Transmission Networks & Risk of HIV Infection in Young Women in KwaZulu-Natal, South Africa

FIDSSA, Cape Town, November 2017

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Associate Scientific Director: CAPRISA
Professor in Clinical Epidemiology, Columbia University
Adjunct Professor in Public Health, University of KwaZulu-Natal
Young women at high HIV risk: Who? Why? What works?

Who - source of infection?
Why so vulnerable?
What works for prevention?

Young women at high HIV risk
Global HIV epidemic at a glance…

In 2016, worldwide there were:

- 36.7 million living with HIV
- 1.0 million HIV deaths
- 1.8 million new infections

Africa has 64% of all the world’s HIV

Source: UNAIDS Global Report 2017
Great progress on increasing HIV treatment but we are lagging in prevention

Number of people receiving antiretroviral therapy, by WHO region, 2003–2016

0% reduction in new infections 2013 - 2015

Africa has 70% of all people with HIV

With <1% of the world’s population, South Africa has 19% of all people living with HIV

Top 10 countries: People living with HIV

1. South Africa - 19%
2. Nigeria - 9%
3. India - 6%
4. Mozambique - 5%
5. Kenya - 4%
6. Uganda - 4%
7. Tanzania - 4%
8. Zimbabwe - 4%
9. Zambia - 3%
10. Malawi - 2%

Remaining countries - 40%

Source: UNAIDS Global Report 2017
Young Women at High Risk

HIV Incidence among Young Women
More than 1/3 New HIV Infections Globally Occur among Young Women in Africa

Estimated number of new HIV infections *per week* among young women aged 15-24 years in East and Southern Africa, 2012
Data source: UNAIDS 2013

<table>
<thead>
<tr>
<th>Country</th>
<th>Number per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>2363</td>
</tr>
<tr>
<td>Uganda</td>
<td>494</td>
</tr>
<tr>
<td>Mozambique</td>
<td>570</td>
</tr>
<tr>
<td>Tanzania</td>
<td>491</td>
</tr>
<tr>
<td>Kenya</td>
<td>468</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>287</td>
</tr>
<tr>
<td>Malawi</td>
<td>262</td>
</tr>
<tr>
<td>Zambia</td>
<td>185</td>
</tr>
<tr>
<td>Lesotho</td>
<td>110</td>
</tr>
<tr>
<td>Swaziland</td>
<td>79</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>64</td>
</tr>
<tr>
<td>Botswana</td>
<td>54</td>
</tr>
<tr>
<td>Namibia</td>
<td>42</td>
</tr>
<tr>
<td>Rwanda</td>
<td>25</td>
</tr>
</tbody>
</table>

Over 7,000 new HIV infections every week among young women globally
HIV in South Africa: Disproportionate burden of HIV in young women

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‡

Young women have up to 8 times more HIV than men
### 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

Quarraisha Abdool Karim,¹,² Ayesha B M Kharsany,¹ Kerry Leask,¹ Fanelisibonge Ntombela,¹ Hilton Humphries,¹ Janet A Frohlich,¹ Natasha Samsunder,¹ Anneke Gröhler,¹ Rachael Dellar,¹ Salim S Abdool Karim¹,²

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>HIV Prevalence (2010) % (95% Confidence Interval)</th>
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HIV phylogenetics reveals Cycle of HIV transmission

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


**Men**
Mean age: 31.5 years (n=79)
Knew HIV status: 22%

Community HIV prevalence in men aged 25-40 years: 40%* (N=1548)

Most young women <25 years acquire HIV from older men (Mean age difference = 8.7 years, CI: 6.8-10.6)

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

Most men & women 25-40 years acquire HIV from similarly aged partners (Mean age difference = 1.1 years, CI: -0.6-2.8)

**Young women <25 years**
Knew HIV status: 23%
62% of male partners are 25-40 years

Community HIV prevalence: 22%* (N=2224)

When young women reach >25 years they continue the cycle

**Women 25-40 years**
Knew HIV status: 43%
63% of male partners are 25-40 years

Community HIV prevalence: 60%* (N=2680)
HIV transmission dynamics: Community-wide phylogenetic study

- 86% consent rate
- People tested for HIV: 9,812
- HIV positive: 36.3% (CI: 35-38) (n=3,969)
- Knew HIV+ status: 59.8% (n=2,337)
- On ARVs: 42.3% (n=1,590)
- Viral load >1000: 47.1% (n=1,847)
- Community-wide phylogenetics: 1,589 viruses sequenced

- Maximum likelihood tree
  Branch support > 90% & Genetic diversity < 4.5%

Phylogenetic linkage = probable recent transmission as long-established infection may be on ART or virus > 4.5% difference
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 young women <25 years acquire HIV from older men (Mean age difference = 8.7 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%

Phylogenetics of 1,589 viruses from 9,812 people

Cycle of HIV transmission in rural KZN
Schematic of sexual networks from clusters with heterosexual transmission

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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)

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

Community HIV prevalence: **59.8%**

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

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Phylogenetics of 1,589 viruses from 9,812 people

Existing HIV prevention strategies - ABCC:
- Abstinence
- Behaviour (Be faithful)
- Condoms (Male & Female)
- Circumcision
- Pre-exposure prophylaxis

HIV in pregnant women in rural South Africa (2001-2013)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=4818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>11.5%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>30.4%</td>
</tr>
<tr>
<td>21-22</td>
<td>39.4%</td>
</tr>
<tr>
<td>23-24</td>
<td>49.5%</td>
</tr>
<tr>
<td>&gt;25</td>
<td>51.9%</td>
</tr>
</tbody>
</table>

Source: Abdool Karim Q, 2014

Which of these are prevention tools for young women in Africa?
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

*(strong recommendation, high-quality evidence)*

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..”
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

Data as at November 2016
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.
CAPRISA 004: First evidence that ARVs prevent sexual transmission of HIV

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

Tenofovir gel also prevents genital herpes in women:
- 51% reduction in HSV-2 incidence
Tenofovir is effective when used...

Association between drug detection and HIV incidence in tenofovir gel studies

**Clinical trials**

**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)

**Effect size (CI)**

39% (6; 60)

15% (-21; 40)

0% (-40, 30)

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

**MTN003/VOICE** – daily Tenofovir gel  
(South Africa, Uganda, Zimbabwe)

**CAPRISA 004** – coital Tenofovir gel  
(South Africa)

**FACTS 001** – coital Tenofovir gel  
(South Africa)

57% (8; 80)

53% (-8; 79)

52% (3, 72)

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\(a\) - Marrazzo et al. NEJM 2015; \(b\) - Kashuba et al. JAIDS 2015; \(c\) - Rees et al. CROI 2015
High vaginal tenofovir concentrations needed at exposure

Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women

Salim S Abdool Karim, Angela DM Kashuba, Lise Werner, Quarraisha Abdool Karim

Probability of HIV infection

Placebo gel

Tenofovir gel TFV ≤1000ng/ml

Tenofovir gel TFV >1000ng/ml

p=0.01*

*comparing women with tenofovir concentration >1000ng/ml vs placebo. Adjusted p=0.03
Pre-existing genital inflammation increases HIV acquisition risk in women

Genital Inflammation and the Risk of HIV Acquisition in Women

Lindi Masson,1,2, a Jo-Ann S. Passmore,1,2,3, a Lenine J. Liebenberg,1, a Lise Werner,1, Cheryl Baxter,1, Kelly B. Arnold,4 Carolyn Williamson,1,2 Francesca Little,5 Leila E. Mansoor,5 Vivek Naranbhai,5 Douglas A. Laufenburger,4 Katharina Ronacher,5 Gerhard Walzl,6 Nigel J. Garrett,7 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

Only 20% of HIV attributed to (or resulted from) an STI (gonorrhoea, chlamydia, trichomonas, HSV-2)

What is the cause of genital inflammation in CAPRISA 004?
**Why: *Prevotella bivia* is strongly associated with inflammation and enhanced HIV acquisition**

<table>
<thead>
<tr>
<th></th>
<th>P. bivia+ OR*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>19.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(95% CI: 4.0-92.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>12.7</td>
<td>p=0.006</td>
</tr>
<tr>
<td>(95% CI: 2.1-77.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*adjusted odds ratio

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

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

*Williams B, et al. IAS 2016*
Inflammation facilitates acquisition of less infectious HIV variants

Cervicovaginal inflammation facilitates acquisition of less infectious HIV variants

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.
Factors undermining topical PrEP efficacy: Vaginal bacterial profiling by mass spectrometry identified 2 major types of women (I / II) from 5 community groups (A-E)

Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women

Nichole R. Klatt¹, *Ryan Cheu¹, *Kenzie Birse²,³, *Alexander S. Zevin¹, *Michelle Perner²,³, *Laura Noël-Romas²,³, Anneke Grobler⁴, Garrett Westmacott⁵, Irene Y. Xie²,³, Jennifer Butler²,³, Leila Mansoor⁴, Lyle R. McKinnon²,³, Jo-Ann S. Passmore⁶,⁴, Quarraisha Abdool Karim⁴,⁷, Salim S. Abdool Karim⁴,⁷, Adam D. Burgener²,³,⁸

Vaginal bacterial profiling by mass spectrometry identified 2 major types of women (I / II) from 5 community groups (A-E)

Overall diversity plot of all women

Average bacterial community group structure for each profile
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
Metabolism of tenofovir by G. vaginalis and Lactobacilli

1) Inoculate NYIII medium with or without TFV, and abiotic controls

L. iners (x15)  G. vaginalis (x15)

+TFV -TFV +TFV -TFV +TFV

2) Sample. Separate cells from culture supernatant by centrifugation. Extract TFV into acetonitrile and analyze on MS

(Tupe)  MS

Intensity

m/z

Culture sample Acetonitrile

▲ = Tenofovir

4 hours:
G. vag vs Abiotic: P<0.0001
G. vag vs. L. iners: P=0.0037
G. vag vs. L. crisp: P=0.0019
L. iners vs L. crisp: P=ns

24 hours:
G. vag vs Abiotic: P<0.0001
G. vag vs. L. iners: P<0.0001
G. vag vs. L. crisp: P<0.0001
L. iners vs L. crisp: P=ns
What: Breaking Cycles of HIV transmission
Based on HIPSS sexual network clusters with heterosexual transmission

VMMC for HIV negative men <25 years
Antiretroviral therapy for HIV+ men >25 years

Need for novel HTC strategies to find missing PPs - Missed opportunities,
Couple HCT, Self-testing
Male responsibility and accountability
Acceptable values and norms

PrEP for women <25 years with SRH services – pH, antibiotics, probiotics

Women 25-40 years Anti-retroviral treatment

PrEP for women <25 years with SRH services – pH, antibiotics, probiotics
What’s in store for new prevention technologies…

- **2-monthly injectable antiretrovirals**
  - Cabotegravir

- **Annual sub-dermal implants**
  - Tenofovir Alafenamide

- **Once-off HIV vaccines**
  - Ad26/Mosiac Alvac/protein

- **3 monthly Broadly neutralising antibodies**
  - VRC01, VRC07 PGT121 CAP256-VRC26

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**Long-acting prophylaxis to overcome adherence problems**
Conclusion

• Reducing HIV in young women could change the course of the epidemic in Africa & reverse current poor global progress in HIV prevention
• Focused effort needed to scale up existing prevention strategies for AGYW and Men & developing new prevention tools including vaccines
• Daily oral PrEP is a start but better options needed; Several promising technologies in the pipeline to overcome adherence challenges
• But we also need to advance knowledge of pathogenesis of HIV infection in women
• Biomedical Interventions 1st step – root cause of vulnerability of women lies in gender-power disparities
IT ALWAYS SEEMS IMPOSSIBLE UNTIL IT'S DONE.

—NELSON MANDELA
ACKNOWLEDGEMENTS

- CAPRISA is funded by:
  - DAIDS, NIAID, National Institutes of Health
  - US Agency for International Development (USAID)
  - President’s Emergency fund for AIDS Relief (PEPFAR)
  - US Centers for Disease Control and Prevention (CDC)
  - South African Dept. of Science & Technology (DST)
  - Gilead Sciences (tenofovir API, TAF API & Truvada)
  - European & Developing Countries Clinical Trials Partnership
  - MACAIDS Fund (via Tides Foundation)
  - Medical Research Council (MRC)
  - National Research Foundation (NRF)
  - The Victor Daitz Foundation

- CAPRISA was established as part of the Comprehensive International Program of Research on AIDS (CIPRA) of the National Institutes of Health (NIH) (grant# AI51794)
## Risk factors for HIV acquisition in female high school students

<table>
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<tr>
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<th>Adjusted OR</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age &lt;18 years</td>
<td>2.67 (1.67-4.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HSV-2 seropositive</td>
<td>4.35 (2.61-7.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experience of pregnancy</td>
<td>1.66 (1.10-2.51)</td>
<td>0.016</td>
</tr>
<tr>
<td>Experience of &gt;1 adult deaths in household</td>
<td>1.97 (1.13-3.44)</td>
<td>0.016</td>
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**SOCIAL as well as BIOLOGICAL vulnerability to infection**

HSV-2 infection increases HIV risk in CAPRISA 004 women

<table>
<thead>
<tr>
<th>HSV-2 incident infections</th>
<th>HSV-2 positive n=58</th>
<th>HSV-2 Negative n=164</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV infections</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>HIV incidence / 100 person-yrs</td>
<td>12.3</td>
<td>5.3</td>
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HR for HIV risk in incident HSV-2: **2.4** (CI: 1.1-5.4), p = **0.03**

Prevalent HPV infection increases HIV risk

<table>
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<th>Women-years (n/N)</th>
<th>HIV Incidence rate (95% CI)</th>
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<tbody>
<tr>
<td>HPV-</td>
<td>330.5 (8/204)</td>
<td>2.4 (1.1 - 4.8)</td>
</tr>
<tr>
<td>HPV+</td>
<td>880.3 (59/575)</td>
<td>6.7 (5.1 - 8.6)</td>
</tr>
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HR for prevalent HPV: **2.8** (CI: 1.3 – 5.9), p=**0.007**

*Multivariate model fitted to HIV incidence adjusting for Study arm, Self-reported condom use, Age, Baseline HSV-2 status, Self-reported sex acts in the last month, and Age at sexual debut.*