Uzun Etkili Tedaviler

Antiretroviral Tedavi

DoÇ. Dr. UlUhan sili

Marmara üniversitesi tıp fakültesi

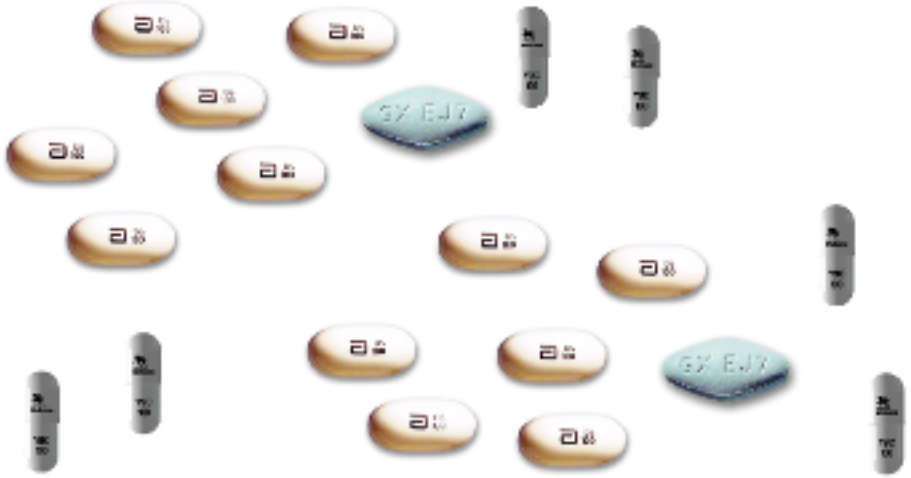
Enfeksiyon hastalıkları ve klinik mikrobiyoloji AD

20 kasım 2021 10:00 – 10:20

MARMARA ÜNİVERSİTESİ 1883 Tıp Fakültesi

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

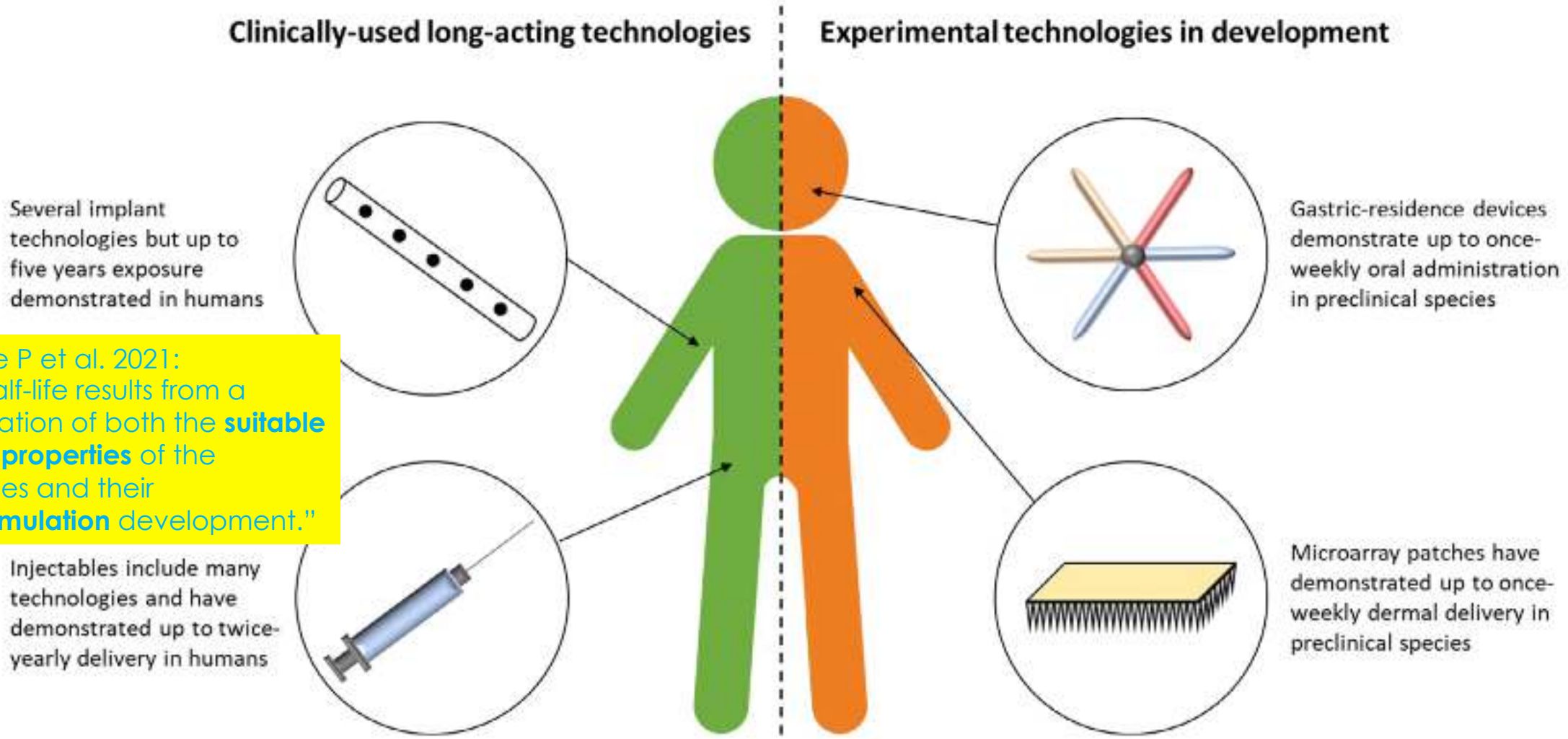
#35YearsOfAIDS

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*
  3. *Terapötik HIV aşıları*

https://www.niaid.nih.gov/diseases-conditions/future-hiv-treatment
6-11-2021



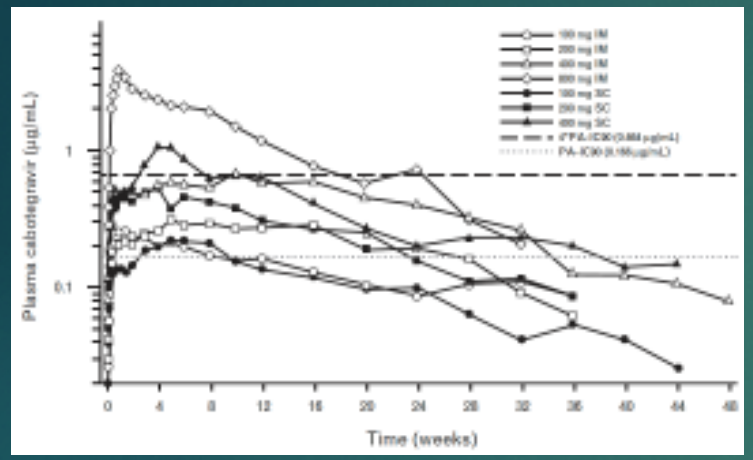
Thoueille P et al. 2021:
"long half-life results from a combination of both the **suitable intrinsic properties** of the molecules and their **nanoformulation** development."

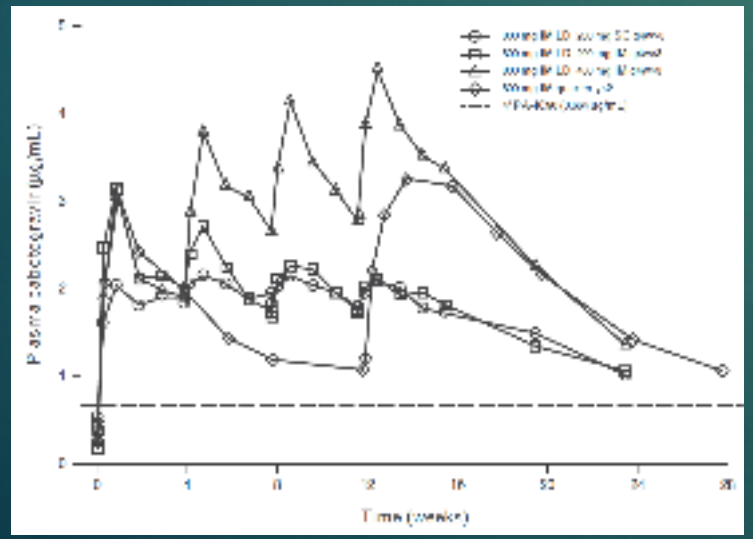
Fig. 1. Examples of long-acting and extended-release drug delivery technologies in preclinical and clinical development for the treatment and prevention of human deficiency virus (HIV) infection.

Formulation and pharmacology of long-acting cabotegravir

Christine Trezza[a], *Susan L. Ford*[a], *William Spreen*[a], *Rennan Pan*[b], *Stephen Piscitelli*[a]

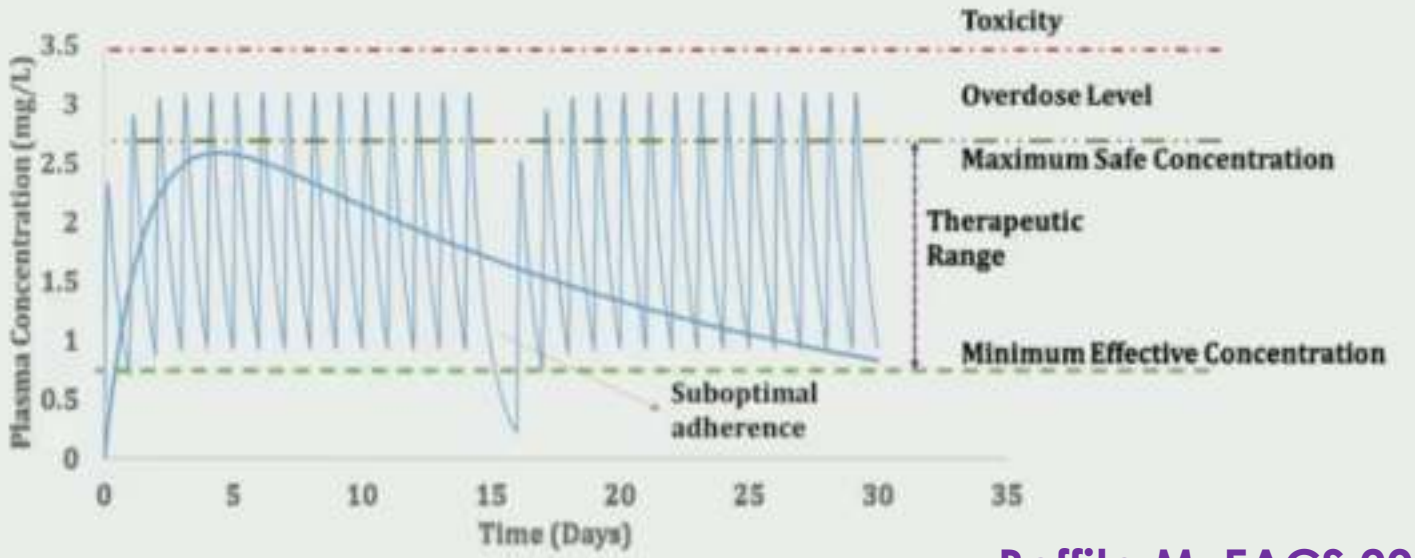
Curr Opin HIV AIDS 2015, 10:239–245





Long-acting PK

Long-acting drugs:
Are slowly absorbed and slowly excreted
Persist in the circulation/tissues
Are effective over a long period of time



Boffito M. EACS 2021

Table 1
Long-acting drugs in development for human immunodeficiency virous (HIV) prevention (Px) and treatment (Tx) by infusion, injection or implant.

Antiretroviral class/agent	Formulation	Development stage
Nucleoside reverse transcriptase inhibitors (NRTI)		
Islatravir (MK-8591)	Implant/Oral	Phase 1/2 (Px)
TAF	Implant	Phase 1/2 (Px)
GS-9131	Implant	Preclinical
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Rilpivirine	Injectable	Phase 3/NDA
Elsulfavirine	Injectable	Preclinical
Protease inhibitors (PI)		
Atazanavir	Injectable	Preclinical
Ritonavir	Injectable	Preclinical
Integrase strand transfer inhibitors (INSTI)		
Cabotegravir	Injectable	Phase 3/NDA, phase 2/3 (Px)
Dolutegravir	Implant	Preclinical (Px)
Raltegravir	Injectable	Preclinical
Entry inhibitors		
Ibalizumab	Intravenous	FDA-approved (Tx)
Leronlimab (PRO 140)	Intravenous and Injectable	Phase 3
Albuvirtide	Intravenous and injectable	Approved in China
bnAbs (e.g. VRC01, VRC07)	Intravenous	Phase 1/2/3
Combinectin	Intravenous	Phase 1
Capsid inhibitors		
Lenacapavir (GS-6207)	Injectable	Phase 2

NDA, New Drug Application; FDA, US Food and Drug Administration; bnAbs, broadly-neutralising antibodies.

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.

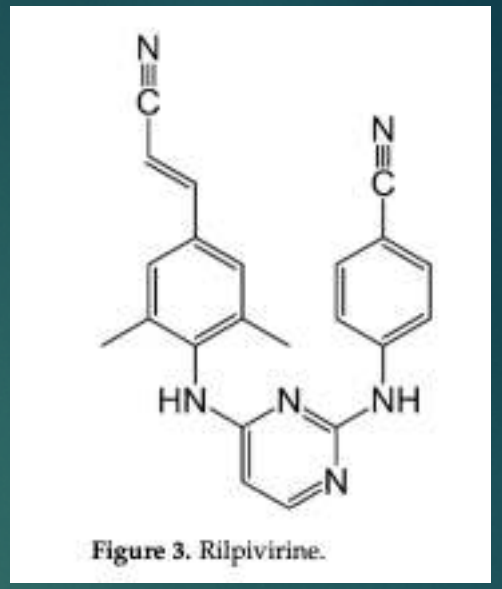


Figure 3. Rilpivirine.

Cabotegravir – *INSTI*

Rilpivirine *NNRTI*

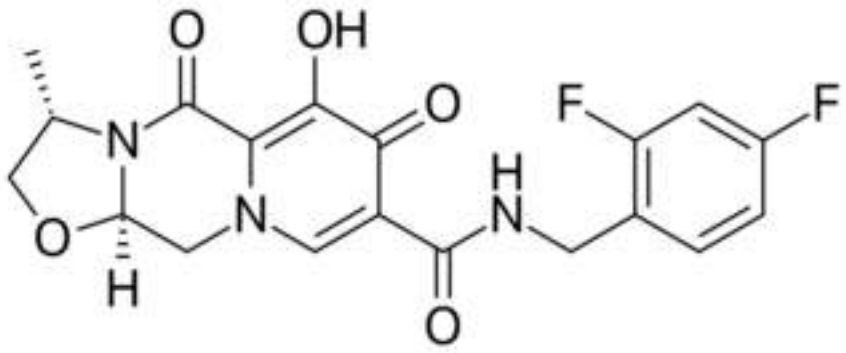
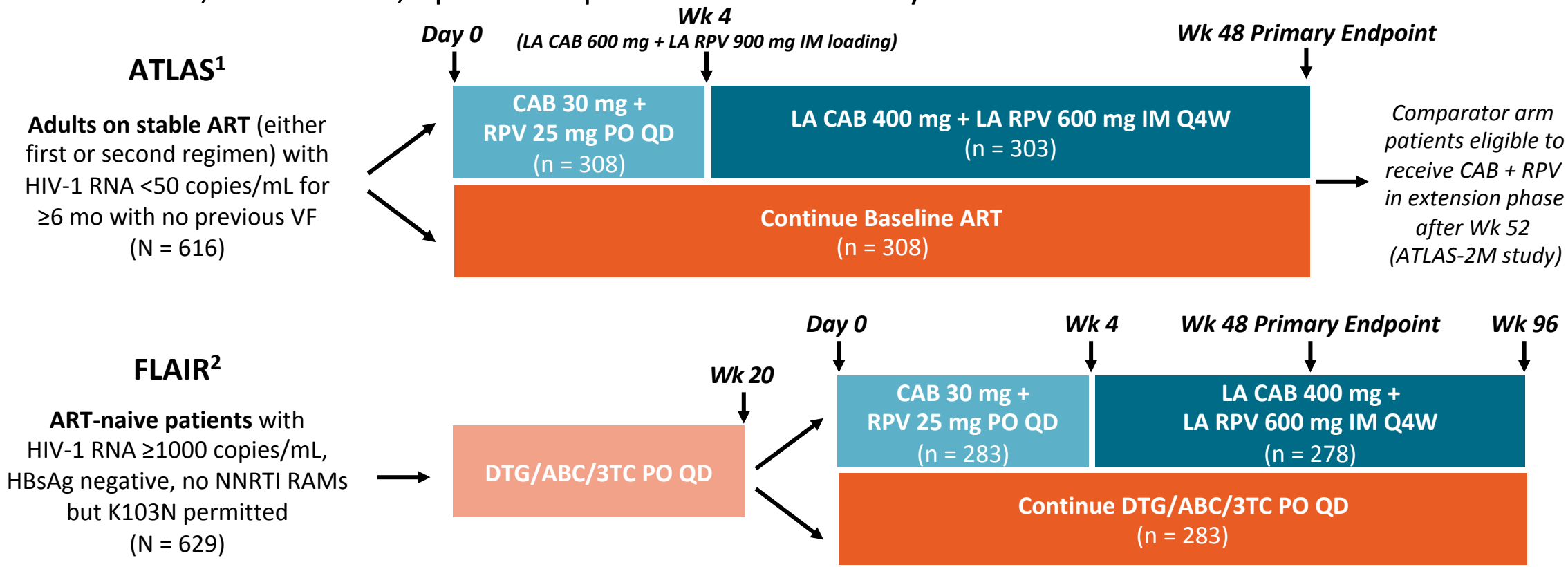


Figure 4. Cabotegravir.

ATLAS ve FLAIR: Oral tedavi ile virolojik baskılama sonrasında uzun etkili intramüsküler CAB + RPV

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

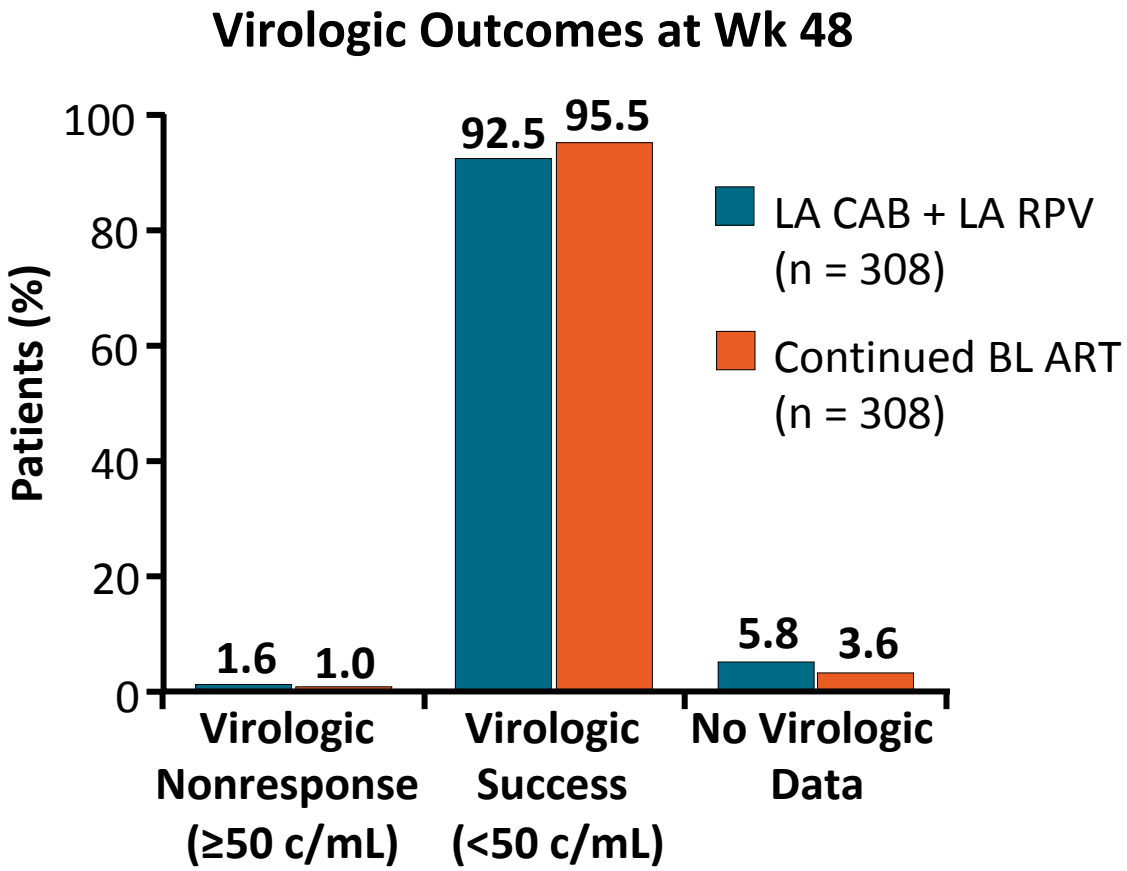


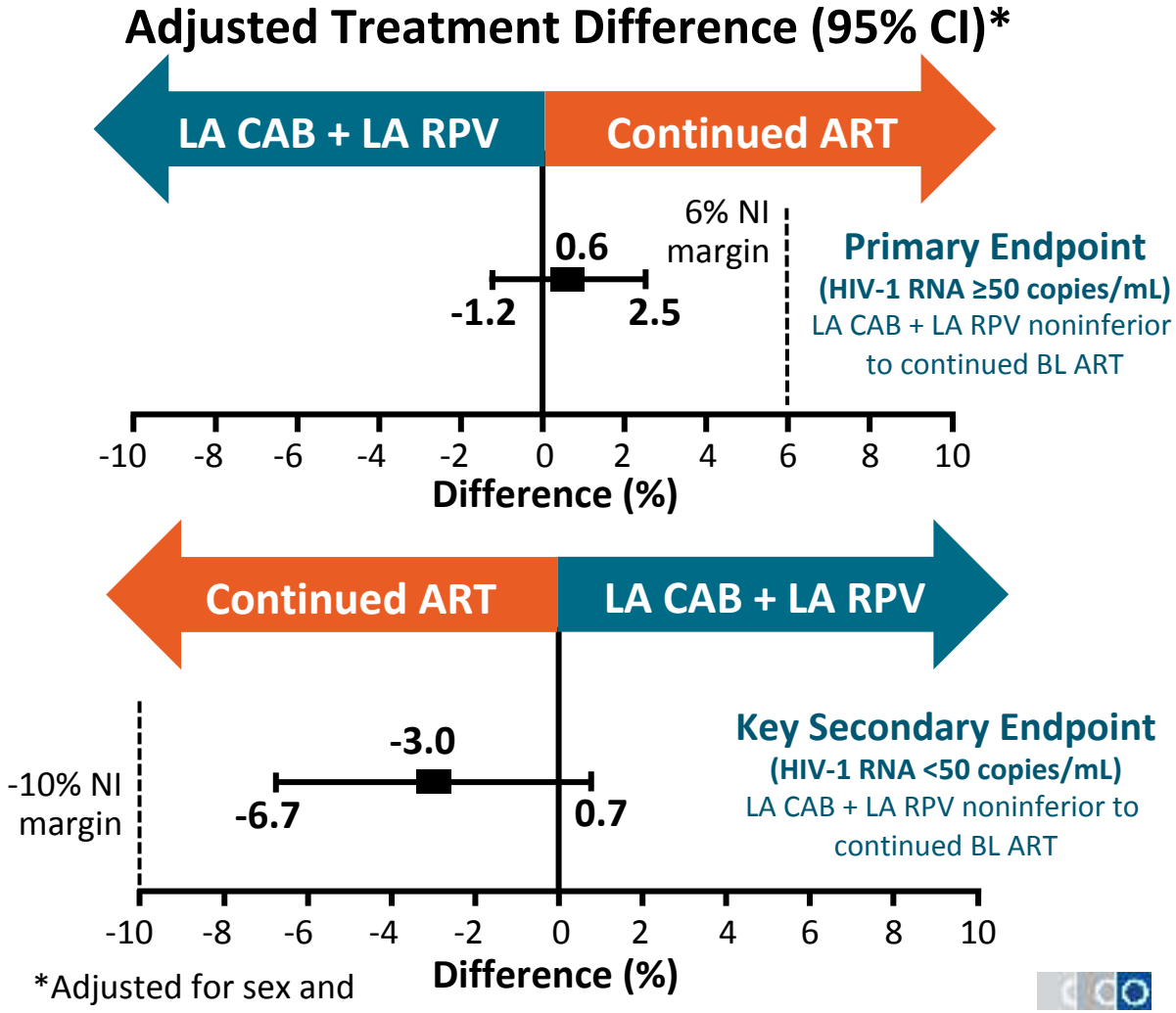
- Primary endpoint for both trials: HIV-1 RNA ≥50 copies/mL at Wk 48 by FDA Snapshot in ITT-E

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

Slide credit: clinicaloptions.com

ATLAS: Virolojik baskılaması olan hastada uzun etkili CAB + RPV veya 3 ilaçlı ART



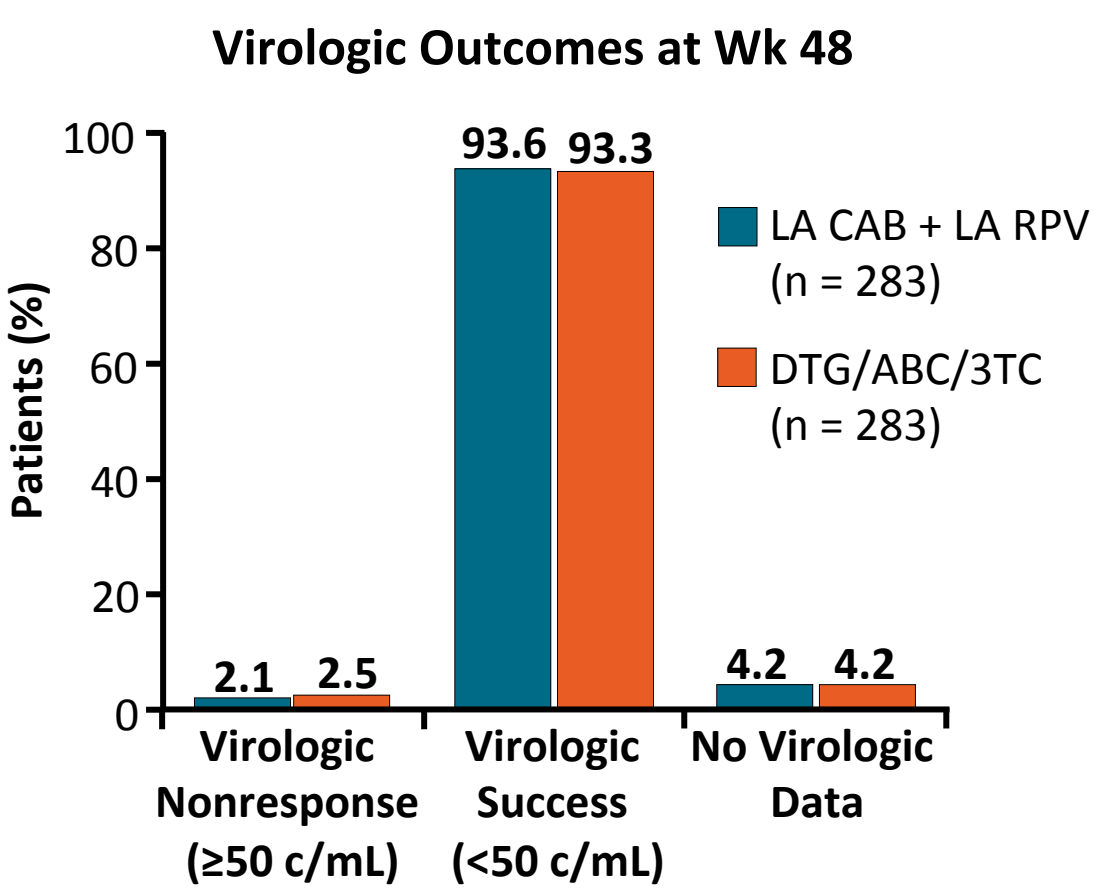


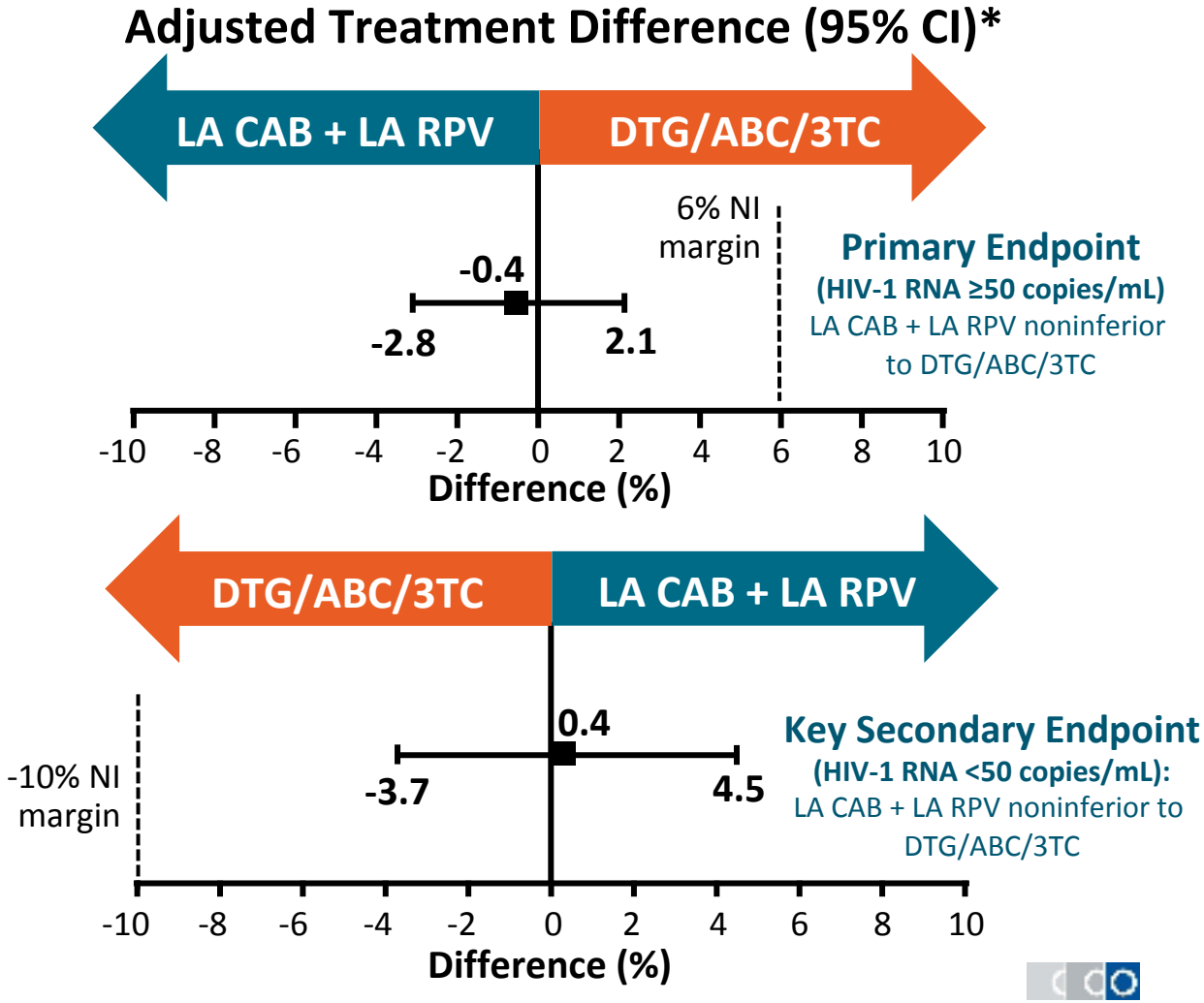
*Adjusted for sex and BL third agent class.

Swindells. NEJM. 2020;382:1112.

Slide credit: clinicaloptions.com

FLAIR: Oral DTG/ABC/3TC ile indüksiyon sonrasında uzun etkili CAB + RPV ile idame





- 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 ve FLAIR: Uzun etkili CAB + RPV tedavisi sırasında ortaya çıkan direnç

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

DTG

S

p. LLR

ILR

p. LLR

ILR

*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.

RT comments

NNRTI

- **K101E** is a non-polymorphic primarily accessory mutation that causes intermediate resistance to NVP and RPV, low-level resistance to EFV, and potentially low-level resistance to ETR. It has a weight of 1.0 in the Tibotec ETR genotypic susceptibility score. It is associated with low-level reductions in DOR susceptibility.
- **V108I** is a relatively non-polymorphic accessory mutation selected in vitro and/or in vivo with each of the NNRTIs. It causes low-level reductions in susceptibility to NVP and DOR. Alone, it does not appear to reduce susceptibility to EFV, ETR, or RPV.
- **E138A** is a common polymorphic accessory mutation weakly selected in patients receiving ETR and RPV. It reduces ETR and RPV susceptibility ~2-fold. It has a weight of 1.5 in the Tibotec ETR genotypic susceptibility score.
- **E138K** is a non-polymorphic mutation selected in a high proportion of patients receiving RPV. It reduces RPV susceptibility by 2 to 3-fold and in combination with K101E or the NRTI-resistance mutation M184I, it is sufficient to cause virological failure on a first-line RPV-containing regimen. **E138K** causes low-level cross-resistance to ETR and possibly to DOR.

IN comments

IN Major

- **G140R** is a nonpolymorphic mutation reported in n macaques receiving CAB pre-exposure prophylaxis and in a person receiving simplification therapy with RPV/CAB. It reduces CAB susceptibility by 7-fold.
- **Q148H/K/R** are non-polymorphic mutations selected by RAL, EVG, and rarely DTG. They nearly always occur in combination with G140A/S or E138K. In this setting they are associated with near complete resistance to RAL and EVG, high-levels of reduction in CAB susceptibility, and intermediate reductions in DTG and BIC susceptibility. The presence of **Q148H/K/R** plus two INSTI DRMs is usually associated with high-level reductions in susceptibility to all INSTIs.
- **N155H** is a non-polymorphic mutation selected in patients receiving RAL, EVG, and rarely DTG. It is associated with high-level reductions in RAL and EVG susceptibility. It causes low-level reductions in DTG susceptibility.

Other

- L74M is a polymorphic accessory mutations commonly selected by each of the INSTIs. In ARV-naive patients, L74M occurs in 0.5% to 5% of patients depending on subtype. **L74I** occurs in 4% to 40% of patients depending on subtype. **L74I** is the consensus amino acid for subtype A6 and does not appear to be selected by INSTI therapy. Alone, **L74M/I** have minimal, if any, effect on INSTI susceptibility. However, L74M and possibly **L74I** reduce susceptibility to each of the INSTIs when they occur with major INSTI-resistance mutations. L74F is a rare nonpolymorphic mutation which also contributes reduced susceptibility when it occurs with other INSTI-resistance mutations.

Dosage Considerations

- There is evidence for high-level **DTG** resistance. If **DTG** is used, it should be administered twice daily.

2019 Update of the Drug Resistance Mutations in HIV-1

IAS–USA *Topics in Antiviral Medicine*

July/August **2019**

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS[25]

Drug	66	74	92	97	118	121	138	140	143	147	148	153	155	263
Bictegravir[26]					G118R		E138K	G140S			**Q148H**			**R263K**
Cabotegravir[27]	T66K				**G118R**		E138A/K/T	G**140**A/C/**R**/S			**Q148H/K/R**	S153F/Y	N155H	**R263K**
Dolutegravir[28]					**G118R**	F121Y	E138A/K/T	G140A/S			**Q148H/K/R**		N155H	**R263K**
Elvitegravir[29]	**T66I**/A/K		**E92Q**/G	T97A		**F121Y**				**S147G**	**Q148H/K/R**		**N155H**	**R263K**
Raltegravir[30]		L74M	E92Q	T97A		**F121Y**	E138A/K	G140A/S	**Y143R/H/C**		**Q148H/K/R**		**N155H**	**R263K**

2019 Update of the Drug Resistance Mutations in HIV-1

IAS–USA *Topics in Antiviral Medicine* July/August **2019**

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[1,11]

	90	98	100	101	103	106	108	138	179	181	188	190	221	225	227	230	234
Doravirine[12]						V106 A I M T					Y188 C L H	G190 E		P225 H	F227 C L R	M230 L	L234 I
Efavirenz			L100 I	K101 P	K103 N S	V106 M	V108 I			Y181 C I	Y188 L	G190 S A		P225 H		M230 L	
Etravirine[13]	V90 I	A98 G	L100 I	K101 E H P		V106 I		E138 A G K Q	V179 D F T	Y181 C I V		G190 S A				M230 L	
Nevirapine			L100 I	K101 P	K103 N S	V106 A M	V108 I			Y181 C I	Y188 C L H	G190 A				M230 L	
Rilpivirine[14]			L100 I	K101 E P				E138 A G K Q R	V179 L	Y181 C I V	Y188 L		H221 Y		F227 C	M230 I L	

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

CLINICAL INFO HIV.gov

Management of the Treatment-Experienced Patient

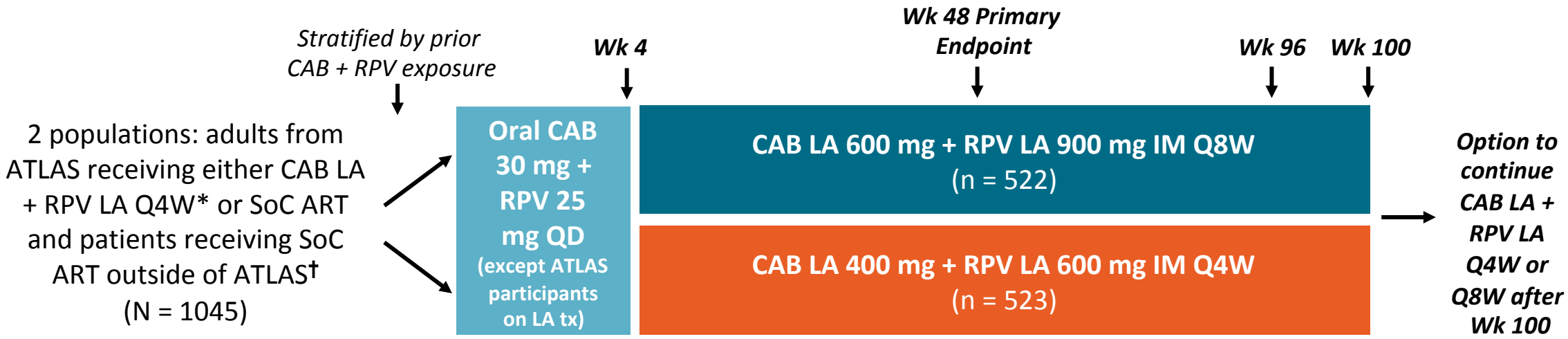
Updated: Jun. 03, 2021
Reviewed: Jun. 03, 2021

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)**.

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

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



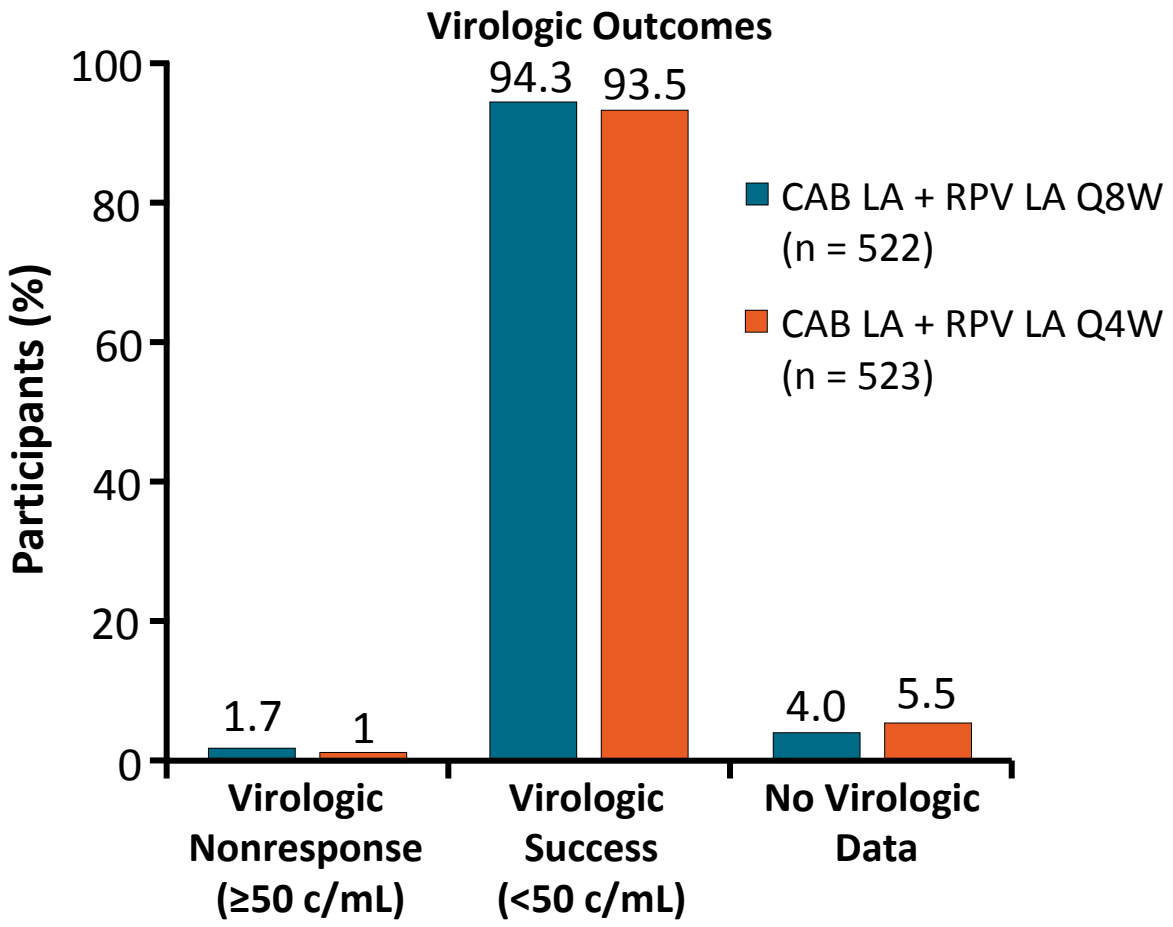
*Participants transitioning from ATLAS must have been on CAB LA + RPV LA Q4W or a current ART regimen through at least Wk 52 and had HIV-1 RNA <50 c/mL at screening. †SoC participants not transitioning from ATLAS study on uninterrupted current regimen (initial or second combined ART) for ≥6 mo prior 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

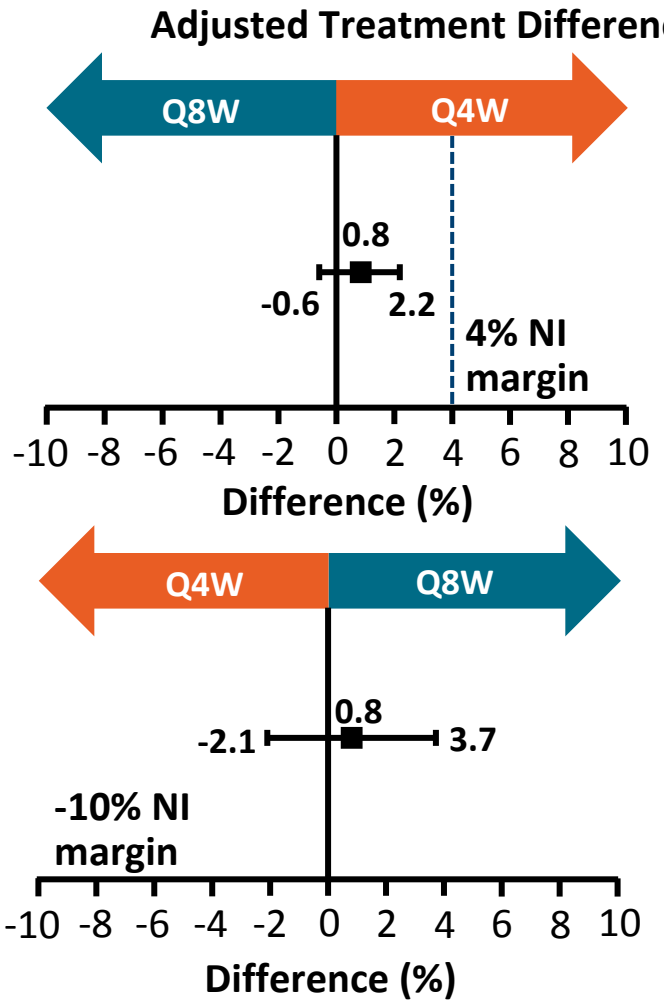
Overton. Lancet. 2021;396:1994.

Slide credit: clinicaloptions.com

ATLAS-2M: 48. hf virolojik sonuçları



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



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

Overton. Lancet. 2021;396:1994.

Slide credit: clinicaloptions.com

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 (UGT1A1) veya RPV (CYP3A) 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 (A5359/ LATITUDE)

- doz atlandığında veya tedavi kesildiğinde direnç çıkma olasılığı var
  - CAB LA yarı ömrü 5.6 – 11.5 hafta
  - RPV LA yarı ömrü 13 – 28 hafta

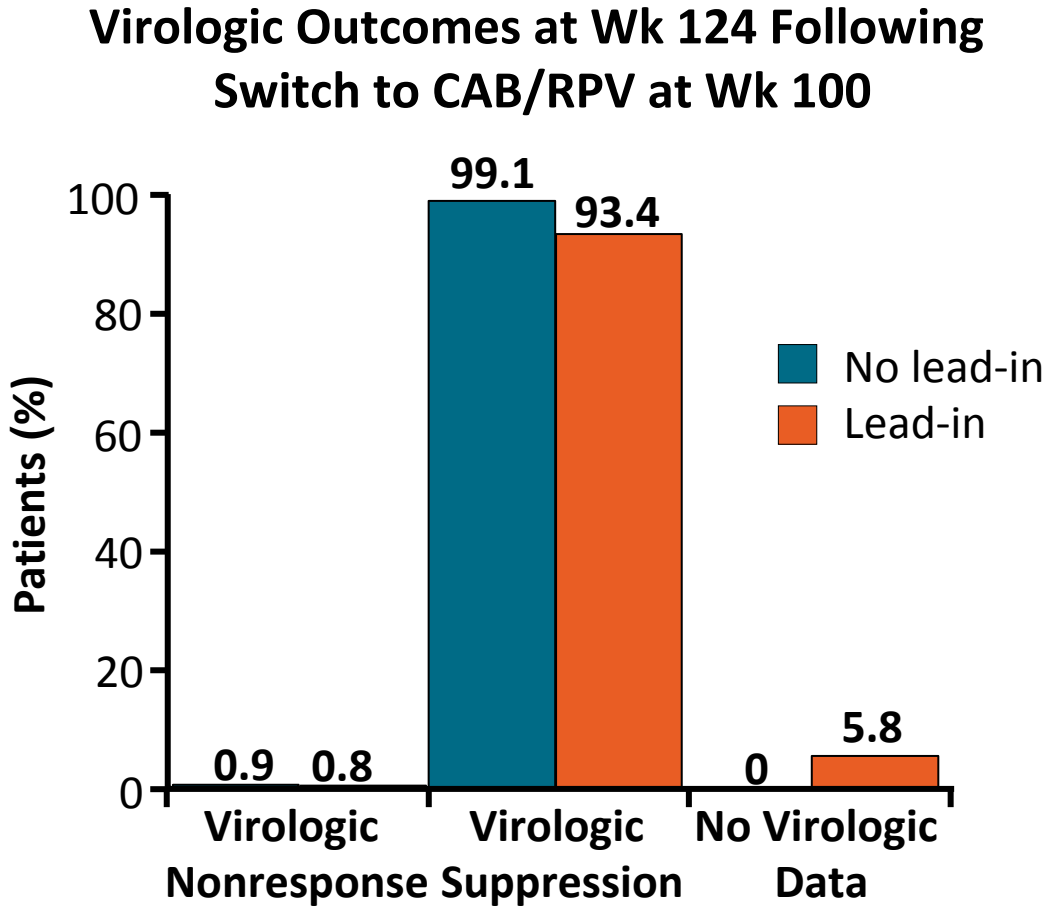
Yan Etkiler

- En sık enjeksiyon bölgesi reaksiyonları
  - hastaların >%80'ninde >1 kez olmuş
  - zamanla azalıyor; >1 sene sonra hastaların %10-30'unda
  - hafif – orta şiddette
  - %99 grade1 veya 2
  - ortanca süre 3 gün

- Diğer bildirilern yan etkiler:
  hipersensitivite, post-enjeksiyon reaksiyonları, hepatotoksisite, depresif hastalık

“Direct to Inject”: Switching to CAB/RPV Without an Oral Lead-in

- FLAIR extension study
  - Participants on DTG/ABC/3TC arm achieving virologic suppression (HIV-1 RNA <50 copies/mL) in 20-wk induction phase could switch to monthly CAB/RPV at Wk 100
  - Switchers randomized to groups with (n = 121) or without (n = 111) an oral CAB + RPV lead-in



D’Amico. J Int AIDS Soc. 2020;23(suppl 7):15.

Slide credit: clinicaloptions.com

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

Table 2. Multivariable logistic regression analysis of confirmed virologic failure through Week 48.

N	Parameter	Full model OR (95% CI), *P*[a]	Backwards elimination model OR (95% CI), *P*[a]
1039	RPV RAM(s) at baseline	30.23 (6.25–>99), <0.001	40.36 (8.81–>99), <0.001
	Log_2 of *post hoc* Week 8 RPV trough concentration	3.85 (1.15–14.29)[b], 0.029	5.00 (1.79–16.67)[b], 0.002
	Baseline HIV-1 subtype A6/A1	2.37 (0.34–22.14), 0.394	5.92 (1.62–22.89), 0.008
	BMI (kg/m^2) at baseline ≥30 kg/m^2	1.08 (0.96–1.22), 0.192	1.13 (1.02–1.24), 0.020
	Prespecified INSTI polymorphism (excluding L74I [excluding mixtures with L74M]) at baseline	0.16 (0.01–1.05), 0.057	0.14 (0.01–0.91), 0.038
	NNRTI RAM(s) (excluding RPV RAMs) at baseline	2.64 (0.72–9.21), 0.137	2.78 (0.78–9.63), 0.111
	Q8W regimen	2.76 (0.65–11.68), 0.164	2.77 (0.67–11.38), 0.156
	L74I (excluding mixtures with L74M) INSTI polymorphism at baseline	2.51 (0.33–13.85), 0.347	Eliminated from model
	Female (sex at birth)	1.09 (0.26–4.36), 0.899	Eliminated from model
	Log_2 of *post hoc* Week 8 CAB trough concentration	0.66 (0.25–1.74), 0.395	Eliminated from model

13 (%1.25) hastada doğrulanmışv irolojik başarısızlık

Cutrell AG et al. AIDS 2021

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

Dosage Considerations

- This virus is predicted to have low-level reduced susceptibility to **RPV**. The use of the combination of CAB/**RPV** should be considered to be relatively contraindicated.

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)

Sanger, popülasyon dizi analizi

	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: nükleozid(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
38	A			Yok
39	A			Yok
47	B			E138A
52	F	Yok	Yok	E138G
85	CRF28_BF	Yok	Yok	K103KN, E138EA
87	B	Yok	M41L,T215D	Yok
65	B	Yok	Yok	E138A

11/104 (%10.5) hastada herhangi düzeyde RPV direnci var

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].

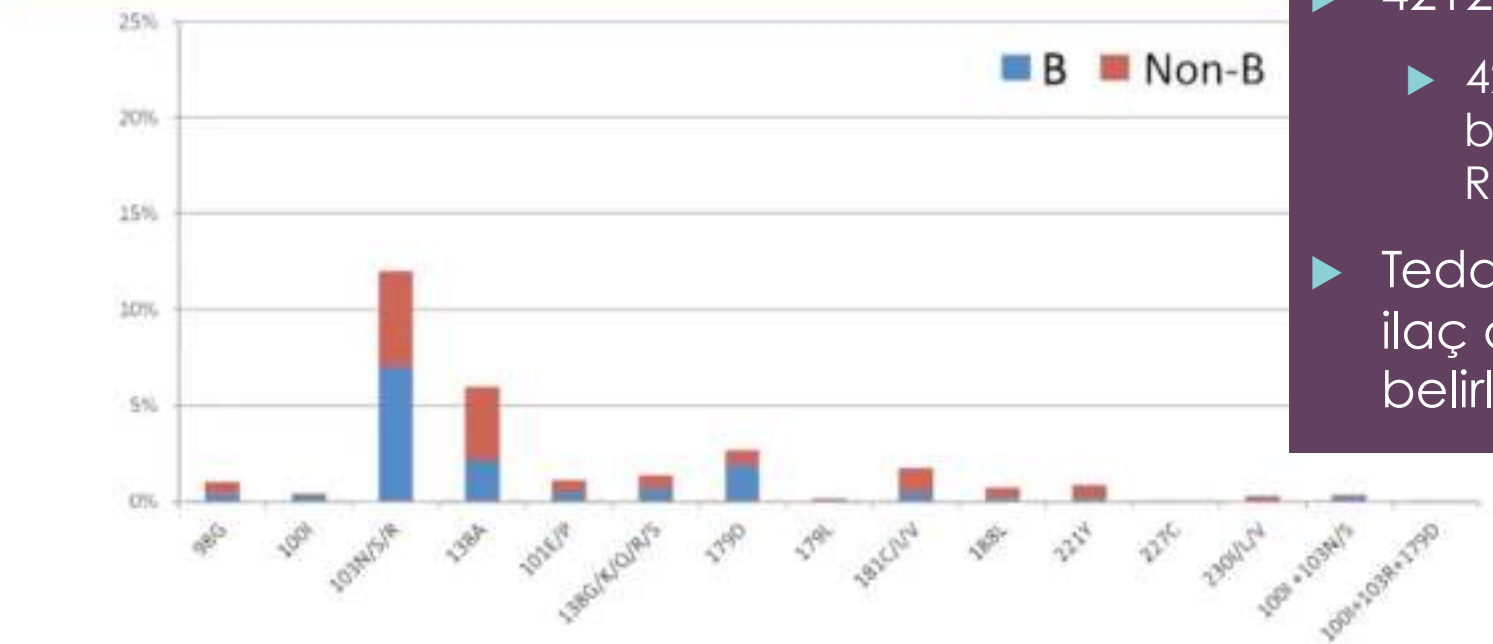
Slide credit: clinicaloptions.com

IAS 2021
18 – 21 July

Prevalence of genotypic baseline risk factors of Cabotegravir + Rilpivirine failure among ARV-naïve patients

Charlotte Charpentier[1], Alexandre Storto[1], Cathia Soulié[1], Valentine Marie Ferré[1], Marc Wirden[2], Véronique Joly[3],

RT RPV mutations



- Prevalence of RPV RAMs: **14.3 %** (no difference between B and non-B)
- **6.2 %** of the sequences were resistant to RPV: 7.4 % in non-B vs 4.2 % in B ($p < 0.0001$) (ANRS algorithm)

- ART naif hastalarda CAB + RPV LA rejimiyle virolojik başarısızlığa yol açabilecek ilaç direnci araştırılmış
- 2010 – 2020 arası genotipik direnç veri seti
- 4212 RT ve IN dizisi değerlendirilmiş
  - 427 (10.1%) dizide CAB + RPV ile virolojik başarısızlığa yol açabilecek (A6/A1 veya RPV RAM) faktör saptanmış
- Tedavi öncesi direnç analizi, aktarılmış ilaç direnci varlığı ve HIV-1 subtipini belirlemek önemli

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

Table 3. Week 48 outcomes by presence of key baseline factors of rilpivirine resistance-associated mutation(s), HIV-1 subtype A6/A1 and BMI at least 30 kg/m^2.

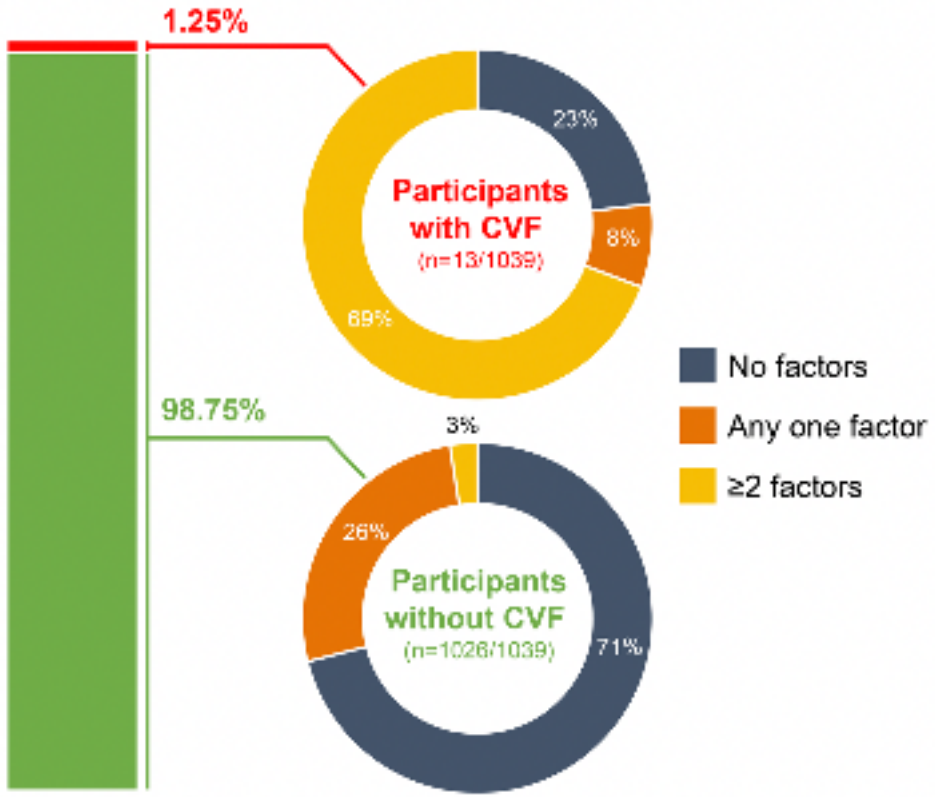
Baseline factors	Virologic success[a] *n* (%)	CVF[b] *n* (%)
None of the three factors	694/732 (94.8)	3/732 (0.41)
Any one of the three baseline factors	261/272 (96.0)	1/272 (0.37)
HIV-1 subtype A6/A1 alone	90/95 (94.7)	1/95 (1.1)
BMI ≥30 kg/m^2 alone	147/153 (96.1)	0/153 (0)
RPV RAM(s) alone	24/24 (100)	0/24 (0)
At least two of the three baseline factors		9/35 (25.7)
RPV RAM(s) + HIV-1 subtype A6/A1		1/3 (33.3)
RPV RAM(s) + BMI ≥30 kg/m^2		3/10 (30.0)
HIV-1 subtype A6/A1 + BMI ≥30 kg/m^2		4/21 (19.0)
All three baseline factors	0/1 (0)	1/1 (100)
TOTAL	980/1039 (94.3)	13/1039 (1.25)
[95% CI (exact method)]	(92.74–95.65)	(0.67–2.13)

Başlangıçta en az 2 faktörün oluşu virolojik başarısızlıkla ilişkili

Cutrell AG et al. AIDS 2021

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

Supplemental Digital Content 7. Week 48 CVF outcome by presence of key baseline factors (RPV RAMs, HIV-1 subtype A6/A1, and BMI ≥30 kg/m²)

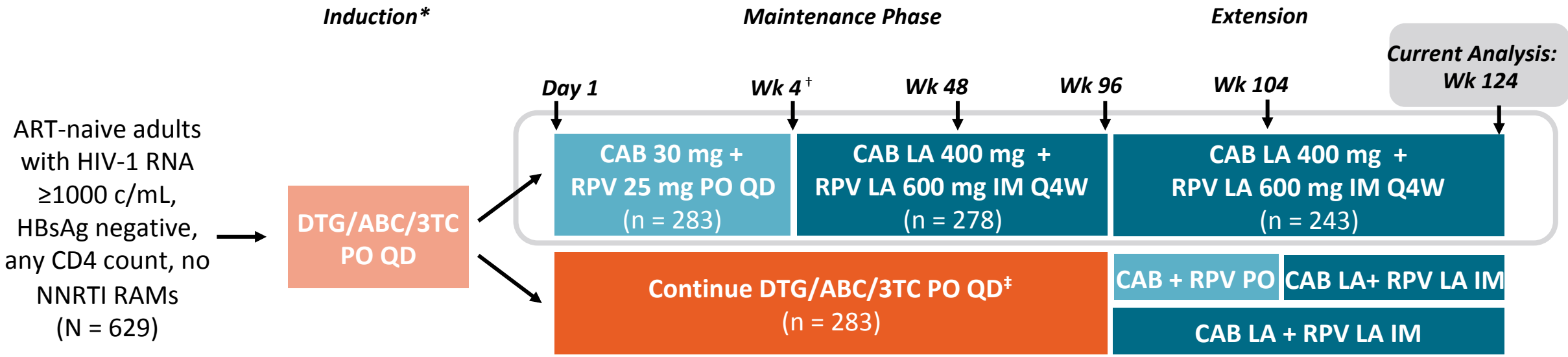


The fact that three of the four significant covariates associated with a potential increased risk of CVF can be considered at baseline may be useful information to clinicians considering long-acting CAB+RPV therapy. In participants with zero or one baseline factor, the CVF rate was less than 0.5%. However, any combination of at least two factors appears to increase CVF risk. Virologically suppressed patients without known or suspected resistance to CAB or RPV are suitable candidates for long-acting CAB+RPV. If the patient's treatment history is unclear, additional consideration may be warranted, particularly if the patient also has an HIV-1 subtype A6/A1 and/or high BMI.

Cutrell AG et al. AIDS 2021

FLAIR 124. hf: Tedavi naif hastalarda uzun etkili Cabotegravir + Rilpivirine

- 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]**

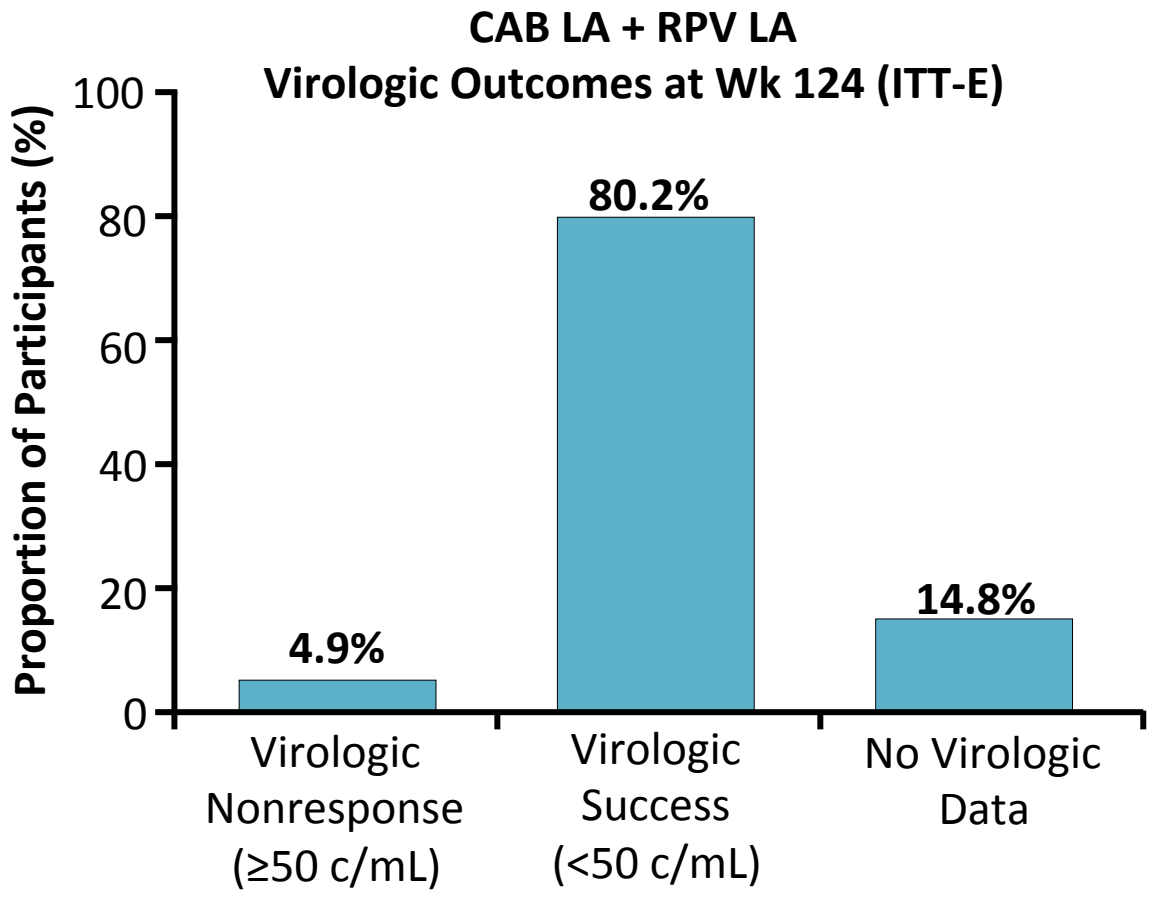
1. Orkin. NEJM. 2020;382:1124. 2. Orkin. Lancet HIV. 2021;8:e185. 3. Orkin. IAS 2021. Abstr OAB0302.

FLAIR: CAB LA + RPV LA ile 124. hf Virolojik Sonuçlar

- 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: Doğrulanmış virolojik kaçışı olan fazladan 1 hasta

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

Stanford University

HIV DRUG RESISTANCE DATABASE

A curated public database to represent, store and analyze HIV drug resistance data.

HOME | GENOTYPE-RX | GENOTYPE-PHENO | GENOTYPE-CLINICAL | HIVDB PROGRAM | ABOUT HIVDB | SUPPORT HIVDB!

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

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	**V106A, V108I, E138G, M230L**
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Susceptible
lamivudine (3TC)	Susceptible
tenofovir (TDF)	Susceptible

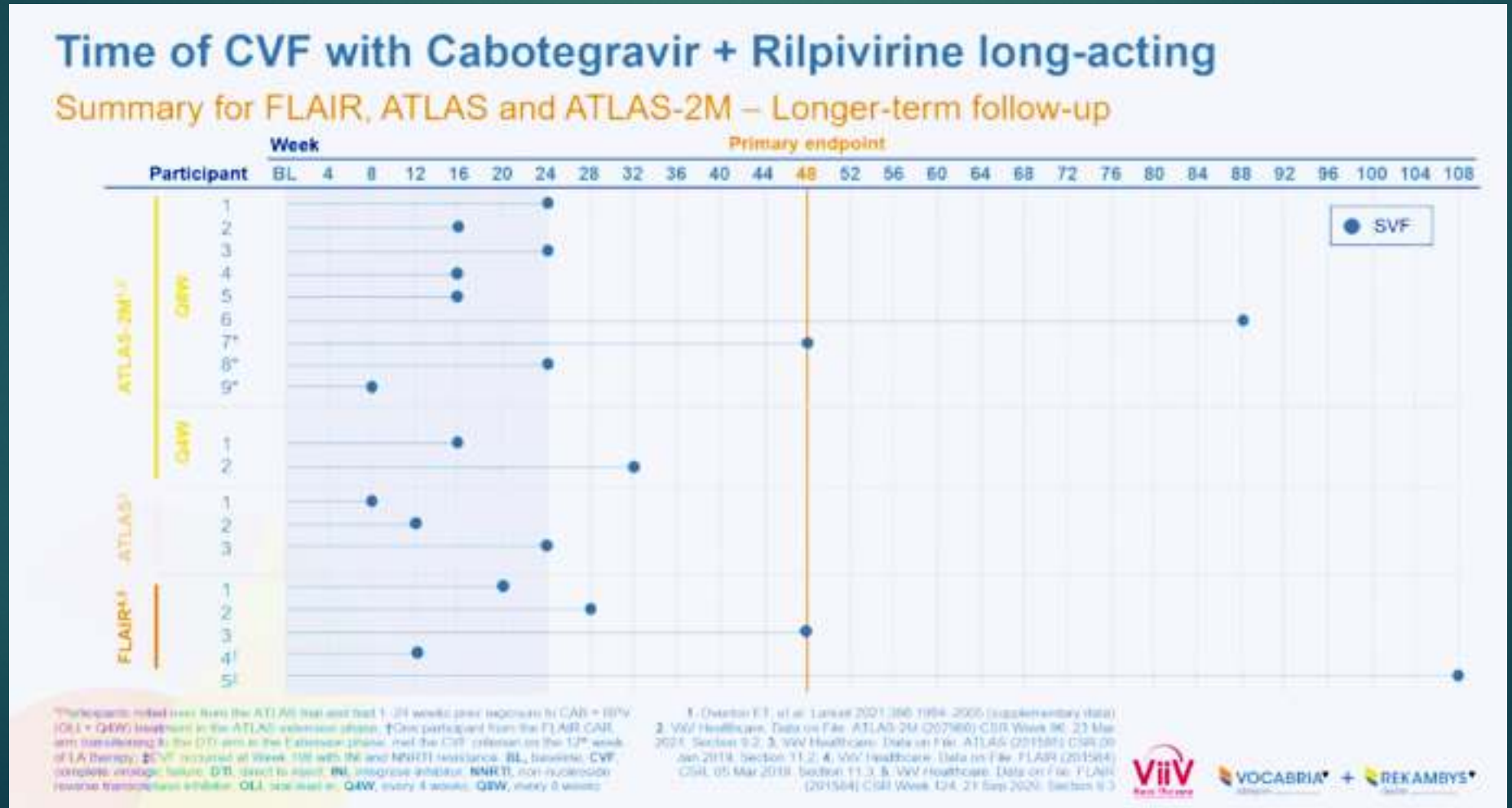
Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	High-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	High-Level Resistance

IN Major Resistance Mutations:	**N155H, R263K**
IN Accessory Resistance Mutations:	None
Other Mutations:	None

Integrase Strand Transfer Inhibitors	
bictegravir (BIC)	High-Level Resistance
cabotegravir (CAB)	High-Level Resistance
dolutegravir (DTG)	High-Level Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

Virolojik kaçış olursa ne zaman olur?

- Virolojik kaçışların çoğu, LA'ya geçiş sonrası **ilk 24 hafta içerisinde** gerçekleşmiş
  Orkin C. EACS 2021. The time for long-acting is now – by ViiV Healthcare



FLAIR: 124.hf güvenlik ve tolere edebilme

- 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 ▪ Pyrexia ▪ Headache ▪ Fatigue	102 (36) 18 (6) 15 (5) 10 (4)	7 (2) 1 (<1) 0 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

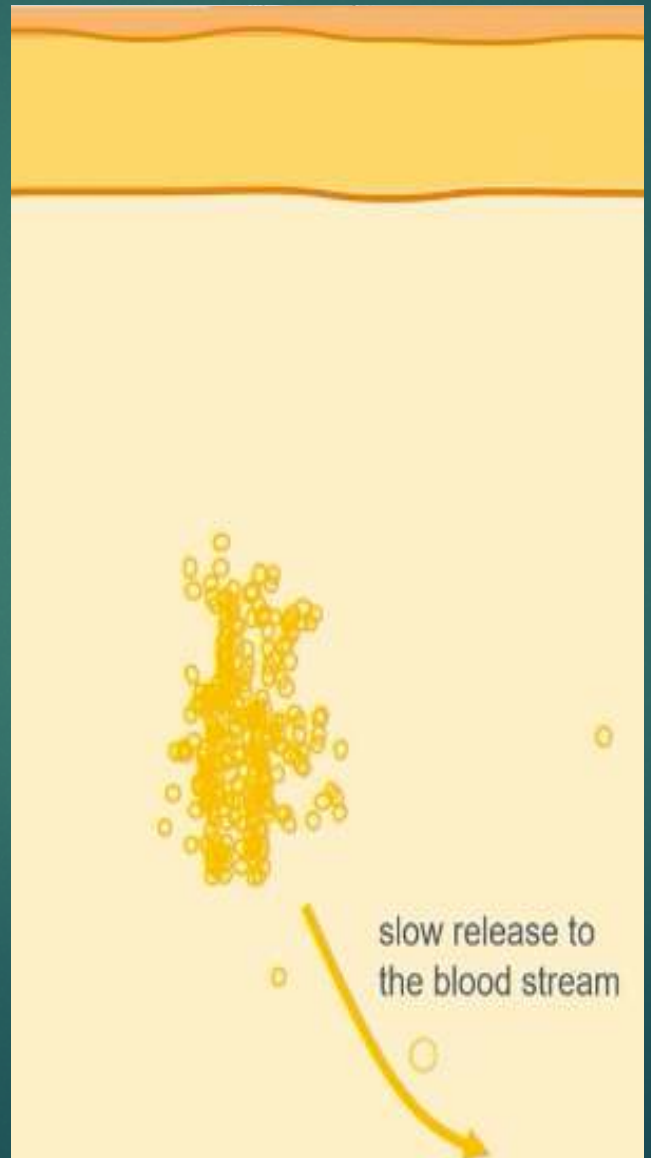
- Injection site reactions (ISR) were most common AE; mostly low-grade
- 17,392 injections; 3,732 ISR events

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

IAS (Ekim 2020): LA CAB + RPV Q4W (AIa)/ Q8W (BIb)
US DHHS (Ağustos 2021): LA CAB + RPV Q4W (AIa)/ Q8W (BIb)
EACS (Ekim 2021): LA CAB + RPV Q8W



- 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

Boffito M. EACS 2021

Review > AIDS Res Hum Retroviruses. 2021 Feb;37(2):75-88. doi: 10.1089/AID.2020.0126. Epub 2020 Dec 7.

The LAIs Are Coming! Implementation Science Considerations for Long-Acting Injectable Antiretroviral Therapy in the United States: A Scoping Review

John T Kanazawa [1], Parya Saberi [2], John A Sauceda [2], Karine Dubé [1]

- Uygulanabilirlik!
- Uzun etkililerin farklı katmanlarda yaşayan HIV hastaları tarafından kabu edilebilirliği
- Maliyet etkinliği?
- Hasta memnuniyeti?
- Hastaların bildirdiği sonuçlar?
- Uygulama için en uygun ortam?

CUSTOMIZE: Arka plan

- 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]

- ***CAB + RPV uzun etkili tedavinin 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: Çalışma Tasarımı

- 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 **(üniversite)**, private practices **(muayenehane)**, AIDS healthcare foundations **(vakıf)**, HMOs **(SGK)**, and federally qualified health centers **(sağlık merkezi)** across the United States
  - 26 providers (physicians, injectors, administrators) from 8 clinics completed surveys **(anket)** 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: Başlangıç Özellikleri

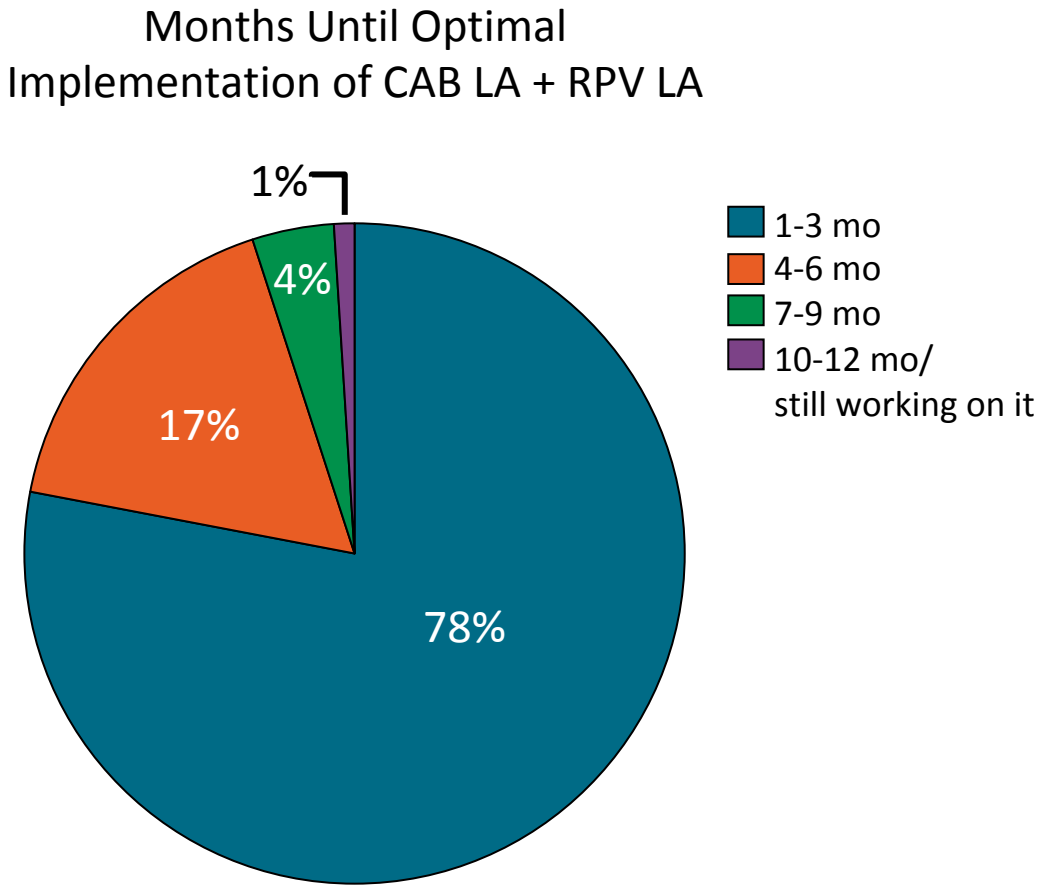
HCP Views of CAB LA + RPV LA Implementation Over Time, %	Baseline (N = 26)	Month 4 (N = 24)	Month 12 (N = 23)
Acceptability by clinic type			
▪ FQHC (n = 8)	84	96	100
▪ University (n = 6)	96	100	100
▪ Private practice (n = 6)	92	88	100
▪ AHF (n = 3)	100	100	100
▪ HMO (n = 3)	92	67	67
Feasibility ***(olabilirlik)*** 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.

Slide credit: clinicaloptions.com

CUSTOMIZE: Uygulamanın oturması için gereken süre ve strateji



- Key strategies for successful **clinic implementation**
  - Good staff communication **(ekip uyumu)**
  - Teamwork **(ekip çalışması)**
  - Use of a web-based treatment planner
- Key implementation strategies for **patient adherence**
  - Good communication about dosing window **(doz aralığı iyi anlatılmalı)**
  - Effective appointment reminder systems **(etkili hatırlatıcı sistem)**
  - Designated staff for appointment tracking **(randevuları ayarlamak için ayrılmış eleman)**

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CUSTOMIZE: Sağlık çalışanı ve hastalar açısından uygulamanın önündeki engeller

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: 12. ay sonuçları ve klinikte geçirilen süre

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: Sonuçlar

- 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

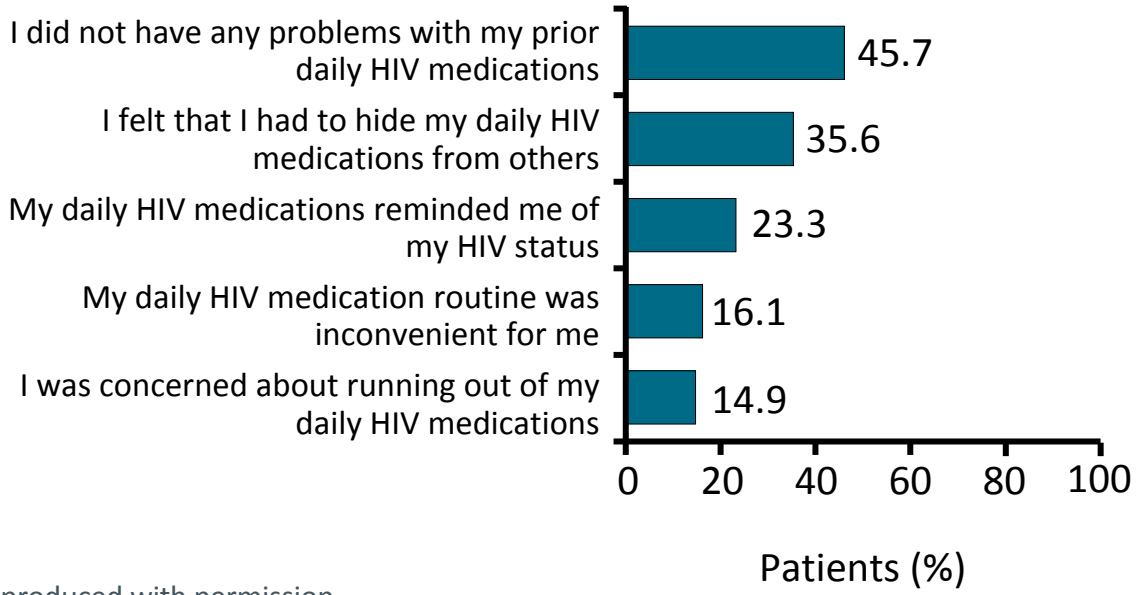
Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

CARISEL: Concerns With Daily HIV Medications Reported at Mo 1

- CARISEL study is assessing the acceptability, appropriateness, and feasibility of LA CAB + RPV injections and implementation support in Belgium, France, Germany, the Netherlands, and Spain
- More than one half of participants (54.3%) reported problems with taking daily oral therapy

"Before participating in this study, did you have any problems with your daily HIV medications?" (n = 421)



Hocqueloux. EACS 2021. Abstr PE2/37. Reproduced with permission.

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Lenacapavir

Kapsid inhibitörü

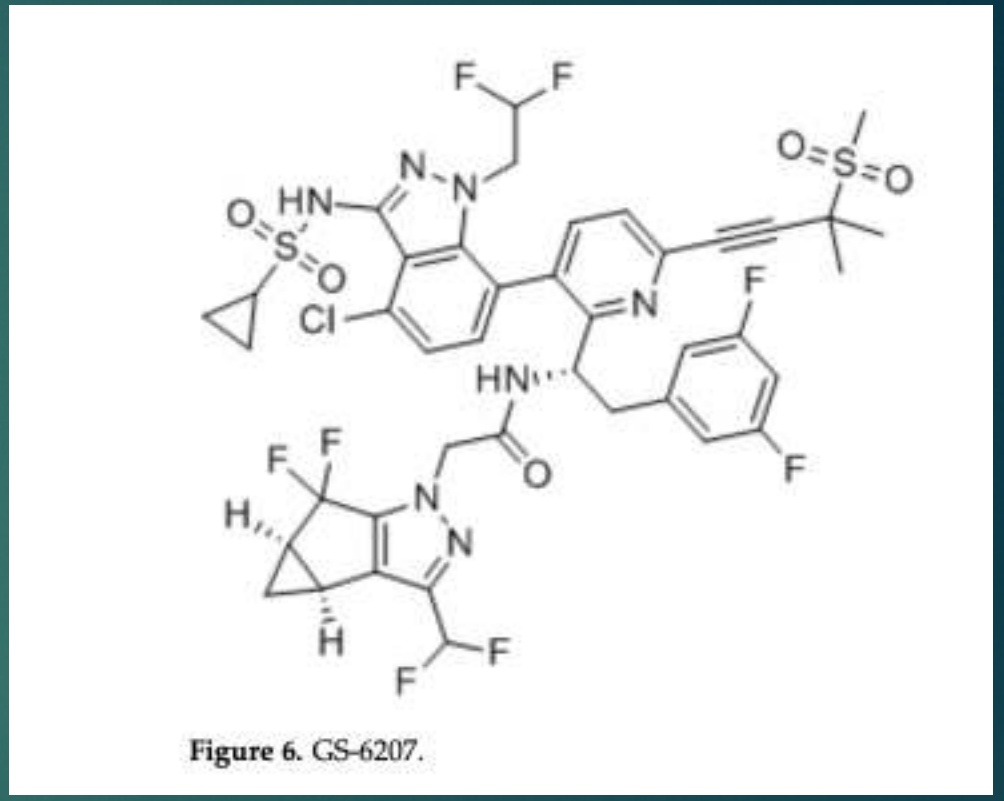
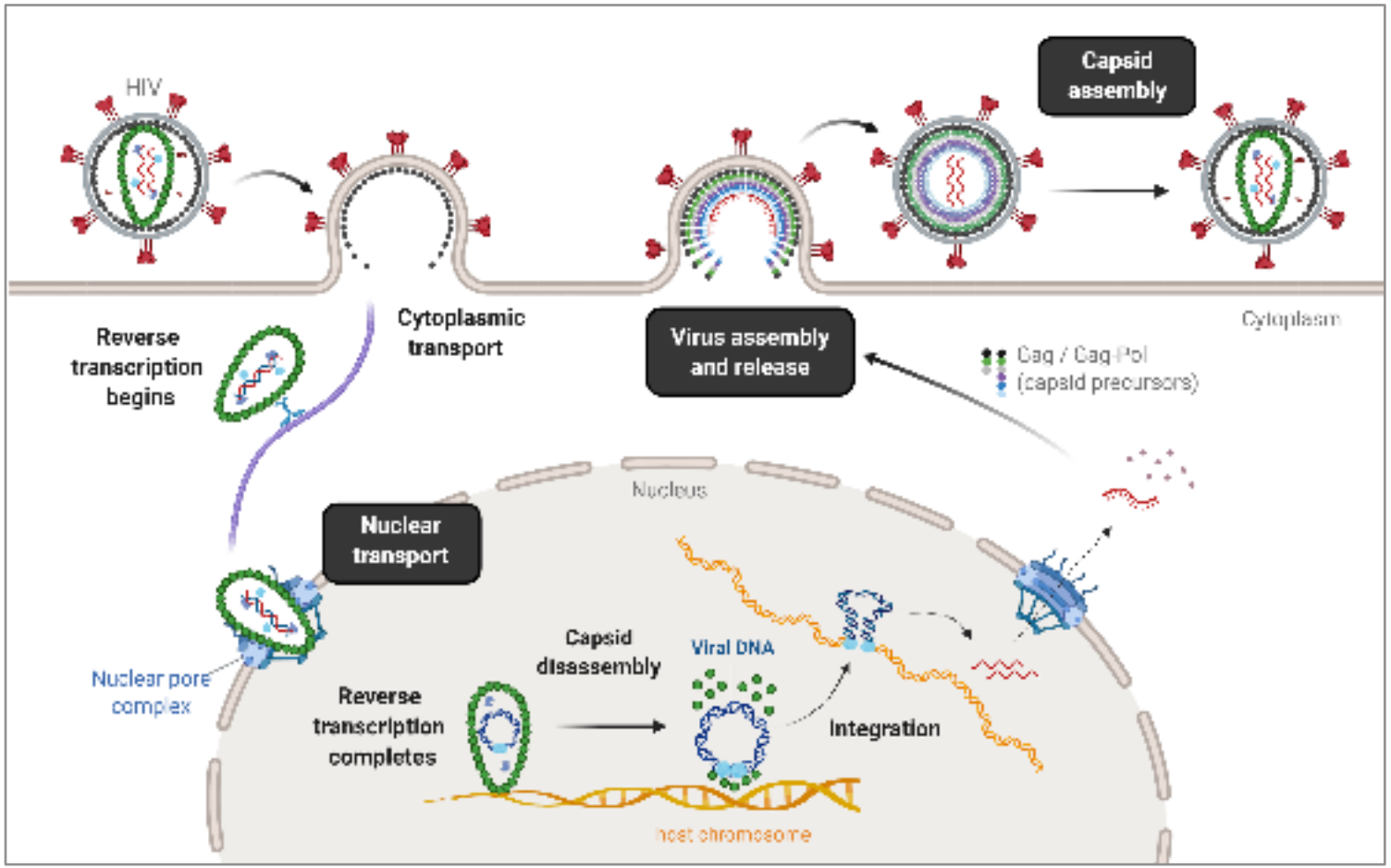


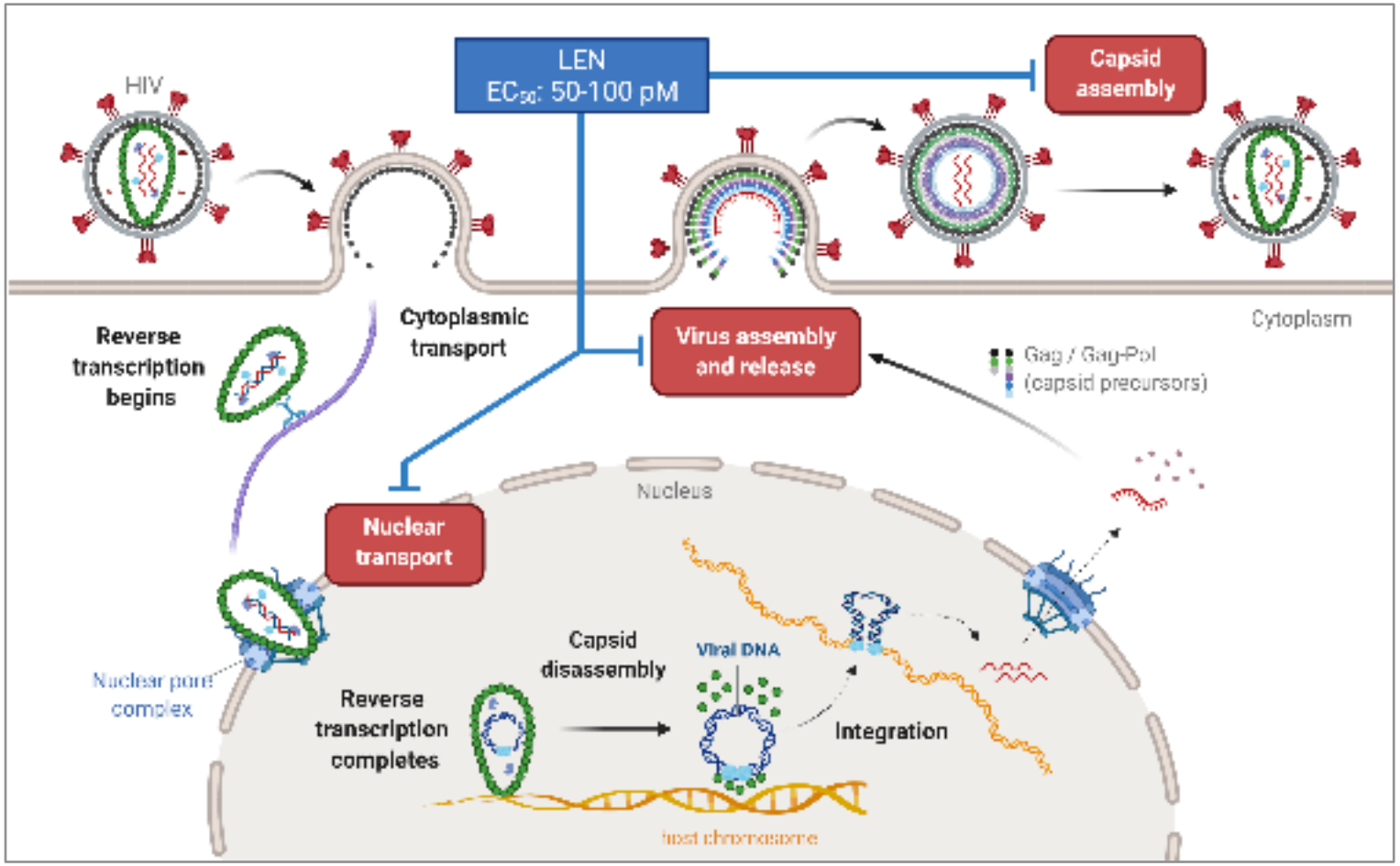
Figure 6. GS-6207.

Kapsid, HIV Replikasyonu Döngüsünün Birden Çok Aşamasında Kritik Önem Taşır



Şekil, aşağıdaki kaynaklara dayalı olarak oluşturulmuştur: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

LEN, HIV Replikasyon Döngüsünün Birden Çok Aşamasını Hedef Alır

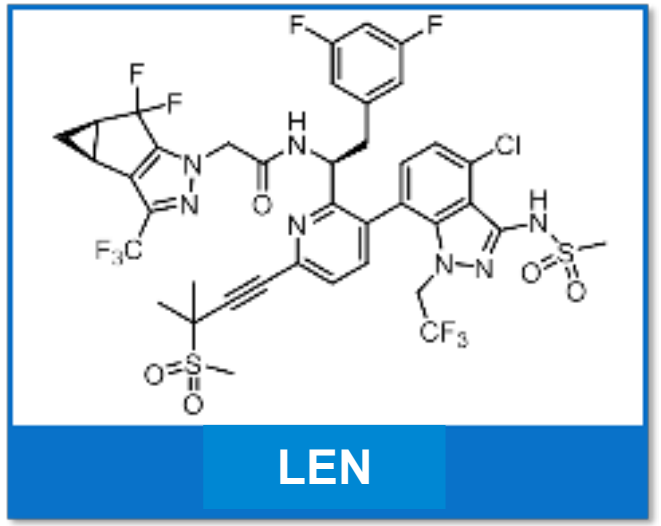


LEN, kapsid komplekslerinin stabilitesini ve/veya taşınmasını modüle ederek HIV yaşam döngüsündeki birçok sürecin inhibisyonuna yol açar

Şekil, aşağıdaki kaynaklara dayalı olarak oluşturulmuştur: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

Genel Bakış

- Özellikleri, düşük dozda uzun etkili enjektabl kullanım için ideal
  - Pikomolar antiviral potens (mevcut ARV'lerden ≥10 kat daha potent)[1]
  - Öngörülen klirensi düşük (hepatik kan akışının <%1'i)[2]
  - Suda çözünürlüğü düşük (pH 2–7'de <1 µM)[2]
- Nonklinik türlerde kanıtlanmış sürekli maruziyet[2]
- Olumlu *in vitro* farmakolojik profil:
  - Çok çeşitli HIV-1 izolatlarına karşı aktif*[1]
  - LEN, mevcut ARV'lere kıyasla benzersiz bir *in vitro* direnç profili sergiler[1]
  - Gag polimorfizmleri ve proteaz mutasyonları bulunan klinik izolatlara karşı pikomolar aktivite ile kendini gösteren yüksek potens[3]
  - HIV ile yaşayan tedavi deneyimsiz ve deneyimli 1500 bireyde, LEN'e karşı *in vitro* dirençle ilişkilendirilen mutasyon görülmedi[4]



* İnsan PBMC'sinde 15 HIV klinik izolatından oluşan panel

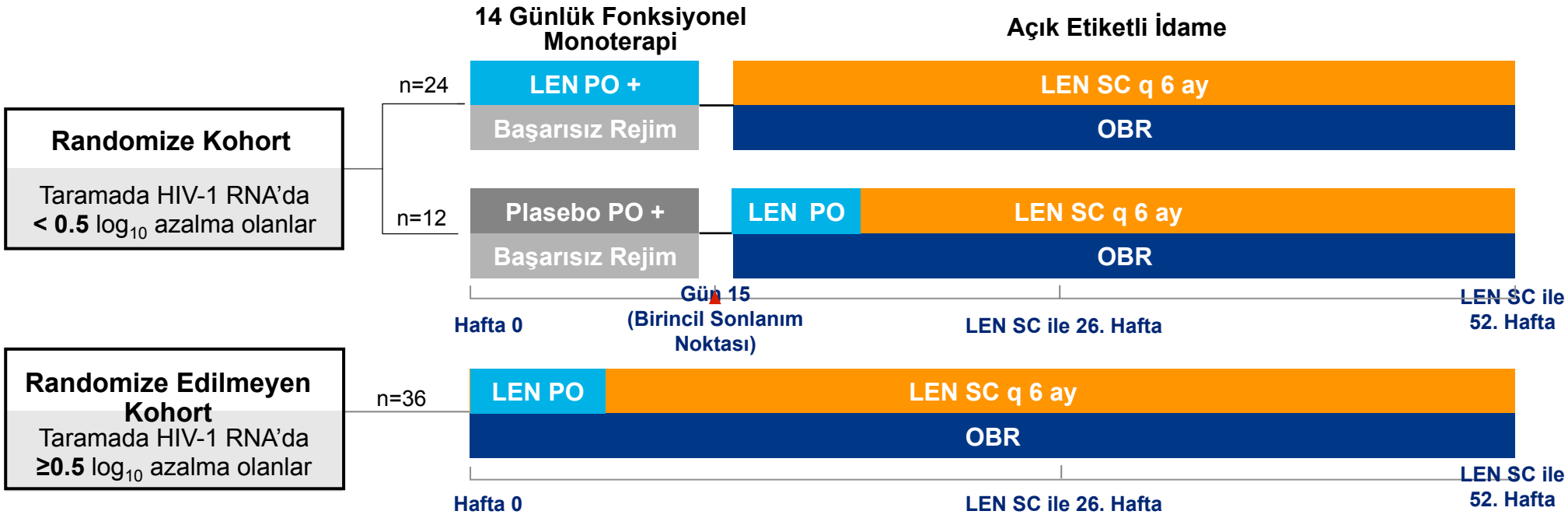
1. Yant SR, et al. CROI 2019. Seattle, WA. 480
2. Zheng J, et al. LEAP 2019. Seattle WA
3. Margot N, et al. EACS 2019. Basel, Switzerland. PE13/22
4. Marcelin AG, et al. EACS 2019. Basel, Switzerland. PE13/15

Önceden Yoğun Tedavi Görmüş HIV ile Yaşayan Bireylerde LEN

Çoklu ilaca dirençli, önceden yoğun tedavi görmüş HIV ile yaşayan bireylerde, başarısız olan rejime ek olarak LEN kullanımını değerlendiren Faz 2/3, kör, plasebo kontrollü çalışma (N=72)

Yoğun Tedavi Görmüş HIV ile Yaşayan Bireyler

- ≥ 12 yaş; ≥ 35 kg
- HIV-1 RNA ≥ 400 k/mL
- **4 ana ARV sınıfının ≥3'ünün her birinden ≥2 ARV'ye direnç***
- **≤ 2 tam aktif ARV seçeneği kalanlar**



Çalışmanın Sonlanım Noktaları

- Birincil: randomize kohortta, başlangıçtan itibaren monoterapinin sonuna kadar HIV-1 RNA'da ≥ 0.5 $\log_{10}$ k/mL azalma olan katılımcıların oranı
- İkincil: randomize kohortta, 26. ve 52. haftalarda HIV-1 RNA < 50 k/mL ve < 200 k/mL olan katılımcıların oranı (FDA Snapshot)

LEN doz rejimi: Oral başlangıç (Gün 1: 600 mg [2 x 300 mg tablet]; Gün 2: 600 mg [2 x 300 mg tablet]; Gün 8: 300 mg), sonrasında 927 mg (2 x 1.5 mL) subkütan idame dozu, q 26 hafta

BL, başlangıç; K, kopya; HTE, yoğun tedavi görmüş; MDR, çoklu ilaç direnci; OBR, optimize edilmiş arka plan rejimi; PO, ağızdan; SC, subkütan

* NRTI, NNRTI, PI, INSTI

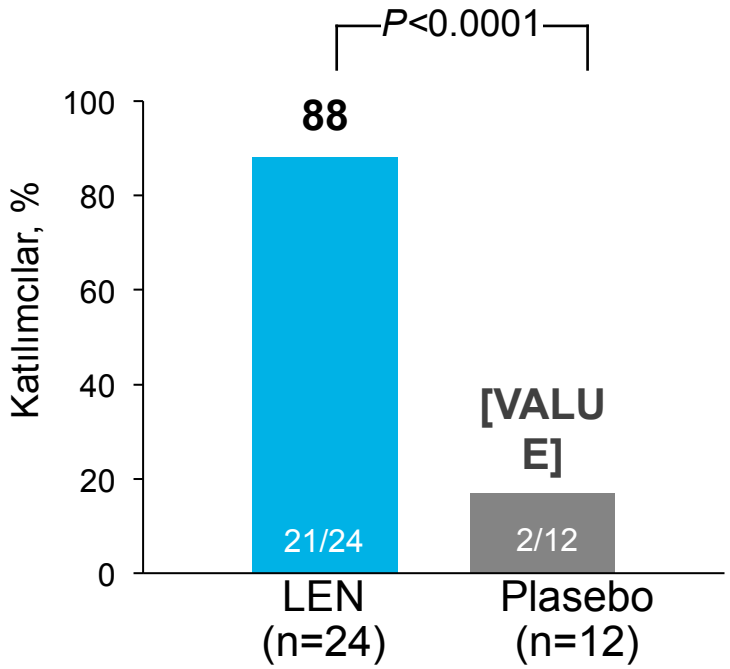
Segal-Maurer S, et al. vCROI 2021. Oral #127

ClinicalTrials.gov URL: https://clinicaltrials.gov/ct2/show/NCT04150068

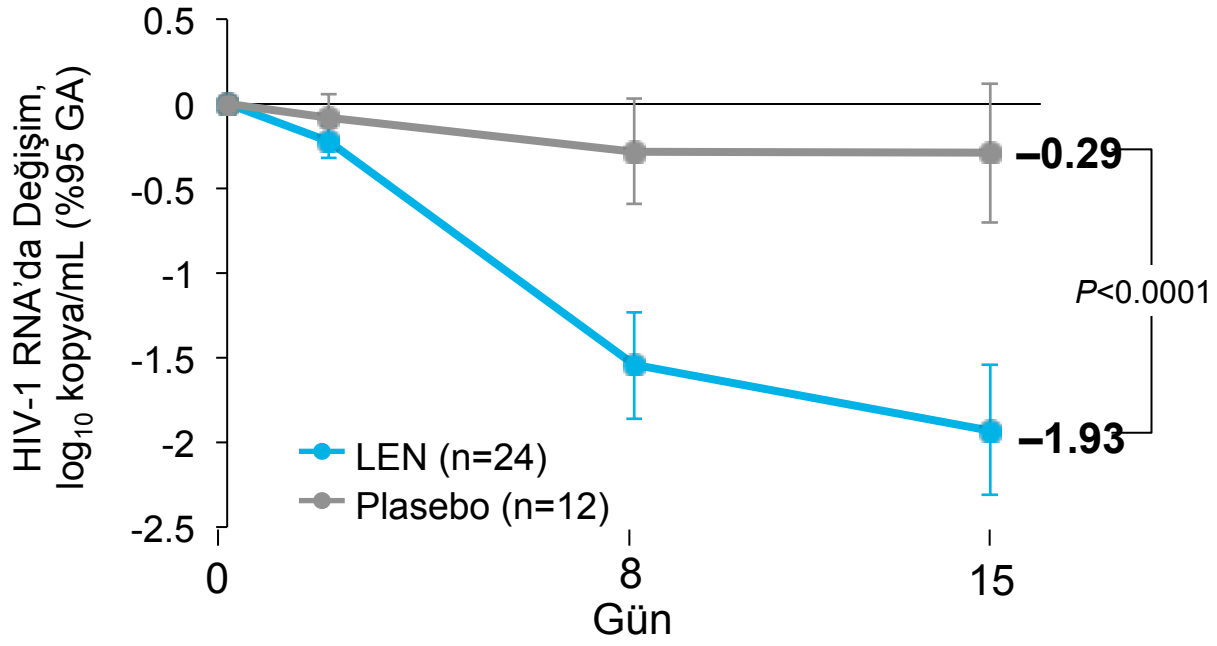
Fonksiyonel Monoterapi Sırasında Antiviral Aktivite

Birincil Sonlanım Noktası

HIV-1 RNA'da ≥ 0.5 log_{10} kopya/mL Azalma Görülenlerin Oranı



Vizite göre HIV-1 RNA'da Ortalama Değişim (%95 GA)

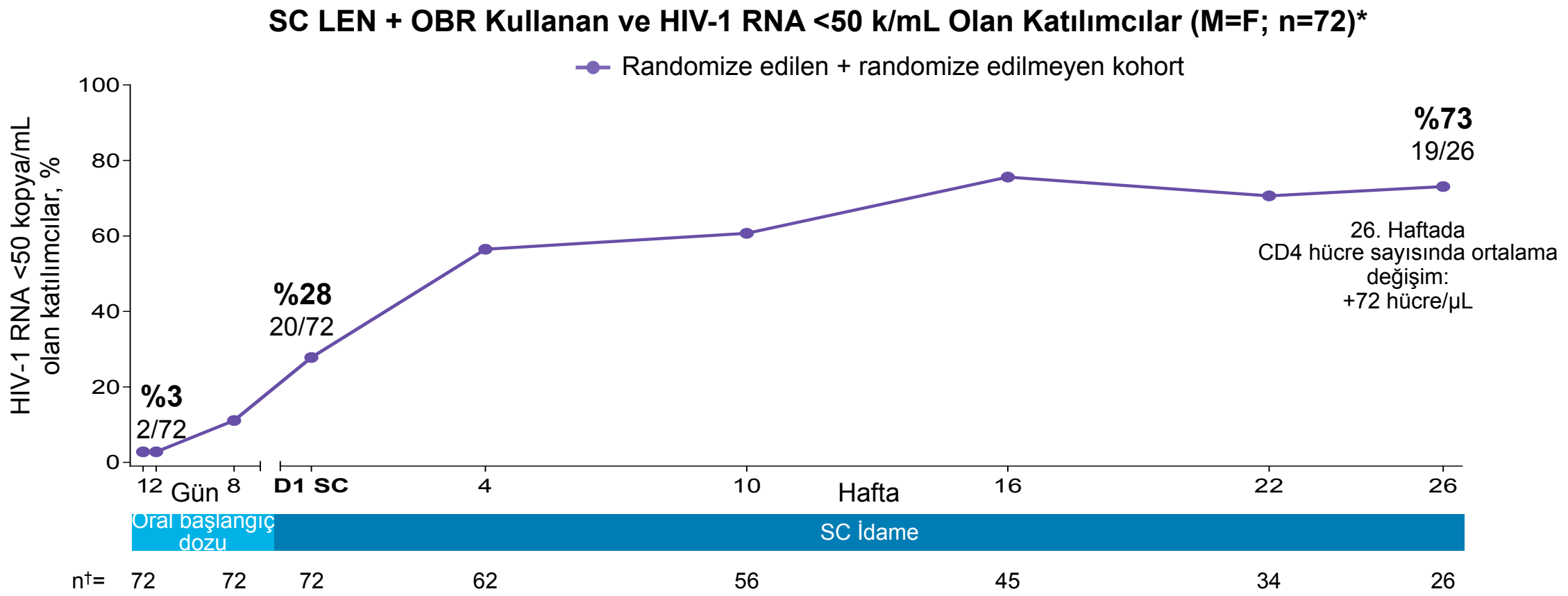


LEN, başarısız olan bir rejime eklendiğinde potent antiviral aktivite gösterdi

HTE, önceden yoğun tedavi görmüş

Segal-Maurer S, et al. vCROI 2021. Oral #127

SC LEN Alanlarda Virolojik Baskılama



LEN, optimize edilmiş bir arka plan rejimi ile birlikte kullanıldığında yüksek virolojik baskılama oranlarına ulaşıldı

OBR, optimize edilmiş arka plan rejimi
* Şubat 2021 ara dönem veri kesim noktası; bu analizde tüm katılımcılar 26. Haftaya ulaşmadı
† Paydalar ≥1 doz SC LEN alan ve çalışma devam ederken veri kesim tarihinde HIV-1 RNA ölçümü mevcut olanlardır; D1 SC, SC LEN'in uygulandığı ilk gün; Kohort 2'deki 2 katılımcıda (randomize edilmeyen kohort) 1. Günde HIV-1 RNA <50 kopya/mL'ydi, ayrıca 1. Günden önce >0.5 log azalma bulunuyordu (muhtemelen tedaviye uyumun iyileşmesi kaynaklı).

Segal-Maurer S, et al. vCROI 2021. Oral #127

Tedaviyle Ortaya Çıkan Direnç

Katılımcı	OBR'de tam aktif ajanlar*	LEN Kullanılan Önceki Vizitlerde	Yeni Gelişen Kapsid Mutasyonları	LEN Kullanılan Sonraki Vizitlerde
#1	Yok	Baskılanmış	M66I, N74D (10. Haftada: 2870 kopya/mL)	OBR'de değişiklik yapılarak 26. haftada yeniden baskılandı+
#2	DRV/COBI,† DTG,† RPV‡	Baskılanmış	M66I (26. haftada: 561 kopya/mL)	OBR'de **hiç değişiklik yapılmadan** 26. haftada yeniden baskılandı

- Yoğun tedavi görmüş, başlangıçta tedavi başarısızlığı ve çoklu ilaç direnci olan ve SC LEN alan 72 katılımcıdan 2'sinde kapsid mutasyonları gelişti
  - Mutasyonlar yüksek düzeyde LEN direncine yol açtı: EC_{50}'de >884 ve 138 kat değişimi (vs WT)
  - M66I mutasyonu viral replikasyonu önemli ölçüde bozmaktadır (%1.5 replikasyon kapasitesi vs WT)

HTE, yoğun tedavi deneyimli; OBR, optimize edilmiş arka plan rejimi; WT, vahşi tip
*OBR'deki diğer ajanlar: Katılımcı #1 - MVC, T20, DTG BID, DRV/COBI, 3TC; Katılımcı #2 - F/TAF
† Günde iki doz (BID)
‡ Fenotip RPV'ye duyarlılık gösterdi; ancak önceden Y181C mutasyonu varlığı, RPV'nin muhtemelen tam aktif olmadığını gösterir.
+ 3TC kesildi ve F/TAF başlandı
Segal-Maurer S, et al. vCROI 2021. Oral #127

LEN'in Güvenliliği ve Tolerabilitesi

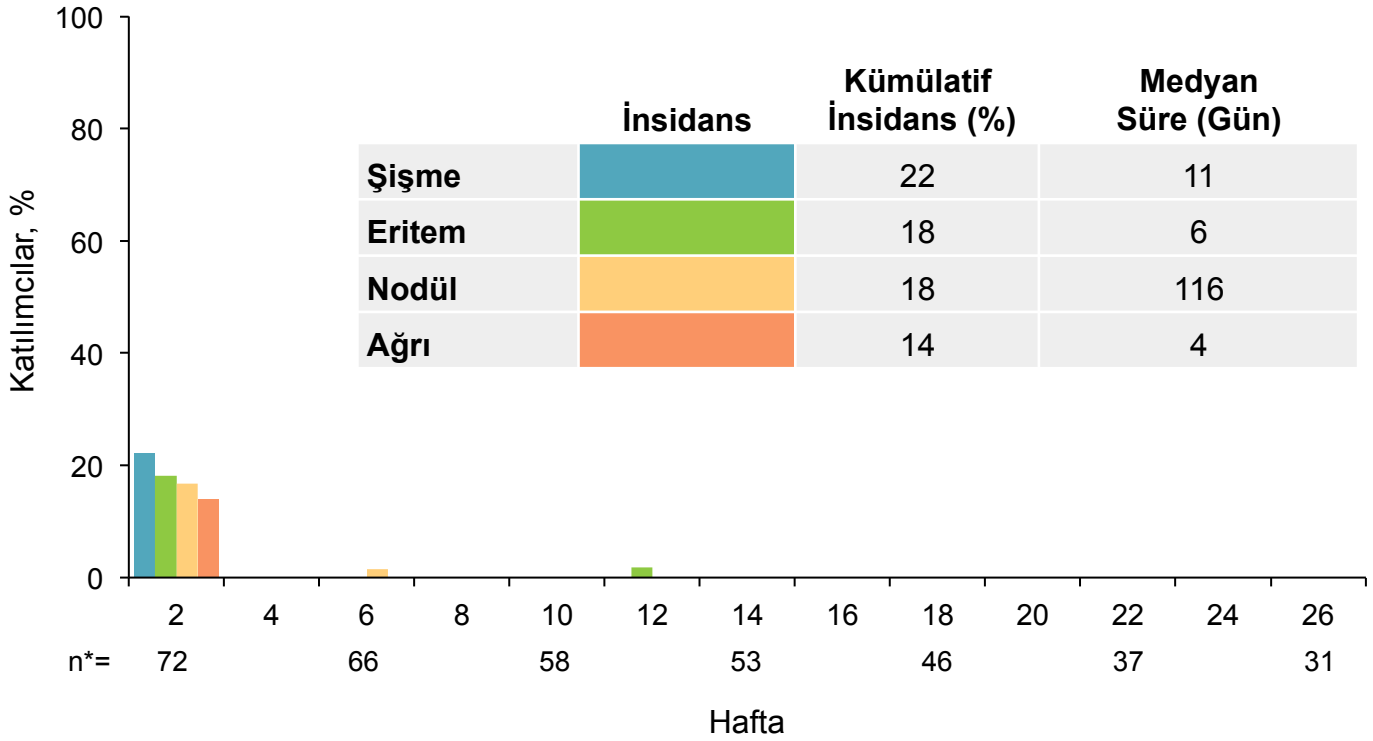
Toplam Güvenlilik

- Çalışma ilacıyla ilişkili ciddi AO görülmedi
- Çalışma ilacının kesilmesine yol açan AO görülmedi

Enjeksiyon Bölgesi Reaksiyonları

- %46'sında (33/72) LEN ile ilişkili ≥1 enjeksiyon bölgesi reaksiyonu vardı
  - Reaksiyonların çoğu Derece 1'di (%82 [27/33]) ve birkaç gün içinde düzeldi
  - Derece 4 reaksiyon görülmedi; bir katılımcıda Derece 3 şişlik ve eritem vardı, sırasıyla 4 ve 8 gün içinde düzeldi
- Nodüller birkaç ay devam etti ve hepsi Derece 1'di
  - Katılımcıların %18'inde bildirildi (%72'sinde nodül bildirmedi)
- Enjeksiyon bölgesi reaksiyonu nedeniyle tedavisi kesilen katılımcı olmadı

Enjeksiyon Bölgesi Reaksiyonları



	İnsidans	Kümülatif İnsidans (%)	Medyan Süre (Gün)
Şişme		22	11
Eritem		18	6
Nodül		18	116
Ağrı		14	4

LEN iyi tolere edildi, tedavinin kesilmesine yol açan AO görülmedi; katılımcıların yarısından azında EBR gözlemlendi

AO, advers olay; EBR, enjeksiyon bölgesi reaksiyonu; CAO, ciddi advers olay
*Çalışmada veya 2 haftalık dönemde çalışmadaki son tarihte yer alan katılımcıların toplam sayısı; Yalnızca LEN ile ilişkili AO'ları içerir, ilişkili olmayanları dışlar (örn. T20)

Segal-Maurer S, et al. vCROI 2021. Oral #127

‡

LEN'in Aktivitesi ve Direnç Karakterizasyonu

Genel Bilgiler[1]

- *In vitro* direnç seçilimleri, kapsiddeki 6 amino asitte ortaya çıkan 7 mutasyonu tanımladı[2]
  - L56I, M66I, Q67H, K70N, K74S/D, T107N
  - Mutasyonların hepsi LEN bağlanma bölgesi ile ilişkili
- Direnç, çoğu mutantta düşük replikasyon kapasitesi ile ilişkili
- 1500 HIV klinik izolatının analizinde LEN mutasyonlarına rastlanmadı[3]
  - PI ile tedavi başarısızlığı olan veya olmayan, tedavi deneyimsiz veya deneyimli
  - LEN'e karşı önceden var olan genotipik direnç yok

LEN ile Seçilen Direnç[1]

HIV-1 Kapsid Sekansı	PhenoSense Gag-Pro (tek döngü)*	
	LEN Kat Değişimi†	Replikasyon kapasitesi, % WT‡
T107N	3.8	32
Q67H	4.8	58
N74D	16	ND
Q67H+N74S	20	15
Q67H+T107N	87	ND
L56I	204	3.6
Q67H+M66I	1,594	ND
Q67H+N74D	>2,700	ND
M66I	>2,700	1.5

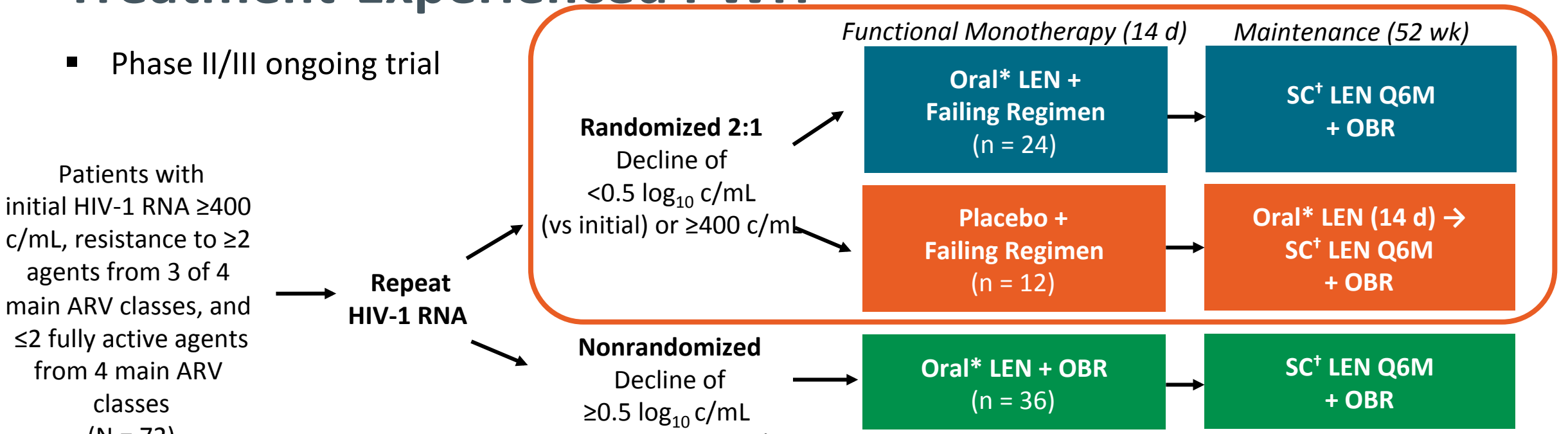
WT, vahşi tip; ND, belirlenmedi; SC, tek döngü
* Sonuçlar, tek ve çok döngülü test formatlarında ve primer hücreler ile hücre dizileri arasında tutarlıydı
† Mutant/WT EC_{50} oranı, PhenoSense Gag-Pro testinde SC reporter HIV-1 ile belirlendi
‡ Referans suş yüzdesi, PhenoSense Gag-Pro testinde SC reporter HIV-1 ile belirlendi

LEN ile seçilen hem tek hem de çift mutasyonlar, LEN duyarlılığını ve fitness'ı azaltır

1. VanderVeen L, et al. vCROI 2021. Oral #128 2. Link J, et al. Nature 2020;584:614-618 3. Marcelin AG, J Antimicrob Chemother 2020;75:1588-1590

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

- Phase II/III ongoing trial



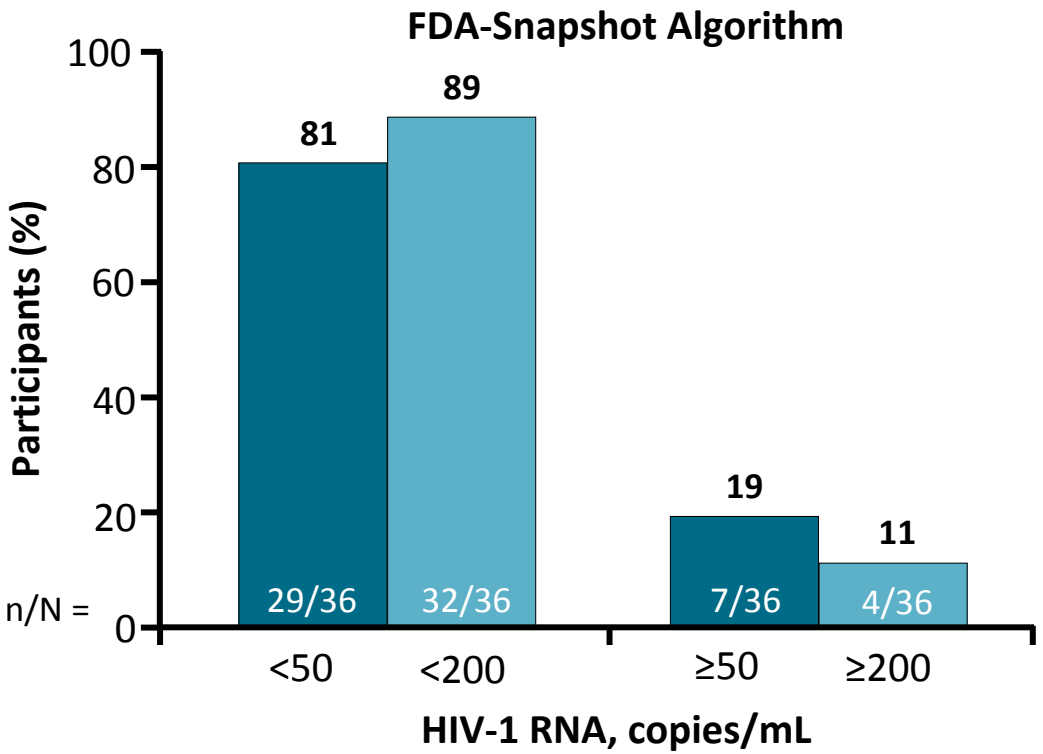
*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8.
†SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.

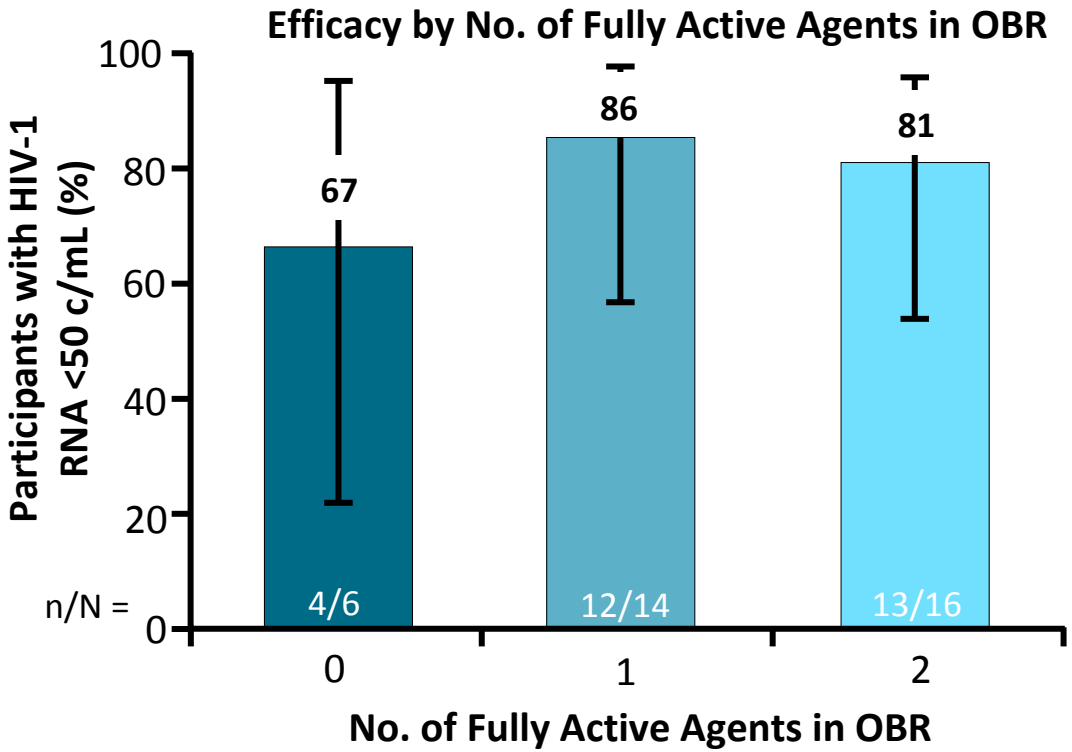
- Participants with known BL resistance to ≥2 drugs in class - NRTI: 99%, NNRTI: 97%, PI: 81%, INSTI: 69%
- Primary endpoint achieved in prior analysis: ≥0.5-log decline in HIV-1 RNA with oral LEN 88% vs placebo 17% at Day 14 in randomized cohort (*P* <.0001)[1]
- **Secondary endpoints: HIV-1 RNA <50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

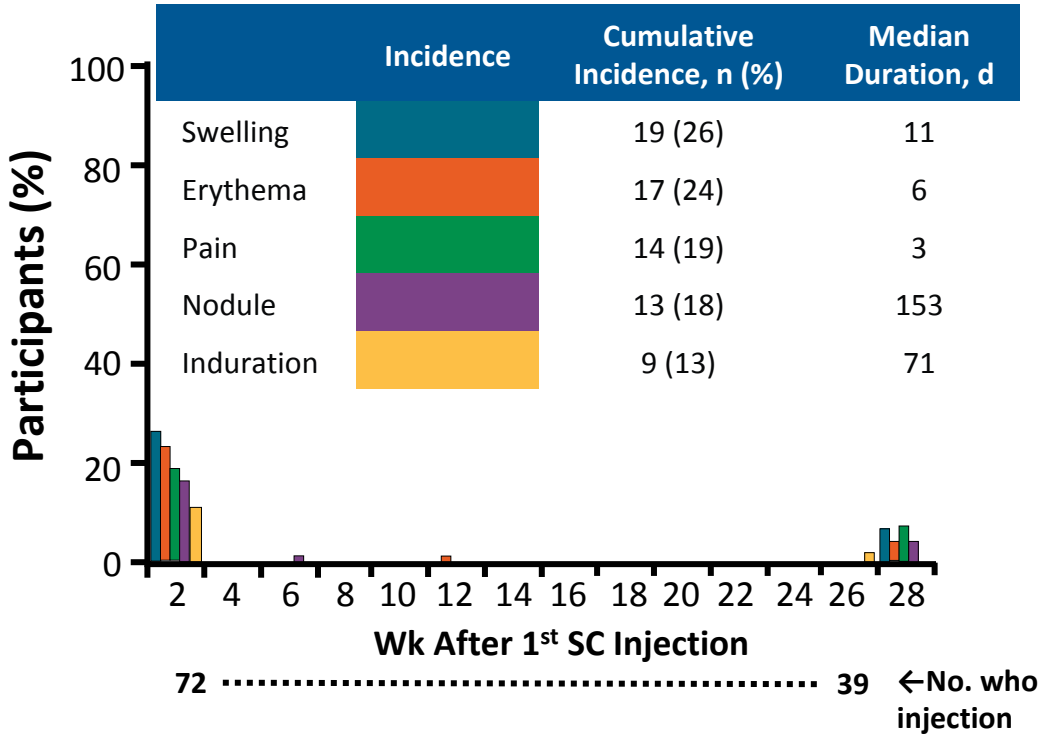
Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

CAPELLA: Wk 26 Safety, Injection Site Reactions in Randomized and Nonrandomized Cohorts

Outcome with incidence ≥5%, n (%)	Total (N = 72)
Adverse event	
▪ Diarrhea	6 (8)
▪ Nausea	6 (8)
▪ Cough	5 (7)
▪ Headache	5 (7)
▪ Pyrexia	5 (7)
▪ Urinary tract infection	5 (7)
▪ Abdominal distension	4 (6)
▪ Arthralgia	4 (6)
▪ Back pain	4 (6)
▪ Constipation	4 (6)
▪ Oral candidiasis	4 (6)
▪ Rash	4 (6)
Any grade 3/4 lab abnormality	19 (26)
▪ Low creatinine clearance/high creatinine	8 (11)
▪ Glycosuria	4 (6)
▪ Nonfasting/fasting hyperglycemia	4 (6)

Injection site reactions (ISRs)



- 56% (40 of 72) had ≥1 ISR related to LEN; 28 grade 1, 2 grade 3, no grade 4
- All 36 patients in randomized cohort received second LEN injection

Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

CAPELLA: Emergent LEN Resistance in Randomized Cohort

Outcome, n (%)	Randomized Cohort (n = 36)
Participants meeting criteria for resistance testing	11 (31)
No emergent LEN resistance	7 (19)
Emergent LEN resistance ▪ M66I ▪ Q67H ▪ K70N/R/S ▪ N74D	 4 1 1 1

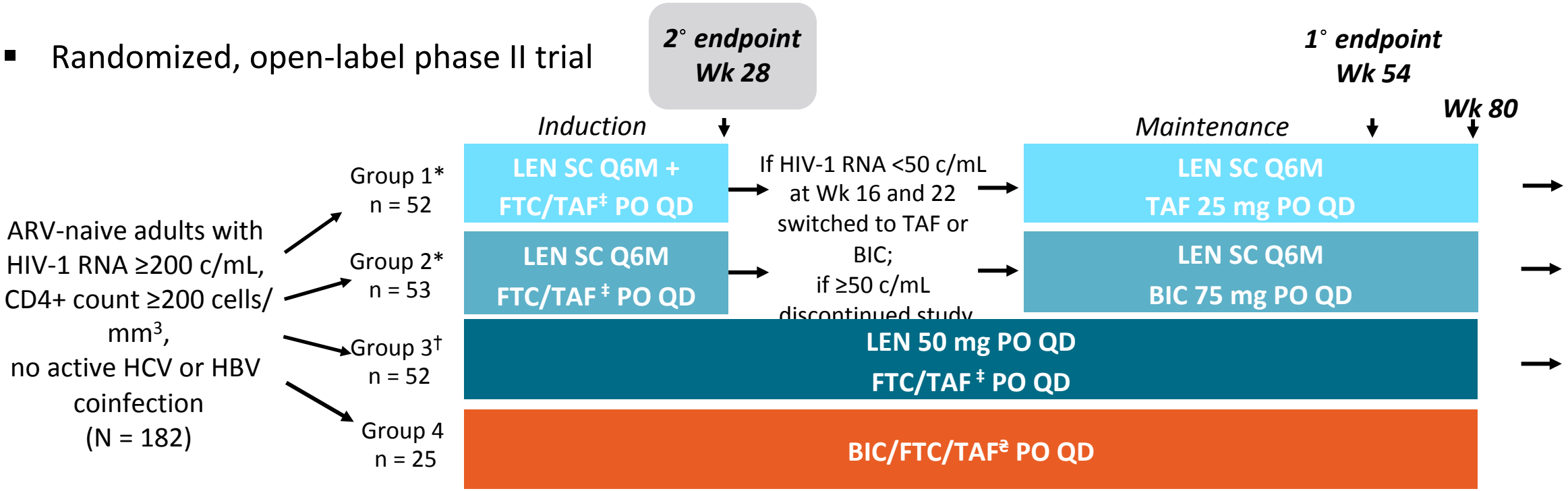
- 4 participants with emergent LEN resistance:
  - All 4 remained on LEN
  - 3 re-suppressed at later visit (2 without, 1 with OBR change)
  - 1 had no fully active agent and never suppressed

Molina. IAS 2021. Abstr OALX01LB02.

Slide credit: clinicaloptions.com

CALIBRATE: Tedavi naif hastalarda lenacapavir (ITT)

- Randomized, open-label phase II trial



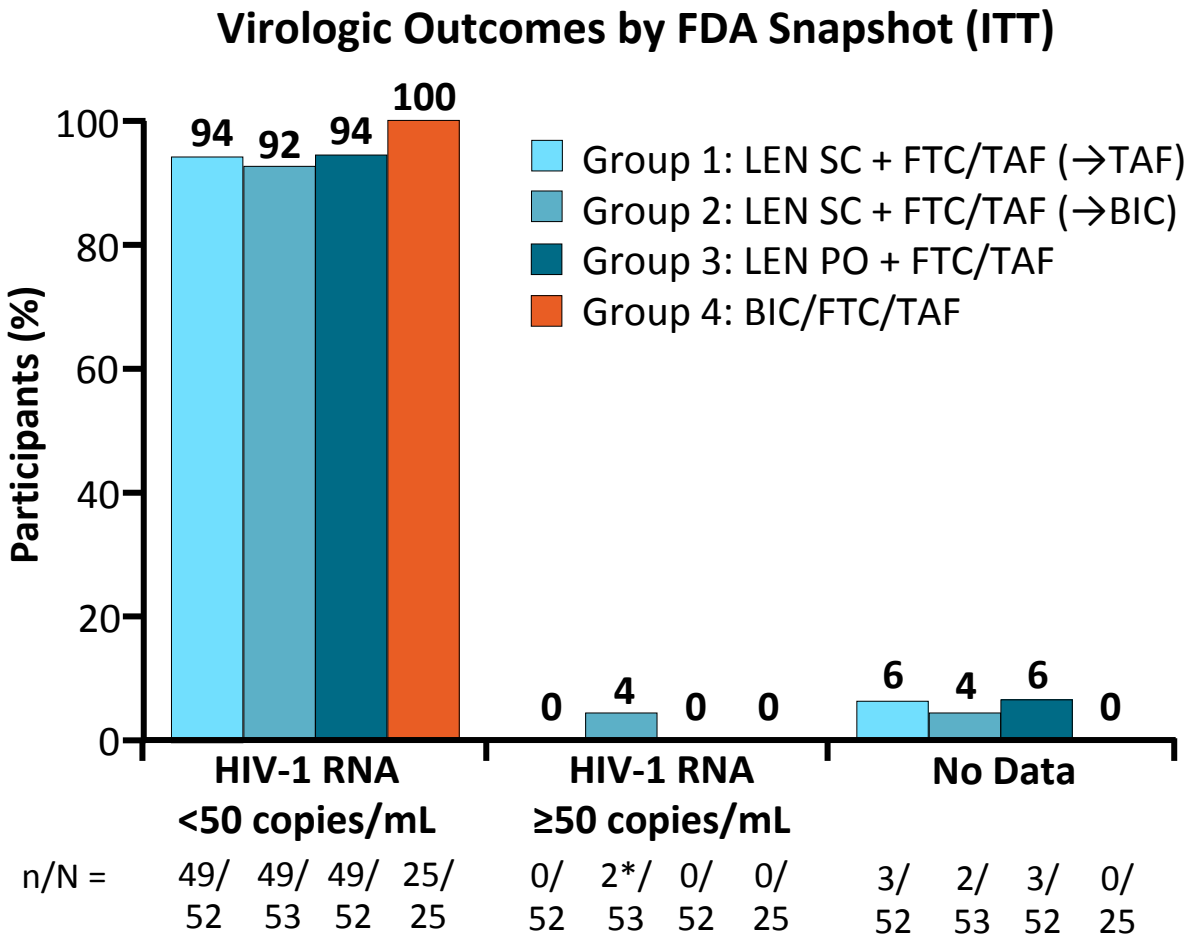
*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M.
†LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ‡FTC/TAF 200/25 mg. ⁂BIC/FTC/TAF 50/200/25 mg.

- 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: 28. hf Virolojik Sonuçlar



*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.

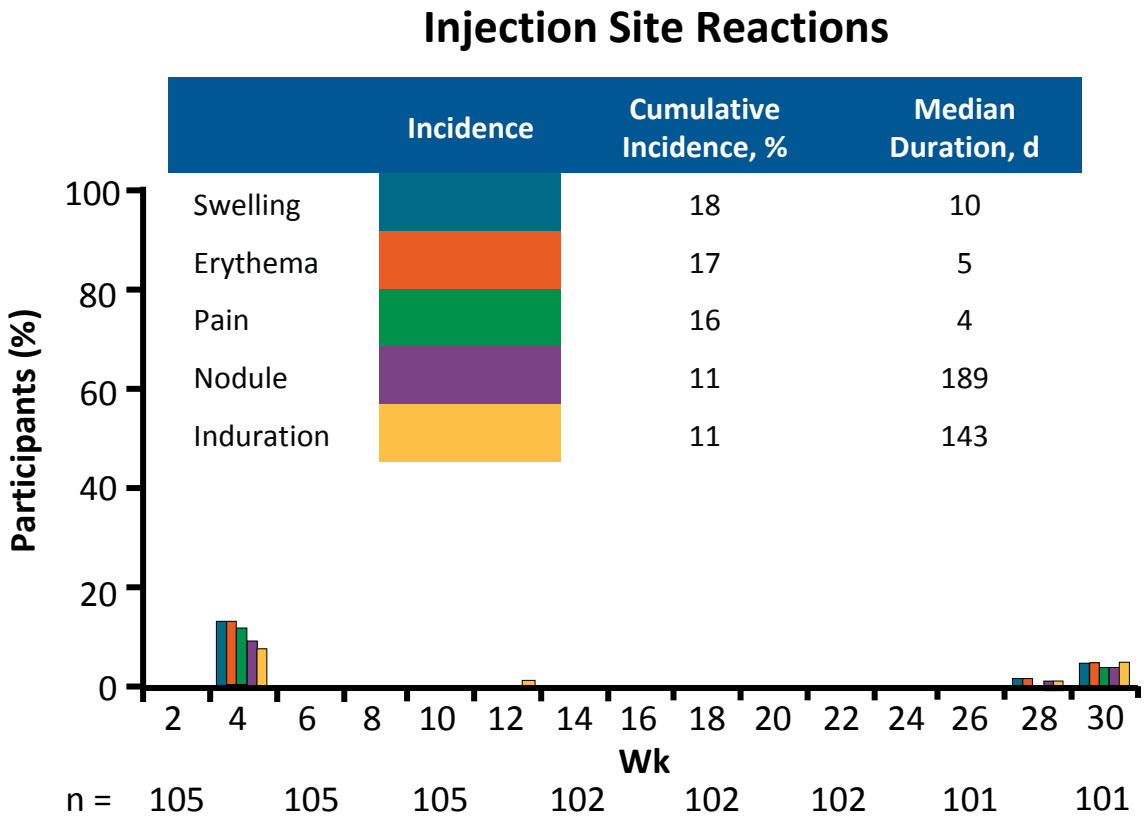
- One participant in **LEN SC + FTC/TAF → BIC** arm had emergent resistance mutations at Wk 10
  - CA: Q67H + K70R (LEN fold change = 20)
  - RT: M184M/I
- Plasma LEN concentrations consistently in target range

Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

CALIBRATE: Advers Olay ve Enjeksiyon Bölgesi Reaksiyonları

- 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

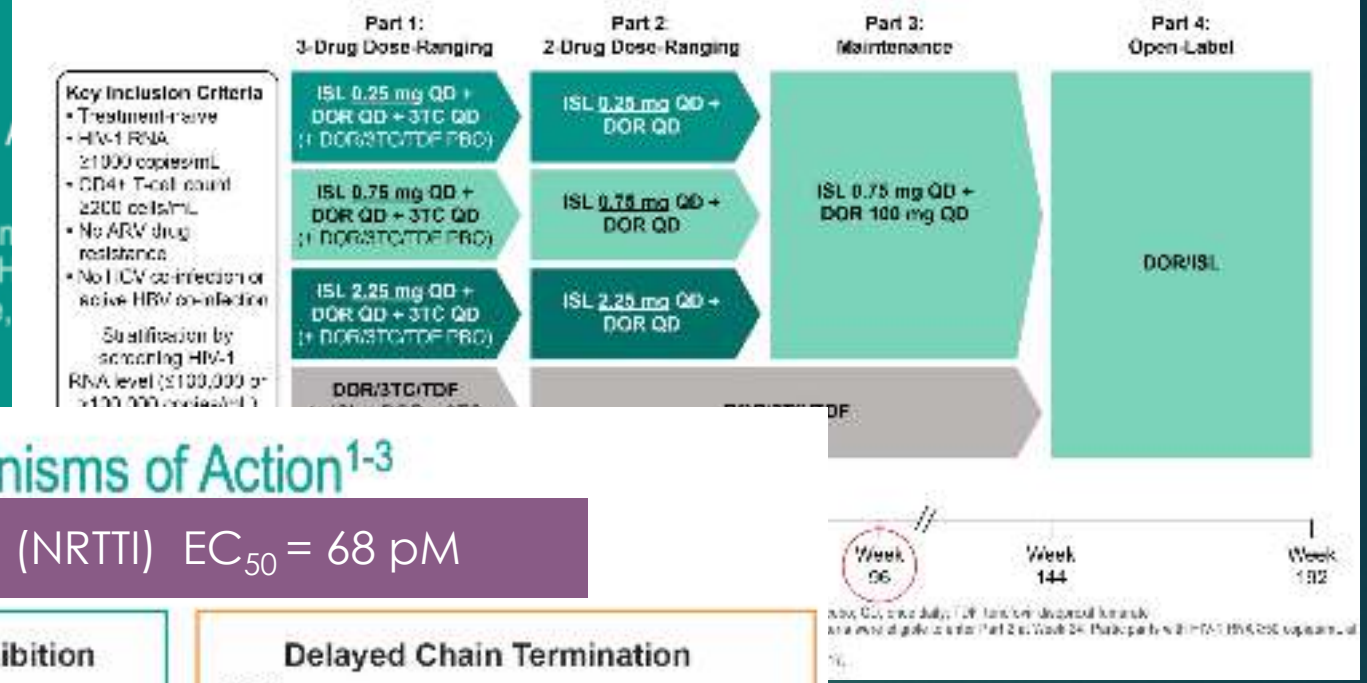
Safety Analysis of Islatravir in Combination With Doravirine in Treatment-Naïve Adults With HIV-1 Infection Through 96 Weeks

D. Cunningham,[1] J.-M. Molina,[2] Y. Yazdanpanah,[3] A. Afani Saud,[4] C. Chahin A
Eves,[6] D. Hepler,[6] C. Hwang,[6] R. Lahoulou,[7] T.A. Correll[6]

[1]Pueblo Family Physicians Ltd, Phoenix, United States, [2]Saint-Louis Hospital an
[3]Bichat Hospital, Paris, France, [4]University of Chile, Santiago, Chile, [5]Hospital H
Temuco, Chile, [6]Merck & Co., Inc., Kenilworth, NJ, United States, [7]MSD France,

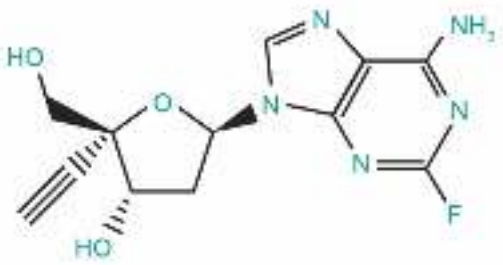
July 18-21, 2
Presented at t
Virtual event (
https://www.ias

MK-8591 Protocol 011: Phase 2 Dose-Ranging Trial of ISL+DOR[a]



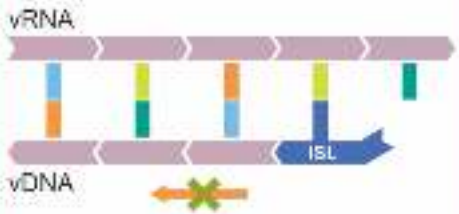
Islatravir (ISL) Has Multiple Mechanisms of Action[1-3]

Nükleosid RT translokasyon inhibitörü (NRTTI) EC_{50} = 68 pM



Multiple mechanisms contribute to the high potency of ISL against HIV-1 (including drug-resistant variants) and its high barrier to resistance

Translocation Inhibition



- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination

- ISL changes vDNA structure such that nucleotide incorporation is prevented
- Because ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- **Viral replication is inhibited**

Gilead and Merck Initiate Phase 2 Study Evaluating an Oral Weekly Combination Regimen of Investigational Lenacapavir and Investigational Islatravir for HIV-1 Treatment in Virologically Suppressed Adults

– This Clinical Study is the First from Merck and Gilead's Collaboration to Develop Potential Long-Acting HIV Treatment Options –

https://www.businesswire.com/news/

ClinicalTrials.gov Identifier: NCT05052996

Actual Study Start Date :	October 5, 2021
Estimated Primary Completion Date :	August 2022
Estimated Study Completion Date :	September 2026

Özet

- En az 3 – 6 aydır virolojik baskılanması (<50 k/mL) olan, daha önce tedavi başarısızlığı veya bilinen/ şüphelenilen ilaç direnci olmayan hastalarda uzun-etkili enjekte edilebilen cabotegravir + rilpivirin idame tedavisi güvenli ve etkili

- Uzun-etkili tedaviler daha sık kullanılacak gibi gözükmekte
  - Lenacapavir + Islatravir = uzun etkili oral veya enjekte edilebilir formülasyon

- Enjeksiyon bölgesi reaksiyonları sık ama şiddeti zamanla azalmakta

- Enjeksiyonların planlanması için poliklinik düzenlemesi gerekmekte
  - Hasta uyumu önemli

Uzun Etkili Tedaviler

Antiretroviral Tedavi

İLGİNİZ İÇİN TEŞEKKÜRLER!

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