A Semi-Mechanistic Population Pharmacokinetic-Pharmacodynamic Model for Tenofovir in Rectal Mucosal Mononuclear Cells of Healthy Volunteers

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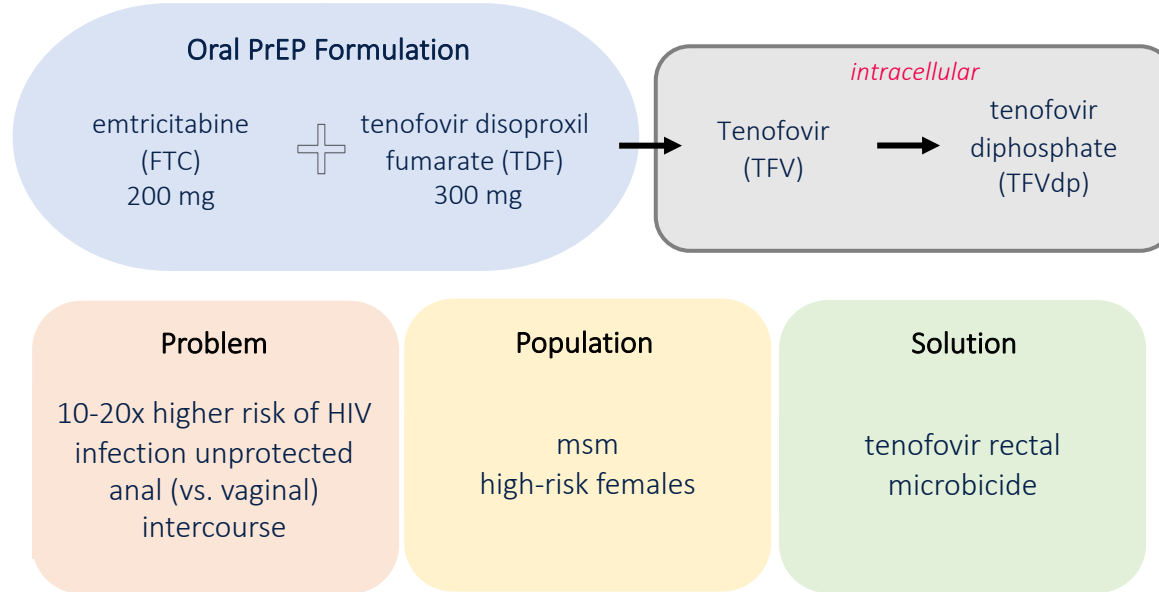
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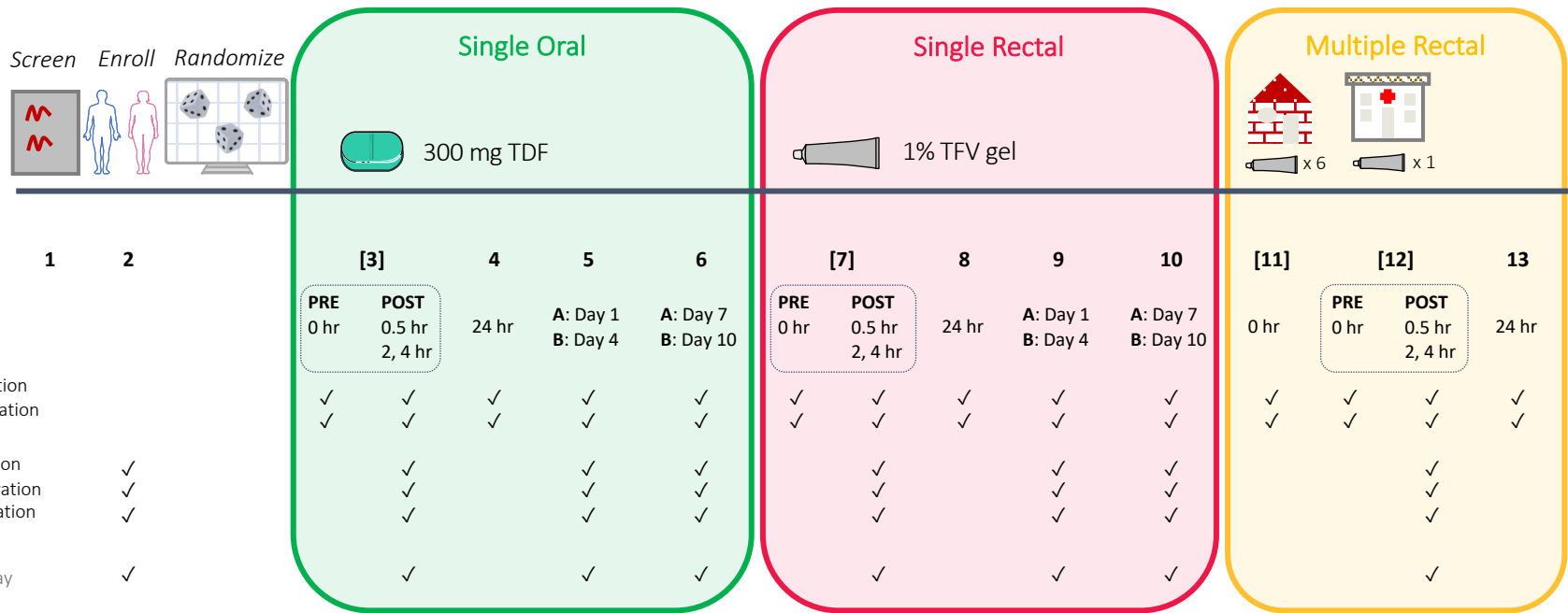03.16.19 • ASCPT 2019 Annual Meeting • Washington, DC

HIV Pre-Exposure Prophylaxis: Topical Product Development

Oral PrEP Formulation

emtricitabine
(FTC)
200 mg

+

tenofovir disoproxil
fumarate (TDF)
300 mg

intracellular

Tenofovir
(TFV) → tenofovir
diphosphate
(TFVdp)

Problem

10-20x higher risk of HIV infection unprotected anal (vs. vaginal) intercourse

Population

msm
high-risk females

Solution

tenofovir rectal microbicide

AIM

Define a tissue-specific prophylactic target tenofovir concentration above which HIV infection is suppressed using pharmacokinetic-pharmacodynamic modeling

The RMP-02/MTN-006 Study[1]: Phase I Pharmacokinetic Study in HIV-1 Seronegative Adults
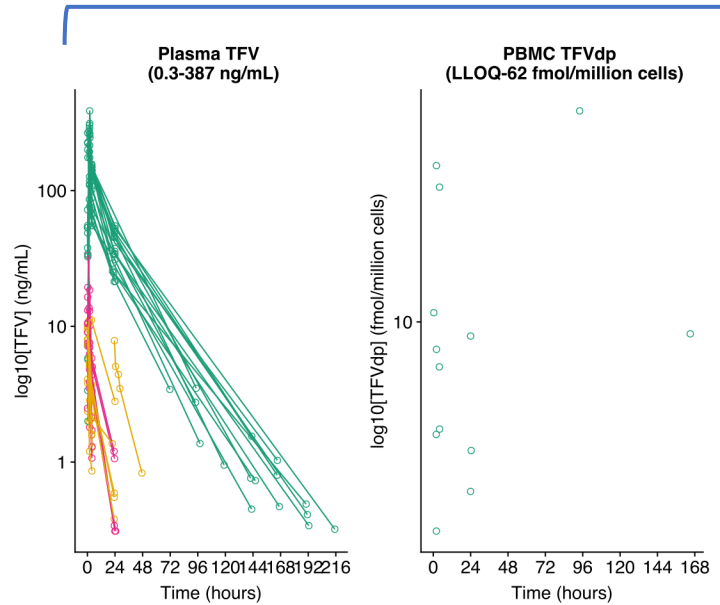

		Single Oral — 300 mg TDF				Single Rectal — 1% TFV gel				Multiple Rectal		
VISIT	**1**	**2**	**[3]**	**4**	**5**	**6**	**[7]**	**8**	**9**	**10**	**[11]**	**[12]**	**13**
	Screen	Enroll	PRE 0 hr / POST 0.5 hr 2, 4 hr	24 hr	A: Day 1 B: Day 4	A: Day 7 B: Day 10	PRE 0 hr / POST 0.5 hr 2, 4 hr	24 hr	A: Day 1 B: Day 4	A: Day 7 B: Day 10	0 hr	PRE 0 hr / POST 0.5 hr 2, 4 hr	24 hr

	1	2	[3] PRE 0 hr	[3] POST 0.5 hr 2,4 hr	4 (24 hr)	5 (A: Day 1 / B: Day 4)	6 (A: Day 7 / B: Day 10)	[7] PRE 0 hr	[7] POST 0.5 hr 2,4 hr	8 (24 hr)	9 (A: Day 1 / B: Day 4)	10 (A: Day 7 / B: Day 10)	[11] 0 hr	[12] PRE 0 hr	[12] POST 0.5 hr 2,4 hr	13 (24 hr)
Plasma Matrices:																
Plasma TFV concentration			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PBMC TFVdp concentration			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Rectal Matrices:																
Tissue TFV concentration		✓		✓		✓	✓		✓		✓	✓			✓	
Tissue TFVdp concentration		✓		✓		✓	✓		✓		✓	✓			✓	
MMC TFVdp concentration		✓		✓		✓	✓		✓		✓	✓			✓	
HIV infectability study:																
p24 explant tissue assay		✓		✓		✓	✓		✓		✓	✓			✓	

Dosing events: [x]

TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFVdp = tenofovir diphosphate
[1]Anton PA, et al. *AIDS Res Hum Retroviruses*. 2012;28(11):1412-21.

Plasma Matrices

Rectal Matrices

Plasma TFV
(0.3-387 ng/mL)

PBMC TFVdp
(LLOQ-62 fmol/million cells)

Tissue TFV
(LLOQ-430 ng/mg)

Tissue TFVdp
(LLOQ-7,188 fmol/mg)

MMC TFVdp
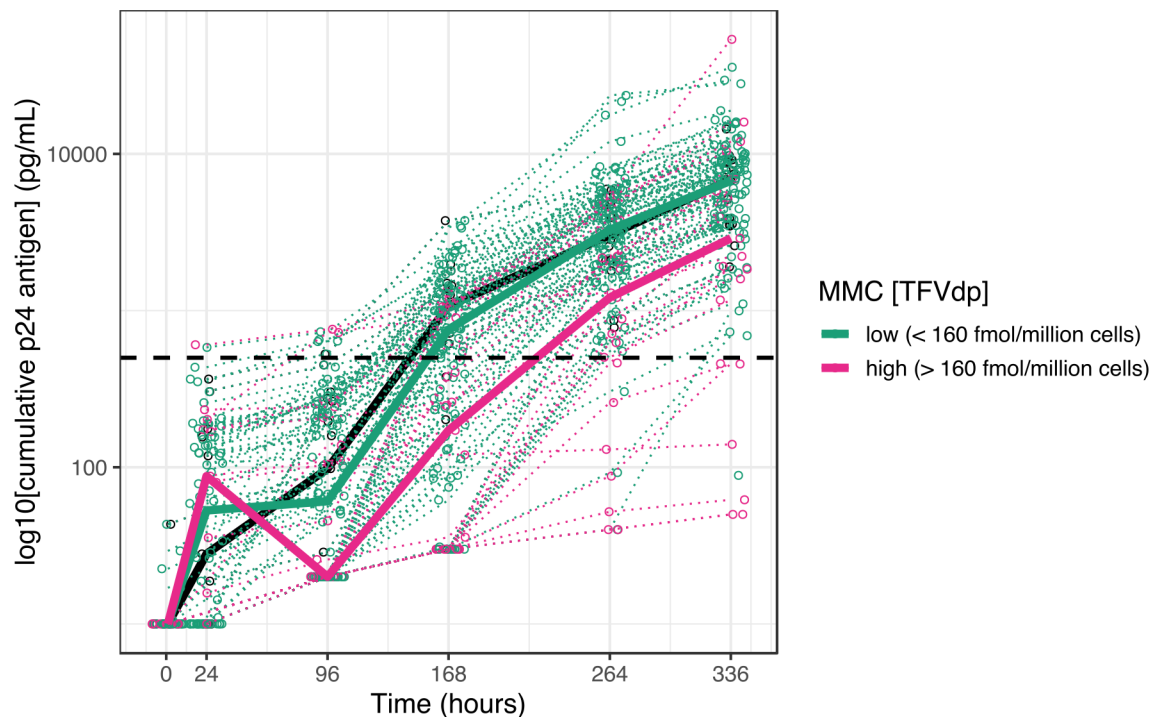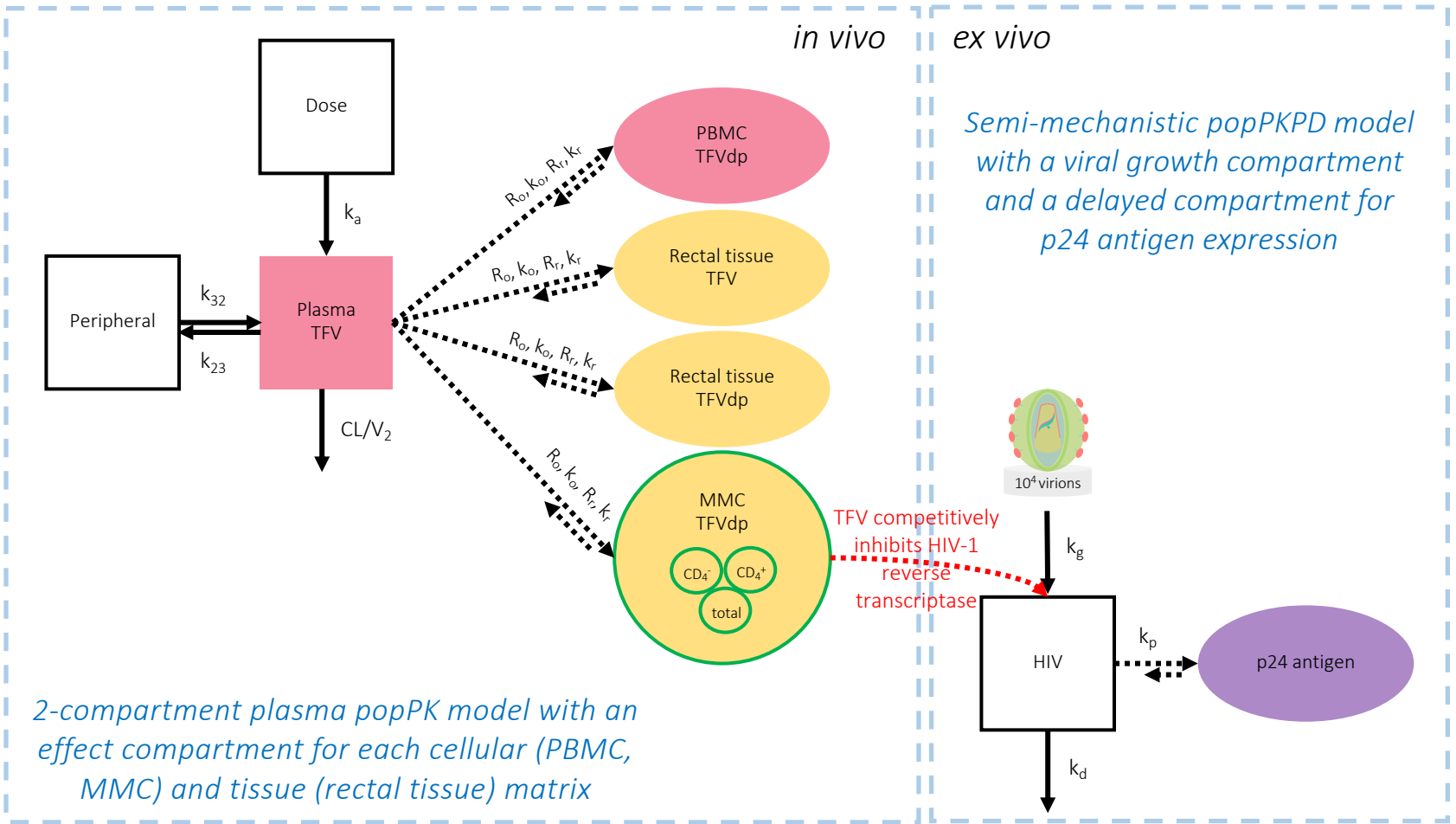**(LLOQ-31,153 fmol/million cells)**

ARM
single oral
single rectal
multiple rectal
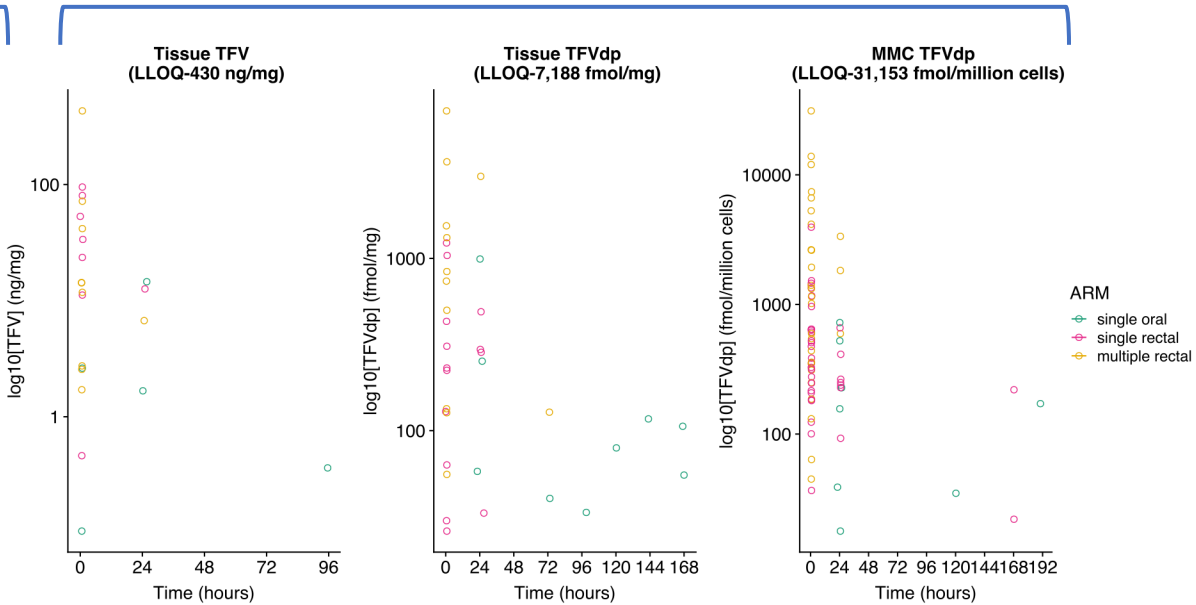
LLOQ = lower limit of quantification; BLQ = below limit of quantification
Concentrations deemed BLQ not included

Cumulative p24 antigen expression decreases with increasing TFVdp drug concentration

MMC [TFVdp]
— low (< 160 fmol/million cells)
— high (> 160 fmol/million cells)

Median (solid, black = baseline); individual (dotted); cumulative p24 antigen level = 500 pg/mL (dashed)
Concentrations deemed BLQ (10 pg/mL) included

in vivo   *ex vivo*

Dose

k_a

Peripheral

k_{32}
k_{23}

Plasma
TFV

CL/V_2

R_o, k_o, R_r, k_r

PBMC
TFVdp

R_o, k_o, R_r, k_r

Rectal tissue
TFV

R_o, k_o, R_r, k_r

Rectal tissue
TFVdp

R_o, k_o, R_r, k_r

MMC
TFVdp

CD_4^- CD_4^+

total

TFV competitively
inhibits HIV-1
reverse
transcriptase

*Semi-mechanistic popPKPD model
with a viral growth compartment
and a delayed compartment for
p24 antigen expression*

10^4 virions

k_g

HIV

k_p

p24 antigen

k_d

*2-compartment plasma popPK model with an
effect compartment for each cellular (PBMC,
MMC) and tissue (rectal tissue) matrix*
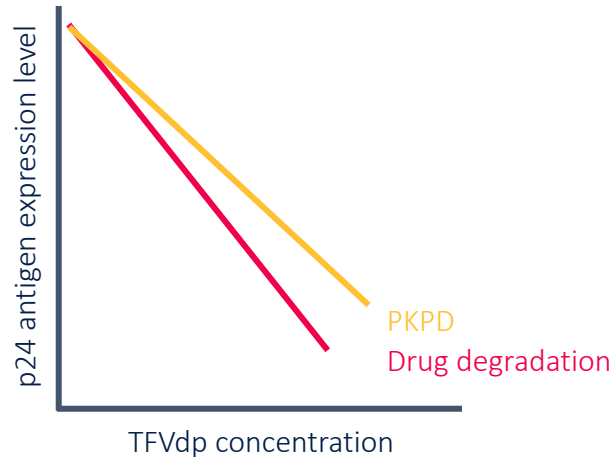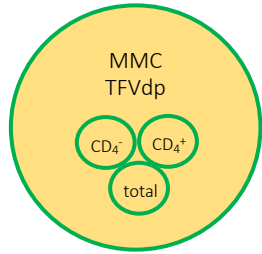
A significant <u>linear</u> PKPD relationship was observed between p24 antigen expression level and TFVdp concentration in MMCs.

The magnitude of the slope is biased without consideration for the rate of drug degradation.

<u>Assumption</u>: constant degradation rate[2] (k_{deg} = 0.0018 h^{-1})

[2]Agrahari, Vivek et al. *Drug testing and analysis* 7.3 (2015): 207-213.

Model Summary and Visual Predictive Checks

Model Description/Parameter	Pharmacokinetic Driver OFV/Significance/Population Estimate (RSE, %)			Inter-individual Variability, %CV (RSE, %)		
	CD_4^-	CD_4^+	TOTAL	CD_4^-	CD_4^+	TOTAL
No treatment effect	8201	8088	8073	-	-	-
Treatment effect	Not significant	Not significant	Not significant	-	-	-
PKPD effect	8168 (dOFV = -33)	8105 (dOFV = +17)	8040 (dOFV = -33)	-	-	-
Drug degradation effect	8161 (dOFV = -40)	8097 (dOFV = +9)	8032 (dOFV = -41)	-	-	-
Slope [(pg/mL)/(fmol/million cells)]	4.20×10^{-4} (9)	8.0×10^{-5} (44)	1.10×10^{-4} (11)	-	2.93 (29)	-
Proportional error [%CV]	86.9 (5)	85.7 (6)	87.6 (6)			
Additive error [pg/mL]	3.53 (10)	3.60 (10)	3.61 (11)			

BASELINE — SINGLE ORAL — SINGLE RECTAL — MULTIPLE RECTAL
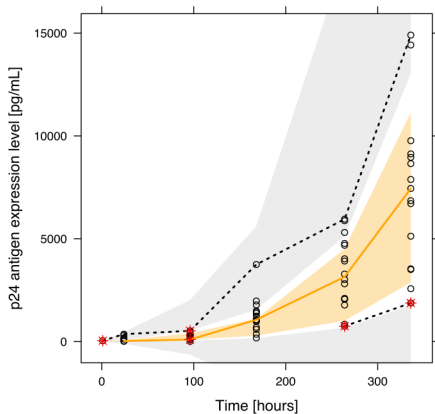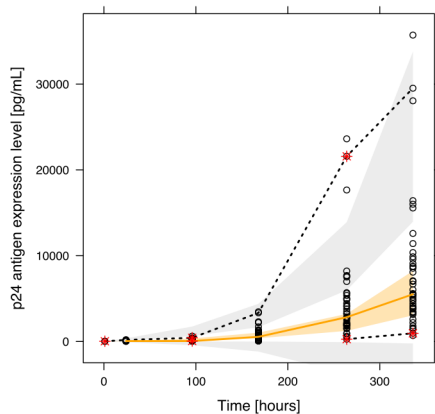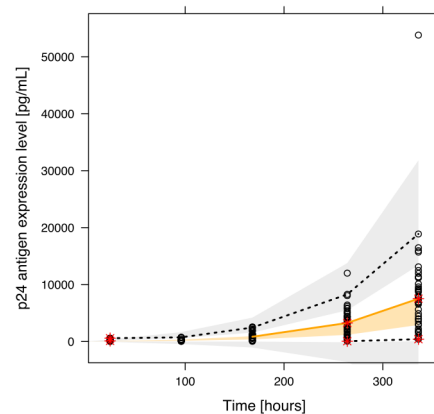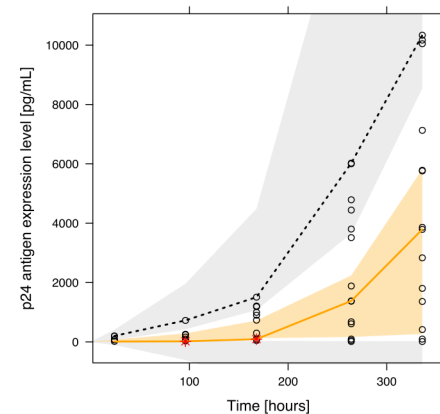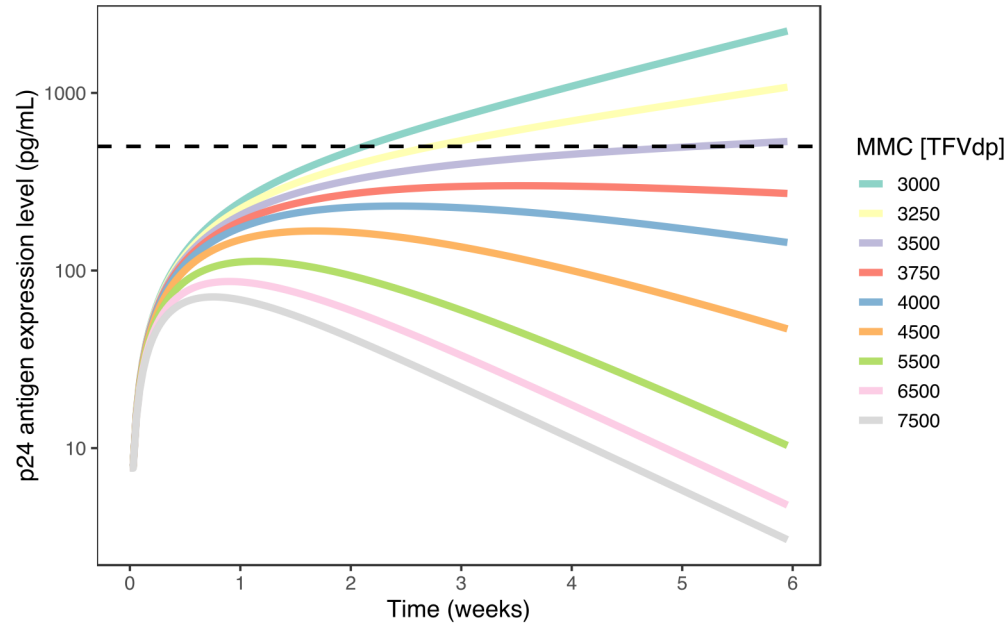
[MMC TFVdp] > 5500 fmol/million cells

Cumulative p24 antigen level = 500 pg/mL (dashed)

Conclusions

*We have established a **dose-concentration-response effect** using **explant tissue** to describe the effect of single (oral and rectal) and multiple (rectal) dose administrations of tenofovir to suppress p24 antigen expression in healthy volunteers.*

Population PK Model

- TFV and TFVdp PK in plasma and rectal matrices were successfully characterized using a multi-compartmental PK model.
- Accumulation of TFVdp in MMCs appears to be higher following rectal compared to oral administration.

Population PKPD Model

- The PKPD relationship appears to be independent of cell type.
- Drug degradation effect in the *ex vivo* assay must be considered to derive unbiased parameter estimates and to maximize the utility of the explant assay.

Tissue-Specific Prophylactic Target TFVdp Concentration

- MMC TFVdp concentrations > 5500 fmol/million cells are desired for full viral suppression (p24 antigen expression profile).