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Acute HIV Infection among Kenyan Infants

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Abstract

Background—Clinical signs and symptoms of acute human immunodeficiency virus (HIV) infection in infants are not well characterized.

Methods—Serial clinical assessments and HIV PCR assays were conducted in a cohort of children born to HIV-seropositive mothers from birth to 2 years of age. Acute HIV infection visits were defined as those up to 3 months prior to and including the visit at which HIV DNA was first detected. Noninfection visits included all visits at which the child had test results negative for HIV, including the last visit at which a test result negative for HIV DNA was obtained in children who later acquired HIV infection. Differences in the prevalence of symptoms at acute infection versus noninfection visits were determined overall and were stratified by age at infection (<2 months vs. ≥2 months). HIV RNA was measured serially in infected infants and was compared between infants with and infants without symptoms of acute HIV infection.

Results—There were 125 acute infection visits (among 56 infants) and 3491 noninfection visits (among 306 infants). Acute HIV infection was associated with rash (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1–2.8), failure to thrive (OR, 1.9; 95% CI, 1.0–3.5), and lymphadenopathy (OR, 2.5; 95% CI, 1.4–4.8). Acute HIV infection was associated with lymphadenopathy (OR, 2.6; 95% CI, 1.3–5.0) in infants <2 months of age and with pneumonia (OR, 3.2; 95% CI, 1.1–9.3) and dehydration (OR, 6.0; 95% CI, 1.9–18.5) in infants ≥2 months of age. Infant peak viral load and mortality were not associated with symptoms of acute HIV infection. However, infants with symptoms had higher viral levels later in the course of infection than did those without symptoms ($P = .05$).

Conclusions—Infants may manifest symptoms early during the course of HIV infection, and symptoms of acute HIV infection may correlate with poor viral control. Rash, failure to thrive, lymphadenopathy, pneumonia, and dehydration may signify acute HIV infection in infants.

Acute primary HIV infection has been characterized by a syndrome including flu-like symptoms, pharyngitis, lymphadenopathy, fever, and meningitis [1, 2]. Among adults with

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HIV infection, those with acute retroviral symptoms have been noted to have poorer clinical outcome than those without symptoms [3, 4]. Less is known regarding pediatric primary HIV infection.

Most children who acquire HIV infection do so during infancy via mother-to-child transmission of HIV [5]. Infancy is a period in which febrile illnesses are fairly common, making it difficult to identify signs and symptoms specific to acute HIV infection. In most settings with a high prevalence of pediatric HIV infection, HIV testing is limited to serologic assays, which are only able to identify infection in children >15 months of age. Determining symptoms and signs that identify pediatric acute HIV infection may be useful for the early diagnosis of HIV infection in children. There have been no studies to date to determine the symptoms typical of early HIV infection acquired during the first few months of life. Late postnatal infection was studied in a single case-control study from West Africa that compared 22 HIV-infected children who acquired illness postnatally with uninfected breastfed control subjects. In this study, acute primary HIV infection was associated with a mononucleosis-like illness, dermatitis, and generalized lymphadenopathy, and acute symptoms during primary infection were not associated with effects on HIV RNA in a limited subset of infants [6].

In a cohort study involving infants born to HIV-infected mothers in Nairobi, Kenya, we compared symptoms and signs among HIV-infected infants seen in the time-window surrounding acute HIV infection with those seen at noninfection visits to determine symptoms and signs that were associated with acute retroviral syndrome in children. In addition, we compared maternal HIV RNA levels and infant HIV RNA peak and set point levels, later viral levels, and mortality in children with and without acute retroviral syndrome during primary HIV infection.

PATIENTS AND METHODS

Clinical characteristics

Procedures related to this cohort of mother-infant pairs have been previously described [7, 8]. In brief, as part of a randomized trial of breastfeeding versus formula feeding involving HIV-infected women in Nairobi, Kenya, HIV-infected women were enrolled during pregnancy after informed consent, and mother-infant pairs were followed up after delivery. The cohort was accrued and observed from 1992 through 1998 and did not receive antiretrovirals. Infants were seen at birth, 6 weeks, 3 months, and quarterly until 2 years of age for HIV DNA PCR assays. HIV RNA assays were performed on blood samples collected at all visits at and after the first visit at which a sample was found to be HIV DNA positive. Clinical assessment was conducted monthly in year 1 and quarterly in year 2 to assess current and past infant clinical symptoms and signs. Clinical evaluation was conducted by 1 of 3 pediatricians (R.N., D.M.N., or G.J.S.) using standardized questionnaires for history and physical examination.

Laboratory characteristics

HIV DNA assays were performed using PCR testing of PBMCs or filter paper samples [9]. HIV RNA levels in maternal and infant plasma were determined using the Gen-Probe TMA assay (Gen-Probe) [10]. Infants were considered to be HIV infected if at least 2 serial PBMC specimens (or filter papers) had detectable HIV DNA or if 1 specimen had detectable HIV DNA and there was not a subsequent specimen available [7]. Virologic testing was performed in Seattle, Washington.

Statistical analysis

All analyses were performed using SPSS, version 12.0 (SPSS) or S-Plus 2000 (Insightful). Infants were excluded from analyses if the timing of their HIV infection was not defined with adequate precision, because this made it infeasible to determine which of their visits should be classified as acute infection visits. Excluded infants included (1) those who never tested HIV DNA negative and who were HIV DNA positive in the first week of life (who may have acquired infection months earlier, in utero) and (2) those whose last HIV DNA–negative test result and first HIV DNA–positive test result were >3 months apart. For the remaining infants, acute infection visits were defined as all clinical assessment visits after the last HIV DNA–negative test result, up to and including the visit at which HIV DNA was first detected. Noninfection visits were visits up to and including the last visit at which an HIV- negative PCR test result was obtained for all infants. Generalized estimating equations with a binomial link and exchangeable correlation structure were used to determine whether there were significant differences in the prevalence of symptoms between acute infection and noninfection visits after controlling for feeding modality, age, and intervisit interval. Age and infant feeding modality are known to influence morbidity and, thus, were adjusted for as confounders, whereas intervisit interval influenced the infant-time denominator and was adjusted to avoid bias caused by differences in the duration of the period over which morbidity was assessed. Analyses were conducted for all infants and were stratified by age at infection (<2 months of age vs. ≥2 months of age). Thus, early infection (at <2 months of age) included infants who were infected in utero, intrapartum, or via early breastfeeding, whereas late infection (at ≥2 months of age) included only infants infected via breastfeeding.

Sensitivity was calculated as the prevalence of a given symptom among all infants known to have acute infection. Specificity was calculated as 1 minus the prevalence of a symptom during non-infection visits. Positive predictive value (PPV) was calculated as (sensitivity × transmission risk)/([sensitivity × transmission risk] +[(1 − specificity) × (1 − transmission risk)]. Negative predictive value (NPV) was calculated as (specificity × [1 − transmission risk]/([specificity × (1 − transmission risk)]+[(1 − sensitivity) × transmission risk)]).

χ^2 test and Pearson's or Fisher's exact tests were used to compare infants infected early (at <2 months of age) with those infected later (at ≥2 months of age) for the presence of symptoms during acute infection. Correlates of the presence of symptoms during acute infection and differences in infant disease progression variables were assessed using Student's *t* tests for continuous variables and χ^2 tests for categorical variables. Kaplan-Meier curves and the log-rank test were used to compare mortality rates among infected infants experiencing symptoms during acute infection and infected infants not experiencing symptoms. Finally, change in plasma HIV RNA load over time was compared between HIV-infected infants experiencing acute retroviral symptoms and those not experiencing symptoms using Loess curves and linear mixed-effects models [11]. Because the presence of acute symptoms was found to significantly modify the effect of change in viral load over time, change in viral load over time is reported stratified by this variable. These analyses were restricted to infants with at least 12 months of follow-up after infection was diagnosed.

RESULTS

Characteristics of Acute Primary HIV Infection

Symptoms during the acute infection window—Of 92 HIV-infected infants, 15 (16%) were infected within the first week of life, and 21 (23%) had >3 months between their last HIV-negative and first HIV-positive test results. The remaining 56 (61%) met all criteria and were included in the analyses. Among these 56 HIV-infected infants, the mean age

during acute infection was 2.6 months (range, 6 days to 15.8 months), with 40 infants (71%) receiving a diagnosis at <2 months and 16 (29%) with late postnatal HIV infection (diagnosed at ≥2 months of age). In infants with early HIV infection (diagnosed at <2 months of age), the mean age during acute infection was 1.0 month (range, 6 days to 1.6 months), whereas for infants with late postnatal infection, the mean age during acute infection was 6.6 months (range, 2.9–15.8 months).

Overall, among the 56 infants, 47 (84%) had at least 1 symptom during the acute infection window period. Cough, cold, skin rash, fever, and lymphadenopathy were each reported in at least 30% of the infants during the acute infection window (table 1). In the overall cohort, acute infection was associated with significantly increased odds of skin rash (OR, 1.8; 95% CI, 1.1–2.8; $P = .02$), failure to thrive (OR, 1.9; 95% CI, 1.0–3.5; $P = .04$), lymphadenopathy (OR, 2.5; 95% CI, 1.4–4.8; $P = .004$), and hospitalization (OR, 3.2; 95% CI, 1.0–9.8; $P = .04$) when compared with noninfection visits in the same infant cohort and adjusting for age, feeding modality, and intervisit interval (table 2). In addition, there were trends for increased odds of hepatomegaly, thrush, and dehydration during acute infection visits in the overall cohort (table 2).

In analyses stratified for timing of infection, among infants infected in the first 2 months of life, lymphadenopathy was significantly more prevalent during acute infection (OR, 2.6; 95% CI, 1.3–5.0; $P = .01$). In infants infected at or after 2 months of age, hospitalization (OR, 4.9; 95% CI, 1.1–21.4; $P = .04$), dehydration (OR, 6.0; 95% CI, 1.9–18.5; $P = .002$), and pneumonia (OR, 3.2; 95% CI, 1.1–9.3; $P = .03$) were significantly more prevalent during acute infection.

Occurrence of symptoms of acute infection by age of infection—Several signs and symptoms were significantly more likely to occur during the acute infection window among infants who were infected at ≥2 months of age, compared with infants infected at <2 months of age (table 2). Cough (OR, 5.0; $P = .01$), fever (OR, 6.7; $P = .002$), failure to thrive (OR, 12.0; $P = .01$), difficulty feeding (OR, 14.8; $P = .001$), diarrhea (OR, 11.4; $P = .005$), pneumonia (OR, 17.7; $P = .006$), and dehydration ($P = .02$) were all significantly more prevalent during acute infection among infants infected at an older age than among those infected at a younger age (table 2).

Sensitivity, specificity, and predictive value of symptoms and signs for acute infection—For all of the symptoms that were more prevalent during acute infection in the overall cohort, sensitivity was low (range, 2.4%–26.4%) and specificity was high (range, 82.2%–98.8%) (table 3). PPVs for each symptom ranged from 33.1% to 62.7%, whereas NPVs ranged from 63.5% to 67.6%, with thrush having the highest PPV (62.7%) and lymphadenopathy having the highest NPV (67.6%). For infants infected during the first 2 months of life, lymphadenopathy had a PPV of 41.6% and an NPV of 79.5%. For infants infected at or after 2 months of life, PPVs for key symptoms identified as more prevalent during acute infection ranged from 15.0% to 41.5%, and NPVs ranged from 88.5%–90.6%.

Correlates of acute infection syndrome during primary HIV infection—Acute infection syndrome in this cohort was de-fined as the presence of any of the signs and symptoms that had a trend for an association with acute infection in the overall cohort (thrush, dehydration, or hepatomegaly) or were significantly associated with acute infection either overall or in analyses stratified by age (skin rash, lymphadenopathy, failure to thrive, hospitalization, and pneumonia) (table 2). To determine the potential association between maternal viral load (and indirectly, maternal viral phenotype) and acute pathogenesis of infant HIV infection, maternal HIV RNA level was compared for infants with and infants without acute infection syndrome. Mean maternal prenatal plasma HIV RNA level among

mothers of infants with acute infection syndrome was 4.89 $\log_{10}$ copies/μL versus 5.09 $\log_{10}$ copies/μL among those without these symptoms (P = .2). In addition, there was no statistically significant association between an infant experiencing acute infection syndrome and maternal socioeconomic status, Cesarean delivery, prematurity, and prenatal maternal $CD4^+$ cell count (data not shown).

Acute Infection Syndrome and Subsequent HIV Disease Course

Markers of HIV disease progression were compared among HIV-infected infants who experienced acute infection syndrome (as defined above) versus HIV-infected infants who did not experience acute infection syndrome. Infant mortality did not differ between infants experiencing acute infection syndrome and those not experiencing this syndrome (figure 1). In addition, there was not a statistically significant difference in mean peak (for the first 2 months after infection) or set point (postpeak) plasma HIV RNA level between infants who experienced acute infection syndrome and infants without symptoms (peak comparison, 6.2 $\log_{10}$ copies/μL [95% CI, 5.7–6.7 $\log_{10}$ copies/μL] vs. 6.2 $\log_{10}$ copies/μL [95% CI, 5.6–6.7 $\log_{10}$ copies/μL]; P = .2; setpoint comparison, 5.7 $\log_{10}$ copies/μL [95% CI, 5.2–6.2 $\log_{10}$ copies/μL] vs. 6.1 $\log_{10}$ copies/μL [95% CI, 5.6–6.5 $\log_{10}$ copies/μL]; P= .3). In the overall cohort, infants with acute symptoms had increased viral levels later in the course of infection than did infants without acute symptoms (P = .02). Because later viral levels may have been lower because of survivor effect, analyses comparing later viral levels were restricted to infants with at least 12 months of follow-up after infection diagnosis. In these analyses, infants with symptoms during acute infection had significantly higher viral levels later in the course of infection than did infants without acute symptoms (figure 2; P = .05). Specifically, among infants with at least 12 months of follow-up after infection diagnosis, infants who did not experience acute infection syndrome had a mean decrease (± SE) in HIV RNA plasma viral load of 0.034 ± 0.010 $\log_{10}$ copies/μL per month after infection (P = .002). Infants who experienced acute infection syndrome had no decrease in viral levels over time (mean increase ± SE, 0.003 ± 0.010 $\log_{10}$ copies/μL per month; P = 0.8). Thus, infants with symptoms of acute infection had significantly higher viral loads during later infection, compared with those infants without symptoms of acute infection. This difference in viral control was independent of feeding modality.

DISCUSSION

In this study, we observed signs and symptoms that were significantly more prevalent at visits that occurred during acute primary HIV infection, compared with noninfection visits in the same cohort. Rash, failure to thrive, lymphadenopathy, hospitalization, hepatomegaly, thrush, dehydration, and pneumonia were more prevalent at visits during acute infection than at other clinic visits. Most signs and symptoms were highly specific but not very sensitive, and they were more likely to occur in older infants than in infants <2 months of age. Maternal HIV RNA load was not predictive of an infant experiencing acute infection syndrome. In addition, acute infection syndrome was not associated with higher peak or set point plasma HIV RNA viral load in the infant or with higher mortality. However, the presence of acute symptoms was associated with significantly higher HIV RNA loads later in infection.

During infection, acute HIV infection and the accompanying host-immune response lead to systemic symptoms, particularly involving lymph nodes, skin, and pharynx [1, 2]. In infant cohorts, particularly in resource-constrained settings, a variety of infections are common throughout infancy, and discriminating symptoms and signs of acute HIV infection is challenging. Several symptoms, such as fever, that are associated with acute HIV infection in adults were seen commonly in both acutely infected and noninfected infants in our cohort and were not significantly associated with acute infection. In addition, because infants

cannot self-report flu-like symptoms—including pharyngeal discomfort, headache, or myalgias—objective symptoms, such as rash, lymphadenopathy, and thrush, were more informative. Unfortunately, none of these signs or symptoms was a highly sensitive predictor of acute infection. Rash was noted in 26.4% of acute infection visits, but it was also noted in 17.8% of noninfection visits. Thrush was associated with the highest PPV overall (62.7%). It should be noted that the predictive values for these signs and symptoms may vary in populations with different infant HIV infection prevalence, which is influenced by interventions to prevent infant HIV infection. However, even in cohorts with a very low prevalence of HIV infection, the sensitivity and specificity of these factors should remain relevant. In addition, current guidelines recommend cotrimoxazole prophylaxis for HIV-exposed infants. This study was conducted prior to these guidelines, and it is plausible that cotrimoxazole prophylaxis would alter the sensitivity and specificity of acute infection markers by decreasing infectious comorbidity in general.

A mononucleosis-like illness, generalized lymphadenopathy, and rash were associated with acute infection in a West African study that compared 22 infants who had late infection with age-matched control subjects [6]. In our cohort, which included both infants with early infection and those with late infection, we also observed that rash and generalized lymphadenopathy were significantly more prevalent during acute infection.

We found that older infants were significantly more likely than infants <2 month of age to experience signs and symptoms during acute infection. Older infants were more likely than younger infants to have fever, cough, diarrhea, failure to thrive, difficulty feeding, dehydration, and pneumonia during acute infection. This may reflect a more mature immune system, with resulting evidence of immune response to acute HIV infection, or these symptoms may be attributable to less effective control of coinfections that could have been better contained earlier in infancy by transplacentally acquired maternal antibodies. Restricting analyses to older infants resulted in noting symptoms specific to acute HIV infection in this subset. Older infants appear to frequently experience a respiratory syndrome involving pneumonia, hospitalization, and dehydration during acute infection.

Studies involving HIV-infected adults show that acute infection syndrome is associated with a faster disease course, including accelerated mortality [3, 4]. We found that infants who experienced acute infection syndrome had higher plasma HIV RNA loads later in infection than did infants who did not experience symptoms during acute infection. However, we did not see an association between this syndrome and increased mortality. As reported previously, overall mortality in this cohort of HIV-infected infants was very high (>40% mortality by 24 months of age), and this mortality was attributable to several causes, some of which were unrelated to HIV infection [8]. The high background mortality rate may have masked any potential effect of acute infection syndrome on mortality.

Our study was unique in determining symptoms associated with acute infection in both young infants <2 months of age and infants who were infected later. We used a sizeable cohort (~400 mother-infant pairs, with a 2-year follow-up period) that included infected and uninfected infants to discriminate symptoms specific for acute infection. The entire cohort of acutely infected infants provided more power to evaluate symptoms, whereas the stratified analyses of younger and older infants allowed evaluation of age-specific symptoms within these smaller strata. Limitations of the study include the fact that the interval in which to assess acute infection for in utero or intrapartum HIV infection was limited to the first 2 months of life. This narrow time-window may have limited our ability to discriminate unique acute infection–defining signs and symptoms for in utero or intrapartum HIV infection.

In this cohort of infants of HIV-infected mothers, we found that infants may manifest symptomatic illness at the time of acute infection. Signs and symptoms that were more prevalent during acute infection included rash, lymphadenopathy, and failure to thrive. Infants infected at ≥2 months of age may be more likely than others to present with pneumonia during acute infection, and they are more likely to experience symptoms, such as fever and dehydration, than are infants who are infected earlier. Acute infection syndrome in infants was not associated with increased early mortality, but it correlated with poor viral control later in infection. The presence of these signs and symptoms may serve to identify infants experiencing primary HIV infection. With expanded HAART access, awareness of acute HIV symptoms during infancy may serve to facilitate the rapid diagnosis of pediatric HIV infection and early referral for treatment.

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References

1. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. New Engl J Med. 1998; 339:33–9. [PubMed: 9647878]
2. Lavreys L, Thompson ML, Martin HL Jr, et al. Primary human immunodeficiency virus type 1 infection: clinical manifestations among women in Mombasa, Kenya. Clin Infect Dis. 2000; 30:486–90. [PubMed: 10722432]
3. Vanhems P, Lambert J, Cooper DA, et al. Severity and prognosis of acute human immunodeficiency virus type 1 illness: a dose-response relationship. Clin Infect Dis. 1998; 26:323–9. [PubMed: 9502449]
4. Lavreys L, Baeten JM, Chohan V, et al. Higher set point plasma viral load and more-severe acute HIV type 1 (HIV-1) illness predict mortality among high-risk HIV-1–infected African women. Clin Infect Dis. 2006; 42:1333–9. [PubMed: 16586394]
5. John GC, Kreiss J. Mother-to-child transmission of human immunodeficiency virus type 1. Epidemiologic reviews. 1996; 18:149–57. [PubMed: 9021309]
6. Rouet F, Elenga N, Msellati P, et al. Primary HIV-1 infection in African children infected through breastfeeding. AIDS. 2002; 16:2303–9. [PubMed: 12441802]
7. Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. JAMA. 2000; 283:1167–74. [PubMed: 10703779]
8. 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; 286:2413–20. [PubMed: 11712936]
9. 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; 37:350–3. [PubMed: 9889216]
10. 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; 38:2688–95. [PubMed: 10878065]
11. Cleveland WS, Devlin SJ. Locally-weighted regression: an approach to regression analysis by local fitting. J Am Stat Assoc. 1988; 83:596–610.

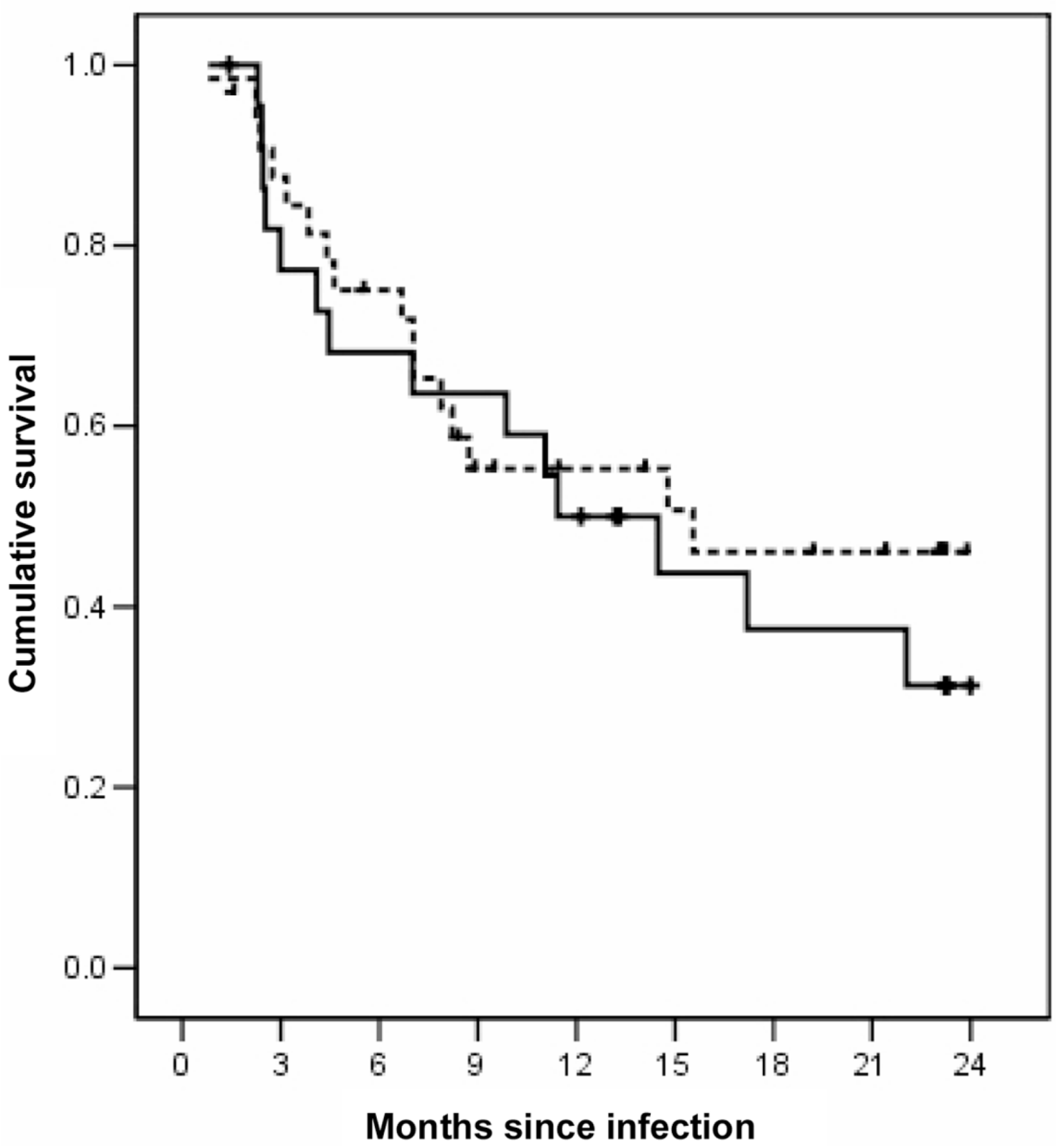

Figure 1.
Infant mortality among infants experiencing acute HIV infection syndrome *(dashed line)* and infants not experiencing acute HIV infection syndrome *(solid line)* (*P* = .5, by log-rank test).

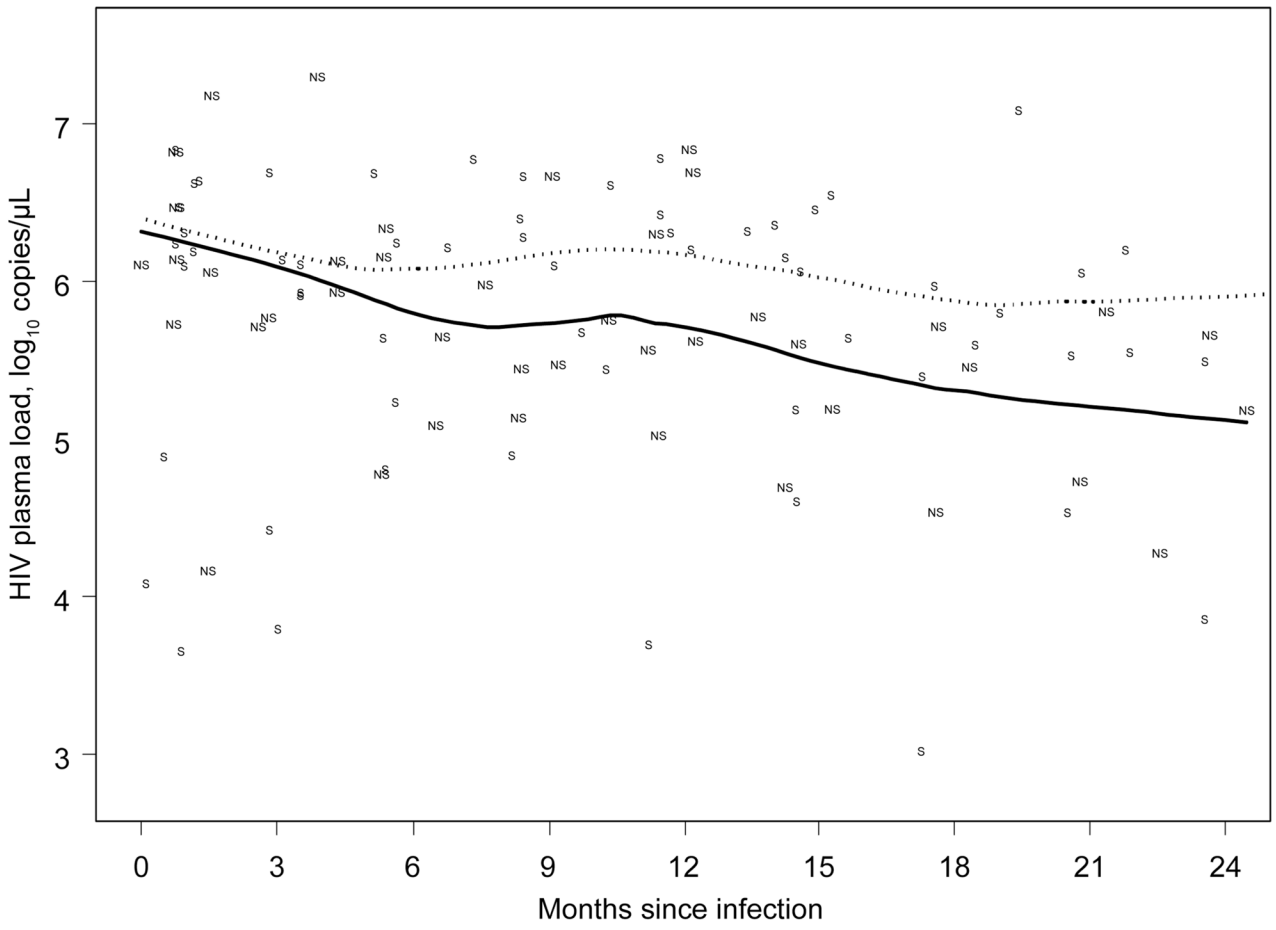

Figure 2.
Plasma HIV load pattern among infants experiencing acute HIV infection syndrome *(S)* and infants not experiencing acute HIV infection syndrome *(NS; solid line)*. The dashed line indicates the mean value for infants experiencing acute HIV infection syndrome, and the solid line indicates the mean value for infants not experiencing acute HIV infection syndrome.

Table 1

Characteristics among infants at acute infection visits.

Clinical characteristic	Percentage of infants with clinical characteristic present at ≥1 acute infection visit (*n* = 56)
Cough[a]	48
Cold[a]	45
Skin rash[a]	39
Fever[a]	32
Lymphadenopathy (≥2 sites)[b]	30
Failure to thrive (<3%)[b]	19
Difficulty feeding[a]	16
Diarrhea[a]	14
Thrush[b]	14
Vomiting[a]	13
Pneumonia[b]	11
Hospitalization[a]	7
Conjunctivitis[b]	5
Dehydration[b]	5
Hepatomegaly[b]	5
Sepsis[b]	4
Wheezing[b]	4
Ear infection[b]	2
Encephalitis[b]	2
Seizure[a]	2
Staccato cough[b]	2
Splenomegaly[b]	0

[a] Since previous visit.

[b] On clinical examination.

Table 2

Symptoms and signs during acute infection window versus symptoms at noninfection visits.

	Overall cohort		Infection diagnosed at <2 months of age[a]		Infection diagnosed at ≥2 months of age[b]	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Cough[c]	1.2 (0.7–1.8)	.5	1.4 (0.8–2.5)	.3	1.8 (0.9–3.7)	.1
Cold[c]	1.1 (0.7–1.7)	.6	1.6 (0.9–2.9)	.1	1.1 (0.6–2.1)	.8
Skin rash[c]	1.8 (1.1–2.8)	.02	1.6 (0.8–2.9)	.2	1.5 (0.6–3.5)	.4
Fever[c]	1.1 (0.7–1.7)	.7	1.8 (0.8–4.1)	.2	1.1 (0.6–2.0)	.8
Lymphadenopathy (≥2 sites)[d]	2.5 (1.4–4.8)	.004	2.6 (1.3–5.0)	.01	1.8 (0.5–6.8)	.4
Failure to thrive (<3%)[d]	1.9 (1.0–3.5)	.04	2.2 (0.6–8.7)	.3	2.0 (0.8–5.2)	.2
Difficulty feeding[c]	0.8 (0.4–1.7)	.6	1.2 (0.3–5.4)	.8	1.2 (0.5–3.2)	.7
Diarrhea[c]	0.7 (0.4–1.4)	.3	0.5 (0.1–2.4)	.4	1.1 (0.5–2.4)	.8
Thrush[d]	1.9 (0.8–4.2)	.1	1.6 (0.7–4.1)	.3	2.7 (0.5–14.9)	.2
Vomiting[c]	0.8 (0.4–1.6)	.5	1.2 (0.5–3.3)	.7	0.7 (0.3–2.0)	.5
Pneumonia[d]	1.3 (0.5–3.5)	.6	0.3 (0.1–1.9)	.2	3.2 (1.1–9.3)	.03
Hospitalization[c]	3.2 (1.0–9.8)	.04	2.4 (0.5–11.2)	.3	4.9 (1.1–21.4)	.04
Conjunctivitis[d]	0.6 (0.2–1.8)	.3	0.4 (0.1–1.6)	.2	1.0 (0.1–7.3)	1.0
Dehydration[d]	2.5 (0.8–8.0)	.1	…[e]	…[e]	6.0 (1.9–18.5)	.002
Hepatomegaly[d]	2.9 (0.8–10.5)	.1	…[e]	…[e]	3.9 (0.8–18.6)	.08

NOTE. Comparisons were performed controlling for age at visit, feeding modality, and time between visits.

[a] Includes 80 acute infection visits among 40 infected infants and 682 noninfection visits among 299 infants.

[b] Includes 45 acute infection visits among 16 infected infants and 2809 noninfection visits among 272 infants.

[c] Since previous visit.

[d] On clinical examination.

[e] Not enough outcomes for model to converge.

Table 3

Sensitivity, specificity, and predictive values of signs and symptoms.

Patient group, variable	Sensitivity, %	Specificity, %	PPV,[a] %	NPV,[a] %
Overall				
Thrush[b]	9.6	96.8	62.7	65.6
Hospitalization[c]	4.0	98.6	61.1	64.6
Lymphadenopathy (≥2 sites)[b]	23.2	90.3	57.5	67.6
Hepatomegaly[b]	3.2	98.4	53.3	64.4
Dehydration[b]	2.4	98.8	52.3	64.3
Skin rash[c]	26.4	82.2	45.5	66.5
Failure to thrive (<3%)[b]	14.2	83.9	33.1	63.5
Infants infected at <2 months of age				
Lymphadenopathy (≥2 sites)[b]	28.8	87.3	41.6	79.5
Cold[c]	30.0	78.6	30.7	78.0
Infants infected at ≥2 months of age				
Dehydration[b]	6.7	98.7	41.5	88.6
Hospitalization[c]	6.7	98.5	37.8	88.6
Hepatomegaly[b]	6.7	98.1	32.1	88.5
Pneumonia[b]	15.6	94.8	28.8	89.2
Cough[c]	57.8	55.2	15.0	90.6

NOTE. Sensitivity and specificity data were determined on the basis of 125 acute infection visits and 3491 noninfection visits overall, 80 acute infection visits and 682 noninfection visits among infants infected at <2 months of age, and 45 acute infection visits and 2809 noninfection visits among infants infected at ≥2 months of age.

[a] Transmission rates among the cohort were estimated to be 36% overall, 24% at <2 months of age, and 12% at ≥2 months of age.

[b] On clinical examination.

[c] Since previous visit.