Maximizing the Benefits of Pre-Exposure Prophylaxis (PrEP)

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Financial Relationships With Commercial Entities

- Dr Buchbinder has participated in research trials that have received provision of medicines from Gilead Sciences, Inc. (Updated 02/20/17)

Learning Objectives

After attending this presentation, learners will be able to:
- Recognize trends in the US HIV Epidemic
- Describe factors influencing PrEP effectiveness in different clinical populations
- Discuss PrEP counseling strategies for clinical practice
Updates in PrEP and HIV Prevention

1. Who needs PrEP most?
   - Epidemiology of new infections

2. PrEP effectiveness
   - Population differences?

3. Counseling considerations
   - Regimens
   - Condoms
   - Safety monitoring

4. Population impact

Who needs PrEP most?

NEW DIAGNOSES IN THE UNITED STATES

ARS 1: What is happening in the US Epidemic?

1. New HIV diagnoses are decreasing in all risk and age groups
2. New HIV diagnoses are rising in African American women
3. New HIV diagnoses are rising in young MSM aged 13-24
4. In 2015, there were more new diagnoses in persons > 45 years than in those <25 years
Diagnoses of HIV Infection among Adults and Adolescents, by Sex
2010–2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.

Stable numbers: now 81% of total
Decline: now 19% of total

Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Transmission Category, 2015—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay. Data have been statistically adjusted to account for missing transmission category. "Other" transmission category not displayed as it comprises less than 1% of cases.

New CDC Data on HIV Infections in the US

Estimated annual HIV infections in the U.S. declined 18% from 2008–2014

New HIV infections declined substantially and statistically in some states and jurisdictions:
- Washington, DC, 10% per year
- Maryland about 9% per year
- Pennsylvania about 7% per year
- Georgia about 6% per year
- New York and North Carolina each about 9% per year
- Illinois about 4% per year
- Texas about 3% per year

Annual HIV infections are falling among gay and bisexual men aged 19–24, but rising among those aged 25–34 years
Diagnoses of HIV Infection among Adults and Adolescents by Age at Diagnosis, 2015—United States

N = 39,393

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay.

Rates of Diagnoses of HIV Infection among Adults and Adolescents 2015—United States and 6 Dependent Areas

N = 39,920  Total Rate = 14.7

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay.

New HIV Diagnoses By MSM And IDU Transmission Category in NYC, 2001-2015

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay.
**POPULATION DIFFERENCES?**

**PrEP Effectiveness**

ARS 2: How do you recommend PrEP be taken?

1. I recommend daily PrEP for both men and women
2. I recommend less than daily dosing for men, but daily dosing for women
3. I recommend PrEP be taken before and after sex, but only for men
4. I recommend peri-coital PrEP for both men and women
5. I don’t recommend anyone take PrEP
TDF/FTC PrEP Effectiveness for MSM
(Excellent, even with high rates of STIs, but not perfect)

- Kaiser Northern California (Marcus et al, JAIDS 2016; 73:540-546)
  - 952 men, 20 women on PrEP
  - 42% annual cumulative incidence STIs
  - 0 HIV infections (2 occurred after d/c’d PrEP)

- PrEP Demo (Liu et al, JAMA Intern Med 2016;176:75-84)
  - 557 MSM and TGW in SF, Miami, DC
  - 51% had STI on follow-up
  - 2 breakthrough infections
    - Pt A: First positive visit 37 days after last dose
    - Pt B: First positive visit 4 weeks after last visit

- Breakthroughs on PrEP
  - 2 MSM HIV-infected while treated for Hep B with daily TDF (Fox et al, Infect Dis Ther 2016; 5:65-71)
  - 1 MSM HIV-infected on TDF/FTC PrEP – multi-drug resistance (Kerr et al, NEJM 2017; 376:5-12)
  - 1 MSM HIV-infected on TDF/FTC PrEP – no resistance (Hornenberg, CROI 2017, Abstract 953)
Acute Infection with a Wild-Type HIV-1 Virus in PrEP User with High TDF Levels

Hoornenborg et al, CROI 2017, Abstract 953

- DBS at 6 and 8 mos, TFV-DP levels >2200 fmol/punch
- At 8 months, developed fever and dysuria
- Antibody positive, Ag negative
- Stopped PrEP: virus detectable 3 weeks later
- No resistance mutations

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IPERGAY: Sex-Driven iPrEP

- 2 tablets 2-24 hours before sex
- 1 tablet every day during sexual activity
- 2 tablets after the last sexual intercourse

On demand PrEP tells you How to Start and How to Stop PrEP

Median # pills/month: 18 (IQR 11-25)
HIV Incidence (mITT Analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (double-blind)</td>
<td>212</td>
<td>6.60 (3.00-11.1)</td>
</tr>
<tr>
<td>TDF/FTC (double-blind)</td>
<td>219</td>
<td>0.91 (0.11-3.30)</td>
</tr>
<tr>
<td>TDF/FTC (open-label)</td>
<td>515</td>
<td>0.19 (0.01-1.08)</td>
</tr>
</tbody>
</table>

Median Follow-up in Open-Label Phase 18.4 months (IQR:17.5-19.1)

97% relative reduction vs. placebo

Planning for the pre-event dose

US online survey, 1013 MSM

- Last anal sex planned?
  - Planned
  - Unplanned

- How far ahead planned?
  - < 1 day
  - 1-2 days
  - > 2 days

MSM Behavior: Intermittent PrEP is not for everyone

- (Un)Planning for sex, Stack et al, JAIDS 2016;71:94-101
  - 3217 MSM in an online survey; 46% had UNPLANNED condomless anal sex in past 3 months

- The “Hope Springs Eternal” study, Parsons et al, JAIDS 2015;68:449-55
  - 92 HIV negative MSM asked to predict sex with casual partner x 30d. Much better at predicting when they WOULDN'T have sex than when they would.
  - “Skip your daily dose only if there is a 0% chance you’ll have sex tomorrow”

- Vacation Sex or “Malaria prophylaxis, 2.0”, Elsesser et al, AIDS Behav, online Nov 4, 2015
  - 7305 MSM online survey: 26% reported condomless anal sex with new partners while on vacation
Vaginal microbial dysbiosis

*The majority of women with dysbiosis are undiagnosed by Nugent score

Healthy vagina

Microbial dysbiosis

An analysis of CAPRISA 004 (tenofovir gel) found that PrEP was only effective in women with lactobacillus-dominant microbiome

Tenoforv gel effective against HIV with Lactobacillus dominance

<table>
<thead>
<tr>
<th>Lactobacillus dominant</th>
<th>Non-Lactobacillus dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>Placebo</td>
</tr>
<tr>
<td>HIV incidence per 100 person-years</td>
<td>2.7</td>
</tr>
<tr>
<td>HIV-1 protection effectiveness</td>
<td>61% (95% CI: 54-68)</td>
</tr>
</tbody>
</table>

Burgener & Klatt, TUSS0605, AIDS 2016

Tenoforv is rapidly depleted by Gardnerella but not Lactobacillus
• 41 healthy, non-pregnant, HIV negative women received daily tenofovir gel or film x 7 days
• Sampling:
  - Baseline vaginal swabs for qPCR and Nugent score
  - Before 7th dose (trough): vaginal fluid and plasma
  - 2 hours after 7th dose (peak): cervical biopsy and plasma
• Association of tenofovir levels and measures of vaginal dysbiosis
  - Vaginal dysbiosis associated with lower levels of tenofovir in vaginal fluid, cervical tissue, plasma
  - Conversely, lactobacillus associated with higher levels of tenofovir in vaginal fluid, cervical tissue, plasma
• Confirms results from CAPRISA 004 suggesting that vaginal microbiota may adversely affect topical tenofovir metabolism

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**Daily Oral PrEP is Effective Among Women with Abnormal Vaginal Microbiota**

From Heffron et al, CROI 2017, Abstract 85

**Parent study: Partners PrEP Study**

1785 HIV uninfected women from Kenya and Uganda with mutually-disclosed HIV infected male partners
(normal liver, renal, hematologic function)

Randomize HIV uninfected partners

PrEP: TDF or FTC/TDF once daily  Placebo once daily

All receiving comprehensive HIV prevention services

Follow up to 36 months

Primary endpoint: incident HIV infection

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**PrEP efficacy was not modified by BV**

Interaction p=0.9

• PrEP was protective against HIV acquisition for each category of Nugent score
• Differences in the levels of HIV prevention efficacy were not statistically significant (interaction p=0.9)
Conclusions

- These data are reassuring that the delivery of oral PrEP to women does not need to be contingent upon testing for BV.
- Given that oral PrEP is metabolized through a systemic process (different from the local process for topical PrEP), a local mediator such as BV may not be expected to modulate the protective benefits.
- The expansion of PrEP delivery to women with substantial HIV risk through models that maximize adherence is of utmost importance.

How long do you need to take PrEP before protected?

**In Blood**

- 89% achieve EC90 after 7 doses
- 98% by 13th dose

**Recommend for MSM**

- Start TDF/FTC PrEP 7 days before
- Continue 28 days after (based on animal data)

**Recommend for Women**

- Unknown how long before: CDC recommends 21 days
- Women need 6-7 doses/week while men only need 4-7 doses

Proportion achieving EC90 of tenofovir in PBMCs

Seifert CID 2015;60:804-810

Need high levels of adherence to protect against injection exposure?

**Bangkok TDF Study in PWID**

- Needed 97.5% adherence under DOT to achieve >80% effectiveness
- May not have the same “forgiveness” with injection exposures
- At CROI 2017, reported 5/11 breakthrough infections despite high adherence under “DOT”
- Garcia-Lerma, Abstract 954
- This study used TDF alone. Would TDF/FTC be more effective?

Martin et al, AIDS 2015;29:819-824
Summary: PrEP Effectiveness

- Highly effective in MSM population
  - Drug "forgiveness" in rectal tissue: achieve high effectiveness if take > 4 pills/week
  - Insufficient data on per-coital dosing if sex < weekly
  - Question patients about anticipated periods of risk (e.g., vacation)

- Highly effective if used daily in women
  - Less "forgiveness" of TDF/FTC in vaginal tissue
  - Maximize benefit from >6 pills/week
  - Appears that vaginal microbiota affects topical but not systemic PrEP

- Appears effective against injection drug use
  - May need high rates of adherence
  - Remember that many women who inject drugs also at risk sexually

Counseling Considerations

COUPLES, CONDOMS, AND SAFETY MONITORING

ARS 3: How would you advise a monogamous HIV “sero-different” couple about condom use?

1. No need for condoms if HIV+ partner is fully virally suppressed
2. No need for condoms if HIV negative partner is on PrEP
3. Both viral suppression and PrEP are needed before stopping condoms
4. Condoms are more effective than ART and/or PrEP
**Potential transmission among treated patients**

- HPTN 052 final results (Cohen et al., NEJM 2016;375:830-839)
  - 36% of transmissions were unlinked (infection from outside partnership)
  - Eight linked infections in couples
    - 4 occurred within 180 days after HIV+ initiated ART
    - 4 occurred after failure of viral suppression in HIV+ partner

- Time VL > 1500 copies (Marks, AIDS 2015, 29:947-954)
  - Cohort of >14,000 patients at 6 HIV clinics followed median of >3 years
  - 90% prescribed ARVs
  - 54% of pts had 1 or more VL > 1500
  - VL > 1500 for 23% of observation time (average 84 days/patient)

**PrEP as a bridge to ART**

- For couples initiating ART at enrollment, PrEP was offered through 6 months, then stopped:
- For couples in which the infected partner delayed or declined ART, PrEP was continued until 6 months after ART initiation:

  - This strategy is supported by mathematical modeling as potentially highly effective and cost-effective (Hallett et al. PLoS Med 2011; Ying et al. JIAS 2015)

**HIV incidence**

- The observed incidence is a 95% reduction compared to expected, a result that was highly statistically significant

- No. of infections observed 4.9 (95% CI 3.9-6.0)
- No. of infections expected 4.0
- 95% reduction 90% CI 87-98%
- P<0.0001

Adapted from Baeten, WEAC0105, AIDS 2016
### Condom Effectiveness

- **Heterosexuals**
  - Meta-analysis of 25 studies, >10,000 couples
  - **Overall effectiveness: 71-77%**

- **MSM**
  - Data from 2 large cohorts
  - **70% effective**
  - Smith et al, JAIDS 2015;68:337-344

### Modest decline in renal function

- In iPrEx OLE and SF Kaiser (Marcus JAIDS 2016), risk of eGFR<70 if:
  - Baseline eGFR<90
  - >40-50 years old

- In Partners PrEP and Partners Demo (Mugwanya JAIDS 2016)
  - Same as above, wt<55kg
  - >75% of creat increases unconfirmed on repeat test
  - No difference 3 vs 6 mo testing

- In Thai IDU study (Martin, CID 2014)
  - No effect of recent IDU
  - Worse with increased age

- All studies
  - Revert near baseline after trial

### Bone Mineral Density: Recovery after Stopping PrEP

- **Minimal bone loss**
- **Recovery after PrEP stopped**

- Similar findings in 16-17 year olds
  - ATN 110
Do STIs modulate the efficacy of PrEP?

- No evidence STIs lower PrEP efficacy in RCTs
  - iPrEx: Syphilis incidence of 7.3/100 py; no interaction with PrEP efficacy (Salomon CID 2014)
  - Partners PrEP: No difference in PrEP efficacy among those with STIs (Murnane AIDS 2013)

- No evidence from open label studies
  - PROUD in UK: 73% with baseline STI & 86% effectiveness of PrEP (McCormack AIDS 2013)
  - US MSM PrEP Demo study: 90/100 p-yr STI incidence & 0.43/100 p-yrs HIV incidence (Liu JAMA Int Med 2015)

PrEP Safety: Summary

- Renal issues rare in HIV negative population with CrCl >90
  - Frequent screening largely leads to unconfirmed issues
  - Increased risk for older, smaller, and those with CrCl 60-90, may warrant closer screening

- BMD decreases relatively small, revert to baseline off PrEP
  - Implications for youth not known

- STIs common in high-risk populations, pre-date PrEP
  - Screening for asymptomatic infection critical
  - Remind pts that PrEP doesn’t protect against other STIs

- Resistance uncommon if uninfected at start
  - Screen for non-specific viral symptoms at start
  - Caution pts about re-starting meds without testing

Population-level Impact

IS PREP SCALE-UP REACHING THE RIGHT PEOPLE?
Transmission risk group | % with PrEP indication | Estimated number (95% CI)
--- | --- | ---
Men who have sex with men, aged 18-59 yrs† | 24.7 | 49,200 (21,200-77,000)
Adults who inject drugs, aged >18 yrs§ | 18.5 | 115,000 (45,000-185,000)
Heterosexually active adults, aged 18-59 yrs¶ | 0.4 | 624,000 (404,000-846,000)
Men** | 0.2 | 157,000 (62,000-252,000)
Women | 0.6 | 468,000 (274,000-662,000)
Total | 24.7% | 1,232,000 (661,000-1,803,000)

*Percentage of all estimated persons in each transmission risk group and demographic subset with PrEP indications.
†Based on 2007–2012 National Health and Nutrition Examination Survey (NHANES) data, weighted as recommended using current population estimates. Risk factors used to define PrEP indications included two or more male sex partners and at least one of the following: any condomless sex or sexually transmitted infection diagnosis in past 12 months.
§Based on 2013 National Survey on Drug Use and Health. Risk factors used to define PrEP indications included injection of heroin, methamphetamine, stimulants, or cocaine, and injecting with a needle used by someone else before them.
¶Based on 2011–2013 National Survey of Family Growth and 2007–2012 NHANES data, weighted as recommended using current population estimates. Risk factors used to define PrEP indications included two or more opposite sex partners and at least one of the following: sex with an HIV positive partner; or any condomless sex in the last 4 weeks and sex with a male who injects drugs or bisexual male (females only) in last 12 months.
**The relative standard error for males was 30.09%.
PrEP Awareness/Attitudes Among Primary Care Providers

- 1500 providers surveyed per year x 6 years
- Increased PrEP awareness over time; in 2015, only 7% had prescribed PrEP
- When PrEP efficacy described as >75%, more than 90% of providers indicated willing to prescribe
- Most common to recommend in stable serodiscordant partnerships
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Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th>Detecting substantial risk of acquiring HIV infection:</th>
<th>Infection Drug Users:</th>
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</thead>
<tbody>
<tr>
<td>Sexual partner with HIV</td>
<td>Infected injecting partner</td>
</tr>
<tr>
<td>Recent drug use (STD)</td>
<td>Sharing injection equipment</td>
</tr>
<tr>
<td>High number of sex partners</td>
<td>Recent drug treatment (but currently not taking)</td>
</tr>
<tr>
<td>History of inconsistent or no condom use</td>
<td></td>
</tr>
<tr>
<td>Commercial sex work</td>
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Clinically eligible:
- Documented negative HIV test before prescribing PrEP
- No contraindications to PrEP
- Normal renal function, no contraindications medications
- Documentation of elevated risk for HIV acquisition
- Recent drug treatment (but currently not taking)

Prescription:
Daily, continuous, avoidance of TDF/FTC 150 mg tablets

Other services:
- Follow-up visits to monitor adherence and assess health
- HIV test, medication adherence counseling, behavioral risk reduction support, side effect management, STD prevention treatment
- At 3 months and every 6 months after, assess renal function
- Every 4 months for those taking TDF
- Do oral health/STD testing
- Assess pregnancy intent
- Pregnancy test every 3 months
- Access to clean needles/syringes and drug treatment services