Early ART initiation is associated with faster decay of the transcriptionally active HIV reservoir

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Background

- Early ART initiation has been associated with smaller HIV reservoirs.
- It is not clear how the timing of ART initiation affects subsets of the "active" HIV-transcribing reservoir.
- To investigate the impact of starting ART in acute vs. chronic infection, we measured different HIV DNA and RNA levels in longitudinal samples obtained before (T1) and up to five timepoints after ART initiation (T2-T5).

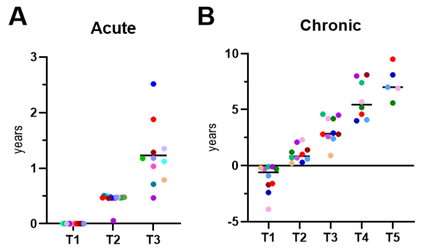


Figure 1. Sampling intervals for individuals starting ART during acute (A) or chronic (B) HIV infection. The y-axis shows time in years relative to the start of ART (y=0). The x-axis indicates timepoints before (T1) and after (T2-T5) starting ART. *Bars indicate medians.*

Hypothesis: Earlier initiation of ART will result in faster decreases in HIV DNA and HIV RNA

Methods

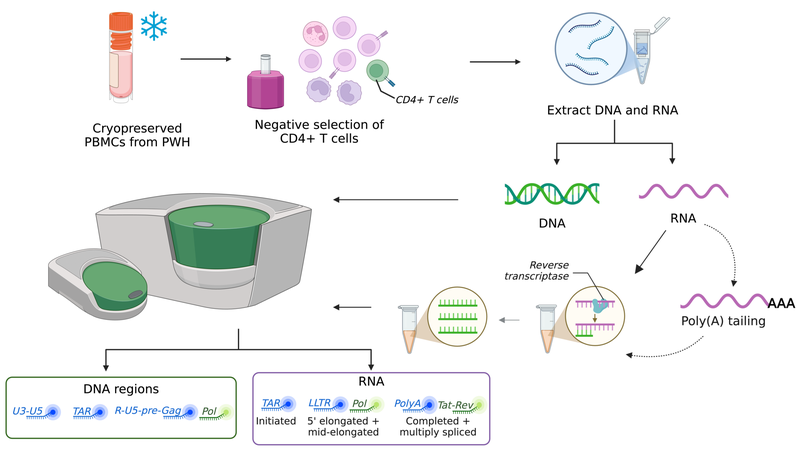


Figure 2. Quantification of HIV-1 DNA and RNA levels in PWH. CD4+T cells were isolated from longitudinal blood samples obtained before ART (T1) and up to 5 timepoints on suppressive ART (T2-T5) from PWH who initiated ART during acute (n=16) or chronic (n=10) HIV infection. HIV DNA and CA-HIV RNA levels were measured by ddPCR and RT-ddPCR, respectively.

Acknowledgments

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ART initiation during **acute infection** preserves immune responses that are both better at killing infected cells and selectively reducing those that transcribe **completed HIV transcripts**

Results

Before ART (T1), levels of some HIV DNA regions (TAR) and HIV transcripts (Pol/mid-transcribed) were higher in acute than chronic infection. However, HIV transcription initiation (HIV RNA/DNA) tended to be lower in acute infection.

DNA region	Acute T1 (copies/10^6)	Chronic T1 (copies/10^6)	P value
TAR	22819	1575	**0.02***
R-U5-pre-Gag	11831	1163	0.20
Pol	235	6.8	0.07
U3-U5	16700	1663	0.08

Table 1A. Median levels of HIV DNA regions during untreated acute or chronic infection (T1). U3-U5, TAR, R-U5-pre-Gag and Pol HIV DNA regions were quantified by ddPCR. *Bold with asterisk(*) indicates statistically significant. Pink indicates trending toward significance.*

HIV transcript	Acute T1 (copies/µg)	Chronic T1 (copies/µg)	P value
Initiated	37080	10332	0.07
5' Elongated	2471	1609	0.36
Unspliced, mid-transcribed	1296	56	**0.003***
Completed	2592	55	0.08
Multiply spliced	130	74	0.73

Table 1B. Median levels of HIV transcripts during untreated acute or chronic infection (T1). Initiated (TAR), 5' elongated (R-U5-pre-Gag), unspliced/mid-transcribed (Pol), completed (PolyA), and multiply spliced (TatRev) HIV transcripts per were quantified by RT-ddPCR.

HIV RNA/DNA ratios	Acute T1	Chronic T1	P value
Initiated	2.1	4.8	0.08
5' Elongated	0.46	0.75	0.80
Unspliced, mid-transcribed	0.96	0.43	0.19
Completed	0.29	0.14	0.30

Table 1C. Median values of HIV RNA per provirus during untreated acute or chronic infection (T1). Each HIV transcript was normalized to the corresponding HIV DNA region to correct for differences in the relative frequency of proviral mutations.

From ART initiation to T2, the decrease in HIV DNA per unit time was greater in those who initiated ART during acute than chronic infection.

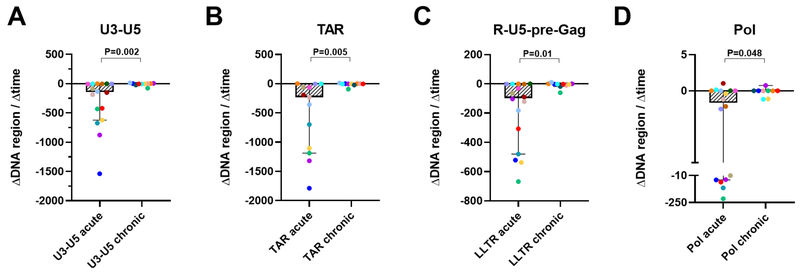


Figure 3. Slope decays of HIV DNA regions from ART initiation to the first timepoint after ART suppression (T2). We measured the change HIV DNA (T2-T1) divided by the time from start of ART to T2. Levels of **A)** U3-U5, **B)** TAR, **C)** R-U5-pre-Gag (LLTR), and **D)** Pol HIV DNA were measured by ddPCR.

Results (continued)

Acute–treated PWH showed a faster decrease in total levels of most HIV transcripts (A-E) and in completed HIV transcripts per provirus (F).

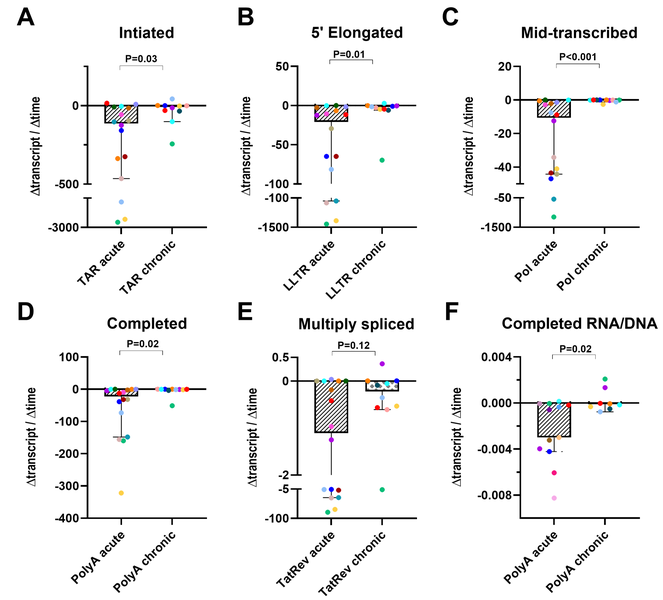


Figure 4. HIV RNA slope decay from the start of ART to after ART initiation (T2). We measured the change in HIV RNA (T2-T1) divided by the change in time from the start of ART to T2 for **A)** initiated (TAR), **B)** 5' elongated (LLTR), **C)** mid-transcribed/unspliced (Pol), **D)** completed (PolyA), and **E)** multiply spliced (TatRev) HIV transcripts. **F)** We also measured the change in completed HIV transcripts per corresponding HIV DNA (T2-T1) from ART start to T2.

Decay half-lives of different HIV DNA regions/proviruses and different HIV transcripts tended to be longer after ART initiation during chronic infection.

A HIV DNA	Acute (weeks)	Chronic (weeks)
TAR	19	160
R-U5-pre-Gag	18	100
Pol	19	370
U3-U5	18	250

B HIV RNA	Acute (weeks)	Chronic (weeks)
Initiated	29	600
Elongated	19	150
Mid/Pol	14	340
Complete	15	140
Spliced	17	91

C IPDA	Acute (weeks)	Chronic (weeks)
5' defective	19	96
3' defective	17	140
Intact	19	120
Total defective	18	96

D IVRA	Acute (weeks)	Chronic (weeks)
5' defective	19	220
3' defective	14	210
Intact	15	160
Total defective	16	220

Table 2A-D. Estimated half-lives of HIV DNA and transcripts. A monophasic decay model was used to estimate the half-life (in weeks) of **A)** HIV DNA regions, **B)** HIV transcripts, **C)** intact and defective HIV DNA, and **D)** intact and defective HIV RNA. *Orange denotes the decay was not statistically significant*,

$$\log_2 y_{ciat} = \mu_i + \alpha_0 + \alpha_{ca} + \beta_{ca} t + \epsilon_{ciat},$$

where cohort c, individual i, assay type a, and time t, account for differences between cohorts and assays

Conclusions

- Before ART, levels of TAR HIV DNA and Pol HIV RNA were higher in acute than chronic infection, but paradoxically, HIV transcription initiation tended to be lower in acute infection (Table 1).
- After ART, acute-treated PWH showed faster declines in all HIV DNA regions (Fig. 3, Table 2) and most HIV transcripts, as well as a trend towards faster decline in completed HIV RNA per provirus (Fig. 4, Table 2).