

# **Population Pharmacokinetics of TFV-DP in Red Blood Cells in HIV-negative and HIV-infected Adults**

Jose Castillo-Mancilla, Sharon Seifert, Jia-Hua Zheng, Amie Meditz, Brandon Klein, L. Anthony Guida, Becky Kerr, Lane R. Bushman and Peter L. Anderson

Division of Infectious Diseases

Colorado Antiviral Pharmacology Laboratory

School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences

University of Colorado-AMC



University of Colorado  
Anschutz Medical Campus

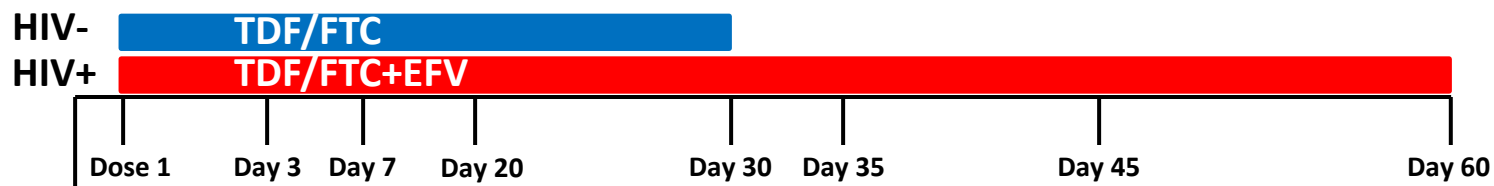
## Background:

- Sustained ARV exposure and adherence critical to treat and prevent HIV.
- TFV-DP accumulates in RBC with a  $t_{1/2}$  of ~17 days.

## Objective:

- To construct a population model to assess the PK of TFV-DP in RBCs.

## Methods:



- NONMEM 7.2.0 with FOCE-I (*ADVAN 2 TRANS 1*) for base model and covariate screens. Model selection: graphical assessments, visual predictive checks and OFV and variance improvements.
- Final models evaluated using forward inclusion/backward elimination.

N=39 participants  
324 samples

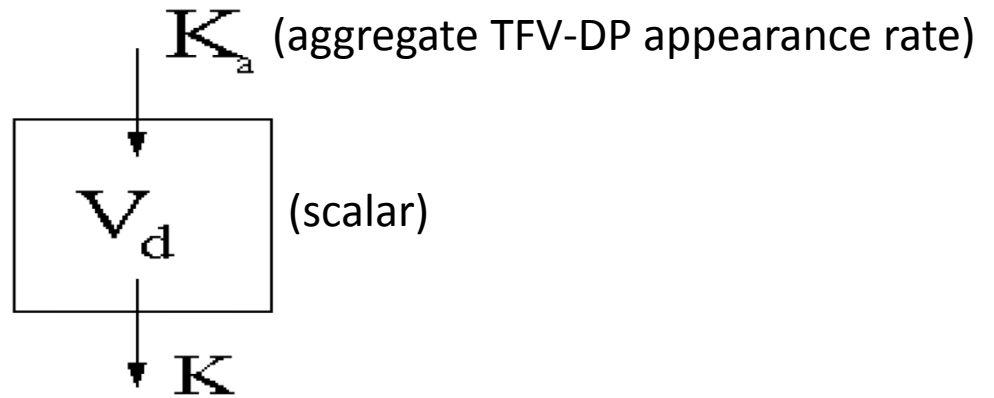


Table 1. Base/Final Model TFV-DP in RBCs Population PK Parameters.

Parameter	Typical Value		IIV
	Estimate	95% CI	CV (%)
$\theta_1$ k (day <sup>-1</sup> ) Half-life: 18.5 days	0.0374	0.0332, 0.0415	21.7
$\theta_2$ V (L) $C_{ss}$ : 131 fmol/10 <sup>6</sup> RBC	27.8	24.6, 30.9	34.1
$\theta_3$ ka (day <sup>-1</sup> )	7.29	4.40, 10.17	110
$\omega_1$	0.047	0.016, 0.077	-
$\omega_2$	0.116	0.044, 0.187	-
$\omega_3$	1.2	0.482, 1.917	-
$\sigma_1$	0.061	0.039, 0.082	-

IIV: Inter-individual variability. CV: Coefficient of variation.

Table 2. Influence of covariates on TFV-DP elimination rate constant (k).

<b>Forward Inclusion</b>	
<b>Covariate</b>	<b><math>\Delta</math>OFV</b>
Base Model	-
Wt	-6.894
Age	-0.652
Gender	-0.026
HIV status	-0.381
eGFR	-0.001
Race	-5.667
TFV CL/F	-0.666
Hct	-0.255
<b>Backward Elimination</b>	
<b>Covariate</b>	<b><math>\Delta</math>OFV</b>
Wt/Race	-
Wt	5.176
Race	6.403

OFV: Objective Function Value.

Forward inclusion ( $p < 0.05$ )

Backward elimination ( $p > 0.01$ ).

## CONCLUSIONS

- This model confirms the long elimination half-life and  $C_{ss}$  of TFV-DP in RBCs and extends research to HIV-infected individuals.
- The lack of covariate influence on k suggests applicability in the multiple populations.
- Prospective validation is required to before it can be used in clinical trials and routine patient care.

# Acknowledgments

## CAVP Laboratory:

PL Anderson  
JJ Kiser  
LR Bushman  
S Seifert  
J Rower  
M Ray  
LA Guida  
JH Zheng  
B Kerr  
B Klein  
L Jimmerson  
H Chen  
K Bushman  
A Hodara  
L Bechtel

## Collaborators:

R Brundage  
E Gardner  
C Wilson  
S MaWhinney  
J Predhomme

## Funding:

Castillo-Mancilla K23 AI104315  
Anderson U01 AI84735

## Study Drug:

Gilead Sciences

## Study Subjects:

All participants in Cell PrEP

