The Adult Long-Acting Pipeline: What comes after Cabotegravir and Rilpivirine?

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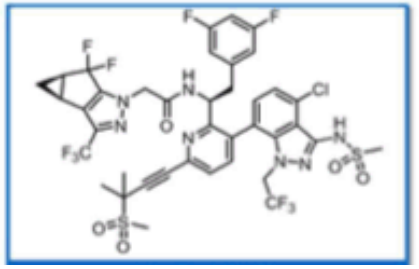
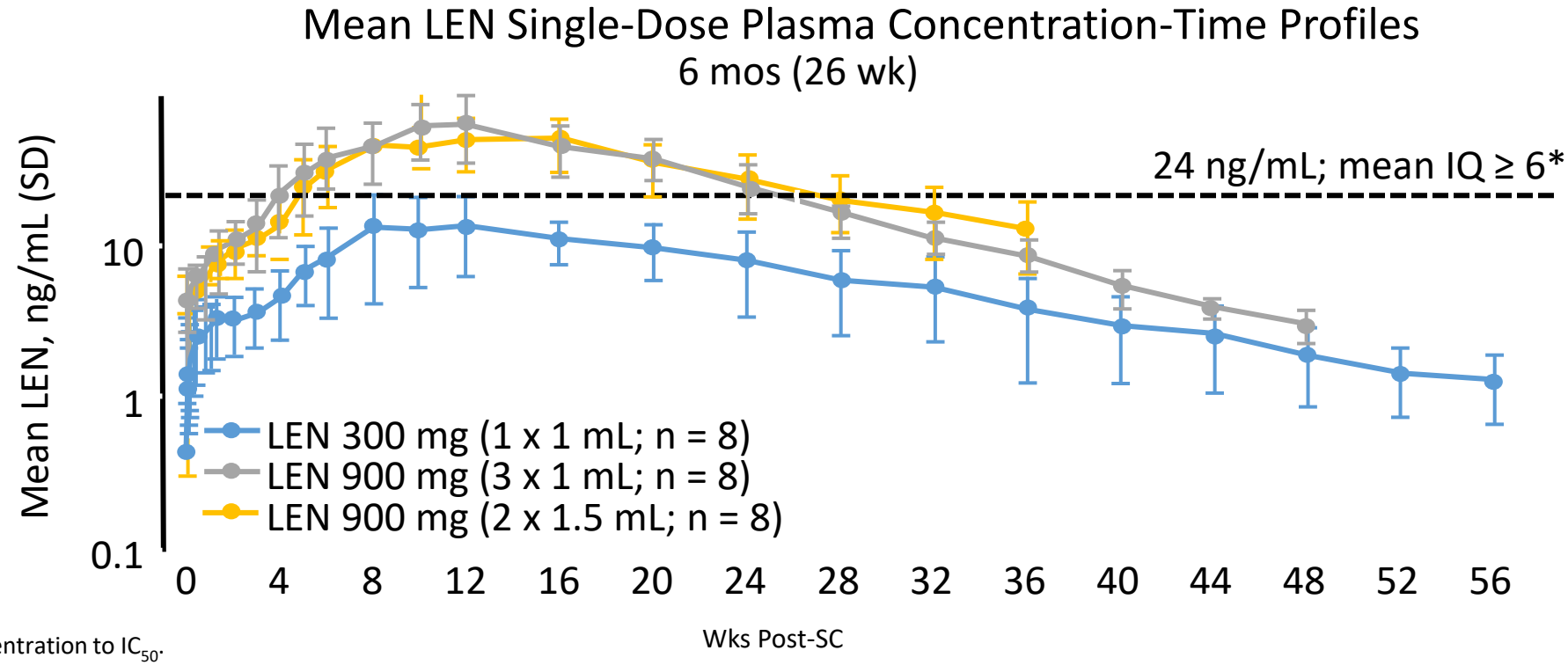
Novel delivery: Subcutaneous ARV's

Lenacapavir (GS-6207) PK Profile



- Lenacapavir (GS-6207): first-in-class selective HIV-1 capsid protein inhibitor / oral and SC long-acting formulations
- Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants
- Supports 6 monthly dosing , maintained target concentrations for 26 weeks

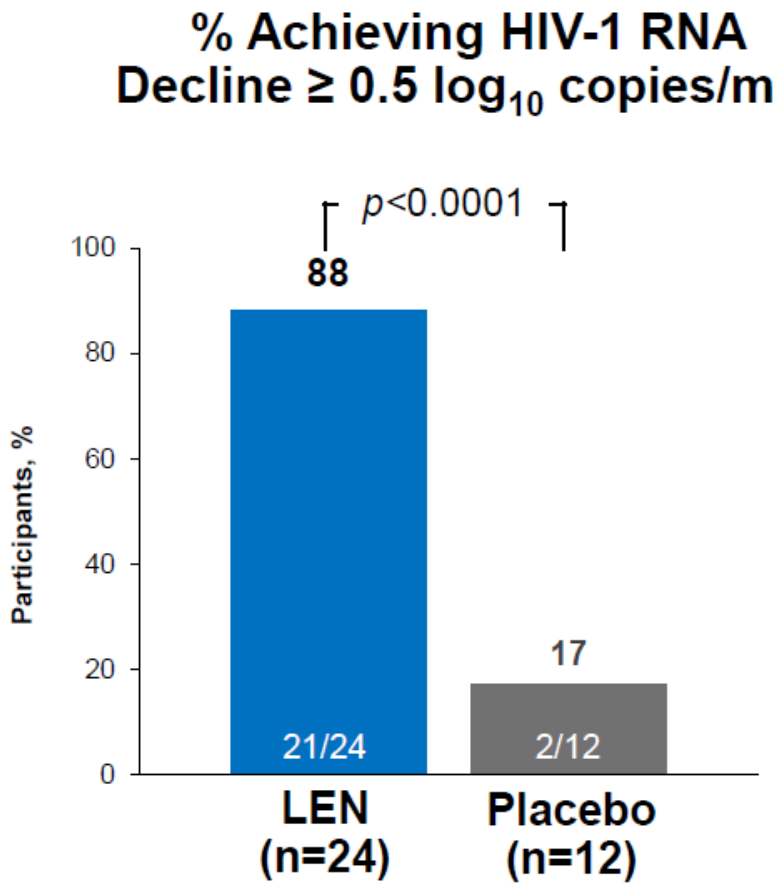
N= 30



*IQ: ratio of LEN plasma concentration to IC_{50}.

Begley. AIDS 2020. Abstr PEB0265

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. Abstr 2228

Novel delivery: Intravenous ARV's

Broadly Neutralizing mAbs in Development

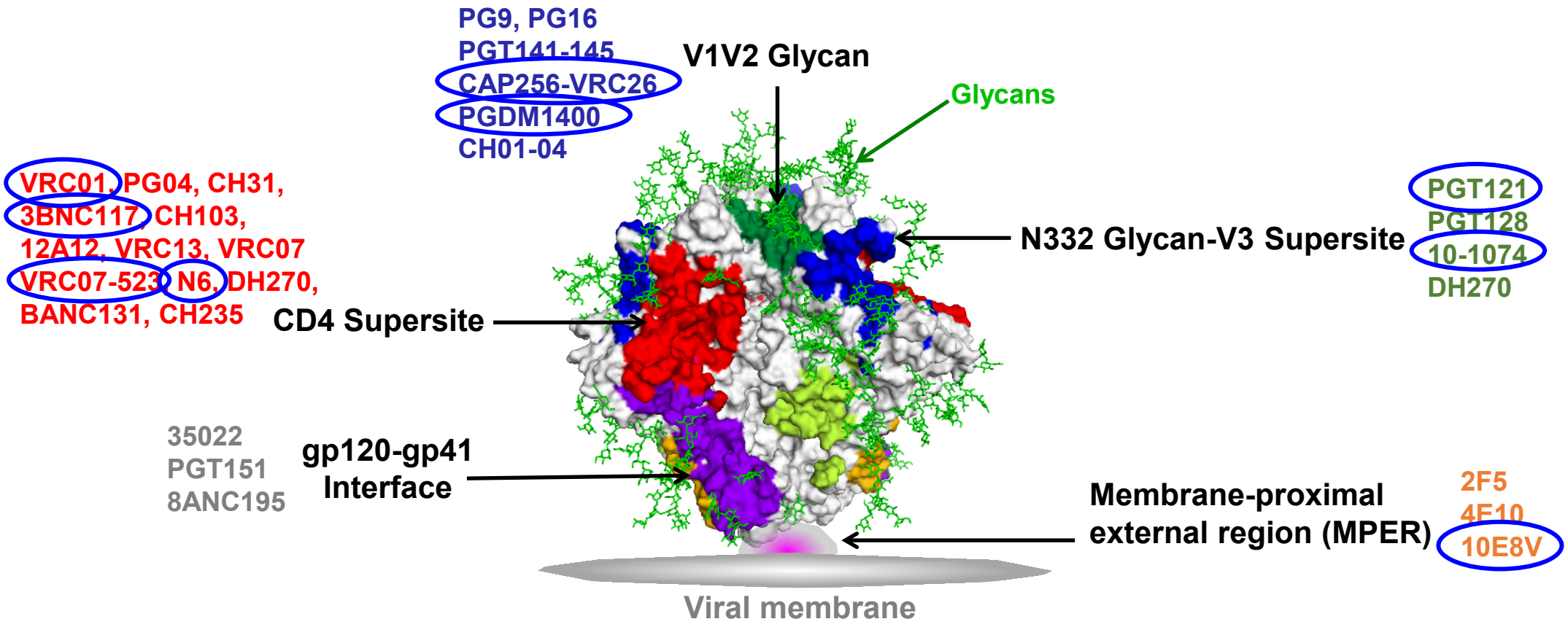
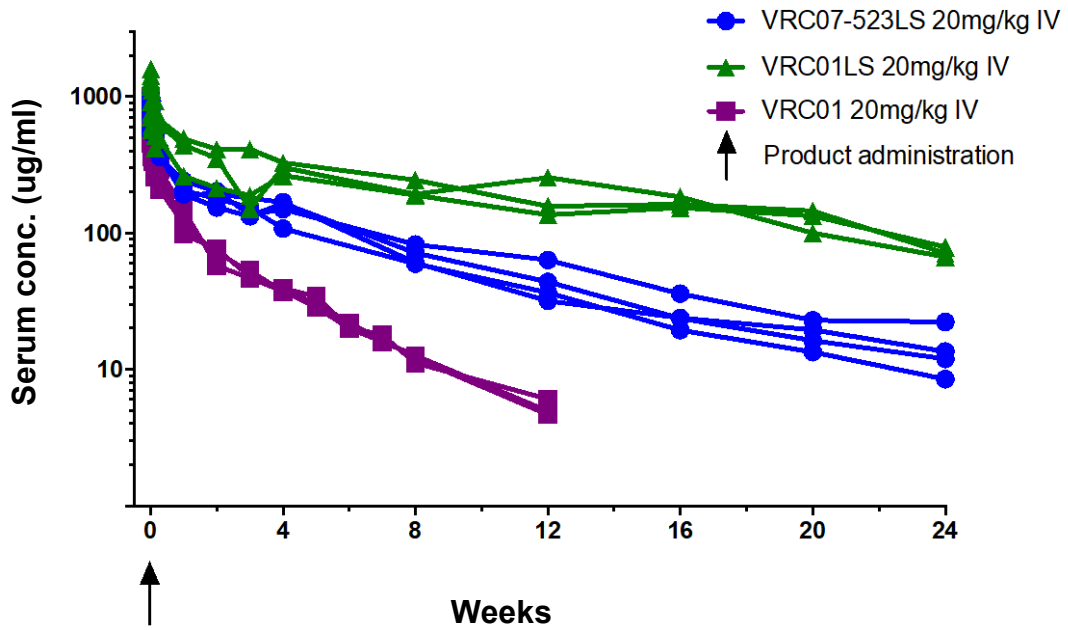


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

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

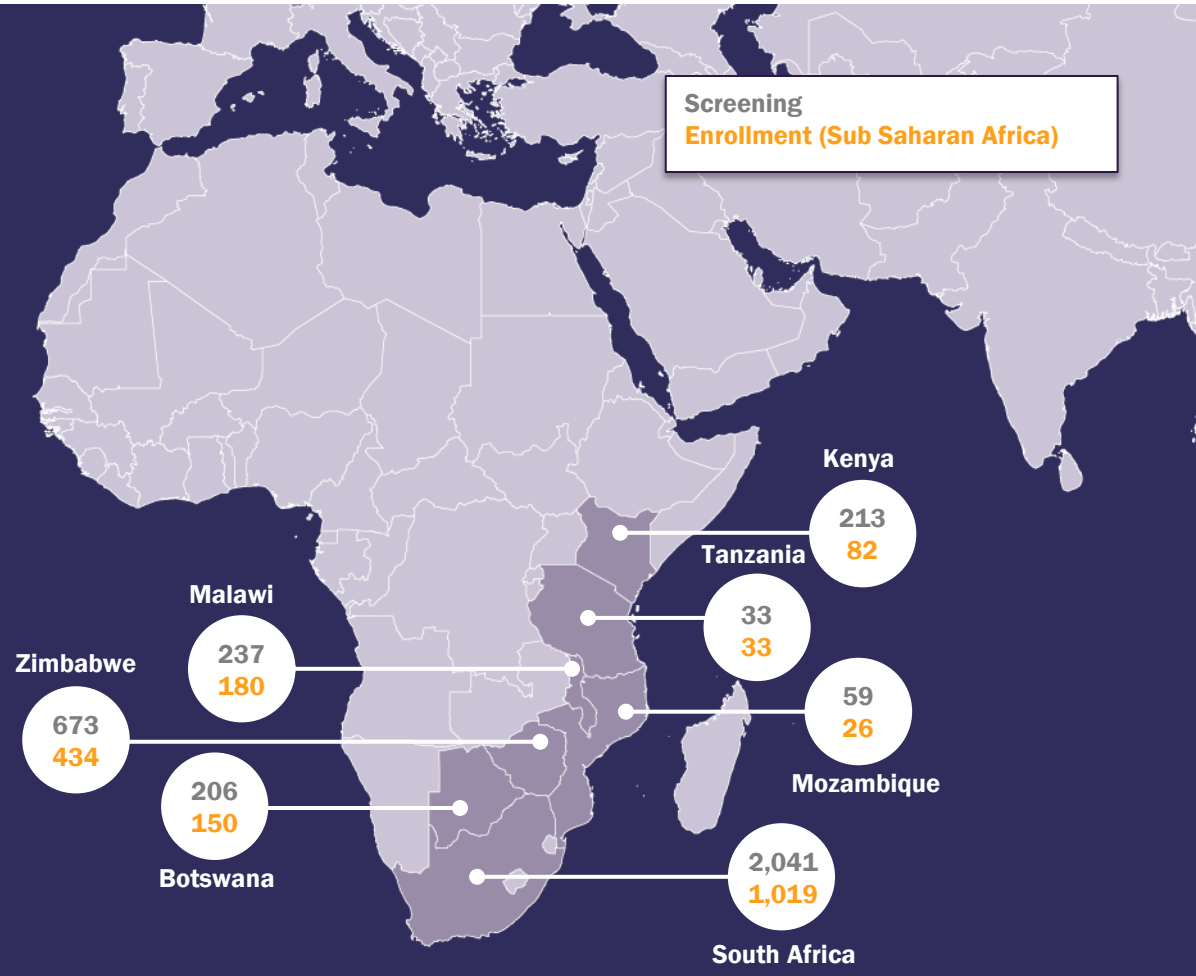
Gaudinski, Ledgerwood et al. Lancet HIV (2019)

HVTN 703/HPTN 081 enrollments

AMP ANTIBODY · MEDIATED · PREVENTION STUDY

Country	Screened	Enrolled
Botswana	206	150
Kenya	213	82
Malawi	237	180
Mozambique	59	26
South Africa	2041	1019
Tanzania	33	33
Zimbabwe	673	434
Total Enrolled		1924

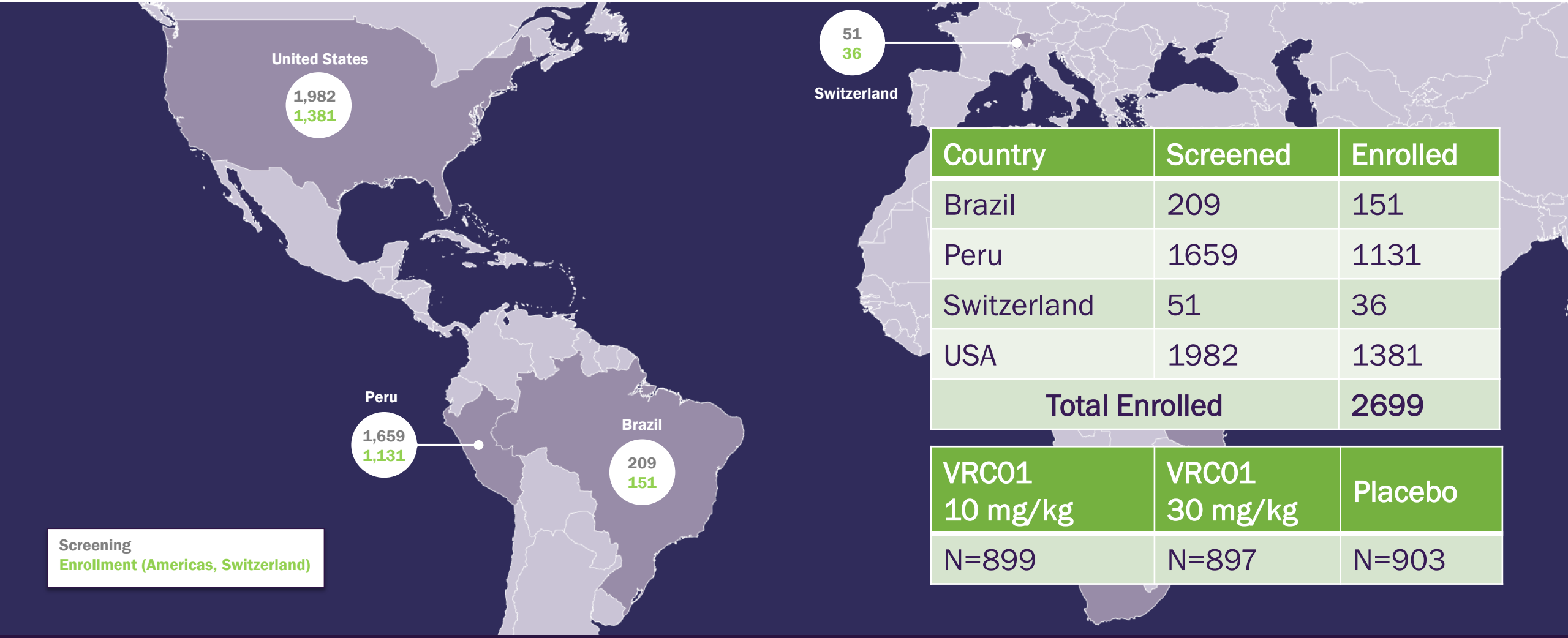
VRC01 10 mg/kg	VRC01 30 mg/kg	Placebo
N=642	N=645	N=637



HIV Prevention Trials Network

HIV VACCINE TRIALS NETWORK

HVTN 704/HPTN 085 enrollments



Country	Screened	Enrolled
Brazil	209	151
Peru	1659	1131
Switzerland	51	36
USA	1982	1381
Total Enrolled		2699

VRC01 10 mg/kg	VRC01 30 mg/kg	Placebo
N=899	N=897	N=903

Prevention with VRC01: The AMP Studies

Table 1: Primary two-sided $\alpha = 0.05$ level Wald-based hypothesis test evaluating equality of the log cumulative hazard functions at τ in the VRC01 pooled vs. control groups.

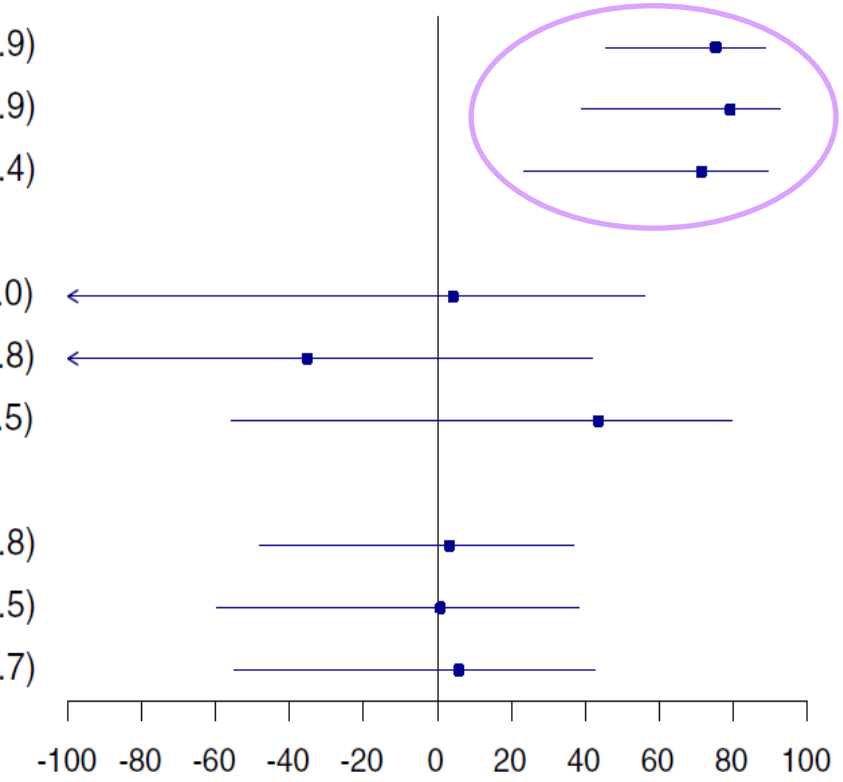
	Total Primary Endpoints (VRC01 vs. Control)	τ (weeks)	Primary Endpoints through τ (VRC01 vs. Control)	Est. Cumulative PE(τ)	95% CI	P-Value
HVTN 704/HPTN 085						
VRC01 Pooled vs. Control	98 (60 vs. 38)	87.0	98 (60 vs. 38)	26.6%	(-11.7% to 51.8%)	0.15
HVTN 703/HPTN 081						
VRC01 Pooled vs. Control	77 (48 vs. 29)	85.9	76 (47 vs. 29)	8.8%	(-45.1% to 42.6%)	0.70
Pooled AMP Trials						
VRC01 Pooled vs. Control	175 (108 vs. 67)	85.9	174 (107 vs. 67)	18.1%	(-12.2% to 40.2%)	0.21

- Estimated PE at the Week 80 visit = 27% for 704/085, 9% for 703/081, 18% pooled
- Prevention efficacy at the Week 80 visit did not significantly differ from zero*

Corey L et al., *N Engl J Med*. 2021; 384: 1003-1014.

Prevention with VRC01: The AMP Studies (Pooled Trials)

Neutralization Resistance Level	Treatment arm	No. of HIV-1 Infections	No. of Person-Years	Rate per 100 Person-Years	PE (95% CI)
<1 µg/ml	Control	19	2203	0.86	
	VRC01 Pooled	9	4427	0.20	75.4 (45.5, 88.9)
	VRC01 10 mg/kg	4	2210	0.18	79.2 (39.1, 92.9)
	VRC01 30 mg/kg	5	2217	0.23	71.5 (23.3, 89.4)
1-3 µg/ml	Control	10	2203	0.45	
	VRC01 Pooled	19	4427	0.43	4.2 (–108.7, 56.0)
	VRC01 10 mg/kg	13	2210	0.59	–35.2 (–214.3, 41.8)
	VRC01 30 mg/kg	6	2217	0.27	43.5 (–55.8, 79.5)
>3 µg/ml	Control	35	2203	1.59	
	VRC01 Pooled	70	4427	1.58	3.3 (–48.0, 36.8)
	VRC01 10 mg/kg	37	2210	1.67	0.9 (–59.7, 38.5)
	VRC01 30 mg/kg	33	2217	1.49	5.8 (–55.1, 42.7)

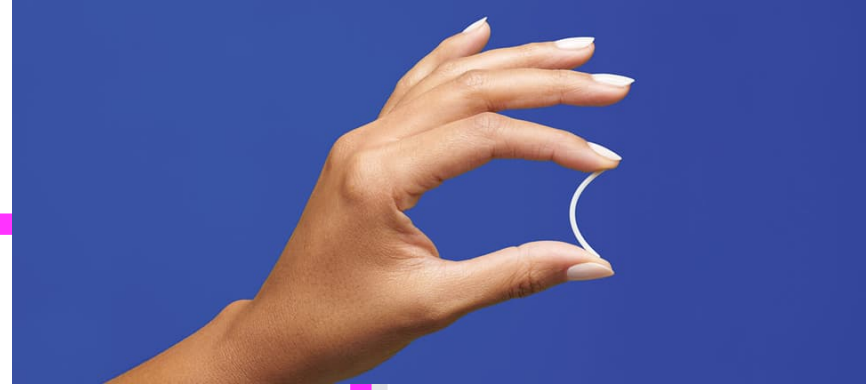


Corey L et al., *N Engl J Med*. 2021; 384: 1003-1014.

Novel delivery: Topical ARV's

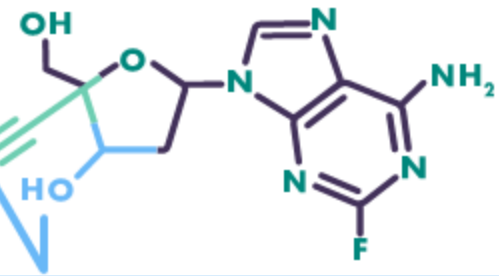
Dapivirine Vaginal Ring – Prevention only!

- Less effective than other prevention strategies in clinical trials
- Removable
  - Susceptible to nonadherence
  - Removal associated with reduced efficacy in clinical trials
- In development as a combination technology
  - Combined with topical hormonal contraception
  - May improve adherence
- Unconventional implementation strategy
  - Developed strictly in a not-for-profit setting
  - Regulated as both a drug and a device



Novel delivery: Implantable ARV's

Islatravir (ISL, MK-8591), a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) with multiple mechanisms of action

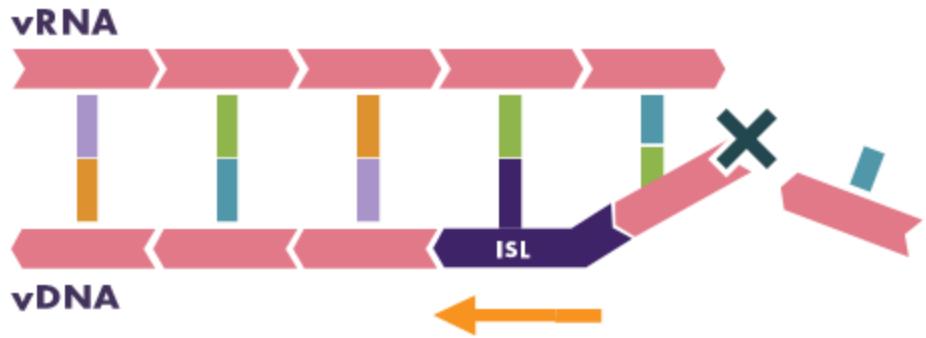


Translocation inhibition
due to the 4'-ethynyl group

- Translocation inhibition prevents the opening of the nucleotide binding site
- Additional nucleotides cannot bind or be incorporated into the viral DNA
- Viral replication is inhibited

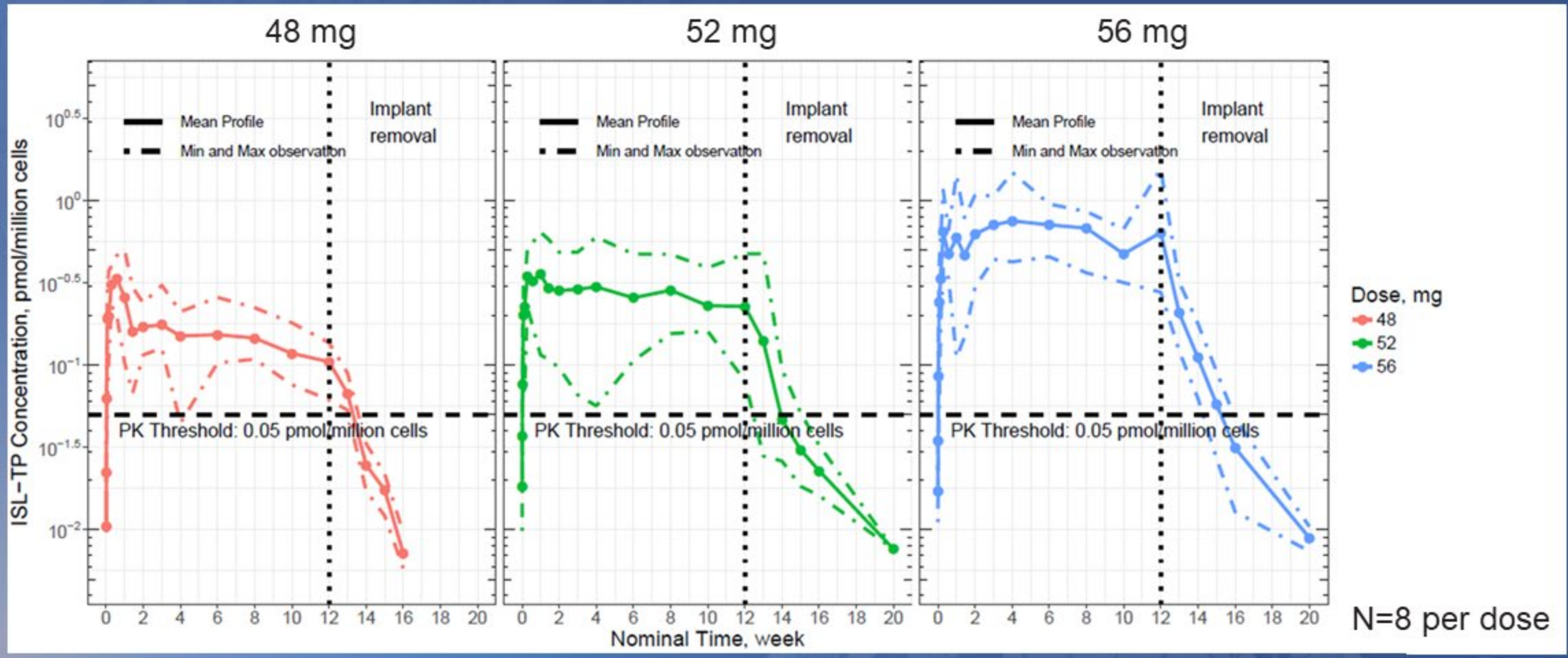
ISL is in clinical development for the treatment and prevention of HIV-1 infection.

Delayed chain termination
due to the 4'-ethynyl and 3'-hydroxyl groups



- ISL incorporation changes the vDNA structure
- If translocation occurs and a nucleotide is added, the structural change prevents further nucleotide incorporation
- Viral replication is inhibited
- As such, ISL is not in the reverse transcriptase (RT) active site and is no longer susceptible to resistance-conferring mutations

Intracellular ISL-TP PK threshold of 0.05 pmol/10^6 cells maintained throughout placement for two highest doses



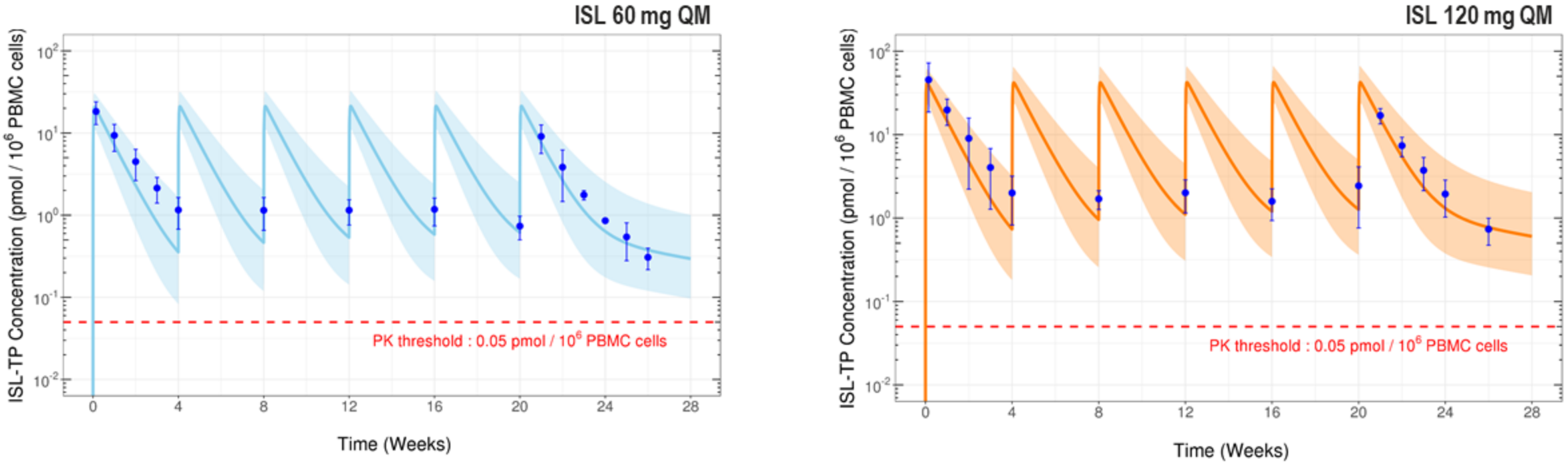
- 56 mg implant ISL-TP concentrations comparable to 62 mg from previous study
- Half-life after removal of implant similar to half-life of orally dosed ISL ($t_{1/2}$ for 56 mg is ~198 hr)

R Matthews et al., CROI 2021.

Novel delivery:
Long-acting Oral ARV's

ISL-TP PK exhibited approximately linear dose proportionality

Mean (SD) ISL-TP concentration-time profile in PBMCs overlaid on population PK model-simulated median (95% PI) ISL-TP concentrations in PBMCs



Population PK simulations assessed the interim observed plasma and PBMC PK data[1]

ISL-TP trough concentrations following 60 mg or 120 mg QM doses were all above the prespecified PK threshold of 0.05 pmol/10^6 PBMCs

ISL, islatravir; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetics; PI, prediction interval; QM, once monthly; SD, standard deviation; TP, triphosphate.

1. Rudd DJ, et al. CROI 2020 (poster).
Hillier et al. HIVR4P (2021).

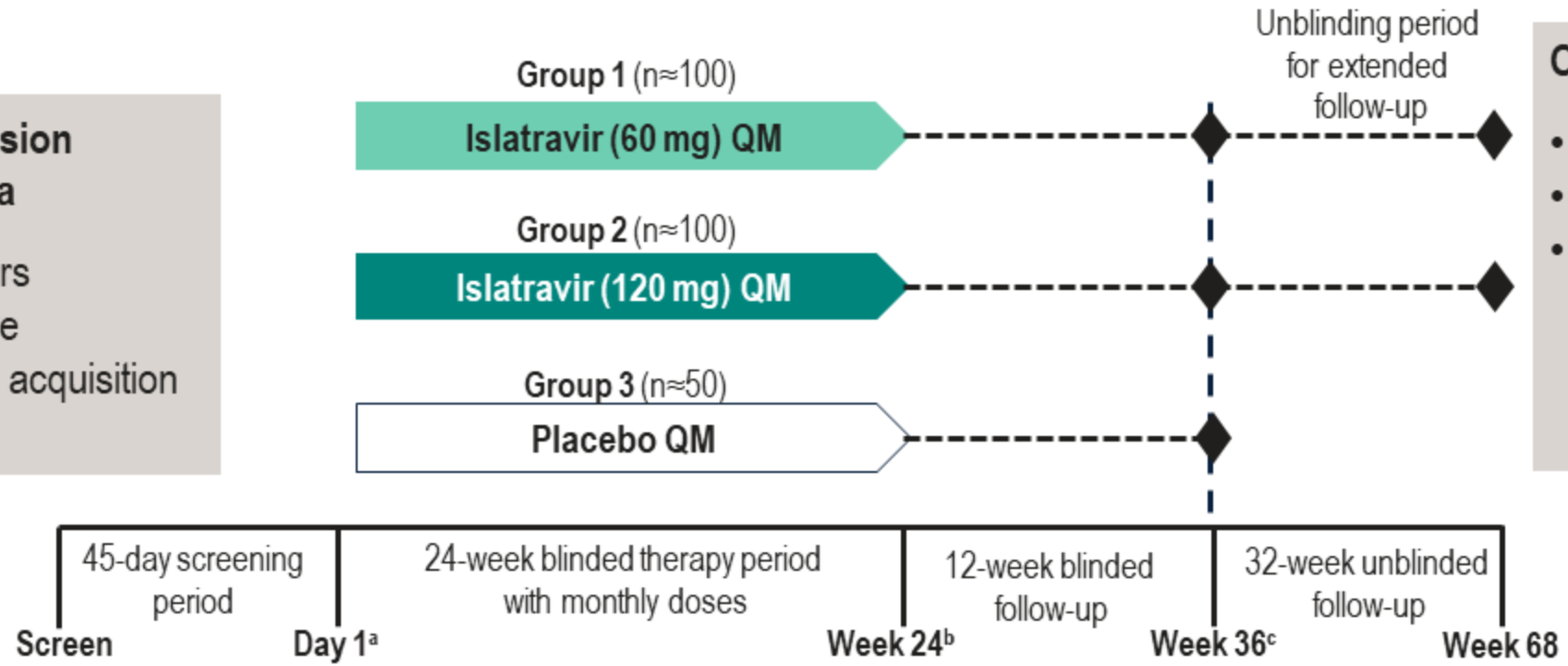
Patel M et al., CROI 2021; Abstract 87

P016 Study design: a Phase 2 study for once-monthly PrEP

Phase 2a, double-blind, randomized, parallel assignment, placebo-controlled, multicenter study in adults at low risk for HIV-1 acquisition

Key inclusion criteria

- Aged 18-65 years
- HIV seronegative
- Low risk for HIV acquisition
- N ≈ 250



Outcome measures

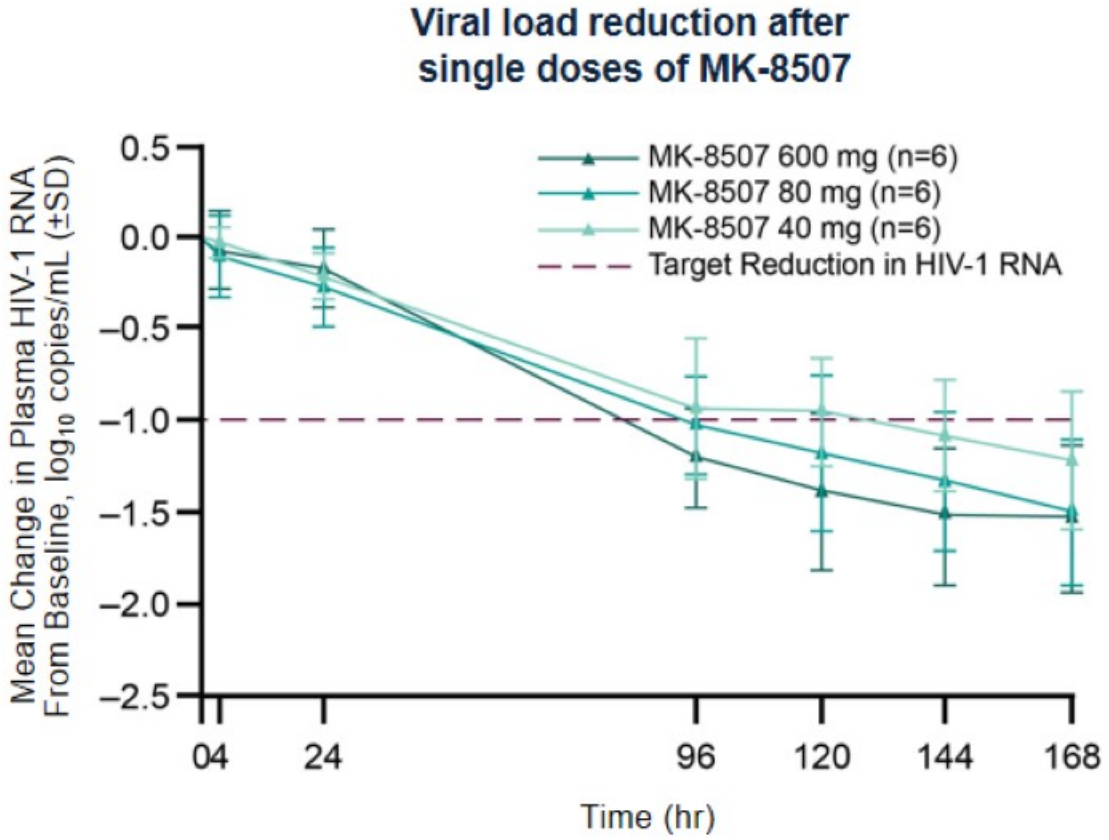
- Safety/tolerability
- PK (ISL/ISL-TP)
- Exploratory
  - PBMC PK
  - Tissue PK
  - Hormonal DDIs

[a]Randomization to study intervention at Day 1 and stratified by sex (female, male) and region (Africa, non-Africa). [b]Sponsor unblinded at Week 24 to allow for an interim evaluation of safety. Participants and investigators/clinical site personnel remain blinded up to Week 36. [c]After Week 36, only participants in the PBMC/PK bridging subset who were randomly assigned to receive ISL will have an additional 32-week extended, unblinded PK follow-up through Week 68.
DDI, drug-drug interaction; ISL, islatravir; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; QM, once monthly; TP, triphosphate. NCT04003103 (P016).
Hillier et al. HIVR4P (2021).

Patel M et al., CROI 2021; Abstract 87

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)



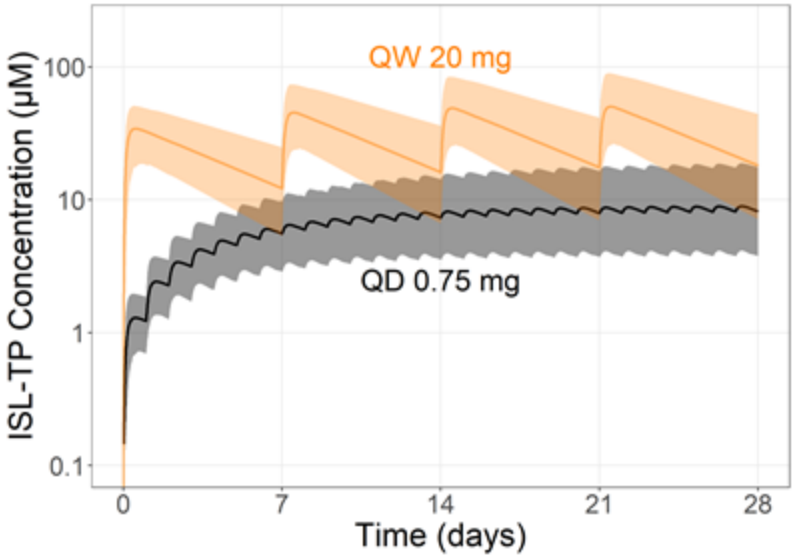
Diamond TL et al, CROI 2021.

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

ISL/MK-8507 oral QW phase 2 dose-ranging study – dose selection framework

ISL
Islatravir

Benchmark ISL-TP
QD vs QW dosing
population PK model



HIV QW phase 2 doses
ISL 20 mg
MK-8507
100, 200, 400 mg

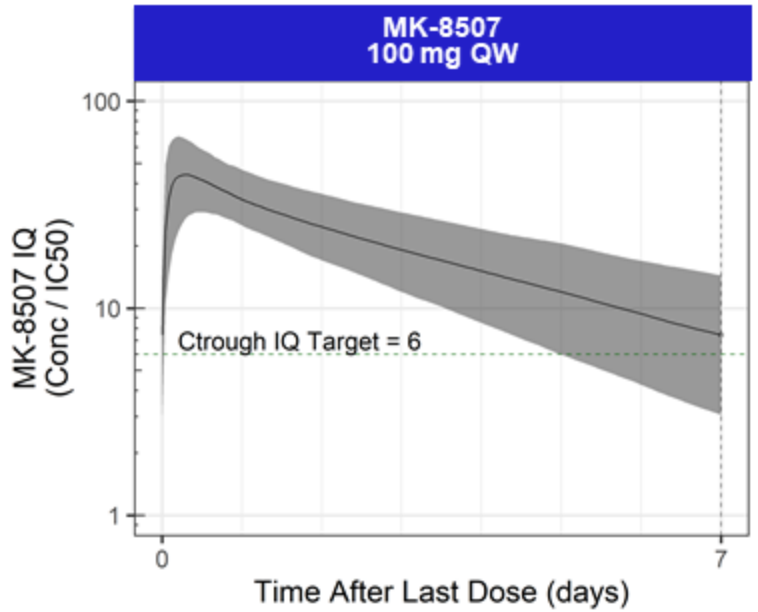
ISL+MK-8507
Viral dynamics modeling (VDM)
- PK (variability); PD (clinical IC_{50})
- IC_{50} shifts (resistance variants)
- Adherence to regimen

Simulations

Predict long-term efficacy
(Percentage of participants with HIV-1 RNA below 50 copies/mL at 48 weeks)

PK target
Population
PK model

MK-8507

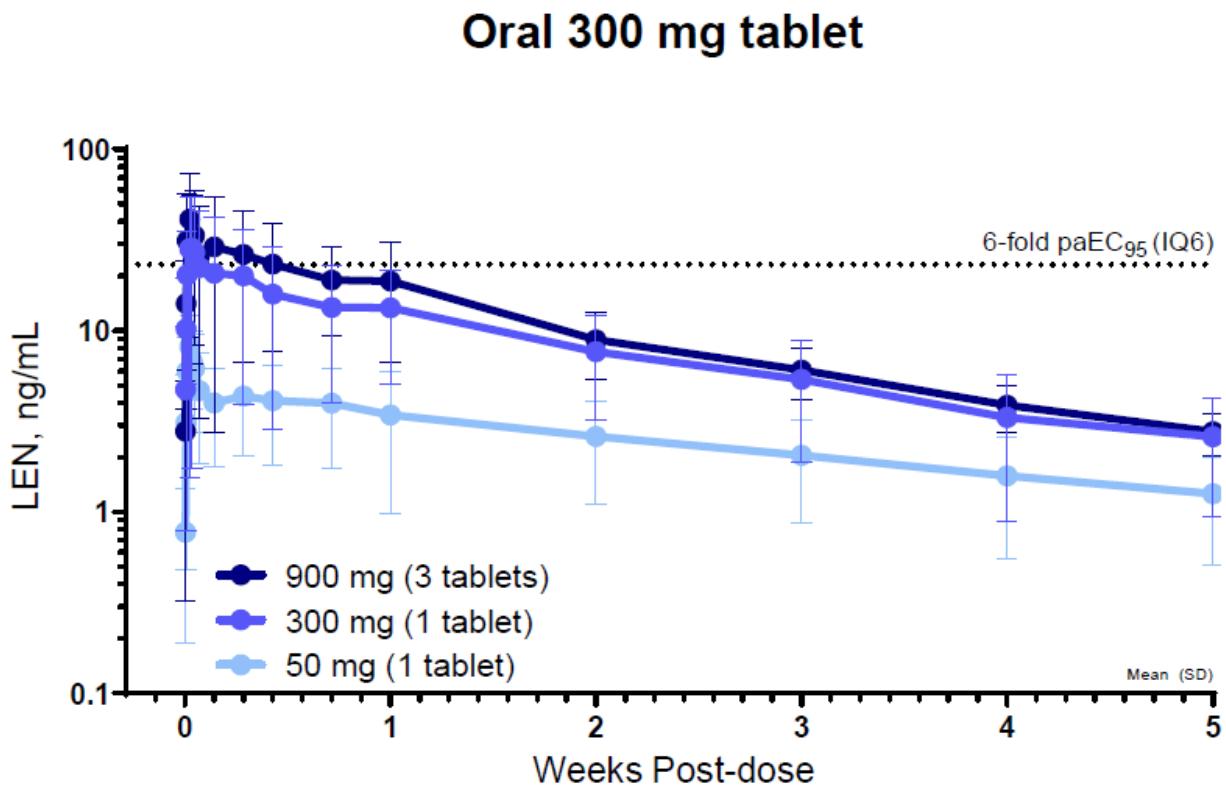


IQ - Inhibitory Quotient ; defined as $\frac{MK-8507\ Concentration}{in-vitro\ IC50}$

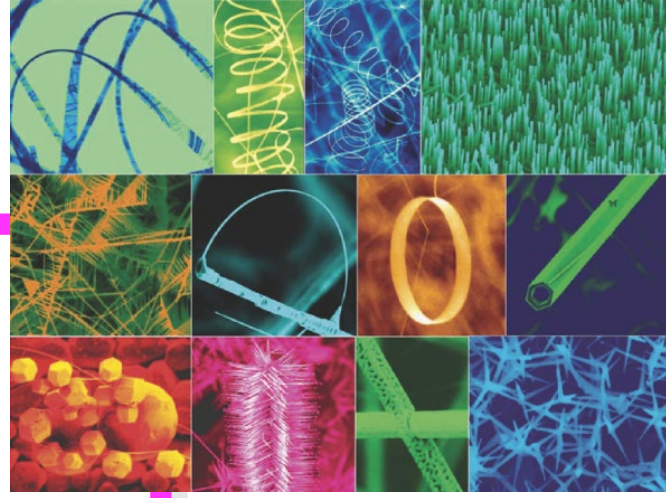
Kandala B et al, CROI 2021.

Oral LEN PK

- Half-life: approximately 12 days
- Significant accumulation with multiple dose
- Oral tablet can be used for:
  - PK loading
  - Lead-in

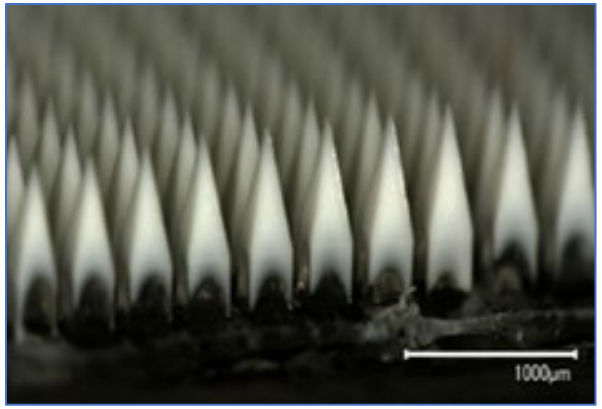


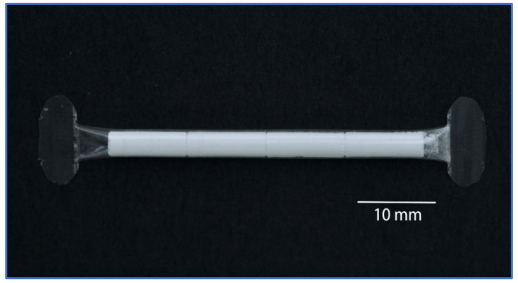
IQ, inhibitory quotient; $paEC_{95}$, protein binding-adjusted 95% effective concentration.
Begley R, et al. CROI 2020

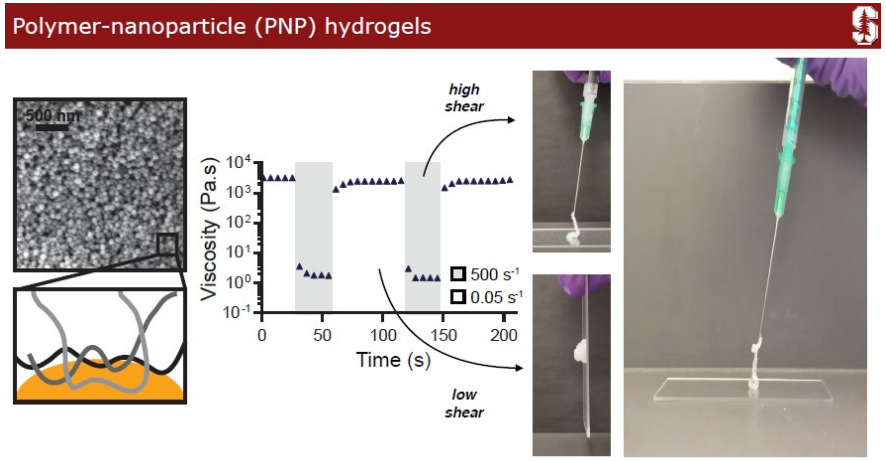


Novel delivery: What will the future hold???

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*

NATURE COMMUNICATIONS | DOI: 10.1038/s41467-017-02294-6 ARTICLE

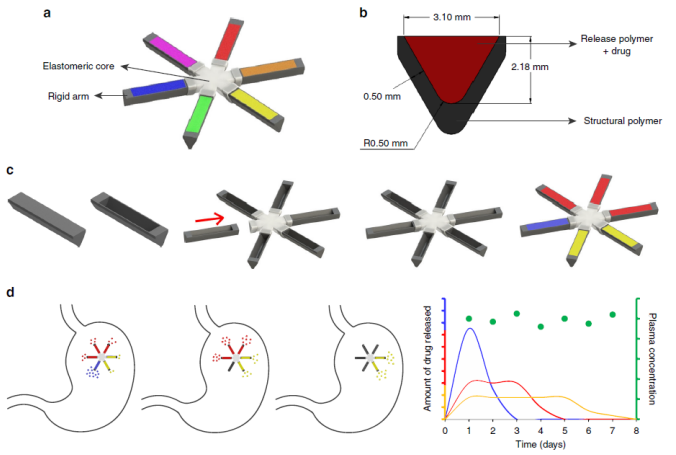
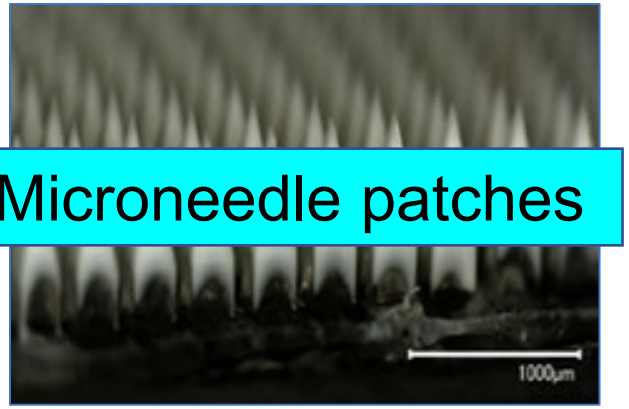


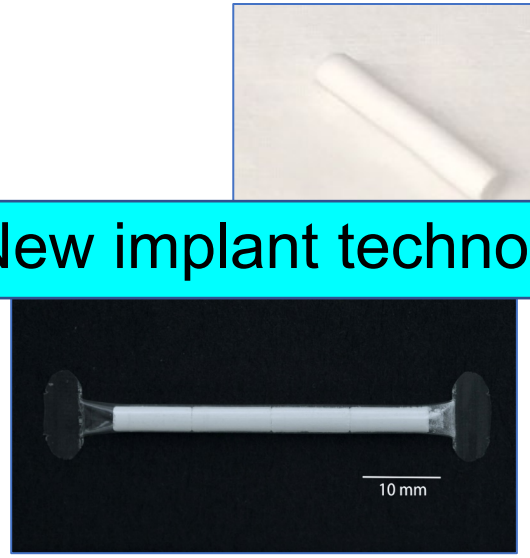
Fig. 1 Concept of oral long acting antiretrovirals. **a** The design of the gastric resident dosage forms. The dosage form consists of an elastomeric core (grey) and six drug loaded arms (multi-coloured). **b** The cross section of the arm. The outer sleeve of the arms is made of a rigid structural polymer 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

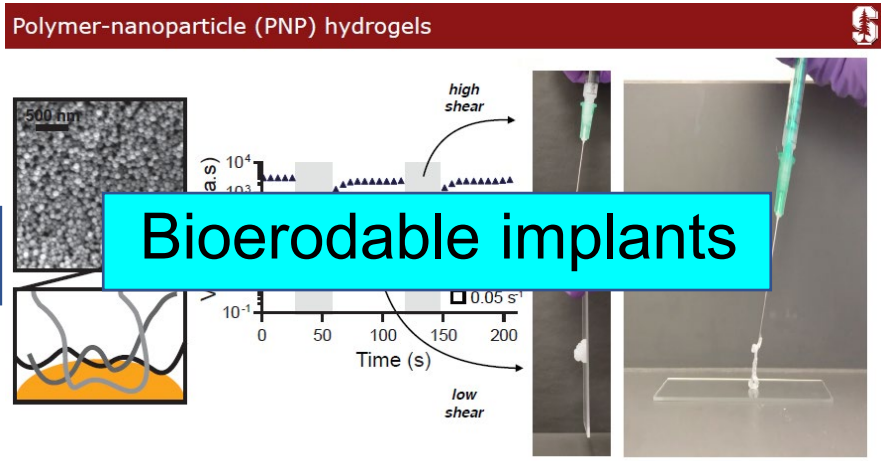
Microneedle patches



New implant technologies



Bioerodable implants



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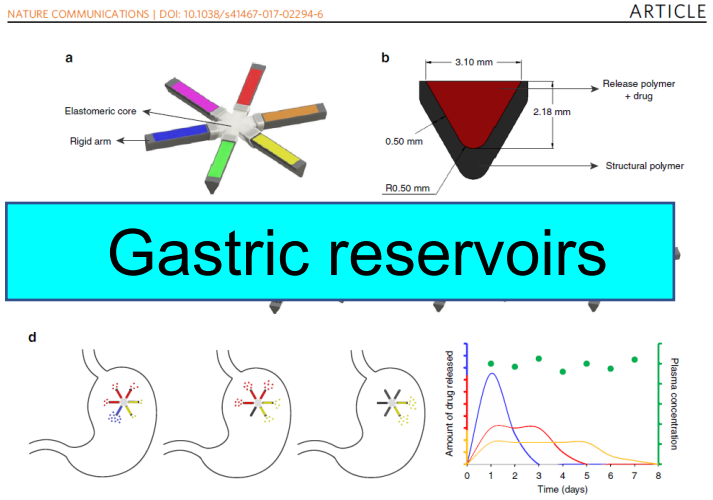
Reduced volume injections

Gastric reservoirs



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Combination technologies

Acknowledgements

Johns Hopkins University
Jane McKenzie-White

ViiV Healthcare
William Spreen
Kimberly Smith

Vaccine Research Center
Richard Koup

UNC
Myron Cohen

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