Effect of ART Start Time, ART Duration, and Elite Control on HIV Transcription

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BACKGROUND:

- **It remains unclear how HIV transcription varies with timing of ART, ART duration, and elite controller status.**
- **To investigate patterns in transcription, we quantified HIV-1 RNA regions from participants enrolled in the Reservoir Assay Validation and Evaluation Network (RAVEN) study.**

ART Start	ART Duration	Samples	Individuals
Early	Short	15	6
Early	Intermediate	15	4
Early	Long	17	6
Chronic	Short	13	4
Chronic	Intermediate	7	4
Chronic	Long	23	8
Elite Controllers	N/A	8	4
Total		98	36

Table 1: RAVEN program samples and participants. Total numbers of samples (column 3) and individuals (column 4) stratified by ART start time (early, chronic), ART duration (short, intermediate, long), and elite controller status.

We hypothesized that HIV transcription would be lower in early-treated participants and elite controllers.

METHODS:

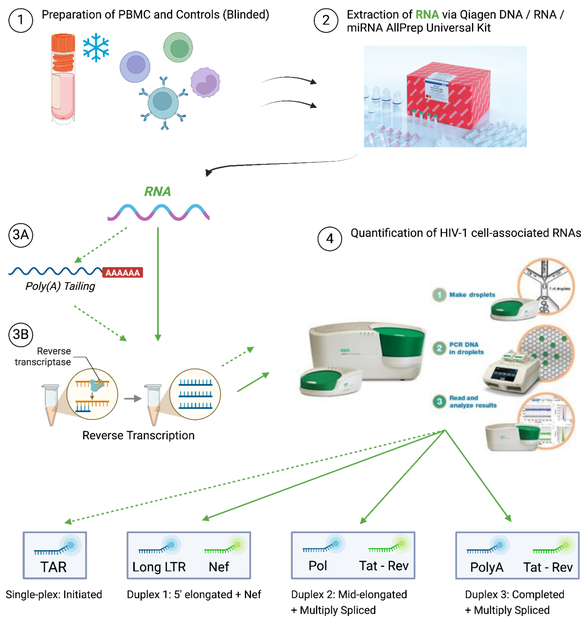


Figure 1: Quantification of HIV-1 RNA Levels in RAVEN cohort. HIV-1 RNA levels were quantified by reverse transcription droplet digital PCR (RT-ddPCR). *"TAR" = Initiated, "Long LTR" = R-U5-pre-Gag (5' elongated), Pol = mid-elongated, "PolyA" = U3-polyA (completed), "Tat-Rev" = multiply spliced. Figure illustrated using BioRender.com*

(1) **Early ART** start may preserve immune responses that limit **HIV transcription initiation**.
(2) **Elite control** mechanisms do not limit HIV transcription initiation, but limit HIV infection frequency and total CA-HIV RNA.

RESULTS:

We observed no differences in CD4+ T cell counts between early-treated PWH, chronic-treated PWH, and elite controllers. Elite controllers had higher CD8+ T cell counts than early-treated PWH, as well as lower total HIV DNA compared to chronic treated PWH.

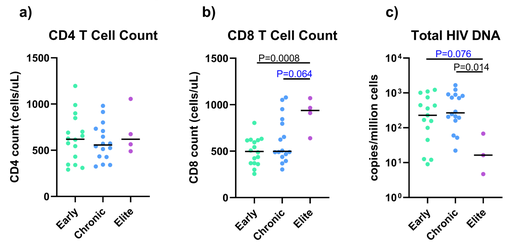
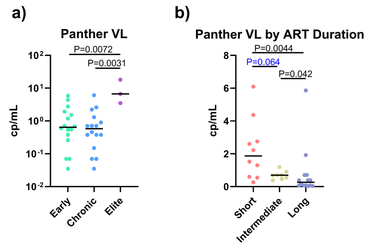


Figure 2: CD4+, CD8+, and total HIV DNA levels in RAVEN participants. Levels of CD4+ T cells (a), CD8+ T cells (b), and total HIV DNA (c) were quantified. *Black bars within the graphs indicate medians. Numbers written in blue indicate trending p-values.*

Plasma HIV RNA was higher in elite controllers than early and chronic treated PWH, and decreased with time on ART.

Figure 3: Plasma HIV RNA in RAVEN participants Plasma HIV RNA levels were determined using the Hologic Panther platform and compared between early-treated PWH, chronic-treated PWH, and elite controllers (a). Plasma HIV RNA levels were also compared by time on ART (b). *Black bars indicate medians, blue numbers indicate trending p-values.*



CA-HIV RNA levels tended to be lower in early-treated PWH and elite controllers than chronic-treated PWH.

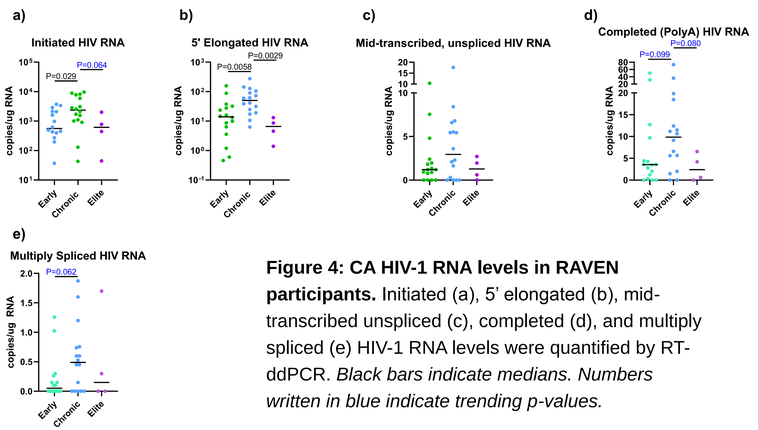


Figure 4: CA HIV-1 RNA levels in RAVEN participants. Initiated (a), 5' elongated (b), mid-transcribed unspliced (c), completed (d), and multiply spliced (e) HIV-1 RNA levels were quantified by RT-ddPCR. *Black bars indicate medians. Numbers written in blue indicate trending p-values.*

RESULTS (cont'd):

HIV transcription per provirus tended to be lower in early-treated PWH than chronic-treated PWH, and higher in elite controllers.

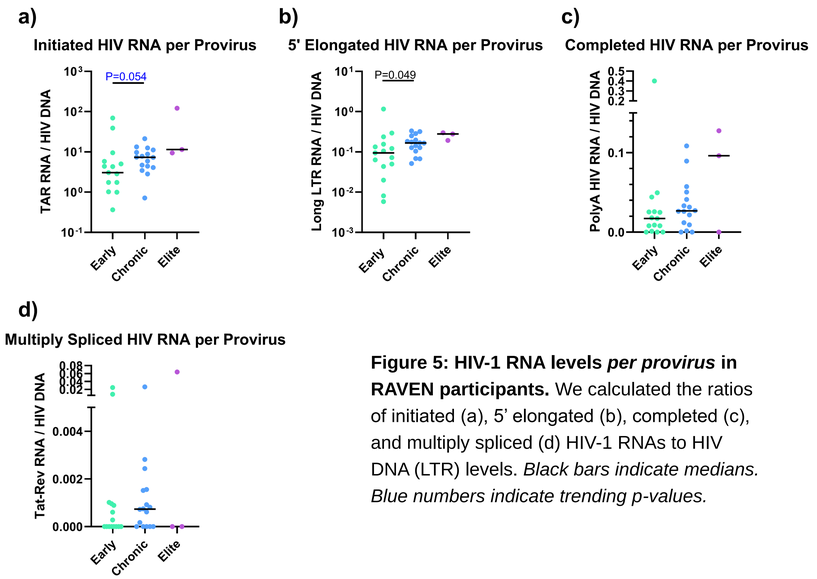


Figure 5: HIV-1 RNA levels *per provirus* in RAVEN participants. We calculated the ratios of initiated (a), 5' elongated (b), completed (c), and multiply spliced (d) HIV-1 RNAs to HIV DNA (LTR) levels. *Black bars indicate medians. Blue numbers indicate trending p-values.*

CONCLUSIONS:

- ❖ **Early-treated PWH may have better immune responses that reduce HIV transcription per provirus (Fig. 5) or enhance the killing of HIV-transcribing cells. These immune responses may wane with longer periods of time before initiating ART.**
- ❖ **The mechanism(s) of elite control do not appear to limit HIV transcriptional initiation (Fig. 5A).**
- ❖ **Elite control mechanism(s) may limit infection frequency by limiting the spread of infection and/or killing HIV-infected cells (Fig. 2).**

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