Association between the Replication Capacity and Mother-to-Child Transmission of HIV-1, in Antiretroviral Drug–Naive Malawian Women

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The replication capacity of the pol gene of HIV is a potentially important determinant of viral fitness and pathogenicity [1]. Ongoing clinical studies are evaluating the potential utility of replication capacity in the management of treatment-experienced [2–5] and treatment-naive [6, 7] patients. The present study examined the association between the replication capacity of HIV-1 and mother-to-child transmission of HIV-1, in antiretroviral drug–naive Malawian women who presented late for delivery (termed “late presenters” in our earlier report of our ongoing nevirapine-and-zidovudine [NVAZ] study [8]). Late presenters in the NVAZ study enrolled too close to delivery to be either tested for HIV-1 or counseled for predelivery antiretroviral prophylaxis. Therefore, immediately after delivery, these women were counseled, and a rapid HIV test was used to determine whether HIV-1 infection was present. Results of the rapid HIV test were confirmed by a conventional ELISA for HIV. All infants born to HIV-infected women received 1 oral dose of nevirapine at birth and were randomized to either receive or not receive an additional 1 week of daily doses of zidovudine syrup [8].

Subjects and methods. At delivery, plasma samples were collected from among, respectively, the 172 transmitters and 780 nontransmitters in the NVAZ trial [8]; in a subsequent study, HIV-1 was subtyped on the basis of phylogenetic analysis of pol gene–region sequences [9], and all women were found to have subtype C HIV-1. All women were also antiretroviral drug–naive when the samples were collected, and they received no antiretroviral drugs during the NVAZ trial. HIV-1–infection status of the infants was determined by methods described elsewhere [8]. In the present study, a woman was classified as a transmitter if her infant was diagnosed with HIV-1 infection either at birth or during the first 6–8 weeks of life, whereas she was classified as a nontransmitter if her infant remained uninfected by 6–8 weeks of age. None of the women delivered by cesarean section, and none delivered twins. All but 1 of the women were breastfeeding at 6 weeks postpartum. The present case-control study of replication capacity included 49 transmitters and 47 nontransmitters, who were randomly selected (i.e., the selection was blinded with respect to HIV-1 load and other clinical or laboratory information) from among, respectively, the 172 transmitters and 780 nontransmitters in the NVAZ trial.
Table 1. Characteristics of study subjects, and comparison of replication capacity of HIV-1 in transmitters and nontransmitters.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Transmitters (n = 49)</th>
<th>Nontransmitters (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>25.8 ± 5.0</td>
<td>24.1 ± 4.5</td>
<td>.09&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parity</td>
<td>3.5 ± 2.0</td>
<td>2.8 ± 1.5</td>
<td>.07&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Regimen (used to treat the infants) of 1 dose of nevirapine only</td>
<td>32/49 (65.3)</td>
<td>27/47 (57.4)</td>
<td>.53&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women with rupture of membranes &lt;4 h before delivery</td>
<td>8/49 (16.3)</td>
<td>4/47 (8.5)</td>
<td>.36</td>
</tr>
<tr>
<td>Women breast-feeding at 6 weeks</td>
<td>42/42 (100.0)</td>
<td>40/41 (97.6)</td>
<td>.49</td>
</tr>
<tr>
<td>HIV-1 load at delivery, log&lt;sub&gt;10&lt;/sub&gt;</td>
<td>5.1 ± 0.5</td>
<td>4.6 ± 0.9</td>
<td>.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Replication capacity, %</td>
<td>37.2 ± 19.3</td>
<td>27.5 ± 18.3</td>
<td>.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NOTE. Data are either mean ± SD or proportion (%) of women, unless otherwise indicated.

<sup>a</sup> By t test.
<sup>b</sup> By Fisher’s exact test.

HIV-1 load was determined by use of the Roche AMPLICOR Monitor Test (version 1.5; Roche Diagnostics). Of the 96 women studied, 1 had an HIV-1 load of <400 copies/mL (the lower detection limit for the assay) and was considered to have an HIV-1 load value of 200 copies/mL (because that is the midpoint between 0 and 400 copies/mL).

Replication capacity was determined by the Monogram Biosciences Clinical Reference Laboratory, which used a modification of the PhenoSense HIV assay [10, 11] and was blinded with respect to the transmission status of the women. In this assay, protease reverse-transcriptase coding sequences from the test sample are transferred to a subtype B–resistance test vector, which, together with an expression plasmid encoding a heterologous envelope protein, is cotransfected into HEK293 cells. Pseudotyped virus particles produced by the transfected cells are used to infect fresh HEK293 cells; in the absence of antiretroviral drugs, the efficiency of infection in a single replication cycle is measured on the basis of the activity of luciferase and is compared with that of a reference strain, to determine the replication capacity. A replication capacity of 100% indicates that the replication capacity of the resistance test vector is the same as the median of a subtype B, wild-type (i.e., drug-sensitive) virus population.

The following statistical methods compared variables in transmitters with those in nontransmitters: t test, for equality of maternal (1) age, (2) parity, and (3) log<sub>10</sub> HIV-1 load at delivery, and (4) replication capacity of HIV-1; and Fisher’s exact test, for equal proportions of each drug regimen used to treat the infants. Multivariate logistic regression for predictors of transmission was performed by use of SAS (version 8.2; SAS Institute). The methods involved Proc Logistic, in which all of the variables considered were forced into the final multivariate model.

In Malawi, the NVAZ trial was approved by the Research and Ethics Committee at the University of Malawi College of Medicine; in the United States, it was approved by the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health. All women gave written informed consent for HIV testing and enrollment in the study.

Results. The present study compared the replication capacity of HIV-1 in Malawian women in the NVAZ trial who did or did not transmit HIV-1 to their infants. Replication capacity was 1.3%–95% in transmitters and 0.32%–76% in nontransmitters; the mean ± SD replication capacity for all maternal plasma samples was 32.5% ± 19.3% and was higher in transmitters (37.2% ± 19.3%) than in nontransmitters (27.5% ± 18.3%) (P = .01, by t test) (table 1 and figure 1). The mean log<sub>10</sub> maternal HIV-1 load at delivery also was higher in transmitters than in nontransmitters (table 1). Mean maternal age

![Figure 1](https://academic.oup.com/jid/article-lookup/10.1093/infdis/jij236/2493979)
The results of the present study do suggest that determinants in the gag/pol-gene region of HIV-1 influence mother-to-child transmission of HIV-1, because, in the PhenoSense HIV assay, this is the only region of the patient’s HIV-1 genome that is inserted into the resistance test vector. This finding may help to direct future studies seeking to identify and define those determinants, thereby expanding our basic understanding of the transmission of HIV-1 in this and other settings. It is possible that such studies might lead to simpler, less expensive methods to identify women at higher risk for transmission, who might benefit from more-intensive intervention. The clinical utility of such assays would be likely to depend on the resources available for prevention of mother-to-child transmission of HIV-1.
Acknowledgments

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References