Tenofovir Diphosphate Benchmarks in Dried Blood Spots in PWH Receiving TAF-Based ART (QUANTI-TAF)

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OBJECTIVES

- We aimed to establish tenofovir-diphosphate/emtricitabine-triphosphate (TFV-DP/FTC-TP) adherence benchmarks in dried blood spots (DBS) for persons with HIV (PWH) receiving tenofovir alafenamide/emtricitabine (TAF/FTC)-based antiretroviral therapy (ART).

BACKGROUND

- TFV-DP/FTC-TP in DBS is strongly associated with current HIV-1 RNA suppression,[1,2] low-level viremia (LLV),[3] and future viremia[4,5] in PWH receiving TDF/FTC-based ART.
- Cellular pharmacology of TFV-DP differs for TDF vs. TAF.[6]

METHODS

- 16-week, prospective, observational, PK study at the University of Colorado Anschutz Medical Campus.
- Adult PWH receiving TAF/FTC-based ART for ≥6 months.
- All regimens contained TAF 25mg and FTC 200mg.
- Concomitant antiretrovirals were: BIC, DTG, RAL, RPV, ETR, DRV/COBI, and DRV/RTV.
- TAF/FTC-based ART tablets were co-encapsulated with an ingestible sensor (ID-Cap System)[7] to directly measure cumulative (enrollment to final visit) and recent (10-day) adherence to aid TFV-DP/FTC-TP interpretations.
- Linear mixed-effects models with backward selection evaluated factors associated with TFV-DP/FTC-TP.
- Results are n (%), median (IQR), or % difference (95% CI).



1 A digital pill with an embedded sensor is ingested (the *ID-Capsule*).

2 The ID-Capsule is activated in the stomach & transmits a radio frequency signal to a wearable device (the *Reader*).

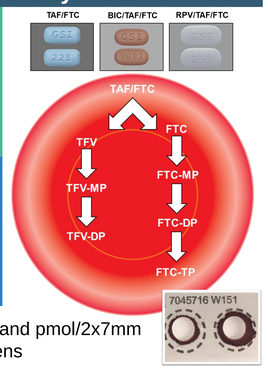
3 The Reader collects and transmits ingestion data to a cloud-based server for the patient to view through a mobile application (the *Patient App*).

4 The ingestion data is securely transmitted and displayed to clinicians on a dashboard (the *Clinician Dashboard*).

Blood was collected in EDTA at monthly visits for DBS

TFV-DP in DBS[6]:
- Phosphorylated anabolite of TFV
- 21 day half-life
- Informs cumulative adherence over the preceding ~6-12 weeks

FTC-TP in DBS[6]:
- Phosphorylated anabolite of FTC
- 35 hour half-life
- Informs recent adherence over the preceding several days



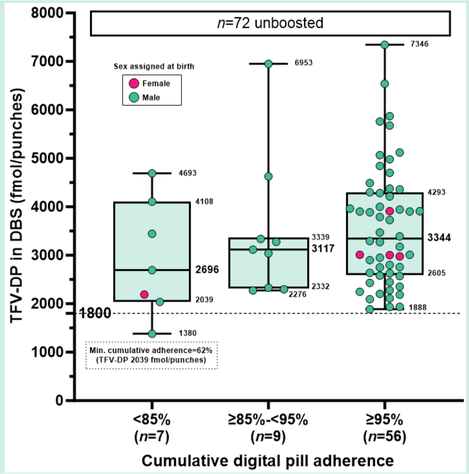
- **LC-MS/MS[8]:** fmol/2x7mm punches (TFV-DP) and pmol/2x7mm punches (FTC-TP) for TAF/FTC-based regimens

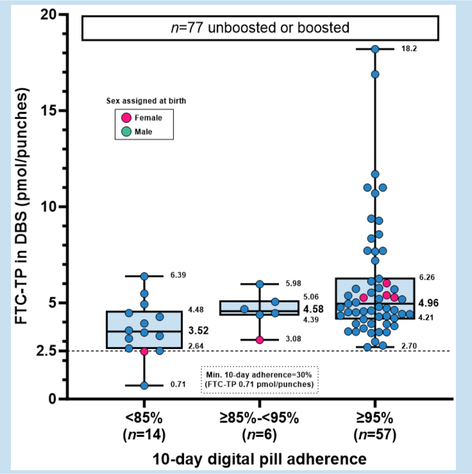
PK-based DBS benchmarks for PWH with ≥85% adherence to TAF/FTC-based ART:

TFV-DP ≥1800 fmol/punches

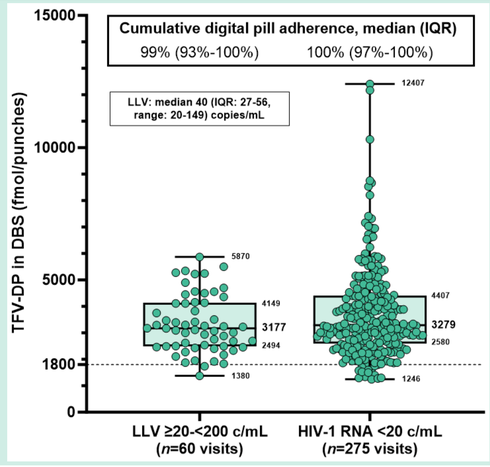
FTC-TP ≥2.5 pmol/punches

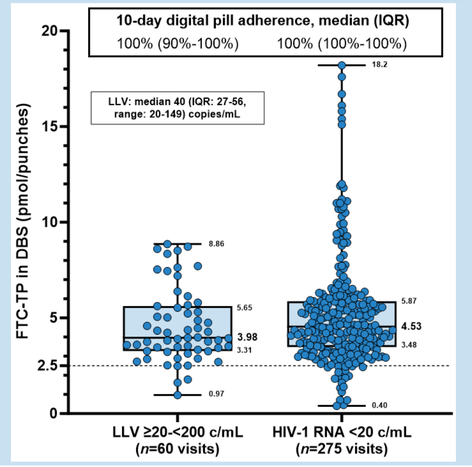
Steady-state (week 12 or 16) DBS concentrations



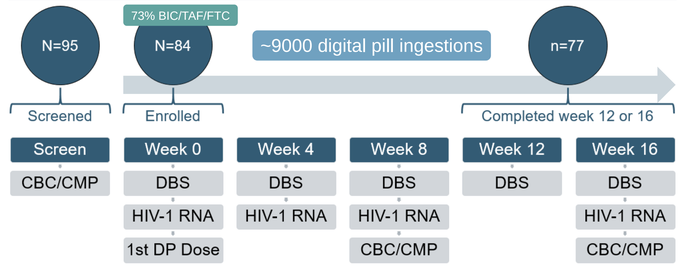


LLV (HIV-1 RNA ≥20-<200 copies/mL) visits versus suppressed (HIV-1 RNA <20 copies/mL) visits





Enrollment flow and baseline characteristics



Baseline characteristics, n (%) or median (IQR)	ART anchor class, n (%)			
	INSTI 74 (88%)	NNRTI 5 (6%)	PI 5 (6%)	Overall 84 (100%)
Sex assigned at birth				
Female	7 (9%)	1 (20%)	1 (20%)	9 (11%)
Male	67 (91%)	4 (80%)	4 (80%)	75 (89%)
Gender identity				
Female	7 (9%)	1 (20%)	1 (20%)	9 (11%)
Male	65 (88%)	4 (80%)	3 (60%)	72 (86%)
Transgender	2 (3%)	0 (0%)	1 (20%)	3 (4%)
Race/ethnicity				
Black	15 (20%)	2 (40%)	3 (60%)	20 (24%)
Hispanic/Latino	16 (22%)	1 (20%)	1 (20%)	18 (21%)
White	43 (58%)	2 (40%)	1 (20%)	46 (55%)
HIV-1 RNA, copies/mL				
<20	62 (84%)	5 (100%)	4 (80%)	71 (85%)
≥20-<200	12 (16%)	0 (0%)	1 (20%)	13 (15%)
Age, years	52 (40-59)	57 (54-58)	57 (54-58)	54 (43-59)
Weight, kg	84 (70-98)	90 (72-100)	75 (72-96)	84 (71-98)
BMI, kg/m^2	28 (23-32)	31 (25-36)	26 (26-31)	28 (23-32)
eGFR, mL/minute/1.73 m^2	84 (69-99)	80 (62-88)	81 (76-93)	83 (69-97)
CD4$^+$ T-cells, cells/mm^3	717 (540-972)	806 (612-836)	476 (418-504)	700 (534-907)
Hematocrit, %	45 (44-48)	45 (43-46)	43 (42-48)	45 (43-48)
Mean corpuscular volume, fL	92 (88-96)	91 (90-95)	92 (92-93)	92 (88-95)
TAF/FTC-based ART duration, months	51 (33-62)	43 (42-44)	62 (57-62)	51 (35-62)

Factors associated with DBS concentrations in multivariable analyses of all available visits (weeks 0-16)

TFV-DP

Adjusting for cumulative adherence, booster status, BMI, and race/ethnicity:

- Every 10% increase in **cumulative adherence** associated with 4.6% increase (95% CI: 0.6%, 8.6%; *P*=0.023).
- **Boosted ART** averaged 146.7% higher (95% CI: 84.7%, 229.5%; *P*<0.0001) versus unboosted.
- Every unit increase in **BMI** associated with 1.2% decrease (95% CI: -2.2%, -0.2%; *P*=0.021).
- **Compared to Blacks**, Whites and Hispanics/Latinos averaged 23.1% (95% CI: 3.4%, 46.5%; *P*=0.020) and 26.2% (95% CI: 3.0%, 54.7%; *P*=0.025) higher, respectively.

FTC-TP

Adjusting for 10-day adherence, BMI, and eGFR:

- Every 10% increase in **10-day adherence** associated with 7.7% increase (95% CI: 5.2%, 10.3%; *P*<0.0001).
- Every unit increase in **BMI** associated with 1.5% decrease (95% CI: -2.6%, -0.4%; *P*=0.011).
- Every 10 mL/min./1.73 m^2 increase in **eGFR** associated with 6.9% decrease (95% CI: -9.9%, -3.9%; *P*<0.0001).

CONCLUSIONS

- We established novel PK-based TFV-DP/FTC-TP adherence benchmarks in DBS for PWH with ≥85% adherence to TAF/FTC-based ART.
- Among PWH with high ART adherence, LLV ≥20-<200 copies/mL was common: 60/335 (18%) visits in 33/84 (39%) participants. No HIV-1 RNA >200 copies/mL was observed during the study (maximum=149 copies/mL).

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References: 1. Castillo-Mancilla et al. 2019, *Clin Infect Dis*. 2. Frasca et al. 2019, *J Antimicrob Chemother*. 3. Castillo-Mancilla et al. 2021, *Open Forum Infect Dis*. 4. Morrow et al. 2019, *J Infect Dis*. 5. Morrow et al. 2021, *AIDS*. 6. Yager et al. 2020, *J Acquir Immune Defic Syndr*. 7. Baumgartner et al. 2021, *JMIR Hum Factors*. 8. Zheng et al. 2016 *J Pharm Biomed Anal*.