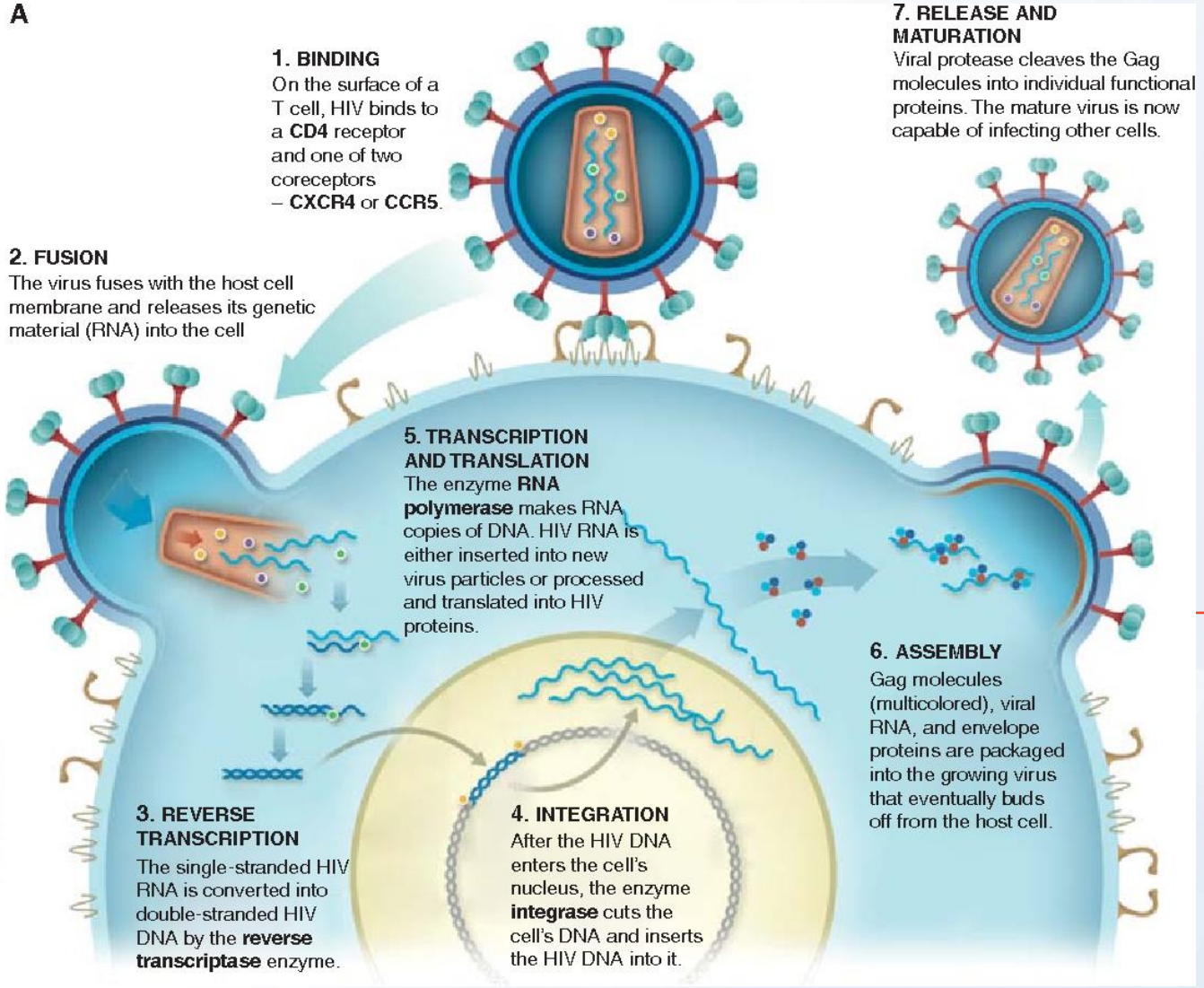
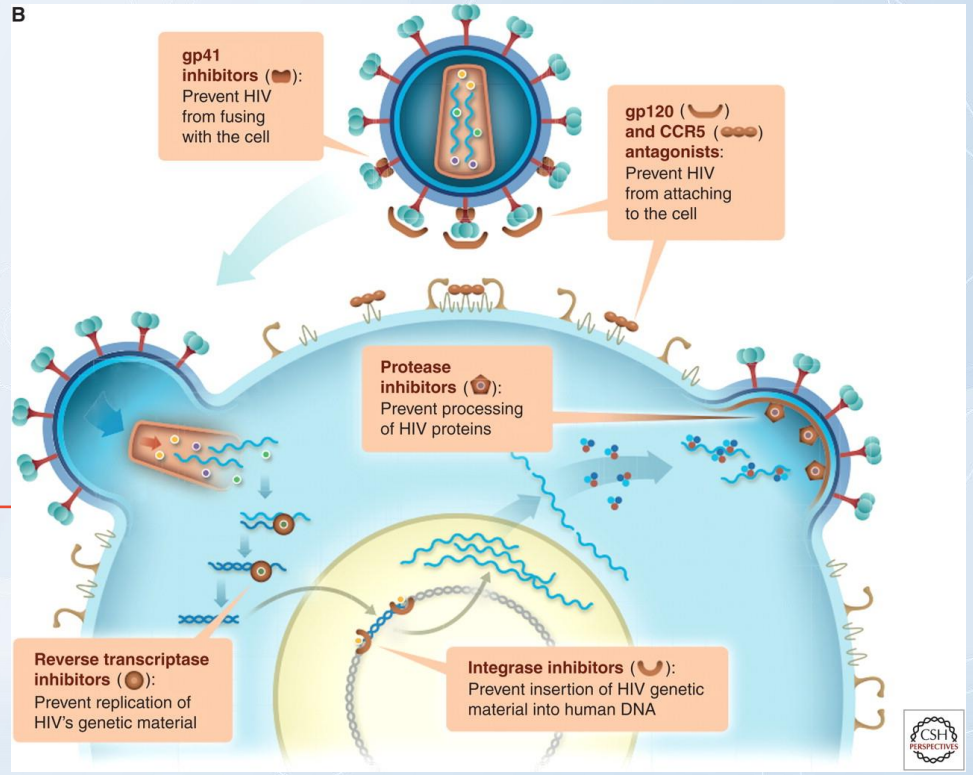
Progress on New Antiretroviral Formulations and Monoclonal Antibodies for HIV Prevention

Nyaradzo M Mgodi (MBChB, MMed)
Principal Investigator
University of Zimbabwe
Clinical Trials Research Centre
nmgodi@uz-ctrc.org

HIV life cycle and mechanism of action of antiretrovirals



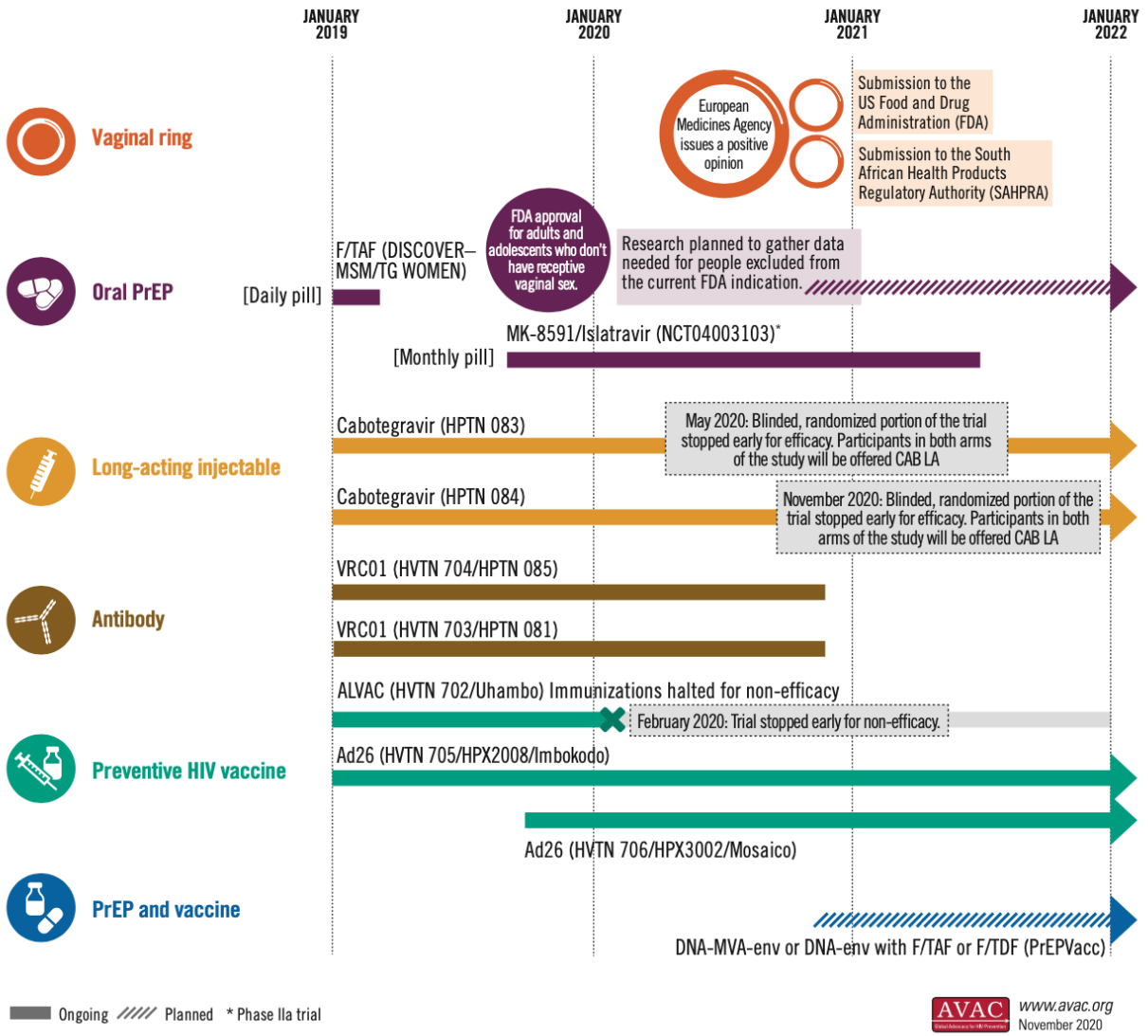


Robin J. Shattock, and Zeda Rosenberg Cold Spring Harb Perspect Med 2012;2:a007385

Advances in HIV/AIDS Management

- Tremendous advances in HIV prevention, diagnostics, and treatment have been made over the last 40 years since HIV-1 was identified
- ART has led to a dramatic shift of AIDS from a fatal disease into a chronic and often stable medical condition
- Antiretroviral drugs are also useful in the prevention field as PEP, PPTCT, TasP and PrEP.
- Long acting injectable products and antiretroviral-based microbicides are currently in late stages of clinical development or regulatory approval
- Gene therapy and the use of bnAbs are also promising approaches to HIV/AIDS management
- On-going or planned research on other novel drug delivery systems

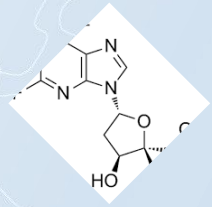
Biomedical HIV Prevention Trials: Results, milestones and more



New Antiretroviral Formulations and Monoclonal Antibodies for HIV Prevention

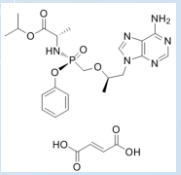
- Oral PrEP
  - Islatravir
  - Tenofovir alafenamide fumarate
- Dapivirine Vaginal Ring
- Long acting Injectable Cabotegravir
- Monoclonal antibodies - VRC01
- Other novel drug delivery systems

Islatravir (EFdA, MK-8591, Merck)



- A First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor with multiple mechanisms of action.
- Intracellularly, ISL is converted to its active triphosphate form which inhibits HIV reverse transcriptase through multiple modes of action.
- Has high potency against HIV-1, HIV-2 and multidrug-resistant variants.
- 10 times as potent as any previous HIV drug hence small doses are effective –
  - Lowers the risk of side effects.
- High barrier to resistance.
- A slow-release yearly implant based on Implanon®/Nexplanon® and once monthly oral dosing could broaden access to PrEP.
- HIV prevention efficacy trial of a long-acting oral ISL among young African women as HIV-1 pre-exposure prophylaxis – MSD/ICRC.

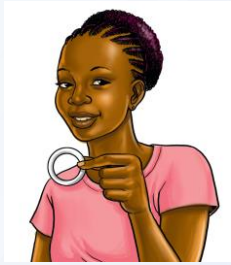
Tenofovir alafenamide fumarate, TAF



- TAF is a prodrug of tenofovir, like Tenofovir disoproxil fumarate (TDF)
- Nucleoside Reverse Transcriptase Inhibitors
- TAF used in combination with Emtricitabine (F/TAF) as an agent for HIV pre-exposure prophylaxis (PrEP).
- TDF is associated with changes in markers of renal function, decreases in bone mineral density and renal toxicity due to high circulating levels of Tenofovir
- TAF is rapidly activated in cells to produce tenofovir disphosphate in HIV-target cell at substantially reduced oral doses of TFV.
- TAF provides effective therapy with approximately 90% lower systemic exposure to tenofovir and therefore improved safety
- Gilead's Phase III Descovy trial in women
- CONRAD's Phase II trial in AGYW - SSA

Dapivirine Vaginal Ring (IPM)

Long-acting PrEP formulated as a flexible silicone ring that slowly releases the antiretroviral dapivirine



- Potential for *better adherence*
- Long acting, strong safety profile
- No related resistance
- Discreet -woman-initiated and controlled.
- Easy to use, scalable

ASPIRE

THE RING STUDY
Developing HIV Prevention for Women

Baeten et al., Nel et al., NEJM 2016

HOPE and DREAM results suggest **interest in**, **adherence to**, **safety** and **effectiveness of** the dapivirine vaginal ring when used in an open-label setting.

Baeten et al., IAS 2019, Nel et al., SA AIDS 2019

HOPE
Out of ASPIRE, there is HOPE

DREAM
Dapivirine Ring Extended Access and Monitoring

Seeking Approval of the Dapivirine Ring

Regulatory Process

IPM applied for approval through European, African and US regulatory authorities

Additional Research

Safety studies of ring and PrEP among adolescent girls, pregnant and breastfeeding women in Africa

Potential Introduction

On 24 July 2020, the European Medicines Agency (EMA) announced a positive opinion about the monthly dapivirine vaginal ring for women ages 18 and older.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden

News 24/07/2020

EMA's human medicines committee (CHMP) has adopted a positive opinion for Dapivirine Vaginal Ring (dapivirine) used to reduce the risk of infection with the human immunodeficiency virus type 1 (HIV-1), in combination with safer sex practices when oral pre-exposure prophylaxis (PrEP) is not used, cannot be used or is not available. Placed in the vagina, the ring slowly releases the antiretroviral medicine dapivirine over a period of 28 days.

This is the eleventh medicine recommended by EMA under EU Medicines for all (EU-M4All), a mechanism that allows the CHMP to assess and give opinions on medicines that are intended for use in countries outside the European Union under Article 58 of Regulation (EC) No 726/2004.

As a result, the ring is closer to being considered for approval for use.

This is a major milestone for women's HIV prevention.

This is a first step to making the ring available for use

- The positive EMA opinion is an important step for the ring, but it is not an approval. This opinion opens the door for ring approval in countries in East and Southern Africa.
- The ring will need to be reviewed by regulators in each country and added into country HIV prevention guidelines.
  - This will be done in coordination with the World Health Organization (WHO).
- It may be possible to begin making the ring available as early as 2021 in some countries.
- IPM will also seek approval from the United States Food and Drug Administration (FDA) so that the ring can be available in the US.

This approval does not apply to adolescent girls, pregnant and breastfeeding women. Safety studies in these groups are on-going – so all adolescent girls and women can use the ring to protect themselves against HIV

The REACH, DELIVER and B-PROTECTED Studies

REACH (MTN-034)

Safety and use of the dapivirine ring and oral PrEP in **adolescent girls and young women ages 16-21**

DELIVER (MTN-042)

Safety of the dapivirine ring and oral PrEP in **pregnant women.**

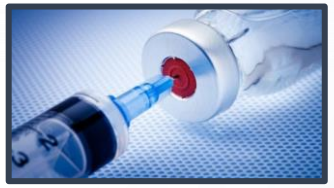
B-PROTECTED (MTN-043)

Safety of the dapivirine ring and oral PrEP in **breastfeeding women**.

Long acting injectable PrEP

Advantages

- Injection every 1-3 months could address adherence issues
- Different drug, not used heavily for treatment -> less concern for resistance/cross-resistance
- People are familiar with injections - highly acceptable
- Women have talked about how injections are more discreet and private than pills or rings



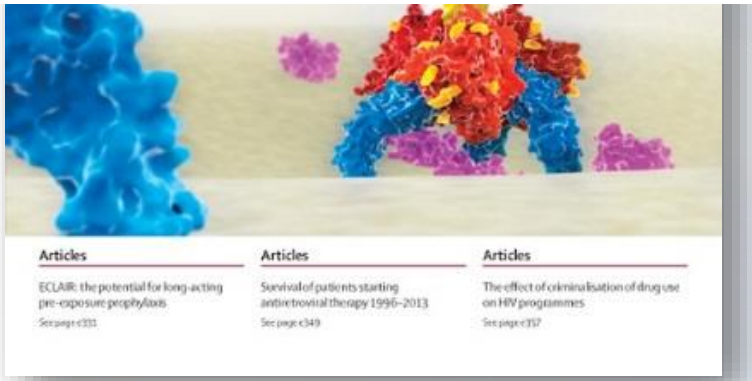
Disadvantages

- Cannot be removed once given
- Confirmation of tolerance before long-acting injection:
  - Oral lead in phase
- Long pharmacologic tail after last injection (up to 48 weeks) → safety and resistance if becomes HIV+
- IM dosing **every** 4 to 8 weeks
- IM injection cannot be removed:
  - Toxicity
  - Desire to stop PrEP

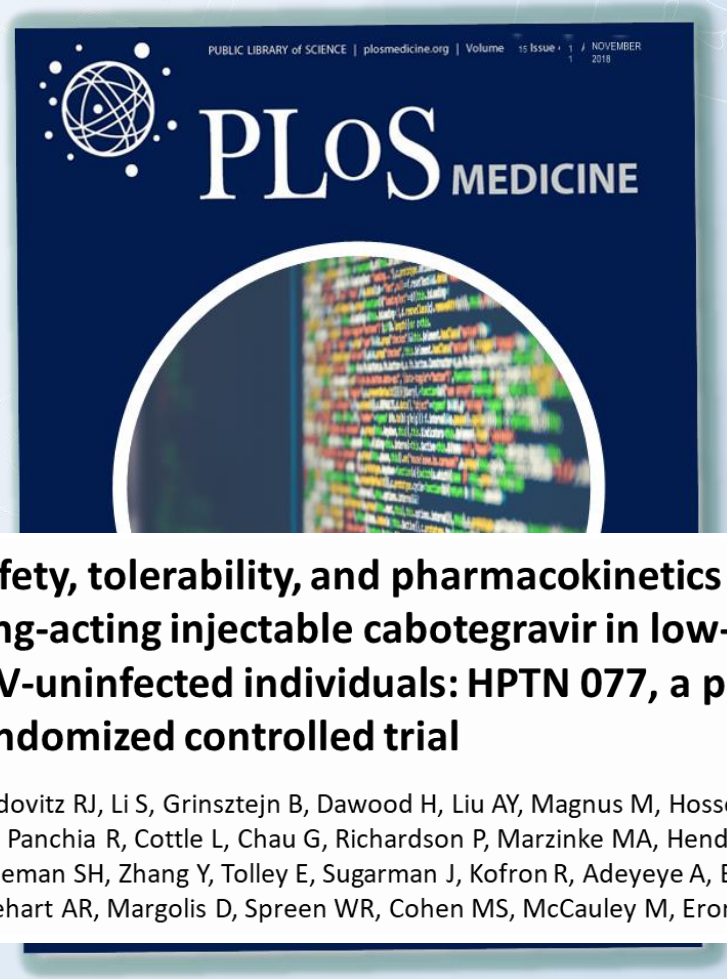
Long-Acting Injectable Cabotegravir (ViiV)

Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial

Martin Markowitz, Ian Frank, Robert M Grant, Kenneth H Mayer, Richard Elion, Deborah Goldstein, Chester Fisher, Magdalena E Sobieszczyk, Joel E Gallant, Hong Van Tieu, Winkler Weinberg, David A Margolis, Krischan J Hudson, Britt S Stancil, Susan L Ford, Parul Patel, Elizabeth Gould, Alex R Rinehart, Kimberly Y Smith, William R Spreen



Lancet HIV. 2017 Aug;4(8):e331-e340



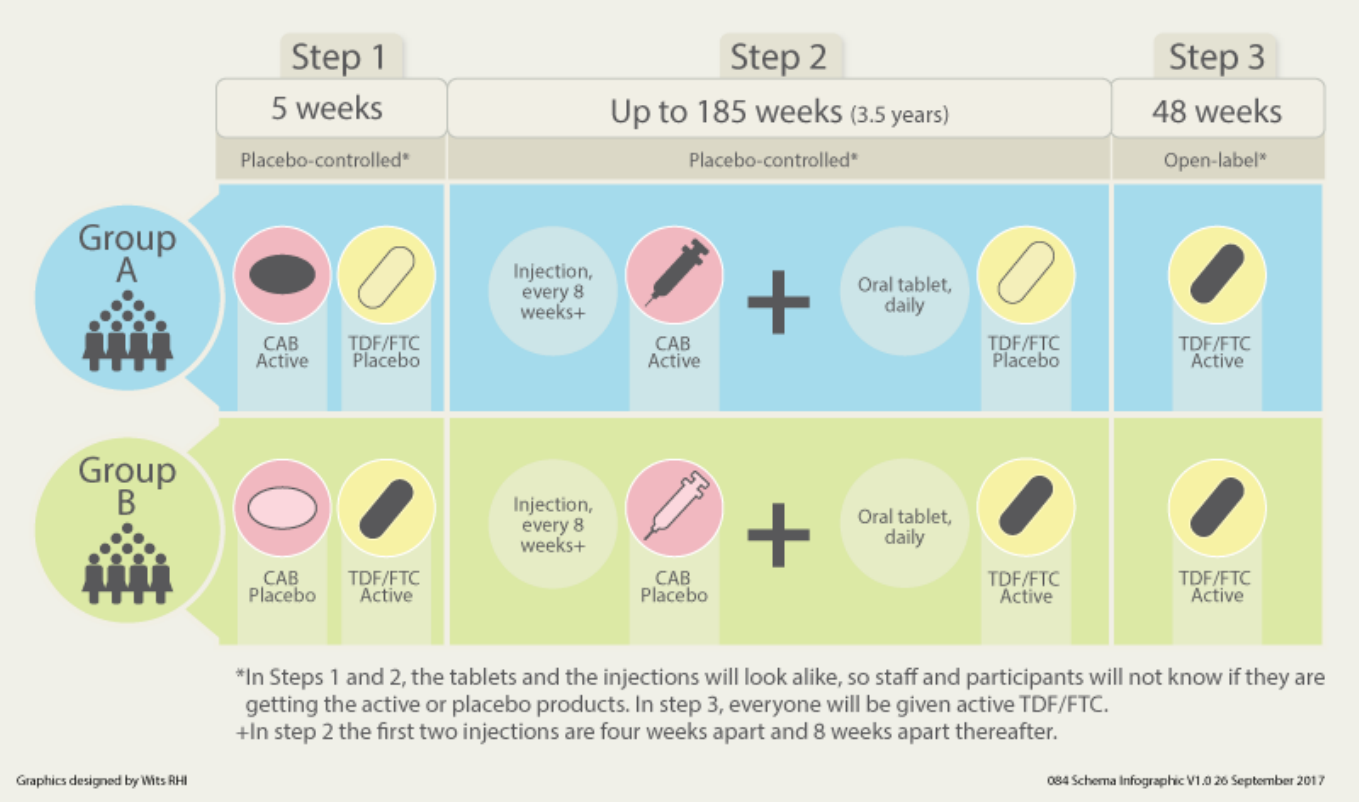
Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

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

HPTN 083 and 084: Phase 3 for CAB LA PrEP ongoing

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)



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

CAB LA – Interim Results

- CAB LA injected once every eight weeks was superior to daily oral FTC/TDF at preventing HIV acquisition in **cisgender men and transgender women who have sex with men** (083)
- And in **cisgender women** (084)
- Both CAB LA and FTC/TDF were safe and well tolerated in both studies
- Most adverse events were mild or moderate and balanced between arms.
- Participants taking active FTC/TDF who wish to use CAB LA will be able to do so as soon as it is available.

CAB LA – Way Forward

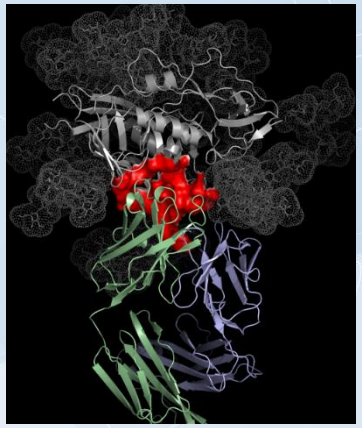
- Two studies HPTN 083-01 and HPTN 084-01 are testing the safety, acceptability, and tolerability of CAB LA among adolescents.
- Too early to know when CAB LA may be available for individuals outside of the HPTN 083 and 084 studies.
- The regulatory approval process for CAB LA requires several steps including review and approval by the U.S. Food and Drug Administration and other regulatory agencies.
- The regulatory approval process for CAB LA requires several steps that need to occur first
  - including review and approval by the U.S. Food and Drug Administration and other regulatory agencies.

Antibody Mediated Prevention

HPTN 081/HVTN 703 and HPTN 085/HVTN 704

Passive Antibody Prevention

Can a passively infused monoclonal antibody VRC01 prevent HIV-1 infection in high-risk adults?



Two harmonized cohorts:

2,700 MSM + TG in North & South America, Switzerland

1,900 Heterosexual women in sub-Saharan Africa

Both trials opened in April/May 2016

AMP ANTIBODY · MEDIATED · PREVENTION STUDY

AMP Study Objectives

PRIMARY

- **Safety & Tolerability of VRC01 infusion**
  - Reactogenicity, AEs, SAEs, discontinuation rates
- **Efficacy to prevent HIV infection**
  - HIV infection by Week 80 in those HIV-negative at enrollment

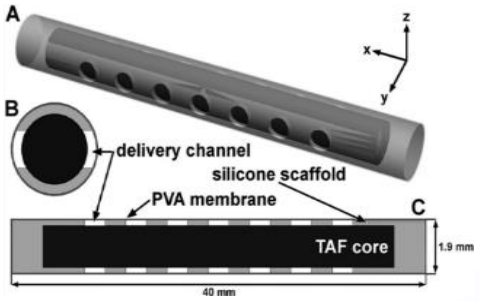
SECONDARY

- **Develop a marker(s) of VRC01 that correlates with the level and antigenic specificity of efficacy and to provide insight into mechanistic correlates of protection**
  - Serum VRC01 concentration
  - Serum mAb mediated neutralization and Fc effector functions to panels of HIV-1 Envs
  - Breakthrough HIV viral sequences in infected people
  - VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants

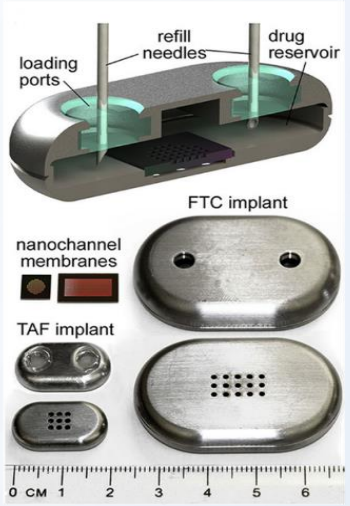
AMP Studies – Way Forward

- We set out to do these test-of-concept AMP studies to establish life-changing concepts – similar to how AZT revolutionized the anti-retroviral field 20 years ago.
- These could fast-track HIV vaccine development and expand the HIV prevention toolbox.
- The primary results of these studies are expected to be released later this year.
- No plans to seek licensure for public use of the VRC01 bnAb.
- Instead, researchers will use what is learned from these proof of concept studies to design studies to evaluate newer antibodies including combinations of antibodies.

Next-Generation: Implantable Drug Delivery Systems

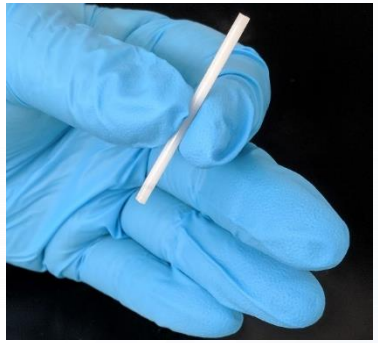


Nondegradable Pod-Type TAF Implant
(Oak Crest Institute of Science)

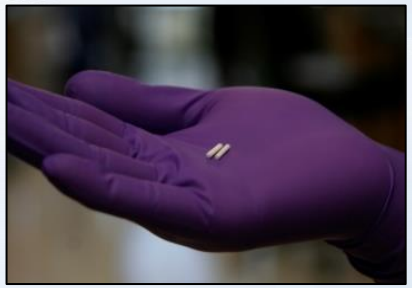


Refillable Transdermal Nanofluidic Implant
(Houston Methodist Research Institute)

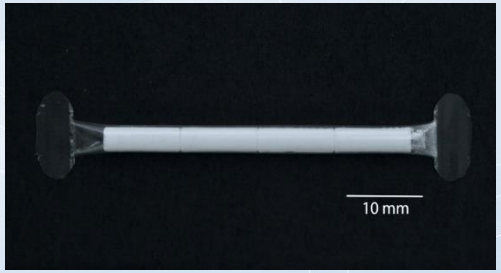
Nondegradable Mini-Pump Implant
(Intarcia Therapeutics)



Biodegradable Reservoir TAF Implant
(RTI International)

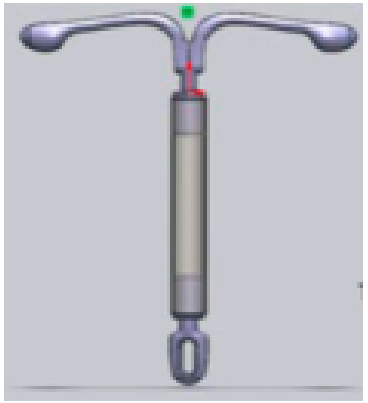


Subdermal Pellet System
(CONRAD)



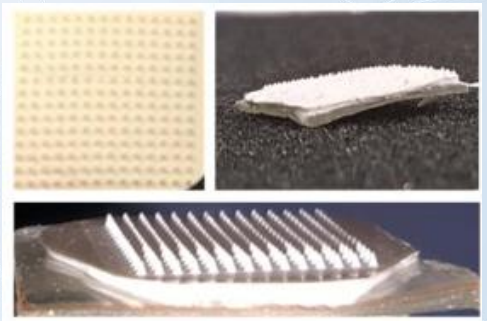
Nondegradable Reservoir CAB Implant
(SLAP HIV-Northwestern University)

Other Novel Drug Delivery Systems in Preclinical Development Pipeline

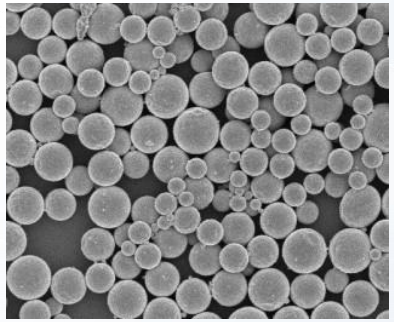


MPT Intrauterine System
(CONRAD)

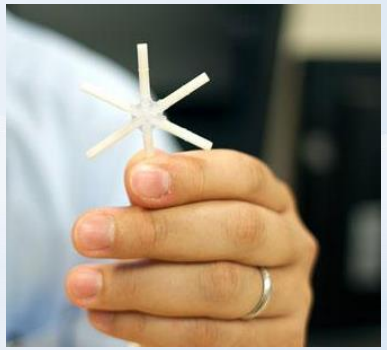
Injectable Depot Systems
(UNC, CONRAD, others)



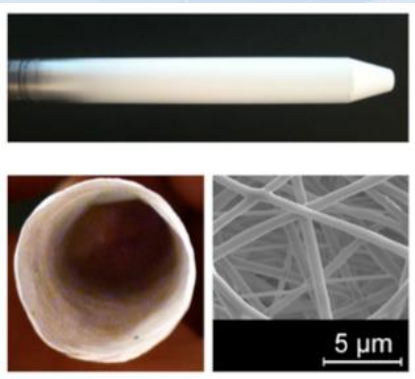
Microarray Needle Transdermal Patch
(PATH, others)



Nano- and Microparticle-Based Delivery Systems
(CONRAD, others)



"Mini-Pillbox" as Once-Weekly Oral Capsule
(MIT/Harvard)



Electrospun Nanofibers
(U. Washington, others)


Thank you