First-line DTG+3TC Reaches Lymph Nodes and Reduces HIV Reservoir Comparable to DTG+FTC/TAF

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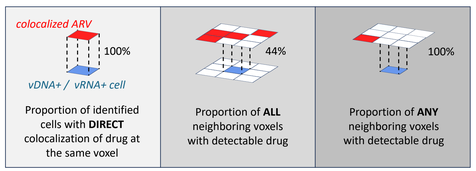
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BACKGROUND

- DUALITY was a randomized, open-label clinical trial showing comparable reductions in peripheral HIV-1 reservoirs in people with HIV (PWH) initiating first-line antiretroviral treatment (ART) with dolutegravir/lamivudine (DTG+3TC, 2DR) or dolutegravir plus emtricitabine/tenofovir alafenamide (DTG+FTC/TAF, 3DR).[1, 2]
- This sub-study aimed to characterize HIV-1 reservoir dynamics within peripheral lymph nodes (LN), a major contributor to HIV reservoir. during the first year of ART and to evaluate antiretroviral pharmacokinetics and spatial drug distribution in relation to viral expression within LN tissue.

METHODS

- 39 participants in the DUALITY study (2DR n=19, 3DR n=20) underwent one ultrasound-guided inguinal LN excision biopsy and paired blood sampling at baseline (week 0) or at weeks 2, 4, 12, or 48 after ART initiation (n=4/arm/timepoint).
- Serial LN cryosections were analyzed using DNA/RNAscope in situ hybridization (ISH) for HIV-1 DNA and RNA (vDNA, vRNA), immunohistochemistry (IHC) for CD20+ B cells and collagen (COL 1) deposition, and mass spectrometry imaging (MSI) for ARV distribution. Parent ARVs and active intracellular metabolites were also measured in tissue homogenate by LC-MS/MS.
- Changes in vDNA and vRNA in LN were analyzed descriptively as ratios of medians week48/week0, with bootstrap-derived 95% CI.
- Spatial overlap of HIV markers and ARVs was assessed by nearest-neighbor analysis of coregistered images (MATLAB), following three approaches:



- Spatial analyses of antiretroviral distribution and colocalization with vDNA+ or vRNA+ cells focused on participants in the 2DR group since TFV concentrations in LN samples were below the LLOQ for MSI.

RESULTS

Table 1. Baseline characteristics of study participants.

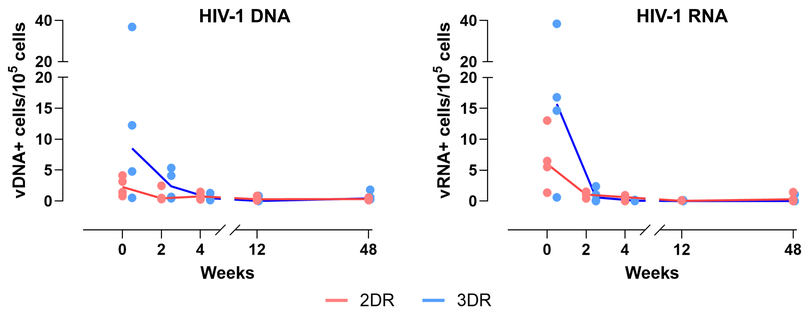
	DTG + 3TC (2DR; n=19)	DTG+FTC/TAF (3DR; n=20)
Age (years)	30.3 (27.0–37.4)	33.5 (27.9–36.0)
Sex at birth, male (n, %)	19 (100.0)	20 (100.0)
pVL (copies/mL)	23,820 (4,921–50,045)	38,264 (14,764–92,314)
CD4⁺ T-cell count (cells/mm^3)	493 (335–607)	448 (392–535)
Total HIV-1 DNA (copies/10^6 CD4⁺ T cells)	1,348 (596–2,426)	1,457 (554–3,751)
Intact HIV-1 DNA (copies/10^6 CD4⁺ T cells)	500 (192–1,197)	775 (183–1,535)
HIV-1 ca-RNA (copies/10^3 copies TBP)	13.6 (6.2–67.9)	6.4 (0.9–42.7)
VIP-SPOT (HAP cells/10^6 CD4⁺ T cells)	16.9 (4.0–34.2)	17.2 (6.6–54.4)

Data are expressed as median and IQR unless when noticed.
Abbreviations: TBP, TATA-binding protein; VIP-SPOT, viral protein spot assay; HAP, human immunodeficiency virus antigen–producing.

References:

1. Bailón L, et al. J Infect Dis 2025;231(3):600-610.
2. Puertas MC, et al. PLoS Pathog 2025;21(9):e1013466.

Figure 1. Viral dynamics in lymph node.



Lines represent medians and dots represent individual data

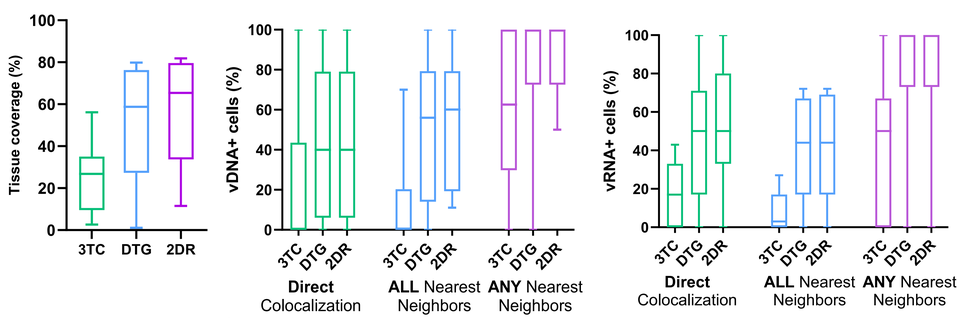
Fold-change (week 48/week 0) was 0.158 (95%CI 0.036–0.416) and 0.049 (0.002–0.532) for vDNA, and 0.055 (0.007–0.692) and 0.001 (<0.001–0.009) for vRNA in the 2DR and 3DR groups, respectively.

Table 2. Drug concentrations in plasma and lymph node (LC/MS-MS).

	N	Plasma	Lymph Node		LN/Plasma Ratio	LN: Plasma Correlation	LN Metabolite/ Parent Ratio	LN Metabolite: Parent Correlation	Inhibitory Reference Value
		ng/mL	μg/g	fmol/10^6 cells		r, (p-value)			
DTG	29	1,290 (620-3,240)	0.261 (0.072-0.739)		0.18 (0.05-0.37)	0.819 (<0.0001)			64*
3TC	14	47.1 (31.1-88.9)	0.078 (0.001-0.286)		1.46 (0.02-6.46)	-0.08 (0.782)			8.7*
3TCtp	14		0.839 (0.008-1.886)	527 (5-1251)			4.19 (0.58-9.16)	0.688 (0.013)	564**
FTC	15	58.7 (40.0-150.0)	0.114 (0.012-0.368)		1.58 (0.24-5.20)	0.278 (0.336)			51*
FTCtp	15		0.342 (0.026-1.652)	258 (15-990)			1.59 (0.57-5.73)	0.366 (0.198)	338**
TFV	15	9.8 (4.4-14.2)	0.044 (0.022-0.108)		4.34 (2.06-11.62)	0.277 (0.340)			2,980*
TFVdp	15		0.145 (0.049-0.550)	104 (35-395)			1.58 (0.57-4.94)	0.518 (0.059)	51***

Data are expressed as median (min-max) * IC90 (ng/ml) ** IC50 (fmol/10^6 cells) *** EC50 (fmol/10^6 cells)

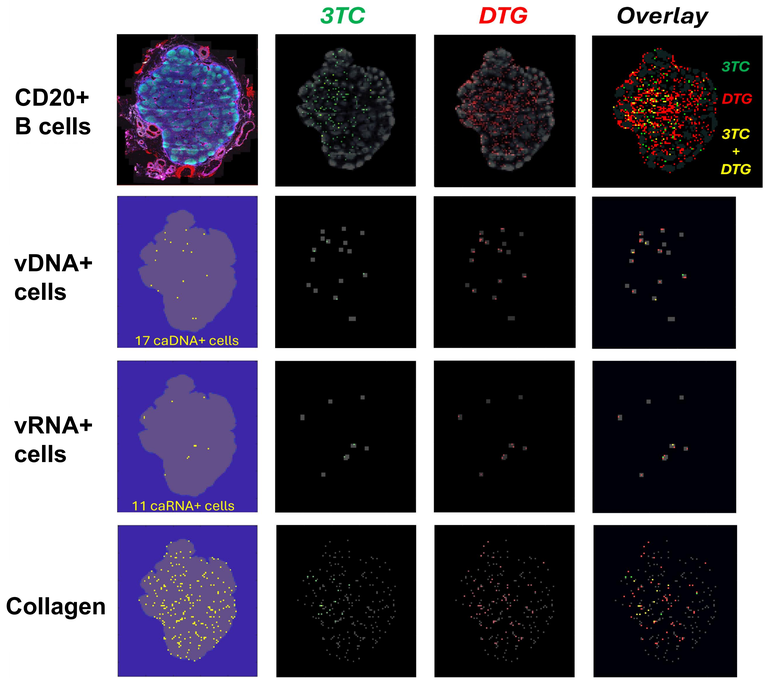
Figure 2. Spatial distribution of 2DR antiretrovirals in lymph node (MSI).



Data are presented as median (min-max)

- All locations where 3TC or DTG were measured by MSI had drug concentrations exceeding relevant in vitro IC90 values.
- 65.3% (11.5-81.8) of LN tissue area was covered by at least one detectable ARV, with 32.0% (3.2-64.0) combined DTG+3TC.
- Nearly all HIV+ cells were exposed to inhibitory ARV concentrations either directly colocalized or at one of the adjacent locations probed by MSI, reflecting their immediate microenvironment (ANY of their nearest neighbors).

Figure 3. Representative spatial colocalization of HIV-1 vDNA+ and vRNA+ cells with antiretroviral drugs.



Spatial distributions of 3TC and DTG in LN (ID 295007, week 2 shown) were evaluated alone or in combination and could be specifically assessed at locations associated with vDNA+ or vRNA+ cells and COL1 expression.

CONCLUSIONS:

- First-line DTG+3TC achieves rapid LN reservoir decline, comparable to triple ART.
- The DTG+3TC regimen penetrates to a high extent within the LN, supporting effective drug delivery to tissue reservoirs.
- By demonstrating effective drug penetration and reservoir suppression in LN, this study addresses concerns regarding reduced drug pressure with DTG/3TC in anatomical sanctuaries.

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