IAS 2019

10TH IAS CONFERENCE ON HIV SCIENCE

Mexico City, Mexico 21-24 July 2019

Long Acting Injectable Agents for PrEP

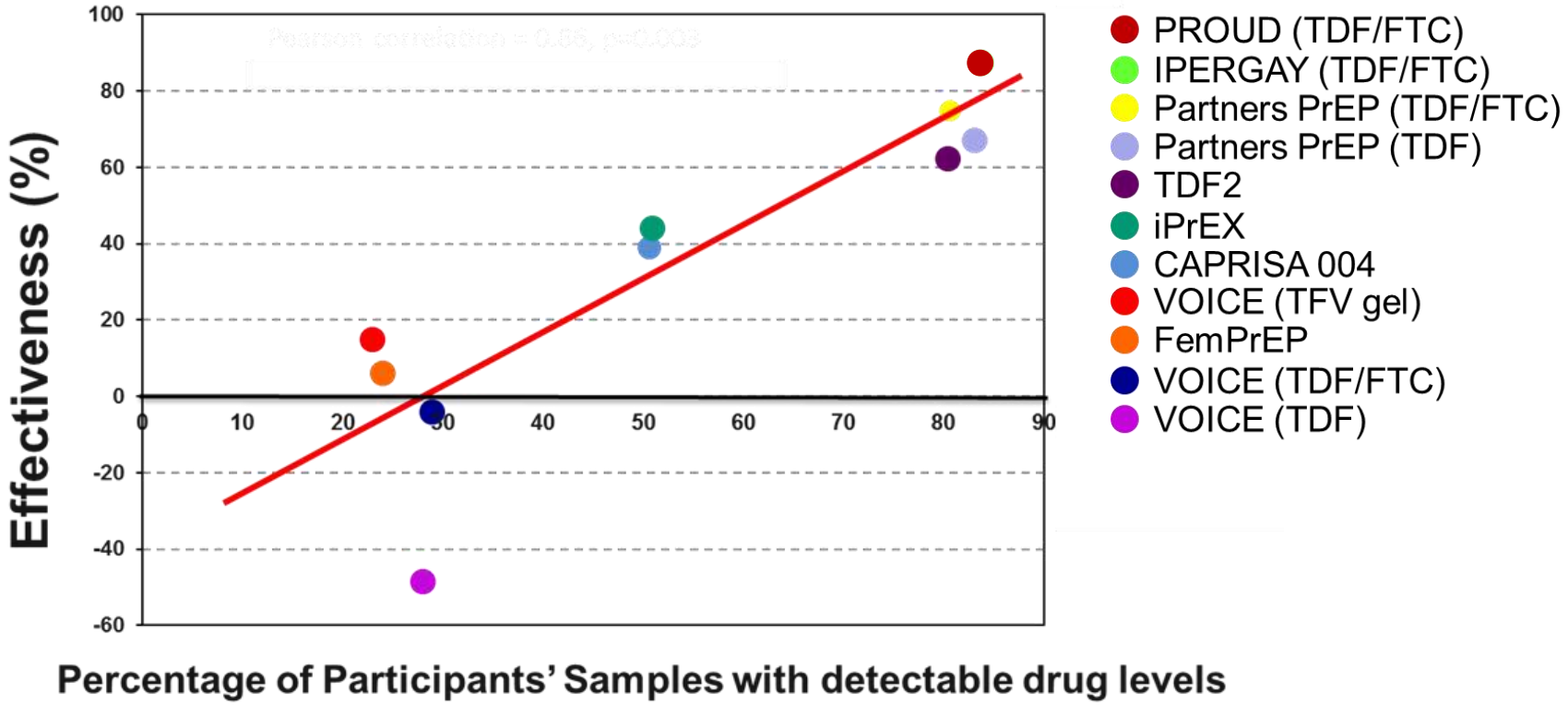
Myron S. Cohen

The University of North Carolina at Chapel Hill

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

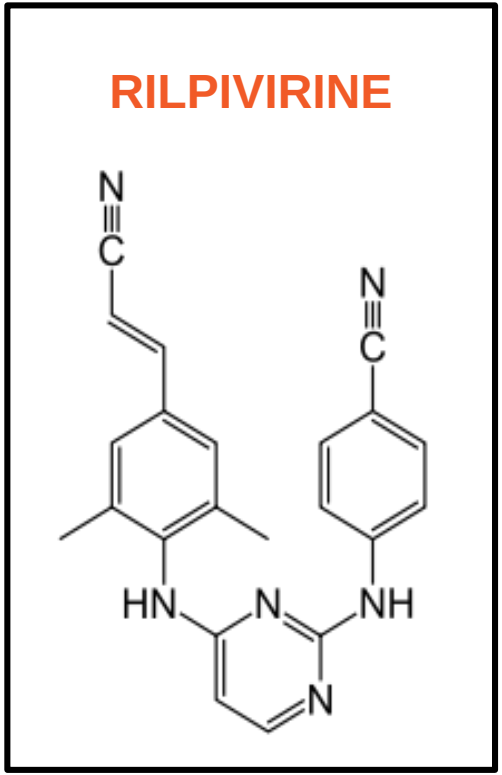
Effectiveness of Daily TDF/FTC in Clinical Trials



SS Abdool Karim, personal communication

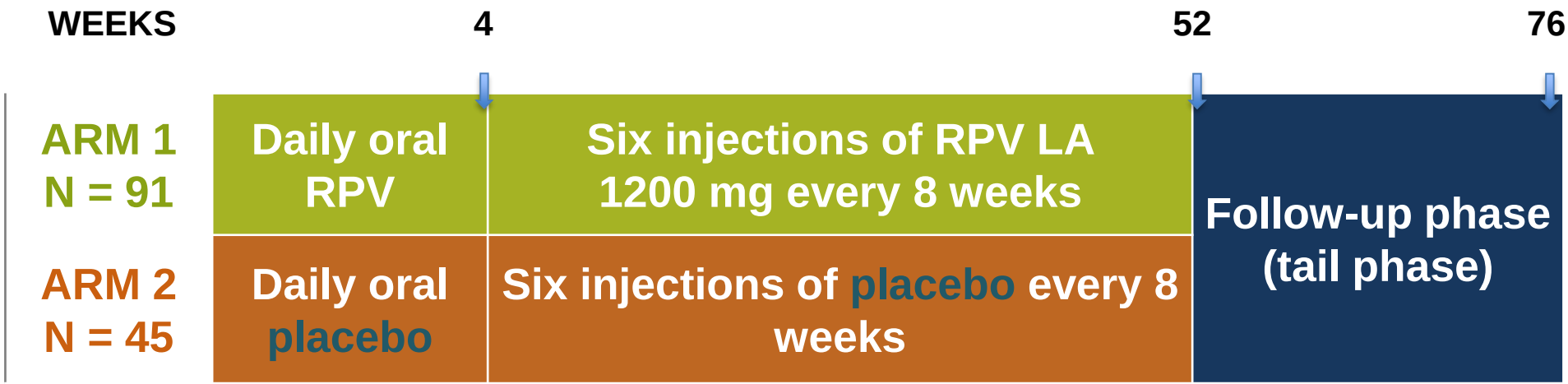
Long-Acting Injectables: Rilpivirine

- **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.

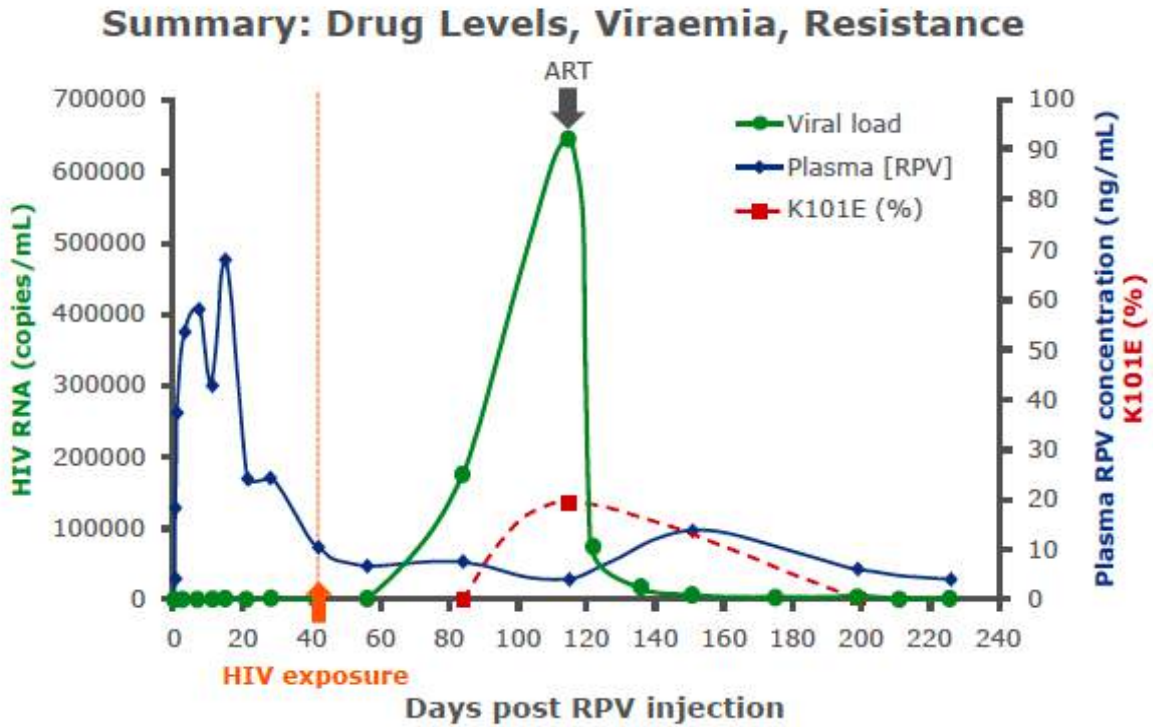


HPTN 076: Phase 2 Safety Results

- Two 2mL IM injections every 8 weeks were safe, well-tolerated, and acceptable to women
- Lower quartile RPV concentrations were consistently above the PA-IC_{90} 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



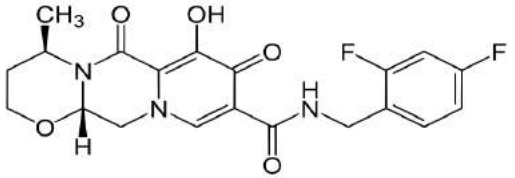
ART = antiretroviral therapy

Penrose K, et al. HIVR4P 2014. Abstract OA27.01

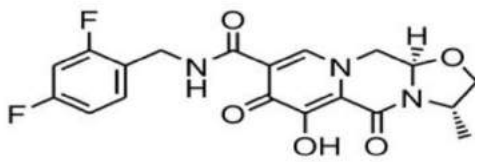
Long-acting Injectables: Cabotegravir

- **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

DOLUTEGRAVIR



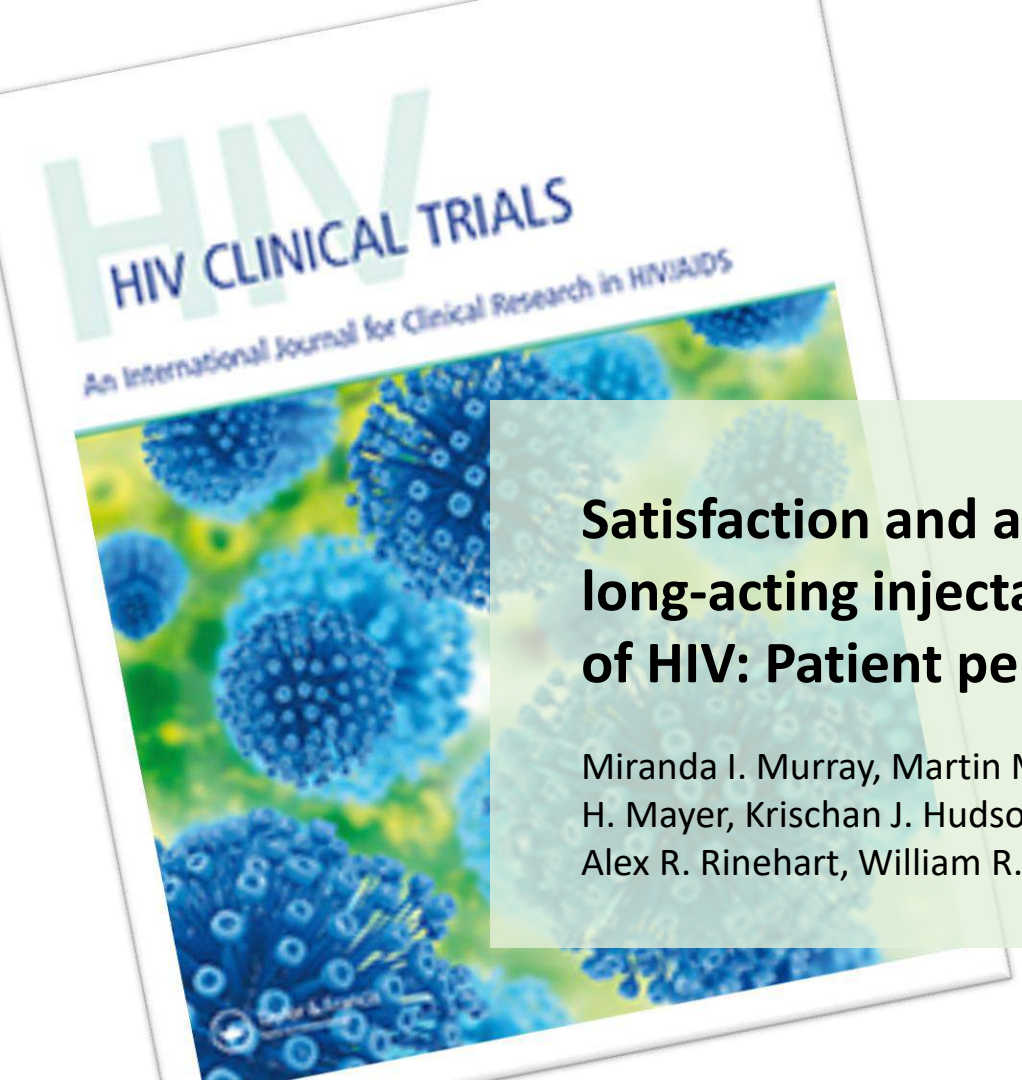
CABOTEGRAVIR



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 Sobieszczyk, 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

Lancet HIV. 2017 Aug;4(8):e331-e340



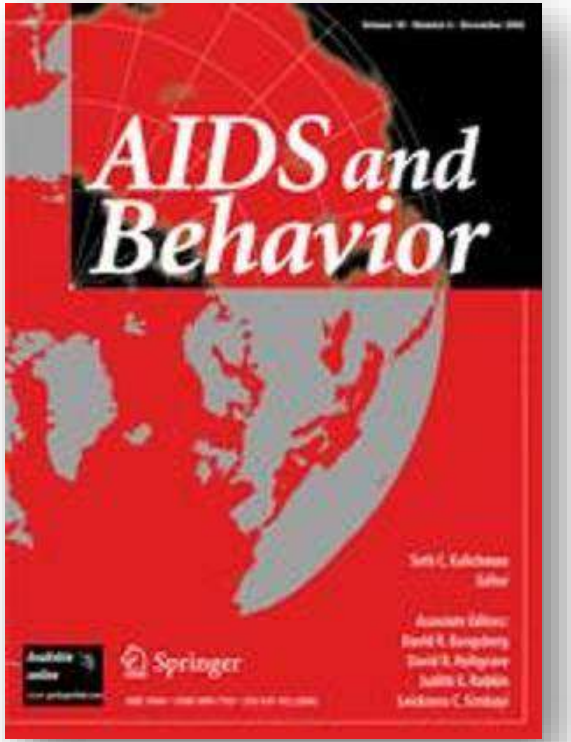
Satisfaction and acceptability of cabotegravir long-acting injectable suspension for prevention of HIV: Patient perspectives from the ECLAIR trial

Miranda I. Murray, Martin Markowitz, Ian Frank, Robert M. Grant, Kenneth H. Mayer, Krischan J. Hudson, Britt S. Stancil, Susan L. Ford, Parul Patel, Alex R. Rinehart, William R. Spreen & David A. Margolis

HIV Clin Trials. 2018 Aug;19(4):129-138

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

Kerrigan D, Mantsios A, Grant R, Markowitz M, Defechereux P, La Mar M, Beckham SW, Hammond P, Margolis D, Murray M



AIDS Behav. 2018 Nov;22(11):3540-3549

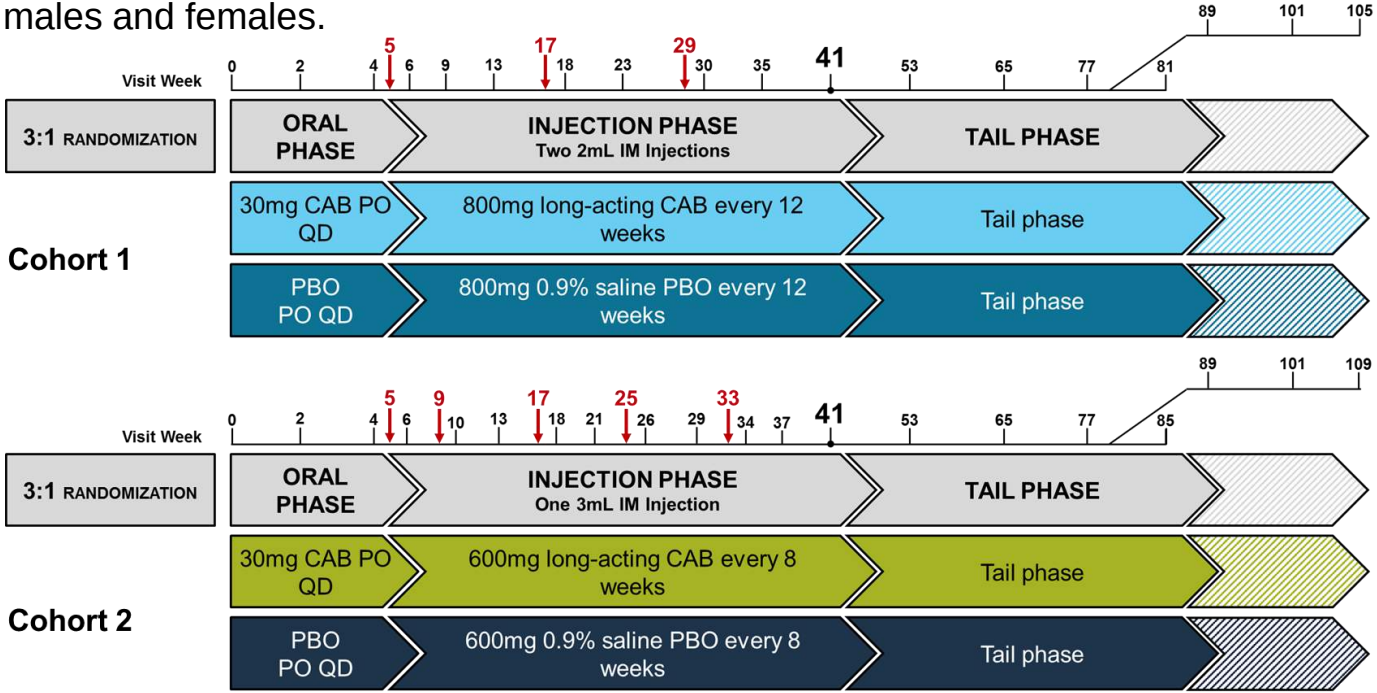
Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M, Hosseinipour MC, Panchia R, Cottle L, Chau G, Richardson P, Marzinke MA, Hendrix CW, Eshleman SH, Zhang Y, Tolley E, Sugarman J, Kofron R, Adeyeye A, Burns D, Rinehart AR, Margolis D, Spreen WR, Cohen MS, McCauley M, Eron JJ

PLoS Med. 2018 Nov 8;15(11):e1002690

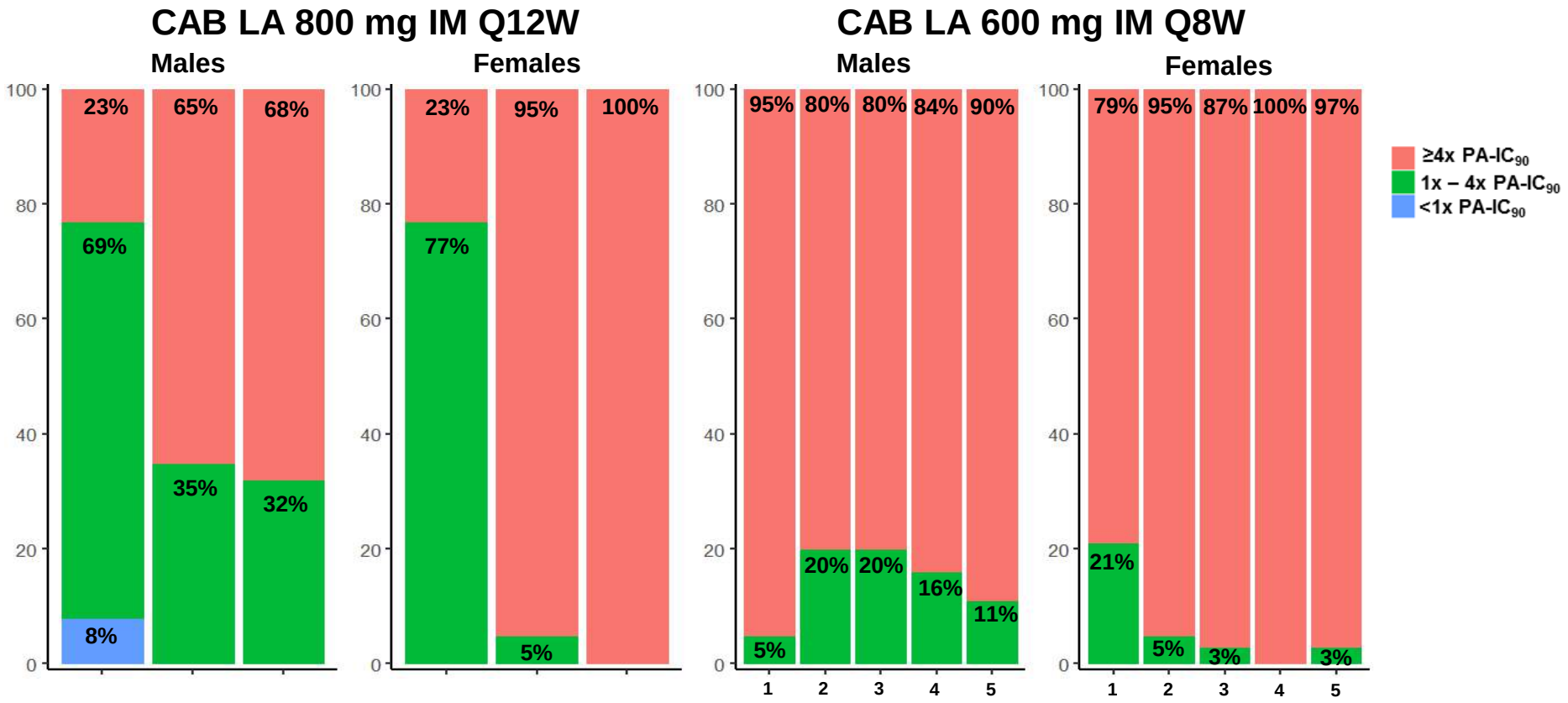
CAB LA in Development: HPTN 077

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



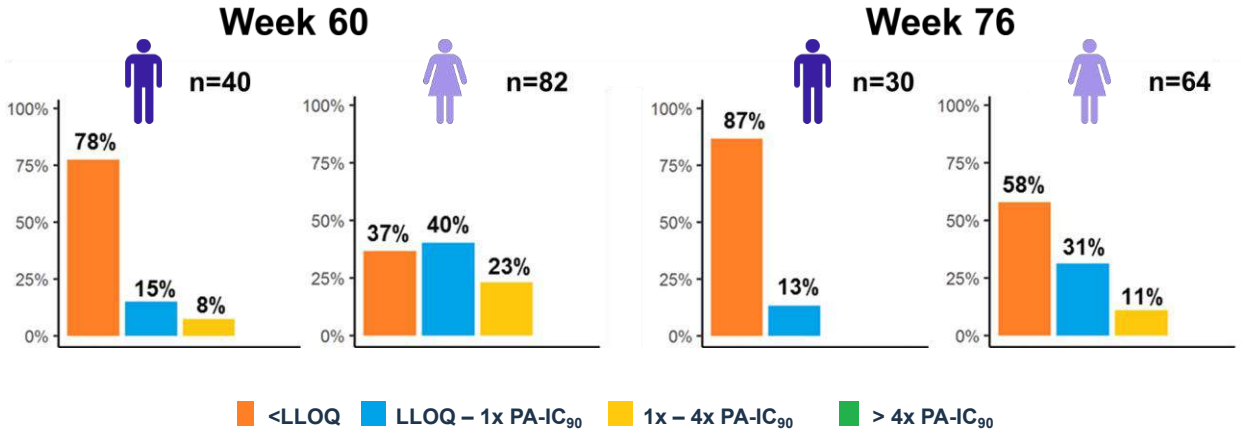
Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

HPTN077: CAB C_τ Following Each Injection



Adapted from Landovitz, R. IAS. 2017

CAB LA Pharmacokinetic Tail

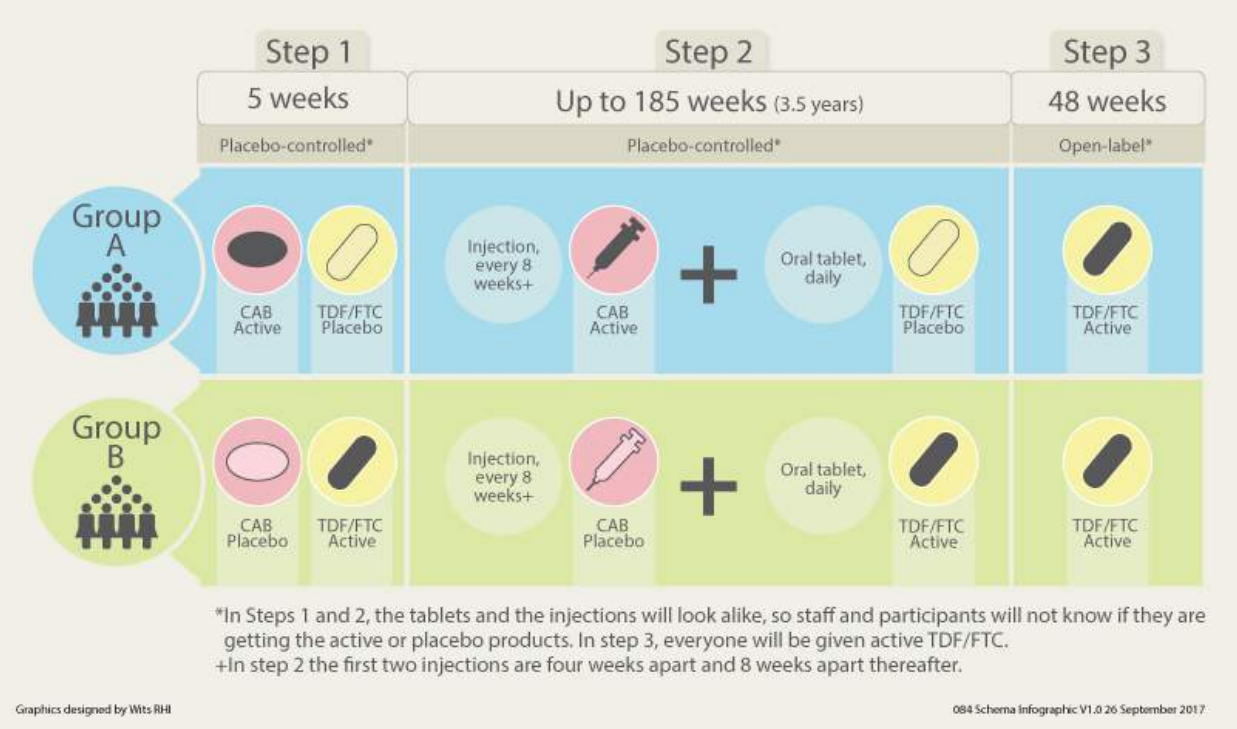


Median time to LLOQ, weeks (range)	42.7 (20.4, 134)	66.3 (17.7, 182)

Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

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)



HPTN
HIV Prevention Trials Network

HPTN 083

PHASE 2B/3 INJECTABLE CABOTEGRAVIR COMPARED 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

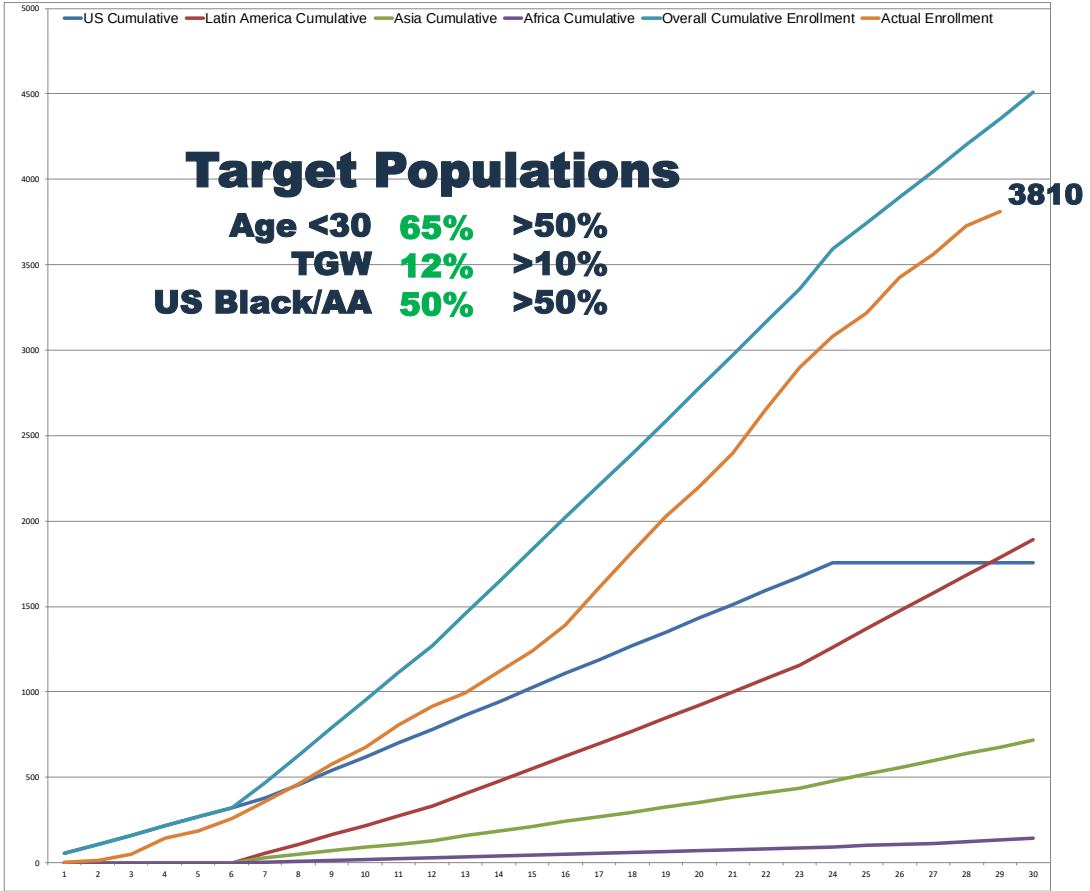
May 9, 2019

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

HPTN
HIV Prevention
Trials Network

Enrollment – May 9



HPTN
HIV Prevention
Trials Network

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

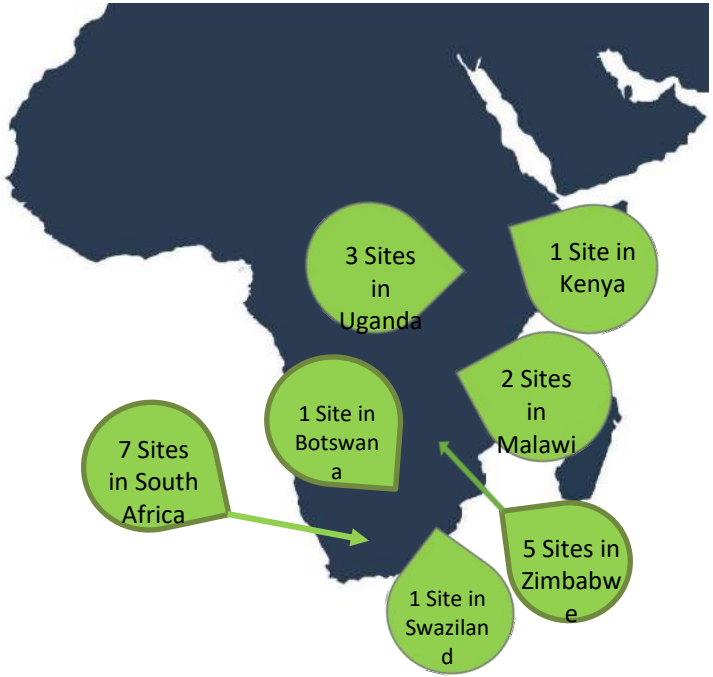
Sinead Delany-Moretlwe
Mina Hosseinipour

NIAID/DAIDS DSMB
November, 2018

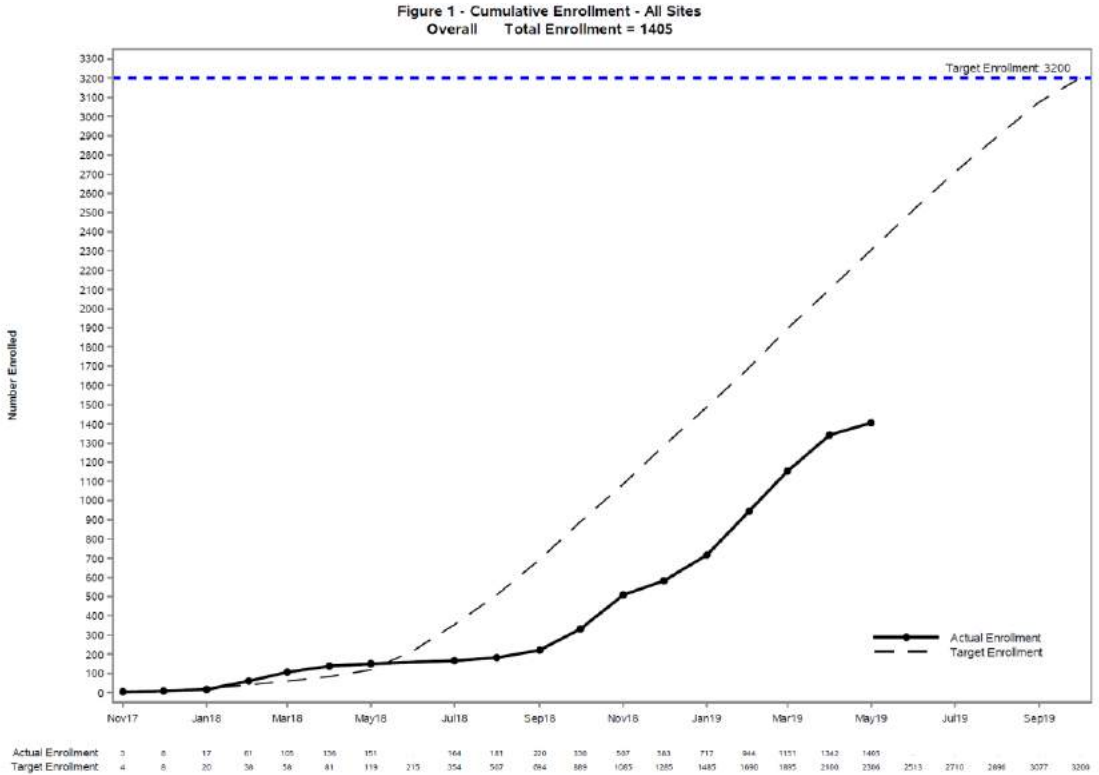
Study Population

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



Enrollment



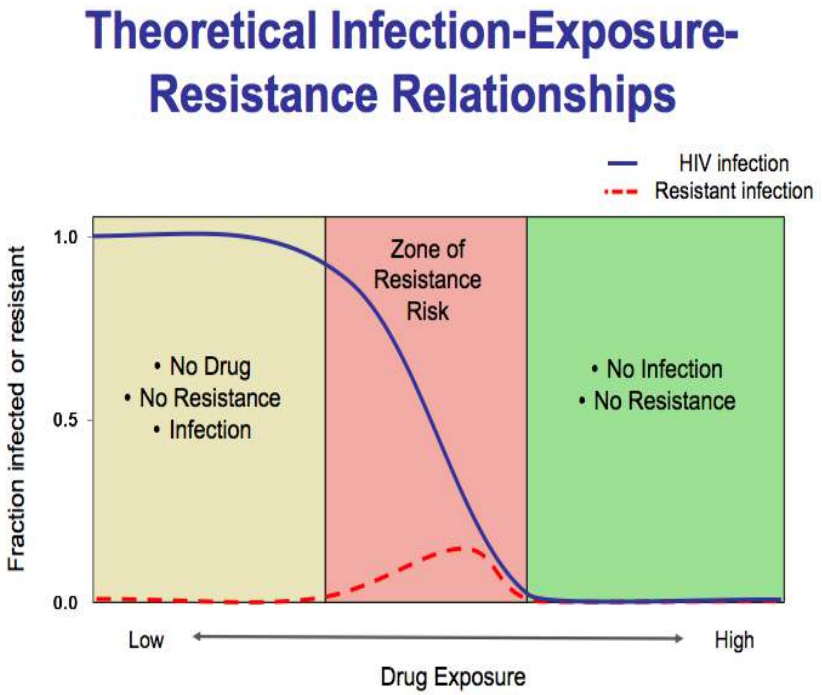
- Almost halfway!
- Current enrolment n=1535
- Since activation of all 20 sites, average enrolment/month 160
- Accrual targeted to complete e/o April 2020

Source: SDMC, data to May 16, 2019

Long-Acting Agents: Good, Bad, or Ugly?

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