“Long acting”: ¿El próximo paso?

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Declaración conflictos de interés

- Financiamiento investigación: MSD
- Asesorías y honorarios: Gador/Gilead, GSK/ViiV

Agenda

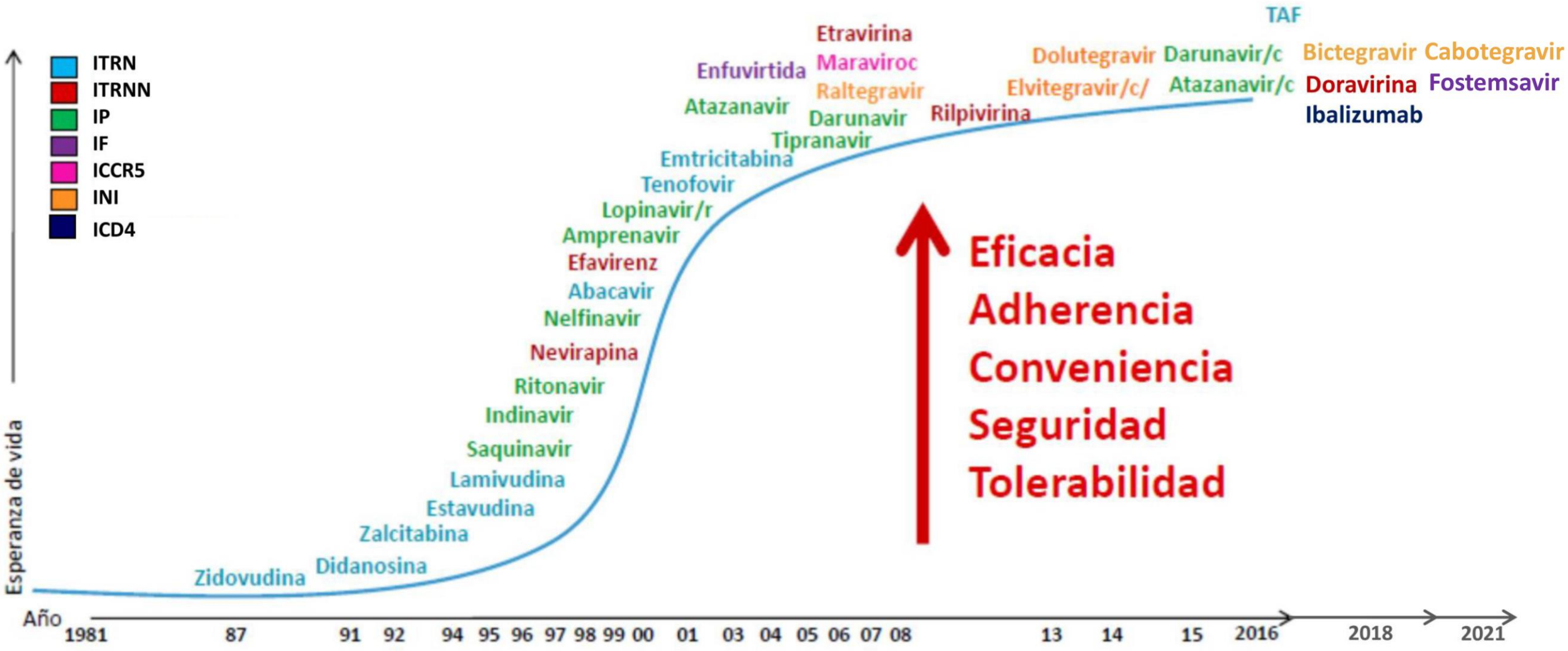
- Introducción
- Modalidades y ARV de larga duración aprobados o en desarrollo
- Cabotegravir-Rilpivirina IM
- Lenacapavir SC
- Islatravir VO
- Anticuerpos neutralizantes de amplio espectro (HIV Broadly Neutralizing Antibodies –bNAbs-) SC

Terapia Antiretroviral 2022

Objetivos:

1) Supresión de la viremia: Indetectabilidad
2) Reconstitución del sistema inmune
3) Reducción de la morbimortalidad
4) Mejor calidad de vida
5) Prevenir la transmisión del VIH

Evolución de la TAR



Introducción

- La TAR moderna es más potente, segura, más simple (regímenes de 1 tableta) y con menos interacciones con otros medicamentos.
- En algunos pacientes que mantienen buena adherencia y supresión virológica, se puede considerar la simplificación u optimización de la TAR, incluyendo el cambio a ARV de larga duración.

DHHS Guidelines. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL. 2022

Introducción (cont.)

- Ello incluye pacientes que tienen EA, interacciones de drogas y/o no desean seguir tomando diariamente ARV.
- Antes de efectuar un cambio a ARV de larga duración, se debe revisar cuidadosamente la historia de TAR incluyendo respuesta virológica, co-infecciones y co-morbilidades, antecedentes de EA asociados a ARV y resistencia acumulada en los casos que haya existido.

DHHS Guidelines. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL. 2022

Los PVVIH están interesados en nuevas terapias ARV de larga duración, para reducir la frecuencia de dosis

"Longer-lasting treatment" (versus daily oral therapy)

61–73%

of PHIV from three independent studies, were **interested in injectable regimens** versus daily oral therapy[1–3]

61%

of 374 participants presenting at an HIV clinic in Houston, Texas reported that they would **'likely'** or **'very likely'** use LA ART formulations[3]

55%

of a cohort of 2,389 PHIV included in the ViiV Positive Perspective 2 Survey, indicated **preference for a LA regimen**[4]

ART, antiretroviral therapy

1. Williams J, et al. Nanomedicine 2013;8:1807–13
2. Derrick B, et al. Open Forum Infect Dis 2018;5:ofy247
3. Dandachi D, et al. AIDS Care 2021;33:801–9
4. de los Rios P, et al. Popul Med 2020;2:23

Modalidades y ARV de larga duración aprobados o en desarrollo

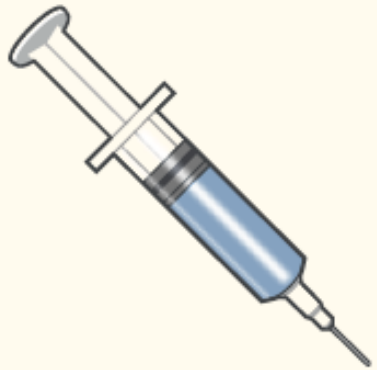
INTRAVAGINAL RING (IVR)

Polymer ring inserted into the vagina releases antiretroviral drug over time.

IMPLANT

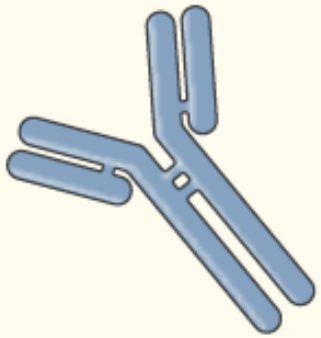
Device implanted in the body releases antiretroviral drug over time.

INJECTABLE

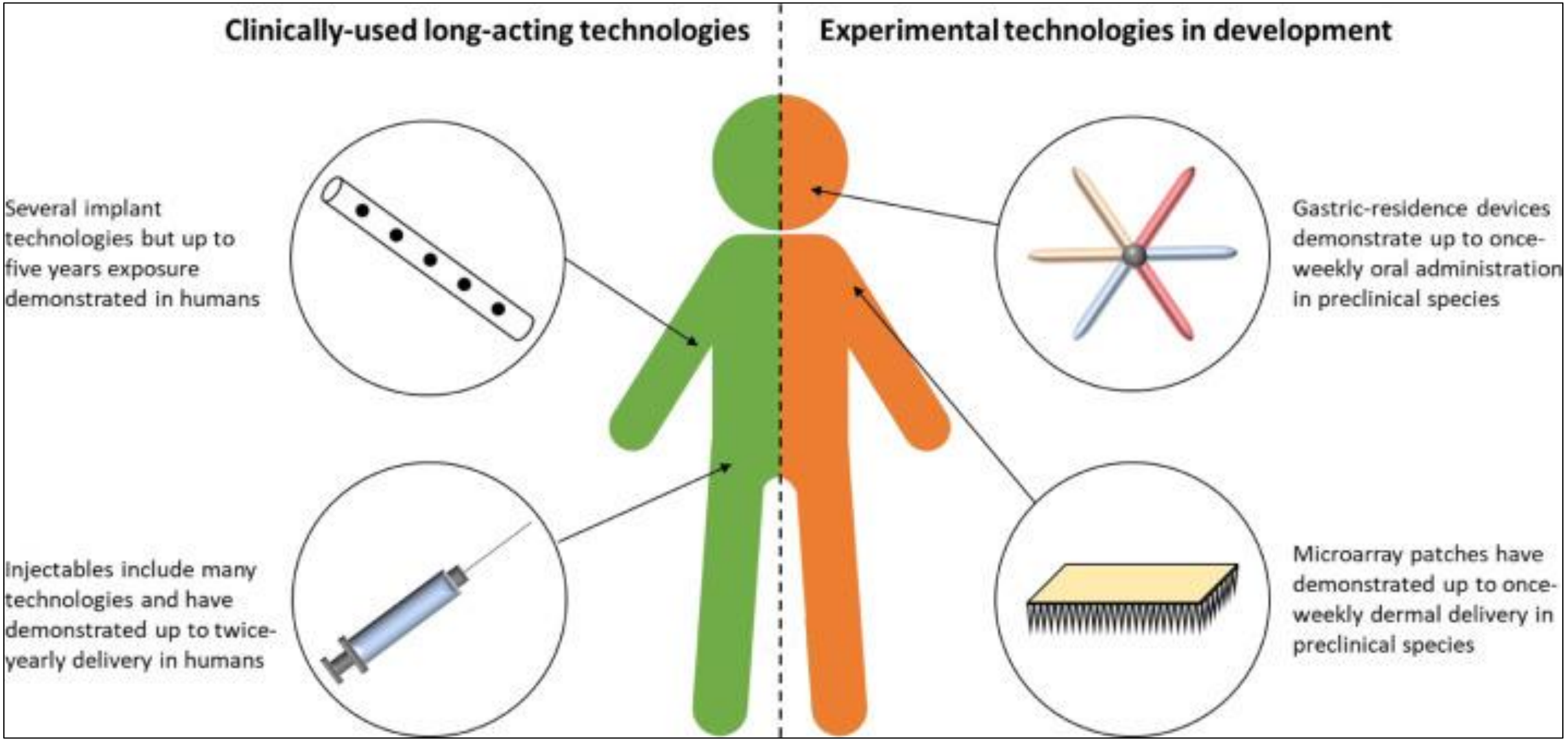


Long-acting antiretroviral drug is injected into the body.

ANTIBODY



Antibody is infused or injected into the body.



Int J Antimicrob Agents. 2021 January ; 57(1): 106220. doi:10.1016/j.ijantimicag.2020.106220.

ARV de larga duración aprobados o en desarrollo

ARV Class	Agent	Formulation	Development Stage
NRTI	Islatravir (MK-8591)	Implant	Phase I
	TAF	Implant	Phase I/II (Px)
	GS-9131	Implant	Preclinical
NNRTI	Rilpivirine	Injectable	Phase III/NDA
	Elsulfavirine	Injectable	Preclinical
PI	Atazanavir	Injectable	Preclinical
	Ritonavir	Injectable	Preclinical
INSTI	Cabotegravir	Injectable	Phase III/NDA, Phase II/III (Px)
	Dolutegravir	Implant	Preclinical (Px)
	Raltegravir	Injectable	Preclinical
Entry Inhibitors	Ibalizumab	Intravenous	FDA Approved (Tx)
	Leronlimab (PRO 140)	Intravenous and Injectable	Phase III
	Albuvirtide	Intravenous and injectable	Approved in China
	bNAbs (e.g., VRC01, VRC07)	Intravenous	Phase I/II/III
	Combinectin	Intravenous	Phase I
Capsid Inhibitors	GS-6207 **(Lenacapavir)**	Injectable	Phase II

ARV = antiretroviral; Px = prevention; Tx = treatment

Int J Antimicrob Agents. 2021 January ; 57(1): 106220. doi:10.1016/j.ijantimicag.2020.106220.

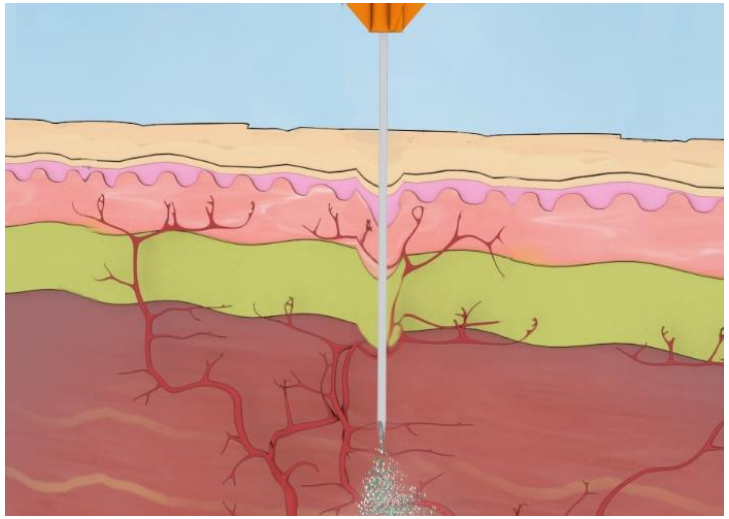
Cabotegravir-Rilpivirina

Attribute	CAB LA[1–4]	RPV LA[1,5–7]
ARV drug class	INI	NNRTI
Oral tablet size ($t_{1/2}$)	30 mg (41 hours)	25 mg (~50 hours)
LA suspension ($t_{1/2}$)	200 mg/mL (5.6–11.5 weeks)	300 mg/mL (13–28 weeks)
Dose – monthly	400 mg (2 mL)	600 mg (2 mL)
Dose – every 2 months	600 mg (3 mL)	900 mg (3 mL)

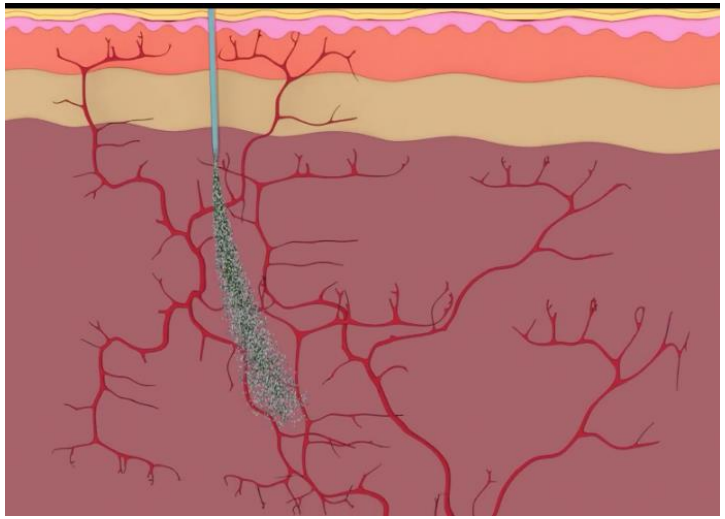
1. Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45; **2.** Ford SL, et al. Antimicrob Agents Chemother 2013;57:5472–7
3. Vocabria EU SmPC. Aug 2022; **4**. Vocabria US PI. Mar 2022; **5.** Rekambys EU SmPC. Feb 2022
6. Edurant EU SmPC. Sep 2021; **7**. Edurant US PI. Mar 2022.

Formulaciones de CAB + RPV LA permiten administration mensual o cada dos meses

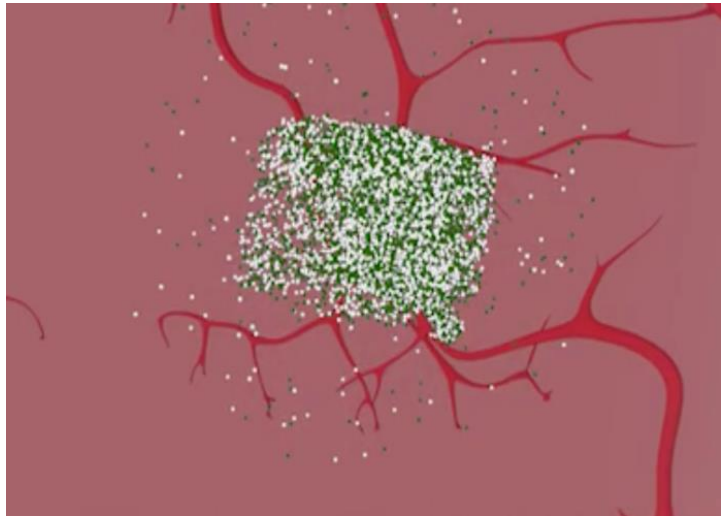
CAB + RPV extended-release suspensions contain finely-milled drug particles suspended in an aqueous vehicle that supports LA dosing:



CAB + RPV LA is administered as separate IM gluteal injection



LA suspension forms a drug depot in the muscle

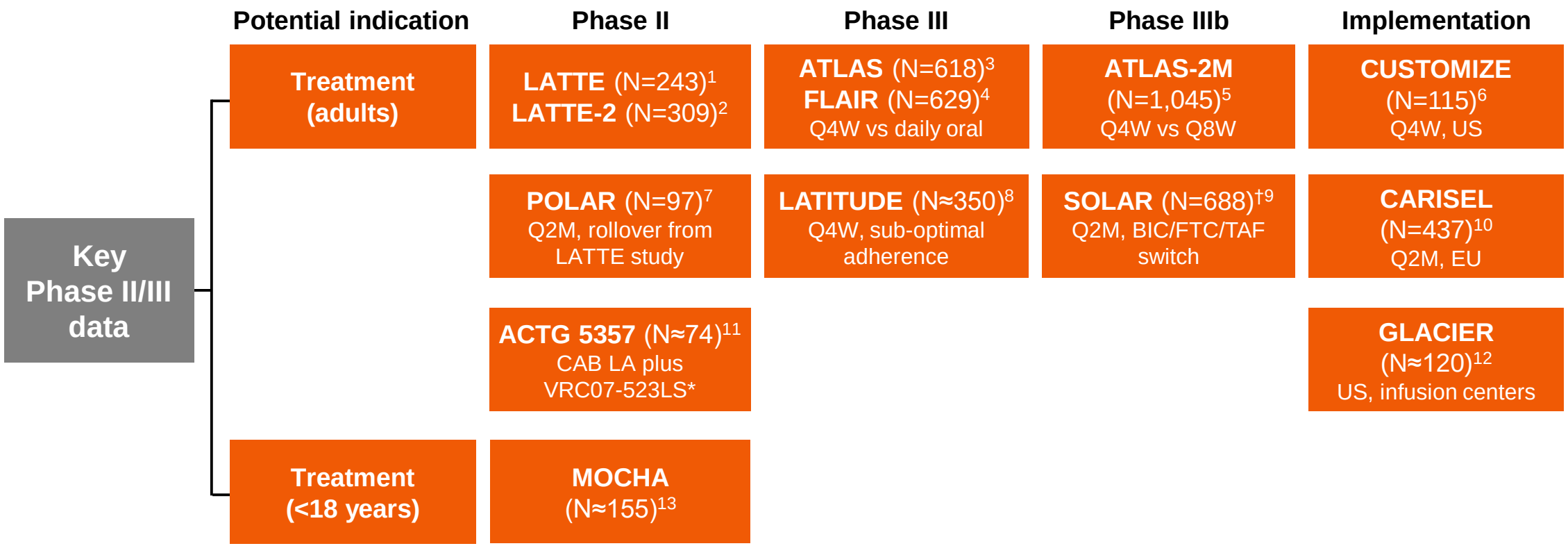


Medications are slowly absorbed from the depot site into the bloodstream

IM, intramuscular

Trezza C, et al. Curr Opin HIV AIDS 2015;10:239–45

CAB LA: Estudios clínicos

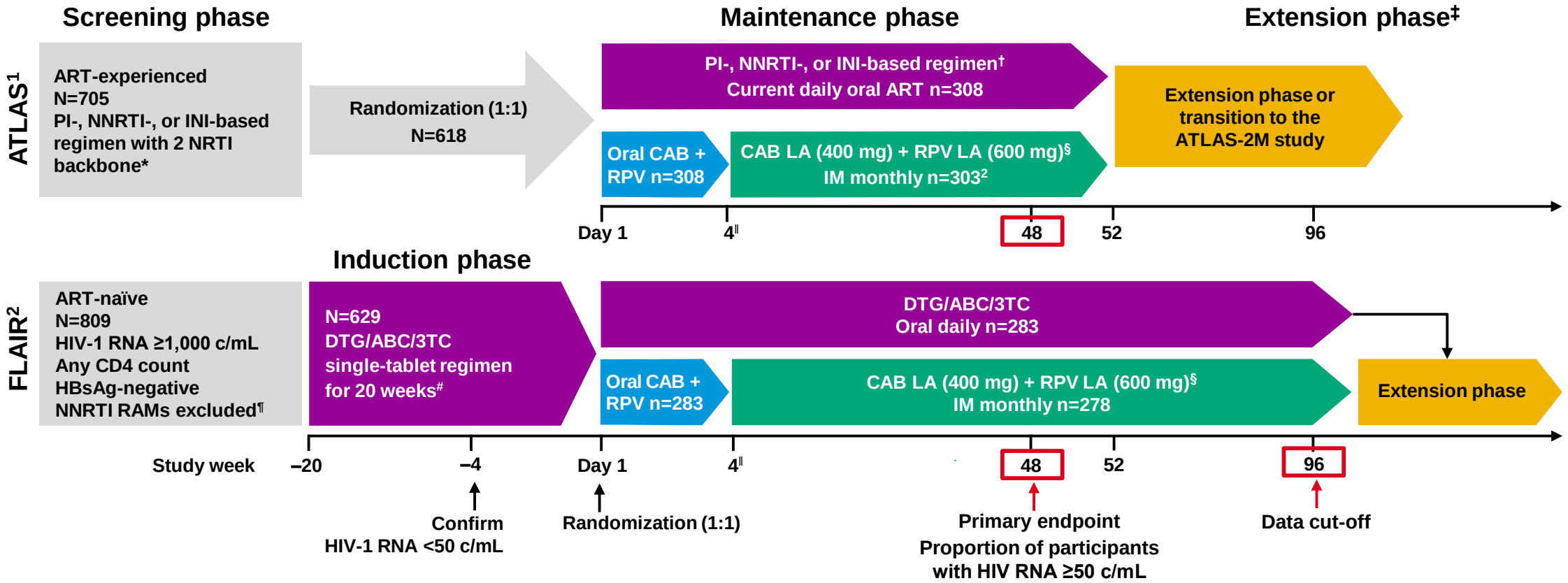


*CAB LA Q4W IM injection in combination with VRC07-523LS (a broadly neutralizing monoclonal antibody) Q8W IV infusion
†The SOLAR study is ongoing but not currently recruiting
BIC, bictegravir; **FTC,** emtricitabine; **IV,** intravenous; **Q2M,** every 2 months; **TAF,** tenofovir alafenamide

1. Margolis DA, et al. Lancet Infect Dis 2015;15:1145–55
2. Margolis DA, et al. Lancet 2017;390:1499–510; **3.** Swindells S, et al. N Engl J Med 2020;382:1112–23
4. Orkin C, et al. N Engl J Med 2020;382:1124–35; **5.** Overton ET, et al. Lancet 2021;396:1994–2005
6. Garris C, et al. IDWeek 2021. Poster 883; **7.** Mills A, et al. AIDS 2021;36:195–203
8. LATITUDE (ACTG 5359). Available at: https://clinicaltrials.gov/ct2/show/NCT03635788 (accessed Sep 2022)
9. SOLAR (213500). Available at: https://clinicaltrials.gov/ct2/show/NCT04542070 (accessed Sep 2022)
10. Hocqueloux et al. EACS 2021. Poster PE2/37
11. ACTG 5357. Available at: https://clinicaltrials.gov/ct2/show/NCT03739996 (accessed Sep 2022)
12. GLACIER. Available at: https://clinicaltrials.gov/ct2/show/NCT04982445 (accessed Sep 2022)
13. MOCHA (IMPAACT 2017). Available at: https://clinicaltrials.gov/ct2/show/NCT03497676 (accessed Sep 2022)

ATLAS y FLAIR: Diseño de los estudios

Phase III, randomized, multicenter, international, open-label, non-inferiority studies



*Uninterrupted ART for 6 months and VL <50 c/mL at screening, 2 × VL <50 c/mL ≤12 months; †INI-based regimen capped at 40% of enrolment. Triumeq excluded from study; ‡Optional switch to CAB + RPV LA at Week 52 for those on CAR; §Participants who withdraw/complete IM CAB + RPV LA must complete 52 weeks of follow-up; ‖Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; ¶NNRTI RAMs except K103N were excluded; #DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive

CD4, cluster of differentiation 4; **HBsAg,** hepatitis B surface antigen; **HLA,** human leukocyte antigen
NRTI, nucleoside reverse transcriptase inhibitor; **PI,** protease inhibitor; **RAM,** resistance-associated mutation

1. Swindells S, et al. AIDS 2022;36:185–194
2. Orkin C, et al. N Engl J Med 2020;382:1124–35

ATLAS y FLAIR: Características basales agrupadas (ITT-E)

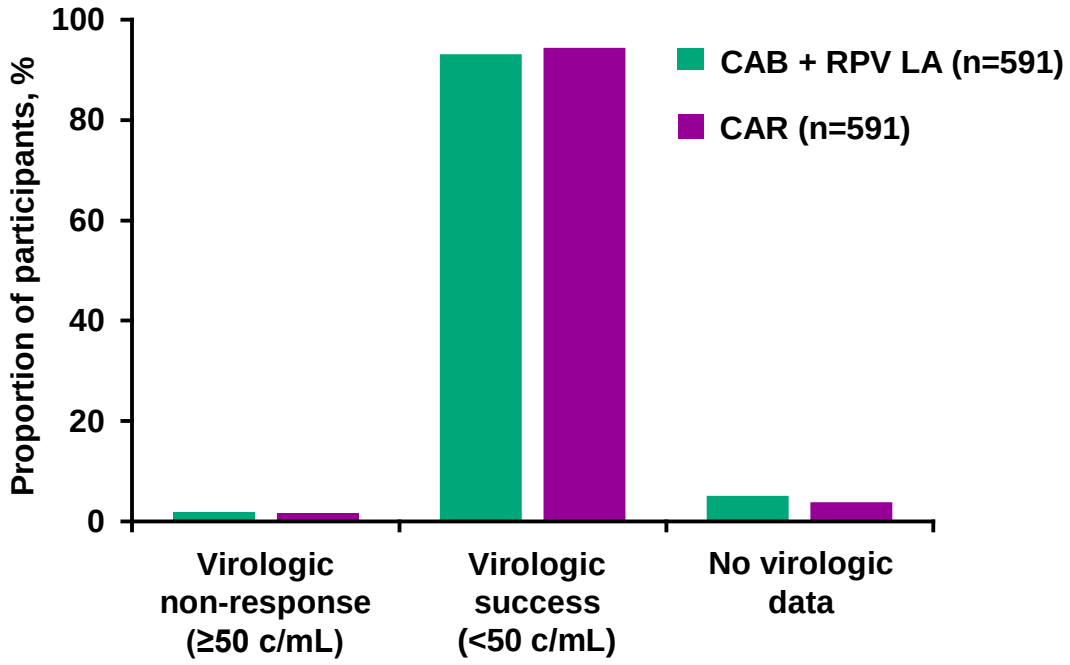
	ATLAS and FLAIR pooled*	
	CAB + RPV LA n=591	CAR n=591
Median age, years (range)	**38 (19–74)**	**38 (18–82)**
Age ≥50 years, n (%)	**99 (17)**	**125 (21)**
Female, n (%)	**162 (27)**	**168 (28)**
Race, n (%)		
White	430 (73)	408 (69)
Black or African American	109 (18)	133 (23)
Other	52 (9)	50 (8)†
Median BMI, kg/m^2 (range)‡	**25 (15–51)**	**25 (13–58)**
Median CD4+ cell count, cells/mm^3 (IQR)	**645 (487–824)**	**641 (480–821)**
HIV-1–HCV co-infection, n (%)	**42 (7)**	**40 (7)**

*BL for FLAIR was Day 1 (maintenance phase)
†Two participants' data are missing
‡Collected at induction BL (Week –20) for FLAIR
BMI, body mass index; **HCV,** hepatitis C virus; **IQR,** interquartile range

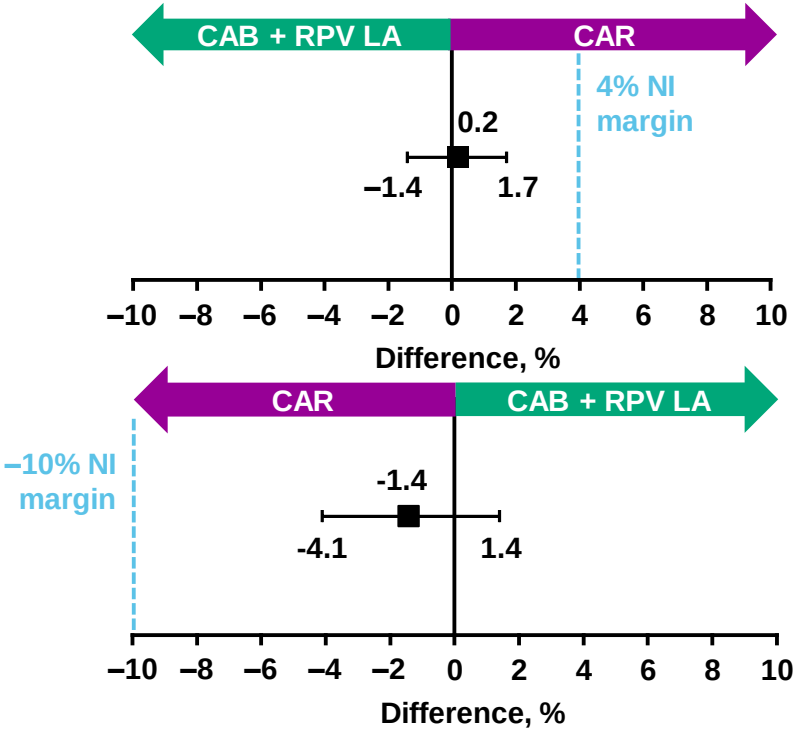
Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506

ATLAS y FLAIR: Desenlaces agrupados a las 48 S (ITT-E)

Virologic outcomes



Treatment differences (95% CI)*



Primary endpoint:

LA non-inferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

Key secondary endpoint:

LA non-inferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

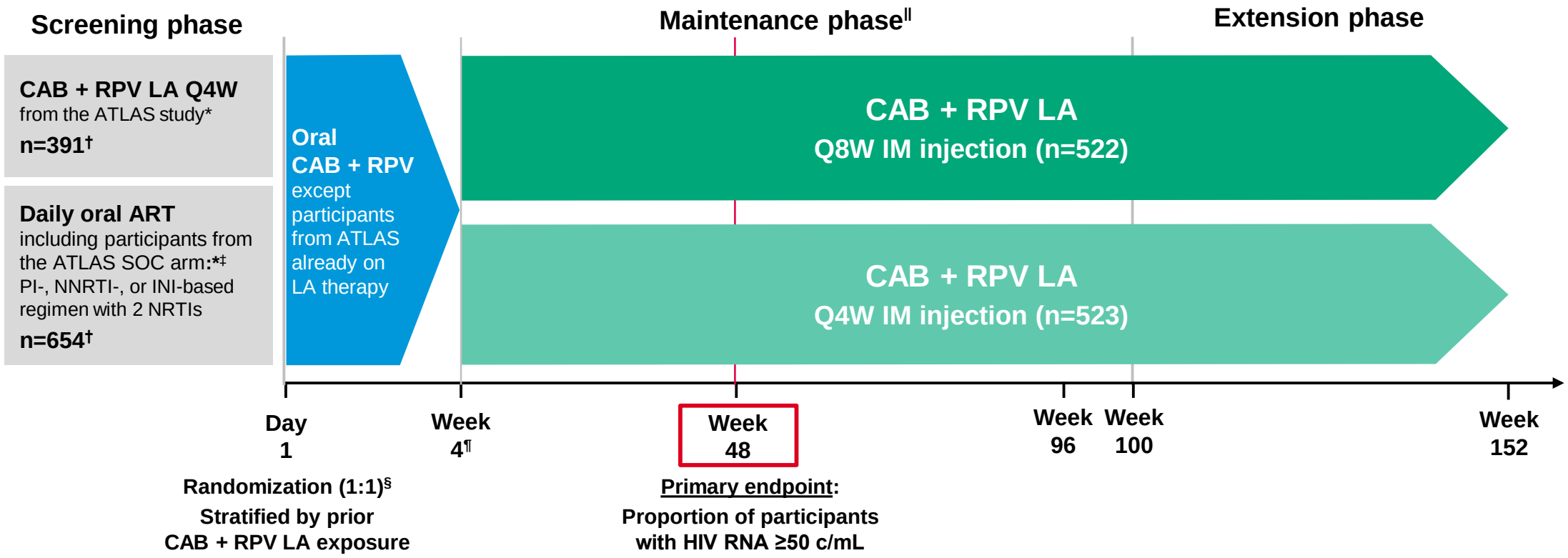
CAB + RPV LA achieved high rates of virologic success and non-inferiority versus CAR for the primary endpoint of HIV-1 RNA ≥50 c/mL at Week 48

*Adjusted for 10 strata
CI, confidence interval; **NI,** non-inferiority

Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506

ATLAS-2M: Diseño del estudio

Phase III, randomized, multicenter, international, open-label, non-inferiority design[1–3]



*Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA <50 c/mL at screening; †ITT-E population; ‡SOC participants not transitioning from the ATLAS study were to be on an uninterrupted current regimen (either the initial or second combined ART regimen) for at least 6 months prior to screening. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to screening, one within the 6–12 month window and one within 6 months prior to screening, was required. Participants were excluded if they had a history of VF or evidence of viral resistance based on the presence of any resistance-associated major INI or NNRTI mutation (except K103N) from prior genotype assay results; §1,149 participants were screened, and 1,049 participants were randomized. Four participants did not receive study drug and therefore were not part of the ITT-E population; ‖Participants who withdraw from the IM regimen must go into 52-weeks long-term follow-up if randomized regimen is not yet locally approved and commercially available; ¶Participants on OLI treatment attended a Week 4 visit to assess tolerability. In participants in the Q4W arm who had an OLI, the first LA dose was CAB 600 mg + RPV 900 mg

OLI, oral lead-in; **SOC,** standard of care

1. Overton ET, et al. Lancet 2021;396:1994–2005
2. Overton ET, et al. CROI 2020. Oral 3334
3. Overton ET, et al. CROI 2022. Poster H03

ATLAS-2M: Características basales (población ITT-E)

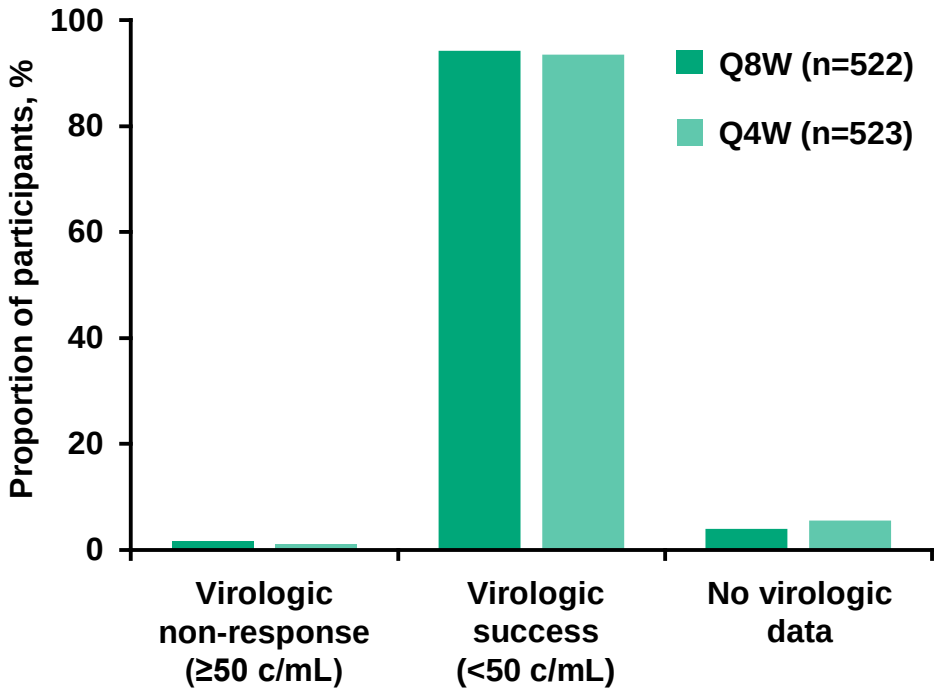
	Q8W n=522	Q4W n=523	Total N=1,045*
Prior exposure to CAB + RPV, n (%)[1]			
None	327 (63)	327 (63)	654 (63)
1–24 weeks	69 (13)	68 (13)	137 (13)
>24 weeks	126 (24)	128 (24)	254 (24)
Median age, years (range)[2]	**42 (20–83)**	**42 (19–75)**	**42 (19–83)**
Age ≥50 years, n (%)	143 (27)	139 (27)	282 (27)
Female (sex at birth), n (%)[1]	**137 (26)**	**143 (27)**	**280 (27)**
Female (participant-reported gender), n (%)[1]	**142 (27)**	**146 (28)**	**288 (28)**
Race, n (%)[1]			
White	370 (71)	393 (75)	763 (73)
Black or African American	101 (19)	90 (17)	191 (18)
Other	51 (10)	40 (8)	91 (9)
Median BMI, kg/m^2 (IQR)[1]	**26 (23–29)**	**26 (23–29)**	**26 (23–29)**
≥30, n (%)	113 (22)	98 (19)	211 (20)
Median CD4 count, cells/mm^3 (IQR)[1]	**642 (499–827)**	**688 (523–878)**	**661 (508–849)**

*1,049 participants were randomized; however, four participants did not receive study drug and therefore were not part of the ITT-E population

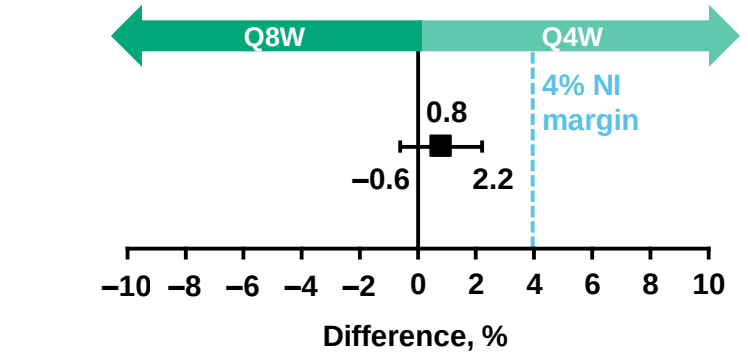
1. Overton ET, et al. Lancet 2021;396:1994–2005
2. Overton ET, et al. CROI 2020. Oral 3334

ATLAS-2M: Resultados virológicos a semana 48 (Snapshot. ITT-E)

Virologic outcomes[1,2]

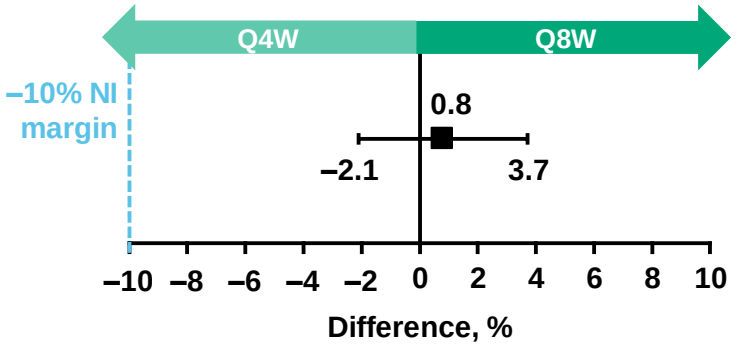


Treatment differences (95% CI)[1,2*]



Primary endpoint:

Q8W non-inferior to Q4W (HIV-1 RNA ≥50 c/mL) at Week 48



Key secondary endpoint:

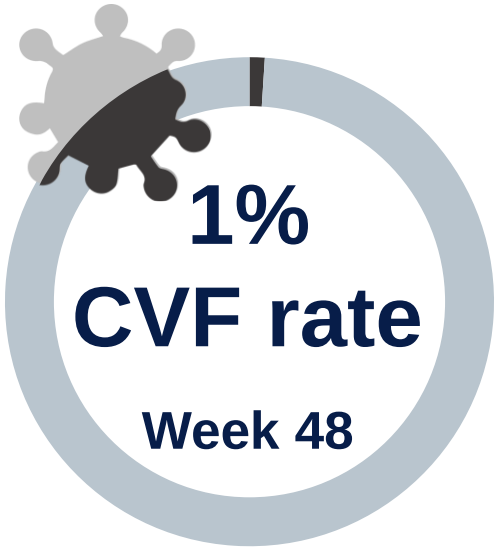
Q8W non-inferior to Q4W (HIV-1 RNA <50 c/mL) at Week 48

CAB + RPV LA Q8W achieved non-inferiority versus Q4W for the primary (HIV-1 RNA ≥50 c/mL) and key secondary (HIV-1 RNA ≥50 c/mL) endpoints at Week 48

*Based on Cochran–Mantel–Haenszel stratified analysis adjusting for the following BL stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks)

1. Overton ET, et al. Lancet 2021;396:1994–2005
2. Overton ET, et al. CROI 2020. Oral 3334

ATLAS, FLAIR y ATLAS-2M: Falla virológica confirmada y Resistencia a CAB + RPV LA a semana 48



CVF
(n=17/1,636*†)[1]

	ATLAS and FLAIR[2]		ATLAS-2M[3]	
n (%)	CAB + RPV LA Q1M N=591	Daily oral ARV N=591	CAB + RPV LA Q2M n=522	CAB + RPV LA Q1M n=523
Participants with CVF	6† (1)	7 (1)	8 (<2)	2 (<1)

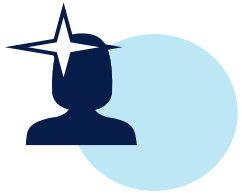
- INI mutation pattern: Q148R/Q, G140R, N155H, E138E/K[2–7]
- NNRTI mutation pattern: E138E/A/K/T/G, K101E, K103N, Y188L, V108I, M230L[2–7]
- 50% (8/16) came from Russian sites where:[2–7]
  - A1/A6 subtype is common[8]
  - L74I is a common polymorphism that was present at BL[9]

- One participant from FLAIR did not re-suppress on 3TC/ZDV/LPV/r[7] while a second participant from ATLAS-2M did not re-suppress because of poor adherence to a bPI regimen[3]

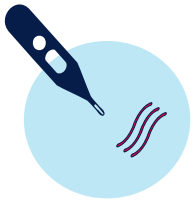
*ATLAS n=308; FLAIR n=283; ATLAS-2M n=1,045
†An additional participant in FLAIR was excluded because CVF occurred prior to receiving LA injection (withdrawn due to false-positive pregancy test)
/r, ritonavir boosted; **bPI,** boosted protease inhibitor; **CVF,** confirmed virologic failure; **LPV,** lopinavir **Q1M,** every 1 month; **ZDV,** zidovudine

1. Cutrell AG, et al. AIDS 2021;35:1333–42; **2.** Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506 **3.** Overton ET, et al. Lancet 2021;396:1994–2005 (and suppl. appendix); **4.** Orkin C, et al. N Engl J Med 2020;382:1124–35 **5.** Swindells S, et al. N Engl J Med 2020;382:1112–23; **6.** ViiV Healthcare. Data on File. REF-150538; **7.** ViiV Healthcare. Data on File. REF-150540 **8.** Hemelaar J, et al. Lancet Infect Dis 2019;19:143–55 (and suppl. appendix); **9.** Lapovok I, et al. Curr HIV Res 2017;15:318–26

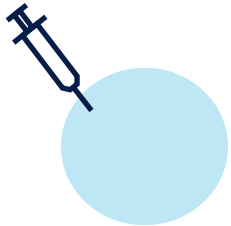
ATLAS, FLAIR y ATLAS-2M: EA mas frecuentes (< 10%) a semana 48



Headache[1,2]



Pyrexia[1,2]



ISRs[1,2]

<2% (n=23/1,636†) of participants discontinued due to injection-related reasons[3,4]

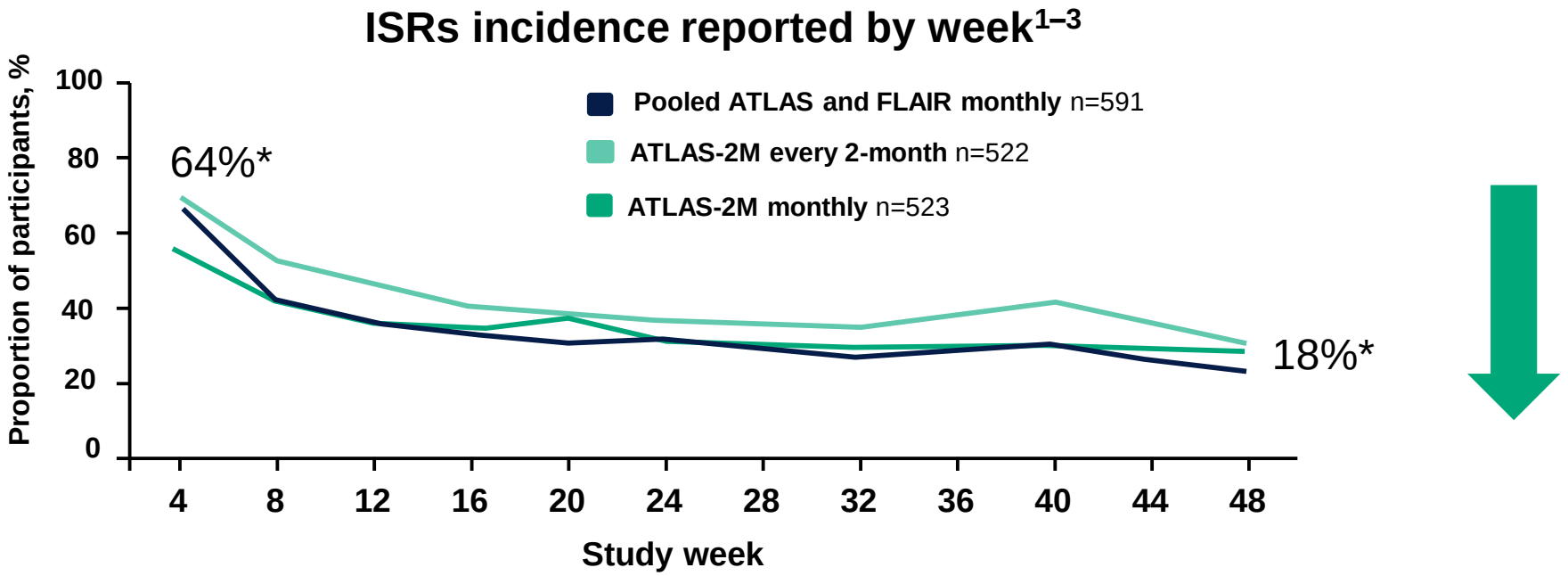
98% (n=9,196/9,322) of ISRs were mild-to-moderate and declined over time[3,4]

3 days median duration[3,4]

*Very common, ≥10%; please refer to the SmPCs for the full list of adverse reactions
†ATLAS n=308; FLAIR n=283; ATLAS-2M n=1,045
SmPC, Summary of Product Characteristics

1. Vocabria EU SmPC. Aug 2022
2. Rekambys EU SmPC. Feb 2022
3. Rizzardini G, et al. J Acquir Immune Defic Syndr 2020;85:498–506 (and suppl. appendix)
4. Overton ET, et al. Lancet 2021;396:1994–2005

ATLAS, FLAIR y ATLAS-2M: Reacciones en el sitio de inyección a CAB + RPV a la semana 48



Reported ISRs decreased over time across the three studies

Long-term follow-up reported number of ISR similar to that observed at the end of the maintenance phases and remained consistent over time[4,5]

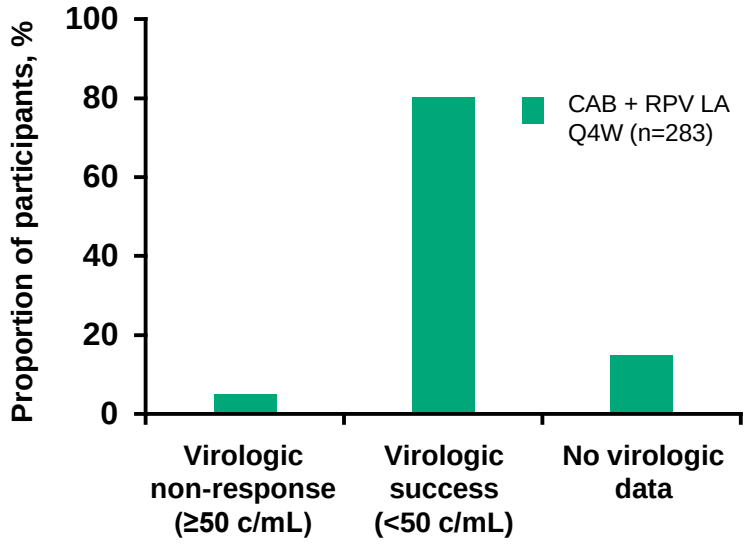
*Average (mean)

1. Orkin C, et al. N Engl J Med 2020;382:1124–35 (and suppl. appendix)
2. Swindells S, et al. N Engl J Med 2020;382:1112–23 (and suppl. appendix)
3. Overton ET, et al. Lancet 2021;396:1994–2005 (and suppl. appendix)
4. Orkin C, et al. Lancet HIV 2021;8:e185–96; **5.** Jäger H, et al. Lancet HIV 2021;8:e679–89

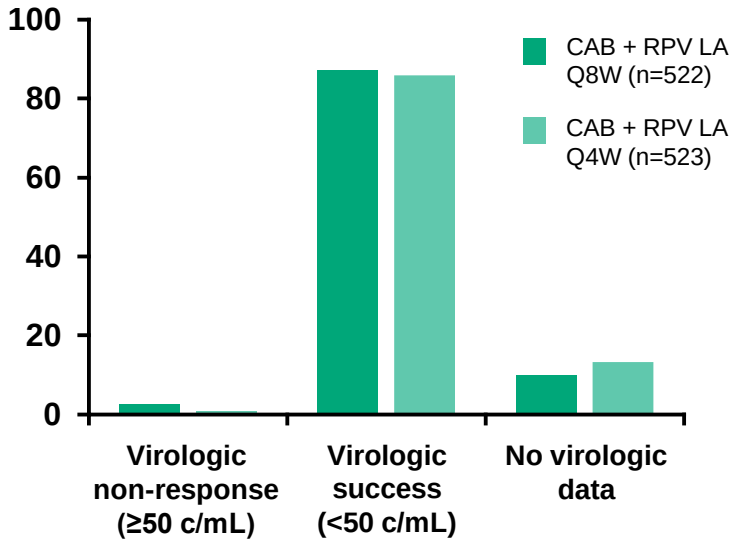
CAB + RPV LA mantiene alta supresión virológica en el largo plazo

Virologic Snapshot outcomes in Phase IIb and III clinical trials (ITT-E)

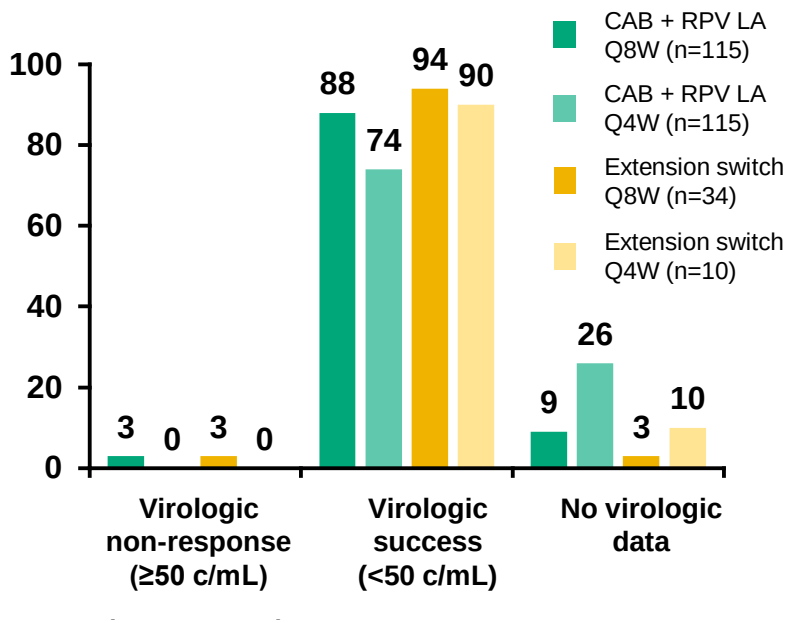
FLAIR Week 124*†[1]



ATLAS-2M Week 152*[2]



LATTE-2 Week 256‡[3]



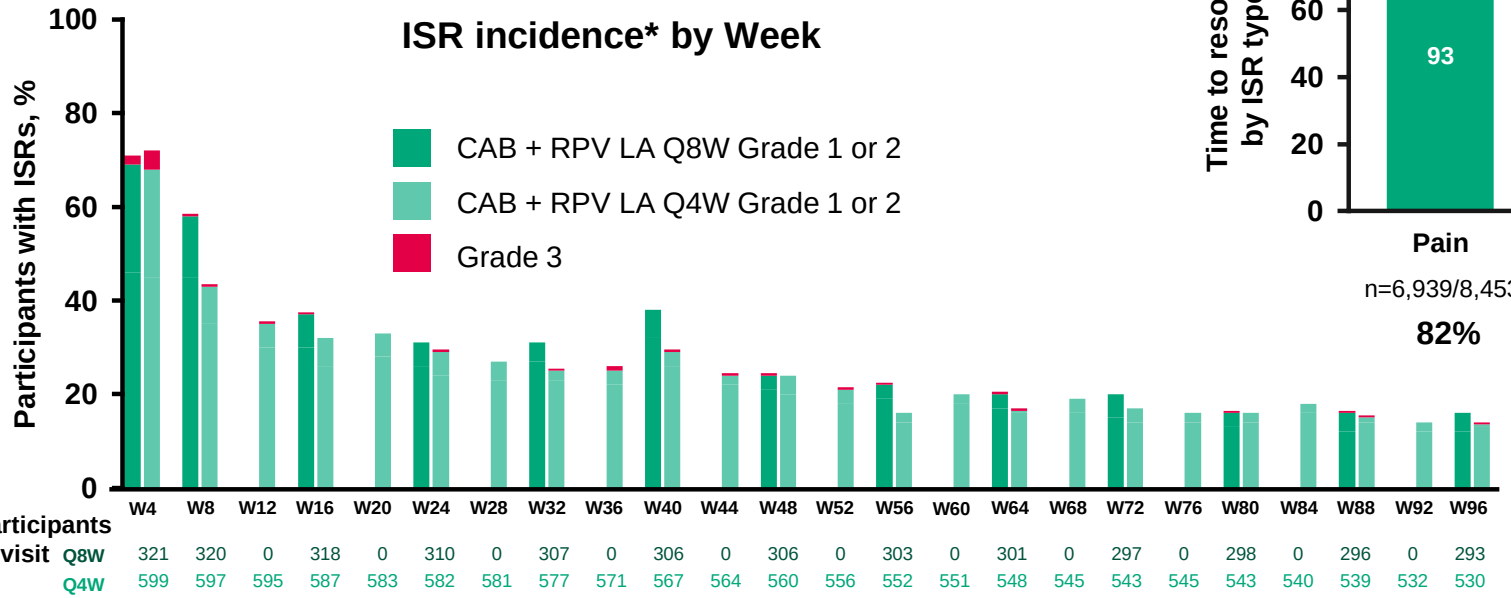
CAB + RPV LA maintained high levels of virologic suppression beyond Week 48[1–3]

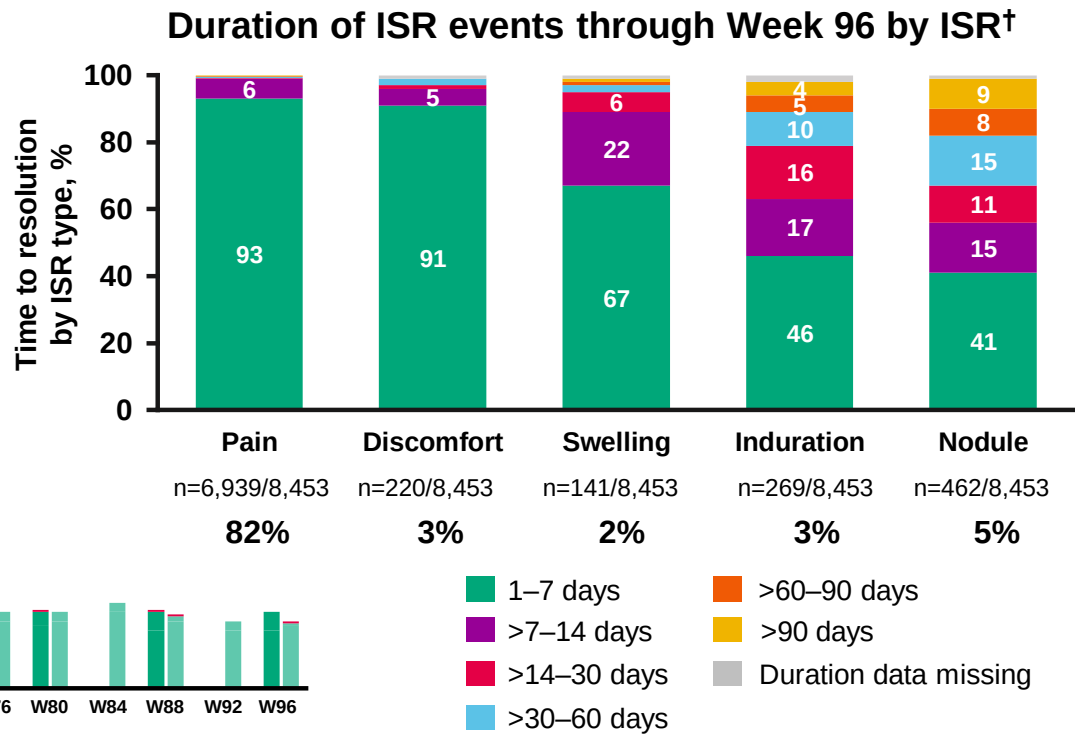
*Primary endpoint: proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 by FDA Snapshot
† No CAR arm at Week 124. Of those with no virologic data at Week 124 (n=42), most were due to discontinuations due to AEs or other non-virologic reasons
‡ Primary endpoints: proportion of participants with viral suppression (HIV <50 c/mL) at Week 32 by FDA snapshot, PVDF and safety events through to Week 96

1. Orkin C, et al. Lancet HIV 2021;8:e668–78
2. Overton ET, et al. CROI 2022. Poster H03
3. Smith GHL, et al. Open Forum Infect Dis 2021;8:ofab439

Análisis agrupado de FLAIR y ATLAS-2M: Incidencia de reacciones en el sitio de inyección disminuyen en el tiempo y se resuelven rápidamente

- 99% of ISRs were Grade 1 and 2, with no Grades 4 and 5 reported
- The median (IQR) duration was 3 days (2–4), with no difference between dosing regimens
- The majority (99%) of ISRs were self-limited



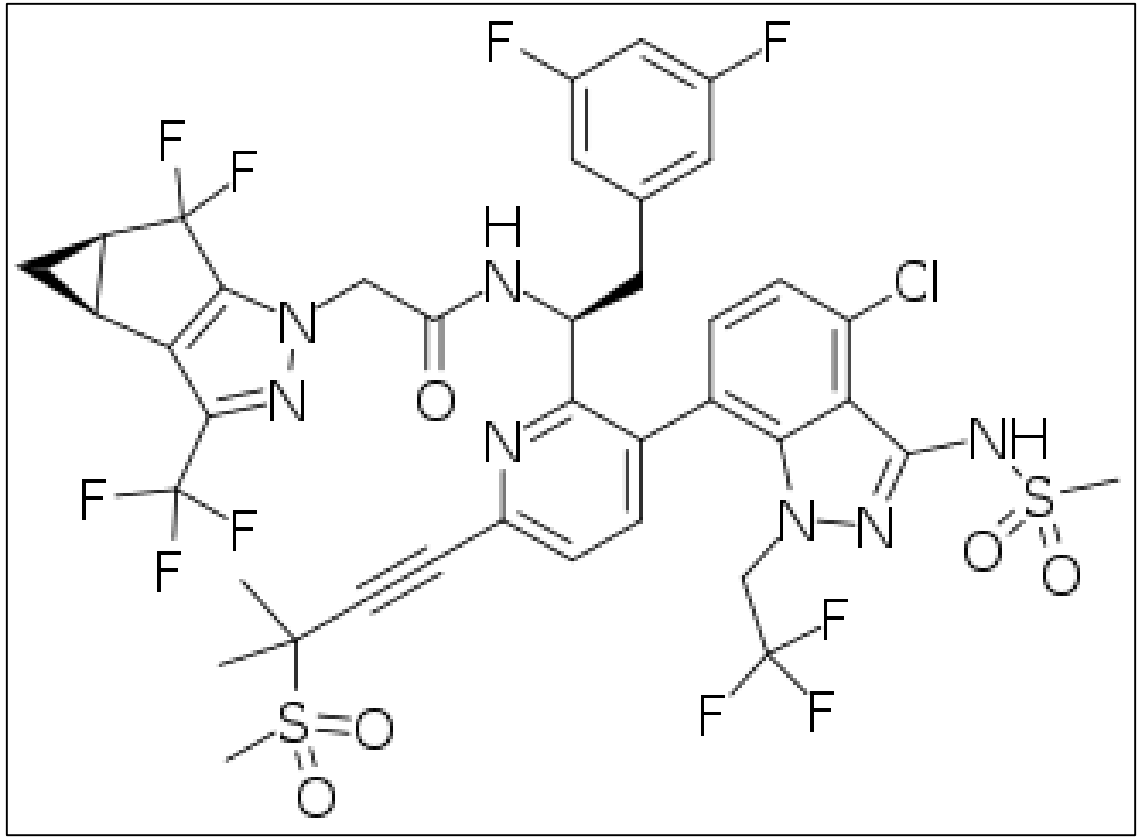


ISR incidence decreased over time and >90% of injection site pain and discomfort, as well as 41–67% of swelling, induration, and nodules resolved within 7 days

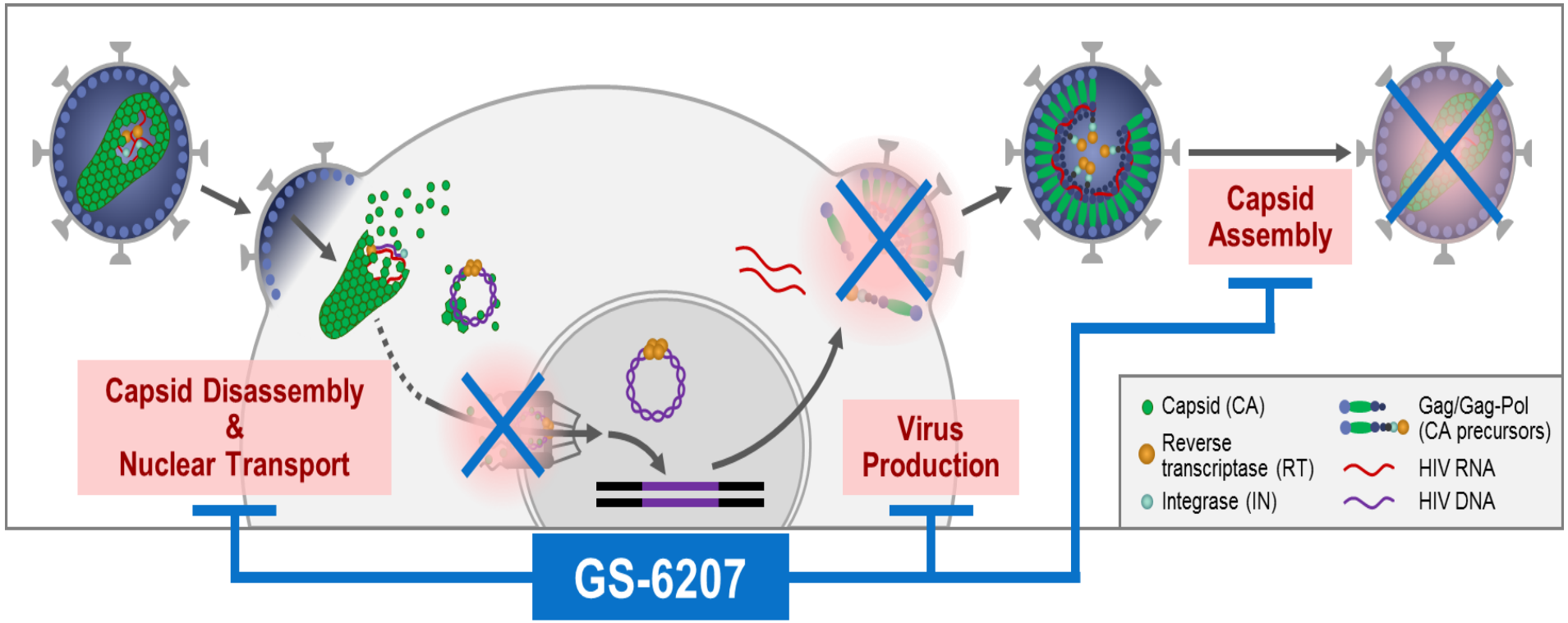
*Incidence is derived relative to the number of participants who received injections at each respective study visit. AE grade is the maximum grade reported by the participant at each visit
†Each ISR event was counted separately. A participant may have had multiple ISR events following a single injection. Top five most common ISRs reported
W, Week

Chamay N, et al. AIDS 2022. Poster EPB182

Lenacapavir (LEN)



Primer inhibidor de cápside del VIH: Mecanismo de acción de Lenacapavir



- GS-6207 inhibits multiple processes essential for viral replication
- GS-6207 modulates the stability and/or transport of capsid complexes

Yant SR, et al. CROI 2019. Seattle, WA. Poster 480
Sager JE, et al. CROI 2019. Seattle, WA. Oral 141

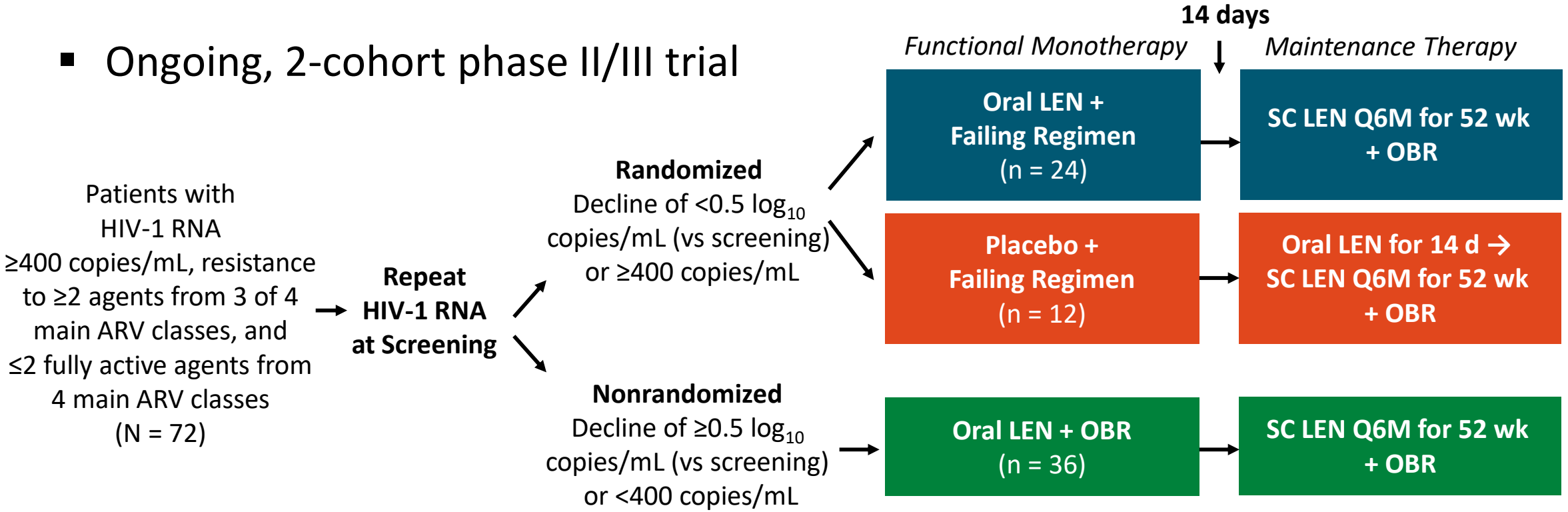
Estudio CAPELLA: Antecedentes

- Lenacapavir: novel, long-acting, HIV-1 capsid inhibitor active in many stages of HIV replication[1,2]
  - Novel MoA may be of benefit in heavily treatment-experienced patients with MDR HIV-1
  - Retains full activity vs NRTI-, NNRTI-, PI-, and INSTI-resistant HIV in vitro[3-5]
  - No observed preexisting capsid mutation resistance[6]
  - Low EC_{50} of 50-100 pM in vitro
  - SC administration with Q6M dosing
- In randomized cohort of ongoing CAPELLA study of LEN in heavily treatment experienced patients:
  - LEN + failing regimen (LEN functional monotherapy) associated with ≥0.5-log decline in HIV-1 RNA in 88% of patients vs 17% with placebo at Day 14[7]
  - LEN + OBR associated with HIV-1 RNA <50 copies/mL in 81% of patients at Wk 26[8]
- Current report presents updated results from CAPELLA through Wk 52[9]

1. Link. Nature. 2020;584:614. 2. Zila. Cell. 2021;184:1032. 3. Margot. Antimicrob Agents Chemother. 2021;65:e02057. 4. VanderVeen. CROI 2021. Abstr 128. 5. Yant. CROI 2019. Abstr 480. 6. Marcelin. J Antimicrob Chemother. 2020;75:1588. 7. Segal-Maurer. CROI 2021. Abstr 127. 8. Molina. IAS 2021. Abstr OALX01LB02. 9. Ogbuagu. CROI 2022. Abstr 491.

CAPELLA: Diseño del estudio

- Ongoing, 2-cohort phase II/III 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 and Q6M thereafter.

- Current analysis: safety and efficacy (FDA Snapshot) of LEN + OBR at Wk 26 and 52

Ogbuagu. CROI 2022. Abstr 491.

Slide credit: clinicaloptions.com

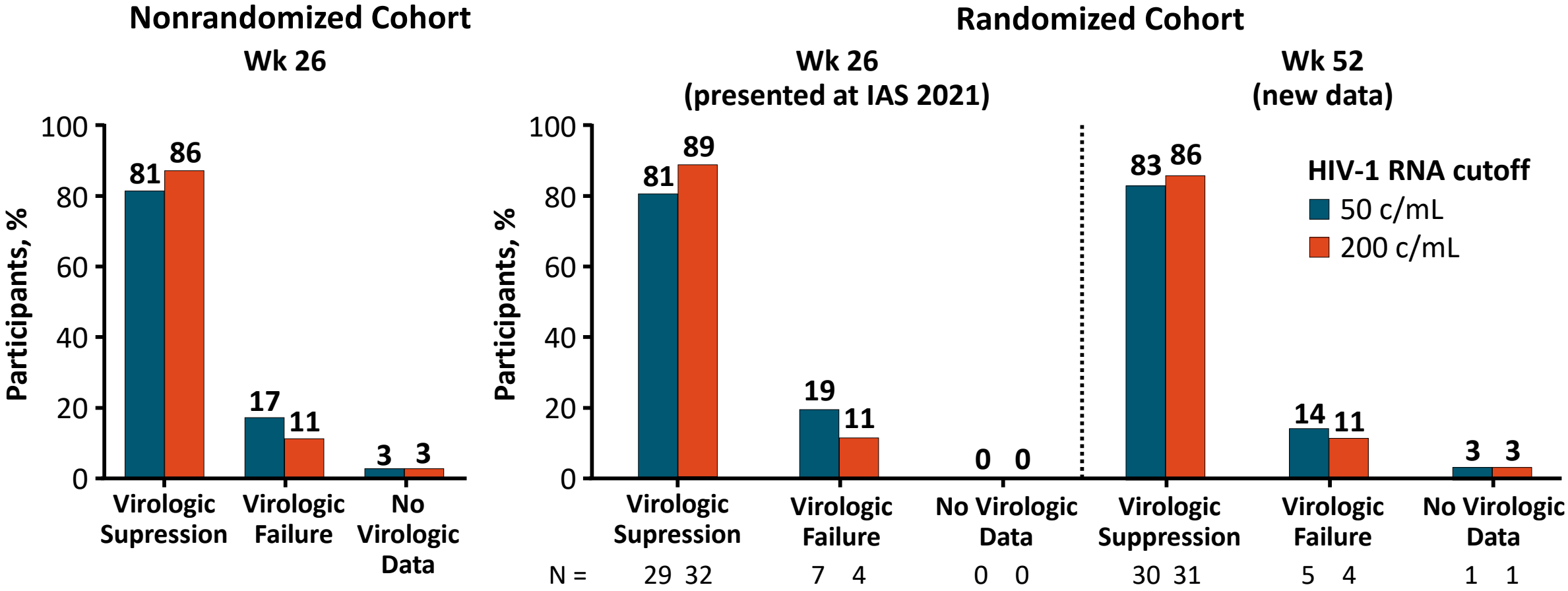
CAPELLA: Características basales de los participantes

Characteristic	Randomized		Nonrandomized	Total (N = 72)
	LEN (n = 24)	Placebo (n = 12)	LEN (n = 36)	
Median age, yr (range)	55 (24-71)	54 (27-59)	49 (23-78)	52 (23-78)
Female at birth, %	29	25	22	25
Black, %	42	55	31	38
Hispanic/Latinx, %	25	36	14	21
Median HIV-1 RNA, log_{10} copies/ml (range) ▪ >75,000 copies/mL, %	4.2 (2.3-5.4) 17	4.9 (4.3-5.3) 50	4.5 (1.3-5.7) 28	4.5 (1.3-5.7) 28
Median CD4+ cell count, cells/mm^3 (range) ▪ ≤200 cells/mm^3, %	172 (16-827) 67	85 (6-237) 92	195 (3-1296) 53	150 (3-1296) 64
Median time since HIV diagnoses, yr (range)	27 (13-39)	26 (14-35)	23 (9-44)	24 (9-44)
Median prior ARVs, n (range)	9 (2-24)	9 (3-22)	13 (3-25)	11 (2-25)
Median ARVs in failing regimen, n (range)	3 (1-7)	3 (2-6)	4 (2-7)	3 (1-7)
Resistance to ≥2 drugs in class, % ▪ NRTI ▪ NNRT ▪ PI ▪ INSTI	 96 92 83 83	 100 100 67 58	 100 100 83 64	 99 97 81 69

Ogbuagu. CROI 2022. Abstr 491.

Slide credit: clinicaloptions.com

CAPELLA: Eficacia de LEN a la semanas 26 y 52



- CD4+ count increased by 83 cells/mm³ at Wk 52 in randomized cohort

Ogbuagu. CROI 2022. Abstr 491. Reproduced with permission.

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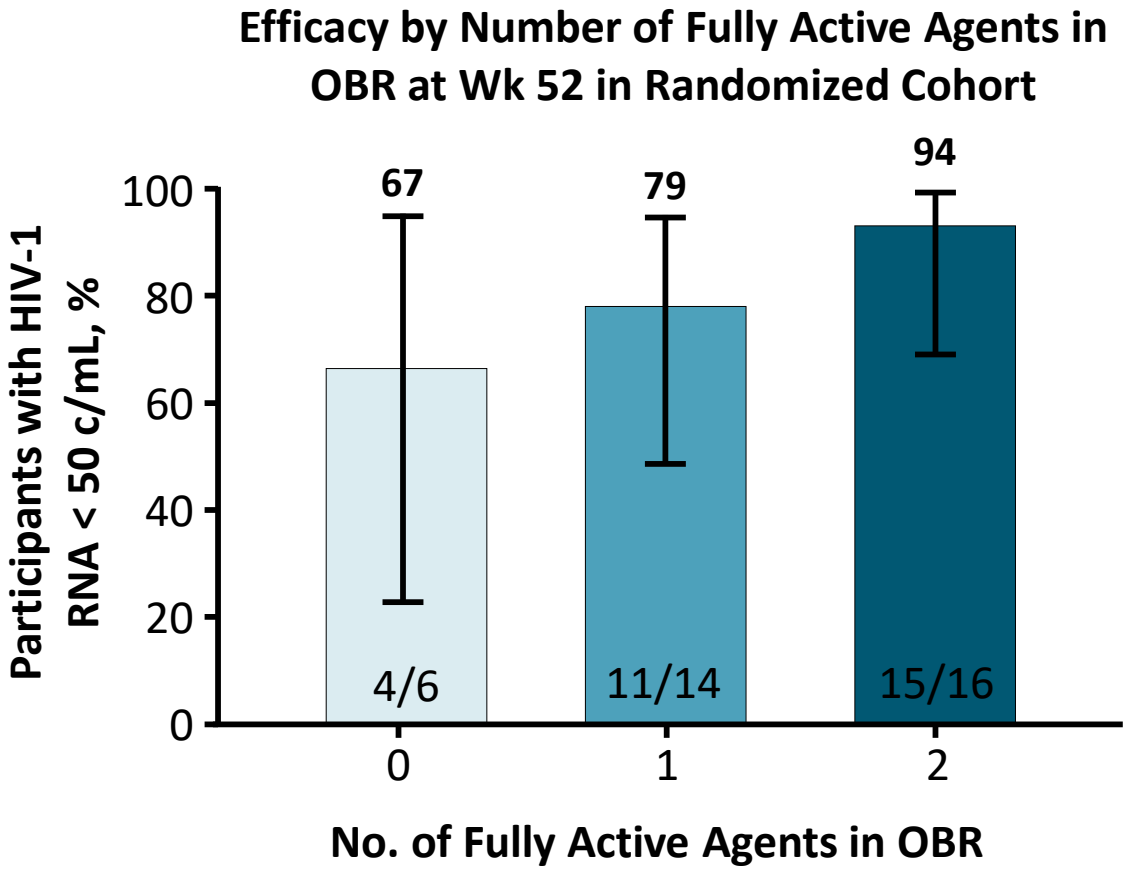
CAPELLA: Eficacia de LEN por ARV activos y emergencia de resistencia



Emergent LEN Resistance, n (%)	Randomized Cohort (n=36)	Nonrandomized Cohort (n =36)
Participants meeting criteria for resistance testing	11 (31)	10 (28)
Emergent LEN resistance	4 (11)	4 (11)
▪ M661	4	2
▪ Q67H/K/N	1	2
▪ K70H/N/R/S	1	3
▪ N74D/H/S	3	0
▪ A105S/T	3	1
▪ T107A/C/N	1	3

- All 8 persons with emergent LEN resistance were high risk for resistance (0 active drugs in OBR, n = 4; inadequate adherence to OBR, n = 4)

Ogbuagu. CROI 2022. Abstr 491. Reproduced with permission.

Slide credit: clinicaloptions.com

CAPELLA: Seguridad a semana 42

- No serious adverse events were attributable to study drug
- Most common adverse events diarrhea, nausea, COVID-19 infection
- Injection-site reactions mostly grade 1/2
  - Discontinuation of study at Wk 52 due to ISR, n = 1
- No other clinically relevant adverse events

Grade 3/4 Adverse Event, n (%)	Trial Population (N = 72)
Low estimated glomerular filtration rate*	14 (10)
Elevated creatinine*	13 (9)
Glycosuria	6 (4)
Hyperglycemia*† (nonfasting or fasting)	6 (3)
Injection-site reaction‡	2 (0.3)

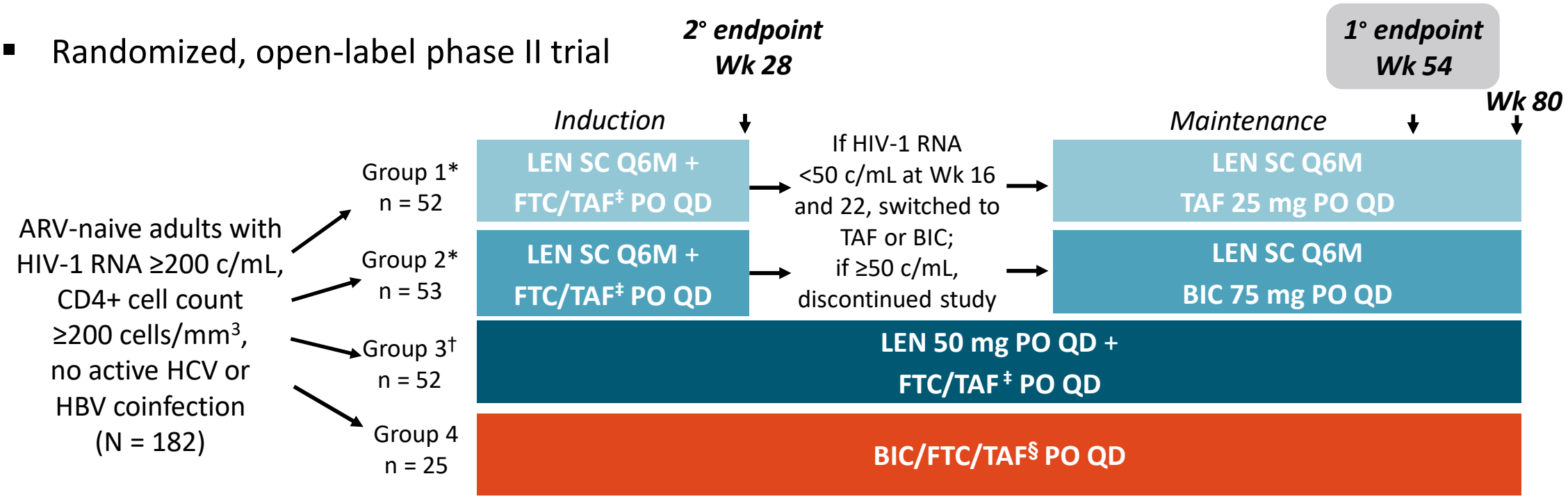
*Transient or unconfirmed. †Related or underlying diabetes.
‡Swelling and erythema, n = 1; pain, n = 1.

Ogbuagu. CROI 2022. Abstr 491.

Slide credit: clinicaloptions.com

CALIBRATE: Diseño del estudio

- 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.

- 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. CROI 2022. Abstr 138.

Slide credit: clinicaloptions.com

CALIBRATE Análisis primario: Características basales

Characteristic	LEN SC + FTC/TAF → TAF (n = 52)	LEN SC + FTC/TAF → BIC (n = 53)	LEN PO + FTC/TAF (n = 52)	BIC/FTC/TAF (n = 25)
Median age, yr (range)	31 (19-61)	28 (19-56)	28 (19-72)	29 (21-61)
Female sex at birth, %	10	2	12	0
Black, %	46	45	60	64
Hispanic/Latinx, %	48	40	46	48
HIV-1 RNA				
▪ Median, log_{10} c/mL (Q1-Q3)	4.27 (3.77-4.63)	4.32 (3.96-4.74)	4.53 (3.82-4.83)	4.37 (4.09-4.77)
▪ >100,000 c/mL, %	10	17	17	16
CD4+ cell count				
▪ Median, cells/mm^3 (Q1-Q3)	404 (320-599)	450 (332-599)	409 (301-600)	482 (393-527)
▪ <200 cells/mm^3, %	0	2	6	0

Gupta. CROI 2022. Abstr 138.

Slide credit: clinicaloptions.com

CALIBRATE Análisis primario: Respuesta virológica a 54s

Virologic Outcome, %	LEN SC + FTC/TAF → TAF (n = 52)	LEN SC + FTC/TAF → BIC (n = 53)	LEN PO + FTC/TAF (n = 52)	BIC/FTC/TAF (n = 25)
FDA snapshot analysis (ITT)				
▪ HIV-1 RNA <50 c/mL	90	85	85	92
▪ HIV-1 RNA ≥50 c/mL	4*	4*†	6‡	0
▪ No data	6	11	10	8
FDA snapshot analysis among patients virologically suppressed at Wk 28				
▪ HIV-1 RNA <50 c/mL	94	92	90	92
▪ HIV-1 RNA ≥50 c/mL	4	0	6	0
▪ No data	2	8	4	8

*3 participants (2 in Group 1 and 1 in Group 2) discontinued due to not having HIV-1 RNA <50 c/mL prior to Wk 28. †1 participant discontinued on Day 2.
‡2 of 3 participants with HIV-1 RNA ≥50 c/mL at Wk 54 were suppressed at a subsequent visit.

- In pooled LEN SC cohort (Groups 1 and 2):
  - 88% achieved and maintained virologic suppression at Wk 54
  - 93% of those virologically suppressed at Wk 28 maintained virologic suppression at Wk 54

Gupta. CROI 2022. Abstr 138.

Slide credit: clinicaloptions.com

CALIBRATE : Resistencia y cambios en recuento LT CD4+

Outcome	LEN SC + FTC/TAF → TAF (n = 52)	LEN SC + FTC/TAF → BIC (n = 53)	LEN PO + FTC/TAF (n = 52)	BIC/FTC/TAF (n = 25)
Mean CD4+ cell count increase from baseline to Wk 54, cells/mm^3	206	212	220	193
Emergent LEN resistance, n	1	0	1[†]	0
▪ Resistance details	Wk 10; Q67H + K70R in CA (20-fold change in LEN susceptibility; preceded by M184M/I in RT*)		Wk 54; Q67H in CA (7-fold change in LEN susceptibility)	

*Pattern suggests incomplete adherence to FTC/TAF. [†]Patient nonadherent to FTC/TAF based on pill count, drug levels.

- Both patients with LEN resistance later resuppressed on regimen of INSTI + 2 NRTI

Gupta. CROI 2022. Abstr 138.

Slide credit: clinicaloptions.com

CALIBRATE Análisis primario: Seguridad a las 54s

- No SAEs or Grade 4 AEs related to study drug; no clinically relevant grade 3/4 lab abnormalities
- Most common AEs in combined LEN arms: headache and nausea (13% each)
- GI AEs with LEN SC vs LEN PO
  - Nausea: 14% vs 12%
  - Diarrhea: 7% vs 10%
  - Vomiting: 4% vs 8%

- Majority of ISRs grade 1 or 2
  - 1 grade 3 (nodule), no grade 4
  - 3 patients discontinued due to ISRs (2 due to grade 1 induration, 1 due to grade 1 erythema and swelling)

ISR	After First SC Dose (Wk 1), %	After Second SC Dose (Wk 26), %	Median Duration, Days
Swelling	14	12	11
Erythema	14	18	5
Pain	15	9	4
Nodule	11	8	195
Induration	9	6	202

Gupta. CROI 2022. Abstr 138.

Slide credit: clinicaloptions.com

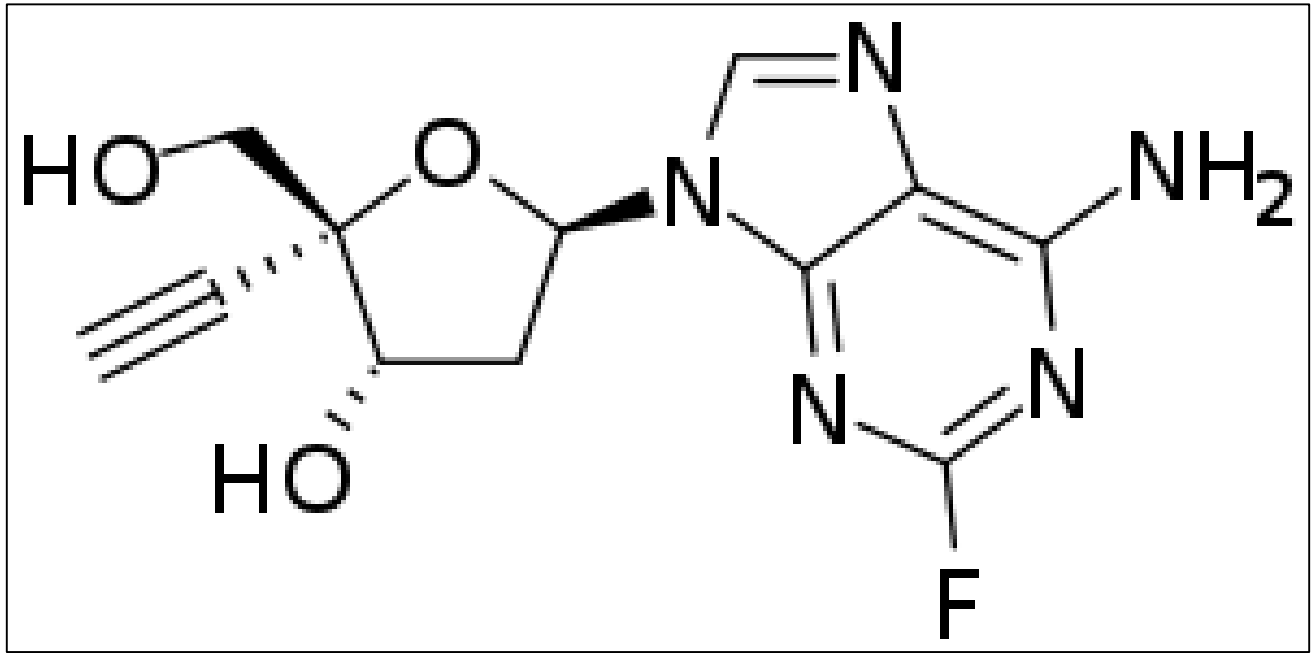
CALIBRATE Análisis primario: Conclusiones

- After 2-wk oral lead-in followed by induction with 6-mo LEN SC + daily FTC/TAF PO, maintenance treatment with 6-mo SC + daily TAF or BIC PO associated with high rates of virologic suppression through Wk 54 in treatment-naive patients
  - LEN SC + FTC/TAF PO → LEN SC + TAF PO: 90%
  - LEN SC + FTC/TAF PO → LEN SC + BIC PO: 85%
  - LEN PO + FTC/TAF PO: 85%
  - BIC/FTC/TAF PO: 92%
- LEN SC and PO well tolerated with infrequent discontinuations

Gupta. CROI 2022. Abstr 138.

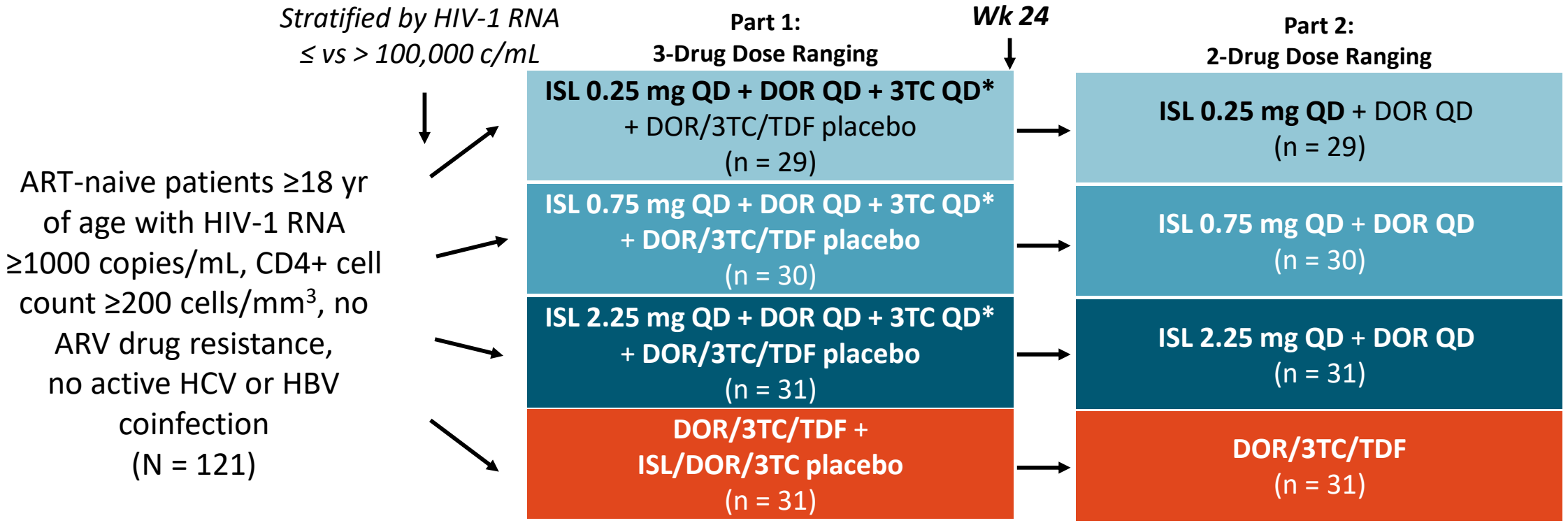
Slide credit: clinicaloptions.com

Islatravir



P011: Islatravir + Doravirine vs DOR/3TC/TDF en pacientes adultos naïve

- **Islatravir: investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI)**
- International, randomized, double-blind phase IIb trial



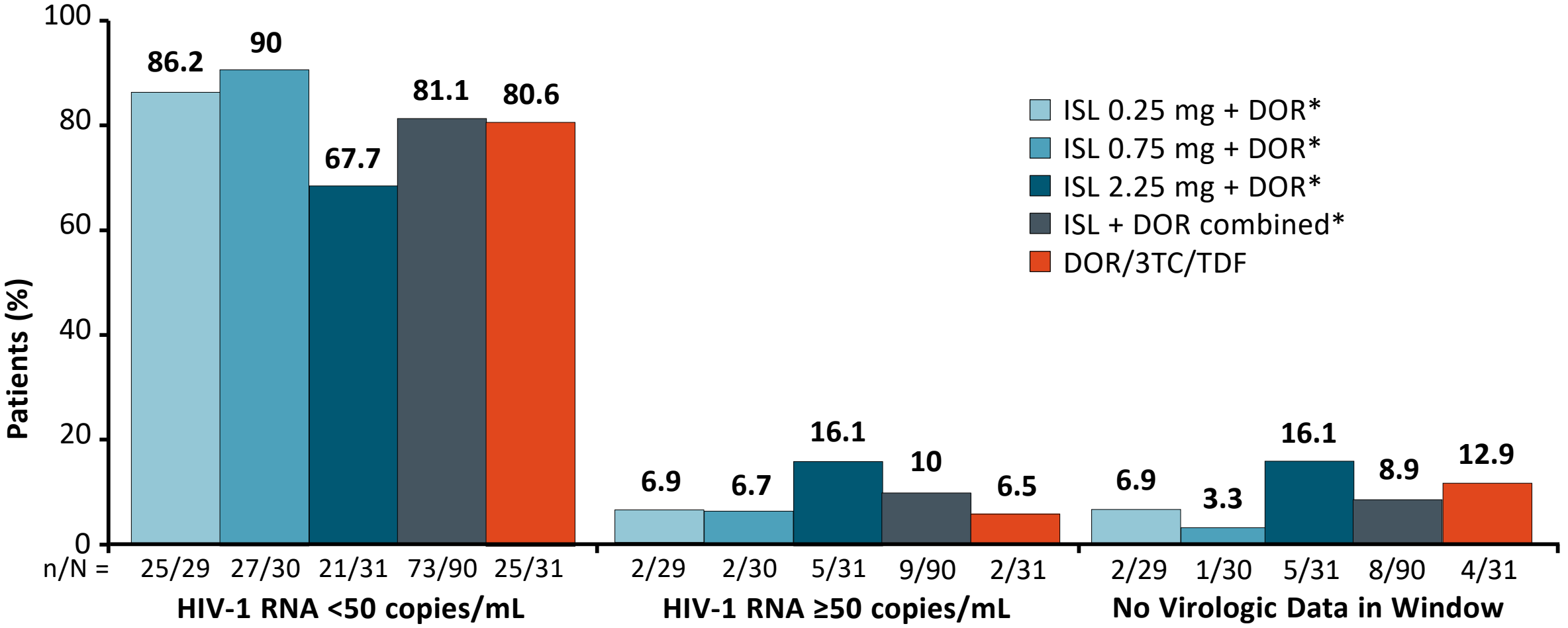
*Patients discontinued 3TC after 24 wk if HIV-1 RNA <50 copies/mL.

- Primary efficacy endpoints: HIV-1 RNA < 50 c/mL at Wk 24 and 48 (FDA Snapshot)

DeJesus. AIDS 2020. Abstr OAB0305.

Slide credit: clinicaloptions.com

P011: Resultados virológicos con Islatravir + Doravirine a semana 96 (FDA Snapshot)



*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during the Wk 24-96 period of the study.

Molina. HIV Glasgow 2020. Abstr O415.

Slide credit: clinicaloptions.com

P011: Resumen acumulado de EA con Islatravir + Doravirine a semana 96

AE, n (%)	ISL 0.25 mg + DOR QD (n = 29)	ISL 0.75 mg + DOR QD (n = 30)	ISL 2.25 mg + DOR QD (n = 31)	DOR/3TC/TDF QD (n = 31)
≥ 1 AE	25 (86.2)	27 (90.0)	22 (71.0)	27 (87.1)
Drug-related AE	0	3 (10.0)	4 (12.9)	7 (22.6)
Serious AE	1 (3.4)	3 (10.0)	1 (3.2)	3 (9.7)
Drug-related serious AE	0	0	0	1 (3.2)
Discontinued due to AE	0	0	2 (6.5)	1 (3.2)
Discontinued due to drug-related AE	0	0	2 (6.5)	1 (3.2)
Deaths	0	0	0	0

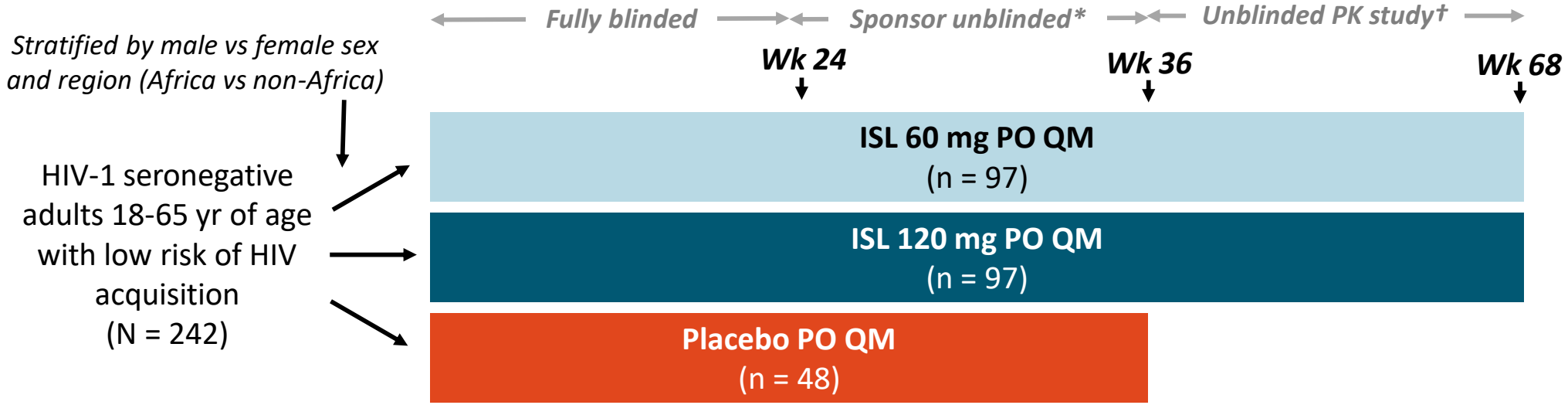
- No new drug-related AEs or discontinuations due to AEs in any ISL+DOR group Wk 48-96
- Most common AE in ISL+DOR groups: headache (11%); in DOR/3TC/TDF: diarrhea (19%)
  - Most events mild, transient, and not related to study treatment; incidence of both AEs similar at Wk 48 and 96

Cunningham. IAS 2021. Abstr OAB0304.

Slide credit: clinicaloptions.com

P016: Islatravir oral una vez al mes para PrEP

- Multicenter, randomized, double-blind, placebo-controlled phase IIa trial:
  67% female, 53% White, 42% Black, median age 31 yr



*Sponsor unblinded at Wk 24 to allow interim safety evaluation. Participants and investigators remain blinded to Wk 36.
†After Wk 36, participants in PBMC/PK Bridging Subset randomized to receive ISL have an additional 32-wk unblinded PK follow-up.

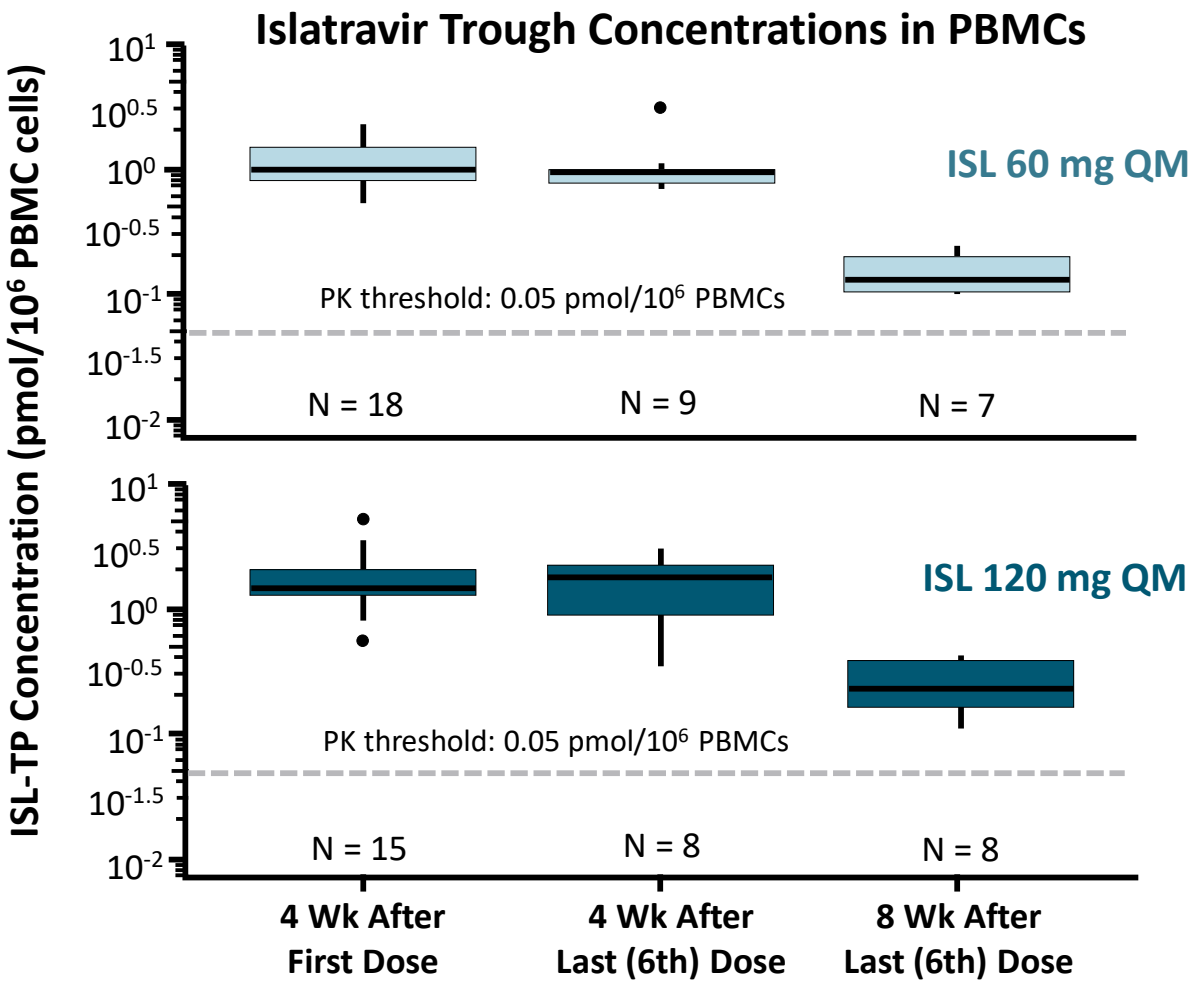
- Primary endpoints: safety/tolerability, pharmacokinetics of ISL-TP (active form of ISL)

Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

P016: Farmacocinética de Wk 24 Islatravir oral a semana 24

- Trough concentrations of ISL-TP (active form of ISL) remained above prespecified PK threshold for HIV prevention for at least 8 wk following last dose



Hillier. IAS 2021. Abstr OALC01LB03.

Slide credit: clinicaloptions.com

Anticuerpos neutralizantes de amplio espectro (HIV Broadly Neutralizing Antibodies –bNAbs-)

Features

- Human monoclonal antibodies able to neutralize wide range of HIV-1 isolates
- Target HIV-1 envelope
- Enhance various effector functions
- Can be genetically engineered to combine multiple specificities or extend half-life

Potential Advantages

- Infrequent dosing
- No cross-resistance with ARVs
- Established paradigms for therapeutic use in other disease areas
- Potential for overcoming adherence challenges and for less stigma
- Potential to enhance HIV-specific immunity

Potential Clinical Uses

- HIV treatment intensification by concomitant use of ART + bNAbs
- Maintenance therapy in virologically suppressed individuals
- HIV immunotherapy: possible treatment alternative (eg, MDR or ART intolerance)
- Prevention: pre- and postexposure prophylaxis; PMTCT (for late presenters)

Slide credit: clinicaloptions.com

¡Muchas gracias!