Microbicides and Antiretroviral Therapy

Kenneth H. Mayer, M.D.
Fenway Health/Beth Israel Deaconess Hospital/Harvard Medical School
Infected Genital Leukocytes and Cell-Associated Virus Transmission
October 19th, 2013
Why Chemoprophylaxis Post-HPTN 052?

- Only few MSM and IDU in HPTN 052, so effectiveness of TasP not fully understood
- HIV incidence has not ↓ in England and Denmark, despite access (Birrell, 2013; Audelin, 2013)
- <1/3\textsuperscript{rd} of PLHIV globally are now on treatment; full access will take years
- Not all PLHIV want to start meds with high CD4 counts, and virologic suppression rates vary
- Serostatus awareness is limited among many
- HIV stigma limits willingness to disclose
- Not either/or; models suggest some synergy
PrEP works, but adherence is critical

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy overall</th>
<th>Drug detected overall</th>
<th>Estimated Risk reduction with drug detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>42%</td>
<td>~50%</td>
<td>92%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>67-75%</td>
<td>82%</td>
<td>86% (TDF) 90% (FTC/TDF)</td>
</tr>
<tr>
<td>TDF-2</td>
<td>62%</td>
<td>80%</td>
<td>78%</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>No efficacy</td>
<td>26%</td>
<td>“adherence too low to assess efficacy”</td>
</tr>
<tr>
<td>VOICE</td>
<td>No efficacy</td>
<td>29%</td>
<td>“ ”</td>
</tr>
</tbody>
</table>
PrEP Concerns

- **Risk Compensation**: not seen in trials
- **Renal insufficiency**: rare, reversible
  - but pts had to have normal function for trials
- **Bone demineralization**: statistically significant, not clinically significant at 18 months, needs f/u
- **Transmission of resistance**
  - Only in pts started on PrEP with acute HIV
  - All but 1 case 184V (XTC R, less fit virus)

*But it is early, and ongoing monitoring needed*
Relative risk reduction in acquiring HIV infection (compared with placebo) based on plasma TFV concentrations (Partners PrEP)
## Improving Adherence Results in Exceedingly High Levels of Protection

- **Partners PrEP adherence sub-study**

- **1,147 couples in Uganda:** those whose three-month pill use dropped below 80% received enhanced counseling which included problem-solving

- **Sub-study also included unannounced home visits; pill use measurement by MEMSCAP**

- **At the end of the study, 14 participants became HIV-infected, none randomized to TDF/FTC**

(Haberer, PLoS Medicine, 2013)
Correlates of Drug Detectability in iPrEX

- 179 samples from 7 sites were evaluated after Wk 24 visit

- Overall detection rate
  - TFV-DP: 50%
  - FTC-TP: 62%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Drug Detected, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>US vs non-US</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>34</td>
<td>97</td>
</tr>
<tr>
<td>Non-US</td>
<td>145</td>
<td>50</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25 yrs</td>
<td>101</td>
<td>73</td>
</tr>
<tr>
<td>&lt; 25 yrs</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Recent reported sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URAI</td>
<td>49</td>
<td>76</td>
</tr>
<tr>
<td>Sex, not URAI</td>
<td>107</td>
<td>59</td>
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<tr>
<td>No sex</td>
<td>23</td>
<td>35</td>
</tr>
</tbody>
</table>

PrEP: An Overview

**Advantages**
- Separates prevention from risk exposure
- Women and men empowerment
- Overcomes negotiations around HIV prevention
- Increased VCT uptake

**Formulation**
- Tablet
- Slow release formulation
- ARV-Microbicides

**When?**
- Daily/Weekly
  - Intermittently
  - When at risk
  - PMTCT

**Challenges**
- ARV-related
  - Drug Resistance
  - Side effects & Long term effects
  - Effects on other viral infections (Hep B/C)
  - Interactions with other drugs (inc. recreational)
  - Adherence
  - Prioritization of available ARV
  - Ethics
  - PrEP vs other prevention options
  - Treating uninfected people
  - Requires regular HIV testing
  - Behaviour changes/Disinhibition/Condom migration
  - Impact on public health
  - Cost (Resources & Drugs)
  - Implementation & Monitoring

**Eligibility**
- Sex workers
- MSM
- IDU
- Most vulnerable
- Serodiscordant couples
- Concurrent relationship
- For all over a certain age (?)

(c) Roger Tatoud
# Key scientific and implementation science questions for PrEP

<table>
<thead>
<tr>
<th>Topic</th>
<th>Key questions</th>
</tr>
</thead>
</table>
| Priority populations | Who should be prioritized for PrEP?  
                          What are key PrEP messages, and how best to disseminate? |
| Uptake             | What is level of interest in PrEP? Who will want PrEP?  
                          How to increase uptake in those who need it most? |
| Adherence          | How will PrEP be used? (adherence, persistence)  
                          How to start/stop PrEP safely?  
                          What are effective strategies to increase PrEP adherence? |
| Sexual behavior    | How will sexual practices change while taking PrEP?  
                          What are best approaches to minimize risk compensation? |
| Safety             | What is long term safety of PrEP? (renal, bone)  
                          What is optimal HIV testing strategy and frequency? |
| Delivery           | Where are PrEP delivery systems best located?  
                          How best to support PrEP providers? |
| Impact             | How can cost-effectiveness of PrEP be maximized?  
                          How should PrEP be prioritized with other prevention strategies? |

Baeten, Haberer, Liu et al JAIDS 2013
<table>
<thead>
<tr>
<th>Trial/project</th>
<th>Sponsor/funder</th>
<th>Type/Category</th>
<th>Location</th>
<th>Population</th>
<th>Design/Key questions</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Demonstration Project</td>
<td>Led by a team of scientists from Kenya, Uganda and the US, funded by NIMH/NIH, USAID and BMGF</td>
<td>Demonstration Project</td>
<td>Kenya, Uganda</td>
<td>Serodiscordant couples</td>
<td>Evaluates HIV prevention preferences among approximately 1,000 HIV serodiscordant couples, adherence to PrEP and ART and interface of reproductive health priorities and ART-based prevention. Will implement PrEP as “bridge” to ART, providing PrEP to HIV-negative partner when HIV-positive partner is not yet on ART due to eligibility based on country guidelines or personal decision.</td>
<td>All four sites open and enrolling as of August 2013; results expected in 2016.</td>
</tr>
<tr>
<td>LVCT and SWOP</td>
<td>Implemented by national partners in each country in collaboration with the World Health Organization, UNAIDS, O’Neill Institute of Georgetown University, London School of Hygiene and Tropical Medicine, Imperial College London; funded by Bill &amp; Melinda Gates Foundation</td>
<td>Demonstration Project</td>
<td>Kenya</td>
<td>Young women, female sex workers and MSM</td>
<td>Aims to introduce PrEP into combination prevention interventions targeting young women, female sex workers and MSM. Formative research underway to assess consumer perceptions and identify potential barriers and opportunities related to introduction. Outcomes include criteria for PrEP indication among young women and a menu of interventions for target populations, including PrEP and feasible delivery options.</td>
<td>Formative research in planning phase; feasibility study report results likely in December 2013.</td>
</tr>
<tr>
<td>Nigerian National Agency for the Control of AIDS</td>
<td></td>
<td>Demonstration Project</td>
<td>Nigeria</td>
<td>Serodiscordant couples</td>
<td>Evaluates the effectiveness of various models for the delivery of PrEP and TasP as part of a combination prevention strategy for 1,200 heterosexual, serodiscordant couples. Couples will be recruited from facilities that provide prevention of vertical transmission, ART and other services. Study sites include Plateau, Edo and Cross River State. Study findings will be used to inform the scale-up of PrEP and TasP as part of a comprehensive national HIV-prevention package.</td>
<td>Formative discussions underway. No start date for demonstration project.</td>
</tr>
<tr>
<td>Wits Reproductive Health and HIV Institute</td>
<td></td>
<td>Demonstration Project</td>
<td>South Africa</td>
<td>Female sex workers</td>
<td>Aims to assess whether oral PrEP and TasP can be rolled out within a combination prevention and care approach tailored to the needs of 605, both HIV-positive and negative, female sex workers age 18 and older. Study sites include Hillbrow and Waterval Boven.</td>
<td>Expected start date of February 2014, with expected completion September 2016.</td>
</tr>
<tr>
<td>Durbar (DMSC) and Ashodaya Samith</td>
<td></td>
<td>Demonstration Project</td>
<td>India</td>
<td>Female and transgender sex workers</td>
<td>Aims to assess the potential introduction of PrEP among female and transgender sex workers. The project includes sex workers part of the Durbar Mahila Samanwaya Committee (DMSC), a brothel-based sex work project in Sonagachi, and also the Ashodaya Samithi project, a CBO for street-based sex workers based in Mysore.</td>
<td>Feasibility study underway from May to September 2013, with results expected in October 2013.</td>
</tr>
<tr>
<td>The Demo Project</td>
<td>National Institute of Allergy and Infectious Diseases of the NIH</td>
<td>Demonstration Project</td>
<td>US (Miami, Florida; San Francisco, California; and Washington, DC)</td>
<td>MSM and transgender women</td>
<td>Aims to enroll 300 HIV-negative MSM and transgender women at City Clinic, while a sister project in Miami will enroll 200 participants in a PrEP regimen. Whitman Walker Clinic in Washington, DC, will also be a site, aiming to enroll approximately 100 participants.</td>
<td>Started October 2012. Expected completion by August 2014.</td>
</tr>
<tr>
<td>East Bay Consortium/CRUSH</td>
<td>California HIV/AIDS Research Program of the University of California</td>
<td>Demonstration Project</td>
<td>US (East Bay, California)</td>
<td>Young MSM of color</td>
<td>Aims to test and link young MSM of color to sexual health services; enhance and evaluate engagement and retention strategies for HIV-positive young MSM of color; and engage and retain HIV-negative young MSM of color in sexual health services, including PrEP.</td>
<td>Started in December 2012.</td>
</tr>
</tbody>
</table>
## PrEP Demo Projects in the US

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (N)</th>
<th>Study design</th>
<th>Sites</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx OLE (Open Label Extension)</td>
<td>300 MSM/trans women enrolled in iPrEx RCT</td>
<td>Open-label daily FTC/TDF for 72 weeks</td>
<td>San Francisco Boston Chicago</td>
<td>Full enrolled; results 2014</td>
</tr>
<tr>
<td>Demo Project</td>
<td>600 MSM/trans women</td>
<td>Open-label daily FTC/TDF for 48 weeks</td>
<td>San Francisco Miami Washington DC</td>
<td>Enrollment Q3 2013, results 2015</td>
</tr>
<tr>
<td>CCTG 595</td>
<td>700 MSM/trans women</td>
<td>Open-label daily FTC/TDF for 48 weeks; Randomized to SMS support vs. SOC</td>
<td>San Diego Long Beach, LA Torrance</td>
<td>Enrollment Q2 2013, results 2016</td>
</tr>
<tr>
<td>PATH-PrEP</td>
<td>375 MSM/trans women</td>
<td>Open-label daily FTC/TDF for 48 weeks for high risk; PEP for low risk</td>
<td>Los Angeles</td>
<td>Enrollment April 2013, results 2017</td>
</tr>
<tr>
<td>CRUSH</td>
<td>150 young MSM of color, high risk women</td>
<td>Open-label daily FTC/TDF</td>
<td>Oakland</td>
<td>Pilot phase: Q1 2013; expanded phase: Q4 2013</td>
</tr>
<tr>
<td>ATN 110 and 113</td>
<td>300 young MSM age 15-22</td>
<td>Open-label daily FTC/TDF for 48 weeks</td>
<td>All 14 ATN sites in US</td>
<td>Enrollment Dec 12, results Q4 2014</td>
</tr>
<tr>
<td>HPTN 073</td>
<td>225 Black MSM</td>
<td>Open-label daily FTC/TDF for 48 weeks</td>
<td>Washington DC, LA, Chapel Hill</td>
<td>Enrollment June 2013, results 2017</td>
</tr>
<tr>
<td>SPARK</td>
<td>~300 MSM and trans women</td>
<td>Open-label daily FTC/TDF; will evaluate PrEP messages and SMS</td>
<td>New York</td>
<td>Enrollment Q4 2013</td>
</tr>
</tbody>
</table>
Strategies to improve PrEP delivery and adherence

New PrEP drugs and dosing strategies

- Rectal Microbicides: MTN-017 (TFV rectal gel)

- Intra-vaginal rings: ASPIRE (Dapivirine)

- Injectable PrEP: HPTN 076 (TMC278)
  HPTN 077 (GSK744)

Novel adherence strategies

Alternative delivery systems and formulations
Regression analysis in iPrEx: 90% reduction in HIV acquisition when TFV-DP > 16 fmol/10^6 cells

Predicted risk reduction:
- 76% with 2 pills/week
- 96% with 4 pills/week
- 99% with 7 pills/week

* Visit when HIV was first discovered

HPTN 067/ADAPT
(Alternative dosing to augment PrEP pill taking)

Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral PrEP with TDF/FTC

6-week lead-in period
1 pill/week DOT before randomization

High risk women and MSM
(New York, Bangkok, Cape Town)

Daily Truvada 1 tablet/d
Regardless of sexual activity
(n = 180)

Time driven Truvada: 1 tablet 2 days/week + 1 post-exposure dose within 2 hours after sex
(n = 180)

Event driven Truvada: 1 tablet prior to sex + 1 post-exposure dose within 2 hours after sex
(n = 180)

Primary Objective: Is intermittent vs. daily dosing associated with equivalent coverage of sex events, lower number of pills used and decreased side effects

R. Grant, F. Van Griensven, et al.
IPERGAY Study Design

Effectiveness of “on demand” PrEP
Randomized placebo-controlled trial

- High risk MSM
- Condomless anal sex with ≥ 2 partners

Full prevention services*
TDF/FTC before and after sex (n=950)

Full prevention services*
placebo before and after sex (n=950)

- Counseling, testing for STI, condoms, vaccination, PEP
- Primary endpoint: HIV infection, 64 events expected
- Incidence of HIV-infection: 3%PY, 50% efficacy, ~ 2000 pts

www.ipergay.fr
MVC 150 Participants

MVC + FTC 150 Participants

MVC + TDF 150 Participants

FTC + TDF 150 Participants

100 MSM

100 MSM

100 MSM

100 MSM

50 Women

50 Women

50 Women

50 Women
Recruit higher-risk HIV-1 serodiscordant couples

Offer/refer for ART for HIV-1+ partners according to current national guidelines

Accepts ART
- Offer PrEP for 6 months to HIV-1– partner
- Continue to counsel HIV-1+ partner on ART

Declines ART
- Offer PrEP to HIV-1– partner

Not yet eligible for ART
- Offer PrEP to HIV-1– partner
- Follow HIV-1+ partner and refer for ART when eligible

ART Prioritization

Partners Demonstration Project: optimizing PrEP & ART for prevention

PrEP as bridge to ART

Timeline: late 2012 to mid 2016
Adolescent PrEP

- ATN 082 enrolled 68 young MSM
- 70% agreed to take PrEP
- Of PrEP users, blood levels indicate about 50% adherence, comparable to self-report
- Lots of psychosocial issues reported
- ATN 110 and 113: open label TDF-FTC plus either group (Many Men, Many Voices) or individual intervention (Personal Cognitive Counseling)
- ATN 110: 18-12 yo; ATN 113: 15-17 yo
PROUD Pilot

MSM reporting UAI
Willing to take a pill now or in 12M

Randomize 500 HIV negative eligible MSM
(exclude if on treatment for hepB)

Risk reduction includes Truvada NOW

Risk reduction includes Truvada in 12M

Follow 3 monthly for up to 24 months (+1m after start truvada)
Online daily diary and monthly questionnaires
The SFDPH Demo Project

- NIAID-funded PrEP Demonstration Project in 600 MSM and transgender women
  - STD clinics in SF, Miami; CHC in DC
- Key objectives:
  - Assess PrEP uptake, adherence, resistance, and sexual behaviors in real-world setting
  - Determine staff and space needed for PrEP delivery
- Study procedures:
  - Provide TDF/FTC PrEP for 48 weeks
  - Study visits at 1 month, then quarterly
  - Safety monitoring (HIV, Cr) at each visit
  - Integrated risk reduction and adherence
Education about pill use
- People who use PrEP more consistently have higher levels of protection against HIV
- Potential side-effects
  - Bloating, soft/more frequent stools, nausea
- Missed Doses
- Developing a routine
- Discussing PrEP with others
- Stopping and restarting PrEP

**WHAT IS PrEP?**

Pre-exposure prophylaxis or PrEP is a new FDA-approved approach to HIV prevention.

PrEP is the use of HIV medications to prevent HIV-negative people from getting HIV from sex.

Clinical studies have shown that PrEP using emtricitabine/tenofovir (Truvada®) is safe and effective.

The more consistently Truvada is taken, the better the protection: In men who have sex with men, Truvada is more than 99% effective in preventing HIV when taken daily.

PrEP should only be started after seeing a health care provider to confirm you are HIV negative.

PrEP also requires ongoing health monitoring. People can get PrEP from demonstration projects or by prescription from a health care providers.

PrEP is covered by many insurance companies and by the drug manufacturer.
Some preliminary impressions (Al Liu)...

Social benefits
- Decreased anxiety
- Increased communication/disclosure
- Increased intimacy / trust
- Increased sense of community / self-efficacy
- Increased sexual pleasure

Social harms
- Stigma – HIV / risky behavior
- Negative health provider encounters

• Anxiety about accessing PrEP after Demo Project
Social Cognitive Model

- Disease prevention
- Pleasure reduction
- Self efficacy
- Safer Sex Adherence

- Depression, anxiety, mental health problems, substance use

Wulfert, Safren, et al., 1999; Journal of Applied Social Psychology
Project PrEPare (Fenway)

• Modeled after “Life-Steps,” (Safren et al) ART adherence intervention
• Modular intervention: 4 weekly visits with nurse and 2 booster sessions.
• Intervention content:
  • CBT-oriented adherence problem-solving
  • Brief motivational interviewing
  • Identification of barriers and solutions
  • Sexual risk-reduction strategies

Optional modules:
• Mental health and substance use issues

Adherence to PrEP was measured daily via Wisepill, and sexual risk taking was assessed by text messages (Lester, 2010)
Diffusion of Innovations
(Everett Rogers, 1962)
Innovation, Communication Channels, Time, Social System
Uptake of ZDV for perinatal prevention

(in 18 states with HIV surveillance)

% 100

Prenatal HIV Test Any ZDV Prenatal ZDV Neonatal ZDV Unk ZDV


ACTG 076 results and PHS guidelines published

Source: Lindegren et al., JAMA 1999; 282:531-38
PrEP Attitudes and Uptake

- Manhunt survey pre/post iPrEX
  - 4,825 MSM: 46 states and 5 Canadian provinces
  - Less than 20% heard of PrEP
  - Less than 1% had used PrEP
  - Majority were interested, depending.....

- Massachusetts MD survey post-CAPRISA
  - Most had heard of CAPRISA 004
  - Some knew that PrEP studies were underway
  - Many concerns about risk compensation, resistance, cost

Krakower et al, PLoS ONE, 2012; White et al, AIDS Pt Care and STDs, 2012
PrEP Use in the US, 2013
(Mera et al, ICAAC, 2013)

- Pharmacy record review (55% of US pharmacies)
- 1,774 pts on PrEP between 1/11 and 3/13
- 53% in 1st half of 2013: increase utilization?
- Median age: 37 y.o. 13.6% <25 y.o.
- Women 47.7% of users
- 49 states; 700 cities; largest N in the South
- Only 37% of PrEP providers also prescribed HAART
- Only 12% of prescribers were ID docs
- Did not capture those in trials (more MSM)
Non Trial PrEP Use at Fenway Health

Dates of Initiation (N=50)
To implement PrEP successfully, it will be essential to engage practicing clinicians.
Practical issue number one is that the people who are going to be prescribing these drugs in theory, who are going to be in the best position, are going to be primary care providers with little or no HIV experience.

–Male, Hospital-based

I think that the idea of adding to what I just did this morning and adding a discussion with my patients about what is their likelihood of having sexual encounters with patients who are HIV-infected, and then on top of that trying to prescribe and get approved medication like Truvada or some other pre-exposure prophylaxis... I just can’t imagine it working in the hands of a primary care doctor.

–Female, Hospital-based
Decrease in HIV Transmission

Maintain Viral Suppression

Treat

Enroll in Care

ART Initiation

Adherence to ART

Maintain Viral Suppression

Linkage To Care

Positive Prevention

Test

HIV Negative

HIV Positive

Address concomitant concerns, e.g. depression, substance use, relationship dynamics

Interventions to Increase Testing

Combination Antiretroviral Prevention

HIV Negative Test

Risk Assessment PrEP, Adherence Counseling

HIV Positive

Increase Testing

Positive Prevention

Adherence to ART

Decrease in HIV Transmission
# Immunoprophylaxis: VRC01 IV or subQ

## VRC01 administration schedule in months (days)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>0</th>
<th>0.5 (14)</th>
<th>1 (28)</th>
<th>1.5 (42)</th>
<th>2 (56)</th>
<th>2.5 (70)</th>
<th>3 (84)</th>
<th>3.5 (98)</th>
<th>4 (112)</th>
<th>4.5 (126)</th>
<th>5 (140)</th>
<th>5.5 (154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>VRC01 40mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>VRC01 40mg/kg IV</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
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</tr>
<tr>
<td>3</td>
<td>20</td>
<td>VRC01 40mg/kg IV</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
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<tr>
<td>4</td>
<td>20</td>
<td>placebo IV</td>
<td>placebo SC</td>
<td>placebo SC</td>
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<td>placebo SC</td>
<td>placebo SC</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr</td>
<td>Subcutaneous (SC) doses administered in the minimum volume at 15 mL/hr using an SC infusion pump</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Thank You

Fenway Clinical, Epidemiological and Behavioral Research Teams
Fenway Medical Department
Slim and Quarraisha Abdool Karim
Jared Baeten
Katie Biello
Susan Buchbinder
Connie Celum
Robert Grant
Sharon Hillier
Doug Krakower
Albert Liu
Sheena McCormack
Matthew Mimiaga
Jean-Michel Molina
David Novak
Jim Rooney
Josh Rosenberger
Steve Safren
Dawn Smith
Roger Tatoud
NIAID, NIMH, NIDA, NICHD, CDC, HRSA, Mass DPH, Gilead
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