HIV, PrEP & adolescent girls and young women: Understanding the evidence

Center for Health & Gender Equity Webinar, November 2016

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Overview

- HIV in adolescent girls and young women
- Evidence on the effectiveness of PrEP in women
- The challenge of PrEP adherence in women
- The vaginal microbiome and PrEP effectiveness
- Biological factors influencing HIV risk in women
- Conclusion
Since 1990 - known that young women have a higher burden of HIV in Africa

Seroprevalence of HIV infection in rural South Africa
AIDS 1992, 6:1535-1539
Quarraisha Abdool Karim, Salim S. Abdool Karim, Bipraj Singh*, Richard Short† and Sipho Ngxongo‡

1990: One of the earliest community-based HIV prevalence surveys in Africa
High rates of HIV in adolescent girls and young women in South Africa

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>HIV Prevalence (2010) % (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15</td>
<td>1.0 (0.0 - 2.2)</td>
</tr>
<tr>
<td>16-17</td>
<td>1.1 (0.2 - 2.0)</td>
</tr>
<tr>
<td>18-19</td>
<td>1.5 (0 - 3.7)</td>
</tr>
<tr>
<td>≥20</td>
<td>1.8 (0 - 3.9)</td>
</tr>
</tbody>
</table>
High rates of HIV in adolescent girls and young women in South Africa

Original Article

Prevalence of HIV, HSV-2 and pregnancy among high school students in rural KwaZulu-Natal, South Africa: a bio-behavioural cross-sectional survey


<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>HIV Prevalence (2010)</th>
<th>Male (n=1252)</th>
<th>Female (n=1423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15</td>
<td>1.0 (0.0 - 2.2)</td>
<td>2.6 (1.2 - 4.0)</td>
<td></td>
</tr>
<tr>
<td>16-17</td>
<td>1.1 (0.2 - 2.0)</td>
<td>6.1 (2.6 - 9.6)</td>
<td></td>
</tr>
<tr>
<td>18-19</td>
<td>1.5 (0 - 3.7)</td>
<td>13.6 (9.0 - 18.1)</td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>1.8 (0 - 3.9)</td>
<td>24.7 (6.3 - 43.1)</td>
<td></td>
</tr>
</tbody>
</table>
Cycle of HIV transmission in rural KZN
Schematic of sexual networks from clusters with heterosexual transmission

**Men 25-40 years** (N=79)
- Knew HIV status: 21.5%
- VL > 50,000: 37.1%
- Community HIV prevalence: **40.3%**

Most men & women 25-40 years acquire HIV from similarly aged partners (Mean age difference = 1.1 years)

**Young women <25 years** (N=43)
- Knew HIV status: 23.3%
- 62% of male partners are 25-40 years
- Community HIV prevalence: **22.3%**

**Women 25-40 years** (N=56)
- Knew HIV status: 42.6%
- 63% of male partners are 25-40 years
- Community HIV prevalence: **59.8%**

39% of the men linked to a woman < 25 are simultaneously also linked to a woman 25-40 years

Most young women <25 years acquire HIV from older men (Mean age difference = 8.7 years)

When young women reach >25 years they continue the cycle

Community HIV prevalence:
- 22.3%
- 40.3%
- 59.8%

Phylogenetics of 1,589 viruses from 9,812 people

Great progress on increasing HIV treatment but we are lagging in prevention

Number of people receiving antiretroviral therapy, by WHO region, 2003–2015

0% reduction in new infections 2013 - 2015

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• The challenge of PrEP adherence in women

• The vaginal microbiome and PrEP effectiveness

• Biological factors influencing HIV risk in women

• Conclusion
July 2010: ARVs prevent HIV in women

First evidence of tenofovir PrEP (in gel) presented at the 2010 International AIDS Conference in Vienna

Tenofovir gel prevents HIV in women
- 39% protection against HIV overall
- 54% effective in women with high adherence
- 74% protection with high tenofovir levels

Tenofovir gel prevents HSV-2 infection in women (NEJM 2015)
- 51% reduction in HSV-2 incidence
November 2010: Oral PrEP prevents HIV in MSM – iPrEx trial

131 infections after randomization

- 48 in FTC/TDF
- 83 in placebo

2499 Men who have sex with Men

Effect of daily TDF-FTC on HIV: 42% (CI: 15% - 63%)

4,758 HIV discordant couples in Kenya & Uganda

Effect of TDF on HIV: 67% (CI: 44% - 81%)
Effect of FTC/TDF on HIV: 75% (CI: 55% - 87%)
Effectiveness of PrEP in men

**Study**

- **IPERGAY** – on demand Truvada (MSM – France)
  - Effect size (CI): 86% (39; 99)

- **PROUD** – daily oral Truvada (MSM – United Kingdom)
  - Effect size (CI): 86% (62; 96)

- **Partners PrEP** – daily Truvada (Discordant couples – Kenya, Uganda)
  - Effect size (CI): 84%* (54; 94)

- **TDF2** – daily Truvada (Heterosexual men - Botswana)
  - Effect size (CI): 82%* (-3; 99)

- **Partners PrEP** – daily oral Tenofovir (Discordant couples – Kenya, Uganda)
  - Effect size (CI): 63%* (20; 83)

- **iPrEx** – daily Truvada (MSM - America’s, Thailand, South Africa)
  - Effect size (CI): 44% (15; 63)

*point estimate for men only
Clinical trials of PrEP in women

**Effect size**

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTN003/VOICE – daily Tenofovir gel</td>
<td>15%</td>
<td>(-21; 40)</td>
</tr>
<tr>
<td>CAPRISA 004 – coital Tenofovir gel</td>
<td>39%</td>
<td>(6; 60)</td>
</tr>
<tr>
<td>FEMPrEP – daily Tenofovir gel</td>
<td>6%</td>
<td>(-52; 41)</td>
</tr>
<tr>
<td>TDF2 – daily TDF/FTC</td>
<td>-4%</td>
<td>(-49; 27)</td>
</tr>
<tr>
<td>Partners PrEP – daily TDF (Viread)</td>
<td>75%*</td>
<td>(24; 94)</td>
</tr>
<tr>
<td>Partners PrEP – daily TDF/FTC</td>
<td>-4%</td>
<td>(-49; 27)</td>
</tr>
<tr>
<td>CAPRISA 004 – coital Tenofovir gel</td>
<td>66%*</td>
<td>(28; 84)</td>
</tr>
<tr>
<td>TDF and TDF/FTC as Oral PrEP</td>
<td>71%*</td>
<td>(37; 87)</td>
</tr>
<tr>
<td>Ring Study – monthly dapivirine vaginal ring</td>
<td>31%</td>
<td>(1; 51)</td>
</tr>
<tr>
<td>ASPIRE – monthly dapivirine vaginal ring</td>
<td>27%</td>
<td>(1; 46)</td>
</tr>
<tr>
<td>FACTS 001 – coital Tenofovir gel</td>
<td>0%</td>
<td>(-40, 30)</td>
</tr>
<tr>
<td>MTN003/VOICE – daily TDF/FTC</td>
<td>-49%</td>
<td>(-129; 3)</td>
</tr>
<tr>
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<td>(-52; 41)</td>
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<td>27%</td>
<td>(1; 46)</td>
</tr>
</tbody>
</table>

Data as at November 2016

**Clinical trials of PrEP in women**

- **TDF2 – daily TDF/FTC**: (Heterosexuals men and women - Botswana)
- **Partners PrEP – daily oral TDF (Viread)**: (Discordant couples – Kenya, Uganda)
- **Partners PrEP – daily TDF/FTC**: (Discordant couples – Kenya, Uganda)
- **FEMPrEP – daily Tenofovir gel**: (Women – Kenya, South Africa, Tanzania)
- **MTN003/VOICE – daily Tenofovir gel**: (Women – South Africa, Uganda, Zimbabwe)
- **MTN003/VOICE – daily TDF**: (Women - South Africa, Uganda, Zimbabwe)
- **CAPRISA 004 – coital Tenofovir gel**: (Women – South Africa)
- **MTN003/VOICE – daily Tenofovir gel**: (Women – South Africa, Uganda, Zimbabwe)
- **FACTS 001 – coital Tenofovir gel**: (Women – South Africa)
- **Ring Study – monthly dapivirine vaginal ring**: (Women – South Africa, Uganda)
- **ASPIRE – monthly dapivirine vaginal ring**: (Women – Malawi, South Africa, Uganda, Zimbabwe)
New WHO policy on PrEP to prevent the spread of HIV by sex

PrEP recommended as global standard for all at high risk, including young women

New WHO PrEP guidelines

“..the use of daily oral pre-exposure prophylaxis is recommended as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches..”
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• Evidence on the effectiveness of PrEP in women
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• Conclusion
High adherence is essential for PrEP

<table>
<thead>
<tr>
<th></th>
<th># HIV</th>
<th>N</th>
<th>HIV incidence</th>
<th>Effect</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TFV</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>High adherers</td>
<td>36</td>
<td>336</td>
<td>4.2</td>
<td>9.3</td>
<td>54%</td>
</tr>
<tr>
<td>(&gt;80% gel adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate adherers</td>
<td>20</td>
<td>181</td>
<td>6.3</td>
<td>10.0</td>
<td>38%</td>
</tr>
<tr>
<td>(50-80% adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low adherers</td>
<td>41</td>
<td>367</td>
<td>6.2</td>
<td>8.6</td>
<td>28%</td>
</tr>
<tr>
<td>(&lt;50% gel adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


CAPRISA 004 was developed... ...“after extensive consultation with international scientific experts and review of monkey challenge data.”

“Just as importantly, it followed detailed consultation with the communities involved.”
Adherence and effectiveness: HIV incidence reductions in relation to drug detection levels

Pearson correlation = 0.84, p = 0.0006

Adherence estimated from drug concentrations

Note: The diameter of circles is proportional to number of HIV infections in the control group. For daily dosing, adherence is based on % of the participants with detected drug. For coital dosing, adherence is estimated on detected drug adjusted for reported recent coitus.
High adherence is essential
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)
15% (-21; 40)

FACTS 001 – coital Tenofovir gel
(Women – South Africa)
0% (-40, 30)

Case-cohort analyses of gel trials:
MTN003/VOICE – daily Tenofovir gel
(South Africa, Uganda, Zimbabwe)
57% (8; 80)

CAPRISA 004 – coital Tenofovir gel
(South Africa)
53% (-8; 79)

FACTS 001 – coital Tenofovir gel
(South Africa)
52% (3, 72)

a - Marrazzo et al. NEJM 2015; b - Kashuba et al. JAIDS 2015; c - Rees et al. CROI 2015
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Factors undermining PrEP efficacy in women: Proteomics reveal diminished tenofovir efficacy in women who do not have vaginal Lactobacilli dominance
Factors undermining PrEP efficacy in women: Vaginal bacterial profiling by mass spectrometry identifies four major community groups.
Factors undermining PrEP efficacy in women:
Proteomics reveal diminished tenofovir efficacy in women who do not have vaginal Lactobacilli dominance

Women with Lactobacillus dominance

Efficacy: 61% (CI: 17; 80)

Women with <50% Lactobacilli

Efficacy: 18% (CI: -65; 60)

HR = 0.39 (CI: 0.20; 0.83)
Logrank p-value = 0.013

HR = 0.82 (95% CI: 0.40; 1.65)
Logrank p-value = 0.760
Vaginal bacteria undermining PrEP efficacy in women

4 hours:
- G. vag vs. L. iners: p=0.0172
- G. vag vs Abiotic: p=0.0360

24 hours:
- G. vag vs. L. iners: p<0.0001
- G. vag vs Abiotic: p=0.0003
Vaginal bacteria undermining PrEP efficacy in women:

Intracellular tenofovir absorption by G. vaginalis

Intracellular tenofovir concentration

Time (hours)

4 hours:
G. vag vs. L. iners: P<0.001

24 hours:
G. vag vs. L. iners: P<0.001
Potential implications for PrEP implementation in women

One approach: Integration of PrEP scale-up with sexual & reproductive health services ie. STI & FP services

Metronidazole treatment to promote a “healthy” (Lactobacillus dominant) vagina

If pH > 4.5
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High risk of acquisition in young women: Role of genital inflammation

Women who later became HIV-infected had pre-infection genital inflammation, only 20% of which was due to the common STIs.

So, what is the cause of the genital inflammation that is enhancing HIV acquisition?

High risk of acquisition in young women: Searching for the cause of genital inflammation in the vaginal microbiome

CVL cytokines
n=120*
IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IP-10, GM-CSF, MCP-1, MIP-1α, MIP-1β, TNF-α

Hierarchical Clustering & Principal Coordinate Analysis

*120 women; 30 with inflammation

V1-V3 16S rDNA Pyrosequencing
n=119 vaginal swabs

QIIME analysis
Separated into Operational Taxonomic Units (OTUs)

3 million 16S sequences
Average: 25,839 sequences / swab

1368 species identified

PAM clustering to define Community State Types (CSTs)

LEfSe to define taxonomic biomarkers of cytokine profiles and HIV acquisition

PICRUSt to predict functional pathways differentiating CSTs

Log-linear regression to estimate Adjusted Relative Risk of HIV associated with taxa

Confirmation of taxonomic assignment and quantitation of bacterial taxa

Metatranscriptomic sequencing on a subset of samples (n=30)

Taxonomy: MetaPhlAn and BLAST analysis of Assembled Contigs

Relevant Taxa quantitated by Real-time PCR

STIs assessed by Real-time PCR

*120 women; 30 with inflammation

USAID From the American People

Center for Infection & Immunity

Columbia University Mailman School of Public Health

Science & Technology

Republic of South Africa

NRF

CAPRISA
High risk of acquisition in young women: In the vaginal microbiome, *Prevotella bivia* enhances HIV acquisition in women exposed to the virus.
High risk of acquisition in young women:
In the vaginal microbiome, *Prevotella bivia* enhances HIV acquisition in women exposed to the virus

<table>
<thead>
<tr>
<th></th>
<th>P. Bivia +</th>
<th>P. Bivia -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (Genital Inflamm +)</td>
<td>10 (37.0%)</td>
<td>17 (63.0%)</td>
</tr>
<tr>
<td>Controls (Genital Inflamm –)</td>
<td>3 (3.3%)</td>
<td>89 (96.7%)</td>
</tr>
</tbody>
</table>

**OR**: 19.2 (95%CI: 4.0-92.4), p<0.001

Women with genital inflammation were 19 times more likely to have *P. bivia*

22 women were HIV positive & had inflammation – 9/22 (41%) had *P. bivia*

* Odds ratio adjusted. Unadjusted OR = 17.5
## Contributions by other organisms that may cause genital infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>HC women N (%)</th>
<th>LC women N (%)</th>
<th>Odds Ratio (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>11 (41%)</td>
<td>14 (15%)</td>
<td>3.8 (1.5-9.8), p=0.007</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>6 (22%)</td>
<td>11 (12%)</td>
<td>2.1 (0.7-6.2), p=0.213</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>1 (4%)</td>
<td>3 (3%)</td>
<td>1.1 (0.2-8.1), p=1.000</td>
</tr>
<tr>
<td>HSV-2 / HSV-1</td>
<td>1 (4%) / 0 (0%)</td>
<td>2 (2%) / 0 (0%)</td>
<td>1.7 (0.2-13.7), p=0.541</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td><em>Haemophilus ducreyi</em></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td><em>Schistosoma</em></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
</tbody>
</table>
In the *P. bivia* microbiome cluster (CST4) there is a higher abundance of genes involved in Lipopolysaccharide (LPS) biosynthesis compared to all other microbiome clusters.

High risk of acquisition in young women:
Potential mechanism: ↑ *P. bivia* = ↑ LPS

* * * * * * *

*p<0.05; **p<0.01; ***p<0.001
Microbial translocation is a cause of systemic immune activation in chronic HIV infection

Jason M Brenchley¹, David A Price¹, Timothy W Schacker², Tedi E Asher¹, Guido Silvestri³, Srinivas Rao⁴, Zachary Kazzaz¹, Ethan Bornstein¹, Olivier Lambotte⁵, Daniel Altmann⁶, Bruce R Blazar⁷, Benigno Rodriguez⁸, Leia Teixeira-Johnson⁸, Alan Landay⁹, Jeffrey N Martin¹⁰, Frederick M Hecht¹⁰, Louis J Picker¹¹, Michael M Lederman⁸, Steven G Deeks¹⁰ & Daniel C Douek¹

Chronic activation of the immune system is a hallmark of progressive HIV infection and better predicts disease outcome than plasma viral load, yet its etiology remains obscure. Here we show that circulating microbial products, probably derived from the gastrointestinal tract, are a cause of HIV-related systemic immune activation. Circulating lipopolysaccharide, which we used as an indicator of microbial translocation, was significantly increased in chronically HIV-infected individuals and in simian immunodeficiency virus (SIV)-infected rhesus macaques (P < 0.002). We show that increased lipopolysaccharide is bioactive in vivo and correlates with measures of innate and adaptive immune activation. Effective antiretroviral therapy seemed to reduce microbial translocation partially. Furthermore, in nonpathogenic SIV infection of sooty mangabeys, microbial translocation did not seem to occur. These data establish a mechanism for chronic immune activation in the context of a compromised gastrointestinal mucosal surface and provide new directions for therapeutic interventions that modify the consequences of acute HIV infection.
Conclusion: HIV risk factors in women

- Genital inflammation
- Other STIs (e.g. HPV)
- Gender-based violence
- Transactional sex
- Low male and/or female condom use
- Age-disparate partnerships
- Depo Provera injectable contraceptive use
- Low adherence to oral PrEP
- Early sexual debut
- >1% abundance of *Prevotella bivia*
- ↓ vaginal lactobacilli (e.g. BV)
- HSV-2 infection
- Depo Provera injectable contraceptive use
- Low adherence to oral PrEP
- Early sexual debut

**Legend:**
- Biological
- Structural
- Behavioural
Conclusion:
Understanding high rates of HIV in young women in Africa:

Implications of new epidemiological, phylogenetic, genomic and proteomic evidence

Most important group that needs to be addressed to reach UNAIDS goal of ending HIV as a public health threat
Key implications of the new results

• New findings from the CAPRISA consortium of researchers from South Africa and North America shed light on why young women in Africa are at such high risk of HIV & how to better protect them from HIV

• Combination prevention in women must now include:
  ▪ Interventions to reduce age-disparate sex in young women & aggressively promote circumcision in young men & PrEP in young women (while Test & Treat is being scaled-up)
  ▪ Interventions to diagnose & treat BV (incl. *Prevotella bivia*)
  ▪ Interventions to link PrEP scale-up with sexual & reproductive health services for vaginal pH testing and treatment for ph>4.5 to promote a “healthy” (Lactobacillus dominant) vagina
Acknowledgements

• Burgener lab, JC Wilt Infectious Disease Research Center
  – Michelle Perner
  – Kenzie Birse
  – Laura Romas
  – Irene Xie
  – Max Abou
  – Jennifer Butler
  – Peter McQueen
  – John Schellenbergh
  – Matthew Cook
  – Lauren Girard
  – Alicia Berard
  – Lani Kotyrba
  – Trisha Vera

• Center for Infection & Immunity
  – W. Ian Lipkin
  – Mara Couto-Rodriguez
  – Simone Formisano
  – Allison Hicks
  – Mansi Vasishtha

• CAPRISA
  – Salim Abdool Karim
  – Quarraisha Abdool Karim
  – Anneke Grobler
  – Leila Mansoor
  – Natasha Samsunder
  – Sinaye Ngcapu
  – Kerry Leask
  – Kim Cousins

• University of Cape Town
  – Jo-Ann Passmore

• CIHR Mucosal Study Team investigators:
  – Lyle McKinnon, Kelly Arnold, Doug Lauffenburger, Kristina Broliden

• Klatt lab, University of Washington
  – Alex Zevin
  – Ryan Cheu
  – Tiffany Hensley-McBain
  – Jennifer Manuzak
  – Charlene Miller
  – Kevin Fogassey
  – Ernesto Coronado
  – Lydia Sweet
  – Arina Wu

• Mass Spectrometry Core (PHAC):
  – Stuart McCorrister, Garrett Westmacott

• National HIV and Retrovirology labs:
  – Paul Sandstrom

CAPRISA 004 study participants, without whom these studies wouldn’t be possible
Acknowledgements

• FUNDERS OF THE INDIVIDUAL PROJECTS
  • PEPFAR
  • Centers for Disease Control and Prevention (CDC)
  • M·A·C AIDS Fund
  • United States Agency for International Development (USAID)
  • Canadian Institutes for Health research (CIHR)

• ADDITIONAL RESEARCH SUPPORT WAS OBTAINED FROM:
  • Department of Science and Technology (DST)
  • National Research Foundation (NRF)
  • South African Medical Research Council (SA MRC)
  • National Institutes of Health (NIH)