The HIV Epidemic: does sex matter?

Linda-Gail Bekker
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University of Cape Town
5th Interest Meeting
Dar Es Salaam.
33.4 M people living with HIV globally

- 2.4 MILLION CHILDREN
- 15.3 MILLION MEN
- 15.7 MILLION WOMEN
Gender matters….

- Epidemiology
- Transmission
  - Response – PK differences, physiology
  - Adverse events- PK and physiology
  - Tolerability –PK and physiology

Opportunistic infections
Prevention efforts
Epidemiology
HIV Incidence by modes of transmission

Percent new infections

- Kenya: 76,315
- Zambia: 74,263
- Uganda: 91,546
- Mozambique: 118,279
- Swaziland: 11,381
- Lesotho: 23,269

Casual heterosexual sex
Men having sex with men
Low risk heterosexual
Clients of female sex workers
Partners of clients of female sex workers
Other
Partners (Casual heterosexual sex)
Injecting drug users

Sources: Kevin De Cock, PEPFAR Implementers MEETING 2009
Draft results from Know your Epidemic project
HIV prevalence among women is higher than men in SSA.
50%
Slightly more than half of all people living with HIV are women and girls.
Women by Marital status

- 1% of women married/living with partner
- 1% of women divorced/separated
- 1% of women widowed

Countries:
- Botswana
- Democratic Republic of the Congo
- United Republic of Tanzania
- Zambia
HIV prevalence among young people in sub-Saharan Africa

HIV prevalence among people 15–24 years old by sex in selected countries in sub-Saharan Africa.

<table>
<thead>
<tr>
<th>Country</th>
<th>15–19 years</th>
<th>20–24 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTSWANA</td>
<td>15–19</td>
<td>20–24</td>
</tr>
<tr>
<td>REPUBLIC OF THE CONGO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LESOTHO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZIMBABWE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: UNAIDS 2010.
10 million youth living with HIV

SOURCE: UNICEF/UNAIDS, 2004; youth age 15 - 24

Kicosehp NGO (support group for people living with HIV/AIDS). Kenya, Africa. © UNAIDS/G. Pirozzi
Disproportionate impact on young girls

2.4 million young boys living with HIV

7.6 million young girls living with HIV

SOURCE: UNICEF/UNAIDS, 2004; young boys/girls age 15 - 24
Risk of acquiring HIV before age 60, if HIV incidence rates stay constant at 2008 levels

![Bar chart showing the risk of acquiring HIV before age 60 for males and females, considering two models: STI-HIV and ASSA2003. The chart indicates a higher risk for females compared to males.](chart.png)
HIV prevalence in pregnant women in rural Vulindlela, South Africa (2005-2008)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>33.0%</td>
</tr>
<tr>
<td>23-24</td>
<td>51.1%</td>
</tr>
</tbody>
</table>
HIV Prevalence: CT township

MSM in community

% of population

AGE

- 15-19
- 20-29
- 30-39
- 40-49
- 50+

Males

Females
FIGURE 1. Proportion of AIDS Cases Among Adults and Adolescents, by Sex and Exposure Category Diagnosed in 2002, United States

Source: U.S. Centers for Disease Control, 2002
Incident infections US 2006

- Black Men: 115.7
- Hispanic/Latino Men: 43.1
- White Men: 19.6
- Black Women: 55.7
- Hispanic/Latino Women: 14.4
- White Women: 3.8
Gender differences over time
Burmese Migrants and Barriers to Access in Thailand

Knowledge about Condoms

Condom Usage

HIV - Causal linkages

Social Economic and power relations among and between MEN and WOMEN along with physiological differences

Determine Women and Men’s risk of infection and their ability to protect themselves effectively

And their respective share of the burden of the epidemic.

Gaps

• Constant surveillance
• Flexibility in responses
• Better design of prevention packages
• Better more appropriate interventions
Transmission risk
Youth in South Africa

• 4.5% of young men and 14.8% of young women (age 15 – 24) are infected
  SOURCE: UNAIDS, 2006

• Almost 16% of pregnant teens (age 15 -19), and almost 33% of pregnant young women (age 20 - 24) are infected
  SOURCE: SA DOH, 2004
Biological vulnerability of young women

• **Ratio of infection 3 : 1** for Males to Females in 15-24 year olds (1.3-12 x higher infection rates)

• Biologic characteristics that make young woman particularly HIV-1 susceptible, including:
  
  – **Cervical ectopy**, which is a common feature of the immature female genital tract,  
    (Plourde et al. J Infect Dis 1994; 170:313-7)
  
  – **Hormonal contraception**, which may increase HIV-1 susceptibility independent of sexual behavior  
    (Lavreys et al. AIDS 2004;18:2179-84)
  
  – **Childbearing** – the peripartum period may be a time of particularly enhanced HIV-1 risk  
    (Gray et al.  Rakai Study Group. 2005)
  
  – **Ovulation less frequent** - vaginal mucus less profuse.

  – **Semen may contain higher viral loads**
Biological vulnerability of Youth generally

- 100M STIs in < 25 yrs every year
- STIs are well-established cofactors for HIV-1 transmission, both susceptibility and infectivity.
- High rates of STIs among adolescents and young adults facilitate HIV-1 transmission to young women and men.
- SA Study of HSV infection showed:
  - Young men 5x incr HIV rate
  - Young female 8x incr HIV rate.
Summary: Phylogenetic analysis of HIV-1 in early infection in the context of a model of random viral evolution allows for the identification of transmitted/early founder virus(es) responsible for productive clinical infection (Keele et al., PNAS 2008).
### Routes and Risks of HIV-1 Transmission

<table>
<thead>
<tr>
<th>HIV invasion site</th>
<th>Anatomical sub-location</th>
<th>Type of epithelium</th>
<th>Transmission medium</th>
<th>Transmission probability per exposure event</th>
<th>Estimated contribution to HIV cases worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female genital tract</strong></td>
<td>Vagina</td>
<td>Squamous, non-keratinized</td>
<td>Semen</td>
<td>1 in 200 to 1 in 2,000</td>
<td>12.6 million</td>
</tr>
<tr>
<td></td>
<td>Ectocervix</td>
<td>Squamous, non-keratinized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocervix</td>
<td>Columnar, single layer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male genital tract</strong></td>
<td>Inner foreskin</td>
<td>Squamous, poorly keratinized</td>
<td>Cervicovaginal and rectal secretions and desquamations</td>
<td>1 in 700 to 1 in 3,000</td>
<td>10.2 million</td>
</tr>
<tr>
<td></td>
<td>Penile urethra</td>
<td>Columnar, stratified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intestinal tract</strong></td>
<td>Rectum</td>
<td>Columnar, single layer</td>
<td>Semen</td>
<td>1 in 20 to 1 in 300</td>
<td>3.9 million</td>
</tr>
<tr>
<td></td>
<td>Upper GI tract</td>
<td>Various</td>
<td>Semen</td>
<td>1 in 2,500</td>
<td>1.5 million</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal blood</td>
<td>1 in 5 - 1 in 10</td>
<td>960,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast Milk</td>
<td>1 in 5 - 1 in 10</td>
<td>960,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal blood</td>
<td>1 in 10 - 1 in 20</td>
<td>480,000</td>
</tr>
<tr>
<td><strong>Placenta</strong></td>
<td>Chorionic villi</td>
<td>Two layer epithelium (cyto and syncytiotrophoblast)</td>
<td>Maternal blood (intrauterine)</td>
<td>1 in 10 - 1 in 20</td>
<td>480,000</td>
</tr>
<tr>
<td><strong>Blood stream</strong></td>
<td>Blood products, IDU</td>
<td></td>
<td></td>
<td>95 in 100 - 1 in 150</td>
<td>2.6 million</td>
</tr>
</tbody>
</table>

Table adapted from the UNAIDS/WHO AIDS epidemic update and Hladik and McElrath (2008), Royce, and Cohen (1997)
Prospective Studies of COCs & HIV Acquisition

Plummer 1991
Sinei 1996*
Kilmarx 1998
Plourde 1994
Heffron 2011
Feldblum 2010
Morrison 2010
Kiddugavu 2003
Kapiga 1998
Saracco 1993
Reid 2010
Laga 1993
Myer 2007
De Vincenzi 1994
Ungchusak 1996

Source: Adapted from Polis (2011)
Prospective Studies of Injectables & HIV Acquisition

Mostly injectable, some OC

- Kilmarx 1998
- Ungchusak 1996
- Watson-Jones 2009
- Feng 2010
- Heffron 2011
- Bulterys 1994
- Baeten 2007
- Myer 2007
- Reid 2010
- Kiddugavu 2003
- Myer 2007

Source: Adapted from Polis (2011)
Gaps

• Why the difference in susceptibility
• Role of contraception
• Role of sex steroids
Physiology

• Some studies have shown:

• Viral loads in women tend to be lower than men at similar CD4 counts.

<table>
<thead>
<tr>
<th>CD4 category</th>
<th>0-199</th>
<th>200-499</th>
<th>&gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female VL lower than male by</td>
<td>40%</td>
<td>48%</td>
<td>57%</td>
</tr>
</tbody>
</table>
Response to treatment

**P=0.01**

**Change from Baseline in Mean CD4+ Count**
(p<0.01 between gender after adjusting for treatment effect)

**Figure 2. Study 903: Change in CD4 Cell Count (144 Weeks)**
Sex may influence the pharmacologic effects of the antiretroviral drugs.

• physiologic differences
  – total body weight, fat distribution, protein binding, gastric motility and acid secretions, glomerular filtration rates, and the influence of sex hormones on drug metabolism (including hormonal contraception).

• Expression and activities of drug transporter genes, proteins, and enzymes involved in phase 1 and 2 biotransformation, eg. P-glycoprotein.
CROI 2012: Patterson, et al.

• metabolism of tenofovir (TDF, Viread) in post-menopausal women (PMW) compared to pre-menopausal women.

• level of tenofovir in the blood and cervicovaginal fluids after the initial dose Truvada and steady-state level of drug exposure after four weeks on the regimen.

W4: PMW had higher levels of tenofovir in both the blood and the cervicovaginal fluids. This difference was significant.
20,328 Patients from 40 RCTS involving 7 drug classes and 16 ARVs

20 % Female (6-68%)
24 % Female in Naïve
15% Female in experienced.
Outcomes: TN

Week 48 Treatment naive: Response rate (HIV RNA <50 copies/mL, 95% CI) difference between female and male for each treatment arm.
Outcomes: TE

Week 48 Treatment experienced: Response rate (HIV RNA <50 copies/mL, 95% CI) difference between female and male for each treatment arm.
Viral load response by age

Week 48: Response rate (<50 copies/mL, 99.75% CI) difference between female and male for each age group

Naive

Experienced

Favors Male

Favors Female

Age > 42

33 < Age ≤ 42

Age ≤ 33
Viralogical response by region

Week 48: Response rate (<50 copies/mL, 99.75%CI) difference between female and male for each region

Region

Naive

Experienced

North America
Europe
C.S. America
North America
Europe
C.S. America

Female and male response rate difference by region

Favors Male

Favors Female
Virological response by region

Week 48: Response rate (<50 copies/mL, 95.75% CI)
difference between female and male for each ethnic group

- Naive
  - Caucasian
  - African American

- Experienced
  - Caucasian
  - African American

Favors Male

Favors Female
Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study.

• 46,201 ART-naïve adults starting ART between January 2002 and December 2009 in eight ART programmes across South Africa.

• Gender differences in mortality, LTFU, virological and immunological outcomes.

» Mornal Cornell, etc for IDEAA.
SA study continued….

- Median age 35 yrs and 65% Female
- Men had shorter time to death and LTFU
- End of study (77 500 py) 67% females in care
- At initiation: men older with lower CD4 and more advanced disease.
- Higher mortality in men (AHR 1.31 (1.2-1.4))
- Men also more at risk for LTFU (AHR 1.2 (1.1-1.28))
- Virological suppression similar at 12, 36, 48 mnth
• Women initiating ART had a higher baseline CD4+ cell count and better CD4+ cell count responses than men over 36 months.

• The median incremental CD4+ cell gains for women and men at 12, 24 and 36 months were 184 vs 154, 87 vs 76 and 56 vs 44 cells/μL respectively.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Med CD4 M/F</th>
<th>Med age M/F</th>
<th>Deaths</th>
<th>Mortality (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11,746</td>
<td>96:115</td>
<td>38:34</td>
<td>1,012</td>
<td>1.17 (1.02, 1.35)</td>
<td>20.49</td>
</tr>
<tr>
<td>2</td>
<td>2,670</td>
<td>89:106</td>
<td>36:32</td>
<td>215</td>
<td>1.23 (0.92, 1.66)</td>
<td>8.52</td>
</tr>
<tr>
<td>3</td>
<td>8,953</td>
<td>94:127</td>
<td>38:34</td>
<td>862</td>
<td>1.58 (1.38, 1.82)</td>
<td>20.49</td>
</tr>
<tr>
<td>4</td>
<td>7,142</td>
<td>82:105</td>
<td>36:31</td>
<td>632</td>
<td>1.26 (1.06, 1.50)</td>
<td>16.32</td>
</tr>
<tr>
<td>5</td>
<td>582</td>
<td>85:127</td>
<td>34:31</td>
<td>21</td>
<td>1.25 (0.52, 3.01)</td>
<td>1.22</td>
</tr>
<tr>
<td>6</td>
<td>3,268</td>
<td>66:103</td>
<td>36:34</td>
<td>195</td>
<td>1.31 (0.98, 1.76)</td>
<td>8.52</td>
</tr>
<tr>
<td>7</td>
<td>10,484</td>
<td>72:93</td>
<td>37:34</td>
<td>909</td>
<td>1.20 (1.04, 1.37)</td>
<td>20.49</td>
</tr>
<tr>
<td>8</td>
<td>1,356</td>
<td>95:125</td>
<td>38:32</td>
<td>103</td>
<td>1.11 (0.69, 1.77)</td>
<td>3.94</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>(I-squared = 42.5%, p = 0.095)</td>
<td></td>
<td></td>
<td>1.28 (1.16, 1.42)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Med: median
M/F: male compared with female
(a) Mortality by gender

![Graph showing mortality by gender over duration on ART (months)].

- **Solid line**: female
- **Dashed line**: male
(b) Loss to follow-up by gender

- female
- male
The graph illustrates the male vs female mortality ratio on ART and non-HIV mortality ratio over a follow-up period of 36 months. The mortality ratio remains relatively stable throughout the follow-up period, with a slight increase towards the end. The data indicates a higher mortality ratio for males compared to females, both on ART and non-HIV conditions.
In summary

• Men often come into care in more advanced state
• Thereafter response to ART virologically comparable
• In a number of studies women tend to respond better immunologically.
  – Pharmacological?
  – Physiological?
  – Behavioural?
Tolerance to ART

• Nevirapine, (NNRTI): rash and hepatitis >women than men.

• Protease inhibitor (PI): gastrointestinal intolerance and metabolic disorders more frequently among women.

• 83% of 60 cases of lactic acidosis with nucleoside reverse transcriptase inhibitors (nRTIs) involved women, and 85% of the 20 fatal cases were in women.
• lipodystrophy: 2258 HIV-infected persons on antiretroviral therapy - morphologic alterations were twice as likely in women.
Bone mineral Density

FIGURE 4. Osteopenia and Osteoporosis in WIHS
Gaps

• Pharmcodynamics
• Physiology
• Role of Sex hormones
• pharmacogenetics
Access and services

• Gender related reasons…….
  • important to investigate presence, causality and appropriate intervention

• Monitor response to interventions
Gaps

- Gender related Health Service Research
- Gender related translational research
- Structural barriers
- Human rights and social justice
OIs: Tuberculosis

• Women less likely to be notified
  – Male : Female 2.25:1 (study from India)

Women more likely to be cured

Male patients outnumbered females in all the unfavorable outcomes like death, failure, and default although none of the differences were statistically significant
HPV and HIV

• Significantly increased risk of cervical disease and CaCx in HIV infected women (Moodley et al., 2005).

• HIV positive women, in Johannesburg presented with invasive cervical cancer almost 10 years earlier than HIV seronegative women (Lomalisa et al., 2000).

• HIV positive women at a greater risk of lower genital tract neoplasias including vulvar and anal cancers (Ferenczy et al., 2003).
HIV and Anti Retroviral Drugs (ARVs)

• With the introduction of ARVs women will live longer and will not die before they develop cervical cancer

• In South Africa has the largest number of people on ARVs worldwide

• At an ARV clinic in Cape Town 93/106 (88%) were HPV positive (Digene HC2)
Genital Human Papillomavirus Prevalence and Human Papillomavirus Concordance in Heterosexual Couples Are Positively Associated with Human Immunodeficiency Virus Coinfection

Zizipho Z. A. Mbulawa,1,3 David Coetzee,2 Dianne J. Marais,1 Mercy Kamupira,2 Eugene Zwane,2 Bruce Allan,1 Deborah Constant,2 Jennifer R. Moodley,2 Margaret Hoffman,2 and Anna-Lise Williamson1,3

The Journal of Infectious Diseases 2009; 199:1514–24
• GENITAL HPV PREVALENCE WAS SIGNIFICANTLY HIGHER AMONG BOTH HIV-INFECTED WOMEN AND MEN THAN AMONG HIV-SERONEGATIVE WOMEN AND MEN

• THERE WAS NO DIFFERENCE IN THE LR-HPV OR HR-HPV PREVALENCE COMPARING HIV+ MEN WITH HIV+ WOMEN.
Prevention Efforts

We Can Do It!
Circumcision and Vaccines

- Step – HVTN 052
- Merck rAd5 vaccine
- Enhanced infection:
  - Men
  - Lack of Male circumcision
  - High background immunity
Likely locations of HIV acquisition in uncircumcised penis

(a)

(b)

McCombe AIDS 2006
### Role of baseline unprotected insertive anal sex

<table>
<thead>
<tr>
<th>Circumcised?</th>
<th>Unprotected insertive anal sex with HIV positive/unknown partner?</th>
<th>N</th>
<th>Hazard ratio (V:P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>359</td>
<td>1.1</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>640</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>359</td>
<td>2.5</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>429</td>
<td>6.1</td>
</tr>
</tbody>
</table>
## Where are we now: PrEP efficacy trial results, March 2012

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>Women</td>
<td>889</td>
<td>39% efficacy vaginal TFV gel</td>
</tr>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2499</td>
<td>44% efficacy FTC/TDF</td>
</tr>
<tr>
<td>TDF2 Study</td>
<td>Young men and women</td>
<td>1200</td>
<td>62% efficacy FTC/TDF</td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>Heterosexual couples</td>
<td>4758</td>
<td>67% efficacy TDF 75% efficacy FTC/TDF</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>High risk women</td>
<td>1950</td>
<td>FTC/TDF = futility</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women</td>
<td>5029</td>
<td>TDF = futility Vaginal TFV gel = futility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FTC/TDF ongoing</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>IDUs</td>
<td>2400</td>
<td>TDF ongoing</td>
</tr>
<tr>
<td>FACTS001</td>
<td>Women</td>
<td>2200</td>
<td>TFV gel enrolling</td>
</tr>
</tbody>
</table>
Adherence, plus

Biology
marginal vaginal concentrations, inflammation, acute infection, etc make PrEP more sensitive to less-than-perfect adherence

Statistical
low adherence (missed doses, missed visits) diminishes statistical power to demonstrate HIV protection

PrEP Efficacy

Jared Baeten CROI 2012
Gaps

- Gender specific prevention packages
- Role of gender in PrEP Effectiveness
- Role of gender in Prep Efficacy
- Female condoms
- Other barrier methods
The Prevention Revolution

“I have always believed that Women are God’s greatest invention”
Archbishop Tutu.
“Sex matters”

Thanks to
- Judith Aberg
- Susan Buchbinder
- Shirien Heidari
- IAS
- DTHC team:
  - Mens Division
  - Womens Division
  - Adolescent Division