

**Truvada® (emtricitabine/tenofovir disoproxil fumarate) for  
Pre-exposure Prophylaxis (PrEP) for HIV-1  
Prevention in Populations at High Risk of  
Sexually Acquired HIV Infection  
NDA 21752 S-30**

***Opening Remarks***

Debra Birnkrant, M.D.  
Director, Division of Antiviral Products  
Antiviral Products Advisory Committee  
May 10, 2012



# NATIONAL HIV/AIDS STRATEGY FOR THE UNITED STATES

JULY 2010



**“We must also move away from thinking that one approach to HIV prevention will work, whether it is condoms, pills, or information. Instead, we need to develop, evaluate, and implement effective prevention strategies and combinations of approaches** including efforts such as expanded HIV testing (since people who know their status are less likely to transmit HIV), education and support to encourage people to reduce risky behaviors, the **strategic use of medications** and biomedical interventions (which have allowed us, for example, to nearly eliminate HIV transmission to newborns), the development of vaccines and microbicides, and the expansion of evidence-based mental health and substance abuse prevention and treatment programs. It is essential that all Americans have access to a shared base of factual information about HIV. The Strategy also provides an opportunity for working together to advance a public health approach to sexual health that includes HIV prevention as one component. To successfully reduce the number of new HIV infections, there must be a concerted effort by the public and private sectors, including government at all levels, individuals, and communities, to:

- Intensify HIV prevention efforts in communities where HIV is most heavily concentrated.
- **Expand targeted efforts to prevent HIV infection using a combination of effective, evidence-based approaches.**
- Educate all Americans about the threat of HIV and how to prevent it.”

# The New England Journal of Medicine

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Volume 331

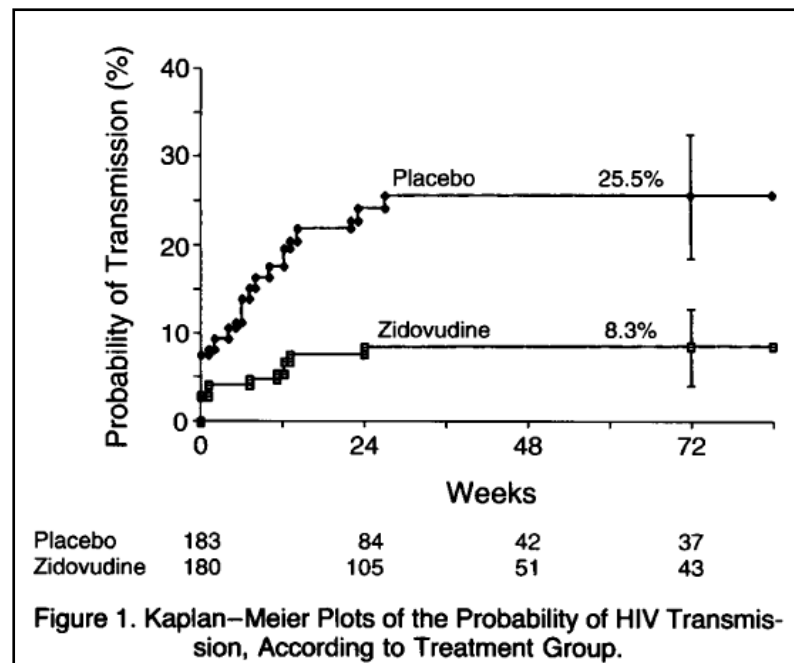
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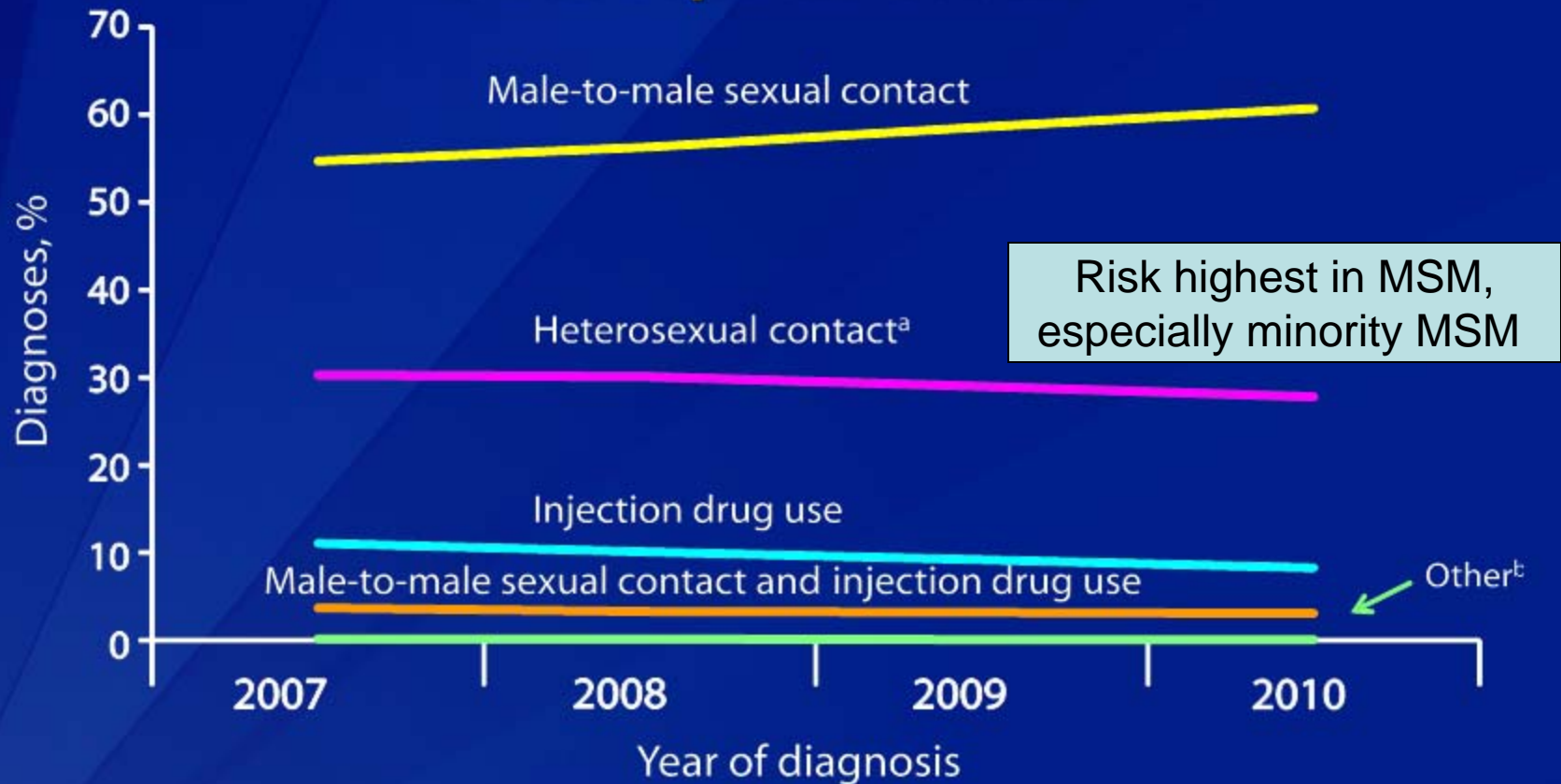
## REDUCTION OF MATERNAL-INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D., GWENDOLYN SCOTT, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL VANDYKE, M.D., MOHAMMED BEY, M.D., WILLIAM SHEARER, M.D., PH.D., ROBERT L. JACOBSON, M.D., ELEANOR JIMENEZ, M.D., EDWARD O'NEILL, M.D., BRIGITTE BAZIN, M.D., JEAN-FRANÇOIS DELFRAISSY, M.D., MARY CULNANE, M.S., ROBERT COOMBS, M.D., PH.D., MARY ELKINS, M.S., JACK MOYE, M.D., PAMELA STRATTON, M.D., AND JAMES BALSLEY, M.D., PH.D.,

FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP\*



# Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2007–2010—46 States and 5 U.S. Dependent Areas



Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing risk-factor information, but not for incomplete reporting.

<sup>a</sup> Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

<sup>b</sup> Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.



# Why Are We Discussing This Topic?

- Truvada® was approved for treatment of HIV-1 infection in combination with other antiretrovirals in 2004
  - Individual components approved earlier: tenofovir in 2001 and emtricitabine in 2003
- Interim CDC guidelines for Truvada for PrEP for high risk MSM posted in 2011
- **Supplemental application provides FDA an opportunity to:**
  - Extensively review and analyze scientific data
  - Inspect clinical trial sites
  - Bring it to a public forum for discussion

# What is PrEP?

- Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs to prevent acquisition of HIV in men and women
  - In combination with other prevention modalities such as condoms and counseling
- Focus today on oral Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate)
  - Priority review (6 months)



# Priority Review

- Manual of Policies and Procedures 6020.3
  - Review classification
    - Priority (6 months) or standard (10 months)
  - Priority review is granted if there is potential for providing significant improvement in the treatment, prevention or diagnosis of a disease when compared to standard applications
  - Truvada® for PrEP was granted a priority review because
    - there is a potential for providing significant improvement in prevention of HIV infection
    - there is no other drug product on the market with an indication for HIV prevention

# Truvada<sup>®</sup>

## (Emtricitabine[FTC]-Tenofovir disoproxil fumarate[TDF])

- Fixed-dose combination tablet of two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) approved for use in combination with other antiretroviral drugs for treatment of HIV infection
- Two-drug combination CANNOT be used to treat HIV
  - Resistance develops rapidly when fewer than three drugs are used at one time
  - Substitutions in HIV reverse transcriptase e.g., emtricitabine (M184V/I) or tenofovir (K65R) can lead to resistance and potentially cross-resistance to other NRTIs



# Role of Truvada® in HIV Treatment

## Panel's Recommendations

- The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naïve patients:
  - efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) (AI)
  - ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) (AI)
  - ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) (AI)
  - raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC) (AI)
- A list of Panel-recommended alternative and acceptable regimens can be found in [Table 5a](#) and [Table 5b](#).
- Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.
- Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, March 2012



# Clinical Trials of Oral PrEP

Trial	Sponsor	Location	Population	Intervention
<b>Phase III, IIb</b>				
<b>iPrEx</b>	NIH/DAIDS	Brazil, Ecuador, Peru, South Africa, Thailand, USA	<b>Adult MSM at high risk</b>	Daily oral <b>FTC/TDF</b>
<b>Partners PrEP</b>	Univ. of Wash	Kenya, Uganda	<b>Serodiscordant couples</b>	Daily oral TDF or <b>FTC/TDF</b>
<b>CDC TDF2</b>	CDC	Botswana	<b>Adult heterosexual men and women</b>	Daily oral <b>FTC/TDF</b>
<b>FEM-PrEP</b>	FHI	Kenya, South Africa, Tanzania	<b>Adult women at high risk</b>	Daily oral <b>FTC/TDF</b>
<b>VOICE</b>	NIH/DAIDS	Uganda, South Africa, Zimbabwe	<b>Adult women</b>	Daily oral <b>FTC/TDF</b> or TDF or tenofovir vaginal gel
<b>Phase II</b>				
<b>CDC 4323</b>	CDC	USA	<b>Adult MSM</b>	Daily oral TDF (Immediate vs. delayed treatment)
<b>FHI PrEP</b>	FHI	Ghana, Cameroon, Nigeria	<b>Adult women at high risk</b>	Daily oral TDF

# Risk Evaluation and Mitigation Strategy - Considerations

- Difficulties in having two systems for dispensing the same drug
  - Need to be able to access Truvada® for treatment, PEP as well as PrEP if new indication is approved
  - One system could be easily circumvented by accessing drug through a different system
    - Truvada® is marketed
    - Individual components are also on the market

# PrEP Risk/Benefit

- In general, PrEP is viewed as another option in the prevention toolbox
- Test and bring more people into treatment
- Reduce risk of acquisition of HIV
- Labeling that includes a PrEP indication could provide
  - Information for individuals and health care providers about benefits and risks, importance of adherence, HIV testing, and safer sex practices including condoms
- Balance protective benefits with:
  - Risk of development/acquisition of resistant HIV-1 variants
  - Toxicity of long term ARV therapy
  - Potential for behavioral compensation



# Advisory Committee Questions

- Risk/benefit assessment
  - Population indication
- Safety assessments
  - Frequency of HIV testing
    - Development of resistance
  - Monitoring for renal/bone toxicity
- Risk mitigation strategies
- Post-marketing trials

# Achieving an AIDS-Free Generation

“...our efforts have helped set the stage for an historic opportunity, one that the world has today: to change the course of this pandemic and usher in an **AIDS-free generation**....”



***Hillary Rodham Clinton***  
*U.S. Secretary of State*  
*NIH Bethesda, November 2011*







# **NDA 21-752 S-030**

## **TRUVADA®**

**(emtricitabine-tenofovir disoproxil fumarate)**

**Pre-exposure Prophylaxis (PrEP) Indication for  
Prevention of Sexually Acquired HIV-1**

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**Antiviral Drugs Advisory Committee Meeting  
May 10, 2012**

**Peter S. Miele, M.D., Medical Officer  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research**

# Agenda

## iPrEx and Partners PrEP Trials

- Efficacy
  - Pre-specified Analyses
  - Exploratory Post-hoc Analyses
- Safety
- Resistance
- Behavioral Changes

# **NDA 21-752/S-030**

## **Proposed indication**

Pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults



# Clinical Trials of Oral PrEP

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<b>VOICE</b>	NIH/DAIDS	Uganda, South Africa, Zimbabwe	<b>Adult women</b>	Daily oral <b>FTC/TDF</b> or TDF or tenofovir vaginal gel
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# **Efficacy**



# Trial Designs

Trial	Population	Randomized (N)	Intervention
<b>iPrEx</b>	<b>Adult MSM at high risk</b>	<b>2499</b>	<b>Daily oral FTC/TDF</b>
<b>Partners PrEP</b>	<b>Heterosexual serodiscordant couples</b>	<b>4747</b>	<b>Daily oral TDF or FTC/TDF</b>

- Randomized, prospective, placebo-controlled
- **Monthly** HIV testing
- Risk reduction counseling, condoms, and treatment of symptomatic STIs provided at every visit
- Powered to show at least 30% efficacy
  - Standard threshold in HIV vaccine and microbicide trials

# iPrEx

## MSM at High Risk

- Any of the following in the past 6 months:
  - No condom use during anal intercourse with male partner who is HIV+ or HIV status is unknown
  - Anal intercourse with > 3-5 male sex partners
  - Exchanged money, gifts, shelter, or drugs for anal sex with a male partner
  - Sexually transmitted infection (STI) - at screening or in the 6 months prior to study entry
  - Inconsistent condom use with HIV+ partner

## iPrEx Outcomes

- 2,499 MSM enrolled
  - Placebo 1248
  - FTC/TDF 1251
- Median duration of exposure: 77.3 weeks (IQR 52.1, 118.9)
- By End of Treatment:

	HIV Seroconversions	Persons (mITT)	Event per 100 PY
Placebo	83	1218	4.2
FTC/TDF	48	1224	2.4

- Risk reduction: 42% (CI 18-60%)

## iPrEx Outcomes

- High self-reported adherence not reliable
  - Poor correlation with detectable drug levels
- Poor self-reported adherence
  - Predictive of undetectable drug levels
- In a sub-study of intracellular drug concentration and HIV seroconversion, estimated risk reduction among subjects with measurable drug concentrations was 87.5% (CI 66-95%) ***as compared with placebo***

# Tenofovir Pharmacokinetics

- Half-lives of tenofovir (TFV-DP) and emtricitabine (FTC-TP) much longer in peripheral mononuclear blood cells (PBMCs)
- Tenofovir half-lives:
  - PBMCs 87-150 hours
  - Plasma 19 hours
- PBMC (intracellular) drug concentrations are more reflective of long-term drug adherence
- PK subgroup analyses focused only on intracellular tenofovir concentrations

# iPrEx

## Subgroup Analysis: Intracellular TFV-DP Concentrations

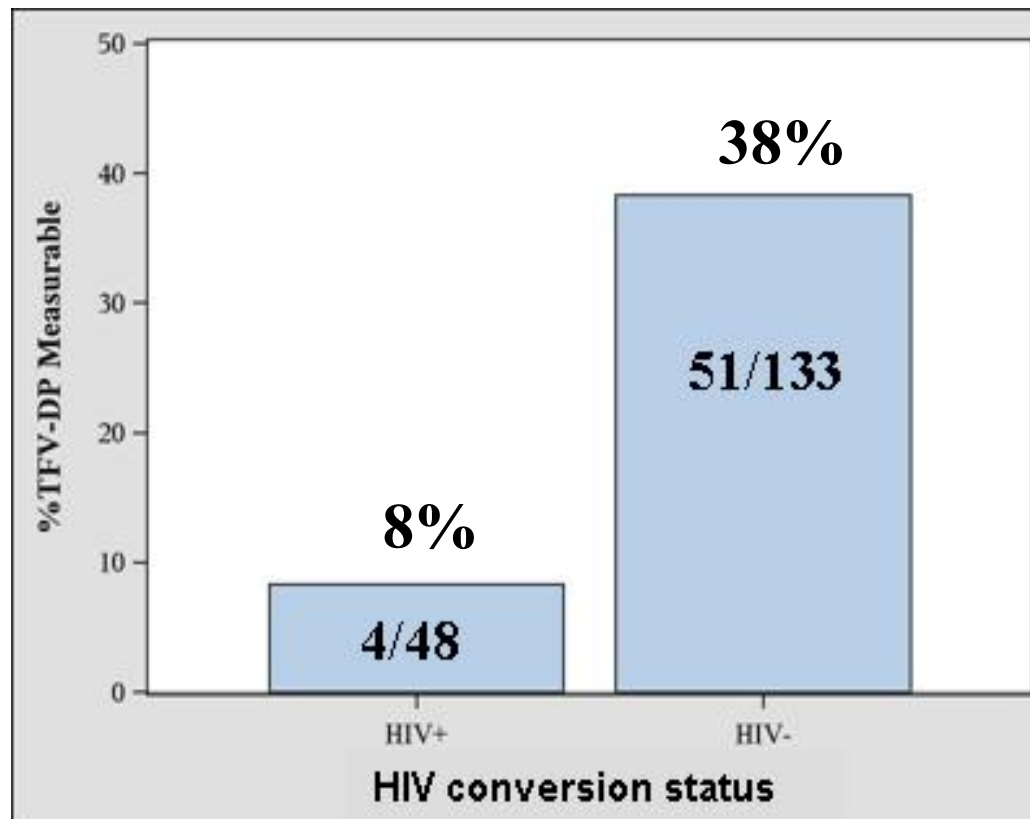
### Methods:

- Blood for PBMCs collected from all subjects at baseline, every 24 weeks and at end of trial (or seroconversion)
- Analysis used PK measurement from study visit retrospectively determined to be closest to the time of HIV infection
- Cases: all 48 HIV seroconverters from FTC/TDF arm
- Controls: 3 uninfected subjects from FTC/TDF arm matched to each seroconverter (n=133). All 3 controls were matched by site and time on treatment and one control was also selected based on positive URAI status



# iPrEx

## Subgroup Analysis: Intracellular TFV-DP Concentrations

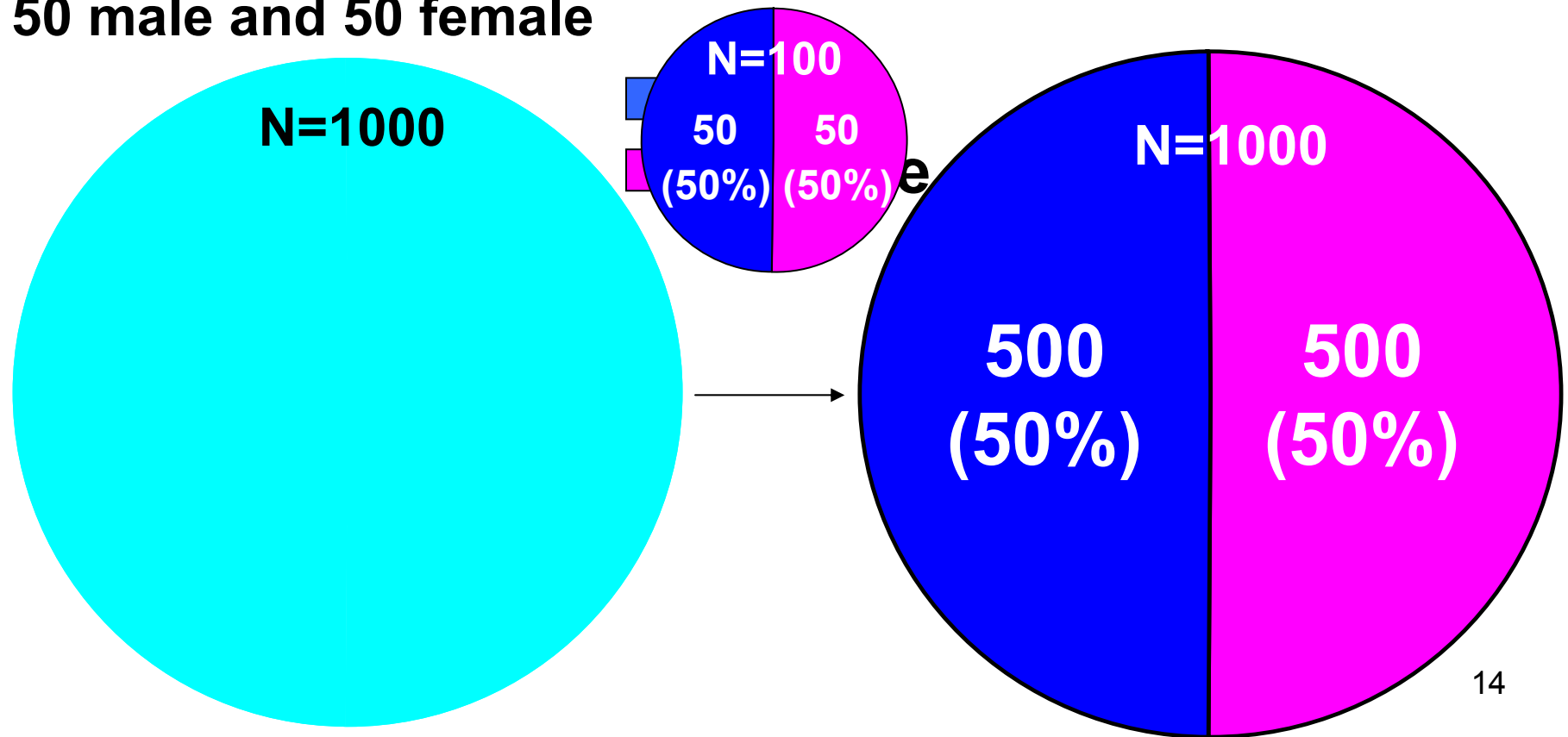


# Assumption Demonstration

Population N=1000 (How many male and female?)

Randomly sample a subset of N=100

50 male and 50 female



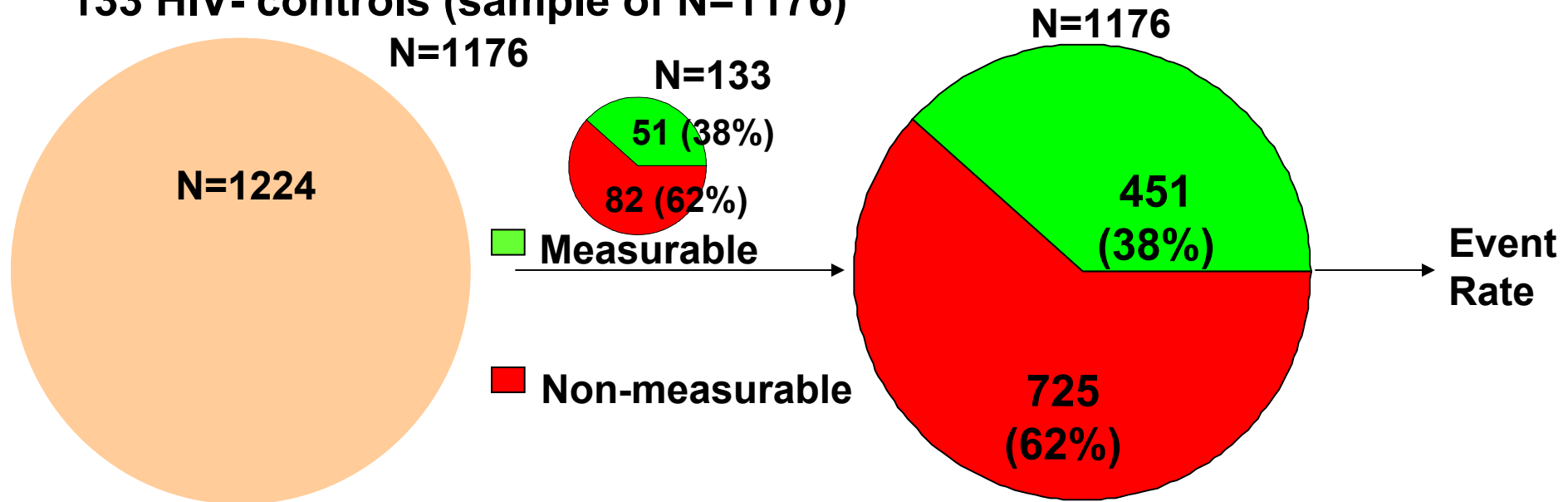
# iPrEx Drug Adherence by Intracellular TFV-DP

48 HIV+:

■ Non-measurable N=44

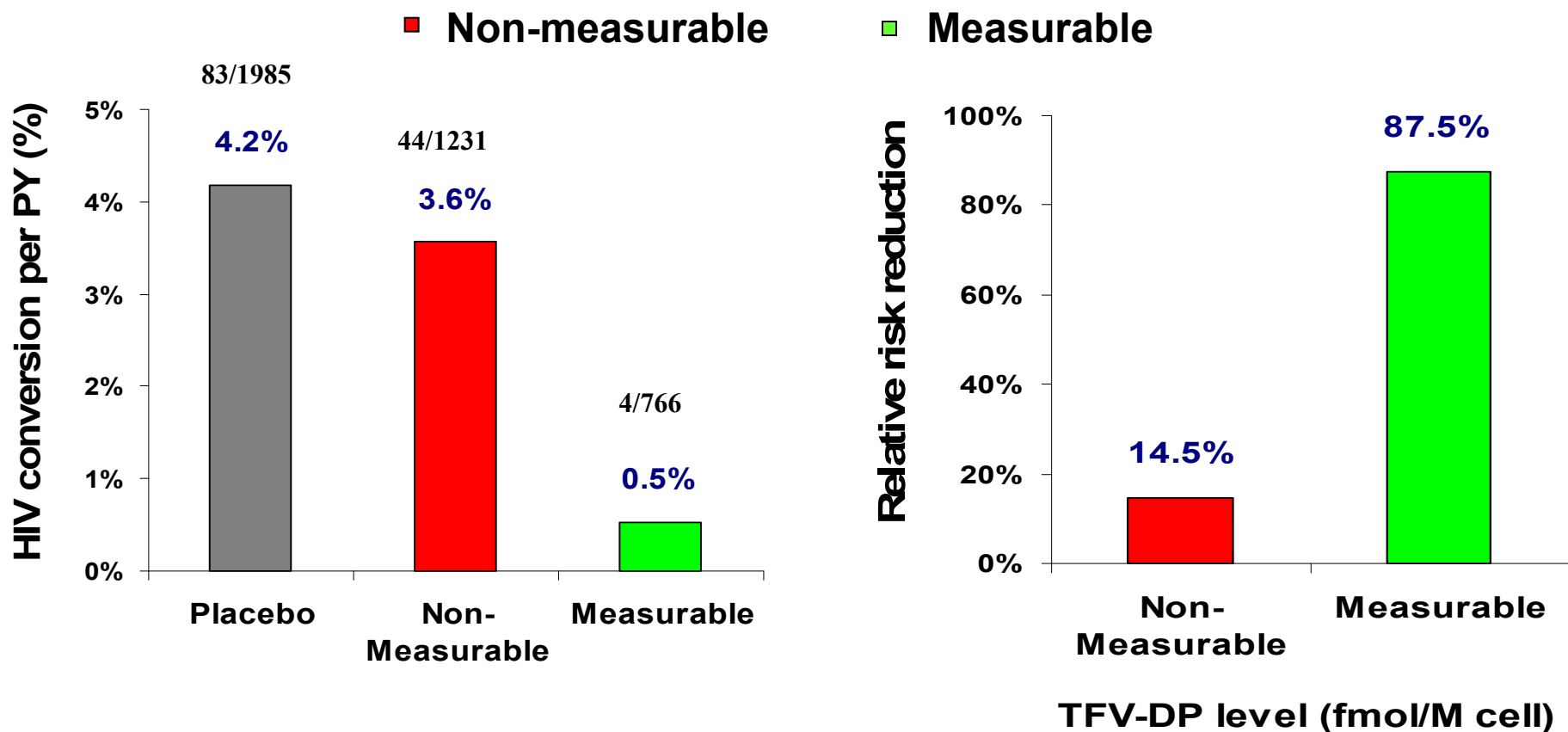
■ Measurable N=4

FTC/TDF treatment group (N=1224)  
1176 HIV-:  
133 HIV- controls (sample of N=1176)



# iPrEx

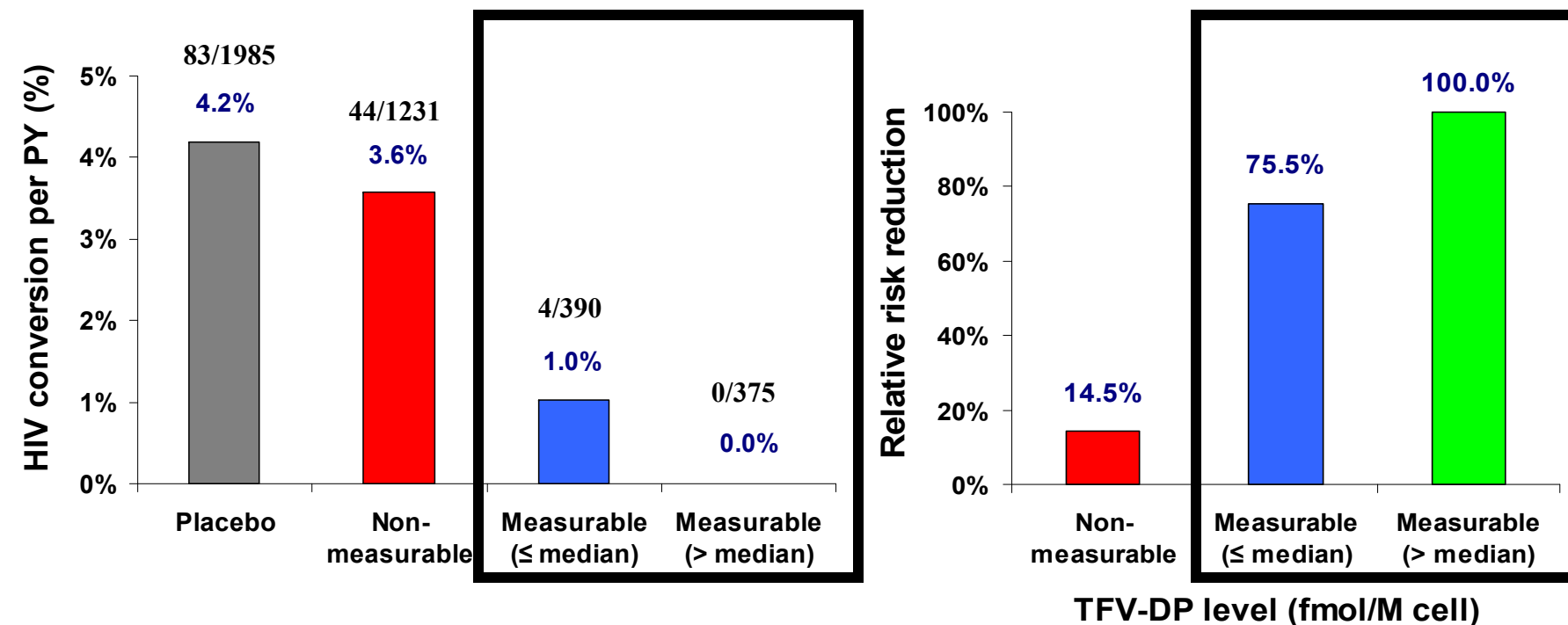
## Adherence by Intracellular TFV-DP Levels: Efficacy



# iPrEx

## Adherence by Intracellular TFV-DP Levels: Efficacy

■ Non-measurable ■ Low measurable ■ High Measurable



Median: 15.6 fmol/M cell



# **iPrEx**

## **Efficacy Summary**

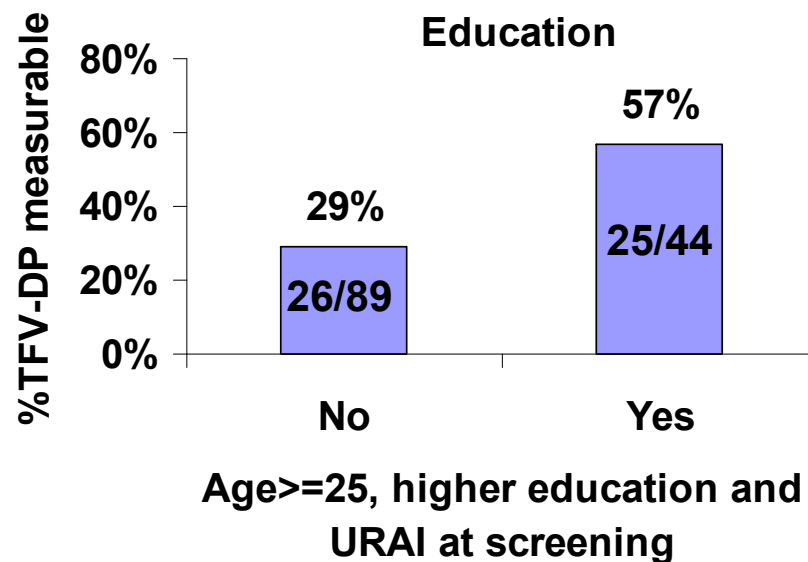
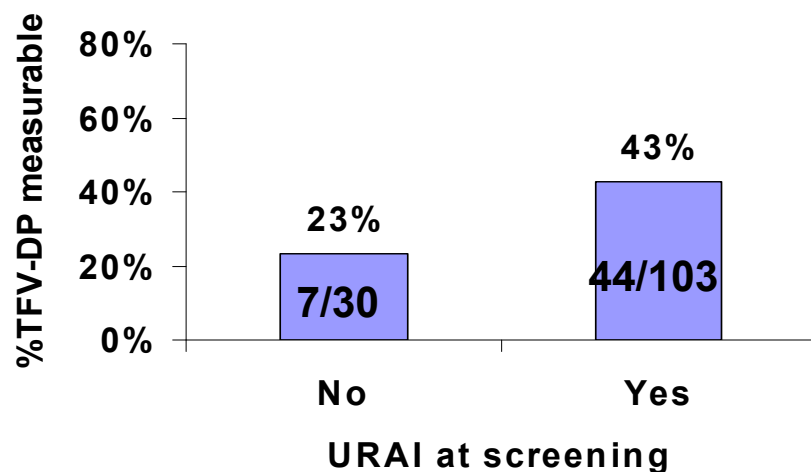
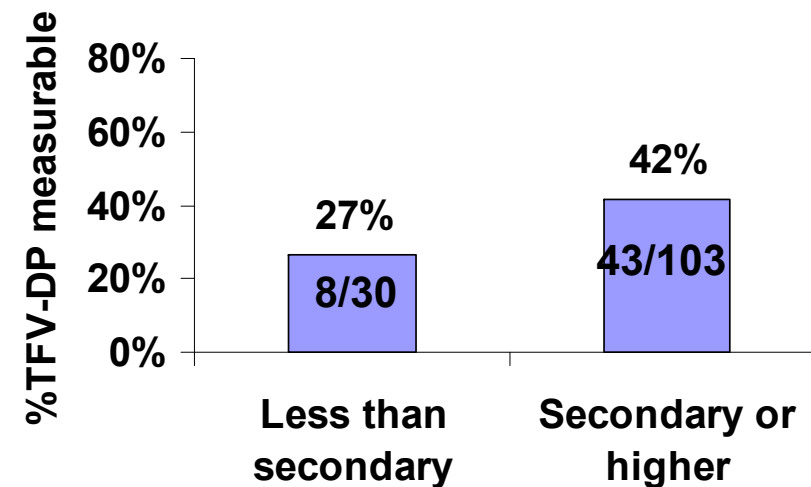
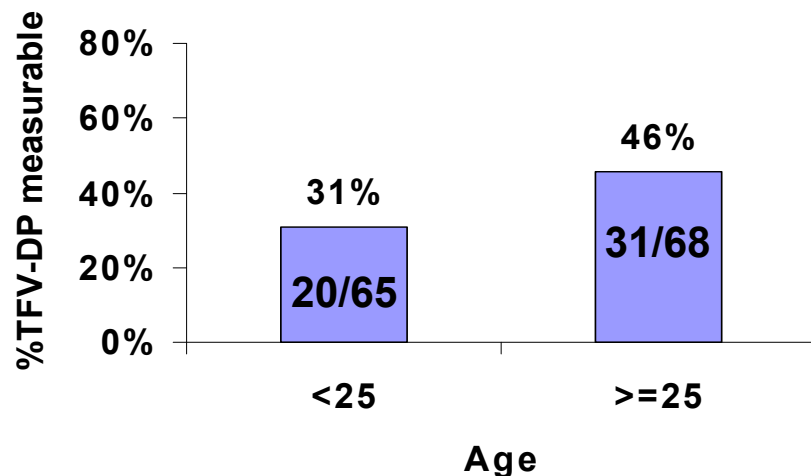
FDA findings similar to iPrEx investigator results





# iPrEx

## Better Adherence: Age, Education, and URAI





# iPrEx

## Risk Reduction in Higher Adherence Subgroups

Subgroup		Event per 100 PY		Relative Risk Reduction
		Placebo	Truvada	
Age	<25	4.5	3.2	28%
	≥ 25	3.8	1.7	56%
Education	Less than Secondary	4.2	3.7	12%
	Secondary or Higher	4.2	2.0	52%
Reported URAI at screening	No	1.5	1.9	-26%
	Yes	5.8	2.7	53%
Age ≥ 25, Secondary/Higher Education and URAI	No	3.9	3.1	23%
	Yes	4.9	0.7	85%



## Partners PrEP Outcomes by Gender

	Men	Women
<b>HIV seroconversion rate (per 100 PY)</b>		
<b>Placebo</b>	<b>1.49</b>	<b>2.81</b>
<b>TDF</b>	<b>0.56</b>	<b>0.81</b>
<b>FTC/TDF</b>	<b>0.24</b>	<b>0.95</b>
<b>Risk Reduction compared with Placebo</b>		
<b>TDF</b>	<b>63%</b> <b>(CI 34-91)</b>	<b>71%</b> <b>(CI 49-94)</b>
<b>FTC/TDF</b>	<b>84%</b> <b>(CI 67-101)</b>	<b>66%</b> <b>(CI 41-92)</b>

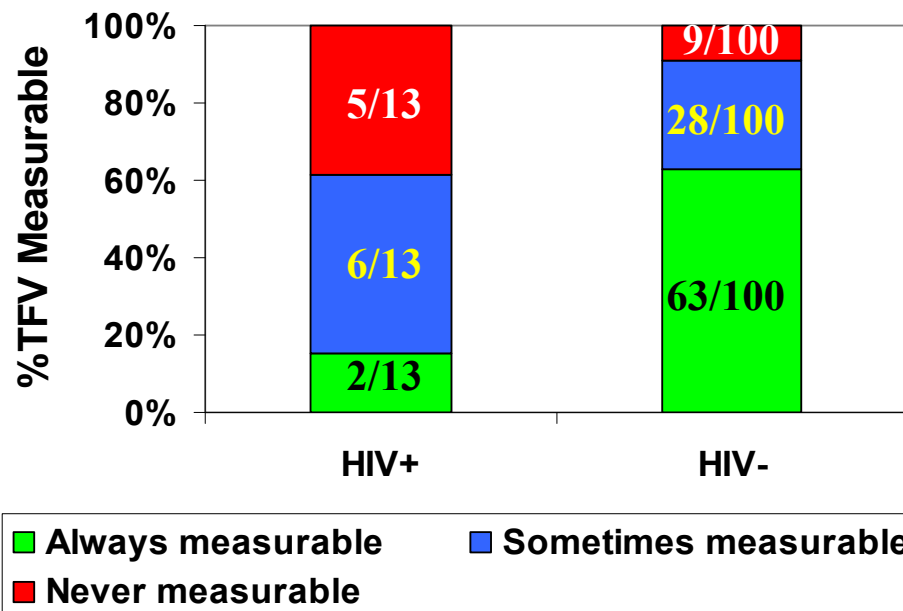
## Partners PrEP Outcomes

- FDA conducted sensitivity analyses to evaluate the impact of:
  - Initiation of ART in the HIV-infected index partner
  - Study drug interruptions in female subjects due to pregnancy/breastfeeding
- Conclusion: no impact on efficacy results

# Partners PrEP

## Subgroup Analysis: Plasma Tenofovir Levels

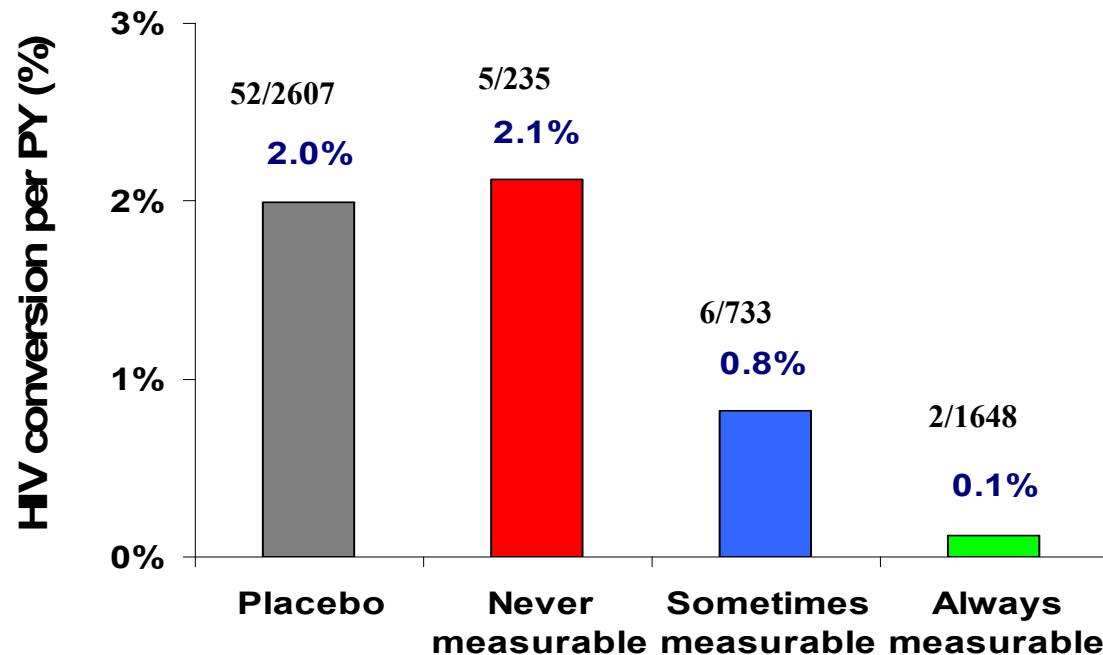
- Case-cohort data: FTC/TDF arm
  - Plasma samples at Month 1, 3, 6, 12, 18, 24, 30, 36
  - Cases = all 13 HIV seroconverters from FTC/TDF arm
  - Cohort = 100 uninfected FTC/TDF subjects, randomly selected



# Partners PrEP

## Adherence by Plasma TFV Levels: Efficacy

■ Never measurable    ■ Sometimes measurable    ■ Always measurable



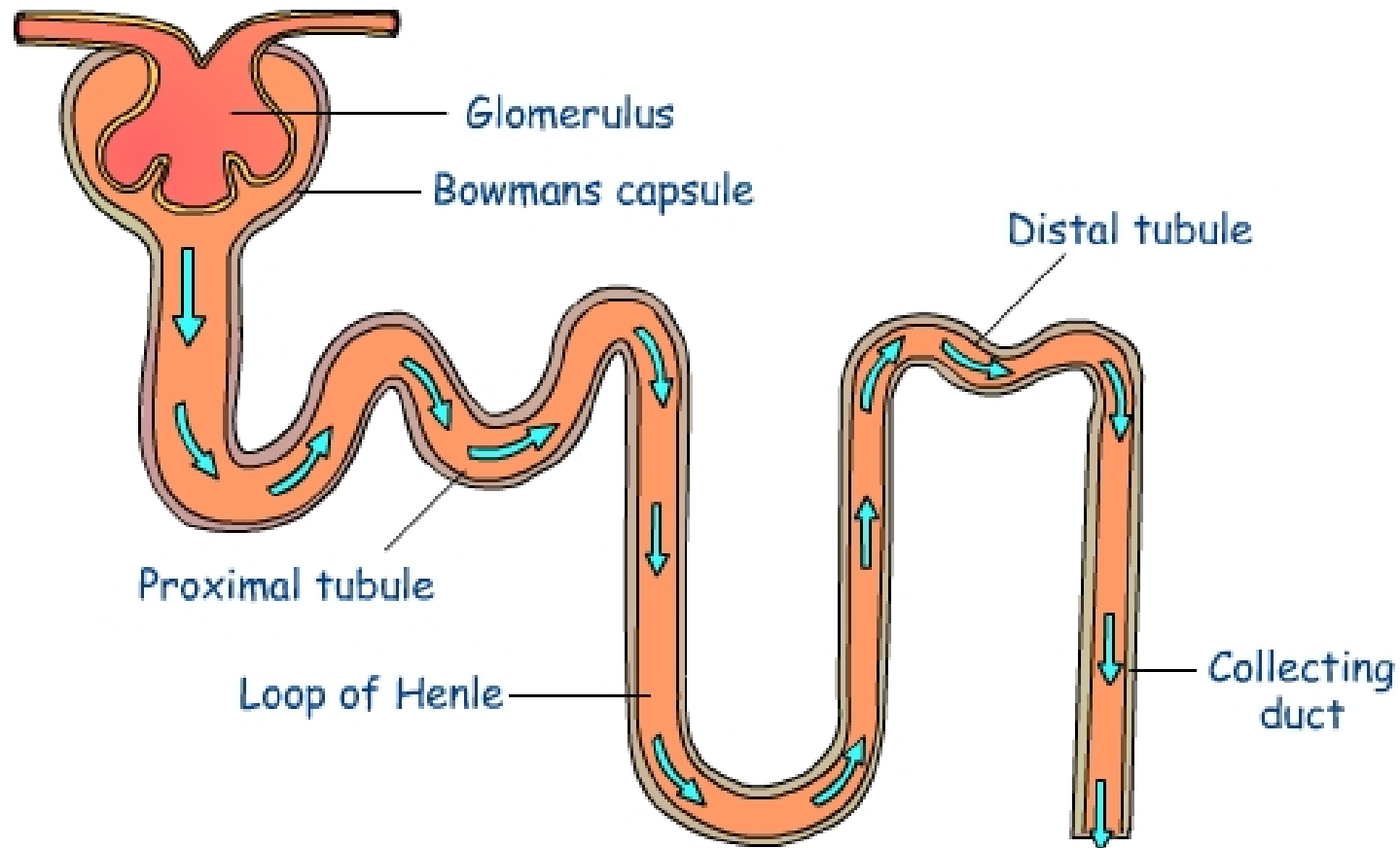


**U.S. Food and Drug Administration**  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

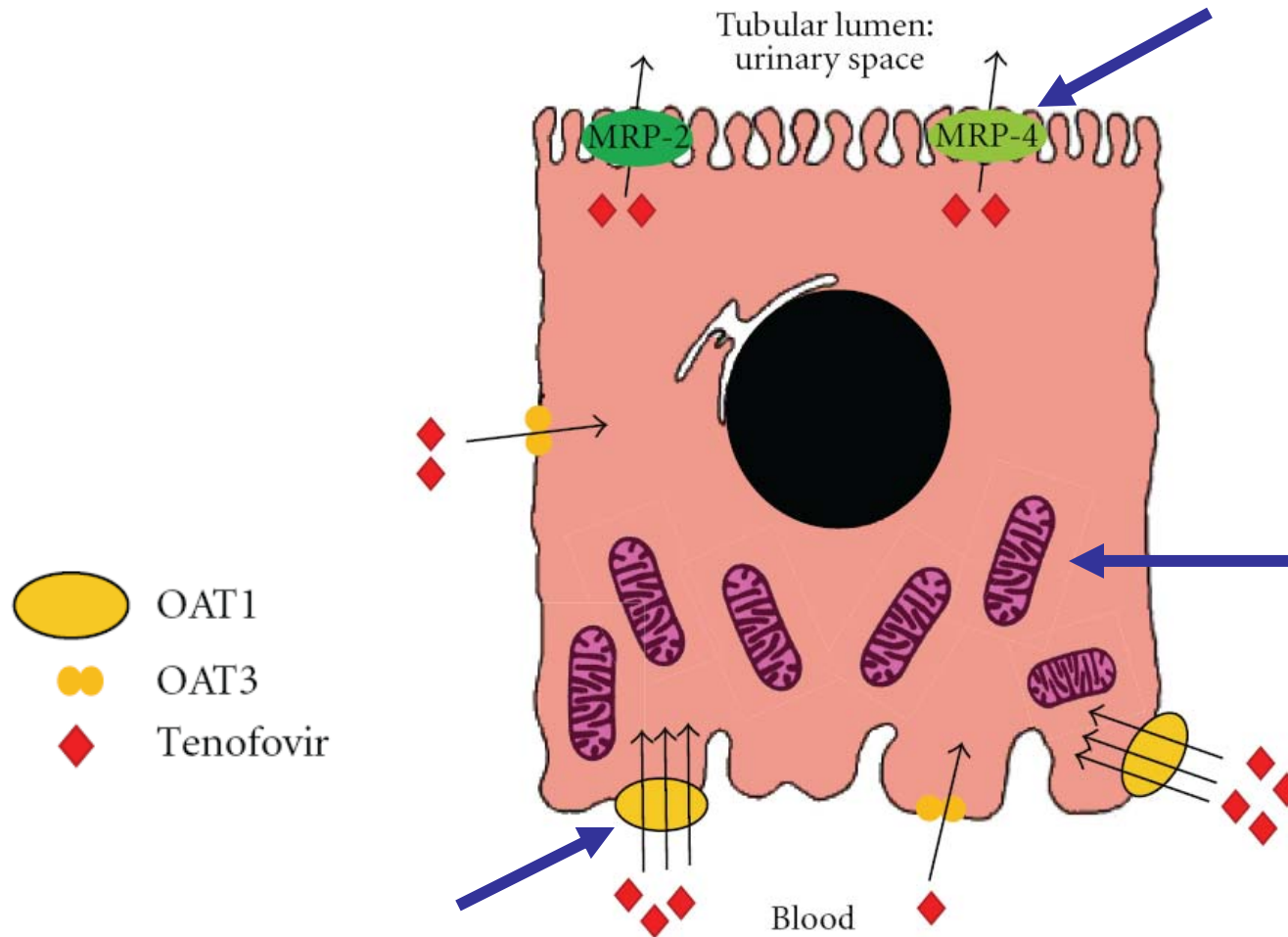
# **Safety Review Focus on Tenofovir**

# Tenofovir Excretion





# Tenofovir Proximal Renal Tubule Cell Transporters



# Tenofovir Renal Tubulopathy

## Clinical Presentation

- Tubular dysfunction may precede decline of renal function
  - May be clinically inapparent
- Severe cases may present as partial or complete Fanconi syndrome, with or without ↓ creatinine clearance\*
  - Appears to occur infrequently
- Proximal tubulopathy may also lead to decreased bone mass due to phosphate wasting or calcitriol (activated Vitamin D) deficiency

# Proximal Renal Tubulopathy

## Laboratory Abnormalities

- Increased fractional excretion of urinary phosphate or uric acid
- Proteinuria,  $\beta$ 2-microglobulinuria
- Non-diabetic glycosuria
- Elevations in serum creatinine, metabolic acidosis
- Decreased activation of Vitamin D into calcitriol
  - $\uparrow$  PTH

# Predictors of Renal Function Decline with Tenofovir

- Low CD4 count, advanced HIV disease
- Older age
- Low body weight
- Lower baseline creatinine clearance
- Type 2 DM, HTN, HCV infection
- Concomitant nephrotoxic drugs
- SNP (genetic variant) of ABCC2 gene

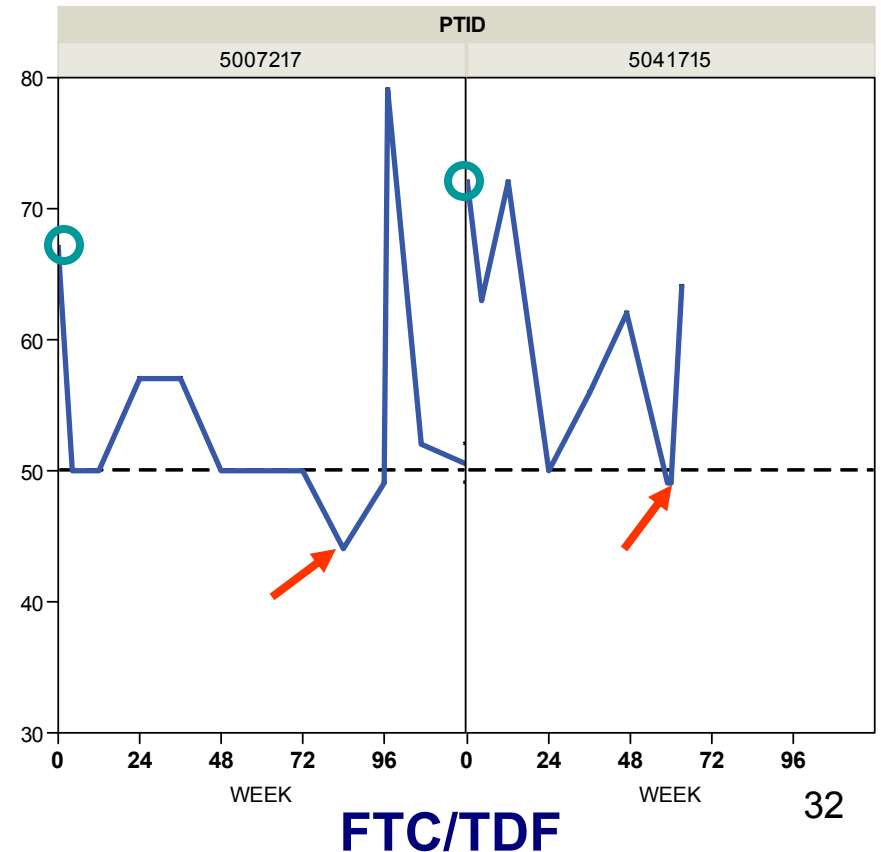
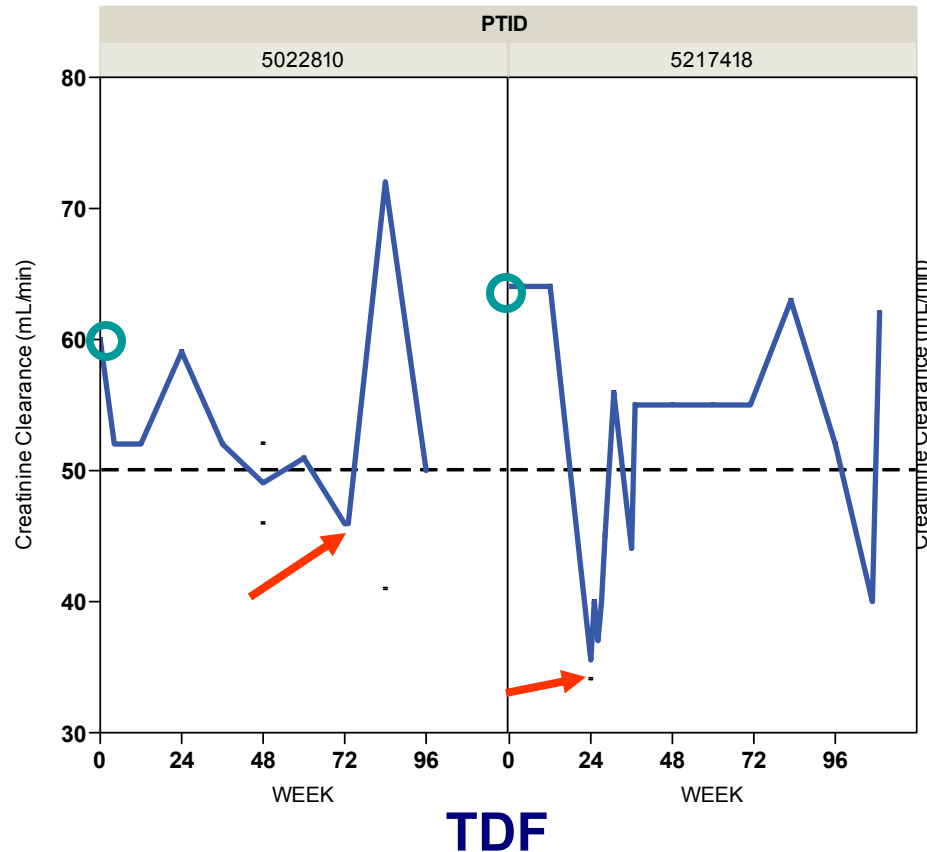
# iPrEx and Partners PrEP

## Review of Safety

- No new adverse events identified
- FTC/TDF well tolerated, few discontinuations for TDF-related adverse events
- iPrEx: 7 subjects interrupted FTC/TDF for creatinine elevations, versus 3 placebo subjects
  - 6 resumed FTC/TDF without further incident
- Partners PrEP: 4 subjects discontinued TDF or FTC/TDF for ↓ creatinine clearance ( $\text{CrCl} \leq 50 \text{ mL/min}$ ), versus 1 placebo subject
  - CrCl returned to  $>50 \text{ mL/min}$  with drug withdrawal

# Partners PrEP

## Discontinuations for Reduced Creatinine Clearance





# PrEP Clinical Trial Data

## Graded Renal Laboratory Events

	CDC 4323 <sup>a</sup>		iPrEx <sup>b</sup>		Partners <sup>b</sup>		
	TDF (N=184)	Placebo (N=186)	TDF/FTC (N=1225)	Placebo (N=1226)	TDF (N=1575)	FTC/TDF (N=1570)	Placebo (N=1573)
<b><i>Elevated Serum Creatinine – n (%)</i></b>							
Grade 1	5 (3)	9 (5)	10 (1)	7 (1)	3 (<1)	6 (<1)	4 (<1)
Grade 2	1 (1)	1 (1)	1 (<1)	1 (<1)	1 (<1)	0	0
Grade 3	0	1 (1)	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
<b><i>Low Serum Phosphorus – n (%)</i></b>							
Grade 1	14 (8)	14 (8)	135 (11)	120 (10)	321 (20)	337 (21)	351 (22)
Grade 2	37 (20)	29 (16)	13 (1)	10 (1)	89 (6)	83 (5)	81 (5)
Grade 3	2 (1)	3 (2)	0	0	11 (1)	12 (1)	10 (1)
Grade 4	0	0	0	0	0	1 (<1)	0

# PrEP Clinical Trial Data

## Urine Abnormalities

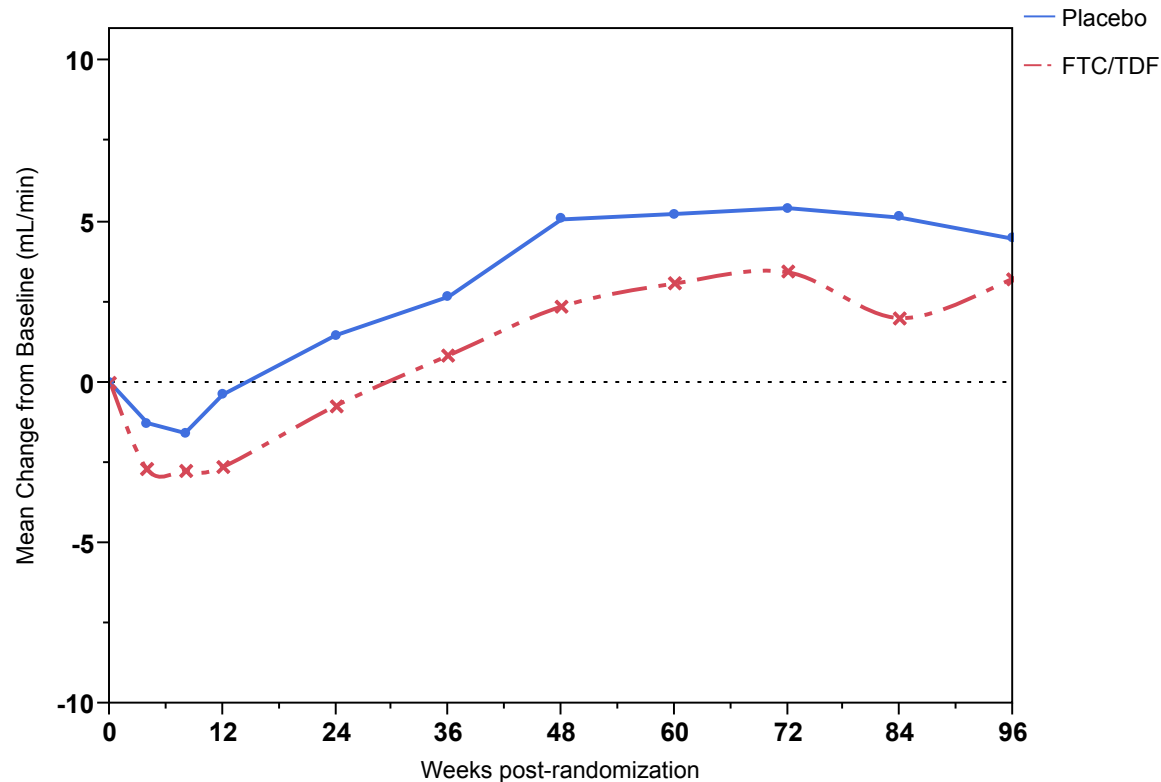
Urinalysis Abnormalities	iPrEx		Partners PrEP		
	FTC/TDF (N=1171)	Placebo (N=1190)	TDF (N=1577)	FTC/TDF (N=1571)	Placebo (N=1574)
Recurrent proteinuria, n (%)	92 (8)	69 (6)	15 (1)	16 (1)	20 (1)
- and graded creatinine increase	5 *	4	0	0	0
Proteinuria with glycosuria, n (%)	6 (<1)	4 (<1)	2 (<1)	2 (<1)	3 (<1)
- and graded hypophosphatemia	5/6	2/4	2/2	1/2	2/3
- and BMD loss >5%	2/5	0	N/A	N/A	N/A

\* Includes subject who permanently discontinued FTC/TDF due to increased creatinine



# iPrEx

## Evaluation of Creatinine Clearance



**Changes in CrCl over time by treatment arm**

## Categorical Analysis of Creatinine Elevations

### Repeated Observation of $\geq 20\%$ Increase over Baseline

Serum Creatinine	CDC 4323		iPrEx		Partners PrEP	
	TDF (N=184)	Placebo (N=181)	FTC/TDF (N=1225)	Placebo (N=1226)	TDF arms (N=3145)	Placebo (N=1573)
<b>Creatinine <math>\geq 20\%</math> from baseline,* n (%)</b>	<b>18</b> <b>(10)</b>	<b>13</b> <b>(7)</b>	<b>136</b> <b>(11)</b>	<b>114</b> <b>(9)</b>	<b>420</b> <b>(13)</b>	<b>138</b> <b>(9)</b>
<b>Baseline Mean Creatinine (mg/dL)</b>	<b>0.91</b>	<b>0.95</b>	<b>0.78</b>	<b>0.76</b>	<b>0.67</b>	<b>0.67</b>
<b><i>At 12 Months</i></b> <b>Mean creatinine (mg/dL)</b>	<b>1.03</b> <b>(+22%)</b>	<b>1.13</b> <b>(+20%)</b>	<b>0.86</b> <b>(+11%)</b>	<b>0.83</b> <b>(+9%)</b>	<b>0.82</b> <b>(+21%)</b>	<b>0.80</b> <b>(+19%)</b>

\*  $\geq 20\%$  increase on more than two visits or on any two consecutive visits

- When available, no correlation with proteinuria or glycosuria
- Corresponding mean serum phosphorus unchanged compared to baseline

# **CDC 4323**

## **Creatinine and Bone Mineral Density Changes from Baseline**

# CDC 4323

## Baseline DEXA Results

- Low bone mineral density (BMD), defined as Z score  $\leq -2.0$ , was observed more frequently than expected in the enrolled MSM population
  - Median age 41 years
- Significant baseline correlates:
  - Amphetamine use (OR 5.9)
  - Inhalants (OR 4.6)
  - MVI/calcium/Vitamin D use (OR -0.26)
- Evaluation of low baseline BMD (16/20)
  - 2 Vitamin D deficiency
  - 1 hypogonadism

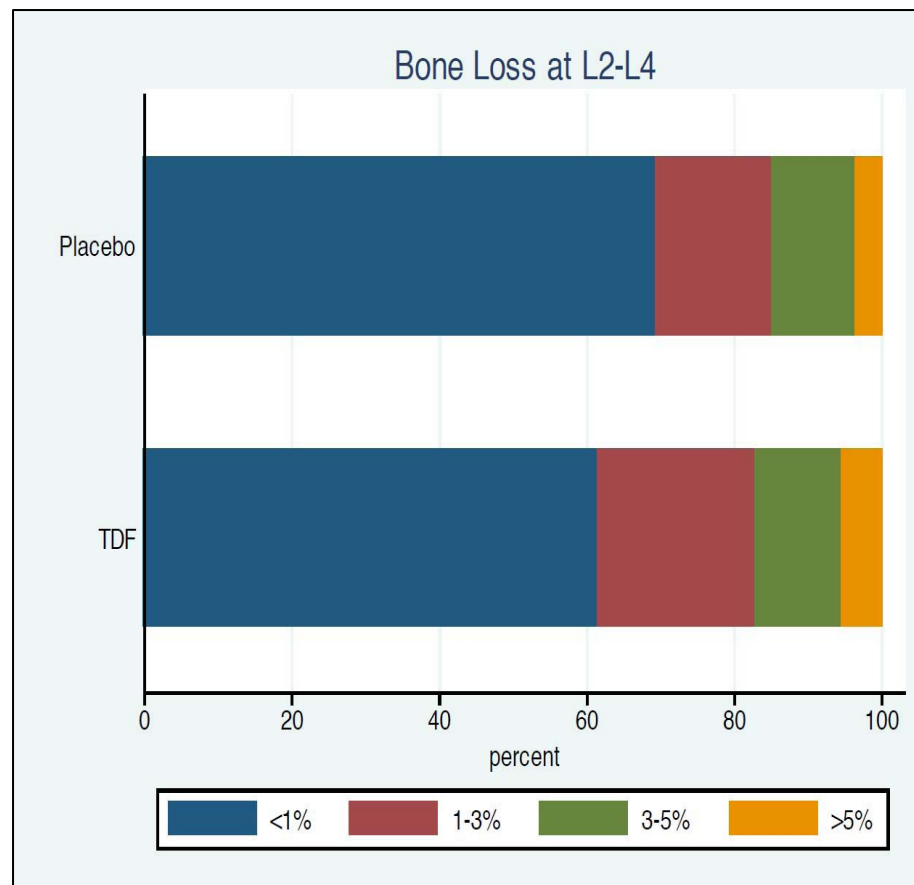
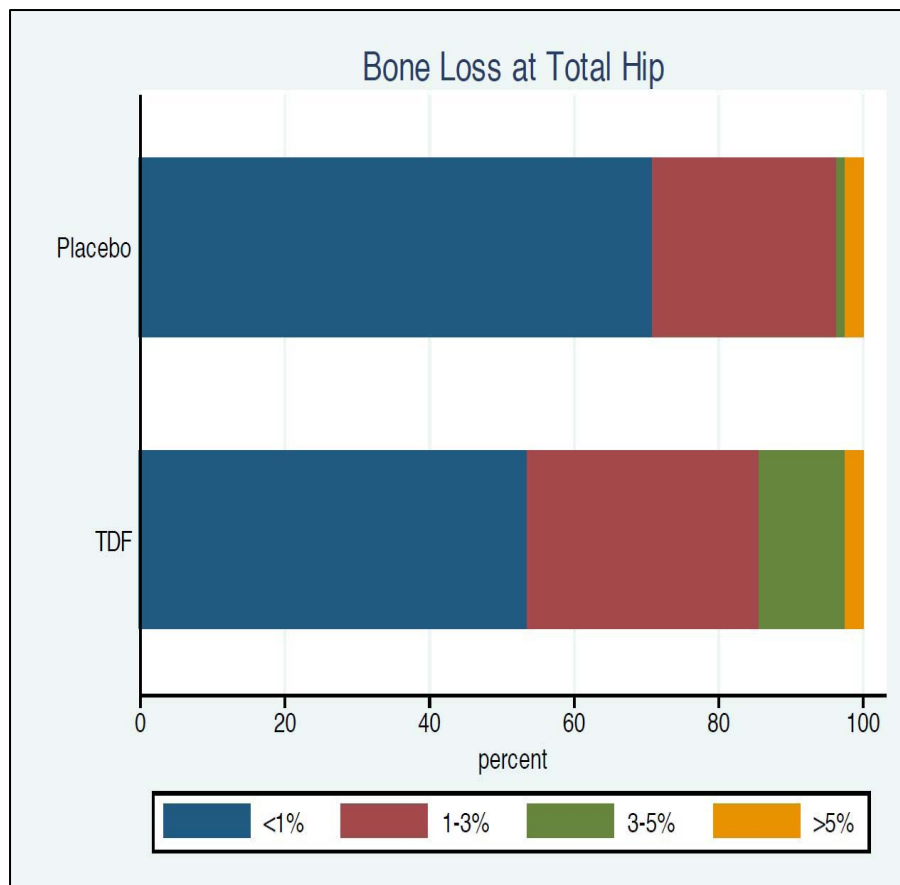
# Reductions in BMD

## Categorical Analyses

- Greater than 3%
  - More than expected BMD loss in healthy men
- Greater than 5%
  - Approximate BMD loss seen in post-menopausal women over a 2 year period

# CDC 4323

## BMD Loss at Month 24 Compared to Baseline



## Creatinine Increase $\geq 20\%$ from Baseline DEXA Scan Findings

	TDF (N=184)	Placebo (N=181)
<b>Creatinine <math>\geq 20\%</math> <math>\uparrow</math> from Baseline, in DEXA substudy</b>	<b>n/N=13/18</b>	<b>n/N=8/13</b>
• and $\geq 3\%$ $\downarrow$ in BMD from Baseline in Total Hip OR Lumbar Spine, n (%)	10/13 (77)	3/8 (37)
– with any $\geq 20\%$ $\uparrow$ Alkaline phosphatase, n (%)	9/10 (90)	2/3 (67)
<b>Creatinine <math>&lt; 20\%</math> <math>\uparrow</math> from Baseline, in DEXA substudy</b>	<b>n/N=81/166</b>	<b>n/N=84/161</b>
• and $\geq 3\%$ $\downarrow$ in BMD from Baseline in Total Hip OR Lumbar Spine, n (%)	46/81 (57)	38/84 (45)
– with any $\geq 20\%$ alkaline phosphatase, n (%)	40/46 (87)	13/38 (34)

# CDC 4323

## New Onset Back Pain

Changes from Baseline at End of Treatment	TDF (n=201)	Placebo (n=199)
New Onset Back Pain, n (%)	18 (9)	10 (5)
Mean age	38	43
Mean % $\Delta$ Creatinine	-3%	0.2%
Mean % $\Delta$ Phosphorus	2%	5%
Mean % $\Delta$ Alkaline Phosphatase	4%	6%
>3% $\downarrow$ in BMD at Total Hip <u>or</u> L1-L4 Spine, n (%)	5 (28)	4 (40)
>5% $\downarrow$ in BMD at Total Hip <u>or</u> L1-L4 Spine, n (%)	4 (22)	3 (30)



# **CDC 4323**

## **Bone Fractures**

### **Tenofovir – 9 subjects**

- 4 single/multiple foot
- 1 2 arms/4 ribs/1 wrist
- 1 4 fractured vertebrae
- 1 clavicle
- 1 hand/elbow
- 1 scaphoid

### **Placebo – 5 subjects**

- 2 single foot
- 1 finger
- 1 hand
- 1 radial head

# Safety Summary

- No serious events related to TDF observed in about 4500 individuals who received TDF or FTC/TDF in 2 large clinical trials and 1 small supportive safety trial.
- Very few subjects (n=6) discontinued TDF or FTC/TDF for decreases in CrCl or increased creatinine.
  - CrCl or creatinine documented to return to baseline in 5/6
- Small, but consistent, increase in incidence of serum creatinine elevation relative to placebo observed across clinical trials
  - Did not appear to correlate with increased risk of clinical events or other laboratory abnormalities
- Small, but significant, reductions in BMD relative to placebo were observed with TDF in 2 trials of MSM

## Safety Summary

- Because long-term significance of BMD reductions are unknown at this time, consider identifying and managing causes of osteoporosis and osteomalacia:
  - Vitamin D deficiency, hypogonadism, tobacco use, others
- This may also assist in identifying individuals for:
  - Baseline and follow-up DEXA scans
  - Vitamin D and calcium supplementation



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# Resistance

# Resistance – Summary

Trial	Drug	<u>NRTI Resistance/Infections</u>	
		On Treatment	Baseline
iPrEx	FTC/TDF	0/48	2/2 (M184V*, M184I)
Partners PrEP	FTC/TDF	0/12	1/3 (M184V*)
	TDF	0/15	2/5 (K65R*, D67N+K70R)
TDF2 (CDC)	FTC/TDF	0/9	1/1 (A62V+K65R+M184V*)

\* Confirmed wild-type virus in pre-treatment sample



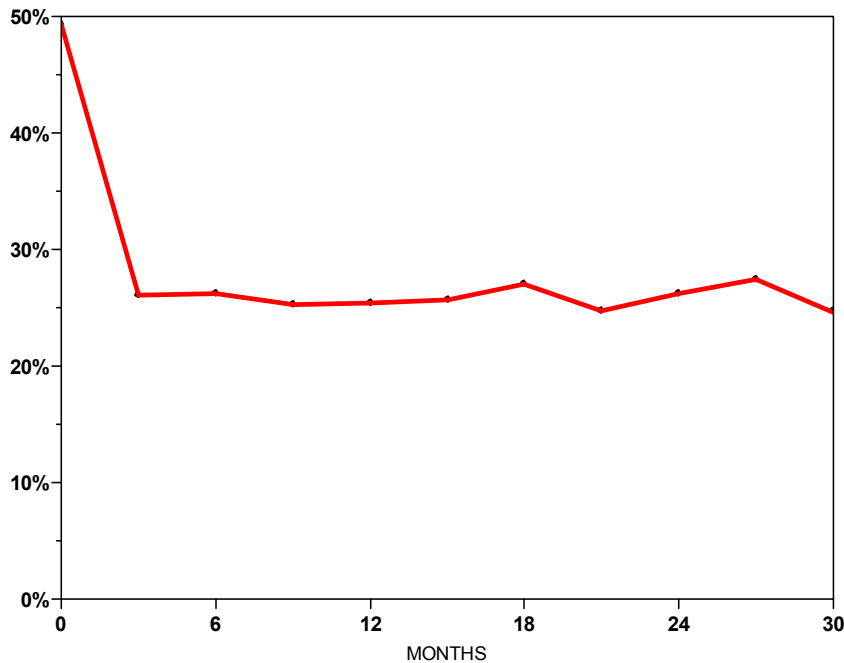
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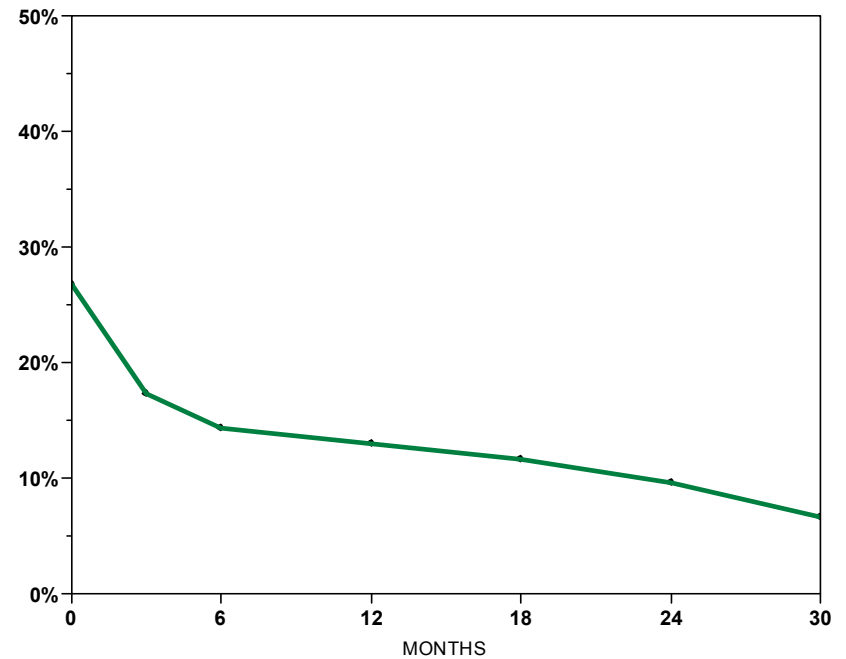
# **Behavioral Changes**

# Behavioral Changes

## Unprotected Sexual Intercourse



**iPrEx**



**Partners PrEP**

# iPrEx

## Sexually Transmitted Infection Rates

Any STI*	FTC/TDF	Placebo
Baseline Prevalence	16%	16%
Post-baseline Incidence (rate per 100 PY)	12.6	12.2

\* Any STI = syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, genital ulcer disease, or herpes simplex virus-2



# Partners PrEP

## Sexually Transmitted Infection Rates

Any STI*	TDF	FTC/TDF	Placebo
Baseline	10%	11%	12%
1-12 Months	3%	3%	3%
13-24 Months	2%	2%	2%

\* Any STI = syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and genital ulcer disease

# Conclusions

- Safety and efficacy of FTC/TDF for the prevention of HIV-1 infection in high risk individuals is supported by two large clinical trials
- Regular HIV testing, adherence and behavioral counseling on safer sex practices, including condom use, are essential components of healthcare delivery around PrEP
- Risk compensation was not observed
- Resistance was identified only in individuals who took TDF or FTC/TDF during early infection, prior to diagnosis
- Careful assessment of risk factors for HIV infection can identify individuals for whom PrEP may be appropriate



# TRUVADA®

(emtricitabine/tenofovir disoproxil fumarate)

## Proposed REMS for TRUVADA for a Pre-exposure Prophylaxis (PrEP) Indication for Prevention of HIV-1 Infection

### Antiviral Drugs Advisory Committee Meeting

May 10, 2012

Carolyn L. Yancey, M.D., Senior Medical Officer  
Division of Risk Management  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

# Agenda

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- Background of a Risk Evaluation and Mitigation Strategy (REMS)
- A REMS for TRUVADA for a PrEP Indication
- Challenges: REMS Assessment Plan

# Background

- Food and Drug Administration Amendments Act (FDAAA) of 2007
  - Amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) of 1938
  - Authorizes FDA to require submission of a Risk Evaluation and Mitigation Strategy (REMS) pre-approval or, post-approval, if the Agency becomes aware of **new safety information** and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug

# Factors to Consider for a REMS

- Estimated size of the population likely to use the product
- Seriousness of the disease or condition that is to be treated with the product
- Expected benefit of the product with respect to the disease or condition
- Expected or actual duration of treatment with a product
- Seriousness of any known or potential adverse events that may be related to a product and the background incidence of such events in the population likely to use the product
- Whether a product is a new molecular entity

# Elements of a REMS

- **A Medication Guide**
  - Provides FDA approved patient-friendly labeling
  - Can be required as part of labeling if FDA determines any of the following:
    - Patient labeling could help prevent serious adverse events
    - Product has serious risks that could affect a patient's decision to use or to continue to use the product
    - Patient adherence to directions is crucial to the product's effectiveness
  - May be few occasions when MG will be included in the REMS
- **Communication Plan**
  - FDA approved materials used to support implementation of a REMS and/or inform healthcare providers about serious risks with the product

# Elements of a REMS

- Elements to Assure Safe Use (ETASU)

To mitigate a serious risk(s) in the labeling may require that:

- A. Healthcare providers who prescribe the drug have particular training or experience or are specially certified
- B. Pharmacies, practitioners or healthcare settings that dispense the drug are specially certified
- C. Drug will be dispensed to patients only in certain health care settings, such as hospitals
- D. Drug will be dispensed to patients with evidence of safe-use conditions
- E. Each patient will be subject to certain monitoring
- F. Each patient will be enrolled in a registry



# Elements of a REMS

- ETASU

- Are not mutually exclusive; in fact, there is considerable overlap among each of the elements to assure safe use
- Some elements to assure safe use include restrictions to drug distribution based on the way a drug is prescribed or dispensed
- Educational materials are important components of several of the ETASU

# Elements of a REMS

- **Timetable for Submission of Assessments**
  - Every REMS for a New Drug Application (NDA) or a Biologic License Application (BLA) must have a Timetable for Submission of Assessments of the REMS
  - Not included in a REMS for an ANDA
  - Must include schedule for submission of assessments
    - No less frequent than 18 months, 3 years, and 7 years
  - REMS can require additional assessments
  - Can be eliminated after 3 years



# What are the Risks for Mitigation with TRUVADA for a PrEP Indication for Prevention of HIV-1 Infection?

## Risks for Mitigation: REMS for TRUVADA for a PrEP Indication

- **Development of Drug Resistance**
  - TRUVADA may not always prevent HIV-1 infection
  - Drug resistant HIV-1 variants may develop in persons continuing to take TRUVADA for a PrEP indication who converted from HIV-1 negative to HIV-1 positive

# Focus of Education: REMS for TRUVADA for a PrEP Indication

- Adherence to:
  - Checking HIV-1 serostatus *prior to* initiating TRUVADA for PrEP
  - Monitoring HIV-1 status *throughout* chronic administration of TRUVADA for a PrEP indication
  - Taking a once-daily, oral dosage regimen
  - Practicing safer sex
- Screening for:
  - Sexually transmitted infections *prior to* and *throughout* administration of TRUVADA for a PrEP indication
  - Signs and symptoms of acute HIV infection *prior to* and *throughout* administration of TRUVADA for a PrEP indication

# Educational Materials in the Public Domain

- Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents (DHHS Panel, March 2012)
- CDC Interim Guidance on HIV Pre-Exposure Prophylaxis for Men Who Have Sex with Men (February 2011)

# Stakeholder Feedback: Forum for Collaborative HIV Research

- Academicians, Federal and State Government, Industry, Public-Private Interest Groups, Public Health
- Stakeholders did not agree with:
  - Restricted drug distribution, mandatory or voluntary registry for prescribers or persons taking TRUVADA for a PrEP indication
  - Documentation of Safe Use Conditions prior to dispensing
    - Negative HIV test result
- Stakeholders agreed that:
  - A restricted risk mitigation program could be circumvented because TRUVADA is approved and marketed in the U. S.
  - Education should be considered in the context of existing preventive initiatives in the public domain
  - Postmarketing surveillance should monitor drug resistant variants, to the extent possible.

# Proposed REMS for TRUVADA for a PrEP Indication

- I. Goals
- II. REMS Elements
  - A. Medication Guide
  - B. Prescriber Training and Education *not linked to restricted drug distribution or access*
  - C. Timetable for Submission of Assessments



# I. GOALS

The goals of the REMS for TRUVADA for a Pre-Exposure Prophylaxis (PREP) indication are:

- To inform and educate prescribers, other healthcare professionals, and individuals at high risk of acquiring HIV-1 infection about:
  - The importance of strict adherence to the recommended dosing regimen
  - The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take TRUVADA, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
  - The fact that TRUVADA for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

## II. REMS Elements

### A. Medication Guide

- A TRUVADA Medication Guide will be dispensed with each TRUVADA prescription in accordance with 21 CFR 208.24
- Single Medication Guide for more than one indication:
  - For education of patients with established HIV -1 infection about the serious risks associated with TRUVADA
  - For education of uninfected individuals taking TRUVADA for a PrEP indication for prevention of HIV-1 infection
    - Risk of continuing to take TRUVADA if they convert from HIV-1 negative to HIV-1 positive
    - Importance of adherence to the comprehensive management plan to reduce the risk of acquiring HIV-1 infection, including adherence to dosing regimen and preventive measures

## II. REMS Elements

### B. Element to Assure Safe Use: Prescriber Training and Education *not linked to restricted distribution or access*

#### – Target Prescribers

- Primary Care Physicians including Internal Medicine, Family Practice and General Medicine
- Infectious Disease Specialists
- Emergency Medicine Physicians
- Obstetricians-Gynecologists
- Addiction Specialists

## II. REMS Elements

### B. Prescriber Training and Education

- Dissemination of safety risk information to relevant professional organizations for outreach to prescribers likely to prescribe TRUVADA for a PrEP indication for prevention of HIV-1 infection
- Educational materials include:
  - Dear Healthcare Provider letter
  - Educational Materials for Providers
  - Training Guide for Healthcare Providers
  - Provider Safety Brochure *and* Individual Safety Brochure: Important Safety Information about TRUVADA for a PrEP Indication
  - Wallet Card - TRUVADA for a PrEP Indication
  - REMS website with access to educational materials

## II. REMS Elements

### C. Timetable for Submission of REMS Assessments

- Periodic REMS assessments will be submitted to FDA according to a specified timetable
  - 6 months, 12 months and annually, thereafter

# A Restricted Distribution Plan

- Not required by FDA for access to TRUVADA because a restricted distribution plan could:
  - Adversely affect access for patients with established HIV infection being treated with TRUVADA
  - Adversely create barriers to access for uninfected individuals taking TRUVADA for a PrEP indication for prevention of HIV-1 infection

# REMS Assessment Plan

- **Surveys**
  - Provider *and* Uninfected Individual Knowledge, Attitude and Behavior Surveys
    - Understanding of key safety risk messages in educational materials
- **Number of prescribers who complete the training and education program**
  - Applicant will maintain a database of providers who completed the training and education program
- **Drug-Use Data for TRUVADA for a PrEP indication**
  - TRUVADA prescriptions *without* concomitant antiretroviral products
  - Number and type of providers, by specialty, who prescribed TRUVADA *without* concomitant antiretroviral products

# REMS Assessment Plan

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- Based on the information submitted to FDA, an assessment and conclusion of whether or not the REMS is meeting its goals, and whether or not a modification to the REMS is needed.



# Challenges: REMS Assessment Plan

- To determine if the REMS impacts:
  - Reducing the number of individuals continuing to take TRUVADA for a PrEP indication who converted from HIV-1 negative to HIV-1 positive
  - Reducing development of drug resistant HIV-1 variants in individuals taking TRUVADA for a PrEP indication
- To determine:
  - Number of individuals taking TRUVADA for a PrEP indication for prevention of HIV-1 infection
    - Challenge: TRUVADA can be prescribed for post-exposure to HIV infection treatment *without* concomitant antiretroviral drugs

# Challenges: REMS Assessment Plan

- No registries in the REMS
  - Physicians prescribing or uninfected individuals taking TRUVADA for a PrEP indication
- No ICD-10 Code\* to identify *uninfected individuals*
- No documentation of Safe Use Conditions
  - No required HIV-1 negative test result for access to TRUVADA for a PrEP indication

\* International Statistical Classification of Diseases and Related Health Problems 10<sup>th</sup> Revision