

# PrEP For Women

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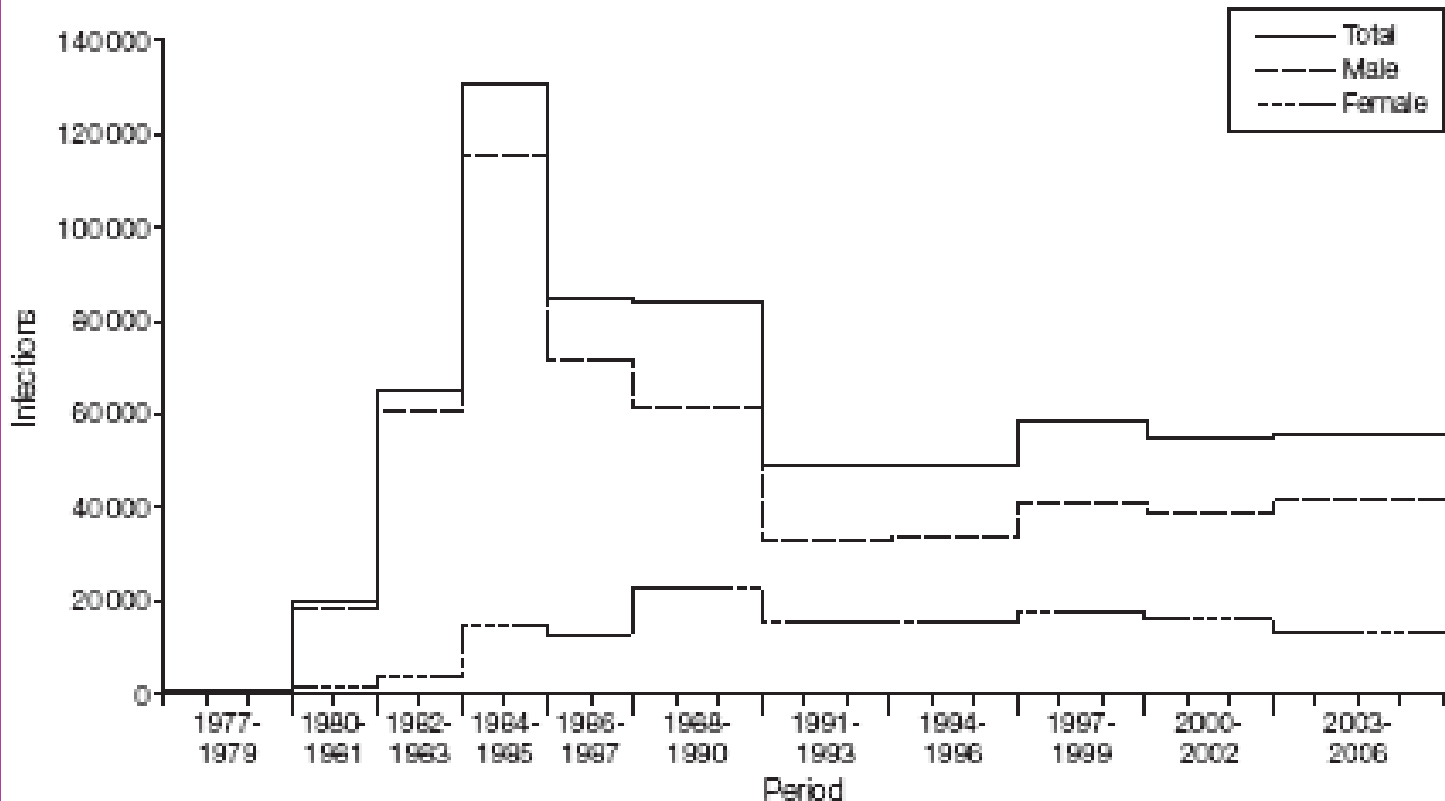
New York City

# Topics to be discussed

- **Why do we need PReP?**
- **What is PReP?**
- **Does it work? Does it work for women?**
- **How much does it cost?**
- **How safe is it?**

# U.S.: New HIV Infections Per Year

**Figure 1.** Estimated New Human Immunodeficiency Virus (HIV) Infections, Extended Back-Calculation Model, 50 US States and the District of Columbia, 1977-2006



**48,100  
in 2009**

Hall JAMA 2008;300:520

Prejean PLoS One 2011;6:e17502

# World Wide: 5 million new cases of HIV each year

Location	# new cases	% of population
North America	65,000	0.6%
South America	210,000	1-2%
Africa	3.5 million	

<http://www.yale.edu/yaw/index.html>

- **The number of women with HIV and AIDS has increased steadily worldwide. By the end of 2005, according to the World Health Organization (WHO), 17.5 million women worldwide were infected with HIV.**

[NIH/NIAID web site](#)

# African Americans

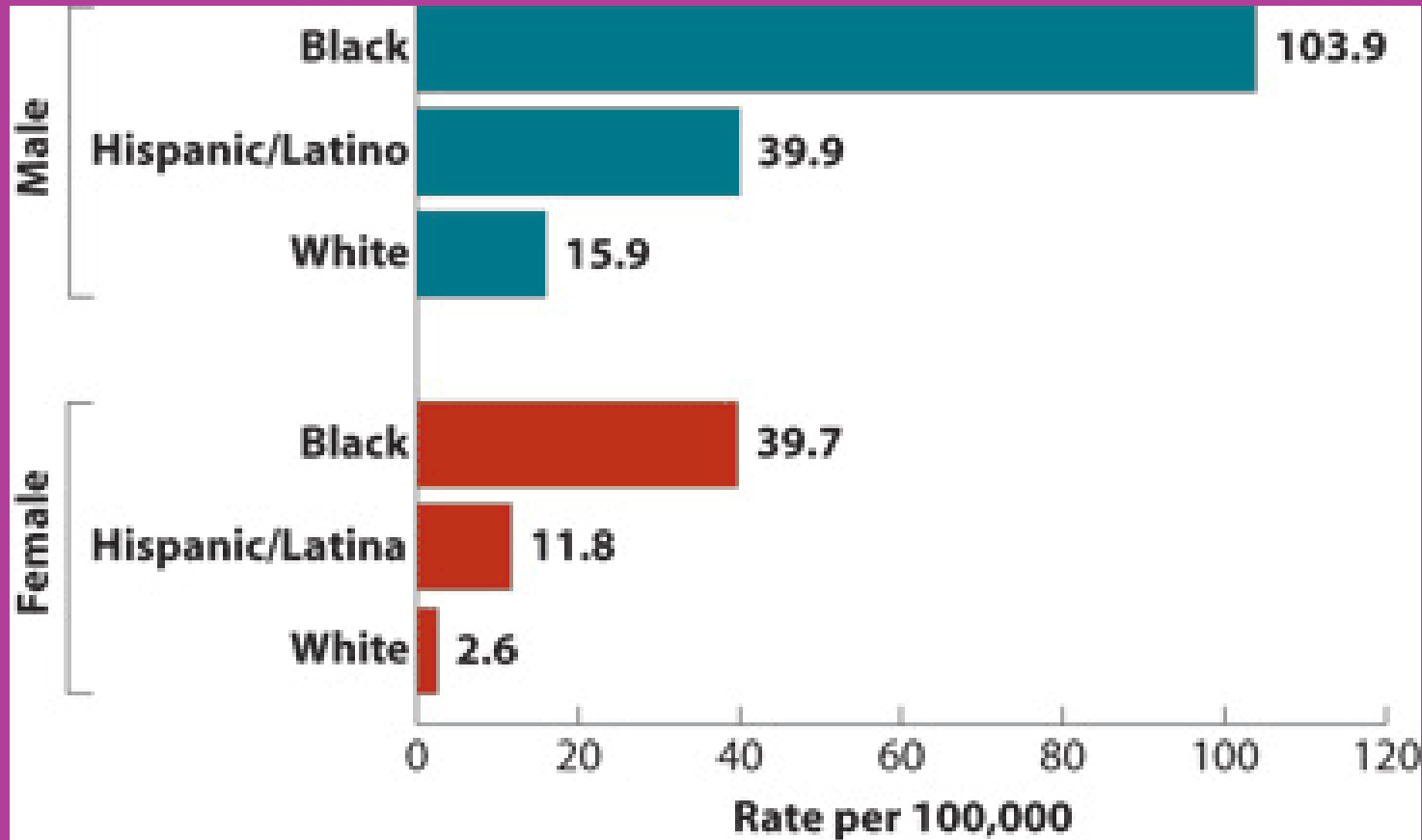
- Among racial/ethnic groups, African Americans face the most severe burden of HIV in the U.S.
- While blacks represent approximately 14% of the U.S. population, they accounted for almost half (46%) of people living with HIV in the U.S. in 2008, as well as an estimated 44% of new infections in 2009. HIV infections among blacks overall have been roughly stable since the early 1990s.

# Hispanics/Latinos

- Hispanics/Latinos represent 16% of the population but accounted for an estimated 17% of people living with HIV in 2008 and 20% of new infections in 2009. HIV infections among Hispanics/Latinos overall have been roughly stable since the early 1990s.
- In 2009, the rate of new HIV infections among Hispanic/Latino men was two and a half times that of white men and the rate among Hispanic/Latino women was four and a half times that of white women.

AIDS.gov June 6, 2012 quoting Prejean et al, 2011

# Estimated Rate of New HIV Infections, 2009, by Gender and Race/Ethnicity



AIDS.gov June 6, 2012



# HIV Prevention Strategies

**A**bstain, **B**e faithful, **C**ondoms,  
**C**ounseling & testing

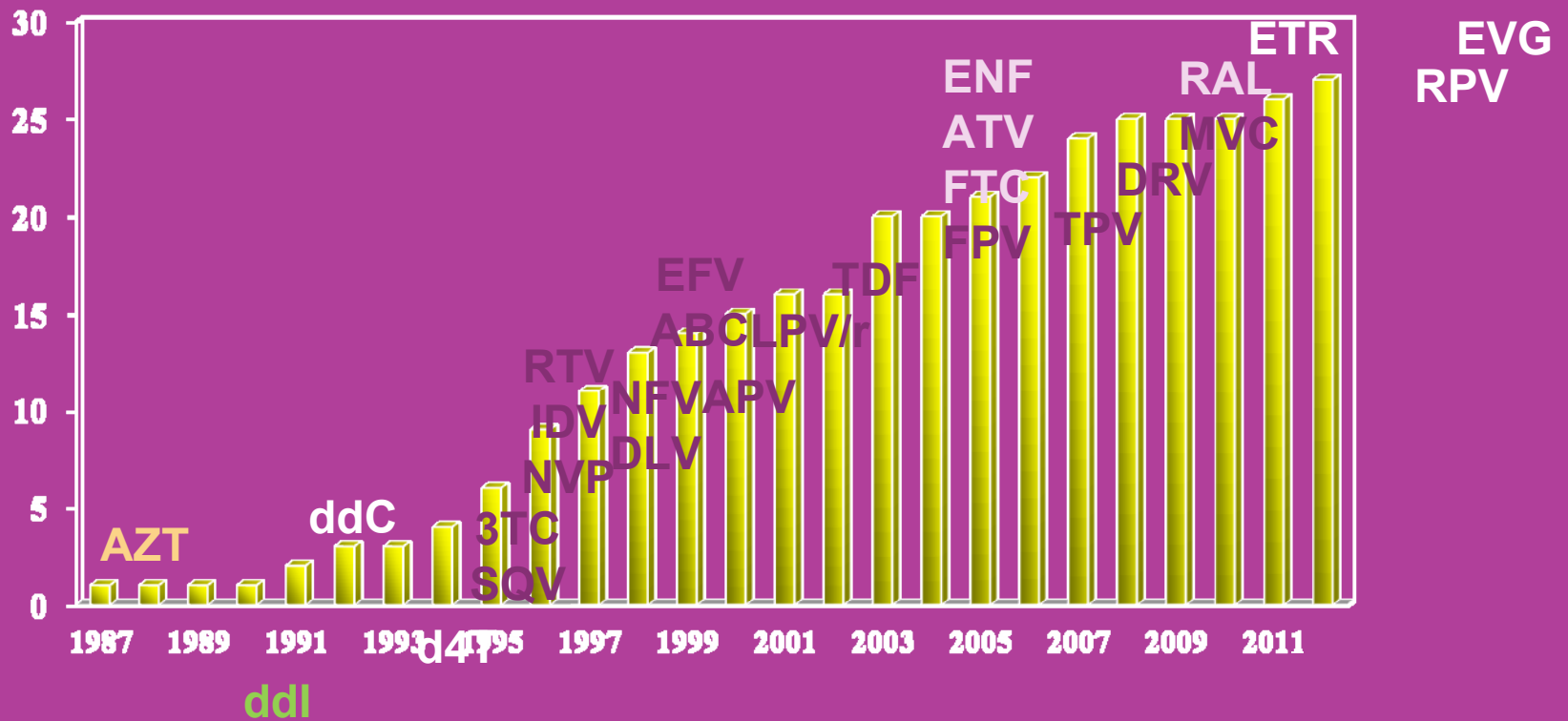
**ABC**

# PrEP = Pre-Exposure Prophylaxis

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- PrEP = an HIV uninfected at-risk individual takes ART.
- By having ART in the bloodstream & genital tract, HIV may be unable to establish infection.
- ART = HIV prevention

# Antiretroviral Drug Approval: 1987 - 2012



# TDF and FTC/TDF for PrEP

Optimal PrEP candidates:

potency, safety, tolerability, and convenience



= TDF (tenofovir)



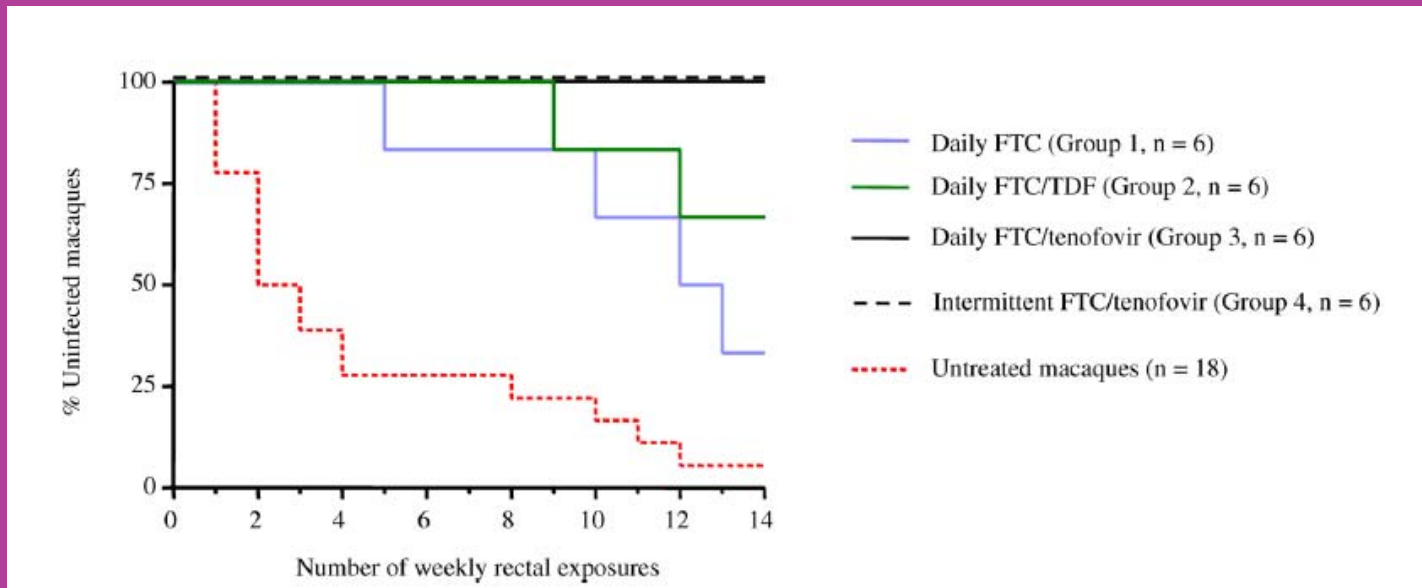
= FTC/TDF (co-formulated emtricitabine + tenofovir)

Potential concerns:

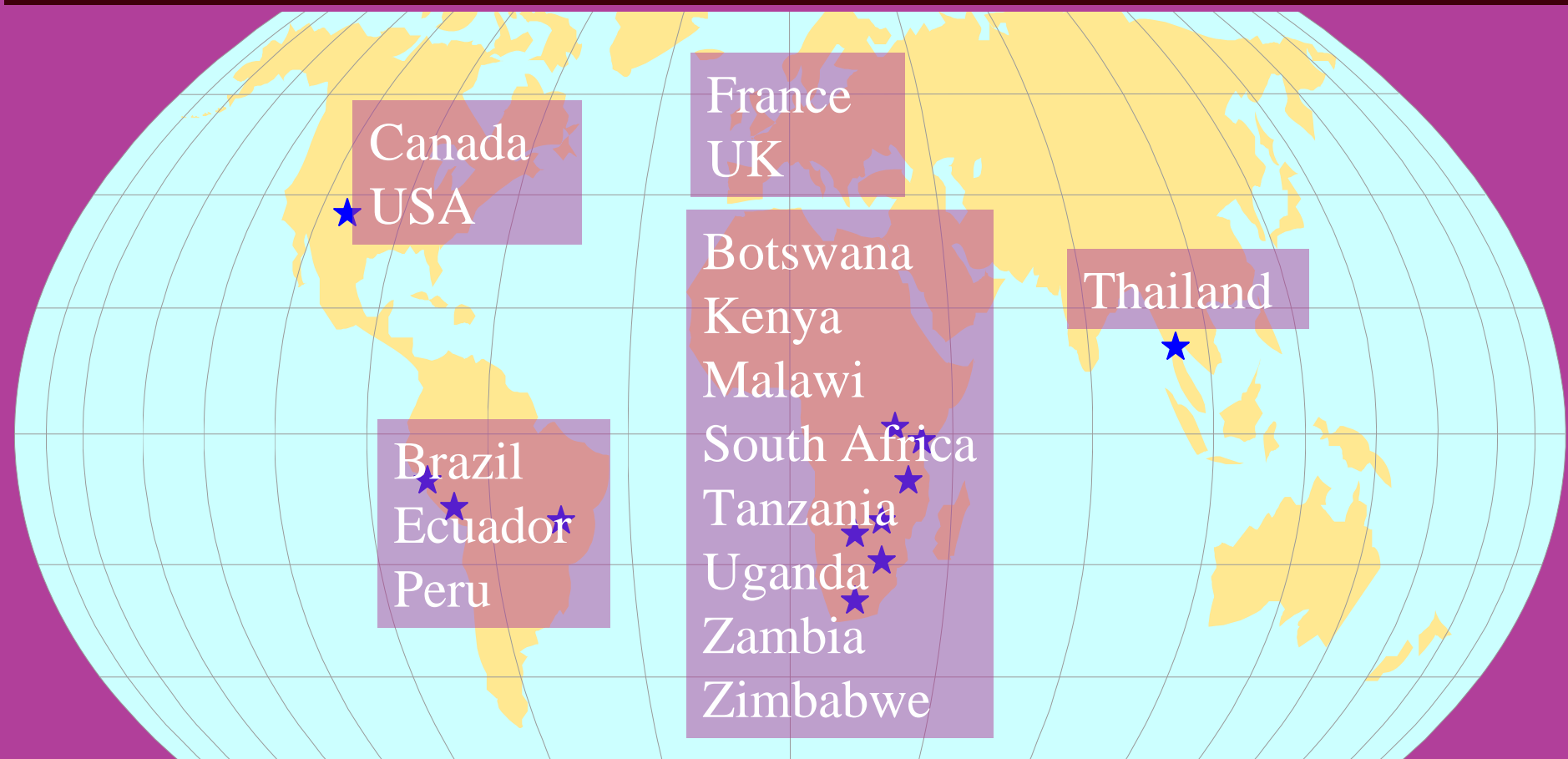
- Used widely; preferred first-line treatment
- Drug resistance
- Toxicities: renal, bone
- Cost >\$10,000/year

# PrEP: Animal Model

Effect of daily and intermittent PrEP in monkeys: SHIV rectal challenge model



# Completed and Current Studies of Oral PrEP



**14 studies and projects, up to 16 countries**

**32,000+ participants**

# PrEP Studies

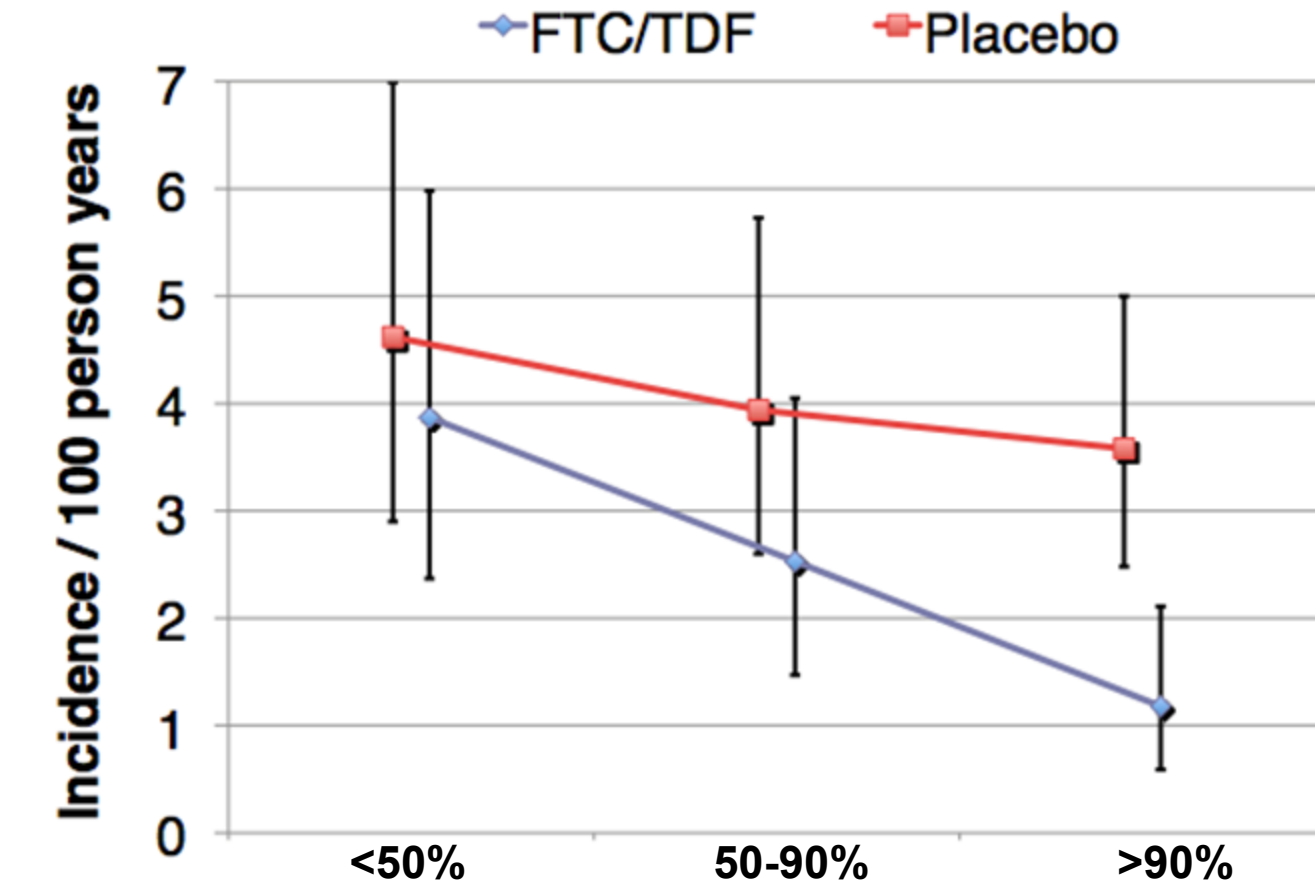
Study (reference)	Study population	Design	Results: Reduction in HIV Infection
<b>IPREX</b> Grant NEJM 2010;363:2587	2499 gay men	TDF/FTC (Truvada) vs. placebo	TDF/FTC: <b>45%</b>  ( <b>92%</b> if drug levels detected)
<b>CDC – TDF-2</b> Thigpen NEJM 2012;367:423	1200 Botswana adults (45% women)	TDF/FTC (Truvada) vs. placebo	TDF/FTC: <b>63%</b>
<b>Partners PREP</b> Baeten NEJM 2012;367:399	4758 discordant Kenya and Uganda couples	TDF (Viread) vs. TDF/FTC (Truvada) vs. placebo	TDF: <b>67%</b> TDF/FTC: <b>75%</b>  (86-90% if TFV detected)

# PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
<b>FEM-PREP</b> Van Damme NEJM 2012;367:411	2120 women in Kenya, South Africa, Tanzania	TDF/FTC (Truvada) vs. placebo	TDF/FTC: <b>6%</b>  (adherence <40%)
<b>VOICE</b> Press release 9/29/11	>5000 women in South Africa, Uganda, Zimbabwe	1% TDF gel vs. placebo; oral TDF, TDF/FTC or placebo	TDF arm stopped early due to futility



# IPREX: Recorded Adherence and Efficacy



% of Visits

18%

33%

49%

**Efficacy**

**16%**

**34%**

**68%**

95% CI

-54 - 54

-20 - 64

36 - 84

# Adverse events

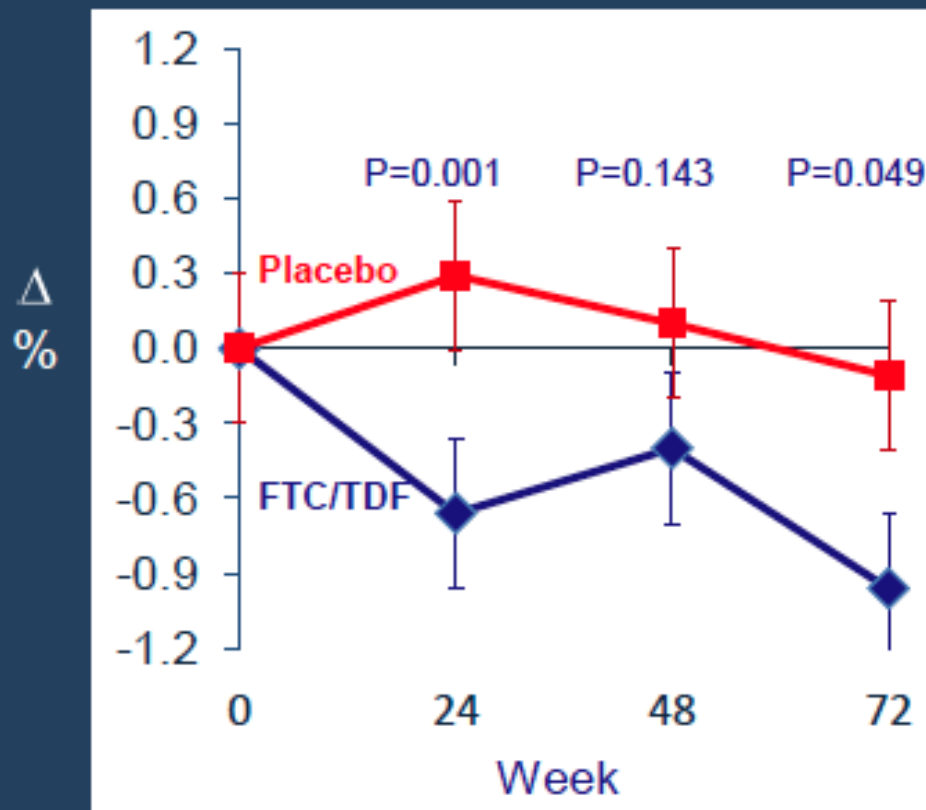
Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
<b>Creatinine Elevated</b>	25 (2%)	28	14 (1%)	15	p=0.08
<b>Headache</b>	56 (4%)	66	41 (3%)	55	p=0.10
<b>Nausea</b>	20 (2%)	22	9 (<1%)	10	p=0.04
<b>Weight Decreased</b>	27 (2%)	34	14 (1%)	19	p=0.04



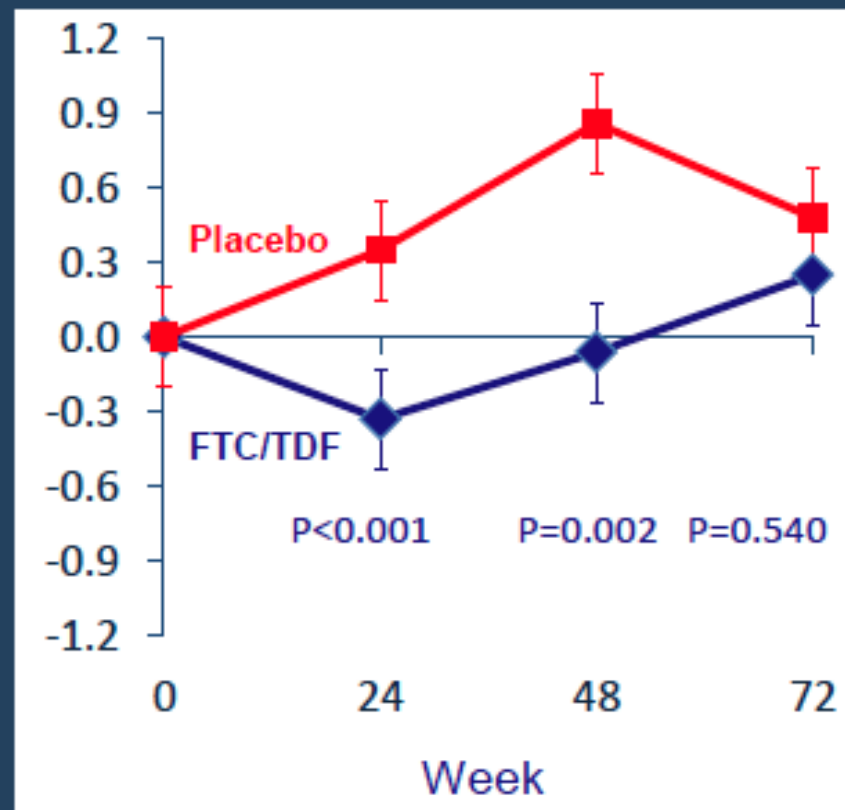
Grant NEJM 2010;363:2587

# PERCENT CHANGES FROM BASELINE IN BMD BY RANDOMIZATION GROUP

## SPINE (L1-L4)



## TOTAL HIP



Placebo	247	199	124	59
FTC/TDF	256	203	124	59

247	199	124	59
256	202	125	59

Mean, SE and P-values by linear mixed model

# Drug Resistance

Genotypic Resistance	HIV Status at Enrollment			
	Infected (N=10)		Uninfected (N=100)	
	Placebo N=8	FTC/TDF N=2	Placebo N=83	FTC/TDF N=48
<b>65R</b>	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>70E</b>	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>184I</b>	0 (0%)	1 (50%)	0 (0%)	0 (0%)
<b>184V</b>	1 (13%)	1 (50%)	0 (0%)	0 (0%)
<b>TDF Resistance</b>	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>FTC Resistance</b>	1 (13%)	2 (100%)	0 (0%)	0 (0%)



# IPREX F/U: Modeling PK

- **Using data from a separate PK study:**
  - **2 doses/week: 76% risk reduction**
  - **4 doses /week: 97% risk reduction**
  - **7 doses/week: 99% risk reduction**

Anderson CROI 2012 #31LB

# Partners PrEP

- 4758 serodiscordant couples in Kenya and Uganda
- HIV- partners 38% women, 62% men; 98% married
- 95% retention; 97% adherence
- unprotected sex 27% at baseline and ↓ during study

	<b>TDF</b>	<b>TDF/FTC</b>	<b>placebo</b>	
<b>Participants</b>	<b>1584</b>	<b>1579</b>	<b>1584</b>	
<b>HIV infections</b>	<b>18</b>	<b>13</b>	<b>47</b>	
<b>Protective efficacy (vs. placebo)</b>	<b>62%</b>	<b>73%</b>		<b>No difference TDF vs. TDF/FTC</b>

- No difference in side effects, lab abnormalities, deaths

# CDC – TDF-2

- Double blind, placebo-controlled study in Botswana
- 18-39 years old, heterosexual, sexually active
- 1200 followed over time (45% women)

	TDF/FTC	Placebo	
<b>N</b>	<b>601</b>	<b>599</b>	
<b>Lost to f/u</b>	<b>9%</b>	<b>10%</b>	
<b>New HIV infections</b>	<b>9</b>	<b>24</b>	<b>Protective efficacy 63%</b>

- No safety differences
- No differences by sex

# **CDC Guidance for PrEP for MSM:**

**(Interim; 1/27/11)**

- **Before starting:**
  - **document HIV Ab- and r/o acute infection**
  - **CrCl  $\geq$ 60, screen for STIs and HBV**
- **Rx TDF/FTC 1 po daily X 90 days**
  - **provide risk reduction, adherence counseling, condoms**
- **On treatment:**
  - **check HIV Ab every 2-3 months**
  - **check BUN/creat at 3 months and yearly**
  - **risk reduction, condoms, STI assessments/rx**

<http://www.cdc.gov/hiv/prep/index.htm>



# **U.S. Food and Drug Administration (FDA) Approval of PrEP (7/16/12)**

- U.S. FDA approves Truvada for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.**

# CDC Guidance for PrEP for heterosexuals (8/9/12)

- Targeted to high-risk individuals, such as those with an HIV+ sex partner.
- It is critical to take PrEP consistently.
- Discuss risks/benefits with pregnant women or those trying to conceive; data are incomplete and mostly from HIV+ women.
- PrEP is not a stand-alone solution.
- Individuals must be confirmed HIV- prior to PrEP; monitor HIV status, side effects, adherence, and risk behaviors.

# WHO Guidance for PrEP (7/20/12)

- ensure that people seeking PrEP are HIV neg
- encourage continued condom use
- check for pre-existing medical conditions (e.g. kidney or bone disease)
- monitor for adverse events
- help people adhere to daily medication
- ensure uninterrupted supply
- test regularly for HIV infection and check for drug resistance if infection is found
- gather cost-benefit information

# Willingness to Take PrEP: **MSM**

## Recruited HIV- MSM (8-11/11)

	<b>Miami</b>	<b>Washington, D.C.</b>
	<b>n=280</b>	<b>n=323</b>
<b>Median age</b>	<b>29</b>	<b>32</b>
<b>Black</b>	<b>18%</b>	<b>28%</b>
<b>White</b>	<b>10%</b>	<b>49%</b>
<b>Hispanic</b>	<b>71%</b>	<b>13%</b>
<b>Other</b>	<b>1%</b>	<b>10%</b>
<b>Had heard of PrEP</b>	<b>15%</b>	<b>30%</b>
<b>Knew anyone on PrEP</b>	<b>3%</b>	<b>3%</b>
<b>Had taken PrEP</b>	<b>0%</b>	<b>0%</b>
<b>Willing to use PrEP</b>	<b>48%</b>	<b>61%</b>

# Attitudes About PrEP: South Carolina

- HIV clinic at the University of South Carolina
- 89 MSM and heterosexual HIV- partners in the relationship  $\geq 6$  months
- Average age 42; 56% men; 70% black, 74% heterosexual; 58% had monthly income of  $\leq$  \$1500
- 58% reported always (100%) using condoms during intercourse after learning their HIV+ partner's status.
- 94% were willing to use PrEP, if available.
- 26% suggested that they would be more likely to have unprotected sex with HIV+ partners with PrEP.
- 27% suggested that it would be difficult to take daily PrEP and also consistently use condoms.

# PrEP Acceptability: South Africa



8 focus groups with 52 adults

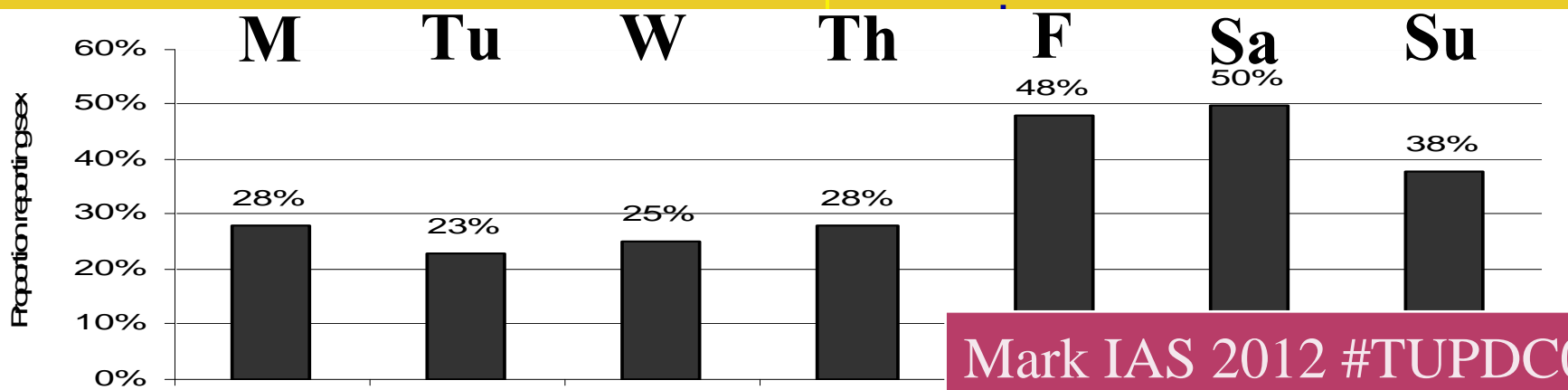
- Acceptability: potential for non-consensual use
- Barriers: PrEP seen as treatment, fear of stigma, risk compensation
- Intermittent PrEP favoured for lower time burden and side effects
- Concerns around intermittent PrEP complexity

## SEXUAL EXPOSURE

- Median 2 sex days in prior week
- 0% reported daily sex as average

## SEXUAL FORECASTING

- 51% forecasted last sex act (men 75% vs. women 32%)
- 77% forecasted some, and 51% all sex events in previous



# Criteria: DAIDS Working Group

- **Safe**
- **Penetrates target tissues**
- **Protects against HIV infection in tissues**
- **Long-lasting activity for convenient dosing**
- **Unique resistance profile or high barrier to resistance**
- **No significant drug-drug interactions**
- **Possibly, not a part of current rx regimens**
- **Affordable, easy to use and implement**

# Antiretroviral Drugs: 2013

## nucleoside/tide RTIs (NRTIs)

- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

## NNRTIs

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)

## protease inhibitors (PIs)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

## entry inhibitors (EIs)

- enfuvirtide (T-20, fusion inh)
- maraviroc (MVC, CCR5 inh)

## integrase inhibitors (IIs)

- raltegravir (RAL)
- elvitegravir (EVG)



# Antiretroviral Drugs: 2013

## nucleoside/tide RTIs (NRTIs)

- lamivudine (3TC)
- emtricitabine (FTC)
- tenofovir (TDF)

## entry inhibitors (EIs)

- maraviroc (MVC, CCR5 inhibitor)

## integrase inhibitors (IIs)

- raltegravir (RAL)

# **Maraviroc for PrEP: Advantages**

- **Entry inhibitor**
- **MVC safety profile X 5 years Gulick IAS 2012**
- **MVC achieves high tissue levels**
  - **3X higher in vaginal secretions Dumond JAIDS 2009**
  - **8-26X higher in rectal tissue Brown JID 2011**
- **MVC prevented HIV infections in animal model Neff PLoS One 2010**
- **MVC drug resistance is uncommon**
- **MVC once-daily dosing possible**  
Rosario Brit J Clin Pharm 2008
- **MVC used uncommonly for HIV treatment**

# MVC for PrEP: Disadvantages

- **Limited safety data in HIV-uninfected individuals**
- **Increased pathogenicity of some viral infections (e.g., West Nile virus)**
- **Other theoretical safety risks**
- **Not labeled for once-daily dosing**
- **Some potential for drug-drug interactions**
- **Not active against X4 virus**

# HPTN 069: NEXT-PrEP

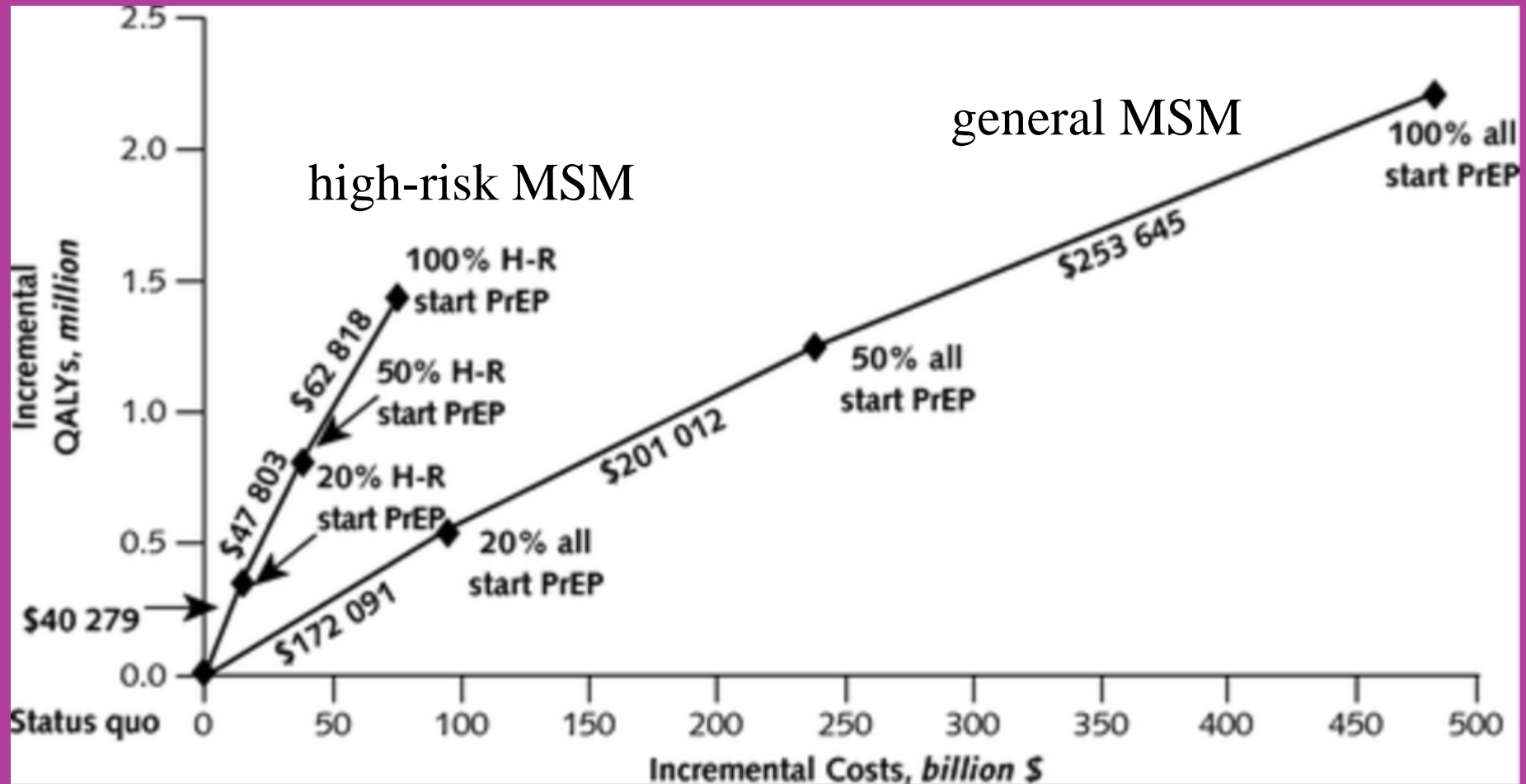
- **Design: Phase II, 4-arm, multisite, study**
- **Study population (N=600)**
  - **At-risk HIV-negative gay men**
  - **At-risk HIV-negative women**
- **Study Treatment:**
  - **MVC monotherapy**
  - **MVC + FTC**
  - **MVC + TDF**
  - **TDF + FTC (control)**
- **Duration: 48 weeks**
- **Primary endpoint: Grade  $\geq 3$  toxicities; time to study treatment discontinuation**

# Newer PrEP Agents

	<b>mechanism</b>	<b>dosing route</b>	<b>dosing frequency</b>	<b>PrEP stage</b>
<b>rilpivirine-LA</b>	NNRTI	injectable, SC	once monthly	Phase 1 pilot
<b>S/GSK 1265744 ('744)</b>	integrase inhibitor	injectable, SC	once monthly (or less)	Phase 1 pilot
<b>ibalizumab</b>	CD4 attachment inhibitor	injectable, SC	once every 1-4 weeks	Phase 1 pilot

# PrEP: Cost-effectiveness in MSM

Assumptions: 20 years of use, PrEP is 44% effective and costs \$10083/year including monitoring



# Cost of Prevention vs Treatment

- **Truvada (in zip code 10011)**
  - \$1,321.04/month (with coupon at Kmart)=
  - \$15,852.48/yr + labs test costs
- **Atripla**
  - \$2,048.58/month with coupon at Duane Reade=
  - \$24,582.96/year + lab test costs

# PrEP: Pros and Cons

## PROS

- Proven efficacy
- FDA approved
- Can be highly effective
- Generally well-tolerated
- Drug resistance not seen
- No risk compensation

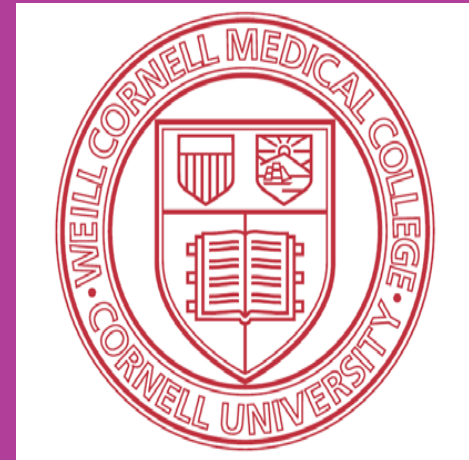
## CONS

- Short-term data
- Daily adherence required
- Side effects
- Drug resistance in acute infection
- Risk compensation could lead to ↓ condoms
- Cost
- Logistics



# Acknowledgments

- **Cornell HIV Clinical Trials Unit (CCTU)**
- **Division of Infectious Diseases**
- **Weill Medical College of Cornell University**
- **AIDS Clinical Trials Group (ACTG)**
- **Division of AIDS, NIAID, NIH**
- **The patient volunteers!**



# Cornell HIV Clinical Trials Unit



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