Combination prevention: Public health and human rights imperatives

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Outline

• The epidemic and response
• What is combination prevention?
• The role of ARVs in prevention: TasP and PrEP
• Implementation and research challenges
• WHO’s approach and guidance
• Human rights and ethical considerations
Still a long way to go to reach 15 million on ART

Estimated gap: CD4 cell count ≤ 350/mm³ but not on ART

Patients receiving ART: 47%

WHO, 2011
## Major inequities persist in access to treatment and prevention

<table>
<thead>
<tr>
<th>PROPORTION OF PEOPLE WHO INJECT DRUGS RECEIVING ART IN LOW AND MIDDLE INCOME COUNTRIES IN EECA REGION 2002-10</th>
<th>2002</th>
<th>2005</th>
<th>2006</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of reporting countries among 26 low- and middle-income countries surveyed</td>
<td>17</td>
<td>21</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>HIV cases among people who inject drugs (% among cumulative reported HIV cases with a known transmission route)</td>
<td>46,052 (71%)</td>
<td>221,849 (77%)</td>
<td>249,982 (77%)</td>
<td>185,565 (62%)</td>
</tr>
<tr>
<td>People who inject drugs receiving antiretroviral therapy (% among the total reported people receiving ART with a known route of transmission)</td>
<td>130 (20%)</td>
<td>4,670 (26%)</td>
<td>5,275 (26%)</td>
<td>7,646 (22%)</td>
</tr>
</tbody>
</table>

Number of people with access to antiretroviral therapy and dying from AIDS-related causes, low- and middle-income countries, 2000–2010
ART coverage significantly decreased individual risk

- AfricaCentre longitudinal surveillance cohort with community and individual data
- Between 2004 and 2011, 1395 HIV seroconversions and over 53,042 person-years of observation (crude HIV incidence rate of 2.63 (95% C.I. 2.50 to 2.77) per 100 person-years
- Every percentage point increase in ART coverage among all HIV+ adults in a community, was associated with a 1.7% decline in the hazard of HIV acquisition ($p < 0.001$)

Maps showing the estimated percentage of HIV+ adults (≥15 years of age) on ART across the Africa Centre’s surveillance area (2004 to 2011)
Knowledge of HIV status remains insufficient

Percentage of women and men who received an HIV test and test results in last 12 months, 2003–2010 (WHO/UNAIDS)
Effective prevention interventions have not been brought to scale

**Goal:**

~ 20 million by 2016

**Total MCs through 2011:**

~1.35 million, 6.5% of target

Male circumcisions performed annually in 14 priority countries in eastern and southern Africa

Source: WHO
Treatment and prevention gap.....

End 2010:

• 6.65 million were receiving ART
• ~7.4 (53%) million in need (CD4 <350)
• ~2.7 million new infections annually

• **Bottom line:**
  – Everyone HIV+ will need ART to survive
  – For every one person placed on treatment around 2.5 are infected
  – Need for sustained efforts combined with innovative approaches to decrease prevention gap
Outline

• Current state of the epidemic and response
• **What is combination prevention?**
• ARV-based prevention: TasP, PrEP
• Implementation and research challenges
• WHO’s approach and guidance
• Costs, human rights and ethical considerations
What is combination prevention?

• Mix of biomedical, behavioral, and structural interventions
• Targets the prevention needs of different populations based upon epidemiological and demographic data
• Includes non-ARV based prevention (condoms, male circumcision, behavior change, etc.) as well as maximizing new prevention opportunities of ARVs
Combination prevention involves multiple disciplines and approaches.
A combination of interventions has more impact than the interventions delivered alone.

Source: Tim Hallett, personal communication
Opportunities for biomedical interventions

Prior to exposure
- Male circumcision
- PMTCT
- Harm reduction for IDU
- Oral PrEP (daily TDF or TDF/FTC)
- Topical PrEP (gels or intra-vaginal rings (microbicides)
- Preventive HIV vaccine

Exposure (pre-coital/coital)
- Oral intermittent PrEP
- Coitally dependent topical PrEP (microbicides)

Exposure (post-injury/-coital)
- Oral post exposure prophylaxis (PEP)

After infection
- ART ≤ 350
- ART ≤ 500
- “Incremental” TasP (SD couples, pregnant women, key populations, TB)
- “Test and Treat”

All have important behavioral components

Adapted from R. Shattock 2011
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New evidence = rapidly changing field
### Biomedical HIV prevention trials

<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>ART for prevention (HPTN052)</td>
<td>96% (82, 99)*</td>
</tr>
</tbody>
</table>

Adapted from Abdool Karim SS, et al. Lancet. 2011
More evidence on the way: 2011 ART for prevention studies

Current HIV Research, 2011, 9, 355-366
HPTN 052: HIV transmissions

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28

Immediate Arm: 1

Delayed Arm: 27

96% reduction in HIV transmission

p < 0.001
Early ART also reduces risk of TB transmission...

<table>
<thead>
<tr>
<th>ART</th>
<th>Control</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB cases</td>
<td>PY at risk</td>
<td>TB cases</td>
</tr>
<tr>
<td>All baseline CD4 counts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badri (2002)</td>
<td>9</td>
<td>375.1</td>
</tr>
<tr>
<td>Cohen (2011)</td>
<td>17</td>
<td>1661.9</td>
</tr>
<tr>
<td>Golub (2007)</td>
<td>221</td>
<td>11627</td>
</tr>
<tr>
<td>Golub (2009)</td>
<td>44</td>
<td>952</td>
</tr>
<tr>
<td>Jerene (2006)</td>
<td>6</td>
<td>162.6</td>
</tr>
<tr>
<td>Lannoy (2008)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miranda (2007)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Samandari (2011)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Santoro-Lopes (2002)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Severe (2010)</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Zhou (2009)</td>
<td>57</td>
<td>5186</td>
</tr>
</tbody>
</table>

Effect: Z = 9.19, p < 0.001; Heterogeneity: I² = 31% (22% - 44%), p = 0.151

Suthar et al 2012, PlosMed, in press

Providing ART for PLHIV prevents TB up to 65%
What is PrEP?

• Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by uninfected people to avoid HIV acquisition
  – Trials have typically evaluated either oral TDF/FTC or TDF alone; studies of other drugs are starting
  – Topical TDF has also been tried as vaginal microbicide
  – Four trials have completed; one was stopped
Demonstrated efficacy of oral PrEP in serodiscordant couples, and men who have sex with men

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Intention to treat&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2499</td>
<td>44% (15-63%)</td>
</tr>
<tr>
<td></td>
<td><strong>Partners</strong></td>
<td><strong>4758</strong> couples</td>
<td><strong>All 75%</strong> (55-87%)</td>
</tr>
<tr>
<td>PrEP</td>
<td>Heterosexual HIV discordant couples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexual men and women</td>
<td></td>
<td><strong>All 62%</strong> (21-83%)</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>Heterosexual women</td>
<td>2056</td>
<td><strong>NS</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> restricted to trials of oral TDF/FTC only as this guidance does not address use of other antiretroviral regimens

<sup>b</sup> excluding only those enrolled participants later found to be infected at randomization and those with no follow-up visit/HIV test

<sup>c</sup> NS= finding not statistically significant
Partners’ PrEP: PrEP among heterosexual men and women

4758 couples, in which HIV+ partner not yet eligible for ART, randomized 1:1:1 to daily oral TDF or FTC/TDF vs placebo

82 HIV infections

17 TDF
13 FTC/TDF
52 placebo

Reduction in HIV acquisition:
TDF = 67% (95% CI 44%-81%)
FTC/TDF = 75% (95% CI 55%-87%)
Combining TasP and PrEP?
HPTN 052: HIV transmissions

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28
- Immediate Arm: 1
- Delayed Arm: 27

Unlinked or TBD Transmissions: 11

Up to 30% of new infections in couples occur outside the primary relationship (Campbell et al PLoS One 2011; Hughes et al. J Infect Dis 2011)

p < 0.001
PrEP as a “niche” intervention? e.g., as bridge to early ART in couples

Recruit higher-risk HIV-1 serodiscordant couples

Offer/refer for ART for HIV-1+ partners according to current national guidelines

Accepts ART
- Offer PrEP for 6 months to HIV-1- partner
- Continue to counsel HIV-1+ partner on ART

Declines ART
- Offer PrEP to HIV-1- partner

Not yet eligible for ART
- Offer PrEP to HIV-1- partner
- Follow HIV-1+ partner and refer for ART when eligible

Source: Baeten & Celum
Outline

• Current state of the epidemic and response
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• ARV-based prevention: TasP, PrEP
• Implementation and research challenges
• WHO’s approach and guidance
• Costs, human rights and ethical considerations
Challenges for implementing TasP / PrEP

• How to optimally combine interventions to achieve best health and prevention impact?
• Can we extrapolate the study results to other groups?
• How to balance benefits and risks? e.g. health and prevention gains vs possible long term effects such as toxicity and resistance
• What threshold of early treatment is needed to achieve viral suppression for population level impact?
Challenges (contd.)

• Using the same drugs in HIV + and in HIV – is problematic. Should drugs can be “reserved” for PrEP? Which ones?

• Repeat testing required for PrEP?

• How to optimize adherence?

• Is a combination approach needed in highly adherent ART users / those with maximum viral suppression?
## Examples of planned implementation research in Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Thailand</th>
<th>Indonesia</th>
<th>Cambodia</th>
<th>Vietnam</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>MSM</td>
<td>MSM FSW</td>
<td>All SD couples FSW ++</td>
<td>All SD couples IDU++</td>
<td>All SD couples MSM</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>To guide future national policy &amp; strategy on earlier ART for MSM and/or FSW</td>
<td>To guide future national policy &amp; strategy on earlier ART for SD couples, FSWs, MSM and/or people who inject drugs</td>
<td>Improve existing policy &amp; strategy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary objective</strong></td>
<td>Feasibility of repeat testing, immediate ART</td>
<td>New HTC approaches &amp; uptake Adherence immediate ART</td>
<td>Feasibility of identifying partner (network approach), early ART, repeat testing</td>
<td>Feasibility improved implementation cascade from KAP HTC to couple FU</td>
<td>Programme strengthening</td>
</tr>
<tr>
<td><strong>ART criteria</strong></td>
<td>Irrespective CD4 TDF-based</td>
<td>Irrespective CD4 TDF-based</td>
<td>Irrespective CD4</td>
<td>Irrespective CD4 TDF-based (possibly FDC)</td>
<td>Irrespective CD4 TDF</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>Outreach internet peers</td>
<td>NGO and public services for MSM and FSW</td>
<td>VCCT/TI sites Pre ART</td>
<td>HTC Methadone sites Pre ART</td>
<td>HTC Pre ART</td>
</tr>
</tbody>
</table>
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WHO ART guidance: 2012/13

- 2012 – ART as prevention in sero-discordant couples
- 2012 – Programmatic update on operational aspects of ARVs for PMTCT (A, B, B+)
- 2012 – Treatment as Prevention programmatic update (9 June 2012)
- 2012 – PrEP rapid advice (July, IAC)
- 2013 WHO consolidated guidance will combine all ARV related guidance for the first time, including use for treatment and prevention
WHO guidance on ART for treatment and prevention in serodiscordant couples

- First formal WHO TasP guidance
- Strongly recommends couples counseling
- Strong recommendation for offering ART in a serodiscordant couple irrespective of CD4 count
- Operational issues are also addressed
### ART Initiation for Serodiscordant Couples

<table>
<thead>
<tr>
<th>ART INITIATION CRITERIA</th>
<th>NUMBER OF COUNTRIES</th>
<th>COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irrespective of CD4 count</td>
<td>8</td>
<td>United States, Canada, Zambia, Europe, Venezuela Argentina (&gt;500) Nigeria (&gt;350), Thailand*(&gt;350)</td>
</tr>
<tr>
<td>ART irrespective of CD4 count in practice</td>
<td>2</td>
<td>China, Rwanda</td>
</tr>
<tr>
<td>350 - 500</td>
<td>1</td>
<td>Mexico</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>Malawi – Lifelong ART irrespective of CD4 count for pregnant women, rationale includes improving health of mother, preventing vertical transmission and preventing of HIV transmission in discordant relationships</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burundi – ART irrespective of CD4 count if partners of HIV-negative pregnant women are HIV-positive</td>
</tr>
</tbody>
</table>

* Expert consultation is recommended
Outlines WHO’s strategy for TasP:

1. Intensify and scale up ART for those with CD4 < 350

2. Identify additional opportunities for TasP (“incremental approach”) in specific populations
   - Recommended for serodiscordant couples
   - Move towards offering ART to all pregnant women (option B+)
   - Explore feasibility in key affected populations
Ethical and human rights issues

- How to prioritize use of ART in absence of universal access: First come, first served? Treat the sickest? Use for TasP? Provide drugs to uninfected persons (PreP)?
  - WHO to hold consultation on ethics of ARV use in the absence of universal access

- Ensuring that testing and treatment remain voluntary, informed, are not coercive and do not inappropriately “target” or stigmatize

- Promoting community-based and driven models of service delivery
*In conclusion...*

The strategic use of ARVs is a key element of combination HIV prevention with a view to ending the HIV epidemic.

Imperatives are to:

- Accelerate and scale-up treatment programmes (CD4 below 350)
- Proactively optimize prevention benefits of ART (TasP)
- Explore possible use of Prep as niche interventions (demonstration projects in countries)
- Scale up other interventions of known effectiveness, including male circumcision, condom use, behavioural
- Address important ethical and human rights issues in programme design and planning – requires close community participation

WHO will issue consolidated ARV guidance (2013) and support implementation research
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