Adherence to Daily Truvada

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Controlling HIV Epidemic

• UNAIDS published HIV prevention Roadmap in Oct 2017 targeting reduction of new infections by 75% (current 1.7 million in 2016 to 500 000 in 2020)

• New infections are concentrated among key populations AGYW, MSM and IDU

• Focus is on Few Pillars:
  - Combination prevention programs
  - behavioral change
  - VMMC and
  - PrEP by provision of daily Truvada
Global HIV Incidence, 2015

Highest disease burden in ECSA

Global Burden of Disease, Lancet HIV 2016
New HIV Infections in Southern and East Africa 2015

- South Africa: 340,000
- Mozambique: 88,000
- Uganda: 100,000
- Zimbabwe: 64,000
- Zambia: 56,000
- Kenya: 56,000
- United Republic of Tanzania: 62,000
- Rest of the region: 64,000

Source: UNAIDS 2016 estimates.
## Evidence of HIV Incidence in the Placebo Arm of Efficacy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>Age</th>
<th>HIV Incidence/100 py</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phambili + 503S</td>
<td>2007-2014</td>
<td>18-35 yrs</td>
<td>5.0</td>
</tr>
<tr>
<td>FACTS 001</td>
<td>2011-2014</td>
<td>18-30 yrs</td>
<td>4.0</td>
</tr>
<tr>
<td>VOICE</td>
<td>2009-2013</td>
<td>18-45 yrs</td>
<td>5.7</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>2012-2015</td>
<td>18-45 yrs</td>
<td>4.5</td>
</tr>
<tr>
<td>The Ring Study</td>
<td>2012-2015</td>
<td>18-45 yrs</td>
<td>6.1</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>2009-2012</td>
<td>18-35 yrs</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Average placebo incidence: 5.1/100 py**
Oral PrEP as another tool to control HIV epidemic

- Oral PrEP is effective when taken as prescribed
- Challenges of adherence among women < 25yr
- Fewer tables (2-3/week) are adequate for rectal protection in MSM compared to 6-7 tablets/week vaginal protection in women
- We need approaches that support PrEP adherence to optimize public health impact of this valuable HIV prevention method – HPTN 082 will provide valuable data
PrEP for HIV Prevention in Men Who Have Sex with Men. Grant et al, 2010

- Truvada had a 44% protection against HIV infection among MSM and transgender women who have sex with men

- Protection increased to 73% with adherence > 90% days covered by daily oral dose of Truvada
Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women.
Baeten et al, Aug 2012

- Truvada had a 75% protection against HIV infection

- TDF was detected in 82% of randomly selected participants

- July 16, 2012 FDA Approved TDF/FTC use as PrEP based on iPrEX and Partners PrEP results
WHO GUIDELINES

September 2015
Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV

2.2 Oral pre-exposure prophylaxis for preventing the acquisition of HIV infection

Recommendation

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).
### WHO Meta-Analysis: PrEP Effectiveness

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
<th>P-value (meta-regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10</td>
<td>0.49 (0.33-0.73)</td>
<td>0.001</td>
<td>--</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;70%)</td>
<td>3</td>
<td>0.30 (0.21-0.45)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate (41-70%)</td>
<td>2</td>
<td>0.55 (0.39-0.76)</td>
<td>&lt;0.0001</td>
<td>0.70</td>
</tr>
<tr>
<td>Low (≤40%)</td>
<td>2</td>
<td>0.95 (0.74-1.23)</td>
<td>0.70</td>
<td>ref</td>
</tr>
<tr>
<td>Mode of Acquisition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>4</td>
<td>0.34 (0.15-0.80)</td>
<td>0.01</td>
<td>0.36</td>
</tr>
<tr>
<td>Vaginal/penile</td>
<td>6</td>
<td>0.54 (0.32-0.90)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Age²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 24 years</td>
<td>3</td>
<td>0.71 (0.47-1.06)</td>
<td>0.09</td>
<td>0.29</td>
</tr>
<tr>
<td>≥25 years</td>
<td>3</td>
<td>0.45 (0.22-0.91)</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Fonner, AIDS 2016

- Prophylaxis of Truvada did not significantly reduce HIV transmission among the 2,120 women in the FEM-PrEP study.

- TDF was detected in only 6% of participants.
Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women, J Marazzo et al, Feb 2015

- Once Daily dosing of oral Truvada was not effective in preventing HIV among women
- Poor adherence to study drug was observed (TDF was detected in <30% of plasma samples from participants)
Effectiveness of tenofovir-based preventions increases with consistent use

Trials
- HPTN 052
- Partners PrEP (TDF/FTC)
- TDF2
- iPrEx
- CAPRISA (tenofovir gel, BAT-24 dosing)
- VOICE (tenofovir gel, daily dosing)
- FEM-PrEP
- VOICE (TDF/FTC)
- VOICE (TDF)

Adapted from Abdool Karim SS, 2011
Oral PrEP in women: heterogeneity of results

- Inadequate adherence at time of HIV risk exposure
- Others:
  - low HIV risk perception
  - lack of motivation to taking daily pill - concerns about side effects
  - HIV stigma associated with pill taking lack of partner/family support
- ? vaginal dysbiosis(vaginal microbiota not dominated by protective lactobacilli species)
Evidence that Efficacy daily Truvada is Not affected by Vaginal Micriobiota status

<table>
<thead>
<tr>
<th></th>
<th>Incidence per 100 person-years (control group)</th>
<th>Incidence per 100 person-years (Tenofovir group)</th>
<th>Tenofovir efficacy (95% CI)</th>
<th>Efficacy in lactobacilli-dominated microbiota (95% CI)</th>
<th>Efficacy in vaginal dysbiosis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PreP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (HIV)</td>
<td>2.8</td>
<td>0.9</td>
<td>71% (37-87)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Sub analysis(HIV)</td>
<td>2.8</td>
<td>0.9</td>
<td>70% (45-84)</td>
<td>77%(43to 90)</td>
<td>73% (6-92)</td>
</tr>
<tr>
<td><strong>CAPRISA 004</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (HIV)</td>
<td>9.1</td>
<td>5.6</td>
<td>39% (6-60)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Subanalysis(HIV)</td>
<td>7.3</td>
<td>4.2</td>
<td>57%(36-96)</td>
<td>61% (11to 84)</td>
<td>18% (-77 to 63)</td>
</tr>
</tbody>
</table>

Renee Heffron et al Lancet HIV, July 2017
How much drug is required to achieve adequate protection from HIV?

- Must achieve adequate concentrations and activity at all vulnerable sites of infection: *Vagina, cervix, rectum*
- Women require 6 or 7 daily oral Truvada/week to be adequately protected from HIV infection (Donnell D, JAIDS 2014)
- MSM/TGF are protected with 4 or 5 tablets/week (Grant, JID 2017)
The Right Concentration

Colorectal Tissue

Female Genital Tract

Emtricitabine Tenofovir-DF Truvada

% Achieving TZMbl EC95 Target Ratio

Doses/Week

Emtricitabine Tenofovir-DF Truvada

% Achieving EC95 Target Ratio

Doses/Week

iPrEx OLE= ↓ HIV incidence by 90% with 2 Truvada doses per week

Partners PrEP= ↓ HIV incidence by 90% with 7 Truvada doses per week

Cottrell et al R4P 2014
The Right Concentration:

**TFVdp In Mucosal Tissues**

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Formulation PK Profiles Compared

- Upper Target (safety)
- Lower Target (efficacy)
- SC or IM Injection
- Implantable & IVR
- Oral Dosing

Courtesy Ariane van der Straten
A Model of HIV Entry Into Female Genital Tract

Epithelial Disruption that allows viral entry
Right time, right place, correct dose to block infection

Hassey, Nature 2010
On Demand PrEP

- Standard oral PrEP is one tablet Truvada/day
- Time Driven: 1 tablet/2x week with a post sex boost
- Event Driven: 1 tablet pre-sex and 1 tablet post sex
- N:B no more than 2 tablets daily or 7 tablets/week
Coverage of Sex Events – Women in Cape Town

Reasons of missed post-sex doses: Not at home, concern about disclosing PrEP use to partner, pills not with me, change in routine, not in the mood to worry.

Sex event defined as vaginal or anal intercourse
Time/Daily $p = 0.0007$, Event/Daily $p < 0.0001$, Time/Event $p = 0.43$

Bekker IAS2015, Vancouver, 2015
Adherence and efficacy in clinical trials, open-label extensions and demonstration projects

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Adherence</th>
<th>Efficacy /Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men who have sex with men (multiple geographic regions)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPrEx</td>
<td>51% by drug detection</td>
<td>44%</td>
</tr>
<tr>
<td>iPrEx OLE</td>
<td>71% by drug detection</td>
<td>49%</td>
</tr>
<tr>
<td>PROUD</td>
<td>86% of days participants would be taking PrEP if everyone’s adherence were 100%</td>
<td>86%</td>
</tr>
<tr>
<td>IPERGAY</td>
<td>Median 16 pills/month by pill count; 43% optimal use, 25% suboptimal use by ACASI</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Serodiscordant couples in Africa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>82% by drug detection</td>
<td>TDF: 67% FTC/TDF: 75%</td>
</tr>
<tr>
<td>Partners Demonstration Project</td>
<td>86% by drug detection</td>
<td>96%</td>
</tr>
</tbody>
</table>

Adapted from Haberer et al, Curr Opin HIV AIDS, 2017
### Incidence Rates for Curable STIs in VOICE study

<table>
<thead>
<tr>
<th>Baseline Risk Factor</th>
<th>Chlamydia Incidence (95% CI)</th>
<th>Gonorrhoea Incidence (95% CI)</th>
<th>Syphilis Incidence (95% CI)</th>
<th>Trichomoniasis Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with Follow-up STI results</td>
<td>4790</td>
<td>4790</td>
<td>4781</td>
<td>4577</td>
</tr>
<tr>
<td>Person Years at Risk</td>
<td>5543.7</td>
<td>5543.7</td>
<td>5533.0</td>
<td>5230.5</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>15.9</td>
<td>3.8</td>
<td>0.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Uganda</td>
<td>9.7</td>
<td>5.9</td>
<td>4.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>4.5</td>
<td>1.1</td>
<td>0.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21 years</td>
<td>26.8</td>
<td>6.8</td>
<td>1.0</td>
<td>7.9</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>3.7</td>
<td>1.5</td>
<td>1.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>16.4</td>
<td>4.1</td>
<td>0.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12.7</td>
<td>2.9</td>
<td>0.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Chirendje ZM, STD, 2017
Current Landscape of oral PrEP

• Several Ongoing demonstration projects targeting FSW, AGYW, MSM (SA, Kenya, Zim etc )
• Some Gaps still remain:
  - Strong advocacy to provide PrEP to high risk populations urgently: Sinead Delany-Moretlwe
  - Need more behavioral research to understand barriers and facilitators of adherence in women
  - Determine efficacy of Intermittent PrEP in women
Summary

- PrEP has tremendous public health benefit through potential significant reduction HIV incidence at risk population
- Some women may choose daily oral Truvada, others vaginal ring, in future IM as their choice of HIV prevention method
- Its all about CHOICES as we have seen successfully in contraceptive method mix
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THANK YOU