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Primary HIV-1 Infection among Infants in Sub-Saharan Africa: HPTN 024

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Abstract

Objective—Our objectives were to assess clinical signs and diagnoses associated with primary HIV-1 infection among infants.

Methods—We analyzed data from a clinical trial (HPTN 024) in sub-Saharan Africa. Study visits were conducted at birth, at 4–6 weeks, and at 3, 6, 9, and 12 months. The study population comprised live born, singleton, first born infants of HIV-1-infected women, with negative HIV-1 RNA assays who were still breastfeeding at 4–6 weeks.

Results—Of 1317 HIV-1-exposed infants, 84 became HIV-1-infected after 4–6 weeks and 1233 remained uninfected. There were 102 primary and 5650 non-primary infection visits. The most common signs were cough and diarrhea, and the most common diagnoses were malaria and pneumonia. Primary infection was associated with significantly increased odds of diarrhea [odds radio (OR)=2.4], pneumonia (OR=3.5), otitis media (OR=3.1), and oral thrush (OR=2.9). For the clinical signs and diagnoses evaluated, sensitivity was low (1â16.7%) and specificity was high (88.2%–99%). Positive predictive values ranged from 0.1–1.4%. Negative predictive values ranged from 28.0–51.1%.

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Conclusions—Certain clinical signs and diagnoses, although more common during primary HIV-1 infection, had low sensitivity and high specificity. Efforts to expand access to laboratory assays for the diagnosis of primary HIV-1 infection among infants of HIV-1-infected women should be emphasized.

Keywords

HIV-1; infant; primary infection

INTRODUCTION

Several studies have evaluated the clinical manifestations of primary, or recent, infection with human immunodeficiency virus type 1 (HIV-1), but there are only limited data regarding this syndrome among infants who acquire the infection from their mothers postnatally (i.e., through breastfeeding). Among adults, primary HIV-1 infection has been described as `a transient symptomatic illness associated with high-titer HIV-1 replication and a robust and expansive immunologic response to the invading pathogen" (1). In two studies of young children, factors associated with primary HIV-1 infection included a mononucleosis-like syndrome, dermatitis, and generalized lymphadenopathy (2) and rash, failure to thrive, lymphadenopathy, pneumonia, and dehydration (3).

The objectives of this analysis were to utilize data collected as part of the HIV Prevention Trials Network (HPTN) 024 protocol: to describe the clinical signs and diagnoses after 4–6 weeks of age among breastfeeding, HIV-1-exposed infants who had negative HIV-1 diagnostic test results by 4–6 weeks of age and who were followed thereafter; to analyze which clinical signs and diagnoses were associated with primary HIV-1 infection among these infants; and to assess the sensitivity, specificity, and predictive values of the clinical signs and diagnoses.

METHODS

The HPTN 024 trial was a randomized, double-blind, placebo-controlled Phase III trial conducted between June 2001 and August 2004 at four sites: Blantyre and Lilongwe, Malawi; Dar es Salaam, Tanzania; and Lusaka, Zambia. The design and results of the trial have been described in detail previously (4). The primary objectives of the trial were to evaluate the efficacy of antibiotics to reduce mother-to-child transmission of HIV-1 and preterm birth. In the trial, eligible women were randomized to receive either antibiotics (metronidazole with erythromycin antenatally and metronidazole with ampicillin intrapartum) or placebo. All HIV-1-infected women participating in HPTN 024 and their infants were provided nevirapine according to the HIVNET 012 regimen for prevention of mother-to-child transmission of HIV-1 (5). Infant study visits were conducted at birth (within the first 48 hours), at four to six weeks, and at three, six, nine, and 12 months. At these visits, the infant's caregiver was interviewed and the infant was examined. Although each clinical site provided counseling regarding the risks and benefits of breast-feeding, replacement feeding or other interventions related to prevention of breastfeeding transmission of HIV-1 infection were not implemented as part of the trial. Antiretroviral treatment for mothers and children was not available at any of the clinical sites at the time the trial was conducted. HPTN 024 was approved by each of the in-country and U.S.-associated Institutional Review Boards or Ethical Committees.

The study population for this analysis comprised live born infants (singletons or, if a multiple gestation, first born infants), born to HIV-1-infected women enrolled in HPTN 024, who had negative HIV-1 RNA assays results at birth and at 4–6 weeks of age, and who were still breastfeeding at the 4–6 week visit (6). Such infants who had positive HIV-1 RNA test results thereafter through the 12-month visit were considered to have acquired HIV-1 infection during

the late postnatal period. HIV-1-uninfected infants were those with negative enzyme immunoassay (EIA) results at 12 months of age, or infants with negative HIV-1 RNA assay results throughout follow-up.

For each infant, a study visit was defined as a *primary infection visit* if the infant's HIV-1 diagnostic test result was positive for the first time at that visit, or if the visit was ≤3 months (92 days) prior to a visit when an infant's diagnostic test result was initially positive and no HIV-1 diagnostic test results were available for that visit. Study visits subsequent to the visit when HIV-1 diagnostic testing was initially positive were not included in the analysis. Study visits when the infant's HIV-1 diagnostic test result was negative, and study visits when no HIV-1 testing was performed but the visit preceded the last visit with a negative HIV-1 diagnostic test result, were defined as *non-primary infection visits*.

HIV-1 diagnostic testing of women was performed according to site-specific procedures including either a rapid test or enzyme-linked immunosorbent assay/Western blot tests. All initially positive HIV-1 test results were confirmed with an additional test on site.

At infant study visits, blood was collected to prepare a dried blood spot (DBS). Nucleic acids were extracted from all of the DBS using the silica bead isolation procedure (7) (bio-Merieux, Durham, NC). HIV-1 RNA was detected using a NASBA technology (bioMerieux NucliSens, GL) for the Malawi and Zambia sites whereas the Roche Amplicor Monitor version 1.5 was used for samples for the Tanzania site in a reference laboratory (University of North Carolina, Chapel Hill, NC). Positive results were confirmed by retesting the same DBS or a subsequent one. DBS specimens from 10% of infants considered to be HIV-1-infected and an equal number who never tested positive were retested in the HPTN Central Laboratory (Johns Hopkins University, Baltimore, USA). The laboratory personnel were not aware of infant HIV-1 infection status or study arm.

The HPTN Central Laboratory reviewed and certified all local laboratories before the initiation of the trial. On a periodic basis throughout the trial, the Central Laboratory verified virologic, serologic, hematologic, immunologic, and biochemical tests based on proficiency panels provided by the College of American Pathology and United Kingdom National External Quality Assessment Service.

Summary statistics (means and proportions) were used to describe the study population. The prevalence of each clinical sign and diagnosis (CSD) was estimated as the proportion of visits when it occurred in primary vs. non-primary infection visits.

Generalized estimating equations (GEE) models, with exchangeable correlation structure, were used to determine statistical significance and to estimate the odds ratio (OR) for each CSD comparing primary to non-primary infection visits. In these univariate models, each CSD was assessed as an outcome variable and visit type (primary vs. non-primary) was the single predictor.

Sensitivity was defined as the prevalence of each CSD during primary infection. Specificity was defined as the probability of not having a CSD during non-primary infection visits. Positive predictive value (PPV) was defined as probability of primary infection given the presence of a CSD, and was computed using the formula:

$$PPV = \Pr(AcuteHIV|CSD)$$

$$PPV = \frac{sensitivity \times \Pr(HIV)}{sensitivity \times \Pr(HIV) + \left[(1 - specificity) \times \left(\Pr\left(\bar{HIV}\right)\right)\right]}$$

Negative predictive value (NPV) was defined as the probability of no primary infection given absence of a CSD and was computed using the formula:

$$NPV = \Pr\left(\bar{Acute}\bar{HIV} \mid \bar{CSD}\right)$$

$$NPV = \frac{specificity \times \Pr\left(\bar{HIV}\right)}{specificity \times \Pr\left(\bar{HIV}\right) + \left[(1 - sensitivity) \times \Pr(HIV)\right]}$$

The HIV-1 transmission rate was assumed to be 7% (6).

RESULTS

Of the 2659 women enrolled in HPTN 024, 2292 were HIV-1-infected. Of these, 2052 delivered live born infants, including 2026 singletons and 26 firstborn twins. Of these live born infants, 1317 had negative HIV-1 RNA assay results at birth and at 4–6 weeks of age, and were still breastfeeding at the 4–6 week visit. Of these 1317 infants, 84 became HIV-1-infected after 4–6 weeks but before 12 months of age and 1233 were uninfected. Characteristics of the study population are shown in Table 1.

Of the 84 HIV-1-infected infants, the mean age of acquisition of HIV-1 infection was 7.6 months (range: 3.0 – 13.6 months). Overall, there were 102 primary infection visits (among the 84 infants who became HIV-1-infected) and 5650 non-primary infection visits among the 84 HIV-1-infected infants (137 visits) and the 1233 infants who remained HIV-1-uninfected (5513 visits). The distribution of clinical visits is shown in Table 2.

The prevalence of CSDs reported at clinical visits, according to visit type, are shown in Table 3. The most common diagnoses were malaria and pneumonia, and the most common clinical signs were cough and diarrhea. Certain CSDs were more likely to be observed during a primary infection visit (Table 4). Specifically, primary infection was associated with significantly increased odds of diarrhea (OR = 2.4), pneumonia (OR = 3.5), otitis media (OR = 3.1), and oral thrush (OR = 2.9).

For the CSDs evaluated, sensitivity was low (1–16.7%) and specificity was high (88.2%–99%). PPVs ranged from 0.1–1.4% with malaria, cough, and diarrhea having the highest PPVs (all 1.4%), and NPVs ranged from 28.0–51.1% (with pneumonia having the highest NPV).

Of the 84 infants who became HIV-1-infected during follow-up, HIV-1 infection was documented to occur within three months of the last negative visit in 36 infants. In other words, 48 infants had interval censored (interval greater than three months) HIV-1 results, making it difficult to precisely define when the infection occurred. To assess the sensitivity of the results to the lack of precision of timing of HIV-1 infection, a secondary analysis excluding the 48 infants with interval censored HIV-1 diagnostic test results was conducted.

Of the 36 HIV-1-infected infants in this secondary analysis, the mean age of infection was 6.1 months (range: 3.0 – 12.3). Overall, there were 36 primary infection visits and 71 non-primary infection visits for these infants. The most common diagnoses at primary infection visits were malaria (19.4%) and pneumonia (8.3%), and the most common clinical signs were cough (22.2%), diarrhea (13.9%), and dermatitis (11.1%). Primary infection was associated with significantly increased odds of cough [odds radio (OR) = 2.4; 95% confidence interval (95% CI): 1.1, 5.4; p = 0.0258] and dermatitis (OR = 3.1; 95%CI: 1.1, 8.8; p = 0.0326). For the CSDs evaluated, sensitivity was generally higher than that observed for the entire cohort of HIV-1-

infected infants (2.8–22.2%), but specificity was similarly high (88.2%–98%). PPVs ranged from 0.2–1.8%, and NPVs ranged from 48.4–51.7%.

Despite the modest differences in sensitivity for certain clinical signs, the results of this secondary analysis were generally comparable to the main study results, with the exception of pneumonia (prevalence: 16% main analysis vs. 8% secondary analysis), non-infectious dermatitis (prevalence: 6% main analysis vs. 11% secondary analysis) and oral thrush (prevalence: 6% main analysis vs. 0% secondary analysis).

DISCUSSION

In our analyses of data regarding this cohort of breastfeeding infants of HIV-1-infected mothers, the most common signs were cough and diarrhea, and the most common diagnoses were malaria and pneumonia. Primary infection was associated with significantly increased odds of diarrhea, pneumonia, otitis media, and oral thrush. However, for the CSDs evaluated, the sensitivity was low and the specificity was high. Malaria, cough, and diarrhea had the highest PPVs (all 1.4%). Pneumonia had the highest NPV (51.1%).

We analyzed data regarding a large cohort of HIV-1-infected women and their infants (both those who remained HIV-1-uninfected and those who acquired HIV-1 infection postnatally). It is important to note that the HPTN 024 trial was not designed to evaluate primary HIV-1 infection in infants. Although the schedule of study visits mirrors what is usually done as part of the routine clinical management of HIV-1-exposed infants (i.e., study visits every three months), this schedule resulted in relatively wide intervals between study visits in terms of assessing the clinical manifestations of primary HIV-1 infection. Diagnoses were made by clinicians at the trial sites, without *a priori* diagnostic criteria imposed by the trial. Therefore, diagnoses were based on clinical findings, with or without laboratory or radiographic studies, and were not necessarily made uniformly across sites. However, the diagnoses made in this cohort of HIV-1-exposed children reflect the existing clinical evaluation and management of such children at these clinical sites.

Primary HIV-1 infection in adults has been associated with fever, rash, oral ulcers, arthralgias, pharyngitis, loss of appetite, weight loss, malaise, and myalgias (8–10). Other clinical features of primary HIV-1 infection include fatigue, lymphadenopathy, night sweats, headaches, vomiting, and diarrhea (11–13). The clinical manifestations of primary HIV-1 infection among infants would be expected to differ from those of adults for three reasons. First, most cases of pediatric HIV infection are acquired through mother-to-child transmission (*in utero*, around the time of birth, and postnatally through breastfeeding). Thus, in contrast to adults, late postnatal transmission of HIV-1 often occurs when the infant's immune system is not completely developed. Secondly, febrile illnesses occur relatively commonly among infants irrespective of the HIV-1 infection status of the mother, thus entailing more difficulty in distinguishing the clinical manifestations of primary HIV-1 infection from the background morbidity in this population. Finally, since infants cannot describe (subjective) symptoms (e.g., headache, myalgias), the clinical manifestations of primary HIV-1 infection generally are limited to (objective) signs (e.g., lymphadenopathy).

To date, there have been only two studies of clinical correlates of primary HIV-1 infection among breastfeeding infants of HIV-1-infected women. Rouet and colleagues conducted a case control study in West Africa, comparing 22 HIV-1-infected children with postnatal acquisition of HIV-1 to controls (breastfed, HIV-1-uninfected children) (2). In this study, primary HIV-1 infection was associated with generalized lymphadenopathy, dermatitis, and a mononucleosis-like illness. Richardson et al evaluated 56 Kenyan infants with 125 primary infection visits and 3491 non-primary infection visits (3). Overall, primary HIV-1 infection was associated with

lymphadenopathy, failure to thrive, and rash. Among infants under the age of two months, primary HIV-1 infection was associated with lymphadenopathy. Among older infants, primary HIV-1 infection was associated with dehydration, pneumonia, and hospitalization. As in our analyses, clinical manifestations of primary HIV-1 infection were highly specific, but with low sensitivity.

Recognition of the timing of acquisition of HIV-1 infection remains important, since early initiation of antiretroviral therapy may provide clinical benefits such as decreasing the risk of neurodevelopmental delay and of life-threatening infections such as *Pneumocystis* pneumonia (14). Beginning in the 1980s, the World Health Organization (WHO) developed clinical case definitions and clinical staging systems for HIV-1 infection (15–18). In addition, the WHO and the United Nations Children's Fund developed the “integrated management of childhood illness” strategy to provide guidelines for the diagnosis and management of ill children at the primary care level (19) However, evaluations of such clinical staging systems, especially among young infants, have had low sensitivity (20–22). The results of our study are consistent with these previous evaluations in suggesting a low sensitivity of clinical diagnosis of HIV-1 infection among infants. However, the WHO has released revised case definitions of HIV-1 infection, to be used for surveillance, and clinical staging classifications for HIV-1-related disease among adults and children (23). Included in these guidelines are clinical criteria for the presumptive diagnosis of severe HIV-1 disease (among HIV-1-seropositive, HIV-1-exposed children younger than 18 months in situations in which virologic testing is not available), such that early initiation of antiretroviral therapy can occur. The results of formal evaluations of these criteria are eagerly anticipated. In the meantime, efforts to expand access to laboratory assays for the diagnosis of HIV-1 infection among infants of HIV-1-infected women should be emphasized.

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Appendix

APPENDIX

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Table 1

Characteristics of the Study Population (N = 1317 mother-infant pairs)

Characteristic		N (%)
Maternal, at enrollment		
Age (years)	≤20	221 (16.8)
	21–29	840 (63.8)
	≥30	256 (19.4)
Education (years)	≤3	259 (19.7)
	4–9	818 (62.1)
	≥10	239 (18.1)
	Missing	1 (0.1)
Marital status	Married/Living with Partner	1203 (91.3)
	Other	114 (8.7)
Electricity in the home	Yes	509 (38.6)
	No	808 (61.4)
Running water in the home	Yes	541 (41.1)
	No	776 (58.9)
CD4+ count (cells/mm^3)	<200	207 (15.7)
	200–499	648 (49.2)
	≥500	327 (24.8)
	Missing	135 (10.3)
Plasma viral load (copies/mL)	< 1,000	112 (8.5)
	≥1000, < 10,000	332 (25.2)
	≥10,000, < 50,000	476 (36.1)
	≥ 50,000	332 (25.2)
	Missing	65 (4.9)
Infant, at birth		
Gestational age < 37 weeks (by fundal height)	Yes	268 (20.3)
	No	1049 (79.7)
Birth weight < 2500 grams	Yes	117 (8.9)
	No	1154 (87.6)
	Missing	46 (3.5)
Gender	Male	681 (51.7)
	Female	636 (48.3)

Table 2

Distribution of Study Visits Performed

Study visit	4–6 weeks	3 months	6 months	9 months	12 months	Total
Primary infection visits, among infants who become infected (n=84) [*]	0	25	31	23	23	**102**
Non-primary infection visits, among infants who become infected (n=84) [†]	83	29	17	8	0	**137**
Number of non-primary infection visits, among infants who remained HIV-1-uninfected (n=1233) [‡]	1194	1199	1160	1075	885	**5513**

[*] Mean age: 7.5 months

[†] Mean age: 2.8 months

[‡] Mean age: 6.0 months

Table 3

Prevalence of Clinical Signs and Diagnoses Reported by Visit Type.

	Visit Type	
	Primary N (%)	**Non-primary N (%)**
Total number of visits	102 (100.0%)	5650 (100.0%)
Clinical signs and diagnoses		
Malaria	17 (16.7%)	665 (11.8%)
Cough	17 (16.7%)	600 (10.6%)
Diarrhea	18 (17.6%)	504 (8.9%)
Pneumonia	16 (15.7%)	289 (5.1%)
Non-infectious (or unspecified) dermatitis	6 (5.9%)	225 (4.0%)
Conjunctivitis	2 (2.0%)	141 (2.5%)
Oral thrush	6 (5.9%)	117 (2.1%)
Anemia	2 (2.0%)	118 (2.1%)
Otitis media	6 (5.9%)	113 (2.0%)
Neonatal sepsis	1 (1.0%)	73 (1.3%)
Fever	1 (1.0%)	56 (1.0%)

Table 4

Odd Ratio Estimates for Clinical Signs and Diagnoses Comparing Primary Infection Visits to Non-Primary Infection Visits (GEE models)

Clinical Signs and Diagnoses	OR (95%CI) for Primary Infection	P-value
Malaria	1.5 (0.9, 2.6)	0.11
Cough	1.7 (1.0, 2.9)	0.06
Diarrhea	2.4 (1.4, 3.9)	0.0012
Pneumonia	3.5 (2.0, 6.2)	<0.0001
Otitis Media	3.1 (1.3, 7.2)	0.0083
Oral Thrush	2.9 (1.2, 6.6)	0.01
Sepsis	0.7 (0.1, 5.7)	0.77
Dermatitis	1.5 (0.7, 3.5)	0.33
Conjuctivitis	0.8 (0.2, 3.3)	0.72
Anemia	1.0 (0.2, 3.8)	0.95
Fever	1.0 (0.1, 6.9)	0.99

Table 5

Sensitivity, Specificity and Predictive Values

Clinical Signs and Diagnoses	Sensitivity (102 visits)	Specificity (5650 visits)	Positive Predictive Value*	Negative Predictive Value*
Malaria	16.7%	88.2%	1.4%	49.6%
Cough	16.7%	89.4%	1.4%	49.9%
Diarrhea	17.6%	91.1%	1.4%	50.7%
Pneumonia	15.7%	94.9%	1.2%	51.1%
Otitis media	5.9%	98.0%	0.4%	49.2%
Oral thrush	5.9%	97.9%	0.5%	49.2%
Neonatal sepsis	1.0%	98.7%	0.1%	48.1%
Anemia	2.0%	97.9%	0.2%	48.2%
Non-infectious (or unspecified) dermatitis	5.9%	96.0%	0.5%	48.7%
Conjunctivitis	2.0%	97.5%	0.2%	48.0%
Fever	1.0%	99.0%	0.1%	48.2%

*HIV-1 transmission rate estimated from cohort is 7%