HIV Transmission to Premature Very Low Birth Weight Infants

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Abstract: There is sparse literature about HIV transmission in preterm infants. Eighty-two HIV-exposed preterm infants received birth polymerase chain reactions (PCRs). Five (6.1%) were HIV positive with all 5 mothers receiving inadequate antiretrovirals. Of the PCR-negative infants, 9 died and 87% of the survivors received further PCR testing which remained negative. With correct care, intrapartum transmission of HIV can virtually be eliminated.

Key Words: prematurity, HIV transmission, prevention of mother to child transmission, very low birth weight, neonatal

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Preterm birth (born before 37 completed weeks) is associated with higher risk of perinatal HIV transmission, especially for those born before 33 weeks.¹⁻³ However, there is limited information about HIV-exposed preterm infants, especially those with very low birth weight (VLBW) (<1500 g). One reason for this may be that in countries with high HIV prevalence, neonatal mortality rates are also high, and these small infants often do not survive.⁴ Treatment and prevention of HIV in premature infants have been termed “the last and first frontiers.”⁵

We have previously shown that it is possible to achieve a low risk of transmission 2.7% (0.7%–14.1%) in extremely low birth weight HIV-exposed infants (<1000 g).⁶ However, this study was limited by the lack of determination of HIV status in the 27% (14/51) of infants who died before the 6-week HIV testing.

The objective of this study was to describe the characteristics and outcomes of a cohort of HIV-exposed VLBW infants.

METHODS

From August 2014 to April 2015, we prospectively enrolled into a database all VLBW babies born at Groote Schuur Hospital (GSH) and New Somerset Hospital (NSH) in Cape Town, South Africa. GSH, one of 2 government tertiary referral centers for the Western Cape Province, delivers about 460 VLBW infants per year, and approximately 40% of these are delivered because of maternal severe pre-eclampsia/hypertension causing maternal or fetal compromise.⁷ NSH is a secondary hospital with about 160 VLBW infants per year.

HIV prevalence in pregnant women is approximately 16%.⁸ Mothers who are not tested for HIV during pregnancy are tested soon after birth. According to provincial protocols, women who test positive during pregnancy are started on triple therapy (once daily fixed dose combination: efavirenz, 600 mg; emtricitabine, 200 mg and tenofovir disoproxil fumarate, 300 mg). During labor, mothers who are known to be HIV positive but not receiving antiretrovirals (ARVs) at the time of delivery are given prophylaxis, which includes nevirapine, zidovudine and tenofovir disoproxil fumarate/emtricitabine. All premature infants are considered high risk of HIV infection regardless of the maternal viral load and are thus started on dual prophylaxis (4 weeks of zidovudine 2 mg/kg twice daily) and at least 6 weeks of nevirapine (2 mg/kg daily for 2 weeks and then 4 mg/kg daily thereafter). Exclusive breastmilk is encouraged for most babies because of its many benefits and the small risk of transmission, especially if the mother’s viral load is low.⁹

However, because of concerns of possible increased transmission in the premature baby, mother’s own milk, if it was available, was pasteurized before administration until she could breast-feed directly. If there was insufficient mother’s milk, the infants either received pasteurized donated milk if they weighed <1200 g or formula if they were >1200 g. The weight cut off was necessitated by limited donor milk stocks.

Information was abstracted from medical records into an Excel database, including maternal ARVs, viral load, comorbidities, pregnancy and delivery outcomes, infant birth weight, estimated gestational age, clinical course, feeding, ARV history and HIV testing results. The polymerase chain reaction (PCR) assay used for infant HIV testing was Roche Cobas Ampliprep/Cobas TaqMan (CAP/CTM), which detects both DNA and RNA. Approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee was obtained for the maintenance of this database.

RESULTS

Eighty-four VLBW infants (77 at GSH and 7 at NSH) were born to 79 women with HIV infection during that period. No infants were excluded from the study. Of the 79 women, 17 (22%) received no antenatal care, and 25 (32%) were diagnosed with HIV during the pregnancy or after delivery. Fifty-seven women (72%) received ARVs at least 1 month before delivery, while 7 (9%) received less than 30 days ARV treatment. Ten women (13%) received no ARVs at all before delivery, and for 5 (6%), the duration of ARV use was unknown. Viral load was undetectable in 37 women (47%), unknown in 25 (32%), <log3 in 4 (5%) and >log3 in 13 (16%).

The infant weights, gestational ages, mode of delivery and deaths are depicted in Figure 1. Twelve babies died before discharge home (2 of these on the first day of life before PCR testing was done). The deaths were predominantly in the babies less than 1000 g, and the overall survival rate (85%) was similar to our background VLBW survival rate (83%). Most of the deliveries (57%) were by cesarean section without labor due to complications of PET.

Of the 84 infants, 82 had an HIV PCR test performed within 48 hours of birth, of which 5 (6%) were PCR positive. All 5 mothers had received either no ARVs or suboptimal antiretroviral therapy duration of 2, 4 or 8 weeks. In all cases, the infants’ dual prophylaxis was converted to triple antiretroviral therapy (zidovudine, lamivudine and nevirapine) within 10 days of life. One infant
died on day 34 from necrotizing enterocolitis; 3 infants achieved virologic suppression, and 1 did not Table 1.

None of the infants who were PCR negative at birth tested positive at either 6 weeks (87% tested) or 10 weeks (49% tested).

Feeding at discharge from GSH and NSH was exclusive breastfeeding 51 (71%), exclusive formula feeding 12 (16%), mixed feeding 7 (10%) and unknown 2 (3%).

DISCUSSION

Mother-to-child transmission of HIV can occur during pregnancy, intrapartum or through breastfeeding. Of these 3 mechanisms, there is evidence that preterm birth differentially affects the risk of intrauterine and intrapartum transmissions.

One of the only advantages to being born preterm is that this decreases exposure time to contract intrauterine HIV. The intrauterine transmission rate for infants born to untreated HIV-infected mothers has been reported to be 1.6% at 28-weeks and 5.1% at 36-weeks gestation.9 Barriers such as skin and mucous membranes are thinner and more friable than in term infants, increasing the risk of transmission when these infants are exposed to conditions such as chorioamnionitis, prolonged rupture of membranes or vaginal birth.10

As maternal viral load is the strongest independent predictor of transmission,11,12 preterm infants are also disadvantaged if their mothers are diagnosed or started on treatment during pregnancy as there is less time before birth to achieve virologic suppression.

Intrauterine transmission in our cohort was higher than expected at 6.1%. All 5 of these pregnancies however could classify as high risk as ARVs were started very late or not at all. Of the 4 who survived to discharge, 3 were virologically suppressed at follow-up, including an infant with birthweight of only 770 g. It would be important to follow up these and other very preterm infants with HIV infection as little is known about their long-term outcomes.

Although our data seem to indicate that it is possible to eliminate intrapartum and breastfeeding transmission in this group of higher risk infants, it must be noted that 13% of our 6-week infants died on day 34 from necrotizing enterocolitis; 3 infants achieved virologic suppression, and 1 did not.

## Table 1.

Characteristics and Outcomes of HIV-infected VLBW Babies

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Baby 1</th>
<th>Baby 2</th>
<th>Baby 3</th>
<th>Baby 4</th>
<th>Baby 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal antiretroviral therapy</td>
<td>None</td>
<td>None</td>
<td>2wk before delivery</td>
<td>4wk before delivery</td>
<td>8wk before delivery</td>
</tr>
<tr>
<td>Maternal viral load</td>
<td>Log 3.4</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Log 4.2</td>
<td>146</td>
</tr>
<tr>
<td>Maternal CD4</td>
<td>195</td>
<td>537</td>
<td>522</td>
<td>116</td>
<td>168</td>
</tr>
<tr>
<td>Maternal HIV diagnosis</td>
<td>Before pregnancy</td>
<td>Postpartum</td>
<td>In this pregnancy</td>
<td>In this pregnancy</td>
<td>In this pregnancy</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>NVD</td>
<td>C/S before labor</td>
<td>NVD</td>
<td>C/S before labor</td>
<td>C/S before labor</td>
</tr>
<tr>
<td>Indication for delivery</td>
<td>Spontaneous preterm labor</td>
<td>Pre-eclampsia with fetal distress</td>
<td>Induction of labor for pre-eclampsia</td>
<td>Pre-eclampsia with fetal distress</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>1100</td>
<td>770</td>
<td>1250</td>
<td>950</td>
<td>1460</td>
</tr>
<tr>
<td>Gestational age</td>
<td>29</td>
<td>29</td>
<td>32</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Gestation age scoring</td>
<td>Ballard</td>
<td>Ballard</td>
<td>Ballard</td>
<td>Early ultrasound</td>
<td>Ballard</td>
</tr>
<tr>
<td>Age at PCR testing</td>
<td>D1</td>
<td>D1</td>
<td>D1</td>
<td>D1</td>
<td>D1</td>
</tr>
<tr>
<td>Age at commencement of triple ART</td>
<td>D5</td>
<td>D6</td>
<td>D6</td>
<td>D7</td>
<td>D7</td>
</tr>
<tr>
<td>Duration of follow-up Outcome</td>
<td>34 d</td>
<td>8 mo</td>
<td>6 mo</td>
<td>4 mo</td>
<td>9 mo</td>
</tr>
<tr>
<td>Outcome</td>
<td>Died of NEC on day 34</td>
<td>LDL viral load Moved back to Zimbabwe</td>
<td>Good growth but unsupressed viral load</td>
<td>LDL viral load Transferred to district services</td>
<td>LDL viral load Transferred to district services</td>
</tr>
</tbody>
</table>

ART indicates antiretroviral treatment; C/S, cesarean section; LDL, lower than detectable limit; NEC, necrotizing enterocolitis; NVD, normal vertex delivery.

FIGURE 1. Weight, gestational age, mode of delivery and outcome of HIV-exposed infants. C/S indicates cesarean section; GA, gestational age; NVD, normal vertex delivery.
PCR results were missing. Prolonged ARV prophylaxis may also suppress viral load sufficiently to reduce sensitivity of PCR testing at 6 weeks. However, as 80% of the cohort were at least partially breast-fed, if any of these babies are subsequently shown to be HIV infected, it will be difficult to determine if the infection occurred intrapartum or through breastfeeding.

It is possible that many of our VLBW infants were over treated when they received 2 prophylactic drugs. Both the UK and US guidelines recommend single drug prophylaxis (zidovudine) when maternal viral loads are <50 copies/mL. Although there are little pharmacodynamic data on ARV use in preterm neonates, zidovudine and nevirapine have both been studied. Prophylactic nevirapine seems to be safe, while zidovudine may exacerbate anemia of prematurity and cause neutropenia. There has also been some speculation that zidovudine may increase the risk of necrotizing enterocolitis in preterm infants.

With correct care, perinatal transmission of HIV can virtually be eliminated even in the most preterm infants. Intrauterine transmission will remain a problem if mothers are not accessing ARV therapy early in their pregnancy.

REFERENCES


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