# Long–Acting Injectable ART

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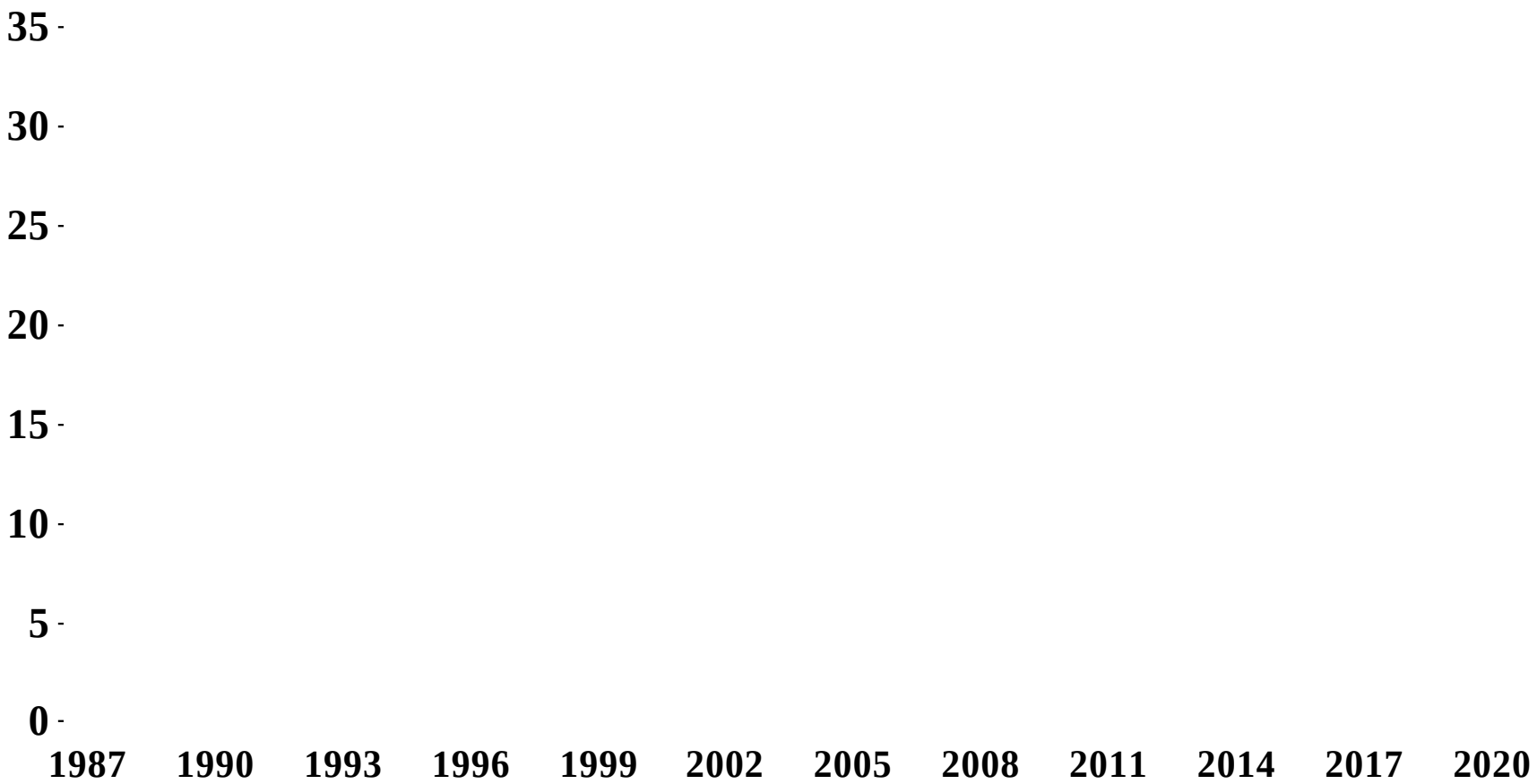
# Disclosures

- No pharmaceutical or device company relationships.
- Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel
- Will discuss investigational antiretroviral agents

# Antiretroviral Drug Approval: 1987 - 2023



# Cabotegravir (CAB)

- Integrase inhibitor similar to dolutegravir
- Potent in people with HIV (5, 10, 30, 60 mg oral)
  Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; injectable
- T1/2 (half-life) 21-50 days(!)
- Supports monthly/bimonthly dosing
- Safety:  ISR (mostly mild) and nodules with subcutaneous dosing
  Spreen JAIDS 2014;67:481

- Phase 1, 2, and 3 studies of IM CAB with/without IM rilpivirine (RPV) for treatment completed

# CAB/RPV: Phase 3 Studies

| Study (reference) | Study population | Design | Result (week 48); f/u reference |
|---|---|---|---|
| FLAIR<br>Orkin<br>NEJM<br>2020;382:1<br>124-1135 | Rx-naïve adults<br>(N=629) | ABC/3TC/DTG X 20 wks → CAB + RPV (oral X 4 wks, then IM monthly) or continue oral regimen<br>(non-inferiority Δ6%) | VS >93%;<br>CAB + RPV **non-inferior** to oral regimen<br><br>IAS 2021: 144 wks |
| ATLAS<br>Swindells<br>NEJM<br>2020;382:1<br>112-1123 | Adults with VS on 2 NRTI + PI, NNRTI, or INSTI<br>(N=616) | continue ART or change to CAB + RPV (oral X 4 weeks, then IM monthly)<br>(non-inferiority Δ6%) | VS >92%;<br>CAB + RPV **non-inferior** to oral regimen<br><br>AIDS 2022;36:185: 96 wks |

# Cabotegravir (CAB)


- EMA Approval 2020; FDA Approval 2021

- **FDA Approved (1/27/21)** Indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ART regimen in those who are virologically suppressed (HIV-1 RNA <50 cpm) on a stable ART regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

- Study of bimonthly dosing
  Overton Lancet 2021 (48 weeks); CID 2023 (152 weeks)
  - Approval every other month dosing: FDA February 2022

- Subanalysis of optional lead-in Orkin Lancet HIV 2021
  - Lead-in optional: FDA March 2022

# IM CAB + IM RPV:

## U.S. DHHS ART Guidelines (March 2023)

## www.clinicalinfo.hiv.gov

- Panel recommends monthly IM CAB + IM RPV as an optimization strategy for people with HIV currently on oral ART with documented viral suppression ≥3 months (AI), who—
  - have no baseline resistance to either medication
  - have no prior virologic failures
  - do not have active HBV infection (unless also receiving an oral HBV active regimen)
  - are not pregnant and are not planning on becoming pregnant
  - are not receiving medications with significant drug interactions with CAB and RPV

# CAB/RPV: Risk factors for Virologic Failure

- 13/1039 (1.25%) participants had confirmed virologic failure (VF) by 48 weeks in ATLAS, FLAIR, ATLAS-2M
- Risk factors for VF identified
- 97% had 0-1 risk factors for VF
  - 0.4% of them had VF
- 3% had ≥2 risk factors for VF
  - 26% of them had VF

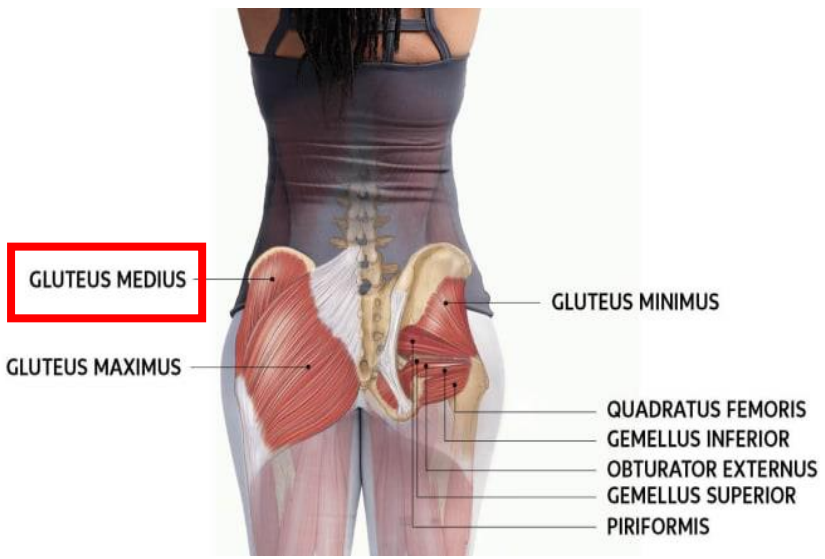
| Parameter | OR |
|---|---|
| RPV RAM(s) at baseline | 40.36 |
| ↓ Week 8 RPV trough concentration | 5.00 |
| Baseline HIV-1 subtype A1/A6 | 5.92 |
| ↑ BMI (kg/m2) at baseline | 1.13 |

Conclusion: VF is an infrequent, multifactorial event with CAB/RPV

Cutrell AIDS 2021;35:1333-1342

# Injectable CAB/RPV: Considerations

- Initiation dose: CAB LA 600 mg + RPV LA 900 mg (3 mL injections at 2 different sites) monthly X 2
- Bimonthly maintenance dose: CAB LA 600 mg + RPV LA 900 mg (3 mL injections at 2 different sites)
- RPV LA requires cold chain storage: 2-8° C.
- Injection into gluteus medius (upper outer quadrant) – Z-track method
  - Private place for injections
  - Obesity, buttock implants, tatoos




US FDA CAB/RPV Package Insert February 2023

# Injectable CAB/RPV: Missed Doses

- Adherence to monthly injection dosing schedule is strongly recommended

- **PLANNED MISSED INJECTIONS** (>7 days)
  - daily oral CAB + RPV starting 2 months after last injection and continued until the day injections are restarted (bridging strategy)
- **UNPLANNED MISSED INJECTIONS**
  - Reassess patient to determine if resumption of injection dosing remains appropriate
  - ≤2 months: resume every other month injections with CAB 600 mg + RPV 900 mg as soon as possible
  - >2 months: re-initiate with CAB 600 mg + RPV 900 mg monthly X 2, then CAB 600 mg + RPV 900 mg every other month

US FDA CAB/RPV Package Insert February 2023

# CAB/RPV Thigh Injections

- Substudy of ATLAS-2M

Figure 1. ATLAS-2M Thigh PK Study Design*

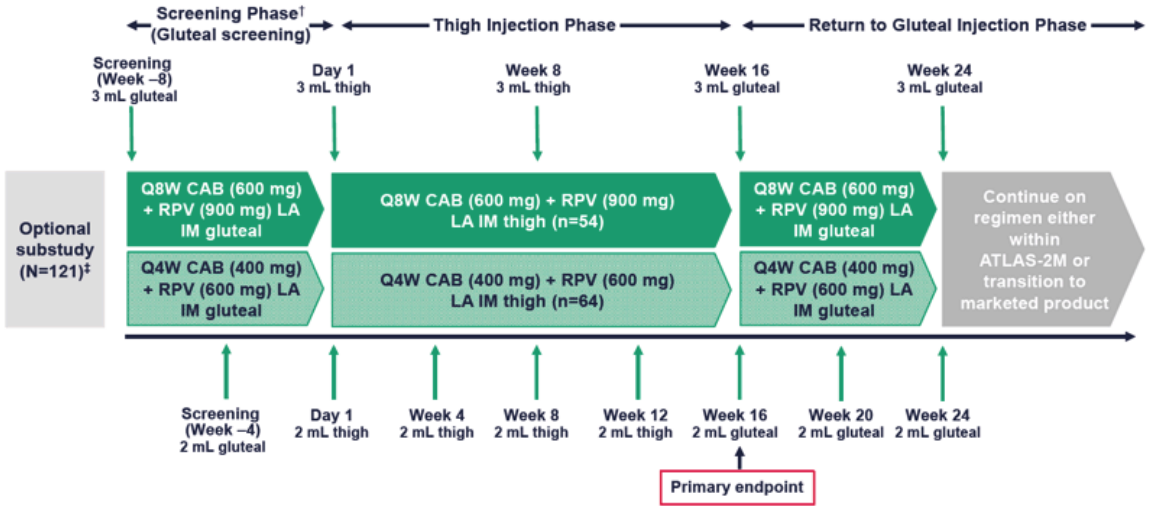
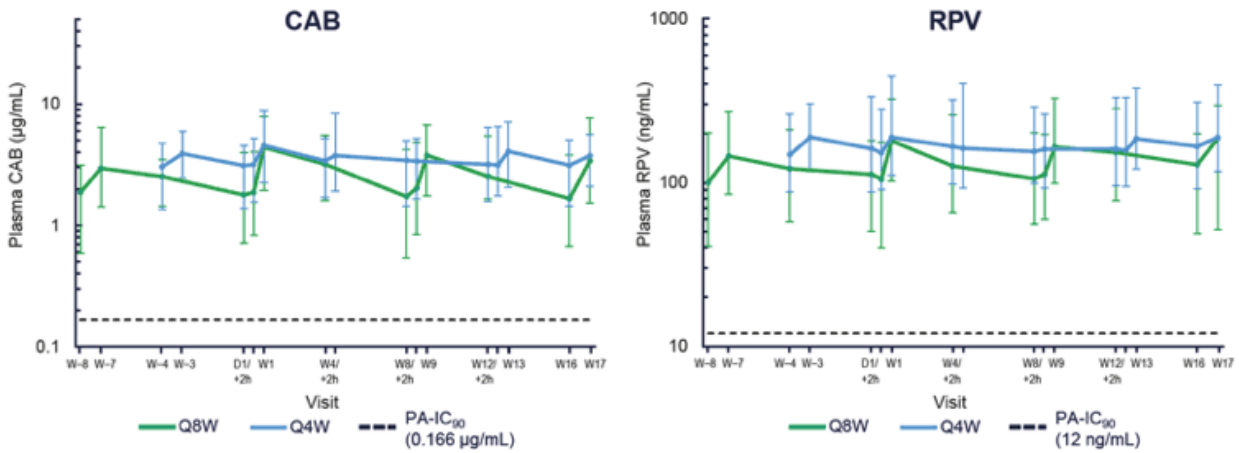



Figure 2. Median (5th, 95th Percentiles) Plasma CAB and RPV Concentration–Time Plots



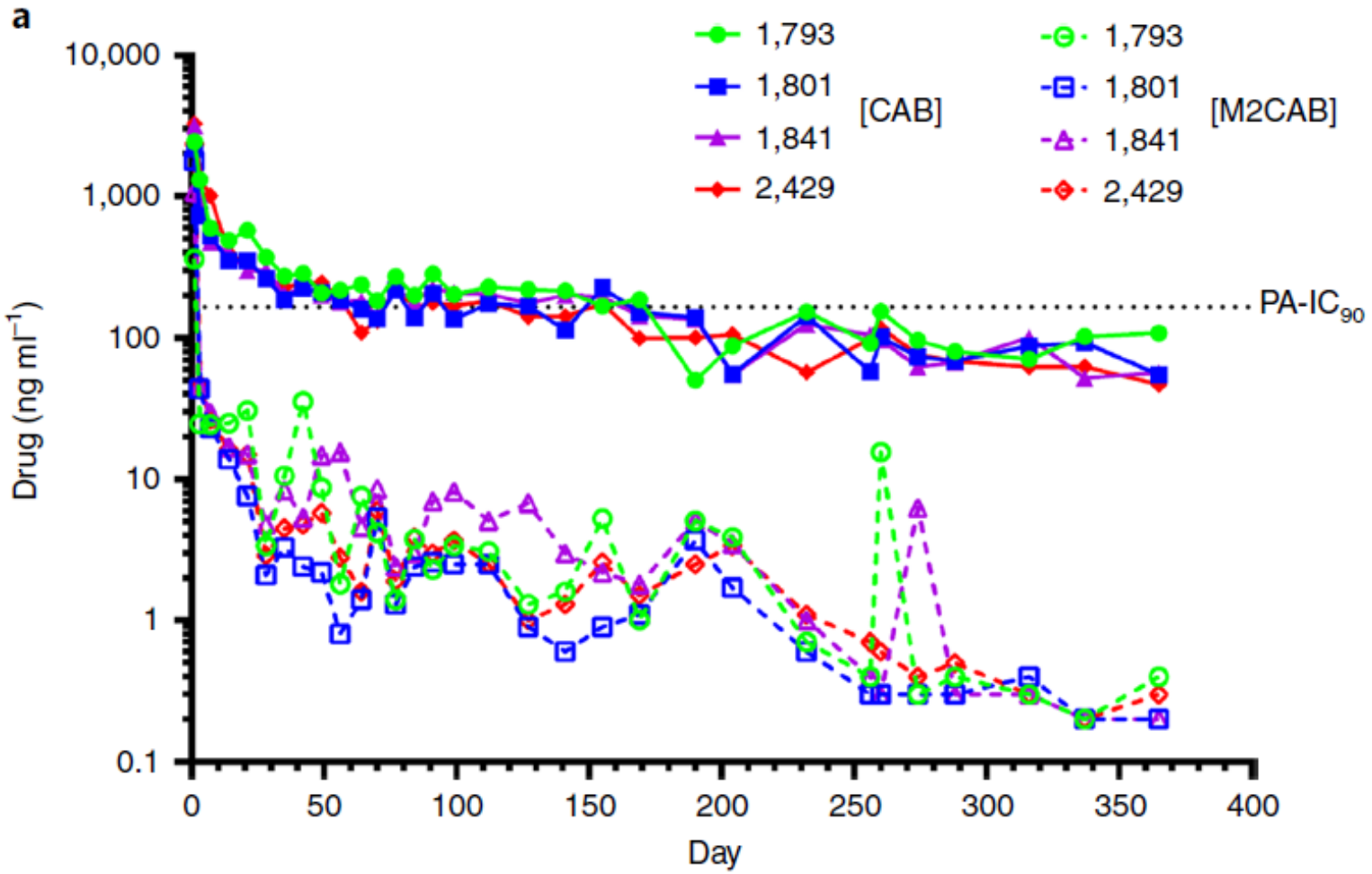

- 30% of pts preferred thigh injections; top reason: ease of access
- Conclusions:
  - No clinically significant differences
  - Support rotational/short-term thigh injections within an established gluteal regimen

Felizarta CROI 2023 #519

# CAB Pro-drug in Rhesus Macaques

- injectable
- extended release
- nanoformulated

- Q6 month dosing!




Kulkarni Nature Materials 2020;19:910-920

# CAB Pro-drug in Rodents

- injectable
- extended-release
- nanoformulated

- yearly dosing!

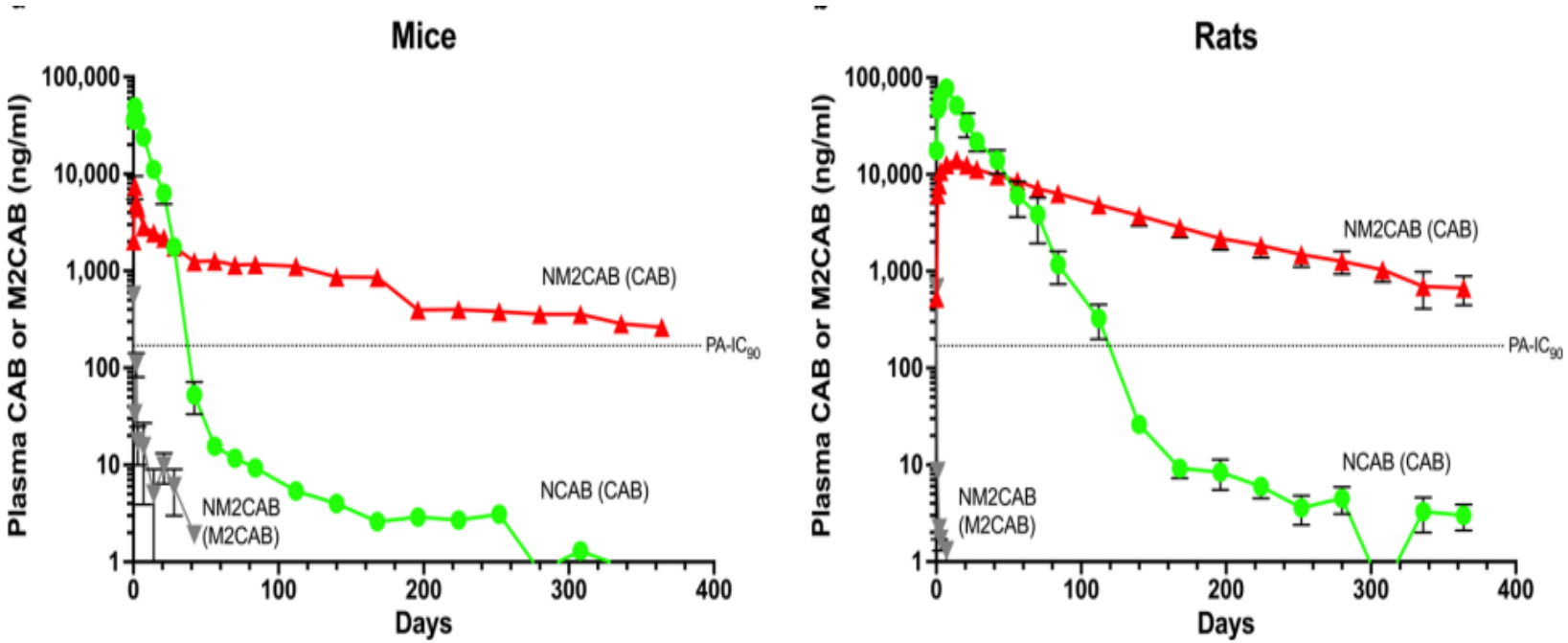
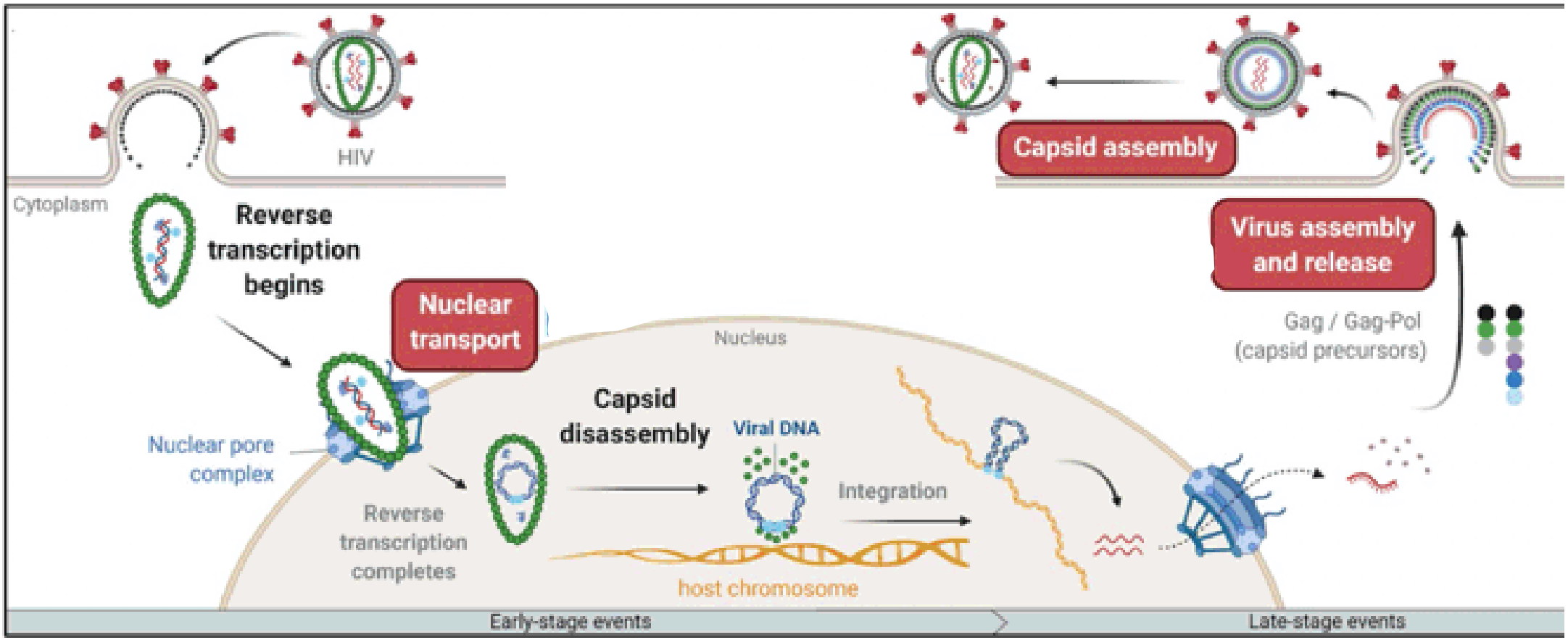



**Fig. 1 Plasma concentration vs. time profiles of CAB and M2CAB plasma concentrations in mice and rats over one year.** Plasma concentration over time was recorded for CAB and M2CAB over one year after a single IM injection (45 mg CAB equivalent/kg) of NCAB or NM2CAB in male Balb/cJ mice (**a**) and male SD rats (**b**). The dotted line indicates the CAB protein-adjusted $IC_{90}$ (PA-$IC_{90}$). For the NM2CAB treatment both the prodrug (M2CAB) and parent (CAB) were measured. Data are expressed as mean ± SEM ($N = 6$ animals per group per time point).

Gautum Nat Commun 2021;12:3453

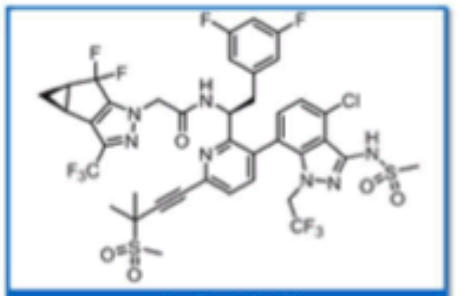
# HIV Capsid Inhibitors




Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

# Lenacapavir (LEN): Investigational Capsid Inhibitor

- Potent antiretroviral activity: $EC_{50}$ 140 pM in PBMC
- ↓ clearance and solubility → long ½ life: 30-43 days
- Oral and SC formulations
- Phase 1 SC Link Nature 2020; 584:614-618



- Phase 2/3 in heavily treatment-experienced: add oral LEN, then at day 15, optimize background ART and add LEN SC q6 months: 26 weeks

Segal-Maurer NEJM 2022;386:1793

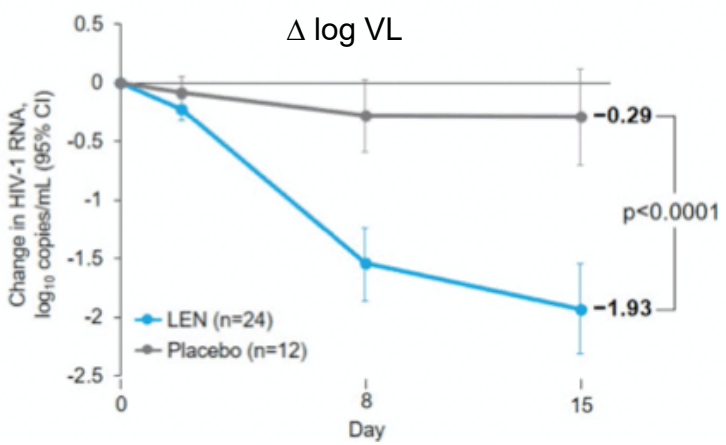
- EMA approved for treatment-experienced August 2022
- FDA approved for treatment experienced December 2022

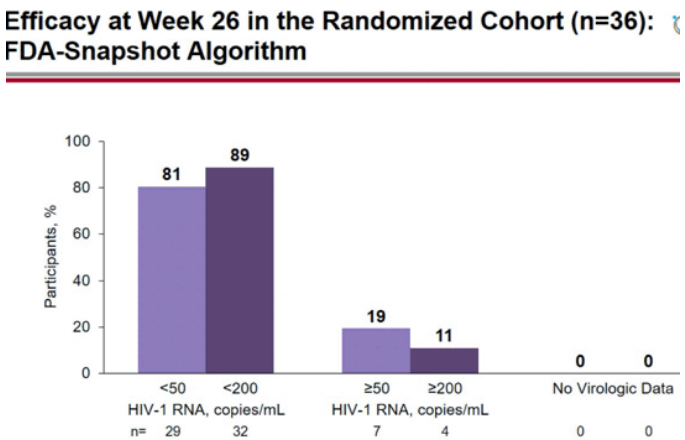

- Phase 2 in treatment naïve: LEN SC q6 months + (TAF/FTC → TAF or BIC): 52 weeks

Gupta Lancet HIV 2023;10:e15-e23

# CAPELLA: LEN in Heavily Treatment-Experienced Pts

- Phase 2/3 randomized, double-blind, placebo-controlled study
- Study population: Pts with MDR HIV (resistant to ≥2 drugs and 3 of 4 classes and confirmed VL >400 and ≤2 fully active agents); (randomized n=36; non-random n=36)
- Study treatment:
  - Randomized cohort (2:1): continue ART + oral **LEN** 600mg d1+2, 300 mg d8 (or placebo), then at d15, optimized ART regimen + sc **LEN** 927 mg q6 months
- Results: **1° endpoint:** % with 0.5 log VL ↓: 88% (**LEN**) vs. 17% (**pbo**) (p<0.001)

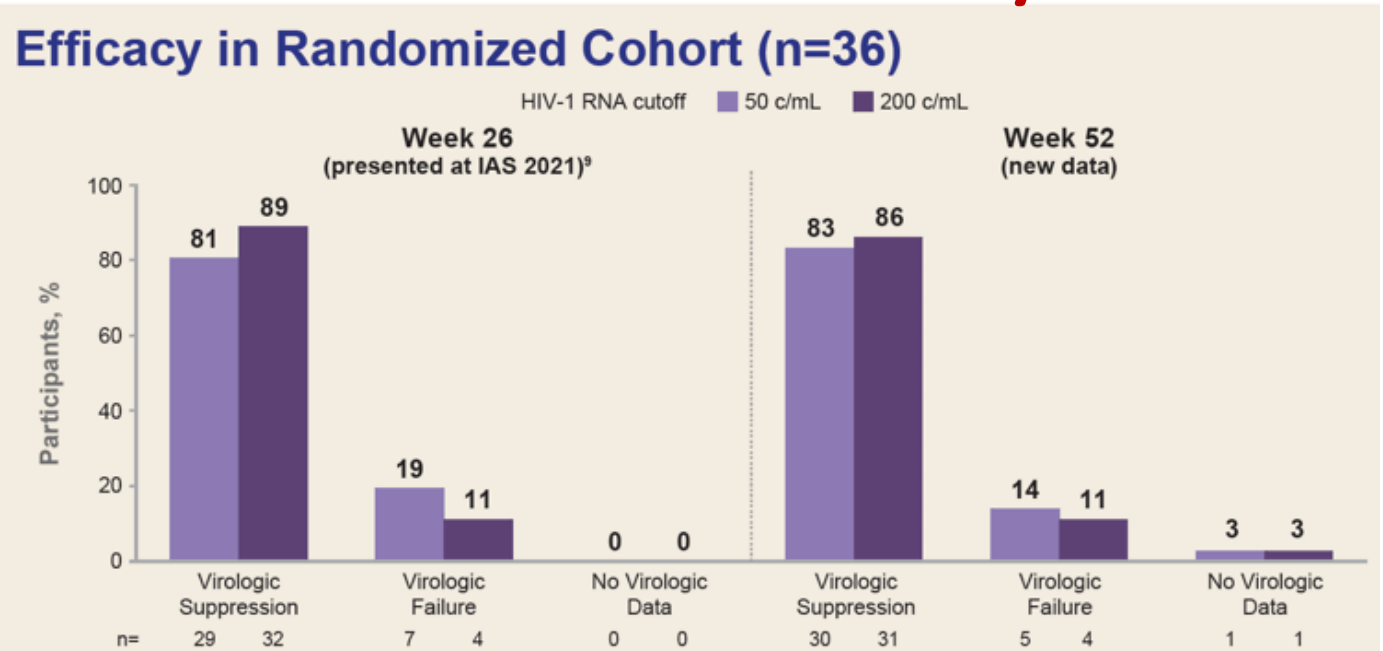


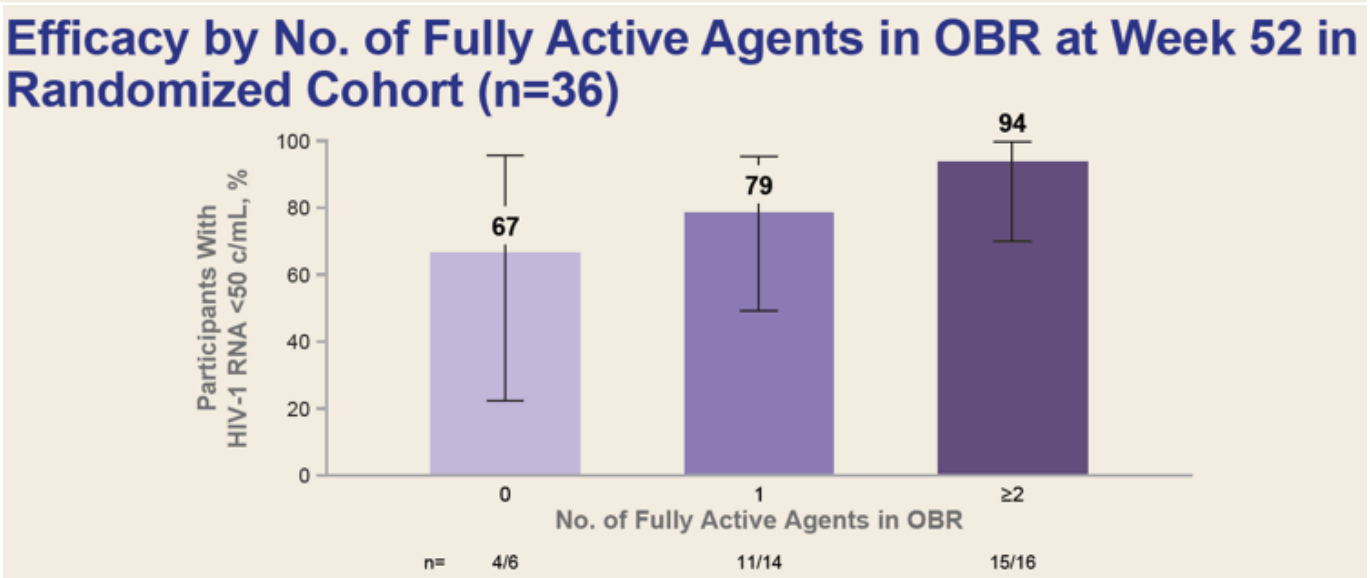




- Generally safe/well-tolerated; 4 developed capsid resistance mutations (M66I, others)
- Conclusion: sustained VS

Segal-Maurer NEJM 2022;386:1793

# CAPELLA: LEN in Heavily Treatment-Experienced Pts

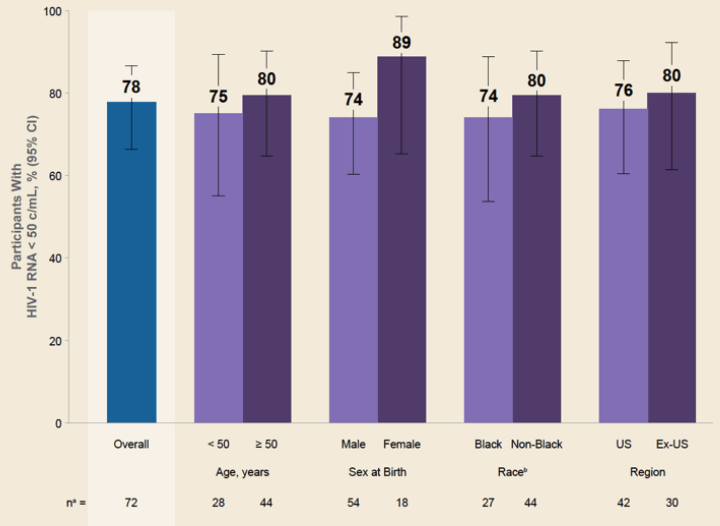



Ogbuagu CROI 2022 #491

# CAPELLA: LEN in Heavily Treatment-Experienced Pts

## Week 52 Efficacy by Demographics

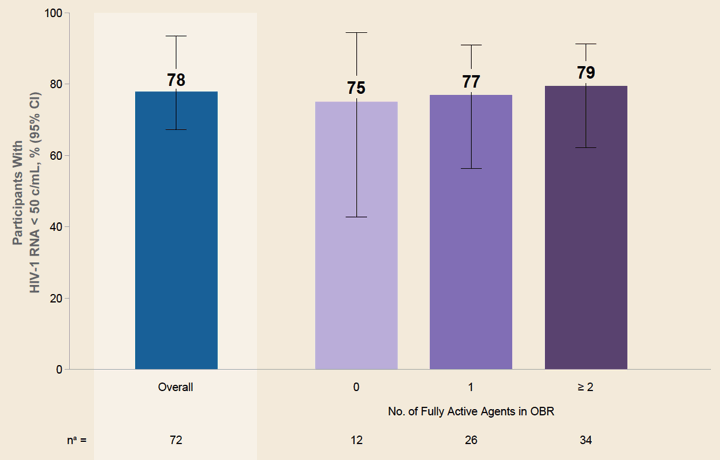



Prespecified subgroup analyses of efficacy at Week 52; post-hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup; [b]1 participant with race reported as "not permitted." CI = confidence interval.

## Week 52 Efficacy by Baseline CD4 and HIV-1 RNA

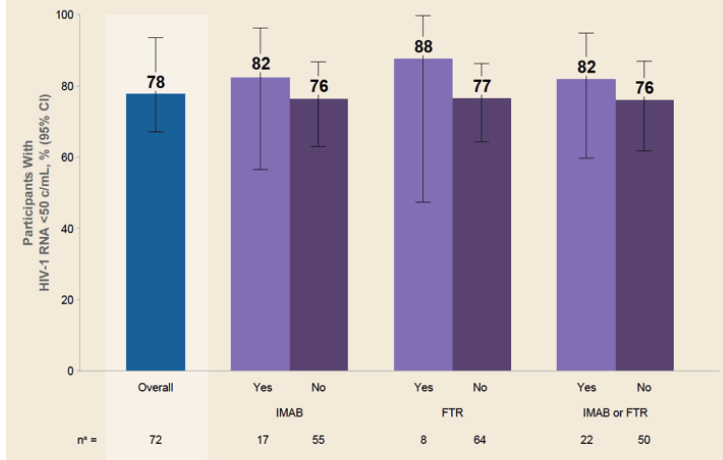

Prespecified subgroup analyses of efficacy at Week 52; in post-hoc analysis, differences between CD4 < and ≥ 200 cells/µL ($P = 0.07$), and between HIV-1 RNA ≤ and > 100,000 c/mL ($P = 0.11$) were not statistically significant. [a]Total n in each subgroup.

## Week 52 Efficacy by Number of Fully Active Agents in OBR




Post hoc subgroup analyses of efficacy at Week 52; post hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup.

## Week 52 Efficacy by Baseline Use of Ibalizumab or Fostemsavir

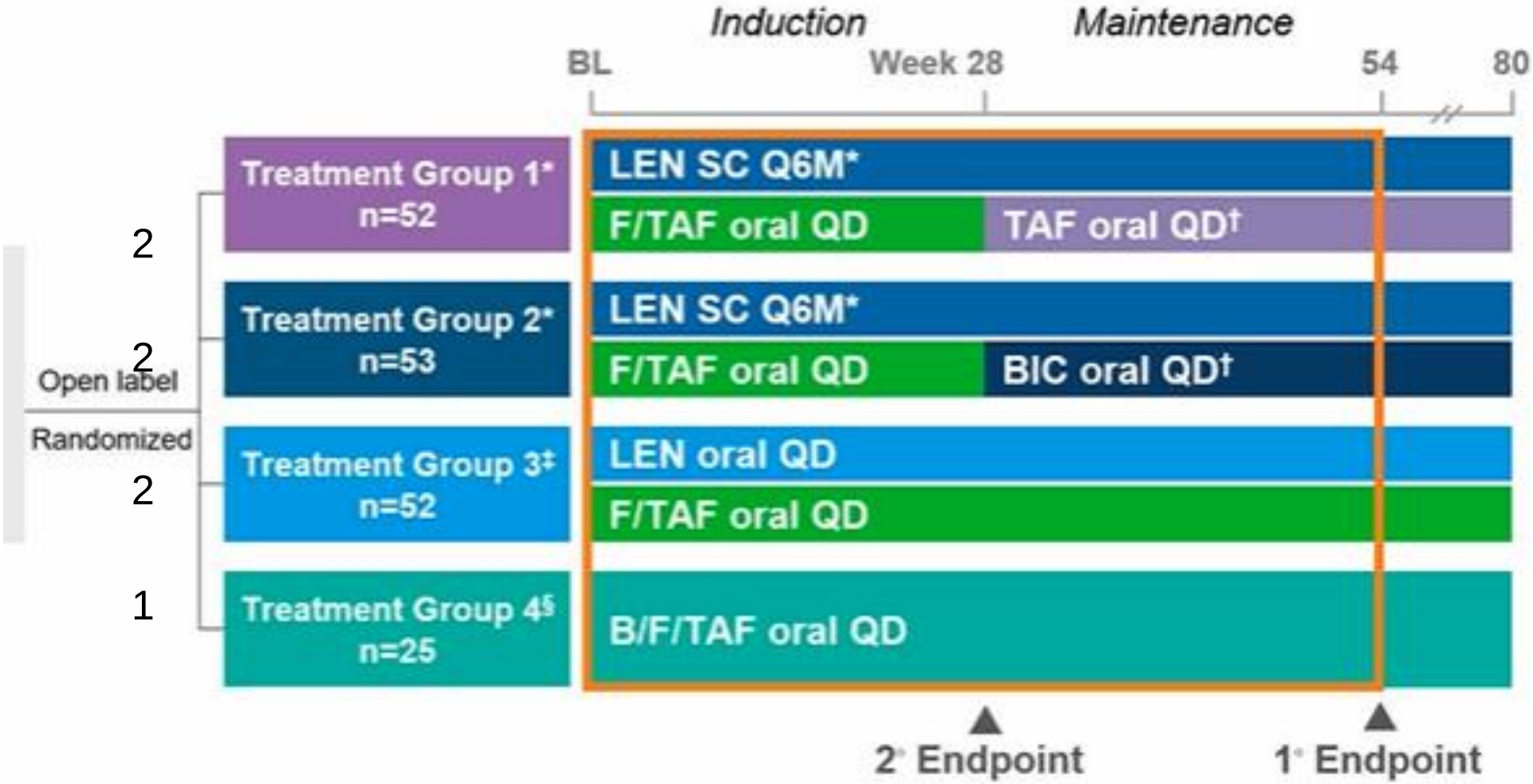



Prespecified subgroup analyses of efficacy at Week 52; post-hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup.

Ogbuagu CROI 2023 #523

# CALIBRATE: Lenacapavir (LEN) in Rx-Naïve Pts

- Ongoing phase 2, randomized, open-label, controlled, induction-maintenance study
- Study population: ART naïve, VL ≥200, CD4 ≥200 (N=182)

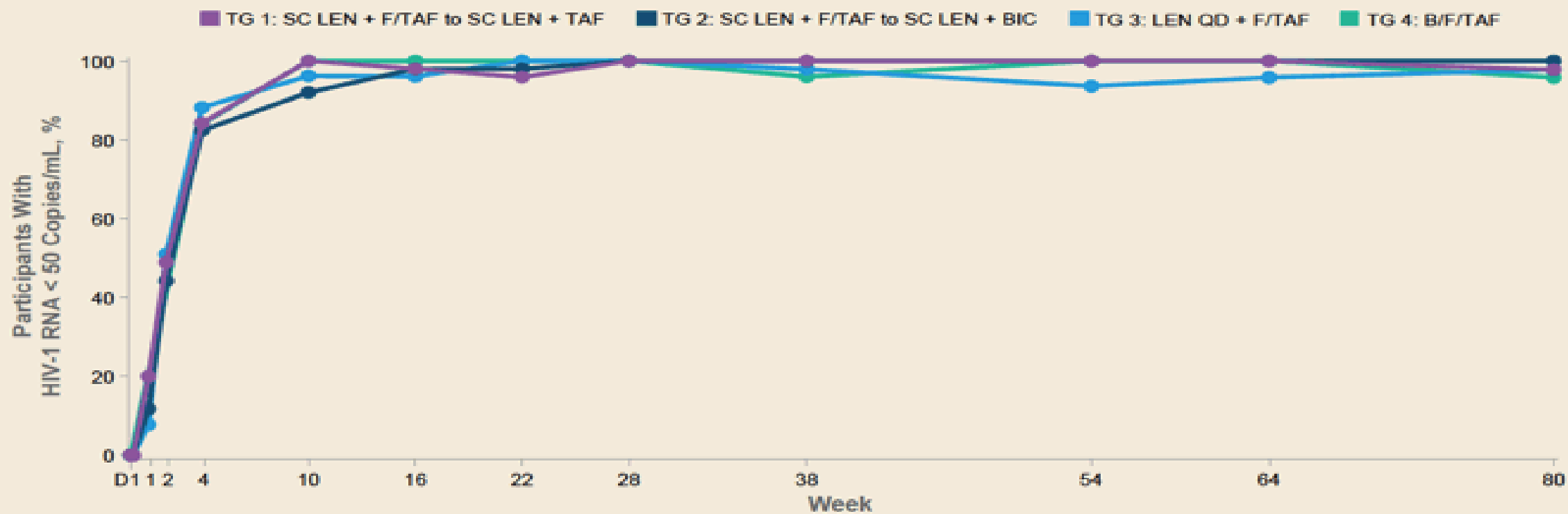



*LEN oral lead in: 600 mg on days 1, 2; 300 mg on day 8; LEN 927 mg SC on day 15

Gupta Lancet HIV 2023;10:e15-e23

# CALIBRATE: Lenacapavir (LEN) in Rx-Naïve Pts

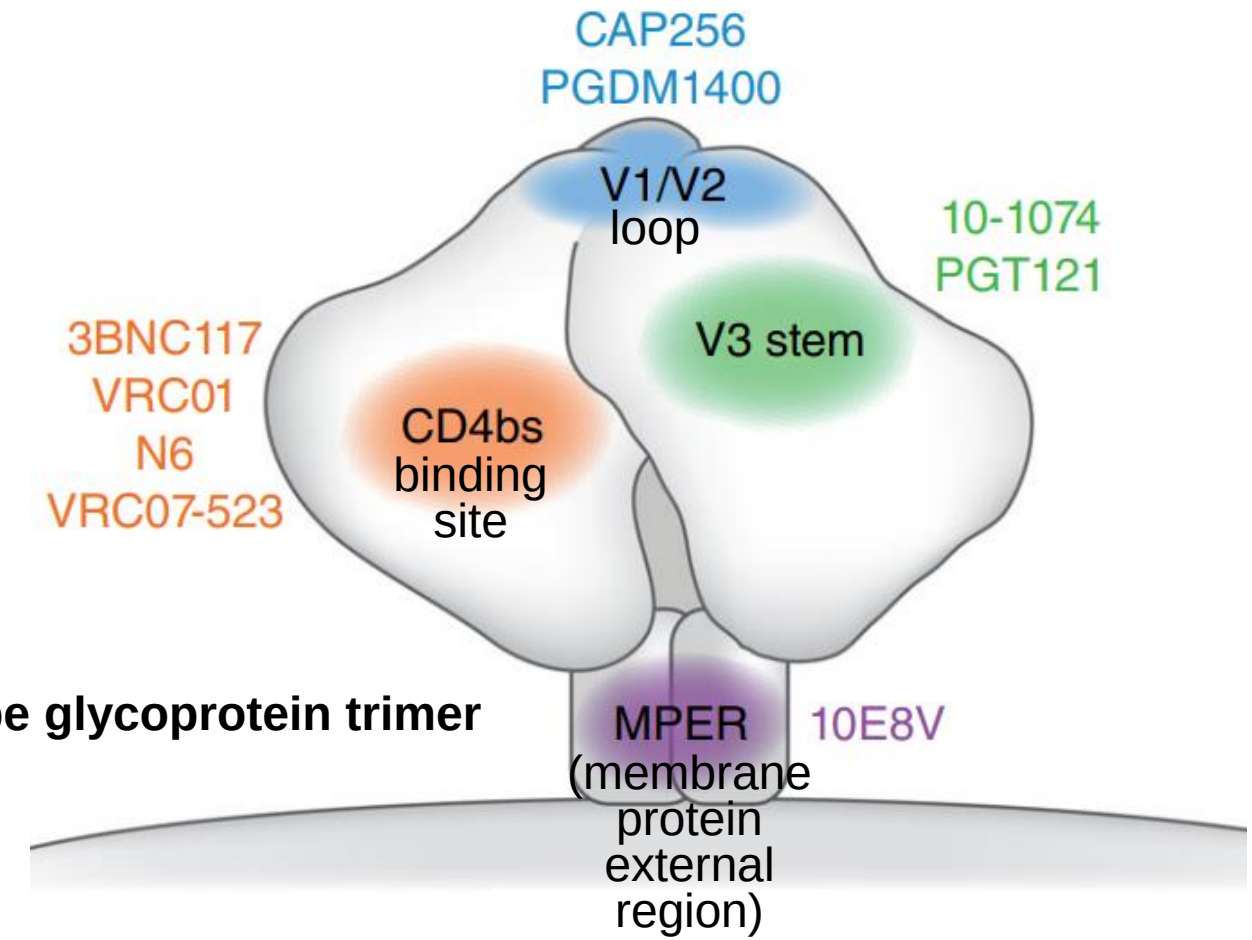
## Participants With HIV-1 RNA < 50 Copies/mL by Visit
### Missing = Excluded (on Treatment)




| | TG 1 n = 46 | TG 2 n = 40 | TG 3 n = 46 | TG 4 n = 25 |
|---|---|---|---|---|
| Participants with HIV-1 RNA < 50 copies/mL, % (n) | 98 (45) | 100 (40) | 98 (45) | 96 (23) |

Gupta Lancet HIV 2023;10:e15-e23
Hagins CROI 2023 #522

# HIV Broadly Neutralizing Antibodies (BNAbs)




**HIV envelope glycoprotein trimer**

Adapted from Caskey Nat Med 2019;25:547-553 (review)

# HIV Broadly Neutralizing Antibodies (BNAbs)

- >17 bNAbs evaluated for safety and PK in humans
- Clinical trials generally demonstrate safety and antiretroviral activity
- "Vaccinal effect": enhancing host immunity
- Strategies to improve potency, breadth, serum half-life and delivery
  - More potent, broader and multi-specific antibodies
  - Longer half-lives → dosing every 2-6 months
  - Subcutaneous dosing

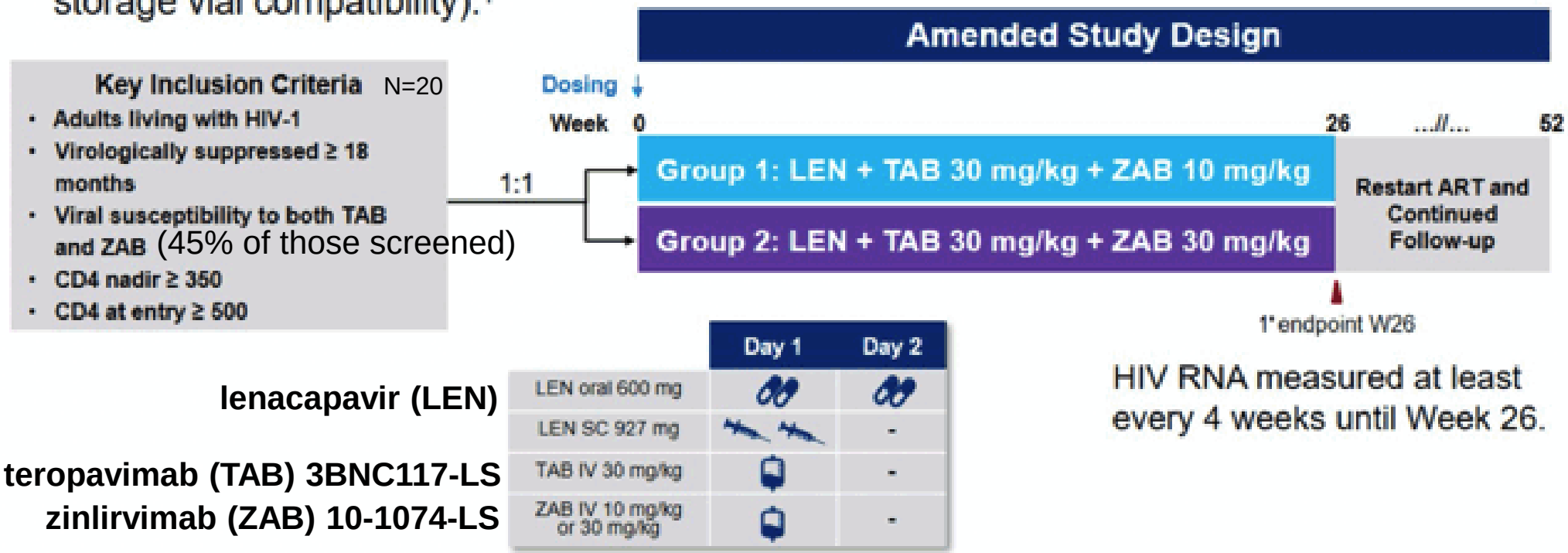
Awan Curr Opin HIV AIDS 2022;17:247-257

- Combination strategies: Phase 1 and 2 studies
  - 2, 3, and 4 BnAb combinations
  - BnAbs + long-acting antiretrovirals
    - ACTG 5357: VRC07-523LS + cabotegravir-LA (NCT03739996)
    - Pilot study: 2 BnAbs + lenacapavir

# Pilot Study: LEN + 2 BNAbs

## Study Design

- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)
- Study design was modified when LEN was unavailable due to temporary clinical hold (for storage vial compatibility).[1]

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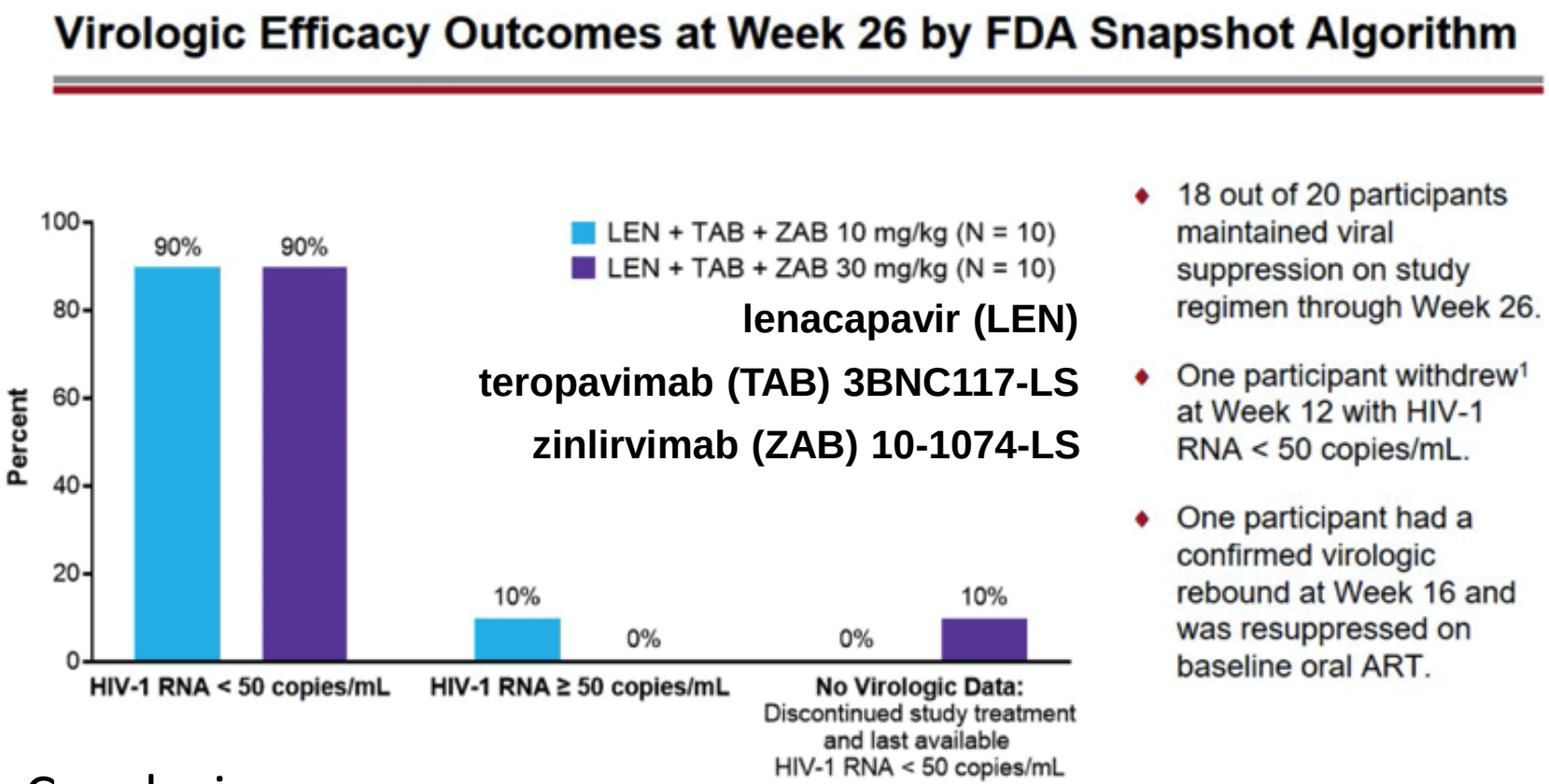
# Pilot Study: LEN + 2 BNAbs

- Results:




- Conclusions:
  - LEN + TAB + ZAB sustained VS in 18/20 pts
  - First 6-month ART regimen

Eron CROI 2023 #193

# Conclusions: LA-Injectable ART

- **Pros:**
  - Efficacious:
    - Phase 3 switch studies with IM RPV/CAB every 2 months
      - Oral lead-in optional
    - Phase 3 study in treatment-experienced with subcutaneous LEN (+ daily oral antiretrovirals) every 6 months
    - Pilot study of IV monoclonal antibodies and LEN every 6 months
  - Generally safe and well-tolerated
  - May ↑ adherence and ↓ concerns about taking ART and stigma

- **Cons:**
  - Logistical, access, and cost constraints
  - More convenient regimens under investigation

- **Overall Conclusion:** One size does NOT fit all – choice and timing are key!

# Acknowledgments


- Cornell HIV Clinical Trials Unit (CCTU)
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- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH
- Alexandra Calmy, Joe Eron, and Chloe Orkin
- HIV iBASE, NATAP, TAG
- The patient volunteers!


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