Doubling dolutegravir dosage reduces HIV persistence markers in ART-treated adults

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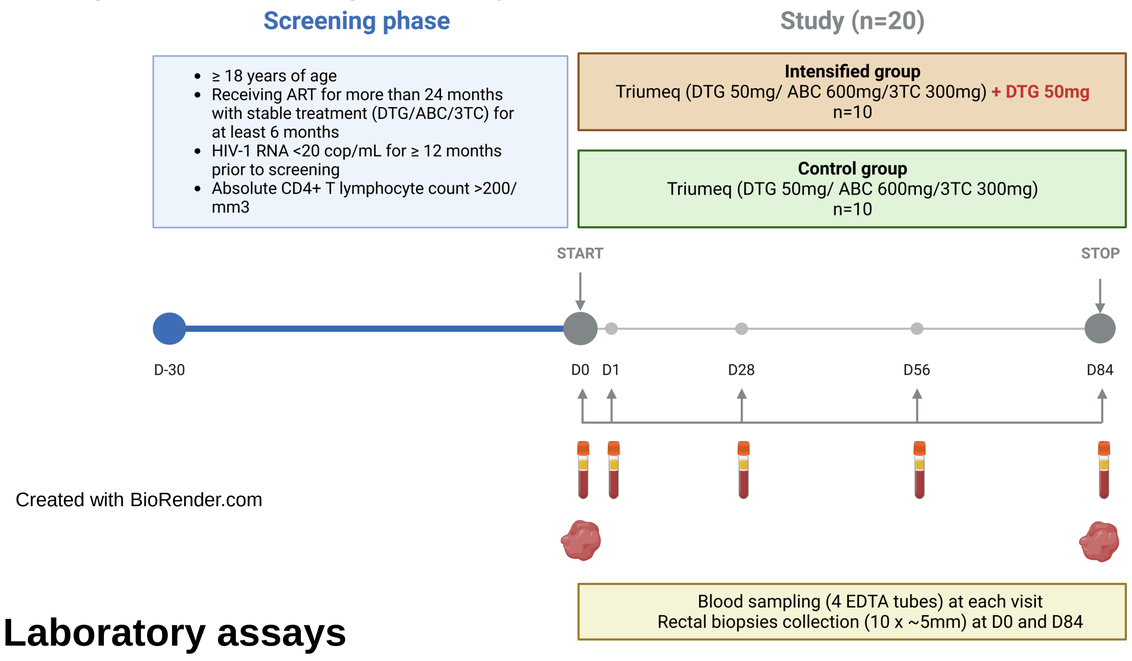
BACKGROUND

- Whether ongoing viral replication occurs in people living with HIV (PLWH) despite antiretroviral therapy (ART) and leads to low-level residual viremia is still debated.
- Here we report on a study, in which we intensified the ART regimen by **doubling dolutegravir (DTG) dosage**. We investigated the impact of this strategy **on HIV blood and tissue latent reservoirs**, **residual viremia**, **immune activation**, and **inflammation**.

MATERIALS AND METHODS

- Twenty HIV-infected adults were enrolled in a phase 3 randomized clinical trial.
- Half of them received additional **50 mg of DTG** for **3 months** as treatment intensification.
- Peripheral blood mononuclear cells (PBMCs), plasma and rectal biopsies were longitudinally collected.



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Laboratory assays

- Concentration of dolutegravir in plasma and in tissue.
- Total HIV DNA, intact HIV DNA (IPDA), cell-associated unspliced (US) HIV RNA in PBMCs and in rectal tissue.
- Single copy assay to determine ultrasensitive plasma viral load.
- Expression of immune activation (HLA-DR, CD38) and exhaustion (PD-1, TIGIT) markers on CD4+ and CD8+ T cells.
- Inflammation by measuring the levels of several plasma biomarkers including sCD14, IL-4, IL-6, IP-10, hsCRP, IFN gamma, and TNF alpha.

RESULTS

- As expected, plasma and tissue DTG concentrations significantly increased between day 0 and day 84 in the intensified group.
- No significant difference in total HIV-1 DNA in PBMCs and in tissue between day 0 and day 84 in both groups.
- However, day84/day0 ratios for both total and intact HIV-1 DNA in PBMCs were significantly lower in the intensified group.
- Significant decreases in US HIV-1 RNA in PBMCs and in ultrasensitive plasma viral load between days 0 and 84 were observed in the intensified group but not in the control group.
- However, intensification had no measurable impact on chronic inflammation or immune activation.

FIGURES

1. DTG concentration increases in plasma and in tissue

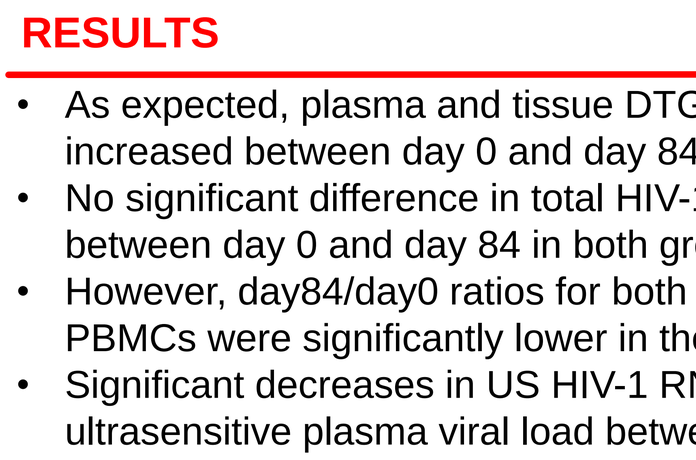


Figure 1: Dolutegravir (DTG) concentrations in plasma and in tissue during intensification.
Evolution of DTG plasma concentration in the control group (A), evolution of DTG plasma concentration in the intensified group (B), evolution of DTG tissue concentration in the control group (C), evolution of DTG tissue concentration in the intensified group (D).

2. DTG intensification reduces HIV persistence markers

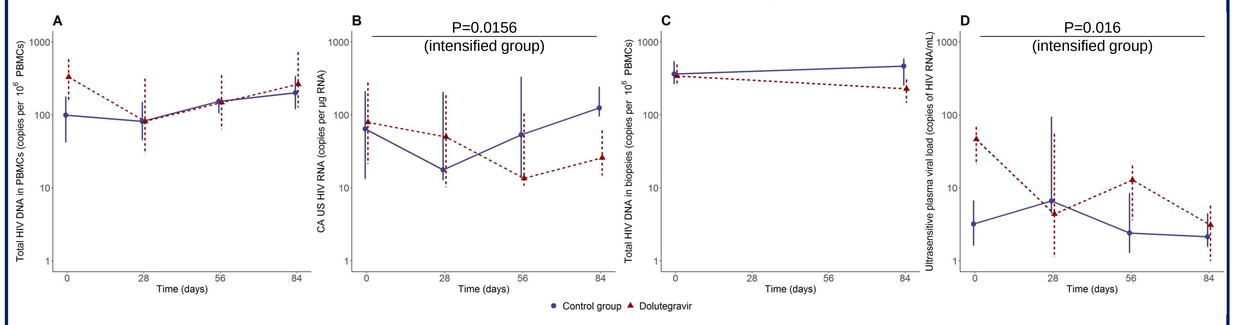


Figure 2a: Virological markers during ART intensification.
Median (IQR) concentrations of total HIV DNA in PBMCs (A), cell-associated unspliced HIV RNA (B), total HIV DNA in rectal biopsies (C) and ultrasensitive plasma viral load (D).

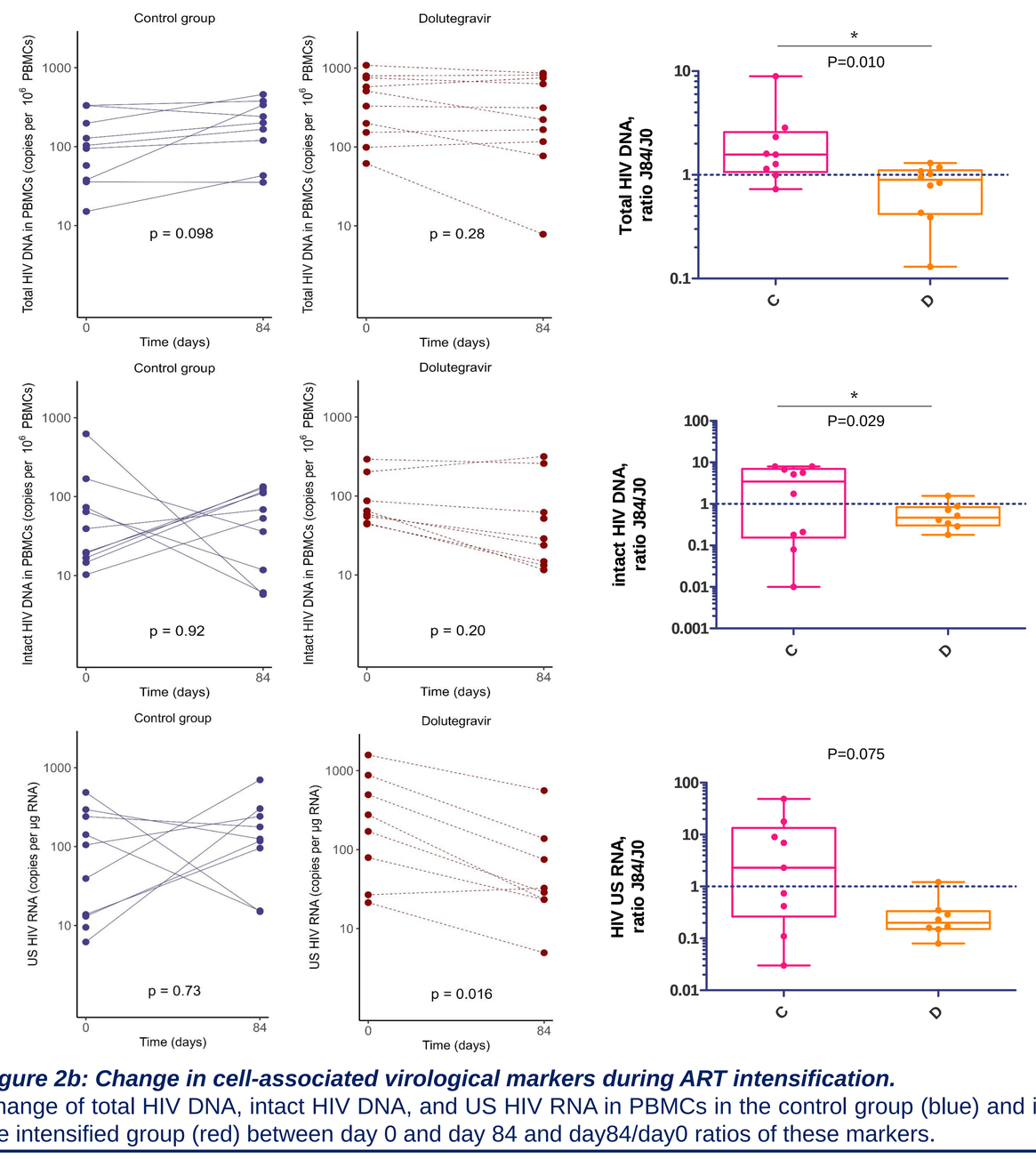


Figure 2b: Change in cell-associated virological markers during ART intensification.
Change of total HIV DNA, intact HIV DNA, and US HIV RNA in PBMCs in the control group (blue) and in the intensified group (red) between day 0 and day 84 and day84/day0 ratios of these markers.

3. DTG intensification doesn't impact immune activation and inflammation

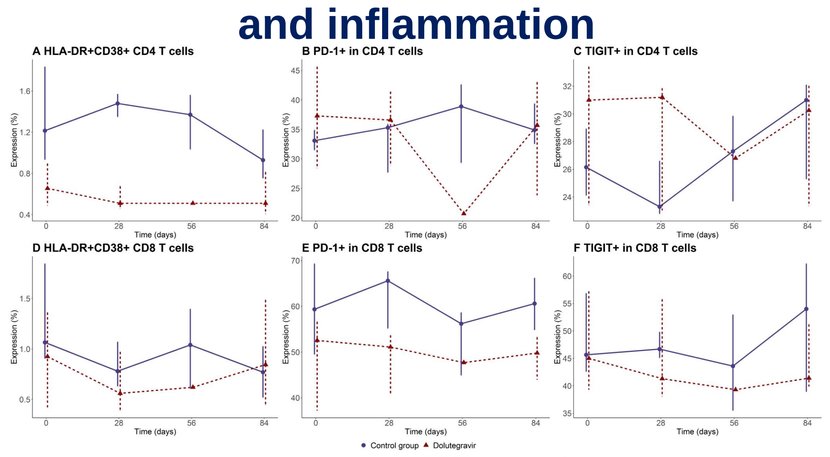
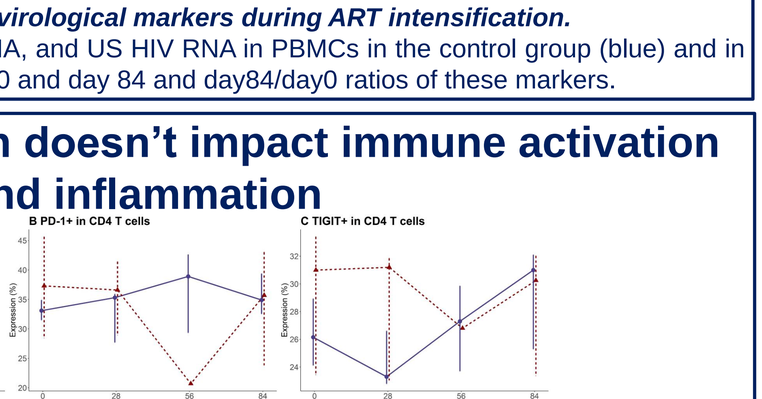


Figure 3: T-cell activation and exhaustion during ART intensification.
Percentage of CD4+ T cells expressing HLA-DR and CD38 (A), PD-1 (B), TIGIT (C) measured by flow cytometry. Percentage of CD8+ T cells expressing HLA-DR and CD38 (D), PD-1 (E), TIGIT (F) measured by flow cytometry.

Figure 4: Biomarkers of inflammation during ART intensification.
Median (IQR) concentrations of sCD14 (A), IL-6 (B), IFN-γ (C) and hsCRP (D). sCD14=soluble CD14, IL-6=interleukin-6, IFN-γ=interferon-gamma, hsCRP=high sensitivity C-reactive protein.



CONCLUSIONS

- Overall, these results suggest ongoing viral replication in some participants.
- If confirmed in larger clinical trials, these results could have an impact on the clinical management of PLWH.

ADDITIONAL KEY INFORMATION

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