Antiretroviral regimen central nervous penetration, viral control, and age of attainment of developmental milestones in early treated HIV-infected infants

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2015

Committee:

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Program Authorized to Offer Degree:

Epidemiology

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Abstract

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Background: Pediatric HIV is associated with an increased risk of neurodevelopmental deficits. We hypothesized that lower cumulative viral load following early antiretroviral treatment (ART), and the use of central nervous system (CNS) penetrating antiretrovirals would improve delays in developmental milestone achievement.

Methods: We conducted a secondary data analysis of a randomized clinical trial of HIV-infected children [Optimizing Pediatric HIV-1 Therapy 03 (OPH03) NCT00428116]. Infants initiated ART and were prospectively followed with 6-monthly CD4 counts, 3-monthly viral loads and monthly assessments of developmental milestone attainment. Viremia copy years were calculated for time periods: 1) up to the earliest age of milestone attainment, 2) at 6 months of age, 3) at 6 months post-ART and 4) up to the earliest age of milestone attainment for milestones

attained in the second year of life while adjusting for viremia copy-years in the first year of life. The CNS penetration effectiveness (CPE) score of initial ART regimen was calculated after adjusting for baseline resistance. Linear regression analysis was used to evaluate the association of viremia copy-years and CPE score of initial ART regimen and age of developmental milestone attainment, adjusting for potential confounders. Logistic regression analysis was used to evaluate the association between viremia copy-years and developmental delay, adjusting for potential confounders.

Results: Among 80 infants initiating ART, median age was 3.7 months [IQR: 2.95, 4.06], 53% were female, baseline median CD4% was 18% [IQR: 14%, 24%], and baseline viral load was 6.58 $\log_{10}$ copies/ml [IQR: 5.98, 7.14]. Median WAZ was -2.35 [IQR: -3.66, -0.93] and HAZ was -1.96 [IQR -3.16, -0.91]. Forty-five (56%) of infants initiated nevirapine-based ART. Mean age in months of sitting unsupported, walking unsupported, monosyllabic speech, and pointing/naming objects and pictures were 7.24 (SD 1.34), 16.64 (SD 3.28), 17.12 (SD 3.06), and 22.78 (SD 4.53), respectively. Median adjusted CPE score of initial ART regimen was 9 [IQR: 9, 10]. There was no association between viremia copy-years and age of developmental milestone attainment using any of the defined methods of copy-year estimation. Higher CPE regimens were associated with earlier supported and unsupported walking in univariate analyses ($p=0.044$ and 0.061), respectively, but these associations were not significant in analyses adjusted for WAZ.

Conclusions: Viremia copy-years (which included time before and after ART) was not associated with developmental milestone attainment while antiretroviral CPE was associated

with earlier walking, suggesting that antiretroviral CSF penetration may be relevant in neurodevelopment. Larger studies are needed to evaluate this association.

Introduction

Children with perinatally acquired HIV infection are vulnerable to neurocognitive problems during development. HIV-associated neurocognitive disorders are thought to be due to viral replication and persistence in the CNS.[1, 2] ART results in viral suppression and immune recovery systemically; however, it remains unclear what impact ART has on CNS viral load and the development of HIV-associated neurocognitive disorders in children. The concept of 'CSF (cerebrospinal fluid) escape,' the presence of detectable viral load in the CSF despite undetectable plasma levels, has been demonstrated to be associated with the development of neurologic symptoms in patients well-controlled on ART.[3, 4] The lack of concordance between HIV-associated neurocognitive disorders and viral suppression is postulated to be due to poor CNS penetration of ART, neuronal injury from inflammatory responses and neurotoxic viral proteins, irreversible neuronal injury prior to ART, and/or neurotoxic effects of ART.[5, 6]

Studies of neurocognitive functioning in ART-treated HIV-infected children reveal lower neurocognitive scores and subtle motor deficits compared to uninfected peers or established norms.[7-12] Initiation of ART in older children does not appear to improve neurocognitive outcomes to catch up completely to expected developmental norms.[13, 14] In one study, preschool aged HIV-infected children experienced neurodevelopmental improvement after approximately one year of ART.[15] Early viral suppression in children <5 years of age is associated with improved neurodevelopment.[16] The CHER study found that infants who received ART before 3 months of age had significantly better neurodevelopmental scores compared to infants for whom ART was deferred.[17] In addition, neurodevelopmental function of infants with early ART in this study was similar to those of HIV-exposed uninfected and HIV-

unexposed infants in all domains except locomotor. A recent study of early treated infants (<5 months old) found that pre-ART low WAZ and low CD4 count correlated with later walking and monosyllabic speech attainment. In this study, infants receiving nevirapine-based regimens had later achievement of monosyllabic speech than infants receiving lopinavir-based regimens.[18] There was a trend for later speech with pre-ART HIV viral loads $>10^6$ copies/mL and 6-month HIV viral load ≥1000 copies/mL but no association between 6-month viral load and age of walking.

HIV plasma viral load has been used as a prognostic measure in clinical practice and research studies. HIV viral load is associated with HIV-related morbidity and mortality.[19, 20] Most research studies use either the peak viral load or the most recent viral load; however, cross-sectional viral load measures do not provide any information about a patient's cumulative viral burden and may under- or over-estimate viral exposure. Viremia copy-years is a measure of cumulative viral burden that estimates the area under the curve using multiple viral load measures at different time points.[21, 22] This measure of cumulative viral burden may be a more accurate measure of viral exposure in studies of the association between viral load and conditions related to systemic inflammation and immune system activation secondary to ongoing HIV replication. In fact, studies in adults have demonstrated the predictive ability of viremia copy-years for HIV-related morbidity and mortality.[22, 23]

ART medications penetrate the CNS to differing extents. Despite viral-suppressing systemic levels there may be low drug concentrations in the CSF, resulting in a CNS reservoir of replicating virus. Studies of the effect of the CPE score of a patient's ART regimen on

neurocognitive outcomes have been conflicting. Shanbhag et al. found no significant association between specific CNS-penetrating drugs and neurocognitive function.[24] Patel et al. found that patients who received high CNS-penetrating regimens were less likely to have HIV encephalopathy compared to patients receiving low-penetrating regimens, but the association was not statistically significant.[25] In one study of infants with viral suppression prior to age 2 years there was a trend towards lower neurocognitive function with higher CPE scoring regimens but the association was not statistically significant.[16]

There are scant data on the neurodevelopmental outcomes of HIV-infected children receiving ART in sub-Saharan Africa. There is evidence that early initiation of ART in infancy will result in improved neurodevelopmental outcomes; however, it remains unclear to what extent other factors may influence this benefit, including virologic failure and CPE scores. This aim of this study was to determine the association between viremia copy-years and CPE score, and neurodevelopment.

Methods

We conducted a secondary data analysis of data collected in a clinical trial of HIV-infected children identified from 2007 to 2009 during routine HIV screening at Nairobi City Council Maternal Child Health clinics and hospital wards. The original randomized clinical trial [Optimizing Pediatric HIV-1 Therapy 03 (OPH03) NCT00428116] enrolled infants initiating ART and randomized them to either receive continuous ART or treatment interruption following a 2-year pre-randomization phase. Details of the original study design have been previously described.[26] Inclusion criteria for the original study included confirmatory positive HIV DNA

test, age <5 months, and no prior ART, except for ART provided as part of PMTCT. This secondary data analysis utilized data collected only during the pre-randomization phase. Ethical approval for OPH03 was obtained from the University of Washington and the University of Nairobi/Kenyatta National Hospital Institutional Review Boards.

Study procedures. Infants initiated ART approximately 2 weeks post-enrollment. First-line ART was two nucleoside reverse transcriptase inhibitors (NRTI) and nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor (NNRTI). Infants who had exposure to NVP via prevention of mother to child transmission (PMTCT) received lopinavir/ritonavir (LPV/r), a boosted protease inhibitor (PI) in place of NVP. Study procedures included monthly clinical visits, every 6-month CD4 counts and every 3-month viral loads. Neurodevelopment was assessed monthly by parental report. Developmental milestones assessed were adopted from the Denver Developmental Screening Test.[27](Table 2) Population-based consensus sequencing was performed on all baseline samples to determine presence of baseline antiretroviral resistance. Resistance was defined as intermediate or high-level according to the Stanford HIV Genotypic Resistance Algorithm.

Viremia copy-years. Viremia copy-years is a time-varying measure of cumulative plasma HIV burden. The trapezoidal rule was used to approximate the area under the viral load curve.(Figure 1) Because viral load measurements were not necessarily performed at the end of the time period of interest, viremia copy-years up to the end of the defined time period of interest was extrapolated using the most recent segment (time interval between 2 consecutive viral load values).[22] Any viral load measures below the level of detection (<250) were recorded as zero

for the viremia copy-years calculations. To test the association between viremia copy-years and age of milestone attainment the earliest age of milestone achievement within the cohort was identified as the time period of interest for each developmental milestone. Viremia copy-years was then calculated for each subject up to the pre-determined milestone-specific age to ensure comparable exposure periods across the cohort. Viremia copy-years was also calculated for pre-defined time periods of interest including: the first 6-, 12-, 18- and 24-months of life for each subject, and 6-, 12- and 18-months post-ART initiation.

Central nervous system penetration effectiveness. The CPE score of initial ART regimen was calculated using the Letendre, et al 2010 ranking system.[28] CPE scores were adjusted for baseline resistance such that any antiretroviral drugs to which a subject had intermediate or high-level resistance were given a CPE score of zero.

Statistical analysis. Weight-for-age (WAZ), height-for-age (HAZ) and weight-for-height (WHZ) Z-scores for growth parameters were calculated using WHO child growth standards. Subjects were categorized as "normal" versus "delayed" based on whether or not they achieved each milestone by the target age defined as the age by which 90% of children are expected to have achieved the milestone based on standardized norms.[27] Linear regression analysis was used to evaluate the association between viremia copy-years and age of developmental milestone attainment, while adjusting for pre-ART WAZ. Logistic regression analysis was used to evaluate the association between viremia copy-years and developmental delay, while adjusting for pre-ART WAZ. Four definitions of viremia copy years were tested: 1) viremia copy-years up to the earliest age of milestone attainment in the cohort, 2) viremia copy-years at 6 months of

age, 3) viremia copy-years at 6 months post-ART, and 4) viremia copy-years up to the earliest age of milestone attainment for milestones attained in the second year of life while adjusting for viremia copy-years in the first year of life. Only developmental milestones that were attained after a child had been on ART for 6-months were included in the 6-months post-ART models. Linear regression analysis was also used to evaluate the association between CPE score of initial ART regimen adjusted for baseline resistance and age of developmental milestone achievement, while adjusting for confounders including most recent log viral load, pre-ART WAZ and age at ART initiation. Analyses were performed using Stata IC version 12.1 (Stata Corp., College Station, TX, USA).

Results:

Cohort Characteristics. Ninety-nine vertically infected infants aged 1.13 to 5 months were enrolled. Eighty (80.8%) infants initiated ART and were included in this analysis.(Table 1) Forty-three (53%) were female, 29 (36%) received PMTCT and 34 (43%) were classified as WHO stage III or IV at enrollment. The median age at enrollment was 3.7 months [IQR: 2.95, 4.06]. Forty-five (56%) infants initiated NVP-based ART and 35 (44%) initiated LPV/r-based ART. Median CPE score of initial ART regimen was 9 [IQR: 9, 10]. Baseline median CD4 count was 1301 cells/mm^3 [IQR: 755, 1953], CD4% was 18% [IQR: 14%, 24%] and viral load was 6.58 $\log_{10}$ copies/ml [IQR: 5.98, 7.14]. Median WAZ was -2.35 [IQR: -3.66, -0.93], HAZ was -1.96 [IQR -3.16, -0.91] and WHZ was -0.63 [IQR: -1.82, 0.53] at baseline. Baseline median years of maternal education was 9 [IQR: 8, 11].

Developmental milestones. The earliest mean age of milestone attainment in the cohort for full neck control, sitting with support, sitting unsupported, walking with support, monosyllabic speech, walking unsupported, throwing toys and pointing/naming objects and pictures were 4.34 (SD 1.13), 5.68 (SD 1.19), 7.24 (SD 1.34), 11.48 (SD 2.42), 16.64 (SD 3.28), 17.12 (SD 3.06),18.88 (SD 2.87) and 22.78 months (SD 4.53), respectively.(Table 2) The proportion of infants with delayed milestone attainment was highly variable between milestones.(Table 2) No infants met criteria for delay for the throws toys milestone.

Viremia copy-years. Median viremia copy-years by age and post-ART are provided in Table 3. Figure 2 shows the inverse exponential relationship between median log viremia copy-years and log viral load by age. The longer children are treated with ART the more likely they are to experience viral suppression. Conversely, cumulative viral load increases with longer ART duration as total viral exposure increases.(Figure 3)

There was no association between viremia copy-years and age of developmental milestone attainment using the earliest age of milestone attainment in the cohort, 6 months of age or 6 months post-ART initiation as the defined period of interest in univariate or multivariate analyses.(Table 4) There was also no association between viremia copy-years and developmental delay in univariate and multivariate analyses.(Table 5) Adjusting for viremia copy-years in the first year of life, viremia copy-years in the second year of life was not associated with either age of developmental milestone attainment or developmental delay in either univariate or adjusted analyses.(Table 6)

Central nervous system penetration effectiveness. There was an association between CPE score and supported walking such that every one unit increase in CPE score was associated with earlier attainment of supporting walking by 17 days (p=0.044). After adjusting for WAZ this association was no longer significant but remained a trend (p=0.061). There was also a trend for an association between CPE score and unsupported walking such that every one unit increase in CPE score was associated with earlier attainment of unsupported walking by 21.87 days (p=0.60). This trend was no longer present after adjusting for WAZ (p=0.12). There was no significant association between CPE score of initial ART regimen adjusted for baseline resistance and age of attainment of the other developmental milestones.(Table 7)

Discussion:

Plasma viral load measures have been invaluable in the care of HIV-infected patients as a marker of viral burden at a single time point; however, cross-sectional viral load measurements fail to provide insight into an individual's cumulative viral burden and may under- or over-estimate viral exposure. In recent years, there has been increasing interest in using viremia copy-years as a marker for cumulative viral exposure. In untreated adults, viremia copy-years has been associated with progression to AIDS, mortality, and morbidity, including AIDS-associated malignancies.[22, 23] In some studies of ART-treated adults, viremia copy-years was more predictive than viral load single time-point measures.[21, 29] It has been proposed that viremia copy-years may represent a better marker of ART response than plasma viral load.[30] Marconi et al. demonstrated that individuals with slow viral load decay had poorer immune reconstitution.[31]

In this study we determined virema copy-years in ART-treated infants. Levels of viremia copy-years in our cohort were much higher than adult ART cohorts. Mugavero et al. calculated a median viremia copy-years of 199,526 copy x years/mL in a cohort of adults initiating ART with a median follow-up duration of 2.7 years; however, this study excluded viral load measures prior to 24 weeks post-ART to capture the effect of cumulative viral load on mortality after allowing for ART response. If we exclude the initial 6 months post-ART then our 12 month post-ART viremia copy-years decreases to 1,299 copy x years/mL. We failed to detect an association between viremia copy-years and age of developmental milestone attainment. There are several possible explanations for our inability to detect an association. The high viral loads and the relatively short time period of follow-up ≤2 years could make it difficult to differentiate between infants with extremely high viral loads for short durations versus infants with moderately high viral loads for longer durations. For example, an infant with a viral load of 2 million copies/mL for 4 months would have the same viremia copy-years as an infant who had a viral load of 6 million copies/mL for two months followed by two months of viral suppression. In this scenario both infants would have the same calculated viremia copy-years but the second child would have experienced high viral loads for only half the duration of the first infant. As early childhood is a period of rapid brain development, it is possible that shorter durations of very high virus levels have a different impact on brain development than longer durations of moderately high virus levels.

Second, most studies to date demonstrating an association between viremia copy-years and HIV-associated outcomes used Cox proportional hazards models. This allows for modelling copy-years viremia as a time-varying covariate while also adjusting for other time-varying covariates

such as CD4 count and time of ART initiation. In contrast, we defined set time periods of interest based on the earliest age of milestone attainment within the cohort in order to maintain a constant exposure period for each child. This approach may have attenuated our ability to detect an association.

Finally, we saw mixed results in our analyses of the association between CPE score of initial ART regimen and age of milestone attainment. In unadjusted analyses, there was a significant association between higher CPE scores and earlier attainment of supported walking as well as a trend for an association between higher CPE scores and earlier attainment of unsupported walking. There have been limited studies to date on the association between CPE score and neurodevelopment. Results of the few studies that have been conducted have been conflicting and likely reflect the fine balance between achieving viral suppression in the CNS and the development of ART related neurotoxicities.[16, 24, 25] Children in our cohort had very little variability in CPE scores even after adjusting for baseline resistance, which decreased our statistical power to be discern CPE effects on milestone attainment.

The main limitations of this study are the small sample size, high attrition rate due to mortality and loss to follow-up, and the use of parental report of milestone achievement. For the early milestones, only one viral load measure was available in which case the calculated copy-years viremia would not provide any additional information beyond that provided by a single cross-sectional viral load measure.

Conclusion: Our study does not support the use of viremia copy-years as a prognostic indicator for neurodevelopmental delay. As our study had many significant limitations, further studies are needed before any definitive conclusions about the utility of viremia copy-years can be made.

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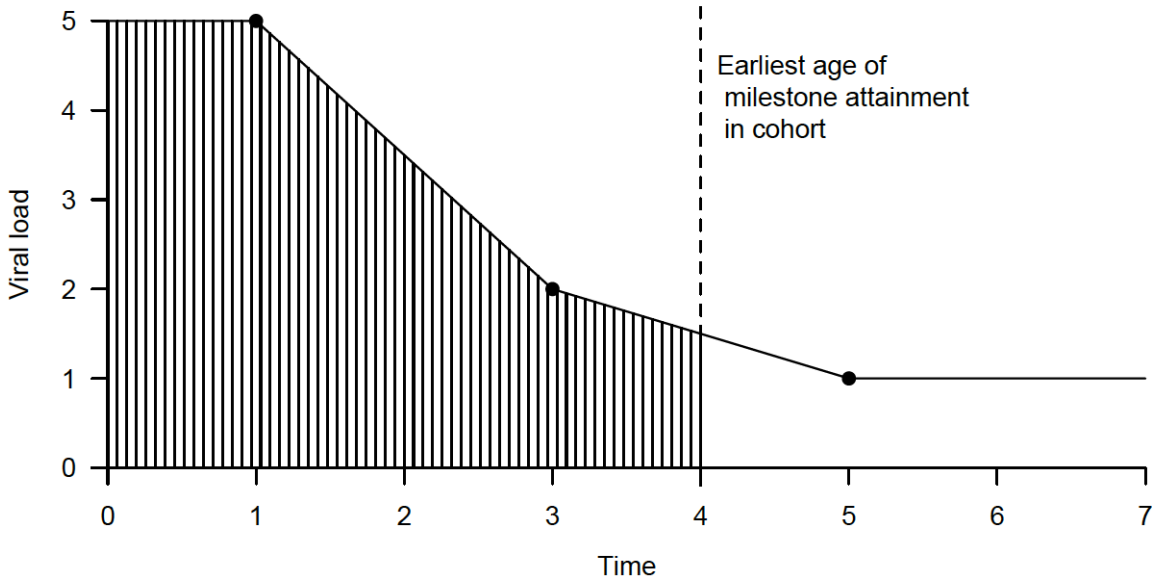
Figure 1. Viremia copy-years, cumulative viral burden, calculated as the area under the curve formed by discrete viral load measures



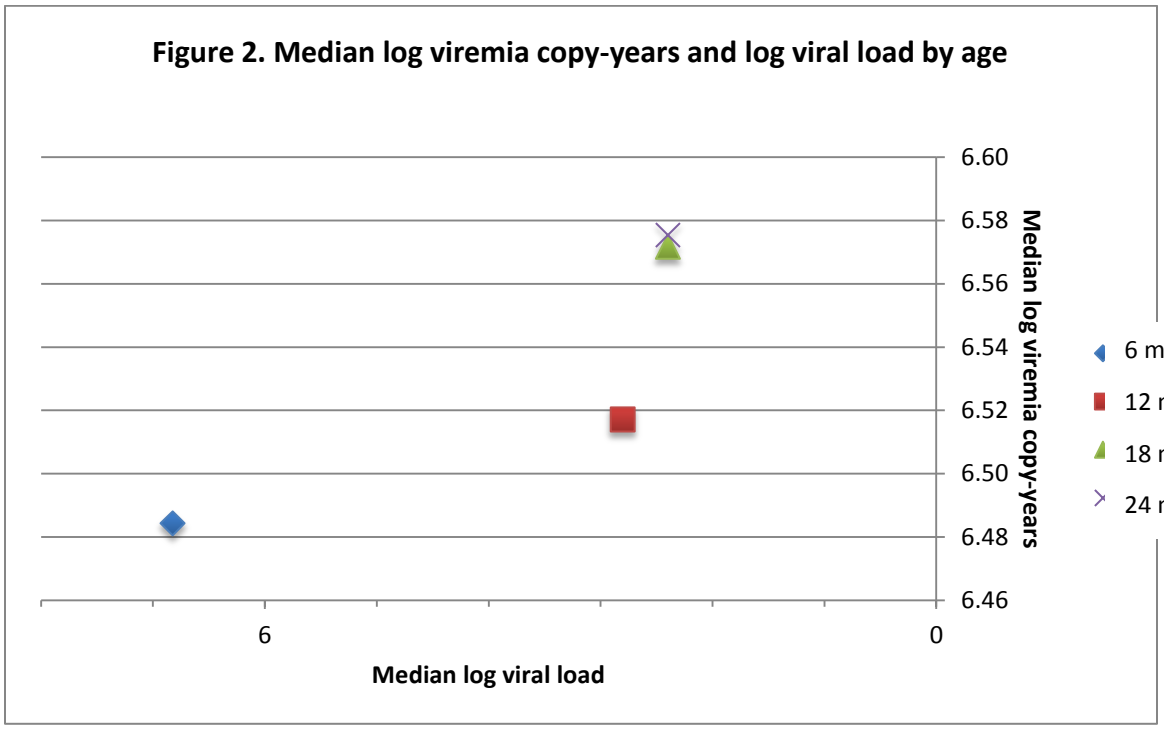
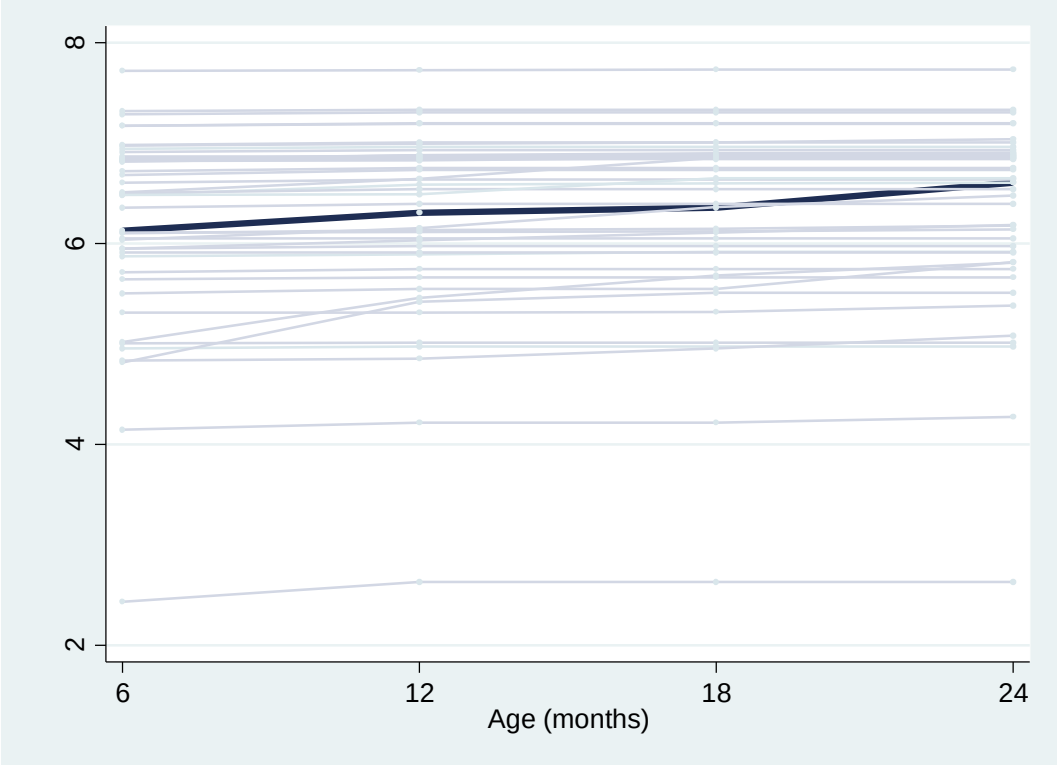


Figure 3. Log viremia copy-years trajectory by patient*



*The dark blue line represents the population median.

Table 1: Baseline characteristics of HIV-infected infants initiating antiretroviral therapy (N=80)

	N	Median or N (%)	IQR
Infant Characteristics			
Age of enrollment (months)	80	3.7	2.95, 4.06
Female	80	43(53%)	--
Received PMTCT	80	29(36%)	--
Ever breastfed	72	62(86%)	--
Prior hospitalization	80	44(55%)	--
CD4 count (cells/mm^3)	80	1301	765, 1907
CD4%	80	18%	14%, 24%
Plasma HIV RNA (log_{10} copies/mL)	70	6.58	5.98, 7.14
WHO Stage III or IV	78	34(43%)	--
WAZ	80	-2.35	-3.66,-0.93
HAZ	80	-1.96	-3.16, -0.91
WHZ	80	-0.63	-1.82, 0.53
Initial ART regimen			
Nevirapine-based	45	56%	--
Lopinavir/ritonavir-based	35	44%	--
CPE score of initial ART regimen	80	9	9, 10
Primary caregiver characteristics			
Biological mother	99	77(96%)	--
Age (years)	79	26	22, 30
Married	80	63(78%)	--
Education (years)	69	9	8, 11

PMTCT: Prevention of mother to child transmission; WHO: World Health Organization; WAZ: Weight for age Z-score; HAZ: Height for age Z-score; WHZ: Weight for height Z-score; ART: Antiretroviral therapy; CPE: Central nervous system penetration effectiveness

Table 2: Age (in months) of milestone attainment and proportion of delayed milestone attainment

	N	Mean (SD) or %	Range	Target age*
Age of achievement of milestones (months)				
Full neck control	73	4.34(1.13)	2.1-7.4	3.7
Sitting with support	63	5.68(1.19)	3.29-8.82	6.2
Sitting unsupported	61	7.24(1.34)	4.44-10.68	6.8
Walking with support	56	11.48(2.42)	7-19.8	13.7
Speech (able to say monosyllables)	53	17.12(3.06)	12.47-25.92	13.3
Walking unsupported	54	16.64(3.28)	11.22-27.57	14.9
Throws toys	55	18.88(2.87)	13.91-27.76	23.6
Points to names objects and pictures	46	22.78(4.53)	14.84-43.45	34.8
Infants with delayed milestone attainment				
Full neck control	54	73%	--	--
Sitting with support	21	33%	--	--
Sitting unsupported	36	59%	--	--
Walking with support	8	14%	--	--
Speech (able to say monosyllables)	49	92%	--	--
Walking unsupported	37	68%	--	--
Throws toys	0	--	--	--
Points to names objects and pictures	21	45%	--	--

*****Age by which 90% of children are expected to have attained the milestone based on standardized norms for the Denver Developmental Screening Test[27]

Table 3. Viremia copy-years and viral load measurements (N=44)*

	Median	IQR
Median viremia copy-years by age (median)		
6 months of age	3,050,389	478,124, 7,073,289
12 months of age	3,289,542	508,180, 7,461,651
18 months of age	3,729,768	518,185, 7,465,797
24 months of age	3,761,594	651,566, 7,808,716
Median copy-years post-ART initiation§		
6 months post-ART	833,203	132,470, 1,690,078
12 months post-ART	907,321	219,952, 1,911,261
18 months post-ART	907,446	220,127, 2,094,713
Median most recent viral load by age		
6 months of age	6,685,200	255,855, $1.74x10^7$
12 months of age	635	250, 50,250
18 months of age	250	250, 12,757
24 months of age	250	250, 62,825
Median most recent viral load post-ART initiation		
6 months post-ART	975	250, 54,275
12 months post-ART	250	250, 32,457
18 months post-ART	250	250, 67,355

*Only includes children with complete follow-up data
§Exposure time starts with ART initiation

Table 4: Association between viremia copy-years and age of developmental milestone achievement

Milestone	Viremia copy-years at youngest age of milestone attainment within the cohort		Viremia copy years at 6 months of age		Viremia copy years 6 months post-ART	
	β	p-value	β	p-value	β	p-value
Unadjusted analyses						
Full neck control	5.65×10^{-8}	0.183	2.72×10^{-8}	0.108	--	--
Sits with support	2.33×10^{-8}	0.427	1.37×10^{-8}	0.448	--	--
Sits unsupported	2.60×10^{-8}	0.320	2.19×10^{-8}	0.313	--	--
Walks with support	-3.91×10^{-9}	0.956	1.63×10^{-8}	0.688	-1.28×10^{-7}	0.457
Monosyllabic speech	2.99×10^{-8}	0.551	2.87×10^{-8}	0.576	1.23×10^{-7}	0.590
Walks unsupported	2.68×10^{-8}	0.618	2.73×10^{-8}	0.620	4.39×10^{-8}	0.857
Throws toys	5.83×10^{-9}	0.901	5.72×10^{-9}	0.905	-1.05×10^{-8}	0.961
Points to objects and pictures	1.31×10^{-8}	0.863	1.79×10^{-8}	0.818	-3.88×10^{-8}	0.910
Adjusted analyses*						
Full neck control	3.91×10^{-8}	0.341	2.03×10^{-8}	0.217	--	--
Sits with support	2.21×10^{-9}	0.934	1.07×10^{-9}	0.948	--	--
Sits unsupported	7.02×10^{-9}	0.766	6.25×10^{-9}	0.751	--	--
Walks with support	-3.44×10^{-8}	0.590	-1.24×10^{-8}	0.737	-1.69×10^{-7}	0.320
Monosyllabic speech	-5.44×10^{-9}	0.906	-8.03×10^{-9}	0.864	-2.07×10^{-8}	0.920
Walks unsupported	-9.97×10^{-9}	0.839	-1.07×10^{-8}	0.833	-1.06×10^{-7}	0.632
Throws toys	-1.85×10^{-8}	0.685	-1.97×10^{-8}	0.672	-1.10×10^{-7}	0.592
Points to objects and pictures	-6.60×10^{-9}	0.932	-2.54×10^{-9}	0.974	-1.26×10^{-7}	0.719

*Model adjusted for pre-ART WAZ

[§]Only milestones that were met after 6 months post-ART were included

Table 5: Association between viremia copy-years and developmental delay

Milestone	OR	p-value	aOR*	p-value
Full neck control	1	0.283	1	0.445
Sits with support	1	0.478	1	0.646
Sits unsupported	1	0.107	1	0.330
Walks with support	1	0.825	1	0.904
Monosyllabic speech	1	0.455	1	0.645
Walks unsupported	1	0.432	1	0.686
Throws toys[§]	--	--	--	--
Points to objects and pictures	1	0.237	1	0.384

*Model adjusted for WHO stage
[§]No delays

Table 6: Association between viremia copy-years and age of developmental milestone attainment and developmental delay during the second year of life adjusted for viremia copy-years during the first year of life

Milestone	Age of milestone attainment				Developmental delay			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	β	p-value	aβ	p-value	OR	p-value	aOR	p-value
Walks with support	-1.25×10^{-7}	0.976	-6.84×10^{-7}	0.877	--[§]	--	--[§]	--
Monosyllabic speech	1.18×10^{-5}	0.594	1.99×10^{-5}	0.317	1	0.640	1	0.758
Walks unsupported	-2.48×10^{-6}	0.757	-3.85×10^{-6}	0.587	1	0.614	1	0.835
Throws toys	-2.04×10^{-7}	0.944	1.35×10^{-6}	0.625	--[¶]	--	--[¶]	--
Points to objects and pictures	-2.83×10^{-6}	0.238	-2.44×10^{-6}	0.312	1	0.265	1	0.382

*Model also adjusted pre-ART WAZ

[§]Delay in the first year of life perfectly predicts delay

[¶]No delays

Table 7: Association between central nervous system penetration effectiveness (CPE) score of initial antiretroviral regimen adjusted for baseline resistance and age of developmental milestone achievement

Milestone	β	p-value	aβ*	p-value
Full neck control	-0.127	0.438	-0.065	0.524
Sits with support	0.191	0.131	0.144	0.145
Sits unsupported	0.058	0.700	0.146	0.187
Walks with support	-0.569	0.044	-0.449	0.061
Monosyllabic speech	0.001	0.997	0.274	0.413
Walks unsupported	-0.729	0.060	-0.518	0.120
Throws toys	0.137	0.688	0.265	0.423
Points to objects and pictures	0.195	0.724	0.291	0.597

*Model adjusted for most recent log viral load, age of ART initiation and pre-ART WAZ