

# A Cohort Study of Health Effects of Human T-Cell Lymphotropic Virus Type I Infection in Jamaican Children

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**ABSTRACT.** *Objective.* Human T-cell lymphotropic virus type I (HTLV-I) infection in childhood is believed to play an important role in risk for adult T-cell leukemia/lymphoma. Although HTLV-I is known to be associated with infective dermatitis in childhood, other HTLV-I-associated morbidity in children has not been well studied. We sought to determine the HTLV-I-associated health effects in Jamaican children.

*Methods.* We compared incidence rates of several health outcomes in 28 HTLV-I-infected and 280 uninfected children clinically followed from age 6 weeks to a maximum of 10 years. Cox proportional hazards regression analysis was used to analyze these prospectively collected data, adjusting for confounding effects of other variables as necessary.

*Results.* HTLV-I-infected children had significantly higher incidence rates of seborrheic dermatitis (rate ratio [RR] = 4.8, 95% confidence interval [CI] = 1.9–12.5), eczema (RR = 3.1, CI = 1.2–7.9) and persistent hyperreflexia (RR = 3.7, CI = 1.6–8.2). Additionally, HTLV-I infected children had increased rates of severe anemia (RR = 2.5, CI = 0.8–7.9) and abnormal lymphocytes (RR = 2.4, CI = 0.8–7.6) that were of borderline statistical significance.

*Conclusions.* Our study suggests that HTLV-I-associated skin diseases of childhood may include seborrheic dermatitis and eczema. Additionally, these data suggest that persistent hyperreflexia of the lower limbs may be an early sign of HTLV-I-associated neurologic involvement in children. Expansion and continued clinical observation of this cohort would be valuable. *Pediatrics* 2003;112:e136–e142. URL: <http://www.pediatrics.org/cgi/content/full/112/2/e136>; HTLV-I, pediatric, morbidity.

ABBREVIATIONS. HTLV-I, human T-cell lymphotropic virus type I; ATL, adult T-cell leukemia/lymphoma; HAM/TSP, HTLV-I-associated

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ated myelopathy or tropical spastic paraparesis; ID, infective dermatitis; WBC, white blood cell; PCR, polymerase chain reaction; RR, rate ratio; CI, confidence interval; SD, seborrheic dermatitis.

Human T-cell lymphotropic virus type I (HTLV-I) causes a rare but almost uniformly fatal T-cell malignancy called adult T-cell leukemia/lymphoma (ATL), and a chronic, debilitating neurologic disease called HTLV-I-associated myelopathy or tropical spastic paraparesis (HAM/TSP).<sup>1,2</sup> HTLV-I is also associated with an inflammatory eye disease, HTLV-I-associated uveitis, and is suggested to be associated with several other inflammatory diseases including arthropathy, Sjögren's syndrome, and polymyositis.<sup>3–6</sup> These diseases occur predominantly among adults. Subclinical conditions associated with HTLV-I infection among adults include lymphadenopathy, an increased prevalence of abnormal lymphocytes and lymphocytosis, which are components of ATL, as well as lymphocytopenia, anemia, and a decreased prevalence of eosinophilia.<sup>7–13</sup> Gait abnormality, a clinical feature of HAM/TSP, was associated with HTLV-I infection in adult US blood donors.<sup>14</sup> Other conditions associated with HTLV-I infection among adults include asthma, electrocardiograph anomaly, and bacterial infections.<sup>9,14,15</sup> Among children, HTLV-I is etiologically associated with infective dermatitis (ID), a severe exudative eczema with usual onset between ages 2 and 3 and abatement of symptoms in puberty.<sup>16,17</sup> With the exception of ID, HTLV-I-associated morbidity in children has not been well studied.

We sought to study health effects of HTLV-I in a cohort of children born to HTLV-I seropositive and seronegative women and clinically observed from 6 weeks of age to a maximum age of 10 years. Specifically, we examined whether, compared with HTLV-I-uninfected children, HTLV-I-infected children had significantly higher rates of signs and symptoms associated with ATL and HAM/TSP, as well as other conditions associated with HTLV-I in adults. Because of the association of HTLV-I with ID in children, we examined whether HTLV-I-infected children had an increased risk of developing skin diseases that represent other eczematous conditions: eczema and seborrheic dermatitis (SD). Finally, because Jamaican dermatologists have observed that children with ID appeared small for their age, we

examined the relationship between HTLV-I infection and physical growth by analyzing height for age.

## METHODS

### Study Population

The study population was described in detail by Wiktor et al<sup>18</sup> in his report on risk factors for maternal-child transmission of HTLV-I in this cohort. Briefly, 9430 pregnant women attending either of 2 antenatal clinics in Kingston, Jamaica, between January 1989 and August 1990 were screened for HTLV-I antibodies. Seropositive status was determined for 350 (3.7%) women, of whom 212 were enrolled along with the 145 seronegative women randomly selected as controls. Mothers donated a blood sample and were interviewed regarding demographic information at enrollment. Of the 357 children born to enrolled mothers, 308 children completed at least 1 clinic visit, including 28 children who became HTLV-I infected, and 280 children who remained seronegative. These children underwent physical examination and phlebotomy, and the mothers responded to questions related to their children's interim health, at clinic visits that occurred every 6 weeks for the first 6 months of life, then every 3 months up to 2 years of age, and every 6 months thereafter up to 10 years of age.

### Demographic and Breastfeeding Information

At enrollment, mothers were interviewed by a nurse about demographic data, and at each clinic visit they were asked about breastfeeding status until weaning. Total income was dichotomized as high ( $\geq$ \$100 Jamaican per week) and low ( $<$ \$100 Jamaican per week). The currency exchange rate at the time of enrollment was \$5.50 Jamaican = \$1.00 United States. All children were breastfed. Duration of breastfeeding was calculated from date of birth to the midpoint between the date of the clinic visit at which the mother reported to have stopped breastfeeding and the preceding clinic visit.

### Clinical Outcomes

At each clinic visit, mothers were interviewed about their child's health, and a physical examination was performed by a study physician, who was blinded to the HTLV-I status of the child. From ages 30 to 120 months, a 20-item skin assessment and a neurologic screening examination were added to the physical examination, and blood was collected for a complete blood count and differential counts. Information on symptoms, intercurrent illness, physical signs, and blood counts were collected on standard forms.

Lymphadenopathy was defined as the presence of lymph nodes  $>1$  cm at a minimum of 2 sites during 1 clinic visit; analysis of this outcome was restricted to data obtained from 30 to 120 months of age. Small stature was defined as height values less than the 5th percentile for sex/age groups, according to the National Center for Health Statistics. Analysis of small stature was also restricted to data collected from 30 to 120 months of age. Determination of all hematologic abnormalities except abnormal lymphocytes were based on age-specific normal values for Jamaican children.<sup>19</sup> Severe anemia was defined as: Hgb  $<9.0$  g/dL (ages: 30–36 months);  $<9.6$  g/dL (ages: 37–66 months) and  $<10.0$  g/dL (ages: 67–120 months). Eosinophilia was defined as  $\geq 800$  eosinophil count per microliter of blood for all ages. Elevated white blood cell (WBC) count was defined as: WBC  $>15.5 \times 10^3/\mu\text{L}$  (ages: 30–66 months); WBC  $>8 \times 10^3/\mu\text{L}$  (ages: 67–114 months); WBC  $>13.5 \times 10^3/\mu\text{L}$  (ages: 115–120 months). Elevated lymphocyte count was defined as lymphocyte count  $>8500/\mu\text{L}$  (ages: 30–120 months). The percent of abnormal lymphocytes was determined by microscopic review of a peripheral blood smear of 100 lymphocytes.

The majority of health outcomes were defined by the first occurrence of the outcome. Seborrheic dermatitis was diagnosed if the child had clinical signs on a least 1 clinic visit, including greasy, red, scaly, usually nonpruritic eruptions predominantly in hair-bearing and intertriginous areas such as scalp, eye brows, eye lashes, perinasal, presternal, postauricular areas as well as the neck, axillae, and groin. However, clinical definitions of eczema and persistent hyperreflexia required detection of these outcomes at multiple clinic visits. The diagnosis of eczema was made if the child had clinical signs of eczema at a minimum of 3 clinic visits.

Clinical signs of eczema vary by age. Eczema was diagnosed between the ages of 1 month and 3 years if clinical signs included an intensely pruritic rash of nonflexural surfaces and the dorsum of the hand, limb, and chest. Eczema was diagnosed between the ages of 4 and 10 years if the child had a dry, papular, and intensely pruritic rash involving scaly patches distributed on the wrist, ankle, antecubital, and popliteal fossae extensor surfaces of limbs, and palms and plantar surfaces of hands and feet. The diagnosis of persistent hyperreflexia was determined if the pediatrician recorded hyperreflexia of the lower limbs (based on a 1–5 scoring system with 1 indicating areflexia and 5 indicating clonus) at a minimum of 2 clinic visits. Regardless of whether the diagnosis required a single or multiple occurrences, the date of diagnosis for all outcomes was the first clinic visit at which the outcome was recorded by the pediatrician.

Referral to clinical specialists occurred only in special circumstances. Cases of skin disease suspected to be ID were referred to a dermatologist for diagnosis during the course of the study. Additionally, at the end of follow-up all children with diagnoses of persistent hyperreflexia who were still enrolled in the study were referred to a pediatric neurologist for examination.

### Laboratory

Heparinized blood was collected at each clinic visit and centrifuged to separate plasma and lymphocytes used for HTLV-I serologic testing and quantification of HTLV-I proviral load, respectively. Plasma was stored at  $-70^\circ\text{C}$  and lymphocytes were stored in liquid nitrogen until withdrawal for testing. Additional fresh blood was collected in an ethylenediaminetetraacetic acid tube for complete blood count and differential counts, which were measured by clinical laboratory technicians using standard methods.

### HTLV-I Infection Status

HTLV-I antibody testing of mothers and offspring had previously been conducted using enzyme-linked immunosorbent assay (Cambridge Bioscience, Cambridge, MA; Dupont, Wilmington, DE; or Genetic Systems, Seattle, WA) and Western blot (Cambridge Bioscience).<sup>18</sup> Among children who were seropositive by enzyme-linked immunosorbent assay from 12 to 24 months of age serial samples obtained up to 24 months of age were tested by Western blot to identify the estimated date of seroconversion. HTLV-I quantitative proviral DNA testing of serial lymphocyte specimens surrounding the estimated date of seroconversion was used to verify the age of infection, determined to be midpoint between the draw dates for the first sample with a positive polymerase chain reaction (PCR) test and the last sample with a negative PCR test.

For HTLV-I proviral load testing, DNA was extracted from  $1 \times 10^6$  cryopreserved peripheral blood mononuclear cells using the PureGene DNA isolation Kit (Gentra Systems, Inc, Minneapolis, MN). Proviral load was measured in 10- $\mu\text{L}$  samples of solutions containing 300 ng of DNA using an ABI PRISM 7700 Sequence Detection System and Taqman PCR Reagent (P/N N808–0230; Perkin Elmer Applied Biosystems, Foster City, CA) in a 96-well format. This assay reliably detects at least 3 copies/ $10^5$  lymphocytes.<sup>20</sup> HTLV-I proviral load was normalized for the number of lymphocytes in each sample by dividing the number of provirus copies by half the count of human endogenous retrovirus 3, which exists as 2 copies per cell.<sup>20</sup> Children who maintained HTLV-I seronegative status for the first 3 years of life were not further tested by Western blot or PCR, and are assumed to be uninfected.

### Vitamin A

Vitamin A was measured as serum retinol at a mean age of 10 months by high performance liquid chromatography (Craft Technologies, Inc, Wilmington, NC). Serum retinol was categorized as low ( $<0.70$   $\mu\text{mol/L}$ ), borderline ( $0.70$   $\mu\text{mol/L}$  to  $1.05$   $\mu\text{mol/L}$ ), or normal ( $>1.05$   $\mu\text{mol/L}$ ).

### Statistical Methods

Separate Cox proportional hazards regression models were used to compute rate ratios (RRs) as measures of the effect of HTLV-I infection on risk of individual health outcomes; 95% confidence intervals (CIs) were calculated to estimate the precision of the RRs. Unless otherwise stated, the RRs presented in the text represent unadjusted RRs. For health outcomes measured at clinic

visits occurring at 30 months to 120 months of age, person-years at risk accrued from the child's age at their 30-month clinic visit for both infected and uninfected children, as the oldest age at infection was 27 months. For health outcomes that were measured from the first clinic visit, HTLV-I status was treated as a time-dependent variable. As such, health outcome events and person-years accumulated among HTLV-I-infected children before their estimated date of infection accrued to the HTLV-I-uninfected study group. Among all children, follow-up ended at their date of diagnosis with a specific health outcome or the date of their last clinic visit, or the end of the study period or their date of death, whichever came first. Potential confounding by child's sex, maternal income, and duration of breastfeeding was examined by including child's sex, dichotomous levels of maternal income, and continuous values of duration of breastfeeding in the regression models. In analyses of health outcomes that were potentially associated with nutritional status (ie, small stature and severe anemia), serum retinol was included as a categorical variable or a dummy variable with 3 levels.

$\chi^2$  and Fisher exact tests were used to compare HTLV-I-infected and -uninfected children with respect to their distribution by sex, income categories, and frequency of specific health outcomes. Wilcoxon rank-sum test was used to compare the distributions of clinical observation periods, duration of breastfeeding, serum retinol, and hematologic parameters between the HTLV-I-infected and -uninfected groups. A 2-sided  $\alpha$  value of 0.05 was used as the criterion for statistical significance. All statistical analyses were conducted using Statistical Analysis Software (SAS Institute, Cary, NC) version 6.03 on a personal computer.

Informed consent was obtained from parents of study participants, and human experimentation guidelines of the US Department of Health and Human Services, the University of the West Indies, Kingston, Jamaica, and the Uniformed Services University of the Health Sciences, Bethesda, Maryland, were followed in the conduct of this clinical research.

## RESULTS

A total of 308 children born to HTLV-I seropositive and seronegative mothers completed at least 1 clinic visit and are included in this analysis. These include 181 children born to HTLV-I seropositive mothers and 127 children born to HTLV-I seronegative mothers. Twenty-eight of the 181 children born to seropositive mothers became infected with HTLV-I at an estimated mean age of 14 months (range: 4–27 months).<sup>18</sup> In this analysis of health affects associated with HTLV-I, we compared the incidence rates of targeted health outcomes ascertained by prospective clinical follow-up in 28 HTLV-I-infected and 280 uninfected children.

HTLV-I-infected children were composed of 57.1% males, compared with 48.2% males among HTLV-I-uninfected children ( $P = .36$ ; Table 1). A nonsignificantly higher proportion of HTLV-I-infected children (35.7%) were born to mothers of low income status, compared with uninfected children (21.0%,  $P = .08$ ). Similar proportions of children in the 2 groups were born at the 2 participating antenatal clinics ( $P = .87$ ). The mean duration of breastfeeding was longer for HTLV-I-infected children (21.6 months) compared with uninfected children (10.3 months;  $P < .0001$ ). The 28 HTLV-I-infected children accumulated a mean of 6.7 years of clinical observation, and the 280 HTLV-I-uninfected children accumulated a mean of 5.5 years of clinical observation ( $P = .81$ ). Of the 308 children who attended at least 1 clinic visit, 82.1% of infected children and 56.1% of uninfected children completed at least 5 years of clinical follow-up and 53.6% of infected children and 36.4% of uninfected children completed 10 years of follow-up.

## Skin Assessment

An examination of skin diseases associated with HTLV-I infection resulted in 1 case of ID that was previously described in a case report.<sup>21</sup> HTLV-I-infected children had an almost fivefold increased rate of SD compared with HTLV-I-uninfected children (RR = 4.8, CI = 1.9–12.5; Table 2). The mean ages at diagnosis for infected (4.9 years) and uninfected children (6.7 years) were not significantly different ( $P = .09$ ). One of the 7 infected children with SD had a previous diagnosis of ID.<sup>21</sup> No child was diagnosed with SD at >2 clinic visits.

HTLV-I-infected children had a greater than two-fold higher rate of eczema compared with HTLV-I-uninfected children (RR = 2.6, CI = 1.1–6.1). The HTLV-I-associated risk of eczema increased after adjusting for duration of breastfeeding, sex, and income (adjusted RR = 3.1, CI = 1.2–7.9; Table 2). HTLV-I-infected and -uninfected children had mean ages of 2.9 years at diagnosis. Five of the 7 HTLV-I infected children with SD also had a diagnosis of eczema, as defined in this analysis, and the other 2

**TABLE 1.** Distribution of Demographic Factors Among HTLV-I-Infected and HTLV-I-Uninfected Jamaican Children

Factor	HTLV-I-Infected (N = 28)	HTLV-I-Uninfected (N = 280)	P Value
Sex			
Male	16 (57.1%)	135 (48.2%)	.36
Female	12	145	
Maternal income*			
Low (<JA\$100/wk)	10 (35.7%)	58 (21.0%)	.08
High ( $\geq$ JA\$100/wk)	18	218	
Hospital clinic			
Jubilee	22 (78.6%)	229 (81.8%)	.87
UWI	6	51	
Duration of breastfeeding (mo)			
Mean	21.6	10.3	< .0001
95% CI	(16.2–27.1)	(9.1–11.6)	
Duration of follow-up (y)			
Mean	6.7	5.5	.81
95% CI	(5.6–7.8)	(5.1–5.9)	

JA\$100 indicates 100 Jamaican dollars; UWI, University of the West Indies.

\* Information on income was missing for 4 HTLV-I seronegative mothers.

**TABLE 2.** Distribution of Health Outcomes and Their Incidence Rates Among HTLV-I-Infected and Uninfected Jamaican Children, and Associated Rate Ratios

Health Outcome	HTLV-I-Infected			HTLV-I Uninfected			RR 95% CI	Adjusted RR* 95% CI
	No. With Outcome	PY F/U	Incidence	No. With Outcome	PY F/Y	Incidence		
Skin assessment‡								
SD	7	124	.056	11	965	.011	4.8 (1.9–12.5)	4.7 (1.7–13.2)
Eczema	8	99	.080	25	821	.030	2.6 (1.1–6.1)	3.1 (1.2–7.9)
Neurologic assessment‡								
Persistent hyperreflexia	9	112	.080	19	896	.021	3.7 (1.6–8.2)	3.6 (1.5–8.8)
Increased muscle tone	2	145	.014	6	965	.006	2.2 (0.4–10.8)	2.0 (0.3–12.5)
Gait abnormality	1	151	.006	15	941	.016	0.4 (0.1–3.5)	0.6 (0.1–5.2)
General physical examination								
Lymphadenopathy	18	136	.132	97	1077	.090	1.4 (0.8–2.3)	1.3 (0.8–2.2)
Heart murmur	11	109	.101	66	697	.095	1.1 (0.6–2.1)	1.1 (0.5–2.1)
Asthma‡	5	125	.040	51	766	.067	0.6 (0.3–1.6)	0.7 (0.3–1.8)
Small stature‡§								
Girls	1	66	.015	10	515	.019	0.7 (0.1–6.1)	2.1 (0.3–17.4)
Boys	2	68	.029	12	393	.030	0.9 (0.2–4.5)	1.1 (0.2–5.6)
Hematologic factors‡								
Severe anemia¶	4	136	.029	13	933	.014	2.5 (0.8–7.9)	2.4§§ (0.6–7.9)
Eosinophilia	8	108	.074	87	611	.142	0.6 (0.3–1.2)	0.8 (0.4–1.6)
Elevated WBC**	11	113	.097	60	798	.075	1.2 (0.6–2.3)	1.0 (0.5–2.1)
Elevated lymphocyte count‡‡	2	143	.014	13	925	.014	1.1 (0.2–4.9)	1.0 (0.2–5.2)
Abnormal lymphocytes (3.0%)	4	142	.028	11	937	.012	2.4 (0.8–7.6)	2.4 (0.7–8.5)
Bacterial infections								
Upper respiratory tract infection	7	31	.225	208	469	.443	0.6 (0.3–1.2)	0.6 (0.3–1.3)
Lower respiratory tract infection	6	151	.039	81	1121	.072	1.2 (0.5–2.7)	0.7 (0.3–1.6)
Ear infection	7	132	.053	61	1293	.047	1.2 (0.6–2.6)	1.2 (0.5–2.7)
Pneumonia	0	216	.000	7	1551	.004	0.0 (0.0–NC)	0.0 (0.0–NC)
Intercurrent illness								
Asthma	5	186	.027	57	1275	.045	0.6 (0.3–1.6)	0.6 (0.2–1.5)
Ear infection	2	204	.010	58	1250	.046	0.3 (0.1–1.2)	0.3 (0.1–1.2)
Pneumonia	0	216	.000	7	1519	.005	0.0 (0.0–NC)	0.0 (0.0–NC)

PY indicates person-years; F/U, follow-up; NC, not calculable.

\* Adjusted for sex and maternal income and duration of breastfeeding.

‡ The total number of children assessed for asthma, lymphadenopathy, small stature, dermatologic, neurologic, and hematologic factors includes 26 HTLV-I infected and 189 uninfected children.

§ Girls: height <83 cm (age: 30 months); <87 (age: 36 months); <91 (age: 42 months); <94 (age: 48 months); <97 (age: 54 months); <100 (age: 60 months); <103 (age: 66 months); <106 (age: 72 months); <110 (age: 78 months); <113 (age: 84 months); <116 (age: 90 months); <118 (age: 96 months); <121 (age: 102 months); <123 (age: 108 months); <125 (age: 114 months); <127 (age: 120 months). Boys: height <85 cm (age: 30 months); <89 (age: 36 months); <92 (age: 42 months); <95 (age: 48 months); <98 (age: 54 months); <101 (age: 60 months); <104 (age: 66 months); <107 (age: 72 months); <110 (age: 78 months); <113 (age: 84 months); <116 (age: 90 months); <119 (age: 96 months); <121 (age: 102 months); <124 (age: 108 months); <126 (age: 114 months); <128 (age: 120 months).

¶ Hemoglobin <9.0 g/dL (ages: 30–36 months); <9.6 g/dL (ages: 37–66 months) and <10.0 g/dL (ages: 67–120 months).

|| Eosinophils >800/μL of blood. \*\*WBC >15.5 × 10<sup>3</sup>/μL (ages: 30–66 months) and >8 × 10<sup>3</sup>/μL (ages: 67–114 months) and >13.5 × 10<sup>3</sup>/μL (ages: 115–120 months).

‡‡ Lymphocyte count >8500 per μL of blood (ages: 30–120 months).

§§ Further adjusted for serum retinol: low (<1.05 μmol/L), normal (≥1.05 μmol/L).

infected children with SD were observed to have eczema at a minimum of 1 clinic visit.

### Neurologic Assessment

HTLV-I-infected children had more than a three-fold higher rate of persistent hyperreflexia of the lower limbs (RR = 3.7, CI = 1.6–8.2; Table 2). Mean ages at diagnosis were similar for infected and uninfected children (4.4 years, 4.6 years, respectively [*P* = .82]). Six of the 9 children with this diagnosis were observed to exhibit hyperreflexia at only the minimum 2 clinic visits, which were required for diagnosis of persistent hyperreflexia, and only 2 of these 6 children had hyperreflexia on consecutive clinic visits. The other 3 children had 3 or 4 clinic visits at which hyperreflexia was observed, all with at least 1

intervening clinic visit at which lower limb reflexes were deemed to be normal.

Of the 28 children with a diagnosis of persistent hyperreflexia, 17 (60%) were available for referral to a pediatric neurologist for further examination after the end of the study period (ages 12–13 years). All 3 of the HTLV-I-infected children and 11 of 14 (78%) uninfected children were diagnosed with hyperreflexia of the lower limbs (*P* = .52). None of these children were diagnosed with clonus, spasticity of the lower limbs, or difficulty walking.

The rate of increased muscle tone was higher among HTLV-I-infected children compared with uninfected children, but only 2 infected children had this outcome (RR = 2.2, CI = 0.4–10.8). Muscle power was normal for all HTLV-I-infected children.

## General Physical Examination

HTLV-I infection was associated with a nonsignificantly elevated risk of lymphadenopathy (RR = 1.4, CI = 0.8–2.3; Table 2). Height for age was used as an indicator of small stature. In univariate analyses HTLV-I was not associated with small stature among boys (RR = 0.9, CI = 0.2–4.5) or girls (RR = 0.8, CI = 0.1–6.1; Table 2). As a marker of nutritional status, serum retinol was examined in association with small stature. Boys with small stature had a lower mean serum retinol level (0.78  $\mu\text{mol/L}$ ) compared with boys without small stature (0.92  $\mu\text{mol/L}$ ;  $P = .05$ ). Among girls, there was no appreciable difference in mean serum retinol by stature (data not shown).

## Hematologic Factors

HTLV-I-infected and -uninfected children had similar mean hemoglobin levels (11.2 g/dL, CI = 10.8–11.6 vs 11.3 g/dL, CI = 11.1–11.5, respectively [ $P = .97$ ]), although the infected children appeared to have a nonsignificantly higher rate of severe anemia (RR = 2.5, CI = 0.8–7.9; Table 2). Examination of available laboratory records for 15 of the 17 HTLV-I-infected and -uninfected children with severely low hemoglobin indicated that 10 of these children had hypochromic microcytic anemia, consistent with iron deficiency. Vitamin A, measured as serum retinol was examined as a marker of nutritional deficiency to assess its association with anemia. Risk of anemia was inversely associated with serum retinol in a trend that was of borderline significance ( $P_{\text{trend}} = 0.08$ ), after adjusting for other factors (Table 2). Risk of severe anemia was also independently associated with low income status (RR = 4.5, CI = 1.0–20.6). The mean ages of diagnosis of severe anemia were similar for infected and uninfected children (2.5 years, 2.6 years, respectively, [ $P = .62$ ]). A greater proportion of HTLV-I-infected children had multiple clinic visits at which severe anemia was diagnosed compared with uninfected children (75.0% vs 39.0%, respectively), although this difference was not statistically significant ( $P = .24$ ). HTLV-I infection was not associated with mild anemia (data not shown).

Frequencies of lymphocytes having abnormal morphology were examined for association with HTLV-I status. In all analyses, abnormal lymphocyte counts were adjusted for WBC count. HTLV-I-infected and -uninfected children had similar rates of abnormal lymphocytes detected at a frequency of 1.0% to 2.0% of all lymphocytes (data not shown). HTLV-I-infected children had a nonsignificantly higher rate of abnormal lymphocytes detected at a higher frequency ( $\geq 3.0\%$ ) compared with HTLV-I-uninfected children (RR = 2.4, CI = 0.8–7.6; Table 2). The mean age at detection of 3.0% abnormal lymphocytes was similar for infected and uninfected children (6.7 years, 5.5 years, respectively,  $P = .41$ ). The most extreme frequency of abnormal lymphocytes detected was 5.0%.

In summary, HTLV-I-infected children had significantly higher incidence rates of eczema, SD, and persistent hyperreflexia compared with uninfected

children. Additionally, infected children had higher incidence rates of severe anemia and abnormal lymphocytes, compared with uninfected children, which were of borderline statistical significance. There was considerable overlap of these health outcomes among HTLV-I-infected children (Fig 1). Among infected children, 5 of the 7 children with SD also had eczema and 6 of the 9 children with persistent hyperreflexia had SD or eczema. Additionally, 3 of the 4 children with diagnoses of severe anemia also had diagnoses of SD, and 2 of these children developed persistent hyperreflexia. Conversely, none of the uninfected children with a 3.0% frequency of abnormal lymphocytes had SD, eczema, persistent hyperreflexia, or severe anemia.

## DISCUSSION

HTLV-I infection in early childhood is believed to be an important factor for development of ATL, an almost uniformly fatal disease. Support for this statement includes the high (>95%) prevalence of HTLV-I among mothers of patients with ATL, suggesting a role for maternal-child HTLV-I transmission in risk for ATL.<sup>22,23</sup> Additionally, the incidence of ATL in the Caribbean is highest among those <40 years of age at diagnosis, suggesting that ATL develops after early childhood infection followed by a latency of 10 to 30 years.<sup>24,25</sup>

ID is the only pediatric disease associated with early childhood HTLV-I infection. It is a severe, exudative eczema usually diagnosed between ages 2 and 3 years and requiring continuous treatment with corticosteroids and antibiotics until abatement of symptoms in puberty.<sup>17</sup> Linking ID with adult disease are case reports of 5 adults with ATL or HAM/TSP who had documented childhood histories of ID, suggesting that ID was a marker of risk for ATL or HAM/TSP.<sup>26–28</sup> Supporting this contention are reports of early childhood skin diseases consistent with ID among a majority of 9 HTLV-I-infected children diagnosed with ATL in childhood, and 4 of 5 infected children diagnosed with HAM/TSP.<sup>29,30</sup> Our study suggests that other skin diseases are associated with HTLV-I infection in childhood, including eczema and SD. These data are consistent with a report of an

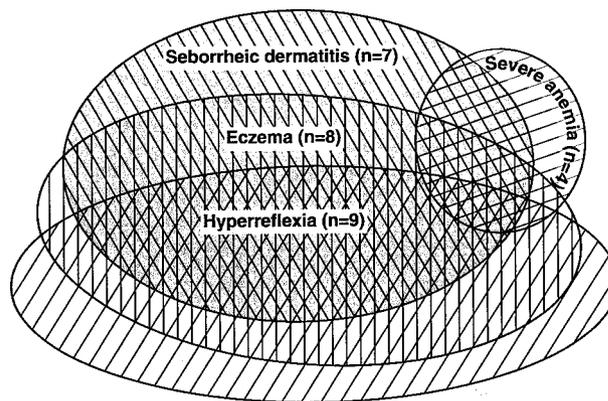


Fig 1. Venn diagram of overlapping health outcomes in HTLV-I-infected children. Spheres represent different HTLV-I-associated health outcomes. Numbers in parentheses indicate the number of children with the health outcome.

increased frequency of skin disease among Jamaican adults subsequent to HTLV-I infection via transfusion, and an association of a history of skin disease with prevalent HTLV-I infection among pregnant women in Brazil.<sup>31,32</sup> Further analysis is being conducted to establish whether these skin diseases among children are associated with a high HTLV-I proviral load, antibody titer, and tax-specific antibody, markers of risk for ATL and HAM/TSP.

HTLV-I-infected children had a significant 3.7-fold higher incidence rate of persistent hyperreflexia of the lower limbs compared with uninfected children. Hyperreflexia was detected subsequently at ages 12 to 13 years among 82.3% of the children available for referral to a single pediatric neurologist based on their diagnosis during our study period. These data suggest that although there was some degree of persistence of this condition over time, there was a lack of progression of this condition. Hyperreflexia of the lower limbs is a feature of HAM/TSP, in addition to spasticity, difficulty walking, weakness of the lower limbs, and bladder dysfunction.<sup>33</sup> Gait abnormality was not associated with HTLV-I infection among the children in this study, although both gait abnormality and hyperreflexia of the lower limbs were associated with HTLV-I seropositive status among adult US blood donors.<sup>14</sup> HAM/TSP, presenting as generalized hyperreflexia and either ankle clonus or hypertonic lower limbs, was diagnosed in a 14-year-old child and a 35-year-old adult who had been diagnosed with ID at ages 2 years and 10 years, respectively.<sup>28</sup> In our study, 4 of the 9 HTLV-I-infected children with persistent hyperreflexia also had SD. Continued follow-up of our cohort is planned to assess progression to spasticity in children with persistent hyperreflexia.

HTLV-I-infected children had a 2.4-fold higher rate of severe anemia compared with uninfected children, which was of borderline statistical significance. These data support an association in children that has been reported in adult HTLV-I carriers in Jamaica and Japan, and Japanese immigrants to Hawaii.<sup>9,10,12</sup> The severe anemia in a majority of these children was documented as hypochromic microcytic anemia, consistent with iron deficiency. A role for nutritional deficiency was supported by the association of anemia with low levels of vitamin A among children in our study. These data are consistent with a significant association of low hemoglobin (<12 g/dL) with low levels of vitamin A among the HTLV-I-infected mothers of children in our study (A. Manns, personal communication, May 5, 2003). It is possible that low vitamin A levels are a marker for nutritional deficiency, including iron deficiency, which may be the cause of HTLV-I-associated anemia among adults, and anemia in children with HTLV-I-associated ID.<sup>17</sup>

HTLV-I-infected children had a 2.4-fold higher rate of abnormal lymphocytes at a frequency of  $\geq 3.0\%$  compared with uninfected children, although this association was of borderline statistical significance. Abnormal lymphocytes at a higher frequency (6.0%) were detected in 30.0% of HTLV-I seropositive adults in Miyazaki, Japan, and were associated with

increased HTLV-I proviral load, increased lymphocyte count, increased activated (CD25+) T-cells, increased CD4:CD8 ratio, decreased serum albumin, and decreased eosinophils.<sup>7,11</sup> The association of abnormal lymphocytes with increased HTLV-I proviral load and activated T lymphocytes suggested that abnormal lymphocytes may be HTLV-I-infected lymphocytes. It is possible that HTLV-I-infected children with  $\geq 3.0\%$  abnormal lymphocytes have an increased proviral load and therefore are more likely to develop HTLV-I-associated disease. The 1 child in our cohort who was diagnosed with both ID and SD had a high proviral load 12 months postinfection, which increased over time, and a 2.2% frequency of abnormal lymphocytes 2 years subsequent to development of ID.<sup>21</sup> Further analysis of HTLV-I proviral load in association with this health outcome is planned.

HTLV-I-infected children in this study did not have appreciably elevated rates of lymphadenopathy, heart murmur, asthma, lymphocytosis, leukocytosis, or bacterial infections and were not protected from developing eosinophilia, although these or analogous conditions (cardiac anomaly) have been associated with HTLV-I infection among adults.<sup>7,9,10,12-14</sup> The presumed shorter duration of HTLV-I infection in children compared with adults, or the small number of infected children in this study may underlie our results.

The authors acknowledge that the results of this study should be interpreted with caution for the following reasons. The modest number of HTLV-I-infected children limited this study's power to detect modest risks. Additionally, the lack of photographs to document skin conditions, and the lack of consistency in detecting hyperreflexia may have resulted in misclassification of these conditions. Furthermore, although physicians were blinded to the HTLV-I status of the children, mothers were not blinded. This may have resulted in higher frequencies of infected children attending clinic for the complete study period. Finally, it is likely that the physicians were aware of the association of HTLV-I with ID among children. The fact that only 1 child in this study was diagnosed with ID suggests that the physician's awareness did not bias diagnosis of this disease. However, it is unknown what effect such awareness may have had on diagnosis of skin diseases in general.

## CONCLUSIONS

We examined the incidence of morbidity in a cohort of HTLV-I-infected and -uninfected children who were clinically observed from 6 weeks to a maximum of 10 years of age. HTLV-I-infected children had significantly higher rates of SD and eczema than uninfected children, possibly expanding the range of HTLV-I-associated skin diseases in children. HTLV-I-infected children also had a significantly higher incidence rate of persistent hyperreflexia, a clinical feature of HAM/TSP. Additionally, HTLV-I-associated morbidity in these children was similar to adults with respect to severe anemia and abnormal lymphocytes, although of borderline statistical sig-

nificance. Expansion and continued observation of this cohort would help to further examine the extended natural history of HTLV-I-associated disease in children.

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