Mother-to-child transmission of HIV in a community-based antiretroviral clinic in South Africa

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Objective. To examine the uptake of ART among pregnant women referred to an ART service and the associated rates and risk factors for vertical HIV transmission.

Method. Retrospective analysis of an observational cohort at a community ART clinic in Cape Town.

Results. Between 2002 and 2008, 367 treatment-naive pregnant women accessed the clinic. The median age was 27.5 years, and median gestation at presentation was 28 weeks. The median baseline CD4 count and viral load were 134 cells/µl and 28 282 copies/ml. Two hundred and sixty-five women (72%) commenced ART before giving birth, 73 women (20%) were referred for prevention of mother-to-child transmission therapy (PMTCT), and 29 (8%) received no intervention. Among ART-eligible women, 13% were lost to follow-up. Of those starting ART, median duration of therapy prior to birth was 7.6 weeks (interquartile range (IQR) 4 - 11.9). The HIV transmission rate was 5.1% (95% confidence interval (CI) 2.8 - 9.0%). Factors associated with transmission were advanced maternal WHO stage disease (odds ratio (OR) 9.57, p=0.02), and follow-up viral load above 50 copies/ml (OR 3.64, p=0.03). Each additional week on ART reduced transmission by 20% (p=0.05). There was no HIV transmission among women who received more than 8 weeks therapy.

Conclusions. The rate of HIV transmission in this study was higher than reported in high-income countries. Prevention of vertical transmission with ART was hindered by women presenting late in pregnancy and with advanced stage of HIV disease. Interventions that facilitate earlier ART commencement and improve programmatic retention of pregnant women are required.

all 3 education sessions, although these had to be attended in due course.

Patients referred after 28 weeks were started on AZT monotherapy at the ANC service while awaiting ART. Zidovudine, lamivudine and nevirapine was the regimen of choice for pregnant women unless contraindicated, in which case an alternative regimen was constructed. ART-naïve women accessing the service between 1 September 2002 and 1 March 2008 were eligible for analysis if they were pregnant at first attendance. Singleton and multiple pregnancies were evaluable.

Women started on triple therapy before birth were categorised as the 'ART' group; women referred back to a maternity outpatient unit for PMTCT and not commenced on ART were categorised as the 'PMTCT' group; and women not started on ART prior to birth with no documented referral for PMTCT or having received AZT prior to birth were categorised as the 'No intervention' group.

Demographic data, WHO staging, treatment outcomes, laboratory results, ART regimens and regimen changes were recorded in a prospectively maintained database for all patients referred to the ART service since the start of the clinic in September 2002. Infant HIV status and age at polymerase chain reaction (PCR) testing were verified using the regional laboratory PCR test database. National guidelines are that PCR testing should take place at 6 weeks of age.¹° Infant HIV status was followed up until September 2008.

Data analysis was by STATA/IC version 10. Fisher’s exact tests and Wilcoxon rank-sum tests were used to compare proportions and medians, respectively. Multiple logistic regression was used to examine the odds of vertical transmission according to maternal clinical characteristics. The upper bound of the rate of transmission was calculated according to Ghent working group formulae.¹⁹ For clinical characteristics. The upper bound of the rate of transmission examine the odds of vertical transmission according to maternal and medians, respectively. Multiple logistic regression was used to compare proportions and Wilcoxon rank-sum tests were used to compare proportions.

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Results
Maternal characteristics
Between 2002 and 2008, 2 350 ART-naïve women were referred for ART, and 367 were identified as pregnant at first clinic attendance. Their median age was 27.5 years (range 15-44); median gestational age 28 weeks (interquartile range (IQR) 24-32), and the median baseline CD4 cell count and viral load were 134/μl (IQR 88-179) and 28 282 copies/ml (IQR 103-74 859) respectively.

Intervention received
Two hundred and sixty-five mothers (73%) started ART prior to giving birth; 73 (20%) were referred back from the ART clinic to the midwife obstetric unit (MOU) for PMTCT, and 29 (8%) had no intervention (Fig. 1). After exclusion of 6 women who were confirmed to be ineligible for ART, 13 refused ART and 7 started ART later. Altogether, 44 out of 346 (12.7%, 95% CI 9.6-16.7%) eligible women were lost to follow-up or refused ART and therefore were not started on ART.

Women who commenced ART started a median of 21 days after enrolment (IQR 14-29); the median period on ART prior to birth was 7.6 weeks (IQR 4-11.9) (Fig. 2). The choice of ART regimen depended on maternal condition. Two hundred and forty-six (93%) started AZT, 3TC and NVP; 12 (5%) commenced d4T, 3TC and NVP owing to anaemia; 6 (2%) started d4T 3TC and EFV owing to TB and advanced pregnancy; and 1 (0.3%) started d4T 3TC and Kaletra. There were 8 regimen changes during pregnancy.

Comparison of PMTCT, ART and No Intervention Received
The demographics and outcomes of the groups of ART and PMTCT were compared (Table I). The PMTCT group were more advanced in their pregnancy, and had higher baseline CD4 cell counts and lower baseline viral loads ($p<0.001$, $p<0.001$, $p=0.013$ respectively). There was no difference in distribution of live births and stillbirths, or in HIV status of infants. The groups that received no intervention were significantly younger than those started on ART ($p=0.002$), and were more likely to have TB ($p=0.015$) and to have stillbirths ($p=0.004$). Both groups gave birth at earlier gestational age than the ART group.

Maternal and pregnancy outcomes
Of the women commenced on ART, 16 (6%) were lost to the programme prior to giving birth. Of these, 9 (3%) were lost to follow-up, 5 (2%) died and 2 were transferred to another ART clinic. Of the 5 deaths, 3 were due to TB and 1 to pneumonia, and the cause of the fifth was unknown. Overall, 34 (9.3%) pregnant women had TB.
The groups of HIV-negative, positive and status-unknown infants born to women commenced on ART were compared (Table II).

### Risk factors for vertical transmission

The groups of HIV-negative, positive and status-unknown infants born to women commenced on ART were compared (Table II). There were 241 births in this group. Median age at PCR was 13 weeks (IQR 10 - 17). Two hundred and six infants were negative (85%), 11 (4.6%) positive, and 24 (10%) of unknown status (Fig. 1). Four of the infants of unknown HIV status died under the age of 17 weeks, and the remaining mothers of 20 infants had been transferred to another clinic, were lost to follow-up, or the infant had not been tested. The mother of infants of unknown status were younger (p=0.018). After exclusion of unknowns, the transmission rate was 5.1% (95% CI 2.8 - 9.0%). The upper bound for the rate of transmission within the ART group estimated by the Ghent working group formulae was 7.83% (95% CI 4.9 - 12.2).19

Crude analysis showed duration of ART before birth to be significantly associated with transmission (p=0.029). All of the mothers who gave birth to HIV-positive infants had less than 8 weeks’ ART prior to delivery. Advanced maternal disease stage (stage III or IV compared with I or II, p=0.01), gestation at enrolment (p=0.036) and first follow-up viral load >50 copies/ml (p=0.018) were also significantly associated. No significant difference was found in HIV status of infant according to maternal ART regimen.

Multivariate analysis of the HIV-positive versus negative infants revealed duration of ART to be an independent predictor of transmission (Table III). Each week reduced risk of transmission by 20% (p=0.005). Additional independent predictor variables were maternal WHO stage at enrolment and viral load at first follow-up.
Women with WHO stage 3 or 4 disease were 9.5 times more likely to transmit (p=0.02) than those at stage 1. Those with incompletely suppressed virus (viral load >50 copies/ml) at 16 weeks on ART had a transmission rate of 10% (95% CI 4 - 20%), whereas those with a viral load of <50 copies/ml had a transmission rate of 3% (95% CI 1 - 8%).

**Discussion**

The HIV transmission rate of those starting HAART during pregnancy was 5.1%, with an upper bound of 7.8% that was higher than rates reported in the developed world.7,8,11 Our study demonstrated that the HIV transmission rate of those starting HAART during pregnancy was 5.1%, with an upper bound of 7.8% that was higher than rates reported in the developed world.7,8,11 Our study demonstrated that the HIV transmission rate of those starting HAART during pregnancy.

The major factor limiting the potential duration of ART was strongly associated with shorter duration of HAART in pregnancy. The potential duration of ART was further restricted because delivery tended to occur early at a median of 38 weeks with 25% of mothers giving birth before 36 weeks' gestation. This limited window of opportunity for ART initiation resulted in a strategy of fast-tracking of women presenting in the third trimester of pregnancy. Fast-tracking may not be an optimal strategy but was considered necessary as an emergency intervention precipitated by late booking. Women accessing ART programmes during pregnancy are significantly more likely to be lost to follow-up than their non-pregnant peers.20,21 The reasons behind poor retention of pregnant women within ART programmes are uncertain; however, too little preparation prior to ART initiation could be a contributing factor.

Lack of treatment readiness was also an important constraint to implementation as 21% of eligible women either refused or delayed commencement of ART to after delivery. Such women had already...
Table III. Risk factors associated with vertical HIV transmission

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 vs. stage 2</td>
<td>1.32</td>
<td>0.1</td>
<td>18.25</td>
</tr>
<tr>
<td>Stage 1 vs. stage 3 and 4</td>
<td>9.68</td>
<td>1.47</td>
<td>63.62</td>
</tr>
<tr>
<td>Age at enrolment</td>
<td>0.85</td>
<td>0.71</td>
<td>1.02</td>
</tr>
<tr>
<td>Weeks on ART prior to birth</td>
<td>0.8</td>
<td>0.64</td>
<td>1.0</td>
</tr>
<tr>
<td>Follow-up viral load &lt;50</td>
<td>5.78</td>
<td>1.17</td>
<td>28.51</td>
</tr>
<tr>
<td>v. &gt;50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up CD4</td>
<td>1</td>
<td>0.1</td>
<td>1.01</td>
</tr>
<tr>
<td>Log baseline viral load</td>
<td>0.73</td>
<td>0.24</td>
<td>2.23</td>
</tr>
<tr>
<td>Baseline CD4</td>
<td>1</td>
<td>0.99</td>
<td>1.02</td>
</tr>
</tbody>
</table>

successfully navigated their way through antenatal booking and referral before attending the ART clinic. As losses may occur at earlier stages of the entire cascade of antenatal clinic attendance, counselling and testing, referral for treatment, initiation of HAART and ongoing adherence to protocol, true losses from the programme are likely to have been even greater.

In the developed world, vertical HIV transmission rates of between 0% and 2.9% have been achieved for women on HAART.¹¹⁻¹³ Triple therapy (HAART) is superior to AZT monotherapy in preventing mother-to-child transmission.⁷⁻⁹ Similarly, in this study, there were no HIV transmissions among women who received at least 8 weeks of therapy before delivery. The overall HIV transmission rate among our patients highlights that the effectiveness of HAART for vertical transmission is affected by the potency of the regimen used and also by other operational constraints. One contributing factor is that the present national ART treatment guidelines restrict HAART to those with AIDS or CD4 <200 cells/µl. Pregnant black women with high viral loads require several weeks of therapy to completely suppress viral load.¹⁰ Our data highlight that the effectiveness of HAART will be greatly increased if women can be encouraged to access antenatal services at an earlier stage of gestation. Antenatal services should also place emphasis on retaining women within care. There were few adverse events related to use of HAART but there were multiple sequelae of untreated HIV. However, a significant proportion of women refused or delayed initiation of HAART. Social marketing of the benefits of HAART is urgently required to overcome the negative messages previously propagated by South Africa's health authorities. The limited window of opportunity for initiating HAART in women presenting later in pregnancy has required fast-tracking them. Whether adequate preparation due to fast-tracking plays a part in the poor retention of pregnant women in HAART programmes must be investigated.

We studied the effectiveness of HAART and did not address important parameters such as mode of delivery, breastfeeding and infant post-exposure prophylaxis. Additionally, pregnancy outcomes of the women referred back for PMTCT were unknown. Direct comparison of the effectiveness of PMTCT v. HAART in this study was therefore not possible. Interpreting the analysis of live v. stillbirths is complex, as women having miscarriages or early stillbirths would not attend the antenatal clinic, which builds in an ascertainment bias. Similarly, longer duration of pregnancy at enrolment emerged as protective, but this may have been because the more advanced the pregnancy, the less time there is for a stillbirth to occur.

The generalisability of the data to other parts of South Africa and the rest of sub-Saharan Africa is difficult to establish. This is one unique programme, and other public sector services may initiate ART more slowly. In other areas, antenatal booking may be later still, and treatment initiation may be further slowed by delays in CD4 enumeration. Further programmatic data are needed.

Summary

The rate of vertical HIV transmission (5.1%) among women commencing ART in this cohort was higher than that reported in the developed world, and was associated with advanced immunodeficiency at presentation and late initiation of HAART. No HIV transmissions occurred among women who received more than 8 weeks of HAART. However, 12.7% of women eligible for ART during pregnancy did not receive it and, in those starting HAART, the median length of therapy before delivery was less than 8 weeks. The effectiveness of HAART will be improved by earlier presentation to antenatal services and subsequent retention in care. Increased uptake of HAART will require social marketing of the considerable benefits of HAART in this patient population.

References


Accepted 12 May 2010.