Forum for Collaborative HIV Research

# Managing PrEP Related Safety Concerns

**Veronica Miller PhD**

**June 12, 2012**

# Sources

- Forum PrEP REMS meeting – August 19, 2011
  - http://www.hivforum.org/index.php?option=com_content&task=view&id=436&Itemid=65
- Strobos et al: Safety considerations in the prevention of HIV transmission by PrEP
  - Forum Annals 2011
- FDA DAVP Advisory Committee
  - May 2012

# Safety Concerns

- PrEP* reduces risk of HIV acquisition
- Potential harms:
  - What will PrEP do to the patient?
  - What will PrEP do to the virus?
  - What will PrEP do to public health?

# 1. Patient

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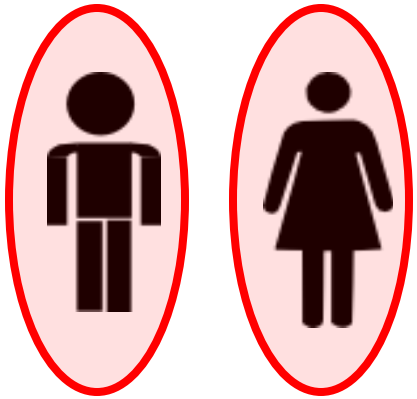
- Benefit:
  - Remain HIV-free

Vs.

- Harm:
  - Drug toxicity



# Clinical Safety Concerns

- Renal
- Bone
- Pregnancy

# 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 (CrCl) ≤ 50 mL/min, versus 1 placebo subject
  - CrCl returned to >50 mL/min with drug withdrawal

# CDC 4323
## Baseline DEXA Results

- Low bone mineral density (BMD), defined as Z score ≤ -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

# 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

# Pregnancy outcomes

| | TOTAL | TDF | FTC/TDF | Placebo |
|---|---|---|---|---|
| **Number of pregnancies** | **288** | 112 | 80 | 96 |
| **Number of pregnancies with outcomes available** data through 30 January 2012 | **262** | 103 | 74 | 85 |
| **Pregnancy outcome** | | | | |
| **Live birth** | **167 (64%)** | 73 (71%) | 40 (54%) | 54 (64%) |
| **Pregnancy loss** | **95 (36%)** | 30 (29%) | 34 (46%) | 31 (36%) |
| ***P-value, vs. placebo*** | | *0.35* | *0.26* | |

PARTNERS PrEP STUDY

Men who have sex with men (MSM) have

**19.3 Higher Odds**

of HIV infection

Baral S, Plos Med 2007

# Safety Considerations in the Prevention of Transmission of HIV by Pre-Exposure Prophylaxis (or "PrEP")

**Strobos J, Hauschild BC, Miller V.**
*Ann Forum Collab HIV Res.* Volume 13 (5): 2011; 1-11
*Forum for Collaborative HIV Research, University of California Berkeley School of Public Health*
On behalf of all moderators and panelists

The use of oral tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (TDF/FTC) to reduce the risk of acquisition of HIV represents a major breakthrough in HIV prevention research. Results from recent pre-exposure prophylaxis (PrEP) trials have demonstrated the efficacy of TDF and TDF/FTC in preventing HIV acquisition in different populations, including men who have sex with men (MSM) and heterosexual men and women.[1]

# Risk:Benefit

acceptable given clear individual benefits. Among some high-risk populations, such as the young black MSM population in the U.S. that experienced a 48% increase in HIV incidence from 2006 to 2009 and where the prevalence of HIV infection may be as high as 28%, ARV-based prevention for uninfected individuals could be considered as valuable as ARV therapy is for HIV-infected individuals[3][4]. However, the individual should be informed about the risks and potential benefits and make his/her own decision about whether to start PrEP. What may be an unacceptable safety risk in some populations may be more acceptable in others. Acquiring HIV infection is a significant and serious risk to these persons. Thus, panelists

# Take Home Message

- For patient safety:
  - Monitor renal and bone parameters
  - Monitor pregnancy

# 2. The Virus

- Concern:
  - selection for drug resistance

# Resistance – Summary

| Trial | Drug | NRTI Resistance/Infections | |
|---|---|---|---|
| | | 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**

# Infrequent Drug Resistance

- **Why?**
  - Risk of seroconversion and drug exposure are **inversely** related
  - No or low drug exposure, no selection by drug, no resistance, but **infection**
  - Good exposure → **no infection & no resistance**

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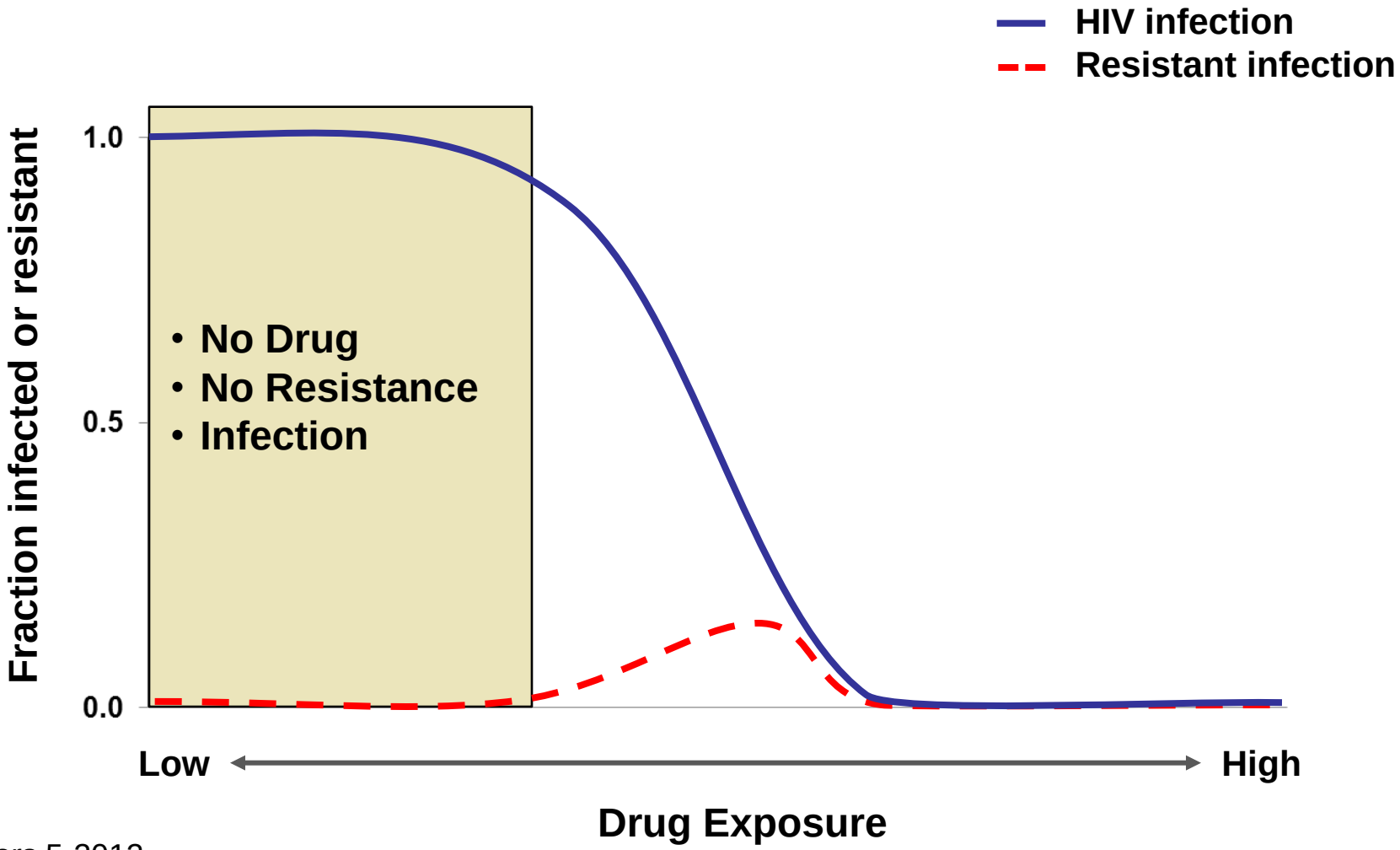
- **Resistance is still possible**
  - At drug exposures that permit infection but also provide selection of resistant variants
  - Appears to be uncommon

# Theoretical Infection-Exposure-Resistance Relationships




Mellors 5-2012

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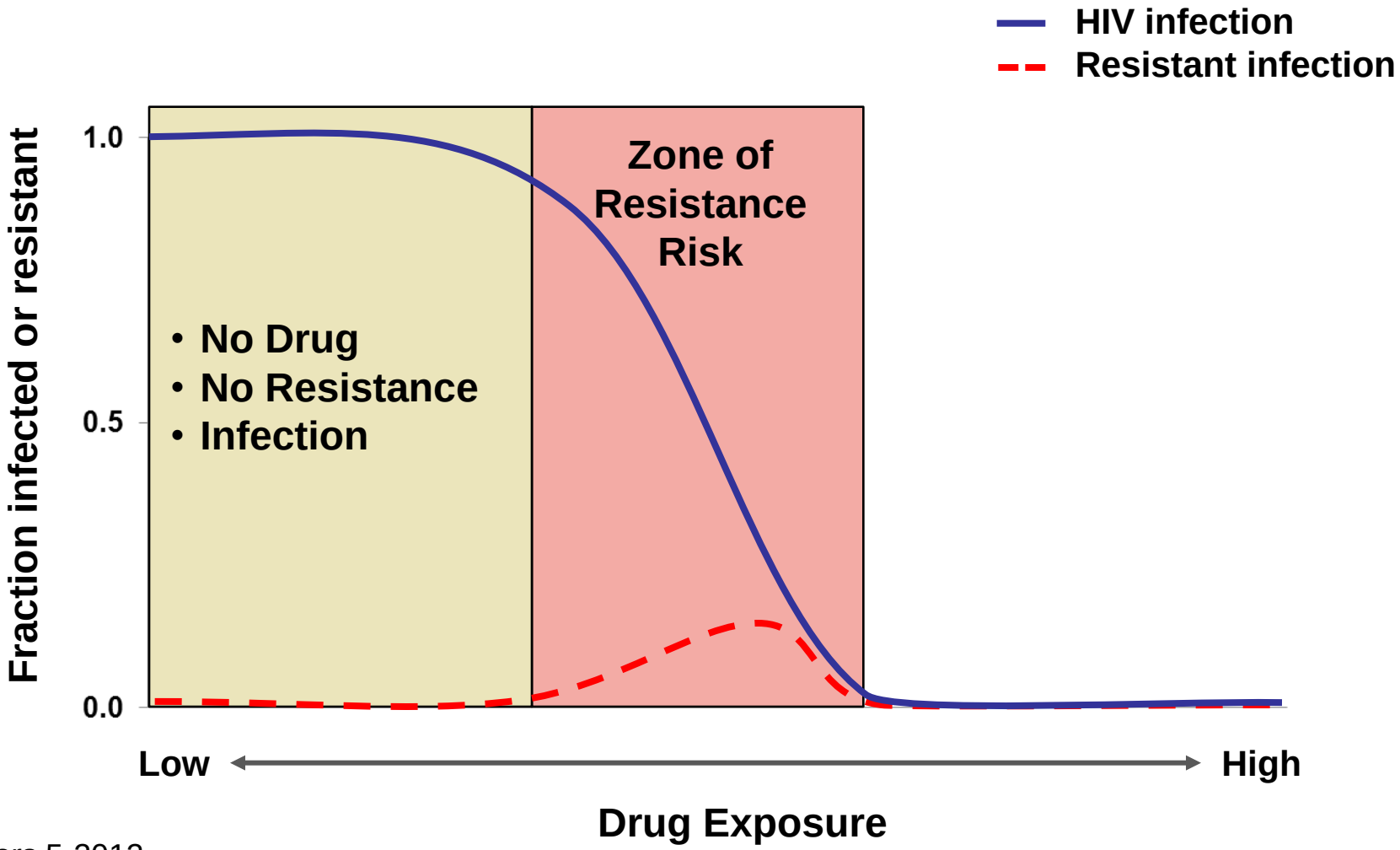


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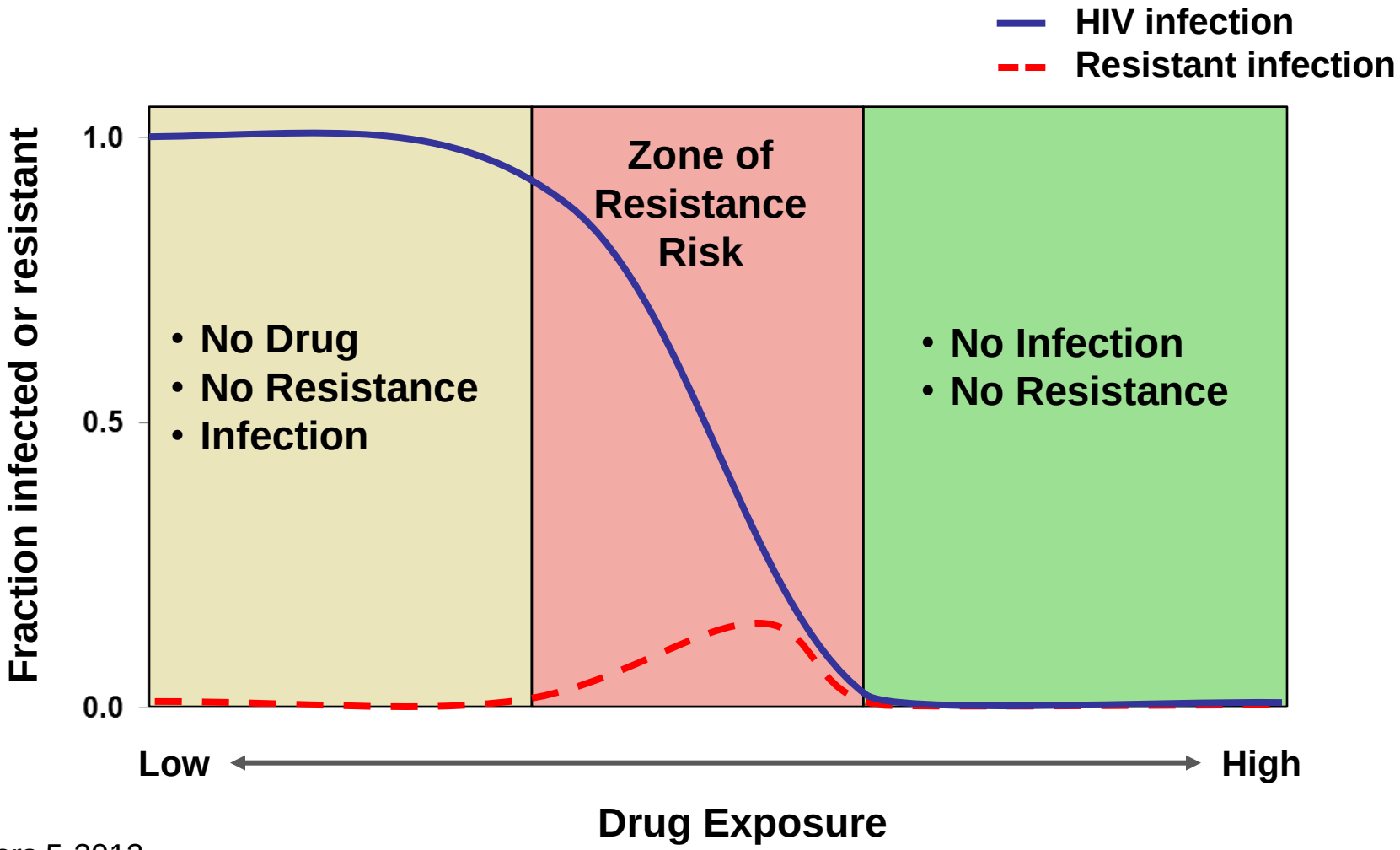


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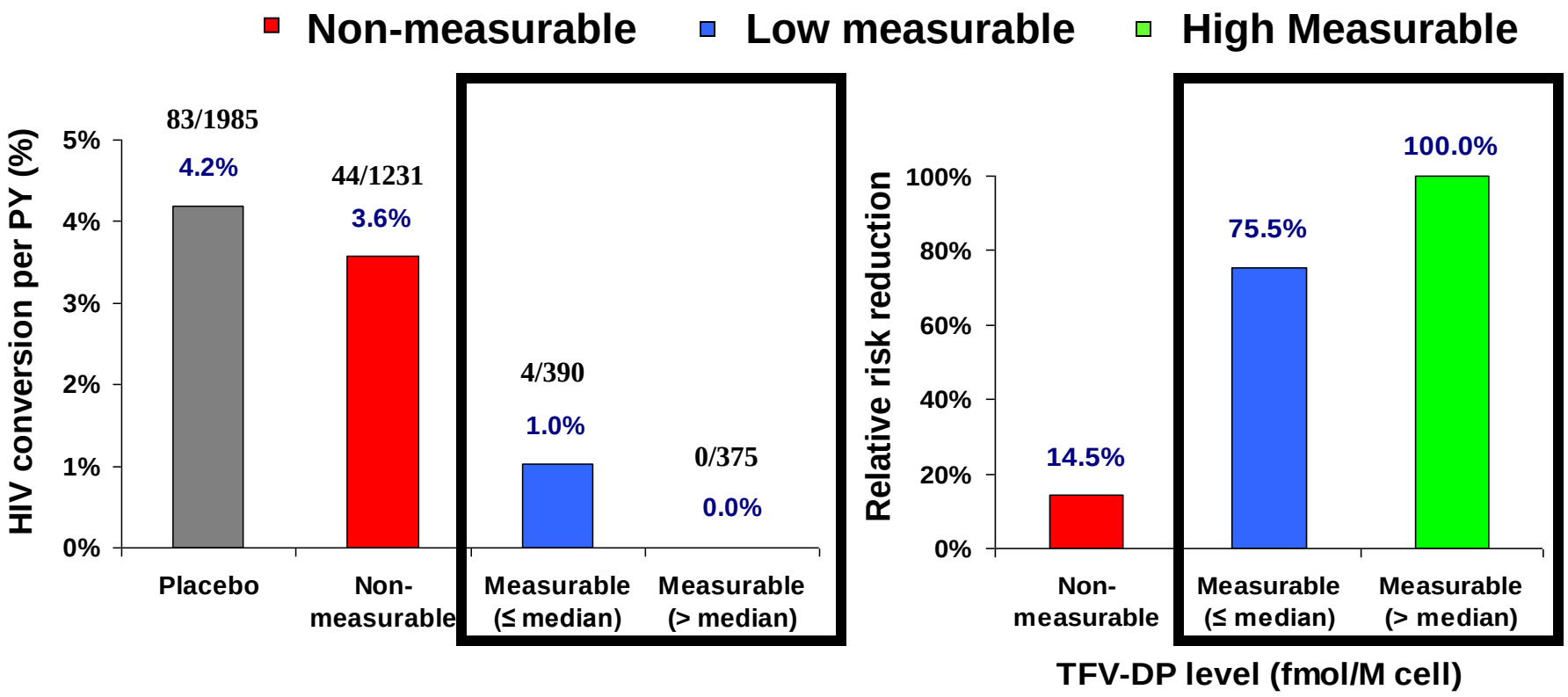
# iPrEx

## Adherence by *Intracellular* TFV-DP Levels: Efficacy

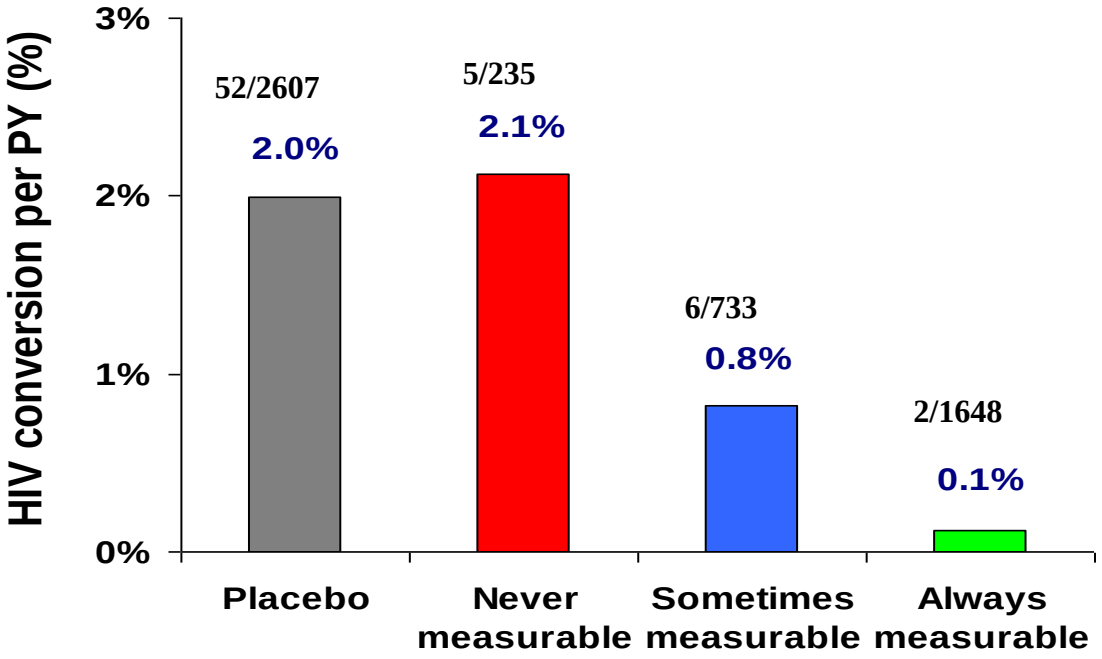



**Median: 15.6 fmol/M cell**

# Partners PrEP

## Adherence by *Plasma* TFV Levels: Efficacy

- Never measurable
- Sometimes measurable
- Always measurable



# Efficacy - Resistance

- If efficacious – no resistance
- Resistance a problem
  - Inconsistent dosing
  - If acutely infected at PrEP initiation

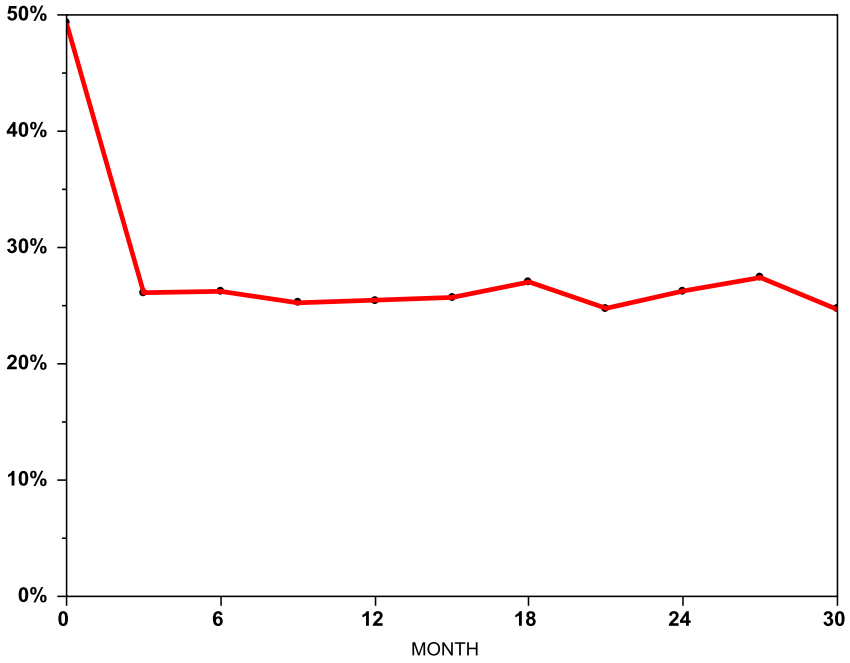
# Take Home Message

- To avoid resistance
  - HIV testing
  - HIV testing
  - HIV testing (and test again)
  - Test for acute infection
- Education
  - Patient
  - Providers
- Adherence support

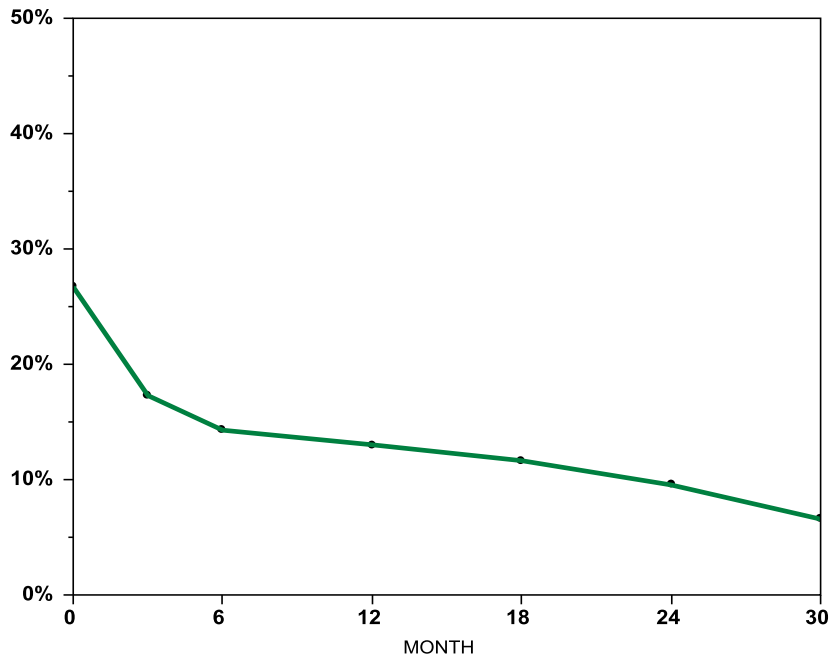
# 3. Public Health

- Concern
  - Behavioral:
    - Patient: adherence
    - Patient: risk compensation
    - Provider: inappropriate prescribing
  - Spread of drug resistant virus

# 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, Trichonomonas 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

# Take Home Message

- Promote public health
  - Patient/provider level
    - Avoid resistance
    - Support adherence
    - Support safe behavior (including prescribing)
  - Population level
    - Monitor programs
      - Access/implementation studies (total of 32,480 individuals)
      - REMS

# REMS

- Risk Evaluation Mitigation Strategies
- FDA Amendment Act (FDAAA)
  - 2007
- Safety related labeling changes
- Safety related post-marketing studies
- Implement REMS

# REMS Strategies

- Potential approaches
  - Education for providers
  - Education for patients
  - Monitoring
  - Restricted access
- Currently under discussion (FDA and sponsor)

In the setting of PrEP, however, panelists concluded that a restricted distribution plan for an ARV drug could not be successfully introduced without also inhibiting access to the same drug for treatment, which would have a potentially devastating impact on HIV management. For example, a

requirement for documentation of negative HIV testing for PrEP would inadvertently have the result of restricting access to treatment for HIV-infected individuals. Restricted-use

Strobos et al Forum Annals 2011

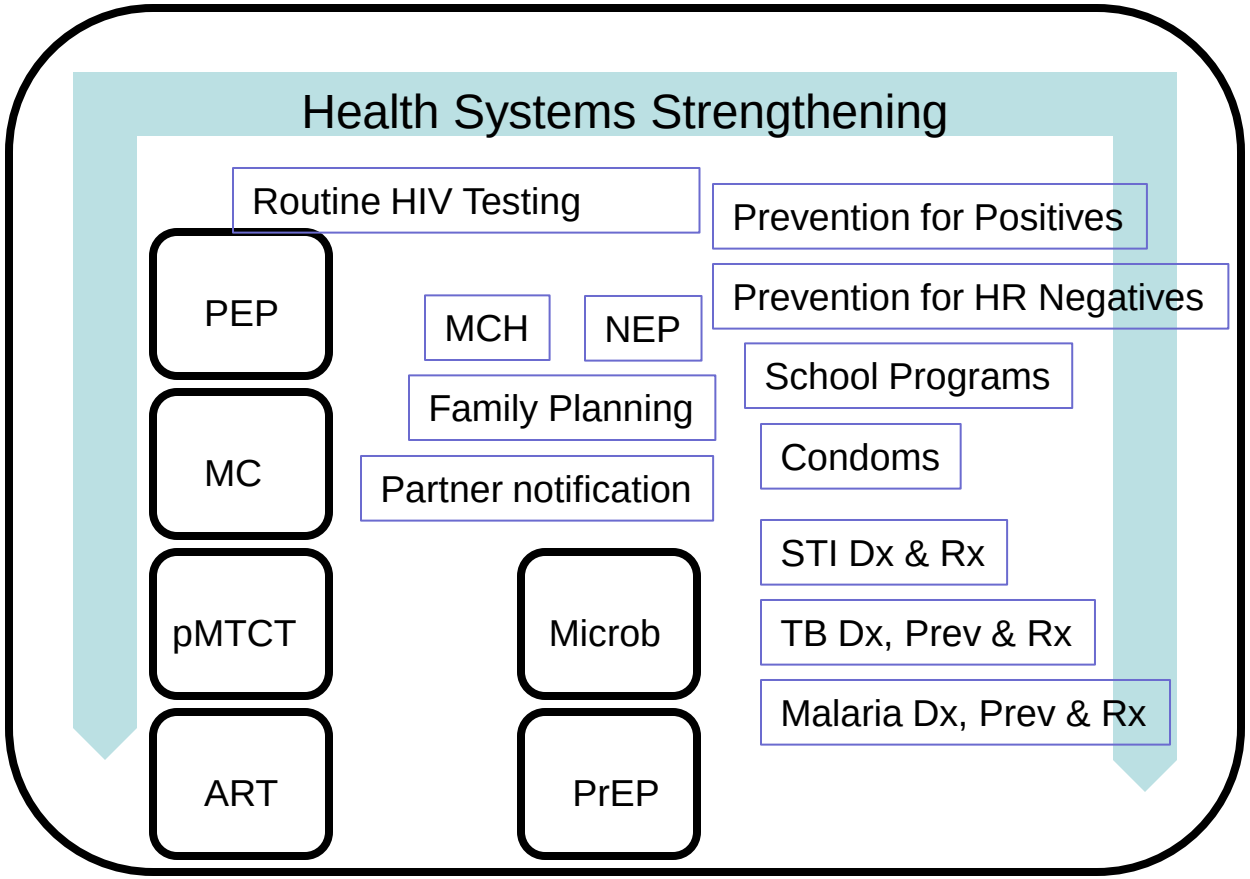
# Additional Considerations

- Role of OTC HIV tests?

# Future Safety Concerns

- Truvada or other regimen specific
  - Drug specific
    - Toxicity
    - Resistance
  - Other
    - Adherence
    - Risk compensation
- Long-acting regimen
  - Drug specific
    - Toxicity
  - Other
    - Risk compensation

# Finding the Synergies

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# Acknowledgements


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