The HIV Prevention Toolbox: More Tools Needed

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Today’s generation of young people is the largest in human history.

UNFPA, 2013

78 million people infected, 39 million people dead

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Worldwide 37m living with HIV today

SSA has 70% of this burden, in most SSA countries close to 60% of people living with HIV are women
Global Picture vrs SSA HIV burden

Sub-Saharan Africa as Share of Global HIV Prevalence, Incidence, and Deaths Compared to Share of World Population, 2013

- **World Population**: Total = 7.1 billion
  - Sub-Saharan Africa: 13%
  - All Other Regions: 87%
- **People Living with HIV**: Total = 35.0 million
  - Sub-Saharan Africa: 71%
  - All Other Regions: 29%
- **New HIV Infections**: Total = 2.1 million
  - Sub-Saharan Africa: 71%
  - All Other Regions: 29%
- **AIDS Deaths**: Total = 1.5 million
  - Sub-Saharan Africa: 73%
  - All Other Regions: 27%

## Burden of HIV in SSA AMP Countries

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>300 000</td>
<td>23.4</td>
<td>160 000</td>
<td>15 000</td>
<td>4 200</td>
</tr>
<tr>
<td>Kenya</td>
<td>1,600 000</td>
<td>6.2</td>
<td>800 000</td>
<td>220 000</td>
<td>62 000</td>
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<tr>
<td>Malawi</td>
<td>910 000</td>
<td>10.0</td>
<td>430 000</td>
<td>170 000</td>
<td>44 000</td>
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<tr>
<td>Mozambique</td>
<td>1,400 000</td>
<td>11.3</td>
<td>750 000</td>
<td>200 000</td>
<td>74 000</td>
</tr>
<tr>
<td>SA</td>
<td>5,600 000</td>
<td>17.3</td>
<td>2,900 000</td>
<td>460 000</td>
<td>270 000</td>
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<tr>
<td>Tanzania</td>
<td>1,800 000</td>
<td>5.6</td>
<td>760 000</td>
<td>230 000</td>
<td>84 000</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>1,200 000</td>
<td>14.9</td>
<td>600 000</td>
<td>200 000</td>
<td>58 000</td>
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New HIV infections in sub-Saharan Africa, 2013

- **23%** South Africa
- **15%** Nigeria
- **10%** Uganda
- **8%** Mozambique
- **5%** United Republic of Tanzania (the)
- **5%** Zimbabwe
- **4%** Zambia
- **3%** Cameroon
- **2%** Malawi
- **2%** Democratic Republic of the Congo (the)
- **1%** Côte d'Ivoire
- **1%** Ethiopia
- **2%** Angola
- **9%** Rest of the region
Annual New HIV Infections in 2013
About half of all new HIV infections in 2014 occurred in 8 ESA countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of new HIV infections in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>340 000</td>
</tr>
<tr>
<td>Uganda</td>
<td>100 000</td>
</tr>
<tr>
<td>Mozambique</td>
<td>88 000</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>64 000</td>
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<tr>
<td>UR Tanzania</td>
<td>62 000</td>
</tr>
<tr>
<td>Kenya</td>
<td>56 000</td>
</tr>
<tr>
<td>Zambia</td>
<td>56 000</td>
</tr>
<tr>
<td>Malawi</td>
<td>42 000</td>
</tr>
</tbody>
</table>

60% new infections occurred in women
Over all Decline of 32% between 2005-2013
HIV in SSA: the Epidemic Among Women

New HIV infections in sub-Saharan Africa, by age and sex, 2013

- In 2013, of the 24.7 million people HIV infected in SSA >50% were women
- Young women are twice as likely to be infected as young men
- Women have fewer HIV prevention options than men

Source: UNAIDS 2013 estimates

UNAIDS Gap Report, 2014
Eastern and Southern Africa: New HIV infections among young people aged 15-24 years

Pleased to notice a decline but burden of disease twice as high in F than M
Controlling HIV Epidemic

• Despite widespread promotion of behavioral modification that include abstinence, correct and persistent use of M or F condom the HIV epidemic continuous to cause enormous burden in SSA particularly in evolving key populations

• A new HIV prevention tool kit that has effective biomedical interventions will help control the epidemic
Randomised controlled trials of medical male circumcision to reduce HIV infection

Rakai, Uganda
Gray et. al. (2007) Lancet; 657 – 66%

Kisumu, Kenya
Bailey et. al. (2007) Lancet; 643 – 56%

Orange Farm, South Africa
Auvert et. al. (2005) PLoS Med; e298 – 61%
Treating HIV-infected People with Antiretrovirals Significantly Reduces Transmission to Partners

Achieved Complete and Sustained Virological Suppression

96% reduction in HIV transmission when ART started in HIV-infected partner at CD4 count of 350-550 compared to <250
FDA Panel Recommends Approval of Drug to Prevent HIV Infection

By Brian Vastag

For the first time in the 30-year battle against the HIV epidemic, a panel of experts has recommended that the Food and Drug Administration approve a drug to give to healthy people to protect against the infection.
What is the Ideal drug for PrEP?

- Drug must be safe, potent, easy to use and acceptable
- High barrier to resistance
  - Ideally, no effect on future ART options
- Adequate concentrations and activity at all vulnerable sites of infection
  - Vagina, cervix, rectum, bloodstream
- Available & affordable
Controlling HIV Epidemic

• Despite widespread promotion of behavioral modification that include abstinence, correct and persistent use of M or F condom the spread of new HIV infections continues mostly in high risk populations.

• High risk populations: discordant couples, MSM, sex workers, cross-border traders, truck drivers, refugees
Biomedical Interventions: Focusing on HIV prevention options for women

- What have we done to combat HIV prevention in women?
- First attempt was development of a microbicide since 1992 has been long, tortuous, with at least 41,000 women from ESA volunteering in these trials
- For a product to be effective, it must get to right place, right time, right dose, high barrier to develop resistance
- Available & affordable
A Model of HIV Entry Into Female Genital Tract

Epithelial Disruption that allows viral entry

Hassey, Nature 2010
Progression in the product pipeline
In past 6 yrs we have seen pivotal, proof of concept PrEP trials

- **Oral pre-exposure prophylaxis (PrEP)**
  Involves taking an ARV tablet by mouth Truvada (combination of tenofovir and emtricitabine) tested in 6 studies

- **Vaginal topical products**
  1% tenofovir gel tested in CAPRISA 004, VOICE, FACTS

- Vaginal ring containing dapavirine tested in ASPIRE and ongoing RING Study
End of TFV gel development for HIV prevention in women?

- At CROI March 2013, VOICE study reported no protection of HIV infection among women using TFV gel as daily regimen

- At CROI Feb 2015, FACTS 001 reported no protection of HIV infection among women using TFV gel BAT regimen used in CAPRISA

- Clearly tenofovir gel was not acceptable for these women as evidenced by low levels (<25%) of detectable tenofovir in swabs collected from genital tract
Conclusions

• Incidence of HIV substantially higher than anticipated
• No study drug significantly reduced risk of HIV acquisition
• Adherence to study products was low, especially among younger, unmarried women
• Results consistent with Fem-PrEP
  • Consider PrEP agents / delivery systems that are long acting and require minimal daily adherence
• Understanding HIV risk perception and biomedical, social and cultural determinants of adherence in this high-risk population urgently needed
What was Impact of VOICE Study

• VOICE was “Game-changer” – removed any reliance on self-reported adherence

• Surprisingly, HIV risk perception was clearly not their greatest concern, particularly in young women < 25yrs

• Objective measurements (PK) of adherence are now obtained during the trial and results discussed with participants as unblinded data across CRS
On the Horizon (ASPIRE and RING Study Results are encouraging

- Phase III safety and effectiveness trial of a vaginal ring containing the ARV dapivirine, replaced every 4 weeks.
  - high level of protection (56% in ASPIRE) women > 21yrs
- Lower adherence and no protection women 18-21 yrs
Effectiveness of tenofovir-based prevention increases with consistent use

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

- To overcome adherence changes observed in many PrEP trials, new ARV based 8 week IM formulations are early testing phases

- LA form of oral Rilpivirine (TMC278 LA) an NNRTI and GSK126744 LA an Intergrase Inhibitor
HPTN 076

- To evaluate the safety and acceptability of the injectable product, TMC278 LA, in healthy, 132 HIV-uninfected women.
- Enrolled 136 women (Harare 52, Capetown 48, and US 36)
- Results expected by 2017
CABOTEGRAVIR: GSK126744 Long Acting (744LA

Favorable attributes for PrEP:

- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

Muller et al, European Journal of Pharmaceutics and Biopharmaceutics, 2011
Spreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012
Long Acting PrEP: Concerns

• Tolerance of two injections (4 ml)
• Safety, as drug “removal” is not possible
• Managing discontinuation (the tail)
  - subtherapeutic levels of ART threaten resistance if HIV is acquired

Long Acting PrEP Opportunity: WOMEN
Modest (31%) protection vaccine recipients in Thai study correlates with neutralizing Abs to a conserved region Region of HIV Envelope
Neutralizing Antibody Epitopes on Native Trimer (since 2009)

gp41 MPER:
2F5, 4E10
10e8

Trimer (gp120/41)
8ANC195
PGT151
35022

V1V2 Glycan:
PG6, PG16, CH01-04
PGT141-45
CAP256-VRC26

N332 Glycan Supersite:
PGT121, PGT128
10-1074

CD4 Binding Site:
VRC01, PG04, CH31
3BNC117, 12A12
CH103, VRC07

HIV-1 viral spike

A phase 2b study will test if passive infusions of monoclonal Ab will prevent HIV infection

Highly selected donors
The HVTN 703/HPTN 081 AMP Study: Filling the Gap

AMP = Antibody Mediated Prevention

This is the idea of using an antibody made by scientists and giving it to people directly, i.e. using an intravenous (IV) infusion, to prevent HIV infections.
HIV prevention Methods in Toolbox

- Education and behavior modification
- Condoms, and other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes, i.e. needle exchange programs
- Interruption of mother-to-child transmission
- Circumcision for female-to-male transmission
- HIV/STI Testing
- Antiretroviral treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)*
- Topical microbicides†
- Intra vaginal rings†
- Vaccination†

*Daily Truvada®; alternate regimens still in research  †Still in research

With thanks to Carl Dieffenbach & Jeff Schouten

HPTN
HIV Prevention Trials Network

HIV VACCINE TRIALS NETWORK
Scientists need to test novel prevention modalities to fill the prevention gap.