Prediction of Intracellular (IC) Tenofovir Diphosphate (TFV-DP) and Emtricitabine Triphosphate (FTC-TP) Concentrations Following Drug Intake Cessation

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SSAT ST STEPHEN'S AIDS TRUST

Background

- Maintaining high level of adherence to antiretrovirals may be aided, in part, by introduction of fixed dose combination tablets
  - Tenofovir disoproxil fumarate (DF)/emtricitabine/efavirenz (Atripla®)
  - Tenofovir DF/emtricitabine/rilpivirine (Eviplera®, Complera®)
- Some patients may miss or delay doses due to specific circumstances e.g. busy lifestyle or personal issues
- Pharmacokinetic (PK) data describing prolonged time-course of antiretrovirals in plasma or peripheral blood mononuclear cells (PBMC) are lacking
- Important for understanding drug behaviour after treatment interruption and improving management of late and missed doses
- Assess appropriateness of compounds for pre-exposure prophylaxis (PrEP)

Background

Eviplera®/Complera®

Co-formulated
Tenofovir DF/emtricitabine/rilpivirine
245/200/25 mg once daily

Europe: No NNRTI, tenofovir or emtricitabine-associated resistance mutations
Viral load ≤100,000 copies/mL[1]

US: Treatment-naïve patients with viral load ≤100,000 copies/mL
Switching virologically suppressed patients (<50 copies/mL)[2]

[1] Gilead Sciences Ltd. EVIPLERA® Summary of Product Characteristics 2014; [2] Gilead Sciences. COMPLERA® Prescribing Information 2014

SSAT048

Open-label, single-treatment arm, PK study at St Stephen's Centre, Chelsea & Westminster Foundation Trust (London, UK)

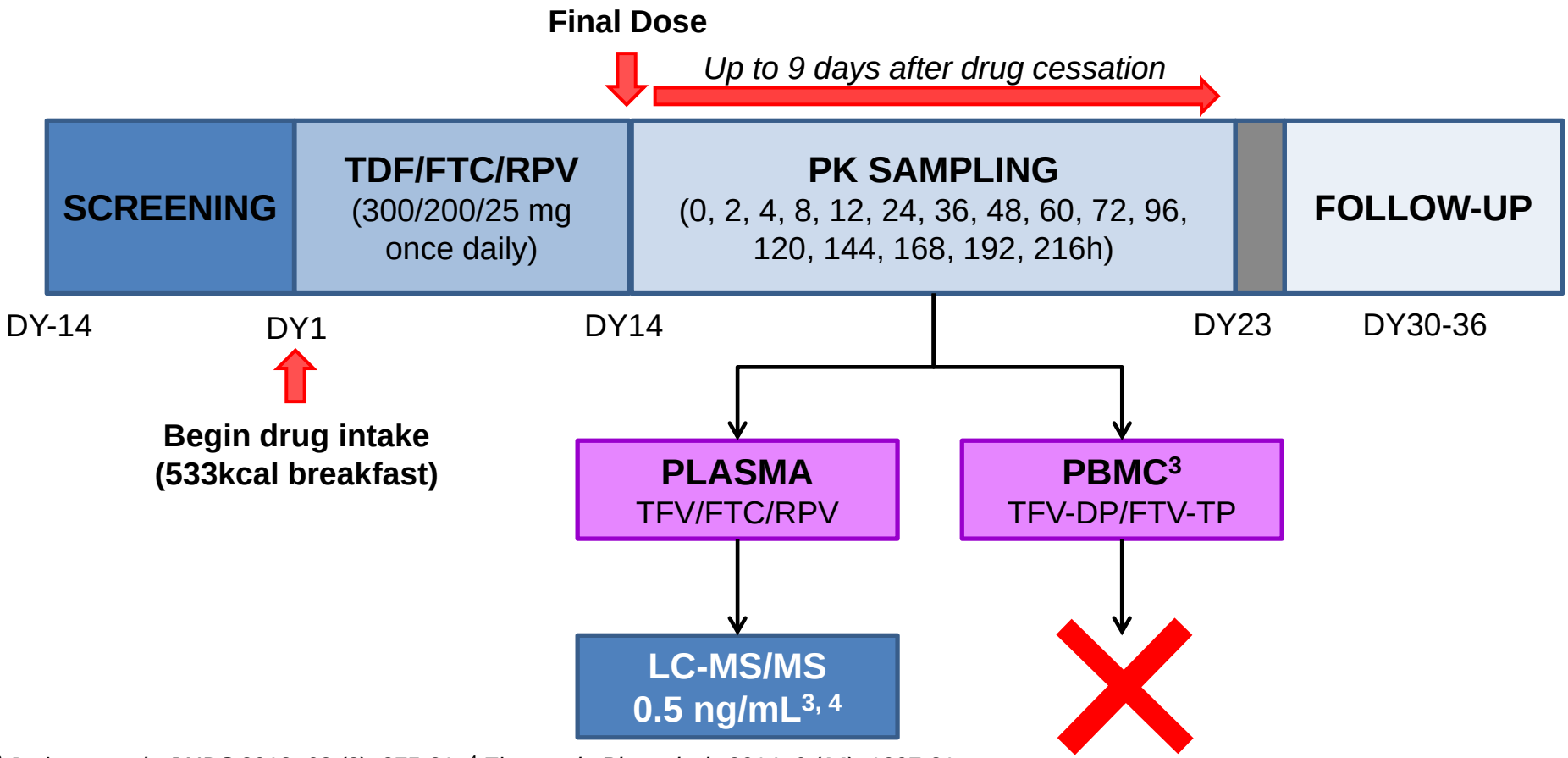
Evaluate plasma PK of tenofovir (TFV), emtricitabine (FTC) and rilpivirine (RPV) and IC TFV-DP and FTC-TP PK in healthy, HIV negative volunteers over 9 days following drug intake cessation

Methods

Study Design & PK Sampling

Inclusion: HIV negative
Healthy male & females
18-60 yr, BMI: 18-35 kg/m^2
Written informed consent

Exclusion: Significant illness e.g. HIV, HCV
Abnormal laboratory parameters
Medications 2 wks prior to study
Use of hormonal birth control



[3] Jackson *et al.*, *JAIDS* 2013; 62 (**3**): 275-81; [4] Else *et al.*, *Bioanalysis* 2014; 6 (**14**): 1907-21

Explore the use of nonlinear mixed effects modelling to predict IC TFV-DP and FTC-TP concentrations from plasma data and prior information

PK Modelling

Prediction of IC TFV-DP and FTC-TP

Time matched plasma and IC data from previous healthy volunteer study (TDF/FTC/EFV, 300/200/600 mg once daily)[3] used as prior information to establish link between plasma TFV and FTC and IC anabolites

Data up to 156 h (6.5 days; EFV study) and 168 h (7 days; RPV study) included

EFV study[3]
n=16 (5 female)

TFV SAMPLES (n/N)
Plasma: 203/206
IC: 183/207
FTCSAMPLES (n/N)
Plasma: 206/206
IC: 207/207

RPV study
n=18 (11 female)

TFV SAMPLES (n/N)
Plasma: 245/251
FTC SAMPLES (n/N)
Plasma: 250/251

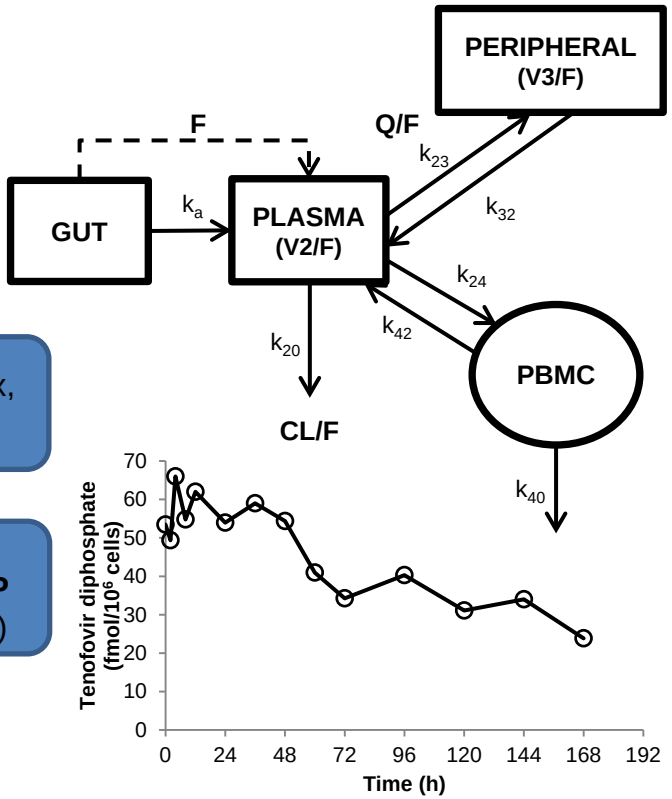
NONMEM (v. 7.2)

Structural Model

Covariate Model → Weight, BMI, sex, age, CrCL

Final Model → **Predictions TFV-DP/FTC-TP** 0-168 h (7 days)

Simulations Visual Predictive Check



[3] Jackson *et al.*, *JAIDS* 2013; 62 (**3**): 275-81

Statistical Analysis

Calculation of TFV-DP and FTC-TP PK Parameters

Individual, model predicted TFV-DP and FTC-TP concentrations used to calculate parameters (WinNonlin Phoenix v. 6.3)

- Area under the curve 0-24 h (AUC_{0-24})
- Area under the curve 0-168 h (AUC_{0-168})
- Maximum concentration (C_{max})
- Concentration 24 h post-dose (C_{24})

Terminal elimination half-lives of TFV-DP and FTC-TP were calculated from the model derived parameter, k_{40}

- $Ln2/k_{40}$

Post-hoc Analysis: comparison with HIV prevention targets

90% risk reduction associated with

- TFV-DP: 16 fmol/10^6 viable PBMCs[5]
- FTC-TP: 3.7 pmol/10^6 viable PBMCs[5]
- Determine proportions below target values 24, 36, 48 and 72 h after stopping drug
- Representing a 12h delay in drug intake and 1-2 missed doses

[5] Anderson *et al.*, *Sci Trans Med* 2012; 4 (**151**): 151ra125

Results

Demographics

	RPV study
Parameter	Median (range) *
Female [n (%)]	11 (61.1)
Age (years)	31 (19-47)
Weight (kg)	75 (60-105)
BMI (kg/m^2)	24 (21-31)
Serum creatinine (µmol/L)	73 (57-104)
Creatinine clearance (CrCL; ml/min/1.73m^2)†	103 (78-146)
Ethnicity [n (%)]	
Caucasian	10 (55.6)
Black-Caribbean	2 (11.1)
Black-African	2 (11.1)
Asian	1 (5.6)
Hispanic	1 (5.6)
Mixed ethnicity	2 (11.1)
Food intake	✓

* *Unless stated otherwise*

† calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[6]

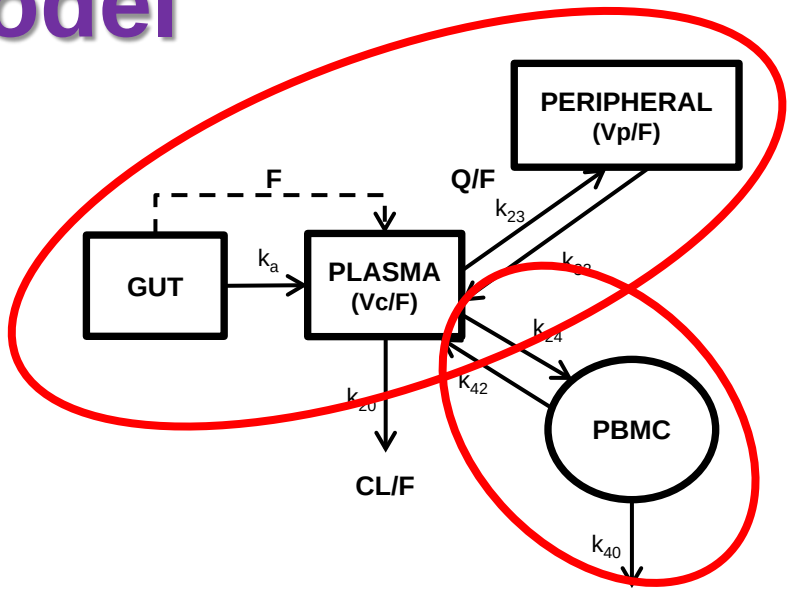
Study drug was well tolerated – no grade 3 or 4 adverse events were reported

[3] Jackson *et al.*, *JAIDS* 2013; 62 (**3**): 275-81; [6] Levey *et al.*, *Ann Inter Med* 2009; 150 (**9**): 604-12

PK Model

FTC Parameters	Estimate (RSE%)	IIV (%) (RSE%)
CL/F (L/h)	19.6 (5.9)	19.1 (29.4)
Vc/F (L)	69.5 (11.0)	45.2 (65.7)
Q/F (L/h)	3.70 (9.1)	
Vp/F (L)	128 (9.5)	18.8 (22.3)
k_a (h^{-1})	0.53 *fix*	
k_{24} (h^{-1})	0.15 (21.8)	60.8 (22.9)
k_{40} (h^{-1})	0.019 (6.1)	
Covariates		
θ_{CrCL} CL/F	0.0077 (30.9)	
Residual error		
Proportional plasma (%)	36.1 (12.9)	
Proportional IC (%)	55.8 (13.3)	

RSE: relative standard error; IIV: interindividual variability
$RSE=SE_{ESTIMATE}/ESTIMATE*100$

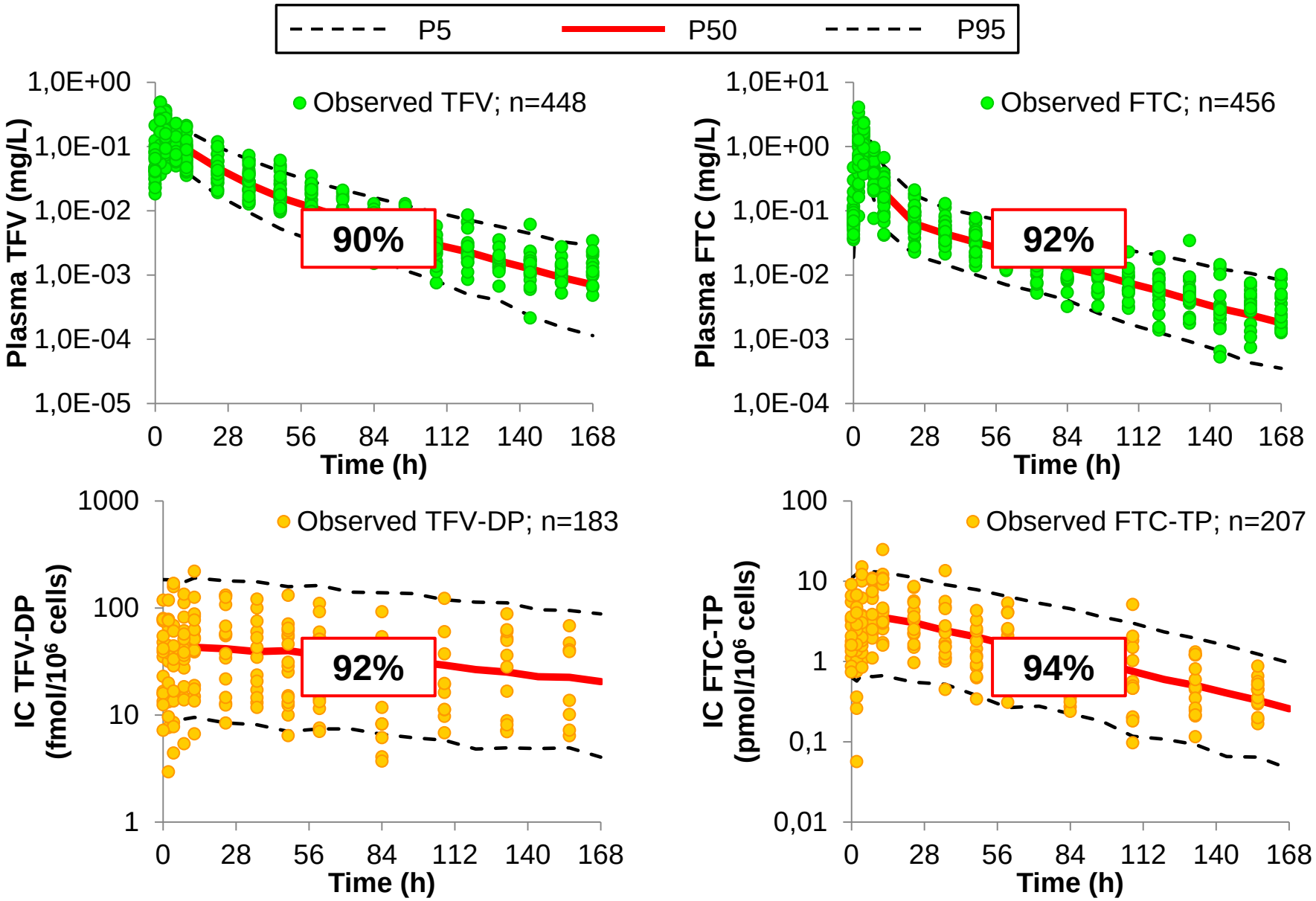


- 2 compartment, 1st order absorption; k_a fixed to 1.05 h^{-1} (TFV)[7], 0.53 h^{-1} (FTC)[8]
- Effect compartment linked to plasma described IC data
- Significant covariates:
  - **Weight** on FTC and TFV clearance and volume parameters
  - **CrCL** on TFV CL/F
  - **Food** effect on F1 (relative increase in F1 of 33% for RPV study vs. EFV study)

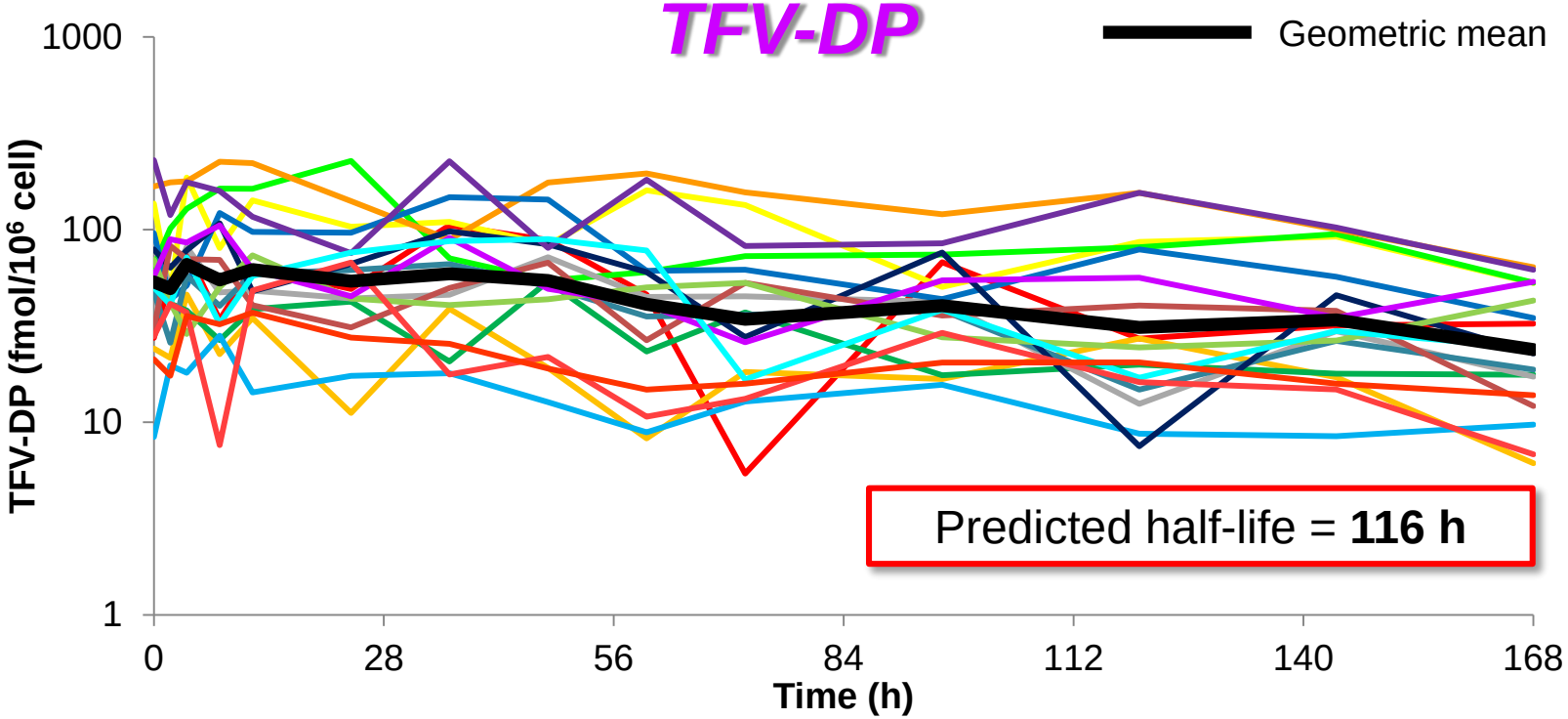
[7] Baheti *et al.*, *AAC* 2011; 55 (**11**): 5294-9;
[8] Valade *et al.*, *AAC* 2014; 58 (**4**): 2256-61

PK Model

Visual Predictive Check



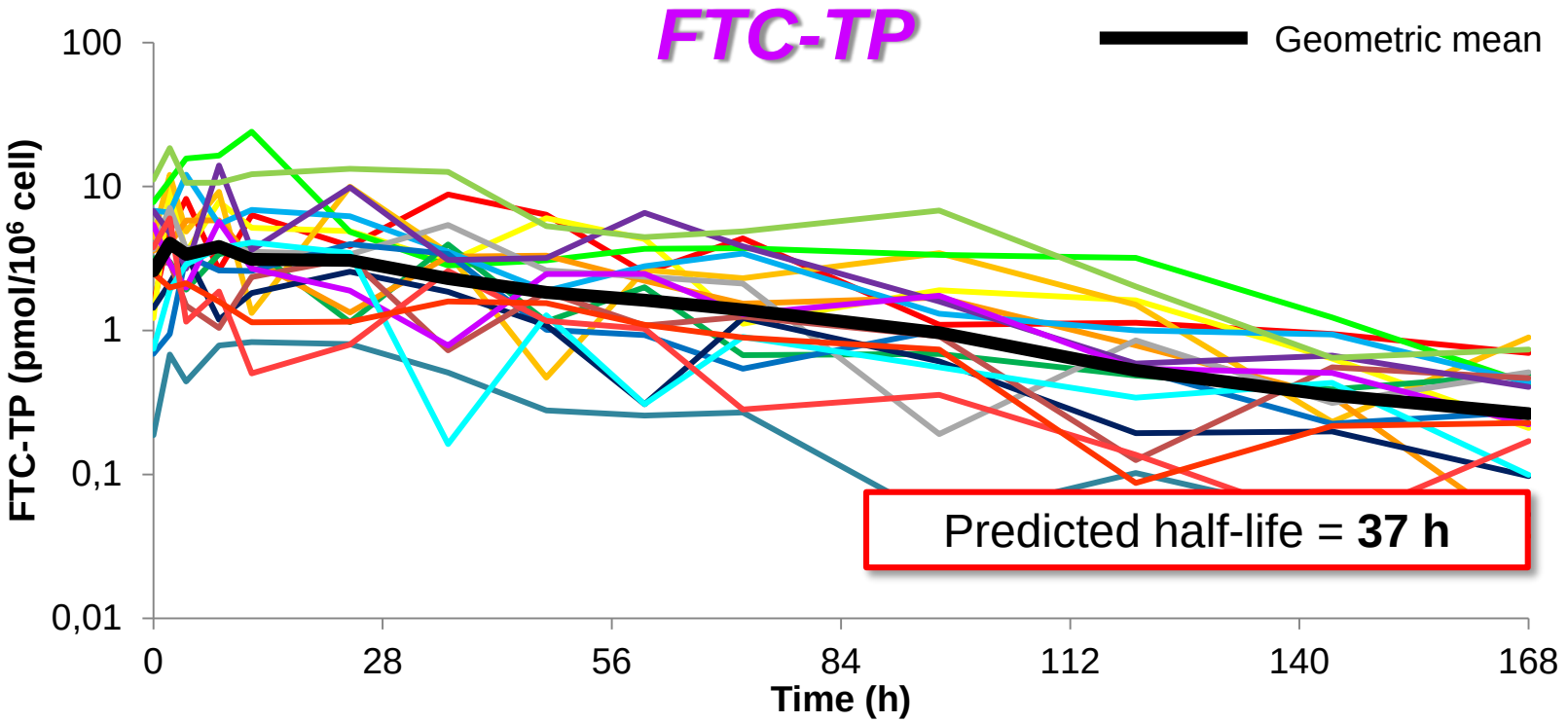
Predicted PK Profiles & Parameters



n=18 volunteers; n=252 predicted TFV-DP concentrations

Parameter	Geometric mean TFV-DP (90% CI)
AUC_{0-24} (fmol.h/10^6 cells)	1456 (1302-2193)
CV%	*66*
AUC_{0-168} (fmol.h/10^6 cells)	7495 (6792-11486)
CV%	*66*
C_{max} (fmol/10^6 cells)	92.2 (83.8-135)
CV%	*60*
C_{24} (fmol/10^6 cells)	54.0 (48.2-87.9)
CV%	*75*

Predicted PK Profiles & Parameters



n=18 volunteers; n=252 predicted FTC-TP concentrations

Parameter	Geometric mean FTC-TP (90% CI)
AUC_{0-24} (pmol.h/10^6 cells)	87.8 (79.2-150)
CV%	*80*
AUC_{0-168} (pmol.h/10^6 cells)	273 (252-440)
CV%	*70*
C_{max} (pmol/10^6 cells)	6.15 (5.73-10.5)
CV%	*75*
C_{24} (pmol/10^6 cells)	3.07 (2.88-5.63)
CV%	*83*

Comparison with HIV Prevention Targets

- Predicted concentrations at 24, 36, 48 and 72 h after stopping drug compared to HIV prevention targets (derived from iPrEx study data; TFV-DP: **16 fmol/10^6 cells**, FTC-TP: **3.7 pmol/10^6 cells**)[5]

Time (h)	TFV-DP		FTC-TP	
	n/N	***%***	***n/N***	***%***
24	1/18	6	10/18	56
36	0/18	0	14/18	78
48	1/18	6	15/18	83
72	4/18	22	15/18	83

- Majority of predicted TFV-DP concentrations **above** its threshold up to 3 days after final dose
- Most of predicted FTC-TP **below** its target between 24-72 h after stopping drug

[5] Anderson *et al.*, *Sci Trans Med* 2012; 4 (**151**): 151ra125

Conclusions

- Prediction of TFV-DP and FTC-TP from plasma data was achieved through inclusion of prior information from a previous healthy volunteer study
- The models, although relatively simplistic, described the data well, but also allows for refinement if further data become available
- TFV plasma concentrations were higher in the RPV study (SSAT048) compared to the EFV study
- Predicted TDF-DP and FTC-TP concentrations were generally in agreement with literature values[5,9-10]

[5] Anderson *et al.*, *Sci Trans Med* 2012; 4 (**151**): 151ra125; [9] Burns *et al.*, *J Clin Pharmacol* 2015; 55 (**6**): 629-38; [10] Wang *et al.*, *AIDS Res Hum Retroviruses* 2004; 20 (**11**): 1173-82

Limitations

- **Assumptions:**
  - RPV and EFV have no or impact on TFV-DP and FTC-TP disposition
  - Increased relative bioavailability assumed to be due to food intake but could be a result of inhibition of renal transporters by RPV or a combination of both
- ***Limitations:***
  - An independent, external validation dataset required to evaluate the model, particularly to confirm TFV-DP and FTC-TP predictions
  - IC rate constants (k_{24}, k_{40}) rely solely on prior data and are a simplification of the ongoing processes they describe

Acknowledgements

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