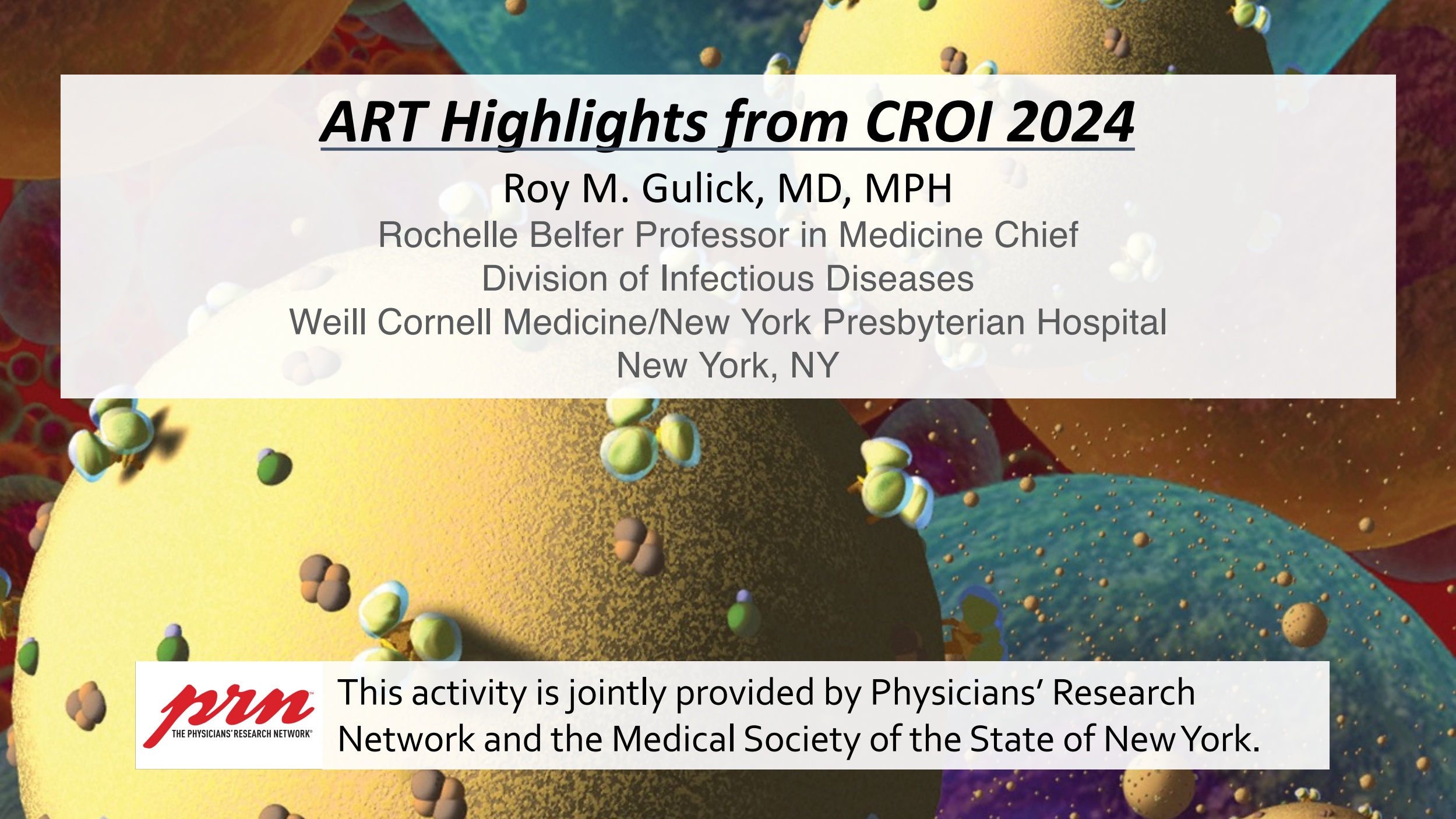
ART Highlights from CROI 2024

Roy M. Gulick, MD, MPH
Rochelle Belfer Professor in Medicine Chief
Division of Infectious Diseases
Weill Cornell Medicine/New York Presbyterian Hospital
New York, NY



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

Disclosures

- none

- 3635 attendees (including 438 virtually)
- 38% of attendees were international
- 73 countries represented

- 1682 submitted abstracts + 220 submitted late breakers
- 966 accepted abstracts + 111 accepted oral presentations

HEADLINES

IMPAACT P1115:
HIV Remission in Very Early Treated Children

- 54 infants with in-utero HIV-1 started ART within 48 hours of birth
  - 2 NRTIs + NVP with LPV/r added later at 42 weeks (up to 294 weeks)
- Offered analytical treatment interruption (ATI) if:
  - No plasma HIV RNA detected after 48 weeks
  - No HIV DNA detected in PBMC
  - Negative HIV serostatus (4th generation ELISA)
- Results:
  - 6 children underwent ATI (Uganda X 4, Tanzania X 1, Zimbabwe X 1)
    - 3 rebounded at 3, 8, and 80 weeks after ATI; 2 of them had acute retroviral syndrome
    - 3 remained suppressed at >44, 48, and 60 weeks after ATI
- Conclusion:
- ART-free remission achieved with very early ART for in-utero HIV

Persaud CROI 2024 #212

DTG Resistance

- **WHO Report** (3/5/24)
  - 91% of people on ART are on DTG (26 million people); $45/year
  - >90% of people taking DTG are suppressed
  - In 4 country surveys
    - Following VF in rx-naïve people, DTG resistance was <1%
    - Following VF in people who were treatment-experienced and had ↑ viral load levels, DTG resistance was 3.9-8.6%, up to >19%

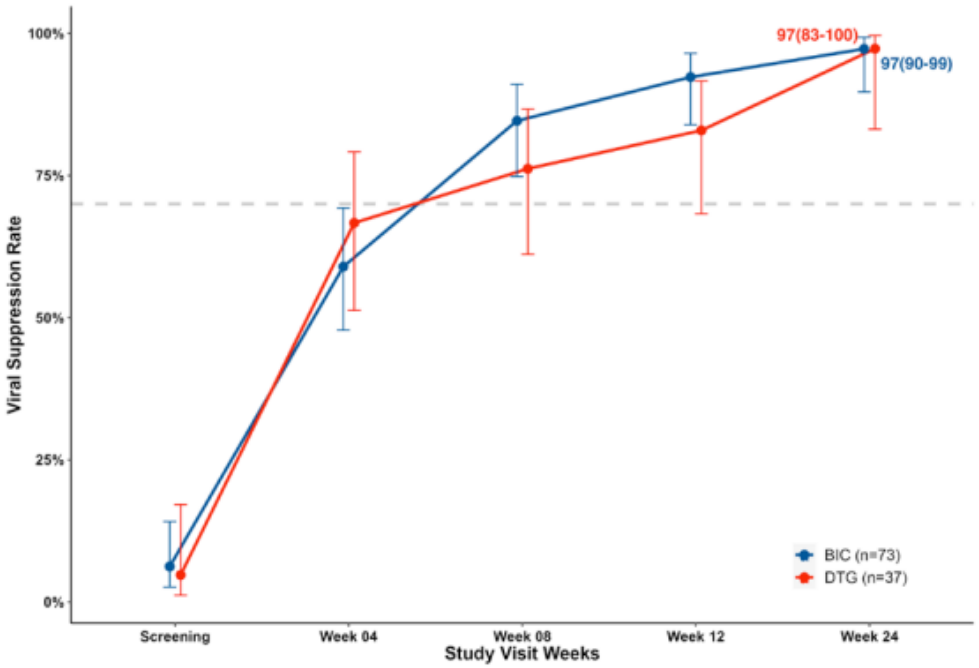
- **A5381** Wallis CROI 2024 #675
  - Cohort study of PWH switching from first-line NNRTI- or second-line PI- to DTG-based regimen with VL >1000 at 13 sites in Africa and Haiti
    - First-line NNRTI switch (N=44) →83% VL <200 at 6 months; no DTG mutations
    - Second-line PI switch (N=165) →67% <200 at 6 months; only 2 had new DTG mutations (G118R, R263K)
    - Viral suppression in both groups declined over 24 months to 76% and 61%
  - Conclusion: Suboptimal VS likely due to adherence issues

Update on Current Antiretrovirals for Treatment

INSIGHT: BIC and RIF Coadministration

- Phase 2b open-label, non-comparative, randomized controlled study
- Study population: PWH with CD4 >50 with TB on a rifampin-based regimen with/without prior ART
  (N=122, 43%F, 42% VL >100K, 59% CD4<200)
- Study treatment: randomized 2:1 to
  - TAF/FTC/BIC bid
  - standard of care (TFV/3TC/DTG + 2nd dose DTG)
- Results:
  - PK: BIC troughs
    - +RIF 0.397 mg/dl; -RIF 2.29 mg/dl); 73% ↓
  - HIV RNA <50 (wk 24): 97% (BIC) and 97% (DTG)

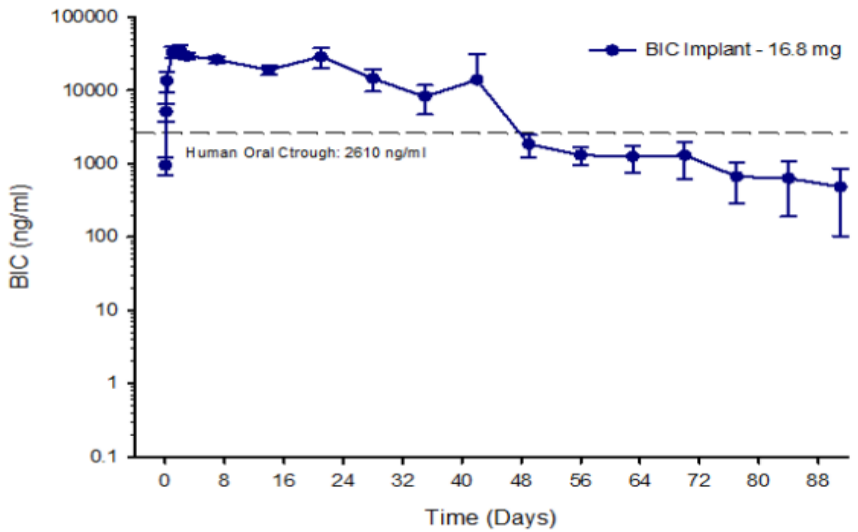
Conclusion: Supports use of BIC bid with RIF



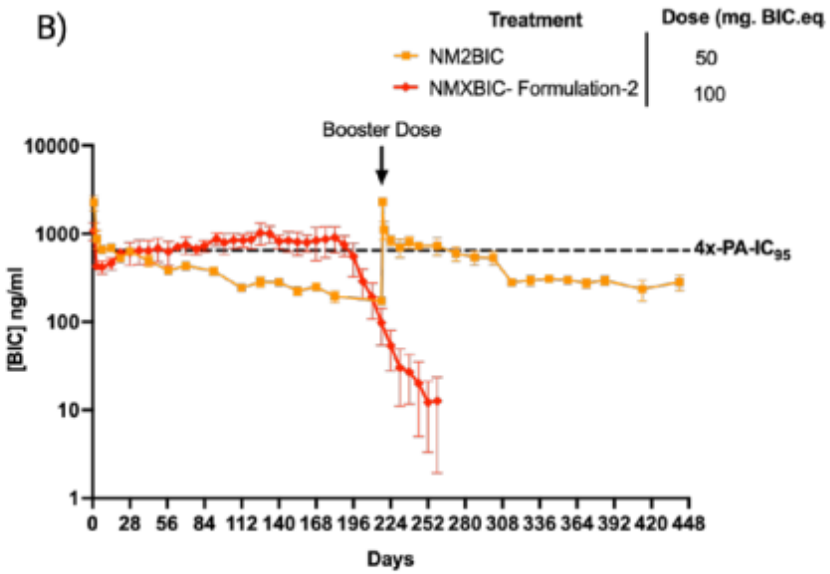
Naidoo CROI 2024 #211

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



Cabotegravir (CAB)

- 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

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

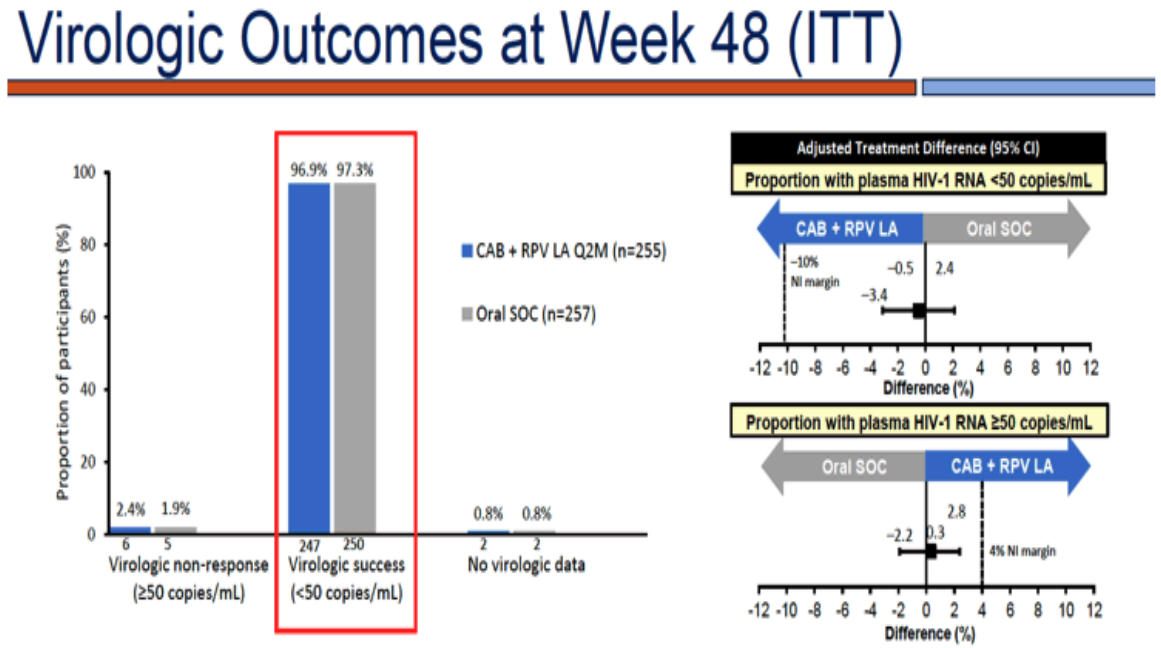
- 2022: FDA approves CAB for PrEP

African CAB/RPV (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)

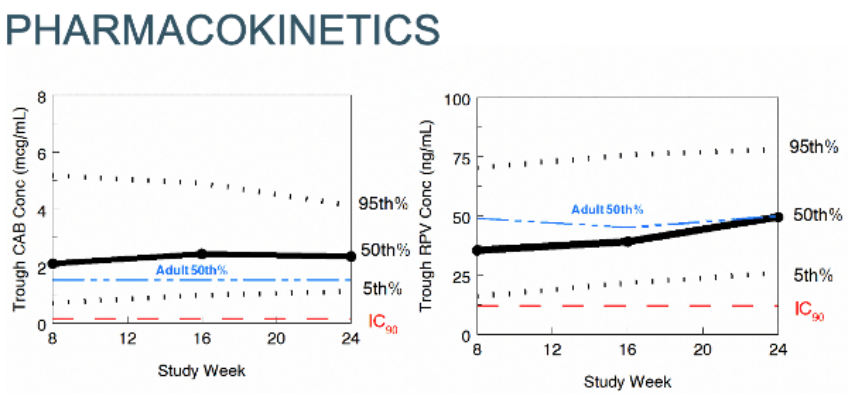
- Study treatment: Continue ART or change to CAB/RPV q8wks
- Results (48 weeks):
  - 4 withdrew (2 in each group)
  - VL <50: 98% (ART) vs. 97% (LA) → met non-inferiority
  - one VF in LA group; one AE (inj site abscess)→D/C
- Conclusion LA safe, effective, non-inferior; may be considered for Africa



Kityo CROI 2024 #122

Adolescents CAB/RPV (MOCHA/IMPAACT 2017)

- Phase 1/2 noncomparative open-label 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

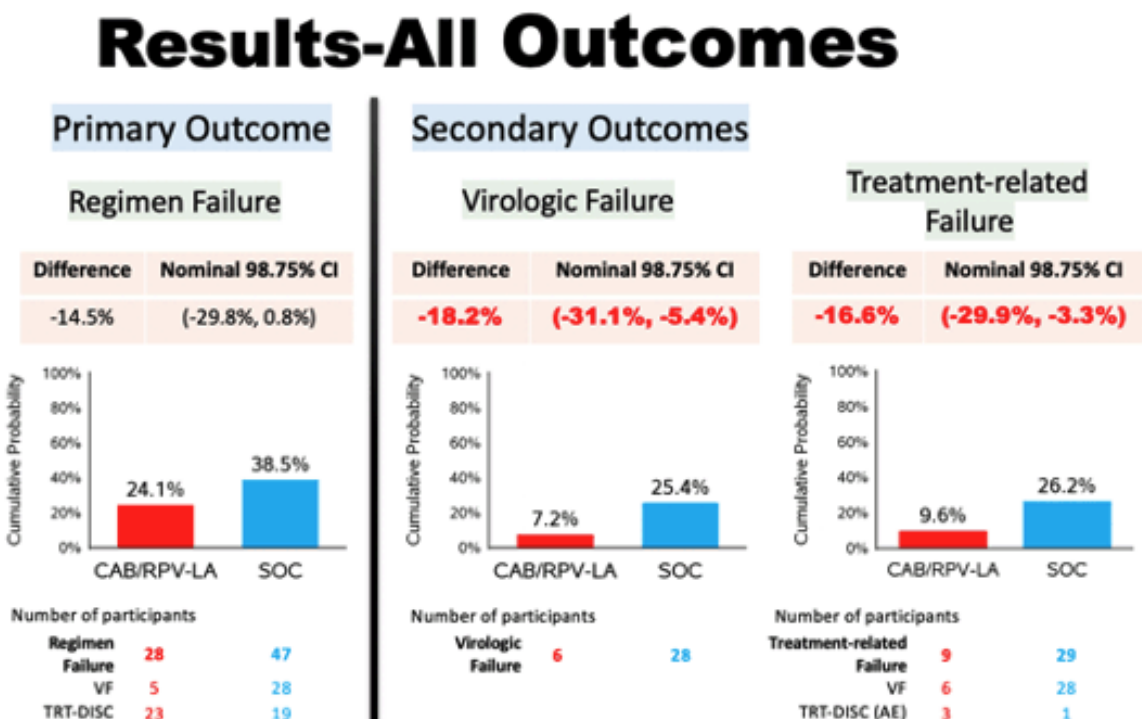


Gaur CROI 2024 #188

A5359 LATITUDE: CAB/RPV in Suboptimal Adherence

- Phase 3 randomized, multicenter, open-label ACTG study; noninferiority Δ10
- 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

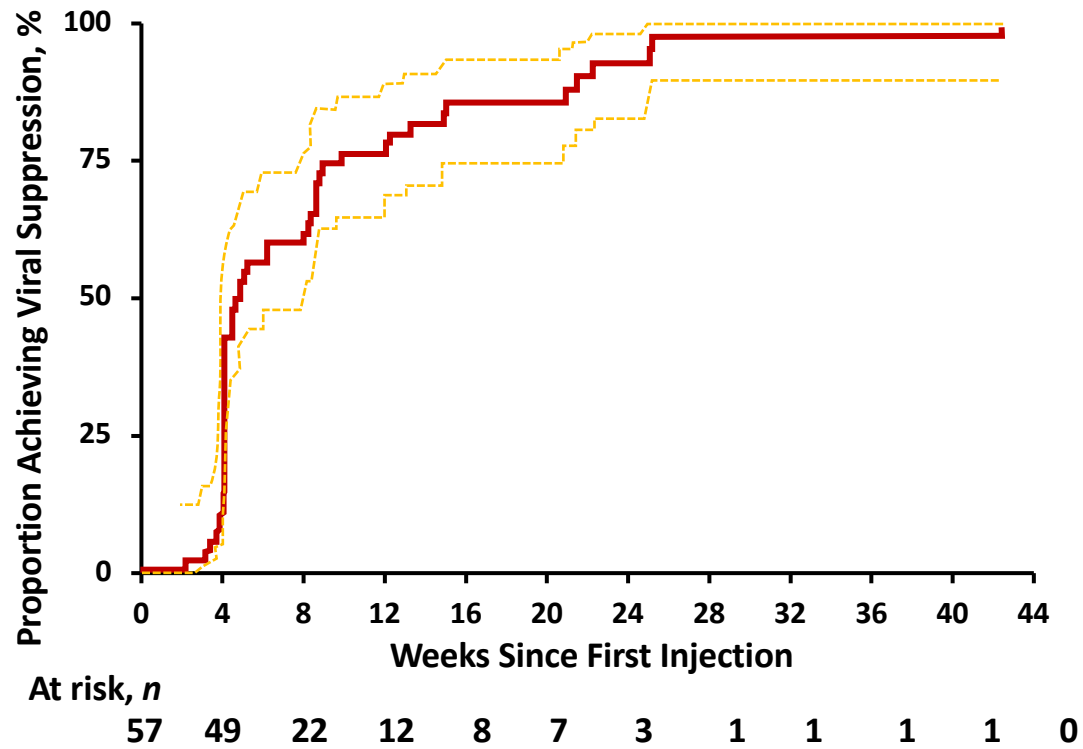


Rana CROI 2024 #212

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).



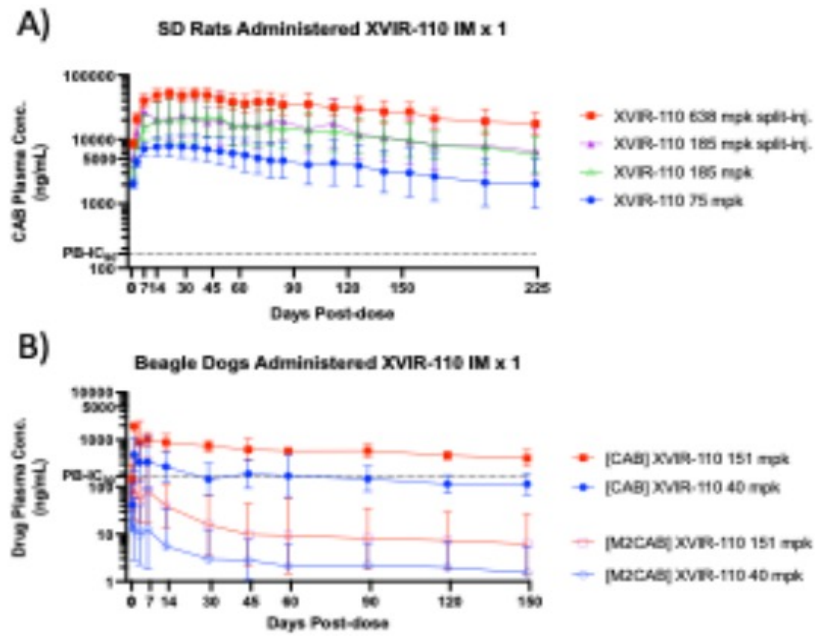
Gandhi Ann Intern Med 2023;176:969-974

Update:
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)

Gandhi CROI 2024 #628

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
  - 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



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: 78% <50 copies/ml Ogbuagu Lancet HIV 2023;10:e497-e505
  - 2-year f/up: 82% <50 copies/ml Ogbuagu IDWeek #1596
  - 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

ARTISTRY-1: Δ to BIC + LEN

- Phase 2 randomized, open-label, multicenter 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
- Next: Phase 3 BIC/LEN STR enrolling!

Mounzer CROI 2024 #642

Case Series: CAB + LEN

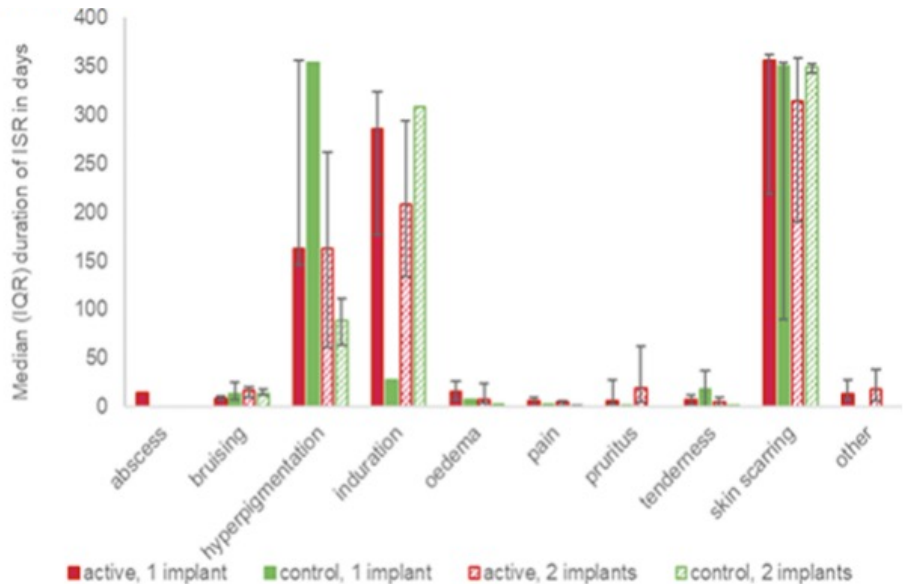
- Case series from UCSF, UCSD, Cleveland, UPenn
- Study population: PWH with adherence challenges to oral ART (N=34, 76%M, 41%B, 38%L, 56% housing insecurity and/or substance use; 71% on CAB q8wks, 47% VS)
- Treatment: CAB q 4 or 8 wks +/- RPV + LEN (oral→q6 mo SQ)
  - 68% added LEN to CAB/RPV, 32% used 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

Update on Current Antiretrovirals for Prevention

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

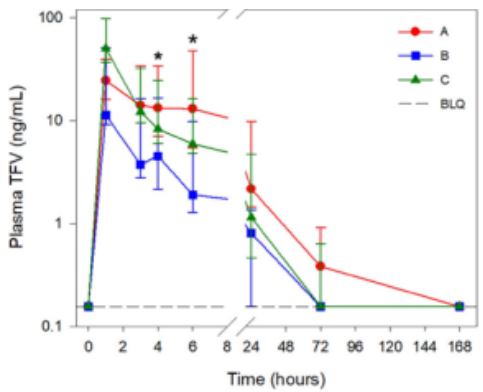
- Phase 1 safety and PK/PD study
- Study population: 9 men
- Study treatment: TFV 660mg in 125 ml hypo-osmolar saline with various sequences:

  (A) 3 TFV douches

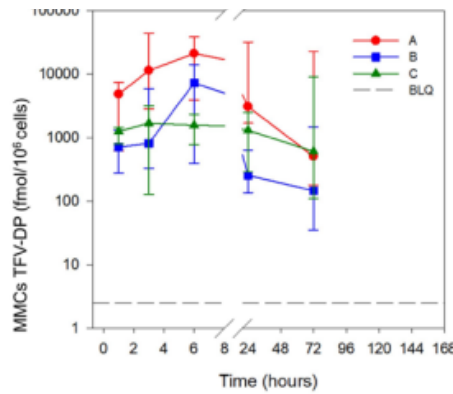
  (B) one TFV douche, then 2 tap water douches

  (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

Pilot Study: TAF/FTC/BIC for PEP

- Cohort study
- Study population: Pts without HIV with confirmed/potential sexual HIV exposure seeking PEP (N=119, 86%MSM, median age 29, 22% prior PEP use)
- Study treatment: baseline HIV testing, changed to TAF/FTC/BIC X 28d
- Results:
  - Of 101 pts with data, 99 completed 28 days of PEP
  - 38% experienced possibly related AE;11% had ≥grade 2 AE
  - no HIV seroconversions

Conclusion: high adherence, generally well-tolerated; no seroconversions Supports use of TAF/FTC/BIC for PEP

Tan CROI 2024 #1134

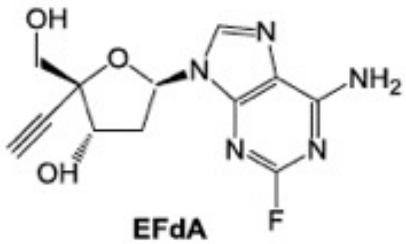
LEN for HIV Prevention

- Lenacapavir (SQ every 6 months)
  - Protected macaques against rectal SHIV challenge
    Bekerman JCI 2023;133:e167818
  - Phase 3 studies (vs. TFV/FTC) www.clinicaltrials.gov
    - PURPOSE 1: Adolescent Girls / Young Women in South Africa and Uganda
    - PURPOSE 2: MSM / TGW in U.S., South Africa, Peru, Brazil
    - PURPOSE 3 / HPTN 102: Cisgender Women in U.S.******
    - PURPOSE 4 / HPTN 103: PUID in U.S.
    - PURPOSE 5: People who would benefit from PrEP - France, UK

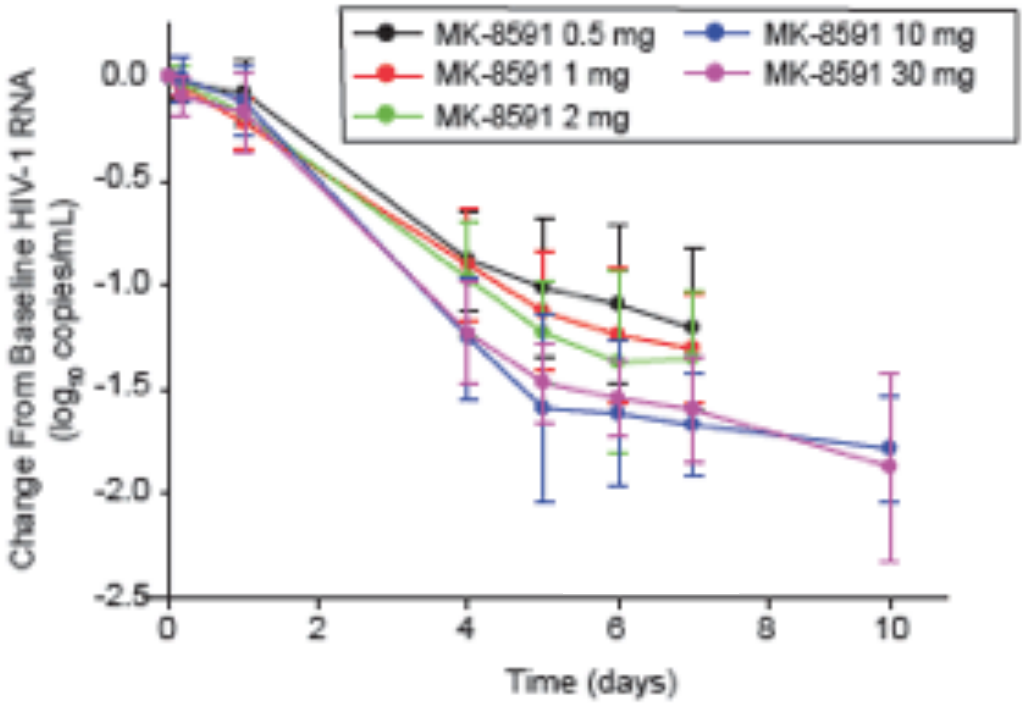
Investigational Agents

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 strains)
- 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, yearly



EFdA



Schurmann Lancet HIV 2020;7:e164-e172

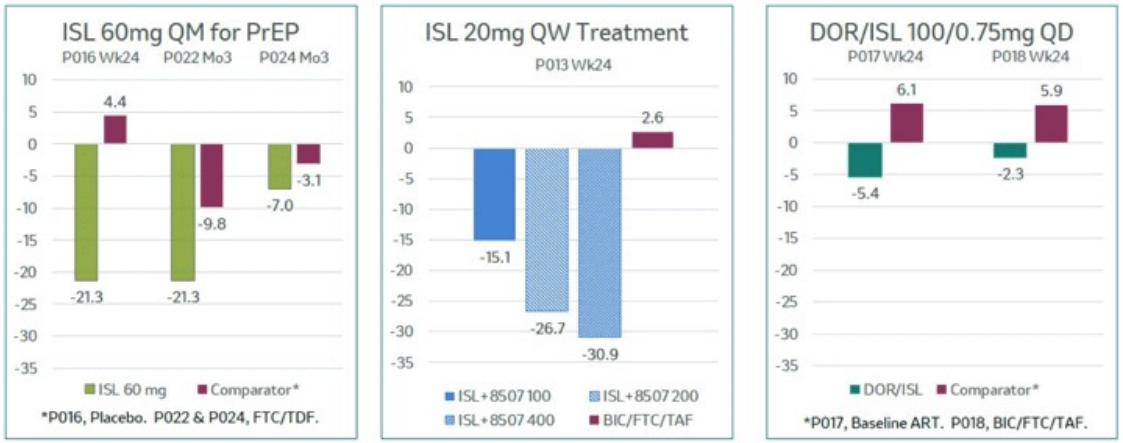
Islatravir (ISL): Phase 3 Studies

- 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 EACS 2023
  - Study 018: Continue TAF/F/BIC or change to ISL/DOR
    - >84% with VL <50 cps/ml at wk 48 Paredes EACS 2023
  - Conclusion: ISL/DOR non-inferior in both studies

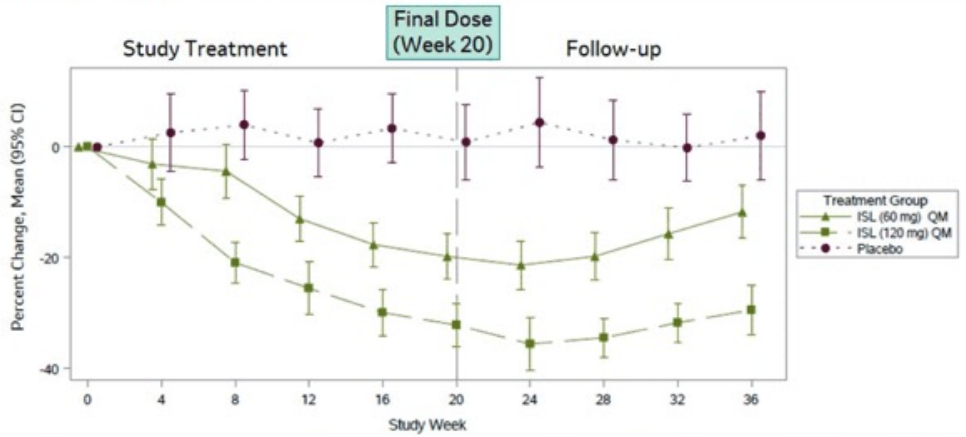
- **Phase 3** study in rx-naïve pts (N=597)
  - ISL/DOR vs. TAF/F/BIC
    - >88% with VL <50 cps/ml at wk 48 in both groups
  - Conclusion: ISL/DOR non-inferior Rockstroh IAS 2023 #OALBX0102

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

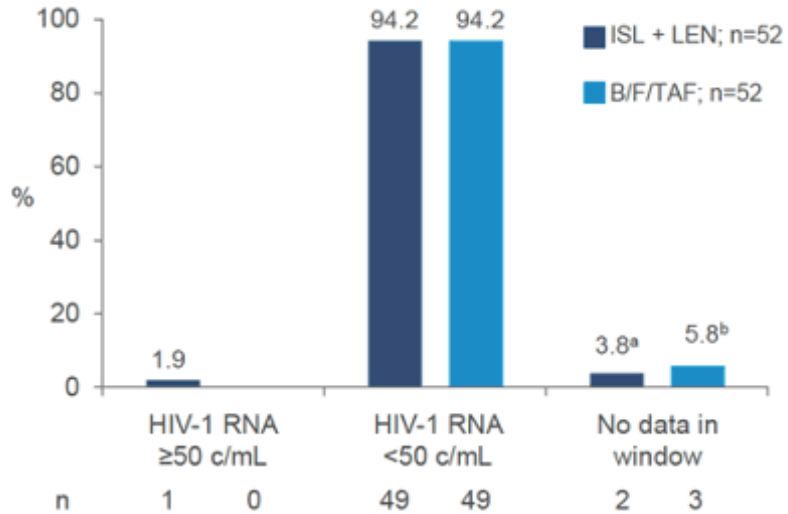


- FDA placed **clinical hold** on studies with oral, injectable, and implantable ISL
- No other blood cell lines affected (other WBC, RBC, platelets)
- No signals in earlier animal or phase 1-2 studies
- Likely mechanism: ↑ISL-TP levels inhibits DNA polymerase-α→ apoptosis
- Not mitochondrial toxicity
- Dose-dependent, reversible, not associated with ↑ infections
- Solution: Modeling suggests 0.25 mg daily / 2 mg weekly optimal

Squires CROI 2023 #192 and Lebron EACS 2023

Weekly Oral Therapy: ISL + LEN

- Phase 2 randomized, open-label, controlled study
- 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; 19%w)
- 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
- Phase 3 enrolling!

Colson CROI 2024 #208

MK-8527 Oral Long-Acting NRTTI

- Prior preclinical and phase 1 studies in people without HIV showed PK supports weekly (or longer) dosing
  Raheem CROI 2024 #638 + Gillespie CROI 2024 #129
- Two Phase 1 oral single-dose studies
- Study population: PWH, ages 18-60 with no prior ART (N=31)
- Study treatment:
  - Single dose of MK-8527: 0.5, 1, 3, or 10 mg
- Results:
  - VL change (copies/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 treatment + prevention

Carstens CROI 2024 #115

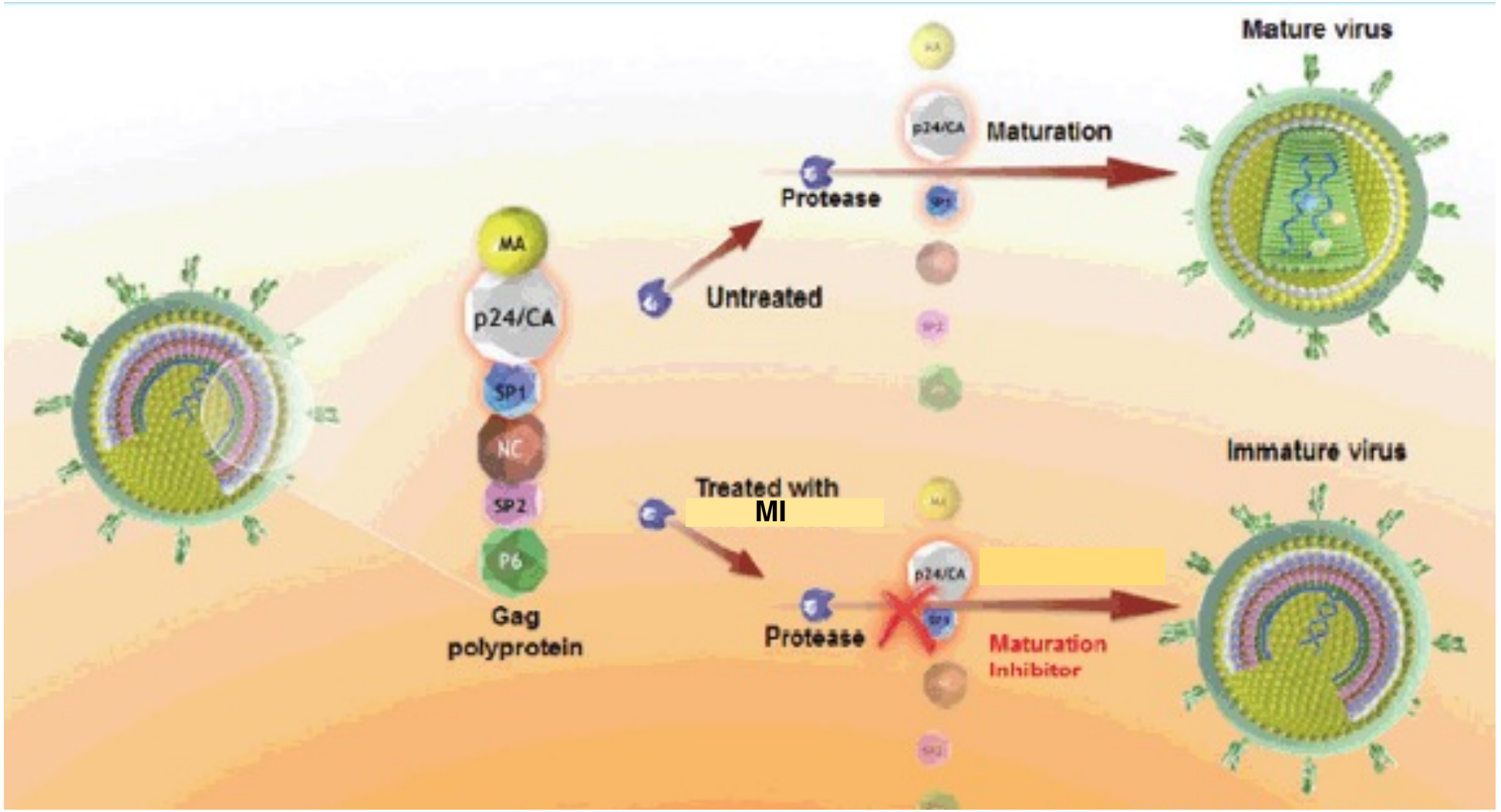
GS-1720 Oral Long-Acting INSTI

- Phase 1b oral open-label multicohort study
- Study population: PWH, rx-naïve or off ART X 12 weeks (N=7)
- Study treatment:
  - GS-1720 450 mg days 1 and 2; followed for 10 days
- Results:
  - Median half-life 9 days
  - Mean HIV RNA ↓ 2.44 log copies/ml (day 11)
  - Generally well-tolerated
  - No rx-emergent INSTI resistance
- Conclusion: Potent antiretroviral activity; PK supportive of weekly dosing; potential for once-weekly regimen

Fichtenbaum CROI 2024 #116

New Mechanisms of Action

HIV Maturation Inhibitors (MI)



Freed CROI 2024 #27

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 2a Joshi EACS 2023
  - Phase 2b: 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 in progress

HIV Broadly Neutralizing Antibodies (bNAbs)

V1/V2 Loop

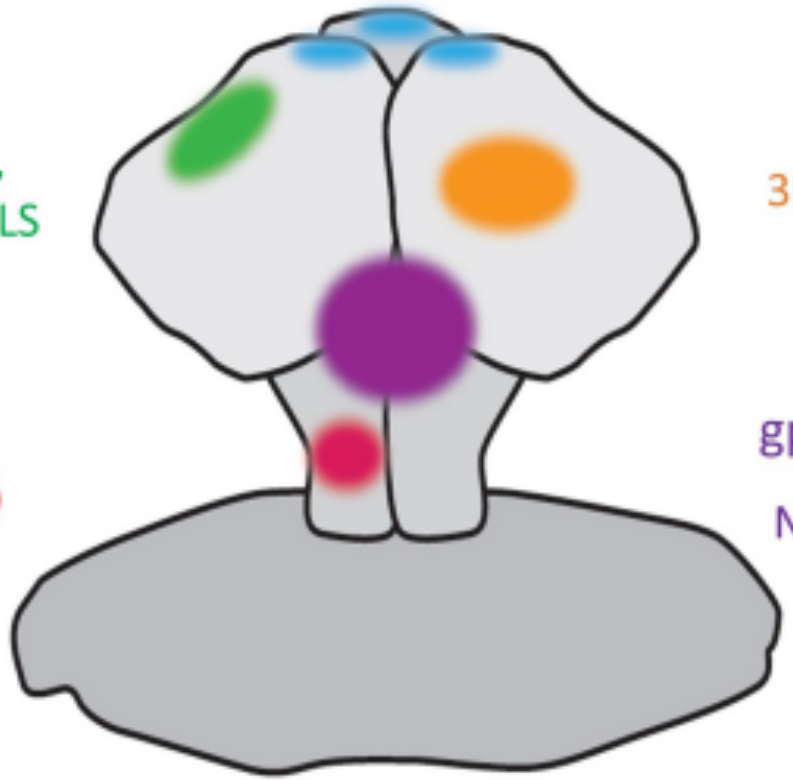
PGDM1400, CAP256V2LS

V3 glycan

10-1074, 10-1074LS,
PGT121, PGT121.414.LS

CD4 binding site

VRC01, VRC01-LS,
3BNC117, 3BNC117-LS,
VRC07-523LS, N6LS



Membrane-proximal external region (MPER)

10E8VLS

gp120-gp41 interface

Not yet in clinical trials

HIV envelope glycoprotein trimer

Adapted from Hsu Front Immunol 2021;12:710044

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

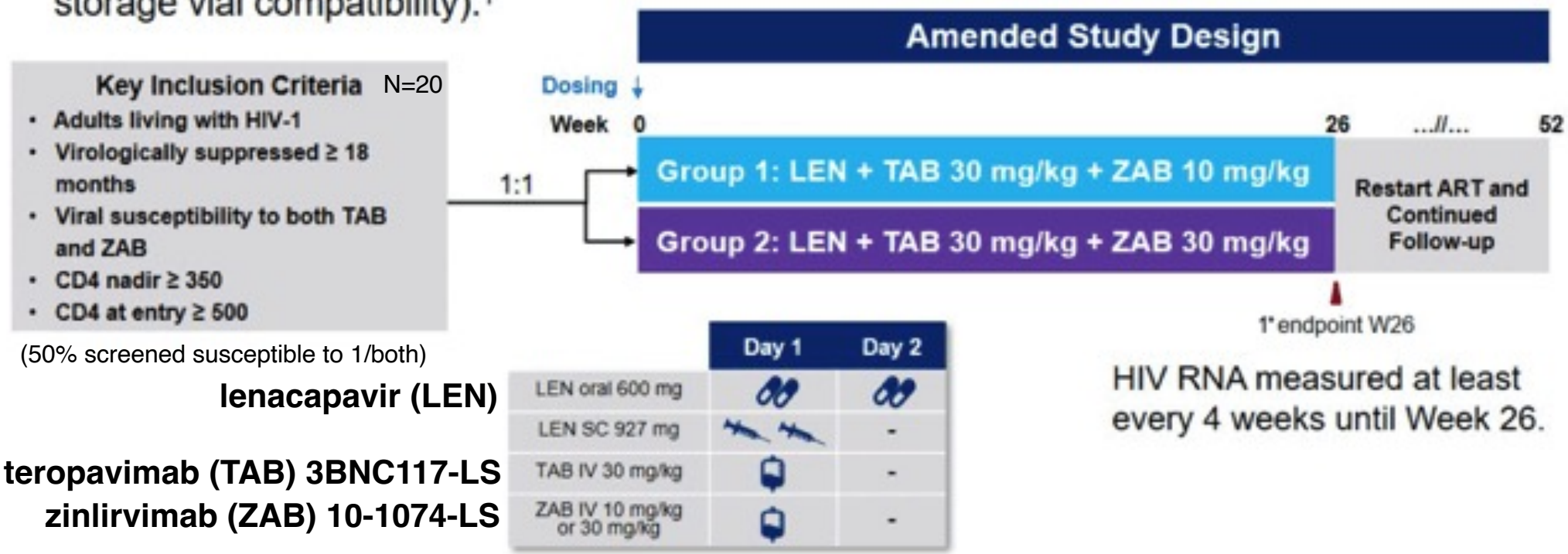
Awan Curr Opin HIV AIDS 2022;17:247-257

- 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

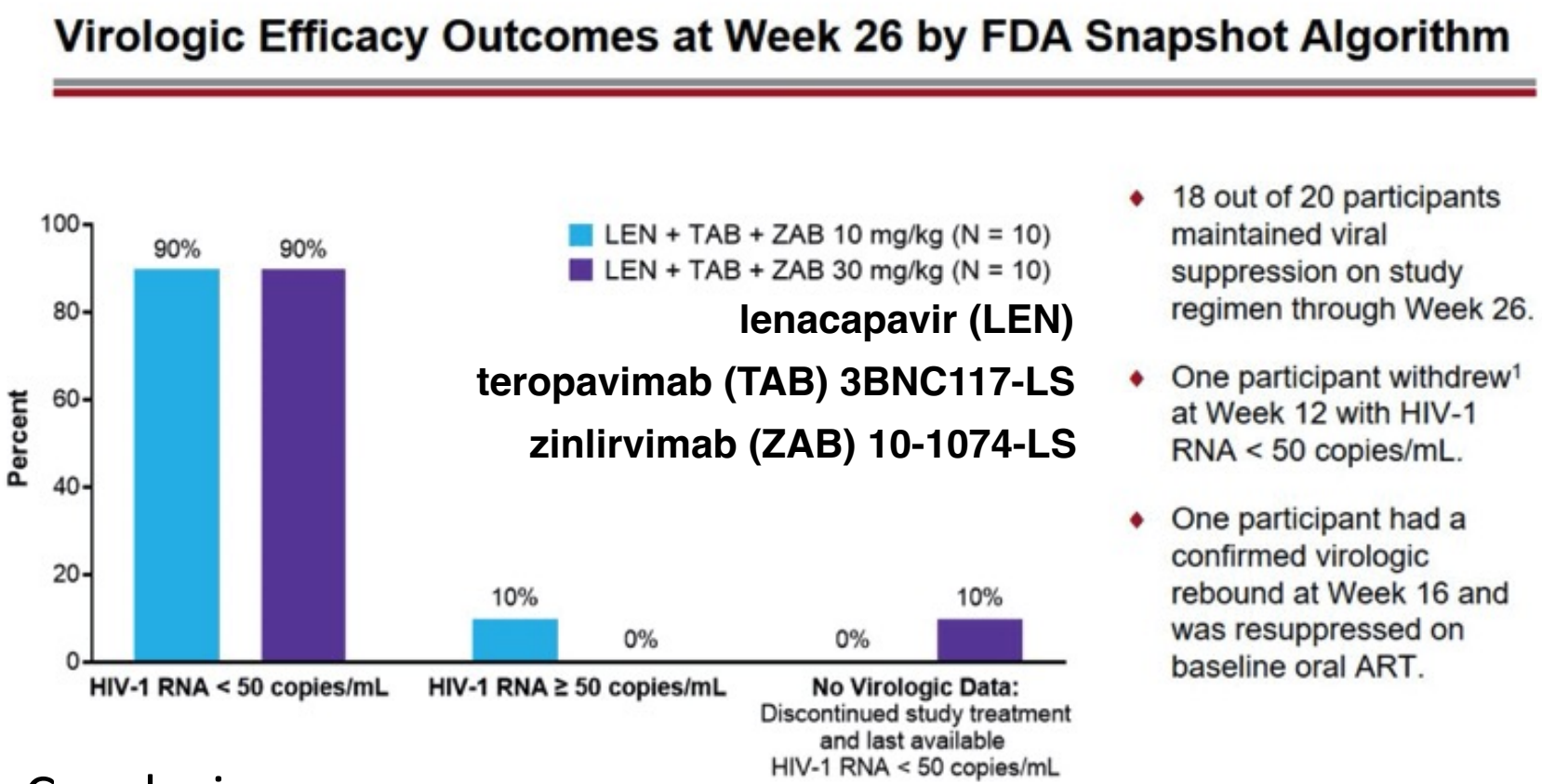
- Randomized, blinded phase 1b study assessing safety and efficacy of a long-acting regimen LEN + TAB + ZAB administered in two different doses. (NCT04811040)
- Study design was modified when LEN was unavailable due to temporary clinical hold (for storage vial compatibility).[1]



Eron Lancet HIV (online 1/30/24)

Pilot Study: LEN + 2 BNAbs

- Results:



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

Eron Lancet HIV (online 1/30/24)

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 Juelg CROI 2024 #121
  - 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

COVID-19
Treatment

Extended Duration Nirmatrelvir/r (NMV/r)

- Phase 2 multinational randomized double-blind study
- Study population: non-hospitalized immunocompromised people over 12 years old with symptomatic COVID-19 within 5 days of dx
- Study procedures:
  - randomized to NMV/r 300/100 mg twice daily for 5, 10, or 15 days
  - nasopharyngeal swabs for PCR and rapid Ag testing: baseline, days 5, 10, 15, 21, 28, 35, 44
- Primary endpoint: NP SARS-CoV-2 RNA below the limit of quantification (2 log cps/ml) from day 15→44
- Results:

  viral suppression rates: 62% (5d), 71% (10d), 66% (15d)

- Conclusion: 5 day of NMV/r is adequate for viral clearance in non-severely immunocompromised patients

Weinstein CROI 2024 #658

AGILE-CST-8 Study: Combination NMV/r + Molnupiravir

- Phase 1 adaptive dose open-label descalation study
- Study population: Adults with mild-moderate acute SARS-CoV-2 infection within 5 days of symptoms (N=24)
- Study treatement: randomized 2:1 to
  - NMV/r 300/100 + MOL 800, 600, or 400 mg bid
  - standard of care
- Results:
  - no dose-limiting toxicities or SAE occurred
  - 14/16 (88%) reported grade 1-2 AE, mostly GI, taste
  - no difference in VL levels at 0-5 days or day 11
  - negative PCR at day 5: 69% (combo) vs. 63% (SOC)
- Conclusion: combo generally well-tolerated; larger studies needed

Khoo CROI 2024 #668

POSITIVES Study: Antiviral Resistance in COVID-19

- Prospective observational cohort study
- Study population: Non-hospitalized pts with acute SARS-CoV-2 infection, treated with nirmatrelvir/ritonavir (N/R; n=53), remdesivir (RDV; n=14), or untreated (n=42)
- Study methods:

  collected nasal swabs 3X/week during first 2 wks after diagnosis

  deep sequencing of nsp5 and nsp 12
- Results:
  - pts who received antivirals were older, more immunosuppressed, had received more vaccinations
  - emergent N/R mutations: 9% (N/R) vs. 05 (untreated) p=0.06
  - mutations generally were <25% of viral population and reverted to wildtype following rx cessation
  - viral rebound 28% (N/R); resistance in 13% with rebound vs. 8% without rebound p=0.6
  - RDV mutations 14% all low frequency and reverted to wildtype
- Conclusion: antiviral mutations emerge, but they are transient, present in minor frequencies and are not associated with viral rebound; risk of widespread resistance remains low

Tamura CROI 2024 #135

CROI 2025: March 9-12

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
- NATAP
- The patient volunteers!

rgulick@med.cornell.edu


Thank You for Your Attendance!
Please visit us at:
www.prn.org