HIV Pre-Exposure Prophylaxis
Can we get closer to ‘virtual HIV elimination’

Nelly Rwamba Mugo, MbChB, MMed Obs/Gyn, MPH

Center for Clinical Research, Kenya Institute of Medical Research (KEMRI)
Departments of Global Health and Medicine, University of Washington

12th INTEREST MEETING
Kigali
May, 29, 2018
Can we answer this question?

YOU HAVE PILLS THAT PREVENT HIV

AND YOU'RE NOT USING THEM?
Disclosure

• My institution received research funding for PrEP and related studies to conduct research at the Thika PHRD-KEMRI clinical trial clinic
  • I have been a principal Investigator for the Partners PrEP clinical trial, Partners Demonstration Project and currently the on-going Partners Scale up Project.

• Source of research funds: Bill & Melinda Gates Foundation, CDC, NIH, PEPFAR, and USAID.
  • For some research studies, medication has been donated by Gilead Sciences.
Outline

▪ The Oral PrEP journey- from Proof of Concept to Scale Up

▪ Global Impact of Oral PrEP Scale up Implementation

▪ What we have learnt about PrEP roll out
  ▪ Kenya Oral PrEP Scale Up Process

▪ PrEP products in the pipeline

▪ Lessons learnt during PrEP scale up
Clinical Trials & Global Guidelines
Leading to Oral PrEP Delivery at Scale

2010/2011  Pivotal clinical trial data in MSM and heterosexuals
2012       FDA approval; WHO recommendation of PrEP for serodiscordant couples & MSM
2014       End of open-label extension trials & consolidated WHO guidelines for KPs
2015 early High impact in demonstration studies
2015 late  WHO guidelines include all persons at high risk
2017       First delivery starts at scale in African settings (DREAMS, Kenya & SA scale-up)

Courtesy of Sharon Hillier & Jared Baeten
Recommendations for oral PrEP is based on strong evidence of effectiveness across different populations
PrEP Effectiveness >> Efficacy!!

In health interventions, we expect that clinical trial efficacy will be the best we can hope for.

PrEP has shown the opposite, with effectiveness in implementation exceeding clinical trials.

Showing that people can recognize their risk, PrEP benefits, & use it effectively.

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Effectiveness</th>
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<tbody>
<tr>
<td>iPrEx = 44% (51% adherent)</td>
<td>PROUD = 86% (nearly all adherent)</td>
</tr>
<tr>
<td>Partners PrEP = 75% (81% adherent)</td>
<td>Partners Demo = 95% (85% adherent)</td>
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</tbody>
</table>

PrEP trials showed higher efficacy for high-risk persons

- In studies with high adherence, 90% protection among those with good drug levels
- Subgroup analyses showed that PrEP is effective for those at greatest HIV risk:
  - Heterosexuals: STIs, HIV+ partner with high viral load  
    Murnane et al. AIDS 2013
  - MSM: Condomless anal sex with HIV+ partner, STIs  
- Adherence higher for persons taking greater risks
PrEP Delivery for MSM

- Effectiveness > 85%
- Adherence over 80%
- Self referral for selecting high risk individuals works
- High STI rates with open label PrEP delivery

What PrEP looks like in real world delivery: HIV-Sero discordant Couples Partners Demonstration Project

• Open-label demonstration among HIV serodiscordant couples in Kenya & Uganda.

• Open access to PrEP and ART.

• Only 4 HIV infections observed, compared with 83 infections expected in a counterfactual simulation model

• None of 4 seroconverters were on PrEP

Baeten et al. WEAC0105 IAS 2016

\[
\begin{align*}
\text{EXPECTED} & : N=83 \text{ infections incidence} = 4.9 \quad (95\% \text{ CI 3.9-6.0}) \\
\text{OBSERVED} & : N=4 \text{ infections incidence} = 0.2 \quad (95\% \text{ CI 0.1-0.6})
\end{align*}
\]

95% reduction (95% CI 87-98%) P<0.001
PrEP & ART: synergy in delivery

• For populations:
  • Risk-targeted PrEP adds to ART (Ying et al. STI World Congress 2013)
    • Increases rates of HIV testing among at risk population
    • & reduces number of undetected infections
    • Increases uptake of ART
Important additional data to inform PrEP scale up

- Randomized Clinical Trials
- Open Label Studies
- Demonstration Projects
- Pilot Delivery
- Wide scale implementation

Delivery Models
Pregnancy
Cost & cost effectiveness
Breast feeding
Risk compensation
Safety
Efficacy
Resistance
Willingness to use
PrEP clinical trials: Adherence key

VOICE & FEM-PrEP
25-30% adherence / No efficacy

iPrEx
51% adherence / 44% efficacy

Bangkok
67% adherence / 49% efficacy

Partners PrEP
81% adherence / 75% efficacy

TDF2
79% adherence / 62% efficacy

Demonstration of PrEP efficacy and safety among diverse populations
## Gender Sub-analysis:
### 3 major PrEP studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number participants</th>
<th>% Female</th>
<th>Participant</th>
<th>Relative reduction - ITT</th>
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</thead>
<tbody>
<tr>
<td><strong>Partners PrEP Study – Kenya, Uganda</strong></td>
<td>4,747</td>
<td>38%</td>
<td>Heterosexual men and women</td>
<td>TDF: 67% (44-81)</td>
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<td>TDF-FTC: 75% (55-87)</td>
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<td>*Adherence was high</td>
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<tr>
<td><em><em>TDF2 Trial</em> - Botswana</em>*</td>
<td>1,219</td>
<td>46%</td>
<td>Heterosexual men and women</td>
<td>TDF-FTC: 62.2% (22-83)</td>
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<td><strong>Bangkok Tenofovir Study</strong></td>
<td>2,413</td>
<td>20%</td>
<td>Male and female drug users from treatment centres.</td>
<td>TDF-FTC: 49% (10-72)</td>
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<td>*Adherence was moderate</td>
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*References:
- Baeten JM. *NEJM* 2012;367:399-410
- Thigpen MC. *NEJM* 2012;367:423-34

*Note: TDF= tenofovir, FTC= emtricitabine.*
PrEP and safety

- Excellent tolerability: transient GI symptoms

- TDF-based PrEP associated with small and non-progressive decline in renal function
  - Accumulated safety evidence suggests we may be able to relax safety monitoring, at least in some patients

- Small decline in BMD, all without clinically relevant toxicity

- Safe in terms of reproductive health
  - Contraception, pregnancy, lactation, male fertility

References:
Mugwanya et al. JAMA Intern Med 2015
Mugwanya JAIDS 2016
Mugwanya J Infect Dis 2016
Mugwanya AIDS 2016
Gandhi et al. CROI 2016
Mugo et al. JAMA 2014
Matthews et al. JAIDS 2013
Murnane et al. AIDS 2014
Heffron et al. AIDS 2014
Were et al. AIDS 2014
PrEP and antiviral resistance

• For PrEP, resistance risk appears nearly completely limited to those with acute infection when starting PrEP. (Lehman et al., JID 2014)

• Importantly, resistance risk is dwarfed by the # of persons protected against HIV:

  2-5 cases of resistance vs. 123 HIV infections averted

• Resistance risk has been modeled to contribute just a fraction to community-level resistance, above and beyond what ART is already contributing, even under the most pessimistic scenarios (Abbas et al., JID 2013)
Pre-exposure prophylaxis works—it’s time to deliver

The science is now clear: oral pre-exposure prophylaxis (PrEP) with a coformulation of tenofovir disoproxil fumarate and emtricitabine (Truvada) significantly reduces the risk of HIV infection among individuals at high risk of HIV infection. The news that PrEP has shown consistent efficacy among those who take it as prescribed should be a cause for celebration, and galvanise action to ensure access to PrEP for those who could benefit the most. But almost 3 years since the US Food and Drug Administration approved it, global access to PrEP is extremely limited. The USA is the only country to have moved forwards with implementation of PrEP. The manufacturer of tenofovir-emtricitabine, Gilead Sciences, has applied for approval in several other countries, but regulatory authorities have generally been slow to act. PrEP demonstration projects exist, but most are fairly small and limited in scope. The cost of PrEP

*Chris Beyrer, Linda-Gail Bekker, Anton Pozniak, Françoise Barré-Sinoussi

Lancet April 18 2015
Population Impact
New HIV diagnoses, deaths, and prevalence, 2006-2016, San Francisco

There was a 51% decline in HIV infections since 2012-2016 associated with:

1. Access to PrEP services
2. Uptake of same-day ART since 2010
3. Collective-impact initiatives by the Getting to Zero consortium

Susan Buchbinder
CROI 2018
Australia: real-life, public health impact of combination prevention

Newly diagnosed HIV cases in New South Wales (including Sydney)

- Educated community and built demand for PrEP among MSM
- PrEP demonstration project at scale
- 25% reduction in the average number of new cases compared to the previous five years.

UK: >6000 on PrEP

- PrEP demand was high without providers or NHS approval
  - Online buying clubs

- 42% decline in new HIV infections & GC among MSM at Dean Street clinic in London in 2015-16

Sheena McCormack IAS 2017
Ultimately, it is about coverage and delivery

- Public health impact will come when PrEP (and ART and other highly effective strategies) are implemented effectively and at scale.

- UNAIDS has called for 3 million persons on PrEP by 2020

UNAIDS 2016
The case of youth & young women
Disproportionate Success in Epidemic Control by Age Group

New HIV Infections by Population and Year

Pediatric (0-14 yrs)  15 - 24 yrs  25 yrs +

2000*
2015*
2020**
Projected

Sources: * UNAIDS AIDS info Online Database, 2016; ** 15-24 yrs age group projected based on Africa Development Forum / World Bank 2015, “Africa’s Demographic Transition: Dividend or Disaster?”
Young African Women at Risk

1 out of 3 new HIV infections are in youth in SSA (15-24yr)

2 out of 3 new HIV infections are in sub-Saharan Africa
Factors that increase young women’s vulnerability to HIV

• Poverty & transactional sex:
  – Young girls have sex with older men to access resources.

• Limited livelihood opportunities:
  – Women’s economic dependence on partner, labor migration, separation of families

• Gender inequality & violence:
  – Women have difficulty negotiating sex or condom use when economically dependent on partner &/or fear violence

• Stigma & discrimination:
  – Prevents those most vulnerable to HIV from accessing HIV testing & services

• Risk-taking & self-efficacy in adolescence

• Limited availability of youth-friendly services
Does PrEP work in young women?

- Yes, if taken; PrEP efficacy ≈70% in all subgroups of women in Partners PrEP
  - Age <30, high risk, high plasma viral load in partner
  - Adherence ≈ 80% based on drug levels

(Murnane, et al, AIDS 2013)

- No efficacy with low uptake in VOICE & FEM-PrEP
  - <30% with drug detected
  - Disconnect between low perceived risk and high STI incidence in FEM-PrEP (Van Damme NEJM 2012)
  - Low uptake due to low risk perception, low motivation for prevention, need for social support and/or challenges with daily pill-taking (remembering, product storage)?
Studies to understand PrEP uptake & adherence among young African women

- HPTN 067 ADAPT (Bekker)
- Plus Pills in Cape Town (Bekker)
- Young women in Kenya (Wanjiru)
- Uptake of PrEP & role of conditional incentives on motivating adherence in Cape Town (Bekker & Celum)
- HPTN 082/HERS: Uptake & adherence to PrEP (Celum & Delany-Moretlwe)
- POWER: Prevention Options Research for Women (Baeten & Celum)
Effective Implementation

- Clear framework & expectations
- Demand creation
  - Positive messaging
  - Champions
- Tools to facilitate uptake
  - Risk assessment tools
  - Decision support tools
- Simple delivery
  - Integrated with other desired services (e.g., FP, STI testing & treatment)
Creating demand for HIV prevention

• Engage the populations we are trying to reach in developing captivating, effective messaging

• Focus on convenience, simple and clear messages about benefits and costs

• Start where we are likely to succeed; learn from early adopters

• Demand creation messages may need to change for ‘late adopters’
Engage with clever messaging

PrEP is like taking anti-malaria pill.
It's a good strategy before you embark on your exotic adventure.

Learn more about PrEP at apcom.org/PrEPARINGASIA
Social Media Campaign

Source: https://www.facebook.com/PrEPKenya/photos
PrEP messaging for young African women

How does PrEP work?
PrEP is an antiretroviral pill, Truvada, which helps HIV-negative people stay negative. When taken regularly, PrEP has been shown to reduce the chance of getting HIV by more than 90%. You should take PrEP every day to be sure you are protected against HIV. When the medicine is in your blood, it will stop HIV from taking hold and spreading in your body. If you want to protect yourself against STIs and have extra HIV protection, use condoms. If you want to prevent pregnancy, use contraception.

THIS IS MY MOMENT
I AM MY OWN WOMAN.
I AM IN CONTROL.

I AM PREPARED
FOR TODAY, FOR THE FUTURE,
FOR LIFE'S TWISTS AND TURNS.

I Ami PrEPPEd
PrEP is a new way to protect yourself from HIV. Taken every day, it helps you stay HIV free. #getPrEPPEd
For the first time in my life – I own my sexuality

It's like a pregnancy pill - if you take a pill you don't get pregnant......if you take PrEP you won't get HIV.

Personal Control
Part of a movement
Implementation tools
WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION

JULY 2017
WHO PrEP Implementation Tool (2017): ‘suggestions, not recommendations’

http://who.int/hiv/pub/prep/prep-implementation-tool
WHO CLINICAL PREP BASICS

Indications for PrEP (by history over the past 6 months):

- HIV-negative AND
- Sexual partner with HIV who is not virally supressed, OR
- Sexually active in a high HIV incidence/prevalence population AND any of the following:
  - Vaginal or anal sexual intercourse without condoms with more than one partner, OR
  - A sexual partner with one or more HIV risk factors, OR
  - A history of a sexually transmitted infection (STI) by lab testing or self-report or syndromic STI treatment, OR
  - Use of post-exposure prophylaxis (PEP), OR
  - Requesting PrEP.

Contraindications:

- HIV-positive
- Estimated creatinine clearance <60 ml/min
- Signs/symptoms of acute HIV infection, probable recent exposure to HIV
- Allergy or contraindication to any medicine in the PrEP regimen.

Rx (example): TDF 300 mg + FTC 200 mg PO daily #90 tablets.

Counselling: Link tablet use with a daily routine.

Develop a plan for contraception or safer conception and for STI prevention.
Keeping it simple: Kenya client encounter form

**Behaviour risk assessment**

Mark all that apply:

- [ ] Sex partner(s) is HIV+ and (mark all that apply):
  - [ ] Not on ART
  - [ ] On ART <6 months
  - [ ] Suspected poor adherence to ART
  - [ ] Detectable HIV viral load
  - [ ] Couple is trying to conceive
- [ ] Sex partner(s) high risk & HIV status is unknown
- [ ] Has sex with >1 partner
- [ ] Ongoing IPV/GBV
- [ ] Transactional sex
- [ ] Recent STI (past 6 months)
- [ ] Recurrent use of post-exposure prophylaxis (PEP)
- [ ] Recurrent sex under influence of alcohol/recreational drugs
- [ ] Inconsistent or no condom use
- [ ] Injection drug use with shared needles and/or syringes
Guidelines on USE of ART for Treating and Prevention HIV infections in Kenya-2016

- **Minimum required laboratory evaluation for PrEP**
- **Baseline creatinine is recommended** but should not delay initiation of PrEP
  - Clients with pre-existing risk for factors for renal impairment every effort should be made to obtain serum creatinine prior to PrEP initiation
- When available HBsAg and HCV serology, if HBsAg neg offer vaccination

### PrEP initiation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Additional steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (HBsAg)</td>
<td></td>
<td>If negative, vaccine series initiated: Yes, No</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
<td>If creatinine is out of range, or CrCl &lt; 50 mL/min, refer for further assessment.</td>
</tr>
</tbody>
</table>

Lab results (Investigations should not delay PrEP initiation. To be recorded when available.)
Getting options into people’s hands

• Finding products that work is not enough
  • The right shoe without a ‘soul’

• We need HIV prevention approaches that:
  • People can use
  • Are less stigmatizing
  • Can be incorporated into daily life
  • Give options and choices
  • Are desirable
  • Can be provided in settings that are less medicalized
PrEP cannot be one size fits all

Tenofovir-containing pills are not feasible for everyone. There is a pipeline of new PrEP prevention products that could deliver additional options.

No single formulation will work or be workable for every person.

Choice will be important to meet diverse needs.

Efficacy, choice & coverage are all critical.
Cabotegravir Studies

- Complete phase one macaque studies
- Completed phase 2 safety studies
  - HPTN 077
    - Injection site pain most common AE, participants had a preference for injectable
- On-going phase three efficacy trials
  - HPTN 084 enrolling 3200 women in Africa ages 18-45 years
  - HPTN 083 enrolling 4500 TGW/MSM in the USA
Intravaginal Ring Studies

• Phase 3 ASPIRE & Ring study results (CROI 2016, NEJM 2016)
  • 27-31% efficacy
• Extended follow up studies; DREAMS & HOPE (CROI 2018)
  • Preliminary data: 47-54% reduction in incidence

• Multipurpose technology rings
  • Completed phase 1 studies, moving to phase 2 studies
    • Dapivirine & levornogestrel
    • Tenofovir & levonorgestrel
    • Dapivirine & Maraviroc IVR
Kenya PrEP Scale Up
Kenya’s PrEP scale-up to reach 20,000

- July 2016: Launch of revised ART guidelines
- November 2016: PrEP implementers meeting
- November 2016 – April 2017: PrEP TWG and subcommittee working group meetings
- May 2017: National PrEP scale-up launch

Courtsey of Jilinde Project
Kenya PrEP Implementation Framework

- Policy Plans, Budgets
- Delivery Considerations
- Demand Creation
- Monitoring & Evaluation
Kenya policy landscape

- **Kenya Strategic Framework (KASF (2014/15-2018/19))**
  - ‘A Kenya free of HIV infections, stigma and AIDS related deaths’
    - Towards reducing new infections by 75%

- **ART Guidelines**
  - 2016 ART guidelines included provision of PrEP for all persons at risk for HIV infection
  - & as part of Prong 1 for eMTCT- prevention of primary infection
May 2017 PrEP launch: Ministry leadership & media engagement
Prioritizing Geography: Initial projects in high burden counties

* GEMS will work in all counties that offer oral PrEP
Kenya National roll out; coordinated by National AIDS Control Program

Guidelines; July 2016
- Inclusion of Prep in Guidelines

Framework 2017
- Formation of TWG
- Development and launch of Framework for Prep implementation

Implementation 2017
- National roll out
  - Training of providers
  - Communication, demand creation
  - Start up of services in multiple facilities
Kenya: Trends in PrEP uptake

Data submission incomplete

Source: www.nascop.org

Now over 20,000
Learning from early adoptors
PrEP in US, 2012 to 2016 (by quarter)

98,732 Unique Individuals Starting FTC/TDF for PrEP:
1,715 in Q3 2012 → 11,827 in Q3 2016

6.9 times increase 2012 - 2016

Low uptake among African American, latino, youth & transgender

This is where Kenya

Some Considerations to make PrEP Delivery Doable

- Nurse led
- Integrated services
- Comprehensive services to maximize impact beyond PrEP
  - Standard testing protocols
  - Not too much fuss about adherence & retention (don’t chase people who don’t come back, not like ART) people can move in and out of PrEP
- Selecting for PrEP eligibility
  - Maybe useful
  - Use to screen in not screen out
  - Let people self select for risk
  - Bottom line, people who turn up and ask for PrEP are likely correctly identifying themselves as benefiting from it
Beyond Prevention: Re energizing combination prevention agenda

- PrEP has catalyzed advocacy for HIV prevention services and re-energized provision of combination prevention services

- Women
  - Female controlled discrete, added protection for sex workers
  - Catalyzing better provision of comprehensive RH services (POWER)
  - High treatable STI prevalence rates (30%)

- Men who have sex with men
  - Inspired by new choice, PrEP has inspired activism with increased demand and advocacy work

- HIV serodiscordant couples (shared responsibility)
  - Safer conception

- In general population
  - Increase HIV testing & identification of people with HIV, linkage to ART
  - Hep B vaccination

- Peers & lay persons- empowering beyond PrEP itself
There have been Sceptics

Caution & Doubt

Helps identify and resolve potential problems
What Has Worked?

Is Global Leadership and National Uptake With a public health agenda

WHO, UNAIDS, Country Specific Guidelines
What do we have to lose if we don’t scale up PrEP

How will history judge us?

4.45pm debate
It is the responsibility of research funding organizations to provide PrEP as standard of care for all participants at risk of HIV infection in all HIV prevention clinical trials
Antiretrovirals for HIV Prevention: Challenges & Opportunities

“Nothing will ever be attempted if all possible objections must first be overcome”
Samuel Johnson (1709-1784)
Asante Sana & Acknowledgements

If you want to go fast, go alone.
If you want to go far, go together.
– African proverb

- presented slides developed by colleagues
  - University of Washington (C. Celum)
  - CROI 2017 presentations
  - WHO consultative meeting
  - Partners in Health Research and Development Thika
  - Scientists in the field

Acknowledge contributions made to science by all study participants, research scientist & funders for research