Pre-Exposure Prophylaxis: A Reality

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thefenwayinstitute.org
Why PrEP? In the TasP Era, Reductions in New HIV Infections are Off Target

FIGURE 2.4. NEW HIV INFECTIONS, ALL AGES, GLOBAL, 1990–2016 AND 2020 TARGET

*The 2020 target is fewer than 500,000 new HIV infections, equivalent to a 75% reduction since 2010.
Source: UNAIDS 2017 estimates.
**Select Daily Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence**

- **VOICE/FEM-PrEP**
  - Efficacy: 0%/6%
  - Adherence: 29%/≤ 37%

- **iPrEx**
  - Efficacy: 44%
  - Adherence: 51%

- **Partners PrEP**
  - Efficacy: 75%
  - Adherence: 81%

- **TDF2**
  - Efficacy: 62%
  - Adherence: 80%

- **PROUD**
  - Efficacy: 86%
  - Adherence: ~100%

*Reduction in HIV incidence vs control.

†Based on pill counts or the detection of study drug in plasma.

Fonner VA, et al. AIDS. 2016
PrEP Safety: Well Tolerated and Rare Discontinuations

- At initiation of PrEP (start-up syndrome)
  - PrEP versus placebo: 1% to 18% versus 0% to 10% experienced nausea, vomiting ± dizziness; Usually ends within the first month
- No difference between PrEP and placebo (overall and by subgroups)
  - Any adverse event (clinical and laboratory) or Grade 3/4 adverse events
- Several studies noted subclinical declines in renal function and bone mineral density among PrEP users
  - Grade 2-4 elevation in creatinine: 0.2%
  - BMD loss: 0.4% to 1.5% across total hip, spine, femoral neck, and trochanter
    - Returned to baseline with withdrawal of PrEP, no increased fracture risk

## PrEP Management

### Prior to PrEP initiation:
- Document negative HIV status prior to prescribing TDF/FTC
- Evaluate for signs or symptoms of acute HIV infection
- If concerned about acute HIV, obtain HIV quantitative PCR prior to rx.
- Evaluate renal function, and exclude patients with CrCl < 60 mg/ml
- Rule out active infection with HBV and document vaccination status
- Review medications to prevent administering counterindicated medications

<table>
<thead>
<tr>
<th>Follow up after PrEP initiation</th>
<th>Schedule follow up visits at least once every 3 months</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Refill PrEP prescription based on adherence to clinical follow-up</td>
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<tr>
<td></td>
<td>Assess adherence and provide follow up adherence counseling</td>
</tr>
<tr>
<td></td>
<td>Obtain HIV test, screen for bacterial STIs, monitor renal function</td>
</tr>
<tr>
<td></td>
<td>For women: perform pregnancy test</td>
</tr>
<tr>
<td></td>
<td>For injection drug users: link to drug treatment services and needle exchange programs</td>
</tr>
</tbody>
</table>

Ridell, Amico, Mayer, JAMA, 2018

- Partners PrEP study and Partners Demonstration Project (n=5359)
- Frequency of clinically relevant decline in creatinine clearance was rare (<1%)
- Baseline covariates associated with creatinine clearance <60 mL/min within 12 months of starting PrEP (hazard ratios)
  - Age ≥45 years (3.4%): 2.5 ($P=0.0008$)
  - Creatinine clearance 60-90 mL/min (4.3%): 74.4 ($P<0.001$)
  - Weight ≤55 kg (2.3%): 2.7 ($P=0.004$)
- These data support US CDC recommendations for 6-monthly creatinine monitoring for people using PrEP

Cumulative Proportion With Impaired Kidney Function at 12 Months

Heterosexual HIV serodiscordant couples:
Creatinine clearance >60 mL/min at entry, PrEP adherence (>80%).
Mugwanya K, et al. JAIDS. 2018;77:206-211.
Clinical Genotypic Drug Resistance With Oral Emtricitabine/Tenofovir DF in the Setting of PrEP

• Resistance was rare in trials
  – Overall risk: 0.05% (5/9222)
  – N needed to treat to harm: 1844
  – Most resistance occurred in people with undiagnosed acute HIV infection

• Multiple HIV infections were averted for every case of resistance
  • Prevented >8 HIV infections for every FTC-resistant infection

<table>
<thead>
<tr>
<th>Study</th>
<th>PrEP Infected</th>
<th>PrEP Incident</th>
<th>Placebo Infected</th>
<th>Placebo Incident</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>2/2</td>
<td>0/48</td>
<td>1/8</td>
<td>0/83</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>1/3</td>
<td>0/13</td>
<td>0/6</td>
<td>0/52</td>
</tr>
<tr>
<td>TDF2</td>
<td>1/1</td>
<td>0/9</td>
<td>0/2</td>
<td>0/24</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>0/1</td>
<td>4/33</td>
<td>0/1</td>
<td>1/35</td>
</tr>
<tr>
<td>VOICE</td>
<td>2/9</td>
<td>1/61</td>
<td>0/1</td>
<td>0/60</td>
</tr>
<tr>
<td>Total</td>
<td>6/16</td>
<td>5/164</td>
<td>1/18</td>
<td>1/254</td>
</tr>
</tbody>
</table>

Is PrEP 100% Protective? NO
HIV Infection Rare with High Adherence to PrEP

<table>
<thead>
<tr>
<th>Patient</th>
<th>PrEP Adherence</th>
<th>Seroconversion</th>
<th>Likely Cause of PrEP Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>43-yr-old MSM[1]</td>
<td>24 mos, supported by pharmacy records, blood concentration analyses, and clinical history</td>
<td>Acquired MDR HIV infection</td>
<td>Exposure to PrEP-resistant, multiclass-resistant HIV strain</td>
</tr>
<tr>
<td>MSM in his 20s[2]</td>
<td>Excellent by self report, supported by blood and hair concentration analyses</td>
<td>Acquired MDR HIV infection after 2 instances of condomless insertive anal intercourse with 2 different partners within 11 weeks before diagnosis</td>
<td>Exposure to PrEP-resistant, multiclass-resistant HIV strain</td>
</tr>
<tr>
<td>50-yr-old MSM[3]</td>
<td>Excellent by self report, supported by blood analyses</td>
<td>Acquired wild-type HIV infection after 2-5 median condomless anal sex partners per day in each month following PrEP initiation</td>
<td>Chronic rectal inflammation +/- trauma</td>
</tr>
</tbody>
</table>

PrEP is not 100% effective, but is highly protective, so to optimize protection and decrease STDs, condoms can be helpful

TDF/FTC PrEP DELAYS SEROCONVERSION

- 25 days vs. 17 days to Feibig V
- 7-fold odds of >100 day delay in site detection of seroconversion
- 0.75 log decrease in viral load
PROUD Study: High PrEP Efficacy in a Real-World Setting

- Significantly ↓ HIV infections with immediate vs deferred PrEP (3 versus 20 cases)
  - HIV infection predated PrEP start (n=1)
  - No drug/not adherent (n=2)
- Number needed to treat to prevent 1 HIV infection: 13
- PrEP was generally well tolerated

iPrEX OLE: PrEP Reduces Incidence of HIV Even With Incomplete Adherence in MSM

- Open-label extension of iPrEX trial; N = 1603 (75% receiving PrEP)
  - 100% adherence was not required to attain full benefit from PrEP
    - Benefit of 4-6 tablets/wk similar to 7 tablets/wk
    - 2-3 tablets/wk also associated with significant risk reduction
- Higher levels of sexual risk taking at baseline associated with greater adherence to PrEP

Grant RM, et al. IAC 2014. Abstract TUAC0105LB.
TDF/FTC PrEP and Women

• ITT estimates range from no protection to 75%
• Post-hoc analyses suggest efficacy >90% when drug consistently taken (Donnell); daily adherence is key
• Oral TDF/FTC has less avidity for cervicovaginal vs. colorectal mucosa, i.e. takes longer to achieve protective concentrations (Patterson)
• But, **daily** TDF/FTC readily achieves protective levels
• Vaginal microbiome (dysbiosis) affects topical TFV concentrations, but **not** systemic (Klatt)
Frequency of any Bacterial STI infection by HIV status and PrEP Use among Male Patients, Fenway Health

Mayer, OFID, 2017
Oral PrEP global roll-out, 2018

- **National roll-out**: Australia, Belgium, Brazil, Canada, Kenya, New Zealand, Norway, Scotland NHS, South Africa (US)
- **Other implementation** (e.g. demonstration projects, pharmacy access, DREAMS)

![World map showing countries implementing Oral PrEP]

*Oral PrEP global implementation:
- National roll-out
- Other implementation*
Number of people taking PrEP globally

Cumulative number starting PrEP

Estimated active users Feb 2018

Half of PrEP users are in the U.S.
Decline sustained in 2017

80% decline in HIV cases since 2015
EPIC-NSW Cohort (N=3700): Targeted PrEP Decreasing HIV Incidence

- Medication possession ratio over 12 months (having enough medication to take PrEP over 12 months)
  - Mean: 83% (95% CI 82%-84%)
- Within cohort HIV infection rate: 0.5/100 person-years
  - 2 infections over 3927 person-years
    - 1 never commenced PrEP
    - 1 took no PrEP for months prior to infection
- Population change in HIV diagnoses over the past 12 months: 32% decline (from 149 to 102 persons)
  - Least reductions
    - Young MSM
    - MSM living outside the central Sydney “gay” suburbs
    - Non-English speaking overseas-born gay men


<table>
<thead>
<tr>
<th>Reduction in HIV Diagnoses (12-month before-after recruitment)</th>
<th>Decline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>32</td>
</tr>
<tr>
<td><strong>Years of age</strong></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>10</td>
</tr>
<tr>
<td>25-34</td>
<td>22</td>
</tr>
<tr>
<td>35-44</td>
<td>44</td>
</tr>
<tr>
<td>&gt;44</td>
<td>48</td>
</tr>
<tr>
<td><strong>Country/region of birth</strong></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>49</td>
</tr>
<tr>
<td>High-income, English speaking</td>
<td>33</td>
</tr>
<tr>
<td>Asia</td>
<td>21</td>
</tr>
<tr>
<td>Other countries</td>
<td>+24</td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td></td>
</tr>
<tr>
<td>Gay Sydney suburbs</td>
<td>52</td>
</tr>
<tr>
<td>Other Sydney</td>
<td>7</td>
</tr>
<tr>
<td>Outside of Sydney</td>
<td>54</td>
</tr>
</tbody>
</table>
Trends in U.S. PrEP Uptake

Estimated 1.1 million people may benefit from PrEP

Mera et al., IAS, 2017; Smith et al., MMWR, 2015

- City-wide getting to zero consortium
  - Coordinated PrEP program
  - Rapid ART program
  - Linkage-engagement in care

- New HIV diagnoses in SF decreased 51% between 2012 (n=453) to 2016 (n=223)
  - Decreases seen among all race/ethnicity groups

PrEP candidates: HIV negative and condomless anal sex OR STI OR HIV-positive partner.
PrEP in the real world: Fenway Health

- Federally qualified community health center with focus on LGBT health
- 35,000 care pts, ~2200 PLHIV, ~7000 HIV- MSM
- 1st PrEP pts in New England: 2011, over past few years: >1000 PrEP starts/year; ~4000 total
- 17 pts who initiated PrEP became infected (<0.5%)
- Reasons for infection: ↓ risk perception, insurance changes, stimulant use
PrEP as a gateway to care: Fenway Health

<table>
<thead>
<tr>
<th>Test</th>
<th>Prevalence Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Flu vaccination</td>
<td>1.57 (1.47-1.67)</td>
</tr>
<tr>
<td>Tobacco screening</td>
<td>1.13 (1.09-1.16)</td>
</tr>
<tr>
<td>Depression screening</td>
<td>1.18 (1.15-1.22)</td>
</tr>
<tr>
<td>Hemoglobin A1c or glucose testing</td>
<td>1.83 (1.75-1.92)</td>
</tr>
<tr>
<td>Hemoglobin A1c testing</td>
<td>0.89 (0.79-1.01)</td>
</tr>
<tr>
<td>Glucose testing</td>
<td>2.03 (1.93-2.14)</td>
</tr>
</tbody>
</table>

Prevalence ratios obtained from Poisson models with generalized estimating equations. Adjusted models included age, gender, race/ethnicity, insurance type, and year, with diabetes, hypertension, and overweight/obesity additionally included in models for hemoglobin A1c and glucose testing.

Marcus et al., CROI, 2018; ms under review
Adherence in clinical practice

• Refill-based PrEP adherence at Kaiser: 92%! with >900 pts f/u
• <5% with <60% adherence (<4/week)
• 2 seroconversions b/c insurance lapses; none among those still on PrEP

<table>
<thead>
<tr>
<th>Factors associated with &lt;80% adherence (N=915)</th>
<th>Risk ratio*</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Black</td>
<td>3.0</td>
<td>(1.7-5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PrEP copay &gt;$50 per month</td>
<td>2.0</td>
<td>(1.2-3.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.6</td>
<td>(1.1-2.3)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

* Risk ratios obtained from Poisson regression with robust variance and adjusted for age, sex, race/ethnicity, socioeconomic status, copay, smoking, drug/alcohol abuse, baseline STI, baseline renal function, hypertension, and diabetes

Marcus et al., JAIDS, July 2016
HIV Acquisition after PrEP Discontinuation (Montreal)

- Retrospective cohort study in MSM who initiated PrEP and returned for at least 1 follow-up visit
Purview paradox

HIV providers:
1^0 care providers should prescribe PrEP

Primary care providers:
PrEP is for specialists

Krakower, AIDS and Behavior, 2014
How to improve chemoprophylaxis effectiveness?

- New oral PrEP drugs and dosing strategies
- Novel adherence strategies
- Alternative delivery systems and formulations
- Vaginal & Rectal Microbicides
- Intravaginal rings (Dapivirine, Tenofovir) +/- Contraception
- Injectable: ARVs and mAbs (Cabotegravir, VRC01)
<table>
<thead>
<tr>
<th>Efficacy Trial</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaginal Ring</strong></td>
<td>HOPE (MTN 025)</td>
<td>Open-label trial of the once-monthly slow-release dapivirine vaginal ring, ongoing in 2,500 women in Malawi, South Africa, Uganda, Zimbabwe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibody</strong></td>
<td>DREAM (IPM 032)</td>
<td>Open-label trial of the once-monthly slow-release dapivirine vaginal ring, ongoing in 1,400 women in South Africa and Uganda</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibody</strong></td>
<td>AMP (HVTN 704/HPTN 085)</td>
<td>Randomized controlled trial of the VRC01 antibody infused every two months, ongoing in 2,700 MSM and transgender men &amp; women in Brazil, Peru, Switzerland and US</td>
<td></td>
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</tr>
<tr>
<td><strong>Antibody</strong></td>
<td>AMP (HVTN 703/HPTN 081)</td>
<td>Randomized controlled trial of the VRC01 antibody infused every two months, ongoing in 1,500 women in Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral PreP</strong></td>
<td>DISCOVER</td>
<td>Randomized controlled trial of once-daily F/TAF as PreP, ongoing in 5,000 MSM and transgender women at approximately 90 sites in Europe and the Americas</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-Acting Injectable</strong></td>
<td>HPTN 083</td>
<td>Randomized controlled trial of injectable cabotegravir every two months, ongoing in 4500 MSM and transgender women in Argentina, Brazil, India, Peru, South Africa, Thailand, US, Vietnam</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-Acting Injectable</strong></td>
<td>HPTN 084</td>
<td>Randomized controlled trial of injectable cabotegravir every two months, planned for 3,200 women in southern and East Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preventive HIV Vaccine</strong></td>
<td>ALVAC/gp120 w/MF59</td>
<td>Randomized controlled trial of ALVAC/gp120 prime-boost with MF59 adjuvant, five doses over 12 months, ongoing in 5,400 men and women in South Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preventive HIV Vaccine</strong></td>
<td>HVTN 702</td>
<td></td>
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<tr>
<td><strong>Preventive HIV Vaccine</strong></td>
<td>HPX2008/HVTN 705</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preventive HIV Vaccine</strong></td>
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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 (3.60-11.1)</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
New technologies and PrEP engagement

- ↑ treatment adherence with text messaging (Lester, Lancet, 2010)
- Daily SMS texting was used to supplement a nurse-delivered PrEP intervention (Safren/Mayer)
- Counseling augmented by electronic diary was associated with ↑ adherence (Amico/Hosek)
- Feedback on drug levels been studied as adjunct to counseling (Landovitz)
- SexPro and MyChoices Apps being developed for young MSM (Buchbinder/Scott/Liu; Mayer/Biello)
- But, augmented lower tech approaches, e.g. home visits, may also be effective (Haberer)
Why the high burden of mental health in HIV?

**Mental Disorder**
- Demographic
  - Age
  - Gender Sexual Orientation
  - Ethnicity
- Biological
  - Chronic immune activation and HPA dysregulation
  - Other Infections (e.g., HCV)
- Community
  - Density
  - Safety / Violence
- Intersecting Stigmas
  - Mental Illness
  - HIV
  - Gender / Sexual Minority
  - Substance Use
  - Sex Work

**HIV**
- SES
  - Income
  - Education
  - Housing and Food: Security/Insecurity
- Environmental
  - Natural Disasters
  - War/Conflict
  - Climate / Water
  - Migration
- Psycho-social
  - Social Support
  - Loss / Bereavement
  - Trauma
  - Gender-based violence
  - Fear of illness
Interventions to Increase HIV and BSTI Testing

Test

HIV negative
Risk assessment PrEP, adherence counseling

HIV positive
Positive prevention

Linkage to care
ART initiation
Retain
Adherence to ART
Enroll in care
Maintain viral suppression

Decrease in HIV and BSTI transmission

Address concomitant concerns:
depression, substance use, relationship dynamics, structural/social issues, STI

Need to Address more than PrEP (and TasP)
Thank You

Rachel Baggaley
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Marcy Gelman
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Doug Krakower
Ken Levine
Julia Marcus
Sheena McCormack
Conall O’Cleirigh

Robert Remien
Steve Safren
Aaron Siegler
Patrick Sullivan

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