

Association of HIV-1 replication capacity with HIV-1 mother-to-child transmission among antiretroviral drug naïve Malawian women (NVAZ trial)



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ABSTRACT

Introduction: HIV *pol* replication capacity is a potentially important determinant of viral fitness and pathogenicity. We examined the association of HIV-1 RC and HIV-1 mother-to-child transmission (MTCT) among antiretroviral drug naïve Malawian women enrolled in the NVAZ late presenter trial. The subtype C HIV-infected women in this trial did not receive any antiretroviral prophylaxis; infants received single dose nevirapine (SD NVP) at birth, and were randomized to either receive or not receive one week of daily zidovudine (ZDV).

Methods: Plasma samples were collected from women at delivery. Study subjects included 52 women whose infants were HIV-1 infected at birth or during the first 6-8 weeks after birth (transmitters) and 48 women whose infants remained uninfected at 6-8 weeks after birth (nontransmitters); 54% of infants received SD NVP only, and 46% of infants received SD NVP plus ZDV. RC was determined using PhenoSense™ HIV (Monogram Biosciences). In this assay, protease-reverse transcriptase coding sequences from the test sample are transferred to a subtype B resistance test vector (RTV), which is co-transfected into cells with a plasmid encoding a heterologous envelope protein. The efficiency of infection in a single replication cycle is compared to that of a reference strain to determine the RC. An RC of 100% indicates that the RC of the RTV is equal to the median of a wild-type (drug sensitive) virus population. For some analyses, RC was log transformed to remove skewness.

Results: The mean RC for the maternal plasma samples was 32% (standard deviation=20%). The mean RC was higher for transmitters 35.3% vs. non-transmitters 27.4% (p=0.02, Wilcoxon test). In a multivariate model, a higher log₁₀ RC was associated with HIV-1 transmission (OR=6.60, 95% CI: 1.23-35.31, p=0.03), adjusting for log₁₀ delivery viral load (OR=2.77, 95% CI: 1.38-5.57, p=0.0043), maternal age (OR = 1.01, 95% CI: 0.88-1.16, p=0.89), parity (OR=1.34, 95% CI: 0.90-2.00, p=0.15) and infant regimen (OR=0.61, 95% CI: 0.23-1.61, p=0.31).

Conclusions: In unadjusted and multivariate models, higher HIV-1 RC was associated with HIV-1 MTCT in Malawian women with subtype C whose infants received either SD NVP or SD NVP plus a short course of ZDV. Further studies are needed to confirm the association of RC and HIV-1 transmission in different HIV-1 subtypes and different clinical settings.

INTRODUCTION

We examined the association of HIV-1 replication capacity (RC) and HIV-1 mother-to-child transmission (MTCT) among pregnant, antiretroviral drug naïve Malawian women who presented late for delivery (NVAZ Study, Lancet 2003;362:1171-7). The women were tested for HIV-1 infection immediately after delivery. None of the women received antiretroviral drugs. Infants born to HIV-infected women were randomized to receive either (SD) nevirapine (NVP) or SD NVP plus one week of daily zidovudine (ZDV).

METHODS

Study Subjects

Women were classified as transmitters if their infant was diagnosed with HIV-1 infection at birth or by 6-8 weeks of age, and as non-transmitters if their infant remained uninfected at 6-8 weeks of age. Fifty two transmitters and 48 non-transmitters were randomly selected within each transmission group from a total of 172 transmitters and 780 non-transmitters, without knowledge of other clinical or laboratory information. HIV-1 subtyping was performed by phylogenetic analysis of *pol* region sequences; all of the women had subtype C HIV-1.

Viral Load Assays

Maternal HIV-1 viral load at delivery was determined using the Roche AMPLICOR Monitor Test, v1.5.

Replication Capacity Assays

RC was measured using a modification of the PhenoSense™ HIV assay. Plasma samples used for RC analysis were collected at the time of delivery.

RESULTS

RC results were obtained for 49 transmitters and 47 non-transmitters. None of the women delivered by C-section, none delivered twins, and all but one were breastfeeding at 6-8 weeks post-partum. The mean RC for all samples was 32% (SD=20%). Mean RC and mean maternal log₁₀ delivery viral load were both higher among transmitters (Table 1, Figure). Mean maternal age and parity were similar among the two groups. The portion of infants receiving SD NVP (vs. SD NVP plus ZDV) was slightly higher among transmitters, consistent with findings from the NVAZ trial. In multiple logistic regression adjusting for log₁₀ HIV-1 viral load, age, parity, and infant regimen, a higher log₁₀ RC was independently associated with HIV-1 transmission (Table 2).

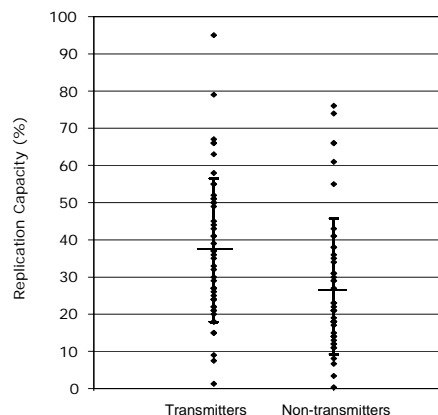
Table 1. Characteristics of study subjects and comparison of RC among transmitters vs. non-transmitters.^a

	Transmitters N=49	Non-transmitters N=47	P-value
Mean Age	25.8 (5.0)	24.1 (4.5)	0.09 ^b
Mean Parity	3.5 (2.0)	2.8 (1.5)	0.07 ^b
Infant regimen = SD NVP only (vs. SD NVP + ZDV)	32/49 (65.3%)	27/47 (57.4%)	0.53 ^c
Mean log ₁₀ viral load	5.1 (0.5)	4.6 (0.9)	0.001 ^b
Mean RC (%)	35.3 (20.3)	27.4 (8.1)	0.02 ^d

^a Numbers in parentheses indicate percentages or standard deviations; P-values are from the t-test^b, Exact test^c, or Wilcoxon test^d

Table 2. Risk factors associated with HIV-1 transmission in a multiple logistic regression model.

Risk factors	Adjusted Odds Ratio (95% CI)	P value (Chi square)
Maternal age (per year)	1.01 (0.88-1.16)	0.89
Parity (per child)	1.34 (0.90-2.00)	0.15
Infant regimen (SD NVP vs. SD NVP + ZDV)	0.61 (0.23-1.61)	0.31
Log ₁₀ viral load (per log increase)	2.77 (1.38-5.57)	0.0043
Log ₁₀ RC (per log increase)	6.60 (1.23-35.31)	0.03



CONCLUSIONS

Higher maternal HIV-1 RC was associated with higher HIV-1 MTCT when the infant received either SD NVP or SD NVP plus a short course of ZDV. This association persisted after controlling for maternal viral load and other factors. The low mean RC of these subtype C samples (32%) is consistent with data from other non-B subtype samples lacking known drug-resistance mutations. This could represent an assay effect (since the test vector backbone is subtype B), or an inherent biological property of non-B viruses. Since the samples studied here are all subtype C, an assay effect should not alter the conclusion that viruses with higher RC are more likely to be transmitted. Further studies are needed to confirm the association of RC and HIV-1 transmission in diverse HIV-1 subtypes, in different clinical settings, and with different routes of HIV-1 transmission. These results also suggest that determinants in the HIV-1 gag/*pol* region influence HIV-1 MTCT, since this is the only region of the patient's HIV-1 genome inserted into the resistance test vector in the RC assay. This finding may help direct future studies to identify and define those determinants, expanding our basic understanding of HIV-1 transmission in this and other settings.