HIV-2 in West Africa. Epidemiological studies
Schim van der Loeff, M.F.

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Survival of HIV-1 and HIV-2 perinatally infected children in The Gambia

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Maarten F Schim van der Loeff 1,2, Andreas Hansmann 1,3, Akum Aveika Awasana 1,
Martin O. Ota 1, Diarmuid O'Donovan 1, Ramu Sarge-Njie 1,4, Koya Ariyoshi 1,5,
Paul Milligan 1, Hilton Whittle 1

(1) the Medical Research Council Laboratories, Fajara, The Gambia; (2) London School of Hygiene & Tropical Medicine, London, UK; (3) Westfälische Wilhelms-Universität, Münster, Germany; (4) National Health Laboratories Services, Banjul, The Gambia; (5) AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan

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ABSTRACT

Background: The risk of mother-to-child transmission (MTCT) of HIV-2 is much lower than that of HIV-1, but the long-term prognosis of perinatally infected HIV-2 children is unknown. We re-visited children who were part of a large MTCT study in The Gambia (conducted 1993 - 97), in order to compare the long-term survival of children perinatally infected with HIV-2 with that of seronegative and of HIV-1 infected children.

Methods: Five to eight years follow-up of a cohort of children born to HIV-negative, HIV-1 positive, and HIV-2 positive mothers.

Results: Seven hundred and seventy-four children were followed up for a median of 6.6 years. Of 17 perinatally HIV-1 infected children, 3 were still alive on 1st July 2001, 2 had been lost to follow up, and 12 had died. The median survival was 2.5 years. Of 8 HIV-2 infected children 5 were still alive, none were lost to follow up and 3 had died. The mortality hazards ratio of both HIV-1 (9.9; 95% Confidence Interval (CI) 5.2-19), and of HIV-2 infected children (3.9; CI 1.2 – 12) was significantly increased compared to children of seronegative mothers. The mortality hazards ratio of HIV uninfected children of HIV-1 or HIV-2 infected mothers was not significantly increased compared to children of seronegative mothers (P = 0.17 and P = 0.5 respectively).

Conclusions: Children with perinatally acquired HIV-2 infection have a higher mortality than children of seronegative mothers. Guidelines for treatment of HIV-1 infected children should be used for treatment of HIV-2 infected children.
HIV-2 in West Africa

Introduction

The majority of the 3 million HIV infections in children world-wide results from mother-to-child transmission (MTCT) [1-3]. The MTCT rate in HIV-1 is between 21% and 43% in breast feeding populations without access to antiretrovirals [4], but can be as low as 1% in women using antiretroviral therapy and delivered by elective caesarean section [5]. The mortality of perinatally infected children in affluent countries has improved dramatically in recent years due to better treatment, notably anti-retroviral treatment [6-9]. Even the median survival in children not on anti-retroviral therapy (ART) is longer than 8 years [6,7,10]. The 5-year probability of survival ranged from 0.60 to 0.75 [6,10,11].

Almost 90% of children with HIV-1 live in sub-Saharan Africa [1], where the survival of children with HIV-1 is much worse. In studies conducted in Africa the survival probability of HIV-1 infected children ranged from 0.66 to 0.80 at 1 year [12-14], and from 0.25 to 0.43 at 5 years [12,15,16]. Reported median survival ranged from 12.4 months to 21 months [13,15,17]. An estimated 8% of all under-5 mortality in sub-Saharan Africa is caused by HIV [18].

The mother-to-child transmission of HIV-2 is estimated to be 4%, one-sixth that of HIV-1 [19]. Survival of adults with HIV-2 is better than in HIV-1 infection [20-22], but few data exist on the survival of children with HIV-2 infection. There are several case reports of presumably perinatally infected children who reached teen [23-25]. To our knowledge, there are no prospective cohort studies of perinatally infected HIV-2 children.

In order to estimate the long-term survival of children with HIV-2 infection, and to compare this with survival in HIV-1 infected and in uninfected children in the same population, we re-visited mother and child pairs four years after the completion of a large observational MTCT study that was conducted between 1993 and 1997 [19,26].
Methods

Perinatal study
Between January 1993 and March 1995 HIV-negative, HIV-1 infected and HIV-2 infected pregnant women were recruited at eight health centres throughout The Gambia. They were followed up at regular intervals up to 18 months postpartum. HIV infection in infants was diagnosed by PCR at 2, 9 and 18 months and by serology at 18 months. Babies were considered infected if they tested HIV seropositive at 18 months of age, or, if this specimen was not available (through death or loss to follow-up) if they tested positive by PCR at 2 or 9 months of age [19]. Infants who died or were lost to follow-up before a first post-natal sample was taken (typically at 2 months), could not be assigned an HIV diagnosis. The survival probability at 18 months was 0.64 (95% confidence interval (CI) 0.37 – 0.82) for the seventeen HIV-1 infected and 1.0 (95%CI 0.63-1.0) for the eight HIV-2 infected children [26].

Field follow-up
From July to November 2001 an attempt was made to visit all 819 women and their children who were seen at least once since their delivery in 1993-5. No visit was planned when the woman had refused participation in the earlier study or when it was known that both mother and child had died. In the latter case the mortality data from the earlier study were used in the analysis. Women were visited by one of three male Gambian field workers, who were unaware of the sero-status of mother and child. The field workers were experienced counsellors in the genito-urinary medicine (GUM) clinic of the Medical Research Council (MRC) Laboratories in Fajara, and were trained to explain the study, and discuss the purpose and meaning of an HIV test. Interviews were conducted in the language of the study participants. A short questionnaire was completed with some key demographic details. The field workers aimed to speak to the study woman, or if she had died, to a close relative, and relied on their information regarding the vital status of the study child. All women were offered a new HIV test.
HIV-2 IN WEST AFRICA

Loss to follow-up was defined as lack of information concerning the survival status of the child as per 1st July 2001. Observation time started at the date of birth, and ended at the date of death, or the date the child was last known to be alive, whichever came first. Children of a twin delivery were both included in the analysis. Time to death was examined using Kaplan-Meier graphs. Cox proportional hazards analysis and log rank tests were performed to compare survival between groups.

Ethics

The study was approved by the Gambia Government / MRC Laboratories Joint Ethics Committee. Participants were asked for verbal informed consent, which was documented by the field worker. In the original study the results of HIV testing had been available from a counsellor based in government health centres. Very few women came to obtain their test results (< 1%), and consequently the current study followed women who were mostly unaware of their HIV status. Instead of offering the result of the test done 6 to 8 years previously, all participants were offered a new HIV test, irrespective of their original HIV status. All newly tested positive subjects were referred for free clinical care to the MRC GUM clinic. Perinatal antiretroviral prophylaxis was not available in The Gambia at the time of birth of the study children. None of the children received antiretroviral therapy or prophylaxis against opportunistic infections during the study period.

Results

Eight hundred and nineteen women had 832 children (including 10 sets of twins). The ten children (all of them HIV-negative) born to HIV-1 and HIV-2 dually infected (HIV-D) women, and 48 stillborn children were excluded, leaving 774 children for analysis. As of 1st July 2001, 104 children (13%) had died, 182 (24%) were lost to follow up, and 488 were alive. The median observation time was 6.6 years (interquartile range (IQR) 1.5–7.5). The rate of loss to follow up was 4.6 (95% CI 4.0–5.3) per 100 person-years of observation, and did not differ by HIV status of mother or child.
Table 1. Survival and mortality hazard ratios of children by mother’s and child’s HIV status, the Gambia 1993-2001.

<table>
<thead>
<tr>
<th>mother’s HIV status</th>
<th>HIV-1</th>
<th>negative</th>
<th>unknown</th>
<th>HIV-2</th>
<th>negative</th>
<th>unknown</th>
<th>negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live-born children</td>
<td>17</td>
<td>64</td>
<td>17</td>
<td>8</td>
<td>194</td>
<td>26</td>
<td>448</td>
</tr>
<tr>
<td>Died (%)</td>
<td>12 (71%)</td>
<td>10 (16%)</td>
<td>7 (41%)</td>
<td>3 (38%)</td>
<td>21 (11%)</td>
<td>11 (42%)</td>
<td>40 (9%)</td>
</tr>
<tr>
<td>Lost during follow-up (%)</td>
<td>2 (12%)</td>
<td>10 (16%)</td>
<td>5 (29%)</td>
<td>0 (0%)</td>
<td>49 (25%)</td>
<td>8 (31%)</td>
<td>108 (24%)</td>
</tr>
<tr>
<td>Infant mortality ratio (95% CI)</td>
<td>235 (68 – 499)</td>
<td>16 (0.4 – 84)</td>
<td>0 (0 – 369)</td>
<td>31 (11 – 66)</td>
<td>54 (35 – 79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 year survival (95%)</td>
<td>59%</td>
<td>93%</td>
<td>100%</td>
<td>96%</td>
<td>(90 – 95)</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>5 year survival (95%)</td>
<td>21%</td>
<td>86%</td>
<td>63%</td>
<td>89%</td>
<td>(88 – 93)</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Mortality hazard ratio (95%)</td>
<td>9.9 (5.2 – 19)</td>
<td>1.6 (0.81 – 3.3)</td>
<td>3.9 (1.2 – 12)</td>
<td>1.2</td>
<td>(0.70 – 2.0)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Log rank test for difference in survival compared to ref. group</td>
<td>0.0005</td>
<td>0.18</td>
<td>0.02</td>
<td>0.5</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval. ref = reference group. The children with unknown HIV status died or were lost to follow-up before a first blood sample could be obtained.
Figure 1. Kaplan-Meier graph comparing survival of HIV-1 infected and HIV-2 infected children, and of children of HIV uninfected mothers. (The Gambia 1993-2001)

Twelve out of 17 HIV-1 infected children died (71%), the median survival being 2.5 years (IQR 1.0–4.5) (see Table 1). The mortality hazards ratio of HIV-1 infected children was 9.9 (CI 5.2–19) compared to children of HIV uninfected mothers (P<0.0005). Three out of 8 HIV-2 infected children died (38%). The median survival could not be calculated, but after 6 years 5 (63%) were still alive (CI 23–86%). The mortality hazard ratio of HIV-2 infected children was 3.9 (CI 1.2–12) compared to children of HIV uninfected mothers (P=0.02). The mortality hazard ratio of HIV-1 infected children was 3.1 (0.87–11) times that of HIV-2 infected children, but this was not significant (P=0.08). Figure 1 compares the survival of HIV-1 and HIV-2 infected children with children born to HIV seronegative women. The characteristics of the eight HIV-2 infected children are listed in Table 2.
<table>
<thead>
<tr>
<th>Child study number</th>
<th>Sex</th>
<th>Earliest recorded weight in kg</th>
<th>Surviv al status</th>
<th>Age in years</th>
<th>Pro- viral load</th>
<th>Antenatal CD4% of mother</th>
<th>Post-partum CD4% of mother</th>
<th>Antenatal log PVL of mother</th>
<th>Survival status of mother</th>
<th>child healthy at time of last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1366591</td>
<td>M</td>
<td>na</td>
<td>D</td>
<td>2.4</td>
<td>111</td>
<td>37</td>
<td>20</td>
<td>2.7</td>
<td>A</td>
<td>na</td>
</tr>
<tr>
<td>1456861</td>
<td>M</td>
<td>2.0</td>
<td>D</td>
<td>2.4</td>
<td>--</td>
<td>12</td>
<td>6</td>
<td>2.4</td>
<td>A</td>
<td>na</td>
</tr>
<tr>
<td>1320521</td>
<td>M</td>
<td>3.0</td>
<td>D</td>
<td>2.7</td>
<td>26</td>
<td>14</td>
<td>19</td>
<td>4.6</td>
<td>A</td>
<td>na</td>
</tr>
<tr>
<td>1429611</td>
<td>F</td>
<td>2.8</td>
<td>A</td>
<td>6.8</td>
<td>130</td>
<td>40</td>
<td>27</td>
<td>4.2</td>
<td>D</td>
<td>Y</td>
</tr>
<tr>
<td>1425001</td>
<td>M</td>
<td>3.7</td>
<td>A</td>
<td>7.0</td>
<td>--</td>
<td>46</td>
<td>39</td>
<td>4.8</td>
<td>A</td>
<td>Y</td>
</tr>
<tr>
<td>1215851</td>
<td>F</td>
<td>3.4</td>
<td>A</td>
<td>7.2</td>
<td>1000</td>
<td>22</td>
<td>50</td>
<td>4.2</td>
<td>A</td>
<td>Y</td>
</tr>
<tr>
<td>1012021</td>
<td>M</td>
<td>3.8</td>
<td>A</td>
<td>7.7</td>
<td>--</td>
<td>32</td>
<td>35</td>
<td>3.4</td>
<td>A</td>
<td>Y</td>
</tr>
<tr>
<td>1010821</td>
<td>F</td>
<td>4.1</td>
<td>A</td>
<td>7.8</td>
<td>--</td>
<td>55</td>
<td>54</td>
<td>2.4</td>
<td>A</td>
<td>Y</td>
</tr>
</tbody>
</table>

a. Weight was recorded a median of 1 day (range 0-16) after birth; b. Age at date of death or date last known to be alive; c. DNA copies per 100,000 peripheral blood mononuclear cells; d. log_{10} RNA copies/ml; e. Mother died 4 years after the child had died; f. Mother died 3 months after the child had died. Abbreviations: A = alive; D = dead; M = male; F = female; na = not applicable; Y = yes; N = no; PVL = plasma viral load.
Survival to the time of the first blood sample was essential for making an HIV diagnosis. A blood sample was not available for 17 (17%) children of HIV-1 infected mothers, and for 26 (11%) children of HIV-2 infected mothers. Therefore we repeated the proportional hazards calculations, conditional on survival up to 4 months. Also in this approach the mortality hazards of HIV-1 and HIV-2 infected children were significantly higher than in children of uninfected mothers (P<0.0005 and P=0.003 respectively).

The mortality hazard ratio of children according to their mothers’ HIV status (and ignoring their own status) was 3.6 (CI 2.2-5.7 ; P<0.0005) for children of HIV-1 infected mothers and 1.8 (CI 1.1-2.8; P=0.012) for children of HIV-2 infected mothers. The mortality hazard of HIV-2 infected children was 3.3 fold (0.98-11) that of uninfected children born to HIV-2 infected mothers (P=0.054). The mortality hazard of HIV-1 infected children was 9.2 fold (CI: 3.9–22) that of uninfected children born to HIV-1 infected mothers (P<0.0005). The overall mortality rate of HIV uninfected children of HIV-1 or HIV-2 seropositive mothers was not significantly different from that in children of HIV uninfected mothers (P=0.17 and P=0.5 respectively). In an analysis excluding the first four months, the mortality hazards of these children were significantly higher (P=0.09 and P=0.02 respectively). The mortality of children whose mothers died in the study was 6.9-fold (CI 4.3-11) that of children whose mothers survived (P<0.0005). This was independent of mother’s HIV status.

Proviral load was available for 11 of 17 HIV-1 infected children; each log, increase of proviral load in the infant was associated with a 1.5 rise (CI 0.89–2.5) in mortality hazard ratio (P=0.13). In HIV-2 children there were only 4 proviral loads done, and no associations were estimated.

None of the following variables were associated with mortality hazard ratios in HIV-1 or HIV-2 infected children: maternal antenatal or postnatal CD4%, maternal plasma viral load, age, parity, or ethnic group, and baby’s sex, but power was low due to small numbers.

Discussion

This study shows that the survival rate of children with perinatally acquired HIV-2 is worse than that of uninfected children, but may be better than in HIV-1 infected children. The mortality of
children with perinatally acquired HIV-1 was similar to that found in other studies [12,13,15,17]:
the median survival time was 2.5 years, and the survival probability at 5 years was 0.21. The
median survival in HIV-2 could not be estimated, but at age 7 years 5/8 of the children were still
alive.

The rate of loss to follow-up was limited with 4.6 per 100 pyo. The observed 4-fold higher
mortality of HIV-2 infected children compared to children of HIV uninfected mothers is likely
to be an underestimate, as diagnosis of HIV-2 infection was conditional on surviving up to the
first sample (typically at 2 months). Twelve children born to HIV-1 infected, and 19 children
born to HIV-2 mothers died or where lost to follow-up before the HIV status could be
established, but some of these may have been infected. Therefore the proportion of infected
children surviving may in fact be lower and the mortality hazard ratio higher than we estimated.
In order to obtain unbiased estimates, hazard ratios were calculated conditional on survival to 4
months. The mortality HR appeared higher than in the overall analysis, confirming an increased
mortality rate in both HIV-1 and HIV-2 infected children.

Perinatally acquired HIV-2 infection may have a better prognosis than perinatally acquired HIV-
1 infection. Although the plasma viral load of the mothers who infected their children with
HIV-2 was high [19], it appears that this does not necessarily lead to a rapid disease progression
in the children. This underlines the importance of host factors in the natural course of HIV-2
infection.

Mothers with HIV-2 must be counselled that they have a small chance of transmitting the
infection to their baby, but if they do, their babies are at increased risk of early death. HIV-2
infected children need antiretroviral treatment and may need prophylaxis against opportunistic
infections. There are few studies on treatment of HIV-2 in adults, [27-29] and none of treatment
of HIV-2 in children. In the absence of HIV-2 specific guidelines and lack of data on PVL, CD4
count and morbidity, we advise that guidelines in use for HIV-1 [30,31] should be followed, with
the exclusion of non-nucleoside analogue reverse transcriptase inhibitors (e.g. nevirapine), which
are not effective against HIV-2. [32]
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HIV-2 in West Africa