Prepping for PrEP

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Overview

• The Health4Men Model and how it facilitates PrEP
• Introduction to PrEP
• Who needs PrEP
• PrEP Evidence
• How to initiate & manage PrEP
• PrEP complications & side effects
• The EJAF Anova H4M PrEP Demo Project
Using the H4M Model to Facilitate Services and PrEP for MSM

H4M promotes and supports MSM healthcare by:

• Providing direct health services at two centres of excellence in MSM sexual healthcare;
• Building a support network of MSM-competent sites;
• Conducting biomedical and operational research on MSM sexual health, and translating our findings into effective intervention models;
• Hosting symposia and think tanks;
Using the H4M Model to Facilitate Services and PrEP for MSM

We promote and support MSM healthcare by:

• Providing training, mentoring and ongoing technical support to health workers in the public sector, in partnership with the Department of Health;
• Conducting prevention and treatment campaigns using mass media, social media and cell phones;
• Producing and distributing guidelines that address prevention, treatment and care for MSM.
• Provide support groups to men living with HIV.
• Providing a platform for piloting of innovative MSM risk reduction interventions such as PrEP
# ART-Based PrEP

| How are antiretrovirals used? | **Oral pill**  
|                             | • Topical gel (microbicide)  
|                             | • Rectal  
|                             | • Vaginal  
|                             | • Injection  
|                             | • Intravaginal ring |
| How often are the antiretrovirals used? | **Daily**  
|                             | • Intermittently  
|                             | • Coitally (before/sex) |
| How many antiretrovirals are used? | **Combination**  
|                             | • Monotherapy |
| What antiretrovirals are used? | **Truvada**  
|                             | • Tenofovir  
|                             | • (Cabotegravir /miravirroc) |

**Post Exposure prophylaxis (PEP)**

**Treatment as Prevention (TasP)**

Combination Prevention with existing and new technologies
Key Populations

TOTAL POPULATION

SEX WORKERS

PEOPLE WHO INJECT DRUGS

MEN WHO HAVE SEX WITH MEN

TG

PRISONERS

Adolescent girls and young women
Vulnerable Populations in South Africa

Specific groups have HIV prevalence above national average (12.2%). They include:

- **Black women aged 20–34 years** (HIV prevalence 31.6%)#
- **MSM** (HIV prevalence 13.7–48.2%)*
- **Sex workers**
- People co-habiting (30.9%)
- Black men aged 25–49 years (25.7%)
- Disabled persons 15 years and older (16.7%)
- High-risk alcohol drinkers 15 years and older (14.3%)
- Recreational drug users (12.7%)

* Marang Men’s Study (2012-13) and Mpumalanga Men’s Study (2014)
National Sex Worker Plan
Ongoing HIV Transmission Despite Expanding ART Access in South Africa

Treatment exposure has doubled from 16.6% in 2008 to 31.2% in 2012.

Source: HSRC, 2012
Core Key Population Services Identified by WHO

- HIV screening and treatment regardless of CD4 count
- Management of HIV related illness
- Appropriate counselling and support
- Prevention – PEP and PrEP*
- Prophylaxis
  - IPT / Fungal / Co-trimoxazole
- STI prevention, screening and treatment
- Malaria prevention (specific provinces)
- Vaccination e.g. hepatitis B, pneumococcal, flu
- Integrated TB services – South Africa

* For populations at significant risk of HIV (3-5%)
HIV Prevention Toolkit

- Microbicides for women
  - Abdool Karim Q, Science 2010

- Male circumcision
  - Gray R, Lancet 2007

- Treatment of STIs
  - Grosskurth H, Lancet 2000

- Female Condoms

- Male Condoms

- HIV Counselling and Testing
  - Coates T, Lancet 2000

- Behavioural Intervention
  - Abstinence
  - Be Faithful

- Oral pre-exposure prophylaxis
  - Grant R, NEJM 2010 (MSM)
  - Baeten J, 2011 (Couples)
  - Paxton L, 2011 (Heterosexuals)

- Post Exposure prophylaxis (PEP)
  - Scheckter M, 2002

- Vaccines
  - Rerks-Ngarm S, NEJM 2009

Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission
# Four Early Trials Demonstrating PrEP Efficacy in Diverse Geographic and Risk Populations

<table>
<thead>
<tr>
<th>Study, population</th>
<th>PrEP agent</th>
<th># of HIV infections</th>
<th>PrEP efficacy (95% CI) publication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP Study</strong></td>
<td></td>
<td></td>
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<tr>
<td>Heterosexual couples</td>
<td>TDF/FTC</td>
<td>13</td>
<td>75% (55-87%)</td>
</tr>
<tr>
<td>Kenya, Uganda (n=4758)</td>
<td>TDF</td>
<td>17</td>
<td>67% (44-81%) Baeten et al. N Engl J Med 2012</td>
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<tr>
<td><strong>TDF2 Study</strong></td>
<td></td>
<td></td>
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<tr>
<td>Botswana (n=1219)</td>
<td>TDF</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>Bangkok Tenofovir Study (BTS)</strong></td>
<td>TDF</td>
<td>17</td>
<td>49% (10-72%) Choopanya et al. Lancet 2013</td>
</tr>
<tr>
<td>IDUs</td>
<td></td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Thailand (n=2413)</td>
<td></td>
<td></td>
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<tr>
<td><strong>iPrEx</strong></td>
<td></td>
<td></td>
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<tr>
<td>MSM</td>
<td>TDF/FTC</td>
<td>36</td>
<td>44% (15-63%) Grant et al. N Engl J Med 2010</td>
</tr>
<tr>
<td>Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499)</td>
<td>TDF</td>
<td>64</td>
<td></td>
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</table>
Partners PrEP: Efficacy and Resistance Results

- Both PrEP arms significantly reduced HIV acquisition risk; similar efficacy in men and women\(^1\)
  - TDF levels correlated with HIV protection
- No differences in serious AEs, creatinine abnormalities across arms
- No evidence of risk compensation

HIV Incidence\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TDF</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Incidence (per 100 PY)</td>
<td>1.99</td>
<td>0.65</td>
<td>0.50</td>
</tr>
</tbody>
</table>

\(67\%\) reduction \((P < .001)\)

\(75\%\) reduction \((P < .001)\)


Slide credit: clinicaloptions.com
Highly anticipated results were reported today from the VOICE trial, which looked at the safety and efficacy of daily oral PrEP and drug-containing vaginal microbicide gel in more than 5,000 women in South Africa, Uganda, and Zimbabwe.

Jeanne Marrazzo, MD, MPH, explained to a packed auditorium at the 20th Retrovirus Conference that these approaches did not prevent new HIV infections in this particular study because most participants didn’t actually use them.

When VOICE—short for Vaginal and Oral Interventions to Control the Epidemic—began enrolling women in September 2009, it had five study groups. Participants were randomized to use one of the following products daily:

- tenofovir gel
- placebo gel
- oral tenofovir tablet
- oral Truvada (the tenofovir/emtricitabine combination)
- oral placebo pill
Preexposure Prophylaxis for HIV Infection among African Women

Van Damme, L et al

- RCT of 2120 HIV negative women in Kenya and Tanzania
- TDF/FTC PrEP versus placebo
- Objectives: effectiveness and safety

Results
- HIV incidence 4.7% PrEP and 5.0% placebo → no difference
- Significantly higher side effects in intervention arm (GIT)

CONCLUSIONS
Prophylaxis with TDF–FTC did not significantly reduce the rate of HIV infection and was associated with increased rates of side effects, as compared with placebo. Despite substantial counseling efforts, drug adherence appeared to be low. (Supported by the U.S. Agency for International Development and others; FEM-PrEP ClinicalTrials.gov number, NCT00625404.)
iPrEX: Daily Oral TDF/FTC PrEP for MSM

- Double-blinded, randomised trial of oral TDF/FTC QD PrEP vs PBO for HIV-negative MSM/TGW at high risk for HIV infection (N = 2499)
- Relative reduction in cumulative risk of HIV infection: 44% with TDF/FTC vs PBO ($P = .005$)[1]
- Approximately 75% risk reduction in those who adhered


Slide credit: clinicaloptions.com
Proud Study UK

- 545 MSM
- Immediate or delayed
- Efficacy = 86% (90% CI: 58–96% \( P = 0.0002 \))
- Number Needed to Treat = 13 (90% CI: 9 – 25)
- There was no difference in the rate of STIs other than HIV

Ipergay France

- 400 high risk MSM
- Sex-based dosing (4 or more doses)
- Efficacy = 86% (95% CI 40-99%, \( P = 0.002 \))
- Number needed to treat for 1 year to prevent 1 infection = 18.
- Also stopped early by DSMB because of high efficacy
- Very sexually active
- Did they not by default get almost daily dosing?

Current evidence supports daily dosing
Indications for PrEP

PrEP should be considered for people who are HIV-negative and at significant risk of acquiring HIV infection

- Any sexually active HIV-negative *MSM* or transgender person who wants PrEP
- *Heterosexual women and men* who want PrEP
- People who inject *drugs*
- Include *adolescents* and *sex workers*
  - especially vulnerable: young MSM and adolescent girls
Contra-indications to PrEP

- HIV-1 infected or evidence of possible acute infection
- Suspicion of window period following potential exposure
- Adolescents <35 kg or <15 years who are not ≥Tanner stage 3
- Poor renal function (creatinine clearance <60 mL/min)
- Other nephrotoxic drugs (e.g., aminoglycosides)
- Unwilling or unable to return for 3-monthly visits
- Pregnant or breastfeeding women
Or more simply...

In the past six months:

1. Have you had sex?
2. Have you had unprotected (condom-less) sex?
3. Have you had sex with partners who are HIV-positive or whose HIV status you did not know?
4. Have you had sex under the influence of alcohol and/or drugs?

Or even more simply...

In the past six months:

1. Have you had sex?
2. Have you had unprotected (condom-less) sex?
Eligibility criteria

1. Anyone identified as being at high risk for HIV exposure
2. No contra-indications to FTC/TDF FDC
3. HIV-negative / not thought to be in the window period
4. Absence of symptoms of acute HIV infection
5. Willing and able to attend 3-monthly visits
6. Willing and able to adhere to PrEP (to take pills)
7. Understands that the protection provided by PrEP is not complete
8. Recurrent use of PEP
Starting PrEP

Screening

PrEP initiation visit

One month follow-up

Three-monthly maintenance visits
Perfect adherence is not required: iPrEx OLE

100% HIV protection was seen with adherence consistent with ≥4 tablets per week

Grant et al. Lancet ID 2014
Lead In and Out Doses

...Or Time to Protection

7 days for anal tissue levels to reach high level steady state

→ Protects against anal acquisition of HIV

20-30 days for vaginal tissue levels to reach high level steady state

→ Protection against vaginal acquisition of HIV
→ May need higher adherence levels for women

28 day lead out time (cf. PEP)
Cycling On or Off PrEP

- PrEP is not a lifelong drug-taking intervention
- PrEP should be used only if there is possible exposure to HIV
  - Risk levels expected to change
  - People will use PrEP for variety of reasons
    - Case example e.g. student / CSW
- People can cycle off PrEP
- This is NOT non-adherence
- Remember lead in and lead out times
Adherence and HIV protection

<table>
<thead>
<tr>
<th></th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
<th>HIV protection estimate with high adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP TDF/FTC arm</td>
<td>81%</td>
<td>75%</td>
<td>90% (tenofovir in blood)</td>
</tr>
<tr>
<td>TDF2</td>
<td>79%</td>
<td>62%</td>
<td>78% (prescription refill)</td>
</tr>
<tr>
<td>BTS</td>
<td>67%</td>
<td>49%</td>
<td>70% - 84% (tenofovir in blood / pill count)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
<td>92% (tenofovir in blood)</td>
</tr>
<tr>
<td>FEM-PrEP &amp; VOICE</td>
<td>&lt;30%</td>
<td>No HIV protection</td>
<td>N/A</td>
</tr>
</tbody>
</table>

When adherence was high, HIV protection is consistent and high

Stopping PrEP

- Positive HIV test
- Request of user
- Safety concerns
  - Creatinine clearance < 60 mL/min
- Risks outweigh benefits
Side Effects

Mild / Predictable / Manageable / No different from placebo in clinical trials

- Headache and malaise
- GI side effects
  - Nausea, weight loss
- Renal toxicity
  - Transient increases in serum creatinine
  - Decreased GFR
- Decreased BMD
  - Less cf HIV-infected individuals on TDF
  - No differences in fracture rates
PrEP and ARV Resistance

Resistance from PrEP was very rare, with only a small number who had acute infection at the time they were started on PrEP.

<table>
<thead>
<tr>
<th></th>
<th># of HIV seroconverters assigned PrEP with HIV resistance</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HIV infected after enrollment</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>0 / 48</td>
</tr>
<tr>
<td>iPrEx</td>
<td>0 / 36</td>
</tr>
<tr>
<td>TDF2</td>
<td>0 / 10</td>
</tr>
</tbody>
</table>

Resistance = K65R (TDF) or M184V/I (FTC) mutations
Risk compensation in PrEP clinical trials

In both iPrEx and Partners PrEP, unprotected sex and STIs were less common over time – suggesting synergy of ongoing risk-reduction counseling along with PrEP.

ACASI behavioural questionnaire
Will PrEP Increase STIs?

• STIs did not increase in PrEP clinical Trials

• Recent meta-analysis (Kajima et al, AIDS 2016, 30:2251–2252)
  - 25 times more likely to get gonorrhoea
  - 11 times more likely to get chlamydial infection
  - 45 times more likely to get syphilis

Increased KP in care
Increased screening and treatment
Hepatitis B and PrEP

- Risk of viral rebound in undiagnosed chronic HBV if PrEP stopped
- Screen for HBsAg and HBsAb
- HBV vaccination if HBsAg+/HBsAb-
- PrEP not contra-indicated in HBV infection
  - Require additional LFT monitoring
- Check LFT after stopping PrEP in chronic HBV
PrEP in Pregnancy and Breastfeeding

- PrEP use at conception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition[^1]

- Data directly related to the safety of PrEP use for a developing fetus are limited

- Potential risks and limited information should be discussed

- TDF and FTC are classified as FDA Pregnancy Category B medications[^2]

- APR: no evidence adverse outcomes in infants exposed to TDF/FTC ART

The SA PrEP Demo Project for MSM

Is NOT A Clinical Research Study

Is A Demonstration Project
Research Study vs. Demonstration Project

What’s the difference?

– We are not proving whether or not PrEP works

– We are not experimenting with a new way of using PrEP

– We are using current guidelines and real world settings

– Standard level of monitoring
SA PrEP Demo: Aims and Objectives

Our Primary Aim:

Assess feasibility of delivering *nurse-driven* PrEP for MSM at a *primary health care level* as part of *combination HIV prevention*
Secondary Aims:

- Assess the knowledge, acceptability and uptake of PrEP and other HIV prevention interventions among HIV-negative MSM
- Characterize the population of MSM who accept PrEP
- Assess retention in the study at 3, 6, 9 and 12 months.
- Monitor patterns of use of PrEP.
- Assess prevention method preferences and acceptability.
- Monitor side effects and safety of PrEP.
- Monitor the HIV status of MSM using PrEP and the emergence of drug resistance among those who acquire HIV.
- Monitor changes in self-reported sexual behaviour in MSM (including reduction or increase of risky sexual behaviour).
- Evaluate the acceptability of the use of cell phone (mHealth) technology to support MSM using PrEP.
- Assess adherence to PrEP medications using therapeutic drug level monitoring
Further Aim

• Leveraging lessons learned from the Demo project to inform design and implementation of PrEP programs in a range of African countries

• Anova Global Programmes

• EQUIP Consortium
Recruit 400 MSM at two sites (CT and Jhb) and maintain on PrEP over two years.
EJAF PrEP Demo: Implementation Lessons

Level of monitoring

- PrEP Demo Project Monitoring:
  - Two HIV neg tests two weeks apart
  - Baseline creatinine and baseline HBV screen
  - Creatinine at month 1, 2 and 3 monthly
  - HCT at month 1, 2 and 3 monthly
  - TDF blood levels at month 1, 2 and 3 monthly

→ Not feasible or necessary
  → No late creatinine elevation identified to date in demo project
  → Not all had positive TDF blood level at month 1 (>85%)

→ SA Clinician Society and NDOH Guidelines more than sufficient
EJAF PrEP Demo: Implementation Lessons

• Nurses are able to provide PrEP
• Required extensive training (3 days)
• Require detailed operational manuals and tools
• Require oversight and mentoring especially in the first month

• Able to educate and provide correct information
• Adherence assessment and support challenging
  – Designing an adherence support package that can be implemented by nurses in <15 minutes...
    • Adapt existing tools and using “next step counselling”
    • Train current lay counsellors
    • Leverage virtual support
Implementation Lessons

– Demand Creation - Community engagement and education activities of Anova were leveraged to create demand for the PrEP via the Demo project.
– Political will
– Civil society support (SANAC)
– Education and knowledge translation
– Health Marketing

Demand has been higher in Cape Town than our planned recruitment rate.
Funding PrEP

Putting in the plug
- Treatment
- Linkage to care
- Better programs
- Support etc

Turning off the tap
- UTT
- PEP
- PrEP
- Condoms and lube
- STI Tx

- Incidence is rising in MSM and other KPs
- All those who are positive will need lifelong (expensive) ART + monitoring
- Proud: PrEP for 13 MSM prevents 1 HIV infection
- IPERGAY: PrEP for 18 MSM prevents 1 HIV infection

→ Front load investment for long term benefits
→ Accurate investment case
Thank You

Meeting sponsors
Elton John Aids Foundation
Anova Health Institute

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#H4MTop2Btm #Wethebrave