Pharmacokinetics and Pharmacodynamics in HIV Prevention

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10th Residential Course on Clincial Pharmacology of Antiretrovirals.
Turin, Italy. 22nd January, 2015

Pre-tenofovir prevention era 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

Aimed to limit systemic toxicity and avoid driving resistance to therapeutic antiretrovirals, whilst achieving high local concentrations...

but failed to prevent HIV infection

Hendrix 2012

The optimal PrEP agent

- Safe
- Penetrates target tissues (rectal, cervical, vaginal)
  - Active against HIV at target tissue
  - reaches effective concentration quickly after dose
- long-lasting activity with convenient dosing

  (increased interval between doses)
- Resistance:
  - high genetic barrier to resistance
  - unique profile if failure
- No significant drug-drug interactions
- Not part of current HIV treatment combinations
- Affordable and easy to use/implement

ARV PrEP; Nevirapine was considered at early stage...

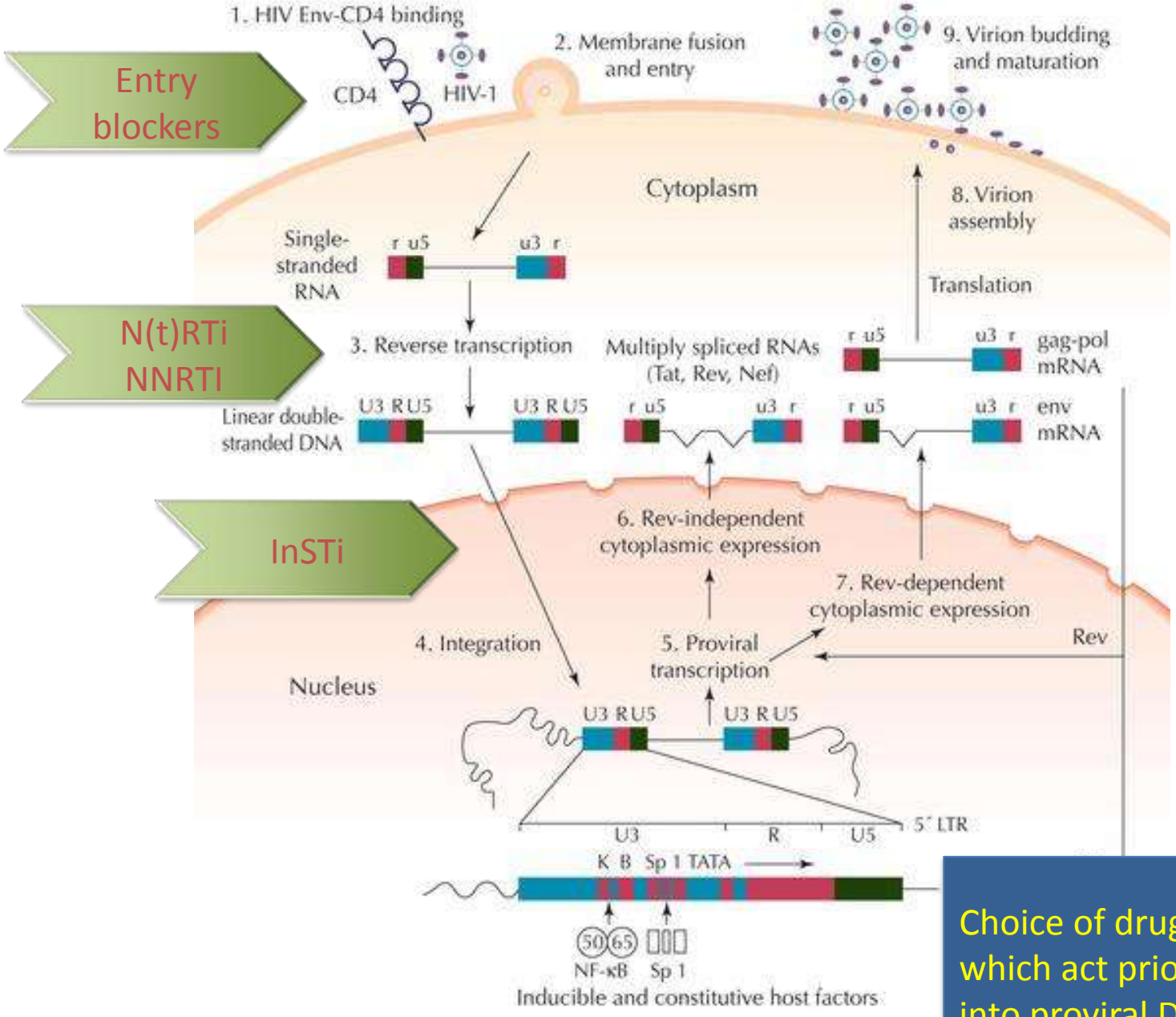
- Jackson JB, et al.

A phase I/II study of nevirapine for pre-exposure prophylaxis of HIV-1 transmission in uninfected subjects at high risk. AIDS. 2003

- 33 volunteers, high risk for HIV-1
- single dose nevirapine
  - once/wk, twice/wk or alternate days for 12 weeks

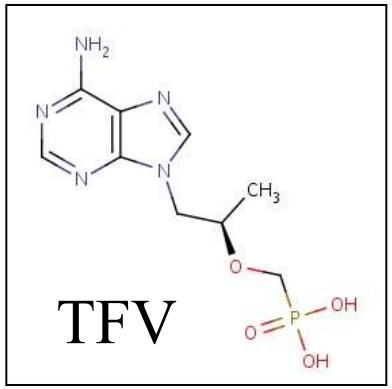
- no seroconversions and C_{trough} above $IC_{50\ for}$ NVP

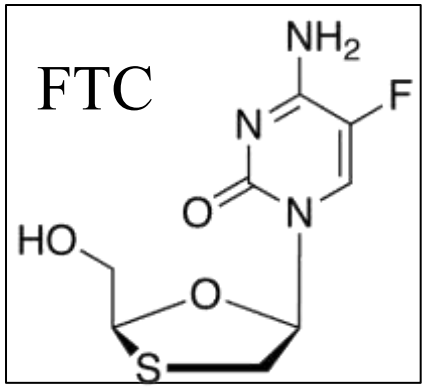
- Potentially favourable PK
- Known efficacy from PTMTC programmes, but safety concern for further development as PrEP



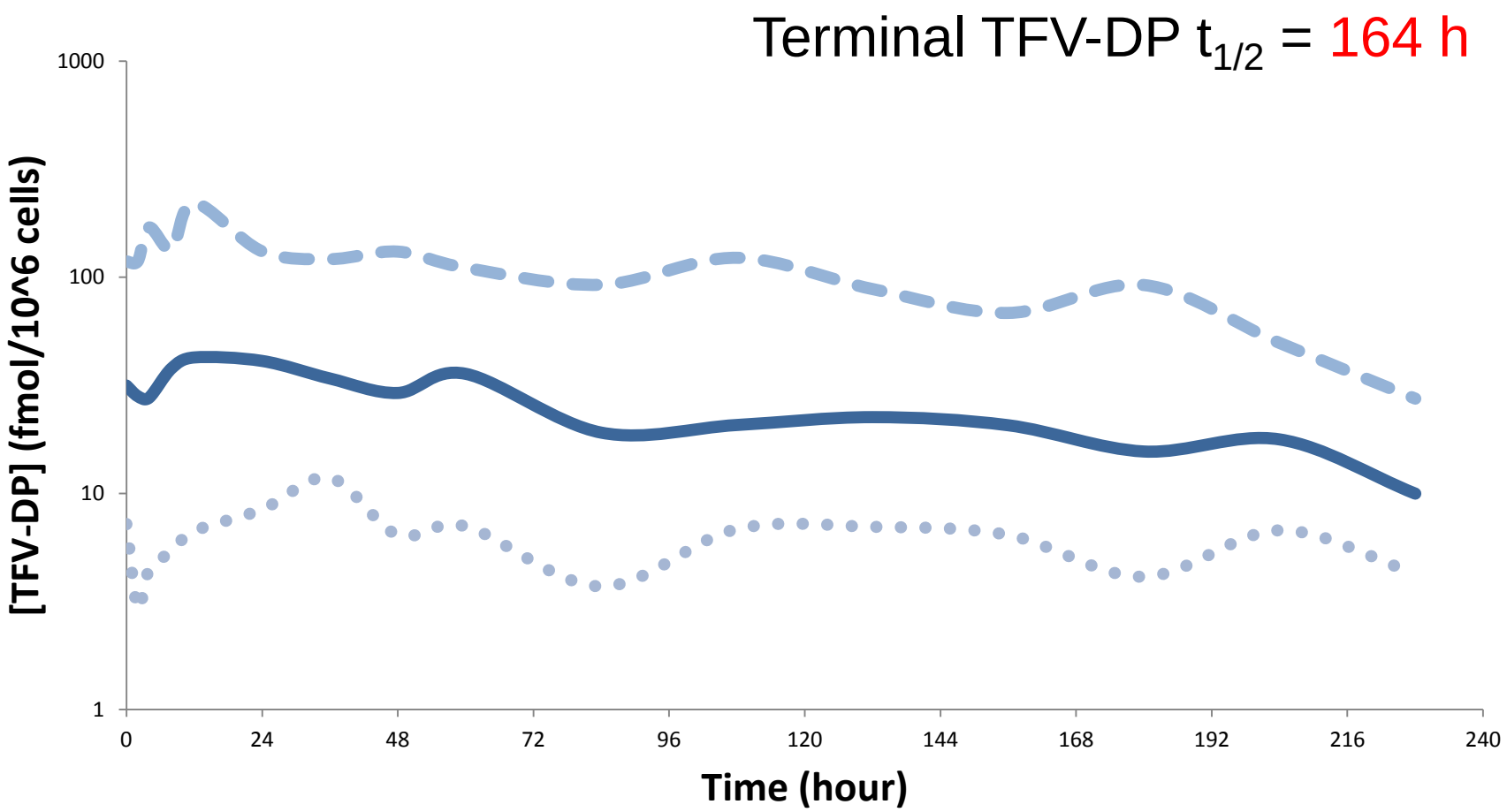
Choice of drug class? - Any which act prior to integration into proviral DNA...

Tenofovir and Emtricitabine





$[TFV\text{-}DP]_{intracellular}$ show prolonged persistence after stopping Atripla

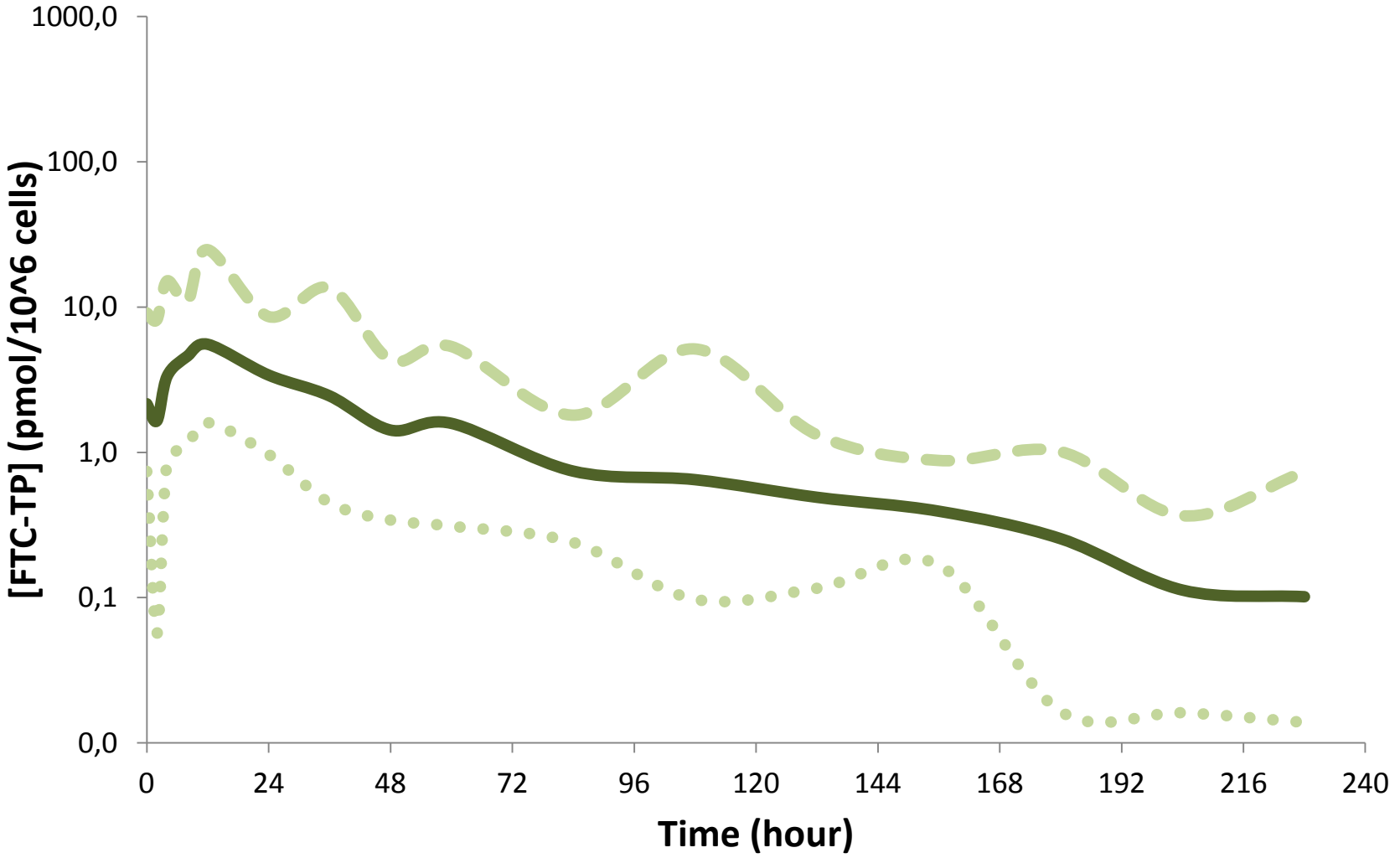


Prolonged $t_{½}$ in PBMC (7 days) compared with 31 hours in plasma.
However, cell activation *in vitro* shown to reduce this → greater exposure variability, particularly in immune cells.

Jackson et al. JAIDS2013

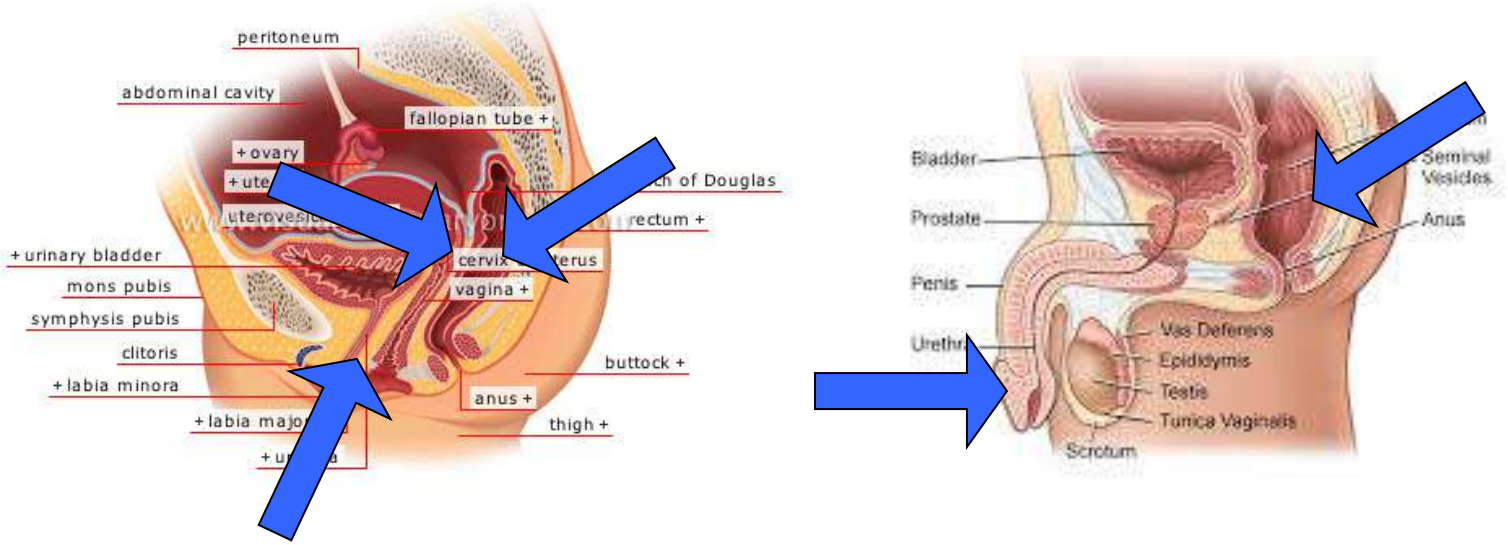
Similarly, FTC-TP has prolonged intracellular persistence relative to plasma

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



Jackson et al. JAIDS2013

Target sites for action



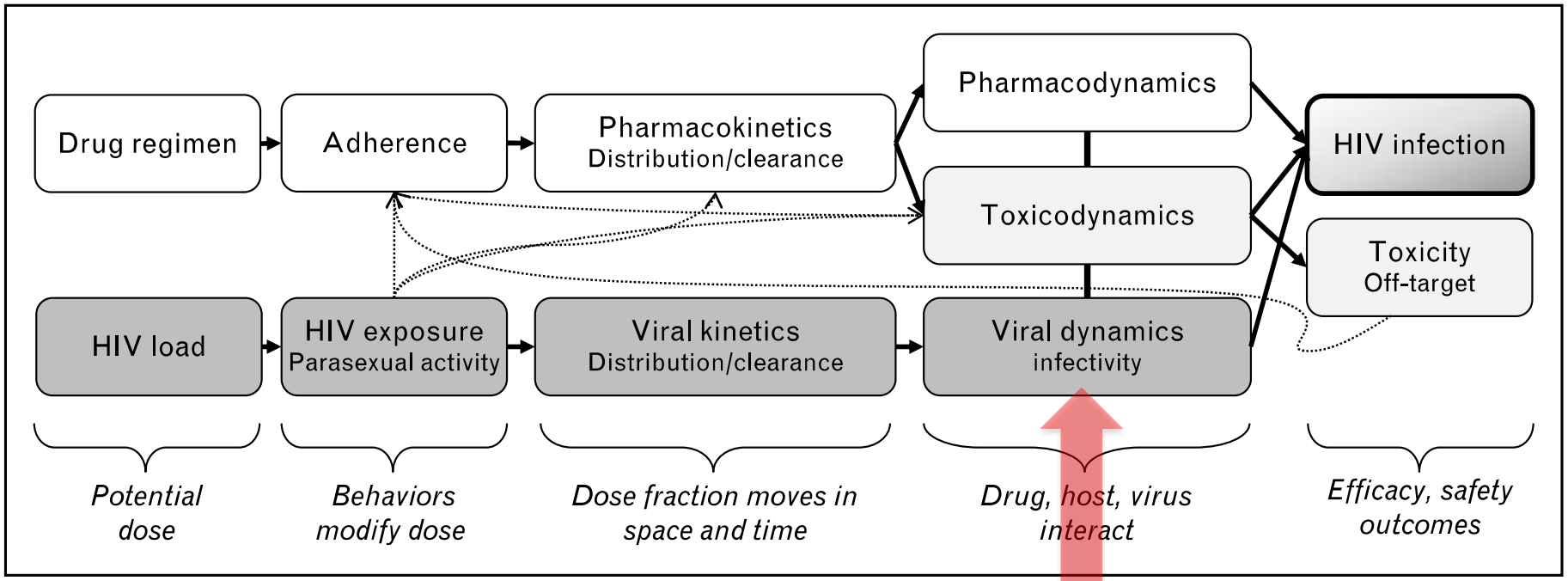
Important considerations for route of dosing:

- oral (systemic) vs. topical (vaginal or rectal)

Also, different compartmental drug partitioning

- between sites: female vaginal vs rectal
- between gender: male rectum vs female rectum

The interaction between PrEP PK and PD effect is highly dependent on viral infectivity factors...



Viral infectivity highly dependent on innate protection at host mucosa... cells affected by infection are at submucosal level.

Per contact probability of infection - 0.5 - 4 % (for homosexual receptive) without PrEP

Founder viruses: usually 1 - 5 in number

Hendrix CW. The clinical pharmacology of antiretrovirals for HIV prevention. Curr Opin HIV AIDS 2012.

Female; topical delivery

- vaginal tenofovir multiple daily doses
  - little accumulation in plasma
  - $[TFV]_{plasma}$ cf. 300mg oral tenofovir
    - 7x lower than C_{trough} and 40x lower than C_{max}

- MTN -001 (oral TDF vs 1% vaginal gel)
  - $[TDF\text{-}DP]_{vaginal\ tissue}$ 130x higher with vaginal than oral dosing

  - this PK study also compared US and African women and picked up differential adherence between groups; by $[TFV]_{predose}$ after prior doses taken at home.
  - ? missed efficacy signal for later

TFV and FTC are so far the only ARV proven effective in prospective PrEP RCTs

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

Lack of surrogate marker for PrEP

the role of CLINICAL PHARMACOLOGY to explain the variable drug responses is usually retrospective

Tenofovir era 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		

Truvada in high risk females

- **no reduction in transmission**

- **subset PK; TFV was detectable in plasma in:**
  - **26 % who did not become infected (NSC) vs 15 % who did (SC)**

  Assay LLOQ 10 ng/mL

Hendrix 2012

Tenofovir generation 2010-2012
PK informed interpretation, not design

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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), LLOQ 10	
	TDF/FTC po QD	**0.75** (0.55-0.87)	0.90 (0.56-0.98)	
CAPRISA004	TFV gel BAT24	**0.39** (0.04-0.60)	> 1000 CVF	0.54 (0.20-0.96)*
VOICE	TFV gel QD	0.0		

Truvada in high risk MSM

- **increased relative risk reduction with detectable drug in plasma**

Hendrix 2012

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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	
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)	
CAPRISA004	TFV gel BAT24	**0.39** (0.04-0.60)	> 1000 CVF	**0.54** (0.20-0.96)*
VOICE	TFV gel QD	0.0		

Topical tenofovir gel applied with coitus increased RRR with:

- **$[tenofovir]_{CVF}$ > 1000 ng/ml**
- **self-reported adherence > 80%**

Hendrix 2012

Tenofovir generation 2010-2012
PK informed interpretation, not design

		RELATIVE RISK REDUCTION (95% CI)		
Similar pattern in all studies; evidence for concentration-response relationship... **$[agent]_{plasma/fluid}$ is dependent on adherence** **Oral drugs work if, and when, taken!**				
CDC TDF2	TDF/FTC po QD	**0.63** (0.22 - 0.83)	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)	
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Hendrix 2012

Can mathematicians help us to understand this?

2012 PLoS ONE 7 (7)

Duwal S, et al

Pharmacokinetics and Pharmacodynamics of the Reverse Transcriptase Inhibitor Tenofovir and Prophylactic Efficacy against HIV-1 Infection.

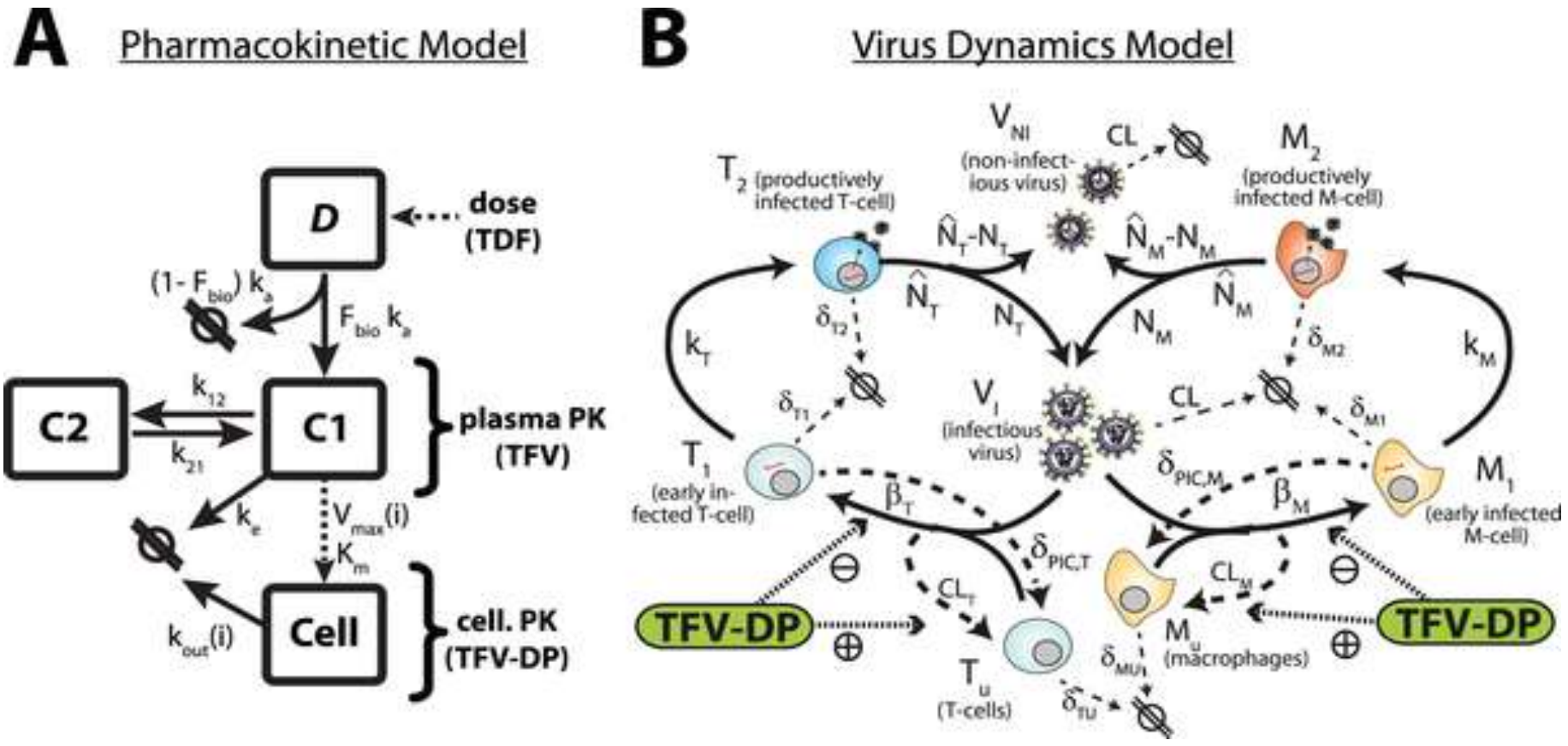
Used published PK data relating $[TFV]_{plasma}$ to $[TFV\text{-}DP]_{intracellular}$

Mathematical models

1. PK of TFV accumulation and intracellular decay
2. Virus dynamics

Combined both to simulate: dosing strategies and size of viral innoculum.

Figure 1. Pharmacokinetic model of TFV and intracellular TFV-DP and model of viral kinetics.



Duwal S, Schütte C, von Kleist M (2012) Pharmacokinetics and Pharmacodynamics of the Reverse Transcriptase Inhibitor Tenofovir and Prophylactic Efficacy against HIV-1 Infection. PLoS ONE 7(7): e40382. doi:10.1371/journal.pone.0040382
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0040382

Figure 3. Predicted TFV-DP intracellular pharmacokinetics following a single dose oral 300 mg TDF and accumulation of TFV-DP after daily 300 mg oral TDF.

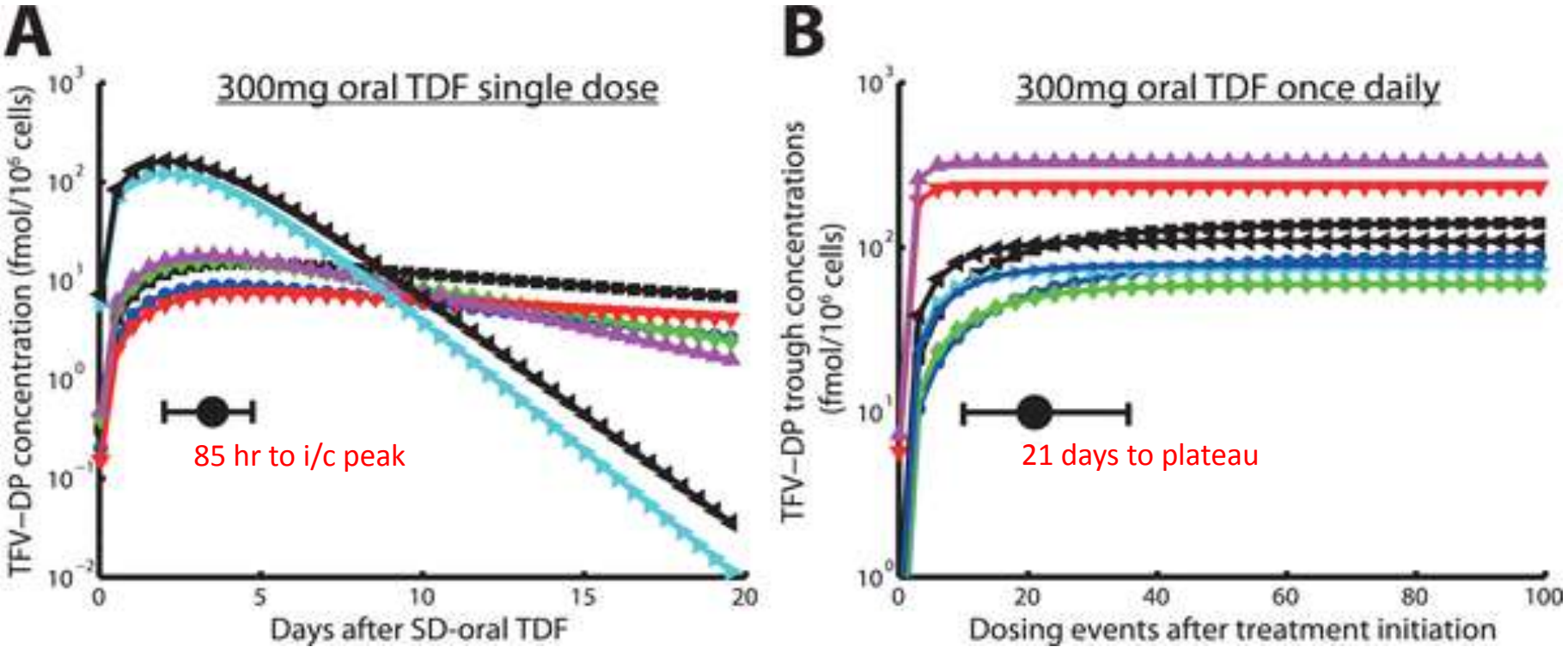


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Figure 4. Viral load log10 kinetics during- and after 28 days of TDF mono-therapy.

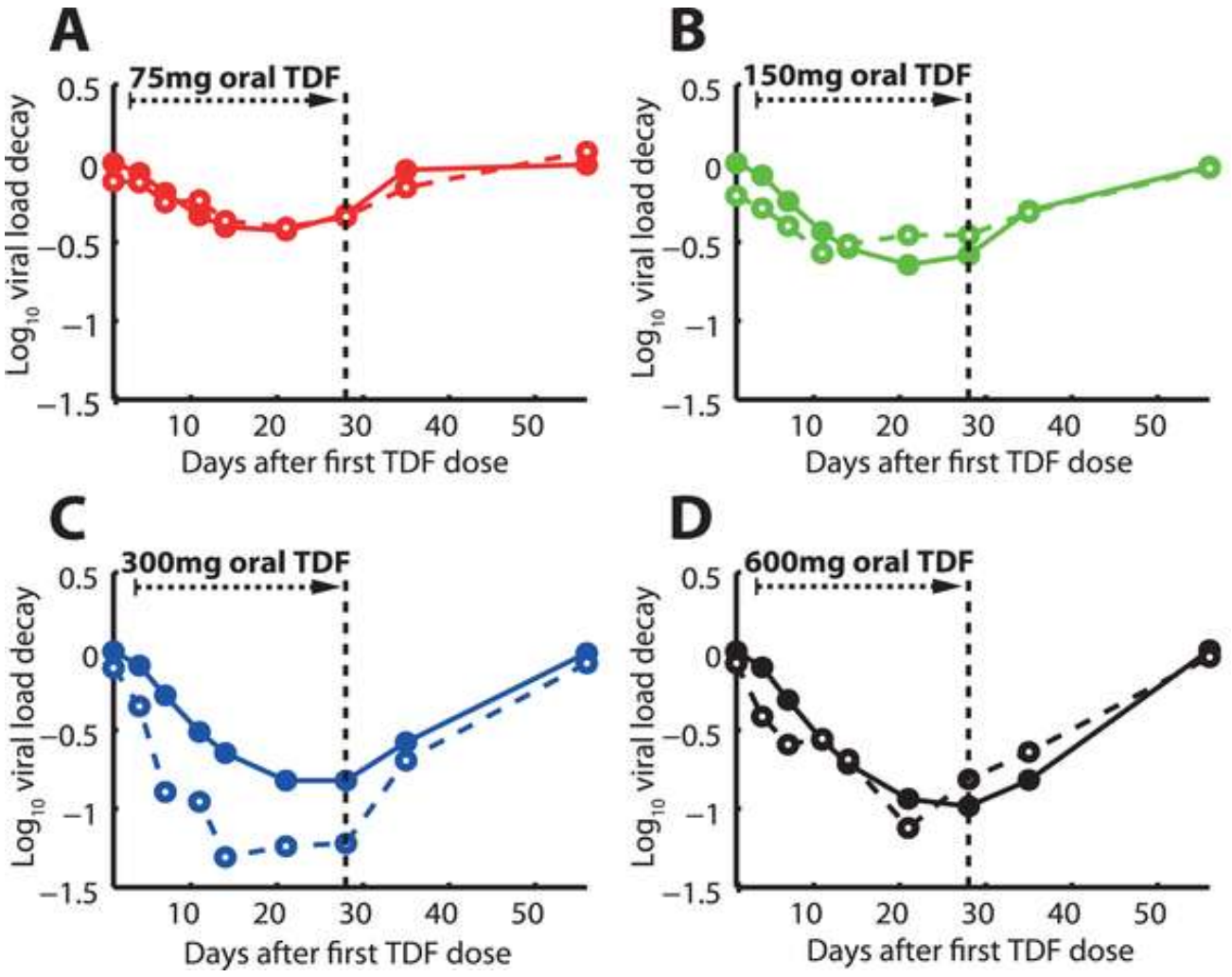

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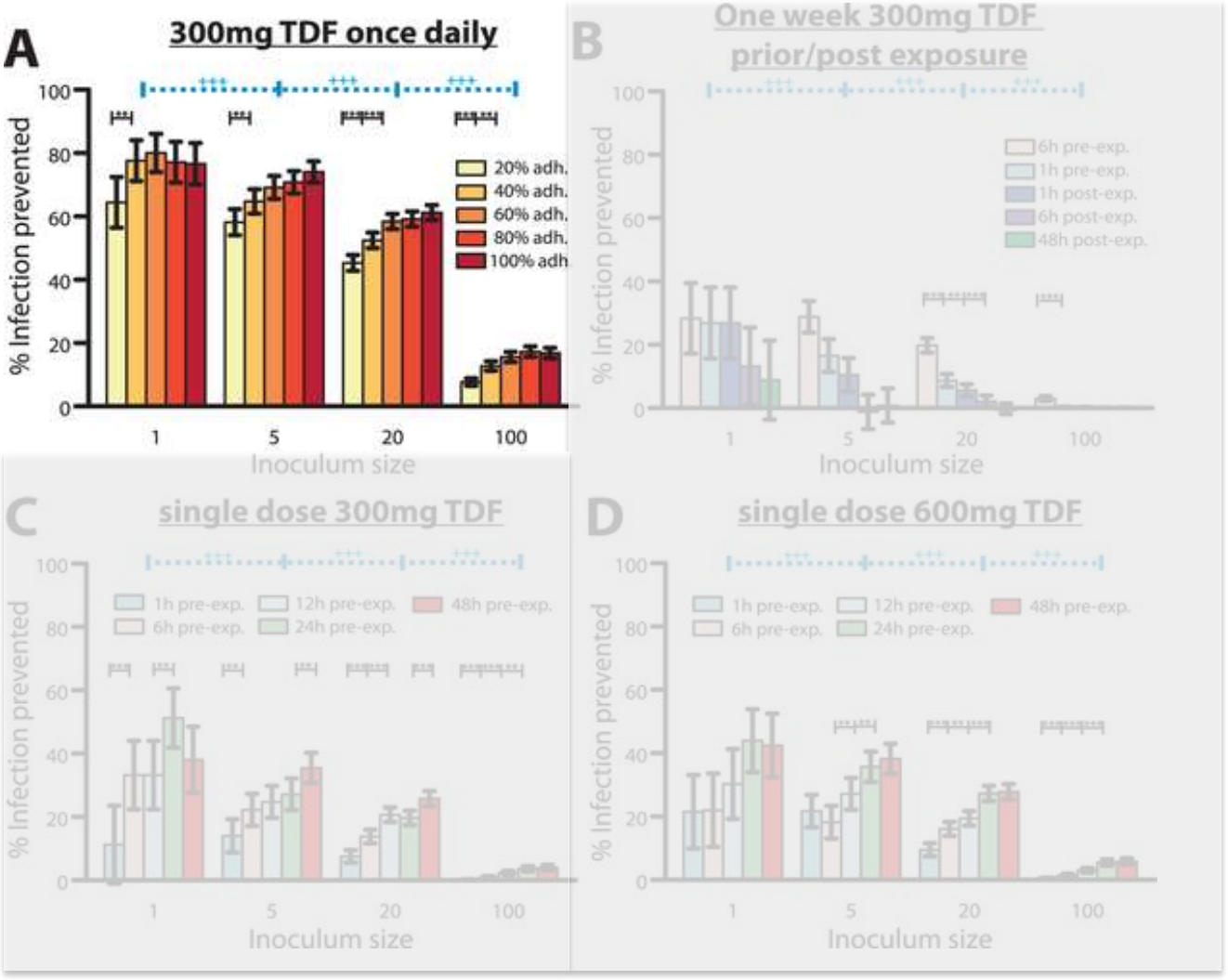
Figure 5. Predicted % infections prevented by distinct TDF-based prophylactic strategies for various parameter sets.



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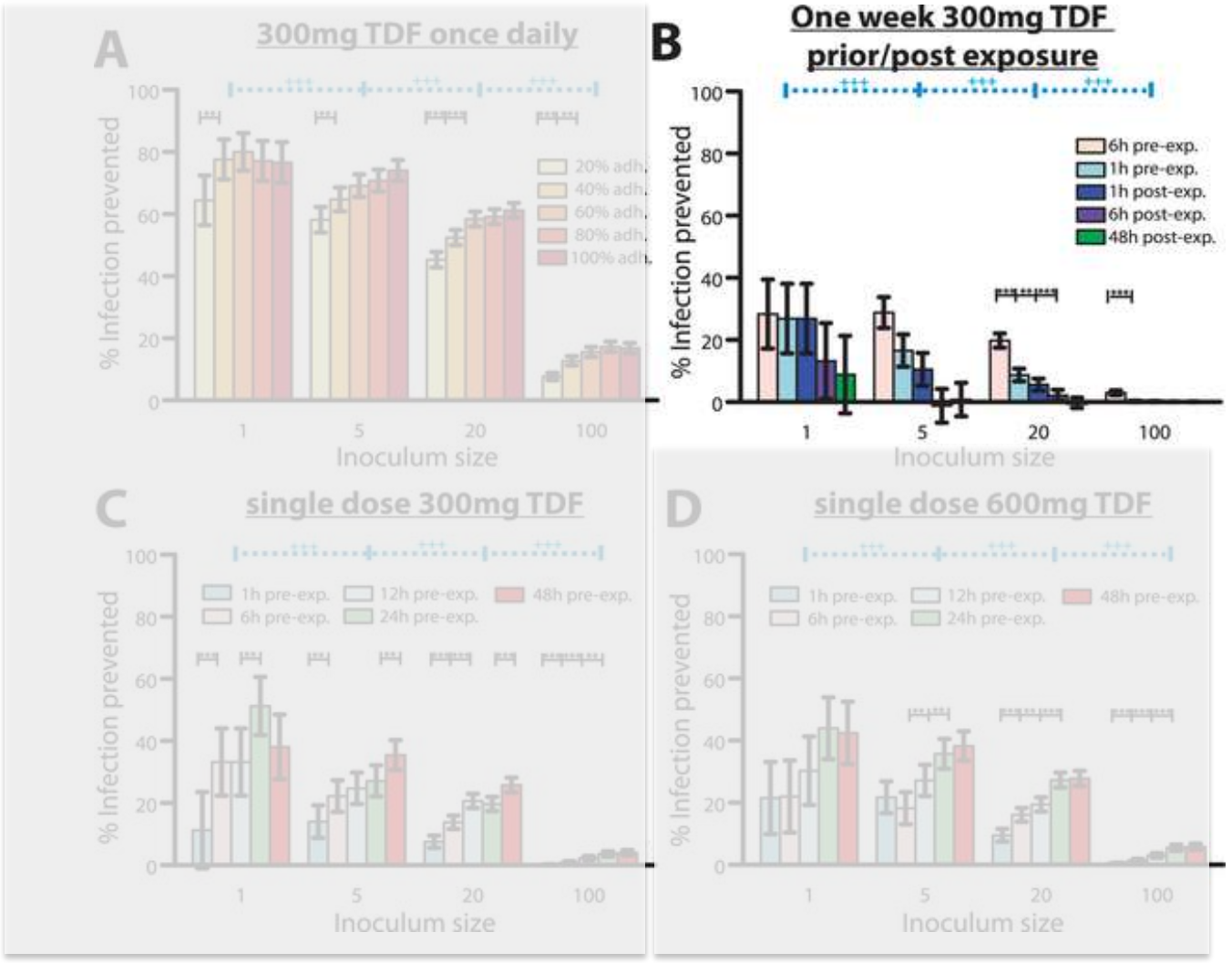

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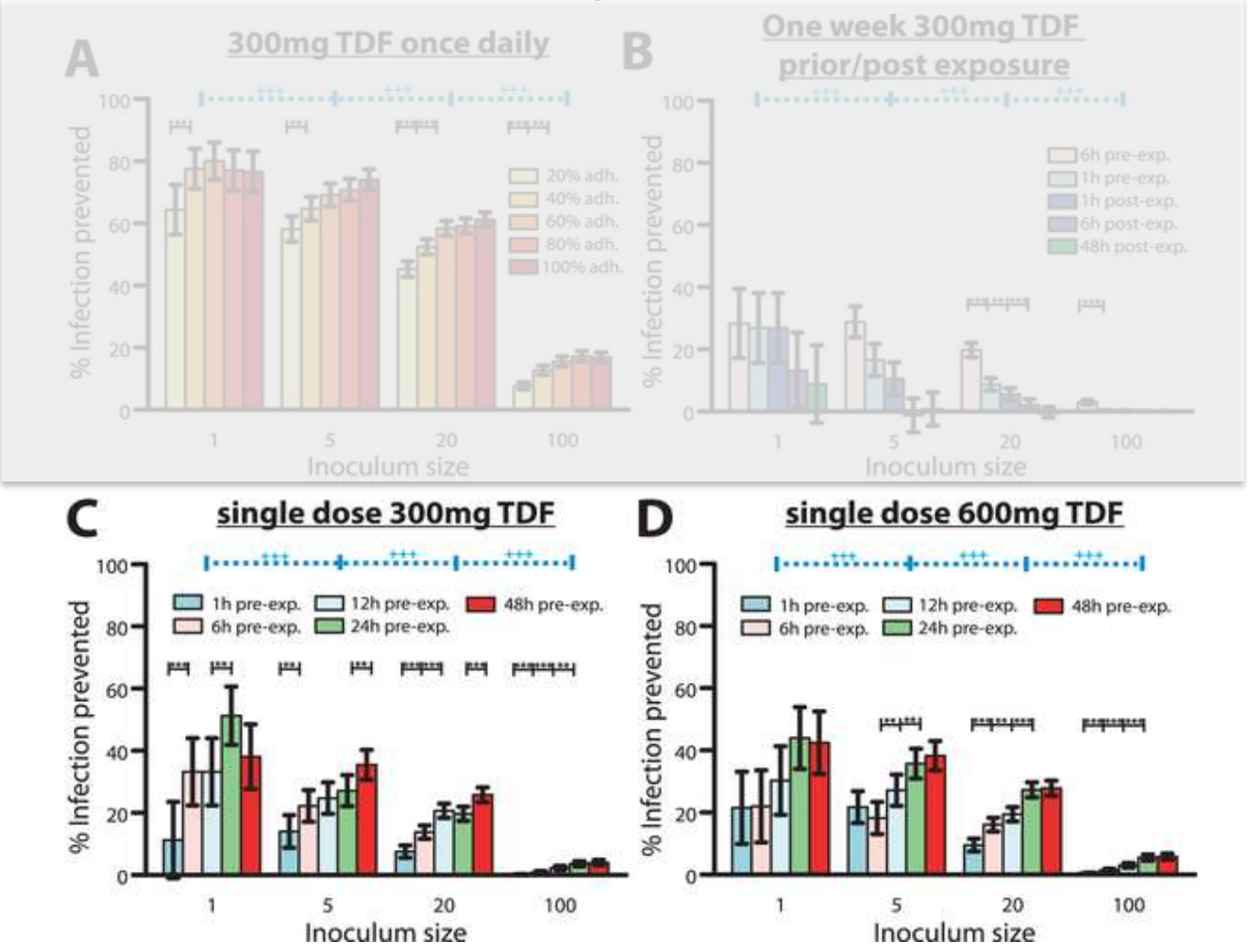

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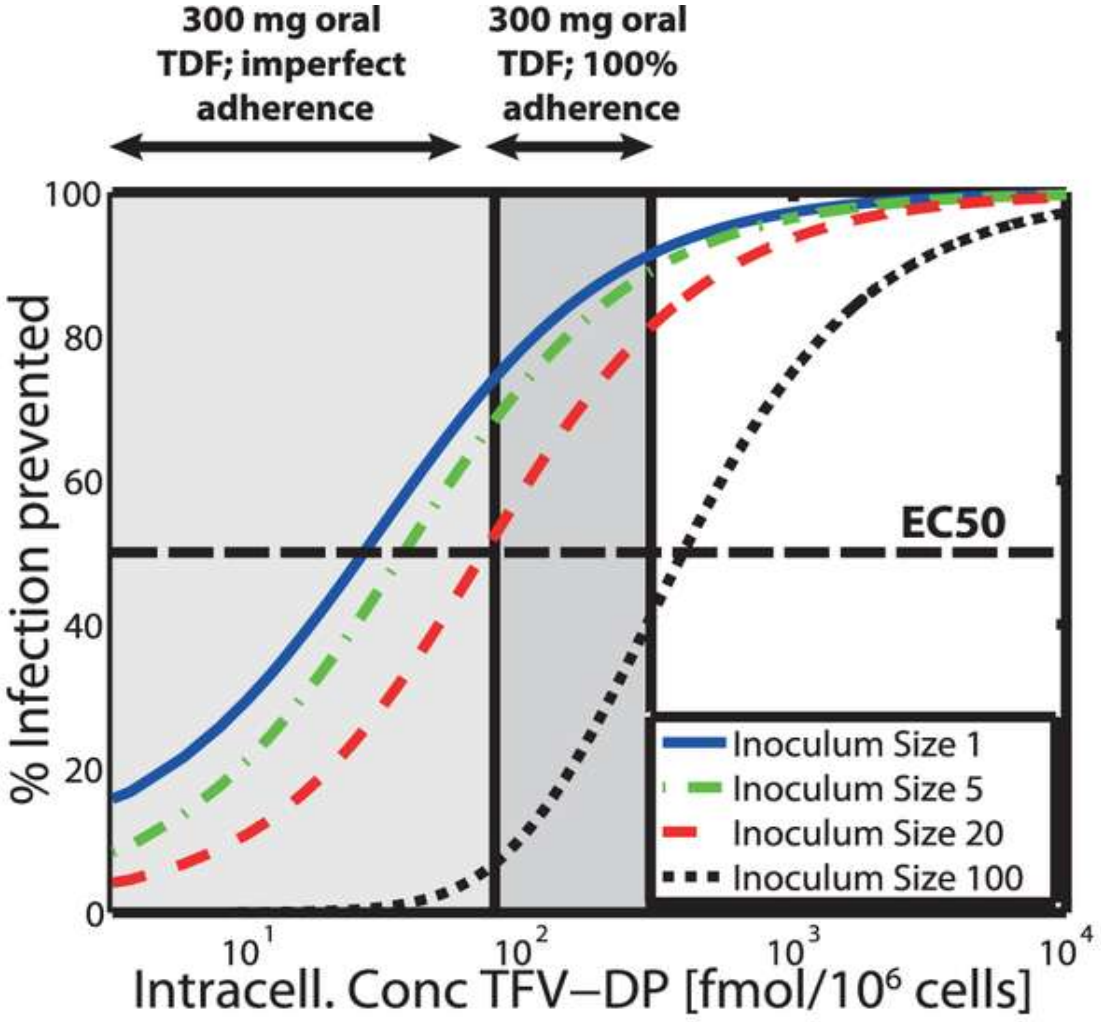
Figure 6. Predicted % infections prevented vs. intracellular TFV-DP concentrations for distinct virus inoculum sizes.



Inoculum size	EC50 [fmol/10^6 cells)
1→	29
5→	40
20→	77
100→	411

Duwal S, Schütte C, von Kleist M (2012) Pharmacokinetics and Pharmacodynamics of the Reverse Transcriptase Inhibitor Tenofovir and Prophylactic Efficacy against HIV-1 Infection. PLoS ONE 7(7): e40382. doi:10.1371/journal.pone.0040382
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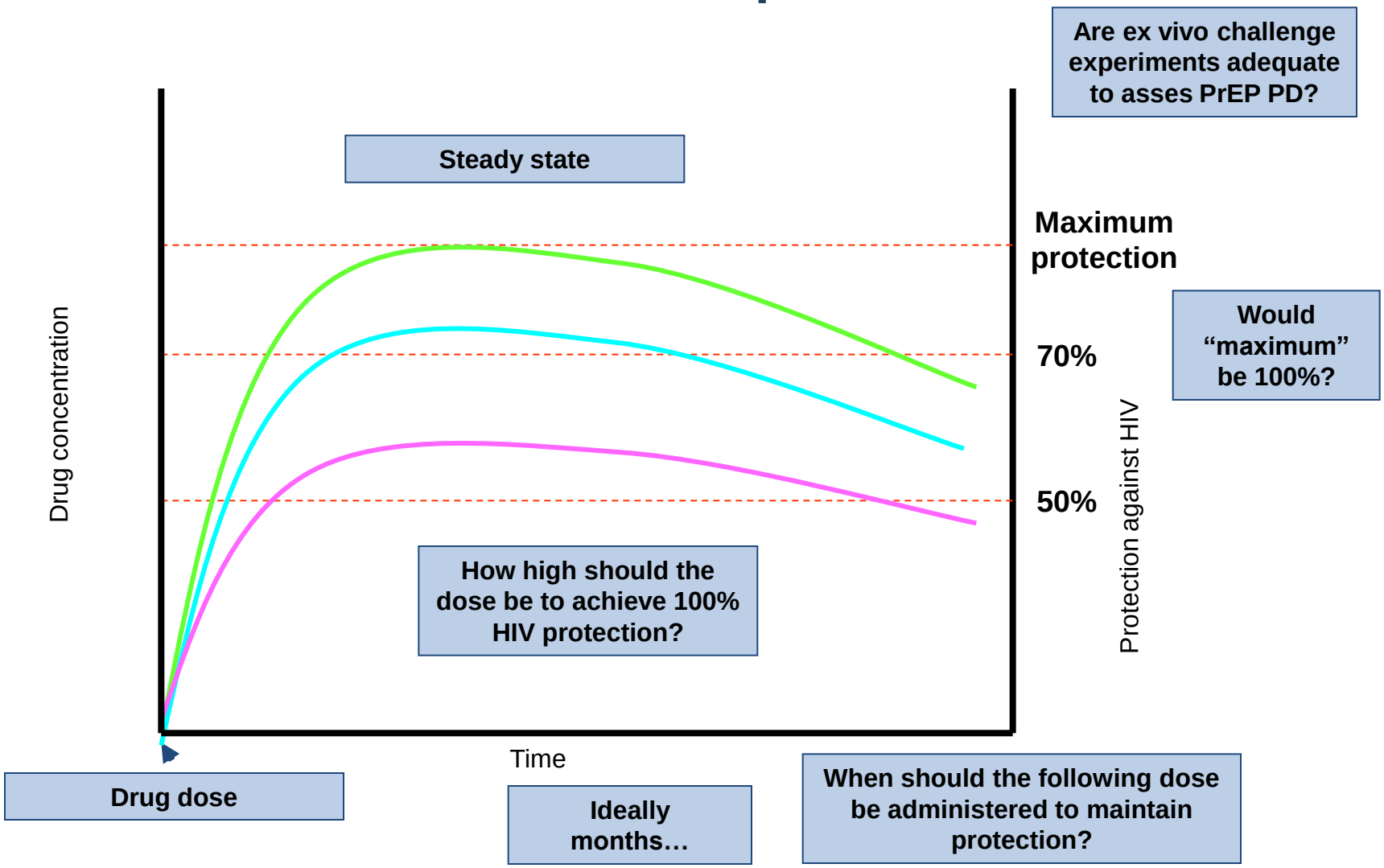
What can we infer from this?

- the accumulation to peak intracellular TDF is slow
- ...so slow, that starting TDF PrEP immediately before a risky encounter is unlikely to offer significant protection. This limits its value for sporadic or episodic use.
- Daily dosing of TDF affords good protection, but this can be overwhelmed by a large amount of virus. Even 100% adherence to QD dosing may not be enough.
- Episodic PrEP may be more suited to drugs such as NNRTI which accumulate to peak concentrations more quickly (e.g. NVP in PMTCT)
- Use of PrEP vs TasP in high endemic regions?
  - probable synergy with test and treat activities, reducing number of undiagnosed transmitters

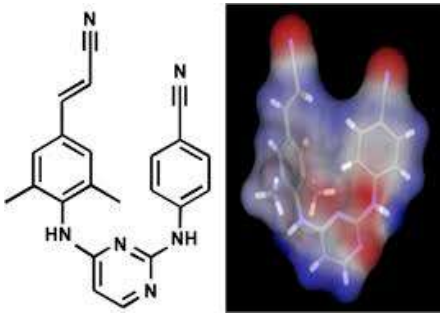
~~Lack of~~ Poor data on concentration-effect relationship



Thanks to Alan Winston and UK PrEP Pharmacology Group

Long-acting formulations for PrEP: TMC278-LA (rilpivirine, RPV)

- Second generation NNRTI



- Potent diarylpyrimidine
- Subnanomolar EC50, long half-life, minimal side-effects
- Injectable formulation (TMC-278LA) is a promising candidate for PrEP
- Solid-drug nanoparticle (nano-milling)
  - formulated as aqueous suspension (300mg/mL) for parenteral use

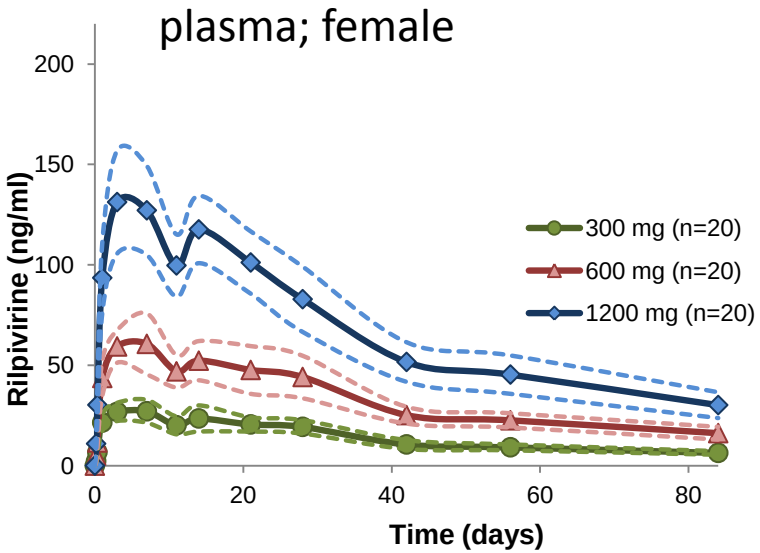
SSAT040: PrEP PK of TMC278LA in HIV-negative volunteers

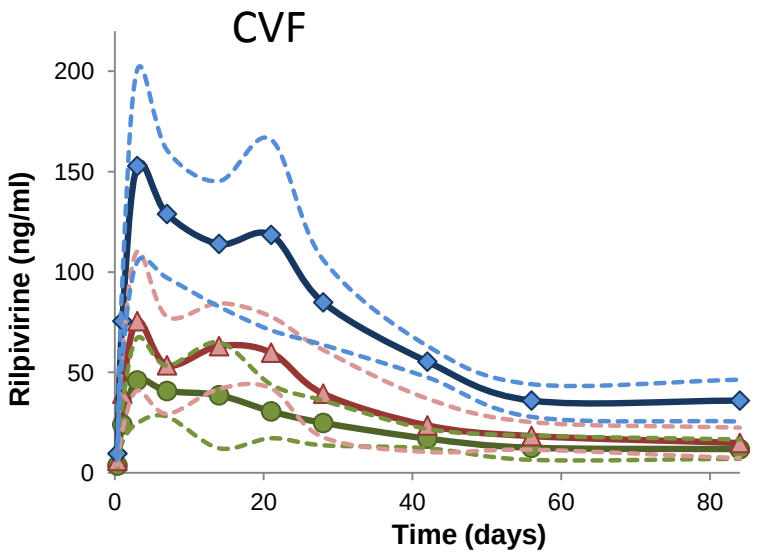
- **HIV negative volunteers (60 female, 6 male)**
- **Aged 18 – 50 years**
- **Low behavioural risk for infection**
- **Female: > 50% of enrolled; self-identified African or African-Caribbean ancestry**
- **Administered 300 (n = 20), 600 (n = 20), 1200 (n = 20) mg RPV-LA IM (gluteus maximus)**

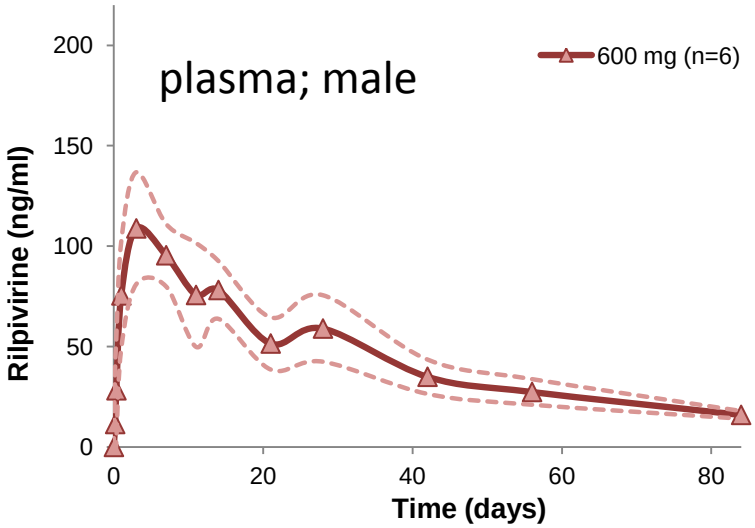
- **Sampling:**
  - **plasma *PK***
  - **cervicovaginal fluid (CVF; females) & rectal fluid (RF; males) *PK***
  - **tissue biopsies: vaginal (VT; females) & rectal (RT; males) *PK***
  - **cervicovaginal lavage (CVL; females) *PK & PD***

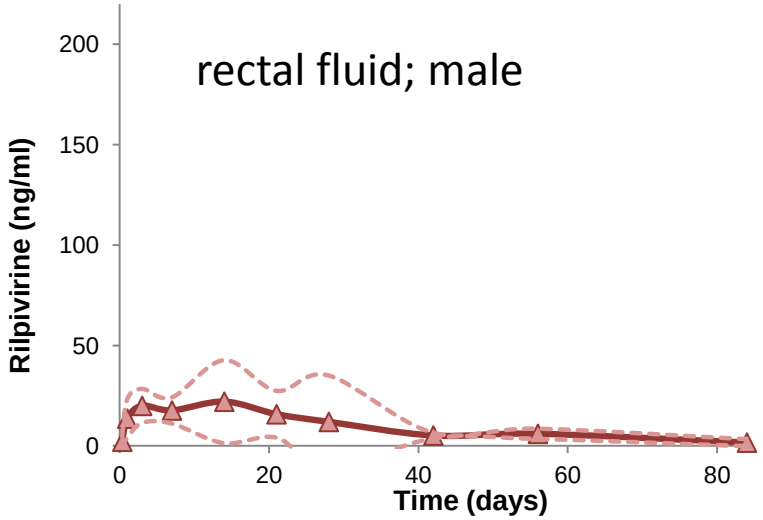
Day	0	0 (4 h)	0 (8h)	1	3	7	11	14	21	28	42	56	84
Plasma PK													
Genital/rectal fluid PK													
Tissue Biopsy (vaginal/rectal)PK													
CVL for PK and PD													

Results: PK plasma and fluid



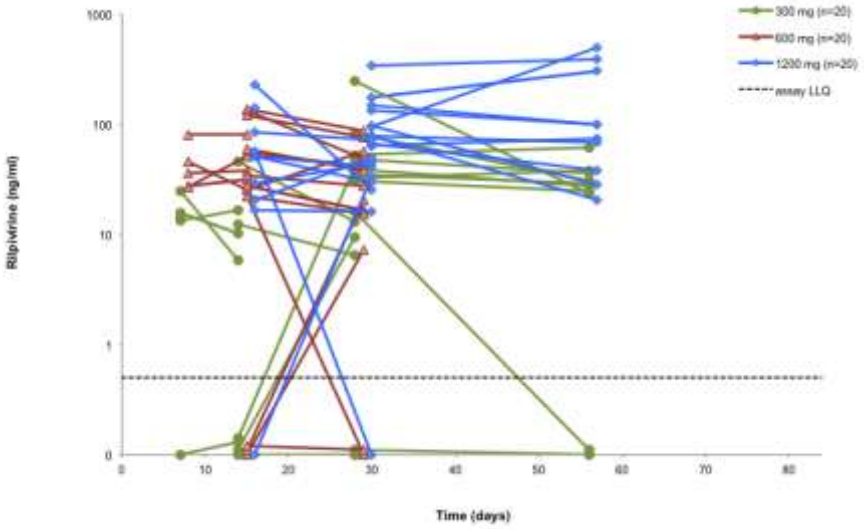




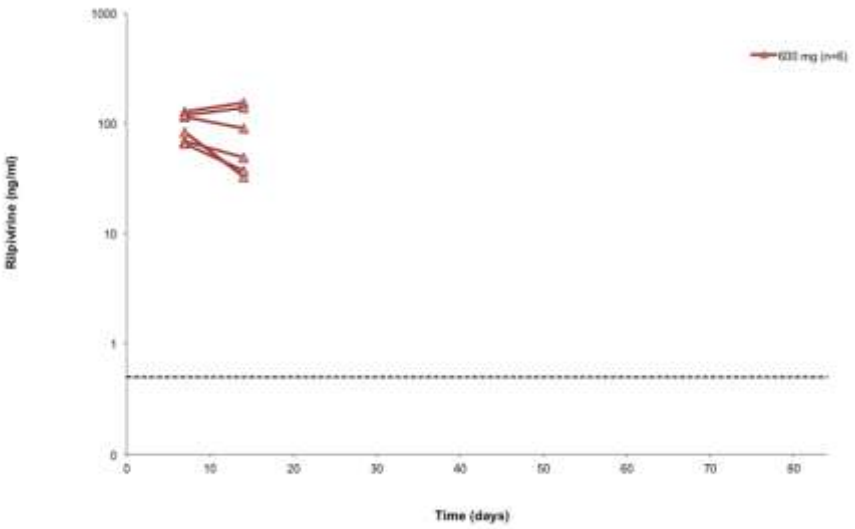


Concentrations in tissue

vaginal

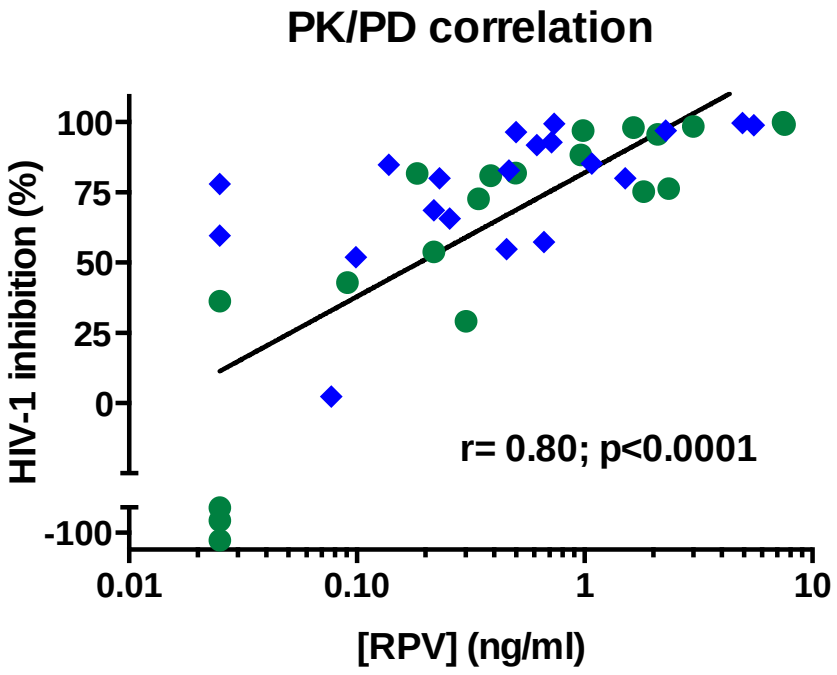


rectal



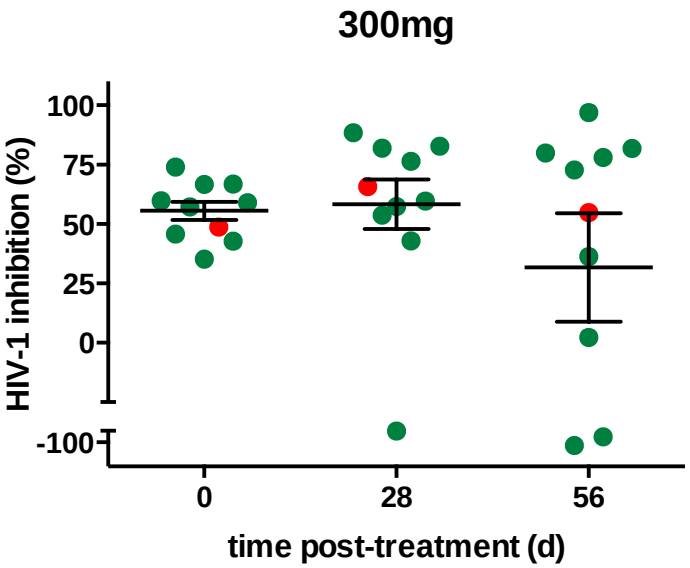
SSAT040: PD Viral data

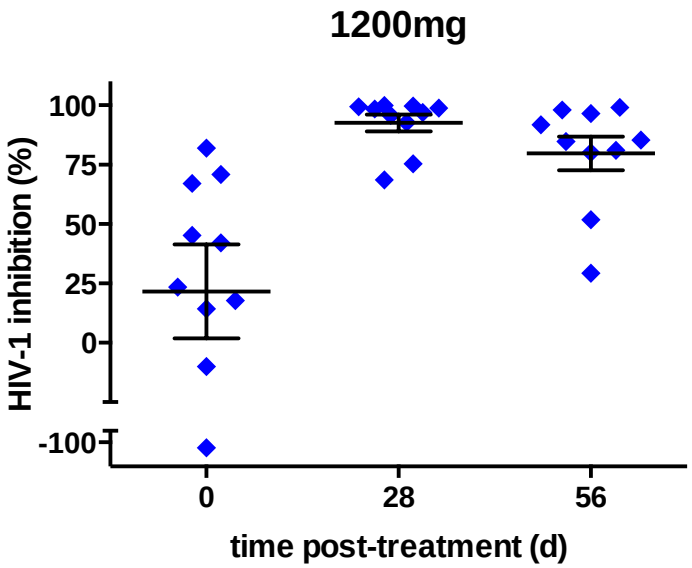
- CVL samples collected by aspiration of 10 mL normal saline (after cervical lavage) at baseline, 28 and 56 days post-dose
- N = 10 on 300mg and N = 10 on 1200mg
- Antiviral activity determined against HIV-1_{BaL} challenge of TZM-bl cells
- PK/PD correlation of all day 28 & 56 data points from both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



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

SSAT040: PD data





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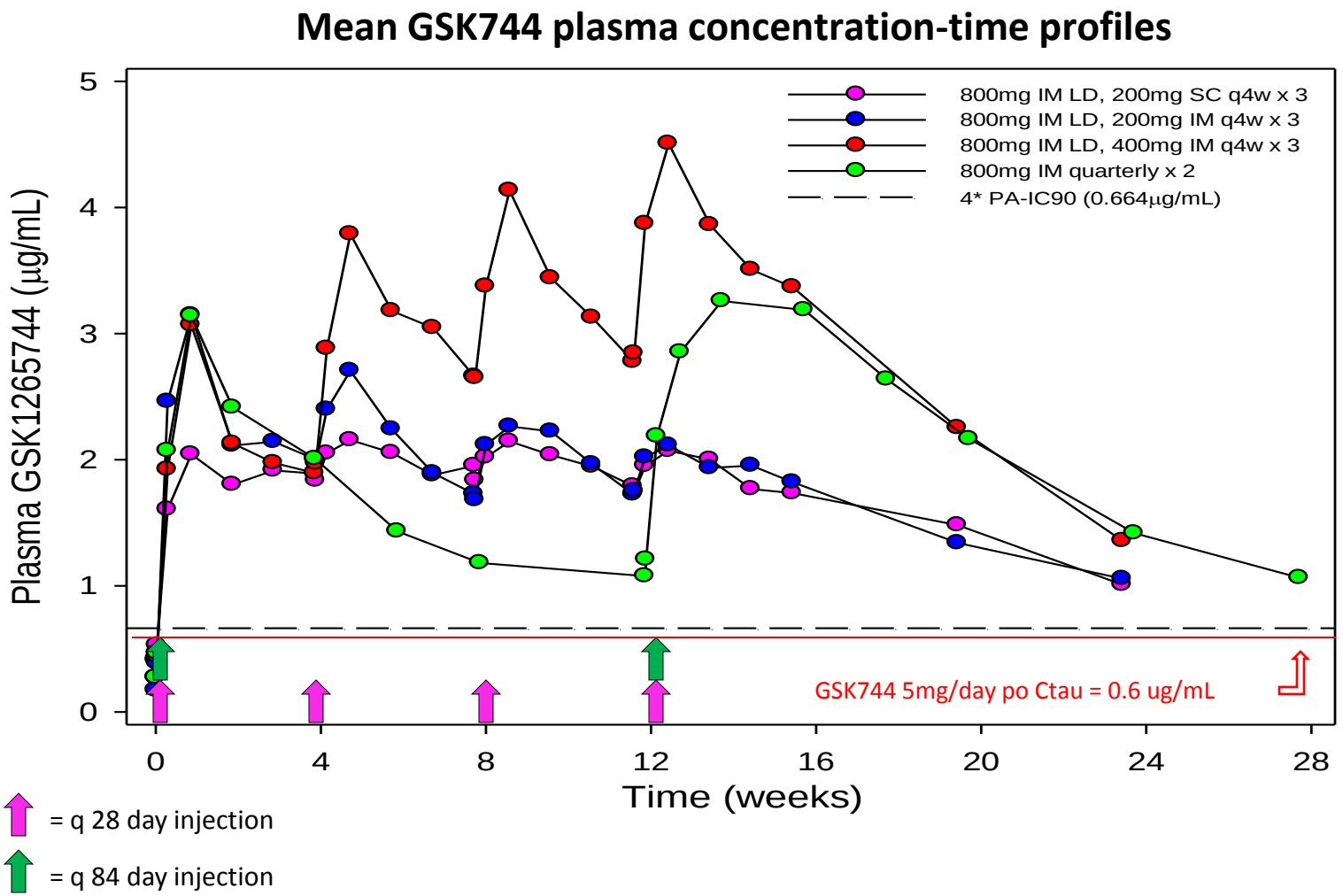
Other LA agents: GSK-744 (cabotegravir) nanosuspension

GSK1265744 = HIV InSTI - analogue of dolutegravir with similar pre-clinical profile



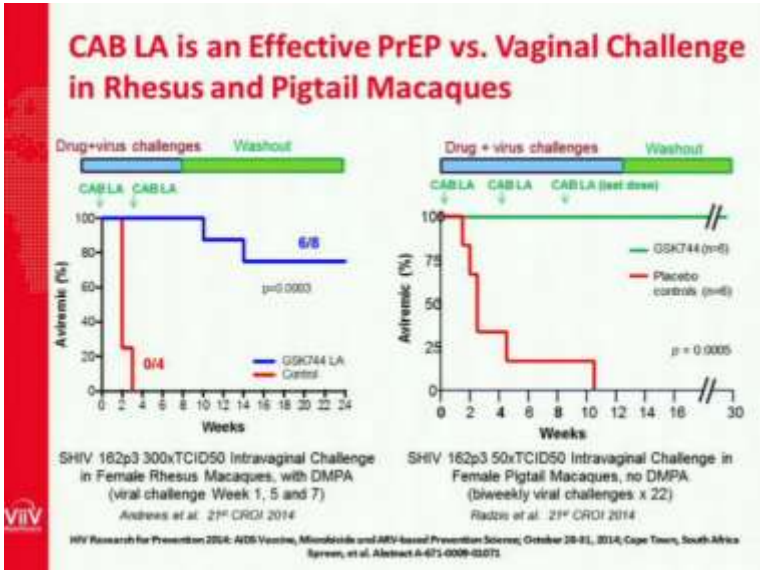
Spreen et al, IAS 2013 Kuala Lumpur, Malaysia

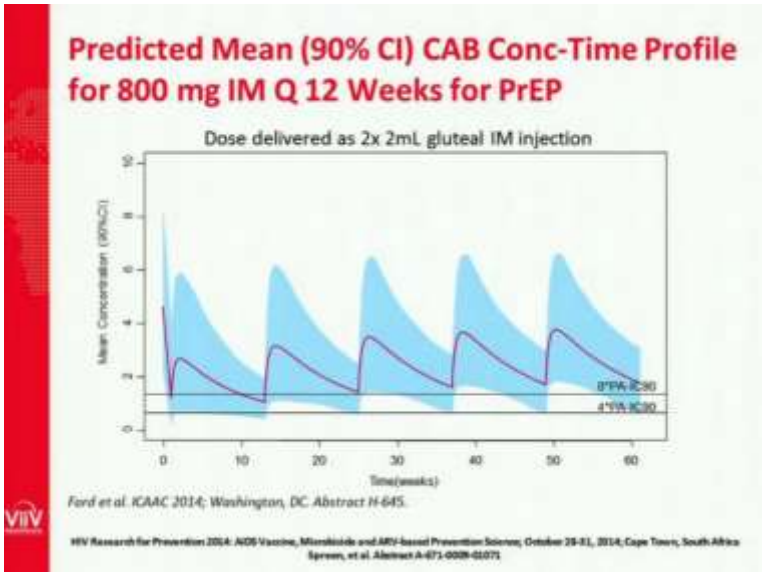
Collectively, human PK data PLUS macaque efficacy data suggest promise for GSK744 as aPrEP agent

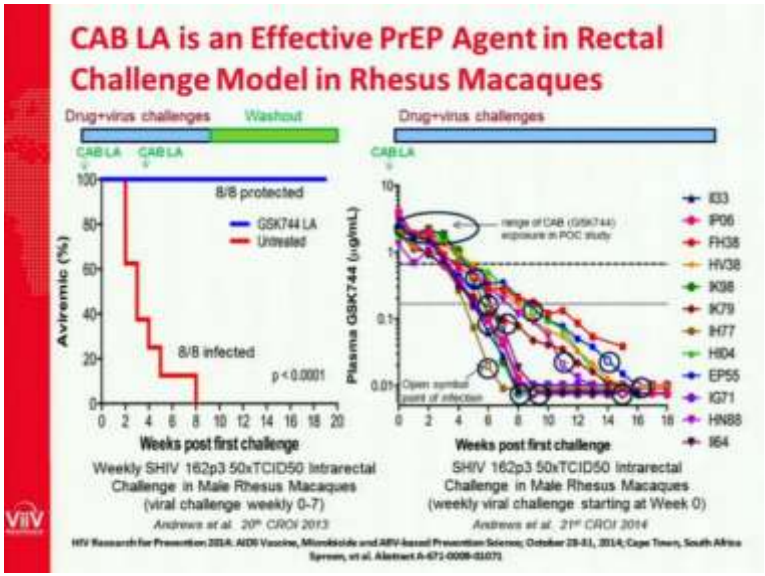
Human PK compartment study

- Healthy volunteers: IM injection
- $t_{1/2}$ = 21 - 50 days
- CV Tissue: plasma GSK744 ratio = 16% to 28%
- Rectal tissue: plasma (male) was ≤ 8%

Proposed 800mg quarterly dosing







GSK1265744 LA and TMC278 LA, together?

Collaborative development (ViiV + Janssen) for treatment

Is it likely that a combination of agents would be used for PrEP?

Cost, funding, affordability are all unknown at this stage

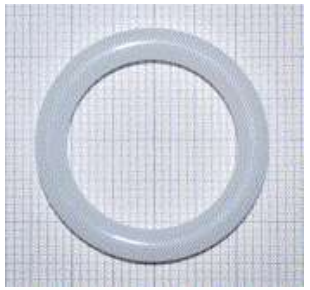
- Both were well tolerated without severe injection site reactions.

- No drug interaction between them

- However, limited repeat-dose experience and none yet to steady-state concentration.

Other Agents

1. Maraviroc
   - Oral PK compartment study, Fox et al (LB @ CROI 2015)
   - HPTN-069 Next-PrEP - phase 2 study with TDF
2. Dapivirine ring
   - NNRTI (TMC120) not for systemic use
   - 2 phase 3 studies ongoing
     - MTN202
     - IPM027



3. Ibalizumab - monoclonal humanised Ab
   - HIV entry blocker

Conclusions

Pharmacokinetics of PrEP is challenging and difficult to define

Single target concentrations are difficult to define.

- compartment: plasma ratios change with time
- efficacy depends on innate host and viral factors
- cellular activation likely lowers concentrations at target tissues
- What is the threshold for SUCCESS?

A combination of:

- modelling predictions based on early PK/PD studies
- clinical data from trials

to guide dosing decisions.

Pragmatically, likely that doses used for PrEP will match doses used for therapy

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