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Opportunistic and Other Infections in HIV-Infected Children in Latin America Compared to a Similar Cohort in the United States

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Abstract

Opportunistic and other infections have declined since the introduction of highly active antiretroviral therapy (HAART) in developed countries but few studies have addressed the impact of HAART in HIV-infected children from developing countries. This study examines the prevalence and incidence of opportunistic and other infections in Latin America during the HAART era. Vertically HIV-infected children enrolled in a cohort study between 2002 and 2007 were followed for the occurrence of 29 targeted infections. Cross-sectional and longitudinal analyses were performed to calculate the prevalence of infections before enrollment and the incidence rates of opportunistic and other infections after enrollment. Comparisons were made with data from a U.S. cohort (PACTG 219C). Of the 731 vertically HIV-infected children 568 (78%) had at least one opportunistic or other infection prior to enrollment. The most prevalent infections were bacterial pneumonia, oral candidiasis, varicella, tuberculosis, herpes zoster, and *Pneumocystis jiroveci* pneumonia. After enrollment, the overall incidence was 23.5 per 100 person-years; the most common infections (per 100 person-years) were bacterial pneumonia (7.8), varicella (3.0), dermatophyte infections (2.9), herpes simplex (2.5), and herpes zoster (1.8). All of these incidence rates were higher than those reported in PACTG 219C. The types and relative distribution of infections among HIV-infected children in Latin America in this study are similar to those seen in the United States but the incidence rates are higher. Further research is necessary to determine the reasons for these higher rates.

Introduction

The introduction of highly active antiretroviral therapy (HAART) has led to HIV becoming a chronic illness with a reduced incidence of opportunistic and other infections and significantly reduced mortality among HIV-infected children.[1,2] In the 219C study of the Pediatric AIDS Clinical Trials Group (PACTG) in the United States the incidence of 29 targeted opportunistic and other infections in the HAART era was uncommon compared to the pre-HAART era.[3] Another U.S.-based study, the Perinatal AIDS Collaborative Transmission Study, found an 86–100% reduction in opportunistic infections in the HAART era, with rates similar to those reported from the 219C study.[4] Not surprisingly, both of these U.S.-based studies found an increased risk of opportunistic infections among those with lower CD4 counts.[3,4] However, data from an Italian pediatric HIV registry demonstrated that severe bacterial infections, particularly pneumonia, still occurred at high rates even in the absence of severe CD4 cell depletion.[5]

Few studies have prospectively analyzed the incidence of opportunistic and other infections in HIV-infected children from Latin America during the HAART era. Studies in Brazil,[6] Chile,[7] Mexico,[8] and Honduras[9] have examined specific opportunistic illnesses, such as cytomegalovirus (CMV) infections, or overall incidence of opportunistic illnesses, but none

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was prospectively performed across a range of sites in the HAART era. This work represents the first regional analysis of opportunistic and other infections among HIV-infected children in Latin America and the Caribbean in the HAART era. We also compare the frequency of first occurrence of specific infectious illnesses in Latin America and the Caribbean to the occurrence of these illnesses in the United States as reported in the PACTG 219C cohort.[3]

Materials and Methods

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) pediatric protocol is a prospective cohort study following HIV-infected children at multiple clinical sites in Latin America. A description of this protocol and the cohort has been published.[10] When enrollment began in the autumn of 2002, HIV-infected infants, children, and adolescents (≤21 years of age) who were receiving care at the participating sites (11 in Brazil and 2 each in Mexico and Argentina) were eligible; in 2006 one site each in Peru and Jamaica was added. The protocol was approved by the ethical review boards of each clinical site, by the sponsoring institution (NICHD), the data management and statistical center (Westat), and the Brazilian National Ethics Committee (CONEP). Informed consent was obtained from adult participants or either parents or guardians of minor participants.

Eligibility for this analysis was limited to vertically infected participants in the NISDI pediatric study. The following data were collected in a standardized fashion during scheduled study visits twice a year: medical history, physical examination, and laboratory evaluations (including flow cytometry and HIV viral load). Height and weight for age[11] and HIV disease classification[12] were determined according to definitions of the CDC. Criteria used for the diagnoses of specific diseases were those developed for NISDI but based upon the criteria used by the PACTG.[3] Infections with a documented causative agent were classified as "proven"; those without documentation were designated "presumed." We targeted 29 infections classified as infectious events B or C in the CDC HIV disease classification system as well as other infections analyzed in the PACTG 219C study in order to provide comparisons. At enrollment into NISDI, information was collected retrospectively regarding all antiretroviral (ARV) regimens since initiation of therapy; additional information regarding ARVs were also collected at each study visit. HAART was defined as any protease inhibitor (PI) and/or nonnucleoside reverse transcriptase inhibitor (NNRTI) therapy. Those not on a PI and/or NNRTI but on some other ARV were classified as other ARV.

Statistical methods

The proportion of children with each of the 29 targeted infections prior to enrollment to the NISDI protocols was calculated based upon retrospective information. Incidence rates (IRs) for the first opportunistic or other infection and 95% confidence intervals (CI) were calculated per 100 person-years under a Poisson distribution for the entire study population during participation on the study; IRs and 95% CI were also calculated for the first occurrence of each of the 29 targeted infections. Person-years of follow-up were calculated from study entry until the first infection or until the end of study participation (withdrawal from the study, death, or end of study); however, a child with a first infection could continue to contribute person-time for different subsequent infections. For analysis purposes, laboratory assays, particularly CD4% and viral load, were those measured at the visit immediately prior to the first occurrence of an opportunistic or other infection. For the description of these numerical variables, we also calculated the median and quartile range (QR). Age was calculated at the time of the infection. All analyses were conducted using the SAS statistical software version 9.0 (SAS Institute Inc., Cary, NC). Incidence rates obtained from NISDI were compared to rates obtained in PACTG 219C[3] using the approximate interval estimation with follow-up data by Rothman.[13]

Results

Characteristics of the study population

Between September 2002 and October 2007, 731 vertically HIV-infected children enrolled in NISDI. As shown in Table 1, 66% were born in Brazil, 56% were girls, 43% were <5 years of age, and 67% were on HAART. These 731 children were on study for a median of 3.9 years (QR 3.3–4.3 years) and contributed 1633 person-years of follow-up to the first infection or end of study for those without infections. Forty-six (6.3%) were lost to follow-up: the sites were unable to locate 17 of the children, 13 moved out of the area, 13 died during follow-up, and 3 withdrew consent.

Prevalence of opportunistic and other infections prior to study entry

Overall, there were 1436 infections reported among 568 (78%) children prior to enrolling in NISDI with 26 of the 29 infections investigated being identified. Bacterial pneumonia was the most common infection for children of all ages. For children older than 1 year of age the most common infections were bacterial pneumonia, varicella, dermatophyte infections, and herpes simplex infections. There were no reports of invasive fungal infections, nontuberculous mycobacterial disease, or bacterial septic arthritis. Table 2 shows the prevalence of the targeted infections compared to those reported in PACTG 219C.[3] Among the seven most common infections seen in the NISDI cohort all except oral candidiasis and herpes zoster were reported at a greater frequency in NISDI, with 95% confidence intervals that did not overlap with those reported from the PACTG cohort. In addition, bacterial abscesses, urinary tract infections, lymphadenitis, herpes simplex, and bacterial meningitis were more prevalent in the NISDI cohort. Only two conditions, dermatophyte infections and lymphoid interstitial pneumonitis, were reported more frequently in the PACTG cohort than in the NISDI cohort.

Incidence of first opportunistic or other infection during the study period

Overall, 383 (52.4%) of the children experienced at least one of the targeted infections during study follow-up. The median age at the first infection was 6 years. Table 1 summarizes the other clinical features for these 383 children prior to their first diagnosed infection. The CD4% was ≥25% in 57% and the viral load was <10,000 copies/ml in 49% of the children who

Table 1. Characteristics of Vertically HIV-Infected Children at Enrollment and at the First Opportunistic Infection After Enrollment on NISDI

Study variable	*At enrollment* N = *731 (%)*	*Experiencing an OI on study* N = *383 (%)*
Country of birth		
Brazil	483 (66.1)	285 (74.4)
Mexico	118 (16.1)	45 (11.8)
Argentina	71 (9.7)	22 (5.7)
Peru	37 (5.1)	20 (5.2)
Jamaica	22 (3.0)	11 (2.9)
Gender		
Male	325 (44.5)	174 (45.4)
Female	406 (55.5)	209 (54.6)
Age (years)		
Median (QR)	5.0 (3.0–9.0)	6.0 (4.0–10.0)
<1	37 (5.1)	11 (2.9)
1-4	275 (37.6)	113 (29.5)
5-9	280 (38.3)	160 (41.8)
≥10	139 (19.0)	99 (25.8)
HIV classification (CDC)		
N	101 (14.0)	39 (10.3)
A	155 (12.5)	76 (20.1)
B	233 (32.3)	128 (33.9)
C	233 (32.3)	135 (35.7)
Missing[a]	9	5
ARV regimen		
PI + NNRTI HAART	55 (7.5)	14 (3.6)
PI HAART	328 (44.9)	186 (48.6)
NNRTI HAART	103 (14.1)	63 (16.4)
Other ARV	127 (17.4)	75 (19.6)
No ARV	118 (16.1)	45 (11.8)
CD4 percent		
Median (QR)	27% (21–34)	26% (19–34)
<15%	74 (11.5)	49 (14.1)
15–24%	187 (29.0)	102 (29.4)
≥25%	384 (59.5)	196 (56.5)
Missing[a]	86	36
HIV viral load (copies/ml)		
Median (QR)	7.9K (0.2–44.3K)	10.5K (0.7–63K)
<1000	225 (31.0)	100 (26.5)
1000–<10,000	156 (21.5)	84 (22.2)
≥10,000	345 (47.5)	194 (51.3)
Missing[a]	5	5
Weight/age (CDC *z*-score)		
≤2SD from the mean	118 (16.2)	60 (15.8)
±2 SD from the mean	601 (82.4)	318 (83.7)
>2SD above the mean	10 (1.4)	2 (0.5)
Missing[a]	2	3
Height/age (CDC z-score)		
≤2 SD from the mean	148 (20.4)	74 (19.5)
±2 SD from the mean	574 (79.2)	304 (80.2)
>2 SD above the mean	3 (0.4)	1 (0.3)
Missing[a]	6	4
BMI percentile		
<5th percentile	68 (9.4)	42 (11.2)
5th<95th percentile	615 (84.8)	321 (85.4)
≥95th percentile	42 (5.8)	13 (3.4)
Missing[a]	6	7

[a]Missing values are not included in percentages.

QR, quartile range represents the 25th and 75th quartile for the population; SD, standard deviation; OI, opportunistic infection; ARV, antiretroviral; PI, protease inhibitor; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; BMI, body mass index.

experienced one of these targeted infections. Forty-nine percent of the study population had received at least one dose of pneumococcal vaccination and 22% had received at least one dose of varicella vaccination by the time of enrollment.

In total, there were 637 incident infections among these 383 children after enrollment attributed to 26 of the 29 infections investigated. There were no reports of invasive fungal infections, bacterial osteomyelitis, or measles. Table 3 summarizes the IRs for each of the targeted infections and presents the comparison between the NISDI cohort and the PACTG 219C cohort. After enrollment, the overall incidence was 23.5 per 100 person-years with the most common infections being bacterial pneumonia, varicella, dermatophyte infections, herpes simplex virus, and herpes zoster. Although similar to the PACTG 219C cohort, in which bacterial pneumonia, herpes zoster, oral candidiasis, dermatophyte infections, and varicella were the five most common infections, our study had significantly higher IRs. Likewise, other infections that were more prevalent prior to enrollment, lymphadenitis, urinary tract infections, and proven diarrhea, also had higher IRs than those seen in the PACTG cohort.

Most cases of diarrhea reported from NISDI were not tested for an etiologic agent, hence were not included in our analyses. If these presumed infectious diarrheas had been included, the IR (6.3 per 100 person-years) would have made this the second most common infection in the NISDI cohort.

No statistical difference was found in CD4% or VL levels between those on HAART and those not on HAART prior to their first infection; thus we present the age, CD4%, and viral load prior to each of these targeted infections without regard to treatment regimen (Table 4). Bacterial pneumonia, was the most common infection for children of all ages. For children older than 1 year of age the most common infections where bacterial pneumonia, varicella, dermatophyte infections, and herpes simplex infections.

Fifty percent or greater of the following CDC class C conditions—bacterial meningitis, cytomegalovirus not retinitis, CNS toxoplasmosis, and *Cryptosporidium* infections—occurred among children whose CD4% was 25% or higher; the majority of bacterial pneumonia, *Pneumocystis jiroveci*, sepsis, and tuberculosis occurred among children with CD4% <25%. All cases of esophageal candidiasis (2), nontuberculous mycobacterial disease (2), and progressive multifocal leukoencephalopathy (2) occurred in children with CD4% less than 15% (data not shown). As we have reported before, during follow-up, 13 patients died, all but two of an infectious cause.[10]

Among the 383 children who had one of the targeted infections, 200 (52.2%) had two or more episodes during the study period. Of the 170 children who had bacterial pneumonia 58 (34.1%) had at least two episodes (29 had two episodes, 12 had three episodes, and 17 had four or more episodes). Of the 60 children who had herpes simplex infections 12 (20%) had at least two episodes (seven had two episodes, three had three episodes, and two had four episodes) (data not shown).

Discussion

In this prospective observational study of vertically HIV-infected children in Latin America we have shown that the relative distribution of 29 targeted infections seen during the

Table 2. Proportion of HIV-Infected Children Reporting Opportunistic and Other Infections Prior to Enrollment in NISDI and PACTG

	NISDI[a]		*PACTG 219C*[3]	
Category	N = *731*	*Percent (95% CI)*[b]	N = *2767*	*Percent (95% CI)*[b]
Overall first infections	568	77.7 (74.7–80.7)		Not reported
Bacterial pneumonia	384	**52.5 (48.9–56.2)**	698	25.2 (23.6–26.8)
Oral candidiasis	212	29.0 (25.7–32.3)	761	27.5 (25.8–29.2)
Varicella	161	**22.0 (19.0–25.0)**	395	14.3 (13.0–15.6)
Tuberculosis	65	**8.9 (6.8–11.0)**	17	0.6 (0.3–0.9)
Herpes zoster	63	8.6 (6.6–10.6)	280	10.0 (9.0–11.2)
Pneumocystis jiroveci	61	**8.3 (6.3–10.3)**	79	2.9 (2.2–3.5)
Diarrhea, proven	56	**7.7 (5.7–9.6)**	104	3.8 (3.1–4.5)
Molluscum contagiosum	56	7.7 (5.7–9.6)	151	5.5 (4.6–6.3)
Abscess, bacterial	48	**6.6 (4.8–8.4)**	5	0.2 (0.0–0.3)
Bacteremia/septicemia	48	6.6 (4.8–8.4)	220	8.0 (6.9–9.0)
Dermatophyte infections	46	6.3 (4.5–8.1)	422	**15.3 (13.9–16.6)**
Urinary tract infections	44	**6.0 (4.3–7.7)**	68	2.5 (1.9–3.0)
Lymphadenitis	40	**5.5 (3.8–7.1)**	11	0.4 (0.2–0.6)
Lymphoid interstitial pneumonitis	39	5.3 (3.7–7.0)	325	**11.8 (10.6–13.0)**
Herpes simplex	27	**3.7 (2.3–5.1)**	24	0.9 (0.5–1.2)
Bacterial meningitis	23	**3.1 (1.9–4.4)**	13	0.5 (0.2–0.7)
Viral hepatitis	15	2.1 (1.0–3.1)	60	2.2 (1.6–2.7)
Cytomegalovirus not retinitis	11	1.5 (0.6–2.4)	49	1.8 (1.3–2.3)
Esophageal/pulmonary candidiasis	10	1.4 (0.5–2.2)	39	1.4 (1.0–1.9)
Toxoplasmosis (CNS)	9	1.2 (0.4–2.0)	5	0.2 (0.0–0.3)
Cytomegalovirus retinitis	6	0.8 (0.2–1.5)	10	0.4 (0.1–0.6)
Measles	5	0.7 (0.1–1.3)	5	0.2 (0.0–0.3)

[a]NISDI also reported three cases of progressive multifocal leukoencephalopathy, two cases of bacterial osteomyelitis, and one each of *Cryptosporidium* and encephalitis.
[b]Higher reporting of specific infections between cohorts shown by **bolded** nonoverlapping intervals.

Table 3. Overall Incidence Rates of First-Time Infections for Categories with Four or More First Events Among Patients Enrolled in NISDI Compared with PACTG 219C

	NISDI[a]			*PACTG 219C*[3]			
Category	*Incident events*	*Person Years*	*IR of events/100 person years (95% CI)*	*Incident events*	*Person Years*	*IR of events/100 person years (95% CI)*	p[b]
Overall first infections[c]	383	1633	23.45 (21.10–25.80)	—	—	—	
Bacterial pneumonia	170	2174	7.82 (6.64–8.99)	123	5726	2.15 (1.79–2.56)	<0.001
Varicella	71	2385	2.98 (2.28–3.67)	29	6623	0.44 (0.29–0.63)	<0.001
Dermatophyte infections	69	2409	2.86 (2.19–3.54)	57	6483	0.88 (0.67–1.14)	<0.001
Herpes simplex virus	60	2440	2.46 (1.84–3.08)	11	7807	0.14 (0.07–0.25)	<0.001
Herpes zoster	45	2460	1.83 (1.29–2.36)	77	6925	1.11 (0.88–1.39)	0.02
Abscess, bacterial[c]	37	2448	1.51 (1.02–2.00)	—	—	—	
Oral candidiasis	36	2466	1.46 (0.98–1.94)	52	5576	0.93 (0.70–1.22)	0.06
Molluscum contagiosum	31	2461	1.26 (0.82–1.70)	23	7392	0.31 (0.20–0.47)	<0.001
Lymphadenitis	22	2495	0.88 (0.51–1.25)	7	7849	0.09 (0.04–0.18)	<0.001
Urinary tract infection	19	2509	0.76 (0.42–1.10)	27	7660	0.35 (0.23–0.51)	0.03
Infectious diarrhea	18	2497	0.72 (0.39–1.05)	9	7552	0.12 (0.05–0.23)	<0.001
P. jiroveci pneumonia	9	2526	0.36 (0.12–0.59)	7	7668	0.09 (0.04–0.19)	0.03
Lymphoid interstitial pneumonitis	7	2533	0.28 (0.07–0.48)	6	6889	0.09 (0.03–0.19)	0.09
Bacterial meningitis[c]	7	2522	0.28 (0.07–0.48)	—	—	—	
Tuberculosis (TB)	7	2523	0.28 (0.07–0.48)	<4	—	—	
Viral hepatitis	6	2525	0.24 (0.05–0.43)	11	7729	0.14 (0.07–0.25)	0.37
Bacteremia/septicemia	5	2529	0.20 (0.02–0.37)	25	7192	0.35 (0.22–0.51)	0.18
CMV not retinitis[c]	4	2534	0.16 (0.0–0.31)	—	—	—	

[a]NISDI reported <4 events for toxoplasmosis (3), non-TB mycobacteria (2), esophageal or pulmonary candidiasis (2), *Cryptosporidium* (2)[c], progressive multifocal leukoencephalopathy (2)[c], CMV retinitis (1), encephalitis (1)[c], septic arthritis, bacterial (1)[c].
[b]Fisher's exact test.
[c]Not reported in PACTG 219C.[3]
IR, incidence rate; CMV, cytomegalovirus.

Table 4. Age, CD4%, and Human Immunodeficiency Virus RNA Prior to First-Time Infections for Diagnostic Categories with Four or More First Events Among Children Participating in the NISDI Pediatric Protocol in Latin America and the Caribbean

		Age					*CD4% prior*[a]				*Viral load*[b]			
	Number of children	*<1*	*1–4*	*5–9*	*≥10*	*IQR (years)*	*<15%*	*15–24%*	*≥25%*	*IQR (%)*	*<1K*	*1K–<10K*	*≥10K*	*IQR (K)*
All first infections	383	11	113	160	99	4–10	49	102	196	19–34	100	84	194	0.7–63
Bacterial pneumonia	170	5	61	70	34	4–9	24	57	73	18–33	35	34	99	3–93
Varicella	71	0	24	37	10	4–8	6	21	37	21–35	24	15	32	0–44
Dermatophyte	69	0	11	31	27	6–11	3	17	43	23–35	25	17	27	0–36
Herpes simplex	60	2	6	29	23	7–11	11	15	30	18–32	16	15	28	0–61
Herpes zoster	45	0	7	17	21	7–12	15	15	14	14–26	6	8	29	2–84
Bacterial abscess	37	0	9	18	10	5–11	3	12	18	22–33	8	12	15	1–36
Oral candidiasis	36	3	14	11	8	3–9	14	10	8	8–25	5	5	26	9–371
Molluscum	31	0	10	15	5	5–9	1	7	21	23–35	5	5	21	3–99
Lymphadenitis	22	0	4	11	7	6–12	2	7	11	16–34	5	2	14	1–62
Urinary tract infections	19	0	6	7	6	3–11	2	4	10	19–32	5	3	11	0–110
Diarrhea, proven	18	2	8	6	2	2–7	5	4	9	14–37	3	4	11	3–196
Pneumocystis jiroveci	9	1	6	1	1	2–19	3	2	4	10–32	0	1	7	38–324
Bacterial meningitis	7	1	1	3	2	3–10	1	2	4	22–40	2	0	4	0–125
LIP	7	1	3	1	2	2–13	0	2	4	17–32	1	1	5	3–182
Tuberculosis	7	1	2	0	4	2–15	2	2	3	13–28	2	4	1	0–9
Viral hepatitis	6	0	1	3	2	8–12	2	2	2	14–31	2	2	2	1–128
Bacteremia septicemia	5	2	1	2	0	0–5	1	2	2	16–25	0	0	4	82–3857

[a]CD4% (87 missing values).
[b]Viral load <400 reported as zero (16 missing values).

HAART era is similar to results from the United States but that the prevalence and IRs are generally higher. Because this study did not begin until 2002, no attempt was made to compare rates in those on HAART versus those not on HAART since all participants could realistically be considered to be treated in the HAART era. However, we were able to compare the NISDI experience in Latin America with the 2767 HIV-infected children enrolled in the U.S. PACTG cohort.[3] The characteristics of the PACTG cohort were similar to NISDI in the enrollment time frame (September 2000 to December 2004), median length of follow-up (3.4 years), median CD4% (30), and the percentage on HAART (69%), but with a lower median viral load (1208 copies/ml) and older median age at enrollment (9.9 years). The IR of any first infection in our study was 23.5 per 100 person-years, and the most common incident infections (bacterial pneumonia, varicella, dermatophyte infections, herpes simplex, and herpes zoster) were more common than in the 219C cohort.[3]

The IR of bacterial pneumonia was higher than has been reported in the 219C study and other studies in the United States and Europe,[3,5] and was similar to the rate seen in the pre-HAART era in Spain[14] and the rate seen after 12 months of HAART in Zambian children.[15] While this should prompt further study, one explanation may well be the difficulty in diagnosing bacterial pneumonia and tuberculosis, especially in children, and the chance that episodes of nonbacterial respiratory illness or tuberculosis were recorded as bacterial.[16] Nevertheless, it is striking that 43% of children with an incident episode of bacterial pneumonia had a CD4% ≥25. This high rate of bacterial pneumonia despite adequate CD4 count has also been seen in the studies in other settings and offers evidence of continued immunologic deficits in the face of effective antiretroviral therapy in children.[3,5,15]

The rate of herpes zoster in our study was higher than the rate reported in the 219C study[3] but was within the range reported in a more detailed examination of herpes zoster among a subset in the 219C study.[17] Interestingly, though, Hispanic ethnicity was associated with higher rates of herpes zoster in another U.S.-based study of HIV-infected children, which may be relevant to the Latin American population that we studied.[18] The higher rate of varicella that we saw may be related to limited use of varicella vaccine in these countries.

In addition to bacterial pneumonia, herpes zoster, varicella, and *Pneumocystis jiroveci* pneumonia, the IRs for the following were also significantly higher in our study compared to results in the 219C study: dermatophyte infections, herpes simplex, molluscum contagiosum, lymphadenitis, urinary tract infections, and infectious diarrhea. The differences between the results for herpes simplex may be related to a much more stringent definition in the 219C study, which counted only episodes refractory to treatment for over 30 days, whereas we include all reported herpes simplex infections. The incidence of several infections was not reported in the 219C report due to very few events. For example, the 219C reported only that there were less than four cases of tuberculosis episodes precluding formal statistical comparison with our NISDI cohort. If we assume there were as many as three tuberculosis cases, the rate would have been 0.04 to 0.05/100 person-years, making tuberculosis substantially more common in the NISDI cohort. The IR for only one targeted infection reported from 219C, sepsis or bacteremia, was higher, but not significantly different than the IR in our study.

The major strengths of this study are the systematic collection of data over a 5-year period with frequent follow-up (every 6 months) that allowed the capture of events between visits. In addition, we used essentially the same classification

system as was used in the 219C cohort study,[3] which facilitated the comparisons across the two cohorts. Some limitations of the study are fewer participants (compared to PACTG 219C) and low rates of rare diseases (for example, CMV retinitis) leading to unstable IRs for some infections reported in NISDI. Also, we relied on reported diagnoses and limited attempts were made to verify the etiologies or confirm the reports.

In conclusion, although the types and relative distribution of infections among HIV-infected children in our Latin American cohort during the HAART era are similar to what has been seen in the United States, the prevalence and incidence rates are higher. Thus, despite access to HAART, there is higher morbidity related to infections among HIV-infected children in Latin America and the Caribbean than in the United States. This may be due, in part, to the higher prevalence of some infections in Latin America (such as diarrhea and tuberculosis), poorer nutritional status of children, socioeconomic factors, health care quality, and other factors. Further research is necessary to determine whether these factors or others are the reasons for these differences in order to identify improved preventive strategies for HIV-infected children living in Latin America and in other countries outside the United States and Europe.

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