# MTN-001
# Phase 2 Adherence and Pharmacokinetic Study of Oral and Vaginal Preparations of Tenofovir

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***…and the MTN-001 Study Group***

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# Questions: Informing RCTs

- Acceptability
  - Do women prefer oral tablets or vaginal gel?
- Adherence
  - Do oral and vaginal dosing have different levels of adherence?
- Pharmacokinetics
  - Do active site drug concentrations vary with dosing form?
  - Is there an additive effect of dosing oral tablet and vaginal gel together?

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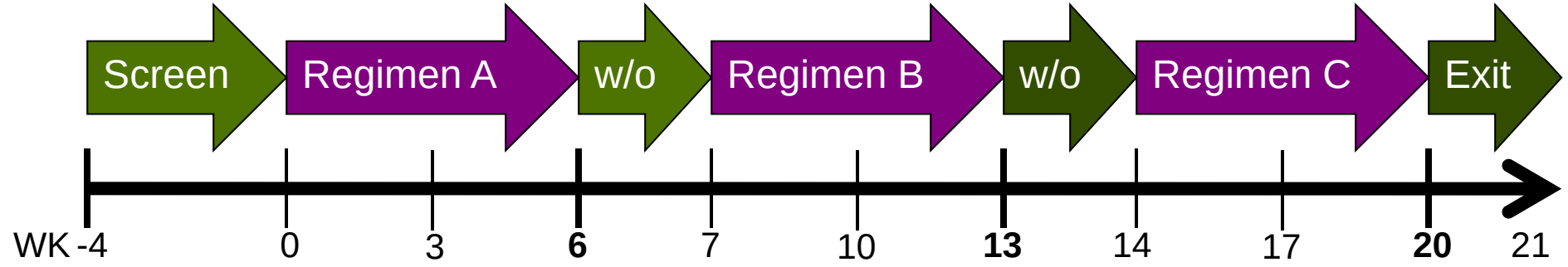
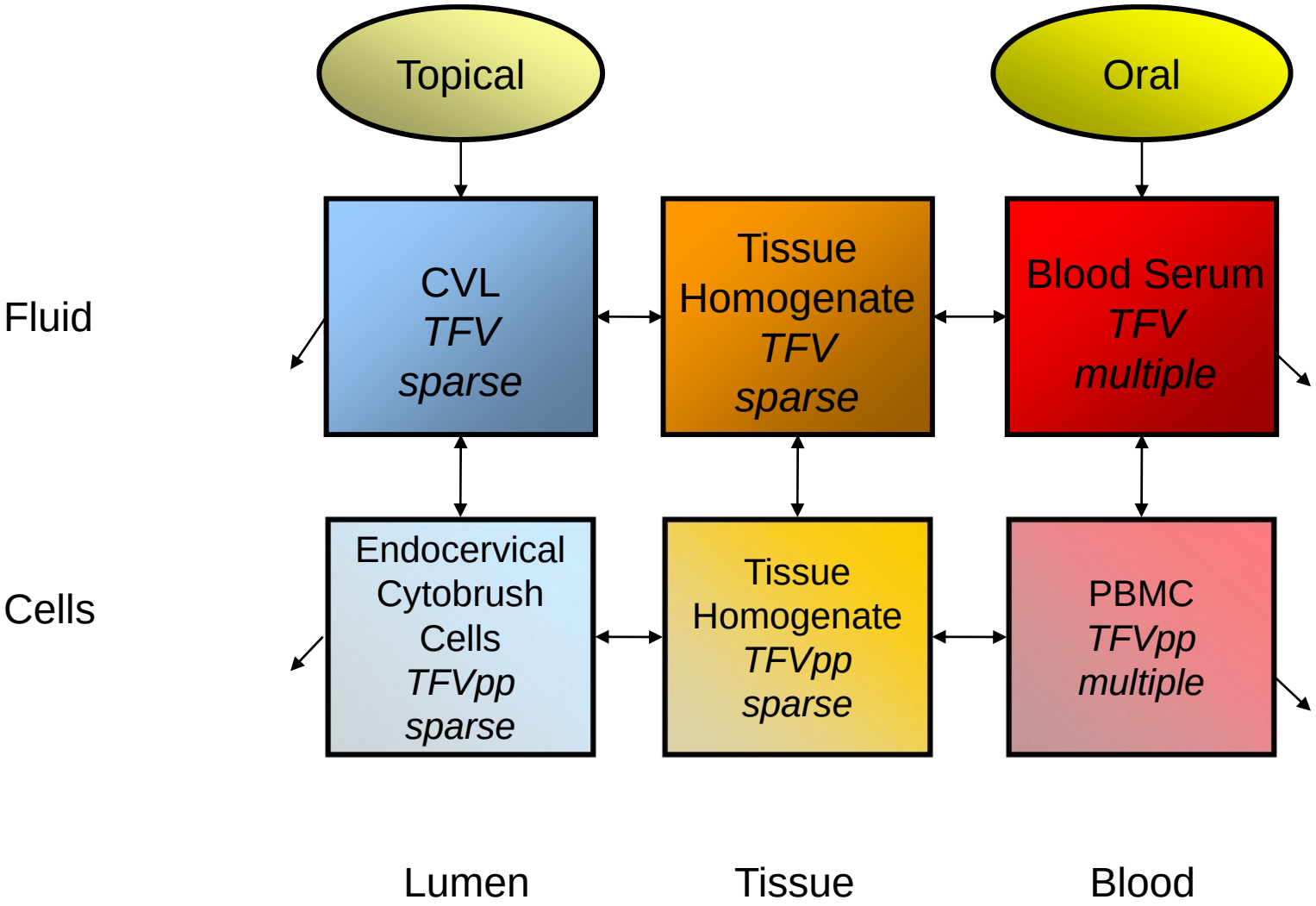
# Study Design

- Three period, open label crossover study
- 144 sexually active, HIV- women, 18-45 y.o., 7 sites
- All receive oral, vaginal, dual – random sequence
  - Daily oral tenofovir disoproxil fumarate (TDF, 300 mg tablet)
  - Daily vaginal tenofovir gel (1% TFV, 40 mg; same as VOICE)
  - Daily oral and vaginal (Dual)
- 21 weeks (3, 6-week periods; 1 week washout)



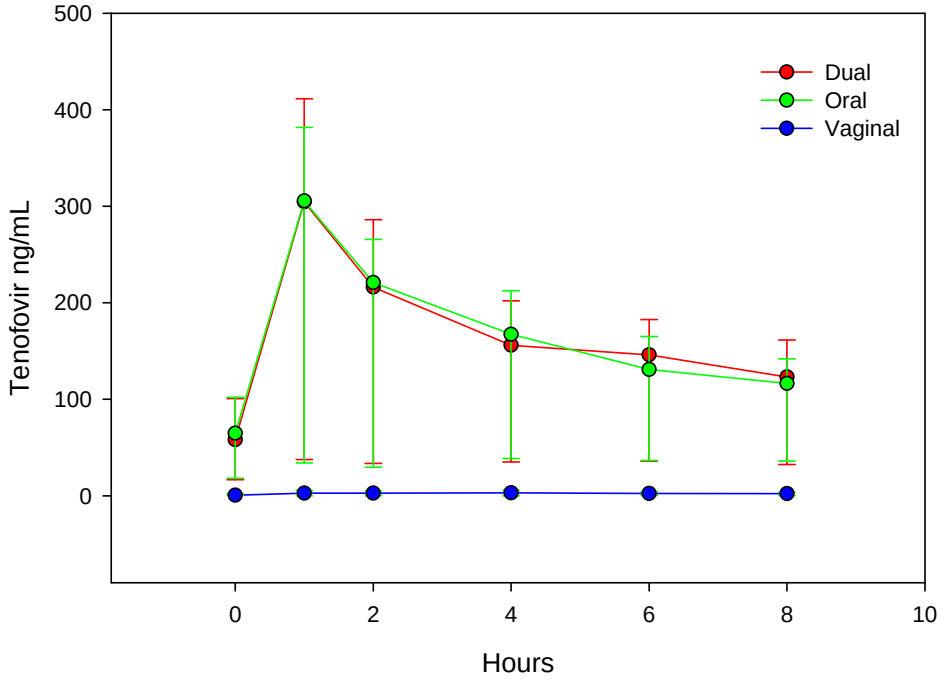

- Safety, adherence, acceptability, PK @ each visit

# Drug Concentration Assessment

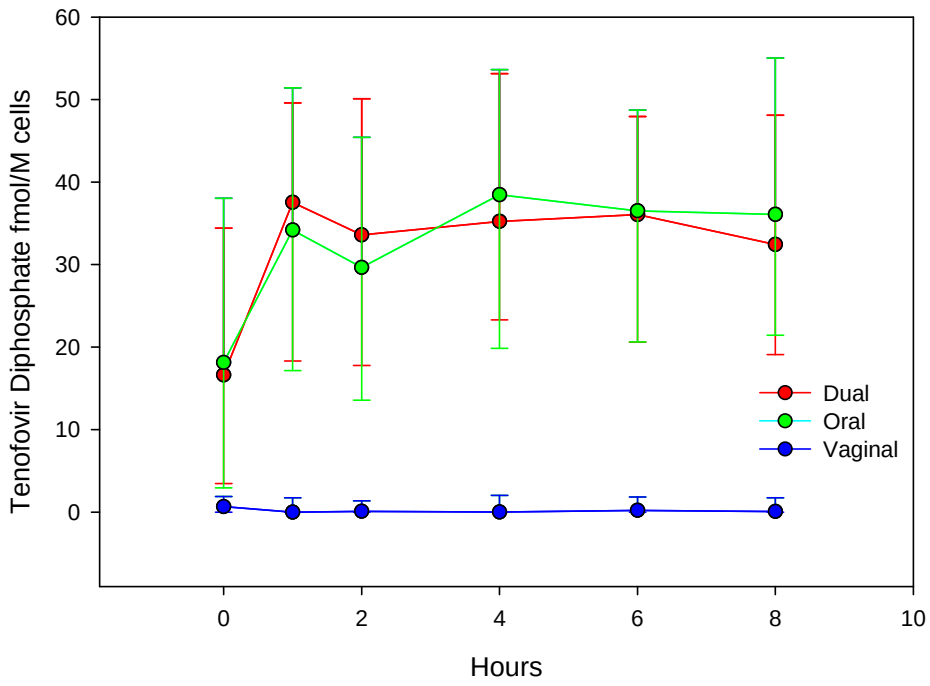


# Serum TFV & PBMC TFV-DP

Serum TFV (median, IQR)




PBMC TFV-DP (median, IQR)




All anatomic sites, except serum, lacked temporal trends over 8 hrs.

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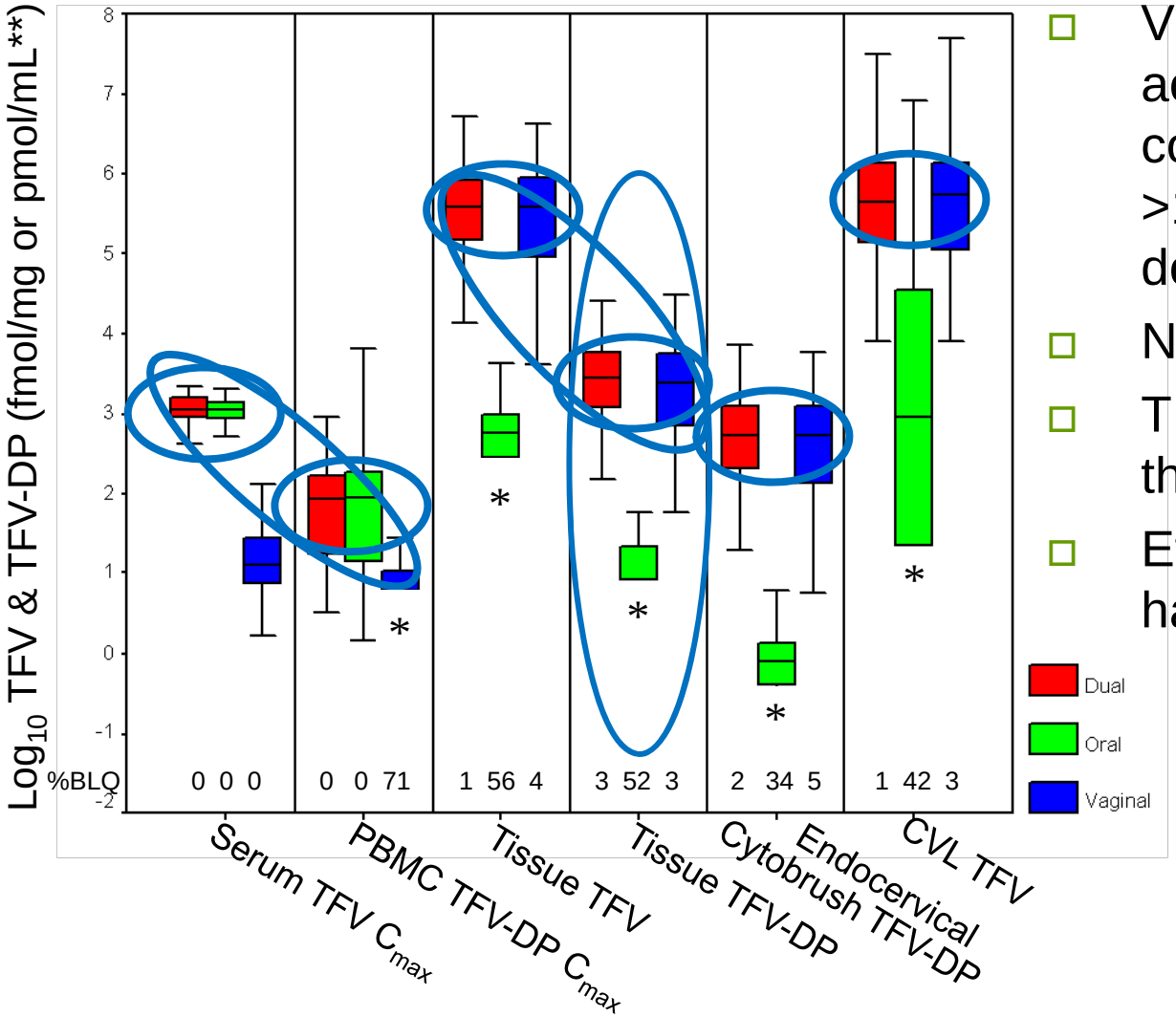
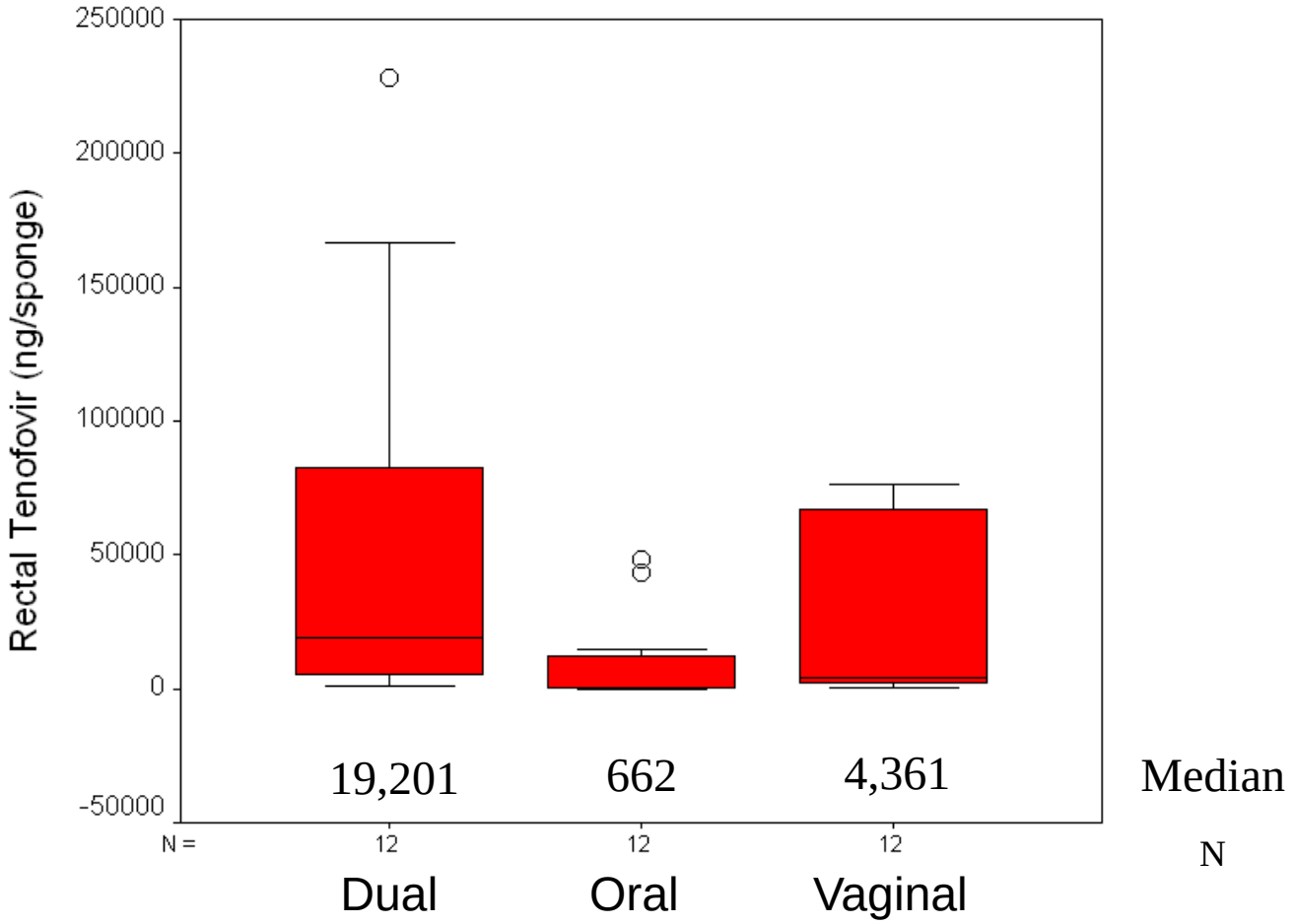
# TFV & TFV-DP by Route & Site




- Vaginal dosing achieves active drug (TFV-DP) concentrations in tissue >100x higher than with oral dosing
- No additive effect of Dual
- TFV-DP ~5-15% of TFV in the same compartment
- Effective concentrations have not been established

*Median <LLOQ, assigned BLQ/2 for median; value **Molar equivalent units assumptions: gm = mL, $10^6$ cells = 0.2uL

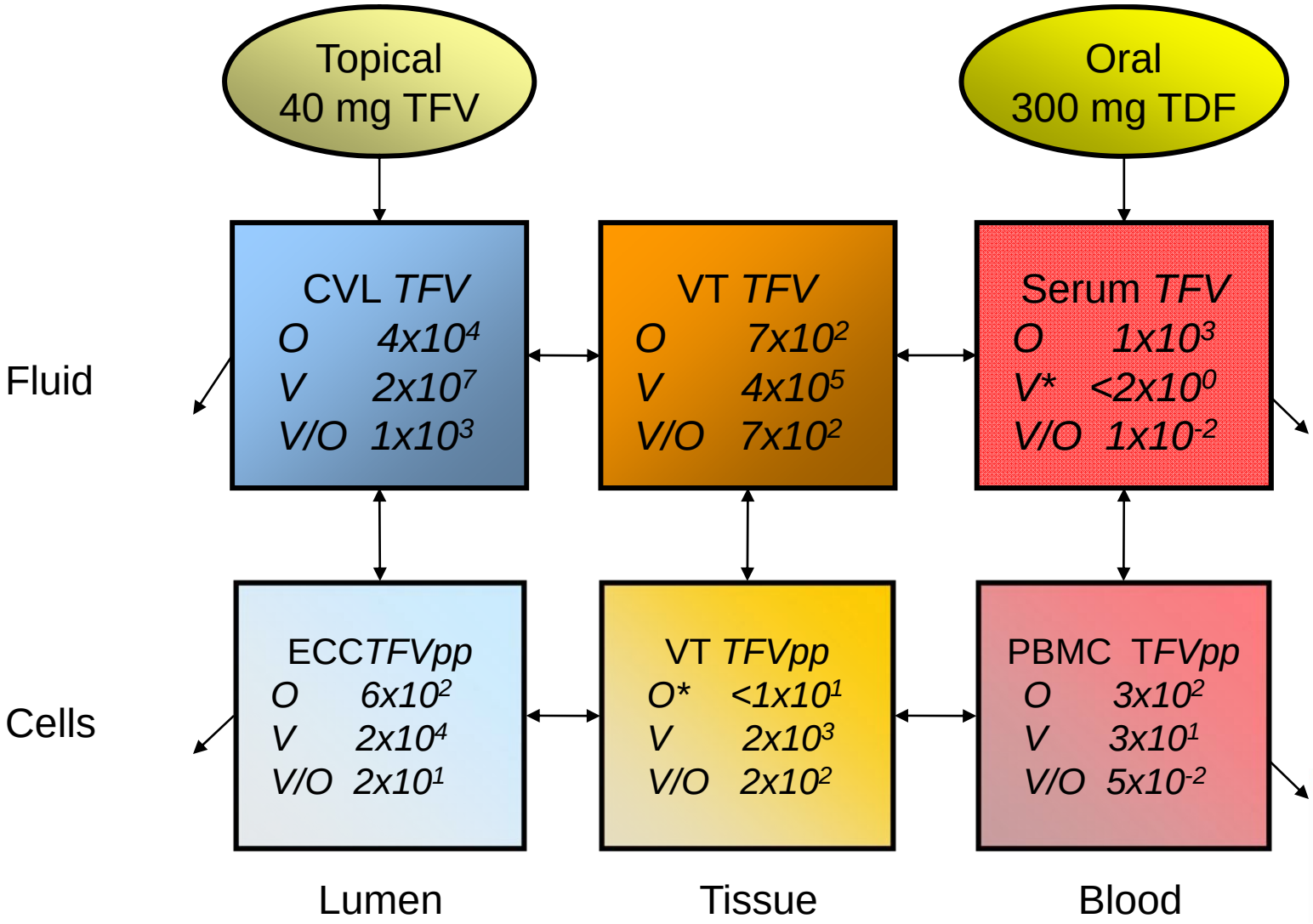
# Rectal Sponge Tenofovir




Friedman p=0.01 comparing among regimens; Dual vs. Oral p=0.01 (Wilcoxon), o/w n.s.

*Numbers are unadjusted for weight.

# TFV Site & Route Variation




All units fmol/mg or pmol/mL
Assumes:
gm = mL
$10^6$ cells=0.2uL
*median BLQ

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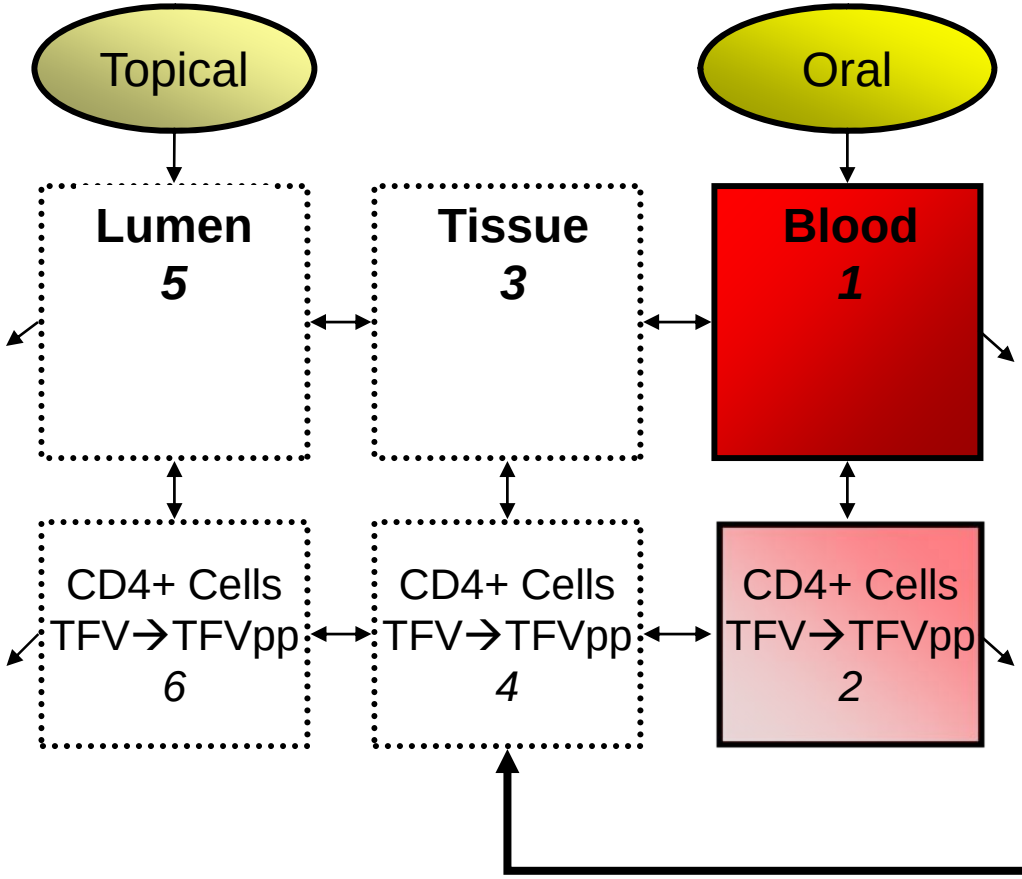
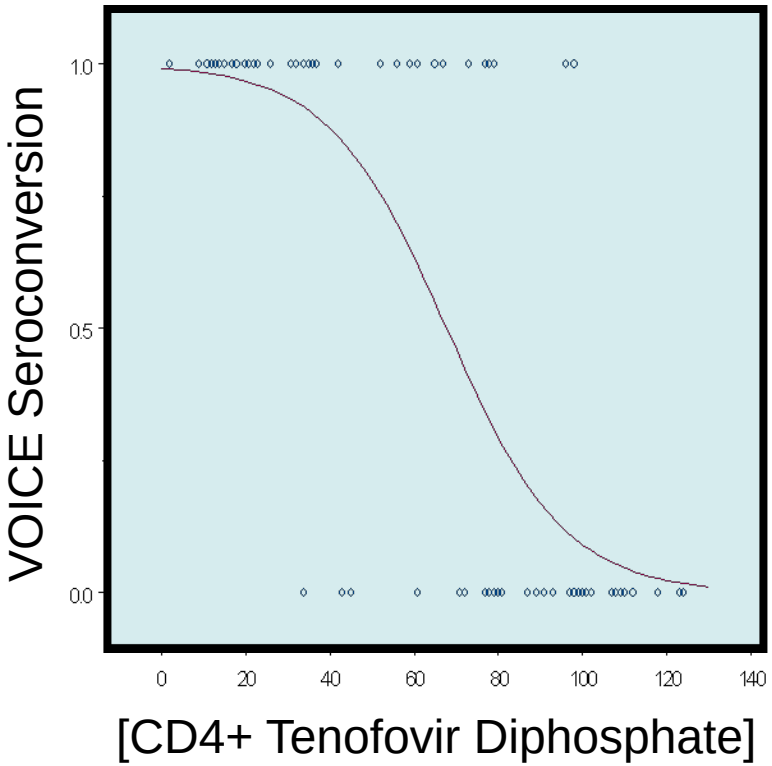
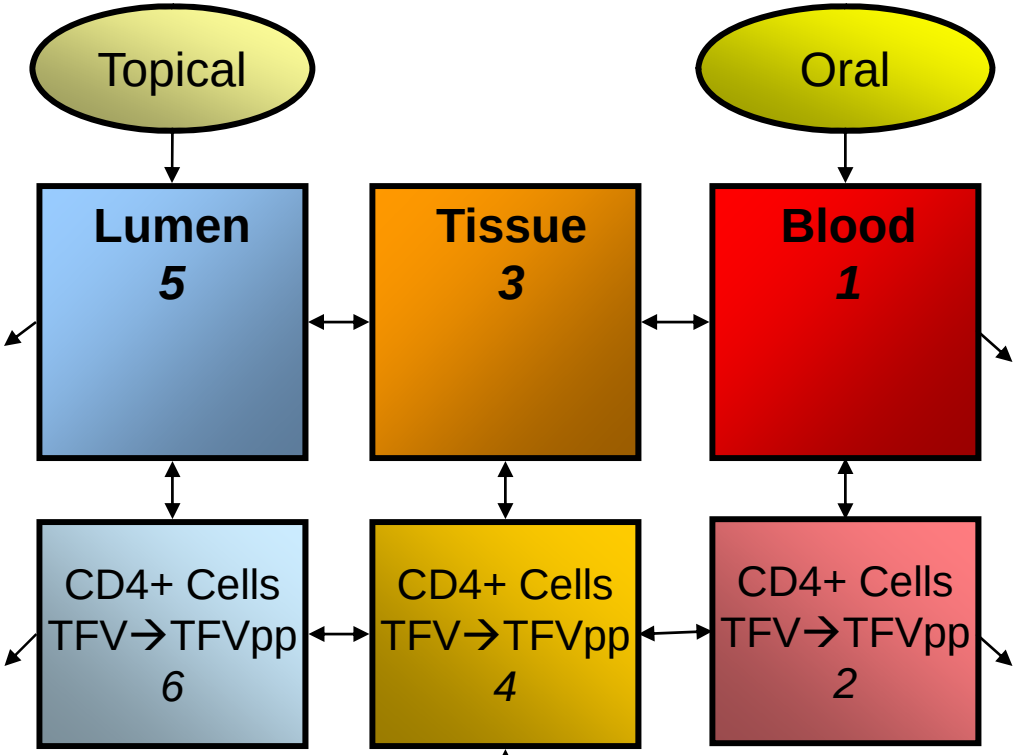
# PK-PD: VOICE Alone

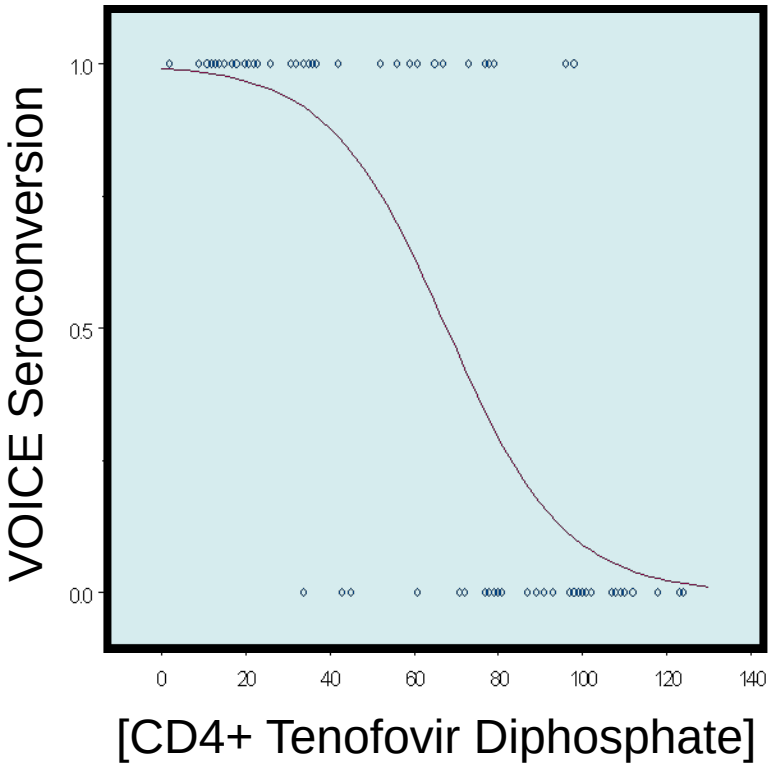



Pharmacokinetic – Pharmacodynamic Link

# PK-PD: VOICE & MTN-001




Pharmacokinetic – Pharmacodynamic Link

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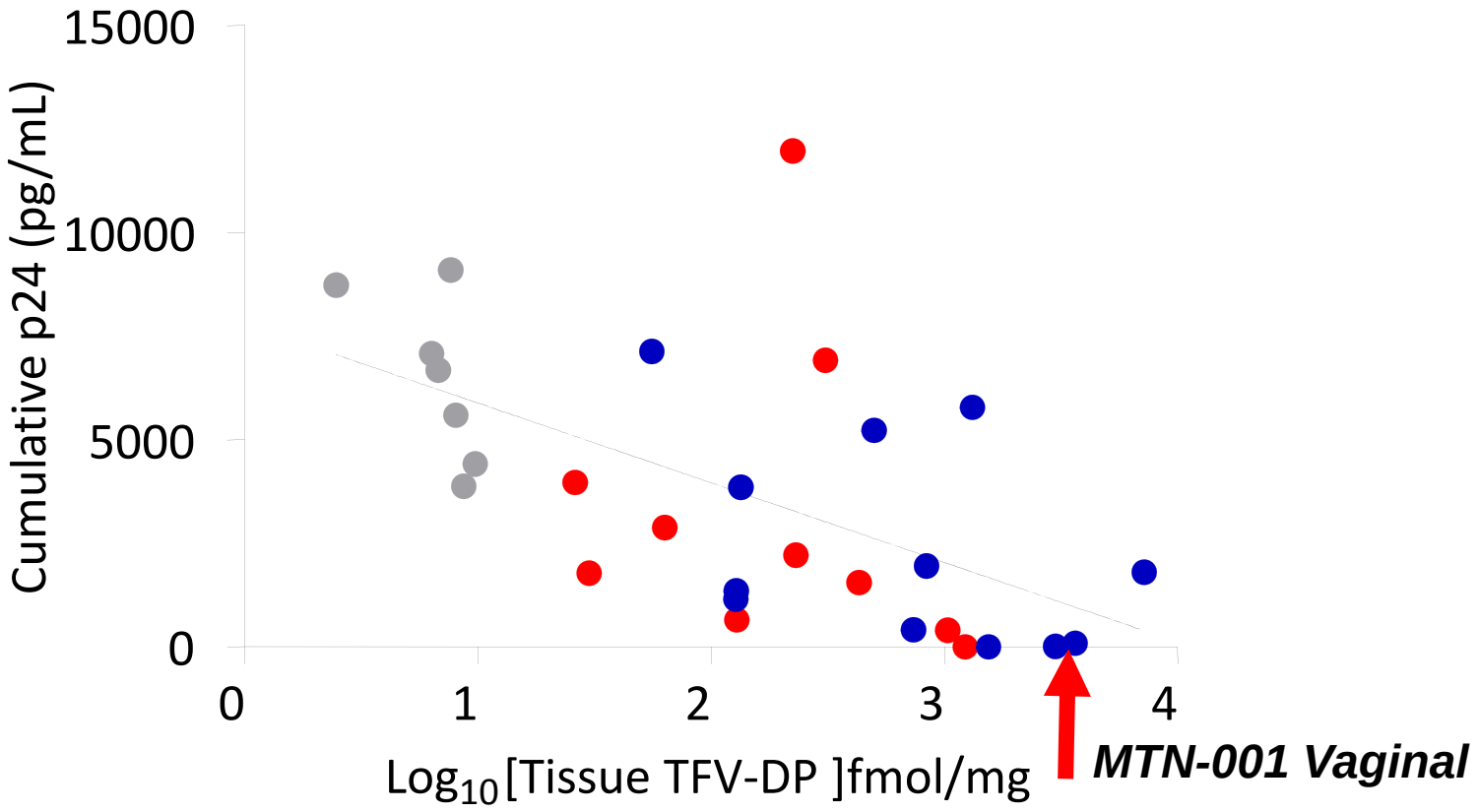
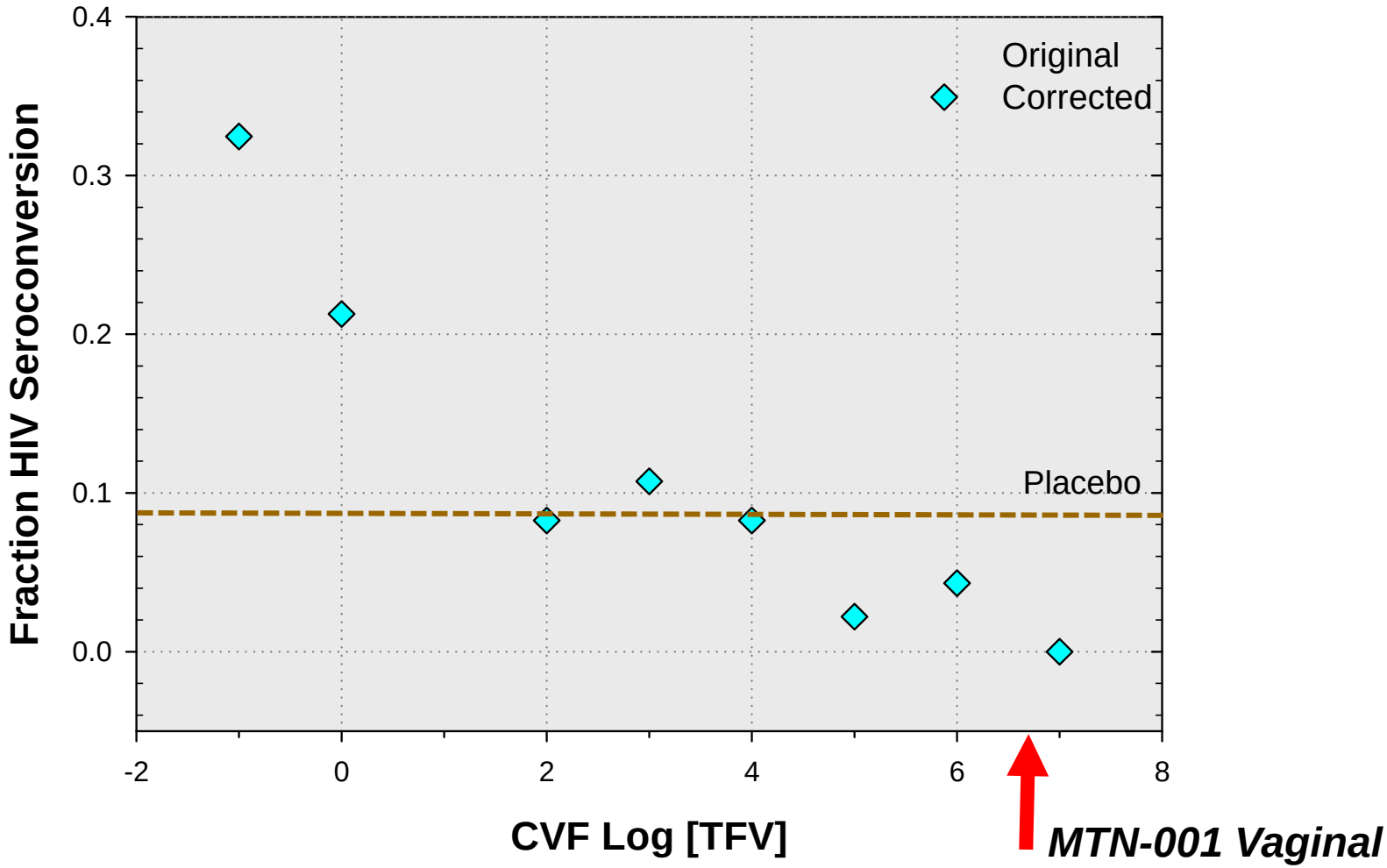
# MTN-006 PK-PD (*Ex vivo*)



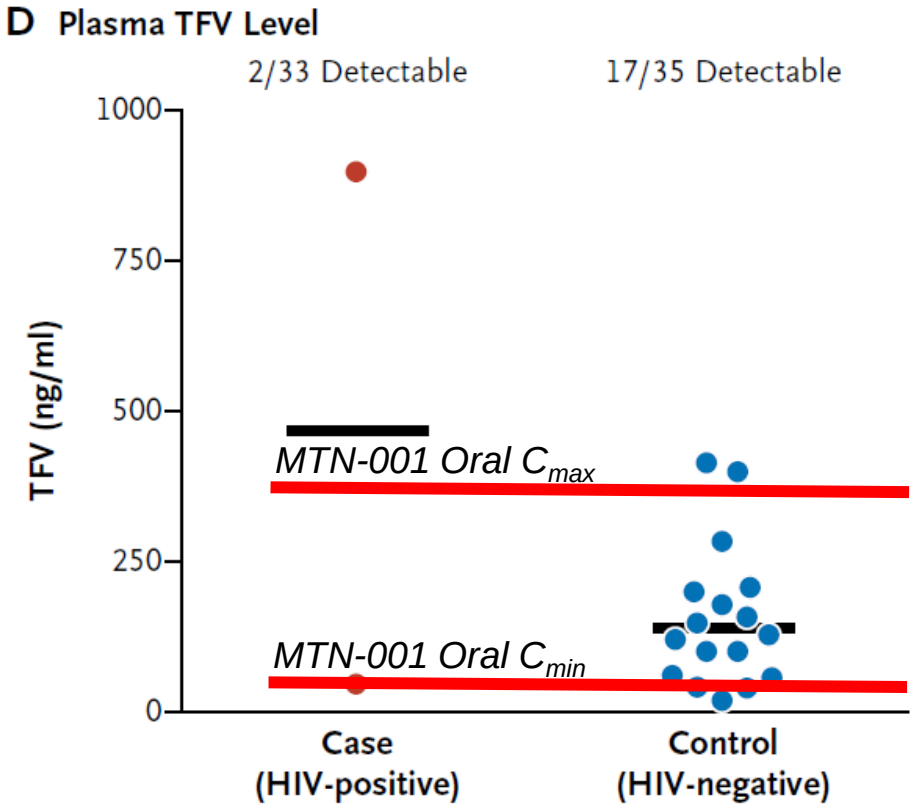

- Virus inhibition correlated with increasing tissue TFV-DP,
- Feasible to assess both dose and response following *in vivo* exposure to drug

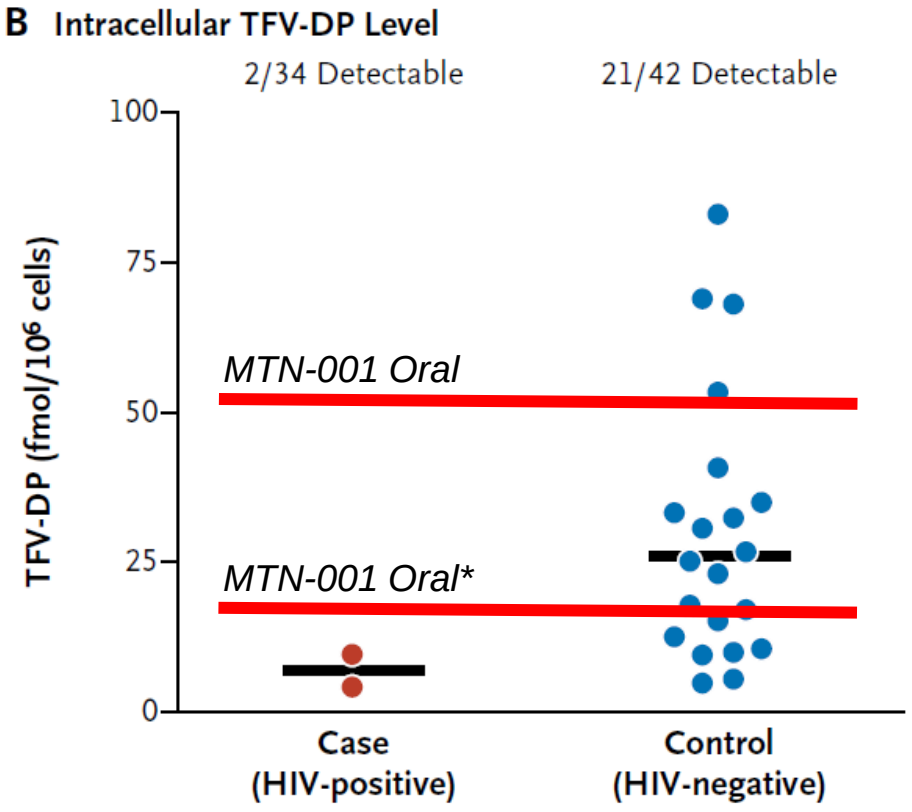
# CAPRISA 004 PK/PD CVF




Modified from Kashuba, *et al*. IAS Vienna 2010

# iPrEX PK/PD Blood




Grant, *et al. New Engl J Med* 2010

*Adjusted 3:1 method differences

# Self-Reported Product Adherence

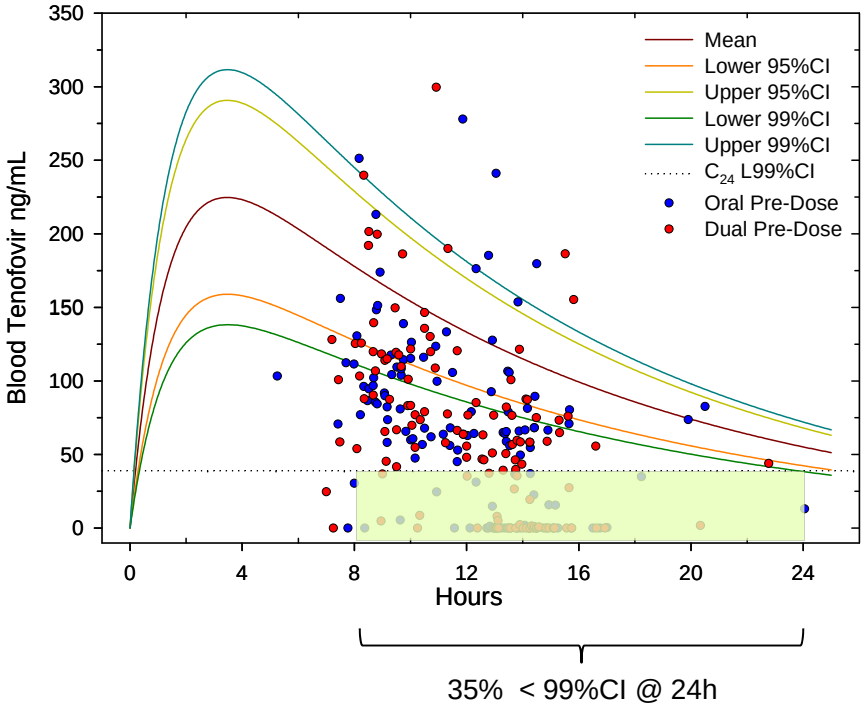
| | Overall | Vaginal Gel | Oral Tablets | Dual |
|---|---|---|---|---|
| | N=851‡ | N=285 | N=282 | N=284 |
| | % | % | % | % |
| **Adherence Measures** | | | | |
| % daily doses taken (mean, SD)† | 94.0 (10.8) | 94.4 (12.2) | 93.9 (10.1) | 93.8 (10.2) |
| >=90% doses taken | 81 | 85 | 79 | 79 |

†p=0.8 (mixed effect model with Gaussian link and fixed effects for treatment, period, sequence; random effect of participant within sequence).
‡N=visits among 144 participants; maximum of 864 possible visits.

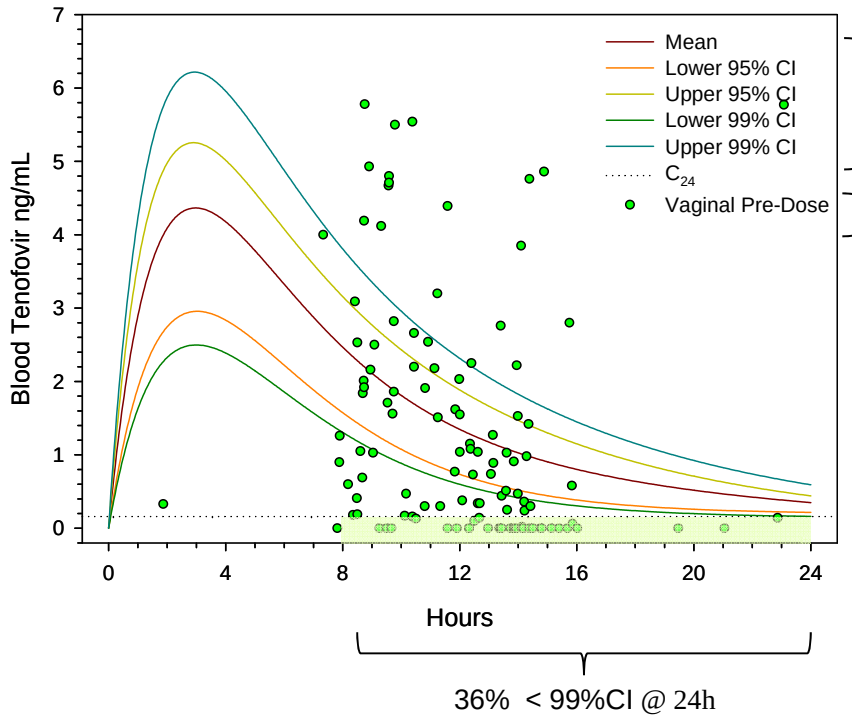
No differences among regimens or across study sites.

# PK as Adherence Measure

***Oral/Dual Dose Phase***




***Vaginal Dose Phase***

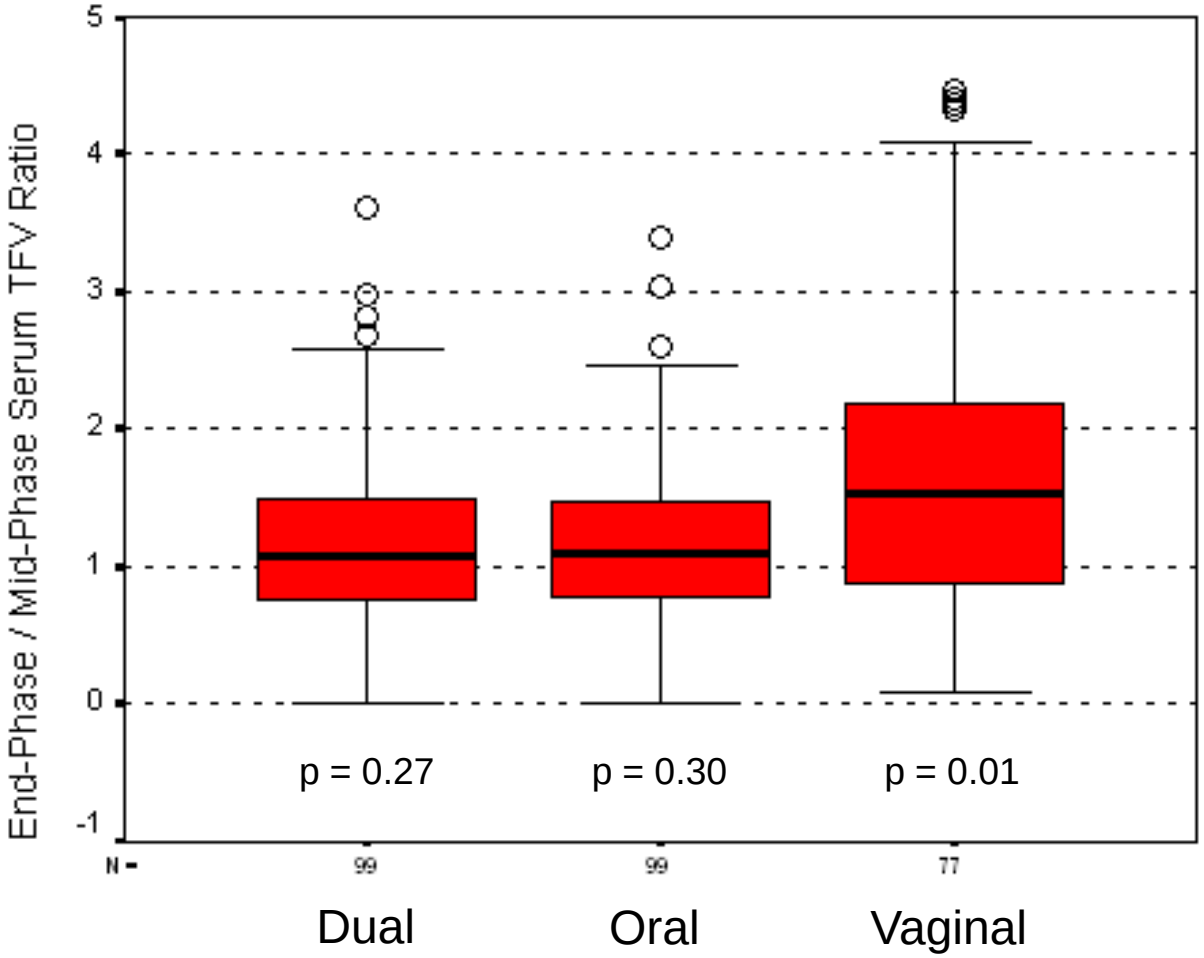



***Expected*** (Witnessed Dose Cohort)

***Actual*** (unobserved MTN-001)

Reference Cohorts: JHU (ICTR, $^{14}$C-TFV), MTN-006, CONRAD Gel Study (Jill Schwartz)

# Mid-Phase vs. End-of-Phase TFV




Adherence appears consistent throughout the 21-week study.

# Summary

- Active drug concentrations (TFV-DP) in vaginal tissue >100-times higher with gel, but “enough” for prevention is yet to be defined
- Dosing oral and vaginal forms together does not increase tissue concentrations more than gel alone
- US women prefer tablet; African women have equal preference & high likelihood of use for both products
- TFV concentrations indicate poor adherence in contrast to self-report; no difference among regimens
- Even with poor adherence, concentrations look promising compared to PK/PD studies

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# Unique Contributions

- Paired comparison oral v. vaginal dose adherence
- Impact of second product on adherence
- Paired comparison of oral v. vaginal PK
- Additive effect of dual route dosing
- Integrated multi-compartment PK model after oral dosing (blood cells, tissue, lumen)
- Comparison of observed v. unobserved PK to assess adherence
- “Connecting the (PK) dots” to relate RCTs (CAPRISA 004, iPrEX, VOICE)

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# Acknowledgements


- Research Participants
- Study Site staff
  - MRC, Botha's Hill, Durban
  - Bronx-Lebanon, NYC
  - CWRU, Cleveland
  - MU-JHU, Kampala
  - U Pitt. CRS, Pittsburgh
  - UAB, Birmingham
  - MRC, Umkomas, Durban
- NIH/DAIDS
- FHI
- SCHARP
- MTN Network Lab
- Clinical Pharmacology Analytical Lab (JHU)
- CONRAD
- Gilead

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# Questions?

# Contributions

- Paired comparison of oral v. vaginal TFV & TFV-DP
- Additive effect of dual route dosing
- Integrated multi-compartment PK model after oral dosing (blood cells, tissue, lumen)
- Comparison of observed v. unobserved PK to assess adherence
- Connecting the sparse PK “dots” to relate RCTs (CAPRISA 004, iPrEX, VOICE)

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# Acceptability

- Likely future use, if effective:
  - 93% oral tablet; 83% gel (p=0.002)
  - Difference driven by lower, different US rates
- Preferences differed by location

| | Overall (%) | Africa (%) | US (%) |
|---|---|---|---|
| Vaginal Gel | 28 | 42 | 14 |
| Oral Tablets | 57 | 40 | 72 |
| Both liked equally | 10 | 14 | 7 |
| Both disliked | 5 | 3 | 7 |

- Many African women said that the gel improved sexual pleasure (Qualitative interviews)

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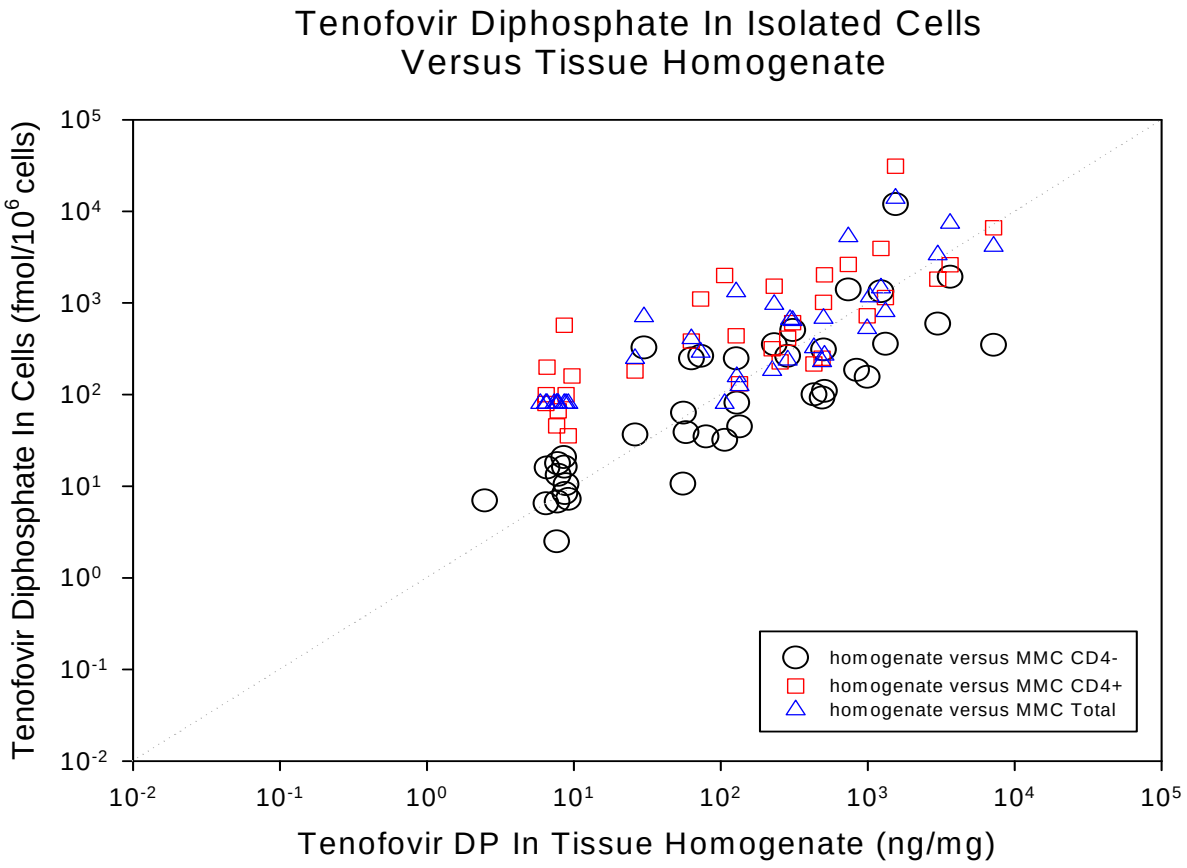
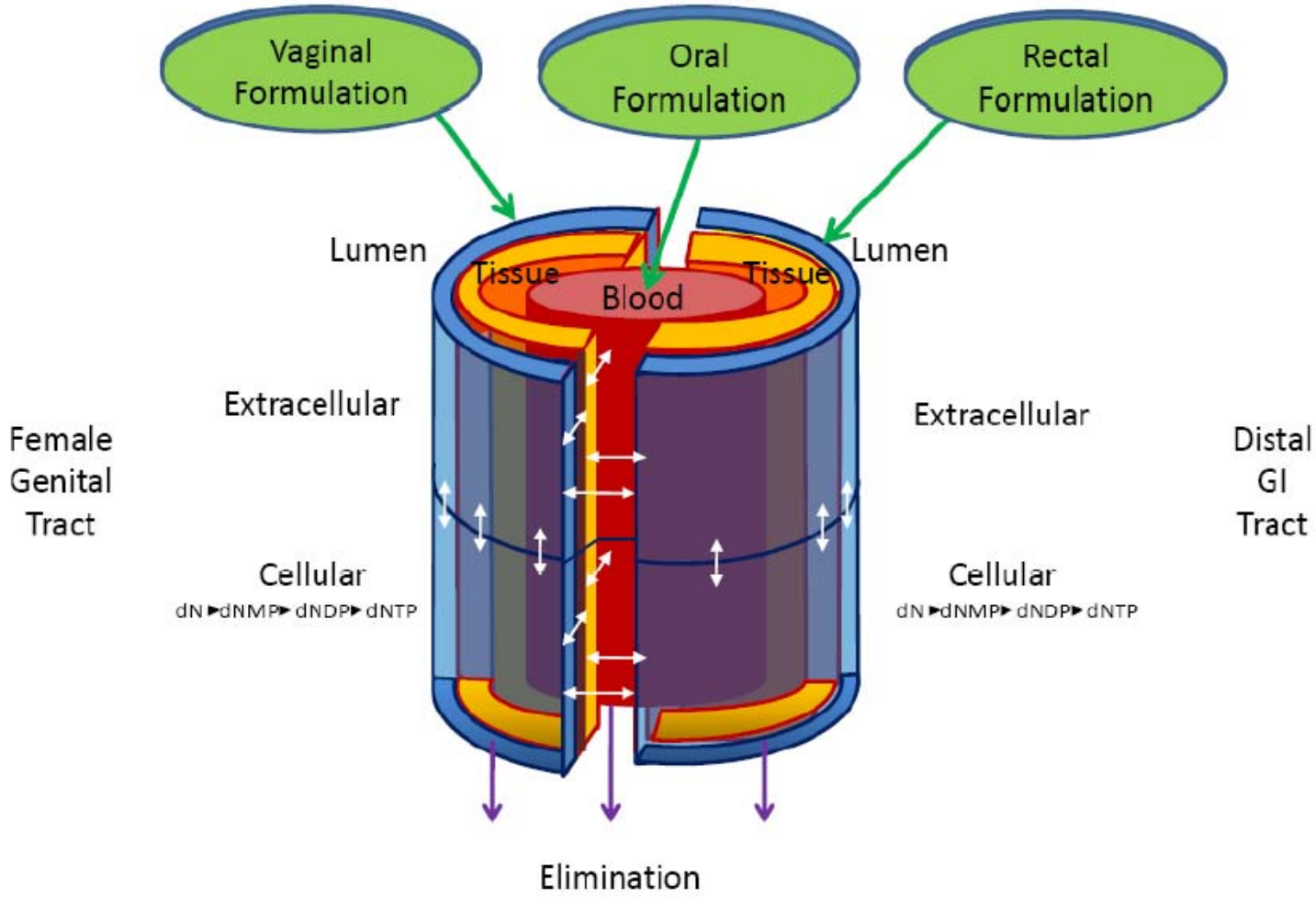
# Relationship Between TFV DP in Tissue Homogenate and Cellular Subsets (potentially for CROI)




Comments:

1. These data demonstrate a relationship between tissue homogenate and cellular subsets for TFV DP
2. Subsets likely do not need to be pursued in future investigations, as homogenate from DP will reflect isolated cellular exposure.

# Multi-Compartmental PK



# PK External Comparisons

| Study | HIV | Other ARVs | N | Route Freq. Duration | Serum TFV $C_{max}$ ng/mL | Serum TFV $C_{tau}$ ng/mL | PBMC TFV-DP $C_{max}$ fmol/M | Tissue TFV ng/mg | Tissue TFV-DP fmol/mg | ECC TFV-DP fmol/M | CVL TFV ng/mL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **MTN-001 (vaginal dosing)** | **-** | **no** | **144** | **V,qd,ss** | **3.7** | **0.6** | **BLQ** | **113** | **$2.3x10^3$** | **$3.3x10^3$** | **$7x10^6$** |
| CAPRISA 004 *Lancet 2010* | - | no | 57 | V,cd,ss | <0.25* | <0.25* | | | | | $5x10^2$ |
| CONRAD TFV Gel 2008 | - | no | 49 | V,qdx14 | 3.4 | 0.3 | | 29 | $2.5x10^4$ | $1.9x10^5$ | $1.8x10^6$ |
| HPTN 050 *AIDS 2006* | - | no | 50 | V,qdx14 | 3 | <3 | | | | | |
| **MTN-001 (oral dosing)** | **-** | **no** | **144** | **O,qd,ss** | **332** | **65** | **52** | **0.2** | **<17** | **118** | **$1x10^4$** |
| iPrEX *NEJM 2010* | - | FTC | 35 | O,qd,ss | 140** | 140** | <5 | | | | |
| CDC Botswana | - | FTC | 18 | O,qd,ss | 223 | 53 | 51 | | | | |
| Barditch-Crovo *AAC 2001* | + | no | 9 | O,qd,ss | 302-375 | 48 | | | | | |
| King *J Chromatog B 2006* | + | yes | 17 | O,qd,ss | | | 69 | | | | |
| Hawkins *JAIDS 2005* | + | yes | 8 | O,qd,ss | | | 90 | | | | |
| Pruvost *J Mass Spectr 2008* | + | yes | 13 | O,qd,ss | | | 165 | | | | |

*Prior coitally-related dose 4-5 days
**Random sample

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# Adverse Events*

- No differences in overall AEs among regimens
- Nausea, diarrhea, headache more common with oral & dual dosing (all <15%)
- Genital symptoms not different by regimen
  - Vaginal 21%, Dual 21%, Oral 18%
- Hypophosphatemia – most common lab AE, transient
  - Vaginal 11%, Dual 15%, Oral 15%
- 17 Grade 3 or 4 AEs
  - 9 hypophosphatemia (4 oral, 2 vaginal, 3 dual)
  - Migraine (only Gr. 4), hives, malaria, procedure, weight loss (2), anemia (2)

*Based on 168 randomized participants, not only 144 evaluable.

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