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INCREASED INCIDENCE OF ASTHMA IN HIV-INFECTED CHILDREN TREATED WITH HAART IN THE NIH WOMEN AND INFANTS TRANSMISSION STUDY

Samuel B. Foster, M.D.^a, Kenneth McIntosh, M.D.^b, Bruce Thompson, Ph.D.^c, Ming Lu, M.S.^c, Wanrong Yin, M.S.^c, Kenneth C. Rich, M.D.^d, Hermann Mendez, M.D.^e, Leslie K. Serchuck, M.D.^f, Clemente Diaz, M.D.^g, Mary E. Paul, M.D.^a, and William T. Shearer, M.D., Ph.D.^a

^aBaylor College of Medicine and Texas Children's Hospital, Department of Pediatrics, Allergy and Immunology Section, Houston, TX

^bChildren's Hospital, Division of Infectious Diseases, Harvard Medical School, Boston, MA

^cClinical Trials & Survey Corp., Baltimore, MD

^dUniversity of Illinois at Chicago, Department of Pediatrics, Chicago, IL

^eState University of New York, Department of Pediatrics, Brooklyn, NY

^fNational Institute of Child Health & Human Development, Pediatric, Adolescent & Maternal AIDS Branch, Bethesda, MD

^gPuerto Rico School of Medicine, Department of Pediatrics, San Juan, PR

Abstract

BACKGROUND—Immunoreconstitution of HIV-infected (HIV+) patients after treatment with highly antiretroviral therapy (HAART) appears to provoke inflammatory diseases.

OBJECTIVE—Determine whether HIV+ children on HAART (HIV+ HAART+) have a higher incidence of asthma than HIV+ children not on HAART (HIV+ HAART−).

METHODS—To investigate this possibility, 2,664 children (193 HIV+, 2,471 HIV−) born to HIV+ women were evaluated for the incidence and prevalence of asthma (i.e., asthma medication use), and change of CD4⁺ T cell percentage with time.

RESULTS—The HIV+ HAART+ children had higher CD4⁺ T cell percentages, lower CD8⁺ T cell percentages, and lower viral burdens than the HIV+ HAART− children ($P \leq 0.05$ to $P \leq 0.01$). The cumulative incidence of asthma medication use in HIV+ HAART+ children at 13.5 year rose to 33.5% vs. 11.5% in HIV+ HAART− children (hazard ratio=3.34, $P=0.01$) and was equal to that in the HIV− children. In children born prior to the HAART era, the prevalence of asthma medication use for HIV+ HAART+ children at 11 years of age was 10.4% vs. 3.8% for HIV+ HAART− children (odds ratio=3.38, $P=0.02$) and was equal to that of the HIV− children. The rate

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Corresponding Author: William T. Shearer, M.D., Ph.D. Texas Children's Hospital, 6621 Fannin Street (MC: FC330.01), Houston, TX 77030, Telephone: 011 (832) 824-1274/Fax: 011 (832) 825-7131, wtsheare@TexasChildrensHospital.org.

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of change of CD4⁺ T cells (percent/year) around the time of first asthma medication for HIV+ HAART+ vs. HIV+ HAART- children was 0.81 vs. -1.43 (P=0.01).

CONCLUSION—The increased incidence of asthma in HIV+ HAART+ children may be driven by immunoreconstitution of CD4⁺ T cells.

CLINICAL IMPLICATIONS—This HIV model of pediatric asthma may yield clues to help explain the epidemic of asthma in the general pediatric population.

Keywords

pediatric HIV infection; CD4⁺ T cell mediated induction of asthma; HAART-produced immunoreconstitution

INTRODUCTION

Asthma or asthma-like conditions can be seen in animal models with pulmonary infections and immunoreconstitution.¹ CD4⁺ T cells are essential for the development of animal models of asthma lose their asthma when depleted of CD4⁺ T cells.^{2,3} B cell-, IgE-, and mast cell-deficient mice may still develop asthma, but CD4⁺ T cell-, STAT6-, and IL-13-deficient mice cannot.⁴ There are studies that document an increase in bronchial hyperresponsiveness and asthma in HIV-infected adults⁵⁻⁸, but other studies do not confirm these findings.^{9,10} For example, Lin and Lazarus⁷ made the seminal observation that a recent CD4⁺ T cell count of ≥ 200 cells/ μ L was significantly associated with current asthma (P=0.01). The weight of this evidence suggests that adults with HIV infection have an increased prevalence of asthma, but most of these studies took place in the pre-HAART era when the immunoreconstitution inflammatory syndrome¹¹ was unknown, and most studies did not stratify patients by their CD4⁺ T cell count.

Galli et al¹² reported a reduced frequency of wheezing (not defined as asthma) in infants with HIV infection who were followed for 2 years of life, but Foster et al¹³ in a single-center retrospective study of 83 older children and young adults reported a several-fold increased asthma prevalence of 34 percent.¹³ In the latter study, there was substantial evidence that antiretroviral medications either restored the CD4⁺ T cell count in children inadequately treated, or preserved the CD4⁺ T cell count in children adequately treated from birth. Gutin and Secord¹⁴ reported in an abstract publication that 24 of 85 children with HIV infection were diagnosed with asthma. Of these 24 children, 65% developed asthma within 3 years of beginning HAART and 22 were immunoreconstituted or immunopreserved at the time of their asthma diagnosis.

To expand on these preliminary findings, investigators of the Women and Infants Transmission Study (WITS), a large multicenter HIV+ pediatric cohort, reviewed the cohort for the incidence and prevalence of asthma, and the results of that investigation are reported herein.

METHODS

Women and Infants Transmission Study

WITS is a prospective natural history, non-interventional study of HIV-infected pregnant women and their offspring conducted by the National Institute of Child Health and Human Development, National Institute of Allergy and Infectious Diseases, National Institute on Drug Abuse, and National Institute of Mental Health from 1988 to 2006 at multiple sites in the United States (Boston and Worcester, MA; Chicago, IL; Houston, TX; New York, NY; and San Juan, PR) with a total enrollment of 193 HIV+ and 2,471 HIV- children. Pregnant

women and their infants began enrollment in 1989 and CD4⁺ T cell and HIV culture/HIV DNA PCR assay were performed at regular intervals: birth, 1, 2, 4, 6, 9, 12 months, and every six months thereafter for HIV+ children and every 12 months thereafter for HIV– children. Similarly, secondary diagnoses of the subjects and their medication use were an integral part of the extensive WITS protocol that were recorded by medical personnel at each WITS study visit.¹⁵ All WITS study data were collected in a systematic manner on case report forms in face-to-face study visits between patient and research nurse and physician-investigator. The institutional review board at each center approved the protocol, and written informed consent was obtained from all parents or legal guardians before study enrollment.

In June 1998, a procedure (randomization mailers using a Bernoulli selection sequence) was instituted to reduce the large cohort of the WITS HIV-uninfected infants by two-thirds. This random selection of HIV– children who would stop WITS follow-up prevented a selection bias from being introduced in the cohort of HIV patients remaining in the study. The medical care of children was not a function of the WITS follow-up protocol visits.

Use of Antiretroviral Medications

All visits for each HIV+ child available for study were categorized into three antiretroviral therapy (ART) eras, and the proportion of visits with HAART was computed for each ART era. In **ART Era I** (before 02/28/94), none of the 127 HIV+ children had received HAART. In **ART Era II** (03/01/94 to 07/31/96), 122 HIV+ children had not received HAART; 8 had 20–40% of visits with HAART. In **ART Era III** (after 07/31/96), 26 HIV+ children had not received HAART, 6 had less than 20% of visits with HAART, 17 had 20–40% of visits with HAART, 18 had 40–60% of visits with HAART, 29 had 60–80% of visits with HAART and 44 had more than 80% of visits with HAART. In WITS HAART is defined as therapy with three drugs in two of the three available classes of ART drugs: 1) nucleoside reverse transcriptase inhibitors (NRTIs), 2) non-nucleoside reverse transcriptase inhibitors (NNRTIs), and 3) protease inhibitors (PIs). Prior to the availability of PIs, 26 children had received one NRTI, 29 had received 2 NRTIs, and 1 had received 1 NRTI plus 1 NNRTI.

Laboratory Studies

Complete blood counts were performed at hospital laboratories that had been certified by the College of American Pathologists or other nationally recognized quality assurance (QA) programs. All sites participated in the laboratory QA program of the AIDS Clinical Trials Group for flow cytometry and the Virology Quality Assessment for HIV culture and HIV DNA PCR assay.¹⁶ For flow cytometry, samples were prepared for staining and analysis by means of whole-blood lysis, as previously published.¹⁷

The diagnosis of HIV infection required two positive assays, HIV culture or HIV DNA PCR. Two-to-three negative HIV assays after 1 month of age were required for the assignment of a child to the HIV– group.

Diagnosis of Asthma

In this prospective analysis of the WITS completed database, asthma was defined in terms of asthma medication use rather than by parental report of wheezing, reactive airways disease, or asthma. Medication use was preferred rather than reported symptoms since most infants with wheezing do not develop asthma¹⁸, and most pediatricians identify the response to asthma medications as necessary in establishing a diagnosis of asthma.¹⁹

All medications were recorded at each study visit from birth for all WITS patients. Short-acting and long-acting bronchodilators (e.g., albuterol), inhaled corticosteroids (e.g.,

fluticasone), and leukotriene antagonists (e.g., montelukast), were all considered asthma medications in this study.

Statistical Analysis

All statistical analyses were performed using SAS. Means, standard deviations and percentages were estimated using Proc Means and Proc Freq, respectively.

Longitudinal data analyses were carried out using general estimating equations (GEE)²⁰ and mixed model analysis of variance.^{21, 22} In some figures, data are presented using three-point moving averages to improve the signal to noise ratio of the curves. Both GEE and mixed models can account for the correlation introduced using this type of smoothing technique through the use of structured correlation matrices for the regression coefficients. Proc Genmod and Proc Mixed were used to carry out these analyses. Multivariate survival analysis models were carried out using the Cox proportional hazards model.²³ Proc Phreg was used to carry out these analyses.

The GEE, mixed model, and the survival analysis models utilized time-dependent HAART-use variables to indicate when a child was and was not taking HAART during a specified interval of time. When performing survival analysis, this analysis technique allows the estimation of beta coefficients that indicate how much a patient's risk of the event being studied is being changed in response to the patient's change in HAART use. For the GEE and mixed model analyses, the beta coefficient indicates how much the expectation of the response variable (e.g., CD4⁺ T cell percentages) changes in response to the patient's change in HAART use. For both of these models, it is possible to output from the SAS analysis a model curve corresponding to the instance in which the patient took HAART over the entire interval. The procedure for survival analyses is presented by Kalbfleisch and Prentice.²⁴ These types of curves are seen in our presentation of the comparison of the HIV+ HAART+, HIV+ HAART-, and HIV- groups in Figure 1. The "cumulative incidences" presented in this figure corresponds to the expected incidences that would be obtained if it were possible to segregate a group of HIV+ children into a group who took HAART for the entire interval and those who did not take HAART for the entire interval. Figure 2 presents a three point moving average of the marginal prevalence of asthma use without using model parameterizations. Figure 3 presents a marginal presentation of the median and interquartile range of CD4⁺ T cell percentages analyzed according to the child's HIV status and HAART therapy at the time of CD4⁺ T cell evaluation. Statistical assessments comparing the curves were done by comparing the change of CD4⁺ T cell percentage/time (slope) coefficients obtained from the Proc Mixed analysis.

In some instances, we have presented pairwise comparison results from analyses that originally had three different parameters. These pairwise comparisons were only generated if the p-value associated with the three-parameter comparison was significant. Once the three-parameter test P-value was declared significant, each pairwise test was carried out using a 0.05 significance level of Hayter.²⁴

All statistical tests were carried out using a 0.05 alpha level to declare statistical significance.

RESULTS

Patient Cohorts

Table 1 summarizes the clinical characteristics of the study subject cohorts by HIV status (HIV+ or HIV-) and whether a HIV+ child ever used HAART (Ever Used HAART, Never Used HAART). The distribution of mean follow-up time (also mean age) among the three

groups was statistically different ($P < 0.001$). The shorter mean follow-up time of the Never Used HAART group is due to the death of many patients in this group (33 out of 80) compared to the Ever Used HAART group (8 out of 113). The shorter follow-up times for the HIV- group is due to randomization of these children out of the WITS protocol (see Methods) ($n = 1,418$), a parent's refusal to allow a child to continue in the study ($n = 502$), and loss to follow-up ($n = 436$). Gender, race/ethnicity, and ability to pay for medical costs (socioeconomic status) did not differ among the three cohorts. All 3 cohorts of the study were predominantly of minority race and ethnic groups and were inner-city dwellers. The percent survival of patients shows that the HIV+ HAART+ group were somewhat older than the HIV+ HAART- children (94.4% vs. 85.5%), respectively. These survival rates are somewhat different from those in Figure 1 (see below) where time-dependent analysis was used to compare the incidence distributions.

Table 2 records the average percentages of $CD4^+$ T cells, $CD8^+$ T cells, $CD4/CD8$ ratio, $CD8^+DR^+$ T cells, and HIV RNA levels at several time points with HAART serving as a time-dependent variable (i.e., children are assigned their respective group depending whether they were or were not taking HAART at the time of the clinic visit). In general, HIV+ children who were on HAART at the time of measurement had higher $CD4^+$ T cell, lower $CD8^+$ T cell, and lower $CD8^+DR^+$ T cell percentages; higher $CD4/CD8$ ratios; and lower viral burdens than the HIV+ children not on HAART ($P \leq 0.05$ to $P \leq 0.01$). The HIV+ HAART+ and HIV+ HAART- children's values at each time were also significantly different from those of the HIV- children ($P \leq 0.05$ to $P \leq 0.01$). Although there were age differences with groups, the GEE analyses and time-dependent covariate analyses that were performed corrected for these age differences through the formation of the respective risk sets and marginal analyses that were evaluated over time.

Survival Analysis Relating HIV Infection and HAART Use (for HIV+ Infants) to the Risk of Initiating Asthma Medication

The time of first asthma medication use for each child was analyzed beginning at 1 month of age and continuing up to 13.5 years of age using a time-dependent Cox Model (Fig 1). The beta coefficients obtained from this analysis and "cumulative incidence curves" compare the expected incidence of asthma medication use for a model group of HIV+ infants taking HAART over the entire follow-up interval, a model group of HIV+ infants not taking HAART at any time over the entire follow-up interval, and the HIV- infants. The cumulative incidence at 13.5 years of age for the model HIV+ HAART+ group was 33.5% and that of HIV- group was approximately 31.2%. In contrast, the cumulative incidence curve for the model HIV+ HAART- group was 11.5%. Using the Cox model estimates to assess whether HIV infection status and HAART therapy (in HIV+ children) was related to the risk of first asthma medication use, the exponential of the difference in the coefficients for HIV+ HAART+ and HIV+ HAART- yielded a hazard ratio (HR) estimate of 3.34 ($P = 0.01$) and the difference between the HIV+ HAART- and HIV- coefficients yielded a HR estimate of 0.33 ($P < 0.01$). The difference between the HIV+ HAART+ and HIV- coefficients was not significant. A Cox analysis model was also used to examine the relationship between asthma medication use and time-dependent treatment with NNRTIs or PIs. The results were similar to those observed in the HAART analysis (data not shown).

Analysis of the Prevalence of Asthma Medication Use

Figure 2 illustrates the prevalence of asthma medication use for children born in the pre-HAART era (prior to 02/28/94) as assessed at the time of each follow-up visit (approximate child's age). The first asthma medication use for all groups was recorded at the 60-month (5-year) visit. Most (65%) of HIV+ HAART+ children had reported asthma medication use on at least two clinic visits. The maximum prevalence of asthma medication use for HIV+

children taking HAART at the same time was 10.4%; the maximum prevalence of asthma medication use in the HIV⁻ group was 10.5%, and the corresponding prevalence for HIV⁺ children not taking HAART at the same time as the asthma medication was 3.8%. All of these maximums are achieved at 132 months (11 years) of follow-up. Using a GEE model analysis, the odds ratio for receiving asthma medication was 3.38 ($P=0.02$) comparing the HIV⁺ HAART⁺ vs. HIV⁺ HAART⁻ groups; 1.40 ($P=0.51$) comparing the HIV⁺ HAART⁺ vs. HIV⁻ groups; and 0.41 ($P=0.15$) comparing the HIV⁺ HAART⁻ vs. HIV⁻ groups.

There were too few HIV⁺ children not taking HAART to allow the statistical analysis of the WITS children born in the ART II (after 03/01/94) and III (after 08/01/96) eras.

Effects of HAART on the Rate of Change of CD4⁺ T Cell Percentage at the Time of the Initiation of Asthma Medication

Mixed model analysis was used to compare CD4⁺ T cell percentage trajectories (percentage/year) among children ages six to ten years indexed by their initiation of asthma medication use (Fig 3). We have chosen to use the CD4⁺ T cell percent since this is a constant indicator of CD4⁺ T cell sufficiency across different children's ages. Assignment of a HIV⁺ child to a HAART group was made at the time of the CD4⁺ T cell percent evaluation (a time-dependent analysis). Data points 3 years before and 3 years after the initiation of asthma medication were recorded at each time according to the child's HIV status and whether or not he or she was taking HAART at that time (HIV⁺ HAART⁺, HIV⁺ HAART⁻ and HIV⁻). The average slopes of the trajectories were: 0.81 percent/year for HIV⁺ HAART⁺ children, -1.43 percent/year for HIV⁺ HAART⁻ children, and 0.15 percent/year for the HIV⁻ children. Analysis of these slope coefficients shows significance for the comparison of HIV⁺ HAART⁺ vs. HIV⁺ HAART⁻ ($P=0.010$) but not for other comparisons: HIV⁺ HAART⁺ vs. HIV⁻ ($P=0.41$) and HIV⁺ HAART⁻ vs. HIV⁻ ($P=0.08$). If data points one year before and one year after the initiation of asthma medication were used to calculate slopes, again significant differences existed between the HIV⁺ HAART⁺ vs. HIV⁺ HAART⁻ children ($P=0.01$) (data not shown).

DISCUSSION

The present large multicenter study of infants born to HIV⁺ women confirms and extends the findings of a smaller single center study.¹³ The cumulative incidence (Fig 1) and the prevalence (Fig 2) of asthma, as assessed by asthma medication use, are higher in HIV⁺ HAART⁺ children as compared to these HIV⁺ HAART⁻ children. Our data show a much lower cumulative incidence and prevalence of asthma in HIV⁺ HAART⁻ children than HIV⁺ HAART⁺ children and a restoration of the risk of asthma when HIV⁺ children were treated with HAART. This pediatric human model of asthma confirms what has been seen in animal models with asthma¹⁻³ and suggests that the loss of CD4⁺ T cells in children with untreated HIV infection protects against asthma, and the gain of CD4⁺ T cells with HAART therapy serves as a risk factor for asthma. Our findings are in agreement with most studies of adult patients with HIV infection⁵⁻⁸ but not other studies.^{9, 10} Most of these adult studies were performed in the pre-HAART era⁶⁻¹⁰ and the timing of HIV infection (adults vs. infants) and immune ontogeny (developed vs. developing) most likely explains the lack of complete agreement. One clear example of the difference between pediatric adult HIV pathogenesis is the rapid rise and persistent (≥ 3 years) elevation in HIV RNA level (hundred thousand to million range) in newborns²⁶ compared to a much lower HIV viral set-point observed 6-8 weeks after infection in adults.

It is possible that the immunoreconstitution of CD4⁺ T cells with HAART therapy plays a role in an inflammatory response as active CD4⁺ T cells initially confront HIV antigens or those of opportunistic organisms colonizing the airway^{27, 28} that results in a clinical state of

bronchial hyperresponsiveness (Fig 3). It is reasonable to speculate that inflammatory cytokines (e.g., IL-4, IL-5, IL-9, IL-13), may participate in this production of asthma.²⁹ Activated CD8⁺ T cells (i.e., DR⁺) may be contributing to a state of pulmonary hypersensitivity as well.³⁰ These activated CD8⁺ T cells have been associated with HIV disease progression and other serious complications of HIV infection, such as encephalopathy.³¹ Virus-specific CD8⁺ T cells can switch from IFN- γ to IL-5 production³² and may be operating in patients with HIV infection who develop asthma on HAART therapy. In another area of clinical immunology, Reveille and Williams³³ have noted the marked change in the pattern of rheumatological complications of HIV infection in adults since the introduction of HAART therapy with the appearance of de novo autoimmune disorders as part of the immunoreconstitution of CD4⁺ T cells.

Several limitations of the present study need mention. The WITS study was not designed to look at the incidence of asthma per se but to focus on HIV infection and its consequences. The diagnosis of asthma and reactive airways disease reported by parents and recorded by WITS medical personnel in the first 1–2 years life of the study subjects suggested an overuse of the diagnosis of asthma as applied to wheezing infants with respiratory syncytial virus or rhinovirus present with asthma-like symptoms (data not shown).^{17, 34–36} Many of these young infants infected with respiratory viruses, particularly those with underlying allergies, indeed go on to have persistent asthma, but a majority have their symptoms remit in a few years. The WITS program did not provide a long-term evaluation of the persistence of asthma symptoms with measurement of pulmonary function.

To mitigate these limitations we established a diagnosis of asthma in the WITS cohort by the use of asthma medications, a more conservative approach than using parental recall of wheezing in infants. We also observed a relatively high incidence of asthma in the HIV– group (roughly equal to that of the model HIV+ HAART+ group). These children might have been exposed to HIV antigens in utero and in the peripartum period, most likely becoming sensitized to HIV antigens and exposed to pro-inflammatory cytokines of the HIV-infected mother. This HIV exposure perhaps renders the HIV– group a non-ideal control against which to compare the incidence of asthma. As the control study subjects lived in inner cities, for the most part, environmental exposures may have contributed to a higher incidence and prevalence of asthma in all groups.³⁷ There is some evidence in the pulmonary literature that HIV-exposed infants had a 20% lower partial forced expiratory flow as compared to historical controls.³⁸ Although the authors at that time discounted an HIV exposure factor as the basis for causation, in retrospect, this may well have played a role in producing this diminution of infant lung function.

There is also a possibility that a treatment-related censoring function with patients who died could have biased our study results. HIV+ infants had a lower risk of death when they were being treated with HAART. However, the nature of the finding presented here suggests that the direction of the bias is to elevate the model incidence curve for the HIV+ HAART– infants. This would occur because the recovery of CD4⁺ T cells predicts resurgence of the risk for asthma (the finding here) and the death-censoring mechanism is selectively eliminating from the analysis asthma information from those infants with the lowest CD4⁺ T cell counts, who would be least likely to develop asthma in our hypothesis.

Despite these limitations, there is reason to continue to explore the interrelationships between HIV infection, HAART treatment, asthma, and CD4⁺ T cells and to expand the study to the evaluation of inflammatory cytokines and activated CD8⁺ T cells. A prospective study of HIV+ patients treated with HAART is now needed that relates pulmonary function data to immune responses. This AIDS model of asthma may hold clues for a better

understanding of molecular and cellular mechanisms responsible for the epidemic of asthma in children.³⁹

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ABBREVIATIONS

ART	antiretroviral therapy
HIV	human immunodeficiency virus type 1
HIV+	HIV infected
HIV	HIV uninfected
HAART	highly active antiretroviral therapy

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Fig. 1.

Survival analysis results for the time-to-first asthma medication use. Cox model estimates relating differences between children according to HIV infection status and HAART use (in the HIV+ group) and respective P values are annotated in the lower right hand portion of the graph. Estimated cumulative incidences for each group at 2, 5, 10, and 13.5 years of age are annotated in the upper left-hand portion of the graph.

Fig. 2. Prevalence of asthma medication use for children born in the pre-HAART era using GEE. Data are presented using a three point moving average. No asthma medications were used by any group before 60 months.

Fig. 3. Median CD4⁺ T cell percentages in children aged six to ten years of age, indexed according to the time of first asthma medication use (Time 0). The slope estimates of CD4⁺ cell percent from the mixed model analysis are annotated in the upper portion of the graph.

Table 1

Patient Cohort Clinical Characteristics of WITS Study Population by HIV Status and HAART Use as Fixed Variables (Ever used or not)

	Ever Used HAART HIV+ (N=113)			Never Used HAART HIV+ (N=80)			HIV- (N=2471)			p-value*
	N Total	n	% (mean)	N Total	N	% (mean)	N Total	n	% (mean)	
Mean follow-up(in years)*	113		(10.4)	80		(3.0)	2471		(2.5)	<.001
Time on HAART (in mos)*	113		(59.4)	80		0.0	2471		(0.0)	<0.001
<i>Survival Rate at 5 years*</i>	113		94.4	80		85.5	2471		87.8	0.1268
Gender										
Male	113	64	56.6	80	33	41.2	2471	1257	50.8	0.107
Female		49	43.3		47	58.7		1214	49.1	
Race/ethnicity										
White		16	14.1		13	16.3		271	11.0	0.195
Black	113	53	46.9	80	29	36.2	2471	1189	48.1	
Other/Missing		44	38.9		38	47.5		1011	40.9	
Insurance coverage										
Self		3	2.8		5	6.4		113	4.6	0.149
Public insurance/aid		78	72.8		59	76.6		1676	68.5	
Private insurance	107	8	7.4	77	6	7.7	2446	345	14.1	
Other individual pays		18	16.8		7	9.0		289	11.8	
Free care/don't pay		0	0.0		0	0.0		23	0.9	

* p-value from a Chi-square or F-test statistic comparing distributions among the 3 groups

Table 2

Average CD4%, CD8%, CD4/CD8 Ratio, CD8⁺DR % and HIV RNA by Age, HIV status, and Grouped according HAART at the Time of the Child's Visit

	HIV+ HAART+						HIV+ HAART-						HIV-					
Infant's Age (in years)	n	CD4%	n	CD8%	n	CD4/CD8 ratio	n	CD4%	n	CD8%	n	CD4/CD8 ratio	n	CD4%	n	CD8%	n	CD4/CD8 ratio
0	2	48.5	2	25.5	2	2.2	124	49.6 [‡]	122	24.0 [‡]	122	2.5 [‡]	1724	54.5	1720	21.1	1720	3.0
0.5	13	43.2 [*]	13	18.7 [*]	13	2.4 [*]	135	32.5 [‡]	133	28.2 [‡]	133	1.4 [‡]	2050	45.9	2040	17.1	2040	3.0
1	18	37.3 ^{*‡}	18	24.4 ^{*‡}	18	1.8 ^{*‡}	119	28.3 [‡]	118	32.9 [‡]	117	1.0 [*]	1679	42.1	1677	19.0	1676	2.5
2	19	31.1 [‡]	19	29.2 ^{*‡}	19	1.3 ^{*‡}	103	26.1 [‡]	103	39.4 [‡]	103	0.8 [*]	769	38.8	766	21.1	766	2.0
5	35	28.9 [‡]	35	37.2 [‡]	35	0.9 [‡]	59	28.7 [‡]	59	39.4 [‡]	59	0.8 [*]	122	38.4	122	23.4	122	1.8
10	53	28.7 [‡]	53	36.0 ^{*‡}	53	0.9 ^{*‡}	22	27.2 [‡]	22	43.3 [‡]	22	0.7 [*]	12	42.7	12	20.7	12	2.2
13.5	19	28.5	19	38.5	19	1.0	3	26.3	3	45.7	3	0.6	0	§	0	§	0	§

Infant's Age (in years)	HIV+ HAART+				HIV+ HAART-				HIV-			
	n	CD8DR%	n	Viral Load (Copies/ml)	n	CD8DR%	n	Viral Load (Copies/ml)	n	CD8DR%	n	Viral Load (Copies/ml)
0	0	§	0	§	1	14.0	76	191,500	1	2.0	0	§
0.5	10	8.3 ^{*‡}	12	267,000	127	14.1 [‡]	121	643,600	1265	4.7	0	§
1	9	12.2 [‡]	18	9,500 [*]	119	19.2 [‡]	108	425,800	1028	6.8	0	§
2	12	17.9 [‡]	19	188,200	103	24.0 [‡]	97	579,100	696	7.5	0	§
5	19	29.1 ^{*‡}	31	41,100	57	21.0 [‡]	46	443,300	90	7.4	0	§
10	0	§	47	41,900	0	§	17	35,100	0	§	0	§
13.5	0	§	11	22,700	0	§	1	2,600	0	§	0	§

Pair-wise comparisons differences significant at P≤0.05 level (red color: P<0.01 level);

* HIV+ HAART+ vs. HIV+ HAART-;

[‡] HIV+ HAART+ vs. HIV-;

[‡] HIV+ HAART- vs. HIV-

§ Insufficient data for analysis

At each time point, HIV+ subjects are assigned to a group by HAART medication, (i.e., HAART+ or HAART-).