HIV DNA and RNA Levels Before and After ART in Natural Controllers and Comparison to Non-Controllers

354

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INTRODUCTION

- HIV-1 elite controllers comprise < 1% of all people with HIV (PWH) and suppress viral loads to <50 copies/mL without antiretroviral therapy (ART).
- Few studies have measured cell-associated (CA) HIV transcripts in elite controllers.
- It is unclear whether administration of ART in elite controllers would lead to reductions in the HIV reservoir or changes to patterns in HIV transcription.

We hypothesized that:

(1) Blocks to HIV transcription will differ between controllers and ART-suppressed non-controllers (NC).

(2) ART will reduce completed and spliced HIV transcripts.

METHODS

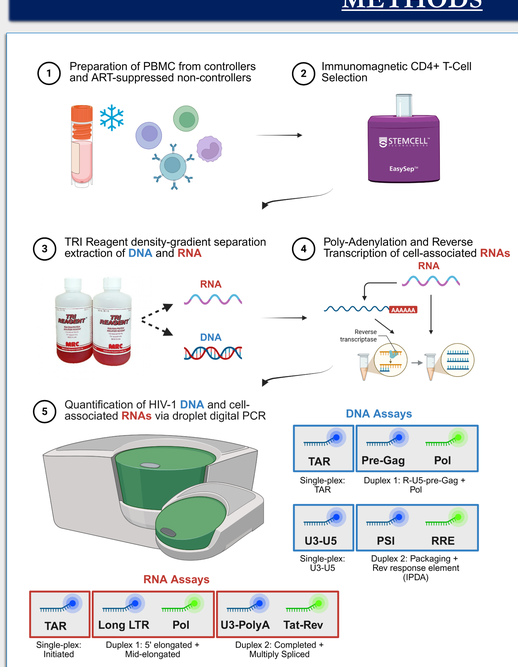


Figure 1: Quantification of HIV DNA and Cell-Associated (CA) RNA. Levels of HIV DNA were quantified by droplet digital PCR (ddPCR). CA-HIV RNA levels were quantified by RT-ddPCR. *For DNA: "TAR" = Trans-Activator Response region, "Pre-Gag" = R-U5-pre-Gag region, "Pol" = Pol region, "U3-U5" = U3-U5 region, "PSI" = Packaging signal, "RRE" = Rev response element. For RNA: "TAR" = Initiated, "Long LTR" = 5' elongated, "Pol" = Mid-elongated, "U3-PolyA" = completed, "Tat-Rev" = multiply spliced.* Figure was illustrated using BioRender.com

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- Natural **HIV control** may be associated with mechanisms that limit production or increase clearance of **completed HIV RNA**.
- In controllers, **ART** reduces **HIV reservoirs**, decreases **HIV RNA**, and increases **CD4 counts**.

RESULTS

Levels of most HIV DNA regions were lower in untreated controllers than ART-suppressed non-controllers (2A). However, we observed no difference in levels of intact HIV DNA (2B).

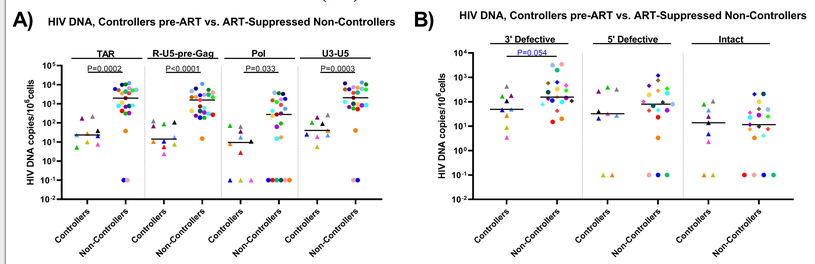


Figure 2: HIV DNA levels in controllers and ART-suppressed non-controllers. Levels of various HIV DNA regions (A) and intact or defective HIV DNA (B) were quantified by ddPCR. *Black bars indicate medians. P-values were calculated using the Mann-Whitney test.*

Total levels of initiated and completed HIV RNA were lower in untreated controllers than ART-suppressed non-controllers (3A). Controllers had paradoxically higher levels per provirus of initiated and 5' elongated HIV transcripts (3B) but a lower ratio of completed/elongated HIV RNA (3C).

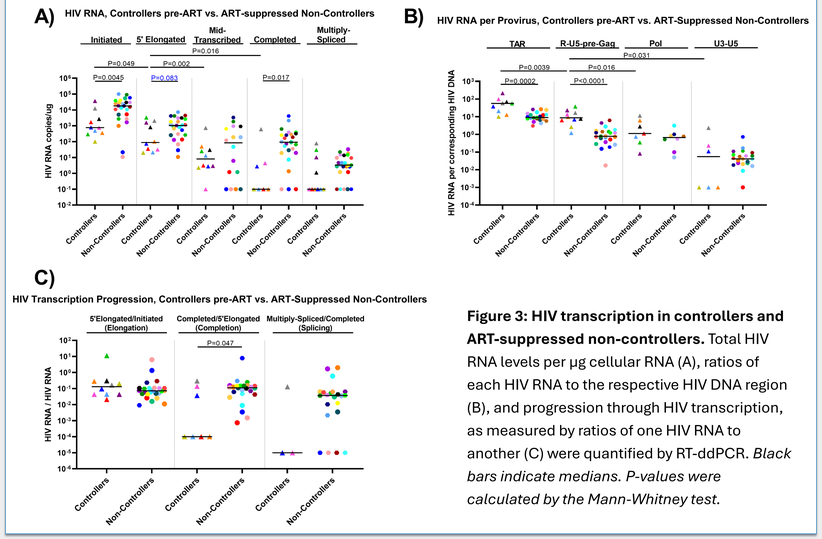


Figure 3: HIV transcription in controllers and ART-suppressed non-controllers. Total HIV RNA levels per µg cellular RNA (A), ratios of each HIV RNA to the respective HIV DNA region (B), and progression through HIV transcription, as measured by ratios of one HIV RNA to another (C) were quantified by RT-ddPCR. *Black bars indicate medians. P-values were calculated by the Mann-Whitney test.*

RESULTS

In controllers, ART increased CD4 counts from T1 to T2 (4A) and tended to increase CD4:CD8 ratios (4B).

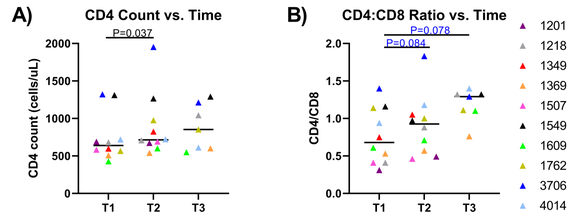


Figure 4: Changes in CD4 counts and CD4:CD8 ratios after starting ART. CD4+ T cell counts (A) and ratios of CD4/CD8 T-cells (B) were measured in controllers before ART start (T1), and at a median of 1.4 yrs (T2) and 4.5 yrs (T3) post-ART. *Black bars indicate medians. P-values were calculated using the Wilcoxon signed-rank test.*

In controllers, ART decreased levels of all HIV DNA regions (5A), intact and defective proviruses (5B), and total levels of initiated, 5' elongated, and possibly mid (Pol) HIV RNA (5C) from T1 to T2.

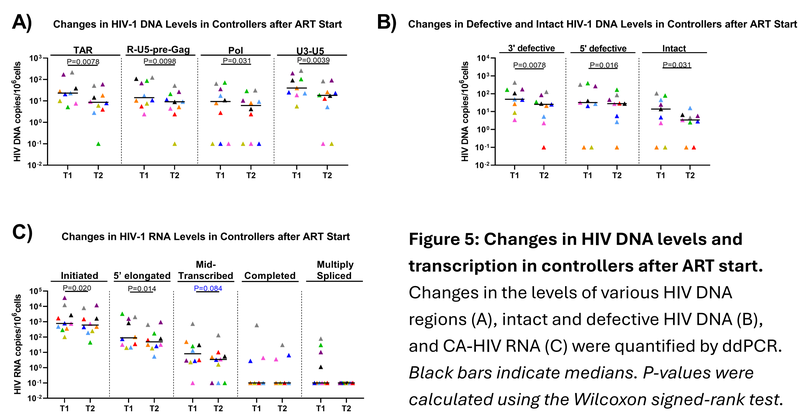


Figure 5: Changes in HIV DNA levels and transcription in controllers after ART start. Changes in the levels of various HIV DNA regions (A), intact and defective HIV DNA (B), and CA-HIV RNA (C) were quantified by ddPCR. *Black bars indicate medians. P-values were calculated using the Wilcoxon signed-rank test.*

CONCLUSIONS

1. Compared to ART, natural control of HIV led to fewer infected cells, higher levels per provirus of short HIV transcripts, and lower proportions of completed HIV transcripts.
2. The ability to clear and/or prevent production of completed HIV RNA may be important for protective immune responses in controllers.
3. ART treatment of controllers increased CD4+ T cell counts, reduced HIV reservoirs, and decreased HIV transcripts, suggesting ART may improve health and should be offered to controllers.