New STI Prevention Agents and Diagnostics

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Head of HIV Pathogenesis & Vaccine Research
Centre for the AIDS Programme of Research in South Africa (CAPRISA)
1. What is the main issue or question the presentation addresses?
   • To provide an overview of the STI landscape in context of HIV prevention in Southern Africa

2. What is the key finding or ‘takeaway message’?
   • Challenges remain with STI care, but there are new opportunities for research and implementation with new technologies and vaccines.

3. How does the research advance HIV prevention efforts?
   • Other STIs increase the risk of HIV acquisition, which means STI solutions are key to HIV prevention.
• The STI burden and Challenges of STI Care in Southern Africa
• Point-of-care Diagnostics to reduce Genital Inflammation and HIV Risk
• The STI Vaccine Pipeline
• The Story of DoxyPEP
• Way forward
New director named at National Institute of Allergy and Infectious Diseases after Fauci’s retirement
Global Burden of STIs, not just HIV

These numbers represent incident cases of chlamydia, gonorrhea, trichomoniatisis and syphilis in 2016.

WHO global regions and the incident cases of four STIs (chlamydia, gonorrhoea, trichomoniatisis and syphilis) from 2016 estimates. The WHO estimates of new cases of these four STIs worldwide in 2020 are shown at the bottom right of the figure.

STI Prevalence remains high in South Africa

STI prevalence: continuously high

Women
Chlamydia: 14.7%
Gonorrhoea: 6.6%

Men
Chlamydia: 6.0%
Gonorrhoea: 3.5%

The Big Elephant in the Room

STI

Advancing STI care in low/middle-income countries: has STI syndromic management reached its use-by date?

Challenges with Syndromic Management

Mlisana, et al. Symptomatic vaginal discharge is a poor predictor of STIs and genital tract inflammation in high-risk women in South Africa, J Infect Dis. 2012 Jul 1;206(1):6-14

### Poor accuracy of syndromic management

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Lab Diagnosis</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>25</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>-</td>
<td>179</td>
<td></td>
<td>723</td>
</tr>
</tbody>
</table>

Sensitivity = 12.3%  **7/8 remain undiagnosed.**
Specificity = 93.8%
PPV = 34.2%
NPV = 80.2%  **2/3 are over-treated.**

### Syndromic vs diagnostic STI care

- Less Expertise required
- Immediate Treatment
- Lower Cost
- Diagnostic Accuracy
  - Monitor Treatment response
  - Reduce HIV Risk
  - STI & Resistance surveillance
Why are STIs important for HIV prevention?

High burden of STIs in women at HIV acquisition

<table>
<thead>
<tr>
<th>Infection</th>
<th>CAPRISA 002 (N=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total %</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>15.4</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>8.3</td>
</tr>
<tr>
<td>Mycoplasma genitalium</td>
<td>8.3</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>10.9</td>
</tr>
<tr>
<td>HSV-2 PCR</td>
<td>8.3</td>
</tr>
<tr>
<td>Syphilis</td>
<td>5.0</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>62.6</td>
</tr>
</tbody>
</table>

Genital inflammation caused by STIs associated with HIV acquisition

Increased HIV susceptibility due to disruption of epithelial barrier and increase in HIV target cells.


To evaluate a model of enhanced STI care to reduce genital inflammation & HIV risk among young women in SA

An alternative STI care approach for young women in South Africa

Point-of-care testing, Immediate Treatment and Expedited partner therapy

Good performance of POC assays

<table>
<thead>
<tr>
<th>POC assay</th>
<th>Positive</th>
<th>Negative</th>
<th>Accuracy with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert CT</td>
<td>37</td>
<td>5</td>
<td>Sensitivity=100% (100% to 100%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>205</td>
<td>Specificity=97.6% (95.6% to 99.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV=88.1% (78.3% to 97.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV=100% (100% to 100%)</td>
</tr>
<tr>
<td>Xpert NG</td>
<td>12</td>
<td>0</td>
<td>Sensitivity=100% (100% to 100%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>235</td>
<td>Specificity=100% (100% to 100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV=100% (100% to 100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV=100% (100% to 100%)</td>
</tr>
<tr>
<td>OSOM TV</td>
<td>6</td>
<td>0</td>
<td>Sensitivity=75.0% (45.0% to 100%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>239</td>
<td>Specificity=100% (100% to 100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV=100% (100% to 100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV=99.2% (98.0% to 100%)</td>
</tr>
</tbody>
</table>

FTD, Fast Track Diagnostics; NG, Neisseria gonorrhoeae; POC, Point-of-care; TV, Trichomonas vaginalis.

**High STI and BV prevalence at baseline**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia trachomatis</td>
<td>18.4*</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>5.2#</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>3.0</td>
</tr>
<tr>
<td>BV or intermediate microbiota</td>
<td>69.3</td>
</tr>
<tr>
<td>Candida</td>
<td>18.0</td>
</tr>
</tbody>
</table>

**Effective STI clearance**

<table>
<thead>
<tr>
<th>Pathogen (N=77)*</th>
<th>Baseline N (%)</th>
<th>Week 6 N (%)</th>
<th>Week 12 N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. trachomatis</td>
<td>35 (45.5)</td>
<td>4 (5.2)</td>
<td>2 (2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>10 (13.0)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>0.041</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>5 (6.5)</td>
<td>2 (2.6)</td>
<td>0 (0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Any of CT, NG or TV</td>
<td>46 (59.7)</td>
<td>6 (7.8)</td>
<td>3 (3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>40 (52.0)</td>
<td>26 (33.8)</td>
<td>19 (24.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>14 (18.2)</td>
<td>7 (9.1)</td>
<td>12 (15.6)</td>
<td>0.668</td>
</tr>
</tbody>
</table>

*Total enrolled 101, but 24 missed either week 6 or month 3 visit

**STI treatment was strongly associated with reduced concentrations of pro-inflammatory cytokines IL-6, IL-1β, TNF-α.**

High Uptake of Expedited Partner Therapy

- 87% accepted EPT, mainly for one partner.
- 89% stated successful EPT, i.e. partner took treatment.
- 17% of women and 6% of partners experienced mild side effects consistent with antibiotic profiles.
- No allergic reactions or social harms reported.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall (N=51)</th>
<th>EPT (N=46)</th>
<th>No EPT (N=5)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td></td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>3.9 (2/51)</td>
<td>2.2 (1/46)</td>
<td>20.0 (1/5)</td>
<td>0.188</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>2.0 (1/51)</td>
<td>0</td>
<td>20.0 (1/5)</td>
<td>0.098</td>
</tr>
<tr>
<td>CT or TV*</td>
<td>5.9 (3/51)</td>
<td>2.2 (1/46)</td>
<td>40.0 (2/5)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*No N. gonorrhoeae cases were detected at 6-week follow-up.
Impact of POC Testing vs Lab-based Testing on STI Management in a large HIV Vaccine Trial

NG/CT Treatment initiation:
eThekwini clinic used POC testing

39 times faster NG/CT Treatment initiation at eThekwini vs Verulam-Isipingo aHR = 39.6, p < 0.001

TV Treatment initiation:
all clinics used POC testing

Fast TV Treatment initiation at all clinics AHR = 0.9, p = 0.770

Pipeline of Point-of-care STI assays

Key features:
- Accurate
- Fast turnaround time
- Simple to operate
- Affordable

New STI Guidelines and NSP STI Policy

- HIV Clinicians Society New STI guidelines
- NSP now includes specific objectives and targets for:
  - common STIs
  - HPV prevention and treatment
  - Hepatitis B and C prevention and treatment


WHO STI Vaccine Roadmap

STI Vaccine Roadmap: Priority Action Areas

1. Obtain better epidemiologic data on infection and disease sequelae
2. Model the theoretical impact of STI vaccines
3. Encourage investment in STI vaccine development
4. Advance basic science and translational research for STI vaccines
5. Expedite clinical development and evaluation
6. Define preferred product characteristics for STI vaccines
7. Plan for vaccine introduction and communication in advance

Twitter@HRPresearch
Chlamydia Vaccine Development

Safety and immunogenicity of the chlamydia vaccine candidate CTH522 adjuvanted with CAF01 liposomes or aluminium hydroxide: a first-in-human, randomised, double-blind, placebo-controlled, phase 1 trial

Vaccines induced anti-CTH522 IgG antibodies in all participants after 5 immunisations

Potential Impact of a Chlamydia Vaccine

Figure 1. A. Prevalence of chlamydia infection in a heterosexual population as a function of time, indicating the impact of a 100% protective vaccine. All model simulations are shown for 100% vaccine coverage before sexual debut (green with median in black), compared with the baseline scenario of no vaccine (red with median in blue). B. Prevalence of chlamydia infection as a function of time for vaccines that wane after a finite duration of 1, 5, or 10 years.

Figure 2. Effects of different male and female coverage rates before sexual debut on the prevalence of chlamydia infection (A) and the incidence of pelvic inflammatory disease (PID) (B) for a 100% protective vaccine. Results are median values for 10 model simulations. The results for 100% coverage of males and females are the same as in figure 1.

Meningococcal B Vaccine and Gonorrhea

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

News

Meningitis vaccine could protect against gonorrhoea, studies find

BMJ 2022; 377 doi: https://doi.org/10.1136/bmj.o997 (Published 19 April 2022)
Cite this as: BMJ 2022;377:o997

Prevention of Neisseria gonorrhoeae With Meningococcal B Vaccine: A Matched Cohort Study in Southern California

Katia J Bruxvoort, Joseph A Lewnard, Lie H Chen, Hung Fu Tseng, Jennifer Chang, Jennifer Yeltman, Jeanne Marrazzo, Lei Qian

Clinical Infectious Diseases, Volume 76, Issue 3, 1 February 2023, Pages e1341-e1349, https://doi.org/10.1093/cid/ciac436
Published: 01 June 2022 Article history

NIH Awards Will Advance Development of Vaccines for Sexually Transmitted Infections

NIAID Announces Four New Cooperative Research Centers

May 9, 2019

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, today announced awards to establish four Cooperative Research Centers (CRCs) focused on developing vaccines to prevent sexually transmitted infections (STIs). The grants, totaling $41.6 million over five years, will support collaborative, multidisciplinary research on the bacteria that cause syphilis, gonorrhea and chlamydia. At the end of the program, each center is expected to identify at least one candidate vaccine ready for testing in clinical trials.

1 U19 AI144177-01
Awardee Organization: University of Connecticut School of Medicine, Farmington, Connecticut
Principal Investigator: Justin Radolf, M.D.
Focus: Syphilis

1 U19 AI144180-01
Awardee Organization: Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland
Principal Investigator: Ann Jerse, Ph.D.
Focus: Gonorrhea

1 U19 AI144182-01
Awardee Organization: Georgia State University, Atlanta, Georgia
Principal Investigator: Cynthia Nau Cornelissen, Ph.D.
Focus: Gonorrhea

1 U19 AI144181-01
Awardee Organization: University of North Carolina Chapel Hill, Chapel Hill, North Carolina
Principal Investigator: Toni Darville, M.D.
Focus: Chlamydia
Use of doxycycline as prophylaxis against bacterial STIs

Two options studied:

<table>
<thead>
<tr>
<th>DoxyPrEP</th>
<th>DoxyPEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline as <strong>pre</strong>-exposure prophylaxis for bacterial STIs</td>
<td>Doxycycline as <strong>post</strong>-exposure prophylaxis for bacterial STIs <strong>24–72 hours</strong> after condomless sex</td>
</tr>
</tbody>
</table>

Bolan et al. OR=0.27 for CT, GC, or TP in HIV(+) MSM using doxy 100mg *daily* *Sex Transm Dis*

Molina et al. 47% reduction in 1st CT or syphilis in HIV(-) MSM on PrEP taking doxyPEP *No effect for GC* *Lancet Infect Dis*

Luetkemeyer et al. 65% reduction in quarterly STIs in PLWH and HIV(-) MSM and TGW on PrEP, w 1+ STI and taking doxyPEP *New Eng J Med*

Molina et al. ANRS 174 *Doxycycline trial*
65% reduction to 1st CT/syphilis/GC/Mgen *CROI 2023*

Stewart, et al. *NO REDUCTION* in incident STIs among nonpregnant cisgender women taking PrEP in Kenya *CROI 2023*

 Courtesy of Alex de Voux, University of Cape Town
The case for and against DoxyPEP

For

• Effective in studies with **MSM populations**

• Doxycycline generally **well tolerated**

• High rates of STIs among persons on HIV PrEP = opportunity for targeted intervention

• Persons on HIV PrEP want **access** to doxyPEP

Against

• ? Not effective among cisgender **women** (?anatomy, resistance, adherence)

• Could promote **antimicrobial resistance**

• **Limited data** available from RCTs

• If bundled with HIV PrEP use, **low use among heterosexual men and women** may limit potential impact
Real-world doxyPEP uptake – San Francisco

Doxy-PEP Uptake Among Patients with a PrEP Visit during Study Interval (N=762)

- 1+ partner AND 1+ STI in p12m (n=333)
  - Doxy-PEP: 246 (74%)
  - No doxy-PEP: 87

- 2+ partners and 0 STI in p12m (n=368)
  - Doxy-PEP: 219 (60%)
  - No doxy-PEP: 149

- 0 STI and ≤1 partner in p12m (n=61)
  - Doxy-PEP: 18 (29%)
  - No doxy-PEP: 43

Bacon et al., STI & HIV 2023 World Congress, Chicago, IL, USA, July 2023
Way forward

• Unacceptably high burden of STIs – urgent need for low-cost diagnostic care solutions in Southern Africa
• Drive development of POC technology for faster, accurate and affordable solutions
• Rapidly evaluate STI vaccine products – if effective against STIs, these trials could have HIV incidence endpoints
• Urgently assess reasons for DoxyPEP limitations among cisgender women
• Engage stakeholders and communities to re-energize STI research and implement solutions
Acknowledgement

• Alison Footman and Mitchell Warren from AVAC
• Alex de Voux, UCT
• SANAC, Remco Peters, Nireshni Mitchev and NSP writing team
• Anne Rompalo, Adrian Mindel and the CAPRISA 083 participants and study team
• Kwabena Asare and the HVTN 702 vaccine trial participants and team
• eThekwini Municipality Health and National DOH teams
• Lenine Liebenberg, Andile Mtshali and the CAPRISA lab team
• Koleka Mlisana and the NHLS STI team
• Many others

Contact: nigel.garrett@caprisa.org
X @nigegarrett