Published in final edited form as:

J Acquir Immune Defic Syndr. 2015 January 1; 68(1): 81–90. doi:10.1097/QAI.0000000000000405.

Maternal HIV status associated with under-five mortality in rural northern Malawi: A prospective cohort study

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Abstract

Background—Under-five mortality is decreasing but with little change in neonatal mortality rates. We examined the effect of maternal HIV-status on under-five mortality and cause of death since widespread availability of antiretroviral therapy in rural Malawi.

Methods—Children born in 2006–2011 in the Karonga demographic surveillance area were included. Maternal HIV-status was available from HIV sero-surveys. Age-specific mortality rate ratios for children born to HIV-positive and HIV-negative mothers were obtained by fitting a Poisson model accounting for child clustering by mother and adjusting for potential confounders. Cause of death was ascertained by verbal autopsy.

Findings—There were 352 deaths among 6913 under-five singleton children followed for 20,754 person-years (py), giving a mortality rate of 17.0/1000py overall, 218/1000py (16.5/1000 live births) in neonates, 20/1000py (17.4/1000 live births) in post-neonatal infants and 8/1000py in 1–4 year-olds. Comparing those born to HIV-positive and HIV-negative mothers, the rate ratio, adjusted for child age, sex, maternal age, parity and drinking water source was 1.5 (95%CI 0.6–3.7) in neonates, 11.5 (95%CI 7.2–18.5) in post-neonatal infants and 4.6 (95%CI 2.7–7.9) in 1–4 year-olds. Birth injury/asphyxia, neonatal sepsis and prematurity contributed >70% of neonatal deaths, while acute infections, malaria, diarrhoea and pneumonia accounted for most deaths in older children.

Conclusions—Maternal HIV status had little effect on neonatal mortality but was associated with much higher mortality in the post-neonatal period and among older children. Greater

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Conflict of interest and source of funding: None of the authors declare any conflict of interest and **source of funding:** the study was funded by Wellcome Trust, grant # 079828/Z/06/Z and 096249/Z/11/A

“Data presented previously at the Global Health Metrics and Evaluation, 2013 Conference in Seattle, Washington, 17–19th June, 2013, and published as abstract in (The Lancet - 17 June 2013 (Vol. 381, Page S29) DOI: 10.1016/S0140-6736(13)61283-0)”

attention to HIV care in pregnant women and mothers should help improve child survival but broader interventions are needed to reduce neonatal mortality.

Keywords

Maternal HIV-status; HIV/AIDS; Mortality; Under-five children; Rural

Introduction

Background

Child mortality remains one of the biggest problems being faced by countries in sub-Saharan Africa.¹ This has been compounded by high HIV prevalence in the region with an estimated 34 million people living with the virus,² the majority of whom are women of child bearing age.³ The proportion of under-five deaths attributable to HIV in Malawi is estimated to be around 13%.²

In Malawi, with an HIV prevalence of between 10-14%, about one million adults and children are estimated to be infected.⁴ HIV prevalence among women in the reproductive age group is estimated at 13%,⁵ and before widespread use of antiretroviral therapy (ART), about 30,000 newborns were infected through mother-to-child transmission every year,⁶ prenatally, during delivery or through breast feeding. Maternal HIV-status also impacts on child mortality indirectly, through death or illness of the mother as a result of HIV/AIDS.⁷⁻¹¹ Between 2005 and 2010, Malawi's under-five child mortality was estimated at 112/1000 children nationally.⁵

Although child mortality is higher in children born to HIV-positive mothers than in children born to HIV-negative mothers,^{8-10, 12-13} Malawi's child mortality has continued to decline⁵ despite high HIV prevalence. We have previously presented data on child mortality from Karonga District demographic surveillance site (DSS) up to 2006.¹⁴⁻¹⁵ Here we present under-five mortality and causes of death from 2006-2012, in the era of widespread antiretroviral therapy (ART), focussing on the contribution of maternal HIV status.

Methods

Study setting

The demographic surveillance area is located in the southern part of Karonga district. The total population is about 35,500 individuals, of whom 6,250 (18%) are children under five years of age.¹⁶ The population earns its living mostly through subsistence farming and fishing from the lake. The area has an adult HIV prevalence of approximately 9%.¹⁷ The community is served by a rural hospital, headed by a clinical officer, and 4 health centres, 3 government run and 1 private. At the time of the study there were two ART clinics available to residents of this area, one 70 km away from the study area which opened in July 2005, and another at the rural hospital within the study area which opened in September 2006.¹⁸ Nevirapine has been available for use in prevention of mother-to-child transmission since 2002. ART was recommended for women in WHO stage 3 or 4 or with CD4 counts of <250 (increased to 350 in 2011).

Demographic surveillance and verbal autopsy

Information about the population is collected and updated through a continuous registration system. This uses village volunteers known as key informants who each month record and report births and deaths, including stillbirths. The information reported by the key informants is complemented by a yearly house-to-house census to update household composition and migration.¹⁸ Each key informant has no more than 40 households under their responsibility.

The key informants report births and deaths to project interviewers at monthly meetings. Birth reports are immediately followed-up by interviewers, who go to the households to register the baby and record information such as date of birth, gender and parents' information. In this area, about 80% of deliveries take place in health facilities. Following a death report, a medically-trained interviewer visits the deceased's household to fill an age-appropriate verbal autopsy form. The form is similar to the INDEPTH verbal autopsy tool, which is an adaptation of the WHO questionnaire. The visit is done as soon as possible after a mourning period of two weeks. Repeat visits are arranged if no-one is found at home during the first visit.

The verbal autopsy forms are reviewed independently by two clinicians who assign a cause of death from a pre-defined hierarchical list. If there is disagreement the forms are reviewed by a third clinician. Full details of the study methods can be found elsewhere.^{16, 18-20}

Socioeconomic surveys

Socioeconomic information such as level of maternal education and household head's occupation, household's source of drinking water, type of dwelling and main source of income was obtained from a socioeconomic survey that runs concurrently with the house-to-house annual re-census.

HIV sero-surveys

Since September 2007, HIV counselling and testing has been offered door-to-door to all individuals aged 15 years and older in the demographic surveillance area. Four rounds of HIV sero-surveys have been conducted from 2007 to 2011, with a participation rate of 55-60% testing at each round.¹⁷ In addition to voluntary testing and counselling, individuals are also asked about previous HIV-testing, including the timing and the results of the most recent test, and also about ART use if the participant reports that they are HIV-positive.¹⁷

Study Population

All children born between September 2006 and December 2011 who were born to a resident of the study area were included in the study. Children were defined as exposed to HIV if they were born to a mother who (a) had a positive HIV test result before the child was born or (b), who tested HIV-positive within one year from the child's birth (since vertical transmission of HIV can also occur during breast feeding). A child was defined as not exposed to HIV if born to a mother who tested negative at any date after the child was born or who tested HIV-negative up to three years before the child was born, and did not have a

positive test within a year of the birth. Children born to mothers whose HIV status was unknown at the time of the child's birth were classified as unknown HIV exposure.

Statistical analysis

First we assessed the distribution of baseline characteristics by child exposure to maternal HIV status using chi-squared test of association. Children with unknown exposure status were included in the analysis as a separate category. Person years of observation (py) were calculated and used as the denominator in the calculation of mortality rates. Person years of observation (time at risk) were calculated from the child's date of birth or in-migration to the earliest of the date of their death, the date of loss to follow-up, or the end of the study (31st December 2012) or 5 years of age. For children who had moved out of the study area and came back, only the time they were in the study area was considered in the calculation of person years.

Because mortality rates and causes of death change rapidly with age, analyses were stratified by age, separating neonatal (0-28 days), post-neonatal (29-365 days) and child (1-4 years). We calculated rates, and rate ratios, using Poisson regression. We allowed for clustering by mother using random effects or robust standard errors. The results were very similar: the results using robust standard errors are presented. We also calculated the proportion of deaths attributable to HIV among HIV-exposed children (the attributable risk percent), and in the whole population (the population attributable fraction, PAF), to measure the impact of maternal HIV on child mortality.

In model building, maternal HIV status was included as the main exposure while child age within the age groups and gender were included as *a-priori* confounders. Adding the other variables one at a time, starting with the variables most strongly associated with the outcome we checked if the RR and or the standard error changed or stayed the same. A change in RR of 10% or more was considered enough evidence of confounding and the variable was left in the model, otherwise it was not included. A noticeable increase in the standard error was evidence of multicollinearity and the variable was dropped from inclusion in the model. Maternal vital status was not included in the multivariable models because of small numbers.

In the multivariable analysis, only records with complete data were included. Data were analysed using STATA version 13 (Stata Corp, College Station, TX, USA). We also checked if there are differences in stillbirth rates between HIV positive and HIV negative mothers. Stillbirth rates were calculated per 1000 live births.

Ethics approval

The study received ethical approval from the National Health Sciences Research Committee of Malawi (protocol number 419) and the Ethics Committee of the London School of Hygiene and Tropical Medicine (protocol number 5081).

Results

Over the period of the study there were 7208 live births to 5266 mothers in the demographic surveillance area. Overall there were 401 deaths before the age of 5 in 21,357 person years of exposure, giving a rate of 18.8/1000py. The mortality rate among singletons was 17.0/1000py (95% CI 15.3-18.8) and among twins/triplets was 78.3/1000py (95%CI 62.6-82.8). Since being a member of a multiple birth was in itself such a strong risk factor for mortality, these children were not included in further analysis. This excluded 295 births and 49 deaths. There was no association between maternal HIV status and twin birth.

During the period of analysis, a total of 115 stillbirths were recorded, giving a stillbirth rate of 15.7/1000 live births. There was a higher proportion of stillbirths born to HIV-positive mothers compared to HIV-negative mothers: 10 were to HIV-positive mothers (representing 3.6% of the births to these mothers) and 91 to HIV-negative mothers (representing 2.1% of births to HIV-negative mothers).

The remaining analysis concentrates on the 6913 live born singleton children. They had 5152 mothers: 3500 (68%) contributed one child, 1544 (30%) contributed two and 108 (2%) contributed more than two. Of these children, 5698 (82.4%) were delivered at a health facility, 918 (13.3%) at home, and 297(4.3%) at a traditional birth attendant. Overall 5,862 (84.8%) were HIV unexposed at birth of whom 250 (4.3%) died; 335 (4.9%) were HIV exposed at birth of whom 55 (16.4%) died; while for 716 (10.4%), maternal exposure to HIV was unknown of whom 47 (6.5%) died.

Table 1 shows the distribution of baseline characteristics and their association with maternal HIV status. HIV-positive mothers tended to be older, more educated, have had at least one previous pregnancy, live nearer to a clinic or the hospital, and to be more likely to come from households with a source of income other than farming, better dwelling construction and access to tap water.

HIV status was missing if the mother was not seen during a sero-survey, or refused to be tested or if the gap between negative and positive tests made the status at birth uncertain. Of the 285 HIV-positive mothers, 52/285 (19%, who were mothers to 65 children) were recorded as being on full ART at the time of the child's birth, 203/285 (71%, 234 children) were not on ART, and ART use was not known for 32/285 (11%) mothers (36 children). Of the 65 children born to HIV positive mothers on ART, 50 (77%) were born after their mother had been on ART for 6 or months and 13 (23%) were born to mothers who had only been on ART for less than 6 months. The extent of missing data on the other variables is shown in table 1.

Table 2 shows child mortality rates and rate ratios by each of the risk factors and by age group. We found no difference in neonatal mortality rate by HIV status of the mother while observing a very strong association between child mortality and maternal HIV status at birth among post-neonates and children aged 1-4 years old. The neonatal mortality rate was 218/1000py (95%CI 181-261), (16.5/1000 live births), post-neonatal mortality 20/1000py (95%CI 17-24), (17.4/1000 live births), and mortality at age 1-4 years 8/1000py (95%CI 9-13). Overall, the mortality rate was 14/1000py (95%CI 12-15) in those whose mothers

were HIV-negative, 62/1000py (95%CI 47-81) in those with HIV-positive mothers and 30/1000py (95%CI 22-40) in those with unknown HIV exposure.

Among the neonates, mortality was highest in the first week of life 784/1000py (95%CI 636-966) compared to 63/1000py (95%CI 43-93) at 7-28 days. The risk of death among neonates born to older mothers was 50% lower, RR 0.5 (95%CI 0.3-0.7) compared to teenage mothers and was higher in primiparous mothers than in those mothers who had given birth before: RR 2.6 (95%CI 1.8-3.8). In the older age groups, mortality rates were much higher in those with HIV-positive mothers, and highest in those whose HIV-positive mothers were already on ART at the time of child birth (though there were small numbers in these groups). Table 3 shows the causes of death by age group and child exposure to maternal HIV status at birth. Marked differences in leading causes of death between the age groups were observed. In age group 0-28 days the three leading causes of death were birth injury/asphyxia (35.1%) followed by neonatal sepsis (29.0%) and prematurity/low birth weight (18.3%). In age group 29-365 days the main causes of death were pneumonia (16.7%), HIV/AIDS (15.0%), diarrhoea (10.0%), malaria (9.2%), and other acute febrile diseases (17.5%). In the 1-4 year age group, malaria (23.7%), diarrhoea (17.0%), HIV/AIDS (7.6%) and other acute febrile diseases (19.5%) were most common.

Overall 26 mothers died during the study period. Of these, 9 (34.6%) died of AIDS, 5 (19.2%) of other communicable diseases, 6 (23.1%) of non-communicable diseases, 5 (19.2%) of maternal causes, and 1 died of external causes. Of the 8 mothers who died and whose children also died, 5 died of AIDS, 1 died of TB, and 2 died of maternal causes. Maternal death increased under-five mortality both one year before and after the mother had died (Table 2), but the numbers of maternal deaths were too few for us to investigate it further in the multivariate analysis.

The proportion of deaths attributable to HIV exposure among those with HIV-positive mothers (the attributable risk percent) or in the population (the population attributable fraction) was highest in the post-neonatal age group (Table 4) and lowest in neonates. In the post-neonatal period, maternal HIV-positivity accounted for more than one third of all deaths.

Table 5 shows results of multivariable models of the association between child mortality and child exposure to maternal HIV status at birth for each age group after adjusting for age within age groups, gender, maternal age, parity and source of drinking water as these are the only variables which confounded the association as described in the methods section above. After adjusting for potential confounding variables and taking into account the effect of child clustering by mother, the rate ratios of mortality in children born to HIV-positive mothers versus children born to HIV-negative mothers were higher than the crude rate ratios in all groups: 1.5 (95% CI 0.6-3.7) among neonates; 11.5 (95% 7.2-18.5) among post-neonatal infants, and 4.6 (95% CI 2.7-7.9) in 1-4 year olds.

Discussion

Overall, child mortality was higher in children born to HIV-positive mothers than those born to HIV-negative mothers, but this effect was only seen after the neonatal period. The main causes of death were different in the different periods. In the older children more than three quarters of the deaths were due to infections. Only a few children had their causes of death classified as AIDS, perhaps reflecting the challenge of assigning AIDS as a cause of death to under-five children using information from verbal autopsies, as noted by others.⁷ In the neonatal period one third of deaths were due to birth injury/asphyxia (in line with other studies),²¹ for which the HIV status of the mother might not play a role. However, half were due to infections or prematurity, so the relatively small effect of HIV exposure is surprising.

Both our neonatal and post-neonatal crude mortality rates were similar to those reported elsewhere in the sub-Saharan region.²²⁻²³ The crude death rate among children born to HIV-positive mothers was very high. It was 9 times higher than the rate in those born to HIV-negative mothers in the post-neonatal period and 4 times higher in children aged 1-4 years. But the difference by HIV status of the mother among neonates was negligible (rate ratio 1.1) and not statistically significant. In a previous study in Karonga district in 1998-2002 we had also found little effect in neonates, crude rate ratio 1.7 (0.7-4.4) compared to rate ratios of 3-5 in the older age groups.²⁴ In a clinic based prospective study in Blantyre, Malawi, the greatest increase in mortality rates was also found in the post-neonatal period.¹³ In Zomba, Malawi, higher mortality for children of HIV-infected mothers was found in each period, including neonates.²⁵ A study in Rwanda found no difference in child mortality by maternal HIV status at 6 months, but observed a significant difference in mortality at 9 months. The lack of an effect of HIV on mortality in the first few weeks of life, despite an increase in the stillbirth rate, has also been reported from South Africa.²⁶ Most studies of the effect of maternal HIV status have not analysed the neonatal and post-neonatal periods separately.

In our study, maternal HIV-positivity accounted for most of the deaths of older children with HIV-positive mothers and one third of all deaths in the post-neonatal period (Table 4). It accounted for only a small proportion of neonatal deaths even among those with HIV-positive mothers, which is consistent with the reported common causes of neonatal death.

Children who lost their mothers were at greater risk of dying than those whose mothers were still alive. This accounted for a small number of deaths, but the effect was large in the post-neonatal period, with 3 babies dying before and another 3 dying after their mothers had died.

Interestingly, the children who were born to mothers who were on ART exhibited higher mortality rates than those born to mothers who were HIV-positive but not on ART. This is in contrast to other studies.²⁷⁻³⁰ This could be a chance finding because numbers were small as only a minority of mothers were already on full ART at the time of their child's birth, but it may also reflect more advanced HIV disease in the mother which is associated with higher mortality in the children.^{8, 31-32}

This is a large, population-based study with long follow-up and minimal loss to follow-up, detailed data on potential confounders and information on causes of death. However, the study was not designed to define the mechanisms underlying this excess mortality in the

HIV exposed child. We had no information on the use of Nevirapine to prevent mother-to-child transmission and there was no HIV DNA testing for infants or routine HIV testing for children. We cannot therefore differentiate HIV-infected children from HIV-exposed and uninfected, who would be expected to have a much lower mortality rate³³ although it may still be higher than that in HIV-unexposed children.³⁴⁻³⁵ Access and use of other interventions known to affect mortality such as, Vitamin A supplementation, midwife attended delivery, completeness of infant vaccine schedules, duration of breastfeeding, were not systematically assessed. Future work will need to focus on understanding modifiable factors and the relative contributions of HIV-infection in the child, inadequate provision of maternal care and biological factors predisposing to serious illness in exposed-uninfected children.

Conclusion

Maternal HIV-positive status at birth has a major impact on child mortality with the relative risk being felt differently across age groups. The new Malawi government policy on preventing mother-to-child transmission using the World Health Organisation Option B+ of “universal life-long ART for all HIV infected pregnant and breastfeeding women regardless of clinical or immunological stage”³⁶ needs to be optimised to prevent more children from getting infected with HIV and maintaining the health of HIV-infected mothers. This can be expected to reduce post-neonatal and child mortality, but different interventions will be needed to reduce neonatal mortality.

Acknowledgements

Dr. Lumbani Munthali

Dr. Terence Tafatatha

Elenaus Mwaiyeghele

Fredrick Kalowebekamo

Lackson Kachiwanda

Vitumbiko Nyirenda

Taniel Njawala

Research was funded by: Wellcome Trust

List of references

1. UNICEF, World Health Organisation, World Bank, United Nations Population Division. Levels and Trends in Child Mortality. UNICEF; New York: 2013.
2. WHO. World Health Statistics. WHO; Geneva: 2013.
3. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic. 2013
4. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic. 2010
5. National Statistical Office (NSO), Macro I. Malawi Demographic and Health Survey 2010. NSO and ICF Macro; Zomba, Malawi, and Calverton, Maryland, USA: 2011.
6. National Statistical Office, UNICEF. Malawi Multiple Indicator Cluster Survey 2006, Final Report. National Statistical Office and UNICEF; Lilongwe, Malawi: 2008.

7. Newell M-L, Brahmbhatt H, Ghys PD. Child mortality and HIV infection in Africa: a review. *AIDS*. Jun; 2004 18(Suppl 2):S27–34. [PubMed: 15319741]
8. Becquet R, Marston M, Dabis F, et al. Children who acquire HIV infection perinatally are at higher risk of early death than those acquiring infection through breastmilk: a meta-analysis. *PLoS One*. 2012; 7(2):e28510. [PubMed: 22383946]
9. Marinda E, Humphrey JH, Iliff PJ, et al. Child mortality according to maternal and infant HIV status in Zimbabwe. *Pediatr Infect Dis J*. Jun; 2007 26(6):519–526. [PubMed: 17529870]
10. Marston M, Becquet R, Zaba B, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. *International journal of epidemiology*. Apr; 2011 40(2):385–396. [PubMed: 21247884]
11. Zaba B, Whitworth J, Marston M, et al. HIV and mortality of mothers and children: evidence from cohort studies in Uganda, Tanzania, and Malawi. *Epidemiology*. May; 2005 16(3):275–280. [PubMed: 15824540]
12. Mugwaneza P, Umutoni NWS, Ruton H, et al. Under-two child mortality according to maternal HIV status in Rwanda: assessing outcomes within the National PMTCT Program. *The Pan African medical journal*. 2011; 9:37. [PubMed: 22145068]
13. Taha TE, Dadabhai SS, Sun J, Rahman MH, Kumwenda J, Kumwenda N. Child Mortality Levels and Trends by HIV Status in Blantyre, Malawi: 1989-2009. *J Acquir Immune Defic Syndr*. Jun 11.2012
14. Jahn A, Floyd S, Crampin AC, et al. Declining child mortality in northern Malawi despite high rates of infection with HIV. *Bulletin of the World Health Organization*. Oct 1; 2010 88(10):746–753. [PubMed: 20931059]
15. Jahn A, Floyd S, McGrath N, et al. Child mortality in rural Malawi: HIV closes the survival gap between the socio-economic strata. *PLoS One*. 2010; 5(6):e11320. [PubMed: 20596521]
16. Crampin AC, Dube A, Mboma S, et al. Profile: The Karonga Health and Demographic Surveillance System. *International journal of epidemiology*. Jun; 2012 41(3):676–685. [PubMed: 22729235]
17. Floyd S, Molesworth A, Dube A, et al. Underestimation of HIV prevalence in surveys when some people already know their status, and ways to reduce the bias. *AIDS*. Aug 7.2012
18. Chihana M, Floyd S, Molesworth A, et al. Adult mortality and probable cause of death in rural northern Malawi in the era of HIV treatment. *Tropical Medicine and International Health*. Aug. 2012 17(8) 2012.
19. Jahn A, Crampin AC, Glynn JR, et al. Evaluation of a village-informant driven demographic surveillance system. *DEMOGRAPHIC RESEARCH*. Mar 23.2007 16(8) 2007.
20. Jahn A, Floyd S, Crampin AC, et al. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet*. May 10; 2008 371(9624):1603–1611. [PubMed: 18468544]
21. Mmbaga BT, Lie RT, Olomi R, Mahande MJ, Kvale G, Daltveit AK. Cause-specific neonatal mortality in a neonatal care unit in Northern Tanzania: a registry based cohort study. *BMC Pediatr*. 2012; 12:116. [PubMed: 22871208]
22. Jasseh M, Webb EL, Jaffar S, et al. Reaching Millennium Development Goal 4 - The Gambia. *Tropical medicine & international health : TM & IH*. Jun 24.2011
23. Garrib A, Jaffar S, Knight S, Bradshaw D, Bennish ML. Rates and causes of child mortality in an area of high HIV prevalence in rural South Africa. *Tropical medicine & international health : TM & IH*. Dec; 2006 11(12):1841–1848. [PubMed: 17176349]
24. Crampin AC, Floyd S, Glynn JR, et al. The long-term impact of HIV and orphanhood on the mortality and physical well-being of children in rural Malawi. *AIDS*. Feb 14; 2003 17(3):389–397. [PubMed: 12556693]
25. Landes M, van Lettow M, Chan AK, Mayuni I, Schouten EJ, Bedell RA. Mortality and health outcomes of HIV-exposed and unexposed children in a PMTCT cohort in Malawi. *PLoS One*. 2012; 7(10):e47337. [PubMed: 23082157]
26. Rollins NC, Coovadia HM, Bland RM, et al. Pregnancy Outcomes in HIV-Infected and Uninfected Women in Rural and Urban South Africa. *J Acquir Immune Defic Syndr*. Mar 1; 2007 44(3):321–328. 2007. [PubMed: 17195768]

27. Lussiana C, Clemente SV, Ghelardi A, Lonardi M, Pulido Tarquino IA, Floridia M. Effectiveness of a prevention of mother-to-child HIV transmission programme in an urban hospital in Angola. *PLoS One*. 2012; 7(4):e36381. [PubMed: 22558455]
28. Ndirangu J, Newell ML, Thorne C, Bland R. Treating HIV-infected mothers reduces under 5 years of age mortality rates to levels seen in children of HIV-uninfected mothers in rural South Africa. *Antivir Ther*. 2012; 17(1):81–90. [PubMed: 22267472]
29. Ndirangu J, Newell M-L, Tanser F, Herbst AJ, Bland R. Decline in early life mortality in a high HIV prevalence rural area of South Africa: evidence of HIV prevention or treatment impact? *AIDS*. Feb 20; 2010 24(4):593–602. [PubMed: 20071975]
30. Ndongoti C, Dabis F, Namale L, et al. [Survival, clinical and biological outcomes of HIV-infected children treated by antiretroviral therapy in Africa: systematic review, 2004–2009]. *Presse Med*. Jul-Aug;2011 40(7-8):e338–357. [PubMed: 21295437]
31. Newell M-L, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet*. Oct 2-8; 2004 364(9441):1236–1243. [PubMed: 15464184]
32. Obimbo EM, Mbori-Ngacha DA, Ochieng JO, et al. Predictors of early mortality in a cohort of human immunodeficiency virus type 1-infected african children. *Pediatric Infectious Disease Journal*. Jun; 2004 23(6):536–543. [PubMed: 15194835]
33. Munyagwa M, Baisley K, Levin J, Brian M, Grosskurth H, Maher D. Mortality of HIV-infected and uninfected children in a longitudinal cohort in rural south-west Uganda during 8 years of follow-up. *Tropical medicine & international health : TM & IH*. Jul; 2012 17(7):836–843. [PubMed: 22591447]
34. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. Mortality in HIV-infected and uninfected children of HIV-infected and uninfected mothers in rural Uganda. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. Apr 1; 2006 41(4):504–508.
35. Kuhn L, Kasonde P, Sinkala M, et al. Does severity of HIV disease in HIV-infected mothers affect mortality and morbidity among their uninfected infants? *Clin Infect Dis*. Dec 1; 2005 41(11): 1654–1661. [PubMed: 16267740]
36. Government of Malawi. Malawi Ministry of Health. Quarterly HIV Programme Report. Quarter 4. Malawi Ministry of Health; Lilongwe (Malawi): 2011.

Table 1
Distribution of baseline characteristics in a cohort study of 6913 under five children, by maternal HIV status at child birth in rural northern Malawi

	Variable	N (%)	Number of children and maternal HIV status at child birth			P value *
			HIV- (n=5,862)	HIV+ (n=335)	HIV status unknown (n=716)	
			n (%)	n (%)	n (%)	
Gender	Male	3,440 (49.8)	2,892 (49.3)	161 (48.1)	387 (54.1)	P=0.65
	Female	3,473 (50.2)	2,970 (50.7)	174 (51.9)	329 (46.0)	
Maternal age	< 20 years	1,474 (21.3)	1,307 (22.3)	15 (4.5)	152 (21.3)	P<0.001
	>= 20 years	5,439 (78.7)	4,555 (77.7)	320 (95.5)	564 (78.7)	
First birth	No	5,229 (75.6)	4,502 (76.8)	303 (90.5)	424 (59.2)	P=0.01
	Yes	1,310 (19.0)	1,194 (20.4)	17 (5.1)	99 (13.8)	
	Missing	1374 (5.4)	166 (2.8)	15 (4.5)	374 (5.4)	
Maternal education	None or primary 1-5	986 (14.3)	855 (14.6)	46 (13.7)	85 (11.9)	P<0.001
	Primary 6-8	3,830 (55.4)	3,408 (58.1)	164 (49.0)	258 (36.0)	
	Secondary/Tertiary	1,657 (24.0)	1,372 (23.4)	111 (33.1)	174 (24.3)	
	Missing	440 (6.4)	227 (3.9)	14 (4.2)	199 (27.8)	
Distance to the nearest clinic	<2.5km	3,396 (49.1)	2,852 (48.7)	202 (60.3)	342 (47.8)	P<0.001
	>=2.5km	3,517 (50.8)	3,010 (51.4)	133 (39.7)	374 (52.2)	
Distance to largest hospital in the area	<5km	1,937 (28.0)	1,551 (26.5)	138 (41.2)	248 (34.6)	P<0.001
	5-9km	2,387 (34.5)	2,033 (34.7)	100 (29.9)	254 (35.5)	
	>=10km	2,589 (37.5)	2,278 (38.9)	97 (29.0)	214 (30.0)	
Occupation of Household head	Farmer	4,516 (65.3)	3,955 (67.5)	207 (61.8)	354 (49.4)	P=0.52
	Professional/Skilled	928 (13.4)	734 (12.5)	56 (16.7)	138 (19.3)	
	Unskilled/Student	1,266 (18.3)	1,077 (18.4)	61 (18.2)	128 (17.9)	
	Missing	203 (2.9)	96 (1.6)	11 (3.3)	96 (13.4)	
Dwelling score	1(Best)	1,176 (17.0)	925 (15.8)	73 (21.8)	178 (24.9)	P=0.02
	2	1,422 (20.6)	1,246 (21.3)	65 (19.4)	111 (15.5)	
	3	2,388 (34.5)	2,094 (35.7)	119 (35.5)	175 (24.4)	
	4 (Worst)	1,647 (23.8)	1,437 (24.5)	68 (20.3)	142 (19.8)	
	Missing	280 (4.1)	160 (2.7)	10 (3.0)	110 (15.4)	
Water source	Tap water	1,625 (23.5)	1,287 (22.0)	130 (38.8)	208 (29.1)	P<0.001
	Borehole	3,598 (52.1)	3,142 (53.6)	154 (46.0)	302 (42.2)	
	Lake/Well	1,410 (20.4)	1,271 (20.2)	40 (11.9)	99 (13.8)	
	Missing	280 (4.1)	162 (2.8)	11 (3.3)	107 (14.9)	
Source of income	Farming	2,997 (43.4)	2,667 (45.5)	115 (34.3)	215 (30.0)	P<0.001
	Employ/Letting property	688 (10.0)	542 (9.3)	38 (911.3)	108 (15.1)	
	Piece wrk/Gathering	1,410 (20.4)	1,243 (21.2)	64 (19.1)	103 (14.4)	
	Trading/Small business	1,542 (19.6)	1,251 (21.3)	108 (32.2)	183 (25.6)	
	Missing	276 (4.0)	159 (2.7)	10 (3.0)	107 (14.9)	

* From Pearson's chi square, for comparison of HIV+ vs HIV- (excluding missing values and the unknown HIV status group)

Univariable analysis of potential risk factors for child mortality by age group in 6913 under five children followed up from September, 2006 to December, 2012 in a cohort study in rural northern Malawi.

Table 2

Variables	Age group 0-28 days				Age group 29-365 days				Age group 1-4 years						
	n	py	Rate/1000py (95% CI)	RR (95%CI)	P value	n	py	Rate/1000py (95% CI)	RR (95%CI)	P value	n	py	Rate/1000py (95% CI)	RR (95%CI)	P value
Overall	114	524	218(181,261)	-	-	120	5965	20 (17,24)	-	-	118	14266	8 (7,10)	-	-
HIV exposure	93	445	209(171,256)	1		64	5143	12 (10,16)	1		93	12695	7 (6,9)	1	
	6	25	237(107,528)	1.1(0.4,2.9)	0.79	32	277	116 (82,164)	9.3 (6.0,14.5)	<0.001	17	587	29 (18,45)	4.0 (2.3,6.7)	<0.001
	15	54	277(167,461)	1.3(0.8,2.3)	0.31	24	545	44 (30,66)	3.5 (2.2,5.7)	<0.001	8	984	8 (4,16)	1.1 (0.5,2.3)	0.78
ARV use by mother	2	5	411(103,1643)	1		12	51	237 (134,417)	1		3	96	31 (10,97)	1	
	4	18	227(85,604)	0.6 (0.1,3.4)	0.52	17	197	86 (54,139)	0.4 (0.2,0.8)	0.02	12	445	27 (15,47)	0.9(0.2,3.1)	0.82
	66	260	254(199,323)	1		56	2960	19 (15,25)	1		67	7023	10 (8,12)	1	
Gender	48	264	182(137,241)	0.7 (0.5,1.1)	0.09	64	3005	21 (17,27)	1.1 (0.8,1.6)	0.51	51	7243	7 (5,9)	0.7 (0.5,1.1)	0.10
	88	112	784 (636,966)	1		58	2760	21 (16,27)	1		90	9481	9 (8,12)	1	
	26	412	63 (43,93)	0.1 (0.05,0.1)	<0.001	62	3205	19 (15,25)	0.9 (0.6,1.3)	0.66	28	4785	6 (4,8)	0.6 (0.4,0.9)	0.03
* Age groups	113	523	216(180,260)	1		114	5952	19 (16, 23)	1		117	14200	8 (7,10)	1	
Vital Status of mother	0	0	0	-	-	3	5	591(191,1832)	31 (9.3,102)	<0.001	1	44	23(3,162)	2.8 (0.4,20)	0.31
	1	0.8	1289(182,9154)	6.0(0.8,46.7)	0.09	3	8	400(129,1340)	21 (7.1,61.1)	<0.001	0	21	-	-	-
	55	258	214(164,278)	1		67	2914	23 (18,29)	1		45	6925	6 (5,9)	1	
Distance to nearest clinic	59	267	221(172,286)	1.0(0.7,1.5)	0.85	53	3050	17 (13,23)	0.8 (0.5,1.1)	0.12	73	7341	10 (8,13)	1.5(1.1,2.2)	0.03
	33	147	225(160,316)	1		27	1661	16 (11,24)	1		21	3874	5 (4,8)	1	
	42	181	232(171,314)	1.0(0.6,1.7)	0.90	40	2064	19 (14,26)	1.2 (0.7,1.9)	0.48	49	4971	10 (7,13)	1.8(1.1,3.0)	0.02
Distance to largest hospital in the area	39	196	199(145,272)	0.9(0.5,1.4)	0.61	53	2240	24 (18,31)	1.5 (0.9,2.3)	0.12	48	5421	9 (7,12)	1.6(1.0,2.7)	0.06
	42	111	380(281,514)	1		28	1245	22 (16,33)	1		22	2790	8 (5,12)	1	
	72	413	174(138,219)	0.5(0.3,0.7)	<0.001	92	4720	19 (16,24)	0.9 (0.6, 1.3)	0.51	96	11476	8 (7,10)	1.1(0.7,1.7)	0.80
Maternal age	65	398	163(128,208)	1		88	4589	19 (16,24)	1		98	11464	9 (7,10)	1	
	42	98	428(316,579)	2.6(1.8,3.8)	<0.001	25	1114	22 (15,33)	1.2 (0.7,1.8)	0.49	16	2526	6 (4,10)	0.7 (0.4,1.3)	0.27
	15	75	200(121,332)	1		19	872	22 (14,34)	1		30	2132	14 (10,20)	1	
First birth	60	290	206(160,266)	1.0 (0.6,1.8)	0.92	61	3352	18 (14,23)	0.8 (0.5,1.5)	0.54	66	8480	8 (6,10)	0.6(0.4,0.9)	0.01
	33	125	263(187,371)	1.3 (0.7,2.4)	0.38	27	1428	19 (13, 28)	0.9 (0.5,1.6)	0.67	21	3405	6 (4,9)	0.4 (0.3,0.8)	0.004
	70	343	204(162,258)	1		83	3944	21 (18,26)	1		90	9882	9 (7,11)	1	
Occupation household head															

Variables	Age group 0-28 days					Age group 29-365 days					Age group 1-4 years						
	n	py	Rate/1000py	(95% CI)	RR (95%CI)	P value	n	py	Rate/1000py	(95% CI)	RR (95%CI)	P value	n	py	Rate/1000py	(95% CI)	RR (95%CI)
Dwelling score	Skilled	20	70	285(184,442)	1.4 (0.8,2.3)	0.21	6	797	8 (3,17)	0.4 (0.2,0.8)	0.02	12	1833	7 (4,12)	0.7(0.4,1.3)	0.28	
	Unskilled/Student	23	96	240(160,362)	1.2 (0.7,1.9)	0.56	22	1083	20 (13,31)	1.0 (0.6,1.5)	0.88	15	2437	6 (4,10)	0.7 (0.4,1.2)	0.16	
	1 (Best)	22	90	245(162,373)	1		15	1020	15 (9,24)	1		14	2375	6 (3,10)	1		
	2	20	106	188(121,291)	0.8 (0.4,1.4)	0.40	26	1224	21 (14,31)	1.4 (0.7,2.6)	0.32	15	3100	5 (3,8)	0.8(0.4,1.7)	0.61	
	3	32	183	175(124,247)	0.7 (0.4,1.3)	0.25	40	2112	19 (14,25)	1.3 (0.7,2.4)	0.38	52	5344	10 (7,13)	1.7(1.0,3.1)	0.07	
	4 (Worst)	36	124	290(209,402)	1.2 (0.7,2.0)	0.60	29	1410	21 (14,29)	1.4 (0.8,2.6)	0.26	34	3229	11 (8,15)	1.7(0.9,3.2)	0.10	
	Tap water	36	122	295(213,408)	1		19	1392	14 (9,21)	1		13	3324	4 (2,7)	1		
Water source	Borehole	56	272	206(158,267)	0.7 (0.5,1.1)	0.12	70	3122	22 (18,28)	1.7 (1.0,2.8)	0.05	72	7638	9 (7,12)	2.2(1.3,4.0)	0.01	
	Lake/Well	18	108	166(105,264)	0.6 (0.3,1.0)	0.06	21	1252	17 (11,26)	1.2(0.7,2.3)	0.49	30	3079	10 (7,14)	2.4(1.3,4.6)	0.01	
	Farming	46	225	204(153,273)	1		53	2596	20 (16,26)	1		53	6517	8 (6,11)	1		
Source of income	Employ/Letting property	14	53	266(158,449)	1.3 (0.7,2.4)	0.37	14	599	23 (14,39)	1.2 (0.6,2.1)	0.63	6	1333	5 (2,10)	0.3(0.1,1.0)	0.04	
	Piece wrk/Gathering	26	108	242(165,355)	1.2 (0.7,1.9)	0.50	21	1233	17 (11,26)	0.8(0.5,1.4)	0.48	32	2927	11 (8,15)	1.2(0.8,1.9)	0.33	
	Trading/Small business	24	118	204(136,305)	1.0 (0.6,1.7)	0.93	22	1340	16 (10,25)	0.8 (0.5,1.4)	0.44	24	3275	7 (5,11)	0.8(0.5,1.3)	0.33	

n= number of children who died

* Age within age group for neonates (younger 6 days, older 7-28 days) -post neonates (younger 2-5months, older 6-11 months) -child 1-4years (younger 1-2yrs, older 3-4yrs).

Table 3

Probable causes of death in 319 under five children by age group and exposure to maternal HIV status at birth in a cohort study of 6913 children between September, 2006 and December, 2011

0-28 days		HIV-		HIV+		Unk		29-365 days		HIV-		HIV+		Unk		1-4 years		N (%)		HIV-		HIV+		Unk	
Causes		N (%)		n		n		Causes		n		n		n		Causes				n		n		n	
Infectious diseases								Infectious diseases								Infectious diseases									
Neonatal sepsis		33 (29.0)		23		2		8		10		5		5		Malaria		28 (23.7)		26		2		0	
Pneumonia		1 (0.9)		1		0		0		18 (15.0)		15		3		Diarrheal		20 (17.0)		12		4		4	
-		-		-		-		-		12 (10.0)		2		0		HIV/AIDS or TB/AIDS		9 (7.6)		0		5		4	
-		-		-		-		-		11 (9.2)		0		1		Pneumonia		3 (2.5)		2		1		0	
-		-		-		-		-		3 (2.5)		1		1		Meningitis		2 (1.7)		2		0		0	
-		-		-		-		-		1 (0.8)		0		1		Other acute febrile dis.		23 (19.5)		21		2		0	
-		-		-		-		-		21 (17.5)		15		4		-		-		-		-		-	
-		-		-		-		-		8 (7.2)		3		0		-		-		-		-		-	
Total infectious		34 (29.8)		24		2		8		94 (78.3)		49		28		Total infectious		85 (72.0)		63		14		8	
Non-comm. dis.								Non-comm. dis.																	
Prematurity/low birth		21 (18.3)		17		1		3		3 (2.5)		0		0		Anemia		4 (3.4)		4		0		0	
Congenital		3 (2.6)		2		1		0		2 (1.7)		2		0		Nutritional		7 (5.9)		5		2		0	
-		-		-		-		-		2 (1.7)		2		0		Central nervous		4 (3.4)		4		0		0	
-		-		-		-		-		2 (1.7)		2		0		Cardiovascular		1 (0.9)		1		0		0	
-		-		-		-		-		2 (1.7)		0		1		Cancer		1 (0.9)		1		0		0	
-		-		-		-		-		-		-		-		Gastro-intestinal		1 (0.9)		1		0		0	
-		-		-		-		-		-		-		-		Respiratory		1 (0.9)		1		0		0	
Total NCD		24 (21.0)		19		2		3		11 (9.2)		6		1		Total NCD		19 (16.1)		17		2		0	
External causes								External causes																	
Birth injury/asphyxia		40 (35.1)		38		0		2		1 (0.8)		1		0		Accident		4 (3.4)		4		0		0	
-		-		-		-		-		-		-		-		Other external		3 (2.5)		3		0		0	
Total external causes		40 (35.1)		38		0		2		1 (0.8)		1		0		Total external causes		7 (5.9)		7		0		0	
Other/Unspec. causes		14 (12.3)		11		2		1		5 (4.2)		2		2		Unspecifiable causes		1 (0.9)		0		1		0	
Missing data		2 (1.8)		1		0		1		9 (7.5)		6		1		Missing data		6 (5.1)		6		0		0	
Overall Total		114		93		6		15		120		64		32		Overall Total		118		93		17		8	

Table 4
HIV/AIDS attributable mortality by age group

	Age group	Attributable mortality fraction as % of observed deaths
For children of infected mothers	Neonatal	11.8
	Post-neonatal	89.2
	Child 1-4 years	74.7
In the population as a whole	Neonatal	3.9
	Post-neonatal	38.1
	Child 1-4 years	11.4

Table 5
Multivariable analysis of the association between mortality and child exposure to mother HIV status in a cohort study of under-five children in rural northern Malawi

Variables	Age group 0-28 days (N=6343)				Age group 29-365 days (N=5866)				Age group 1-4 years (N=4806)			
	n/N	py	Adjusted RRs (95% CI) [^]	P value	n/N	py	Adjusted RRs (95% CI) [^]	P value	n/N	py	Adjusted RRs (95% CI) [^]	P value
HIV exposure												
No	84/5562	422	1		59/5466	4910	1		89/5278	12393	1	
Yes	6/313	24	1.5 (0.6,3.7)	0.43	29/304	260	11.5 (7.2,18.5)	<0.001	16/269	557	4.6 (2.7,7.9)	<0.001
Unknown	13/468	35	1.8 (1.0,3.3)	0.05	16/452	387	3.9 (2.2,6.7)	<0.001	6/397	840	1.1 (0.6,4.0)	0.87
*Age groups												
Younger	80/6343	103	1		50/6220	2552	1		84/5921	9164	1	
Older	23/6261	378	0.1 (0.0,0.1)	<0.001	54/6069	3005	1.0 (0.6,1.4)	0.85	27/3477	4625	0.7 (0.4,1.0)	0.06
Sex												
Male	59/3147	238	1		50/3082	2752	1		64/2946	6794	1	
Female	44/3196	243	0.7 (0.5,1.1)	0.14	54/3140	2804	1.1 (0.7, 1.6)	0.63	47/2998	6995	0.7 (0.5,1.0)	0.09
Maternal age												
< 20years	35/1288	97	1		24/1250	1109	1		19/1186	2639	1	
>=20years	68/5055	384	0.8 (0.4,1.6)	0.47	80/4972	4449	0.6 (0.3,1.2)	0.17	92/4758	11150	0.9 (0.5,1.8)	0.79
First birth												
No	64/5082	387	1		83/5003	4479	1		95/4793	11304	1	
Yes	39/1261	95	2.1 (1.1,4.0)	0.03	21/1219	1078	1.0 (0.5,2.2)	0.95	16/1151	2885	0.80 (0.4,1.7)	0.56
Water source												
Tap water	35/1525	115	1		17/1485	1319	1		13/1411	3286	1	
Borehole	51/3441	261	0.7 (0.4,1.1)	0.09	68/3385	3024	2.3 (1.3,3.9)	0.003	68/3232	7470	2.6 (1.4,4.8)	0.002
Lake/Well	17/1377	105	0.6 (0.3,1.0)	0.06	19/1352	1215	1.7 (0.9,3.3)	0.11	30/1301	3033	2.9 (1.5,5.6)	0.002

[^] Adjusted for variables in the table and child clustering by mother

* Age within age group for neonates (younger 6 days, older 7-28 days) -post neonates (younger 2-5months, older 6-11 months) -child 1-4years (younger 1-2yrs, older 3-4yrs).