PrEP
For Women

Valery Hughes FNP
Research Nurse Practitioner
Cornell Clinical Trials Unit
Weill Medical College of Cornell University
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

Hall JAMA 2008;300:520
Prejean PLoS One 2011;6:e17502
World Wide: 5 million new cases of HIV each year

<table>
<thead>
<tr>
<th>Location</th>
<th># new cases</th>
<th>% of population</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>65,000</td>
<td>0.6%</td>
</tr>
<tr>
<td>South America</td>
<td>210,000</td>
<td>1-2%</td>
</tr>
<tr>
<td>Africa</td>
<td>3.5 million</td>
<td></td>
</tr>
</tbody>
</table>

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.
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.

AIDS.gov  June 6, 2012
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

Abstain, Be faithful, Condoms, Counseling & testing

ABC

Adapted from Ramjee IAS Meeting 2006, #TUPL02
PrEP = Pre-Exposure Prophylaxis

- **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**
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

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

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Results: Reduction in HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEM-PREP</strong></td>
<td>2120 women in Kenya, South Africa, Tanzania</td>
<td>TDF/FTC (Truvada) vs. placebo</td>
<td>TDF/FTC: 6% (adherence &lt;40%)</td>
</tr>
<tr>
<td>Van Damme NEJM 2012;367:411</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td>&gt;5000 women in South Africa, Uganda, Zimbabwe</td>
<td>1% TDF gel vs. placebo; oral TDF, TDF/FTC or placebo</td>
<td>TDF arm stopped early due to futility</td>
</tr>
<tr>
<td>Press release 9/29/11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IPREX: Recorded Adherence and Efficacy

Efficacy
- FTC/TDF: 16% (95% CI: -54 - 54)
- Placebo: 34% (95% CI: -20 - 64)

Incidence / 100 person years

% of Visits
- <50%: 18%
- 50-90%: 33%
- >90%: 49%

Grant et al, CROI 2010
## Adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TDF/FTC</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Events</td>
<td>n (%)</td>
</tr>
<tr>
<td>Creatinine Elevated</td>
<td>25 (2%)</td>
<td>28</td>
<td>14 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>56 (4%)</td>
<td>66</td>
<td>41 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (2%)</td>
<td>22</td>
<td>9 (&lt;1%)</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>27 (2%)</td>
<td>34</td>
<td>14 (1%)</td>
</tr>
</tbody>
</table>

Grant NEJM 2010;363:2587
PERCENT CHANGES FROM BASELINE IN BMD BY RANDOMIZATION GROUP

SPINE (L1-L4)

TOTAL HIP

Δ %

Week

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

Mean, SE and P-values by linear mixed model

### Drug Resistance

<table>
<thead>
<tr>
<th>Genotypic Resistance</th>
<th>HIV Status at Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infected (N=10)</td>
</tr>
<tr>
<td></td>
<td>Placebo N=8</td>
</tr>
<tr>
<td>65R</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>70E</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>184I</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>184V</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>TDF Resistance</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>FTC Resistance</td>
<td>1 (13%)</td>
</tr>
</tbody>
</table>

Grant NEJM 2010;363:2587
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

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>TDF/FTC</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>1584</td>
<td>1579</td>
<td>1584</td>
</tr>
<tr>
<td>HIV infections</td>
<td>18</td>
<td>13</td>
<td>47</td>
</tr>
<tr>
<td>Protective efficacy</td>
<td>62%</td>
<td>73%</td>
<td>No difference TDF vs. TDF/FTC</td>
</tr>
<tr>
<td>(vs. placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No difference in side effects, lab abnormalities, deaths

Baeten IAS 2011 #MOAX0106
CDC – TDF-2

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

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>601</td>
<td>599</td>
</tr>
<tr>
<td>Lost to f/u</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>New HIV infections</td>
<td>9</td>
<td>24</td>
</tr>
</tbody>
</table>

- No safety differences
- No differences by sex

Thigpen IAS 2011 #WELBC01
CDC Guidance for PrEP for MSM:
(Interim; 1/27/11)

- **Before starting:**
  - document HIV Ab- and r/o acute infection
  - CrCl ≥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. 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)

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

Metsch IAS 2012 #TuPDC0301
Attitudes About PrEP: South Carolina

- HIV clinic at the University of South Carolina
- 89 MSM and heterosexual HIV- partners in the relationship >6 months
- Average age 42; 56% men; 70% black, 74% heterosexual; 58% had monthly income of ≤ $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.

Tripathi IAS 2012 # TuPDC0302
**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 week

---

**Daily Sexual Activity**

<table>
<thead>
<tr>
<th>Day</th>
<th>Proportion Reporting Sex (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>28%</td>
</tr>
<tr>
<td>Tu</td>
<td>23%</td>
</tr>
<tr>
<td>W</td>
<td>25%</td>
</tr>
<tr>
<td>Th</td>
<td>28%</td>
</tr>
<tr>
<td>F</td>
<td>48%</td>
</tr>
<tr>
<td>Sa</td>
<td>50%</td>
</tr>
<tr>
<td>Su</td>
<td>38%</td>
</tr>
</tbody>
</table>

Mark IAS 2012 #TUPDC0303
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

<table>
<thead>
<tr>
<th>Nucleoside/tide RTIs (NRTIs)</th>
<th>Entry inhibitors (EIs)</th>
<th>Integrase inhibitors (IIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamivudine (3TC)</td>
<td>maraviroc (MVC, CCR5 inhibitor)</td>
<td>raltegravir (RAL)</td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 ≥3 toxicities; time to study treatment discontinuation
## Newer PrEP Agents

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

<table>
<thead>
<tr>
<th><strong>PROS</strong></th>
<th><strong>CONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Proven efficacy</td>
<td>- Short-term data</td>
</tr>
<tr>
<td>- FDA approved</td>
<td>- Daily adherence required</td>
</tr>
<tr>
<td>- Can be highly effective</td>
<td>- Side effects</td>
</tr>
<tr>
<td>- Generally well-tolerated</td>
<td>- Drug resistance in acute infection</td>
</tr>
<tr>
<td>- Drug resistance not seen</td>
<td>- Risk compensation could lead to ↓ condoms</td>
</tr>
<tr>
<td>- No risk compensation</td>
<td>- Cost</td>
</tr>
<tr>
<td></td>
<td>- Logistics</td>
</tr>
</tbody>
</table>
Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
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- Division of AIDS, NIAID, NIH
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Valery
Kirsis

Veronica
Kristie
Marshall
Trip
Tim
Joanne