Towards HIV eradication

HIV prevention research in adolescents

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I have no conflicts of interest to declare
Presentation Outline

• State of the epidemic in adolescents
• Biomedical HIV prevention
  • Oral PrEP
  • Intra-vaginal rings
  • Antibodies
  • Novel DDSs
• Conclusion
Presentation Outline

• **State of the epidemic in adolescents**
  • Biomedical HIV prevention
    • Oral PrEP
    • Intra-vaginal rings
    • Antibodies
    • Novel DDSs
  • Conclusion
State of the Epidemic in Adolescents

• Despite global progress in the last decade, adolescents still bear a disproportionate burden of the HIV/AIDS disease

<table>
<thead>
<tr>
<th></th>
<th>Adolescents 10-19</th>
<th>Girls 10-19</th>
<th>Boys 10-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of adolescents living with HIV</td>
<td>1.6 million [1.1 million – 2.3 million]</td>
<td>970,000 [540,000 – 1.4 million]</td>
<td>580,000 [510,000 – 950,000]</td>
</tr>
<tr>
<td>Estimated number of adolescents newly infected with HIV</td>
<td>190,000 [59,000 – 380,000]</td>
<td>140,000 [29,000 – 280,000]</td>
<td>50,000 [8,600 – 120,000]</td>
</tr>
<tr>
<td>Estimated number of adolescents dying of AIDS-related causes</td>
<td>33,000 [22,000 – 47,000]</td>
<td>16,000 [10,000 – 24,000]</td>
<td>16,000 [12,000 – 23,000]</td>
</tr>
</tbody>
</table>

• Eastern and Southern Africa – the region most affected by HIV – 19% of adolescent girls and 14% of adolescent boys aged 15-19 have been tested for HIV in the past 12 months and received the result of the last test.

2018 HIV Estimates: UNAIDS/UNICEF database
The Youth Bulge

Particularly pronounced in sub-Saharan Africa

• High rates of HIV in young women and men remain unchecked
• If prevention isn’t effectively targeted to this population, early gains in the fight against the epidemic will be reversed.

Big Data Real People, AVAC Report, 2016
Slow decline in new infections among adolescents

Annual number of new infections

Age 15-19


250,000 - 260,000
280,000 290,000 310,000 330,000 350,000 370,000

Slow decline in new infections among adolescents

Annual number of new HIV infections among children and adolescents, by age, 2018–2030

UNICEF special report | December 2018
Global targets from the Super-Fast-Track framework for ending AIDS in children, adolescents and young women by 2020

**START FREE**
Eliminate new HIV infections among children (aged 0–14) by reducing the number of children newly infected annually to less than 20,000 by 2020.

**STAY FREE**
Reduce the number of new HIV infections among adolescents and young women (aged 10–24) to less than 100,000 by 2020.

**AIDS FREE**
Provide 1.4 million children (aged 0–14) and 1 million adolescents (aged 15–19) with HIV treatment by 2020.
Start free, stay free, AIDS free

Preventing new HIV infections
- Use of digital platforms to disseminate info
- Biomedical interventions for HIV prevention

Treatment and retention in care
- Family centred testing
- Peer-support
- Point of Care testing

Cross-cutting approaches
- Adolescent friendly services
- Cash and care
- Targeted community outreach for adolescents
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  - Antibodies
  - Novel DDSs
- Conclusion
Oral PrEP

- Shows a clear dose-response relationship of protection and adherence.

- Protection modelled to be 99% when taken 7 days per week as prescribed.

- Modelled data suggest some forgiveness of missed doses for protection against rectal exposures

- Protection against vaginal exposures is modelled to be much less forgiving of missed doses.

- Urgent need for PrEP agents that have more convenient dosing schedules.
Adolescents and Oral PrEP

Currently, indications for PrEP including initial and follow-up prescribing and testing procedures are the same for adolescents and adults.

Adolescents’ access to PrEP is dependent upon several external factors including parental consent and involvement, confidentiality, and access to healthcare providers who are knowledgeable and trained to prescribe PrEP.

Additional concerns that potentially limit adolescents’ access to PrEP include stigma, psychological burden and potential adverse health effects such as decreased bone mineral density.

HPTN 082

Uptake and adherence to daily oral TDF/FTC PrEP in HIV negative young (16-25 yrs) Southern African women

Why was the HPTN 082 study done?

To find ways to help young women in southern Africa start and take daily oral pre-exposure prophylaxis (PrEP) consistently
451 young women (ages 16-25) enrolled at 3 sites in 2 countries

- Average age of participants was 21 Age range 16-25
- There were no safety concerns related to tablet use by participants
- Most women took PrEP in the first three months.
- About 1 out of 4 of these women had high adherence to oral PrEP
- At six months about half of the women were taking PrEP.
- About 1 in 5 of them had high adherence
- Women who perceived themselves to be at risk of HIV were motivated to use and had higher adherence at 6 months
- Many young women are interested and willing to start taking oral PrEP
- However, there are challenges for young women to take daily oral PrEP
- Longer-acting PrEP & choice of options will likely increase uptake, adherence & persistence (i.e., effective coverage)
Dapivirine Vaginal Ring (IPM)

Long-acting PrEP formulated as a flexible silicone ring that slowly releases the antiretroviral dapivirine

- Potential for **better adherence**
- Long acting, strong safety profile
- No related resistance
- Discreet - woman-initiated and controlled.
- Easy to use, scalable

HOPE and DREAM results suggest **interest in, adherence to, safety and effectiveness of** the dapivirine vaginal ring when used in an open-label setting.

27% reduction

31% reduction

Baeten et al., Nel et al., NEJM 2016

Dapivirine Vaginal Ring is currently under regulatory review by the European Medicines Agency (EMA) through an Article 58 application.
HOPE Study: The details

• 1,456 women enrolled at 14 sites in 4 countries
• HOPE participants could choose if they wanted to use the ring or not
• Average age of participants was 31
  • Age range 20-49
• Procedures
  • Clinical exams; STI, HIV and pregnancy testing; counselling and sample collection
HOPE Study: Summary

• Most women chose to use the ring, and they used it more than in the earlier study of the ring
• The ring is very safe
• The ring reduces HIV risk
MTN 034: REACH

• Next steps in understanding HIV prevention in young African women.
• **Purpose:** To assess safety and adherence of the Dapivirine (25 mg) Vaginal ring and Truvada (FTC /TDF) Tablet amongst African adolescent and young women.
• **Study Population:** Healthy, HIV-uninfected, 300 adolescent females (15 - 17 years old) and 150 young women (18-21 years old) on effective contraception.
REACH: MTN-034

Daily oral TDF/FTC PrEP

Monthly dapivirine VR

EMPOWER YOUNG WOMEN
Longer-acting, systemic HIV prevention products represent a product development priority

**Improved product profile = potential for greater adherence**

- Less user-dependent, safer, more effective
- More forgiving
- More compatible with women’s lifestyles (particularly in SSA)
- More preferable – Abstract #64, Donaldson *et al*
- Longer duration of protection
- Fewer follow-up visits to clinic

Drug development strategies to improve favourable characteristics: nano-formulations; prodrugs; devices
Long acting injectable PrEP

Advantages
• Injection every 1-3 months could address adherence issues
• Different drug, not used heavily for treatment -> less concern for resistance/cross-resistance
• People are familiar with injections - highly acceptable
• Women have talked about how injections are more discreet and private than pills or rings

Disadvantages
• Cannot be removed once given
• Confirmation of tolerance before long-acting injection:
  • Oral lead in phase
• Long pharmacologic tail after last injection (up to 48 weeks) → safety and resistance if becomes HIV+
• IM dosing every 4 to 8 weeks
• IM injection cannot be removed:
  • Toxicity
  • Desire to stop PrEP
Cabotegravir Long-Acting Injectable (ViiV)

Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial

Martin Markowitz, Ian Fest, Robert M Grant, Kenneth H Mayer, Richard Ellen, Deborah Goldstein, Chester Fisher, Magdalena E Szewczyk, Joel E Gallant, Hong Van Tuij, Winifred Winkleberg, David A Margolis, Richard J Hasbrou, Brits S Sturck, Susan I Fund, Parul Patel, Elizabeth Gould, Alex R Brelant, Kimberly P Smith, William K Speer


Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial


HIV Life Cycle: No Cabotegravir
HIV Life Cycle: With Cabotegravir
Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)

Graph designed by Ric Uhl

Courtesy of M. Cohen, IAS 2019
There is a long history of using antibodies to prevent viral infections

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>PRODUCT DESCRIPTION</th>
<th>INDICATION</th>
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<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
<td>Prevention (travel)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
<td>Prevention in High Risk Infants</td>
</tr>
<tr>
<td>VZ</td>
<td>Varicella Zoster Immune Globulin</td>
<td>Post Exposure</td>
</tr>
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</table>

And, most effective vaccines induce antibodies that neutralize the pathogen.

Can an antibody be used to prevent HIV?

Thanks to John Mascola for this slide.
Neutralizing Antibodies Preventing HIV Infection
Multiple antibody neutralization against HIV

Thanks to Lisa Donohue for this video.
IslaTravir (EFdA, MK-8591, Merck)
A First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI)
With Multiple Mechanisms of Action

**Oral Pill**
- Once-monthly
- Clinical status: Phase 1/2

**Subdermal Implant**
- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator
- Potential to last at least 1 year
- In Phase 1: generally well tolerated, with no discontinuations due to an AE and no severe implant-related AEs
Next-Generation: Implantable Drug Delivery Systems

- Nondegradable Pod-Type TAF Implant (Oak Crest Institute of Science)
- Nondegradable Mini-Pump Implant (Intarcia Therapeutics)
- Refillable Transdermal Nanofluidic Implant (Houston Methodist Research Institute)
- Biodegradable Reservoir TAF Implant (RTI International)
- Subdermal Pellet System (CONRAD)
- Nondegradable Reservoir CAB Implant (SLAP HIV-Northwestern University)
Other Novel Drug Delivery Systems in Preclinical Development Pipeline

- MPT Intrauterine System (CONRAD)
- Injectable Depot Systems (UNC, CONRAD, others)
- Microarray Needle Transdermal Patch (PATH, others)
- Nano- and Microparticle-Based Delivery Systems (CONRAD, others)
- “Mini-Pillbox” as Once-Weekly Oral Capsule (MIT/Harvard)
- Electrospun Nanofibers (U. Washington, others)
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Being an adolescent is complicated!

What if I can’t use a condom?

Adolescents are less likely to:
- Use condoms
- Access PrEP
- Access contraception
- Be tested
- Be on ART
- Be suppressed

More likely to:
- Experiment with sexuality
- Experiment with drugs
- Fall out of care
- Have high levels of drug resistance

Sources: Demographic and Health Surveys 2014—2017, PHIAs
Towards HIV eradication

HIV prevention (research) in adolescents

To beat the epidemic, we need to focus more on adolescents and young people.

Excluding adolescents from novel product development delays evaluation in that age group and delays access for this vulnerable group.

If this age group is ignored, these youngsters age up and become blessers and parents, so the cycle of transmission continues.

Attention to the social determinants of health is vital to address these gaps.
Thank you