Extra/Intra-cellular Nucleoside/tide Semen Pharmacology: Implications for Eradication

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Abstract 406

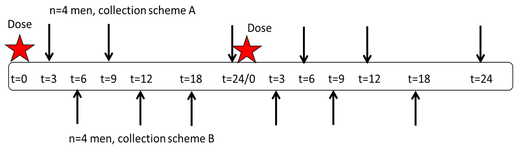
BACKGROUND

- The male genital tract (MGT) is a putative HIV reservoir and potential barrier to cure. (1)
- Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and emtricitabine (FTC) are widely-used nuclear reverse transcriptase inhibitors (NRTIs). (2)
- Seminal mononuclear cell (SMC) concentrations of tenofovir diphosphate (TFVdp), emtricitabine triphosphate (FTCtp), and the concentrations of their competitive endogenous nucleotides (deoxyadenosine triphosphate [dATP], deoxycytidine triphosphate [dCTP], respectively) may inform effective dosing regimens for HIV cure.

METHODS

CLINICAL STUDY

- 8 HIV+, 8 HIV- men receiving TDF (300mg) and 8 HIV+ men receiving TAF (10mg or 25mg), with FTC (200mg), provided 6 blood (BP) and seminal plasma (SP) samples over 48 hours.



SAMPLE ANALYSIS

- Peripheral blood mononuclear cells (PBMC) and SMC isolated from BP/SP.
- Concentrations of TFVdp, FTCtp, dATP, dCTP in PBMC and SMC; tenofovir (TFV), FTC, and TAF in BP and SP measured via LC-MS/MS. (3,4)

STATISTICAL/DATA ANALYSIS

- Noncompartmental analysis (Phoenix WinNonlin v6.3, Certara) generated areas under the curve (AUCs) for SP, BP, and PBMC analytes. Concentration over 24hrs ($C_{ss,ave}$) was computed (AUC/24hrs) to compare matrices.
- SMC samples were pooled across a visit for 12 men due to low cell counts.
- For PBMC/SMC concentrations below the limit of quantification (LOQ), ½ of the sample LOQ was imputed.

RESULTS

	HIV+ TAF (n=8)	HIV+ TDF (n=8)	HIV- TDF (n=8)
AGE (years)	45.5 (34 – 52)	36.5 (33 – 41)	30.5 (24 – 39)
BMI (kg/m^2)	28.8 (25 – 31)	29.8 (27 – 33)	28.3 (24 – 32)
eGFR (mL/min)	109 (97 – 122)	133 (117 – 154)	115 (109 – 149)
African-American	5	7	5
Caucasian	2	0	3
Mixed Race	1	1	0

Table 1. Baseline demographics of participants, presented as median (interquartile range [IQR]) or number. BMI: Body Mass Index, eGFR: estimated glomerular filtration rate

	HIV+ TAF (n=8)	HIV+ TDF (n=8)
EVG+Cobi	3	3
DRV + Cobi	2	0
DTG+DRV+ Cobi	1	0
RAL	1	1
RPV	1	2
EFV	0	1
ATV/r	0	1

Table2. Concomitant antiretrovirals of HIV+ men. TAF subjects receiving EVG+Cobi and DRV+Cobi received TAF 10mg; all others received TAF 25mg.
EVG: elvitegravir,
Cobi: cobicistat,
DRV: darunavir,
DTG: dolutegravir,
RAL: raltegravir,
RPV: rilpivirine,
EFV: efavirenz,
ATV/r: atazanavir/ritonavir

	Tenofovir (TFV)					
	TFV BP $C_{ss,ave}$ (ng/mL)	TFV SP $C_{ss,ave}$ (ng/mL)	TFVdp PBMC $C_{ss,ave}$ (fmol/10^6 cells)	TFVdp SMC $C_{ss,ave}$ (fmol/10^6 cells)	dATP PBMC $C_{ss,ave}$ (fmol/10^6 cells)	dATP SMC $C_{ss,ave}$ (fmol/10^6 cells)
HIV- TDF/ FTC	103 (54, 177)	112 (58, 235)	119 (76, 174)	21 (4.2, 91)	115 (93, 153)	65 (3.5, 94)
HIV+ TDF/ FTC	110 (74, 174)	181 (70, 330)	174 (115, 239)	21 (5.7, 88)	128 (101, 172)	33 (7.2, 61)
HIV+ TAF/ FTC	14 (12,17)	121 (70, 189)	935 (684, 2024)	35 (24, 78)	144 (116, 236)	43 (27, 73)
	Emtricitabine (FTC)					
	FTC BP $C_{ss,ave}$ (ng/mL)	FTC SP $C_{ss,ave}$ (ng/mL)	FTCtp PBMC $C_{ss,ave}$ (fmol/10^6 cells)	FTCtp SMC $C_{ss,ave}$ (fmol/10^6 cells)	dCTP PBMC $C_{ss,ave}$ (fmol/10^6 cells)	dCTP SMC $C_{ss,ave}$ (fmol/10^6 cells)
HIV- TDF/ FTC	287 (111, 668)	1030 (516, 1990)	6135 (3889, 8303)	90 (34, 193)	571 (468, 745)	115 (4.9, 241)
HIV+ TDF/ FTC	251 (116, 649)	1330 (830, 2343)	6038 (4465, 10088)	59 (22, 119)	590 (462, 825)	71 (30, 123)
HIV+ TAF/ FTC	393 (142, 858)	1930 (876, 3070)	8242 (5602, 13480)	179 (108, 395)	628 (531, 1084)	83 (38, 179)

Table 3. Median steady state concentrations ($C_{ss,ave}$) for individual anabolites following TDF and TAF administration. In HIV+ men receiving TAF, TFV BP concentrations were approximately 10-fold lower compared to TFV BP in men receiving TDF, with the expected increase in PBMC TVFdp concentrations. TFV SP concentrations and TFVdp SMC concentrations were similar regardless of TFV dosage form. FTC BP concentrations were approximately 10-fold lower than SP concentrations, though FTCtp PBMC concentrations were approximately 10-fold higher than SMC.

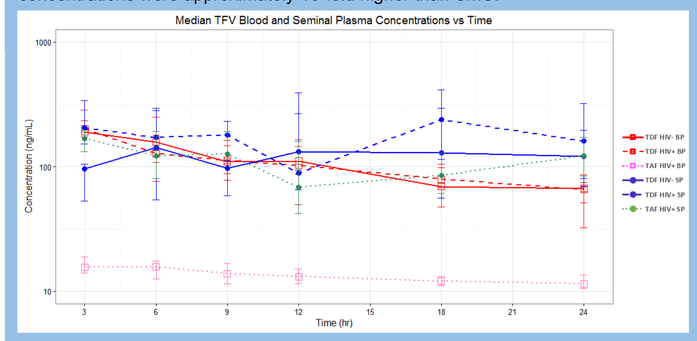


Figure 1. Median/IQR Tenofovir (TFV) Concentrations in the blood plasma (BP) and seminal plasma (SP) following TDF and TAF administration. Median TFV BP concentrations following TAF administration were approximately 10 times lower compared TDF administration as expected (5). TFV SP concentrations following TDF administration are consistent with previous reports (6, 7); TFV concentrations following TAF administration were similar to those seen with TDF administration.

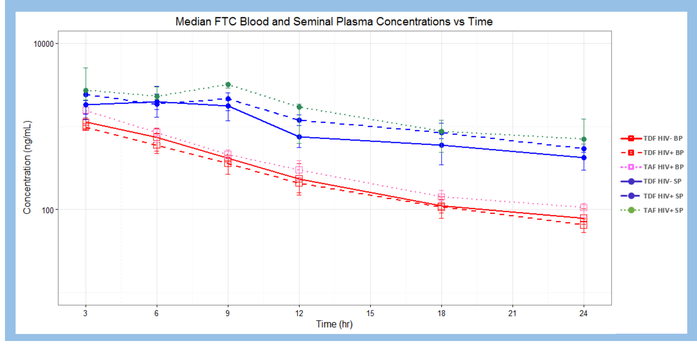


Figure 2. Median/IQR Emtricitabine (FTC) Concentrations in the blood plasma (BP) and seminal plasma (SP) following Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) administration. FTC SP concentrations were consistent with previous reports. (8)

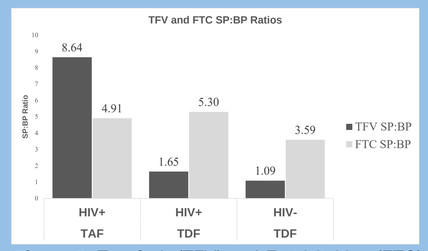


Figure 3. Tenofovir (TFV) and Emtricitabine (FTC) Seminal Plasma (SP) to Blood Plasma (BP) $C_{ss,ave}$ ratios, by group. Elevated TFV SP concentrations in men receiving TAF drove the higher SP:BP ratio observed in this group.

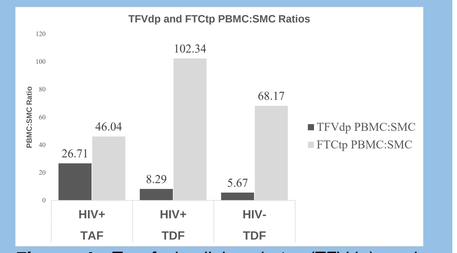


Figure 4. Tenofovir diphosphate (TFVdp) and Emtricitabine triphosphate (FTCtp) PBMC to SMC $C_{ss,ave}$ ratios, by group. TFVdp PBMC: SMC ratios following TAF administration were approximately 4 times higher than TDF administration.

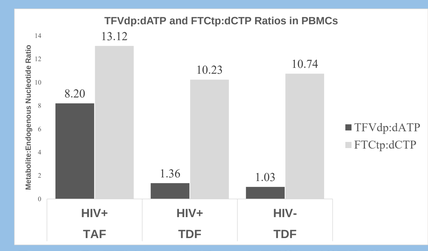


Figure 5. TFVdp: dATP and FTCtp:dCTP $C_{ss,ave}$ ratios in PBMCs, by group. The TFVdp:dATP ratio was approximately 8 times higher following TAF administration.

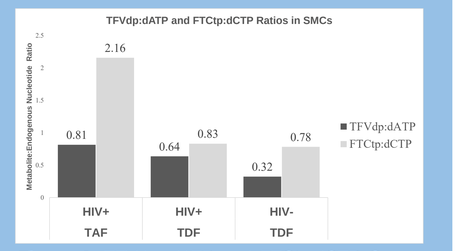


Figure 6. TFVdp: dATP and FTCtp:dCTP $C_{ss,ave}$ ratios in SMCs, by group. The FTCtp:dCTP ratio was approximately 2 times higher following TAF administration.

CONCLUSIONS

- High TFV concentrations in SP after TAF dosing were unexpected.
  - Cathepsin A in the male genital tract (MGT) and differing drug transporter affinities for TAF and TFV may explain these findings.
  - Results suggest that MGT distribution of TAF differs from TDF.
- As previously observed with lamivudine, FTCtp concentrations are lower in SMCs than PBMCs, despite high SP FTC concentrations. (9)
- Role of NRTI triphosphate:endogenous nucleotide ratios may inform ability to protect cells during a “shock and kill” cure strategy.(10)
- Population pharmacokinetic modeling is underway to further describe these data and probe mechanisms of MGT distribution.

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