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

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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 during 1993–1997), 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, three were still alive on 1 July 2001, two had been lost to follow-up, and 12 had died. The median survival was 2.5 years. Of eight HIV-2 infected children five were still alive, none were lost to follow-up and three 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 with 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 that of 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.

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Introduction

The majority of the 3 million HIV infections in children worldwide 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 antiretroviral therapy (ART) [4], but can be as low as 1% in women using ART and delivered by elective Cesarean section [5]. The mortality of perinatally infected children in affluent countries has improved dramatically in recent years due to better treatment, notably ART [6–9]. Even the median survival in children not on ART is longer than 8 years [6,7,10]. The 5-year probability of survival ranges 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 mortality under the age of 5 years in sub-Saharan Africa is caused by HIV [18].

The MTCT of HIV-2 is estimated to be 4%, one-sixth that of HIV-1 [19]. Survival of adults infected by HIV-2 is better than those with HIV-1 [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 have reached teenage [23–25]. To our knowledge, there are no prospective cohort studies of perinatally infected HIV-2 children.

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 4 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 17 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 1993–1995. 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.

Statistical analysis

Loss to follow-up was defined as lack of information concerning the survival status of the child as per 1 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 6–8 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 ART or prophylaxis against opportunistic infections during the study period.

Results

A total of 832 children were born to the 819 women (this included 10 sets of twins). The 10 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 1 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.

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 eight HIV-2 infected children died (38%). The median survival could not be calculated, but after 6 years five (63%; CI, 23–86%) were still alive. The mortality hazard ratio (HR) of HIV-2 infected children was 3.9 (CI, 1.2–12) compared to children of HIV uninfected mothers ($P = 0.02$). The mortality HR of HIV-1 infected children was 3.1 (CI, 0.87–11) times that of HIV-2 infected children, but this was not significant ($P = 0.08$). Fig. 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.

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 HR 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-

Table 1. Survival and mortality hazard ratios of children by mother's and child's HIV status, the Gambia 1993–2001.

	Mother's HIV status					
	HIV-1		HIV-2		Negative	
	HIV-1	Negative	HIV-2	Negative	Unknown ^a	Negative
Live-born children	17	64	8	194	26	448
Died (%)	12 (71%)	10 (16%)	3 (38%)	21 (11%)	11 (42%)	40 (9%)
Lost during follow-up (%)	2 (12%)	10 (16%)	0 (0%)	49 (25%)	8 (31%)	108 (24%)
Infant mortality ratio (95% CI)	235 (68–499)	16 (0.4–84)	0 (0–369)	31 (11–66)	54 (35–79)	93% (90–95)
2-Year survival (95% CI)	59% (33–82%)	93% (83–97%)	100% (63–100%)	96% (93–98%)	93% (90–95)	91% (88–93)
5-Year survival (95% CI)	21% (5–44%)	86% (73–93%)	63% (23–86%)	89% (83–93%)	91% (88–93)	1 (reference)
Mortality hazard ratio (95% CI)	9.9 (5.2–19)	1.6 (0.81–3.3)	3.9 (1.2–12)	1.2 (0.70–2.0)	1 (reference)	–
Log rank test for difference in survival compared to reference group	< 0.0005	0.18	0.02	0.5	–	–
Mortality hazard ratio conditional on survival to 4 months (95% CI)	19 (9.3–38)	2.7 (1.3–5.6)	6.3 (1.9–21)	2.0 (1.1–3.6)	1 (reference)	–
Mortality hazard ratio conditional on survival to 18 months (95% CI)	22 (9.5–53)	3.6 (1.6–8.1)	9.3 (2.7–32)	2.2 (1.1–4.4)	1 (reference)	–

^aChildren with unknown HIV status died or were lost to follow-up before a first blood sample could be obtained. CI, Confidence interval.

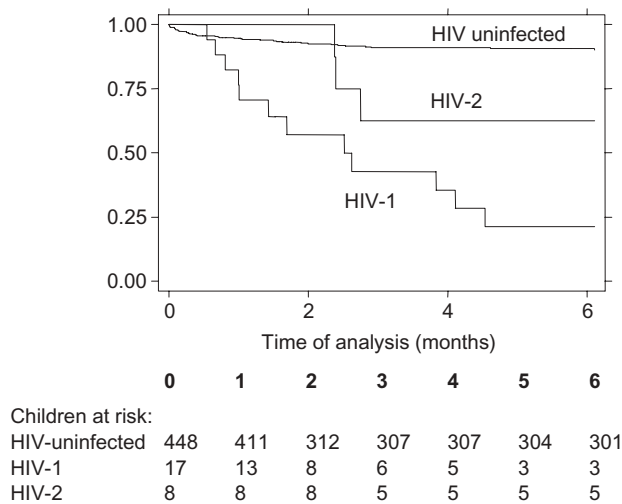


Figure 1. Kaplan-Meier graph comparing survival of HIV-1 infected and HIV-2 infected children, and of children of HIV uninfected mothers. (The Gambia 1993–2001).

fold (CI, 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 4 months, the mortality hazards of these children were significantly higher ($P=0.009$ and $P=0.02$, respectively). The mortality of children whose mothers died during the study was 6.9-fold (CI, 4.3–11) that of children whose mothers survived ($P<0.0005$). This was independent of the mother’s HIV status.

Proviral load was available for 11 of 17 HIV-1 infected children; each \log_{10} increase of proviral load (DNA copies per 100 000 peripheral blood mononuclear cells) in the infant was associated with a 1.5 rise (CI, 0.89–2.5) in mortality HR ($P=0.13$). In HIV-2 children there were only four proviral loads done, and no associations were estimated.

None of the following variables were associated with mortality HR in HIV-1 or HIV-2 infected children: maternal antenatal or postnatal CD4 percentage, 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

Table 2. Characteristics of eight perinatally infected HIV-2 infected children, The Gambia, 1993–2001.

Child study number	Sex	Earliest recorded weight (kg) ^a	Survival status	Age (years) ^b	Proviral load ^c	Antenatal CD4% of mother	Post-partum CD4% of mother	\log_{10} antenatal plasma viral load of mother ^d	Survival status of mother	Child healthy at time of last visit
1366591	M	n.a	Dead	2.4	111	37	20	2.7	Alive	n.a.
1456861	M	2.0	Dead	2.4	–	12	6	2.4	Alive ^e	n.a.
1320521	M	3.0	Dead	2.7	26	14	19	4.6	Alive ^f	n.a.
1429611	F	2.8	Alive	6.8	130	40	27	4.2	Dead	Y
1425001	M	3.7	Alive	7.0	–	46	39	4.8	Alive	Y
1215851	F	3.4	Alive	7.2	1000	22	50	4.2	Alive	Y
1012021	M	3.8	Alive	7.7	–	32	35	3.4	Alive	Y
1010821	F	4.1	Alive	7.8	–	55	54	2.4	Alive	Y

^aWeight was recorded a median of 1 day (range, 0–16 days) after birth. ^bAge at date of death or date last known to be alive. ^cDNA copies per 100 000 peripheral blood mononuclear cells. ^d \log_{10} RNA copies/ml. ^eMother died 4 years after the child had died. ^fMother died 3 months after the child had died. M, Male; F, female; n.a., not applicable; Y, yes; N, no.

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 five out of eight of the children were still alive.

The rate of loss to follow-up was limited with 4.6 per 100 person years of observation. The observed fourfold 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 mothers, and 19 children born to HIV-2 mothers died or were 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 HR higher than we estimated. In order to obtain unbiased estimates, HR 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 and if they do transmit their babies are at increased risk of early death. HIV-2 infected children need ART and may also 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 plasma viral load, CD4 cell 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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