EMERGING ISSUES IN HIV PREVENTION

NEAETC IAS UPDATE, AUGUST 11TH, 2015

KENNETH H. MAYER, M.D.

Disclosures: Unrestricted Educational and Research Grants from Gilead Sciences

thefenwayinstitute.org
Case #1

• Pt is a 42 year old gay man who recently became HIV-infected. His CD4 count is 870 cells/mm³ and his viral load is 75,000 copies/ml.

• He recently began a relationship with an HIV-uninfected man and they do not want to use condoms
A. Would recommend that he start treatment just to protect his partner, since there’s no health benefit for the patient to start so soon

B. Would recommend that he initiate treatment if he is ready to do so, because it would be good for his health, and could protect his partner

C. Would recommend that he tell his partner to start PrEP, to protect himself, but it is too early for the patient to start treatment
TasP, HPTN 052
90-90-90
PrEP Implementation
New approaches
Infusions and injections
HPTN 052 (Final Results): Stable Heterosexual Couples

**Phase 3 study**
Americas, African, Asian sites

**Stable, healthy, sexually active, serodiscordant couples**
CD4 350-550 cells/mm³

Randomization 1:1

**Early ART**
CD4 350 to 550 cells/mm³

**Delayed ART**
CD4 <250 cells/mm³

Similar baseline demographic characteristics and sexual history/behavior both arms and between HIV-negative partner and HIV-positive, treatment naïve index patient

**Primary Endpoints**
- Transmission
  - Virologically linked transmission events
- Clinical
  - WHO stage 4 clinical events
  - Pulmonary TB
  - Severe bacterial infection and/or death

**Status of Participants**
Enrolled (2010; n=1763 enrolled)
Remained in trial
  - 2011 (n=1642)
  - 2015 (n=1535)

HPTN 052 (2011 Results) : HIV Prevention in Stable Heterosexual

- DSMB halts trials after a median follow-up: 1.7 years
  - HIV RNA <400 copies/mL
    - Early ART: 90%
    - Delayed ART: 93%
- Linked HIV transmission to HIV-negative partner (n=28)
  - Early therapy (n=1)
    - 0.1 per 100 person-years
  - Delayed therapy (n=27)
    - 1.7 per 100 person-years
- Early ART led to a 96% reduction of sexual transmission of HIV in serodiscordant couples

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PY f/u</td>
<td>All partner infections # (rate)</td>
<td>Linked partner infections # (rate)</td>
</tr>
<tr>
<td>Total</td>
<td>3482</td>
<td>46 (1.32)</td>
<td>37 (1.06)</td>
</tr>
<tr>
<td>Early</td>
<td>1751</td>
<td>4 (0.23)</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td>Delayed</td>
<td>1731</td>
<td>42 (2.43)</td>
<td>36 (2.08)</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>0.09</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>91%</td>
<td>97%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Rate = # of events/ 100 PY
Risk reduction = 1 – rate ratio
Linked = index to partner transmission
HPTN 052 Conclusions

- 8 linked partner infections diagnosed AFTER the index partner started ART:
  - 4 infections likely occurred before (or soon after) the index partner started ART
  - 4 infections occurred after the index failed ART (mainly non-adherence)
- No index-to-partner (linked) HIV transmissions were observed when the index pt was stably suppressed
- ART is highly effective for prevention of sexual transmission of HIV

- But, 63% of transmissions were from outside partners!
HPTN 052 (2011 Results): Clinical Events

Median follow-up: 2.1 years (1.6-2.9). Patients in the delayed arm initiating ART (24%).

HIV Transmission According to Sexual Behavior Reported by HIV-Negative Partner

- Overall HIV transmission rate
- Zero through condomless sex with a partner on ART (HIV RNA <200 copies/mL), despite a significant number of sex acts
- Uncertainty over the upper limit of risk remains
- Particularly with receptive anal sex with ejaculation
- Additional follow-up needed to provide more precise estimates for transmission risk
- Duration of prior ART without transmission may have selected for lowest risk discordant couples

**Rate of Couple Transmission (per 100 Couple-Years Follow-Up)**

- **Heterosexual (Male)**
  - Vaginal sex with ejaculation (192 CYFU)

- **Heterosexual (Female)**
  - Vaginal sex (272 CYFU)

- **MSM**
  - Receptive anal sex:
    - With ejaculation (93 CYFU)
    - Without ejaculation (157 CYFU)
  - Insertive anal sex (262 CYFU)

CYFU: couple-years follow-up.

Opposites Attract: MSM Couples

HIV ‘Treatment as Prevention’: *Opposites Attract*

<table>
<thead>
<tr>
<th>Type of condomless anal intercourse (CLAI) reported by HIV-negative partner</th>
<th>Linked transmissions (n)</th>
<th>Couple-years of follow up (CYFU)</th>
<th>No. of CLAI acts</th>
<th>Incidence rate per 100 CYFU (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0</td>
<td>149.96</td>
<td>5,905</td>
<td>0 (0-2.46)</td>
</tr>
<tr>
<td>Any CLAI</td>
<td>0</td>
<td>90.83</td>
<td>5,905</td>
<td>0 (0-4.06)</td>
</tr>
<tr>
<td>Insertive CLAI</td>
<td>0</td>
<td>77.87</td>
<td>3,569</td>
<td>0 (0-4.74)</td>
</tr>
<tr>
<td>Receptive CLAI</td>
<td>0</td>
<td>57.08</td>
<td>2,337</td>
<td>0 (0-6.46)</td>
</tr>
<tr>
<td>Any CLAI when VL &lt;200 copies</td>
<td>0</td>
<td>88.59</td>
<td>5,656</td>
<td>0 (0-4.16)</td>
</tr>
<tr>
<td>Any CLAI when VL &gt;200 copies</td>
<td>0</td>
<td>2.00</td>
<td>237</td>
<td>0 (0-184.31)</td>
</tr>
</tbody>
</table>

(Grulich et al., 2015, CROI)
Protection from whom?
Non-monogamy is common: consider protection from other partners

- Any sex with outside partners in previous 3 months:

- Any condomless anal intercourse with outside partners in previous 3 months:

B Bavinton et al IAS 2015 abstract TUAC0306
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

Target 1: 90% of HIV+ people diagnosed
36.9 million

Target 2: 90% of diagnosed people on ART
33.2 million

Target 3: 90% of people on ART with HIV RNA suppression
29.5 million

Viral Suppression
73%

Global Estimates (2014-15) vs the Gap to reach 90-90-90 Targets

HIV Positive People: 36.9 million

Breakpoint 1: 13.4 million Undiagnosed
Breakpoint 2: 14.9 million not treated
Breakpoint 3: 15.3 million Not Virally Suppressed

Diagnosed: 19.8 million

On ART: 15.0 million

Viral Suppression <1000 (ITT)*: 11.6 million


www.ias2015.org
Target 2 vs Target 3:
Percentage of diagnosed people on ART, versus HIV RNA suppression when on ART

*Average from: Botswana, Burkina Faso, Mali, Cameroon, Cote d'Ivoire, Kenya, Senegal, Uganda, Malawi, Mozambique, Nigeria, Senegal, South Africa, Tanzania, Uganda, Zimbabwe, Zambia.
Correlation between HIV treatment and incidence

1.1% (0.8%-1.4%) reduction in HIV incidence, for each 1.0% increase in treatment coverage.

TasP Trial Sites in Africa
**SEARCH Key Questions**

- Can a population-based ART test and treat strategy “shut down” new HIV infections? *
  *As part of combination prevention*
- What are the additional gains?  
  (maternal child health, TB, education, household earning power?)
- What is the best way to do it?
- What would it cost?
- Can efficient HIV chronic care models be adapted to establish care for other chronic diseases (hypertension and diabetes)\(\text{?}\)

**SEARCH: Cluster randomized trial of universal vs. standard ART**

**Intervention**

- ART at all CD4+  
  Annual & targeted testing  
  Enhanced linkage & retention

- 16 communities  
  \(n = 10,000\) each

**Community Health Campaign**

- HIV Screening/Diagnosis  
  Malaria testing & care  
  HTN and Diabetes testing  
  Maternal/child health

- 16 communities  
  \(n = 10,000\) each

**Community Health**

- HIV incidence  
- HIV population viral metrics  
- AIDS  
- Maternal and child health  
- TB  
- NCD (HT, DM)

**Outcomes Year 3 and 5**

**SEARCH Partners**

- PEPFAR  
- NIH  
- WHO  
- World Bank  
- UNAIDS  
- Gilead Sciences  
- Uganda MOH  
- Kenya MOH
Leaks in the cascade may reduce TasP effectiveness: SF example (and Australian paradox, De Wit, AIDS Impact, 2015)

Figure 1.2 New HIV diagnoses, deaths, and prevalence, 2006-2013, San Francisco

HIV Cascade of Care: Missed Opportunities in the US

HIV-Infected: >25 Years of Age (n=896,800)

- 12% Unaware of Infection
- ~73% Diagnosed
- ~40% Linked to Care
- ~28% Retained in Care
- 60% Unaware of Infection

HIV-Infected: 13-29 Years of Age (n=78,949)

- 25% Diagnosed
- 11% Linked to Care
- 6% Retained in Care
- 6% Viral Suppression

Disparities persist between black and other MSM throughout treatment cascade (24 comparative studies)

- **Undiagnosed HIV**
  - OR, 6.38 (4.33-9.39)

- **Diagnosed HIV+**
  - OR, 3.00 (2.06-4.40)

- **ART utilization/access**
  - OR, 0.56 (0.41-0.76)

- >200 CD4 cells/mm³ before ART initiation
  - OR, 0.50 (0.33-0.76)

- **Healthcare visits**
  - OR, 0.61 (0.42-0.90)

- **ART adherence**
  - OR, 0.50 (0.33-0.76)

- **HIV suppression**
  - OR, 0.51 (0.31-0.83)

- **Lower income (<$20k)**
  - OR, 3.42 (1.94-6.01)

- **Health insurance**
  - OR, 0.47 (0.29-0.77)

- **Viral Suppression**

  "To eliminate difference in viral suppression, **an estimated additional 38,920 black MSM and 17,043 Latino MSM would need to be on treatment** to raise viral suppression to levels on par with white MSM aware of their infection (56%)."  
  - (Hall, 2013)

---

(Millett, 2012)
Acute HIV infection: impact on the spread of HIV and transmission of drug resistance

S. Yerly\textsuperscript{a}, S. Vora\textsuperscript{a}, P. Rizzardi\textsuperscript{b}, J.-P. Chave\textsuperscript{f}, P. L. Vernazza\textsuperscript{c}, M. Flepp\textsuperscript{d}, A. Telenti\textsuperscript{b}, M. Battegay\textsuperscript{e}, A.-L. Veuthey\textsuperscript{g}, J.-P. Bru\textsuperscript{h}, M. Rickenbach\textsuperscript{i}, B. Hirschel\textsuperscript{a}, L. Perrin\textsuperscript{a} and the Swiss HIV Cohort Study\textsuperscript{*}

Objective: To assess the impact of primary HIV infection (PHI) on the spread of HIV and the temporal trends in transmission of HIV drug resistance between 1996 and 1999 in Switzerland.

Methods: Sequencing of the genes for reverse transcriptase (RT) and protease was performed for 197 individuals with documented PHI. Phylogenetic analyses were confronted with epidemiological data.

Results: Significant clustering was demonstrated for 29\% of the RT sequences. All these cases occurred closely together in time and place; contact tracing demonstrated transmission at the time of PHI in 30\% of them. Genotypic drug resistance was detected in 8.6\% of PHI individuals in 1996, 14.6\% in 1997, 8.8\% in 1998 and 5.0\% in 1999. Drug-resistant variants were identified in 11.3\% of individuals infected by heterosexual contacts, 6.1\% by homosexual contacts, 13\% of intravenous drug users and more frequently in men (10.4\%) than women (2.6\%). Potential factors involved in the recent decrease of transmission of drug-resistant variants include increase of HIV non-B subtypes from 23\% in 1996 to 35\% in 1999 (only one non-B subtype had resistance mutations) and a steady increase of patients with undetectable viraemia as documented in Swiss HIV Cohort Study (10\% in 1996 vs 53\% in 1999).

Conclusions: Phylogenetic and epidemiological analyses underline the impact of PHI in the spread of HIV. Moreover, this study indicates that drug resistance transmission may have decreased recently in Switzerland through the increased frequency of infection with HIV non-B subtypes and the steady increase of patients with undetectable viraemia.

\textsuperscript{*}© 2001 Lippincott Williams & Wilkins

\textit{AIDS} 2001, 15:2287–2292
What is your current practice and experience with the use of pre-exposure prophylaxis to prevent HIV transmission?

A. I have not prescribed PrEP, because I have concerns about the practice
B. I have not prescribed PrEP, because I have not had requests, but would consider doing so
C. I have only prescribed PrEP to HIV-uninfected partners of my HIV-infected patients
D. I have prescribed PrEP for HIV-uninfected, high risk men who have sex with men, and other at risk people
Clinical trial evidence for oral and topical tenofovir-based prevention (April 2015)

- **Partners PrEP - daily oral TDF/FTC**
  - Discordant couples - Kenya, Uganda
  - Effect size: 75% (55; 87)

- **Partners PrEP - daily oral tenofovir**
  - Discordant couples - Kenya, Uganda
  - Effect size: 67% (44; 81)

- **iPrEx - daily oral TDF/FTC**
  - MSM - North and South America, Thailand, South Africa
  - Effect size: 44% (15; 63)

- **PROUD - daily TDF/FTC**
  - MSM - UK
  - Effect size: 86% (58; 96) (90% CI)

- **IPERGAY - intermittent TDF/FTC**
  - MSM - France, Canada
  - Effect size: 86% (40; 69)

- **TDF2 - daily TDF/FTC**
  - Heterosexual men and women - Botswana
  - Effect size: 62% (22; 84)

- **CAPRISA 004 - “BAT-24” dosing vaginal tenofovir gel**
  - Women - South Africa
  - Effect size: 39% (6; 60)

- **FACTS 001 - “BAT-24” dosing vaginal tenofovir gel**
  - Women - South Africa
  - Effect size: 0% (-1; 2)

- **MTN 003/Voice - daily vaginal dosing tenofovir gel**
  - Women - South Africa, Uganda, Zimbabwe
  - Effect size: 15% (-21; 40)

- **FEMPrEP - daily oral TDF/FTC**
  - Women - Kenya, South Africa, Tanzania
  - Effect size: 6% (-52; 41)

- **MTN 003/Voice - daily oral TDF/FTC**
  - Women - South Africa, Uganda, Zimbabwe
  - Effect size: -4% (-49; 27)

- **MTN 003/Voice - daily oral tenofovir**
  - Women - South Africa, Uganda, Zimbabwe
  - Effect size: -49% (-129; 3)

- **People who inject drugs**
  - Bangkok tenofovir study – daily oral tenofovir
    - (IDUs - Thailand)
    - Effect size: 49% (10; 72)

PrEP works, but adherence is key

Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA

AVAC Report 2013: Research & Reality
www.avac.org/report2013
PrEP is well-tolerated, discontinuations rare because of AEs

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Comparison</th>
<th>Statistics for each study</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BKK TDF Study</td>
<td>Men and Women</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 0.979</td>
<td>0.797</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.203</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value -0.202</td>
<td>p-Value 0.840</td>
</tr>
<tr>
<td>CDC Safety Study</td>
<td>MSM</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 1.357</td>
<td>0.899</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.420</td>
</tr>
<tr>
<td>FEMPrEP</td>
<td>Women</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 1.446</td>
<td>0.855</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.445</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value 1.042</td>
<td>p-Value 0.169</td>
</tr>
<tr>
<td>IAVI Kenya Study</td>
<td>MSM and FSW</td>
<td>multiple PrEP dosing</td>
<td>Risk ratio 4.592</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>81.944</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value 1.037</td>
<td>p-Value 0.300</td>
</tr>
<tr>
<td>IAVI Uganda Study</td>
<td>Men and Women</td>
<td>multiple PrEP</td>
<td>Risk ratio 0.170</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value -1.097</td>
<td>p-Value 0.272</td>
</tr>
<tr>
<td>Ipergay</td>
<td>MSM</td>
<td>intermittent PrEP</td>
<td>Risk ratio 1.226</td>
<td>0.622</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.420</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value 0.589</td>
<td>p-Value 0.556</td>
</tr>
<tr>
<td>iPrEx</td>
<td>MSM and TG</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 0.919</td>
<td>0.747</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.129</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value -0.806</td>
<td>p-Value 0.420</td>
</tr>
<tr>
<td>Partners PrEP- Main</td>
<td>Men and Women</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 1.077</td>
<td>0.954</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.215</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value 1.194</td>
<td>p-Value 0.233</td>
</tr>
<tr>
<td>Project PrEPare</td>
<td>MSM</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 2.850</td>
<td>0.324</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.069</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value 0.944</td>
<td>p-Value 0.345</td>
</tr>
<tr>
<td>TDF2</td>
<td>Men and Women</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 0.652</td>
<td>0.370</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.150</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value -1.477</td>
<td>p-Value 0.140</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women- All PrEP</td>
<td>daily PrEP vs. placebo</td>
<td>Risk ratio 0.925</td>
<td>0.746</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.147</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-Value -0.713</td>
<td>p-Value 0.476</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.916</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.127</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.305</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.760</td>
</tr>
</tbody>
</table>

Favours PrEP  Favours Placebo

- No difference in proportion of participants reporting any adverse event (RR=1.01, 95% CI: 0.99-1.03, p=0.27) or any grade 3 or 4 adverse event comparing PrEP to placebo study arms.
- Several studies noted subclinical declines in renal functioning and bone mineral density among PrEP users.
## PrEP: Risk, Compensation, Adherence, Coverage

<table>
<thead>
<tr>
<th>Best Case: “risky” person is highly adherent (good coverage)</th>
<th>→→</th>
<th>No HIV transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst case: “risky” person is not adherent (poor coverage)</td>
<td>→→</td>
<td>HIV Transmission; selection for resistance</td>
</tr>
</tbody>
</table>

- Risk compensation? Not often relevant
  - Possible, not often seen in studies to date
  - But what if condoms are never used?

- Match counseling messages and prevention intervention to risk →→ Requires discussion with clinician
UK GU Med Clinics: PROUD Study

• Significantly fewer new HIV infections with immediate versus deferred PrEP (3 versus 19 cases)
  – 86% reduction ($P=0.0002$)
  – Number needed to treat to prevent 1 infection: 13

• PEP used by 31% in deferred arm

• Preliminary analysis found that risk behaviors were similar between the 2 arms

PEP: post-exposure prophylaxis.

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
  - Injectables: ARVs and mAbs
“Forgiveness”
Tenofovir Concentration: Rectal>Cervical>Vaginal

Patterson KB et al. Sci Transl Med. 2011.
CORRELATES OF PREP PROTECTION  
(GRANT ET AL, LANCET ID, 2014)

<table>
<thead>
<tr>
<th></th>
<th>BLQ</th>
<th>LLOQ to &lt;350 fmol per punch</th>
<th>350-699 fmol per punch</th>
<th>700-1249 fmol per punch</th>
<th>≥1250 fmol per punch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated dose (tablets per week)</td>
<td>None</td>
<td>&lt;2</td>
<td>2-3</td>
<td>4-6</td>
<td>7</td>
</tr>
<tr>
<td>Follow-up (% of visits)</td>
<td>25%</td>
<td>26%</td>
<td>12%</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>HIV infections (n)</td>
<td>18</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Person-years per infection</td>
<td>384</td>
<td>399</td>
<td>179</td>
<td>316</td>
<td>181</td>
</tr>
<tr>
<td>HIV incidence (95% CI)</td>
<td>4.70 (2.99-7.76)</td>
<td>2.25 (1.19-4.79)</td>
<td>0.56 (0.00-2.50)</td>
<td>0.00 (0.00-0.61)</td>
<td>0.00 (0.00-1.06)</td>
</tr>
<tr>
<td>HR vs previous placebo (95% CI)*</td>
<td>1.55 (0.88-2.56)</td>
<td>0.69 (0.32-1.32)</td>
<td>0.19 (0.01-0.88)</td>
<td>0.00 (0.00-0.25)</td>
<td>0.00 (0.00-0.50)</td>
</tr>
<tr>
<td>HR vs concurrent off-PrEP (95% CI)†</td>
<td>1.25 (0.60-2.64)</td>
<td>0.56 (0.23-1.31)</td>
<td>0.16 (0.01-0.79)</td>
<td>0.00 (0.00-0.21)</td>
<td>0.00 (0.00-0.43)</td>
</tr>
</tbody>
</table>

HR=hazard ratio. PrEP=pre-exposure prophylaxis. BLQ=below limit of quantification. LLOQ=lower limit of quantification. *Adjusted for study site. †Adjusted for study site, age, number of sexual partners, non-condom receptive anal intercourse, and syphilis. Drug concentration measurements were not available for 5% of visits.

Table 2: Effect of tenofovir diphosphate in dried blood spots on HIV infection.
ANRS Ipergay Trial: Event-Driven PrEP

- Significantly fewer new HIV infections with intermittent PrEP versus placebo (2 versus 14 cases)
  - 86% reduction after a mean follow-up of 13 months ($P=0.002$)
- Safety of on-demand PrEP was similar to placebo except for GI adverse events
- Adherence to PrEP was good, supporting the acceptability of on-demand PrEP

Median number of pills/month (IQR): 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm (p=0.84)

48 participants (12%) received PEP
25 (13%) in the TDF/FTC arm and 23 (11%) in the placebo arm (p=0.73)
HPTN 067/ADAPT Study: Proportion Achieving Detectable Tenofovir Concentrations at Week 30

Cape Town (WSM)

Patients (%)

Daily | Time | Event
--- | --- | ---
32% | 46% | 66%

Bangkok (MSM/TGW)

Patients (%)

Daily | Time | Event
--- | --- | ---
86% | 95% | 91%

Harlem (MSM/TGW)

Patients (%)

Daily | Time | Event
--- | --- | ---
39% | 50% | 56%

With sex in the past 7 days.
Cape Town and Bangkok (tenofovir diphosphate >9.1 fmol/M PBMC).
Harlem (tenofovir ≥5 ng/mL plasma).

Partners Demonstration Project: TasP and PrEP

- Open-label prospective study
  - Heterosexual discordant couples not using ART or PrEP in Kenya & Uganda
  - At high risk for HIV transmission based on risk scoring tool
  - ART per national guidelines (treat all seropositive partners in a discordant relationship)
  - PrEP (open-label emtricitabine/tenofovir DF) until HIV-positive partner is on therapy for 6 months as a ‘bridge’ to ART

- 858 person-years of follow-up
- 95% uptake of PrEP and 80% on ART

HIV Incidence

TDF2 Study:
Open-Label Extension (Botswana)

• Offered PrEP with efficacy during the TDF2 study (n=267)
  – Started PrEP (n=229)
    • Most felt at risk or their partner was at risk ($P \leq 0.02$)
• Completed 12 months of follow-up: 54%
  – ~70% of those completing follow-up perceived their HIV risk to medium or high at baseline ($P=0.03$)
• Severe adverse events (n=10)
  – Grade 3 hypophosphatemia (n=6, 2 discontinued); grade 3 hyperamylasemia (n=3), grade 1 hypercreatinemia
• Next steps
  – Motivations and risk behaviors
  – Drug levels and adherence

ATN 110: PrEP Demonstration Project and Safety Study for Young MSMs in the US

- Phase 2, open-label study
  - 18 to 22 years old
  - Self reports evidence of high risk for acquiring HIV
  - HIV negative

- Primary objectives
  - Safety data on emtricitabine/tenofovir DF
  - Acceptability, patterns of use, rates of adherence, drug exposure
  - Patterns of sexual behavior

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enrolled (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>20.2</td>
</tr>
<tr>
<td>White/black/Hispanic/Asian (%)</td>
<td>21/53/17/2</td>
</tr>
<tr>
<td>Gay/bisexual (%)</td>
<td>78/14</td>
</tr>
<tr>
<td>Completed high school/some college (%)</td>
<td>34/45</td>
</tr>
<tr>
<td>Not currently working (%)</td>
<td>30.2</td>
</tr>
<tr>
<td>Partners in past month (number)</td>
<td>5</td>
</tr>
<tr>
<td>Condomless sex (%)</td>
<td>81</td>
</tr>
<tr>
<td>Condomless receptive anal intercourse with last partner (%)</td>
<td>58</td>
</tr>
<tr>
<td>Any positive STI test (%)</td>
<td>22</td>
</tr>
</tbody>
</table>

High risk for HIV: condomless anal intercourse with an HIV-infected male partner or a male partner of unknown HIV status; anal intercourse with ≥3 male sex partners; exchange of money, gifts, shelter, or drugs for anal sex with a male partner; sex with a male partner and has had a STI; sexual partner of an HIV-infected male with whom condoms were not consistently used; or at least one episode of anal intercourse where the condom broke or slipped off.

ATN 110: Main Outcomes of PrEP Demonstration Project and Safety Study for Young MSM

- **Safety**
  - Discontinued (n=25)
  - Treatment-related adverse events (n=3)
    - Nausea, weight loss, headache (all grade 3)
  - HIV seroconversions (n=4)
    - HIV incidence: 3.29/100 person-years
    - No drug resistance
- **Sexual behavior and adherence**
  - STI diagnoses remained constant over time
  - Higher adherence and tenofovir diphosphate levels among those participating in condomless sex and condomless receptive anal intercourse
  - Adherence decreased for all participants over time

New technologies and PrEP adherence

- ↑ treatment adherence with text messaging (Lester, Lancet, 2010)

- Wisepill: used in Life-Steps HAART adherence intervention modified for PrEP, including daily SMS with pts →84% drug levels c/w daily use at 6 months (Mayer/Safren)

- Electronic diaries studied in SF and Chicago was associated with ↑ adherence (Amico/Hosek)

- SexPro App with diary features and adherence support, tested in NYC, SF, Lima and Rio (Buchbinder)

- Feedback on drug levels been studied as adjunct to counseling (Landovitz)
New PrEP Starts per Quarter

Total Unique Individuals = 8,512

IMS National Prescription Database accounts for approx. 39% of all TVD prescriptions
iPrEx Open Label PrEP in San Francisco:

81% still on PrEP at 12 months,¹
92% on PrEP use 4+ tablets per week.²

1. Grant Lancet ID 2014 14(9):820-9;
2. Estimated from dried blood spots in iPrEx OLE in San Francisco.
Fenway Health: PrEP Experience

- 85.5% of initiators still on PrEP; Longest: 3.8 years
- 79.7% White; 8% Black; 12.3% Latino
- 95.1% identified as gay
- 158 zip codes
- “Gayborhood” <10%
- Private Ins: 80.7%; Medicare: 9%; Medicaid: 8.7%
- 25.9% who d/c’ed PrEP, initiated again
- More than 30 prescribers
New England providers perceived numerous barriers to prescribing PrEP (Krakower, PLOS ONE, in press 2015)

- Lack of patient requests: 7% not a barrier, 22% minor barrier, 45% moderate barrier, 26% major barrier.
- Concerns about insurance coverage: 10% not a barrier, 26% minor barrier, 31% moderate barrier, 32% major barrier.
- Clinicians not trained to prescribe PrEP: 14% not a barrier, 22% minor barrier, 30% moderate barrier, 35% major barrier.
- Clinicians not aware of CDC guidance: 19% not a barrier, 22% minor barrier, 33% moderate barrier, 25% major barrier.
- Time constraints: 22% not a barrier, 38% minor barrier, 31% moderate barrier, 9% major barrier.
- Clinicians not aware of PrEP: 23% not a barrier, 27% minor barrier, 31% moderate barrier, 20% major barrier.
- Limited # at-risk patients: 27% not a barrier, 33% minor barrier, 25% moderate barrier, 15% major barrier.

Numbers represent percentage for each response category: not a barrier, minor barrier, moderate barrier, major barrier. Bars total to 100%.
Antiretrovirals alone are not sufficient

Interventions to Increase Testing

- Test
  - HIV Negative
    - Risk Assessment
    - PrEP, Adherence Counseling
  - HIV Positive
    - Linkage To Care
    - Positive Prevention
- Enroll in Care
  - ART Initiation
  - Treat
    - Adherence to ART
  - Maintain Viral Suppression

Decrease in HIV Transmission

Address concomitant concerns: depression, substance use, relationship dynamics
Many thanks

Salim Abdool Karim
Stef Baral
Steve Boswell
Mike Cohen
Heidi Crane
Carlos Del Rio
Marcy Gelman
David Glidden
Andrew Grulich
Diane Havlir
Sybil Hosek
Bill Kapogiannis
Beryl Koblin
Doug Krakower
Raphy Landovitz
Jim Rooney
Steve Safren
Patrick Sullivan
Rodney Vanderwarker
Mitchell Warren

TFI Biomed, Behavioral, Epi and Data Teams
Study Participants

Grants from: NIAID, NIMH, NIDA, NIAAA, NICHD, HRSA, CDC, Gilead