TFV-DP & FTC-TP IN BLOOD CELL SUBSETS OF PERSONS WITH HIV

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University of Colorado Anschutz Medical Campus

Vincent Mainella[1], Jose Castillo-Mancilla[2], Brian Branchford[3], Seth Hosford[1], Bethany Johnson[1], Ye Ji Choi[1], Pang Xiong[1], Martin Williams[1], Jia-Hua Zheng[1], Lane Bushman[1], Jennifer Kiser[1], Peter Anderson[1], Kristina M. Brooks[1]

[1]University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences; Aurora, CO [2]University of Colorado School of Medicine; Aurora, CO [3]Medical Sciences Institute Versiti; Milwaukee, WI

BACKGROUND

Nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) are anabolized to their active forms within multiple cell types, but data have been primarily focused on red blood cells, dried blood spots (DBS) and peripheral blood mononuclear cells (PBMCs) to date. Understanding the extent to which N(t)RTIs accumulate in other major blood cells may inform clinicians' understanding of ART efficacy and toxicity, such as cardiometabolic effects.

The overall goals of our study were to examine the cell pharmacology and platelet effects of abacavir (ABC)/lamivudine (3TC) and tenofovir alafenamide (TAF)/emtricitabine (FTC) in persons with HIV (PWH).

OBJECTIVES

To establish tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) concentrations in different cell types of persons with HIV (PWH) and compare them with historical data in persons without HIV (PWOH).

METHODS

- PWH receiving TAF 25mg/FTC 200mg as part of clinical care with HIV VL <200 c/mL for ≥6 months prior to entry were eligible (NCT04301661)
- Adherence was monitored via video directly observed therapy for 28±3 days prior to the study visit.
- PK samples were collected 2±1 hrs following an observed dose. Blood samples were processed for dried blood spots (DBS), peripheral blood mononuclear cells (PBMCs), neutrophils, and platelets.
- LC-MS/MS methods were used to quantify phosphorylated anabolites across all cell types.[1]
- Data in PWOH originated from TAF-DBS (NCT02962739).[2,3] Cellular concentrations by HIV status were compared using linear regression models to control for adherence and time after dose (SAS v9.4).
- To depict relative intracellular drug concentrations between cell types, cell concentrations (per 10^6 cells) were normalized to cell volume using the following conversions:
  - RBC: 90 fL; PBMC: 282 fL, neutrophils: 300 fL, & platelet: 10.9 fL

RESULTS

Table 1. Baseline Characteristics

	PWH (N=13)[a]	PWOH (N=30)
Age, median (range)	42 (26-64)	29 (18-41)
Male, n (%)	12 (92%)	16 (53.3%)
Race, n (%)		
White	8 (62%)	24 (80%)
Black/African American	1 (8%)	5 (16.7%)
Asian	1 (8%)	0
More than one race	2 (15%)	0
Unknown/Unreported	1 (8%)	1 (3.3%)
Hispanic/Latino, n (%)	4 (31%)	5 (16.7%)
Weight (kg), median (range)	71 (58-117)	75 (56.7-118.2)
Adherence, median (range)	96% (89-100%)	67% (33-100%)

[a] Concomitant ARVs included bictegravir (n=12) and rilpivirine with raltegravir (n=1).

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In PWH vs. PWOH: TFV-DP and FTC-TP did not significantly differ in PBMC and neutrophils, FTC-TP was higher in platelets and TFV-DP was higher in both DBS and platelets

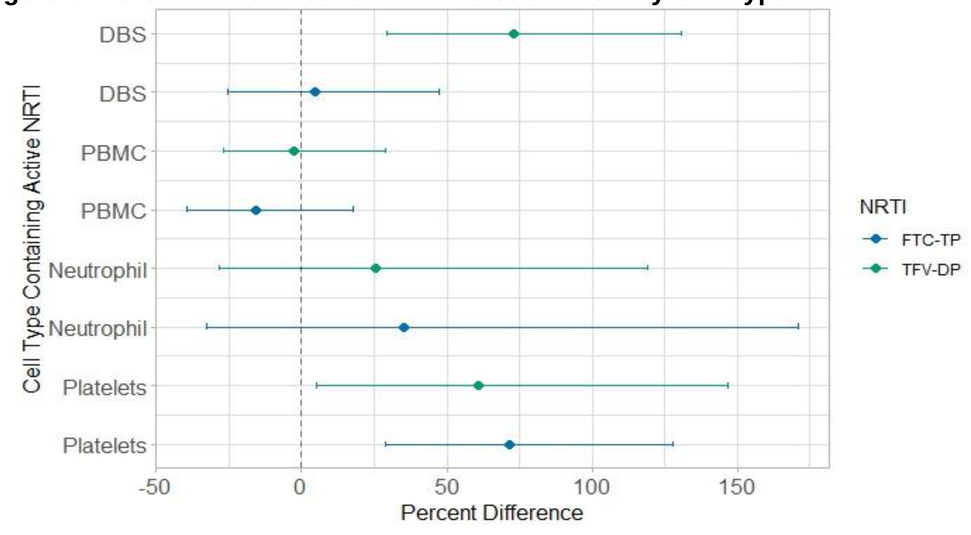
RESULTS

Table 2. Intracellular Concentrations by Cell-Type

Cell Type	TFV-DP (fmol) PWH (n=13)[a]	TFV-DP (fmol) Percent Difference (95% CI)[b]	TFV-DP (fmol) P-value	FTC-TP (pmol) PWH (n=13)[a]	FTC-TP (pmol) Percent Difference (95% CI)[b]	FTC-TP (pmol) P-value
DBS (/2x7mm punch)	2963 (1826-4767)	73.0% (29.6%, 131%)	0.0004	4.84 (2.1-7.96)	4.61% (-25.7%, 47.4%)	0.79
PBMC (/10^6 cells)	619 (397-1193)	-2.76% (-26.8%, 29.1%)	0.84	6.72 (4.46-13.1)	-15.6% (-39.5%, 17.9%)	0.31
Neutrophils (/10^6 cells)	334 (121-880)	25.3% (-28.3%, 119%)	0.42	5.37 (1.54-10.9)	35.1% (-32.6%, 171%)	0.39
Platelets (/10^6 cells)						
MP fraction	7.37 (3.93-11.6)	--	0.03	0.059 (0.035-0.13)	--	0.0005
DP fraction	2.55 (1.26-5.21)	--		0.077 (0.045-0.12)	--	
TP fraction	10.0 (6.31-17.4)	61% (4.9%, 147%)		0.15 (0.059-0.22)	71.4% (28.9%, 128%)	

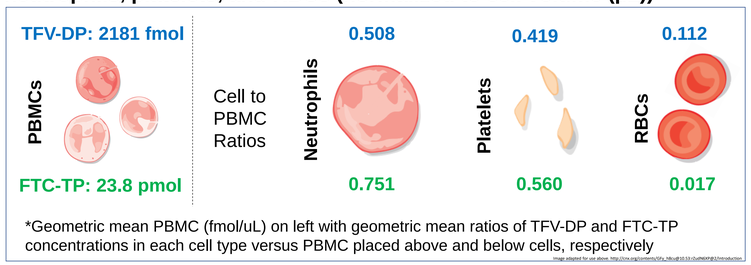
[a]Data presented as geometric mean (range) [b]PWH compared to PWOH; point estimates reflect adjustment for adherence and time since last dose across all cell types.

Figure 1: Percent Difference for PWH versus PWOH by Cell Type



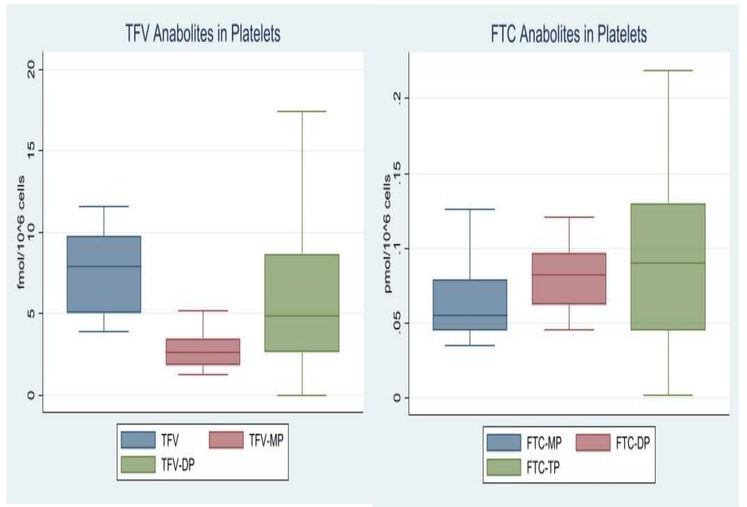
RESULTS

Figure 2. Comparison of TAF and FTC cell loading in PBMCs, neutrophils, platelets, and RBCs (normalized to cell volume (µL))



*Geometric mean PBMC (fmol/uL) on left with geometric mean ratios of TFV-DP and FTC-TP concentrations in each cell type versus PBMC placed above and below cells, respectively

Figure 3. Phosphorylated fractions of TFV and FTC in platelets



CONCLUSIONS

- Higher TFV-DP in DBS is consistent with previous studies in PWH.[4]
- Findings indicative of higher TFV-DP and FTC-TP concentrations in platelets versus PWOH are novel and suggest an undescribed difference in cell-specific physiology in PWH.
- These results are hypothesis generating and may relate in part to increased platelet activation in PWH relative to PWOH shown in previous studies.[5]
- Cellular data with ABC/3TC and comparisons of metabolic effects in platelets may help provide further insight into intracellular processes.

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