CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS

From Consensus to Implementation

22-24 September 2013
Queen Elizabeth II Conference Centre, London

Pharmacology Lessons from Chemoprophylaxis Studies

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Pre tenofovir generation 1996-2009
PK did not inform trials

Study Drug	Mechanism of Action	Sample Size	Seroconversions		Hazard Ratio (95% CI)
			Active	Placebo	
Nonoxynol 9	Surfactant	892	**59**	45	1.5 (1.0–2.2)
Savvy (C31G)	Surfactant	2,153	**21**	12	1.7 (0.9–3.5)
Cellulose Sulfate	Polyanion	1,333	**23**	11	0.8 (0.3–1.8)
Carraguard	Polyanion	6,202	134	**151**	0.9 (0.7–1.1)
Pro2000	Polyanion	*3,099	36	**51**	0.7 (0.5–1.1) 0.6 (on Rx, p=0.04)
Pro2000 (MRC)	Polyanion	9,385	**145**	143	1.00 (0.79–1.26)

In parallel with RCT, in vitro studies demonstrate toxicity for 3 of these products
*4-arm study, 1,550 enrolled in Pro2000 and placebo gel arms

Hendrix 2012

Tenofovir generation 2010-2012
PK informed interpretation, not design

		RELATIVE RISK REDUCTION (95% CI)		
STUDY	REGIMEN	ALL PARTICIPANTS	DRUG DETECTABLE	ADHERENCE
FEM-PrEP	TDF/FTC po QD	0.0 (-0.73-0.42)	SC 15%, NSC 26%, NS, LLOQ 10	
VOICE	TDF po QD	0.0		
iPrEX	TDF/FTC po QD	0.42 (0.15-0.63)	0.92 (0.44-0.99), LLQ 10	
CDC TDF2	TDF/FTC po QD	0.63 (0.2200.83)	SC 50%, NSC 80%, LLOQ 0.3	0.78 (0.41-0.94)
Partners	TDF po QD	0.67 (0.44-0.81)	0.86 (0.57-0.95), LLOQ 0.3	
	TDF/FTC po QD	0.75 (0.55-0.87)	0.90 (0.56-0.98)	
CAPRISA	TFV gel BAT24	0.39 (0.04-0.60)	> 1000 CVF	0.54 (0.20-0.96)*
VOICE	TFV get QD	0.0		

Hendrix 2012

IDEALLY

Large RCTs should contain sparse PK assessment

Linked to smaller formal/intensive PK studies

- Importance of understanding concentration-response
- Factors affecting dose selection
- Future trial design

The optimal PrEp agent

- Safe
- Penetrates target tissues
- Protect against HIV in tissue
- Demonstrates long-lasting activity with convenient dosing
- Unique drug resistance profile / high genetic barrier to resistance
- No significant drug-drug interactions
- Not part of current HIV treatment combinations
- Affordable and easy to use/implement

TFV and FTC are the only ARVs proven efficacious in prospective randomised clinical PrEP trials

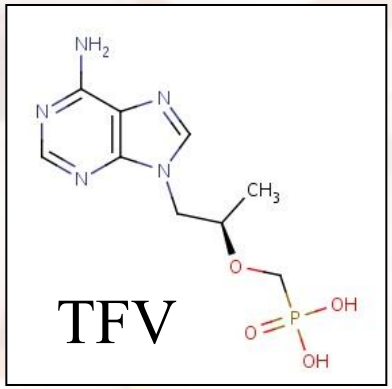
↓

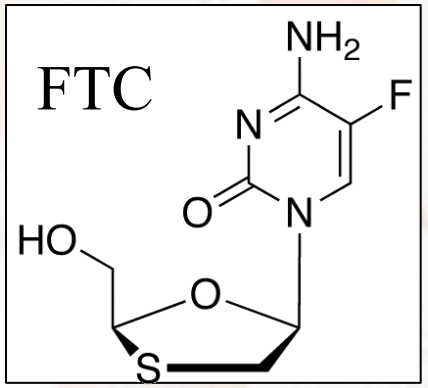
HIV acquisition is the primary outcome used / large sample size CTs

↓

Lack of surrogate marker for PrEP

Important role of CLINICAL PHARMACOLOGY to explain the variable drug responses

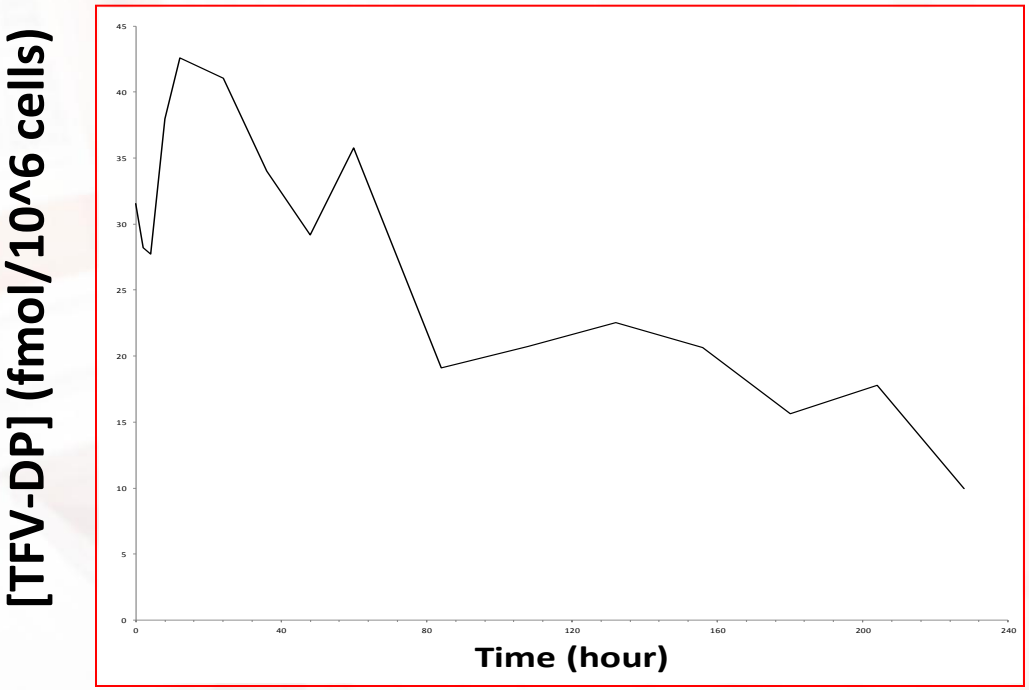

TFV


FTC

Proviral DNA
Viral RNA
RT
RT
Proviral DNA
Viral RNA

Tenofovir, emtricitabine intracellular and plasma, and efavirenz plasma concentration decay following drug intake cessation: implications for HIV treatment and prevention.

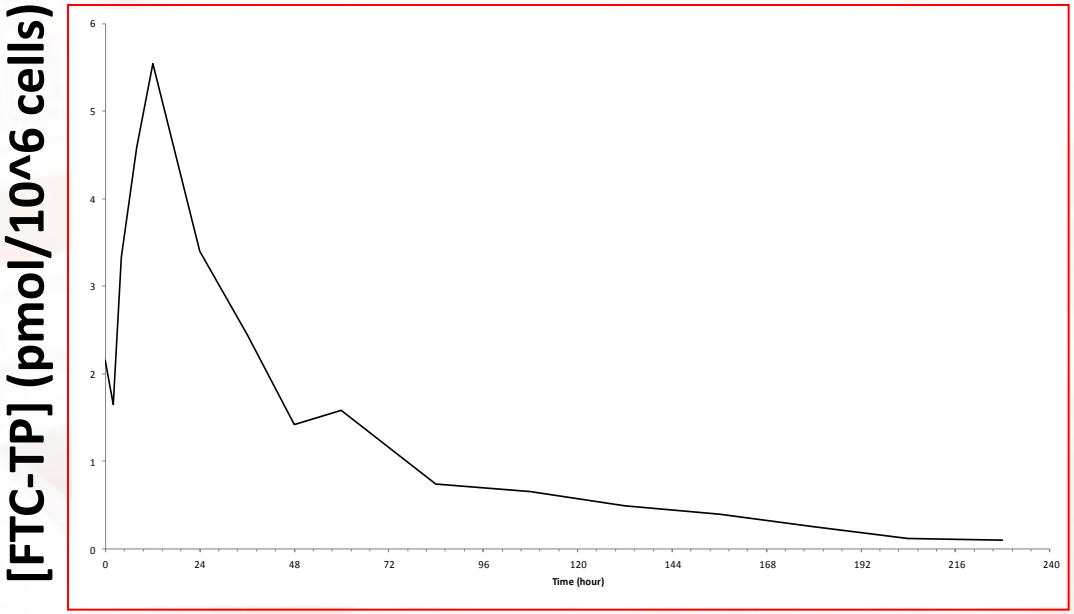
Terminal TFV-DP $t_{1/2}$ = 164 h



Jackson et al. JAIDS2013

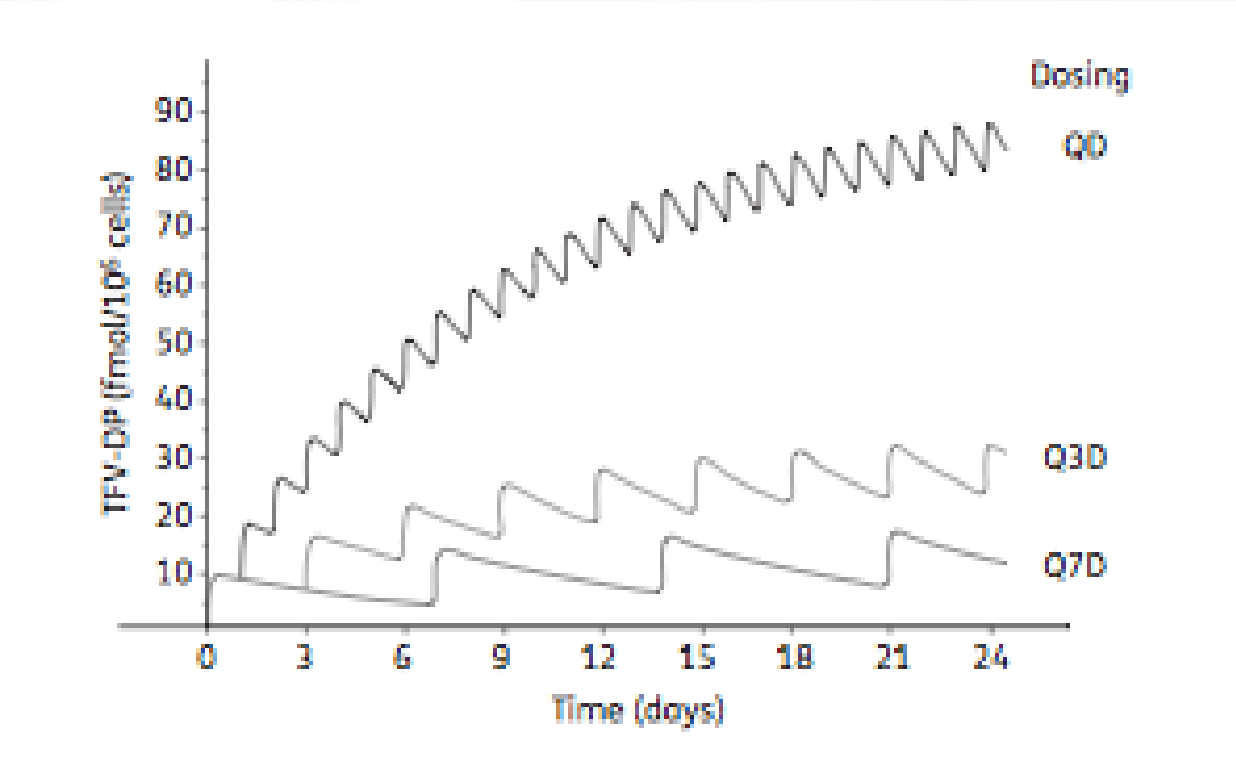
Tenofovir, emtricitabine intracellular and plasma, and efavirenz plasma concentration decay following drug intake cessation: implications for HIV treatment and prevention.

Terminal FTC-TP $t_{1/2}$ = 39 h



Jackson et al. JAIDS2013

Predicted TFV-DP accumulation to steady-state in humans with 3 different dosing strategies



STRAND: Directly observed dosing showed TFV-DP concentrations that corresponded with HIV risk reduction of 76% for 2 doses per week, 96% for 4 doses per week, 99% for 7 doses per week

Anderson et al. JAC 2010; Anderson et al. STM 2012

Within study concentration-response comparison

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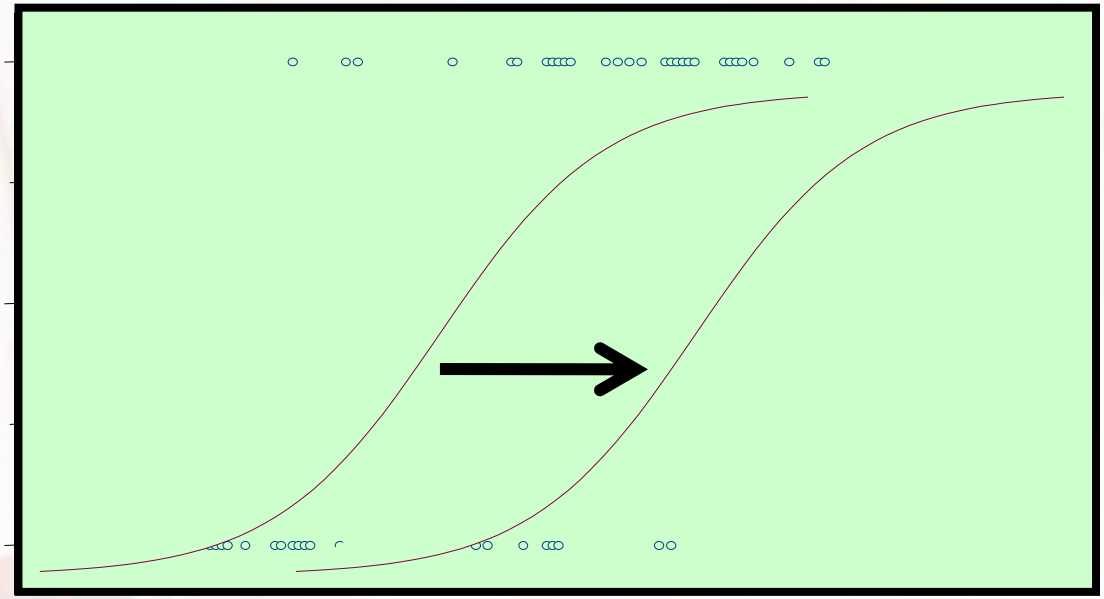
VOICE	TFV get QD	0.0		

***** *INCREASED RR REDUCTION WITH DETECTABLE DRUG IN PLASMA*

***** *INCREASED RR REDUCTION WITH >80% ADH and [CVF]>1000ng/mL*

Hendrix 2012

Sources of PHARMACODYNAMIC variability



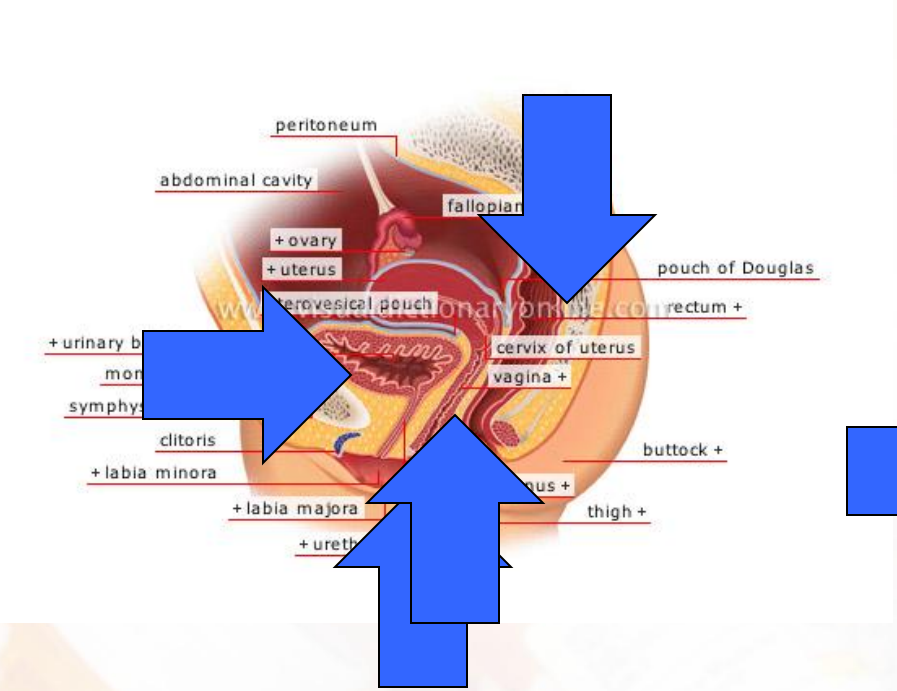
- Virological factors
- Immunological factors
- Host biology/genetics
- Adherence
- PK
- Drug interactions
- Tissue penetration
- Cell type
- Toxicity
- ETC…

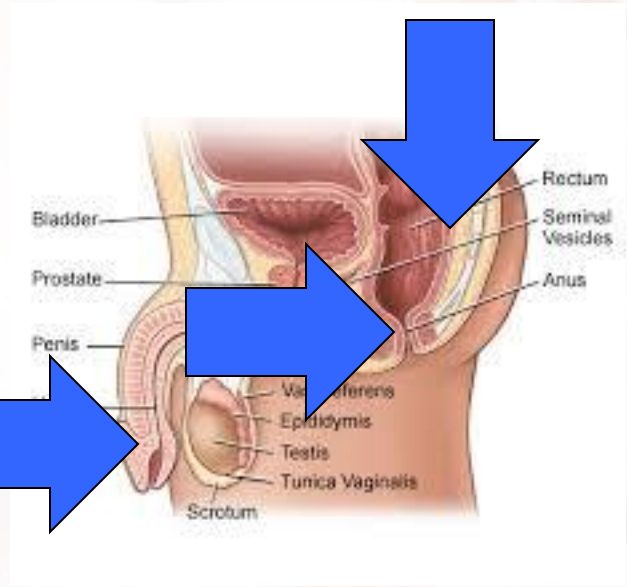
Hendrix, *et al Ann Rev Pharm Toxicol* 2009

Gaps?

- Fundamental HIV transmission biology incompletely understood
  - What is the site of action to target?
  - What is the required duration of action?
- Validation of animal models and *ex vivo* HIV challenge
- Clinical proof-of-concept design needed

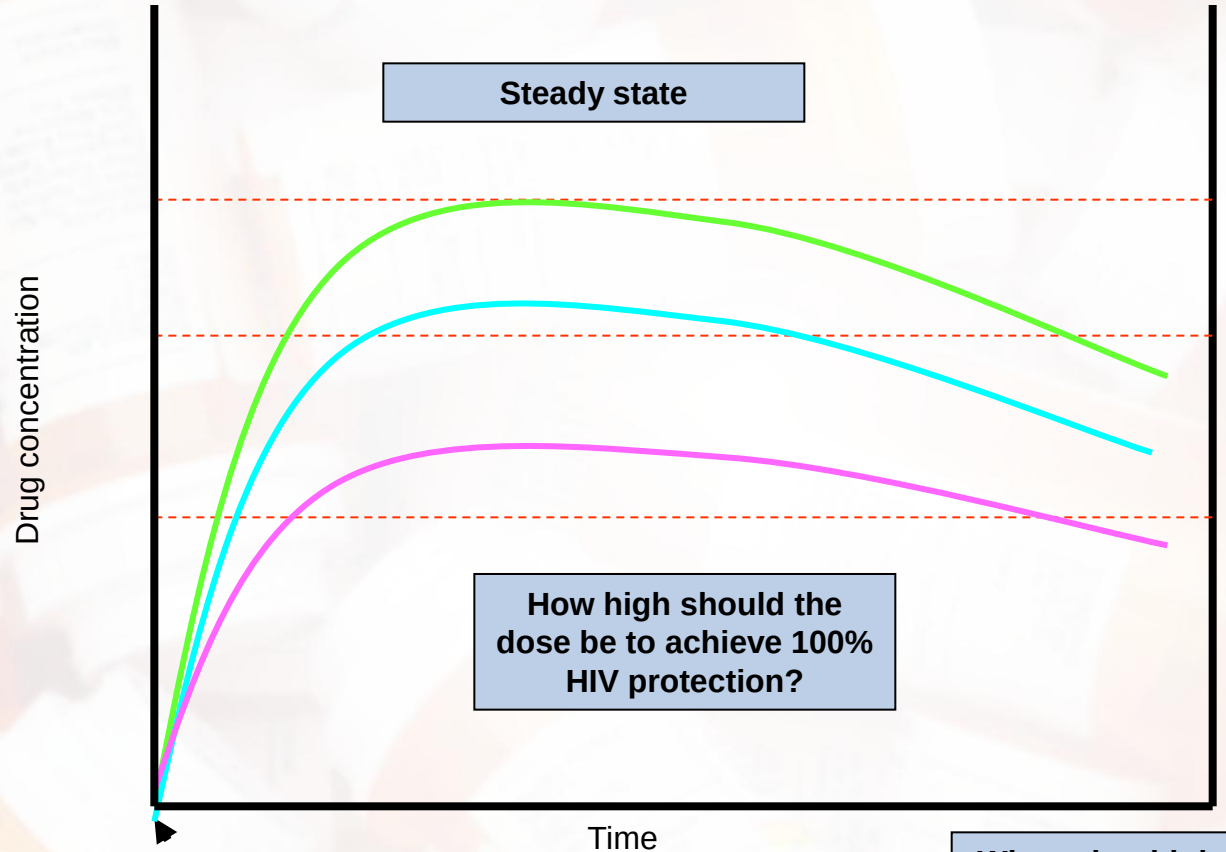
What are the drug distribution targets?





Lack of data on concentration-effect relationship

or poor



Are ex vivo challenge experiments adequate to asses PrEP PDs?

Would "maximum" be 100%?

How high should the dose be to achieve 100% HIV protection?

Ideally months…

When should the following dose be administered to maintain protection?

Thanks to Alan Winston and UK PrEP Pharmacology Group

SSAT040

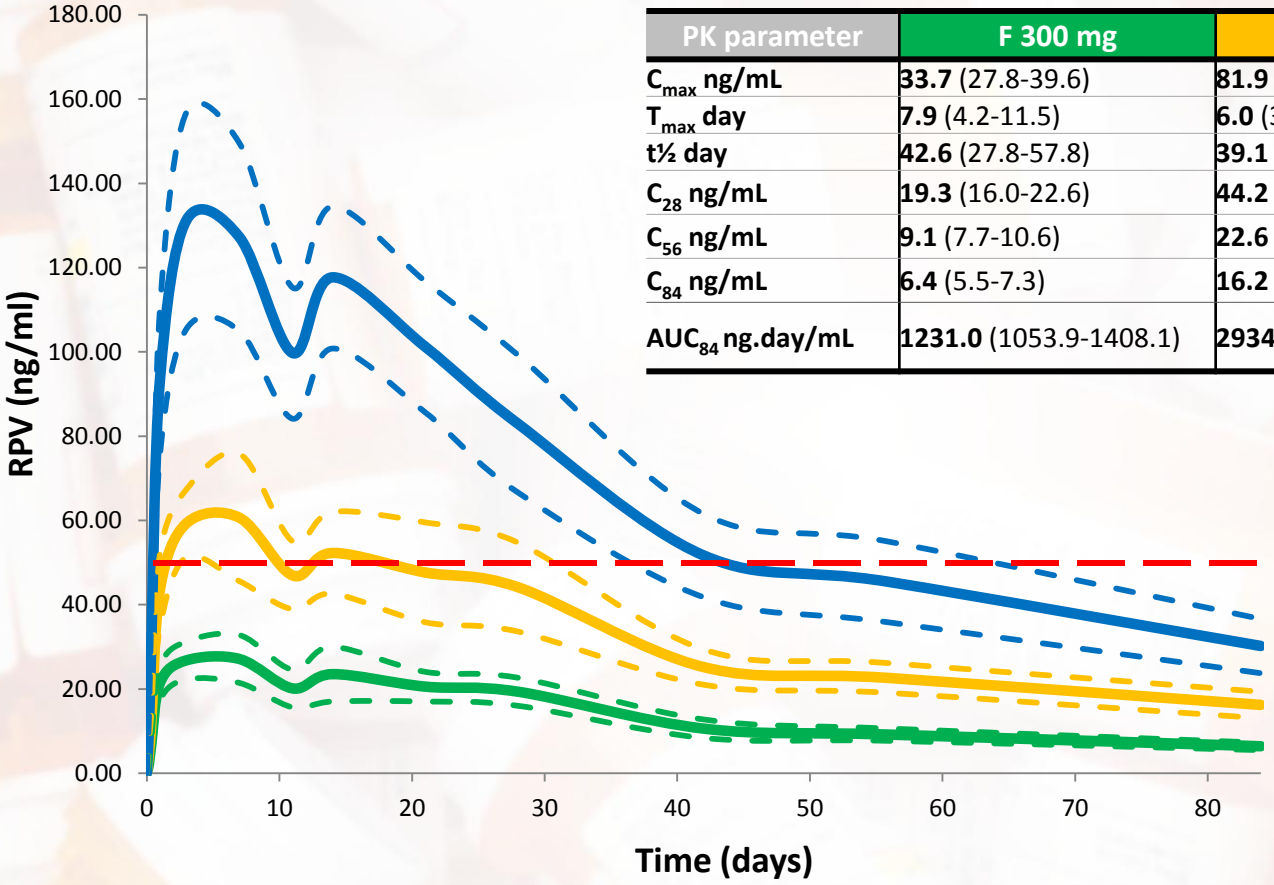
A pharmacokinetic evaluation of the exposure and distribution of TMC278LA for use as pre-exposure prophylaxis, in plasma and genital tract / rectal compartments, following a single intramuscular dose at different doses in HIV negative healthy volunteers.

- **HIV negative volunteers (60 female, 6 male)**
- **Aged 18 – 50 years**
- **Low behavioural risk for infection**
- **Female: > 50% of enrolled; self-identified African or African-Caribbean ancestry**
- **Administered 300 (n = 20), 600 (n = 20), 1200 (n = 20) mg RPV-LA (G001 formulation) intramuscularly (gluteus maximus)**
- **Sampling:**
  - **plasma *PK***
  - **cervicovaginal fluid (CVF; females) & rectal fluid (RF; males) *PK***
  - **tissue biopsies: vaginal (VT; females) & rectal (RT; males) *PK***
  - **cervicovaginal lavage (CVL; females) *PK & PD***

Day	0	0 (4 h)	0 (8h)	1	3	7	11	14	21	28	42	56	84
Plasma PK													
Genital/rectal fluid PK													
Tissue Biopsy (vaginal/rectal)PK													
CVL for PK and PD													

PLASMA 300, 600 & 1200 mg doses:

Dose proportionality: geometric mean (90% CI)



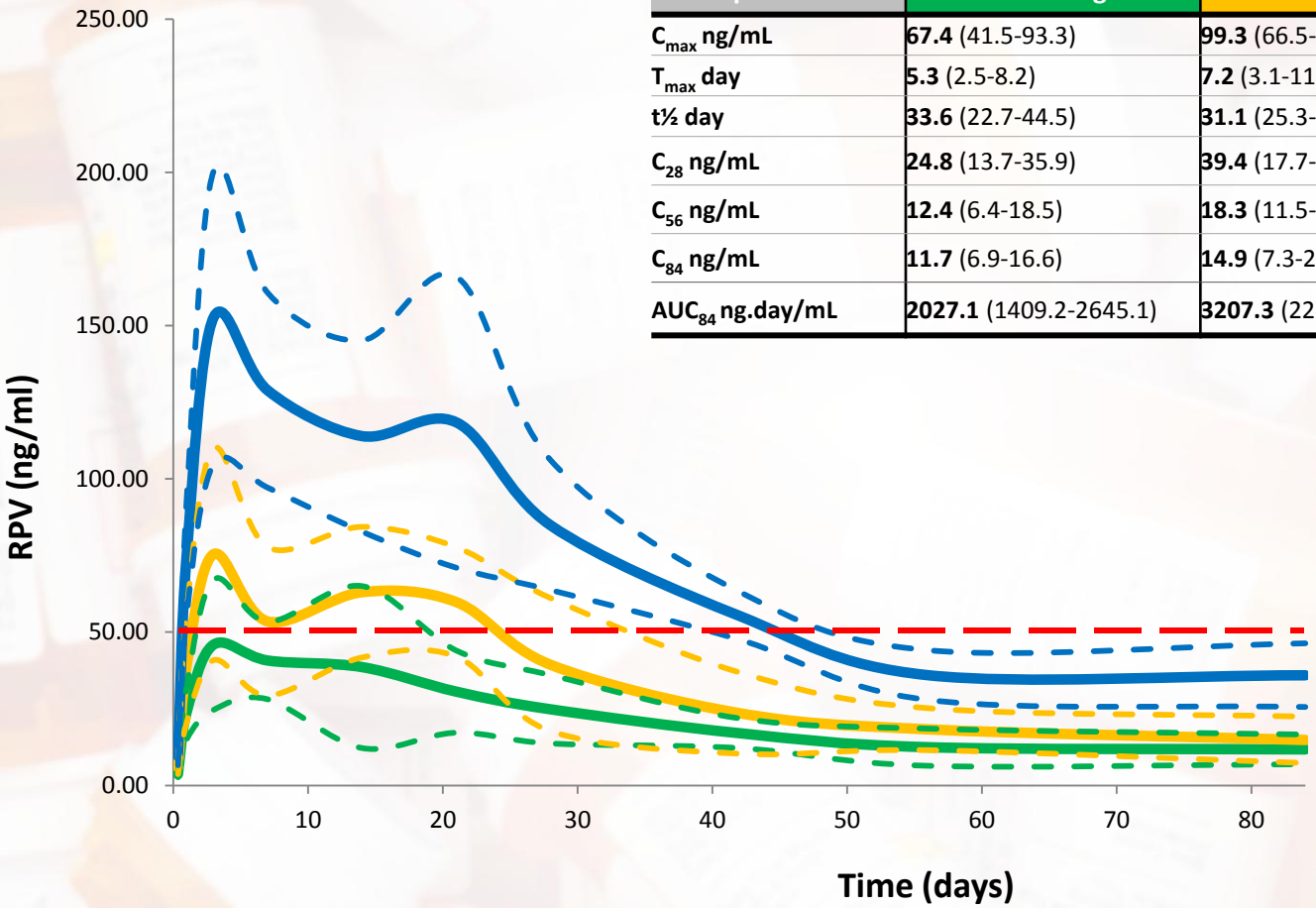
PK parameter	F 300 mg	F 600 mg	F 1200 mg
C_{max} ng/mL	**33.7** (27.8-39.6)	**81.9** (68.7-95.1)	**160.2** (137.5-182.9)
T_{max} day	**7.9** (4.2-11.5)	**6.0** (3.4-8.6)	**6.2** (4.3-8.1)
t½ day	**42.6** (27.8-57.8)	**39.1** (33.4-44.9)	**38.2** (29.8-46.6)
C_{28} ng/mL	**19.3** (16.0-22.6)	**44.2** (33.6-54.7)	**82.9** (66.6-99.1)
C_{56} ng/mL	**9.1** (7.7-10.6)	**22.6** (19.1-26.1)	**45.3** (35.8-54.9)
C_{84} ng/mL	**6.4** (5.5-7.3)	**16.2** (13.0-19.3)	**30.2** (23.7-36.6)
AUC_{84} ng.day/mL	**1231.0** (1053.9-1408.1)	**2934** (2568.5-3300.4)	**5981.6** (5155.9-6807.4)

TARGET?

CVF 300, 600 & 1200 mg doses:

Dose proportionality: geometric mean (90% CI)

PK parameter	F 300 mg	F 600 mg	F 1200 mg
C_{max} ng/mL	**67.4** (41.5-93.3)	**99.3** (66.5-132.1)	**199.9** (154.7-245.1)
T_{max} day	**5.3** (2.5-8.2)	**7.2** (3.1-11.3)	**8.5** (5.06-11.9)
t½ day	**33.6** (22.7-44.5)	**31.1** (25.3-36.8)	**43.7** (31.1-56.4)
C_{28} ng/mL	**24.8** (13.7-35.9)	**39.4** (17.7-61.1)	**84.8** (63.7-106.1)
C_{56} ng/mL	**12.4** (6.4-18.5)	**18.3** (11.5-25.1)	**35.9** (27.8-44.1)
C_{84} ng/mL	**11.7** (6.9-16.6)	**14.9** (7.3-22.4)	**35.9** (25.5-46.3)
AUC_{84} ng.day/mL	**2027.1** (1409.2-2645.1)	**3207.3** (2262.4-4152.1)	**6499.5** (5264.2-7734.7)

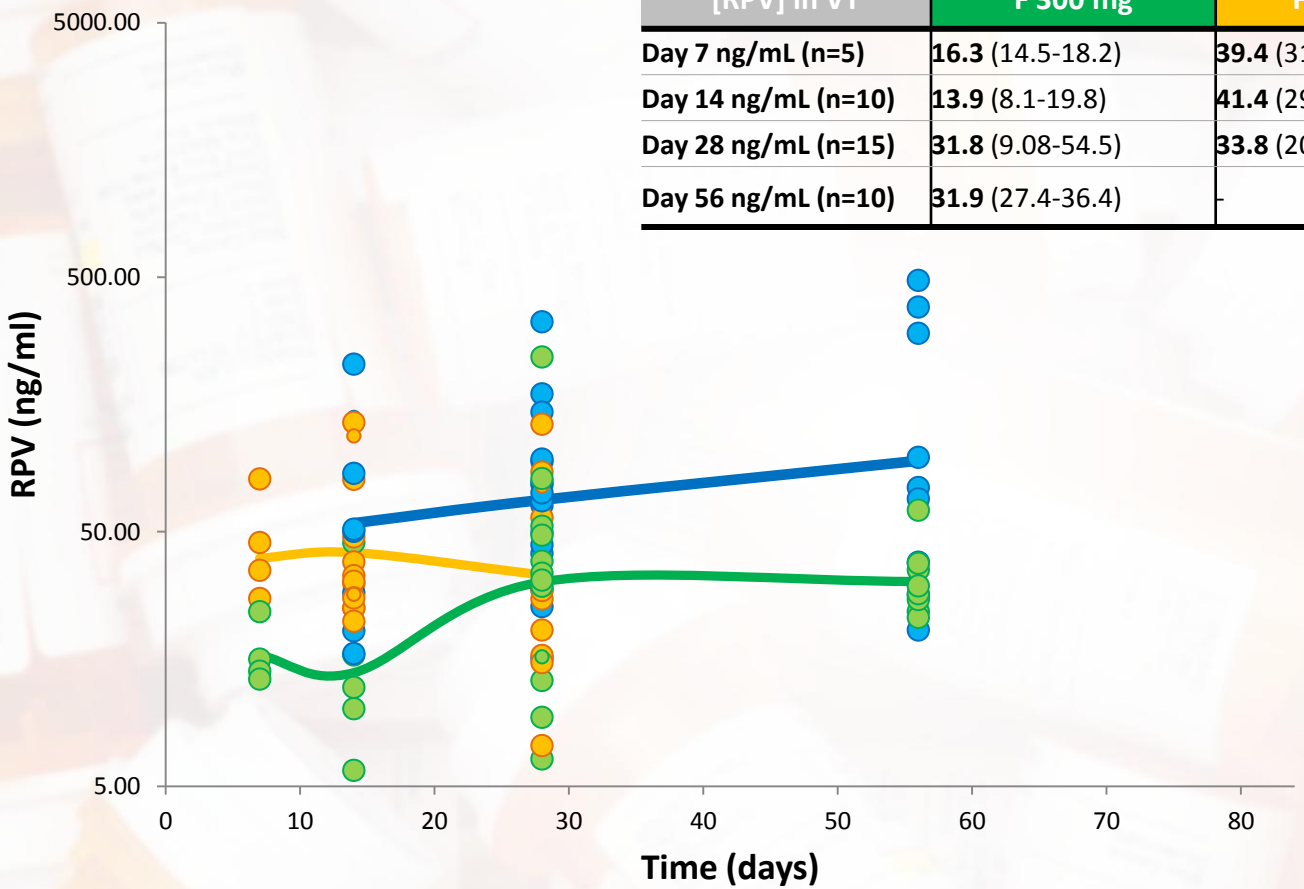


TARGET?

VT 300, 600 & 1200 mg doses:

Dose proportionality: geometric mean (90% CI)

[RPV] in VT	F 300 mg	F 600 mg	F 1200 mg
Day 7 ng/mL (n=5)	**16.3** (14.5-18.2)	**39.4** (31.2-47.6)	-
Day 14 ng/mL (n=10)	**13.9** (8.1-19.8)	**41.4** (29.1-53.7)	**53.9** (28.6-79.3)
Day 28 ng/mL (n=15)	**31.8** (9.08-54.5)	**33.8** (20.3-47.3)	**66.6** (38.8-94.4)
Day 56 ng/mL (n=10)	**31.9** (27.4-36.4)	-	**94.9** (33.3-156.6)



-A subject tested positive for HIV antibodies on study day 84

-HIV viral load on study day 56 = 370 copies,/mL
-HIV viral load on study day 84 = 175060 copies,/mL

-Received the lowest studied dose of 300 mg IM

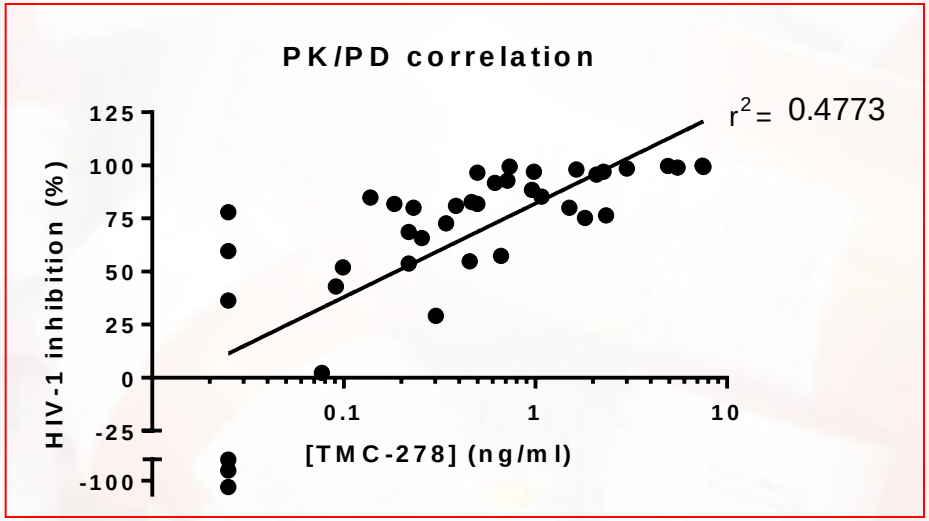
-Plasma [RPV] = 24.3 ng/mL on day 28
10.5 ng/mL on day 42 (presumed exposure to HIV)
6.8 ng/mL on day 56
7.5 ng/mL on day 84

-CVF [RPV] = 32.9 ng/mL on day 28
18.3 ng/mL on day 42 (presumed exposure to HIV)
11.2 ng/mL on day 56
14.0 ng/mL on day 84

May suggest that higher exposures of RPV are needed to protect against HIV infection

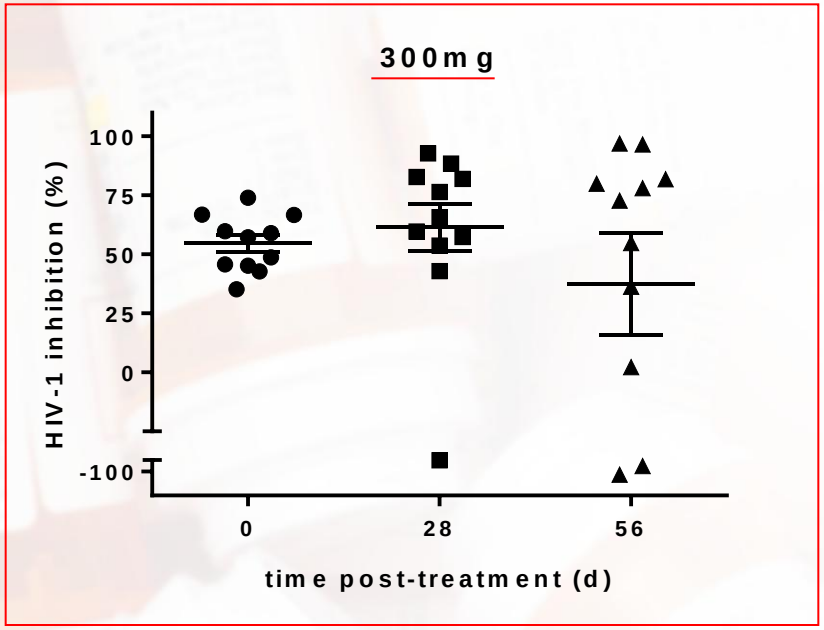
SSAT040: PD data

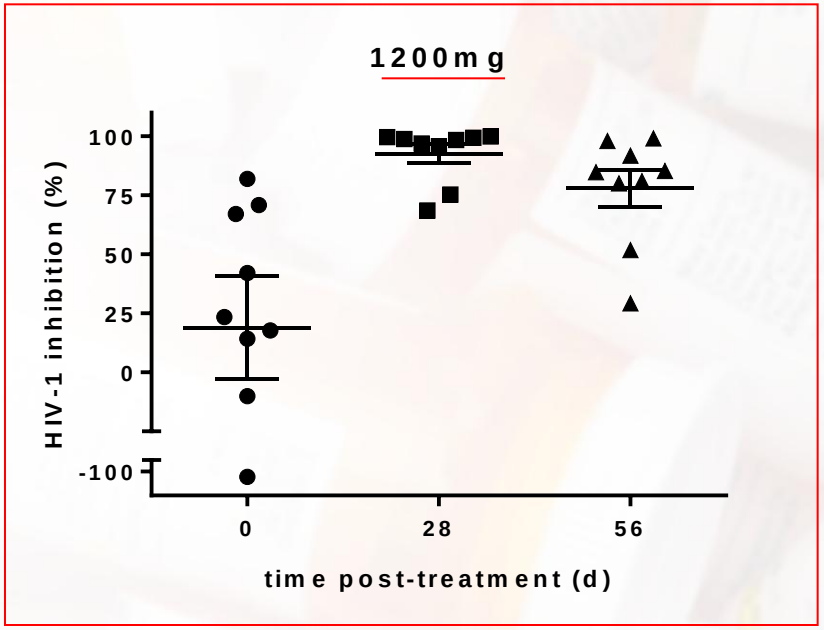
- CVL samples collected by aspiration of 10 mL normal saline (after cervical lavage) at baseline, 28 and 56 days post-dose
- N = 10 on 300mg and N = 10 on 1200mg
- Antiviral activity determined against HIV-1BaL challenge of TZM-bl cells
- PK/PD correlation established using all data points from both doses



Thanks to Betsy Harold and Pedro Mesquita, Albert Einstein College of Medicine.

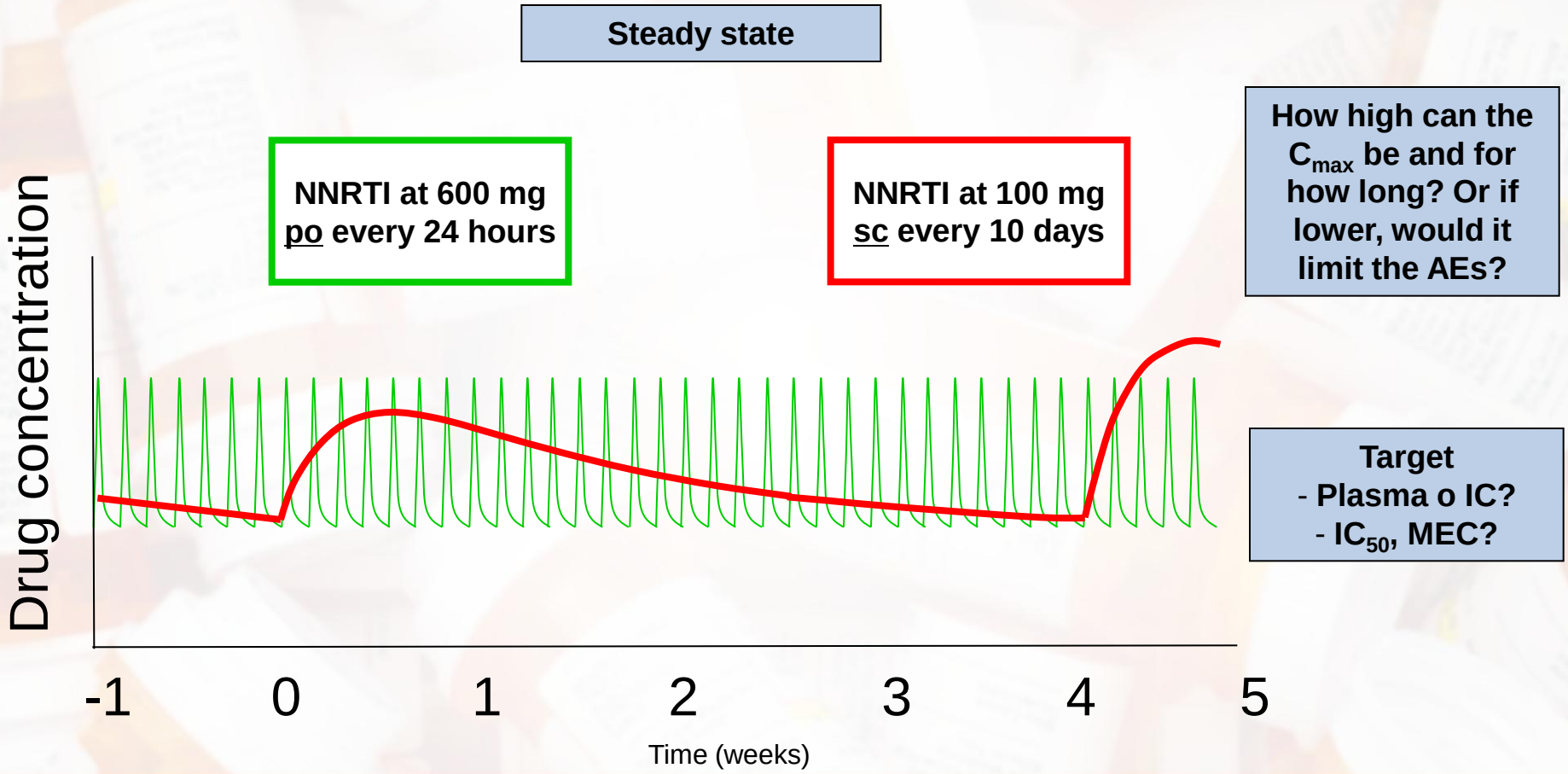
SSAT040: PD data





Thanks to Betsy Harold and Pedro Mesquita, Albert Einstein College of Medicine.

Simulation of drug concentration profiles following multiple dosing of immediate release vs. extended release: higher versus lower dose?

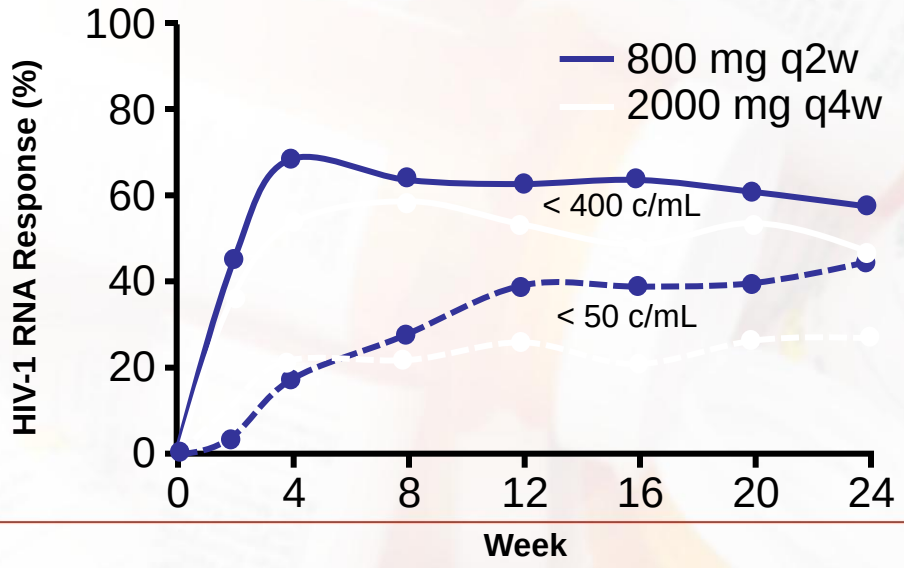


Safety and Efficacy of Ibalizumab + OBR in Treatment-Experienced Patients

- Humanized monoclonal antibody to non-HIV binding epitope of CD4
- Blocks HIV-1 entry into cell
- TMB-202: randomized, double-blind phase IIb study in heavily treatment-experienced patients
  - **800 mg IV q2w + OBR (n = 59)**
  - **2000 mg IV q4w + OBR (n = 54)**

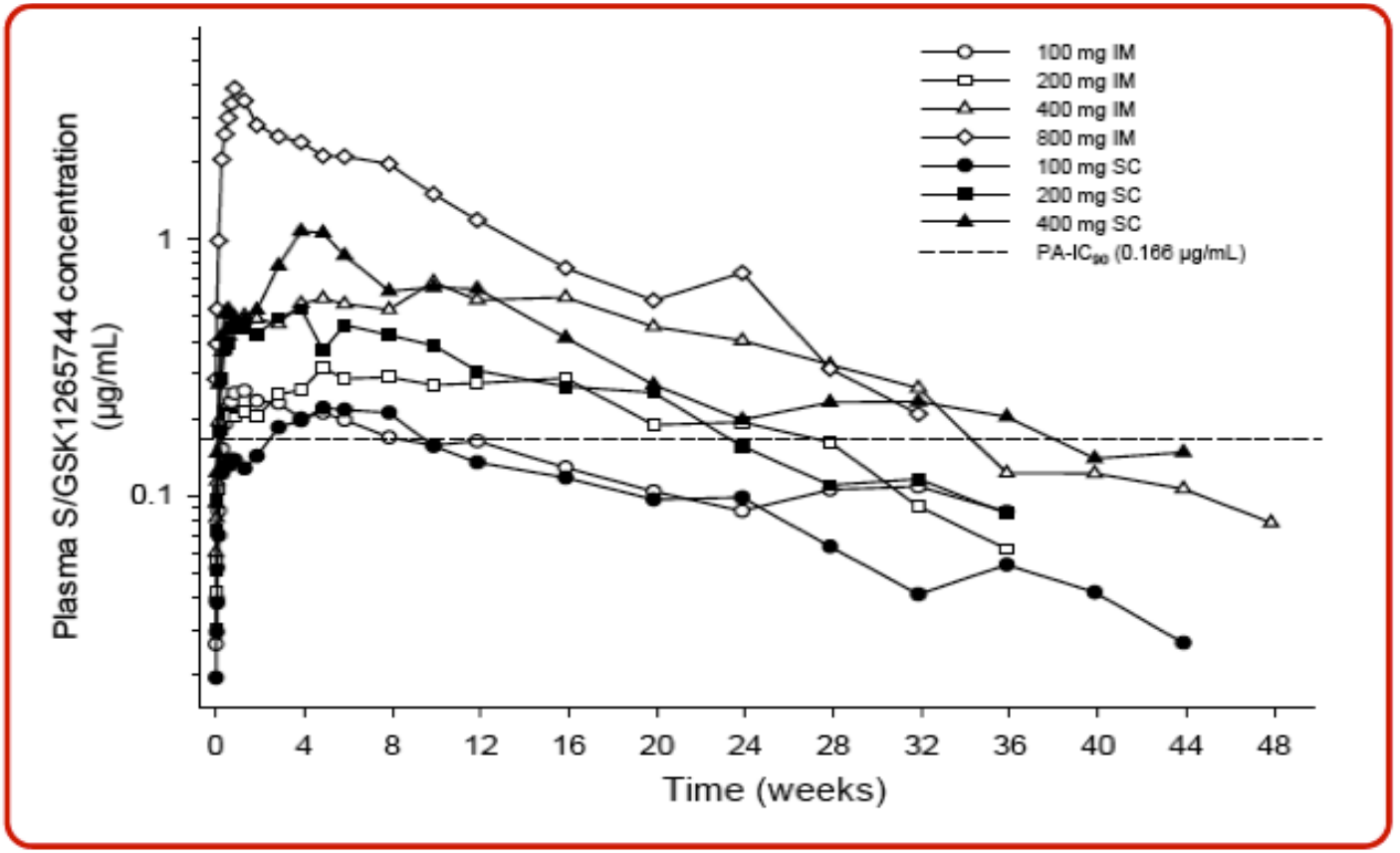
OBR contained ≥ 1 active agent

- HIV-1 RNA < 50 at wk 24
  - **44% in 800 mg q2w arm**
  - **28% in 2000 mg q4w arm**
- No d/c due to study drug
- Phase I trial ongoing assessing s.c. administration



Khanlou et al, ICAAC 2011. *Thank you to CCO.*

Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration



Spreen et al, IAS 2012. *Thank you to NATAP.*

Human PK data PLUS macaque efficacy data suggest real promise for GSK744 as an agent for PrEP

IWCPHT-2013

- Administered as IM injection to healthy volunteers in a long-acting nanosuspension formulation
- $t_{1/2}$ = 21 - 50 days
- 400 mg IM either a single IM injection or split into 2 x 200 mg IM injections
- Median ratio of GSK744 concentrations in cervicovaginal tissue to plasma ranged from 16% to 28%
- Median ratio of rectal tissue to plasma (obtained only from male participants) was ≤ 8%
- Association between higher tissue concentrations with higher plasma concentrations suggests low tissue concentrations may be improved with higher doses

CROI-2013

- Efficacy of GSK744 for PrEP in 8 macaques that received IM doses of GSK744 at two time points 4 weeks apart
- 8 macaques receiving placebo became infected with SHIV
- None of the 8 treated macaques had detectable virus 3 weeks after the final viral challenge

Collectively, human PK data PLUS macaque efficacy data suggest real promise for GSK744 as an agent for PrEP

First study of repeat dose co-administration of GSK1265744 and TMC278 long-acting parenteral nanosuspensions: pharmacokinetics, safety, and tolerability in healthy adults

Spreen et al. IAS 2013

PrEP = SINGLE AGENT?

- GSK744 LAP and TMC278 LA formulations were generally safe and well tolerated - with mild-moderate ISR in majority subjects
- GSK744 LAP PK indicated that q 4 wks or less frequent injections will maintain plasma concentrations > 4x PA-IC_{90}
- TMC278 LA PK suggested q 4 wks injections give plasma concentrations comparable to oral RPV 25 mg OD

New Approaches to Antiretroviral Drug Delivery: Challenges and Opportunities

Marta Boffito[1]; Akil Jackson[1]; Andrew Owen[2]; Stephen Becker[3]

[1]St. Stephen's Centre, Chelsea and Westminster Hospital, London, UK; [2]University of Liverpool, Liverpool, UK; [3]Bill and Melinda Gates Foundation, Seattle, WA, USA.

In press

Conclusions

Small clinical pharmacology studies inform:

- concentration-response in PrEP RCTs
- adherence
- concentrations in anatomic site of HIV acquisition
- how to achieve “target” concentrations

Early planning and completion of clinical pharmacology studies is improving the drug development process for the next generation of PrEP agents.