Intact HIV DNA Decay during 15 Years of Suppressive ART: Comparisons by Timing of ART Initiation

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BACKGROUND

- Latent reservoirs of proviral HIV DNA integrated into CD4+ T-cells represent the major barrier to HIV cure.
- People who initiate antiretroviral therapy (ART) during acute HIV have small HIV reservoirs, but this population is uncommon.
- Despite rapid seeding of HIV reservoirs, there appears to be some early plasticity, with similar HIV DNA levels observed 6-12 months after ART initiation during Fiebig stages II-V of acute HIV.
- It is unclear when the period of plasticity of the HIV reservoir ends and just how early may be early "enough" to improve disease outcomes and optimize the potential to achieve HIV remission.
- We evaluated how the time between seroconversion and ART initiation impacts HIV reservoir decay during up to 15 years of suppressive ART to clarify reservoir pathogenesis and inform future studies of strategies to achieve HIV remission.

Earlier ART initiation was associated with lower levels of intact proviral DNA in PBMCs that persisted through 10-15 years of suppressive ART but did not affect the slope of HIV reservoir decay.

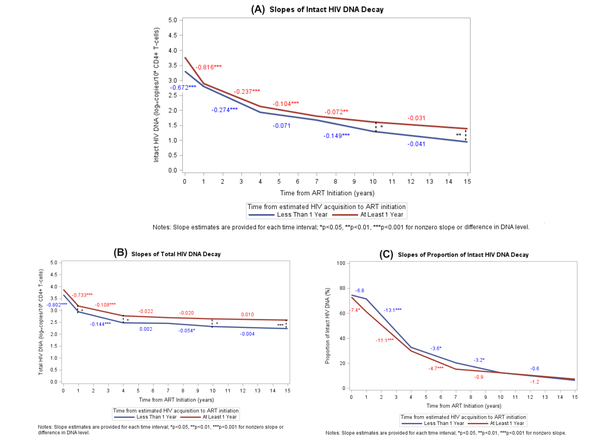
MATERIALS AND METHODS

- The U.S. Military HIV Natural History Study (NHS) enrolls adult U.S. Department of Defense beneficiaries with HIV.
  - Because U.S. service members are routinely tested for HIV every 1-2 years, many NHS participants have well-defined dates of estimated HIV seroconversion.
- We identified NHS participants with known HIV seroconversion windows who achieved HIV RNA <400 copies/mL within 1 year of starting ART, maintained suppressive ART for at least 10 years, and had stored peripheral blood mononuclear cell (PBMC) specimens at years 4, 7, and 10 after ART initiation.
  - If available, samples were also analyzed from years 0, 1, and/or 15.
- PBMCs were analyzed using the intact proviral DNA assay (IPDA) to separately quantify intact and defective proviruses.
- We created linear spline models for intact HIV DNA, total HIV DNA, and proportion of intact HIV DNA based on time between estimated HIV seroconversion and ART initiation (<1 year vs. ≥1 year), with knots at 1, 4, 7, and 10 years on ART.
- Models were adjusted for age, race/ethnicity, CD4 count, and viral load at ART initiation.
- Correlations between intact and total HIV DNA were assessed using Spearman's rank correlation coefficient.

RESULTS

- Among 83 participants, the median age at ART initiation was 34.3 years (IQR: 29.2-41.5), 23 (27.7%) started ART within one year of estimated HIV seroconversion (21 within 3-12 months), and 82 (98.8%) were male (Table 1).
- There were similar patterns of decay of intact HIV DNA, total HIV DNA, and proportion of intact HIV DNA between time to ART initiation groups.
  - The slope of reservoir decay did not vary based on the time of ART initiation (Figure 1).
  - Decay of intact HIV DNA continued through year 10 of ART (Figure 1A).
    - Intact HIV DNA was consistently lower in the earlier ART initiation group (1.18 vs. 1.67 log_{10}copies/10^6 CD4+ T-cells at 10 years, p<0.05; 0.76 vs. 1.64 log_{10}copies/10^6 CD4+ T-cells at 15 years, p<0.01).
  - Decay of total HIV DNA plateaued around year 4 of ART (Figure 1B).
    - Total HIV DNA was consistently lower in the earlier ART initiation group (2.88 vs. 3.32 log_{10}copies/10^6 CD4+ T-cells at 1 year, p<0.05; 2.46 vs. 2.77 log_{10}copies/10^6 CD4+ T-cells at 4 years, p<0.05; 2.28 vs. 2.61 log_{10}copies/10^6 CD4+ T-cells at 10 years, p<0.05; 2.07 vs. 2.80 log_{10}copies/10^6 CD4+ T-cells at 15 years, p<0.001).
  - Proportion of total HIV DNA that is intact decreased rapidly until about 4 years on ART and then more slowly thereafter and did not vary by the timing of ART initiation (Figure 2C).
- Correlations between intact and total HIV DNA were strongly positive at all time points for both groups (range: 0.824-0.964; p<0.001).

Figure 1: Slopes of Proviral DNA Decay in Peripheral Blood Mononuclear Cells, by Timing of ART Initiation



Notes: Slope estimates are provided for each time interval; *p<0.05, **p<0.01, ***p<0.001 for nonzero slope or difference in DNA level.

Adjusted linear spline models were used to evaluate the slopes of decay in log-transformed intact HIV DNA (Panel A), total HIV DNA (Panel B), and proportion of intact HIV DNA (Panel C) based on time between estimated HIV seroconversion and ART initiation (<1 year vs. ≥1 year), with knots at 1, 4, 7, and 10 years on ART.

Table 1: Demographics and HIV-related Characteristics by Time from Estimated HIV Seroconversion to Antiretroviral Therapy Initiation

	Time to ART Initiation: Less than 1 Year n=23 (27.7%)	Time to ART Initiation: At Least 1 Year n=60 (72.3%)	P
Age at HIV Seroconversion (years)	30.9[26.7-33.3]	33.2[26.6-37.6]	0.1471
Age at ART Initiation (years)	31.8[27.0-34.2]	38.2[30.1-42.6]	**0.0021**
Sex			1.0000
Male	23(100.0)	59(98.3)	
Female	0(0.0)	1(1.7)	
Race			0.2572
African American	13(56.5)	24(40.0)	
Caucasian	9(39.1)	27(45.0)	
Hispanic/Other	1(4.4)	9(15.0)	
HIV Seroconversion Era			**0.0305**
Prior to 1996	1(4.4)	19(31.7)	
1996 - 2000	7(30.4)	11(18.3)	
2000 - Current	15(65.2)	30(50.0)	
ART Initiation Era			0.7314
1995-2000	7(30.4)	16(26.7)	
2000+	16(69.6)	44(73.3)	
First ART regimen			0.9740
NNRTI	14(60.9)	35(58.3)	
Unboosted PI	5(21.7)	11(18.3)	
Old Dual Therapy	1(4.4)	5(8.3)	
Triple NRTI	1(4.4)	4(6.7)	
Boosted PI	1(4.4)	3(5.0)	
Mono	1(4.4)	1(1.7)	
NRTI not ABV	0(0.0)	1(1.7)	
CD4 at ART Initiation (cells/μL)			0.9671
0-200	2(8.7)	8(13.3)	
201-350	10(43.5)	24(40.0)	
351-500	7(30.4)	15(25.0)	
501+	4(17.4)	10(16.7)	
Missing	0(0.0)	3(5.0)	
Viral Load at ART Initiation (log_{10}copies/mL)			0.2054
<5.0	14(60.9)	45(75.0)	
5.0+	8(34.8)	13(21.7)	
Missing	1(4.4)	2(3.3)	

Abbreviations: ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor: ABV, abacavir.

Continuous variables are presented as median [Q1-Q3]. Mann-Whitney U test and Chi-square/Fisher's exact test were used to calculate p-values for continuous and categorical variables, respectively (excluding missing). Statistically significant differences between groups (p<0.05) are shown in **bold**.

CONCLUSIONS:

- Earlier ART initiation was associated with lower levels of intact proviral DNA in PBMCs that persisted through 15 years of suppressive ART, at which point they were about 50% smaller in the early-treated group.
- Significant reservoir decay was observed through 10 years of ART, regardless of Athe timing of ART initiation.
- Future studies of curative interventions may consider enrolling participants who initiated ART within one year of year of estimated HIV seroconversion, particularly those with a long history of suppressive ART.

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