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PrEP and Serodiscordant Couples
FDA approved emtricitabine/tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (PrEP) in 2012
HIV Prevention

PrEP  
92% Efficiency

Condom Use  
80% Efficiency
28yo G2P1001 presented for initial prenatal care visit at 22wks. She was seen in various EDs and OB triage x several visits.

- She did not have any notable medical illnesses
- FOB was not present
- She screened positive for IPV but was not ready to leave FOB
- NOB screening tests: (-)HIV, (+)syphilis (-)gc/ct
- Prenatal course uneventful – 28wk labs normal, (-)repeat gc/ct
- Delivered a healthy BB at 38wks
- Infant feeding method was breastfeeding upon discharge from hospital
One Patient’s Story (continued)

- BB hospitalized for failure to thrive and diffuse LAD
- Diagnosed with HIV infection at 7 mos old
- FOB disclosed he was living with HIV
  - For quite some time
  - Not prescribed HAART because of active alcoholism
- This happened in 2007
Lifetime Risk of HIV by State

New HIV diagnosis: in 2016, Black women accounted for over 61% of the new HIV diagnoses among women.
HIV Transmission Category in Women: by Race

Majority of cases are secondary to heterosexual sex
Some racial difference in IDU

CDC- 2016 Diagnosis of HIV in female adults and adolescents in U.S.
# Oral PrEP Clinical Trials

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Participants</th>
<th>N</th>
<th>Drug</th>
<th>% reduction in acquisition of HIV infection a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2499</td>
<td>TDF/FTC</td>
<td>42</td>
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<tr>
<td><strong>Partners PrEP</strong></td>
<td><strong>Heterosexual serodiscordant couples</strong></td>
<td>4747</td>
<td>TDF</td>
<td>67</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>75</td>
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<tr>
<td>TDF 2</td>
<td>Heterosexually active men and women</td>
<td>1200</td>
<td>TDF/FTC</td>
<td>62</td>
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<tr>
<td>Bangkok Tenofovir Study</td>
<td>IV Drug Users</td>
<td>2413</td>
<td>TDF</td>
<td>49</td>
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<tr>
<td>Fem-PrEP</td>
<td>Heterosexually active women</td>
<td>1951</td>
<td>TDF/FTC</td>
<td>6(^c)</td>
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<tr>
<td>VOICE</td>
<td>Heterosexually active women</td>
<td>5029</td>
<td>TDF/FTC</td>
<td>- 4(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Modified Intent to Treat

\(^b\) Excluded only those enrolled patients later found to be infected at randomization and those with no follow-up visit or HIV test

\(^c\) On-demand" regimen constitutes: FTC/TDF or 2 placebo < 24 hrs prior to sexual intercourse exposure 1 FTC/TDF or placebo dose 24 hrs after; and a final dose 48 hrs after

Gibson, S. et al. AIDS 2016; Durban, South Africa #FRAE0104


PrEP Effectiveness in Women

• Adherence
  • If it isn’t taken, it will not work!
  • Self-report, pill counts underestimates true adherence
  • In clinical trial: did not know if taking placebo or not

• Perception of risk
  • VOICE trial (9%/yr HIV incidence in women <25)
    • <30% had detectable drug levels
  • FEM-PrEP trial (5%/yr HIV incidence)
    • 70% of women reported feeling at little risk for HIV

• Stigma, risk, and vulnerability (e.g. economic, power differentials)
PrEP Effectiveness in Women

• Poor drug penetration into vaginal tissue compared with rectal tissue
  • Missed pills less forgiving in women
• Genital inflammation or breaks in mucosa
  • Related to menopause (i.e. lack of estrogen), STIs
• Greater susceptibility in women vs hetero men
  • Greater surface area, longer contact with seminal fluid
PrEP in Women: Effectiveness

• Meta-analysis of 5 RCTs of oral PrEP among women
  • 3 reported evidence of effectiveness and 2 did not
  • **Estimates by adherence** (based on plasma drug levels)
    • 25% adherence: *no protection* (RR 1.19 95% CI: 0.89 – 1.61)
    • 50% adherence: 32% *protective* (RR 0.68 95% CI: 0.53 – 0.88)
    • 75% adherence: 61% *protective* (RR 0.39 95% CI: 0.25 – 0.60)

• “90%” effective for women
  • **Partners PrEP (HIV serodiscordant couples) subgroup analysis**
    • ~20% HIV(+) partners initiated ARV (higher among men)
    • Condomless sex decreased (27% at start → 9% at month 24)
    • Less exposure to persons with acute HIV infection
      • Higher viral loads assoc with higher transmission risk

Hanscom B, Janes H, Guarino P. JAIDS 2016; 73(5):606-608
Challenges

- **Provider-level**
  - Identifying women who are at-risk
  - Which provider best suited to prescribe
  - OBG, family planning, ID

- **Patient-level**
  - Awareness of PrEP (<10%)
  - Recognizing and understanding risk
  - Medication adherence in the face of daily life
ACOG PB: PrEP Use in Heterosexual Women

- HIV-negative and at substantial risk for HIV acquisition
  - Sexually active with a partner living with HIV
  - Living in a high HIV prevalence area or social network AND
  - Does not regularly use condoms during sex with partner of unknown HIV status
  - Recent sexually transmitted infection
  - Exchange sex for drugs, housing, money, etc
  - Incarceration
  - Use injection drugs
  - Abuse alcohol
  - Partner of unknown status with any of the above factors
PrEP Utilization by Sex

- U.S. retail pharmacy data 2012-2015

- PrEP use among female patients << male patients
- Highlights the difficulty in identifying women at risk

Bush S et al ASM 2016
In 2015, of the 13% of prescriptions filled by women, only 17% of those were among AA women.
Retrospective cohort
- Pregnant patients who had PNC and delivered at JHH in 2012
- >1600 women

Eligibility for PrEP defined as:
- Prior or current sexually transmitted infection
- Sexual partner living with HIV

Over 10% of our patients were eligible for PrEP
PrEP Safety during Pregnancy and Breastfeeding

- No randomized trials
  - Demonstration project (n=30): no difference in birth outcomes or infant growth

- Safety data are from women living with HIV or hepatitis B
  - No increased risk of birth defects, stillbirth, PTD, LBW

- WHO systematic review: safe during pregnancy/lactation
  - Tenofovir serum levels was undetectable in 94% breastfed babies
    - Tenofovir is mostly not bioavailable: must be given as prodrug TDF

Siberry 2012; Siberry 2014; Gibb 2012; Mugo JAMA 2014; CROI 2014; CDC Practice Guidelines 2014; Mofenson LM AIDS 2016 epub; Mugganya KK PLOS One 2016; Heffron AIDS 2018
# U.S. Women with Indications for PrEP

<table>
<thead>
<tr>
<th># U.S. people at-risk for HIV</th>
<th>Total Heterosexual Adults</th>
<th>1.2 million [661,000 – 1.8 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterosexual Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>624,000</td>
<td>[404,000 – 846,000]</td>
</tr>
<tr>
<td>MSM</td>
<td>468,000</td>
<td>[274,000 – 662,000]</td>
</tr>
<tr>
<td></td>
<td>492,000</td>
<td>[212,000 – 772,000]</td>
</tr>
</tbody>
</table>

- CDC definition of substantial risk among heterosexual adults
  - 18-59 yo, not known to be HIV-positive, sex with 2 or more opposite sex partners in past 12 months AND 1 of the following:
    - Condomless sex in last 4 weeks AND sex with a partner who is IVDU
    - For women: sex with a bisexual male sex partner in past 12 months

<table>
<thead>
<tr>
<th>Heterosexual Adults</th>
<th>1 in 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1 in 167</td>
</tr>
<tr>
<td>Heterosexual Men</td>
<td>1 in 500</td>
</tr>
<tr>
<td>MSM</td>
<td>1 in 4</td>
</tr>
</tbody>
</table>

Smith DK, Van Handel M, Wolitski RJ et al; MMWR 2015; 64 (46); 1291-1295
Introduction

Universal Prenatal HIV Counseling and Testing

Preconception Care

ARV Prophylaxis

Scheduled C-section (when indicated)

Avoidance of Breast Feeding

U.S. HIV Perinatal Transmission is now <1%
A focus on appropriate overall medical care for HIV-infected couples is the best way to prevent HIV infection of infants.

Every HIV-infected infant is a sentinel event representing missed opportunities for prevention.
Who Desires Children?

• Partner who desires child (3/4 of HIV+ men and women desiring children)

• Fewer children (almost 40% desiring children had no previous children)

• Younger age

• Higher self-ratings of health
  • not related to CD4/viral load
Reasons HIV+ Men and Women Desire Children

• Leave a legacy
• Cope with loss (including replacing child HIV)
• To be loved and accepted
• To be taken care of
• Pregnancy has social/cultural
• Want to live “normal” life
Reproductive Options for HIV
Broader Family Planning Landscape

- Preconception care (PCC) for people living with HIV (PLWH) historically understudied

- Important dimension of FP/HIV

- PCC encompasses not only pregnancy prevention but also safe childbearing
Family Planning and Planning for a Family: Why is This Important?

- **High rates of unintended pregnancy**: of 382 women in the Medical Monitoring Project, 85% had one or more unplanned pregnancy after knowing their HIV status (JAIDS 2014;65:350)

- **High rates of HIV serodiscordance (SDC) among sexual partnerships**: more than half of HIV+ individuals have HIV- partners

- **HIV has an adverse effect on fertility and there is potential improvement in fertility with ART**

- **High rates of comorbidities potentially affecting maternal or fetal health: depression, interpersonal violence**

- **Fertility desires and intentions among HIV+ women**: Most studies show that pregnancy desires and reproductive decision-making are similar between HIV-infected and HIV-uninfected women
Goals of Preconception counseling for PLWH

Promote planned pregnancies

Prevention of unintended pregnancy

Support safer conception strategies: Sero-concordant and sero-discordant couples

Prevent mother to child transmission of HIV

Optimize maternal and infant health outcomes

Optimize maternal and infant health outcomes
Preconception Care: what can women’s health providers do?

- **Recommend HIV testing of both partners**
  - For serodiscordant couples: discuss *Treatment as prevention* (TasP) or *Pre-exposure prophylaxis* (PrEP)
  - Discuss safer sexual practices

- **Assess childbearing plans/desires of HIV+ women on regular basis**
  - If desires children, ask about timing
  - If does not desire pregnancy currently, ensure access to effective contraception
  - Perform or refer for preconception counseling/care if desires to conceive
What is PCC for PLWH?

- Assessment
- Screening
- Counseling
- Prevention and Treatment Services
Preconception Counseling and Care

- Comprehensive family planning and preconception care is part of routine primary care and is recommended by CDC, ACOG, and other national organizations.

- **Purpose:**
  - Prevention of unintended pregnancies.
  - Optimization of maternal health prior to pregnancy.
  - Prevention of perinatal transmission.
  - Prevention of HIV transmission to an uninfected partner while trying to conceive including the use of PrEP
Case #1

33yo healthy woman presented to Ob/Gyn clinic with her husband for preconception counseling. They wanted to have a biological child together.

• Her husband was living with HIV
  • He was taking antiretroviral therapy and had an undetectable viral load for several years
• She had never been pregnant and had never tried to get pregnant
• Negative intimate partner violence screen

Would you offer her PrEP?
PrEP Use in Heterosexual Women

- HIV-negative and **at substantial risk** for HIV acquisition
  - Sexually active with a partner living with HIV
  - Living in a high HIV prevalence area or social network AND
    - Does not regularly use condoms during sex with partner of unknown HIV status
    - Recent sexually transmitted infection
    - Exchange sex for drugs, housing, money, etc
    - Incarceration
    - Use injection drugs
    - Abuse alcohol
    - Partner of unknown status with any of the above factors
Conception Options for HIV Serodiscordant Couples

• **Antiretroviral therapy is the most important intervention**
  - ARV for HIV+ partner as prevention (HPTN 052)
  - Pre-exposure prophylaxis (PrEP) for HIV- partner as well?
• Screen and treat sexually transmitted infections
• Undetectable viral load for HIV+ partner
  - HIV+ woman: timed condomless sex, artificial insemination
  - HIV+ man: timed condomless sex; assisted reproductive technology, i.e. semen washing with intrauterine insemination, IVF/ICSI

Reproductive Options for HIV Concordant and Serodiscordant Couples.

- PrEP is recommended with conception via sexual intercourse without a condom (counsel first) when VL is unknown or viral suppression is not attained to reduce risk of HIV transmission
  - Counsel couples to limit sex (sans condoms) to peak fertility times

- PrEP may be used to minimize risk of transmission of HIV with discordant couples.
  - Unclear if PrEP with viral suppression further reduces the risk of Sexual transmission
  - Studies are currently evaluating the efficacy of PrEP in conception
  - Only TDF and Emtricitabine is currently approved for use as PrEP
**PrEP**

- **Peri-conception PrEP**
  - Very few data to date on periconception PrEP; studies under way.
  - Infected partner should be on ART with fully suppressed HIV viral load.
  - Once daily tenofovir/emtricitabine is currently FDA approved for PrEP; CDC recommends 1 month before and 1 month after conception attempted.
  - No reported increase in congenital anomalies for children whose mothers were exposed to tenofovir or emtricitabine during first trimester.
PrEP

- If used in serodiscordant couples counseling should include
  - Potential risks and benefits
  - Alternatives for safer conception
  - Start PrEP in the un-infected partner one month prior to conception
  - Continue PrEP one month after conception is attempted.
  - Follow Recommended Laboratory testing
    - Including HIV testing at baseline and every 3 months
  - Educate about symptoms of acute HIV infection
  - If HIV infection is documented discontinue PrEP ARV agents.
Case #2

28yo woman presented for prenatal care at 24 weeks of gestation. This was her 2\textsuperscript{nd} pregnancy. Her male partner was not present.

\begin{itemize}
  \item She did not have any chronic medical illnesses
  \item She tested negative for HIV but positive for syphilis at the initial prenatal visit
  \item Male partner with unknown HIV status
  \item She reported he can be physically abusive at times and abuses alcohol
\end{itemize}

Would you offer her PrEP?
HIV and Pregnancy

- Pregnancy may be time of enhanced risk of HIV acquisition
  - Unclear if biologic and/or behavioral
- Greater risk of mother-to-child transmission (MTCT) if seroconversion happens during pregnancy or breastfeeding
- 2144 pregnant WLHIV in NY (2002-2004)
  - Only 1.4% were seroconversions, but these accounted for 23.4% of all MTCT cases
- CDC analysis of 10 states
  - 1.4% seroconversions among 4006 pregnant WLHIV
  - MTCT: 29.3% in acute HIV vs. 4.8% in chronic HIV

Case #3

36yo healthy woman presented to Ob/Gyn for her routine annual examination

- Had 2 male sexual partners
  - One was a long-term casual partner and the other was a main partner
  - Unknown HIV status of partners but patient thought they were negative

- Tested positive for both trichomonas and gonorrhea

- HIV test was negative

Would you offer her PrEP?
PrEP Use in Heterosexual Women

- HIV-negative and at substantial risk for HIV acquisition
  - Sexually active with a partner living with HIV
  - Living in a high HIV prevalence area or social network AND
    - Does not regularly use condoms during sex with partner of unknown HIV status
  - Recent sexually transmitted infection
  - Exchange sex for drugs, housing, money, etc
  - Incarceration
  - Use injection drugs
  - Abuse alcohol
  - Partner of unknown status with any of the above factors

ACOG Practice Bulletin No 595 May 2014
On the Horizon

- Studies of alternatives to daily dosing
- Studies of alternative antiretrovirals (MVC, RPV)
- Studies of alternative formulations: intravaginal rings, films, injectables
- Multipurpose technology (antiretroviral combined with contraceptive)
- Qualitative projects involving women at-risk
Conclusion

• **PrEP** is another tool for HIV prevention, but should be part of a comprehensive risk reduction package

• **Good adherence** is critical to PrEP effectiveness-need better measures, better support and more forgiving regimens

• Use of PrEP must take into account risk, risk perception, and fertility plans and desires
Case Follow-up

• Case #1 (attempting pregnancy): offered PrEP but declined
  • Conceived after 1st unprotected intercourse
  • Remained HIV-uninfected
  • Delivered last year

• Case #2 (pregnant): PrEP not available yet (2010)
  • Seroconverted during breastfeeding
    • Male partner was living with HIV but did not disclose
    • Infant tested positive

• Case #3 (annual exam): offered PrEP but declined
  • Did not think she was at risk
  • Remains HIV-uninfected
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Trial</th>
<th>#</th>
<th>Population</th>
<th>Status</th>
<th>Location</th>
<th>PrEP Status</th>
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</thead>
<tbody>
<tr>
<td>Oral PrEP: Daily oral F/TAF</td>
<td>Discover</td>
<td>5,400</td>
<td>MSM &amp; transgender</td>
<td>Fully enrolled</td>
<td>Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, UK, US</td>
<td>Oral TDF/FTC as part of active control in double-dummy, double-blind design</td>
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<tr>
<td>bNAb: VRC01 infused every 2 months</td>
<td>HVTN 704/ HPTN 085</td>
<td>2,700</td>
<td>MSM &amp; transgender</td>
<td>Enrolling</td>
<td>Brazil, Peru, Switzerland, US</td>
<td>Access to oral FTC/TDF PrEP offered at no drug cost to every participant</td>
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<tr>
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<td>HVTN 703/ HPTN 081</td>
<td>1,500</td>
<td>Sexually active women</td>
<td>Enrolling</td>
<td>Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe</td>
<td>Oral TDF/FTC discussed in IC, risk reduction counseling sessions, and referral systems</td>
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<tr>
<td>Vax: ALVAC/gp120</td>
<td>HVTN 702</td>
<td>5,400</td>
<td>Sexually active women &amp; men</td>
<td>Enrolling</td>
<td>South Africa</td>
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<td>MF59 adjuvant boost, 5 doses in 12 months</td>
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<td>Long-acting Injectable: cabotegravir every</td>
<td>HPTN 083</td>
<td>4,500</td>
<td>MSM &amp; transgender</td>
<td>Enrolling</td>
<td>Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam</td>
<td>Oral TDF/FTC as part of active control in double-dummy, double-blind design</td>
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<td>two months</td>
<td>HPTN 084</td>
<td>3,200</td>
<td>Sexually active women</td>
<td>Enrolling</td>
<td>Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe</td>
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<tr>
<td>HC/HIV: evaluating 3 contraceptives for</td>
<td>ECHO</td>
<td>7,800</td>
<td>Sexually active women</td>
<td>Fully enrolled</td>
<td>Kenya, South Africa, Swaziland, Zambia</td>
<td>Participants interested in oral TDF/FTC referred as programs become available in each study community</td>
</tr>
<tr>
<td>possible increased risk</td>
<td></td>
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<tr>
<td>Vax: Ad26/Mosaic + gp140 boost, 4 doses in</td>
<td>HPX2008/ HVTN705</td>
<td>2,600</td>
<td>Sexually active women</td>
<td>Enrolling</td>
<td>Malawi, Mozambique, South Africa, Zambia, Zimbabwe</td>
<td>TBD</td>
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<tr>
<td>12 months</td>
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<tr>
<td>Ring/PrEP: dapivirine ring and oral TDF/FTC</td>
<td>MTN 034/IPM 045/REACH</td>
<td>300</td>
<td>Sexually active women</td>
<td>Planned 2018</td>
<td>Kenya, South Africa, Uganda, Zimbabwe</td>
<td>Open-label cross-over; all will try both ring and oral, then choose</td>
</tr>
</tbody>
</table>
90% Daily PrEP can reduce the risk of sexually acquired HIV by more than 90%.

70% Daily PrEP can reduce the risk of HIV infection among people who inject drugs by more than 70%.

1 in 3 1 in 3 primary care doctors and nurses haven’t heard about PrEP.