

SCIENCE SPOTLIGHT



Persistent HIV Transcription and Variable ARV Levels in Lymph Nodes during ART

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Background, Objectives and Methods



■ Background:

- ❖ The ability of antiretroviral (ARV) drugs to penetrate and suppress viral replication in tissue reservoir sites is critical for HIV remission. The lymph node (LN) has been shown to be a pharmacologic sanctuary for some ARVs; the penetration of abacavir (CBV-triphosphate) and maraviroc (MVC) in the LN is not known.

■ Objective:

- ❖ To evaluate ARV levels in peripheral blood and the LN, and their impact on HIV transcription in LNs in participants of the RV254 acute infection cohort in Bangkok.

■ Methods:

- ❖ Group 1 (n=6): initiated and continued ART with 2 NRTI and DTG and MVC.
- ❖ Group 2 (n=12): initiated ART with 2 NRTI and EFV and switched from EFV to DTG.
- ❖ HIV-RNA+ and HIV-DNA+ cells were measured by RNAscope.
- ❖ ARV levels were quantified by LC/MS/MS, and values referenced to *in-vitro* inhibitory concentrations to give an inhibitory quotient (IQ).

Participant Characteristics at Lymph Node Biopsy



Characteristics	Groups 1+2 (N=18)	Group 1 (n=6)	Group 2 (n=12)	P-value
ART duration, wks, median	109 (24 - 252)	44 (24 - 54)	135 (86 - 252)	<0.001
DTG duration, wks, median	59 (24 - 82)	44 (24 - 54)	63 (42 - 82)	0.002
ART regimen				
ABC/3TC + DTG/MVC	3 (16.7)	3 (50)	-	
TDF/3TC + DTG/MVC	3 (16.7)	3 (50)	-	
ABC/3TC + DTG	11 (61.1)	-	11 (91.7)	
TDF/3TC + DTG	1 (5.6)	-	1 (8.3)	
Plasma HIV-RNA (<20 cpm)	18/18	6/6	12/12	

HIV-RNA and -DNA Levels in Lymph Nodes

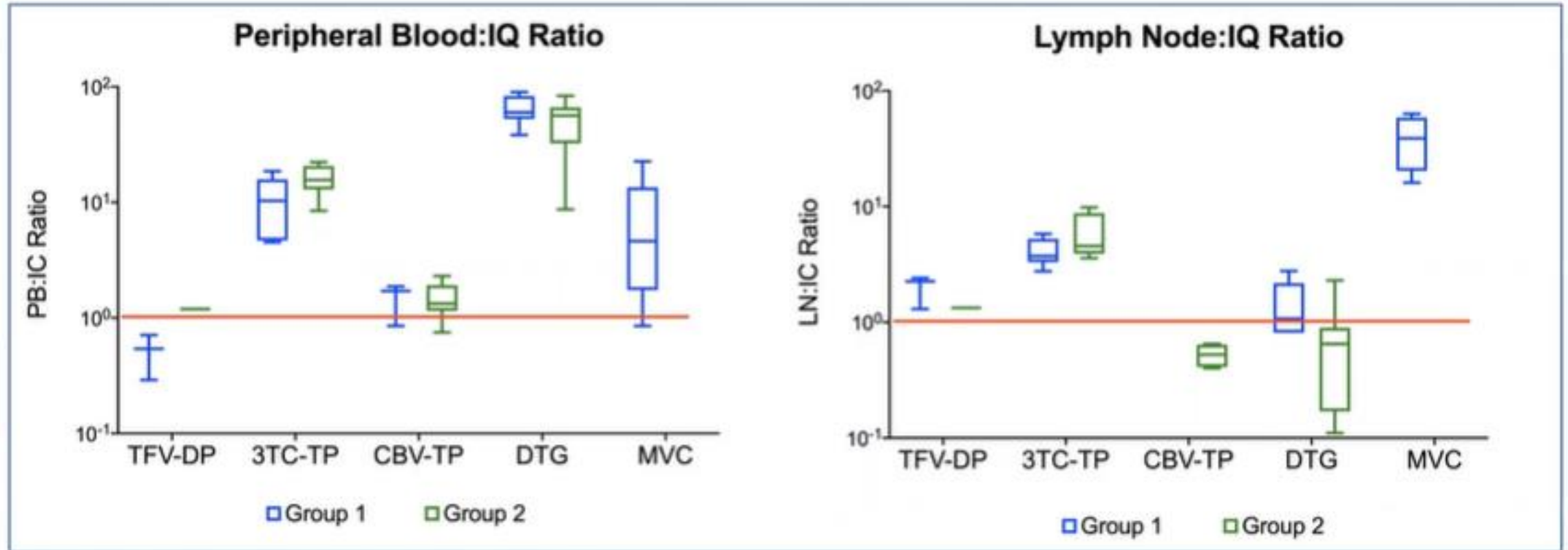


HIV Measure	Groups 1+2 (N=18)	Group 1 (n=6)	Group 2 (n=12)	P-value
HIV in Lymph Node, median (min-max)				
RNAscope (+ cells/g tissue)	9.14 (5.3-27.6 E+04)	7.14 (5.3-10.9 E+04)	9.98 (5.5-27.6 E+04)	0.111
DNAscope (+ cells/g tissue)	26.23 (10.5-76.9 E+04)	16.91 (13.5-54.3 E+04)	30.34 (10.5-76.9 E+04)	0.512

Group 1: ART with 2 NRTI and DTG and MVC
Group 2: ART with 2 NRTI switched from EFV to DTG

Inhibitory Quotient Ratios

Peripheral Blood (PBMC or Plasma) and in Lymph Nodes



The Inhibitory Quotient (IQ) is the ratio of drug concentration (in peripheral blood or LN) to the *in vitro* IC₅₀ or IC₉₀
Group 1: ART with 2 NRTI and DTG and MVC
Group 2: ART with 2 NRTI switched from EFV to DTG

Observations and Implications



- Ongoing viral expression as measured by RNAscope in LN was seen in all participants despite suppression of plasma HIV-RNA in 100% to < 20 copies/mL.
- A trend was observed for lower levels of RNA+ cells in LN in the DTG + MVC group vs. the DTG group.
- PBMC levels of cell-associated HIV-RNA and total HIV-DNA were not different between groups (data not shown).
- Plasma and PBMC concentrations of ARVs were consistent with prior data.
- CBV-TP levels in the LN were commonly not quantifiable and $<IC_{50}$. MVC LN levels, however, were uniformly quantifiable and 39-fold higher than IC_{90} .
 - ❖ Enhanced LN penetration of MVC is consistent with tissue distribution studies in rats (Xenobiotica, 2008; 38:1330-9. DOI: 10.1080/00498250802447409).
- The trend for lower LN RNA+ expression in the DTG+MVC group may be consistent with enhanced anti-HIV potency in the LN, which led to a greater reduction in the pool of infected cells. Further exploration of this observation is warranted.

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