IAS 2019
10TH IAS CONFERENCE ON HIV SCIENCE
Mexico City, Mexico  21-24 July 2019
Long Acting Injectable Agents for PrEP

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Dr. Cohen is disclosing the following potential conflicts as recommended by the Conference:

- HIV Prevention Trials Network Co-PI
- Consulting: Merck, Gilead
- Stockholder and equity: None to report.
- Patents and intellectual property: None to report.
- Board of Directors Qura
Effectiveness of Daily TDF/FTC in Clinical Trials

SS Abdool Karim, personal communication
Long-Acting Injectables: Rilpivirine

- Rilpivirine LA is a long-acting nanosuspension for delivery via IM injection (regulatory approvals for HIV treatment in combination with other ART agents – in development with CAB LA)
- **Agent class:** Non-nucleoside reverse transcriptase inhibitor
- **Half-life:**
  - Oral: 45 hours
  - Injectable: 90 days
HPTN 076: RPV LA in low-risk HIV-uninfected women

Objective: To evaluate the safety and acceptability of rilpivirine LA in healthy, HIV-uninfected females.

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>52</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
<td>Daily oral RPV</td>
<td>Six injections of RPV LA 1200 mg every 8 weeks</td>
<td>Follow-up phase (tail phase)</td>
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<tr>
<td>N = 91</td>
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<tr>
<td>ARM 2</td>
<td>Daily oral placebo</td>
<td>Six injections of placebo every 8 weeks</td>
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<td>N = 45</td>
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HPTN 076: Phase 2 Safety Results

- Two 2mL IM injections every 8 weeks were safe, well-tolerated, and acceptable to women
- Lower quartile RPV concentrations were consistently above the PA-IC₉₀ 8 weeks post injection at all time points
- Cold chain required

Bekker LG, CROI 2017. Abstract 421 LB.
Seroconversion during pharmacokinetic tail after 300 mg IM dose

Summary: Drug Levels, Viraemia, Resistance

ART = antiretroviral therapy

Penrose K, et al. HIVR4P 2014. Abstract OA27.01
Long-acting Injectables: Cabotegravir

- Cabotegravir LA is a long-acting suspension for delivery via IM injection (Currently in advanced development for Maintenance of virologic suppression [with RPV LA] and PrEP-monotherapy)
- Agent class: Strand-transfer integrase inhibitor
- Half-life:
  - Oral: 40 hours
  - Injectable: 40-65 days
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 Frank, Robert M Grant, Kenneth H Mayer, Richard Elion, Deborah Goldstein, Chester Fisher, Magdalena E Sabieszczyk, Joel E Gallant, Hong Van Tieu, Winkler Weinberg, David A Margolis, Krischan J Hudson, Britt S Stancil, Susan L Ford, Parul Patel, Elizabeth Gould, Alex R Rinehart, Kimberly Y Smith, William R Spreen

Satisfaction and acceptability of cabotegravir long-acting injectable suspension for prevention of HIV: Patient perspectives from the ECLAIR trial

Expanding the Menu of HIV Prevention Options: A Qualitative Study of Experiences with Long-Acting Injectable Cabotegravir as PrEP in the Context of a Phase II Trial in the United States

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

Objective: To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.

HPTN077: CAB Cₜ Following Each Injection

Adapted from Landovitz, R. IAS. 2017

CAB LA 800 mg IM Q12W
Males: 23% ≥4x PA-IC₅₀, 65% 1x - 4x PA-IC₅₀, 68% <1x PA-IC₅₀
Females: 23% ≥4x PA-IC₅₀, 95% 1x - 4x PA-IC₅₀, 100% <1x PA-IC₅₀

CAB LA 600 mg IM Q8W
Males: 95% ≥4x PA-IC₅₀, 80% 1x - 4x PA-IC₅₀, 84% <1x PA-IC₅₀
Females: 79% ≥4x PA-IC₅₀, 95% 1x - 4x PA-IC₅₀, 87% <1x PA-IC₅₀
CAB LA Pharmacokinetic Tail

Week 60

- Males: 78% <LLOQ, 15% LLOQ – 1x PA-IC90, 8% 1x – 4x PA-IC90, 8% >4x PA-IC90
- Females: 37% <LLOQ, 40% LLOQ – 1x PA-IC90, 23% 1x – 4x PA-IC90, 8% >4x PA-IC90

Week 76

- Males: 87% <LLOQ, 13% LLOQ – 1x PA-IC90, 4% 1x – 4x PA-IC90, 8% >4x PA-IC90
- Females: 58% <LLOQ, 31% LLOQ – 1x PA-IC90, 11% 1x – 4x PA-IC90, 8% >4x PA-IC90

Median time to LLOQ, weeks (range)

- Males: 42.7 (20.4, 134)
- Females: 66.3 (17.7, 182)

HPTN 083 and 084: Phase 3 for CAB LA PrEP

**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)

*In Steps 1 and 2, the tablets and the injections will look alike, so staff and participants will not know if they are getting the active or placebo products. In step 3, everyone will be given active TDF/FTC. + In step 2 the first two injections are four weeks apart and 8 weeks apart thereafter.*

Graphics designed by: White Bill
HPTN 083

PHASE 2B/3 INJECTABLE CABOTEGRAVIR COMPARSED TO DAILY ORAL TDF/FTC FOR PREP IN CISGENDER MEN AND TRANSGENDER WOMEN WHO HAVE SEX WITH MEN

Raphael Landovitz
Beatriz Grinjsten

NIAID/DAIDS DSMB
May 9, 2019
Status of Site Activation

• 27 US sites
  – Enrollment closed as of 3/11/19

• 11 South American Sites
  – Final site activated 3/11/19
  – Enrollment ongoing

• 4 Asian sites
  – Screening closed as of 4/22/19
  – Enrollment nearly complete

• 1 African site
  – Enrollment nearly complete
Target Populations

- Age <30: 65% >50%
- TGW: 12% >10%
- US Black/AA: 50% >50%

Enrollment – May 9
HPTN 084

A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

Sinead Delany-Moretlwe
Mina Hosseinipour

NIAID/DAIDS DSMB
November, 2018
Study Population

3,200 women who have sex with men
- Female
- HIV negative
- Age 18-45 years
- Sexually active (vaginal intercourse twice in past 30 days)
- **Modified VOICE Risk Score 3**
- Not pregnant or breastfeeding
- No previous enrollment in vaccine trial and no co-enrollment in other HIV prevention trials
- No contraindications to either agent

5 Sites in Zimbabwe
3 Sites in Botswana
2 Sites in Malawi
1 Site in Uganda
1 Site in Swaziland
1 Site in Kenya
5 Sites in South Africa
7 Sites in South Africa
Enrollment

• Almost halfway!
• Current enrolment \( n=1535 \)
• Since activation of all 20 sites, average enrolment/month 160
• Accrual targeted to complete e/o April 2020

Source: SDMC, data to May 16, 2019
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 et al, Lancet HIV 2017;4:e331-40
The name Biomedical Prevention Implementation Collaborative or “BioPIC” for short, reflects our objectives

**BIOPIC OBJECTIVES**

1. Using CAB-LA as an initial example, develop and fine-tune an overarching product introduction framework that is adaptable to any future biomedical prevention, enabling stakeholders to quickly convert positive clinical trial results into public health impact.

2. Develop a comprehensive, coordinated product introduction agenda and access strategy in parallel with the clinical trials and ahead of their completion to ensure successful and rapid introduction of CAB-LA.
Challenges in Development of CAB-LA as PreP

• Recruitment and retention!
• Reduced HIV incidence (GOOD NEWS) with more ART, behavior change compromises anticipated “endpoints”
• Will CAB-LA PrEP “overwhelm” STIs
• Analysis may be complicated: ITT vs “As treated”
THANK YOU FOR LISTENING