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HIV Prevention
Trials Network

Injectable Pre-Exposure Prophylaxis for HIV Prevention

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HPTN/IMPAACT Network Meeting 2016

Clinical Trial Evidence for HIV Prevention Options (February 2016)

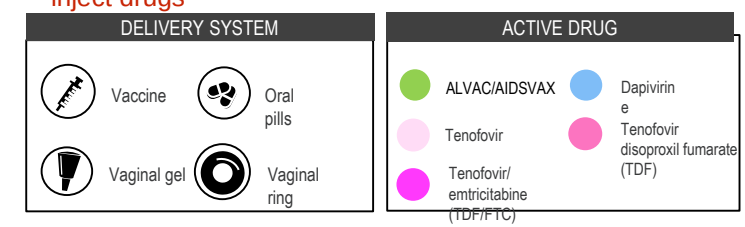
AVAC
Global Advocacy for HIV Prevention

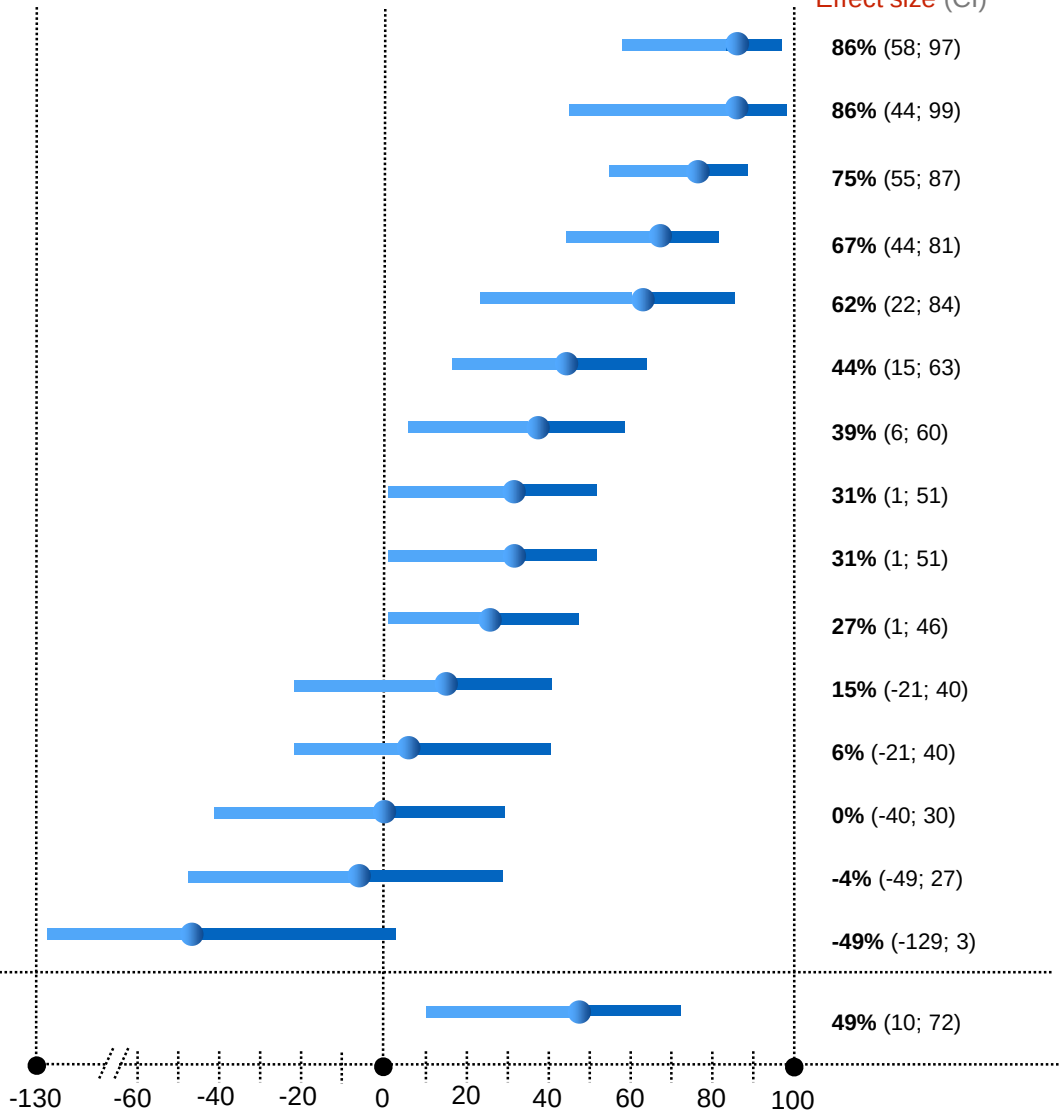
Effect size (CI)

Prevention of sexual transmission

PROUD – daily oral TDF/FTC (MSM – United Kingdom)	**86%** (58; 97)
IPERGAY – event-driven TDF/FTC (MSM – Canada, France)	**86%** (44; 99)
Partners PrEP – daily oral TDF/FTC (Serodiscordant couples – Kenya, Uganda)	**75%** (55; 87)
Partners PrEP – daily oral TDF (Serodiscordant couples – Kenya, Uganda)	**67%** (44; 81)
TDF2 – daily TDF/FTC (Heterosexual men and women – Botswana)	**62%** (22; 84)
iPrEx – daily oral TDF/FTC (MSM – North and South America, South Africa, Thailand)	**44%** (15; 63)
CAPRISA 004 – BAT-24 dosing vaginal tenofovir gel (Women – South Africa)	**39%** (6; 60)
RV 144 – six injectable ALVAC/AIDSVAX (Heterosexual men and women – Thailand)	**31%** (1; 51)
The Ring Study – monthly vaginal ring containing dapivirine (Women – South Africa, Uganda)	**31%** (1; 51)
ASPIRE – monthly vaginal ring containing dapivirine (Women – Malawi, South Africa, Uganda, Zimbabwe)	**27%** (1; 46)
MTN 003/VOICE – daily dosing vaginal tenofovir gel (Women – South Africa, Uganda, Zimbabwe)	**15%** (-21; 40)
FEM-PrEP – daily oral TDF/FTC (Women – Kenya, South Africa, Tanzania)	**6%** (-21; 40)
FACTS 001 – event-driven vaginal tenofovir gel (Women – South Africa)	**0%** (-40; 30)
MTN 003/VOICE – daily oral TDF/FTC (Women – South Africa, Uganda, Zimbabwe)	**-4%** (-49; 27)
MTN 003/VOICE – daily oral TDF (Women – South Africa, Uganda, Zimbabwe)	**-49%** (-129; 3)
Bangkok Tenofovir Study – daily oral TDF (PWID– Thailand)	**49%** (10; 72)

Prevention in people who inject drugs





Adapted from: Salim S. Abdool Karim, CAPRISA

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The PrEP Pipeline: Looking past TDF/FTC

- Maraviroc – HPTN 069/ACTG A5305[1]
- TAF – Macaque protection (?) but low tissue levels[2]
- Long Acting Therapies
  - Rilpivirine (TMC278) – HPTN 076
  - Cabotegravir (GSK1265744) – HPTN 077/HPTN 083/ ÉCLAIR[3]
  - Immunotherapies – VRC01
  - Implantable devices
- More on Intermittent (i)PrEP
- Special populations
  - HPTN 073 – BMSM[4]
  - ATN 110/113 – Youth[5,6]
- Combinations of interventions

1. Gulick RM, CROI 2016
2. Garrett K, CROI 2016
3. Markowitz M, CROI 2016
4. Wheeler D, CROI 2016
5. Hosek S, IAS 2016; Mulligan K Compl 2016.

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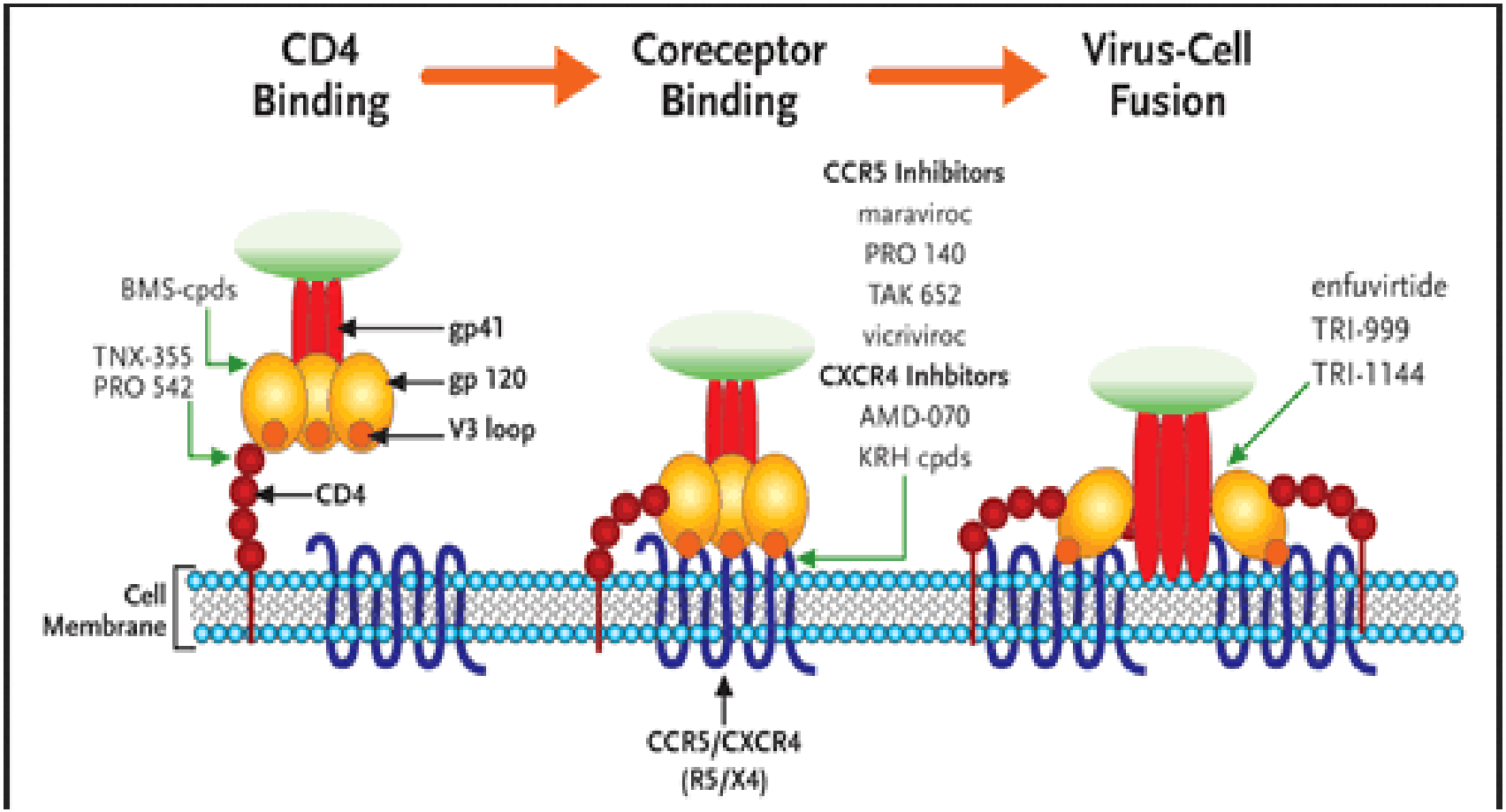
HPTN 069 / ACTG A5305

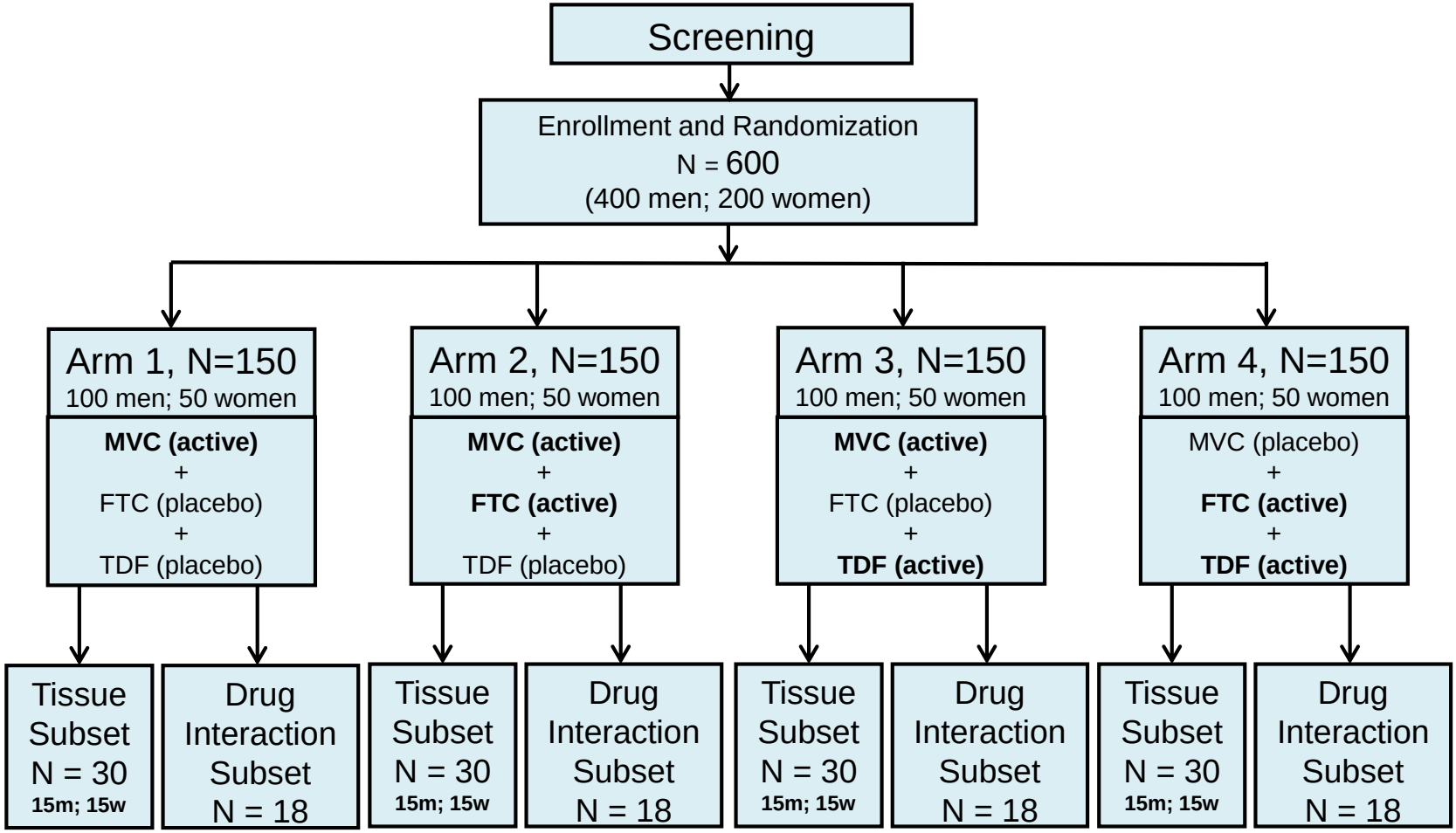
A phase 2 safety study designed to answer:

Could daily oral maraviroc, a CCR5 receptor antagonist, be a next-gen PrEP agent for men and/or women?

Maraviroc – HPTN 069/ACTG A5305



HPTN 069 / ACTG A5305



NEXT PrEP
AN HPTN/ACTG STUDY

HPTN 069 / ACTG A5305: Participants

- **N = 406** individuals enrolled
- 100% male at birth; 7 (2%) transgender
- Median age 30 (range 18, 70)
- 28% black, 22% Latino, 62% white, 10% other (participants could report more than one)
- 20% high school education or less, 67% some college or more, 13% advanced degrees

- 31 (8%) had 34 STIs during study screening:
  - 15 (4%) chlamydia, 5 (1%) gonorrhea, 14 (3%) syphilis

HPTN 069 / A5305: Results

- **No differences by study arm in:**
  - proportion who discontinued study drugs (p=0.6)
  - time to permanent study drug discontinuation (p=0.6)

- **There were 67 grade 3-4 AEs**
  - No differences in occurrence or rate among the study arms (p>0.05 in pairwise comparisons)

- **90 (22%) had 115 STI diagnosed during study f/u**

- **Plasma Drug Concentrations**:
  - Random subset across 4 study arms (n=160)
  - All study drugs in regimen detectable in 83% (week 24) and 77% (week 48)
    - No differences between the study arms (p>0.3)

HPTN 069 / A5305: HIV Infections

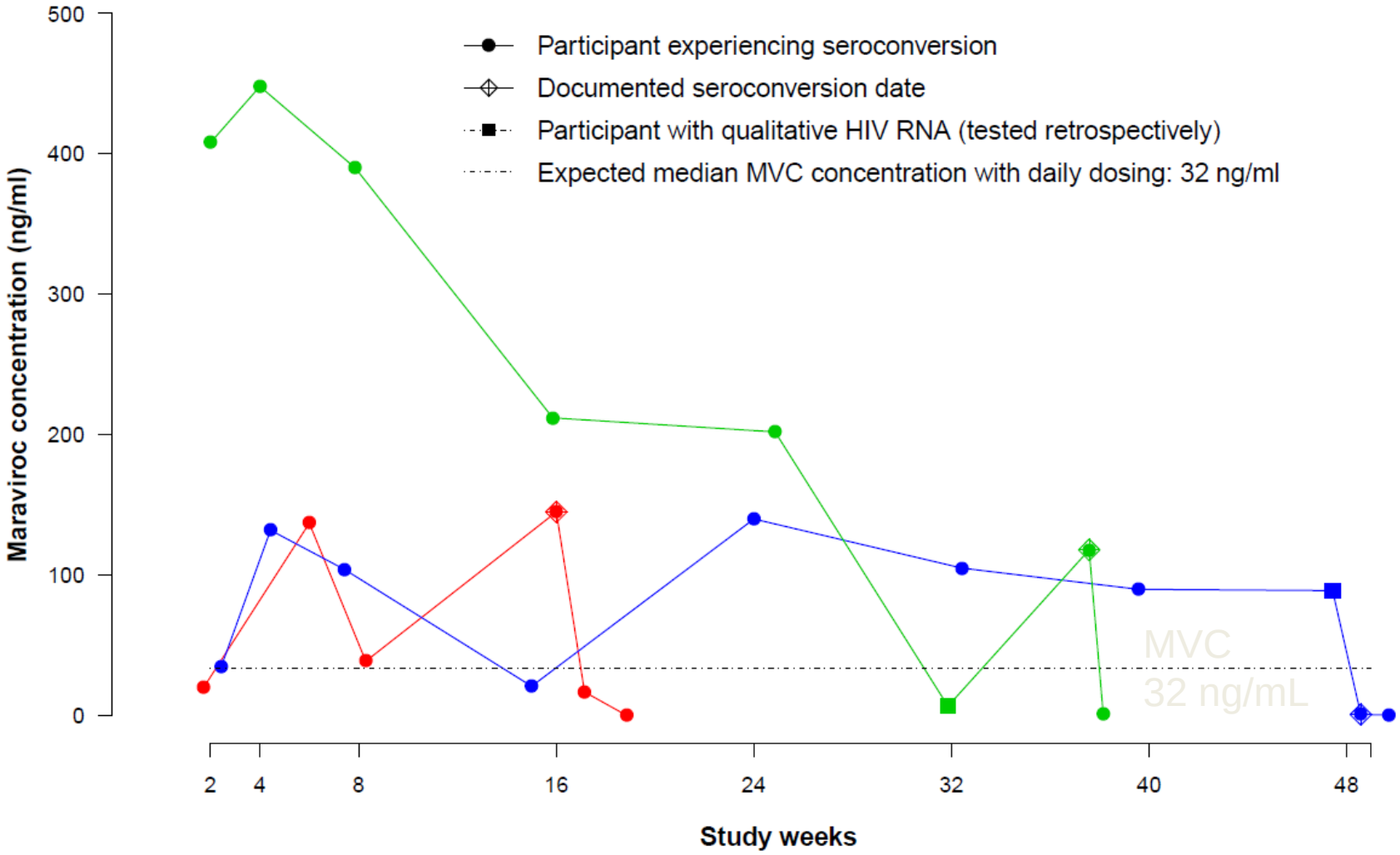
- 5 new HIV infections during the study
- Annual incidence rate 1.4% [95% CI: 0.8%, 2.3%]

#	Demos. (age, race/ ethnicity, HIV risk)	Study arm	First reactive HIV+ test (week)	HIV RNA (cps/mL)	CD4 cells (/mm^3)	HIV trop-ism	Geno-typic drug resis-tance	Plasma drug conc. at serocon-version visit (ng/mL)*
1	**20, black MSM**	MVC+ TDF	4	122,150	357	R5	none	MVC=0† TFV=0
2	**61, Asian MSM**	MVC alone	16	981	294	R5	none	MVC=145
3	**21, mixed MSM**	MVC alone	24	106,240	325	R5	none	MVC=0†
4	**35, white MSM**	MVC alone	32	13,626	828	R5	none	MVC=6.7
5	**36, black MSM**	MVC alone	48	52,191	804	R5	none	MVC=0.7

* expected pre-dose steady state MVC = 32 ng/ml

† undetectable plasma drug concentrations at every study visit

HPTN 069 / A5305: Study Drug Concs. in New HIV Infections



Note: 2 others with new HIV infection had undetectable study drug at every visit.

HPTN 076

A phase 2 safety study designed to answer:

Could injectable rilpivirine, a FDA-approved NNRTI in its oral formulation, be a useful sustained-release PrEP agent?

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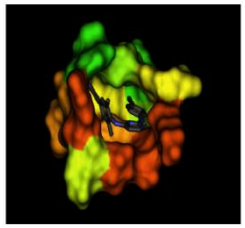
Long Acting Rilpivirine (TMC278) HPTN 076: Phase 2 Safety

- TMC278 LA is a novel poloxamer 338-containing formulation of TMC278. TMC278 LA is long-acting suspension and well-suited for delivery via IM injection
- HPTN 076 enrolling at 4 sites, low-risk HIV-uninfected women (NY, NJ, Zim, SA)
- Fully enrolled, Data available 2017



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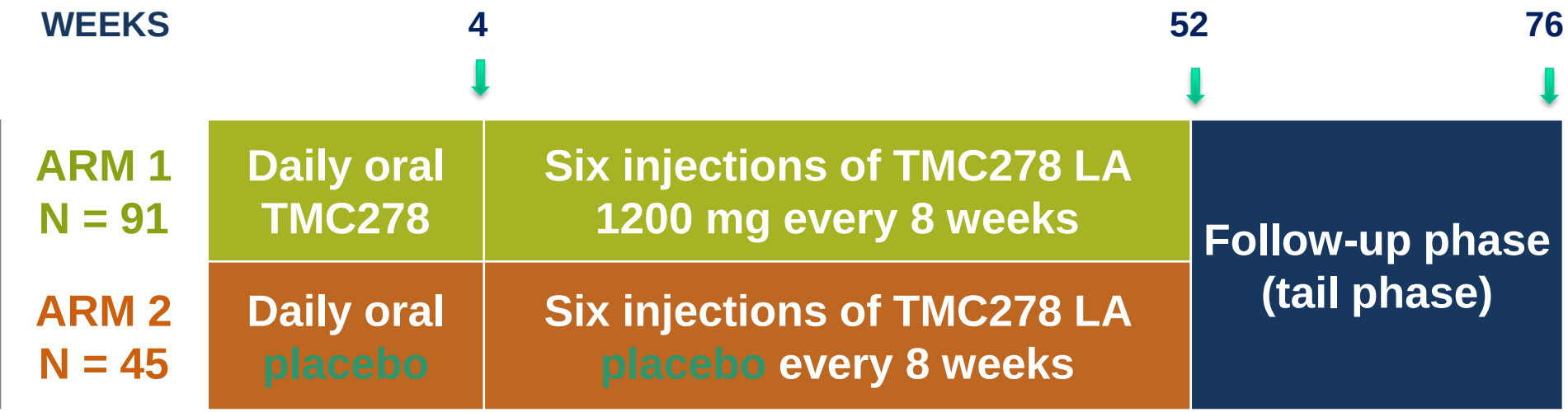
HPTN 076: Safety and acceptability of injectable rilpivirine(TMC278 LA) for PrEP

136 HIV-uninfected, women ages 18-45 years



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HPTN 076 – Study Sites and Status

US Sites

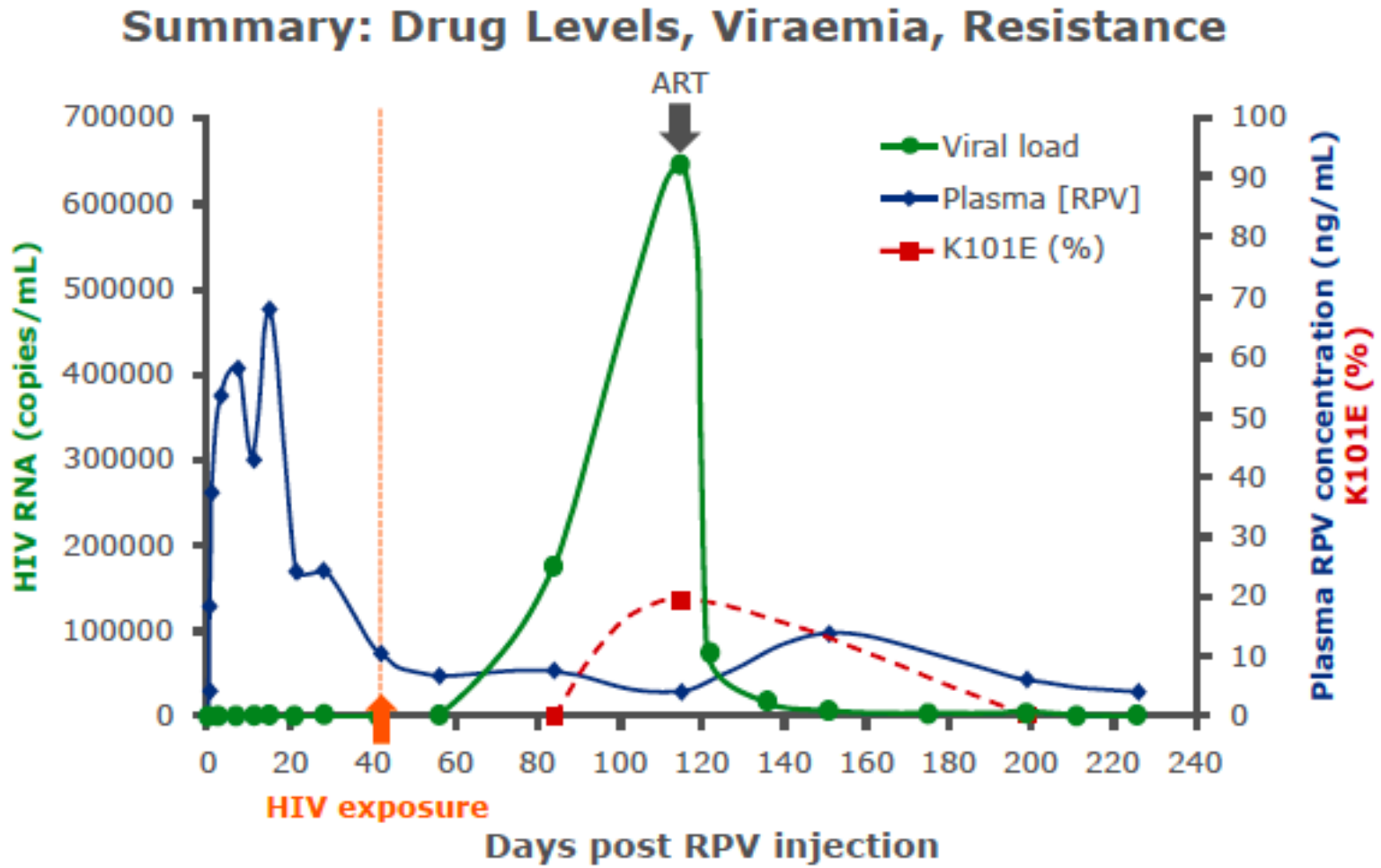
- Bronx, NY
- Newark, NJ

International Sites

- Cape Town, South Africa
- Harare, Zimbabwe

Primary Endpoint- September, 2016
Last Study Visit- February, 2017

SSAT040: Seroconversion Event During Washout of 300 mg



ART = antiretroviral therapy

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

CABOTEGRAVIR

The artist formerly known as GSK1265744
Or “744”

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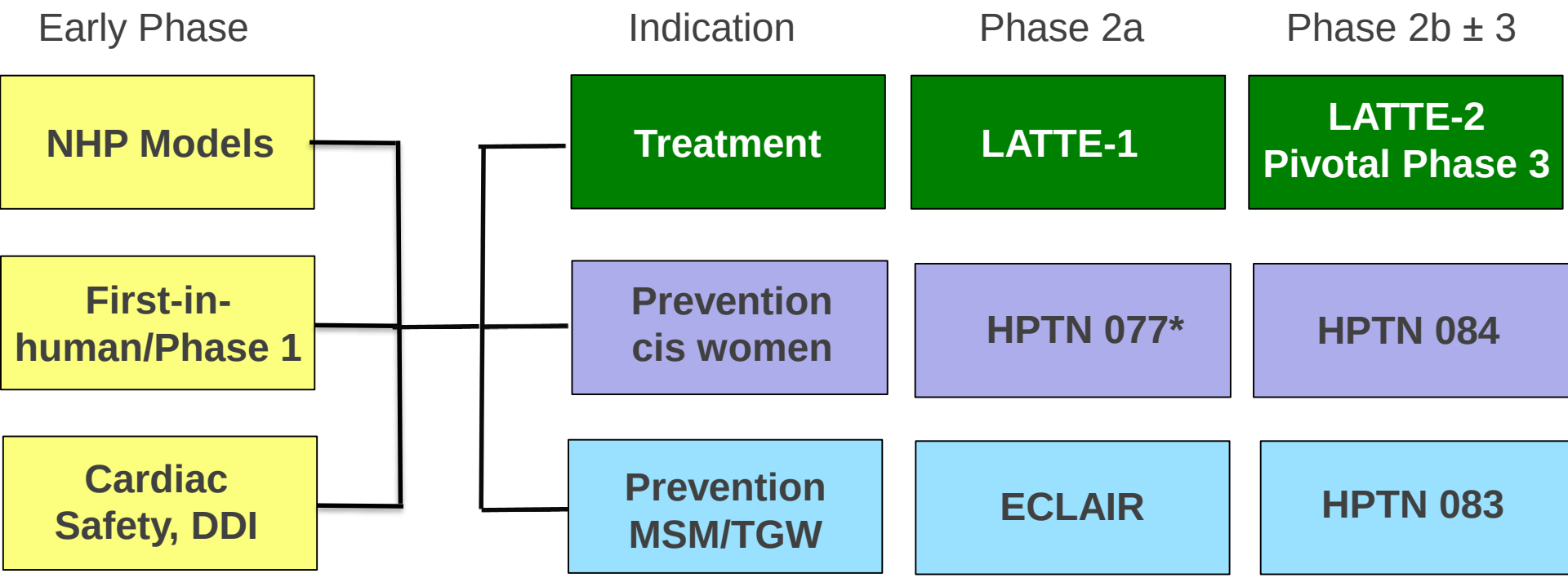
Cabotegravir (GSK 1265744) development



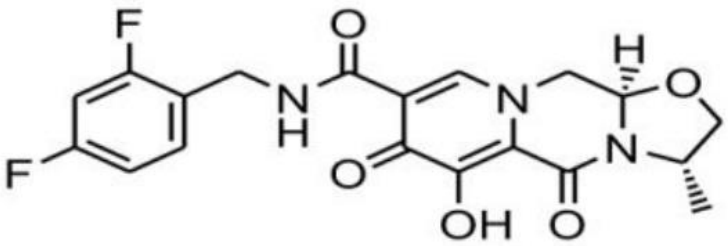
HPTN 077

A phase 2 safety study designed to answer:

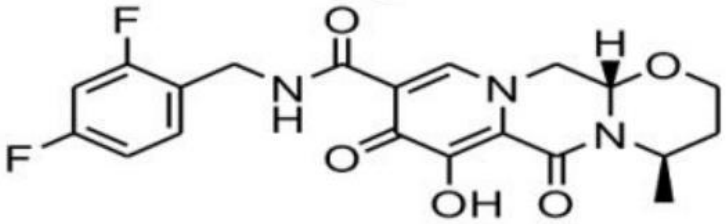
Could injectable cabotegravir, a NON-FDA-approved integrase inhibitor (currently being developed for HIV treatment in parallel) be a useful sustained-release PrEP agent in women (and men) globally?

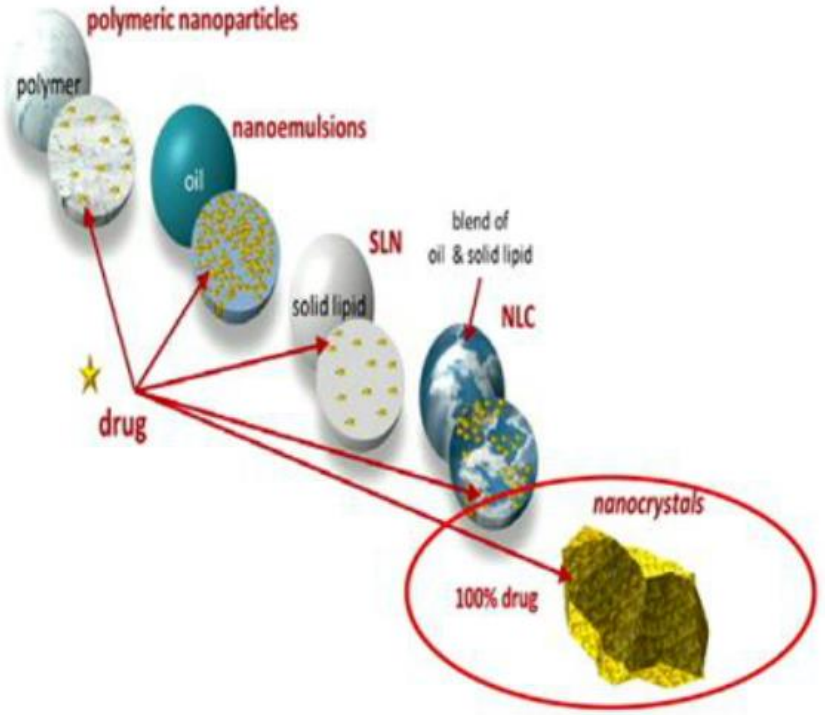
CABOTEGRAVIR: GSK126744 Long Acting (744 LA)

GSK1265744 (GSK744)



Dolutegravir





Favorable attributes for PrEP:

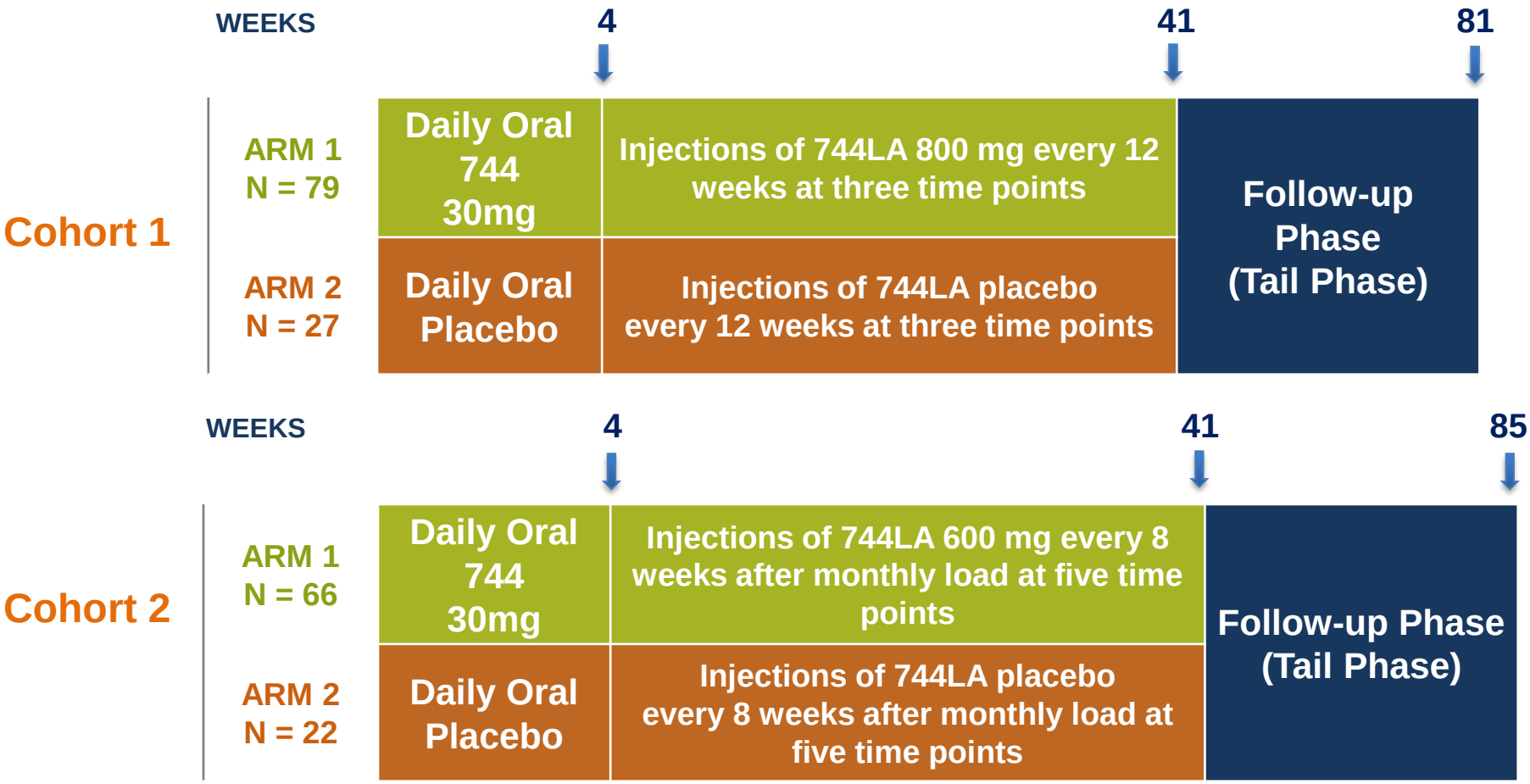
- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

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

Long Acting Cabotegravir
HPTN 077 – Phase 2a

A Phase 2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, Cabotregravir, in HIV-uninfected Men and Women

200 HIV-uninfected, Ages 18-65



HPTN 077 – Phase 2a

US Sites

- Los Angeles, California
- San Francisco, California
- Washington, DC
- Chapel Hill, North Carolina

International Sites

- Soweto, South Africa
- Vulindlela, South Africa
- Lilongwe, Malawi
- Rio de Janeiro, Brazil

Fully Enrolled as of May 27, 2016
67% Women

Primary Endpoint- March, 2017
Last Study Visit- January, 2018

ECLAIR

A ViiV-sponsored phase 2 safety study designed to answer:

Could injectable cabotegravir, a NON-FDA-approved integrase inhibitor (currently being developed for HIV treatment in parallel) be a useful sustained-release PrEP agent in US-based men?

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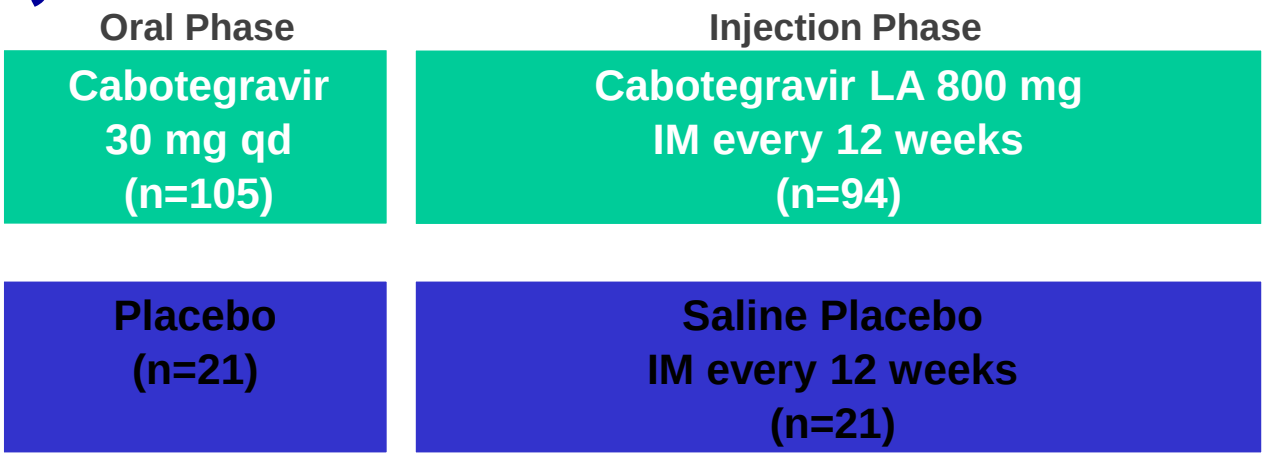
ÉCLAIR: Cabotegravir LA for PrEP in Low-Risk, HIV-Uninfected Men

Phase 2a

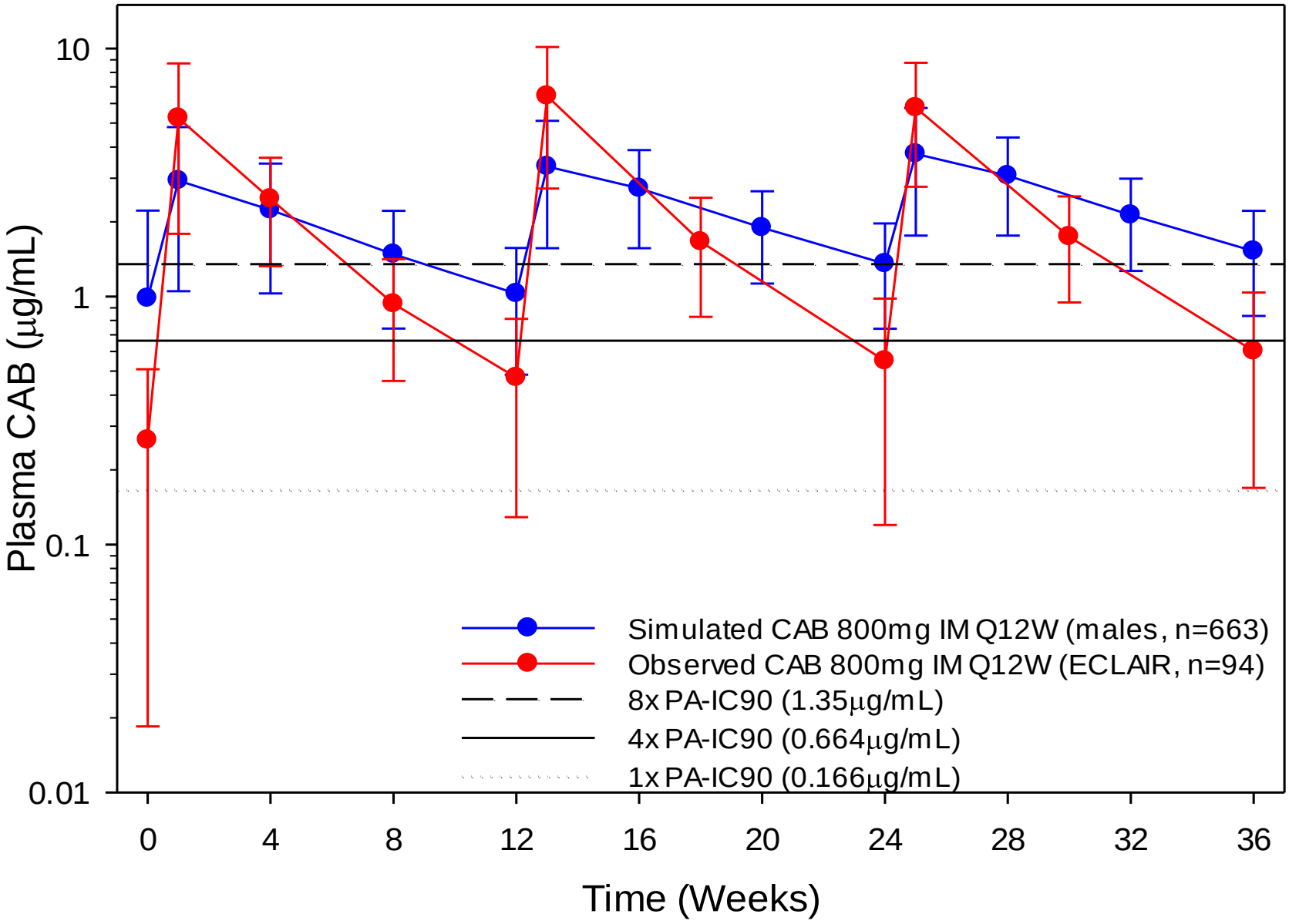
Double-blind
Men 18 to 65 years of age
Low-risk of acquiring HIV
No PEP or ART
No liver disease
5:1 randomization



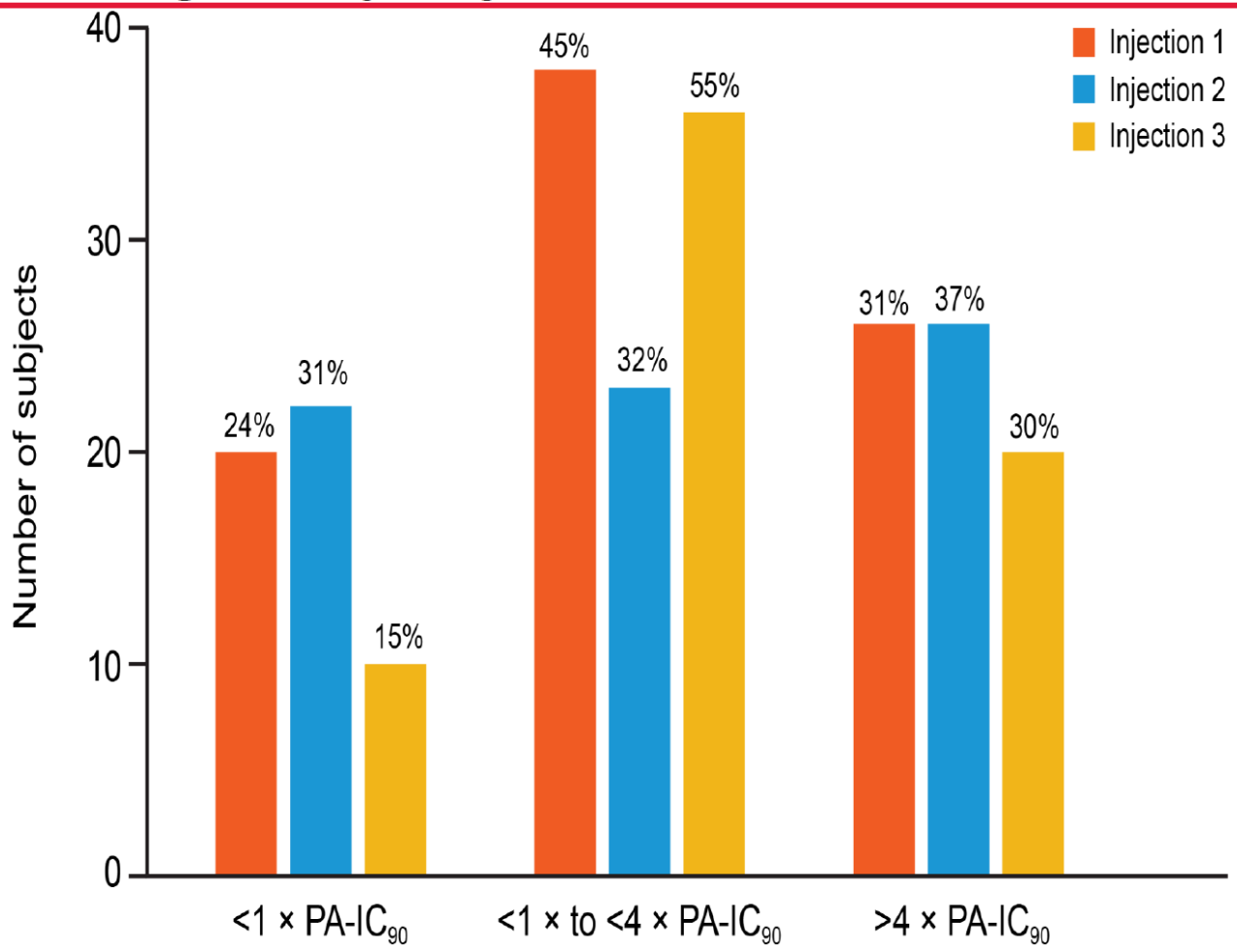
Baseline characteristics (cabotegravir oral phase):
- Median age: 31 years.
- White/black race/ethnicity: 56%/31%.
- Hispanic/Latino race/ethnicity: 15%.
- Median height: 176 cm.
- Median BMI: 26 kg/m^2.
- Risk for HIV acquisition:
  - Homosexual contact: 85%.
  - Heterosexual contact: 21%
  - Occupational exposure: 2%.

Markowitz M, et al. 23rd CROI. Boston, 2016. Abstract 106.

Mean (SD) Plasma CAB Conc-Time Profiles following 800mg IM Q12W in ÉCLAIR and Predicted in original Phase 2 Model (Sparse Time Points)



Numbers of Subjects in CAB Concentration Ranges by Injection Visit - ÉCLAIR



Multi-stakeholder Input to Dose-finding

HPTN 083 Team Leadership

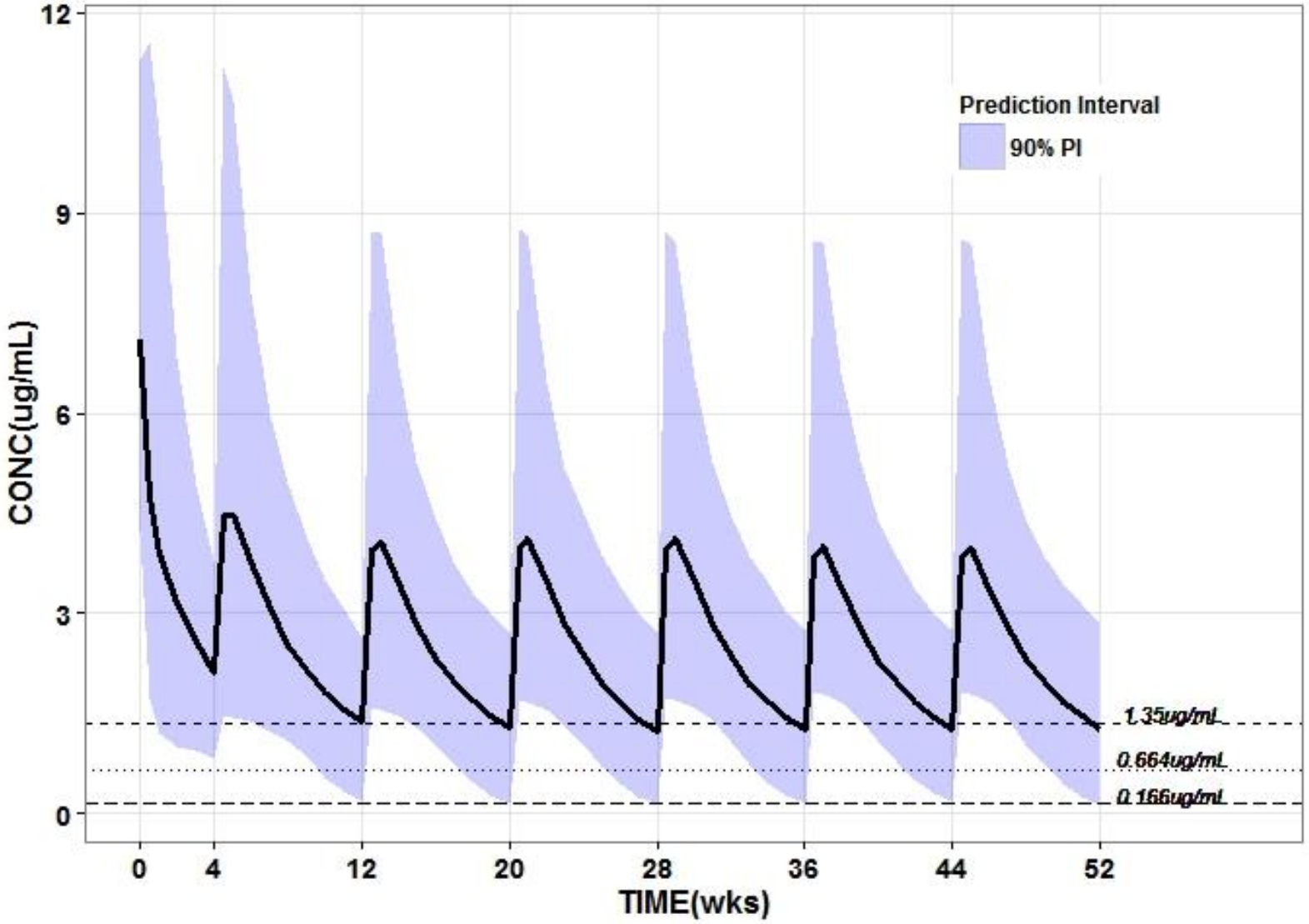
HPTN Network Leadership

HPTN Laboratory Center Leadership

NIH/DAIDS

ViiV

Simulated Median (90% PI) Conc-Time profile following (CAB) LA 600mg IM at Day 1, Week 4 and Q8W thereafter in Males (Updated PopPK Model)



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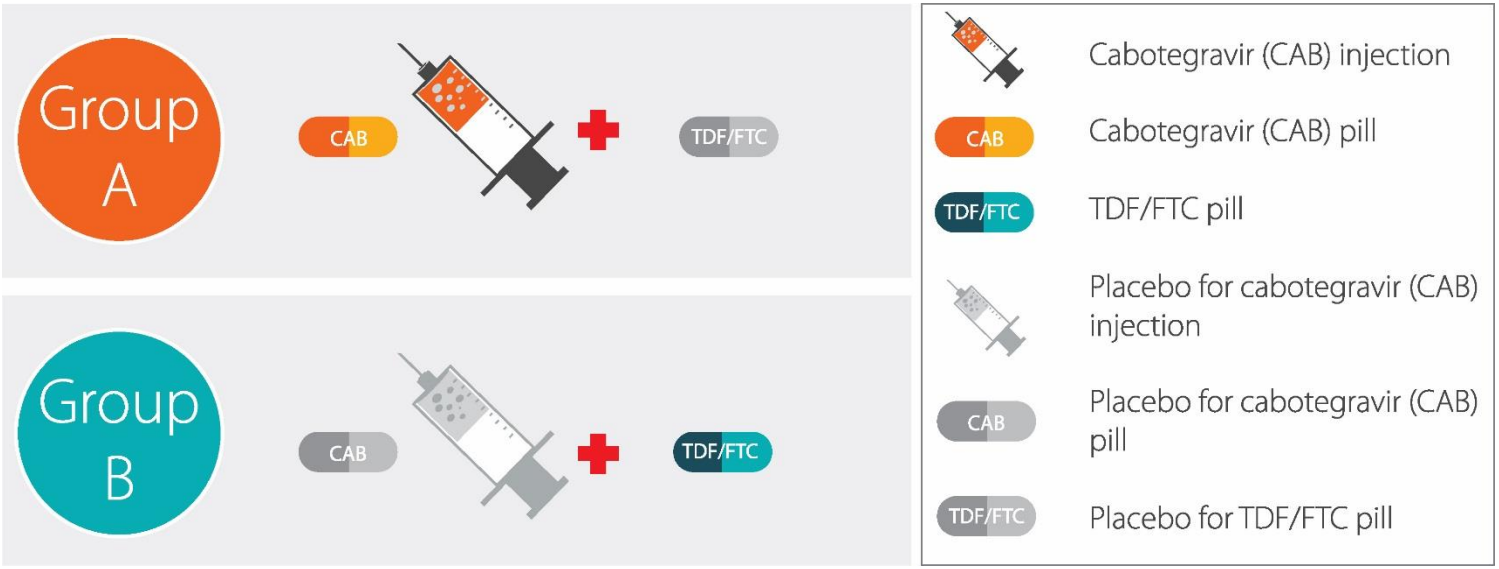
HPTN 083: Treatment Arms



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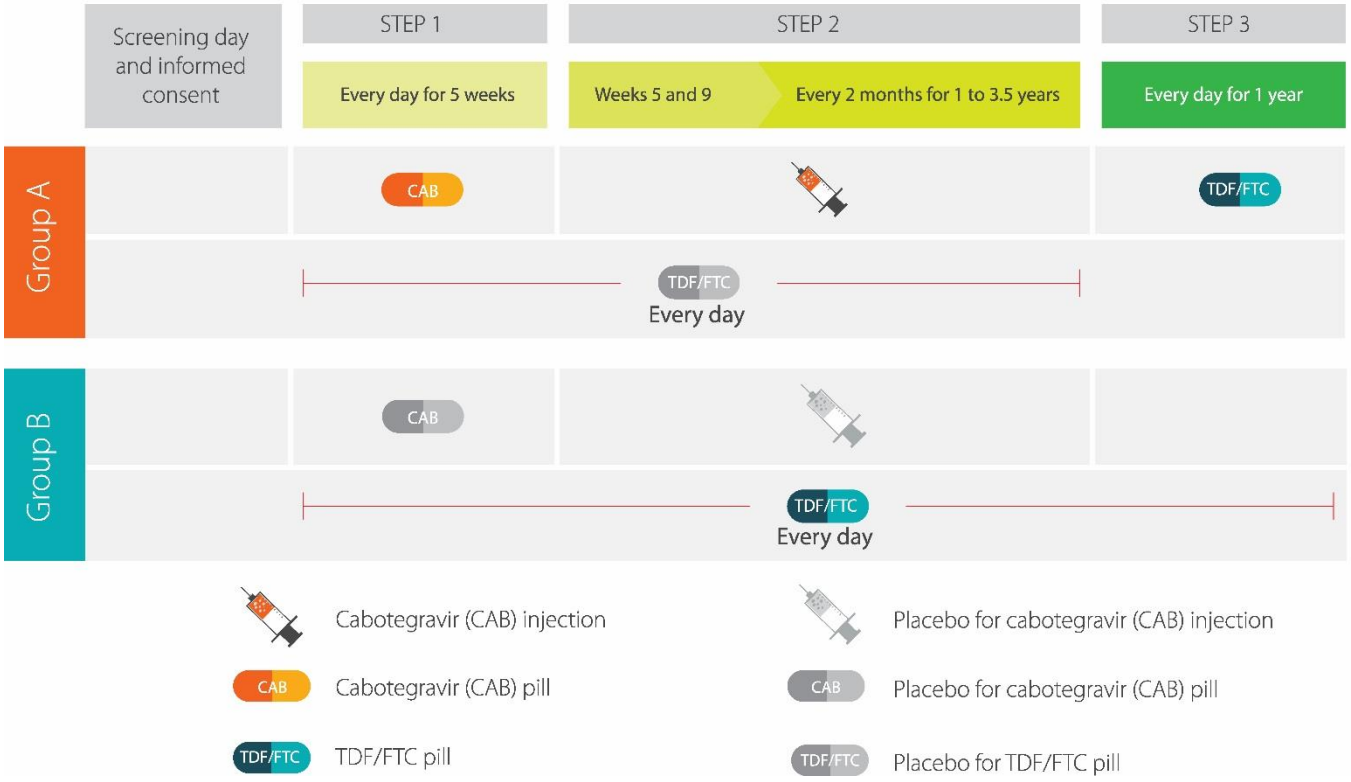
HPTN 083: A "3 STEP" Study



Protocol Objectives

Primary Objectives

-Efficacy of CAB vs. TDF/FTC

-Safety of CAB vs. TDF/FTC

Secondary Objectives

-Efficacy in pre-specified subgroups of CAB vs. TDF/FTC

-Kidney, liver, and bone safety in CAB vs. TDF/FTC

-ART resistance in seroconverters on CAB vs. TDF/FTC

-HIV incidence based on strata of study product adherence

-Acceptability and preferences for oral vs. injectable PrEP

Tertiary Objectives

-Rates, patterns, correlates of adherence

-Changes in sexual risk behavior (self-report and biomarkers, i.e., STIs)

-Cost effectiveness considerations

Study Population

Cis-MSM and TGW, 18 yo or older, at high-risk for HIV acquisition defined as:

- **In past 6 months: Any ncRAI; >5 partners; stimulant drug use; rectal or urethral STI**

Enrollment goals:

- *Minimum* 50% of US enrollment BMSM (~ 950)

- Overall minimum 10%TGW (~ 450)

- Overall > 50% under age 30

HPTN 083 Sites

South Africa

- Groote Schuur HIV CRS

Asia (Thailand and Vietnam)

- CMU HIV Prevention CRS
- Silom Community Clinic CRS
- Thai Red Cross (TRC-ARC) CRS
- Yen Hoa Health Clinic CRS

Latin America (Argentina, Brazil, Peru)

- Fundación Huésped CRS
- Hospital General de Agudos JM Ramos Mejía CRS
- Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS
- Hospital Nossa Senhora da Conceiçao CRS
- University of Sao Paulo CRS
- Centro de Referencia e Treinamento DST/AIDS CRS
- Asociacion Civil Selva Amazonica (ACSA) CRS
- Barranco CRS
- San Miguel CRS
- CITBM CRS
- Via Libre CRS

United States

- Alabama CRS
- Adolescent and Young Adult Research at the CORE Center (AYAR at CORE) CRS
- Bridge HIV CRS/ East Bay AIDS Center (EBAC) CRS
- Bronx Prevention Research Center CRS
- Chapel Hill CRS
- Children's Hospital Colorado CRS
- Cincinnati CRS
- Fenway Health (FH) CRS
- George Washington University CRS
- Greensboro CRS
- Harlem Prevention Center CRS
- Hope Clinic of the Emory Vaccine Center CRS
- Houston AIDS Research Team (HART) CRS
- Johns Hopkins University CRS
- New Jersey Medical School CRS
- New Orleans Adolescent Trials Unit CRS
- New York Blood Center CRS
- Ohio State University CRS
- Penn Prevention CRS
- Ponce de Leon Center CRS
- St. Jude Children's Research Hospital CRS
- UCLA CARE Center CRS
- UCLA Vine Street Clinic CRS
- UIC Project WISH CRS
- University of Miami AIDS Clinical Research Unit (ACRU) CRS
- Washington University Therapeutics (WT) CRS
- Weill Cornell Chelsea CRS

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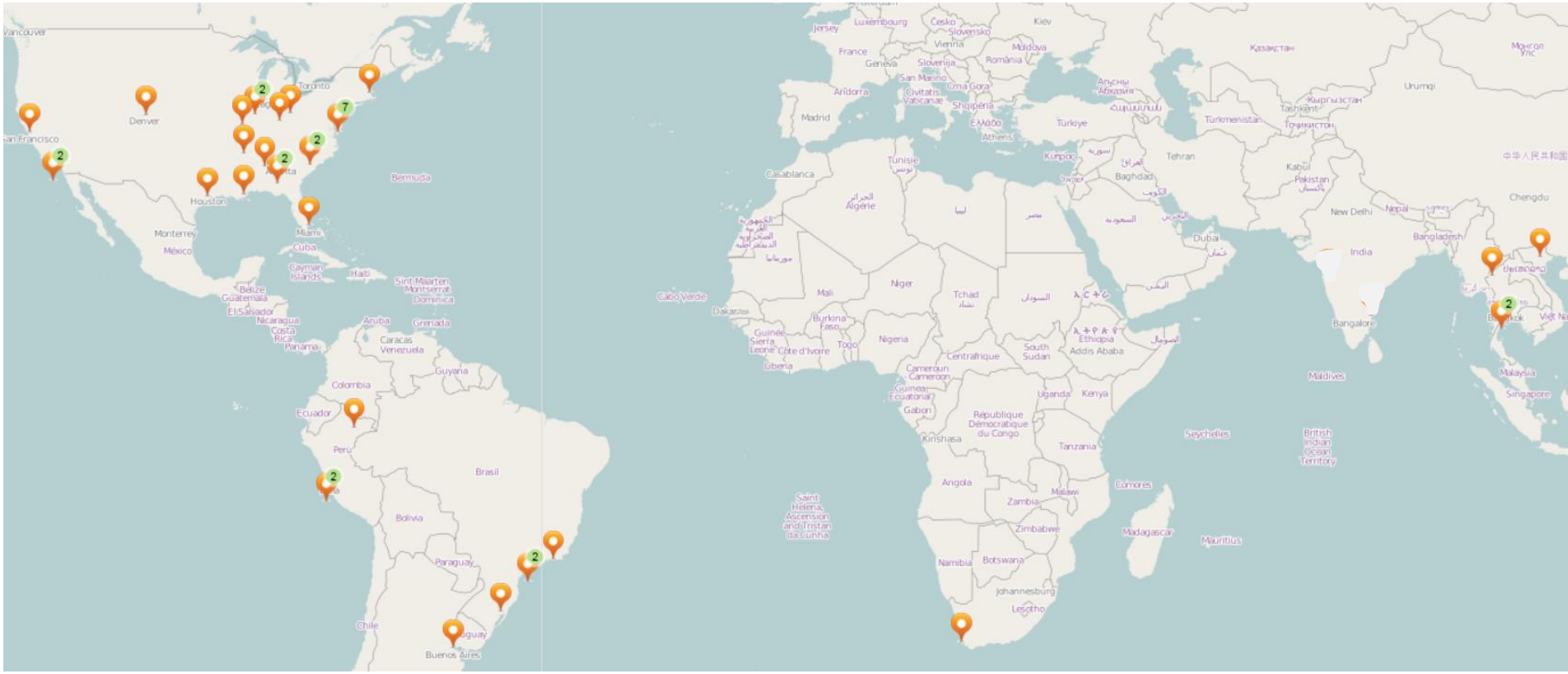
HPTN 083 Sites – Phase 2b/3

42 Sites in 7 Countries



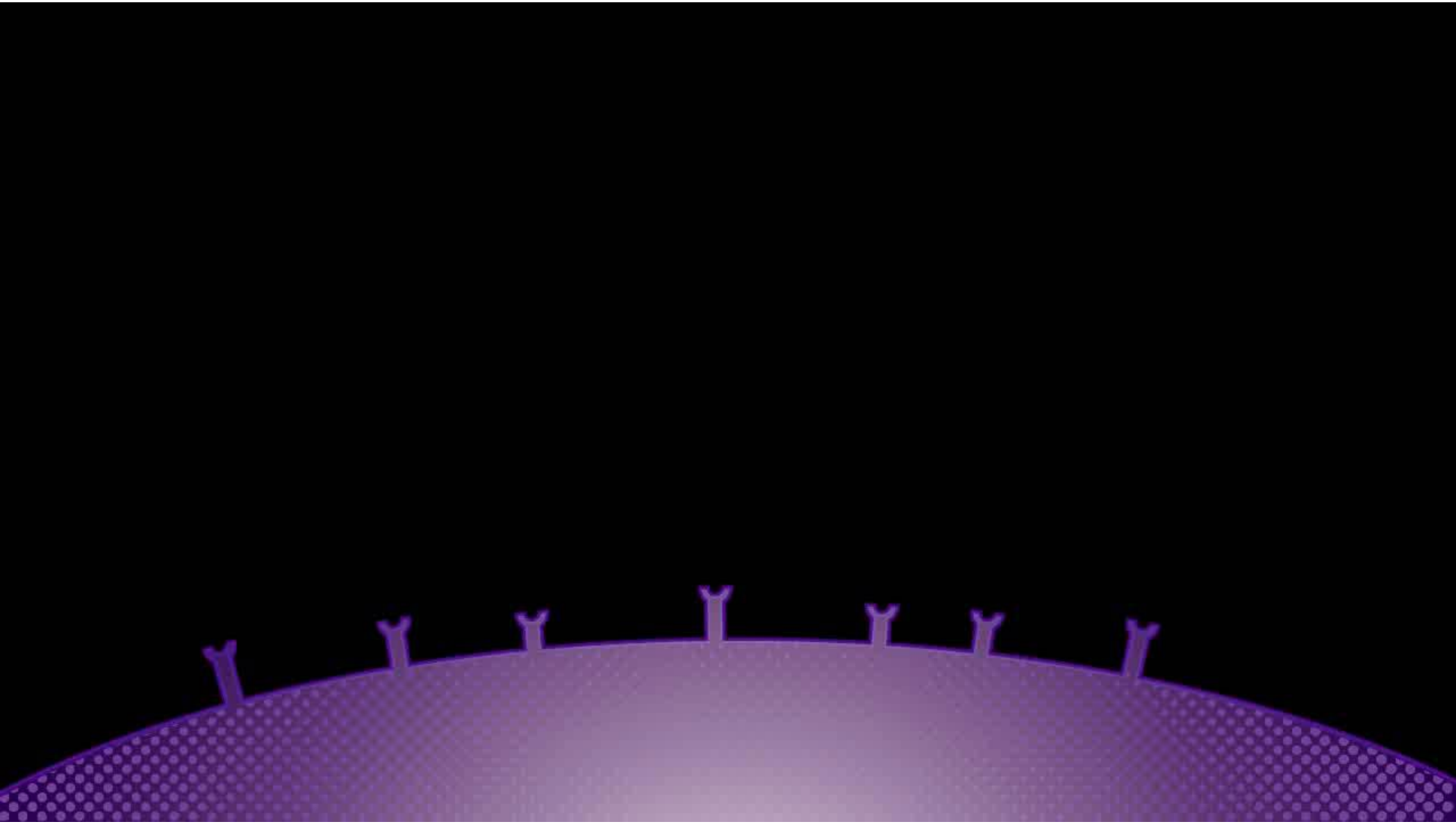
Anticipated Start – 3rd Q 2016 US Sites
Non-US TBD*
***Based on local regulatory approvals**

Antibody Mediated Prevention

HPTN 081/HVTN 703, HPTN 085/HVTN 704

How Do Antibodies Prevent Infection?

One Way: Neutralization



The 3 Study Groups

North & South America:

2700 Men and Transgender Individuals Who Have Sex With Men, age 18-50, HIV-negative

1. Lower dose VRC01, 10 mg/kg (900)
2. Higher dose VRC01, 30 mg/kg (900)
3. Placebo (900)

The 3 Study Groups in Africa

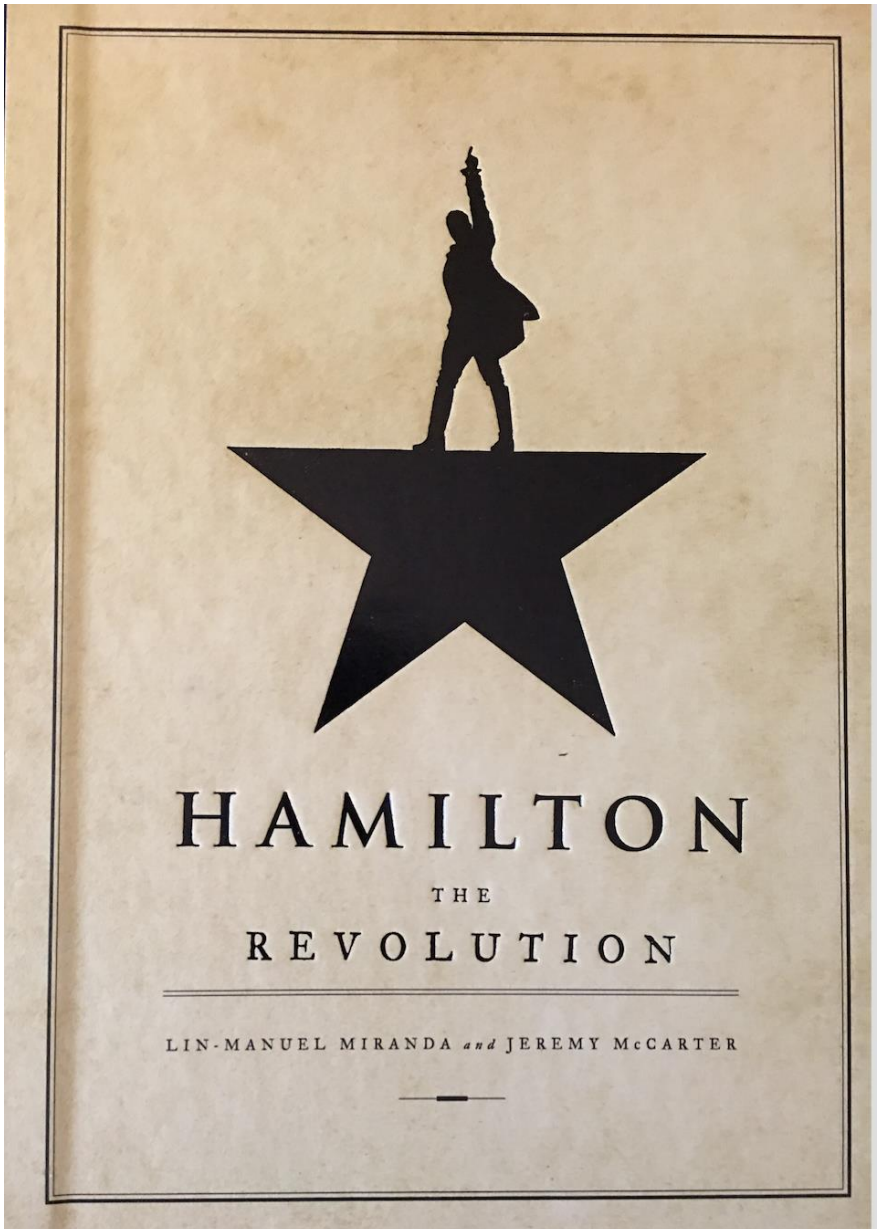
1500 HIV-negative Heterosexual Women, age 18-50

1. Lower dose VRC01, 10 mg/kg (500)
2. Higher dose VRC01, 30 mg/kg (500)
3. Placebo (500)

AMP Study Arms

Regimen	HVTN 704/HPTN 085 (MSM and transgender persons in N. & S. America)	HVTN 703/HPTN 081 (Sub-Saharan African women)	Total	Note
VRC01 10 mg/kg	900	500	2,800	Infusions every 8 weeks through Week 72 (10 total infusions per participant)
VRC01 30 mg/kg	900	500		
Control	900	500	1,400	
Total	**2,700**	**1,500**	**4,200**	

Access to PrEP where possible


HAMILTON
THE
REVOLUTION
LIN-MANUEL MIRANDA and JEREMY McCARTER

Thank You