HIV PrEP (Pre-exposure Prophylaxis) 
Past, Present and Future

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Professor of Medicine, UNC-Chapel Hill School of Medicine
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Disclosures

♦ In the past 2 years

– I have been an employee of the University of North Carolina at Chapel Hill, School of Medicine.
– I attended an HIV prevention advisory board meeting for Viiv Health Care.
– I have not held any investments in the pharmaceutical organizations, medical devices companies or communications firms.
– In the past 2 years I have received research support from the NIH, Aidsfonds, USAID, WHO.
Today’s Talk

- Intro to PrEP
- PrEP research studies
- PrEP in Practice
- Injectables under evaluation
- Next PrEP- Implants
- Conclusion
CURRENT HIV PREVENTION STRATEGIES

- BNABs/Vaccines? in the field
  - Microbicides for women
    - Grant R, NEJM 2010 (MSM)
    - Baeten J, 2011 (Couples)
    - Paxton L, 2011 (Heterosexuals)
  - Oral pre-exposure prophylaxis (PEP)
    - Scheckter M, 2002

- Male circumcision
  - Gray R, Lancet 2007

- Treatment of STIs
  - Grosskurth H, Lancet 2000

- Female Condoms

- Male Condoms

- HIV Counselling and Testing
  - Coates T, Lancet 2000

- Treatment for prevention
  - - Abstinence
  - - Be Faithful

Slide Credit (HPTN, Karim & Cohen)
What is PrEP?

PrEP as a concept is to take a medicine or product to prevent disease for the period of risk exposure
- Malaria prophylaxis
- PCP prophylaxis

For HIV, PrEP (Pre-Exposure Prophylaxis) is the use of antiretroviral medications (ARVs) or products to reduce the risk of HIV acquisition in HIV-negative people.
Why Tenofovir/Emtricitabine Truvada®?

- Limited side effects and strong safety profile
- Relatively long duration of action in the body
- Less likelihood of drug resistance
- Strong protective effect against in animal models
PrEP Efficacy versus Adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy</th>
<th>Adherence</th>
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<tbody>
<tr>
<td>VOICE Tenofovir</td>
<td>-49</td>
<td>28</td>
</tr>
<tr>
<td>VOICE Truvada</td>
<td>-4</td>
<td>29</td>
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<tr>
<td>Fem PrEP</td>
<td>6</td>
<td>37</td>
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<tr>
<td>VOICE Tenofovir Gel</td>
<td>15</td>
<td>23</td>
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<td>CAPRISA 004</td>
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<td>iPrEX</td>
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<tr>
<td>Bangkok Tenofovir</td>
<td>49</td>
<td>67</td>
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<tr>
<td>Study</td>
<td>62</td>
<td>81</td>
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<tr>
<td>TDF2</td>
<td>67</td>
<td>83</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>75</td>
<td>81</td>
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<tr>
<td>Tenofovir</td>
<td>86</td>
<td>86</td>
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<tr>
<td>Truvada</td>
<td>86</td>
<td>91</td>
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<tr>
<td>PROUD</td>
<td>86</td>
<td>91</td>
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<tr>
<td>IPERGAY</td>
<td>86</td>
<td>91</td>
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K. Rivet Amico and Michael J. Stirratt
TDF/FTC was FDA Approved for use for Prevention on July 16, 2012

BUT... success depends on adherence.
PrEP approvals

PRE-EXPOSURE PROPHYLAXIS (PrEP)
WHO EXPANDS RECOMMENDATION ON ORAL PRE-EXPOSURE PROPHYLAXIS OF HIV INFECTION (PrEP)

NOVEMBER 2015
PrEP Recommendations

- Should be targeted to HIV negative individuals at increased risk for HIV infection
- Should be taken daily
- Women who are pregnant or trying to conceive should discuss potential risks and benefits with a health care provider
- Should be delivered as part of a comprehensive HIV prevention package
Enter Implementation Science
To Prevent HIV and Control the Epidemic

Key Populations:
MSM, IVDU, AGYW, FSW, Discordant Couples, Prisoners, Pregnant Women, STI clients

ART clinics, Family Planning Clinics, Outpatient, Mobile Outreach Clinics, Pharmacy, Schools, Bars

Peer Support, Social Networks, Health Care provider model, Stakeholders

A package approach to HIV prevention
Commentary

PrEP implementation research in Africa: what is new?

Frances M Cowan¹,², Sinead Delany-Moretlwe³, Eduard J Sanders⁴,⁵, Nelly R Mugo⁶,⁷,⁸, Fernand A Guedou⁹, Michel Alary¹⁰, Luc Behanzin⁹, Owen Mugurungi¹¹ and Linda-Gail Bekker¹²

⁵Corresponding author: Frances M Cowan, Department of International Public Health, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 SQA, UK. (frances.cowan@lstmed.ac.uk)
PrEP demonstration Projects- South Africa: 12 + and counting

♦ Oral:
  - Adolescents: Pluspills (DTHF), UNICEF/UNITAID (DTHF)
  - Adolescent girls/YW: 3P (DTHF), POWER (WRI, DTHF) HPTN 082 (WRI, DTHC),
  - Sex workers: NDoH, WRI
  - MSM: Sibanye (DTHF), EJF (Anova/DTHF)

♦ Topical:
  - HOPE OLE, DREAM OLE, MTN 034
The final risk score included the following predictors:

- having a male partner with unknown HIV status
- number of lifetime sexual partners
- syphilis
- bacterial vaginosis (BV)
- vaginal candidiasis

Score > 6 associated with incidence of 7.3/100 py
Risk Scores

An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African Women.


- Age
- married/living with a partner
- partner provides financial/material support
- partner with other partners,
- alcohol use,
- curable STI,
- HSV-2 serostatus

- Score > 5
  - Incidence of >5/100py
Modeling

COST-EFFECTIVENESS OF PREEXPOSURE PROPHYLAXIS ACROSS COUNTIES IN WESTERN KENYA - CROI 2017 abstract 1037

- Infections averted per 1000 person years of PrEP
Providing time-limited PrEP to the partners of migrant miners, as opposed to providing PrEP all year, would improve the cost per infection averted by 7.5-fold.

For the cost per infection averted to be below US$3000 (cost effective), at least 85% of PrEP users would need to be good adherers and PrEP would need to be cheaper than US$115 per person per year.
IS ORAL TDF/FTC ENOUGH?
Why do we need additional PrEP formulations?

• Some people may have difficulty or prefer not to take a pill every day

• Some may not be able to take may have side effects / toxicity to oral Truvada

• Truvada is part of many first line regimens, concern for resistance

• More Effective Regimens may be available

• No one size fits all!
New Oral Drugs
DISCOVER Trial

- Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (FTC/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection (DISCOVER)

- Phase 3 double blind, placebo controlled
- Compares TDF/FTC to TAF/FTC
- Outcome- Acquisition of HIV
More Choice
Comparing Effectiveness

More effective
Less than 1 pregnancy per 100 women in one year

- Implants
- IUD
- Female Sterilization
- Vasectomy

Less effective
About 30 pregnancies per 100 women in one year

- Injectable
- LAM
- Pills
- Male or Female Condoms
- Diaphragm
- Fertility Awareness Methods
-Withdrawal
- Spermicides
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

Corresponding author: Ellen H Luecke, 351 California Street, Suite 500, San Francisco, CA 94104, USA. Tel: +(415) 848 1392. (eluecke@rti.org)

Figure 1. MTN-003D stage 2 HIV prevention potential product formulation discussion card.
Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study

Ellen H Luecke¹, Helen Cheng¹, Kubashni Woeber², Teopista Nakyanzi³, Imelda C Mudekunye-Mahaka⁴ and Ariane van der Straten¹⁵ on behalf of the MTN-003D Study Team

¹Corresponding author: Ellen H Luecke, 351 California Street, Suite 500, San Francisco, CA 94104, USA. Tel: +(415) 848 1392. (eluecke@rti.org)
Abstract #9: The drug will help protect my tomorrow”: Awareness, willingness, and preferences to use pre-exposure prophylaxis (PrEP) among female sex workers in Lilongwe, Malawi
The Next Generation of PrEP

- Oral daily maraviroc: HPTN 069
- TAF
- An injectable long acting ART
  - TMC 278LA (rilpivirine): HPTN 076
  - GSK1265744LA (integrase inhibitor): HPTN 077
- Monoclonal antibodies?
  - Ibaluzimab (TMB-355)
  - VRC01-7, other antibodies
- Vectored immunoprophylaxis (VIP)??

_Baltimore et al. Nature 481:81, Blood 129:4571_
Injectable PrEP – Advantages and Disadvantages

♦ **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+
Rilpivirine Long Acting

• Rilpivirine (RPV), a next generation NNRTI, has demonstrated in vitro and in vivo activity against wild-type and NNRTI resistant isolates

• Long acting rilpivirine injectable nanosuspension available

• No safety concerns observed
HPTN 076:
Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for PrEP
HPTN 076 Design

136 HIV-uninfected, ages 18-45

WEEKS

4

52

76

ARM 1
N = 91

Daily Oral TMC278
Six doses of injections of TMC278 LA every 8 weeks
Follow-up phase (tail phase)

ARM 2
N = 45

Daily oral placebo
Six doses of injections of TMC278 LA placebo every 8 weeks

Primary objective: Evaluate the safety of TMC278 LA, through 48 weeks after initial injection in women in sub-Saharan Africa and the U.S.
**HPTN 076 High Level Overview**

- **Oral Run-in (4 Weeks)**
- **Injection Phase (40 Weeks)**
- **Follow-up (32 Weeks)**

**Acceptability Questionnaires**

**Rectal & Vaginal Fluid Collection**

**Tissue Subset:**
- Vaginal Biopsy

**N = 136**

4 sites:
- Bronx, NY
- Newark, NJ
- Cape Town, SA
- Harare, Zimbabwe

**Subset:**
- Focus Group Discussions
## PARTICIPANT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=136)</th>
<th>African Sites (N=100)</th>
<th>US Sites (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>31 years (IQR: 25,38)</td>
<td>31 years (IQR: 22,37)</td>
<td>32 years (IQR: 28,40)</td>
</tr>
<tr>
<td><strong>Median Weight</strong></td>
<td>75 kg (IQR: 64,89)</td>
<td>72 kg (IQR: 63,87)</td>
<td>83 kg (IQR: 72,100)</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td>46% married</td>
<td>56% married</td>
<td>19% married</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>94% Black</td>
<td>100% Black</td>
<td>78% Black</td>
</tr>
<tr>
<td><strong>Employment Status</strong></td>
<td>60% unemployed</td>
<td>65% unemployed</td>
<td>47% unemployed</td>
</tr>
</tbody>
</table>
PARTICIPANTS’ SAFETY DATA

• 122 (42 P, 80 LA) women received at least one injection; 98 (34 P, 64 LA) received all six injections.
  – Transient Grade ≥2 liver abnormalities occurred in 9 (11%) LA participants compared with 4 (10%) in the P arm.
  – 3 LA participants (4%) developed Grade ≥3 injection site reactions compared with 0 (0%) in the P arm.
• No significant difference was observed between the two arms and study product was well-tolerated.
DRUG CONCS: PARTICIPANTS RECEIVING ALL 6 INJECTIONS (64)
ACCEPTABILITY
ACCEPTABILITY

Attributes DISLIKED

- Nothing
- No HIV prevention
- Painful
- Side Effects
- No Reversal
- Not discreet
- Provided by HCP
- Cost
- Other

3b.

- Placebo
- TMC 278 LA
At the last injection visit, 73% of women strongly agreed that they would think about using – and 61% that they would definitely use – a PrEP injectable in the future.
CABOTEGRAVIR: GSK126744 Long Acting (744LA)

Favorable attributes for PrEP:
- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

Muller et al, European Journal of Pharmaceutics and Biopharaceutics, 2011
Sreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012
INJECTABLE CABOTEGRAVIR
HPTN 077

A PHASE IIA STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF THE INVESTIGATIONAL INJECTABLE HIV INTEGRASE INHIBITOR, GSK1265744, IN HIV-UNINFECTED MEN AND WOMEN
HPTN 077: Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Long-acting Cabotegravir (CAB LA) in HIV-uninfected Men and Women

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARM 1</strong>&lt;br&gt;N = 79</td>
<td><strong>ARM 1</strong>&lt;br&gt;N = 66</td>
</tr>
<tr>
<td>Daily Oral&lt;br&gt;744 30 mg</td>
<td>Daily Oral&lt;br&gt;744 30 mg</td>
</tr>
<tr>
<td>CAB Injections LA 800 mg every 12 weeks at 3 visits</td>
<td>CAB Injections LA 600 mg every 8 weeks after monthly load at 5 visits</td>
</tr>
<tr>
<td><strong>Follow-up Phase (Tail Phase)</strong></td>
<td><strong>Follow-up Phase (Tail Phase)</strong></td>
</tr>
<tr>
<td><strong>ARM 2</strong>&lt;br&gt;N = 27</td>
<td><strong>ARM 2</strong>&lt;br&gt;N = 22</td>
</tr>
<tr>
<td>Daily Oral&lt;br&gt;Placebo</td>
<td>Daily Oral&lt;br&gt;Placebo</td>
</tr>
<tr>
<td>CAB Injections LA placebo every 12 weeks at 3 visits</td>
<td>CAB Injections LA placebo every 8 weeks after monthly load at 5 visits</td>
</tr>
</tbody>
</table>

200 HIV-uninfected, age 18-65
CAB LA PrEP Phase 2 Safety and PK Studies

**CAB LA 200mg/mL gluteal IM**

- **Follow-Up Phase**
  - 1°analysis
  - W41
  - W53
  - W65
  - W77
  - W81

**CAB LA 30 mg PO qd**

- **Placebo PO qd**

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**ECLAIR - all subjects**

- IM
- IM
- IM
- IM
- IM
- IM
- IM

**HPTN 077 - Cohort 1**

- IM
- IM
- IM
- IM
- IM
- IM
- IM

**HPTN 077 - Cohort 2**

- IM
- IM
- IM
- IM
- IM
- IM
- IM

**800mg q12 wks**

- (2 x 2mL)

**600mg q8 wks**

- (1 x 3mL)

---

**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)

---

**ViiV ECLAIR Study (NCT02076178)**

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

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- HIV negative, at-risk adults (excluding high risk)
- Drug PK sampling (blood plasma) in all study participants
CAB LA PrEP Phase 2 Safety and PK Studies

Primary Results to be presented at IAS 2017

- 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)

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- Two Cohorts (800 and 600mg IM)
- 3:1 randomization
- 67% enrolment of women
- US, Brazil, SA, Malawi (8 sites)
HPTN 083-
Phase 3 injectable Cabotegravir compared to daily oral TDF/FTC for PrEP in MSM

HPTN 084
Phase 3 injectable Cabotegravir compared to daily oral TDF/FTC for PrEP in women
45 HPTN 083 Research Sites Worldwide
4500 MSM
17-20 HPTN 084 Research Sites Sub-Saharan Africa
3200 Women

- 6 Sites in South Africa
- 1 Site in Kenya
- 2 Sites in Uganda
- 2 Sites in Malawi
- 5 Sites in Zimbabwe
- 1 Site in Botswana
Primary Objectives of HPTN 084

- To evaluate the relative safety and efficacy of CAB (oral run-in and injections) vs. daily oral TDF/FTC for HIV prevention.
HPTN 084: Study Design

• Phase 3 double blind, double dummy trial of CAB LA vs. TDF/FTC in women
  • Studies in NHP and HIV-infected participants support the potential of CAB LA to protect women from HIV acquisition
  • Active comparison with current TDF/FTC in women from Sub-Saharan Africa
  • Wide range in efficacy estimates for TDF/FTC make estimation of a non-inferiority margin challenging
Group A

Screening day and informed consent

STEP 1
Every day for 5 weeks

- CAB

STEP 2
Weeks 5 and 9

- TDF/FTC (Every day)

STEP 3
Every 2 months for 1 to 3.5 years

- Placebo for cabotegravir (CAB) injection
- Placebo for cabotegravir (CAB) pill

Group B

STEP 1
Every day for 48 weeks

- CAB

STEP 2
Weeks 5 and 9

- TDF/FTC (Every day)

STEP 3
Every 2 months for 1 to 3.5 years

- Placebo for TDF/FTC pill
- Placebo for cabotegravir (CAB) injection

TDF/FTC pill
CAB
Cabotegravir (CAB) injection
Placebo for TDF/FTC pill
Placebo for cabotegravir (CAB) injection

HPTN
HIV Prevention Trials Network
AFTER INJECTABLES
Subcutaneous PrEP Implants
Modeled After Implanon/Nexplanon Contraception

- Simple insertion AND removal
- Long-acting (months to years)
- PrEP + contraception?
- Current development:
  - TAF, EFdA (MK-8591)

CROI updates on implants

- **Abstract 420: IN VITRO AND IN VIVO EVALUATION OF BIODEGRADABLE IMPLANT CONTAINING TAF FOR HIV PREP**
  - Animal Study (Rabbit)
  - Polycaprolactone (PCL) is used as a biodegradable thin film to deliver TAF
  - Dose Dependent release
  - In vivo depletion by 14-21 days

- **Abstract 422LB: TRANSCUTANEOUS REFILLABLE NANOFLOWIDIC IMPLANT FOR CONSTANT DELIVERY OF HIV PREP**
  - Macaque model
  - Nanofluidic Implant
  - The implant demonstrated sustained release of both TAF and FTC for over 83 days.

*Durham, et al.  
Chua et al.*
Conclusions: HIV Prevention 2017

• TDF/FTC is an effective PrEP regimen

• PrEP demonstration projects and Implementation science studies will inform scale-up of PrEP services.

• Long acting antiviral agents will serve as critical new tools for prevention of HIV

• Ultimately, new tools are being developed to improve choices for PrEP, leading to improved combination prevention of HIV
THANK YOU!
TO ALL WHO DEVELOPED AND PARTICIPATED IN THESE MANY STUDIES, TO THOSE WHO HELPED WITH THIS TALK AND SLIDES
HPTN 083 AND 077 TEAMS (RAPHY LANDOVITZ), HPTN 084 (SINEAD DELANY-MORETLWE), HPTN 076 (LINDA GAIL BEKKER) HPTN COMMUNITY AND SUPPORT TEAMS MYRON S. COHEN, AND TO ALL THE FUNDERS