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Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine

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Abstract

Objective—To determine whether prior exposure to single-dose nevirapine (NVP) for prevention of mother-to-child HIV transmission (PMTCT) is associated with attenuated CD4 cell response, death, or clinical treatment failure in women starting antiretroviral therapy (ART) containing non-nucleoside reverse transcriptase inhibitors (NNRTI).

Methods—Open cohort evaluation of outcomes for women in program sites across Zambia. HIV treatment was provided according to Zambian/World Health Organization guidelines.

Results—Peripartum NVP exposure status was known for 6740 women initiating NNRTI-containing ART, of whom 751 (11%) reported prior use of NVP for PMTCT. There was no significant difference in mean CD4 cell change between those exposed or unexposed to NVP at 6 (+202 versus +182 cells/μl; $P=0.20$) or 12 (+201 versus +211 cells/μl; $P=0.60$) months. Multivariable analyses showed no significant differences in mortality [adjusted hazard ratio (HR), 1.2; 95% confidence interval (CI), 0.8–1.8] or clinical treatment failure (adjusted HR, 1.1; 95% CI, 0.8–1.5). Comparison of recent NVP exposure with remote exposure suggested a less favorable CD4 cell response at 6 (+150 versus +219 cells/μl; $P=0.06$) and 12 (+149 versus +215 cells/μl; $P=0.39$) months. Women with recent NVP exposure also had a trend towards elevated risk for clinical treatment failure (adjusted HR, 1.6; 95% CI, 0.9–2.7).

Conclusion—Exposure to maternal single-dose NVP was not associated with substantially different short-term treatment outcomes. However, evidence was suggestive that exposure within 6

months of ART initiation may be a risk factor for poor treatment outcomes, highlighting the importance of ART screening and initiation early in pregnancy.

Keywords

HIV; nevirapine; mother-to-child transmission of HIV; clinical outcomes; Zambia; Africa; antiretroviral therapy

Introduction

Since the demonstration in 1999 that the combination of intrapartum and neonatal single-dose nevirapine (NVP) was a simple and effective method for perinatal HIV prophylaxis [1,2], this has become a cornerstone for preventing mother-to-child HIV transmission (PMTCT) in many developing world settings [3–8]. While the low cost and simplicity of this intervention has allowed widespread implementation in resource-constrained settings, use of single-dose NVP may come at a price. Studies have shown that 20–75% of women develop resistance mutations to non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral drugs in the weeks following delivery [9–12]. NNRTI resistance has also been described when single-dose NVP is added to antenatal zidovudine or combination lamivudine–zidovudine in the antenatal period [13,14].

At present, the clinical significance of these resistance mutations is uncertain [15]. As HIV treatment becomes increasingly available in developing world settings, however, there are strong concerns that prior NVP exposure could compromise the effectiveness of combination antiretroviral regimens that include NNRTIs [16]. Studies from Thailand [14] and Botswana [17] suggest an increased risk of virological failure among women with prior NVP exposure when that exposure occurs within 6 months of initiating antiretroviral therapy (ART). This concern is particularly relevant for countries such as Zambia, where resource and infrastructure constraints have led to a heavy reliance on NVP for PMTCT at the present time and where current ART scale-up efforts utilize NNRTI-based regimens for first-line therapy.

Methods

Clinical and immune responses were compared among women with and without a history of NVP use who were currently receiving NNRTI-containing ART across 26 public ART clinics in Zambia. This setting is well suited for such an evaluation because of robust programs for both PMTCT [3] and ART provision [18]. At the start of 2007, 52 919 individual doses of NVP had been distributed to HIV-infected pregnant women, while 26 590 women had initiated ART.

Across all ART sites, clinical flow, patient care, and medical documentation have been standardized in accordance with the Zambian national guidelines for adult HIV treatment [19], which closely follow those outlined by the World Health Organization (WHO) [20]. In the first months of the program, ART was initiated in individuals with either CD4 cell count <200 cells/μl or WHO stage 3 or 4. Since 2005, the Zambian guidelines have been revised to exclude ART eligibility for patients in WHO stage 3 with CD4 cell count >350 cells/μl. First-line drug regimens in Zambia comprise two nucleoside reverse transcriptase inhibitors (lamivudine with either zidovudine or stavudine) and one NNRTI (NVP or efavirenz).

In our setting, routine testing for HIV viral load or viral drug resistance is not available as part of treatment monitoring. Instead, patients are switched to second-line drug regimens based on clinical and immunological (CD4 cell) criteria, such as the development of new opportunistic infections or the return of CD4 cell counts to (or below) pretreatment levels. Since several

months are required for immunological reconstitution, a patient must be adherent to ART for a minimum of 3 months before a second-line regimen is considered [20].

At each site, patient information is collected on a comprehensive set of clinical care forms based on national treatment guidelines. Each patient visit generates a paper form, and selected data from that form are entered by clerical staff at the clinical facility. Through these procedures, key individual indicators are collected in a large database for monitoring and reporting, including demographic characteristics, medical history, laboratory results, pharmacy dispensations, and vital status [21]. Previous exposure to single-dose NVP is ascertained through patient's ART history, collected at the enrollment visit. In May 2005, the Lusaka District clinical care forms were revised to elicit more detailed history of ART, including date and number of NVP exposures for PMTCT. New patients are asked these questions at time of enrollment. For those already enrolled into care, this information was obtained at the next clinical visit following introduction of the new forms.

For the present analysis, patients were categorized as "active" if they attended their last scheduled clinic and/or pharmacy visit within 30 days of their appointment date. "Dead" patients were so classified only after confirmation from family members, friends, or clinic staff. "Inactive" patients had formally withdrawn from the HIV treatment program. "Late" patients were more than 30 days overdue for their last scheduled visit and could not be located via community health worker contact tracing. Censorship of patient outcomes began at the last patient contact for late patients. For inactive or dead patients, it was based on the date of report or date of death.

Outcome measures were mean CD4 cell count change, survival, and treatment failure. Patients were classified as having failed their first-line ART regimen if they met any of the following criteria: (1) worsening WHO stage after 3 months on ART, (2) fall in CD4 cell count to below 95% of the pretreatment level after at least 3 months on therapy, or (3) death. Comparisons were made between women previously exposed and unexposed to single-dose NVP. In order to determine what effect the timing of NVP exposure may have on patient outcomes, the exposed population was also stratified according to the interval between drug ingestion and ART initiation. The categories of "recent" (i.e., <6 months between NVP ingestion and ART initiation) and "remote" (i.e., ≥6 months) NVP exposure were used based on conventions established by previous work [17].

To determine the optimal study population, women with known NVP status (i.e., exposed or unexposed) were grouped as: (1) those with NVP exposure status determined at time of enrolment, and (2) those with NVP exposure status missing at time of enrollment but determined at some point after initiating NNRTI-based ART. To assess similarity between these groups, the proportion of NVP-exposed women within each was compared. There was a higher proportion of women with NVP exposure among those whose status was determined after ART initiation than among those whose status was recorded at enrollment (40% versus 11%, $P < 0.0001$). This was thought to result from ascertainment bias. Among women who had already started ART and returned for clinic visits later in care, it appeared that health-care workers were less likely to document status information if they denied previous NVP use. In an effort to minimize selection biases, the primary analysis was limited to women with NVP exposure status determined at time of enrollment (the "primary evaluation cohort"). The one exception was a supplementary comparison of recent and remote NVP exposure, where all women with known NVP exposure were included in the analysis. It was reasoned that differences in exposure ascertainment were unlikely to influence comparisons within the NVP exposed group itself. Secondary analyses were performed on the larger cohort of women.

To compare various demographic and medical characteristics among members of our study population, categorical variables were analyzed using either Pearson's χ^2 test or Fisher's exact test. Two-tailed t-tests were used for normally distributed continuous variables, while Wilcoxon rank-sum tests compared parameter medians when distribution was not believed to be normal. Log-rank tests were used to evaluate differences in survival and treatment failure using Kaplan–Meier analysis. Cox proportional hazards models were used to assess the risk of death and treatment failure [22]. These multivariate analyses were performed with covariates significant at a $P \leq 0.10$ level in bivariate analysis comparing NVP-exposed and NVP-unexposed women. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA). This analysis, using routinely collected clinical data, was deemed exempt [23] from human subjects review by the Institutional Review Boards of the University of Zambia (Lusaka, Zambia), the University of Alabama at Birmingham (Birmingham, Alabama, USA), and the US Centers for Disease Control and Prevention (Atlanta, Georgia, USA).

Results

From April 1, 2004 to July 31, 2006, NNRTI-containing ART was initiated by 6740 women with known exposure status. In the primary evaluation cohort, 751 (11%) reported previous use of single-dose NVP for PMTCT. The remaining 5989 (89%) had no history of NVP exposure (Fig. 1). As of July 31, 2006, 157 (2.3%) withdrew from the program and 1563 (23.2%) were late for a scheduled visit. NVP-exposed women were somewhat less likely to be late or to have withdrawn than were unexposed women (22% versus 27%; $P = 0.006$). Of the remaining 5020 women who were neither late nor withdrawn, 290 (5.7%) were known to have died [crude mortality rate, 9.5/100 person-years; 95% confidence interval (CI), 8.5–10.7]. Women without previous NVP exposure had lower CD4 cell count and higher WHO stage. They were also older, had a higher average body mass index (BMI), and were more frequently undergoing treatment for active tuberculosis at time of enrollment (Table 1).

CD4 cell response

Among the 229 NVP-exposed women with CD4 cell count data at baseline and at 6 months, the mean increase was 202 cells/ μ l (SD, 218). Of the 1530 NVP-unexposed women with corresponding data available, the mean increase was 182 cells/ μ l (SD, 166) ($P = 0.20$). Among the 110 NVP-exposed women with CD4 cell count data at baseline and at 12 months, the mean increase was 201 cells/ μ l (SD, 206). Among the 659 NVP-unexposed women with data available, the mean increase was 211 cells/ μ l (SD, 182) ($P = 0.60$). After adjusting for baseline WHO stage, CD4 cell count, tuberculosis status, BMI, and age, the observed CD4 response did not differ significantly between the two exposure groups at 6 and 12 months (Fig. 2).

Mortality and treatment failure

In Kaplan–Meier analysis, there was no difference in the overall mortality between NVP-exposed (8.0%) and NVP-unexposed (7.5%) groups at 12 months ($P = 0.56$; Fig. 3a). In Cox proportional hazard models, risk of death was not significantly increased among NVP-exposed women in either unadjusted [hazard ratio (HR), 0.9; 95% CI, 0.6–1.3] or adjusted (adjusted HR, 1.2; 95% CI, 0.8–1.8) regression models (Table 2). Similar results were noted when the composite outcome of treatment failure was analyzed via Kaplan–Meier analysis (15.9% versus 14.1% $P = 0.58$; Fig. 3b) and Cox proportional hazards models (adjusted HR, 1.1; 95% CI, 0.8–1.5; Table 2).

Effect of nevirapine exposure timing on patient outcomes

Of the 751 with reported NVP exposure, 434 (58%) had exposure timing information available. Median interval between NVP exposure and ART initiation was 15.6 months (interquartile range, 7.5–29.9). Of these, 81 (19%) ingested the drug within 6 months of starting therapy. The remaining 353 (81%) reported remote (i.e. 6 months or greater) NVP exposure.

When the CD4 cell count response was compared between women with recent exposure and those with remote exposure using a two-sided t-test, there was a suggestion of a less favorable CD4 cell response at 6 (+150 versus +219 cells/ μ l; $P=0.06$) and 12 (+149 versus +215 cells/ μ l; $P=0.39$) months. In Kaplan–Meier analysis, mortality (log-rank P value =0.85) and treatment failure (log-rank P value =0.55) between the two groups were similar when compared with women previously unexposed to NVP. In a Cox proportional hazards model controlling for baseline WHO stage, CD4 cell count, tuberculosis status, BMI, and age, women with recent (adjusted HR, 0.9; 95% CI, 0.2–3.5) and remote (adjusted HR, 0.8; 95% CI, 0.4–1.7) exposure to NVP had similar risk of mortality when compared with those with no exposure. These findings remained consistent when the composite outcome of treatment failure was evaluated for recent NVP exposure (adjusted HR, 1.0; 95% CI, 0.4–2.4) and remote NVP exposure (adjusted HR, 0.8; 95% CI, 0.5–1.3).

A secondary analysis was performed that included all women with self-reported NVP status, regardless of the timing of status ascertainment (7339). Overall, 988 (13%) were exposed to NVP, of whom 691 had information regarding timing of exposure: 128 were recent exposures and 563 were remote. The remaining 6351 (87%) were not exposed to NVP. In this expanded cohort, the trend towards attenuated CD4 cell response among those with recent NVP exposure was still apparent at 6 (+150 and +190 cells/ μ l, respectively; $P=0.21$) and 12 (+162 and +214 cells/ μ l, respectively; $P=0.24$) months when compared with those with remote NVP exposure. In a multivariable analysis, there was no statistically significant differences in mortality when women with recent (adjusted HR, 1.0; 95% CI, 0.3–3.1) or remote (adjusted HR, 0.6; 95% CI, 0.3–1.2) NVP exposure were compared with those with no exposure. When the outcome of treatment failure was evaluated, women with recent exposure trended toward higher likelihood of treatment failure (adjusted HR, 1.6; 95% CI, 0.9–2.7) when compared with NVP-unexposed women. No difference was noted for those with remote NVP exposure compared with no NVP exposure (adjusted HR, 0.8; 95% CI, 0.5–1.1).

Discussion

Since it was first noted in 2001 [9], the selection for NNRTI-related resistance mutations following single-dose NVP has led to concerns regarding future treatment options for women using the regimen for PMTCT. Like others [17,24], we found no significant differences in CD4 cell response among NVP-exposed and NVP-unexposed women at 6 and 12 months on ART. We also observed similar trends in early survival and treatment response between the groups. These findings have particular relevance to African health systems that rely heavily on NVP in both PMTCT and ART services.

We believe that our analysis contributes significantly to the growing literature on HIV treatment outcomes following NVP exposure for PMTCT. These results provide some reassurance that the resistance mutations detected after use of single-dose NVP may not substantially temper the early (i.e. 1 year) effectiveness of subsequent NNRTI-containing ART. We recognize, however, that differences in treatment outcomes may be difficult to detect in settings like Zambia, where the relatively high prevalence of infectious diseases (e.g., malaria, tuberculosis) can lead to greater adult mortality, regardless of HIV status. Clinical and survival

analyses are likely needed – alongside measures of virological treatment failure – if locally relevant scientific conclusions are to be reached.

Similar to another study [17], we observed a moderately increased risk for treatment failure among women with NVP exposure less than 6 months prior to ART initiation. There was also the suggestion that women with recent NVP exposure had less favorable CD4 cell responses at 6 and 12 months. While our findings may be underpowered and are not definitive, they emphasize the benefits of early ART screening among HIV-infected pregnant women via clinical staging and CD4 cell testing [25]. Pregnant women identified as eligible for HIV treatment should start ART in antenatal care: to maximize the benefits for mother and infant and to minimize the number who will initiate therapy after recent NVP exposure.

An interesting secondary finding was the protective effect of low CD4 cell counts on clinical treatment failure. In our multivariable model, women with lower baseline cell counts (i.e. <50 cells/ μ l or 50–200 cells/ μ l) appeared at less risk for this outcome than those with baseline CD4 cell counts >200 cells/ μ l. We have observed this phenomenon in other analyses [18] and believe it is artifactually related to our CD4 cell-based criterion for clinical treatment failure (i.e., a fall in CD4 cell count to below the pretreatment baseline). Women within these CD4 cell count categories may be less likely to meet this definition because their already low cell counts simply cannot fall further. Given the lack of standardized definitions for clinical treatment failure [20], we believe that further investigation is needed to elucidate this phenomenon.

Strengths of this analysis included its relatively large sample size and its “real world” program perspective. The primary limitation of the study was the duration of follow-up. It is possible that, when dealing with clinical outcomes such as mortality and treatment failure, longer follow-up periods (2 years or more) may be needed in order for differences between the comparison groups to manifest. Sensitive surrogate markers such as HIV-1 viral load allow a more critical evaluation of this question; unfortunately, in Zambia, this capacity is not widespread. Another potential limitation was our reliance on patient self-report to determine NVP exposure. Although we believe self-report is a reasonable approach, we recognize that misclassification could bias the study results toward a finding of no difference between comparison groups. Lastly, while this is one of the largest cohorts yet available to study this question, the sample may still be too small to exclude subtle differences in treatment outcomes. We detected no differences in survival or treatment failure between NVP-exposed and NVP-unexposed women; however, our available sample size had only 53% power to detect an HR value of 1.10 between the groups when $\alpha = 0.05$. For 80% power and $\alpha = 0.05$, the minimum detectable difference was an HR value of 1.14.

In summary, in this large ART cohort in Zambia, exposure to NVP for PMTCT was not associated with substantially attenuated maternal immune response or worse clinical outcomes over the first 12 months following treatment initiation. While these early results are reassuring, long-term follow-up is critically needed to understand the full impact of NVP exposure on subsequent NNRTI-based treatment regimens. The effect of NVP exposure timing on clinical outcomes requires further delineation, particularly among women reporting recent NVP use. In the meantime, links between PMTCT and ART services should be strengthened, so that women requiring ART start therapy prior to delivery and thus avoid treatment initiation following NVP exposure occurring less than 6 months previously. Single-dose NVP – used either alone or in combination with other antiretroviral drugs – should also remain an important PMTCT option in settings where more intensive regimens for HIV prophylaxis are not yet feasible.

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Fig. 1. Description of primary evaluation cohort, comprising HIV-infected women initiating antiretroviral therapy (ART) with nevirapine (NVP) exposure status determined at time of enrollment, April 2004 to July 2006, Zambia.

Fig. 2. Changes in mean CD4 cell count at 6 and 12 months among women with nevirapine exposure and non-exposure determined at time of enrollment, April 2004 to July 2006, Zambia
Results were controlled for baseline World Health Organization stage, CD4 cell count, tuberculosis status, body mass index, and age; CD4 cell responses were adjusted to the mean value of each variable.

Fig. 3.

One-year mortality alone (a) and treatment failure including death (b) among women with nevirapine (NVP) exposure and non-exposure determined at time of enrollment, April 2004 to July 2006, Zambia.

Comparison of HIV-infected women initiating antiretroviral therapy across 26 clinics, categorized according to nevirapine exposure and non-exposure documented at time of enrollment, April 2004 to July 2006, Zambia.

	NVP exposed			NVP unexposed			P value
	No.	Value		No.	Value		
Median age [years (IQR)]	751	29 (26-33)		5989	34 (29-40)		<0.0001 ^a
Mean weight [kg (SD)]	710	52.1 (9.6)		5674	52.4 (10.6)		0.48 ^b
Mean body mass index [kg/m ² (SD)]	645	20.3 (3.7)		4378	20.7 (4.2)		0.01 ^b
Median parity (IQR)	689	3 (2-5)		5819	3 (2-5)		0.41 ^a
Median gravidity (IQR)	689	3 (2-4)		5813	3 (2-5)		0.95 ^a
Mean CD4 cell count [cells/μl (SD)]	689	170.1 (121.4)		5110	143.0 (121.6)		<0.001 ^b
CD4 cell count <50 cells/μl [No. (%)]	687	78 (11)		5108	1003 (20)		<0.001 ^c
Mean hemoglobin [g/l (SD)]	579	109 (68)		4599	107 (142)		0.62 ^b
Hemoglobin <8 g/l [No. (%)]	579	48 (8)		4599	536 (12)		0.03 ^c
Tuberculosis (active) [No. (%)]	751	50 (7)		5989	632 (11)		<0.001 ^c
WHO stage at entry [No. (%)]	743			5846			<0.001 ^c
1		105 (14)			513 (9)		
2		198 (27)			1242 (21)		
3		386 (52)			3398 (58)		
4		54 (7)			693 (12)		
Mean months of follow-up in ART program (SD)	743	8.0 (5.4)		5878	7.4 (5.7)		0.03 ^b

NVP, nevirapine; IQR, interquartile range (Q1–Q3); ART, antiretroviral therapy; WHO, World Health Organization.

^aWilcoxon rank-sum test.
^bStudent's t-test.
^cPearson's χ^2 test.

Table 2

Factors associated with death or treatment failure among women with nevirapine exposure status determined at time of enrollment, April 2004 to July 2006, Zambia.

	Death			Treatment failure		
	No.	Crude HR (95% CI)	Adjusted HR (95% CI) (n =3647)	No.	Crude HR (95% CI)	Adjusted HR (95% CI) (n =3671)
Prior NVP use	5020	0.9 (0.6–1.3)	1.2 (0.8–1.8)	5048	1.1 (0.8–1.4)	1.1 (0.8–1.5)
WHO stage	4933			4961		
1 and 2		Ref	Ref		Ref	Ref
3		2.0 (1.5–2.7)	2.0 (1.4–3.0)		1.7 (1.4–2.2)	1.6 (1.2–2.1)
4		3.8 (2.6–5.5)	3.5 (2.2–5.6)		2.7 (2.0–3.6)	2.4 (1.7–3.4)
CD4 cell count (cells/ μ l)	4396			4424		
≥ 200		Ref	Ref		Ref	Ref
50–200		1.5 (1.0–2.2)	1.6 (1.0–2.4)		0.6 (0.5–0.7)	0.6 (0.5–0.8)
<50		4.0 (2.7–5.9)	3.1 (2.0–4.8)		1.0 (0.7–1.2)	0.8 (0.6–1.1)
Tuberculosis	5020	1.4 (1.0–2.0)	0.8 (0.5–1.2)	5048	1.1 (0.8–1.4)	0.7 (0.5–1.0)
Body mass index <16 kg/ m^2	4139	4.3 (3.2–5.8)	3.1 (2.2–4.3)	4163	2.8 (2.2–3.7)	2.4 (1.8–3.2)

HR, hazard ratio; CI, confidence interval; NVP, nevirapine; WHO, World Health Organization.

^a Age and time trend included in model as continuous variables.