Female Sex is Associated with Continuous Decline in Intact HIV-1 Proviruses during Long-Term Antiretroviral Therapy

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Background

1. HIV-1 infection cannot be cured in most people due to persistence of a latent reservoir, despite long-term suppressive antiretroviral therapy (ART).
2. Understanding the long-term dynamics of intact HIV-1 proviruses during suppressive ART is critical for developing HIV-1 cure strategies.
3. Sex and sex hormones have been shown to regulate immunity and are associated with prominent differences in HIV acute and chronic infection [1, 2]. Their association with HIV-1 reservoir remains under-characterized.

Methods

1. Retrospective analysis of people with HIV (PWH) on ≥10 years of suppressive ART from University of Pittsburgh (MACS cohort, male assigned at birth only) and University of California, San Francisco (WIHS cohort, female assigend at birth only).
2. Intact, defective and total HIV-1 proviral DNA levels were measured by intact proviral DNA assay (IPDA™).
3. Hormone levels including testosterone (T), estradiol (E) and follicle-stimulating hormone (FSH) were measured at Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Cytokines were measured using ELISA.
4. Patterns of intact proviruses decline:
   -Continuous declines (D_C)
   -Declines initially then rises later (D_LR)
   -No declines (ND)
5. We used generalized estimation equation (GEE) to estimate between-group differences among the intact proviral dynamics groups with repeated measurement.

Results

Table 1. Baseline characteristics

Characteristics	Overall (n=35)	Female (n=18)	Male (n=17)	P
Age at ART initiation, years (IQR)	38 (33, 43)	38 (29, 45)	41 (37, 43)	0.8
Age at viral load suppression, years (IQR)	45 (39, 50)	42 (37, 47)	48 (42, 52)	0.07
Race				0.01
African American	9 (26%)	6 (33%)	3 (18%)	
Caucasian	21 (60%)	7 (39%)	14 (82%)	
Other	5 (14%)	5 (28%)	0 (0%)	
Hispanic ethnicity	3 (8.6%)	2 (11%)	1 (5.9%)	>0.9

Main Findings

1. Nearly half of PWH on suppressive ART did not show persistent decline in intact proviral HIV-1 DNA.

2. Female sex assigned at birth and rapid viral suppression were associated with persistent proviral decline.

3. In female participants, IL-6 was negatively associated with intact proviruses. In male participants, D-dimer was negatively associated with intact proviruses. This may suggest a differential correlation between inflammation and HIV-1 persistence in male and female PWH.

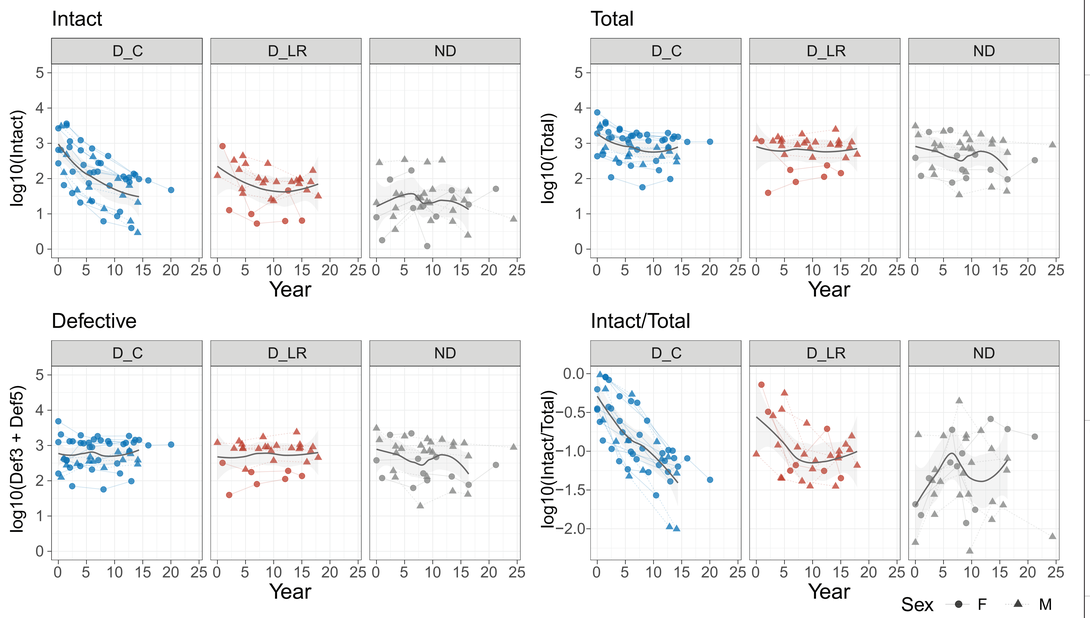


Figure 1. Intact, total, defective and intact/total ratio during long-term suppressive ART. Three patterns of intact HIV-1 proviral DNA decline were identified. x-axis, years since sustained viral suppression.

Despite distinct patterns in intact provirus decline, three groups had comparable total and defective proviral levels (P>0.05 in D_C vs. D_LR and D_C vs. ND, GEE, adjusting for sex and race) .

Table 2. Characteristics associated with different patterns of intact provirus decline.

Characteristics	D_C (n=16)	D_LR (n=8)	ND (n=11)	P
Sex				0.04
Female	12 (75%)	2 (25%)	4 (36%)	
Male	4 (25%)	6 (75%)	7 (64%)	
Age at ART initiation , years (IQR)	38 (29, 42)	39 (32, 45)	41 (37, 49)	0.4
Age at viral load suppression , years (IQR)	41 (39, 45)	48 (43, 52)	49 (45, 54)	0.04
Nadir CD4 cell count (cells/mm^3)	236 (185, 288)	232 (138, 374)	216 (189, 403)	>0.9
CD4/CD8 ratio , lowest in record (IQR)	0.29 (0.21, 0.36)	0.30 (0.18, 0.37)	0.48 (0.21, 0.58)	0.3
CD4/CD8 ratio, highest in record (IQR)	1.27 (1.08, 1.58)	1.30 (1.02, 1.82)	1.90 (0.83, 2.96)	0.6

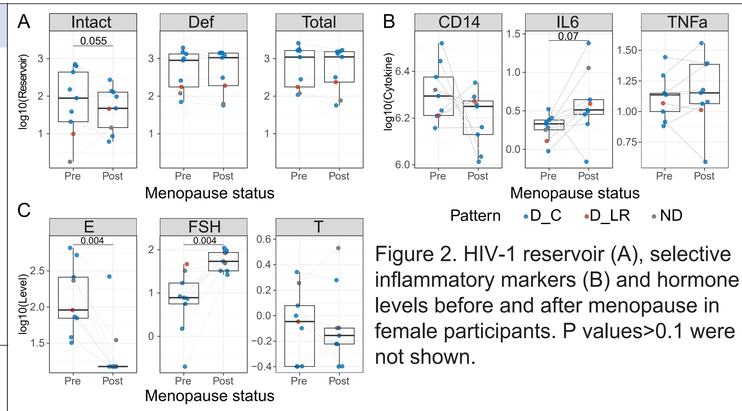


Figure 2. HIV-1 reservoir (A), selective inflammatory markers (B) and hormone levels before and after menopause in female participants. P values>0.1 were not shown.

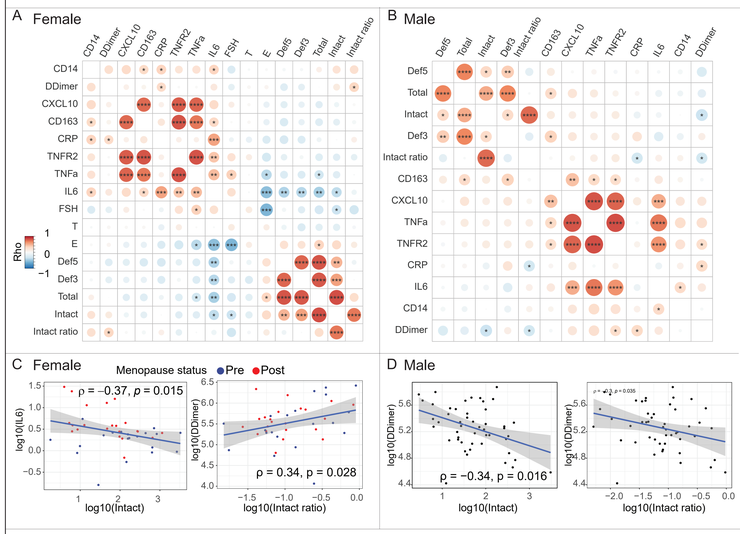


Figure 3. Correlation between inflammatory cytokines, HIV-1 proviral levels, and hormone levels. Spearman correlation matrix in female (A) and male (B) participants with HIV. (C) Correlation between intact proviruses and IL-6, Intact proviral ratio (intact/total proviruses) and D-dimer levels in female participants with HIV. (D) Correlation between intact proviruses and D-dimer; intact ratio and D-dimer in male participants with HIV.

Limitations

- Small sample size
- Several confounders including years to viral suppression
- Most participants started treatment in 1990s with old ART regimens.

References

1. Ziegler and Altfeld, Curr Opin HIV AIDS. 2016; 11(2):209–215
2. Gianella et al., Clin Infect Dis. 2022;75(1):73-80.

Acknowledgement

All the MWCCS participants, clinical staff.
Funding support: Rustbelt Center for AIDS Research (P30 AI036219), U01-HL146208 and U01-HL146242.