CROI 2018
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Tenofovir HIV-1 plasma prophylactic concentration: iPrEX, VOICE, Partners meta-analysis

Katarina Vucicevic[1], Craig Hendrix[2], María García-Cremades[1], Leah Jarlsberg[1], Robert Grant[3], Connie L. Celum[4], Jared Baeten[4], Jeanne Marrazzo[5], Peter Anderson[6], David Glidden[7], Radojka M. Savic[1]*

[1]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA; [2]Division of Clinical Pharmacology, Department of Medicine, Johns Hopkins University, Baltimore, MD; [3]Department of Medicine, University of California San Francisco, San Francisco, CA; [4]Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA; [5]Division of Infectious Diseases, University of Alabama at Birmingham Medical Center, Birmingham, Alabama; [6]Department of Pharmaceutical Sciences, University of Colorado, Denver; [7]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA

Background & Aims

Efficacy of oral tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) is variable across and within randomized clinical trials (RCTs): ranging from ~49 to 75% compared to placebo[1-3]

Tenofovir (TFV) plasma levels are variable across and within RCTs[1-3], being mainly attributed to adherence, but may also be due to variability in drug disposition and sampling time relative to administered dose

Sigmoid relationship between response and TFV concentration across RCTs[4]

Prophylactic TFV plasma levels are not fully characterized.

Objective of the analysis was to:

- assess adherence patterns based on the time-course of TFV plasma concentrations
- address sources of variability in pharmacokinetics (PK) and in the clinical outcomes within and among 3 RCTs
- establish TFV exposure-response relationship using HIV-1 infection
- define target TFV plasma prophylactic concentration.

Participants & Data

- Participants assigned to oral active arms of iPrEX (men or transgender women who have sex with men)[1], VOICE (young unmarried African women)[2], Partners PrEP trial (HIV-1 negative partner in heterosexual couples)[3] were considered
- 300 mg of TDF daily with/without 200 mg emtricitabine (FTC)
- Adherence to the treatment estimated on 4 week-follow-up, and it was rather high based on self-reports and pill counts in the returned box
- Single blood draw per specific visit was obtained, and multiple samples across follow-up visits were available per participants
- Lower limit of quantifications (LLOQs): 10 ng/mL[1], 0.31 ng/mL[2,3]
- Efficacy assessed every 4 weeks. The primary efficacy endpoint was seropositivity in previously HIV-1 negative subject defined by the HIV-1 serologic testing algorithm
- Participants with at least one TFV concentration obtained up to 100 h post-dose were included in model development
- PK samples were matched with visit-specific HIV-1 status and pill adherence

Results

Table 1. Participants characteristics

CHARACTERISTIC	number (%)/ mean (range)
Participants	2354
Participants/trial **iPrEX** **VOICE** **Partners PrEP**	 671 (28.5%) 736 (31.3%) 947 (40.2%)
Male participants	1167 (49.6%)
Age (years)	29.4 (18 – 64)
Body weight (kg)	65 (36.7 – 153.8)
CrCl (mL/min) set to 140 mL/min (M), 130 mL/min (F)	120.3 (44 – 443)
PK samples	7868
Median PK samples per participant	3 (1 – 16)
Range of quantifiable TFV conc. (ng/mL)	0.313 – 899
BLQ samples	3396 (43.2%)
Participants with at least one BLQ	1179 (50.1%)
HIV-1 seroconversions	204

Fig. 2. Estimated individual visit-specific probability of drug intake (P).
Red – concentration not included in PK model.
Dot– seroconversion event

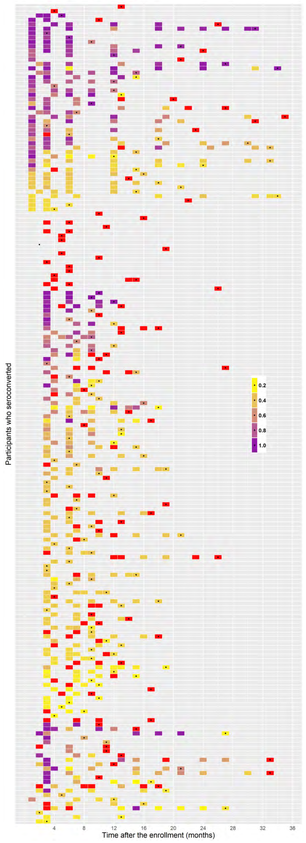


Fig 1. TFV raw data and fitted two-compartment model

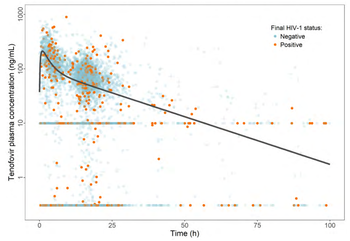


Table 2. Estimated parameters of adherence-PK-outcome model

PARAMETER	estimate (%RSE)
Ka (h^{-1})	2.28 (5)
Vc (L)	561 (11)
Vp (L)	825 (23)
Q (L/h)	112 (12)
CL (L/h)	68.5 (3)
Effect of CrCl on CL (linear)	0.0054 (11.2)
IIV of CL (%)	29.9 (6)
F1 (SUBPOP1)	100%
PROBABILITY (SUBPOP1)	0.63 (3)
F1 (SUBPOP2)	0%
PROBABILITY (SUBPOP2)	0.37
Additive error (ng/mL)	40.1 (7)
Proportional error (CV%)	64.7 (6)
EC50 (ng/mL)	23.6 (16)
gamma	1.96 (16)

Fig.3. Histogram represents the distribution of the observed data. Distribution of TFV model-predicted Cavg vs participants' HIV-1 status. Fitted logistic regression curve

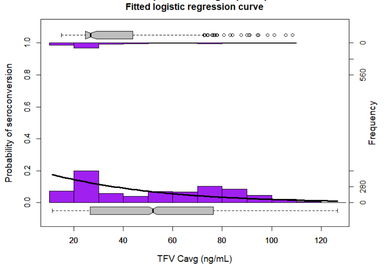


Fig 4. Simulated survival curve based on the PK-outcome model

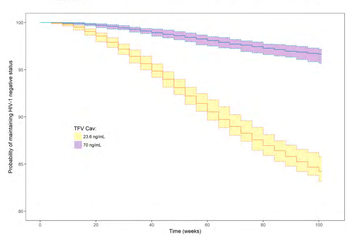
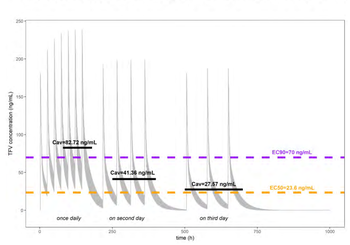


Fig 5. Simulated PK profile based on different adherence patter



Methods

- Individual level data meta-analysis
- Nonlinear mixed effects modeling approach, NONMEM software (v. 7.3)
- Sources of the PK and outcome variability were examined. Predefined parameter-covariate relations in SCM tool and Emax, sigmoidal Emax shapes of these relations were tested
- Adherence-PK model: two-compartment disposition; relative bioavailability (F) adjusted for adherence correction; M3 method; between- and within-individual mixture model approach
- Individual average steady-state TFV concentration (Cavg) was calculated
- PK-outcome model: sequential; binary logistic regression; survival model with time-varying Surge hazard distribution best fitted time-to-event data
- Model evaluation: numerical and graphical diagnostics

Conclusions & Implications

- Model estimated individual visit-specific probability of F=100% used as surrogate of adherence was different from reported pill adherence values, showing great inter- and intra-individual variability
- Estimated population PK parameters are in agreement with previous reports
- Our study shows that 90% decrease in the probability of HIV-1 infection may be attained by targeting average steady-state TFV plasma level of 70 ng/mL
- Opportunity for patient-centered PrEP management (adherence and low-PK based dosing regimen interventions) in everyday clinical practice
- Developed model can be used as a tool for clinical trial simulations towards determining optimal study designs of up-coming novel TDF formulations

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ACKNOWLEDGMENTS.

This project has received funding from the Bill & Melinda Gates Foundation. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation.

VOICE was designed and implemented by the Microbicide Trials Network (MTN) funded by the National Institute of Allergy and Infectious Diseases through individual grants (UM1AI068633, UM1AI068615 and UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

University of California San Francisco

MTN microbicide trials network

* rada.savic@ucsf.edu