A New Era of Highly-Effective HIV Prevention in Primary Care Part II

Antiretrovirals for HIV Prevention: PEP and PrEP in Clinical Practice

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Learning objectives

At the end of this webinar, participants will be able to:

- Explain how non-occupational post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) are used for HIV prevention
- Summarize the major research findings on PEP and PrEP
- Identify how to access current recommendations on the use of PrEP and PEP in clinical practice
HIV Prevention: New Opportunities, New Challenges

Decrease Infectiousness
- Barrier protection
- Blood screening
- IDU harm reduction
- Antiretroviral therapy (PMTCT, treat infected partners)
- STI treatment

Decrease Host Susceptibility
- Barrier protection
- Infection control
- Circumcision
- PEP, PrEP
- Topical microbicides
- Vaccines
- STI treatment

Alter Behavior
- Condom and HIV testing promotion
- Individual interventions
- Couples interventions
- Community-based interventions
- Structural interventions
Post-Exposure Prophylaxis (PEP) vs. Pre-Exposure Prophylaxis (PrEP)

- **What are they?** Medication or immunotherapy before or following an exposure to an infectious agent to prevent or stop a disease.

- **PEP** is intended to be used after an acute exposure; **PrEP** presumes recurrent exposures.

- **PEP Examples:**
  - Immune globulin after Hepatitis exposure
  - Antibiotics after meningococcal outbreak

- **PrEP Example:**
  - Antimalarial chemoprophylaxis for travelers
PEP and PrEP: Background

- The use of ART after HIV exposure has been recommended by CDC and WHO for over a decade

- Randomized controlled trials of PEP have not demonstrated the superiority of one regimen over another

- Recent trials have demonstrated PrEP efficacy

- Hard to study because sexual HIV transmission is not very efficient, and ethically, researchers must counsel participants about safer sex, and provide appropriate mental health and medical referrals

- PEP and PrEP trials take time and are costly
HIV Transmission Efficiency

- **Sexual transmission**
  - Penile-vaginal: about 1 per 1,000
  - Penile-anal: more efficient, 1 to 3%
  - Oral sex: less efficient, case reports

- **Injection drug use** – efficient (depending on needle size and amount of blood exposure)

- **Mother-to-child** – 20-30%

- **Blood transfusion** – very efficient (>90%)

- **Accidental needle stick** – about 3 per 1,000

- **Co-factors**: source viral load; concomitant STDs
Post-Exposure Prophylaxis (PEP)
Polling Question

How familiar are you with the use of PEP after non-occupational HIV exposure?

A. Very familiar
B. Moderately familiar
C. A little familiar
D. Not at all familiar
Rationale for PEP

- **Early HIV infection**
  - Immune cells in mucous membranes & skin
  - Migration of HIV into lymph nodes
  - HIV detectable in blood within 3-5 days “window of opportunity”

- **Animal studies**
  - Protection is variable: mode of exposure, animal model, specific drugs, duration of treatment
  - But, generally protective

Studies in Humans

- Health Care Workers - Needlesticks
  - Cardo, MMWR, (Add Citation) Case-Control study
  - Basis for Occupational PEP

- Mother-Child Transmission
  - ACTG 076 (AZT)
  - HIVNET 012 (Nevirapine)
  - Basis for Non-Occupational

- 28 day regimen based on animal data
PEP in Brazilian MSM  
(Schechter, JAIDS, 2004)

- High-risk MSM educated about PEP use and given AZT/3TC “Starter Packs”

- Told to take for 28 days
  - ~1/3 did not engage in risky behavior
  - 1/3 were risky and used PEP
  - 1/3 were risky and didn’t use PEP
PEP in Brazilian MSM  
(Schechter, JAIDS, 2004)

- Results:
  - 10 acute infections among those who didn’t use PEP (seroconversion rate: 4.7%)
  - Only one new infection in PEP users (<1%)
- 92% adherence
- Highly motivated cohort
- >70% side effects
- Best proof of concept
San Francisco Experience

- 401 patients (94% sexual exposures)
  - 40% anal receptive, 27% anal insertive
  - 43% with known HIV+ source
  - 78% completed 4 weeks of therapy

- 6 month follow up:
  - 74% decrease in unprotected sex
  - 9.6% had increase in risk behaviors
  - 12 month follow up: 17% repeated PEP

Martin J, CROI, 2001
Concerns about PEP Risks

- Possible increase in risk behaviors of general population because a “morning after” pill exists?
- Possible serious adverse effects from treatment?
- Potential selection for resistant virus?
- Evidence tells us that these risks are likely minimal (CDC MMWR, 2005)
PEP in Practice – The Basics

- Providing PEP is a skill that can be in EVERY primary care provider’s tool kit
- Antiretrovirals initiated within 72 hours after exposure
- Indicated for exposures of “substantial risk”
- 28 days of antiretroviral therapy
- Perform HIV antibody testing at 1, 3, and 6 months post-exposure
- Not appropriate for those with multiple sexual or IDU exposures over time
CDC and HRSA Guidelines

- Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States (MMWR 2005;54(No. RR-2)
  - [www.cdc.gov/mmwr/PDF/rr/rr5402.pdf](http://www.cdc.gov/mmwr/PDF/rr/rr5402.pdf)

- Clinical Guidance: Nonoccupational PEP (HRSA HAB)
Fenway Health’s PEP Program

- Multidisciplinary team approach
- 24 hour access to a clinician
- Medical evaluation: including laboratory testing at baseline, 28 days and 3 months
- Medications: 2 vs. 3 drugs
- Counseling and mental health referral
- Screen for STIs, Hep B, Hep C
- Regimens have evolved over several years
Choice of Drugs for PEP

- No head-to-head comparisons
- Two-drug regimens often preferred b/c of simplicity of one pill once a day
- Three-drug regimens may be used to anticipate resistance if source is treatment-experienced

(Mayer, JAIDS, 2011)
Choice of Drugs for PEP

- Trend towards using TDF/FTC vs. AZT/3TC
- 3rd drug: can’t use NVP b/c hepatitis, EFV b/c CNS side effects, ATV b/c of ↑ jaundice
- CDC guidelines suggest Lopinavir/r, some use Darunavir/r as boosted PI
- Raltegravir: well tolerated

(Mayer, JAIDS, 2011)
Contribute to National Data Collection through the Nonoccupational HIV PEP Registry

Call toll-free: 1-877-HIV-1PEP
Fax: 1-877-HIV-7PEP
On-line Provider Registration & Data Submission:
www.hivpepregistry.org
Pre-Exposure Prophylaxis (PrEP)
Polling Questions

Approximately when did you first hear about PrEP to prevent HIV infection?
A. When the PrEP trials began
B. When the results from the trials were announced
C. When the FDA approved it
D. When I signed up for this webinar series
E. Don’t remember
F. Other
Clinical Trial Evidence that Antiretroviral Drugs Prevent HIV Transmission

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for prevention (HPTN 052)</td>
<td>96% (73; 99)</td>
</tr>
<tr>
<td>PrEP for discordant couples (Partners PrEP with FTC/TDF)</td>
<td>73% (49; 85)</td>
</tr>
<tr>
<td>PrEP for heterosexuals* (Botswana TDF2 with FTC/TDF)</td>
<td>63% (21; 48)</td>
</tr>
<tr>
<td>Medical male circumcision (Orange Farm, Rakai, Kisumu)</td>
<td>54% (38; 66)</td>
</tr>
<tr>
<td>PrEP for MSMs (iPrEX with FTC/TDF)</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>STD treatment* (Mwanza)</td>
<td>42% (21; 58)</td>
</tr>
<tr>
<td>Microbicide* (CAPRISA 004 tenofovir gel)</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>HIV Vaccine* (Thai RV144)</td>
<td>31% (1; 51)</td>
</tr>
</tbody>
</table>

*Other trials were negative
First Demonstration that Oral PrEP works: Nov 23, 2010

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Pre-Exposure Prophylaxis Initiative (iPrEx)

Sites | 11
Participants | 2499

iPrEx: Efficacy

- Efficacy through study end (mITT): 42% (95% CI: 18% to 60%)

\[ P = 0.002 \]
# iPrEx: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>FTC/TDF (n = 1251)</th>
<th>Placebo (n = 1248)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 event</td>
<td>12% 248</td>
<td>13% 285</td>
<td>.51</td>
</tr>
<tr>
<td>Death</td>
<td>&lt; 1 1</td>
<td>&lt; 1 4</td>
<td>.18</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>5% 76</td>
<td>5% 87</td>
<td>.57</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>2% 28</td>
<td>1% 15</td>
<td>.08</td>
</tr>
<tr>
<td>Creatinine elevation confirmed on next visit</td>
<td>0.4% 7</td>
<td>0% 0</td>
<td>.06</td>
</tr>
</tbody>
</table>

iPrEx: Percent Bone Mineral Density Changes

iPrEx: Condom Use With High-Risk Sex

Partners PrEP: Both PrEP Strategies Significantly Reduce HIV Acquisition

- Both PrEP strategies associated with significant reduction in HIV acquisition vs placebo in both men and women
  - TDF efficacy: 71% in women, 63% in men
  - TDF/FTC efficacy: 66% in women, 84% in men

<table>
<thead>
<tr>
<th>Primary Efficacy Outcome, mITT Analysis</th>
<th>TDF (n = 1584)</th>
<th>TDF/FTC (n = 1579)</th>
<th>Placebo (n = 1584)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV acquisitions, n</td>
<td>17</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>HIV incidence/100 PY</td>
<td>0.65</td>
<td>0.50</td>
<td>1.99</td>
</tr>
<tr>
<td>Efficacy vs placebo, % (95% CI)</td>
<td>67 (44-81)</td>
<td>75 (55-87)</td>
<td>--</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>--</td>
</tr>
</tbody>
</table>

TDF2: PrEP With TDF/FTC Significantly Reduces HIV Acquisition

- 9 vs 24 patients seroconverted in TDF/FTC vs placebo arms, respectively
- Overall protective efficacy of TDF/FTC: 62.6% (95% CI: 21.5-83.4; \( P = .0133 \))

![Graph showing time to seroconversion](image)

PrEP Works Together with Other HIV Prevention Strategies

- Ongoing HIV counseling and testing, condoms, risk reduction, male circumcision, treatment of STIs *plus PrEP* synergize to maximally reduce HIV risk

Disappointing Results of PrEP in Women: FEM-PrEP and VOICE

- Placebo-controlled studies with African women
- VOICE regimen: oral TDF; oral TDF/FTC; vaginal TFV gel [2]
- All stopped early for lack of efficacy except VOICE oral TDF/FTC arm (ongoing)
- FEM-PrEP: evidence of lack of adherence

1. Van Damme L, et al N Engl J Med. 2012 Jul 11. [Epub ahead of print]. 2. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.
Why was oral and topical PrEP ineffective for some women?

- Adherence?
- Pharmacology?
- Genital Tract Inflammation, STDs?
- Viral challenge from partners?
## PrEP (Like ART) Works When Taken

<table>
<thead>
<tr>
<th>Partners PrEP*[^1]</th>
<th>81</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF2[^2]</td>
<td>79</td>
<td>62</td>
</tr>
<tr>
<td>iPrEx[^3]</td>
<td>51</td>
<td>44</td>
</tr>
</tbody>
</table>

* ^TDF/FTC arm

**There is a clear dose-response between evidence of PrEP use and efficacy**

Correlates of Drug Detectability

- 179 samples from 7 sites (2 US, 4 South America, 1 South Africa) were evaluated after week 24 visit

- Overall detection rate
  - TFV-DP: 50%
  - FTC-TP: 62%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Drug Detected, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>34</td>
<td>97</td>
</tr>
<tr>
<td>Non-US</td>
<td>145</td>
<td>50</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25 yrs</td>
<td>101</td>
<td>73</td>
</tr>
<tr>
<td>&lt; 25 yrs</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Recent reported sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URAI</td>
<td>49</td>
<td>76</td>
</tr>
<tr>
<td>Sex, not URAI</td>
<td>107</td>
<td>59</td>
</tr>
<tr>
<td>No sex</td>
<td>23</td>
<td>35</td>
</tr>
</tbody>
</table>
Peri-Exposure Prophylaxis in Macaques With Oral FTC/TDF

- Macaque model of rectal transmission of HIV
  - Rectal exposure with R5 virus inoculum (10 TCID$_{50}$)
- 2 doses of FTC/TDF
  - Before SHIV exposure (-)
  - After SHIV exposure (+)
- Extended window of protection
  - Associated with extended long intracellular persistence of drug
- No drug resistance in macaques failing PrEP

Protection From SHIV
On July 16, 2012, the US FDA approved oral TDF/FTC to reduce the risk of HIV infection in high-risk HIV-uninfected adults who may engage in sexual activity with HIV-infected partners.

TDF/FTC, taken daily, is to be used in combination with safer sex practices.
The “PrEP Package” in Practice

- It’s a pill and a process: for optimal effect
- Once daily TDF/FTC PLUS behavioral interventions
- It should only be considered for patients at high-risk of HIV infection
- Adherence is key! Patients must commit to taking a daily pill and to coming in for follow-up visits every 2-3 months
PrEP Guidelines from CDC

- CDC Interim guidelines for PrEP

- CDC Compendium of Evidence-Based Behavioral HIV Interventions
  www.cdc.gov/hiv/topics/research/prs/prs_rep_debi.htm
PrEP Resources from The Fenway Institute

Guide for Clinicians

INTRODUCING THE “PrEP PACKAGE” FOR ENHANCED HIV PREVENTION: A Practical Guide for Clinicians

Guide for Consumers

PROTECTING YOURSELF FROM HIV THROUGH PRE-EXPOSURE PROPHYLAXIS (PrEP): What You Need to Know

www.lgbthealtheducation.org
PrEP Resources from Gilead Sciences

- Checklist for Prescribers
- Initiation of PrEP
- Information for Consumers

www.truvadapreprems.com
Key elements of CDC`s guidance on PrEP

- Determine Eligibility (negative HIV test, at high-risk for HIV acquisition, able to be adherent and return for regular follow-up)
- Screen/treat for STDs, screen/vaccinate for Hep B
- Prescribe tenofovir-emtricitabine
- Provide condoms and risk-reduction counseling
- Monitor closely (at 1 month, then q 2-3 month: HIV testing, follow BUN/Cr, repeated risk assessment and counseling)
Other Key Points about PrEP

- Important to make PrEP available to highest-risk individuals
- Insurance coverage is case by case (being reviewed by payors)
- Inform patients of GI/nausea side effects in 5% of patients (usually resolves within days or weeks)
- Long-term safety data are not yet available, but can look at safety data of HIV-infected on ART
How many potential US PrEP users?

- **NHANES (2001-2006)**
  - 1.8 million men aged 18-59 reported sex with a man in prior year and self-identify as gay
    - 47% reported >2 MSM partners in past year
    - 83% HIV-uninfected

- No condom use during most recent sex was 39% (National Sex Behavior Survey)

- **275,000** uninfected gay men with >2 male sex partners in past year and no condom use at last anal sex

- **Up to 200,000** HIV discordant couples

Immediately after iPrEx, PrEP awareness increased; interest and use were stable.

Changes in PrEP Awareness, Interest, and Experience after iPrEx

(Krakower et al, PLoS ONE, 2012)

- **Heard of PrEP**
  - Before iPrEx: 12.5%
  - After iPrEx: 19.0%

- **Would use PrEP**
  - Before iPrEx: 76.1%
  - After iPrEx: 78.5%

- **Have Used PrEP**
  - Before iPrEx: 0.7%
  - After iPrEx: 0.9%
Clinical Screening Index Predictive of Incident HIV Infection among US MSM

- Screening index included (over past 6 months):
  - n male partners
  - n HIV-infected partners
  - n URA with any partner
  - n UIA with HIV-infected partners
  - poppers
  - amphetamines

- Score 0-47; >10 assoc with 84% sensitivity; 45% specificity

D Smith et al, JAIDS, 2012
Combination Antiretroviral Prevention

Interventions

- Test
  - HIV Negative
    - Risk Assessment
      - PrEP, Adherence Counseling
  - HIV Positive
    - Positive Prevention

- Enroll in Care
  - ART Initiation
  - Treat
    - Adherence to ART
  - Maintain Viral Suppression

- Linkage To Care

- Decrease in HIV Transmission

Address concomitant concerns, e.g. depression, substance use, relationship dynamics

[Image: thefenwayinstitute.org]
Thank You

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Steve Safren
Dawn Smith

NIAID, NIMH, NIDA, NICHD, CDC, HRSA, Mass DPH, Gilead

www.thefenwayinstitute.org
SUPPLEMENTAL SLIDES

Biomedical Prevention: Looking to the Future
What about Treatment as Prevention?
HPTN 052: ↓ HIV Transmission by HAART

Total HIV-1 Transmission Events: 39 (4 in immediate arm and 35 in delayed arm; \( P < .0001 \))

Linked Transmissions: 28

- Delayed Arm: 27
- Immediate Arm: 1

Unlinked or TBD Transmissions: 11

Single transmission in patient in immediate HAART arm believed to have occurred close to time therapy began and prior to suppression of genital tract HIV

\[ P < .001 \]

HPTN 052 Limitations

- Many couples are short-lived and do not disclose
- Some people may never disclose
- Stigma about testing and revealing status
- Only 3% of couples in HPTN 052 were MSM
- Not either, or.......
- PrEP combined with ART for prevention can decrease epidemic more rapidly (Hallett, Walensky)
- Can less frequent dosing or new agents be comparably effective?
- Can topical chemoprophylaxis lead to less frequent monitoring?
What about intermittent PrEP?

- IAVI studies in East Africa: MSM and FSW, small size, but many missed post-coital doses
- HPTN 066: dose proportionality study of different PrEP schedules, sampling mucosal tissues
- HPTN 067: MSM in Bangkok and NYC, and high risk women in Capetown, to compare adherence to coitally dependent vs. fixed intermittent PrEP.
- Ipergay: getting underway in France, 2 doses before risky sex, and 1 post-coital
## New Antiretrovirals for Prevention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Status</th>
<th>Developers/Sponsors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapivirine (gel and ring)</td>
<td>NNRTI</td>
<td>Phase 1/2</td>
<td>Tibotec/IPM</td>
</tr>
<tr>
<td>UC-781 (gel)</td>
<td>NNRTI</td>
<td>Phase 1/2</td>
<td>CONRAD MTN</td>
</tr>
<tr>
<td>MIV-150 (gel)</td>
<td>NNRTI</td>
<td>Phase 1</td>
<td>Population Council</td>
</tr>
<tr>
<td>BMS-793 (?)</td>
<td>gp120 inhibitor</td>
<td>Pre-clinical</td>
<td>BMS/IPM</td>
</tr>
<tr>
<td>L644 peptide (?)</td>
<td>gp120 inhibitor</td>
<td>Pre-clinical</td>
<td>Merck/IPM</td>
</tr>
<tr>
<td>Maraviroc (oral and ring)</td>
<td>CCR5 inhibitor</td>
<td>Phase 1</td>
<td>ViiV/IPM HPTN/MTN</td>
</tr>
<tr>
<td>TMC278 (injectable)</td>
<td>NNRTI</td>
<td>Phase 1</td>
<td>Tibotec</td>
</tr>
</tbody>
</table>
NEXT-PrEP (HPTN 069)

- Maraviroc alone
- Maraviroc-FTC
- Maraviroc-TDF
- TDF-FTC
- 400 U.S. MSM, 200 women
  12 sites (ACTG+HPTN)
- Substudies to assess PK, co-receptor occupancy, immunohistology
- Currently enrolling
- Basis for future comparative PrEP trial
Demo Projects to Enhance Adherence

- In Weltel study (Kenya), weekly SMS message and phone support reported adherence and rates of virologic suppression for HIV+ pts
- SF adapting this for use in PrEP with weekly SMS messages to check in
- Fenway: 2 new projects:
  - R34 (Mayer/Safren) to develop evidence-based adherence intervention
  - R21 (Mimiaga/Mitty) to study stimulant using MSM to develop PreP package

Lester Lancet 2010
CAPRISA 004: First Proof of Concept that Chemoprophylaxis works

What about Topical Microbicides?

- Vaginal Gel: waiting for the tie breaker: the FACTS study
- Vaginal gel not tolerated rectally b/c glycerin (MTN 006)
- MTN 007: Phase 1 study of reformulated tenofovir 1% gel
- Reduced glycerin tenofovir 1% gel
  - Reduced incidence and severity of GI adverse events
  - No significant changes in histology, inflammatory markers, and epithelial sloughing
  - Improved acceptability
- Further safety study in humans is planned
  - MTN-017: phase 2 rectal safety study