ARV-BASED PREVENTION STRATEGIES: MAKING SENSE OF PrEP, PEP & TasP

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National University Hospital
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Overview

• Prevention remains critical to controlling and ending HIV/AIDS

• ARV-based strategies are essential as part of an overall comprehensive prevention plan

• Definitions:
  - PrEP = pre-exposure prophylaxis
  - PEP = post-exposure prophylaxis
  - TasP = treatment as prevention
HIV Prevention: Increasing Choices

Decrease Source of HIV Infection
- Barrier protection
- Blood screening
- Harm reduction for PWUD
- ART
  - Maternal-to-child transmission
  - Decrease partner’s viral load
  - Treatment of acute HIV infection

Decrease Host Susceptibility to HIV Infection
- Barrier protection
- Circumcision
- Vaccines
- Immunoprophylaxis
- ART
  - Oral
  - Topical (Gel, Film, Ring)
  - Injectable

Alter Behavior: Exposure, Adherence
- Condom promotion
- Individual-level interventions
- Couples interventions
- Community-based interventions
- Structural interventions

Slide courtesy of Kenneth H. Mayer, Melbourne AIDS2014
HIV PREVENTION

- PEP
- PrEP
- PMTCT
- TasP
- Male Circumcision
- Male & Female Condoms
- Microbicides
- STI Treatment
- Needle Exchange
PrEP

• PrEP means taking an anti-HIV pill daily, or in advance of exposure, to prevent HIV infection

• Daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults

• Acute and chronic HIV infection must be excluded by symptom history and HIV testing immediately before PrEP is prescribed

• The only medication regimen approved by the Food and Drug Administration and recommended for PrEP is daily TDF 300 mg co-formulated with FTC 200 mg (Truvada)
Regulatory approval for PrEP

www.avac.org/prep
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Control</th>
<th>Limitations</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agent</td>
<td>Control</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>TDF/FTC (n = 1251)</td>
<td>Placebo (n = 1248)</td>
<td>Adherence</td>
<td>High</td>
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<tr>
<td>iPrEx Trial</td>
<td>Phase 3</td>
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<tr>
<td>US MSM Safety Trial</td>
<td>Phase 2</td>
<td>TDF (n = 201)</td>
<td>Placebo (n = 199)</td>
<td>Minimal</td>
<td>High</td>
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<tr>
<td></td>
<td></td>
<td>TDF/FTC (n = 1589)</td>
<td>Placebo (n = 1586)</td>
<td>Minimal</td>
<td>High</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Phase 3</td>
<td>TDF/FTC (n = 611)</td>
<td>Placebo (n = 608)</td>
<td>High loss to follow-up; modest sample size</td>
<td>Moderate</td>
</tr>
<tr>
<td>TDF2</td>
<td>Phase 2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>TDF/FTC (n = 1062)</td>
<td>Placebo (n = 1058)</td>
<td>Stopped at interim analysis, limited follow-up time; very low adherence to drug regimen</td>
<td>Low</td>
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<td></td>
<td>West African Trial</td>
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<tr>
<td></td>
<td></td>
<td>TDF (n = 469)</td>
<td>Placebo (n = 467)</td>
<td>Stopped early for operational concerns; small sample size; limited follow-up time on assigned drug</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC (n = 1007)</td>
<td>Placebo (n = 1009)</td>
<td>TDF arm stopped at interim analysis (futility); very low adherence to drug regimen in both TDF and TDF/FTC arms</td>
<td>Low</td>
</tr>
<tr>
<td>VOICE</td>
<td>Phase 2B</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>TDF (n = 1204)</td>
<td>Placebo (n = 1207)</td>
<td>Minimal</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC (n = 1207)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BTS</td>
<td>Phase 3</td>
<td></td>
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<td></td>
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</tr>
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</table>
**Table 3: Evidence Summary—HIV Incidence Findings**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Analyses—HIV incidence (mITT)</th>
<th>Effect — HR [Efficacy Estimate] (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agent</td>
<td>Control</td>
</tr>
<tr>
<td>iPrEx (MSM)</td>
<td>36 infections among 1224 persons</td>
<td>64 infections among 1217 persons</td>
</tr>
<tr>
<td>PROUD</td>
<td>15 infections among 1606 persons</td>
<td></td>
</tr>
<tr>
<td>TDF2 (heterosexual men and women)</td>
<td>9 infections among 601 persons 1.2 infections/100 person-years</td>
<td>24 infections among 1130 persons 3.1 infections per 100 person-years</td>
</tr>
<tr>
<td>FEM-PrEP (heterosexual women)</td>
<td>33 infections among 1024 persons 4.7 infections per 100 person-years</td>
<td>35 infections among 1016 persons 5.0 infections per 100 person-years</td>
</tr>
<tr>
<td>West African Trial (heterosexual women)</td>
<td>2 infections among 427 persons 0.86 infections per 100 person-years</td>
<td>6 infections among 434 persons 2.48 infections per 100 person-years</td>
</tr>
<tr>
<td>VOICE (heterosexual women)</td>
<td>TDF 52 infections among 993 persons 6.3 infections per 100 person-years TDF/FTC 61 infections among 985 persons 4.7 infections per 100 person-years</td>
<td>35 infections among 1010 persons 4.2 infections per 100 person-years</td>
</tr>
<tr>
<td>BTS (injection drug users)</td>
<td>17 infections among 1204 persons 0.35 infections per 100 person-years</td>
<td>33 infections among 1217 persons 0.68 infections per 100 person-years</td>
</tr>
</tbody>
</table>

mITT: modified intent to treat analysis; HR: hazard ratio.

*Not statistically significant.*
High Levels of Adherence are Feasible: US PrEP Demonstration Project (2012-2014)

STD clinics in San Francisco, Miami, Washington, DC (n=831)
MSM, transgender women
Clinic referrals (63%)
Self-referrals (37%) and clinic referrals
Offered up to 48 weeks of open-label emtricitabine/tenofovir DF
Accepted PrEP: 60.4%
77% had TDF-DP levels consistent with taking >4 doses/week
PrEP use associated with higher-risk sexual behaviors

BLD: below limit of detection.


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**Tenofovir-DP Levels (Week 4)**

- **Miami** (n=157) - 52%
- **Washington, DC** (n=100) - 35%
- **San Francisco** (n=300) - 14%

<table>
<thead>
<tr>
<th>Doses/Week:</th>
<th>&lt;2</th>
<th>&lt;2</th>
<th>2</th>
<th>&gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLD</td>
<td>5%</td>
<td>11%</td>
<td>18%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt;250</td>
<td>2%</td>
<td>4%</td>
<td>4%</td>
<td>43%</td>
</tr>
<tr>
<td>250-550</td>
<td>0%</td>
<td>2%</td>
<td>27%</td>
<td>40%</td>
</tr>
<tr>
<td>&gt;550-950</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td>52%</td>
</tr>
<tr>
<td>&gt;950</td>
<td>14%</td>
<td>4%</td>
<td>35%</td>
<td>14%</td>
</tr>
</tbody>
</table>

*Femtomole/punch: measure of flux density.*
PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

Percentage of participants' samples that had detectable drug levels vs. Effectiveness (%)

Pearson correlation = 0.86, p=0.003

Source: Salim S. Abdool Karim, CAPRISA
ARV-Based Prevention Pipeline (March 2014)

**PRE-CLINICAL**
- IPM
- Pop Council
- IPM
- Pop Council
- IPM
- IPCP NIAID
- IPM
- Pop Council
- IPM
- ImQuest
- IPM
- Pop Council
- RTI
- CDC
- Mintaka
- IPM
- Pop Council
- IPM
- Pop Council

**PHASE I**
- IPM
- GSK
- CONRAD
- Janssen
- CONRAD
- TaiMed
- CONRAD
- IPM
- Pop Council

**PHASE II**
- HPTN/ACTG
- CONRAD
- TDF
- IPM

**PHASE III**
- CONRAD
- IPM
- Gilead

**PHASE IV**
- DAR
- Darunavir
- DAP
- Dapivirine
- GRF
- Griffithsin
- DS003
- DS003 (BMS793)
- IQP
- IQP-0528
- MIV 150
- 5P12
- 5P12-RANTES
- 744
- GSK 744
- MAb
- Monoclonal antibody
- No drug tested currently

**ACTIVE DRUG**
- TFV
- Tenofovir
- TFV
- Tenofovir prodrug
- TDF
- Tenofovir disoproxil fumarate
- TDF/FTC
- Tenofovir disoproxil fumarate/emtricitabine
- TFV/FTC
- Tenofovir/emtricitabine
- TMC 278
- Ripivirine
- MIV 150
- Raltegravir

**DELIVERY SYSTEM**
- Oral pills
- Vaginal tablet
- Vaginal gel
- Rectal gel
- Vaginal ring
- Long acting injectable
- Vaginal film
- Thin film polymer
- PBS
- Phosphate buffered saline
- Nano-fiber

<table>
<thead>
<tr>
<th></th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detecting substantial risk of acquiring HIV infection</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
</tr>
<tr>
<td></td>
<td>Recent bacterial STI</td>
<td>Recent bacterial STI</td>
<td>Sharing injection equipment</td>
</tr>
<tr>
<td></td>
<td>High number of sex partners</td>
<td>High number of sex partners</td>
<td>Recent drug treatment (but currently injecting)</td>
</tr>
<tr>
<td></td>
<td>History of inconsistent or no condom use</td>
<td>History of inconsistent or no condom use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Commercial sex work</td>
<td>Commercial sex work</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In high-prevalence area or network</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically eligible</td>
<td>Documented negative HIV test result before prescribing PrEP</td>
<td>No signs/symptoms of acute HIV infection</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Normal renal function, no contraindicated medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Documented hepatitis B virus infection and vaccination status</td>
<td></td>
</tr>
<tr>
<td>Prescription</td>
<td>Daily, continuing, oral doses of TDF/FTC (Truvada), (\leq 90)-day supply</td>
<td></td>
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</tr>
<tr>
<td>Other services</td>
<td>Follow-up visits at least every 3 months to provide the following:</td>
<td>HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment</td>
<td>Access to clean needles/syringes and drug treatment services</td>
</tr>
<tr>
<td></td>
<td>Do oral/rectal STI testing</td>
<td>Assess pregnancy intent</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy test every 3 months</td>
<td></td>
</tr>
</tbody>
</table>
HIV PREVENTION

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- Male Circumcision
- STI Treatment
- Male & Female Condoms
- Microbicides
PEP

- PEP is a course of HIV medication that may block HIV infection & taken after a potential exposure has already occurred.
- **NOT a “morning-after pill” → MONTH-AFTER PILLS**
- PEP is most commonly used by healthcare workers after needlestick injuries, and by people following sexual exposure.
- PEP is most effective when begun soon after the exposure, less effective as time increases.
  - PEP should be started as soon as possible after the exposure, preferably within hours.
  - Point at which no benefit may be gained is not defined; in animal studies less effective if started >72 hours after exposure.
- **Optimal duration unknown - 4 weeks appears protective in occupational and animal studies.**
  - PEP should be taken for 4 weeks, if tolerated.
Evidence for PEP

- RCT-free zone

- It is not possible to carry out randomized trials comparing PEP to no treatment in humans, as this would involve denying some exposed patients treatment

- Evidence comes from animal models, human observational studies (largely in HCW on occupational PEP) and extrapolation from prevention of mother-to-child transmission of HIV by short courses of ART in newborns
Effectiveness of PEP

• Case-control study of needlestick injuries to health-care workers given AZT → 81% decrease in the risk for acquiring HIV

• High-risk HIV incidence cohort in Brazil, AZT + 3TC were administered to 200 homosexual and bisexual men. Seroincidence was 0.7 per 100 person-years (one seroconversion) among men who took nPEP and 4.1 per 100 person-years among men who did not take nPEP (11 seroconversions)
  Abstract 225, 8th CROI, Chicago, Illinois, February 4--8, 2001
  Abstract 492, 7th CROI, San Francisco, California, January 30--February 2, 2000

• Other studies - sexual assault survivors in Brazil and South Africa
HIV PREVENTION

- Needle Exchange
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- TasP
- Microbicides
TasP

• The use of ART in HIV+ individuals to preserve their health AND reduce the risk of transmitting the virus

• HPTN 052 - enrolled 1,763 serodiscordant heterosexual couples. It asked whether initiating treatment in the HIV-positive partner could help reduce the risk of sexual transmission of HIV to the HIV-negative partner and found that immediately initiating therapy reduced the risk of HIV transmission by 96%

• PARTNER - found similarly high levels of protection among heterosexual and gay serodiscordant couples
• Range of other trials many of which also support the prevention benefit of expanding access to treatment. These data support ongoing efforts to expand global access to ART...
2013 WHO ARV guidelines can decrease new infections and deaths

WHO 2013 guidelines recommend initiating ART in HIV positive people with CD4 cell counts of 500 or below. Implementing these guidelines will reduce infections and save lives.

Annual HIV Infections in 2015

2010 Guidelines

36%

2013 Guidelines

3.5 million additional new HIV infections averted

Annual HIV-related deaths in 2015

2010 Guidelines

39%

2013 Guidelines

3 million additional lives saved


AVAC Report 2013: Research & Reality

www.avac.org/report2013
THE TIPPING POINT: MOVING FROM RHETORIC TO REAL
MILESTONES FOR ENDING AIDS

METHODOLOGY
The analysis used modelling to build a prevention advocacy agenda around ending AIDS. The targets set reflect best-case scenario calculations based on published modeling and epidemiologic data, as well as analysis provided by experts in the field. Data projections were crosschecked with modelers and epidemiologists. Modelling data is tracked and updated to ensure the most recent metrics are used, and real-time data is included and analyzed as available.

GLOBAL TIPPING POINT

Additionally, the pace at which treatment and prevention are scaled up is key. To reach the tipping point the rate at which people are started on treatment should accelerate immediately.

HIV PREVENTION AND THE TIPPING POINT
A country can reach the tipping point and then cross back—returning to a situation where incidence outstrips rate of ART initiation. That’s why it is essential to achieve optimal coverage rates of high-impact prevention including voluntary medical male circumcision, male and female condoms and harm reduction. Newer strategies such as PrEP and, eventually, a microbicide or vaccine should also be used for maximum impact. Milestones are needed for prevention interventions, too. These include coverage goals for VMMC, condom availability and more.

COUNTRIES THAT HAVE REACHED THE TIPPING POINT

TIPPING POINT COUNTRY EXAMPLES

BOTSWANA
New Infections in Botswana in 2012: 12,000
Increase in Patients on Treatment in Botswana in 2012: 25,614
Tipping Point Ratio: 0.47

KENYA
New Infections in Kenya in 2012: 98,000
Increase in Patients on Treatment in Kenya in 2012: 65,044
Tipping Point Ratio: 1.5

www.avac.org/prevention-option/treatment-prevention
Thank you