Greater Virologic Control in Infants Initiated on ART Before 6 Months of Age

Stephanie Shiau[1], Ashraf Coovadia[2], Karl-Gunter Technau[2], Renate Strehlau[2], Leigh Martens[2], Francoise Pinillos[2], Elaine J. Abrams[1], Louise Kuhn[1]

[1]Columbia University, New York, NY, USA, [2]University of the Witwatersrand, Johannesburg, South Africa

Columbia University MAILMAN SCHOOL OF PUBLIC HEALTH

Stephanie Shiau, MPH
Columbia University
G.H. Sergievsky Center
622 W 168th Street PH 19-110
New York, NY 10032
212-305-2424
ss2568@columbia.edu

Abstract

Background: The recent report of an HIV-infected infant with viral control post-antiretroviral therapy (ART) interruption brings to light the possibility of "functional cure" for infants initiated on ART close to birth. However, there are limited data on the effects of early ART initiation before 6 months of age on the establishment and persistence of viral reservoirs. Here, we examine viral dynamics post-ART initiation by age at initiation.

Methodology: Viral dynamics by age at ART initiation (<6 months vs. 6-24 months) was evaluated in 3 cohorts at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. Children in Cohort 1 were initiated on ritonavir-boosted lopinavir (LPV/r)-based ART <24 months of age and randomized to remain on LPV/r or switch to nevirapine after achieving viral suppression. Children 3-5 years of age at enrollment in Cohort 2 were suppressed on LPV/r and randomized to remain on LPV/r or switch to efavirenz. Cohort 3 included children in routine services starting ART <24 months of age.

Results: Of 323 children in Cohort 1, HIV RNA levels were higher pre-ART in 102 children <6 months at ART start vs. 221 children 6-24 months at ART start (75.6 vs. 58.4% >750,000 copies/mL (cpm); 4.7 vs. 10.7% <100,000 cpm, p=0.02) but time to and likelihood of achieving viral suppression were similar by age at ART start, suggesting faster trajectories of decline in the younger children. Of 195 children who achieved suppression and were randomized in Cohort 1, mean plasma HIV RNA was 64 cpm in 54 children who started ART <6 months vs. 1502 copies/mL if 6-24 months (NS) after a median of 9 months of ART. Children <6 months at ART start were less likely to fail (>1000 cpm) by 52 weeks post-randomization (p=0.02, adjusted for group). The failures were primarily in those switched to nevirapine. In those retained on LPV/r where failure was rare, children <6 months at ART start were less likely to blip >50 cpm by 52 weeks post-randomization (p=0.04, adjusted for group). Of 300 children in Cohort 2, children <6 months at ART start were less likely to blip above 50 cpm than children 6-24 months at ART start (p=0.002). Of 239 children in Cohort 3, children who started ART <6 months were more likely to suppress <1000 cpm by 6 months (54.8%) than those starting 6-12 months (31.4%) or 12-24 months (35.9%) (p=0.03).

Conclusions: Across three separate cohorts, we observed greater virologic control in infants initiating ART <6 months of age. These results are consistent with the notion that early initiation of ART may limit formation of the long-lasting viral reservoir in infants.

Introduction

- The recent report of an HIV-infected infant with viral control post-antiretroviral therapy (ART) interruption brings to light the possibility of "functional cure" for infants initiated on ART close to birth.
- Emerging evidence indicates early initiation of ART, albeit not as early as the Mississippi baby, has critical benefits for young HIV-infected children at the greatest risk for death and disease progression, including reduced morbidity and mortality and improved clinical outcomes.
- However, less is known about the effects of early ART initiation before 6 months of age on the establishment and persistence of viral reservoirs.
- Here, we examine viral dynamics post-ART initiation by age at initiation (<6 months vs. 6-24 months).

Acknowledgements

This study was supported by funding from the National Institute of Child Health & Human Development (HD 47177, HD 61255) and the Secure the Future Foundation (RES 219).

Methods

Study Design

Figure 1. Johannesburg, South Africa



- We evaluated viral dynamics by age at ART initiation (<6 months vs. 6-24 months) in 3 cohorts at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa (**Figure 1**).
- Cohort 1 (NEVEREST 2): Children were initiated on ritonavir-boosted lopinavir (LPV/r)-based ART <24 months of age and randomized to remain on LPV/r or switch to nevirapine after achieving viral suppression.
- Cohort 2 (NEVEREST 3): Children were 3-5 years of age at enrollment and suppressed on LPV/r. Children were randomized to remain on LPV/r or switch to efavirenz. We included children who initiated ART <24 months of age.
- Cohort 3 (FInHDER): Children were participants in a surveillance study of newly-diagnosed HIV-infected infants and young children. We included children who initiated ART <24 months of age.

Statistical Analysis

- First, virologic suppression between age at ART start categories (<6 months vs. 6-24 months) was assessed. For Cohort 1, viral load trajectory since ART start was compared between groups. For Cohort 3, proportions of children with suppressed viral load 6 months after starting ART were compared between groups.
- Second, virologic control between age at ART start categories (<6 months and 6-24 months) was assessed. For Cohort 1, Kaplan-Meier methods and log-rank tests were used to describe time to virologic outcomes between groups. For Cohort 2, viral load categories of children at scheduled visits were compared between groups.

Results

Characteristics

- The three cohorts had similar pretreatment characteristics (**Table 1**).

Table 1. Pretreatment characteristics of children from 3 cohorts at Rahima Moosa Mother and Child Hospital

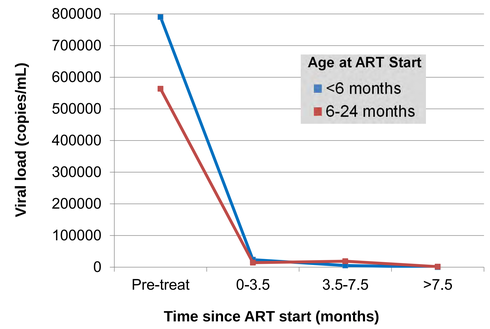
Characteristic	Cohort 1 (Neverest 2) N=323	Cohort 2 (Neverest 3) N=293	Cohort 3 (FInHDER) N=236
Sex, N (%)			
Male	168 (52.0)	137 (46.8)	112 (47.5)
Female	155 (48.0)	156 (53.2)	124 (52.5)
Age at ART start (months), N (%)			
<6	102 (31.6)	136 (46.4)	114 (48.3)
6-12	115 (35.6)	79 (27.0)	59 (25.0)
12-24	106 (32.8)	78 (26.6)	63 (26.7)
Mean ± SD	10.1 ± 5.8	8.9 ± 6.3	8.6 ± 6.5
HIV-1 RNA (copies/mL), N (%)			
<100,000	25 (8.8)	38 (15.4)	22 (10.8)
100,000-750,000	78 (27.6)	75 (30.5)	64 (31.5)
≥750,000	180 (63.6)	133 (54.1)	117 (57.6)
CD4 count (cells/mm^3), Mean ± SD	1007 ± 754	1213 ± 793	1260 ± 1193
CD4 percent, Median (IQR)	17.7 (12.3, 24.1)	20.1 (13.4, 27.9)	20.2 (13.1, 30.0)

Main Finding 1: Age at ART start influenced initial viral suppression

Cohort 1 (Neverest 2)

- Of 323 children in Cohort 1, HIV RNA levels were higher pre-ART in 102 children <6 months at ART start vs. 221 children 6-24 months at ART start (75.6 vs. 58.4% >750,000 copies/mL (cpm); 4.7 vs. 10.7% <100,000 cpm, p=0.02)
- Time to and likelihood of achieving viral suppression were similar by age at ART start, suggesting faster trajectories of decline in the younger children (**Figure 2**).

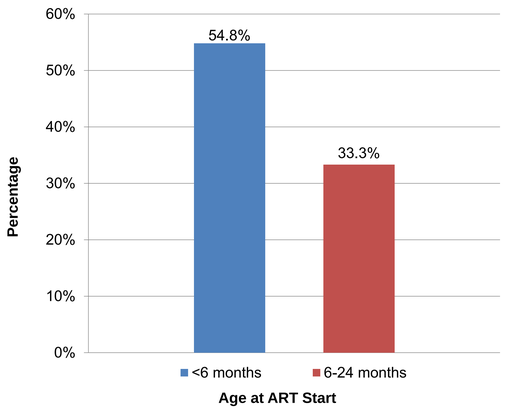
Figure 2. Viral load trajectory since ART start



Cohort 3 (FInHDER)

- Of 236 children in the cohort with a known date of ART initiation, 145 had a 6 month viral load available for analysis.
- Children who started ART <6 months of age were more likely to suppress <1000 cpm by 6 months (54.8%) than those starting ART 6-24 months of age (33.3%) (**Figure 3**).

Figure 3. Percentage of children with suppressed VL <1000 copies/mL 6 months after ART start

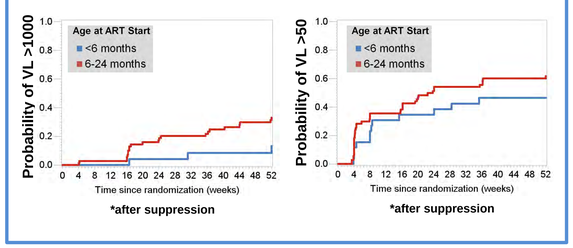


Main Finding 2: Age at ART start influenced virologic control after viral suppression

Cohort 1 (Neverest 2 once suppressed)

- Children <6 months at ART start were less likely to fail (>1000 cpm) by 52 weeks post-randomization (p=0.02, adjusted for group) (**Figure 4**). The failures were primarily in those switched to nevirapine.
- In those retained on LPV/r where failure was rare, children <6 months at ART start were less likely to blip >50 cpm by 52 weeks post-randomization (p=0.04, adjusted for group) (**Figure 4**).

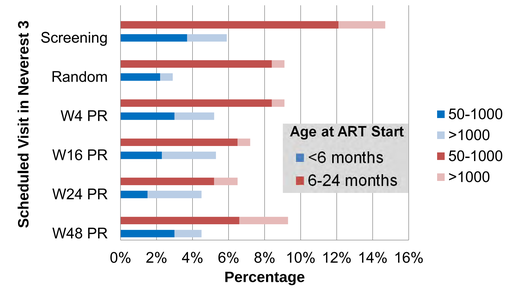
Figure 4.



Cohort 2 (Neverest 3)

- Of 293 children in Cohort 2, children <6 months at ART start were less likely to blip above 50 cpm than children 6-24 months at ART start (**Figure 5**).

Figure 5. Percentage of children with VL 50-1000 and VL >1000 copies/mL at scheduled visits



Conclusions

- Across three separate cohorts, we observed greater virologic control in infants initiating ART <6 months of age compared to infants initiating ART 6-24 months of age.
- These results are consistent with the notion that early initiation of ART may limit formation of the long-lasting viral reservoir in infants.