Translating the Science to End New HIV Infections in Kenya

Perspectives, Practices and Lessons

Nairobi, 28 - 30 May 2017
AIDS 2016 Post-Conference Workshop
Setting the Stage

Overview of key messages from the AIDS 2016 conference with implications for local policy and practice

Kenneth Ngure
School of Public Health
Jomo Kenyatta University of Agriculture and Technology
Outline:

- PrEP
  - Efficacy to Effectiveness
  - Pregnancy
  - Products in the pipeline
- Vaginal Rings
- ART
  - Promise Study
  - Search Study
- Vaccines
- Gender
- Policy Implications
Efficacy  ➡  Effectiveness
Overall evidence for PrEP

**Study**

- **IPERGAY – on demand Truvada**
  (MSM – France)
  Effect size (CI): 86% (39; 99)

- **PROUD – daily oral Truvada**
  (MSM – United Kingdom)
  Effect size (CI): 86% (62; 96)

- **Partners PrEP – daily Truvada**
  (Discordant couples – Kenya, Uganda)
  Effect size (CI): 75% (55; 87)

- **Partners PrEP – daily oral Tenofovir**
  (Discordant couples – Kenya, Uganda)
  Effect size (CI): 67% (44; 81)

- **TDF2 – daily Truvada**
  (Heterosexuals men and women- Botswana)
  Effect size (CI): 62% (22; 84)

- **iPrEx – daily Truvada**
  (MSM - America’s, Thailand, South Africa)
  Effect size (CI): 44% (15; 63)

- **FEMPrEP – daily Truvada**
  (Women – Kenya, South Africa, Tanzania)
  Effect size (CI): 6% (-52; 41)

- **MTN003/VOICE – daily Truvada**
  (Women – South Africa, Uganda, Zimbabwe)
  Effect size (CI): -4% (-49; 27)

- **MTN003/VOICE – daily Viread**
  (Women - South Africa, Uganda, Zimbabwe)
  Effect size (CI): -49% (-129; 3)

- **CAPRISA 004 – coital Tenofovir gel**
  (Women – South Africa)
  Effect size (CI): 39% (6; 60)

- **MTN003/VOICE – daily Tenofovir gel**
  (Women – South Africa, Uganda, Zimbabwe)
  Effect size (CI): 15% (-21; 40)

- **FACTS 001 – coital Tenofovir gel**
  (Women – South Africa)
  Effect size (CI): 0% (-40, 30)

Celum, AIDS 2016
Moving PrEP from evidence to implementation requires…

- Not being paralyzed by inconsistent efficacy results
  - Understanding low adherence in some populations

- Demonstration projects of targeted PrEP as part of combination prevention to populations with high HIV incidence
  - Define who wants it, how long they use it, when & how to discontinue PrEP

Celum, AIDS 2016
Demonstration projects for new innovations in prevention

• The pathway from a clinical trial results to programmatic roll-out is not fully defined for a new prevention intervention.

• Demonstration projects have been called for as part of the pathway to scale-up of PrEP
  – including in Kenya and Uganda, which had hosted one of the pivotal clinical trials of PrEP for HIV prevention, among HIV serodiscordant couples (the Partners PrEP Study)

Graphic: AVAC
Partners Demonstration Project

- For couples initiating ART at enrollment, PrEP was offered through 6 months, then stopped:
  - HIV+ partner
  - HIV- partner
  - PrEP
  - PrEP prior to viral suppression in HIV+ partner
  - Protection through sustained ART use

- For couples in which the infected partner delayed or declined ART, PrEP was continued until 6 months after ART initiation:
  - HIV+ partner
  - ART delayed
  - HIV- partner
  - PrEP
  - PrEP prior to ART initiation and then prior to viral suppression in HIV+ partner
  - Protection through sustained ART use

- This strategy is supported by mathematical modeling as potentially highly effective and cost-effective (Hallett et al. PLoS Med 2011; Ying et al. JIAS 2015)

Baeten, AIDS 2016
The observed incidence is a **95% reduction** compared to expected, a result that was highly statistically significant.
Pregnancy
There are multiple and complex personal, social and cultural factors that motivate women to conceive naturally even when the risk of HIV acquisition is high.
Pregnancy & PrEP Guidelines

• South Africa guidelines do not include PrEP use in pregnancy
  – Kenya guidelines include use in Pregnancy in specific populations
  – Uganda guidelines in process

• US practice, HIV-serodiscordant couples have been provided PrEP for periconception use (HIVE-HIVPrEP)
  – What is the balance between risk of use and none use among women at high risk
  – Do we need more pregnancy safety data? (Heather Watts presentation)

Mugo, AIDS 2016
Is there willingness to use PrEP?

Partners Demonstration Project
• Pregnant HIV uninfected women were given an option to continue using PrEP in pregnancy
  – 88% of the women chose to use PrEP
  – Analysis of birth outcomes on-going

Mugo, AIDS 2016
Summary

• Public health delivery requires products that are safe during peri-conception period
  • Majority of pregnancies are known after use of products
  • Fertility desire is global
    - PrEP provides cost effective options for implementation of safer conception options for women & men at risk for HIV infection
• Pregnancy increases HIV risk and requires protection
• PrEP is an important tool for elimination of mother to child HIV transmission and should be considered as part of PMTCT programs

Mugo, AIDS 2016
PrEP Products in the Pipeline
PrEP Products in the Pipeline

- **Injectable PrEP products**: completed phase 1 safety studies & cohort studies
  - HPTN 069/ACTG 5305: Phase II Study of Maraviroc-Based Regimens for HIV PrEP in MSM (CROI 2016 abstract 103)
  - Long-acting Oral and Parental Dosing of MK-8591 for HIV treatment or prophlaxix (CROI 2016 abstract 98)
  - ÉCLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men (CROI abstract 106)
  - Cabotegravir Long-Acting Injection Protects Macaques Against Intravenous Challenge (CROI 2016 abstract 105)

Other abstracts at IAS 2016

- **Long acting PrEP products will require special consideration for use among young women**
  - Tail product after cessation of use & implications for safety & resistance (PMTCT)
  - Inadvertent use among unintended pregnancy & infant safety (infant well being & resistance virus, infant plasma levels & breast milk levels)

-- Mugo, AIDS 2016
Vaginal Rings
Why a vaginal ring for prevention?

**Longer Acting:**
- Used monthly or longer = sustained release of drug
- May help with consistent use
- Higher adherence → increased effectiveness

**Ease of Use:**
- Women can insert (and remove) the ring themselves
- Little or no impact on sexual activity
- Cheap to make, distribute, and monitor

**Safety:**
- Topical delivery minimizes systemic drug exposure, which may both reduce potential side effects, interface well with reproductive health choices, and respond to patient preferences

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

*Vaginal rings are used in the US and Europe to deliver contraception*

Baeten, AIDS 2016
The dapivirine vaginal ring

• Flexible silicone vaginal ring developed by the International Partnership for Microbicides (IPM)
  – Slow release of dapivirine over a month
  – Potential for further development for longer (e.g., 3 months) use
  – Potential to add medications for multipurpose prevention

• Two Phase III trials – ASPIRE and The Ring Study – conducted in parallel to enable rapid regulatory submission if ring found safe and effective
  – N=4588, 4 countries, mean age=26, most unmarried

Baeten, AIDS 2016
The dapivirine ring was effective

27% reduction
P=0.046

31% reduction
P=0.04

Baeten et al. & Nel et al. NEJM 2016

Baeten, AIDS 2016
HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

- Age 18-21: -27% (-133,31) placebo incidence 5.4%/yr
- Age 22-26: 56% (19,76) placebo incidence 6.1%/yr
- Age 27-45: 51% (8,74) placebo incidence 3.0%/yr

Adherence measures were statistically significantly lower among women 18-21 years compared to women >21 years.
The dapivirine ring was safe

• No safety risk in ASPIRE/Ring Study:
  – SAEs, genital Aes, etc.
  – No increased risk of HIV resistance in seroconverters & no interference with ART response
  – No evidence of adverse effects for women who became pregnant

consistent with minimal systemic absorption

Baeten, AIDS 2016
HIV protection was higher with higher adherence

When taking into account residual levels of dapivirine in the ring (a marker of its use) – HIV protection with greater use was 55%, 59%, 75%, & 92% across several analyses.

More dapivirine released = more use = more protection

Brown et al., AIDS2016 abstract
After ASPIRE and The Ring Study: open-label studies (underway Q3 2016)

<table>
<thead>
<tr>
<th></th>
<th>ASPIRE/Ring Study</th>
<th>HOPE/DREAM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, blinded phase III</td>
<td>Open-label phase IIIB w/ no randomization or blinding</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td>Unproven efficacy, may be placebo, unproven safety</td>
<td>Proven to prevent HIV, proven safe</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>Determine whether the ring was effective and safe</td>
<td>Show whether women will use the ring, when given the opportunity</td>
</tr>
</tbody>
</table>

Baeten, AIDS 2016
Looking ahead to combination products

The idea:
Many women at risk of HIV also want family planning. Why not combine HIV prevention with contraception?

• For example, a long-wearing ring (90 days) that could provide dual-protection against HIV and pregnancy
  • 4 rings would provide HIV prevention and contraception for a year

• In development:
  – Tenofovir / levonorgestrol ring (CONRAD) [MTN-038]
  – Dapivirine / levonorgestrol ring (IPM) [MTN-030/036]
ART
PROMISE study

- Multi-country study (India & SSA)
- WHO recommends ART to all people living with HIV (PLHIV) regardless of CD4 count
- Immediate ART eligibility to be associated with lower mortality, improved immune function, and reduced household HIV incidence
- Continuing ART for postpartum women is safe and associated with fewer WHO Stage 2/3 events vs. stopping ART
- However, among women not on ART, there was low initial acceptance of early ART after initial counseling.
SEARCH Study

• Conducted in rural Kenya and Uganda

• Community-based approach to HIV testing combined with a ‘test and treat’ model of antiretroviral treatment (ART) access

• Increased the proportion of adults in these communities who were virally suppressed from 45% to 81% over two years.

• Significant advance toward achieving the UNAIDS 90-90-90 targets.
Vaccines
HVTN 100

- South African study of a modified version of the RV144 regimen, the only HIV vaccine regimen to show efficacy to date

- Adapted the RV144 regimen to make it specific to the southern Africa’s Clade C HIV subtype

- Adjuvant changed to elicit a more powerful immune response, and added a booster to prolong protection

- The successful study provided the green light for a larger efficacy trial of the improved regimen, which, if successful, could lead to a licensed HIV vaccine in South Africa and the world’s first preventive HIV vaccine
Gender
Why does gender matter?

For KEY and PRIORITY populations

- Sex workers FSW, MSW
- MSM
- Incarceration
- Fishermen
- Transgender
- YWAG
- PWID
A critical problem to address:
One third of new HIV infections globally occur in young African women

• In context of ART scale up with 40% of HIV+ persons on ART & 6 million medical male circumcisions performed by end of 2013
• Need to implement effective primary prevention strategies
Celum, AIDS 2016
Vulnerability

AMONG WOMEN – especially Adolescent girls and Young Women (AGYW)

- Power dynamics and decision making
- Education
- Poverty
- Biology

Bukusi, AIDS 2016
Prevention options for young African women

• High HIV risk and lesser HIV protection for young African women makes us up our game for finding new prevention strategies for this group
  – Acceptability & adherence? Especially open-label context
  – Biological factors that may influence safety & efficacy

• MTN-034/REACH: open-label study will evaluate the safety of and adherence to the monthly dapivirine ring and daily oral PrEP in 300 girls and young women ages 16-21 in 3 countries – and also their preferences for each

Baeten, AIDS 2016
She’s keeping herself for marriage...
What about you?
Vulnerability

AMONG MEN

• Social norms on masculinity
  – often assume that men are knowledgeable and experienced when it comes to sexual issues.

• Generally men have poor health seeking behaviour,
  – Do not access health services within the facilities and
  – reduces the chances of being diagnosed and early initiation of treatment / prevention

Where are the men??
“Where are the men?”

- Symposia session, “Engaging Men in Care in HIV Treatment: Closing the Treatment and Survival Gap,” turned the spotlight to men’s participation in treatment.

- Men living with HIV not only engage in treatment at lower levels than women…they also experience worse outcomes, including a 37% higher likelihood of death than women when on HIV treatment.

- Need to engage and retain men and boys in HIV testing and treatment – a key but often overlooked component of a stronger AIDS response.
You mean you’re not CIRCUMCISED!

Stand Proud. Get Circumcised.

For more information about Safe Male Circumcision visit the nearest health facility where you see the SMC sign or call the National Health Hotline on 031 2500 600 or 0800-200 600 OR Type SMC (leave a space) your question and send to 8198.
Policy Implications
PrEP works and works very well, when taken

PrEP is a safe prevention option

The risks are small and the benefits are real

In other populations offered open label PrEP, uptake and effectiveness have been very high

Need to evaluate whether young women in Africa are motivated and able to take PrEP

Celum, AIDS 2016
New WHO guidance: ARVs for prevention

New WHO ARV Guidelines
“..the use of daily oral pre-exposure prophylaxis is recommended as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.”

Celum, AIDS 2016
Choice Matters

- Products must be used to be effective
- People’s preferences and needs are not all the same
  - Analogy: for contraception, women regularly weigh side effects, efficacy, life burden, and “medicalization” when making choices
- People want options so they can make choices

We are naïve if we think one option will work for all, or that people will use something just because we made it

Baeten, AIDS 2016
Looking ahead … getting the right products into people’s hands

• Finding products that work is *not enough*
• We need HIV prevention approaches that are
  • Less stigmatizing
  • Can be incorporated into daily life
  • Are desirable and provided in settings that are less medicalized

Baeten, AIDS 2016
Is HIV epidemic control achievable? Without a vaccine or cure?

Yes, HIV epidemic control is achievable! However, a vaccine or cure is essential for elimination!

Source: Cremin I. et al. AIDS 2013

Celum, AIDS 2016
Acknowledgements

- IAS and NACC for organizing the preconference
- Study participants of all highlighted studies
- Study teams including: PrEP Research Teams & ASPIRE Research Team
- Funders including: BMGF, NIH, USAID, Gilead for study donations
- Connie Celum, Elizabeth Brown, Elizabeth Bukusi, Jared Baeten, Nelly Mugo, Renee Heffron for sharing their slides