HIV PrEP

A Brief Introduction to HIV prevention

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Slides courtesy of Patrick Milligan, MD
Learning Objectives

- Discuss the epidemiology of HIV infection
- Briefly review literature regarding PrEP efficacy
- Review the recommended PrEP protocol and how you can do this in your practice
- Explore PrEP safety
HIV Epidemiology

- There are approximately 1.2 million people in the US living with HIV and 36.7 million people worldwide.

- Despite prevention efforts and treatment of infected patients, there are still 50,000 new HIV infections in the US each year and up to 2.5 million worldwide.

- Health disparities exist with higher rates among racial minorities, MSM, and transgender people.
What is PrEP?

- **Pre-Exposure Prophylaxis**

- Prescription of daily antiretrovirals medication to high-risk HIV negative individuals to prevent infection
  - Tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg
  - **TDF/FTC**
  - **Truvada 1 tablet by mouth daily**
1984: HIV virus first isolated

1987: AZT is FDA approved

1995: first use of HAART

1995: Macaque study shows pre-treatment with tenofovir prevents SIV infection

2001: Tenofovir is FDA approved

2004: Truvada (TDF/FTC) is FDA approved

2007: WHO guidelines recommend use of AZT/3TC for PEP


2010: iPrEx

2012: Truvada (TDF/FTC) is FDA approved for PrEP

2012: Partners PrEP

2013: Bangkok Tenofovir Study
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Pop</th>
<th>Treatment</th>
<th>Adherence</th>
<th>Efficacy (RRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>2499</td>
<td>MSM</td>
<td>TDF/FTC</td>
<td>~50%</td>
<td>Overall Drug + 44%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>4747</td>
<td>Discordant couples</td>
<td>TDF/FTC TDF</td>
<td>~80%</td>
<td>TDF/FTC TDF 75-90%</td>
</tr>
<tr>
<td>Bangkok Tenofovir</td>
<td>2413</td>
<td>IDU</td>
<td>TDF</td>
<td>~70%</td>
<td>Overall Drug + 49%</td>
</tr>
<tr>
<td>TDF 2</td>
<td>1219</td>
<td>Hetero M + F</td>
<td>TDF/FTC</td>
<td>84%</td>
<td>62%</td>
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<tr>
<td>TDF Safety</td>
<td>936</td>
<td>African women</td>
<td>TDF</td>
<td>69%</td>
<td>35%</td>
</tr>
<tr>
<td>Fem PrEP</td>
<td>2120</td>
<td>African women</td>
<td>TDF/FTC</td>
<td>~35%</td>
<td>18%</td>
</tr>
<tr>
<td>VOICE</td>
<td>5029</td>
<td>African women</td>
<td>TDF/FTC TDF TFV gel</td>
<td>~30%</td>
<td>TDF/FTC TDF - 4.4%</td>
</tr>
<tr>
<td>PROUD</td>
<td>545</td>
<td>MSM</td>
<td>TDF/FTC</td>
<td></td>
<td>86%</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>414</td>
<td>MSM</td>
<td>TDF/FTC (PRN)</td>
<td>~44%</td>
<td>86%</td>
</tr>
</tbody>
</table>
Basics of Providing PrEP Services

- Use of TDF/FTC as PrEP in select populations has been shown to be safe and effective at preventing HIV infection.

- TDF and FTC have been the most studied drugs because of convenient half-life and high concentrations in genital mucosa.

- PrEP is just one component of what should be a multi-faceted approach to HIV prevention:
  - Risk modification
    - Safe sex practices
    - Drug counseling/treatment
    - Needle exchange programs
  - Partner treatment
  - Frequent testing for high risk individuals.
Basics of Providing PrEP Services

- PrEP is NOT lifelong – need for PrEP should be reassessed regularly

- Given the substantial size of the at-risk population, prescription of PrEP should not be limited to ID providers
“How To” Guide for Providing PrEP
Key Steps to PrEP Management

- **Initial Visit**
  - **Risk assessment**
    - Confirm prescription drug coverage
    - Screen for symptoms of acute HIV
    - Rule out recent (<72 hrs) high risk exposure
    - Confirm HIV negative
      - Antibody within past 7 days (ideally 4th Gen assay)
      - Viral Load
  - Baseline lab testing
    - CrCl
    - Hepatitis B sAg and sAb
    - +/- pregnancy testing
  - Counseling/Risk modification
CDC Guidelines

- MSM (not in a monogamous relationship with HIV- partner)
  - History of inconsistent or no condom use
  - Commercial sex work
  - High number of sex partners
  - Any STI in past 6 months
  - Ongoing sexual relationship with known HIV + partner
- Heterosexual Men and Women*
  - Same as above
- Injection drug users (with IDU of non-prescribed med in past 6 mo)
  - Sharing of injection equipment in past 6 months
  - In drug treatment program (methadone, etc.) – but currently injecting
  - High-risk sexual behavior, HIV positive partner
New York State Dept of Health

- MSM who engage in unprotected anal intercourse
- Serodiscordant sexual relationship – AKA known infected partner
- Transgender individuals engaging in high-risk sexual behaviors
- Transactional sex – sex for money, drugs or housing
- Injection drug users
  - Share equipment
  - Multiple daily injections
  - Injection of cocaine or methamphetamine
  - High-risk sexual behaviors
- Use of stimulants (e.g. meth) with high-risk sexual behaviors
- History of 1 or more anogenital STI in the past 12 months
- Recent use of nPEP with ongoing risk
Key Steps to PrEP Management

- **Initial Visit**
  - Risk assessment
  - Confirm prescription drug coverage
  - Screen for symptoms of acute HIV
  - Rule out recent (<72 hrs) high risk exposure → PEP
  - Confirm HIV negative
    - Antibody within past 7 days (ideally 4th Gen assay)
    - Viral Load
  - Baseline lab testing
    - CrCl
    - Hepatitis B sAg and sAb
    - +/- pregnancy testing
  - Counseling/Risk modification
Key Steps to PrEP Management

- **Initiation Visit**
  - Review Labs
  - Counseling
  - Provide prescription*

- **90 Day Visit (and subsequent 3 mo visits)**
  - HIV Ab screen
  - Risk assessment
  - Creatinine (repeated at least every 6 months)
  - STI testing – recommended every 6 months or with sx; can elect to test more frequently
  - Counseling/Risk Modification
  - Assess adherence
  - Re-prescribe PrEP
### Signs of acute HIV infection

<table>
<thead>
<tr>
<th>Features</th>
<th>Overall (n = 375)</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>75%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>49%</td>
</tr>
<tr>
<td>Skin rash</td>
<td>48%</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>40%</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>39%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>30%</td>
</tr>
<tr>
<td>Night sweats</td>
<td>28%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27%</td>
</tr>
</tbody>
</table>
Figure: Clinician Determination of HIV Status for PrEP Provision

1. **HIV immunoassay blood test** (rapid test if available)
   - **Negative**
   - **Indeterminate**
   - **Positive**
     - **Consider HIV + (pending confirmatory testing)**

2. **Indeterminate**
   - **Signs/symptoms of acute HIV infection anytime in prior 4 weeks**
     - **HIV -**
       - **No**
       - **Yes**
         - **Option 1 (Preferred)**
           - Send blood for HIV antibody/antigen assay*
             - **Positive**
             - **HIV +**
             - **HIV -**
             - **HIV - Eligible for PrEP**
             - **HIV + Not Eligible for PrEP**
             - **HIV Status Unclear**
             - **Defer PrEP decision**
           - **Negative**

3. **Positive**
   - **Option 2**
     - Send blood for HIV-1 viral load (VL) assay
       - **VL ≥3,000 copies/ml**
       - **VL <3,000 copies/ml**
         - **HIV +**
         - **HIV + Retest VL**
         - **Defer PrEP decision**

4. **Option 3**
   - Retest antibody in one month
   - Defer PrEP decision

* send blood for HIV-1 viral load (VL) assay
Simplified PrEP Algorithm

**Intake Visit**
- risk assessment
- check creatinine
- check Hep B sAg
- check Hep B sAb
- check HIV Viral Load
- verify insurance

**Initiation Visit**
(<7 days from Intake)
- verify labs
- counseling
- additional HBV counseling if needed

**90 Day Visit**
- counseling
- pill count
- check Cr
- HIV Ab
- risk assessment

**Prescribe PrEP:**
TDF/FTC for 30 days, 2 refills

**60 Day Visit**
- counseling
- pill count
- optional HIV Ab

**30 Day Visit**
- counseling
- pill count
- optional HIV Ab

**Risk Assessment**
Negative or CrCl < 60

**VL Pos**
- repeat HIV Ab
- refer for cART

**VL Neg**
- PrEP Contra-indicated
PrEP and Safety Concerns

- Hepatitis B infection

- Adverse drug reactions
  - Side effects: nausea, diarrhea, abd pain, rash, headache
  - Renal/hepatic dysfunction
  - Bone mineral density changes

- Development of HIV resistance
  - Acutely infected at initiation
  - Conversion while on PrEP
## Interpretation of Hep B testing

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total anti-HBc</th>
<th>IgM anti-HBc</th>
<th>anti-HBs</th>
<th>Interpretation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>—</td>
<td>Negative</td>
<td>Susceptible</td>
<td>Vaccinate</td>
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<tr>
<td>Negative</td>
<td>Positive</td>
<td>—</td>
<td>Positive*</td>
<td>Immune (natural infection)</td>
<td>Document</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>—</td>
<td>Positive*</td>
<td>Immune (prior vaccination)</td>
<td>Document</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Chronic HBV infection</td>
<td>Evaluate for treatment</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Acute HBV infection</td>
<td>Follow and evaluate for treatment</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>—</td>
<td>Negative</td>
<td>Unclear—could be:</td>
<td>Case-by-case evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Resolved infection (most common)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• False-positive anti-HBc; susceptible</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• “low level” chronic infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Resolving acute infection</td>
<td></td>
</tr>
</tbody>
</table>

* = seroprotective levels of >10 mIU/mL
Kidney and Bone Health

- Potential proximal tubular disease with TDF
- All PrEP trials have had eGFR < 60 ml/min as an exclusion criterion
- PrEP is contraindicated if eGFR is < 60
- Trend toward decline in BMD at 2 of 3 sites
  - Fem neck: -1.1%  p=0.004
  - Hip total: -0.8%  p=0.003
  - L-spine: -0.7%  p= 0.11
- iPlex – early in trial, greater BMD loss in spine and hip, but no significant difference at weeks 48 and 72, respectively
October 2019 Descovy approved by FDA for PreP

- Tenofovir alafenamide + emtricitabine

- Approval based on Discover 3 trial

- RCT of F/TAF (200 mg/25 mg) or F/TDF (200 mg/300 mg), followed for up to 96 weeks
  - Adherence measured through pill counts and TDM
  - F/TAF arm, incidence rate ratio of 0.16 per 100 person-years
  - F/TDF arm, incidence rate ratio of 0.34 per 100 person-years

- Approval does not include cisgender women
**PrEP and HIV Resistance Mutations**

<table>
<thead>
<tr>
<th>Study</th>
<th>M184V</th>
<th>K65R</th>
<th>placebo</th>
<th>M184V</th>
<th>K65R</th>
<th>n (PrEP)</th>
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<tbody>
<tr>
<td>iPrEx</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1226</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3163</td>
</tr>
<tr>
<td>BTS</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1204</td>
</tr>
<tr>
<td>TDF 2</td>
<td>1*</td>
<td>1*</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>611</td>
</tr>
<tr>
<td>US MSM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>201</td>
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<tr>
<td>FemPrEP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1062</td>
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<tr>
<td>VOICE</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2974</td>
</tr>
</tbody>
</table>

13 in 10,441 (0.125%) treated compared to 2 in 7679 (0.026%) placebo. NNH = 1010

If only trials with good drug adherence are considered, “on-treatment” rate of resistance is 1/6405 – same as rate with placebo.
Summary and Take-Home Points

- Use of TDF/FTC as PrEP is one part of a multi-armed strategy to prevent new HIV infections

- PrEP only works if you take it
  - With detectable tenofovir levels, PrEP was 90% effective

- Currently only daily TDF/FTC or TAF/FTC is approved

- Initial PrEP visit should include:
  - Confirmation of HIV seronegativity
  - HBV and Cr testing
  - Risk Assessment
Summary and Take-Home Points

- Follow-up PrEP visits should include:
  - HIV testing every 3 months
  - Creatinine every 6 months
  - Repeat risk assessment to confirm need for PrEP
  - Counseling for risk modification

- PrEP is generally safe and well tolerated
  - Minimal changes in serum creatinine and BMD
  - Few transient side effects

- Risk of HIV resistance is minimal and can be lessened by:
  - Ruling out acute infection
  - Increasing adherence to therapy

- PrEP is expensive, but not compared to the cost of HIV treatment
References


References


- McCormack S, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 22LB.

- Molina JM, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 23LB.

- Mulligan K, et.al. 18th CROI; Seattle, WA; Feb 2011. Abst. 94LB.


References


THANK YOU!