65.4%) but of no statistical significance due to the limited sample sizes. For example, within NVP+ (36 randomized to efavirenz and 34 to lopinavir/ritonavir), the power to detect the difference of 75% versus 61.8% is only 15%. There was also no significant difference between efavirenz and lopinavir/ritonavir in CD4 changes (overall $p=0.35$), within the NVP+ ($p=0.45$) or the NVP- ($p=0.10$) subgroup.

Discussion

In this subgroup analysis of the Phidisa II trial, we found no association between self-reported prior nevirapine use and immunologic and virologic outcomes at 6-month post initiation of efavirenz- or lopinavir/ritonavir-based cART. Our findings are different from the ACTG 5208 trial study, which found significantly poorer outcomes (primary endpoint defined as death or confirmed virologic failure) among sd-NVP exposed women when commenced on a nevirapine-containing regimen compared to a lopinavir/ritonavir-containing regimen⁹. In the ACTG trial, the rate of reaching primary endpoint declined with a longer duration between sd-NVP exposure and the initiation of NVP-based cART.

Unlike the ACTG and other studies, efavirenz instead of nevirapine-based cART was used in our study. Although significant cross resistance exists between efavirenz and nevirapine, for patients with susceptible virus, there may be difference in viral responses between the two NNRTIs. The 2NN study, which compared efavirenz vs. nevirapine-based cART, showed a trend towards better virologic outcomes in the efavirenz-treated subjects than those who received nevirapine-based regimens.¹² Similar results were recently reported in Botswana, where virologic failure was seen more frequently in nevirapine-based cART than efavirenz-based therapy¹³. There could possibly be difference in virologic responses to efavirenz vs. nevirapine in the presence of some NNRTI mutations, which cannot be further investigated in this study. Our data also support the results from other trials comparing efavirenz vs. lopinavir/ritonavir-based regimen, where overall, higher rates of virologic suppression were seen in treatment naïve subjects treated with efavirenz than lopinavir/ritonavir.^{13, 14}

There are several limitations to our study. First, this is a post-hoc analysis of a larger study, only a small number of patients reported prior use of nevirapine. The patients were not stratified by prior nevirapine exposure and women with prior nevirapine may differ from nevirapine-naïve women in terms of unmeasured characteristics that could influence outcome. We used multivariate linear and logistic regression to correct for measured baseline imbalances. Second, prior nevirapine use was based on patient recall and not on actual documentation. This was also the case in other studies in resource-limited countries, as medical record is almost non-existence in many settings. Since the patients were to have received < 7 days of antiretroviral therapy, we made an assumption that reports of nevirapine use were based on sd-NVP. We selected subjects who did not report use of other antiretroviral drugs, however, it is possible, that some women might have received short course of cART without reporting to the research team. Thirdly, the time lapse from sd-NVP

use to initiation of cART, was not documented, it is possible that some women might have received sd-NVP more than six months before enrollment into the trial, making it more likely for them to have good virologic response to an NNRTI-based regimen.⁷ Lastly, since resistance testing is not available for routine clinical care in South Africa, the presence of antiretroviral resistance at baseline and at failure cannot be determined.

Despite these limitations, in our analysis, 75% of the women who reported prior nevirapine exposure achieved HIV RNA <400 copies/mL 6 months after starting an efavirenz-based regimen. This response is similar to those without a history of nevirapine exposure. Our small retrospective analysis shows that efavirenz-based regimen, which is amongst the first line cART in Africa, remains as a viable option for some women who received sd-NVP. If available, HIV RNA monitoring will be very useful in detecting early virologic non-response or failure so as to commence a second line regimen sooner rather than later. With the move to using cART instead of ssd-NVP for PMTCT in many countries including South Africa, it is hopeful that NNRTI-resistance from sd-NVP may become a problem of the past.

Acknowledgments

The authors wish to acknowledge the support of the Phidisa Executive Committee, the dedication of the site investigators and staff, and the enrollment of the study participants.

Funding Sources: Funding of this project is provided by the South African Military Health Service and the National Institute of Allergy and Infectious Diseases, NIH, USA

References

1. Marseille E, Kahn JG, Mmiro F, et al. Cost effectiveness of single-dose nevirapine regimen for mothers and babies to decrease vertical HIV-1 transmission in sub-Saharan Africa. *Lancet*. Sep 4; 1999 354(9181):803–809. [PubMed: 10485721]
2. Flys TS, Donnell D, Mwatha A, et al. Persistence of K103N-containing HIV-1 variants after single-dose nevirapine for prevention of HIV-1 mother-to-child transmission. *J Infect Dis*. Mar 1; 2007 195(5):711–715. [PubMed: 17262714]
3. Arrive E, Newell ML, Ekouevi DK, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int J Epidemiol*. Oct; 2007 36(5):1009–1021. [PubMed: 17533166]
4. Eshleman SH, Guay LA, Mwatha A, et al. Comparison of nevirapine (NVP) resistance in Ugandan women 7 days vs. 6–8 weeks after single-dose nvp prophylaxis: HIVNET 012. *AIDS Res Hum Retroviruses*. Jun; 2004 20(6):595–599. [PubMed: 15242535]
5. WHO. Rapid Advice: antiretroviral therapy for HIV infection in adults and adolescents.; Accessed June. 2009. p. 2010 <http://www.who.int/hiv/pub/arv/advice/en/index.html>.
6. WHO. Prioritizing second-line antiretroviral drugs for adults and adolescents: a public health approach.; World Health Organization. Accessed April. 2007. p. 2009 http://www.who.int/hiv/pub/meetingreports/art_meeting/en/index.html.
7. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med*. Jul 15; 2004 351(3):229–240. [PubMed: 15247339]
8. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med*. Jan 11; 2007 356(2):135–147. [PubMed: 17215531]
9. Lockman, S. Lopinavir/ritonavir + tenofovir/emtricitabine is superior to nevirapine + tenofovir/emtricitabine for women with prior exposure to single dose nevirapine: ACTG: A5208 (“OCTANE”). Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Canada. February 8–11, 2009; 2009. Abs 94 LB
10. Coovadia A, Hunt G, Abrams EJ, et al. Persistent Minority K103N Mutations among Women Exposed to Single-Dose Nevirapine and Virologic Response to Nonnucleoside Reverse-Transcriptase Inhibitor-Based Therapy. *Clin Infect Dis*. 2009; 48(4):462–72. [PubMed: 19133804]

11. Ratsela A, Polis M, the Phidisa II Study Group. Phidisa II: A randomized 2×2 factorial trial comparing initial therapy of efavirenz with lopinavir/ritonavir and zidovudine+didanosine with stavudine+lamivudine in treatment-naïve HIV-infected persons with <200 CD4+ cells/mm³ or a prior AIDS diagnosis. *Journal of Infectious Diseases*. 2010 in press.
12. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. Apr 17; 2004 363(9417):1253–1263. [PubMed: 15094269]
13. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. May 15; 2008 358(20):2095–2106. [PubMed: 18480202]
14. Sierra-Madero J, Villasis-Keever A, Mendez P, et al. Prospective, randomized, open label trial of Efavirenz vs Lopinavir/Ritonavir in HIV+ treatment-naïve subjects with CD4+<200 cell/mm³ in Mexico. *J Acquir Immune Defic Syndr*. Apr; 2010 53(5):582–588. [PubMed: 20090545]

Table 1

Pre-cART Baseline Characteristics of Subjects With (NVP+) and Without (NVP-) Prior Single Dose Nevirapine Therapy

	NVP+	NVP-	P-value
N	86	392	
Age [yrs. mean (range)]	32.0(23.5, 42.9)	34.7(18.5, 56.6)	<0.001
CD4+ T cell count [cells/mm ³ , mean (SD)]	117.7(72.9)	109.6(71.6)	0.363
Log ₁₀ HIV RNA [copies/mL, mean (SD)]	4.96(0.56)	4.94(0.67)	0.787
Hemoglobin [g/dL, mean (SD)]	11.88(1.53)	11.47(1.53)	0.031
Body mass index [kg/m ² , mean (SD)]	27.6(6.2)	25.6(5.3)	0.008
WHO Stage 3 or 4 (percent)	39.5%	45.9%	0.284

Table 2

Virologic and CD4 Responses to Efavirenz (EFV)- or Lopinavir/ritonavir (LPV/r)-Based Regimens at 6 Months

	NVP+	NVP-	P-value
N	70 ¹	326 ²	
% with HIV RNA < 400 copies/mL at 6 months			
All Patients	68.6%	69.9%	0.89
EFV	75.0%	74.7%	1.00
LPV/r	61.8%	65.4%	0.70
Mean CD4 (cells/mm ³) change from baseline			
All Patients	+120.4	+115.5	0.67
EFV	+127.9	+108.5	0.22
LPV/r	+112.3	+122.6	0.55

NVP+ = prior nevirapine use; NVP- = no prior nevirapine use; EFV = efavirenz; LPV/r = lopinavir/ritonavir

¹ 36 randomized to EFV-based and 34 randomized to LPV/r-based regimens

² 163 randomized to EFV-based and 163 randomized to LPV/r-based regimens