Alterations in Cardiac and Pulmonary Function in Pediatric Rapid Human Immunodeficiency Virus Type 1 Disease Progressors

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ABSTRACT. *Objective.* **Infants with human immunodeficiency virus type 1 (HIV-1) can be divided into rapid progressors (RPs) and non-rapid progressors (non-RPs) based on symptoms and immunologic status, but detailed information about cardiac and pulmonary function in RP and non-RP children needs to be adequately described.**

Methodology. **Cardiac, pulmonary, and immunologic data and HIV-1 RNA burden were periodically measured in 3 groups: group I, 205 vertically infected children enrolled from 1990 to 1994 and followed through 1996; group II, a prospectively studied cohort enrolled at birth that included 93 infected (group IIa); and 463 noninfected infants (group IIb).**

Results. **Mean respiratory rates were generally higher in group IIa RP than non-RP children throughout the period of follow-up, achieving statistical signifance at 1 month, 12 months, 24 months, 30 months, and 48 months of follow-up. Non-RP and group IIb (HIV-uninfected children) had similar mean respiratory rates from birth to 5 years of age.**

Significant differences in mean respiratory rates were found between group I RP and non-RP at 7 age intervals over the first 6 years of life. Mean respiratory rates were higher in RP than in non-RP at <1 year, 2.0 years, 2.5 years, 3.0 years, 3.5 years, 4.0 years, and 6.0 years of age.

Mean heart rates in group IIa RP, non-RP, and group IIb differed at every age. Rapid progressors had higher mean heart rates than non-RP at all ages through 24 months. Mean heart rates at 30 months through 60 months of age were similar for RP and non-RP children. Non-RP children had higher mean heart rates than did group IIb at 8 months, 24 months, 36 months, 42 months, 48 months, 54 months, and 60 months of age.

In group I, RP had higher mean heart rates than non-RP at 2.0 years, 2.5 years, 3.0 years, and 4.0 years of age. After 4 years of age, the non-RP and RP had similar mean heart rates.

Mean fractional shortening differed between the 3 group II subsets (RP, non-RP, and IIb) at 4, 8, 12, 16, and 20 months of age. Although mean fractional shortening was lower in RP than in non-RP in group II at all time points between 1 and 20 months, the mean fractional shortening was significantly lower in RP only at 8 months when restricting the statistical comparisons to the 2 HIV-infected groups (RP and non-RP). Mean fractional shortening increased in the first 8 months of life followed by a gradual decline through 5 years of age among group IIb children. No significant differences among the 3 groups in mean fractional shortening were detected after 20 months of age.

In group I, differences between RP and non-RP in mean fractional shortening were detected at 1.5, 2.0, 2.5, and 3.0 years of age. After 3 years of age, group means for fractional shortening in RP and non-RP did not differ. Because of the limited data from the first months of the group I patients, it could not be determined whether this group experienced the gradual early rise in mean fractional shortening seen in the group II infants.

In group IIa, RP had more clinical (eg, oxygen saturation <96%) and chest radiographic abnormalities (eg, cardiomegaly) at 18 months of life. RP also had significantly higher 5-year cumulative mortality than non-RP, higher HIV-1 viral burdens than non-RP, and lower $CD8^+$ T-cell counts.

Conclusions. **Rapid disease progression in HIV-1-infected infants is associated with significant alterations in heart and lung function: increased respiratory rate, increased heart rate, and decreased fractional shortening. The same children exhibited the anticipated significantly increased 5-year cumulative mortality, increased serum HIV-1 RNA load, and decreased $CD8^+$ (cytotoxic) T-cell counts. Measurements of cardiopulmonary function in HIV-1-infected children seem to be useful in the total assessment of HIV-1 disease progression.** *Pediatrics* **2000; 105(1). URL: http://www.pediatrics.org/cgi/content/full/105/1/e9; *human immunodeficiency virus infections, human immunodeficiency virus type 1, child, infant, newborn, diseases, disease progression, cohort studies, lung, heart.***

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The members of the P^2C^2 HIV Study Group are listed in the "Appendix."

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ABBREVIATIONS. RP, rapid progressor; HIV-1, human immunodeficiency virus type 1; AIDS, acquired immodeficiency syndrome; LIP/PLH, lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia; P^2C^2 HIV Study, Pediatric Pulmonary and

Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus Study; CDC, Centers for Disease Control and Prevention; non-RP, non-rapid progressor; CI, confidence interval; WITS, Women and Infants Transmission Study.

Rapid progressors (RPs) in pediatric human immunodeficiency virus type 1 (HIV-1) infection have been defined as children up to 2 years of age who had an acquired immunodeficiency syndrome (AIDS) -defining condition (other than lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia [LIP/PLH]) or severe immunosuppression in the first year of life.[1] In general, children with vertical HIV infection have shorter clinical latent periods and more rapid disease progression than do other individuals with HIV infection.[2–6]

The Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus Study (P^2C^2 HIV Study) has shown that structural and functional abnormalities of the heart are among the earliest abnormalities to appear in pediatric HIV infection.[7] Pulmonary abnormalities were also found, including a high incidence of acute pneumonia during the first year of life.[8] Immunologic abnormalities included progressively abnormal low $CD4^+$ and high $CD8^+$ T-cell counts in HIV-1-infected children followed from birth, and extremely low $CD4^+$ T-cell counts associated with advanced disease.[9] High HIV-1 burden also has been associated with rapid disease progression and mortality risk in children.[10–12]

Because the cardiovascular and respiratory systems are at least secondarily affected by HIV-1 disease in children, it would be of considerable benefit to determine whether HIV-1 disease progression manifests itself in quantitative and progressive alterations of cardiovascular and respiratory function. It would be important, for example, for physicians to be able to suspect the RP status merely by making conventional examinations of heart or lung function. This study, therefore, uses prospective and retrospective data from the P^2C^2 HIV Study to examine changes in cardiac and pulmonary systems associated with categories of progressive HIV-1 disease in children.

METHODS

Study Population

The P^2C^2 HIV Study population has been described fully elsewhere, with explanations of recruitment, examinations, laboratory and clinical tests, quality assessment, and data analysis.[13] Briefly, 205 infants and children with diagnosed HIV-1 infection were enrolled between 1990 and 1993 and were followed on protocol for up to 6 years of age (group I). A second group of 600 study subjects enrolled at birth (beginning in 1990) and followed prospectively for up to 6 years comprised 93 HIV-1-infected (group IIa), 463 HIV-1-noninfected (group IIb), and 44 HIV-1-indeterminate infants. Infants and children in group I were examined at least every 6 months, and those in group II at least every 3 months. Over 90% of group I and group IIa study subjects took antiretroviral medications (principally zidovudine and ideoxyinosine) at some time during the study period; 21 children in group I and 7 children in group IIa took protease inhibitors (Ritonavir, Nelfinavir, Saquinavir, or Indinavir), but all children were over 2 years of age when started; 43% of group I and 28% of group IIa study subjects received intravenous immunoglobulin at some time during the study period.

The 44 infants of indeterminate HIV-1 infection status born to 41 mothers were excluded from all analyses: 35 were lost to follow-up and 9 died before the required virologic testing (eg, only 1 positive HIV-1 culture result with ≥1 negative HIV-1 culture results or awaiting a confirmatory antibody test at ≥15 months of age). Longitudinal data were very limited on these cases. Demographic characteristics for these 44 infants were similar to the cohorts described in the study. Most were black (n = 23, 52.3%) and 47.7% were female (n = 21).

Definitions of HIV-1 Disease Progression in Study Subjects

The definitions of HIV-1 disease progression children were based on several studies.[1–6] For purposes of this study, the definitions are: 1) RP—had an AIDS-defining condition (other than LIP/PLH), or severe immunosuppression (Centers for Disease Control and Prevention [CDC] immunologic category 3), or both, in the first year of life;[14] and 2) non-rapid progressors (non-RP)—did not meet criteria for rapid progressors.

Disease progression categories for infants dying or lost to follow-up before 1 year of age were assigned based on available symptom and immunology data.

Examinations of Subjects

Examinations of subjects included periodic physical examinations and measurements of blood (complete blood count), lymphocyte phenotypes ($CD4^+$ and $CD8^+$ T-cell counts), and cardiac function (through echocardiograms); all laboratory tests and interpretation of physical measurements were quality controlled as described in the reference paper.[13] Lymphocyte phenotypes were determined in laboratories certified by the AIDS Clinical Trials Group in quality-assured fashion and z scores for normal age-adjusted $CD4^+$ and $CD8^+$ T-cell counts were taken from Mofenson et al.[15] Respiratory rate was measured while the child was quietly breathing and awake; observations were conducted for 1 full minute by a trained observer. Tachypnea was defined as a respiratory rate at or above the 95th percentile based on age.[16] Oxygen saturation was determined by pulse oximetry (Nellcor Inc, Hayward, CA). Recordings were made for a 10-minute period. A saturation of <96% was considered abnormal.

Chest radiographs of group II subjects were obtained at 3, 12, and 18 months of age and read by a radiologist at each center using standardized reporting forms to record parenchymal consolidation, adenopathy, cardiomegaly, nodular densities, reticular densities, and bronchovascular markings. Quality assurance was centrally coordinated as previously reported.[17] Reticular densities and increased bronchovascular markings categories were combined for the analyses because the quality assurance studies revealed that inter-reader agreement was greatly improved when the categories were combined.[17] In the absence of lung biopsy-proven diagnosis, presumptive LIP/PLH was defined as the appearance of nodules on chest radiograph that persisted for longer than 2 months.

Serum was obtained on 76 group II patients and on 166 group I children. After being frozen at −70°C at a central repository and thawed once, serum was analyzed for HIV-1 RNA concentration by quantitative HIV-1 RNA polymerase chain reaction using the Amplicor HIV-1 Monitor Test (Roche Diagnostic Systems, Branchburg, NJ) at the laboratory of Dr Thomas Quinn; 1 technician performed all the assays; the lower limit of detection of the assay was 400 copies/mL, as previously described.[10]

Statistical Analysis

To assess whether there were changes with age, a longitudinal repeated measures analysis was performed for serum HIV-1 RNA (log base 10), respiratory rate, heart rate, fractional shortening, and lymphocyte phenotypes (cube-root transformation). Specifically, a linear model using restricted maximum likelihood estimation and either an unstructured variance–covariance form or heterogeneous compound symmetry form among repeated measurements was fit for each outcome. Covariate adjustment was made for HIV-1 status, disease progression category, age category, and HIV-1 status by age. The results were summarized with adjusted means and 95% confidence intervals by HIV-1 status and age category. All statistical tests were two-sided and a P value ≤.05 was considered statistically significant. For the group II cohort, a

Bonferroni adjustment for multiple comparisons was utilized at each age (resulting in a statistical significance level of $P \leq .02$). A logistic regression model using generalized estimating equations that adjusted for the correlation between repeating tests from each child was used to compare clinical and chest radiographic findings by disease progression. The cumulative mortality rate for each cohort by disease progression was estimated by the Kaplan-Meier method. Cumulative mortality rates among groups were compared with two-sided log-rank tests. Confidence intervals (95%) were calculated for the 5-year mortality rates.

RESULTS

Classification of HIV-1 Disease Progression in Study Subjects

In the cohort of 93 group IIa infants, 45 (48.4%) could be classified as RP and 48 as non-RP. Most of the children were black ($n = 41$, 44.1%) or Hispanic ($n = 32$, 34.4%), and 52.7% ($n = 49$) were female. The reasons for classifying these infants as RP were their low $CD4^+$ cell counts (33.3%), their development of CDC class C symptoms (24.4%), or both reasons (42.2%; Table 1).

In the 205 group I children enrolled at a median age of 23 months, 71 (34.6%) could be classified as RP and 134 (65.4%) as non-RP. Only 22 children (10.7%) were asymptomatic at enrollment. Most of the children were black ($n = 89$; 43.4%) or Hispanic ($n = 82$; 40.0%), and 54.1% ($n = 111$) were female. The median age of RP at enrollment was 8.4 months, and the mean $CD4^+$ cell count and z score were 515 cells/μL and -1.80, indicative of severe immunosuppression. The reasons for classifying these children as RP were low $CD4^+$ cell counts (7.0%), CDC class C symptoms in the first year of life (53.5%), or both reasons (39.4%; Table 1).

Respiratory Rate, Heart Rate, and Fractional Shortening

Figure 1 describes the respiratory rate, heart rate, and fractional shortening in group II (A–C) and group I (D–F) subjects.

Mean respiratory rates were generally higher in group IIa RP than non-RP children throughout the period of follow-up, achieving statistical signifance at 1 month ($P = .01$), 12 months ($P < .001$), 24 months ($P = .003$), 30 months ($P = .003$), and 48 months of age ($P = .003$). Non-RP and group IIb (HIV-uninfected children) had similar mean respiratory rates from birth to 5 years of age.

Significant differences in mean respiratory rates were found between group I RP and non-RP children at 7 age intervals over the first 6 years of life. Mean respiratory rates were higher in RP children than in non-RP at <1 year ($P = .05$), 2.0 years ($P = .02$), 2.5 years ($P = .003$), 3.0 years ($P = .03$), 3.5 years ($P = .002$), 4.0 years ($P = .05$), and 6.0 years ($P = .003$).

Mean heart rates in group IIa RP, non-RP, and group IIb differed at every age (Fig 1B). Rapid progressors had higher mean heart rates than non-RP at all ages through 24 months ($P < .001$ at 1, 4, and 20 months; $P = .02$ at 8 months; $P = .009$ at 12 months; $P = .001$ at 16 months; and $P = .01$ at 24 months). Mean heart rates at 30 months through 60 months were similar for RP and non-RP. Non-RP had higher mean heart rates than did group IIb at 8 months ($P = .01$), 24 months ($P = .02$), 36 months ($P = .008$), 42 months ($P = .001$), 48 months ($P = .002$), 54 months ($P = .002$), and 60 months ($P < .001$).

In group I, RP had higher mean heart rates than non-RP at 2.0 years ($P = .006$), 2.5 years ($P = .05$), 3.0 years ($P < .001$), and 4.0 years of age ($P = .01$). After 4 years of age, the non-RP and RP had similar mean heart rates.

As shown in Fig 1C, mean fractional shortening differed among the 3 group II subsets (RP, non-RP, and IIb) at 4, 8, 12, 16, and 20 months of age ($P = .02$, $<.001$, $<.001$, .05, and .04, respectively). Although mean fractional shortening was lower in RP than in non-RP in group II at all time points between 1 and 20 months, the mean fractional shortening was significantly lower in RP only at 8 months ($P = .005$) when restricting the statistical comparisons to the 2 HIV-infected groups (RP and non-RP). Mean fractional shortening increased in the first 8 months of life followed by a gradual decline through 5 years of age among group IIb children. No significant differences between the 3 groups in mean fractional shortening were detected after 20 months of age.

In group I, differences between RP and non-RP in mean fractional shortening were detected at 1.5, 2.0, 2.5, and 3.0 years of age (Fig 1F; $P = .004$, .04, $<.001$,

TABLE 1. Demographic and Clinical Characteristics of Children in Groups I and II

Characteristic	Group I (Established Infection)				Group II (Prospectively Enrolled From Birth)					
	HIV-Infected ($n = 205$)				HIV-Infected (IIa) ($n = 93$)				HIV-Uninfected (IIb) ($n = 463$)	
	RP ($n = 71$)		Non-RP ($n = 134$)		RP ($n = 45$)		Non-RP ($n = 48$)			
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Race										
Black	35	49.3	54	40.3	22	48.9	19	39.6	245	52.9
Hispanic	27	38.0	55	41.0	16	35.6	16	33.3	138	29.8
White	8	11.3	20	14.9	5	11.1	10	20.8	54	11.7
Other	1	1.4	5	3.7	2	4.4	3	6.3	26	.2
Sex										
Male	34	47.9	60	44.8	25	55.6	19	39.6	249	53.8
Female	37	52.1	74	55.2	20	44.4	29	60.4	214	46.2
Reasons classified as RP										
Class C symptoms only	38	53.5			11	24.4				
Low $CD4^+$ cell counts only	5	7.0			15	33.3				
Both	28	39.4			19	42.2				

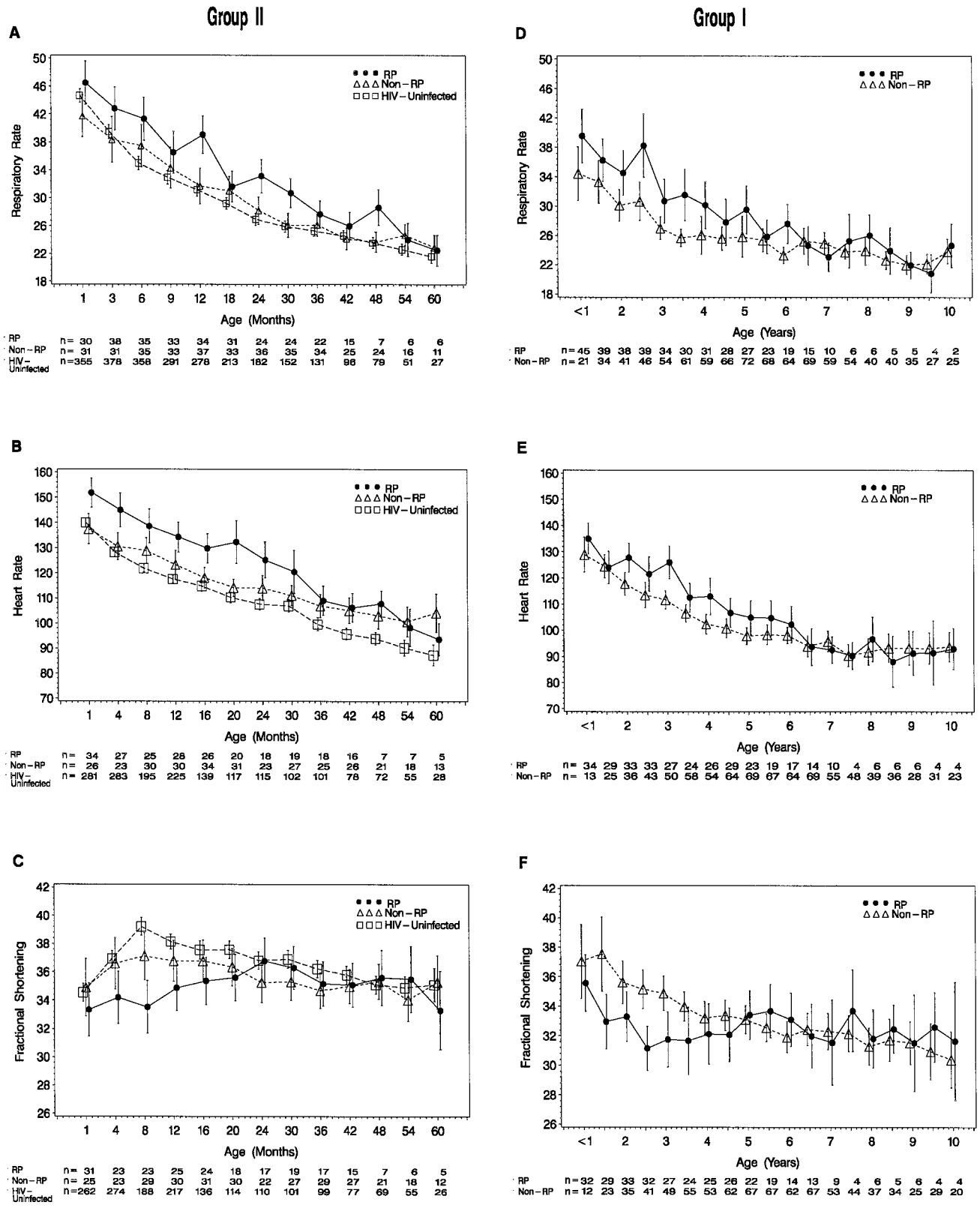

Fig 1. Longitudinal changes in mean respiratory rate, heart rate, and fractional shortening by age. The time trend lines are the model-based means and 95% confidence intervals. A and D, Respiratory rate (breaths/minute) for group II children (n = 45 RP; n = 47 non-RP; and n = 456 HIV-1-uninfected) and group I children (n = 71 RP and n = 126 non-RP). B and E, Heart rate (bpm) for group II children (n = 42 RP; n = 46 non-RP; and n = 435 HIV-1-uninfected) and group I children (n = 64 RP and n = 124 non-RP). C and F, Fractional shortening (%) for group II children (n = 41 RP; n = 45 non-RP; and n = 428 HIV-1-uninfected) and group I children (n = 64 RP and n = 121 non-RP).

and .005, respectively). After 3 years of age, group means for fractional shortening in RP and non-RP did not differ. Because of the limited data from the first months of the group I patients, it could not be determined whether this group experienced the gradual early rise in mean fractional shortening seen in the group II infants.

Data trends remained similar to those in Fig 1 after we excluded any measurement made within 2 weeks of a clinical examination in which the child had either an acute upper respiratory tract infection (rhinitis, pharyngitis, or otitis) or lower respiratory tract infection (croup, airway hyperreactivity/bronchiolitis, or pneumonia). The analyses were also adjusted for hemoglobin levels, but most of the differences in respiratory rate, heart rate, and fractional shortening remained significant. Statistical analyses comparing the group II RP infants that died to those that survived did not suggest that early death contributed heavily to the observed differences found in the first year of life between RR and non-RP infants. Mean fractional shortening at 8 months of age was 33.5% for RP infants and 37.1% for non-RP infants. For RP infants that died, mean fractional shortening at 8 months was 33.9% and 33.4% for RP infants that did not die. The mean heart rate at 8 months was 139 bpm and 136 bpm, respectively, for RP infants that died and RP infants that survived. Mean heart rate for non-RP infants was 129 bpm at 8 months of age. Respiratory rates were also similar between RP children that died and RP survivors at 9 months, but at 1 year the mean respiratory rate was 46 breaths/minute for those that died and 38 breaths/minute for those that did not die. The mean respiratory rate for non-RP at 1 year was 32 breaths/minute. Generally, mean heart rates and respiratory rates were higher for RP children that died, compared with RP survivors, but these differences were not statistically significant but the sample sizes were small. No significant differences were observed in mean heart rate, mean respiratory rate, or mean fractional shortening between RP with and without encephalopathy in the first year of life.

Cardiopulmonary Findings in Group II Children

The cardiopulmonary findings of group II children at 12 and 18 months of age are presented in Table 2. Tachypnea and oxygen saturation are analyzed first for all the children and then excluding those with acute upper and lower respiratory infections within 2 weeks of illness. In many categories, there are significant differences between group IIa RP and non-RP children (at 12 or 18 months of age or both). Oxygen saturation below 96% and cardiomegaly on chest radiographs were more common among RP than among non-RP infants ($P = .04$ and .007, respectively). Although nodular densities on radiographs were more common in RP than in non-RP children ($P = .003$), no difference was noted between RP and non-RP children for reticular densities/increased bronchovascular markings.

No cases of LIP were identified in the first year of life in the group II cohort. Of the 4 RP infants with nodular densities on chest radiograph at 12 months of age, none had a LIP diagnosis. A presumptive diagnosis of LIP required radiographic changes consistent with the LIP diagnosis for longer than 2 months. A definitive diagnosis of LIP required tissue confirmation. At 18 months, 7 RP children had nodular densities on chest radiograph but only 3 RP children had presumptive LIP ($n = 2$; ages = 12.1 and 15.3 months) or tissue confirmed LIP ($n = 1$; age = 15.3 months).

Mortality, Serum HIV-1 RNA Load, and CD8$^+$ T-Cell Counts in Group II Children

The 5-year follow-up analysis of mortality revealed significant differences in RP and non-RP subjects in group II (Fig 2A). Of the 45 group IIa infants designated as RP, 24 had died by 5 years of age, and none were lost to follow-up. The cumulative mortality of the RP at 5 years was 57.7% (95% confidence

TABLE 2. Clinical and Chest Radiograph Findings in Group II by Disease Progression Category at 12 and 18 Months of Age

Finding	12 Months						18 Months						*P* Value* (RP vs Non-RP)
	RP		Non-RP		HIV		RP		Non-RP		HIV		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Tachypnea	5/34	14.7	1/35	2.9	3/278	1.1	2/28	7.1	3/33	9.1	7/220	3.2	.26
Tachypnea†	3/24	12.5	0/19	.0	2/182	1.1	2/18	11.1	1/25	4.0	3/149	2.0	.10
Oxygen saturation <96%	3/33	9.1	0/34	.0	8/281	2.9	6/29	20.7	2/31	6.5	5/222	2.3	.02
Oxygen saturation <96%†	1/23	4.4	0/19	.0	2/187	1.1	4/20	20.0	0/23	.0	3/153	2.0	.04
Parenchymal consolidation‡	1/34	2.9	1/34	2.9	9/276	3.3	5/28	17.9	3/33	9.1	3/185	1.6	.28
Adenopathy (hilar)‡	2/34	5.9	0/34	.0	1/276	.4	3/28	10.7	1/33	3.0	0/185	.0	.09
Nodular densities‡	4/34	11.8	0/34	.0	0/276	.0	7/28	25.0	0/33	.0	0/185	.0	.003
Reticular densities‡/ bronchovascular markings§	6/34	17.7	5/34	14.7	7/276	2.5	6/28	21.4	2/33	6.1	6/185	3.2	.18
Nodular/reticular/or bronchovascular markings	8/34	23.5	5/34	14.7	7/276	2.5	9/28	32.1	2/33	6.1	6/185	3.2	.02
Cardiomegaly (radiograph)‖	5/34	14.7	0/34	.0	1/276	.4	7/28	25.0	2/33	6.1	5/185	2.7	.007

* The *P* value for RP versus non-RP compares the 2 groups across the ages using a logistic regression analysis for correlated data, except when the non-RP group did not have an event [nodular densities] ($P = .11$ and .003 at 12 and 18 months by Fisher's exact test and oxygen saturation <96% ($P = .99$ and $P = .04$).
† Excludes children with acute upper or lower respiratory infections within 2 weeks of the clinical examination (awake/quiet only).
‡ Parenchymal consolidation, adenopathy, nodular densities, and reticular densities are considered present if coded as "present definite."
§ Bronchovascular markings noted as "increased."
‖ Cardiomegaly noted as "heart enlarged."

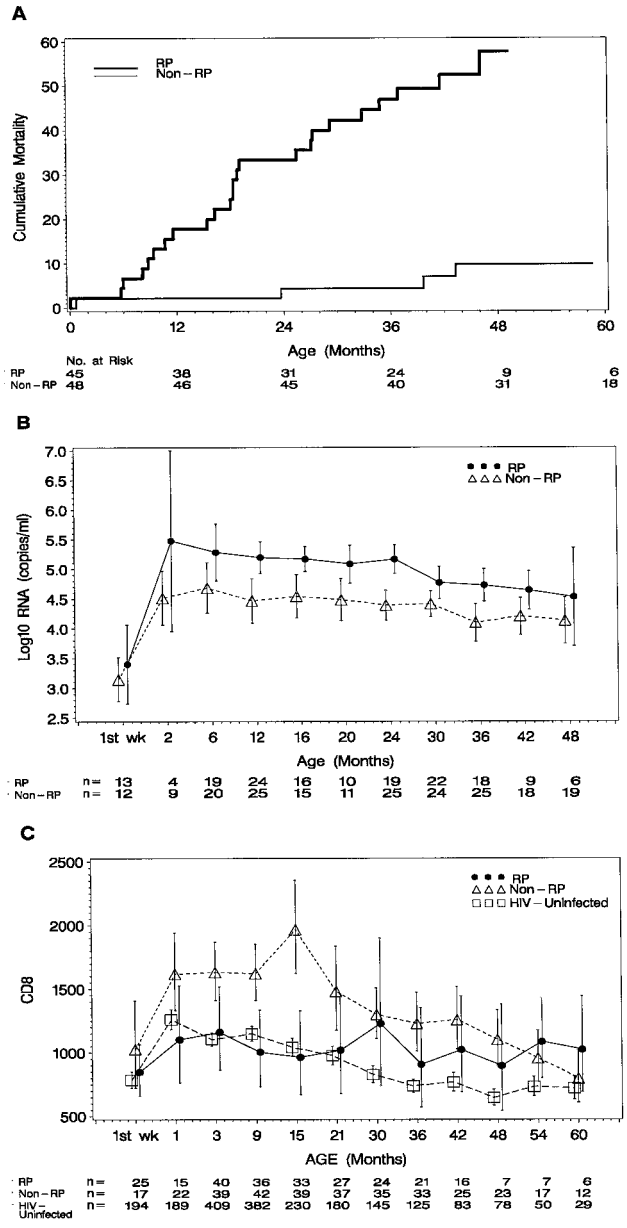

Fig 2. Cumulative mortality and longitudinal changes in HIV-1 viral burden and CD8$^+$ T-cell counts. A, Cumulative mortality by age among 93 group II HIV-1-infected children (n = 45 RP and n = 48 non-RP). B, Longitudinal changes in mean $\log_{10}$ HIV-1 RNA burden by age for 76 group II children (n = 34 RP and n = 42 non-RP). C, CD8$^+$ T-cell counts for n = 45 RP, n = 47 non-RP, and 461 HIV-1-uninfected children.

interval [CI]: 41.2–74.3). Of the group that died, 83% had died by 3 years of age. The cumulative mortality at 5 years of age was 9.8% (95% CI: .6–19.0; n = 5 deaths) for non-RP ($P < .001$; RP vs non-RP). In group I the 5-year (after enrollment) cumulative mortality rate for RP was 48.3% (95% CI: 36.1–60.6; n = 32 deaths); and for non-RP it was 28.7% (95% CI: 20.5–36.9; n = 35 deaths; $P = .004$ RP vs non-RP; data not shown).

Among the 76 group IIa children with at least 1 RNA measurement, 34 were RP and 42 non-RP. At 12 months of age, the geometric mean RNA was 157 000 RNA copies/mL for RP and 29 000 RNA copies/mL for non-RP ($P = .002$). At 2 years of age, mean RNA levels were also higher in the RP ($P < .001$; geometric mean: 147 000 for RP and 25 000 for non-RP). Over the first 4 years of life, mean RNA was significantly higher in RP children than in non-RP ($P = .001$; Fig 2B). Group I RP had higher mean HIV-1 RNA levels than non-RP among the younger (≤1.5 and 1.5–2.0 years of age) children ($P = .06$ and $P < .001$); however, mean RNA levels in RP and non-RP were similar at most ages above 2 years (data not shown).

Mean CD8$^+$ T-cell counts in RP were lower at 9 and 15 months ($P = .003$ and $P < .001$) than in non-RP (Fig 2C). Rapid progressors and non-RP had similar mean profiles for total lymphocyte count and CD8$^+$ T-cells after 21 months of age.

DISCUSSION

Perhaps the most useful assessment of the HIV-1 disease progression categories is in group IIa patients, and in the comparison between group IIa and IIb, all whom were followed prospectively from birth. Here, the label RP conveys quantitative differences (RP vs non-RP vs IIb) measured in cardiac (heart rate and fractional shortening) and pulmonary (respiratory rate) function. Rapid progressors, both in the prospective group and group I, had faster heart rates, lower fractional shortening, and higher respiratory rates (Fig 1A–F). For example, in group II the mean RP respiratory rate at 1 year of age was 39 breaths per minute and the non-RP mean was 32. The IIa RP mean heart rate at 1 year of age was 130 bpm, more than 10 bpm faster than the rate in both non-RP (mean: 118) and noninfected children (mean: 115). The RP mean heart rate remained significantly higher than both other groups through 24 months. Fractional shortening in group IIa RP infants at 8 months of age was 33.5%, significantly lower than the 37.1% figure for non-RP infants. The difference in fractional shortening disappeared by 20 months of age. To a certain extent, these differences in various body systems in the RP infants are expected, in that the patients are much sicker than those infants in the non-RP or IIb groups. However, the differences detected in the first 2 years of the study, eg, fractional shortening, possibly imply selective early age effects in the RP category. Because none of the HIV-1-infected patients were taking current highly active antiretroviral therapy from birth, it is possible that the clinical appearance and expression of the RP category in the current treatment era will be different from what was observed in this study.

Additional cardiac studies of group I patients reveal a relationship between cardiac and immune dysfunction[18] and show that depressed left ventricular fractional shortening is a risk factor for mortality.[19] Similar studies of group IIa children are in progress.[20] Of 34 children who died between 1 and 5 years of age, 3 died of cardiac disease, 18 had chronic heart disease, and 59% (20/34) had chronic pulmonary disease.[21] In the same study, of 16 children who died older than 5 years of age, 4 died from cardiac disease, 9 had chronic heart disease, and 50% (8/16) had chronic lung disease. Table 2 indicates the amount of pulmonary disease in the group II children, showing the important pulmonary abnormali-

ties among HIV-infected infants, as previously reported.[8] The hypoxia observed in RP children most likely is a result of shunting of blood attributable to chronic inflammation or ventilation:perfusion mismatch.

Our definitions of RP are further supported by the marked differences in mortality between RP and non-RP children. Group IIa RP children had a 58% probability of dying by 5 years of follow-up compared with group IIa non-RP children (10%). Similarly, the HIV-1 RNA load in group IIa RP children was significantly higher than in group IIa non-RP children. The immunologic findings can be understood in the context of current concepts of pathogenesis of HIV-1 infection. Compared with group IIa non-RP patients, the group IIa RP have depressed $CD8^+$ T-cell counts. This finding is consistent with a loss of the cytotoxic $CD8^+$ T-cells, which contributes to rapid HIV-1 disease progression.[22] Taken together, the increased 5-year mortality data, increased HIV-1 RNA load, and lower $CD8^+$ T-cell counts in group IIa RP reinforce the special nature of the RP category suggested by measurements of cardiopulmonary function.

Although the designation of RP status in the patients in this study described a unique set of patients, assessed by multiple and different measurements, we noticed that the proportion of RP (48.4%) in our patient groups was higher than in groups described in other studies, eg, 26% in the Women and Infants Transmission Study (WITS).[10] When the WITS definition of RP (class C symptoms or death by 18 months of age) was applied to our group IIa cohort, it reduced the number of infants classified as RP to 43%. We also applied other definitions of RP and obtained the following results: class C symptoms by 12 months of age, 32.3%; and class C symptoms or death by 12 months, 36.6%. To further compare the results of using different definitions of RP, we plotted the plasma HIV RNA concentrations of RP versus non-RP using all 3 definitions. We found that by any definition of RP, the RP group had statistically significantly elevated RNA levels, very similar to the data in Fig 2B (data not shown). Therefore, we believe that the RP group identified in the present study is somewhat larger than, but otherwise equivalent to, those in other published studies. Three of the clinical sites had some subjects who were also WITS subjects, but they accounted for only 31% of the cohort.

The differences between the RP cohorts as to the reasons for classifying these infants as RP might be attributable to several factors. Selection bias was minimal in the group II, because the HIV-1 infection status was unknown before enrollment. Because the group II cohort was followed from birth, more frequent measurement of CD4 cell counts in the first year of life might account for the higher percentage classified as RP based on low CD4 cell counts only in group II RP. Because we did not recruit the group I cohort from birth (average: 23 months of age), many children with low $CD4^+$ cell count alone would have been missed.

CONCLUSION

In summary, in this 5-year study of 205 children with established HIV-1 infection and 93 HIV-1-infected children followed from birth, there were category-specific, quantitative differences, such as heart rate, respiratory rate, and fractional shortening in children identified as RP by CDC class C disease or immunologic category 3. These same children experienced a much higher death rate, had higher HIV-1 RNA burden, and had lower $CD8^+$ T-cell counts than non-RP children. Our findings suggest that subclinical cardiac and pulmonary functional abnormalities are present in RP patients and may be contributing factors to their poor outcome.

APPENDIX

A complete list of study participants can be found in reference 12.

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