Long Acting Injectable Cabotegravir for PrEP

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Conflict of Interest Disclosure Statement

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AETC AIDS Education & Training Center Program South Central

Learning Objectives

1. Describe pertinent pharmacology of the novel PrEP medication cabotegravir.
2. Recognize available clinical trial data on cabotegravir for PrEP.

Cabotegravir (CAB) Pharmacology

Mechanism: integrase strand transfer inhibitor (INSTI)

- Prevents viral DNA integration into host genome & inhibits HIV replication
- Analog of dolutegravir
- Oral and injectable forms

Half-life (T½)

- Intramuscular (IM) or Subcutaneous (SC) -5.6 to 11.5 weeks
- Oral (po)- 41 hours

https://aidsinfo.nih.gov/drugs/513/cabotegravir/0/professional

HPTN 083 study

Purpose: Evaluate the safety and efficacy of cabotegravir long acting (CAB LA) for PrEP in cisgender men and transgender women who have sex with men (MSM and TGWSM) without HIV

Study Design: randomized, double-blinded.

Planned enrollment for 4500, increased to 5000 after interim analysis

Sites: 47- South Africa, Thailand, Vietnam, Argentina, Brazil, Peru, USA

Primary Outcomes:

- # of documented HIV infections over 4 years
- # of grade 2 or higher clinical and laboratory AEs

https://www.hptn.org/research/studies/hptn083

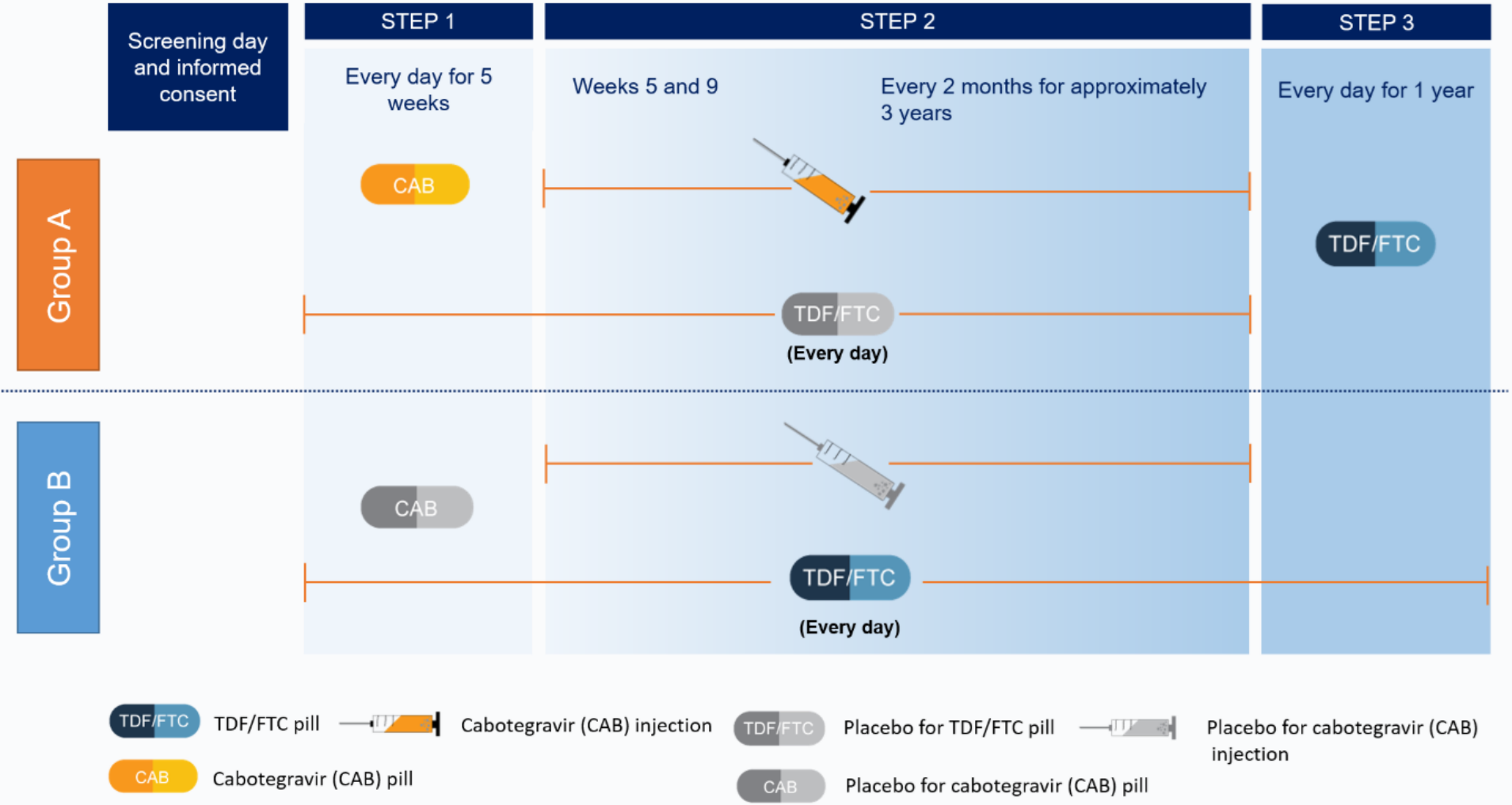
HPTN 083 study

Notable inclusion criteria:

- 18 yo and older
- MSM or TGWSM
- High risk for sexually acquiring HIV (self-report) in last 6 months
- Hepatitis B virus surface antigen negative
- CrCl (Cockcroft-Gault) ≥ 60mL/min (consider *not* enrolling 60-70mL/min)

Notable exclusion criteria:

- Active, recent (<90 days) injection drug use
- Clinically significant cardiovascular disease
- Inflammatory skin conditions that compromise safety of IM injection
- Current or chronic history of liver disease
- Coagulopathy that would contraindicate IM injection
- Egg or soy allergies



https://www.hptn.org/research/studies/hptn083

Interim Review

- Study began in November 2016
- n= 4566
  - 66% of the study population were <30 yo
  - 12.4% transgender women
  - 18.5% black
- 50 people acquired HIV
  - 12- cabotegravir long acting (CAB LA) arm
  - 38- daily oral tenofovir disoproxil fumarate(TDF) /emtricitabine (FTC) arm

Interim Review

- HIV incidence rate
  - CAB LA: **0.38%** (95% CI 0.2-0.66%)
  - TDF/FTC: **1.21%** (95% CI 0.86-1.66%)

- **66% fewer infections with CAB LA vs. TDF/FTC**

- May 14, 2020- Data & safety monitoring board (DSMB) found CAB LA *highly effective* in preventing HIV
  - All study participants now be offered injectable PrEP
  - Study terminated early

Companion Study- HPTN 084

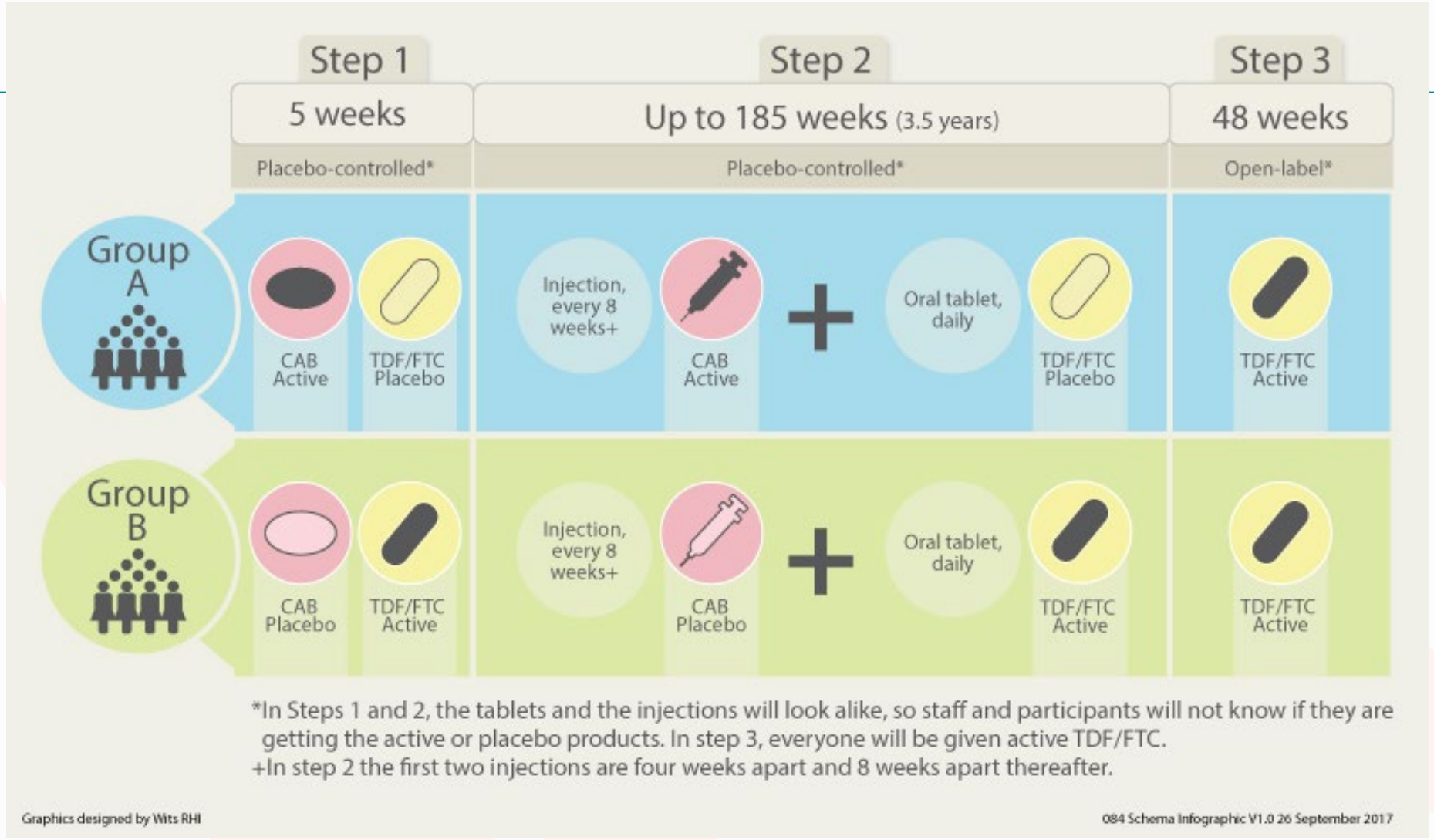
Purpose: evaluate the safety and efficacy of CAB LA for PrEP in cisgender women without HIV

Study Design: randomized, double-blinded; 3,224 ciswomen aged 18 to 45, not pregnant or breastfeeding, on contraception

Sites: 7 countries in sub-Saharan Africa

Primary Outcomes:

- # of documented HIV infections over 4 years
- # of grade 2 or higher clinical and laboratory AEs



https://www.hptn.org/research/studies/hptn084

Interim Review

- Study began in November 2017
- n= 3224
  - 57% of the study population were <25 yo
  - 82% percent not living with a partner
  - 55% reported 2+ partners in the past month
  - 34% had a primary partner PWH or unknown HIV status
- 38 people acquired HIV
  - 4- CAB LA arm (2 with recent CAB injection)
  - 34- daily oral TDF/FTC arm

Interim Review

- HIV incidence rate
  - CAB LA: **0.21%** (95% CI 0.06-0.54%)
  - TDF/FTC: **1.79%** (95% CI 1.24-2.51%)

- **89% fewer infections with CAB LA** vs. TDF/FTC

- November 9, 2020- DSMB found CAB LA *highly effective* in preventing HIV
  - All study participants now be offered injectable PrEP
  - Study terminated early

Adverse Events

HPTN 083 trial- 4,566 participants

- Injection site reactions (ISR): 81% CAB vs. 31% placebo
- Majority were grade 1 or 2
- 2.2% of CAB LA participants discontinued due to injection site reaction AE
- Other AEs more common in CAB LA group:
  - Increased blood glucose levels, pyrexia, nasopharyngitis, weight gain (1.3kg vs. 0.3kg TDF/FTC)
  - Weight gain equal by week 40- 1.08kg vs. 1.07kg

Adverse Events

HPTN 084 trial- 3,224participants

- ISR: 32% CAB vs. 9% placebo
- Grade 2+ ISR: 7% CAB vs. 1% placebo
- Zero participants discontinued due to injection site reaction AE
- Other AEs more common in CAB LA group:
  - Immediate weight gain (0.42kg CAB [95% CI 0.3 – 0.54]) p<0.001
  - Overall, increase in both arms (not significant, p=0.12)
    - CAB +2.4 kg/year
    - TDF/FTC +2.2 kg/year

Cabotegravir (CAB) Drug Interactions

- Metabolism
  - UGT1A1 (major) & UGT1A9 (minor); minimal CYP-mediated role
  - Unchanged in feces (58.5%) & as a metabolite in urine (26.8%)

- Rifampin- suboptimal CAB concentrations

- Rifabutin- modest effect on CAB concentration, still suppressed VL in people with HIV (PWH)

- **No interaction expected with:**
  - UGT1A1 or 1A9 inhibitors (i.e. atazanavir)
  - UGT inducers (i.e. phenobarbital)
    - However, *potent* UGT inducers predicted to significantly ↓ CAB concentrations (i.e. carbamazepine)
  - Oral contraceptives containing levonorgestrel and ethinyl estradiol

Prescribing HIV LA PrEP

- Approval December 20, 2021
  - Monthly injections by a healthcare professional x 2 months, followed by every other month injections
  - “May use” an oral lead in for one month to assess tolerability
- ICD-10 Codes:
  - Z20.6 Contact with and (suspected) Exposure to HIV
  - Z20.2 Contact with and (suspected) Exposure to infections with a predominantly sexual mode of transmission
- If insured, may require prior authorization or copay card
- If no insurance or large copay:
  - Medication Assistance Program: 1-800-226-2056 or online at https://www.gileadadvancingaccess.com/
  - Patient Advocate Foundation: https://www.copays.org/diseases/hiv-aids-and-prevention

Summary

- Cabotegravir appears to be overall well-tolerated
- Minimal drug interactions
- Long-acting formulation allows for every 8-week dosing
  - CAB in MSM & TGWSM - **66% lower** HIV risk vs. TDF/FTC
  - CAB in ciswomen - **89% lower** HIV risk vs. TDF/FTC
- Usage in clinics may be complex due to insurance, capacity, logistics

Resources

- Clinical Consultation Center http://nccc.ucsf.edu/
  - HIV Management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP line
  - HCV Management
  - Substance Use Management
- AETC National HIV Curriculum https://aidsetc.org/nhc
- Core Concepts - Primary Care Management - Basic HIV Primary Care - National HIV Curriculum (uw.edu)
- AETC National Coordinating Resource Center https://targethiv.org/library/aetc-national-coordinating-resource-center-0
- Additional trainings scaetcecho@salud.unm.edu

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Resources

- https://aidsinfo.nih.gov/drugs/513/cabotegravir/0/professional
- https://aidsinfo.nih.gov/clinical-trials/details/NCT02720094
- https://www.hptn.org/research/studies/hptn083
- https://www.niaid.nih.gov/news-events/long-acting-injectable-drug-prevents-hiv-among-men-who-have-sex-men-and-transgender
- https://www.hiv.gov/blog/long-acting-injectable-form-hiv-prevention-outperforms-daily-pill-nih-study?utm_source=email&utm_medium=email&utm_campaign=ias20200706&utm_content=federalresponse