Treatment of HIV with long-acting agents

Charles Flexner, MD
Johns Hopkins University

DIVISION OF
CLINICAL
PHARMACOLOGY

How close are we to having approved long acting treatments for HIV?

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

David A Margolis, Juan Gonzalez-Garcia, Hans-Jürgen Stellbrink, Joseph J Eron, Yazdan Yazdanpanah, Daniel Podzamczer, Thomas Lutz, Jonathan B Angel, Gary J Richmond, Bonaventura Clotet, Felix Gutierrez, Louis Sloan, Marty St Clair, Miranda Murray, Susan L Ford, Joseph Mrus, Parul Patel, Herta Crauwels, Sandy K Griffith, Kenneth C Sutton, David Dorey, Kimberly Y Smith, Peter E Williams, William R Spreen*

Summary

Background Cabotegravir and rilpivirine are antiretroviral drugs in development as long-acting injectable formulations. The LATTE-2 study evaluated long-acting cabotegravir plus rilpivirine for maintenance of HIV-1 viral suppression through 96 weeks.

Methods In this randomised, phase 2b, open-label study, treatment-naive adults infected with HIV-1 initially received oral cabotegravir 30 mg plus abacavir–lamivudine 600–300 mg once daily. The objective of this study was to select an intramuscular dosing regimen based on a comparison of the antiviral activity, tolerability, and safety of the two intramuscular dosing regimens relative to oral cabotegravir plus abacavir–lamivudine. After a 20-week induction period on oral cabotegravir plus abacavir–lamivudine, patients with viral suppression (plasma HIV-1 RNA <50 copies per mL) were randomly assigned (2:2:1) to intramuscular long-acting cabotegravir plus rilpivirine at 4-week intervals (long-acting cabotegravir 400 mg plus rilpivirine 600 mg; two 2 mL injections) or 8-week intervals (long-acting cabotegravir 600 mg plus rilpivirine 900 mg; two 3 mL injections) or continued oral cabotegravir plus abacavir

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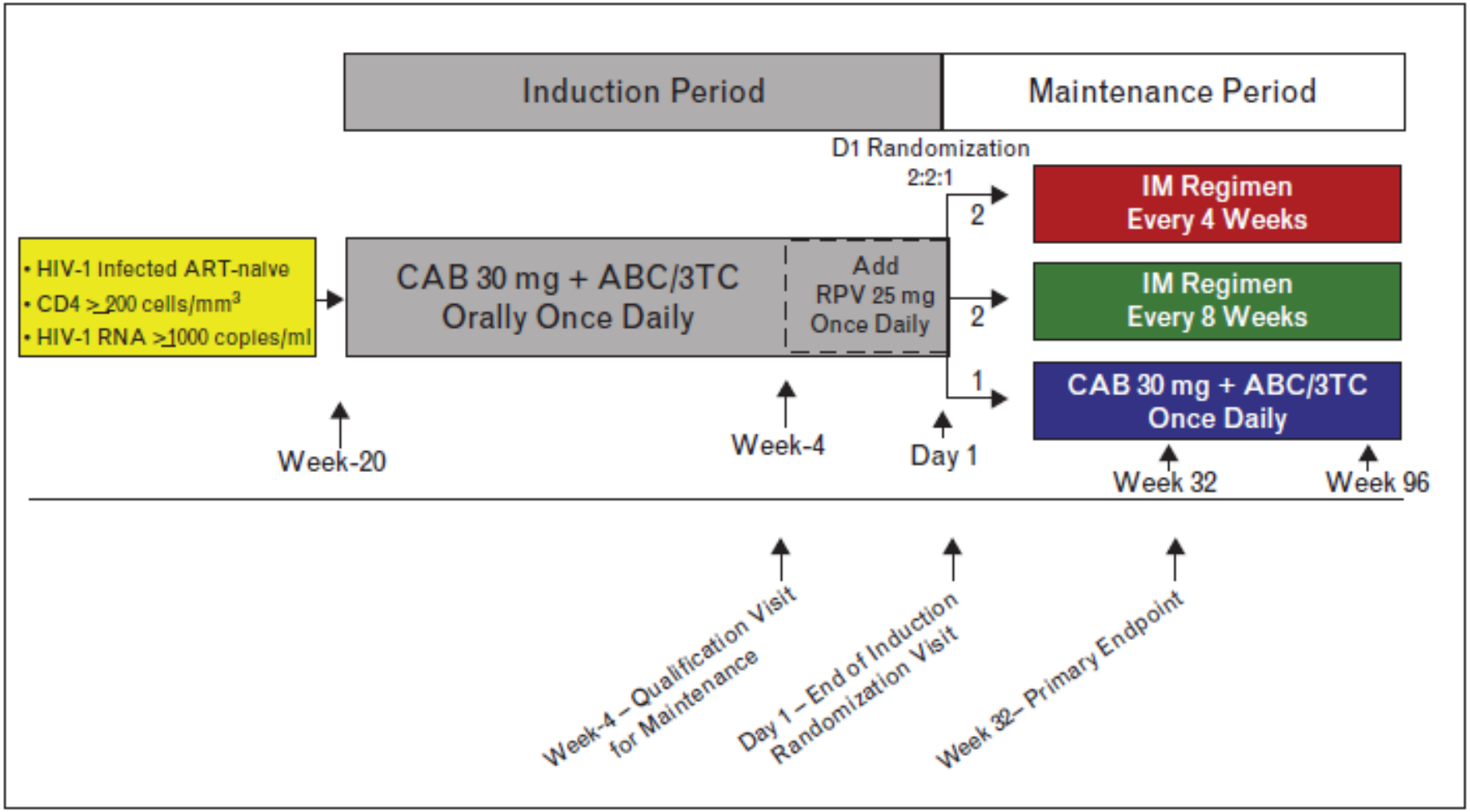
See Comment page 1468

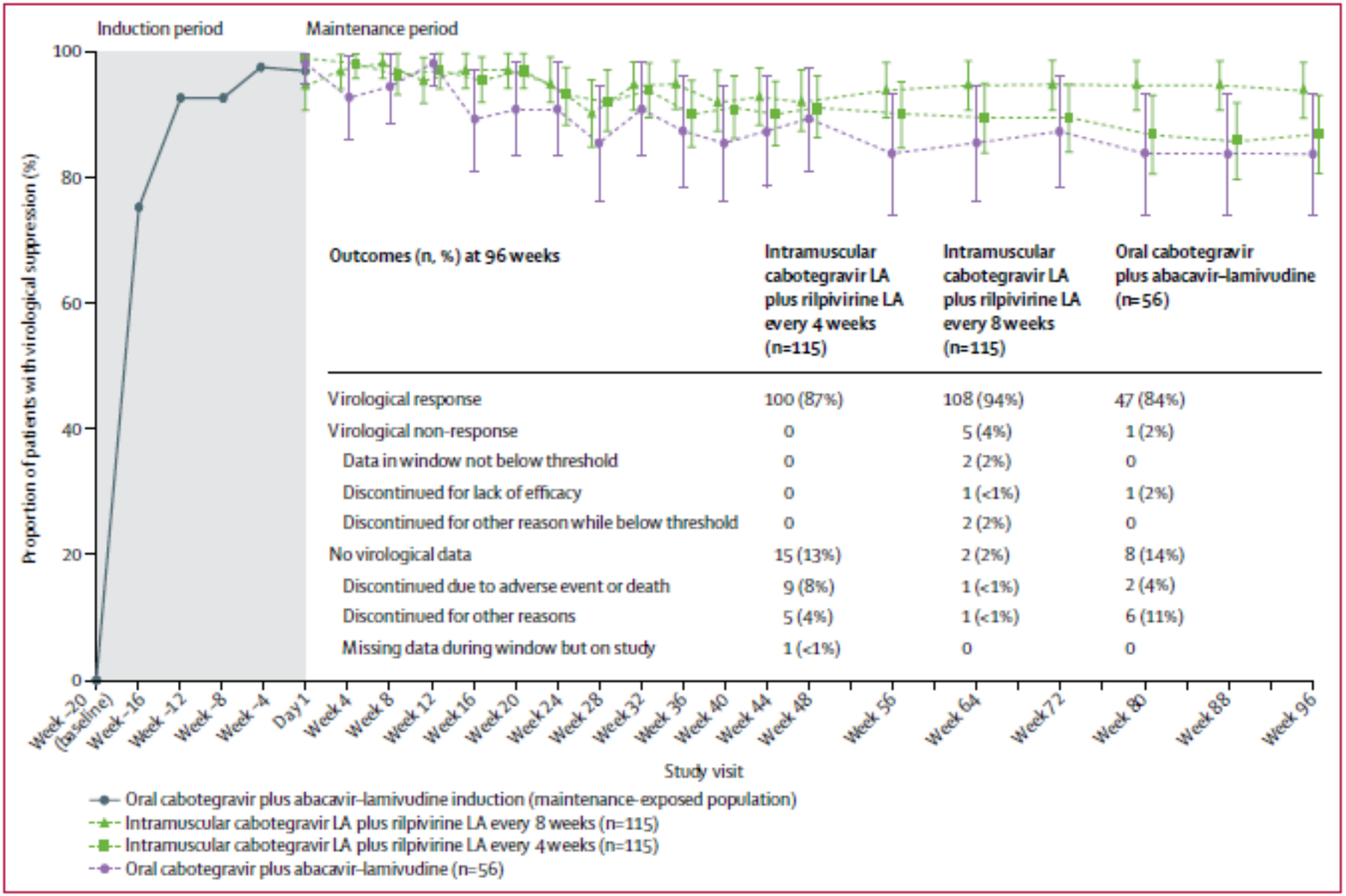
ViiV Healthcare, Research Triangle Park, NC, USA (D A Margolis MD, M St Clair BS, J Mrus MD, Parul Patel PharmD, S K Griffith Pharm D, K C Sutton MA, K Y Smith MD, W R Spreen Pharm D); **Hospital**

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

LATTE-2 Study Design



Margolis and Boffito, *Current Opinion HIV AIDS* 2015; 4: 246



Outcomes (n, %) at 96 weeks	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

Figure 2: **Proportion of patients with HIV-1 RNA concentration less than 50 copies per mL (FDA snapshot algorithm) by visit in the maintenance-exposed population and snapshot outcomes at week 96**

Error bars show 95% CIs, derived using the normal approximation. FDA=US Food and Drug Administration. LA=long-acting.

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

Tolerability of injectable RPV and CBT

	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)		Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)		Oral cabotegravir plus abacavir–lamivudine (n=56)	
	Grade 1–4†	Grade 3–4‡	Grade 1–4†	Grade 3–4‡	Grade 1–4†	Grade 3–4‡
(Continued from previous page)						
Injection-site discolouration	6 (5%)	0	3 (3%)	0	0	0
Dyspepsia	6 (5%)	0	1 (<1%)	0	1 (2%)	0
Asthenia	3 (3%)	0	2 (2%)	0	3 (5%)	0

Data are n (%). LA=long-acting. *Includes all post-baseline induction period and maintenance period adverse events, as well as long-term follow-up period adverse events for patients withdrawing from intramuscular dosing that occurred within 35 or 63 days (4-week group or 8-week group) of the last maintenance period intramuscular injection until up to and including the start date of the long-term follow-up period on oral highly active antiretroviral treatment. †At least 10% in any treatment group for total adverse events and at least 5% in any treatment group for treatment-related adverse events. ‡Includes only events listed in the grade 1–4 column; other grade 3–4 events that did not meet the 5% or 10% cutoff for the grade 1–4 column are not shown.

Table 2: Summary of total adverse events and treatment-related adverse events through week 96 in the safety maintenance population

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

Patient satisfaction with injectable RPV and CBT

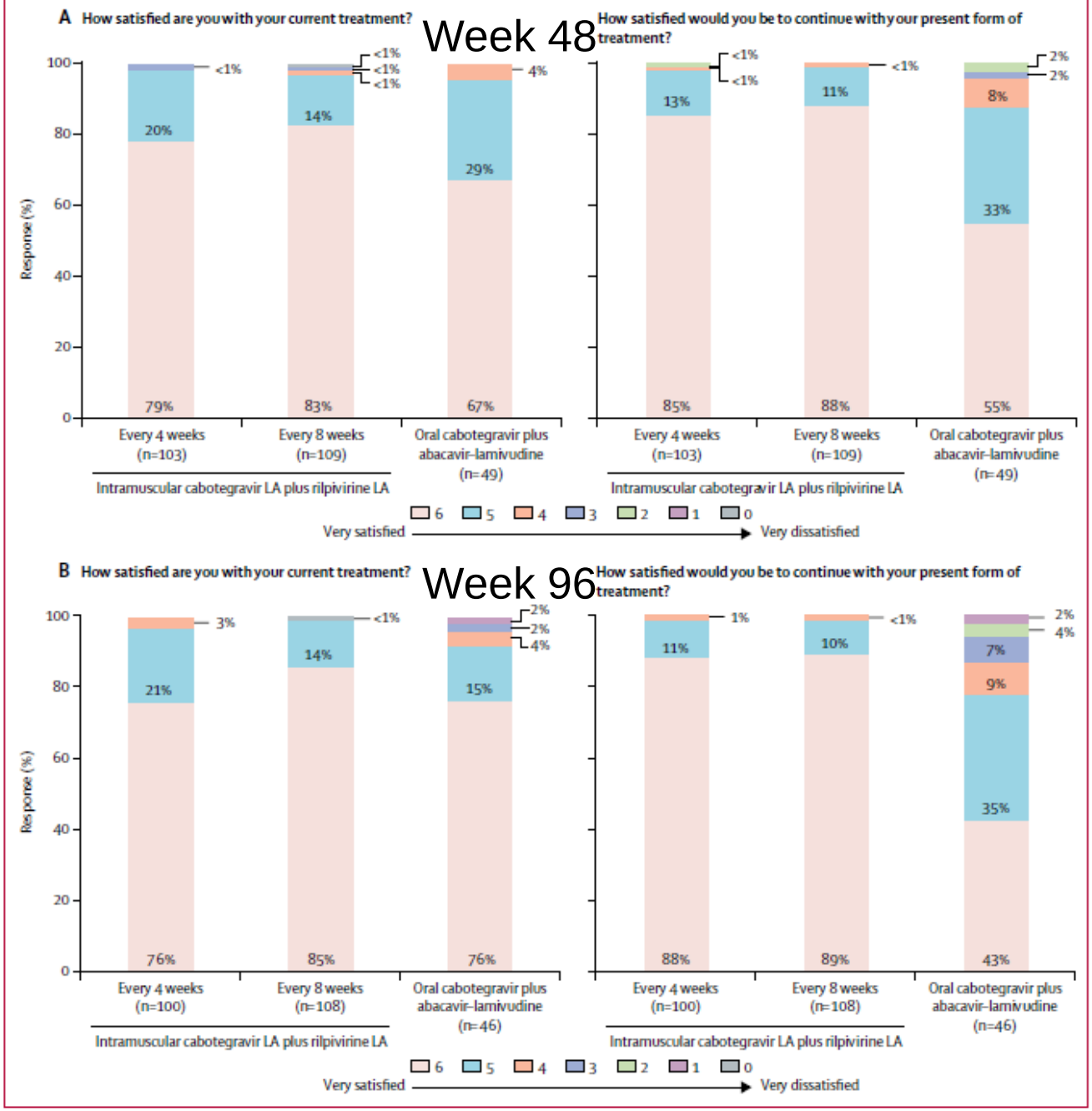


Figure 4: **Summary of patient-reported outcomes at (A) week 48 (maintenance treatment) and (B) week 96**
The data are based on the observed case dataset of patients who completed questionnaires at week 48 and week 96 (HIV Treatment Satisfaction Questionnaire, status version). LA=long-acting.

Is a 2-drug LA regimen adequate for HIV treatment?

Juluca

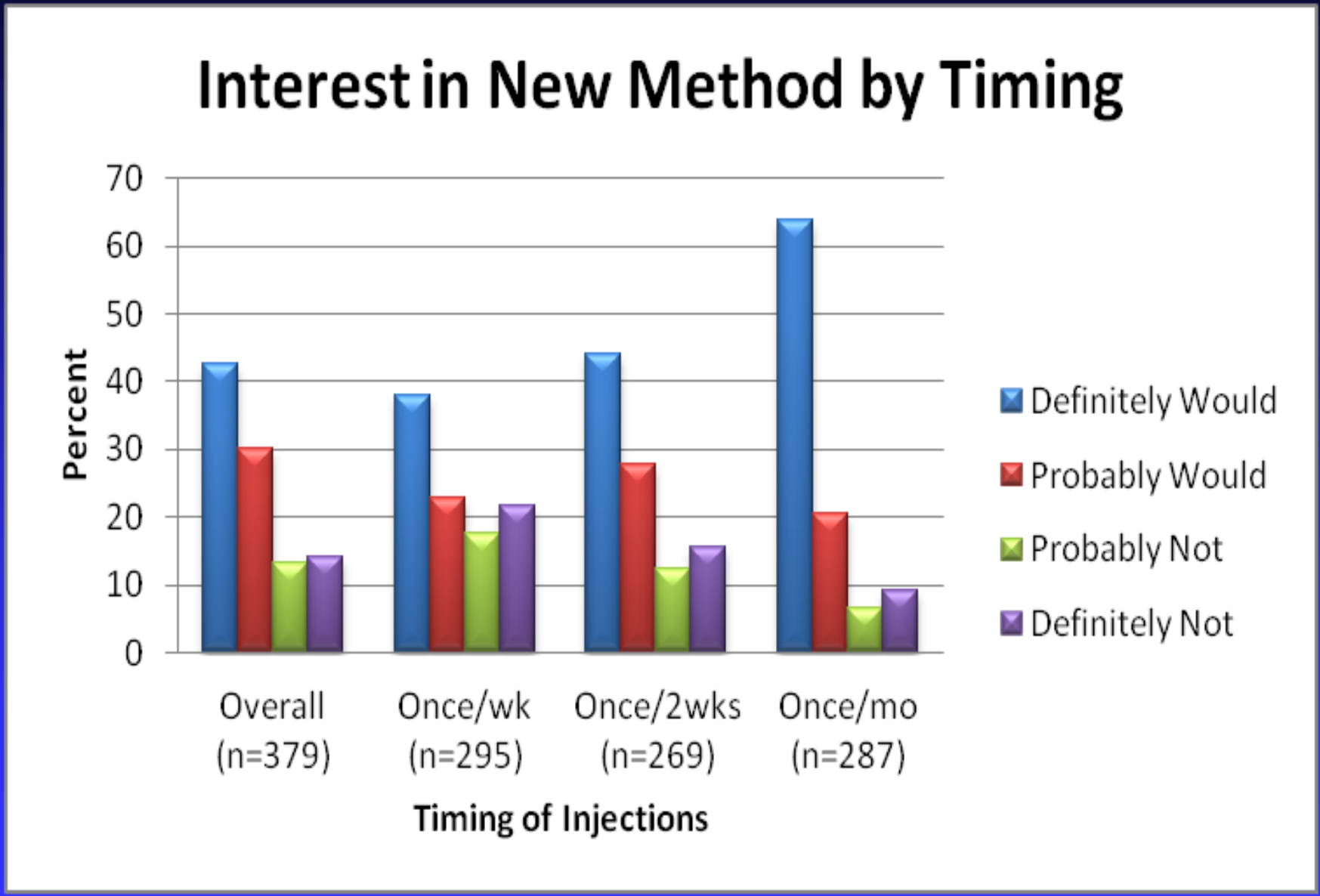
dolutegravir 50 mg/
rilpivirine 25 mg tablets

What’s the evidence that patients want to switch from oral once-daily pills to long acting formulations?

LA/ER: What's the attraction?

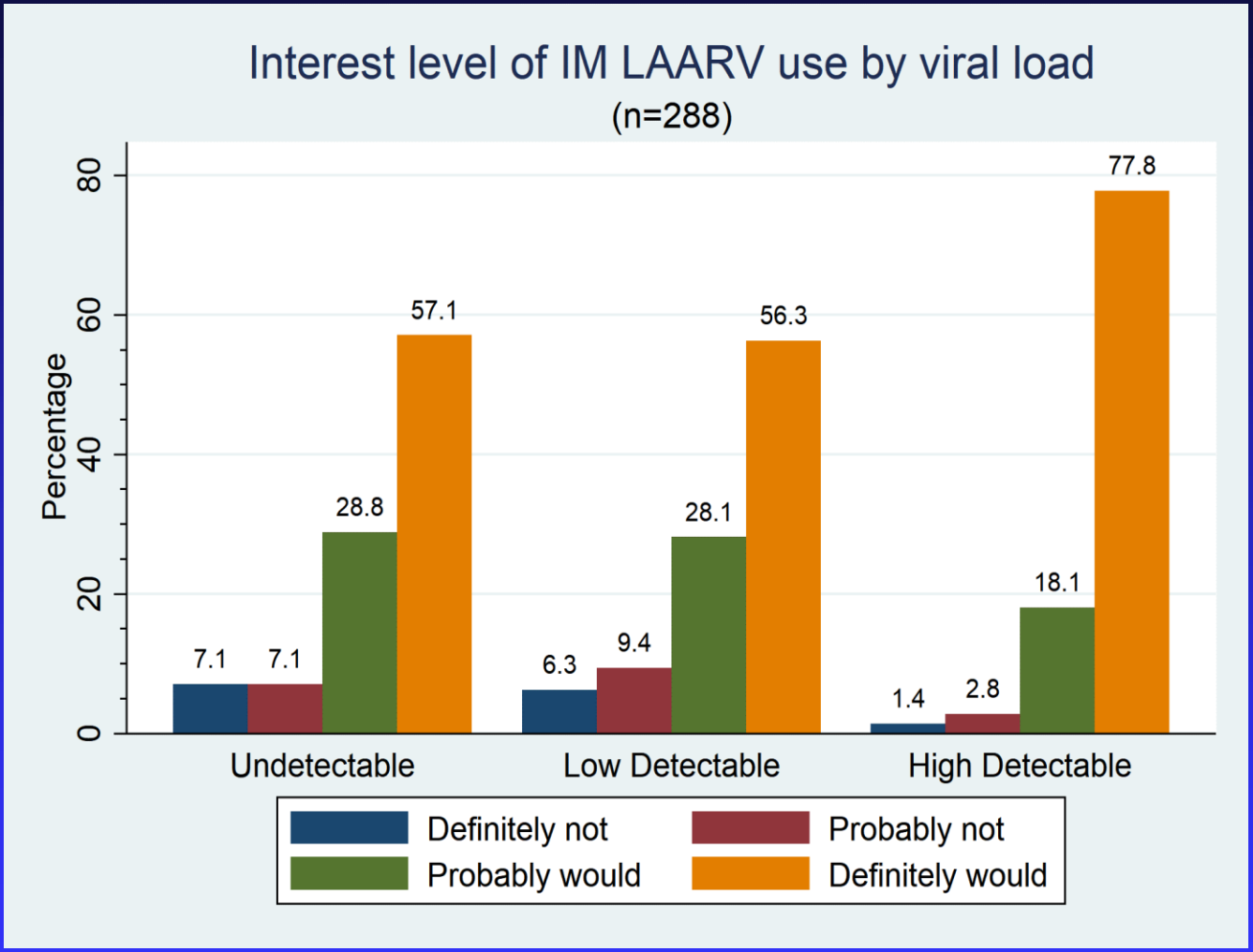
- Infrequent dosing
  - Long apparent $T_{1/2}$
- Lower drug dose needed (nanoformulation)
- Prevents poor adherence
- Possibility of directly observed therapy
- Tissue targeting (LN/macrophage uptake)
- Use in patients with pill fatigue
- Better protection of health privacy
- Avoids treatment-related HIV stigma

NanoART Survey - Adults



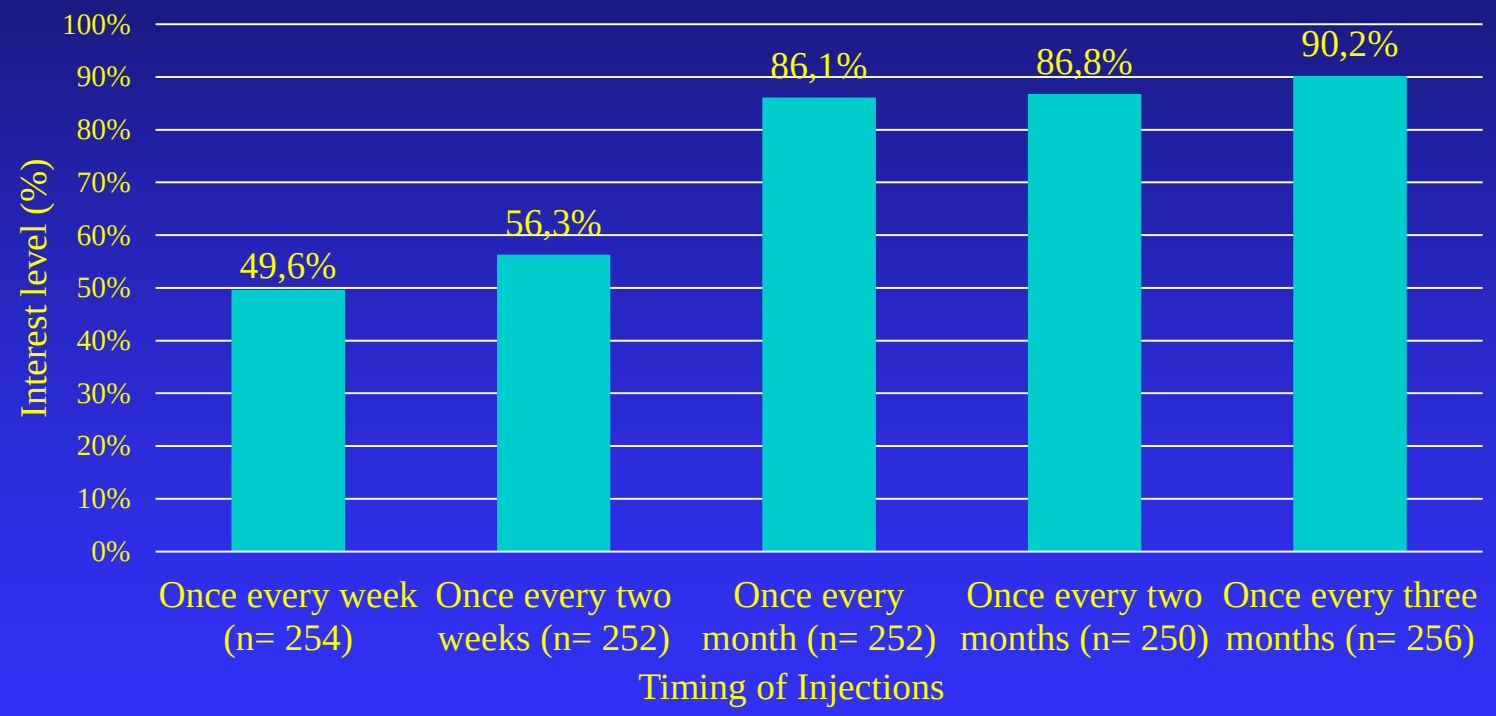
- J. Williams et al., *Nanomedicine (Lond.)* 2013; 8: 1807

NanoART Survey - Adolescents



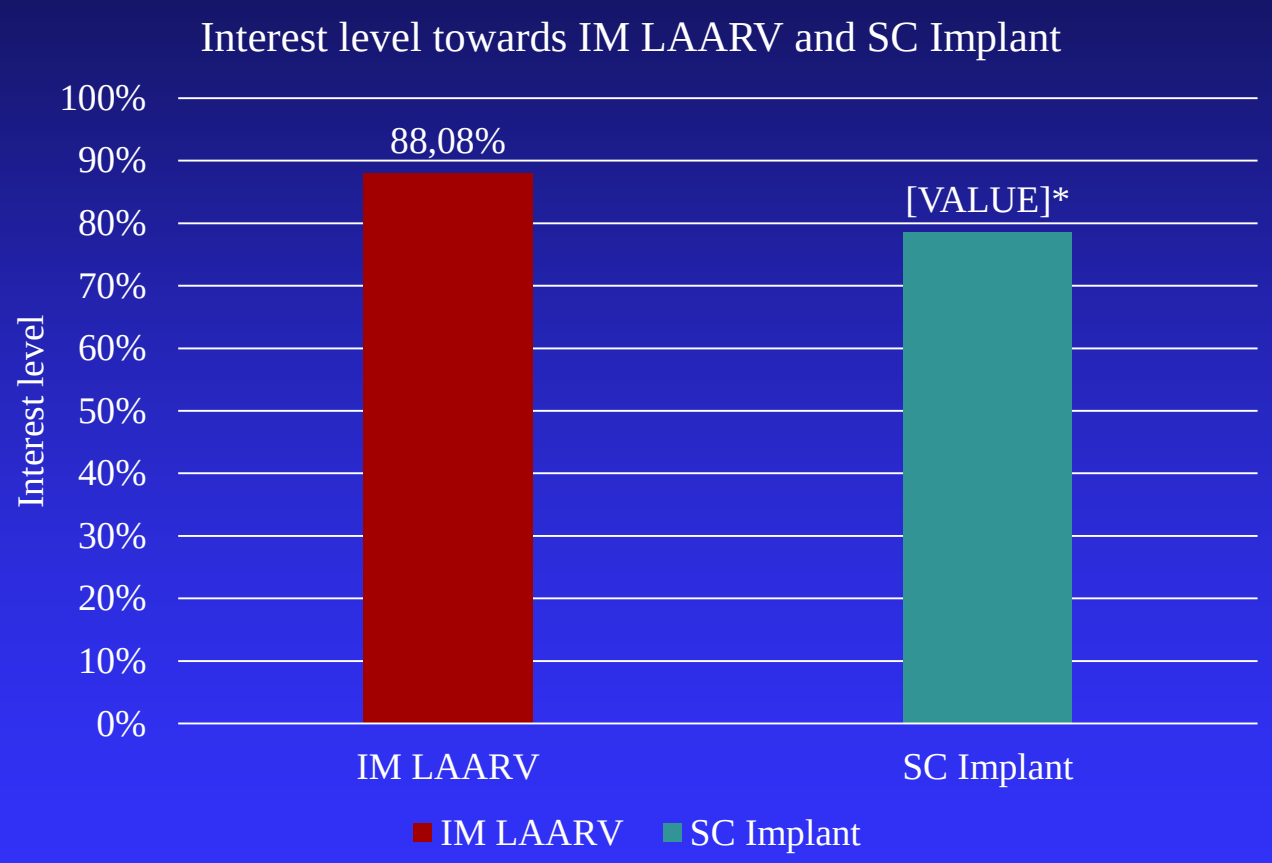
- Weld E. et al., Poster presentation; IAS Paris 2017

Level of interest as a function of dosing frequency



- Weld E. et al., Poster presentation; IAS Paris 2017

Level of interest: injection or implant?

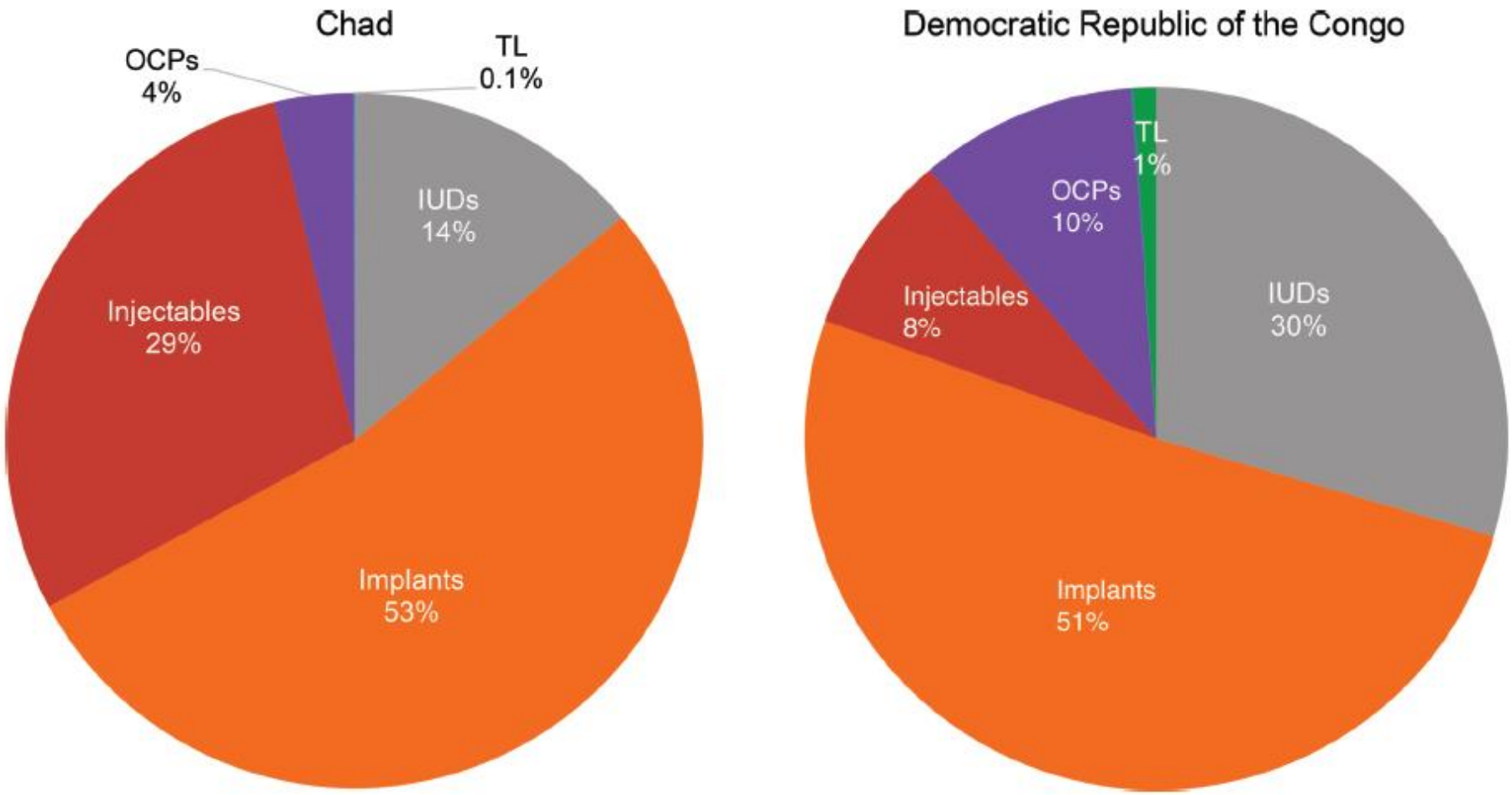


- Weld E. et al., Poster presentation; IAS Paris 2017

What’s the evidence that patients will switch from oral once-daily pills to long acting formulations?

Uptake of contraceptive implants in SSA

FIGURE 1. Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad[a] and DRC, June 2011 to November 2015



- Rattan J et al., *Global Health: Sci Prac* 2016; 4: Suppl 2

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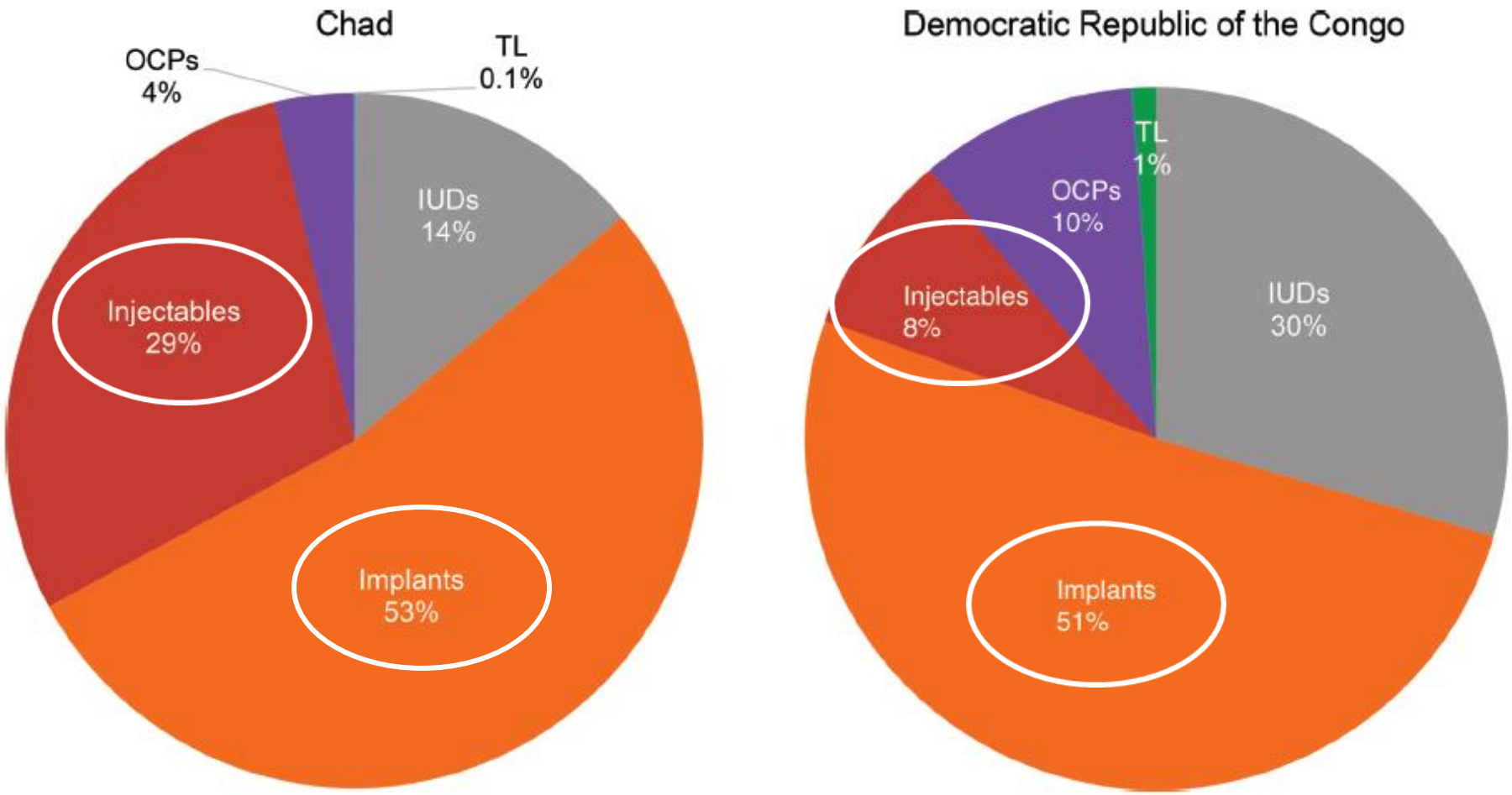


- Rattan J et al., *Global Health: Sci Prac* 2016; 4: Suppl 2

Novel LA/ER technologies: What’s in the pipeline?

Novel LA/ER technologies: Implants

Long Acting ARV Implants

- Potential advantages over injectables
  - Removable
  - More consistent and predictable drug release
  - PK not dependent on injection site
  - May remain in place for years (inert, non-degradable subcutaneous versions)
- Potential disadvantages over injectables
  - Specialized device required for insertion
  - Minor surgical procedure to remove
  - Regulated as both a drug and a device
  - Difficulty moving to a generic marketplace

LA ARV Implants – Tenofovir Alafenamide

See also CROI 2017 Abstract 420

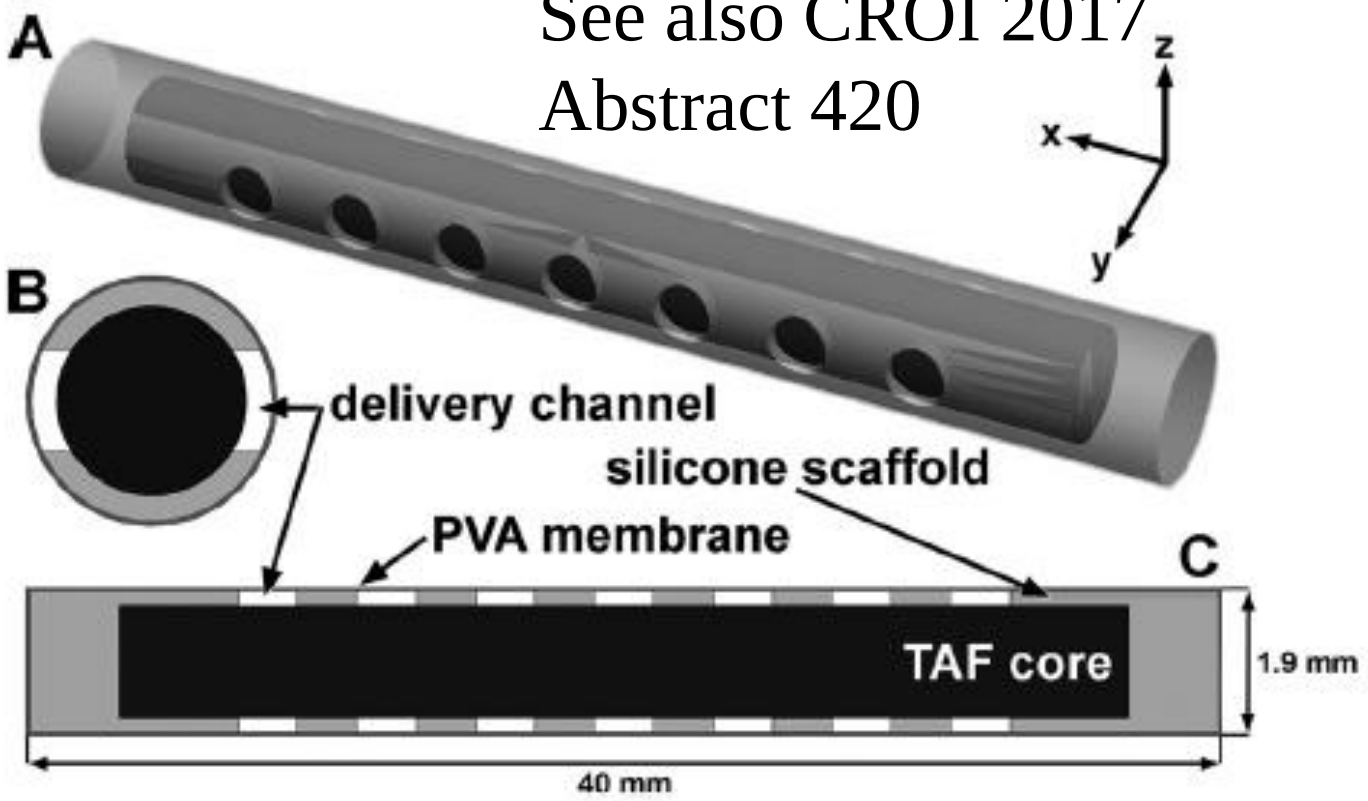


FIG 1 Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the *y-z* (B) and *x-y* planes (C).

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

LA ARV Implants – Tenofovir Alafenamide

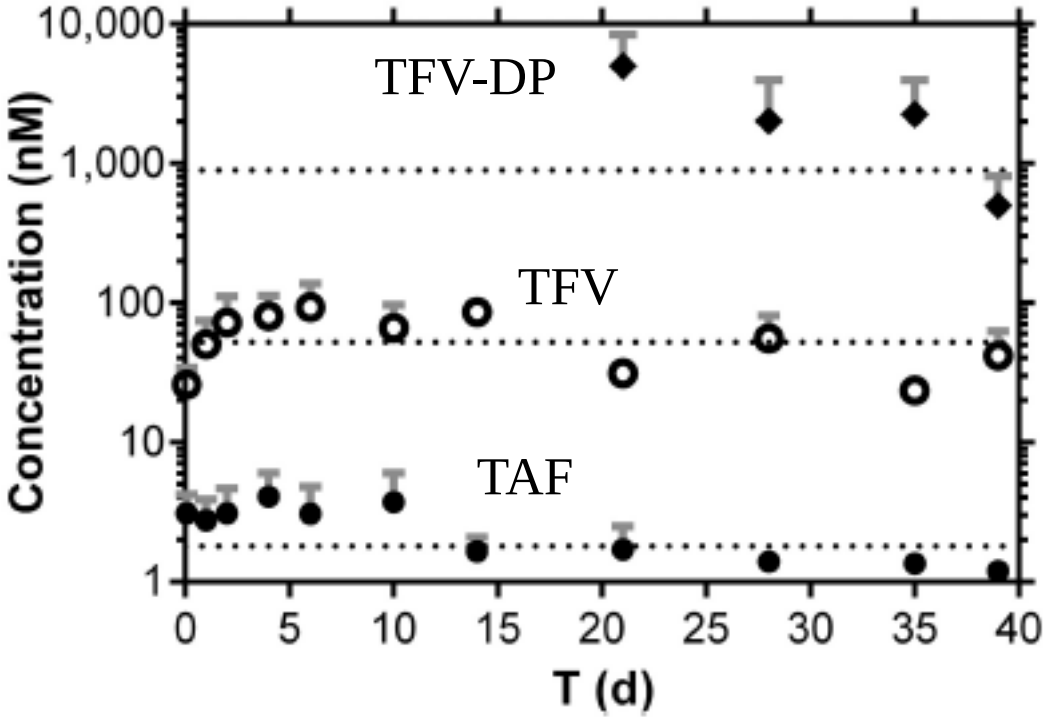
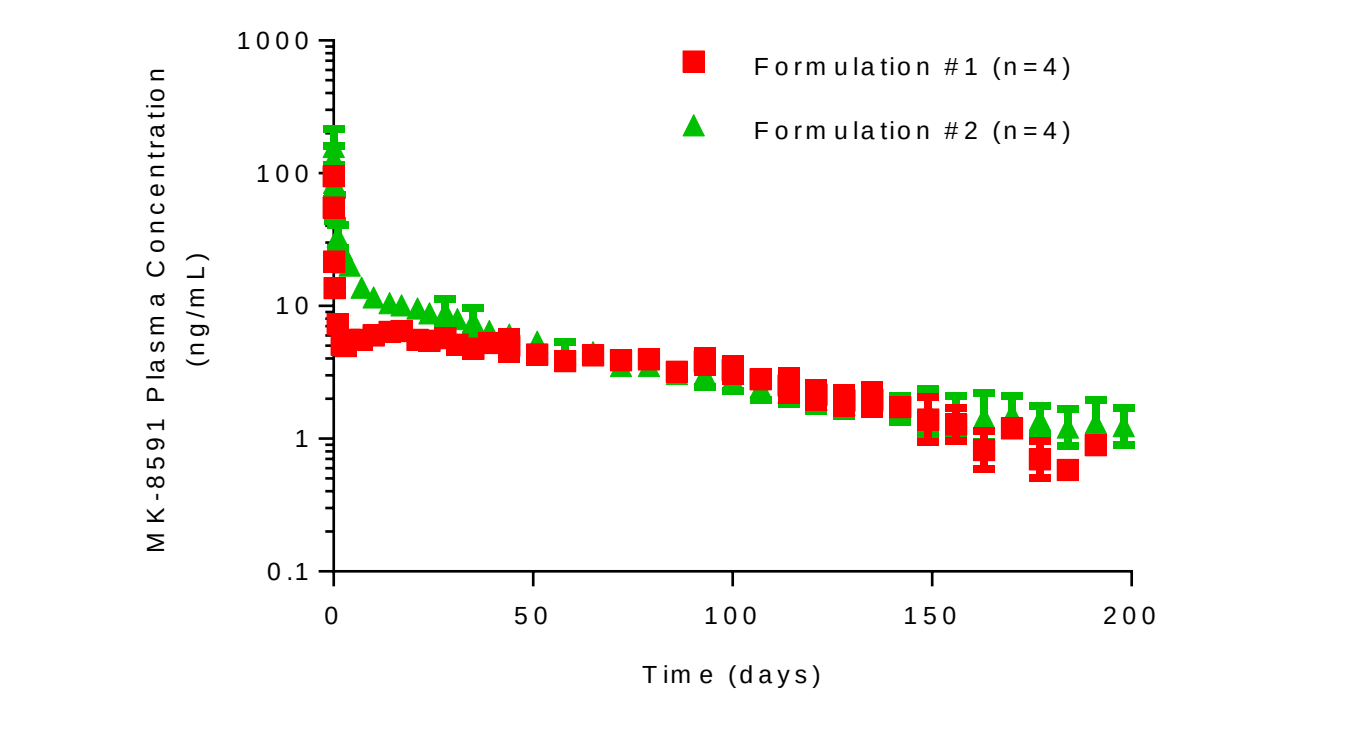


FIG 3 Subdermal implantation of TAF LA prototype device in beagle dogs maintains sustained drug levels with low systemic exposure to TAF and TFV with concomitant, efficient PBMC loading with TFV-DP. Pharmacokinetic profiles of plasma TAF (closed circles) and TFV (open circles) and PBMC TFV-DP (closed 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.

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

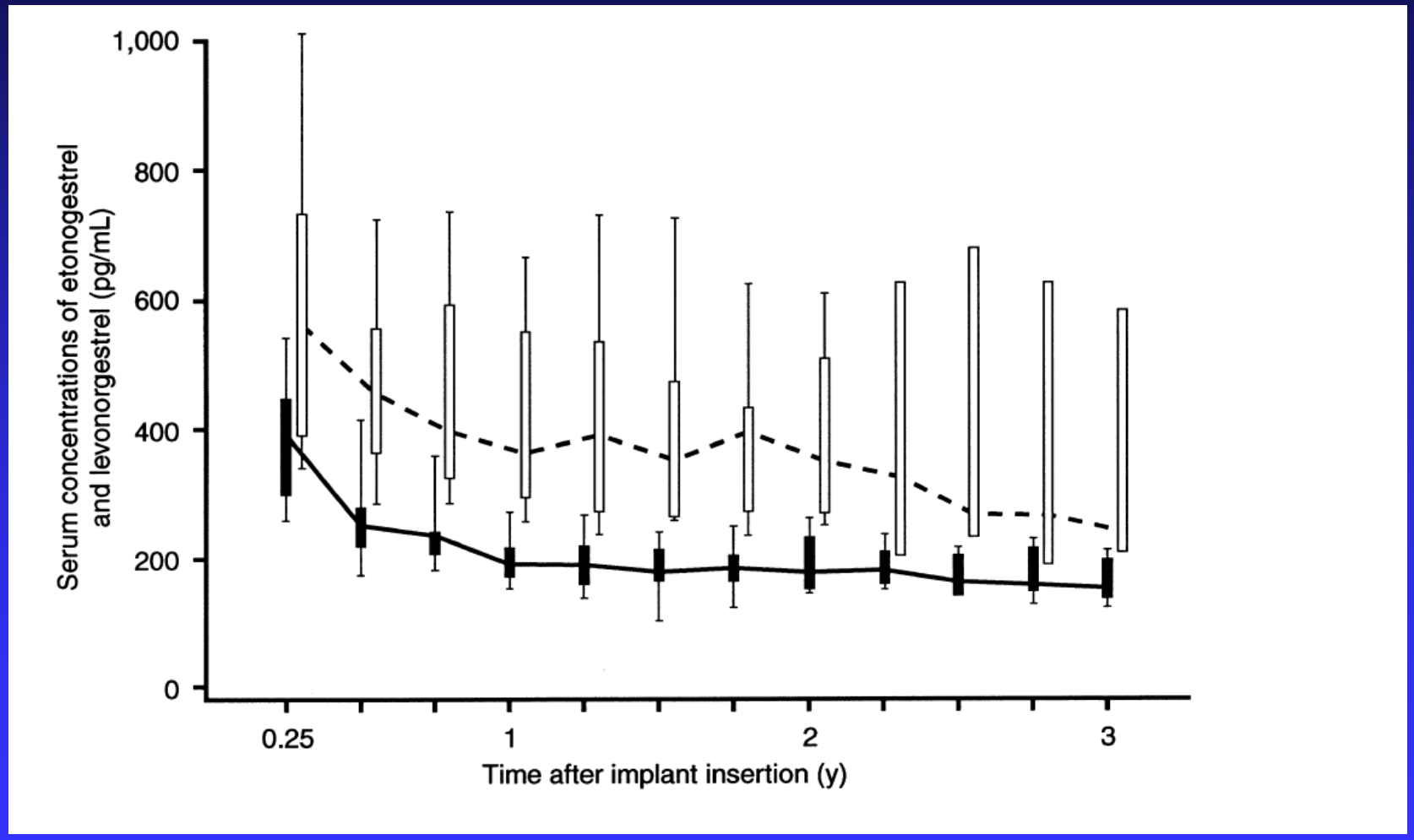
MK-8591 (EFdA) Implant Formulations Release Effective Drug Levels for >180 days



- >180-day extended release from solid state formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

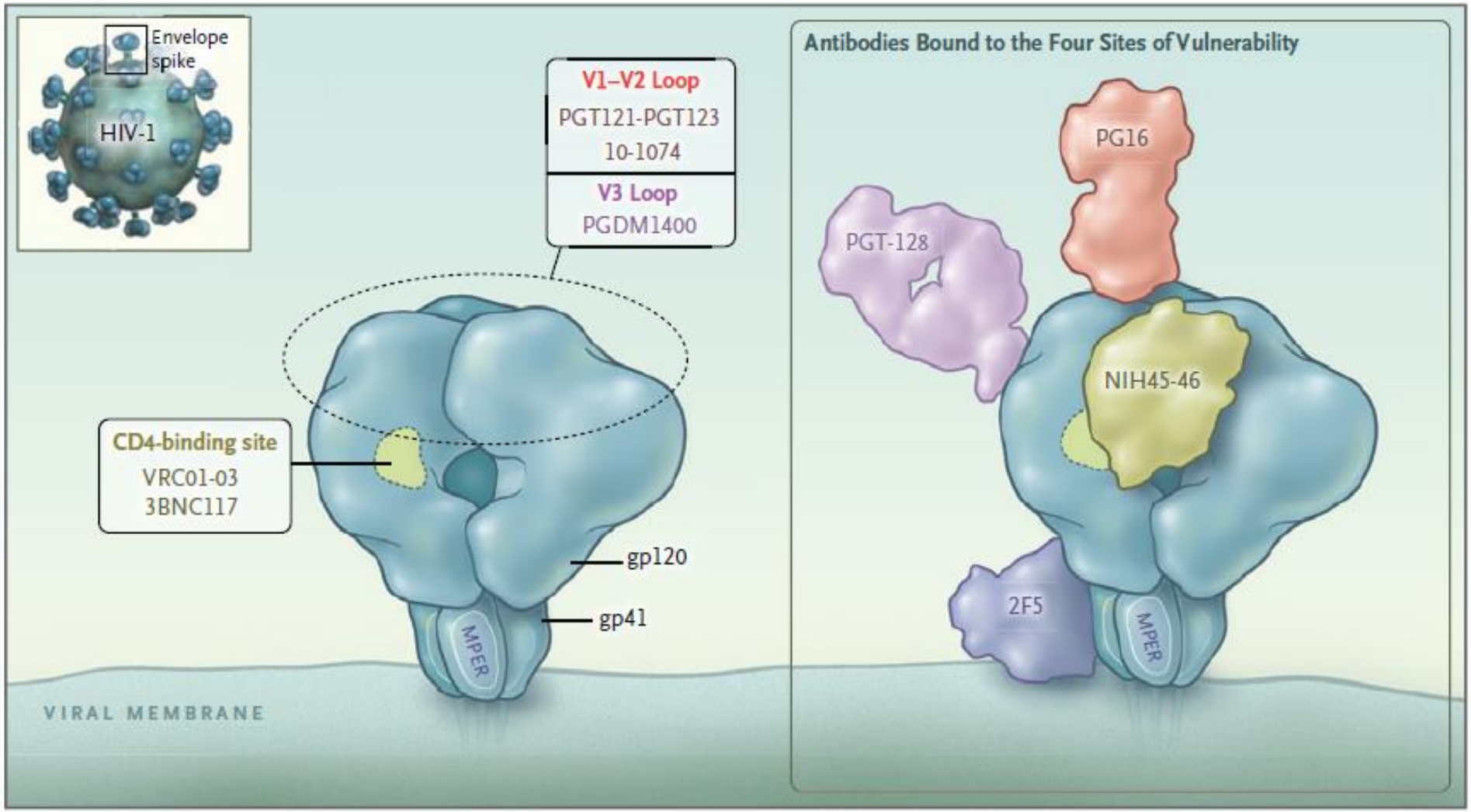
- Grobler JA et al. CROI, 2/22-2/25, 2016, Boston, MA

Etonogestrel and levonorgestrel serum concentrations for 3 years following a single implant



- Makarainen et al., *Fertility & Sterility* 1998; 69: 716

LA/ER Drugs: Broadly-neutralizing monoclonal antibodies



HIV-1 Spike Protein, Showing Sites Targeted by Broadly Neutralizing Monoclonal Antibodies.

The inset shows the virus with its surface spikes. The left panel shows target sites of monoclonal antibodies in clinical development. The right panel illustrates the binding of four different broadly neutralizing antibodies.

Caskey et al., *New Engl J Med* 2016; 375: 2019

PK profile of VRC01-LS

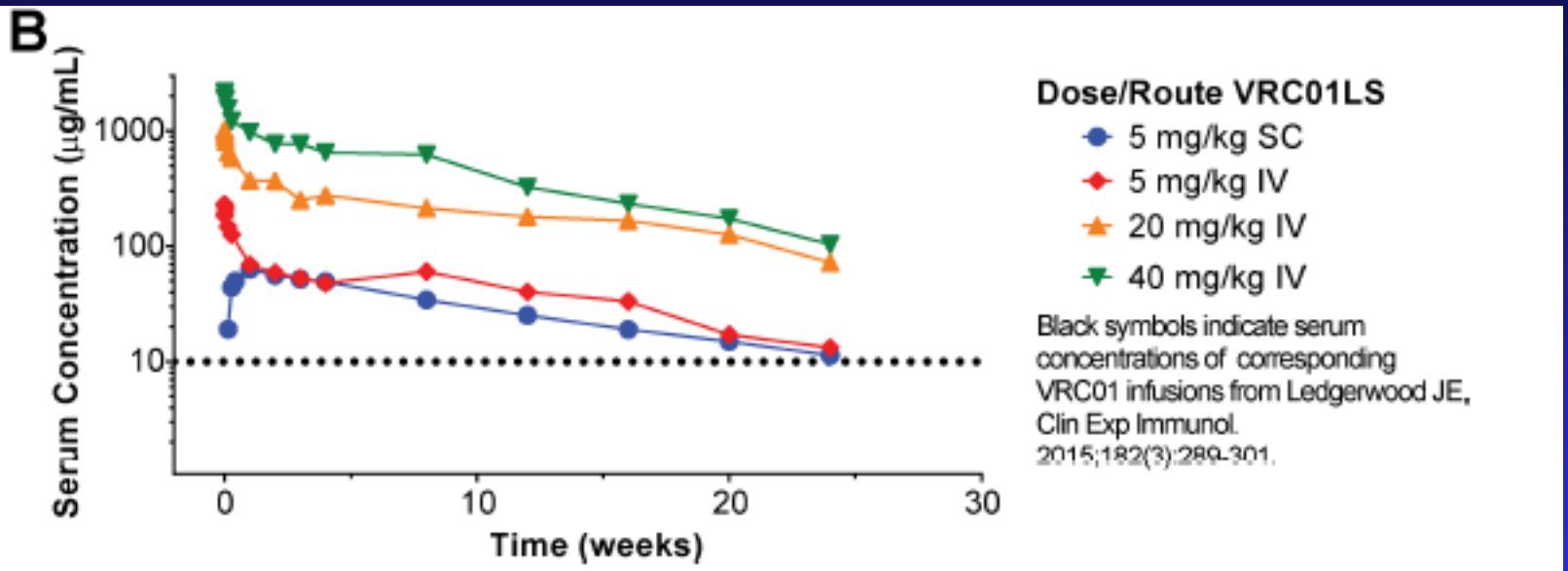


Fig 2. Measurement of antibody serum concentration (µg/mL). (A) Serum VRC01LS concentrations (colored plots) are shown from first measurement through week 24 after a single administration. The infusion dose and route are as specified in the legend. All values are the mean of duplicate samples run in different wells within the same plate. Previously published VRC01 concentrations based on historical data (black plots) after administration at weeks 0 and 4 are shown for comparison. (B) Geometric mean serum VRC01LS concentrations per group over time. The dotted line at 10 µg/mL on each graph is shown as a reference value. IV, intravenous; SC, subcutaneous.

https://doi.org/10.1371/journal.pmed.1002493.g002

Gaudinski MR et al., *PLoS Med* 2018; January 24

Broadly-neutralizing monoclonal antibodies

- Potential advantages
  - Humanized, well-tolerated
  - "Extendification" possible
    - LA version of VRC01 in clinical development
  - May induce beneficial host cell-mediated immunity
    - ADCC responses
  - Use in prevention applications, PrEP
- Potential disadvantages
  - Expensive
  - Intravenous route of administration
  - Pre-existing resistance commonplace
  - Select for resistance viruses

Novel LA/ER technologies: Once-weekly oral dosing?

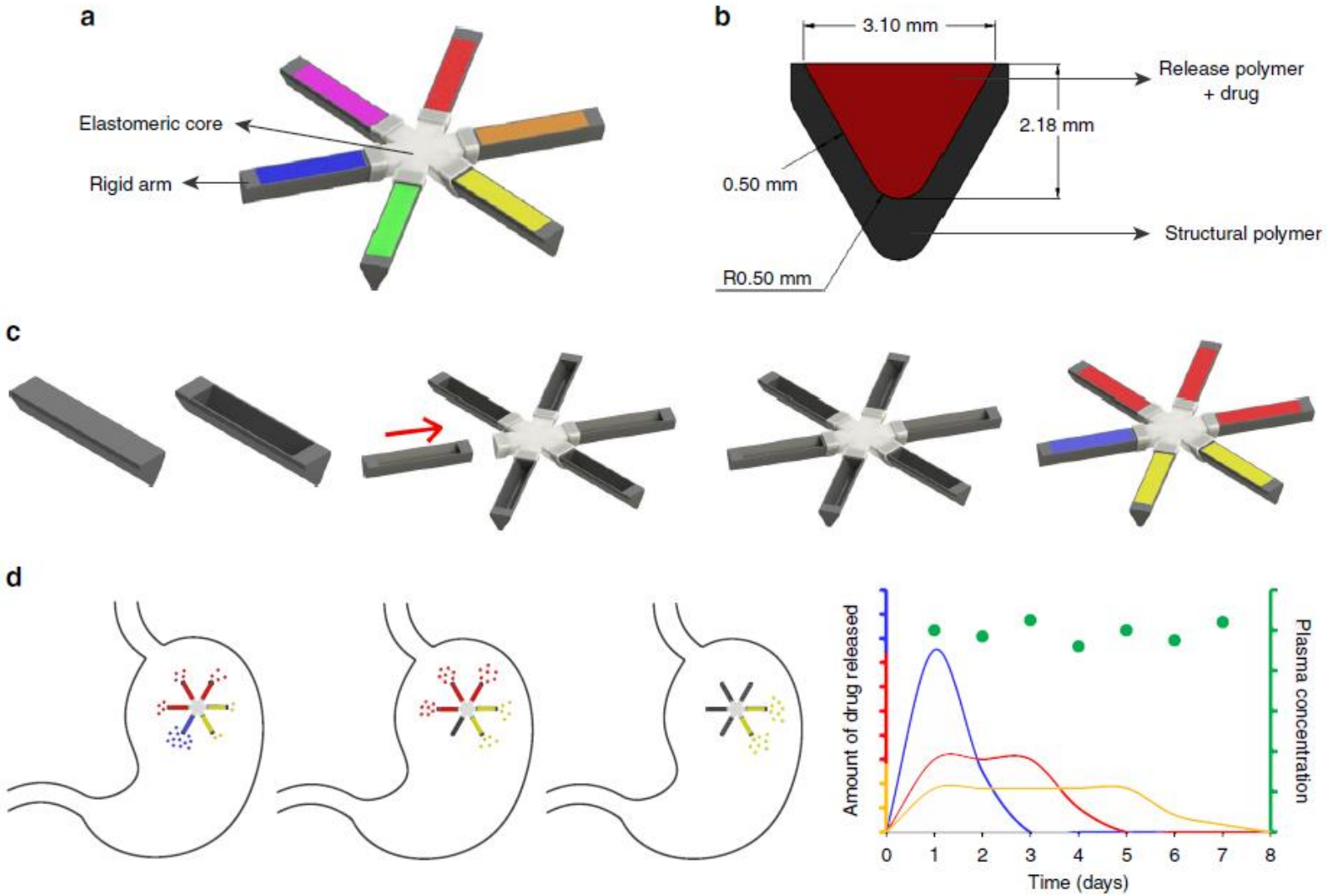
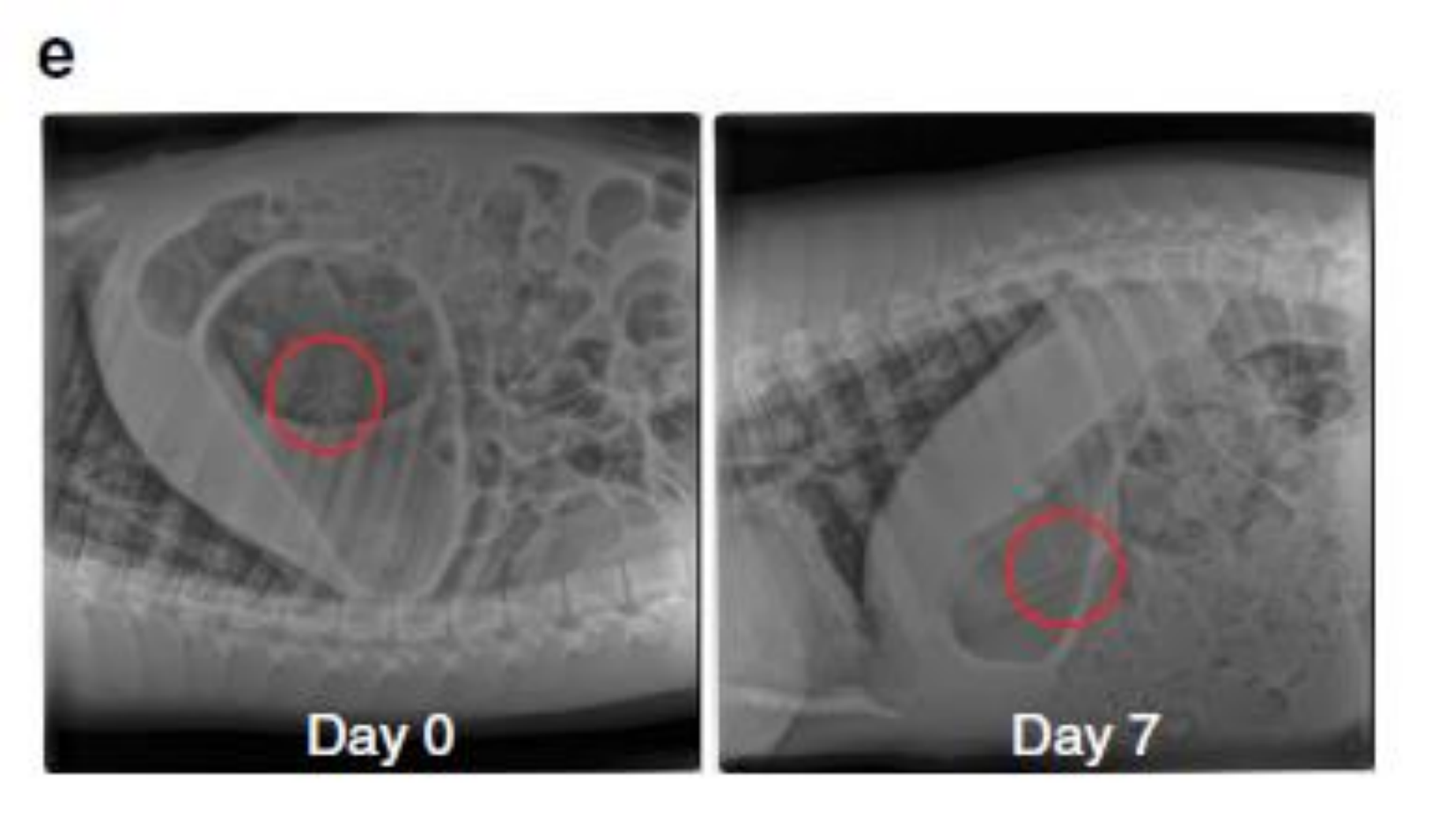


Fig. 1 Concept of oral long acting antiretrovirals. **a** The design of the gastric resident dosage forms. The dosage form consists of an elastomeric core (grey) and six drug loaded arms (multi-coloured). **b** The cross section of the arm. The outer sleeve of the arms is made of a rigid structural polymer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

Persistence of an oral gastric reservoir for ARV release



- Kirtane et al. *Nature Comm* 2018

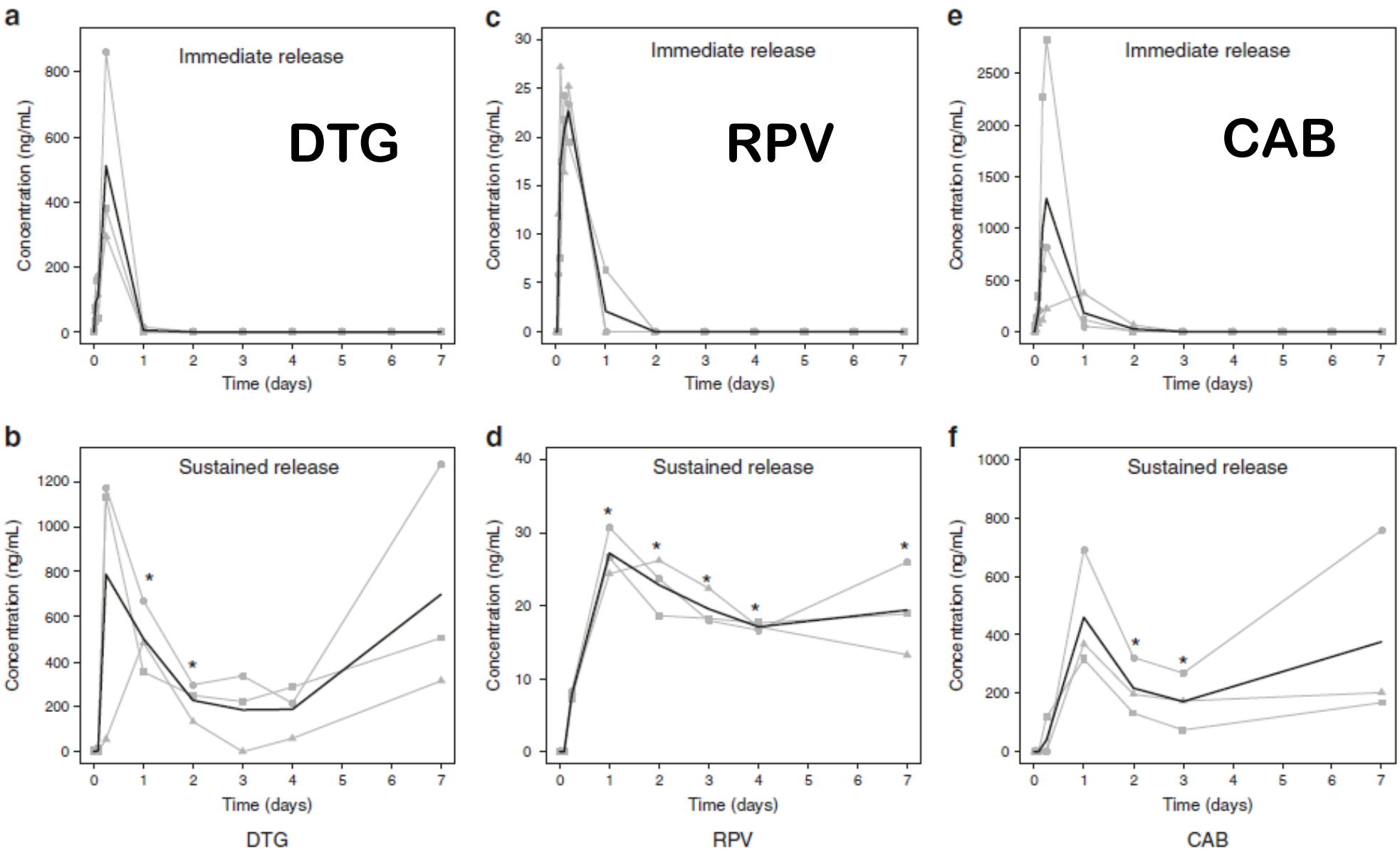


Fig. 4 Plasma pharmacokinetics of immediate release and sustained release antiretrovirals. The concentration time profiles of (**a**) DTG immediate release (**b**), DTG sustained release (**c**), RPV immediate release (**d**), RPV sustained release (**e**), CAB immediate release and (**f**) CAB sustained release are shown. Each dosage form was tested in three animals, and plasma samples from each animal were processed three times. Data was first averaged within each animal (shown by the grey lines) and then between animals in each treatment group (shown by the black line). *indicates $p < 0.05$, two sample t test comparing sustained release formulations and immediate release formulations at matching time points

Gastric resident "starfish"

- Potential advantages over parenteral formulations
  - Convenient, self-administered
  - Multiple ARV's in a single device
  - Spontaneous degradation for GI elimination
  - Removable (by endoscopy)
- Potential disadvantages over parenteral formulations
  - Published device is very large for oral administration
  - Dosing interval limitation of 1-2 weeks (?)
  - GI tolerability in humans unknown
  - Possibility of gastrointestinal ulceration and obstruction
  - Unknown food and antacid effects

Treatment of HIV with long-acting agents: how away far is it?

Treatment of HIV with long-acting agents: how away far is it?

Not very!!!

leap

Long-Acting/Extended Release Antiretroviral Resource Program

http://longactinghiv.org

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Who We Are

Funded by an R24 grant from the National Institutes of Health, the mission of LEAP is 3-fold:

1. To support scientific innovation through investigator access to broad-based scientific expertise including the pharmaceutical industry.
2. To develop a communications and data hub to support investigators in this field
3. To provide a Modeling and Simulation Core Service that helps investigators identify the most promising approaches to the development of new products.

LEARN MORE

Funding Opportunities

Finding funds for research can be a challenge. The following resources are provided to help guide your

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