PrEP prospects in RSA:

Where are we within our generalized epidemic??

Linda-Gail Bekker
The Desmond Tutu HIV Centre, UCT.
HPTN meeting
Washington 2013
...in the 'leading cause of death' event, the continent's new number one...
ART PrEP contributions….

Topical

- CAPRISA 004: 1% TDF gel; BAT24; 889 women; PE: 39%
- VOICE 1% gel arm: Daily; 5029 women; Futility
ART PrEP contributions....

Topical

- FACTS 001: 1% TDF gel; BAT 24; 2600 women; ongoing
- Ring Studies, Aspire: Dapivirine Ring; ongoing
- MTN 017: 1% TDF gel rectal microbicide in MSM; pending.
- FACTS 002: 1% TDF safety in adolescents: pending
ART PrEP contributions....

Systemic

- Global iPrEx: Daily TDF/FTC; 2499 MSM; PE 44%
- FEMPREP: Daily TDF/FTC 1950 women; Futility
- VOICE TDF and TDF/FTC arms: Daily; 5029 women; Futility
SA Opinion leaders

• “the entire sexually active population are high risk. Is PREP feasible in this setting?”

• “an intervention this weak, and with studies showing that adherence is critical but dreadful, should not be standard of care.”
People feel as though PrEP is important in South Africa

Do you think that PrEP should be an important part of the prevention plan for your country?

- a) No, not at all important and should be given no attention
- b) It is important, but there are other things that are more important
- c) Very important and should be given lots of attention
- d) No opinion

- 2.9%
- 5.0%
- 44.5%
- 47.5%
The majority of people feel that microbicides are very important in South Africa.
National Strategic Plan for HIV and AIDS, STIs and TB, 2012-2016

• Reduce new infections by means of combination prevention by 50% (75% in vertical infection, 50% in high risk)
Key populations....

• Key populations for HIV services include: young women between the ages of 15 and 24 years; people living close to national roads and in informal settlements; young people not attending school; people with the lowest socio-economic status; uncircumcised men; people with disabilities; sex workers and their clients; people who abuse alcohol and illegal substances; men who have sex with men; and transgender persons.
HIV Prevalence: CT township

MSM in community

AGE

%
SA PrEP Guidelines

• Recognises
  – MSM a significant key population at risk for HIV in RSA
  – Evidence for an effective biomedical prevention
  – Must be combined with other behavioural and structural interventions
  – Can formulate a “package for MSM”
  – Truvada available in RSA.
  – Have an ethical and moral obligation to make sure guidance available to do this safely.
  – May add discordant couple amendment…..
Ongoing work in PrEP
iPrEx was a randomized controlled trial of daily oral FTC/TDF PrEP versus placebo for prevention of HIV acquisition in men who have sex with men and transgendered women (MSMTG).\textsuperscript{1}

- Average age 24 years,
- Placebo incidence 3.9 / 100py.

Randomization to receive PrEP provided 44\% additional reduction in HIV incidence (MITT).\textsuperscript{1}

Risk reduction was
- 96\% if drug concentrations were commensurate with use of 4 tablets per week;\textsuperscript{2}
- 99\% if drug concentrations were commensurate with use of 7 tablets per week.\textsuperscript{2}

\textsuperscript{1}Grant et al, \textit{NEJM} 2010; \textsuperscript{2}Anderson et al, \textit{Science Translational Medicine}, 2012.
iPrEx Open Label Extension (OLE)

• All participants previously enrolled in iPrEx were eligible to enroll in the iPrEx OLE.
  – Visits in the blinded randomized phase of the main iPrEx study occurred through November 2010, except substudy visits not considered here.
  – iPrEx OLE started as soon as all applicable authorities approved the modified protocol (enrollment from June 2011 to June 2012).

• 1529 (65%) iPrEx participants enrolled in OLE
• In Cape Town: 88 MSM enrolled in iPrEx (85%)
• 55 enrolled in OLE (98%)
Factors Associated with Enrollment in OLE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Enrolled in OLE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Condomless Receptive Anal Intercourse</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>No</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Yes</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>Age</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>&lt;25</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>25-30</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>27%</td>
<td>73%</td>
</tr>
<tr>
<td>Prior Randomization Group</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td>Placebo</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td>Drug Detected in Randomized Phase</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Never</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Any</td>
<td>28%</td>
<td>72%</td>
</tr>
</tbody>
</table>
HIV Incidence by Study Period; During the gap, 78 infections, 3.7 / 100py

<table>
<thead>
<tr>
<th>Group</th>
<th>TDF Di-Phosphat e fmol/ M vPBMC</th>
<th>Randomized Phase Events / PY Rate (95% CI)</th>
<th>Gap Phase Events / PY Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>83 / 2113 3.9 (3.1 to 4.8)</td>
<td>43 / 1044 4.1 (3.1 to 5.6)</td>
</tr>
<tr>
<td>FTC/TDF F</td>
<td>&lt;10</td>
<td>46 / 1500 3.1 (2.2 to 4.0)</td>
<td>35 / 1048 3.3 (2.4 to 4.7)</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>2 / 624 0.3 (0 to 0.08)</td>
<td></td>
</tr>
</tbody>
</table>
Cape Town OLE

- Declined OLE Enrollment: 15
- Relocation: 5
- Life-Style Change: 9
- Availability: 1

- OLE Enrollment: 55
- Initiated Drug: 40
- SC (Pre-OLE): 8
- Declined Drug: 7

- Declined Drug: 7
- Life-Style Change: 6
- Side Effects: 1

- Discontinued drug: 9
- SC : 4 (<25YRS)
- Side effects : 2
- Lifestyle change : 2
- Personal Choice: 1

Adherence on drug levels >70%
Lesson?

• When told something works-
• People who have had a chance to experience a product-
• Can make healthy decisions about whether to use it or not-
• Suggesting they CAN and WILL align their risk and need for protection…..
MSM package?

Which ingredients?
Prevention Packages for MSM in Southern Africa

Emory University
Desmond Tutu HIV Foundation,
HSRC(PE)
Johns Hopkins University
University of California, Los Angeles
400 MSM enrolled and followed
# MP3 Standard and Enhanced Prevention Packages

## Standard Package
- Choice condoms
- Risk-reduction counseling
- HIV testing and counseling
- Linkage to care for HIV+ men

## Enhanced Package
- Standard package components
- Enhanced condom selection
- Condom-compatible lube
- Couples HIV testing and counseling and home testing
- Pre-Exposure prophylaxis
Post-VOICE

• In a case-cohort subset, TFV was detected on average in 28% of available quarterly plasma samples among participants randomized to TDF, 29% to TDF/FTC, and 22% to TFV gel.

• Predictors of plasma TFV detection in the case cohort group were being married, age >25 years, and reporting a primary male partner >28 years. No safety concerns were identified.
Will it work?
Will people take/use it??
What is the approach?

- Prep
- Pills
- Prep LA
- Vaccine
- Microbicide gel
- Microbicide ring
- MMC
- Treat partner
- LIFESTYLE
- CLIENT CENTRED PROTECTION
- RISK
- PREFERENCE
- CHOICE
Acceptability of oral intermittent pre-exposure prophylaxis as a biomedical HIV prevention strategy: Results from the South African ADAPT (HPTN 067) Preparatory Study

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¹Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town; ²Center for Health Intervention and Prevention, University of Connecticut; ³Gladstone Institute of Virology and Immunology; ⁴University of California; ⁵Department of Medicine, University of Cape Town

Oral Abstract TUPDC0303
XIX International AIDS Conference
Washington, DC, USA
July 24, 2012
Background/ Methods

• Intermittent PrEP dosing or iPrEP (time- or event-driven) is being explored for the sake of convenience, cost-effectiveness and reduction in side effects

• Acceptability data in at-risk communities is needed to evaluate likely uptake and potential impact

  ✓ 8 focus groups in Cape Town, South Africa - 6 with adults, 2 with counselors working in high-incidence populations (n-52)
  ✓ Semi-structured guide and sexual exposure/ forecasting survey
  ✓ Framework analysis for qualitative data
Results

ACCEPTABILITY

• PreP acceptability due to potential for non-consensual use
• Barriers: aversion to novelty, PrEP seen as treatment, fear of stigma, risk compensation
• iPrEP favoured for lower time burden and side effects
• Concerns around iPrEP complexity

SEXUAL EXPOSURE

• Median of 2 sex days in previous week
• 0% reported daily sex as average
• Highest sex activity over weekends

SEXUAL FORECASTING

• 51% forecasted last sex act (men 75% vs. women 32%)
• 77% forecasted some, and 51% all sex events in previous week
• 88 sex days reported in previous week, of which 67% were forecasted.
HPTN 067 : ADAPT

A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)

- Alternative
- Dosing
- to Augment PrEP
- Pill
- Taking

= ADAPT
Primary Objective:

- To test the hypothesis that recommending **intermittent** (non-daily) usage of oral FTC/TDF chemoprophylaxis, compared with recommending daily usage, will be associated with:
  - **Equivalent coverage** of sex events with pre- and post-exposure dosing
  - **Lower number of pills** needed for coverage and fewer pills used
  - **Decreased self-reported symptoms/side effects** (both severity and frequency) during 24 weeks of self-administered use
Secondary Objectives:

– Develop objective measures of drug exposure among PrEP users by **obtaining steady state PK** during a 6 week directly-observed therapy (DOT) phase

– To **describe safety outcomes** among PrEP users and resistance among any seroconverters

– Assess **differences between arms in the acceptability** of different PrEP regimens and in perceptions of advantages and disadvantages of different regimens
Secondary Objectives (cont):

- Assess **differences by arm in adherence**
- Evaluate the **potential influence of PrEP usage on**
  - changes in **sexual behavior**,  
  - **planning** for sex,  
  - **prediction of risky** situations, and  
  - **recognition of possible HIV exposure** from baseline to final on-drug assessment in relation to PrEP optimism
Study Sites:

• Cape Town (WSM) – F/up almost complete

• Bangkok (MSM)- enrolling

• Harlem (MSM)-enrolling
Study Design: 3 arms

• **Daily:**
  - One tablet of FTC/TDF once a day regardless of sexual activity

• **Time Driven:**
  - One tablet of FTC/TDF 2 days/week and a post-exposure booster dose within 2 hours after sexual intercourse

• **Event Driven:**
  - One tablet of FTC/TDF prior to sexual intercourse & a post-exposure booster dose within 2 hours of sexual intercourse
Randomization Scheme

300mg TDF/200mg FTC Tablets (Truvada®)

Week 6 Randomization

Arm 1 Daily
- 120 MSM
- 60 WSM

Arm 2 Time-driven
- 120 MSM
- 60 WSM

Arm 3 Event-driven
- 120 MSM
- 60 WSM
292 screened, 191 enrolled, 179 randomised
Median age: 26 yrs
80% unmarried.
Women tend not to carry pills with them. Given unpredictable nature of sex, makes remembering even more difficult:

“Another thing that made it difficult was that maybe on a Saturday – okay, let’s say you took your pills at seven in the evening. Now you get ready and leave the house before seven. When you have already arrived at your destination, you then recall that you haven’t taken your pills along. And then you tell yourself that you’re going to make up for it tomorrow. And then I would take two the next day.” (Daily arm participant)
Fear of association with chronic illness and/or HIV

Some people might be embarrassed about taking the pills, you know… Like, it’s something that I first experienced. I thought: “I have to keep so many pills on me as if I am a sickly person.” (Event arm participant)

I don’t think it will be acceptable because some people are scared of the fact that this pill is being taken by positive people – they are looking for people who are negative. They are scared and say: ‘I would never take it!’ (Daily arm participant)
Study participation has health promoting effects

Well, I didn’t even think about testing. I just told myself I would deal with it when I get it [HIV]. So coming here and being tested, I started thinking ‘let me start protecting myself’, maybe there will be a difference…Yes, that was encouraging because I told myself that from today I will never make that mistake again (Time arm participant)
Future access to PrEP might include information or counseling groups

They should be given knowledge about these pills...In the way that it happens here at the clinic. Like at the clinic, you’re not just given the pills. You are first told what the pills are for and then you take them. If maybe someone just goes to the chemist and buys them there, perhaps they won’t tell them what these pills will do to them. (Time arm participant)

There should be groups like these being held where they are, so that they can be told about these pills...In the area where they stay...(Event arm participant)
Lessons?

- Peoples’ needs vary
- Peoples’ needs vary over time
- People have preferences
- Perhaps HIV protection should be tailored to need and preference….??
Targeted Prevention Packages

- CSW
- IDU
- MSM
- PMTCT
- Adolescents
CHAMPS: CHoices for Adolescent Methods of Prevention in SA.

1. Literature Review.
2. Pilot studies of biomedical technologies.
4. Design of clinical trials.
CHAMPS

Pilot 1. Circumcision
- MMC vs TMC

Pilot 2. PrEP
Truvada
- Adherence
- Monitoring
- Risk

Pilot 3. Routes
- Injectable
- Oral
- Ring

Pilot 4. Choices
Longer acting Injectables: HPTN 076

- Non-nucleoside reverse transcriptase inhibitor: Rilpivirine (Janssen)
- Oral ART: Edurant (25mg) once per day
- Complera: Combination treatment with FTC/TDF
- ECHO and THRIVE
HPTN 076

• 3 Phase I clinical trials of parenteral formulations of TMC278 LA in HIV-negative, healthy participants have been completed.

• 1 trial is ongoing.

• Between these four clinical trials, >70 individuals have been exposed to TMC278 LA.
HPTN 076

- Doses of 1200, 600, 300mg IMI have been used
- No grade 3 or 4 adverse events
- Pain and tenderness at injection site
- Rash (less frequent than EFV)
- Vial is 2ml = 600mg
HPTN 076

• PHASE II SAFETY AND ACCEPTABILITY OF AN INVESTIGATIONAL INJECTABLE AGENT, TMC278 LA, FOR PRE-EXPOSURE PROPHYLAXIS

• TMC278 LA (1200 mg (2x 2ml) dose administered every 8 weeks) in HIV-seronegative women in SSA and in the United States (US). 2:1 randomisation

• 160 healthy women (18-45 yrs)

Emavundeli CRS, Spilhaus CRS, NJMS CRS, Bronx-Lebanon CRS
Client centred prevention....

Pill  Gel  Vaginal film  Vaginal ring  Injectable

Choice, preference, risk, lifestyle......
Acknowledgements

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- MP3-CHAMPS
- HPTN, DAIDS.
- Comrades in the prevention revolution.