HIV Prevention Without A Vaccine

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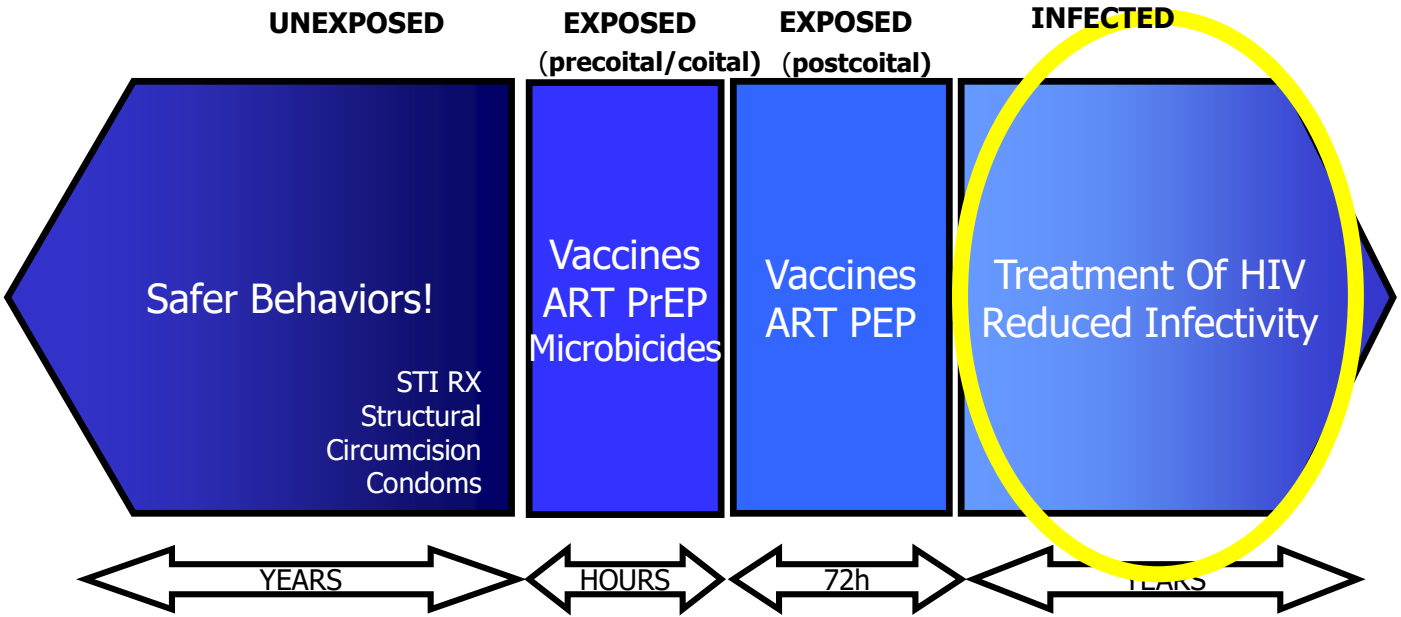
Associate Vice Chancellor for Global Heath

Four Prevention Opportunities

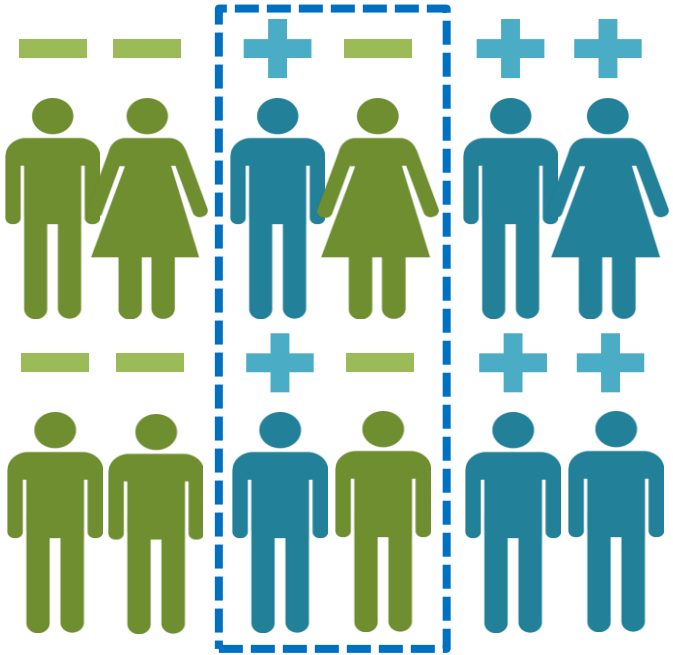
Cohen et al, JCI, 2008
Cohen IAS 2008



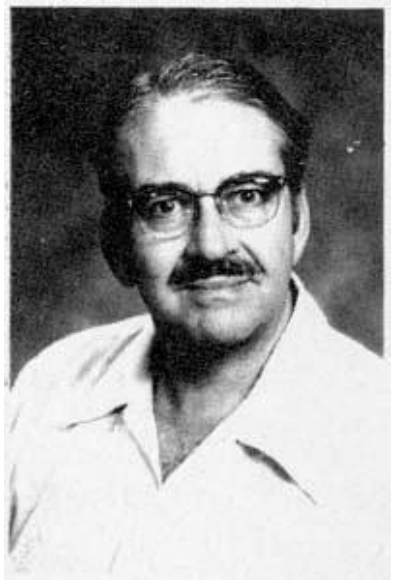
A Simple Prevention Idea

Reduce HIV in genital secretions with ART!

Could HIV transmission be prevented in discordant couples?



Proving the negative:
Difficult, if not impossible



"In some circumstances it can be safely assumed that if a certain event had occurred, evidence of it could be discovered by qualified investigators.

In such circumstances it is perfectly reasonable to take the ***absence of proof of its occurrence*** as positive proof of its non-occurrence."

Copi, Introduction to Logic (1953), p. 95

Summarized by Dr. Pietro Vernazza

UNDETECTABLE = UNTRANSMITTABLE

Prevention Access Campaign

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2019 VOL. 381 NO. 3

ORIGINAL ARTICLE

Effect of Universal Testing and Treatment HIV Incidence — HPTN 071 (PopART)

R.J. Hayes, D. Donnell, S. Floyd, N. Mandla, J. Bwalya, K. Sabapathy, et al.

EDITORIAL

HIV-1 Epidemic Control –

Salim S. Abdool Karim, M.B., Ch.B., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana

J. Makhema, K.E. Wirth, M. Pretorius Holme, T. Gaolathe, M. Mmalane, et al.

ORIGINAL ARTICLE

HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

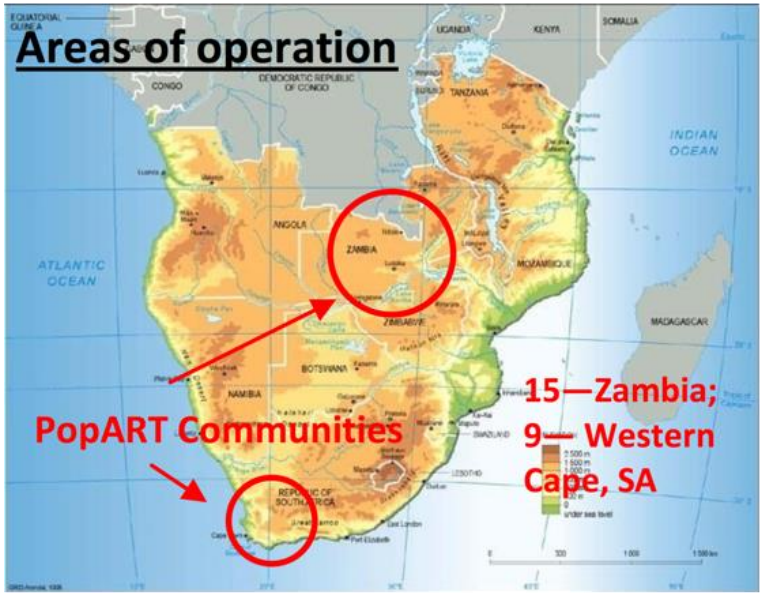
D.V. Havlir, L.B. Balzer, E.D. Charlebois, T.D. Clark, D. Kwarisiima, J. Ayieko, et al.

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

Universal testing and universal treatment, to reduce HIV incidence.



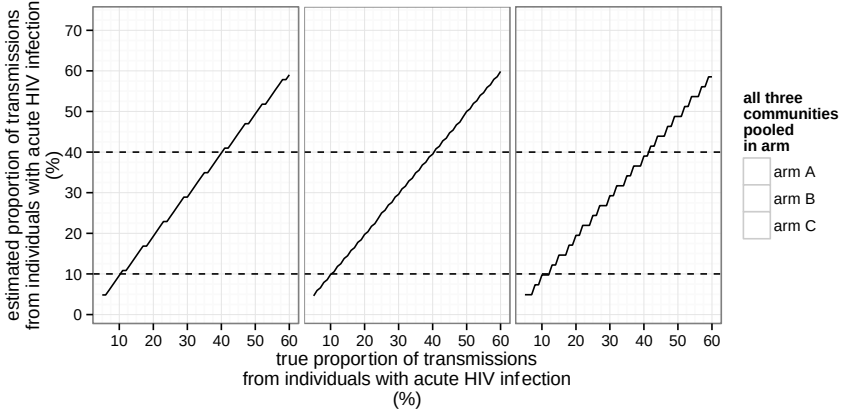
- 1.2m individuals
- 21 communities 25,000-125,000
- HIV+ 15-25%
- HIV+ on ART 15-30%
- HIV incidence ~1.5%

Approaching end of year 3 of intervention, will end after 4 years of intervention (3 years of follow up)

Molecular Epidemiology to Inform HIV Prevention

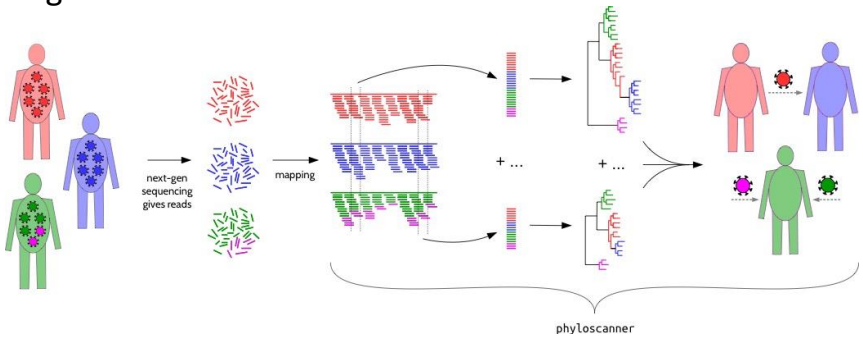
PopART HPTN 071

Study is powered based on detecting transmission events



Example: power for primary aim 1

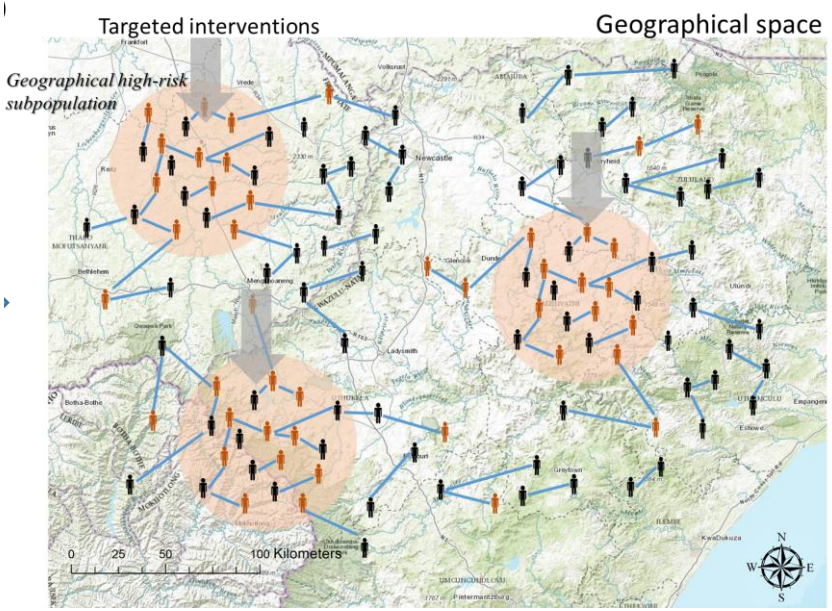
Using new methods for detecting transmission events (with direction) using deep-sequence whole genome data:

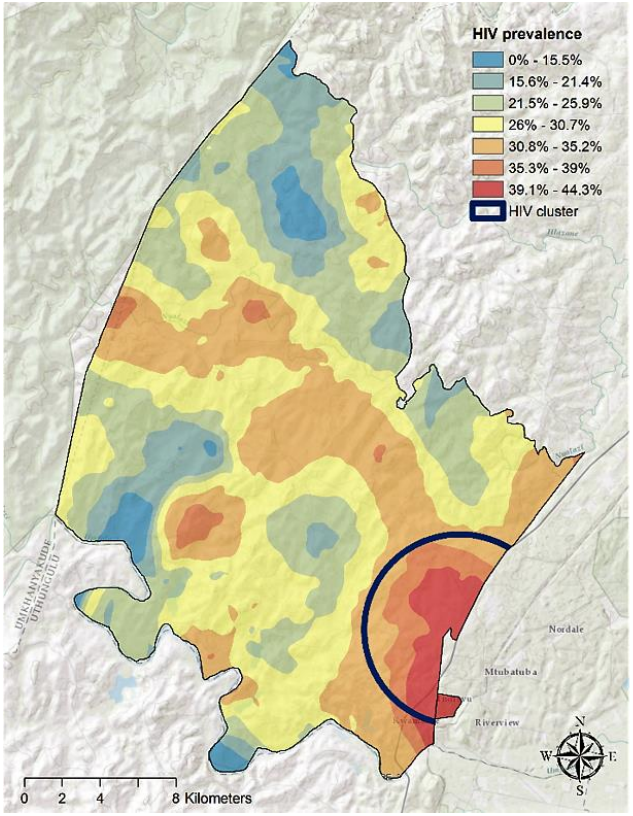


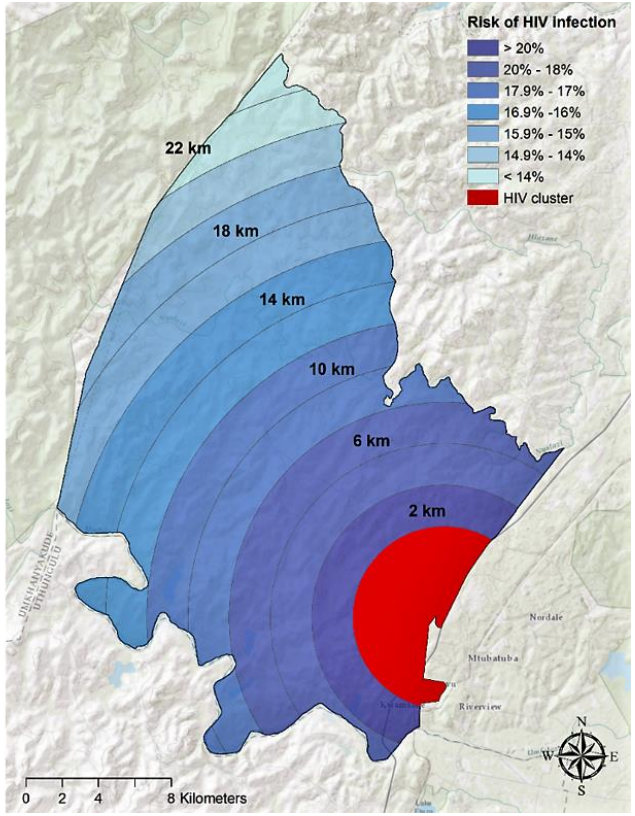
Wymant et al Biorxiv 2017

Geographical space

- HIV ‘hot-spots’ can behave as the highly connected nodes of in the transmission network




HIV prevalence
0% - 15.5%
15.6% - 21.4%
21.5% - 25.9%
26% - 30.7%
30.8% - 35.2%
35.3% - 39%
39.1% - 44.3%
HIV cluster
Nordale
Mtubatuba
Riverview
0 2 4 8 Kilometers
N
W
E
S


Risk of HIV infection
> 20%
20% - 18%
17.9% - 17%
16.9% -16%
15.9% - 15%
14.9% - 14%
< 14%
HIV cluster
22 km
18 km
14 km
10 km
6 km
2 km
Nordale
Mtubatuba
Riverview
0 2 4 8 Kilometers
N
W
E
S

Phylogenetic Analysis and Attributable Risk HPTN 071 Zambia Communities (PANGEA)

- Resistance (?)
- Untreated People (?)

  -acute HIV (?)

  -”in-migration” into a community (?)

  -young men as a key population (?)

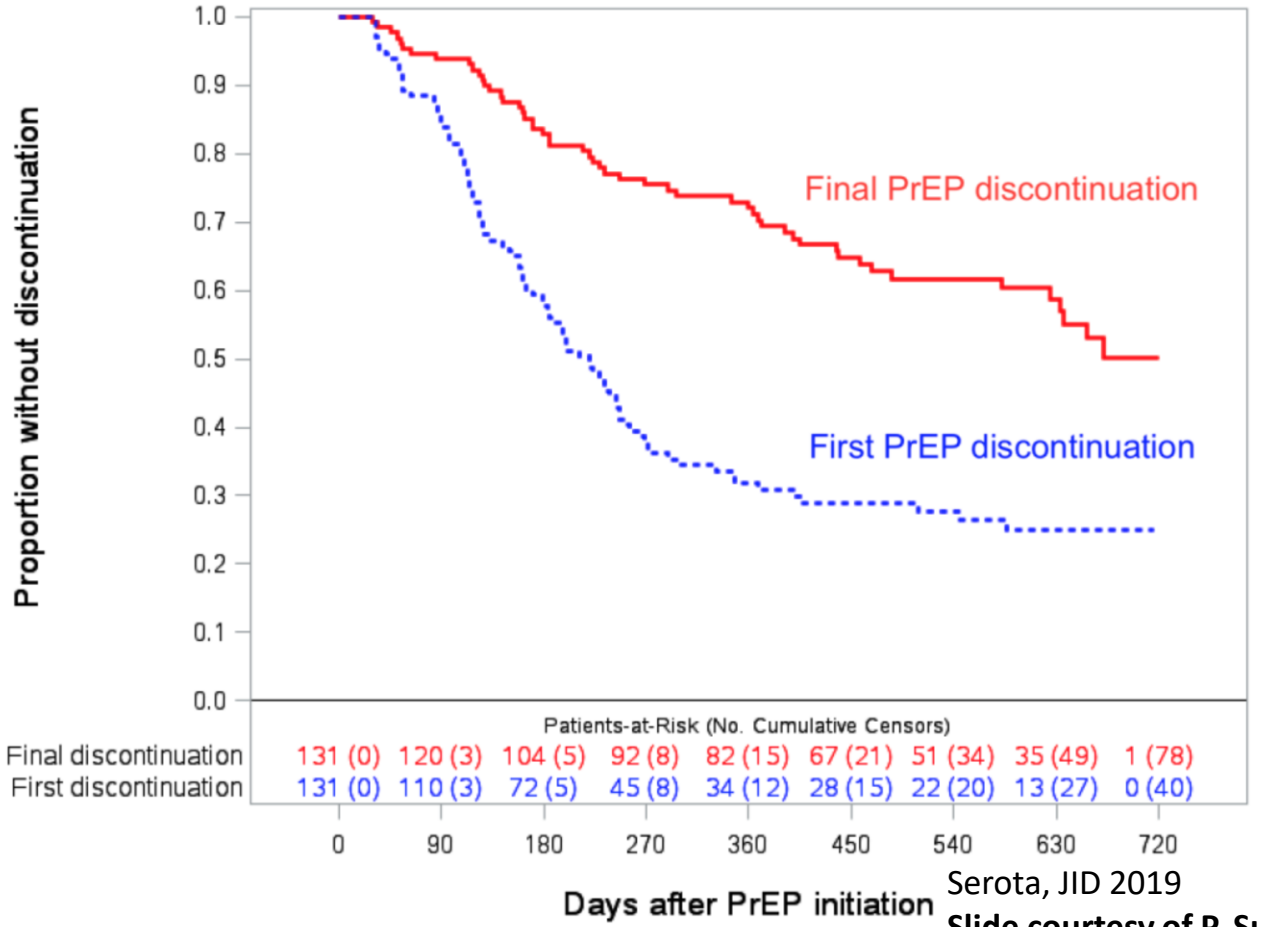
TDF/FTC was FDA Approved for use for Prevention on July 16, 2012

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?



Serota, JID 2019

Slide courtesy of P. Sullivan

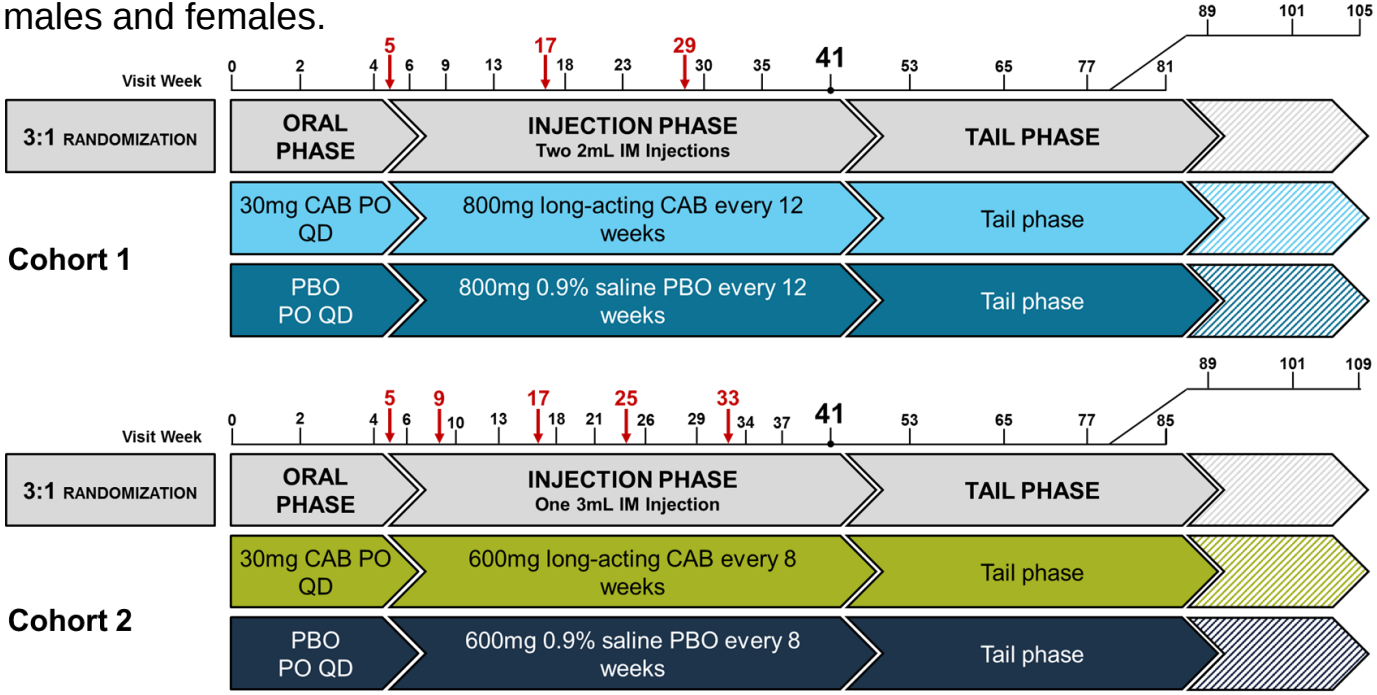
Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

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

PLoS Med. 2018 Nov 8;15(11):e1002690

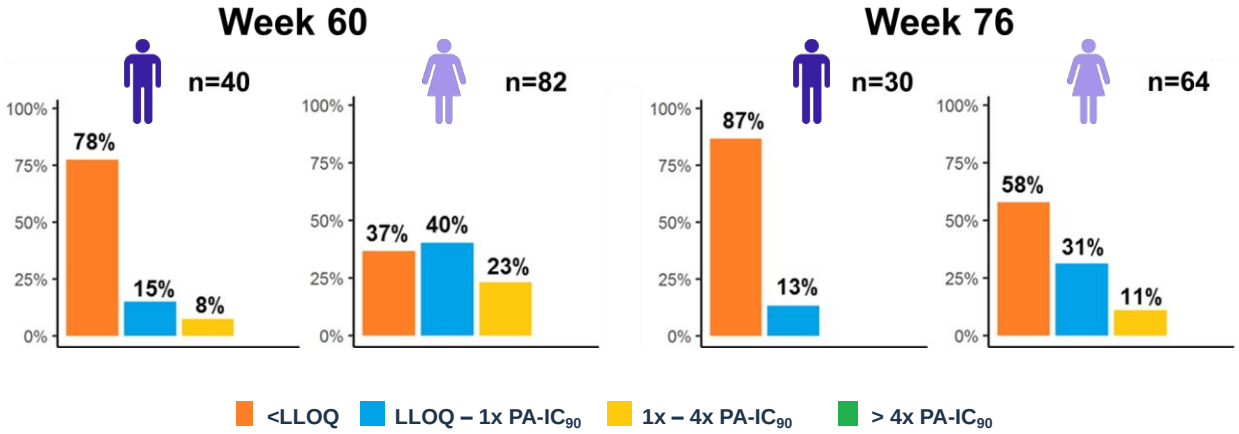
CAB LA in Development: HPTN 077

Objective: To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.



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

CAB LA Pharmacokinetic Tail

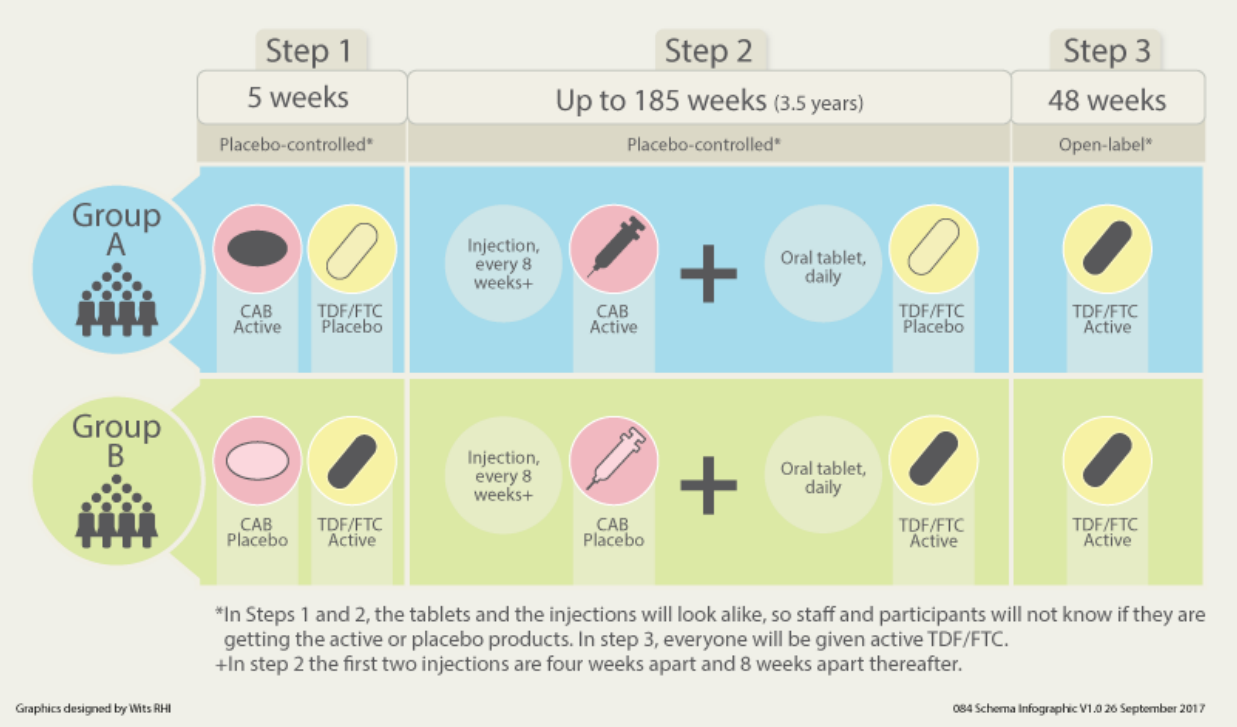


Median time to LLOQ, weeks (range)	42.7 (20.4, 134)	66.3 (17.7, 182)

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

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
HIV Prevention
Trials Network

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

Status of Enrollment: n=4500

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

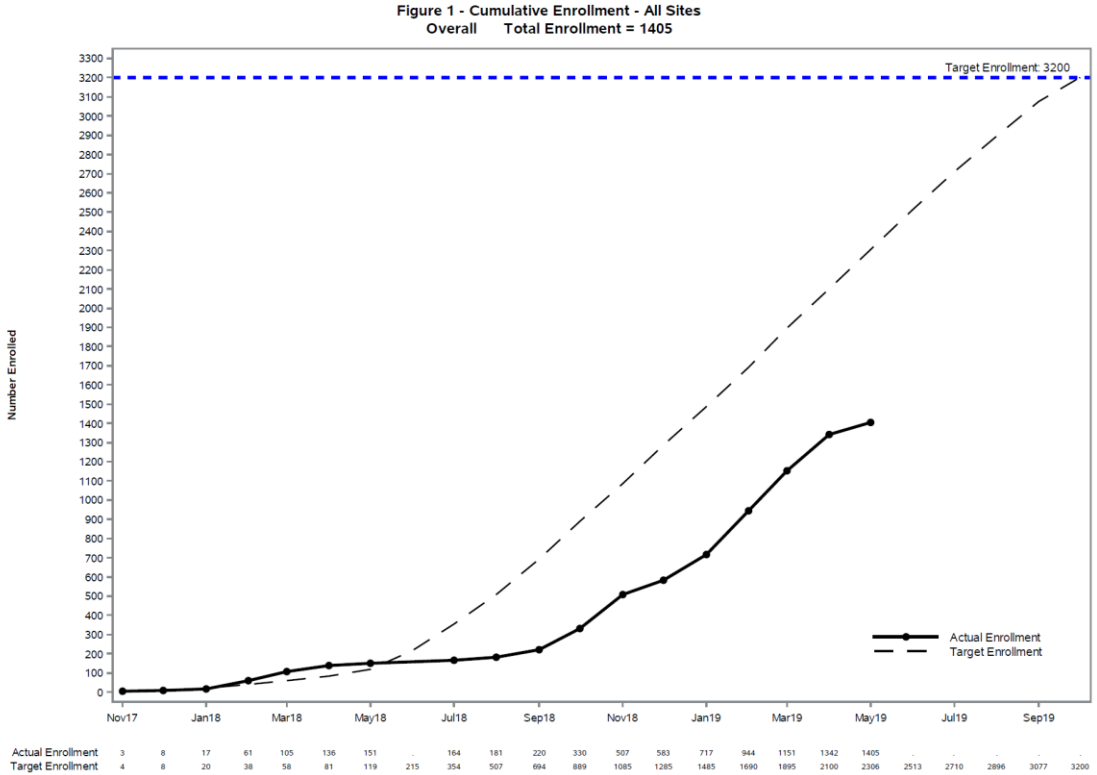
The study is essentially fully enrolled (!!) with consideration of additional enrollment

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

Enrollment



- Current enrolment n=2178
- Since activation of all 20 sites, average enrolment/month 160
- Accrual targeted to complete e/o April 2020

Source: SDMC, data to May 16, 2019

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”

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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

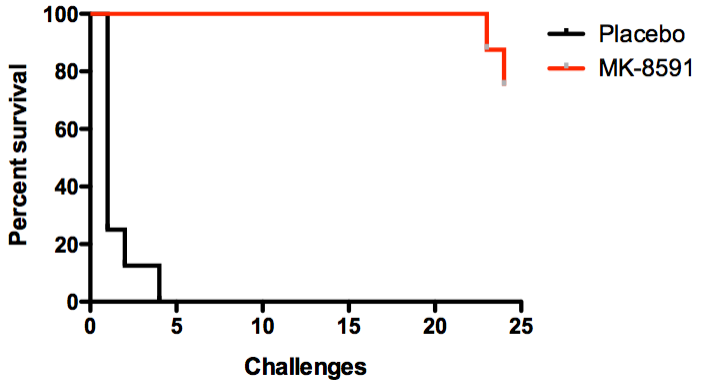
Recruitment Status : Not yet recruiting

First Posted : July 1, 2019

Last Update Posted : August 15, 2019

See **Contacts and Locations**

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

LA Implants

Matrix vs. Reservoir

Renewable vs. biodegradable

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

TAF Implant: silicone/PVA

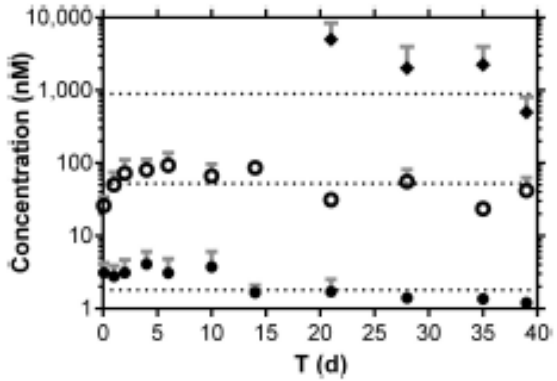


FIG 3 Subdermal implantation of TAF LA prototype device in beagle dogs maintains sustained drug levels with low systemic exposure to TAF and TFV with concomitant, efficient PBMC loading with TFV-DP. Pharmacokinetic profiles of plasma TAF (closed circles) and TFV (open circles) and PBMC TFV-DP (closed diamonds). Each data point represents the means ± standard deviations from four beagle dogs, and dotted lines correspond to the median concentrations for each analyte over the 40-day study. Note that TFV-DP levels were measured only after day 20.

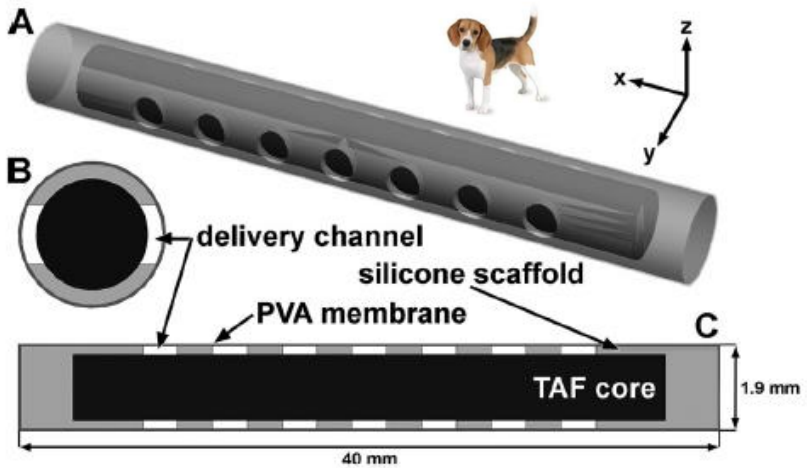
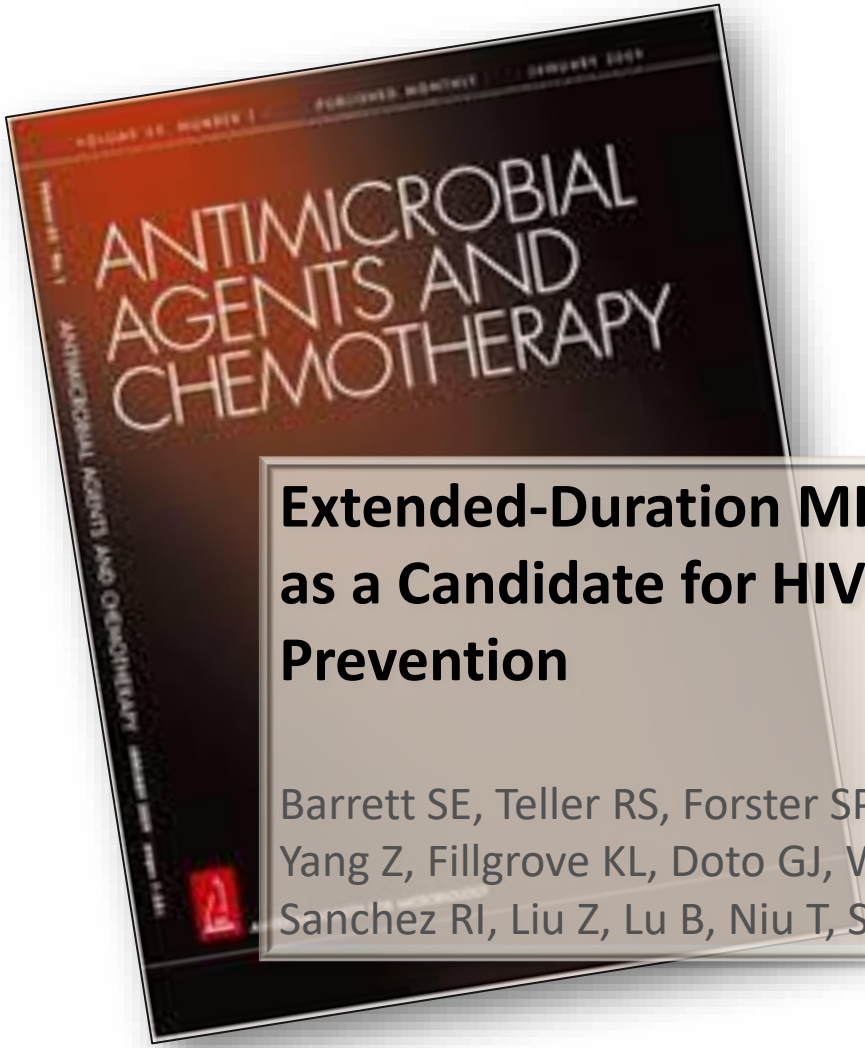


FIG 1 Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the *y-z* (B) and *x-y* planes (C).

M Gunawardana et al., *Antimicrob Agents Chemother* 2015; 59: 3913

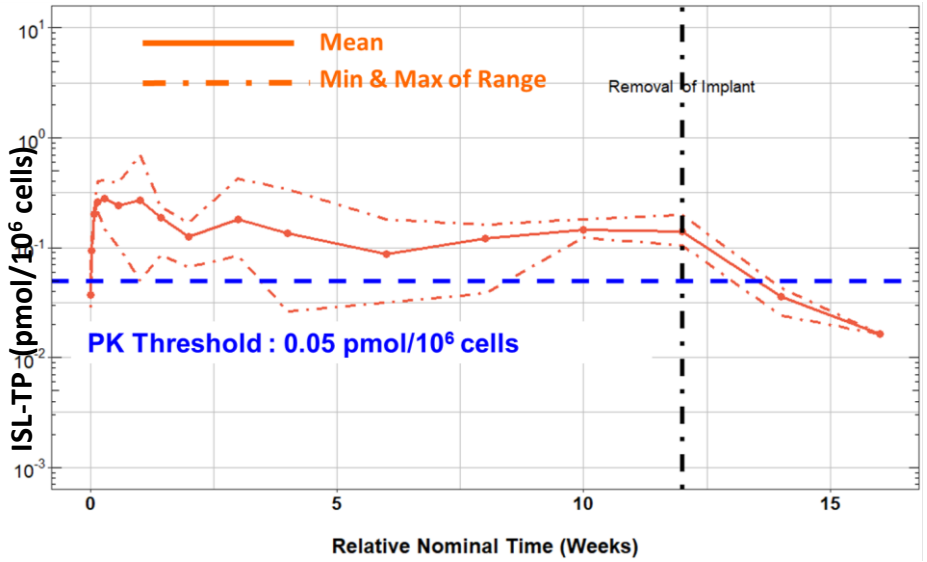


Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

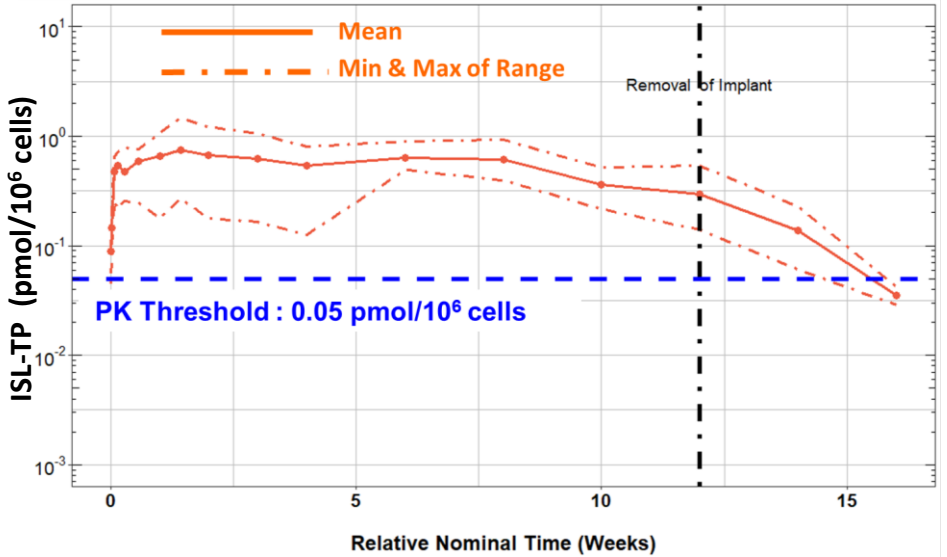
Barrett SE, Teller RS, Forster SP, Li L, Mackey MA, Skomski D, Yang Z, Fillgrove KL, Doto GJ, Wood SL, Lebron J, Grobler JA, Sanchez RI, Liu Z, Lu B, Niu T, Sun L, Gindy ME

Antimicrob Agents Chemother. 2018 Sep 24;62(10)

ISL-TP Target Maintained ≥12 months



62 mg Implant



- Ratio of TP/plasma remains fairly constant at ~1000:1 – consistent with oral dosing
- Half-life after removal of implant similar to half-life of orally dosed ISL

Matthews R., TUAC0401LB IAS 2019 (Mexico City)

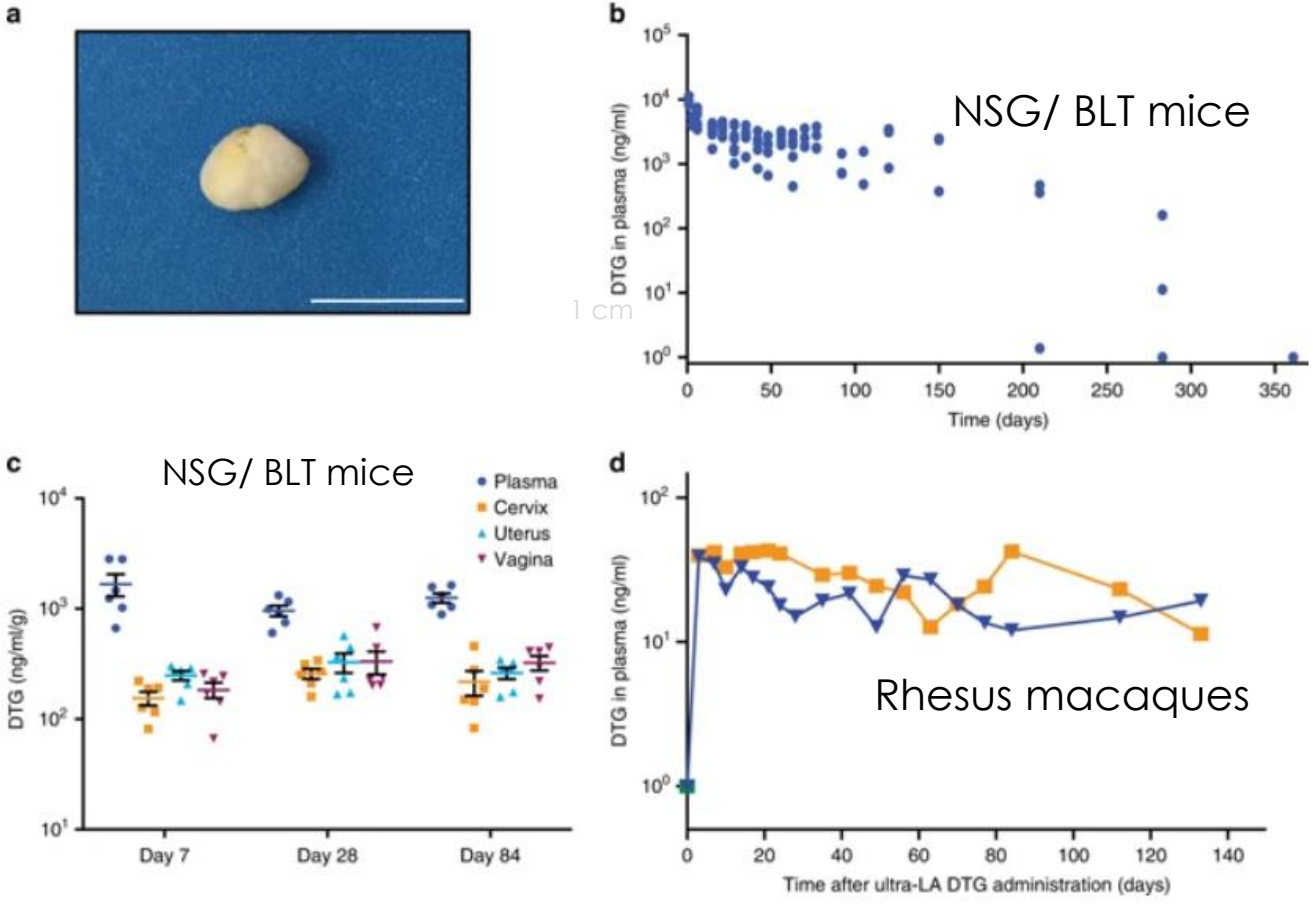
Ultra Long-Acting Dolutegravir (sol-gel)

What is PrEP [DTG] target?

- **[DTG]should be ≥ 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., Ultra-long-acting removable drug delivery system for HIV treatment and prevention. *Nature Communications* **9**, Article number: 4156 (2018). SPRING-1 Van Lunzen Lancet ID 2012; Reese et al Drug Metab Disp (2013) 41: 353.

Slide Courtesy of Ethel Weld



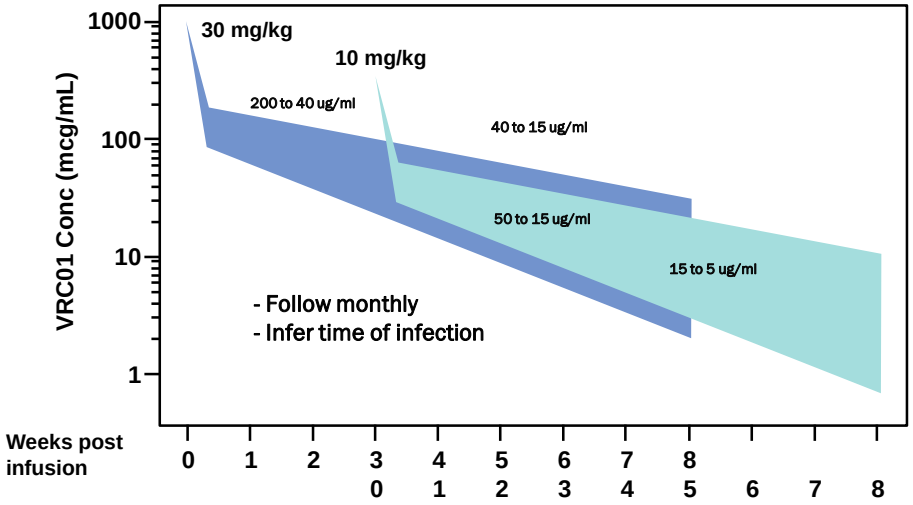
The AMP Studies: phase 2b proof of concept trials designed to test the efficacy of VRC01 antibody to prevent HIV acquisition

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)

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:

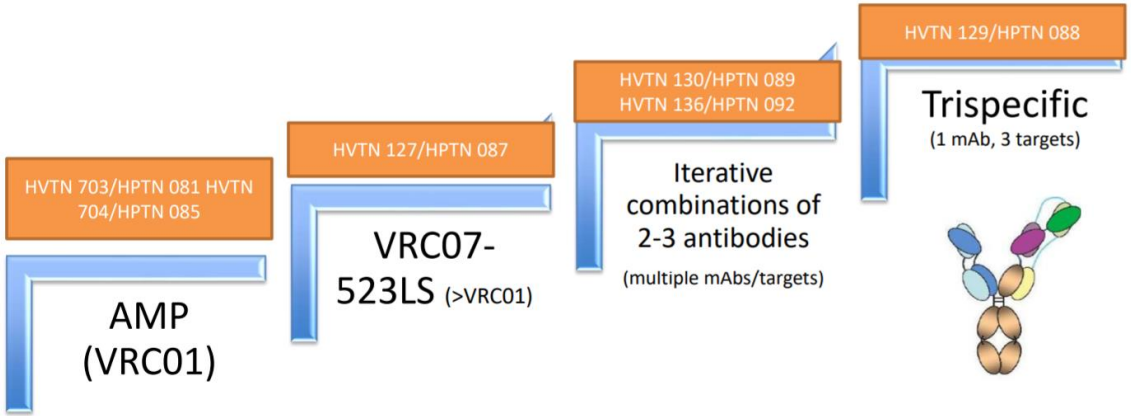
- Safety
- **Efficacy (Week 80)**

Secondary Objectives:

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

Slide courtesy of Ethel Weld

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



http://www.hvtn.org/en/science/HVTN-studies/AMPstudy.html

Ngodi NM, IAS July 2019 (Mexico City)

THANK YOU FOR LISTENING