Novel HIV Prevention Methods for Women

State of the art injectables, rings, and antibody-mediated prevention

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Conflict of Interest Disclosure

• I have no potential conflict of interest to report
Presentation Outline

• Background
• Dapivirine intravaginal rings
• Antibody mediated HIV prevention
• Long acting injectable PrEP in HIV-1 prevention
• Conclusion
Current HIV Prevention Strategies

- Male circumcision
  - Gray R, Lancet 2007

- Intravaginal Rings
  - Nel et al 2016

- Treatment of STIs
  - Grosskurth H, Lancet 2000

- Male Condoms

- Female Condoms

- HIV Counselling and Testing
  - Coates T, Lancet 2000

- Microbicides for women
  - Abdool Karim Q, Science 2010

- Oral pre-exposure prophylaxis
  - Grant R, NEJM 2010 (MSM)
  - Baeten J, 2011 (Couples)
  - Paxton L, 2011 (Heterosexuals)

- Post Exposure prophylaxis (PEP)
  - Scheckter M, 2002

- Treatment for prevention
  - Abstinence
  - Be Faithful

- BNABs/Vaccines in the field
Pre-exposure Prophylaxis (PrEP) for HIV Prevention

• Daily pill (a combination ARV marketed as Truvada) approved for prevention of acquisition of HIV in guidelines
• The WHO has recommended oral PrEP for HIV-negative people at substantial risk of HIV
• Many trials contributed towards these recommendations
• Phase III PrEP trials used daily oral tenofovir-based pills:
  ✓ **Potent:** Broad and potent activity (all HIV subtypes)
  ✓ **Safe:** Favorable safety and tolerability
  ✓ **Easy:** Low pill burden, no food restrictions, few drug interactions
Adherence Correlates with Efficacy

Adherence (%) adjudicated by drug levels

Pearson correlation = 0.86, p=0.003

Abdool Karim, SS IAS 2014
Is Oral PrEP Enough?

What are the Alternatives to Oral PrEP?
Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study

Ellen H Luecke, Helen Cheng, Kubashni Woeber, Teopista Nakyanzi, Imelda C Mudekunye-Mahaka and Ariane van der Straten on behalf of the MTN-003D Study Team

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Figure 1. MTN-003D stage 2 HIV prevention potential product formulation discussion card.
Research article

Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study

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It is all About Choices!

- Even the most effective product cannot protect against HIV if it is not used
- A product that best suits one’s lifestyle and needs is more likely to be used
- Women’s preferences are not all the same - just as women have choices in contraception, they should have choices for HIV prevention, too
The Dapivirine Vaginal Ring

- The dapivirine ring was developed by the International Partnership for Microbicides (IPM)
- The ring contains an ARV -- dapivirine -- to offer women potentially longer-acting protection against HIV
- It is the first vaginal ring being tested for HIV prevention
- The ring is designed to be worn for a month at a time
  - The ring slowly releases dapivirine into the cervix and vagina over the month it is worn
Why test a vaginal ring for HIV prevention?

**Longer Acting:**
A monthly product may help with consistent use
Higher adherence → increased effectiveness

**Ease of Use:**
Flexible ring, can be self-inserted
Little or no impact on sexual activity

**Safety:**
Studies have shown the ring is safe to use and has very few side effects

**Privacy:**
Vaginal rings can be inserted and removed in private
Rarely felt by women or male partners
Dapivirine Vaginal Ring

• Two phase III clinical trials showed that a monthly vaginal ring containing dapivirine was:
  • well tolerated and
  • reduced HIV-1 incidence by approximately 30% compared to placebo.

• Protection was strongly linked to adherence
• Women >25 years more adherent

Baeten et al., Nel et al., NEJM 2016
Open-label Extension Trials
IPM 032 and MTN-025

• Two ongoing Phase IIIb, multi-center, open-label follow-on trials in follow up to the two pivotal Phase III trials

• Primary study objectives are to continue –
  o evaluating safety
  o assessing adherence to ring use

• Former Phase III participants who tested HIV-1 negative and were not pregnant at the time of screening were eligible to enroll in the OLE trials
Simulating an OLE Placebo Arm: Bootstrap Method

Step 1
Sample equivalent number of placebo participants from Specific Phase III Trial, with replacement, matching for:
• Age, STI at enrolment, research center

Step 2
Calculate HIV-1 incidence rate per 100 Person Years (PY) of follow-up

Step 3
Repeat the first two steps 10,000 times, resulting in 10,000 HIV incidence rates

Step 4
Based on 10,000 records:
• Calculate the mean
• Obtain 95% CI from ordered 250th, 9750th records

IPM 027/The Ring Study:
3.9 per 100 PY
95% CI: 2.9-4.9

MTN-020/ASPIRE
4.1 per 100 PY
95% CI: 3.2-5.1 ;L,
Interim Results: 
HIV-1 Incidence

<table>
<thead>
<tr>
<th></th>
<th>IPM 032/DREAM</th>
<th>MTN-025/HOPE</th>
</tr>
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<tbody>
<tr>
<td>HIV-1 seroconversions</td>
<td>11 in 623 PY</td>
<td>12 in 616 PY</td>
</tr>
<tr>
<td>HIV-1 incidence</td>
<td>1.8 per 100 PY</td>
<td>1.9 per 100 PY</td>
</tr>
<tr>
<td></td>
<td>95% CI: 0.9-3.2</td>
<td>95% CI: 1.2-3.0</td>
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<tr>
<td>Based on 10,000 bootstrap samples, HIV-1 incidence in the modelled placebo group is</td>
<td>3.9 (95% CI: 2.9-4.9) per 100 PY</td>
<td>4.1 (95% CI 3.2-5.1) per 100 PY</td>
</tr>
</tbody>
</table>

The HIV-1 incidence of 1.8 per 100 PY observed in DREAM, and 1.9 per 100 PY observed in HOPE, did not occur in these 10,000 samplings.

Data cut-off 29 Sep ’17 and 06 Oct ’17 respectively
Dapivirine Vaginal Ring - Summary

• Interim results from these open-label extension trials of the dapivirine vaginal ring indicate:
  • High uptake
  • High adherence, and
  • HIV-1 incidence has been half of the expected rate.

• These are the first data to assess use of the dapivirine vaginal ring and HIV-1 protection in an open-label context.

• Dapivirine Vaginal Ring is currently under regulatory review by the European Medicines Agency (EMA) through an Article 58 application.
Dapivirine Vaginal Ring - Summary

• Procedure allows EMA, in cooperation with the World Health Organization (WHO), to provide a scientific opinion on the safety, efficacy and quality of medicines
  • marketed exclusively outside of the European Union - specifically in low- and middle-income countries
  • diseases of major public health interest.

• Should the EMA grant a positive opinion, IPM will seek WHO prequalification, which many national regulatory agencies in African countries consider in their regulatory reviews.
Dapivirine Vaginal Ring – Thank you
Can antibodies be used to prevent HIV-1 infections?
Passive Antibody Protection

• An alternative approach to prevention and/or treatment of infectious diseases is passive administration of antibodies

Can antibodies be used to prevent HIV-1 infections?

• Can we use an antibody made by scientists and give it to people directly to prevent HIV infections?
Neutralizing Antibodies Preventing HIV Infection

An example of a neutralising antibody is VRC01
Passive Antibody Prevention
Can a passively infused monoclonal antibody VRC01 prevent HIV-1 infection in high risk adults?

Two harmonized cohorts:

2,700 MSM + TG in North & South America, Switzerland
1,900 Heterosexual women in sub-Saharan Africa

Both trials opened in April/May 2016
AMP in sub-Saharan Africa

7 Countries

20 Sites
The Main AMP Study Questions

• Is the VRC01 antibody safe to give to people?
• Are people able to “tolerate” the antibody without becoming too uncomfortable?
• Does the antibody lower people’s chances of getting infected with HIV?
• If the antibody does lower people’s chances of getting infected with HIV, how much of it is needed to provide protection from HIV?
The AMP Study in SSA: Selected Eligibility Criteria

• Women, 18-40 years of age
• HIV uninfected
• Risk behavior related criteria:
  • Female who has had vaginal or anal intercourse with a male partner in the past 6 months
  • All volunteers in a mutually monogamous relationship with an HIV(-) partner for > 1 year are excluded.
• Volunteers with clinically significant medical conditions are excluded
AMP Studies

HVTN 703/ HPTN 081
African Women

- **1567** enrolled
- **82%**
- **95%** retention through **17,368** clinic visits
- **99%** adherence of **7852** infusions

HVTN 704/ HPTN 085
MSM + TG

- **2367** enrolled
- **88%**
- **94%** retention through **28,471** clinic visits
- **100%** adherence of **12,861** infusions
HVTN 127/HPTN 087: Study Status
• A phase 1 clinical trial to evaluate the safety and drug levels of VRC07-523LS, administered to healthy, HIV-uninfected adults.
• Study activated on 2 February

HPTN 088
• A Phase I clinical trial to evaluate the safety, pharmacokinetics, and functional activity of a tri-specific antibody, SAR441236, in healthy, HIV-1 uninfected adults. Under development

HPTN 089
• A Phase I clinical trial to evaluate the safety, pharmacokinetics, and functional activity of a combination of VRC07-523LS, PGT121, and PGDM1400 in healthy, HIV-1 uninfected adults. Under development
What about long acting injectable PrEP in HIV-1 prevention?
Long acting injectable PrEP in HIV-1 prevention

Advantages
• Injection every 1-3 months could address adherence issues
• Different drug, not used heavily for treatment -> less concern for resistance/cross-resistance

Disadvantages
• Cannot be removed once given → prolonged side effects
• Long pharmacologic tail after last injection
  (up to 48 weeks)
→ safety and resistance if becomes HIV+
Long-Acting Injectable Cabotegravir for PrEP Well Tolerated in HPTN 077: Results Support Dosing Regimens in HPTN 083 and HPTN 084

Jul 25, 2017

133 women enrolled
33% 18-24 years
Well tolerated and feasible
HPTN-084

- 3,200 women
- 18 - 45
- HIV negative
- Sexually active, Voice score > 2
- In general good health per clinical and laboratory assessments
- Willing to undergo all study procedures
- 20 research sites in 7 countries in Sub-Saharan Africa
- Expected HIV incidence > 3.5/100 person years
HPTN 084

Giving Women Control of HIV Prevention: How Injectable PrEP Could Change Everything

Efficacy of injectable cabotegravir for PrEP in HIV-uninfected women

140 women enrolled to date

31% 18-24 years SSA
Long acting injectable PrEP in HIV-1 prevention

- PrEP effectiveness compromised by need for regular adherence
- Effective injectable LA formulations represent the next generation of PrEP.
- Obviate the need for a daily or peri-coital pill-taking activity
- Do not entirely solve **adherence** problems
- Need for **oral lead-in phase**
- **Long tail phase** – may pose a challenge

Conclusion

• Reasonable likelihood that we will conquer
• It will take our combined effort to curb the epidemic...
  • Through bNAb's or
  • An HIV vaccine
  • An intra-vaginal ring
  • Oral PrEP
  • Long acting injectable agent
  • A combination of all or some of these.

“*The secret is to gang up on the problem (HIV), rather than compete against each other*” - adapted, Thomas Stallkamp
Thank you