

# **HIV Prevention 2020**



**Myron S. Cohen, MD**

**Yeargan-Bate Eminent Professor  
Medicine, Microbiology and Public Health  
Director, Institute for Global Health & Infectious Diseases  
Associate Vice Chancellor for Global Health**



## Viewpoint

March 8, 2019

# HIV in the United States Getting to Zero Transmissions by 2030

Ingrid Katz, MD, MHS<sup>1,2</sup>; Ashish K. Jha, MD, MPH<sup>1,3</sup>

*JAMA*. 2019;321(12):1153-1154. doi:10.1001/jama.2019.1817

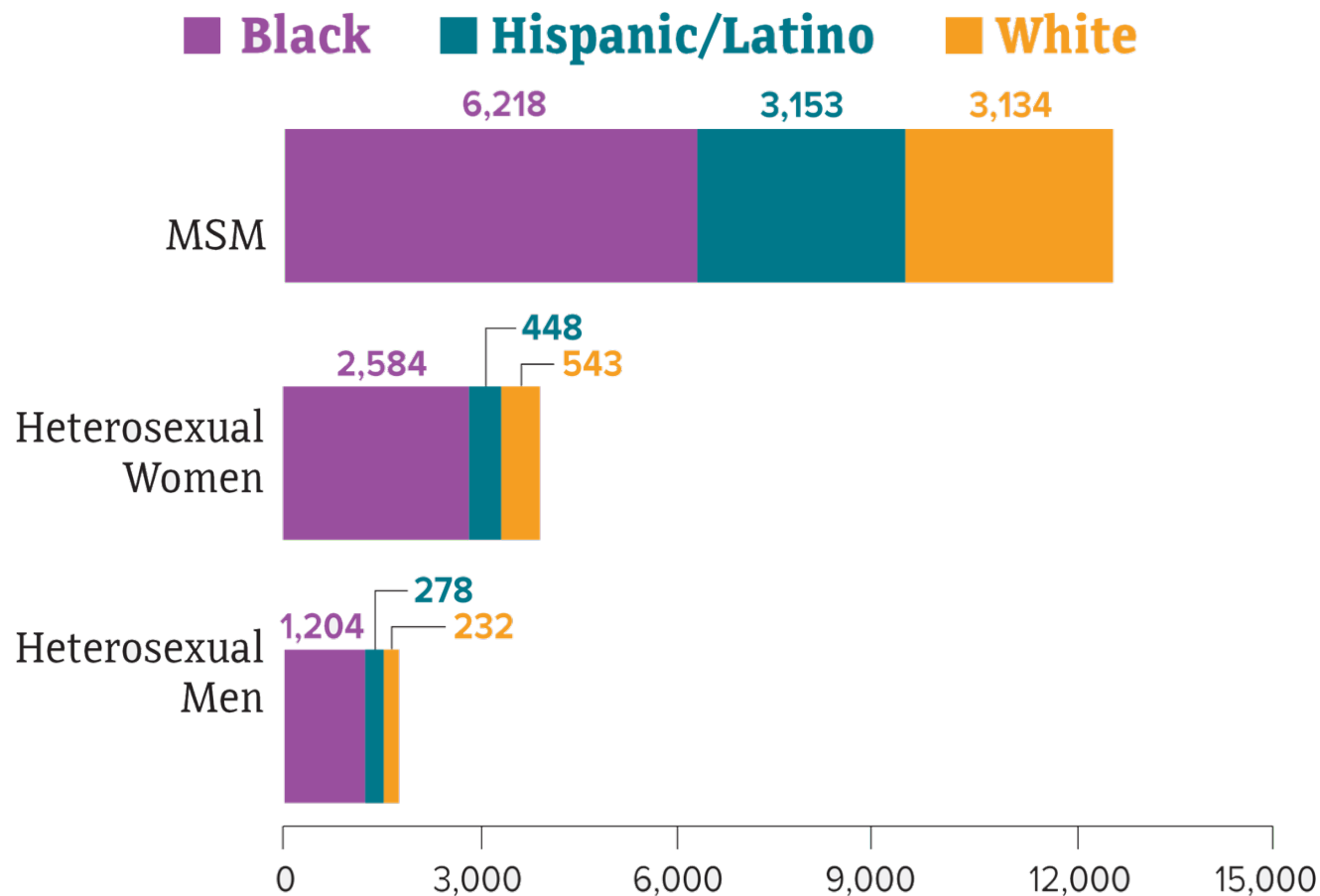
## Editorial

February 7, 2019

# Ending the HIV Epidemic A Plan for the United States

Anthony S. Fauci, MD<sup>1</sup>; Robert R. Redfield, MD<sup>2</sup>; George Sigounas, MS, PhD<sup>3</sup>; [et al](#)

*JAMA*. 2019;321(9):844-845. doi:10.1001/jama.2019.1343



## New HIV diagnoses In the Southern US

Black MSM accounts for most of the new HIV-1 diagnoses in the south, however, rates of new infections are surging among Hispanic/Latino MSM in the south in recent years.

\* Includes the three most affected racial/ethnic groups in each category

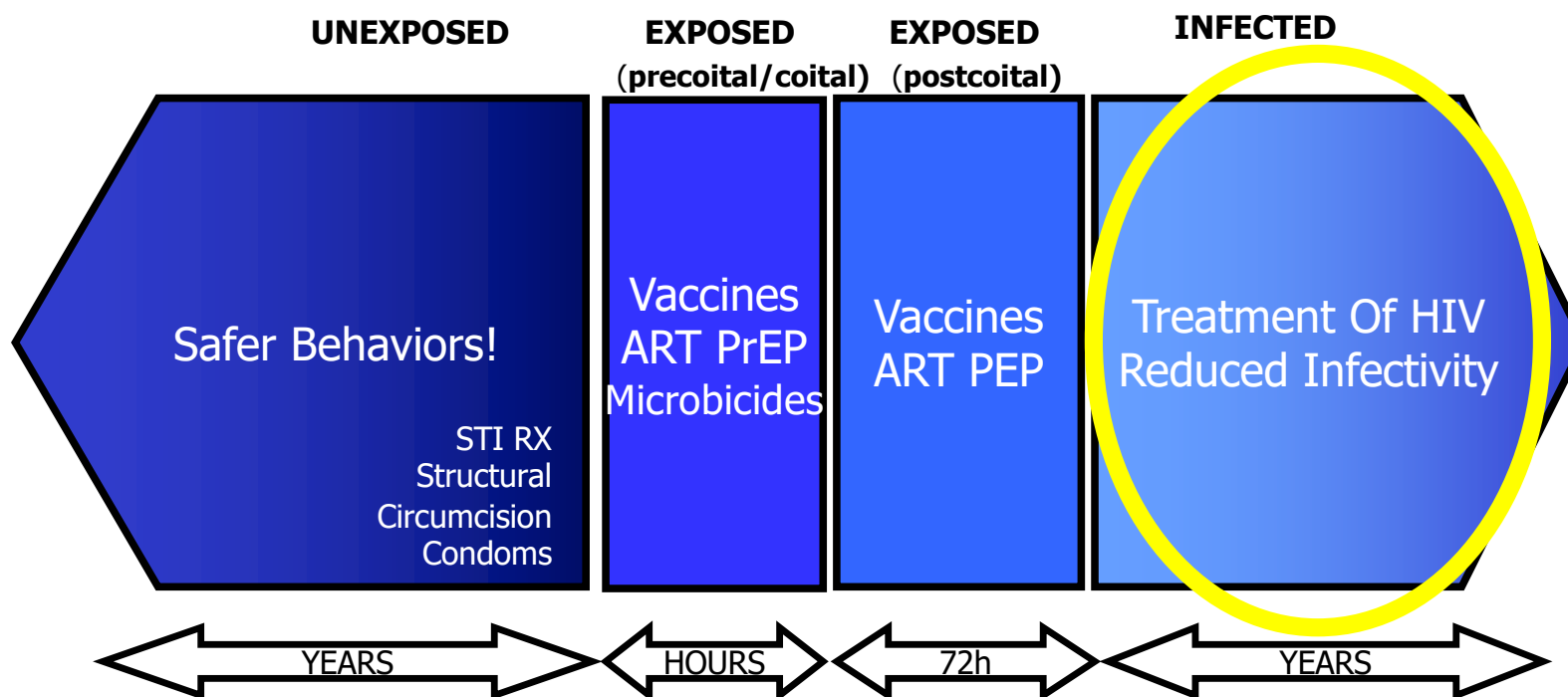
# “Ending the HIV Epidemic” Four Strategies

- ✓ Increase Testing and Diagnosis
- ✓ Improve the Treatment Cascade
- ✓ PrEP to protect individuals at risk
- ✓ Rapid detection and response to HIV-1 transmission outbreak clusters



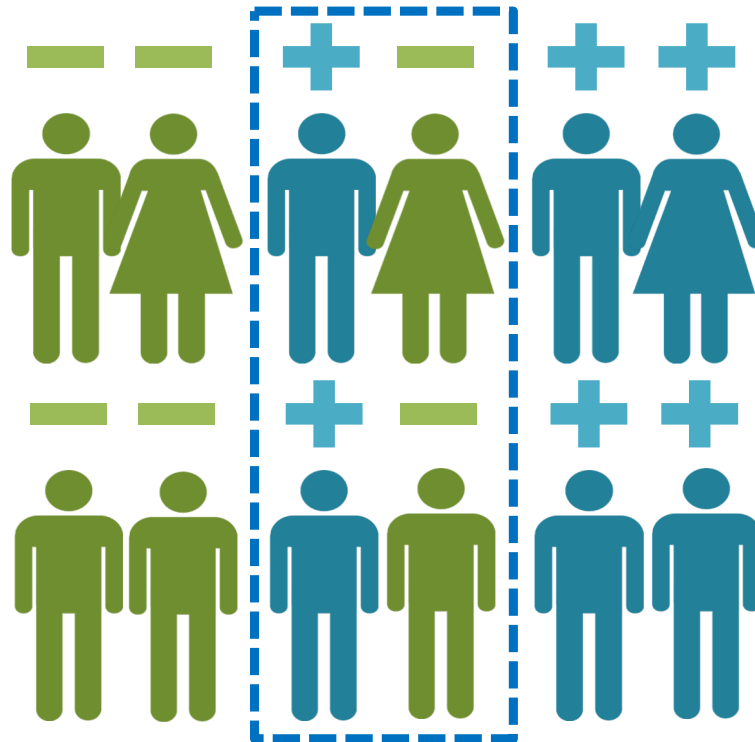
# Four Prevention Opportunities

*Cohen et al, JCI, 2008*  
*Cohen IAS 2008*



# Treatment as Prevention

Reduce HIV in genital secretions with ART!



“The results have galvanized efforts to end the world’s AIDS epidemic in a way that would have been inconceivable even a year ago”

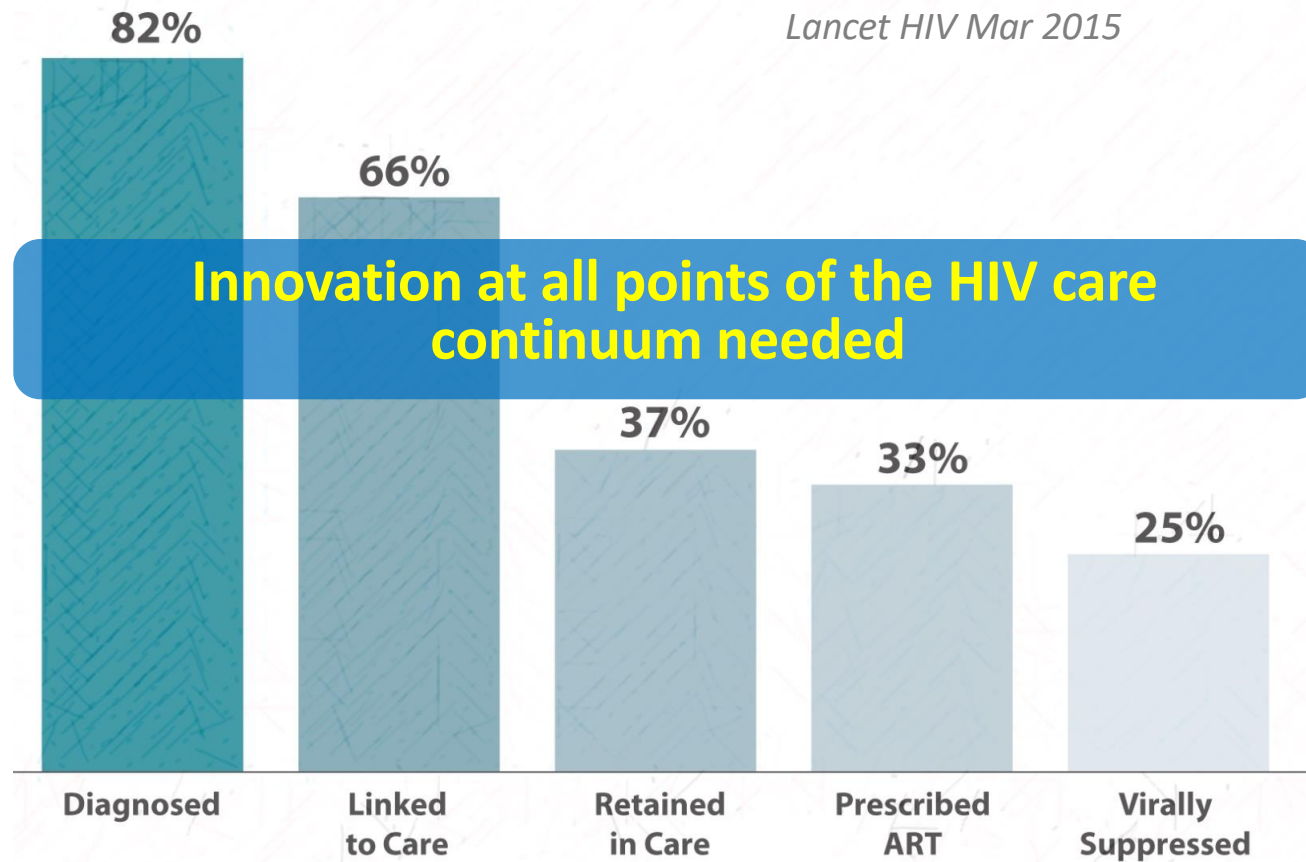


Bruce Alberts,  
editor of Science





# “End of AIDS on the horizon, but innovation is needed”



## Community Based TasP

- ANRS South Africa (*NEJM, NS*)
- Botswana (*IAS, 30% Reduction*)
- SEARCH (*IAS, 2018, NS*)
- HPTN 071/POPART (*CROI 2019*) ??

**Treatment serves as prevention, but imperfectly.**

# Why is “Treatment as Prevention” Imperfect?

- Magnitude of Coverage
- ART Resistance
- Specific Untreated People
  - acute HIV
  - “in-migration” into a community
  - young men as a key population

ATTRIBUTABLE RISK FOR EACH?



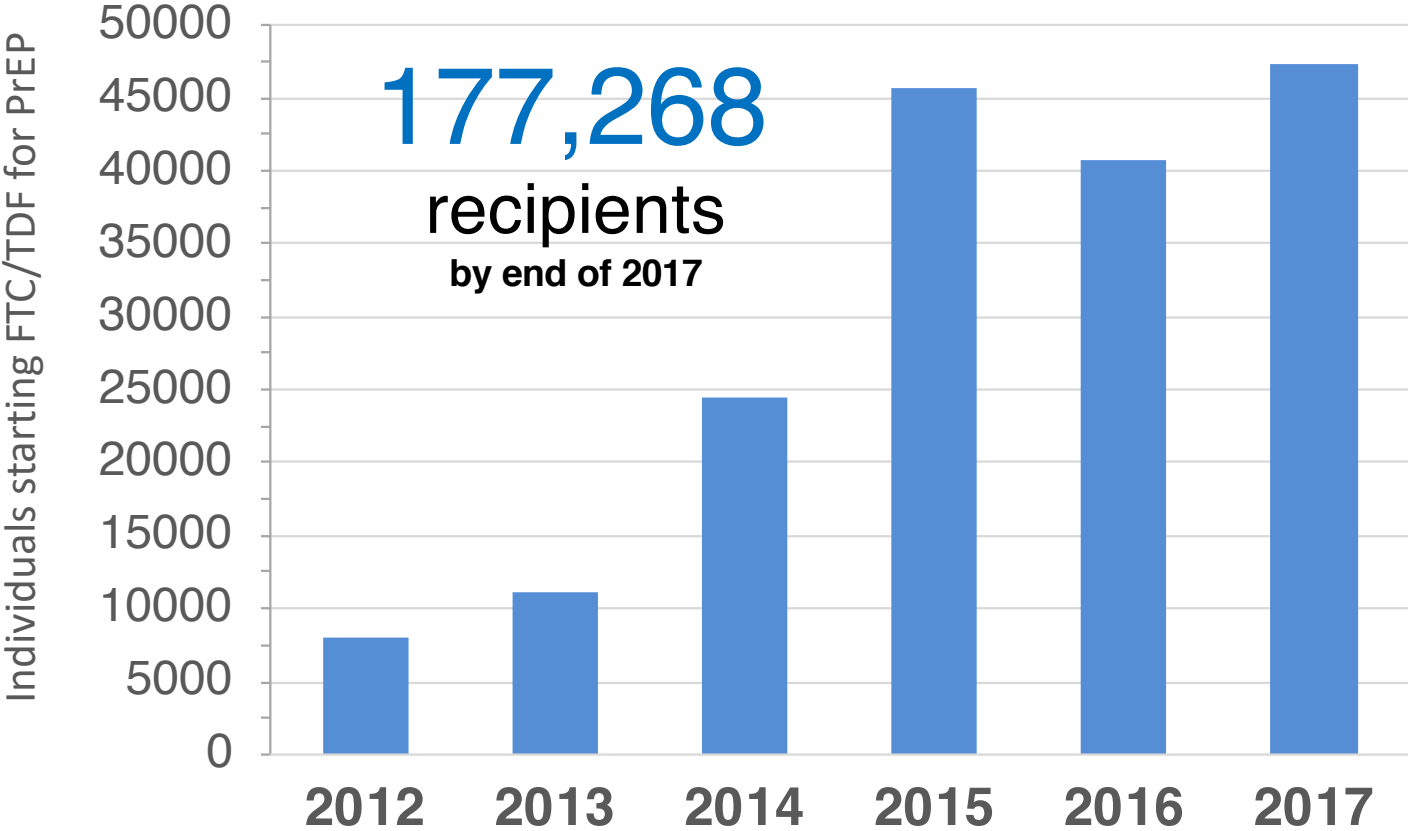
# **TDF/FTC was FDA Approved for use for Prevention on July 16, 2012**

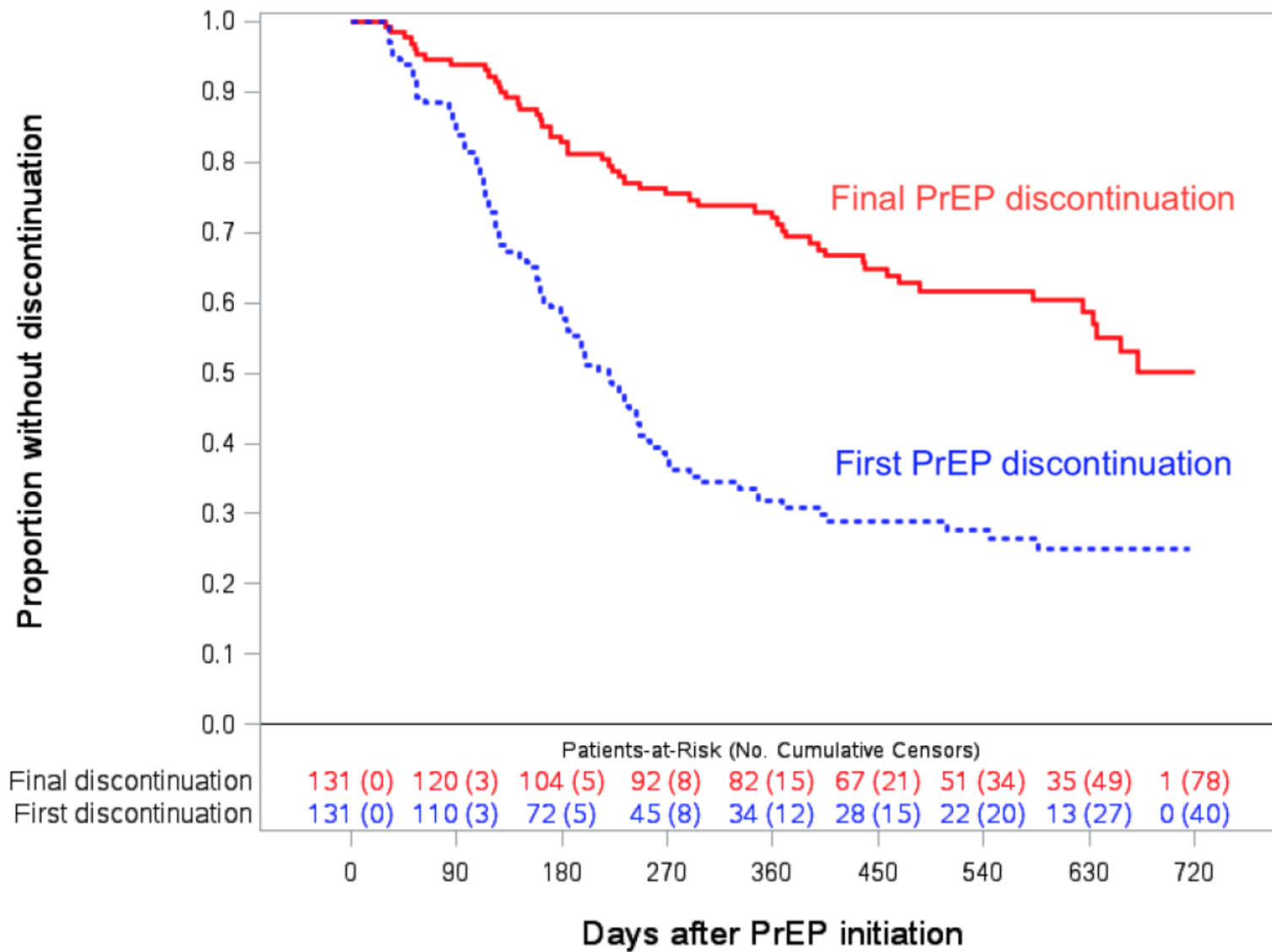
- Success depends entirely on adherence
- Alternatives to daily dosing are possible
- Truvada PrEP uptake has been limited to date
- Perhaps longer acting agents will prove more attractive?





# PrEP use has increased in the US...





Serota, JID 2019  
 Slide courtesy of P. Sullivan

# THE PHASE 3 DISCOVER STUDY: DAILY F/TAF OR F/TDF FOR HIV PRE-EXPOSURE PROPHYLAXIS

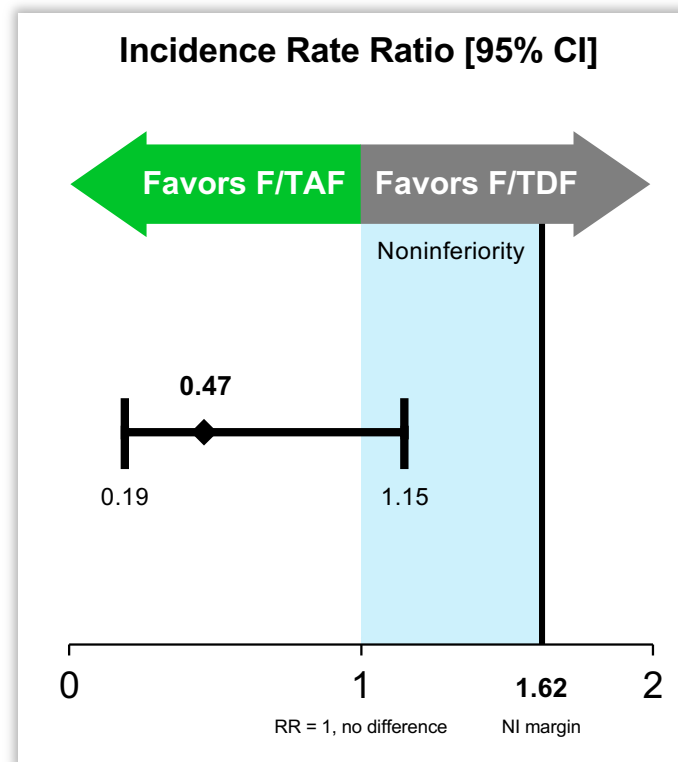
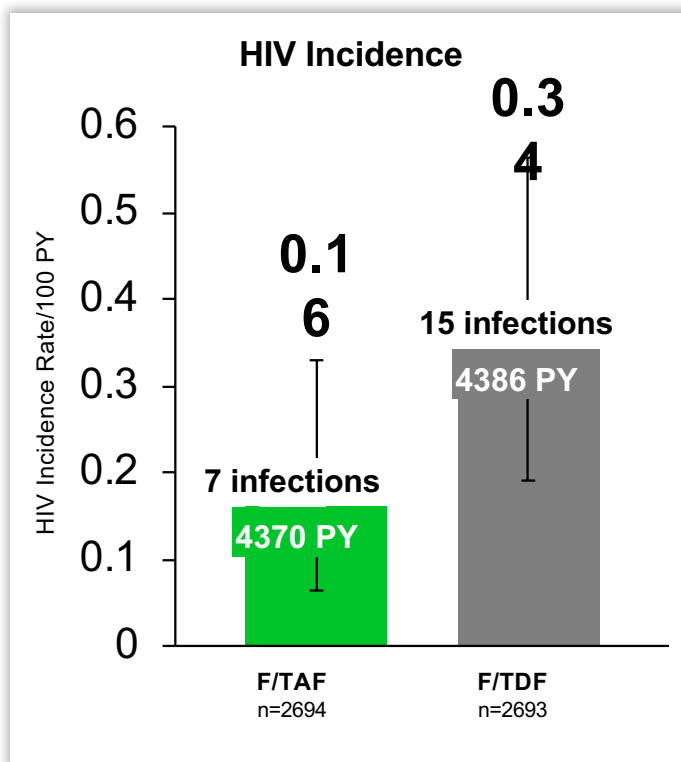
**Brad Hare<sup>1</sup>, Pep Coll<sup>2</sup>, Peter Ruane<sup>3</sup>, Jean-Michel Molina<sup>4</sup>,  
Kenneth Mayer<sup>5</sup>,  
Heiko Jessen<sup>6</sup>, Robert Grant<sup>7</sup>, Joss De Wet<sup>8</sup>, Melanie  
Thompson<sup>9</sup>, Edwin DeJesus<sup>10</sup>, Ramin Ebrahimi<sup>11</sup>,  
Robertino Mera<sup>11</sup>, Moupali Das<sup>11</sup>, Diana Brainard<sup>11</sup>, Scott  
McCallister<sup>11</sup>**

<sup>1</sup>Kaiser-Permanente, San Francisco, CA; <sup>2</sup>Institut de Recerca de la Sida, Barcelona, Spain; <sup>3</sup>Ruane Clinical Research, Los Angeles, CA; <sup>4</sup>University of Paris Diderot, France; <sup>5</sup>Harvard T.H. Chan School of Public Health, Boston, MA; <sup>6</sup>Praxis Jessen, Academic Teaching Clinic of Charité, Universitätsmedizin, Berlin, Germany; <sup>7</sup>University of California, San Francisco, San Francisco, CA; <sup>8</sup>Spectrum Health,

# DISCOVER: F/TAF vs. F/TDF



22 HIV infections in 8756 PY of follow-up



**F/TAF is non-inferior to F/TDF for HIV prevention**

CI, confidence interval; RR, rate ratio.  
Hare B, et al. CROI 2019. Oral 104LB

# Monthly Dapivirine Rings

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- Flexible silicone vaginal ring developed
- Woman-initiated
  - Self-inserted monthly
  - Discreet
- Slowly releases the NNRTI dapivirine
- Reduced women's HIV-1 risk by ~30% in 2 phase 3 trials
- Data from open-label studies show greater use and potentially greater risk reduction
- **Under regulatory review??**
  - NNRTI, non-nucleoside reverse transcriptase inhibitor

Nel A, et al. NEJM. 2016;375:2133-2143

Baeten J, et al. NEJM. 2016;375:2121-2132

Baeten J, et al. CROI 2018. #143LB

Nel A, et al. CROI 2018, #144LB

# Long Acting Parenteral PrEP



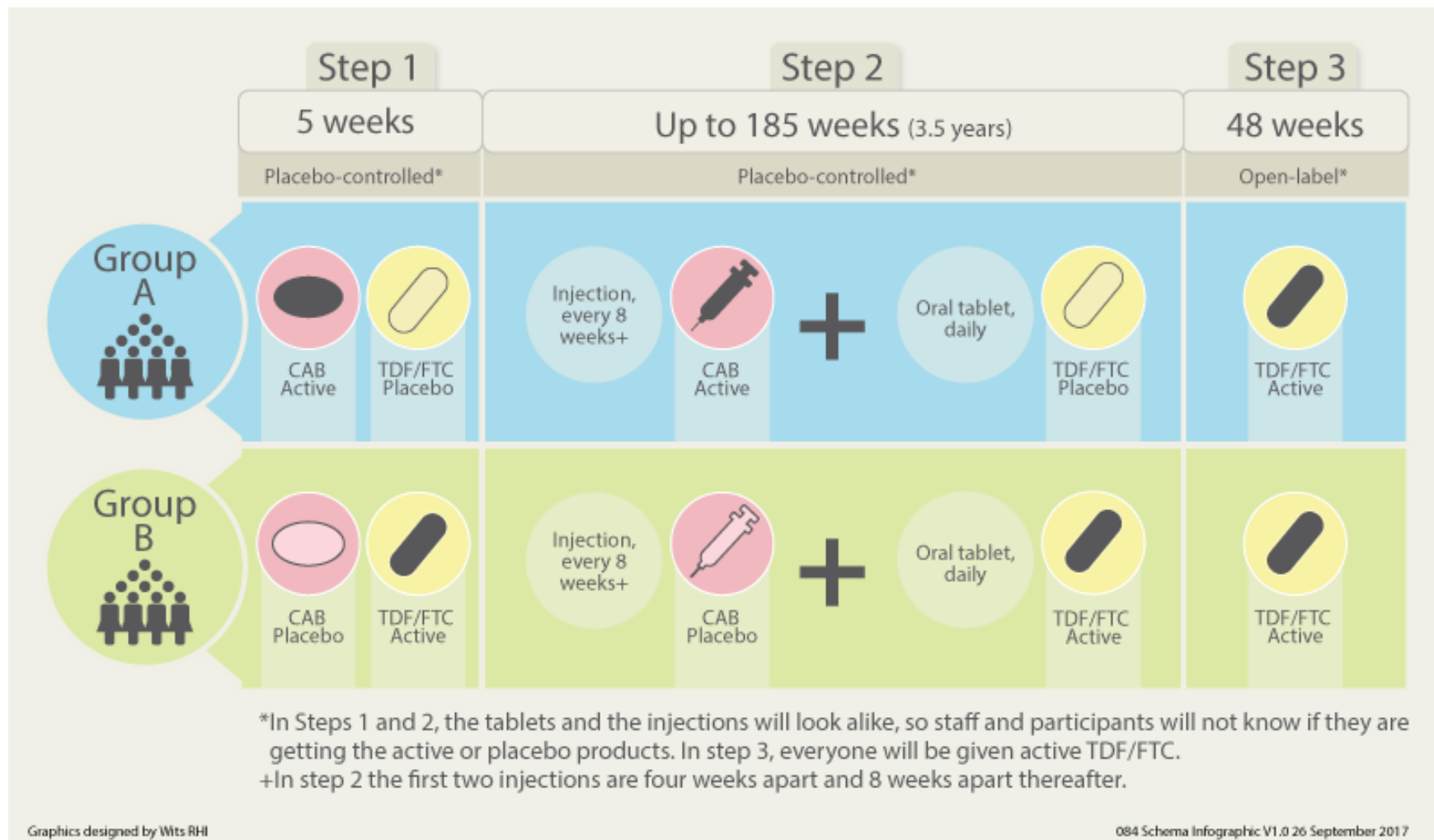


## **Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial**

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

# 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 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**

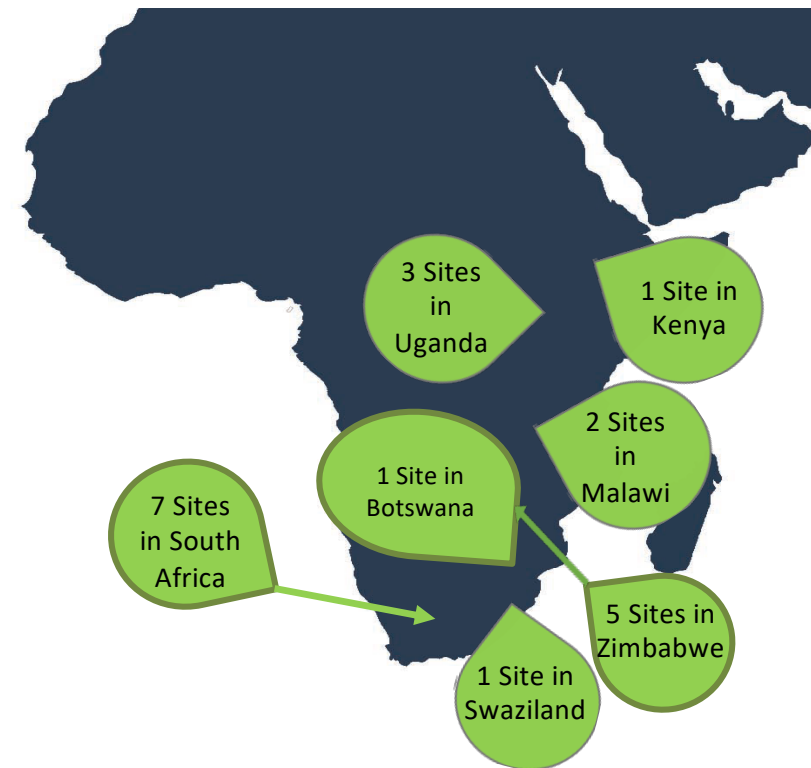
- 27 US sites
- 11 South American sites
- 4 Asian sites
- 1 African site

**The study is essentially fully enrolled (!!)  
with additional enrollment of 500 subjects**

## 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

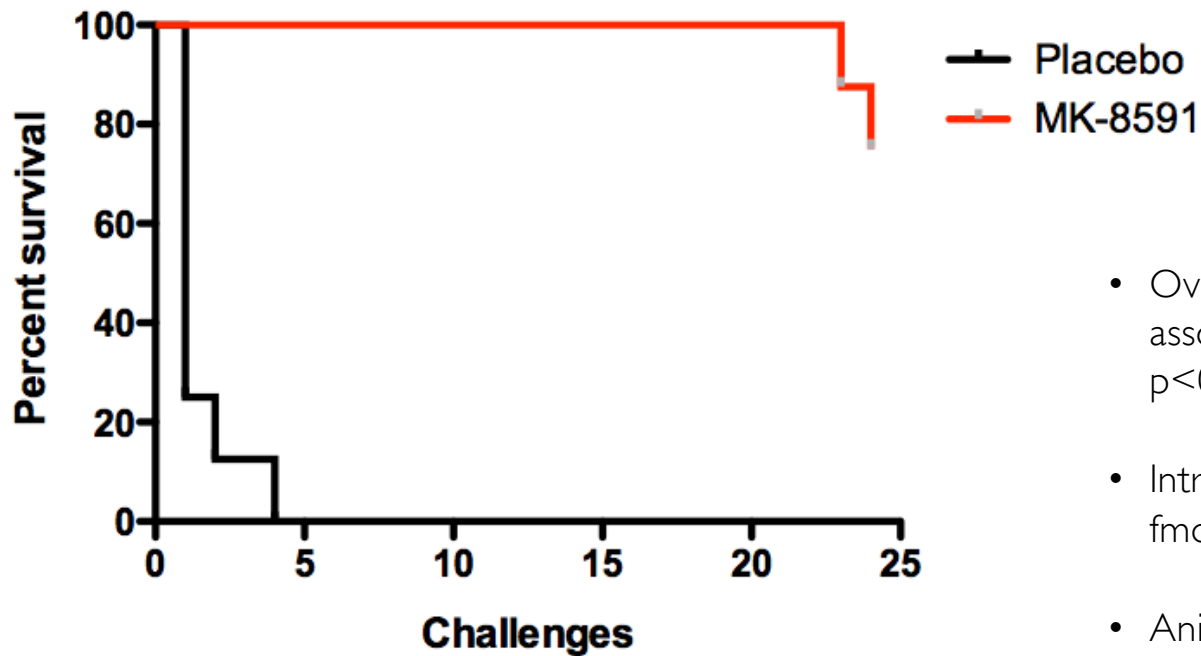




## Challenges in Development of CAB-LA as PreP

- Recruitment and retention!
- **Reduced HIV incidence compromises anticipated endpoints**
- Will CAB-LA PrEP “overwhelm” STIs
- Analysis may be complicated: ITT vs “As treated”

MK-8591 at 3.9, 1.3, 0.43 and 0.1 mg/kg is highly protective against infection with SHIV109CP3 (Phase 2 study q month pill launching)



- Overall, treatment with MK-8591 at all 4 doses was associated with a 41.47-fold lower risk of infection,  $p < 0.0001$ , log rank test
- Intracellular levels of MK-8591-TP at or above 24 fmol/ $10^6$  PBMC is associated with 92% protection
- Animals treated with 0.1 mg/kg dose are 7.2-fold less likely to be infected,  $p = 0.0004$  log rank test

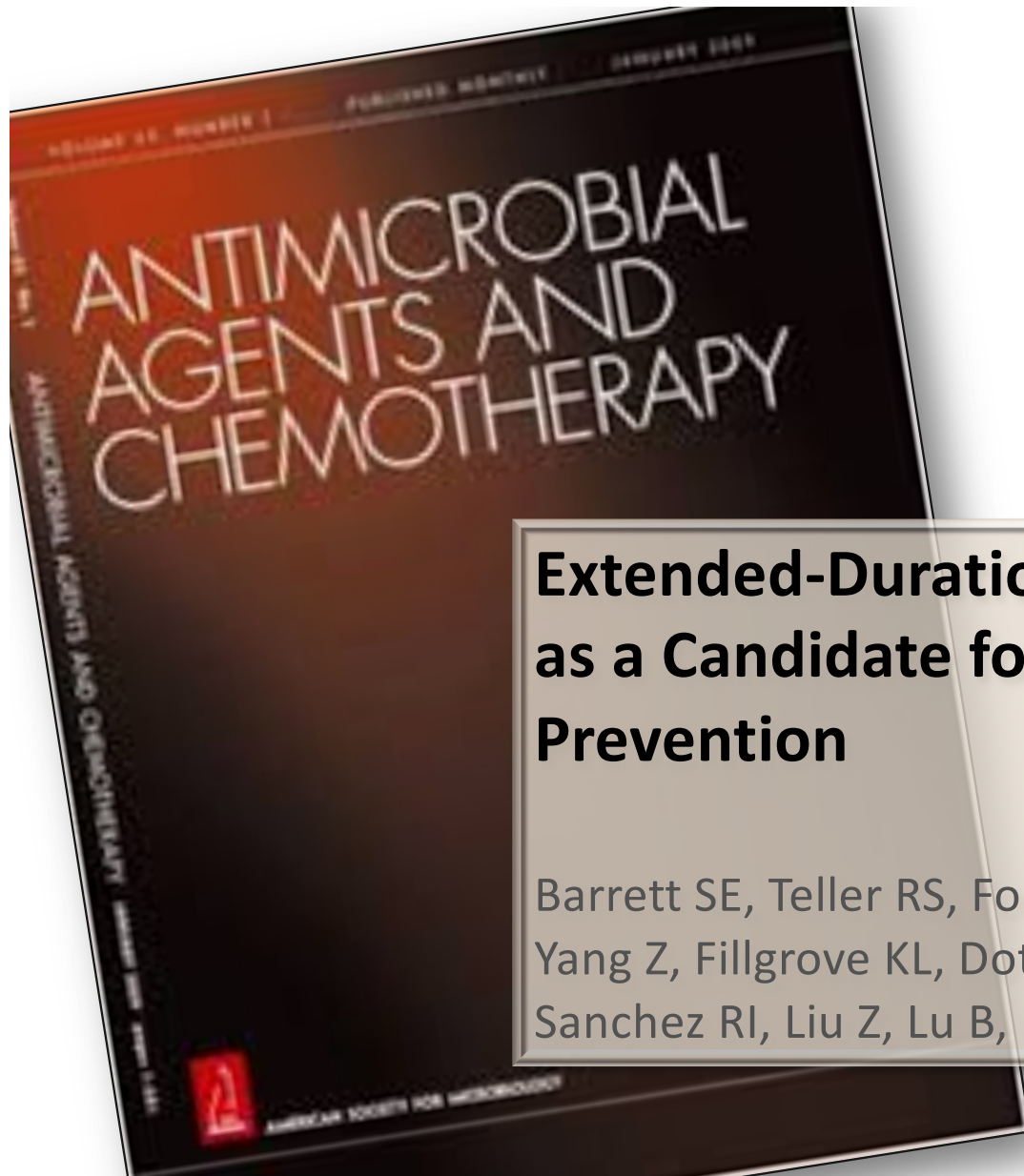
**Safety and Pharmacokinetics of Oral Islatravir (MK-8591) Once Monthly  
in Participants at Low Risk of Human Immunodeficiency Virus 1  
(HIV-1) Infection (MK-8591-016)**

ClinicalTrials.gov Identifier: NCT04003103

Recruitment Status : Not yet recruiting

First Posted : July 1, 2019

Last Update Posted : August 15, 2019



## **Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention**

Barrett SE, Teller RS, Forster SP, Li L, Mackey MA, Skomski D,  
Yang Z, Fillgrove KL, Doto GJ, Wood SL, Lebron J, Grobler JA,  
Sanchez RI, Liu Z, Lu B, Niu T, Sun L, Gindy ME

# LA Implants

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Matrix vs. Reservoir

Renewable vs. biodegradable

- MK-8591 (Islatravir)
- Cabotegravir (Northwestern, ViiV)
- TAF (Oakcrest, Houston, RTI, Northwestern)
- Dolutegravir (Sol-Gel)



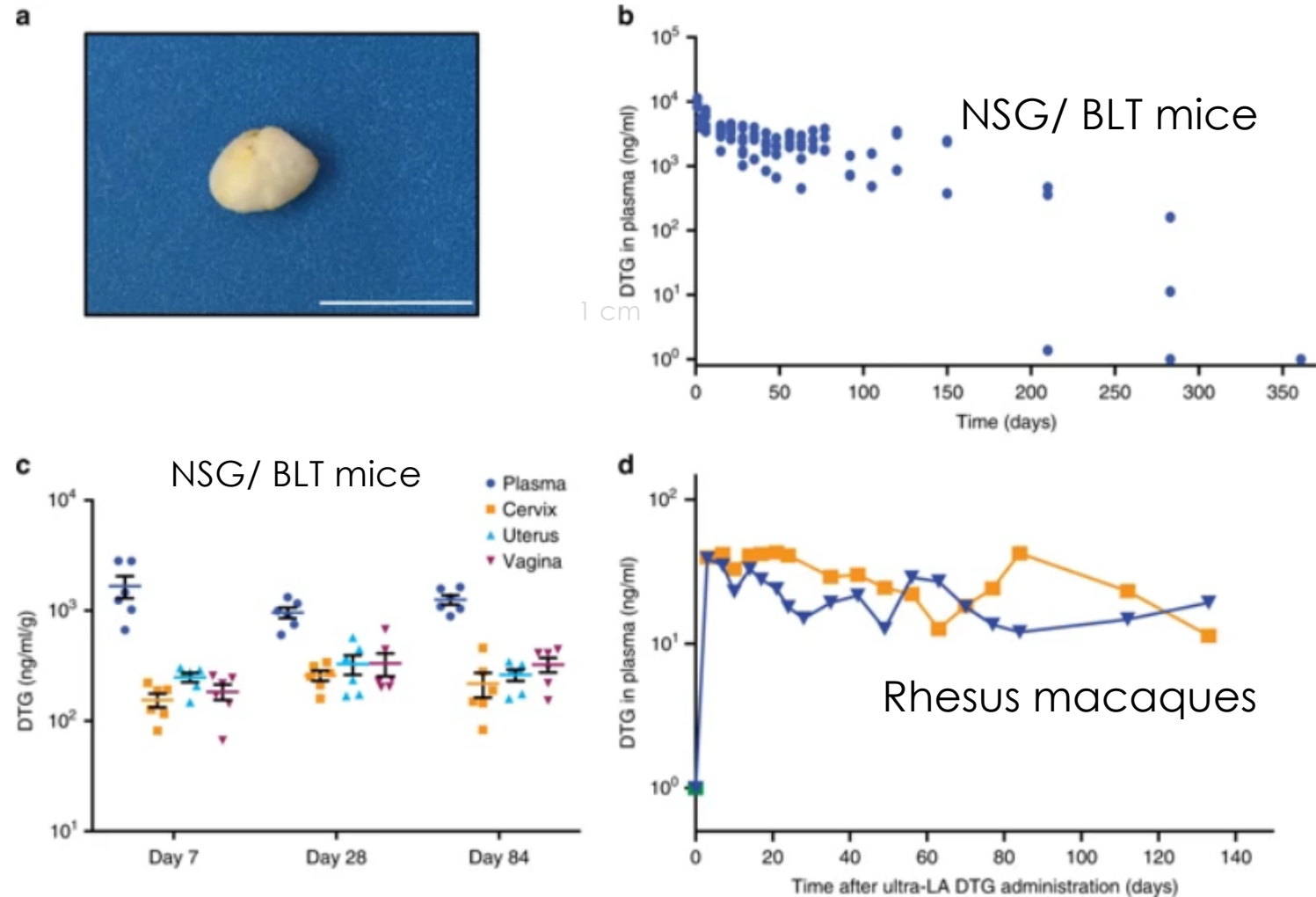
# Ultra Long-Acting Dolutegravir (sol-gel)

## What is PrEP [DTG] target?

- [DTG] should be  $\geq C_T$  observed at 10 mg once daily (0.30 mcg/mL)
- =  $EC_{90}$  based on  $E_{max}$  model from PK/PD analysis of monotherapy study
- With 50 mg daily,  $C_T$  is 1.20 mcg/mL;
  - 0.30 mcg/mL is 25% of that value

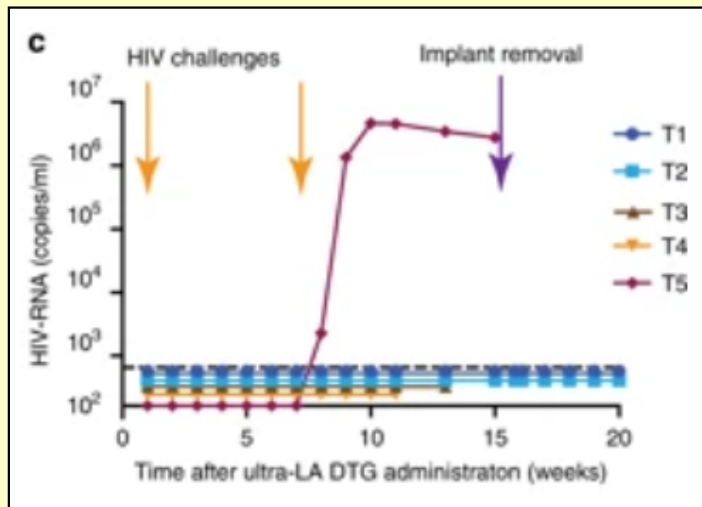
Kovarova M et al., Nature Communications 2018  
Van Lunzen Lancet ID 2012  
Reese et al Drug Metab Disp 2013

Slide Courtesy of Ethel Weld

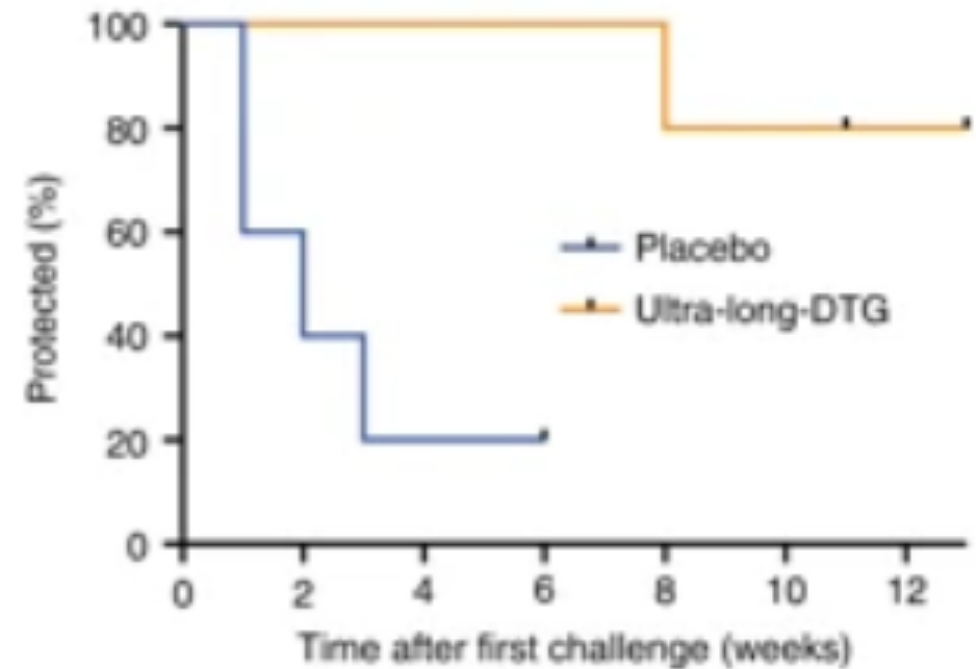


# Ultra LA DTG Antiviral Effect

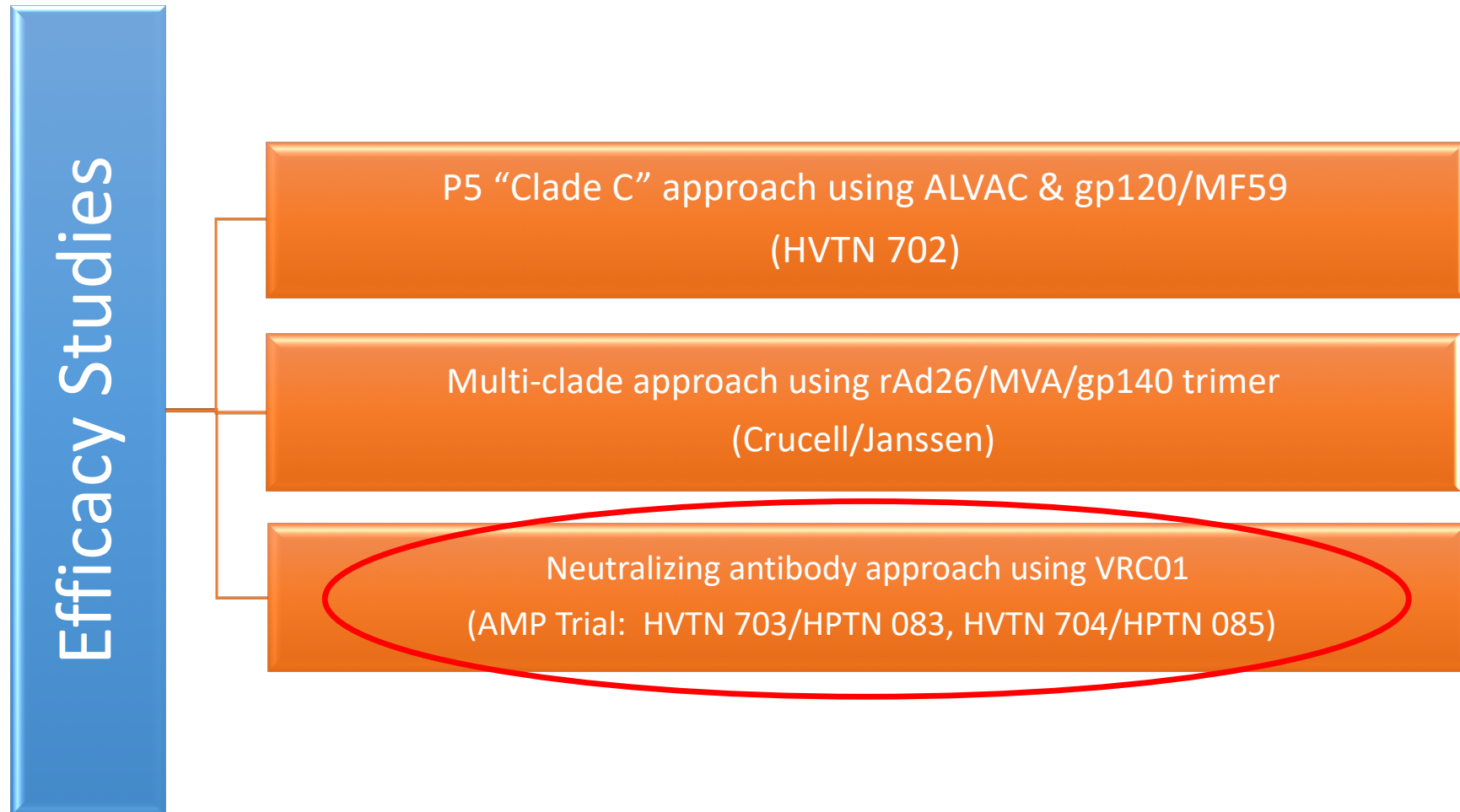
- BLT mice challenge



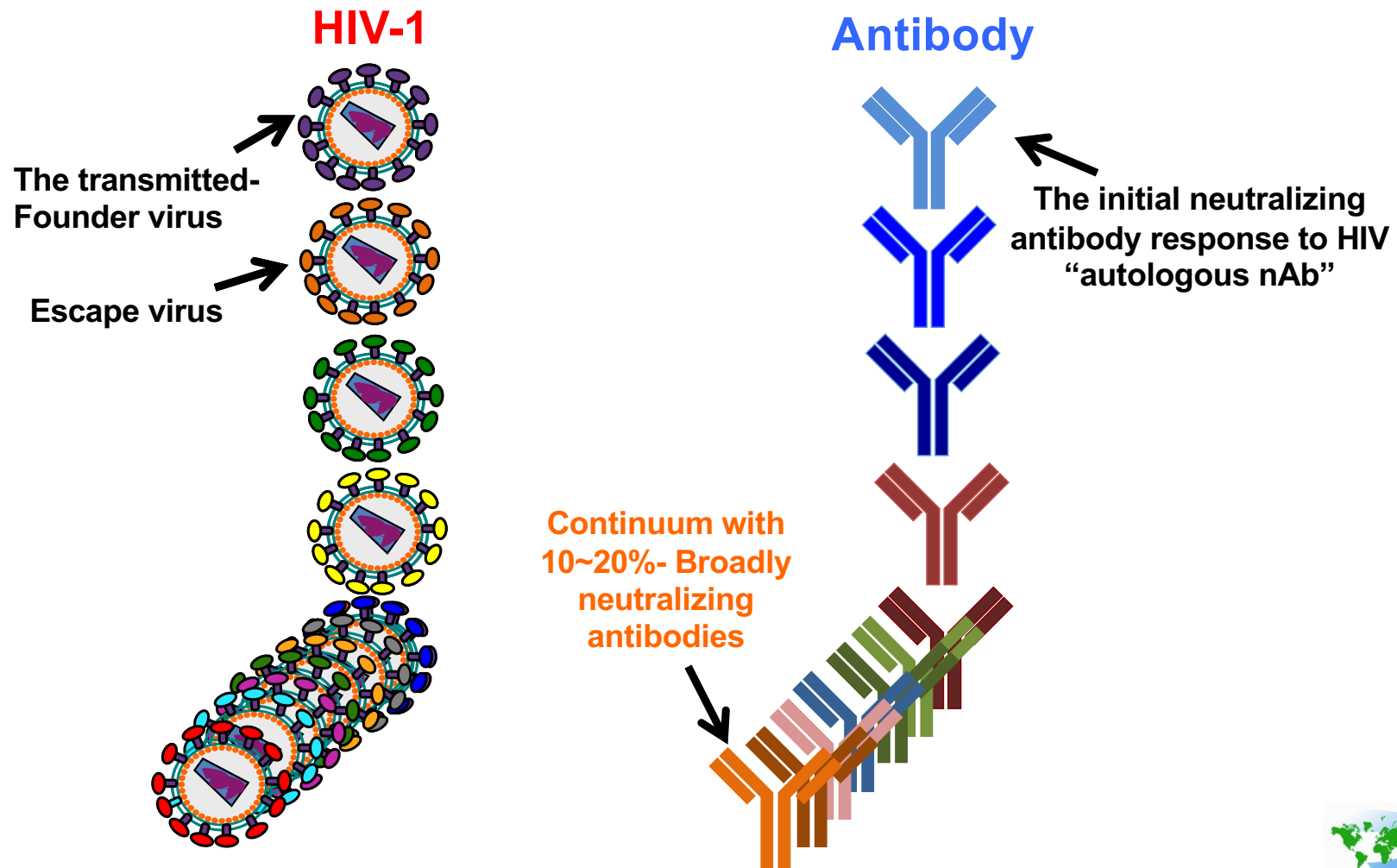
- 80% protection from repeated vaginal challenge (positive controls 4/5 HIV+)



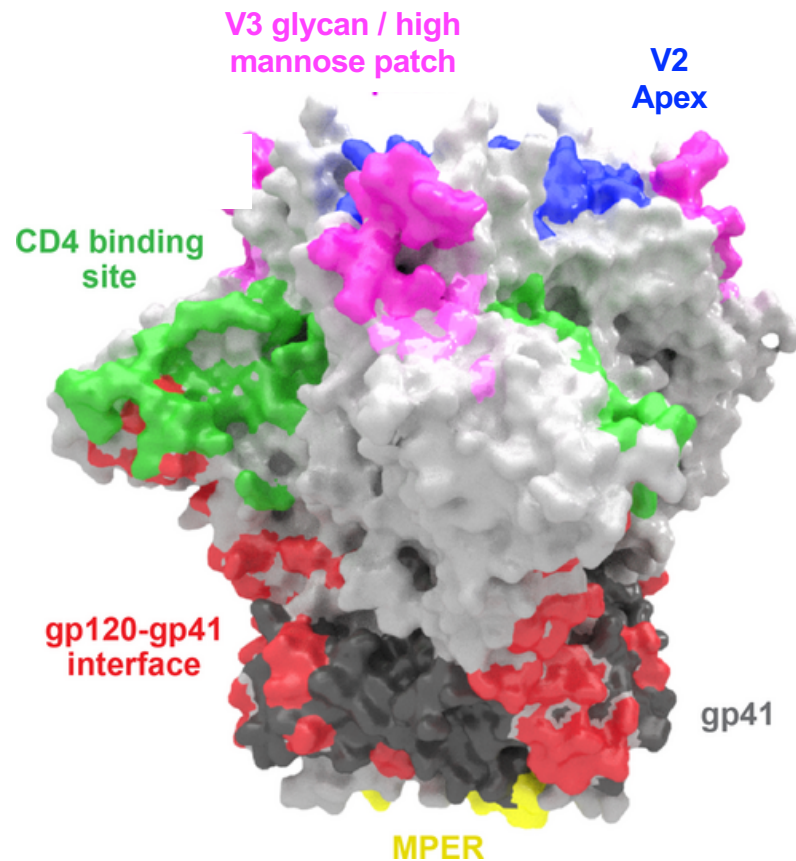
# Vaccine Strategies 2019



# Development of Broad Neutralizing Antibodies (BnABs)



# bnAb Activities



HIV-1 Trimer

## CD4bs

- VRC01, VRC07.523LS, 3BNC117, N6

## V3 glycan

- 10-1074

## MPER

- 10E8

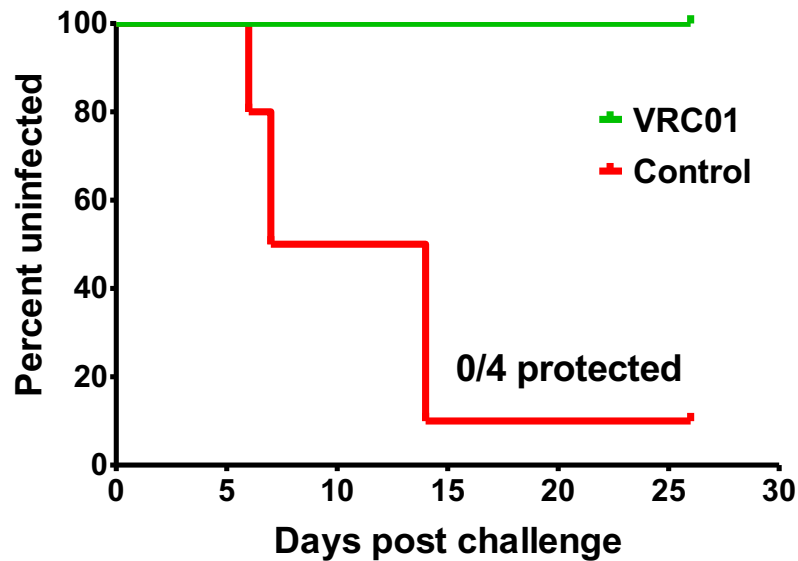
## V2 glycan/Apex

- CAP256

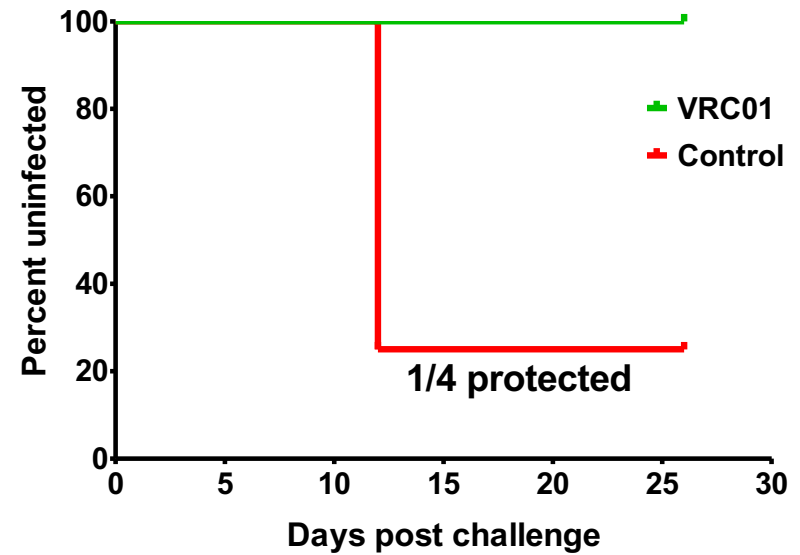
# VRC01 Protects against Mucosal SHIV162P3 Challenge in NHP

20 mg/kg infusion of VRC01

**RECTAL CHALLENGE**  
4/4 protected



**VAGINAL CHALLENGE**  
4/4 protected



# The AMP Studies: Phase 2b Proof-of-Concept Trials Designed to Test the Efficacy of VRC01 Antibody to Prevent HIV Acquisition

**AMP = Antibody Mediated Prevention**

**Two harmonized protocols**

**HVTN 704/HPTN 085**

**(MSM and TG in the Americas &  
Europe)**



**HVTN 703/HPTN 081**

**(Women in sub-Saharan Africa)**



# The AMP Studies: phase 2b proof of concept trials designed to test the efficacy of VRC01 antibody to prevent HIV acquisition

AMP = Antibody Mediated Prevention

## Two harmonized protocols:

- HVTN 704/HPTN 085 (MSM and TG in the Americas & Europe)
  - HVTN 703/HPTN 081 (Women in sub-Saharan Africa)

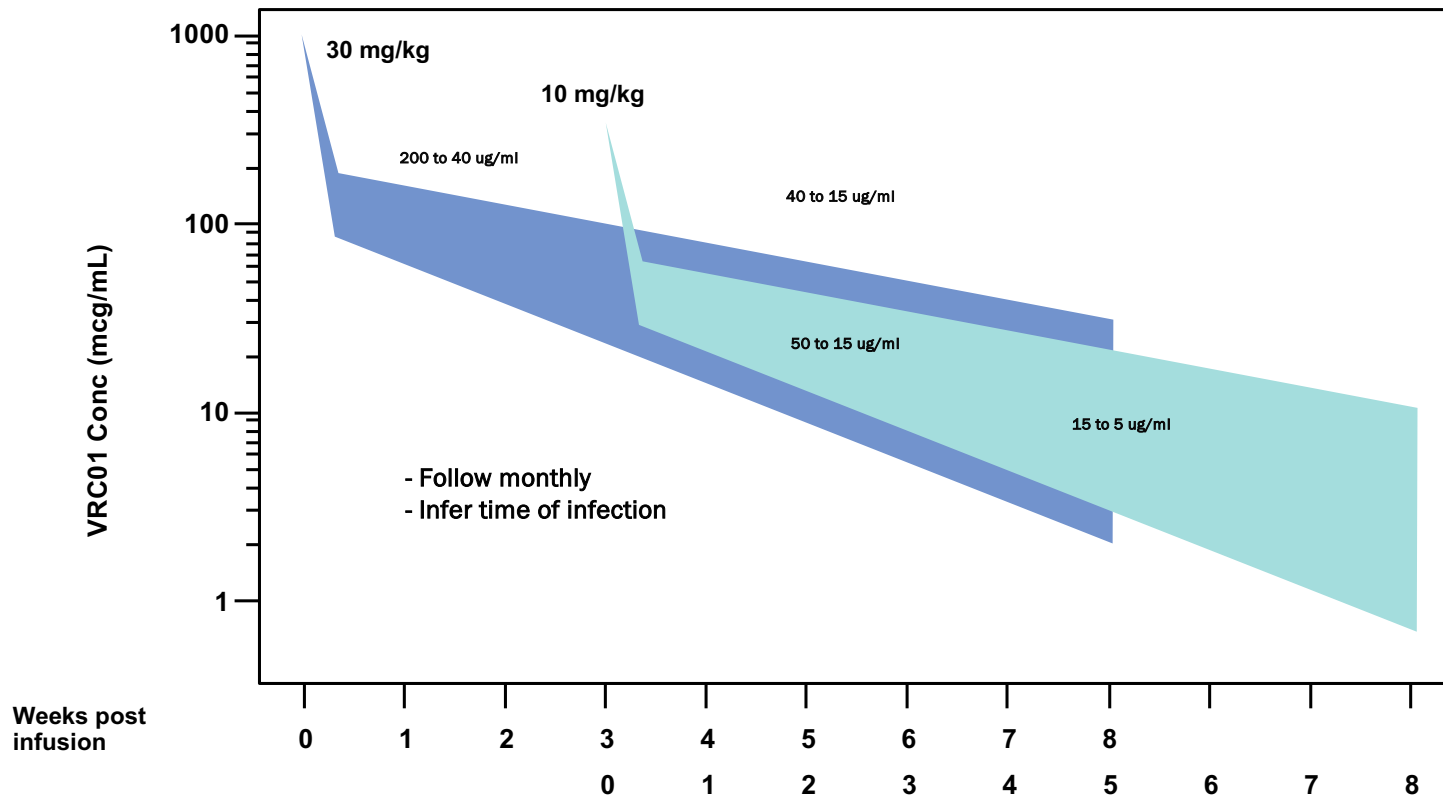


## The AMP Studies: Highlights

Cohort	IV Treatment	n=	Schedule
North + South American MSM (2400) HVTN 704 / HPTN 085	VRC01 10 mg/kg	800	Every 8 wks x 10 doses
	VRC01 30 mg/kg	800	
	Placebo Control	800	
Sub-Saharan African women (1500) HVTN 703 / HPTN 081	VRC01 10 mg/kg	500	Every 8 wks x 10 doses
	VRC01 30 mg/kg	500	
	Placebo Control	500	

- **Two different infusion doses:**  
Important to know if lower dose of 10 mg/kg can protect
- **Powered to associate mAb serum level with protection**

# Study Designed with two dosages to span a range of VRC01 concentrations and power to detect reduced acquisition and sieving



## Sieving:

All infection viral Envs are cloned and tested for neutralization sensitivity to VR01

Does VRC01 have the ability to exclude acquisition of HIV variants deemed as “sensitive” to the antibody



# bNAbs

## First-Gen: VRC01

(HVTN 703/ HPTN 081 & HVTN 704/HPTN 085)

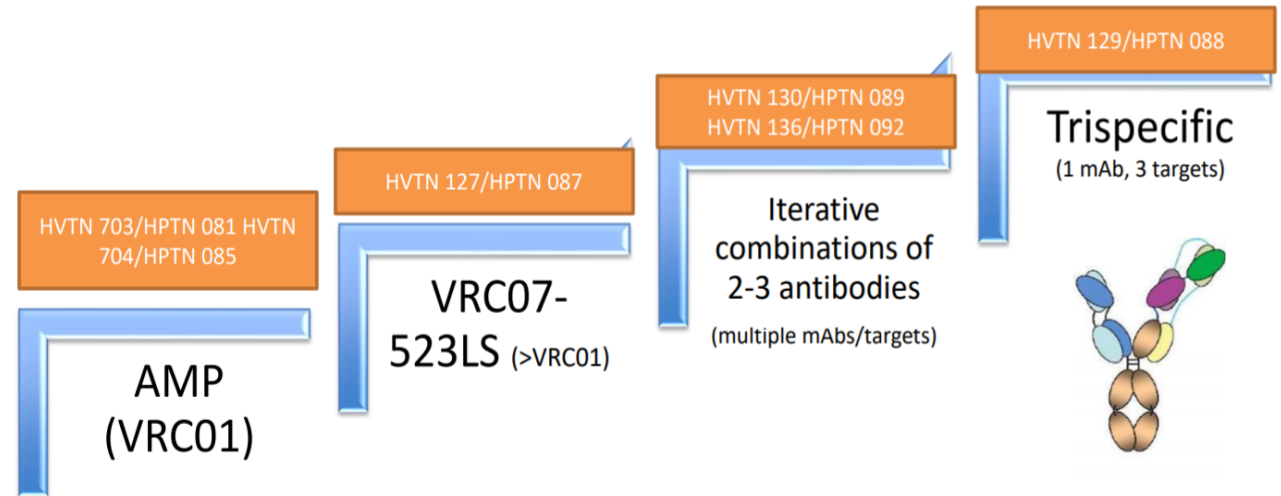
### Primary Objectives:

- Safety
- **Efficacy (Week 80)**

### Secondary Objectives:

- **VRC01 concentration**
- mAb effector functions
- Genotypes/ effector functions/ sensitivity to neutralization of breakthroughs

**Next-gen bNAbs:** re-engineered, more potent VRC07, combos of mAbs, combos of bnAbs with different specificities into single molecule, trispecific mAbs



# The Big Picture

- HIV prevention research results are driving global HIV prevention
- TASP and PrEP need to find their way(s) to INTEGRATED STRATEGIES
- Global HIV Prevention remains too unfocused for maximal benefit
- US End the Epidemic is a major attempt at an integrated strategy

THANK YOU FOR LISTENING

