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INFECTIOUS DISEASE

Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa

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Background Previously, HIV epidemic models have used a double Weibull curve to represent high initial and late mortality of HIV-infected children, without distinguishing timing of infection (peri- or post-natally). With more data on timing of infection, which may be associated with disease progression, a separate representation of children infected early and late was proposed.

Methods Paediatric survival post-HIV infection without anti-retroviral treatment was calculated using pooled data from 12 studies with known timing of HIV infection. Children were grouped into perinatally or post-natally infected. Net mortality was calculated using cause-deleted life tables to give survival as if HIV was the only competing cause of death. To extend the curve beyond the available data, children surviving beyond 2.5 years post infection were assumed to have the same survival as young adults. Double Weibull curves were fitted to both extended survival curves to represent survival of children infected perinatally or through breastfeeding.

Results Those children infected perinatally had a much higher risk of dying than those infected through breastfeeding, even allowing for background mortality. The final-fitted double Weibull curves gave 75% survival at 5 months after infection for perinatally infected, and 1.1 years for post-natally infected children. An estimated 25% of the early infected children would still be alive at 10.6 years compared with 16.9 years for those infected through breastfeeding.

Conclusions The increase in available data has enabled separation of child mortality patterns by timing of infection allowing improvement and more flexibility in modelling of paediatric HIV infection and survival.

Keywords HIV, survival, paediatric

Introduction

Until recently, survival of HIV-infected children in the absence of causes of death unrelated to HIV has been modelled using a double Weibull curve that represents the mortality experienced by HIV-infected children irrespective of their time of infection from birth.[1,2] The double Weibull curve has been used as it is one of the few functional forms that can describe high initial mortality along with rising mortality at older ages. However, in a pooled analysis, Newell *et al*.[3] showed that mortality in the 2 years following infection was lower for children who acquired HIV via breastfeeding (post-natal infection) than those with perinatal infection.[3] To improve modelling of the HIV epidemic, a separate representation of children infected early and late was thus deemed appropriate. Indeed, new data have become available from clinical trials that provide information on HIV status of children from birth and allow an accurate estimation of age at infection and sufficient follow-up time to allow assessment of the risk of dying. These data are in accordance with the differences shown by Newell *et al*.[4]

It has been suggested that the impact of age at infection may be due to background mortality patterns.[5] Removing background mortality did have a slightly larger effect in those infected at older ages where background mortality is higher but it did not explain the differences in survival from age at infection in adults. However, such effects are more extreme in childhood where the differences between neonatal and post-neonatal mortality are much greater than the differences in mortality rates in adults within 1 month or 1–12 months after infection. Therefore, some of the differences in time since infection shown by Newell *et al*.[3] might be attributable to background mortality in the neonatal period.

This article investigates the effect of background mortality on survival post infection of children by time of infection for up to 2.5 years following acquisition of infection. In order to bridge the gap in the data between children and young adults, survival curves are further extended beyond the available data by using survival of young adults and model curves fitted to the net survival of each of these groups for use in HIV modelling.

Methods

Data

Data from 12 clinical trials and cohort studies in Southern, Eastern and Western Africa (Table 1) were included in a pooled analysis where all the data were combined into the same data set. Interventions in these studies were various peripartum anti-retroviral prophylactic regimens,[6–14] vitamin A[15] and birth canal cleansing.[16] These trials represent the vast majority of the clinical research studies performed since the mid-90s on the African continent on prevention of mother-to-child transmission of HIV. Most study sites ($n = 8$) were situated in reference hospitals of capital or large cities; three studies were based in antenatal care clinics, or a mixture of the two, and one in a mixture of both urban and rural settings. The ZVITAMBO study accounted for 51% of the person-years of exposure for HIV-infected children. The median follow-up time ranged from 300 to 1096 days, and studies tested at regular intervals in the first 18 months. Some studies explicitly stated that they provided free medical treatment at time of follow-up and in between follow-up visits.

Inclusion criteria

Data collected in time periods when anti-retroviral treatment was widely available cannot be used in the analysis as they would not represent the survival from HIV per se. However, it would be incorrect to censor children at time of treatment initiation as this would mean we were selecting out those who were going to die thereby biasing the results to give much lower mortality. Anti-retroviral treatment became available in the MASHI trial on 1 October 2002 so follow-up was rightly censored at this point. Anti-retroviral treatment was not available during the time of the other trials.

Mortality analysis

Date of infection was taken to be the midpoint between the last negative test and the first positive HIV test (antibody or PCR depending on age). Where there was no negative test for those infected early, the midpoint between birth and first positive test was taken. A sensitivity analysis was undertaken to assess how results varied according to the date imputed.

Children were grouped by infection status (infected and uninfected) and time of infection (perinatal,

Table 1 Summary of trials in the analysis with ART interventions for individual site analysis, numbers are for children of HIV-positive mothers, number of deaths are in brackets

Trial	Arm	Mother PMTCT	Child PMTCT[a]	Total	Uninfected	Infection status			HIV status unknown/ indeterminant
						Early	Late	Unknown	
ANRS 049a (7)	ANRSA_N2	None	None	78 (22)	55 (4)	15 (14)	2 (1)	5 (2)	1 (1)
	ANRSA_N3	None	None	123 (30)	79 (4)	11 (9)	7 (2)	11 (6)	15 (9)
	ANRSA_T2	ZDV	None	77 (11)	59 (3)	6 (3)	5 (0)	3 (3)	4 (2)
	ANRSA_T3	ZDV	None	123 (25)	88 (3)	6 (6)	8 (4)	10 (5)	11 (7)
ANRS 049b (16)	ANRSB_N	None	None	51 (11)	36 (2)	0 (0)	2 (1)	4 (3)	9 (5)
	ANRSB_T1	None	None	53 (15)	35 (2)	1 (1)	3 (1)	4 (4)	10 (7)
ANRS 12010 Ditrame Plus (13)	Diatrame Plus	ZDV + NVP or CBV + NVP	ZDV + NVP	747 (79)	689 (54)	40 (20)	18(5)	0 (0)	0 (0)
Good Start (9)	Paarl	NVP	sdNVP	149 (7)	107 (0)	12 (4)	3 (0)	6 (2)	21 (1)
	Rietvlei	NVP	sdNVP	192 (34)	80 (0)	23 (13)	8 (0)	11 (1)	70 (20)
	Umlazi	NVP	sdNVP	324 (26)	184 (0)	33 (10)	12 (0)	14 (3)	81 (13)
MASHI (12)	MASHI_0	CBV + NVP, ZDV, ZDV + sdNVP	ZDV + sdNVP	600 (42)	551 (30)	26 (9)	11 (3)	4 (0)	8 (0)
	MASHI_1	CBV + NVP, ZDV, ZDV + sdN	ZDV + sdNVP	600 (43)	541 (33)	30 (8)	16 (2)	0 (0)	13 (0)
MB (17)	MB_N	None	None	197 (45)	132 (15)	27 (16)	19 (2)	13 (7)	6 (5)
MITRA Plus (10)	MITRA Plus	ZDV + 3TC + NVP	ZDV + 3TC	441 (35)	415 (26)	16 (6)	8 (2)	2 (1)	0(0)
PETRA (11)	PETRA_A	ZDV/3TC	ZDV/3TC	366 (37)	301 (12)	11 (4)	28 (10)	13 (6)	13 (5)
	PETRA_B	ZDV/3TC	ZDV/3TC	371 (52)	294 (21)	24 (8)	21 (9)	14 (8)	18 (6)
	PETRA_C	ZDV/3TC	None	368 (47)	286 (15)	37 (14)	20 (4)	10 (5)	15 (9)
	PETRA_D	None	None	353 (48)	264 (11)	38 (17)	18 (2)	19 (11)	14 (7)
RETRO (14)	RETRO_N	None	None	133 (29)	86 (4)	26 (11)	10 (4)	2 (1)	9 (9)
	RETRO_T1	ZDV	None	128 (10)	96 (1)	15 (8)	13 (0)	2 (0)	2 (1)
VITA (15)	VITA_N	None	None	325 (23)	239 (5)	58 (14)	8 (1)	4 (0)	16 (3)
	VITA_T1	None	None	335 (26)	245 (6)	53 (15)	14 (2)	6 (1)	17 (2)
VTS (6)	VTS	NVP	sdNVP	1422 (198)	979 (40)	127 (77)	70 (20)	52 (29)	194 (32)
Zvitambo (8)	Zvitambo	None	None	4495 (881)	3115 (251)	727 (427)	257 (46)	355 (152)	41 (5)

[a]Up to 7 days post-partum. ART, anti-retroviral therapy; CBV, Combivir (ZDV + 3TC); NVP, nevirapine; sdNVP, single-dose NVP; ZDV, zidovudine.

breastfeeding or post-natal period, status unknown) as defined by Newell *et al*.[3] Those with unknown timing of infection were not used in the analysis beyond looking at their overall mortality compared with those with known timing of infection. Kaplan–Meier analysis was used to calculate survival curves. Uninfected children of positive mothers were used to estimate mortality from non-HIV-related causes when calculating net survival.

Prior to decisions on pooling data on the effect on the mortality hazards of the child receiving anti-retroviral drugs in the first 7 days of life for PMTCT post-exposure prophylaxis and possible regional differences, a piece-wise Weibull model was constructed adjusting for duration of follow-up (to allow for changing composition due to differing follow-up times across studies) and study of origin to assess whether data should be excluded or analysed separately.

Calculating net survival

Methods to calculate paediatric survival have been described in detail elsewhere.[1] In brief, the net survival probability, $l_A(x)$, if HIV-related mortality is the only operative cause of death, can be calculated from the proportions of HIV-infected children surviving to age x, $l_{O+A}(x)$, and the proportion of uninfected children surviving to age x, $l_O(x)$, using the usual relationship for cause-deleted life tables:

$$l_A(x) = \frac{l_{O+A}(x)}{l_O(x)}$$

To make the distribution of the HIV-negative children similar to that of the HIV-infected children, the HIV-negative ones were weighted so that their distribution by entry into observation, study group and timing of start of risk exposure matched those of the HIV-infected children.

Newell *et al*. showed that infected infants experience different rates of progression through the disease stages leading to AIDS and death, with those who acquired the infection *in utero* experiencing a more rapid progression than those acquiring the infection around the time of delivery or during breastfeeding.

As noted, the double Weibull provides a good functional representation of paediatric survival curve as it allows for initial high mortality followed by rising mortality at later time points,[1,18] taking the form:

$$l_A(x) = \pi \cdot \exp\left\{-[\lambda_1 \cdot x]^{\mu_1}\right\} + (1-\pi) \cdot \exp\left\{-[\lambda_2 \cdot x]^{\mu_2}\right\}$$

By studying the empirical curves depicting net survival by time since infection we produce two functional representations: one for those with perinatal infection and one for those with infection through breastfeeding.

External constraints were introduced to extend the curve beyond the follow-up time provided by the studies, and these data were used until 20 subjects were remaining, which was deemed as a point at which the results could not be seen as reliable due to small numbers. Recently, a pooled study has been published[5,19] showing survival post infection in adults by age of infection using data from low- and middle-income countries. This showed a more favourable survival for those adults infected at a younger age, and similar results were found in studies from higher-income countries in the pre-ART era.[20] A reasonable assumption we could thus consider is that the net HIV mortality rates of infected children at long durations of infection are no higher than the rates experienced by HIV-infected young adults below age 25 years. The net survival of adults from HIV is described by the single Weibull curve:

$$l_A(x) = \exp[-\lambda \cdot x^{\mu}]$$

Results

A total of 1930 infected children with known timing of infection were included in the analysis, contributing 1576 person years of follow-up. The median age at last follow-up or death was 1.0 years (range: fraction of a day to 4.39 years) for infected children and 1.49 years (range: fraction of a day to 11.39 years)

Table 2 Follow-up and outcome by child's HIV infection status and timing of infection

	Number at start	Total person-years	Deaths	Follow-up in years	
				Median	Maximum
Infected					
Perinatally	1340	1095.38	699	0.64	4.39
Through breastfeeding	590	480.66	120	0.65	4.17
Timing unknown	615	590.34	254	0.86	3.77
Uninfected					
Mother positive	8384	11 457.84	493	1.49	11.39
Mother negative	1584	2633.18	51	1.83	4.48
Unknown infection status					
Mother positive	9484	11 296.43	250	1.02	3.28

for uninfected children of HIV-positive mothers. Of the 1930 infected children, timing of infection was considered early for 1340, late for 590 and unknown for 615 (Table 2).

Figure 1 shows the cumulative survival of these children by timing of infection. Median age of survival was 348 days for those infected perinatally, but was not reached by 2.0 years when only 20 subjects remained for those infected through breastfeeding, and therefore could not be calculated. The survival of children for whom the mode of infection was unknown was intermediate, suggesting that this category was made up of children infected perinatally and through breastfeeding. The mortality hazard of those children infected through breastfeeding was 0.39 [95% confidence interval (CI) 0.32–0.46], lower than for those infected perinatally. The mortality data of uninfected children which are used to compute non-HIV-related mortality risks for those infected perinatally, showed, as expected, higher mortality and worse survival than those of the uninfected children used to compute the equivalent risks for those infected through breastfeeding. Mortality of uninfected children included in these trials was very low with an overall infant mortality rate of 4 per 1000, i.e. lower than in most sub-Saharan African populations generally. Changing the imputed infection date for early infection to be birth for children who only had a positive, and no negative, test had almost no effect on the results. This is also true of the later infected children, assuming the date of infection to be the earliest possible date (last negative test) or the latest possible date (first positive test) date.

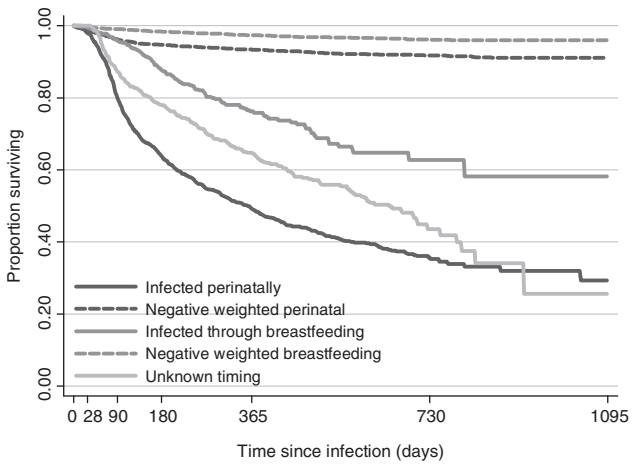

Figure 1 Survival from time of infection by timing of HIV infection and weighted survival of uninfected children

Differentials by region and peripartum anti-retroviral treatment

Differences in survival by region and whether the child received peripartum anti-retroviral intervention in the first 7 days of life were assessed using piece-wise Weibull models; these were adjusted for study. After adjusting for study, no mortality differences were seen across the regions or between children who received peripartum preventative anti-retroviral treatment in the first 7 days of life (Table 3).

Timing of late infection

The late infection group was split further into four groups. A Weibull piece-wise model adjusting for duration of follow-up and trial showed a decrease in the gross mortality the later the child is infected (Table 4). Figure 2 shows the increasing improvement in survival with later age at infection.

Net survival

Removing all other causes of mortality to give survival as if HIV was the only cause of death only slightly raised survival for both those infected perinatally or through breastfeeding (Figure 3). The resulting net survival at 1 year post infection for those infected perinatally was 52% and for those infected through breastfeeding 78% (Table 5).

Table 3 Hazard ratios (HR) of survival for HIV Infection perinatally and through breastfeeding

	Perinatal infection		Infection through breastfeeding	
	Adjusted for duration of follow-up HR (95% CI)	Adjusted for duration of follow-up and study HR (95% CI)	Adjusted for duration of follow-up HR (95% CI)	Adjusted for duration of follow-up and study HR (95% CI)
Region				
Eastern Africa	1	1	1	1
Southern Africa	1.60 (1.19–2.16)**	1.54 (0.85–2.82)	0.69 (0.44–1.08)	0.59 (0.20–1.73)
Western Africa	1.39 (0.96–2.01)	1.67 (0.21–13.03)	0.87 (0.44–1.74)	2.19 (0.37–12.92)
Child PMTCT ARV				
No	1	1	1	1
Yes	1.22 (1.00–1.49)*	1.20 (0.62–2.34)	0.69 (0.47–1.00)*	0.41 (0.16–1.02)

*$P < 0.05$; **$P < 0.01$. ARV, antiretroviral prophylaxis.

Extending the observed net curve

Weibull curves were fitted to the net survival of adults post infection in East Africa by age at infection which gave a median time of survival of 20 years for 15- to 24-year olds ($\lambda = 0.002$; $\mu = 2.195$) decreasing to 14 years for ages 35–44 years ($\lambda = 0.025$, $\mu = 1.532$).[5] Assuming that children who survive for 2.5 years following perinatal infection and 2 years following infection through breastfeeding (the maximum follow-up time with greater than 20 subjects remaining) do not have a worse survival than young adults at the equivalent time post infection, the net curve was extended using the probabilities of dying between years since infection x and x+1 for adults at the same point in time. Double Weibull curves were then fitted to the extended net survival (Figure 4).

Table 6 gives a summary of the curve fits to the extended net survival. The final double Weibull curves give a median survival at 1.1 years for perinatal infection and 9.4 years for infection through breastfeeding. This predicts a survival of 33% at 5 years from time of infection for those infected perinatally and 60% for those infected through breastfeeding. At 20 years, this is 9% and 16%, respectively.

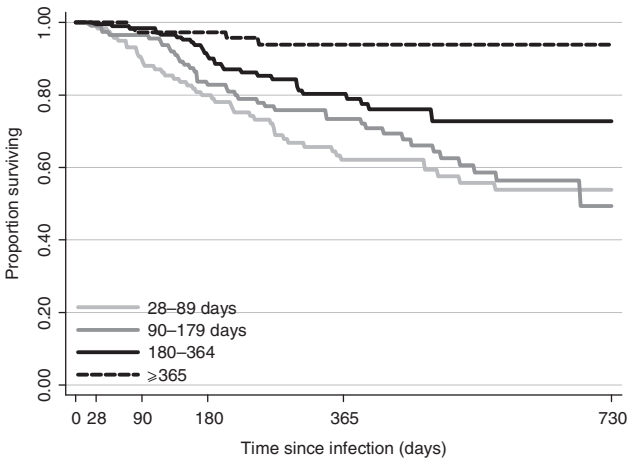

Figure 2 Survival from time of infection by age at infection for those infected through breastfeeding

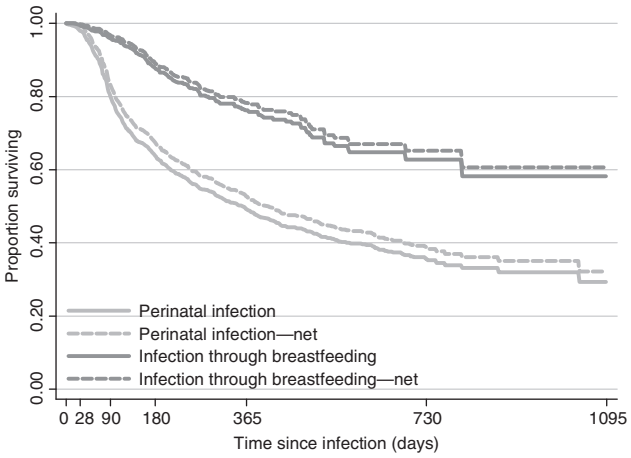

Figure 3 Net and gross survival from time since infection for infection perinatally and through breastfeeding

Discussion

The current analysis produced separate survival schedules for children infected perinatally and those infected through breastfeeding, with a median survival of 1.1 and 9.4 years, respectively. The use of these updated schedules in mathematical modelling of the HIV epidemic among children is expected to constitute a major improvement over the past approach with a unique survival schedule applied to all children. This has extended work done by Newell *et al*. suggesting a possible mortality difference by timing of vertical infection by adding new data that have become available and extending the survival curves using the net survival of young adults from HIV. The differences in survival are substantial at 5 years after infection, with only 33% of those infected perinatally surviving compared with 60% of those infected through breastfeeding. At 20 years after infection the difference is smaller at 16% compared with 9%; this is mainly because in the absence of evidence to suggest that either one should be higher we have applied the same mortality schedule to both groups after 2.5 years.

The analysis further shows that there are also differences in survival within those who are infected through breastfeeding with a more favourable survival

Table 4 HRs for those with late HIV infection

	Adjusted for duration of follow-up and trial
	HR (95% CI)
Region	
Eastern Africa	1
Southern Africa	0.57 (0.2–1.67)
Western Africa	2.48 (0.42–14.78)
Peripartum ARV	
No	1
Yes	0.4 (0.16–1.01)
Age at infection (days)	
28–90	1
90–180	0.81 (0.52–1.27)
180–365	0.53 (0.33–0.85)**
⩾365	0.16 (0.06–0.42)***

**$P < 0.01$; ***$P < 0.001$.

the later the time of infection, and these differences still persisted after taking into account background mortality.

We found no difference between the survival of those HIV-infected infants treated and not treated with peripartum anti-retrovirals to prevent mother-to-child transmission and therefore included these children in the analysis. We do not question the effectiveness of PMTCT interventions to reduce the risk of transmission of HIV. However, our data suggest that where an infant acquires infection in spite of PMTCT exposure, mortality levels are similar to those infants infected without exposure to PMTCT. Regional differences in survival by timing of infection were not seen once heterogeneity between trials was accounted for; therefore, with these current data we pooled data from all regions into the same data set to generate one curve to represent all children. These data are only from sub-Saharan Africa with 51% of the person-years of exposure coming from the ZVITAMBO trial in Zimbabwe.[8] Regional differentials between sub-Saharan Africa and Thailand were seen in adults;[19] therefore, adding data from other regions would help confirm whether such differences exist for the mortality of HIV-positive children, although we acknowledge that fewer HIV-exposed children are breastfed in Asia or South America than in sub-Saharan Africa.

Although breastfeeding is an important factor in child survival,[21] we have not excluded those who were never breastfed. Without knowing the breastfeeding trends in the general population we cannot tell how representative this sample is. Even if we had excluded this 12% from this analysis, the impact on the overall highly unfavourable survival curve would be minimal.

Background mortality had very little effect on the differences in survival post-infection for both early

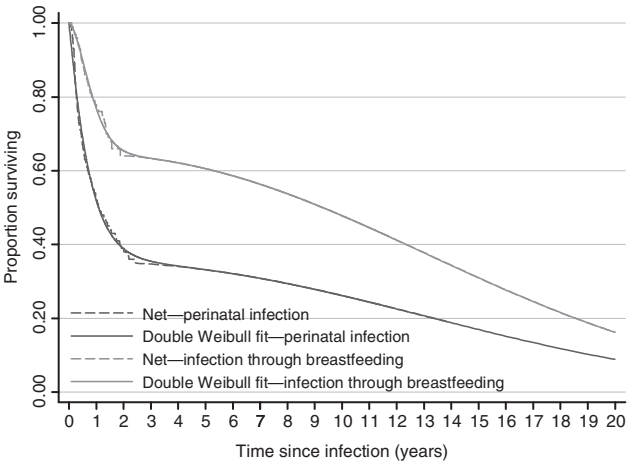

Figure 4 Double Weibull curves fitted to extended net survival functions for early and late HIV infection. Curves were fitted using the net probability of survival of adults age 15–24 years after 2.5 years of follow-up for perinatal infection and 2.0 years for those infected through breastfeeding

Table 5 Probability of survival for HIV-infected children and uninfected children to time × by timing of infection

	Time×							
	1 day	7 days	28 days	90 days	180 days	1 year	2 years	2.5 years
Perinatal infection								
Uninfected (weighted)	1	1	0.99	0.96	0.95	0.93	0.92	0.91
Infected	1	1	0.98	0.80	0.64	0.49	0.35	0.32
Net survival	1	1	0.99	0.83	0.67	0.52	0.39	0.35
Net Weibull	0.99	0.96	0.9	0.79	0.69	0.54	0.37	0.32
Infection through breastfeeding								
Uninfected (weighted)	1	1	1	0.99	0.98	0.97	0.96	0.96
Infected	1	1	0.99	0.96	0.88	0.76	0.62	0.58
Net survival	1	1	1	0.97	0.89	0.78	0.64	0.60
Net Weibull	1	0.99	0.98	0.94	0.89	0.79	0.63	0.56

Table 6 Summary of curve fits to the extended net survival (using adult survival) for those infected with HIV perinatally and through breastfeeding from time of infection

	Parameters					**Percentiles**			**Net mortality risks (per thousand)**	
Time of infection	π	λ_1	μ_1	λ_2	μ_2	75%	50%	25%	1q0	5q0
Perinatal	0.65	1.34	1.06	0.06	2.19	0.38	1.09	10.61	481	626
Breastfeeding	0.35	1.03	1.66	0.06	2.19	1.09	9.24	16.91	232	396

and late infection. All the data come from clinical trials or research studies within which background mortality, taken from the uninfected children of infected mothers, apparently was much lower than in the corresponding communities. The overall HIV-negative infant mortality rate in the current analysis was 4 per 1000. The Demographic and Health Surveys[22] give infant mortality rates in the 10 years preceding each survey. Estimates for urban areas ranged from 41 in South Africa 2003 to 72 in Tanzania in 2004–05, all indicating a much higher mortality in the general population in many of the places the trials took place. The difference is evident even if we allow for the fact that the DHS figure includes the mortality of HIV-infected children and that the studies mainly took place at the later end of these periods (i.e. if infant mortality decreases over time we would expect a lower mortality rate in the trial). It strongly suggests that the mortality of uninfected children involved in the trials is lower than that in the general population, possibly due to increased access to healthcare services due to study participation; therefore, in the general population one might expect to see a larger difference between net and gross mortality.

We have used the mortality of HIV-negative children of positive mothers as a reference in this analysis. Therefore the resulting net mortality does not take into account the added negative effect of having an HIV-positive mother. There is evidence to suggest that there is a difference in the mortality of HIV-negative children born to HIV-positive mothers compared with HIV-negative mothers. The Rakai study[23] found that overall, for those <2 years of age, $C(x<2)=1.3$, where $C(x)$ is the ratio between uninfected children of infected mothers compared with those of uninfected mothers at age x, but there was some evidence of variation of $C(x)$ with age, with $C(x<1)=1.1$, and $C(1<x<2)=1.8$. A study in Kampala[24] showed a similar pattern with the same overall value for $C(x<2)=1.3$ and a similar increase with age on subdivision of the interval.

The model curves beyond 2.5 years rely on what is known about adult survival and assume that children are like younger adults with respect to mortality patterns. Further investigation is needed about whether this is a valid assumption, especially for children infected early. The inclusion of more data from other trials might increase our knowledge of net child survival beyond 2.5 years and give a more accurate picture and more knowledge on how child survival compares with young adult survival. However these data are currently scarce and with the increase in antiretroviral treatment in children it is unlikely that any further data will become available. It is possible that data on time to treatment need and time to death from treatment by timing of infection might help inform us further.

The aim of this analysis was to improve modelling of the HIV epidemic by providing a separate representation of children infected perinatally and through breastfeeding. This analysis is an update on work done previously[1,2] and has used more detailed data from studies that can provide the timing of HIV infection of a child.

The increase in data available and the construction of separate survival curves for children infected perinatally and through breastfeeding allow for a clear improvement in the modelling of the HIV epidemic and is being used in the UNAIDS spectrum package to project the HIV epidemic.[25]

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Conflict of interest: None declared.

KEY MESSAGES

- Children infected perinatally with HIV have a much higher risk of dying than those infected through breastfeeding.
- Differences seen in the survival of children infected perinatally with HIV and through breastfeeding cannot be explained by differences in background mortality, which is much higher in the neonatal period.
- The use of two separate curves to describe the net survival from perinatal and breastfeeding HIV infection improves the realism of child survival when modelling the HIV epidemic.

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Appendix 1

Composition of the UNAIDS Child survival group.

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