Dolutegravir Increases B Cells and Resting Memory B Cells in Blood and Lymph Nodes in RV254

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BACKGROUND

Early initiation of antiretroviral therapy (ART) in acute HIV infection (AHI) could help preempt evasion and damage of the immune system by HIV. Treatment of AHI with ART improves long term virologic suppression and clinical outcomes for the individual. Moreover, B cell abnormalities can be found in HIV infected participants, especially reduced resting memory (RM) and increased activated memory (AM) B cells and can be reversed by ART. Combination ART is the standard of care for all individuals with HIV infection, including AHI. Currently, use of the integrase inhibitor dolutegravir (DTG) and double nucleoside reverse transcriptase inhibitor (2NRTIs) is the new standard regimen. DTG can block HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells. However, the influence of these drugs on the recovery of immune cells in blood and lymph node (LN) tissue has not been well studied. To address this, we assessed differences in B cell populations in Thai participants randomized to switch from 2NRTI+EFV (3TC/TDF/EFV) to 2NRTI+DTG (3TC/EFV/DTG).

MATERIALS AND METHODS

Cryopreserved peripheral blood mononuclear cells (PBMCs) and lymph node mononuclear cells (LNMCs) from 27 AHI treated Thai participants enrolled in the RV254 cohort were analyzed. Participants were grouped based on ART regimen: those randomized to switch from 2NRTI+EFV to 2NRTI+DTG (n=13; 6-22 months EFV followed by 9-20 months DTG) and those who remained on 3TC/TDF/EFV (range 6-22 months) (n=14). Eighteen uninfected individuals (HIV$^-$) enrolled in RV304 were included for comparison. B cells were characterized by flow cytometry. All these participants fulfilled demographic and clinical data are included in Table 1. These cohorts are under the Chulalongkorn University (Bangkok, Thailand) and Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD, USA) IRB approved clinical study. *$p < 0.05$; **$p < 0.005$; ***$p < 0.0005$; ****$p < 0.00005$ (Kruskal-Wallis test)*

STUDY PARTICIPANTS

Table 1. Clinical characterization of study participants.

Study Cohorts	ART	Number of participants	Median CD4+ T cells (cells/cu.mm.)	Median plasma HIV-RNA (copies/ml)
RV254gr.1	ABC/3TC/EFV	14	613 (336-1,633)	< 20
RV254 gr.2	ABC/3TC/DTG	13	566 (467-1,382)	< 20
RV304A	No	18	-	-

CONCLUSIONS

- Switching from 2NRTI+EFV to 2NRTI+DTG could aid in recovery of B cell populations in both blood and LN
- Higher frequencies of B cells and RM B cells in both PBMCs and LNMCs after switching from 2NRTI+EFV to 2NRTI+DTG
- 2NRTI+DTG treated participants had fewer AM and TLM B cells, the latter of which have an exhausted phenotype.
- Plasmablast and plasma cells increased in people on 2NRTI+DTG
- Frequencies of GC B cells tended to be higher in participants on 2NRTI+DTG

These data suggest that switching from EFV to DTG may be beneficial to limit activation and exhaustion in the B cell compartment of participants who initiated treatment in AHI.

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RESULTS

I. Total and resting memory B cells in people on ART with DTG or EFV based regimen

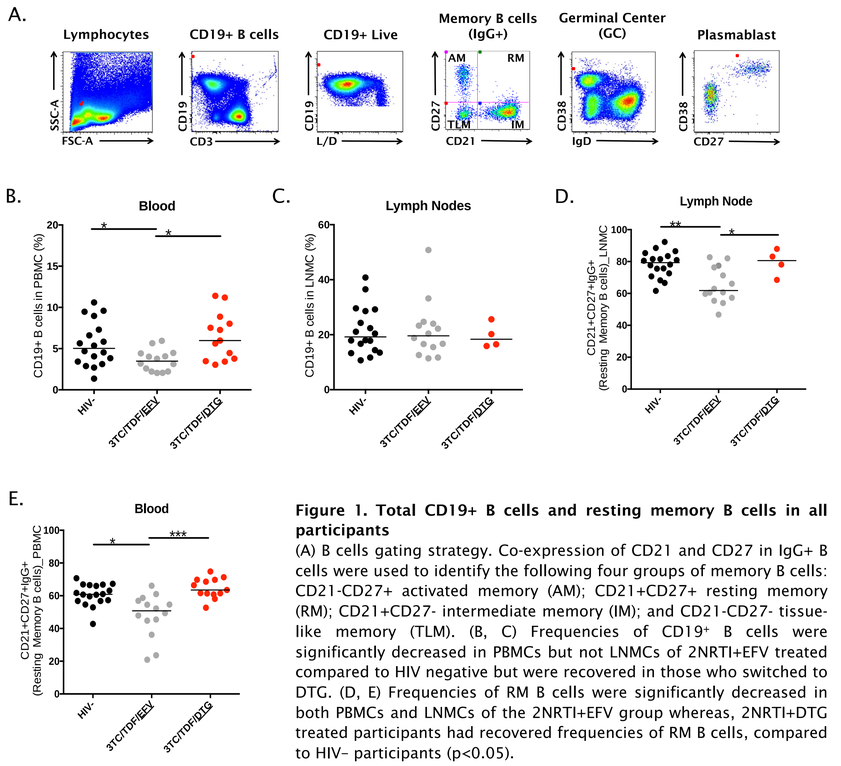


Figure 1. Total CD19+ B cells and resting memory B cells in all participants
(A) B cells gating strategy. Co-expression of CD21 and CD27 in IgG+ B cells were used to identify the following four groups of memory B cells: CD21-CD27+ activated memory (AM); CD21+CD27+ resting memory (RM); CD21+CD27- intermediate memory (IM); and CD21-CD27- tissue-like memory (TLM). (B, C) Frequencies of CD19$^+$ B cells were significantly decreased in PBMCs but not LNMCs of 2NRTI+EFV treated compared to HIV negative but were recovered in those who switched to DTG. (D, E) Frequencies of RM B cells were significantly decreased in both PBMCs and LNMCs of the 2NRTI+EFV group whereas, 2NRTI+DTG treated participants had recovered frequencies of RM B cells, compared to HIV- participants ($p<0.05$).

II. Decreased frequencies of AM and TLM B cells in people on ART with DTG

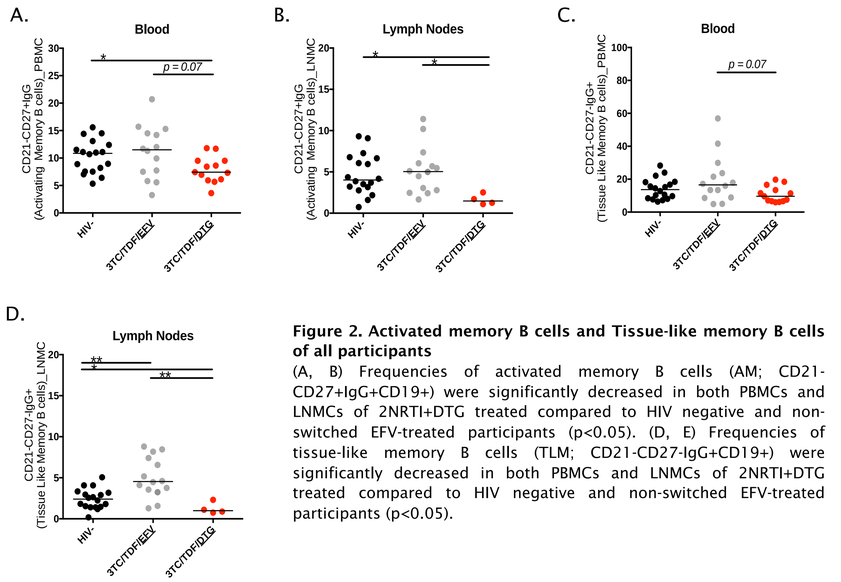


Figure 2. Activated memory B cells and Tissue-like memory B cells of all participants
(A, B) Frequencies of activated memory B cells (AM; CD21-CD27+IgG+CD19+) were significantly decreased in both PBMCs and LNMCs of 2NRTI+DTG treated compared to HIV negative and non-switched EFV-treated participants ($p<0.05$). (D, E) Frequencies of tissue-like memory B cells (TLM; CD21-CD27-IgG+CD19+) were significantly decreased in both PBMCs and LNMCs of 2NRTI+DTG treated compared to HIV negative and non-switched EFV-treated participants ($p<0.05$).

III. Increased frequencies of plasmablasts, plasma cells and germinal center (GC) B cells in people on ART with DTG

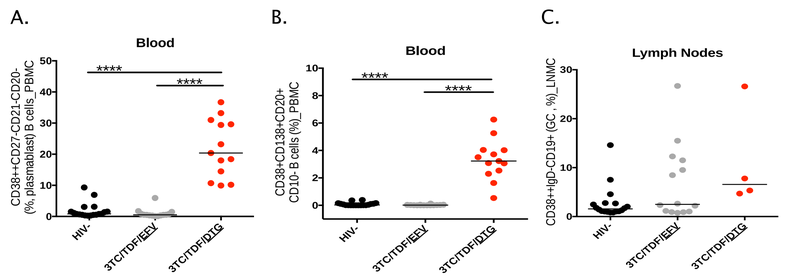


Figure 3. Plasmablasts, plasma cells and germinal center B cells of all participants
(A) Plasmablast B cells were gated as CD38hiCD27+CD21-CD20-CD19+ (B) plasma B cells were gated as CD38+CD138+CD20+CD10-CD19+ (C) Germinal center (GC) B cells were gated as CD38hiIgD-CD19$^+$ at each group. (A, B) Frequencies of plasmablasts and plasma cells in people on 2NRTI+DTG were significantly increased compared to HIV- participants and non-switched EFV-treated participants ($p<0.05$). (C) Frequencies of GC B cells in participants on 2NRTI+DTG tended to be higher than in HIV- participants and non-switched EFV-treated participants.

IV. Proliferating and activating T cells in LN

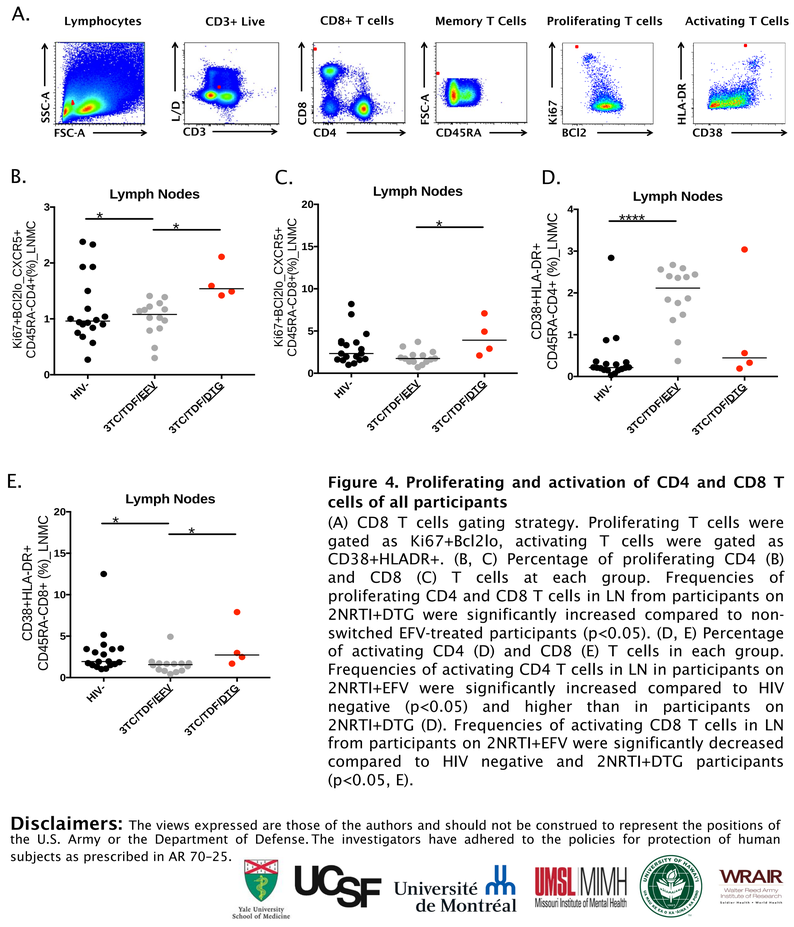


Figure 4. Proliferating and activation of CD4 and CD8 T cells of all participants
(A) CD8 T cells gating strategy. Proliferating T cells were gated as Ki67+Bcl2lo, activating T cells were gated as CD38+HLADR+. (B, C) Percentage of proliferating CD4 (B) and CD8 (C) T cells at each group. Frequencies of proliferating CD4 and CD8 T cells in LN from participants on 2NRTI+DTG were significantly increased compared to non-switched EFV-treated participants ($p<0.05$). (D, E) Percentage of activating CD4 (D) and CD8 (E) T cells in each group. Frequencies of activating CD4 T cells in LN in participants on 2NRTI+EFV were significantly increased compared to HIV negative ($p<0.05$) and higher than in participants on 2NRTI+DTG (D). Frequencies of activating CD8 T cells in LN from participants on 2NRTI+EFV were significantly decreased compared to HIV negative and 2NRTI+DTG participants ($p<0.05$, E).

Disclaimers: The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense. The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70-25.