Reviewing the HIV Prevention Landscape and Addressing the HPTN Research Gaps

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Outline

- Overview of Prevention Landscape
- Overview of HPTN Scientific Agenda
- Operationalizing Research Priorities into Research Studies
- HPTN Concept Sheet
Decline in New Infections

Global New HIV Infections

Number of New Infections

Year

UNAIDS. Ending AIDS. Progress towards the 90-90-90 targets, 2017
Geographic Hotspots

> 40,000 new infections per week
36.7 million people living with HIV

(UNAIDS 2016)
Priority and key populations

- Sex Workers
- PWID
- MSM
- Transgender people
- Sexual partners of key populations
- Rest of population

UNAIDS. Ending AIDS. Progress towards the 90-90-90 targets, 2017
HIV Prevention Approaches and Tools

Decrease Risk of Transmission
- Barrier protection
- Screening of blood and blood products
- Harm reduction for PWID
- Antiretroviral Therapy
  - PMTCT
  - Horizontal transmission
- STI Treatment

Decrease Risk of Acquisition
- Barrier protection
- Voluntary medical male circumcision (VMMC)
- Pre Exposure Prophylaxis (PrEP)
- Post Exposure Prophylaxis
- Vaccines
- STI Treatment

Alter Behavior
- Condom and HIV testing promotion
- Individual interventions
- Community-based interventions
- Structural interventions

Adapted from Ken Mayer
Biomedical Products for Prevention

**Demonstrated Efficacy**
- VMMC
- TasP
- Oral PrEP

**Submitted for Approval**
- Vaginal Ring

**Under Investigation**
- Vaccines
- Injectable PrEP
- AMP
- Implant
Can voluntary medical male circumcision be used to prevent HIV acquisition?

- **Design:** RCTs evaluate if circumcision can prevent HIV acquisition in men

- **Studies:**
  - ANRS 1265 (S. Africa): 18-24y men (n= 3,274)
  - Rakai, Uganda: 15-49 y (n=4,996)
  - Kisumu, Kenya: 18-24 y (n=2,784)

- **Results:** Men who were circumcised had a 51-60% lower incidence of HIV infection than men in the uncircumcised groups

HPTN 052 – Use of ART for Prevention in Serodiscordant Couples

Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm³

Randomization

Early ART
CD4 350-550

Delayed ART
CD4 ≤ 250

Primary Transmission Endpoint
Virologically-linked partner infections

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death
1,763 sero-discordant couples (97% heterosexual)
• HIV infected partners: 890 men, 873 women

39 HIV Transmissions
28 linked HIV transmissions

Immediate ART:
1 transmission

Delayed ART:
27 transmissions

96% Protection
Can ARVs be used prophylactically to prevent HIV acquisition?

- Design: RCTs conducted in HIV negative populations evaluating oral pre exposure prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTC/TDF arm</td>
<td>81%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Effectiveness is correlated with adherence

Donnell et al CROI 2012
Grant et al N Engl J Med 2010
Can a vaginal ring be used to deliver topical PrEP to women?

- Vaginal ring (VR) containing dapivirine (DPV) is under evaluation for pre-exposure prophylaxis (PrEP) for HIV prevention among women.
Behavioral Interventions for Prevention of HIV Acquisition

• Decrease risk behaviors
• Increase protective behaviors
• Increase uptake and adherence to biomedical products

Harm Reduction
– Needle and Syringe Exchange Programs
– Medically Assisted Therapy

Counseling

Socioeconomic interventions
HPTN 068: Effects of Cash Transfer For the Prevention of HIV in Young South African Women

Enrollment: 2,537 ♀ 13-20 yrs

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,263</td>
<td>1,274</td>
</tr>
<tr>
<td>Cash transfer conditional on school attendance</td>
<td>No cash</td>
</tr>
</tbody>
</table>

Primary outcome: Primary HIV Incidence
HPTN 068: Key Findings

Incidence Outcomes
• Overall HIV Incidence: 1.8%
  – Among 16 year olds: 1%
  – >20 years: 5%
• No difference in HIV incidence
• No difference in HSV-2 incidence

School Attendance Outcomes
• High school attendance in both study arms was high
  – Three fold high risk of HIV infection in school drop out to non-drop outs
• School enrollment and attendance were protective for HIV acquisition irrespective of study arm
Optimizing Intervention Efficacy

Behavioral Interventions
- NSP
- OST
- Condoms
- Counseling

Biomedical Interventions
- TasP
- PrEP
- VMMC

Combination & Integrated Strategies
Overview of HPTN Scientific Agenda

• Integrated Strategies Agenda
  – TasP (HPTN 071, HPTN 074, HPTN 078)

• PrEP Agenda
  – Optimizing oral PrEP (HPTN 073, HPTN 082)
  – New PrEP (HPTN 083, HPTN 084, HPTN 086, AMP, other phase I bNAbs)

• Recruitment Feasibility
  – HPTN 075
HPTN 071 - PopART

- Community-based, RCT evaluating the impact of a combination HIV prevention package on HIV incidence
- Total estimated 1 million participants testing TREATMENT as PREVENTION on a community Level

<table>
<thead>
<tr>
<th>Arm A/B</th>
<th>Arm C</th>
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<tbody>
<tr>
<td>Full PopART intervention</td>
<td>Standard of care at current service provision levels,</td>
</tr>
<tr>
<td></td>
<td>including ART irrespective of CD4 count or clinical stage</td>
</tr>
<tr>
<td>ART irrespective of CD4 count</td>
<td></td>
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<tr>
<td>or clinical stage</td>
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</table>

**Primary Outcome:** HIV Incidence Measured in Population Cohort (PC)
- 2,500 randomly selected adults from each community cluster (about 52,000)
- Followed at 12, 24 and 36 months
HPTN 071 PopART Interventions

- Intervention Arm Components delivered by Community HIV Care Providers (CHiPs):
  - Offering voluntary HIV counseling and testing annually through a house-to-house campaign
  - Linking those with HIV to care at the local health center
  - Offering ART to all those who are HIV-infected, irrespective of CD4+ count or clinical stage
  - Promoting voluntary medical male circumcision (VMMC) for men who test HIV-negative
  - Promoting services for the prevention of mother-to-child transmission (PMTCT) to HIV-infected pregnant women
  - Referral for treatment of sexually transmitted infections
  - Providing condoms in the community
  - Screening and referral for tuberculosis (TB)
HPTN 074: Can TasP be used to prevent HIV acquisition in PWID?

A study comparing an integrated intervention including supported ART to standard of care for PWID

Results:

- 502 indexes and 806 partners enrolled with good retention
- Indexes in the intervention arm had better outcomes:
  - Higher ART use, viral suppression, MAT use
  - Lower mortality
- Partners of index participants in the intervention arm had lower mortality.
- All incident HIV infections among partners occurred in the SOC arm.
HPTN 078: Can an integrated strategy using TasP be used to help HIV infected MSM achieve and maintain viral suppression?

Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States

Study Design
HPTN 073: Can we optimize oral PrEP for black MSM?

• Study was designed to answer:
  – What is the feasibility of recruitment and retention of cohort of HIV-negative Black MSM?
  – What is the feasibility, acceptability and effectiveness of Coordinated Clinical Care Coordination (C4) intervention to enhance uptake and adherence with oral daily PrEP?

• Findings
  – Recruitment and retention of Black MSM in US is feasible
  – Implementation of C4 feasible and acceptable
  – C4 associated with uptake and adherence with oral PrEP
  – Engagement of HPTN Black Caucus advantageous in design and implementation of the study
HPTN 082: Can we optimize oral PrEP for young women?

HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women

Study Population

- Uninfected women
- Ages 16-25 yrs
- Johannesburg & Cape Town, South Africa
- Harare, Zimbabwe

Target Enrollment

- 400 women who accept PrEP at enrollment
- ≤ 200 women who decline PrEP at enrollment

Primary objectives:

- Assess the proportion and characteristics of women who accept versus decline PrEP
- Assess PrEP adherence using drug levels in young women
HPTN 075: Can African MSM be recruited into a prevention research study?

Feasibility & Acceptability

Preliminary Results:

- Recruiting and retention of MSM from sub-Saharan Africa is feasible
- With sufficient preparation such studies can be implemented minimizing social harms
- Implementing studies with this population enables acceptance by healthcare workers and CABs.
Long-acting Agents for HIV Prevention

**Long-acting injectable ARVs**

- Cabotegravir:
  - HPTN 083
  - HPTN 084
  - HPTN 086

**Broadly-neutralizing antibodies**

- VRC01:
  - HVTN 703/HPTN 081
  - HVTN 704/HPTN 085
  - Other BNAbs
    - HVTN 127/HPTN 087
    - HVTN 129/HPTN 088
    - HVTN 130/HPTN 089

**Implants**

- SLAP
  - HPTN ???
Additional Priority Populations

• Continue work with MSM, substance users, and women of child bearing age (HPTN 075, HPTN 078, AMP, HPTN 074, HPTN 083, HPTN 084)
• Set protocol specific or country specific enrollment quotas for populations deemed most vulnerable (HPTN 083)
• Heterosexual men in Africa (HPTN 071)
• Research focusing on and inclusive of transgender people (including transgender men) (HPTN 083, AMP)
HIV Prevention Package

• Include discussions of viral suppression for all participants (regardless of sero-status) enrolled in research conducted by the HPTN
  – HPTN 052, TasP (071, 074, 078)

• Establish PrEP access as part of the HIV prevention package for research conducted by the HPTN
Behavioral Research

- Include strong behavioral components with biomedical research
  - In all studies, what are new/additional behavioral interventions not being included
- Utilize results from research to develop demonstration projects (i.e. HPTN 073)
- Focused research on chemical sex and blood sharing (blue-toothing)
Questions?
Operationalizing Epidemic Priorities into Research Studies

• Example:
  – Young Women and Adolescents in sub-Saharan Africa
3.9 million young people in SSA aged 15-24 years are living with HIV
Three-quarters are young women
Every minute, a young woman is newly infected with HIV.

As a result of their lower economic, socio-cultural status in many countries, women and girls are disadvantaged when it comes to negotiating safe sex, accessing HIV prevention information and services.

11-45%
Between 11% and 45% of adolescents who report that their first sexual experience was non-consensual.

Women living with HIV are more likely to experience violations of their sexual and reproductive rights, including forced sterilizations.

Two-thirds of the world’s newly diagnosed women are adults.

In many countries, customary practices or power relations undermine women’s autonomy to HIV, and reduce their ability to cope with the disease and its impact.

32/94
Women living with HIV are not regularly included in formal processes to plan and review the national HIV response in 32 out of 94 countries.

40%
Approximately 40% of women aged 15-24 in the developing world have the potential to benefit from targeted programmes before they are 18 years old.

More than one-third of women under 20 die in childbirth.

2x
Globally, every woman aged 15-24 is at least twice as vulnerable to HIV as her male counterpart.

HIV is the leading cause of death of women of reproductive age.

Only 1 out of 5 women is available for sex in Sub-Saharan Africa.

Globally, less than 2% of young women have comprehensive and cascade knowledge of HIV.
PrEP as part of combination for young women in SSA

• How do you create demand?
  – Motivations and characteristics of young women who accept PrEP

• How do you support effective use?
  – What does adherence support look like for young women?
    • Counselling, SMS, clubs
    • Drug feedback levels
    • Targeted/intensification for those who need more support?
Translating epidemic priority to research studies

HPTN 082: Design

HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women

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**Primary objectives:**
- Assess the proportion and characteristics of women who accept versus decline PrEP
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**HPTN Q82 HERS**
- Randomize PrEP Acceptors 1:1
- SOC and offer PrEP (≤200 women)
- Provide PrEP, enhanced adherence support, SOC (~200 women)
- Provide PrEP, standard adherence support, SOC (~200 women)

**In-depth interviews about women’s decisions to use PrEP, adhere to PrEP, and acceptability.** (~75 total, including acceptors and decliners)

**Standard Adherence Support**
- CBT counseling
- SMS texting
- Adherence clubs

**Enhanced Adherence Support**
- CBT counseling
- SMS texting
- Adherence clubs
- Drug level feedback counseling
Overview of HIV Prevention Landscape

• Where should we focus our resources?
  – Geographic Hotspots
  – Priority and key populations

• What are our available tools?
  – Biomedical Interventions
  – Behavioral Interventions
  – Combination/Integrated Strategies
Summary of Purpose and Rationale

- This should include introduction and background literature to set the context of the proposed research
- Specify the principal aim(s), rationale, relevant background, overall design for Phase I/II trials
- Describe critical pathway to efficacy evaluation
- Indicate relevance to the long-term global goals of HPTN
Study Design

• Specify the type of study proposed, e.g., whether it is a Phase I, IIA, IIB, or III randomized clinical trial, observational, nested case control study, etc.
Description of the Intervention

- Describe intervention (e.g. drug/regimen, counseling program), specify study arms, including control if applicable
Endpoints

• Specify the primary endpoints such as seroconversion, dose-limiting toxicity, specific behavioral outcomes (either primary or secondary endpoints).
Study Population

- Specify sample size, the principal inclusion and exclusion criteria, recruitment source(s), appropriateness of the proposed study population for the proposed concept, and other salient characteristics.
Product-related Considerations

• Is an IND needed?
• Is the product and placebo available in sufficient quantity for the proposed study?
• From whom?
• Is there a plan to manufacture sufficient quantities for any proposed follow-on studies?
Timeframe

- Specify expected duration of accrual and follow-up, and any contingencies for development/implementation (e.g. final product selection/dosage to await results of ongoing study)
HPTN 082

- Brief background - high annual HIV incidence rates of 5-6%
- Rationale – if PrEP delivered with supportive interventions, adherence will improve and PrEP will be efficacious
- Target population - HIV-uninfected women at risk 16-25 years
- Study design – offer open label PrEP, counseling, SMS, adherence clubs, drug level feedback (per randomization)
- Key outcomes – PrEP uptake and adherence
- Study assessments – behavioral data, uptake, ARV drug levels
- Estimated sample size – 400 who accept PrEP at enrollment, up to 200 decline PrEP at enrollment
- Potential impact on the target population – will identify key elements to maximize uptake and adherence to oral PrEP
Science Generation of Concepts to Protocols

- Concept Plan
- Concept Not Approved
- HPTN EC Reviews and Scores
- Concept Approved
- Protocol Development by Protocol Team
- HPTN SRC Review and Approval

- DAIDS PSRC review and approval
- DAIDS regulatory review and approval
- DAIDS medical or program officer review and approval
- DAIDS RAB Chief sign-off on final version 1.0

Final protocol version to sites for preparation of site-specific consent forms and submission to IRBs/ECs
ACKNOWLEDGEMENTS

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