PrEP: evolving use, lessons learned and progress in the development of new prevention products

Sinead Delany-Moretlwe, MBBCh PhD
University of the Witwatersrand, South Africa
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• I have received drug donations for a PrEP demonstration project from Gilead Sciences
Overview

• Evolving PrEP use

• Lessons learned for scale up

• Future ART-based HIV prevention products
The promise of PrEP

15 randomised controlled trials
- PrEP safe and effective
- Level of protection strongly correlated with adherence
- Cost-effective in populations with incidence ≥3% per annum
- Goal: 3 million on PrEP by 2020

Source: WHO, 2015
By Q1 2019, PrEP Reviewed by 40 regulatory authorities Included in >68 country programmes 465,000 people on PrEP world wide
In 46 studies worldwide, seroconversion rates comparable to clinical trials

- 46 individual studies of TDF/FTC as PrEP
- 10,609 HIV-1 negative participants
- 9,936 person-years

Results
- 91 new HIV infections
- Incidence 0.92/100 py
- 36% new infections >30 days post-PrEP dose

- Adherence is key to PREP effectiveness – most infections appeared to occur in the absence of consistent PrEP use

Baeten, HIV R4P 2018
Ultimate goal: prevention-effective adherence

Goal: prevention-effective adherence
i.e. PrEP use during periods of HIV exposure to achieve public health impact

Lessons learned about new contraceptive product introduction

• Technology will not achieve potential if health system does not have the will or capacity to provide new options with sufficient quality of care

• Introduction of new products hampered by:
  • Stigma, social barriers
  • Provider bias
  • Limited infrastructure for distribution and promotion
  • Limited investment in training, communication and outreach
  • Limited data

• Slow acceptance is not always evidence of lack of acceptability

Source: Delany-Moretiwe, 2016; Pleaner, 2017
Five PrEP controversies, SA AIDS 2017

- Pregnancy and breastfeeding
- Time to protection
- PrEP messaging
- Risk compensation
- Cost
Five PrEP controversies, SA AIDS 2017

Demonstration projects >> National scale up
Experience of 50,000 initiations

✓ Pregnancy and breastfeeding
✓ Time to protection
✓ PrEP messaging
✓ Risk compensation
✓ Cost
Effective scale up of PrEP requires

• Demand creation
• Demedicalised and streamlined delivery
• Integrated services
• Differentiated models of adherence support
Demand creation: Positive PrEP messaging in South Africa

Learn about PrEP
- PrEP is the use of anti-HIV medication.
- Does PrEP provide other protection?
- PrEP is another option for HIV prevention.
- What is the difference between PrEP, PEP, and ART?
- Is PrEP for me?

www.myprep.co.za
Task shifting and demedicalised approaches

| ART | • is sometimes medically complicated  
|     | • needs life-long adherence without breaks  
| PrEP | • is for the most part not medically complex  
|      | • needs adherence during periods at risk  
|      | • is not needed with risk is not present  

• Minimize time & burden
  • Online information to support decision-making, and help people identify clinics where they can access PrEP
  • Self-testing
• Same day PrEP starts
  • Growing evidence that medical monitoring not a pre-requisite in a healthy young population
  • Reduces costs
• Reduce barriers in access through task-shifting
  • Pharmacy or nurse-managed PrEP delivery
  • Mobile services
Service integration

- Responsive to user needs
- PrEP ideally delivered as part of a package of sexual and reproductive health services
  - Enhance engagement in care
  - Provide ongoing choice in the context of changing risk
  - Refills for PrEP and contraception, opportunity to add STI testing
  - Programme benefits, efficiency, cost
  - Platform to introduce new products
- Other services e.g. GBV screening

Delany-Moretiwe, CROI 2019 poster 995
Differentiated models of adherence support

One size does not fit all…

PrEP persistence among only participants beyond 1 month

- High adherence >700 fmol/punch associated with no. sexual partners, partners HIV serostatus, no depression, disclosure of PrEP use and attending a clubs

Source: Rousseau-Jemwa, HIV R4P 2018; Celum, CROI poster #0994 and #0995
Differentiated models of adherence support

- SOC adherence counseling plus:
  - **WhatsApp groups:** ~50 participants/group with staff facilitator and PrEP ambassador who introduce topics and monitor content
  - **Two-way SMS messages:** Weekly messages asking, “Are you fine, girlfriend?”

- Non-responders also receive:
  - **Monthly counseling visits** with problem-focused counseling
  - **Drug-level feedback** based on TFV-DP levels at M2 and M6 visits
Effective implementation requires

- Demand creation
- Demedicalised and streamlined delivery
- Integrated services
- Differentiated models of adherence support
- Long acting products
Current Status: Alternative Formulations

- **Oral & vaginal formulations**
  - Daily F-TAF (Discover trial)
  - “On demand” (Periodic Dosing of TDF/FTC; 3 days/4 doses, Ipergay)
  - Dapivirine vaginal ring under EMA review

- **Long-acting Injectable** bi-monthly
  - Cabotegravir IM vs. TDF/FTC PO--Phase 2B/3 HPTN 083 & 084
  - Rilpivirine (withdrawn from PrEP development)

- **On Demand + Behavioral congruence**
  - Gels, films, inserts, suppositories
  - Lubricant - DPV applied as lubricant, MTN-033
  - Douche - TFV/prodrug (TDF, TAF, CMX-157)

- **Longer-acting Implantable**
  - TAF silicone/PVA rod OCIS
  - TAF biodegradable implant, RTI
  - Cabotegravir, Rilpivirine,TAF, CMX-157 NU UM1

Slide adapted from Craig Hendrix
Monthly Dapivirine Ring

- Flexible silicone vaginal ring developed by IPM
- Woman-initiated
  - Self-inserted monthly
  - Discreet
- Slowly releases ARV dapivirine
- Reduced women’s HIV-1 risk by ~30% in two Phase III trials
- Interim data from open-label studies show greater use and suggest ~50% risk reduction
- Under regulatory review
  - Additional studies in adolescents, pregnant and breastfeeding women ongoing

Preferences for long-acting PrEP

Women from SA, Zim, Ug

<table>
<thead>
<tr>
<th>Preferred Product</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectables</td>
<td>40</td>
</tr>
<tr>
<td>Implants</td>
<td>37</td>
</tr>
<tr>
<td>Vaginal Ring</td>
<td>20</td>
</tr>
<tr>
<td>Oral Tablets</td>
<td>15</td>
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<tr>
<td>Vaginal Film</td>
<td>12</td>
</tr>
<tr>
<td>Vaginal Suppository</td>
<td>12</td>
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<tr>
<td>Vaginal Gel</td>
<td>11</td>
</tr>
<tr>
<td>Cervical Barrier</td>
<td>6</td>
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</tbody>
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Luecke, JIAS 2016
Cabotegravir

- Experimental
- GSK1265744 = Cabotegravir
- Integrase inhibitor
- High genetic barrier to resistance
- PK profile – allows 1-3 month injectable dosing using nanosuspension formulation
- Oral formulation also available
- Developed for both treatment and prevention
CAB LA - the PK tail
CAB LA - the PK tail

• When administering agents with long $t_{1/2}$ in non-removable method

• May require oral lead-in to assess toxicity before administering LA formulation

• May have prolonged sub-therapeutic tail; great concern for poorly adherent

Markowitz, Lancet HIV 2017; Slide modified from John Mellors, FDA 2012
CAB LA PrEP Ph II and PK studies

- HIV negative, at-risk adults (excluding high risk)
- Drug PK sampling (blood plasma) in all study participants

**ViiV ECLAIR Study** (NCT02076178)
- n=126 (all injections complete)
- 800 mg IM
- 5:1 randomization
- Men including MSM
- US only (10 sites)

**HPTN 077 Study** (NCT02178800)
- n=200 (110 Cohort 1; 90 Cohort 2)
- Two Cohorts (800 and 600mg IM)
- 3:1 randomization
- 67% enrolment of women
- US, Brazil, SA, Malawi (8 sites)
**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)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
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</thead>
<tbody>
<tr>
<td><strong>5 weeks</strong></td>
<td><strong>Up to 185 weeks (3.5 years)</strong></td>
<td><strong>48 weeks (about 11 months)</strong></td>
</tr>
<tr>
<td>Placebo-controlled*</td>
<td>Placebo-controlled*</td>
<td>Open-label*</td>
</tr>
<tr>
<td><strong>Group A</strong></td>
<td><strong>Group B</strong></td>
<td></td>
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<tr>
<td>CAB Active</td>
<td>CAB Placebo</td>
<td>CAB Placebo</td>
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<tr>
<td>TDF/FTC Placebo</td>
<td>TDF/FTC Active</td>
<td>TDF/FTC Active</td>
</tr>
<tr>
<td>Injection, every 8 weeks+</td>
<td>Injection, every 8 weeks+</td>
<td>Injection, every 8 weeks+</td>
</tr>
<tr>
<td>Oral tablet, daily</td>
<td>Oral tablet, daily</td>
<td>Oral tablet, daily</td>
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Primary outcome: HIV incidence
In May 2018, WHO, FDA, EMA and SAHPRA released advisories on the issue of reported neural tube defects in women taking dolutegravir during pregnancy in Botswana.

- 4 out of 426 women taking DTG around the time of conception (0.9%) compared to 0.1% in women taking other antiretrovirals.
- Final results due for release in Q2 2019.

Implications for conception on HPTN 084?
CAB LA in women

• HPTN 084 protocol modified
  • Require women to be on a long-acting contraceptive at enrolment
  • No evidence of drug-drug interactions with contraceptives
    • Will expand the dataset to include data on DMPA, NET-EN and etonorgestrel
    • Target pregnancy incidence <3%

• For those that become pregnant
  • Unblinding at confirmed pregnancy visit
  • Referral for early ultrasound and follow up
  • Plan for co-enrolment in a protocol to assess CAB PK in breastmilk and infant plasma

• Planned ancillary safety and acceptability study in adolescents 16-18 yo
Subcutaneous implants

- Simple insertion AND reversible with removal
- Long lasting (months to year)
- More consistent and predictable drug release
- Potential for multipurpose
- Current development
  - CAB, TAF, MK8591
  - Reservoirs, osmotic pumps

- Clinical trials pending
  - CAPRISA 018 PH I/II TAF subdermal implant MK8591

Gunawardana, 2015; Flexner, 2018; Kovarova, 2018
Multi-purpose technologies

Co-formulated:
Multiple Active Pharmaceutical Ingredient formulated into a single dose

Co-administered:
Two independent products used together

Co-packaged:
Two different doses packaged together in a single product for simultaneous co-use

Also injections, implants
Conclusions

• Oral PrEP has been a vanguard product

• To achieve global targets we will have to focus on demedicalising and streamlining services so that they facilitate greater PrEP use

• Long acting products will solve some but not all of these challenges

• A range of options are ultimately better
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