Integrating PrEP with Early Antiretroviral Initiation

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May 3rd, 2018
The Key Paradigm: Test and Treat (when ready)

HPTN 052: Treatment as Prevention

Public Health Benefit

Begin treatment at any CD4+ T-cell count

START and Temprano Studies: Early Treatment

Individual Health Benefit
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

*Reduction in HIV incidence vs control.
†Based on pill counts or the detection of study drug in plasma.

**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%

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

**Proud**
- Efficacy 86%
- Adherence ~100%

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

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

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*Ridell, Amico, Mayer, JAMA, 2018*
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

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)
Number of people taking PrEP globally

Cumulative number starting PrEP

Estimated active users Feb 2018

Half of PrEP users are in the U.S.
HIV Decline at Dean Street - UK

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

### Reduction in HIV Diagnoses (12-month before-after recruitment)

<table>
<thead>
<tr>
<th></th>
<th>Decline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>32</td>
</tr>
<tr>
<td>Years of age</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>Country/region of birth</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>Area of residence</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
PrEPVu: Matching PrEP Uptake to PrEP Need

Prevalence of PrEP Users per 100,000 Population
Q2 2017

PrEP-to-Need Ratio (PnR)
Q2 2017

- 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%) compared to >2% of those who did not use PrEP
- Reasons for infection: ↓ risk perception, insurance changes, stimulant use
### PrEP as a gateway to care: Fenway Health

Adjusted prevalence ratios (95% CI) comparing receipt of primary care between PrEP users and individuals not prescribed PrEP – Fenway, 2012-2016 (N=5,857)

<table>
<thead>
<tr>
<th>Service</th>
<th>Prevalence Ratio (95% CI)</th>
</tr>
</thead>
<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

### Factors associated with <80% adherence (N=915)

<table>
<thead>
<tr>
<th>Factor</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

**FIGURE 1**

- **Individuals initiating PrEP (N=1258)**
  - Consistent PrEP use: 36% (N=450)
  - Periodic PrEP use: 9% (N=114)
  - Reported PrEP stop: 17% (N=214)
  - Lost to follow-up: 38% (N=480)

Greenwald et al, CROI 2018, abstract 1038
HIV providers:  
10 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

Vaginal & Rectal Microbicides

Intravaginal rings (Dapivirine, Tenofovir) +/- Contraception

Novel adherence strategies

Alternative delivery systems and formulations

Injectables: ARVs and mAbs (Cabotegravir, VRC01)
## 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?

**Demographic**
- Age
- Gender
- Sexual Orientation
- Ethnicity

**Biological**
- Chronic immune activation and HPA dysregulation
- Other Infections (e.g., HCV)

**Community**
- Density
- Safety / Violence

**Mental Disorder**
- Mental Illness
- HIV
- Gender / Sexual Minority
- Substance Use
- Sex Work

**Intersecting Stigmas**
- Mental Illness
- HIV
- Gender / Sexual Minority
- Substance Use
- Sex Work

**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

Why the high burden of mental health in HIV?
Need to Address more than PrEP (and TasP)

Interventions to Increase HIV and BSTI Testing

- Test
  - HIV negative
  - HIV positive
  - Positive prevention

- Enroll in care
  - ART initiation
  - Retain
  - Adherence to ART

Risk assessment PrEP, adherence counseling

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

Decrease in HIV and BSTI transmission

Maintain viral suppression
Thank You

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Steve Safren
Aaron Siegler
Patrick Sullivan

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