

# A Multi-Compartment, Single and Multiple Dose Pharmacokinetic Study of the Vaginal Candidate Microbicide 1% Tenofovir Gel

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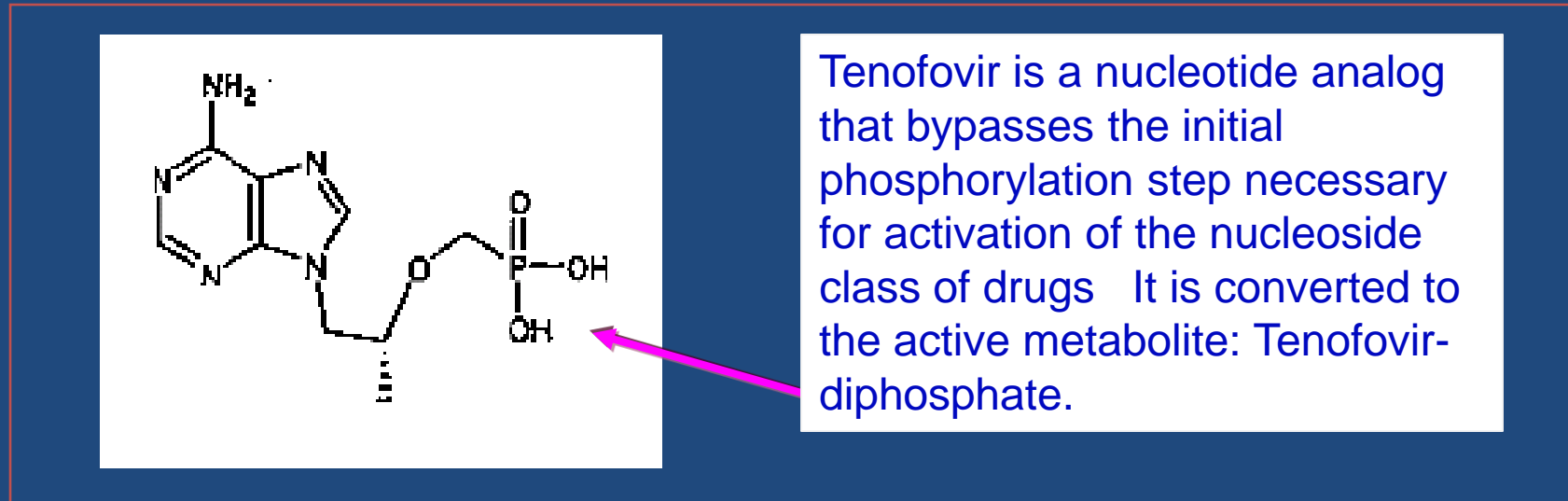
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## Introduction

Tenofovir (TFV) gel is being evaluated as a microbicide in two HIV prevention studies with pericoital and daily regimens. To inhibit viral replication locally, adequate levels in the genital tract is critical, however the window of protection afforded by vaginal application and the ideal dosing strategy has yet to be fully determined.

Figure 1. Tenofovir



## Materials and Methods

This multi-center study recruited 49 women at three sites for a single-dose (4ml) of TFV gel followed by two weeks of once or twice-daily dosing. A subset of participants at one of the three sites (Pittsburgh) who completed the first two phases of the study was asked to participate in a third phase with sample collection at 12 hours after an additional single dose.

### Objective

- To assess local and systemic absorption and concentration of TFV after a single dose and after 14 days of once or twice-daily dosing.

### Endpoints

- TFV concentration after single TFV gel vaginal dose and after two weeks of once or twice-daily dosing in the local genital tract compartment [cervicovaginal fluid (CVF), endocervical cells (ECC) and vaginal tissue].
- Cmax and Tmax of TFV after single TFV gel vaginal dose and after two weeks of once or twice-daily dosing in the systemic compartment.

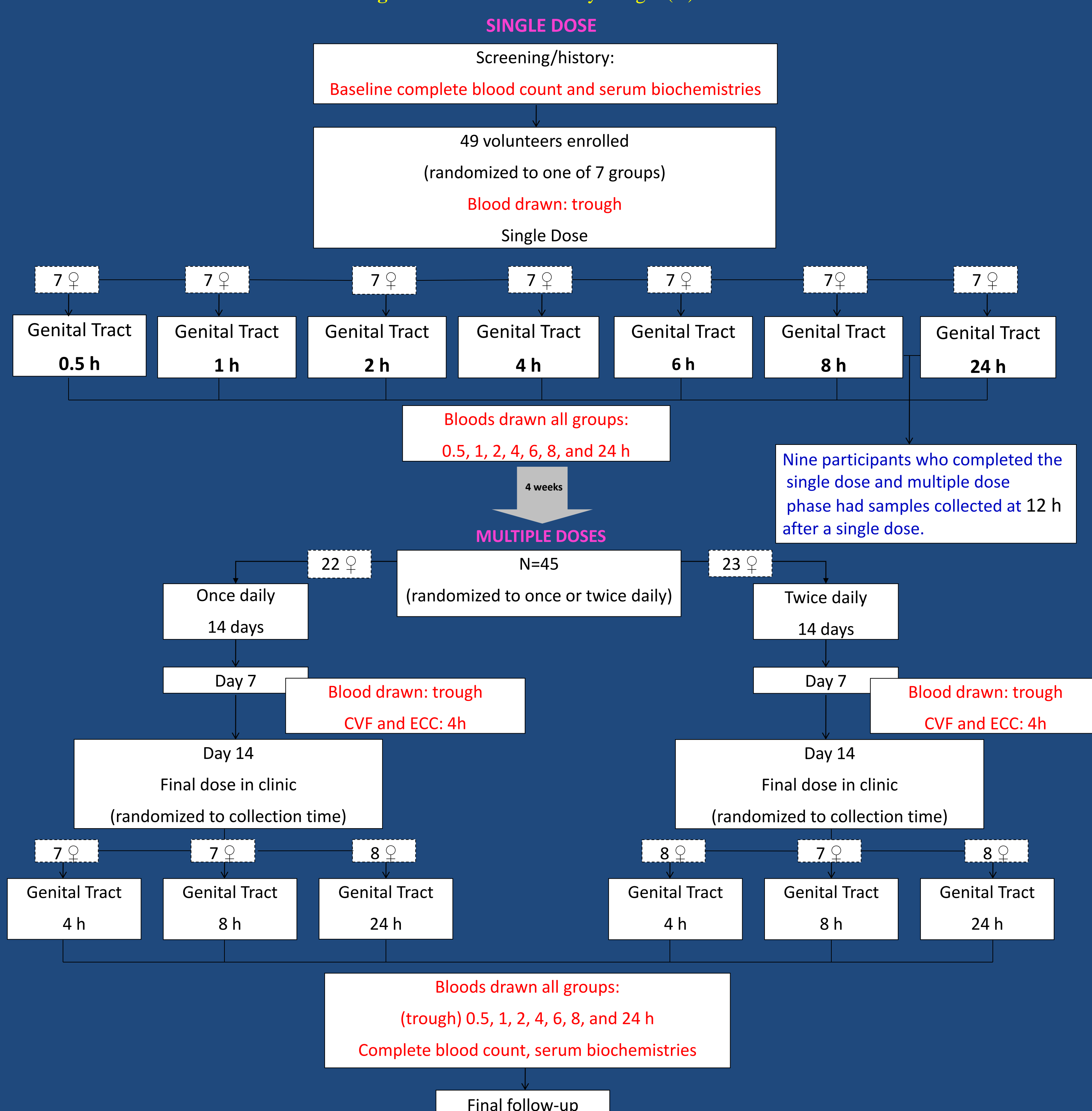
### Design

- Multiple sites (University of Pittsburgh, PA; Advances in Health, TX; PROFAMILIA, Dominican Republic).
- Study Visits: Screening; Enrollment (single dose phase); Multiple Dose Initial Visit; One week FU; Two week FU; third phase (Pittsburgh); Final Visit.

### Procedures

- Participants were randomized to 0.5, 1, 2, 4, 6, 8, or 24 hr after single dose (SD) and to 4, 8 or 24 hr after multiple doses (MD) for collection of genital tract specimens (CVF, ECC, and vaginal biopsies).
- Blood was drawn at all seven times after SD and MD.
- TFV was measured in peripheral blood plasma (BP), CVF and vaginal tissue.
- The active metabolite [TFV-diphosphate (DP)] was measured in ECC and vaginal tissue using LC/MS.

Figure 2. Tenofovir PK study design. (N)=49



## Results

Table 1. Demographic Characteristics (N=49)

Median Age (range)	35 (20-45)
Ethnicity	
Hispanic/ Latina	26 (53%)
Race	
Black	17 (35%)
White	10 (20%)
More than one race	22 (45%)
Mean Body Mass Index (SD)	30 (6.9)

Table 2. Related Adverse Events

Seventeen of 48 (35%) women reported 59 adverse events that were at least possibly related.

System Organ Class/Preferred Term	N=48		
	No. events	No. women	% of Women
<b>Gastrointestinal Disorders</b>			
Nausea	2	2	4.2
Abdominal Pain	1	1	2.1
<b>Reproductive System and Breast D/O</b>			
Metrorrhagia	9	6	12.5
Pruritus Genital	25	6	12.5
Vaginal Discharge	5	4	8.3
Vaginal Burning Sensation	3	3	6.3
Vaginal Odour	6	3	6.3
Vulvovaginal Discomfort	3	3	6.3
Genital Erosion	1	1	2.1
Vaginal Candidiasis	1	1	2.1
<b>Skin and Tissue D/O</b>			
Rash Papular	1	1	2.1
Skin Irritation	1	1	2.1
Skin Odour	1	1	2.1
TOTAL	59	17	35.4

Table 3. Median (IQR) Pharmacokinetic Parameters

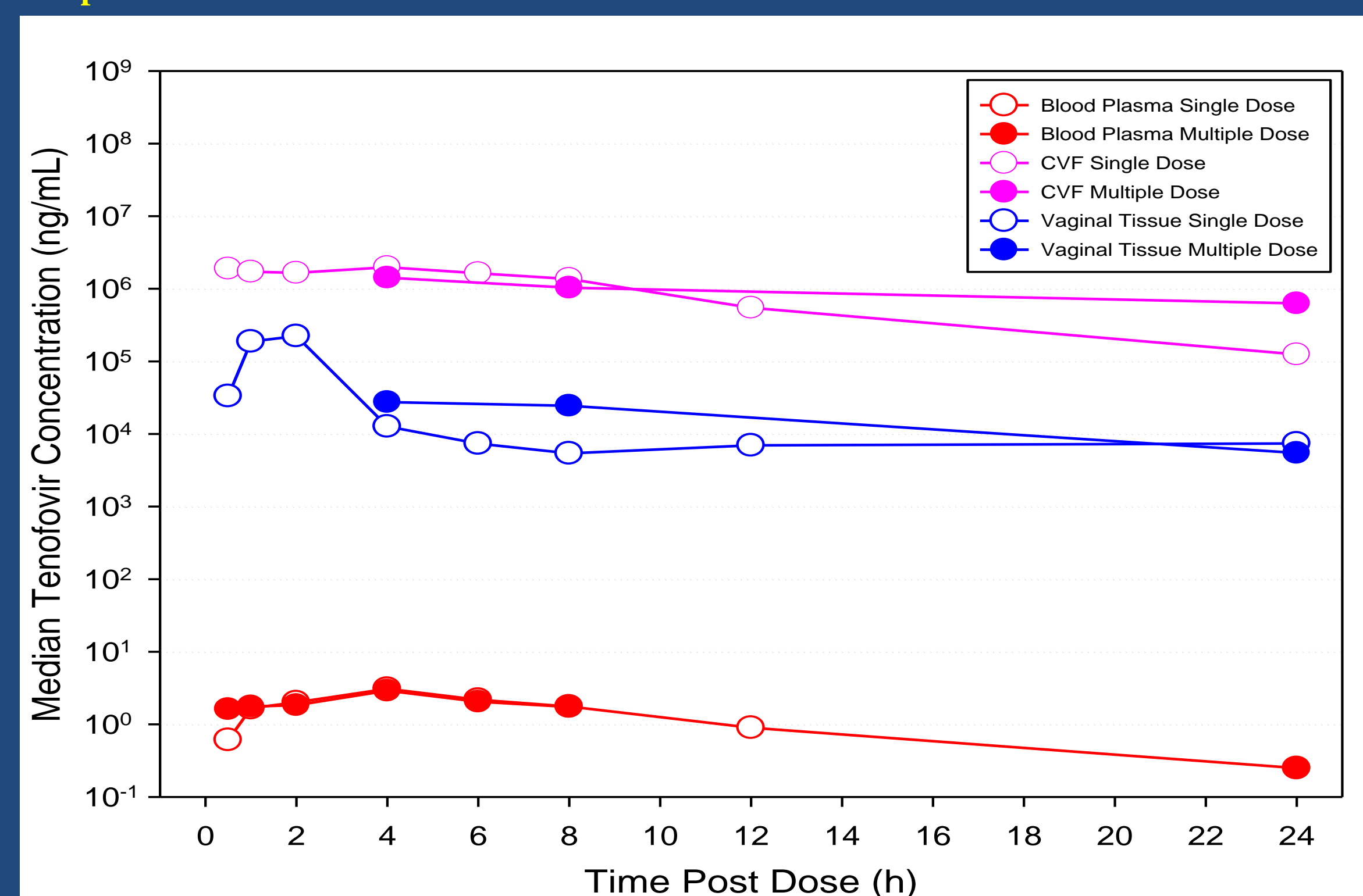
Analyte, Matrix, Dose Frequency	Cmax (ng/mL)	Tmax (hr)	AUC <sub>24h</sub> (hr*ng/mL)	C <sub>24h</sub> (ng/mL)
TFV BP SD	4.0 (1.5-9.1)	4 (2-6)	36.4 (13.5-69.6)	0.3 (0.3-0.5)
TFV BP MD	3.4 (2.4-6.1)	4 (2-6)	37.2 (24.6-62.6)	0.3 (0.3-0.6)
TFV CVF SD <sup>1</sup>	1.9 x 10 <sup>6</sup>	4	18.6 x 10 <sup>6</sup>	0.1 x 10 <sup>6</sup>
TFV CVF MD <sup>1</sup>	1.4 x 10 <sup>6</sup>	4	18.2 x 10 <sup>6</sup>	0.6 x 10 <sup>6</sup>
TFV Vaginal Tissue SD	2.2 x 10 <sup>5</sup>	2	6.1 x 10 <sup>5</sup>	7.4 x 10 <sup>3</sup>
TFV Vaginal Tissue MD	2.7 x 10 <sup>4</sup>	4	2.9 x 10 <sup>5</sup>	5.5 x 10 <sup>3</sup>
TFV-DP ECC SD <sup>1,2</sup>	33.6 x 10 <sup>4</sup>	4	259.9 x 10 <sup>4</sup>	3.5 x 10 <sup>4</sup>
TFV-DP ECC MD <sup>1,2</sup>	16.2 x 10 <sup>4</sup>	8	205.1 x 10 <sup>4</sup>	3.1 x 10 <sup>4</sup>
TFV-DP Vaginal Tissue SD <sup>3</sup>	1.8 x 10 <sup>3</sup>	1	4.3 x 10 <sup>3</sup>	n/a
TFV-DP Vaginal Tissue MD <sup>3</sup>	1.5 x 10 <sup>3</sup>	8	2.1 x 10 <sup>4</sup>	5.8 x 10 <sup>2</sup>

<sup>1</sup>Estimated from 4, 8 & 24 hour samples

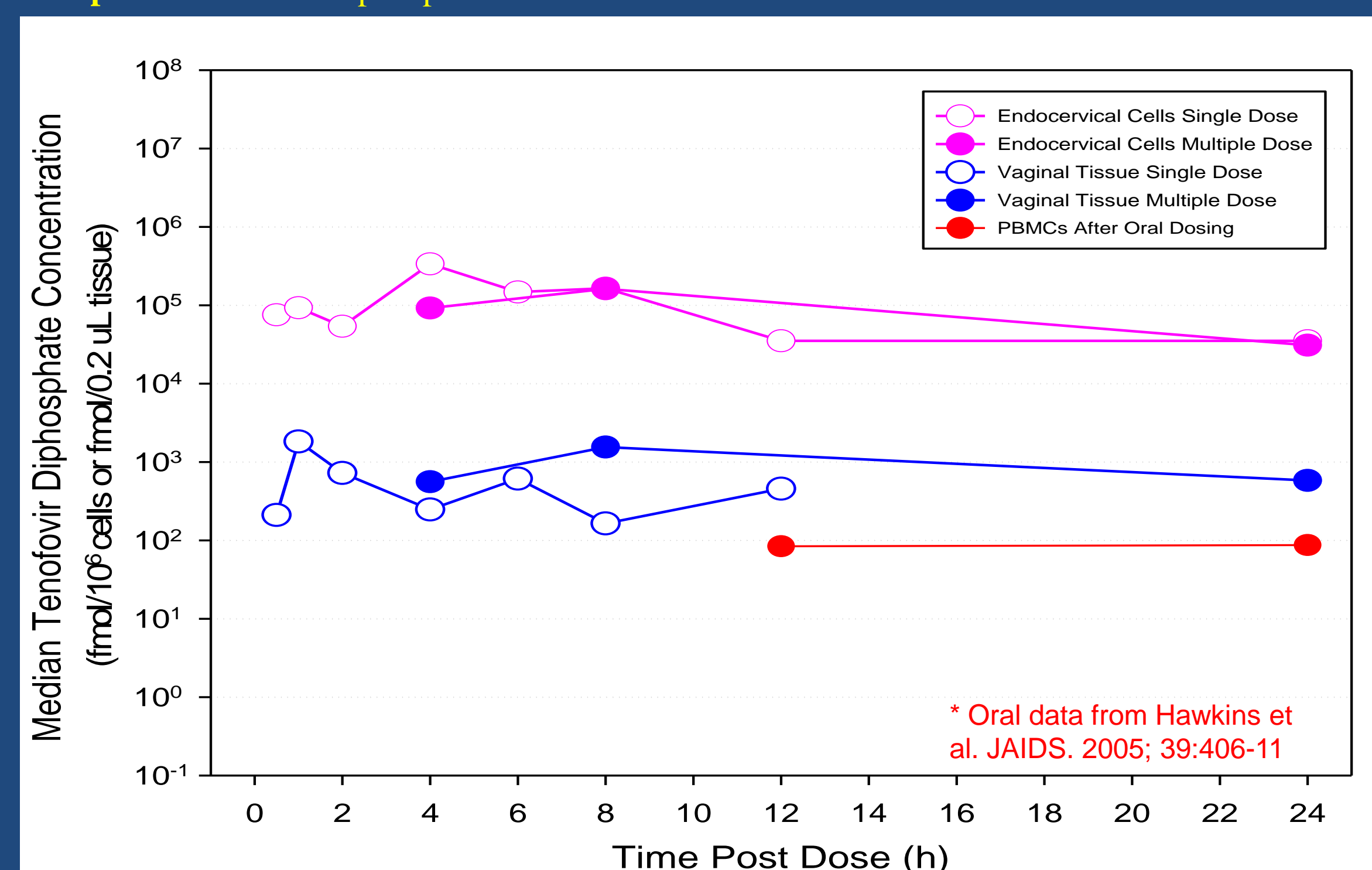
<sup>2</sup>Cmax and C<sub>24h</sub> in fmol/10<sup>6</sup> cells; AUC<sub>24h</sub> in hr\*fmol/10<sup>6</sup> cells

<sup>3</sup>Cmax and C<sub>24h</sub> in fmol/0.2 uL; AUC<sub>24h</sub> in hr\* fmol/0.2 uL

Graph 1. Tenofovir Pharmacokinetics



Graph 2. Tenofovir Diphosphate Pharmacokinetics



For Graphs 1 & 2: Vaginal Tissue Single Dose data available from this preliminary tissue analysis consist of 36 samples (including 9 from the 12 hr time point) which were analyzed for TFV and TFV-DP. Twenty-one samples analyzed in the interim analysis are excluded from these graphs because a novel diphosphate method was developed and the initial data is not comparable. Available Vaginal Tissue Multiple Dose data consist of 45 samples which were analyzed for TFV and TFV-DP.

For Graph 2: 15/36 (42%) single dose samples and 17/45 (38%) multiple dose samples had TFV-DP concentrations above the limit of detection (4.5fmol/0.2uL). Only those with measurable levels are represented on this graph.

## Conclusions

TFV exposure was low in blood plasma (1 to <15% of the levels following 300 mg oral exposure with Tenofovir disoproxil fumarate) and high in cervical vaginal fluid up to 24 hours following single and multiple dose vaginal exposure.

TFV-DP concentrations were high in endocervical cells up to 24 hours following single and multiple dose vaginal exposure.

TFV-DP was detectable in about 40% of the vaginal tissue biopsy samples at exposures similar to, or up to 2 logs greater than what is seen in peripheral blood mononuclear cells after oral exposure.

Results show that single dose and multiple dose TFV gel exposure lead to high genital tract levels up to 24 hours post dose and support further study of pericoital and once-daily dosing of TFV gel as potential strategies.

## Acknowledgments

- This poster was made possible through support provided by the U.S. Agency for International Development, under the terms of Award Number GPO-A-00-05-00041-00. The opinions expressed do not necessarily reflect the views of the U.S. Agency for International Development.
- The Tenofovir gel for this study was donated by Gilead Sciences.
- The analytical expertise of Nicole White and Eric Kraft from the UNC CFAR Clinical Pharmacology and Analytical Chemistry Laboratory in generating plasma, cervicovaginal, and tissue data is greatly appreciated.
- The clinical monitoring of this study by Susan Ju and the assistance with the preparation of this poster by Lamia Khiali are greatly appreciated.