Realizing the Promise of PrEP

CATIE Forum
October 15, 2015
Darrell Tan MD FRCPC PhD
Learning objectives

• To review existing data regarding the efficacy, effectiveness, and main clinical concerns about PrEP

• To propose a roadmap to broader PrEP implementation, including key challenges and opportunities for PrEP to achieve its public health potential in Canada

• To provide examples of work already underway in Canada and the U.S. that can inform the road ahead
Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H.,

• 2499 MSM / transgender F in 6 countries
  – USA, Peru, Ecuador, Brazil, Thailand, S Africa
• Randomized to daily TDF/FTC vs placebo
• Followed for 3324 person-years (median 1.2y)
• All received package of HIV prevention services
  – HIV testing, counseling, STI testing/treatment, condoms

NEJM 2010;363:2587
Figure 2. Kaplan–Meier Estimates of Time to HIV Infection (Modified Intention-to-Treat Population).

The cumulative probability of HIV acquisition is shown for the two study groups. The efficacy of preexposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate (FTC–TDF) was 44%, as compared with placebo (P = 0.005). The inset graph shows a more detailed version of the overall graph up to a probability of 0.10.
PrEP Trials Have Shown Efficacy in MSM, Heterosexual Men and Women, and IDUs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population/Setting</th>
<th>Intervention</th>
<th>HIV Infections, n</th>
<th>Reduction in HIV Infection Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEX[^1]  (N = 2499)</td>
<td>MSM, transgender women, 11 sites in US, South America, Africa, Thailand</td>
<td>TDF/FTC</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>Thai IDU[^4]  (N = 2413)</td>
<td>Volunteers from 17 drug treatment centers in Thailand</td>
<td>TDF</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

FDA NEWS RELEASE

For Immediate Release: July 16, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves first drug for reducing the risk of sexually acquired HIV infection

Evidence-based approach enhances existing prevention strategies

Today, the U.S. Food and Drug Administration approved Truvada (emtricitabine/tenofovir disoproxil fumarate), the first drug approved to reduce the risk of HIV infection in adults at high risk. Truvada, taken daily, is to be used for pre-exposure prophylaxis (PrEP) in combination with safer sexual practices to reduce the risk of sexually acquired HIV infection in adults at high risk.
Concerns about PrEP:
1. Adherence / Efficacy

*PrEP (like ART) works, but only if you take it!*

<table>
<thead>
<tr>
<th>Study</th>
<th>Blood Samples With TFV Detected, %</th>
<th>HIV Protection Efficacy in Randomized Comparison, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP[1]</td>
<td>81</td>
<td>75</td>
</tr>
<tr>
<td>TDF2[2]</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>Thai IDU[4]</td>
<td>67</td>
<td>49</td>
</tr>
<tr>
<td>iPrEx[3]</td>
<td>51</td>
<td>44</td>
</tr>
</tbody>
</table>

iPrEx OLE: Efficacy as a function of drug concentrations in MSM

Follow-up %
- 26%
- 12%
- 21%
- 12%

Risk Reduction
- 44%
- 84%
- 100%
- 100%

95% CI
- -31 to 77%
- 21 to 99%
- 86 to 100%
- 100%

(published online July 22, 2014)

Grant WAC Melbourne 2014;
Grant et al, Lancet Infectious Diseases, published online July 22, 2014
Study Design

Randomized, multicenter, open-label pilot study in the UK

High-risk, HIV-uninfected MSM engaging in CAI
N=545

Immediate (IMM) FTC/TDF
(n=276)

Deferred (DEF) FTC/TDF
(start at Month 12)
(n=269)

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

Oct 2014: the PROUD Trial Steering Committee announced that participants on the deferred arm of the study, who had not yet started PrEP, would be offered the opportunity to begin PrEP ahead of schedule

CAI: Condomless anal intercourse
All subjects received comprehensive HIV prevention services, including condoms, risk-reduction counseling, testing and treatment for sexually transmitted infections, and HIV pre- and post-test counseling
Results

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

**HIV Incidence**

<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>22</td>
<td>453</td>
<td>4.9 (3.4-6.8)</td>
</tr>
<tr>
<td>Immediate</td>
<td>3</td>
<td>239</td>
<td>1.3 (0.4-3.0)</td>
</tr>
<tr>
<td>Deferred</td>
<td>19</td>
<td>214</td>
<td>8.9 (6.0-12.7)</td>
</tr>
</tbody>
</table>

- FTC/TDF prescribed to IMM participants covered 86% of days in follow-up
- Use of post-exposure prophylaxis by arm:
  - IMM: 13 subjects (5%); 15 prescriptions
  - DEF: 83 subjects (31%); 174 prescriptions

86% (90% CI 58-96%) Risk Reduction $P=0.0002$
Number needed to treat=13 (90% CI: 9-25)
Concerns about PrEP:
2. Risk compensation – sexually transmitted infections

<table>
<thead>
<tr>
<th>Anal sex partners in past 90 days, median (IQR)</th>
<th>Baseline, n=539</th>
<th>Month 12, n=349</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMM</td>
<td>DEF</td>
</tr>
<tr>
<td>Total</td>
<td>10.5 (5-20)</td>
<td>10 (4-20)</td>
</tr>
<tr>
<td>Condomless receptive</td>
<td>3 (1-5)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Condomless insertive</td>
<td>2.5 (1-6)</td>
<td>3 (1-7)</td>
</tr>
</tbody>
</table>

No significant differences in STIs between the deferred and immediate arms

McCormack S, et al. CROI 2015; Seattle, WA. #22LB
On October 2014, the DSMB recommended that the placebo arm be discontinued and patients be offered switching into the treatment arm.

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

Study Design

"On-demand" FTC/TDF treatment
All participants received a package of preventative measures:
- counselling
- repeated HIV testing
- screening & treatment for other STIs
- HBV vaccination
- condoms and gel

Double-blind, randomized

"On-demand" FTC/TDF placebo
"On-demand" regimen constitutes:
- 2 FTC/TDF or 2 placebo 2 - 24 hrs prior to sexual intercourse exposure
- 1 FTC/TDF or placebo 24 hrs and then 48 hrs after first intake

Primary endpoint: HIV seroconversion
Secondary endpoints: Sexual behavior, safety events, adherence
IPERGAY: On-Demand PrEP

Kaplan-Meier Estimates of Time to HIV-1 Infection*

![Graph showing Kaplan-Meier estimates of time to HIV-1 infection.]

**86% relative reduction (95% CI: 40-99, *P*=0.002)**

16 subjects infected (PBO=14; FTC/TDF=2)

Number need to treat: 18 for 1 year to prevent 1 HIV infection

* mITT Population
† Log-rank test

Molina J, et al. CROI 2015; Seattle, WA. #23LB
## Concerns about PrEP: 3. HIV Drug Resistance

<table>
<thead>
<tr>
<th>Study</th>
<th>Infected on Study</th>
<th>Unrecognized Baseline Infections$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infected, $n$</td>
<td>Resistant to FTC or TDF, $n$</td>
</tr>
</tbody>
</table>
| iPrEx$^1$ | 100 (36 on FTC/TDF, 64 on placebo) | None | 10 (2 on FTC/TDF, 8 on placebo) | 2 on FTC/TDF (M184V/I); 1 on placebo (M184V)$^*$_
| Partners PrEP$^2$ | 103 (21 on FTC/TDF, 30 on TDF, 52 on placebo) | 3 on FTC/TDF (2 M184I/V, 1 M184I/V + K65R); 1 on TDF (M184I/V); 2 on placebo (M184I/V)$^†$ | 18 (4 on FTC/TDF, 8 on TDF, 6 on placebo) | 2 on FTC/TDF (M184V); 1 on TDF (K65R/K70E) |
| TDF$^3$ | 33 (9 on FTC/TDF, 24 on placebo) | 1 on placebo (K65R <1%)$^†$ | 3 (1 on FTC/TDF, 2 on placebo) | 1 on FTC/TDF (K65R, M184V, A62V) |
| FEM-PrEP$^4$ | 68 (33 on FTC/TDF, 35 on placebo) | 1 on placebo (M184V)$^*$, 4 on FTC/TDF (M184V/I)$^‡$ | 5 (1 on FTC/TDF, 4 on placebo) | None |
| VOICE$^5$ | 312 | 1 on FTC/TDF (M184V/I) | 22 | 2 on FTC/TDF (M184V) |

8 / 129 = 6.2% 6 / 16 = 37.5%

$^*$ Using ultra-deep sequencing

† Transmitted (primary) resistance can occur independent of PrEP, which likely explains resistance in the placebo arm

‡ 1 probable and 2 possible transmitted resistance; 1 uncertain timing of infection (HIV RNA detectable at first follow-up visit)

§ Infection + incomplete suppression of replication by FTC/TDF selects resistance; transmitted (primary) resistance can occur, independent of PrEP, which likely explains resistance in the placebo arm

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2. Lehman D, et al. CROI 2014; Boston. #590LB
5. Parikh, et al. CROI 2014; Boston. #594
PREPARATORY-5

“Canada’s first demonstration project of open-label, oral TDF/FTC-based PrEP”
PREPARATORY-5 Trial

- 1-year ‘Demonstration Project’ in 50 gbMSM
  - Acceptability, adherence, tolerability, toxicity, HIV, STIs
  - Point-of-care HIV testing
- High demand continuing well after enrollment complete
- Community-based research objectives

Referrals:
1. Hassle Free
2. Other CBOs
3. Ads

Screening visit
If eligible and consents

Objective 1: Quantify CBO referrals
Objective 2: Screen for syndemic health problems

Period 1
Baseline visit

Period 2
Month 1 visit

Period 3
Month 3 visit

Period 4
Month 6 visit

Period 5
Month 9 visit

Mo. 12 Final visit

Objective 3: CBO-based adherence support intervention

Objective 4:
Define and begin implementing a CBO ‘Action Agenda’ on PrEP

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Summary: What we know about PrEP in late 2015

- **PrEP** is very **effective** at preventing HIV in gbMSM, IDU and heterosexual men & women when used consistently & correctly

- **Intermittent** PrEP use may be a possibility in select circumstances, but current recommendations are for daily PrEP only

- **PrEP** is **safe** and well **tolerated**

- Careful monitoring for **STIs** and HIV drug **resistance** is important
A roadmap for delivering PrEP at scale

ACCESS
CANDIDATES
PROVIDERS
INTEGRATION
MONITORING & RESEARCH
1. Widespread public ACCESS to PrEP

- Health Canada regulatory approval
  - All prescribing in Canada is currently off-label
  - Application submitted August 2015
  - Will greatly facilitate: coverage, policies, programs

- Public coverage
  - Cost is $883.03 CAD / month
  - Almost all current users using private insurance
  - Position of private payers unclear
  - Truvada® patent ends July 2017
  - Financial assistance program?
2. Strategies for identifying PrEP CANDIDATES

• A) Patient-initiated
  – Need for community awareness

• B) Provider-initiated
  – Clinicians and/or service providers

• C) Public health-initiated?
  – In response to new diagnoses
2. Pathways for identifying PrEP candidates

Increasing community awareness

Proportion of MSM at HFC aware of PrEP

- Feb-Jul 2010: 11.7%
- Apr-Jun 2013: 26.7%
- Nov 2014-Apr 2015: 28%
2. Pathways for identifying PrEP candidates

Uptake of PrEP may be limited because few gay men think they are at risk of HIV infection

Toronto study highlights disconnect between 'objective' and 'subjective' assessments of risk

Roger Pebody
2. Pathways for identifying PrEP candidates

Hypothetical ‘PrEP Cascade’

n=420 MSM at Hassle Free Clinic
3. Knowledgeable, culturally competent PrEP PROVIDERS

• “I went through a sort of like bad part five years ago. I was just feeling lots of anxiety and I knew it was because I was gay, but I’d try to spin it off to something else... So I went to my doctor and I was like, “I think I know why I’m so anxious all the time.” And she’s like, “Why?” And I was like, “I’m gay.” And then she was like, “I know lots of people that are becoming gay now.” And I was like, “Oh, okay.” And so it just reminded me that a lot of doctors are not really well versed with dealing with people who are gay. And it didn’t come from a bad place from her, I just think it came from ignorance and that’s why I never felt comfortable talking to her about anything else.”
Decentralized delivery by trained clinicians

- Awareness among most clinicians remains low
- PrEP delivery is straightforward, but time-consuming
  - Proper STI screening, adherence counseling, timing of appointments vs Rx renewals, addressing syndemics...

- Nurses
  - Public health / sexual health clinics

- Primary care providers
  - Directories of knowledgeable, gay-friendly MDs

- Resources for clinicians
  - Clinical practice guidelines
  - Phone lines
Preparation for PrEP: Perceptions and Readiness of Canadian Physicians for the Implementation of HIV Pre-Exposure Prophylaxis

Malika Sharma¹, James Wilton², Heather Senn³, Shawn Fowler⁴, Darrell H. S. Tan¹,³,⁴,⁵

¹ Division of Infectious Diseases, University of Toronto, Toronto, Ontario, Canada, ² Canadian AIDS Treatment Information Exchange, Toronto, Ontario, Canada, ³ Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, ⁴ Hassle Free Clinic, Toronto, Ontario, Canada, ⁵ Division of Infectious Diseases, St Michael’s Hospital, Toronto, Ontario, Canada

Minimum level of HIV prevention efficacy respondents thought necessary for regulatory approval, stratified by current opinion on whether PrEP should be Health Canada approved:

- **NO**
  - Median (IQR) 75% (50-90%)

- **YES**
  - Median (IQR) 50% (40-70%)
4. INTEGRATION with other HIV prevention & health services

• Combination prevention programs
  – Biomedical (eg. PEP, STIs, vaccines...)
  – Behavioural (eg. condoms, adherence...)
  – Mental health (eg. mood, substance use...)
  – Social (eg. housing, employment...)

• Comprehensive care out of PrEP clinic

• Linkage models
5. Embedded **MONITORING** and **RESEARCH**

- Comprehensive monitoring & evaluation
  - Minimum data set – cohort study
  - Administrative data
- Embedded research
  - Biomedical, clinical, behavioural, public health, social
  - Readiness for future prevention technologies
Acknowledgements

All our study participants who make this research possible

- St. Michael’s Hospital
  - Alex Schnubb
  - Erin Moses
  - Ahmed Bayoumi
  - Kevin Gough
  - Sharmistha Mishra
  - Deborah Yoong
  - Mark Naccarato
  - Andrew Pinto

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  - Isaac Bogoch
  - Janet Raboud

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The End