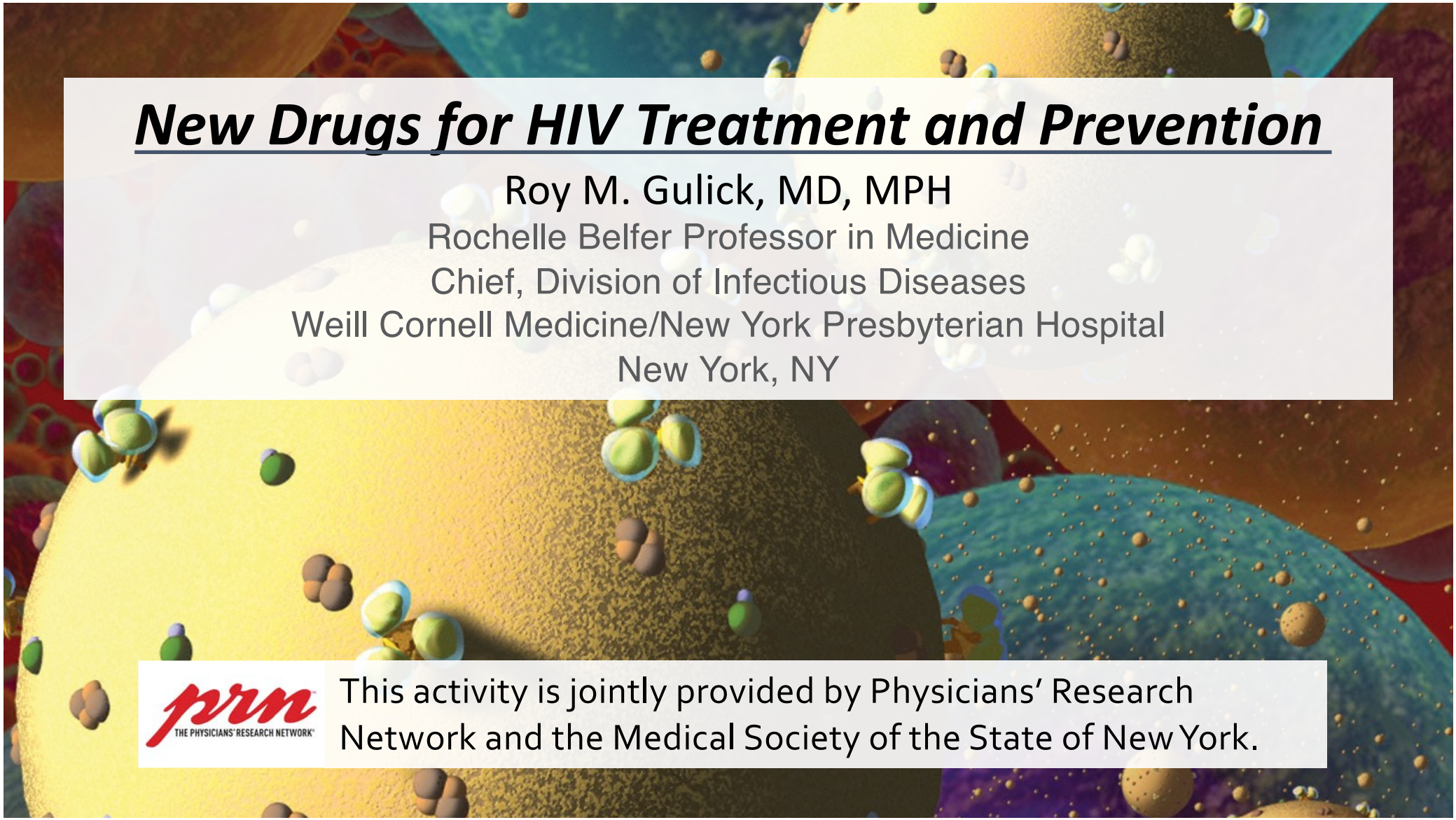

New Drugs for HIV Treatment and Prevention

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This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

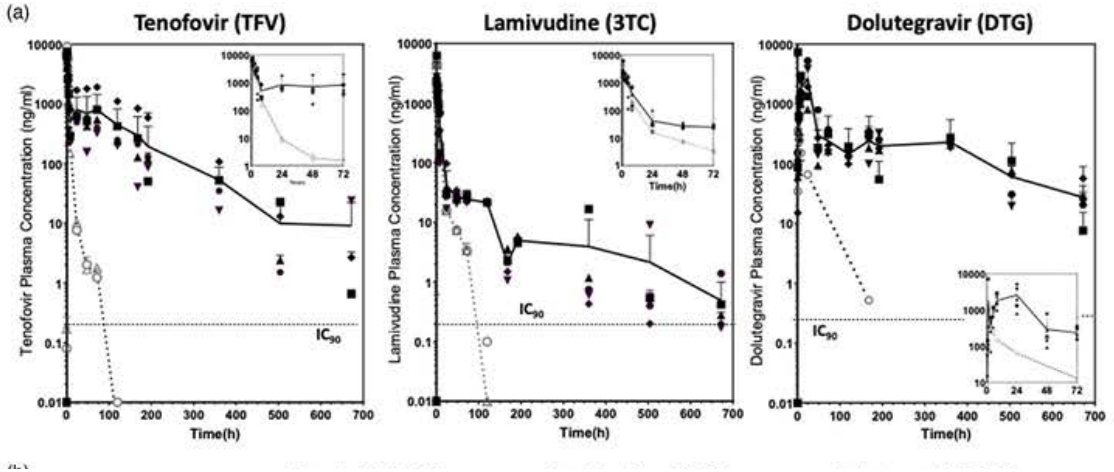
Disclosures

- none

Current Antiretrovirals: New Formulations and Strategies -- NRTIs

TFV/3TC/DTG (TLD): New Formulation

- TFV/3TC/DTG
  - First-line ART regimen; BUT disparate physical-chemical properties
- Drug-combination-nanoparticle (DcNP) technology
  - TLD stabilized and assembled with lipid excipients; suitable for SQ injection
  - Single dose in non-human primates (N=7, 3 dosing levels)

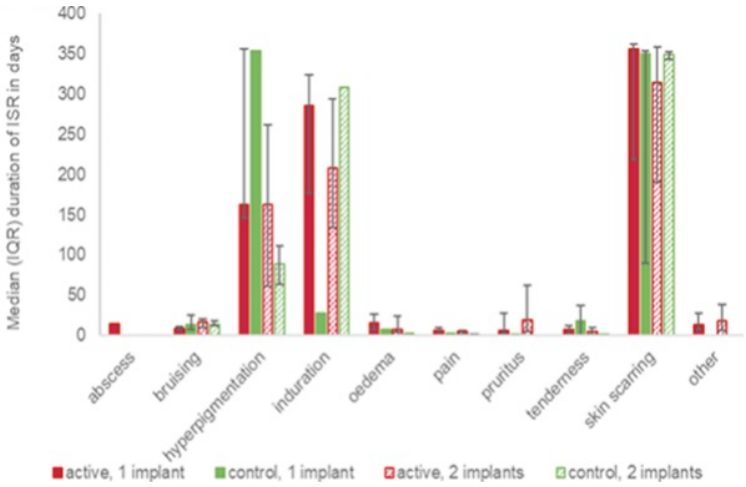


- Conclusion: 4-week subcutaneous dosing possible

Perazzolo AIDS 2023;37:2131-2136

CAPRISA 018: TAF Implants

- Phase 1 first-in-human study
- Study population: South African women without HIV and at low risk for HIV
- Study treatment: Micro-tableted TAF formulated in a silicone elastomer subdermal implant:
  - Group 1 (TAF 110 mg implant X 4 wks; n=6);
  - Group 2 (randomized 4:1 to 1 or 2 TAF implants or placebo X 48 weeks, n=30)
- Results (48 weeks):
  - Prolonged insertion site reactions: hyperpigmentation, induration, scarring
  - In group 2, 11 (37%) withdrew early [10 in TAF arm] due to ISR
  - TFV-DP PK targets not reached in most participants
- Conclusion: suboptimal tolerability and PK; further work necessary



Gengiah CROI 2024 #123 and #1136

DREAM-03 Study: TFV Rectal Douche

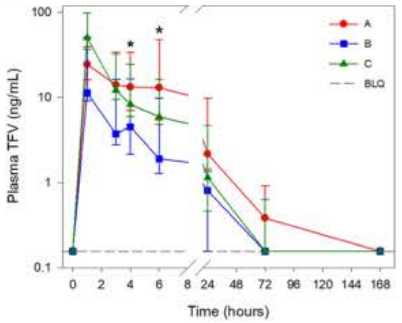
- **Phase 1** safety and PK/PD study
- Study population: 9 men
- Study treatment: TFV 660mg in 125 ml hypo-osmolar saline with various sequences:

  (A) 3 TFV douches

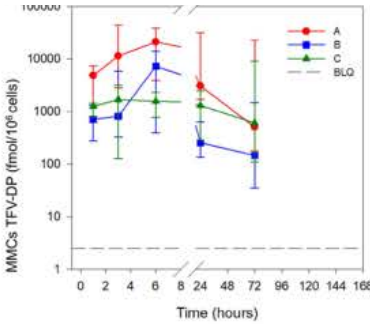
  (B) one TFV douche, then 2 tap water douches

  (C) 2 tap water douches, then one TFV douche

plasma



rectal mucosa



- Results:
  - no >grade 2 study-related adverse events
  - higher plasma TFV concentrations in A vs. B
  - trend towards higher rectal mucosal TFV in A and C vs. B
  - HIV replication (ex-vivo challenge): concentration response A > B or C
- Conclusion: well-tolerated; sequence important, medicated douche should come last

Zheng CROI 2024 #612

- **HPTN 106:** Phase 2 cross-over study of rectal vs. oral TFV – coming soon!

Current Antiretrovirals: New Formulations and Strategies -- INSTIs

Cabotegravir (CAB)

- Integrase inhibitor similar to similar to dolutegravir
- Potent in people with HIV (5, 10, 30, 60 mg oral)
  Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; injectable
- Phase 3 studies of IM CAB/rilpivirine (RPV) for treatment switch demonstrated non-inferiority to standard oral treatment regimens
  - Orkin NEJM 2020;382:1124
  - Swindells NEJM 2020;382:1112
  - Overton Lancet 2021;396:1994

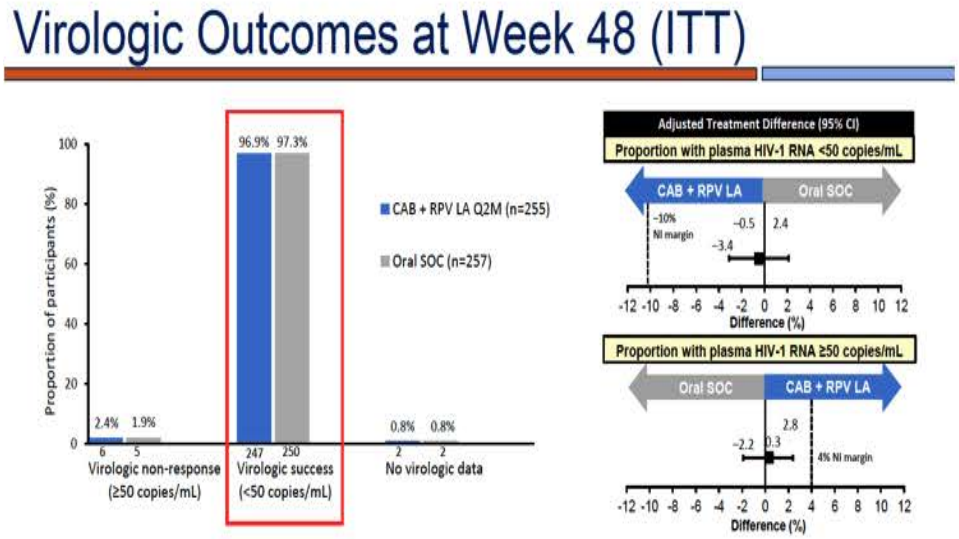
- In 2021, FDA approved combination of IM CAB + RPV for switch treatment monthly
  - For patients undetectable on ART without a history of virologic failure, drug resistance, or chronic HBV infection
- In 2022, FDA approved IM CAB/RPV every other month; made lead-in dosing optional; and approved CAB for PrEP

CAB/RPV in Africa (CARES)

- **Phase 3b** randomized, multicenter, open-label study at 8 African sites; noninferiority Δ10%; VL monitored q24 weeks
- Study population: PWH on TDF + 3TC/FTC + EFV/NVP/DTG with VL <50

(N=512, 58% F, 92% on DTG, 74% with prior NNRTI, 14% with archived RPV mutations, 57% subtype A1)

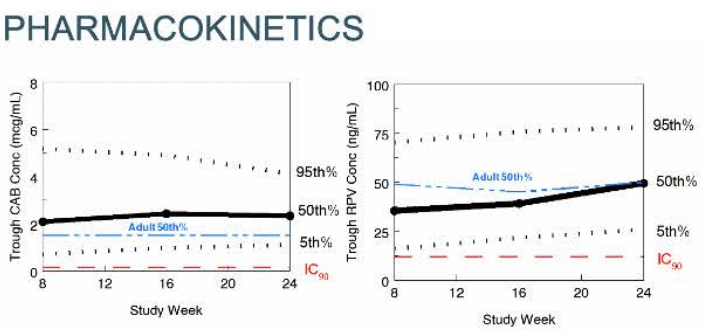
- Study treatment:
  Continue ART or change to CAB/RPV q8wks
- Results (48 weeks):
  - 4 withdrew (2 in each group)
  - VL <50: 97% (ART) vs. 96% (LA) → met non-inferiority
  - 2 VF in LA group, both with resistance
  - 1 discontinuation for injection site abscess
- Conclusion LA safe, effective, non-inferior; may be considered for Africa



Kityo Lancet ID 2024;24:1083-1092

CAB/RPV in Adolescents (MOCHA/IMPAACT 2017)

- **Phase 1/2** noncomparative open-label, noncomparative study in 5 countries
- Study population: PWH aged 12-18 suppressed on ART (N=144, average age 15, 49% boys, 74% Black)
- Study treatment: Switch ART to oral CAB/RPV X 4 wks, then IM CAB/RPV q4 wks X 1, then q2 mos through 24 weeks
- Results (24 weeks):
  - 141/144 completed study; no virologic failure
  - no AE → d/c occurred
  - 35% reported ISR
    - 91% grade 1 and 86% resolved within 7d; 2 grade 3 ISR (pain, abscess)
  - CAB PK similar to adults; 1 pt had low CAB concentration at wk 24
- Conclusion: supports using CAB/RPV as switch in virally suppressed adolescents



Gaur CROI 2024 #188
Gaur Lancet HIV 2024;1:e211-e221

MOCHA / IMPAACT 2017: Week 48

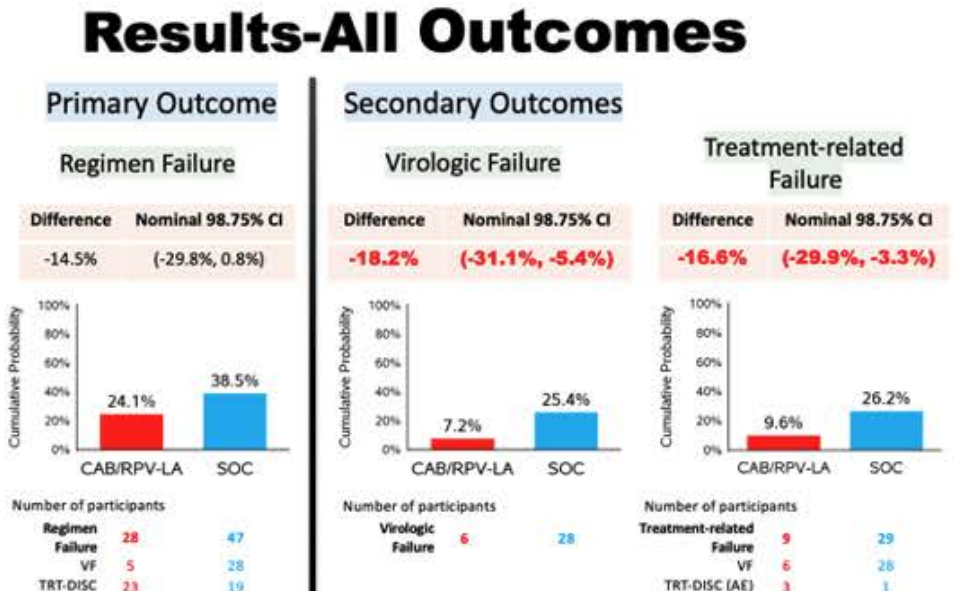
- **Results (week 48):**
- **PK:** Median pre-dose CAB and RPV concentrations at week 48 approximated those in adults and were above respective protein-adjusted IC_{90}
- **Virologic:**
  - VL <50 cps/ml (FDA snapshot): 97%
  - VL <50 cps/ml (on treatment, n=140): 100%
  - Virologic failure (2 consecutive HIV-1 RNA ≥200 c/mL): 0%
- **Questionnaire** (on treatment, n=140): 100% preferred LA injections to daily oral treatment

Guar AIDS 2024 #OAB2606LB

A5359 LATITUDE: CAB/RPV in Suboptimal Adherence

- **Phase 3** randomized, multicenter, open-label ACTG study; noninferiority $\Delta 10$
- Study population: PWH with hx of suboptimal adherence (persistent VL >200 or lost to follow-up)
- Study treatment:
  - Step 1: Continue oral ART with cash incentives up to 24 wks (N=434, 70%M, 64%B, 17%L, 5% TG, 14% PUID) ---- if VL<200→
  - Step 2: Continue oral ART or change to CAB/RPV q4wks X 52 wks (n=294)
- Results:
  - DSMB stopped study early due to significant difference

Conclusion: Considering all endpoints, CAB/RPV superior to oral ART in PWH with adherence challenges

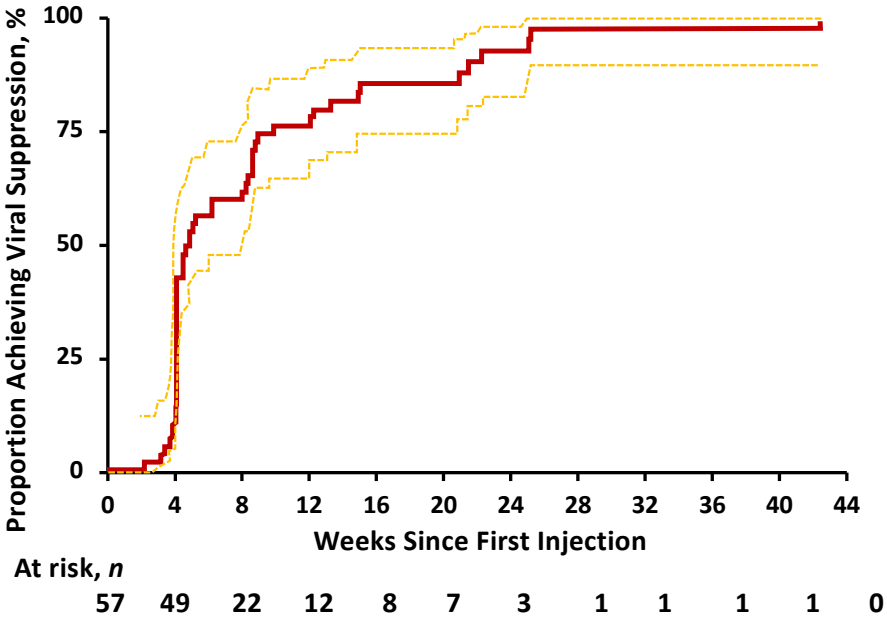


Rana CROI 2024 #212

CAB/RPV in Unsuppressed: UCSF

- Demonstration project
- 133 clinic patients started on CAB/RPV
  - Average age 46 (range 25-68), 88% men, 62% non-white
  - 42% unstable housing or homeless, 34% substance use
  - 76 suppressed on oral ART; 57 with viremia
- Results:
  - 54 of 57 (98%) had virologic suppression by median 33 weeks
  - 1 had 2 log ↓ in viral load
  - 2 (1.5%) had virologic failure
- Conclusion:
  - CAB/RPV suppresses VL, even with viremia and suboptimal adherence

Figure. Kaplan-Meier curve of probability of achieving virologic suppression (viral load <30 copies/mL) with long-acting anti-retroviral therapy (n=57).



Gandhi Ann Intern Med 2023;176:969-974

Update: Gandhi CROI 2024 #628

88 viremic pts enrolled; 60 ≥32 weeks of f/up; at wk 24, 51 (85%) VL <50 cps/ml, 4 VL >50 cps/ml, 5 missing data

Of those with VL >50, 2 had resistance (RT E138K, INSTI R263K; RT L100I, Y181I)

Guidelines: CAB/RPV in Viremic Patients

- **US DHHS (9/12/24)** Based on very limited data, the Panel recommends the use of LA CAB/RPV on a case-by-case basis in select individuals with persistent virologic failure despite intensive adherence support on oral ART, who have no evidence of resistance to CAB or RPV, and with shared decision-making between providers and people with HIV **(CIII).**
- The Panel notes that people with HIV and their providers must be aware of the significant risk of developing resistance to NNRTIs, and particularly integrase strand transfer inhibitors (INSTIs) if virologic failure occurs on LA CAB/RPV. Such resistance may limit future treatment options and may also lead to HIV transmission.

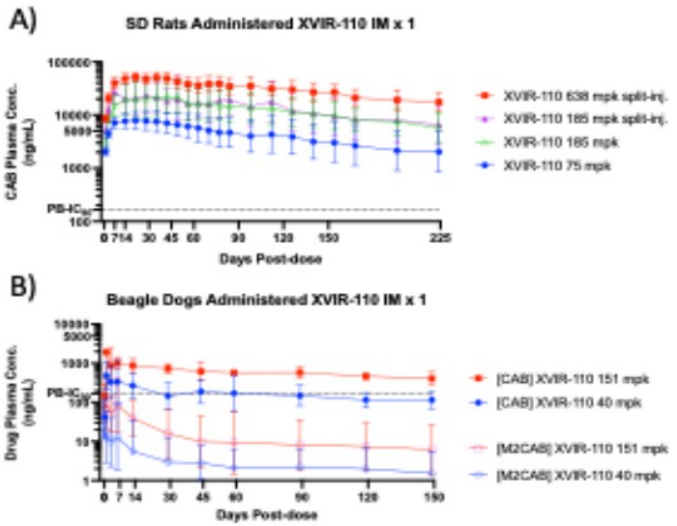
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv

CAB: New Formulations

- Current formulation: CAB 200 mg/ml q2 months
- New formulations:
  - CAB 200 mg/ml with recombinant human hyaluronidase (HU) SQ and CAB 400 mg/ml SQ or IM
    Han CROI 2024 #130
    - CAB 200 + HU → stopped due to ISR; PK did not support longer dosing intervals
    - CAB 400 → favorable safety/PK supporting **≥q4 month dosing**

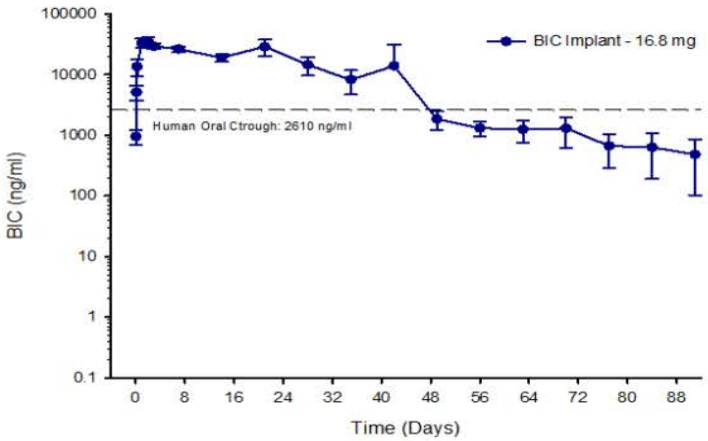
    FURTHER CLINICAL STUDIES PLANNED!

  - Cabotegravir stearate (XVIR-110): CAB prodrug
    Kearney CROI 2024 #656
    - Forms depots with protracted elimination half-life
      → extended release suspension for IM injection
    - Single IM injections in rats and dogs
    - Results:
    - Conclusion: Suggests **q6 month or q year dosing**

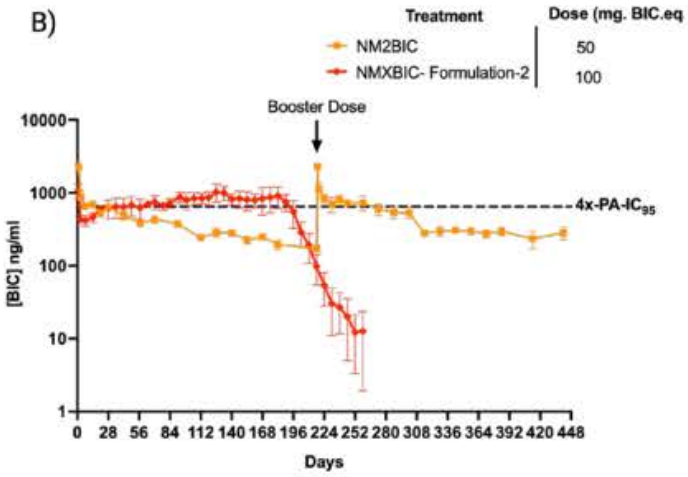


New INSTI Formulations

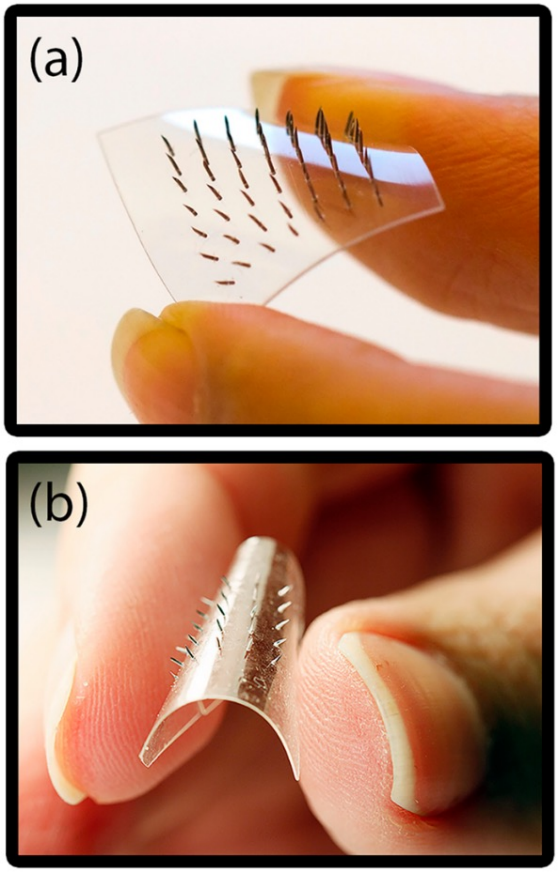
- BIC LA solid nanoparticle injectable Arshad CROI 2024 #653
  - Pre-clinical in rats; single injection
  - PK: plasma concentrations exceeded the human oral stead-state Ctrough within 3 hours and for 42 days
  - No visible ISR
- Similar data with DTG LA Le CROI 2024 #1137



- BIC LA pro-drugs Nayan CROI 2024 #654
  - Dimeric (MXBIC) and monomeric (M2BIC) injectable nanosuspensions
  - Pre-clinical in rats and rhesus macaques, single IM injections
  - NMXBIC formulations PK:
    - BIC concentrations >PA-IC95 for >6 months in rats and macaques
    - Short PK tail with rapid decay in rhesus macaques
  - Conclusion: High plasma BIC exposure with potential for q6month dosing and short PK tail

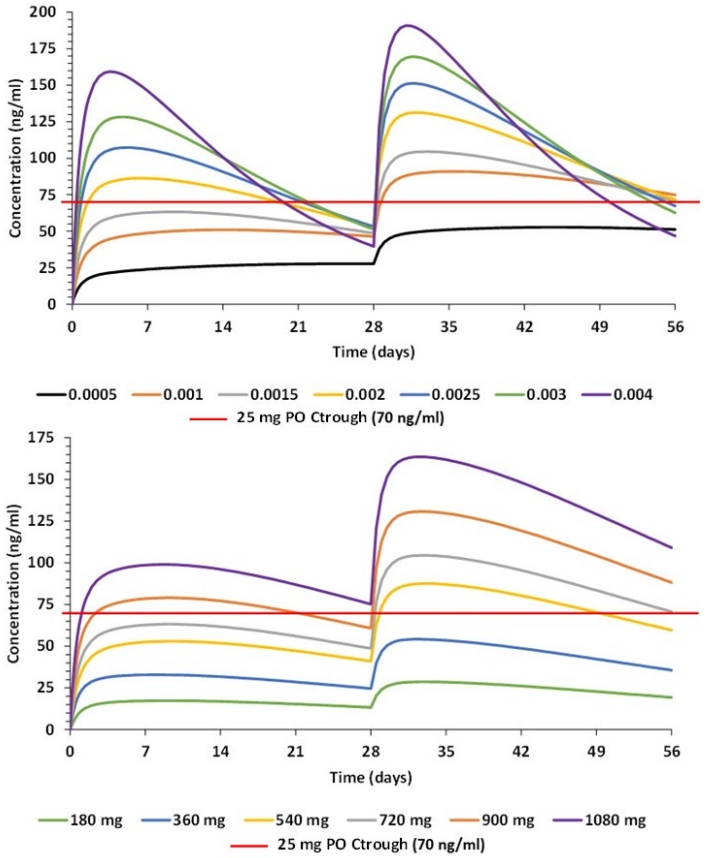


CAB -- Microneedle Patches



Rajabi PLoS One 2016;11:e0166330

Estimated cabotegravir concentrations after applying a 30-60 cm^2 microneedle patch (adults)



Rajoli Eur J Pharm Biopharm 2019;144:101-109
Volpe-Zanutto J Control Release 2022;348:771

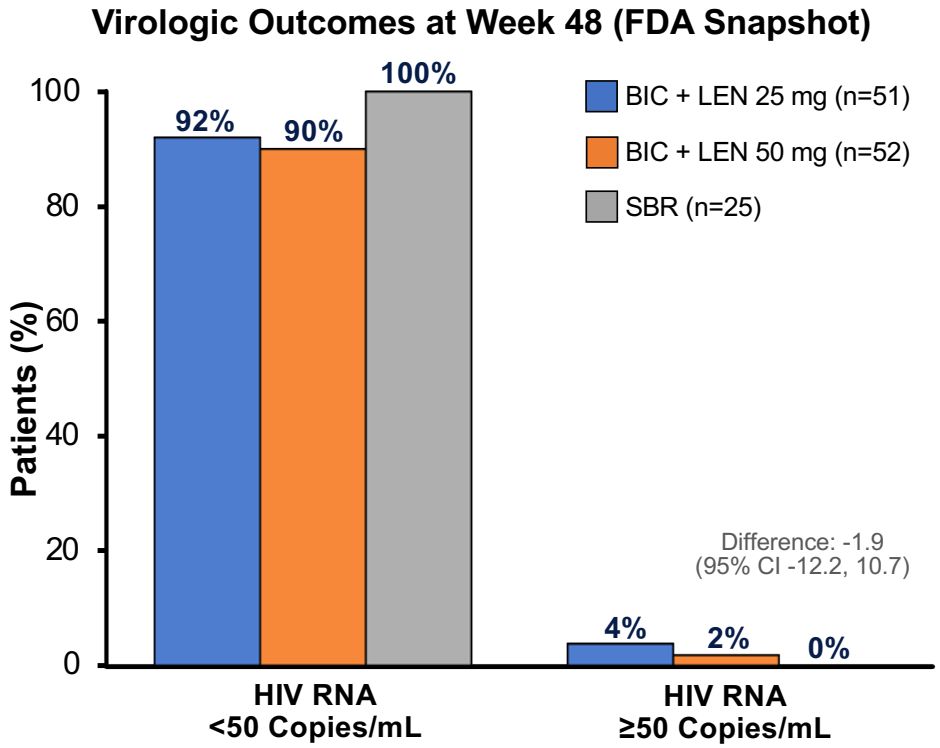
Current Antiretrovirals: New Formulations and Strategies -- Capsid Inhibitors

ARIISTRY-1: Lenacapavir (LEN) + Bictegravir (BIC)

- **Phase 2** randomized, open-label, multicenter, switch study
- Study population: PWH VS on a stable multi-tablet ART regimen (N=128, 19%F, 31%B, 16%L, median age 60, median 3-tab ART)
- Study treatment: randomized 2:2:1 to
  - BIC 75 mg + LEN 25 mg daily
  - BIC 75 mg + LEN 50 mg daily
  - Continue baseline regimen
- Results (24 wks):
  - VL <50: 96% (BIC+LEN 25), 96% (BIC+LEN 50), 100% (baseline ART)
  - VL ≥50: 1 participant (BIC+LEN 50) who resuprressed on same regimen
  - Missing data: 2 pts (BIC+LEN 25) + 1 pt (BIC+LEN 50)
- Conclusion: BIC + LEN highly effective

Mounzer CROI 2024 #642

ARTISTRY-1 Study: 48-week Results



- Conclusions:
  - maintained viral suppression; CD4 cell gains were comparable across groups
  - regimens were generally well tolerated, regardless of lenacapavir dose

Mounzer IAS 2024 #OAB2602

- Phase 3 using single-pill formulation of BIC/LEN enrolling!

Case Series: Lenacapavir (LEN) + Cabotegravir (CAB)

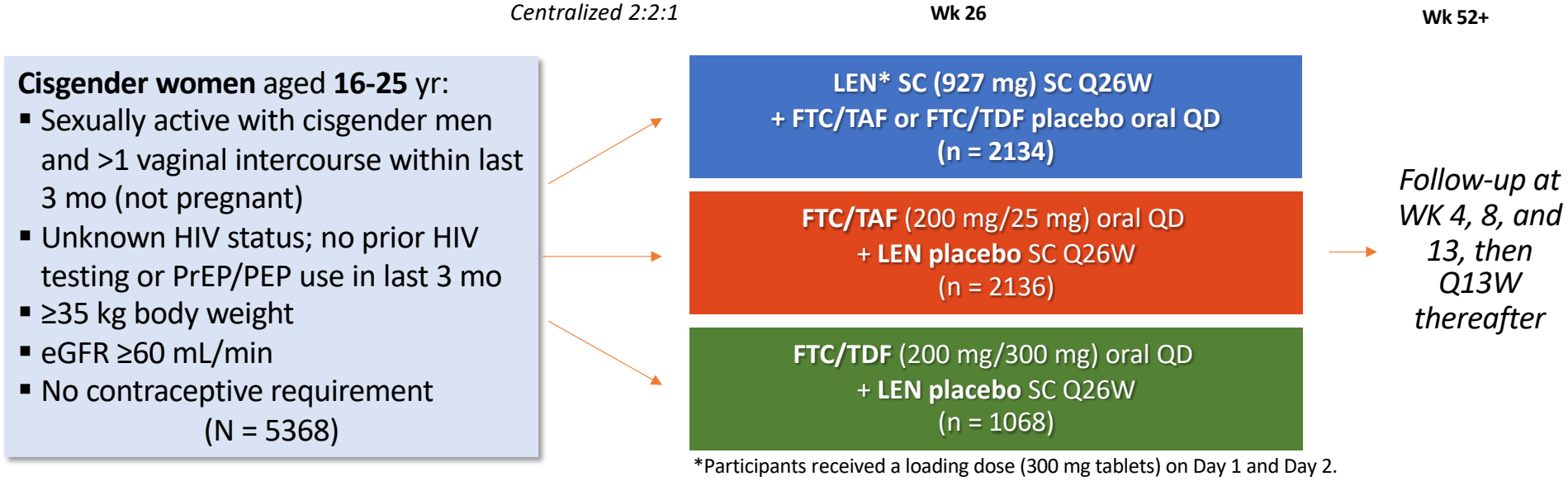
- Case series from UCSF, UCSD, Cleveland, UPenn
- Study population: PWH with adherence challenges to oral ART (N=34, 76%M, 41%B, 38%L, 56% housing insecurity and/or substance use; 71% on CAB q8wks, 47% VS)
- Treatment: LEN (oral→q6 mo SQ) + CAB q 4 or 8 wks +/- RPV
  - 68% added LEN to CAB/RPV, 32% used LEN/CAB without RPV
- Results:
  - Reasons for adding LEN: 59% NNRTI resistance, 15% INSTI mutations, 18% high VL when starting CAB/RPV, 12% viremia on CAB/RPV
  - 32/34 (94%) suppressed VL<75 copies/ml after starting LEN
- Conclusion: supports a clinical trial Gandhi CROI 2024 #629

- **ACTG 5431:** LEN-CAB in viremic pts with adherence challenges

LEN for HIV Prevention

PURPOSE 1: Twice-Yearly LEN Injections vs Daily Oral Tenofovir as PrEP in Cisgender Women

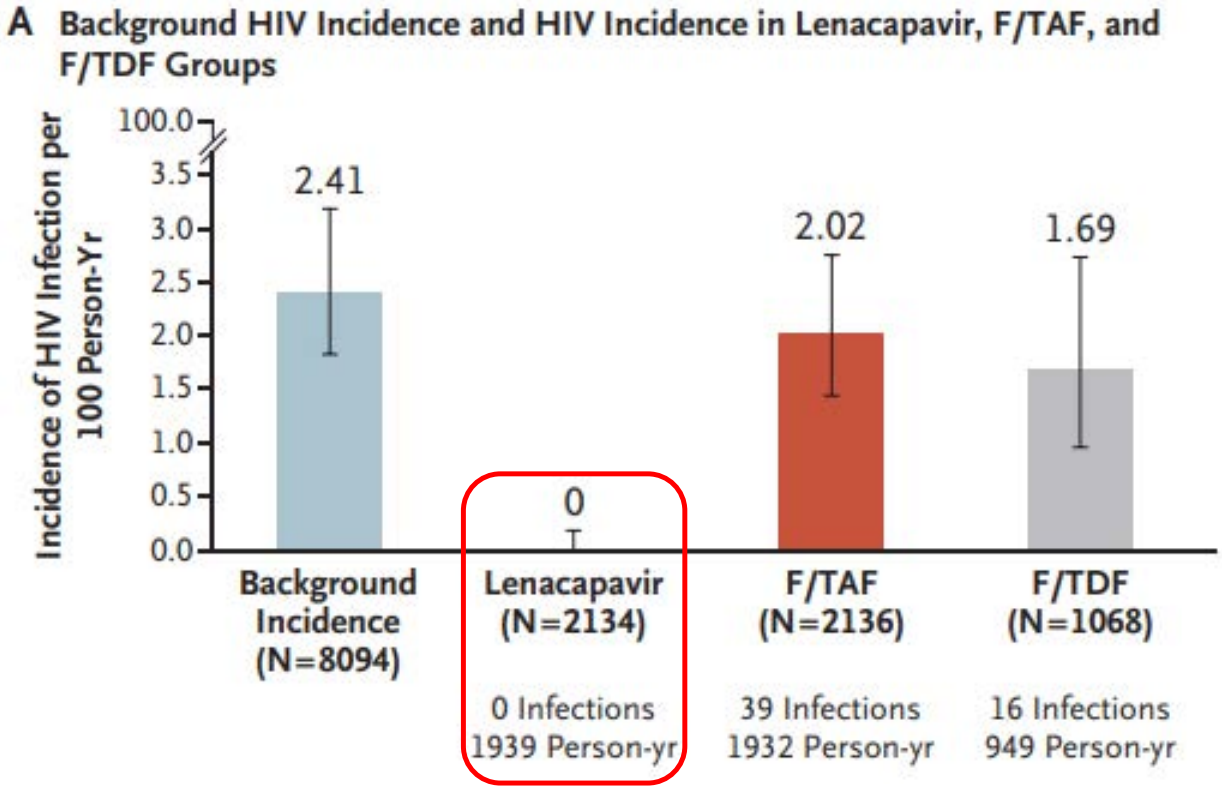
- Randomized, double-blind phase III trial in South Africa and Uganda using counterfactual design



Study stopped early by DSMB!

Bekker AIDS 2024 #SS0407
Bekker NEJM 2024 [Epub 6/24/24]

Results: Efficacy of injectable LEN for PrEP

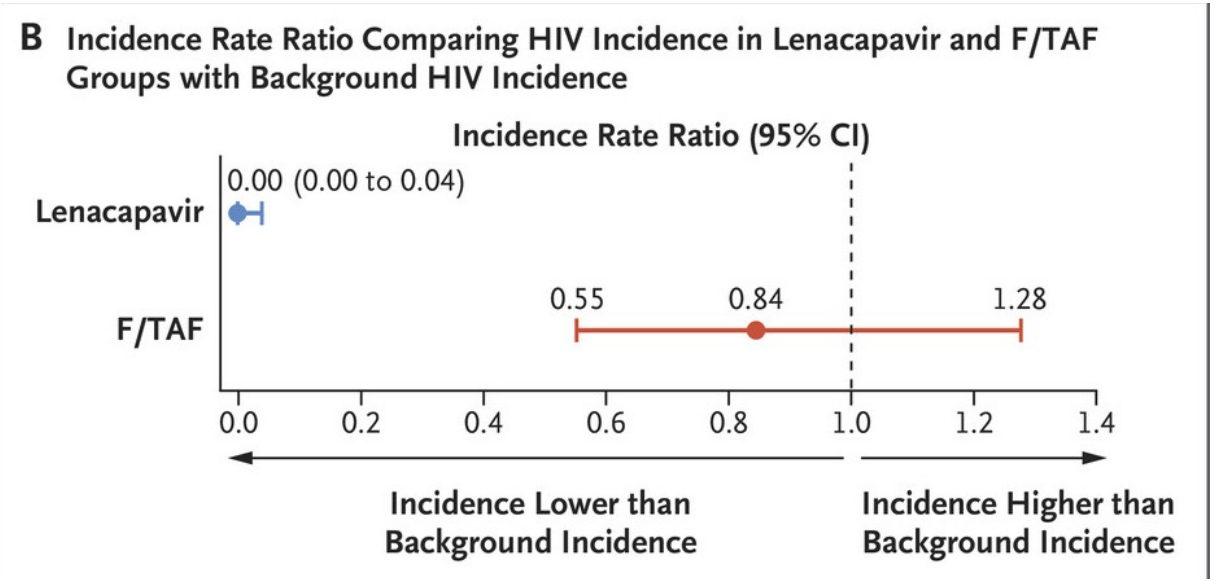


LEN associated with fewer GI adverse events than orals.
ISR were common, but led to discontinuation in only 0.2%.

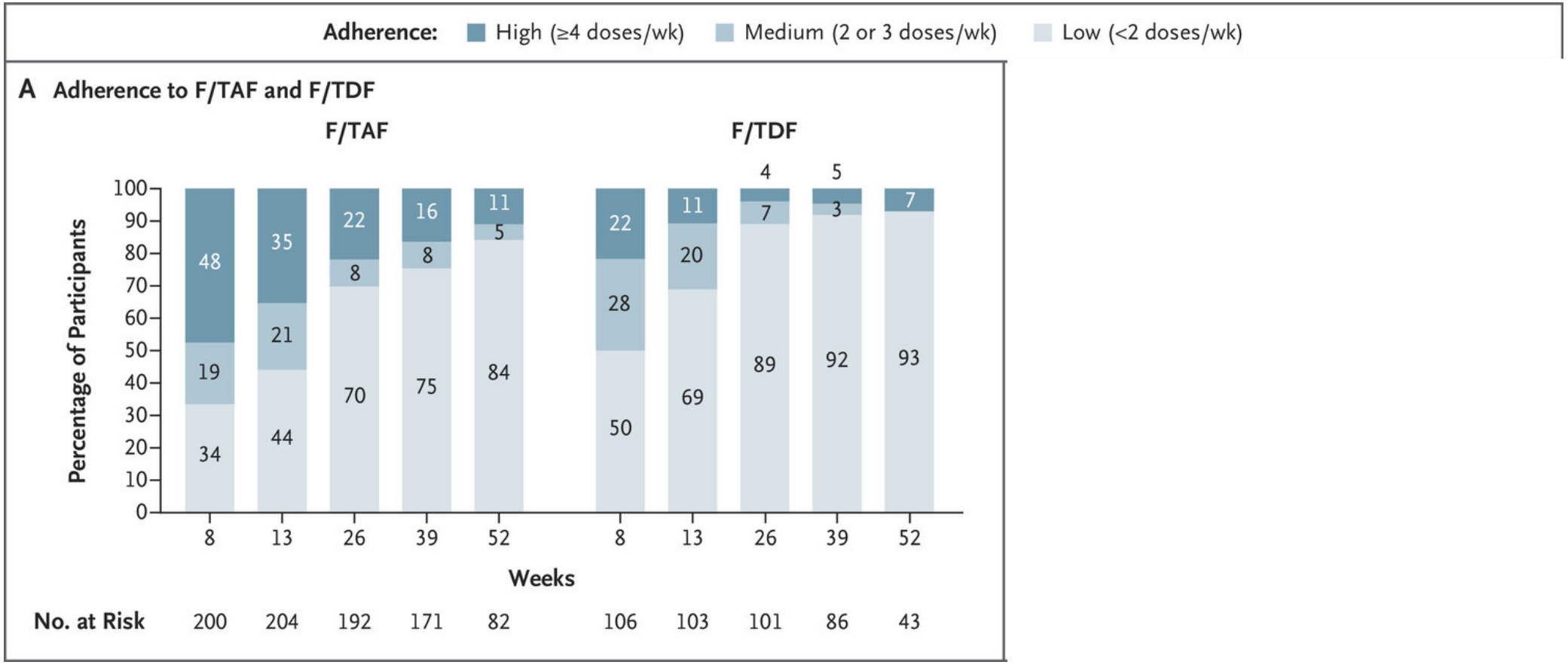
Bekker AIDS 2024 #SS0407 + Bekker NEJM 2024 [Epub 6/24/24]

Efficacy results compared with background incidence

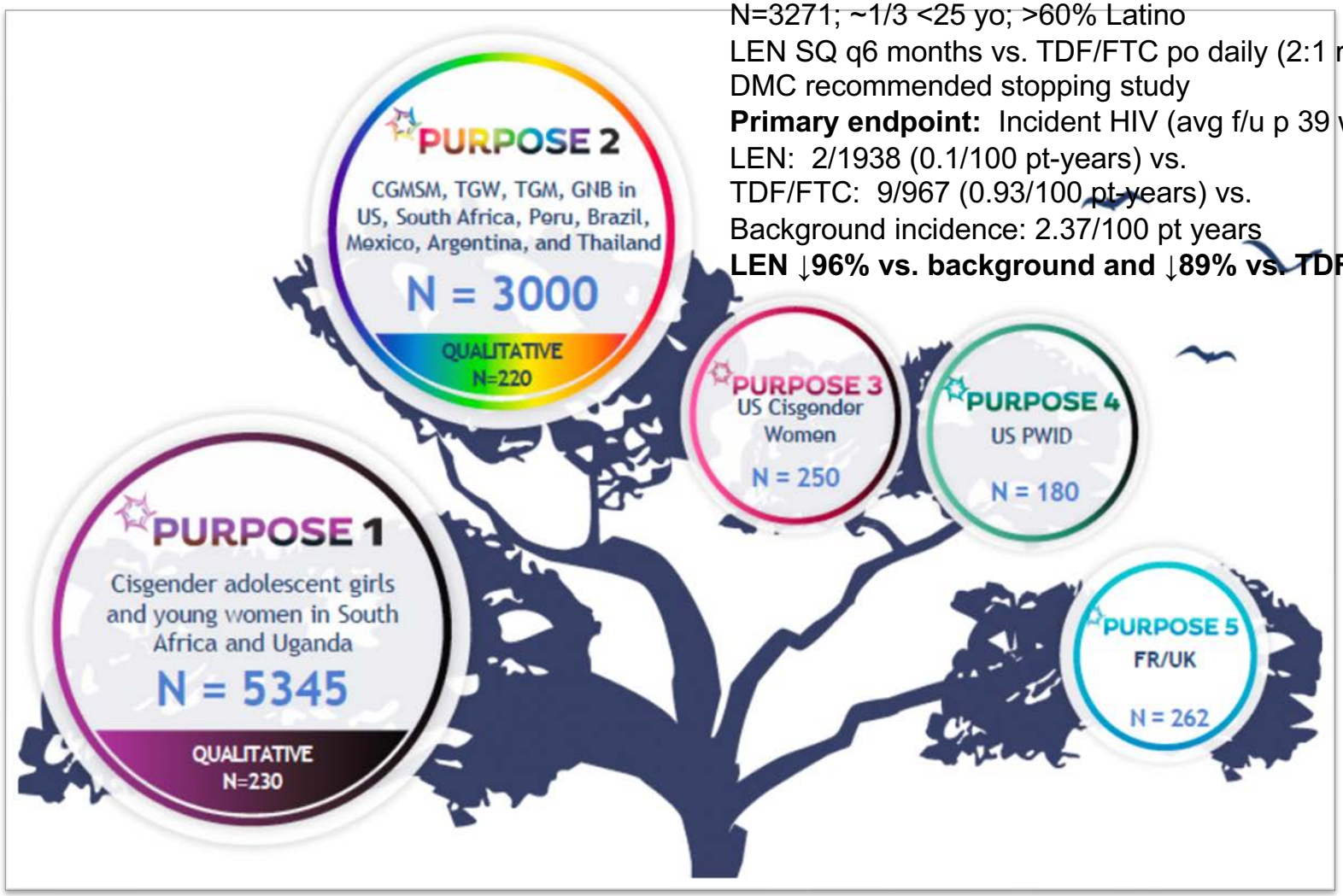
1. LEN significantly better
2. TAF/FTC not significantly better



Bekker AIDS 2024 #SS0407 + Bekker NEJM 2024 [Epub 6/24/24]



Bekker AIDS 2024 #SS0407 + Bekker NEJM 2024 [Epub 6/24/24]

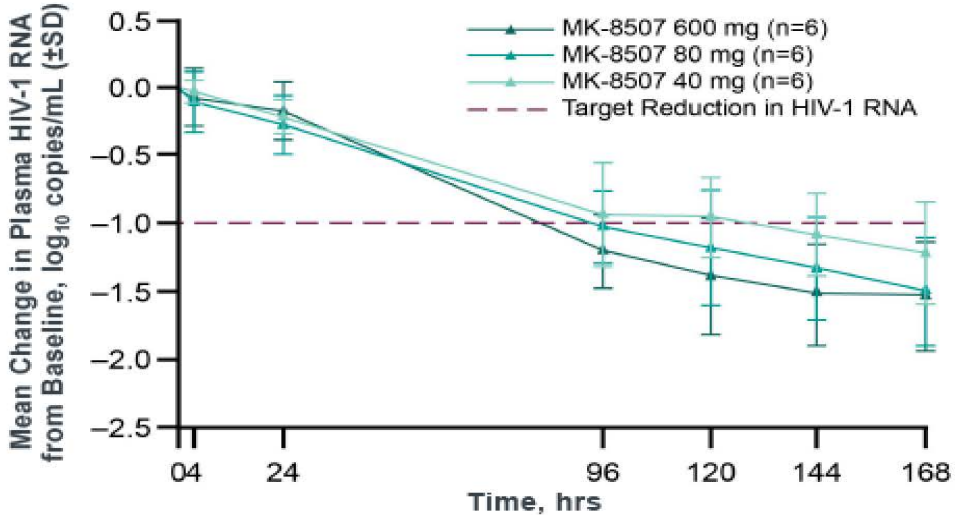


Press Release 9/12/24 and Kelley R4P 10/24:
N=3271; ~1/3 <25 yo; >60% Latino
LEN SQ q6 months vs. TDF/FTC po daily (2:1 randomization)
DMC recommended stopping study
Primary endpoint: Incident HIV (avg f/u p 39 weeks):
LEN: 2/1938 (0.1/100 pt-years) vs.
TDF/FTC: 9/967 (0.93/100 pt-years) vs.
Background incidence: 2.37/100 pt years
LEN ↓96% vs. background and ↓89% vs. TDF/FTC

Investigational Agents
-- NNRTI

Ulonivirine (ULO, MK-8507): Investigational NNRTI

- Potent in vitro (IC50 ~50nM); active in vitro against common NNRTI-resistant variants
- $T_{1/2}$ ~ 70 hours -- supports once-weekly oral dosing Ankrom AAC 2021;65:e0093521
- ↓ CNS side effects
- Phase 1 study (N=18)
  - HIV+ rx-naïve, VL≥10,000, CD4 >200, no NNRTI mutations. no HBV/HCV
  - Single doses tested: 40, 80, 600 mg
  - Results:
    - Generally well-tolerated
    - 1 pt with F227C (uncommon NNRTI mutation)

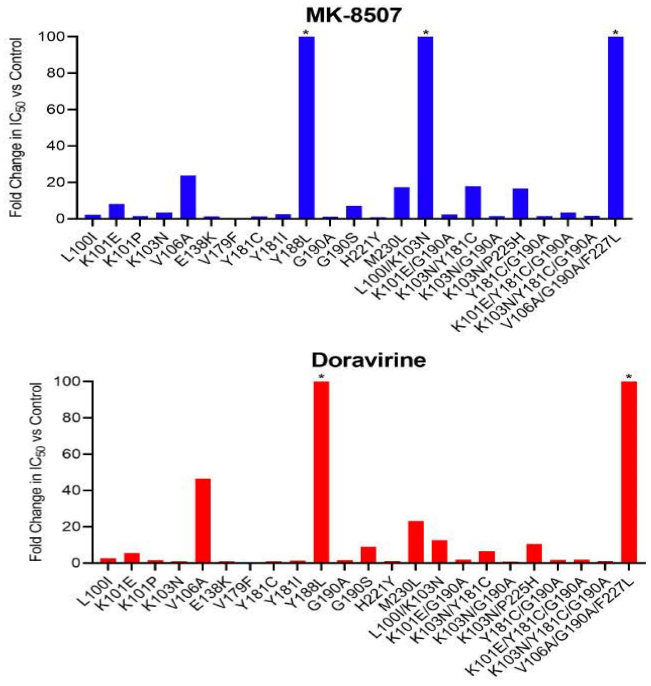


  - Conclusion: Supports weekly combination rx studies
- Future studies: ISL + ULO qweek

Schurmann JAIDS;2022:191-198

Ulonivirine (MK-8507): Investigational NNRTI

- Drug resistance Diamond CROI 2021 abstract #129
  - V106A was primary mutation with subtype B
  - V106M was primary mutation with subtypes A
  - <5 fold ↓ against K103N, K181C, G190A
  - Similar to doravirine



- Phase 2 study:
  - MK-8507 (100, 200 or 400 mg) + oral ISL 20 mg weekly dosing
  - ↓lymph/CD4 counts
  - Development paused Press Release November 2021

Bavtavirine (GS-5894): Investigational NNRTI

- Active in vitro against NNRTI-resistant viral strains Lansdon CROI 2024 #636
- PK supports weekly dosing
- Phase 1 enrolled, in progress clinicaltrials.gov/NCT05585307
  - Study population: PWN with no prior treatment (N=13)
  - 10 days monotherapy
    - PK, dose selection, antiretroviral activity

Investigational Agents
-- INSTI

GS-1720 Oral Long-Acting INSTI

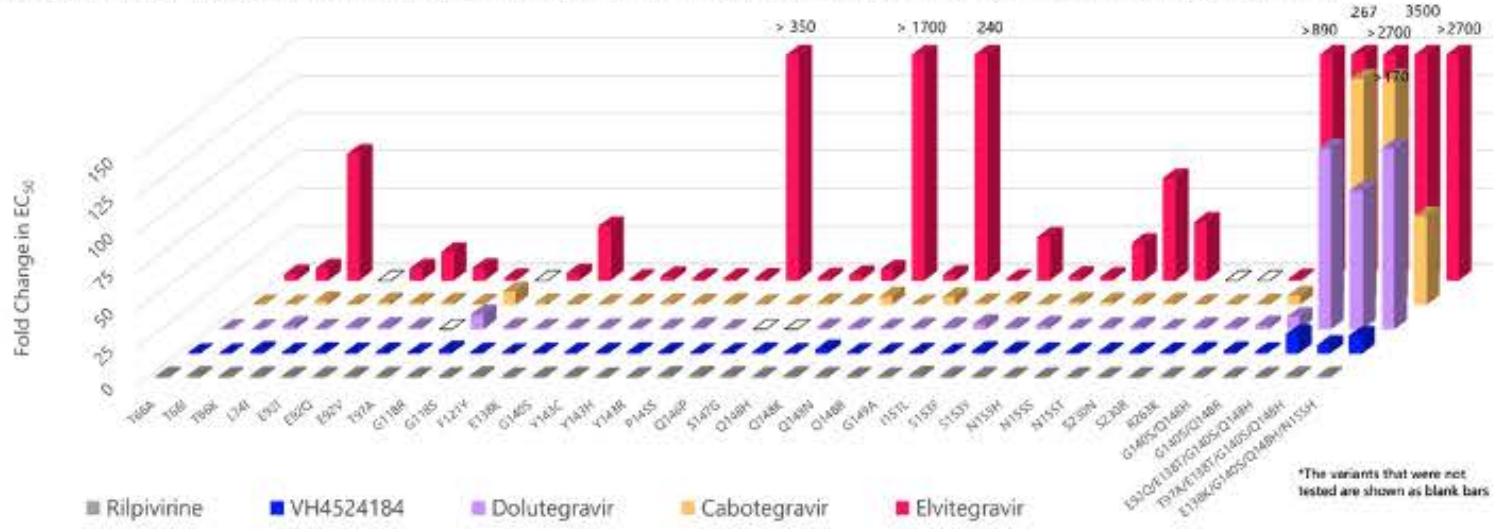
- **Preclinical:** Potent HIV IC50 6.2nM; no resistance after 16 passages; 7X ↑ potency (vs. BIC) in clinical PBMC isolates Hansen IAS 2024 #THPEA025
- **Phase 1a:** single oral doses: GS-1720 50, 150, 450, 1350 mg or placebo (8 pts without HIV/cohort) Shaik IAS 2024 #WEPEB117
  - Results: median half-life 9.3 days, non-linear PK, generally well-tolerated
- **Phase 1b:** oral open-label multicohort study Fichtenbaum CROI 2024 #116
- Study population: PWH, rx-naïve or off ART X 12 weeks (N=7)
- Study treatment: GS-1720 450 mg days 1 + 2; followed for 10 days
- Results:
  - Median half-life 9 days, allowing weekly oral dosing
  - Mean HIV RNA ↓ 2.44 log copies/ml (day 11); No rx-emergent INSTI resistance
  - Generally well-tolerated
- Other inj INSTIs: GS-6212 (q3mo), GS-1212 (q6mo), GS-3242 (q6mo)

VH184 – "3rd Generation" INSTI: In vitro

- Antiviral activity measured against lab and clinical isolates
- HIV integrase enzyme IC50 5.8 nM; HIV proviral DNA IC50 0.46nM
- HIV in vitro passage with VH-184 X 112 days: no mutations

Resistance Profiles:

The fold changes in EC_{50} values of VH4524184 against a panel of HIV-1 molecular clones harboring INSTI-resistant associated mutations*



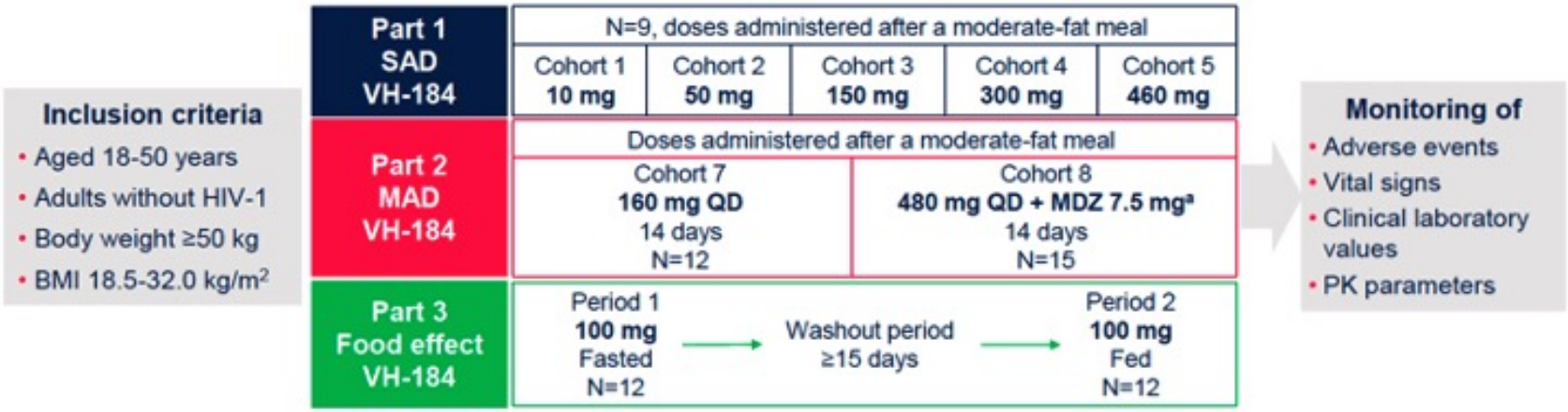
- **VH4524184 (VH-184, S-365598) exhibits a superior resistance profile against first- and second-generation INSTI-resistant variants**
- **There was no significant decrease in the anti-HIV-1 activity of VH-184 observed for any of the single mutants**

Seki IAS 2024 #WEPEB114

VH184 – "3rd Generation" INSTI: Phase 1

- VH4524184 (VH-184): third-generation long-acting INSTI; t ½ 24 hours

Double-blind, randomized, placebo-controlled, phase 1, first-time-in-human study of VH-184



- Results: 84 participants (VH184 n=63; placebo n=21)
  - Dose-proportional ↑ concentrations up to 300mg
  - Minimal impact on midazolam (CYP3A4 substrate); moderate +food effect
  - Generally safe and well-tolerated

Rogg IAS 2024 #OAB2603

Investigational Agents
-- Capsid Inhibitors

GS-4182: Pre-Clinical + Phase 1

- Oral Prodrug of LEN; undergoes conversion to LEN in the gut
- **Preclinical:** Subramanian AIDS 2024 #WEPEA031
  - favorable in vitro and animal model solubility, permeability, and metabolism
- **Phase 1:** Randomized, blinded, placebo-controlled Shaik AIDS 2024 #WEPEB117
- Single and multiple ascending doses of GS-4182 in pts without HIV (N=28)
  - Single doses 200 + 600 mg; multiple doses 200 mg weekly X 6 weeks
- Results
  - GS-4182 undetected in most pts
  - With GS-4182 200 mg, LEN concentrations similar to levels with LEN 300 mg
  - With GS-4182 600 mg, LEN concentrations double levels with LEN 600 mg
  - Generally safe and well-tolerated
- Conclusion: Favorable PK; supports further development as oral weekly drug
- **Next: Phase 2:** GS-4182 + GS-1720 weekly recruiting

VH-280 and VH-499: Capsid Inhibitors

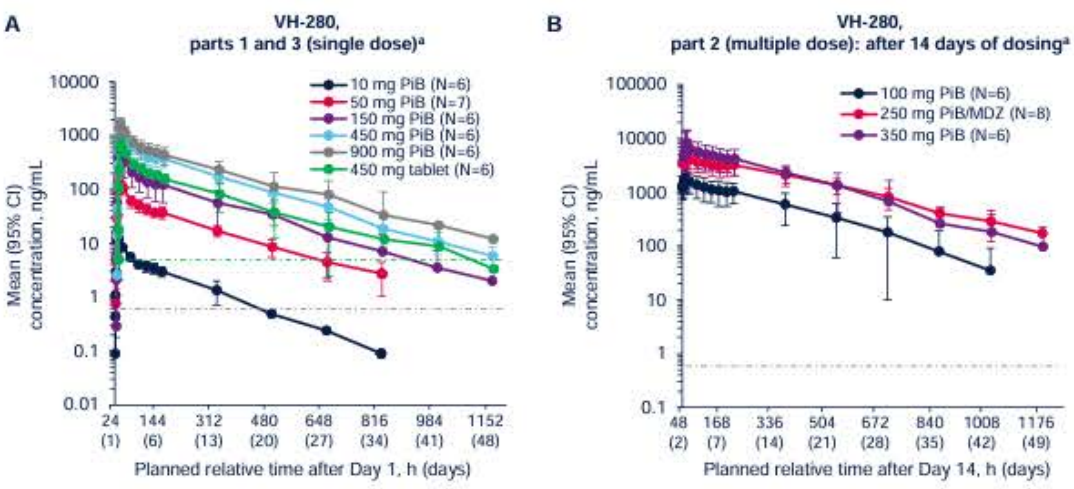
- **Preclinical:**
  - VH-280 and VH-499 each bind to the mature capsid hexamer, binding contact similar to LEN
  - Inhibit both early and late stages of the HIV life cycle; early 9-14X↑; between reverse transcription and integration; also inhibit nuclear import and integration
  - Potent in vitro: HIV EC50 93 pM (VH-280) and 23 pM (VH-499)
  - Capsid resistance mutations (L56I, M66I, Q67H, N74D, A105E, T107N, Q67H/N74D) also ↓ susceptibility to VH-280 and VH-499
  - VH-280 and VH-499 select Q67H, A105E, T107A/D/N singly, in pairs, and in triples
  - Conclusion: supports clinical development

Wang IAS 2024 #WEPEA027

VH-280: Capsid Inhibitor

- **Phase 1:**
  - Double-blind, randomized, placebo-controlled study
  - Adults without HIV (N=73)
  - Single and multiple doses
    - Dose proportional
    - Exceeded target levels
  - Terminal half-life >6 days
  - With/without midazolam
    - No change; no CYP3A4
  - Generally well-tolerated

Figure 2. Mean Plasma VH-280 Concentration vs Time Plots in (A) Parts 1 and 3 and (B) Part 2 (Semi-logarithmic Scale): PK Population



- Conclusion: Supports further development as a long-acting HIV treatment

Griesel IAS 2024 #THPEB093

- **Phase 2** enrolled

VH-499: Capsid Inhibitor

- **Phase 1:**
  - Double-blind, randomized, placebo-controlled studv
  - Adults without HIV (N=73)
  - Single and multiple doses
    - Less-than-dose proportional
    - Exceeded target levels
  - Terminal half-life >2 days
  - With/without midazolam
    - No change; no CYP3A4
  - Generally well-tolerated

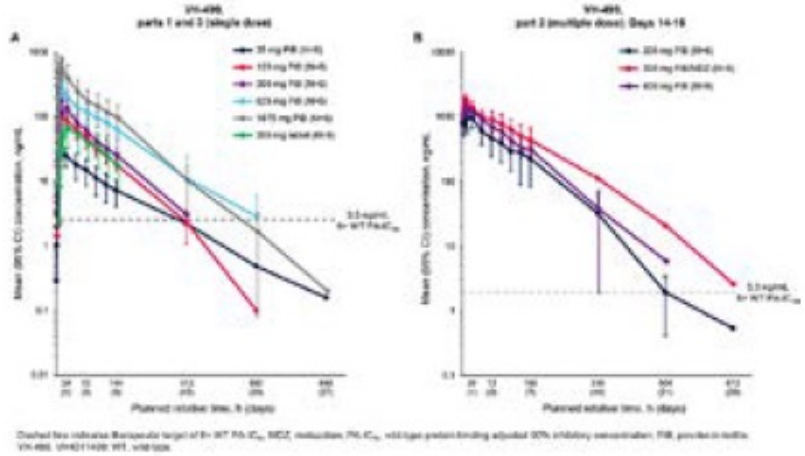


Figure. Mean plasma VH-499 concentration-time plots in (A) parts 1 and 3 and (B) part 2 (semi-logarithmic scale).

- Conclusion: Supports further development as a long-acting HIV treatment

Thakkar IAS 2024 #WEPEB105

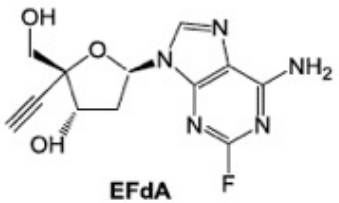
- **Phase 2** enrolled

New Mechanisms of Action

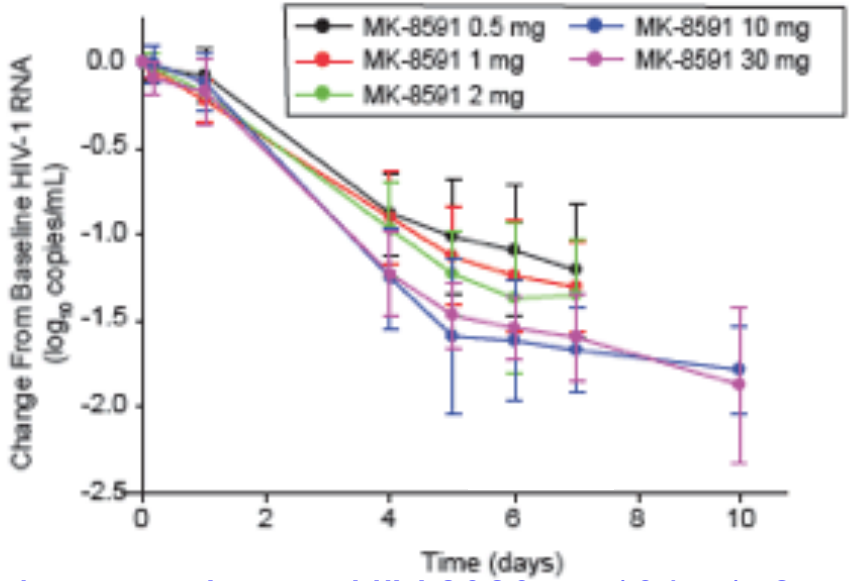
Investigational Agents – NRTTI

Islatravir (ISL)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; MK-8591; EFdA
- DNA chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Half-life = 50-60 hours in plasma
- No drug-drug interactions anticipated
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR)
- Low-dose and parenteral formulations
- **Phase 1b:** single oral dose
- **Phase 2** in rx-naïve: ISL+DOR
  Molina JAIDS 2022;91:68-72
- Infrequent dosing for treatment/prevention
  - daily, weekly, monthly
- GS-1614: ISL pro-drug q3 month injection dosing



EFdA



Schurmann Lancet HIV 2020;7:e164-e172

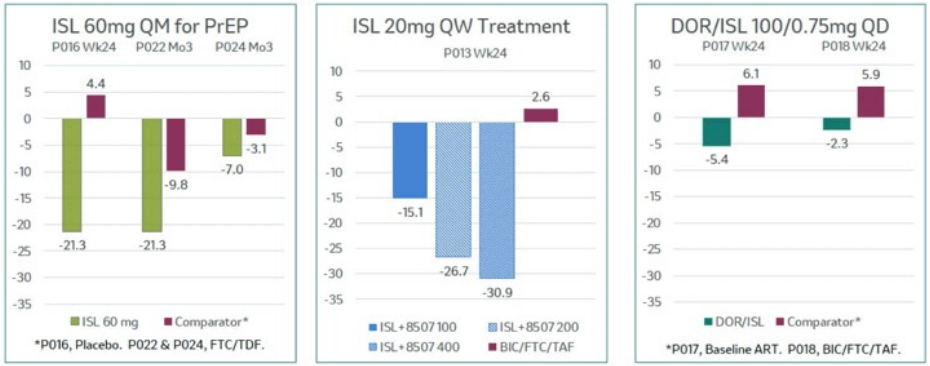
Islatravir (ISL): Phase 3 Studies

- Two **Phase 3 switch** studies (total N=1313 on suppressive ART)
  - Study 017: Continue ART or change to ISL/DOR
    - >86% with VL <50 cps/ml at wk 96 Molina Lancet HIV 2024;11:e369
  - Study 018: Continue TAF/F/BIC or change to ISL/DOR
    - >84% with VL <50 cps/ml at wk 48 Mills Lancet HIV 2024;11:e357
  - Conclusion: ISL/DOR non-inferior in both studies

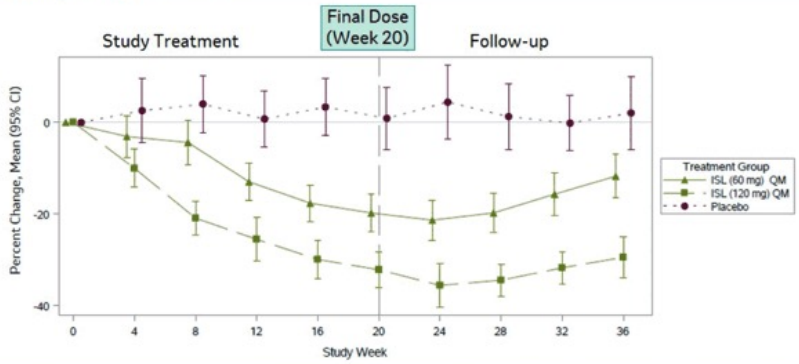
- **Phase 3** study in rx-naïve pts (N=597)
  - ISL/DOR vs. TAF/F/BIC
    - >88% with VL <50 cps/ml at wk 48 in both groups
  - Conclusion: ISL/DOR non-inferior Rockstroh IAS 2023 #OALBX0102

Islatravir (ISL) – Lymphocyte Toxicity

Total Lymphocyte Count, Mean % Change from Baseline



Phase 2 ISL Dose-Ranging Study in HIV-1 Low-Risk (MK8591-016)
Total Lymphocyte Count

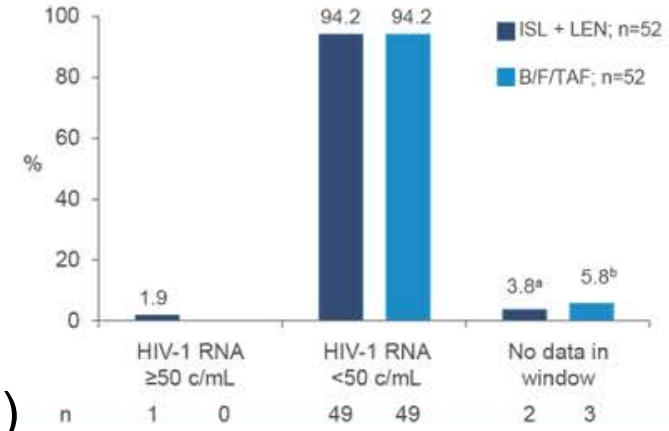


- FDA placed **clinical hold** on studies with oral, injectable, and implantable ISL
- No other blood cell lines affected (other WBC, RBC, platelets)
- No signals in earlier animal or phase 1-2 studies
- Likely mechanism: ↑ISL-TP levels inhibits DNA polymerase-α→ apoptosis
- Not mitochondrial toxicity
- Dose-dependent, reversible, not associated with ↑ infections
- Solution: Modeling suggests 0.1 mg daily / 3-5 mg weekly optimal

Squires CROI 2023 #192, Kim CPT Pharmacometrics Syst Pharmacol (epub 8/20/24)

Weekly Oral Therapy: ISL + LEN

- **Phase 2** randomized, open-label, controlled study Colson CROI 2024 #208
- Study population: PWH on TAF/FTC/BIC with VL <50 at least 24 weeks without prior VF, CD4 ≥350/mm^3, absolute lymphocyte count ≥900/mm^3, no active/occult HBV (N=104)
- Study treatment:
  - **ISL** 2 mg + **LEN** 300 mg weekly oral dosing
  - TAF/FTC/BIC daily dosing
- Results (24 wks);
  - VL <50: 94% (ISL + LEN wkly) vs. 94% (T/F/BIC)
  - CD4: -57 (ISL + LEN wkly) vs. -4 (T/F/BIC) (p=0.3)
  - ALC: -0.01 (ISL + LEN wkly) vs. -0.04 (T/F/BIC) (p=0.6)

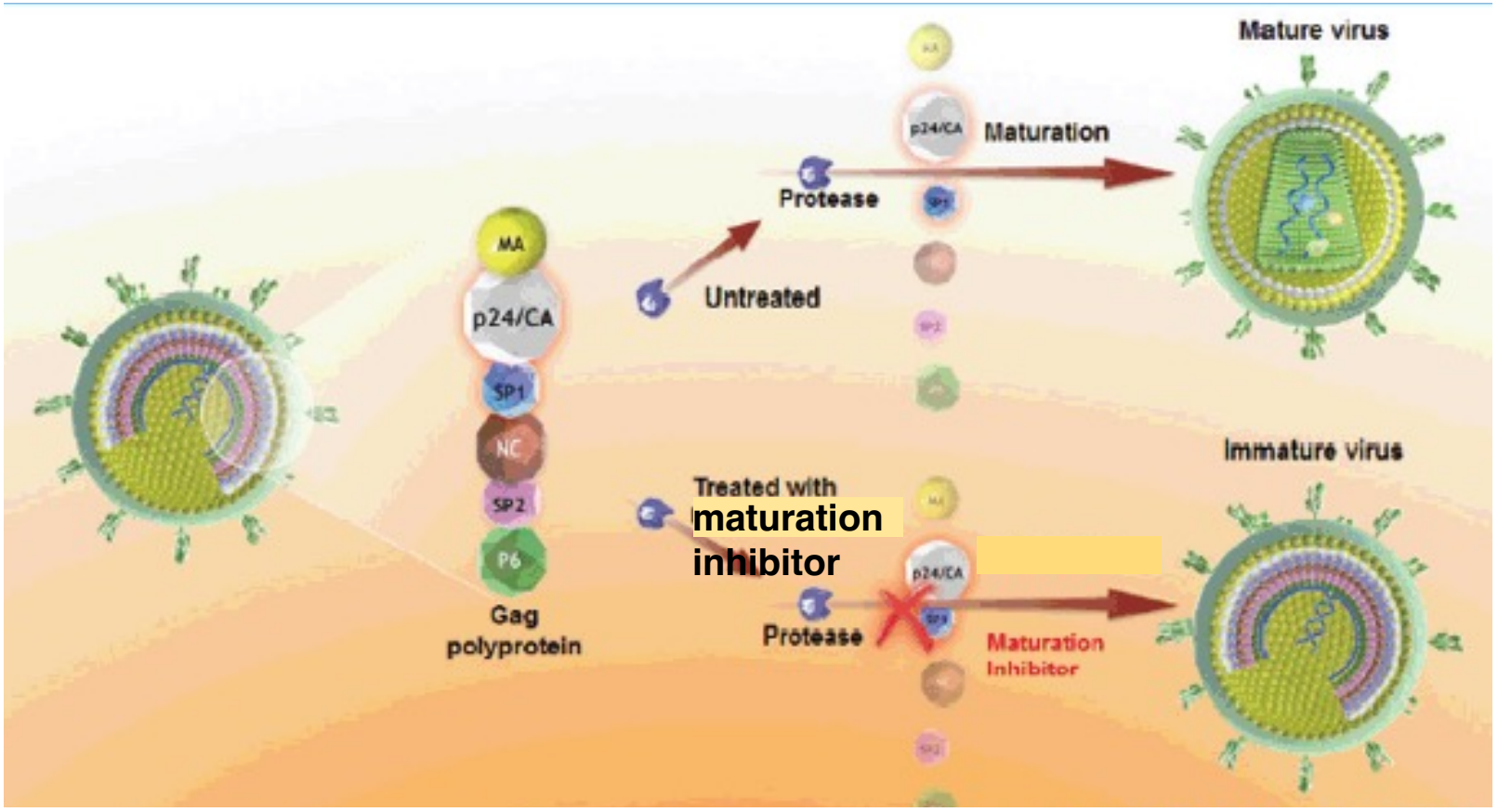


- Conclusion: First oral weekly regimen efficacious/well-tolerated
- Week 48: ISL + LEN wkly 94% VL <50 Colson IDWeek Late Breaker #577

MK-8527 Oral Long-Acting NRTTI

- People without HIV showed PK ($t_{1/2}$ 200-300 hrs) supports weekly-monthly oral dosing Raheem CROI 2024 #638 + Gillespie CROI 2024 #129
- Two **Phase 1** oral single-dose studies Carstens CROI 2024 #115
  - Study population: PWH, ages 18-60 with no prior ART (N=31)
  - Study treatment: Single doses of MK-8527: 0.5, 1, 3, or 10 mg
- Results:
  - VL (log c/ml at day 7): -1.39 (0.5 mg), -1.21 (1 mg), -1.66 (3 mg), -1.39 (10 mg)
  - Generally well-tolerated
- Conclusion: Single doses as low as 0.5 mg achieved >1 log copies/ml decreases at day 7; potential for rx + prevention
- Weekly oral PrEP with MK-8527 protects rhesus macaques from rectal SHIV challenge Diamond R4P 2024
- Phase 2 monthly oral PrEP enrolling!

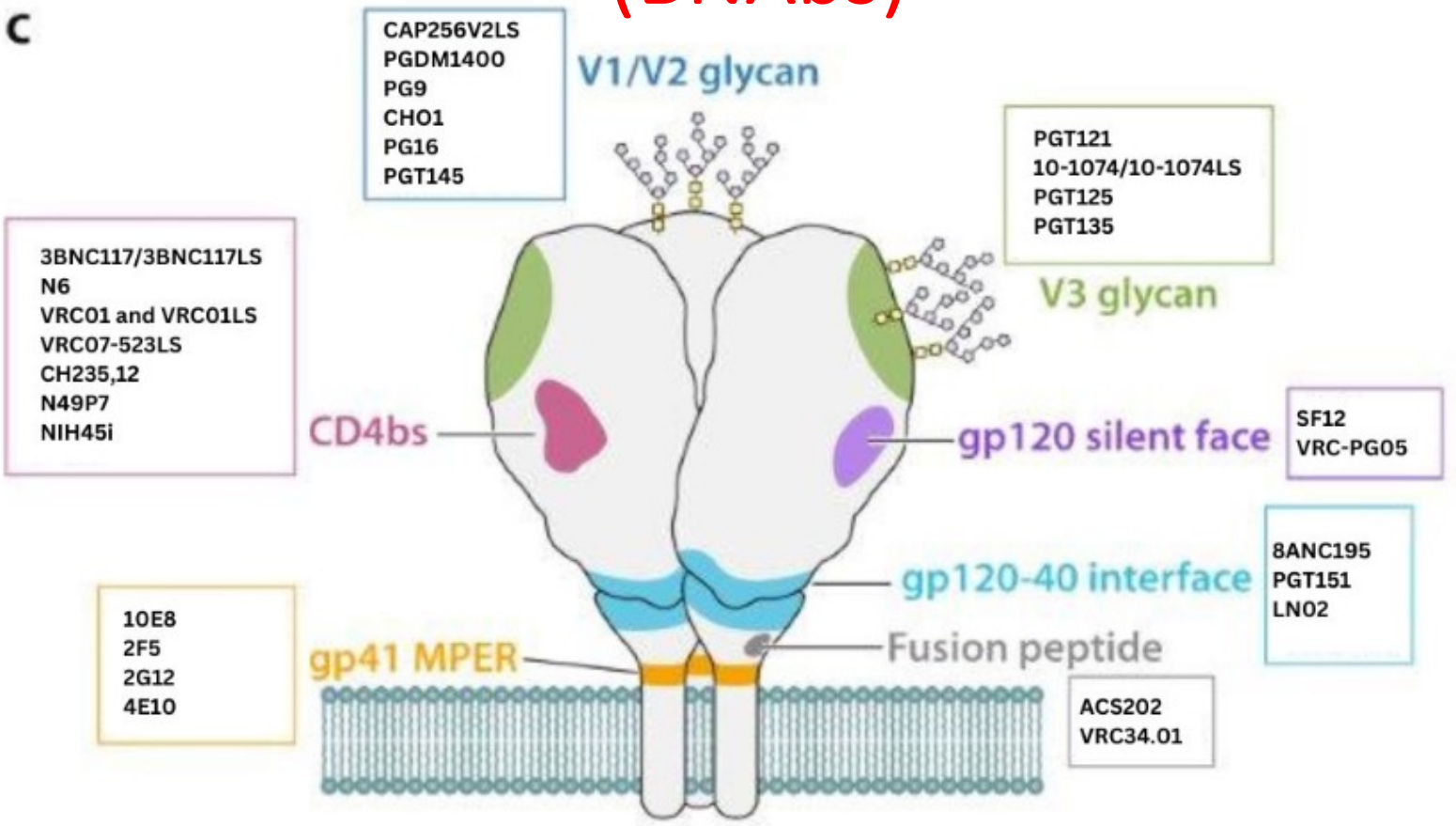
HIV Maturation Inhibitors (MI)



HIV Maturation Inhibitors (MI)

- **bevirimat** – **Phase 2** McCallister 2008 XVII HIV Drug Resistance Conference #8
  - ~50% of rx-experienced pts had no response due to gp120 polymorphisms
- **GSK 3532795/BMS-955176** – **Phase 2b**
  - TDF/FTC + '795: 76-83% <40 cps/ml
  - GI intolerance Morales-Ramirez PLoS One 2018;13:e0205368
- **GSK 2838232** – **Phase 2a**
  - '232 + cobicistat: up to ↓1.7 log cps/ml at 10 days
  - need for boosting DeJesus CID 2020;71:1255-1262
- **GSK 3640254** – **Phase 2b** Joshi EACS 2023
  - VL <50 at week 24: 77-95% ('254 at 3 doses + DTG) vs. 86% (DTG + 3TC)
  - "Not differentiated enough from existing 2-drug daily regimens"
- **VH-3739937** –
  - Preclinical: EC50 1-5 nM; active against prior MI polymorphisms McAuliffe CROI 2024 #633
  - **Phase 1:** long half-life; potential for weekly oral dosing Benn Pharmacol Res Perspect 2023;11:e01093
  - **Phase 2b** studies stopped due to "preliminary findings in a preclinical study of a similar maturation inhibitor" Press Release 10/2/24

HIV Broadly Neutralizing Antibodies (BNAbs)



Mahomed Clin Micro Rvw 2024;37:e0015222

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

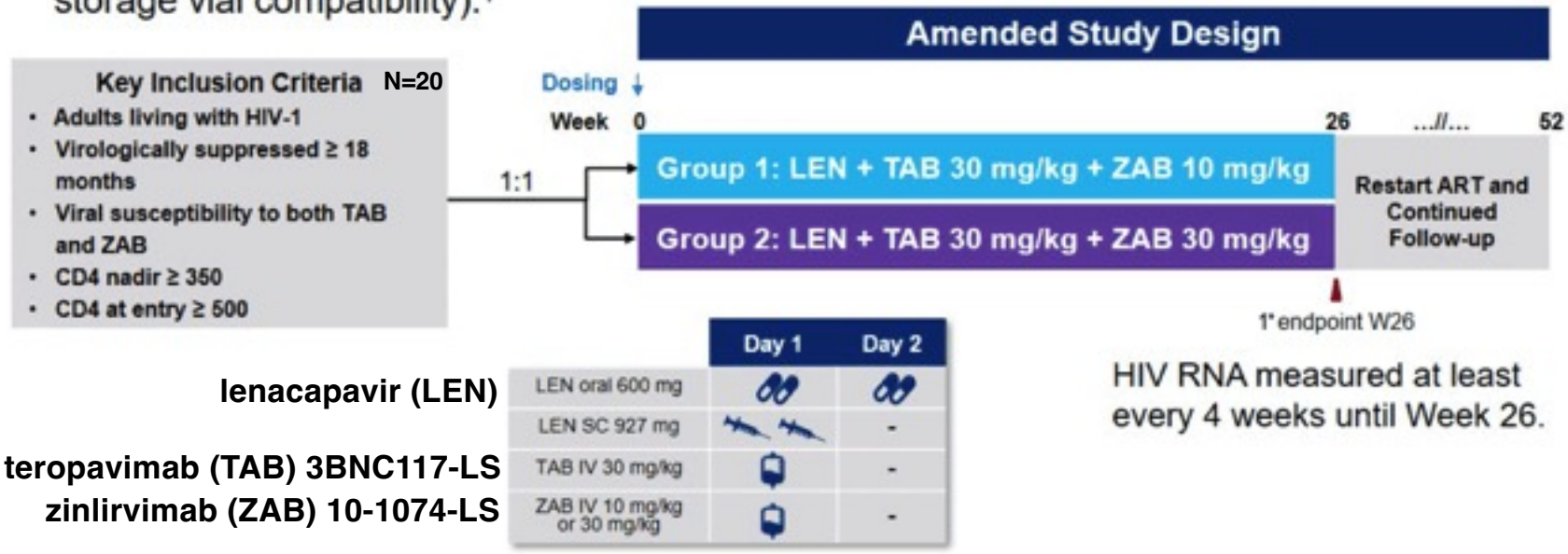
Awan Curr Opin HIV AIDS 2022;17:247-257

- Combination strategies: **Phase 1 and 2** studies
  - 2, 3, and 4 BnAb combinations
  - BnAbs + long-acting ARV (CAB or LEN)

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]

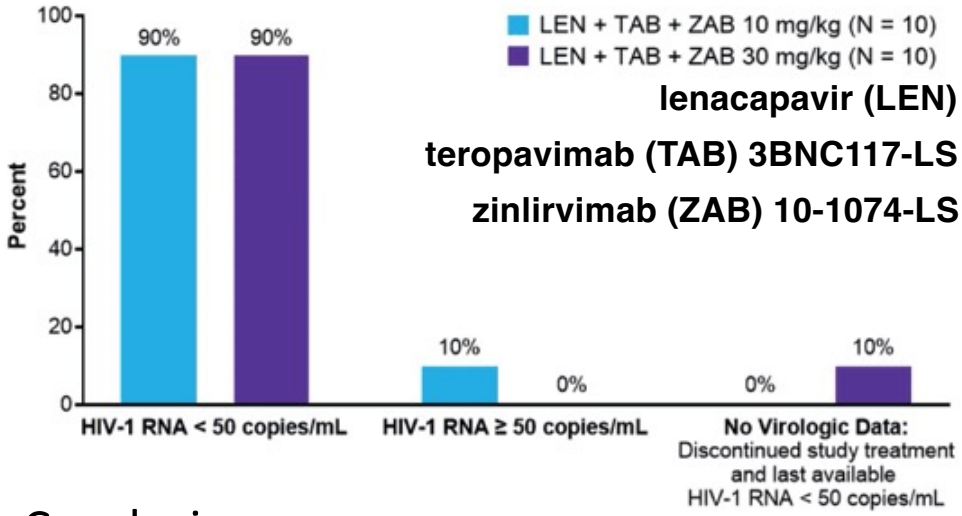


Eron Lancet HIV 2024;11:e146-e155

Pilot Study: LEN + 2 BNAbs

- Results:

Virologic Efficacy Outcomes at Week 26 by FDA Snapshot Algorithm



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

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

Eron Lancet HIV 2024;11:e146-e155

LEN + 2 BnAbs Pilot Study (Part 2)

- **Pilot study**, identical design
- Study population: PWH with VL <50 on ART X 1.5 years, CD4 nadir ≥350, current CD4 ≥500, high-level sensitivity to TAB or ZAB but not both (N=11, 3F, 4B)
- Study treatment (single dose): LEN SQ + TAB IV 30 mg/kg + ZAB IV at 2 doses (10 and 30 mg/kg)
- Result (26 weeks):
  - no study drug-related d/c
  - 8/10 maintained VS (group 1 [ZAB 10] 2/4; group 2 [ZAB 30] 6/6)
  - 2 VF
    - one sensitive to TAB had COVID-19 at rebound
    - one sensitive to ZAB
    - Both rebounded with VL <100 cps/ml; no resistance
- Conclusion: well-tolerated; VS maintained at higher bNAB dose
- Phase 2 in pts sensitive to BOTH MoAbs enrolled

Eron CROI 2024 #120

A5357: CAB + VRC07-523LS

- **Phase 2** single-arm clinical trial
- Study population: PWH with VS on ART X 2 years, CD4 ≥350, VRC07-523S susceptible (IC50 0.25ug/mL and max % inhibition >98% on Monogram Phenosense Mab Assay)
- Study treatment:

  Step 1 (N=74, 26%F, 51% WNH): oral CAB +2 NRTI X 4-5 weeks, ---- if VS→

  Step 2 (n=71): IV VRC07-523LS q8wks + LA CAB q4wks X 48 wks

  Step 3: return to baseline ART regimen
- Result (48 weeks):
  - 61 (86%) completed step 2 + 10 (14%) stopped early (5 VF [confirmed VL >200], 1 death, 4 pt/MD request)
  - 5 (7%) had VF; 3 of VF had VL 51-200 cps/ml at week 4; one VF had R263K mutation; all had therapeutic CAB concentrations and VRC levels >100X IC50
  - 12 (17%) met primary safety endpoint: 15% with ≥grade 3 AEs (chills, myalgia, fatigue)
- Conclusion: VRC07-523LS + CAB safe; most maintained VS, "observed vulnerabilities should inform future bNAb strategies" (tolerability, virologic suppression, resistance issues)

Taiwo CROI 2024 #119

Other bNAB Studies

- 3 bNAb combination Julg CROI 2024 #121 + Nat Med (9/12/24)
  - PGT121 (V3 glycan supersite) + PGDM1400 (V2 apex) + VRC07-523LS (CD4 binding site)
  - 12 PWH on ART, no baseline susceptibility testing
    - 10 (83%) with VS for at least 28 weeks; 2 with early rebound had baseline resistance to PGT121 or PGDM1400
  - Conclusion: 3 bNAb cocktail provides VS

- A5377 Tsibris CROI 2024 #118
  - SAR441236 Trispecific Ab: combines VRC01 (CD4 binding site) + PGDM1400 (v1/v2 glycan binding site) + 10E8v4 (MPER) into one molecule with LS for half-life extension
  - **Phase 1** study of escalating single doses (N=52)
  - Conclusion: Safe, well-tolerated, favorable PK similar to other Ab; supports further development of multispecific bNAbs

ART: Potential Future Regimens

Oral

- Once weekly
  - LEN/ISL, ULO+ ISL, GS-4182 + GS-1720, and other 2-drug combos

Injectables

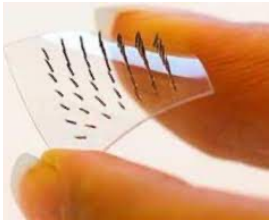
- Every 3-12 months
  - CAB (new formulations) and other INSTIs, LEN, monoclonal antibodies

Implants (removable; refillable; biodegradable)

- Every 6-12 months: TAF, DTG, others

Patches

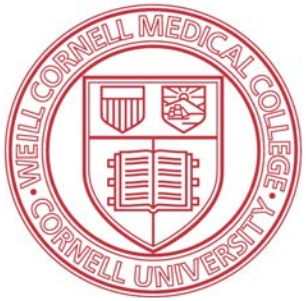
- CAB, TAF



+ new formulations, pro-drugs, and mechanisms of action: NRTTI, MI, bNAbs

Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH
- For slides:
  - Alexandra Calmy, Raj Gandhi, James McMahon, Chloe Orkin, Paul Sax, Melanie Thompson; HIV iBASE, NATAP, TAG
- The patient volunteers!

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EXTRA SLIDES

New and Investigational ART Agents

R.M. Gulick, MD, MPH

Rochelle Belfer Professor in Medicine

Chief, Division of Infectious Diseases

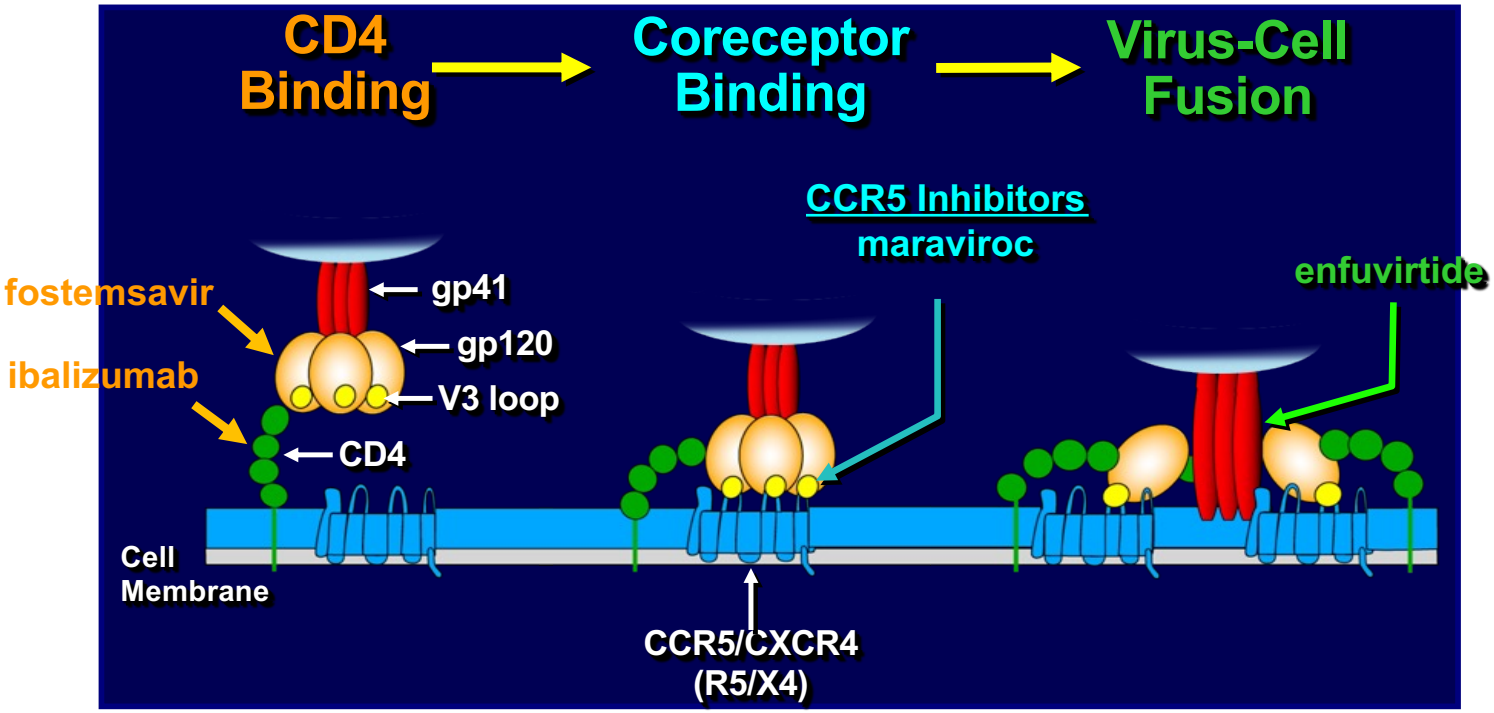
Weill Cornell Medicine

New York City, USA

New and Investigational ART Agents (partial list)

	NRTI	NNRTI	PI	EI	II	CI	MI	bNAb
Recently FDA-approved				fostemsavir	cabotegravir	lenacapavir		
Phase 3	azvudine islatravir	KM023 (ACC007)		albuvirtide semzuvolimab (UB-421)				
Phase 2	censavudine	elsulfavirine ulonivirine (MK-8507)	TMC 310911	cenicriviroc PF-232798	STP0404		GSK-254	VH3810109 N6LS PG121 PGDM1400 teropavimab VRC07-LS zinlirvimab
Phase 1/2	elvucitabine GS-1614 MK-8527	GS-5894	TMB-607	CPT31 lipovirtide temsavir	GS-1720 VH4524184	VH4004280 VH4011499	HRF-4467	

HIV Entry Inhibitors

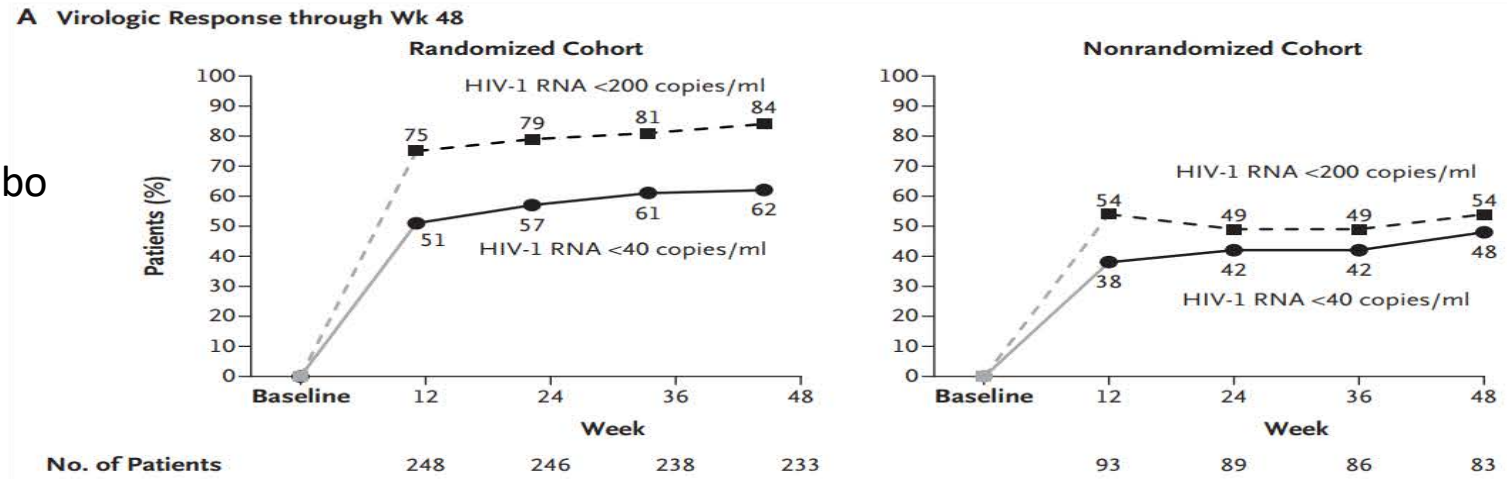


Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- **Phase 3** BRIGHTE Study Kozal NEJM 2020;382:1232-1243
  - Treatment-experienced patients with MDR HIV (N=272)
  - 2 cohorts
    - 1 remaining ART option: randomized to +/- **FTR** X 8d, then OBR + open-label **FTR**
    - No remaining ART options: OBR + open-label **FTR**
  - Results:

    Day 8 VL Δ (log cps/ml): 0.8 **FTR** vs. 0.2 pbo (p<0.001)

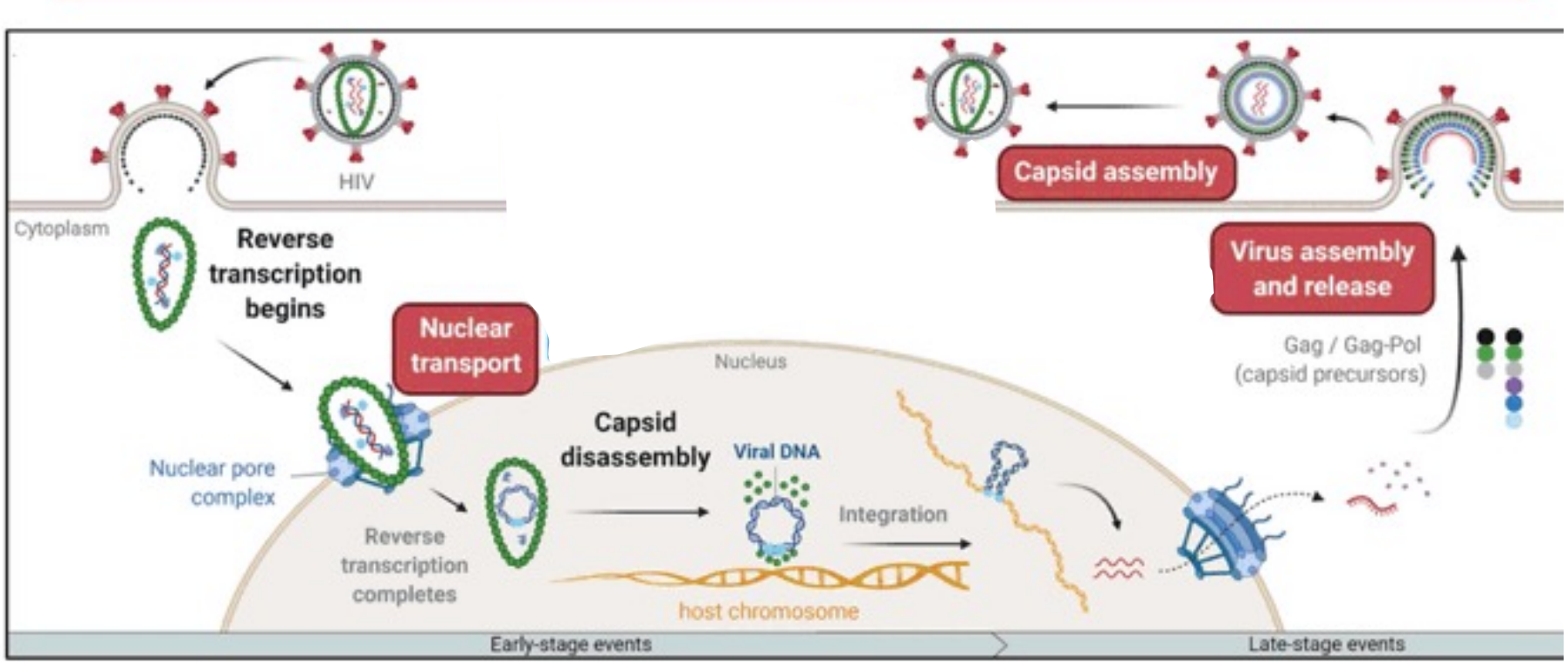


  - FDA approved for MDR HIV in 2020
    - 2-year data: Lataillade Lancet HIV 2020;7:e740-751
    - 5-year data: Aberg Infect Dis Ther 2023;12:2321-2335

Guidelines: CAB/RPV in Viremic Patients

- IAS-USA Sax JAMA 2024;331:1060-1061
- When supported by intensive follow-up and case management services, injectable CAB-RPV may be considered for people with viremia who meet the criteria below when no other treatment options are effective due to a patient's persistent inability to take oral ART (rating AIIa under the conditions described).
  - Unable to take oral ART consistently despite extensive efforts and clinical support
  - High risk of HIV disease progression (CD4 cell count <200/µL or history of AIDS-defining complications)
  - Virus susceptible to both CAB and RPV

HIV Capsid Inhibitors



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

Lenacapavir (LEN): Capsid Inhibitor

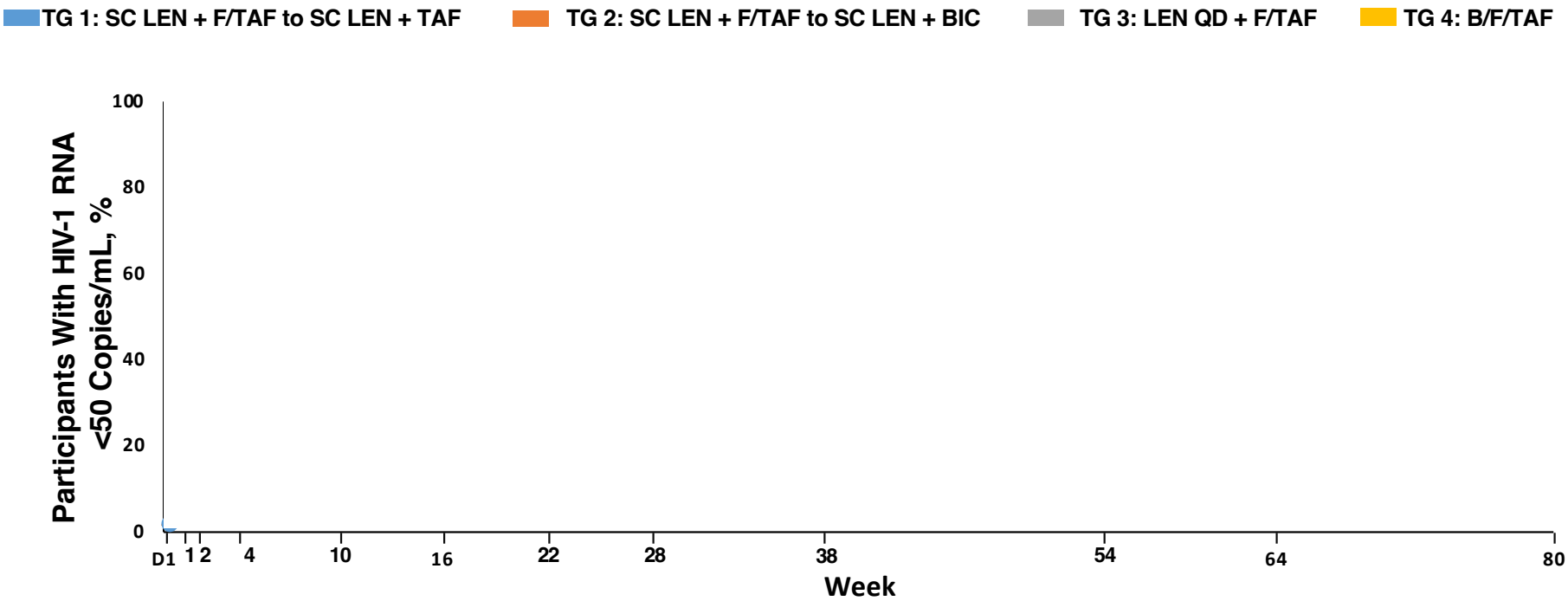
- **Phase 2/3** in heavily treatment-experienced (N=72): add oral LEN, then at day 15, optimize background ART and add LEN SC q6 months: ~82% <50 cps/ml at 26 weeks Segal-Maurer NEJM 2022;386:1793
  - FDA approved for heavily treatment-experienced pts in 2022

  - 52-week f/up: 30 of 36 (83%) <50 copies/ml Ogbuagu Lancet HIV 2023;10:e497-e505
  - 2-year f/up: 44 of 54 (82%) <50 copies/ml Ogbuagu CID 2024 (epub 8/29/24)
  - 12 (17%) with no fully active agents in OBR → 8 had VL <50 through 2 years Ogbuagu CROI 2024 #630

- Daily and weekly oral rx regimens; q6 month injectable rx regimens

CALIBRATE: LEN Phase 2 in Rx-Naïve Pts

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



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