HIV Long Acting Injectables - The Treatment of the Future, Now.

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LEARNING OBJECTIVES

1. Discuss why patients may desire long-acting antiretroviral therapy for HIV treatment and prevention
2. Review basic clinical pharmacology of the long-acting antiretroviral therapies currently available
3. Identify patients who are the best candidates for long-acting antiretroviral therapies
4. Discuss costs and review the process for obtaining access to long-acting antiretroviral therapy

Question 1

Which of the following is TRUE regarding CAB/RPV?

A. Contraindicated with PPIs
B. Only approved for Q 1 month dosing
C. Must be refrigerated
D. Not well tolerated by patients

Question 2

Which of the following is a reason PLWH might prefer an injectable therapy option vs oral therapy option?

A. Privacy
B. Adherence
C. Tolerability
D. All of the above

Question 3

When administering Cabotegravir LAI for HIV prevention (PrEP), which of the following lab tests must be obtained at each visit?

A. CMP
B. CBC
C. Lipid Panel
D. HIV ab/ag

Question 4

Which of the following has been identified as a risk factor for CAB/RPV failure?

A. BMI $\geq$ 30
B. Previous treatment with DTG/RPV
C. HIV Subtype B
D. Older age

Question 5

What is the biggest barrier to HIV LAI for treatment and prevention?

A. Tolerability
B. Medication Costs
C. Patient Interest
D. Efficacy

FDA Approval of HIV Medicines

1981: First AIDS cases are reported in the United States.

'85-'89

1987
Zidovudine (NRTI)

'90-'94

1991
Didanosine* (NRTI)

1992
Zalcitabine* (NRTI)

1994
Stavudine* (NRTI)

'95-'99

1995
Lamivudine (NRTI)
Saquinavir (PI)

1996
Indinavir* (PI)
Nevirapine (NNRTI)
Ritonavir (PI)

1997
Combivir (FDC)
Delavirdine* (NNRTI)
Nelfinavir* (PI)

1998
Abacavir (NRTI)
Efavirenz (NNRTI)

1999
Amprenavir* (PI)

'00-'04

2000
Didanosine EC* (NRTI)
Kaletra (FDC)
Trizivir (FDC)

2001
Tenofovir DF (NRTI)

2003
Atazanavir (PI)
Emtricitabine (NRTI)
Enfuvirtide (FI)
Fosamprenavir (PI)

2004
Epzicom (FDC)
Truvada (FDC)

'05-'09

2005
Tipranavir (PI)

2006
Atripla (FDC)
Darunavir (PI)

2007
Maraviroc (CA)
Raltegravir (INSTI)

2008
Etravirine (NNRTI)

'10-'14

2011
Complera (FDC)
Nevirapine XR (NNRTI)
Rilpivirine (NNRTI)

2012
Stribild (FDC)

2013
Dolutegravir (INSTI)

2014
Cobicistat (PE)
Elvitegravir* (INSTI)
Triumeq (FDC)

'15-'19

2015
Evotaz (FDC)
Genvoya (FDC)
Prezcobix (FDC)

2016
Descovy (FDC)
Odefsey (FDC)

2017
Juluca (FDC)

2018
Biktarvy (FDC)
Cimduo (FDC)
Delstrigo (FDC)
Dovarivine (NNRTI)
Ibalizumab-uiyk (PAI)
Symfi (FDC)
Symfi Lo (FDC)
Symtuza (FDC)
Temixys (FDC)

2019
Dovato (FDC)

'20-'24

2020
Fostemsavir (AI)

2021
Cabenuva (FDC)
Cabotegravir (INSTI)

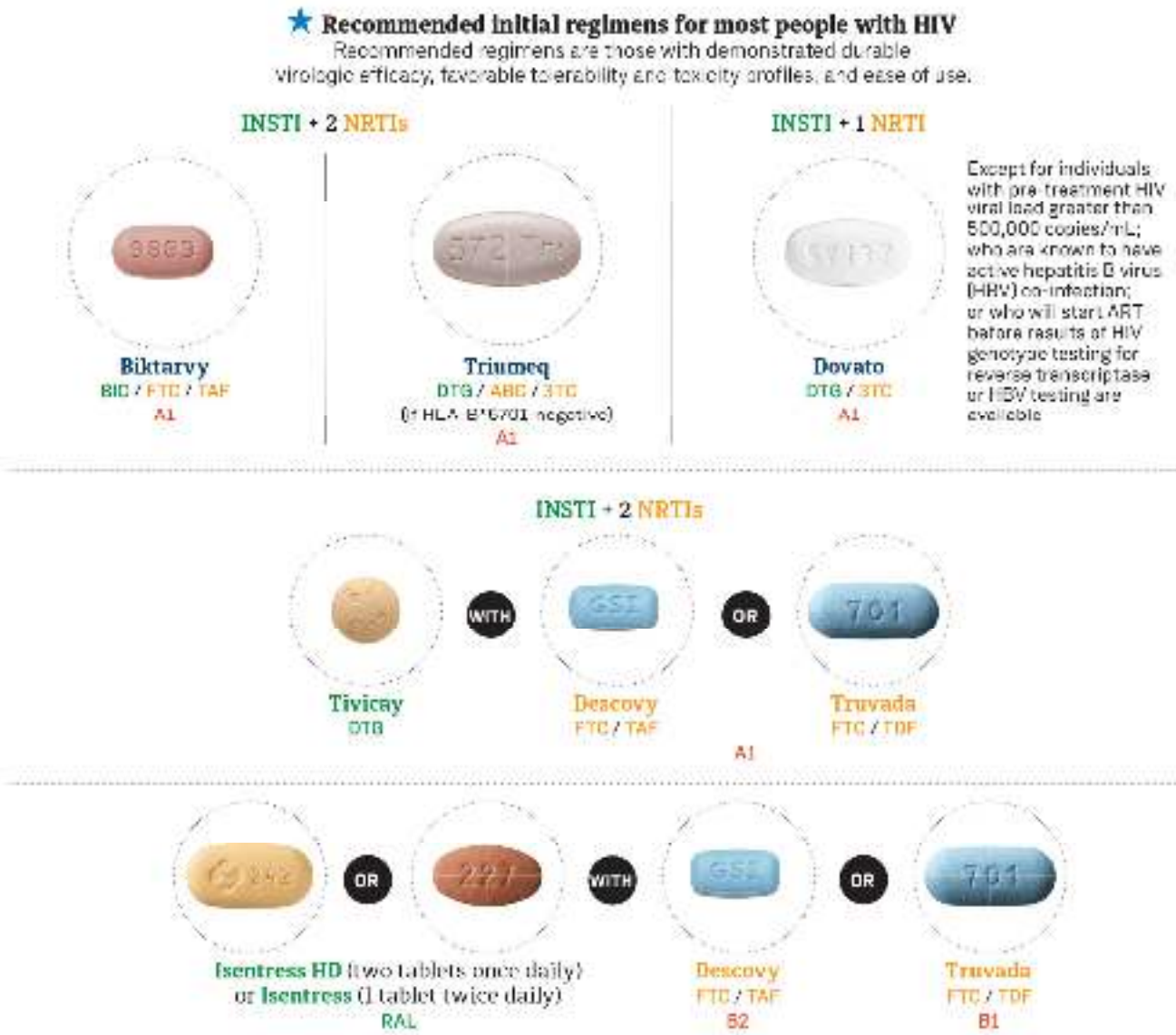
2022
Lenacapavir (CI)

Drug Class Abbreviations:
AI: Attachment Inhibitor; **CA**: CCR5 Antagonist; **FDC**: Fixed-Dose Combination; **FI**: Fusion Inhibitor; **INSTI**: Integrase Inhibitor; **NNRTI**: Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI**: Nucleoside Reverse Transcriptase Inhibitor; **PE**: Pharmacokinetic Enhancer; **PI**: Protease Inhibitor; **PAI**: Post-Attachment Inhibitor

HIVinfo.NIH.gov

***Note:** Drugs with an asterisk are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.

WHAT TO START?



DHHS Guidelines, Accessed 2023

DO WE EVEN NEED NEW DRUGS?

- Options for heavily treatment experienced patients
- More convenience
- PrEP options

NEW HORIZONS IN THERAPY

Patient desires

- Freedom from stigma
- Decreased pill burden or side effects

Ideal long-acting ARV characteristics

- Potent
- Extended dosing intervals
- Low volume injections
- Patient self-administration

Cabotegravir + Rilpivirine

CABENUVA

INJECTABLE CAB/RPV

Consists of:

- Cabotegravir extended-release injectable suspension
  - Integrase inhibitor (INSTI)
  - White to light pink color
- Rilpivirine extended-release injectable suspension
  - Non-nucleoside reverse transcriptase inhibitor (NNRTI)
  - White to off-white color

For intramuscular (IM) use

FDA approved on January 21st, 2021

RILPIVIRINE (EDURANT®)

- Found in: Complera, Odefsey, Juluca
- Contraindicated with PPIs
- Lacks potency and a high barrier to resistance
- Must be taken with food (a full meal) to increase absorption

CABOTEGRAVIR (VOCABRIA®)

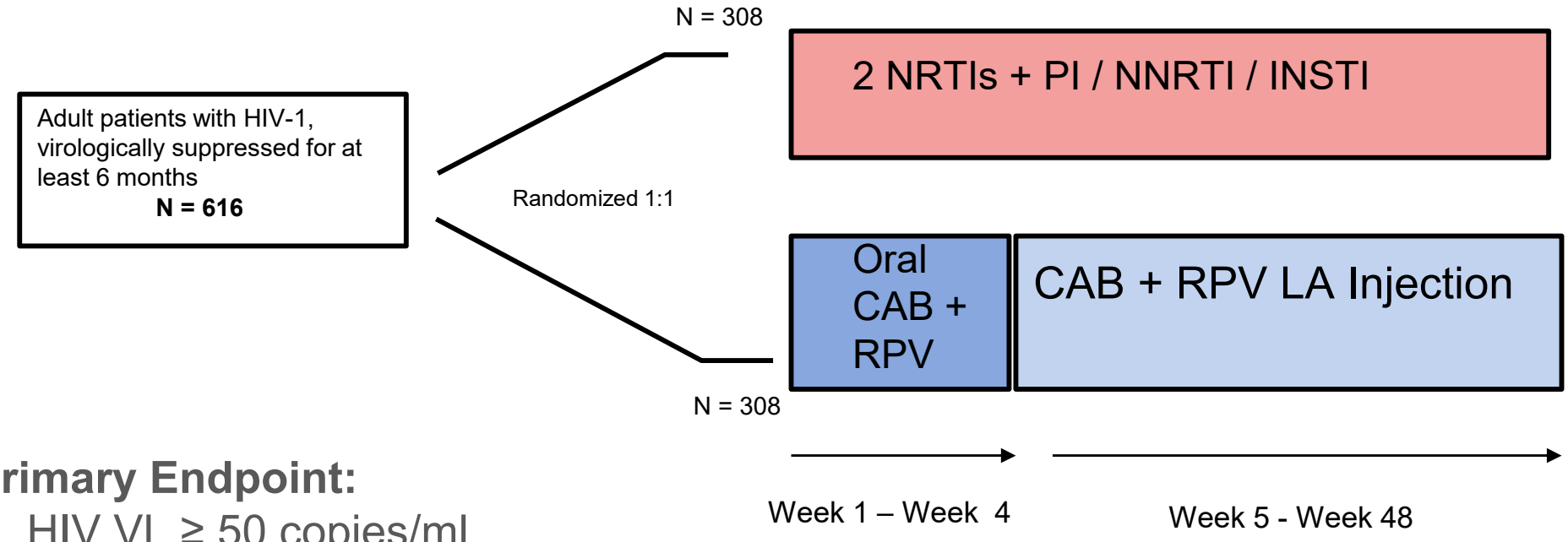
- Brand new agent – Similar to dolutegravir
- Moderate barrier against HIV resistance but less than DTG, BIC
- Adverse effects appear similar to those of dolutegravir

CAB/RPV (CABENUVA®)

- Approved for switch in stable suppressed patients (VL<50)
- No history of treatment failure or known/suspected resistance to CAB or RPV

ATLAS & FLAIR

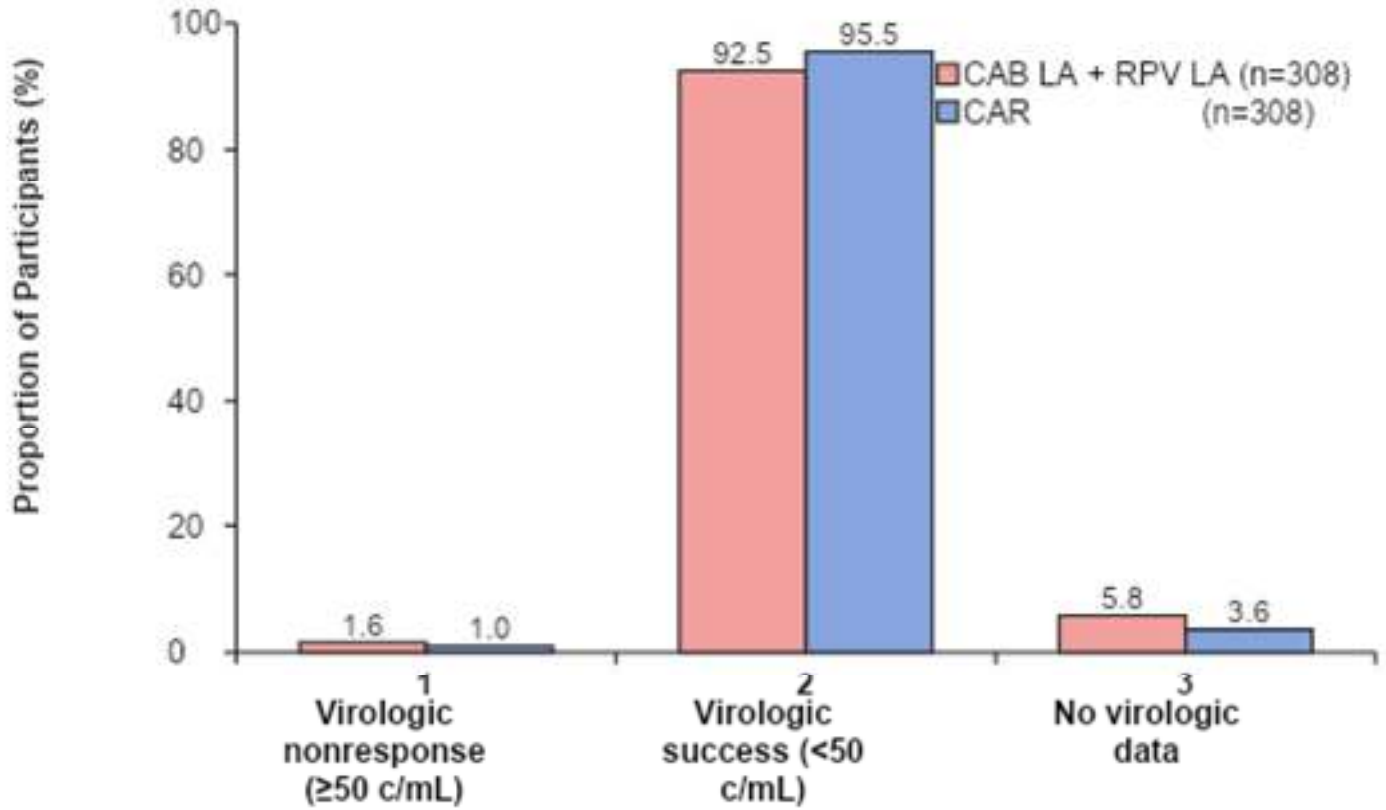
ATLAS Study Design



Primary Endpoint:

- HIV VL ≥ 50 copies/mL

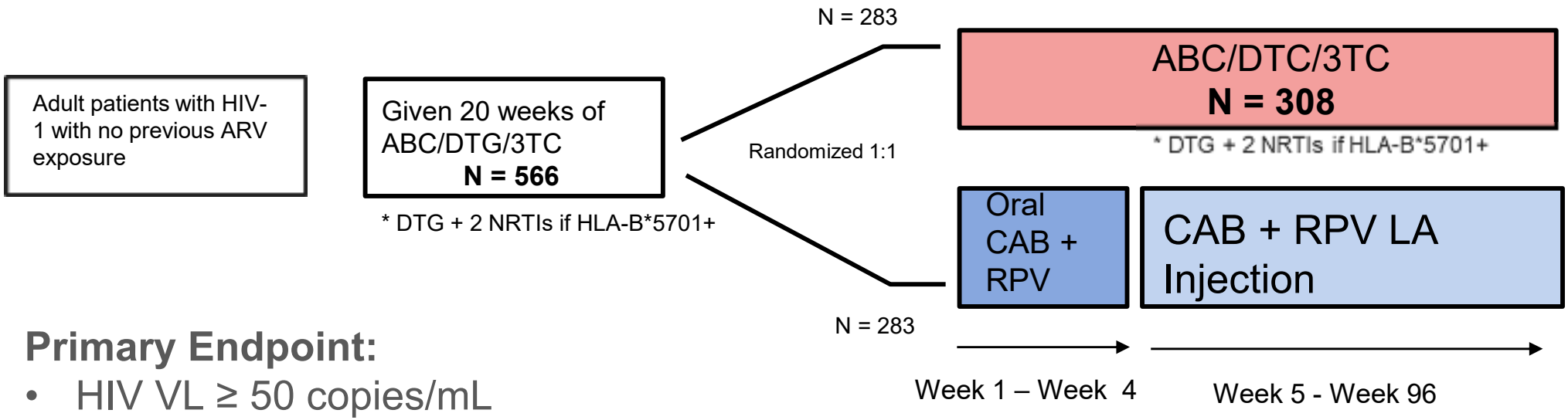
ATLAS Results



Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.

ATLAS & FLAIR

FLAIR Study Design



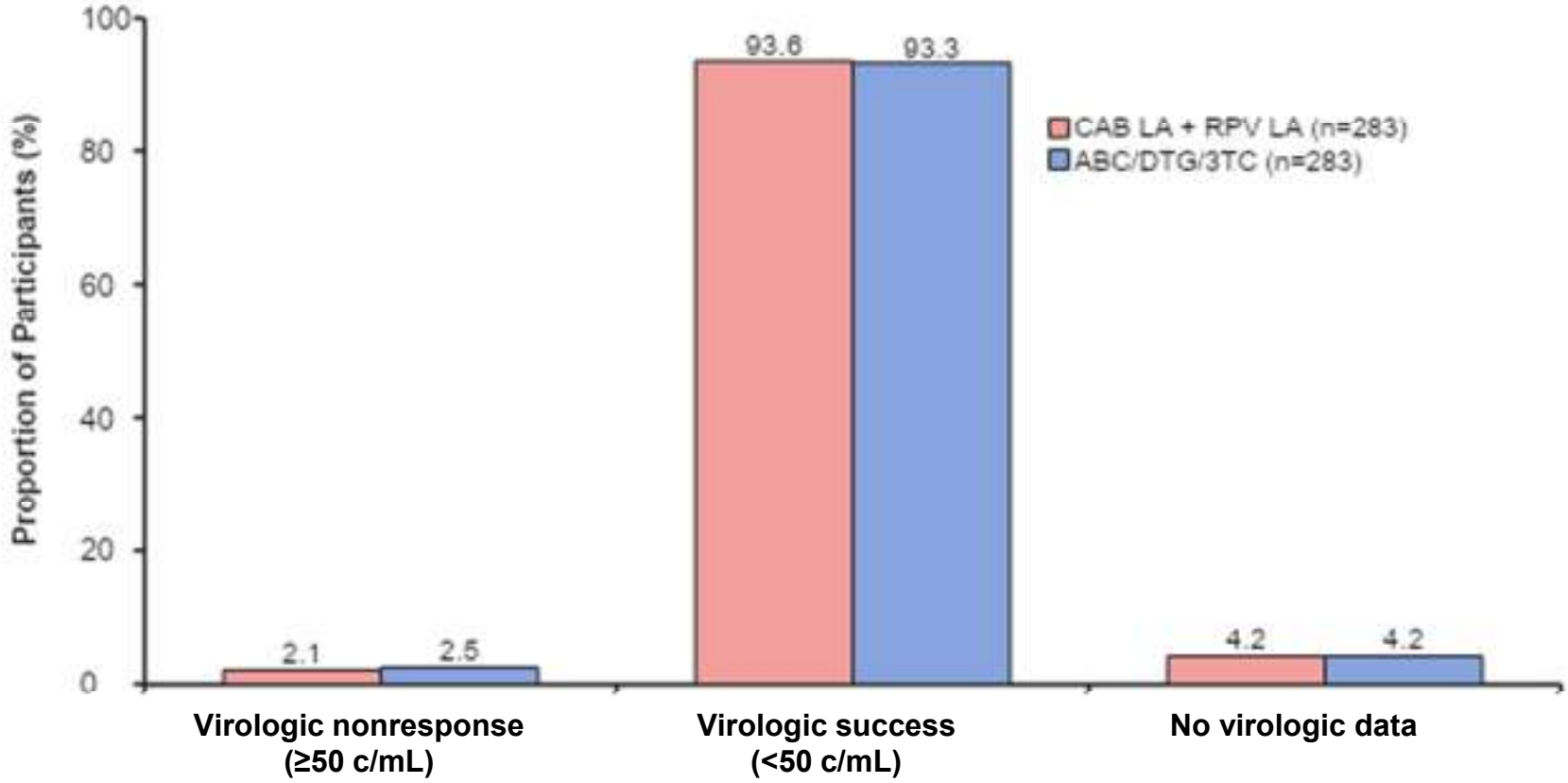
Primary Endpoint:

- HIV VL ≥ 50 copies/mL @ 48 weeks

Secondary Endpoint:

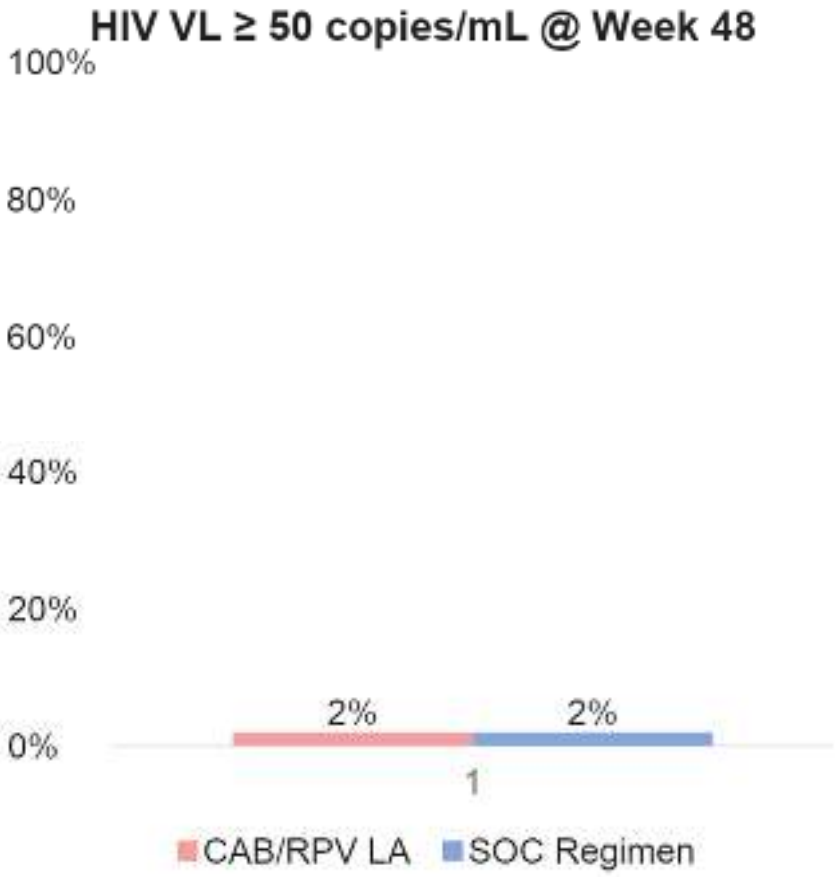
- HIV VL ≥ 50 copies/mL @ 96 weeks

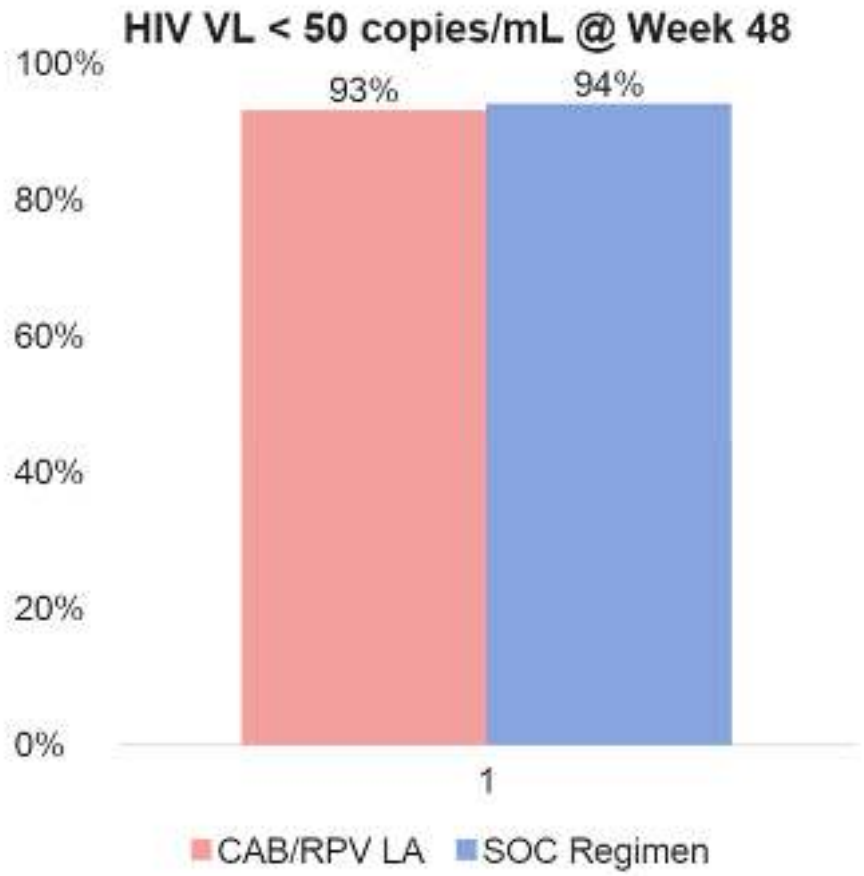
FLAIR Results



Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947

Pooled Analysis – ATLAS + FLAIR





Rizzardini JAIDS 2020

ATLAS & FLAIR - Safety

Table 3. Safety Overview, Excluding ISRs, Through Week 48 in Maintenance Phase

	CAB + RPV LA N=591	CAR N=591
Any AE	505 (86%)	444 (75%)
Any Grade 3/4/5 AE*	44 (7%)	35 (6%)
Any drug-related AE	165 (28%)	35 (6%)
Any Grade 3/4/5 drug-related AE*	8 (1%)	1 (<1%)
Any AEs leading to withdrawal	17 (3%)	9 (2%)
Any serious AE	24 (4%)	25 (4%)
Serious AEs related to study treatment†	1 (<1%)	1 (<1%)
Common AEs (≥5%)		
Nasopharyngitis	108 (18%)	90 (15%)
Headache	73 (12%)	38 (6%)
Upper respiratory tract infection	70 (12%)	53 (9%)
Diarrhea	54 (9%)	40 (7%)
Back pain	43 (7%)	23 (4%)
Influenza	42 (7%)	34 (6%)
Pyrexia	43 (7%)	13 (2%)
AEs of special interest		
Anxiety	27 (5%)	20 (3%)
Depression	16 (3%)	14 (2%)
Suicidal ideation/behavior	4 (<1%)	5 (<1%)

*There was only one (<1%) participant with Grade 5 AE in the CAR arm; †Serious AEs related to study treatment: LA arm – arthritis; CAR arm – suicidal ideation.

Mean (SD) weight change at week 48 from baseline was an increase of 2.34 kg (5.67) and 1.17 kg (5.22) in the LA and CAR arms, respectively.

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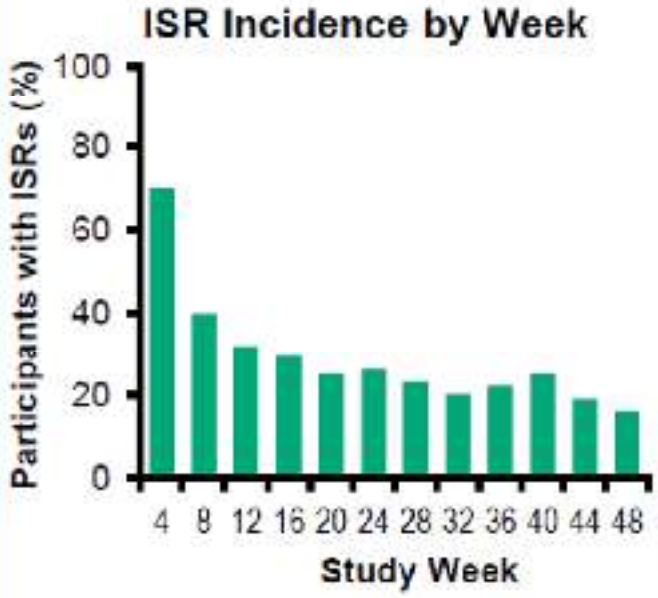
ATLAS & FLAIR - Safety

Figure 5. Pooled Injection Site Reactions



Event	CAB + RPV LA N=591
Participants receiving injections, n	581
Injections given, n	14682
ISR events, n (%)	3663 (24.9)
Pain	3087 (84.3)
Nodule	140 (3.8)
Induration	136 (3.7)
Swelling	86 (2.3)
Grade 3 ISR pain	32 (0.9)
Median duration of ISRs, days	3
Participants with ISR leading to withdrawal, n (%)	6 (1)

Bars represent incidence of onset ISRs relative to the most recent IM injection visit.

- The majority (99%, 3628/3663) of ISRs were Grade 1–2 and most (88%) resolved within ≤7 days

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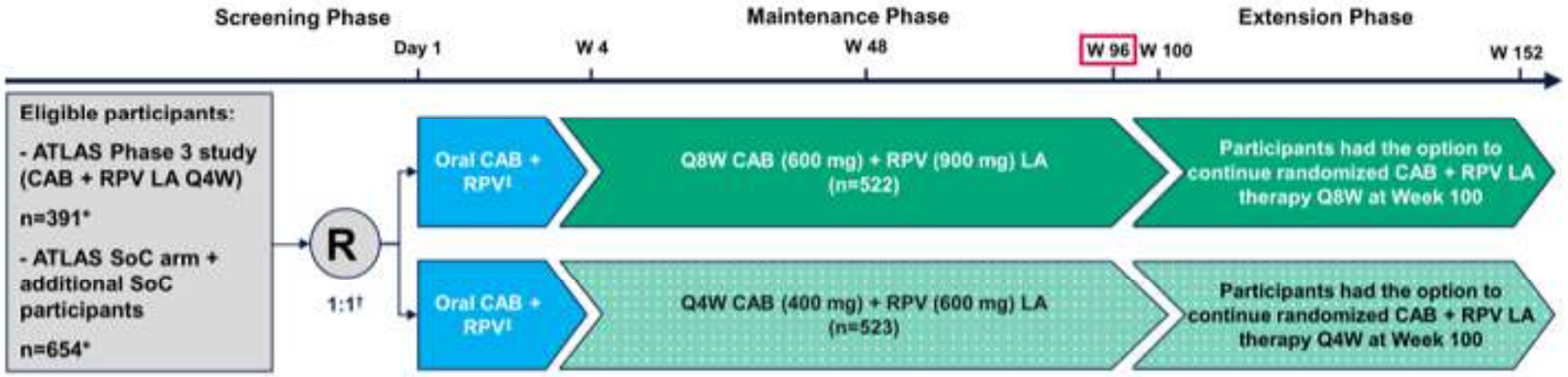
ATLAS-2M

ATLAS-2M Week 96: Study Design

Phase 3b, randomized, multicenter, parallel-group, noninferiority, open-label study

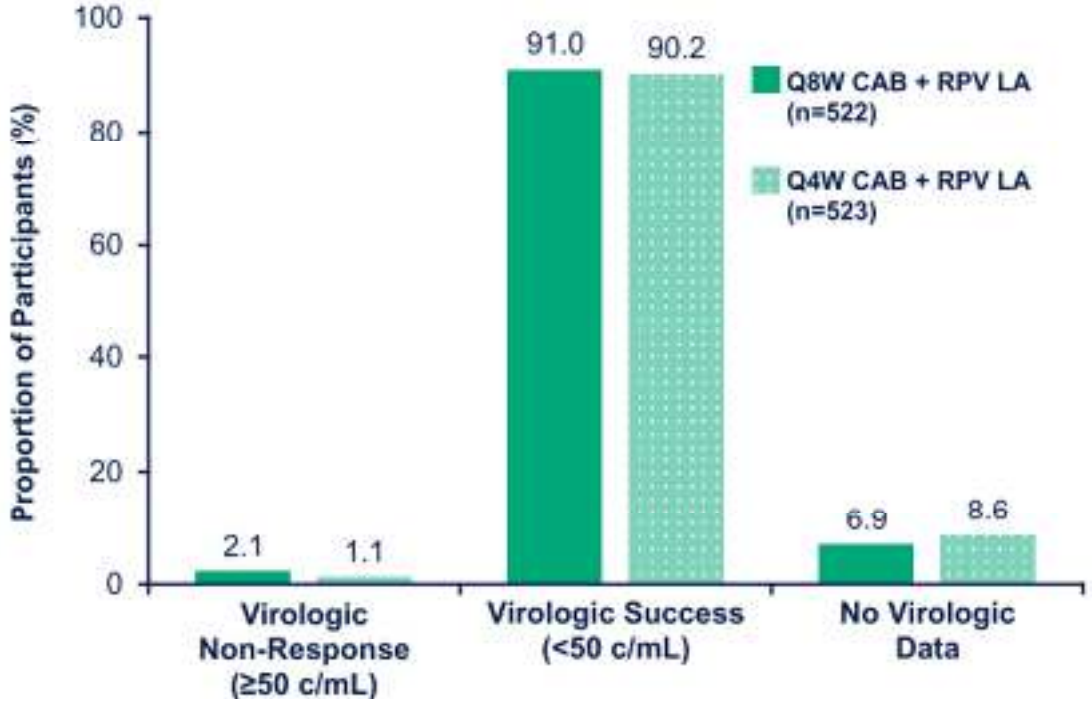


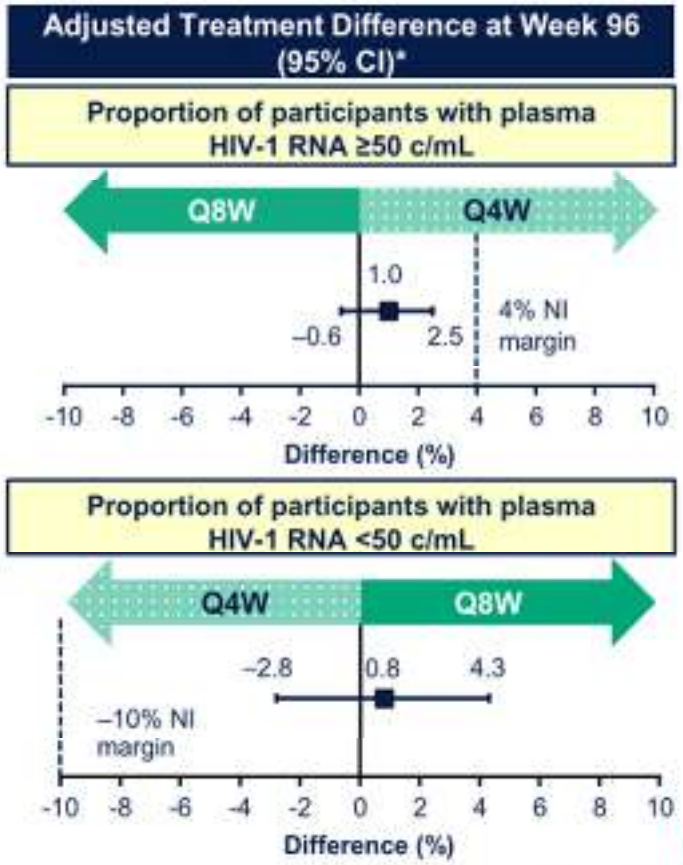
- The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)
- Secondary endpoints included the proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)
- Other endpoints assessed at Week 96 included the incidence of CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL), incidence of viral resistance in participants with CVF, and safety and tolerability

Jaeger CROI 2021

ATLAS-2M Results

ATLAS-2M Week 96: Virologic Snapshot Outcomes for ITT-E: CAB + RPV LA Continued to Maintain High Levels of Viral Suppression





*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks). CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Conference on Retroviruses and Opportunistic Infections: March 6-10, 2021; Virtual

Jaeger et al. CROI 2021; Virtual. Science Spotlight

Jaeger CROI 2021

CAB/RPV TREATMENT FAILURES

- Multivariate post hoc analysis of the confirmed virologic failures in ATLAS, FLAIR, ATLAS-2M (n=23/1431)
  - About 1% in each study
- CVF was rare and associated with the presence of at least 2 baseline factors: RPV resistance mutations, BMI≥30, HIV-1 subtype A6/A1

Orkin et al. CID June 2023

CAB/RPV TREATMENT FAILURES

Three Baseline Factors:
RPV RAMs, Subtype A6/A1, and BMI ≥30 kg/m^2

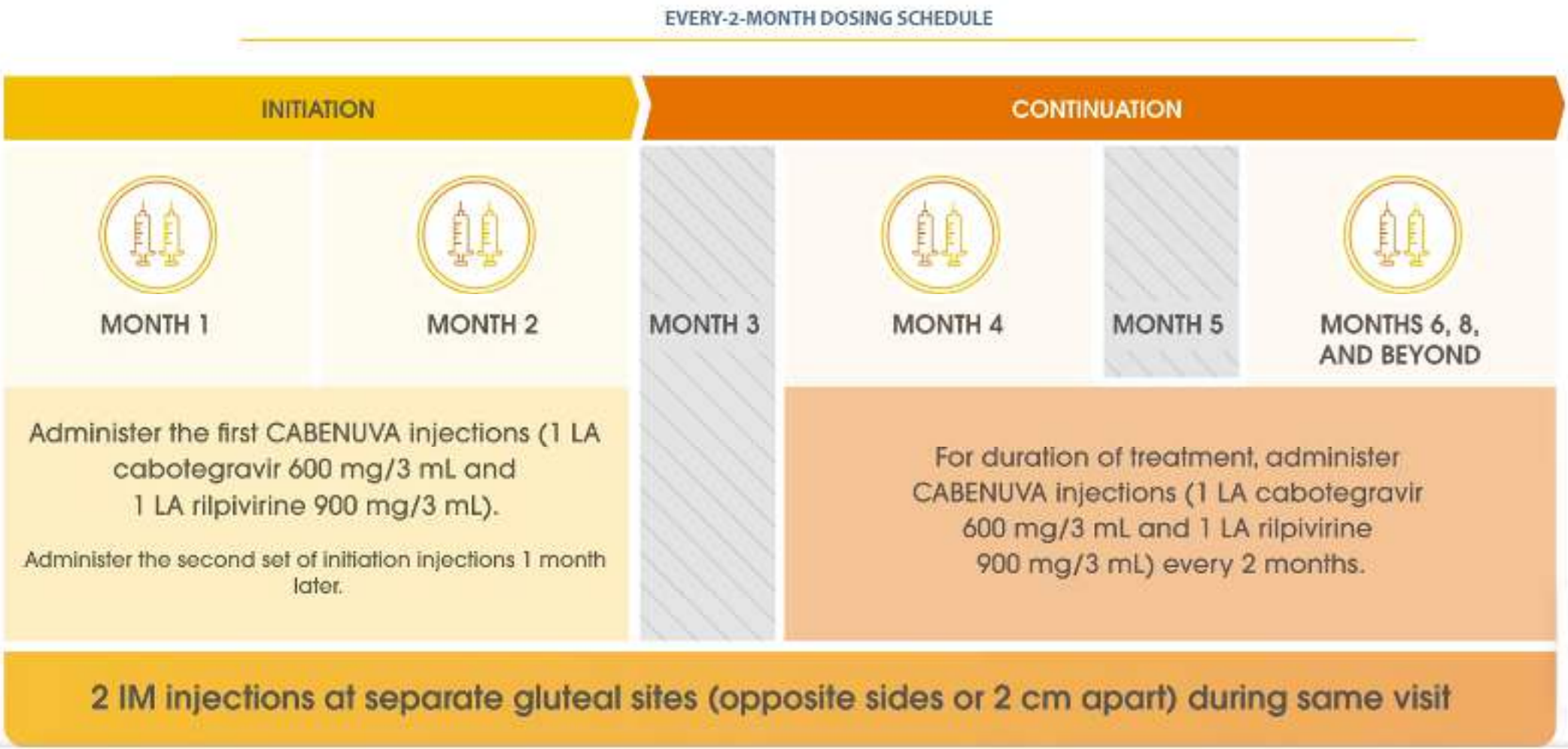
Baseline Factors (Number)	Virologic Suppression, n (%)[b]	CVF, n (%)[c]
0	844/970 (87.0)	4/970 (0.4)[d]
1	343/404 (84.9)	8/404 (2.0)[e]
≥2	44/57 (77.2)	11/57 (19.3)[f]
TOTAL	1231/1431 (86.0)	23/1431 (1.6)
(95% CI)	(84.1–87.8)	(1.0–2.4)
		18/1224 (1.47)[j]

Orkin et al. CID June 2023

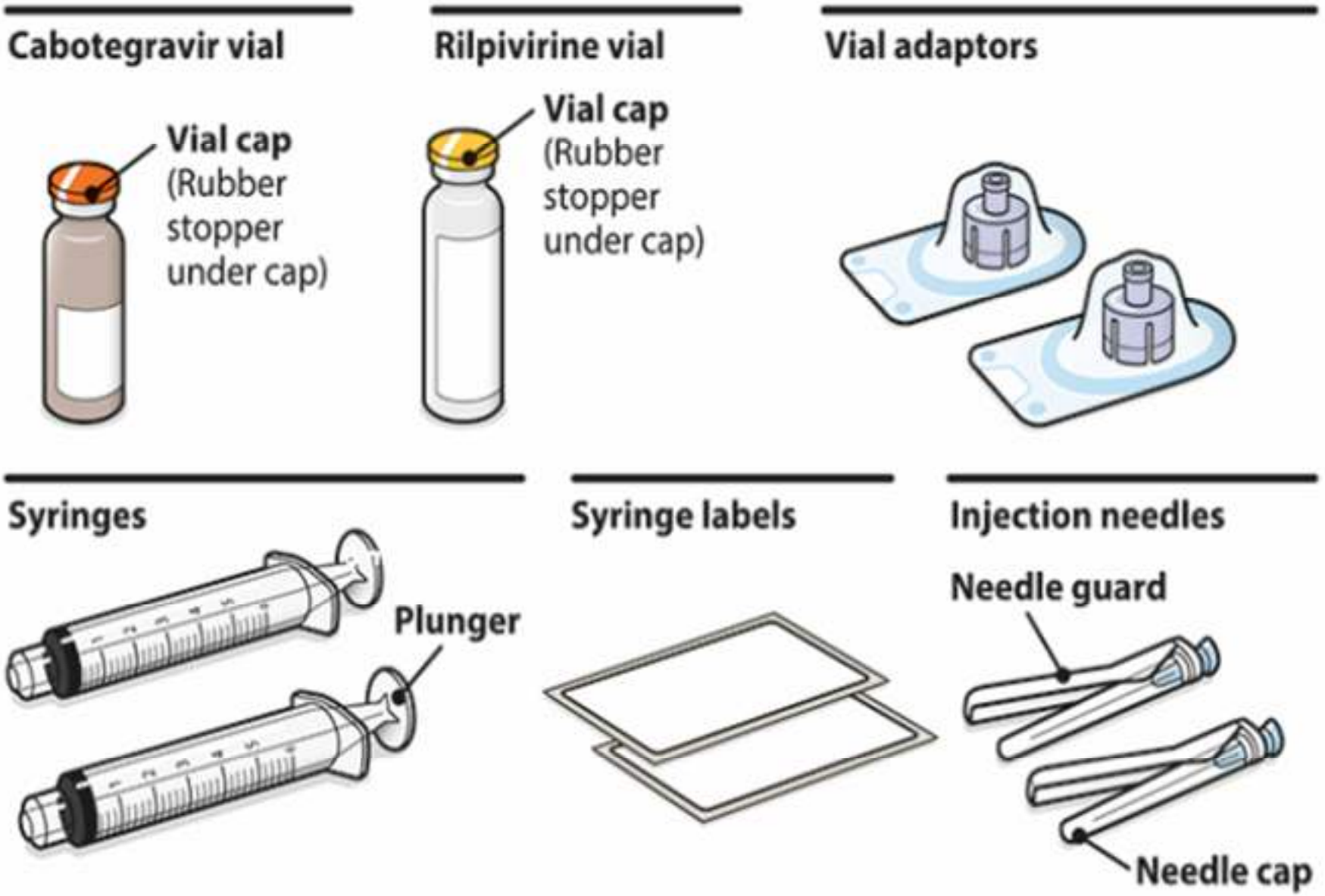
DOSAGE AND ADMINISTRATION

- Injectable CAB/RPV is for IM gluteal injection only
  - Cabotegravir and rilpivirine are administered as two different injections at separate gluteal injection sites (on opposite sides or 2 cm apart) during the same visit

CABENUVA DOSING SCHEDULE



CABENUVA KITS



ADMINISTRATION INSTRUCTIONS

- CAB/RPV should be removed from the refrigerator at least 15 minutes prior to preparing the injections to allow the medications to come to room temperature
- The vials may remain in the carton at room temperature for up to 6 hours
- Once the suspensions have been drawn into syringes, they should be administered as soon as possible, but may remain in the syringes for up to 2 hours
- Consider the BMI of the patient to ensure that the needle length is sufficient to reach the gluteus muscle

ADHERENCE

- CAB/RPV must be administered by a healthcare professional
- Patient must agree to required monthly injection dosing schedule
- Patients should be counseled on the importance of adherence to scheduled dosing visits to help maintain viral suppression and avoid potential development of resistance with missed doses
- CAB/RPV may be given up to 7 days before or after the date the patient is scheduled to receive monthly injections

RESTARTING AFTER PLANNED MISSED INJECTIONS

Your patient is restarting injections after planned missed injections.

How much time has passed since their missed Target Treatment Date?

≤1 month since Missed Target Treatment Date

Resume injections on final day of oral therapy. Continue with every-2-month dosing schedule thereafter.

>1 month since Missed Target Treatment Date

Repeat initiation injections on final day of oral therapy 1 month apart for 2 consecutive months. Continue with every-2-month dosing schedule thereafter.

RESTARTING AFTER UNPLANNED MISSED INJECTIONS

Adherence to scheduled injections visits is important.

Your patient missed the Target Treatment Date by >7 days and did not plan for it by taking oral therapy.

Clinically reassess the patient to determine whether long-acting treatment remains appropriate.

How much time has passed since their missed Target Treatment Date?

≤1 month since Missed Target Treatment Date

Resume injections as soon as possible. Continue with every-2-month dosing schedule thereafter.

>1 month since Missed Target Treatment Date

Repeat initiation injections as soon as possible 1 month apart for 2 consecutive months. Continue every-2-month dosing schedule thereafter.

CAB/RPV (CABENUVA®)

- Contraindicated with
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Rifabutin, rifampin, rifapentine
  - St Johns wort
  - Dexamethasone (more than a single dose treatment)

- ADRs: injection site reactions, fatigue, fever, headache, nausea, musculoskeletal pain

Cabotegravir

APRETUDE

INJECTABLE CABOTEGRAVIR

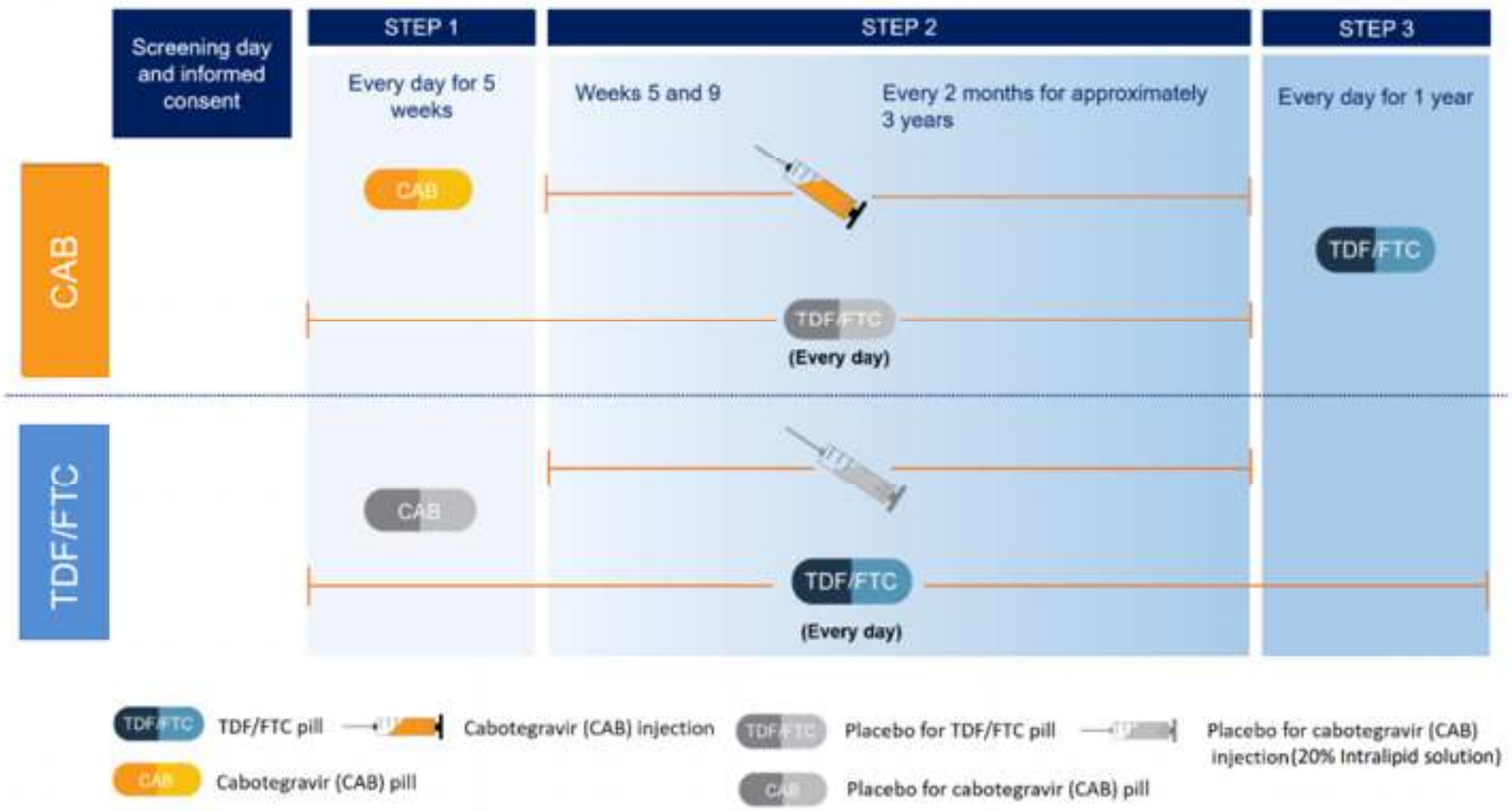
- Consists of:
  - Cabotegravir extended-release injectable suspension
    - Integrase inhibitor (INSTI)
    - White to light pink color
  - For intramuscular (IM) use

- FDA approved December 20, 2021

CABOTEGRAVIR (APRETUDE®)

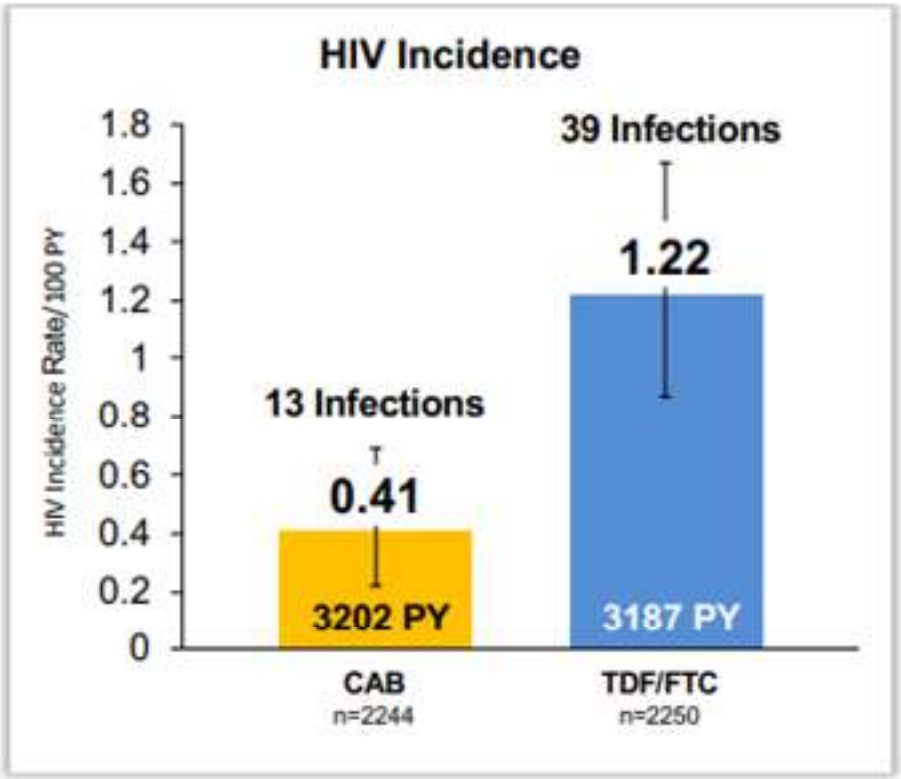
- Approved for pre-exposure prophylaxis (PrEP) in ALL populations

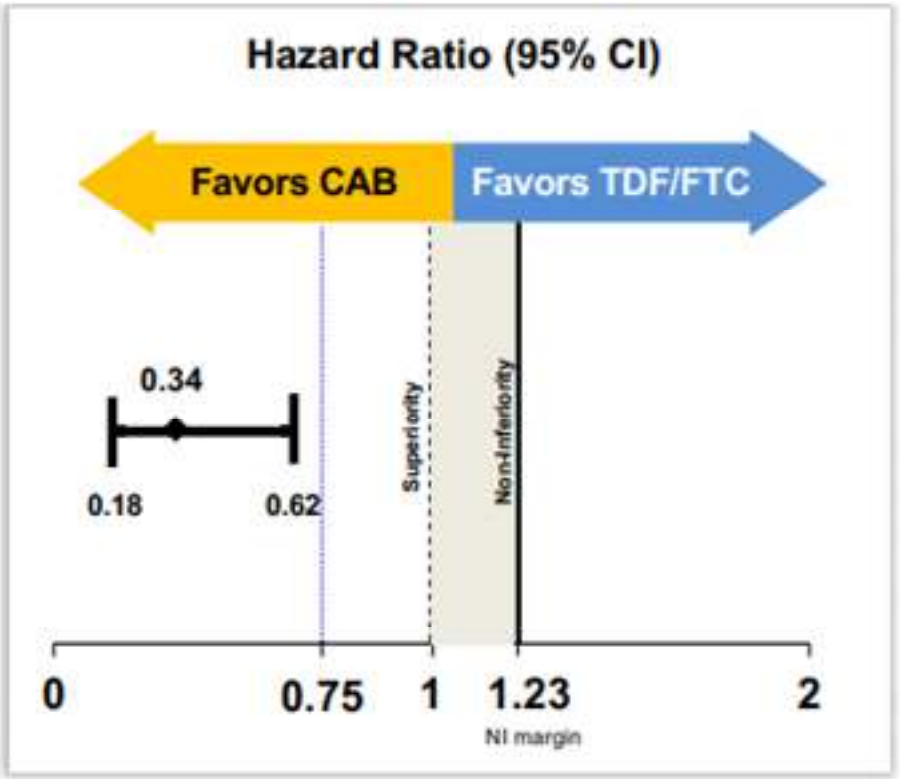
CAB for PrEP: HPTN 083



Landovitz et al. AIDS 2020, #OAXLB01

CAB for PrEP: HPTN 083





CI, confidence interval

- 66% reduction in risk of HIV infection in CAB group
- CAB well tolerated, ISR

Landovitz et al. AIDS 2020, #OAXLB01

CAB for PrEP: HPTN 084

- Planned enrollment of 3,200 cis-women in sub-Saharan Africa as risk for HIV acquisition

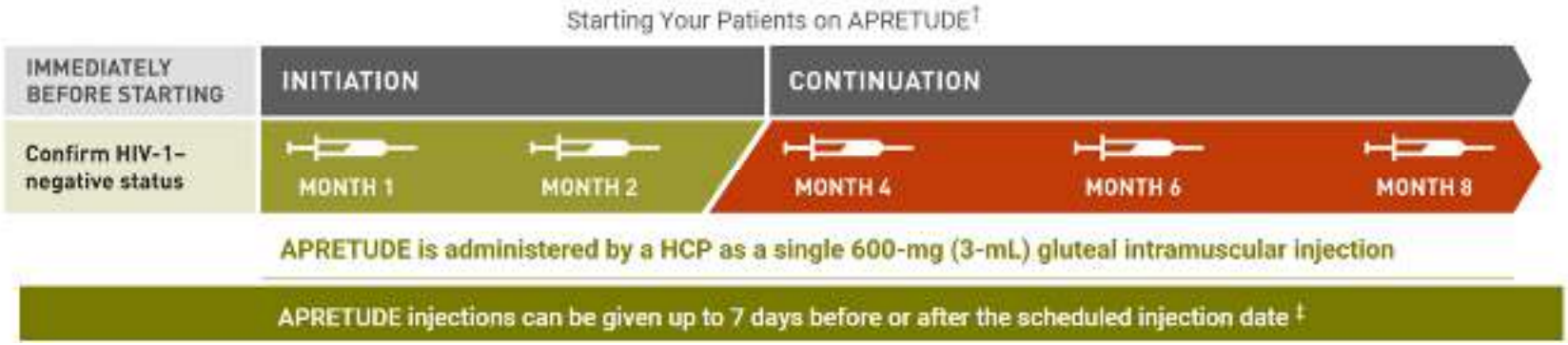
https://www.hptn.org/research/studies/hptn084#views-field-field-public-files

CAB for PrEP: HPTN 084

- Stopped early in November 2020, was designed to go to 2022
- 3223 cisgender women enrolled
- CAB was superior to TDF/FTC at preventing HIV
- HIV incidence
  - 0.21% in CAB group, n=4
  - 1.79% in TDF/FTC group, n=38

https://www.084life.org/study-results/

CAB for PrEP (Apretude®)



HIV-1 testing and APRETUDE

PRE-INITIATION VISIT

Screen for HIV-1 infection.

- If HIV-1 negative, begin benefit verification before initiating APRETUDE

INITIATION AND CONTINUATION INJECTIONS

Individuals must be tested prior to initiating APRETUDE or oral cabotegravir and with each subsequent injection.

- Use a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infecton
  - If an antigen/antibody test was used and was negative, confirm results with an HIV RNA test
  - Results of confirmatory HIV RNA test can be pending at the time of administration

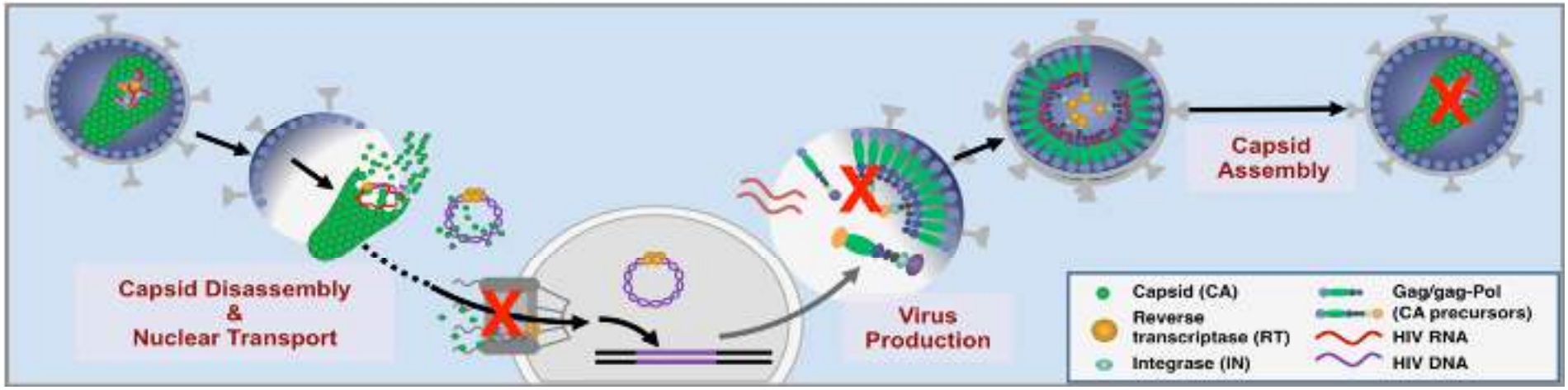
ADMINISTRATION

- Similar to Cabenuva (CAB/RPV)
  - Does not need to be refrigerated
  - One injection vs two injections
- ADRs: injection site reactions, pyrexia, vasovagal rxns, weight gain (1.5-4kg)
- Contraindicated with
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
  - Rifabutin, rifampin, rifapentine
  - St Johns wort

OTHER INJECTIONS

LENACAPAVIR

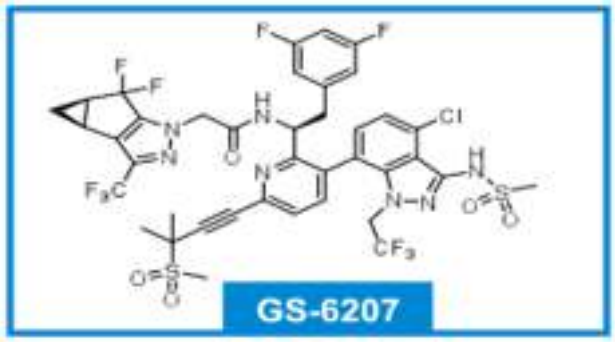
HIV CAPSID INHIBITOR



Sager et al. CROI 2019, #141

LENACAPAVIR (LEN): CAPSID INHIBITOR

- First in-class inhibitor of HIV capsid inhibitor with picomolar potency
- Given as subcutaneous suspension
  - Also has oral formulation in trials
- In-vitro: active against HIV-1 variants and resistant strains
- Low clearance and low solubility very long half life
- In clinical trials, for both treatment and PrEP

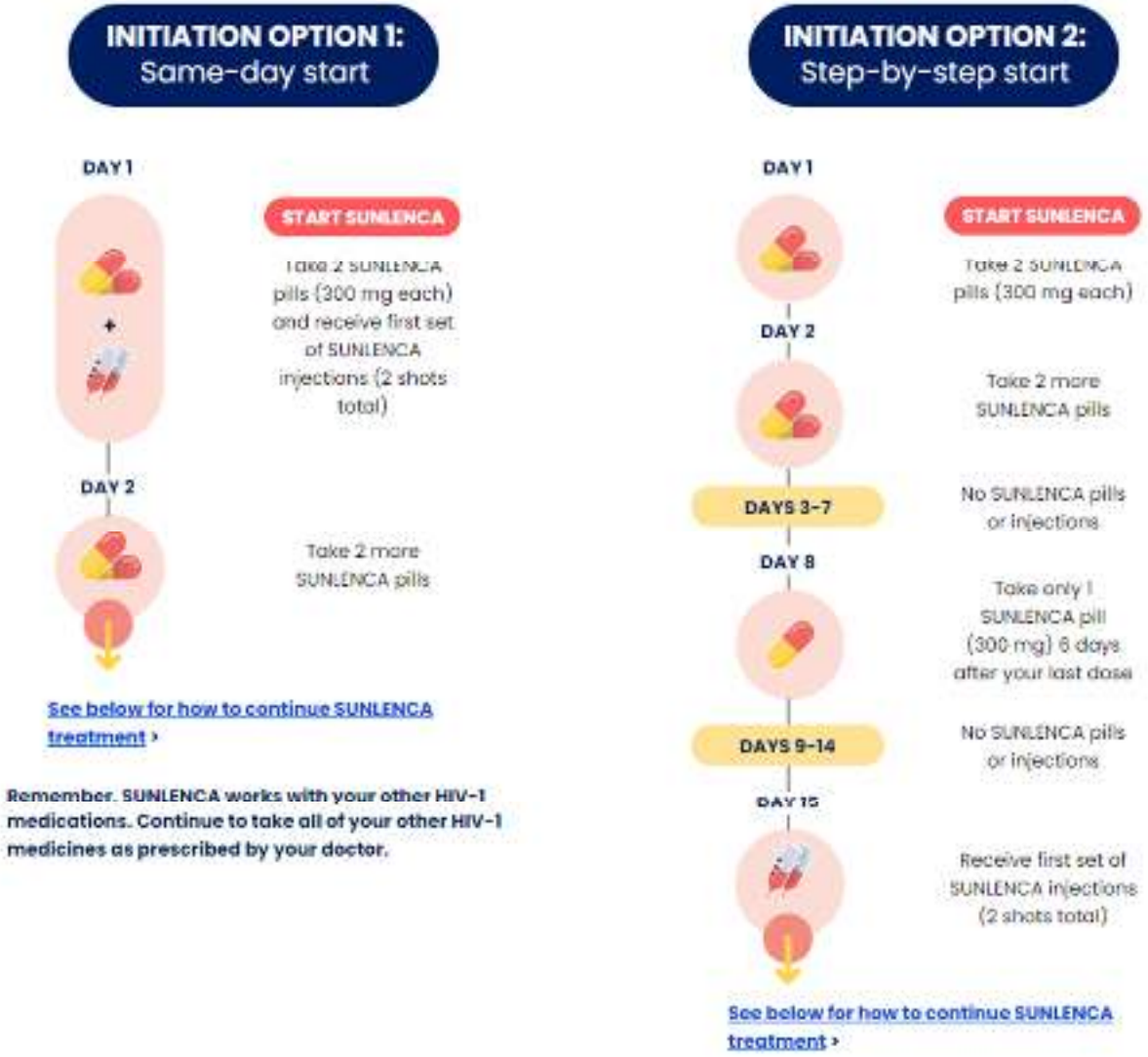


Sager et al. CROI 2019, #141

SUNLENCA®

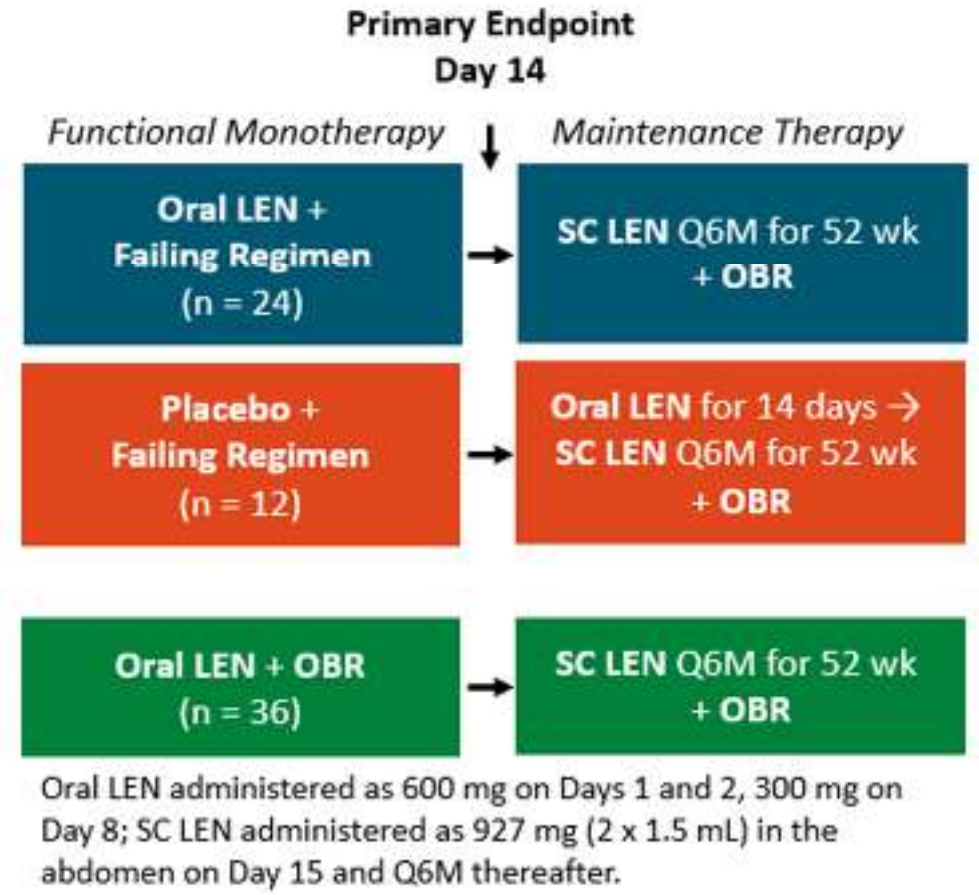
- Approved in December 2022
- Every 6mo subcutaneous injection for patients with multi-drug resistant HIV
- NOT a standalone regimen

SUNLENCA®


INITIATION OPTION 1:
Same-day start
DAY 1
START SUNLENCA
Take 2 SUNLENCA pills (300 mg each) and receive first set of SUNLENCA injections (2 shots total)
DAY 2
Take 2 more SUNLENCA pills
See below for how to continue SUNLENCA treatment ›
Remember, SUNLENCA works with your other HIV-1 medications. Continue to take all of your other HIV-1 medicines as prescribed by your doctor.
INITIATION OPTION 2:
Step-by-step start
DAY 1
START SUNLENCA
Take 2 SUNLENCA pills (300 mg each)
DAY 2
Take 2 more SUNLENCA pills
DAYS 3–7
No SUNLENCA pills or injections
DAY 8
Take only 1 SUNLENCA pill (300 mg) 6 days after your last dose
DAYS 9–14
No SUNLENCA pills or injections
DAY 15
Receive first set of SUNLENCA injections (2 shots total)
See below for how to continue SUNLENCA treatment ›

CAPELLA Trial

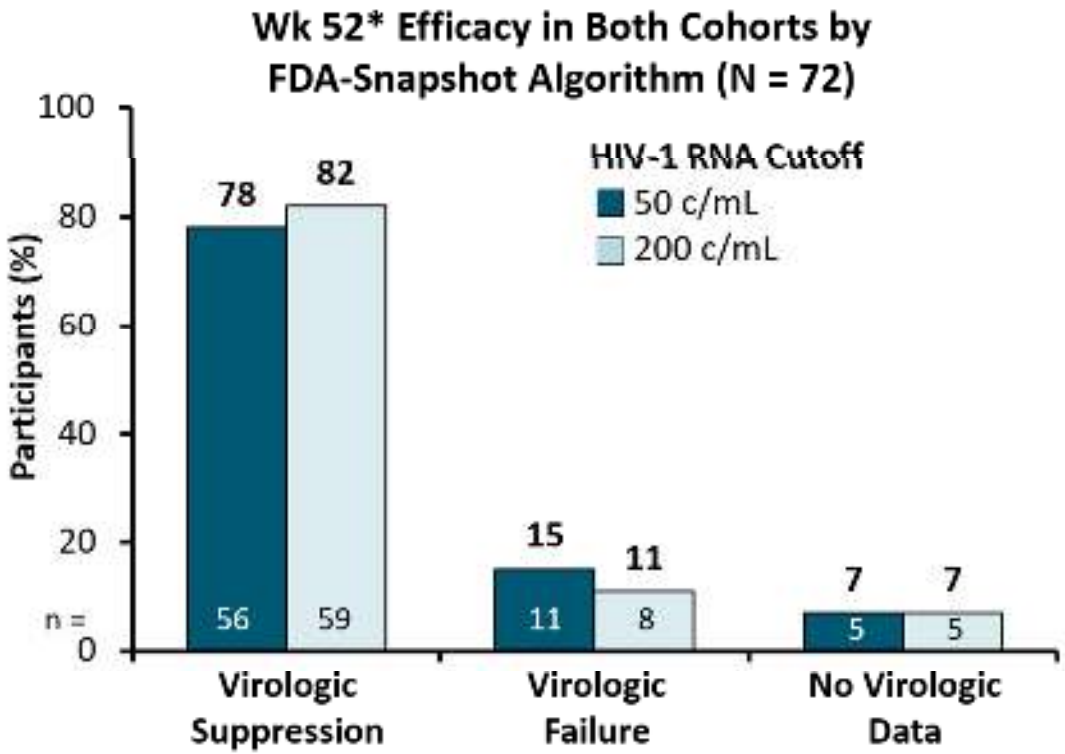
- Phase 2/3 trial
- Persons with HIV-1 RNA ≥400 copies/mL, resistance to ≥2 agents from 3 of 4 main ARV classes, ≤2 fully active agents from 4 main ARV classes (N = 72)

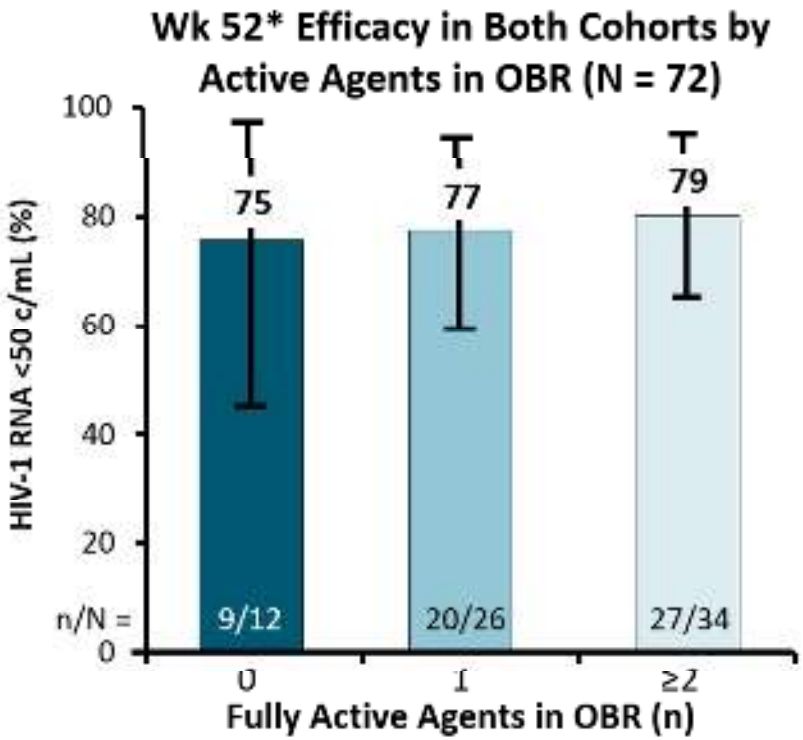


Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

Ogbuagu. IDWeek 2022. Abstr 1585.
Slide credit: clinicaloptions.com

CAPELLA Trial: 52 Week Efficacy





*By Wk 52, 17 participants took ≥1 dose or oral LEN bridging (300 mg QW) because of FDA clinical hold on SC LEN.

- 9 patients developed LEN resistance, all continued. 5 were non adherent to OBR and 4 had no fully active drugs in OBR

Ogbuagu. IDWeek 2022. Abstr 1585.
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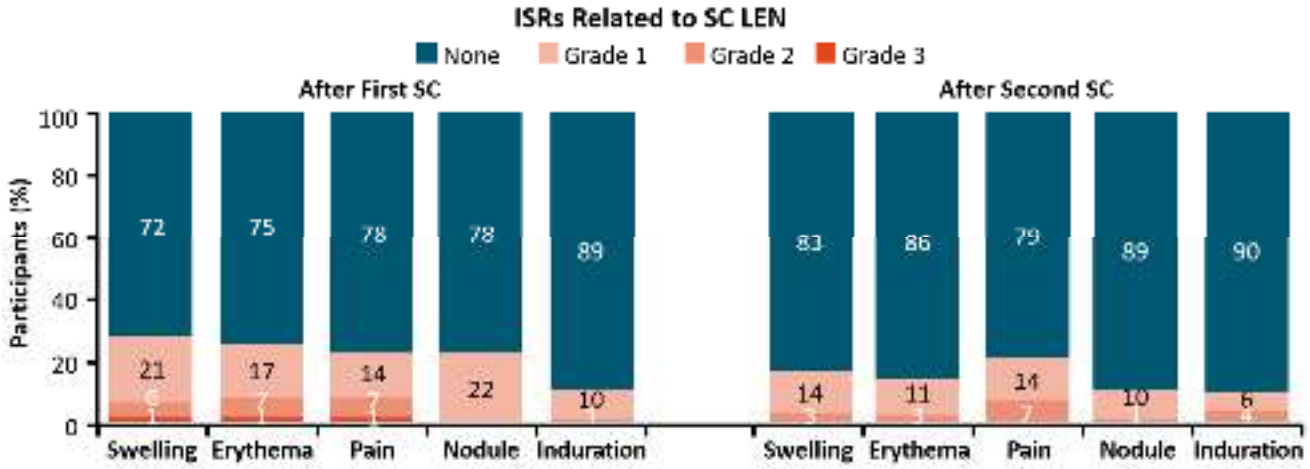
CAPELLA Trial: 52 Week Safety

Any-Grade AEs Other Than ISRs in ≥10% of Participants, n (%)	LEN + OBR (N = 72)
Diarrhea	10 (14)
Nausea	10 (14)
Constipation	9 (13)
Cough	8 (11)
Pyrexia	8 (11)



- No serious AE's considered related to study drug

Ogbuagu. IDWeek 2022. Abstr 1585.
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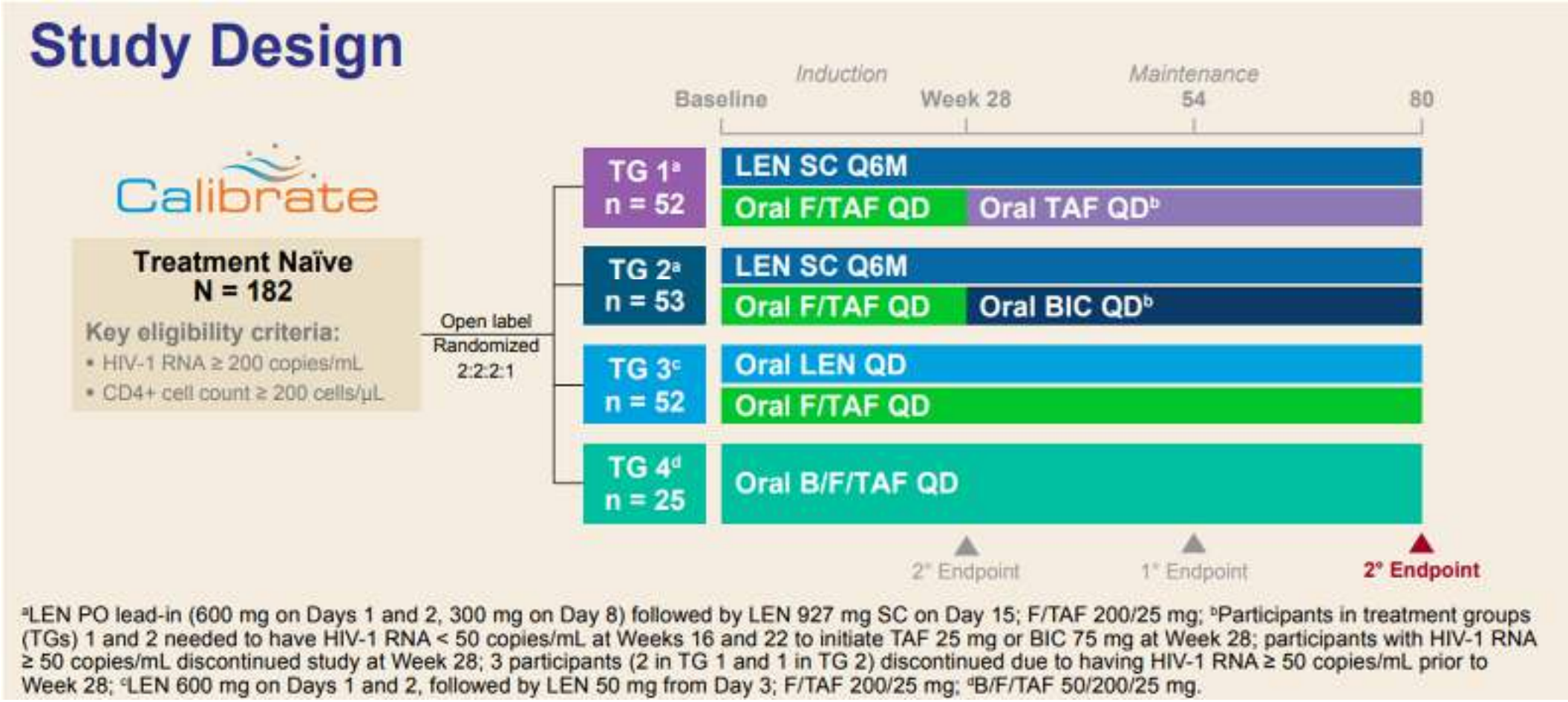
CALIBRATE Trial

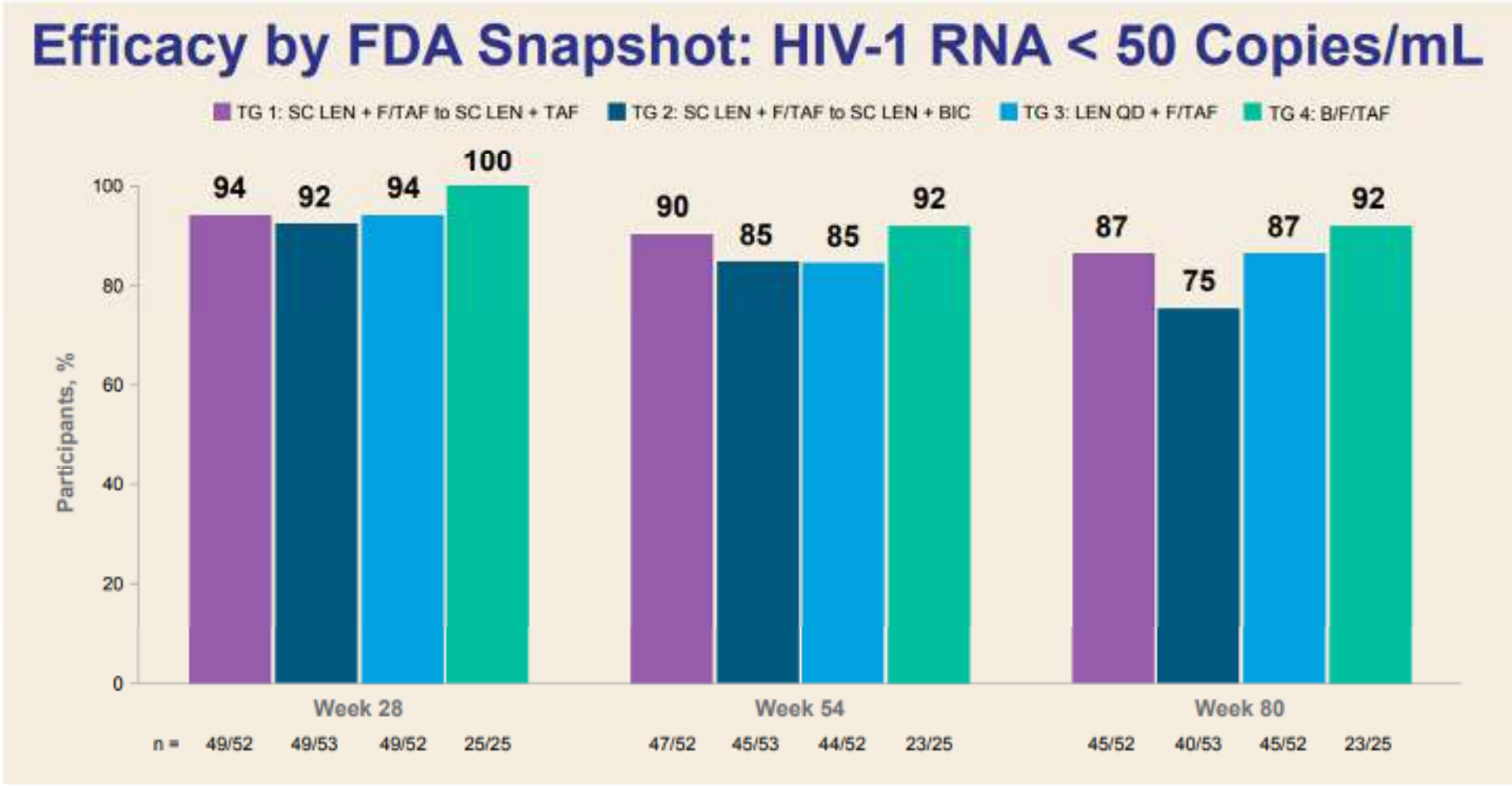
- Ongoing, phase 2, open-label study in treatment naïve patients



[a]LEN PO lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN 927 mg SC on Day 15; F/TAF 200/25 mg; [b]Participants in treatment groups (TGs) 1 and 2 needed to have HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate TAF 25 mg or BIC 75 mg at Week 28; participants with HIV-1 RNA ≥ 50 copies/mL discontinued study at Week 28; 3 participants (2 in TG 1 and 1 in TG 2) discontinued due to having HIV-1 RNA ≥ 50 copies/mL prior to Week 28; [c]LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; [d]B/F/TAF 50/200/25 mg.

Hagins et al. CROI 203. Poster 522.

CALIBRATE Trial: 80 Week Efficacy



Hagins et al. CROI 203. Poster 522.

CALIBRATE Trial: 80 Week Safety

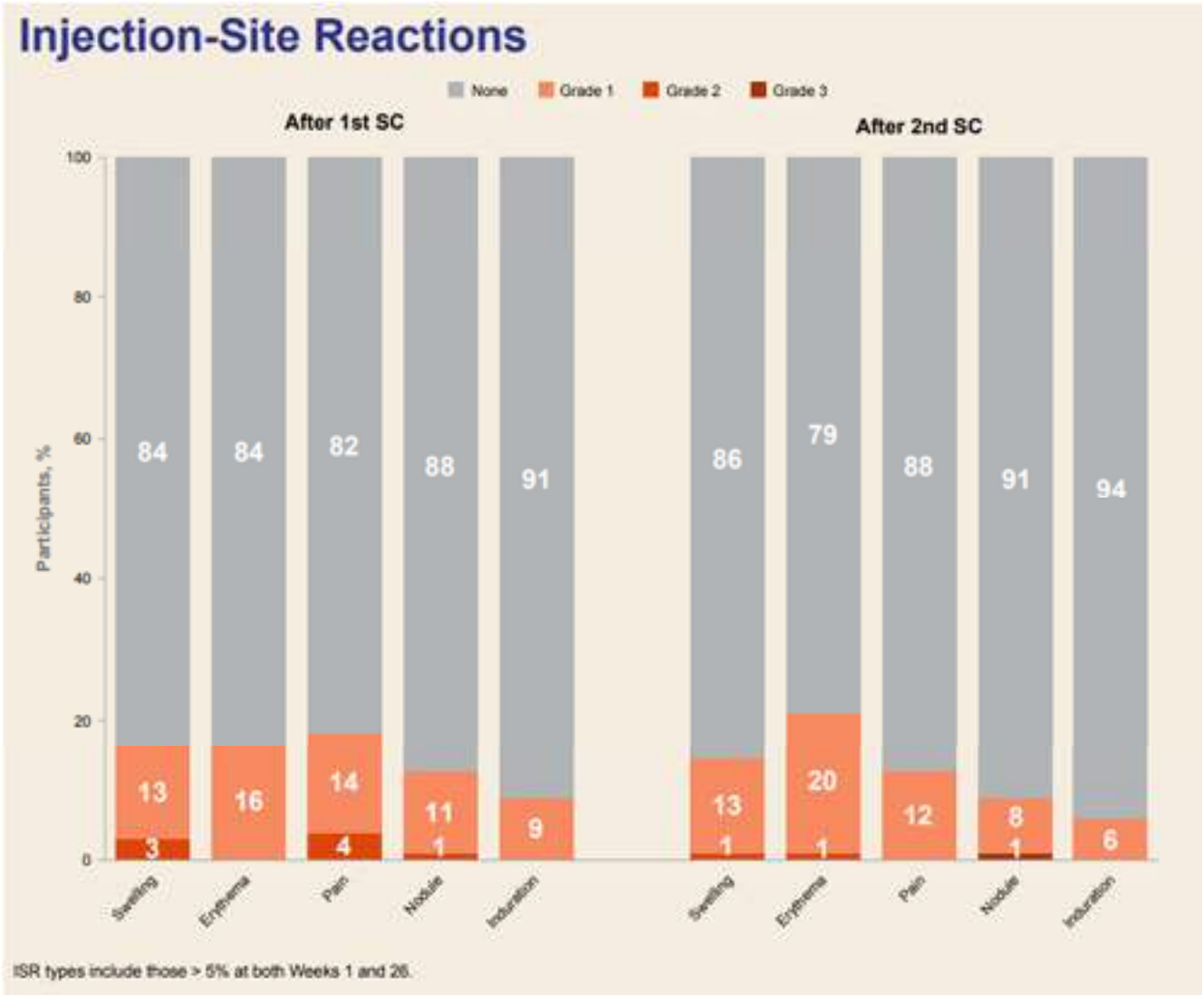
Adverse Events (Excluding ISRs)

≥ 10% of Participants in LEN total, %	LEN Total TGs 1-3 n = 157	B/F/TAF TG 4 n = 25
Headache	16	12
Nausea	13	4
COVID-19	13	16
Syphilis	11	16
Influenza	11	0
Diarrhea	10	8

ISRs = injection-site reactions.

Hagins et al. CROI 203. Poster 522.

CALIBRATE Trial: 80 Week Safety



Hagins et al. CROI 203. Poster 522.

OTHERS

- Ibalizumab (Trogarzo)
- Islatravir + Doravirine Implants?
- Once weekly PO regimens

WHO MIGHT BENEFIT?

Patients who:

- Have issues with tablet size
- Have issues with stigma
- Trouble remembering to take their meds
- Can commit to attend appointments
- Drug interactions
- Have resistance to current options

CHALLENGES

- **Insurance coverage**
- **Patient factors**
  - Pregnancy potential
  - Managing adverse effects
  - Drug drug interactions
  - Body composition
- **Office factors**
  - Drug acquisition and storage
  - Scheduling visits
  - Missed appointments
  - Patient screening
  - Injection vs infusion

SUMMARY

- Injectable and other long-acting ARV therapy have great potential for both HIV treatment and prevention
- Patients may face challenges with access and administration but also may prefer this to traditional oral therapy

Question 1

Which of the following is TRUE regarding CAB/RPV?

A. Contraindicated with PPIs
B. Only approved for Q 1 month dosing
C. Must be refrigerated
D. Not well tolerated by patients

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Question 2

Which of the following is a reason PLWH might prefer an injectable therapy option vs oral therapy option?

A. Privacy
B. Adherence
C. Tolerability
D. All of the above

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A. Privacy
B. Adherence
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D. All of the above

Question 3

When administering Cabotegravir LAI for HIV prevention (PrEP), which of the following lab tests must be obtained at each visit?

A. CMP
B. CBC
C. Lipid Panel
D. HIV ab/ag

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Question 4

Which of the following has been identified as a risk factor for CAB/RPV failure?

A. BMI $\geq$ 30
B. Previous treatment with DTG/RPV
C. HIV Subtype B
D. Older age

Question 4

Which of the following has been identified as a risk factor for CAB/RPV failure?

A. **BMI ≥ 30**
B. Previous treatment with DTG/RPV
C. HIV Subtype B
D. Older age

Question 5

What is the biggest barrier to HIV LAI for treatment and prevention?

A. Tolerability
B. Medication Costs
C. Patient Interest
D. Efficacy

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Questions?

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