15th International Conference on
HIV TREATMENT AND
PREVENTION ADHERENCE

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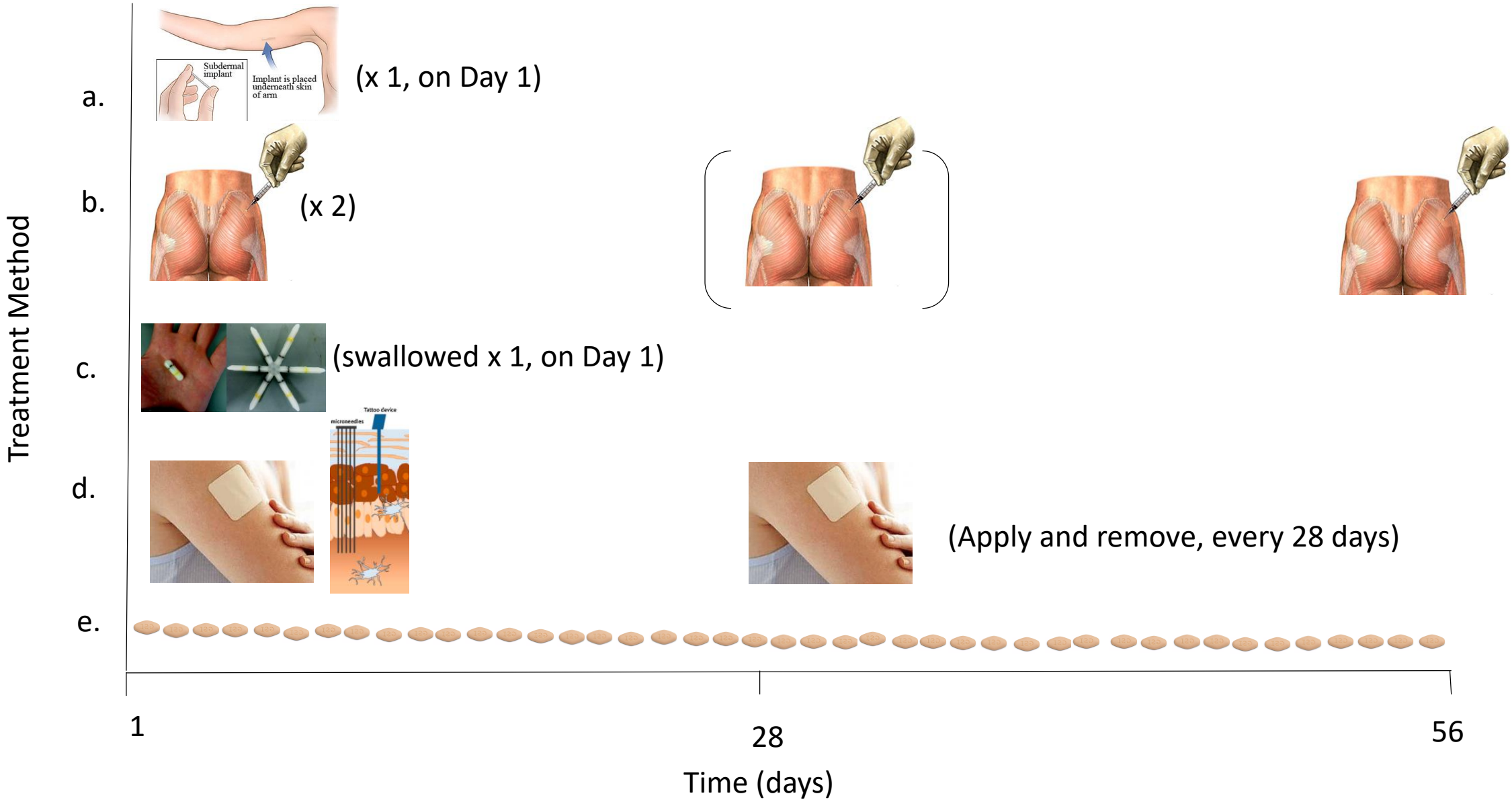
Long-Acting ART: What is on the Horizon? Are we Ready?

Outline of Talk

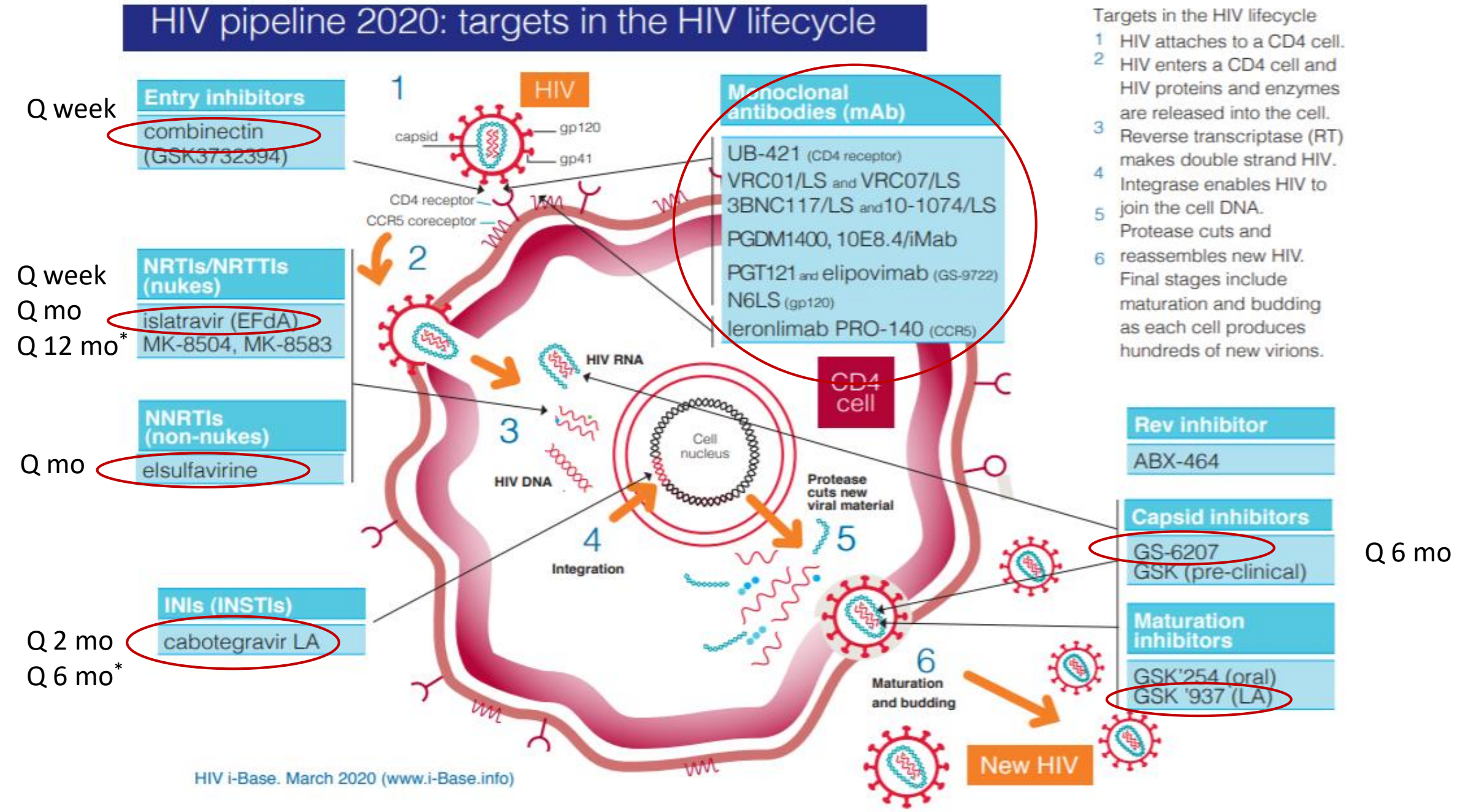
- Formulation & Delivery Fixes for Adherence Issues
- Long-Acting ART: What are the new Aspects?
- Long-Acting ART: What is coming?
- CAB-LA and RPV-LA: On the Near Horizon
  - The New Frontiers
- ART Implants: On the Far Horizon
- Are We Ready?
  - Gaps in Existing Technologies & Knowledge
  - What Are the Questions?

Delivery & Formulation Fixes for Adherence Issues



Healthwise, Inc.; drugs.com (A.D.A.M.); latimes.com; Gilead Sciences; dailymail.co.uk; brooksinbeta.com; Alkilani AZ, *Pharmaceutics* **2015**, *7*(4), 438-470

HIV pipeline 2020: targets in the HIV lifecycle



Targets in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrase enables HIV to join the cell DNA.
5. Protease cuts and
6. reassembles new HIV. Final stages include maturation and budding as each cell produces hundreds of new virions.

= long-acting approach

*= as PrEP

Long-Acting ART[1] (LA-ART): What is Coming?

- Cabotegravir long-acting (CAB-LA) & Rilpivirine long-acting (RPV-LA)
- Islatravir (ISV; aka MK-8591, aka EfDA)
  - Implant: q 6-12 months
  - Oral: q day – q week (q Month as PrEP)
- Lenacapavir (aka GS-6207)
  - SC: q 6 months
  - PO: q week
- [Broadly neutralizing antibodies (bNAbs)]

Swindells S, et al, N Engl J Med. 2020 Mar 4. doi: 10.1056/NEJMoa1904398; Orkin C., et al. Abstract 140, CROI March 9, 2019, Seattle WA; Orkin C, et al., Abstract 482LB, Virtual CROI March 10, 2020; Daar E et al, Abstract 469, Virtual CROI March 2020; Overton ET et al, Abstract 34, Virtual CROI March 2020; Matthews R., TUAC0401LB, IAS 2019 (Mexico City); Barrett SE et al. *Antimicrob Agents Chemother* 2018; DOI: 10.1128/AAC.01058-18; Nel A., 9th SA AIDS Conference, Durban ICC 11-14 June 2019; Baeten J., IAS 2019, Mexico City, MX; Johnson LM, et al, *Pharmaceutics* 2019 Jul 4;11(7) [1]ART: antiretrovirals

LA-ART: What are the *new* aspects?

- **Centering non-adherence**, accommodating without blame
- **DOT by definition** (distinct from non-observed therapies)
  - De-linkage of individual behaviour from viral suppression
    - Until we investigate home self-injections
- Pay for Performance (P4P4P) ?easier than with daily oral strategies
  - Decrease in number of daily actions that need to be performed by PLWH
  - **Adherence as a function of the number of daily actions needed** is of interest
- Understanding real-world tolerability
  - **Trade-off** between ⬇ frequency of dosing and acceptability of ISR, AEs
- *Frequency* of ***clinic visits*** *higher* (q Month) than with daily ART (q 6-12 months)
- What will the **real-world frequency of missed injections**/ resistance be?
- **Pricing**, **availability**, Ryan White/ ADAP, Administration/ personnel

Brantley AD et al., *Public Health Rep* 2018 Nov-Dec; 133(2 Suppl): 75S–86S. PMCID: PMC6262523

Rates of viral suppression after 6, 12, and 24 months of enrollment among patients enrolled in the Health Models pay-for-performance program[a] at 3 urban HIV clinics, New Orleans and Baton Rouge, Louisiana, September 2013–September 2016

Characteristic	Total Enrolled in Health Models, No. (%)	Baseline[b]		6 Months After Enrollment			12 Months After Enrollment			24 Months After Enrollment		
		Virally Suppressed, No. (%)[c,d]	*P* Value[e]	Virally Suppressed, No. (%)[c,d]	*P* Value[e]	Percentage- Point Difference From Enrollment	Virally Suppressed, No. (%)[c,d]	*P* Value[e]	Percentage- Point Difference From 6 Months	Virally Suppressed, No. (%)[c,d]	*P* Value[e]	Percentage- Point Difference From 12 Months
Total	2076 (100.0)	1198/2074 (57.8)	NA	1453/1767 (82.2)	NA	24.4	1474/1783 (82.7)	NA	0.5	1084/1265 (85.7)	NA	3.0

Timeline & Important Milestones

Long Acting Cabotegravir & Rilpivirine

Regulatory

- **Health Canada Approves CABENUVA™** — Mar 2019
- **FDA Submission** — Apr 2019
- **Dec. 21, 2019:** FDA issues **Complete Response Letter** to ViiV and Janssen for Long-acting CAB and RPV, citing concerns re:CMC (Chemistry, Manufacturing & Controls)
- **FDA Declines** — Dec 2019
- **FDA Resubmission** — Aug 2020
- **EMA CHMP Positive Opinion** — Oct 2020
- **FDA Approval** — ????

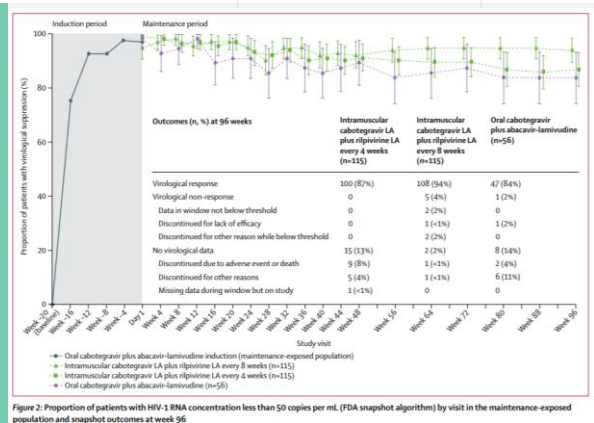
<2017	2018	2019	2020	2021
Clinical Studies				
LATTE-1 **LATTE-2**		**FLAIR** **ATLAS**	**ATLAS-2M** **POLAR**	**CUSTOMIZE (U.S.)** **CARISEL (Europe)**
Importance				
		FLAIR: HIV VL<50 c/mL: • 93.6% CAB/RPV LA • 93.3% oral ART Troughs> 4XPA IC90 ATLAS: Switch to qM LA CAB/RPV Non-inferior to oral ART	ATLAS: q2M == q4wk 98% preferred LA-ART 94% preferred q2M to qM. POLAR: 90/97 LATTE participants chose LA-CAB/LA-RPV (not PO) • Durable suppression w q2M	First trials to explore implementation aspects of LA-ART • High acceptability • Perceived barriers

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

Swindells S, et al, N Engl J Med. 2020 Mar 4. doi: 10.1056/NEJMoa1904398; Orkin C., et al. Abstract 140, CROI March 9, 2019, Seattle WA; Orkin C, et al., Abstract 482LB, Virtual CROI March 10, 2020; Daar E et al, Abstract 469, Virtual CROI March 2020;

Provider Thoughts on Feasibility of LA-ART (CAB/RPV)

CUSTOMIZE study
N= 449 providers
Providing care during ATLAS-2M study
Europe, N. America, Asia, Africa, Latin America

- Primary outcome: overall feasibility of qmonth CAB-LA and RPV-LA
- Logistical barriers, benefits

Table 2. Provider Clinical Concerns With LA ART (Very/Somewhat Concerned):

	N (293)	%
Patients not returning to clinic on time for injection appointments	224	79.7
Risk of resistance for patients not adherent to injections	195	69.4
Patients moving out of the area	182	64.8
Patients switching to a different provider	154	54.8
Drug interactions and comorbidities (e.g. TB, HCV)	138	49.1
Taking a patient off CAB LA + RPV LA and switching to oral ART	120	42.7
The oral lead-in phase before starting injections	68	24.2

Table 2 shows providers top concerns about patient management all focused on patients' adhering to injection schedules:

- **Patients not returning to the clinic on time** for injection appointments (80%).
- **Risk of resistance** due to non-adherence to injection schedule (69%).
- Fear of patients **moving out of area** was mentioned by more than half (65%).

Figure 1. Barriers to LA ART Appointment Adherence: Frequency by Region

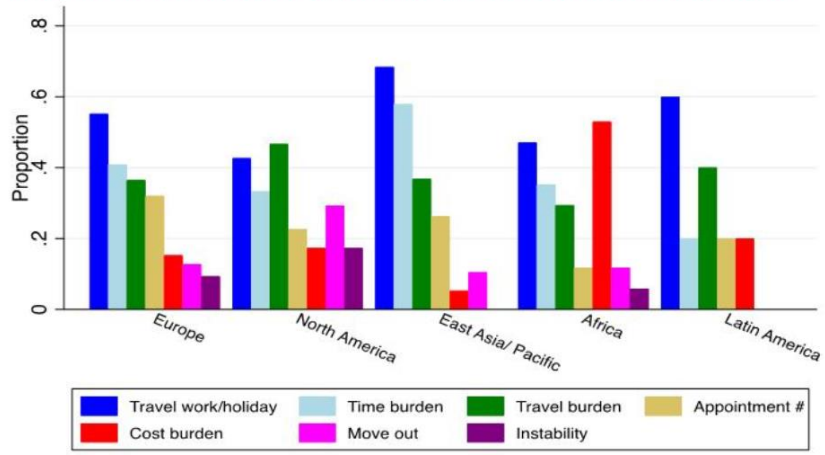
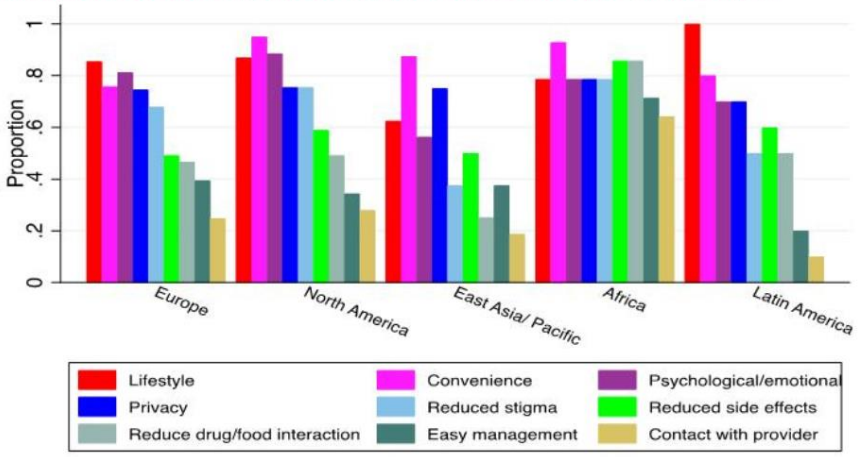
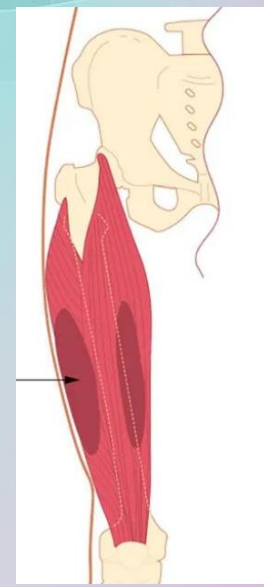


Figure 2. Benefits of Injectable LA ART Regimen: Frequency by Region



The New Frontiers for IM LA-CAB and LA-RPV

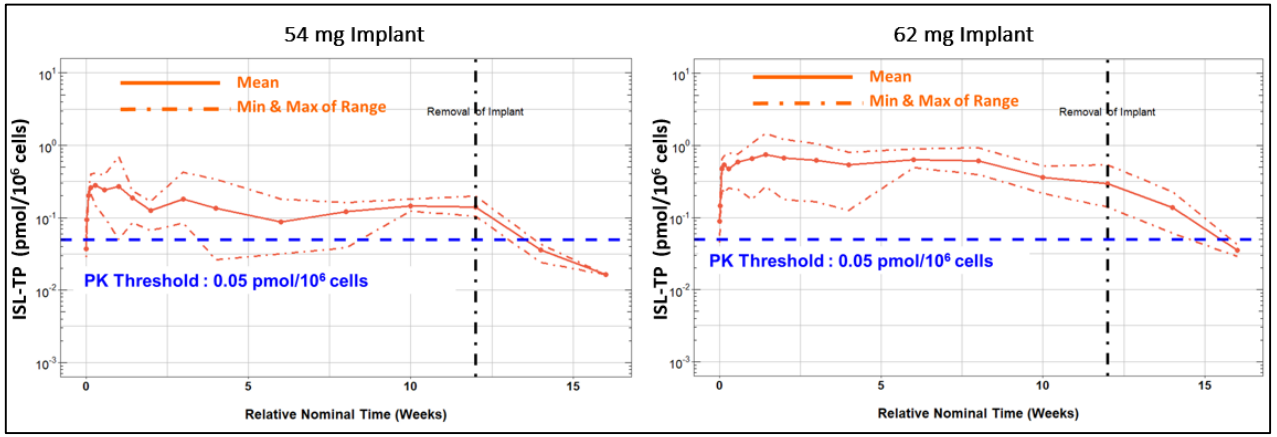
- Frequency of HIV RNA PCR checks?
  - Align with injections? Space out if remain suppressed?
- Therapeutic Drug Monitoring (TDM)
  - Check levels prior to injection? Individualized dosing frequency?
- Lower injection volume
- Identifying best candidates for LA-ART?
  - Patient-centered approaches
  - Eligibility scoring/ success predictors
- *Where* and *by whom* should injections be given?
  - Clinics? Community-based organizations? Pharmacies? Home? Public health settings?
  - Visiting health worker? RN? PLWH (*vastus lateralis?)*

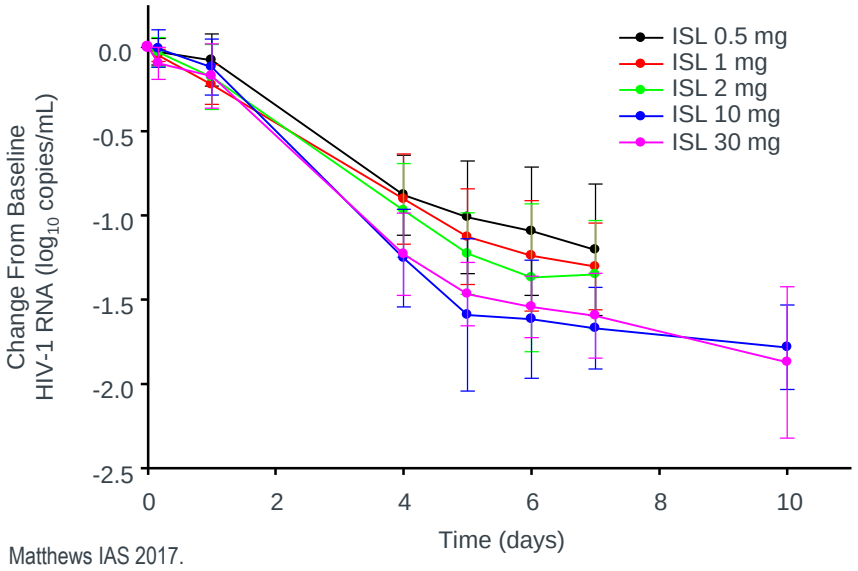


Islatravir (ISL; EFdA; MK-8591)

- *Oral*
  - Linear PK for parent (plasma) and active triphosphate (TP) in PBMCs
    - **Half-life of parent ISL: 50-60 hr**
    - **Half-life of active ISL-TP in PBMCs: 120-177 hr**
  - Antiviral efficacy observed in monotherapy after single doses as low as 0.5 mg

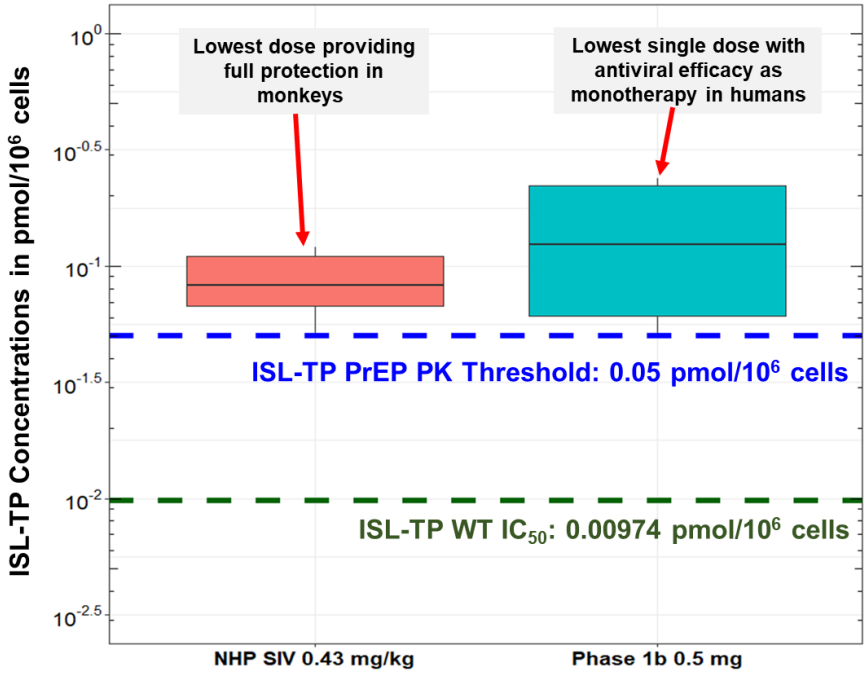
Implant





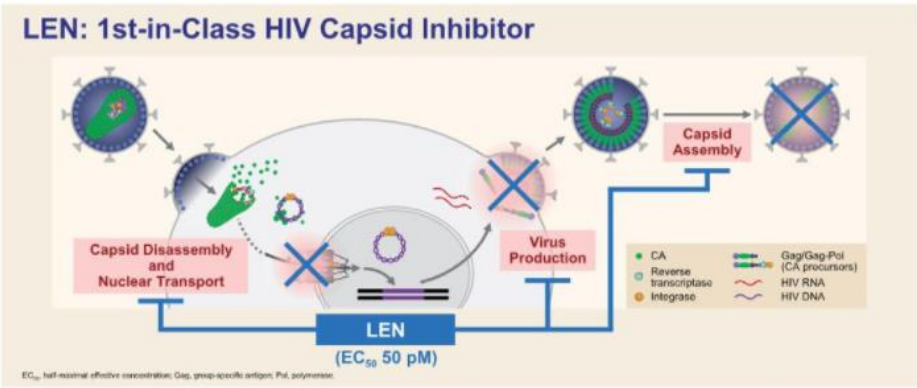
Matthews IAS 2017.

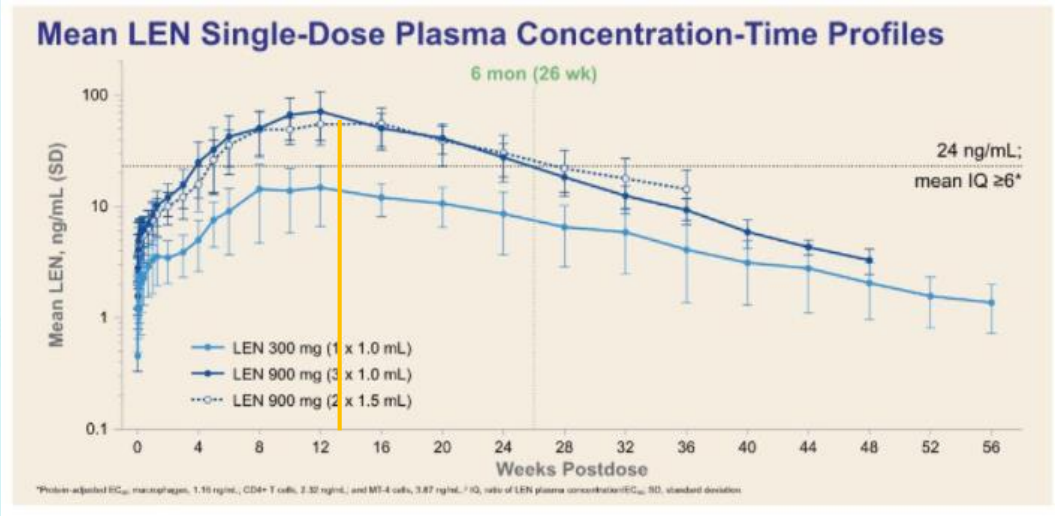
PK-PD Modeling: supports PrEP threshold 0.05 pmol/10^6 cells



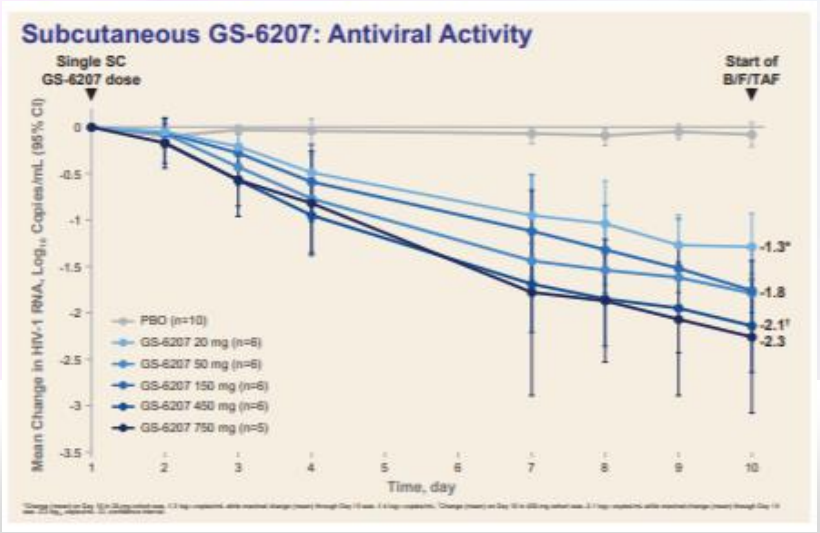
Matthews R., TUAC0401LB, IAS 2019 (Mexico City).

Lenacapavir (LEN)





- FIC, Inhibits multiple capsid protein dependent functions
- Potent antiviral activity:



$T_{1/2\ (SC)}$= 49-65 days; $T_{1/2\ (PO)}$= 11-13 days

- No food effect
- Oral dosing: **q 1 week**
- Subcutaneous dosing: **q 6 months** (oral lead-in 2/2 slow initial release)

Begley R, et al. PEB 0265: Lenacapavir sustained delivery formulation supports 6-month dosing interval AIDS 2020; Daar E, et al. Poster 3691: Dose-Response Relationship of Subcutaneous Long-Acting HIV Capsid Inhibitor GS-6207, Virtual CROI March 8-11, 2020.

ART Implants on the Horizon

Advantages	Disadvantages
Swift/easy removal at the end of treatment or in setting of adverse effects	Specialized device w need for training/sterility/ equipment/ procedure for insertion & removal
No oral lead-in required	Minor surgical procedure required to remove
No oral TDF/FTC needed to protect during subtherapeutic PK 'tail'	Must be removed at the end of product lifespan
Lower dose/day	Impossible to discern from palpation how long the device has been in place
Can remain in place for years (require less interaction with healthcare system)	Can migrate from original insertion site to a place where palpation is difficult (esp. in beagles)
More consistent and predictable drug release kinetics	Regulated as both a drug and a device
PK properties may not depend on injection site	More complex uptake into generic marketplaces
Palpable under skin indicating its presence	Visibility (arm) & possible stigma
Radio-opaque for visualization in case of unintended subcutaneous migration	
Biodegradable versions also possible	
Avoid high injection volumes	

Weld ED et al, *Current Opinion in HIV and AIDS* 15(1):33-41, January 2020.

Implant type	Model	Drug name	Size	Dose (mg/day)	Duration of levels/activity
Nonbioerodable					
1. Granulated drug core, PVA coating, permeable silicone tubes [35]	Rats	Nevirapine (NVP)			90 days
2. Pure drug powder core, platinum microperforated silicone tubing, PVA coating [11]	Beagle dogs	Tenofovir alafenamide (TAF)	1.9 x 4.0 mm	*In vivo* release rate: 1.07 mg/day (Human doses down to 0.15 mg/day)	40 days
3. Refillable nonpolymer nanochannel delivery implant (NDI)[15▪] - Titanium drug reservoir - Silicone nanochannel membrane - Twoi sealable refillable silicone drug loading ports	Rhesus macaques	Tenofovir alafenamide (TAF) and Emtricitabine (FTC)	FTC: 43 mm x 28.5 mm x 8.7 mm; 250 nm nanochannel TAF: 5 mm x 20 mm x 12.3 mm; 20 nm nano-channel	*In vitro:* TAF: 0.21 ± 0.03 mg/ day FTC: 2.67 ± 0.35 mg/day	83 days (TFV-DP); 28 days (FTC-DP)
4. Silicone-based transdermal matrix-based (drug-in-adhesive) patch w polyisobutylene adhesives [5▪]	Dermatomed human cadaver skin	Tenofovir alafenamide (TAF)	7 × 7 cm	Permeation flux of 7 μg/cm^2/h (extrapolates to 8.4 mg TAF/day)	1 week (in vitro)
5. Biocompatible polymer blended with entecavir via hot melt extrudates and polymer coated tablets (both administered subcutaneously) [16]	Rats (Wistar han)	Entecavir (ETV)	Dose 350 mg/kg		87 days
6. Titanium osmotic mini-pump system (Medici DDS™) [36]		TDF-FTC	'match-stick sized'		6 months to 12 months
7. Biodegradable and nonbiodegradable matrix-based polymer with islatravir [37▪▪] - HME process: barrel temp above melting point for polymer but below melting temp for drug→ solid crystalline drug in polymer matrix	Rats, NHP	Islatravir (ISL) aka EFdA (MK-8591)	2 mm × 40 mm	> 10 μg/day for entire study	> 6 months (for 40 wt% and 60 wt% MK-8591 in PCL, and 50 wt% MK-8591 in EVA) >12 months (for 60 wt% MK-8591 in PCL implants)
8. Biodegradable and nonbiodegradable matrix-based polymer [23▪▪,37▪▪] (same polymer and applicator as Nexplanon)	Humans (healthy volunteers) (N=16; 12 drug and 4 placebo)	Islatravir (ISL) aka EFdA (MK-8591)	2 mm × 40 mm	54 and 62 mg (0.17 mg/day)	12 months+
Bioerodable					
9. Ultra-long-acting removable DTG/PLGA/NMP in 0.3 : 1:2 ratio [25▪▪] (formulation optimized for *mice*, not macaques)	Rhesus macaque (treatment)	Dolutegravir (DTG)		100 mg	
10. Ultra-long-acting removable DTG/PLGA/NMP in 0.3:1:2 ratio [25▪▪] (formulation optimized for mice)	Humanized BLT mouse (prevention)	Dolutegravir (DTG)	1 cm	250 mg/kg (5.5–7.0 mg DTG in 50–80 μl)	> 5 months (flat shape of concentration: time curve at 140 days)
11. Reservoir-style implant [26▪] (extruded tube of a biodegradable polymer, PCL, filled w TAF and castor oil excipient in 2 : 1 ratio)	*In vitro*	Tenofovir alafenamide (TAF)	1, 4, and 7 cm (length) Wall thickness 100 μm	Release rates: 0.28 ± 0.06 mg/day (100 μm thickness) Range from 0.15 mg/day (for 200 μm thickness) to 0.91 mg/day (for 45 μm thickness)	180 days (in vitro)

Islatravir

6-12 months

Weld ED, et al, COHA 15(1):33-41, January 2020.

Need for Multipurpose Implants

- **ART plus…**
  - **Contraception**
  - **Opiate substitution therapy**
  - **Antipsychotic**

Drug and indication	Materials	Dose (mg/day)	Duration	Size
Etonorgestrel (Implanon; Nexplanon) *Hormonal contraception*	Ethylene vinyl acetate (EVA) copolymer, barium sulfate, magnesium stearate	65 mg (0.06 mg/day)	3 years	2 × 40 mm (1 rod)
Levonorgestrel (Norplant; Jadelle) *Hormonal contraception*	Dimethylsiloxane/ methylvinylsiloxane core in thin-walled silicone (provided w. disposable trocar)	150 mg (0.03–0.04 mg/day (p 12 months)	5 years	2.5 × 43 mm (2 rods)
Buprenorphine (Probuphine) (subcutaneous) *Matrix-style implant for maintenance treatment of opioid addiction*	Drug released through four individual poly(ethylene-vinyl acetate) (EVA) rods	80 mg buprenorphine hydrochloride (0.44 mg/day)	6 months	2.5 x 26 mm
Risperidone subcutaneous implant [32–34] *Schizophrenia*	Risperidone	375, 48, 720, or 960 mg (2, 2.7, 4, and 5.3 mg/day, respectively)	6 months	*Not mentioned in primary publication*

Weld ED, et al, COHA 15(1):33-41, January 2020.

Gaps in Existing Technologies

- Multipurpose Treatment and Prevention (combined LA-ART & contraception)
- LA ART for prevention of vertical transmission (PMTCT); PrEP in pregnancy
- LA ART for Hepatitis B
- ISL, LCV, bNAbs, CAB/RPV: What are the partners? How well do the PK profiles need to match? How do you study DDIs? Are oral forms needed?
- TAF +/- FTC implants: local tissue necrosis issue Su JT et al, *AAC*, 2020 Feb 21;64(3)
- First principles & modeling to predict which molecules and formulations will cause local toxicity

“Both the science and the art of medicine are advanced by **curiosity**.”

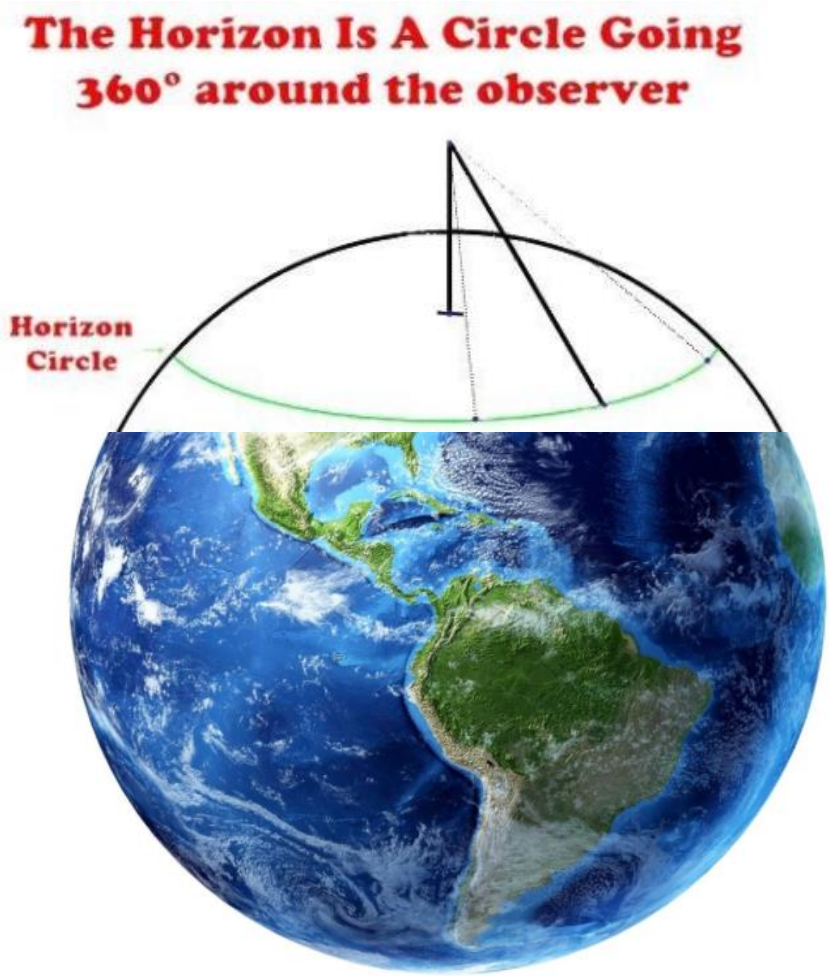
–Faith Fitzgerald, Ann Int Med 1999; 130:70-72

“What is the answer?”

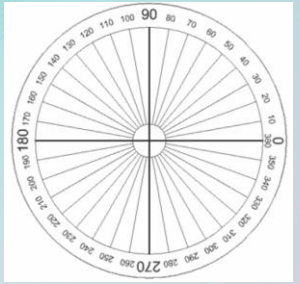
--Gertrude Stein, on her deathbed. Then, when no answer came from Alice B. Toklas:

“In that case, **what is the question**?”

Different Domains of LA-ART Horizon



- Efficacy
- Safety
- Quality of Life
- Tolerability/ Acceptability
- Cost
- Logistics
- Monitoring
- Stigma
- Adherence



THANK YOU!

IAPAC & Adherence 2020 Conference
Catherine Orrell
Robert Remien
Conference organizers
Jonathon Hess
Faculty & Attendees

Mentors/ Wayfinders

Kelly Dooley
Allison Agwu
Charlie Flexner
Craig Hendrix
Richard Chaisson
Leah Rubin

Funders

- NIH/NIAID R24 AI118397 (Long-Acting/ Extended Release Antiretroviral Resource Program (LEAP))
- Johns Hopkins University Center for AIDS Research P30AI094189 (Adolescent and Young Adult Scientific Working Group micro-grant; Junior Faculty Retention Funding)
- Johns Hopkins Clinical Research Scholars KL2 Award
- Pearl M. Stetler Research Award for Women Physicians
- NIH T32 GM066691-11 & GM066691-12, NIGMS

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https://www.hopkinsmedicine.org/news/publications/hiv-aids-timeline/timeline.html