Long Acting ART for Treatment and PrEP

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Disclosures

I have received honoraria, travel sponsorship and research grants from:

- Gilead Sciences
- Janssen
- MSD
- ViiV Healthcare

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

BUT… success depends on adherence.

Long Acting – What's the attraction?

- Prevents poor adherence
- Infrequent dosing
- Use in patients with pill fatigue /aversion?
- Better protects health privacy
- Lower overall drug dose

Yearly intake of ARV by regimen

Regimen	Daily Dose (mg)	Yearly dose (g)
3-Drug Regimens:		
DRV/r + FTC/TDF	800/100 + 200/300	511.0
RAL + F/TAF	800 + 200/10	368.7
DTG/ABC/3TC	50/600/300	346.8
EVG/c/FTC/TAF	150/150/200/10	186.2
2-Drug Regimens:		
DTG + 3TC	50 + 300	127.8
DTG + RPV	50 + 25	27.4
$CAB_{oral} + RPV_{oral}$	30 + 25	20.1
$CAB_{im} + RPV_{im}$	400 + 600 (every 2 mo)	6g

Will there be demand for long-acting formulations?

Lessons from the contraceptive pill

Women choose **multiple** modalities:

Oral

Long acting injectable

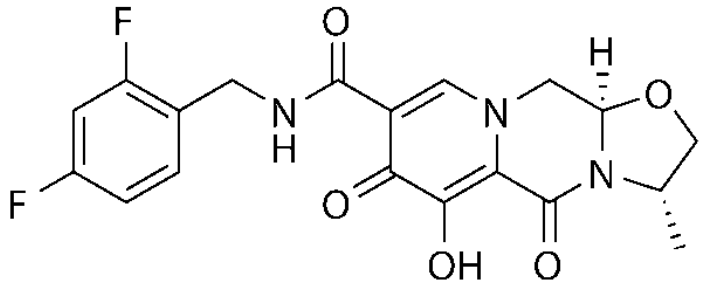
Topical (Coil)
Implantable

LA formulations: Pros and Cons

- **PROS**
- – Allow =monthly dosing
- – Tolerated well to date
- – More convenient
- – Less stigma
- – May promote adherence
- – Potential for DOT?

- **CONS**
- – Some require i.m. injection
- – Long-term tolerability?
- – Very long terminal ½-life
- – Cannot be self-administered
- – Potential for resistance in
- non-adherent patients

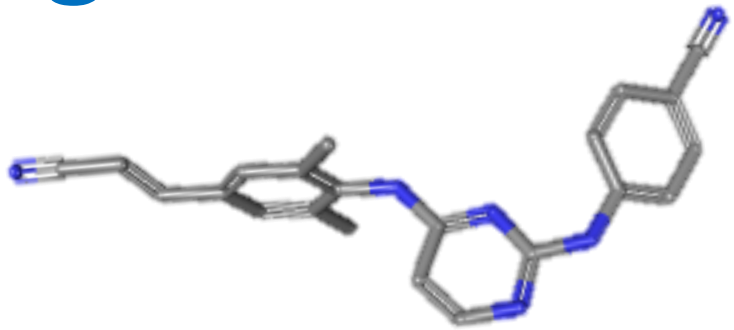
Most advanced Long – Acting Formulations



CABOTEGRAVIR

- UGT1A1 (minor 1A9) metabolism
- Low DDI potential as victim or perpetrator
- Animal studies support PreP
- Loading dose increased to 600mg im
- Treatment dose 400mg im q 4w

Spreen HIV-HEPPK 16 and 17



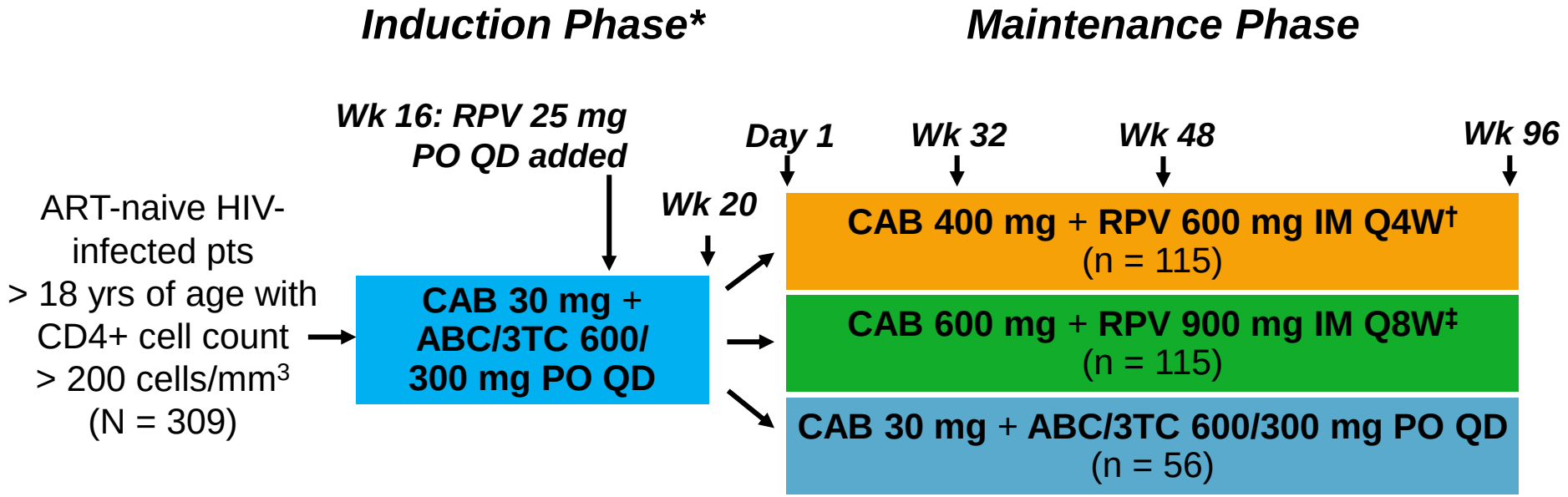
RILPIVIRINE LA

- Terminal T½ 30-90 days (G001)
- CYP3A4 substrate
- Low DDI potential as victim or perpetrator
- Animal studies support PreP
- Loading dose increased to 900mg im
- Treatment dose 600mg im q 4w

Crawels HIV-HEPPK 16 and 17

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label, randomized phase IIb study
  - Cabotegravir: INSTI formulated as oral tablet and for long-acting IM injection



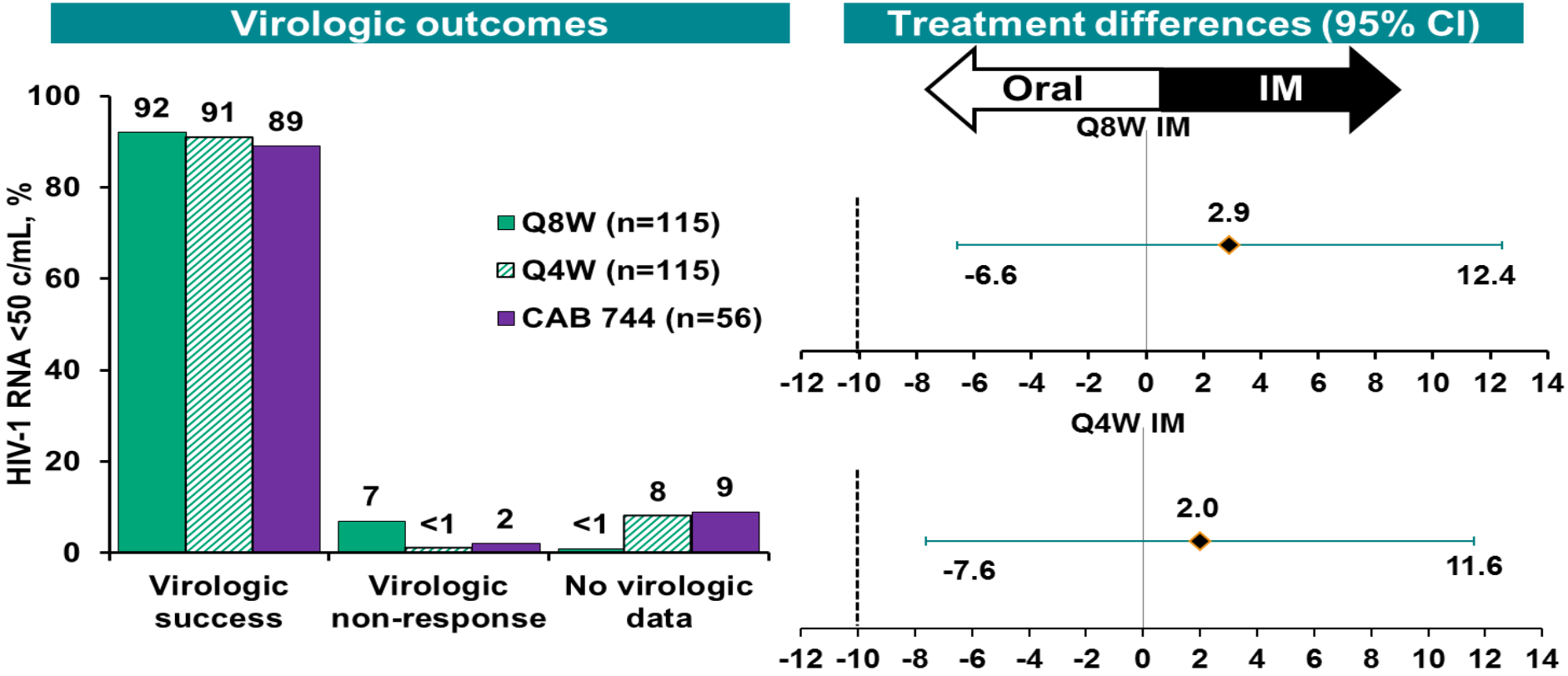
*Pts with HIV-1 RNA < 50 copies/mL from Wks 16-20 continued to maintenance phase. †CAB loading dose at Day 1. ‡CAB loading doses at Day 1 and Wk 4.

- Injections were 2-3 mL, IM (gluteal region), provider administered

Margolis DA, et al. Lancet. 2017;390:1499-1510.

Switch to Long acting Injectables LATTE-2

HIV-1 RNA <50 c/mL at Week 48: ITT-ME (Snapshot)



Both Q8W and Q4W comparable to Oral CAB at Week 48[a]

[a]Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

LATTE-2 Week 48 Results: A/Es

99% of ISRs for pts receiving injectable therapy

grade 1 (82%) or 2 (17%); none grade 4

Most frequent ISRs: pain (67%), nodules (7%), swelling (6%)

2/230 pts (< 1%) withdrew for ISRs (both in Q8W arm)

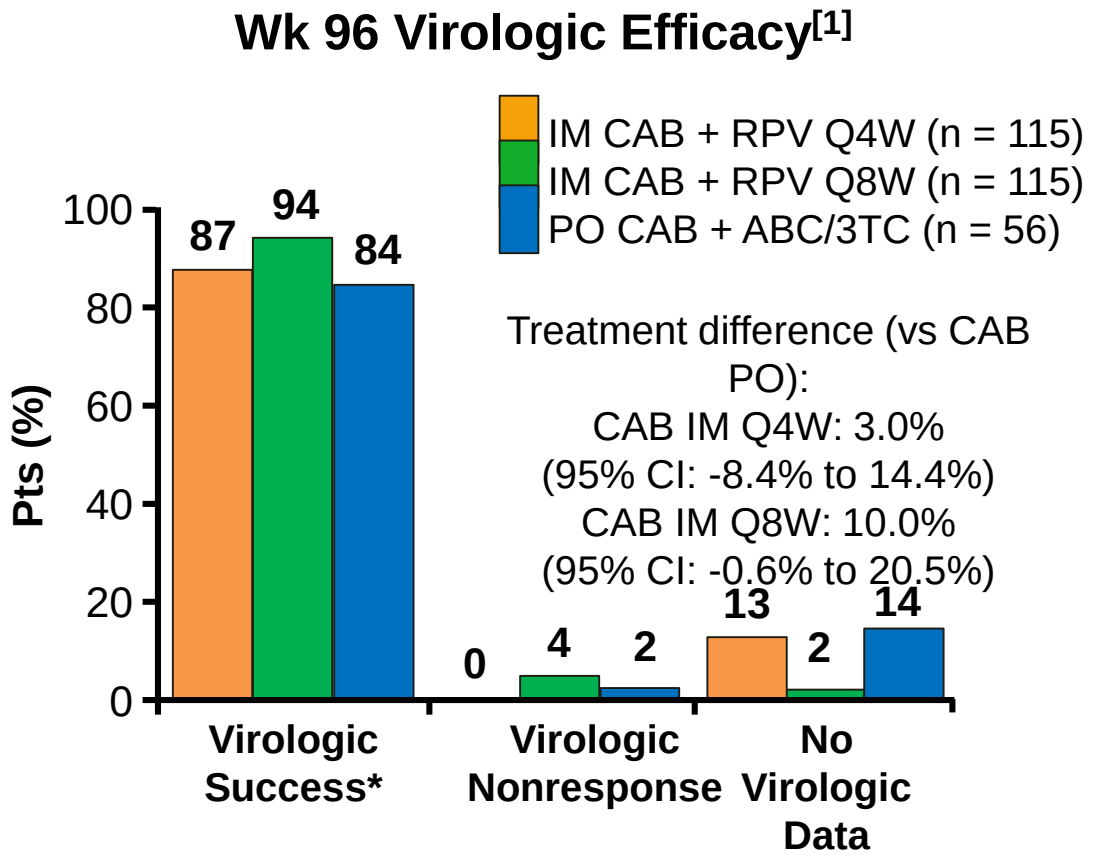
AEs leading to withdrawal

Pooled Q4W/Q8W IM arms, 4%

PO arm, 2%

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Sustainable response
LATTE-2: 96-Wk Results



*HIV-1 RNA < 50 copies/mL.

- Withdrawals between Wks 48 and 96:
  - CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent)
  - CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving IM CAB very satisfied to continue present treatment vs 43% receiving PO CAB
- Phase III maintenance trials (ATLAS and FLAIR) assessing Q4W dose;
- ATLAS-2M comparing Q4W and Q8W doses[2-4]

LATTE-2: Resistance data

- 3 participants met protocol-defined criteria for virological failure
  - 1 in oral dosing arm: no PR, RT or IN resistance mutations
  - 2 in Q8W injection arm:
    - One with R269R/G mixture in IN (no fold-change)
    - One with K103N, E138G, K238T in RT and Q148R in IN (resistant to NNRTIs, RAL, EVG, CAB but DTG sens)

Margolis DA et al Lancet 2017

Long-Acting Cabotegravir for PrEP

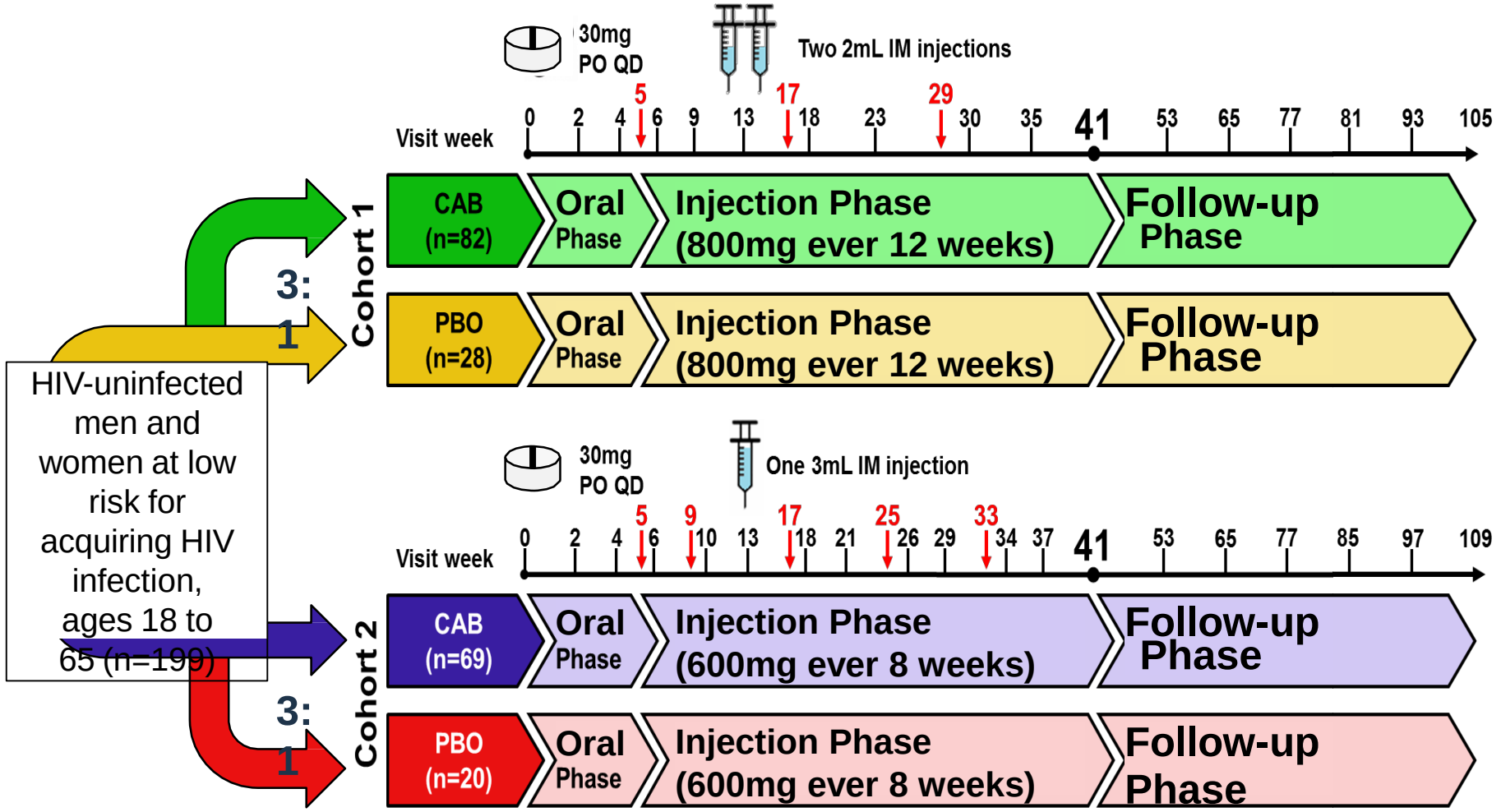
CAB Trial	Design and Findings
ECLAIR[1] ▪ Phase IIa (N = 127)	▪ **CAB LA IM (Q12W)** vs PBO IM for men at low risk for HIV infection ▪ Encouraging results in terms of pt satisfaction and safety
HPTN 077[2] ▪ Phase IIa (N = 199)	▪ **CAB LA IM (Q8W or Q12W)** vs PBO IM for men and women at low risk for HIV infection ▪ Q8W dosing consistently met prespecified PK targets
HPTN 083/084[3,4] ▪ Phase IIb/III (planned N = 4500/3200)	▪ **CAB LA IM (Q8W after 2 injections 4 wks apart)** vs **TDF/FTC PO QD** for MSM/TGW (083) or women (084) at high risk for HIV infection; trial now recruiting (estimated completion: 2022)

Considerations: may remove need for QD tablets; however, less control of drug intake and same potential for subinhibitory concentrations if doses missed

For all trials, an oral CAB phase preceded the injection phase.

1. Markowitz M, et al. Lancet HIV. 2017;4:e331-e340. 2. Landovitz R, et al. IAS 2017. Abstract TUAC0106LB. 3. ClinicalTrials.gov. NCT02720094. 4. ClinicalTrials.gov. NCT03164564.

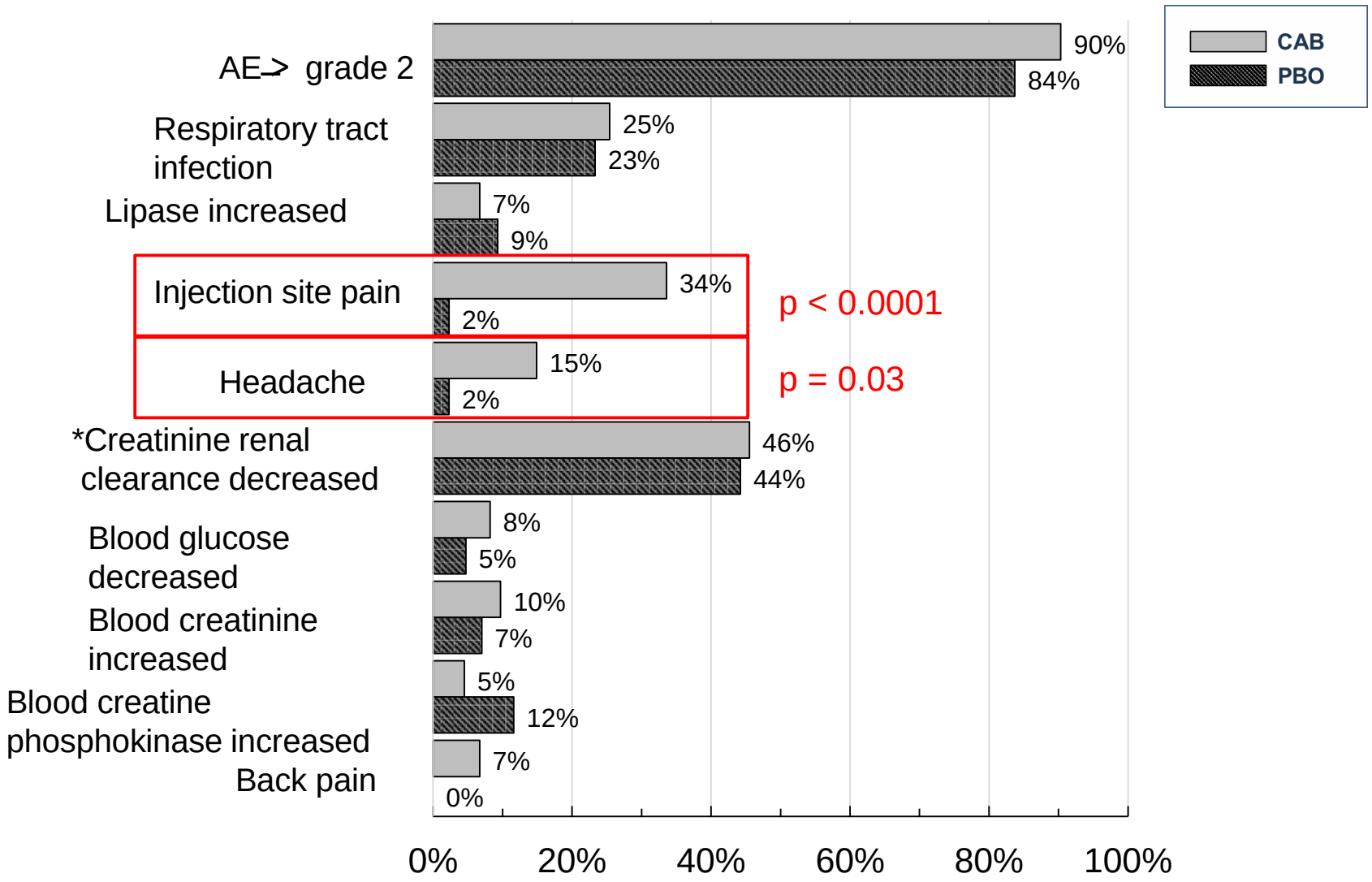
HPTN 077 Study Design



Landovitz R, et al, 9th IAS, Paris, 2017. Abstract #TUAC0106LB

Grade 2 or Higher AE's Experienced by >5% of Any Arm

n=177
(CAB 134, PBO 43)



* Grade 2: < 90 to 60 ml/min or 10 to < 30% decrease from participant's baseline.
Grade 3: < 60 to 30 ml/min or 30 to < 50% decrease from participant's baseline.

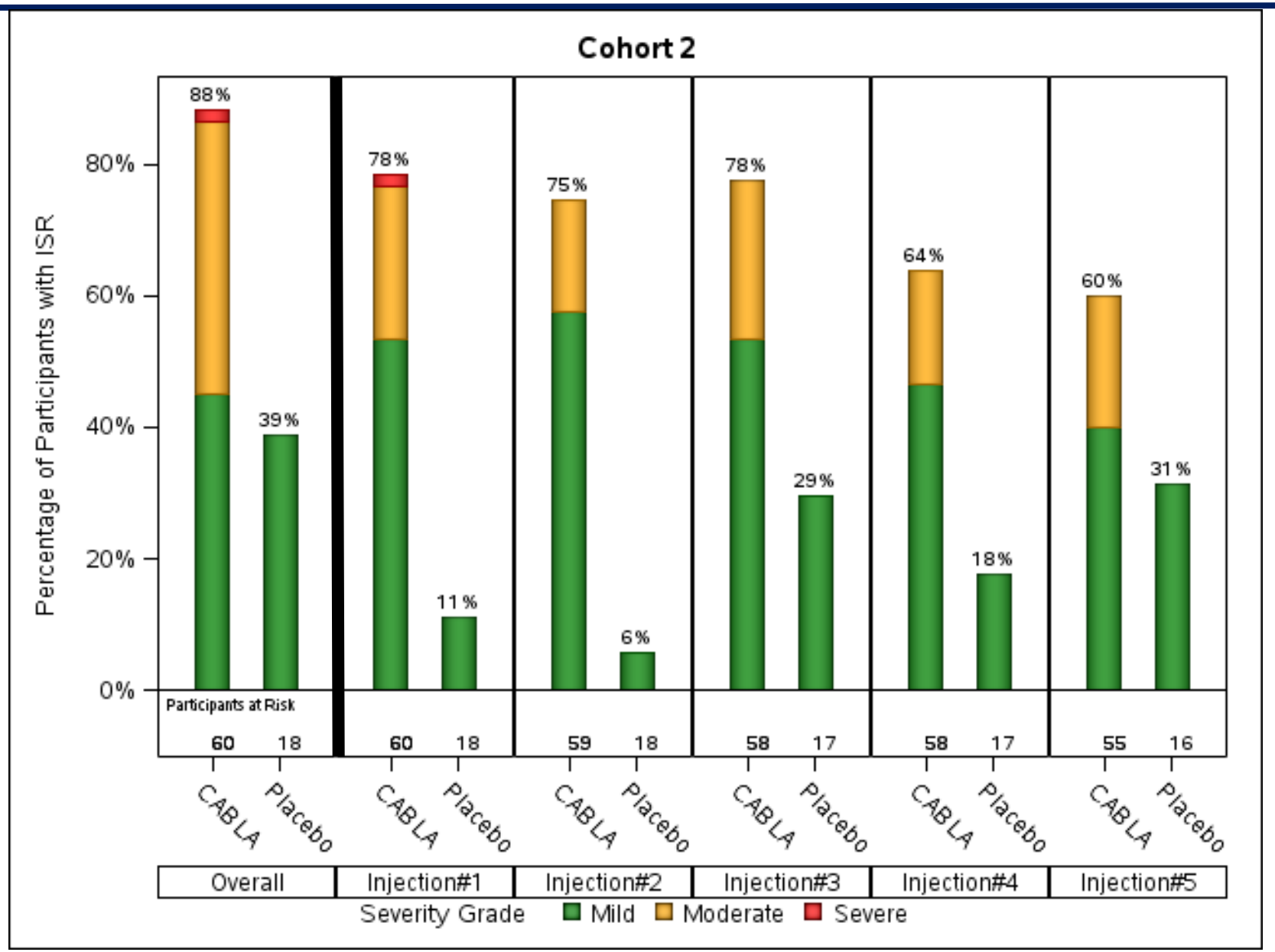
Landovitz R, et al, 9th IAS, Paris, 2017. Abstract

Other clinically significant events

- Active Arm Discontinuations due to clinical AE, n=12
  - Gastrointestinal, n=1
  - Rash, n=3
  - Nervous system, n=8
    - Seizure, n=1
- Seroconversion, Active CAB (Cohort 1)
  - Detected Study W77 (48W after final injection)
  - CAB levels BLOQ at W53 and 77
  - Wild type virus

Landovitz R, et al, 9th IAS, Paris, 2017. Abstract #TUAC0106LB

Percentage of Participants with ISR



Landovitz R, et al, 9th IAS, Paris, 2017. Abstract #TUAC0106LB

LA IM injectable ARVs for Treatment: Other Candidates

Name	Man.	Status	Clinical trials	Results Exp.	Notes
EFdA, MK-8591	Merck	Phase 2b	• Drive2SIMPLIFY	• 2020	• Phase 2B study with DOR + 3TC
GS-9131	Gilead	No ongoing LA clinical activity	• Preliminary data presented at CROI 2017		• Favorable resistance profile • Favorable synergistic effect when combined with other ARVs • Must overcome manufacturing challenges in order to bring down cost and allow for further study
GS-CA1	Gilead	Phase 2	• Phase 1B studies		• Capsid inhibitor with high potency, phase 1 studies suggested monthly or longer injections are possible • Currently being developed as an injection for use in Phase 2
VRC01	NIAID VRC	Phase 1/2	• VRC 601 • VRC 602		• Monoclonal antibody • Ongoing studies in adults and infants
Elsulfavirine or VM1500A	Viorim	Phase 2B	• Currently under review for oral use		• PK and Phase 2B studies show that this drug could be developed into a LA IM injection • Similar profile to Efavirenz with fewer AEs in clinical trials
Ibalizumab	TaiMed Biologics	Phase 3	• TMB-202 • TMB-301		• Monoclonal antibody, very high potency • 2017 results suggest drug resistance problems

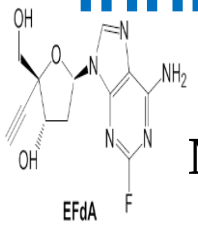
Emerging LA PrEP Strategies

Strategy	Examples
Long-acting ARVs	▪ Cabotegravir LA IM injection Q12W well tolerated in phase IIa study (ÉCLAIR)[1] ▪ MK-8591 (EFdA) has extended half-life in early-phase studies[2]
HIV vaccines	▪ HVTN100 vaccine met immunogenic criteria required to move into phase IIb efficacy studies[3] ▪ Other vaccine concepts in earlier phases of study
Broadly neutralizing antibodies	▪ VRC01, 3BNC117 bNAbs have extended half-lives in early studies,[4,5] efficacy trials under way

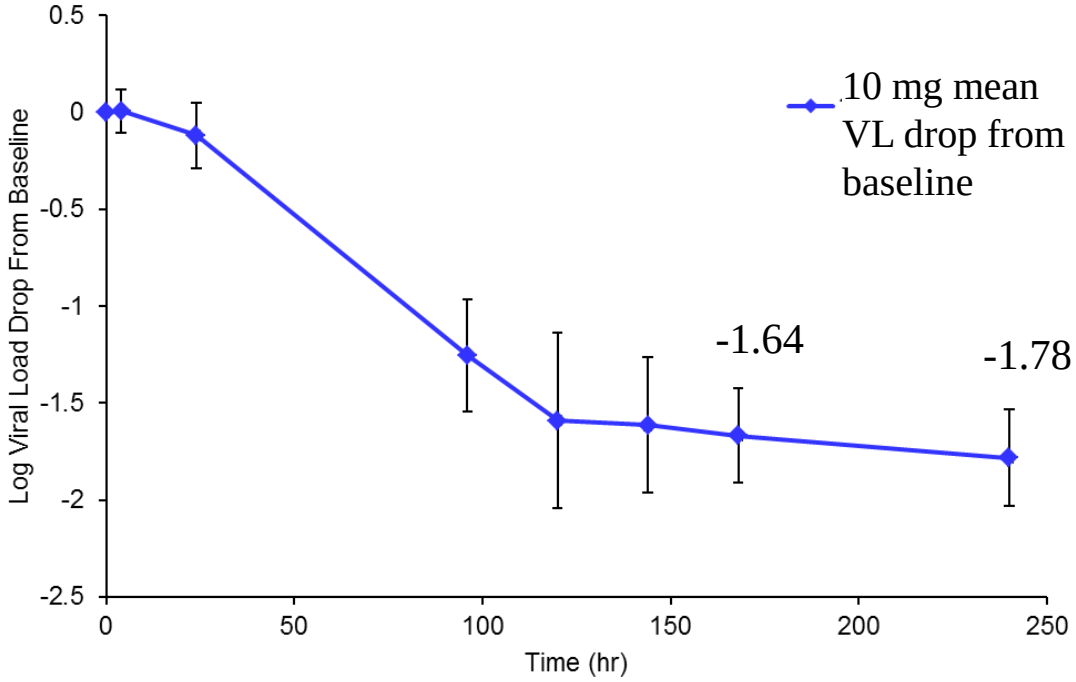
1. Markowitz M, et al. Lancet HIV. 2017;[Epub ahead of print]. 2. Friedman EJ, et al. CROI 2016. Abstract 437LB. 3. Bekker LG, et al. IAC 2016. Abstract TUAX0102LB. 4. Caskey M, et al. Nature. 2015;522:487-491. 5. Lynch RM, et al. Sci Transl Med. 2015;7:319ra206.

Other LA drugs for treatment or PrEP

MK-8591 (EFdA) Nucleoside reverse transcriptase translocation inhibitor



MK-8591 is Effective in HIV patients when Dosed Once-Weekly: Results from ongoing Ph1b study

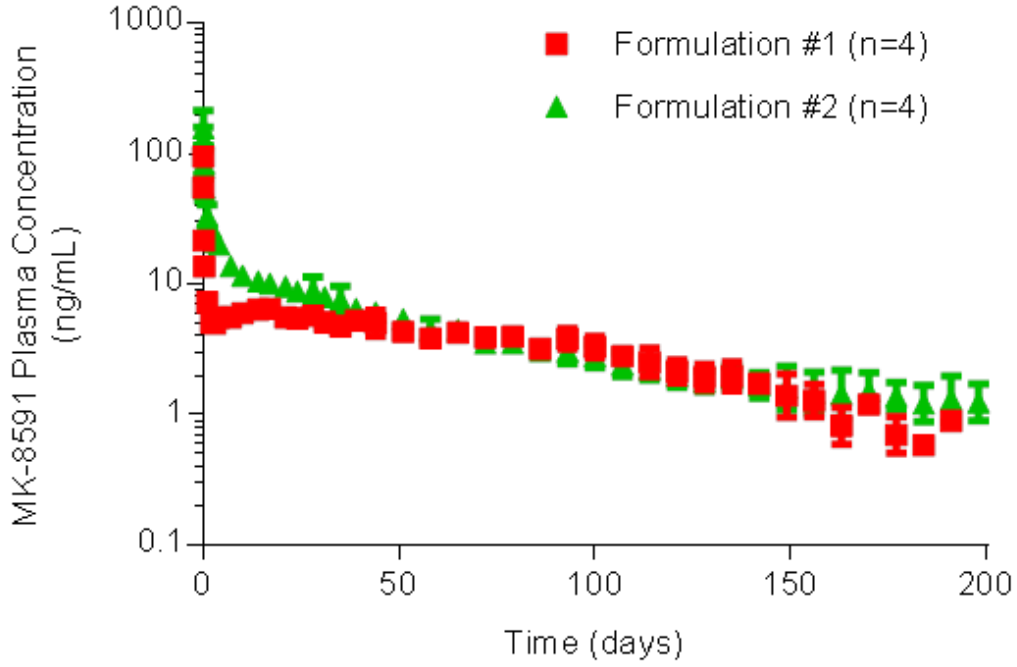


A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10

Friedman, et al., CROI 2016 Poster# 437LB

Potential for a drug in an implant

MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days

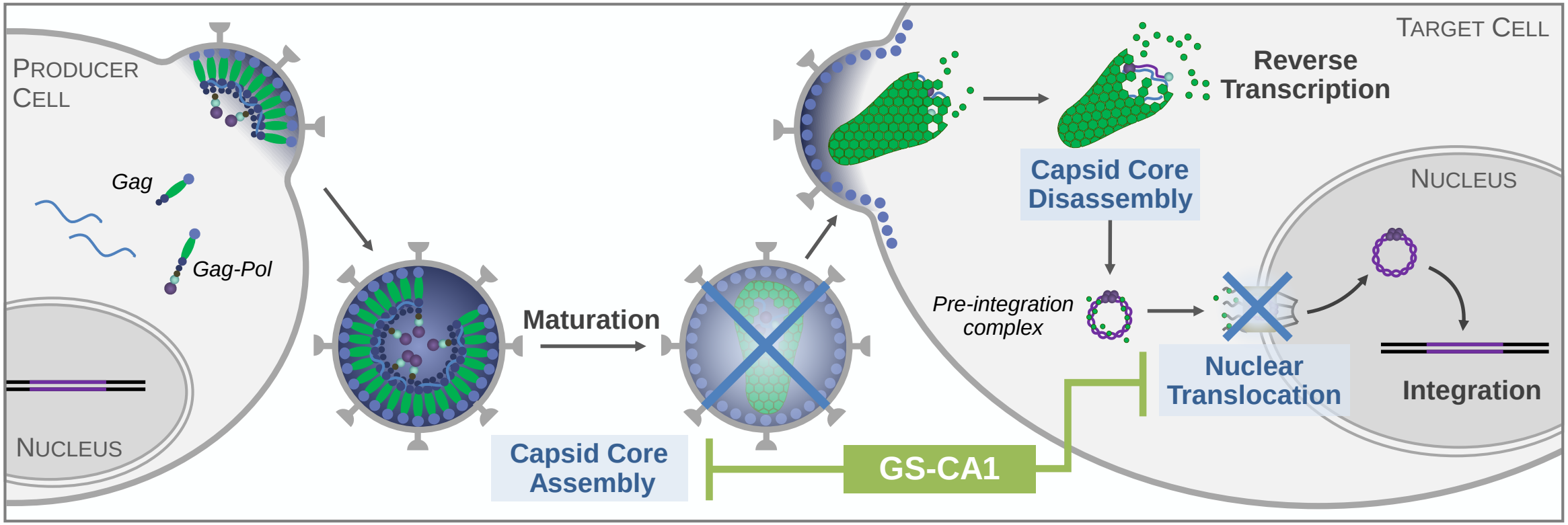


Low dose amenable to extended-duration parenteral formulation

Grobler et al CROI 2016

GS-CA1 -Capsid Inhibitor

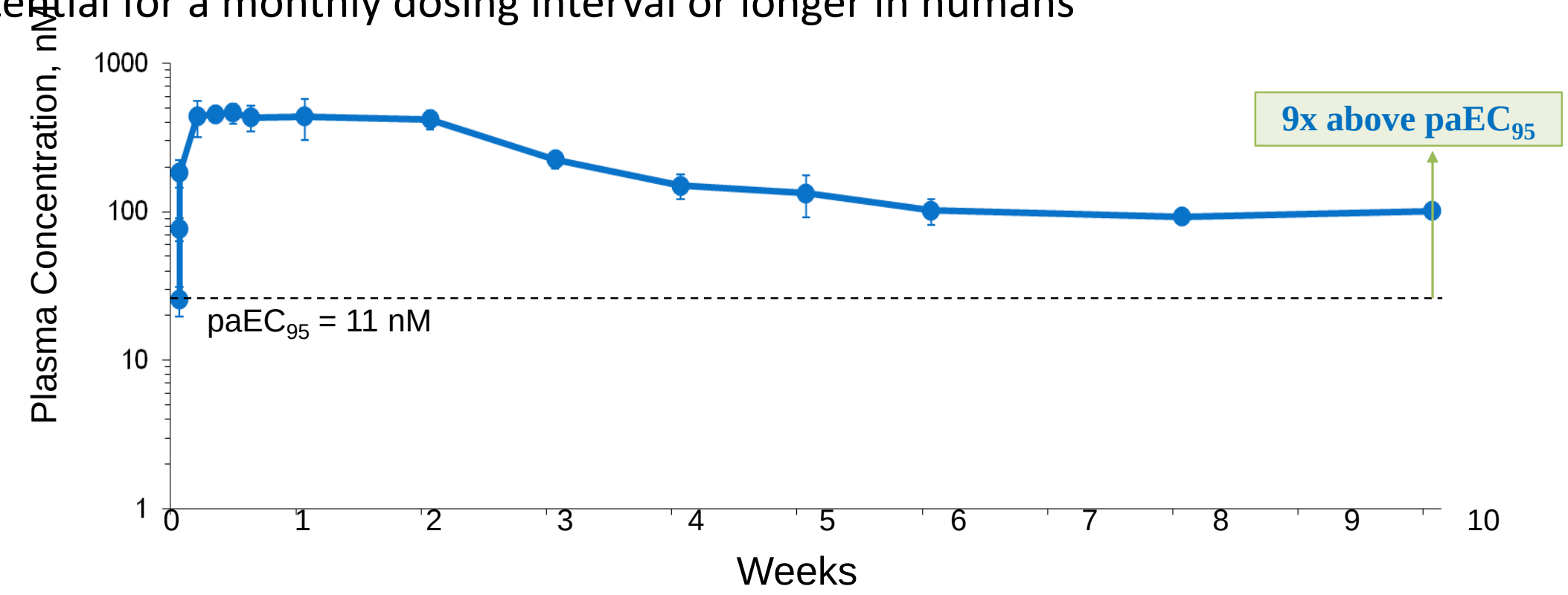
Mode of Action Summary



GS-CA1 Pharmacokinetics in Rats

Extended Release Formulation

- Single subcutaneous injection maintains plasma concentrations well above $paEC_{95}$ for >10 wks
- Potential for a monthly dosing interval or longer in humans

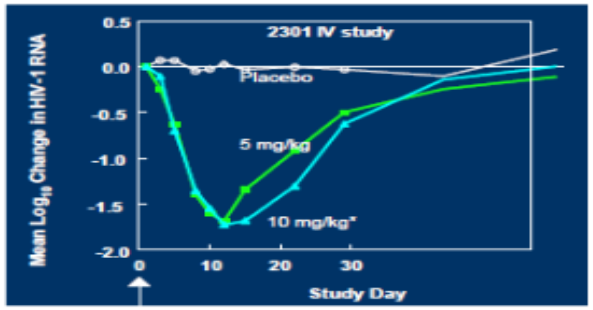


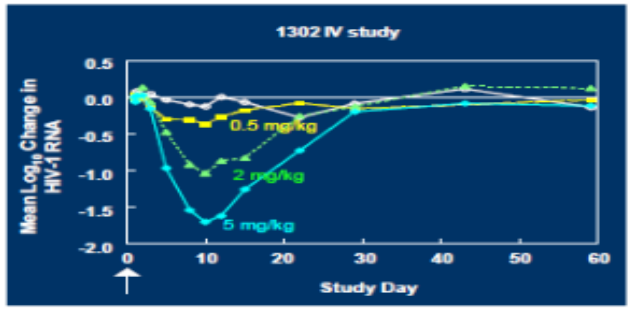
Monoclonal Antibody against CCR5

PRO-140 phase 1-2 trial results

Intravenous Administration

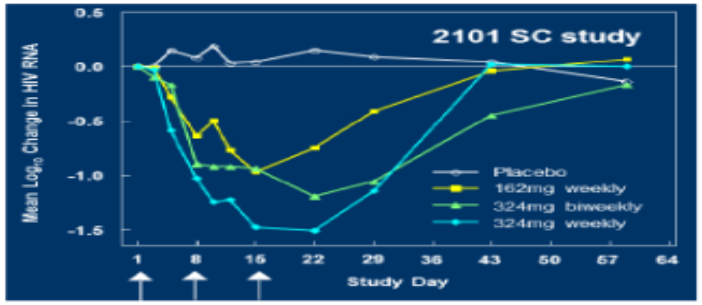
Significant single-dose viral load reductions over 3-week period





Subcutaneous Administration

First proof of concept for a long-acting, self-administrable HIV drug administered weekly or bi-monthly



Study	Route	Treatment Groups	Reference
PRO 140 1302	IV	▪ Placebo (n=9) ▪ 0.5 mg/kg single dose (n=10) ▪ 2 mg/kg single dose (n=10) ▪ 5 mg/kg single dose (n=10)	Jacobson et al., J. Infect. Dis. 198:1345, 2008
PRO 140 2301	IV	▪ Placebo (n=11) ▪ 5 mg/kg single dose (n=10) ▪ 10 mg/kg single dose (n=10)	Jacobson et al., AAC, 54:4137, 2010
PRO 140 2101	SC	▪ Placebo (n=10) ▪ 162 mg Days 1, 8, 15 (n=11) ▪ 324 mg Days 1, 15 (n=12) ▪ 324 mg Days 1, 8, 15 (n=11)	Jacobson et al., J. Inf. Dis. 201:1481, 2010

mAb against CCR5
Pro140 monotherapy in ART suppressed patients

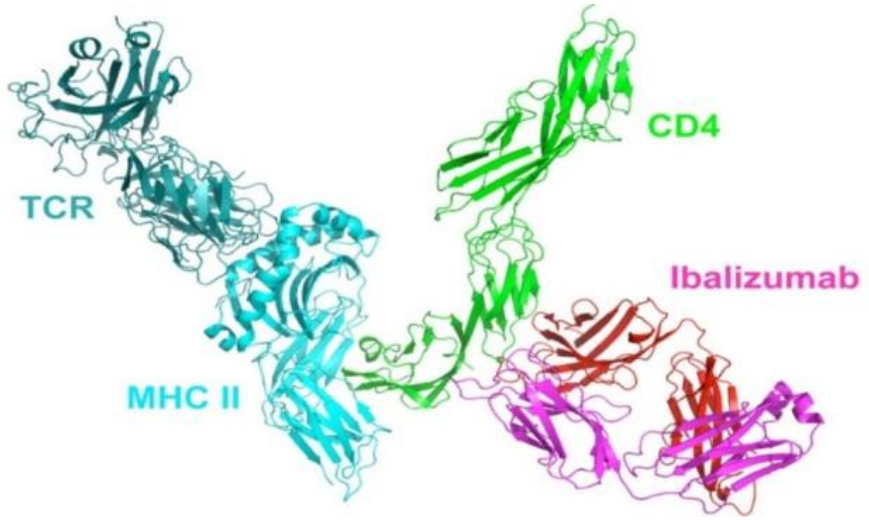
- **39 HIV-infected patients on suppressive ART**
- **R5 virus by Monogram Trofile DNA assay**
- **16 continued self-administration sc after week 13**
- **15 eligible participants (median CD4 586 cells/mm3)**
- – 11 remained suppressed on PRO140 for >1 year
- – 3 VF; one moved away from study site
- – No change in co-receptor usage or susceptibility
- **No anti-PRO140 antibodies detected**

- Lalezari J et al CROI 2017

Ibalizumab – Long-Acting, Monoclonal Antibody

- Active against HIV-1 resistant to all approved ARV agents
- Binds to CD4 to prevent HIV attachment
- Initial development as IV infusion to be administered every 2 weeks

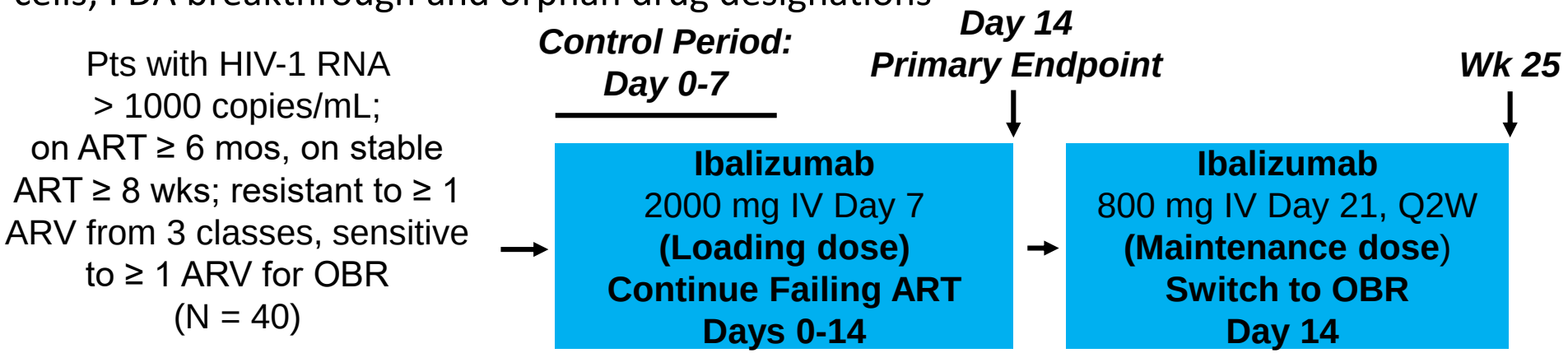
- In treatment-experienced patients (n=40) with resistance to approved ARV agents, After 24 weeks of treatment (with optimized background regimen):
  - Mean VL decrease of 1.6 $\log_{10}$ from Baseline (55% with ≥1 $\log_{10}$; 48% with ≥2 $\log_{10}$)
  - 43% of patients had VL of <50 copies; 50% with <200 copies
- Adverse reactions were mild to moderate



Lewis et al. Croi 2017 Abstract #449LB

TMB-301: Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Single-arm, open-label phase III trial[1]
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14
  - **Ibalizumab:** humanized mAb to CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells; FDA breakthrough and orphan drug designations



- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance
- TMB-311: pts who completed Wk 24 of TMB-301 could continue to receive ibalizumab for an additional 24 wks (N = 27)[2]

1. Lewis S, et al. CROI 2017. Abstract 449LB. 2. Emu B, et al. IDWeek 2017. Abstract 1686.

TMB-301/-311: Key Results

Virologic Outcome With Ibalizumab	TMB-301		TMB-311
	Day 14[1] (N = 40)	Wk 24[2] (N = 40)	Wk 48[3] (N = 27)
≥ 0.5 log_{10} HIV-1 RNA decrease, %	83*	NR	NR
≥ 1.0 log_{10} HIV-1 RNA decrease, %	60	55	NR
≥ 2.0 log_{10} HIV-1 RNA decrease, %	NR	48	NR
Mean log_{10} HIV-1 RNA decrease	1.1	1.6	NR
HIV-1 RNA < 50 copies/mL, %	NR	43	59
HIV-1 RNA < 200 copies/mL, %	NR	50	63

*P < .0001 vs 3% at end of control period.

- Wk 24: 9 pts reported 17 serious AEs; 1 drug-related serious AE (IRIS) resulted in d/c
- Wk 48 TEAEs (all mild/moderate): upper respiratory tract infection, 15%; diarrhea, 11%; rashes, 7%

1. Lalezari J, et al. IDWeek 2016. Abstract LB-6. 2. Lewis S, et al. CROI 2017. Abstract 449LB.
3. Emu B, et al. IDWeek 2017. Abstract 1686.

Broadly Neutralizing Antibodies (bNAbs) for HIV Prevention

- VRC01: monoclonal antibody directed against the HIV-1 CD4 binding site[1]
  - Terminal half-life in PK study: ~ 15 days; demonstrated antiviral activity in HIV-infected pts
  - Randomized phase II prevention trials now under way
    - Low-dose/high-dose IV VRC01 or placebo Q8W for adults at high risk for HIV infection
    - MSM/TGW (North/South America) and women (sub-Saharan Africa); planned overall enrollment: N = 4200

- Other bNAbs in development: 3BNC117, 10-1074[

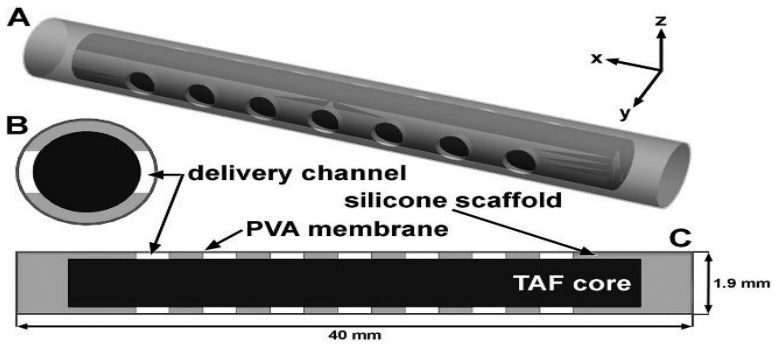
Dapivirine Vaginal Ring for HIV Prevention

HIV Protection Efficacy vs Placebo, %	ASPIRE/MTN-020[1] (N = 2629)	IPM 027/Ring[2] (N = 1959)
Overall	27 (95% CI: 1-46; *P* = .05)	30.7 (95% CI: 0.90-51.5; *P* = .04)
Age > 21 yrs	56 (95% CI: 31-71; *P* < .001)	37.5 (95% CI: 3.49-59.5)

- HOPE (ASPIRE) and DREAM (IPM 027/Ring) programs implementing open-label extension dapivirine ring studies

1. Baeten JM, et al. N Engl J Med. 2016;375:2121-2132. 2. Nel A, et al. N Engl J Med. 2016;375:2133-2143.

Long Acting Implants



- **Potential advantages over injectables**
  - **Removable**
  - **More consistent drug release**
  - **Could remain in place for years.**
- **Potential disadvantages over injectables.**
  - **Specialised device required for insertion**
  - **Removal?**
  - **Regulated as both a drug and device.**
  - **Generic marketplace?**

Schlesinger E et al Pharm Res 2016; 33: 1649-1656; *Gunawardana M et al; AAC; 2015; 59: 3913-3919*

Long Acting – Oral

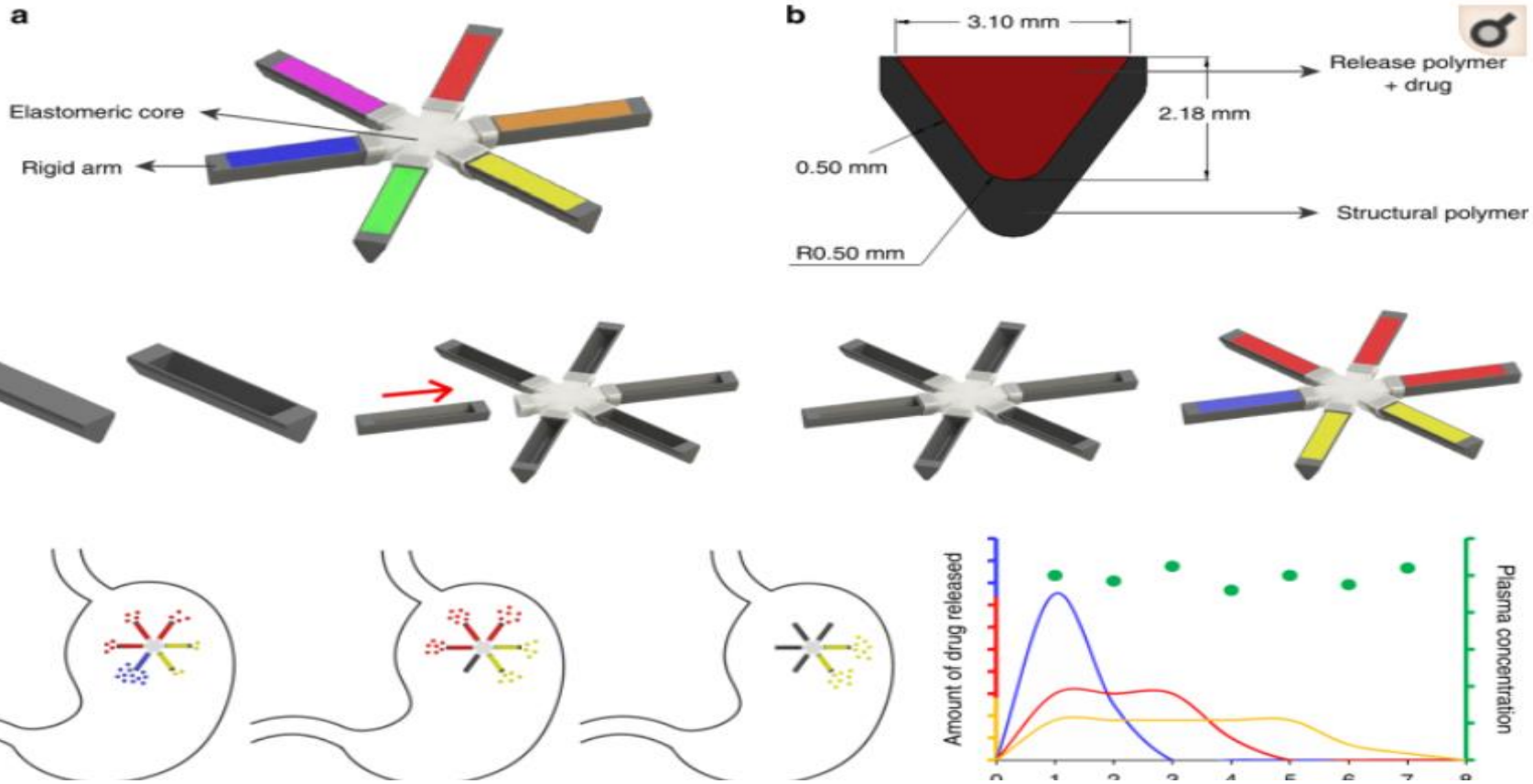
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-02294-6 OPEN

Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy

Ameya R. Kirtane[1], Omar Abouzid[1,2], Daniel Minahan[1], Taylor Bensel[1], Alison L. Hill[3], Christian Selinger[4], Anna Bershteyn[4], Morgan Craig[3], Shirley S. Mo[3], Hormoz Mazdiyasni[1], Cody Cleveland[1,5], Jaimie Rogner[1], Young-Ah Lucy Lee[1], Lucas Booth[1], Farhad Javid, Sarah J. Wu[6], Tyler Grant[7], Andrew M. Bellinger[7], Boris Nikolic[8], Alison Hayward[1], Lowell Wood[4], Philip A. Eckhoff[4], Martin A. Nowak[3], Robert Langer[1,9,10] & Giovanni Traverso[1,5]



Nature Comms 2018; Jan 9th

Key Questions With Long-Acting ART

- Can we move away from daily oral therapy for HIV?
- Are emerging long-acting therapies as effective as oral therapies?
- What about toxicity?
- Is self-administration feasible? Is it desirable?
- What pts might be ideal candidates for long-acting therapy?
- How can resistance be prevented if pts miss doses?
- Can these agents be used as PrEP?