Updates in HIV Prevention:  
A Focus on PrEP and PEP 

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Disclosure

Betty J. Dong, PharmD has no conflicts of interest to disclose.
Learning Objectives

After successfully completing this presentation, participants should be able to:

• Identify appropriate candidates for pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).

• List appropriate treatment regimens for PrEP and PEP

• Identify side effects, drug interactions, and monitoring parameters to ensure the safe and effective use of PrEP and PEP.

• Provide effective patient counseling and strategies to prevent HIV infection.
What is the Reported Efficacy of PrEP in the Real World Setting?

1. 46%
2. 55%
3. 66%
4. 75%
5. 86%
PrEP has been found to be less effective in which of the following persons?

1) Men who have sex with men
2) Intravenous drug users
3) Discordant couples
4) Women
5) Adolescents
6) d and e
Which is the Recommended Initial Regimen Recommended for Post-exposure Prophylaxis (PEP) by the CDC?

1) Tenofovir/emtricitabine + darunavir/ritonavir
2) Tenofovir/emtricitabine/efavirenz (Atripla)
3) Tenofovir/emtricitabine + dolutegravir
4) Tenofovir/emtricitabine/elvitegravir/cobicistat (Stribild)
5) Abacavir/lamivudine/dolutegravir (Triumeq)
6) Carbotegravir + rilpivirine
What is the Longest Time (in Hours) Following An Risky Exposure When PEP is Still Recommended to be Given?

1) 2
2) 6
3) 12
4) 24
5) 72
Undiagnosed/Unaware HIV+ Persons Contribute to New HIV Infections

1.2 million persons are living with HIV in the US
50,000 new infections per year

About 87% (1,000,000) aware
About 16% (200,000) unaware

- 30% with undetectable HIV RNA, 850,000 can transmit HIV infection
- 2,000 new HIV infections each year are sexual transmissions (e.g. MSM)

If all diagnosed + 57% reduction in unprotected sexual exposures
31% reduction in new infections

Skarbinski J et al. JAMA Intern Med. 2015;175(4):588-596
The Need for HIV Prevention: Continued HIV Risk

- ~50,000 new infections/year
- MSM: ~ 67% new infections
- Females: 87% due to heterosexual contact

Estimated new HIV infections in the United States for the most affected subpopulations, 2010-2014

- Male-to-male sexual contact (67%)
- Heterosexual contact (17%)
- IDU (4%)
- Male-to-male sexual contact and IDU (3%)
- Other (1%)
Diagnoses of HIV Infection among Adults and Adolescents, by Age at Diagnosis, 2014—United States

N = 43,899

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
HIV Prevention Strategies

Comprehensive Prevention Strategies:
condoms, clean needles, safe sex, risk reduction, education
Case Presentation

AK is a 32 year old HIV infected female who is well known to your pharmacy. She is not on ART but they plan to have a child. CD4 650 cells/mm³, VL 65,000 c/ml

BG, her husband, is HIV negative. He asks if there is anything that can protect him and the pregnancy from becoming HIV infected.

Questions:

a) What is BG’s risk of getting HIV infection?
b) What can AK do to prevent HIV transmission to her partner?
c) Provide education and counseling to BG about protecting him and the pregnancy/baby from HIV infection.
Risks of Sexual HIV Transmission

Single contact w/ contaminated blood/body fluids

Risks of sexual contact/episode: anal>vaginal

- Insertive vaginal 0.04% (1/2500)
- Insertive anal risk 0.06% (1/1666)
- Receptive vaginal 0.08% (1/1250)
- Receptive anal risk 0.82-1.4% (1/122- 1/71)

- Oral sex
  - Insertive partner: very low risk
  - Receptive partner: very low risk

- Baby risk: < 1% if undetectable VL in mother during preg & prophylaxis of mother and baby
Can Antiretroviral Therapy (ART) Prevent HIV Transmission?

- **Benefits of Offering and Treating All HIV+ with ART:**
  - To reduce HIV viral load and infectiousness
  - To reduce risk of HIV transmission to uninfected partner

- **HIV Treatment as Prevention:**
  - “Test and Treat”: A Public health approach to prevent HIV transmission
  - Reduce community viral loads and lower rate of new infections
  - San Francisco Depart Public Health and Zuckerberg SF General Hospital ARV “Getting to Zero” Eliminate HIV within 10 years
  - NYC 2nd city to offer ART to all
HIV+ sexually active serodiscordant couples

CD4+ of HIV+ partner: 350-550 cells/mm$^3$
(N = 1763 couples)

Immediate ART
Start ART at CD4+ cell count 350-550 cells/mm$^3$
(n = 886 couples)

Delayed ART
Start ART at CD4+ cell count ≤ 250 cells/mm$^3$*
(n = 877 couples)

Primary efficacy endpoint: virologically linked HIV transmission

Primary clinical endpoints: WHO stage 4 events, pulmTB, severe bacterial infection and/or death

Couples received intensive counseling on risk reduction and condom use


*Based on 2 consecutive values ≤ 250 cells/mm$^3$. 
HIV Transmission Reduced 93% with Immediate ART (5.5 yr F/U)

Total HIV-1 Transmission: n=78
HIV incidence 0.9%
(19 in immediate arm and 59 in delayed arm; $P < .0001$)

Linked Transmissions: 46

Delayed Arm: 43
Immediate Arm: 3

Unlinked Transmissions: 26
(14 immed; 12 delayed)

$P < .001$

PrEP Outline

1. **What is PrEP?**  How Effective is it?

2. Who are Candidates for PrEP

3. Pharmacokinetic Data

4. Safety of PrEP
What is Pre-exposure (PrEP) Prophylaxis?

- After exposure to HIV, infection may become established.
- PrEP is providing antiretroviral medication(s) or prophylaxis to an HIV-uninfected individual before potential HIV exposure.
- Pre-exposure prophylaxis begun earlier before exposure may prevent infection.
Pre-exposure Prophylaxis (PrEP)

- Tenofovir/emtricitabine (Truvada®): FDA approval in July 2012 for adults

- One tablet daily continuously with/without food to prevent HIV exposure

- Achieves sustained concentrations in blood

- Penetrates into genital secretions: rectal >> cervix/vaginal

- Data in monkeys show protection with daily, 3 days pre-exposure, 2 hr post rectal
## PrEP Clinical Trials Results

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Participants</th>
<th>Number</th>
<th>Drug</th>
<th>mITT a efficacy of % reduction in acquisition of HIV infection b</th>
<th>Adherence-adjusted efficacy based on TDF detection in blood c</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Men who have sex with men (MSM)</td>
<td>2499</td>
<td>TDF/FTC</td>
<td>42 (18-60)</td>
<td>92 (40-99)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>HIV discordant couples</td>
<td>4747</td>
<td>TDF</td>
<td>67 (44-81)</td>
<td>86 (67-94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>75 (55-87)</td>
<td>90 (58-98)</td>
</tr>
<tr>
<td>TDF 2</td>
<td>Heterosexually men/women</td>
<td>1200</td>
<td>TDF/FTC</td>
<td>62 (22-83)</td>
<td>84 NS</td>
</tr>
<tr>
<td>Bangkok</td>
<td>IDU</td>
<td>2413</td>
<td>TDF</td>
<td>49 (10-72)</td>
<td>74 (2-91)</td>
</tr>
<tr>
<td>PROUD</td>
<td>MSM</td>
<td>500</td>
<td>TDF/FTC</td>
<td>86 (58-96)</td>
<td>-----</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>MSM</td>
<td>400</td>
<td>on demand</td>
<td>86 (40-99)</td>
<td>-----</td>
</tr>
<tr>
<td>US PrEP Demo</td>
<td>MSM, Transgender</td>
<td>437</td>
<td>TDF/FTC</td>
<td>NS</td>
<td>-----</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>Heterosexually active women</td>
<td>1951</td>
<td>TDF/FTC</td>
<td>NS</td>
<td>-----</td>
</tr>
<tr>
<td>VOICE</td>
<td>Heterosexually active women</td>
<td>5029</td>
<td>TDF/FTC</td>
<td>NS</td>
<td>-----</td>
</tr>
</tbody>
</table>

Notes:
- mITT: Modified Intent To Treat
- %: Percentage
- (95% CI): 95% Confidence Interval

References:
- Molin, J. et al. CROI 2015; Seattle, WA. #23LB; McCormack S, et al. CROI 2015; Seattle, WA. #22LB
PrEP: Adherence = Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Adherence</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx¹</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Partners PrEP³</td>
<td>81%</td>
<td>75%</td>
</tr>
<tr>
<td>Bangkok²</td>
<td>67%</td>
<td>49%</td>
</tr>
<tr>
<td>TDF²</td>
<td>84%</td>
<td>62%</td>
</tr>
<tr>
<td>FEM-PrEP⁵ &amp; VOICE⁶</td>
<td>≤30%</td>
<td>No efficacy</td>
</tr>
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PROUD: Pragmatic Open-Label Randomized PrEP Trial

Randomized, multi-center, open-label pilot in 13 UK STD clinics; 11/29/12-4/30/14

High-risk, HIV-uninfected MSM engaging in CAI N=544

Immediate (IMM) TVD (n=275)

Deferred (DEF) TVD (start at Month 12) (n=269)

Primary endpoint: HIV seroconversion between randomization and Month 12
Secondary endpoints: Safety, adherence, sexual behavior, resistance development

Oct 13, 2014: the PROUD Trial Steering Committee announced that all deferred participants would be offered the opportunity to begin PrEP ahead of schedule

PROUD: Pragmatic Open-Label Randomized Trial of Pre-Exposure Prophylaxis

### Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Infections, n</th>
<th>Follow-up (PY)</th>
<th>Incidence/100 person-years (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>23</td>
<td>504</td>
<td>4.9 (3.4-6.8)</td>
</tr>
<tr>
<td>Immediate</td>
<td>3</td>
<td>243 (94%)</td>
<td>1.2 (0.4-3.0)</td>
</tr>
<tr>
<td>Deferred</td>
<td>20</td>
<td>222 (90%)</td>
<td>9.0 (6.0-12.7)</td>
</tr>
</tbody>
</table>

Side effects: n=21 subjects w/ nausea, HA, arthralgia; ↑Scr d/c (n=3)

Risk reduction 86% (90% CI: 64%-96%) (p=0.0001)

Number needed to treat=13 (90% CI: 9-25)/with 1 year of PrEP to prevent 1 HIV infection

IPERGAY: On-Demand PrEP

Study Duration: 2/22/2012 thru 10/23/2014: Mean F/U = 9.3 months (4.9 to 20.6)

High-risk, HIV-uninfected MSM N=400
- Condomless anal sex with ≥2 partners within 6 months
- eGFR > 60 mL/min

Double-blind, randomized

“On-demand” TDF/FTC treatment (n=199)
All participants received a package of comprehensive preventative measures:
- counseling
- repeated HIV testing
- screening & treatment for other STIs
- HBV and HAV vaccination
- condoms and gel

“On-demand” TDF/FTC placebo (n=201)

Primary endpoint: HIV seroconversion
Secondary endpoints: Sexual behavior, safety events, adherence

Oct. 2014, the DSMB recommended that the placebo arm be discontinued and patients be offered switching into the treatment arm.

Total tablets = 4 tablets for HIV prophylaxis

“On-demand” regimen constitutes:
- LD: 2 TDF/FTC or 2 placebo 2-24 hours with food before sexual exposure
- 1 TDF/FTC or placebo 24 hours and then 48 hrs after first intake
- Multiple exposures: one tablet daily until the last exposure, then last 2 tablets
- If< 1 week between exposures, LD=1 tablet only

IPERGAY Results: On-Demand PrEP

- **16 HIV infections**
  - PBO=14 (incidence: 6.6/100 PY)
  - TDF/FTC=2 (incidence: 0.91/100 PY)

- Average 15 pills/month (11-21)

- Adherence: pill counts, TDF/FTC levels
  - 28% did not take TDF/FTC or PBO
  - 43% correct; 29% suboptimal dose
  - No resistance noted

- ADR: TDF/FTC vs PBO: higher GI/renal
  - GI: 14% vs 5% (p=0.002)
  - Renal: 18% vs 10% (p=0.03)

- NNT: 18/year to prevent 1 infection
- 86% reduction (95% CI: 40-98, p=0.002)

On demand regimen was effective among high-risk MSM with frequent sex (median of 10 sex acts/month and 8 partners every two months).

Suggest that 3-4 days/week (on average) may be effective.

However, short study duration

CDC cautions:
- similar efficacy among MSM with less frequent sex less or among other populations at high risk for HIV infection.
- recommends daily dosing of PrEP and urges people at substantial risk for HIV infection and their health care providers to continue to follow current CDC guidelines

US PrEP Demo Project

- Prospective, open-label demonstration project assessing PrEP
- 557 MSM and transgender women in SF, Miami, Wash DC
- TDF/FTC provided at no costs over 48 weeks @ STI clinics
- 80 to 86% adherence by pill counts, self report and drug level
- 4 or more tablets weekly → 99% HIV protection
- 2 HIV infections (0.43 infections per 100 person yrs)
- Higher study drop out rates (30-37.5% ) in AA, younger men, lower socioeconomic status, and those without prior knowledge of PrEP
- Lower TDF levels in AA, unstable housing, and Miami patients.
- STI rates were high

Liu A et al. JAMA Intern Med 2016;176:75-84
Oral TDF/FTC PrEP for Adolescent MSM

ATN 113: observational, open-label, single-arm feasibility study
- US MSM, 15-17 yrs with CAI with ≥ 3 high-risk partners/behaviors for HIV infection
- n=2864 prescreened but only 79 enrolled
- Week 48 outcomes (40% n=32 stopped)
  - 3 infections; w/ undetectable TFV-DP levels
  - HIV incidence: 6.41/100 PY (95% CI: 4.9-25.8)
  - Adherence declined over time
  - ADR: weight loss 10-19%


ATN 110: MC, open label, feasibility study
- US MSM, 18-22 yrs high-risk behavior for HIV infection
- n=200 (mean age 20 yrs)
- Week 48 results (25 stopped PrEP d/t choice or ADR)
  - 4 infections w/ undetectable TFV-DP levels
  - HIV incidence: 3.29/100 py
  - ADR: grade 3 nausea, wt loss, HA
  - Adherence:
    - lowest in AA, highest in white/Latino men
    - >700 TFV-DP levels: declined over time

Hosek S, et al 8th IAS Conf, Abst TUAC0204LB

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Wk 4</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>Wk 36</th>
<th>Wk 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFV-DP levels &gt; 700 fmol/punch*</td>
<td>60.0</td>
<td>52.4</td>
<td>55.0</td>
<td>31.5</td>
<td>22.7</td>
<td>28.2</td>
</tr>
</tbody>
</table>

*Equivalent to adherence for ≥ 4 days.
What is the Reported Efficacy of PreP in the Real World Setting?

1. 40%
2. 55%
3. 60%
4. 75%
5. 86%
PrEP has been found to be less effective in which of the following persons?

1) Men who have sex with men
2) Intravenous drug users
3) Discordant couples
4) Women
5) Adolescents
6) d and e
PrEP Outline

1. PrEP Efficacy

2. Candidates for PrEP

3. Pharmacokinetic Data

4. Safety of PrEP
PrEP is recommended as one prevention option for the following adults at substantial risk of HIV acquisition
- Sexually active MSM
- Heterosexually active men and women
- Injection drug users

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### Potential indicators of substantial risk of acquiring HIV infection

**MSM**
- HIV-positive sexual partner
- Recent bacterial STI
- High number of sex partners
- History of inconsistent or no condom use
- Commercial sex work

**Heterosexual Women and Men**
- HIV-positive sexual partner
- Recent bacterial STI
- High number of sex partners
- History of inconsistent or no condom use
- Commercial sex work
- In high-prevalence area or network

**Injection Drug Users**
- HIV-positive injecting partner
- Sharing injection equipment
- Recent drug treatment (but currently injecting)

---

Checklist: Is patient a PrEP Candidate?

- Are they at substantial risk of HIV infection?
  - report behaviors or situations that place them at risk for frequently recurring HIV exposures (e.g., IDU or sex without condoms)
  - report receipt of ≥1 course of PEP in the past year

- Are they able to adhere to a once-daily tablet regimen?

- What is their likely tolerance of possible adverse effects?

- Are they able to maintain follow-up appointments?

- Are there any economic issues or other concerns?
CDC PrEP Guidance for Adults at High Risk through Heterosexual Sex/MSM

Determine eligibility

• Confirm high risk for acquiring HIV

• Document HIV/HBV status

• Confirm pregnancy negative (Can be used in pregnancy)

• Confirm CrCL > 60 mL/min

• Screen STD and HCV and treat if necessary

• Avoid PrEP in breastfeeding women
CDC Guidance: Pre-Exposure Prophylaxis (PrEP) for Adults at High Risk thru Heterosexual Sex/MSM

**BEGIN PREP**

- Ensure HIV negative (HIV Ab, HIV RNA)
- Tenofovir/emtricitabine (Truvada) one tablet daily with/without food
- Dispense max of 90 days/per rx
- Adherence counseling
- Provide comprehensive prevention: Risk reduction, condoms, needle exchange, etc

**MONITORING**

- HIV test q 2-3 mo and if PrEP stopped
- Pregnancy test q 2-3 mo
- Assess adherence/continuing risks vs benefits
- Monitor Scr/bone loss
- If HIV+, refer to care

MMWR 2011; 60;65; NEJM 2012;367:399
## PrEP Outline

1. PrEP Efficacy
2. Candidates for PrEP
3. **Pharmacokinetic Data**
4. Safety of PrEP
2014 USPHS/CDC Guidelines for PrEP: Time to Achieve Steady State Levels of TFV-DP

- Time from initiation of daily oral doses of TDF/FTC to maximal protection against HIV infection is unknown

- Pharmacokinetic studies conducted with HIV-uninfected men and women provide preliminary data on the lead-time required to achieve steady state levels of TFV-DP in peripheral blood mononuclear cells, rectal, and vaginal tissues.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Time to Achieve Steady State Levels of TFV-DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal tissue</td>
<td>~7 days</td>
</tr>
<tr>
<td>Blood</td>
<td>~20 days</td>
</tr>
<tr>
<td>Cervicovaginal tissues</td>
<td>~20 days</td>
</tr>
<tr>
<td>Penile tissues</td>
<td>No data available</td>
</tr>
</tbody>
</table>
Fig. 1 TFV-DP concentrations in the STRAND and iPrEx trials.


TFV-DP 16 fmol assoc w/ 90% HIV vs PBO
## PrEP Outline

1. PrEP Efficacy
2. Candidates for PrEP
3. Pharmacokinetic Data
4. **Safety of PrEP**
PrEP Side Effects

- Transient
- GI: nausea, vomiting, abd discomfort, diarrhea
- Headache, fatigue, dizziness
- Weight loss
- Provide supportive care
  - Anti-emetics, anti-diarrheals, analgesics
- Counseling
Tenofovir/Emtricitabine Renal Toxicities

HIV+: renal dysfunction ≤2%, Fanconi’s syndrome (reabsorption failure in proximal tubules), DM insipidus
- ↑Scr, ↓PO4, proteinuria, glycosuria, metabolic acidosis
- Onset: weeks-months
- Risk factors: renal dx, dehydration, DM, HTN, nephrotoxins, proteinuria
- Monitor: baseline SCr/UA for glu/prot, PO4, q 3 mo
- Stop if proteinuria>500 mg/24 hr, ↑BUN/SCr, CrCl<60
- Usually reversible after stopping TDF
- Pt education: hydration, avoid nephrotoxins
Renal:

- n = 2499 HIV-negative subjects in iPrEx study
- A mild, non-progressive decrease in CrCL (CG), reversible and managed with routine monitoring. Did not vary by race, age, or HTN hx
  - Affected by NSAID use
    - -3.4 mL/min (+NSAID) vs. -0.3 mL/min (no NSAID), P = 0.04

<table>
<thead>
<tr>
<th></th>
<th>TVD</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4</td>
<td>-2.4</td>
<td>-1.1</td>
<td>0.02</td>
</tr>
<tr>
<td>At Stop</td>
<td>+0.3</td>
<td>+1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Post-stop</td>
<td>-0.1</td>
<td>0.0</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Change in Creatinine Clearance from Baseline (mL/min)*

Decline in eGFR Resolves Within Weeks of Discontinuing TDF or FTC/TDF for PrEP

- Partners PrEP: daily oral TDF PrEP vs. FTC/TDF PrEP vs. PBO among African HIV-negative men and women (N=4747) with normal baseline renal function
- Mean eGFR was 2-3 mL/min lower on PrEP vs. PBO ($P < 0.01$) at first post-study visit
- >96% of participants had >75% eGFR reversion to baseline levels by 8 weeks of study drug discontinuation

Mugwanya, K. CROI 2015, Seattle, WA #981
Renal Monitoring for PrEP

- Obtain baseline Scr and estimated CrCL
- Avoid fixed dose TDF/FTC if CrCl is less than 60 mL/min.
- If decrease in CrCl is observed while on PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.
- Maintain good hydration
- Avoid concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs)
Tenofovir and Bone Abnormalities

MSM in CDC PrEP Study
- 0.8-1.1% net ↓ BMD at femoral > hip during 1st 12 mo
- No further BMD decline at 24 mo
- 6 fractures vs 4 PBO but study not designed/powered

HIV+: ART ↓ BMD 0.8-1.7% during 24-48 wks, then stabilize
- Tenofovir ↓ 0.7 to 1% BMD @ 24 wks hip > lumbar
- Boosted protease inhibitors; OR 1.5 (ie. ATV, LPV/r)

↑ risk of osteoporotic fractures (retropective VA study)
- Tenofovir 12%

CID 2010; 51:937; CID 2011; 52:1061; Curr Opin Infect Dis 2010;23:1; Plos One 2011;6:e23688;
JAMA 2004;292:191; CID 2010; 51:963
BMD Substudy of iPrEx: TDF/FTC PrEP vs Placebo in HIV-Neg High-Risk MSM/TGW

iPrEx: double-blind, randomized trial (N = 2499): 44% relative reduction in cumulative HIV risk with TDF/FTC vs PBO ($P = .005$)

iPrEx DXA BMD substudy (N = 498)
- Small net decrease in spine (-0.91%) and total hip (-0.61%) BMD with TDF/FTC vs PBO at Wk 24 ($P = .001$ for both); no difference in fracture rate between groups ($P = .62$)

Current analysis evaluated BMD changes after PrEP stop visit

BMD Substudy of iPrEx: BMD Recovery After Discontinuation of TDF/FTC PrEP

Data compared for TFV-DP < or ≥ 16 fmol/M viable PBMC, concentration associated with 90% reduction in HIV infection risk in MSM/TGW

<table>
<thead>
<tr>
<th>Change in BMD From iPrEx Enrollment (%)</th>
<th>Hip</th>
<th>Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 25 Yrs</td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td></td>
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<tr>
<td>Wk 24 TFV-DP &lt; 16</td>
<td></td>
<td></td>
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<tr>
<td>Wk 24 TFV-DP ≥ 16</td>
<td></td>
<td></td>
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<tr>
<td>Age ≥ 25 Yrs</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Wk 24 TFV-DP &lt; 16</td>
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<tr>
<td>Wk 24 TFV-DP ≥ 16</td>
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</tbody>
</table>
PrEP in Clinical Practice: What Are the Barriers to PrEP Uptake?

Users
- Unaware of HIV risk,
- PrEP availability, or how to access it
- No or delayed access to clinical preventive care
- Uninsured or unable to pay
- Adherence challenges
- Concern about disclosure and stigma

Providers
- Unaware of intervention
- Uncertain how to deliver the intervention
- Wary of complexity and time involved
- Discomfort with assessing candidacy
- Uncertain how to bill for intervention

n=155 clinicians from specialties for which PrEP prescribing may be feasible.
Numbers represent percentage of each response.

Key Concerns, Challenges, and Unanswered Questions for PrEP

- Who is most likely to benefit?: Less protective for women and adolescents
- Will risky behaviors and safe sex be abandoned? How to maintain comprehensive prevention: safer sex, condom use, behavioral modifications
- Will long term toxicities increase? HIV- persons/fetus? renal, bone loss?
- How to maintain logistics of adherence and ongoing monitoring for efficacy, toxicity, and resistance?
- Will drug resistance with poor adherence?
Case Report: Multiclass Resistant HIV Infection Despite High Adherence to PrEP

43-yr-old MSM acquired multiclass resistant HIV-1 infection following 24 mos of oral once-daily TDF/FTC PrEP

Pharmacy records, blood concentration analyses, and clinical history support recent and long-term adherence to PrEP

PrEP failure likely result of exposure to PrEP-resistant, multiclass resistant HIV-1 strain

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mutations Detected on Day 7 Following p24-Positive Test</th>
<th>Estimated Fold-Change in IC$_{50}$ or Change in Response (Drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>41L, 67G, 69D, 70R, 184V, 215E</td>
<td>1.9x (ABC), 61x (3TC), 38x (FTC), 1.3x (TDF)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>181C</td>
<td>43x (NVP)</td>
</tr>
<tr>
<td>PI</td>
<td>10I</td>
<td>No relevant change</td>
</tr>
<tr>
<td>INSTI</td>
<td>51Y, 92Q</td>
<td>Reduced (RAL, DTG), resistant (EVG),</td>
</tr>
</tbody>
</table>

Knox DC, et al. CROI 2016. Abstract 169aLB.
What’s in the Future for PrEP

- Carbotegravir: potent INSTI formulated as oral tablet and as long acting IM injection q 12 weeks
- Maraviroc
- Dapavirine:
  - Silicone elastomer vaginal ring containing dapivirine 25 mg every 4 wks
  - Insert and remove the vaginal ring and wear it for the entire month.
  - Sustained adherence associated with 92% reduction in risk of HIV

Pharmacist Roles in Providing PrEP

- Ensure negative HIV Ab/HBV test, and pregnancy before starting PrEP
- Offer HBV vaccination if appropriate
- Familiar with use and interpretation of OTC HIV test
- Knowledge about HIV and its transmission
- Acquisition of PrEP: authentic sources, funding
- Counseling and education if starting/dispensing PrEP
  - Safe sex/condom use/risk reduction with PrEP
  - Minimize side effects of TDF+ FTC/ reduce self D/C
  - Reminders about HIV/preg testing every 2-3 mo
  - Avoiding nephrotoxins; increase hydration
  - Recognition of the signs/sx acute HIV infection
  - Long term toxicity or fetal exposure unknown
- Linkage/referral of patients for HIV care

After exposure to HIV, infection may become established

Post-exposure prophylaxis (started ASAP after exposure) reduces the chance of infection
Post-Exposure Prophylaxis (PEP)

- Antiretrovirals given after risky exposure to prevent HIV

- Occupational PEP
  - After needle-stick, muco-cutaneous or cutaneous exposures to blood or infectious body fluids

- Non-occupational PEP (nPEP):
  - After risky sex/condom breakage, IVDU, sexual assault, found needles

- Evaluate exposure mode, fluid exposed to, HIV status of source patient, and risk factors of source patient.

2016 nPEP  CDC Guidelines ; MMWR Recomm Rep 2005;54(RR-9):1-17
Case Presentation: PEP

- FG is a pharmacist in a community pharmacy who often provides immunization and POCT testing.
- After giving a influenza vaccination, FG sustains a NS
- FG is concerned about transmission of HIV.
- How common and risky is this exposure?
- What counseling and treatment should FG receive at this time?
Risks of HIV Transmission

- Single contact w/ contaminated blood/body fluids
  - Blood transfusion before 1985 (HIV-1) and
    - 1992 (HIV-2): HIV risks 1:2,100,000
  - Needle-sharing IVDU: 0.67% (1/150)
  - Needlestick 1/400 (0.23%) to HIV+ source patient (SP)
    - Deep NS
    - Visibly bloody needle
    - High HIV viral load (much lower risk if undetectable HIV viral load)
  - Non-intact skin/mucous membrane exposures 1/1000

- No Risks: Non-bloody saliva, vomitus, urine, feces, sweat, tears and respiratory secretions
Needlestick Injuries in Retail Pharmacy Chain 2000-2011

2150 pharmacists at 805 chain pharmacies in 25 states certified to provide immunization (lancet injuries n=5 excluded)

28 syringe injuries occurred after use/before disposal
  - During use of the sharp (n=6)
  - Putting into sharps container (n=5)
  - Disassembling (n=2)
  - Sharps left in inappropriate place (n=2)
  - Other (n=4)

14 NS injuries in 2010 (none 2000-2007): No BBP infections documented:

Incidence
  - 0-3.62 per 100,000 vaccinations
  - 0-5.65 per 1000 immunizing pharmacists

Chain’s written policies/procedures comprehensive and c/w OSHA BBP standards

Likely preventable and underestimation actual incidence

Infection Control and Hosp Epidemiology 2012;33:1156
Case Presentation: PEP

FG is a pharmacist in a community pharmacy who often provides immunization and POCT testing.

After giving a influenza vaccination, FG sustains a NS

FG is concerned about transmission of HIV.

How common and risky is this exposure?

What counseling and treatment should FG receive at this time?
Post-Exposure Prophylaxis (PEP) Evaluation

- Is time of exposure within the “window” for PEP?
  - No human studies—start ASAP after exposure
  - Within 72 hr (CDC) based on animal data
  - Within 36 hr (NYC) based on animal data

- Risks (ARV toxicity) vs. benefits (~80% risk reduction)

- No infections reported by CDC since 2002 for occupational exposures

- Evaluate risks for HBV and HCV infection
Post-Exposure Prophylaxis (PEP)

- Duration of therapy is 28 days:
  - Tenofovir/emtricitabine (Truvada) one daily PLUS
    - Raltegravir (Isentress) 400 mg bid
    OR
    - Dolutegravir (Tivicay) 50 mg daily
  - Alternate: Tenofovir/emtricitabine (Truvada) one daily PLUS darunavir (Prezista) 800 mg and ritonavir (Norvir) 100 mg daily
  - Avoid NNRTI
  - If SP HIV+, provide sensitive ARVs (e.g. PI)

CDC 2016 nonoccupational guidelines: [http://stacks.cdc.gov/view/cdc/38856](http://stacks.cdc.gov/view/cdc/38856)
Monitoring Post-Exposure Prophylaxis

- **Side effects:**
  - Tenofovir/emtricitabine: GI, headache, renal/bone abnormalities
  - Raltegravir (RAL): myalgias, creatine kinase (rare)
  - Dolutegravir (DTG): insomnia, headache, false ↑ Scr

- **Drug interactions:** Al++/Mg/Ca cations

- **Laboratory**
  - HIV Ag/Ab test baseline, 6 wks, 4 mo (if SP HCV+ 6 and 12 mo)
  - Scr baseline, repeat 2 weeks and prn
  - AST/ALT baseline, repeat 2 weeks and prn
  - HCV Ab baseline, 3 and 6 mo (if + HCV SP: obtain HCV VL @ 6 wks)

What is the Longest Time (in Hours) Following an Risky Exposure When PEP is Still Recommended to be Given?

1) 2
2) 6
3) 12
4) 24
5) 72
Which is the Recommended Initial Regimen Recommended for Post-exposure Prophylaxis (PEP) by the CDC?

1) Tenofovir/emtricitabine + darunavir/ritonavir
2) Tenofovir/emtricitabine/efavirenz (Atripla)
3) Tenofovir/emtricitabine + dolutegravir
4) Tenofovir/emtricitabine/elvitegravir/cobicistat (Stribild)
5) Abacavir/lamivudine/dolutegravir (Triumeq)
6) Carbotegravir + rilpivirine
Additional HIV Prevention Strategies (if time permits)
Is Safe Sex/Condoms Still Necessary if Your HIV VL is Undetectable?

- HIV suppression in blood is different from vaginal/rectal fluids
- Tenofovir achieves higher rectal than vaginal levels
- Detectable HIV RNA in semen with undetectable HIV VL in blood
  - 6.6% (n=20/304 HIV+)
  - 25% (n=21/83) of HIV+ MSM with co-infections with STI/genital inflammation
- HIV viral shedding is not uncommon even if undetectable HIV VL
- HIV shedding increased by STI/urethritis and genital inflammation

Lambert-Niclot S et al AIDS 2012 Feb 29; Politch JA et al. AIDS 2012 March 23
Male Circumcision Reduces Risk of HIV Infection in Heterosexual Men Globally

- Studies show circumcision reduces risk of HIV infection by 50-60%  
  - RR: 0.42 (95% CI: 0.34-0.54) Meta-analysis (n=27 studies) sub-Saharan Africa; 15 adjusted for confounding factors
  - RR: 0.40 (95% CI: 0.24-0.68; $P < .001$) ANRS 1265 (n=3274) South Africa RCT circumcision immediately vs end of month
  - RR: 0.47 (95% CI: 0.28-0.78) 2784 men Kenya RCT immediate vs delayed circumcision; 24 mo
  - RR 0.49 (95% CI: 0.26-0.93) US STD clinic visits AA heterosexual men with HIV+ exposure (n 394) vs unknown exposure (n = 40,177)

HVTN100: Investigational HIV-1 Vaccine for HIV-Uninfected South African Adults

- Double-blind, randomized, placebo-controlled phase I/II trial
  - South African adults (N = 252) randomized to vaccine (n = 210) or placebo (n = 42)
  - Vaccine: clade C ALVAC-HIV (vCP2438) and bivalent subtype C gp120/MF59
  - Vaccination schedule: ALVAC-HIV @ 0,1mo; ALVAC-HIV gp120/MF59 @ 3, 6, 12 mo (booster)

- Goal: 4 prespecified immunogenetic criteria required to enter into phase IIb efficacy studies
  1. Develop IgG-binding Abs to ≥ 2 of 3 gp120 vaccine antigens (LL of 95% CI ≥ 75%)
  2. Non-inferior IgG-binding Ab magnitude to 2 of 3 gp120 vaccine antigens vs RV144 (previous vaccine trial)
  3. Non-inferior response rate of Env-specific CD4+ T cells expressing IL-2, IFN-gamma, or CD40L vs RV144 (difference within 30%)
  4. Develop IgG-binding Abs to ≥ 1 clade C V1V2 Ags/tags (LL of 95% CI ≥ 56%)

Prevention of HIV Transmission: What Probably Works?

Abstinence
Male Circumcision
Clean Needles
Undetectable viral load
Condoms
PrEP
PEP
Additional HIV References and Resources

Conference on Retrovirus and Opportunistic Infections (CROI 2016) [http://retroconference.org/]
Clinical Care Options HIV :
   [http://www.clinicaloptions.com]
HIV Insite: [http://hivinsite.ucsf.edu]
HIV-Associated Resources on the Web. ([http://www.iasusa.org])
PrEP Watch ([http://www.prepwatch.org/])
Global HIV Prevention ([http://www.avac.org/ht/d/sp/i/262/pid/262])
Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV— United States, 2016
The CCC provides clinicians of all experience levels cost-free, timely, and expert responses to questions on:

- HIV/AIDS management (testing, ARVs, co-infection, care)
- Occupational and non-occupational exposure management
- Management of HIV in pregnant mothers and their infants
- Considerations in providing PrEP as part of HIV prevention
- Substance use evaluation and management
Thank You!

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Session Code:

1. Write down the course code. Space has been provided in the daily program-at-a-glance sections of your program book.

2. To claim credit: Go to www.cshp.org/cpe before December 1, 2016.