Published in final edited form as:
J Acquir Immune Defic Syndr. 2012 October 1; 61(2): 226–234. doi:10.1097/QAI.0b013e3182618eea.

Child Mortality Levels and Trends by HIV Status in Blantyre, Malawi: 1989-2009

Taha E. Taha, MBBS PhD[1], **Sufia S. Dadabhai, MHS PhD**[1], **Jin Sun, MSc**[1], **M. Hafizur Rahman, MBBS DrPH**[2], **Johnstone Kumwenda, MBChB FRCP**[3], and **Newton Kumwenda, MPH PhD**[1]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

[2]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

[3]Department of Medicine, College of Medicine, University of Malawi, Blantyre, Malawi

Abstract

Introduction—Continuous evaluation of child survival is needed in sub-Saharan Africa where HIV prevalence among women of reproductive age continues to be high. We examined mortality levels and trends over a period of ~20 years among HIV-unexposed and exposed children in Blantyre, Malawi.

Methods—Data from five prospective cohort studies conducted at a single research site from 1989-2009 were analyzed. In these studies, children born to HIV-infected and uninfected mothers were enrolled at birth and followed longitudinally for at least two years. Information on socio-demographic, HIV infection status, survival and associated risk factors was collected in all studies. Mortality rates were estimated using birth-cohort analyses stratified by maternal and infant HIV status. Multivariate Cox regression models were used to determine risk factors associated with mortality.

Results—The analysis included 8,286 children. From 1989-1995, overall mortality rates (per 100 person-years) in these clinic-based cohorts remained comparable among HIV-uninfected children born to HIV-uninfected mothers (range 3.3-6.9) or to HIV-infected mothers (range 2.5-7.5). From 1989-2009, overall mortality remained high among all children born to HIV-infected mothers (range 6.3-19.3), and among children who themselves became infected (range 15.6-57.4, 1994-2009). Only lower birth weight was consistently and significantly ($P<0.05$) associated with higher child mortality.

Conclusions—HIV infection among mothers and children contributed to high levels of child mortality in the African setting in the pre-treatment era. In addition to services that prevent mother-to-child transmission of HIV, other programs are needed to improve child survival by lowering HIV-unrelated mortality through innovative interventions that strengthen health infrastructure.

Contact Information for Corresponding Author: Taha E. Taha MD PhD Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology 615 N. Wolfe Street, E7138, Baltimore, MD 21205 Ph 410 614 5255; Fax 443 287 5188; ttaha@jhsph.edu.

Disclaimer The findings reported in this manuscript represent the conclusions of the authors' and do not represent the views of their institutions or of the study sponsors.

Conflicts of Interest and Source of Funding: All authors declare no conflicts of interest.

Keywords

birth weight; child mortality; cohort effect; HIV; Malawi; Sub-Saharan Africa

Introduction

In the early 1980s, simple interventions such as the provision of safe water supply, child immunizations, use of oral rehydration therapy and increases in maternal education led to substantial gains in child survival in sub-Saharan Africa.[1] However, the HIV epidemic has had a negative impact on child survival and may have reversed declining mortality trends.[2,3] In 2000, administering single-dose nevirapine (sdNVP) to an HIV-infected mother and her newborn was found to substantially decrease mother-to-child transmission (MTCT) of HIV.[4] Additional strategies such as infant extended antiretroviral prophylaxis and maternal highly active antiretroviral therapy (HAART) for prophylaxis and treatment have also become available.[5-7] Nonetheless, several reports suggest stagnant or high levels of child mortality in sub-Saharan Africa.[8,9]

In this analysis, data collected over 20 years (1989-2009) from multiple prospective studies at a single research site in Malawi are presented. It is rare to have longitudinal data on mortality among children by HIV status. Even though the data presented are from hospital-based studies, rather than community-based, collectively, they are useful for examining trends over time by maternal and child HIV status. We examine and summarize child mortality levels and trends and assess risk factors associated with mortality.

Methods

Data from five prospective HIV research studies conducted in Blantyre, Malawi from 1989 to 2009 are included in this analysis: ICAR (International Collaborative AIDS Research, 1989-92),[10] PAVE (Preparation for AIDS Vaccine Evaluation, 1993-95),[10] PAVE2-HIVNET (HIV Network, 1994-97),[11] NVAZ (NVP/zidovudine [ZDV or AZT], 2000-03),[12,13] and PEPI (Post-Exposure Prophylaxis of Infants, 2004-09).[6,14] In each study, women were screened from the same geographic areas and enrolled at the same government referral hospital (Queen Elizabeth Central Hospital [QECH]) and surrounding health centers. QECH is the largest referral hospital in the southern region of Malawi and women attending QECH are mostly urban populations..

Key study characteristics are summarized in Table 1. The study designs were similar: all were prospective cohort studies in which children (and their mothers) were followed longitudinally from time of birth to at least two years of age. Women were counseled and screened for HIV either antenatally or when they presented for delivery in the hospital. All studies enrolled HIV-infected women; three studies from the early period of the Malawi's HIV epidemic (ICAR, PAVE and PAVE2-HIVNET) also enrolled HIV-uninfected women to mask the HIV status of enrolled women and to provide a comparison group. ICAR, PAVE and PAVE2-HIVNET (1989-97) were observational studies to determine rates of MTCT of HIV and risk factors associated with transmission. NVAZ and PEPI (2000-2009) were clinical trials to determine the efficacy of interventions to reduce MTCT of HIV (NVAZ: short course post-exposure prophylaxis with NVP/AZT; PEPI: extended infant post-exposure prophylaxis with NVP and ZDV). All studies were approved by ethical review committees in the United States (Johns Hopkins Bloomberg School of Public Health) and Malawi (College of Medicine and Ministry of Health ethics committees). Women were counseled and signed informed consent forms.

HIV status was determined using HIV ELISA and Western blot testing. Rapid testing was used in the PEPI study. Study questionnaires were administered to collect demographic, behavioral and clinical information. Physical examinations were performed on both mother and infant at each visit. The schedule of follow-up visits was generally similar across studies and included visits at 6-9 weeks and 12 weeks postpartum, and then every three months until study completion.

The infant HIV testing strategy changed over time. For the earlier studies, ICAR and PAVE, infants were tested for HIV using serology (ELISA and Western blot tests). At that time, sensitive PCR testing methods were not available and almost all infant HIV studies in Africa relied on serological testing at age 12 months or later. A major limitation of this strategy is that infants could be lost before age 12 months due to death or other causes. PCR testing of infant blood samples for HIV was used in the PAVE2-HIVNET, NVAZ and PEPI studies.

Due to these differences in infant HIV testing methods, we separately compared mortality of infants born to HIV-infected and uninfected mothers from time of birth in the ICAR and PAVE studies (1989-1995). Using infant HIV infection status after 12 months would have limited mortality analyses to the period after one year of age. In PAVE2-HIVET, NVAZ and PEPI (1994-2009), which used PCR to establish infant HIV infection from time of birth, mortality is analyzed based on infant (rather than maternal) HIV infection status; mortality of HIV-infected children is compared with mortality of HIV-uninfected children.

The PAVE2-HIVNET study was a follow-up study of a large trial[15] that enrolled both HIV-infected and uninfected women. In PAVE2-HIVNET, infants born to HIV-infected women with known HIV status from time of birth and a sample of infants born to HIV-uninfected women were enrolled after they had survived the first year. Therefore, in the PAVE2-HIVNET study, mortality estimates for only year two are included. This study provided an opportunity to estimate mortality based on both maternal HIV and infant HIV infection status based on PCR. NVAZ and PEPI enrolled only HIV-infected women.

Mortality rates were calculated taking into account the year of birth (cohort) and age at time of event, which could be either death or censoring due to loss to follow-up or study termination. Methods for birth cohort analyses have been described extensively in the literature.[16,17] To assess changes in mortality across time, children were grouped by year of birth, rather than age; for example, rather than reporting one mortality rate for all children 0-12 months, using birth cohort analysis, we were able to report multiple rates for 0-12 month olds based on the year they were born. Children were grouped into 2-year birth cohorts beginning with the 1989-91 cohort and ending with the 2007-08 cohort. For mortality rates, the numerator was the number of child deaths in a particular age window (e.g. 0-12 months) and the denominator was person-years children contributed from birth to death or censoring during the same age window. The mortality rates, expressed per 100 person-years (PYs), and exact 95% confidence intervals (CI) are presented for each birth cohort, by age group (0-12 months, 12-24 months and, for the earlier studies, 24-36 months). Infant, child and overall mortality rates were considered comparable within and between cohorts when 95% CI overlapped.

Risk factors for child mortality for each cohort were analyzed using Cox proportional hazard models. The proportionality assumption for the Cox model was checked using graphical and statistical methods and was generally met, with one exception: birth weight. However, upon including an interaction term in the model between infant age (our time variable) and birth weight, inferences were not affected; the direction, strength and significance of the associations were not altered. Thus we present the most parsimonious model, without the interaction term. The selection of these factors was based on epidemiological relevance,

statistical significance in univariate models at the $P<0.05$ level, biological considerations, and the availability of the same risk factor data across all studies to allow comparison of underlying trends. These factors included infant gender, birth weight, birth year, infant age, maternal age, parity, education and having electricity at home as an indicator of socio-economic status (SES). In the multivariate models, infant age was excluded because it was highly correlated with birth year. All *P* values presented are two-sided and considered statistically significant at <0.05. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

At the time of ICAR, PAVE, PAVE2 and NVAZ, most women in Malawi were breastfeeding for 24 months. The World Health Organization (WHO) breastfeeding recommendations for women with HIV infection were not implemented until 2003 and were adopted only in the most recent cohort, the PEPI study. Because almost all women were breastfeeding, we did not include this variable in the analyses of risk factors for all cohorts. However, we examined the effect of breastfeeding as a time-varying covariate in separate models and using data from the NVAZ study (2000-03), where no change in breastfeeding was adopted, and the PEPI study (2004-09), where women were counseled to follow WHO recommendations at that time.[18]

Results

Overall, 8,212 mothers and 8,286 children were included in this analysis from the five studies (1989-2009). Of these, 2,860 (1,438 HIV-infected and 1,422 HIV-uninfected) women and 2,909 infants were included from the ICAR, PAVE and PAVE2-HIVNET studies (1989-97). Additionally, 5,352 HIV-infected mothers, 1,022 HIV-infected infants and 4,355 HIV-uninfected infants were included from the NVAZ and PEPI studies (2000-09). There were no major differences at baseline in socio-demographic characteristics of women and children recruited from 1989 to 2009. Characteristics including mean maternal age, parity, education, infant gender, and mean infant birth weight were comparable among HIV-infected women and their children across all studies, and among HIV-uninfected women and their children in ICAR, PAVE and PAVE2-HIVNET. Additional information from the specific studies is provided in the references in Table 1. In all cohorts, with the exception of the most recent PEPI study cohort who received counseling to wean infants early, the frequency of breastfeeding was over 90% at 12 months postpartum.

Table 2 shows that from 1989-95, the cohort-age-specific mortality rates among children (0-36 months) born to HIV-infected mothers were consistently several folds higher than the mortality rates of children born to HIV-uninfected mothers, with a few exceptions when the number of observations was small. During 1989-91 the mortality rate of infants (0-12 months) born to HIV-infected mothers was 26.5 per 100 PYs (95% CI 21.9-31.8) compared to 8.6 per 100 PYs among infants of HIV-uninfected mothers (95% CI 6.2-11.6), giving a rate ratio of 3.1. There were no substantial changes in mortality rates during the years 1989-95 among children born to HIV-infected mothers, or to uninfected mothers, as evidenced by overlapping 95% CI (Table 2: mortality rates in columns 4,7,10 and 13). Similarly, from 2000 to 2008, among children (infected and uninfected) born to HIV-infected mothers, there was fluctuation in mortality rates but no consistent increase or decline. Relative to the 1989-95 period, it appears that mortality rates started to decline in the later years from 2000-08 in both the 0-12 and 12-24 month age groups. Of note, from 2004 onward, in keeping with national guidelines, all HIV-infected mothers were counseled at each visit to breast-feed exclusively for 6 months and to consider weaning thereafter.

The mortality rates of HIV-infected and uninfected children from 1994-2004 (PAVE2-HIVNET and NVAZ) are shown in Table 3. Mortality rates from 2004-09 (PEPI) are shown in Table 4. The cohort-age-specific mortality rates were consistently higher in HIV-infected children compared to those in HIV-uninfected children (e.g., in 1994-95 the mortality of HIV-infected children [12-24 months] was 38.5 versus 5.7 per 100 PYs in HIV-uninfected children, giving a rate ratio of 6.8). Similar to mortality trends of children born to HIV-infected or uninfected women during the earlier years (1989-95), there were no substantial changes over time in the mortality rates of HIV-infected or HIV-uninfected children during the later years (1994-2004 and 2004-09; Tables 3 and 4, columns 5, 8 and 11). The 95% CIs overlapped across time points within each cohort. Also, despite differences in time periods when these studies were conducted, the mortality rates of HIV-uninfected children shown in Tables 3 and 4 (1994-2009) were comparable to the mortality rates of children born to HIV-uninfected mothers shown in Table 2 (1989-95). The overall mortality rates of children born to HIV infected mothers shown in Table 2 (column 13) were lower than mortality rates shown in Tables 3 and 4 (column 11) when the child was HIV-infected.

Risk factors associated with child mortality are presented in Table 5. The only variable associated with lower child mortality in all models from 1989-2009 was infant birth weight. After adjusting for other factors, higher birth weight (per 100 grams) was associated with lower mortality (aHR 0.89-0.96). Higher SES (as indicated by the electricity in the household) was also associated with lower child mortality in most adjusted models (aHR 0.47-0.87), particularly in the earlier period (1989-95). In the earlier period, in models A and C (children born to HIV-infected mothers and children born to HIV-infected or uninfected mothers, respectively) infant birth year was significantly ($p<0.05$) associated with lower mortality (aHR 0.83 and 0.86). Additional analyses that adjusted for breastfeeding in the PEPI and NVAZ studies (data not shown in tables), indicated that breastfeeding was strongly associated with lower mortality for both HIV-infected (aHR 0.45, $p<0.0001$) and uninfected infants (aHR 0.446, $p<0.001$) and overall (aHR 0.69, $p=0.02$), after controlling for other factors.

Discussion

This analysis examined mortality data by HIV status from several prospective HIV studies serially conducted in the pre-treatment era in Malawi, from 1989 to 2009. As reported in previous studies from sub-Saharan Africa,[19,20] in the current analysis, mortality among HIV-infected children was substantially higher than among uninfected children. This pattern was also observed among children of HIV-infected mothers compared to those with HIV-uninfected mothers. The mortality of children born to HIV-infected mothers was lower than in children who were themselves infected because children born to infected mothers include both HIV-infected and uninfected infants; typically, there are more uninfected than infected infants. It was not possible to avoid this limitation in the earlier studies when infant HIV testing with PCR was not available.

Mortality differences by HIV status persisted in all cohorts and time periods. In Malawi, where HIV prevalence is high among women of reproductive age, only supportive HIV services were possible prior to introduction of effective programs to prevent MTCT of HIV and antiretroviral treatment. The lack of consistent mortality declines may be a reflection of the limited services available for HIV infected women and their children. HAART became available in 2006 in Malawi, toward the end of the study period in this analysis; mothers and children in the later studies, though eligible for HAART, were not on treatment and this could have led to the sustained high child mortality. The mortality rates reported here serve as baseline levels from which to monitor changes in mortality resulting from the introduction and expansion in antiretroviral treatment coverage.

The risk factor independently associated with higher mortality in this analysis was lower birth weight (Table 5). In communities where malnutrition is common, it appears that low birth weight may have long-term consequences. In Malawi, several studies have reported high prevalence of child stunting, underweight and wasting.[21,22]

A study of seven randomized trials in East, West and South Africa reported mortality rates among children up to age 24 months (born before 2000) of 4.1 and 37.4 deaths per 100 child-years among HIV-uninfected and infected children, respectively (rate ratio 9.1).[23] Mortality was associated with maternal death and timing of infant HIV infection but not breastfeeding. Our results from this time period were similar for HIV-infected children but higher among uninfected children (5.7 deaths/100 PY in 1994-95 and 6.0 in 2000-1) suggesting the background risk of death, independent of HIV, may have been higher in our population than in the seven trials. A similar pattern was observed in a separate pooled analysis by Marston et al.[24] This disparity may help explain why mortality did not consistently or substantially decline in our study population over time. Neighboring Zambia has seen child mortality decline over the same time period as in our study. This may be due to the earlier roll-out of interventions and higher HAART coverage (85% of all those in need of treatment compared to 63% in Malawi).[25]

Child immunization coverage for diphtheria, tetanus, pertussis, poliomyelitis and BCG has generally remained high in Malawi. According to the 2010 Malawi Demographic and Health Survey (MDHS), coverage in Blantyre steadily decreased between 1992 and 2004, but rebounded by 2010. In 2010, nationally, 81% of children were fully immunized by 24 months (versus 64% in 2004), with coverage lower in Blantyre (74%) than nationally. The immunization program in Malawi could be re-examined to identify additional vaccines to combat respiratory and diarrheal disease, in particular rotavirus. The addition of the pneumococcal vaccine in late 2011 is anticipated to have a significant impact on child health.

Furthermore, maternal care should be strengthened before, during and after pregnancy to ensure better care for the child. For example, while sdNVP and opt-out HIV testing for pregnant women were adopted in Malawi in 2001 and 2006, respectively, and are nearly universal, HAART for pregnant and breastfeeding mothers, infant feeding counseling and safer obstetric practices at the time of delivery are reaching only one-half of the women who need them.[26] These interventions are efficacious but implementation has been slow and coverage inadequate[25,27]; they were also not routinely implemented at the time of these studies. Not surprisingly, despite the increase in HAART coverage for adults in Africa, pediatric HIV treatment is yet to reach the adult coverage levels.[28,29]

These interventions have the potential to reduce child mortality among HIV-exposed infants, but not among mothers and children not infected with HIV. In addition to continued efforts to improve vaccination and PMTCT service coverage, other factors contributing to mortality must be ascertained and addressed to achieve improvements in overall child survival. Studies have previously reported on clinical morbidity patterns and the nutritional status of HIV-infected and uninfected children in Malawi.[30-33] These studies also provided preliminary data on causes of death, mostly from history and verbal autopsy. Diarrheal, respiratory (including TB) and parasitic diseases in addition to nutritional deficiencies remain the major causes.[34] Innovative and rapid diagnostic tools are needed to identify these common pediatric infections to guide clinical care.

The weaknesses of the health care system in resource-constrained settings, including a shortage of trained personnel, medical supplies and efficient clinic operations, have been extensively discussed.[35-37] Strengthening the health care system and structural interventions

will be vital to improve survival of children and their mothers. UNAIDS and WHO have also recognized the importance of integrating HIV interventions into family planning, maternal and child health services.[38]

Similar to the trends we observed, during the earlier years (1990-99), Malawi national survey data showed no substantial declines in under-five child mortality.[39] However, more recent survey data for Blantyre District show reductions in infant mortality (from 90 deaths per 1000 live births and in 1994-20004 to 69/1000 in 2000-10) and overall child mortality (from 69 deaths per 1000 children aged 12-59 months to 44), though not neonatal mortality.[39,40] These data are based on household, cross-sectional surveys conducted every 5 years, and are not stratified by HIV infection. The studies in this paper were clinic-based. Women who attend clinics are likely a selected population, representative of urban and suburban women at higher risk than the survey population. MDHS also excluded women with a pregnancy or birth in the two months prior to the survey. Direct comparisons between study and survey data should be made cautiously.

The socio-demographic characteristics of the 2010 survey population from Blantyre District and the PEPI study population, which overlaps most closely in time with MDHS, were both similar and different. Similar proportions of households had electricity. More women in PEPI completed some primary or secondary school (53% and 36% respectively) than in the MDHS (43% and 24%). Similar proportions of men completed some primary education (32% and 34%), but only 29% in Blantyre District completed some secondary school versus 64% among husbands of mothers in PEPI. Most (92%) PEPI mothers were married compared to 59% in a stable union in the MDHS data. These differences between the survey and study populations may partially explain differences in child mortality trends.

Some limitations to the analysis were inevitable. Despite our efforts to search for secular trends and stratify for seasonal changes over time, some underlying social and environmental changes were not measured and may have affected the interpretation of results. The clinic-based nature of these studies may limit generalizability of findings beyond populations in similar settings. Our estimates could be regarded as minimum estimates, since they refer to children in research studies who had access to better health care than outside research settings. Other factors such as selection criteria in the recent clinical trials may limit comparability of findings to survey data.

A major strength of this investigation is the ability to analyze data from several cohort studies, an opportunity that is rare due to the time, cost and logistical constraints of conducting these studies. They had a similar design and were conducted in the same hospital and health centers by a single research project. Unlike national survey data in Malawi, these studies provided information on biological factors including infant HIV status. With expanding access to HIV treatment, these data from the pre-treatment era, prior to treatment scale-up, will be valuable for long-term comparisons to determine the population level impact of current and future interventions.

Acknowledgments

We are indebted to the mothers and children who enrolled in these studies. We thank the investigators, study coordinators and technical staff in Malawi who participated in the original design and conduct of the ICAR, PAVE, PAVE2-HIVNET, NVAZ and PEPI studies.

Funding: The ICAR, PAVE and HIVNET studies were supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, grants PO1-AI-26499, R21-AI-33874-01, NO1-CP-33005, and NO1-AI-35173-117. The NVAZ study was funded by the Fogarty International Center, National Institutes of Health (AIDS FIRCA Award #5R03TW01199 and Supplement), and the Doris Duke Charitable Foundation, New York. The PEPI study was supported by a cooperative agreement from the Centers for Disease Control and

Prevention and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Health, 5-U50-PS022061-05; award U50-CC0222061.

References

1. Claeson M, Gillespie D, Mshinda H, et al. Knowledge into action for child survival. Lancet. Jul; 2003 362(9380):323–327. [PubMed: 12892965]
2. 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]
3. Adetunji, J.; Bos, ER. Levels and Trends in Mortality in Sub-Saharan Africa: An Overview. In: Jamison, DT.; Feachem, RG.; Makgoba, MW., et al., editors. Disease and Mortality in Sub-Saharan Africa. 2nd ed. Washington (DC): 2006.
4. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. Sep; 1999 354(9181):795–802. [PubMed: 10485720]
5. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med. Jun; 2010 362(24):2271–2281. [PubMed: 20554982]
6. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med. Jul; 2008 359(2):119–129. [PubMed: 18525035]
7. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med. Jun; 2010 362(24):2282–2294. [PubMed: 20554983]
8. Bradshaw D, Dorrington R. Child mortality in South Africa--we have lost touch. S Afr Med J. Aug; 2007 97(8):582–583. [PubMed: 17952212]
9. Mwalali P, Ngui E. Reduction in maternal and child mortality in sub-Saharan Africa: the yo-yo effect in delivering on the promises. J Health Care Poor Underserved. 2009; 20(4 Suppl):149–169. [PubMed: 20168039]
10. Taha TE, Dallabetta GA, Hoover DR, et al. Trends of HIV-1 and sexually transmitted diseases among pregnant and postpartum women in urban Malawi. AIDS. Jan; 1998 12(2):197–203. [PubMed: 9468369]
11. Miotti PG, Taha TE, Kumwenda NI, et al. HIV transmission through breastfeeding: a study in Malawi. JAMA. Aug; 1999 282(8):744–749. [PubMed: 10463709]
12. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. JAMA. Jul; 2004 292(2): 202–209. [PubMed: 15249569]
13. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. Lancet. Oct; 2003 362(9391):1171–1177. [PubMed: 14568737]
14. Taha TE, Li Q, Hoover DR, et al. Postexposure prophylaxis of breastfeeding HIV-exposed infants with antiretroviral drugs to age 14 weeks: updated efficacy results of the PEPI-Malawi trial. J Acquir Immune Defic Syndr. Aug 1; 2011 57(4):319–325. [PubMed: 21423025]
15. Biggar RJ, Miotti PG, Taha TE, et al. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. Lancet. Jun; 1996 347(9016):1647–1650. [PubMed: 8642957]
16. Szklo, M.; Nieto, FJ. Epidemiology: Beyond the Basics. 2nd ed. Jones and Bartlett Publishers; Sudbury, MA: 2006.
17. Breslow, NE.; Day, NE. Statistical Methods in Cancer Research. Vol. Volume I: The analysis of case-control studies. IARC Scientific Publications, Inc.; Lyon, France: 1980.
18. WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Towards Universal Access - Recommendations for a public health approach. World Health Organization; Geneva: 2006.
19. 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]

20. 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. J Acquir Immune Defic Syndr. Apr; 2006 41(4):504–508. [PubMed: 16652060]
21. Aiga H, Matsuoka S, Kuroiwa C, et al. Malnutrition among children in rural Malawian fish-farming households. Trans R Soc Trop Med Hyg. Aug; 2009 103(8):827–833. [PubMed: 19409590]
22. Maleta K, Virtanen SM, Espo M, et al. Childhood malnutrition and its predictors in rural Malawi. Paediatr Perinat Epidemiol. Oct; 2003 17(4):384–390. [PubMed: 14629321]
23. Newell ML, 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]
24. 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. Int J Epidemiol. Apr; 2011 40(2):385–396. [PubMed: 21247884]
25. WHO. UNAIDS. UNICEF. [Accessed May 16, 2011] Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector: Progress report. 2010. http://www.who.int/hiv/pub/2010progressreport/report/en/index.html
26. UNICEF. [Accessed June 10, 2011] Malawi: PMTCT Factsheet. 2010. http://www.unicef.org/aids/files/Malawi_PMTCTFactsheet_2010.pdf
27. UNAIDS. UNAIDS report on the global AIDS epidemic 2010. Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva: 2011.
28. Meyers T, Moultrie H, Naidoo K, et al. Challenges to pediatric HIV care and treatment in South Africa. J Infect Dis. Dec; 2007 196(Suppl 3):S474–481. [PubMed: 18181697]
29. Bowen A, Palasanthiran P, Sohn AH. Global challenges in the development and delivery of paediatric antiretrovirals. Drug Discov Today. Jun; 2008 13(11-12):530–535. [PubMed: 18549980]
30. Taha TE, Graham SM, Kumwenda NI, et al. Morbidity among human immunodeficiency virus-1-infected and -uninfected African children [electronic article]. Pediatrics. Dec.2000 106(6):E77. [PubMed: 11099620]
31. Taha T, Nour S, Li Q, et al. The effect of human immunodeficiency virus and breastfeeding on the nutritional status of African children. Pediatr Infect Dis J. Jun; 2010 29(6):514–518. [PubMed: 20054287]
32. Chilongozi D, Wang L, Brown L, et al. Morbidity and mortality among a cohort of human immunodeficiency virus type 1-infected and uninfected pregnant women and their infants from Malawi, Zambia, and Tanzania. Pediatr Infect Dis J. Sep; 2008 27(9):808–814. [PubMed: 18679152]
33. Graham SM, Walsh AL, Molyneux EM, et al. Clinical presentation of non-typhoidal Salmonella bacteraemia in Malawian children. Trans R Soc Trop Med Hyg. May-Jun;2000 94(3):310–314. [PubMed: 10975008]
34. Jones G, Steketee RW, Black RE, et al. How many child deaths can we prevent this year? Lancet. Jul; 2003 362(9377):65–71. [PubMed: 12853204]
35. Travis P, Bennett S, Haines A, et al. Overcoming health-systems constraints to achieve the Millennium Development Goals. Lancet. Sep; 2004 364(9437):900–906. [PubMed: 15351199]
36. Barnighausen T, Bloom DE, Humair S. Human resources for treating HIV/AIDS: needs, capacities, and gaps. AIDS Patient Care STDS. Nov; 2007 21(11):799–812. [PubMed: 17944556]
37. Thomas LS, Jina R, Tint KS, et al. Making systems work: the hard part of improving maternal health services in South Africa. Reprod Health Matters. Nov; 2007 15(30):38–49. [PubMed: 17938069]
38. UNAIDS. The Global Plan Towards the Elimination of New Infections Among Children and Keeping Their Mothers Alive. Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva: 2011.
39. Malawi Demographic and Health Survey 2004: Final Report: National Statistics Office of Malawi (Zomba, Malawi) and ORC Macro (Calverton, USA). 2005.

40. Malawi Demographic and Health Survey 2010: Preliminary Report: National Statistics Office of Malawi (Zomba, Malawi) and MEASURE DHS/ICF Macro (Calverton, USA). 2011.

Table 1

Characteristics of Studies Included in Analysis

	Total follow-uptime/ median follow-up time (months)	Sample size (N)	Reference	Design and objective	Enrollment	HIV testing – mother	HIV testing – infant	Breastfeeding recommendations
ICAR 1989-92	36/ 24.4	1359	Taha 1998[10]	Longitudinal cohort study; determine incidence of HIV infection, and rates and risk factors for MTCT of HIV	HIV-uninfected and HIV-infected women and their infants	ELISA/ Western blot	ELISA/Western blot at age 12 months or later	No recommendations to stop breastfeeding at a specific time postnatally for either HIV-uninfected or HIV-infected women
PAVE 1993-95	36/ 15.0	849	Taha 1998[10]	Longitudinal cohort study; determine incidence of HIV infection, and rates and risk factors for MTCT of HIV	HIV-uninfected and HIV-infected women and their infants	ELISA/ Western blot	ELISA/Western blot at age 12 months or later	
PAVE2-HIVNET 1994-97	24/ 19.3[a]	701	Miotti 1999[11]	Longitudinal cohort study; determine rates of MTCT of HIV due to breastfeeding and associated risk factors	HIV-unexposed and HIV-exposed infants who survived to age 1 year	ELISA/ Western blot	PCR testing from birth	
NVAZ 2000-03	24/ 21.2	1914	Taha 2003[13] and 2004[12]	Randomized clinical trial; determine efficacy of short-course infant antiviral prophylaxis to prevent MTCT of HIV	HIV-infected women and their infants	ELISA/ Western blot	PCR testing from birth	
PEPI 2004-09	24/ 24	3357	Kumwenda 2008[6] and Taha 2011[14]	Randomized clinical trial; determine efficacy extended infant antiviral prophylaxis to prevent MTCT of HIV	HIV-infected women and their infants	Rapid HIV test and ELISA/ Western blot	PCR testing from birth	HIV-infected mothers counseled to exclusively breastfeed up to 6 months postpartum and to wean thereafter

ELISA, enzyme-linked immunosorbent assay; HIVNET, HIV Network; ICAR, International Collaboration for AIDS Research; MTCT, mother-to-child-transmission of HIV; NVAZ, Nevirapine and Zidovudine; PAVE, Preparation for AIDS Vaccine Evaluation; PCR, polymerase chain reaction; PEPI, Post-exposure Prophylaxis of Infants

[a]Participants enrolled at age 12 months.

Table 2

Cohort-Age-Specific Mortality Rates among Children Born to HIV-Uninfected and Infected Mothers from 1989–1995 and to HIV-Infected Mothers from 2000-2008, Blantyre, Malawi

		Age 0–12 months			Age 12–24 months			Age 24–36 months			Overall		
# of children (1)	Birth year (2)	deaths/ PY (3)	rate/ 100PY (4)	95%CI (5)	deaths/ PY (6)	rate/ 100PY (7)	95%CI (8)	deaths/ PY (9)	rate/ 100PY (10)	95%CI (11)	deaths/ PY (12)	rate/ 100PY (13)	95% CI (14)
Mother HIV-uninfected (infants uninfected)													
576	1989–91	42/488.1	8.6	6.2, 11.6	14/378.9	3.7	2.0, 6.2	7/299.0	2.3	0.9, 4.8	63/1166.0	5.4	4.2, 6.9
120	1991–92	3/101.3	3.0	0.6, 8.6	3/79.6	3.8	0.8, 11.0	2/60.0	3.3	0.4, 12.0	8/240.9	3.3	1.4, 6.5
638	1993–94	36/510.2	7.1	4.9, 9.7	8/151.6	5.3	2.3, 10.4	2/5.5	36.1	4.4, 131.3	46/667.3	6.9	5.0, 9.2
108	1994–95[a]	-	-	-	6/95.2	6.3	2.3, 13.7	0/48.0	0.0	-	6/143.2	4.2	1.5, 9.1
Mother HIV-infected (both uninfected and infected infants)													
572	1989–91	116/437.0	26.5	21.9, 31.8	38/288.7	13.2	9.3, 18.1	24/214.7	11.2	7.2, 16.6	178/940.4	18.9	16.3,21.9
91	1991–92	13/77.5	16.8	8.9, 28.7	10/54.3	18.4	8.8, 33.9	2/43.1	4.6	0.6, 16.8	25/174.9	14.3	9.3,21.1
211	1993–94	29/153.4	18.9	12.7, 27.2	8/47.5	16.8	7.3, 33.2	2/1.4	142.9	17.3,516.1	39/202.3	19.3	13.7, 26.4
593	1994–95[a]	-	-		66/498.7	13.2	10.2, 16.8	17/229.8	7.4	4.3, 11.8	83/728.5	11.4	9.1,14.1
693	2000–01	82/579.3	14.2	11.3, 17.4	31/391.8	7.9	5.4, 10.9	-	-	-	113/971.1	11.6	9.6, 13.9
863	2001–02	116/718.4	16.1	13.2, 19.2	45/511.1	8.8	6.4, 11.6	-	-	-	161/1229.5	13.1	11.2, 15.2
326	2002–03	27/278.8	9.7	6.4, 13.7	3/195.2	1.5	0.3, 3.7	-	-	-	30/474.0	6.3	4.3, 8.8
32	2003–04	3/24.4	12.3	2.5, 29.7	0/10.0	0.0	-	-	-	-	3/34.4	8.7	1.8, 21.0
341	2004–05[b]	40/294.2	13.6	9.7, 18.1	18/252.5	7.1	4.2, 10.8	-	-	-	58/546.8	10.6	8.1, 13.5
1152	2005–06	128/969.8	13.2	11.0, 15.6	62/802.7	7.7	5.9, 9.8	-	-	-	190/1772.5	10.7	9.2, 12.3
1159	2006–07	82/939.7	8.7	6.9, 10.7	86/856.8	10.0	8.0, 12.3	-	-	-	168/1796.5	9.4	8.0, 10.8
705	2007–08	52/591.3	8.8	6.6, 11.3	24/432.9	5.5	3.6, 8.0	-	-	-	76/1024.2	7.4	5.8, 9.2

CI, confidence interval; PY, person-years.

[a] Data for 1994-95 are from PAVE2-HIVNET, which enrolled infants after they survived to age 12 months. Thus, we do not report data for age 0-12 months.

[b] As of 2004, HIV-infected women in Malawi were recommended to exclusively breastfeed for 6 months and then wean thereafter.

Table 3

Cohort-Age-Specific Child Mortality Rates among HIV-Exposed Children, by Child HIV Status, 1994–2004, Blantyre, Malawi

			Age 0–12 months			Age 12–24 months			Overall		
Study/ Arm (1)	**# of children (2)**	**Birth year (3)**	**deaths/ PY (4)**	**rate/ 100PY (5)**	**95%CI (6)**	**deaths/ PY (7)**	**rate/ 100PY (8)**	**95%CI (9)**	**deaths/ PY (10)**	**rate/ 100PY (11)**	**95%CI (12)**
Child HIV-uninfected											
PAVE2/ NVAZ	439	1994–95[a]	-	-	-	22/384.6	5.7	3.6, 8.7	22/384.6	5.7	3.6, 8.7
	528	2000-01	34/450.4	7.5	5.2, 10.5	12/319.2	3.8	1.9, 6.6	46/769.6	6.0	4.4, 8.0
	652	2001-02	52/551.6	9.4	7.0, 12.4	10/409.2	2.4	1.2, 4.5	62/960.8	6.5	4.9, 8.3
	262	2002-03	10/227.9	4.4	2.1, 8.1	0/169.5	0.0	-	10/397.4	2.5	1.2, 4.6
	26	2003-04	2/19.3	10.4	1.3, 37.4	0/8.6	0.0	-	2/27.9	7.2	0.9, 25.9
Child HIV-infected											
PAVE2/ NVAZ	154	1994–95[a]	-	-	-	44/114.1	38.5	28.0, 51.8	44/114.1	38.5	28.0, 51.8
	165	2000-01	48/128.9	37.2	27.5, 49.4	19/72.5	26.2	15.8, 40.9	67/201.4	33.3	25.8, 42.3
	211	2001-02	64/166.8	38.4	29.6, 49.0	35/101.8	34.4	24.0, 47.8	99/268.6	36.9	30.0, 44.9
	64	2002-03	17/50.9	33.4	19.5, 53.5	3/25.7	11.7	2.4, 34.1	20/76.6	26.1	16.0, 40.3
	6	2003-04	1/5.0	20.0	0.5, 111.4	0/1.4	0.0	-	1/6.4	15.6	0.4, 87.1

CI, confidence interval; HIVNET, HIV Network; NVAZ, Nevirapine and Zidovudine; PAVE, Preparation for AIDS Vaccine Evaluation; PY, person-years.

[a]Data for 1994-95 are from PAVE2-HIVNET, which enrolled infants after they survived to age 12 months. Thus, we do not report data for age 0-12 months.

Table 4

Cohort-Age-Specific Child Mortality Rates by Child HIV Status, 2004-2009, Blantyre, Malawi

			Age 0–12 months			Age 12–24 months			Overall		
Study/ Arm (1)	**# of children (2)**	**Birth year (3)**	**deaths/ PY (4)**	**rate/ 100PY (5)**	**95% CI (6)**	**deaths/ PY (7)**	**rate/ 100PY (8)**	**95% CI (9)**	**deaths/ PY (10)**	**rate/ 100PY (11)**	**95% CI (12)**
Child HIV-uninfected											
PEPI Control	90	2004-05	7/76.9	9.1	3.7, 18.8	4/69.1	5.8	1.6, 14.8	11/146.0	7.5	3.8, 13.5
	303	2005-06	17/253.1	6.7	3.9, 10.7	7/214.7	3.3	1.3, 6.7	24/467.8	5.1	3.3, 7.6
	473	2006-09	37/393.6	9.4	6.6, 13.0	13/313.8	4.1	2.2, 7.1	50/707.4	7.1	5.2, 9.3
PEPI Treatment	185	2004-05	7/166.5	4.2	1.7, 8.7	5/155.5	3.2	1.0, 7.5	12/322.0	3.7	1.9, 6.5
	636	2005-06	56/542.8	10.3	7.8, 13.4	20/466.6	4.3	2.6, 6.6	76/1009.4	7.5	5.9, 9.4
	1,104	2006-09	68/953.2	7.1	5.5, 9.1	21/745.9	2.8	1.7, 4.3	89/1699.1	5.2	4.2, 6.4
Child HIV-infected											
PEPI Control	25	2004-05	11/17.2	64.0	31.9, 114.4	3/7.2	41.7	8.6, 121.8	14/24.4	57.4	31.4, 96.3
	76	2005-06	20/62.5	32.0	19.6, 49.4	12/42.4	28.3	14.6, 49.4	32/104.9	30.5	20.9, 43.1
	106	2006-09	29/90.5	32.0	21.5, 46.0	16/58.1	27.5	15.7, 44.7	45/148.6	30.3	22.1, 40.5
PEPI Treatment	41	2004-05	15/33.5	44.8	25.1, 73.9	6/20.6	29.1	10.7, 63.4	21/54.1	38.8	24.0, 59.3
	137	2005-06	35/111.4	31.4	21.9, 43.7	23/79.0	29.1	18.5, 43.7	58/190.4	30.5	23.1, 39.4
	181	2006-09	36/159.1	22.6	15.9, 31.3	24/106.2	22.6	14.5, 33.6	60/265.3	22.6	17.3, 29.1

CI, confidence interval; PEPI, Post-exposure Prophylaxis of Infants; PY, person-years.

Table 5

Association of Risk Factors with Child Mortality in Blantyre, Malawi, 1989-2009

	Univariate models			Multivariate models		
	Hazard ratio	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Model A) Children born to HIV-infected mothers, 1989–1995						
Infant gender (male vs. female)	1.15	0.91, 1.46	0.24	1.27	0.96, 1.68	0.10
Infant birth weight (per 100 grams)	0.91	0.89, 0.93	<0.0001	0.92	0.89, 0.94	<0.0001
Infant birth year (per 1 calendar year)	0.80	0.73, 0.88	<0.0001	0.83	0.74, 0.92	0.0007
Infant age (per 1 month)	0.63	0.60, 0.66	<0.0001	-	-	-
Mother age (per 1 year)	1.00	0.98, 1.03	0.77	1.03	0.99, 1.08	0.15
Electricity (yes vs. no)	0.68	0.50, 0.92	0.01	0.63	0.43, 0.93	0.02
Mother education (schooling vs. no schooling)	0.83	0.57, 1.21	0.34	-	-	-
Parity	1.04	0.98, 1.11	0.22	0.98	0.87, 1.10	0.69
Model B) Children born to HIV-uninfected mothers, 1989–1995						
Infant gender (male vs. female)	1.02	0.70, 1.48	0.92	1.25	0.79, 1.99	0.35
Infant birth weight (per 100 grams)	0.87	0.84, 0.90	<0.0001	0.89	0.85, 0.94	<0.0001
Infant birth year (per 1 calendar year)	0.95	0.79, 1.14	0.58	0.82	0.65, 1.03	0.08
Infant age (per 1 month)	0.17	0.13, 0.24	<0.0001	-	-	-
Mother age (per 1 year)	0.98	0.95, 1.01	0.28	1.02	0.95, 1.08	0.63
Electricity (yes vs. no)	0.42	0.23, 0.77	0.005	0.47	0.22, 0.98	0.04
Mother education (schooling vs. no schooling)	0.69	0.43, 1.12	0.13	-	-	-
Parity	1.02	0.93, 1.12	0.72	0.98	0.84, 1.15	0.78
Model C) Children born to HIV-infected or -uninfected mothers, 1989–1995						
Infant gender (male vs. female)	1.12	0.92, 1.37	0.28	1.30	1.02, 1.66	0.03
Infant birth weight (per 100 grams)	0.89	0.87, 0.90	<0.0001	0.90	0.88, 0.92	<0.0001
Infant birth year (per 1 calendar year)	0.86	0.79, 0.94	0.0007	0.86	0.78, 0.95	0.003
Infant age (per 1 month)	0.56	0.53, 0.59	<0.0001	-	-	-
Mother age (per 1 year)	0.99	0.97, 1.01	0.24	1.02	0.99, 1.06	0.20
Electricity (yes vs. no)	0.64	0.49, 0.83	0.0009	0.61	0.43, 0.85	0.004
Mother education (schooling vs. no schooling)	0.87	0.65, 1.16	0.34	-	-	-

	Univariate models			Multivariate models		
	Hazard ratio	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Parity	1.00	0.95, 1.05	0.90	0.96	0.87, 1.05	0.32
Model D) HIV-infected children (PEPI intervention arm excluded), 1994–2009						
Infant gender (male vs. female)	0.85	0.68, 1.06	0.14	0.88	0.71, 1.10	0.27
Infant birth weight (per 100 grams)	0.96	0.94, 0.98	0.0006	0.96	0.94, 0.99	0.002
Infant birth year (per 1 calendar year)	0.99	0.95, 1.04	0.71	1.00	0.96, 1.05	0.91
Infant age (per 1 month)	0.48	0.44, 0.52	<0.0001	-	-	-
Mother age (per 1 year)	0.99	0.97, 1.01	0.42	0.98	0.95, 1.02	0.25
Electricity (yes vs. no)	0.72	0.55, 0.93	0.01	0.78	0.59, 1.01	0.06
Mother education (schooling vs. no schooling)	0.85	0.60, 1.19	0.33	-	-	-
Parity	1.01	0.94, 1.07	0.88	1.06	0.96, 1.17	0.29
Model E) HIV-uninfected children (PEPI intervention arm excluded), 1994–2009						
Infant gender (male vs. female)	1.02	0.78, 1.32	0.90	1.11	0.85, 1.44	0.45
Infant birth weight (per 100 grams)	0.93	0.91, 0.96	<0.0001	0.93	0.90, 0.96	<0.0001
Infant birth year (per 1 calendar year)	1.04	0.99, 1.10	0.12	1.05	1.00, 1.10	0.08
Infant age (per 1 month)	0.34	0.30, 0.39	<0.0001	-	-	-
Mother age (per 1 year)	1.00	0.97, 1.03	0.97	1.01	0.97, 1.05	0.68
Electricity (yes vs. no)	0.84	0.63, 1.13	0.26	0.87	0.64, 1.17	0.35
Mother education (schooling vs. no schooling)	0.85	0.57, 1.27	0.42	-	-	-
Parity	0.99	0.91, 1.07	0.72	0.97	0.87, 1.09	0.64
Model F) HIV-infected and -uninfected children (PEPI intervention arm excluded), 1994–2009						
Infant gender (male vs. female)	0.85	0.72, 1.00	0.05	0.91	0.76, 1.07	0.24
Infant birth weight (per 100 grams)	0.94	0.92, 0.96	<0.0001	0.94	0.92, 0.96	<0.001
Infant birth year (per 1 calendar year)	1.00	0.96, 1.03	0.87	1.01	0.97, 1.04	0.76
Infant age (per 1 month)	0.42	0.39, 0.45	<0.0001	-	-	-
Mother age (per 1 year)	1.00	0.98, 1.01	0.62	1.00	0.97, 1.02	0.92
Electricity (yes vs. no)	0.77	0.63, 0.93	0.01	0.81	0.66, 0.98	0.03
Mother education (schooling vs. no schooling)	0.84	0.65, 1.09	0.20	-	-	-
Parity	0.99	0.94, 1.04	0.73	1.00	0.93, 1.08	0.97

CI, confidence interval; PEPI, Post-exposure Prophylaxis of Infants.

Children from the PEPI intervention arm were excluded because the intervention, extended antiretroviral prophylaxis up to age 14 weeks, was highly effective in reducing transmission but was not the standard of care. Therefore, we included only the control arm that did not receive extended antiretroviral prophylaxis.