Published in final edited form as:
J Paediatr Child Health. 2014 March ; 50(3): 189–195. doi:10.1111/jpc.12454.

Risk Factors for Mortality among HIV-exposed and HIV-unexposed Infants Admitted to a Neonatal Intensive Care Unit in Botswana

Rebecca M. Zash[1,5], **Olubunmi Ajose-Popoola**[2], **Ketil Stordal**[3,4], **Sajini Souda**[5], **Anthony Ogwu**[5], **Scott Dryden-Peterson**[5,6], **Kathleen Powis**[5,7,8], **Shahin Lockman**[5,6,8], **Joe Makhema**[5], **Max Essex**[5,8], and **Roger L. Shapiro**[1,5,8]

[1] Division of Infectious Disease, Beth Israel Deaconess Medical Center, 110 Francis Street, Boston, MA 02215

[2] Department of Otolaryngology Head & Neck Surgery, University of California, Irvine Medical Center, Building 56, 101 The City Drive South, Orange, California 92868 USA

[3] Princess Marina Hospital, Gaborone, Botswana

[4] Norwegian Institute of Public Health, Oslo, Norway

[5] Botswana–Harvard AIDS Institute Partnership for HIV Research and Education, Gaborone, Botswana

[6] Infectious Diseases Unit, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02215 USA

[7] Massachusetts General Hospital Departments of Internal Medicine and Pediatrics, 55 Fruit St, Boston, MA 02114

[8] Department of Immunology and Infectious Diseases, Harvard School of Public Health, 665 Huntington Avenue FXB 301, Boston, Massachusetts 02115

Abstract

Aim—Newborns admitted to neonatal intensive care units (NNU) in resource limited settings face high risk of mortality but the epidemiology of these deaths is poorly understood. We describe risk factors for NNU mortality in an area with high prevalence of HIV.

Methods—We performed a prospective cohort study of infants admitted to the NNU at a public referral hospital in Gaborone, Botswana. The primary outcome was neonatal death, defined as death within 28 days of a live delivery. Cox proportional hazard models were used to evaluate risk factors for mortality.

Results—From October 2008 to April 2009, 449 neonates were admitted to the NNU. Cumulative mortality was 24.5% (110/449). Factors associated with increased risk of death included lack of enteral feeding (HR 18.8, 95% CI 10.3, 34.2), gestational age <28 weeks (HR 2.0, 95% CI 1.1, 3.8) and APGAR score <7 at 10 minutes (HR 2.5, 95% CI 1.5, 4.2). Among 348

Corresponding Author Division of Infectious Diseases Beth Israel Deaconess Medical Center, Lowry Medical Office Building, Suite GB, 110 Francis Street, Boston, MA 02215, rzash@bidmc.harvard.edu, (ph) 617-667-7706, (fax) 617-667-7626.

(78%) infants who were fed, there was no difference in mortality between infants who were breastfed compared with those who were formula fed or had mixed feeding (p=0.76). There was no significant mortality difference by HIV exposure status; 35 (28%) of 128 HIV-exposed infants died compared with 55 (21%) of 272 HIV-unexposed infants (p=0.19).

Conclusions—This study identified low Apgar scores, extreme prematurity, and lack of enteral feeding as the most important risk factors for mortality in this NNU setting. HIV exposure and formula feeding were not significantly associated with death in neonates who were very ill.

Keywords

Botswana; neonatal intensive care units; neonatal mortality; HIV; feeding method

Introduction

Significant gains have been made in the past decade toward the United Nations Development Goal of reducing under-5 mortality[1,2]. However, the slowest gains have occurred in sub-Saharan Africa, where 50% of all childhood deaths now occur (increased from 33% in 1990)[3], and neonatal mortality (death <28 days) has remained of particular concern[4,5]. In 2009, an estimated 30% (1.1 million) of all childhood deaths in Sub-Saharan Africa occurred in the first 28 days of life[3,6]. It is believed that the HIV epidemic in Sub-Saharan Africa has contributed to neonatal mortality through direct infant HIV infection, poor maternal health and increases in adverse birth outcomes, increased vulnerability of HIV-exposed but uninfected infants, and in some cases the early introduction of infant formula rather than exclusive breastfeeding[7]. There is a poor understanding of the epidemiology of these events, as data on early death are often difficult to gather[8]. In Botswana, a country where over 90% of women receive antenatal care and deliver in hospitals, there was a 400% increase in child mortality from 1991 to 2003 which coincided with the spread of the HIV epidemic[9]. This increase was not from mother-to-child HIV transmission (MTCT) alone, as HIV-exposed but uninfected infants also have increased mortality[10].

In previous studies, we identified early formula feeding as the strongest risk factor for neonatal mortality in a cohort of infants born to women who enrolled during pregnancy[10]. However, while these data were representative of deaths among all HIV-exposed infants, they did not focus on the highest risk hospitalized infants. Because most women in Botswana deliver in hospitals, a very high percentage of early deaths occur in the hospital setting; where tertiary care is available, the majority of neonatal deaths occur in the Neonatal Unit (NNU). We set out to better understand risk factors for neonatal mortality in the NNU at Princess Marina Hospital (PMH) in Gaborone, where the highest level of clinical care in the country's public hospital system was available. We hypothesized that risk factors for mortality in the NNU setting might differ from those identified in previous studies among infants who had been discharged to the outpatient setting[10, 11, 12, 13, 14, 15].

Materials and Methods

We performed a prospective cohort study and included all infants <28 days old admitted to the PMH NNU between October 2008 and April 2009. PMH is a large tertiary referral hospital in Gaborone, Botswana. During the study period, the PMH NNU was staffed by two full-time pediatricians, and from 3-5 nurses and 2-3 non-specialist medical officers; it can accommodate up to 60 infants and is rarely over capacity. Gowns, gloves, soap and water are routinely available to all health care personnel. Approval to perform the study was granted by human subjects committees in Botswana and at the Harvard School of Public Health.

Data were abstracted daily from the infant medical records. Neonatal variables that were collected at entry included location of birth, admission diagnosis, gestational age at birth, birth weight, Apgar score at 1, 5 and 10 minutes, and congenital abnormalities. Prospective collection occurred to record feeding method, medical complications, antibiotic use, need for resuscitation, laboratory and culture results, and discharge diagnosis. Maternal data were abstracted from obstetric records and included age, frequency of prenatal care, demographics, obstetrical history, HIV status, CD4 count, highly active antiretroviral therapy (HAART) regimen at the time of delivery and complications during labor and delivery.

Gestational age was estimated using reported last menstrual period (LMP). Prematurity was defined as an infant delivered <37 weeks gestation. Birth weight was categorized as normal (>2500g), low (1500g-2500g), very low (1000g-1499g), and extremely low (<1000g). Infant feeding was categorized as exclusive breast feeding, exclusive formula feeding, mixed feeding (which included infants who were documented to receive both breast milk and formula), and infants who had no documentation of being fed by either method (NPO). Infants were considered HIV-exposed if their mother had a positive HIV test any time prior to delivery or immediately postpartum. HIV-unexposed infants included those whose mothers had a documented negative HIV test during pregnancy or immediately postpartum. Infants born to women with no documented HIV test were considered to have unknown HIV exposure.

The primary outcome of interest was in-hospital neonatal death (NND), defined as death within 28 days of a live delivery. Infants were considered to be alive if there was no record of death at last hospital contact or by 28 days of life. The cause of death was determined by the first discharge diagnosis.

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina, USA). Kaplan-Meier plots were used to estimate the cumulative incidence of neonatal mortality according to HIV-exposure and feeding status and analyzed with a log-rank test. Cox proportional hazards regression model was used to calculate hazard ratios (HR) and associated 95% confidence intervals (CI) for both unadjusted and adjusted analysis. Potential risk factors for neonatal death were considered for inclusion in the final model if they were significant in univariate analysis ($p<0.05$). Respiratory distress and sepsis were then excluded because they were determined to mediate the effect of preterm

delivery and low Apgar score. Maternal HIV status was included in the final model because previous studies showed it was an important risk factor. Due to correlation between preterm delivery and low birth weight, risk factors included in the final model were assessed for multi-collinearity in a logistic regression model.

Results

Data were abstracted for 449 consecutive NNU admissions of neonates < 28 days old (Table 1). Seventy percent of these infants were born at PMH while 18% were referred from district hospitals, 7% from the Gaborone City Clinic (GCC), 3% were delivered at home and 2% were unknown. Median gestational age at birth was 34 weeks [IQR 30,39] and ranged from 20-45 weeks. Preterm and very preterm delivery were common, with 280 (62%) of infants born < 37 weeks gestation and 9% born < 28 weeks of gestation. Only 38% weighed ≥ 2500g at birth; 32% were low birth weight (2499g-1500g), 23% were very low birth weight (1000g-1499g), and 8% were extremely low birth weight (<1000g). The most common primary admission diagnoses for infants was prematurity (45%) followed by asphyxia/low Apgar score (16%), respiratory distress (8%), jaundice (4%), meconium aspiration (4%) and congenital abnormality (4%).

HIV-exposed infants were not disproportionally represented in NNU admissions. One hundred and twenty eight (29%) infants were HIV-exposed, 272 (60%) were HIV-unexposed, and 49 (11%) had unknown HIV exposure status. During this same time period, 772/3044 (25%) of women delivering at PMH were HIV positive. However, HIV-exposed infants were more likely to be premature, to have lower birth weight, and to be born to older multiparous women (data not shown).

The median length of stay in the NNU was 5 days [IQR 2,15 days]. Fifty-eight percent of infants received ventilation by ambubag and 8.5% were given adrenaline during resuscitation at delivery. Ten percent of infants were intubated in the NNU (3-4 ventilators were available during the study period). Over the course of the stay in the NNU, 7.6% of infants had a red blood cell transfusion and 1.8% received platelets. Overall, 295 (66%) infants received antibiotics. Of these, 90% initially received IV ampicillin and gentamicin, which is first line therapy for sepsis in Botswana. Additional antibiotics used included IV vancomycin, cefotaxime, metronidazole, cloxacillin, ciprofloxacin, piperacillin/tazobactam or amikacin, and 17% of infants were either started or switched to one of these agents.

Discharge diagnoses did not differ by HIV exposure status (Table 2). The most common diagnoses were prematurity (27%), respiratory distress (15%), sepsis (13%), and birth trauma/asphyxia (12%). Four infants (0.9%) were diagnosed with necrotizing entercolitis (2 breast fed, 1 formula fed and 1 NPO). Of 40 positive blood cultures in septic infants, *S. aureus* was isolated in 35%; of these, 71% of isolates were methicillin-sensitive and 29% were Methicillin-resistant. Gram negative rods accounted for 58% of isolates, including *Klebsiella spp*. (25%), E. Coli (25%) and Pseudomonas (7.5%). The other three isolates were *Streptococcus spp.* (7.5%). There was no difference in the prevalence of sepsis between HIV-exposed and HIV-unexposed infants (p=0.92) (Table 2).

In accordance with Botswana's infant feeding recommendations, feeding strategies differed significantly by HIV exposure status ($p < 0.0001$). Only four HIV exposed infants were breast fed while 89% of HIV unexposed infants who initiated feeding were breastfed. Only 40 (9%) infants were both formula and breastfed, 94% of whom were HIV unexposed. Sixty-seven (15%) neonates were NPO in the NNU, and the proportion did not differ by HIV-exposure status (p=0.33).

The total number of neonatal deaths was 110 (25%). More than half (54%) of all deaths occurred between 1 day and 1 week and 20% of deaths occurred within 24 hours of birth (Figure 1). The most common diagnoses among neonates who died were prematurity (30%), followed by respiratory distress (19%), sepsis (17%) and low Apgar/birth asphyxia (13%). Among full term neonates, the most common cause of death was birth injury/asphyxia (50%), and among neonates surviving more than one week, sepsis was the leading cause of death (37%). None of the 15 neonates admitted for diarrhea or abdominal distention died. There was no significant mortality difference by HIV exposure status; 35 (27%) of 130 HIV-exposed neonates died compared with 55 (20%) of 271 HIV-unexposed neonates (p=0.19) (Figure 2).

Being very preterm (HR 2.0, 95% CI 1.1, 3.8), being NPO (HR 18.8, 95% CI 10.3, 34.2), and having an Apgar score <7 at 10 minutes (HR 2.5, 95% CI 1.5, 4.2) were all associated with an increased risk of death in adjusted analyses (Table 3). Of infants categorized as NPO, 60/67 (90%) died in the NNU, and 80% of these deaths occurred within 4 days. NPO infants were more likely to be very preterm ($p<0.001$) and very low birth weight ($p<0.001$). Most NPO infants (80%) were documented to have received IV fluids. Among fed infants, there was no difference in the risk for mortality between those who received any formula compared with those who received any breast milk (p=0.76) (Figure 2).

No infant in the NNU was tested for or diagnosed with HIV. Maternal characteristics such as age, parity, and prenatal care did not affect the mortality risk. Maternal CD4 cell count, viral load, HAART regimen during pregnancy and intrapartum ART as well as neonatal ARV prophylaxis were not documented with sufficient completeness to assess as risk factors among HIV exposed infants.

Discussion

To our knowledge, this is the first prospective study of mortality in a neonatal intensive care unit in Botswana. Neonatal mortality was very high, with the majority of deaths occurring in the first week of life among very preterm infants. Neither HIV exposure nor formula feeding increased the risk of death in the NNU setting.

The epidemiology of neonatal mortality in Southern Africa is not well understood. The cumulative mortality in this high-risk NNU population was 24.5%, similar to that found in intensive care settings in other resource poor settings such as Benin[16], Ethiopia[17], Nigeria[18] and Saudi Arabia[19], but higher than the 3.8% neonatal mortality found in a private hospital NICU in South Africa[20]. Mortality differences may in part reflect the ability to resuscitate very preterm infants and other factors related to resource availability[3]. Our results are

consistent with previous studies of neonatal mortality in Sub Saharan Africa that have identified preterm birth, low birth weight, and neonatal infection as important risk factors for neonatal mortality[21-30]. In the NNU setting, lack of enteral feeding was the strongest predictor for mortality even after adjusting for prematurity, birthweight and APGAR score. It is likely that NPO status is a marker for very high-risk infants, where death occurred prior to feeding or where feeding was felt to be unsafe but this study cannot rule out the possibility that improved focus on infant feeding could improve outcomes in some cases..

Formula feeding has been associated with early infant mortality in other studies from Southern Africa[10, 31, 32, 33]. However, we did not identify feeding method as a mortality risk factor in the NNU. The controlled NNU setting may mitigate factors that lead to excess risk from formula feeding, such as use of contaminated water, not mixing enough formula into water and not receiving supplemental IV fluids if dehydration occurs. This finding may be reassuring for those caring for critically ill children where breastfeeding is logistically challenging or when antiretroviral prophylaxis is not available for PMTCT. However, given the high mortality among infants prior to any feeding, this study may have limited power to detect differences between breast and formula feeding. Larger studies would be required to exclude less than a 1.6-fold mortality difference between feeding groups. Finally, feeding method was tightly linked to maternal HIV status in our study, because of Botswana infant feeding guidelines. Although we cannot exclude the possibility of confounding that masked a true feeding effect, it seems unlikely that HIV exposure would be protective.

There were a large number of positive blood cultures in our sample (40), though the total number of blood cultures sent was not recorded. It is possible that some proportion of these could represent nosocomial infections and that improvements in hygiene could improve infant outcomes in the NNU. However, this cannot be systematically assessed as we did not collect data about line-placement or other invasive procedures, there were no antibiotic susceptibilities (other than MRSA). Also, we did not did we assess the availability of sterile equipment, cleaning products or staff hygiene practices.

The proportion of HIV-exposed infants in the NNU was similar to the proportion born at the hospital, and we did not detect a significant survival difference by maternal HIV status. There was no increased rate of sepsis by maternal HIV status, and no difference in antibiotic usage to suggest increased rates of infection. Prior studies outside the NNU setting have found that HIV-exposed but uninfected infants have significantly higher mortality than HIV-unexposed infants, even when controlling for maternal factors[5, 11]. We believe that the higher level of care in the NNU, and the overall severity of illness in all infants, may have masked any early differences by maternal HIV status, if present. We did identify that HIV-exposed infants were more likely to be premature and to have lower mean birth weight than unexposed infants, similar to our findings in general surveillance at the hospital[34]. We could not specifically assess risk factors for mortality by infant HIV status, as no infants in this study were tested for HIV infection (routine HIV PCR testing of HIV-exposed infants in Botswana occurs at 6 weeks of life). In addition, we lacked maternal HIV RNA at delivery and other potential risk factors specific to HIV-exposed infants.

Our study had several limitations. The maternal obstetric record was often incomplete, and we were not able to assess the contribution of maternal immunologic or nutritional status on neonatal mortality. The calculation of gestational age by the use of the LMP is less precise than use of ultrasound, though we do not expect significant differences in gestational age calculations by HIV-exposure or feeding method. This study did not include mortality that occurred after infant discharge or among non-NNU infants. Because we lacked a comparator group of discharged neonates living in the outpatient setting, this study was not intended as an overall assessment of all neonatal mortality. Rather, our focus was to describe outcomes and risk factors specific to the NNU setting.

In conclusion, our study highlights the high rate of neonatal mortality in the NNU setting and identifies low Apgar scores, extreme prematurity, and lack of enteral feeding as the most important risk factors for mortality. This study also provides cautious reassurance that critically ill HIV-exposed formula fed infants are not more likely to die, once admitted to a NNU, when compared with critically ill HIV-unexposed breastfed infants. While it is unlikely that there will be sufficient resources in much of the developing world to markedly improve outcomes for very low birth weight (<1500g) and very premature (<28 weeks gestation) infants, there is certainly room to improve. Further study is required to know whether interventions such as parenteral feeding and appropriate IV fluid resuscitation, management of sepsis guided by antimicrobial susceptibility patterns, increased number of mechanical ventilators in the NNU, or improved obstetric care to minimize preterm deliveries will lead to decreased neonatal mortality.

Acknowledgments

We are grateful to the staff of maternity ward and special care baby unit at Princess Marina Hospital and to our research assistants, Kelebogile Binda, Onalenna Nthase and Itereleng Kelapile. We would like to thank the Pasteur Clinical Research Program, Office of Enrichment Programs at Harvard Medical School and the Doris Duke Clinical Research Foundation for providing financial support for this study. This work was also conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from Harvard University and its affiliated academic health care centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.

References

1. United Nations General Assembly. United Nations Millennium Declaration. A/RES/55/2. United Nations; New York, NY: 2000. http://www.un.org/millenniumgoals/childhealth.shtml
2. United Nations. The Millennium Development Goals Report 2009. United Nations Department of Economic and Social Affairs; New York: 2009.
3. Lozano R, Wang H, Foreman KJ, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet. 2011; 378:1139–65. [PubMed: 21937100]
4. Rajaratnam JK, Marcus JR, Flaxman AD, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970–2010: a systematic analysis of progress towards Millennium Development Goal 4. Lancet. 2010; 375:1988–2008. [PubMed: 20546887]
5. Axelson H, Bergh AM, Chopra M, et al. Sub-Saharan Africa's mothers, newborns, and children: where and why do they die? PLoS Med. 2010; 7(6):e1000294. [PubMed: 20574524]

6. Oestergaard MZ, Inoue M, Yoshida S, et al. United Nations Inter-Agency Group for Child Mortality Estimation and the Child Health Epidemiology Reference Group. Neonatal mortality levels for 193 countries in 2009 with trends since 1990: a systematic analysis of progress, projections, and priorities. PLoS Med. 2011; 8(8):e1001080. [PubMed: 21918640]
7. Shapiro RL, Lockman S. Mortality among HIV-exposed infants: the first and final frontier. Clin Infect Dis. 2010; 50(3):445–7. [PubMed: 20047482]
8. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet. 2005; 365:891–900. [PubMed: 15752534]
9. Inter-Agency Task Team (IATT) on the Prevention of HIV infection among Pregnant Women, Mothers, and their Children. PMTCT and Pediatric Care and Treatment Situation Analysis. Botswana: 2006.
10. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. JAMA. 2006; 296:794–805. [PubMed: 16905785]
11. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F, Ghent International AIDS Society (IAS) Working Group on HIV Infection in Women and Children. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004; 364:1236–43. [PubMed: 15464184]
12. Kuhn L, Aldrovandi GM, Sinkala M, et al. Effects of early, abrupt weaning for HIV-free survival of children in Zambia. N Engl J Med. 2008; 359:130–141. [PubMed: 18525036]
13. Marinda E, Humphrey JH, Iliff PJ, et al. Child mortality according to maternal and infant HIV status in Zimbabwe. Pediatr Infect Dis J. 2007; 26:519–526. [PubMed: 17529870]
14. 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]
15. 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. 2006; 41(4):504–8. [PubMed: 16652060]
16. Omoigberale AI, Sadoh WE, Nwaneri DU. A 4 year review of neonatal outcome at the University of Benin Teaching Hospital, Benin City. Niger J Clin Pract. 2010; 13(3):321–5. [PubMed: 20857794]
17. Woldehanna TD, Idejene ET. Neonatal mortality in a teaching hospital, North Western Ethiopia. Cent Afr J Med. 2005; 51(3-4):30–3. [PubMed: 17892229]
18. Orimadegun AE, Akinbami FO, Tongo OO, Okereke JO. Comparison of neonates born outside and inside hospitals in a children emergency unit, southwest of Nigeria. Pediatr Emerg Care. 2008; 24(6):354–8. [PubMed: 18562876]
19. Arafa MA, Alshehri MA. Predictors of neonatal mortality in the intensive care unit in Abha, Saudi Arabia. Saudi Med J. 2003; 24(12):1374–6. [PubMed: 14710287]
20. Pepler PT, Uys DW, Nel DG. Predicting mortality and length-of-stay for neonatal admissions to private hospital neonatal intensive care units: a Southern African retrospective study. Afr Health Sci. 2012; 12(2):166–173. [PubMed: 23056023]
21. Schrag SJ, Cutland CL, Zell ER, et al. PoPS Trial Team. Risk Factors for Neonatal Sepsis and Perinatal Death among Infants Enrolled in the Prevention of Perinatal Sepsis Trial, Soweto, South Africa. Pediatr Infect Dis J. 2012; 31:821–6. [PubMed: 22565291]
22. Kayode GA, Adekanmbi VT, Uthman OA. Risk factors and a predictive model for under-five mortality in Nigeria: evidence from Nigeria demographic and health survey. BMC Pregnancy Childbirth. 2012; 12:10. [PubMed: 22373182]
23. McCurdy RJ, Kjerulff KH, Zhu J. Prenatal care associated with reduction of neonatal mortality in Sub-Saharan Africa: evidence from Demographic and Health Surveys. Acta Obstet Gynecol Scand. 2011; 90(7):779–90. [PubMed: 21426311]
24. Hole MK, Olmsted K, Kiromera A, Chamberlain L. A neonatal resuscitation curriculum in Malawi, Africa: did it change in-hospital mortality? Int J Pediatr. 2012:408689. 2012. [PubMed: 22164184]

25. Engmann C, Matendo R, Kinoshita R, et al. Stillbirth and early neonatal mortality in rural Central Africa. Int J Gynaecol Obstet. 2009; 105(2):112–7. [PubMed: 19201402]
26. Diallo AH, Meda N, Ouédraogo WT, Cousens S, Tylleskar T, PROMISE-EBF Study Group. A prospective study on neonatal mortality and its predictors in a rural area in Burkina Faso: can MDG-4 be met by 2015? J Perinatol. 2011; 31(10):656–63. [PubMed: 21372798]
27. Engmann C. Improving neonatal mortality in sub-Saharan Africa: any cause for optimism? J Perinatol. 2011; 31(12):745–8. [PubMed: 22124515]
28. Darmstadt GL, Bhutta ZA, Cousens S, et al. Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet. 2005; 365:977–988. [PubMed: 15767001]
29. Zupan J. Perinatal Mortality in Developing Countries. N Eng J Med. 2005; 352:2047–2048.
30. Forssas E, Gissler M, Sihvonen M, Hemminki E. Maternal predictors of perinatal mortality: the role of birth weight. Int J Epidemiol. 1999; 28:475–478. [PubMed: 10405851]
31. Kuhn L, Aldrovandi GM, Sinkala M, et al. Effects of Early, Abrupt Weaning for HIV-free Survival of Children in Zambia. N Engl J Med. 2008; 359:130–41. [PubMed: 18525036]
32. Cournil A, De Vincenzi I, Gaillard P, et al. Kesho Bora Study Group. Relationship between mortality and feeding modality among children born to HIV-infected mothers in a research setting: The Kesho Bora Study. AIDS. 2012 DOI:10.1097/QAD.0b013e32835d5226.
33. Fawzy A, Arpadi S, Kankasa C, et al. Early weaning increases diarrhea morbidity and mortality among uninfected children born to HIV-infected mothers in Zambia. J Infect Dis. 2011; 203:1222–30. [PubMed: 21459815]
34. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis. 2012; 206:1695–705. [PubMed: 23066160]

'What is already known on this topic'

- HIV-exposed uninfected infants have an increased risk of neonatal mortality compared with HIV-unexposed infants in the general population
- Early formula feeding is a risk factor for neonatal mortality among HIV-exposed infants outside of the NNU setting
- Neonatal mortality increased 400% in Botswana from 1991-2003, coinciding with the HIV epidemic

'What this paper adds'

- HIV-exposure did not increase the risk of neonatal mortality in the NNU setting
- Infants who were formula fed or had mixed feeding were not at increased risk of death compared with those who were exclusively breast fed
- The most important risk factor for neonatal mortality was the lack of any enteral feeding (NPO)

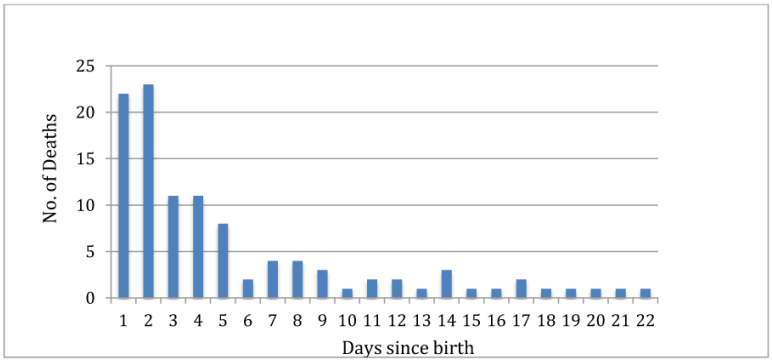

Figure 1.
Timing of Neonatal Deaths at the Neonatal Intensive Care Unit, Princess Marina Hospital, Gaborone, Botswana

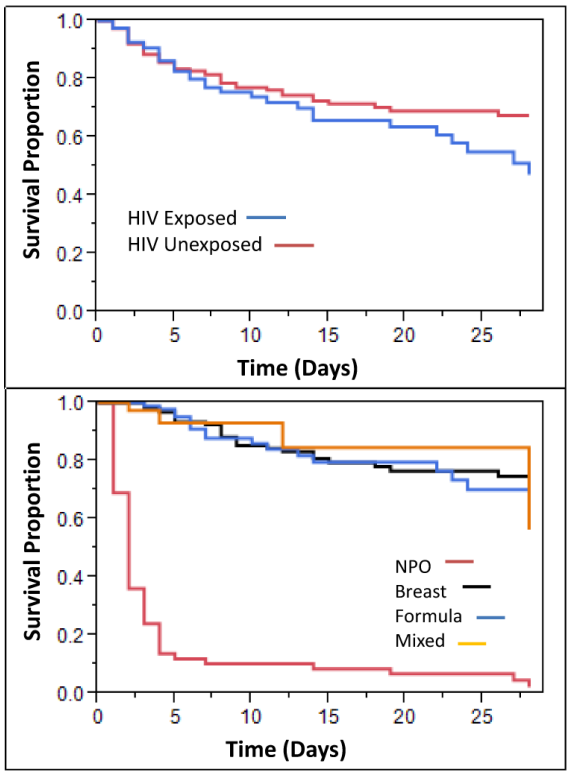

Figure 2.
Survival by HIV-exposure Status and Feeding Method

Table 1

Maternal and Infant Characteristics of Infant NNU Admissions

	Number of Infants (%) N=449
Maternal Age	27 (6%)
<18	381 (85%)
18-35	34 (8%)
>35	7 (2%)
Missing	
Maternal Parity	115 (26%)
Nulliparous	145 (32%)
Multiparous (gravid 1-3)	4 (1%)
Multiparous (gravid >=4)	185 (41%)
Missing	
Place of Birth	315 (70%)
Princess Marina Hospital	80 (18%)
District Hospitals	30 (7%)
Gaborone City Clinic	15 (3%)
Home	9 (2%)
Other	0
Missing	
Infant Gender	230 (51%)
Male	219 (49%)
Female	0
Missing	
Gestational Age at Birth	42 (9%)
<28 weeks	238 (53%)
28-36 weeks	168 (37%)
≥37 weeks	1 (1%)
Missing	
Birth weight	36 (8%)
<1000g	102 (23%)
1000-1499g	142 (32%)
1500-2499g	169 (38%)
>=2500	0
Missing	
Apgar Score	178 (40%)
<7 at 1 minute	105 (23%)
<7 at 5 minutes	60 (13%)
<7 at 10 minutes	
Feeding Strategy	67 (15%)
NPO	201 (45%)
Exclusive Breastfeeding	132 (29%)
Exclusive Formula	40 (9%)
Mixed Feeding	9 (2%)
Missing	
HIV Exposure Status	128 (29%)
HIV-Exposed	272 (61%)
HIV-Unexposed	49 (11%)
Unknown	

Table 2

Causes of Neonatal Mortality in the NNU, by HIV Exposure Status*

Diagnosis	HIV-Exposed Infants (N=35)	HIV-Unexposed Infants (N=55)	P-value
Premature Delivery	16 (45.7%)	20 (36.4%)	0.38
Sepsis	8 (22.9%)	12 (21.9%)	0.92
Low Apgar Score/Asphyxia	5 (14.3%)	9 (16.4%)	0.79
Other	2 (5.8%)	7 (12.7%)	0.48
Respiratory Distress	4 (11.4%)	3 (5.5%)	0.42
Meconium Aspiration	0	1 (1.8%)	--
Hydrocephalus/Myelomeningocele	0	1 (1.8%)	--

* primary discharge diagnosis for all babies who died

Table 3

Risk Factors for Neonatal Mortality among Infants Admitted to the NNU

	Total Deaths (N, % with characteristic that died)	Unadjusted HR (95%CI)	p-value	Adjusted HR* (95%CI)	p-value
Gestational Age <28 weeks 28-36 weeks 37-42 weeks >42 weeks	31 (74%) 74 (31%) 21 (14%) 3 (20%)	4.1 (2.3, 7.1) 1.2 (0.7, 2.0) 1.0 1.6 (0.5, 5.4)	<.0001	2.0 (1.1, 3.8)	0.03
Birth weight <1500g 1500-2499g >=2500g	70 (54%) 87 (33%) 23 (13%)	2.7 (1.7, 4.4) 0.8 (0.4, 1.5) 1.0	<.0001	0.99 (0.96, 1.02)**	0.61
Feeding status NPO Breast feeding Formula Feeding or mixed feeding	60 (90%) 17 (13%) 31 (13%)	19.8 (13.3, 9.5)^ 0.92 (0.5, 1.6)# 1.0	<.0001 0.76	18.8 (10.3, 34.2)	<.0001
HIV-exposed **HIV-unexposed**	35 (28%) 55 (21%)	1.14 (0.95, 1.4) 1.0	0.16	1.0 (0.6, 1.7)	0.92
Sepsis **No Sepsis**	30 (36%) 80 (22%)	1.6 (1.0, 2.4) 1.0	0.04	--	--
Respiratory Failure **No Respiratory Failure**	33 (35%) 77 (22%)	1.8 (1.2, 2.7) 1.0	0.007		
Maternal Age < 18 years 18-35 years >35 years	7 (26%) 89 (28%) 5 (15%)	1.1 (0.5, 2.4) 1.0 0.4 (0.2, 1.2)	0.76 0.16	-	-
Maternal Parity Primigravid Multiparous (0-3) Multiparous (>=4)	16 (14%) 38 (30%) 3 (18%)	0.67 (0.2, 2.3) 1.3 (0.4, 4.2) 1.0	0.52 0.67	--	--
Place of Birth All Referral PMH	48 (36.3%) 62 (19.9%)	1.5 (1.1, 2.2) 1.0	0.03	1.1 (0.6, 1.9)	0.75
APGAR score <7 at 10 minutes >=7 at 10 minutes	36 (60.0%) 65 (18.3%)	4.4 (2.9, 6.7) 1.0	<0.001	2.5 (1.5, 4.2)	0.0007

*adjusted for birthweight (continuous variable), premature birth <28 weeks, NPO status, Apgar Score at 10 min, place of birth, and HIV exposure,

**per 100g increase in neonatal birthweight,

^NPO status compared to any feeding,

#Exclusive breastfeeding compared to exclusive formula feeding or mixed feeding, excluding NPO infants