Long-acting Cabotegravir (CAB LA) for PrEP

Programmatic Update – 12 Oct 2019

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Cabotegravir LA (CAB LA)

- CAB is an investigational HIV integrase strand transfer inhibitor in Phase 3 development for HIV treatment and prevention
- LA formulation is low solubility crystalline drug suspended in aqueous vehicle for intramuscular injection
  - No requirement for protection from light or refrigeration
  - Shelf life: 36 months at up to 30˚C, do not freeze
- Phase 2b HIV treatment studies (with rilpivirine LA) demonstrate potent anti-HIV activity and a high barrier to resistance
- NHP studies demonstrate high level protection against rectal[1], vaginal[2,3], parenteral[4], or penile[5] SIV/SHIV challenges
- Strong preclinical/clinical data package supports ongoing Phase 3 program for HIV PrEP

[1]Andrews *et al. Science.* 2014;343(6175):1151-4, [2]Radzio *et al. Sci Transl Med.* 2015;7(270):270ra5,
[3]Andrews *et al. Sci Transl Med.* 2015;7(270):270ra4, [4]Andrews et al. AIDS. 2017;31(4):461-7,
[5]Dobard *et al.* Abstract 83. 25th Conference on Retroviruses and Opportunistic Infections; March 4-7, 2018; Boston, Massachusetts

CAB LA Potential Indications

HIV Treatment (with rilpivirine LA)

- CAB LA + RPV LA once every 1 or 2 monthly IM injection as a two-drug maintenance regimen for HIV-infected patients
- CAB + RPV attributes support LA approach
  - Different MOA, resistance profiles, metabolic pathways
  - Lack of drug interaction between CAB and RPV [1]
  - Initial LA trials support q4-8 week synchronous dosing schedule
  - Oral formulations to facilitate treatment initiation, oral-bridging and discontinuation strategies
  - Well-established and favorable oral RPV safety profile

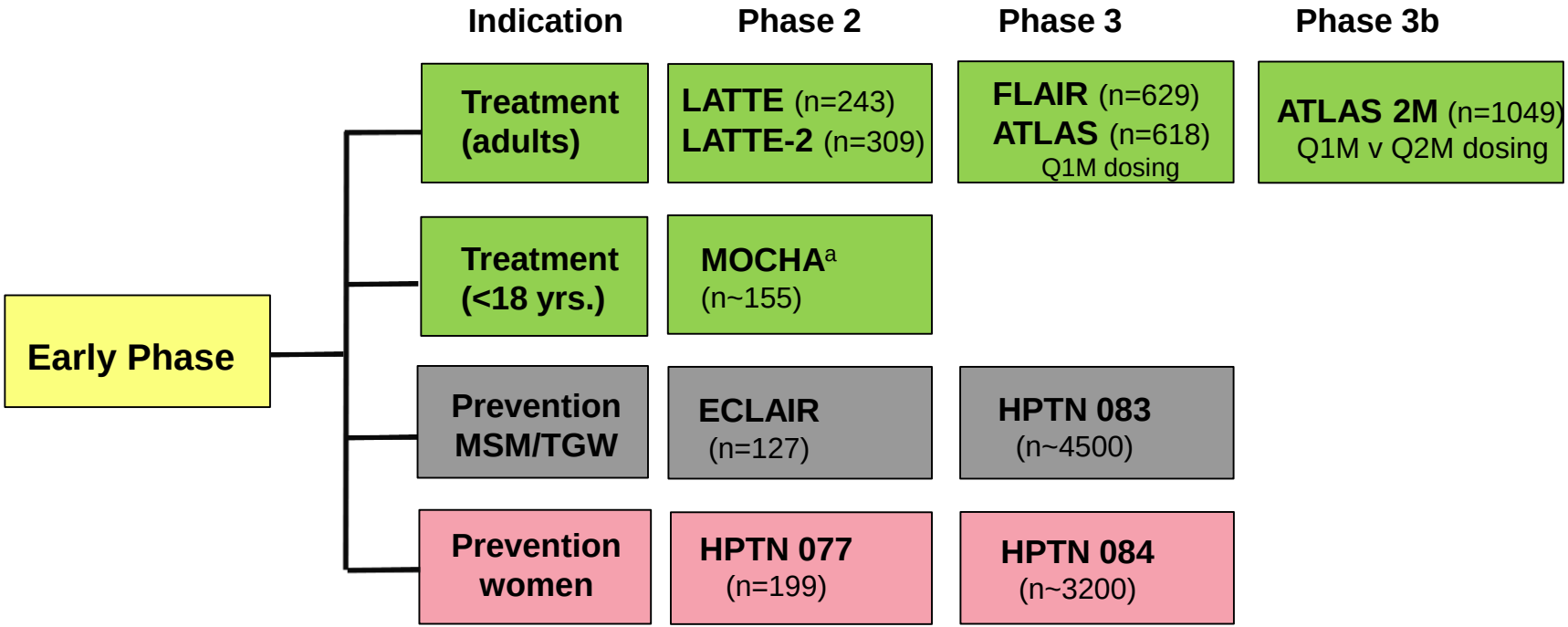
HIV PrEP (CAB monotherapy)

- CAB LA IM once every 2 months, to reduce risk of sexually acquired HIV-1 infection (combined with safer sex practices)
- Potential to deliver with LA contraception in family planning setting

[1] Ford S, AAC 2013:57, 5472-7

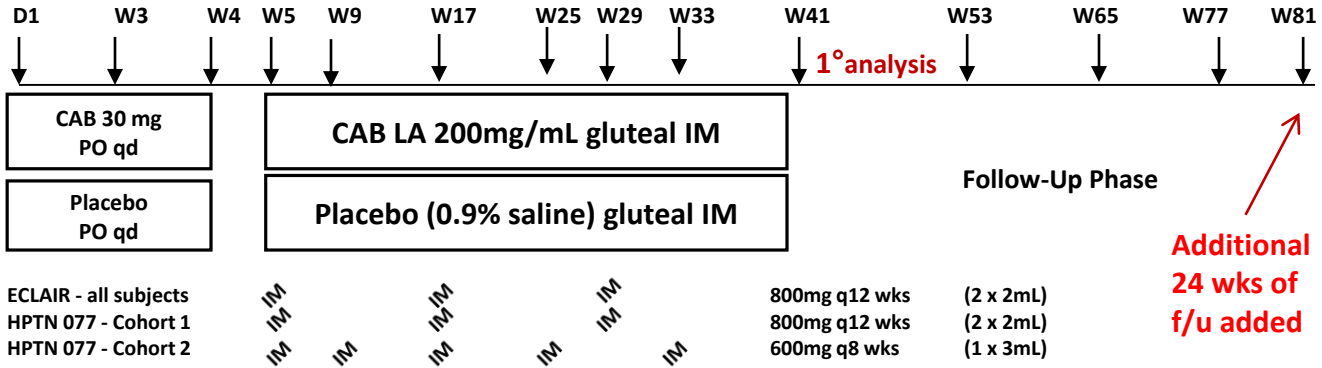
CAB LA Development Program

Simultaneous Global Registration Programs for Treatment and Prevention



[a] MOCHA (IMPAACT 2017) Phase 1/2 study will provide supportive information for HIV prevention in adolescents

CAB LA PrEP Phase 2 Safety and PK Studies

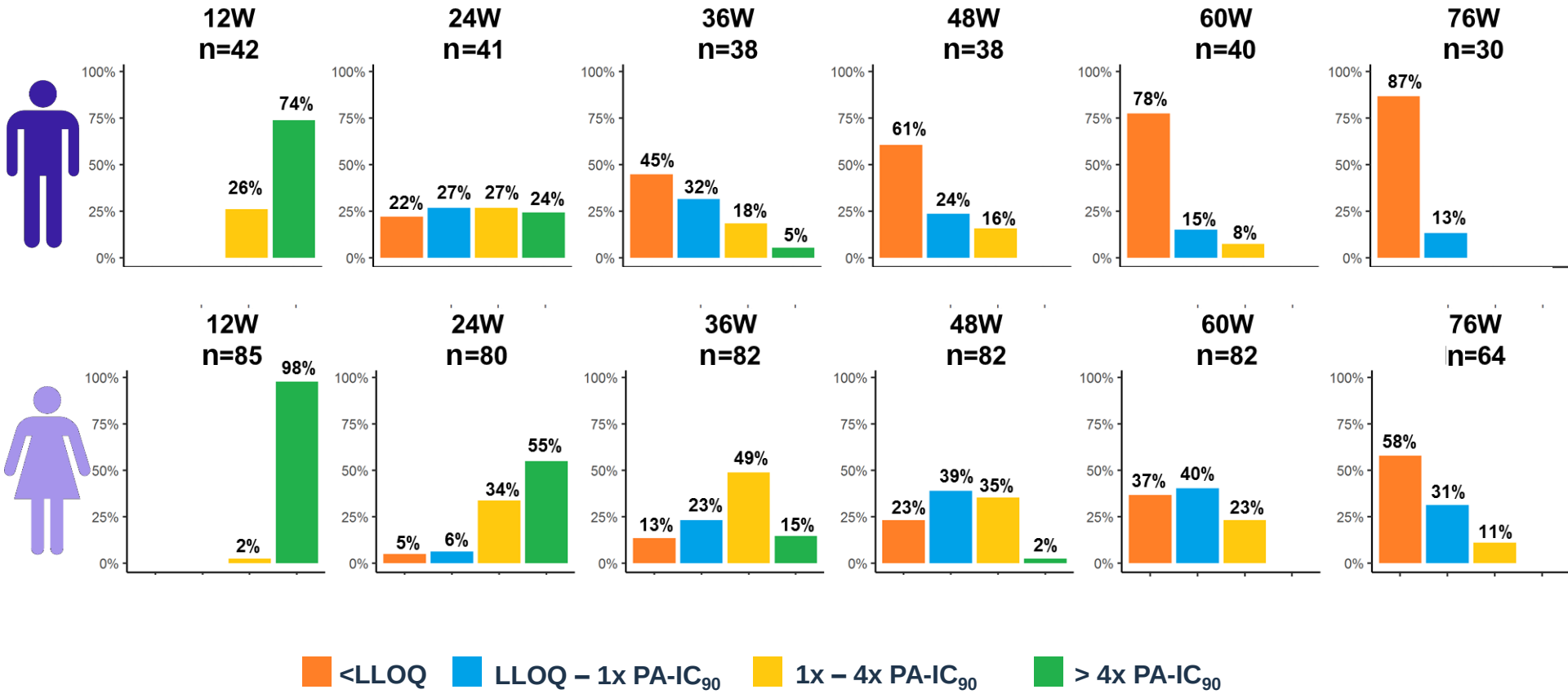


- HIV negative, at-risk adults (excluding high risk)
- Drug PK sampling (blood plasma) in all study participants

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

HPTN 077 Study (NCT02178800)
- n=199 (110 Cohort 1; 89 Cohort 2) ongoing
- Two Cohorts (800 and 600mg IM)
- 3:1 randomization
- 60% enrolment of women
- US, Brazil, SA, Malawi (8 sites)

CAB LA pharmacokinetic tail by sex at birth

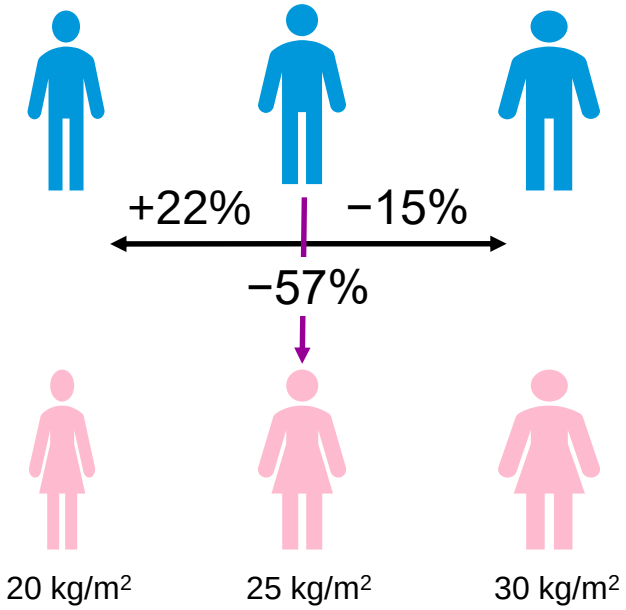


<LLOQ | LLOQ – 1x PA-IC_{90} | 1x – 4x PA-IC_{90} | > 4x PA-IC_{90}

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

CAB Absorption Slower in Females and Individuals of Higher BMI – Results in Lower Peaks, Higher Troughs

Absorption Rate:



Each covariate alone was associated with <15% change in steady-state trough

CAB PK supports a Q8W PrEP regimen without need for demographic-driven dosing

BMI, body mass index; CAB, cabotegravir; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; Q8W, every 8 weeks.

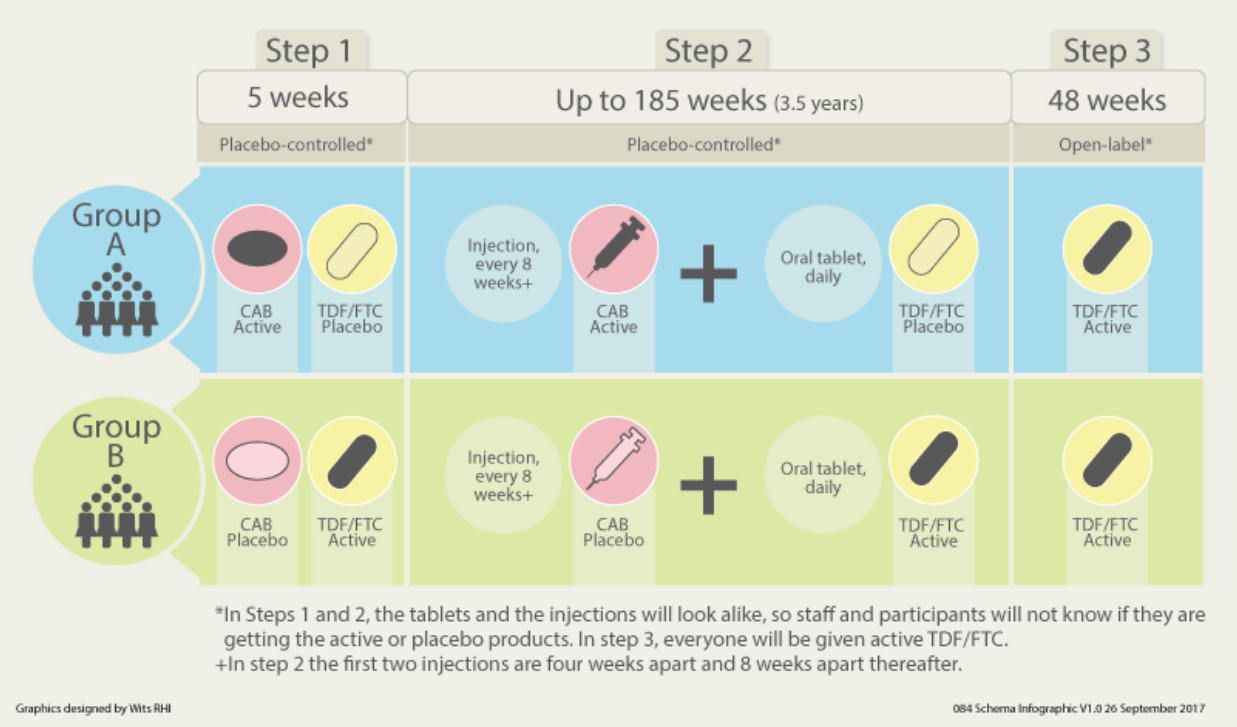
Han et al. HIVR4P 2018; Madrid, Spain. Slides OA15.05

CAB LA for PrEP – Phase 2a Summary (HIV-uninfected, low-risk persons)

- Two placebo-controlled studies (ECLAIR, HPTN 077) were conducted in 325 HIV-uninfected, low-risk men (including MSM) and women in geographically relevant populations (US, Brazil, S Africa, Malawi)
- Two different doses were evaluated
  - q12w 800 mg dose (2 x 2 ml injections)
  - q8w 600 mg dose (1 x 3 ml injection)
- Injections were safe and well-tolerated with no major clinical/lab findings
  - d/c due to injection intolerability were low (5/245, 2%)
  - Similar to treatment program, pain greatest with first injection but decreases for all subsequent injections
- q12w dose did not meet prespecified plasma PK targets in males and the q8w 600 mg dose was chosen for both genders in Ph3 efficacy studies
- Characterization of the PK tail out to 76 wks post final injection
  - no additional safety concerns during the tail phase
  - clearance rates are longer for women and higher BMI persons
    - 42% of women and 13% of men had detectable plasma levels of CAB at 76 wks
- Patient reported outcomes in both studies show acceptable levels of injection pain and high levels of satisfaction vs oral dosing (Kerrigan et al. *HIV Clin Trials* 2018, Tolley R4P 2018)

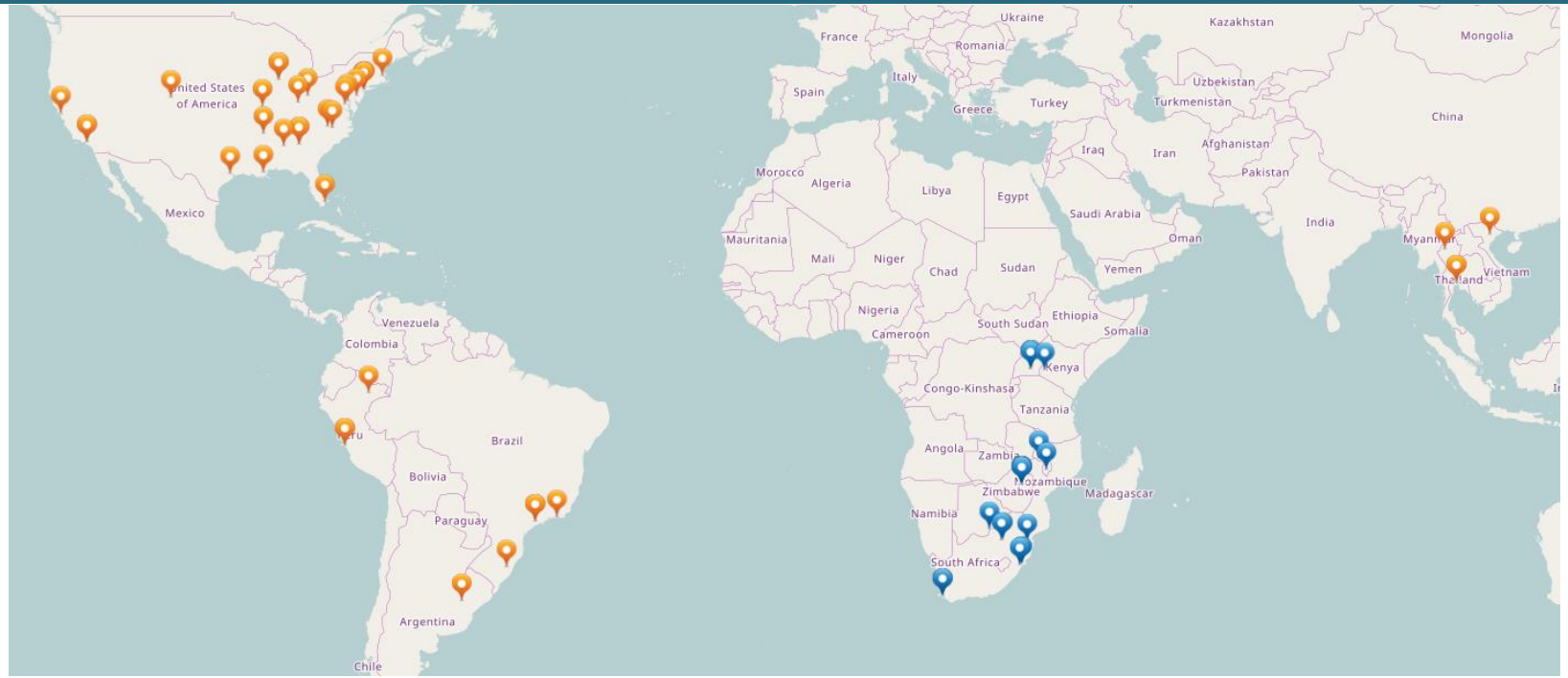
HPTN 083 and 084: Phase 3 for CAB LA PrEP

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)



Landovitz, R4P 2018

A Global Public-Private Partnership



- Multiple research collaborations with Aaron Diamond, CDC, and NIH (pre-clinical to Phase 2)
- Phase 3 registrational studies - 65 sites across 13 countries
  - sponsored by DAIDS (NIH)
  - jointly funded by NIH, ViiV, and Bill & Melinda Gates Foundation (HPTN 084 only)
  - study product provided by Gilead Sciences and ViiV

Trial Considerations for the Ongoing Phase 3 Efficacy Trials

- Both trials address global, diverse populations most at risk of HIV acquisition
  - HPTN 083 – 4500 MSM/transgender women (TGW) in N and S America, Africa, and Asia with special recruitment emphasis on persons <30 yo, TGW, Black MSM (US sites only)
  - HPTN 084 – 3200 women (>18 yo) in 7 sub-Saharan African countries

- Both trials are endpoint driven (not time-bound) – conclusion depends on accumulation of endpoints (seroconversions) and/or person-years of drug exposure

- Due to disparate outcomes in different populations in earlier TVD PrEP trials, *the studies are designed to assess different outcomes against the same comparator*
  - non-inferiority to daily, oral TVD in MSM/TGW (HPTN 083)
  - superiority to daily, oral TVD in young, African women (HPTN 084)

- Successful conduct of both ongoing studies is due to:
  - robust scientific and technical collaboration with the NIH and HPTN
  - **significant and unique public-private funding partnership with NIH, ViiV Healthcare, and the Bill & Melinda Gates Foundation (HPTN 084 only)**

HPTN 083 Update

- **4507/4500** enrolled at 44/44 sites
  - 101% overall; US at 100%, Asia at 104%, LatAm at 102%, and Africa at 101%

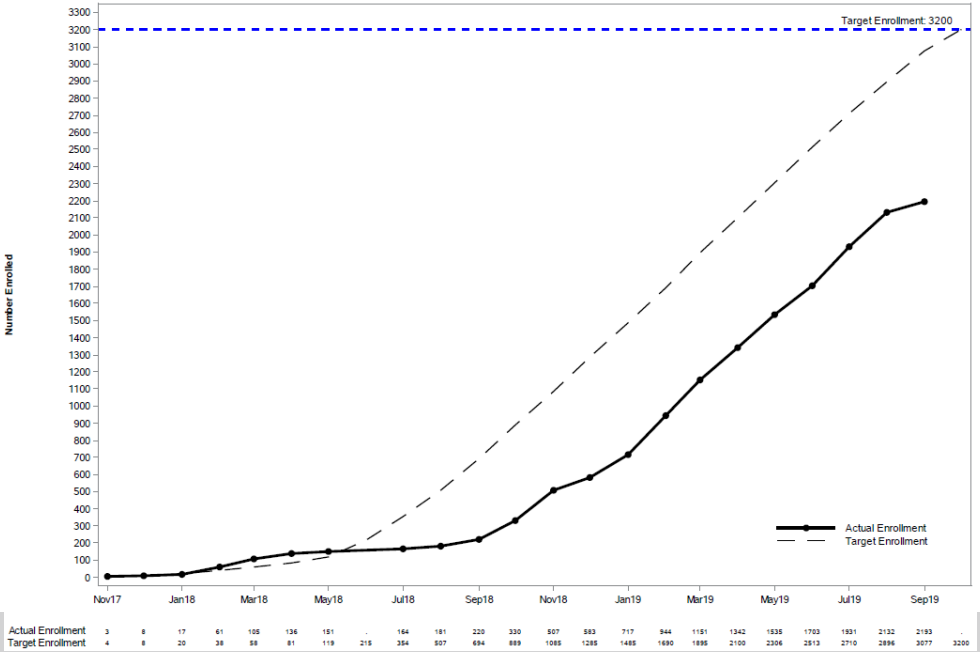
- **Enrolment is complete!**

- Key population enrolment (target):
  - 66% <30 yo (50%)
    - 40% between 18 to 24 yo
  - 12% TGW (10%)
  - 50% Black MSM (50%)

- Upcoming progress checks
  - SMC 08 Oct
  - DSMB 05 Nov

HPTN 084 Update

- **2448/3200 (77%)** enrolled at 20/20 activated sites in 7 SSA countries
  - Enrolment rate is 200/mo
- **Complete enrolment projected 2Q20**
- Upcoming progress checks
  - SMC 02 Oct
  - DSMB 05 Nov
- No plans at this time to relax LARC requirement



HPTN 084 = NCT03164564

HPTN 084 Update (cont.)

- Substudies soon to start
  - Pregnancy/neonatal (N=25 mother/infant pairs)
    - Outcomes of mother and infant
    - Plasma PK at each trimester, PK in cord blood and breast milk
    - After breast feeding, mother can return as open lable to original randomized arm
  - Drug-drug interactions with LARC (N=180, 60/LARC)
    - Effect of TDF/FTC or CAB LA on plasma concentrations of DMPA, Net-EN, and etonorgestrel (implant)
  - Prospective qualitative substudy (N=104)
    - Repeated in-depth interviews to collect preferences for and experiences with CAB LA vs other potential prevention methods
    - Waiting room observations

Adolescent PrEP Studies Update

- Designed to collect safety and tolerability data in adolescents
  - Efficacy from adult studies
  - PK from pediatric treatment study (P2017, MOCHA)
  - Data to be used at same time as adult regulatory submission

- MSM/TGW (HPTN 083-1)
  - 3 US (ATN) sites (N=50)
- AGYW (HPTN 084-1)
  - 3 sites total in S Africa, Uganda, Zimbabwe (N=50)

- Enroll ≤17yo and ≤50kg
  - May lower weight to ≥35kg if PK supports
- Receive 5 injections for only 1 year and then transition to 48 wks daily, oral TDF/FTC

- Projected 1Q20 starts for both studies

Clinical Considerations with Programmatic Implications

Oral Lead-in (OLI)

- Implemented in all prevention studies as safety check before injection given higher bar for risk/benefit in HIV-uninfected people
  - No key safety signals have been observed in Ph2 or Ph3 studies to date
- With combined safety data from treatment program, intent is to ask regulators to make OLI requirement optional

PK Tail

- Clinical relevance of PK tail is unknown
- Coverage of the PK tail with oral TDF/FTC in Ph3 trials is an artifact of the trial design
  - Requirement for use in real world will come from Ph3 and demo project results
- The window of time after a final injection during which development of resistance is theoretically possible is unknown and may be learned from Ph3 results and real world use
  - If selection of resistant virus occurs, virus is likely to be unfit to replicate (but needs to be verified)
- Recommendations for use in pregnancy are unavailable at this time
  - Requirement for use of long-acting contraception in HPTN 084 hampers collection of maternal/fetal outcome data
  - Longer half-life in women and lack of data make it difficult to make any pregnancy recommendations
  - DTG NTD issue also clouds any recommendations