Development of a Tenofovir Disoproxil Fumarate IVR for Prevention of HIV & HSV

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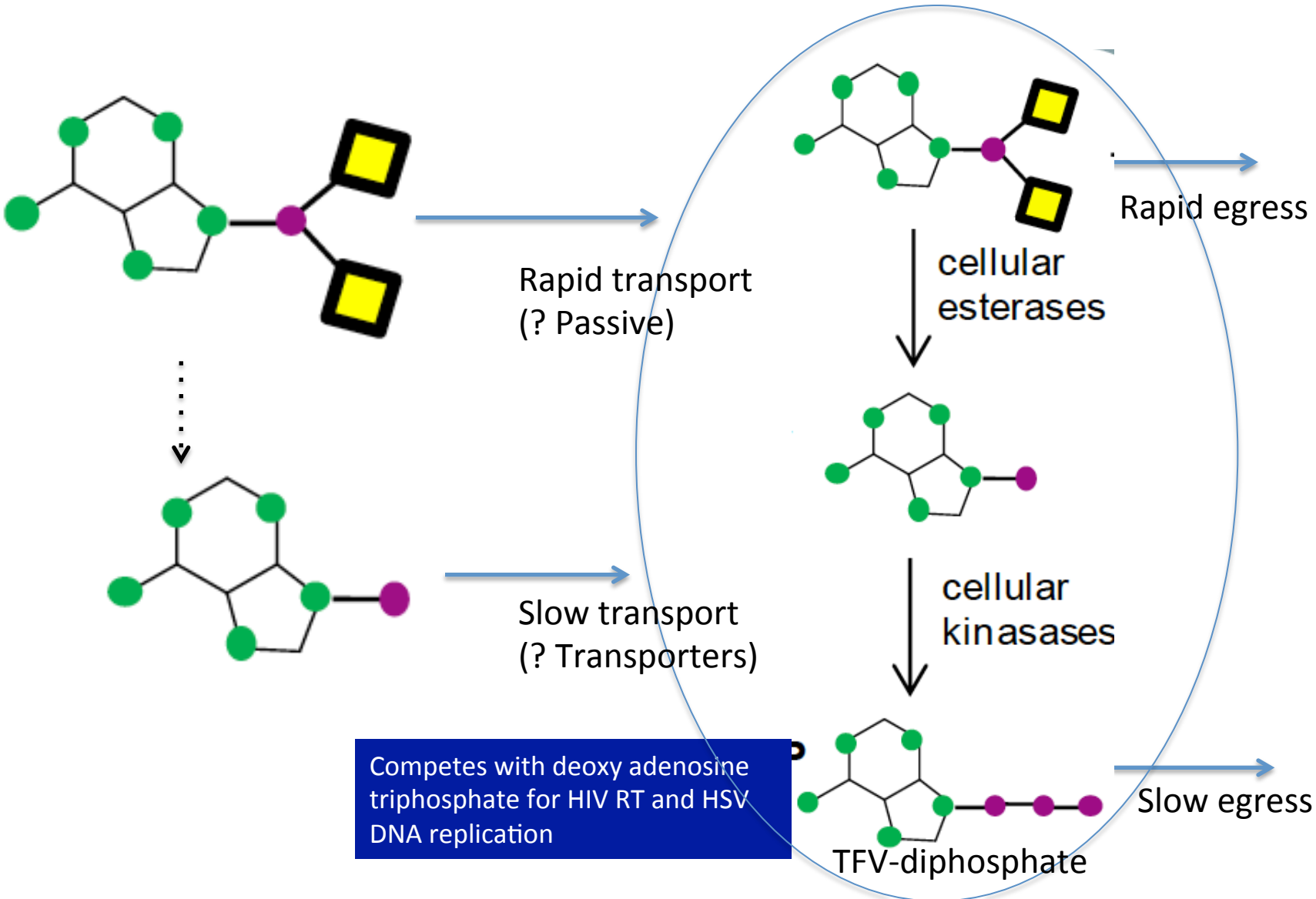
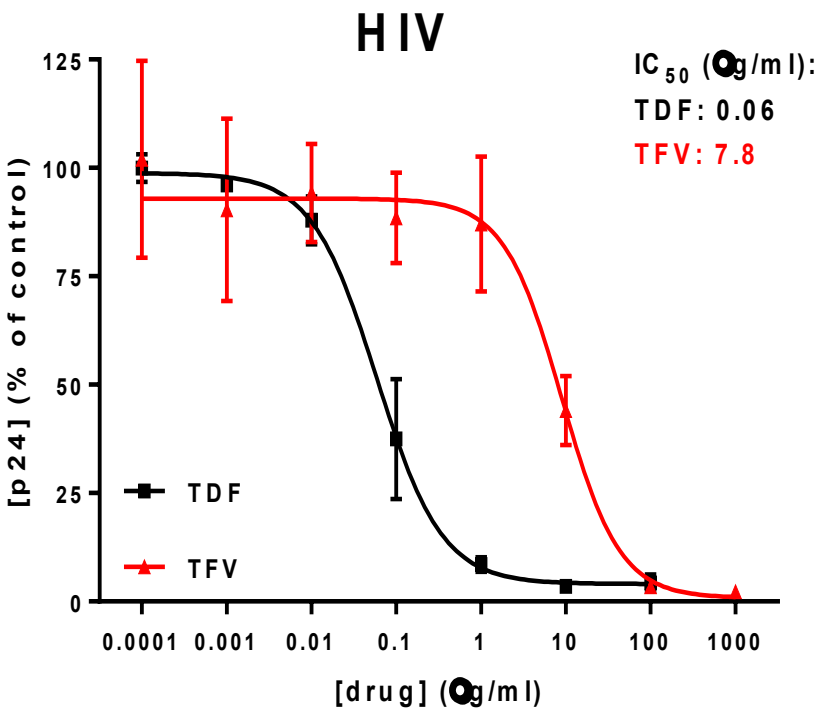
Overview

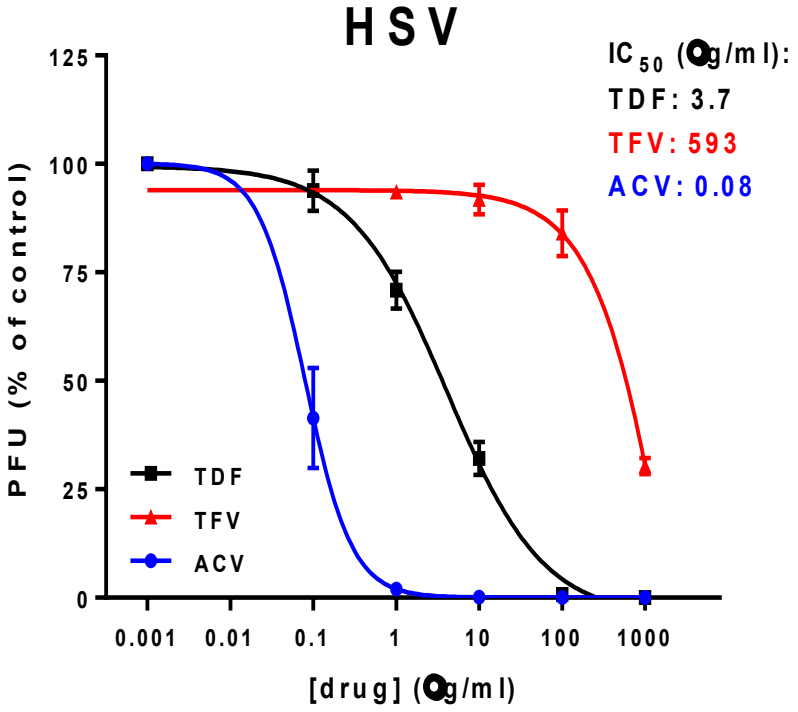
- Why tenofovir disoproxil fumarate (TDF)?
  - In vitro and animal model data
- Why IVR design?
- Phase 1 single site PK/safety study initiated December, 2013
  - Albert Einstein College of Medicine/Montefiore Medical Center
- Future directions

Tenofovir Disoproxil Fumarate vs. Tenofovir



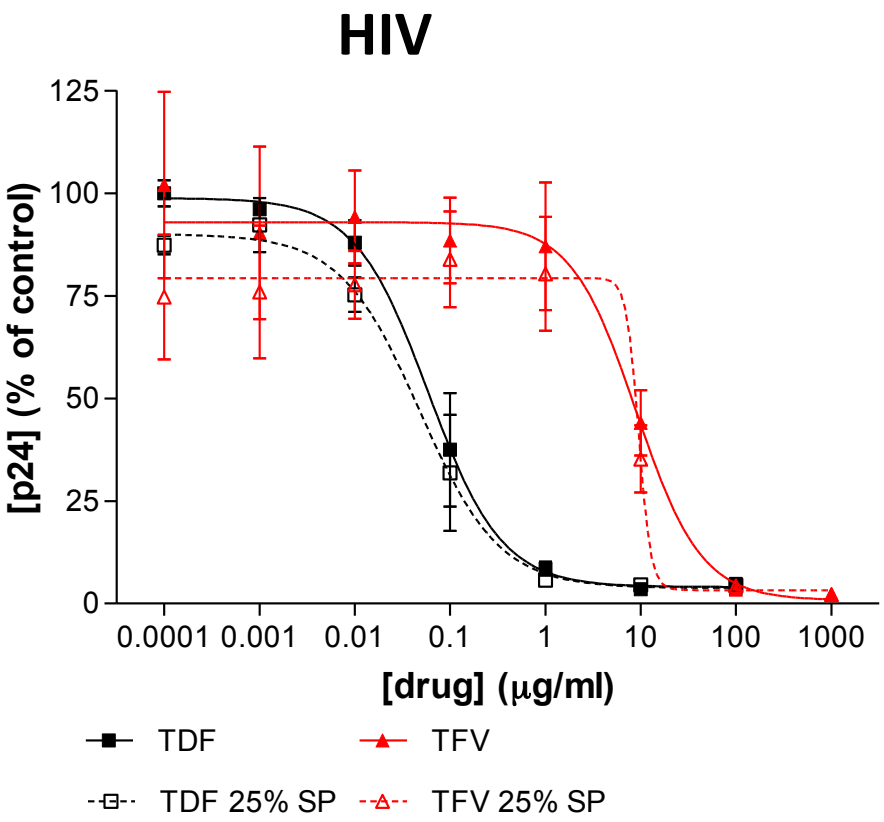
TDF more Potent than TFV against HIV & HSV-2

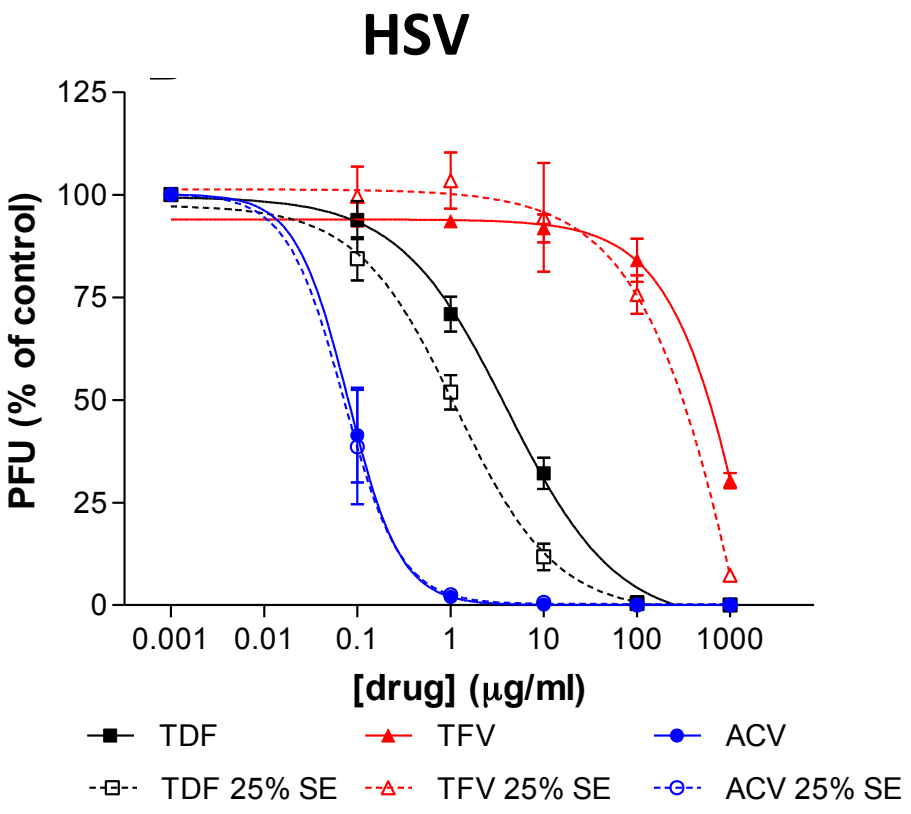




Mesquita, Rastogi et al; J Antimic Chemo, 2012

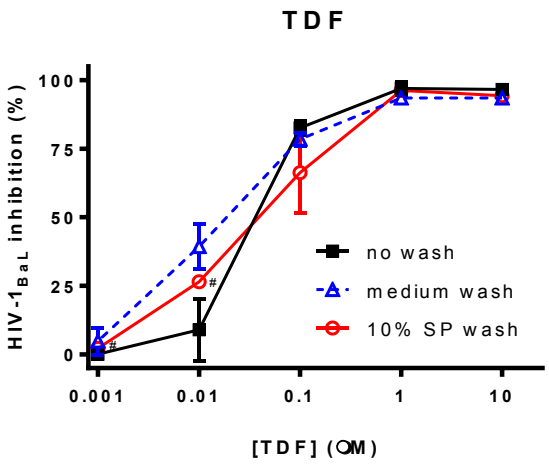
Retains Activity when Virus Introduced in Semen/Seminal Plasma

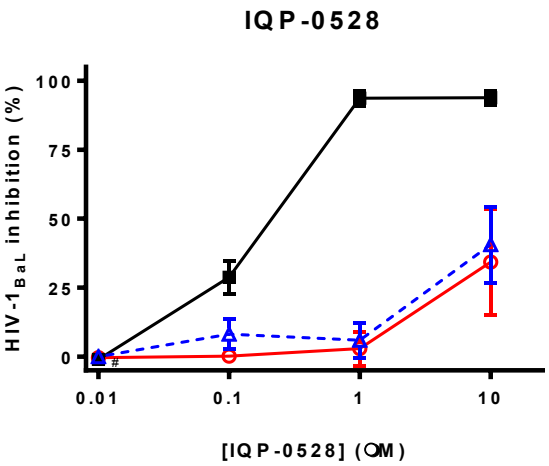


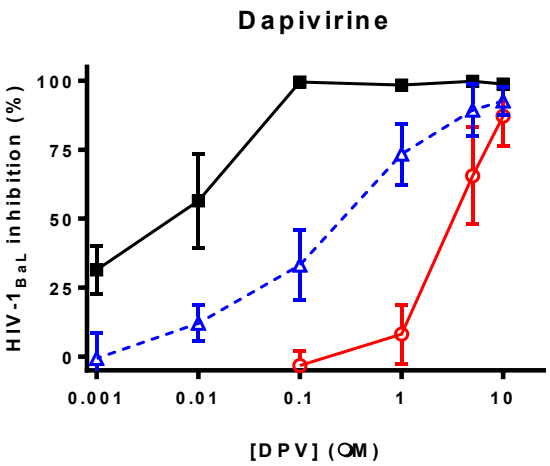


Mesquita, Rastogi et al; J Antimic Chemo, 2012

TDF Retains Activity following Washout



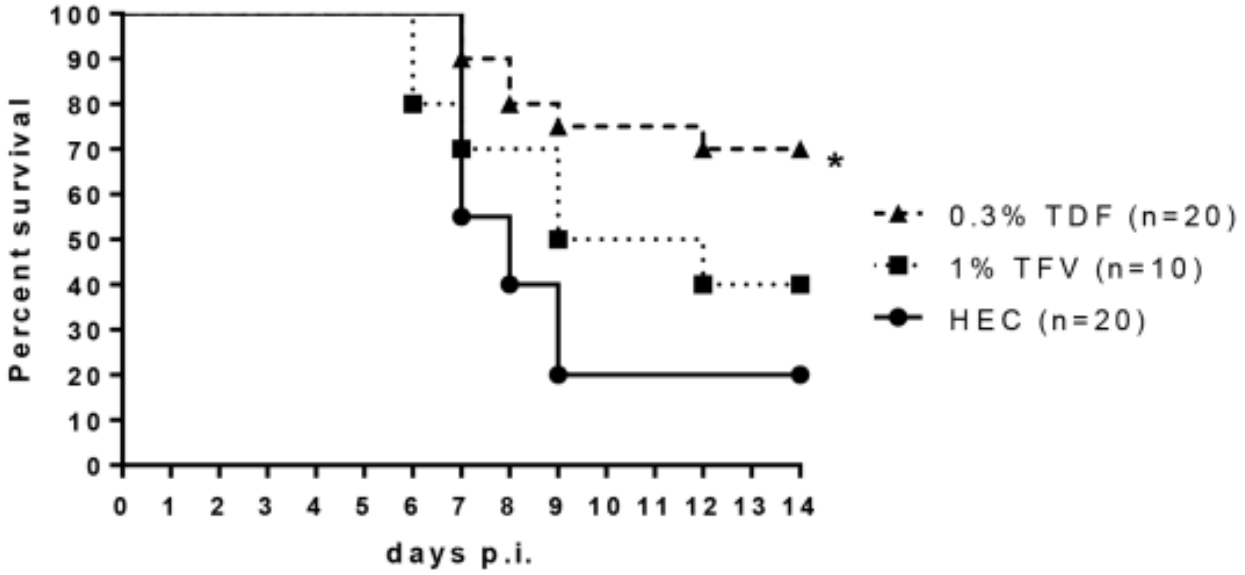




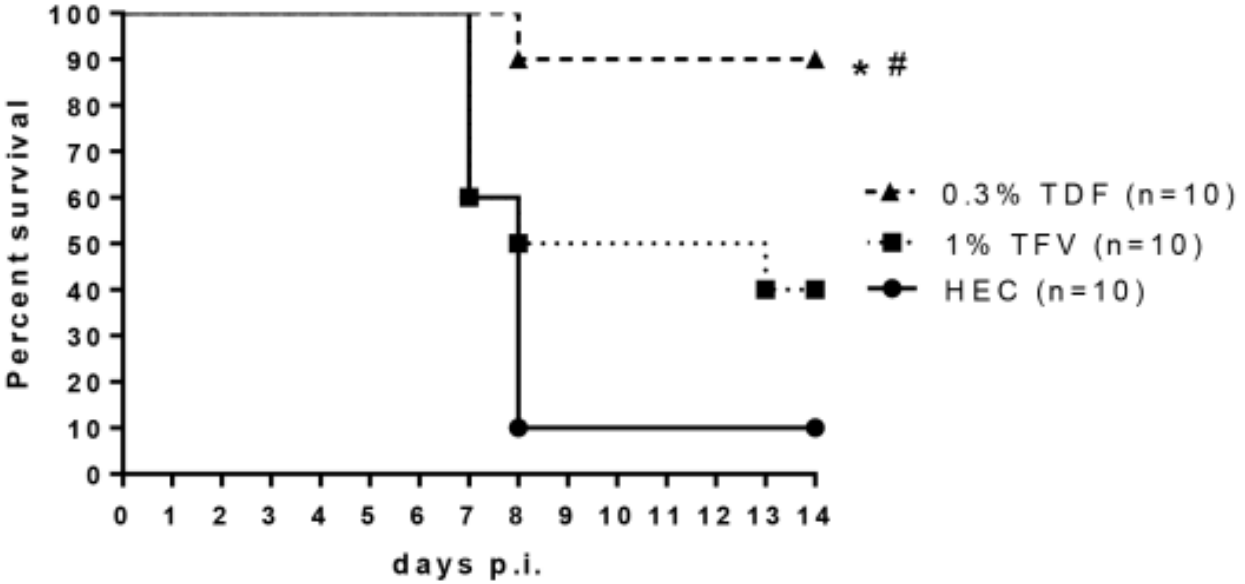
Mesquita, Retrovirology, 2013

TDF Provides Greater Protection than TFV against HSV-2 in Murine Model

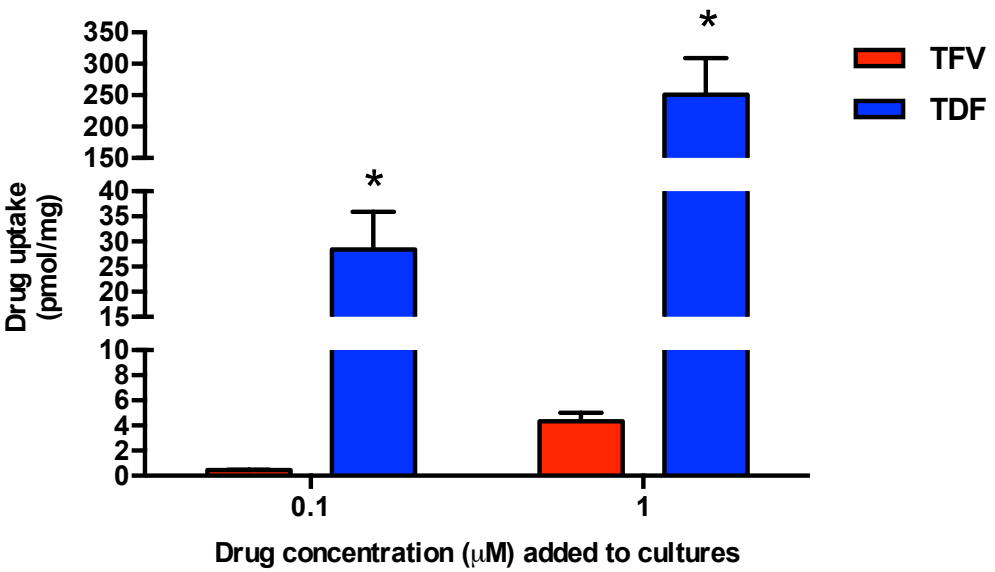
BAT24 Dosing



Daily Dosing



Increased protection with TDF reflects greater intracellular uptake



- No significant increase in inflammatory cytokines or chemokines in vaginal washes
- No change in cytokine, chemokine or mitochondrial gene expression in RNA extracted from genital tract tissue in mice treated with twice-daily 0.3% TDF gel
- No histological changes relative to HEC treated mice
- Ring eluants had no deleterious impact on epithelial barrier integrity in dual chamber model

Nixon et al, AAC, 2013

Why Intravaginal Rings (IVR)?

- Optimal delivery strategy for TDF
- Rings may overcome some of the difficulties with adherence
- Behavioral studies support IVR strategy with caveats:
  - Women may remove rings
    - To ascertain "that it is still there"
    - During menstruation
    - Possibly in association with sex
  - No behavioral acceptability data comparing 30 d vs. longer duration rings

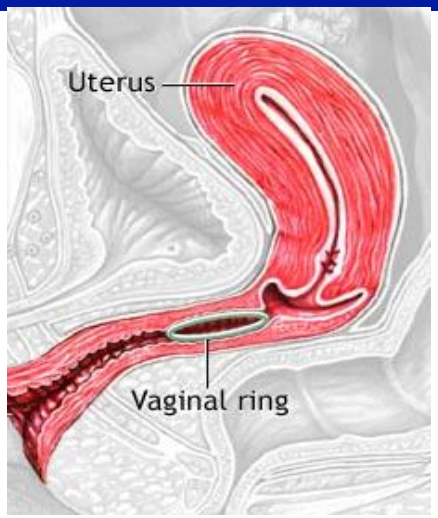
Intravaginal Rings for Sustained Delivery

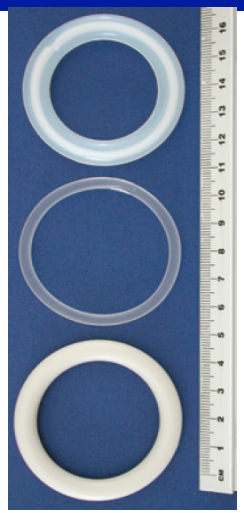
Dapivirine
MVC

Matrix

TFV
TDF

Reservoir





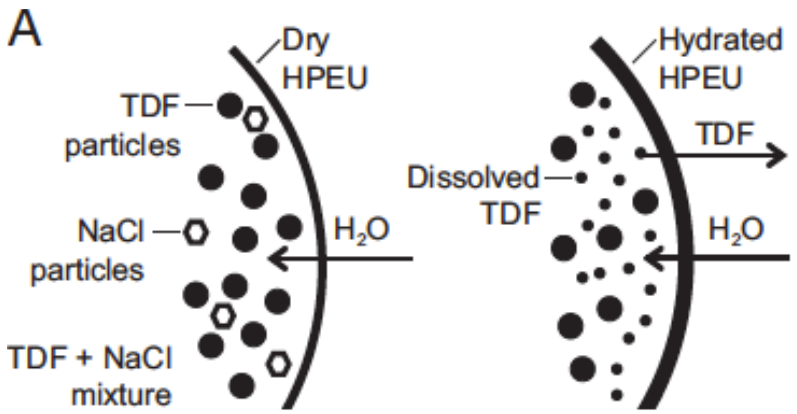
Estring
22 mL

Nuvaring
4.3 mL

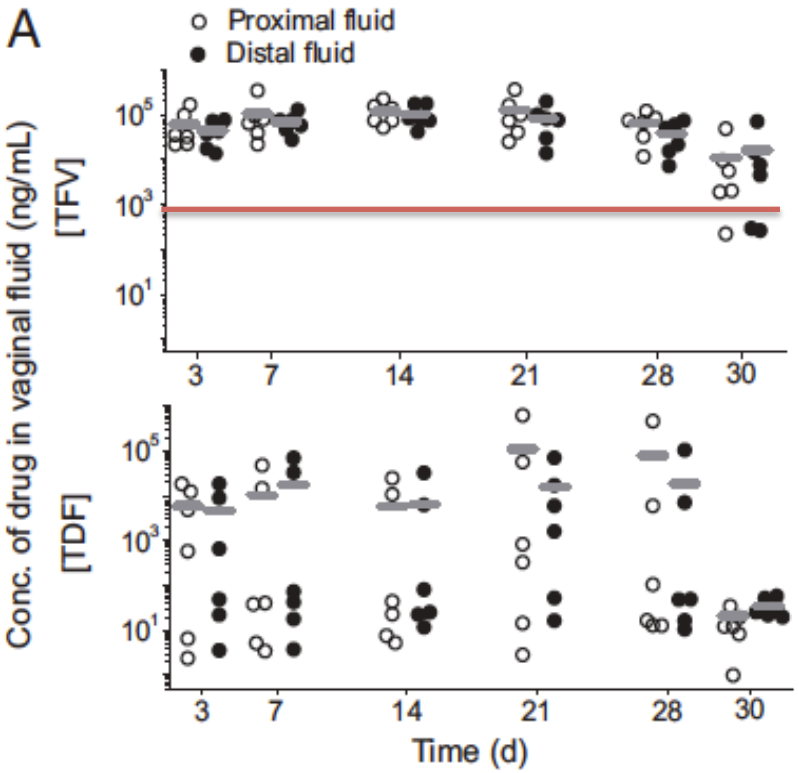
Femring
18 mL

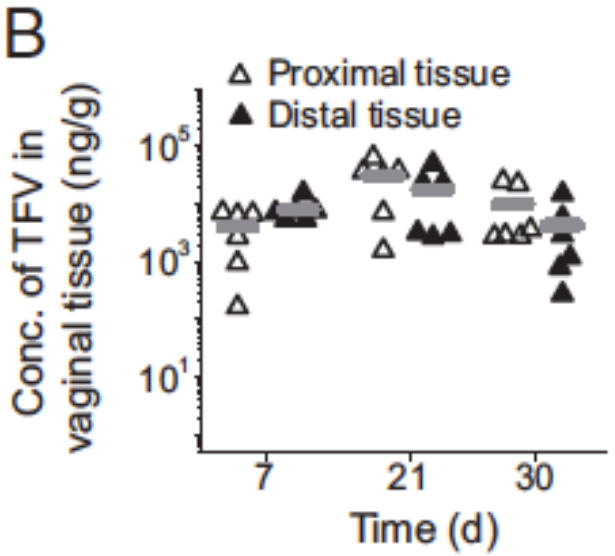
www.nlm.nih.gov
Malcolm, K. et al., *J. Antimicrob. Chemother.* 2005, 56: 954-6

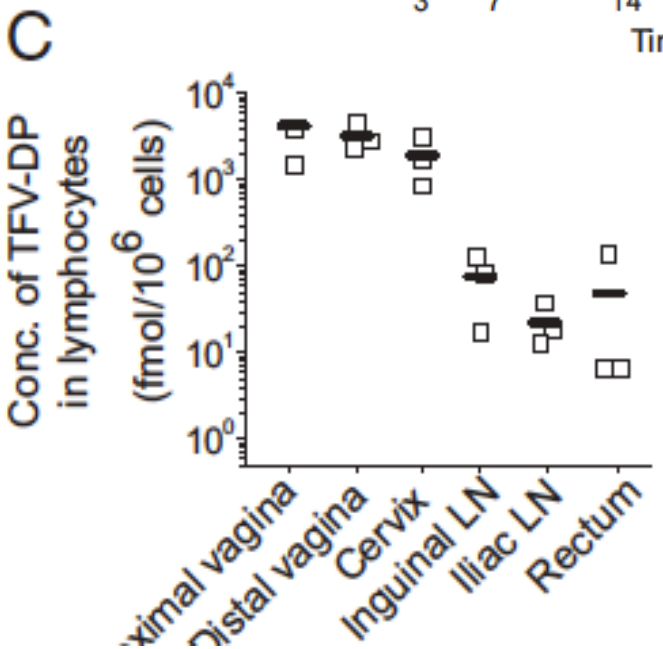
- Matrix devices exhibit drug release rates that decrease with time
- **Reservoir devices rate controlling membrane that allow for more consistent drug flux**
- **TDF reservoir IVR designed using polyurethane**
  - Vaginal fluid is driven into the core resulting in TDF elution;
  - NaCl aids in solubilizing drug in the core to drive release through wall



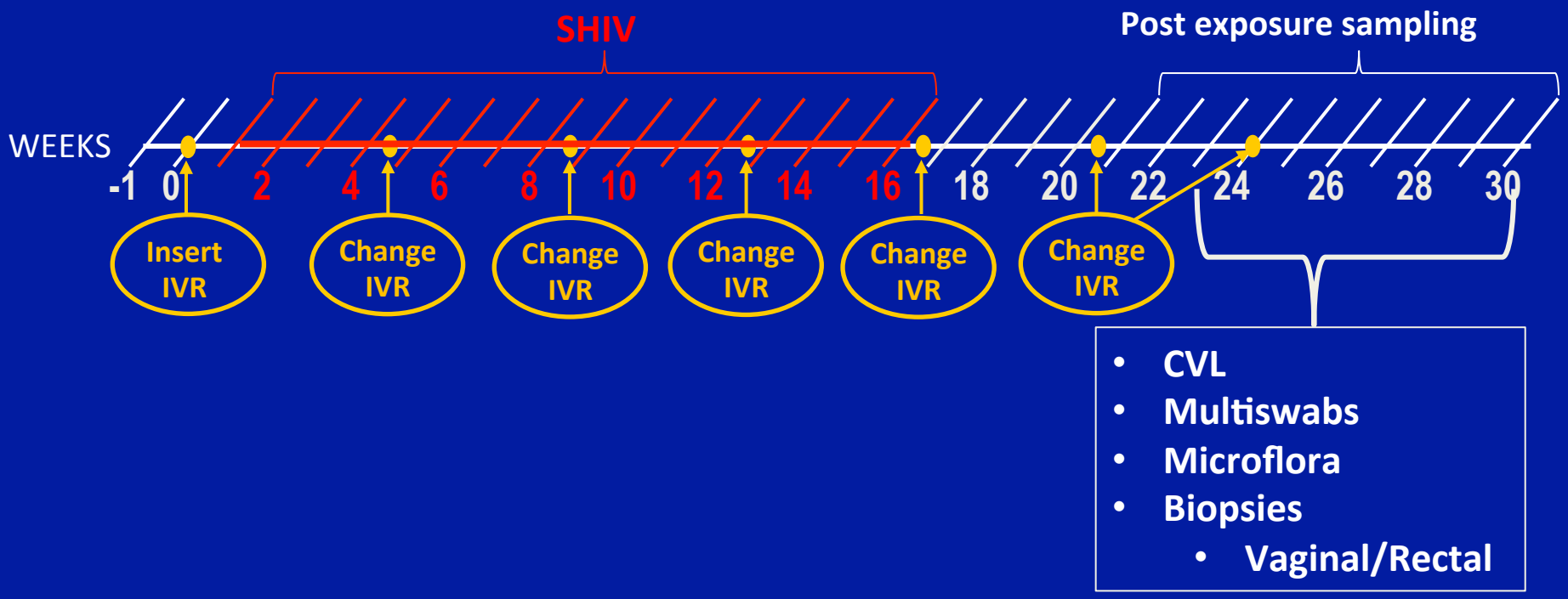
TDF/TFV in vaginal secretions and tissue in 28 d macaque study



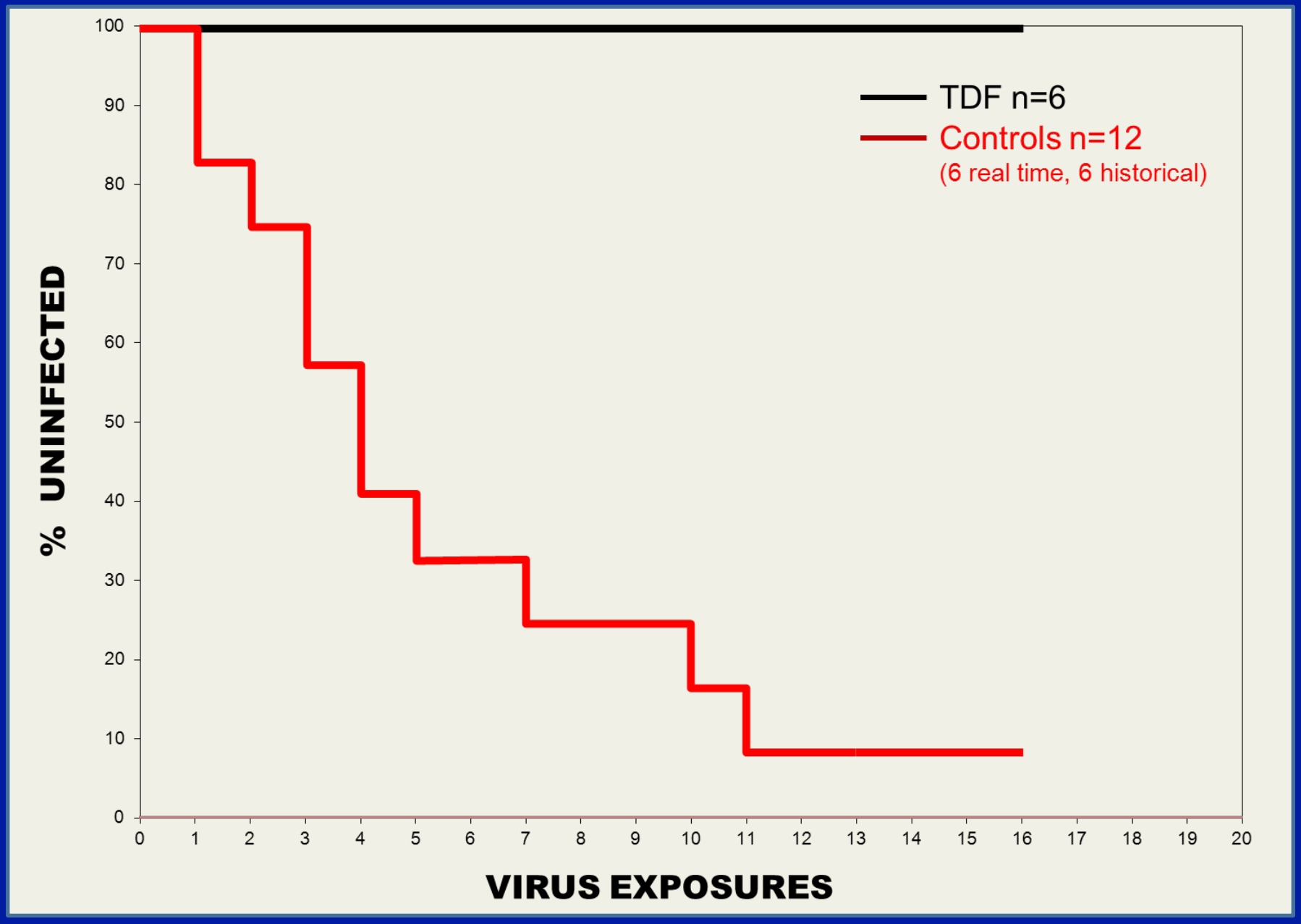




Efficacy Study in Macaques

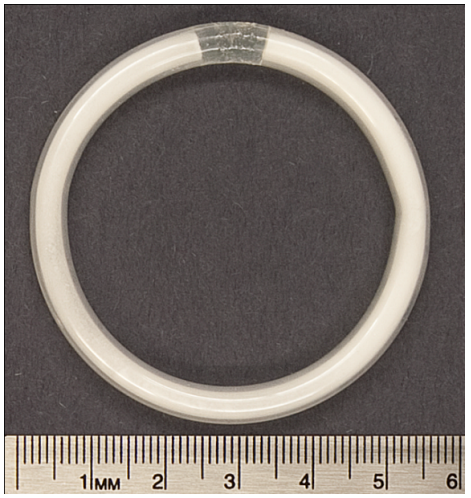


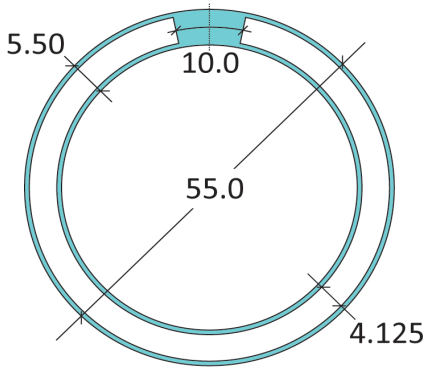
Smith et al, PNAS, 2013


TDF n=6
Controls n=12
(6 real time, 6 historical)
% UNINFECTED
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
VIRUS EXPOSURES

Target product profile

- **Human IVR design**
  - Reservoir polyurethane ring
  - HydroThane™ AL 25-93A (20 wt% swelling polymer)
    Advansource Biomaterials
  - IVR dimensions: 55 mm x 5.5 mm
  - Tubing wall thickness: 0.7 mm
  - Amount of core material:
    - TDF = 360±54 mg
    - NaCl = 60±9 mg
  - Release duration = 30 days
  - Average release rate = 5.5 ± 1.5 mg/day
  - Average F_{10} = 1.04 ± 0.08 N
    (force to compress 10%)



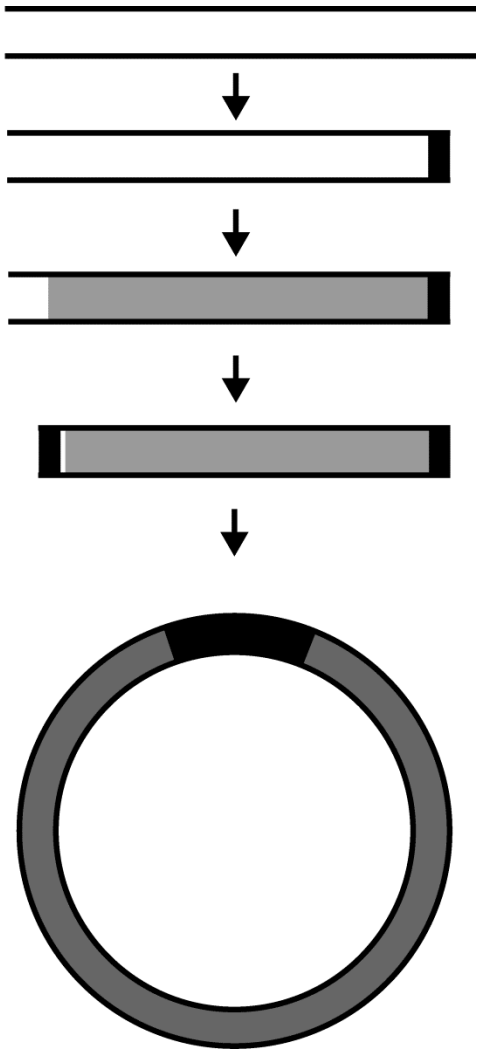


Dimensions in mm

IVR fabrication

- Steps involved
  1. Extrude tubing
  2. Cut tubing to 171 mm
  3. Seal 1st tubing end
  4. Fill tube with TDF/NaCl mixture
  5. Seal 2nd end of filled tube
  6. Weld sealed ends to make an IVR
  7. Anneal to get a circular shape
  8. Package
  9. Incubate at 65°C for 5 days for wall loading

Final device



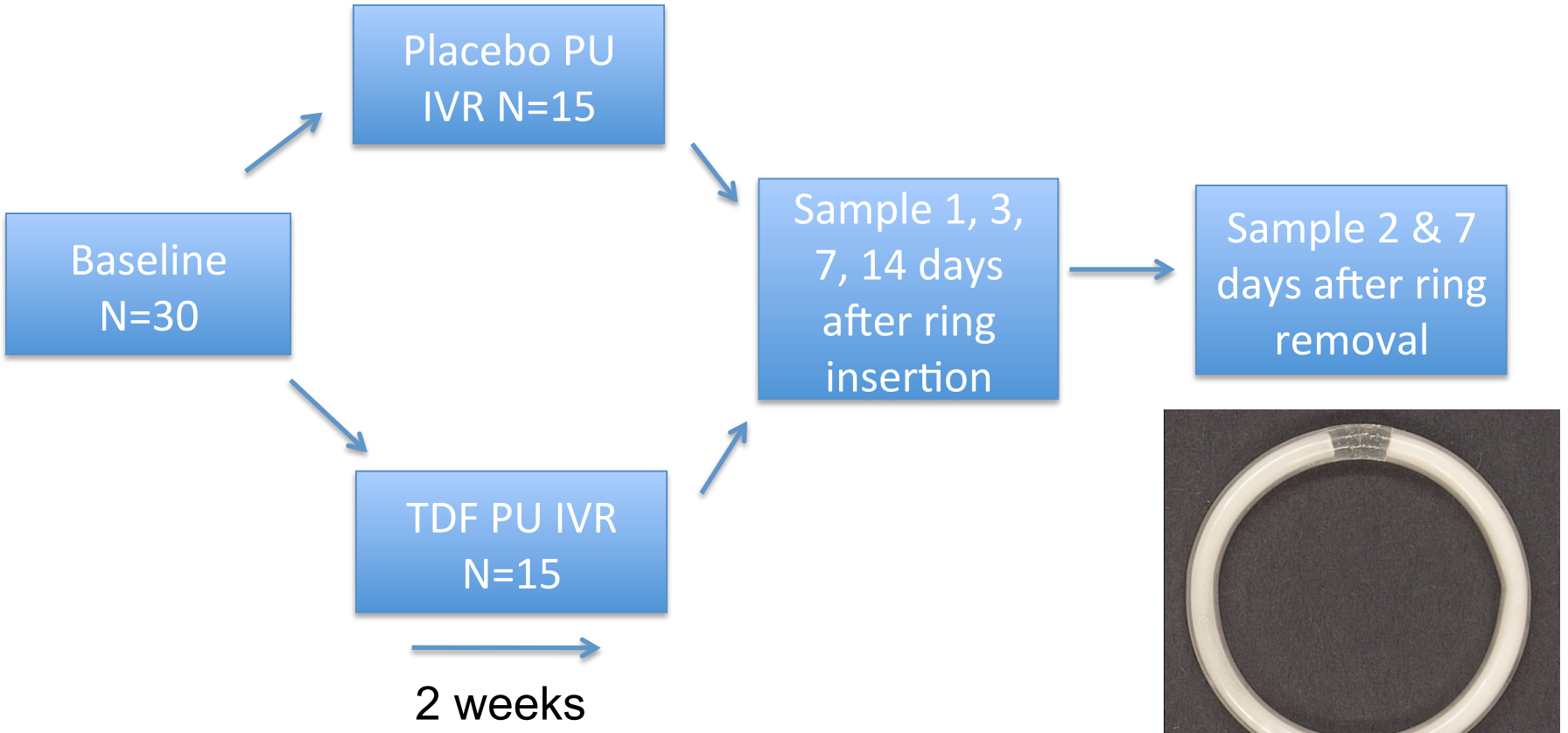
Phase 1 Trial

Randomized, Single-Site, Safety, Pharmacokinetic, and Acceptability Study of a Tenofovir Disoproxil Fumarate Reservoir and Placebo Polyurethane Intravaginal Ring

TDF IVR-001

IND 116 945

Study Design



Schema of Study Design

	Visit 1: Screen	Visit 2 Enrollment	Visit 3 D0	Visit 4 D1	Visit 5 D3-5	Visit 6: D7	Call D10	Visit 7 D14	Visit 8 D16-18	Visit 9 D21
			IVR Insertion →					IVR Removal		
Assessment AEs/Pelvic Exam	X	X*	X*	X	X	X		X*	X	X*
Blood, genital tract PK			X	X	X	X		X	X	X
Tissue PK/PD		X						X		

*Colposcopy

Exploratory outcomes: Drug levels using dried blood spots, PD in biopsies and fluid, mucosal immune mediators and microbiota

Proposed next steps

- Phase 1 study initiated in December with plan to complete by September 2014
  - Interim PK analysis in April/May
- If results (PK, safety, acceptability) favorable, propose Phase 2 expanded PK/safety study:
  - Focus on young (18-25) US and African sexual active women
  - 6 months of ring use
  - Primary endpoints: PK, safety, adherence
  - Exploratory endpoints: PD, HSV shedding, mucosal immunity including microbiome