PREPARING FOR PREP: FROM THEORY TO PRACTICE

Key Populations

Dr Oscar Radebe
Preparing for the End of HIV

• Until recently there has been exciting new advances in clinical research focusing on HIV prevention for high risk groups.

• New data on Prep studies have given researchers, scientists, politicians, clinicians to respond to the continent’s HIV epidemic on a global scale.
Preparing for the End of HIV

Theory
Scientific Research

Implementation Process

Practice
Prescribing Prep

Anova Health Institute
Why do We Need PrEP?

• 7400 new infections daily
• (600 in SA women daily)
• 15 Million in MLIC need ART
• 5.2 Million on ART by 2010
• For every 1 on ART another 2 infected.
Key Populations

Key populations are those most likely to be exposed to HIV or to transmit it.

- People who inject drugs
- Men who have sex with men (MSM)
- Commercial sex workers
- Transgender persons
- Prisoners
- Migrants
At Risk Populations in South Africa

- Young women 15 to 24 years old
- Young people not attending school; girls who drop out of school
- People from low socio-economic groups
- People living close to national roads and in informal settlements
- Uncircumcised men
- Persons with disabilities and mental disorders
- Sex workers and their clients
- People who abuse alcohol and illegal substances
- Men who have sex with men
- Transgender persons
Why Prioritise MSM in a Predominantly Heterosexual Epidemic?

MSM are at high risk of HIV transmission and acquisition

• Gay and bisexual men account for **63% of new infections** in the US, and African American men in this group account for more new infections than any other subgroup.

• **Increased HIV risk** compared to general population (OR 3.8 in Africa) [Baral et al 2007]

• Soweto Men’s Study MSM HIV prevalence = 20%
  • High rates of unprotected sex
  • High rates of sex with men and with women [Lane 2009]

• JEMS study, South Africa:
  MSM HIV prevalence = **43%** [HSRC 2009]
Global Prevalence of HIV in MSM

Gay men and other MSM shoulder a disproportionate burden of the HIV epidemic in virtually every country that reports reliable HIV surveillance data.

Key Population:
Relatively high HIV / STI Risk
AND
Relatively limited access to health services

HIV Prevalence

Overall Prevalence

- Cape Town: 22.3%
- Durban: 48.2%
- Johannesburg: 26.8%

Prevalence by Age

- Cape Town: 13.1% (18–24), 27.8% (25+)
- Durban: 39.3% (18–24), 71.1% (25+)
- Johannesburg: 17.1% (18–24), 36.7% (25+)
Marang Study Summary

- Largest MSM Surveillance Study in SA
- Some methodological problems
  - Sex workers in Cape Town
  - Students in Durban
  - Jhb possibly the most representative
- High HIV rates and sub-optimal HIV knowledge
- High degrees of bisexuality and concurrency
- Ongoing risky behaviours (e.g. alcohol, low condom use and repeat HIV testing)
- Experience of stigma from health providers
## Risk of HIV Transmission

<table>
<thead>
<tr>
<th>Type of contact</th>
<th>Transmission Risk (per 10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive anal intercourse</td>
<td>50</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>10</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>6.5</td>
</tr>
<tr>
<td>Insertive vaginal intercourse</td>
<td>5</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>1</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>0.5</td>
</tr>
</tbody>
</table>

UAI 20 times more risky than for vaginal
# Novel HIV Prevention Intervention Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime-boost HIV Vaccine (Thai RV144)</td>
<td>31% (1, 51)</td>
</tr>
<tr>
<td>1% tenofovir gel (Caprisa 004, Karim et al.)</td>
<td>39% (6, 60)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in MSM (iPrEx, Grant et al 2010)</td>
<td>44% (15, 63)</td>
</tr>
<tr>
<td>Medical male circumcision (MMC) (Orange Farm, Rakai, Kisumu)</td>
<td>57% (42, 68)</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in heterosexuals (TDF2, CDC)</td>
<td>63% (22, 83)*</td>
</tr>
<tr>
<td>TDF oral-PrEP in serodiscordant Partner (Partners PrEP)</td>
<td>62% (34, 78)*</td>
</tr>
<tr>
<td>TDF/FTC oral-PrEP in serodiscordant Partner (Partners PrEP)</td>
<td>73% (49, 85)*</td>
</tr>
<tr>
<td>Immediate ART for positive Partners (HPTN052)</td>
<td>96% (82, 99)*</td>
</tr>
</tbody>
</table>
## 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  
• (Maraviroc) |

- **Post Exposure prophylaxis (PEP)**
- **Treatment as Prevention (TasP)**
- **Combination Prevention with existing and new technologies**
Regulatory Approval for Daily TDF/FTC for Prevention in Host Countries

- TDF/FTC approved for prevention
  - United States

- Regulatory application filed for a prevention indication for TDF/FTC
  - Brazil
  - South Africa
  - Thailand

- Host countries with no regulatory application filed for prevention
  - Australia
  - Botswana
  - Canada
  - Ecuador
  - France
  - Germany
  - Kenya
  - Peru
  - Tanzania
  - Thailand
  - Uganda
  - United Kingdom
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>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%)</td>
</tr>
<tr>
<td><strong>TDF2 Study</strong></td>
<td>TDF/FTC</td>
<td>10</td>
<td>62% (16-83%)</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td></td>
<td></td>
<td></td>
</tr>
<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%)</td>
</tr>
<tr>
<td>IDUs</td>
<td></td>
<td></td>
<td>Choopanya et al. Lancet 2013</td>
</tr>
<tr>
<td>Thailand (n=2413)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>TDF/FTC</td>
<td>36</td>
<td>44% (15-63%)</td>
</tr>
<tr>
<td>MSM</td>
<td></td>
<td></td>
<td>Grant et al. N Engl J Med 2010</td>
</tr>
<tr>
<td>Brazil, Ecuador, Peru, South Africa, Thailand, US (n=2499)</td>
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</table>
iPrEx

- Using ART in negative patients on a long term basis to reduce infection risk if they are exposed to the virus
- Seems safe
- High adherence
- Global iPrEx Study

2499 MSM & TG: Truvada daily pill vs placebo → 44% reduction in HIV transmission (95% confidence interval, 15% to 63%; p = 0.005)
iPrEx Study Design & Results

- High Risk MSM
- Randomized 1:1 Daily Oral PREP
- FTC/TDF vs Placebo
- Followed Monthly on Drug for:
  - HIV seroconversion
  - Adverse Events
  - Metabolic Effects
  - HBV Flares among HBsAg+
  - Risk Behavior & STIs
  - Adherence
  - If Infected
    - Drug Resistance
    - Viral Load
    - CD4+ T Cell Count
HIV Infections

110 in total (100 incident, 10 at baseline)

At least on specimen with undetectable RNA for all incident seroconverters
Efficacy (MITT) 44% (15-63%)
Infection Numbers: 64 – 36 = 28 averted

Cumulative Probability of HIV Infection

- Placebo
- FTC/TDF

P = 0.0045

N =
Placebo: 1248 1194 1108 1005 852 674 546 444 370 258 137 60
FTC/TDF: 1251 1188 1097 988 848 693 558 447 367 267 147 65

New England Journal of Medicine, online Nov 23, 2010
PROUD Study, United Kingdom

MSM reporting UAI
Willing to take a pill now or in 12M

Randomize 500 HIV negative eligible MSM
(exclude if on treatment for hepB)

Risk reduction includes Truvada immediately
Risk reduction includes Truvada in 12 months

Follow 3 monthly for up to 24 months (+1m after start truvada)

Outcome: HIV incidence in immediate vs deferred arm
Among MSM in the UK, delivery of PrEP (compared to randomization to deferred access to PrEP) was so effective in preventing HIV that the deferred arm was discontinued early.

- At baseline, the population was at considerable HIV risk: in the year prior to enrollment 25% had gonorrhea, 10% had syphilis, 40% used PEP, & 74% had recreational drug use.
PROUD Study UK

- 545 MSM recruited to take Truvada PrEP
- Immediate or delayed initiation with 24 months follow up
- Study stopped early by DSMB as efficacy dictates that continuing would be unethical
- Efficacy = 86% (90% CI: 58 – 96%) P-value = 0.0002
- Number Needed to Treat = 13 (90% CI: 9 – 25)
- HIV incidence amongst gay men in England is much higher than what was thought.
- There was no difference in the rate of STIs other than HIV
- The use of Truvada for PrEP was safe and concerns about resistance are minimal.
- PrEP can be delivered as part as routine HIV reduction package
IPERGAY France

- RCT of Truvada versus placebo in 400 recruited high risk MSM
- Sex-based dosing (4 or more doses)
- Relative RR of HIV incidence was 86% (95% CI 40% to 99%, P = 0.002)
- Number needed to treat for 1 year to prevent 1 infection was 18.
- Also stopped early by DSMB because of high efficacy

- Very sexually active
- Did they not by default get almost daily dosing?
PrEP Works For High-risk People

Subgroup analyses of PrEP trials show that PrEP is effective for those at greatest HIV risk:

- **Heterosexuals (Partners PrEP)**  
  - Reporting sex without condoms  
  - With an STI  
  - With an HIV+ partner who has a high plasma HIV viral load  
  - Women <30 years of age

- **MSM (iPrEx)**  
  - Used cocaine  
  - Had syphilis  
  - Had anal sex with an HIV+ partner

- HIV protection estimates for these subgroups were often **higher** than for the trial population as a whole, because adherence was often greater for persons taking greater risks
PrEP Safety

• Rates of death, serious adverse events, and laboratory abnormalities (including renal dysfunction) were low and not significantly different between those taking PrEP and those taking placebo.

• PrEP was well tolerated.
  • Adverse effects occurred in minority of subjects.
  • GI adverse effects (e.g., nausea) more common in those receiving PrEP than placebo.
    • Occurred in < 10% and primarily during the first month only (PrEP “start up” symptoms).

• PrEP associated with a small change (~1%) in bone mineral density but no increased risk of fracture.
Adherence and HIV protection

<table>
<thead>
<tr>
<th>Study</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><strong>Partners PrEP</strong></td>
<td>81%</td>
<td>75%</td>
<td>90% (tenofovir in blood)</td>
</tr>
<tr>
<td><strong>TDF/FTC arm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TDF2</strong></td>
<td>79%</td>
<td>62%</td>
<td>78% (prescription refill)</td>
</tr>
<tr>
<td><strong>BTS</strong></td>
<td>67%</td>
<td>49%</td>
<td>70% - 84% (tenofovir in blood / pill count)</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>51%</td>
<td>44%</td>
<td>92% (tenofovir in blood)</td>
</tr>
<tr>
<td><strong>FEM-PrEP &amp; VOICE</strong></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

Oral PrEP Adherence

Longitudinal analysis of tenofovir detection in blood samples from persons on PrEP has shown that, for those who were taking PrEP, adherence was frequently consistent over time:

Partners PrEP Study, Baeten et al., Lancet ID 2014
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
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>
</thead>
<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.
Prescribing PrEP

- **Risk assessment**
  - PrEP is indicated for those at high HIV risk

- **Eligibility**
  - HIV negative, adequate renal function, HBV testing

- **Follow-up**
  - Prescribe for daily use, periodic HIV testing (3-monthly), counsel about risk-reduction

- **PrEP Cycling**
  - PrEP is not meant to be life-long = for periods of highest risk
Does anybody know if there is a prep doctor in Morgantown, West Virginia??

My six month PrEP anniversary tonight!

Are you a #PrEPWarrior? Get the shirt to prove it. Team Friendly Northeast Ohio needs one more order in the next 6 hours for the fifth batch of these shirts to go into production!

#PrEPWarrior
Show your PrEP pride and help fight the stigma.
teespring.com
Concerns About PrEP Delivery

• Who pays? (DOH keen but not committed)
• Bundling with other services (e.g., FP for women or HAST clinics, doctor or nurse driven)
• Community delivery to create demand and reduce burden on facilities?
• Minimise frequent visits and costs
• Risk screening for targeting (e.g. condomless anal receptive sex for MSM, risk score for serodiscordant couples)
• Adherence monitoring?
Prep implementation process in South Africa

**Preparation**
- Theory: Science & Research (Global and Local)
- Implementing partners providing Technical assistance

**Planning**
- NDOH buy in
- SANAC: LGBTI sector, all sectors/Political engagement

**Practice**
- Training & mentoring HCW on Prep
- Knowledge, acceptability of Prep as part of prevention of KP
- Constant supply of Prep
- Monitoring side effects of Prep

**Levels**
- **PROVINCIAL LEVEL**
- **DISTRICT & SUB-DISTRICT LEVEL**
- **FACILITY LEVEL**
- **COMMUNITY – CREATE DEMAND**
Health4Men Professional

http://www.health4men.co.za/health4men-professional/
Thank You

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Anova Health Institute

Contact:
– Oscar Radebe
– 011 581 5060
– radebe@anovahealth.co.za

www.anovahealth.co.za
www.health4men.co.za
info@health4men.co.za

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