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CD4⁺ cell count and risk for antiretroviral drug resistance among women using peripartum nevirapine for perinatal HIV prevention

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Abstract

Objective—To determine the association between antenatal CD4⁺ cell count and development of viral drug resistance following use of peripartum nevirapine (NVP) for perinatal HIV prevention.

Design—Secondary analysis of data from previously conducted randomized control trial.

Setting—Lusaka, Zambia.

Population—HIV positive pregnant women.

Methods—We analyzed data from a clinical trial of single-dose tenofovir/emtricitabine (TDF/FTC) to reduce viral drug resistance associated with peripartum NVP. The trial population was categorized according to antenatal CD4⁺ cell count (200–350 cells/uL, 351–500 cells/uL, and >500 cells/uL).

Main outcome measures—Relative risk for acquiring drug resistance—determined by consensus sequencing and oligonucleotide ligation assay (OLA)—was estimated using multivariable logistic regression.

Results—Of 397 study participants, 119 (30%) had a CD4⁺ count of 200–350 cells/uL, 135 (34%) had a CD4⁺ count of 351–500 cells/uL, and 143 (36%) had a CD4⁺ count >500 cells/uL. Among women receiving no intervention, risk for drug resistance appeared to increase as CD4⁺ cell count decreased. Participants with CD4⁺ cell counts of 200–350 cells/uL randomized to the study arm had the lowest risk, suggesting higher efficacy of the intervention within this stratum.

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DISCLOSURE OF INTERESTS

None of the authors have declared financial conflicts of interest.

CONTRIBUTION TO AUTHORSHIP

BD interpreted the analysis, drafted the paper and substantially revised it. JM participated substantially in data interpretation and manuscript revision. MSL analyzed study data, interpreted analysis and substantially revised the paper. FM implemented study, interpreted analysis and substantially revised the paper. NTC designed the study, interpreted analysis and substantially revised the paper. CJC participated substantially in data interpretation and manuscript revision. LMF participated substantially in data interpretation and manuscript revision. JSAS designed the study, interpreted the analysis, and substantially revised the manuscript. BHC designed the study, interpreted the analysis, drafted the paper, and substantially revised the manuscript.

These results were consistent at two and six weeks, regardless of how drug resistance was measured.

Conclusion—Women with CD4⁺ cell counts of 200–350 cells/uL may be at increased risk for viral drug resistance following use of peripartum NVP. Given the high prevalence of NVP resistance and the clear benefits of treatment, antiretroviral therapy should be initiated among pregnant women with CD4⁺ cell counts $\leq$ 350 cells/uL.

Keywords

HIV; antiretroviral therapy; non-nucleoside reverse transcriptase inhibitor; resistance; prevention of mother-to-child transmission; CD4⁺ cell count

INTRODUCTION

Whether alone or in combination with other drugs, intrapartum and neonatal nevirapine (NVP) regimens have become a cornerstone for prevention of mother-to-child transmission (PMTCT) in resource-constrained settings over the past decade.^{1–3} While these regimens have proven effective, they are associated with the selection of NVP-resistant variants in the weeks and months following ingestion;^{4,5} when non-nucleoside reverse transcriptase inhibitor (NNRI)-based antiretroviral therapy (ART) is used subsequently, treatment outcomes may be compromised.^{6–9} To mitigate this risk, the World Health Organization (WHO) has recommended use of adjuvant antiretroviral regimens (i.e., combination antiretroviral “tails”) following single-dose NVP.¹⁰

Severity of HIV disease is an important predictor for NNRTI resistance following use of peripartum NVP. Higher circulating plasma concentrations of HIV-1 (i.e., viral load) at time of delivery, for example, have been shown to correlate with increased risk for NNRTI resistance. In a randomized trial, we found that higher circulating viral concentration at delivery was associated with higher rates of NNRTI-related drug resistance at 6 weeks postpartum following use of intrapartum NVP.¹¹ Similar results have been demonstrated in studies from Uganda, where a log₁₀ increase in plasma HIV-1 viral load was associated with 3.97-fold increase in risk (95% confidence interval [CI]=1.54–10.20) for resistant virus,⁵ and from Cote d’Ivoire, where a one log₁₀ increase was associated with a 3.10-fold increase in risk (95% CI=1.00–13.28).¹² Maternal HIV-1 viral load at delivery, however, is not useful in stratifying risk for developing NNRTI-related viral drug resistance, since it is poorly accessible in most settings where peripartum NVP is used. For this reason, we investigated the association between NNRTI-related viral drug resistance and another indicator of HIV disease severity: antepartum CD4⁺ cell count.

METHODS

We analyzed data from a previously reported clinical trial in Lusaka, Zambia. The study design and methods have been described elsewhere.^{11,13,14} Briefly, candidates were screened for study eligibility between 28 to 38 weeks and excluded from consideration if they had previous exposure to any antiretroviral drugs (including for PMTCT) or if they met the Zambian national guidelines to initiate HIV treatment (CD4⁺ cell counts $<$ 200 cells/uL, WHO stage 4, and CD4⁺ cell count $<$ 350 cells/uL and WHO stage 3). According to local guidelines, all study-eligible women were offered short-course antenatal ZDV and intrapartum NVP for perinatal HIV prevention. Participants were randomly allocated to receive either single-dose tenofovir/emtricitabine (TDF/FTC) or no study drug alongside routinely prescribed intrapartum NVP when they presented in active labor at the delivery ward. No additional antiretroviral drugs were given in the subsequent postpartum period.

Postpartum follow-up included visits at 2 and 6 weeks, where maternal specimens were collected for drug resistance testing. These included standard consensus sequencing¹¹ and an ultra-sensitive oligonucleotide ligation assay (OLA) capable of detecting quasi-species populations of 2% or greater.¹³ For consensus sequencing, samples were identified as NNRTI resistant if they contained the mutations L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/L/H, G190A, P225H, or P236L.¹¹ For OLA, virus was categorized as NNRTI resistant if they tested positive for K103N (AAY sequence), V106M (ATG sequence), Y181C (TGY sequence), or G190A (GCA sequence) mutations.¹³ Individuals below the viral load threshold of 2,000 copies/mL for consensus sequencing and 1,000 copies/mL for OLA were categorized as non-resistant.

We stratified our population according to antenatal CD4⁺ cell count: 200–350 cells/uL, 351–500 cells/uL, and >500 cells/uL. Because ART eligibility was an exclusion criterion for our study – since these women were offered immediate ART – none of our study participants had a CD4⁺ cell count less than 200 cells/uL. CD4⁺ classifications were based on documented results from up to three months prior to study enrollment. Using multivariable logistic regression, we sought to determine associations between CD4⁺ cell count and NNRTI resistance at 2 weeks and 6 weeks. In preliminary analysis, we observed differences in efficacy of the TDF/FTC intervention across CD4⁺ cell count strata (Figure 1), suggesting it is an effect modifier in the relationship between antenatal CD4⁺ cell count and NNRTI resistance postpartum. For this reason, we stratified our analysis by both CD4⁺ cell count and study arm, modeling consensus sequencing and OLA outcomes separately. Statistical analyses were performed using SAS version 9.1.3 (Cary, North Carolina). This study was approved by the University of Zambia Research Ethics Committee (Lusaka, Zambia), the Institutional Review Boards at the University of Alabama at Birmingham (Birmingham, AL, USA), the Childrens Hospital Los Angeles (Los Angeles, CA, USA), and the Seattle Children's Hospital (Seattle, WA, USA).

RESULTS

Between March 16, 2005 and February 13, 2007, 397 HIV-infected women met eligibility criteria and were randomized to one of two study arms. As previously reported, the maternal, infant, and delivery characteristics between the two groups were not significantly different. When the intervention and control arms were compared, they were found to be similar across key demographic and medical characteristics, including age (median 26 years vs. 24 years, $p = 0.16$), gravidity (median 3 vs. 3, $p = 0.71$), and parity (median 2 vs. 2, $p = 0.69$).¹¹ Of the 397 study participants, 119 (30%) had CD4⁺ cell count of 200–350 cells/uL, 135 (34%) had CD4⁺ cell count of 351–500 cells/uL, and 143 (36%) had CD4⁺ cell count >500 cells/uL. For consensus sequencing, results for 347 (87%) specimens were available at 2 weeks and 339 (85%) were available at 6 weeks. For OLA, results for 328 (83%) were available at 2 weeks and 315 (79%) were available at 6 weeks. Reasons for missing results included missed visit, lost specimen, PCR amplification failure, and indeterminate results.^{11,13}

When measured by consensus sequencing, the prevalence of NNRTI resistance at two weeks postpartum was 6% (7/121) for women with CD4⁺ cell counts of >500 cells/uL; 7% (8/120) for women with CD4⁺ cell counts of 351–500 cells/uL; and 11% (12/106) for women with CD4⁺ cell counts of 200–350 cells/uL (p for trend = 0.13). At six weeks postpartum, prevalence was 13% (16/122) for women with CD4⁺ cell counts of >500 cells/uL; 17% (20/117) for women with CD4⁺ cell counts of 351–500 cells/uL; and 25% (25/100) for women with CD4⁺ cell counts of 200–350 cells/uL (p for trend = 0.02). When measured by OLA, the prevalence of NNRTI resistance at two weeks postpartum was 10% (11/114) for women with CD4⁺ cell counts of >500 cells/uL; 13% (15/116) for women with CD4⁺ cell

counts of 351–500 cells/uL; and 14% (14/98) for women with CD4⁺ cell counts of 200–350 cells/uL (*p* for trend = 0.30). At six weeks postpartum, prevalence was 24% (27/112) for women with CD4⁺ cell counts of >500 cells/uL; 32% (35/109) for women with CD4⁺ cell counts of 351–500 cells/uL; and 35% (33/94) for women with CD4⁺ cell counts of 200–350 cells/uL (*p* for trend = 0.08).

To appropriately account for the effect modification by the TDF/FTC intervention, we then stratified the population both by antenatal CD4⁺ cell count and the study arm. Women with CD4⁺ cell counts >500 cells/uL, who were randomized to the control arm, served as the reference group and all comparisons were adjusted for HIV-1 viral load at delivery. Several trends are noteworthy (Table 1). Within the control arm, the risk for NNRTI resistance increased as CD4⁺ cell count decreased categorically. Among women randomized to the TDF/FTC study intervention, the risk for NNRTI resistance was substantively lower in the CD4⁺ 200–350 cells/uL category. These trends were consistent at two weeks and at six weeks, when NNRTI resistance was measured both by consensus sequencing or OLA.

DISCUSSION

Women with lower CD4⁺ cell counts during pregnancy appeared to be at greater risk for NNRTI-related viral drug resistance following use of short-course antenatal ZDV and peripartum NVP for perinatal HIV prevention, though this trend did not reach statistical significance. We demonstrated the highest risk for viral drug resistance at the lowest CD4⁺ stratum (i.e., 200–350 cells/uL) among women receiving no intervention, with six-week estimates of 41% by consensus sequencing and 56% by ultrasensitive OLA. That the efficacy of our single-dose TDF/FTC intervention was most pronounced among women within this lowest CD4⁺ stratum was reassuring. However, these results emphasize the importance of risk stratification by antenatal CD4⁺ screening and initiation of ART for all women with CD4⁺ cell count ≤350 cells/uL during pregnancy.

Although we analyzed data from a rigorously conducted randomized trial, we note several limitations to this study. Consistent with our previous analyses,^{11,13} we considered all specimens below a specific HIV-1 viral load threshold (<2,000 copies/mL for consensus sequencing and <1,000 copies/mL for OLA) as non-resistant. To keep our analysis consistent with our previous work, we also used the different HIV-1 viral load thresholds for consensus sequencing (<2,000 copies/mL) and OLA (<1,000 copies/mL). Since the two analyses are parallel – and we do not compare results obtained by the two assays – these differences did not affect our findings. We did not collect data regarding the duration of HIV infection among our participants, a potential confounder to our analysis. However, most of our participants were newly diagnosed with HIV in this index pregnancy and, given their relatively healthy status, were likely early in the course of the disease. Finally, because the study did not stratify enrollment according to antenatal CD4⁺ cell count, our sample size was relatively small within each CD4⁺ category. Larger populations should be studied to better understand the relationship between CD4⁺ cell count and selection for NNRTI-related viral drug resistance, and confirm the trends observed in this analysis.

The objective of this study was to identify individuals at high risk for selecting for NNRTI-related viral drug resistance following use of short-course antenatal ZDV and peripartum NVP. We stratified our study population by baseline CD4⁺ cell count since it is an important indicator of HIV disease progression and has become an important component of PMTCT programs worldwide.¹⁵ Among women included in our analysis, those with the lowest CD4⁺ cell counts (i.e., 200–350 cells/uL) during pregnancy appeared to have the highest risk for NNRTI drug resistance in the postpartum period, although this did not reach statistical significance. Women with CD4⁺ cell counts lower than 200 cells/mL were not eligible for

our study since, according to the Zambian national guidelines, ART was indicated. However, the even greater risk for NNRTI resistance can probably be extrapolated. In report of the TOPS study, for example, McIntyre and colleagues demonstrated substantially higher rates of NNRTI resistance when comparing women with CD4⁺ cell counts ≤200 /uL to those >200 /uL, even when provided a “tail” of adjuvant ZDV-lamivudine (3TC) afterwards.¹⁶

CONCLUSION

These results provide further support for ART eligibility among pregnant women with CD4⁺ cell counts ≤350 cells/uL. Although recent WHO guidelines for PMTCT have adopted this higher CD4⁺ threshold, timely initiation of ART remains a challenge in many African settings.¹⁰ Laboratory capacity to perform CD4⁺ screening may not be available;¹⁷ even when such services are accessible, PMTCT and ART may be housed in separate departments and referral systems may be inefficient.^{18,19} Novel public health strategies are urgently needed to bridge this gap.²⁰ In settings where ART is poorly accessible for pregnant women, or in settings where the <200 cell/uL threshold is still used to determine ART eligibility, use of antiretroviral “tail” regimens for peripartum NVP are critically needed to reduce selection of NNRTI-related viral drug resistance, particularly for women with CD4⁺ cell counts between 200 and 350 cells/uL.

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DETAILS OF ETHICS APPROVAL

This study was approved by the University of Zambia Research Ethics Committee (Lusaka, Zambia) on September 23, 2004, reference number 005-06-04 and the Institutional Review Board at the University of Alabama at Birmingham (Birmingham, AL, USA) on July 26, 2004, IRB identification number IRB00000726.

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Figure 1.

Efficacy of adjuvant single-dose tenofovir-emtricitabine (TDF/FTC) stratified across different antenatal CD4+ cell counts, using the control arm as the reference group. This analysis demonstrates that our TDF/FTC intervention was an effect modifier in the relationship between antenatal CD4+ cell count and viral drug resistance. Our study intervention appeared to have greater efficacy among with lower antenatal CD4+ cell counts (i.e., 200–350 cells/ μ L) at both two and six weeks postpartum, regardless of the assay used to detect viral drug resistance.

Table 1

Risk for non-nucleoside reverse transcriptase inhibitor-related viral drug resistance according to study arm allocation and CD4⁺ count strata

Study arm	Antenatal CD4 ⁺ cell count	Two week NNRTI resistance		Six week NNRTI resistance	
		Prevalence	Adjusted* odds ratio (95% CI)	Prevalence	Adjusted* odds ratio (95% CI)
<i>Consensus sequencing[§]</i>					
Control	>500 cells/μL	5 / 69 (7.3%)	Ref	12 / 69 (17.4%)	Ref
Control	351 – 500 cells/μL	5 / 53 (9.4%)	1.45 (0.36 – 5.88)	11 / 53 (20.8%)	1.20 (0.46 – 3.15)
Control	200 – 350 cells/μL	11 / 47 (23.4%)	3.54 (1.01 – 12.43)	18 / 44 (40.9%)	2.67 (1.07 – 6.67)
Intervention	>500 cells/μL	2 / 52 (3.9%)	0.54 (0.09 – 3.18)	4 / 53 (7.6%)	0.39 (0.11 – 1.35)
Intervention	351 – 500 cells/μL	3 / 67 (4.5%)	0.53 (0.11 – 2.58)	9 / 64 (14.1%)	0.65 (0.24 – 1.76)
Intervention	200 – 350 cells/μL	1 / 59 (1.7%)	0.19 (0.02 – 1.83)	7 / 56 (12.5%)	0.45 (0.15 – 1.35)
<i>Oligonucleotide ligation assay[‡]</i>					
Control	>500 cells/μL	7 / 64 (10.9%)	Ref	19 / 64 (29.7%)	Ref
Control	351 – 500 cells/μL	9 / 51 (17.7%)	1.90 (0.57 – 6.39)	22 / 51 (43.1%)	2.17 (0.93 – 5.06)
Control	200 – 350 cells/μL	12 / 44 (27.3%)	3.50 (1.10 – 11.16)	25 / 45 (55.6%)	2.80 (1.19 – 6.56)
Intervention	>500 cells/μL	4 / 50 (8.0%)	0.98 (0.24 – 3.96)	8 / 48 (16.7%)	0.58 (0.22 – 1.57)
Intervention	351 – 500 cells/μL	6 / 65 (9.2%)	0.97 (0.27 – 3.47)	13 / 58 (22.4%)	0.60 (0.24 – 1.48)
Intervention	200 – 350 cells/μL	2 / 54 (3.7%)	0.33 (0.06 – 1.86)	8 / 49 (16.3%)	0.38 (0.14 – 1.04)

* Adjusted for HIV-1 viral load at delivery

[§] All specimens under 2,000 copies/mL were considered non-resistant

[‡] All specimens under 1,000 copies/mL were considered non-resistant