ART for Prevention… What Happens Next?

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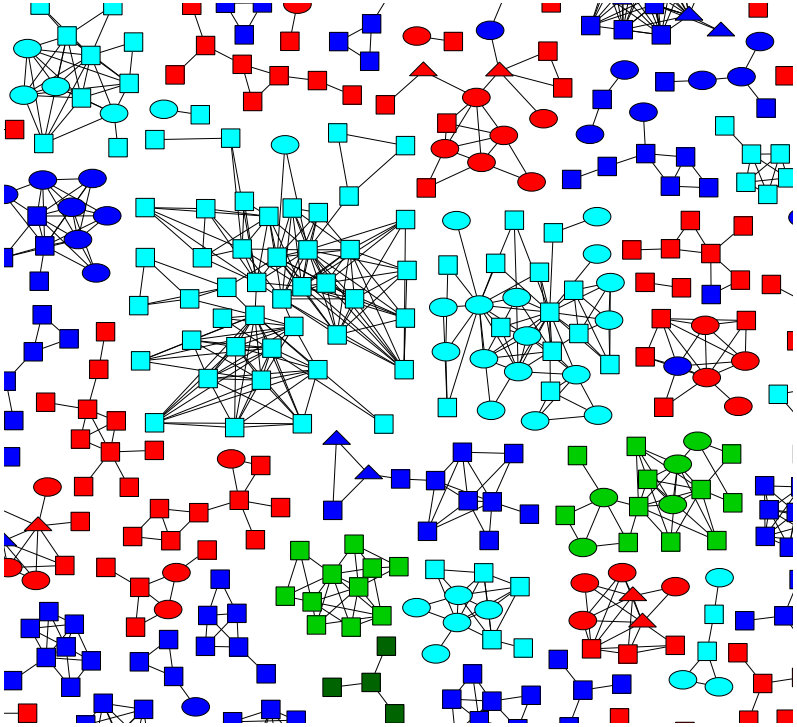
How do transmission networks drive epidemics?



HIV Transmission Networks among USA, Central America and Mexico

Avilla-Rios, Wertheim, Dennis, Mehta, CROI 2015 Abstract #242

HIV transmission is shaped by:

- Geography
- Uneven distribution of risk behaviors
- Transmission mode
- Stage of Infection
- Prevention requires attention to the infected and unifected

Adapted from: Kouyos CROI 2014

Treatment as Prevention

- By 2020, 90% of all people living with HIV will know their HIV status.
- By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
- By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

90-90-90 An ambitious treatment target to help end the AIDS epidemic

The Belief in “TASP”

- Heterosexual transmission: HPTN052!
- MSM: Observational studies forthcoming
- PWID: HPTN 074 enrolled

HIV-Infected Participants in HPTN 052

2010: 1,763 enrolled (HIV-infected)

2011: 1,642 remained in the trial (96%)

2015: 1,535 remained in the trial (87%)

Overall: 9,822 person-years follow-up

HPTN 052: Partner Infections (ITT) Total and Linked (*NEJM July 2016*)

	April 2005-May 2011			May 2011-May 2015			Overall		
	PY f/u	All partner infections # (rate)	Linked partner infections # (rate)	PY f/u	All partner infections # (rate)	Linked partner infections # (rate)	PY f/u	All partner infections # (rate)	Linked partner infections # (rate)
Early arm	1751	4 (0.23)	1 (0.06)	2563	15 (0.59)	2 (0.08)	4314	19 (0.44)	3 (0.07)
Delayed arm	1731	42 (2.43)	36 (2.08)	2449	17 (0.69)	7 (0.29)	4180	59 (1.41)	43 (1.03)
Risk reduction		91%	97%		14%	72%		69%	93%

- Unlinked transmissions 1/300 PY
- 8 linked partner infections were diagnosed AFTER index partner started ART
  - 4 linked partner infections likely occurred before or soon after index partner started ART
  - 4 linked partner infections occurred after index failed ART

Linked = index-to-partner transmission likely

Pre-Exposure Prophylaxis

Optimization of use of TDF/FTC
Identification of new PrEP agents

PrEP Demonstration Studies

- 28 Truvada studies worldwide (per Gilead)
- 16,000 Study Subjects
- Multiple designs

HPTN 067: Pharmacokinetic and Behavioral Study of Daily versus Non-Daily oral FTC/TDF for PrEP

Randomization to:

- Daily Time Driven:
- Twice weekly with a post-intercourse dose
- Event-driven: Before and after intercourse

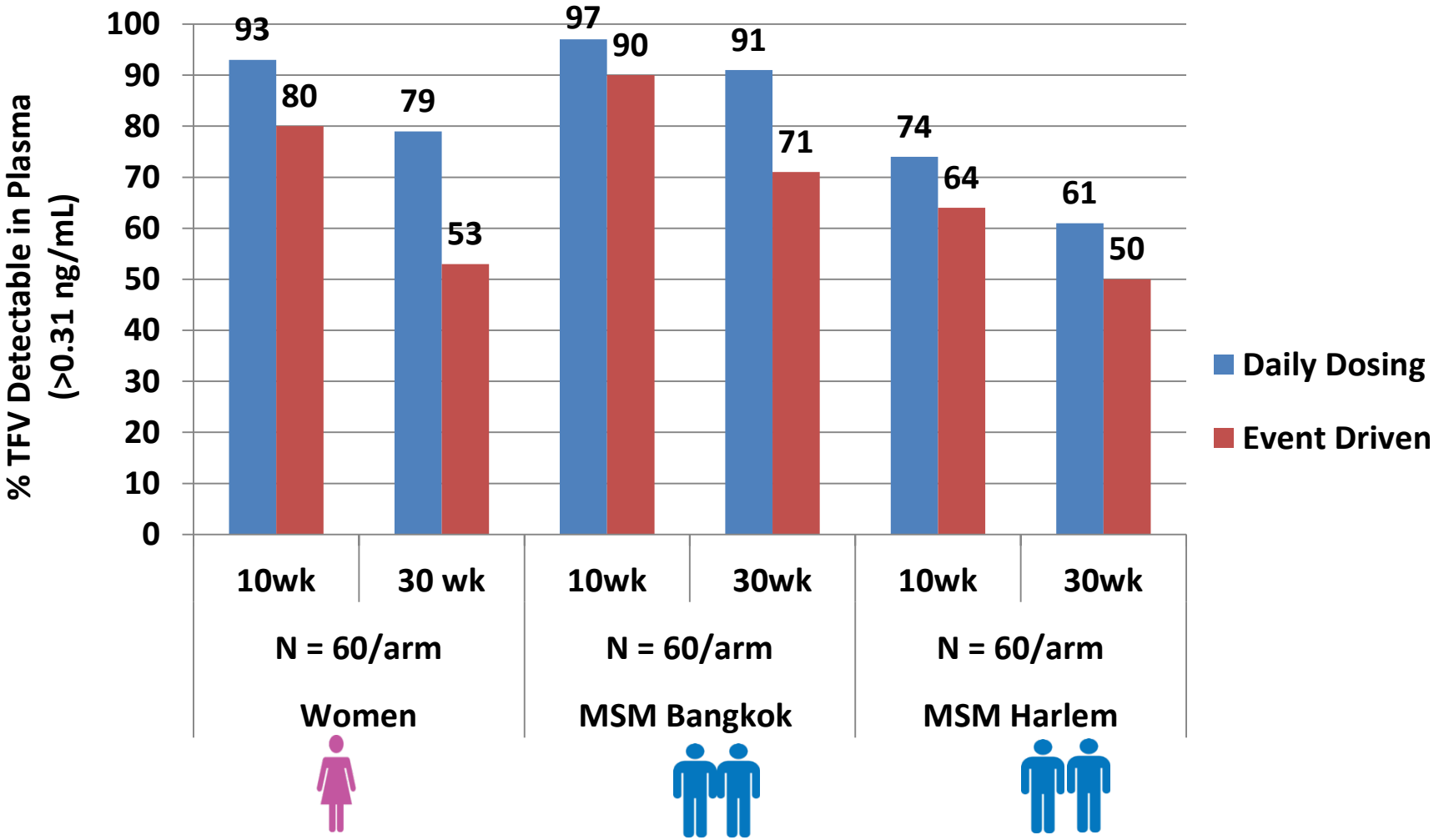
- Women: Cape Town, SA
- MSM: Harlem, NY
  Bangkok, Thailand

Primary objectives:

Compare daily versus non-daily arms:

- coverage of sex events
- number of pills pills for coverage
- side effects

HPTN 067: Adherence in participants reporting sex in the past 7 days



HPTN 073: Uptake of and adherence to TDF/FTC PrEP among Black MSM in the US (Vanguard Study)

Enrollment	226
Population	BMSM/HIV-
Study Duration: 12 M	

HIV negative BMSM

→

Provide PrEP
Daily Oral TDF/FTC

+

Client Centered Care Coordination (C4)

Washington,DC
Los Angeles, CA
Raleigh, NC

Results at CROI 2016

CROI 2016

HPTN 082: Uptake and adherence to daily oral TDF/FTC PrEP in young Southern African women (Vanguard Study)

Study Population

HIV-Uninfected women
Ages 16-25 yrs

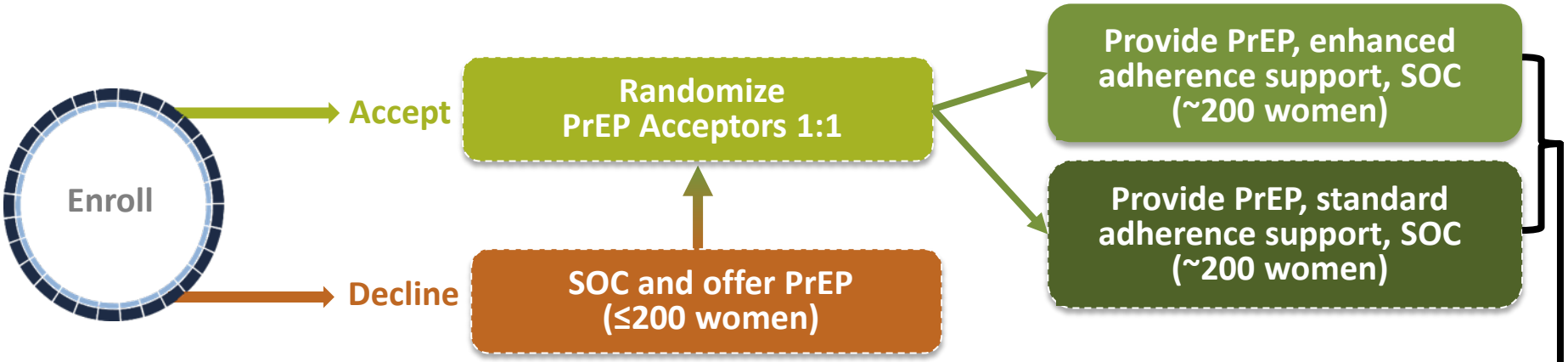
Target Enrollment

- 400 women who accept PrEP at enrollment
- ≤ 200 women who decline PrEP at enrollment

Sites
South Africa (2)
Zimbabwe

Study Design

PrEP = Daily oral FTC/TDF



IDI to explore factors that influence decisions to use, to adhere to, and acceptability of PrEP in the first 3 months after PrEP acceptance
(~75 total, including acceptors and decliners)

Standard Adherence Support	Enhanced Adherence Support
• CBT counseling	• CBT counseling
• SMS texting	• SMS texting
• Adherence clubs	• Adherence clubs
	• Drug level feedback counseling

Primary objectives:

- Assess the proportion and characteristics women who accept versus decline PrEP
- Assess PrEP adherence using drug levels in young women

HPTN 069 – Safety and tolerability of Maraviroc


406/400


188/200

Study Design	Phase 2 Double-blind Randomized
Location	13 sites – U.S. only

Study arms	
Arm 1	MVC
Arm 2	MVC+FTC/TDF
Arm 3	MVC+FTC
Arm 4	TDF

Study Status

Follow-up completed April 2015

Presentation of final results at CROI 2016

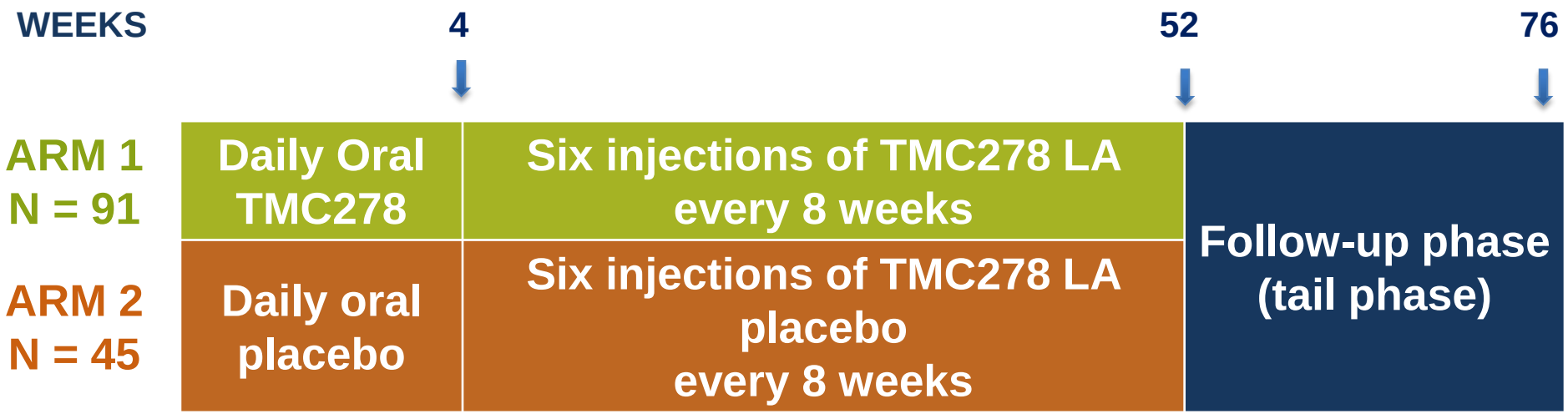
Follow-up completed November 2015

Abstract of final results to be submitted to AIDS 2016

Long Acting Parenteral PrEP

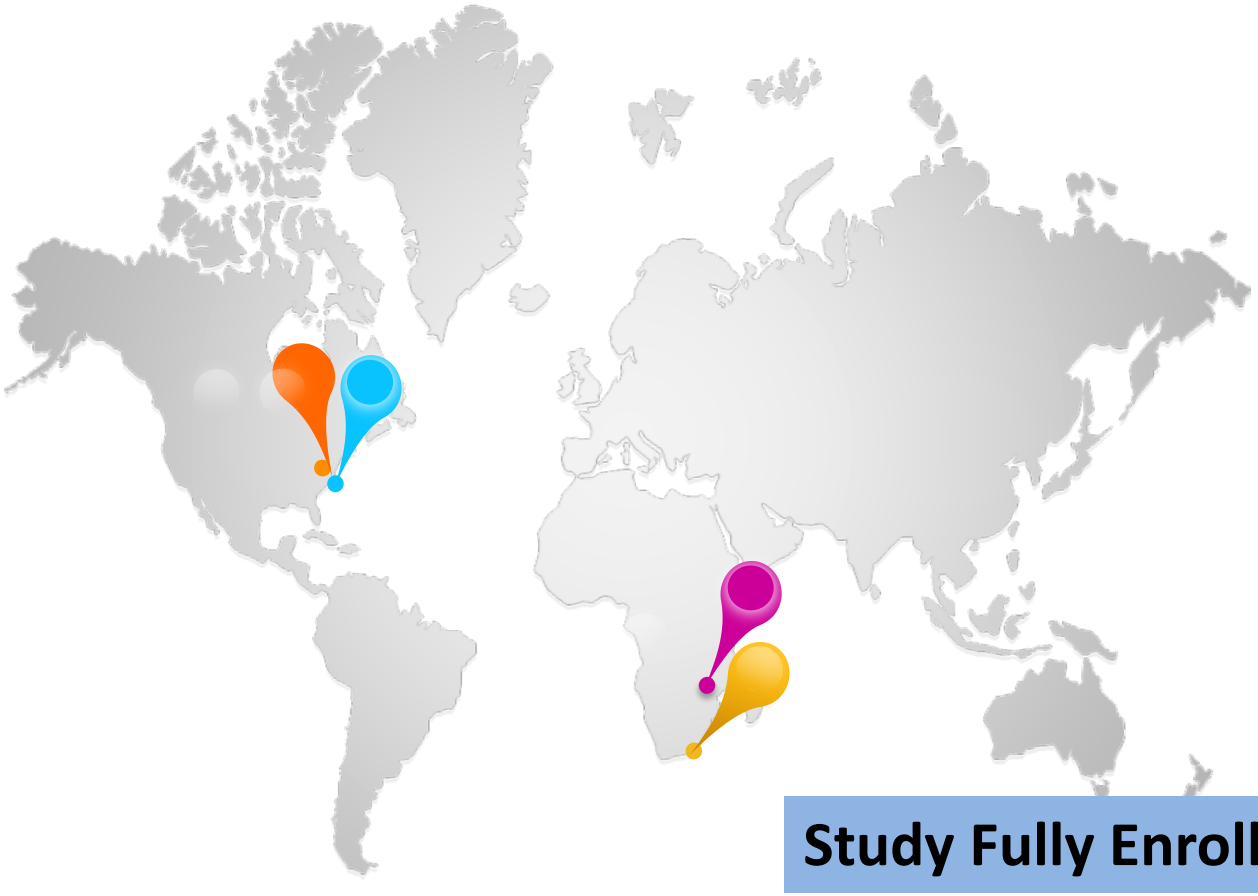
HPTN 076: Safety and acceptability of injectable rilpivirine for PrEP

136 HIV-uninfected, women ages 18-45 years



Primary objective: Evaluate the safety of injectable rilpivirine through 48 weeks in women in SSA and the U.S.

HPTN 076 – Study Sites and Status



US Sites

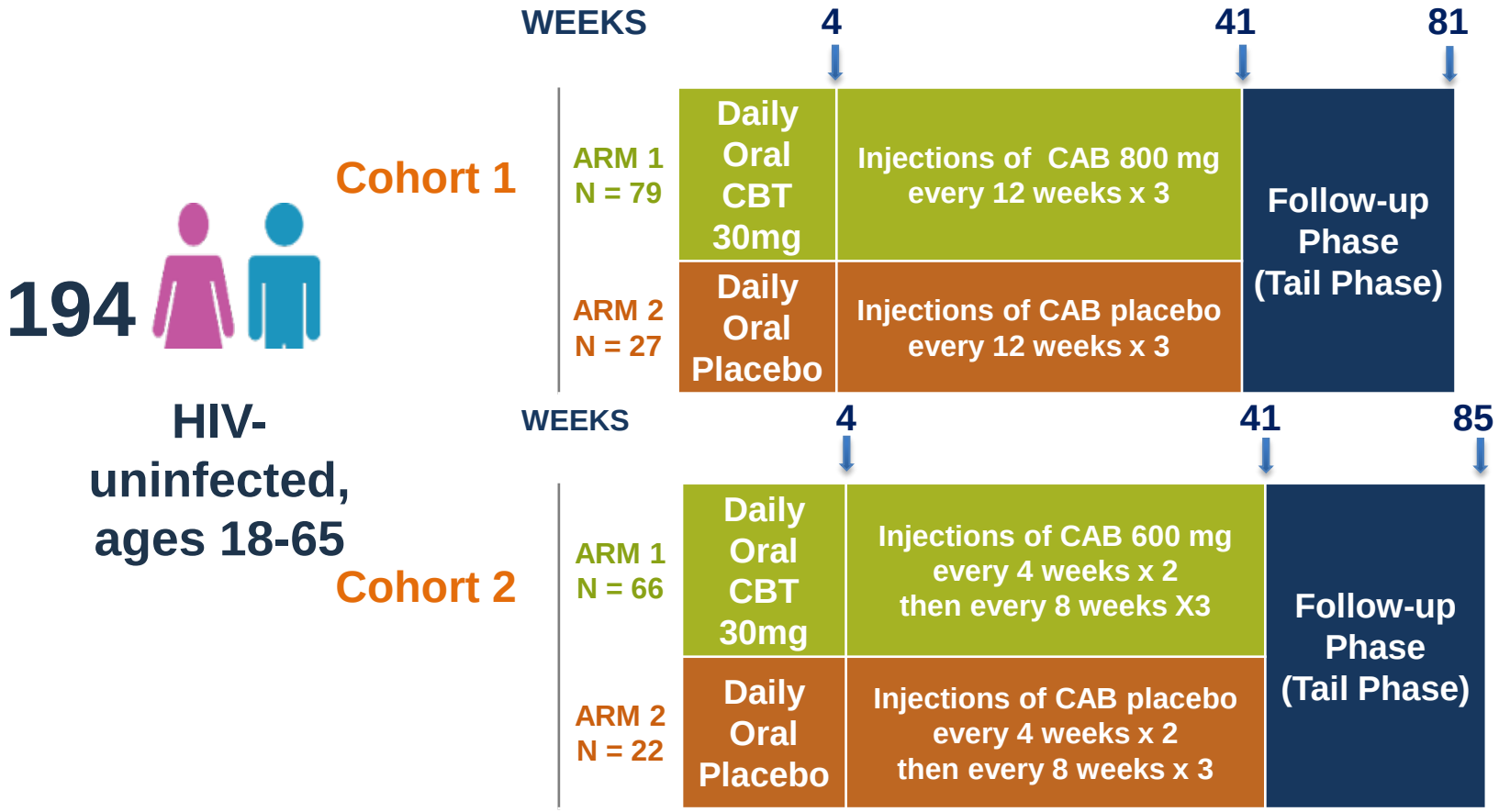
- Bronx, NY
- Newark, NJ

International Sites

- Cape Town, South Africa
- Harare, Zimbabwe

Study Fully Enrolled

HPTN 077: Safety, tolerability and pharmacokinetics of injectable cabotegravir (CAB) in men and women



Primary objective: Evaluate the safety and tolerability of the injectable CAB in HIV-uninfected men and women

HPTN 077 – Study Sites

US Sites

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

International Sites

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

Cohort 1: Enrollment complete (113)
Cohort 2: Target enrollment (88)

PrEP RCT Design and Monitoring

- When is a placebo control defensible?
- Is the design superiority or non-inferiority?
- Is the trial product blinded or unblinded?
- How intensive is the adherence monitoring and adherence support for oral PrEP?
- How do we design stopping rules to adapt to adherence?
- Is the trial feasible? If not, what are alternative designs approaches?

HPTN 083: Efficacy of injectable cabotegravir (CAB) for PrEP in MSM and transgender women

- N = 4500;
- Goals: 10% TGW overall; 50% of US BMSM; 50% overall < 30 year old
- Study duration: 3-5 years
- Sites in North and South America; Asia; SSA (limited)

	CAB	TDF/FTC
Step 1	Daily oral CAB and oral TDF/FTC placebo	Daily oral TDF/FTC and oral CAB placebo
Step 2	CAB injection x 2, 4 weeks apart then every 8 weeks plus daily oral TDF/FTC placebo	Placebo injection x 2, 4 weeks apart then every 8 weeks plus daily oral TDF/FTC
Step 3	Open-label daily oral TDF/FTC to cover the PK tail, for up to 48 weeks	

Primary objective: HIV Incidence

HPTN 084: Cabotegravir PrEP for Women

- Dr. Sinead Delaney Protocol Chair
- Study design under discussion

  -unblended, superiority?

NOTE PARTNERSHIP BETWEEN NIH/HPTN and VIIV, PEPFAR, USAID, and BMGF

Blinded versus Unblinded

HPTN
HIV Prevention Trials Network

Blinded

- Participants
  - Receive both injection and pills
  - Know if pill is active, will only work if taken
- Question answered
  - Closer to efficacy of drug itself
  - Difference in characteristics of adherers minimal

Unblinded

- Participants
  - Receive either injection or pill
  - Those on pill know it will work only if taken
- Question answered
  - Closer to effectiveness of intervention
  - Adherer characteristics will differ between arms
  - Behavior changes are possible

MK-8591 (Efda) CROI 2016!

HPTN
HIV Prevention
Trials Network

-EC50 in PBMCs of 0.2 nM
-Half life in PBMCs100 hours

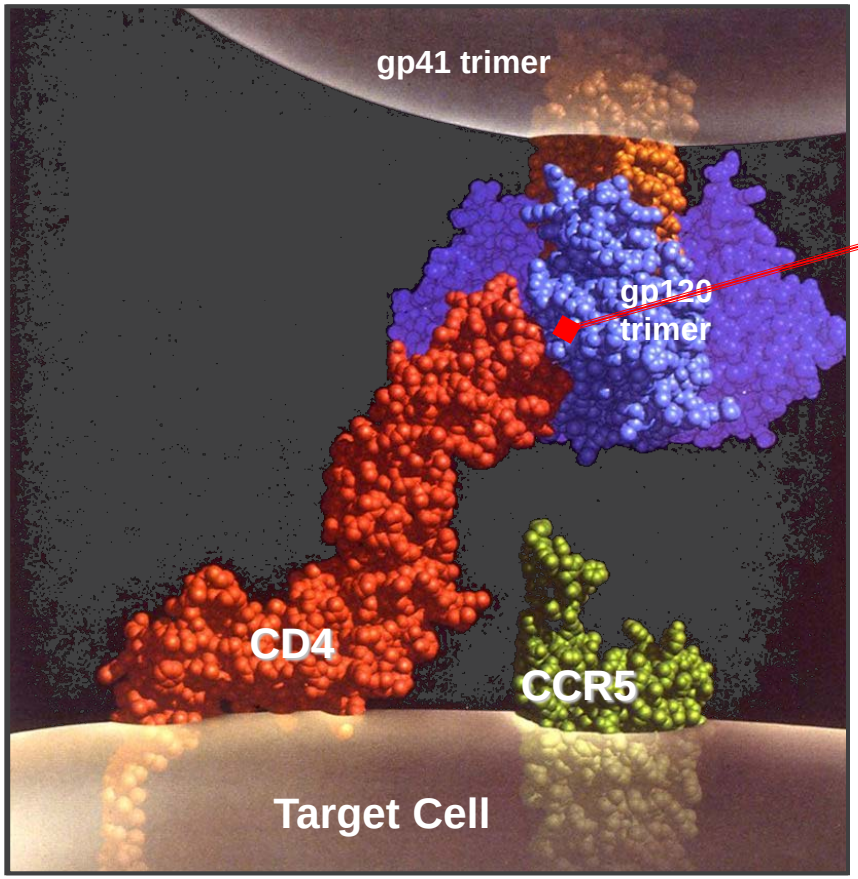
HIV treatment?
Peroral weekly prevention?
Development of a long acting implant
BC and PrEP implant combined?
The best drug development plan?

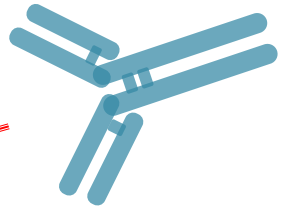
The AMP Studies

AMP = Antibody Mediated Prevention

Broad neutralizing monoclonal antibodies (BnABS) to prevent HIV infection.

VRC01 Blocks Attachment to CD4





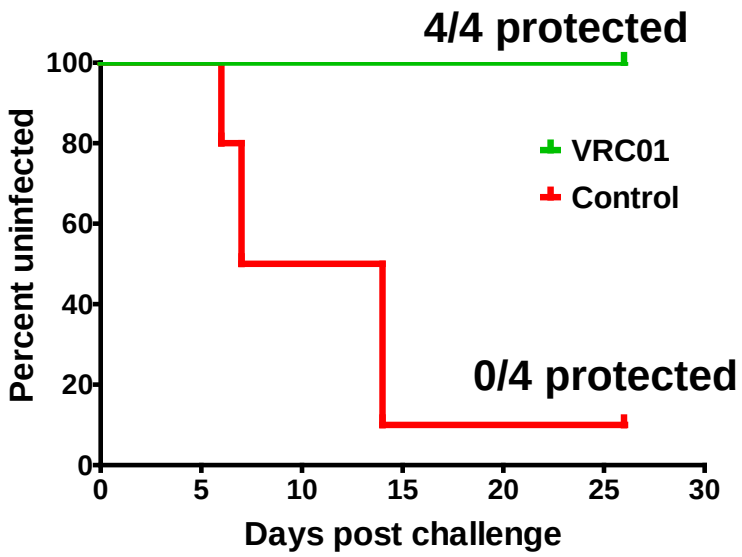
CD4 binding site on gp120 is functionally conserved: All viruses must bind CD4

VRC01 neutralize ~ 90% of diverse viral isolates

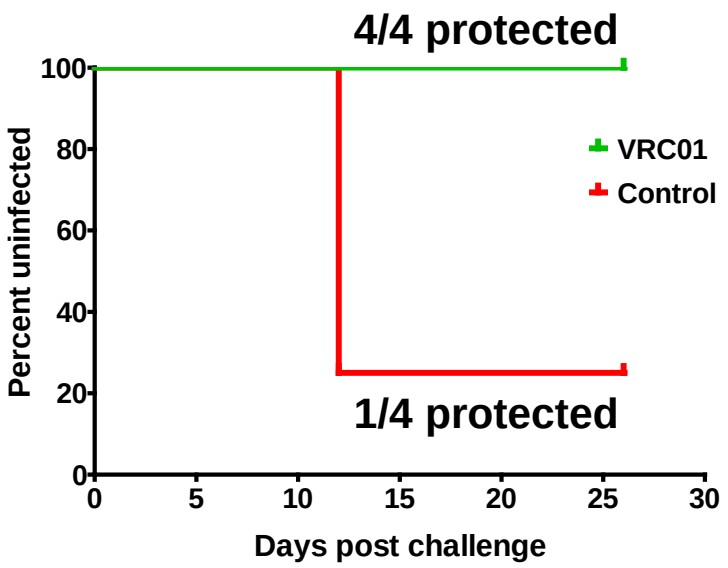
VRC01 Protects against Mucosal SHIV-Challenge in Non-human Primates

20 mg/kg infusion of VRC01: Challenge with SHIV SF162P3

RECTAL CHALLENGE



VAGINAL CHALLENGE



- Pegu et al. Science Transl Med (2014)
- Ko et al. Nature (2014)
- Rudicell et al. J Virol (2014)

nature International weekly journal of science

LETTER

doi:10.1038/nature17677

A single injection of anti-HIV-1 antibodies protects against repeated SHIV challenges

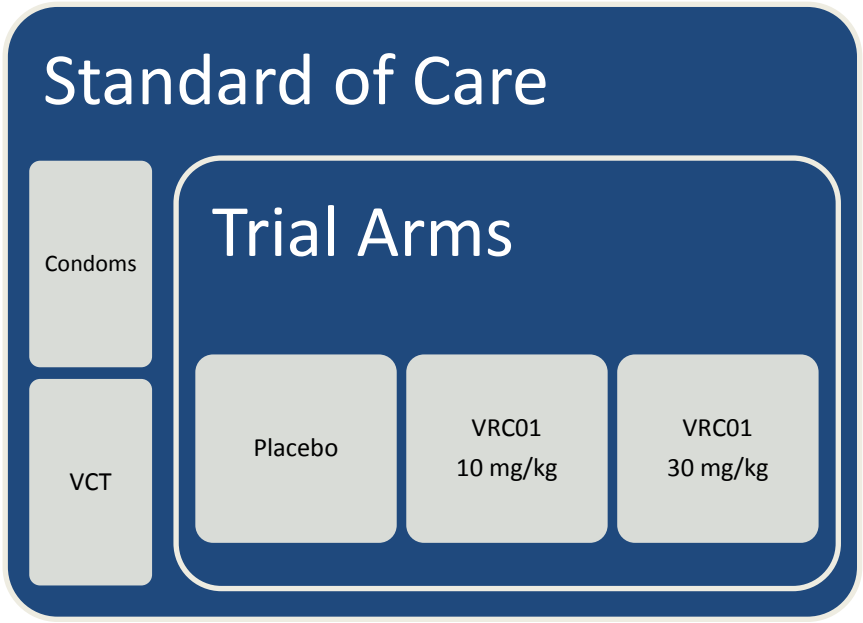
Rajeev Gautam[1]*, Yoshiaki Nishimura[1]*, Amarendra Pegu[2], Martha C. Nason[3], Florian Klein[4,5,6], Anna Gazumyan[4], Jovana Golijanin[4], Alicia Buckler-White[1], Reza Sadjadpour[1], Keyun Wang[2], Zachary Mankoff[2], Stephen D. Schmidt[2], Jeffrey D. Lifson[7], John R. Mascola[2], Michel C. Nussenzweig[4,8] & Malcolm A. Martin[1]

The Main Hypotheses of the AMP Trial

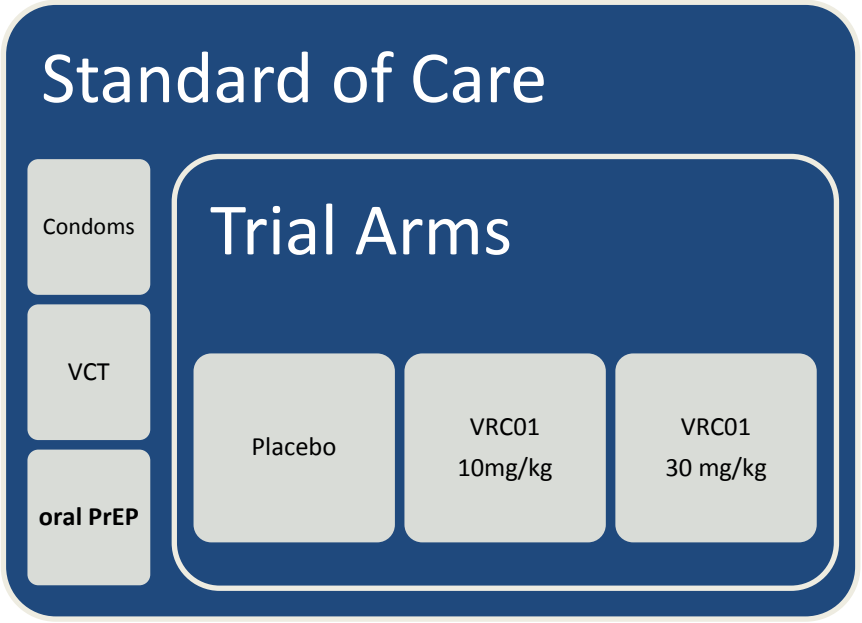
- Administration of this broadly neutralizing antibody will reduce acquisition of HIV infection in these high risk populations;
- The concentration of antibody in serum will be directly associated with the rate of protection; that is, higher levels of antibodies will give greater rates of protection than lower levels; and
- Breakthrough isolates will have greater resistance to neutralization and will exhibit molecular signatures associated with escape from neutralization.

Superiority Trial: VRC01

Sites without access to oral PrEP



Sites with access to oral PrEP



Ethical imperative to improve prevention products:

- What is the "SOC" support for uptake of PrEP (ease of access, adherence support)?
- How and why is this support different when PrEP is a study drug?

When is a placebo control defensible?

Existing proof of concept in humans

- FTC/TDF success in prevention provides proof of concept for ART drugs for prevention
- Credible, but unproven, that other ARTs will prevent infections
- Comparator needs to be TDF/FTC

No existing proof on concept in humans

- Monoclonal antibodies and vaccines do not have convincing evidence for HIV prevention in humans
- Placebo required to provide evidence of effect
- Rigorous attention given to access to FTC/TDF in context of trial populations

HVTN 704/HPTN 085 (AMP): VRC 01 for PrEP in MSM & TG in the Americas

Enrolled participants
2700 MSM & TG 18 to 50 years old
Study duration
92 weeks (infusions given through week 72)

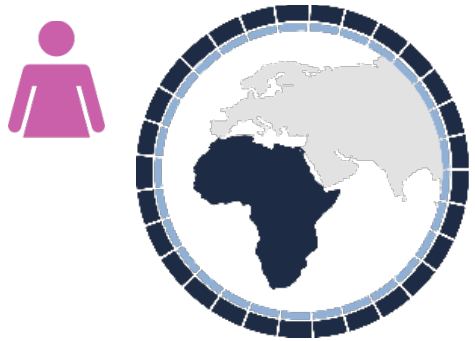
Regimen	Target Sample	
VRC01 10 mg/kg	900	Infusions every 8 weeks through Week 72 >150 enrolled!
VRC01 30 mg/kg	900	
Control	900	
Total	**2700**	

HIV-1 tests administered at baseline and every 4 weeks through the Week 92 visit

Primary objective: HIV incidence, safety and tolerability

HVTN 703/HPTN 081 (AMP) VRC 01 for PrEP in Women in SSA

Enrolled participants
1500 South African Women 18 to 50 years old
Study duration
92 weeks (infusions given through week 72)



Regimen	Target Sample	
VRC01 10 mg/kg	500	Infusions every 8 weeks through Week 72 > 12 enrolled
VRC01 30 mg/kg	500	
Control	500	
Total	**1500**	

HIV-1 tests administered at baseline and every 4 weeks through the Week 92 visit

Primary objective: HIV incidence, safety and tolerability

THANK YOU FOR LISTENING