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Pediatric HIV-1 in Kenya: Pattern and Correlates of Viral Load and Association With Mortality

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Abstract

Background—There is limited information regarding the pattern and correlates of viral replication in vertically HIV-1–infected children and its role on their outcomes in resource-limited settings.

Methods—HIV-1–infected infants were followed from birth to 24 months. Serial HIV-1 RNA levels were compared in infants infected in utero (<48 hours), peripartum (48 hours–1 month), and late postnatal (after 1 month). Cofactors for viral peak [highest viral load (VL) within 6 months of infection] and set point and mortality were determined.

Results—Among 85 HIV-1–infected infants, 24 were infected in utero, 41 peripartum, 13 late postnatal; 7 had no 48-hour assay. HIV-1 VL set point was significantly lower in infants infected >1 month vs. ≤1 month (5.59 vs. 6.24 $\log_{10}$ copies per milliliter, $P = 0.01$). Maternal VL correlated with peak infant VL ($P < 0.001$). Univariately, infant peak and set point VL and 6-month CD4% <15% predicted mortality; and 6-month CD4% <15% remained independently predictive in multivariate analyses (hazard ratio = 4.85, 95% confidence interval: 1.90 to 12.36).

Conclusions—Infants infected after the age of 1 month contained virus better than infants infected before 1 month of age. Maternal VL predicted infant VL, which, in turn was associated with early mortality.

Keywords

HIV-1; mortality; pathogenesis; pediatric; timing of HIV-1 infection; viral load

INTRODUCTION

Control of HIV-1 viremia is a crucial determinant of disease course in HIV-1–infected individuals. Peak and set point plasma viral levels in infants have been observed to be considerably higher than those in adults.[1] Inferior control of viremia in infants may partly explain their more rapid course of HIV-1 disease compared with adults. Peak plasma viremia

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during initial months after primary infection has been shown to be associated with disease progression in children.[2–7] Control of virus after initial peak plasma viremia differs between adults and children. In adults, after an initial peak, viral levels decline rapidly and stabilize at a fairly constant "set point" within 6–12 months after primary infection, and viral set point is associated with long-term disease course.[1,8] In children, viral levels may fail to decline after initial peak in plasma viral levels or have a less rapid decline than that observed in adults.[2,9] Infant set point is difficult to define, and less is known regarding the predictive role of set point on infant HIV-1 progression.

Longitudinal data on HIV-1 viral load (VL) in African HIV-1–infected children is limited. In the setting of high incidence of infectious diseases and malnutrition, both of which may influence control of viremia, it is possible that levels of viremia differ from those observed among children in the industrialized world. In addition, in contrast to European/US cohorts, a substantial number of pediatric HIV-1 infections in Africa are acquired via breastfeeding, and it is plausible that timing and route of acquisition of HIV-1 may influence subsequent course of HIV-1 in infancy. As pediatric HIV-1 treatment programs expand, it is important to determine predictors of viral control in African cohorts to inform development of regionally specific guidelines regarding treatment initiation. We previously described cofactors for mortality in a cohort of HIV-1–infected children, without access to infant viral levels.[10] We subsequently determined the pattern and correlates of infant HIV-1 VL and its association with mortality in a larger group of infants derived from the same cohort.

METHODS

Cohort and Clinical Procedures

This was a prospective cohort study involving HIV-1–infected infants from a perinatal cohort in Nairobi, Kenya, recruited between 1999 and 2003.[10] Written informed consent was obtained from mothers for themselves and their infants, and the study was reviewed and approved by the University of Washington institutional review board and Kenyatta National Hospital Ethical Review Committee. HIV-1–seropositive women received short-course zidovudine for prevention of infant HIV-1[11] and fed their infants as per their preference after counseling. Infants were seen monthly until 1 year and quarterly until 2 years or death. Study physicians examined the children and interviewed mothers regarding infant health. Infant blood was obtained within 48 hours of birth and at 1, 3, 6, 9, and 12 months for HIV-1 detection and RNA levels. Once a child was identified to be HIV-1 infected, CD4 counts were performed on subsequent samples; further samples were obtained at 15, 18, 21, and 24 months. Children received trimethoprim/sulfamethoxazole prophylaxis, treatment of outpatient illnesses, and referral for hospitalization. Programs with provision of highly active antiretroviral therapy (HAART) became available in 2004, and eligible children were referred to these programs. Data from children who initiated HAART were censored after HAART initiation.

Laboratory Procedures

HIV-1 *gag* DNA assays were conducted on filter paper dried blood spots and HIV-1 RNA assays on plasma specimens.[12] Infants with either a positive HIV-1 DNA or RNA assay on at least 2 time points were considered positive unless there were no specimens collected after detection of HIV-1, in which case the single result was considered positive. HIV-1 RNA assays were performed on all retrospectively collected samples from the visit before the first positive filter paper result until end of follow-up, using the Gen-Probe HIV-1 viral load assay, which is sensitive for detection of Kenyan HIV-1 subtypes A, C, and D.[13] Timing of infection was defined by the earliest HIV-1 detection. The lower limit of detection for the assay was 7 copies per milliliter and no specimens in this study fell below this lower limit of detection.

Total white cell counts, lymphocyte differential count, and percentage of CD4 and CD8 lymphocytes were determined on fresh anticoagulated blood samples using flow cytometry (Facscan; Becton Dickinson, Mountainview, CA).

Data Analysis

In utero infection was defined as detection of HIV-1 in the first 48 hours of life. Peripartum HIV-1 infection was defined as occurring >48 hours but before 1 month of life. Thus, peripartum HIV-1 infection included HIV-1 acquired late in utero, intrapartum, or via early breastfeeding. Late postpartum infections were defined as infections detected after 1 month of life. Infants who were detected to have HIV-1 during the first month of life but who did not have an assay in the first 48 hours of life were determined to have "early" HIV-1 infection but could not be included in other analyses that required more precise timing of infection (ie, in utero, peripartum). Infants who lacked assays at or before 1 month were included in "overall"summaries but were excluded from analyses involving timing of infection.

The pattern of VL over time since infection for children infected in utero, peripartum, and late through breastfeeding was assessed graphically using Loess curves. VLs were log transformed. Peak VL was defined as the maximum VL level attained during the first 6 months post infection, and set point VL was defined as the first available VL measurement occurring ≥1.5 months after peak VL. Previous studies have used a narrower window (<2 months) to define peak; however, a longer window of 6 months allowed us to capture most peak events in all 3 groups.[8] The difference between VL at birth and peak VL for infants infected in utero was tested using the paired *t* test.

Peak and set point VLs for infants infected in utero, peripartum, and late were compared using the Student *t* test. To determine correlates of infant peak and set point VL, continuous covariates of interest were dichotomized at the median (eg, maternal age) or a clinically relevant value (eg, maternal CD4 count <350 cells/mm^3 and $\log_{10}$ maternal VL > 10^5 copies/mL). Linear regression was used to assess the effects of these correlates on peak and set point VL, and Pearson correlation coefficient was used to assess the correlations between maternal VL and infant VL.

To determine the risk of mortality in the first 2 years of life associated with peak VL, set point VL, and infant CD4% <15%, univariate Cox proportional hazards models were performed, with time from HIV-1 infection to death as outcome. Person-time was calculated with start time as the time of first detection of HIV-1 and stop time as time of death or if the infant survived, the time of last follow-up visit. Multivariate analysis were conducted to determine independent predictive value of HIV-1 RNA peak, HIV-1 RNA set point, and 6-month CD4% <15% on mortality, using the continuous measures of these covariates. The final model only included 1 measure of HIV-1 RNA because RNA peak and RNA set point were colinear.

RESULTS

Cohort Characteristics

The analysis included 85 HIV-1–infected infants. Mothers of the 85 infants had a median age of 25 years (range: 18—38 years), had received a median of 8 years education (range: 0—14 years). Seventy-one (84%) were married, and 66 (78%) lived in single-room houses (Table 1). Eighty-two percent of women received antenatal zidovudine, and 79% delivered vaginally. Maternal CD4 count as measured at ~32 weeks gestation ranged from 6 to 880 cells per microliter, with a median of 365 cells per microliter; 17 women (20%) had CD4 <200 cells per microliter. Median maternal VL (plasma RNA) at ~32 weeks gestation was 5.19 $\log_{10}$ copies per milliliter with an interquartile range of 4.75–5.66. After zidovudine, this dropped

by delivery to a median of 4.69 $\log_{10}$ copies per milliliter (interquartile range: 4.04–5.27 copies). During 2-year follow-up, 8 mothers (9%) died.

Infants were born at median gestation of 40 weeks (range: 33–40 weeks), with a median birth weight of 3.0 kg (range: 1.6–4.0 kg). Thirty-nine infants (46%) were female and 72 (86%) breastfed. HIV-1 infection occurred in utero in 24 (28%), peripartum in 41 (48%), indeterminate (either in utero/peripartum) in 7 (8%), and late postpartum in 13 (15%). Among 52 infants who lived ~6 months after HIV infection and had CD4 assays at that time, median CD4 was 1350 (range: 61–3692) cells, and median CD4% was 20 (range: 3%–40%); 16 of these 52 infants (31%) had CD4% <15%. The infants were followed up to a median age of 12 months after birth (range: 1–29 months) and for a median of 11 months after infection (range: 0–25 months). Death in the first 2 years of life occurred in 47 infants (55%) at a median age of 7.5 months (range: 0–24 months), with a median time from infection to death of 7.3 months (range: 0–24 months) (Table 1).

Pattern of VL

Figure 1 shows HIV-1 RNA levels over time for infants infected in utero (n = 24), peripartum (n = 41), and late (n = 13). Infants infected in utero had a lower initial HIV-1 RNA level (5.09 $\log_{10}$ copies/mL) than subsequent levels, likely due to prenatal/intrapartum zidovudine dosing ($P < 0.001$ for difference between birth and peak). After birth, HIV-1 RNA levels increased and reached a plateau of ~6.5 $\log_{10}$ copies per milliliter gradually decreasing thereafter. Infants infected after birth but before 1 month had a generally flat slope with a slight decrease over time. Infants infected late postpartum had initial peaking of HIV-1 RNA at 6.76 $\log_{10}$ copies per milliliter, with a well-defined decrease to levels significantly below infants infected earlier.

Comparison of Peak and Set Point VL in Infants Infected In Utero, Peripartum, and Late Postnatally

Peak plasma RNA levels were available for all 85 infants. Mean peak for the cohort was 6.79 $\log_{10}$ copies per milliliter [95% confidence interval (CI): 6.63 to 6.94] (Table 2). Peak viral levels did not differ significantly between infants infected in utero, peripartum, and late postnatally (6.49, 6.95, and 6.76 $\log_{10}$ copies/mL, respectively, $P = 0.3$, 0.4 for in utero or peripartum vs. late postnatally). Set point plasma RNA levels were available for 59 infants because several infants died or were lost to follow-up before set point. Median set point for the 59 infants was 6.13 $\log_{10}$ copies per milliliter (95% CI: 5.93 to 6.32). Set point levels of HIV-1 RNA were lower among infants infected late postnatally (5.59 $\log_{10}$ copies/mL) than among those infected in utero (6.11 $\log_{10}$ copies/mL $P = 0.1$) or peripartum (6.28 $\log_{10}$ copies/mL, $P = 0.03$). Infants infected late postnatally had significantly lower HIV-1 RNA set point levels than all infants infected early (<1 month) including in utero, peripartum, or early undefined ($P = 0.01$). Three additional definitions of set point were used in addition to the 1 above (first VL ≥ 6 weeks after peak with peak defined as occurring during the first 6 months post infection: (1) first VL at least 6 weeks after peak (occurring any time during follow-up), (2) first VL at least 6 weeks after peak VL (restricted to the first 12 months), or (3) nadir VL after peak (occurring in the first 6 months). In all 3 definitions of set point, late-infected infants (>1 month) had significantly lower set point than early infected infants ($P = 0.04$, 0.001, 0.007, respectively).

Cofactors for Peak and Set Point Viral Levels

Vaginal delivery, breastfeeding, zidovudine use, and maternal CD4 count <350 cells were not associated with infant HIV-1 peak or set point VL (Table 3). Maternal viral levels $>10^5$ copies per milliliter during pregnancy were associated with significantly higher peak and had a trend for higher set point in HIV-1–infected infants overall ($P = 0.01$ and 0.09, respectively). Higher maternal viral levels during pregnancy were associated with significantly higher infant peak

viral levels in infants infected in utero, peripartum, and with a strong trend among those infected late ($P = 0.05, 0.05, 0.06$, respectively), despite low numbers in each of these groups of infants. Among infants infected late, male sex was associated with a higher peak VL and trend for higher set point VL compared with females ($P = 0.02$, $P = 0.06$, respectively).

The correlations between maternal prenatal or delivery HIV-1 RNA and infant HIV-1 peak and set point levels are summarized in Table 4. Overall and in each subset of infants based on timing of infection, maternal HIV-1 RNA (before zidovudine) was significantly correlated with infant peak HIV-1 RNA levels with correlation coefficients ranging from 0.45 to 0.78 ($P < 0.001$ to $P = 0.02$, Table 4). Maternal HIV-1 RNA (before zidovudine) was also significantly correlated with infant set point VL levels overall and in peripartum-infected infants, and the relationship was linear (correlation coefficient 0.31 and 0.38, $P = 0.02$ and $P = 0.04$, respectively). Maternal VL at delivery was associated with infant peak VL overall and among infants infected late postnatally ($P = 0.009$, $P = 0.008$) but not with set point. Notably, because there were fewer data available for maternal delivery HIV-1 RNA and infant set point VL, there was less power to detect associations than for analyses assessing maternal prenatal HIV-1 RNA or infant peak VL.

Cofactors for Mortality

The incidence of mortality after HIV-1 infection was 30.1 per 100 person-years overall, with higher mortality among infants infected ≤1 month (30.9 per 100 person-years) than in those infected after 1 month (20.4 per 100 person-years), however, this difference did not achieve statistical significance [hazard ratio (HR) = 2.32, 95% CI: 0.53 to 10.09, $P = 0.3$]. There were no significant interactions between timing of infection and peak VL, set point VL, or 6-month CD4% < 15%, so results were not stratified by timing of infection. Restricting analyses to the 46 children for whom there were complete data on all 3 covariates, peak and set point viral levels and 6-month CD4% <15%, were all significantly associated with mortality in univariate analyses (Table 5). These 46 infants did not differ significantly from the 39 excluded infants in terms of peak VL, set point VL, and 6-month CD4%. In multivariate analysis of the overall cohort, 6-month CD4% <15% remained a significant independent predictor of mortality, whereas set point was not significant in a model including both covariates. Results were similar in a multivariate model including 6-month CD4% <15% and peak VL, suggesting that 6-month CD4% <15% may be the most predictive marker of mortality for children who lived to 6 months of age. Using World Health Organization 2006 guidelines treatment initiation of <25% (rather than previous guidelines of <15%) resulted in a trend for increased mortality (HR = 3.16, 95% CI: 0.93 to 10.81, $P = 0.07$) in univariate analysis and in multivariate analysis (HR = 2.45, 95% CI: 0.69 to 8.73, $P = 0.2$). The majority (67%) of 6-month olds had CD4 <25%, whereas 31% had CD4 <15%.

DISCUSSION

In this cohort of HIV-1–infected infants followed for up to 2 years, we made several important observations relevant to HIV-1 pathogenesis in infancy. First, infants who acquired infection after the first month of life demonstrated markedly improved control of HIV-1 replication compared with infants infected earlier. Second, maternal HIV-1 RNA predicted infant peak HIV-1 levels. Finally, infant HIV-1 peak and set point VL and 6-month CD4% were predictive of mortality, with 6-month CD4% being the most predictive.

Infants have a much more aggressive course of HIV-1 infection than adults, with 1–2 $\log_{10}$ higher HIV-1 RNA levels and high (~50%) mortality in the first years of infection.[10,14] Patterns of HIV-1 replication during infancy have not been well characterized in settings where breast milk transmission of HIV-1 is prevalent. In this cohort, we observed that HIV-1 viral control differed between infants infected after 1 month of age “late” and those infected before 1 month

"early." Late-infected infants demonstrated a pattern of viral control more similar to that seen in adults—with substantial decline in HIV-1 RNA after peak, whereas early infected infants had sustained high levels of viral replication. Thus, although peak levels did not differ between late-infected and early infected infants, set point viral levels were significantly lower in infants infected late than early. We noted significantly lower set point in late-infected infants using 4 different criteria for set point. Our findings contrast with that of a Malawian cohort in which late-infected children did not contain HIV-1 better than early infected but concur with another study in which older hemophiliac children (>2 years) had adult-like control of HIV-1 compared with perinatally infected children, suggesting that age at HIV-1 acquisition influences control of viral replication.[8,9] Our observation confirms and extend our previous observations in a different Kenyan cohort in which late-infected infants had a viral set point 0.8 $\log_{10}$ copies per milliliter lower than early infected infants ($P = 0.01$), and mortality was 10% in late-infected infants vs. 65% in early infected infants ($P < 0.0001$).[1,15] The previous cohort had greater power to note a highly significant mortality risk difference, did not receive antiretroviral prophylaxis to prevent infant HIV-1, and had a different definition of early/late timing (<2/>2 months) due to different blood collection schedule and different definition of set point. The fact that we observed consistent significant differences between early and late infant HIV-1 infections in 2 distinct cohorts despite several methodological differences strengthens the evidence that timing of HIV-1 acquisition alters infant HIV-1 pathogenesis.

Improved control of HIV-1 among late-infected infants may reflect enhanced immune responses.[16,17] The latest "late" infection in our cohort occurred at 6 months, suggesting that if immune control was responsible for the better course of late infant infection, immune function improved within the first few months of life. Early $CD8^+$ T-cell responses may be compromised by deficiencies in $CD4^+$ T-helper cell and dendritic cell function or suppressed due to high levels of circulating T regulatory cells.[18–21] Alternatively, it is possible that phenotype/selection of virus or presentation of virus to host immune cells differs in breast milk transmission from peripartum transmission resulting in less efficient viral replication in late-infected infants.

Previous studies have noted decreased levels of HIV-1 RNA at birth among infants with in utero HIV-1 acquisition.[9,22] Similarly, our study noted among in utero infected infants that HIV-1 RNA levels were lower at birth than subsequently, likely due to intrapartum zidovudine. For providers, it is important to note that among infants who received combined or alternative antiretroviral prophylaxis regimens, lower viral levels may be observed in the first weeks of life, limiting predictive value. One study has noted peaking in infant viral levels within the first 2 weeks of life; we could not assess this in our cohort because the first blood sampling after 48 hours occurred at 1 month.[23] In contrast to previous studies, we did not observe higher viral levels in early infected female infants.[24] Among late-infected infants, viral levels were ~1.0 $\log_{10}$ copies per milliliter higher in males, perhaps due to similar unexplained mechanisms that lead to higher levels of HIV-1 RNA in adult males than females and increased risk of late postnatal HIV-1 transmission in males.[25,26]

In our study, maternal HIV-1 RNA level significantly predicted infant HIV-1 RNA ($r = 0.45$, $P < 0.001$).[22,27] Ioannidis et al[27] conducted a meta-analysis of 574 HIV-1–infected infants from European/US cohorts in which maternal HIV-1 RNA correlated with early infant HIV-1 RNA ($r = 0.26$, $P < 0.001$). Rouet et al[22] noted an association between maternal HIV-1 RNA at delivery and infant HIV-1 VL in a West African study ($r = 0.27$, $P = 0.02$). Our study was unique in demonstrating associations between maternal and infant HIV-1 RNA both in overall and in stratified analyses of infants infected in utero, peripartum, and late despite low numbers in each of these groups of infants. Thus, regardless of the mode of acquisition of infant HIV-1, it seems that either maternal viral phenotype or shared maternal–infant characteristics influence viral replication in the infant. Studies from the simian immunodeficiency virus/macaque model

clearly demonstrate that the phenotype and inherent replication fitness of the virus is a key determinant of viral set point levels, suggesting that characteristics of the maternal virus may play a major role in the levels of virus replication in the infant.[28] Whether it is viral replication fitness per se or the antigenic properties of the virus and/or the subsequent ability of the host to respond is unclear. Finally, shared human leukocyte antigen or capacity to mobilize cellular immune responses may explain shared poor progression. If the latter are the main determinants of infant progression, reducing maternal HIV-1 RNA level to reduce transmission may not decrease infant HIV-1 progression in those who are not protected from infection.

Previous studies have noted that baseline RNA and CD4 levels are independently predictive of progression.[3,7] In this cohort, peak and set point viral HIV-1 RNA levels and 6-month CD4% <15% all predicted infant mortality in univariate analyses; 6-month CD4% <15% was the most predictive in multivariate analyses. Unfortunately, we did not collect earlier CD4% data in the majority of infants. Our observation of the predictive value of 6-month CD4% <15% and its relative merit compared with VL is reassuring for clinicians in settings in which viral levels may not be accessible. Recent World Health Organization guidelines suggest using CD4 <25% rather than <15%. The majority of infants had CD4 <25% (67%), and this cut-off was not as specific a predictor of mortality risk as CD4 <15%.

In summary, this study demonstrates that maternal VL predicts infant VL, that infants infected early contain virus more poorly than those infected late, that high VL is predictive of increased mortality, and that CD4 counts were most independently predictive of survival outcome in HIV-1–infected infants. These findings are important for defining pathogenesis and management of infants with HIV-1.

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REFERENCES

1. Richardson BA, Mbori-Ngacha D, Lavreys L, et al. Comparison of human immunodeficiency virus type 1 viral loads in Kenyan women, men, and infants during primary and early infection. J Virol 2003;77:7120–7123. [PubMed: 12768032]
2. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. N Engl J Med 1997;336:1337–1342. [PubMed: 9134873]
3. Mofenson LM, Korelitz J, Meyer WA III, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. J Infect Dis 1997;175:1029–1038. [PubMed: 9129063]
4. Dickover RE, Dillon M, Leung KM, et al. Early prognostic indicators in primary perinatal human immunodeficiency virus type 1 infection: importance of viral RNA and the timing of transmission on long-term outcome. J Infect Dis 1998;178:375–387. [PubMed: 9697717]
5. Kalish LA, McIntosh K, Read JS, et al. Evaluation of human immunodeficiency virus (HIV) type 1 load, CD4 T cell level, and clinical class as time-fixed and time-varying markers of disease progression in HIV-1-infected children. J Infect Dis 1999;180:1514–1520. [PubMed: 10515810]
6. Rich KC, Fowler MG, Mofenson LM, et al. Maternal and infant factors predicting disease progression in human immunodeficiency virus type 1-infected infants. Women and Infants Transmission Study Group. Pediatrics 2000;105:e8. [PubMed: 10617745]

7. Kaufmann GR, Cunningham P, Zaunders J, et al. Impact of early HIV-1 RNA and T-lymphocyte dynamics during primary HIV-1 infection on the subsequent course of HIV-1 RNA levels and CD4+ T-lymphocyte counts in the first year of HIV-1 infection. Sydney Primary HIV Infection Study Group. J Acquir Immune Defic Syndr 1999;22:437–444. [PubMed: 10961604]
8. Engels EA, Rosenberg PS, Katki H, et al. Trends in human immunodeficiency virus type 1 (HIV-1) load among HIV-1-infected children with hemophilia. J Infect Dis 2001;184:364–368. [PubMed: 11443565]
9. Biggar RJ, Janes M, Pilon R, et al. Virus levels in untreated African infants infected with human immunodeficiency virus type 1. J Infect Dis 1999;180:1838–1843. [PubMed: 10558939]
10. Obimbo EM, Mbori-Ngacha DA, Ochieng JO, et al. Predictors of early mortality in a cohort of human immunodeficiency virus type 1-infected African children. Pediatr Infect Dis J 2004;23:536–543. [PubMed: 15194835]
11. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet 1999;353:773–780. [PubMed: 10459957]
12. Panteleeff DD, John G, Nduati R, et al. Rapid method for screening dried blood samples on filter paper for human immunodeficiency virus type 1 DNA. J Clin Microbiol 1999;37:350–353. [PubMed: 9889216]
13. Emery S, Bodrug S, Richardson BA, et al. Evaluation of performance of the Gen-Probe human immunodeficiency virus type 1 viral load assay using primary subtype A, C, and D isolates from Kenya. J Clin Microbiol 2000;38:2688–2695. [PubMed: 10878065]
14. 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 2004;364:1236–1243. [PubMed: 15464184]
15. Mbori-Ngacha D, Nduati R, John G, et al. Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: a randomized clinical trial. JAMA 2001;286:2413–2420. [PubMed: 11712936]
16. Sandberg JK, Fast NM, Jordan KA, et al. HIV-specific CD8+ T cell function in children with vertically acquired HIV-1 infection is critically influenced by age and the state of the CD4+ T cell compartment. J Immunol 2003;170:4403–4410. [PubMed: 12682278]
17. Lohman BL, Slyker JA, Richardson BA, et al. Longitudinal assessment of human immunodeficiency virus type 1 (HIV-1)-specific gamma interferon responses during the first year of life in HIV-1-infected infants. J Virol 2005;79:8121–8130. [PubMed: 15956557]
18. Velilla PA, Rugeles MT, Chougnet CA. Defective antigen-presenting cell function in human neonates. Clin Immunol 2006;121:251–259. [PubMed: 17010668]
19. Vekemans J, Ota MO, Wang EC, et al. T cell responses to vaccines in infants: defective IFNgamma production after oral polio vaccination. Clin Exp Immunol 2002;127:495–498. [PubMed: 11966766]
20. Adkins B. Neonatal T cell function. J Pediatr Gastroenterol Nutr 2005;40:S5–S7. [PubMed: 15805855]
21. Legrand FA, Nixon DF, Loo CP, et al. Strong HIV-1-specific T cell responses in HIV-1-exposed uninfected infants and neonates revealed after regulatory T cell removal. PLoS ONE 2006;1:e102. [PubMed: 17183635]
22. Rouet F, Sakarovitch C, Msellati P, et al. Pediatric viral human immunodeficiency virus type 1 RNA levels, timing of infection, and disease progression in African HIV-1-infected children. Pediatrics 2003;112:e289. [PubMed: 14523214]
23. Biggar RJ, Broadhead R, Janes M, et al. Viral levels in newborn African infants undergoing primary HIV-1 infection. AIDS 2001;15:1311–1313. [PubMed: 11426078]
24. Newell ML, Gray L, Thorne C, Cortina-Borja MC, Peckham C. Level and pattern of HIV-1-RNA viral load over age: differences between girls and boys? AIDS 2002;16:97–104. [PubMed: 11741167]
25. Napravnik S, Poole C, Thomas JC, et al. Gender difference in HIV RNA levels: a meta-analysis of published studies. J Acquir Immune Defic Syndr 2002;31:11–19. [PubMed: 12352145]
26. The Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. J Infect Dis 2004;189:2154–2166. [PubMed: 15181561]

27. Ioannidis JP, Tatsioni A, Abrams EJ, et al. Maternal viral load and rate of disease progression among vertically HIV-1-infected children: an international meta-analysis. AIDS 2004;18:99–108. [PubMed: 15090835]

28. Kimata JT, Kuller L, Anderson DB, et al. Emerging cytopathic and antigenic simian immunodeficiency virus variants influence AIDS progression. Nat Med 1999;5:535–541. [PubMed: 10229230]

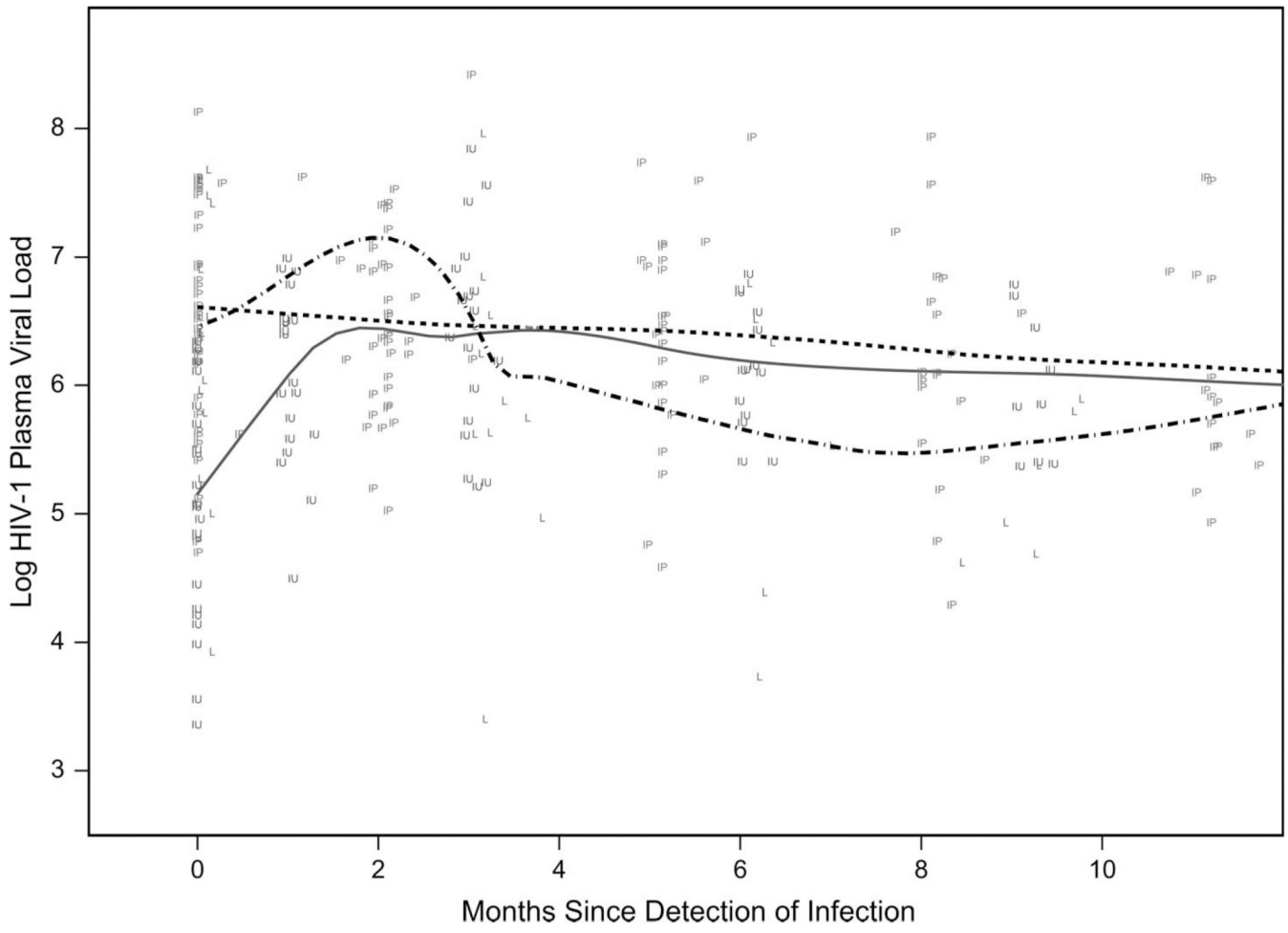

FIGURE 1.

HIV-1 RNA levels since infection by timing of infection (in utero, peripartum, and late postpartum). —, infants with in utero transmission; – – –, infants with peripartum transmission; .–.–, infants with late transmission.

TABLE 1

Description of the Cohort, Sociodemographics and Maternal and Infant Clinical Characteristics

Characteristic	Median Value (range or IQR) or Frequency (%)	n*
Maternal sociodemographic characteristics		
Maternal age in yrs	25 (18–38)	83
Maternal years of education	8 (0–14)	85
Number living in one-roomed house	66 (78)	85
Number married	71 (84)	85
Maternal obstetric and clinical characteristics		
Number receiving antenatal zidovudine	67 (82)	82
Number with vaginal delivery	66 (79)	84
Maternal CD4 count, cells/μL	365 (6–880)	84
Maternal deaths	8 (9)	85
Maternal VL at 32-week gestation, $\log_{10}$ copies/mL	5.19 (4.75–5.66)	82
Maternal VL at delivery, $\log_{10}$ copies/mL	4.69 (4.04–5.27)	69
Infant characteristics		
Gestational age in weeks	40 (33–44)	76
Birth weight in kg	3.0 (1.6–4.0)	84
Number breastfed from birth	72 (86)	84
Number female	39 (46)	85
Timing of HIV-1 infection		
Intrauterine	24 (28)	85
Peripartum	41 (48)	
Indeterminate intrauterine/peripartum	7 (8)	
Late postpartum	13 (15)	
CD4 count at ~6 months after infection, cells/μL	1350 (61–3692)	52
CD4% at ~6 months postinfection, cells/μL	21 (3–40)	52
Duration of follow-up, mo	12 (0–29)	85
Follow-up duration after infection, mo	11 (0–25)	85
No. infant deaths in first 2 years of life	47 (55)	85
Age at death, mo	7.5 (0–24)	47
Time from infection to death, mo	7.3 (0–24)	47

IQR, interquartile range.

*Number of infants for whom data on this characteristic was available.

TABLE 2

Infant HIV-1 RNA Levels in Infants Infected Early or Late

Characteristic	Mean (95% CI) Log_{10} Values	n*
Highest VL in first 6 months post infection (peak)		
Infected at or before 1 month	6.79 (6.62 to 6.96)	72
Infected in utero	6.49 (6.18 to 6.80)	24
Infected peripartum	6.95 (6.73 to 7.17	41
Infected early at indeterminate time (48-hour specimen not available but infected by 1 month)	6.86 (6.29 to 7.43)	7
Infected late postpartum	6.76 (6.33 to 7.19)	13
All infants	6.79 (6.63 to 6.94)	85
Set point VL		
Infected at or before 1 month	6.24 (6.05 to 6.42)†	49
Infected in utero	6.11 (5.84 to 6.38)	15
Infected peripartum	6.28 (6.01 to 6.54)	31
Infected early at indeterminate time	6.46 (6.12 to 6.80)	3
Infected late postpartum	5.59 (4.87 to 6.32)†	10
All infants	6.13 (5.93 to 6.32)	59

*Number of infants for whom data on this characteristic was available.

†Significantly lower set point for late infected than early infected ($P = 0.01$).

TABLE 3

Correlates of Infant Peak and Set Point Viral Load: Difference in Viral Load Between Infants With and Without Stated Characteristic

	Overall		In utero	
Characteristic	**Peak, n = 85**	**Set Point, n = 59**	**Peak, n = 24**	**Set Point, n = 15**
Vaginal delivery	−0.32 (−0.70 to 0.05), $P = 0.09$	−0.05 (−0.54 to 0.45), $P = 0.9$	−0.40 (−1.23 to 0.44), $P = 0.3$	0.19 (−0.62 to 1.00), $P = 0.6$
Breastfeeding	0.26 (−0.17 to 0.69), $P = 0.2$	0.20 (−0.45 to 0.85), $P = 0.5$	0.14 (−0.58 to 0.87), $P = 0.7$	0.23 (−0.57 to 1.04), $P = 0.5$
Received zidovudine	0.10 (−0.30 to 0.50), $P = 0.6$	0.25 (−0.29 to 0.80), $P = 0.4$	−0.37 (−1.17 to 0.43), $P = 0.4$	−0.60 (−1.33 to 0.14), $P = 0.1$
Male	0.18 (−0.13 to 0.48), $P = 0.2$	−0.01 (−0.41 to 0.38), $P = 0.9$	−0.13 (−0.76 to 0.49), $P = 0.7$	−0.15 (−0.71 to 0.41), $P = 0.6$
Maternal CD4 count <350 cells/mm^3	0.19 (−0.12 to 0.50), $P = 0.2$	0.02 (−0.39 to 0.42), $P = 0.9$	0.40 (−0.25 to 1.05), $P = 0.2$	−0.09 (−0.91 to 0.73), $P = 0.8$
Maternal VL at 32 weeks >10^5copies/mL	0.55 (0.24 to 0.86), $P = 0.01$	0.34 (−0.05 to 0.72), $P = 0.09$	0.61 (0.01 to 1.22), $P = 0.05$	0.18 (−0.40 to 0.76), $P = 0.5$
Maternal VL at delivery >10^5copies/mL	0.32 (−0.04 to 0.69), $P = 0.08$	0.17 (−0.34 to 0.68), $P = 0.5$	0.65 (−0.20 to 1.51), $P = 0.1$	NA*

Peripartum		Late	
Peak, n = 41	**Set Point, n = 31**	**Peak, n = 13**	**Set Point, n = 10**
−0.40 (−0.92 to 0.13), $P = 0.1$	−0.12 (−0.78 to 0.54), $P = 0.7$	−0.23 (−1.20 to 0.74), $P = 0.6$	−0.34 (−2.03 to 1.36), $P = 0.7$
0.23 (−0.39 to 0.86), $P = 0.5$	0.35 (−0.45 to 1.15), $P = 0.4$	NA*	NA*
0.40 (−0.15 to 0.94), $P = 0.2$	0.58 (−0.13 to 1.29), $P = 0.1$	−0.82 (−2.41 to 0.77), $P = 0.3$	0.99 (−1.51 to 3.48), $P = 0.4$
0.21 (−0.24 to 0.65), $P = 0.4$	−0.18 (−0.73 to 0.36), $P = 0.5$	0.99 (0.16 to 1.81), $P = 0.02$	1.30 (−0.05 to 2.65), $P = 0.06$
0.05 (−0.40 to 0.49), $P = 0.8$	0.21 (−0.33 to 0.75), $P = 0.4$	0.29 (−0.85 to 1.42), $P = 0.6$	−0.06 (−1.99 to 1.86), $P = 0.9$
0.47 (0.01 to 0.93), $P = 0.05$	0.47 (−0.06 to 1.00), $P = 0.08$	0.79 (−0.05 to 1.62), $P = 0.06$	0.47 (−1.09 to 2.03), 0.5
−0.16 (−0.62 to 0.31), $P = 0.5$	−0.22 (−0.80 to 0.36), $P = 0.4$	0.80 (−0.05 to 1.64), $P = 0.06$	1.11 (−0.54 to 2.76), $P = 0.2$

All numbers show difference in VL between the 2 levels of the cofactor [regression coefficients (95% CI)].

*NA = All infants fall into same category of cofactor.

TABLE 4

Relationship Between Maternal and Infant HIV-1 RNA Levels

	Overall	In Utero	Peripartum	Late
Correlation of maternal HIV-1 RNA with infant peak HIV-1 RNA level*				
Maternal HIV-1 RNA at 32 weeks gestation	0.453, $P < 0.001$	0.501, $P = 0.02$	0.771, $P < 0.001$	0.780, $P = 0.002$
Maternal HIV-1 RNA at delivery	0.311, $P = 0.009$	0.266, $P = 0.2$	0.07, $P = 0.7$	0.72, $P = 0.008$
Correlation of maternal HIV-1 RNA with infant set point HIV-1 RNA level				
Maternal HIV-1 RNA at 32 weeks gestation	0.309, $P = 0.02$	0.26, $P = 0.3$	0.378, $P = 0.04$	0.355, $P = 0.3$
Maternal HIV-1 RNA at delivery	0.143, $P = 0.3$	0.43, $P = 0.1$	−0.04, $P = 0.8$	0.321, $P = 0.4$

*Pearson correlation coefficient.

TABLE 5

Correlates of Mortality

Covariate	Univariate HR (95% CI), *P* Value	Multivariate HR* (95% CI), *P* Value
Peak VL (log_{10})	1.98 (1.0 to 3.95) $P = 0.05$	
Set point VL (log_{10})	2.14 (1.15 to 4.33), $P = 0.04$	1.59 (0.73 to 3.48), $P = 0.2$
6-month CD4% <15%	5.74 (2.34 to 14.07), $P < 0.001$	4.85 (1.90 to 12.36), $P = 0.001$

*Only set point VL was used in multivariate analysis because peak and set point were colinear.