Impact of Antiretroviral Therapy (ART) Intensification on HIV-1 Virologic Markers (ACTG A5324)

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BACKGROUND

In people living with HIV-1 (PWH) on effective antiretroviral therapy (ART), neurocognitive disorders (ND) may arise from continued residual replication, including in the central nervous system (CNS), despite control of plasma viremia.

Hypothesis: The A5324 trial evaluated if ART intensification with dolutegravir (DTG) or DTG with maraviroc (MVC) could reduce residual replication and improve neurocognitive performance (NP).

- NDs in PWH may be due to persistent low-level HIV-1 replication during ART. If this is true, then ART drugs that distribute better into the CNS might better suppress HIV-1 replication in this protected compartment and treat NDs.
- Also, some studies with integrase inhibitor intensification have observed potential effects on residual replication.
- Both DTG, a second-generation integrase inhibitor, and MVC, a CCR5-inhibitor, achieve therapeutic concentrations in the CNS. Moreover, the target of MVC is the main co-receptor used by HIV-1 in CNS.
- In A5324, ART intensification did not improve NDs in PWH (Letendre, 2023). Here we evaluated virological markers from the periphery to determine if we could detect an impact on the HIV-1 reservoir or residual replication.

METHODS

Trial design

- A randomized, double-blind, placebo-controlled 96-week trial of ART intensification in PWH with NDs
  - **Arm 1:** dual placebo (PBO)
  - **Arm 2:** DTG + PBO
  - **Arm 3:** DTG + MVC

Sample collection

- Plasma and PBMC were collected at baseline, week 2, week 4, and week 12.

Virological assays

- HIV-1 cell-associated DNA (caDNA), ddPCR
- HIV-1 cell-associated RNA (caRNA), RT-ddPCR
- HIV-1 cell-associated 2-LTR circle (ca2LTR), ddPCR
- plasma HIV-1 RNA, low copy assay

191 individuals were enrolled

- Stratified by nadir CD4⁺ T cell count and ND severity
- 171 participants were analyzed for virological markers from blood (PBMC and plasma).
- Excluded participants either went off study treatment prior to week 12 or did not have data available at all necessary timepoints for evaluation.

In PWH with neurocognitive impairment, the HIV-1 peripheral reservoir and residual replication <u>were unaffected</u> by 12 weeks of ART intensification and <u>did not relate to</u> neurocognitive performance

RESULTS

Comparison of several key characteristics at baseline demonstrates the randomization was successful and the groups are well-balanced.

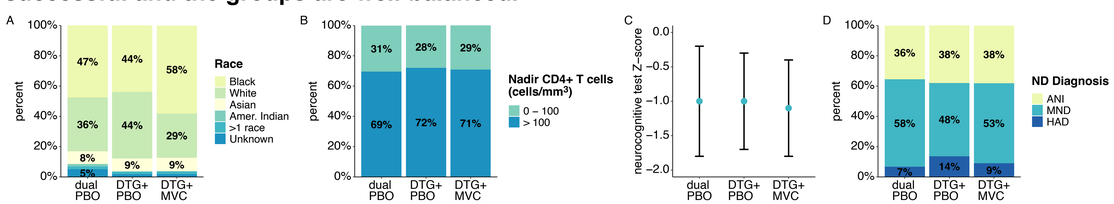


Figure 1: Baseline characteristics (A) Race, (B) Nadir CD4+ T cells (cells/mm^3), (C) Average normalized neurocognitive test Z-score, (D) ND Diagnosis are shown. For the neurocognitive test Z-score results (C), the mean and standard deviation are shown, and all other remaining plots display the baseline characteristic category proportions for each arm. In (D) HIV-associated neurocognitive disorder (HAND) categories were utilized and abbreviated as follows asymptomatic neurocognitive Impairment (ANI), mild neurocognitive disorder (MND), or HIV-associated dementia (HAD).

Detection and levels of HIV-1 caDNA and caRNA did not change significantly during first 12 weeks of intensification.

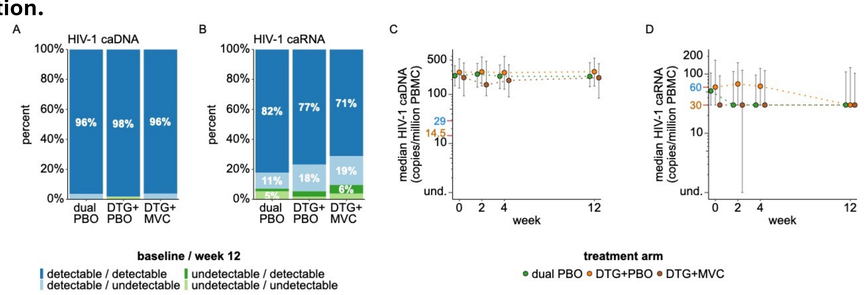


Figure 2: HIV-1 caDNA (A) and HIV-1 caRNA (B) results were divided into four categories based on the combination of detection between baseline and week 12. The median values and the Q1 and Q3 range for HIV-1 caDNA (C) or HIV-1 caRNA (D) is plotted for each arm and timepoint examined. Detectable results below the LLoQ were set to one-half the LLoQ and undetectable values (und.) were set to zero. The LLoQ and one-half LLoQ values of each of each assay are shown on each axis in blue and orange text, respectively.

Detection of HIV-1 ca2LTR differed significantly in the DTG+MVC arm at week 2-4, with a higher proportion undetectable at week 2-4, but the difference was diminished by week 12.

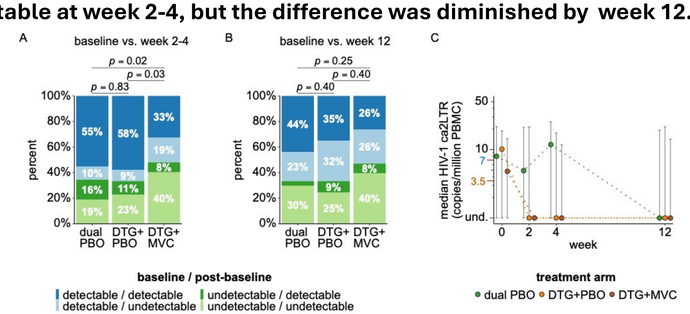


Figure 3: HIV-1 ca2LTR results were categorized based on the combination of detection between baseline and (A) avg. of week 2-4 (B) or week 12. A chi-squared test was applied to test for differences in detection between arms and the P-value (p) for each test is shown above the bar graphs. (C) The median values and the Q1 and Q3 range is plotted for each arm and timepoint examined. Detectable results below the LLoQ were set to one-half the LLoQ and undetectable values (und.) were set to zero. The LLoQ and one-half LLoQ values are shown on the axis in blue and orange text, respectively.

Detection of HIV-1 plasma RNA did not differ between arms and a greater proportion of participants experienced an increase in HIV-1 plasma RNA in the DTG+MVC arm.

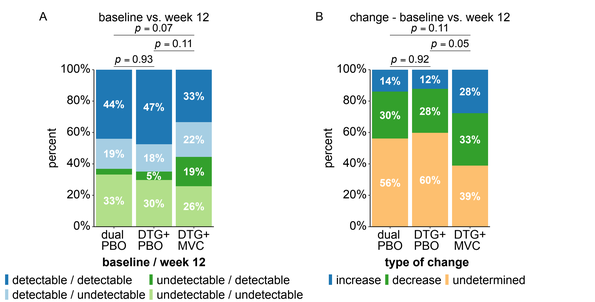


Figure 4: (A) HIV-1 plasma RNA results were categorized based on the combination of detection between baseline and week 12. (B) HIV-1 plasma RNA results were categorized according to whether a participant experienced a change in level (increase or decrease) or If baseline and week 12 results were below the LLoQ the change was undetermined. A chi-squared test was applied to test for differences in detection or change between arms and the P-value (p) for each test is shown above the bar graphs.

HIV-1 markers and the normalized average neurocognitive performance (Z-score) are not strongly correlated.

	HIV-1 marker[2]	Correlation with total Z-score[3]	P-Value[3]
Baseline	caDNA	-0.02	0.79
	caRNA	-0.07	0.34
	ca2LTR	0.01	0.91
	plasma RNA	-0.02	0.75
Change from baseline[1]	caDNA	0.02	0.81
	caRNA	-0.11	0.16
	ca2LTR	0.15	0.05
	plasma RNA	-0.09	0.25

[1] Change from baseline and week 48 (Z-score) or week 12 (HIV-1 marker)
[2] HIV-1 marker quantitative results were utilized in this correlation analysis
[3] Spearman Correlation

CONCLUSIONS

- ART intensification with DTG or DTG+MVC over 12 weeks did not significantly impact the peripheral HIV-1 reservoir or residual replication, consistent with other studies of ART intensification.
- Although, detection of HIV-1 ca2LTR at week 2-4 differed significantly in DTG+MVC arm compared to the other arms a higher proportion of individuals were undetectable for HIV-1 ca2LTR in the DTG+MVC at baseline. This difference may have influenced the initial significance that was then diminished by week 12.
- We observed a larger proportion of individuals that experienced in increase in HIV-1 plasma RNA in the DTG+MVC arm, however plasma RNA levels remain well suppressed in most individuals (< 50 copies/mL).
- An important limitation of this study is that all virological measurements were taken from the periphery, so effects on the HIV-1 reservoir and residual replication in the CNS were not directly measured.