



ART for Prevention: The Next Generation

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HPTN Domestic WG Retreat

3/4/10

HIV PREVENTION 2010

DECREASE SOURCE OF INFECTION

- Barrier protection
- Blood screening
- IDU harm reduction
- Antiretroviral Therapy
 - PMTCT
 - Rx infected partners
- STI Treatment

DECREASE HOST SUSCEPTIBILITY

- Barrier protection
- Infection Control
- Circumcision
- PEP
- Oral PREP
- Topical Microbicides
- Vaccines
- STI Treatment

ALTER BEHAVIOR

- Condom and HIV testing promotion
- Individual interventions
- Couples interventions
- Community-based interventions
- Structural interventions (e.g., economic)

PrEP Clinical Trials: 2010

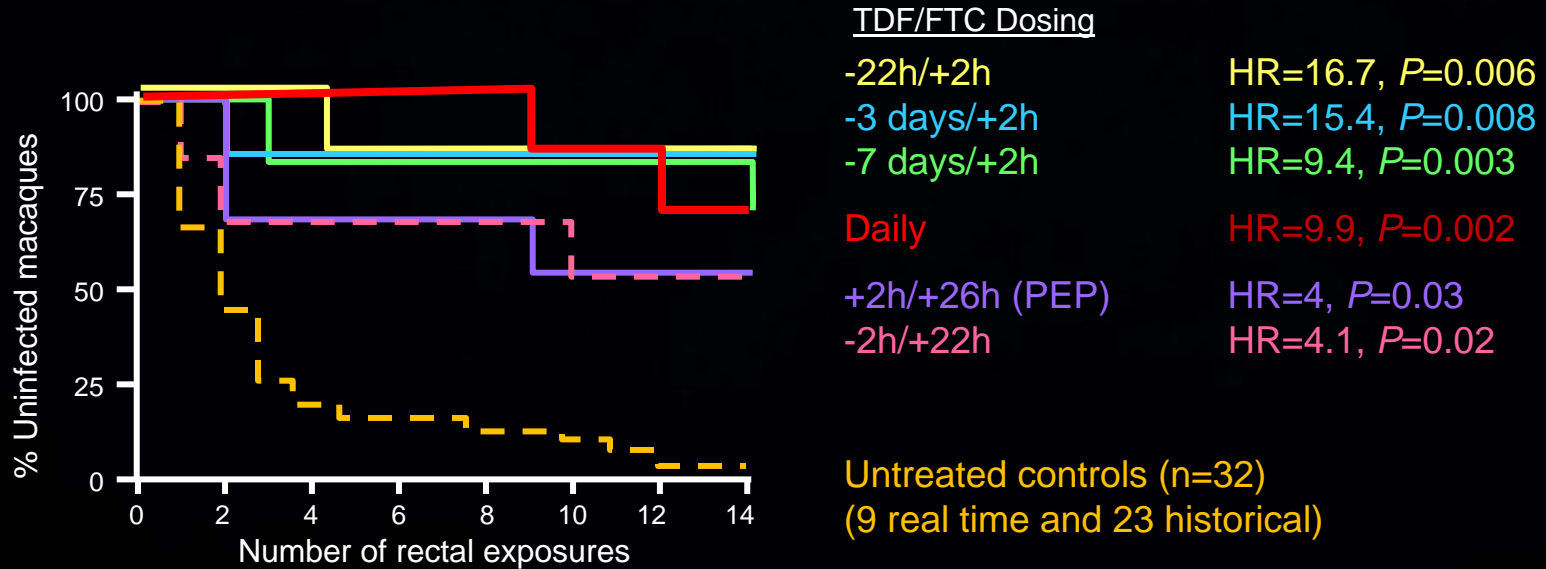
<u>Study Name</u> <u>Location</u>	<u>Funder</u>	<u>Population</u>	<u>Intervention</u>	<u>Results Available</u>
<u>CDC 4940</u> Botswana	CDC	1,200 Het. Men & Women	Daily Oral TDF, TDF/FTC	2010
<u>CDC 4323</u> USA	CDC	400 MSM	Daily Oral TDF	2010
<u>CDC 4370</u> Thailand	CDC	2400 IDU	Daily Oral TDF	2010
<u>CAPRISA 004</u> South Africa	USAID	900 women	Pre/Post Coital 1% TFV Gel	2010
<u>IPREX</u> Peru, Ecuador, Brazil, USA, Thailand, South Africa	NIH, BMGF	3,000 MSM	Daily Oral TDF/FTC	2010

PrEP Efficacy Trials: Beyond 2010

<u>Study Name</u> <u>Location</u>	<u>Funder</u>	<u>Population</u>	<u>Intervention</u>	<u>Results Available</u>
<u>Partners PREP</u> Kenya, Uganda	BMGF	3,900 Het. Discord. Couples	Daily Oral TDF	2012
<u>FEM PREP</u> Kenya, Malawi, South Africa, Tanzania, Zambia	USAID, BMGF	3,900 Women	Daily Oral TDF	2012
<u>Voice</u> South Africa, Uganda, Zambia, Zimbabwe	MTN/ NIH	5,000 Women	Daily Oral TDF, TDF/FTC, and Tenofovir Gel	2013

Intermittent PrEP/PEP in Macaques with TDF/FTC

- Animal model of rectal transmission of HIV
 - 6 groups challenged with physiologic inoculum of R5 virus (10 TCID₅₀)
 - 2 doses of TDF/FTC given before (-) or after (+) challenge



- Extended window of protection associated with long IC
- No drug resistance on macaques failing PrEP/PEP

Intermittent PrEP: 2/10

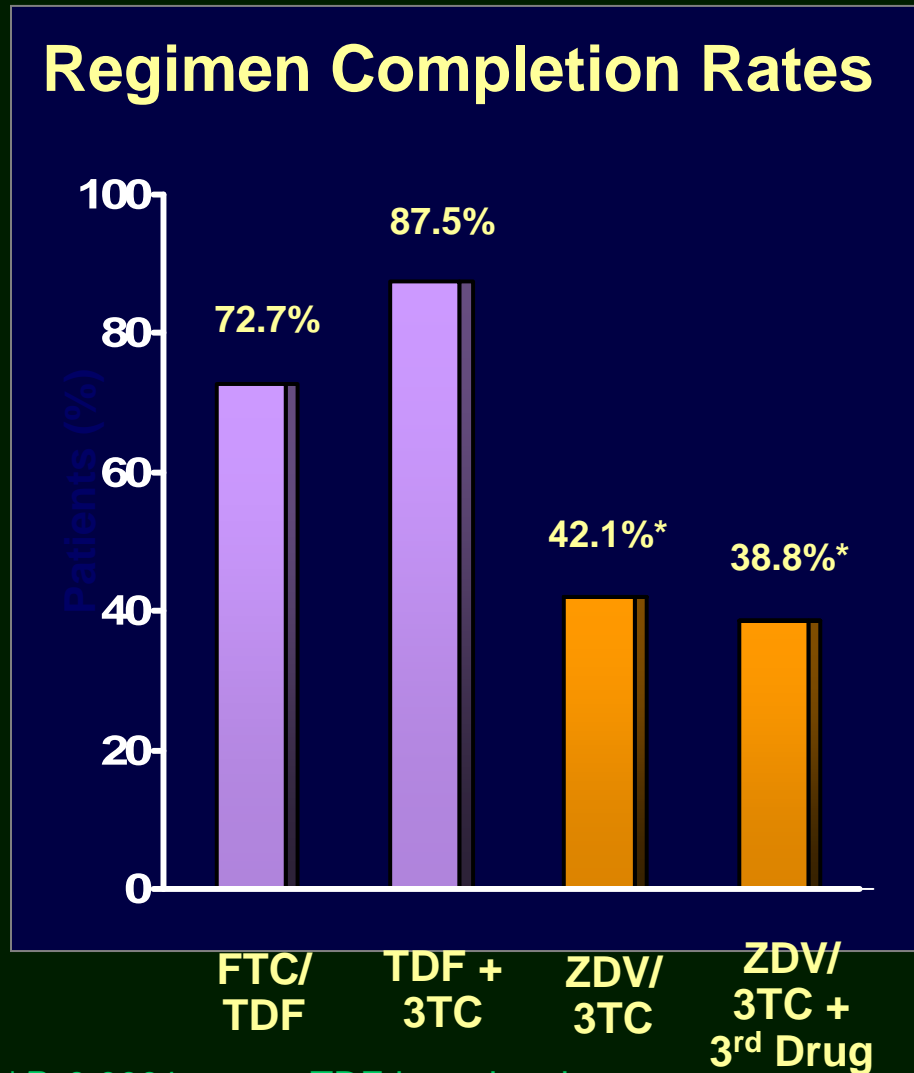
- **IAVI E001/002**: Discordant couples, MSM and FSW in Kenya and Uganda (N=150)
- **HPTN 066**: Domestic; intensive PK study evaluating TDF/FTC genital and rectal secretion/tissue concentrations after different dosing strategies (N=24)
- **HPTN 067**: High risk women and MSM in high prevalence areas, to assess acceptability of, and adherence to, fixed interval vs. coitally-dependent IPREP (N=360)

What if TDF+/- FTC PrEP “Works”?

- If it is a “home run” would still want other options, given increasing use of TDF/FTC as first line HAART
- If the signal is more ambiguous (e.g. decreased efficacy if non-adherent) would want other options
- Ideally block other steps in HIV life cycle (e.g. binding or integration)
- Could some drugs be developed just for prevention?
- New Co-formulations targeting more than one step in HIV life cycle could be considered if Pharma was agreeable
- What makes sense for the next generation of PrEP?

Tenofovir + Emtricitabine or Lamivudine for Non-Occupational PEP

- Mainly MSM
- Side effects common, some more prevalent with TDF (e.g. diarrhea), but tended to be mild
- Persistence and intensity of symptoms led to discontinuation in AZT arms



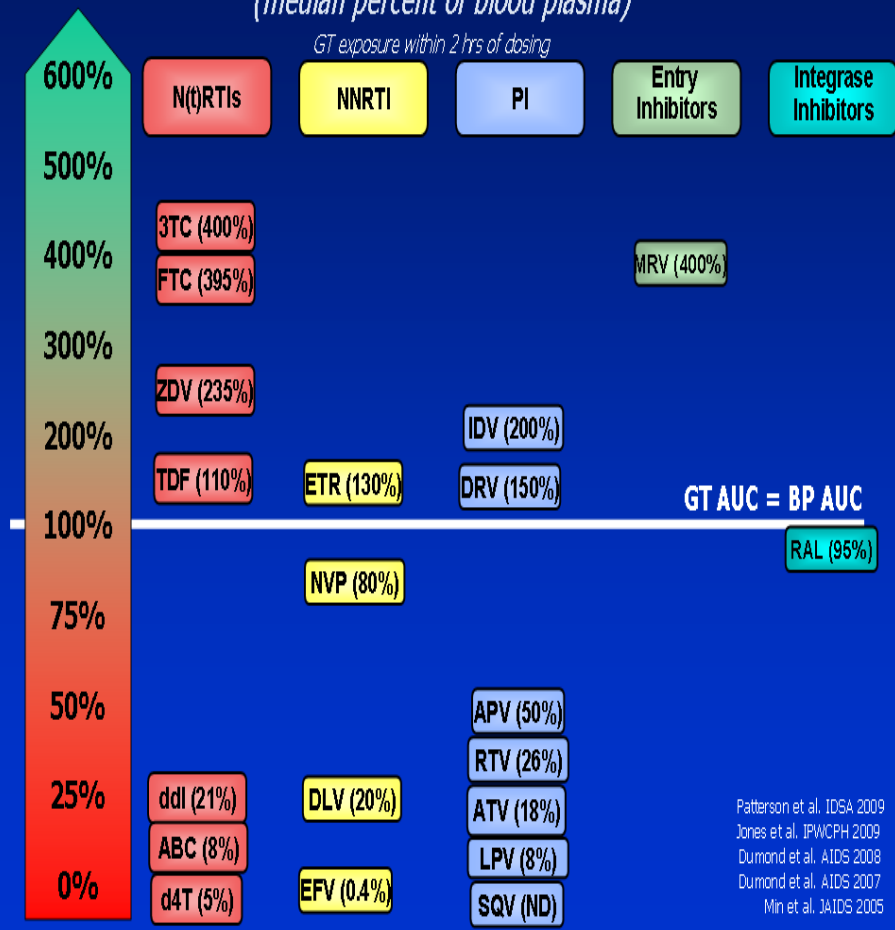
Genital:Blood Antiretroviral Concentrations

(A. Kashuba)

Systemic PrEP For Women

Female Genital Tract Exposure
(median percent of blood plasma)

GT exposure within 2 hrs of dosing

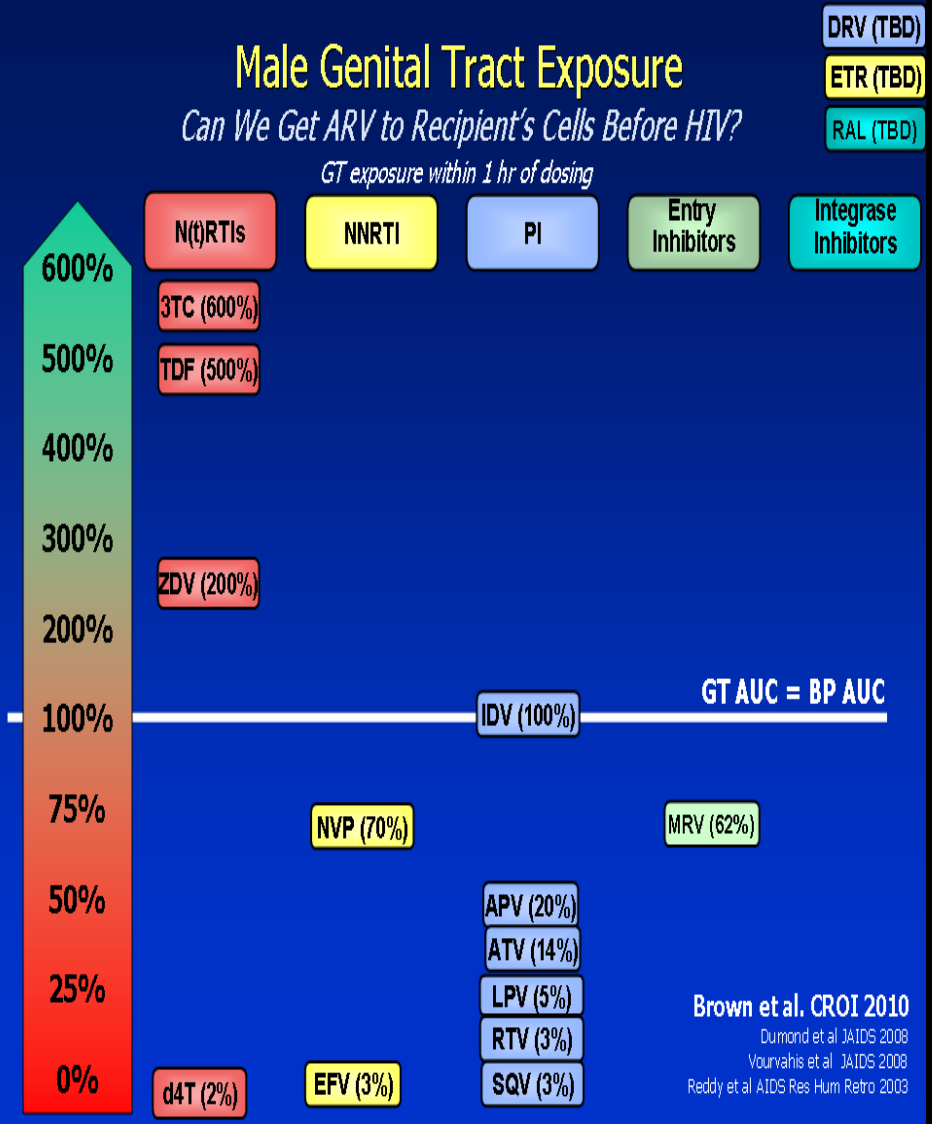


Patterson et al. IDGA 2009
Jones et al. IPWCPH 2009
Dumond et al. AIDS 2008
Dumond et al. AIDS 2007
Min et al. JAIDS 2005

Male Genital Tract Exposure

Can We Get ARV to Recipient's Cells Before HIV?

GT exposure within 1 hr of dosing

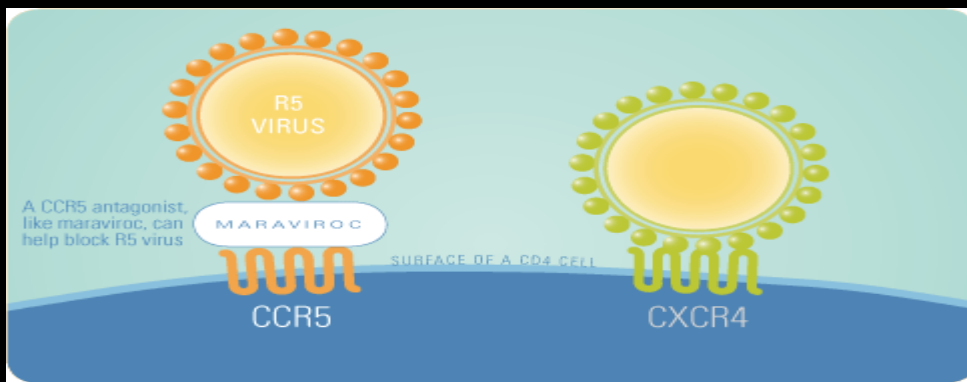


Brown et al. CROI 2010
Dumond et al. JAIDS 2008
Vourvahis et al. JAIDS 2008
Reddy et al. AIDS Res Hum Retro 2003

DRV (TBD)
ETR (TBD)
RAL (TBD)

Raltegravir and Darunavir in the Genital Tract

- RAL concentrations in cervicovaginal fluid were 2.3-fold greater than plasma, 16-fold greater than wild type IC_{50} .
Clavel, CROI 2010, Session 44, 2/19
- RAL Semen-to-blood plasma concentration ratio ranged from 1.62 at 2-4 hours post-dosing to 6.45 later, suggesting drug accumulation and persistence.
Bonora, CROI, Session 44, 2/19
- Median Darunavir semen-to-blood plasma ratio was about 1, many fold greater than the EC_{50} of wild-type virus, corrected for protein-binding.
Taylor, CROI 2010, Session 44, 2/19
Lambert-Niclot, CROI 2010, Session 44, 2/19



Maraviroc Chemoprophylaxis?

- MVC concentrations in rectal tissue were 10-fold higher than in vaginal tissue, which was 2-fold higher than in blood, but seminal levels were 38% less than blood. (30% of MVC excreted unchanged in stool)
Brown, CROI 2010, Session 24; Tiraboschi, CROI 2010
- Gel-formulated MVC protected macaques from vaginal SHIV challenge at 3mg/ml concentrations. Protection declined as time between dosing and challenge grew. Did not protect vs. X4 challenge. Veazey, CROI 2010, Session 24, 2/19
- Extremely well-tolerated, but not used much clinically.

Long History of Maraviroc for PrEP

- Mentioned as a priority ART for prevention issue in HPTN recompetition application
- Several meetings with Pfizer as they developed its therapeutic and safety profile (last one at IAS in Capetown)
- Trip Gulick, one of the PIs of MVC therapeutic efficacy trials expressed interest in MVC potential for prevention
- 2009: creation of ViiV, merger of HIV/AIDS portfolio of Pfizer and GSK, meaning that MVC and 3TC could be co-formulated
- 2/18/10: meeting to discuss MVC PrEP

Tolerability and Adherence of MVC-3TC versus TDF-FTC for PrEP in high risk MSM

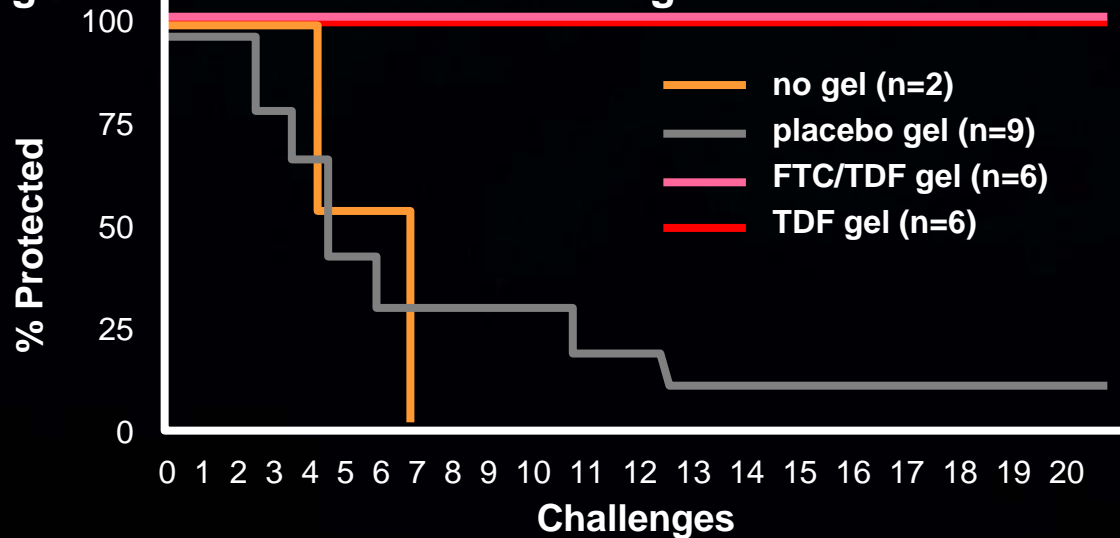
- Rationale: prior to any efficacy trial, will want to know if the side effect profile and adherence with MVC-3TC is at least comparable (if not better than) TDF-FTC
- Design: double dummy RCT
- Would model study design on CDC expanded safety study in MSM (e.g. N around 400) and power it on anticipated level of adherence between study arms.
- Would do the study in US, given ViiV sensitivity to issues raised by international prevention studies

Issues for Discussion

- **Population:** High risk US MSM are readily recruited into PrEP trials (more than 600 already in IPrEX and CDC) and don't have pregnancy issues **vs.** desire for diversity and studies in U.S. women might have applicability to international settings.
- **Leadership:** HPTN has expertise with prevention, but ACTG has experience with MVC for rx, and DAIDS would like cross-network collaboration
- **Protocol team expertise** should include investigators who have done PrEP trials, worked with MVC, as well as pharmacologists, behavioral science adherence experts

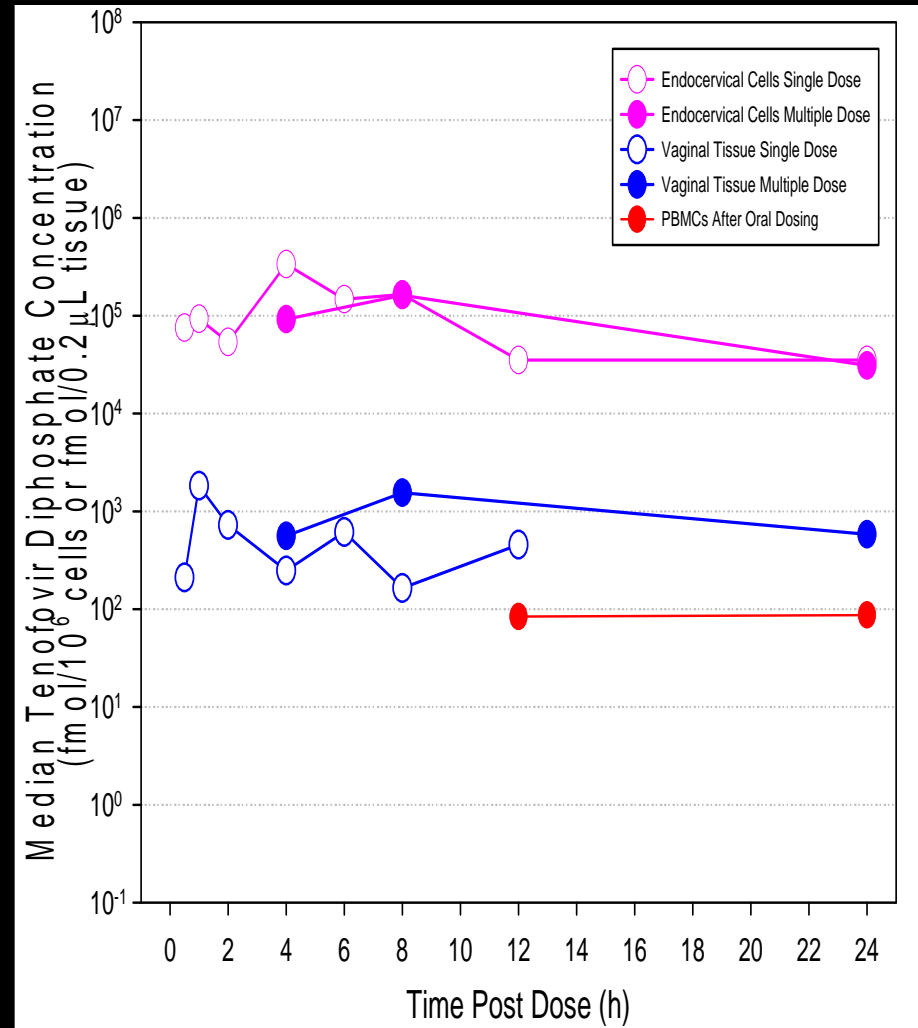
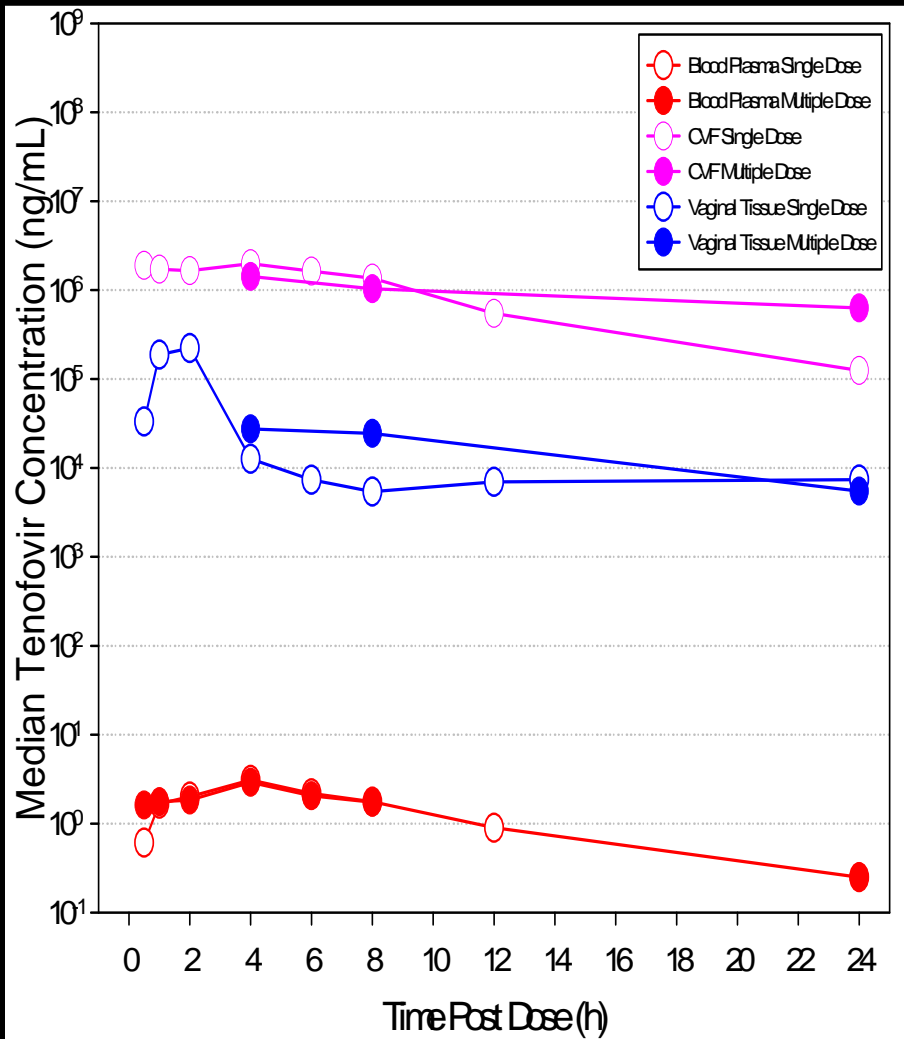
Topical PrEP in Macaques with TDF or TDF/FTC

- Study to assess most effective modality for topical ARV gels
- 1% TDF or 1% TDF/5% FTC gels in 23 macaques
 - Gel (matrix + preservatives) clear, viscous, odorless, stable at 37° x 6 months
 - 3 ml gel applied 30 mins before vaginal challenge with R5 virus inoculum (10 TCID₅₀)
 - Challenges 2x/week for total 20 challenges



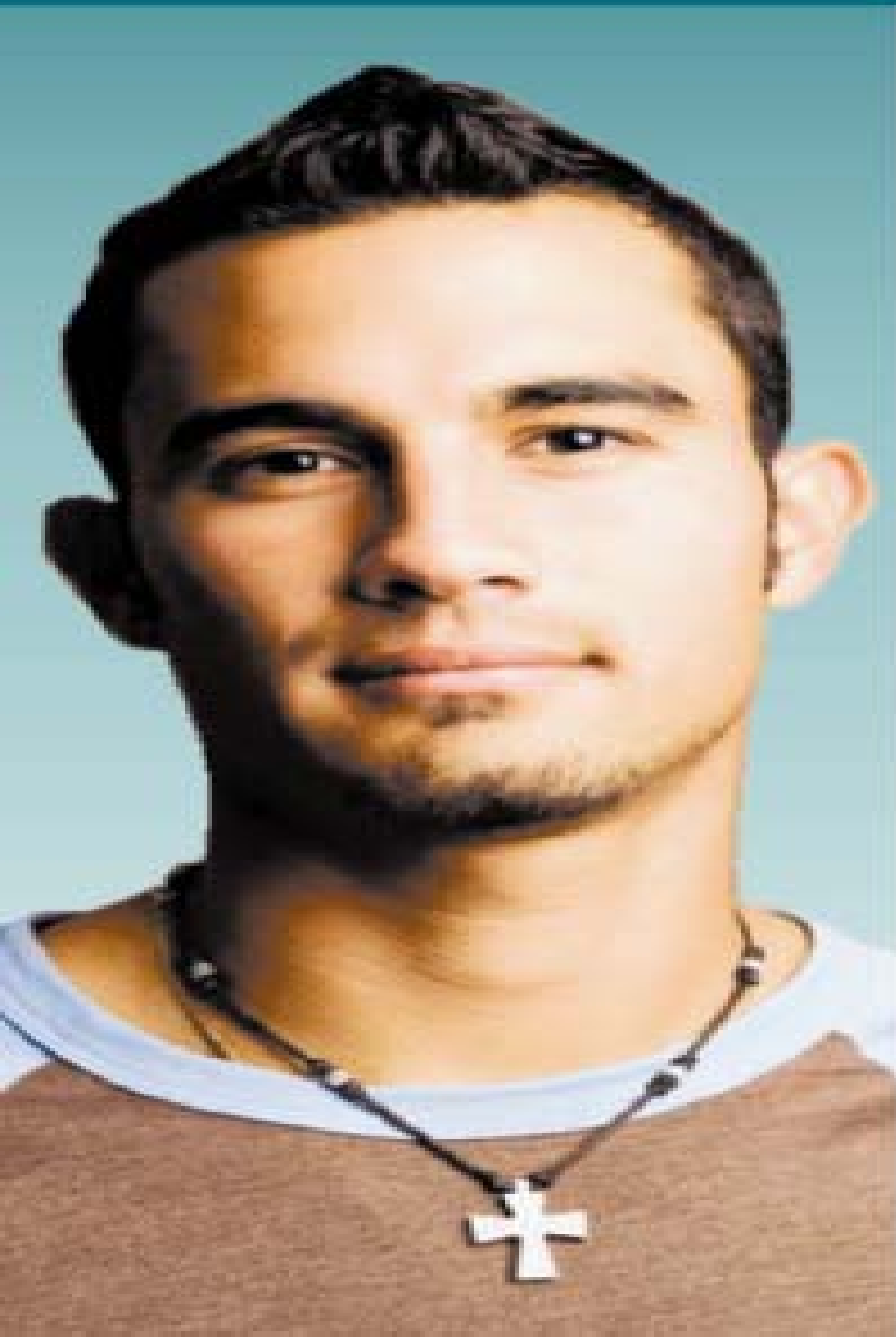
Compartmental Concentrations

After Single and Multiple Doses of 1% Tenofovir Gel in Humans



New Antiretroviral Topical Microbicides

Compound	Mechanism	Developers/ Sponsors	Status
Dapivirine	NNRTI	Tibotec/IPM	Phase I/II (gel, ring)
UC-781	NNRTI	Conrad/NIH/ MTN	Phase I/II
MIV-150	NNRTI	Population Council	Phase I
BMS-793	gp 120 blocker	BMS/IPM	Pre-Clinical
L644 Peptide	gp 41 blocker	Merck/IPM	Pre-Clinical
Maraviroc	CCR5 blocker	Pfizer/IPM	Pre-Clinical
M167, M872, M882	CCR5 blocker	Merck, IPM	Pre-Clinical



Can one Pill a day **PREVENT HIV?**

HIV-Negative Gay/Bi Men Needed to Participate in Research. Project PrEPare 2. This study will test if a daily medication can prevent HIV-infection in HIV-negative men.

Be: HIV-negative, 18+, and sexually active.

Interested? Please call Fenway Community Health.

 **Fenway**

7 Haviland St.
Boston, MA
02115

617.927.6450
or visit the website at
www.fenwayhealth.org/prep2

Preexposure Antiretroviral Prophylaxis Attitudes in High-Risk Boston Area Men Who Report Having Sex With Men: Limited Knowledge and Experience but Potential for Increased Utilization After Education

Matthew J. Mimiaga, ScD, MPH,*† Patricia Case, ScD, MPH,*‡ Carey V. Johnson, ScM,*
Steven A. Safren, PhD,*† and Kenneth H. Mayer, MD*§

J Acquir Immune Defic Syndr • Volume 50, Number 1, January 1, 2009

- 227 Boston MSM
- One had used PrEP
- 19% had heard of it
- 74% indicated an interest in using PrEP after education
- Similar findings to Liu, et al in SF (*JAIDS*, 2008) and CDC's Gay Pride surveys (*Kellerman et al, JAIDS*, 2006)

Predictors of intent to use

	<u>O.R.</u>
-Lower income	13.0
-Less education	7.7
-No perceived side effects	3.5
-Not having to pay	4.2



Not Panacea nor Pandora, but a Labyrinth

- Treatment as Prevention: Earlier treatment is inevitable, given evidence of benefits of HAART. Challenges: Resources needed to train providers, access to sustained treatment; adherence, STI management, risk compensation
- ART for Uninfected Persons: Biological plausibility, proof-of-concept soon. Challenges: Need to define optimal drugs, frequency of dosing, mode of drug delivery; as well as risk for development of resistance, chronic toxicities; access, adherence, STI management, risk compensation