Tenofovir Concentration in the Female Genital Tract

Jill L Schwartz, MD

The Microbicide Challenge is a Tall Order…

In order to prevent HIV infection we have to:

- Deliver the *appropriate* concentration of TFV
- To the *appropriate* biological site
- For the *appropriate* duration
- And avoid side effects and resistance

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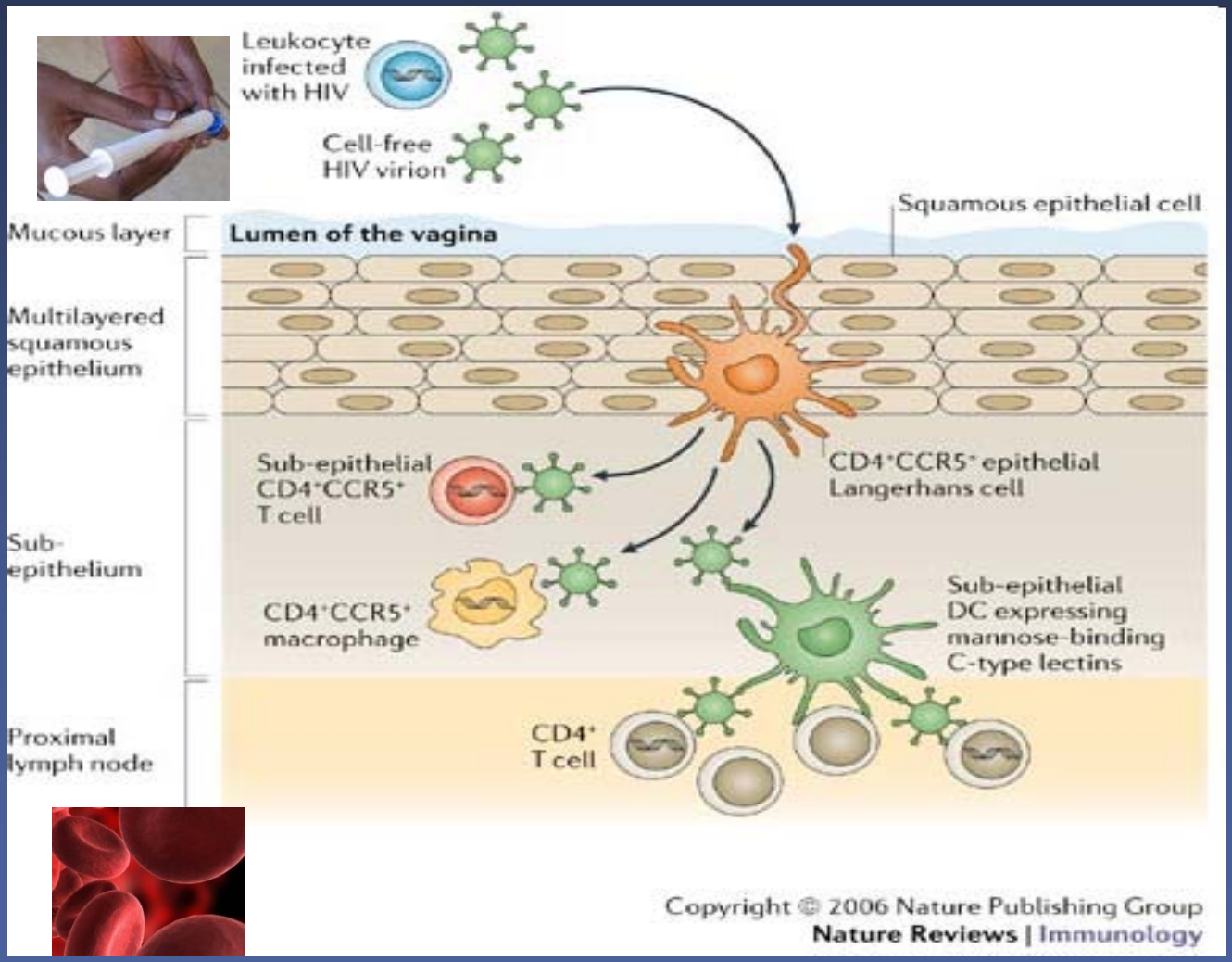
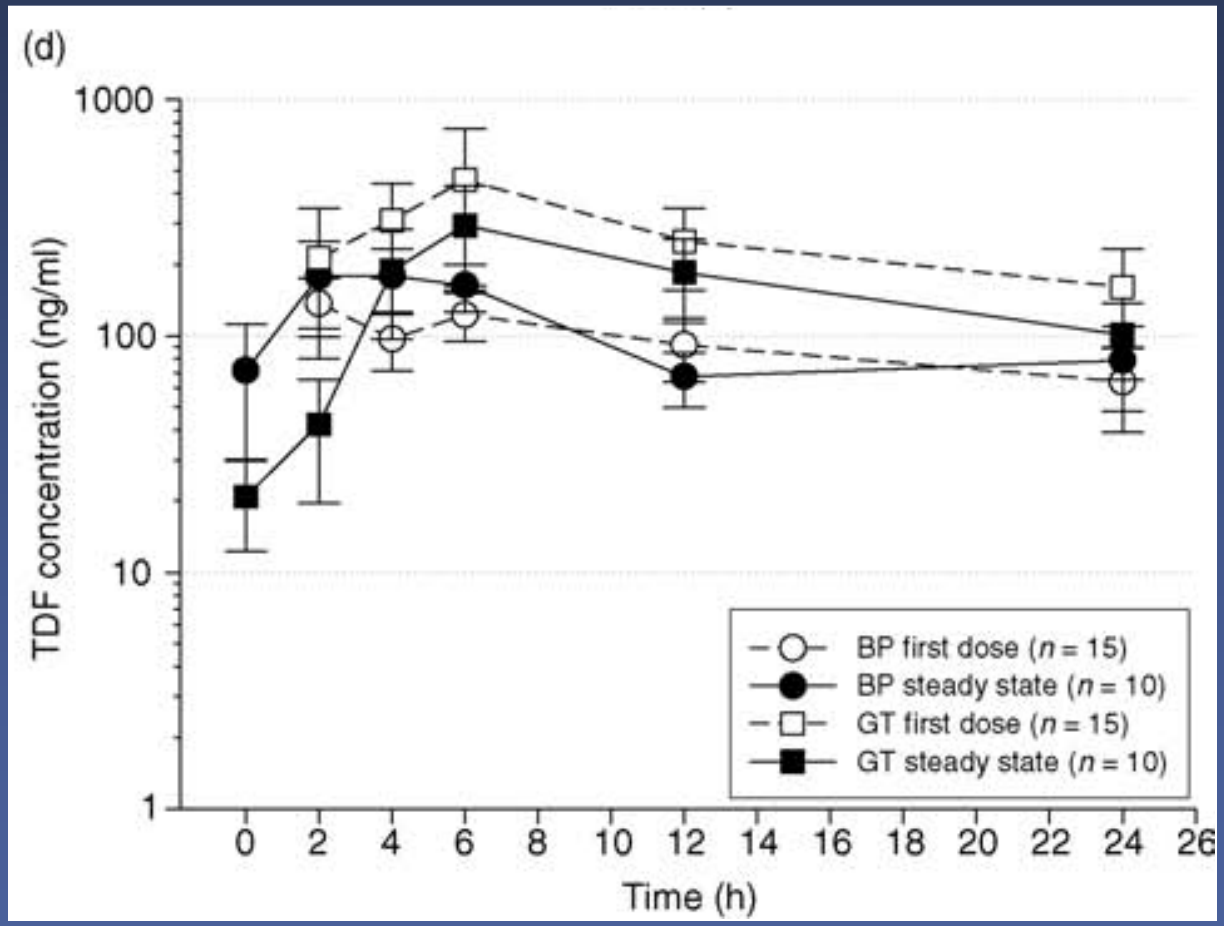
Why Are Pharmacokinetic Data Collected

- Inform clinical trials for selection of drug dose and dosing frequency
- Provide biologic plausibility to interpret clinical trial results

Where do the drugs need to be?



ORAL TDF
TFV in blood plasma (BP) and genital tract (GT)
After 1st dose and Steady State



Dumond et al. AIDS 2007

TFV gel Clinical Safety and PK Studies

Study	N (# TFV)	Arms	Endpoints			
			Safety (includes AEs)			PK
			Colpo	Cyto-kines	Flora	
HPTN O50 ***Safety study in HIV- & HIV+***	**84**	**0.3 vs 1% QD or BID for 2 weeks**	√			√
MTN 059 ***Expanded Safety***	**200 (100)**	**4 arms: Daily or Coitally Tenofovir or placebo for 6 months**	√	√	√	√
CONRAD PK	**49**	**Single dose then 2-weeks (once or twice-daily)**				√
MTN 001 ***Crossover safety and PK***	**144**	**6-weeks oral 6-weeks vaginal 6-weeks oral + vaginal**		√	√	√

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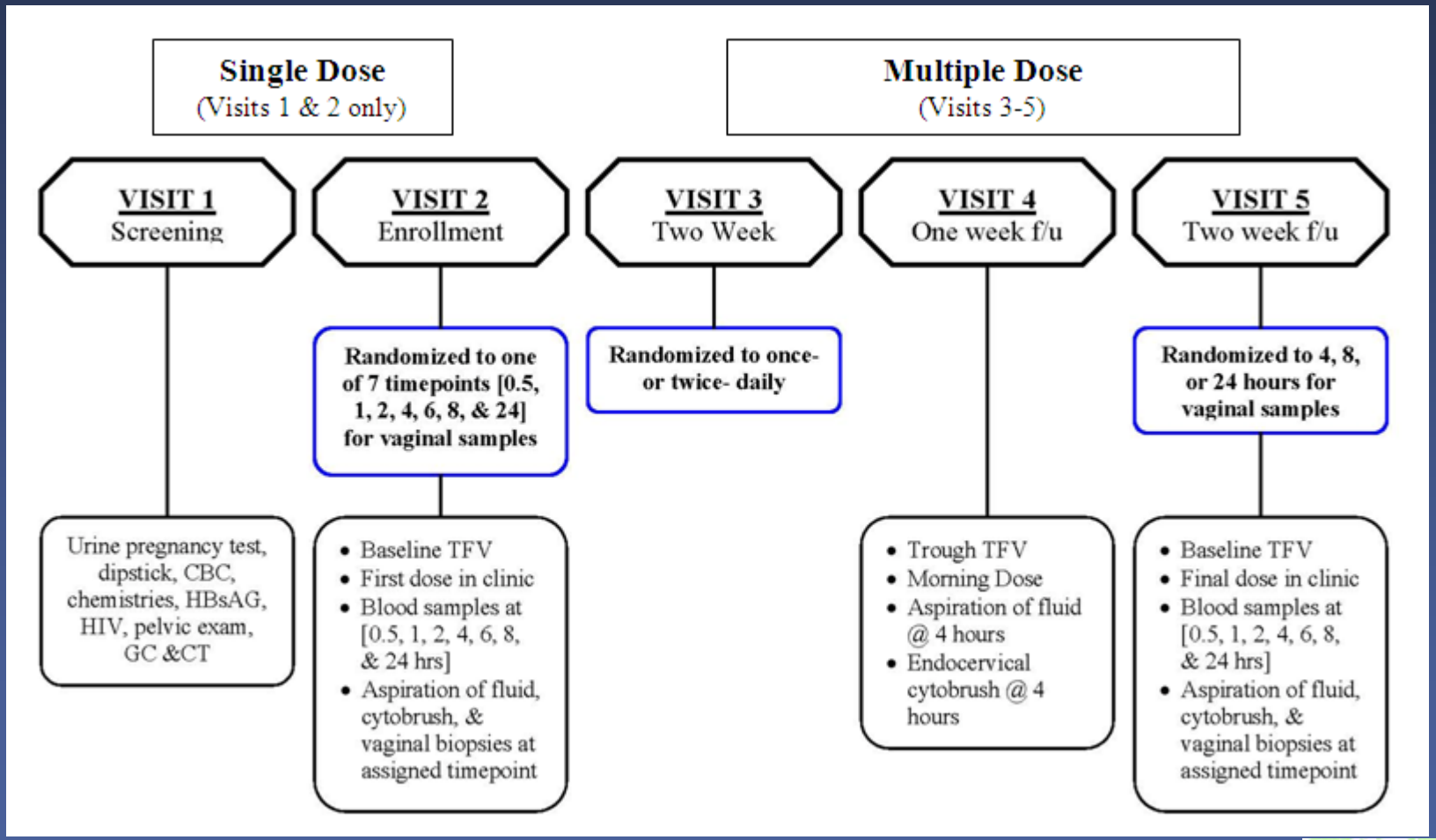
Tenofovir PK Study Design
N=49



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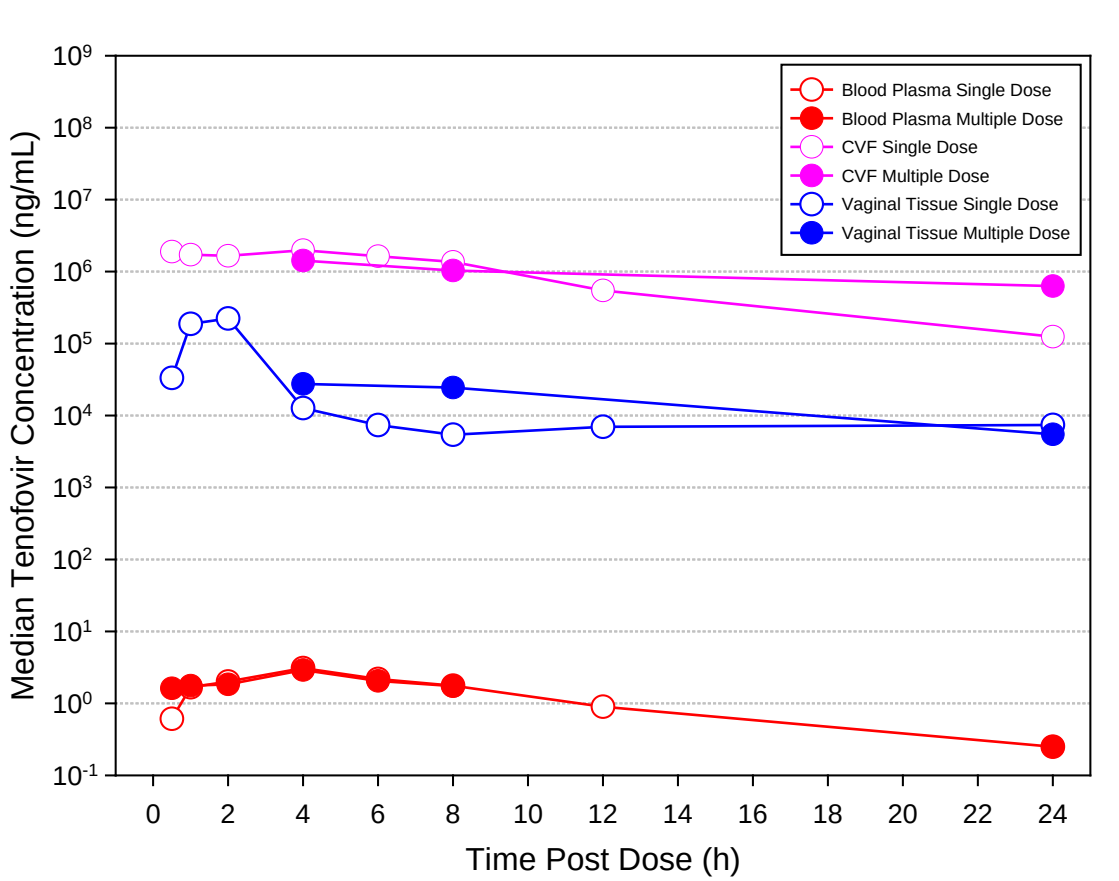
Tenofovir Pharmacokinetics



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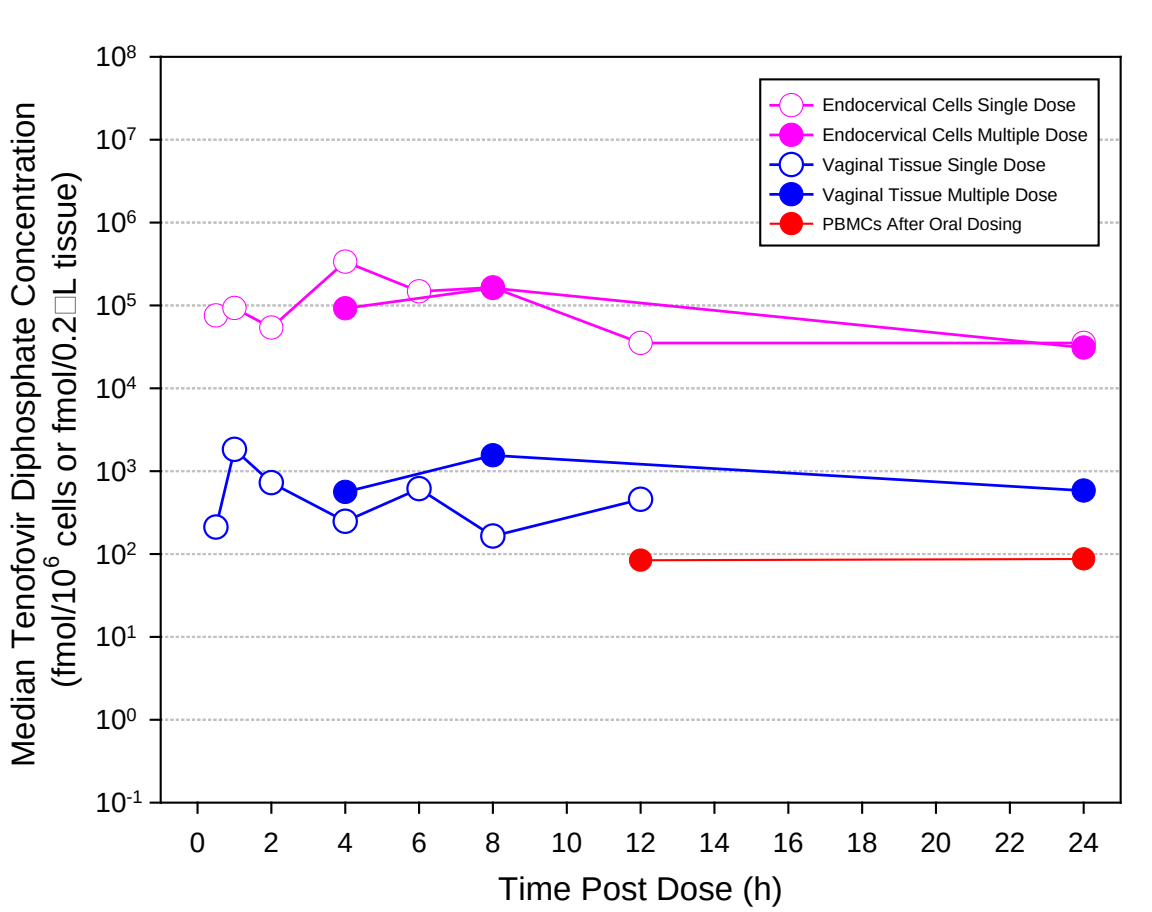
Tenofovir Diphosphate Pharmacokinetics



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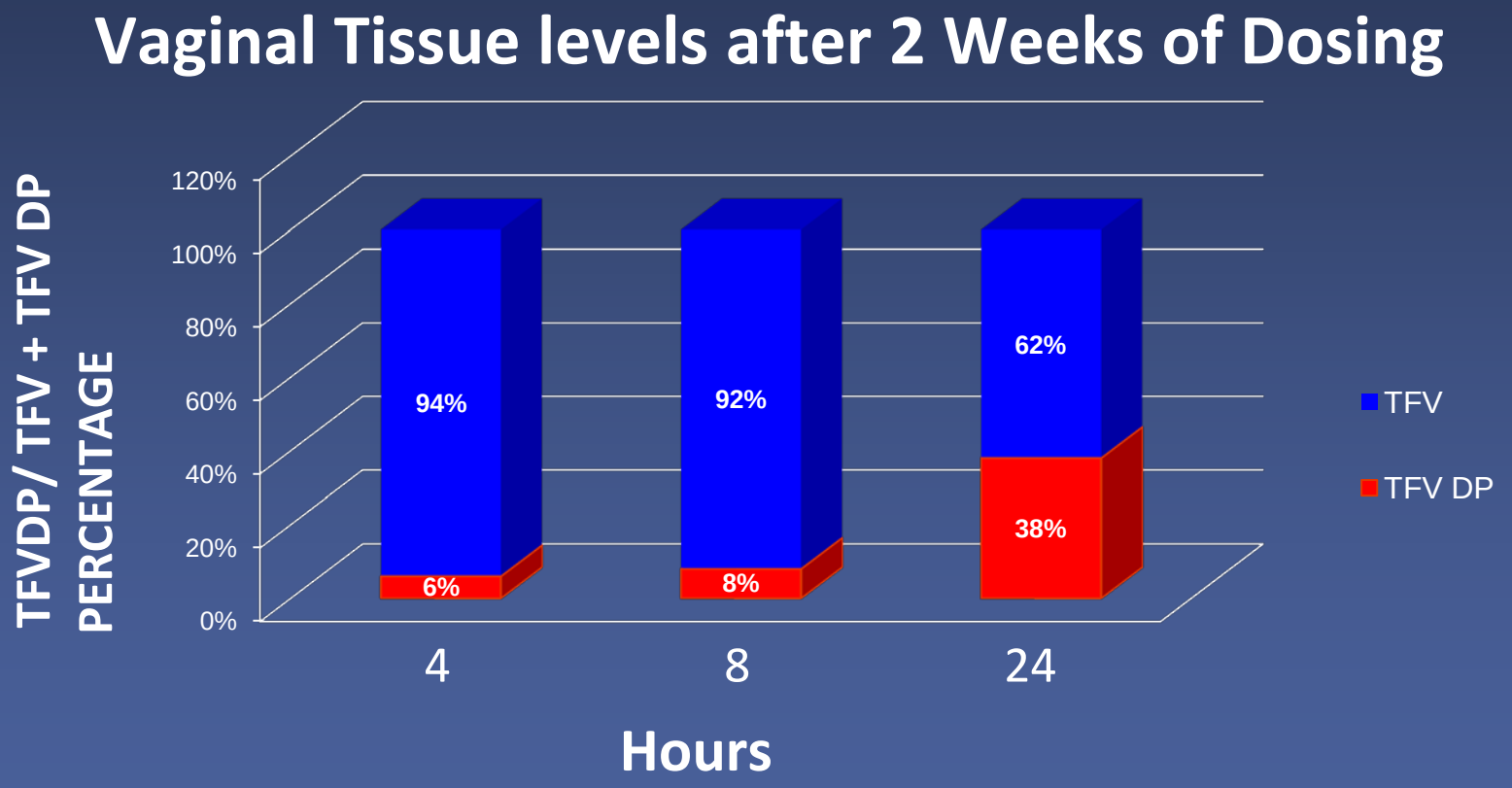
What percentage of total tenofovir is in the active metabolite form?



Median (IQR) Parameters Blood Plasma

Analyte, Matrix, Dose Frequency	Cmax (ng/mL)	Tmax (hr)	AUC_{24h} (hr*ng/mL)	C_{24h}(ng/mL)
TFV Single Dose	4.0 (1.5-9.1)	4 (2-6)	36.4 (13.5-69.6)	0.3 (0.3-0.5)
TFV Multiple Dose	3.4 (2.4-6.1)	4 (2-6)	37.2 (24.6-62.6)	0.3 (0.3-0.6)
TDF (oral) 300 mg	3.0×10^2	1	2.3×10^3	--

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Median PK Parameters TFV-DP in Genital Tract

Analyte, Matrix, Dose Frequency	Cmax (ng/mL)	Tmax (hr)	AUC_{24h} (hr*ng/mL)	C_{24h}(ng/mL)
TFV-DP ECC Single Dose [1]	7.5×10^5	4	58.1×10^5	0.8×10^5
TFV-DP ECC Multiple Dose [1]	3.6×10^5	8	44.5×10^5	0.5×10^5
TFV-DP Tissue Single Dose[1]	0.5×10^3	4	1.7×10^3	n/a
TFV-DP Tissue Multiple Dose[1]	3.1×10^3	8	43.4×10^3	1.3×10^3
TDF (oral) 300 mg Blood Plasma	3.0×10^2	1	2.3×10^3	--

[1] Estimated from 4, 8 and 24 hour samples

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What do we know about TFV in Genital Tract?

Oral:

- GT exposure within 2 hrs of oral dose
- TFV reached peak conc by 6 hours
- GT conc. were at or above BP conc 4h after dose and remained higher

Intravaginal:

- TFV high in vaginal tissue (10^4-10^5 ng/ml)
- TFV-DP high in ECC (10^5 ng/ml) and vaginal tissue (10^3 ng/ml)

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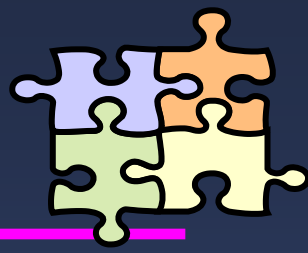
What will other ongoing studies tell us? More pieces to the puzzle…



- TFV010—
  - Mucosal Immunity: cytokines, antimicrobial proteins and endogenous activity, ECC TFV-DP (Results M2010)
- MTN001—
  - Genital Tract PK with oral vs intravaginal administration
- PK in Pregnancy—
  - 002—PK in blood, amniotic fluid, fetal cord blood, placenta and endometrium after single dose
  - 008---PK after 7 days in pregnancy and lactation
- Rectal Studies—
  - 006 --To compare PK among oral TDF, rectal TFV gel & placebo gel

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What do we still need to know?

- TFV-DP levels in cell populations (immune vs. epithelial cells)
- TFV-DP conversion—need to stabilize samples
- What drug levels are needed and where?

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