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Timing of Antiretroviral Therapy Initiation and its Impact on Disease Progression in Perinatal Human Immunodeficiency Virus-1 Infection

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Abstract

Objective—Treatment with highly active antiretroviral therapy (HAART) reduces overall perinatal HIV-1 related mortality. The impact of timing of HAART initiation on reduction of morbidity is not well-defined. We evaluated the association of timing of HAART initiation on progression to moderate or severe disease.

Methods—Retrospective, population-based study of 196 perinatally HIV-infected children followed from birth in northern California from 1988 to 2009.

Results—Of 196 children, 58% received HAART and were followed for a median of 6.2 years after HAART initiation. HAART use was associated with improved survival to age 5 years: 50% no HAART vs. 88% HAART, $p < 0.0001$. However, the advantage of initial HAART over mono or dual therapy transitioning to HAART was small and not statistically significant ($p = 0.23$). Starting HAART before the development of moderate or severe disease delayed the median age of diagnosis of moderate disease from 0.4 years (IQR [0.3–0.8]) without HAART to 3.0 years (IQR 1.9–5.8], $p < .0001$) with HAART. HAART initiation after progression to moderate or severe disease was associated with decreased progression to severe disease or death, respectively (moderate to severe: 8% (3/36) HAART vs. 84% (70/83) no HAART, $p < 0.0001$; severe to death: 9% (6/68) HAART vs. 73% (49/67) no HAART, $p < 0.0001$).

Conclusion—In perinatal HIV infection, HAART is associated with delayed progression and reduced mortality regardless of disease severity at HAART initiation. This finding reinforces U.S. guidelines regarding HAART initiation at >1 year of age if children present with most clinical category B diagnoses, regardless of CD4 measurements or plasma HIV RNA level.

Keywords

perinatal; HIV-1; highly active antiretroviral therapy (HAART); timing of onset

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Introduction

Early highly active antiretroviral therapy (HAART) for children with perinatal human immunodeficiency virus (HIV) infection decreases mortality and progression to Centers for Disease Control (CDC) category C disease^{1, 2, 3}. Current U.S. and World Health Organization (WHO) guidelines recommend HAART initiation in HIV-infected children younger than 12 and 24 months^{4, 5}, but due to lack of evidence about the role of HAART in asymptomatic older children, recommendations regarding when to initiate HAART in children >1 year of age vary by organization. Hospital-based surveillance data suggest that more than half of perinatal transmissions are associated with neglected HIV prevention measures⁶, which might lead to delays in HIV-1 diagnosis and HAART initiation. In resource-poor settings, many children present to medical attention after the time recommended for early HAART initiation⁴; moreover, because of insufficient resources, only 36% of children worldwide receive appropriate HAART⁴.

Before the HAART era, approximately 10–20% of children with perinatal HIV developed profound early immunosuppression and severe clinical disease in the first 12 months of life^{7–10}. Although it is not clinically possible to predict which children will be “rapid progressors” during infancy, it is important to balance the timing of later progression of HIV disease with the complications of lifelong HAART: long term side-effects, development of resistance, and lack of evidence about HAART’s long-term durability in the pediatric population.

After 1 year of age, current U.S. guidelines recommend initiation of HAART for children with significant symptoms (CDC clinical category C or most category B conditions) regardless of CD4 percentage/count or plasma HIV RNA level⁵. HAART initiation is also recommended for children who meet age-specific immunologic criteria⁵. Reduced mortality from opportunistic infections has been documented in the HAART era¹¹ as well as a reduced frequency of specific category B/C clinical diagnoses among HIV-infected children^{12–14}. HAART use in HIV-infected infants in the first 12 weeks of life while CD4 lymphocyte percentages are greater than 25 percent has been shown to decrease infant mortality¹. However, to our knowledge, the impact of the timing of HAART initiation at specific clinical and immunologic stages on disease progression has not been well-defined.

Since the prevalence of perinatal HIV-infection in the U.S. is low, well-powered domestic clinical trials are difficult to conduct and longitudinal, population-based studies are used to evaluate the timing and complications of long-term HAART use. The CDC has called for perinatal HIV surveillance as a component of a comprehensive HIV prevention strategy¹⁵. We previously published data from a cohort of perinatally infected children born from 1988–2000, who were followed to 3 years of age. We showed that very early treatment with any antiretrovirals improved outcomes and that HAART was associated with decreased HIV progression to clinical category C diagnoses and death in the first 3 years of life². In the current study, we evaluate the impact of HAART on progression to moderate disease, as well as to severe disease or death and extend our observations to children born between 1988–2008, followed through 2009.

Methods

Study Design

The study population was identified through Stanford University’s Pediatric Spectrum of Disease (PSD) surveillance project, as previously described². PSD was a longitudinal, multi-center pediatric HIV surveillance study which concluded in 2009, involving the major referral hospitals in Northern California with pediatric HIV clinics. It followed all children

born to known HIV positive mothers and all children later identified as HIV infected. The surveillance area comprises 12 counties in Northern California, with a total population of approximately 10 million. A single study nurse visited each study site in six month intervals to collect, from medical records, initial information on newly identified children and updated information on previously identified children. Race/ethnicity was defined by the participants.

To maintain confidentiality and prevent duplication of records, each patient was assigned an anonymous unique identifier with which s/he was entered into a standardized database. The study was approved yearly at Stanford University and the Institutional Review Board at each surveillance hospital.

Subjects

Children were included in the current study if they had perinatal HIV infection, were born during 1988–2008, and followed at a surveillance hospital from: (i) age ≤ 14 months if they were US born; or (ii) age ≤ 6 months if they were born outside the US. This distinction ensures that foreign-born children received early medical care equivalent to US-born infants. Children lost to follow-up at age < 2 months or within 1 month of their initial HIV evaluation were excluded from the study. The study children were followed until their End of Follow-Up (EFU) due to death, transition to adult HIV care, or lapse in care of > 18 months. When children were not seen in clinic for > 18 months their EFU was at their last visit before treatment lapse, even if they later returned to care.

We grouped patients, according to their date of birth, in three cohorts reflecting major temporal changes in the guidelines for the management of pediatric HIV: early — 1988–1991; intermediate — 1992–1995; and late — 1996–2008. The early cohort represents a period characterized by delayed HIV-1 diagnoses and lack of effective antiretrovirals. The intermediate cohort represents improved HIV-1 identification and treatment: the 1990 FDA's approval of zidovudine, the 1992 guidelines recommending prophylaxis for *Pneumocystis jiroveci* pneumonia^{16, 17}, the advent of the PACTG 076 trial¹⁸. The late cohort represents the effects of the 1995 recommendations for prenatal HIV-1 testing, the 1996 introduction of the protease inhibitor, and the advent of HAART^{19, 20}.

Disease Progression

Moderate and severe immune suppression, as well as category B and C diagnoses were defined according to the CDC 1994 and 2008 Revised Classification System for children < 13 and 13–18, respectively^{21, 22}. One exception was that children who had multiple clinical diagnoses of severe bacterial infections were considered to have a category C diagnosis in the absence of culture data. Children who had mild immunosuppression and at most a clinical category A diagnosis were referred to as having mild disease. Children who had either moderate/severe immunosuppression or a clinical category B/C diagnosis were referred to as having a moderate or severe disease, respectively. Progression was defined as a more advanced disease stage after baseline evaluation. The baseline disease status could be mild, moderate, or severe, and children could progress directly from mild to severe disease²³.

Use of Antiretrovirals

All FDA approved antiretroviral agents prescribed by the treating physician, except those for prophylaxis of mother-to-child transmission not continued beyond 6 weeks of life, were considered in the study. These drugs are classified as: Protease Inhibitor (PI), Non-nucleoside Reverse Transcriptase Inhibitors, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI), Integrase Inhibitors, and Fusion Inhibitors. HAART was defined as at

least 3 antiretrovirals of two classes⁵. Regimens with 3–4 NRTIs were considered dual therapy. Ritonavir, when used in combination with other PIs for pharmacologic boosting, was not considered as an individual agent. Throughout the study three categories of antiretroviral regimens (ARVs) were considered: none, mono or dual (M/D) and HAART. In the analysis, an ARV was considered to be in use at a particular date if it had been given continuously during the month prior to that date. One month was chosen to allow sufficient time for therapeutic onset, as previously described².

Statistical Analysis

The main outcomes were: 'percent of' and 'age at' EFU, progression to moderate/severe disease or death (Events). These were analyzed relative to birth cohort and administered ARVs. Unless otherwise specified, discrete variables were compared with the 2-sided Fisher's exact test; continuous variables with the Kruskal-Wallis test. Kaplan Meier curves describe 'Time to Events'; event-free survival among groups was compared with the log-rank test. Throughout the manuscript, age, time between disease stages and time from treatment to disease progression, are presented in years as medians with the associated interquartile range: Median (25%-75%). The analysis was performed using SAS 9.2 (SAS Institute Inc, Cary NC). P-value<0.05 was considered statistically significant.

Results

Study Population

One hundred ninety-six infants with perinatal HIV infection are included in the analysis. HIV testing was done in the first month of life for 51% (99/196), and before the age of 4 months for an additional 24% (49/196). Sixty (31%) of the 196 children died of HIV-related causes. More than half of the surviving 136 children were still followed in participating clinics at study completion and 35% of the censored children returned to care (Table 1). Of the 43 participants who did not return to care, 22/43(51%) had documented transitions in care (Table 1). Since the survival of the 17 who moved from the study area cannot be confirmed, the 38/196(19%) remaining children represent the true rate of loss-to-follow up.

The median age at HIV-related death of children in the study was 1.9 (1.0–3.4) years; the children who remained in care to the study completion were followed for 12.6 (7.5–15.6) years (Table 1). More than half of the children who were lost to follow-up remained in care for more than 6 years (Table 1); those children who later returned to care were followed to 10.2 (5.3–14.2) years of age.

As expected, the risk of death decreased significantly in the later birth cohorts (Table 2, Figure 1a). While the probability that children in the early cohort would survive to age 5 was 47%, it increased to 66% and 98% in the intermediate and late cohorts respectively. If children survived the first 5 years, their subsequent risk of death was low: 14% (4/28), 0% (0/36), and 0% (0/26) in the early, intermediate and late cohorts, respectively. None of the children died at age>9 years, although they were followed to maximum ages of 19, 17, and 13 years in the early-late cohorts, respectively.

Of note, morbidity also declined across cohorts, with the percentage of children progressing to CDC clinical category C diagnoses declining from 70% in the early cohort to 38% in the late cohort ($p<0.005$, Table 2). The progression of 191/196 children, for which baseline information was available, from baseline to EFU through various disease stages is presented in Figure 2.

Association of HAART Initiation and Overall Mortality

Of the 196 children in the study, 113 (58%) received HAART: 84% were followed for more than 1 year and half for at least 6.2 years after HAART initiation. In children followed to age 5 years, survival was 88% with HAART vs. 50% without HAART, $p<0.0001$. None of the 21 children who initiated HAART at age<4 months died; half of these children were followed for more than 4.5 years and up to 11 years. In comparison, the probability of surviving to 4.5 years without HAART was only 62% ($p=0.004$, log-rank test). Notably, HAART initiation, compared to no HAART, was associated with reduced mortality even after subjects had already progressed to moderate or severe disease (Figures 3b & 3c, $p<0.0001$).

HAART Initiated Before Moderate or Severe Disease

HAART use was associated with a delayed time and reduced proportion of children progressing to moderate disease (Figure 1c). Among the 131 children with documented clinical/immunological data prior to severe disease: 62% (13/21) of children treated with HAART progressed to moderate disease compared to 97% (107/110) of children who did not receive HAART ($p<0.0001$). HAART compared to no HAART also delayed the age at progression to moderate disease from 0.4 (0.3–0.8) years to 3.0 (1.9–5.8) years ($p=0.0001$). Similarly, in children with mild disease at baseline, HAART use was associated with reduced and delayed progression to moderate disease by approximately 3 years, but >50% of these children still progressed to moderate disease (Figure 3a).

In addition to reducing and delaying progression to moderate disease, children who received HAART demonstrated progression to moderate disease primarily as laboratory-based immunosuppression rather than clinical disease. Of the children receiving HAART: 77% (10/13) progressed via immunosuppression, 62% were never diagnosed with a clinical category B condition, and none ever had a clinical category C condition. Of children who did not receive HAART: only 44%, (47/107) progressed via immunosuppression, most (86%) had a clinical category B condition and 47% had later a clinical category C condition ($p=0.001$).

HAART Initiated after Moderate Disease and before Severe Disease

HAART use after progression to moderate disease was associated with a decreased proportion of children progressing to severe disease and death. Only 8% (3/36) of children who received HAART after the onset of moderate disease progressed to severe disease, and none died (Figure 3b). In comparison, 84% (70/83) of children who did not receive HAART after progressing to moderate disease progressed to severe disease and 4% (3/83) died without progressing to severe disease (Figure 3b, $p<0.0001$).

HAART initiated even after development of a clinical category B diagnosis was associated with reduced further progression. There were 88 children who had a clinical category B diagnosis before progressing to severe disease, 22 (25%) of whom started HAART. These children were followed for a median of 5.4 (1.8–9.1) and up to 10.9 years after HAART initiation, with only 3 (14%) progressing to severe disease. Of note, only 2 children, both of whom started HAART more than 2 months after their category B diagnosis, developed a clinical category C diagnosis. In contrast, of the 66 (75%) children who did not receive HAART after a clinical category B diagnosis, 54 (82%) progressed to category C diagnosis within 0.8 (0.2–1.5) years. The 12 without further progression were followed for 1.0 (0.4–2.7) and up to 15.2 years.

HAART Initiated After Severe Disease

HAART initiation among children who progressed to severe disease was associated with increased survival: 91% (62/68) survived who received HAART compared to 27% (18/67) who did not receive HAART ($p<0.0001$, Figure 3c). HAART administration was not associated with delaying death after identification of severe disease ($p=0.15$).

While receipt of HAART improved survival after progression to severe disease, 13 children treated only with M/D remained alive through a median follow-up of 4.1 years (2.6–6.0) after progressing to severe disease to a median age of 5.4 years (3.8–7.3) (Figure 3c). Moreover, 76% (47/62) of the children who survived with HAART were treated with M/D for up to 12.7 years after progression to severe disease and before transitioning to HAART; 14 (30%) of these children were treated with M/D for more than 5 years before starting HAART. There were 65 children in the study who had severe disease at initial evaluation (62 at baseline, 3 after ARV); all had progressed to severe disease by 22 months of age, with 75% progressing by 6 months. Survival with vs. without HAART by cohort was: early cohort - 100% (3/3) vs. 17% (4/24), intermediate cohort - 70% (7/10) vs. 21% (3/14), late cohort - 93% (13/14) vs. 0/0.

Discussion

This study demonstrates the effect of the timing of HAART initiation on progression to all stages of CDC-defined perinatal HIV infection within a US-based longitudinal cohort. We found that HAART was associated with reduced and delayed clinical and immunologic progression regardless of disease stage at initiation. The effect of HAART in preventing progression to clinical category C and death in children younger than 3 years of age has been previously demonstrated by our study group²; others have demonstrated HAART-related declines in morbidity and mortality for the treatment of perinatal HIV-1 infection^{1, 24, 25}. In this study we demonstrated that a reduction in disease progression and mortality occurred regardless of the disease stage at HAART initiation.

A prospective randomized controlled trial in South Africa reported a 76% decrease in death or pre-defined clinical or immunologic failure when HAART was initiated in the first 12 weeks of life, compared to children who received HAART after their CD4 percent decreased to <20% or specific clinical criteria were met¹. While not prospective, we describe a wider range of ages and immunologic stages at HAART initiation and still clearly demonstrate the benefit of HAART even after progression to moderate disease, both in decreasing death and progression to severe disease. This benefit persisted through a median 6.2 years of longitudinal post-HAART follow-up. Other differences in the studies may be related to differences in secondary factors related to nutrition and endemic diseases.

Progression to moderate disease was associated primarily with laboratory rather than clinical disease progression. However, even with HAART initiation, more than half of the children progressed to moderate disease although progression was reduced and delayed by about 3 years. Although HAART did not prevent progression to moderate disease, HAART initiation before clinical or immunologic progression was associated with a significant reduction in progression to moderate disease.

With 22 years of longitudinal patient follow-up, our study is among those with the longest published follow-up of children with perinatal HIV infection^{24, 26–28}. In our study children were followed for up to 14 years (the maximum possible) after HAART administration, half of them for more than 6.2 years after HAART initiation. We report HAART's durable survival effect, even when started after progression to severe disease. All the children who died despite receiving HAART either stopped HAART or delayed HAART initiation until

1.5–3.5 years after progression to severe disease. This highlights the importance of timely HAART initiation after progression to severe disease.

Although prospective, our study was not randomized and data collection was limited to information documented by providers at the participating facilities. Incomplete capture of perinatally infected children may also have biased outcomes. However, we previously demonstrated the high capture rate in our population-based study, thus reducing recruitment bias²⁹. To standardize data collection, one individual extracted data from patient records during the entire study period in all the participating facilities. Our data are limited by 19% loss to follow-up in the earlier birth cohorts, however this rate is lower than was reported in other observational studies of perinatal HIV^{12,30}. Also, more than half of the loss to follow-up occurred after 6 years of age, and those children who were lost to follow-up and then returned to care were followed to median age of 10.2 (5.3–14.2) years.

Current US guidelines suggest HAART initiation at >1 year of age if children present with most clinical category B diagnoses, regardless of CD4 measurements or viral load. Our findings support this recommendation by showing that HAART initiation even after progression to moderate disease is associated with a dramatic reduction of progression to severe disease and death. Current recommendations also suggest that treatment can be considered for children ≥1 year of age with no/mild symptoms, plasma HIV RNA <100,000 copies/mL, and no evidence of laboratory-based immunosuppression. Our study suggests that it may be reasonable to perform watchful waiting in children older than 12 months who have access to close medical follow-up and present to care without evidence of clinical category B diagnoses or laboratory-based immunosuppression. Further studies are needed to confirm these findings.

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Drs. Sturt, Halpern, and Maldonado were responsible for manuscript drafting, data analysis and interpretation. Dr. Halpern was responsible for statistical analysis. Dr. Maldonado was responsible for study conception and design and obtaining funding. Dr. Halpern had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Barbara Sullivan, RN was responsible for data collection.

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Figure 1. Event-Free Survival of 196 Perinatally HIV-Infected Children Followed from Infancy
 Figure 1a: Survival by Birth Cohort

Figure 1b: Survival by ARVs Administered before the End of Follow-up

Figure 1c: Moderate Disease-Free Survival by ARVs Administered before Progression to Moderate Disease or End of Follow-up*

ARV= antiretroviral medications used for treatment, M/D= mono or dual therapy, HAART= highly active antiretroviral therapy

*Only includes 131 children who did not progress directly to severe disease

Figure 2. Disease Progression of Study Children with Known Baseline

Progression from baseline (mild, moderate, or severe disease), through moderate and/or severe disease, to the end of follow-up (status: alive or dead).

Age - age, in years, at the indicated stage of disease progression: median (25%-75%).

Baseline - disease progression at the 1st visit after HIV evaluation.

* For 5 children the baseline disease stage could not be determined. All started AZT before progression to moderate/severe disease and received HAART by 10 months of age. Disease progression in these children was: 3- severe, 1- moderate, 1 - mild. All were alive at end of follow-up at ages 2, 4.5, 8.7, 17.4 & 18.2 years.

Figure 3. Disease Progression Following Administration of Antiretrovirals

Figure 3a: Progression from Mild Disease, by the Most Advanced ARV Administered before Progression to Moderate/Severe Disease or End of Follow-Up.

Figure 3b: Progression from Moderate Disease, by the Most Advanced ARV Administered before Progression to Severe Disease or End of Follow-Up.

Figure 3c: Progression from Severe Disease, by the Most Advanced ARV Administered before Progression to End of Follow-Up.

Age - age, in years, at the indicated stage of disease progression: Median (25%-75%). Status at End of Follow-up: Dead or Alive.

* 119: 54 progressed from mild; 62 had moderate disease at baseline; 4 baseline could not be determined. In addition, 1 child who had no ARV died 1 day after being diagnosed with bacterial sepsis at age 4 months (progression from mild).

** 135: 32 progressed from mild through moderate; 3 progressed directly from mild; 35 progressed from baseline moderate; 62 at baseline; 3 baseline could not be determined.

† One child progressed by immune suppression only; two children had clinical category C conditions.

†† The child was diagnosed with bacterial pneumonia at his last follow-up visit. He returned to care after a lapse of 2 years and was further followed (alive) to age 5.3 years.

^Four children stopped ARV for more than one month before death.

^^Two children stopped HAART before death.

Table 1
Status at EFU of 196 Perinatally HIV-infected Children Followed from Infancy

	Followed at Study Completion	Censored Before Study Completion		Died, HIV-related
		LTFU	Returned to Care After >18m Lapse	
All Study Subjects	70 (36%)	43 ^a (22%)	23 ^b (12%)	60 (31%)
Birth Cohorts				
1	10 (14%)	16 (37%)	4 (17%)	36 (60%)
2	27 (39%)	16 (37%)	8 (35%)	23 (38%)
3	33 (47%)	11 (26%)	11 (48%)	1 (2%)
Age at EFU	12.6 (7.5–15.6)	6.0 (1.5–11.1)	3.0 (1.6–7.3)	1.9 (1.0–3.4)
Disease Progression at EFU				
Moderate	24 (34%)	13 (30%)	6 (26%)	7 (7%)
Severe	43 (61%)	29 (67%)	10 (44%)	56 (93%)
ARV at EFU				
None	4 (6%)	8 (19%)	8 (35%)	15 (25%)
M/D	6 (9%)	15 (35%)	5 (22%)	41 (68%)
HAART	60 (86%)	20 (47%)	10 (43%)	4 (7%)

Since not all children received antiretrovirals, not all columns add to 100 percent.

Abbreviations: ARV= antiretrovirals used for treatment, EFU= End of Follow-Up, LTFU= Lost to Follow-Up, M/D= mono or dual therapy, HAART= highly active antiretroviral therapy, m= months, y= years

^a 17 moved from study area, 3 transferred to other clinics, 1 transferred to adult care, 1 died of child abuse, 21 LTFU

^b 1 died from HIV-related conditions 5.6 years after leaving care (age 9.5 years). Ten are still followed in participating clinics.

Table 2
Demographics, Antiretroviral Use, Progression, and Survival of 196 Perinatally HIV-infected Children Followed from Infancy

Characteristic	N (%) ^c	% ^d with Early ^e ARV	First ARV			Most Advanced ARV ^a				Outcome		Age at End of Follow-Up (y) ^b	
			Age at 1 st ARV(m) ^b	% ^d M/D	% ^d HAART	% ^d M/D	% ^d HAART	% ^d With Cdx	% ^d Died	Dead	Alive		
All	196	16%	6 (3–12)	76%	15%	33%	58%	54%	31%	1.9 (1.0–3.4)	9.2 (3.3–14.1)		
Demographics													
Gender													
Male	88 (45%)	9% ¹	6 (3–11)	77%	16%	36%	56%	55%	27%	1.9 (1.3–3.3)	8.9 (3.0–14.3)		
Female	108 (55%)	22%	5 (2–13)	74%	14%	30%	58%	53%	33%	1.7 (0.8–3.4)	9.2 (3.4–13.0)		
Race													
White	57 (29%)	18%	5 (3–12)	79%	16%	39%	56%	63%	39%	2.5 (1.2–3.2)	10.7 (3.8–12.9)		
Black	82 (42%)	16%	7 (3–13)	74%	16%	28%	62%	51%	24%	2.1 (1.0–4.1)	9.6 (3.0–14.2)		
Hispanic	45 (23%)	13%	5 (3–9)	69%	13%	31%	51%	51%	33%	1.2 (0.7–2.3)	5.7 (1.6–13.2)		
Other	12 (6%)	25%	6 (2–13)	92%	8%	42%	58%	33%	25%	1.5, 1.8, 2.1	6.0 (4.4–12.2)		
Cohort													
1988–1991	66 (34%)	5% ²	10 (6–18) ²	82% ²	0% ²	50% ²	32% ²	70% ³	56% ²	2.1 (1.1–3.9)	16.8 (7.2–18.1) ²		
1991–1995	74 (38%)	11%	6 (3–11)	89%	3%	38%	54%	51%	31%	1.8 (0.7–2.7)	12.6 (3.8–14.2)		
1996–2008	56 (29%)	38%	3 (0–6)	50%	48%	5%	93%	38%	2%	0.6	4.6 (2.5–10.7)		
ARV regimen													
None	19 (10%) ^f	----	----	----	----	----	----	53%	53%	0.5 (0.4–1.0)	1.5 (1.2–1.8)		
First ARV													
M/D	148 (76%)	19%	6 (3–12)	100%	0%	43%	57%	57%	32% ¹	2.3 (1.5–3.9)	12.3 (5.3–15.2) ²		
HAART	29 (16%)	15%	4 (2–13)	0%	100%	0%	100%	38%	7%	0.6, 2.7	4.4 (1.8–8.5)		
Most Advanced ARV^a													
M/D	64 (33%)	12% ³	8 (3–12)	100%	0%	100%	0%	69% ³	69% ²	2.0 (1.4–3.5)	4.0 (1.4–7.3) ³		
HAART	113 (58%)	25%	5 (2–11)	74%	26%	0%	100%	45%	5%	3.9 (2.7–4.6)	11.5 (4.5–14.4)		

Since not all children received ARVs, not all columns add to 100%.

Abbreviations: ARV= antiretrovirals used for treatment, M/D= mono or dual therapy, HAART= highly active antiretroviral therapy, Cdx= CDC clinical category C disease, m= months, y= years

^aFor 87% of the records the most advanced ARV was the regimen children received at the end of follow-up (EFU). Exceptions at EFU were: 9 children transitioned from HAART to dual therapy; 16 children stopped ARV before EFU (6 M/D, 10 HAART).

^bMedian (Inter Quartile Range); Ages are given for cases where there were up to 3 children.

^cPercentage of the 196 children in the study

^dPercentage of the number of children specified by the characteristic in column 1

^eEarly Treatment – treatment started at age ≤ 61 days

^fBy cohorts: 1988–1991 – 12 children, 1992–1995 – 6 children, 1996–2008 – 1 child.

P-values for Comparison of Vertically Grouped Covariates:

- ¹ p<0.05
- ² p<0.005
- ³ p<0.0001