Uzun Etkili Tedaviler

II. Türkiye EKMUD HIV Akademisi

DOÇ. DR. ULULHAN SİLİ

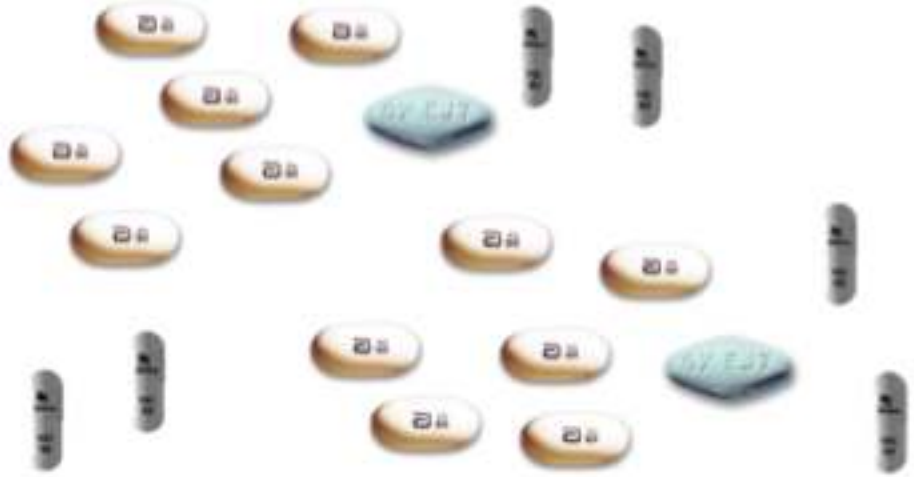
MARMARA ÜNİVERSİTESİ TIP FAKÜLTESİ

ENFEKSİYON HASTALIKLARI VE KLİNİK MİKROBİYOLOJİ AD

4 EYLÜL 2021 10:00 – 10:30

Antiretroviral therapy for HIV infection

In the 1990s



Up to 20 pills daily, taken at different intervals throughout the day

Today

As little as 1 pill per day, delivering multiple drugs

#35YearsOfAIDS

HIV tedavisinin geleceği

- Uzun etkili tedavilerin geliştirilmesi
  - günlük doz alımı yerine haftada bir, ayda bir veya daha aralıklı doz alımı
  - uyumu daha kolay, daha az toksik ve daha maliyet etkin olabilir

- 3 tip ajan çalışılmakta
  1. Uzun-etkili ilaçlar (long-acting drugs)
  2. Geniş nötralize eden antikorlar (broadly neutralizing antibodies)
  3. Terapötik HIV aşıları

https://www.niaid.nih.gov/diseases-conditions/future-hiv-treatment
30-8-2021

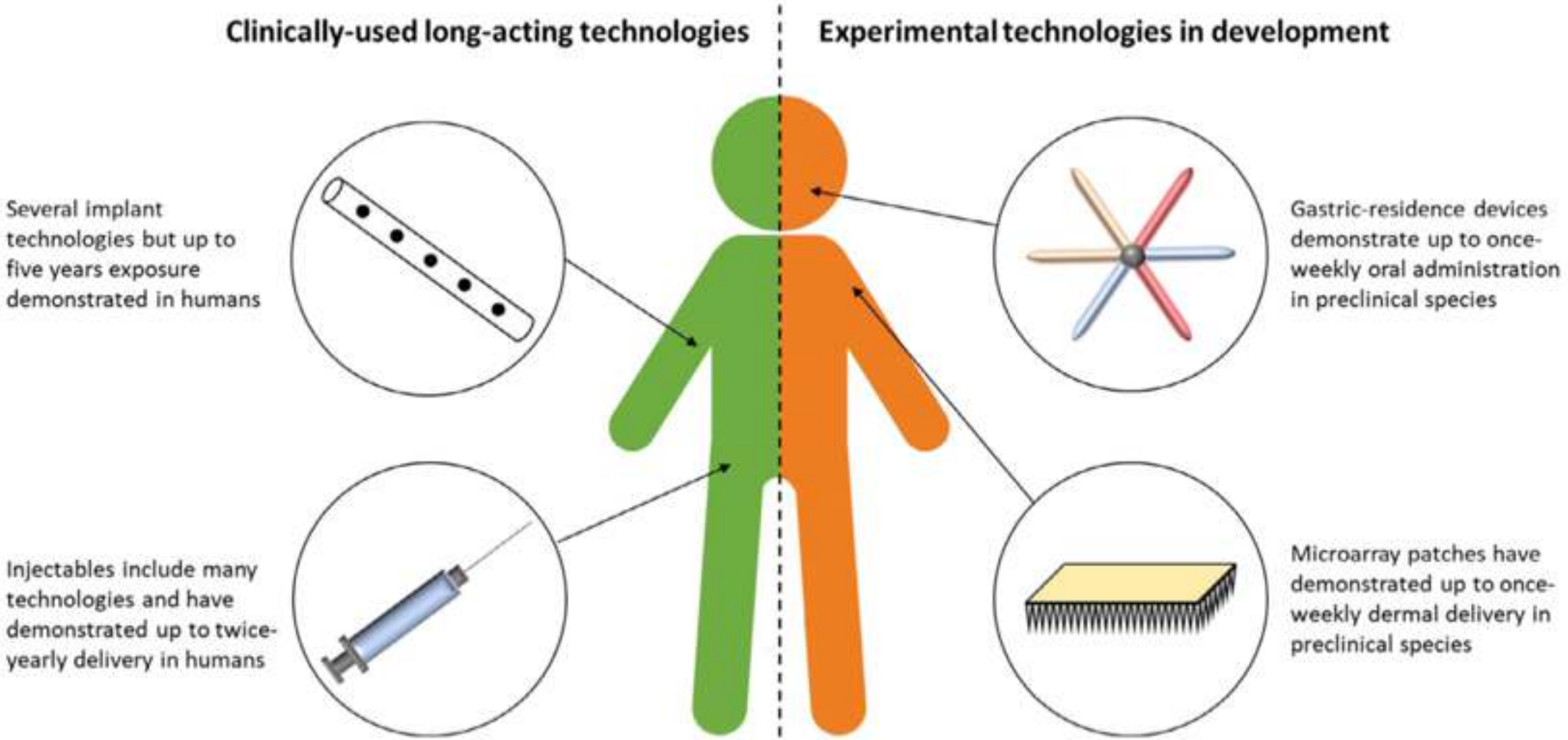


Fig. 1. Examples of long-acting and extended-release drug delivery technologies in preclinical and clinical development for the treatment and prevention of human deficiency virus (HIV) infection.

Long-Acting Antiretroviral Therapies for HIV Treatment and Prevention

More treatment options and modalities are now available for patients.

BY ERIC F. EGELUND, PHARMD, PHD; AND JESSICA HUSTON, PHARMD

Contagion® • June 2021

TABLE. Sample of Long-Acting Formulations for Treatment and PrEP Under Development With Proposed Regimens

DRUG	MOA	FORMULATION	PREP/TREATMENT	FREQUENCY
Cabotegravir	Integrase inhibitor	Injectable	Treatment PrEP	Every 4 weeks Every 8 weeks
Dapivirine	NNRTI	Vaginal Ring	PrEP	Every 3 months
Islatravir	NRTTI	Oral	Treatment Treatment PrEP	Once daily Once weekly Once monthly
Islatravir	NRTTI	Implant	PrEP	Once yearly
Lenacapavir	Capsid inhibitor	Oral	Treatment	Once weekly
Lenacapavir	Capsid inhibitor	Injectable	PrEP	Twice yearly
VRC01	bNAb	Intravenous	PrEP	Every 8 weeks

bNAb, broadly neutralizing antibody; MOA, mechanism of action; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTTI, nucleoside reverse transcriptase translocation inhibitor; PrEP, preexposure prophylaxis.

Table 1.

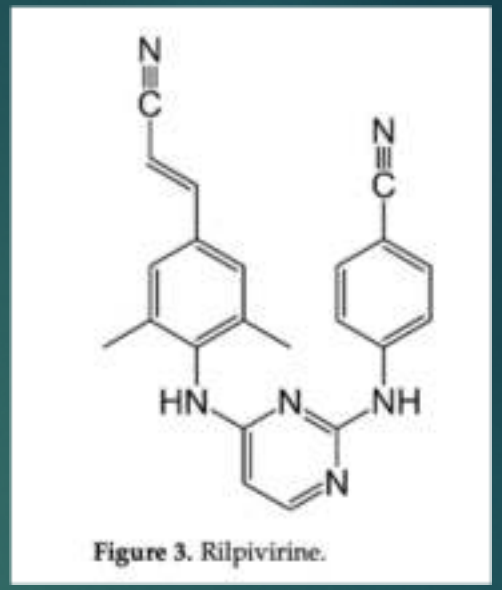


Figure 3. Rilpivirine.

Cabotegravir – *INSTI*

Rilpivirine *NNRTI*

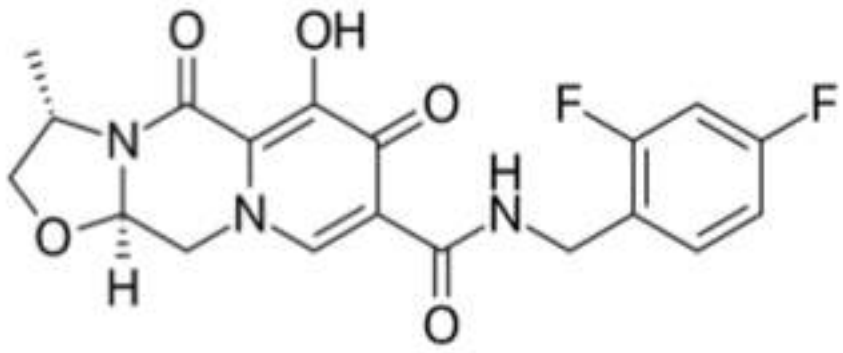
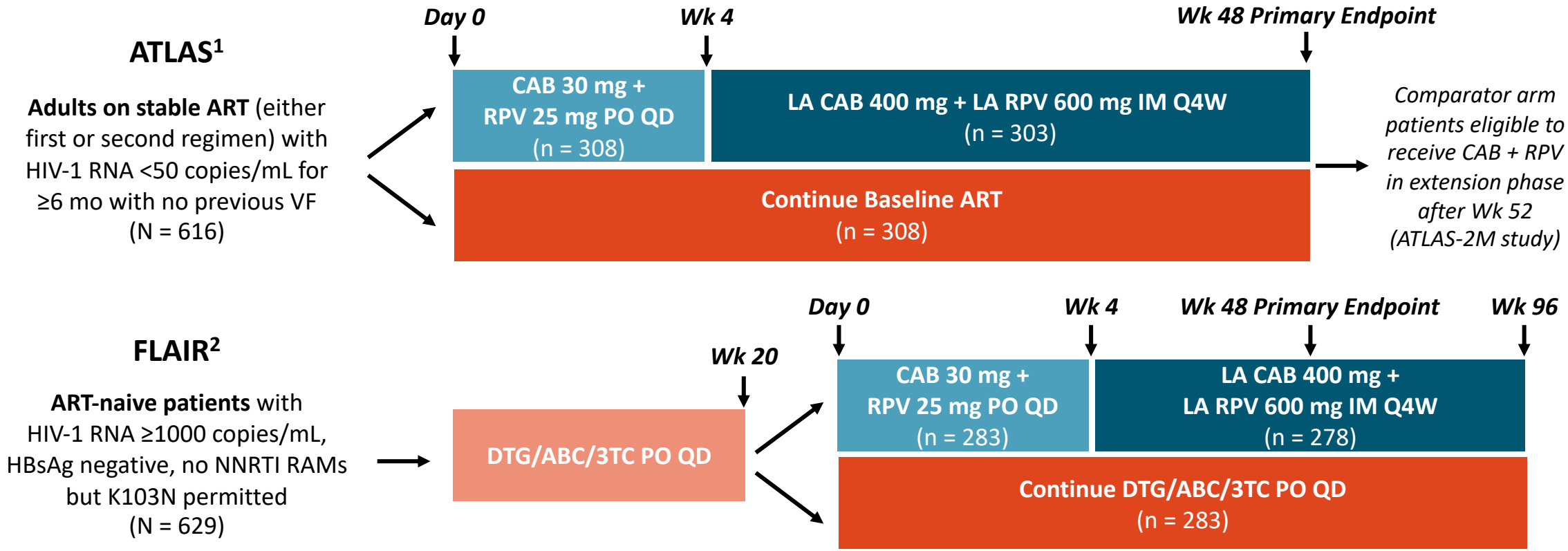


Figure 4. Cabotegravir.

ATLAS and FLAIR: LA Intramuscular CAB + RPV After Initial Virologic Suppression With Oral Therapy

- Multicenter, randomized, open-label phase III noninferiority trials

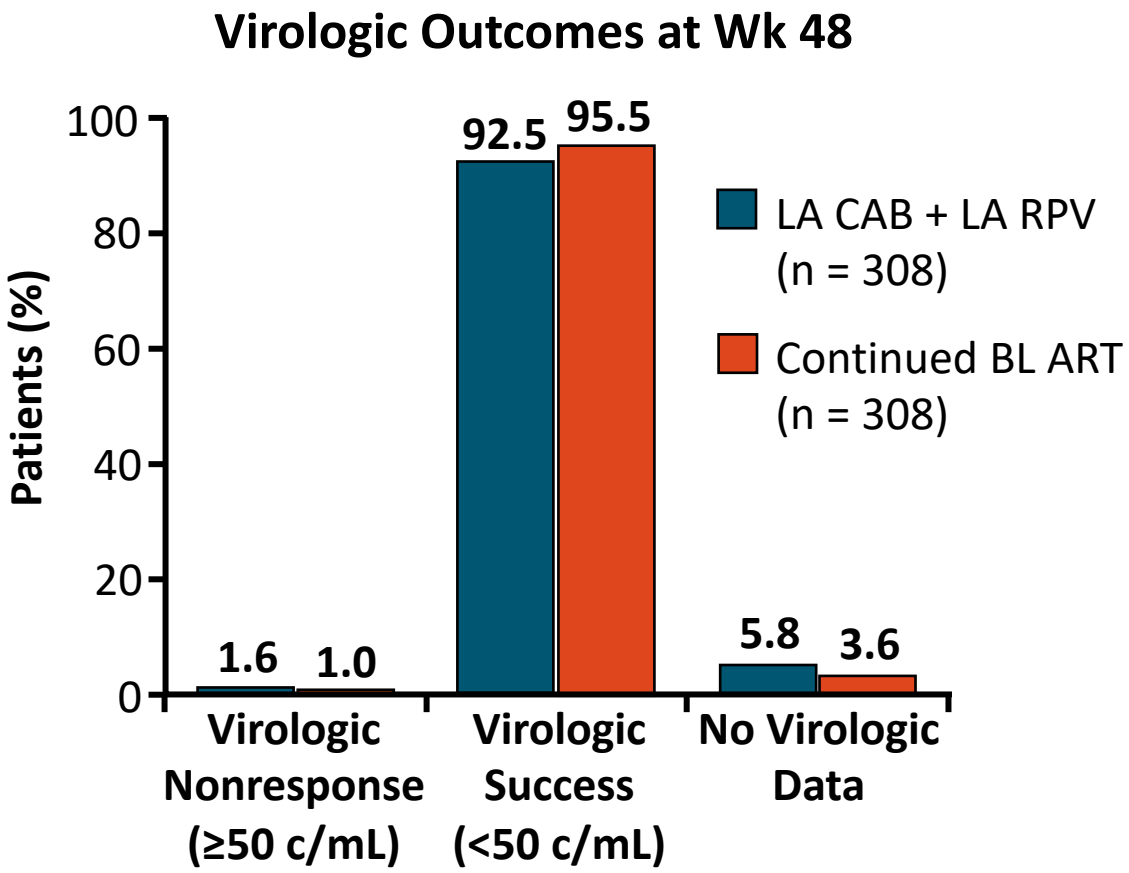


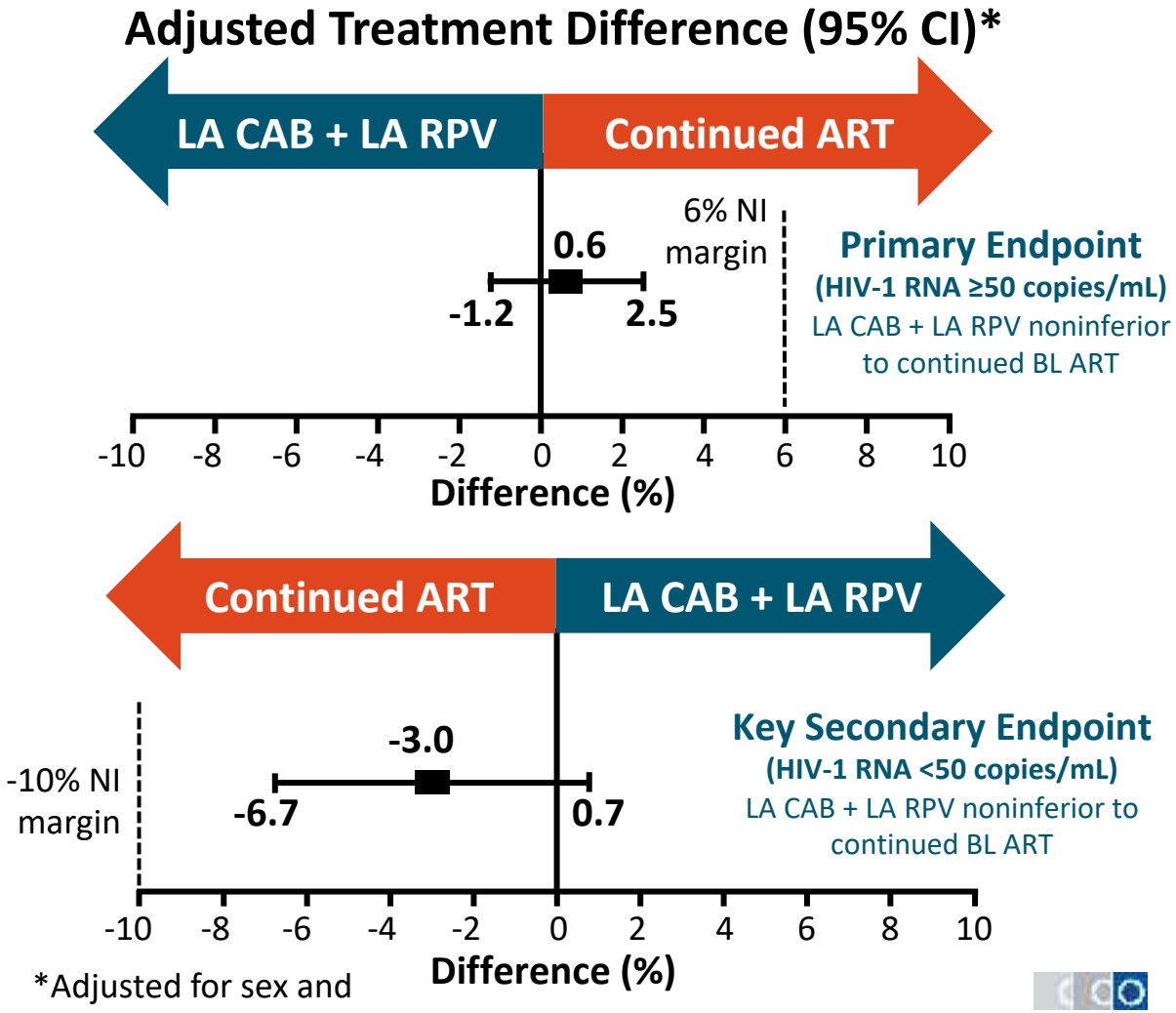
- Primary endpoint for both trials: HIV-1 RNA ≥50 copies/mL at Wk 48 by FDA Snapshot in ITT-E

1. Swindells. NEJM. 2020;382:1112. 2. Orkin. NEJM. 2020;382:1124.

Slide credit: clinicaloptions.com

ATLAS: Switch to LA CAB + RPV vs Continued 3-Drug ART in Virologically Suppressed Adults



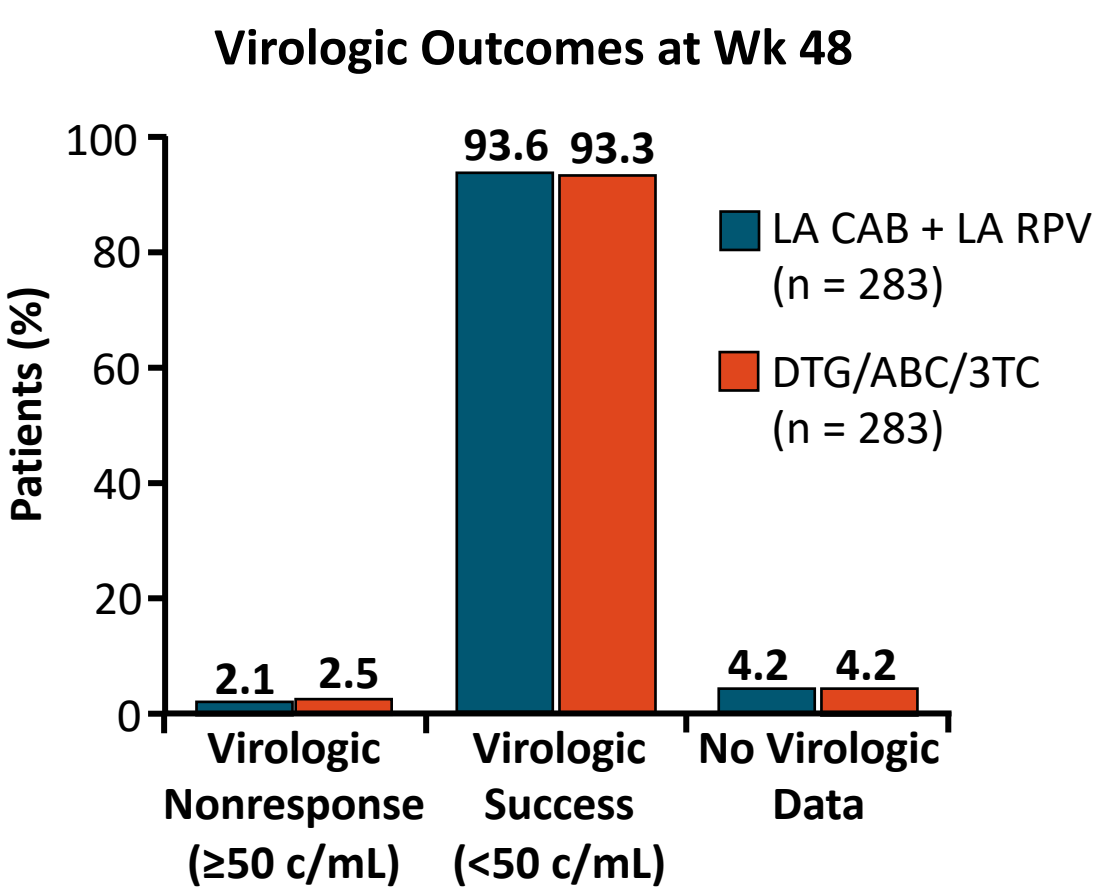


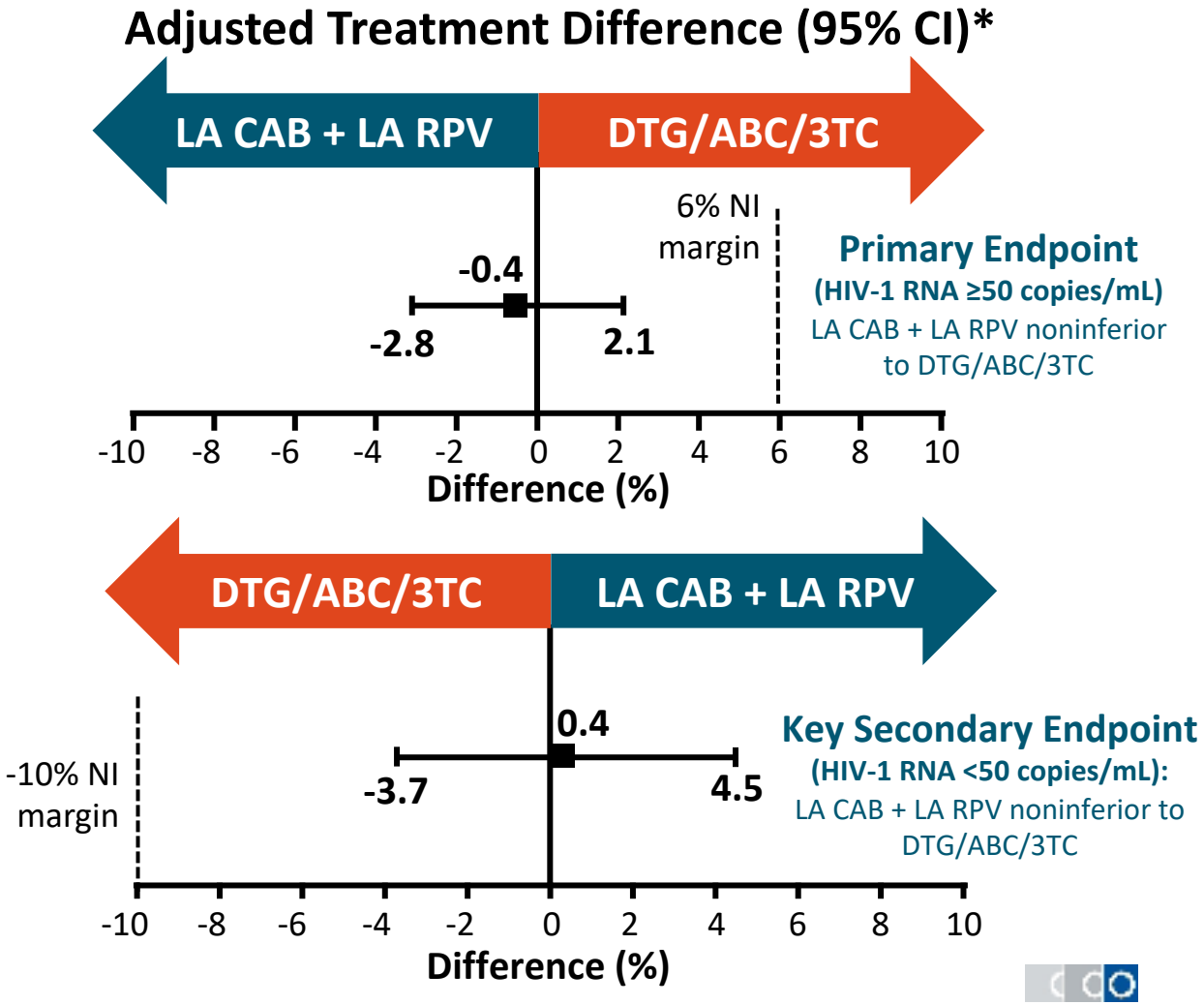
*Adjusted for sex and BL third agent class.

Swindells. NEJM. 2020;382:1112.

Slide credit: clinicaloptions.com

FLAIR: LA CAB + RPV Maintenance After Oral DTG/ABC/3TC Induction





- Noninferiority also observed at Wk 96
- No additional CVF during Wk 48 to 96 in CAB + RPV arm

Orkin. NEJM. 2020;382:1124. Orkin. CROI 2020. Abstr 482LB.

*Adjusted for sex, BL HIV-1 RNA (<vs ≥100,000 c/mL).

Slide credit: clinicaloptions.com

ATLAS and FLAIR: Treatment-Emergent Resistance With Long-Acting CAB + RPV

Study	Sex	Country	HIV-1 Subtype	Wk of Failure	NNRTI RAMs		INSTI RAMs*	
					Baseline	Failure	Baseline	Failure
ATLAS[1]	F	Russia	A/A1	8	E138E/A	E138A	L74I	L74I
	F	France	AG	12	V108V/I, E138K	V108I, E138K	None	None
	M	Russia	A/A1	20	None	E138E/K	L74I	L74I, N155H
FLAIR[2]	F	Russia	A1	20	None	E138E/A/K/T	L74I	L74I, Q148R
	M	Russia	A1	28	None	K101E	L74I	L74I, G140R
	F	Russia	A1	48	None	E138K	L74I	L74I, Q148R

*L74I not considered an INSTI RAM by IAS-USA guidance; not expected to affect CAB sensitivity.

- 101/483 patients had BL L74I in FLAIR: n = 64 from Russia, n = 60 with subtype A[3]
  - Presence of this polymorphism did not negatively affect proportion achieving HIV-1 RNA <50 copies/mL at Wk 48
  - At Wk 96, no additional cases of treatment-emergent resistance[4]

1. Swindells. CROI 2019. Abstr 139. 2. Orkin. CROI 2019. Abstr 140LB. 3. Overton. IAS 2019. Abstr MOPEB257. 4. Orkin. CROI 2020. Abstr 482LB.

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

CLINICAL INFO HIV.gov

Management of the Treatment-Experienced Patient

Updated: Jun. 03, 2021
Reviewed: Jun. 03, 2021

Optimizing Antiretroviral Therapy in the Setting of Viral Suppression

- A long-acting ARV regimen, such as the combination of injectable cabotegravir and rilpivirine, is an optimization option for patients who are engaged with their health care, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs **(AI)**.

Uzun etkili antiretroviral tedavi
DHHS/NIH 3-6-2021

- ”uzun etkili” : haftada bir veya daha uzun aralıklı *long-acting injectable (LAI)*
- 2018: ilk LAI onaylandı; ibalizumab (anti-CD4 monoklonal), iv

- Ocak 2021: FDA → LAI INSTI (cabotegravir, CAB) + NNRTI (rilpivirine, RPV)
  - tedavi başarısızlığı öyküsü olmayacak
  - CAB veya RPV’ye karşı bilinen veya şüphelenilen direnç mutasyonu olmayacak
  - aktif veya gizli HBV enfeksiyonu yok (HBV’ye etkili tedavi almıyorsa)
  - gebe değil ve planlamıyor
  - CAB veya RPV ile ciddi etkileşen ilaç almıyor olacak
  - en az 3-6 aylık virolojik baskılama (HIV-1 RNA <50 k/mL) olan hastalarda oral başlangıçtan (~1 aylık, toleransı görmek üzere) sonra CAB ve RPV’nin farklı ventrogluteal bölgelere aylık intramüsküler enjeksiyonu

Uzun etkili antiretroviral tedavi
DHHS/NIH 3-6-2021

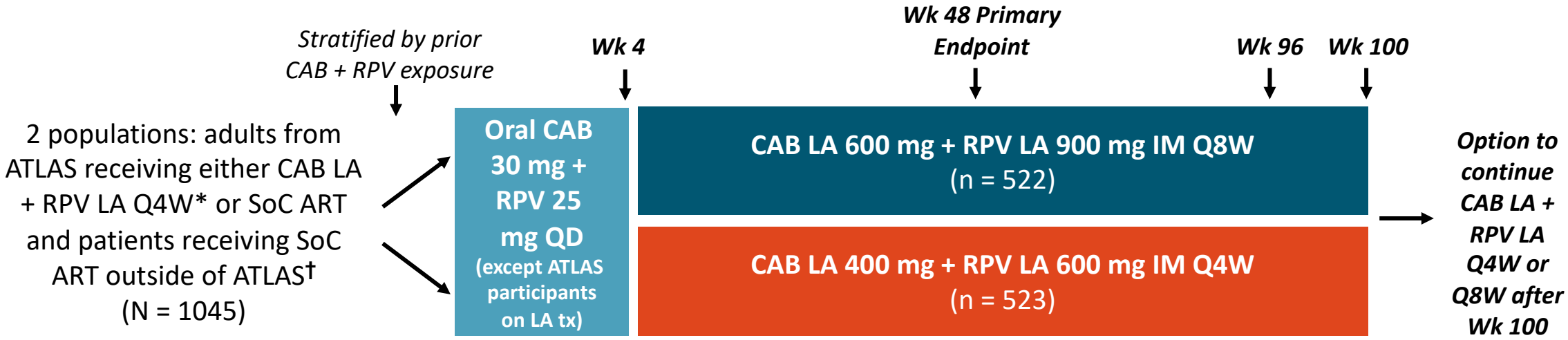
- avantajları
  - azalmış doz sıklığı
  - tablet yorgunluğuna çare
  - günlük ilaç alımı ile ilişkili stigmayı azaltma
  - uyumu iyi takip edebilme

- klinik çalışmalar iyi uyumu olan ve en az 6 aydır virolojik supresyonu olan iyi takipli poliklinik hastaları ile yapılmış
  - uyum sorunu olan veya viremik kontrolü iyi olmayan hastalarla çalışma sürüyor

- doz atlandığında veya tedavi kesildiğinde direnç çıkma olasılığı var

ATLAS-2M: Cabotegravir + Rilpivirine IM Q8W vs Q4W

- Multicenter, randomized, open-label phase III noninferiority trial



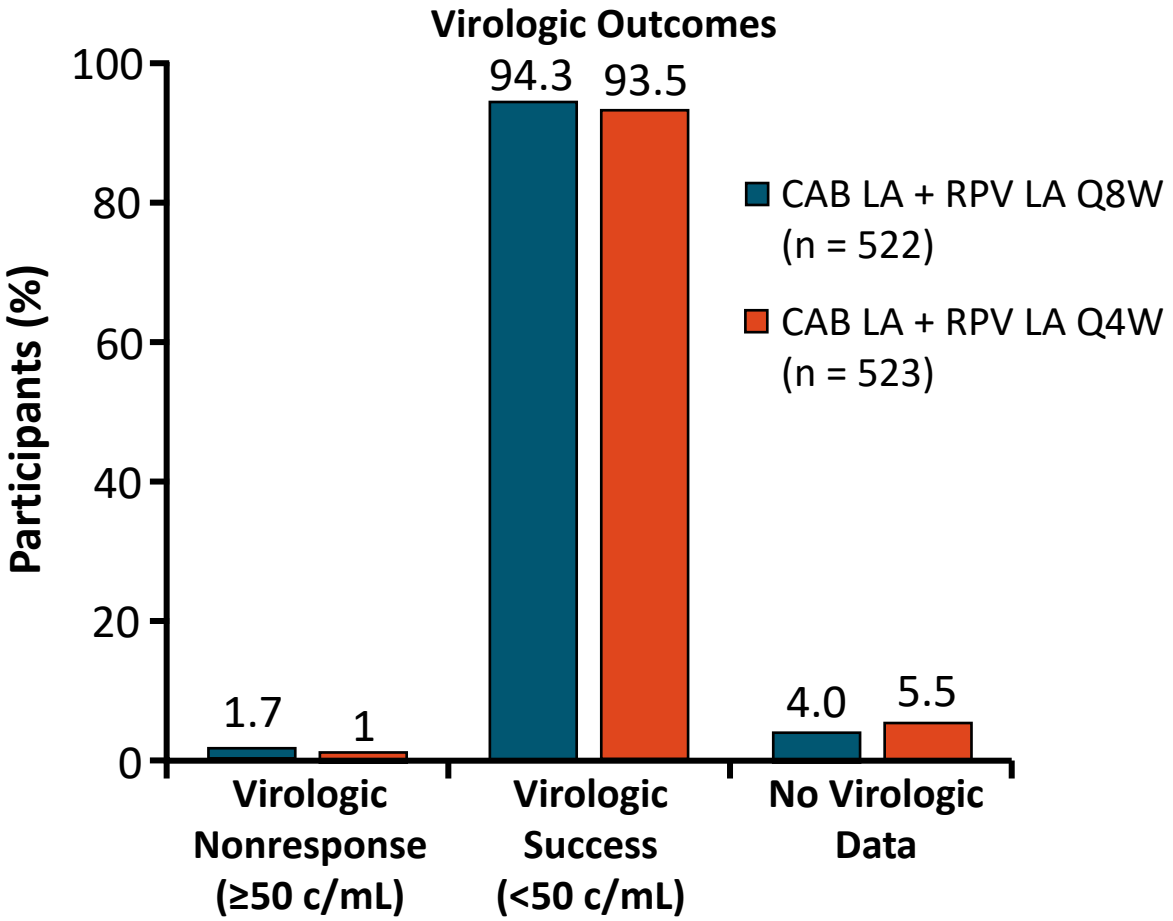
*Participants transitioning from ATLAS must have been on CAB LA + RPV LA Q4W or a current ART regimen through at least Wk 52 and had HIV-1 RNA <50 c/mL at screening. †SoC participants not transitioning from ATLAS study on uninterrupted current regimen (initial or second combined ART) for ≥6 mo prior to screening and documented evidence of ≥2 plasma HIV-1 RNA <50 c/mL in 12 mo prior to screening (one 6-12 mo and one within 6 mo prior to screening). Participants excluded if history of VF or if prior genotype results show any major INSTI or NNRTI mutations (except K103N).

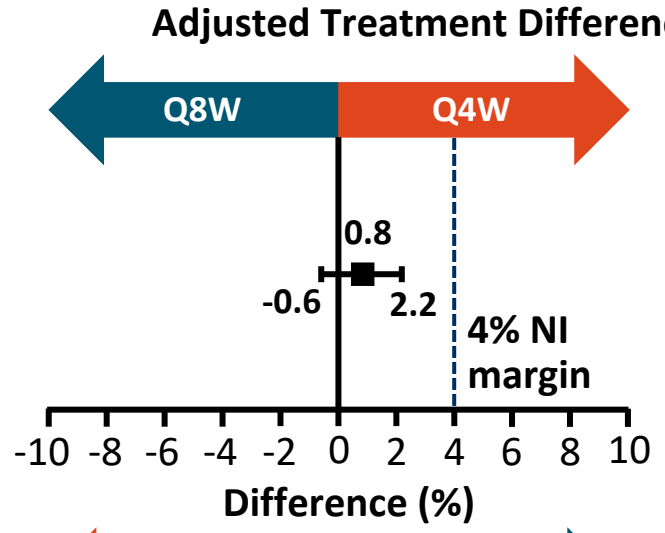
- Primary endpoint: HIV-1 RNA ≥50 copies/mL at Wk 48 by FDA snapshot in ITT-E
- Secondary endpoints: HIV-1 RNA <50 copies/mL at Wk 48 by FDA snapshot in ITT-E, safety and tolerability, VF, resistance, and treatment preference

Overton. Lancet. 2021;396:1994.

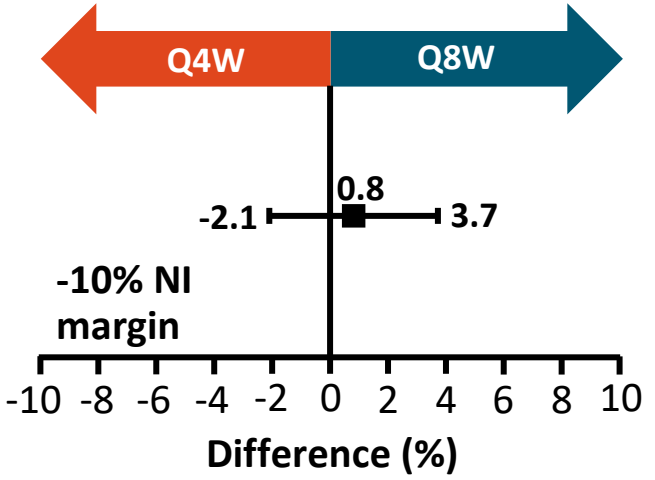
Slide credit: clinicaloptions.com

ATLAS-2M: Virologic Outcomes at Wk 48 in ITT-E by FDA Snapshot





Primary endpoint (HIV-1 RNA ≥50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W



Key secondary endpoint (HIV-1 RNA <50 c/mL): CAB LA + RPV LA Q8W noninferior to Q4W

*Based on Cochran-Mantel-Haenszel analysis adjusting for prior CAB + RPV exposure.

Overton. Lancet. 2021;396:1994.

Slide credit: clinicaloptions.com

Current HIV Research, 2018, *16*, 216-221

RESEARCH ARTICLE

Assessment of Transmitted HIV-1 Drug Resistance Mutations Using Ultra-Deep Pyrosequencing in a Turkish Cohort

Uluhan Sili[a,*], Burak Aksu[b], Aysun Tekin[a], Ufuk Hasdemir[b], Guner Soyletir[b] and Volkan Korten[a]

[a]*Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey;* [b]*Department of Medical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey*

The most frequent NNRTI PDRM was at the 138th position of reverse transcriptase (38.9%, n=14). Thirteen patients had E138A; 22.2% (n=8) of whom were at ≥20% level while 13.9% (n=5) were within minority variants, and one patient had E138K within minority variants. E138A mutation is not included in TDRM surveillance because of its highly polymorphic nature.

Drug resistance interpretation: RT — HIVDB 9.0 (2021-02-22)

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	**E138A**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors		Non-nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Susceptible	**doravirine (DOR)**	Susceptible
zidovudine (AZT)	Susceptible	**efavirenz (EFV)**	Susceptible
emtricitabine (FTC)	Susceptible	**etravirine (ETR)**	Potential Low-Level Resistance
lamivudine (3TC)	Susceptible	**nevirapine (NVP)**	Susceptible
tenofovir (TDF)	Susceptible	**rilpivirine (RPV)**	Low-Level Resistance

Table 2. List of transmitted drug resistance mutations detected.

Patient No.	TDRM Mutation	Frequency (%)
NRTI		
2	M41L	97.73
	T215D	77.50
	T215E*	4.50
18	T215D*	2.43
19	T215D*	3.36
22	M184I	100.00
26	T215D	25.00
49	K219Q*	2.26
NNRTI		
2	Y188H*	6.59
	P225H*	6.50
3	P225H*	2.50
8	P225H*	12.90
	Y188H*	6.55
PI		
36	D30N*	2.84
38	V32I*	3.13
50	M46I*	6.32

* minority variants (≥2% – <20%)
NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleos(t)ide reverse transcriptase inhibitors; PI, protease inhibitors.

XXXVIII. Türk Mikrobiyoloji Kongresi

HIV-1 ile enfekte, tedavi naif olgularda ilaç direnci mutasyonlarının ve HIV-1 alt tiplerinin araştırılması

Rabia Can Sarınoğlu,
Uluhan Sili, Burak Aksu, Ufuk Hasdemir, Güner Söyletir
Volkan Korten.
Marmara Üniversitesi Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı.
Marmara Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları Anabilim Dalı.
Kasım, 2018

Naif hastalarda tedavi öncesi ilaç direnci mutasyonları ve aktarılmış ilaç direnci mutasyonları oranları (n = 104)

	Tedavi öncesi ilaç direnci mutasyonları n (%)	Aktarılmış ilaç direnci mutasyonları n (%)
NRTI	8 (7,69)	4 (3,85)
NNRTI	12 (11,54)	4 (3,85)
PI	1 (0,96)	1 (0,96)
Herhangi	21 (20,19)	9 (8,65)

NNRTI; non-nükleozid revers transkriptaz inhibitörleri, NRTI; nükleoz(t)id revers transkriptaz inhibitörleri, PI;proteaz inhibitörleri

Hasta No	Genotip	Proteaz	NRTI	NNRTI
460	B	Yok	M41L,T215L	Yok
471	B	Yok	Yok	E138A
479	CRF43_02G	Yok	Yok	K103N,V179E
484	G + CRF02_AG	Yok	Yok	K103N, V179E
482	A	M46L	Yok	Yok
490	B	Yok	Yok	K103N
502	A	Yok	A62V	Yok
505	B	Yok	E44D	Yok
517	B+CRF02_AG	Yok	Yok	E138A
14	B+CRF02_AG	Yok	Yok	E138A
15	B+CRF02_AG	Yok	Yok	E138A
23	B	Yok	M41L,T215D	Yok
28	B + CRF02_AG	Yok	Yok	E138A
35	B	Yok	M41L,T215D	Yok
38	A	Yok	A62V	Yok
39	A	Yok	A62V	Yok
47	B	Yok	Yok	E138A
52	F	Yok	Yok	E138G
85	CRF28_BF	Yok	Yok	K103KN, E138EA
87	B	Yok	M41L,T215D	Yok
65	B	Yok	Yok	E138A

Factors That May Contribute to Risk of Treatment Failure With Long-Acting CAB/RPV

- Post hoc analysis of phase III data (Wk 48)
  - ATLAS and FLAIR (Q4W dosing)
  - ATLAS-2M (Q4W and Q8W dosing)
- Backwards elimination model (10 covariates)
- Factors associated with increased odds of confirmed virologic failure:
  - RPV RAMs at baseline (OR: 40.36; *P* <.001)
  - Log_2 of post hoc Wk 8 RPV trough concentration (OR: 5.00; *P* = .002)
  - Baseline HIV-1 subtype A6/A1 (OR: 5.92; *P* = .008)
  - BMI ≥30 kg/m^2 at baseline (OR: 1.13; *P* = .020)
- Q8W dosing was not a significant factor

Baseline Factors	Patients, % (n)*	CVF, % (n)	HIV-1 RNA <50 c/mL, % (n)
None	70.5 (732)	0.41 (3)	94.8 (694)
1	26.2 (272)	0.37 (1)	96.0 (261)
≥2	3.37 (35)	25.71 (9)	71.4 (25)

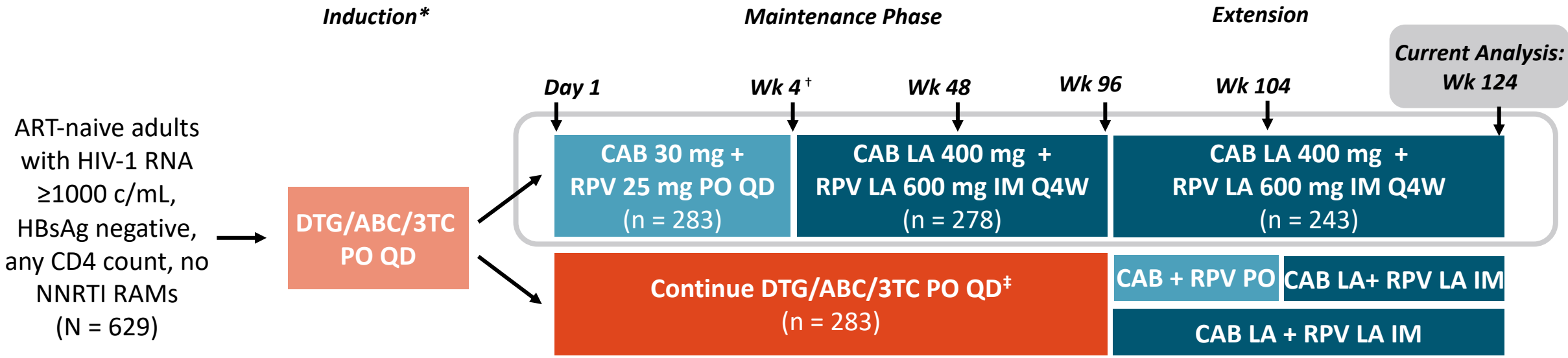
*For CVF analysis, N = 1039

Cutrell. AIDS. 2021;[Epub].

Slide credit: clinicaloptions.com

FLAIR Wk 124: Long-Acting Cabotegravir + Rilpivirine for Treatment-Naive PWH

- Multicenter, randomized, open-label phase III non-inferiority trial



*Patients with HIV-1 RNA <50 c/mL at end of induction continued to maintenance phase. † Loading dose: CAB LA 600 mg IM + RPV LA 900 mg IM; regular dosing begun at Wk 8.

- Previous analysis demonstrated noninferiority of switching virologically suppressed participants from daily oral DTG/ABC/3TC to monthly injections of CAB + RPV LA IM over 96 wk[1,2]

- **Wk 124 endpoints: HIV-1 RNA ≥50 and <50 c/mL, confirmed virologic failure, safety/tolerability[3]**

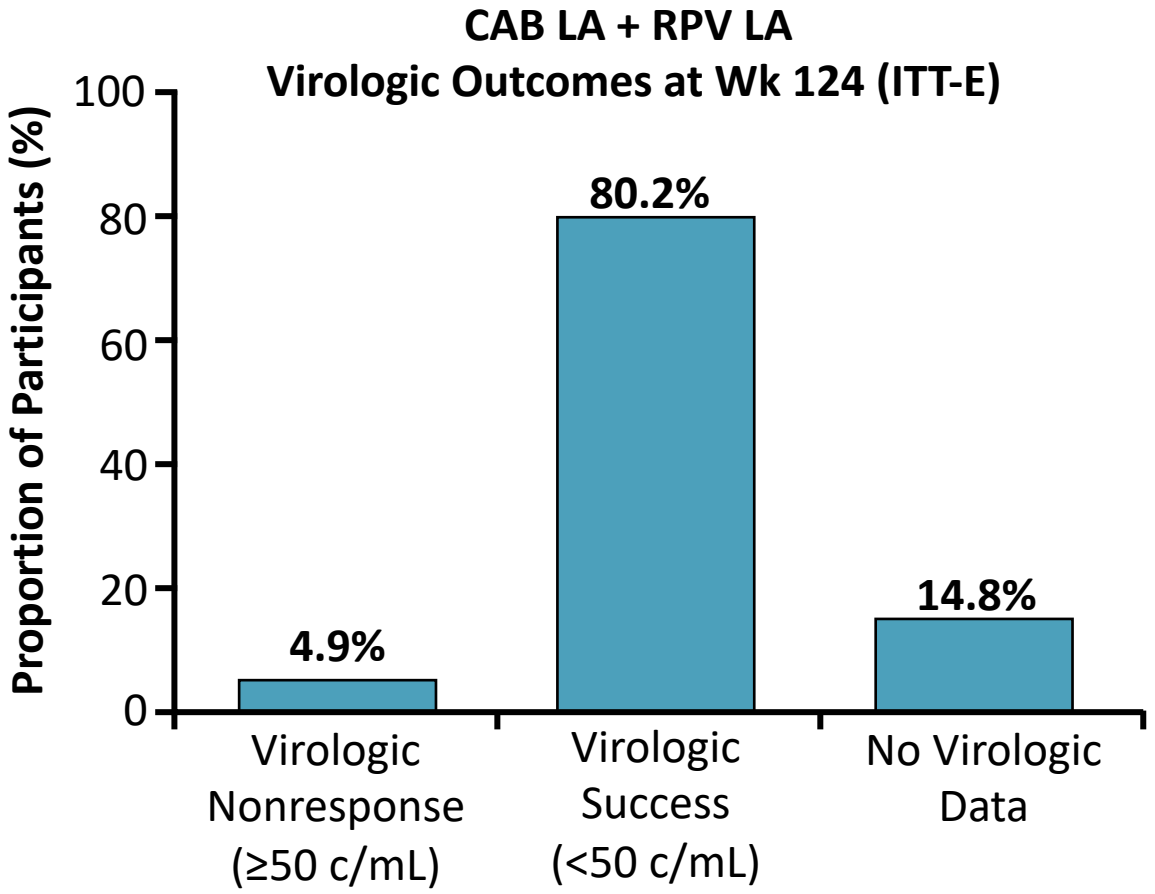
1. Orkin. NEJM. 2020;382:1124. 2. Orkin. Lancet HIV. 2021;8:e185. 3. Orkin. IAS 2021. Abstr OAB0302.

FLAIR: Wk 124 Virologic Snapshot Outcomes With CAB LA + RPV LA

- 229 participants ongoing
- Since Wk 96 analysis
  - 5 additional participants had HIV-1 RNA ≥50 c/mL
  - 1 additional participant had CVF
  - 13 additional participants not recorded as suppressed, most due to non-virologic reasons

Virologic Outcome, n (%)	Wk 96	Wk 124
Nonresponse (≥50 c/mL)	9 (3.2)	14 (4.9)
Success (<50 c/mL)	245 (86.6)	227 (80.2)
No virologic data	29 (10.2)	42 (14.8)
Confirmed virologic failure*	4 (1.4)	5 (1.8)

*2 consecutive plasma HIV-1 RNA ≥200 c/mL; 1 additional patient since Wk 96 analysis



Orkin. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

FLAIR: Additional CVF Patient Characteristics

Characteristic (Wk 108)	
Sex at birth	Male
BMI, kg/m^2	24.7
HIV-1 subtype	A6
Baseline RAMs	None
Viral load at suspected/confirmed virologic failure, copies/mL	887/1112
Treatment-emergent NNRTI RAMs	V106V/A, V108V/I, E138G, M230L
Treatment-emergent INSTI RAMs	N155H, R263K
Wk 8 troughs: CAB µg/mL/RPV ng/mL	1.05/24.6*
Wk 108 troughs: CAB µg/mL/RPV ng/mL	1.73/79.5

- Resuppressed to HIV-1 RNA <50 c/mL at 3 mo on EFV/FTC/TDF

*By comparison, Wk 8 CAB and RPV geometric mean (5th, 95th percentile) for the FLAIR population was 1.56 µg/mL (0.551, 3.61) and 41.2 ng/mL (17.9, 92.7), respectively.

Orkin. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

FLAIR: Wk 124 Safety and Tolerability

- Safety profile at Wk 124 consistent with earlier analyses

Adverse event, n (%)	CAB LA + RPV LA Wk 124 (n = 283)	Increase Since Wk 96
Any AE	271 (96)	7 (2)
Grade 3/4 AE	38 (13)	9 (3)
Drug-related AE	102 (36)	7 (2)
▪ Pyrexia	18 (6)	1 (<1)
▪ Headache	15 (5)	0
▪ Fatigue	10 (4)	3 (1)
Drug-related grade 3/4 AE	5 (2)	1 (<1)
AE leading to withdrawal	15 (5)	1 (<1)
Any serious AE	33 (12)	2 (1)
Drug-related serious AE	1 (<1)	0
Fatal AE	0	0

- Injection site reactions (ISR) were most common AE; mostly low-grade
- 17,392 injections; 3,732 ISR events

ISR outcome	CAB LA + RPV LA Wk 124 (n = 283)
No. injections	17,392
ISR events	3732
Pain, n (% of injections)	3131 (18)
Nodule, n (% of injections)	162 (<1)
Induration, n (% of injections)	158 (<1)
Median duration of ISR, days	3
Withdrawals due to ISR, n (% of participants)	7 (2)

Orkin. IAS 2021. Abstr OAB0302.

Slide credit: clinicaloptions.com

- ayrı ventrogluteal bölgelere i.m. enjeksiyon
- BMI ≥30 kg/m2 ise daha uzun iğne ucu kullan
- +4°C'de saklanıyor; enjeksiyondan önce ≥15 dk oda sıcaklığında olmalı
- planlanan enjeksiyondan 7 gün önce veya sonra yapılabilir
- >7 gün geçmiş ise oral veya im tamamlama yap

CUSTOMIZE: Background

- LA intramuscular injection of CAB + RPV approved by FDA and recommended by treatment guidelines for the maintenance of virologic suppression in PLWH[1,2]
- Current real-world study analyzes the implementation of provider-administered CAB LA + RPV LA in diverse US healthcare settings and outcomes after 12 months[3]

- *Uygulanabilirliği gerçek yaşamda test edilmiş*

1. US Department of Health and Human Services. aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/15/virologic-failure.
2. Saag. JAMA. 2020;324:1651. 3. D'Amico. Glasgow HIV 2020. Abstr O414. 4. Czarnogorski. IAS 2021. Abstr OAD0705.

CUSTOMIZE: Study Design

- Phase IIIb, hybrid III implementation-effectiveness study of monthly CAB LA + RPV LA injection
  - Quantitative and qualitative data collected from July 2019 to October 2020 to examine barriers to, facilitators of, and effective strategies for regimen delivery
  - Clinic types included universities, private practices, AIDS healthcare foundations, HMOs, and federally qualified health centers across the United States
  - 26 providers (physicians, injectors, administrators) from 8 clinics completed surveys and interviews at baseline, interim (Month 4), and Month 12
  - 109 patients received monthly CAB LA + RPV LA (following 1-mo oral lead-in) and completed surveys
    - 86% men, 57% white, 37% black, median BMI 27 (17-55) kg/m^2

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Baseline Characteristics

HCP Views of CAB LA + RPV LA Implementation Over Time, %	Baseline (N = 26)	Month 4 (N = 24)	Month 12 (N = 23)
Acceptability by clinic type			
▪ FQHC (n = 8)	84	96	100
▪ University (n = 6)	96	100	100
▪ Private practice (n = 6)	92	88	100
▪ AHF (n = 3)	100	100	100
▪ HMO (n = 3)	92	67	67
Feasibility *(olabilirlik)* of CAB + RPV LA			
▪ Seems implementable- *uygulanabilir*	96	88	96
▪ Seems possible- *olası*	100	88	96
▪ Seems doable- *yapılabilir*	96	83	96
▪ Seems easy to administer- *kolaylık*	69	79	91

- Despite COVID-19, acceptability *(kabul edilebilirlik)* scores increased between Months 4 and 12
- Adherence to ±7-day administration window was 94% through Month 12; nonadherence was accounted for by:
  - Early dosing (4%)
  - Late dosing (<1%)
  - Coverage with oral CAB + RPV due to COVID-19 (<1%)

Czarnogorski. IAS 2021. Abstr OAD0705.

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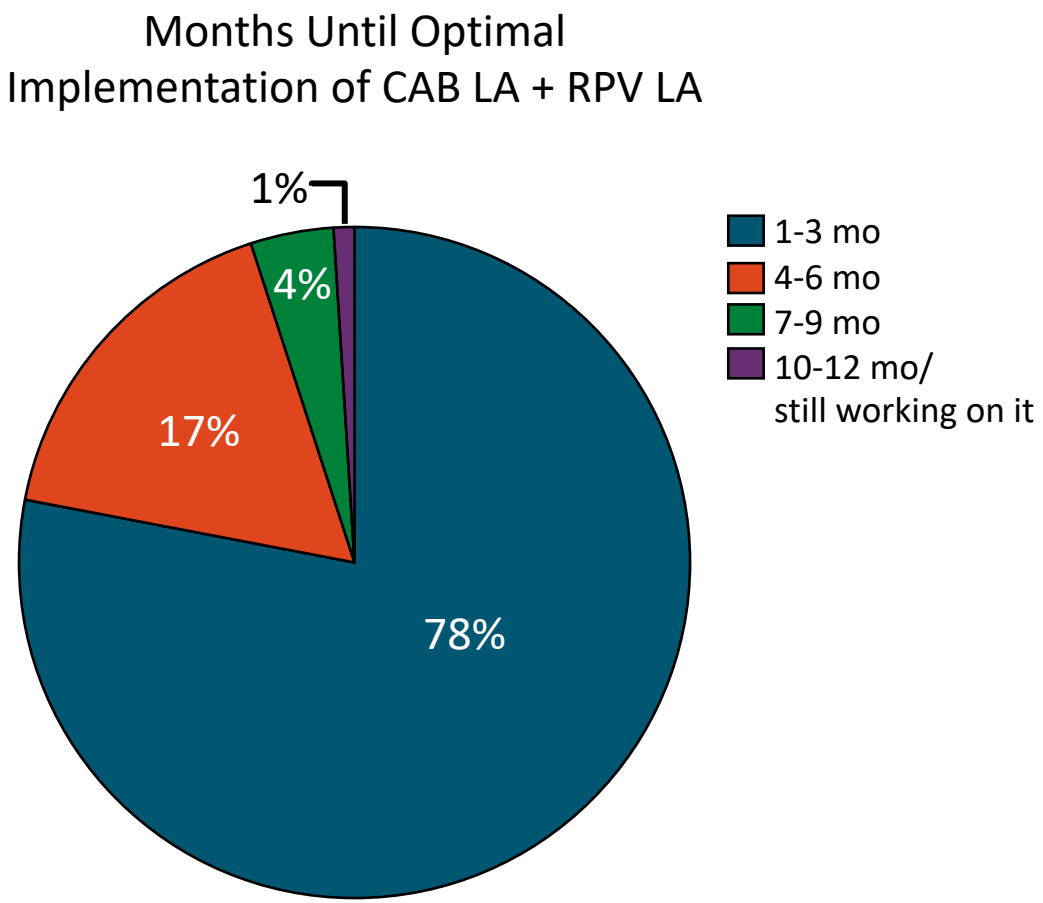
CUSTOMIZE: Time and Strategies for Optimal Implementation



- Key strategies for successful **clinic implementation**
  - Good staff communication
  - Teamwork
  - Use of a web-based treatment planner
- Key implementation strategies for **patient adherence**
  - Good communication about dosing window
  - Effective appointment reminder systems
  - Designated staff for appointment tracking

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: HCP and Patient Implementation Barriers

Perceived Barriers to CAB LA + RPV LA Implementation Among HCPs Over Time, %	Baseline (N = 26)	Month 4 (N = 24)	Month 12 (N = 23)
Patient ability to keep monthly appointment	81	38	39
Patient transportation for monthly appointment	77	38	43
Flagging/awareness of missed visits	73	46	22
Staff resourcing for clinic flow	54	38	17
Rescheduling missed visits	50	21	26
Patients failing treatment due to missed dose/visit	50	17	13
Management of patients with other needs	50	33	22
Injection-site soreness	46	42	48

- 74% of patients reported no interference with monthly injection visits
- Perceived barriers to monthly injectable CAP LA + RPV LA implementation inconsistent between patients and providers

Perceived Barriers to CAB LA + RPV LA Implementation at Month 12, %	Patients (N = 102)	HCPs (N = 23)
Injection pain/soreness	15	48
Patient transportation	3	43
Rescheduling missed visits	1	26
Scheduling injection visits	2	17

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Clinical Outcomes at Month 12 and Time Spent in Clinic

Virologic Outcome at Month 12, n (%)	Patients (N = 115)
Virologic success (<50 copies/mL)	101 (88)
Virologic nonresponse (≥50 copies/mL)	0
No virologic data ▪ Discontinued due to AE or death ▪ Discontinued for other reasons ▪ On study but missing data in window	14 (12) 5 (4)* 8 (7) 1 (1)†
Scheduling injection visits	2

* 2 deaths, both unrelated to study treatment.
† Due to COVID-19.

- Tolerability and safety of monthly CAB LA + RPV LA through Month 12 consistent with phase III data
  - Fatigue (5%) and headache (5%) were most common non-ISR drug-related AEs
  - 2 (2%) patients withdrew due to ISRs
- 93% of patients thought time spent in clinic for CAB LA + RPV LA injection was extremely/very acceptable
- Median duration of visit length decreased over time
  - Month 1: 57 min
  - Month 11: 34 min

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Impact of COVID-19

- 93% of patients maintained monthly CAB LA + RPV LA dosing schedule despite COVID-19 disruptions; remainder used temporary oral therapy (7%; CAB + RPV or alternative ART) or rescheduled LA injections (<1%)
- 19% of study patients (19/102) had a COVID-19–impacted visit (missed/rescheduled visit, quarantine, COVID-19 diagnosis, clinic closure)
  - CAB + RPV LA acceptability and treatment preference remained high among these individuals
- At Month 12, 97% of study patients reported they will continue to use monthly CAB LA + RPV LA

Patient Perspectives of CAB LA + RPV LA at Month 12, %	Impacted by COVID-19 (n = 19)	Not Impacted by COVID-19 (n = 83)	Total (N = 102)
Acceptability	97	98	98
Treatment preference			
▪ CAB LA + RPV LA	95	92	92
▪ Daily oral tablet regimen	5	2	3
▪ No preference	0	6	5

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Conclusions

- In this implementation-effectiveness study of monthly injectable CAP LA + RPV LA:
  - Healthcare staff across clinic types found implementation both feasible and acceptable despite disruptions due to COVID-19
  - 78% of healthcare staff indicated that optimal implementation of the regimen was achieved in 1-3 mo
  - HCPs' perceived barriers to implementation decreased by Month 12; 74% of patients reported that nothing was interfering with monthly injection visits
  - Treatment was effective and well tolerated across a variety of real-world clinic settings, consistent with the phase III clinical program
- Investigators concluded that key success factors for monthly injectable CAB LA + RPV LA were:
  - Selecting patients with good historical adherence to appointments
  - Having dedicated, clinically trained staff responsible for managing appointments, rescheduling, and setting reminders

Czarnogorski. IAS 2021. Abstr OAD0705.

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Lenacapavir

Capsid inhibitörü

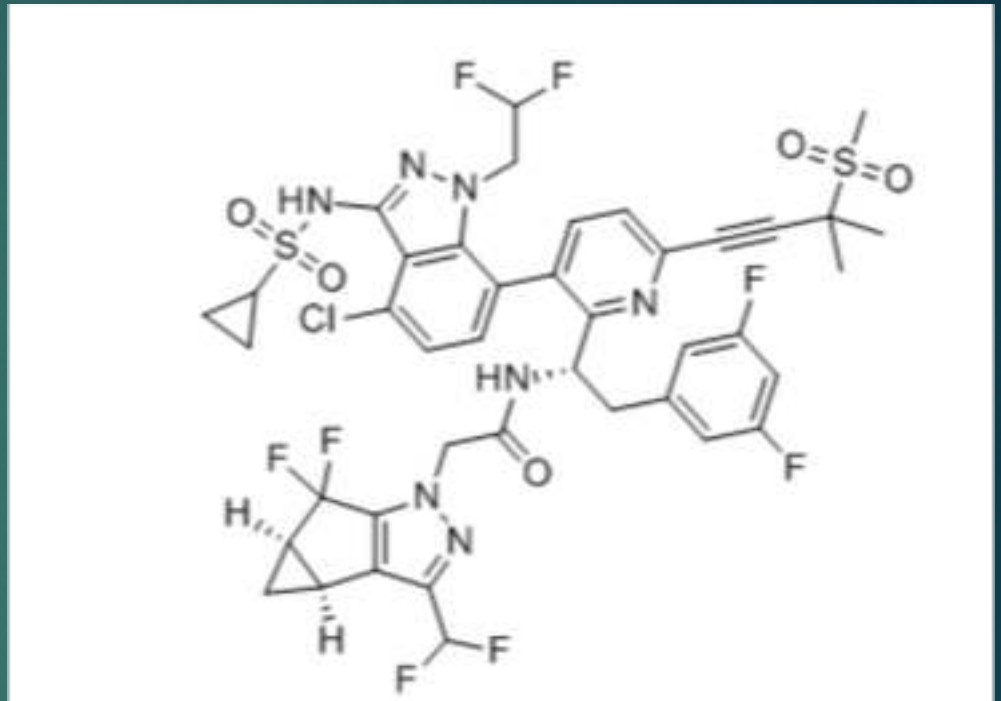
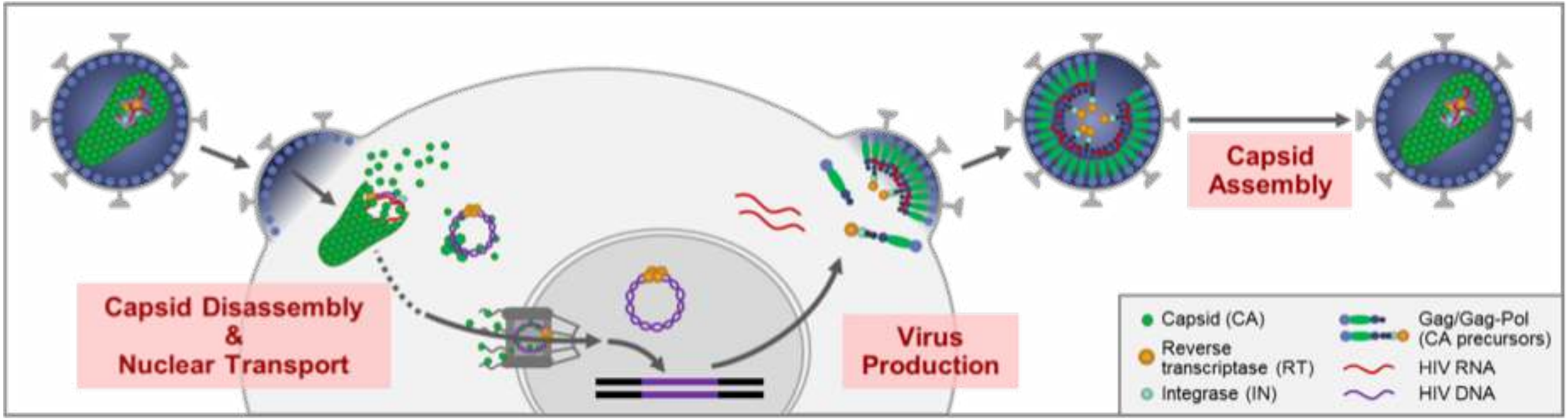


Figure 6. GS-6207.

First-in-Class HIV Capsid Inhibitor: Mechanism of Action

HIV capsid is essential at multiple stages in the viral life cycle

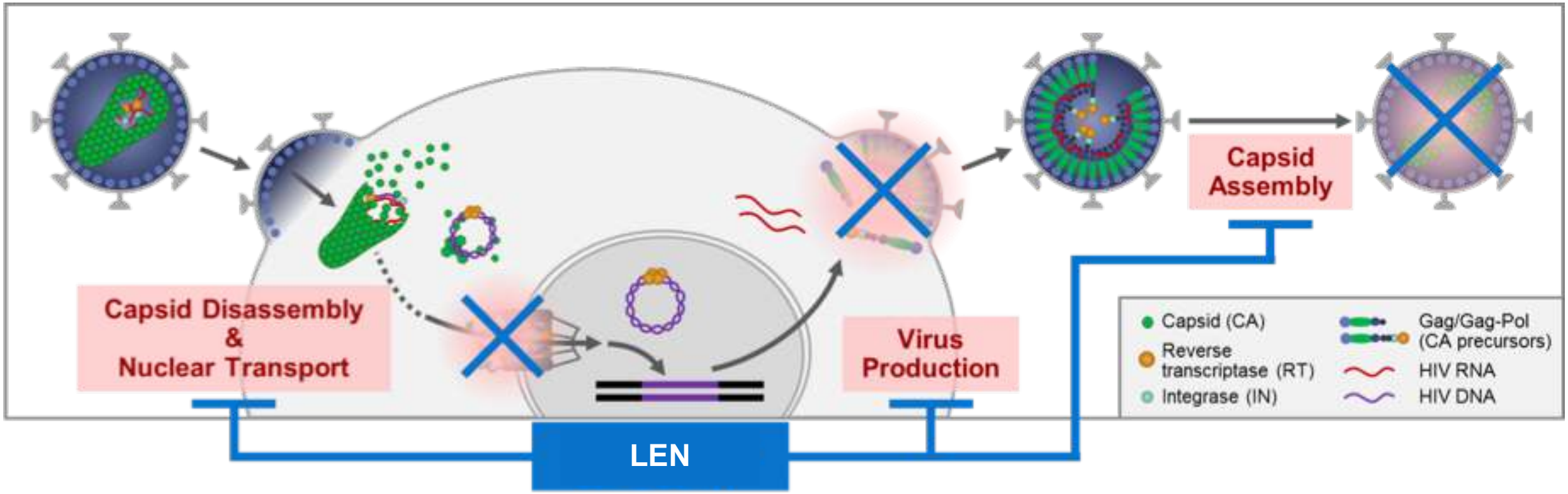


LEN is a first-in-class HIV capsid (CA) inhibitor with a multi-stage mode of action and picomolar potency (EC_{50} = 50pM)

Margot N, et al. EACS 2019. Basel, Switzerland. PE13/22

First-in-Class HIV Capsid Inhibitor: Mechanism of Action

HIV capsid is essential at multiple stages in the viral life cycle

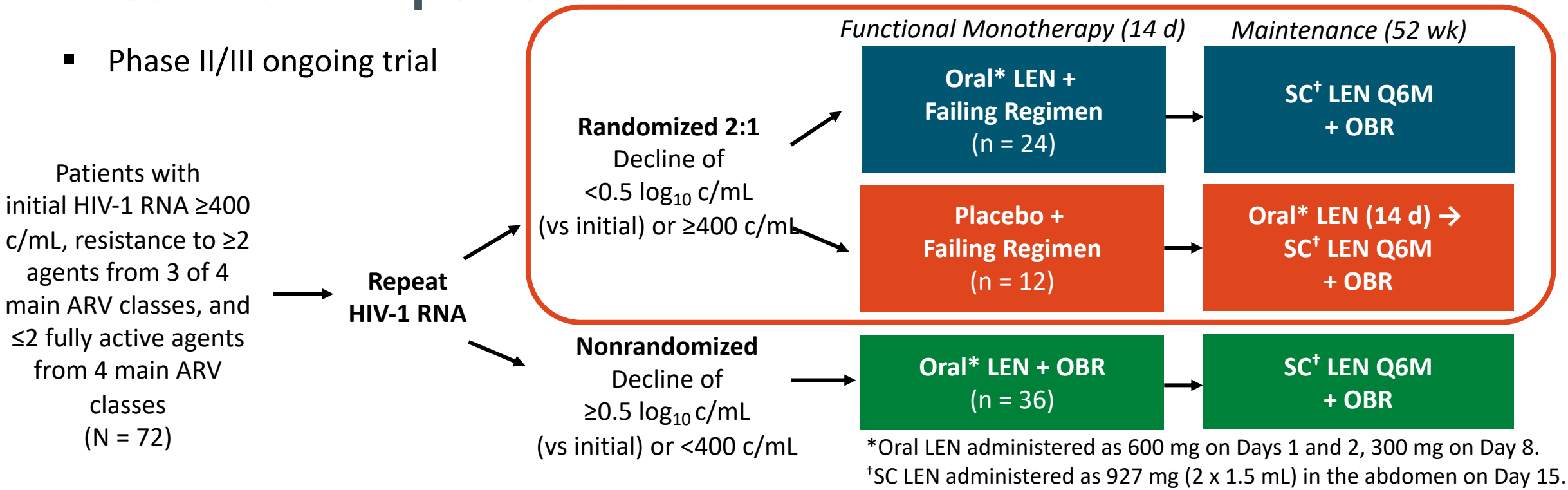


LEN inhibits CA-mediated nuclear entry of viral DNA, HIV assembly, and proper capsid formation, functions essential for viral replication

Margot N, et al. EACS 2019. Basel, Switzerland. PE13/22

CAPELLA: Wk 26 Analysis of Lenacapavir in Heavily Treatment-Experienced PWH

- Phase II/III ongoing trial



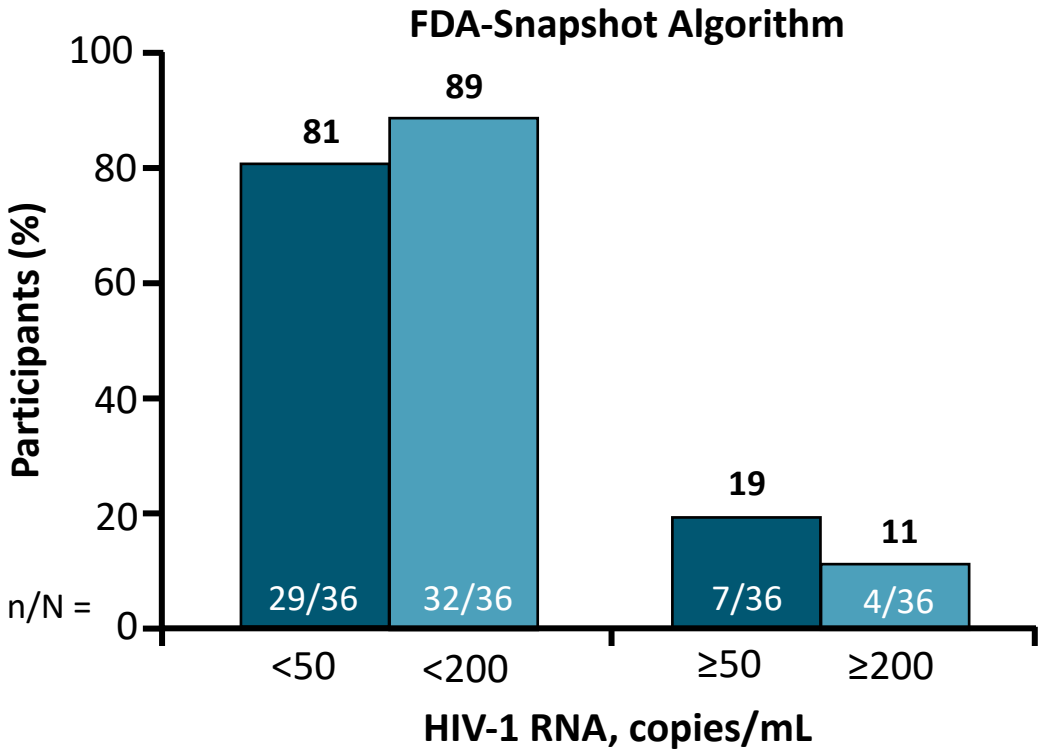
*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8.
†SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.

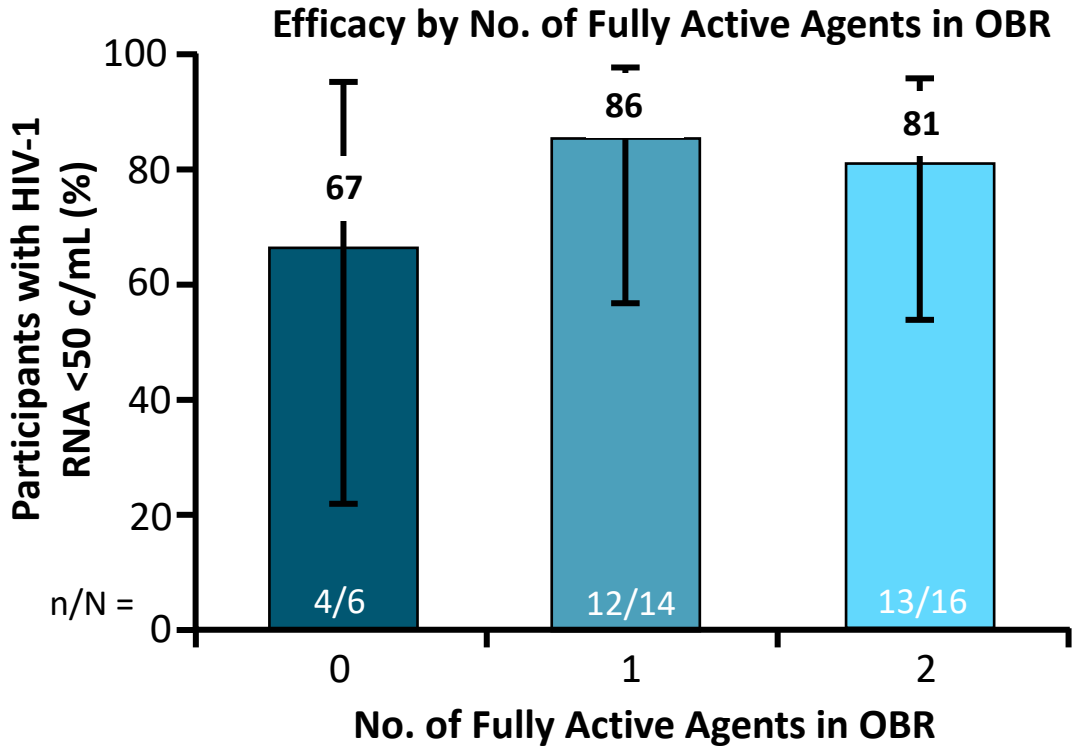
- Participants with known BL resistance to ≥2 drugs in class - NRTI: 99%, NNRTI: 97%, PI: 81%, INSTI: 69%
- Primary endpoint achieved in prior analysis: ≥0.5-log decline in HIV-1 RNA with oral LEN 88% vs placebo 17% at Day 14 in randomized cohort (*P* <.0001)[1]
- **Secondary endpoints: HIV-1 RNA <50 c/mL, <200 c/mL at Wk 26 in randomized cohort**[2]

1. Segal-Maurer. CROI 2021. 2. Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

CAPELLA Secondary Endpoints: Wk 26 Efficacy in Randomized Cohort





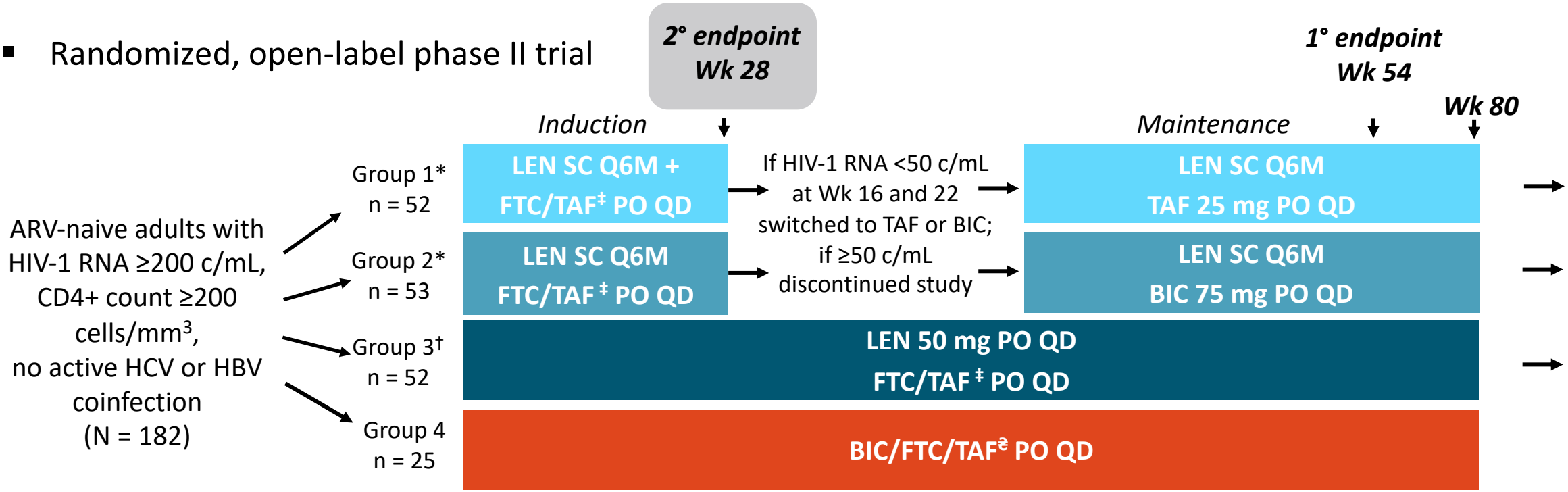
- **Mean change in CD4+ cell count: +81 cells/mm^3**
- Proportion of participants with very low CD4+ cell count (<50 cells/mm^3) **decreased from 22% (8 of 36) at baseline** to **0% (0 of 34) at Wk 26**

Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

CALIBRATE: Lenacapavir in Treatment-Naive PWH

- Randomized, open-label phase II trial



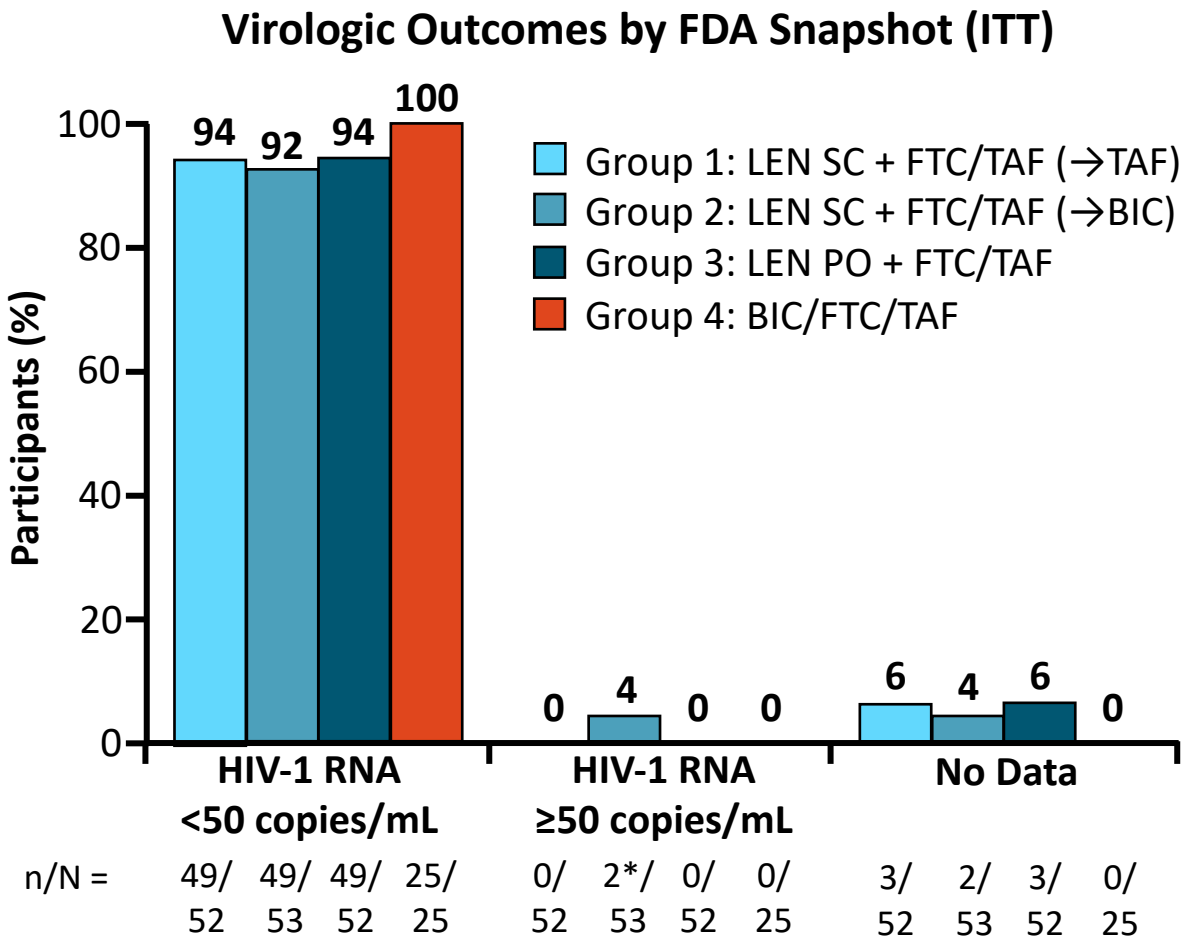
*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M.
†LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ‡FTC/TAF 200/25 mg. ⁂BIC/FTC/TAF 50/200/25 mg.

- Participants at baseline: median age 29 yr; 93% male; 52% Black race; 45% Latinx ethnicity
- Primary outcome: proportion with HIV-1 RNA <50 c/mL at Wk 54; **secondary outcomes: proportion with HIV-1 RNA <50 c/mL at Wk 28**, 38, and 80; change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Wk 28, 38, 54, and 80

Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

CALIBRATE: Wk 28 Virologic Outcomes



*1 discontinuation due to not meeting a protocol criterion of HIV-1 RNA <50 c/mL prior to Wk 28; 1 participant discontinued on Day 2.

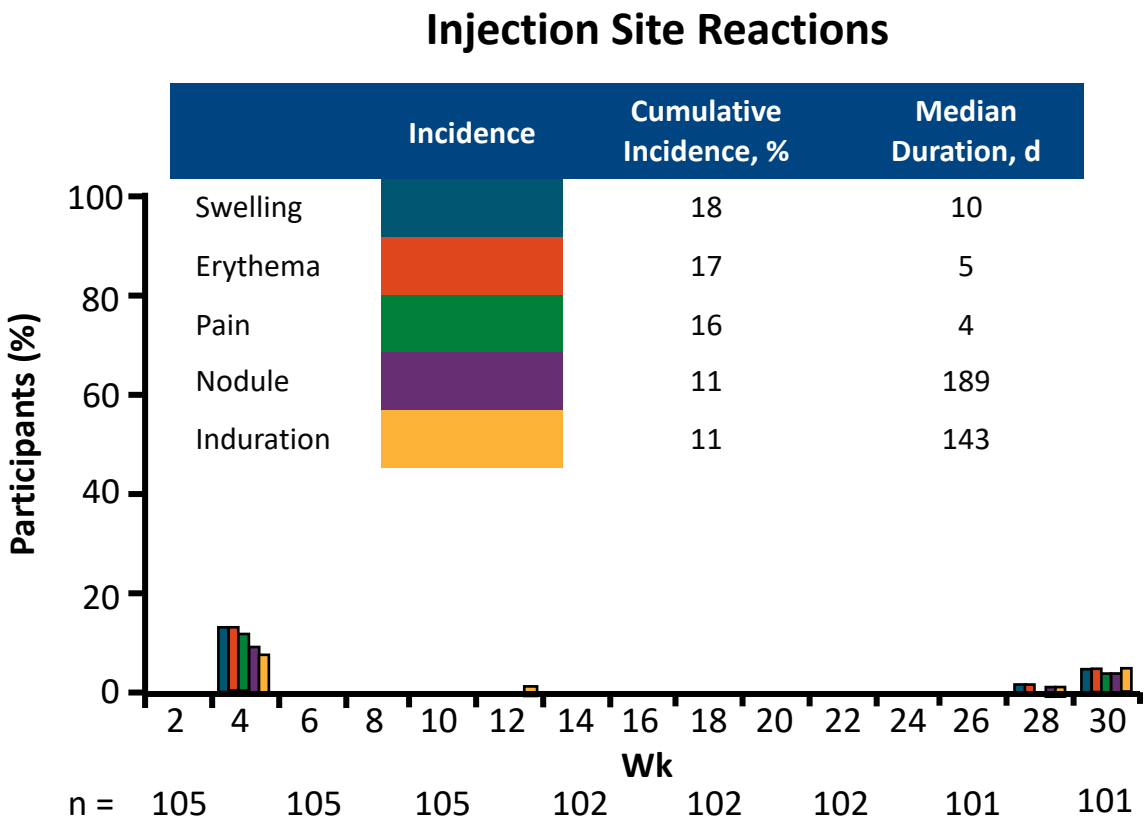
- One participant in **LEN SC + FTC/TAF → BIC** arm had emergent resistance mutations at Wk 10
  - CA: Q67H + K70R (LEN fold change = 20)
  - RT: M184M/I
- Plasma LEN concentrations consistently in target range

Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

CALIBRATE: Adverse Events and Injection Site Reactions

- LEN was well tolerated with favorable safety profile
  - No SAEs or grade 4 AEs related to study drug
  - Most common AEs: headache and nausea (11% each)
  - GI AEs in SC vs oral LEN:
    - Nausea: 12% vs 8%
    - Diarrhea: 6% vs 8%
- ISRs in 39% of participants; 83% were grade 1 and generally resolved in days
- 2 discontinuations due to ISRs (grade 1 injection site induration)



Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

Özet

- En az 3 aydır virolojik baskılanması olan, daha önce tedavi başarısızlığı veya bilinen/ şüphelenilen ilaç direnci olmayan hastalarda uzun-etkili enjekte edilebilen CAB + RPV güvenli ve etkili
- Uzun-etkili tedaviler daha sık kullanılacak gibi gözükmekte
  - Lenacapavir + Islatravir = uzun etkili oral ve enjekte edilebilir formülasyon
- Enjeksiyon bölgesi reaksiyonları sık ama zamanla azalmakta
- Enjeksiyonların planlanması için poliklinik düzenlemesi gerekecek
  - Hasta uyumu önemli

Uzun Etkili Tedaviler

II. Türkiye EKMUD HIV Akademisi

İLGİNİZ İÇİN TEŞEKKÜRLER!

DOÇ. DR. ULUHAN SİLİ

MARMARA ÜNİVERSİTESİ TIP FAKÜLTESİ

ENFEKSİYON HASTALIKLARI VE KLİNİK MİKROBİYOLOJİ AD

uluhan@hotmail.com

MARMARA ÜNİVERSİTESİ 1883 | Tıp Fakültesi