CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS

Treatment as Prevention and Pre-Exposure Prophylaxis

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Royal Garden Hotel, London

Sponsored by:
British HIV Association
In partnership with:
PrEP: Setting the Stage

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Beth Israel Deaconess Medical Center
Harvard Medical School
HIV Prevention: New Opportunities, New Challenges

**Decrease Infectiousness**
- Barrier protection
- Blood screening
- IDU harm reduction
- Antiretroviral therapy (PMTCT, treat infected partners)
- STI treatment

**Decrease Host Susceptibility**
- Barrier protection
- Infection control
- Circumcision
- PEP, PrEP
- Topical microbicides
- Vaccines
- STI treatment

**Alter Behavior**
- Condom and HIV testing promotion
- Individual interventions
- Couples interventions
- Community-based interventions
- Structural interventions
Clinical Trial Evidence that Antiretroviral Drugs Prevent HIV Transmission

Study

Treatment for prevention
(HPTN 052)

PrEP for discordant couples
Partners PrEP with FTC/TDF

PrEP for heterosexuals
Botswana TDF2 with FTC/TDF

Medical male circumcision*
Orange Farm, Rakai, Kisumu

PrEP for MSMs
(iPrEX with FTC/TDF)

STD treatment*
Mwanza

Microbicide*
(CAPRISA 004 tenofovir gel)

HIV Vaccine
(Thai RV144)

Effect size (CI)

96% (73; 99)
73% (49; 85)
63% (21; 48)
54% (38; 66)
44% (15; 63)
42% (21; 58)
39% (6; 60)
31% (1; 51)

Abdool Karim SS & Q. Antiretroviral prophylaxis...Lancet 2011;378:e23-5
HPTN 052 Limitations

- Many couples are short-lived and do not disclose
- Some people may never disclose: MSM, SW
- Stigma about testing and revealing status
- Only 3% of couples in HPTN 052 were MSM
- Not either, or........
- PrEP combined with ART for prevention can decrease epidemic more rapidly (Hallett, Walensky)
- Can less frequent dosing or new agents be comparably effective?
- Can topical chemoprophylaxis lead to less frequent monitoring?
CAPRISA 004 Results: HIV Incidence

Overall

HIV Incidence Rate (%)

Follow-Up (months)  Placebo  Tenofovir DF gel
12  10.5%  5.2%  50% (P=0.007)
30  9.1%  5.6%  39% (P=0.017)

By Adherence

HIV Incidence Rate (%)

By Adherence Level (months)  Placebo  Tenofovir DF gel
>80%  9.3%  4.2%  54% (P=0.025)
50%-80%  10.0%  6.3%  38% (P=0.34)
<50%  8.6%  6.2%  28% (P=0.30)

Nov 2010: Oral TDF/FTC PrEP prevents HIV in MSM – iPrEx trial

131 infections after randomization
- 48 in FTC/TDF
- 83 in placebo

- Primary HIV analysis (1 May): 44% protection
- At the end of the study: 42% (95% CI 18%-60%)
- No effect on HSV-2

TDF-DP drug levels in blood << EC50 for HSV
Partners PrEP Study: Tenofovir Levels Correlate with HIV Protection

- Case cohort study of 30 seroconverters in active arms vs. 200 uninfected subjects randomly selected from active arms
- Plasma TDF levels at months 1, 3, 6, 12, 18, 24, 30, 36 + seroconversion visit

Subjects with Detectable Tenofovir Levels and Risk Reduction

<table>
<thead>
<tr>
<th></th>
<th>Cases (TDF = 17, FTC/TDF = 12)</th>
<th>Cohort (N=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visits prior to seroconversion</td>
<td>Seroconversion visits</td>
</tr>
<tr>
<td>TDF</td>
<td>35/63</td>
<td>6/17</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>20/36</td>
<td>3/12</td>
</tr>
</tbody>
</table>

- Relative risk reduction associated with detectable tenofovir
  - TDF arm: 86% (95% CI: 57%, 95%)
  - FTC/TDF arm: 90% (95% CI: 56%, 98%)

Predictors of detection – Recent report of sex

Anderson et al, CROI 2011

- 76% in those reporting URAI vs 59% reporting sex w/o URAI vs 35% reporting no sex in preceding 12 weeks (P=0.003).

- Trend suggests drug use associated with recent report of sex/URAI.
Why was oral and topical PrEP ineffective for some women?

- Adherence?
- Pharmacology?
- Genital Tract Inflammation, STDs?
- Viral challenge from partners?
TDF-DP Levels in PBMC with 2-7 days DOT
Understanding iPrEx results

"Consistent" dosing
16 fmol/10^6 cells

"Inconsistent" dosing
ARV-based HIV Prevention Timeline **

As of February 2012

* Trial end-dates are estimates; due to the nature of clinical trials the actual dates may change. For full trial details, see www.avac.org/trials.

** Not all trials included are effectiveness trials. Trials included on this list are mainly phase II/IIb, III/IIIb and IV trials.
PERCENT CHANGES FROM BASELINE IN BMD BY RANDOMIZATION GROUP

SPINE (L1-L4)

TOTAL HIP

Week

Placebo 247 199 124 59
FTC/TDF 256 203 124 59

Placebo 247 199 124 59
FTC/TDF 256 202 125 59

Mean, SE and P-values by linear mixed model

Mulligan et al, CROI 2011 abstract 94LB
Peri-Exposure Prophylaxis in Macaques With Oral FTC/TDF

- Macaque model of rectal transmission of HIV
  - Rectal exposure with R5 virus inoculum (10 TCID<sub>50</sub>)
- 2 doses of FTC/TDF
  - Before SHIV exposure (-)
  - After SHIV exposure (+)
- Extended window of protection
  - Associated with extended long intracellular persistence of drug
- No drug resistance in macaques failing PrEP

Anal sex frequency
Thai MSM

Van Griensven, JIAS 2010
What about intermittent PrEP?

- **IAVI** studies in East Africa: MSM and FSW, small size, but many missed post-coital doses.
- **HPTN 066**: dose proportionality study of weekly TDF/FTC, twice weekly, and double dose twice weekly. DOT. Sampling blood, mucosal secretions and tissues.
- **HPTN 067**: MSM in Bangkok and NYC, and high risk women in Capetown, to compare adherence to coitally dependent vs. fixed intermittent PrEP.
- **Ipergay**: getting underway
Adherence to different PrEP dosing, MEMs
RCT in Kenya MSM and FSW

Priddy, PLOS One, in press
# New Antiretrovirals for Prevention

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism</th>
<th>Status</th>
<th>Developers/Sponsors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapivirine (gel and ring)</td>
<td>NNRTI</td>
<td>Phase 1/2 (gel ring)</td>
<td>Tibotec/IPM</td>
</tr>
<tr>
<td>UC-781 (gel)</td>
<td>NNRTI</td>
<td>Phase 1/2</td>
<td>CONRAD/MTN</td>
</tr>
<tr>
<td>MIV-150 (gel)</td>
<td>NNRTI</td>
<td>Phase 1</td>
<td>Population Council</td>
</tr>
<tr>
<td>BMS-793 (?)</td>
<td>gp120 inhibitor</td>
<td>Pre-clinical</td>
<td>BMS/IPM</td>
</tr>
<tr>
<td>L644 peptide (?)</td>
<td>gp120 inhibitor</td>
<td>Pre-clinical</td>
<td>Merck/IPM</td>
</tr>
<tr>
<td>Maraviroc (oral and ring)</td>
<td>CCR5 inhibitor</td>
<td>Phase 1</td>
<td>ViiV/IPM/HPTN/MTN</td>
</tr>
<tr>
<td>TMC278 (injectable)</td>
<td>NNRTI</td>
<td>Phase 1</td>
<td>Tibotec</td>
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Social Cognitive Model

Disease prevention → Pleasure reduction

Pleasure reduction → Self efficacy

Self efficacy → Safer Sex Adherence

Safer Sex Adherence → Depression, anxiety, mental health problems, substance use

Social Models → Disease prevention

Wulfert, Safren, et al., 1999; Journal of Applied Social Psychology
Demo Projects to Enhance Adherence

• In Weltel study (Kenya), weekly SMS message and phone support reported adherence and rates of virologic suppression
• SF adapting this for use in PrEP with weekly SMS messages to check in
• Fenway: 2 new projects:
  • R34 (Mayer/Safren) to develop evidence-based adherence intervention
  • R21 (Mimiaga/Mitty) to study stimulant using MSM to develop PrEP package
Youth

- **ATN 082**: 58 young MSM in Chicago randomized to PrEP vs placebo
- 46 enrolled in iPrEx OLE, 70% used PrEP
- Of PrEP users, blood levels indicate about 50% adherence, comparable to self-report
- Youth enjoyed integrated Next Step Counseling
- Lots of interim visits for social issues
- No seroconversions
- **ATN 110/113**: PrEP demo projects for youth, ages 15-18 and 18 and above, getting underway
Antiretrovirals for Prevention 6/12

- Clinical trials provided proof of concept, but…
- How do we optimize effectiveness?
- Integration of treatment as prevention with other services (e.g. mental health)
- Define best drugs for each indication
- Define the role of intermittent dosing
- Define whether oral or topical is preferable
- Affordability and Scalability
- Optimize Prevention Packages
Combination Antiretroviral Prevention

Interventions to Increase Testing

Test
- HIV Negative
  - Risk Assessment
    - PrEP, Adherence Counseling
  - Address concomitant concerns, e.g. depression, substance use, relationship dynamics
- HIV Positive
  - Positive Prevention
  - Linkage To Care

Enroll in Care
- ART Initiation
- Treat
- Adherence to ART
  - Maintain Viral Suppression

Decrease in HIV Transmission

Treat
- Enroll in Care
- ART Initiation
  - Treat
  - Adherence to ART
    - Maintain Viral Suppression

Linkage To Care
- Enroll in Care
  - ART Initiation
  - Treat
    - Adherence to ART
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Decrease in HIV Transmission
- Treat
  - Enroll in Care
    - ART Initiation
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Thank You

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