State of ART: Prevention of HIV in Young Women

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Overview

- High burden of HIV in young women in Africa
- HIV prevention technologies for women
  - Tenofovir Pre-Exposure Prophylaxis (PrEP)
- Why the high HIV risk in young women in Africa?
  - Behaviour and Biology
  - Genital inflammation as a key risk factor (IL-17 biomarker)
  - Higher HIV risk = more low infectivity viruses transmitted
  - Impact of the vaginal microbiome on HIV risk
  - What is causing inflammation?
- What does the future hold?
  - Long acting slow release products – implants, injectables, tablets
  - Combination bnAbs as passive immunisation
  - Vaccines, MPTs
- Conclusion
Each day, there are about 5,000 new HIV infections globally. 54% in Eastern and Southern Africa. ± 1,000 are in adolescent girls and young women.
Globally we are lagging in HIV prevention…

16% reduction in new infections 2013 - 2017

New HIV infections among adults (15+)

1.9 million in 2013

1.6 million in 2017

500,000 (2020 Target)

Source: Adapted from UNAIDS Fast-track Report
3 major challenges – EECA, vulnerable sub-groups (YBMSM in USA) & youth bulge in Africa

Increasing new HIV infections in Eastern Europe and central Asia

High HIV rates in vulnerable sub-groups such as young black MSM in US

The youth bulge in Africa is increasing the number of adolescents and rates in young women are still high. Hence, more HIV infections in young people in southern Africa

Disproportionately high burden of HIV in young women in Sub-Saharan Africa

Young women 15-24 years have up to 6 times more HIV compared to their male peers
HIV remains high in hyper-epidemics
How to slow the high HIV rates in women?

Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study


Community-based house-to-house HIV prevalence survey  N = 9812

Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study


<table>
<thead>
<tr>
<th>Women age group</th>
<th>Age difference with male partners</th>
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<tbody>
<tr>
<td>16-20</td>
<td>11.5 yrs</td>
</tr>
<tr>
<td>21-25</td>
<td>7.0 yrs</td>
</tr>
<tr>
<td>26-30</td>
<td>1.5 yrs</td>
</tr>
<tr>
<td>31-35</td>
<td>1.7 yrs</td>
</tr>
<tr>
<td>36-40</td>
<td>0.7 yrs</td>
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**Infection Pathway**

- Very young women acquire HIV from men, on average, 8 years older.
- High HIV incidence men mean age 27 years (range 23-35 years).
- Men and women > 24 years usually acquire HIV from similarly aged partners.
- High HIV risk women mean age 18 years (range 16-23 years).
- High HIV prevalence women mean age 26 years (range 24-29 years).
- Pathways
- Time: Cycle repeats itself
Preventing the sexual spread of HIV:

- Existing accepted proven HIV prevention strategies - ABCCC:
  - Abstinence
  - Behaviour (Be faithful)
  - Condoms (Male & Female)
  - Circumcision (Medical Male)
  - Counselling and Testing

Which of these are prevention tools for young women in Africa?
Long road to WHO 2015 oral PrEP guideline

Oral PrEP: 7 years - from 1st RCT → increasing implementation

Fem-PrEP (SA, Kenya, Tanzania)
PrEP no↓ HIV (†)

US FDA approval of
TDF/FTC for PrEP

Proud (UK)
PrEP 86 % ↓
HIV (MSM)

SA National
PrEP program

EMA approval of TDF/FTC for
PrEP

iPrEX (multi site)
PrEP 44% ↓
HIV (MSM)

Voice
PrEP & gel no↓
HIV (†)

PrEP 44% ↓
HIV (MSM)

BBK TDF
PrEP 49%↓ HIV
(PWID)

iPerGay (France)
PrEP 86% ↓
HIV (MSM)

Numerous demo projects and OLE

First WHO PrEP GL
for demo projects
MSM, TG & SDC

WHO PrEP KP rec
for PrEP for KP (except
PWID) (as part of KP GL)

WHO enabling PrEP rec
for all at ‘substantial HIV risk
PWID (as part of KP GL)

WHO PrEP implementation
tool

WHO PrEP issues
for adolescents

WHO update
on PrEP use
during pregnancy &
BF

CAPRISA 004
Tenofovir
gel (39% ↓
HIV †)

BostwanaTDF2
PrEP 62% ↓
HIV († & †)

WHO PrEP KP rec
for PrEP for KP (except
PWID) (as part of KP GL)

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World Health
Organization
Status of adoption of WHO’s oral PrEP recommendation (as at June 2018)
Access for young people remains a challenge
Tenofovir is only effective when used…

Association between drug detection and HIV incidence in tenofovir gel studies

**Clinical trials**

- **CAPRISA 004** – coital Tenofovir gel
  (Women – South Africa)
  - Effect size (CI): 39% (6; 60)

- **MTN003/VOICE** – daily Tenofovir gel
  (Women – South Africa, Uganda, Zimbabwe)
  - Effect size (CI): 15% (-21; 40)

- **FACTS 001** – coital Tenofovir gel
  (Women – South Africa)
  - Effect size (CI): 0% (-40, 30)

**Case-cohort analyses of gel trials:**

- **MTN003/VOICE** – daily Tenofovir gel
  (South Africa, Uganda, Zimbabwe)
  - Effect size (CI): 57% (8; 80)\(^a\)

- **CAPRISA 004** – coital Tenofovir gel
  (South Africa)
  - Effect size (CI): 53% (-8; 79)\(^b\)

- **FACTS 001** – coital Tenofovir gel
  (South Africa)
  - Effect size (CI): 52% (3, 72)\(^c\)

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\(^a\) - Marrazzo et al. NEJM 2015; \(^b\) - Kashuba et al. JAIDS 2015; \(^c\) - Rees et al. CROI 2015
Biology: Genital inflammation increases HIV acquisition risk in women

Genital Inflammation and the Risk of HIV Acquisition in Women

Lindi Masson,1,2,5 Jo-Ann S. Passmore,1,2,3,5 Lenine J. Liebenberg,1,5 Lise Werner,1,5 Cheryl Baxter,1,5 Kelly B. Arnold,6 Carolyn Williamson,1,2 Francesca Little,5 Leila E. Mansoor,1 Vivek Naranbhai,1 Douglas A. Lauffenburger,1 Katharina Ronacher,5 Gerhard Walzl,5 Nigel J. Garrett,1 Brent L. Williams,7 Mara Couto-Rodriguez,7 Mady Hornig,7 W. Ian Lipkin,7 Anneke Grobler,1 Quarraisha Abdool Karim,1,8 and Salim S. Abdool Karim1,8

![Genital Inflammation and the Risk of HIV Acquisition in Women](image)

Later became HIV-infected (n=58)  Remained HIV-uninfected (n=58)
Genital inflammation increases risk of HIV & affects topical PrEP

Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women

Lyle R McKinnon¹⁻³,⁹, Lenine J Liebenberg¹,³,⁹, Nonhlanhla Yende-Zuma¹, Derseree Archary¹,³, Sinaye Ngcapu¹,³, Aida Sivro¹⁻³, Nico Nagelkerke², Jose Gerardo Garcia Lerma⁴, Angela D Kashuba⁵, Lindi Masson¹,⁶, Leila E Mansoor¹, Quarraisha Abdool Karim¹,⁷, Salim S Abdool Karim¹,⁷ & Jo-Ann S Passmore¹,⁶,⁸

Genital inflammation (>5/9 cytokines) increased the risk of HIV acquisition 2.4 fold (95% CI: 1.4 to 4.2) p=0.002
IL-17 central to inflammatory cascade in the female genital tract

Relationship between female genital tract infections, mucosal interleukin-17 production and local T helper type 17 cells


IL-17 concentrations elevated in women with bacterial STIs, but lower in those with candidal infections

IL-17 production in female genital tract associated with genital inflammation
Inflammatory cytokines → influx of HIV-susceptible target CD4+ cells

Increased levels of inflammatory cytokines in the female reproductive tract are associated with altered expression of proteases, mucosal barrier proteins, and an influx of HIV-susceptible target cells.

Kelly B Arnold1,13, Adam Burgener2,3,4,13, Kenzie Birse2,3, Laura Romas2,3, Laura J Dunphy1, Kamnoosh Shahabi5, Max Abou5, Garrett R Westmacott6, Stuart McCorrister6, Jessie Kwatampora7, Billy Nyanga7, Joshua Kimani3,7, Lindi Masson8,9, Lenine J Liebenberg9, Salim S Abdool Karim9,10, Jo-Ann S Passmore8,8,11, Douglas A Lauffenburger1, Rupert Kaul5,7,12,14 and Lyle R McKinnon5,7,9,14

Significant 2-fold increase in CD4+ T-cells in the endocervix of individuals with elevated mucosal cytokines.
Low infectivity viruses dominate in GI

Cervicovaginal Inflammation Facilitates Acquisition of Less Infectious HIV Variants

Philippe Selhorst,1,a Lindi Masson,1,2,a Sherazaan D. Ismail,1 Natasha Samsunder,2 Nigel Garrett,2 Leila E. Mansoor,2 Quarraisha Abdool Karim,2,4 Salim S. Abdool Karim,2,4 Jo-Ann S. Passmore,1,2,3,b and Carolyn Williamson1,3,b

Only 2/11 (18%) women who did not have pre-infection genital inflammation were infected by viruses with low infectivity (RLU/RT <median), compared to 11/16 (69%) women with inflammation

Viral infectivity was calculated as Relative Light Units (RLUs) generated per picogram Reverse Transcriptase (RT) activity in each stock as measured by Roche’s colorimetric RT assay (Switzerland)
The vaginal microbiome: key factor in HIV risk and topical PrEP efficacy

Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women

Nichele R. Klatt,1+ Ryan Cheu,1† Kenzie Birse,2,3‡ Alexander S. Zevin,1‡ Michelle Perner,2,3‡ Laura Noël-Romas,2,3‡ Anneke Grobler,4 Garrett Westmacott,5 Irene Y. Xie,2,3 Jennifer Butler,2,3 Leila Mansoor,4 Lyle R. McKinnon,3,4 Jo-Ann S. Passmore,6,4 Quarraisha Abdoel Karim,4,7 Salim S. Abdoel Karim,4,7 Adam D. Burgener2,3,8+†

Women with Lactobacillus dominance

Women with <50% Lactobacilli

Overall diversity plot of all women
What is causing inflammation and vulnerability to HIV in women?

<table>
<thead>
<tr>
<th>P. bivia+ OR*</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>HC</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 4.0-92.4)</td>
</tr>
<tr>
<td>HIV+</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 2.1-77.8)</td>
</tr>
</tbody>
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*adjusted odds ratio

22 women were HIV positive & had inflammation – 9/22 (41%) had *P. Bivia* in the vaginal microbiome

Women with *P. bivia* were 19 times more likely to have genital inflammation and 13 times more likely to acquire HIV
Hormonal contraception and HIV risk

- Several observational studies show hormonal contraception increases the risk of HIV acquisition.
- A meta analysis including 18 studies, 37,124 women (43,613 woman-years) and 1,830 incident HIV infections concluded:
  - DMPA may increase HIV risk: aHR 1.43 (95% CI 1.23–1.67)
Result from RCT assessing hormonal contraception and HIV risk

HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial

Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium

- **HR for HIV acquisition were:**
  - $1.04$ (96% CI $0.82–1.33$, $p=0.72$) for DMPA vs copper IUD,
  - $1.23$ (0.95–1.59, $p=0.097$) for DMPA vs LNG implant
  - $1.18$ (0.91–1.53, $p=0.19$) for copper IUD vs LNG implant

- The RCT found no difference in HIV risk among the methods evaluated, and all methods were safe and highly effective
All women within a PrEP trial may not benefit equally.

Ph 1 Tnf ring – genital ulceration – early stop.

No protection in young women <21 years
(-27%; 95% CI: -133 to 31; p = 0.45)
New prevention technologies in development and testing...

Two Monthly injectable antiretrovirals:
- Cabotegravir
- Rilpivirine

Annual sub-dermal implants:
- Cabotegravir TAF
- EFDA

HIV vaccines:
- Mosiac vaccine

Combination broadly neutralising antibodies:
- CAP256, VRC07 & PGT121
Conclusion

• Reducing high rates of HIV in young women in Africa is key to the control of the global HIV epidemic – behaviour, biology and structural drivers

• Genital inflammation is a major HIV risk factor
  – Vaginal microbiome impacts HIV risk & PrEP efficacy
  – Research underway to understand causes of genital inflammation & Evaluation of products to address vaginal dysbiosis

• Daily oral Tenofovir/Emtricitabine great start – enhance access

• High priority: Additional Prevention Tools for Women
  – Need less user adherence-dependent strategies
    • Injectables, Implants, New more potent and non-daily oral drugs
    • Vaccines
    • Multi-purpose technologies
    • Combination bnAbs as passive immunisation
      – if effective, identifies the immunogens for active vaccination
The future of technologies to prevent HIV in women

- More potent oral ARVs
  - eg monthly tablets
- Injectable ARVs
- 2-3 monthly
- ARV vaginal rings
- Annual ARV implants
- More potent oral ARVs eg monthly tablets
- HIV vaccines
- Combination Broadly neutralising antibodies
- Truvada
- Altering the vaginal microbiome - Treat vaginal dysbiosis
- Multi-purpose technologies
Biomedical Interventions – first step

• Root cause: gender-power dynamics
  – Gender based violence
    • Young boys and girls life trajectories
    – Globalization, Poverty, & Commodification of Women
• Enabling rapid access
  – Early inclusion in product development & evaluation
  – Overcoming legal and ethical barriers
  – Implementation: Peer-peer led interventions
• New communication technologies
  – Dating sites and increased HIV risk
  – Access to information and support
• Adolescence to adulthood – complex challenge
• We won’t end AIDS in young women and adolescent girls tomorrow…….. but it has to be part of our vision for an AIDS-free generation
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  • Lyle McKinnon, CAPRISA & University of Manitoba

• Research teams involving >200 scientists & students

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“After climbing a great hill, one only finds out that there are many more hills to climb”

(Nelson Mandela)