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Addition of extended zidovudine to extended nevirapine prophylaxis reduces nevirapine resistance in infants who were HIV infected *in utero*

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Abstract

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CONTRIBUTION OF AUTHORS All authors contributed to preparation of the manuscript. In addition, individual authors had the following contributions to the study:

J Lidstrom Performed resistance testing; analyzed resistance data and drafted the manuscript.

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BACKGROUND—In the PEPI-Malawi trial, most women received single dose nevirapine (sdNVP) at delivery, and infants in the extended study arms received sdNVP plus 1 week of daily zidovudine (ZDV), followed by either extended daily NVP or extended daily NVP+ZDV up to 14 weeks of age. While extended NVP prophylaxis reduces the risk of postnatal HIV transmission, it may increase the risk of NVP resistance among infants who are HIV-infected despite prophylaxis.

METHODS—We analyzed 88 infants in the PEPI-Malawi trial with *in utero* HIV infection who received prophylaxis for a median of 6 weeks prior to HIV diagnosis. HIV genotyping was performed using the ViroSeq HIV Genotyping System.

RESULTS—At 14 weeks of age, the proportion of infants with NVP resistance was lower in the extended NVP+ZDV arm than in the extended NVP arm (28/45=62.2% vs. 37/43=86.0%, $p=0.015$). None of the infants had ZDV resistance. Addition of extended ZDV to extended NVP was associated with reduced risk of NVP resistance at 14 weeks if prophylaxis was stopped by 6 weeks (54.5% vs. 85.7%, $p=0.007$), but not if prophylaxis was continued beyond 6 weeks (83.3% vs. 87.5%, $p=1.00$).

CONCLUSIONS—Addition of extended ZDV to extended NVP prophylaxis significantly reduced the risk of NVP resistance at 14 weeks in infants with *in utero* HIV infection, provided that HIV infection was diagnosed and the prophylaxis was stopped by 6 weeks of age.

Keywords

HIV-1; resistance; infants; Malawi; nevirapine

INTRODUCTION

Two recent clinical trials (SWEN and PEPI-Malawi) demonstrated that providing infants with daily extended nevirapine (NVP) prophylaxis to 6–14 weeks of age decreases the risk of postnatal mother-to-infant transmission of HIV (MTCT) compared to shorter regimens, such as single dose NVP (sdNVP) or sdNVP plus 1 week of daily zidovudine (ZDV) [1,2]. In PEPI-Malawi [2], HIV-infected women who presented early in labor received sdNVP (approximately 70% of women), while those who presented too late in labor for counseling, HIV testing, and sdNVP administration did not. Infants of both early and late presenters were randomized at birth to receive either: (1) sdNVP plus 1 week of daily ZDV (the control regimen), (2) the control regimen followed by daily NVP to age 14 weeks (extended NVP arm), or (3) the control regimen followed by daily NVP+ZDV to age 14 weeks (extended NVP+ZDV arm). Infants were tested for HIV at birth, 1, 3, 6, 9 and 14 weeks, and at subsequent study visits. Prophylaxis was stopped as soon as possible after infants were diagnosed with HIV infection. The risk of MTCT at 9 months was similar in the two extended study arms, among infants who were HIV-uninfected at birth [2]. Infants who received extended NVP+ZDV had a higher rate of adverse events deemed to be possibly related to ZDV (mostly neutropenia) than those using extended NVP alone; however, most of those events were transient [2].

While extended NVP prophylaxis is intended for infants who are HIV-uninfected at birth, the HIV infection status of an infant born to an HIV-infected woman is often not known at the time when antiretroviral (ARV) prophylaxis regimens are initiated. Administration of NVP-based prophylaxis to infants with undiagnosed HIV infection puts those infants at risk for acquiring NVP resistance. When sdNVP is used for prophylaxis, infants with *in utero* HIV infection are more likely to develop NVP resistance than infants with intrapartum or postnatal HIV infection [3]. In the SWEN study, Ugandan infants with *in utero* HIV infection who received either sdNVP or sdNVP plus daily NVP up to 6 weeks of age were at high risk of developing NVP resistance [4].

Early provision of ARV treatment to HIV-infected infants in the first few months of life has been shown to decrease morbidity and mortality, compared to delaying therapy until symptoms develop or until the infant meets CD4 criteria for initiation of therapy [5]. Most first-line treatment regimens for children include a non-nucleoside reverse transcriptase inhibitor (NNRTI) [6], and prior sdNVP exposure can compromise treatment response [7,8]. In infants with *in utero* HIV infection, exposure to extended NVP prophylaxis prior to HIV diagnosis is also likely to compromise their response to subsequent ARV treatment if resistant HIV variants are selected, but this has not yet been studied.

In the NVAZ studies in Malawi, the risk of NVP resistance after sdNVP exposure was reduced in HIV-infected infants when infants also received 1 week of daily ZDV prophylaxis [9]. It is not known whether the addition of ZDV prophylaxis to extended NVP prophylaxis reduces the risk of NVP resistance in infants who received these drugs prior to HIV diagnosis. In this study, we examined NVP resistance in infants in the PEPI-Malawi study with *in utero* HIV infection who received either extended NVP or extended NVP +ZDV prophylaxis prior to confirmation of their HIV infection. Infants with *in utero* HIV infection were not included in the primary efficacy analysis of the PEPI-Malawi study [2], but were followed in the trial.

METHODS

Samples used for analysis

The details of the PEPI-Malawi study are described elsewhere [2]. In this study, 161 of the infants enrolled in the extended prophylaxis arms by December 2007 had *in utero* HIV infection (79 in the extended NVP arm, 82 in the extended NVP+ZDV arm). Plasma collected at 14 weeks of age (20–75 µl) was available from 105 (65.2%) of those infants (49 in the extended NVP arm, 56 in the extended NVP+ZDV arm). Some infants also had a sample tested from an earlier visit, if prophylaxis was stopped before 14 weeks. The 56 infants who did not have a 14-week sample available included 33 infants who did not have a 14-week study visit and 23 infants whose 14-week sample was used for other trial-related testing.

HIV genotyping

Plasma samples were analyzed using the ViroSeq HIV-1 Genotyping System, v2.8 (Celera, Alameda, CA). Sequences were analyzed for the presence of mutations associated with NVP and ZDV resistance [10]. HIV subtypes were determined by phylogenetic analysis as previously described [11], using PHYLIP v3.66.

Statistical Analysis

Proportions were compared with exact tests and means/medians were compared by rank tests or by signed rank tests for paired observations. Multivariate logistic regression models were fit to simultaneously evaluate the independent associations of covariates with probability of NVP resistance.

Ethical considerations

Written informed consent was obtained from all women for participation in the PEPI-Malawi study. The study was approved by Institutional Review Boards in Malawi and the U.S. as described [2], including the U.S. Centers for Disease Control and Prevention.

RESULTS

HIV genotyping results were obtained for 88 (83.8%) of 105 infants with available 14-week samples (43 infants in the extended NVP arm, 45 infants from the extended NVP+ZDV arm). All 88 infants had subtype C infection. Among these infants, prophylaxis was discontinued at a median of 6 weeks of age in both study arms (range 1–14 weeks). We found no significant difference between the 88 infants with genotyping results and the 73 infants without genotyping results in terms of study regimen (the proportion of infants in the extended NVP arm was 43/88=48.9% vs. 36/73=49.3%, $p=1.00$), maternal sdNVP administration (the proportion of infants whose mothers received sdNVP was 62/88=70.5% vs. 41/73=56.2%, $p=0.07$), duration of prophylaxis (the proportion of infants who stopped prophylaxis before or at 6 weeks of age was 68/88=77.3% vs. 57/73=78.1%, $p=1.00$), or median maternal pre-NVP HIV log viral load (4.63, interquartile range: 4.15–4.90, vs. 4.71, interquartile range: 4.02–5.02, $p=0.71$).

Among the 88 infants with HIV genotyping results, the proportion of infants with one or more NVP resistance mutation detected in the 14-week sample was lower in the extended NVP+ZDV arm than in the extended NVP arm (28/45=62.2% vs. 37/43=86.0%, $p=0.015$). This association was still observed in a multivariate model (odds ratio (OR): 4.76, 95% confidence limits (CI): 1.48, 15.3, $p=0.01$) after adjusting for infant age when prophylaxis was stopped (by 6 weeks of age vs. after 6 weeks), median maternal pre-NVP viral load, and administration of maternal sdNVP. None of the other variables in the model were statistically associated with NVP resistance (prophylaxis stopped by vs. after 6 weeks: OR=0.35, 95% CI=0.08–1.41, $p=0.14$; median maternal HIV RNA, per log unit increase: OR=0.99, 95% CI=0.38–2.56, $p=0.98$; maternal sdNVP yes/no: OR=1.38, 95% CI=0.44–4.30, $p=0.58$). The reduced risk of NVP resistance was observed in the subgroup of infants with extended NVP+ZDV whose prophylaxis was stopped by 6 weeks (18/33=54.5% for extended NVP+ZDV vs. 30/35=85.7% for extended NVP, $p=0.007$), but not in the subgroup of infants whose prophylaxis was continued after 6 weeks (10/12=83.3% for extended NVP+ZDV vs. 7/8=87.5% for extended NVP, $p=1.00$, Fisher's test, Figure 1).

None of the infants had ZDV resistance detected in the 14-week sample, consistent with the high genetic threshold for ZDV resistance [12]. However, two infants in the extended NVP arm and one infant in the extended NVP+ZDV arm had one or more mutations associated with resistance to other nucleoside reverse transcriptase inhibitors (NRTIs); all three of the corresponding mothers initiated HAART for their own health prior to the 14-week visit. Among the 88 infants with HIV genotyping results, only one other woman initiated HAART prior to 14 weeks post-partum; her infant did not have any NRTI mutations detected. Because the number of women initiating HAART by 14 weeks was small (total: 4/88=4.5%), it was not possible to include maternal HAART in the multivariate model presented above.

Fifty-one infants who had genotyping results from the 14-week study visit also had a sample available from the visit when prophylaxis was stopped. HIV genotyping was successful for 33 of those samples (16 from the extended NVP arm, 17 from the extended NVP+ZDV arm, Table 1). Phylogenetic analysis of the resulting sequences confirmed that paired samples were from the same infant (data not shown). Among the 33 infants with paired samples, the proportion of infants who had NVP resistance at the time when prophylaxis was stopped was significantly higher in the extended NVP arm than in the extended NVP+ZDV arm (16/16=100% vs. 11/17=64.7%, $p=0.018$). When prophylaxis was stopped, the mean number of NVP resistance mutations detected per infant was also significantly higher in the extended NVP arm than in the extended NVP+ZDV arm (2.1 vs. 0.71, $p<0.0001$, Wilcoxon rank test). However, this difference had almost vanished by 14 weeks of age (1.2 vs. 0.94,

p=0.34, Wilcoxon rank test). In the extended NVP arm, there was a statistically significant decrease in the number of mutations detected per infant between the time prophylaxis was stopped and at 14 weeks (2.1 vs. 1.2, p=0.01, signed rank test, Table 1). In contrast, in the extended NVP+ZDV arm, the numbers of mutations detected per infant increased between the time prophylaxis was stopped and 14 weeks, but the change was not statistically significant (0.71 vs. 0.94, p=0.44, Table 1).

DISCUSSION

In this study, we found that the majority of infants with *in utero* HIV infection who received extended NVP prophylaxis (without extended ZDV prophylaxis) prior to diagnosis of HIV infection had detectable NVP resistance, both at the time that prophylaxis was stopped (if before 14 weeks, 16/16=100% of infants) and at 14 weeks of age (37/43=86.0% of infants). The proportion of infants with NVP resistance was significantly lower, both at the time when prophylaxis was stopped and at 14 weeks, when infants received extended ZDV prophylaxis in addition to extended NVP. The reduction in NVP resistance at 14 weeks in the extended NVP+ZDV arm compared to the extended NVP arm was statistically significant among the subset of infants who stopped prophylaxis by 6 weeks of age, but was not apparent in the subset of infants who received more than 6 weeks of prophylaxis. Infants in the extended NVP arm also had a significantly higher frequency of NVP resistance mutations at the time when prophylaxis was stopped, compared to infants in the extended NVP+ZDV arm. As expected, NVP mutations that developed when infants received extended NVP without ZDV tended to fade from detection after the NVP prophylaxis was stopped. In contrast, we hypothesized that NVP resistance mutations would accumulate in HIV-infected infants in the NVP+ZDV arm after prophylaxis was stopped because NVP has longer half-life than ZDV. In this case, ZDV would be cleared before NVP, leaving the infants exposed to NVP alone for a week or more. While we did see an accumulation of NVP mutations in the extended NVP+ZDV arm after prophylaxis was stopped, this effect was not statistically significant, possibly due to the small number of infants analyzed. Further studies are needed to determine whether the risk of NVP resistance can be reduced in HIV-infected infants who were exposed to extended NVP+ZDV prophylaxis, by stopping NVP first, and then providing a short ZDV tail after the NVP is stopped.

In the SWEN study, NVP resistance was frequently detected in HIV-infected infants who received up to six weeks of extended NVP prophylaxis prior to diagnosis of HIV infection [4,13]. However, it is difficult to compare the risk of resistance in HIV-infected infants in the SWEN study and in this study because of differences in the prophylactic regimens, the prevalent HIV subtypes, and other factors. Furthermore, this study included only infants with *in utero* HIV infection. Infants who are HIV-infected *in utero* are more likely to acquire NVP resistance after sdNVP compared to infants who acquire HIV infection at or after birth [3].

Infants with *in utero* HIV infection generally have higher HIV viral loads during the first two months of life than infants who are HIV-infected during or after delivery [14], and infants who are HIV-infected by three months of age progress more rapidly to AIDS than those who are infected later [15]. Therefore, infants with *in utero* HIV infection may be among those most likely to benefit from early initiation of HAART. Results from the CHER Study indicate that initiation of HAART in HIV-infected infants within the first three months of life can dramatically decrease infant mortality in resource-limited settings [5]. Therefore, there is increased momentum for early HIV diagnosis and ARV treatment initiation in HIV-infected infants, regardless of CD4 cell count.

In settings where NVP-based regimens are used to prevent MTCT, our findings underscore the importance of determining the HIV infection status of infants as close to the time of delivery as possible, to minimize the risk of NVP resistance. If infant infection status cannot be determined before starting an extended NVP regimen for prevention of MTCT, addition of extended ZDV to extended NVP may help to reduce this risk. In this study, in infants with *in utero* HIV infection whose prophylaxis was stopped by 6 weeks of age, addition of extended ZDV to extended NVP prophylaxis significantly reduced the risk of NVP resistance at 14 weeks. The high risk of NVP resistance in this setting suggests that infants who are HIV-infected despite extended NVP prophylaxis may benefit from use of a protease inhibitor-based regimen for HIV treatment.

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Figure 1. NVP resistance at 14 weeks in infants with *in utero* HIV

The figure shows the proportion of infants in the extended NVP arm (triangles) and the extended NVP+ZDV arm (squares) with one or more NVP resistance mutation detected at 14 weeks of age. Prophylaxis was stopped when diagnosis of infant HIV infection was confirmed. Data are presented separately for infants whose prophylaxis was stopped at ≤3 weeks, 6 weeks, 9 weeks, and 14 weeks (full study regimen). Prophylaxis was stopped by 6 weeks in a total of 33 infants in the extended NVP+ZDV arm and 35 infants in the extended NVP arm; prophylaxis was continued beyond 6 weeks in a total of 12 infants in the extended NVP+ZDV arm and 8 infants in the extended NVP arm.

Table 1

NVP resistance mutations detected in infants receiving extended NVP or extended NVP+ZDV prophylaxis.

Infant	Weeks of prophylaxis	NVP resistance at end of prophylaxis	NVP resistance at 14 weeks	P value
Extended NVP				
1	3	<i>K103N, Y188H, Y188L</i>	Y181C	
2	6	Y181C	Y181C	
3	6	<i>K103N, Y181C</i>	WT	
4	6	K103N	K103N, Y181C	
5	6	<i>K103N, Y181C</i>	Y181C	
6	6	K103N, <i>Y181C, Y188C</i>	K103N	
7	6	Y181C	Y181C	
8	6	Y181C	Y181C	
9	6	<i>K103N, G190A</i>	Y181C	
10	6	Y181C, <i>Y188C</i>	Y181C	
11	6	<i>V106A, G190A, F227L</i>	Y181C	
12	6	Y181C	Y181C	
13	6	<i>V108I, Y181C</i>	Y181C	
14	6	<i>K103N, V106A, V108I, Y181C</i>	G190A	
15	9	K103N, Y181C	K103N, Y181C	
16	9	K103N, Y181C, G190A	K103N, Y181C, G190A	
<hr/>				
Mean # mutations		2.1	1.2	0.01 ^a
Median # mutations		2	1	
<hr/>				
Extended NVP+ ZDV				
17	3	WT	Y181C	
18	3	WT	K103N, Y181C	
19	3	Y181C	Y181C	
20	3	WT	WT	
21	6	<i>V106A</i>	Y181C	
22	6	G190A	K103N, G190A	
23	6	Y181C	Y181C	
24	6	K103N	K103N	
25	6	WT	Y181C	
26	6	K181C	Y181C	
27	6	WT	K103N	
28	6	G190A	G190A	
29	6	G190A	Y181C, G190A*	
30	6	<i>V106A</i>	WT	
31	6	<i>V106M, G190A</i>	WT	
32	6	WT	WT	
33	9	Y188C	Y188C	

Infant	Weeks of prophylaxis	NVP resistance at end of prophylaxis	NVP resistance at 14 weeks	P value
Mean # mutations		0.71	0.94	0.44 ^a
Median # mutations		1	1	

^a Signed rank test, end of prophylaxis vs. 14 weeks.