Reservoir Size and Dynamics by Age at Virologic Suppression and Sex in Youth with Perinatal HIV-1

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— BACKGROUND —

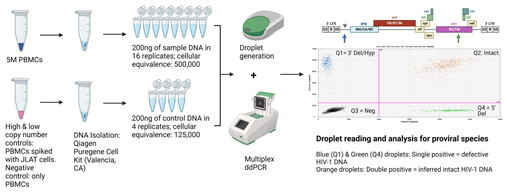
- Longitudinal studies on HIV-1 reservoir size and dynamics in youth with perinatal HIV-1 and long-term viral suppression (VS) are limited by the large amount of blood volume required for purifying sufficient CD4+ T cells to quantify the reservoir by viral outgrowth and inducible assays.
- In a previous study, we reported on differences in the decay of total HIV-1 infected cells persisting on ART by age at VS [1]. This study used a single-plex ddPCR assay that was limited by the inability to distinguish intact and defective proviral genomes, and therefore was not a direct measure of the reservoir size.
- The Intact Proviral DNA Assay (IPDA) permits quantification of intact and defective proviral genomes, providing a novel approach to quantify the HIV-1 reservoir on small numbers of nonviable cells in long-term biorepositories [2].

— OBJECTIVE —

To evaluate the size and dynamics of the HIV-1 reservoir over longitudinal follow-up by age at virologic suppression and sex at birth using the IPDA among youth with perinatal HIV-1 in the U.S.

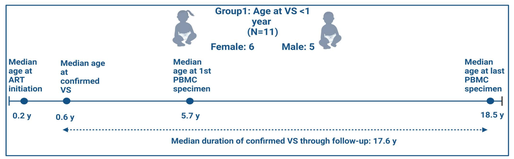
— METHODS —

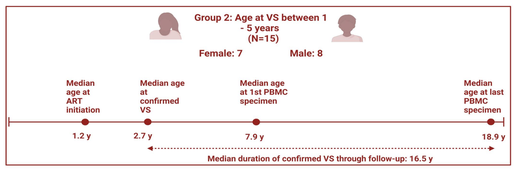
Figure 1: Schematic of Intact Proviral DNA Assay (IPDA) used to quantify HIV-1 reservoir size.



Study Population: Pediatric HIV/AIDS Cohort Study (PHACS)

Figure 2: Summary demographics of the study population.





PHACS (www.phacsstudy.org) Adolescent Master Protocol (AMP)/AMP Up: prospective cohort studies of the outcomes of perinatal HIV infection in the U.S.

Statistical Methods

- Distributions of sociodemographic data, HIV-1-specific characteristics (ART, CD4, plasma viral load), PBMC availability, and PBMC HIV-1 DNA concentrations were described by age at confirmed VS and sex at birth.
- Locally weighted scatterplot smoothing (LOESS) plots were used to graphically summarize the relationship between time since VS and the trajectories of total, intact, 5'-del, and 3'-del/hypermutated proviral HIV-1 DNA, for all study participants, and then stratified by age at confirmed VS to inform appropriate age groupings and model building decisions, including knot placement for piecewise regression.
- Piecewise linear mixed effects models were fit to estimate trajectories of each outcome measure over follow-up by age at confirmed VS and sex at birth.

— RESULTS —

Overall Cohort Data

- HIV-1 quantified in 26/27 eligible participants.
- **PBMCs were primarily collected between 5 to <15 years of VS (median of 8 specimens per participant over a median of 17.3 years of VS).**

Years since VS:	5-<10 years	10-<15 years
Median Number of PBMCs Analyzed (IQR)	509,156.6 (420,331.1, 586,321.2)	520,113.6 (453,575.9, 591,098.9)
Median Assay Limit of Detection (LOD) Copies/10^6 PBMCs (IQR)	2.0 (1.7, 2.4)	1.9 (1.7, 2.2)
Median HIV-1 DNA Copies/10^6 PBMCs (IQR)		
Total HIV-1 DNA	58.5 (29.6, 120.3)	56.1 (23.5, 134.9)
Intact HIV-1 DNA	4.1 (1.2, 8.6)	3.1 (1.0, 10.1)
5' Del HIV-1 DNA	22.7 (9.7, 44.8)	16.9 (6.2, 41.7)
3' Del/Hypermutated HIV-1 DNA	36.0 (11.5, 77.4)	33.5 (13.3, 82.7)

With ***early sustained virologic suppression*** at a median of 7.8 months of age, HIV-1 ***reservoir size*** was ***smaller*** by age 5 years compared with ***late virologic suppression*** at a median of 2.7 years of age. This smaller size was maintained through adolescence.

Among youth with ***late virologic suppression***, ***sex differences*** in the ***reservoir size*** were observed with females having larger reservoir size.

These findings have ***relevance*** for considerations of ***age at VS and sex at birth*** in developing ***ART-free remission approaches*** for ***perinatal HIV-1 infection.***

The reservoir size was smaller among early suppressed individuals with perinatal HIV-1

Figure 3A: LOESS plots over actual data points.

Open circles – values below LOD were set to LOD/2

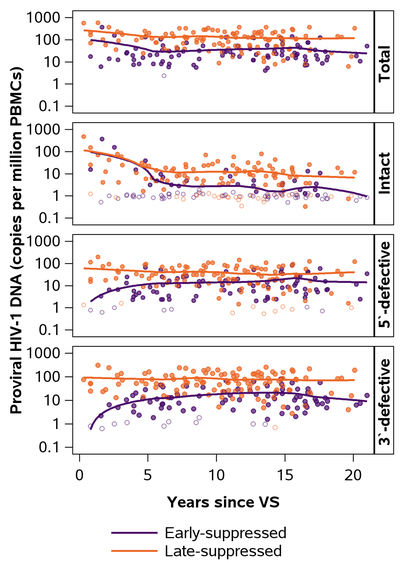
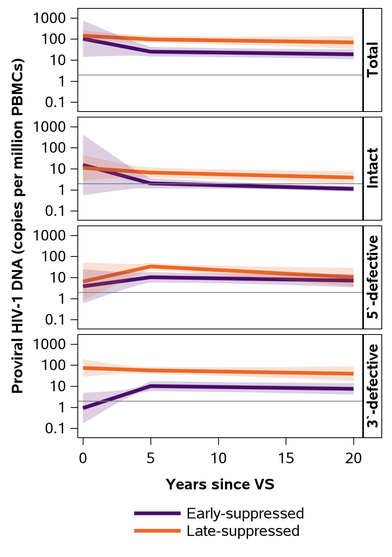


Figure 3B: Estimated proviral HIV-1 DNA trajectories.

Values below LOD were set to LOD/2.



Years since VS:	5-<10 years		10-<15 years	
Median HIV-1 DNA Copies/10^6 PBMCs (IQR)	Early Suppressed	Late Suppressed	Early Suppressed	Late Suppressed
Total HIV-1 DNA	20.0 (8.1, 32.9)	113.2 (68.3, 204.4)	28.0 (18.8, 53.1)	103.3 (47.0, 188.8)
Intact HIV-1 DNA	1.2 (0.9, 3.1)	6.4 (3.0, 18.3)	1.1 (1.0, 2.9)	6.3 (1.0, 14.5)
5' Del HIV-1 DNA	9.0 (2.4, 16.4)	34.7 (21.0, 65.6)	10.5 (5.7, 17.6)	19.6 (7.3, 54.9)
3' Del/Hypermutated HIV-1 DNA	7.3 (3.6, 15.4)	57.6 (34.7, 137.9)	16.5 (6.4, 29.0)	56.8 (24.2, 121.1)

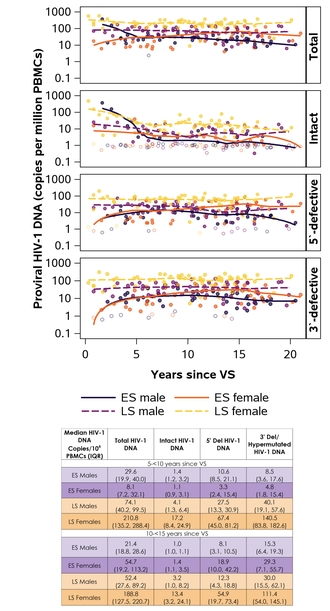
Estimated mean (95% CI) proviral HIV-1 DNA copies/10^6 PBMCs	Total HIV-1 DNA	Intact HIV-1 DNA	5' Del HIV-1 DNA	3' Del/Hypermutated HIV-1 DNA
5 years since VS				
Early Suppressed	25.1 (14.8, 42.7)	2.0 (1.2, 3.5)	10.3 (5.9, 18.2)	10.2 (5.9, 17.5)
Late Suppressed	96.6 (65.6, 142.1)	6.6 (3.7, 11.8)	33.6 (22.8, 49.6)	56.5 (38.4, 83.0)
10 years since VS				
Early Suppressed	22.9 (14.0, 37.4)	1.7 (1.1, 2.5)	9.1 (5.3, 15.6)	9.2 (5.3, 15.8)
Late Suppressed	86.6 (57.1, 131.3)	5.5 (3.2, 9.4)	22.7 (14.0, 36.7)	50.1 (31.9, 78.7)
15 years since VS				
Early Suppressed	20.8 (12.6, 34.3)	1.4 (1.0, 1.8)	8.1 (4.4, 14.7)	8.3 (4.7, 14.8)
Late Suppressed	77.7 (45.7, 132.1)	4.6 (2.5, 8.3)	15.3 (7.4, 31.8)	44.5 (24.2, 81.7)

- For the time intervals evaluated, the median HIV-1 proviral loads were lower in the early suppressed group compared with the late suppressed group. In both groups, there was an overabundance of 5'Del and 3' Del/Hypermutated HIV-1 DNA.
- Median intact proviral HIV-1 DNA copies/10^6 PBMCs for the early suppressed group were close to the median limit of detection.

Females had larger reservoir size compared to males with late virologic suppression in perinatal HIV-1

Figure 4A: LOESS plots over actual data points.

Open circles – values below LOD were set to LOD/2

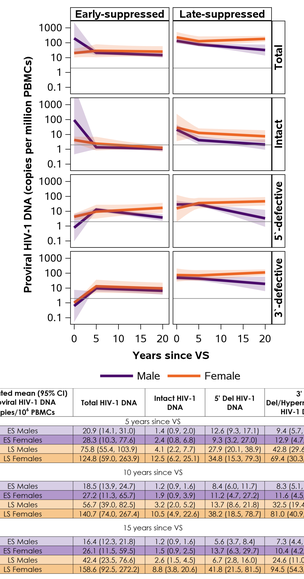


Median HIV-1 DNA Copies/10^6 PBMCs (IQR)	Total HIV-1 DNA	Intact HIV-1 DNA	5' Del HIV-1 DNA	3' Del/ Hypermutated HIV-1 DNA
5-<10 years since VS				
ES Males	29.6 (19.9, 40.0)	1.4 (1.2, 3.2)	10.6 (8.5, 21.1)	8.5 (3.6, 17.6)
ES Females	8.1 (7.2, 32.1)	1.1 (0.9, 3.1)	3.3 (2.4, 15.4)	4.8 (1.8, 13.4)
LS Males	74.1 (40.2, 99.5)	4.1 (1.3, 6.4)	27.5 (13.3, 30.9)	40.1 (19.1, 57.6)
LS Females	210.8 (135.2, 288.4)	17.2 (8.4, 24.9)	67.4 (45.0, 81.2)	140.5 (83.8, 182.6)
10-<15 years since VS				
ES Males	21.4 (18.8, 28.6)	1.0 (1.0, 1.1)	8.1 (3.1, 10.5)	15.3 (6.4, 19.3)
ES Females	54.7 (19.2, 113.2)	1.4 (1.1, 3.5)	18.9 (10.0, 42.2)	29.3 (7.1, 55.7)
LS Males	52.4 (27.6, 89.2)	3.2 (1.0, 8.2)	12.3 (4.3, 18.8)	30.0 (15.5, 62.1)
LS Females	188.8 (127.5, 220.7)	13.4 (3.2, 24.1)	54.9 (19.7, 73.4)	111.4 (54.0, 145.1)

Figure 4B: Estimated proviral HIV-1 DNA trajectories.

++Intact HIV-1 slope uncertain due to high number of undetectable values++

Values below LOD were set to LOD/2.



Estimated mean (95% CI) proviral HIV-1 DNA copies/10^6 PBMCs	Total HIV-1 DNA	Intact HIV-1 DNA	5' Del HIV-1 DNA	3' Del/Hypermutated HIV-1 DNA
5 years since VS				
ES Males	20.9 (14.1, 31.0)	1.4 (0.9, 2.0)	12.6 (9.3, 17.1)	9.4 (5.7, 15.5)
ES Females	28.3 (10.3, 77.6)	2.4 (0.8, 6.8)	9.3 (3.2, 27.0)	12.9 (4.7, 35.7)
LS Males	75.8 (55.4, 103.9)	4.1 (2.2, 7.7)	27.9 (20.1, 38.9)	42.8 (29.6, 61.8)
LS Females	124.8 (59.0, 263.9)	12.5 (6.2, 25.1)	34.8 (15.3, 79.3)	69.4 (30.3, 159.1)
10 years since VS				
ES Males	18.5 (13.9, 24.7)	1.2 (0.9, 1.6)	8.4 (6.0, 11.7)	8.3 (5.1, 13.3)
ES Females	27.2 (11.3, 65.7)	1.9 (0.9, 3.9)	11.2 (4.7, 27.2)	11.6 (4.9, 29.5)
LS Males	56.7 (39.0, 82.5)	3.2 (2.0, 5.2)	13.7 (8.6, 21.8)	32.5 (19.4, 54.4)
LS Females	140.7 (74.0, 267.4)	10.5 (4.9, 22.6)	38.2 (18.5, 78.7)	81.0 (40.9, 160.2)
15 years since VS				
ES Males	16.4 (12.3, 21.8)	1.2 (0.9, 1.6)	5.6 (3.7, 8.4)	7.3 (4.4, 12.2)
ES Females	26.1 (11.5, 59.5)	1.5 (0.9, 2.5)	13.7 (6.3, 29.7)	10.4 (4.7, 23.4)
LS Males	42.4 (23.5, 76.6)	2.6 (1.5, 4.5)	6.7 (2.8, 16.0)	24.6 (11.0, 54.9)
LS Females	158.6 (92.5, 272.2)	8.8 (3.8, 20.6)	41.8 (21.5, 81.5)	94.5 (54.3, 164.4)

- Between 5-<10 years since VS, ES females had lower total and defective HIV-1 DNA than ES males. Between 10-<15 years since VS, the total and defective HIV-1 DNA proviral species were higher for ES females.
- However, with late suppression, total proviral HIV-1 DNA and intact proviral DNA were higher in females across both time intervals (5-<10 years and 10-<15 years since VS) compared to males. These data indicate larger reservoir sizes in females with late virologic suppression.
- Estimated mean slopes of total HIV-1 DNA from 5 to <15 years were similar by sex among ES but differed among LS: total HIV-1 DNA increased by 2.4% per year for females and decreased by 5.6% per year for males.

— CONCLUSIONS —

- **Age at virologic suppression influences reservoir size in long standing perinatal HIV-1 infections.**
- **Data from this study uncovered the importance of investigating sex differences when evaluating reservoir size in perinatal HIV-1 infection.**

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