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Long Term Follow-up of Children in the HIVNET 012 Perinatal HIV Prevention Trial: Five-Year Growth and Survival

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Abstract

Objectives—To describe five year growth, survival and long-term safety among children exposed to nevirapine or zidovudine in an African perinatal prevention trial, HIVNET 012.

Methods—All study children who were alive at eighteen months of age were eligible for an extended follow-up study. Children whose families consented were enrolled and evaluated every six months from 24 to 60 months. At each visit, history, physical exam and growth measures were taken. From these measurements Z scores based on World Health Organization (WHO) standards were computed. Serious adverse event data were collected. Data from the initial and extended follow-up cohorts were included in the analysis.

Results—528 study children were alive at age 18 months, and 491 (426 HIV uninfected; 65 infected) were enrolled into the follow-up study. Both exposed but uninfected children and HIV infected children were substantially below WHO growth standards for weight and height. Head circumference Z scores for uninfected children were comparable to WHO norms. Five-year survival rates were 93% for uninfected children versus 43% for infected children. Long-term safety and growth outcomes in the two study arms were similar.

Conclusions—Both infected and uninfected children in the five-year HIVNET 012 follow-up showed poor height and weight growth outcomes, underscoring the need for early nutritional interventions to improve long-term growth of *all* infants born to HIV-infected women in resource limited settings. Likewise, the low five year survival among HIV infected children support the importance of early initiation of antiretroviral therapy. Both peripartum nevirapine and zidovudine were safe.

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Conflict of Interest
None of the authors have a conflict of interest.

Introduction

HIV/AIDS continues to have a profound effect on the health of children worldwide. Despite advances in prevention of mother to child HIV transmission (PMTCT), an estimated 330,000 children become infected through mother to child transmission (MTCT) in resource limited settings (RLS) each year.[1]

In the U.S. and Europe, the effects of HIV on pediatric growth, morbidity, and mortality have been studied extensively among both HIV infected and exposed uninfected children through prospective perinatal cohort studies. These studies have longitudinally tracked the growth and development, complications of HIV and treatment, hospitalizations, quality of life and survival of children born to HIV infected women, [2–6] prior to and following the availability of potent combinations of pediatric antiretroviral treatment.

However, in resource limited settings, with the largest pediatric HIV burden, there is a paucity of literature addressing the long term growth and survival of infants born to HIV infected women, including whether there are any late sequelae of exposure to perinatal antiretroviral (ARV) interventions. The limited numbers of published research studies have focused primarily on comparisons of infant morbidity and mortality in children below 36 months born to HIV infected mothers.[7–11]

The HIVNET 012 clinical trial,[9] which followed HIV exposed infants from birth to 18 months of age; and its companion rollover protocol, which followed participant children from 24 months up to age five years, provided a unique opportunity to address longer term growth, morbidity and survival as well as to assess potential late sequelae from short peripartum ARV exposure. The overall aim of this analysis was to compare the long term growth and survival among the HIV infected and uninfected children in the HIVNET 012 cohorts during a time period when antiretroviral treatment (ART) was not widely available. In addition, we examined the most common causes of hospitalizations in HIV uninfected and infected infants. Lastly we monitored for any late sequelae over the first five years of life among children born to mothers in the short course zidovudine (ZDV) compared to the nevirapine (NVP) study arms of HIVNET 012

Methods

Study Design

HIVNET 012 was a phase IIB randomized trial conducted to evaluate the safety and efficacy of peripartum nevirapine (NVP) or zidovudine (ZDV) in HIV infected Ugandan women and their infants for PMTCT. The study design, methods and outcomes were previously reported.[9] Longitudinal data were collected prospectively on a cohort of mother-infant pairs enrolled in the primary HIVNET 012 study from pregnancy through 18 months of age. Additional data were collected prospectively from HIVNET 012 participants who consented and enrolled in a roll-over extended follow-up observational study of children from 24 to 60 months of age. The Ugandan and Johns Hopkins institutional review boards approved both the primary and the extended follow-up protocols.

Study population

The extended follow-up study was conducted at the Makerere University-Johns Hopkins University (MU-JHU) Research Clinic in Kampala, Uganda from November 1999 to June 2004. This analysis includes all first-born HIVNET 012 infants followed from birth through 18 months of age in the primary study and those subsequently enrolled and followed in the extended follow-up study.

Procedures

Children born to HIV infected mothers in HIVNET 012 trial were prospectively followed for 18 months to determine drug safety, HIV infection rate and mortality.[9] Children enrolled in the follow-up study were seen every six months from 24 months through 60 months of age. At each visit, a history was obtained including breastfeeding status, current and interim illnesses, interim medications and serious adverse events and a routine physical examination was performed. The exam also included anthropometric measurements (weight, height, head circumference) and neurological assessment and neurodevelopmental screening, each done by trained staff using standardized procedures. Weight was measured using a balance beam scale and height was measured using either a wooden stadiometer or height rod (0.1 cm scale). Laboratory evaluations were done in HIV infected infants only including complete blood count (CBC), CD4 cell count and HIV RNA PCR at each visit. The neurodevelopmental screening was done every 6 months at follow up visits using the Denver developmental screening test (DDST) that evaluated four developmental domains: gross motor, fine motor, social contact and language skills. The HIVNET 012 children's performance was scored against the DDST age and gender normed age performance ranges as either Pass or Fail.

All study participants had access to free well and sick child care, growth monitoring, diagnosis and treatment of illnesses at the research clinic. Cotrimoxazole prophylaxis was provided to all HIV infected children and to18.44% (92/499) of HIV exposed infants during the first year of life. Combination pediatric ART was not available in Uganda during most of the period of follow-up. However, three children were started on ART in the final year of the five year follow-up. Study doctors collected all information during clinic visits using standardized medical forms. Children requiring hospitalization were referred to the Mulago National Referral Hospital. During hospitalizations, study staff abstracted pertinent clinical information, laboratory data, and discharge diagnoses from hospital records utilizing a standardized data collection form. Attempts to determine cause of death through family interviews were done for all participants who died at home during the 60 month follow-up period.

Statistical Methods

Infant Growth Analysis—Weight, height, weight-for-height, head circumference and body mass index were used to assess infant growth. Each outcome was standardized (Z score) for age and gender using World Health Organization (WHO) normal values.[12]

To estimate the effect of HIV-1 infection on infant growth through 5 years of age, for each standardized growth outcome we included trend for infant age, HIV infection status (time

dependent), and trend for time since HIV-infection, allowing a random intercept for each infant. Similar analyses were conducted for comparison of randomization arms (NVP versus ZDV).

Infant Mortality—Kaplan Meier methods were used to compute five year survival rates of infected and uninfected infants. Since 79% of HIV infections occurred by 8 weeks of age and follow-up time was through 5 years, infants were classified as infected versus uninfected, regardless of the actual time of infection. In a second analysis, infected infants were divided into 3 groups-identified as infected at birth, infected after birth up to 8 weeks and infected after 8 weeks of age. Cox proportional hazards regression was used to estimate the hazard ratio for death for HIV infected vs. uninfected infants. Infection status was defined as a time dependent covariate, and adjusted for baseline maternal log10 viral load.

Morbidity—The frequency of infant causes of hospitalization and death were compared using Chi-square tests. An infant could contribute to multiple categories, but each infant was only counted once within a category. Hematology results between ZDV and NVP arms were compared using t-tests at each visit for infected infants.

Long term safety between 2–5 years—The outcomes of hospitalizations, SAE, neurological exams and diagnoses, Denver developmental assessments and mortality between the ZDV and NVP arms were compared using Chi squared test and log rank tests.

All analyses were conducted using SAS version 9 (SAS Institute Inc., Cary, NC, USA).

Results

There were 651 births in HIVNET 012, of which 627 were included in this analysis (Figure 1). Four infants were stillborn, 13 were not first born infants, and 7 were excluded because their HIV status was unknown. Of these 627, 128 became HIV infected before 18 months of age: 59 infected at birth, 42 after birth but before 8 weeks of age and 27 after 8 weeks of age. At 18 months, 528 (84%) children were alive and in follow-up, of which 491 (93%) were consented (426 uninfected and 65 infected) and enrolled in the 5 year follow-up protocol. Of these, 18 children died, 26 were lost to follow-up, and 447 completed follow-up to 5 years of age, giving 91% retention in the extended follow-up study. The median duration of breastfeeding was 9 months (95% CI 8.8–10.3 AZT and 8.8(7.9–9.7 NVP group). There were 308 children randomized to the NVP arm, 302 to the ZDV arm and 17 to the placebo. The mean birth weight of the uninfected children was 3.15kg (SE 0.019) compared to 3.02 (SE 0.64) for the children infected at birth. There were no significant differences in infant gender, birth-weight and maternal age based on infant infection status.

Infant Growth Analysis—Mean growth in HIV infected infants was significantly lower than uninfected infants for weight, height and head circumference over the five year follow-up. (Figure 2). On average an HIV infected infant weighed 0.15 standard deviations (SD) less than an uninfected infant, in the first year after becoming infected ($p<0.0001$). In the same period, they were 0.2 SD shorter ($P <0.0001$). Our model predicts that at 5 years of

age, the weight of a study participant infant infected at birth would be 1.6 standard deviations less than the WHO normal, while an uninfected infant would be 0.9 SD less.

Table 1 shows the proportion of HIV infected and uninfected children with weight for age (WAZ) and height for age (HAZ) below −2 and −3 standard deviations at different time points. By 12 months of age 14% of HIV infected children had WAZ below −3SD compared to 5.4% in the uninfected children (p = 0.0040). This difference peaked at 3 years with 14.3% of HIV infected children with WAZ below −3SD compared to 1.1% of uninfected children (p = 0.0072), then steadily declined. The infected children were also significantly shorter than the uninfected children from 6 months through 5 years (6 months p = 0.0020, 60 months p = 0.0019). In regards to Weight for Height (WAH) Z scores, HIV infected children had significantly lower WAHZ scores at 12 and 18 months: at 12 months 7 % of HIV infected children had evidence of wasting with WAHZ scores below −3SD compared to 1.7 % of uninfected children (p = 0.0049). This difference peaked at 18 months with 7.3% of HIV infected children with WAHZ below −3SD compared to 0.5% of uninfected children (p <.0001), then steadily declined. There was no difference between infants assigned to NVP or ZDV in any growth outcomes after adjusting for HIV-1 infection status (data not shown). Assessment of secondary microcephaly identified 9 infants with head circumference < −3 SD, 7 infants randomized to NVP and 2 infants in the ZDV arm, HR = 3.2 (95% CI 0.7–15.5), p = 0.14.

Infant Mortality—Five-year survival in the HIV exposed uninfected children was 93% (95% CI 90%–95%) compared to 43% (95% CI 35%–53%) in the HIV infected infants (p< 0.0001) (Figure 3a). Stratifying by time of infection, infants infected at birth and those after birth but before 8 weeks of age, show a 5 year survival proportion of 39% (95% CI 26%–57%) and 39% (95% CI 28%–54%) respectively, whereas those infected after 8 weeks of age had a 61% (95% CI 44%–83%) survival (Figure 3b). Over 50% of the deaths in the infected children occurred within the first 2 years of life. If an infected child survives to age two, the chance of surviving to age five were greater than 70%, irrespective of time of infection.

The leading cause of death during the 5 year period for the infected children was diarrhea and its complications (SDC Table 1a), accounting for 42.9% of deaths, followed by pneumonia (31.4%). In the uninfected children, malaria (22.9%) and diarrhea (22.9%) combined contributed to close to 50% of the deaths. There was no difference in the three (99%) and five (98%) year survival in the uninfected children in ZDV and NVP arms (p=0.90).

Cotrimoxazole exposure and infant mortality: There was no difference in the survival between HIV uninfected infants exposed to Cotrimoxazole (93.5%) or not exposed to Cotrimoxazole (94.8%) (p= 0.73).

Morbidity findings

There were significant differences in the proportion of infected and uninfected children hospitalized for each of the leading five causes of hospitalization (SDC Table 1b). Malaria was the overall leading cause of hospital admission (21.9%). For infected children, however,

pneumonia was the leading cause of hospitalization (41.4%) followed by malaria (30.5%) and diarrhea (29.7%). Among uninfected children, the leading causes of hospitalizations were malaria (19.6%), anemia (9.2%), and pneumonia (8.2%). There were no differences in the proportion of children ever hospitalized between the ZDV and the NVP arms.(15.1% vs 12.7% P=0.46).

Hematological findings

There were no significant differences in hemoglobin concentrations, platelet counts, absolute neutrophil counts and CD4 cell counts in HIV infected infants in the ZDV and NVP arms throughout the 60 month period.

Developmental and Neurological Evaluations

There were no differences between the proportion of children who passed the Denver Developmental Assessment evaluations in the two study arms which were done at every 6 month visit and based on a combined analyses of all serial neurodevelopmental assessments: Gross motor assessment 82.7% vs 84.8% for ZDV vs NVP (p=0.55), Fine motor assessment 77.3% vs 80.1% for ZDV vs NVP(p=0.50), Social assessment 86.3% vs 84.55% for ZDV vs NVP(p=0.599) and Language assessment 7.94% vs 5.78% for ZDV vs NVP (p =0.38). Likewise, there were no statistical differences between the study arms in the proportion of children who experienced a neurological abnormality between two and five years (3.66% vs 3.96% for ZDV vs NVP) (p=0.87).

Discussion

This study examined growth patterns, long term safety of peripartum antiretroviral prophylaxis, morbidity and five year survival of children enrolled in the HIVNET 012 trial. It is one of only a few studies[13] that has monitored the long term growth and survival patterns of children born to HIV infected mothers in resource limited settings in the era before pediatric antiretroviral treatment was widely available. It is also unique in being the only study to date that has compared longitudinal growth patterns across treatment arms among children perinatally exposed to peripartum nevirapine and zidovudine, the most commonly used antiretrovirals for perinatal prevention in resource limited settings. Of importance, we found sustained lower weight and height compared to WHO growth standards in exposed but uninfected infants as well as infected children. In contrast, normal brain growth based on head circumference measurements was preserved among the uninfected children over the five year follow-up. Not surprisingly we found substantially lower weight, height, and head circumference among infected relative to uninfected children in this cohort.

The consistent poor growth through age five years in both HIV infected and uninfected children in the HIVNET 012 cohort likely reflects the high background rates of early childhood malnutrition, growth faltering and stunting seen in resource limited countries such as Uganda[14]. The pathogenesis of the poor growth is most likely multi-factorial with widespread poverty, low calorie weaning foods, unhygienic food preparation and feeding practices leading to diarrheal disease. Among the HIV infected children, rapid HIV disease

progression could also have contributed to the early severe malnutrition observed between 12–24 months of age. The longitudinal growth patterns between the Ugandan infected versus uninfected children in the HIVNET 012 cohort showed similar patterns to cohorts of perinatally HIV infected children in European and US cohorts with infected children having lower Z scores for all parameters.[15]

Five-year survival among HIV exposed uninfected children in the HIVNET 012 follow- up study cohort was significantly higher than that of the infected children (93% versus 43 %); and also slightly higher than overall Uganda national vital statistics for under five year survival (91% in 2011).[16] The higher HIVNET 012 five year survival of the uninfected children compared to these Uganda national data is encouraging and demonstrates that comprehensive medical care and close monitoring of children born to HIV infected women in RLS can substantially reduce pediatric mortality. Our study participants had access to medications for acute medical conditions as well as Cotrimoxazole prophylaxis for a proportion of exposed infants during the first year of life. This cheap and cost effective intervention could also have contributed to the high survival rates in the uninfected children in HIVNET 012, potentially related to reductions in malaria and diarrheal diseases. A study done in Uganda found a protective role of Cotrimoxazole in reducing malaria infections and improving survival in HIV affected families.[17]

The poor survival of the HIV infected children in the HIVNET 012 studies reflects an era when antiretroviral therapy (ART) was generally unavailable in Uganda. This low survival is similar to rates seen in other African studies of infected children in the pre-ART treatment era[7–11] but contrasts with the five year survival among perinatally HIV infected children in the U.S and Europe, which was close to 70% prior to the availability of ART[18–20]. Increased vulnerability of infected children to pneumonia, malaria, and diarrhea also contributed to the higher mortality seen among this group. The finding that children who became infected during breastfeeding compared to in utero or at birth, had better survival is of interest. We hypothesize that this may be related to more mature immune response repertoire to the HIV virus among older infants and/or protective effects afforded by maternal humoral or other protective factors in breast milk.

The low mortality in uninfected children and the lack of differences in hospitalizations SAE, neurological exams and Denver Developmental assessment between the two drug arms that have different toxicity profiles are reassuring concerning the long term safety of short course peripartum ARV exposure. There were also no significant differences in the hematologic parameters in HIV infected children exposed to peripartum NVP and ZDV.

Important strengths of the HIVNET 012 follow-up study include its prospective nature, extremely low loss to follow-up over the five year period of the study; documentation of serious adverse events in a standardized manner, the longitudinal physical growth measurements obtained by trained staff using calibrated measuring equipment.

There were certain limitations to the data available in the HIVNET 012 follow-up study. While follow-up was generally high, 7% of children from the original HIVNET 012 study were not available for the follow-up study. In addition, hospitalization and outpatient death

diagnoses were based mainly on clinical diagnosis as no autopsies were available to look more formally at specific causes of death. We also assumed that Cotrimoxazole prescribed and dispensed to infants was ingested by the participants. Lastly, CBC and CD4 cell counts were only available for HIV infected children after 18 months of age.

The growth, morbidity and mortality findings in this study emphasize the heightened vulnerability of HIV uninfected infants as well as HIV infected children born to HIV infected women. The growth findings highlight the need for early nutritional monitoring, counseling and support for HIV exposed infants in RLS to reduce mortality and the risk of failure-to-thrive. Nutritional supplementation should be directed towards those with growth faltering or overt under nutrition. There is a critical need for early identification of HIV infected infants in the first several months of life followed by rapid introduction of antiretrovirals for infected infants in order to reduce the high mortality for HIV infected children.[21]

Given the availability of donor funding for both pediatric and adult ARV as well increased availability of PCR diagnostics for early infant HIV diagnosis, there is cause for optimism that major improvements in under five survival can be achieved in the next several years among HIV infected children in RLS such as Uganda. Early detection and aggressive management of pneumonia and diarrhea in HIV infected children will also go a long way in reducing mortality in this population.

Careful attention must also be given to providing comprehensive long term quality care to HIV exposed uninfected children, who represent an extremely vulnerable population of children. Maternal Child health (MCH) clinics in high prevalence RLS should 1) emphasize early identification of HIV exposed but uninfected infants; 2) train clinic staff to routinely carry out low cost growth monitoring including the plotting and review of growth charts; 3) provide early nutritional interventions for uninfected infants and children who demonstrate a drop off in their growth parameters; 4) ensure high levels of immunization through regular attendance at well child clinics; 5) offer Cotrimoxazole to all HIV exposed infants in the first year of life and 6) provide timely treatment for acute pediatric illnesses like malaria, diarrhea and pneumonia that contribute significantly to morbidity and mortality in this group. To achieve this, international donor funding in concert with incountry resources will be required to strengthen the overall MCH infrastructure in most resource limited settings.

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References

1. [Accessed 05 April, 2013] http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf
2. Moye J, Rich KC, Kalish LA, et al. Natural history of somatic growth in infants born to women infected with Human Immunodeficiency virus. J Pediatr. 1996; 128 (1):58–69. [PubMed: 8551422]
3. Bertolli J, Hsu HW, Sukalac T, et al. Hospitalisation trends among children and Youths with Perinatal Human immunodeficiency virus infection 1990–2002. Pediatr Infect Dis J. 2006; (7):628–633. [PubMed: 16804434]
4. Tovo PA, de Martino M, Gabiano C, et al. Prognostic factors and survival in children with perinatal HIV -1 infection. The Italian Register for HIV-1 Infections in Children. Lancet. 1992; 339:1249–1253. [PubMed: 1349667]
5. European collaborative study. Fluctuations in symptoms in HIV infected children: The first 10 years of life. Pediatrics. 2001; 108:116–122. [PubMed: 11433063]
6. Blanche S, Tardieu M, Duliege A, et al. Longitudinal study of 94 symptomatic infants with perinatally acquired human immunodeficiency virus infection. Evidence for a bimodal expression of clinical and biological symptoms. Am J Dis Child. 1990; 144 (11):1210–1215. [PubMed: 1978551]
7. Taha TE, Kumwenda NI, Broadhead RL, et al. Mortality after the first year of life among human immunodeficiency virus type1-infected and uninfected children. Pediatr Infect Dis J. 1999; 18(8): 689–694. [PubMed: 10462337]
8. Taha TE, Graham SM, Kumwenda NI, et al. Morbidity among human Immunodeficiency virus 1 -infected and uninfected African children. Pediatrics. 2000; 106(6):E 77.
9. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and single dose Nevirapine compared with Zidovudine for prevention of mother to child transmission of HIV- 1 in Kampala, Uganda: 18 months follow up of the HIVNET 012 randomised trial. Lancet. 2003; 362(9387):859–868. [PubMed: 13678973]
10. Mbori–Ngacha D, Nduati R, John G, et al. Morbidity and Mortality in breast fed and formula fed infants of HIV- 1 infected women. JAMA. 2001; 286(19):2413–2420. [PubMed: 11712936]
11. Newell ML, Coovadia H, Cortina–Borja M, et al. 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(9441):1236–1243. [PubMed: 15464184]
12. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for- height and body mass index-for-age: Methods and development. Geneva: World Health Organization; 2006. Available at: http://www.who.int/childgrowth/standards/technical_report/en/index.html
13. Spira R, Lepage P, Dabis F, et al. Natural history of Human Immunodeficiency virus type 1 infection in children : A five year prospective study in Rwanda. Pediatrics. 1999; 104:Pe 56.
14. Bridge A, Kipp W, Konde-Lule J, et al. Nutritional status of young children in AIDS affected households and controls in Uganda. Am J Trop Med Hyg. 2006; 74(5):926–931. [PubMed: 16687705]
15. Newell ML, Borja MC, et al. European Collaborative study. Height weight and growth in children born to mothers with HIV infection in Europe. Pediatrics. 2003; 111:e52–60. [PubMed: 12509595]
16. The state of the World's Children. 2012. Available at http://www.unicef.org/uganda/UNICEF_UGANDA_
17. Mermin J, Ekwaru JP, Liechty CA, et al. Effect of Cotrimoxazole prophylaxis, antiretroviral therapy and insecticide treated bed nets on the frequency of malaria in HIV-1 infected adults in Uganda; a prospective cohort study. Lancet. 2006; 367 (9518):1256–1261. [PubMed: 16631881]
18. Kline M, Paul ME, Bohannon B, et al. Characteristics of children surviving to 5 years of age or older with Vertically Acquired HIV Infection. Pediatr AIDS HIV Infect. 1995; 6(6):350–353. [PubMed: 11361459]
19. Blanche S, Newell ML, Mayaux MJ, et al. Morbidity and Mortality in European children vertically infected by HIV-1. The French Pediatric HIV Infection Study Group and European Collaborative Study. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 14:442–50. [PubMed: 9170419]

20. The European Collaborative Study. natural history of vertically acquired human immunodeficiency virus-1 infection. Pediatrics. 1994; 94:815–819. [PubMed: 7970995]

21. Violari A, Cotton MF. CHER Study Team, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008; 359:2233–44. [PubMed: 19020325]

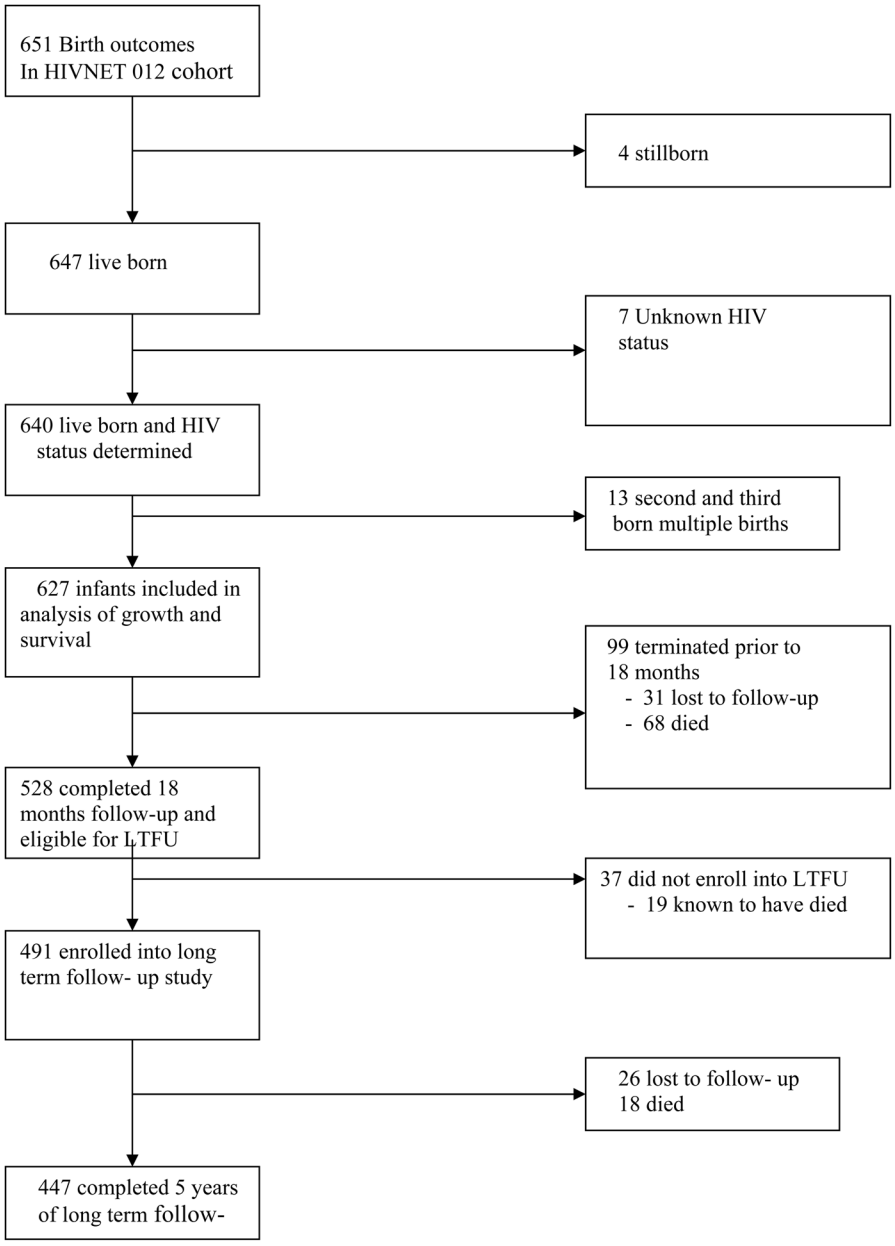

Figure 1.
Study Flow Chart, Infants Included in the Growth Analysis

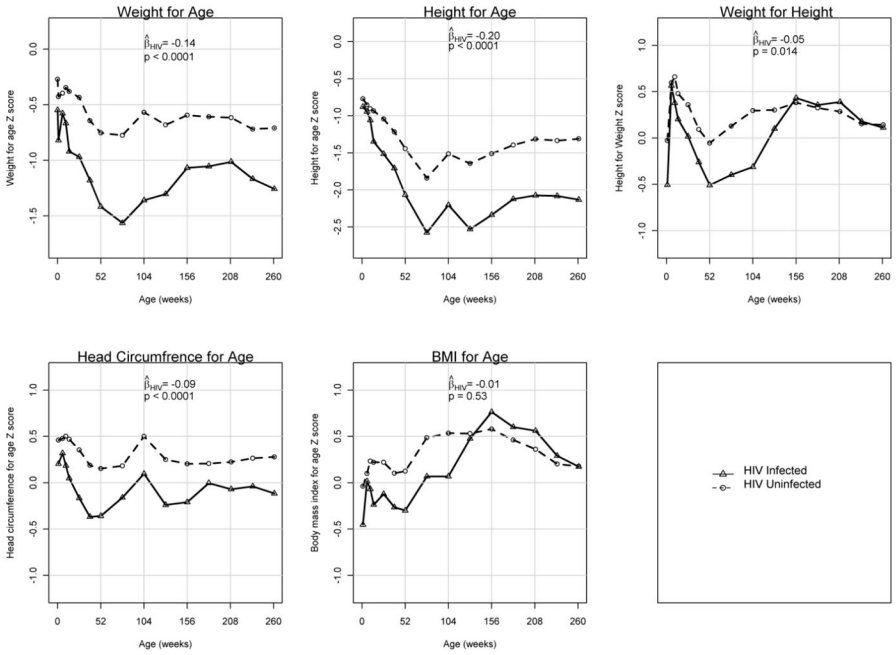

Figure 2.

Infant Growth (Z scores) by HIV-1 Infection Status and Age in Weeks

Plots of mean group values for each growth Z score at each study visit. βHIV estimates the mean difference in Z score between HIV uninfected and infected infants

Figure 3a:

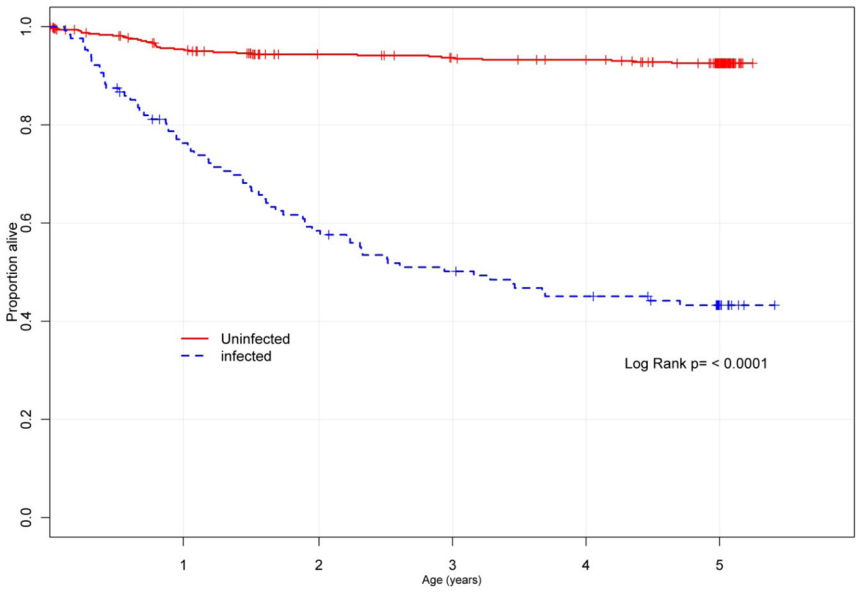

Figure 3b:

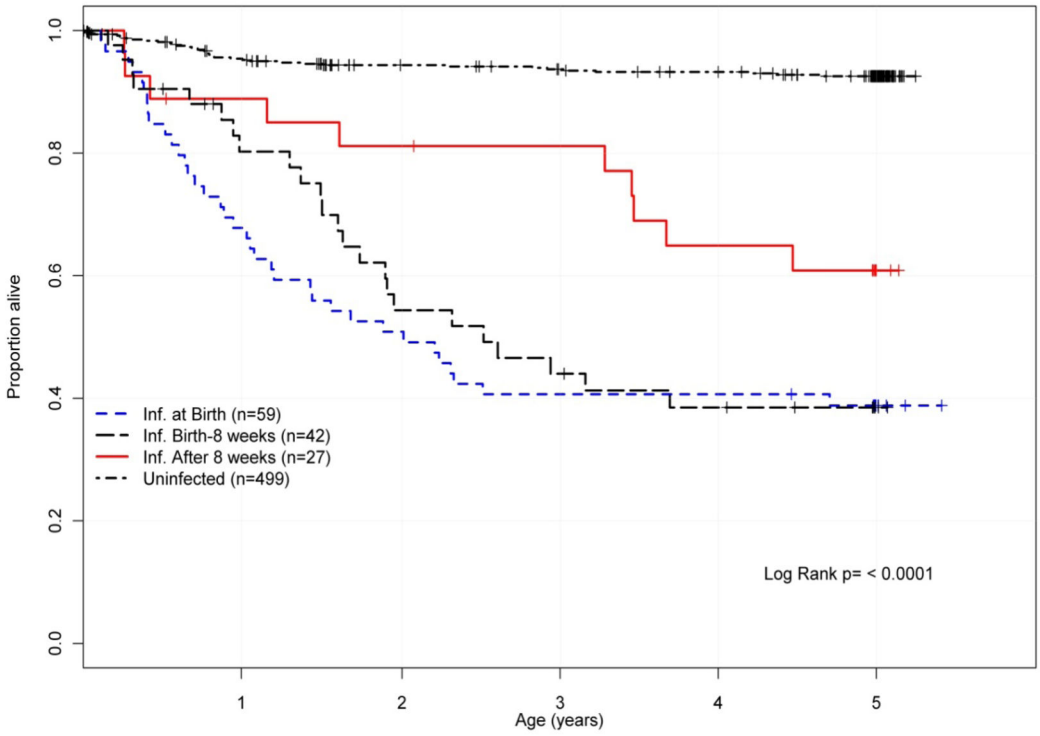

Figure 3.

Figure 3a: Kaplan Meier Plot of Infant Survival by HIV Infection Status

Estimated 5 year survival was 93% (95% CI 90–95%), HIV uninfected infants and 43% (95% CI 35–53%) for HIV infected.

Figure 3b: Kaplan Meier Plot of Infant Survival by Timing of HIV infection

Estimated 5 year survival was 93% (95% CI: 90–95%), HIV uninfected infants; 61% (95% CI: 44–83%), HIV infected after 8 weeks; 39% (95% CI: 28–54%) HIV infected between birth and 8 weeks; 39% (95% CI 26–57%) HIV infected at birth.

Table 1

Proportion of Infants below 2 and 3 Standard Deviations, by Time Dependent HIV Infection Status

	Below 2 SD			Below 3 SD		
	Uninfected	Infected		Uninfected	Infected	
	Number (%)	Number (%)	P value[Ψ]	Number (%)	Number (%)	P value[Ψ]
Birth						
Weight for Age	21/556 (3.8%)	5/59 (8.5%)	0.0882	3/556 (0.5%)	1/59 (1.7%)	0.2939
Month 6						
Weight for Age	42/472 (8.9%)	22/93 (23.7%)	<.0001	14/472 (3.0%)	8/93 (8.6%)	0.0102
Height for Age	86/471 (18.3%)	37/93 (39.8%)	<.0001	16/471 (3.4%)	10/93 (10.8%)	0.0020
Weight for height	16/471 (3.4%)	8/92 (8.7%)	0.0214	5/471 (1.1%)	0/92 (0.0%)	0.3209
Month 12						
Weight for Age	65/459 (14.2%)	28/86 (32.6%)	<.0001	25/459 (5.4%)	12/86 (14.0%)	0.0040
Height for Age	138/459 (30.1%)	42/86 (48.8%)	0.0007	40/459 (8.7%)	18/86 (20.9%)	0.0007
Weight for height	24/459 (5.2%)	11/86 (12.8%)	0.0087	8/459(1.7%)	6/86 (7.0%)	0.0049
Month 18						
Weight for Age	54/443 (12.2%)	28/83 (33.7%)	<.0001	15/443 (3.4%)	14/83 (16.9%)	<.0001
Height for Age	187/443 (42.2%)	58/83 (69.9%)	<.0001	67/443 (15.1%)	27/83 (32.5%)	0.0001
Weight for height	11/442 (2.5%)	9/82 (11.0%)	0.0002	2/442 (0.5%)	6/82 (7.3%)	<.0001
Month 36						
Weight for Age	26/369 (7.0%)	13/55 (23.6%)	<.0001	6/369 (1.6%)	5/55 (9.1%)	0.0012
Height for Age	97/360 (26.9%)	33/51 (64.7%)	<.0001	28/360 (7.8%)	15/51 (29.4%)	<.0001
Weight for height	0/360 (0.0%)	1/52 (1.9%)	0.0084	0/360 (0%)	0/52 (0%)	-
Month 48						
Weight for Age	22/387 (5.7%)	10/51 (19.6%)	0.0003	4/387 (1.0%)	2/51 (3.9%)	0.0953
Height for Age	85/378 (22.5%)	28/50 (56.0%)	<.0001	14/378 (3.7%)	9/50 (18.0%)	<.0001
Weight for height	4/378 (1.1%)	2/51 (3.9%)	0.1021	1/378 (0.3%)	0/51(0.0%)	0.7131
Month 60						
Weight for Age	24/375 (6.4%)	12/44 (27.3%)	<.0001	6/375 (1.6%)	0/44 (0.0%)	0.3980

	Below 2 SD			Below 3 SD		
	Uninfected	Infected		Uninfected	Infected	
	Number (%)	Number (%)	P value[Ψ]	Number (%)	Number (%)	P value[Ψ]
Height for Age	78/374 (20.9%)	25/44 (56.8%)	<.0001	21/374 (5.6%)	8/44 (18.2%)	0.0019
Weight for height	1/375 (0.3%)	1/48 (2.1%)	0.0841	1/375 (0.3%)	0/48(0.0%)	0.7202

[Ψ]Chi-Square test