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Antiretroviral Treatment of U.S. Children with Perinatally-Acquired HIV Infection: Temporal Changes in Therapy between 1991 and 2009 and Predictors of Immunologic and Virologic Outcomes

Russell B. Van Dyke, MD¹, Kunjal Patel, DSc, MPH^{2,3}, George K. Siberry, MD, MPH⁴, Sandra K. Burchett, MD⁵, Stephen A. Spector, MD⁶, Miriam C. Chernoff, PhD³, Jennifer S. Read, MD, MPH⁴, Lynne M. Mofenson, MD⁴, and George R. Seage III, DSc, MPH^{2,3} for the Pediatric HIV/AIDS Cohort Study

¹ Tulane University Health Sciences Center, New Orleans, LA

² Department of Epidemiology, Harvard School of Public Health, Boston MA

³ Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

⁴ Pediatric Adolescent Maternal AIDS Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, Bethesda, MD

⁵ Children's Hospital, Boston, MA

⁶ University of California, San Diego, La Jolla, CA

Abstract

Background—Advances in therapy have allowed children with perinatal HIV infection in the U.S. to survive into adolescence. We sought to describe the disease status of a large cohort of such children and identify predictors of their current CD4 count and HIV viral load (VL).

Methods—The Pediatric HIV/AIDS Cohort Study AMP Protocol is an ongoing prospective study conducted at 15 sites in the U.S. Between 2007 and 2009, we enrolled a population-based sample of 451 children with perinatal HIV who were 7–16 years of age at entry.

Corresponding author: Russell B. Van Dyke, MD, Department of Pediatrics, TB-8, Tulane University Health Sciences Center, 1440 Canal St, Suite 1600, New Orleans, LA, 70112., vandyke@tulane.edu, Phone: 504-988-2570, Fax: 504-988-3805.

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Results—The median age of subjects at entry was 12.2 years, 53% were female, 70% were African-American, and 24% Hispanic. Their median entry CD4% was 33% and 78% had a CD4% $\geq 25\%$; 68% had a suppressed VL. The more recent birth cohorts (1994–2002) had a significantly higher CD4% over time than the earliest birth cohort (1991–1993). The significant independent predictors of a higher CD4% at entry were a suppressed entry VL, a higher nadir CD4%, and starting antiretroviral therapy (ART) at a younger age. The mean CD4% at entry for children with a nadir CD4% $\geq 25\%$ was 9.5 percentage points higher than for those with a nadir CD4% $< 15\%$ ($p < 0.001$). Independent predictors of a suppressed entry VL were membership in a recent birth cohort, male gender, HAART use at entry and fewer prior ART regimens.

Conclusion—Most children with perinatal HIV maintain virologic suppression and good CD4 values. Earlier treatment results in better immune outcome.

Keywords

Human Immunodeficiency virus; antiretroviral therapy; pediatrics; HIV viral load; CD4 count

Introduction

Most HIV-infected children acquire their infection through mother-to-child transmission (MTCT). In 1994, it was demonstrated that antiretroviral therapy (ART) administered to the pregnant woman and her newborn can prevent MTCT.¹ Treatment of the HIV-infected pregnant woman with highly active combination antiretroviral therapy (HAART) reduces the rate of MTCT from 25–30% to less than 2%.² Thus, most children currently living in the US with perinatally-acquired HIV infections (perinatal HIV) are between 13 and 19 years of age.³ Having been infected since birth or early infancy, many of these children have received multiple antiretroviral therapy (ART) regimens, often starting with what is now considered suboptimal therapy before the availability of HAART.⁴ In 1996, the availability of HAART enabled suppression of viral replication in most children⁵ with consequent improvement in their immunologic status,^{5–7} fewer opportunistic infections and other complications of HIV^{8,9}, improved survival,^{5,10,11} and an improved quality of life.¹²

As children with perinatal HIV infection age into adolescence and adulthood, it is important to monitor the course of their infection, with particular attention paid to complications of both HIV and ART.¹³ The Adolescent Master Protocol (AMP), a component of the Pediatric HIV/AIDS Cohort Study, is a prospective cohort study designed to define the impact of HIV infection and ART on pre-adolescents and adolescents with perinatal HIV infection. The goal of this analysis is to describe the HIV disease status and immune function of children with perinatal HIV infection in the AMP cohort at study entry and to relate these findings to their previous treatment and medical history. We hypothesize that children in more recent birth cohorts will have improved outcomes because of earlier access to advances in ART.

Methods

We conducted the study at 15 sites in the U.S., including Puerto Rico, with enrollment occurring between March 2007 and December 2009. Children with perinatally-acquired HIV were eligible if they were born to an HIV-infected mother, were between 7 and 16 years of age, and had either: (1) been previously enrolled in an approved longitudinal cohort study or (2) medical record documentation since birth of their medical history, including ART use, plasma HIV RNA concentrations (viral loads), and lymphocyte subsets. This age range was chosen to allow us to observe the children as they progressed through adolescence. Approved cohort studies included the International Maternal Pediatric Adolescent AIDS Clinical Trials protocols 219 and 219C¹⁴, which were earlier prospective studies designed to

evaluate the long-term effects of HIV infection and *in utero* and postnatal exposure to ART, and the Women and Infants Transmission Study¹⁵, a longitudinal study of HIV-infected pregnant women and their infants. The protocol was approved by the institutional review board (IRB) of each participating site and the Harvard School of Public Health. Written informed consent was obtained from each child's parent or legal guardian. Assent was obtained from child participants according to local IRB guidelines.

This analysis utilized data collected at the entry study visit, including sociodemographic and clinical characteristics, and historical data. Race and ethnicity were reported by the parent or guardian. The history of ART use, HIV viral loads, lymphocyte subsets, and the CDC clinical classification¹⁶ were abstracted from medical records and obtained from databases of prior studies. We utilized CD4+ T cell percentages (CD4%) since normal values vary less by age in young children than do normal absolute CD4+ cell count values.¹⁷ Since many viral load results were obtained prior to the availability of ultrasensitive RNA assays, we used a viral load 400 copies/mL to indicate viral suppression. An ART regimen change was defined as a change in one or more drugs. HAART was defined as the concomitant use of at least three drugs from at least two classes of antiretroviral (ARV) drugs. ARV classes were: nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, integrase inhibitors, and entry inhibitors (CCR5 antagonists).

We divided the study population into four birth cohorts (1991–1993, 1994–1995, 1996–1997, 1998–2002) which correspond to changes in the availability and use of ARV drugs over time. We compared entry characteristics across birth cohorts using the Kruskal-Wallis test for continuous characteristics, the Cochran-Armitage trend test for binomial proportions, and the Chi-Square test for multi-category characteristics. To assess differences in CD4% over time between birth cohorts, we fit a linear mixed effects model with CD4% at time *t* as the outcome and birth cohort as the independent variable. We assumed a constant difference over time between birth cohorts.

To identify independent predictors of the CD4% at study entry, we fit univariable linear regression models with the following variables: birth cohort, age at entry, gender, race, ethnicity, CDC clinical classification at entry, viral load at entry, nadir CD4%, peak viral load, age at ART initiation, use of HAART as first regimen, use of HAART at entry, number of ART regimens used prior to entry, and total duration of ART. To identify independent predictors of a detectable viral load (>400 RNA copies/mL) at entry, we conducted a similar analyses using logistic regression but excluded viral load at entry and nadir CD4%. We included variables of clinical interest and those associated with CD4% at entry or detectable viral load at entry with a log-likelihood *p*-value ≤ 0.10 in final multivariable linear or logistic regression models respectively. Among collinear univariable predictors, we chose one to be included in multivariable analyses based on univariable effect sizes. We conducted analyses using SAS version 9.2 (SAS Institute, Cary, NC).

Results

The study population comprised all 451 HIV-infected children enrolled in the AMP. Their median age at entry was 12.2 years, 53% were female, 70% were African American, and 24% Hispanic (Table 1). Twenty-four percent of the subjects had a prior AIDS-defining condition (CDC Class C). Their median CD4% at entry was 33% and 78% had a CD4% ≥ 25%. The majority (68%) had a viral load ≤ 400 copies/mL. The most common regimen at entry was PI-containing HAART (70%) followed by NNRTI-containing HAART (16%). Their median duration of ART was 11.4 years with a median lifetime use of seven individual ARV drugs and five different regimens. (Table 1)

The ART the subjects received prior to 1994 consisted principally of one or two NRTI agents (Figure 1). Since 1997, HAART has predominated, with PI-containing HAART being the most common regimen since 1998. Between 1999 and 2006, HAART containing both a PI and an NNRTI was the second most common regimen. In 2006, it was replaced by NNRTI-containing HAART. Among the NRTIs, zidovudine use peaked in 1997 when it was taken by 54% of subjects; its use has fallen since, being taken by 36% of subjects in 2008. (see Supplement Digital Content 1, Figure 3) Likewise, the proportion of subjects receiving didanosine peaked at 50% in 1996 and fell to 23% by 2008. The most commonly used NRTIs since 1998 are lamivudine and stavudine, although the use of stavudine decreased from 58% of subjects in 2002 to 27% in 2008. Use of abacavir, tenofovir, and emtricitabine has increased since 2000, being taken by 32%, 25%, and 22% of subjects in 2008, respectively. Among the NNRTIs, use of nevirapine peaked in 2000 at 22% of subjects and fell to 8% in 2008, while use of efavirenz has increased, peaking at 21% in 2008. (see Supplement Digital Content 2, Figure 4) Nelfinavir was the most frequently used PI between 1997 and 2003; its use peaked at 42% of subjects in 2000 and fell to 15% in 2008. (see Supplement Digital Content 3, Figure 5) Since 2004, lopinavir/ritonavir has been the most frequently used PI and its use has increased over time, rising to 44% in 2008. Use of ritonavir as a single PI peaked in 1998 at 19% of subjects. Use of atazanavir has increased since 2003 and was used by 14% of subjects in 2008. Other PIs were taken by no more than 5% of subjects in 2008.

Entry demographic and clinical characteristics by birth cohort are presented in Table 1. The nadir and entry median CD4% were significantly higher among the more recent birth cohorts. The nadir CD4% for all subjects occurred at a median of 4.8 years of age and occurred at a younger age among the more recent birth cohorts. Children in the more recent birth cohorts were less likely to have an entry CD4<15%, reflecting severe immunosuppression, more likely to have an undetectable entry viral load, and less likely to have had a prior AIDS-defining condition (CDC class C events). ART was initiated at an earlier age in more recent birth cohorts, while earlier birth cohorts had significantly greater ART experience prior to study entry as measured by total duration of ART and total number of regimens.

The mean CD4% of each birth cohort by age is shown in Figure 2. The three most recent birth cohorts (1994–1995, 1996–1997 and 1998–2002) had significantly higher CD4% over time as compared to the earliest birth cohort (1991–1993). All birth cohorts demonstrate a modest ongoing decline in their mean CD4% starting between 5 and 10 years of age.

The significant predictors of CD4% at entry by univariable analyses were birth cohort, age at entry, CDC clinical classification, viral load at entry, nadir CD4%, use of HAART as the first ART regimen, use of HAART at entry, number of regimens used prior to entry, and total duration of ART. (Table 2) In multivariable analysis, however, only a suppressed viral load at entry, a higher nadir CD4%, and a younger age at initiation of ART remained as significant independent predictors of a higher CD4% at entry. (Table 2) Use of HAART at entry, fewer total ART regimens prior to entry, and a shorter total duration of ART were marginally associated with a higher CD4% at entry. The nature of the first ART regimen (HAART or not) did not independently predict entry CD4%. The mean CD4% at entry for children with a suppressed entry viral load (≤ 400 copies/mL) was 8.3 percentage points higher than the mean CD4% of children with a detectable entry viral load ($p < 0.001$). Children with a nadir CD4% $\geq 15\%$ had a significantly higher mean CD4% at entry than those with a nadir CD4% $< 15\%$. The mean CD4% at entry in those with a nadir CD4% $\geq 25\%$ was 9.5 percentage points higher than for those with a nadir CD4% $< 15\%$ ($p < 0.001$).

The significant predictors of viral load at entry by univariable analyses were birth cohort, age at entry, gender, use of HAART as the first ART regimen, use of HAART at entry, and number of regimens received prior to entry. (Table 3) In multivariable analysis, membership in an earlier birth cohort, female gender, no use of HAART at entry, and receipt of a greater number of ART regimens prior to entry remained significant independent predictors of a detectable viral load (>400 copies/mL) at entry. The recent birth cohorts (1996–2002) were more likely to have an undetectable viral load at entry compared to the 1991–1993 birth cohort, after adjustment for all univariable predictors of viral load. Receipt of HAART at entry was significantly associated with an 80% decrease in the risk of detectable entry viral load compared to not receiving HAART at entry, with similar results for PI-containing HAART and HAART without a PI (data not shown). For every one regimen increase in the total number of regimens used prior to entry, there was a 10% increase in the risk of detectable viral load at entry.

Discussion

The children we describe are the pioneering survivors among children with perinatal HIV in the US. Maternal use of ARVs during pregnancy and other interventions have made MTCT rare in the US, with fewer than 250 infants estimated to acquire perinatal HIV each year.¹⁸ Thus, the majority of children currently living with perinatal HIV in the U.S. were born prior to the implementation of effective interventions to prevent MTCT. These children have grown up during a period of expanding availability of ART and changing treatment guidelines. Many initially received single or dual NRTI therapy, now considered suboptimal therapy, which often results in incomplete suppression of viral replication and the selection of drug-resistant virus. As treatment options have expanded, many children have received multiple ART regimens.⁴ Other challenges these children have faced include a limited number of agents available in pediatric formulations and the difficulty in maintaining adherence to therapy.¹⁹

The children in this cohort benefited from these advances in therapy, surviving to late childhood or adolescence. Most received single or dual NRTI therapy until 1996 when the PIs zidovudine and zalcitabine became available. Although zidovudine use began in 1994, its use as a component of HAART was initially limited. Since 1997, most subjects have received HAART containing a PI, with a smaller proportion receiving an NNRTI or both a PI and an NNRTI. Since 2004, the fixed combination of lopinavir boosted with zidovudine has been the most commonly used PI. In 2008, 27% of subjects were receiving stavudine, a drug now recommended for use “only in special circumstances” by the US pediatric treatment guidelines.²⁰ However, it was an “alternative” regimen in the 2006 guidelines²¹ and most subjects were receiving it as part of a second ART regimen where stavudine is more likely to be used. In addition, stavudine toxicity is uncommon in children.¹⁴ Use of the newer classes of drugs, including fusion inhibitors, CCR5 antagonists, and integrase inhibitors, has been limited in children but is increasing recently. These children have had extensive ART experience, starting therapy at a median of 0.8 years of age and receiving a median of 11.4 years of therapy. Overall, they have been exposed to a median of seven different ARVs.

Despite these challenges, most of our subjects had virologic suppression (68%) and a normal CD4 percentage of $\geq 25\%$ (78%) at study entry. This is noteworthy since 24% had previously experienced an AIDS-defining condition. Among 263 children studied in 2001 by the HIV Research network (HIVRN) cohort study, which included four sites across the United States, fewer children achieved virologic suppression (43%) and more had an AIDS diagnosis (30%) at a mean of 8.5 years of age. However, children in the HIVRN cohort were more likely to have a CD4% $\geq 25\%$ (88%).²² Likewise, among 205 infected children in a Northern California cohort born between 1988 and 2001, 40% had developed an AIDS

diagnosis at a median of three years of age, compared to only 18% of those in our 1998–2002 birth cohort.²³ However, the children in our study were older at entry, and children with a prior AIDS-defining condition are less likely to survive to an older age.

The outcomes of children in the different birth cohorts differed significantly. Children in the more recent birth cohorts had a higher CD4 percentage and a greater likelihood of virologic suppression at study entry. They initiated ART at an earlier age, were more likely to have received HAART as their initial regimen, and received fewer total ART regimens. Throughout their life, they maintained a significantly higher mean CD4% than the earlier birth cohorts (Figure 2), and also had a higher nadir CD4%. All four birth cohorts demonstrate a modest fall in CD4% starting between 5 and 10 years of age. Children and adults who maintain viral suppression with HAART therapy continue to have an ongoing increase in their CD4+ T cells over at least 6 years of therapy.^{24,25} Thus, this fall in CD4% likely represents those subjects without viral suppression, who comprise one-third of subjects at entry. The improved immune and virologic status of later birth cohorts resulted in better clinical outcomes, with significantly fewer children developing AIDS (CDC Class C, $p=0.004$). A previous study found a similar rate of progression to AIDS (21%) among their latest birth cohort (1996–2001), which was significantly lower than that of their earlier birth cohorts.²³ The lower median peak viral loads observed in our earlier birth cohorts are likely because viral load testing was not generally available until 2000, when these subjects were older and already receiving ART, as reflected in their age at peak viral load and age at starting ART.

The important independent predictors of a higher CD4% at entry were a suppressed viral load at entry, a higher nadir CD4% prior to entry, and starting ART at a younger age, suggesting a benefit from starting ART at an earlier age and a higher CD4%. Several studies have shown that children initiating therapy with lower CD4 counts ultimately achieve CD4 counts that are lower than those who start therapy at higher CD4 values.^{5,6,26} In a large European study, predictors of the CD4 cell response to therapy included the baseline CD4 count, being treatment naive when starting HAART, and the CDC clinical classification.²⁷ The long-term consequences of achieving lower, albeit normal, CD4% values is unclear, although several studies suggest a continued reduction in the risk of death and progression to AIDS with further increases in the CD4 count or percentage above normal values.^{28–30} Since the goal of therapy is to maximally restore and maintain immune function, initiating therapy at a higher nadir CD4% will result in higher overall CD4 values and fewer subjects with abnormally low CD4 values. This supports the current U.S. treatment guidelines for HIV-infected children which recommend initiating therapy at higher CD4 values than previously suggested.²⁰ The association of a higher CD4% at entry with fewer ART regimens and a shorter total duration of ART suggests a lower frequency of ART-resistant virus in these subjects.

The independent predictors of a suppressed viral load at entry (≤ 400 copies/mL) were membership in a more recent birth cohort, male gender, receipt of HAART at entry, and receipt of fewer prior ART regimens. Subjects in earlier cohorts received more individual agents and regimens and commonly started therapy with a less potent regimen prior to receiving HAART, increasing the likelihood for development of drug-resistant virus. Multi-drug resistance could be one reason that 14% of subjects were not receiving HAART at entry. The association of gender with virologic response is of borderline significance but warrants further study in children. The CD4 cell response to ART is not related to gender in children⁵ and there is little evidence of an effect of gender in the CD4 or virologic response in adults.³¹ Subjects in recent birth cohorts benefited from having HAART available for initial therapy as well as access to a greater number of ARV drugs. (Figure 1) It is expected that use of HAART, rather than a less potent regimen, will result in viral suppression. Both

poor adherence to therapy and ARV drug resistance are likely to account for the association of virologic failure with a larger total number of regimens. We are currently collecting data on viral resistance testing which will clarify the impact of viral resistance on treatment failure.

A limitation of the study is that subjects whose families were willing to participate may not be representative of all children with perinatal HIV in the US. However, the study includes a large number of children from multiple sites. In addition, they were cared for by centers experienced in treating pediatric HIV and likely represent outcomes resulting from optimal care.

In conclusion, most children with perinatal HIV infection are achieving virologic suppression and normal CD4+ lymphocyte counts despite having extensive treatment experience. Children who started ART at a younger age and who had a higher nadir CD4% were more likely to achieve a higher CD4%. Likewise, viral suppression was more likely among children who were members of a recent birth cohort, who were receiving HAART, and had fewer prior ART regimens. Advances in ART for children over the past two decades have substantially improved the outcome for children with perinatally-acquired HIV infection surviving to adolescence and young adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Trends in antiretroviral therapy use from 1993–2008. HAART: highly active combination antiretroviral therapy; NRTI: nucleoside/nucleotide reverse-transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; FI: fusion inhibitor; II: integrase inhibitor; EI: entry inhibitor.

Figure 2.
Mean CD4% by age for each birth cohort and estimated difference in mean CD4% between birth cohorts.

Table 1

Characteristics of subjects by birth cohort at study entry

Characteristic	Total	Birth Cohort				p
		1991–1993	1994–1995	1996–1997	1998–2002	
N	451	104	119	92	136	-
Age (years), Median (Q1, Q3)	12.2 (9.9, 14.2)	15.0 (14.3, 15.7)	13.4 (12.6, 14.3)	11.3 (10.8, 11.9)	8.8 (8.0, 9.6)	-
Female gender, N (%)	241 (53)	49 (47)	70 (59)	47 (51)	75 (55)	0.45 ^a
Race, N (%)						
African-American	316 (70)	73 (70)	81 (68)	67 (73)	95 (70)	0.82 ^b
White	98 (22)	20 (19)	28 (24)	17 (18)	33 (24)	
Hispanic ethnicity, N (%)	109 (24)	22 (21)	35 (29)	17 (18)	35 (26)	0.29 ^b
CDC class, N (%)						
N/A	217 (48)	39 (38)	47 (40)	46 (50)	85 (63)	0.004 ^b
B	120 (27)	33 (32)	39 (33)	23 (25)	25 (18)	
C	106 (24)	28 (27)	32 (27)	22 (24)	24 (18)	
CD4 (cells/mm ³), median (Q1, Q3)	728 (530, 966)	578 (409, 773)	648 (504, 866)	763 (569, 989)	873 (666, 1122)	<0.001 ^c
CD4%, median (Q1, Q3)	33 (27, 38)	31 (22, 36)	32 (26, 38)	33 (28, 40)	34 (29, 40)	<0.001 ^c
CD4%, N (%)						
<15	22 (5)	8 (8)	8 (7)	3 (3)	3 (2)	0.008 ^b
15–24	75 (17)	28 (27)	18 (15)	12 (13)	17 (13)	
≥ 25	351 (78)	67 (65)	93 (78)	77 (84)	114 (85)	
Nadir CD4%, median (Q1, Q3)	19 (12, 25)	14 (10, 21)	17 (10, 24)	20 (14, 27)	22 (17, 27)	<0.001 ^c
Age (years) at nadir CD4%, median	4.8 (1.7, 8.6)	7.2 (3.2, 11.8)	5.3 (1.9, 10.6)	4.9 (1.4, 8.4)	2.9 (1.2, 6.9)	<0.001 ^c
Viral load ≤ 400 copies/mL, N (%)	305 (68)	62 (60)	69 (58)	70 (76)	104 (78)	<0.001 ^a

Characteristic	Total	Birth Cohort				p
		1991–1993	1994–1995	1996–1997	1998–2002	
Peak viral load (copies/mL), median (Q1, Q3)	317,000 (76,800, 750,000)	200,000 (48,500, 545,000)	205,000 (56,900, 606,000)	448,000 (135,000, 750,000)	502,000 (120,000, 750,000)	<0.001 ^c
Age at peak viral load (years), median (Q1, Q3)	2.8 (0.7, 7.2)	6.6 (4.7, 11.9)	4.2 (2.3, 9.4)	1.0 (0.4, 3.3)	0.7 (0.2, 2.6)	<0.001 ^c
ART ^d , median						
Age (years) ART initiated (Q1, Q3)	0.8 (0.3, 2.5)	1.7 (0.7, 3.2)	1.4 (0.4, 3.2)	0.4 (0.2, 1.8)	0.4 (0.2, 1.2)	<0.001 ^c
HAART ^e as first regimen, N (%)	157 (35)	10 (10)	22 (19)	33 (36)	92 (69)	<0.001 ^a
Total duration on ART (years) (Q1, Q3)	11.4 (9.1, 13.2)	13.5 (11.9, 15.6)	12.8 (10.9, 14.1)	11.9 (10.3, 12.7)	9.1 (7.9, 10.1)	<0.001 ^c
Total # of regimens	5 (3, 7)	6 (4, 9)	6 (4, 7)	4 (3, 7)	4 (2, 5)	<0.001 ^c
Total # of HAART ^e regimens	3 (2, 5)	3 (2, 5)	3 (2, 5)	3 (2, 5)	3 (2, 4)	0.15 ^c
Total # of ART agents	7 (5, 9)	8 (6, 11)	7 (6, 10)	7 (5, 8)	6 (4, 7)	<0.001 ^c

^a Cochran-Armitage p-value

^b Chi-square p-value

^c Kruskal-Wallis p-value

^d Antiretroviral therapy

^e Highly active antiretroviral therapy

Table 2

Univariable and Multivariable Predictors of CD4% at Entry

Characteristic	Difference in CD4 % (95% CI)	<i>p</i>	Adjusted Difference in CD4 % (95% CI)	<i>p</i>
Birth cohort				
1991–1993	Referent		Referent	
1994–1995	2.5 (−0.1, 5.1)	<0.001	1.2 (−1.0, 3.4)	0.25
1996–1997	4.7 (1.9, 7.4)		0.1 (−2.4, 2.6)	
1998–2002	5.2 (2.7, 7.7)		−1.5 (−4.6, 1.6)	
Age at entry	−0.8 (−1.1, −0.4)	<0.001	--	--
Gender				
Male	−0.04 (−1.9, 1.8)	0.96	--	--
Female	Referent			
Race				
White/Other	Referent	0.30	--	--
African-American	−1.2 (−3.3, 1.0)			
Ethnicity				
Hispanic	−0.8 (−3.0, 1.3)	0.45	--	--
Not Hispanic	Referent			
CDC class at entry				
Not C	Referent	<0.001	Referent	0.72
C	−3.7 (−5.8, −1.5)		−0.3 (−2.2, 1.5)	
Viral load at entry				
≤ 400 copies/mL	9.4 (7.6, 11.2)	<0.001	8.3 (6.5, 10.0)	<0.001
> 400 copies/mL	Referent		Referent	
Nadir CD4%				
< 15%	Referent	<0.001	Referent	<0.001
15–24%	4.3 (2.3, 6.2)		3.3 (1.4, 5.2)	
≥ 25%	10.8 (8.6, 13.0)		9.5 (7.4, 11.6)	
Peak viral load (copies/mL)				
<10,000	2.6 (−1.6, 6.8)	0.37	--	--
10,000–100,000	−0.6 (−2.9, 1.6)			
≥ 100,000	Referent			
Age at ART initiation ^{a,b}	−0.3 (−0.7, 0.1)	0.17	−0.6 (−1.1, −0.1)	0.01
First regimen ^{b,c}				
HAART	2.2 (0.2, 4.1)	0.03	0.4 (−1.7, 2.4)	0.73
Not HAART	Referent		Referent	

Characteristic	Difference in CD4 % (95% CI)	<i>p</i>	Adjusted Difference in CD4 % (95% CI)	<i>p</i>
ART use at entry ^{a,c}				
HAART	4.5 (1.9, 7.1)	<0.001	2.2 (−0.1, 4.6)	0.06
Not HAART	Referent		Referent	
Total # of regimens	−0.8 (−1.0, −0.5)	<0.001	−0.3 (−0.5, 0.0)	0.05
Total duration on ART ^a				
< 10 years	2.2 (0.3, 4.1)	0.03	2.3 (0.0, 4.6)	0.05
≥ 10 years	Referent		Referent	

^a ART: antiretroviral therapy

^b Note: The 4 children who never initiated ART were excluded when evaluating this association.

^c HAART: highly active antiretroviral therapy

Table 3

Univariable and Multivariable Predictors of a Detectable Viral Load (>400 copies/mL) at Entry

Characteristic	Odds Ratio (95% CI)	<i>p</i>	Adjusted Odds Ratio (95% CI)	<i>p</i>
Birth cohort				
1991–1993	Referent	<0.001	Referent	0.02
1994–1995	1.1 (0.6, 1.9)		1.2 (0.7, 2.2)	
1996–1997	0.5 (0.3, 0.9)		0.5 (0.2, 1.0)	
1998–2002	0.4 (0.2, 0.8)		0.5 (0.2, 1.1)	
Age at entry	1.1 (1.1, 1.2)	<0.001	--	--
Gender				
Male	0.6 (0.4, 1.0)	0.03	0.6 (0.4, 1.0)	0.04
Female	Referent		Referent	
Race				
White/Other	Referent	0.36	--	--
African-American	1.2 (0.8, 2.0)			
Ethnicity				
Hispanic	1.0 (0.6, 1.5)	0.88	--	--
Not Hispanic	Referent			
CDC class at entry				
Not C	Referent	0.47	--	--
C	1.2 (0.7, 1.9)			
Peak viral load (copies/mL)				
<10,000	1.0 (0.4, 2.5)	0.57	--	--
10,000–100,000	1.3 (0.8, 2.1)			
≥ 100,000	Referent			
Age at ART initiation ^{a,b}	1.0 (0.9, 1.1)	0.93	1.0 (0.9, 1.1)	0.82
First regimen ^{b,c}				
HAART	0.6 (0.4, 1.0)	0.03	1.4 (0.7, 2.6)	0.32
Not HAART	Referent		Referent	
ART use at entry ^{a,c}				
HAART	0.2 (0.1, 0.4)	<0.001	0.2 (0.1, 0.4)	<0.001
Not HAART	Referent		Referent	
Total # of regimens	1.1 (1.1, 1.2)	<0.001	1.1 (1.1, 1.2)	<0.001
Total duration on ART ^a				
< 10 years	0.7 (0.5, 1.1)	0.17	--	--
≥ 10 years	Referent			

^a ART: antiretroviral therapy

^b Note: The 4 children who never initiated ART were excluded when evaluating this association.

^c HAART: highly active antiretroviral therapy