HPTN Pipeline
Something Old, Something New

Myron S. Cohen
Wafaa El-Sadr
on behalf of the HPTN
HPTN Mission

The HIV Prevention Trials Network (HPTN) advances HIV prevention through research:

• Integrated HIV prevention strategies
• Improve pre-exposure prophylaxis (PrEP)
• New strategies for key populations
New Tools for HIV Prevention
Pre-exposure prophylaxis 2.0: new drugs and technologies in the pipeline


Introduction
Despite major advances in HIV treatment and prevention, the HIV pandemic continues to pose a major global public health challenge. As of 2017, 36.9 million people were estimated to be living with HIV of whom 22.3% were unaware of their infection status. The rapid scale-up of antiretroviral therapy (ART) as a global priority in the fundamental strategy used to tackle the pandemic, with treatment back for treatment and prevention. Studies of HIV-discordant couples show the role of ART and correlates of dying, in particular plasma and intracellular drug concentrations, with a 96% risk reduction in MSM estimated their drug concentrations consistent with taking an average of four or more doses per week. Importantly, pharmacokinetic studies have shown substantially lower concentrations of tenosin disulfate in vaginal tissue than in rectal tissues (rectal tenosin disulfate concentration was 100-times higher than that observed in vaginal and cervical tissue after a single dose), with six to seven doses per week needed to reach vaginal and
Effectiveness of TDF/FTC in Placebo-Controlled Clinical Trials

**iPrEx (TDF/FTC)**
- 42% protection
- CI: 15-63

**FEM-PreP (TDF/FTC)**
- 6% protection
- CI: -52-41

**TDF2 (TDF/FTC)**
- 49% protection
- CI: 22-81
- 80% protection
- CI: 25-97

**Partners PrEP**
- 71% protection
- CI: 37-87
- 63% protection
- CI: 20-83
- 66% protection
- CI: 28-84
- 84% protection
- CI: 54-94

**VOICE (TDF/FTC)**
- 49% protection
- CI: +3 to -129
- 44% protection
- CI: +27 to -149

**PROUD (TDF/FTC)**
- 86% protection
- CI: 64-96

**IPERGAY (TDF/FTC)**
- 86% protection
- CI: 40-99

Landovitz RJ et al. AIDS 2020, #OAXLB0101
“PrEP 2.0”: Trials of Novel PrEP Agents

**ASPIRE** (Dapivirine)
- Incidence rate: 0.30%
- CI: 1 – 46

**Ring** (Dapivirine)
- Incidence rate: 0.16%
- CI: 1 – 51

**DISCOVER** (TDF/FTC)
- Incidence rate: 0.30%

**DISCOVER** (TAF/FTC)
- Incidence rate: 0.16%

Landovitz RJ et al. AIDS 2020, #OAXLB0101
PrEP use in young African women in HPTN 082: Effect of drug level feedback


on behalf of the HPTN 082 Study Team
646 were accessed for eligibility

- 129 were not eligible, including:
  - 50 unable to enroll within 45 days of screening
  - 29 HIV positive at screening
  - 21 pregnant or planning pregnancy
  - 10 with VOICE score <5

451 enrolled

24 declined PrEP

427 underwent randomization

215 were assigned to receive drug level feedback plus standard adherence support

- Retention:
  - Month 1: 204/215 (95%)
  - Month 2: 191/215 (89%)
  - Month 3: 191/215 (89%)
  - Month 6: 183/215 (85%)
  - Month 9: 173/214 (81%)
  - Month 12: 184/215 (86%)

- 179 included in the intent-to-treat analysis for month 6 primary outcome
  - 4 missing DBS sample for drug level at month 6

212 were assigned to receive standard adherence support

- Retention:
  - Month 1: 191/212 (90%)
  - Month 2: 180/212 (85%)
  - Month 3: 190/212 (90%)
  - Month 6: 183/212 (85%)
  - Month 9: 180/212 (81%)
  - Month 12: 181/212 (85%)

- 184 included in the intent-to-treat analysis for month 6 primary outcome
  - 4 missing DBS sample for drug level at month 6

26 lost to follow-up

28 lost to follow-up

4 HIV infections

179 included in the intent-to-treat analysis for month 6 primary outcome

184 included in the intent-to-treat analysis for month 6 primary outcome

4 HIV infections
HPTN 082: Results

- 95% PrEP uptake (95%) among young women.
- No effect of drug level feedback on proportions with detectable TFV-DP or high adherence by arm at 6 months.
- Women who perceived themselves to be at risk of HIV and were motivated to use PrEP (HPRM score) had higher adherence at 6 months.
- Adherence declined significantly after month 3.
- Low HIV incidence (1%) given the risk profile of this cohort.
PrEP: Today

Truvada
Approved July 2012

Descovy
Approved October 2019
PrEP: Tomorrow?

Cabotegravir

Capsid Inhibitors

Rings

Implants

Transdermal Needles and Patches
HIV Incidence
CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up
1.4 (IQR 0.8-1.9) years median per-participant follow-up
Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY

HIV Incidence

<table>
<thead>
<tr>
<th>CAB</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2244</td>
<td>n=2250</td>
</tr>
<tr>
<td>13 Infections</td>
<td>39 Infections</td>
</tr>
<tr>
<td>0.41</td>
<td>1.22</td>
</tr>
<tr>
<td>3202 PY</td>
<td>3187 PY</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)

- Favors CAB (0.34, 0.18-0.62)
- Favors TDF/FTC (1.23)

CI, confidence interval

Landovitz RJ et al. AIDS 2020, #OAXLB0101
Infection despite continuous, on-time CAB injections
Long-Acting Cabotegravir (CAB LA): Planning for Global Success in At-Risk Populations

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BACKGROUND

In order for promising HIV prevention technologies to have the greatest public health impact, the time from the delivery of Phase 3 efficacy results to product introduction must be shortened. Additional clinical research and implementation questions that are not addressed in Phase 3 efficacy studies must be accounted for across a broad range of key-affected populations to ensure and maximize successful delivery and uptake.

Long-acting cabotegravir (CAB LA) is an investigational agent that is being evaluated as a single 3ml injection administered every 8 weeks for HIV prophylaxis. The safety and efficacy of CAB LA is being measured against the current standard of care daily, oral TDF/FTC in two ongoing Phase 3 trials:

• 5000 HIV-uninfected cisgender men (MSM) and transgender women (TGW) who have sex with men in 43 sites in 7 countries in North and South America, Africa, and Asia (HPTN 083)
• 3200 HIV-uninfected cisgender women in 20 sites in 17 countries in sub-Saharan Africa (HPTN 084)

HPTN 084 initiated in December 2016 and has enrolled 4957/5000 MSM/TGW. At a planned Data and Safety Monitoring Board (DSMB) in May 2020, the DSMB:
• recommended that the blinded part of the study be stopped early for successfully meeting its specified objectives.
• The study results showed that CAB LA, administered every eight weeks, provided high efficacy compared to cisgender men and TGW.
• Despite the promising findings from HPTN 083, we still do not know if CAB LA prevents HIV in cisgender women.
• All HPTN 084 participants were informed of the DSMB outcome for HPTN 083.
• At the DSMB review in May 2020, the DSMB recommended that HPTN 084 continue.

HPTN 084 initiated in November 2017 and has enrolled 3032/3200 cisgender women.
• The blinded phase of HPTN 083 in MSM/TGW has been stopped due to efficacy of CAB LA when compared to TDF/FTC.
• The Phase 3 efficacy trial (HPTN 084) in cisgender women in sub-Saharan Africa is ongoing.
• Open-Label Extensions are planned for participants in HPTN 083 and HPTN 084.
• Studies in adolescent males (HPTN 083-01) and females (HPTN 084-01) are about to begin.
• Activities required for successful product introduction and access in lower and middle income countries have been identified and prioritized by BioPIC.
• The routes of HIV acquisition are different, and the drugs may behave differently in cisgender women compared to cisgender men and TGW.
• HPTN 084 will also provide important safety data in cisgender women of reproductive potential.
• HPTN 084 sub-studies will generate data on any LARC/CAB LA drug interactions, and quantify CAB LA drug concentrations in mother-infant pairs at delivery.
• The DSMB will continue to review trial progress.

PHASE III EFFICACY TRIAL UPDATES

HPTN 083 initiated in December 2016 and has enrolled 4957/5000 MSM/TGW. At a planned Data and Safety Monitoring Board (DSMB) in May 2020, the DSMB:
• recommended that the blinded part of the study be stopped early for successfully meeting its specified objectives.
• The study results showed that CAB LA, administered every eight weeks, provided high efficacy compared to TDF/FTC.
• All participants will be unblinded and offered CAB LA.

• The studies in adolescent males (HPTN 083-01) and adolescent females (HPTN 084-01) are about to begin.

For more information see:
http://www.hptn.org

For additional information on BioPIC, please visit bio-pi.org.

Presented at the 23rd International AIDS Conference (AIDS 2020)
6-10 July 2020
Online
Poster Number: 1BPE028L
Cabotegravir Research Going Forward

• HPTN 084 (Cabotegravir for women) ongoing
• HPTN 083-01 and 084-01 (Cabotegravir for adolescents)
• Cabotegravir/rilpivirine for discordant couples?
• Cabotegravir pharmacology in pregnant women?
• Cabotegravir every 8 weeks prenatal prevention?
• Cabotegravir and levonorgestrel combined?
• Other???
New PrEP Agents and Approaches

• Other New ARVs
  - Islatravir (MSK 8591; potent pill or implant)
  - Lenacaprevir (G 6207, sub Q)

• New Devices
  - Dapivirine Rings (Favorable EMA Regulatory Review)
  - Implants
  - Transdermal needles and patches
MK-8591 at 3.9, 1.3, 0.43 and 0.1 mg/kg is highly protective against infection with SHIV109CP3

Overall, treatment with MK-8591 at all 4 doses was associated with a 41.47-fold lower risk of infection, p<0.0001, log rank test

Intracellular levels of MK-8591-TP at or above 24 fmol/10^6 PBMC is associated with 92% protection

Animals treated with 0.1 mg/kg dose are 7.2-fold less likely to be infected, p=0.0004 log rank test
Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

LA Implants

Matrix vs. Reservoir
Renewable vs. biodegradable

• EFDA (Ilatravir, Merck)

• Cabotegravir (Northwestern, ViiV)

• TAF (Oakcrest, Houston, RTI, Northwestern)
Safety and PK of Subcutaneous GS-6207, a Novel HIV-1 Capsid Inhibitor

Jennifer E. Sager, Rebecca Begley, Martin S. Rhee, Steve K. West, Amber Silva, John Ling, Scott D. Schroeder, Winston C. Tse, Anita Mathias

Gilead Sciences Inc. Foster City, CA

Conference on Retroviruses and Opportunistic Infections (CROI 2019)
Seattle, WA, 4–7 March 2019
Oral presentation O-13
Results

Sustained Delivery Supports Dosing Interval of at least 12 Weeks

- At doses ≥100 mg, GS-6207 plasma concentrations at 12 weeks were above the $\text{paEC}_{95}$ of 3.87 ng/mL

$^*$EC$_{50}$ determined in MT-4 T-Cell Line with WT HIV-1 (IIIB strain). C$_{95}$: GS-6207 plasma concentration on Day 84. IQ: Inhibitory quotient; $\text{paEC}_{95}$: protein adjusted EC$_{95}$
Multipurpose Technologies for Prevention

OPPORTUNITIES AND CHALLENGES

Sharon Hillier, PhD
Richard Sweet Professor of Reproductive Infectious Disease
University of Pittsburgh School of Medicine
Departments of Obstetrics, Gynecology and Reproductive Sciences and Microbiology and Molecular Genetics
Magee-Womens Research Institute
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Delivery Options for MPTs

**Co-formulated:**
Multiple API formulated into a single dose

**Co-administered:**
Two independent products used together

**Co-packaged:**
Two different doses packaged together in a single product for simultaneous co-use

- Vaginal ring containing ARV plus LNG
- Two implantable rods, one containing ARV, the second containing contraceptive
- Two tablets, one containing ARV, the second containing contraceptive
Development of Broadly Neutralizing Antibodies (BnAbs)

HIV-1

The transmitted-Founder virus
Escape virus

Antibody

Continuum with 10~20%- Broadly neutralizing antibodies

The initial neutralizing antibody response to HIV “autologous nAb”
The AMP Studies: Phase 2b Proof-of-Concept Trials Designed to Test Efficacy of VRC01 Antibody to Prevent HIV Acquisition

**AMP = Antibody Mediated Prevention**

Two harmonized protocols

HVTN 704/HPTN 085  
(MSM and TG in the Americas & Europe)

HVTN 703/HPTN 081  
(Women in sub-Saharan Africa)

MSM, men who have sex with men; TG, transgender

The AMP Studies: Objectives & Endpoints

- **Safety & tolerability of VRC01 infusions**
  - Reactogenicity, AEs, SAEs
  - Efficacy to prevent HIV infection
    - HIV infection by Week 80 in those HIV-negative at enrollment

- **Develop a marker(s) of VRC01 that correlates with the level and antigenic specificity of efficacy and provides insight into mechanistic correlates of protection**
  - Serum VRC01 concentration
  - Serum VRC01-mediated neutralization and Fc effector functions
  - Breakthrough HIV viral sequences in infected people
  - VRC01 neutralization sensitivity of, & effector functions against HIV strains from infected trial participants from the earliest point available

**TRIAL COMPLETED; RESULTS WILL BE PUBLISHED IN 2020!!**
Theoretical combinations of mAbs

Adapted from M Cohen and T Gamble
Integrated Strategies

Biomedical Interventions

Behavioral Interventions

Structural Interventions
Transgender People and HIV Prevention: What We Know and What We Need to Know, a Call to Action

Kenneth H. Mayer, MD,* Beatriz Grinsztejn, MD, PhD,† and Wafaa M. El-Sadr, MD, MPH, MPA‡

Abstract: Transgender people have been disproportionately affected by HIV, particularly transgender women. Their increased vulnerability to HIV is due to multiple issues, including biological (e.g., increased efficiency of HIV transmission through receptive anal sex), epidemiological (e.g., increased likelihood of having HIV-infected people and to implement these interventions in ways that are culturally congruent and health promoting.

Key Words: HIV prevention, transgender, HIV/AIDS

(J Acquir Immun Defic Syndr 2016;72:S207–S209)
Integrated Strategies: HPTN 091

- Immediate Intervention Arm
  - 310 TGW Enrolled
  - Randomization 1:1 Assignment
- Deferred Intervention Arm

**PrEP Provision**
- STI Screening & Treatment

**Co-Located Services**
- Gender Affirming Hormone Therapy
- Peer Health Navigation Using Strengths-Based Case Management

**Linkage to Services**
- Gender affirming hormone therapy and case management services

- **PrEP Provision**
  - STI Screening & Treatment

- **Co-located Services**
  - Gender Affirming Hormone Therapy
  - Peer health navigation using strengths-based case management

**Timeline**
- (0-6 months)
- (6-18 months)
• Objectives
  1. To assess acceptability and feasibility of delivering integrated HIV prevention services co-located with gender-affirming hormone therapy (GAHT) and peer-delivered health navigation supported by strengths-based case management (SBCM) for TGW.
  2. To assess PrEP uptake and adherence (including PrEP persistence) in both the Immediate Intervention Arm and the Deferred Intervention Arm.

• Study Sites:
  – Rio de Janeiro
  – Houston
  – San Francisco
  – New York
  – Philadelphia
HPTN 094

INTEGRA: A Vanguard Study of Health Service Delivery in a Mobile Unit to Link Persons who Inject Drugs to Care and Prevention for Addiction, HIV, HCV and Primary Care

Steven Shoptaw PhD
Nabila El-Bassel PhD
Integrated Strategies: HPTN 094  
Mobile Health Delivery for PrEP, TasP and MOUD

• Does providing “one stop” integrated services delivered in a mobile health delivery unit – particularly medication for opioid use disorder (MOUD) and HIV treatment and prevention medications – to PWID improve uptake and adherence compared to a control arm that provides referrals to existing services in bricks-and-mortar facilities?

• Two-arm, individually randomized, controlled, open label study.

• 885 participants allotted in 1:1 ratio to intervention and control arms
Overview HPTN 094

- RCT of a mobile unit to deliver “one stop” integrated health services – particularly medications for opioid use disorder (MOUD) and HIV treatment and prevention – compared to an active control arm that receives peer navigation to health services in the community for people who inject opioids living with HIV or at risk
- Primary outcomes: uptake and use of MOUD, and uptake and use of antiretroviral therapy (ART) or pre-exposure prophylaxis (PrEP) at 26 weeks
- Secondary outcomes: continued use of MOUD and ART meds at 52 weeks; psychological and health outcomes at 26 and 52 weeks; COVID-19 factors
- Impact (cost-effectiveness, mathematical modeling) and implementation factors (mixed methods to identify barriers and facilitators of the interventions) will contextualize findings from the efficacy analysis
Integrated Strategies: HPTN 094
Advancing the Ending the HIV Epidemic Initiative with a $109 Million Investment in 57 Areas of the United States

August 03, 2020

Eugene McCray, M.D., Director, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC

Gail Bolan, M.D., Director of the Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC

Jonathan Mermin, M.D., M.P.H., RADM and Assistant Surgeon General, USPHS, Director, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC

#endHIVepidemic
Ending the HIV Epidemic: The AHEAD Dashboard
July 30, 2020

Harold J. Phillips, MRP
Office of Infectious Disease and HIV/AIDS Policy
U.S. Department of Health and Human Services

Four strategies to achieve our goal of ending the HIV epidemic in the U.S. by 2030:

• **Diagnose** all people with HIV as early as possible.
• **Treat** people with HIV rapidly and effectively to reach sustained viral suppression.
• **Prevent** new HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).
• **Respond** quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.
Reduction in HIV Incidence
(measured by HIV recency assessment after 3-year intervention)

Reduction in Black MSM vulnerable to infection (PrEP)
(measured by PrEP use in cross-sectional assessments)

Increased PrEP uptake
Increased PrEP adherence

Intervention Level
IC = Community
Io = Organizational
Ip = Interpersonal
Ii = Individual

Increased ART uptake
Increased ART adherence

Peer support

Health equity

Social media influencers

HIV/STI testing

Intersectional stigma reduction

Multi-level social support

Individual-level agency

Multi-level intersectional stigma

Structural barriers to healthcare services

Increased HIV and STI Testing

Intersectional stigma reduction

Reduction in Black MSM who are infectious
(measured by viral suppression in surveillance data)

Reduction in Black MSM vulnerable to infection (PrEP)

Reduction in HIV Incidence
(measured by HIV recency assessment after 3-year intervention)
HPTN 096 is a Partnership

Sponsor and Funder

NIH
National Institutes of Health
Turning Discovery Into Health

Other Partners

CDC
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

HRSA
Health Resources & Services Administration
THANK YOU!
TO ALL WHO DEVELOPED AND
PARTICIPATED IN THESE MANY STUDIES,
TO THOSE WHO HELPED WITH THIS TALK,
AND TO ALL THE FUNDERS