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Lower respiratory tract infections among human immunodeficiency virus-exposed, uninfected infants☆

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SUMMARY

Objectives: To evaluate whether maternal HIV disease severity during pregnancy is associated with an increased likelihood of lower respiratory tract infections (LRTIs) in HIV-exposed, uninfected infants.
Methods: HIV-exposed, uninfected, singleton, term infants enrolled in the NISDI Perinatal Study, with birth weight >2500 g were followed from birth until 6 months of age. LRTI diagnoses, hospitalizations, and associated factors were assessed.
Results: Of 547 infants, 103 (18.8%) experienced 116 episodes of LRTI (incidence = 0.84 LRTIs/100 child-weeks). Most (81%) episodes were bronchiolitis. Forty-nine (9.0%) infants were hospitalized at least once with an LRTI. There were 53 hospitalizations (45.7%) for 116 LRTI episodes. None of these infants were breastfed. The odds of LRTI in infants whose mothers had CD4% <14 at enrollment were 4.4 times those of infants whose mothers had CD4% ≥29 ($p = 0.003$). The odds of LRTI in infants with a CD4+ count (cells/mm^3) <750 at hospital discharge were 16.0 times those of infants with CD4+ ≥750 ($p = 0.002$). Maternal CD4+ decline and infant hemoglobin at the 6–12 week visit were associated with infant LRTIs after 6–12 weeks and before 6 months of age.
Conclusions: Acute bronchiolitis is common and frequently severe among HIV-exposed, uninfected infants aged 6 months or less. Lower maternal and infant CD4+ values were associated with a higher risk of infant LRTIs. Further understanding of the immunological mechanisms of severe LRTIs is needed.

1. Introduction

In utero exposure to the human immunodeficiency virus (HIV) may adversely affect the exposed infant's immune system development, possibly due to exposure to HIV proteins or even HIV particles during fetal life,[1,2] maternal and/or fetal cytokine imbalance,[3] and/or the known inhibition of bone marrow function by antiretrovirals.[4] Qualitative differences in T cell function[1,5,6] and cell-mediated immune responses to unrelated antigens[7] in HIV-exposed, uninfected infants are consistent with immunosuppressive effects of in utero HIV exposure, and may persist over time.[8] However, the clinical significance of these observations has not been completely explored.

We recently described infectious disease morbidity among HIV-exposed but uninfected infants from Latin America and the Caribbean during the first 6 months of life.[9] In the current analysis, we characterize LRTI episodes experienced by HIV-exposed, uninfected infants enrolled in the NICHD International Site Development Initiative (NISDI) Perinatal Study and assess risk

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factors for acquisition of and hospitalization for LRTIs during the first 6 months of life. We hypothesized that, after controlling for confounders, maternal clinical HIV disease severity and degree of immunosuppression during pregnancy would increase the likelihood of occurrence of and hospitalization for LRTIs in this population.

2. Materials and methods

2.1. NISDI perinatal study

The NISDI Perinatal Study is a prospective cohort study of HIV-infected women and their infants at clinical sites in Argentina, the Bahamas, Brazil, Jamaica, Mexico, and Peru.[10] Enrollment began in September 2002 and is ongoing. All enrolled women had to have access to both antiretroviral prophylaxis and alternatives to breast milk. HIV-infected women were enrolled into the study during pregnancy, and followed until 6 months postpartum. A medical history was obtained, and a physical examination was conducted at each visit. Laboratory studies were conducted at most visits. Their infants were evaluated prior to hospital discharge following birth, at 6–12 weeks, and at 6 months of age. At each infant study visit, a medical history was obtained, a physical examination (with assessments of growth and of morbidity) was performed, and laboratory studies (flow cytometry and HIV diagnostic assays, hematology and biochemical assays) were performed. As part of the interval history, information was collected regarding infant signs and symptoms, diagnoses, medications, and hospitalizations. Although not required by the NISDI protocol, infants were usually followed monthly at the study sites to assess growth and morbidity. Further, when an infant became ill, mothers were advised to seek medical attention at the clinical site and, if medical attention was obtained, clinical, radiographic, and/or laboratory documentation was available at the site. Otherwise, when medical care was obtained at another clinical center, the medical records were requested. Diagnoses were reported at each site by the site clinician. Criteria used by all sites for the diagnosis of specific diseases were those developed for the NISDI.

Infants were considered HIV-uninfected if they had: (1) two or more negative HIV virologic assays (e.g., HIV culture or HIV DNA PCR), with one test performed at age 1 month or older and one performed at age 4 months or older, and no positive virologic tests; (2) one positive HIV virologic assay followed by two negative HIV virologic tests (with at least one performed after age 4 months); or (3) two negative HIV antibody test results, with at least one performed after age 6 months.

2.2. Study population and definitions

The study population comprised singleton, term (>37 completed weeks of gestation), HIV-exposed but uninfected infants enrolled in the NISDI Perinatal Study as of March 1, 2006, who weighed >2500 g at birth and completed 6 months of follow-up. Infants with severe underlying cardiovascular or pulmonary conditions were excluded from this analysis. Due to the small numbers of subjects enrolled in other countries, the analysis was restricted to infants born to women enrolled in Brazil and Argentina.

An LRTI was defined as having occurred when either a definitive or a presumptive diagnosis of an LRTI was recorded. An infection was considered incident if the infant had been free of any signs and symptoms consistent with the same LRTI for at least 7 days prior to the incident event. Due to possible overlap in clinical diagnoses of bronchiolitis and bronchitis in this age group, these two diagnoses were categorized as 'bronchiolitis'.

Disease severity was ascertained based on the severity of bronchospasm and/or dyspnea occurring within 5 days of the diagnosis of an LRTI. An infant was classified as having severe disease if he/she presented with grade ≥3 dyspnea and/or grade ≥3 bronchospasm.[11] Infant hemoglobin values for age were classified as normal or abnormal (grade ≥1) according to established criteria.[11]

Infant gestational age at birth (completed weeks) was determined by obstetrical estimation or by pediatric newborn exam. Growth standard reference values were used for categorizing subjects' weight for age at birth.[12] Maternal clinical disease staging was performed with the use of the Centers for Disease Control and Prevention classification system.[13] Considering that immunizations against *Haemophilus influenzae* type b would only be completed by 6 months of age, and that *Streptococcus pneumoniae* immunization was not mandatory in the vaccination guidelines of either country, these immunizations were not taken into consideration in the evaluation of risk factors for LRTI. None of the infants received respiratory syncytial virus (RSV) prophylaxis.

2.3. Statistical analysis

The primary outcomes of interest were occurrence of and hospitalizations due to LRTIs. Frequencies of LRTIs were calculated according to the age at the initial diagnosis. Further, in order to analyze the occurrence of LRTIs in relation to immunologic (CD4+) and other (hemoglobin) laboratory indicators, data were analyzed according to LRTI events occurring after a study visit. Thus, two main study periods were analyzed: after hospital discharge (including the neonatal period and post-neonatal LRTI events occurring before the 6–12 week visit) and LRTIs occurring after the 6–12 week visit. By analyzing the data this way, we guaranteed that outcomes (LRTIs) occurred after potential risk factors occurred. Infant CD4+ decline was calculated by estimating *Z*-scores for the distribution of the entire NISDI study population at birth and at the 6–12 week visit. Decline was defined as a negative value of the *Z*-score when subtracting the *Z*-score value at the 6–12 week visit from that at the hospital discharge visit. Maternal CD4+ decline was estimated by subtracting the *Z*-score at hospital discharge from that at enrollment.

Incidence rates were calculated using person-weeks as the denominator, and the 95% confidence intervals (95% CI) were calculated using Fisher's exact method. Proportions were estimated, and 95% CIs for proportions were calculated using the exact binomial method. Associations of categorical variables with LRTIs before and after the 6–12 week visit were evaluated using the Fisher–Freeman–Halton exact test. Variables at least marginally associated with LRTIs ($p \leq 0.20$) were considered candidates for the multivariable logistic regression modeling. Both stepwise selection and backward elimination strategies were applied to determine whether both selection procedures arrived at the same parsimonious model (using a 5% significance level).

3. Results

3.1. Derivation and characteristics of the study population

As of March 2006, a total of 988 HIV-infected pregnant women had been enrolled into the NISDI Perinatal Study, of whom 910 were enrolled in Argentina or Brazil. Of these enrollments, 877 (96.4%) represented the first enrollment into the study. These 877 women delivered 794 singleton, live born infants. Birth data were not available for eight infants. Of the remaining 786 infants, 707 (89.9%) were followed through the 6-month study visit. Among these 707 infants, seven were HIV-infected, 25 were of indeterminate HIV infection status, and 675 were HIV-uninfected. Of these

Table 1
Characteristics of the study population ($N = 547$) and risk of LRTI before and after the 6–12 week visit

Characteristic	$N = 547$	Before the 6–12 week visit[a]			After the 6–12 week visit		
		LRTI ($n = 23$ (4.2%)) n (%)	Univariate OR (95% CI)	p[b]	LRTI ($n = 85$ (15.5%)) n (%)	Univariate OR (95% CI)	p[b]
Maternal country of residence							
Brazil	378 (69.1)	13 (3.4)	1	0.2	62 (16.4)	1	0.4
Argentina	169 (30.9)	10 (5.9)	1.8 (0.8–4.1)		23 (13.6)	0.8 (0.5–1.4)	
Maternal age at delivery (years)							
<20	30 (5.5)	1 (3.3)	0.8 (0.1–6.5)	0.9	7 (23.3)	1.6 (0.7–4.0)	
20–29	320 (58.7)	13 (4.1)	1		50 (15.6)	1	
>29	195 (35.8)	9 (4.6)	1.1 (0.5–2.7)		28 (14.4)	0.9 (0.6–1.5)	
Missing	2	0			0		
Maternal education (years)							
≥13	20 (3.7)	0 (0)	1	0.50	1 (5)	1	0.29
7–12	344 (62.9)	13 (3.8)	NA		51 (14.8)	3.3 (0.4–25.2)	
0–6	183 (33.5)	10 (5.5)	NA		33 (18.0)	4.2 (0.5–32.3)	
Gainful employment outside of the home							
Yes	121 (22.1)	2 (1.7)	1	0.13	22 (18.2)	1	0.39
No	426 (77.9)	21 (4.9)	3.1 (0.7–13.4)		63 (14.8)	0.8 (0.5–1.3)	
Number of persons in the household							
1–3	245 (44.8)	6 (2.4)	1	0.09	36 (14.7)	1	0.6
≥4	302 (55.2)	17 (5.6)	2.4 (0.9–6.1)		49 (16.2)	1.1 (0.7–1.8)	
Maternal CD4+ count at enrollment (cells/mm^3)							
≥500	174 (32.4)	8 (4.6)	1	0.5	24 (13.8)	1	0.63
200–499	302 (56.2)	11 (3.6)	0.8 (0.3–2.0)		51 (16.9)	1.3 (0.8–2.2)	
<200	61 (11.4)	4 (6.6)	1.5 (0.4–5.0)		8 (13.1)	0.9 (0.4–2.2)	
Missing	10	0			2		
Maternal CD4% at enrollment							
<14	32 (6.5)	4 (12.5)	2.7 (0.8–9.1)	0.07	3 (9.4)	0.7 (0.2–2.3)	0.60
14–28	219 (44.4)	7 (3.2)	0.6 (0.2–1.6)		35 (16.0)	1.2 (0.7–2.0)	
≥29	242 (49.1)	12 (5.0)	1		33 (13.6)	1	
Missing	54	0			14		
Maternal CD4+ count at hospital discharge (cells/mm^3)							
≥500	222 (43.7)	9 (4.1)	1	0.59	31 (14.0)	1	0.49
200–499	243 (47.8)	9 (3.7)	0.9 (0.4–2.3)		44 (18.1)	1.4 (0.8–2.3)	
<200	43 (8.5)	3 (7.0)	1.8 (0.5–6.8)		7 (16.3)	1.2 (0.5–2.9)	
Missing	39	2			3		
Maternal CD4% at hospital discharge							
<14	26 (5.5)	2 (7.7)	2.0 (0.4–9.7)	0.52	4 (15.4%)	1	0.49
14–28	167 (35.4)	8 (4.8)	1.2 (0.5–3.1)		27 (16.2%)	1.4 (0.8–2.3)	
≥29	279 (59.1)	11 (3.9)	1		42 (15.1%)	1.2 (0.5–2.9)	
Missing	75	2			12		
Maternal CD4+ decline							
No	259 (51.8)	12 (4.6)	1	0.7	35 (13.5)	1	0.14
Yes	241 (48.2)	9 (3.7)	0.8 (0.3–1.9)		45 (18.7)	1.5 (0.9–2.4)	
Missing	47	2			5		
Maternal plasma viral load at enrollment (copies/ml)							
<1000	314 (58.6)	13 (4.1)	1	0.8	43 (13.7)	1	0.45
1000–10 000	113 (21.1)	4 (3.5)	0.8 (0.3–2.7)		20 (17.7)	1.4 (0.8–2.4)	
≥10 000	109 (20.3)	6 (5.5)	1.3 (0.5–3.6)		19 (17.4)	1.3 (0.7–2.4)	
Missing	11	0			3		
Maternal plasma viral load at hospital discharge (copies/ml)							
<1000	433 (84.5)	18 (4.2)	1	0.43	73 (16.9)	1	0.07
1000–10 000	51 (10.0)	1 (2.0)	0.5 (0.1–3.5)		3 (5.9)	0.3 (0.1–1.0)	
≥10 000	28 (5.5)	2 (7.1)	1.8 (0.4–8.1)		6 (21.4)	1.3 (0.5–3.4)	
Missing	35	2			3		
Maternal HIV clinical stage at enrollment							
A	473 (86.5)	18 (3.8)	1	0.19	75 (15.9)	1	0.87
B	34 (6.2)	3 (8.8)	2.4 (0.7–8.8)		4 (11.8)	0.7 (0.2–2.1)	
C	40 (7.3)	2 (5)	1.3 (0.3–6.0)		6 (15)	0.9 (0.4–2.3)	
Maternal HIV clinical stage at hospital discharge							
A	472 (86.3)	18 (3.8)	1	0.23	75 (15.9)	1	0.84
B	35 (6.4)	3 (8.6)	2.4 (0.7–8.4)		4 (11.4)	0.7 (0.2–2.0)	
C	40 (7.3)	2 (5)	1.3 (0.3–5.9)		6 (15)	0.9 (0.4–2.3)	
Gender							
Female	261 (47.7)	9 (3.4)	1	0.52	34 (13.0)	1	0.1
Male	286 (52.3)	14 (4.9)	1.4 (0.6–3.4)		51 (17.8)	1.4 (0.9–2.3)	

Table 1 (*Continued*)

Characteristic	N = 547	Before the 6–12 week visit[a]			After the 6–12 week visit		
		LRTI (n = 23 (4.2%)) n (%)	Univariate OR (95% CI)	p[b]	LRTI (n = 85 (15.5%)) n (%)	Univariate OR (95% CI)	p[b]
Weight for age percentile at birth							
≥5th	531 (97.1)	23 (4.3)	1	1.00	82 (15.4)	1	0.7
<5th	16 (2.9)	0	NA		3 (18.8)	1.3 (0.4–4.5)	
Infant CD4+ count at hospital discharge (cells/mm^3)							
<750	8 (1.8)	2 (25)	10.2 (1.9–4.9)	0.03	0 (0)	NA	1.0
≥750	441 (98.2)	14 (3.2)	1		85 (19.3)	1	
Missing	98	7			0		
Infant CD4% at hospital discharge							
15–24	4 (1.0)	1 (25)	8.8 (0.9–89.7)	0.15	0 (0)	NA	1.0
≥25	411 (99.0)	15 (3.6)	1		77 (18.7)	1	
Missing	132	7			8		
Infant CD4+ count at 6–12 week visit (cells/mm^3)							
<750	7 (1.5)				0 (0)	NA	0.36
≥750	451 (98.5)				85 (18.8)	1	
Missing	89				0		
Infant CD4% at 6–12 week visit							
<25	126 (25.4)				27 (21.4)	1.5 (0.9–2.6)	0.1
≥25	386 (74.6)				58 (15.0)	1	
Missing	35				0		
Infant CD4+ decline							
Yes	48 (12.3)				11 (22.9)	1.6 (0.8–3.3)	0.2
No	342 (87.7)				54 (15.8)	1	
Missing	157				20		
Infant hemoglobin at hospital discharge							
Normal	353 (76.1)	13 (3.7)	1	1.00	52 (14.7)	1	0.10
Abnormal	111 (23.9)	4 (3.6)	1.0 (0.31–3.1)		24 (21.6)	1.6 (0.9–2.7)	
Missing	83	6			9		
Infant hemoglobin at 6–12 week visit							
Normal	341 (72.4)				40 (11.7)	1	<0.001
Abnormal	130 (27.6)				43 (33.1)	3.7 (2.3–6.1)	
Missing	76				2		

LRTI, lower respiratory tract infection; OR, odds ratio; CI, confidence interval; NA, not applicable (OR not calculated due to 0 value in a cell).
[a] Grayed area indicates that values are not applicable for this age group.
[b] *p*-Value using Fisher–Freeman–Halton exact test.

675 HIV-uninfected infants, 563 had a gestational age of ≥37 weeks and a birth weight of ≥2500 g. A total of 16 infants were excluded from the analysis due to underlying severe cardiovascular (*n* = 12; pulmonary valve stenosis, tricuspid valve insufficiency, ventricular septal defect, patent ductus arteriosus, foramen ovale) or pulmonary conditions (*n* = 5; pulmonary hypertension, meconium aspiration); one infant had both cardiovascular and pulmonary conditions. Thus, a total of 547 infants were eligible for this analysis and contributed 13 734 person-weeks of follow-up time. Adherence to study visits at 6–12 weeks and at 6 months was 100%. The average number and range of days between laboratory assessments and the occurrence of the LRTI were: hemoglobin mean 62 days (4–138) and CD4 cell count mean 32 days (2–140).

The main characteristics of the study population are shown in Table 1. Most infants were from Brazil (69.1%). Only two infants received any breast milk. All infants received HIV perinatal transmission prophylaxis with zidovudine (median duration 44 days). Some mothers reported substance use during pregnancy (tobacco (22.1%), alcohol (9.3%), marijuana (2.2%), cocaine (2.7%)). All of them used antiretrovirals during pregnancy either as prophylaxis (58.7%) or treatment (41.3%). Most children (97.1%) were above the 5th percentile of weight for age, and 16 (2.9%) weighed exactly 2500 g. In univariate analysis, only infant CD4 count at hospital discharge was significantly associated with LRTI before the 6–12 week visit, and infant hemoglobin at the 6–12 week visit was significantly associated with LRTI after the 6–12 week visit.

3.2. Occurrence of and hospitalization for LRTIs

Of 547 infants, 103 (18.8%) experienced 116 LRTIs with a mean of 1.1 events per infant (Table 2). The overall incidence rate of LRTIs was 0.84 per 100 child-weeks (95% CI 0.7–1.0). No LRTIs occurred during the first 6 days of life. Overall, there were 53 hospitalizations for 116 episodes of LRTI. Forty-nine of 547 (9.0%) infants were hospitalized at least once with an LRTI. Of 41 hospitalizations due to bronchiolitis, the median duration of hospitalization was 5 days (range 1–30 days). Of 12 hospitalizations due to pneumonia, the median duration of hospitalization was 7 days (range 4–19 days). No infant died due to an LRTI or related complications.

Ten infants had two episodes of bronchiolitis; one was diagnosed with bronchiolitis and then pneumonia 3 weeks later, and one was diagnosed with two different episodes of pneumonia. Among 22 episodes of pneumonia, 16 (72.7%) had consistent radiographic findings. The remaining six (27.3%) did not have chest X-rays and diagnosis was based on clinical findings. In one episode (4.5%), microbiology data confirmed the etiology as being RSV. Disease was classified as severe in 2/22 (9.1%) episodes of pneumonia and 12/94 (12.8%) episodes of bronchiolitis. LRTIs had a seasonal distribution (Figure 1), with most events occurring during June and July of each year (winter in Brazil and Argentina), and the fewest during the summer months (December, January and February). Hospitalization occurred in 12/22 (54.5%) episodes of pneumonia and in 41/94 (43.6%) episodes of bronchiolitis.

Table 2
Incidence of LRTIs by type of LRTI and age at onset of infection

Type of LRTI	Age				Infants (*n*)	Episodes (*n*)	Cumulative incidence per 100 children[a] (95% CI)	Incidence per 100 child-weeks (95% CI)	Hospitalizations[b] *n* (%) (95% CI)
	7–27 days		≥28 days						
	Episodes	Hospitalizations *n* (%)	Episodes	Hospitalizations *n* (%)					
Pneumonia	2	2 (100)	20	10 (50)	20	22	3.7 (2.2–5.6)	0.16 (0.1–0.2)	12 (54.5) (32.2–75.6)
Bronchiolitis	6	5 (83.3)	88	36 (40.9)	83	94	15.2 (12.3–18.5)	0.68 (0.5–0.8)	41 (43.6) (33.4–54.2)
Total	8	7 (87.5)	108	46 (42.6)	103	116	18.8 (15.6–22.4)	0.84 (0.7–1.0)	53 (45.7) (36.4–55.2)

LRTI, lower respiratory tract infection; CI, confidence interval.
[a] (Number of infants with ≥1 LRTI episode/total number of infants) × 100.
[b] Episodes of hospitalization for LRTIs/number of episodes of LRTIs.

Overall, severe disease was reported in 13/103 (12.6%) infants with LRTI and in 13/49 (26.5%) hospitalized infants. Among infants with bronchiolitis and pneumonia, 12/83 (14.5%) and 2/20 (10%) had severe disease, respectively. All children with severe disease were hospitalized (data not shown).

3.3. Factors associated with the occurrence of LRTIs

Only eight infections occurred during the neonatal period, which prevented separate analysis of neonatal LRTIs. With respect to LRTIs before the 6–12 week visit, factors considered for multivariable analyses were: maternal country of residence, the number of persons in the household, maternal gainful employment outside of the home, maternal CD4 percentage at enrollment, maternal HIV clinical stage at enrollment, and infant CD4+ count and CD4 percentage at hospital discharge following birth. Factors associated with LRTIs before the 6–12 week visit in multivariable analyses (Table 3) were maternal CD4 percentage at enrollment and infant CD4+ count at hospital discharge.

In terms of LRTIs after the 6–12 week visit, variables included in multivariable analyses were: maternal CD4+ decline (from enrollment to hospital discharge), maternal plasma viral load at hospital discharge, infant gender, infant CD4 percentage at the 6–12 week visit, infant CD4+ decline, and infant hemoglobin at hospital discharge and at the 6–12 week visit. Infant hemoglobin at the 6–12 week visit and maternal CD4 decline were associated with LRTI after 6–12 weeks (Table 3).

3.4. Factors associated with hospitalizations for LRTIs

In univariate analysis, four or more persons in the household (OR 2.5; 95% CI 1.1–5.7) and length for age $<5^{th}$ percentile at birth (OR 5.9; 95%CI 1.2–28.6) were significantly associated with hospitalization among children who had an LRTI. Also, all children with acute dyspnea (grade ≥4) and bronchospasm and/or dyspnea (grade ≥3) were hospitalized. We attempted to model all variables that met inclusion criteria for modeling (i.e., $p \leq 0.2$), but after both backward and forward elimination processes, no variable met the 0.05 criterion. Data were also analyzed taking into account only those 83 infants with bronchiolitis episodes, of whom 38 were hospitalized. A higher number of persons in the household ($p = 0.04$) and bronchospasm and/or dyspnea grade ≥3 ($p < 0.0001$) were associated with hospitalization (data not shown).

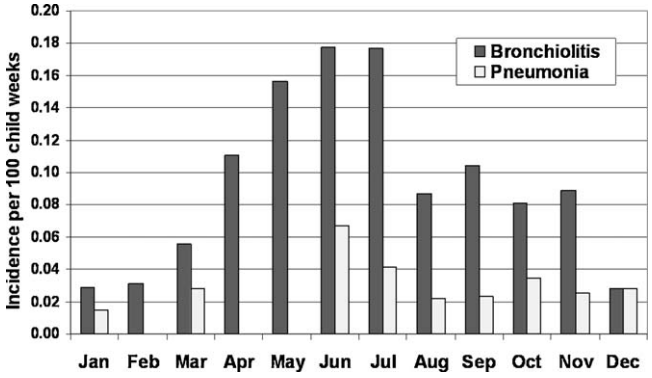

Figure 1. Incidence rate of LRTIs per 100 child-weeks according to month of the year.

4. Discussion

In this study, approximately 20% of infants (0.7–1.0/100 child-weeks) experienced at least one episode of acute LRTI during the first 6 months of life. Most (81%) of these episodes were bronchiolitis, a significant proportion of them (45.7%) required hospitalization, and 12.1% of the episodes presented as severe clinical disease. After controlling for known risk factors, we found that lower maternal and infant CD4+ values were associated with an increased likelihood of LRTI among infants before the 6–12 week visit. Maternal CD4+ decline and infant hemoglobin at the

Table 3
Multivariable analysis of factors associated with LRTIs among infants before the 6–12 week visit and after the 6–12 week visit

	N = 547	LRTI *n* (%)	OR (95% CI)	Adjusted OR (95% CI)
Before the 6–12 week visit				
Maternal CD4% at enrollment				
<14	32	4 (12.5)	2.7 (0.8–9.1)	4.4 (1.2–16.0)[a]
14–28	219	7 (3.2)	0.6 (0.2–1.6)	0.4 (0.1–1.6)
≥29	242	12 (5.0)	1	1
Missing	54			
Infant CD4+ count at hospital discharge (cells/mm^3)				
<750	8	2 (25)	10.2 (1.8–54.9)	16.0 (2.7–96.1)[b]
≥750	441	14 (3.2)	1	1
Missing	98			
After the 6–12 week visit				
Maternal CD4+ decline				
No	259	35 (13.5)	1	1
Yes	241	45 (18.7)	1.5 (0.9–2.4)	1.7 (1.0–2.8)
Missing	47	5		
Infant hemoglobin at 6–12 week visit				
Normal	341	40 (11.7)	1	1
Abnormal	130	43 (33.1)	3.7 (2.3–6.1)	3.5 (2.1 – 6.0)
Missing	76	2		

LRTI, lower respiratory tract infection; OR, odds ratio; CI, confidence interval.
[a] $p = 0.003$.
[b] $p = 0.002$.

6–12 week visit were associated with an increased likelihood of acute LRTI among infants after the 6–12 week visit.

It has been well documented that HIV-infected infants are at increased risk of LRTIs as compared to HIV-uninfected infants, even if they are breastfed.[14] However, it is not known whether HIV-uninfected exposed infants are more susceptible to LRTIs than are infants born to HIV-uninfected mothers. Limited data on respiratory symptoms or pneumonia episodes in African cohorts have suggested that they occur with similar frequency in HIV-exposed and -unexposed infants in that setting.[14]

Although a control group of infants born to HIV-uninfected mothers was not available in our study, a comparison with the most recent available data from a Brazilian community-based study[15] showed that the frequency of LRTIs in the NISDI cohort of HIV-uninfected infants was similar to the 20% prevalence of all respiratory tract infections (RTIs) in infants. However, this study[15] did not differentiate between LRTI and upper RTI. If we conservatively assume that RTIs in infants born to HIV-uninfected mothers are equally distributed between LRTIs and upper RTIs, we conclude that HIV-uninfected, exposed infants have twice as many LRTIs as infants born to HIV-uninfected mothers. Still, taking into account that the intensity of respiratory viral epidemics, that the disease severity varies geographically and temporally, and that breastfeeding reduces the risk of respiratory infections in young infants,[16] a concurrent control group of infants born to HIV-uninfected mothers who were not breastfed from a similar sociodemographic background would be required to address the question of whether HIV-uninfected infants born to HIV-infected mothers were more susceptible to LRTIs than infants born to HIV-uninfected mothers. Due to the lack of a control group, we focused this analysis on characterization of LRTIs and risk factors (especially maternal HIV infection characteristics) for LRTIs.

Community-based studies have shown that acute respiratory symptoms in otherwise healthy infants occur frequently, with virus being identified in 70% to 80% of these episodes, including those presenting as LRTI.[17,18] Although the etiologic agents of the LRTIs in our study subjects were usually not identified, various factors (the young age at presentation, the characterization of the clinical diagnosis as bronchiolitis with wheezing in the great majority of the infants, and the occurrence of a well defined seasonal pattern with an outbreak during late autumn and winter) suggest that most of these infections were caused by viruses. Even those episodes characterized as pneumonia could be primarily or secondarily related to a viral infection in these infants, since most occurred after the peak incidence of bronchiolitis.

In our study, we restricted the analysis to otherwise healthy, term HIV-exposed but uninfected infants. In order to test our hypothesis, we used logistic regression analysis controlling for socioeconomic background, household crowding, maternal tobacco use, maternal employment, and maternal education (which are well-defined correlates of respiratory disease among infants from less privileged populations[19]). Besides abnormal infant hemoglobin at the 6–12 week visit being a predictor of the occurrence of LRTIs in infants older than 6–12 weeks, the odds of LRTI were two- to four-fold greater among infants whose mothers had greater immunosuppression during pregnancy. The magnitude of this association suggests that maternal immunological dysfunction due to HIV infection increases the risk of LRTI, as has been demonstrated for overall infant morbidity[9] and mortality.[20] Considering further the strong association found by us between lower infant CD4+ lymphocyte counts at birth and the occurrence of LRTIs, our results are consistent with previously published reports of the effects of maternal HIV infection on immune cells numbers, maturation and/or function of exposed infants.[1,5–8,21] However, the exact nature of immunological characteristics which predispose some HIV-uninfected infants to acquire LRTIs deserves further investigation, including evaluation of the role of passively-acquired specific antibodies.

In developed countries, where hospitalization data are used as a surrogate for disease severity, the highest reported rates of admissions for acute episodes of RSV-associated bronchiolitis range from 10% to 20% for preterm infants, with the highest rates occurring among those with underlying disease,[22] while only approximately 3% of term or near term otherwise healthy infants are hospitalized.[23] In order to analyze whether rates of hospitalization observed in this study could be explained by the hospital admission practices for HIV-uninfected infants at the research study sites due to socioeconomic conditions (as indicated by general guidelines of LRTI management in these countries[24]), we also evaluated disease severity based on the occurrence of moderate or life-threatening bronchospasm and/or dyspnea. As expected, severe disease (which occurred among 12.6% of infants) perfectly predicted hospitalization. Variables indicating socioeconomic status, such as years of maternal education or maternal gainful employment, did not predict hospital admissions. However, at the univariate level, household crowding, a circumstance usually associated with low socioeconomic status and with the occurrence and severity of LRTIs,[25,26] was found to be associated with hospitalization in this cohort. Taking into account that it was not possible to control completely for confounders, and that two thirds of infants who were admitted did not have severe illness, we cannot rule out whether family and household conditions influenced the physician's decision to hospitalize the infant. Despite 26.5% of hospitalized infants having severe disease, this rate is still higher than those reported for term infants. These findings suggest that it will be important to investigate whether the immune profile of HIV-uninfected infants predisposes them to increased LRTI severity either due to decreased cellular immunity, low virus-specific antibodies, or increased severity of inflammatory responses, as has been recently explored for unexposed infants.[27–29] The possibility of long term sequelae for young infants with bronchiolitis episodes[30] calls further attention to this issue.

This study is limited due to the lack of a control group of infants born to HIV-uninfected mothers. Missing values for some key variables, such as infant CD4 cell counts and hemoglobin values at hospital discharge, might have decreased statistical power in multivariable analysis.

This study demonstrates that LRTIs (primarily acute bronchiolitis) are common and frequently severe among HIV-exposed, uninfected, non-breastfed Latin American infants during the first 6 months of life. We have shown that the immunological status of both the mother and the infant are associated with an increased risk of LRTI during the first 6 months of life. Further understanding of the immunological mechanisms of severe disease may help in avoiding sequelae and in the development of interventions.

Conflict of interest

No authors have any conflict of interest to declare.

Ethical approval

The ethics review boards at each clinical site, the sponsoring institution (NICHD), and the coordinating center (Westat) approved this study. Written informed consent was obtained from all subjects.

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Appendix A. NISDI Perinatal Study Group

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