HIV UPDATE 2023
CONNECTICUT INFECTIOUS DISEASE SOCIETY MEETING

- **David S. Rubin MD**
- **Medical Director**
- **Circle Care Center**
- **Norwalk, CT**

DISCLOSURES:

- SPEAKER – VIIV HEALTHCARE
- ADVISORY BOARDS – THERATECHNOLOGIES
- RESEARCH SUPPORT – CYTODYN, SANGAMO THERAPEUTICS, GILEAD SCIENCES

HIGHLIGHTS OF ART

GUIDELINE UPDATES

1. RECOMMENDATIONS ON WHEN AND WHAT TO START

2. RAPID START

3.BREAST FEEDING

4. USPSTF HIV PREP

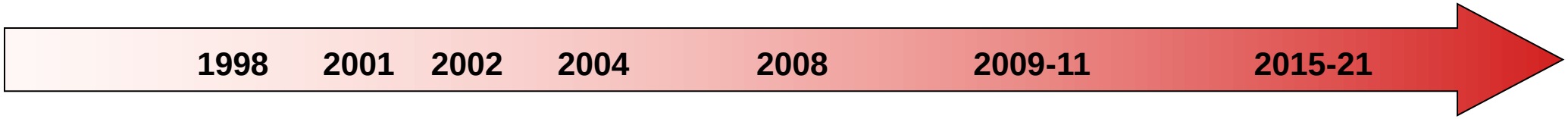
LATEST DATA ON NEWEST AGENTS

1. CAB+RPV

2. LENACAPRAVIR

3. PREP
    A. CAB LA/LEVI SYNDROME
    B. DOXYPEP
    C. PIPELINE

Evolution to Initiating Treatment Immediately to Improve Outcomes



FACTOR	RECOMMENDATION FOR TREATMENT						
AIDS	Treat	Treat	Treat	Treat	Treat	Treat	Treat
CD4	<500	• Recommended at <200 • Offer at <350 • Individualize decision at >350			• Recommended <350 • Risks/Benefits >350	• Recommended <500 • Favor/Optional >500	Treat immediately following diagnosis, or as soon as possible, to increase uptake of ART and linkage to care, decrease time to viral suppression, and improve rate of viral suppression
Viral Load	>20,000	>55,000		>100,000	No specific viral load		
Other Factors					Pregnant women HBV co-infected HIVAN		ART recommended for HIV-infected individuals to reduce morbidity and mortality, and for the prevention of HIV transmission

DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, Jan 2022. Available at: http://aidsinfo.nih.gov/guidelines. Accessed Feb 2022.

Recommendations for When to Start ART

Guideline	Recommendation (Strength/Quality)
DHHS[1]	• ART is recommended for all individuals with HIV, regardless of CD4 cell count, to reduce the morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI)** • ART should be initiated immediately, or as soon as possible, after HIV diagnosis to increase the uptake of ART and linkage to care, decrease the time to viral suppression, and improve the rate of suppression among persons with HIV **(AII)** • When initiating ART, it is important to educate patients regarding benefits of ART, and to deploy strategies to optimize care engagement and treatment adherence **(AIII)**

IAS-USA[2]	• ART should be initiated as soon as possible after diagnosis, ideally within 7 days, including on the same day as diagnosis or at the first clinic visit if the patient is ready and there is no suspicion for a concurrent OI **(AIII)**
	• Structural barriers that could delay receipt of ART (including same-day), and impede care engagement, continuous ART access, and ART adherence should be identified and addressed using evidence-informed strategies **AIIa)**
	• Initiation of ART at the time of diagnosis of acute HIV infection is recommended **(AIIa)**
	• Initiation of ART is recommended within 2 weeks of initiation of treatment for most OIs
	  • In active TB without evidence of TBM, ART should be initiated within 2 weeks after initiation of TB treatment, especially when CD4 cell count <50 cells/μL **(AIa)**
	  • In TBM, high-dose steroids should be initiated along with TB treatment and ART should be initiated within 2 weeks after starting TB treatment and steroids **(BIa)**
	  • For individuals with cryptococcal meningitis with access to close monitoring and supportive care for AEs, ART should be initiated 2–4 weeks after starting antifungal therapy **(BIIb)**; ART-naïve individuals who have asymptomatic cryptococcal antigenemia and a negative lumbar puncture result with no evidence of cryptococcal meningitis should start ART immediately **(BIII)**
	  • Initiation of ART is recommended immediately in the setting of a new diagnosis of cancer with attention to DDIs **(BIIa)**

EACS[3]	• ART is recommended in all PLWH, irrespective of CD4 count • Starting ART on the same day after diagnosis is feasible and acceptable for newly-diagnosed individuals • Nevertheless, assessment of the readiness to start ART is essential to allow to express the person's preference and not feel pressured to start ART immediately, unless clinically indicated

DDI, drug-drug interaction; OI, opportunistic infection; TB, tuberculosis; TBM, tuberculous meningitis

1. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, Sept 2022. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed Nov 2022; 2. Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society–USA Panel. JAMA. 2023;329(1):63–84. Available at https://jamanetwork.com/journals/jama/fullarticle/2799240. Accessed January 2023; 3. EACS. Guidelines Version 11.1, October 2022. Available at https://eacs.sanfordguide.com/. Accessed November 2022

Global Recommended Initial ART Regimens

IAS-USA 2022[1]
FOR MOST PEOPLE WITH HIV
BIC[±]/FTC/TAF[¥]
DTG[±] + TAF[¥]/FTC or TDF[¥]/(FTC or 3TC)
DTG[±]/3TC[¤]

DHHS 2022[2]
FOR MOST PEOPLE WITH HIV WITH NO HISTORY OF CAB-LA PrEP
BIC/FTC/TAF[‡]
DTG/3TC[‡]/ABC[**]
DTG + (TAF or TDF)[*] + (FTC or 3TC[‡])
DTG/3TC[§]
FOR MOST PEOPLE WITH HIV WITH A HISTORY OF CAB-LA PrEP[§§]
bDRV + (TAF or TDF)[*] + (FTC or 3TC[‡])

EACS 2022[3]
RECOMMENDED REGIMENS[Ω]
BIC/FTC/TAF[II]
DTG + ABC/3TC[I,II] or DTG/ABC/3TC[I,II]
DTG + (TAF/FTC or TDF/XTC)[II,III]
RAL[‡] + TAF/FTC or TDF/XTC[II,III,IV]
XTC + DTG or 3TC/DTG[II,V]
DOR + (TAF/FTC or TDF/XTC) or TDF/3TC/DOR[II,III,VI]

Click on the blue annotation symbols to access footnotes

Recommended for rapid start

1. Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society–USA Panel. JAMA. 2023;329(1):63–84. Available at:https://jamanetwork.com/journals/jama/fullarticle/2799240. Accessed January 2023
2. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, Sept 2022. Available at:https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed Nov 2022.
3. EACS. Guidelines Version 11.1, October 2022. Available at https://eacs.sanfordguide.com/. Accessed November 2022

Recommendations for Rapid/Immediate ART Initiation

IAS-USA 2022[1]	DHHS 2022[2, 3]	EACS 2022[4]
• ART initiation as soon as possible after diagnosis, ideally within 7 days, including on the same day as diagnosis or at the first clinic visit if the patient is ready and there is no suspicion for a concurrent opportunistic infection. • Only triple therapy is recommended for rapid ART start	• ART should be started immediately or as soon as possible after diagnosis for adults and children of all ages • Only triple therapy is recommended for rapid ART start	• ART is recommended in all adult PLWH irrespective of CD4 counts • If ART is to be initiated before genotypic testing results are available, it is recommended to select a first line regimen with a high barrier to resistance

Recommended Regimens (Adults)			
	No CAB-LA PrEP	CAB-LA PrEP	
BIC/FTC/TAF	**BIC/FTC/TAF**		PI/b or second generation INSTI
DTG + TAF/FTC or TDF/(FTC or 3TC)	DTG + (TAF or TDF) + (FTC or 3TC)		
	(DRV/r or DRV/c) + (TAF or TDF) + (3TC or FTC)	(DRV/r or DRV/c) + (TAF or TDF) + (3TC or FTC)	

1. Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society–USA Panel. JAMA. 2023;329(1):63–84. Available at https://jamanetwork.com/journals/jama/fullarticle/2799240. Accessed January 2023
2. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, Sept 2022. Available at: : https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. Accessed Nov 2022.
3. DHHS. Guidelines for the use of Antiretroviral Agents in Pediatric HIV Infection, Apr 2022. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf. Accessed 29 Nov. 2022
4. EACS. Guidelines Version 11.1, October 2022. Available at: https://eacs.sanfordguide.com. Accessed November 2022

Updated DHHS Guidance for Women Living with HIV who Desire to Breastfeed

Infant Feeding Considerations	
Health benefits from breastfeeding	**Infant:** lower risk of infants developing asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome, gastrointestinal infections, and necrotizing enterocolitis **Breastfeeding parent:** decreased risk of hypertension; type 2 diabetes, and breast and ovarian cancers
Equity Considerations	Black women are disproportionately affected by HIV People of color experience a greater burden of many health conditions that may be alleviated by breastfeeding
Cultural Considerations	Environmental, social, familial, and personal pressures to consider breastfeeding Fear that not breastfeeding would lead to disclosure of their HIV status

Individuals with HIV with a consistently suppressed viral load during pregnancy (at minimum 3rd trimester) should be counseled on formula feeding, banked donor milk, or breastfeeding

Maintaining viral suppression during pregnancy and postpartum decreases breastfeeding transmission risk to less than 1%, but not zero

Breastfeeding should be stopped immediately in the case of a detectable viral load

DHHS guidelines recommend to support parental choice through shared decision making, not a specific infant feeding mode

1. Levison et al. CROI 2023 OA-6; 2. DHHS. Perinatal Guidelines. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. January 2023. Accessed Feb 2023.

United States Preventive Services Task Force (USPSTF) Recommendation for PrEP

2019 Recommendation Summary	Grade
The USPSTF recommends that clinicians offer PrEP with effective antiretroviral therapy to persons who are at high risk of HIV acquisition	**A**

2021 DHHS Guidance

- **On June 11, 2019, the USPSTF released a recommendation with a Grade A rating that clinicians offer PrEP with effective antiretroviral therapy to persons who are at high risk of HIV acquisition**
- **When medically/clinically appropriate, health insurance plans covered by the ACA must cover certain PrEP medications and PrEP related ancillary tests and services (e.g. HIV testing, renal monitoring, adherence counseling) consistent with the USPSTF recommendation without cost sharing for plan or policy years beginning on or after June 30, 2020**
- **When PrEP is deemed medically necessary for an individual specified in the USPSTF recommendation, as determined by the individual's health care provider, it would not be reasonable to restrict the number of times an individual can restart PrEP**
- **Individuals with health insurance plans covered by the ACA must have access with no cost-sharing to the PrEP medication that is medically appropriate for them, as determined by the individual's healthcare provider**
- **Plans must have an easily accessible, transparent, and sufficiently expedient exceptions process if using reasonable medical management techniques**

The USPSTF recommendation for PrEP medication includes a combination of baseline and monitoring services, which are essential to the efficacy and implementation of PrEP

ACA, Affordable Care Act; PrEP, pre-exposure prophylaxis

Preexposure Prophylaxis for the Prevention of HIV Infection US Preventive Services Task Force Recommendation Statement, *JAMA*. 2019;321(22):2203-2213. doi:10.1001/jama.2019.6390.
FAQs Accessible at: https://www.dol.gov/sites/dolgov/files/EBSA/about-ebsa/our-activities/resource-center/faqs/aca-part-47.pdf

Long-Acting CAB + RPV in a Safety Net Clinic Population: Background

- LA CAB + RPV for HIV treatment has shown promise in adherence-challenged populations but has been studied only in and is
  FDA approved only for use in PWH with virologic suppression
  - 1.4% virologic failure rate reported among PWH with virologic suppression in phase III FLAIR and ATLAS trials[1,2]
  - 68% of virologic failures occurred by 24 wk[1,2]
- Current study evaluated efficacy of LA CAB + RPV in an urban safety net HIV clinic that serves primarily publicly insured PWH with high rates of adherence barriers (eg, housing instability, mental illness, and substance use)[3]

1. Orkin. NEJM. 2020;382:1124. 2. Swindells. NEJM. 2020;382:1112. 3. Gandhi. CROI 2023. Abstr 518.

Long-Acting CAB + RPV in a Safety Net Clinic Population: Study Design

- Study population started on LA CAB + RPV between June 2021 and November 2022 at Ward 86 HIV Clinic in San Francisco
  - No entry requirement for virologic suppression or prior use of oral ART
  - Required to express willingness to come to clinic every 4 wk, provide contact information, and accept outreach from staff
  - Exclusion criterion of presence of RPV or INSTI mutations added after 2 virologic failures occurred
- Analysis summarized patient characteristics, median and range of injections received, and viral suppression outcomes, stratified by HIV-1 RNA ≥30 copies/mL at initiation of LA CAB + RPV

Gandhi. CROI 2023. Abstr 518.

Long-Acting CAB + RPV in a Safety Net Clinic Population: Baseline Characteristics

Characteristic	Ward 86 Patients (N = 133)
Median age, yr (range)	45 (38-45)
Gender, n (%)	
▪ Cisgender man	117 (88)
▪ Cisgender woman	11 (8)
▪ Transgender woman	5 (4)
Race/ethnicity, n (%)	
▪ Black	21 (16)
▪ Latinx	50 (38)
▪ White	43 (32)
▪ Multiracial	19 (14)
Housing, n (%)	
▪ Unstable	77 (58)
▪ Stable	45 (34)
▪ Experiencing homelessness	11 (8)

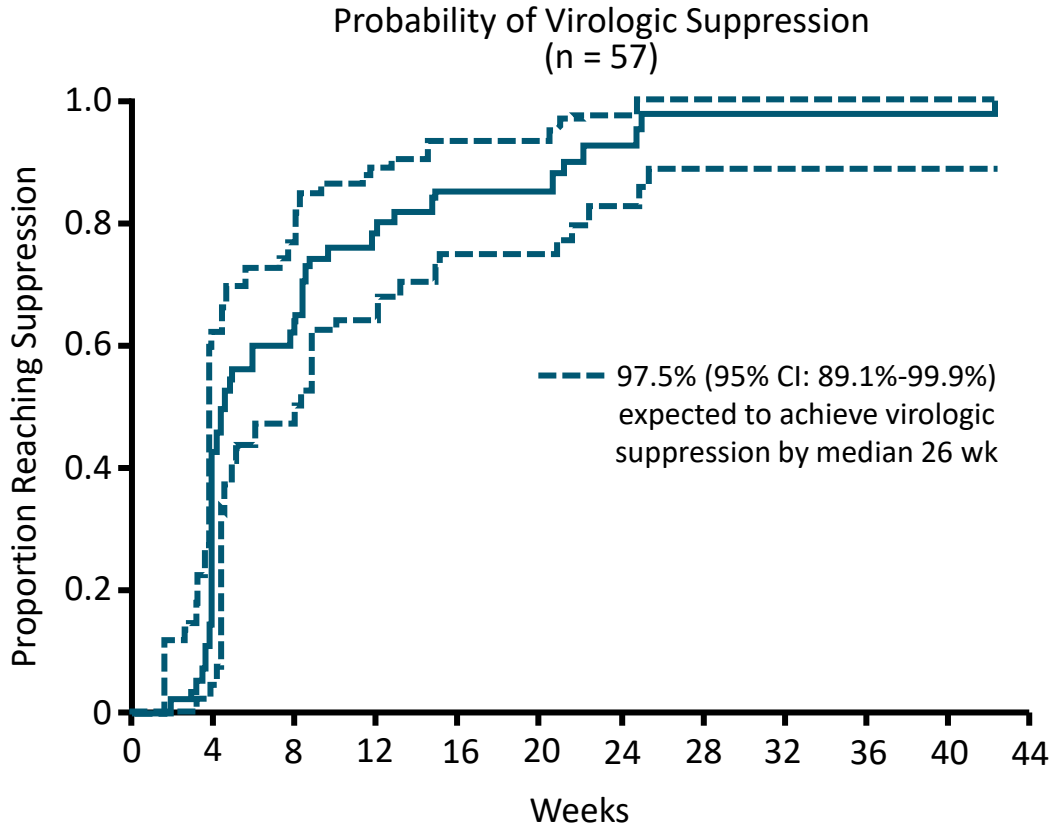
Characteristic	Ward 86 Patients (N = 133)
Insurance, n (%)	
▪ Medicare/Medicaid/both	130 (98)
▪ ADAP	3 (2)
Current stimulant use, n (%)	44 (33)
Major mental illness, n (%)	51 (38)
Virologically nonsuppressed (>30 copies/mL), n (%)	57 (43)
Mean $\log_{10}$ HIV-1 RNA (SD)	4.21 (1.30)
Median CD4 count, cells/mm^3 (IQR)	
▪ Virologically suppressed	616 (395-818)
▪ Virologically nonsuppressed	215 (75-402)

Gandhi. CROI 2023. Abstr 518.

Slide credit: clinicaloptions.com

Long-Acting CAB + RPV in a Safety Net Clinic Population: Results

- 74% (95% CI: 66%-81%) received on-time injections
- 100% (95% CI: 94%-100%) of those with virologic suppression (n = 76) remained suppressed during the follow-up period
- At median of 33 days, 55 of 57 without virologic suppression achieved virologic suppression
- 1.5% virologic failure rate among total population studied



- 2 virologic failures by <24 wk; both had minor mutations, and this led to study protocol update

Gandhi. CROI 2023. Abstr 518. Reproduced with permission.

Slide credit: clinicaloptions.com

Long-Acting CAB + RPV in a Safety Net Clinic Population: Investigators' Conclusions

- In a population of PWH with high rates of adherence barriers, starting LA CAB + RPV showed highly successful virologic outcomes
  - In PWH with virologic suppression at baseline, no virologic failures
  - In PWH without virologic suppression at baseline, 96% achieved virologic suppression
  - Virologic failures occurred by <24 wk due to resistance mutations
- Overall virologic failure rate of 1.5% in this population with and without virologic suppression at baseline was similar to 1.4% rate in phase III trials of PWH
  with virologic suppression
- Investigators suggested that LA CAB + RPV may be effective in patients with adherence challenges unable to achieve or maintain viral suppression on oral ART

Gandhi. CROI 2023. Abstr 518.

Use of CABENUVA in Viremic Patients

Compassionate Use[1]

Of the 35 PLWH receiving CAB + RPV LA via the compassionate use program, 28 (80%) entered with detectable viremia (HIV-1 RNA ≥50 copies/mL; median 60,300 c/mL). Virological suppression was achieved in 16/28 (57%), 13 of whom had taken three or more prior ART regimens.

UCSF Safety Net[2]

133 patients described (68% non-white race, 66% unstable housing/homelessness, 33% current stimulant use). 57 patients started on CAB + RPV LA with detectable viremia. After median of 26 weeks, all have achieved viral suppression, 2 with early virologic failure. 55/57 (96%) suppressed. Both with failure could not take oral ART.

OPERA[3]

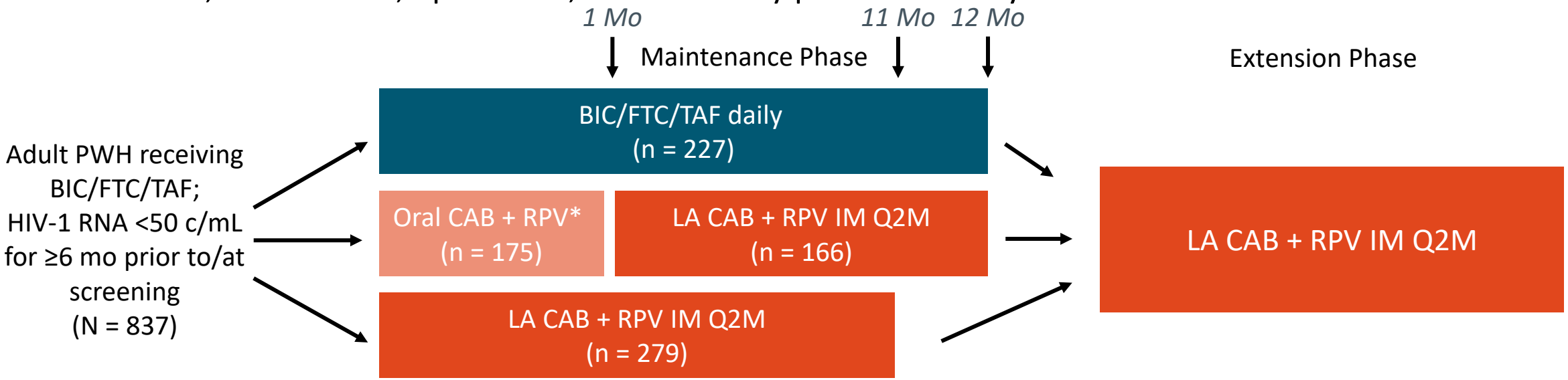
383 received their first CAB + RPV LA injections during the eligibility period (1/21/21-2/28/22). 28 (7%) were viremic (VL ≥ 200 copies/ml) at BL. 89% remained on treatment at the end of follow up (median duration of 4.4 months). For those with repeat VL, 91% (19/21) achieved VL < 200 copies/ml.

HIV Drug Therapy Glasgow; October 23-26, 2022; Virtual and Glasgow, Scotland

1. D'Amico R et al. HIV Med 2022;1-10.
2. Gandhi M. CROI . CROI 2023; Virtual and Seattle, WA. Poster 518.
3. Sension MG et al. ID Week 2022; Oct 19-23, 2022; Washington DC and Virtual.

SOLAR: Randomized Switch to LA CAB + RPV From BIC/FTC/TAF

- Multicenter, randomized, open-label, noninferiority phase IIIb study



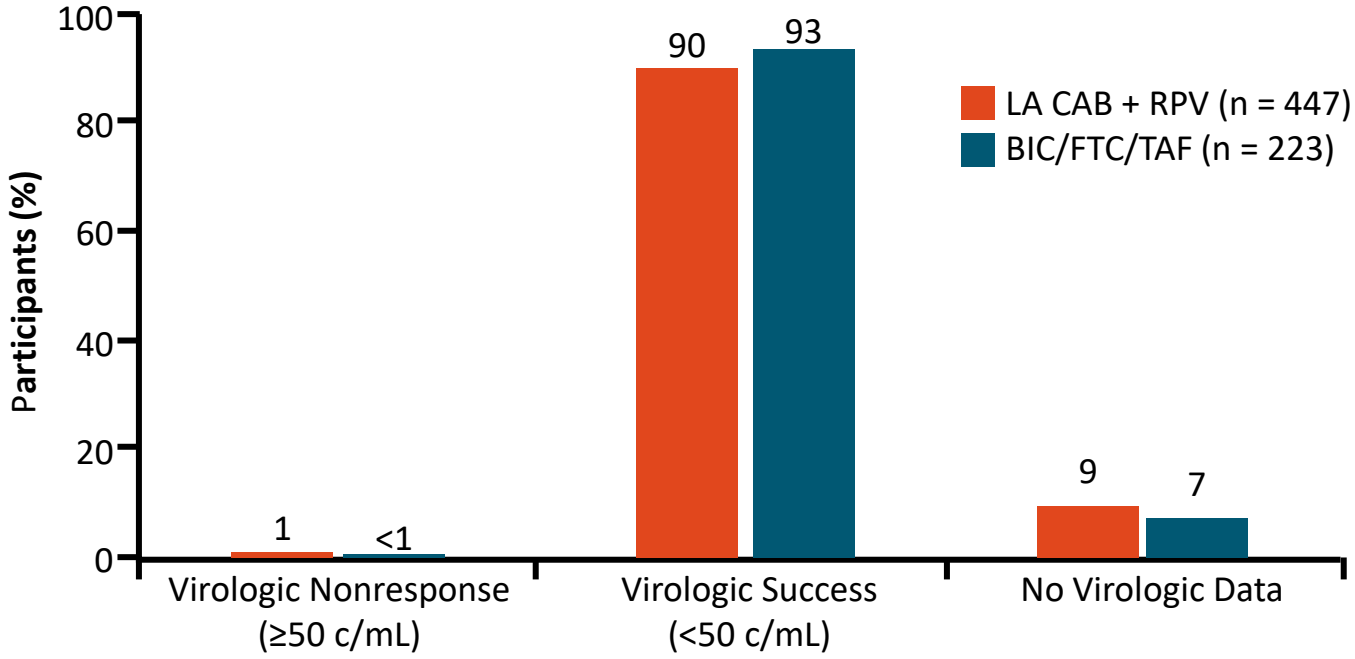
*Patients randomized to LA arm chose between 1 mo OLI or starting with injections.

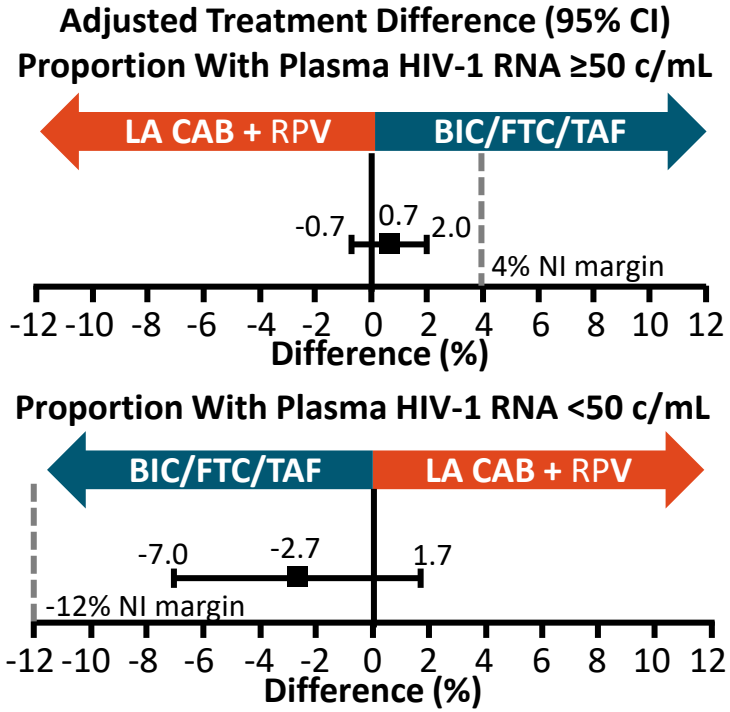
- Endpoints assessed at Mo 12 (Mo 11 for those who started with injections) in mITT-E population
  - Proportion of patients with plasma HIV-1 RNA ≥50 c/mL (primary endpoint) and <50 c/mL
  - Incidence of CVF (2 consecutive HIV-1 RNA ≥200 c/mL)
  - Safety and tolerability
  - Treatment satisfaction (HIVTSQs) and patient preference for therapy

Ramgopal. CROI 2023. Abstr 191.

Slide credit: clinicaloptions.com

SOLAR: Virologic Outcomes at 12 Mo in mITT-E





- LA CAB + RPV noninferior virologic efficacy to BIC/FTC/TAF at 12 mo
- 2 (0.4%) people receiving LA CAB + RPV in mITT-E population met CVF criterion
  - Associated with development of RPV and INSTI RAMs on treatment

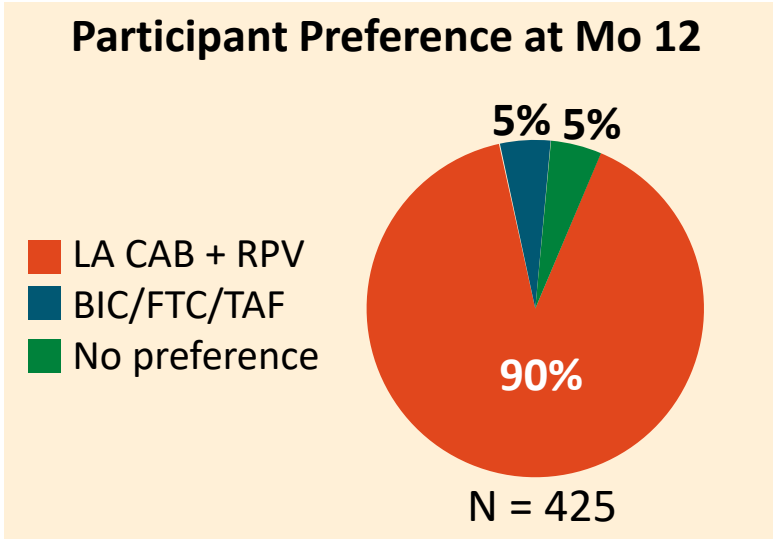
Ramgopal. CROI 2023. Abstr 191.

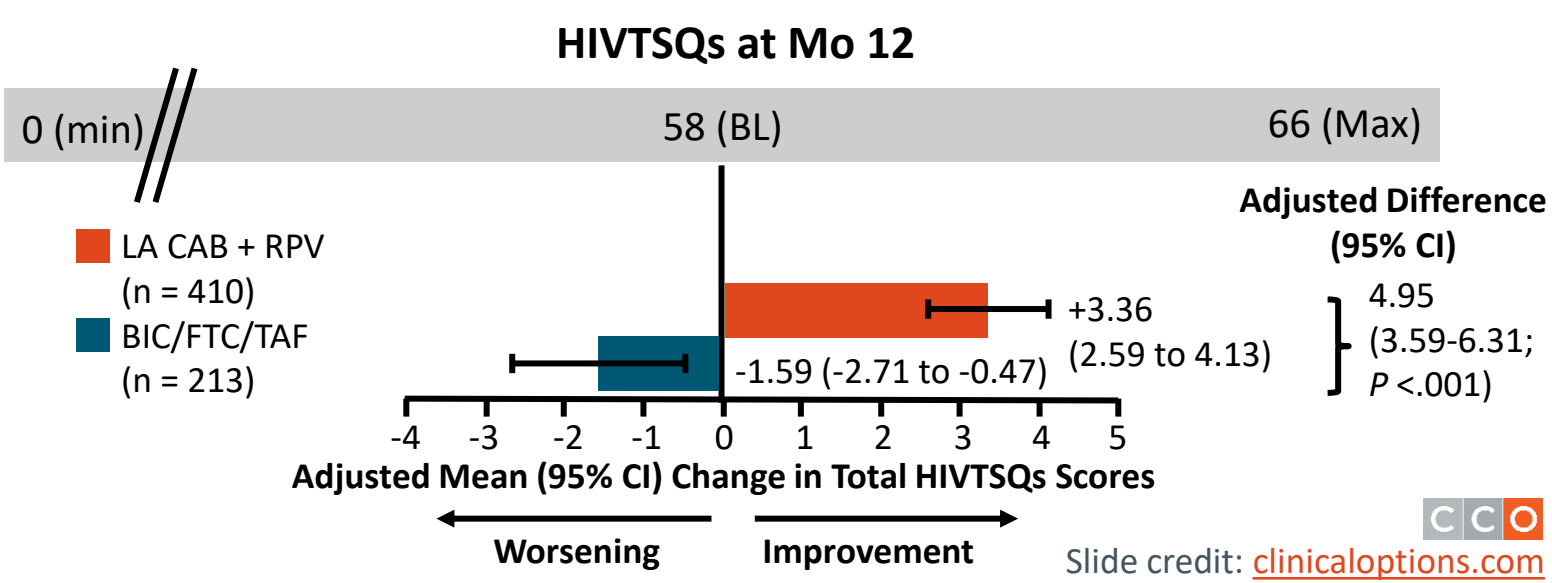
Slide credit: clinicaloptions.com

SOLAR: Safety and Treatment Satisfaction

Adverse Events, n (%)	LA CAB + RPV (n = 454)	BIC/FTC/TAF (n = 227)
Any AE	349 (77)	172 (76)
Grade ≥3 AEs	42 (9)	26 (11)
Treatment withdrawal due to AEs	16 (4)	2 (<1)

- 98% of ISRs with LA CAB + RPV were grade 1/2 and lasted for median of 3 days





Ramgopal. CROI 2023. Abstr 191.

Slide credit: clinicaloptions.com

Guideline-Based Definitions and Management: HTE PLWH

EACS[1]

When a 2–3-drug active regimen cannot be constructed, a drug with a new mechanism of action, such as FTR or IBA, can be added.
In any cases of monotherapy, consider access to experimental drug therapy through early access program or clinical trials

IAS-USA[2]

In the setting of multiclass resistance (3-class resistance), the next regimen should be constructed using drugs from new classes, if available (evidence rating: BIII); e.g., FTR (Alb) or IBA (BII), with at least one additional active drug in an optimized ART regimen

DHHS[3]

Failing regimen	Resistance considerations	New regimen options	Goal
Drug resistance **with fully active treatment** options	• Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen	• Two fully active agents, at least one of which has a high barrier to resistance; otherwise, three fully active agents are preferred • Partially active drugs may be used when no other options are available • Consider using an ARV drug with a different mechanism of action	• Resuppression
Multiple or extensive drug resistance **with few treatment** options	• Use past and current genotypic and phenotypic resistance testing to guide ART • Confirm with viral tropism assay when use of MVC is considered • Consult an expert in drug resistance, if needed	• Identify as many active or partially active drugs as possible based on resistance test results • Consider using an ARV drug with a different mechanism of action (i.e., IBA, FTR) • Clinical trials or expanded access programs for investigational agents may be available • Discontinuation of ARV drugs **is not recommended**	• Resuppression, if possible • Otherwise, keeping viral load as low as possible and CD4 count as high as possible

DHHS; the US Department of Health and Human Services; EACS, European AIDS Clinical Society; FTR, fostemsavir; IAS-USA, International Antiviral Society–USA; IBA, ibalizumab

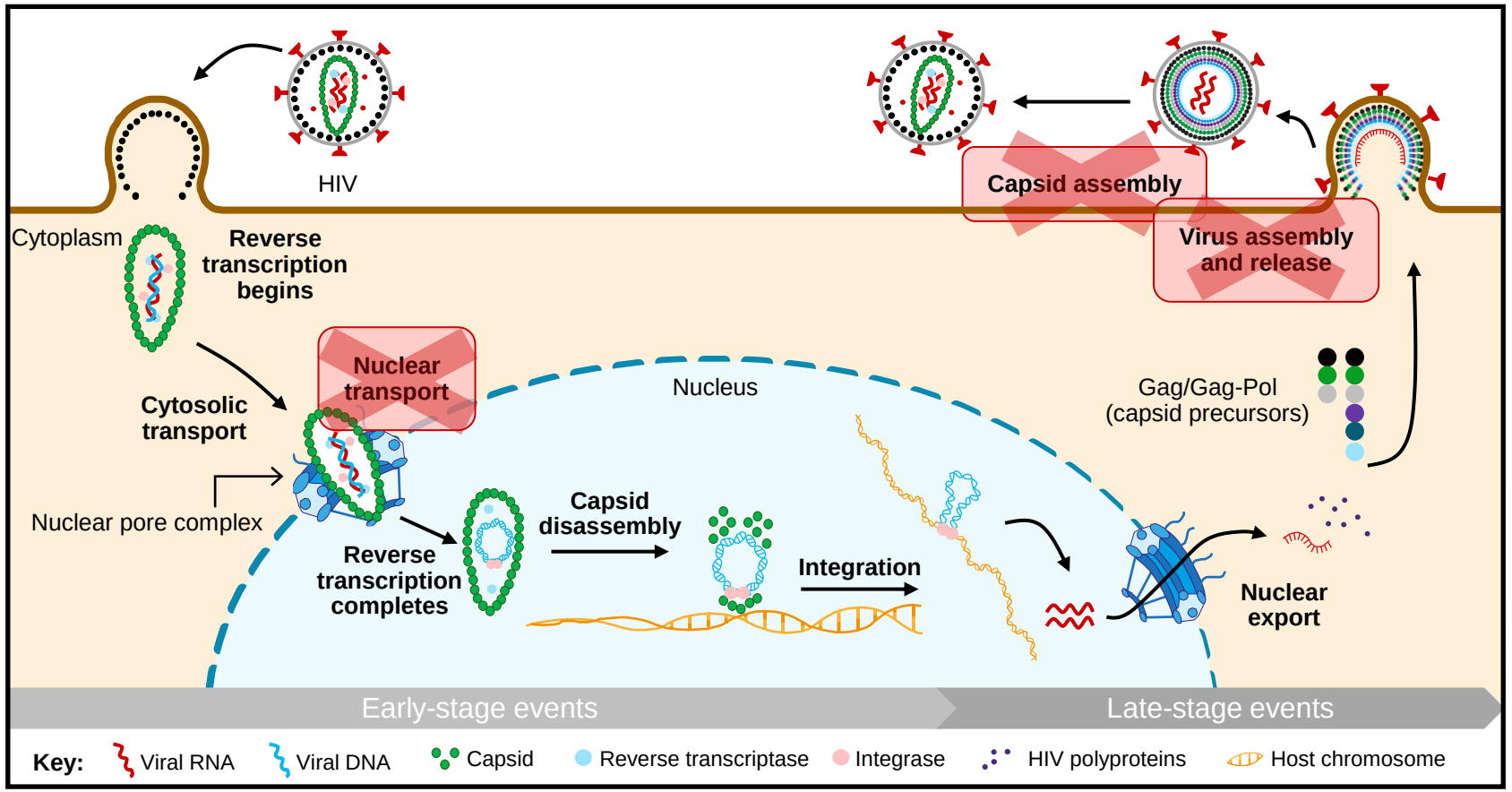
1. EACS Guidelines version 11.1, Oct 2022. https://eacs.sanfordguide.com/ (accessed Nov. 20, 2022); 2. Saag MS, et al. JAMA 2020;324(16):1651-1669;
3. DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Sept 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed Nov. 20, 2022)

LEN Targets Multiple Stages of the HIV Replication Cycle

Click here or scan the QR code for video

LEN
EC_{50}: 50 – 100 pM

Interrupts
multiple distinct stages
of the viral lifecycle



LEN binds directly between capsid protein subunits, modulating the stability and/or transport of capsid complexes, leading to inhibition of essential steps of the viral lifecycle

Figure developed based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T, et al. vCROI 2021, Oral 22; Muller B, et al. vCROI 2021, Oral 19; Pathak VK, et al. vCROI 2021, Oral 20; Ganser-Pornillos B, et al. vCROI 2021, Oral 21. EC_{50}, 50% effective concentration of half maximal response

Study Design

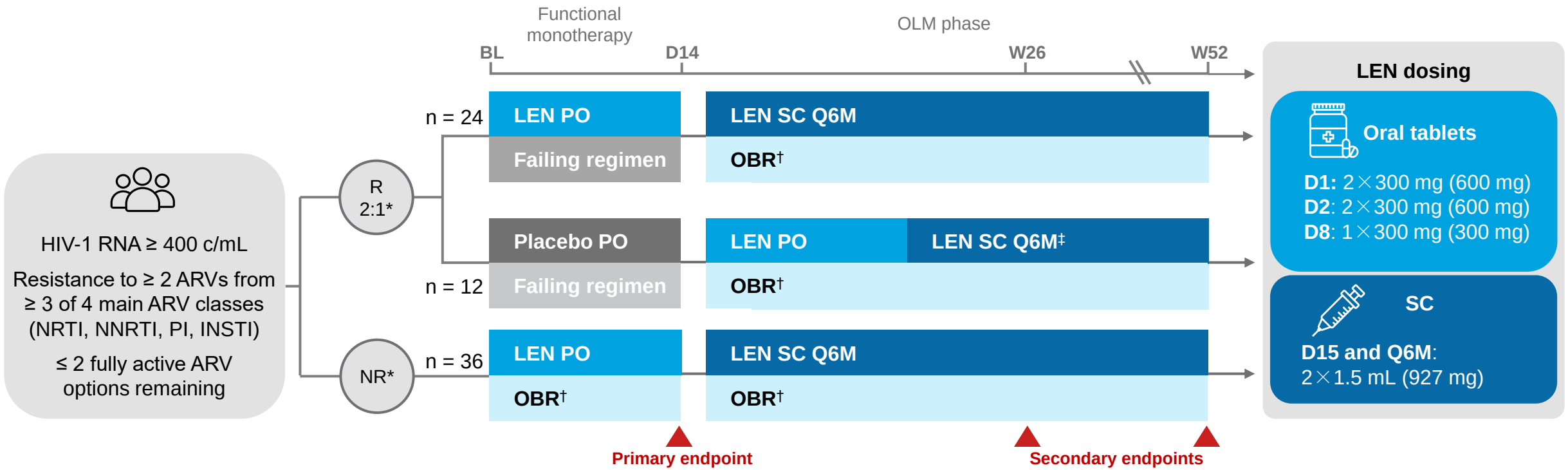
N = 72

HTE PLWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

Primary: ≥ 0.5 $\log_{10}$ c/mL reduction in HIV-1 RNA from BL at D15
Secondary: HIV-1 RNA < 50 c/mL and < 200 c/mL at W26 and W52 (FDA Snapshot)

2019–present (ongoing)



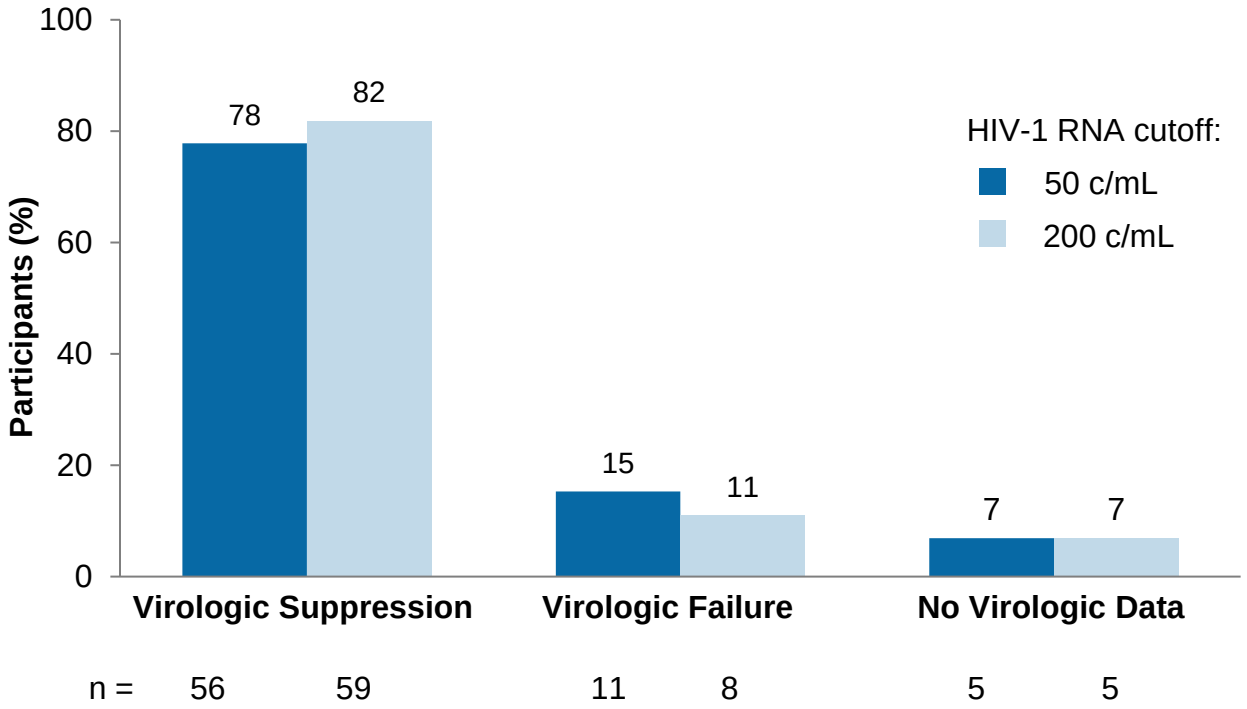
*Participants with < 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥ 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the nonrandomized cohort; †Investigational agents (e.g., FTR) permitted; ATV, ATV/c, ATV/r, EFV, ETR, NVP, TPV not permitted

BL, baseline; D, day; FDA, U.S. Food and Drug Administration; HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized; OBR, optimized background regimen; OLM, open-label maintenance; PO, by mouth; Q6M, every 6 months; R, randomized

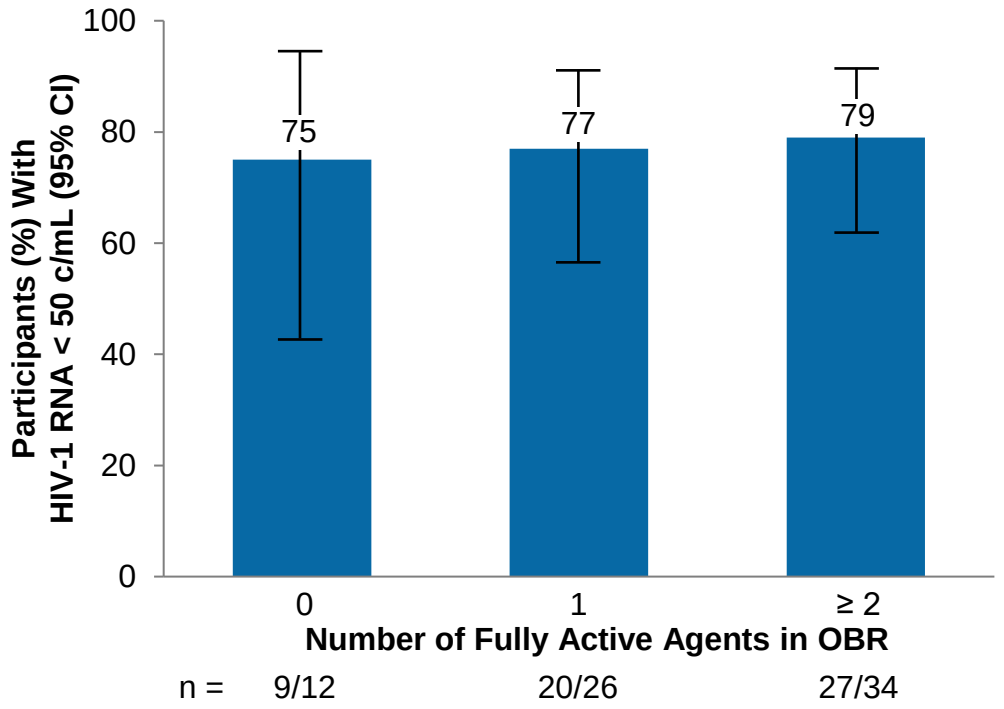
1. Molina JM, et al. vIAS 2021, Oral OALX01LB02; 2. Segal-Maurer S, et al. vCROI 2021, Oral 127; 3. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803

Efficacy at Week 52: Randomized and Nonrandomized Cohorts

Combined Efficacy at Week 52 in Both Cohorts (N = 72)*



Efficacy by Number of Fully Active Agents in OBR (N = 72)*



In HTE PLWH with MDR, LEN in combination with an OBR maintained high rates of virologic suppression at Week 52 in both cohorts

*Due to the clinical hold on SC LEN by the FDA during the study, by Week 52, 17 participants took ≥ 1 dose of oral LEN bridging (300 mg QW)
HTE, heavily treatment-experienced; MDR, multidrug resistance; OBR, optimized background regimen; QW, once weekly
Ogbuagu O, et al. IDWeek 2022, Oral 1585

Study Design

N = 182

Treatment-naïve PLWH with HIV-1 RNA ≥ 200 c/mL and no HBV or HCV[2]

Outcomes[2]

Primary (W54): HIV-1 RNA < 50 c/mL at W54. Secondary (W28, 38 & 80): HIV-1 RNA < 50 c/mL, and change from BL in log_{10} HIV-1 RNA and CD4 count

2019–present (ongoing)

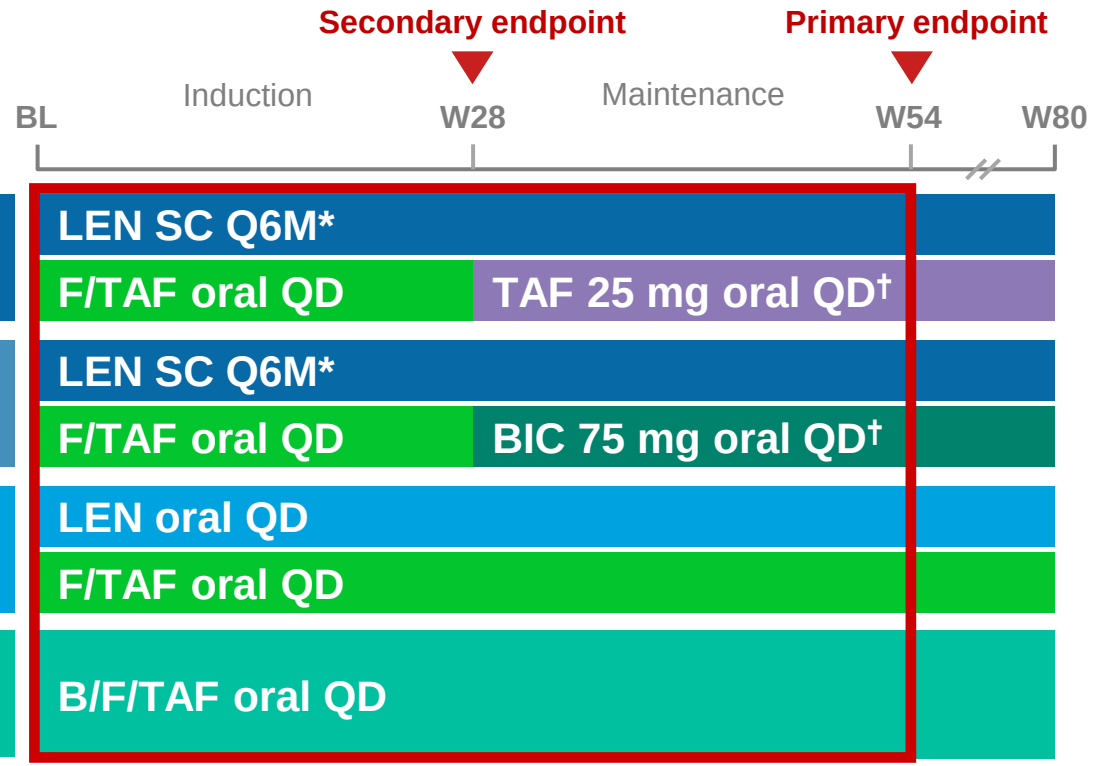
ART-naïve PLWH[1]

HIV-1 RNA ≥ 200 c/mL

CD4 count ≥ 200 cells/μL

No HBV or HCV

2:2:2:1

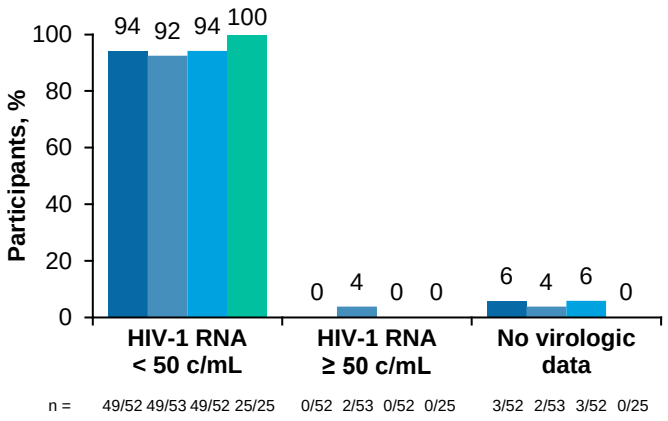


*LEN oral initiation (600 mg on Day 1 and 2, 300 mg on Day 8), followed by LEN SC 927 mg on Day 15; F/TAF, 200/25 mg; †Participants in treatment group 1 and 2 required HIV-1 RNA < 50 c/mL at Week 16 and Week 22 to initiate either TAF or BIC at Week 28; those with HIV-1 RNA ≥ 50 c/mL discontinued study at Week 28; ‡LEN 600 mg on Day 1 and 2, followed by LEN 50 mg from Day 3; F/TAF, 200/25 mg; §B/F/TAF, 50/200/25 mg. BL, baseline; Q6M, every 6 months (Q26 weeks)

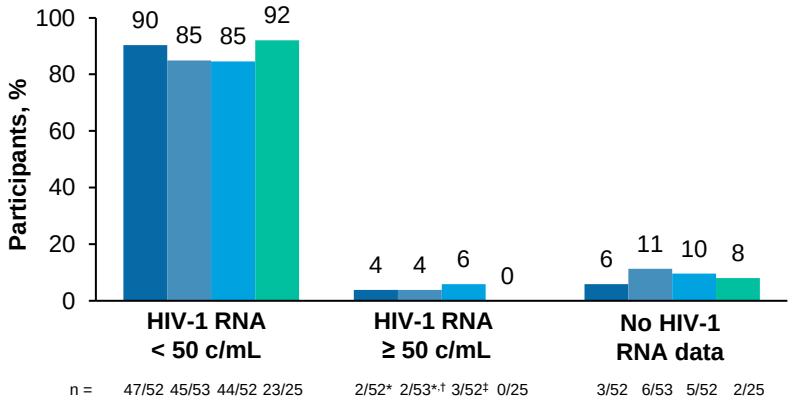
1. Gupta SK, et al. CROI 2022, 2. Oral 138; Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04143594?term=lenacapavir%2C+calibrate&cond=hiv&draw=2&rank=1 (accessed March 4, 2022)

Efficacy at Week 28 and 54

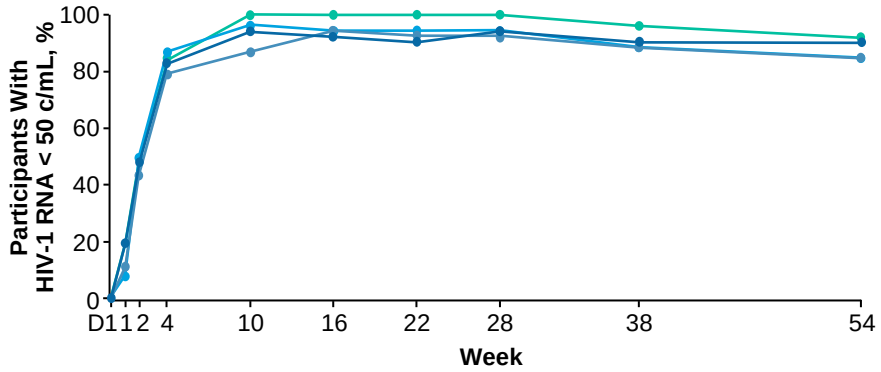
Virologic Outcome at Week 28 (FDA Snapshot; intent-to-treat)



Efficacy at Week 54 (FDA Snapshot)



Participants With HIV-1 RNA < 50 c/mL by Visit (M = F; On Treatment)



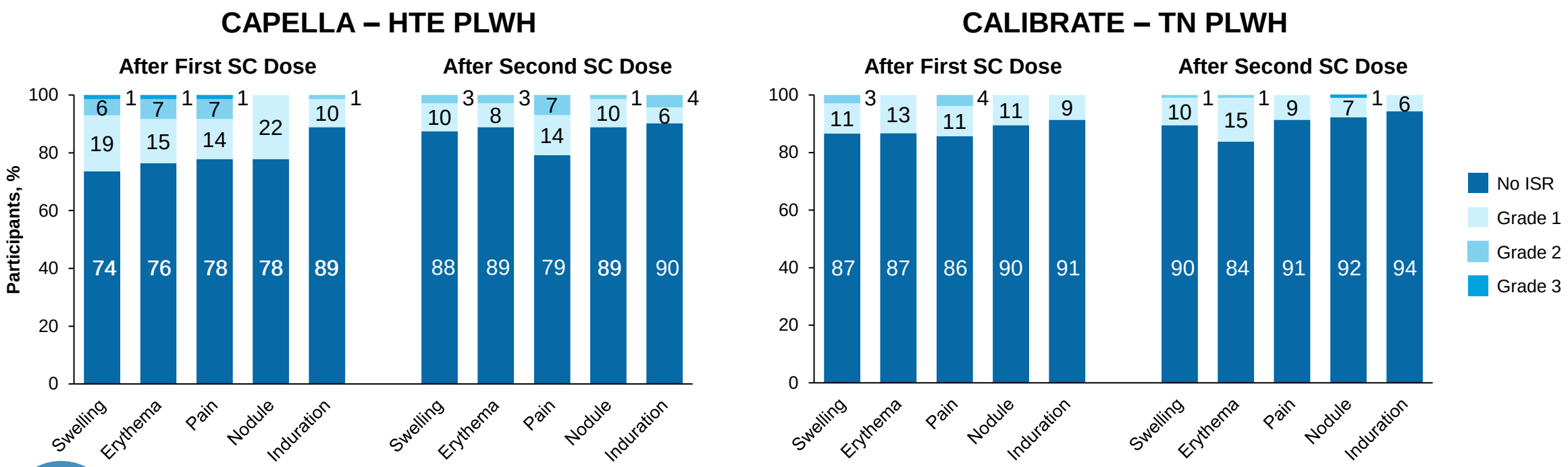
- In the pooled SC LEN group (TG 1 + 2) at Week 54:
  - 88% (92/105) achieved and maintained viral suppression
  - 93% (91/98) of participants who were virally suppressed at Week 28 maintained viral suppression

In TN PLWH, SC LEN in combination with oral F/TAF, TAF or BIC, and oral LEN in combination with F/TAF, rapidly achieved and maintained high rates of viral suppression at 1 year

*3 participants (2 in TG 1 and 1 in TG 2) discontinued on account of not meeting the protocol criteria of having HIV-1 RNA < 50 c/mL prior to Week 28; †1 participant discontinued on Day 2 (TG 2); ‡2 of the 3 participants (TG 3) with HIV-1 RNA ≥ 50 c/mL at Week 54 were suppressed in the subsequent visit. D, Day; FDA, U.S. Food and Drug Administration; M = F, missing = failure; TG, treatment group; TN, treatment-naïve

Gupta SK, et al. CROI 2022, Oral 138

Incidence of ISRs Related to SC LEN*

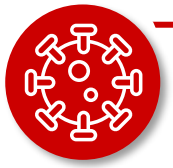


- **Most ISRs were Grade 1** (42% [30/72] in CAPELLA and 48% [49/103] in CALIBRATE), and incidence generally declined from 1st to 2nd injection
- No serious or Grade 4 ISRs were reported; 3 participants (2%) had Grade 3 ISRs
- 4/174 (2%) participants discontinued due to ISR, all of which were Grade 1 and participant driven†

LEN was generally well tolerated, with most participants (70–90%) experiencing no ISRs of swelling, erythema, pain, nodule or induration. Only 2% (4/175) of participants discontinued LEN due to ISRs

*Only includes AEs related to LEN as determined by the investigator and excludes those not related to it; includes ISRs > 10% in both studies; †CAPELLA: Grade 1 nodule discontinuation at Day 379; CALIBRATE: Grade 1 induration discontinuation at Day 211; Grade 1 induration discontinuation at Day 156, and Grade 1 erythema and swelling discontinuation at Day 399
HTE, heavily treatment-experienced; ISR, injection-site reaction; TN, treatment-naïve
Kumar P, et al. AIDS 2022, Poster EPB184

Summary



LEN is a novel, first-in-class capsid inhibitor blocking multiple essential steps of the HIV viral lifecycle

LEN has characteristics supporting its use as a LAO and SC injectable

- Demonstrated picomolar potency, synergy and lack of cross resistance with other ARVs

In CAPELLA, Q6M LEN combined with OBR demonstrated potent antiviral activity, high rates of VS, low rates of treatment-emergent resistance, and was generally well tolerated in HTE PLWH

Adherence to an OBR with LEN is important in order to avoid LEN resistance

LEN is being developed as a foundational agent for new long-acting regimens for HIV treatment and prevention, with the goal of offering a diverse range of options to address individual needs and preferences

HTE, heavily-treatment experienced; LAO, long-acting oral; OBR, optimized background regimen; Q6M, every 6 months; VS, viral suppression

LEVI Syndrome: Background

- For HIV PrEP, LA CAB efficacy superior to oral FTC/TDF in HPTN 083 (cisgender MSM and TGW) and HPTN 084 (cisgender women)[1]
- In HPTN 083, 6 cases of HIV infection occurred despite on-time LA CAB injections
  - Rapid and Ag/Ab tests often fail to detect HIV infection due to viral suppression and delayed/diminished Ab expression that can persist for months after infection, even after injection discontinuation
- Delayed detection of HIV infection may result in delayed ART start, ongoing HIV transmission, and emergence of INSTI resistance
- Current report describes case from HPTN 083 of patient who received LA CAB PrEP with LEVI syndrome[2]
  - Report also examined retrospective lab testing and genotyping

1. www.hptn.org/research/studies. 2. Eshleman. CROI 2023. Abstr 160.

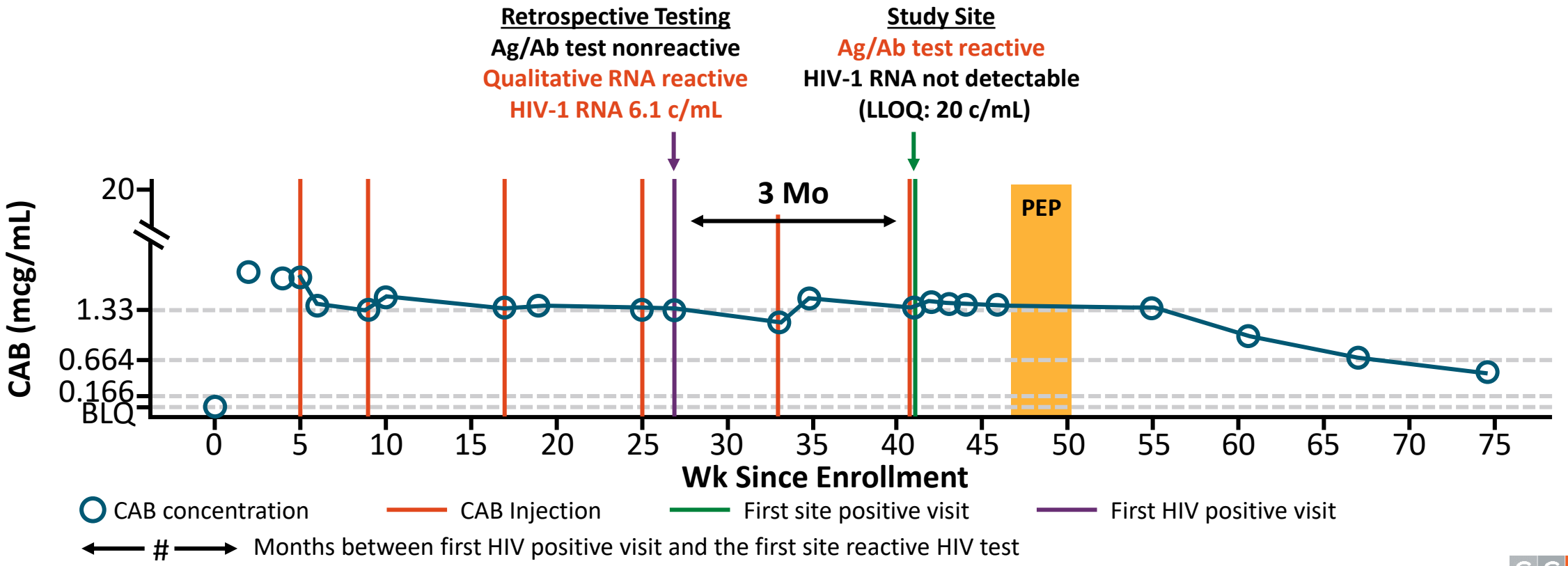
HIV-1 RNA Screening During PrEP With LA CAB

- Recommendations for HIV-1 RNA screening during PrEP with LA CAB
  - Included in prescribing information
  - Recommended by CDC in US
  - Not included in WHO guidelines
  - Not included in HPTN 083 and HPTN 084 protocols

Cabotegravir/rilpivirine PI. CDC PrEP for HIV Prevention Guidelines 2021.
WHO LA CAB for HIV Prevention Guidelines 2022. Eshleman. CROI 2023. Abstr 160.

LEVI Syndrome Patient Case: Detection of Infection

- Retrospective sensitive HIV-1 RNA testing detected HIV infection 3 mo earlier than study site

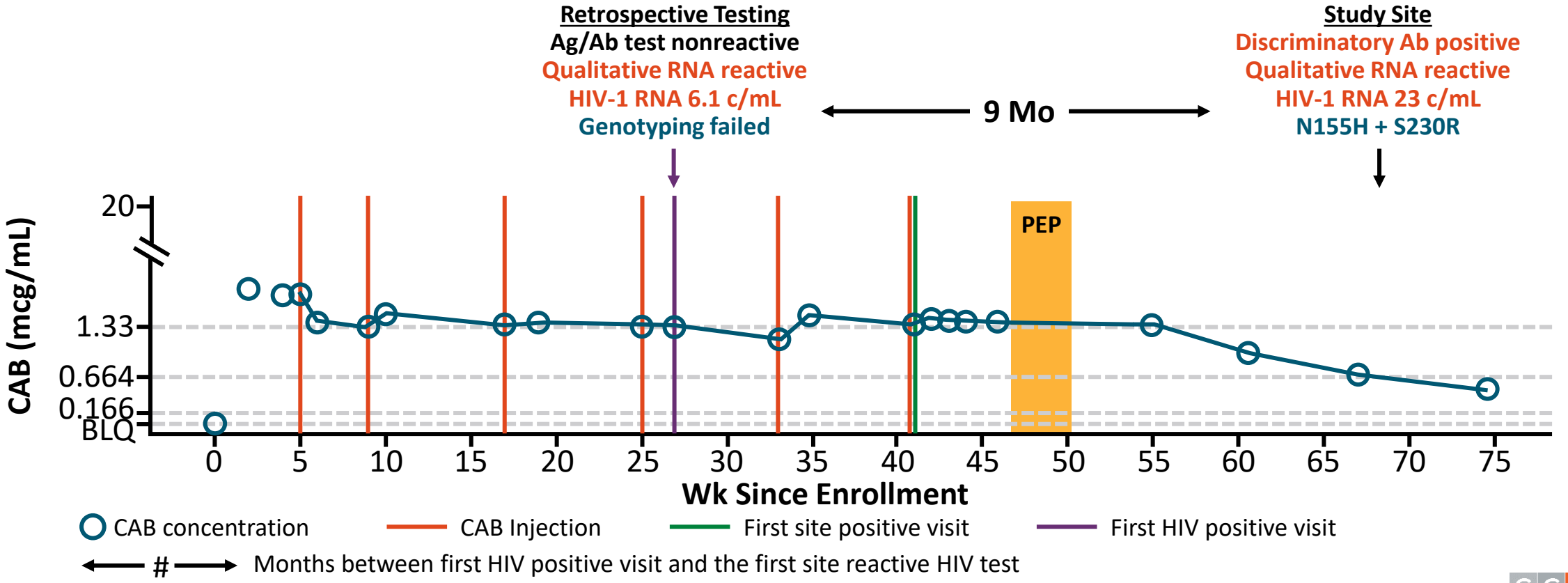


Eshleman. CROI 2023. Abstr 160. Reproduced with permission.

Slide credit: clinicaloptions.com

LEVI Syndrome Patient Case: Confirmation of Infection

- HIV infection not confirmed by study site until after 9 mo from first HIV+ visit
- Retrospective genotyping failed at first HIV+ visit (HIV-1 RNA 6.1 c/mL) and detected INSTI resistance at study site HIV+ visit (HIV-1 RNA 23 c/mL)



Eshleman. CROI 2023. Abstr 160. Reproduced with permission.

Slide credit: clinicaloptions.com

LEVI Syndrome Patient Case: Assay Reversion

Days since 1st HIV+ visit	Rapid test	Ag/Ab test	Qualitative RNA test, LLOD 30 c/mL	Confirmatory Ab test	HIV-1 RNA (c/mL) LLOD 40 c/mL or single copy	HIV-1 DNA (c/mL) LLOD 4.09 c/10^6 cells
0	NR	NR	R		6.1	
42	NR	NR	NR			
55	NR	NR	R		ND	
98	NR	NR	NR			
105	R	R	NR	NEG		Detect <LLOD
112	NR	R	NR	NEG		
119	NR	NR	NR			
132	NR	R	NR	INDET		ND
195	R	NR	NR			Detect <LLOD
235	NR	R	NR	INDET		
280	NR	R	R	NEG	<40	Detect 5.8
333	R	R	R	INDET	<40	

11 mos

Eshleman. CROI 2023. Abstr 160. Reproduced with permission.

Slide credit: clinicaloptions.com

AHI vs LEVI Syndrome With LA CAB PrEP

Feature	AHI	LEVI
Cause	Phase of natural HIV infection	LA ARV for PrEP
Onset	New infection	Infection during PrEP; initiation of PrEP during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Minimal, variable, often no symptoms reported
Detection	Ag/Ab, RNA (including point-of-care and pooled tests), DNA, and total nucleic acid assays	Ultrasensitive RNA assay (often low/undetectable HIV-1 RNA and HIV-1 DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 wk (until Ab detection)	Mo (until viral breakthrough, drug clearance, or ART start); can persist mo after ARV is discontinued
Transmission	Very likely	Unlikely (except possibly via blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when HIV-1 RNA is low)

Eshleman. CROI 2023. Abstr 160.

Slide credit: clinicaloptions.com

INSTI Resistance Occurring During PrEP With LA CAB

- In HPTN 083, INSTI resistance occurred in 10/18 cases within 6 mo of first HIV+ visit
  - INSTI resistance was not observed if first HIV+ visit >6 mo after LA CAB injection
  - Most infections detected by retrospective sensitive HIV-1 RNA assay before INSTI resistance emerged
- HIV-1 RNA screening being considered in ongoing HPTN 083 and HPTN 084 studies

Eshleman. CROI 2023. Abstr 160.

Slide credit: clinicaloptions.com

Investigators' Conclusions

- HIV infections rare with on-time LA CAB injections for PrEP
  - Detection of HIV infection may be delayed if rapid or less-sensitive assays used
- HIV-1 RNA assays may detect infections earlier and avoid development of resistance
- More research needed to:
  - Evaluate use of HIV-1 RNA screening during PrEP with LA CAB
  - Determine if LEVI syndrome occurs with other LA PrEP agents

Eshleman. CROI 2023. Abstr 160.

Prevention of STIs in the DOXYVAC and DOXYPEP Studies in MSM and TGW

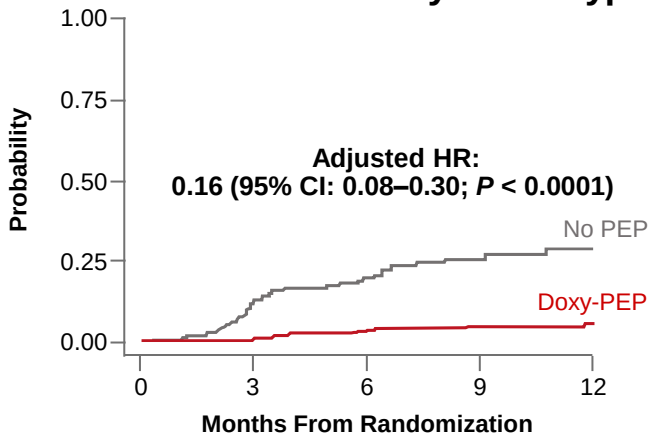
ANRS 174 DOXYVAC Study:[1]
MSM on PrEP (N = 720)
Randomized 2:1 to doxy-PEP* or no PEP (both with/without 4CMenB vaccine)

DOXYPEP Study:[2]
MSM and TGW PLWH or on PrEP (N = 637)
Randomized 2:1 to doxy-PEP* or SoC

Outcomes

ANRS 174 DOXYVAC study: Time to first chlamydia/syphilis infection and impact of 4CMenB vaccine on time to first episode of gonorrhea infection
DOXYPEP study: *S. aureus* colonization and doxycycline resistance

DOXYVAC Study: Time to First Chlamydia or Syphilis Infection†,[1]



No. at risk:

No PEP	170	137	99	47	22
Doxy-PEP	332	271	220	144	83

Chlamydia or syphilis infections:

- **No PEP: n = 36**
  Incidence rate: 35.4/100 PY
- **Doxy-PEP: n = 13**
  Incidence rate: 5.6/100 PY

DOXYPEP Study: *S. Aureus* Colonization and Doxycycline Resistance[2]

	Doxy-PEP treatment group	
	***S. aureus* colonization**	**Doxycycline resistance**
Baseline (N = 428)	44%	5%
Month 6 (n = 360)	29%	13%
Month 12 (n = 222)	31%	13%

Doxy-PEP group:

↓ **14%; *P* < 0.01**
Absolute **decrease** in *S. aureus* colonization

↑ **8%; *P* < 0.01**
Absolute **increase** in doxycycline resistance at month 6 maintained at month 12

In a single oral dose pharmacology study of doxycycline, doxycycline efficiently distributed to mucosal sites of STI exposure, and mucosal doxycycline concentrations exceeded MIC for *C. trachomatis* and *T. pallidum* to a greater extent than for *N. gonorrhoeae*[3]

Doxy-PEP decreased STI incidence in MSM[1] and was associated with a 14% absolute reduction in *S. aureus* colonization with an 8% increase in doxycycline resistance in MSM and TGW[2]

*200 mg within 72 hours of exposure; †No interaction between doxy-PEP and 4CMenB vaccine. ANRS, Agence Nationale de Recherches sur le SIDA; doxy, doxycycline; HR, hazard ratio; MIC, minimum inhibitory concentration; PY, person-years; SoC, standard of care; TGW, transgender women

1. Molina JM, et al. CROI 2023, Oral 119; 2. Luetkemeyer A, et al. CROI 2023, Oral 120; 3. Haaland R, et al. CROI 2023, Oral 118

Pipeline: Modalities of PrEP Administration – Preclinical/Investigational

Vaginal PrEP Efficacy of Biodegradable Islatravir in Macaques[1]

- Biodegradable implant to deliver ART and hormonal contraceptives and eliminate need for replacement
- PK, safety and efficacy titration reported for a biodegradable SC ISL implant in macaques
- 5/6 animals were protected with plasma ISL levels of ≥ 1.4 nM
- Plasma ISL levels of 1 and 2 implants were equivalent to 0.25 mg and 0.75 mg, respectively

Minimal site reactions and high vaginal efficacy with clinically relevant ISL levels[1]

Extended Postexposure Protection Against SHIV Vaginal Infection with TAF/EVG Inserts[2]

- Rapidly dissolving TAF/EVG (20 mg/16 mg) inserts for on-demand prophylaxis have demonstrated protection against rectal and vaginal SHIV exposure
- Current study evaluated the window of vaginal PEP efficacy in macaques
- 100%, 94% and 77% protection against vaginal SHIV infection when given 4, 8 or 24 hours after exposure, respectively

Data inform the timing of insert application and support clinical development of TAF/EVG inserts for on-demand prophylaxis[2]

Pharmacokinetic and X-ray Imaging of Long-Acting CAB *In Situ* Forming Implant[3]

- CAB IM in liquid form transforms into a removable *in-situ* implant and can be co-formulated with multiple therapies
- Protective plasma concentration ≥180 days may reduce dosing frequency
- Potential for shorter PK tail after removal, although complete CAB elimination not achieved
- Reversible, easily removable and biodegradable at 6 months post-administration

CAB implant may overcome limitations with current long-acting injectables[3]

1. Daly MB, et al. CROI 2023, Oral 989; 2. Makarova N, et al. CROI 2023 Oral 990; 3. Young IC, et al. CROI 2023, Oral 991

Acknowledgements:

Clinical Care Options, Gilead Sciences and Viiv Healthcare