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Long-Term Effects of Highly Active Antiretroviral Therapy on CD4+ Cell Evolution among Children and Adolescents Infected with HIV: 5 Years and Counting

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Abstract

Background—Lower percentages of $CD4^+$ T lymphocytes are associated with adverse clinical outcomes among children and adolescents infected with human immunodeficiency virus (HIV). $CD4^+$ lymphocyte percentage generally increases with receipt of highly active antiretroviral therapy (HAART), but long-term follow-up is required to assess whether these increases in $CD4^+$ cell percentage are maintained and whether they lead to normal $CD4^+$ cell percentages in children with severe immunosuppression.

Methods—The study population included 1236 children and adolescents perinatally infected with HIV who were enrolled in a US-based multicenter prospective cohort study (Pediatric AIDS Clinical Trials Group 219/219C) and who were not receiving HAART at study initiation. We estimated the effects of HAART, HAART with protease inhibitors, and HAART with nonnucleoside reverse-transcriptase inhibitors on $CD4^+$ cell percentage, using marginal structural models to account for confounding by severity.

Results—Initiation of any type of HAART increased $CD4^+$ cell percentage by 2.34% (95% confidence interval, 1.35%–3.33%) in the first year, relative to noninitiation of HAART. The substantial increases in $CD4^+$ cell percentage observed after the first year of experience with these combination therapies were followed by relatively smaller increases that continued for 5 years after initiation. Although larger increases in $CD4^+$ cell percentage were observed among children with a greater degree of immunosuppression at baseline, the mean $CD4^+$ cell percentage after 5 years of HAART did not reach normal levels.

Conclusions—Our study supports the initiation of HAART in children before severe immunosuppression occurs for long-term maintenance of normal $CD4^+$ cell percentages. This

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beneficial result must be weighed against the evidence of potential adverse events associated with the prolonged use of such therapy.

Among children and adolescents infected with HIV, low $CD4^+$ T lymphocyte counts have been associated with weight growth failure [1] and mortality [1–5]. $CD4^+$ cells serve as important immunologic markers of HIV disease progression that facilitate both clinical decision-making about when to initiate antiretroviral therapy and clinical monitoring of treatment effectiveness and drug resistance. Use of HAART has been associated with improved clinical outcomes, such as growth [6, 7] and survival of HIV-infected children [8, 9]. These associations are likely to be partly mediated through the effect of HAART on $CD4^+$ cell counts. Numerous studies have found an association between combination antiretroviral therapy and increases in $CD4^+$ cell count in children [10–24]. However, the majority of these studies included only small numbers of children and/or had follow-up periods of <1 year [10–21]. Of the studies evaluating the association between HAART and $CD4^+$ cells, 2 recent studies observed >200 children for >1 year [22, 23]. These studies compared $CD4^+$ cell percentage before initiation with $CD4^+$ cell percentage after initiation and found substantial improvements in $CD4^+$ cell percentage after the first year of therapy, followed by relatively smaller increases in the subsequent years. These immediate and prolonged effects were particularly observed among younger children (<5 years of age) and those children who initiated HAART with low $CD4^+$ cell percentages (<15%).

Our study aimed to evaluate whether the $CD4^+$ cell percentage increases associated with HAART were sustained for >5 years after HAART initiation and whether these increases resulted in a $CD4^+$ cell percentage >25%, a level considered to be the lower limit of normal for children >1 year of age [25]. We further aimed to evaluate separately HAART including a protease inhibitor (PI) and HAART including a nonnucleoside reverse-transcriptase inhibitor (NNRTI). Either PIs or NNRTIs are strongly recommended for inclusion in initial regimens for HIV-infected children [26] and are a basis for the definition of HAART. We investigated the mean change in $CD4^+$ cell percentage after HAART exposure, because $CD4^+$ cell percentage is a more stable measure of $CD4^+$ lymphocytes in children than is absolute $CD4^+$ cell count [25].

PATIENTS, MATERIALS, AND METHODS

The study population included participants from Pediatric AIDS Clinical Trials Group (PACTG) Protocols 219 and 219C, both of which are longitudinal prospective studies designed to evaluate the long-term effects of HIV infection and in utero and postnatal exposure to antiretroviral therapy. Beginning in April 1993, infected and uninfected children from >80 study sites in the United States were eligible for enrollment in PACTG 219 and for subsequent enrollment in 219C if they were born to HIV-infected mothers and were younger than 21 years of age at study entry. These studies were approved by the human subjects review boards at each participating institution, and written informed consent was obtained from each child’s parent or legal guardian. The population eligible for this study included 1236 perinatally infected children enrolled in PACTG 219 or 219C from 1 January 1996 through 30 June 2006 who were HAART naive at their baseline visit and had complete data on covariates of interest at some point before HAART initiation. This period includes the introduction of PIs into clinical practice and captures data on those children who initiated HAART.

At each study visit, data on sociodemographic characteristics, clinical diagnoses, antiretroviral therapies received, and laboratory measurements of $CD4^+$ cell percentage, total lymphocyte count, WBC count, hematocrit, and albumin level were collected. These laboratory measures have been previously identified as possible predictors of clinical

progression in pediatric HIV infection [27, 28] and were, therefore, considered to be potential confounders of the effect of HAART on $CD4^+$ cell percentage. Clinical diagnoses were reviewed by a study physician and classified as category C or N/A/B on the basis of the Centers for Disease Control and Prevention (CDC) criteria for classification of HIV disease in children <13 years of age and ⩾13 years of age [29, 30]. HIV RNA measurements were not routinely collected before 2000, because they were not available when PACTG 219 was designed and were not standardized for pediatrics until the late 1990s [31].

HAART exposure was defined as the concomitant use of ⩾3 drugs from ⩾2 classes of HIV therapy. HIV drugs are classified into 3 main categories: nucleoside and/or nucleotide reverse-transcriptase inhibitors (NRTIs), NNRTIs, and PIs. HAART with PI was defined as a HAART regimen containing a PI, and HAART with NNRTI was defined as a HAART regimen containing an NNRTI (the 2 categories were not mutually exclusive). To evaluate the effects of treatment over time, patients in the HAART, HAART with PI, and HAART with NNRTI groups were classified into categories of years since the initiation of first HAART treatment. Once a participant initiated HAART, he or she was considered to be receiving therapy for the length of the follow-up period. In PACTG 219, actual dates of initiation of medication or dates of changes in the use of medications were not available. In accordance with a previous PACTG 219 study [8], we assumed that the midpoint between the first visit date at which the use of a new medication was recorded and the date of the prior visit was the date of initiation of that medication. We also conducted analyses in which the date of initiation was randomly assigned (unconditionally or conditionally on the basis of $CD4^+$ cell percentage) during the interval between the 2 visits. These analyses resulted in similar estimates of the effect of HAART on $CD4^+$ cell percentage.

Each child was able to contribute a maximum of 10 person-visits of follow-up beginning with his or her baseline visit and ending with (1) the patient's final follow-up visit, (2) the first visit with missing $CD4^+$ cell percentage data, or (3) 30 June 2006 (i.e., completion of study), whichever came first. In analyses of HAART with PI and HAART with NNRTI, children were censored on the last visit before switching to HAART regimens that did not include a PI and that did not include an NNRTI, respectively. For those children who enrolled in PACTG 219 before the start of the study period (1 January 1996), the first study visit after this date was set as the baseline visit. For children who enrolled after 1 January 1996 in either PACTG 219 or 219C, the first study visit was set as the baseline visit. For participants who were missing baseline data for any time-varying covariate, baseline was redefined as the first visit with complete data. Children with previous or current use of HAART at the baseline visit were excluded.

To estimate the effect of HAART on mean change in $CD4^+$ cell percentage, we fit a repeated-measures linear regression model with $CD4^+$ cell percentage at year t as the outcome and with the following covariates: an indicator for ever having received HAART by year $t-1$, age, sex, race or ethnicity, week of follow-up, calendar year, baseline CDC clinical category, baseline $CD4^+$ cell percentage, baseline total lymphocyte count, baseline WBC count, baseline hematocrit, and baseline albumin level. To account for within-subject correlation caused by repeated measures, we fit this model using generalized estimating equations. To appropriately control for time-varying confounders, we weighted each child at each year by the inverse of the probability that they received their actual treatment history, given their measured time-varying covariates. Under the assumption of no unmeasured confounders, this model, which has parameters that are those of a marginal structural model [32, 33], estimates the difference in mean $CD4^+$ cell percentage for those patients who initiated HAART, compared with those who did not initiate HAART. We used similar models to estimate the effect of HAART with PI and HAART with NNRTI on the mean $CD4^+$ cell percentage.

We estimated stabilized inverse probability weights for initiating HAART and for censoring at the time of each visit [32–34]. For each child and each visit, the denominator of the weight is informally the probability that they received their actual treatment history and remained uncensored up to that time, conditional on their past covariate history. These weights create a statistical population in which the probabilities of treatment and censoring are unrelated to the time-varying confounders included in the models used to estimate weights [34]. Unlike conventional unweighted models, inverse probability weighted models may appropriately adjust for time-varying confounders that are affected by prior HAART use or are on the causal pathway between HAART and changes in $CD4^+$ cell percentage [32, 33, 35]. We estimated the weights by fitting pooled logistic regression models for the probability of HAART initiation and censoring at each visit, given baseline and past time-varying covariates [32, 33]. The covariates included in these models were age, sex, race or ethnicity, year of follow-up, and calendar year at baseline, together with baseline and time-varying values for CDC clinical category, $CD4^+$ cell percentage, total lymphocyte count, WBC count, hematocrit, and albumin level. Year of follow-up and time-varying $CD4^+$ cell percentage were modeled using flexible cubic splines with knots at the fifth, 25th, 50th, 75th, and 95th percentiles of the year of follow-up and $CD4^+$ cell percentage, respectively. Data were structured for analysis purposes into 1-year intervals, and covariate information was carried forward from the most recently observed value when data were missing. For model comparison purposes, an unweighted generalized estimating equation model including only baseline covariates and a standard unweighted generalized estimating equation model including both baseline and time-varying covariates were used to estimate the effect of HAART, HAART with PI, and HAART with NNRTI on $CD4^+$ cell percentage.

RESULTS

Characteristics of the 1236 participants at baseline are presented in table 1. At baseline, 29% of participants were <5 years of age, 51% were female, 56% were black, 20% had a $CD4^+$ cell percentage <15%, and 28% had CDC clinical category C disease. In the analysis of the overall effects of HAART on $CD4^+$ cell percentage, the median length of follow-up for the entire cohort was 3 years (interquartile range, 1–7 years). A total of 330 participants (27%) remained in follow-up through 30 June 2006; the remaining 906 (73%) were censored at the first visit with missing $CD4^+$ cell percentage data. There were 3043 HAART-free person-years of follow-up, and 610 participants (49%) initiated HAART; these participants had a total of 3109 person-years of follow-up while receiving HAART. Among the HAART initiators, the median cumulative exposure was 3 years (interquartile range, 1–7 years). The corresponding follow-up characteristics for the HAART with PI and HAART with NNRTI analyses are presented in table 2.

Of the 610 initial HAART regimens, 387 (63%) included only PIs in combination with NRTIs, of which nelfinavir (177 regimens; 46%) and ritonavir (174 regimens; 45%) were the most common. Sixty-seven (11%) of the initial HAART regimens included only NNRTIs in combination with NRTIs; efavirenz was used in 34 (51%) of these regimens, and nevirapine was used in 33 (49%). Of the initial HAART regimens, 156 included both PIs and NNRTIs with NRTIs; nevirapine was the most common NNRTI used, in combination with ritonavir in 61 (39%) of the regimens and nelfinavir in 46 (29%). Most HAART regimens included 2 NRTIs, the most common combinations being lamivudine with either stavudine (107 [33%] of 329) or zidovudine (92 [28%] of 329).

Table 3 presents estimates of the effects of HAART on mean $CD4^+$ cell percentage by years since HAART initiation. All 3 HAART exposures resulted in a >2% increase in $CD4^+$ cell percentage after 1 year of therapy, compared with no HAART exposure. A small increase in $CD4^+$ cell percentage was observed each year after the large increase in the first year after

initiation. This steady trend extended at least 5 years after combination therapy initiation. Similar to previous analyses, the largest increases in $CD4^+$ cell percentage during the years since combination therapy initiation were observed in those children with the lowest baseline $CD4^+$ cell percentage. After 1 year of HAART, children with a $CD4^+$ cell percentage <15% at baseline experienced a 4.44% increase (95% CI, 2.27%–6.62%) in $CD4^+$ cell percentage, compared with a 2.78% increase (95% CI, 1.52%–4.03%) among children with a $CD4^+$ cell percentage of 15%–24% at baseline and a 1.19% increase (95% CI, 0.01%–2.38%) among children with a $CD4^+$ cell percentage ⩾25% at baseline. Despite the greater increase in $CD4^+$ cell percentage, however, the mean $CD4^+$ cell percentage of children with a $CD4^+$ cell percentage <15% at baseline did not recover to a level >25%, even 5 years after HAART initiation (figure 1). Age at baseline did not modify these effects further. The effect of years since initiation of HAART with PI and years since initiation of HAART with NNRTI showed the same pattern of change by $CD4^+$ cell percentage and age at baseline.

As expected, conventional unweighted regression models yielded attenuated estimates. The estimated difference in mean $CD4^+$ cell percentage after 1 year of HAART use versus no HAART was 1.76% (95% CI, 0.83%–2.70%) in an unweighted repeated-measures model with baseline covariates only and was 0.76% (95% CI, 0.18%–1.35%) when the time-varying covariates were added to the model.

DISCUSSION

Our findings suggest that the initial increases in $CD4^+$ cell percentage observed in the first year after HAART initiation are sustained for at least 5 years after HAART initiation among children and adolescents infected with HIV and that greater increases occur among those with the greatest degree of immunosuppression. Our findings also suggest that PI-based and NNRTI-based HAART regimens cause similar increases in mean $CD4^+$ cell percentage. Although age at baseline did not significantly modify these findings, larger improvements in $CD4^+$ cell percentage attributable to HAART initiation were observed among younger children (<5 years of age), compared with older children (⩾5 years of age). This is consistent with previous studies evaluating $CD4^+$ cell response to HAART and may support the hypothesis of greater thymic activity among young children [14, 22, 23]. However, the differences between the age groups could be attributable to alternative explanations, such as adherence issues among adolescents [22] or a survivor effect.

Although the ideal goal of long-term therapy is to recover $CD4^+$ cell percentage to normal levels, only 36% of children with $CD4^+$ cell percentage <15% and 59% of children with $CD4^+$ cell percentages of 15%–24% at baseline achieved $CD4^+$ cell percentages ⩾25% at 5 years after HAART initiation. Given these descriptive findings, we evaluated whether HAART initiation was associated with normal $CD4^+$ cell percentage values after adjustment for time-dependent confounding and found that HAART initiation was associated with 2-fold greater odds of normal $CD4^+$ cell percentage, compared with noninitiation of HAART (OR, 2.26; 95% CI, 1.65–3.10). Similarly, initiation of HAART with PI and initiation of HAART with NNRTI were associated with normal $CD4^+$ cell percentage values, compared with noninitiation (OR for HAART with PI, 2.63 [95% CI, 1.87–3.68]; OR for HAART with NNRTI, 4.69 [95% CI, 2.63– 8.34]).

Our results were consistent with the previous PACTG 219 study investigating the effect of PI-based HAART on $CD4^+$ cell percentage [22]. Although that study used different approaches to examine this association, both studies found HAART with PI to be associated with significant increases in $CD4^+$ cell percentage that were maintained over time. The previous PACTG 219 study estimated the mean changes in $CD4^+$ cell percentage from

baseline to 3 years after initiation of HAART with PI. Our approach aimed to estimate the effect of initiating HAART on $CD4^+$ cell percentage, compared with not initiating HAART. This approach used a non-HAART comparison group to account for changes in $CD4^+$ cell percentage over time that were unrelated to HAART initiation, such as age-related changes in $CD4^+$ cell percentage [25].

Our results are not directly comparable to those of Walker et al. [23], because those authors compared HAART use with no use of any antiretroviral therapy. We were unable to compare the effect of HAART on $CD4^+$ cell percentage with the effect of no treatment, because only 20 children in our cohort had no experience with antiretroviral therapy. These treatment-naive children were more likely to have enrolled in the later years of the study than in the earlier years.

To obtain a completely unbiased estimate of the effect of HAART on $CD4^+$ cell percentage, information on all potential confounders of the association is a necessity. Although we were able to control for some important confounders, such as age and CDC clinical category, we were unable to adjust for potential confounding by plasma HIV RNA level (i.e., viral load), because this information was not routinely collected or available until 2000. If clinicians were using viral load information to make treatment initiation decisions during our study period, then the HAART-associated increases in $CD4^+$ cell percentage reported in our study may be underestimated.

In this study, children were required to be naive to HAART at study entry; therefore, a large percentage (56%) of subjects in PACTG 219/219C were ineligible for our study because of previous HAART exposure. This was especially true for subjects who enrolled after 2000. This exclusion allowed for the observation of treatment history prior to HAART initiation and the identification of predictors of HAART initiation. We therefore needed to make the "no confounding" assumption for therapy initiation but not for therapy continuation.

Also, we assumed that children continued to receive HAART after initiation. This assumption was correct for 87% of 3109 person-years after HAART initiation. However, because 13% of the visits occurred among persons who had stopped using HAART, our analysis did not attempt to estimate the effect of continuous HAART versus no HAART, but the effect of HAART initiation (the "intention-to-treat effect") versus no HAART in a hypothetical randomized clinical trial in which (1) participants were randomly assigned to begin continuous HAART at different visits, (2) all participants initially complied and began HAART at their assigned visit, and (3) 13% later discontinued HAART. Because many of the study participants who discontinued HAART did so because of toxicity (rather than for nonmedical reasons), it is this intention-to-treat effect, not the effect of continuous HAART use, that would be a parameter of public health interest. This is because, had we estimated the effect of continuous HAART, we would have been estimating the effect of forcing people to continue therapy even in the presence of toxicity (something that did not occur in reality).

In conclusion, this study assessed the long-term effect of HAART initiation on $CD4^+$ cell percentage among children and adolescents infected with HIV. Overall, HAART initiation was associated with a significant increase in $CD4^+$ cell percentage. The substantial increases in $CD4^+$ cell percentage observed after the first year of HAART were followed by relatively smaller increases continuing for at least 5 years after initiation. Although larger increases in $CD4^+$ cell percentage were observed among children with a greater degree of immunosuppression at baseline, their mean $CD4^+$ cell percentage after 5 years of HAART treatment did not approach normal levels. This study adds to previous studies that have addressed the debate about when to initiate HAART in children. Although our study

supports the initiation of HAART in children before severe immunosuppression occurs to maintain normal $CD4^+$ cell percentages, this beneficial result must be weighed against evidence of potential adverse events associated with the prolonged use of such therapy [22, 36–40]. Continued follow-up is therefore required, not only to observe long-term events, but also to determine if the effects of HAART on $CD4^+$ cell percentage are maintained beyond the 5-year period documented in this study and whether children who initiate HAART at low $CD4^+$ cell percentages eventually rebound to normal levels.

PACTG 219/219C STUDY TEAM

The following institutions and individuals participated in PACTG Protocol 219C, by order of enrollment. Baylor Texas Children's Hospital: Mary E. Paul, Chivon D. Jackson, Faith Minglana, and Heidi Schwarzwald; University of Florida, Jacksonville: Mobeen H. Rathore, Ayesha Mirza, Kristy Champion, and Almer Mendoza; Chicago Children's Memorial Hospital: R. Yogev and E. Chadwick; University of Puerto Rico, University Children's Hospital AIDS Program: Irma L. Febo, Licette Lugo, Ruth Santos, and Ibet Heyer; Bronx Lebanon Hospital Center: M. Purswani, S. Baksi, E. Stuard, and M. Dummit; San Juan Hospital: M. Acevedo, M. Gonzalez, L. Fabregas, and M. E. Texidor; University of Miami: Gwendolyn B. Scott, Charles D. Mitchell, Claudia Florez, and Joan Gamber; University of Medicine & Dentistry of New Jersey: Arlene Bardeguez, Arry Dieudonne, Linda Bettica, and Juliette Johnson; Charity Hospital of New Orleans & Earl K. Long Early Intervention Clinic: M. Silio, T. Alchediak, C. Boe, M. Cowie, and R. Van Dyke; University of California at San Diego Mother, Child & Adolescent HIV Program: Stephen A. Spector, Rolando M. Viani, Mary Caffery, and Kimberly Norris; Howard University: Sohail Rana, Helga Finke, Patricia Yu, and Jhoanna Roa; Jacobi Medical Center: M. Donovan, R. Serrano, M. Burey, and R. Auguste; St. Christopher's Hospital for Children, Philadelphia: J. Chen and J. Foster; Baystate Medical Center Children's Hospital: B. W. Stechenberg, D. J. Fisher, A. M. Johnston, and M. Toye; Los Angeles County Medical Center/University of Southern California: J. Homans, M. Neely, L. S. Spencer, and A. Kovacs; Children's Hospital Boston: S. Burchett and N. Karthas; Children's Hospital of Michigan: E. Moore and C. Cromer; St. Jude Children's Research Hospital, Memphis: Aditya Gaur, Katherine Knapp, Nehali Patel, and Marion Donohoe; New York University School of Medicine/ Bellevue Hospital: Maryam Minter, Thomas Hastings, Seham Akleh, and William Borkowsky; The Children's Hospital at Downstate: E. Handelsman, H. J. Moallem, D. M. Swindell, and J. M. Kaye; The Columbia Presbyterian Medical Center & Cornell University New York Presbyterian Hospital: A. Higgins, M. Foca, P. LaRussa, and A. Gershon; The Children's Hospital of Philadelphia: Steven D. Douglas, Richard M. Rutstein, Carol A. Vincent, and Patricia C. Coburn; Children's Hospital of Oakland: Ann Petru, Teresa Courville, Katherine Eng, and Karen Gold; University of California, San Francisco, Moffitt Hospital: Diane W. Wara, Nicole Tilton, and Mica Muscat; Children's Hospital, University of Colorado, Denver: E. McFarland and C. Salbenblatt; Johns Hopkins University Department of Pediatrics: N. Hutton, B. Griffith, M. Joyner, and C. Kiefner; Children's Hospital and Regional Medical Center, University of Washington: Michele Acker, Ann J. Melvin, Kathleen M. Mohan, and Suzanne Phelps; Metropolitan Hospital Center: Mahrukh Bamji, Indu Pathak, Savita Manwani, and Ekta Patel; Children's National Medical Center: Diana Dobbins, Deidre Wimbley, Tracy Perron, and Hans Spiegel; University of Massachusetts Medical School: K. Luzuriaga and R. Moriarty; University of Alabama at Birmingham: R. Pass and M. Crain; University of Maryland School of Medicine: D. Watson, J. Farley, K. Klipner, and C. Hilyard; Schneider Children's Hospital: V. R. Bonagura, S. J. Schuval, C. Colter, and L. Campbell; Boston Medical Center: Stephen I. Pelton, E. R. Cooper, Lauren Kay, and Ann Marie Regan; University of Illinois: K. C. Rich, K. Hayani, M. Bicchinella, and J. Camacho; State University of New York, Stony Brook: Sharon Nachman, Denise Ferraro, Jane Perillo, and Michele Kelly; North Broward Hospital

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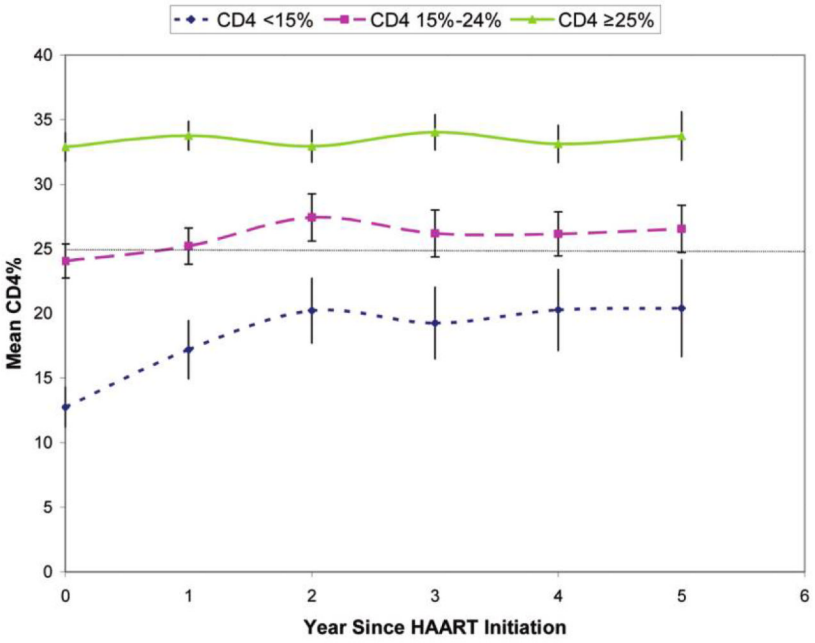

Number of Patients by Year Since HAART Initiation

<15%	137	99	82	61	52	42
15%-24%	177	145	130	108	97	86
≥25%	296	253	216	189	155	131
Total	610	497	428	358	304	259

Figure 1.

Mean $CD4^+$ cell percentage by year since HAART initiation and $CD4^+$ cell percentage at baseline for 610 patients who initiated HAART.

Table 1

Baseline demographic and clinical characteristics of 1236 HIV-positive participants enrolled in Pediatric AIDS Clinical Trials Group protocols 219 and 219C during the period 1 January 1996–30 June 2006.

Characteristic	No. (%) of patients (n = 1236)
Antiretroviral therapy[a]	
Non-HAART regimen	1236 (100)
HAART regimen	0 (0)
Age	
<5 years	354 (29)
⩾5 years	882 (71)
Sex	
Female	627 (51)
Male	609 (49)
Race or ethnicity	
White/Asian/other	176 (14)
Black	690 (56)
Hispanic	370 (30)
Year of study entry	
1996	819 (66)
1997	155 (13)
1998–2000	102 (8)
2001–2006	160 (13)
Centers for Disease Control and Prevention clinical category	
N/A/B	885 (72)
C	351 (28)
$CD4^+$ cell percentage	
<15%	257 (20)
15%–24%	304 (25)
⩾25%	675 (55)
Total lymphocyte count	
<1500 cells/μL	225 (18)
⩾1500 cells/μL	1011 (82)

Characteristic	No. (%) of patients (*n* = 1236)
WBC count	
<3000 cells/μL	82 (7)
⩾3000 cells/μL	1154 (93)
Hematocrit	
<35%	528 (43)
⩾35%	708 (57)
Albumin level	
⩽4.0 g/dL	419 (34)
>4.0 g/dL	817 (66)

[a] No children had experienced HAART at baseline, because this was one of the inclusion criteria.

Table 2

Clinical characteristics of the participants in the HAART, HAART with protease inhibitor (PI), and HAART with nonnucleoside reverse-transcriptase inhibitor (NNRTI) analyses at follow-up.

Variable	HAART[a]	HAART with PI[b]	HAART with NNRTI[c]
Duration of follow-up, median years (interquartile range)	3 (1–7)	2 (1–6)	1 (0–3)
No. of patients with HAART initiation	610	543	223
Cumulative exposure, median years (IQR)	3 (1–7)	3 (1–7)	2 (1–5)
No. (%) of patients remaining in follow-up through 30 June 2006[d]	330 (27)	263 (21)	155 (12)
No. (%) of patients censored at first follow-up with missing $CD4^+$ cell percentage data[d]	906 (73)	851 (69)	614 (50)
No. (%) of patients censored because of switching regimen[d]	…	122 (10)	467 (30)

[a] The HAART group (n = 610) includes HAART with only PI (n = 387), HAART with only NNRTI (n = 67), and HAART with both PI and NNRTI (n = 156).

[b] The HAART with PI group (n = 543) includes HAART with only PI (n = 387) and HAART with both PI and NNRTI (n = 156).

[c] The HAART with NNRTI group (n = 223) includes HAART with only NNRTI (n = 67) and HAART with both PI and NNRTI (n = 156).

[d] n = 1236.

Table 3

Effect of HAART, HAART with protease inhibitor (PI), and HAART with nonnucleoside reverse-transcriptase inhibitor (NNRTI) initiation on mean $CD4^+$ cell percentage, compared with noninitiation of HAART, overall and by $CD4^+$ cell percentage at baseline.

	Difference in mean $CD4^+$ cell percentage between patients with HAART initiation and patients without HAART intiation (95% CI)			
Variable	**After 1 year of HAART**	**After 2 years of HAART**	**After 3 years of HAART**	**After 5 years of HAART**
HAART	2.34 (1.35–3.33)	3.32 (1.87–4.77)	3.68 (2.04–5.32)	4.42 (2.09–6.76)
All age groups				
$CD4^+$ cell percentage <15%	4.44 (2.27–6.62)	7.96 (5.71–10.22)	7.22 (4.61–9.83)	8.93 (4.94–12.91)
$CD4^+$ cell percentage 15%–24%	2.78 (1.52–4.03)	5.26 (3.03–7.49)	4.39 (2.37–6.42)	5.55 (3.18–7.91)
$CD4^+$ cell percentage ⩾25%	1.19 (0.01–2.38)	0.39 (−1.12 to 1.90)	2.12 (0.26–3.98)	2.31 (−0.36 to 4.98)
Age <5 years				
$CD4^+$ cell percentage <15%	6.59 (1.76–11.42)	10.61 (5.89–15.33)	11.89 (6.69–17.08)	6.85 (−3.53 to 17.23)
$CD4^+$ cell percentage 15%–24%	3.84 (1.29–6.39)	6.07 (2.97–9.18)	3.94 (0.76–7.12)	4.32 (0.82–7.82)
$CD4^+$ cell percentage ⩾25%	0.77 (−0.95 to 2.49)	−0.33 (−2.42 to 1.76)	2.53 (−0.24 to 5.29)	4.47 (0.87–8.08)
Age ⩾5 years				
$CD4^+$ cell percentage <15%	3.72 (1.22–6.22)	7.06 (4.42–9.69)	5.74 (2.82–8.66)	9.39 (5.15–13.64)
$CD4^+$ cell percentage 15%–24%	2.29 (0.80–3.77)	4.89 (2.03–7.75)	4.59 (2.16–7.03)	6.10 (3.44–8.77)
$CD4^+$ cell percentage ⩾25%	1.46 (0.09–2.84)	0.84 (−0.88 to 2.55)	1.85 (−0.08 to 3.79)	0.69 (−2.15 to 3.52)
HAART with PI	2.70 (1.62–3.78)	3.59 (2.14–5.03)	4.45 (2.66–6.24)	4.23 (1.56–6.90)
All age groups				
$CD4^+$ cell percentage <15%	5.34 (2.87–7.82)	9.94 (7.33–12.56)	8.10 (4.96–11.25)	9.84 (5.25–14.43)
$CD4^+$ cell percentage 15%–24%	3.32 (1.95–4.68)	4.98 (3.16–6.80)	6.12 (3.92–8.33)	6.04 (3.24–8.83)
$CD4^+$ cell percentage ⩾25%	1.22 (−0.06 to 2.51)	0.78 (−0.86 to 2.43)	2.67 (0.64–4.70)	1.78 (−1.46 to 5.03)
Age <5 years				
$CD4^+$ cell percentage <15%	6.93 (1.58–12.29)	14.55 (9.67–19.43)	12.86 (6.85–18.88)	10.29 (−2.50 to 23.08)

Variable	Difference in mean CD4+ cell percentage between patients with HAART initiation and patients without HAART intiation (95% CI)			
	After 1 year of HAART	After 2 years of HAART	After 3 years of HAART	After 5 years of HAART
CD4+ cell percentage 15%–24%	4.17 (1.58–6.76)	6.23 (2.87–9.58)	5.41 (1.82–9.00)	4.35 (0.22–8.48)
CD4+ cell percentage ⩾25%	0.70 (−1.15 to 2.55)	0.16 (−2.12 to 2.44)	3.29 (0.27–6.31)	4.06 (0.04–8.07)
Age⩾ 5 years				
CD4+ cell percentage <15%	4.78 (1.82–7.73)	8.27 (5.18–11.36)	6.40 (2.81–10.00)	9.70 (5.29–14.10)
CD4+ cell percentage 15%–24%	2.92 (1.29–4.56)	4.41 (2.28–6.53)	6.42 (3.80–9.04)	6.74 (3.47–10.00)
CD4+ cell percentage ⩾25%	1.59 (0.07–3.11)	1.20 (−0.70 to 3.09)	2.23 (0.10–4.36)	0.10 (−3.82 to 4.02)
HAART with NNRTI	2.82 (1.26–4.38)	4.05 (1.74–6.36)	5.61 (3.26–7.96)	6.61 (2.75–10.48)
All age groups				
CD4+ cell percentage <15%	7.65 (4.21–11.08)	13.23 (9.02–17.43)	12.10 (6.32–17.89)	9.76 (0.56–18.95)
CD4+ cell percentage 15%–24%	4.31 (2.10–6.52)	6.10 (2.05–10.14)	7.10 (3.05–11.14)	10.29 (6.46–14.13)
CD4+ cell percentage ⩾25%	0.30 (−1.52 to 2.13)	0.71 (−1.55 to 2.97)	3.55 (1.10–6.00)	3.88 (−1.31 to 9.08)
Age <5 years				
CD4+ cell percentage <15%	11.41 (3.35–19.47)	13.93 (4.37–23.49)	21.35 (10.56–32.15)	11.73 (8.65–14.81)
CD4+ cell percentage 15%–24%	4.96 (0.08–9.84)	3.51 (−4.70 to 11.71)	6.15 (−2.02 to 14.32)	7.30 (−0.25 to 14.85)
CD4+ cell percentage ⩾25%	−0.45 (−3.42 to 2.51)	−1.12 (−4.44 to 2.20)	5.19 (1.65–8.74)	7.02 (3.82–10.22)
Age< 5 years				
CD4+ cell percentage <15%	6.44 (2.76–10.11)	12.85 (8.84–16.87)	10.00 (4.20–15.81)	9.29 (−1.85 to 20.43)
CD4+ cell percentage 15%–24%	4.03 (1.42–6.63)	7.27 (2.45–12.08)	7.56 (2.79–12.34)	12.19 (8.23–16.14)
CD4+ cell percentage ⩾25%	0.79 (−1.43 to 3.01)	1.99 (−0.58 to 4.56)	2.48 (−0.24 to 5.19)	1.62 (−6.00 to 9.23)