Asymptomatic STIs – The Anova Health Institute Experience

Dr Kevin Rebe
Overview

• Background and Context

• Epidemiology in South African women

• Epidemiology in MSM

• Health4men ASTI Study

• Hepatitis C in South Africa
Asymptomatic STIs

- Syphilis
- Hepatitis and other sexual viruses
- HIV
- Gonorrhoea (GC)
- Chlamydial infection (CT)

Majority of non-urethral GC and CT are likely to be asymptomatic in key populations
Why STIs Matter?

• Common in all sub-populations

• Key populations are at high risk of both HIV and STI

• HIV sero-conversion is associated with
  – Genital ulceration (e.g. syphilis and HSV2)
  – Rectal gonorrhoea and chlamydia
  – Anal warts

• There are NO ongoing STI surveillance programs for key populations (MSM) in South Africa

• Syndromic treatment of STIs will fail to diagnose most cases of anal and pharyngeal STIs as they are frequently asymptomatic

• Lack of systematic state sector directed screening results in a deficit of specimens at the NHLS to allow for early detection of increasing antibiotic resistance
• Cross sectional survey at 25 Primary Health Care facilities in Mopani
• Random consecutive sampling of 600 participants
• Sexual history and risk factor questionnaire completed
• Physical examination
• Swabs taken from pharynx, vagina and anus
• PCR-based screening for gonorrhea and Chlamydial infection (PrestoPlus CT-NG-TV assay)
# Cross-Sectional Study of Genital, Rectal, and Pharyngeal Chlamydia and Gonorrhea in Women in Rural South Africa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) or Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30 (18–49)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Sepedi</td>
<td>310 (53)</td>
</tr>
<tr>
<td>Shangaan</td>
<td>260 (44)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (3.2)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>347 (58)</td>
</tr>
<tr>
<td>Married/engaged</td>
<td>256 (42)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>444 (74)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
</tr>
<tr>
<td>HIV-infected</td>
<td>187 (31)</td>
</tr>
<tr>
<td>HIV-uninfected*</td>
<td>274 (46)</td>
</tr>
<tr>
<td>Unknown</td>
<td>139 (23)</td>
</tr>
<tr>
<td>On antiretroviral therapy</td>
<td>100 (53)</td>
</tr>
<tr>
<td>On co-trimoxazole prophylaxis</td>
<td>61 (10)</td>
</tr>
<tr>
<td>Pregnant</td>
<td>103 (17)</td>
</tr>
<tr>
<td>Any history of VDS</td>
<td>130 (22)</td>
</tr>
<tr>
<td>Any history of GUS</td>
<td>46 (7.6)</td>
</tr>
</tbody>
</table>

*Reported to have tested negative for HIV less than 6 months before inclusion.

GUS indicates genital ulcer syndrome.
Cross-Sectional Study of Genital, Rectal, and Pharyngeal Chlamydia and Gonorrhea in Women in Rural South Africa

149 (25%) diagnosed with STI at any site (95% CI 21-28%)

Figure 1. Prevalence of chlamydia and gonorrhea infection by anatomical site in African women. Bars show prevalence with 95% CI of chlamydial (dark gray) and gonococcal (light gray) infection.
### Cross-Sectional Study of Genital, Rectal, and Pharyngeal Chlamydia and Gonorrhea in Women in Rural South Africa

**Reported Symptoms**
- **Chlamydia**: 26/93 (28%) women with genital chlamydial infection
- **Gonorrhea**: 18/58 (31%) women with gonococcal infection

**Rectal infection was not associated with reported unprotected anal intercourse**

### TABLE 3. Validity of Symptoms and Signs for Indicating Genital and Rectal Chlamydial and Gonorrheal Infection in African Women

<table>
<thead>
<tr>
<th>Symptoms of genital infection (n = 589)</th>
<th>Chlamydia*, % (95% CI)</th>
<th>Gonorrhea*, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>28 (19–37)</td>
<td>31 (19–43)</td>
</tr>
<tr>
<td>Specificity</td>
<td>63 (59–67)</td>
<td>64 (60–68)</td>
</tr>
<tr>
<td>PPV</td>
<td>12 (8.0–17)</td>
<td>8.6 (4.8–12)</td>
</tr>
<tr>
<td>NPV</td>
<td>82 (79–86)</td>
<td>89 (86–93)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms or signs of genital infection (n = 591)</th>
<th>Chlamydia*, % (95% CI)</th>
<th>Gonorrhea*, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>39 (29–49)</td>
<td>43 (30–56)</td>
</tr>
<tr>
<td>Specificity</td>
<td>52 (47–56)</td>
<td>53 (48–57)</td>
</tr>
<tr>
<td>PPV</td>
<td>13 (9.3–17)</td>
<td>9.0 (5.7–12)</td>
</tr>
<tr>
<td>NPV</td>
<td>82 (78–86)</td>
<td>89 (86–93)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms of rectal infection (n = 595)</th>
<th>Chlamydia*, % (95% CI)</th>
<th>Gonorrhea*, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>7.1 (0–15)</td>
<td>20 (0–40)</td>
</tr>
<tr>
<td>Specificity</td>
<td>88 (85–90)</td>
<td>88 (86–91)</td>
</tr>
<tr>
<td>PPV</td>
<td>4.2 (0–8.9)</td>
<td>4.2 (0–8.9)</td>
</tr>
<tr>
<td>NPV</td>
<td>93 (90–95)</td>
<td>98 (96–99)</td>
</tr>
</tbody>
</table>
• Most women with chlamydia and gonorrhea did not report any symptoms

• most women reporting symptoms did not have any chlamydial or gonococcal infection.

• As such, most infections would remain untreated if symptoms alone are used to screen and treat women for STI.

• Brings into question the validity of a syndromic approach for STI control

• Unrecognized infection puts many women at increased risk for long-term complications and contributes to a continuously high rate of transmission in the population.
Pilot STI screening service for HIV positive adults in a busy state-sector OPD clinic in urban Jhb

1109 PLWHA (551 men and 558 women)

Mean age 35 years for women and 38 years for men ($P<0.001$)

Overall reported condom use was approximately 66%

Urine (men) and endocervical swabs (women) were collected for PCR screening for:

- Neisseria gonorrhoeae (NG),
- Chlamydia trachomatis (CT),
- Trichomonas vaginalis (TV)
- Mycoplasma genitalium (MG) [in-house real-time MPCR, Rotor-Gene 3000 platform (Corbett Robotics Pty Ltd, Sydney, Australia)]
# Urethritis/Cervicitis Pathogen Prevalence and Associated Risk Factors Among Asymptomatic HIV-Infected Patients in South Africa

## TABLE 2. Frequency Distribution of Laboratory Diagnoses by Patients’ Gender

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n/N (%)</th>
<th>Male n/N (%)</th>
<th>Female n/N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence of urethritis and cervicitis pathogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em> (NG)</td>
<td>60/1108 (5.4)</td>
<td>24/550 (4.4)</td>
<td>36/558 (6.4)</td>
<td>0.127</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em> (CT)</td>
<td>23/1108 (2.1)</td>
<td>11/550 (2.0)</td>
<td>12/558 (2.2)</td>
<td>0.861</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em> (TV)</td>
<td>84/1108 (7.6)</td>
<td>27/550 (4.9)</td>
<td>57/558 (10.2)</td>
<td>0.001</td>
</tr>
<tr>
<td><em>Mycoplasma genitalium</em> (MG)</td>
<td>68/1108 (6.1)</td>
<td>39/550 (7.1)</td>
<td>29/558 (5.2)</td>
<td>0.189</td>
</tr>
<tr>
<td>Any pathogen (NG/CT/TV/MG)</td>
<td>209/1108 (18.9)</td>
<td>90/550 (16.4)</td>
<td>119/558 (21.3)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Other female genital tract infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>N/A</td>
<td>N/A</td>
<td>155/553 (28.0)</td>
<td>—</td>
</tr>
<tr>
<td><em>Candida</em> species on microscopy</td>
<td>N/A</td>
<td>N/A</td>
<td>101/553 (18.3)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Seroprevalence of syphilis and HSV-2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPR seroreactive</td>
<td>26/1106 (2.4)</td>
<td>13/550 (2.4)</td>
<td>13/556 (2.3)</td>
<td>0.978</td>
</tr>
<tr>
<td>TPPA seroreactive</td>
<td>237/1106 (21.4)</td>
<td>133/550 (24.2)</td>
<td>104/556 (18.7)</td>
<td>0.026</td>
</tr>
<tr>
<td>HSV-2 IgG seropositive</td>
<td>942/1106 (85.2)</td>
<td>463/550 (84.2)</td>
<td>479/556 (86.2)</td>
<td>0.357</td>
</tr>
</tbody>
</table>

Note: denominators vary due to missing slides or lack of serum samples.
Study Findings and Conclusions

A substantial “silent” burden of urethritis/cervicitis pathogens among PLWHA who are asymptomatic for genital discharges and/or their complications

Overall prevalence:
- 7.6% for trichomoniasis
- 6.1% for mycoplasma
- 5.4% for gonorrhoea
- 2.1% for chlamydial infection

Screened population was characterized by:
- Suboptimal condom use
- Low levels of knowledge of partners’ HIV serostatus
- Recent sexual intercourse with more than one partner
As STI co-infections may undermine future efforts to use ART for HIV prevention by increasing genital secretion infectiousness, there are potential benefits to be gained from strengthening STI screening activities within existing HIV treatment programs.
Mathematical model of sexual behaviour patterns in South Africa to determine incidence of HIV, SV, syphilis, chancroid, gonorrhoea, chlamydial infection, trichomoniasis, bacterial vaginosis and vaginal candidiasis

Assumptions about health seeking behaviour and treatment effectiveness were based on South African survey data. The model was fitted to available STI prevalence data.

In women aged between 15 and 49, syndromic management resulted in:

• 33% (95% CI: 23-43%) decline in syphilis prevalence
• 6% (95% CI: 3-11%) reduction in gonorrhoea prevalence
• 5% (95% CI: 1-13%) reduction in the prevalence of bacterial vaginosis and chancroid.

However:

• No detection of asymptomatic STIs
• Much of the decrease in prevalence in 1995-2005 could be ascribed to increased condom use and AIDS mortality
MSM and STI’s

Less threatening way to attract men into care

Can then engage for HIV testing and management

Treating STIs:

– Maintains mucosal integrity
– Less mucosal inflammation
– Lowers viral load in HIV positives
High Risk Sexual Behaviours Ongoing among MSM

• STI rates remain high
  – MSM account for 55% of new HIV infections
  – MSM account for 58% of new syphilis diagnoses

• 25% thought to be acquired through oral sex

• Why?
  – HIV complacency in the HAART era
  – Prevention messaging fatigue
  – Internet has changed the sexual market place by making anonymous sex dates easier
  – Increases in crystal methamphetamine use
Recent Syphilis and Rectal Gonorrhoea and/or Chlamydial Infections Are Associated with HIV Seroconversion in MSM

- 541 MSM with rectal NG / CT observed for 1197 person years
- 27 incident HIV infections (5%)
- Annual incidence 2.25% (95% CI 1.49-3.26)

### Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early syphilis within the past 2 years</td>
<td>3.94 (1.18-13.10)</td>
<td>4.04 (1.19-13.79)</td>
</tr>
<tr>
<td>&gt;2 CT/NG rectal infections within the past 2 years</td>
<td>8.16 (2.39-27.88)</td>
<td>8.85 (2.57-30.40)</td>
</tr>
</tbody>
</table>

Bernstein et al.  JAIDS 2010;53:537-543
A Little Anatomy

**Pharyngeal**
- Receptive oral sex
- Rimming

**Urethral**
- Penetrative oral sex
- Penetrative anal sex

**Anal**
- Receptive anal sex
- ?Rimming
- ?Sex toys
Recommended Screening for ASTIs

CDC (and various USA & EU guidelines)
- Yearly syphilis
- PCR screening of pharynx, anus and urethra based on sexual history
  - PCR’s are expensive and not accessible locally or feasible for most of Africa

WHO: Presumptive STI treatment for at risk MSM
- Reported UAI in the last year PLUS
- Partner with an STI OR
- Multiple partners
  - Large numbers of patients would get unnecessary treatment and increasing antibiotic resistance is a concern
43 HIV negative MSM enrolled as pre study for a PrEP trial in Kenya

Recruited from a group of MSM considered to be at high HIV risk

PCR screening for gonorrhea and chlamydia infection was performed
(GenProbe Aptima 2 Combo)

MSM provided self collected urine and a clinician collected swab

Clinical assessment

Anoscopy for those reporting receptive anal intercourse
# High prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections among HIV-1 negative men who have sex with men in coastal Kenya

Eduard J Sanders, Alexander N Thiong'o, Haile Selassie Okuku, et al.

*Sex Transm Infect* 2010 86: 440-441 originally published online July 23, 2010

## Table 1  Prevalence of *Chlamydia* and gonorrhoea in HIV-1 negative MSM, by sexual orientation of MSM, Coastal Kenya

<table>
<thead>
<tr>
<th>Sexual orientation</th>
<th>Chlamydia (CT)</th>
<th>Gonorrhoea (GC)</th>
<th>CT or NG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urethra N (%)</td>
<td>Rectum N (%)</td>
<td>Urethra N (%)</td>
</tr>
<tr>
<td>All MSM (n=43)</td>
<td>5 (12)</td>
<td>3 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>MSM only (n=13)</td>
<td>_</td>
<td>3 (23)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>MSMW (n=30)</td>
<td>5 (17)</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

2 MSM were symptomatic (1 urethral pain and 1 anal pain)

MSM-only had a higher prevalence of rectal or any infection than MSMW (46% vs 17%, p.0.04)
8000 Clients ever in care
Approx 50% HIV positive
>850 positive on DOH ART

50% of clinical visits are STI related

- Operational research
- Substance-abuse harm-reduction
The ASTI Study at Health4men

Symptomatic and Asymptomatic STI Screening among MSM.
Rebe, K, Lewis D, Myer L, Struthers, H, McIntyre JA

- Funding from PEPFAR / USAID via Anova Health Institute
- Prospective study, sequential sample
- 200 MSM recruited between Jan-Jul 2012
- Socio-behavioral and symptom questionnaire
- Detailed clinical examination for STIs
- HIV, syphilis screening
- PCR for GC and CT at 3 anatomical sites
- Validation of an in-house PCR kit
ASTI Specimen Collection

- Blood for syphilis and HIV screening
- Dirty urine
- Pharyngeal swab (clinician administered)
- Anal swab (clinician administered)
- Specimens and serum stored
ASTI Study Aims

- Describe the burden of asymptomatic STIs
- Identify risk factors associated with positive PCRs
- Calculate the NNT (number needed to test)
- Assess cost-efficacy of using PCR
- Develop a locally applicable screening algorithm
- Raise awareness in private and public sector
- Advocacy for PCR screening
Provisional Results

Raw, uncleaned data
All percentages are approximate only

<table>
<thead>
<tr>
<th>Indicator</th>
<th>No</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total MSM participants</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Transgender</td>
<td>15</td>
<td>7.5</td>
</tr>
<tr>
<td>History of transactional sex</td>
<td>77</td>
<td>38.5</td>
</tr>
<tr>
<td>HIV positive</td>
<td>88</td>
<td>44%</td>
</tr>
<tr>
<td>New HIV diagnoses</td>
<td>8</td>
<td>4%</td>
</tr>
<tr>
<td>New syphilis diagnoses</td>
<td>18</td>
<td>9%</td>
</tr>
<tr>
<td>Total PCR + for GC or CT</td>
<td>63</td>
<td>(31%)</td>
</tr>
<tr>
<td>Symptomatic PCR +</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic PCR +</td>
<td>48</td>
<td>(24%)</td>
</tr>
</tbody>
</table>

Rebe K et al, Unpublished
Provisional Results

SSTI and ASTI (Gonorrhoea and Chlamydia) by site of infection

Rebe K et al, In Press
Provisional Results

In univariate analysis, ASTI was strongly associated with:

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transgender identity</td>
<td>OR = 4.09, CI 1.38- 12.12</td>
</tr>
<tr>
<td>&gt;5 male sex partners within the past 12 months</td>
<td>OR = 2.56, CI 1.16- 5.62</td>
</tr>
<tr>
<td>Engaging in transactional sex in the past year</td>
<td>OR = 2.33, CI 1.13- 4.79</td>
</tr>
</tbody>
</table>

No association between ASTI and HIV status

Rebe K et al, Unpublished
ASTI - Summary

- STIs and ASTIs were common in sexually active MSM
- ASTIs may be increasing HIV transmission risk?
- PCR is now the preferred screening method for GC /CT
- PCR screening standard in GUM clinic in the developed world
- Sexual behavior based screening algorithms and development of cost-effective in-house PCR platforms should make this intervention relevant for Africa, especially in view of high detection rates
- Sentinal screening of MSM and other key populations should form part of South Africa’s STI response
- Should we treat ASTIs using WHO empiric guidance
GC Treatment Failures

• Treatment failures reported from:
  • Slovenia (ceftriaxone failure), Europe, Canada and the USA (cefixime failure)

→ 3 cases isolated in MSM (2 Jhb and 1 Cape Town)

→ One had definitive treatment failure following two courses of empiric treatment with cefixime

Lewis, D. NICD Communiqué. 2012
GC Epidemiology in MSM

STIs are increasing among MSM globally despite prevention programs*

MSM experience barriers to health care access**
- Stigma and prejudice from health care workers
- Heteronormative health programs
- MSM under-researched and under-resourced
- Current in-country STI guidelines not inclusive of MSM sexual health care needs

5/43 (12%) of MSM in coastal Kenya screened positive for GC***

EXPLORE Study: GC prevalence 5.5%; Incidence 11.2/100 person-years#

Median GC prevalence in MSM = 15.3%##

* Das, M. PLOS One 2010; Cowan, S. JAIDS 2012
** Rebe, K. SA HIV J 2013
*** Sanders, E.J. Sex Transm Dis. 2010
# Morris, S. CID. 2006
South African STI Guidelines

• Guidelines are not responsive to needs of MSM
  – Lack of guidance regarding anal and oral infections
  – Lack of resistance surveillance in a vulnerable population

Undertreated GC promotes HIV transmission

MSM prevalence already high → high community viral load

Highly effective HIV transmission in UAI (20 X vaginal sex risk.)

Untreated urethritis increases seminal HIV viral load by a factor of approximately 10.
Hepatitis C

- 3% of the global population are infected with hepatitis C (HCV).
- Transmission is mostly parenteral via needles.
- Heterosexual sex transmission is uncommon.
- MSM are at increased risk of HIV and HCV.
- From limited data the local prevalence of HCV is 0.03%-1%.
- Co-infection rates and risk factors in our local HIV population is not known.

Hepatitis C

- 313 HIV positive participants screened for HCV
  - 170 (54%) MSM from Ivan Toms Clinic
  - 143 (46%) non-MSM from Groote Schuur

- 10 (3.2%) overall tested positive for HCV
  - 9 (5.3%) in MSM
  - 1 (0.7%) in non-MSM (p=0.024)
## Hepatitis C

<table>
<thead>
<tr>
<th>Risk</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug use</td>
<td>5.2</td>
<td>0.8-33.2</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Intravenous</td>
<td>3.1</td>
<td>1.2-8.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Inhaled</td>
<td>2.8</td>
<td>0.8-9.9</td>
<td>P=0.028</td>
</tr>
<tr>
<td>Oral</td>
<td>1.4</td>
<td>0.8-2.4</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Nasal</td>
<td>2.0</td>
<td>1.0-4.4</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Rectal</td>
<td>1.4</td>
<td>0.9-2.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Sex with CSW</td>
<td>1.6</td>
<td>0.8-3.0</td>
<td>P=0.018</td>
</tr>
</tbody>
</table>

### Conclusions

Local HCV prevalence in HIV positive patients is underestimated. The risk seems to be limited to the MSM sub-group. Targeted HCV testing in this group is warranted.

Thank You

- PEPFAR/USAID
- Anova Health Institute
- D Lewis (NICD)
- L Gumede
- G De Swardt
- G Jobson
- H Struthers
- C Bamford
- J McIntyre

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