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Treating HIV infected mothers reduces mortality in children under 5 years of age to levels seen in children of HIV uninfected mothers: evidence from rural South Africa

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Abstract

Background—Maternal and child survival are highly correlated, but the contribution of HIV infection on this relationship, and in particular the impact of HIV treatment has not been quantified. We estimate the association between maternal HIV and treatment and under-5 child mortality in a rural population in South Africa.

Methods—All children born between January 2000-January 2007 in the Africa Centre Demographic Surveillance Area were included. Maternal HIV status information was available from HIV surveillance; maternal antiretroviral treatment (ART) from the HIV Treatment Programme database and linked to surveillance data. Mortality rates were computed as deaths per 1000 person-years observed. Time-varying maternal HIV effect (positive, negative, ART) on U5MR was assessed in Cox regression, adjusting for other factors associated with under-5 mortality.

Results—9,068 mothers delivered 12,052 children, of whom 947 (7.9%) died before age 5. Infant mortality rate (IMR) declined by 49% from 69.0 in 2000 to 35.5 in 2006 deaths per 1000 person-years observed; a significantly decline was observed post-ART (2004-2006). The estimated proportion of deaths across all age groups were higher among the children born to the HIV-positive and HIV-not reported status women than among children of HIV-negative women. Multivariably, mortality in children of mothers on ART was not significantly different from children of HIV-negative mothers (aHR 1.29, 0.53-3.17; p=0.572).

Conclusions—These findings highlight the importance of maternal HIV treatment with direct benefits of improved survival among all children under-5. Timely HIV treatment for eligible women is required to benefit both mothers and children.

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Authors' contributions

J.N. was responsible for overall statistical analysis and writing of the first draft of the paper; M-L.N. originally suggested the idea of linking surveillance and ARTemis data and provided oversight of the analysis approach and writing of the paper; C.T. gave constructive comments during writing; R.B. gave constructive comments during analysis and writing of the paper and all authors substantially contributed to, and approved, the final manuscript.

Disclosure statement

We declare that we have no conflict of interest.

Introduction

Maternal HIV infection affects child mortality directly through mother-to-child transmission or indirectly through maternal ill-health [1-4]. A mother's death has a negative impact on child health, even in the absence of transmission to the child; uninfected children of infected mothers may be more likely to be orphaned and thus be at higher risk of child mortality than children brought up by their own mothers [5-7].

Sub-Saharan Africa is the most heavily HIV-affected region in the world, with 67% of global new HIV infections in 2008, and 72% of AIDS-related deaths [8]. In South Africa, home to the world's largest population of people living with HIV (5.7 million), child mortality rates have continued to increase since 1990, coinciding with the rapid rise in HIV prevalence in pregnant women from 1% in 1990 to more than 29% in 2008 [9, 10]. South Africa will fall short of achieving Millennium Development Goal 4 (MDG4) to reduce under-5 mortality by two-thirds from baseline 60 deaths per 1000 live-births by year 2015 [11].

Antiretroviral therapy (ART), which substantially delays HIV disease progression, is contributing to a decline in adult HIV-related mortality at a population level [12, 13]. Recent evidence suggests that declining early child mortality at a population level is similarly associated with expanding HIV treatment services [14]; in an earlier study in this rural area we estimated that the effect of maternal ART provision was greater than the impact of programmes delivering single-dose nevirapine (sdNVP) to prevent mother-to-child transmission, presumably because survival of infected mothers benefits both infected and uninfected children [14]. However, the association between survival of HIV infected mothers on ART and child survival at an individual level remains unquantified.

We investigated under-5 mortality in a largely rural population of KwaZulu-Natal, South Africa, with high HIV prevalence [15, 16], and quantify the association between maternal survival and child mortality, through linkage of mother and child records from demographic surveillance and an HIV treatment programme.

Methods

The Africa Centre Demographic Surveillance Area (DSA), Umkhanyakude district, northern KwaZulu-Natal, covers 438 km² and nearly 90,000 Zulu-speaking people, including 22,600 women of child-bearing age, in 11,000 households. The area is predominantly rural; the main sources of income are waged employment and state pensions [17].

Since 2000, data including births, deaths, migration, and vaccination history are supplied by a key informant on all resident and non-resident household members during bi-annual household visits [18]. Further, since 2003, annual HIV surveillance documents the HIV status of consenting resident women aged 15-49 years and men aged 15-54 years [19]. Written informed consent allowing use of routine data was obtained from all participants. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

All children born between 1 January 2000 and 1 January 2007 (to allow at least 3 years of observation for children born post-2004 and for mothers of children born pre-2004 to have initiated ART before their children turned 5 years) to women enrolled in the Africa Centre surveillance were included. Twin births are at increased mortality risk [7] as are first born children [20]. We classified pregnancy as singleton or twin and birth order into three groups: first, second/third or fourth/later born. A count of household assets, closest to date of birth, (classified as ≤ 5 or >5) was used to indicate economic household status [21]. Previous child

death and previous fetal death have been associated with increased risk of death of subsequent children [14]; the former was defined as a child death (age <5 years) prior to the birth of index child. Last known maternal vital status at or before end of observation was classified as 'alive', 'dead' or 'unknown'.

The Department of Health Hlabisa HIV Treatment and Care Programme, initiated in late 2004, is supported by the Africa Centre for Health and Population Studies (www.africacentre.ac.za), with funding from PEPFAR. The programme provides free services at the 17 local government primary health care clinics (PHC) [22, 23]; 6 of which are located in the DSA. We used data regarding maternal antiretroviral treatment (ART) from the ARTemis database (an operational database of HIV-infected people on antiretroviral treatment) [22]; independent data were linked to the HIV surveillance data using the national South African identification number, a unique identifier in both datasets, and other identifiers where needed. Ethical approval for this linkage was obtained. Some women have ART information but no HIV surveillance data, as they have accessed treatment but not the surveillance. By end-2006, the last birth date in the cohort, 396 women were initiated on ART, rising to 2,172 by the end of observation [22]. A PMTCT programme was introduced in 2001 and established at all primary health care clinics by end 2002 [24] with sdNVP provided to all HIV-infected women and their infants. In 2007, sdNVP uptake in babies born to infected women was estimated at 54% [25]. The PMTCT programme changed in late-2008 in the district to include Zidovudine (AZT) from 28 weeks of pregnancy. Further changes came into effect from April 2010, when all HIV-infected pregnant women with a CD4 count ≥ 350 cell/mm³ are started on life-long ART, while those not eligible for ART are provided with AZT during pregnancy from 14 weeks [26]. We previously estimated the median duration of exclusive breastfeeding in this setting as 177 (IQR 150-180) and 175 days (IQR 137-180) in HIV-negative and HIV-positive women respectively with exclusive breastfeeding support provided by well trained lay counselors for 6 months [27]. 14.1% of exclusively breastfed infants were infected with HIV by age 6 weeks and 19.5% by 6 months of age [28].

Maternal HIV status based on data from the HIV surveillance was classified into known (to us, from surveillance) negative, not-reported, known positive (including unknown at birth of child but HIV-negative before pregnancy and positive after delivery) and 'On ART (from the HIV Treatment clinical database)' for children whose mothers were initiated on ART within 5 years post-delivery before 31st December 2009. Date of initiation is also recorded. The study included 12 mothers who began HAART before delivery; overall, an estimated maximum 12% of women would have been eligible for ART with a CD4 below the cut-off for eligibility at the time [24].

Statistical methods

Infant and child mortality rates were computed as deaths per 1000 person-years observed. For descriptive analysis, a chi-square test was used for categorical variables and two-sample test of proportions for independent proportions. Survival by age group was estimated by Kaplan-Meier method and Cox regression analysis was used to investigate the effect of maternal HIV status on U5MR, in a time-varying approach, adjusting for factors known to be associated with mortality. Observation time was censored at change of maternal HIV status to 'On ART' and at seroconversion from HIV-negative to positive status reflecting the end of the former category and the start of the latter. For mothers who were on ART since before birth time was set to 0. For variables with missing data, we included 'unknown' as a category in the model to retain overall denominators. For each child, the observation time was taken as time from birth until death within the five years, date of fifth birthday, end of observation (31 December 2009) or date last seen, whichever came first. In multivariable

analysis, all variables with a statistically significant association univariately were included. Goodness of fit of the final models was assessed using the likelihood-based Akaike information criteria (AIC) [29]. Estimated mortality rates were obtained from the predicted survivor function of the Cox regression model. We used Stata (Version 11.0, Stata Corporation, College Station, Texas, USA), which allows the analysis of continuous and time-dependent covariates.

Results

Nine hundred and forty-seven children died before 5 years of age from 12,052 live-births to 9,068 women (Table 1). Total number of child-years' follow-up was 47,482. A total of 307 (3.4%) mothers initiated ART within 5 years post-delivery; 12 (3.9%) women were initiated before delivery (and continued beyond) with median time to delivery of 1.8 months [Interquartile range (IQR) 0.7-10.6]. 193 (7.5%) of 2,591 HIV-positive and 114 (2.3%) of 4,860 'HIV-not reported' mothers initiated ART. 12 (3.9%) of mothers initiated ART within 6 months of delivery, 17 (5.5%) between 6 months and 1 year of age, 55 (17.9%) between 1-2 years, 60 (19.5%) between 2-3 years and 151 (49.2%) initiated between 3-5 years of the child's age. Women who initiated ART were older, more educated, had the index child as their first born, and among those with more than one child, a significantly larger proportion (15.7% vs. 4.7%, $p=0.018$) reported previous history of child death (age <5 years) prior to birth of the index child compared to those not initiated on ART.

Median age of mothers was 24 years (IQR 20-30); most had post primary education. Although only a small percentage (4.2%) of children had mothers who had died, these children had higher mortality than those whose mothers were alive (Table 1). Similarly, mortality rate was higher in children of infected women who never initiated ART than those whose mothers were initiated (Table 1).

Trends in all-cause age-standardized mortality rates are shown in Figure 1. The infant mortality rate (IMR; <12 months) declined by 49% from 69.0 in 2000 to 35.5 in 2006 deaths per 1000 person-years observed. A significant decline in the IMR was observed after roll-out of ART (2004-2006). Mortality in the age group 12-24 months declined by 27% and among the children aged 25-60 months by 60%, from a peak in 2002 to 2006, with slight declines observed in the latter age group after roll-out of ART (Figure 1). Crude mortality rates among children born to HIV-negative mothers remained relatively stable averaging 10.5 deaths per 1000 person-years from 2000 to 2006. Mortality rates among children born to HIV-positive mothers declined by 33% from 53.1 in 2003 (at the start of HIV surveillance) to 35.8 in 2006 deaths per 1000 person-years observed and averaged 41.3 deaths per 1000 person-years over the period. In further Kaplan-Meier survival analysis, we estimate that 3.9% of children of HIV-negative, 11% of HIV-not reported and 12.8% of HIV-positive mothers would have died by 5 years of age (Figure 2).

Overall, the estimated proportion of children dying decreased with increasing child age (Table 2). The estimated proportions of deaths across all age groups were higher among the children born to HIV-positive and HIV-not reported status women than among the children of HIV-negative women.

Factors associated with under-5 mortality

The 12,052 children were followed for a total of 48,396 child-years of follow up; median follow-up time was 3.9 years (IQR 3.1-4.9). Children who died were more likely to have been born at home, born in peri-urban or rural areas, to somewhat older mothers and mothers with primary school education only, and to mothers not initiated on ART (Table 1). In univariate and multivariable analyses of the overall cohort, compared to the relevant

reference categories, children from multiple births were at a significantly increased hazard of death, as were first born children, those born at home, born in peri-urban or rural areas, to mothers between 20 and 30 years old, with primary education only, and with a history of child death (Table 3). Children born in households with fewer assets were at increased hazard of death in unadjusted, but not adjusted analyses. Overall, children whose mothers had died were at a 3-fold increased hazard of death, compared to children whose mothers were alive in both univariate and multivariate analyses.

Children of mothers reported to be HIV infected, at birth or who seroconverted postpartum, or with HIV-not reported status were at four-fold and two-fold respectively significantly increased hazard of dying compared to children of HIV-uninfected mothers in both univariate and multivariate analyses. The mortality in children while their mother was on ART was not significantly different from that of HIV-negative mothers (Table 3).

Additionally, in a separate analysis in children born to HIV-positive mothers only, children whose mothers initiated ART had a significantly reduced hazard of death than children whose mothers did not initiate ART (adjusted hazard ratio 0.32, 95% CI 0.13-0.78; $p=0.012$).

Discussion

We present all-cause age-standardized mortality rates among children in a largely rural South African surveillance site and show significantly declining infant mortality rates after ART roll-out. Slight declines in mortality were observed in the children aged 25-60 months after ART roll-out. The peak in mortality in 2003 in the <12 months group is due to a drop in the number of live-births that year, rather than an increase in the number of deaths, with a net decrease observed in the resident population that year, especially among women [30].

The decline in child mortality occurred despite continuing high HIV incidence and prevalence [16, 17, 19]. The contribution of HIV infection to child mortality has been previously reported, with child mortality rates expected to rise proportionately to the prevalence of HIV [31-34]. It has been suggested that the effect of HIV on child mortality would be more marked in Southern than other parts of Africa because of lower underlying (non HIV) mortality rates [6, 31, 35], which makes the reversal of the trend in child mortality rates despite continued high HIV prevalence and incidence in our study all the more remarkable.

Children born after 2004 will have been observed only for 3-4 years and under-5 mortality for them is thus incompletely assessed in the Cox regression analysis. The declining trend in recent years may be partially explained by this, although given that most under-5 mortality is in the first year of life the extent of this will be limited. Further, as there will have been more women on ART from 2006 onwards [22], the effect of maternal survival associated with ART would have been under-estimated.

Children born to HIV-infected mothers are more vulnerable compared to those of uninfected mothers [3, 20]. We show here that children of women who were HIV infected and not initiated on ART were four times more likely to die than children of uninfected mothers. We also show that women initiated on ART postpartum more likely reported previous child death than those not initiated, indicating vulnerability. Overall, HIV-related adult mortality at a population level declined in the area by 39% between 2003 and 2006 following ART roll out [36]. This, coupled with the decline in estimated proportion of children dying after birth with increasing number of mothers on ART, is in line with a maternal ART effect at an individual level in an area where adult deaths attributable to HIV declined from 83% to 70% after ART roll out [36]. As maternal ART keeps an infected mother alive, there will be an

indirect effect of reducing child mortality in both her infected and uninfected children [14, 36]. Additionally, in a separate analysis, we confirm the effect of maternal survival on child survival, allowing for other factors known to be associated with mortality, with children of infected mothers on ART having a significantly reduced hazard of death than those without ART.

Access to ART could have impacted on household assets, for instance when people in the lower socio-economic status dispose household assets to cover substantial expenditure for health care [37]. However, in this setting with high unemployment, and high HIV prevalence, the impact of HIV on mortality is greater than the impact of household wealth on mortality [14].

Although not all mothers participated in the HIV surveillance, and we thus did not have information on the maternal HIV status during the early years for all children, children of HIV infected mothers, as well as those of not reported HIV status were less likely to die if their mothers were initiated on ART. This, coupled with the fact that children of the HIV-not reported status mothers had high hazards of death, with a similar trend to those of the HIV infected mothers, would suggest that a substantial number of the women in this group were likely to have been HIV-positive during the index pregnancy in this high HIV setting.

We also show that children whose mothers had died were three times more likely to have died than children of surviving mothers, independent of maternal HIV status. A mother's vital status may be associated with child mortality as present mothers may spend more time caring for their children than absent mothers; without the protection of mothers or dependable caregivers, children may be disadvantaged [38]. Further, the effect of maternal survival has been shown to impact on child mortality independent of maternal HIV infection status [2], with the year before and following a mother's death being particularly risky times for their children [39, 40].

We show that one-third of the mothers initiated ART during the breastfeeding period. This, coupled with the high rates of exclusive breastfeeding in the setting account for the relatively low rates of post-natal transmission [25, 27]. Further, mortality risk in children infected through breastfeeding is substantially less than in those infected perinatally [3].

Our results confirm the negative effect of twin births [2, 7] on child mortality as well as first born births [7], rural and peri-urban births [24, 41] and low maternal education [2]. Additionally, our findings draw attention to the importance of place of delivery to the survival of children. We show that children born at home are at significantly increased risk of death compared to those born in a health facility, though this is largely related to the first 2 years of life [42]. Increasing access to care is important in rural areas where a tenth of children are born at home and two-thirds of the population travel an hour or more to the nearest facility [12].

Only a limited number of women known to have been initiated on ART could be linked to the surveillance data, partially because the largest primary health care clinic in the programme is positioned near the edge of the surveillance area and accessed by people not covered by the demographic and HIV surveillance. For instance, of a total of 2,172 women initiated on ART in this clinic, only 774 (35.6%) were linked to the surveillance, 307 (39.7%) of whom met the inclusion criteria of having initiated ART within 5 years post-delivery of the index child. 153 (19.8%) of 774 children died before their HIV infected mothers initiated on ART; median time from child death to mother initiation was 3.6 months (IQR 1.9-5.4). Only 7 (0.9%) of the 774 mothers died after their child had died and before they could be initiated on ART. These 153 children would have been correctly allocated to the mother not on ART group; in the mothers on ART, especially when initiated sometime

after delivery, we may have some selection bias with higher likelihood of child survival as the child would have to survive until that time. As mortality risk declines with age of child, we thus may overall underestimate the potential effect of maternal ART on child mortality. Although we may thus have underestimated the effect of maternal ART, there is no evidence to suggest that people outside of the surveillance area are substantially different from those within. Further, only about half of eligible adults participate in each HIV surveillance round, although for the household surveillance coverage is nearly 100%. [17] Possible reasons for non-consent include survey fatigue and knowledge of HIV status from voluntary counseling and testing in the public health services freely available in the community. Therefore, although we are confident about the reliability of the overall denominator and the number of deaths in either children or mothers, we are less confident about the HIV infection status of all women; hence the inclusion of the not-reported category.

Infants less than one year of age on HIV treatment were rare with only 1 in 2006 and 1 in 2007 [25]. The poor ART coverage of children in this setting due to a number of reasons: firstly, the programme was only started in late-2004 and although there has been rapid scale up of adult initiations [43], the numbers of infants on ART has experienced a slow growth. Further, infant diagnosis remains a problem even now, partly attributable to the slow turnaround of PCR results from the centralized provincial laboratory, lack of information on the antenatal HIV status of the mother on the child's immunization card leading to missed opportunities of identifying HIV exposed children during immunization uptake, poor integration of PMTCT, TB and ART services, and lack of clear HIV testing guidelines for children until very recently.

We lack information on child HIV infection status and individual access to PMTCT could thus not directly be controlled for in our analyses. However, we do have information as to the service delivery at the primary health care clinic level, and know that coverage was not complete and the only PMTCT available was sdNVP which has a limited effect, especially since some infants, for example those born outside health care facilities, may not have received the infant component of this PMTCT [14]. PMTCT, with sdNVP, is estimated to reduce HIV transmission from 20 to 12% [44], and can potentially affect child mortality through reducing the number of infected children. Assuming a 30% HIV prevalence, PMTCT with sdNPV would avoid infection in 2 out of 30 infants born to HIV-positive mothers and thus prevent 2 HIV deaths in these children, although not necessarily in the first five years of life. Treatment of infected children with ART would have kept infected children alive by delaying disease progression [45]. However, very few children were on ART by end-December 2009 [23].

In conclusion, with a functional HIV treatment programme and accurate linkage with longitudinal surveillance data, benefits for survival of children at individual level can be shown. These findings confirm and expand the previous indirect evidence of an association between HIV treatment programme and population early child mortality, and highlight the importance of maternal HIV treatment with direct benefits of improved survival among all their children under-5 years. Therefore, timely introduction of HIV treatment in all eligible women is of utmost importance if further significant reductions in under-5 mortality are expected, which is necessary if MDG4 is to be realised.

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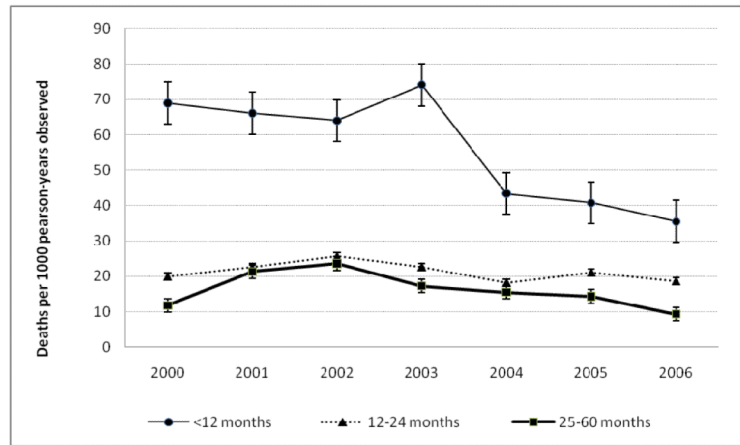


Figure 1. All-cause age-standardized child mortality rates by age group, KwaZulu-Natal, South Africa, 2000-2006

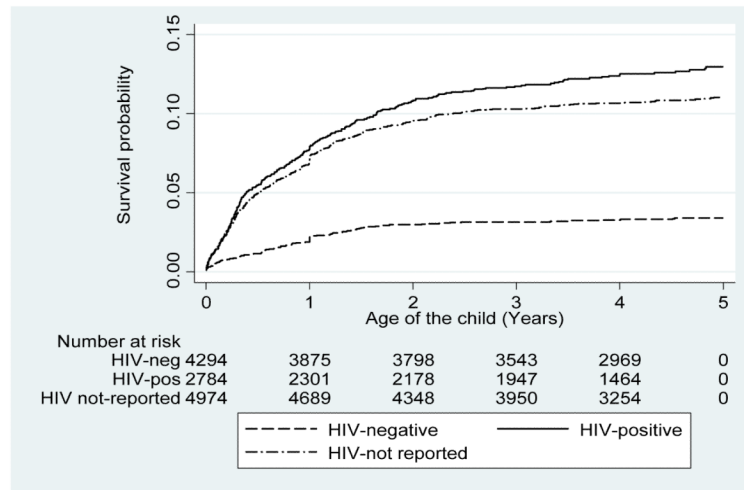


Figure 2. Estimated unadjusted under-5 mortality by maternal HIV status at child birth

Table 1

Distribution of demographic variables and risk factors of children born at ACDIS, 2000-2007

Characteristic	Alive (n=11 105) Number (%)	Dead(n=947) Number (%)	P	Mortality rate per 1000 live births
Sex				
Male	5,501 (49.5)	446 (47.1)		74.9
Female	5,604 (52.8)	501 (52.8)	0.158	82.1
Multipregnancy				
Singleton	10,295 (92.7)	888 (93.8)		79.4
Twin	352 (3.2)	49 (5.2)		122.2
Unknown	458 (4.1)	10 (1.0)	0.006	21.4
Birth order				
First born	4,468 (40.2)	387 (40.9)		79.7
Second/third	3,943 (35.6)	377 (39.8)		87.3
Fourth/later	2,236 (20.1)	173 (18.3)		71.8
Unknown	458 (4.1)	10 (1.0)	<0.001	21.4
Delivery location				
Homestead	1,149 (10.4)	139 (14.7)		107.9
Clinic	2,773 (24.9)	266 (28.1)		87.5
Hospital	5,889 (53.0)	465 (49.1)		73.2
Unknown	1, 294 (11.7)	77 (8.1)	<0.001	56.2
Area of birth				
Rural	6,961 (62.7)	602 (63.6)		79.6
Peri-urban	3,305 (29.8)	314 (33.2)		86.8
Urban	508 (4.6)	29 (3.1)		54.0
Unknown	331 (2.9)	2 (0.2)	<0.001	6.0
Household assets				
<=5	2,001 (18.0)	211 (22.3)		95.4
>5	8,556 (77.1)	718 (75.8)		77.4
Unknown	548 (4.9)	18 (1.9)	<0.001	31.8
Maternal characteristics				
Age (years)				
<20	2,532 (22.8)	179 (18.9)		66.0
20-30	5,243 (47.2)	526 (55.5)		91.2
>30	2,519 (22.7)	203 (21.4)		74.6
Unknown	811 (7.3)	39 (4.1)	0.001	45.9
Education				
At least Primary	2,751 (24.8)	266 (28.1)		88.2
Post primary	7,708 (69.4)	624 (65.9)		74.9
Unknown	646 (5.8)	57 (6.0)	0.065	81.1
Previous Fetal death				
No	10,413 (93.8)	906 (95.7)		80.0
Yes	361 (3.3)	39 (4.1)		97.5

Characteristic	Alive (n=11 105) Number (%)	Dead(n=947) Number (%)	P	Mortality rate per 1000 live births
Unknown	331 (2.9)	2 (0.2)	<0.001	6.0
Previous Child death				
No	10,524 (94.8)	866 (91.5)		76.0
Yes	250 (2.3)	79 (8.3)		240.1
Unknown	331 (2.9)	2 (0.2)	<0.001	6.0
Vital status				
Alive	10,386 (93.5)	788 (83.2)		70.5
Died	367 (3.3)	144 (15.2)		281.8
Unknown	352 (3.2)	15 (1.6)	<0.001	40.8
HIV Status				
HIV-negative	4, 146 (37.3)	148 (15.5)		34.5
HIV-not reported	4,418 (39.8)	442 (46.7)		90.9
HIV-positive	2,242 (20.2)	349 (36.9)		134.7
On ART	299 (2.7)	8 (0.8)	<0.001	26.1

* ACDIS stands for Africa Centre Demographic Information System. P is for the difference between the children who died and those who were alive.

Table 2
 Estimated proportion of children dying by infant age and maternal HIV status at child birth

Group	< 12 months		12-24 months		25-60 months	
	n	Proportion	n	Proportion	n	Proportion
All	601		232		114	
HIV-negative	79	13.14	41	17.67	12	10.52
HIV-not reported	317	52.74	102	43.96	54	47.36
HIV-positive	205	34.10	89	38.36	48	42.10

Table 3

Risk of mortality before age 5 years by maternal and child characteristics

Characteristic	Events/total 947/12,052	Unadjusted	Adjusted	P
		HR (95% CI) P	HR (95% CI)	
Multipregnancy				
Singleton	888/11,183	1.00 1.62 (1.21-2.16)	1.00	
Twin	49/401	0.001 0.31 (0.16-0.57)	1.60 (1.20-2.14)	0.001
Unknown	10/468	<0.001	0.30 (0.09-1.06)	0.057
Birth order				
Second/third	377/4,320	1.00 0.91 (0.79-1.05)	1.00	
First born	387/4,855	0.207 0.81 (0.67-0.97)	1.28 (1.09-1.51)	0.003
Fourth/later	173/2,409	0.020 0.28 (0.15-0.52)	0.85 (0.69-1.06)	0.154
Unknown	10/468	<0.001	-	
Delivery location				
Hospital	465/6,354	1.00 1.21 (1.04-1.40)	1.00	
Primary health Clinic	266/3,039	0.015 1.49 (1.23-1.79)	1.18 (1.01-1.37)	0.035
Homestead	139/1,288	<0.001 0.80 (0.62-1.01)	1.36 (1.12-1.67)	0.002
Unknown	77/1,371	0.065	0.93 (0.72-1.20)	0.523
Area of birth				
Urban	29/537	1.00 1.42 (0.98-2.07)	1.00	
Peri-urban	602/7,563	0.063 1.60 (1.09-2.34)	1.48 (1.01-2.17)	0.043
Rural	314/3,619	0.015 0.13 (0.03-0.55)	1.50 (1.02-2.21)	0.043
Unknown	2/333	0.006	-	
Environmental variables				
Household assets				
>5	718/9,274	1.00 1.24 (1.06-1.44)	1.00	
5	211/2,212	0.007 0.46 (0.29-0.75)	1.10 (0.94-1.29)	0.221
Unknown	18/566	0.220	0.74 (0.44-1.21)	0.216
Birth season				

Characteristic	Events/total 947/12,052	Unadjusted	Adjusted	P
		HR (95% CI) P	HR (95% CI)	
Apr-Sept	470/6,173	1.00 1.15 (1.01-1.30)	1.00	
Oct-Mar	477/5,546	0.037	1.12 (0.99-1.27)	0.080
Mothers characteristics				
Age (years)				
<20	179/2,711	1.00 1.43 (1.20-1.69)	1.00	
20-30	526/5,769	<0.001 1.13 (0.93-1.39)	1.28 (1.07-1.56)	0.009
>30	203/2,722	0.221 0.76 (0.54-1.07)	1.26 (0.96-1.63)	0.089
Unknown	39/850	0.117	1.15 (0.76-1.74)	0.511
Education				
Post primary	624/8,332	1.00 1.17 (1.01-1.35)	1.00	
At least primary	266/3,017	0.031 1.31 (0.99-1.72)	1.21 (1.04-1.42)	0.017
Unknown	57/703	0.051	2.74 (2.00-3.75)	<0.001
Previous Fetal death				
No	906/11,319	1.00 1.24 (0.90-1.71)	-	
Yes	39/400	0.185 0.09 (0.02-0.36)	-	
Unknown	2/333	0.001	-	
Previous Child death				
No	866/11,390	1.00 3.39 (2.69-4.27)	1.00	
Yes	79/329	<0.001 0.09 (0.02-0.38)	2.69 (2.12-3.42)	<0.001
Unknown	2/333	0.001	-	
Vital status				
Alive	788/11,174	1.00 4.61 (3.86-5.51)	1.00	
Died	144/525	<0.001 0.58 (0.35-0.97)	3.05 (2.54-3.67)	<0.001
Unknown	15/353	0.036	1.29 (0.54-3.13)	0.534
HIV Status				
HIV-negative	148/4,294	1.00 2.93 (2.43-3.55)	1.00	
HIV-not reported	442/4,860	<0.001 4.88 (4.02-5.92)	2.52 (2.07-3.06)	<0.001

Characteristic	Events/total 947/12,052	Unadjusted	Adjusted	P
		HR (95% CI) P	HR (95% CI)	
HIV-positive	349/2,591	<0.001 1.12 (0.49-2.53)	4.22 (3.46-5.15)	<0.001
On ART	8/307	0.456	1.29 (0.53-3.17)	0.570