What's in the Pipeline? Long-acting Drugs for Treatment and Prevention!

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DIVISION OF CLINICAL PHARMACOLOGY

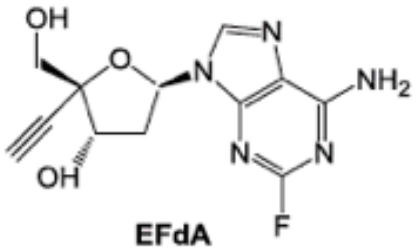
leap

Disclosures

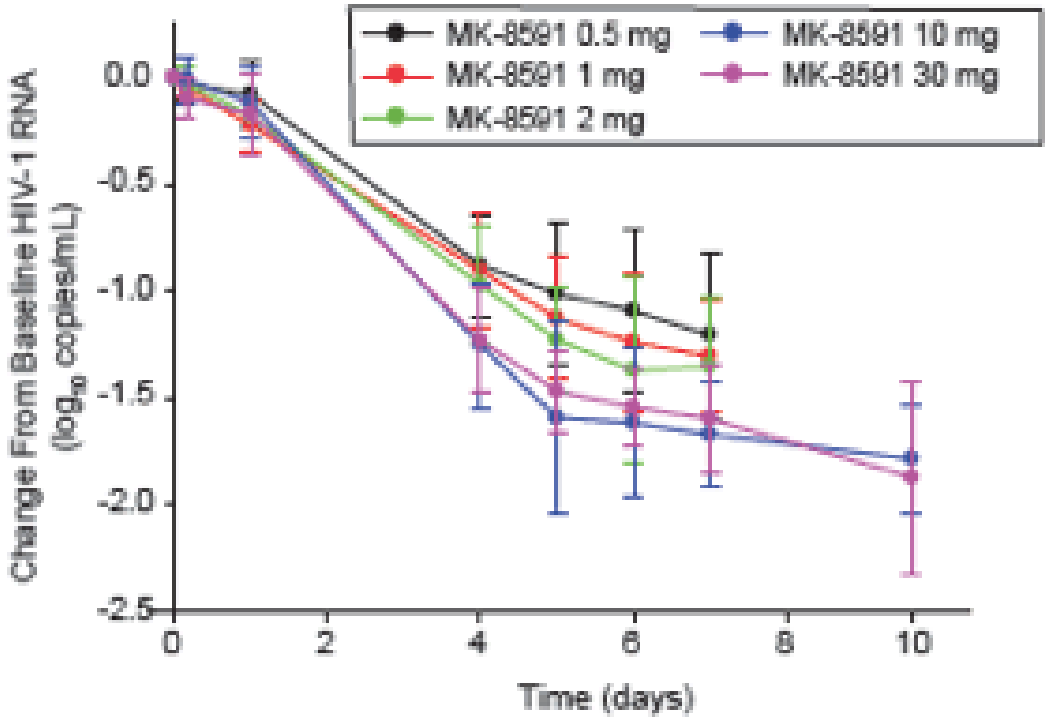
- Dr. Flexner has disclosed that during the past 24 months he has served as a paid consultant for Gilead Sciences, Merck, Janssen and ViiV Healthcare, and serves on the Scientific Advisory Board for Navigen.
- He is also a co-inventor on two issued patents related to the development of long-acting formulations for delivery of antiretroviral drugs.

Novel delivery:
Long-acting Oral ARV's

Islatravir (ISL)



- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; MK-8591; EFdA
- DNA chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Half-life = 50-60 hours in plasma
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Oral weekly version for treatment, and oral monthly version for PrEP



Schurmann et al. Lancet HIV 2020;7:e164-e172

https://www.fiercebiotech.com/biotech/merck-pauses-very-important-hiv-program-after-seeing-red-flag-phase-2-trial-once-weekly; see also https://www.biopharmadive.com/news/merck-isltravir-hiv-safety-signal-combination/610348/

Biotech

Merck pauses 'very important' HIV program after seeing red flag in phase 2 trial of once-weekly combo

by Nick Paul Taylor |
Nov 19, 2021 7:15am

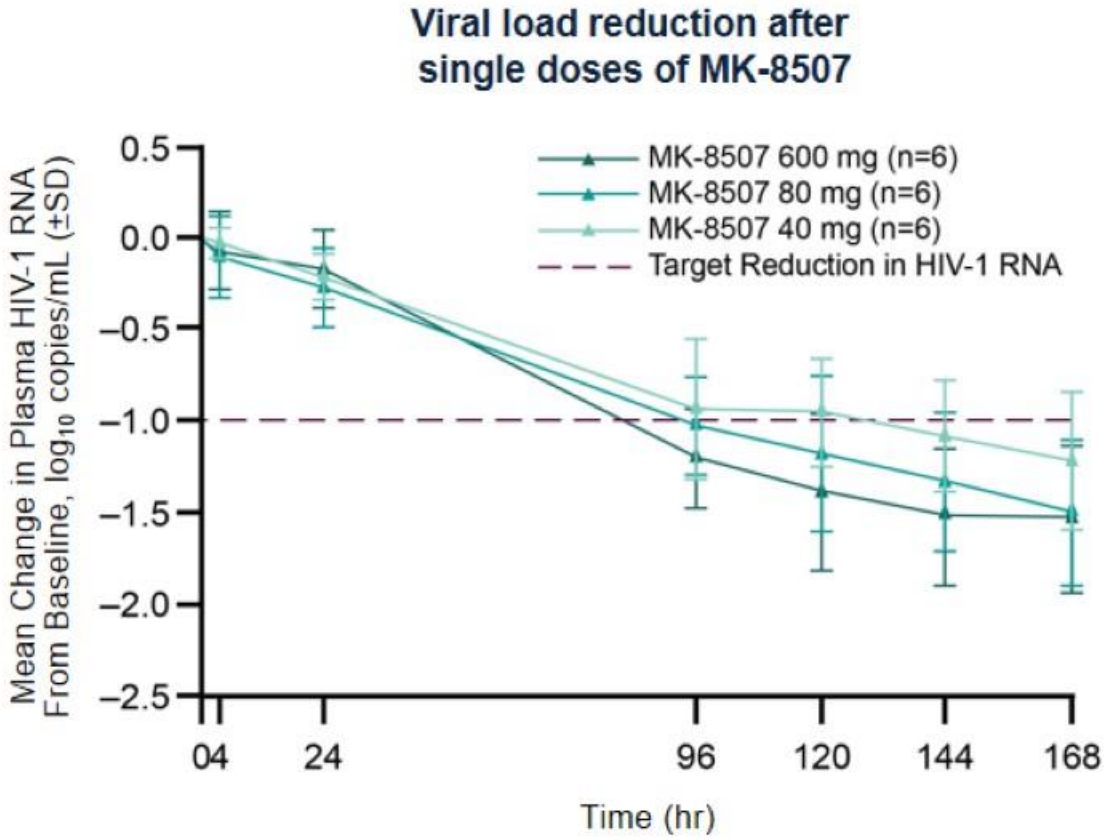
In response to MK-8507 combination data, Merck went over the results from other clinical trials of islatravir. (Merck & Co.)

A “very important” part of Merck’s HIV strategy has come off the rails. Just months after talking up the importance of MK-8507, Merck has **paused** development of the asset in response to mid-phase data that also raised questions about the backbone of all the company’s planned HIV regimens.

Merck paused development of MK-8507 after seeing decreases in white blood cells in HIV patients who took the non-nucleoside reverse transcriptase inhibitor in combination with backbone therapy islatravir in a phase 2 clinical trial. The external data monitoring committee concluded the

MK-8507, a once-weekly NNRTI for HIV-1 treatment

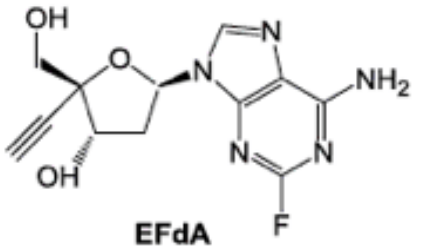
- In vitro IC_{50} (100% NHS)=51.3nM
- Mean plasma $t_{1/2}$ ~70 hours in humans supports once-weekly dosing
- Generally well tolerated with single doses up to 1200 mg and 3x weekly doses up to 400 mg
- Single oral doses of MK-8507 as low as 40 mg reduced mean plasma HIV-1 RNA levels >1 log for up to 7 days in treatment-naïve PLWH
- Phase 2 study of MK-8507 in combination with islatravir is planned (NCT04564547)



Diamond T et al. CROI 2021

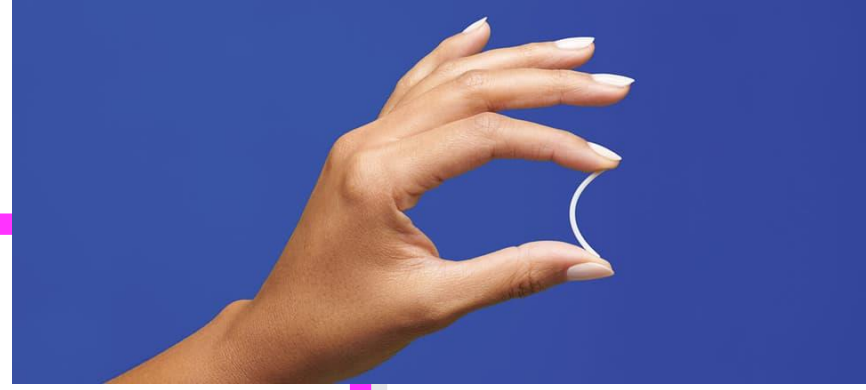
IC_{50}, half-maximal inhibitory concentration; NHS, normal human serum; PLWH, people living with HIV

Islatravir-associated lymphopenia



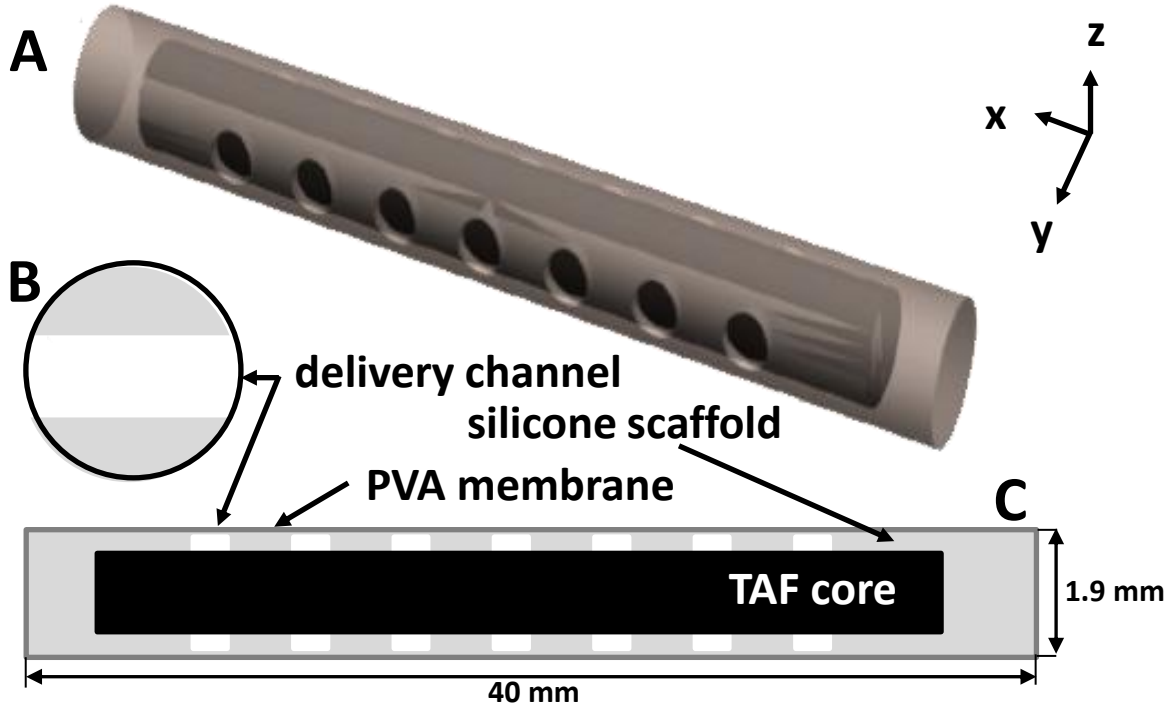
EFdA

- Will lower doses of ISL meet safety and efficacy targets?
- Are there patient populations for whom ISL would never be an appropriate drug?
- Could there be delivery platforms (like implants) that would not produce lymphopenia?



Novel delivery: Implantable ARV’s

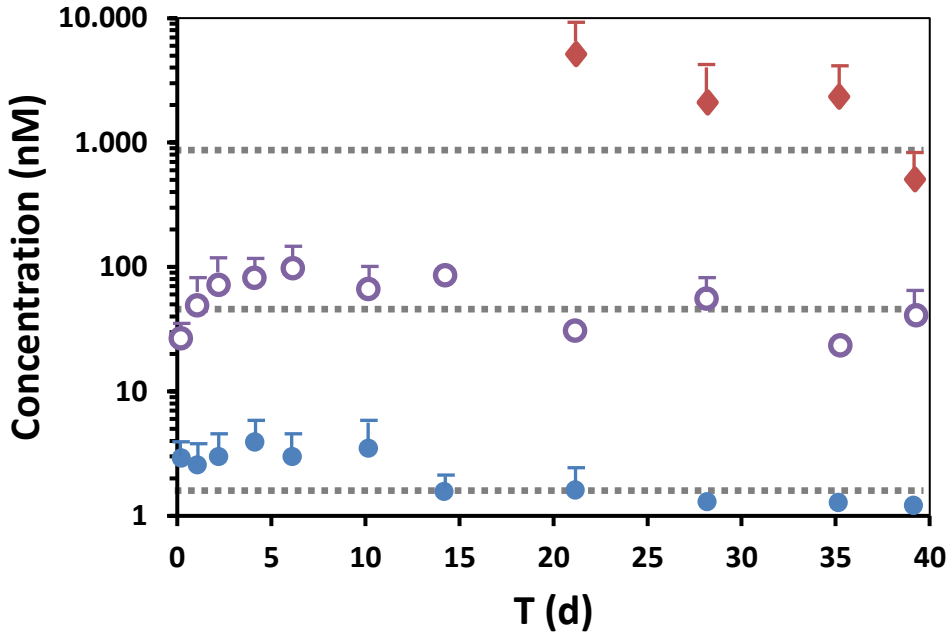
LA ARV Implants – Tenofovir Alafenamide



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

LA ARV Implants – Tenofovir Alafenamide



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.

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

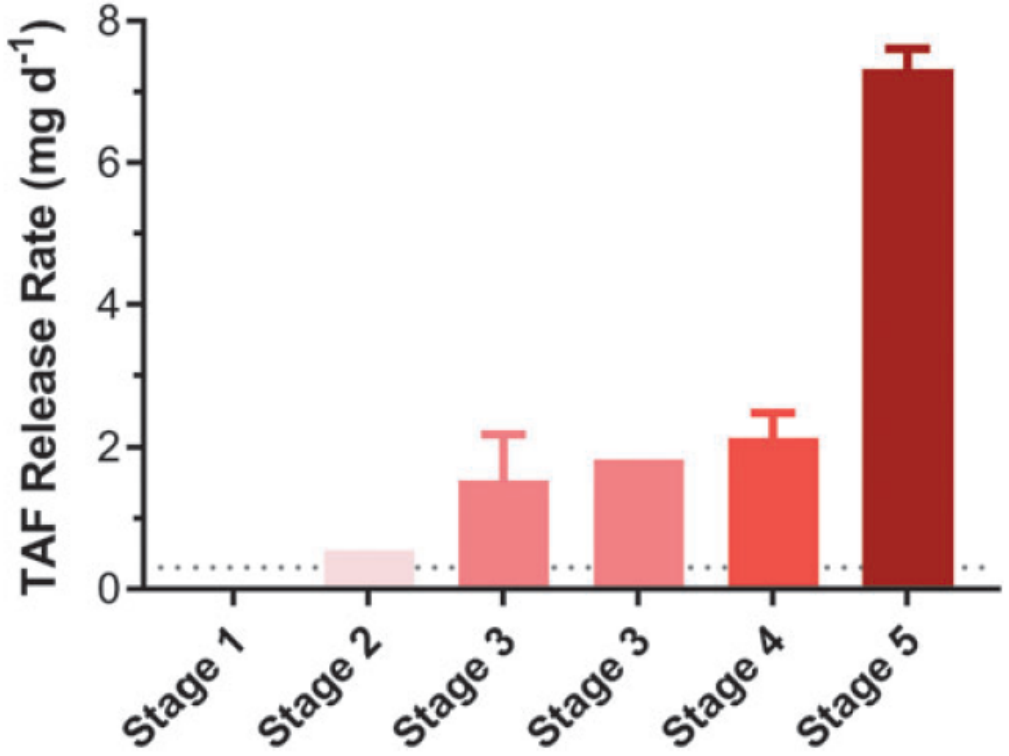
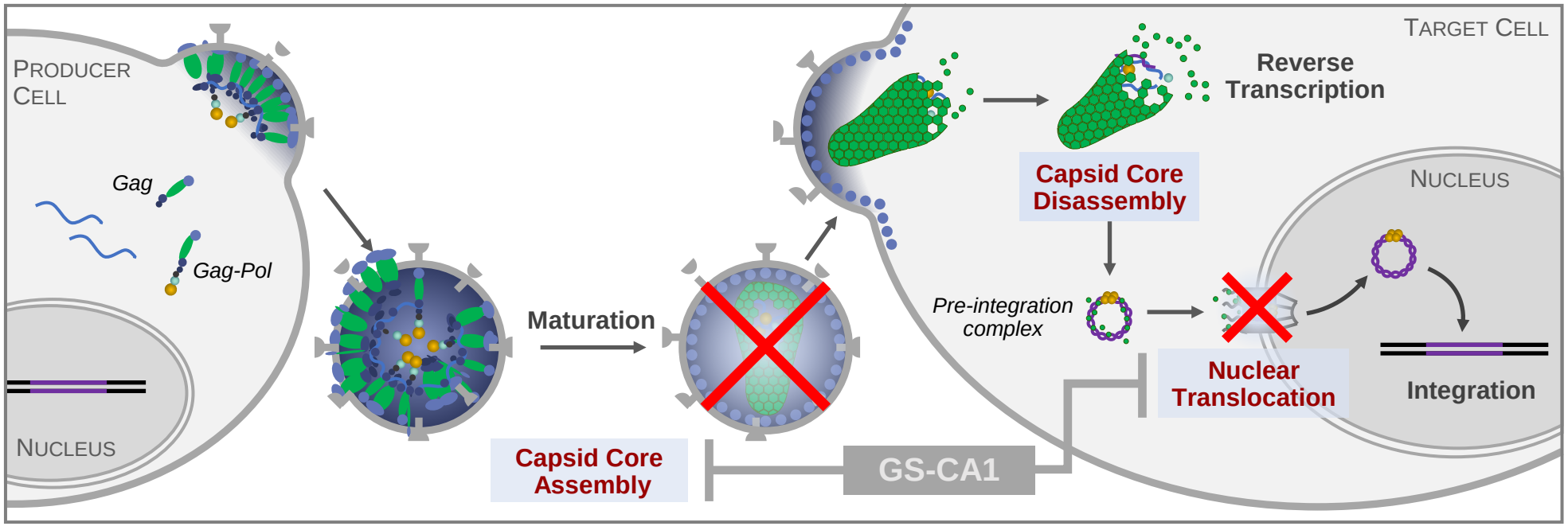


FIG. 4. Stage 1, scab, slight erythema; stage 2, slight swelling at dose site, scab, slight edema; stage 3, mild-to-moderate edema, scab, swelling, ocular discharge, emesis; stage 4, macroscopic descriptions of swelling and/or firmness in the interscapular implant sites, no expressible fluid; stage 5, slight swelling, emesis, red-tinged material at dose site and yellow discharge; mild edema, mild erythema.

- From Romano J et al., AIDS RESEARCH AND HUMAN RETROVIRUSES Volume 37, Number 6, 2021

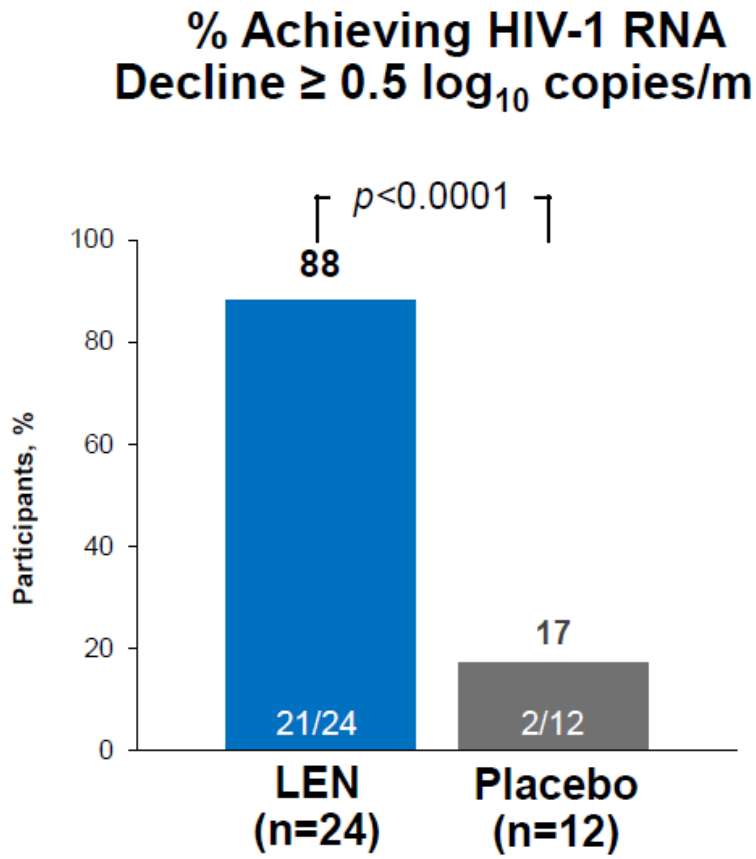
Novel delivery: Subcutaneous ARV's

HIV Capsid Inhibitors: Mechanism of Action



Yant et al., Nat Med 2019; 25:1377-1384

CAPELLA: Phase 2/3 in heavily treatment-experienced PWH
Primary endpoint achieved (press release in Nov 2020)

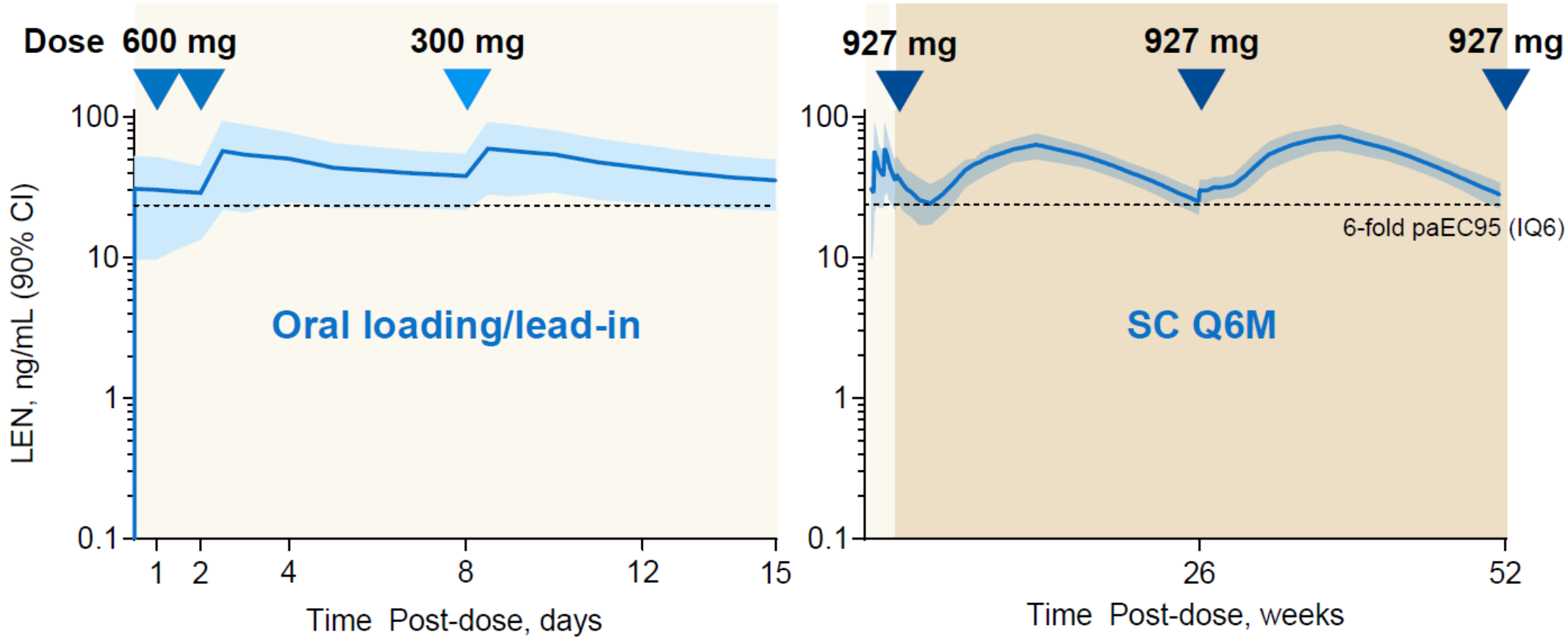


- LEN was generally safe and well-tolerated
- The study is ongoing

Oral 2228 on Tue (09 March 2021)
By Segal-Maurer S et al.
Potent antiviral activity of lenacapavir in phase 2/3 in heavily ART-experienced PWH

Segal-Maurer et al. CROI 2021; abstract 2228

Putting oral and SC together
Predicted LEN PK for Phase 2/3 LEN regimen



CI, confidence interval.
Begley R, et al. AIDS 2020 (previously presented as SC 900 mg, but revised based on further data)

Novel delivery: Intravenous ARV’s

Broadly Neutralizing mAbs in Development

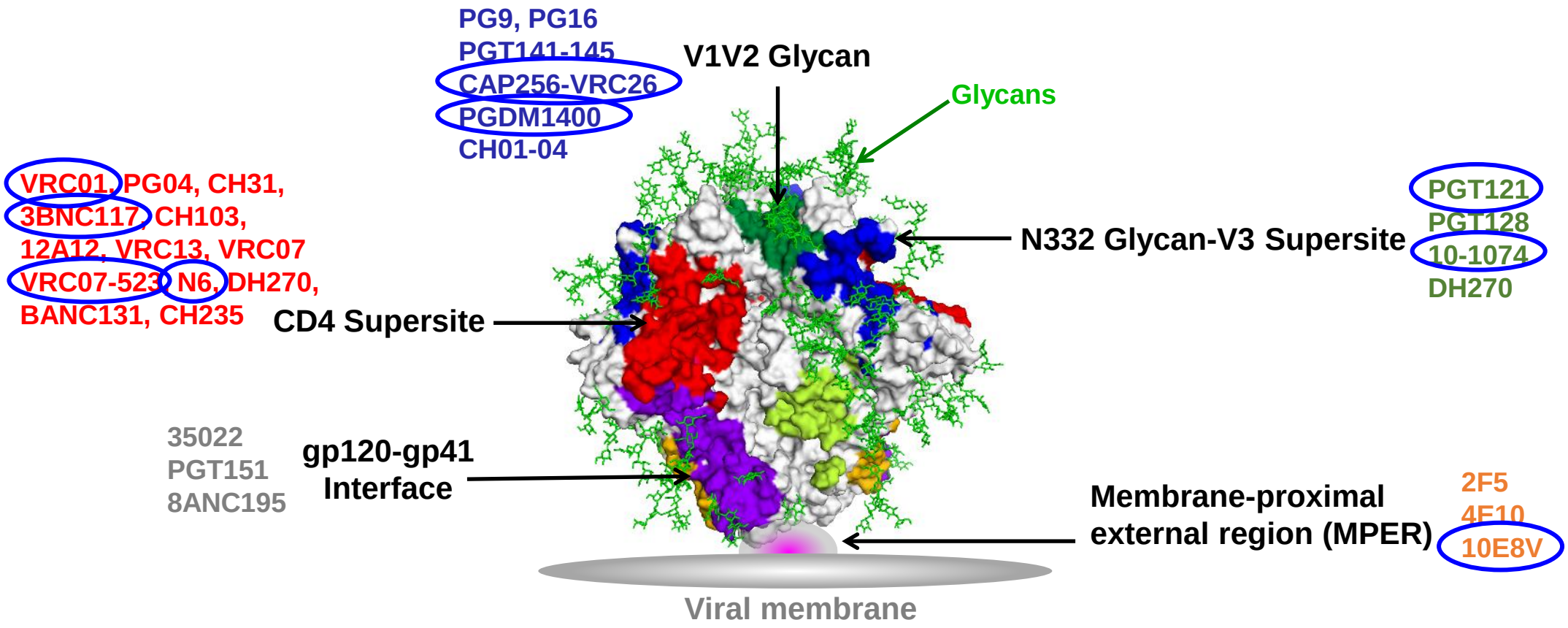
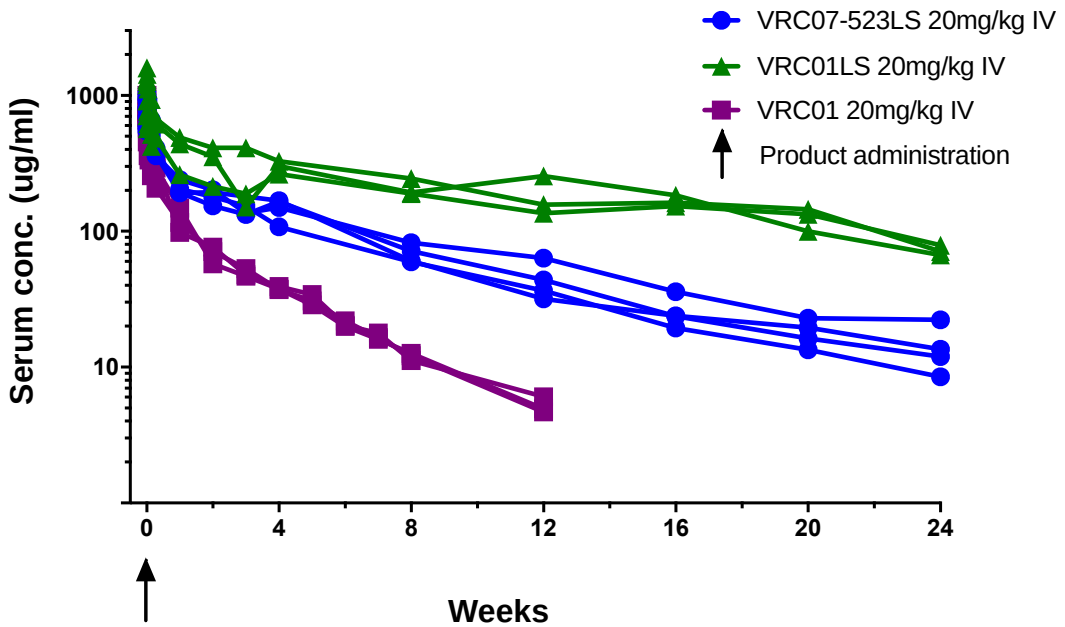


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

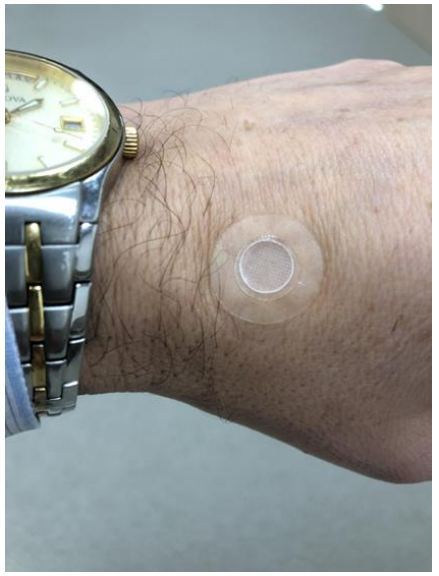
VRC07-523LS and VRC01LS serum conc.



Trough at 12 weeks is 3-fold lower
Trough at 16 to 24 weeks is 5-fold lower

→ **But overall, serum neut is better for VRC07-523LS vs VRC01LS**

Gaudinski, Ledgerwood et al. Lancet HIV (2019)

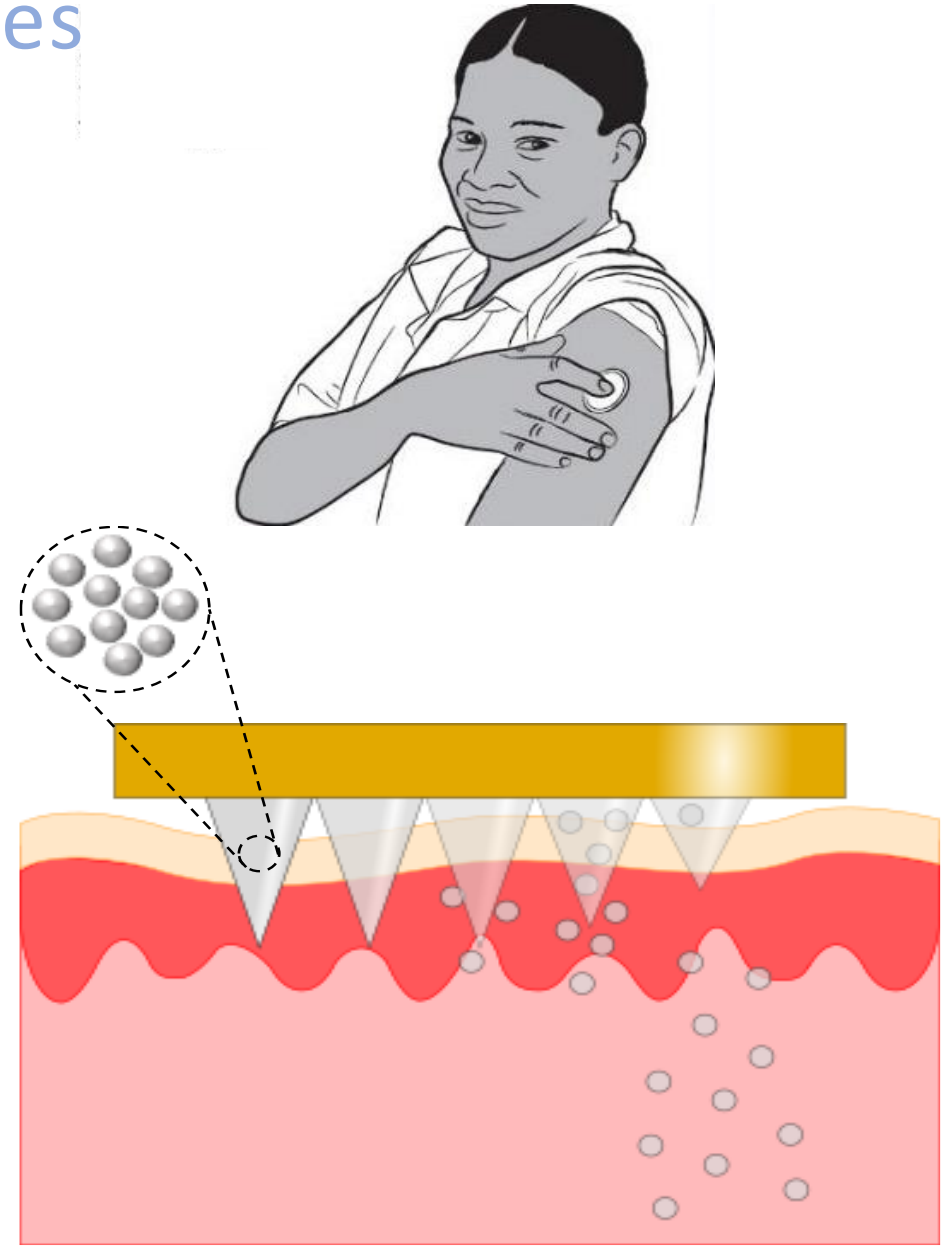


Novel delivery: Transdermal ARV's

Formulation and Application of LA ART

Microarray Patches

- **Load nanoformulated drugs at high concentration into aqueous gels**
- **Cast into mould**
- **Dry and add border adhesive and occlusive backing layer to form microarray patch (MAP)**
- **Baseplate should readily detach upon microneedle dissolution in skin**
- **Nanoformulated drugs deposited in viable skin layers for sustained release and absorption by rich dermal microcirculation**

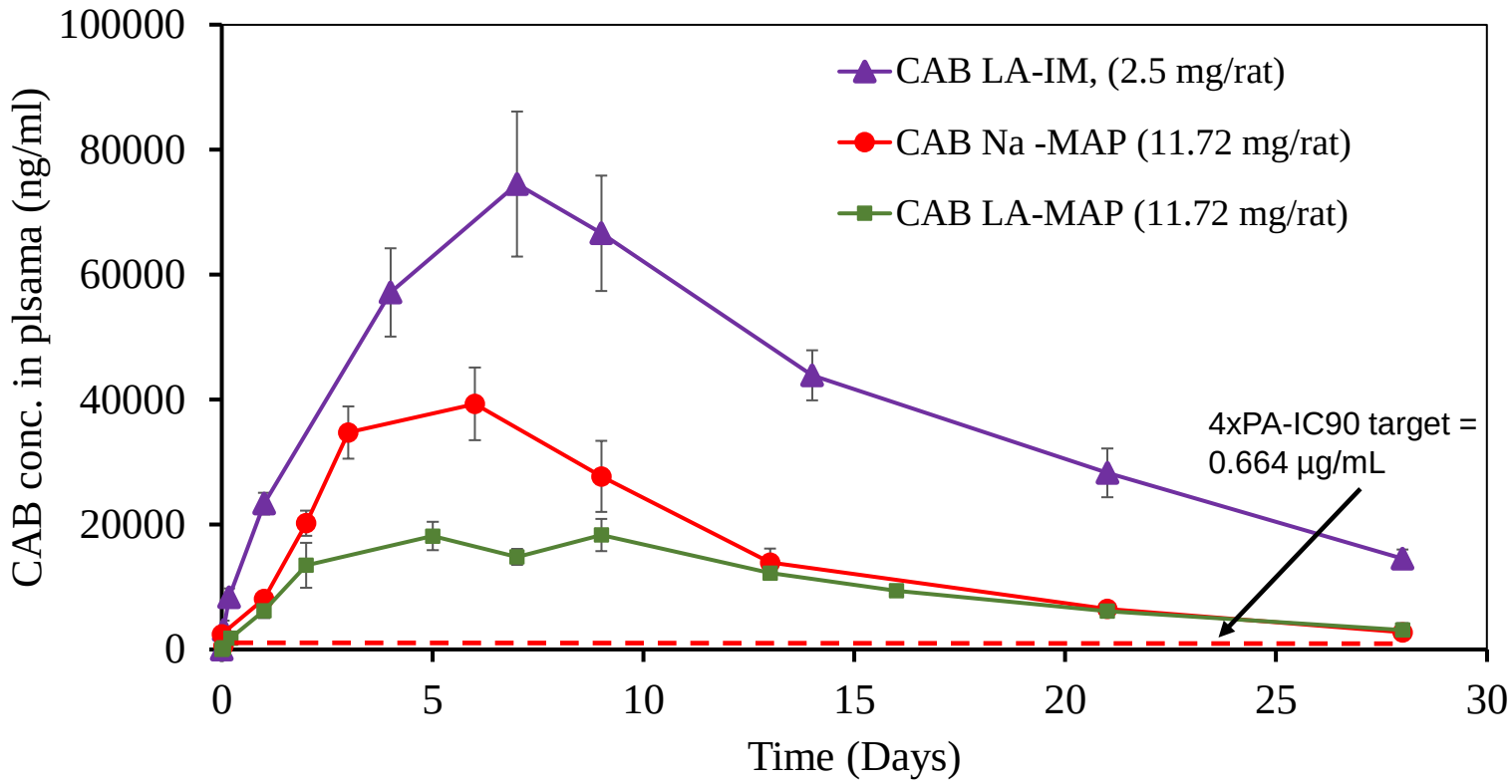


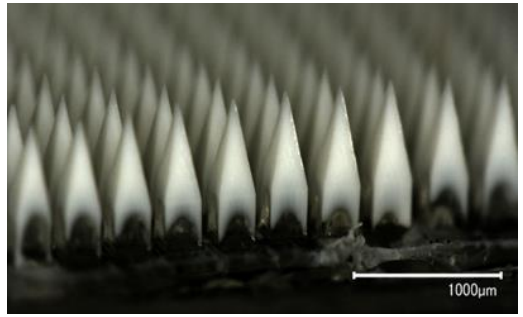
PEPFAR U.S. President's Emergency Plan for AIDS Relief

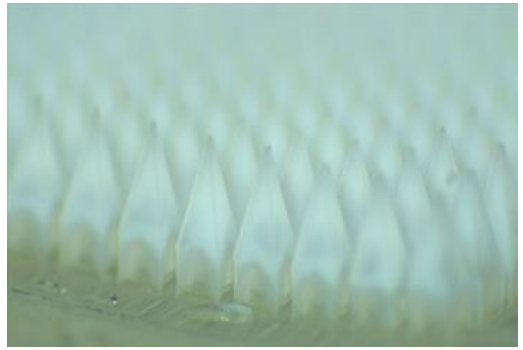
USAID FROM THE AMERICAN PEOPLE

PATH

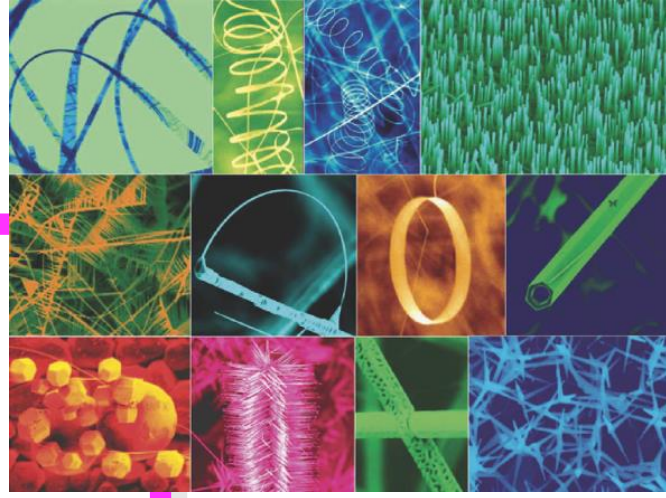
Cabotegravir Microarray Patch – PK profile comparison





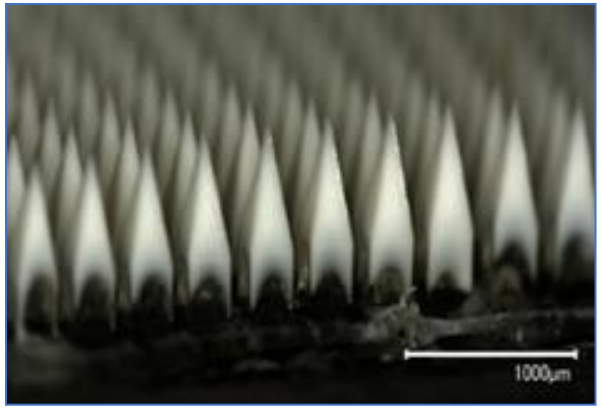


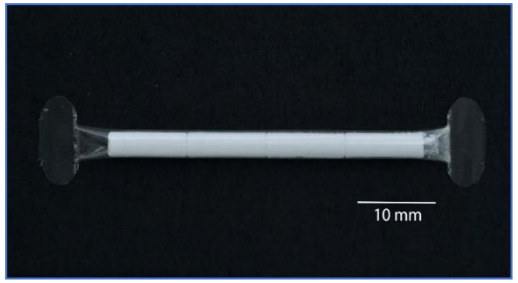
- Courtesy Prof. Ryan Donnelly

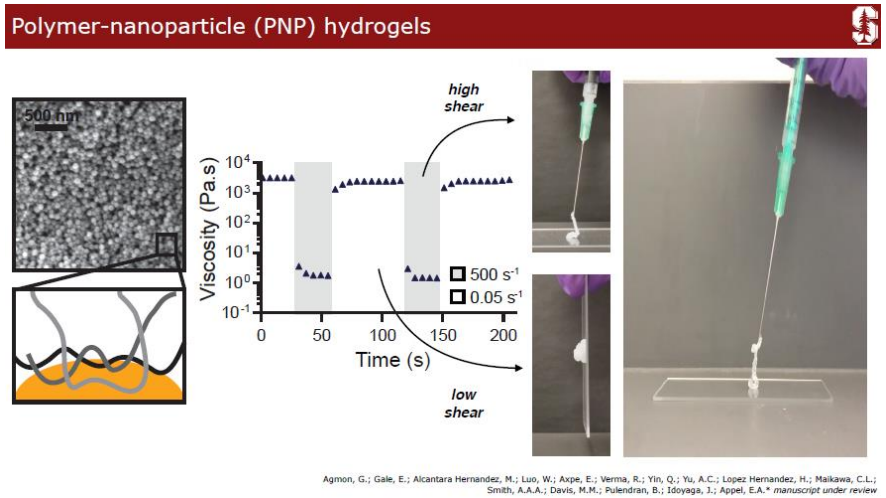


Novel delivery: What will the future hold???

The ARV Drug Delivery Pipeline







Agmon, G.; Gale, E.; Alcantara Hernandez, M.; Luo, W.; Axpe, E.; Verma, R.; Yin, Q.; Yu, A.C.; Lopez Hernandez, H.; Maikawa, C.L.; Smith, A.A.A.; Davis, M.M.; Pulendran, B.; Idoyaga, J.; Appel, E.A.* *manuscript under review*

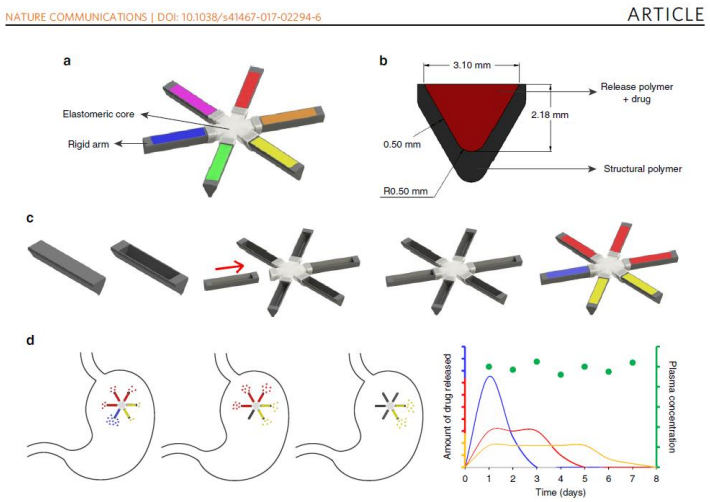
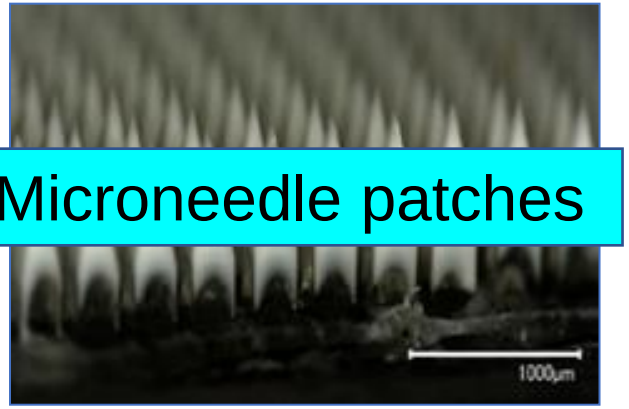


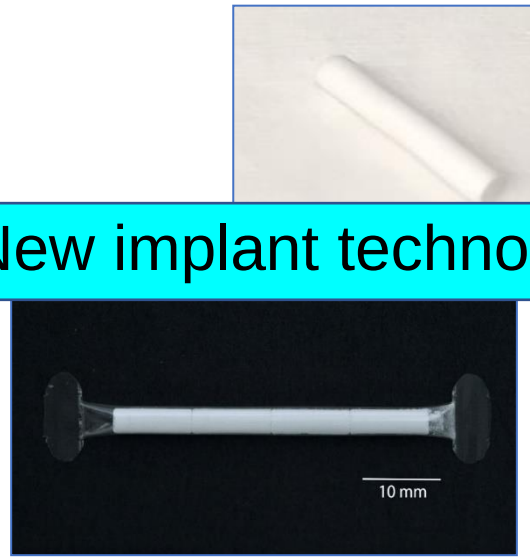
Fig. 1 Concept of oral long acting antiretrovirals. **a** The design of the gastric resident dosage forms. The dosage form consists of an elastomeric core (grey) and six drug loaded arms (multi-coloured). **b** The cross section of the arm. The outer sleeve of the arms is made of a rigid structural polymer which provides the arm its mechanical strength. This sleeve is then filled with a drug-polymer matrix which releases the drug at a desired rate. **c** The manufacturing scheme of the dosage form. The expected performance of the dosage form in vivo is shown in **d**. The dosage form is loaded with three different polymers (blue, red and yellow) which release the drug at different rates. Selection of appropriate polymers may result in almost constant and sustained plasma drug concentrations. It should be noted that **d** is a schematic representing an ideal system, and is not experimentally obtained data

The ARV Drug Delivery Pipeline

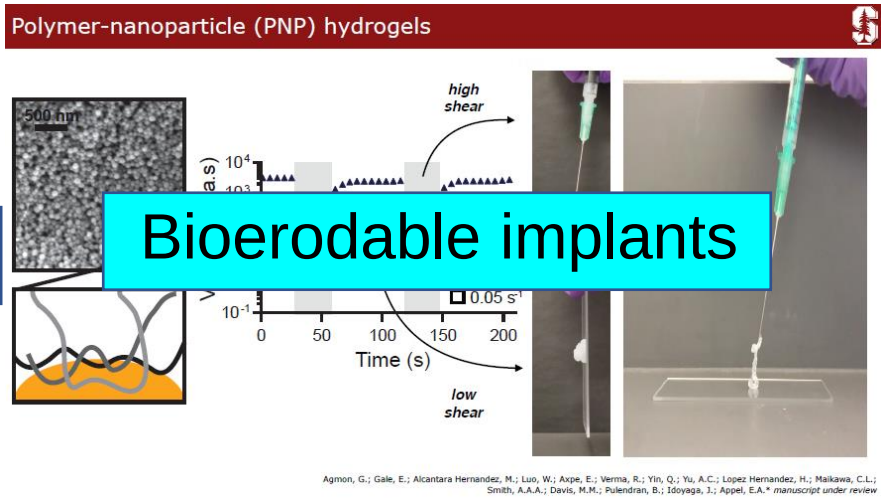
Microneedle patches



New implant technologies



Bioerodable implants



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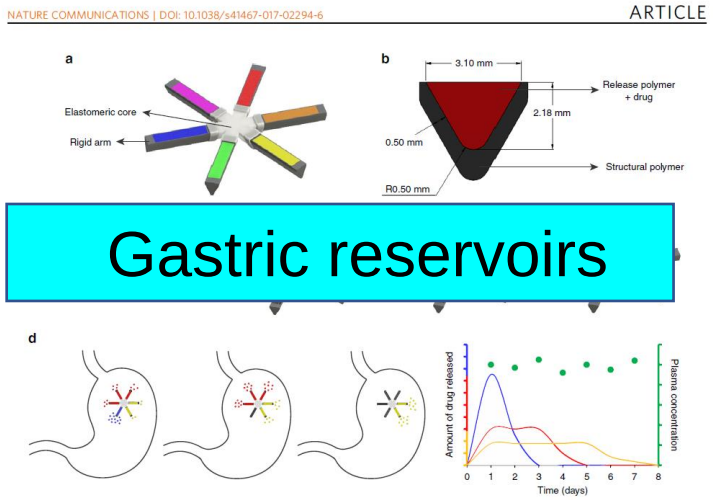
Reduced volume injections

Gastric reservoirs



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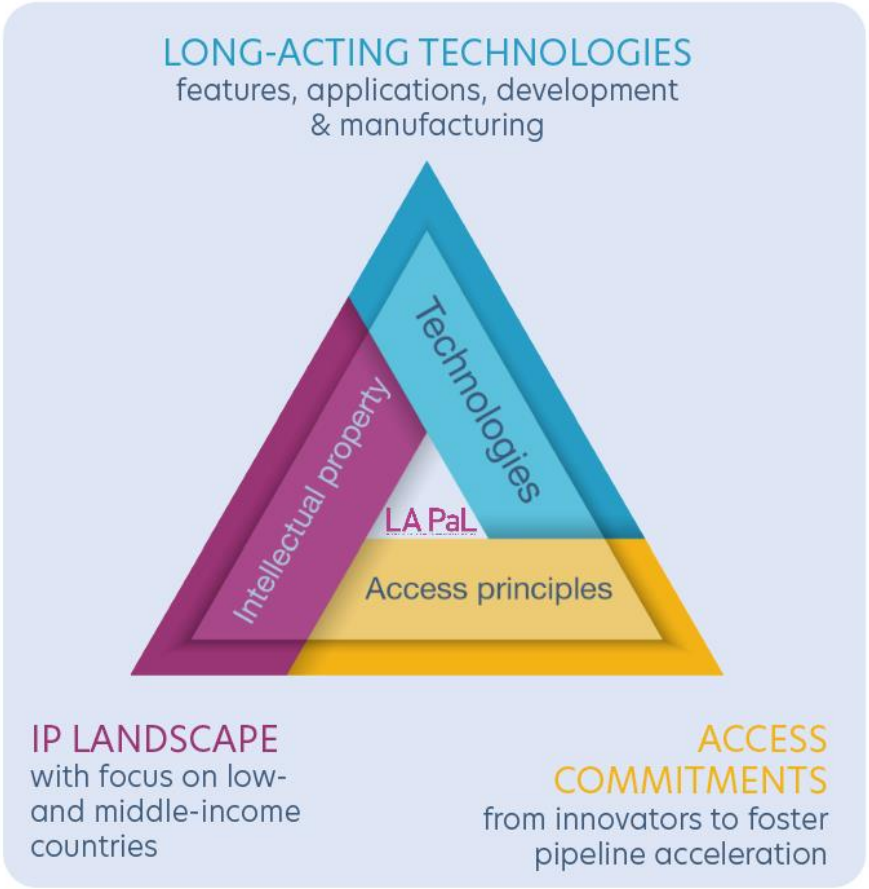
Combination technologies

LAPaL

Long-acting technologies patents and licences database

A free online resource that provides information on technical features and IP status of selected long-acting technologies and their potential applications, in particular, in the fields of HIV, viral hepatitis, tuberculosis and malaria.



Acknowledgements

Johns Hopkins University

Jane McKenzie-White

Melissa Davey-Rothwell

David Thomas

Ana Cervantes

Vaccine Research Center

Richard Koup

UNC

Myron Cohen

Queen's University, Belfast

Ryan Donnelly

Merck

Jay Grobler

Randy Matthews

Tracy Diamond

Bhargava Kandala

Gilead

Martin Rhee

James Rooney

FUNDING SOURCES

Bill and Melinda Gates Foundation

NIAID, R24 AI-118397 (LEAP)

NIAID, R01 AI-114405

leap

longactinghiv.org