Valencia, 21 octubre de 2020

Perspectivas terapéuticas para el paciente con VIH

M JOSÉ GALINDO PUERTO

UNIDAD DE ENFERMEDADES INFECCIOSAS

HOSPITAL CLÍNICO UNIVERSITARIO DE VALENCIA

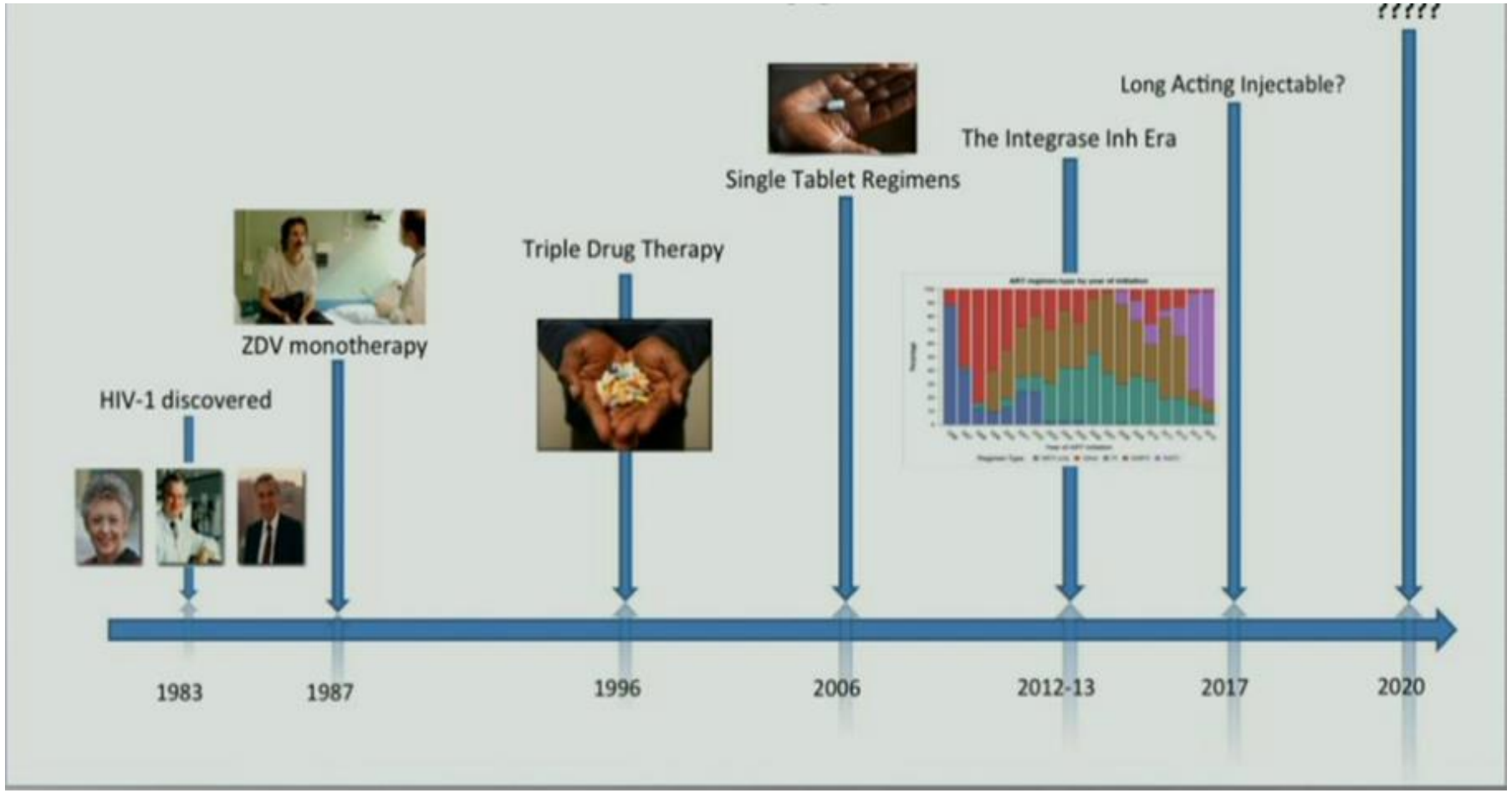
concepto

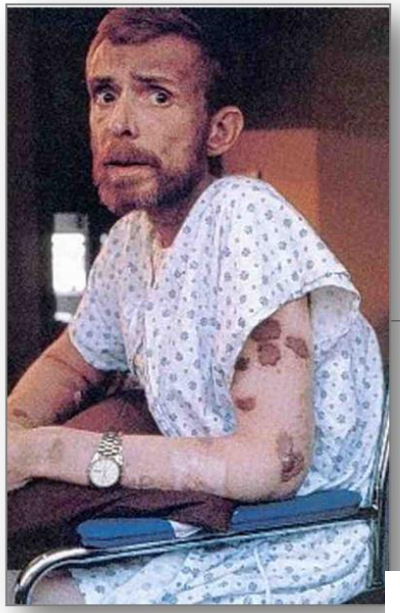
1. Arte que enseña el modo de representar en una superficie los objetos, en la forma y disposición con que aparecen a la vista
2. Obra o representación ejecutada con este arte
3. Conjunto de objetos que desde un punto determinado se presentan a la vista del espectador, especialmente cuando están lejanos
4. Apariencia o representación engañosa y falaz de las cosas
5. Punto de vista desde el cual se considera o se analiza un asunto
6. Visión, considerada en principio más ajustada a la realidad, que viene favorecida por la observación ya distante, espacial o temporalmente de cualquier hecho o fenómeno
7. Contingencia que puede preverse en el curso de algún negocio

¿perspectivas terapéuticas?

- De qué punto partimos
- Qué hay disponible
- Qué nos gustaría tener

Evolución del tratamiento antirretroviral





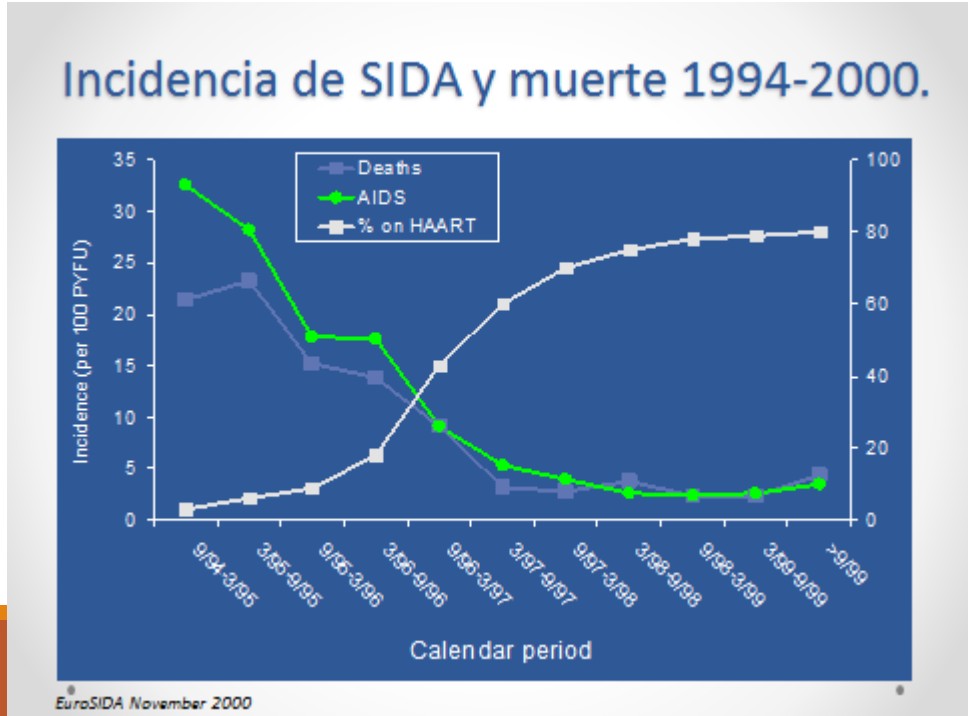
¿Perspectiva?

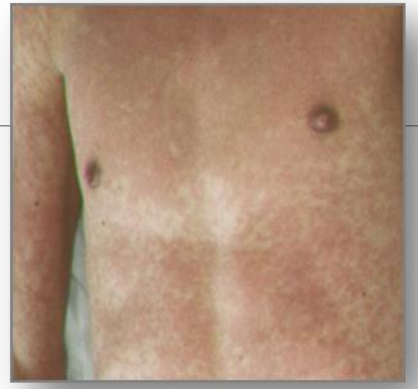
Elevada mortalidad

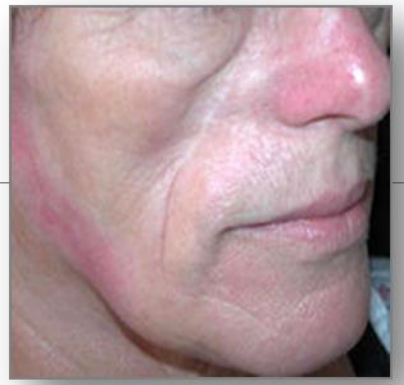
"El SIDA está matando a más personas que todas las guerras y catástrofes mundiales habidas hasta ahora" (Nelson Mandela).

¿Expectativa?

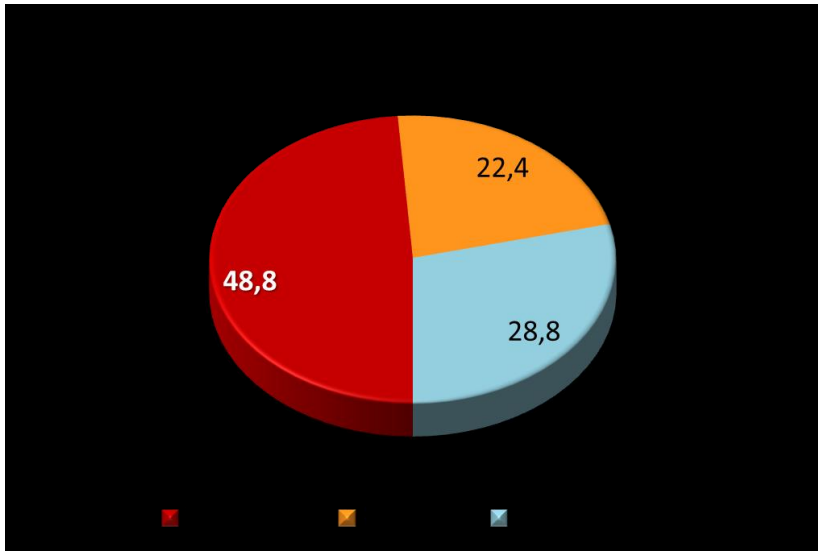
Un tratamiento eficaz







¿Perspectiva?



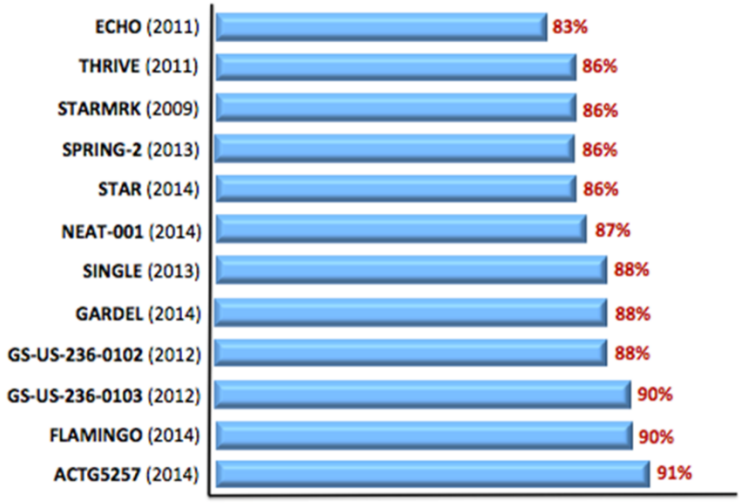
¿Expectativa?

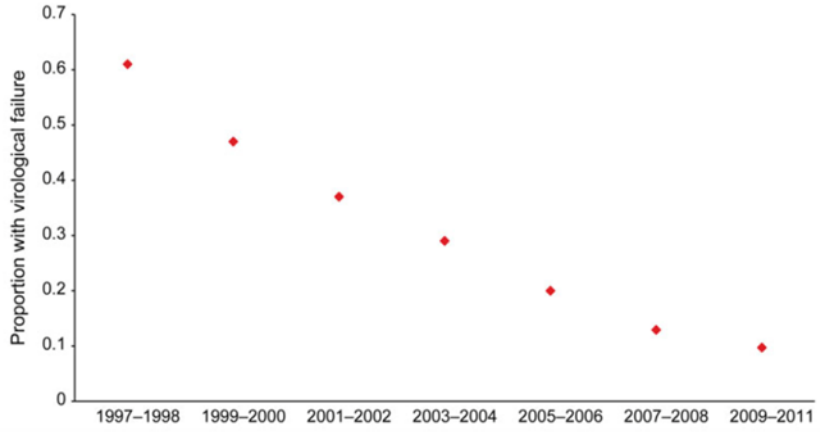
Vivir mejor

Un tratamiento eficaz pero con menos efectos secundarios y más cómodo

Chen RY, et al. *Clin Infect Dis* 2003; 37:714-22.

Eficacia virológica a 48 semanas en los últimos ensayos clínicos aleatorizados con regímenes de TAR de 1ª línea



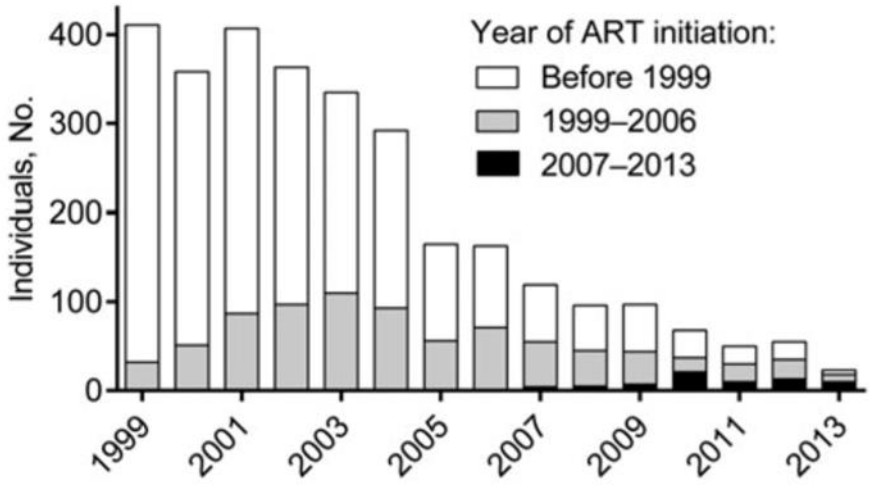


Fracaso virológico

¿Expectativa?

Más comodidad
Menos efectos adversos
Curación

¿Perspectiva?



Resistencia

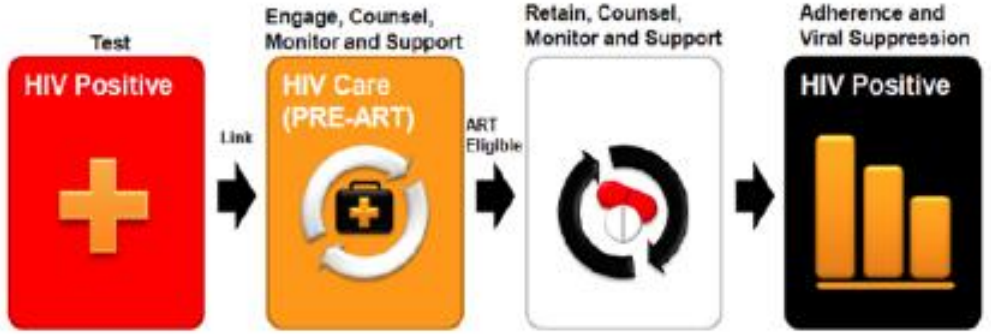
Delaugerre C, et al. *Clin Infect Dis* 2015; 60:463-472.

Scherrer AU. *Clin Infect Dis* 2016, 62, 1310-1317.

‘Beyond Viral Suppression’:
Es necesario un “Cuarto 90”

*Adapted from: UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. 2014. Available at http://unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed on 25 April 2016

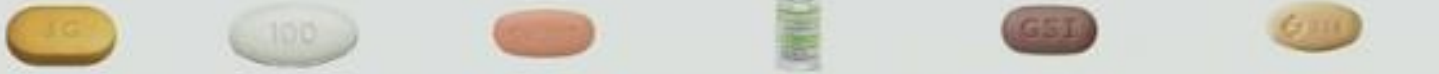
Continuidad asistencial de la infección por el VIH



El Sadr W, et al. *19th CROI*, Seattle, WA; March 5-8, 2012. Abstract 18.
McNairy ML and El Sadr W. *AIDS* 2012; 26:1735-1738.

HIV Glasgow, 28-31 October 2018, Glasgow, UK

New molecules and combinations, 2018 FDA approval (brand names)



SYMTUZA	DOLU-TDF-3TC (DOLU-TAF-FTC)	JULUKA	TROGARZO	BIKTARVY	DELSTRIGO
Darunavir / COBI / TAF / FTC		Dolutegravir+ rilpivirine	Ibalizumab	Bictegravir/TAF/FTC	Doravirine + tenofovir DF + lamivudine
The first PI-based 3-in-1 combination	A 3-in-1 attractive combination, WHO recommanded, in generic formulation (FDA tentative approval)	The first 2-in-1 combination approved for maintenance	The first mAb against HIV-1 to receive FDA approval and is currently indicated for use as salvage therapy	A new low-milligram integrase inhibitor-based FDC	New once daily NNRTI with TDF and 3TC (generics)

Orkin C et al, J Int AIDS Soc 2018 21(S8):e25187 O212

Stellbrink et al, J Int AIDS Soc 2018 21(S8):e25187 O211

2018 has been an important year for HIV research with 5 drugs or combo, **including the first in class monoclonal Ab (ibalizumab)** – One drug has been approved only for use in China (albuvirtide, injectable fusion inhibitor)

Alexandra Calmy

HIV/AIDS Unit, Geneva University Hospitals, Geneva, Switzerland

Late Breakers / Hot Topics

New ARV drugs and strategies

HIV Drug Therapy GLASGOW 2018

TABLA DE ANTIRRETROVIRALES

grupo de trabajo sobre tratamientos del VIH

Bictegravir/ emtricitabina/tenofovir alafenamida	*Biktarvy*		Comprimido que contiene 50mg de bictegravir, 200mg de emtricitabina, 25mg de tenofovir alafenamida	Un comprimido al día
Darunavir/cobicistat/ emtricitabina/tenofovir alafenamida	*Symtuza*		Comprimido que contiene 800mg de darunavir, 150mg de cobicistat, 200mg de emtricitabina, 10mg de tenofovir alafenamida	Un comprimido al día
Dolutegravir/abacavir/ lamivudina	*Triumeq*		Comprimido que contiene 50mg de dolutegravir, 600mg de abacavir, 300mg de lamivudina	Un comprimido al día
Dolutegravir/rilpivirina	*Juluca*		Comprimido que contiene 50mg de dolutegravir y 25mg de rilpivirina	Un comprimido al día
Doravirina/lamivudina/ tenofovir disoproxil fumarato	*Delstrigo*		Comprimido que contiene 100mg de doravirina, 300mg de lamivudina, 245mg de tenofovir disoproxil fumarato	Un comprimido al día
Efavirenz/emtricitabina/ tenofovir disoproxil fumarato Medicamento genérico, su aspecto puede variar			Comprimido que contiene 600mg de efavirenz, 200mg de emtricitabina, 245mg de tenofovir disoproxil fumarato	Un comprimido al día
Elvitegravir/cobicistat/ emtricitabina/tenofovir alafenamida	*Genvoya*		Comprimido que contiene 150mg de elvitegravir, 150mg de cobicistat, 200mg de emtricitabina, 10mg de tenofovir alafenamida	Un comprimido al día
Elvitegravir/cobicistat/ emtricitabina/tenofovir disoproxil fumarato	*Stribild*		Comprimido que contiene 150mg de elvitegravir 150mg de cobicistat 200mg de emtricitabina 245mg de tenofovir disoproxil fumarato	Un comprimido al día
Rilpivirina/ emtricitabina/tenofovir alafenamida	*Odefsey*		Comprimido que contiene 25mg de rilpivirina, 200mg de emtricitabina, 25mg de tenofovir alafenamida	Un comprimido al día
Rilpivirina/ emtricitabina/tenofovir disoproxil fumarato	*Eviplera*		Comprimido que contiene 25mg de rilpivirina, 200mg de emtricitabina, 245mg de tenofovir disoproxil fumarato	Un comprimido al día


Prevención Del VIH
Circumcisión masculina [1-3]
Intervenciones conductuales
Treatment of STIs[4]
CLINIC
HIV consejo y prueba[5]
Condón femenino
Condón masculino
Microbicidas para mujeres[13]
profilaxis preexposición [9-12]
HSH, parejas, heterosexuales, UDIs
Tratamiento como prevención[6,7]
Profilaxis postexposición[8]
PEP
Note: PMTCT, screening transfusions, harm reduction, universal precautions, etc have not been included. This is focused on reducing sexual transmission.
1. Auvert et al. PLoS Med 2005;2:e298. 2. Gray et al. Lancet 2007;369:657-66. 3. Bailey et al. Lancet 2007;369:643-56. 4. Grosskurth et al. Lancet 2000;355:1981-7. 5. Sweat et al. Lancet. 2000;356:113-21. 6. Donnell et al. Lancet 2010;375:2092-8. 7. Cohen et al. NEJM 2011;365:493-505. 8. Schechter et al. JAIDS 2004;35:519-25. 9. Grant et al. NEJM 2010;363:2587-99 (MSM). 10. Mujugira et al. PLoS One 2011;6:e25828 (couples). 11. Paxton et al. Curr Opin HIV AIDS 2012;7:557-62 (heterosexuals). 12. Choopanya et al. Lancet. 2013;381:2083-90 (IDU). 13. Abdool Karim et al. Science 2010;329:1168-74

Pero estábamos hablando de expectativas, y hasta ahora lo hemos hecho de realidades y hemos revisado la situación actual

Expectativas

Paciente:

- ¿para cuándo la cura?
- ¿hay algo nuevo doctor?

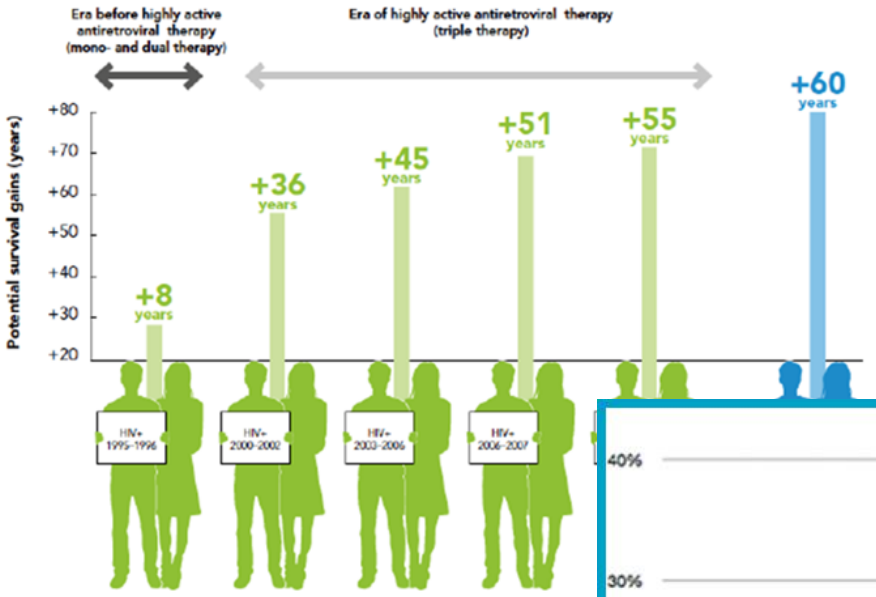
Médico:

- mejorar supervivencia con calidad de vida
- Mejorar tratamiento
- curación


¿QUÉ IMPORTAN LOS AÑOS? LO QUE REALMENTE IMPORTA ES COMPROBAR QUE AL FIN DE CUENTAS LA MEJOR EDAD DE LA VIDA ES ESTAR VIVO
Reflexiones para TI y para Mí

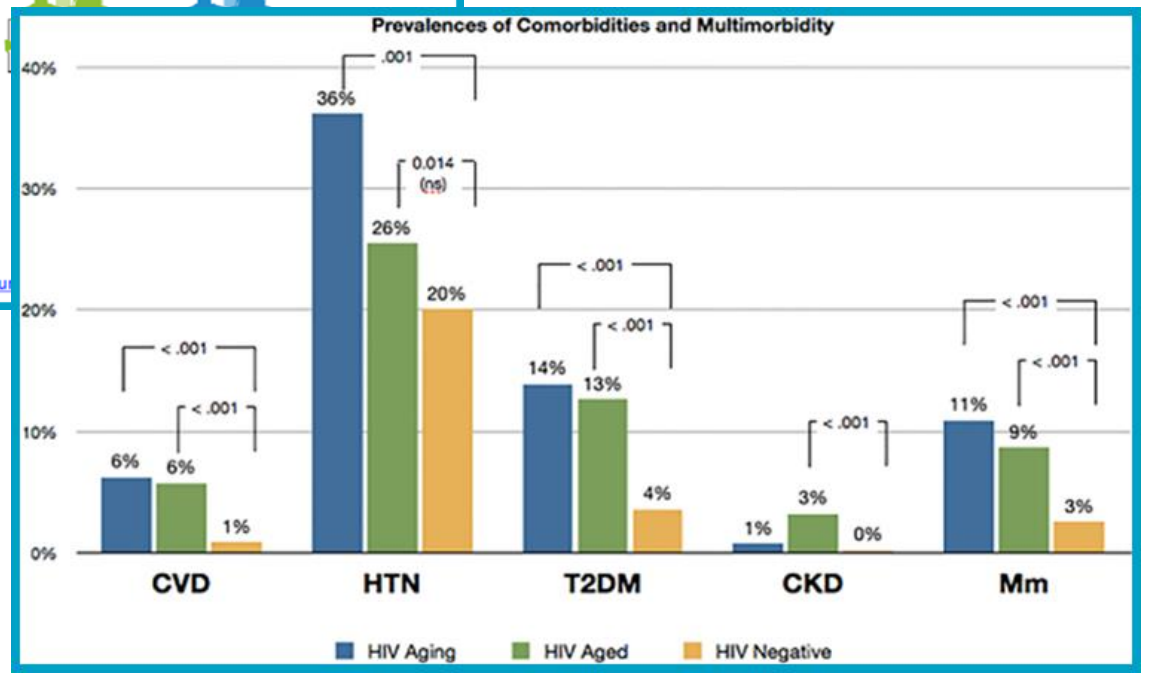

No se trata de añadir años a la vida....
sino vida a los años

Impacto del TAR sobre las expectativas de vida
(Persona de 20 años en un país con altos recursos económicos)



Source: Adapted from Lohse et al, 2007; Hoog et al, 2008, May et al, 2011 & Hogg et al, 2013.

http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/u

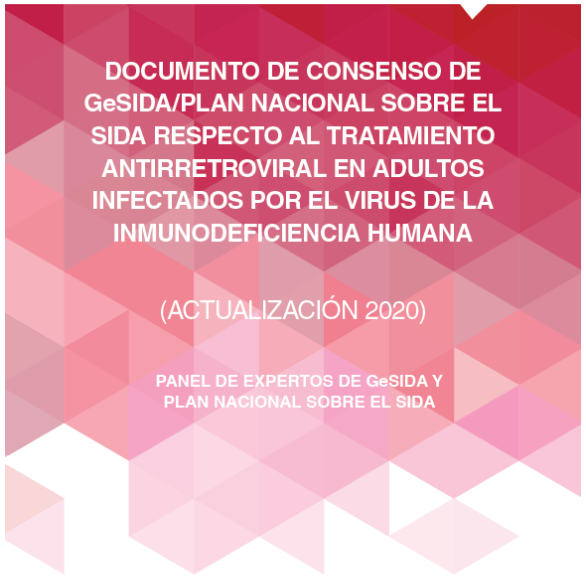


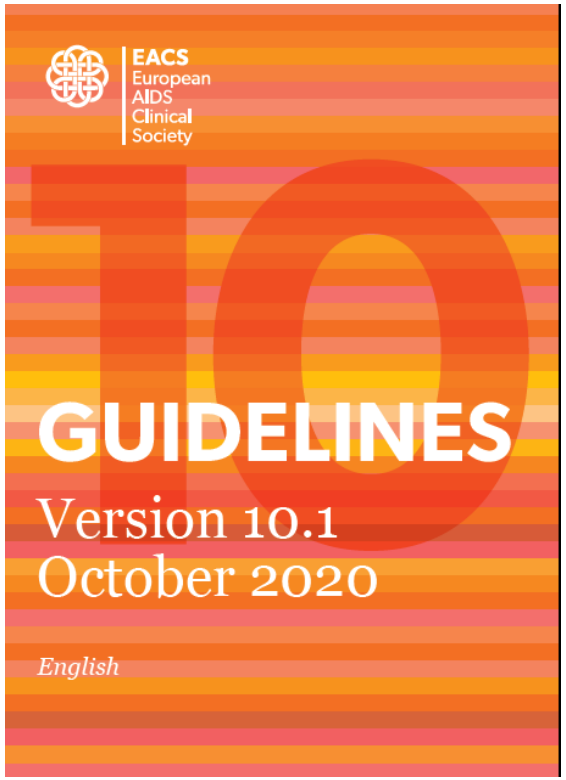
[redacted]

¿perspectivas terapéuticas?

- De qué punto partimos
- Qué hay disponible
- Qué nos gustaría tener

Las guías actúan como elementos de referencia





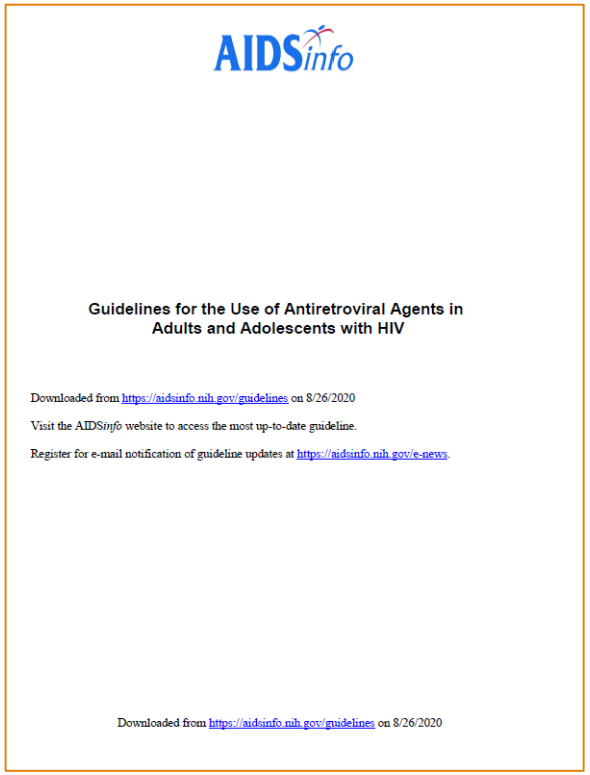


Tabla 2. Recomendaciones sobre TAR de inicio en pacientes con infección por el VIH-1

Recomendaciones
Se recomienda la administración de TAR a todos los pacientes con infección por VIH-1[1] **(A-I)**
El TAR debe iniciarse tan pronto como sea posible tras el diagnóstico[2] **(A-II)**

Tabla 3. Combinaciones de TAR de inicio recomendadas†

3er Fármaco	Pauta†	Comentarios‡
Preferentes. *Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia no inferior a otras pautas también consideradas actualmente como preferentes o superior frente a otras pautas y presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas*		
INI	BIC/FTC/TAF	
	DTG/ABC/3TC	-ABC está contraindicado en pacientes con HLA-B*5701 positivo -DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces. -No utilizar en pacientes con hepatitis B crónica
	DTG+FTC/TAF**	- DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces
	RAL+FTC/TAF*	-RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas
	DTG/3TC	- No recomendado en pacientes con cifra basal de CD4+ menor de 200/µL - DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces - No utilizar en pacientes con hepatitis crónica por VHB
Alternativas. *Pautas eficaces, pero que no se consideran preferentes bien porque su eficacia ha resultado inferior a las pautas preferentes en ensayos clínicos o no se han comparado con pautas preferentes, o porque tienen desventajas potenciales o restricciones en su indicación. Pueden ser, sin embargo, de elección en subgrupos de pacientes o en casos especiales*		
INI	EVG/c/FTC/TAF	-Es imprescindible evaluar posibles interacciones.
IP potenciado	DRV/c/FTC/TAF o DRV/r+FTC/TAF**	-Es imprescindible evaluar posibles interacciones.
ITINN	DOR+FTC/TAF*, ***	-Existe la combinación de DOR/3TC/TDF en comprimido único, que puede utilizarse siempre que se excluya la presencia de alteración renal o de osteopenia/osteoporosis, y no existan factores de riesgo para desarrollarlas.
	RPV/FTC/TAF*	-No indicado en pacientes con CVP >100.000 copias/mL. -Realizar previamente un estudio genotípico que descarte mutaciones de resistencia a ITINN. -Contraindicado si se utilizan inhibidores de la bomba de protones. -Se debe tomar siempre con una comida.

DOCUMENTO DE CONSENSO DE GeSIDA/PLAN NACIONAL SOBRE EL

Box 2. Recommended Initial Antiretroviral Therapy (ART) Regimens

Recommended for Most People With HIV[a]

- Bictegravir/tenofovir alafenamide/emtricitabine (evidence rating: AIa)
- Dolutegravir plus (all evidence ratings: AIa)
  - Tenofovir alafenamide/emtricitabine
  - Tenofovir disoproxil fumarate/emtricitabine
  - Tenofovir disoproxil fumarate/lamivudine
- Dolutegravir/lamivudine with caveats[b] (evidence rating: AIa)

Recommended in the Setting of Opportunistic Infection Treatment

- Dolutegravir (50 mg twice daily), efavirenz (600 mg/d), or raltegravir (800 mg twice daily) plus 2 nucleoside reverse transcription inhibitors is recommended for initial ART in people with HIV who have active tuberculosis and are receiving a rifamycin-based tuberculosis treatment regimen (evidence rating: AIa)
- Bictegravir with rifampin is not recommended due to drug-drug interactions (evidence rating: AIIa)
- Boosted protease inhibitors are recommended only if an integrase strand transfer inhibitor–based or efavirenz-based regimen is not an option (evidence rating: AIa); if possible, rifabutin (150 mg/d) should be substituted for rifampin in the tuberculosis treatment regimen if a protease inhibitor–based regimen must be used (evidence rating: BIII)

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2020 Recommendations of the International Antiviral Society–USA Panel

Michael S. Saag, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Melanie A. Thompson, MD; Paul E. Sax, MD; Davey M. Smith, MD; Constance A. Benson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

Table 2. Other Recommended Initial Antiretroviral Therapy (ART) Regimens[a]

Regimens[b]	Potential uses and cautions
• Darunavir/cobicistat/tenofovir alafenamide/emtricitabine[c] • Darunavir/cobicistat plus tenofovir disoproxil fumarate/lamivudine[d]	• Potential use for patients with known or suspected pretherapy multidrug resistance • Potential use for patients who have resistance to InSTIs • Potential use for patients at high risk of poor adherence[e]
• Dolutegravir/abacavir/lamivudine	• Caution for patients with kidney insufficiency[f]
• Doravirine/tenofovir disoproxil fumarate/lamivudine[c] • Doravirine plus tenofovir alafenamide/emtricitabine • Doravirine plus tenofovir disoproxil fumarate/lamividine[c]	• Potential use for patients who are intolerant to InSTIs
• Efavirenz (400 mg or 600 mg) plus tenofovir disoproxil fumarate/lamivudine[c,d] • Efavirenz (400 mg or 600 mg) plus tenofovir disoproxil fumarate/emtricitabine	• Potential use for patients being treated for co-infection with HIV and tuberculosis • Potential use for patients who are pregnant or intend to become pregnant
• Raltegravir plus tenofovir alafenamide/emtricitabine • Raltegravir plus tenofovir disoproxil fumarate/emtricitabine • Raltegravir plus tenofovir disoproxil fumarate/lamivudine[d]	• Potential use for patients at high risk of drug-drug interactions • Potential use for patients who are intolerant to other InSTI initial regimens • Potential use for patients with child-bearing potential who are trying to conceive • Potential use for patients who are sexually active and not consistently using contraception
• Rilpivirine/tenofovir alafenamide/emtricitabine[c,g] • Rilpivirine plus tenofovir disoproxil fumarate/lamivudine[d,g]	• Potential use for patients who are intolerant to InSTIs • Small pill size is an advantage for some patients

Tabla 4. Recomendaciones sobre la necesidad de cambio de TAR, asumiendo que se mantendrá la supresión virológica

TAR actual	Motivo del cambio	Necesidad de cambio	Recomendación
TDF	Osteopenia/osteoporosis	Obligado	A-I
TDF	Disminución del FGe o disfunción tubular, si se demuestra una acción directa de TDF y se corrigen otros factores	Variable, dependiendo de la magnitud de descenso del FGe. Obligado si se desarrolla insuficiencia renal o parámetros de disfunción tubular	A-I
EFV o DTG	Sintomatología del SNC: mareo, trastornos del sueño	Obligado	A-I
EFV o DTG	Toxicidad del SNC *subclínica*	No se ha demostrado beneficio	A-II
IP/r	Diarrea u otros síntomas gastrointestinales asociados a ritonavir	Obligado	A-III
IP/r	Dislipidemia, alto riesgo cardiovascular	Variable. No se ha demostrado que el cambio sea mejor que el uso de hipolipemiantes ni el impacto sobre el riesgo cardio-vascular	B-II
Múltiples comprimidos	Comprimido único	No se ha demostrado que el cambio sea necesario en la mayoría de los pacientes	B-III
DTG BIC, COBI, TAF	Teratogenicidad peri concepción Sin datos de seguridad en embarazo	Obligado en en mujeres que deciden quedarse embarazadas	A-II A-III

Tabla 5. Recomendaciones sobre cambios entre FAR, con el motivo de cambio y la evidencia sobre la eficacia del cambio

TAR actual	Motivos del cambio*	TAR nuevo**	Recomendación**
Cambio a regímenes que siguen incluyendo 3 fármacos			
TDF TDF/FTC	Evitar los efectos de TDF sobre riñón y/o hueso	ABC TAF/FTC	A-II A-I
ABC/3TC	Decisión clínica	TAF/FTC	A-I
ITINN + 2 ITIAN	Evitar los efectos de TDF sobre riñón y/o hueso; Decisión clínica; Evitar toxicidad de los ITINN (especialmente de EFV sobre SNC); Disminución del número de comprimidos; Evitar interacciones	BIC/FTC/TAF EVG/c/FTC/TAF DTG/ABC/3TC RAL + 2 ITIAN DOR/3TC/TDF[b] RPV/FTC/TAF	A-III A-I A-I A-I A-I A-I
ATV/r DRV/r 800/100 mg	Disminución del número de comprimidos	ATV/c DRV/c	A-I
IP/p + 2 ITIAN[a]	Evitar los efectos de TDF sobre riñón y/o hueso; Decisión clínica; Dislipemia o síntomas gastrointestinales por IP/p; Disminución del número de comprimidos; Evitar interacciones	BIC/FTC/TAF EVG/c/FTC/TAF DTG/ABC/3TC DTG + 2 ITIAN RAL + 2 ITIAN DOR/3TC/TDF[b] RPV/FTC/TAF DRV/c/FTC/TAF	A-I A-III, A-I A-I A-I A-I A-I A-III A-I
INI + 2 ITIAN	Decisión clínica; Disminución del número de comprimidos	BIC/FTC/TAF DTG/ABC/3TC	A-I A-I
Cambio a regímenes con menos de 3 fármacos[a]			
IP/p + 2 ITIAN[a]	Evitar efectos adversos del régimen actual; Simplificación	DRV/p o ATV/p + 3TC	A-I
IP/p o ITINN o INI + 2 ITIAN[a]	Evitar efectos adversos del régimen actual; Simplificación; Evitar interacciones	DTG/3TC DTG/RPV	A-I A-I
IP/p + 2 ITIAN Regímenes varios	Evitar efectos adversos del régimen actual; Simplificación	DTG + DRV/p	A-I, A-II

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention
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Michael S. Saag, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Melani
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Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MI

Box 3. Key Recommendations for When and How to Switch Antiretroviral Therapy (ART) Regimens

- Review of the patient's ART regimen history, regimen tolerability, co-medications, food requirements, cost, and results from prior resistance tests is recommended before any treatment changes are made (evidence rating: AIa).
- HIV viral load assessment is recommended 1 month after switching regimens (evidence rating: BIII).

Switching When the Patient Has Achieved Viral Suppression

- Patients with HIV and hepatitis B virus (HBV) co-infection who are switching therapy should continue taking tenofovir alafenamide or tenofovir disoproxil fumarate (evidence rating: AIII) unless these drugs are contraindicated. Switching to a regimen including lamivudine or emtricitabine and excluding tenofovir alafenamide or tenofovir disoproxil fumarate will not maintain suppression of chronic HBV and is not recommended; alternative HBV suppressive therapy is recommended (evidence rating: AIIa).
- In patients with nucleoside reverse transcriptase inhibitor (nRTI) resistance mutations, switching from a boosted protease inhibitor (PI) to a regimen containing a drug with a low genetic barrier to resistance (eg, nonnucleoside reverse transcriptase inhibitor [NNRTI] or raltegravir) is not recommended (evidence rating: AIa).
- In the setting of viral suppression, switching from a 3-drug regimen to an oral 2-drug regimen is an appropriate strategy to manage toxic effects, intolerance, adherence, or patient preference provided both agents are fully active (evidence rating: AIa). Recommended regimens include dolutegravir/rilpivirine (evidence rating: AIa), a boosted PI with lamivudine (evidence rating: AIa), dolutegravir/lamivudine (evidence rating: AIa) or a long-acting injectable 2-drug regimen of cabotegravir and rilpivirine dosed every 4 weeks (evidence rating: AIa) or every 8 weeks (evidence rating: BIb) pending approval by regulatory bodies and availability.
- Monotherapy with boosted PIs or dolutegravir is not recommended (evidence rating: AIIa).
- Review of co-medications is recommended to ensure no change in tenofovir alafenamide dosing is needed (evidence rating: BIII).

Switching for Virological Failure

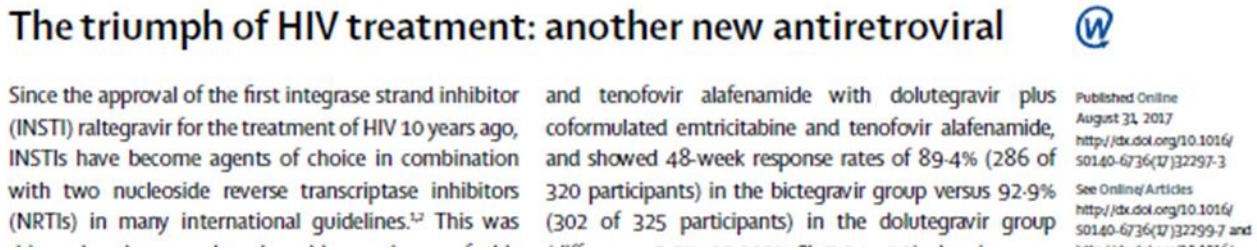
- Resistance testing is recommended while the patient is taking the failing ART regimen (evidence rating: AIa) or within 4 weeks of stopping ART (evidence rating: AIIa).
- Virological failure (defined as HIV RNA level >200 copies/mL) should be confirmed and, if resistance is identified, a prompt switch to another active regimen using the results of current and past resistance testing is recommended (evidence rating: BIIa).
- Adding a single active agent to a failing regimen is not recommended (evidence rating: AIa).
- Dolutegravir plus 2 nRTIs (with ≥1 active drug determined by genotypic testing) is recommended after initial treatment failure with an NNRTI (evidence rating: AIa).
- A boosted PI plus 2 nRTIs (with ≥1 active nRTI) is recommended for initial treatment failure of an integrase strand transfer inhibitor–containing regimen (evidence rating: AIII).
- Dolutegravir (dosed twice daily) plus at least 1 fully active other agent is recommended in the setting of raltegravir or elvitegravir resistance (evidence rating: BIII).
- Virological failure due to resistance mutations is rare with PIs (evidence rating: AIa). Support for adherence or an alternative regimen that improves adherence, tolerability, or both is recommended (evidence rating: AIII)
- In the setting of multiclass resistance (3-class resistance), the next regimen should be constructed using drugs from new classes if available (evidence rating: BIII); eg, fostemsavir (evidence rating: AIb) or ibalizumab (evidence rating: BII) with at least 1 additional active drug in an optimized ART regimen.

Clinical Studies of Recommended First-line INSTIs

Trial	INSTI Regimen	Comparator	Wks	Outcome vs Comparator
GS-1489[1]	**BIC**/FTC/TAF	DTG/ABC/3TC	96	Noninferior
GS-1490[2]	**BIC**/FTC/TAF	DTG + FTC/TAF	96	Noninferior
SINGLE[3]	**DTG** + ABC/3TC	EFV/FTC/TDF	144	Favors INSTI
FLAMINGO[4]	**DTG** + 2 NRTIs	DRV + RTV + 2 NRTIs	96	Favors INSTI
SPRING-2[5]	**DTG** + 2 NRTIs	RAL + 2 NRTIs	96	Noninferior
ARIA[6]	**DTG**/ABC/3TC	ATV + RTV + FTC/TDF	48	Favors INSTI
GEMINI-1/2[7]	**DTG** + 3TC	DTG + FTC/TDF	96	Noninferior
ACTG A5257[8]	**RAL** + FTC/TDF	ATV or DRV + RTV + FTC/TDF	96	Favors INSTI
STARTMRK[9]	**RAL** + FTC/TDF	EFV + FTC/TDF	240	Favors INSTI

- Rates of discontinuation for AEs numerically lower with INSTIs vs PIs or NNRTIs and no BIC or DTG resistance detected in these trials

1. Wohl. Lancet HIV. 2019;6:e355. 2. Stellbrink. Lancet HIV. 2019;6:e364. 3. Walmsley. JAIDS. 2015;70:515.
4. Molina. Lancet HIV. 2015;2:e127. 5. Raffi. Lancet Infect Dis. 2013;13:927. 6. Orrell. Lancet HIV. 2017;4:e536.
7. Cahn. JAIDS. 2020;83:310. 8. Lennox. Ann Intern Med. 2014;161:461. 9. Rockstroh. JAIDS. 2013;63:77.



The triumph of HIV treatment: another new antiretroviral

Since the approval of the first integrase strand inhibitor (INSTI) raltegravir for the treatment of HIV 10 years ago, INSTIs have become agents of choice in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in many international guidelines.[1,2] This was

and tenofovir alafenamide with dolutegravir plus coformulated emtricitabine and tenofovir alafenamide, and showed 48-week response rates of 89·4% (286 of 320 participants) in the bictegravir group versus 92·9% (302 of 325 participants) in the dolutegravir group

Published Online
August 31, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32297-3

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(17)32299-7 and

Bictegravir

Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial

Brar, Eric S Daar,

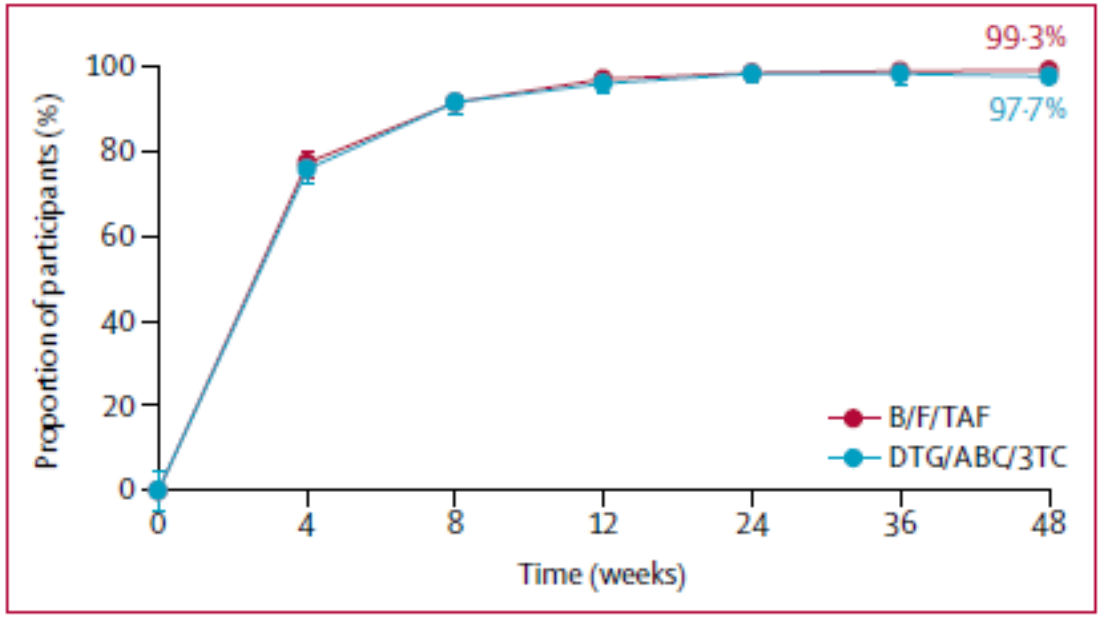


***Figure 2*: Proportion of participants with HIV-1 RNA less than 50 copies per mL**
Missing-as-excluded analysis. Error bars represent 95% CIs. B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine.

Published Online
August 31, 2017

Bictegravir… dolutegrav… HIV-1 infec… phase 3, ra… …nide versus …treatment of …d, multicentre, …rial

Joel Gallant, Adriano Laz… David Wohl, Jürgen Rocks… Indira Brar, Eric S Daar, …k

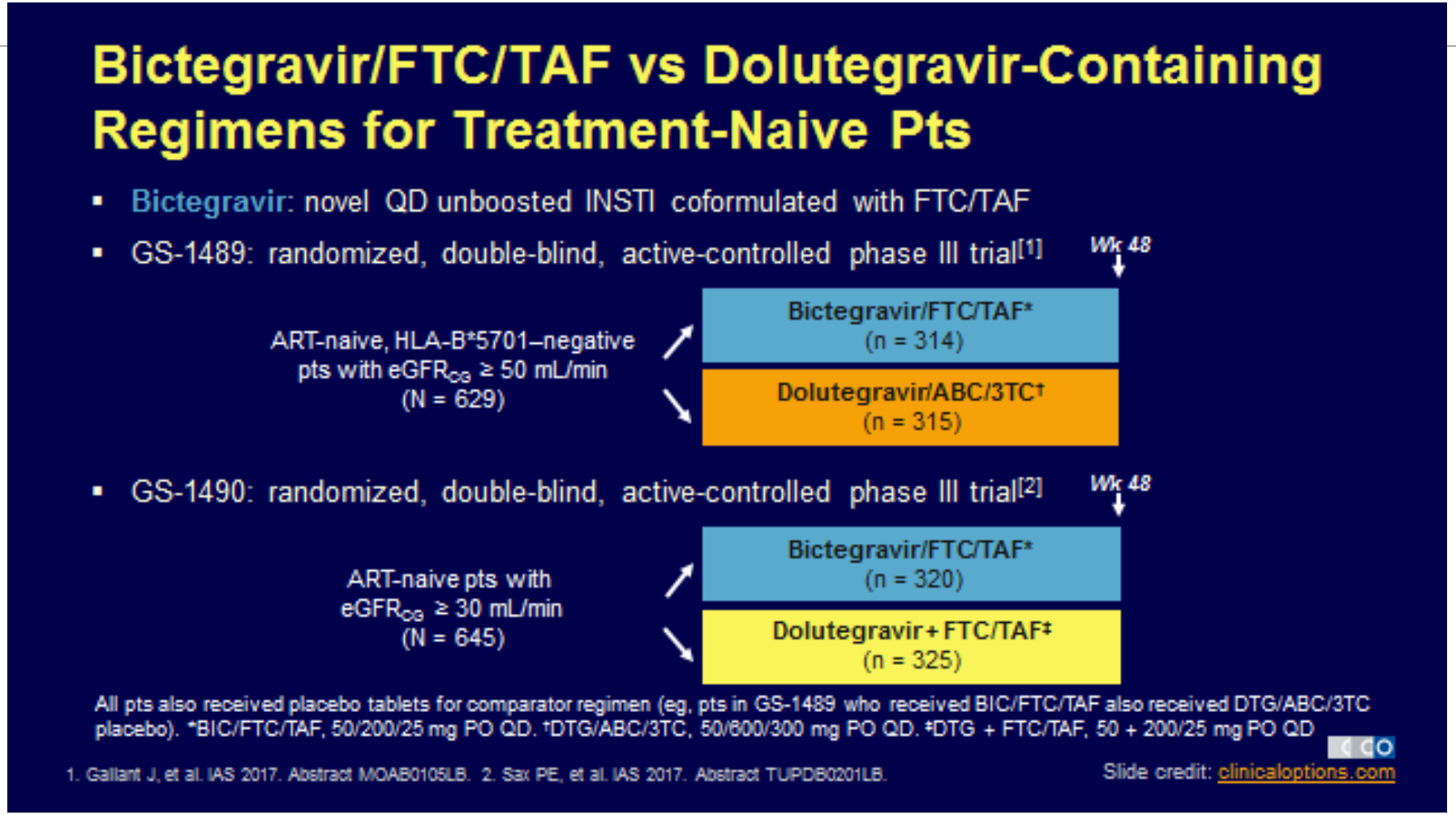
	B/F/TAF group (n=314)	DTG/ABC/3TC group (n=315)
Any adverse event	265 (84%)	283 (90%)
Grade 3 or 4 adverse event	23 (7%)	24 (8%)
Serious adverse event	19 (6%)	25 (8%)
Drug-related adverse event	82 (26%)	127 (40%)
Drug-related serious adverse event	1 (<1%)	1 (<1%)
Any adverse event leading to study drug discontinuation	0	4 (1%)*
Adverse events occurring with ≥5% incidence in either group		
Nausea	32 (10%)	72 (23%)
Diarrhoea	40 (13%)	41 (13%)
Headache	36 (11%)	43 (14%)
Upper respiratory tract infection	20 (6%)	34 (11%)
Nasopharyngitis	23 (7%)	29 (9%)
Fatigue	19 (6%)	27 (9%)
Syphilis	12 (4%)	25 (8%)
Insomnia	14 (4%)	20 (6%)
Arthralgia	11 (4%)	19 (6%)
Vomiting	12 (4%)	17 (5%)
Cough	20 (6%)	8 (3%)
Bronchitis	10 (3%)	16 (5%)
Abdominal pain	9 (3%)	16 (5%)

Data are n (%). B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine. *Chronic pancreatitis and steatorrhoea (n=1), nausea and generalised rash (n=1), depression (n=1), and thrombocytopenia (n=1).

Table 3: **Adverse events**

Published Online August 31, 2017

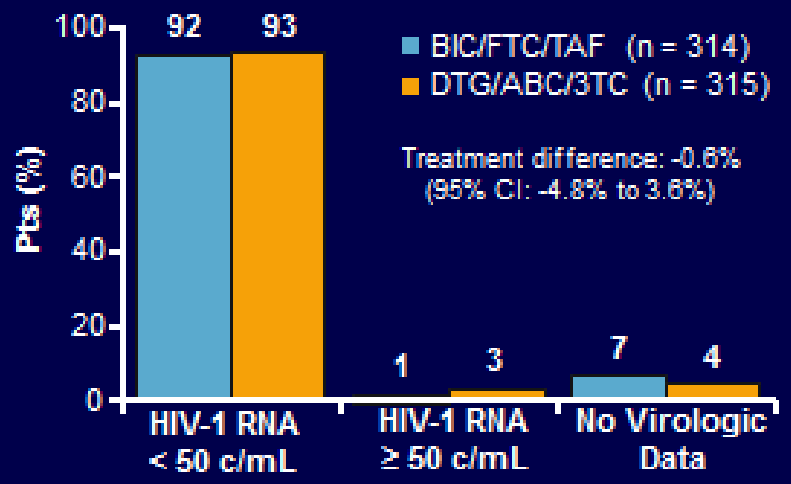
Nueva integrasa en STR



Nueva integrasa en STR

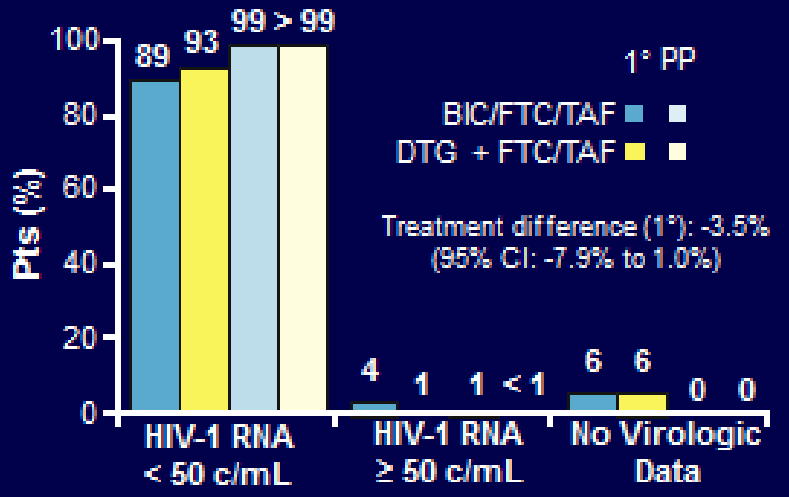
BIC/FTC/TAF vs DTG-Containing Regimens: Key Efficacy Findings

GS-1489: Wk 48 Virologic Efficacy[1]



- No resistance for any regimen components detected for either group

GS-1490: Wk 48 Virologic Efficacy[2]



- No resistance for any regimen components detected for either group

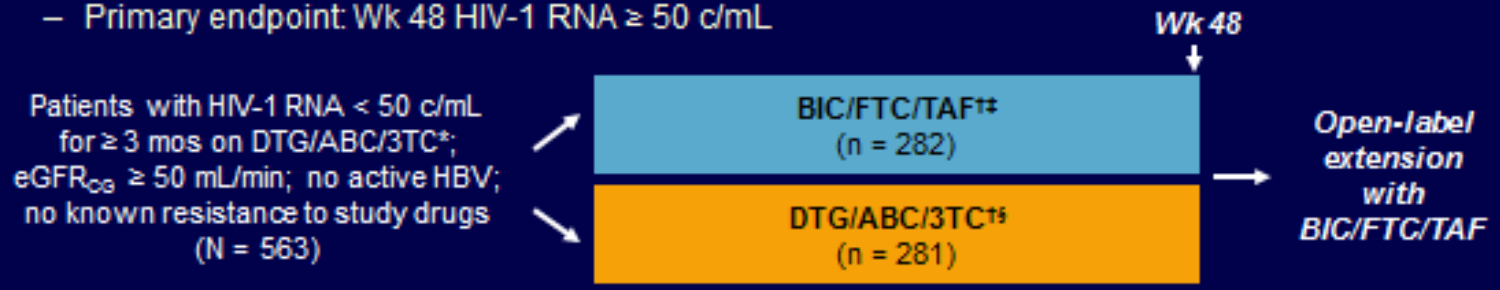
1. Gallant J, et al. IAS 2017. Abstract MOAB0105LB. Reproduced with permission.
2. Sax PE, et al. IAS 2017. Abstract TUPDB0201LB. Reproduced with permission.

Slide credit: clinicaloptions.com

Y en cambio de tratamiento

Study 380-1844: Switch From Suppressive DTG/ABC/3TC to BIC/FTC/TAF

- BIC/FTC/TAF: once-daily STR with novel, unboosted INSTI; now FDA approved for treatment-naive patients and virologically suppressed patients with no history of treatment failure or resistance to regimen components
- 380-1844: randomized, double-blind, international, active-controlled phase III trial
  - Primary endpoint: Wk 48 HIV-1 RNA ≥ 50 c/mL



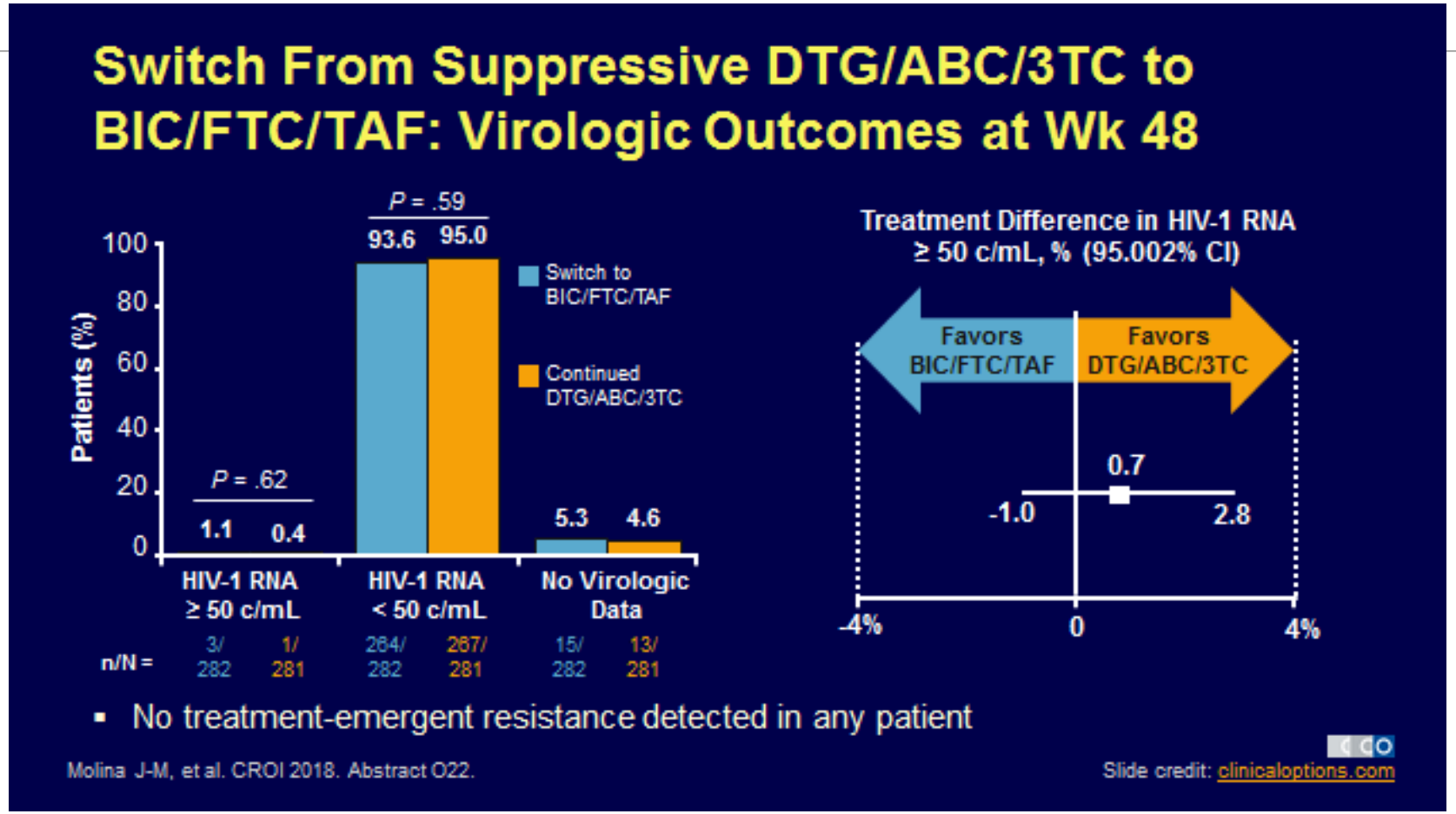
- Baseline: male sex, 88% to 90%; black race, 21% to 22%; median age, 45-47 yrs; median CD4+ cell count, 661-732 cells/mm^3; median eGFR$_{CG}$, 101 mL/min

*Could be STR or as separate components. †All patients also received placebo tablets for comparator regimen. ‡BIC/FTC/TAF 50/200/25 mg PO QD. §DTG/ABC/3TC 50/600/300 mg PO QD.

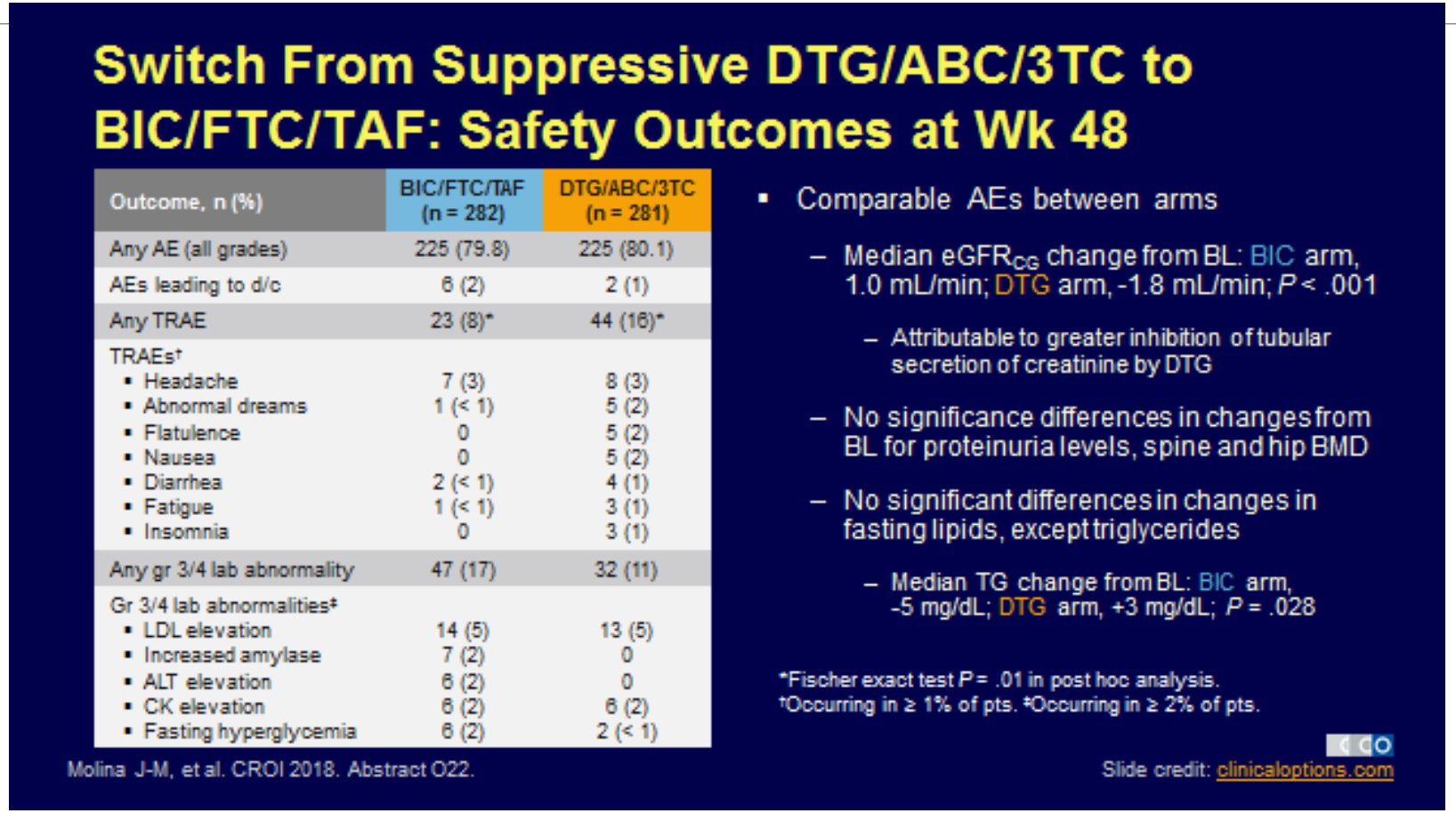
Molina J-M, et al. CROI 2018. Abstract O22.

Slide credit: clinicaloptions.com

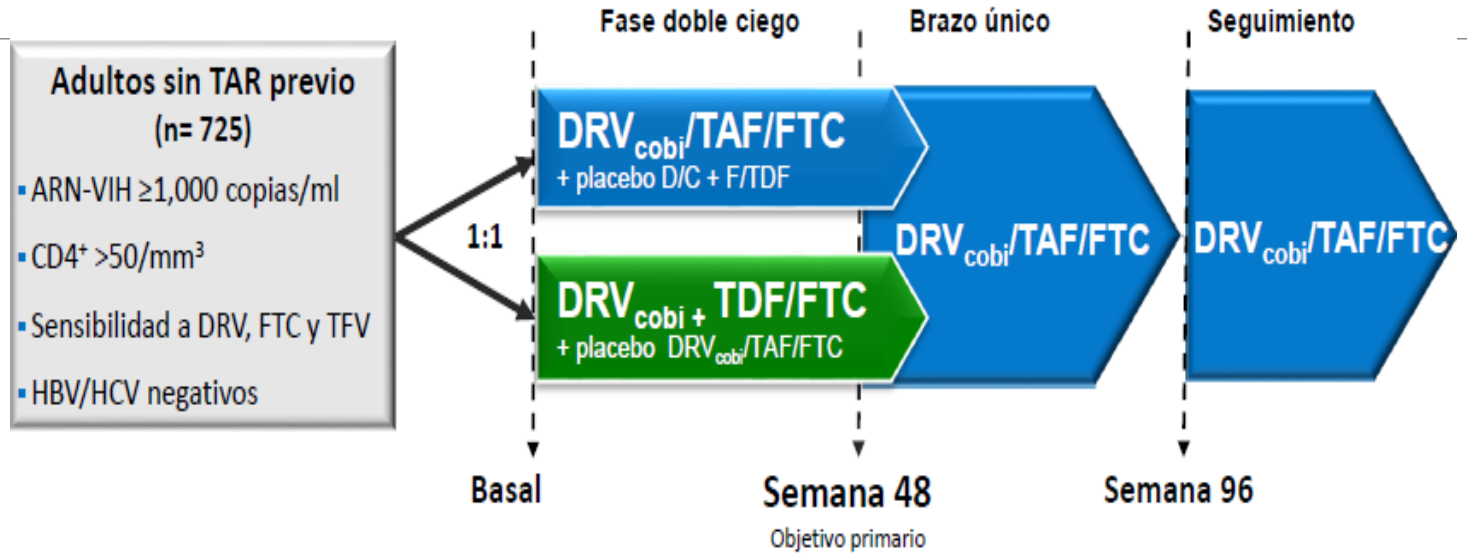
Y en cambio de tratamiento



Y en cambio de tratamiento



Estudio AMBER D/C/F/TAF vs. DRV/c + FTC/TDF



- **Objetivo primario:** evaluar la no inferioridad de D/C/F/TAF vs. DRV/c + FTC/TDF según la proporción de pacientes con CV <50 copias/ml a las 48 semanas

Phase 3, Randomised, Double-blind, International,* Multicentre Trial *

121 sites in USA, Canada, Belgium, France, Germany, Italy, Poland, Russia, Spain, UK

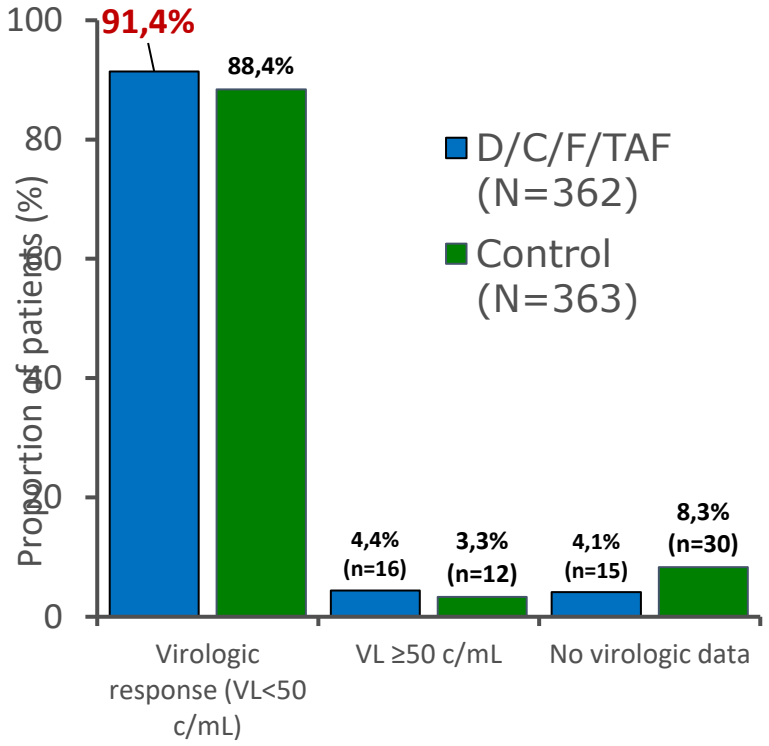
†Lower limit of 95% CI of stratified Mantel-Haenszel difference between D/C/F/TAF and control >–10%

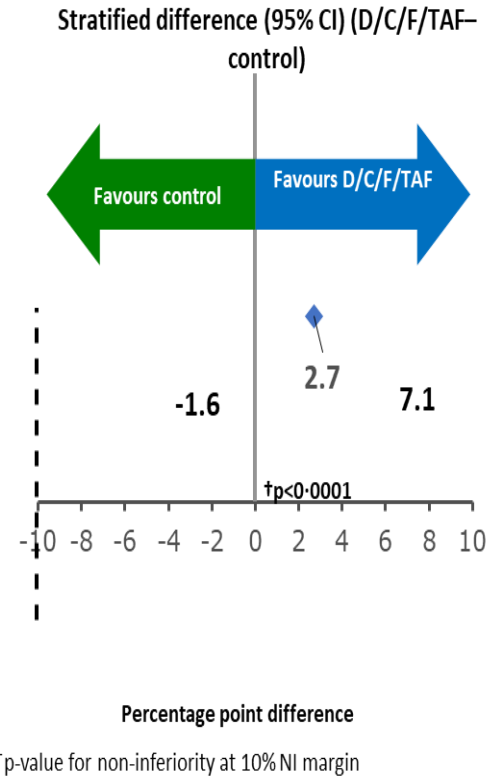
(NI margin 10%; FDA-Snapshot algorithm)

Estudio AMBER
D/C/F/TAF no inferior al control

D/C/F/TAF non-inferior to control

Lower bound 95% CI >–10%





†p-value for non-inferiority at 10% NI margin

*(FDA Snapshot; VL<50 c/mL) (ITT)

Estudio AMBER: Análisis de resistencias a semana 48

	DRV_{cobi}/TAF/FTC n= 362	Control n= 363
Fracasos virológicos con genotipos basales y en FV*, n	7	2
Desarrollo de mutaciones (IAS 2015) durante el estudio, n		
Mutaciones a DRV	0	0
Mutaciones primarias a IPs	0	0
Mutaciones a Análogos	1 (M184I/V)†	0

*Post-baseline genotyping/phenotyping performed for patients who met the criteria for protocol-defined virologic failure (virologic non-response, virologic rebound, and/or viraemic at final timepoint) and who had VL ≥400 c/mL at failure (unconfirmed or confirmed failure) or at later time points

†Patient had K103N at screening, indicating transmitted NNRTI (efavirenz/nevirapine) resistance, and developed M184I/V, conferring resistance to FTC and 3TC

Estudio AMBER: Efectos adversos s 48

Incidence, n (%)	D/C/F/TAF N=362	Control N=363
≥1 AE, any grade	312 (86.2)	307 (84.6)
≥1 grade 3–4 AE	19 (5.2)	22 (6.1)
≥1 serious AE	17 (4.7)	21 (5.8)
≥1 AE leading to permanent discontinuation	7 (1.9)	16 (4.4)
Deaths	0	0
AEs at least possibly related to study drug		
Any	126 (34.8)	151 (41.6)
Most common (≥5% either arm)		
Diarrhoea†	31 (8.6)	40 (11.0)
Rash	22 (6.1)	14 (3.9)
Nausea	20 (5.5)	36 (9.9)

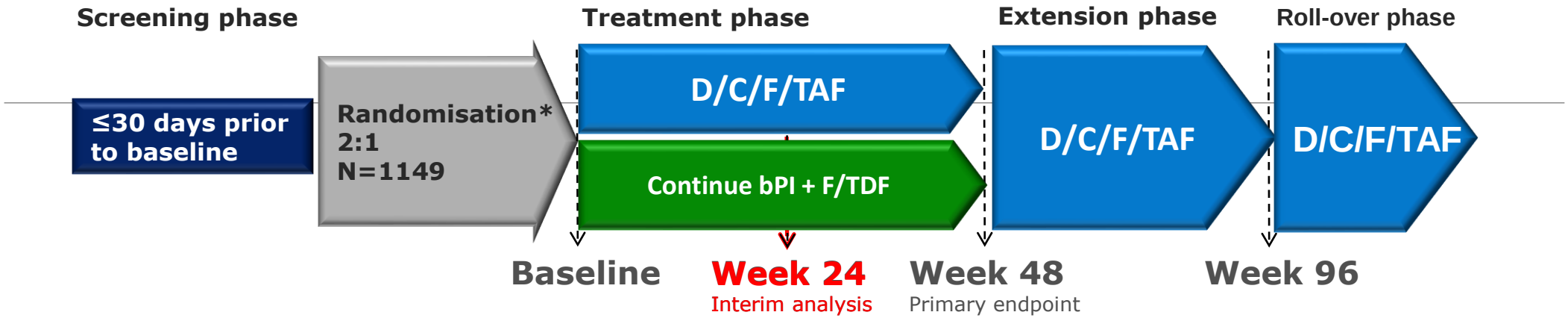
Ninguna discontinuación por EA óseos, renales o del SNC

Más del 90% de los pacientes toleran el tratamiento - 1,9% de discontinuaciones por EA

†Most cases were mild: Grade 1: 24 (6.6%) vs 32 (8.8%); Grade 2: 7 (1.9%) vs 8 (2.2%)

CNS, central nervous system

EMERALD: Open-label, Randomised, Multicentre, Parallel-group, Non-inferiority Phase III Trial



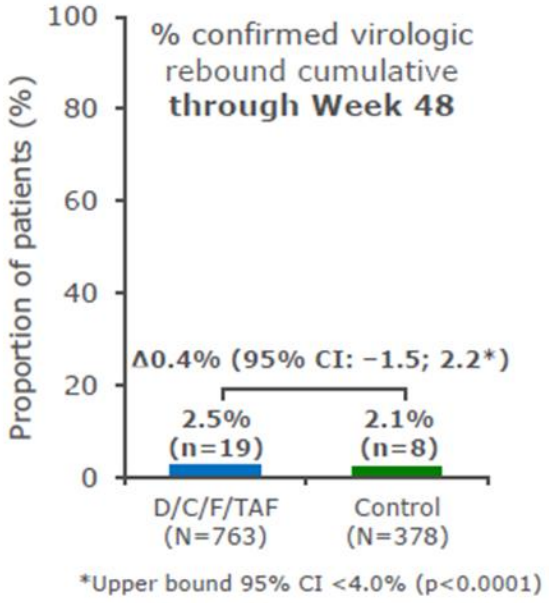
Objective: Non-inferiority and safety of switching to D/C/F/TAF vs continuing bPI + FTC/TDF regimens in virologically suppressed HIV-1-infected adults at Week 48

Key inclusion criteria:

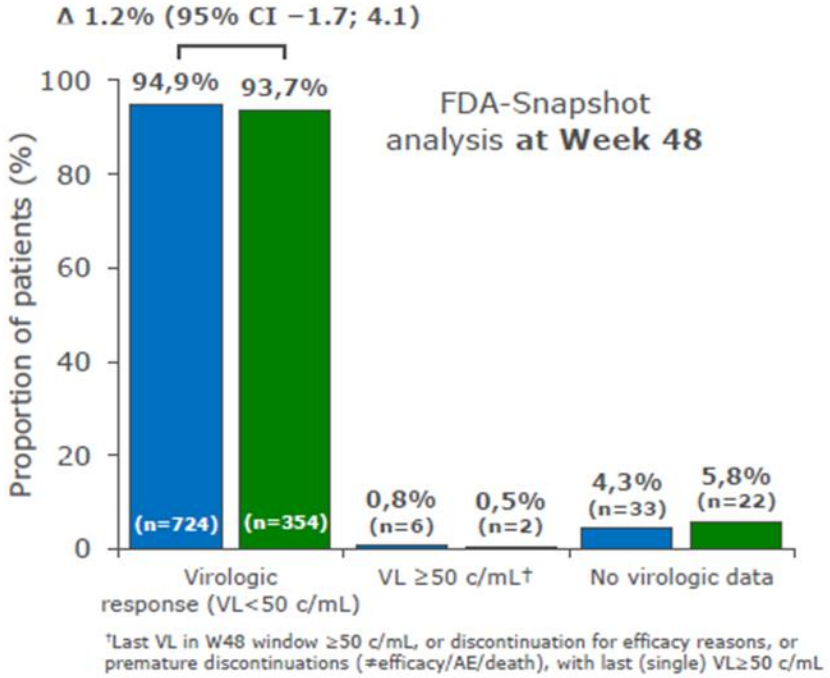
- Previous ART VF allowed
- Absence of history of VF on DRV, and if historical genotype available, absence of DRV RAMs†
- Viral load (VL) <50 c/mL for ≥2 months before screening; one VL≥50 and <200 c/mL within 12 months prior to screening allowed
- Creatinine clearance (by Cockcroft-Gault) ≥50 mL/min

*Stratified by bPI (protease inhibitor boosted with low-dose ritonavir or cobicistat) at screening;
†DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V (IAS-USA)

Week 48 Efficacy



*Upper bound 95% CI <4.0% (p<0.0001)



†Last VL in W48 window ≥50 c/mL, or discontinuation for efficacy reasons, or premature discontinuations (≠efficacy/AE/death), with last (single) VL≥50 c/mL

- No discontinuations for efficacy reasons
- Most rebounders (12/19 D/C/F/TAF and 4/8 control) resuppressed (<50 c/mL) at Week 48

Pero tenemos novedades

GeSIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

DOCUMENTO DE CONS
GeSIDA/PLAN NACIONAL
SIDA RESPECTO AL TRA
ANTIRRETROVIRAL EN
INFECTADOS POR EL VI
INMUNODEFICIENCIA

(ACTUALIZACIÓN 2

SECRETARÍA GENERAL

3er Fármaco	Pauta†	Comentarios‡
Preferentes.	*Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia no inferior a otras pautas también consideradas actualmente como preferentes o superior frente a otras pautas y presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas*	
INI	BIC/FTC/TAF	
	DTG/ABC/3TC	-ABC está contraindicado en pacientes con HLA-B*5701 positivo -DTG no debe utilizarse en mujeres que deseen quedarse embarazadas o mujeres en edad fértil que no utilicen medidas anticonceptivas eficaces. -No utilizar en pacientes con hepatitis B crónica
	DTG+FTC/TAF**	
	RAL+FTC/TAF*	
	DTG/3TC	
Alternativas.	*Pautas eficaces, pero que no se consideran preferentes bien porque su eficacia ha resultado inferior a las pautas preferentes en ensayos clínicos o no se han comparado con pautas preferentes, o porque tienen desventajas potenciales o restricciones en su indicación. Pueden ser, sin embargo, de elección en subgrupos de pacientes o en casos especiales*	
INI	EVG/c/FTC/TAF	-Es imprescindible evaluar posibles interacciones.
IP potenciado	DRV/c/FTC/TAF o DRV/r+FTC/TAF**	-Es imprescindible evaluar posibles interacciones.
ITINN	DOR+FTC/TAF*, ***	-Existe la combinación de DOR/3TC/TDF en comprimido único, que puede utilizarse siempre que se excluya la presencia de alteración renal o de osteopenia/osteoporosis, y no existan factores de riesgo para desarrollarlas.
	RPV/FTC/TAF*	-No indicado en pacientes con CVP >100.000 copias/mL. -Realizar previamente un estudio genotípico que descarte mutaciones de resistencia a ITINN. -Contraindicado si se utilizan inhibidores de la bomba de protones. -Se debe tomar siempre con una comida.

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doravirina

Estudiado en dos ensayos de fase 3, aleatorizados, multicéntricos, doble ciego y con control activo para valorar la eficacia y seguridad de DOR en combinación con otros ARV [1,2]

Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus–1 Infection: Week 48 Results of the DRIVE-AHEAD Trial

Chloe Orkin,[1,2] Kathleen E. Squires,[3,a] Jean-Michel Molina,[4] Paul E. Sax,[5] Wing-Wai Wong,[6] Otto Sussmann,[7] Richard Kaplan,[8] Lisa Lupinacci,[9] Anthony Rodgers,[9] Xia Xu,[9] Gina Lin,[9] Sushma Kumar,[9] Peter Sklar,[9] Bach-Yen Nguyen,[9] George J. Hanna,[9] Carey Hwang,[9] and Elizabeth A. Martin[9]; for the DRIVE-AHEAD Study Group

CID 2019 Feb 1; 68(4):535-544

Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial

Jean-Michel Molina, Kathleen Squires, Paul E Sax, Pedro Cahn, Johan Lombaard, Edwin DeJesus, Ming-Tain Lai, Xia Xu, Anthony Rodgers, Lisa Lupinacci, Sushma Kumar, Peter Sklar, Bach-Yen Nguyen, George J Hanna, Carey Hwang, for the DRIVE-FORWARD Study Group

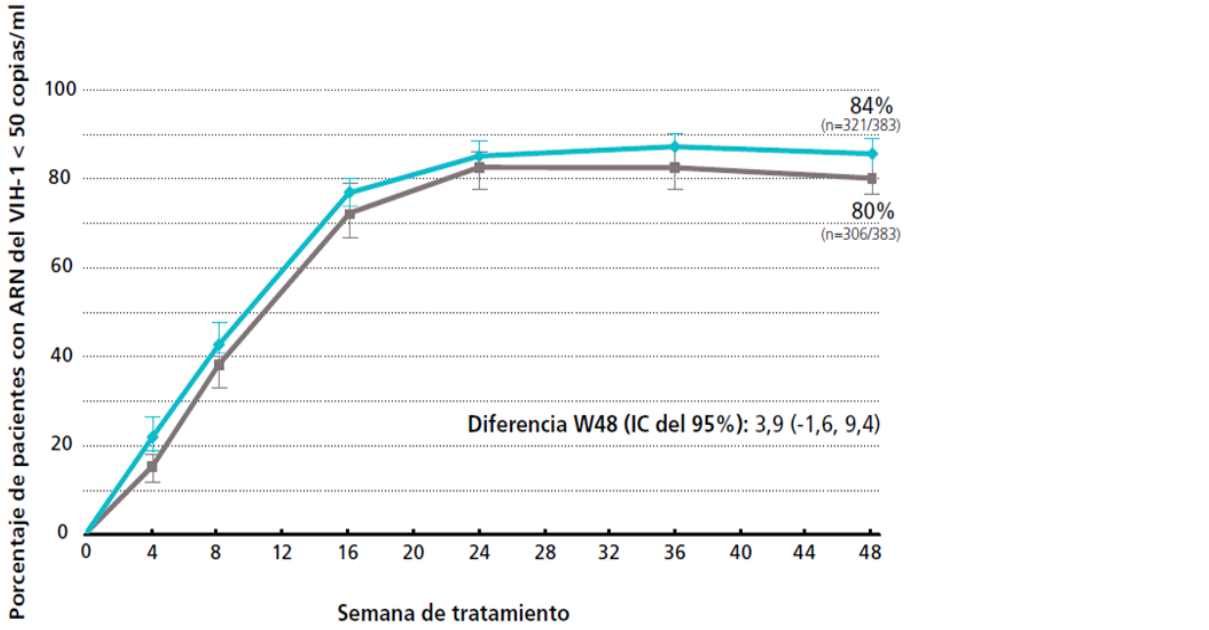
www.thelancet.com/hiv Published online March 25, 2018 http://dx.doi.org/10.1016/S2352-3018(18)30021-3

Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial

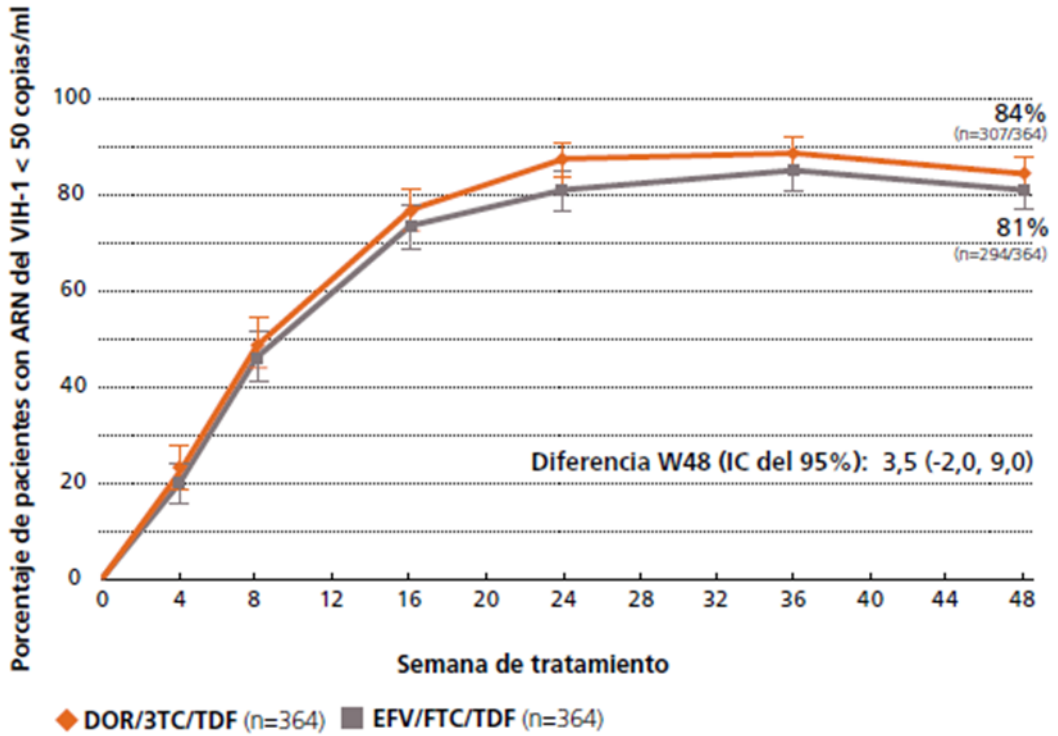
Jean-Michel Molina, Kathleen Squires, Paul E Sax, Pedro Cahn, Johan Lombaard, Edwin Delesus. Mina-Tain Lai. Anthony Rodgers, Lisa Lupinacci, Sushma Kumar, Peter Sklar, George J Hanna, Carey Hwang, Elizabeth Anne Marti p*

Lancet HIV 2020; 7: 16–26

DRIVE FORWARD



DRIVE AHEAD



Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial

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Lancet HIV 2020; 7: 16–26

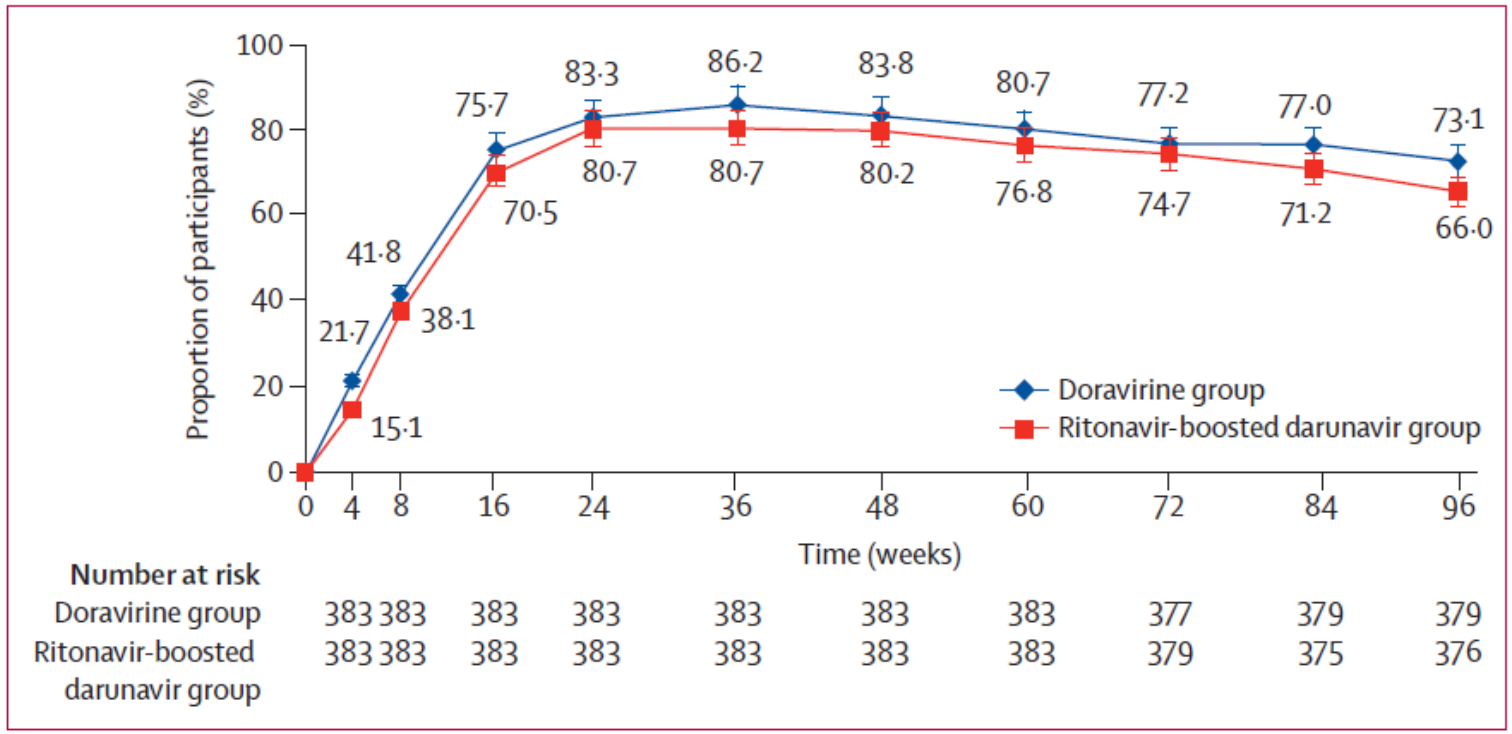
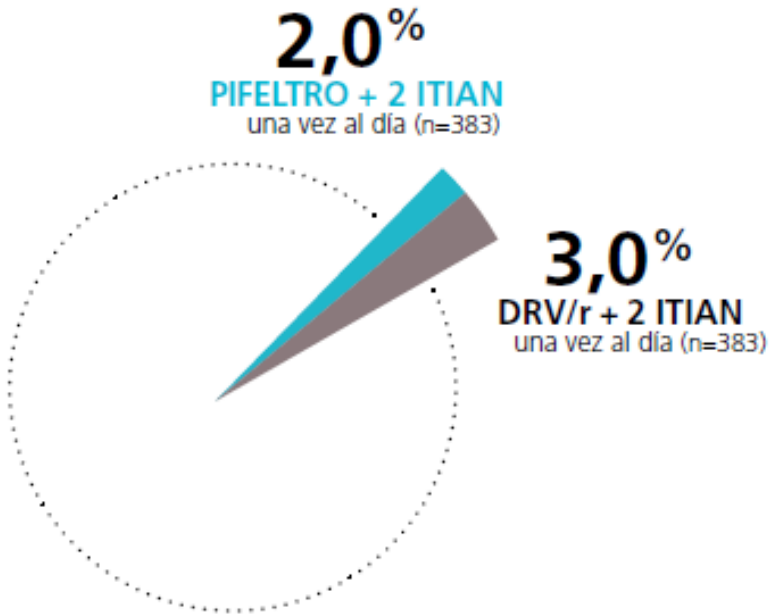


Figure 2: Proportion of participants with plasma HIV-1 RNA concentration of less than 50 copies per mL until week 96

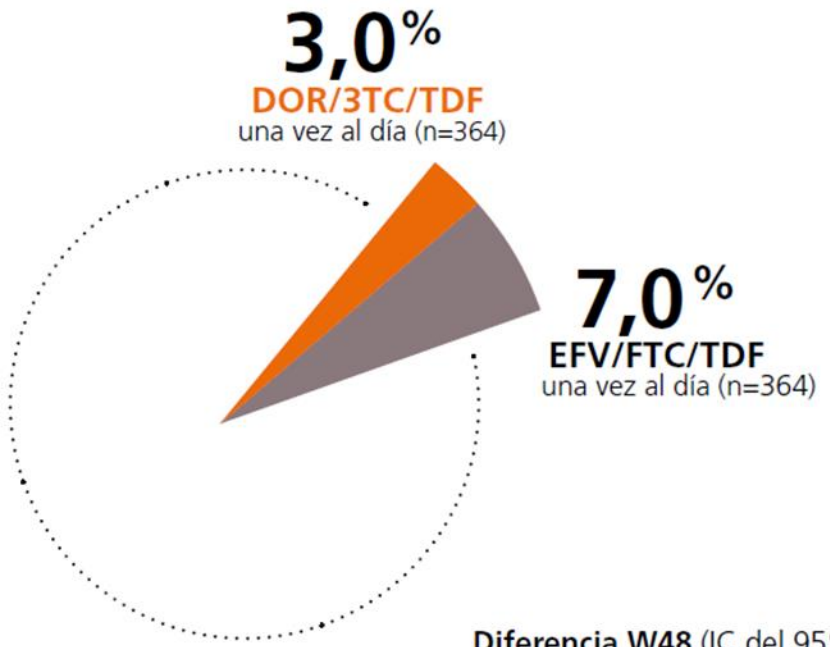
Un estudio de 48 semanas en pacientes adultos con VIH-1 no tratados previamente mostró:

Tasa de discontinuaciones durante 48 semanas[1,2]

DRIVE FORWARD



DRIVE AHEAD



Diferencia W48 (IC del 95%) -3.6 (-6.9, -0.5)

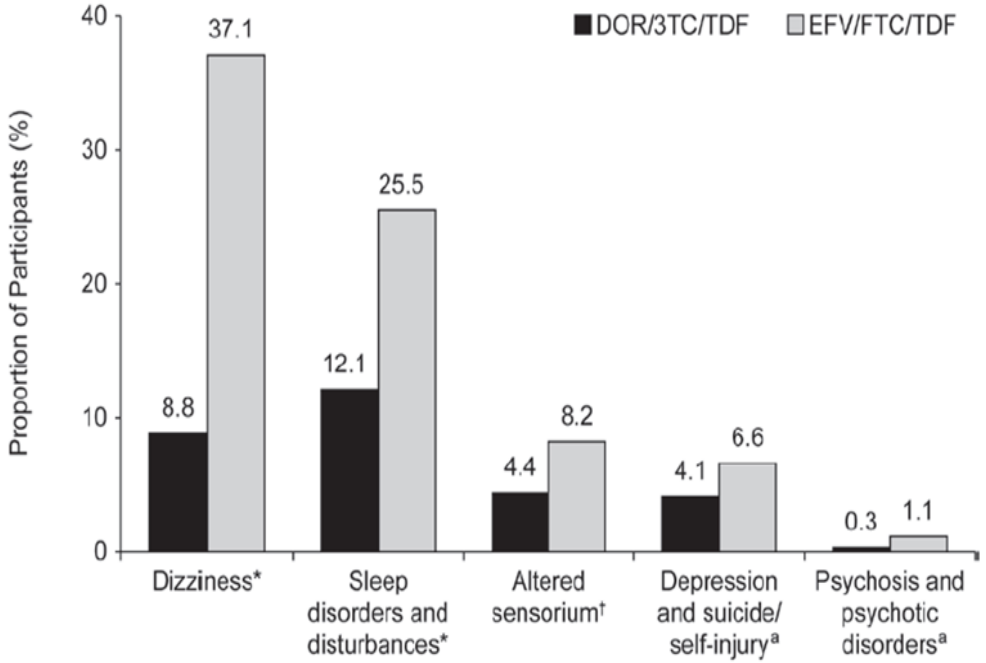
1. Molina JM et al. *Lancet HIV*. 2018;5(5):e211-e220. doi:10.1016/S2352-3018(18)30021-3.
2. Orkin C et al. Clin Infect Dis. 2019;68(4):535-544.

Número significativamente menor de acontecimientos adversos neuropsiquiátricos en tres categorías predefinidas[1]

DRIVE AHEAD

Comparación de los pacientes que sufrieron acontecimientos adversos neuropsiquiátricos en las tres categorías predeterminadas de mareo, trastornos y alteraciones del sueño y alteración del nivel de consciencia con DOR/3TC/TDF y con EFV/FTC/TDF[1,a]

[a] n=364 para cada grupo de tratamiento.[1]



Mareo

4 veces MENOS

9% DOR/3TC/TDF

37% EFV/FTC/TDF

P<0.001[b]

Trastornos y alteraciones del sueño

2 veces MENOS

12% DOR/3TC/TDF

25% EFV/FTC/TDF

P≤0,001[b]

Alteración del nivel de consciencia[c]

2 veces MENOS

4% DOR/3TC/TDF

8% EFV/FTC/TDF

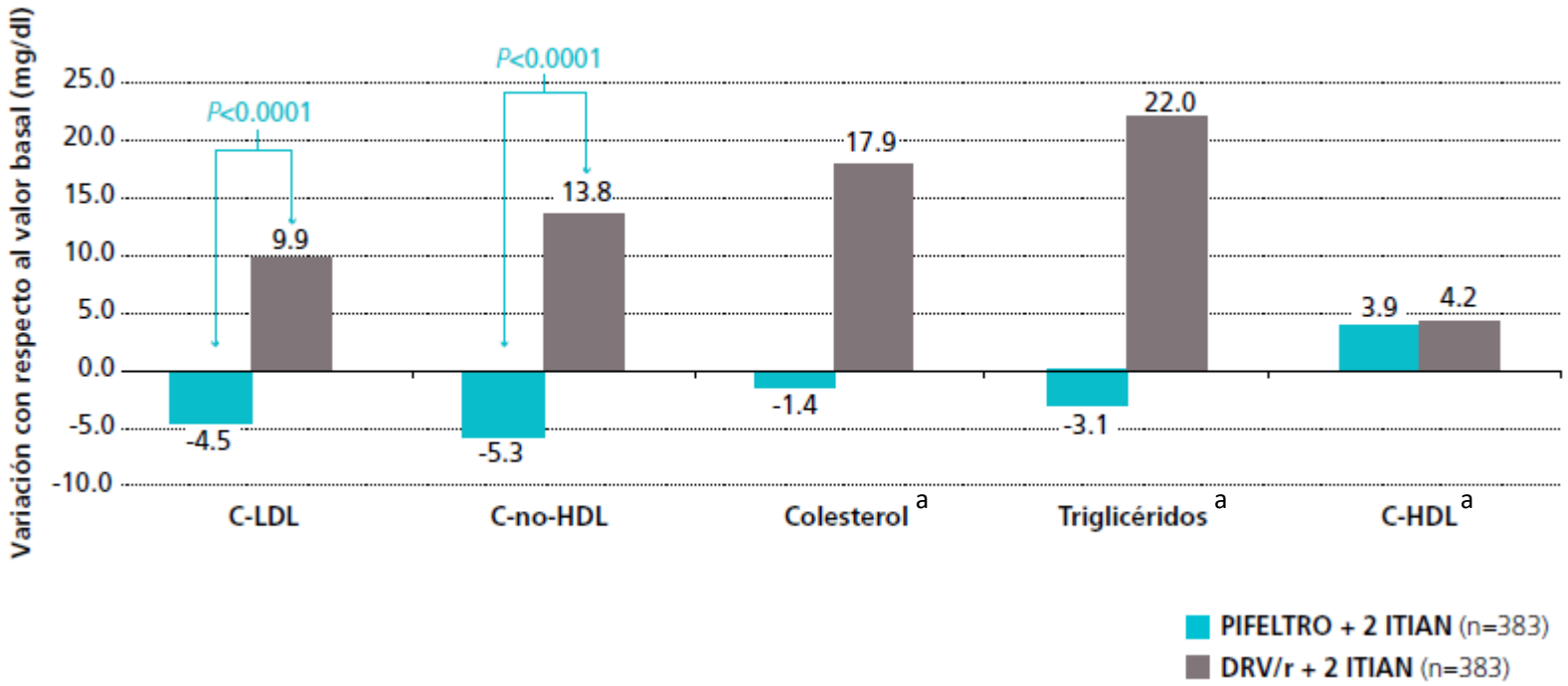
P=0,033[b]

[b] Los IC del 95% se calcularon con el método de Miettinen y Nurminen.[1]
[c] Incapacidad para pensar con claridad o concentrarse.[1]

1. Orkin C et al. *Clin Infect Dis*. 2019;68(4):535-544.

Un estudio de 48 semanas en pacientes adultos con VIH-1 no tratados previamente mostró:

Perfil lipídico superior frente a DRV/r[1]



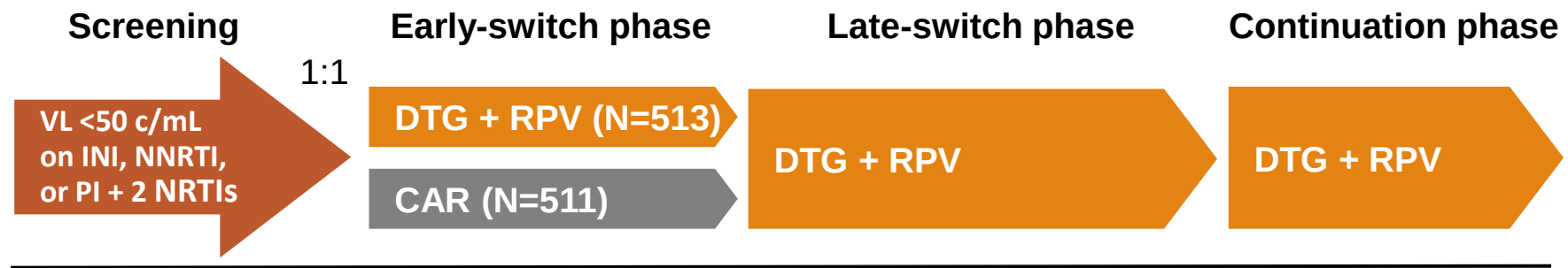
[a]No se predefinieron análisis estadísticos en estas categorías.

1. Molina JM et al. *Lancet HIV*. 2018;5(5):e211-e220. doi:10.1016/S2352-3018(18)30021-3.

OPCIONES DOBLES TERAPIAS

SWORD-1 and -2: Phase III Study Design

Identically designed, randomised, multicentre, open-label, parallel-group, non-inferiority studies



Inclusion criteria

- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV-negative

Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)*

Countries:

Argentina, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, United Kingdom, United States

*8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

HBV, hepatitis B virus; ITT(-E), intent to treat (- exposed); NRTI, nucleoside reverse transcriptase inhibitor

Llibre JM, et al. CROI 2017. Oral Presentation 44LB. Llibre JM, et al. Lancet. 2018;391:839-849.

SWORD-1 and -2: Snapshot Outcomes at Week 48

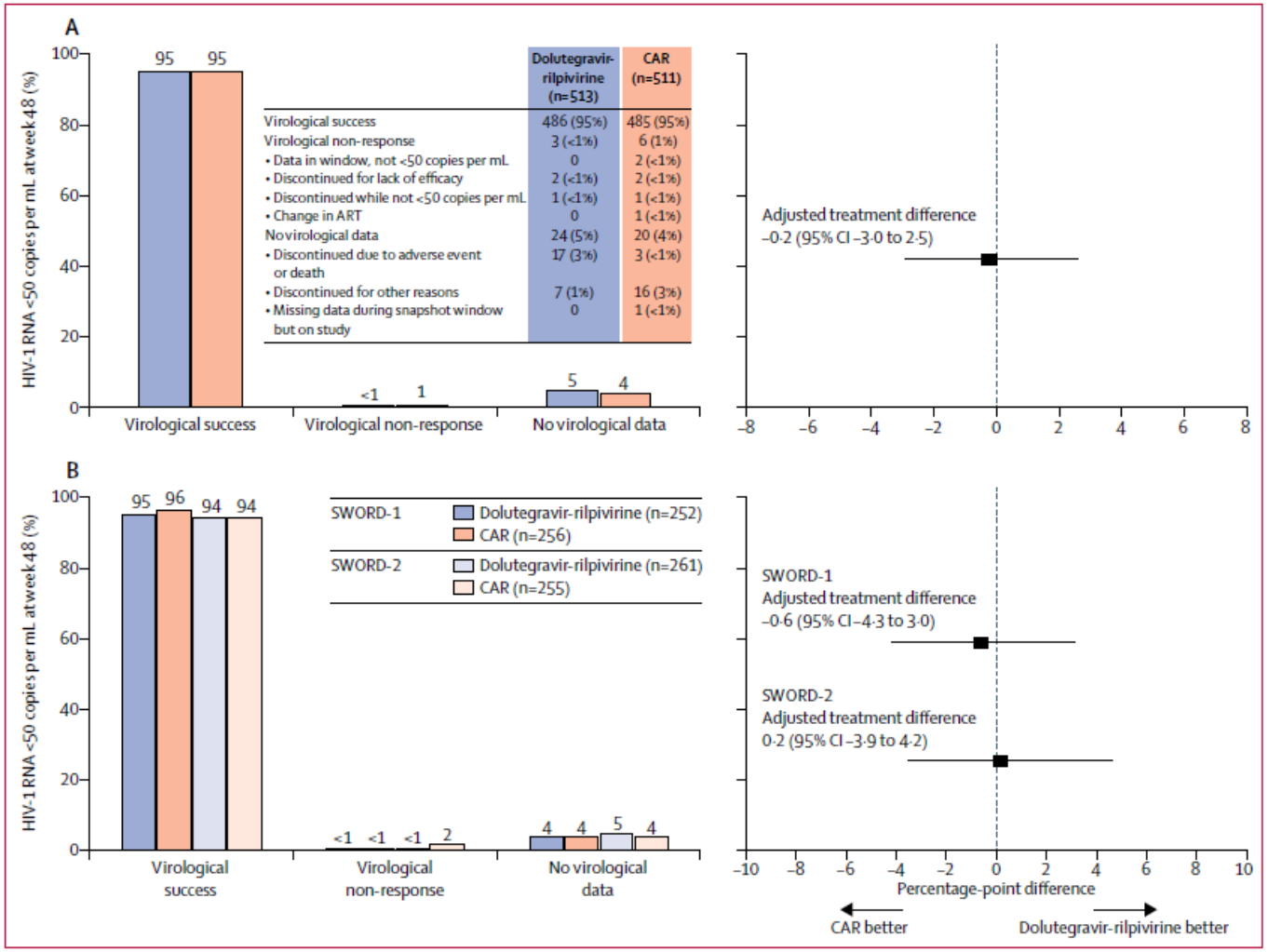
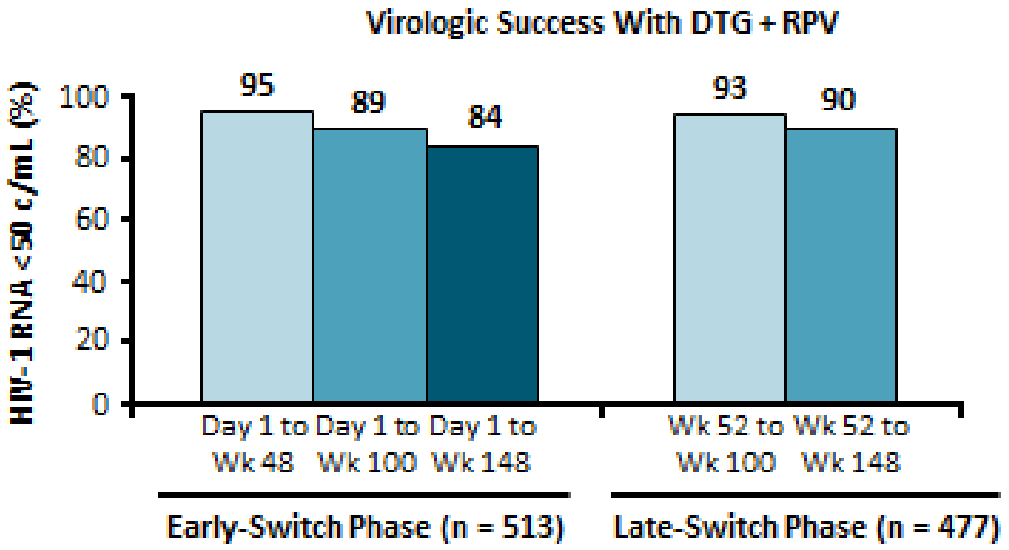


Figure 2: **Virological outcomes at week 48 (US Food and Drug Administration snapshot) in the pooled SWORD-1 and SWORD-2 intention-to-treat study population (A) and separated by study (B)**

Treatment difference was adjusted for age and baseline third-agent class. CAR=current antiretroviral regimen. ART=antiretroviral therapy.

Llibre JM, et al. Lancet. 2018 Mar 3;391:839-849.

SWORD-1 and -2: Efficacy of DTG + RPV to 3 Yrs (Wk 148)



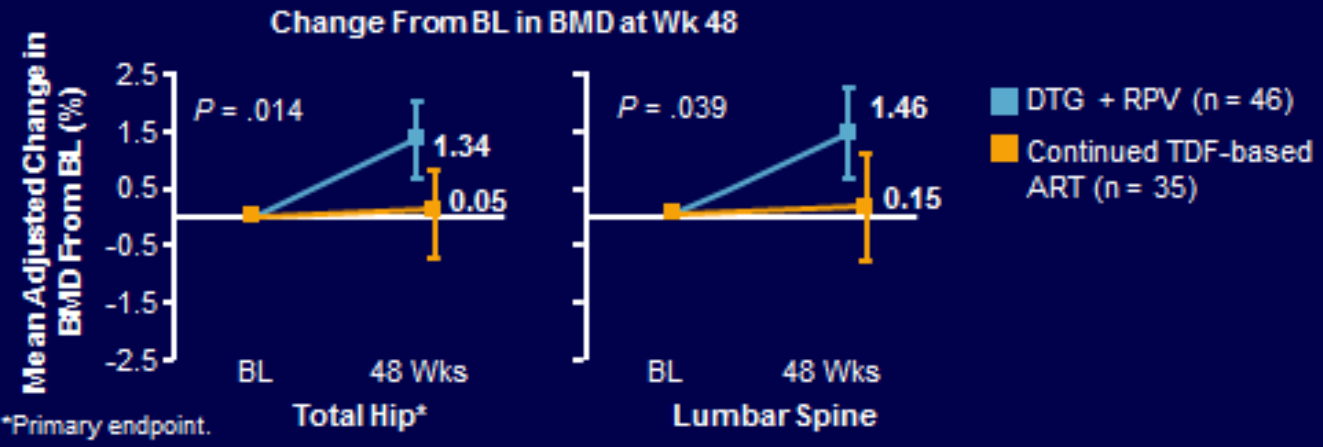
Aboud. AIDS 2018. Abstr THPE8047. van Wyk. BHIVA 2019. Poster P008.

Slide credit: clinicaloptions.com

Densidad mineral ósea

SWORD 1 & 2 Substudy: BMD Impact of Switch From TDF-Based ART to DTG + RPV

- Randomized, open-label, multicenter phase III trials demonstrated that switch to DTG + RPV noninferior to remaining on baseline ART at Wk 48 in virologically suppressed pts[1]
- Current analysis assessed BMD in pts who continued on TDF-containing triple ART regimen or switched from TDF-containing triple ART to DTG + RPV (N = 102)[2]



1. Llibre JM, et al. CROI 2017. Abstract 44LB. 2. McComsey G, et al. IAS 2017. Abstract TUPDB0205LB. Reproduced with permission.

Slide credit: clinicaloptions.com

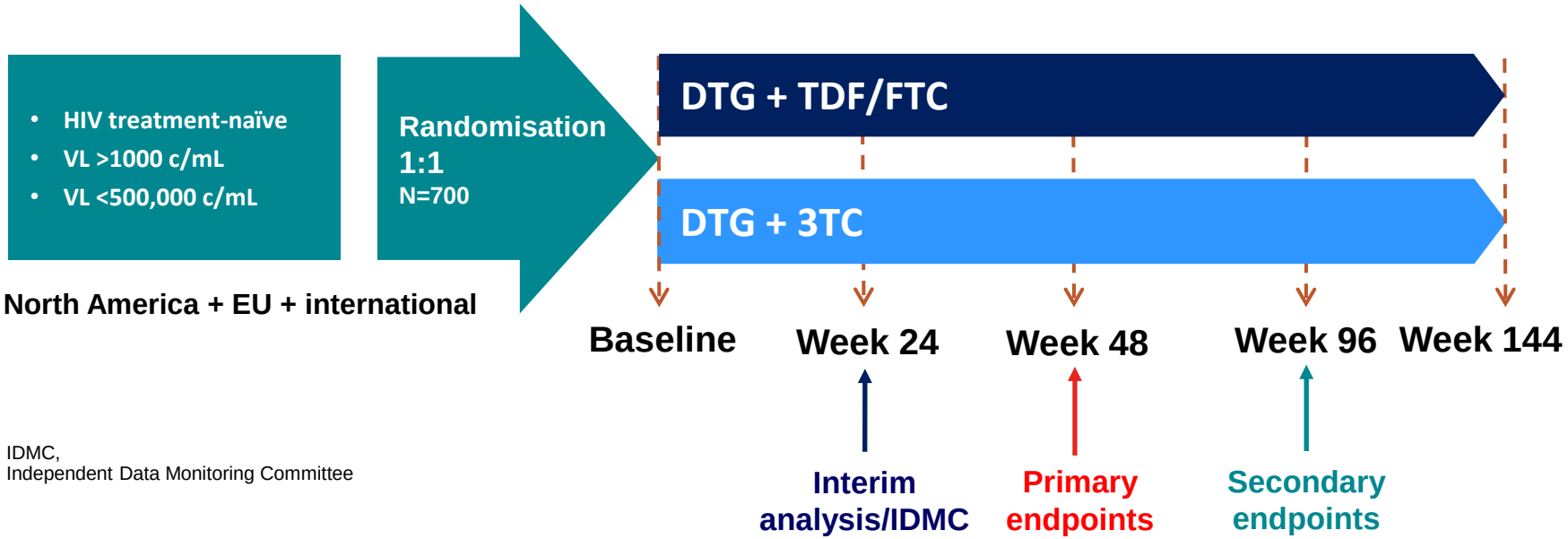
GEMINI-1 and -2: Study Design

Phase III, randomised, double-blind, multicentre, non-inferiority study[1,2]

Objective: to demonstrate the non-inferior antiviral activity of DTG + 3TC QD compared with DTG + TDF/FTC QD over 48 weeks in HIV-1-infected ART-naïve subjects[1,2]

Primary endpoint: the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (missing, switch or discontinuation = failure)[1,2]

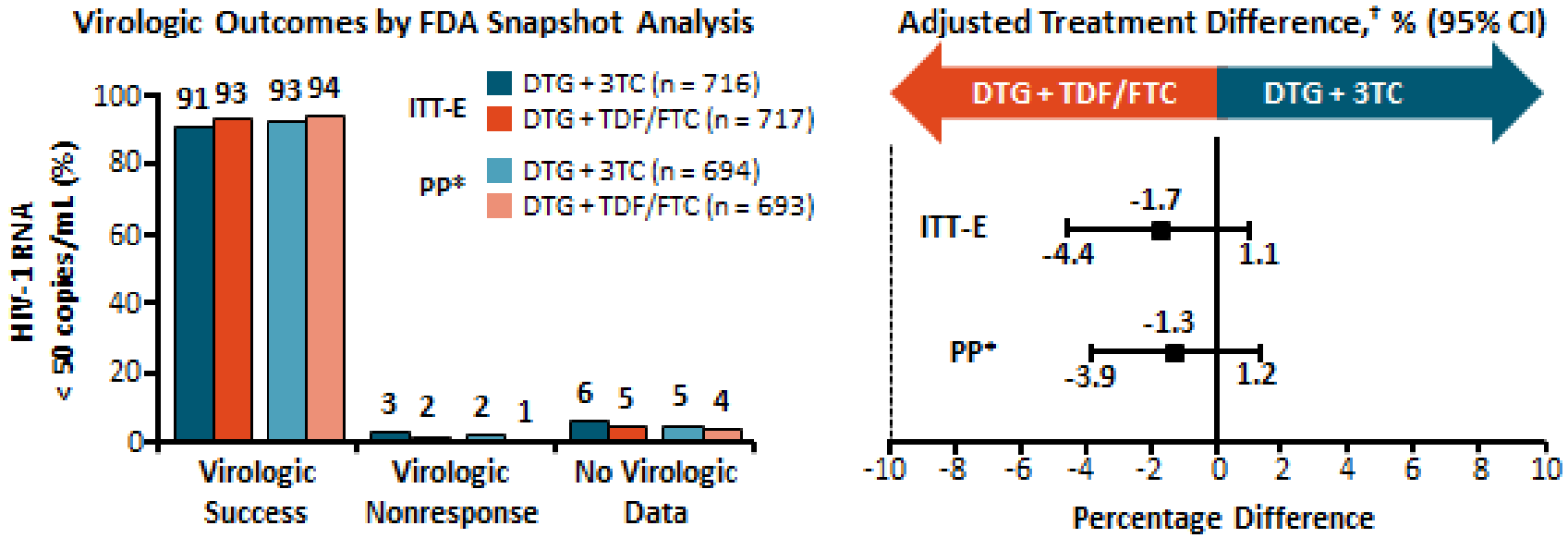
- non-inferiority margin: 10%[1,2]



IDMC,
Independent Data Monitoring Committee

1. GEMINI-1. Available from: https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed Aug 2017
2. GEMINI-2. Available from: https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed Aug 2017

GEMINI-1 and -2: Virologic Response at Wk 48

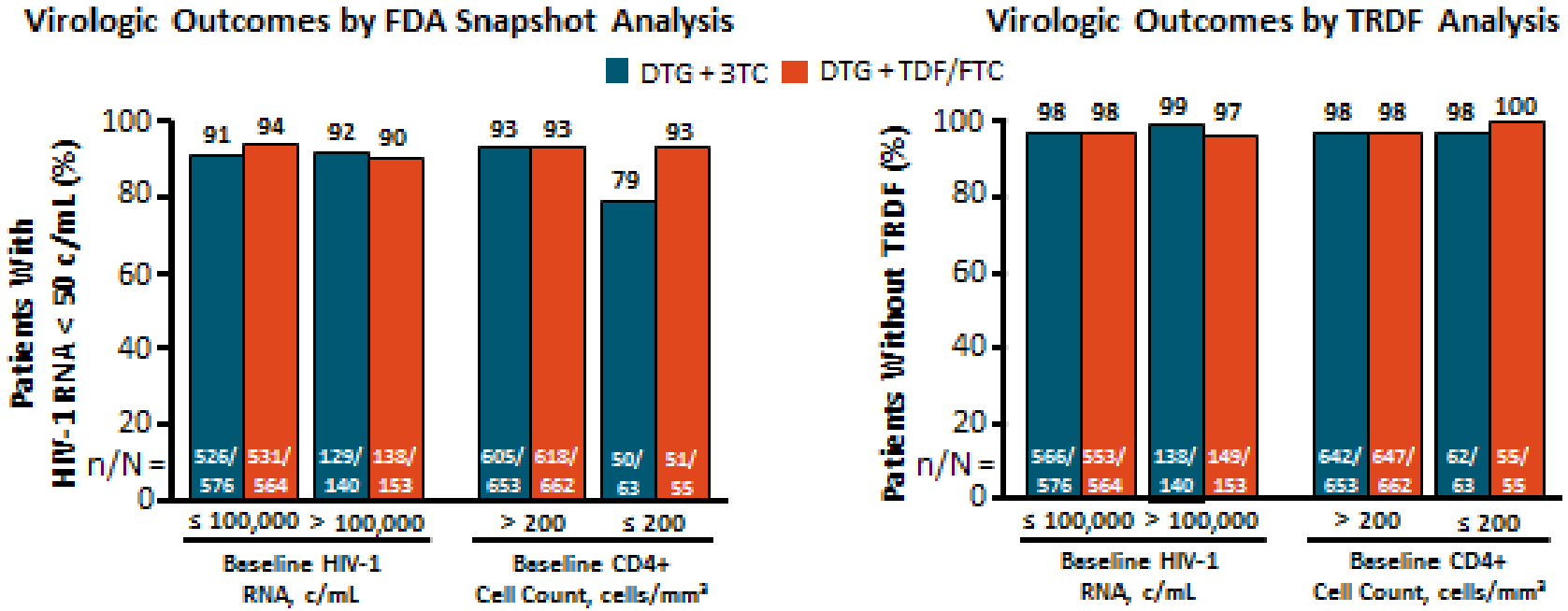


*ITT-E population excluding significant protocol violations.
†Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count (≤ vs > 200 cells/mm³), and study (GEMINI-1 vs GEMINI-2).

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

Slide credit: clinicaloptions.com

GEMINI-1 and -2: Virologic Response at Wk 48 by Baseline HIV-1 RNA and CD4+ Cell Count



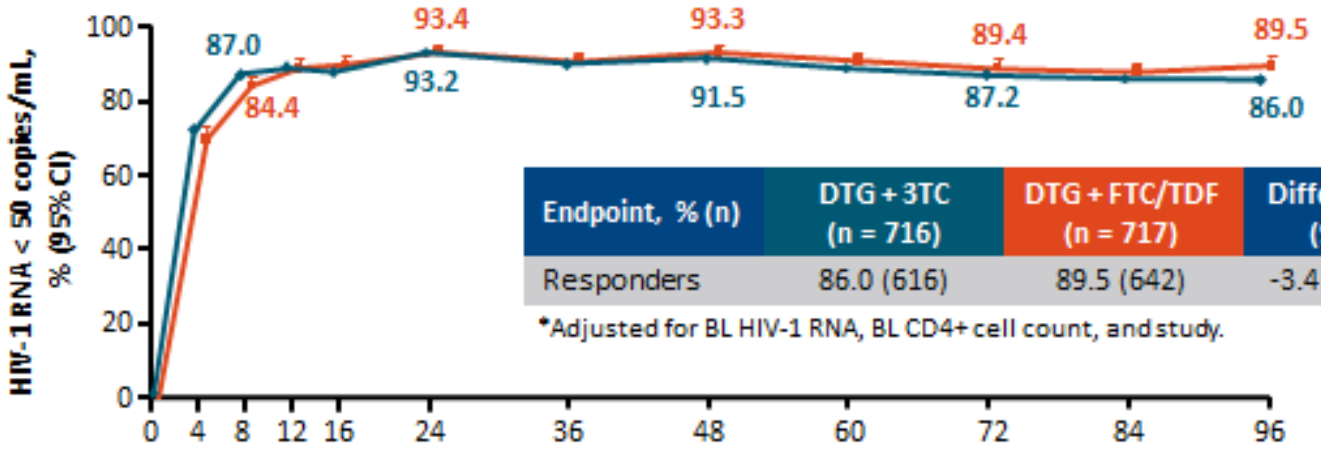
- TRDF includes confirmed virologic withdrawal, withdrawal for lack of efficacy or treatment-related AEs, and participants meeting protocol-defined stopping criteria

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

Slide credit: clinicaloptions.com

GEMINI-1 and -2: Virologic Response Through Wk 96

- In ART-naive adults, DTG + 3TC met criteria for **noninferior efficacy** vs DTG + FTC/TDF at Wk 96
- No treatment-emergent resistance observed in patients with CVW



Endpoint, % (n)	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)	Difference,* % (95% CI)
Responders	86.0 (616)	89.5 (642)	-3.4 (-6.7 to 0)

*Adjusted for BL HIV-1 RNA, BL CD4+ cell count, and study.

Cahn. IAS 2019. Abstr WEAB0404LB.

Slide credit: clinicaloptions.com

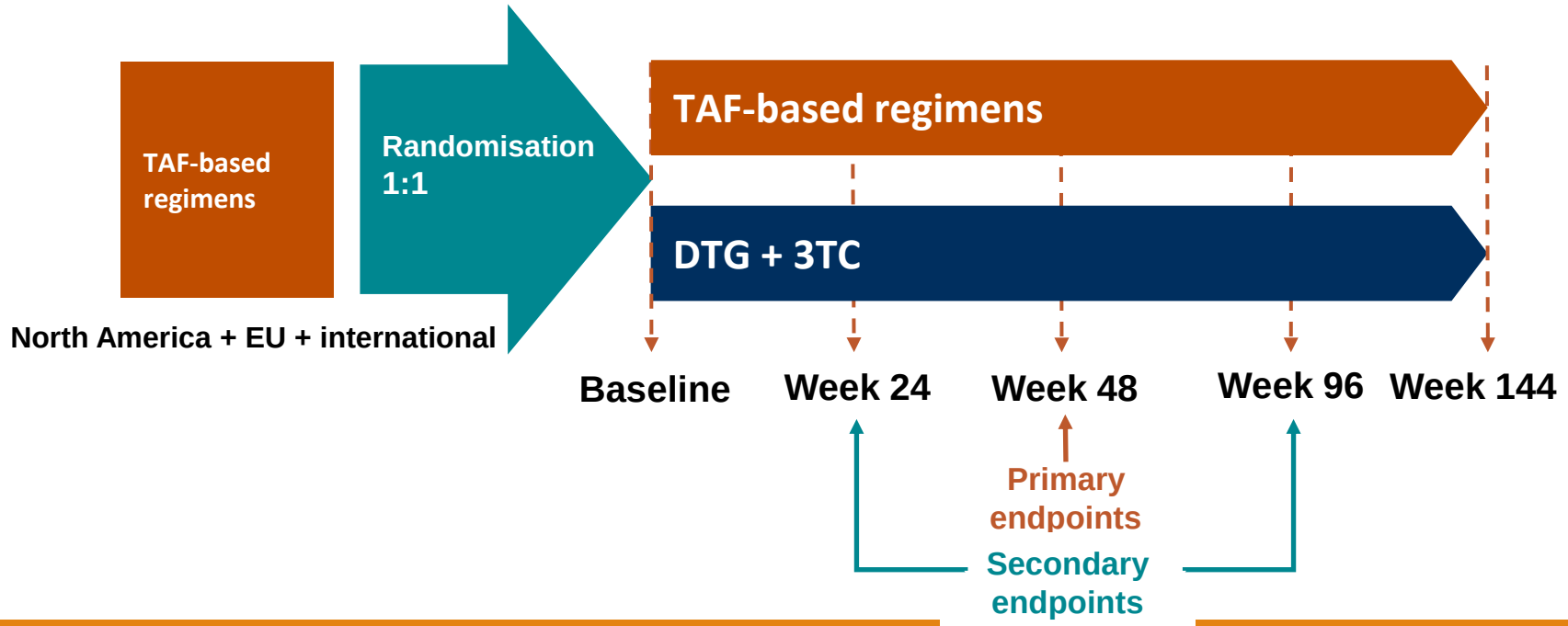
TANGO: Switch Study Design

Phase III, randomised, multicentre, parallel-group, non-inferiority study

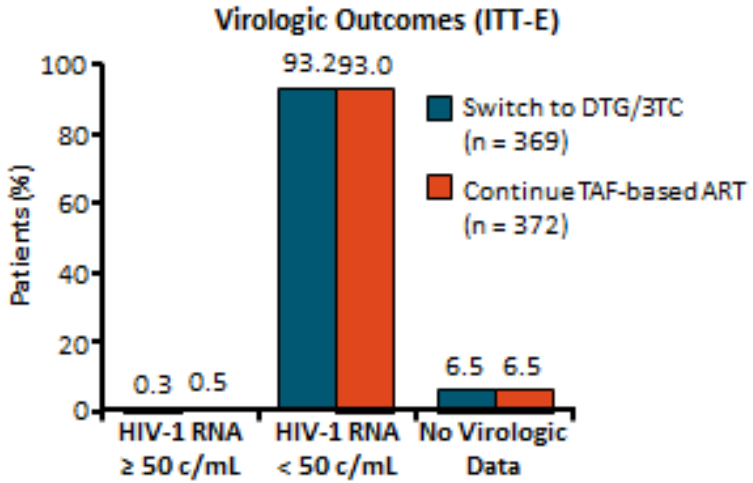
Objective: to demonstrate non-inferior antiviral activity of switching to DTG + 3TC QD compared with continuation of current ARV regimen over 48 weeks in HIV-1-infected ART-experienced subjects

Primary endpoint: the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the ITT-E population

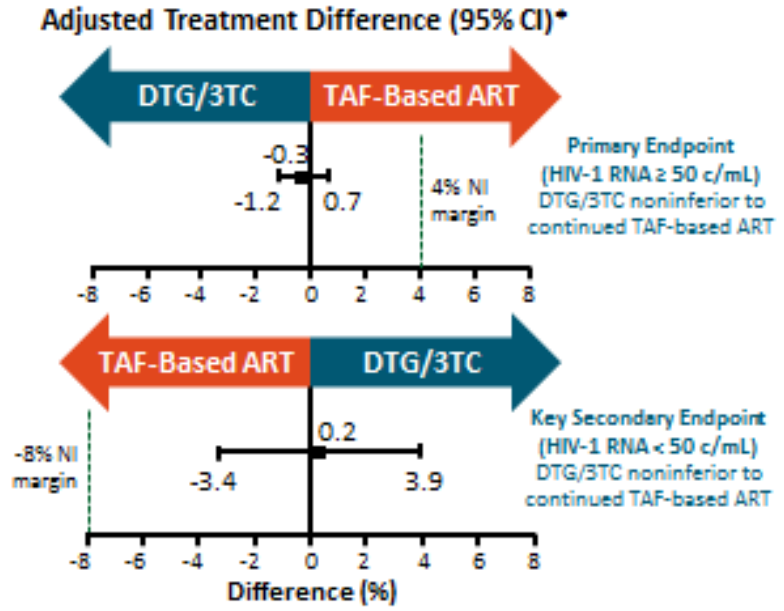
- non-inferiority margin = 4%; Week 48 primary endpoint



TANGO: Virologic Outcomes by FDA Snapshot at Wk 48



- No CVW in DTG/3TC arm, CVW in 1 (< 1%) patient in TAF-based ART arm; no resistance detected at failure
- All 7 patients (4 in DTG/3TC group, 3 in TAF-based ART group) with proviral M184V/I mutation at baseline maintained HIV-1 RNA < 50 c/mL at Wk 48



*Adjusted for baseline third agent class.

van Wyk. IAS 2019. Abstr WEAB0403LB.

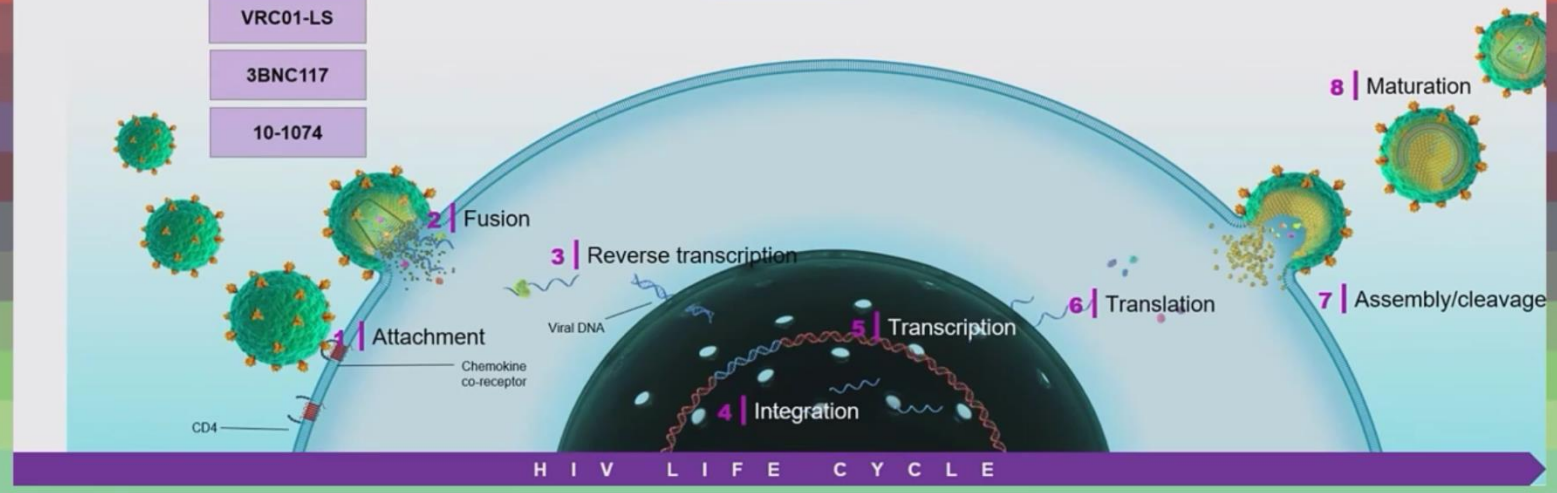
Slide credit: clinicaloptions.com

Y seguimos teniendo novedades, muy interesantes

Más opciones: nuevas formas de administración

Potential for LA or non-oral delivery

Entry/fusion inhibitor	bNAb	NRTI/NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor	TLR 7 agonist
Albuvirtide	UB-421	Islatravir	Elsulfavirine	MK-2048	ATV LA IM	GS-6207	GSK3739937	
Combinectin	PRO-140	TAF implant	RPV LA	RAL LA IM	RTV LA IM			
	VRC07-LS			CAB LA IM				
	VRC01-LS							
	3BNC117							
	10-1074							



Cabotegravir Long-Acting (LA) Injectable Nanosuspension

Bill Spreen, for ViiV Healthcare & GSK Development Team

17th HIV-HEPPK – June 2016

Studies of Long-Acting Cabotegravir + Long-Acting Rilpivirine

Study	Phase	Study Population	Switch Regimen
LATTE-2[1]	IIb	▪ ART-naive receiving CAB PO + ABC/3TC PO	CAB IM + RPV IM Q4W or Q8W
ATLAS[2]	III	▪ ART-experienced with **long-term suppression** on INSTI, NNRTI, or PI-based ART	CAB IM + RPV IM Q4W
FLAIR[3]	III	▪ ART-naive with **recent suppression** on DTG/ABC/3TC	CAB IM + RPV IM Q4W
ATLAS-2M[4]	III	▪ Suppressed on INSTI, NNRTI, or PI-based ART ▪ Participants with **long-term suppression** from ATLAS	CAB IM + RPV IM Q4W or Q8W

1. Margolis. Lancet. 2017;390:1499. 2. NCT02951052. 3. NCT02938520. 4. NCT03299049.

Slide credit: clinicaloptions.com

CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS IS NONINFERIOR TO MONTHLY DOSING: WEEK 48 RESULTS FROM THE ATLAS-2M STUDY

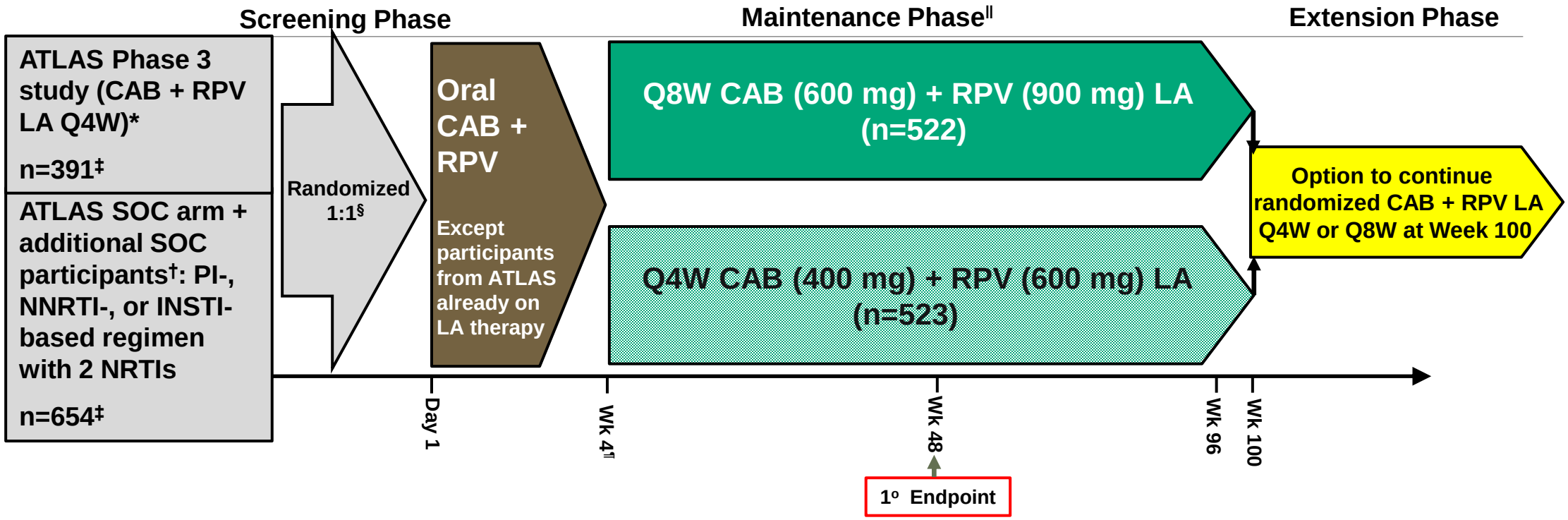
Edgar T. Overton[1], Gary Richmond[2], Giuliano Rizzardini[3], Hans Jaeger[4], Catherine Orrell[5], Firaya Nagimova[6], Fritz Bredeek[7], Miguel García Deltoro[8], Paul D. Benn[9], Yuanyuan Wang[10], Krischan J. Hudson[11], David A. Margolis[11], Kimberly Y. Smith[11], Peter E. Williams[12], William Spreen[11]

[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]Broward Health Medical Center, Fort Lauderdale, FL, USA; [3]Fatebenefratelli Sacco Hospital, Milan, Italy; [4]MVZ Karlsplatz, HIV Research and Clinical Care Center, Munich, Germany; [5]Desmond Tutu HIV Foundation, University of Cape Town Medical School, Cape Town, South Africa; [6]Republic Center for the Prevention and Control of AIDS and Infectious Diseases, Russia; [7]Metropolis Medical, San Francisco, CA, USA; [8]General Hospital of Valencia, Valencia, Spain; [9]ViiV Healthcare, Brentford, UK; [10]GlaxoSmithKline, Collegeville, PA, USA; [11]ViiV Healthcare, Research Triangle Park, NC, USA; [12]Janssen Research & Development, Beerse, Belgium

Conference on Retroviruses and Opportunistic Infections; March 8–11, 2020; Boston, Massachusetts

ATLAS-2M Study Design

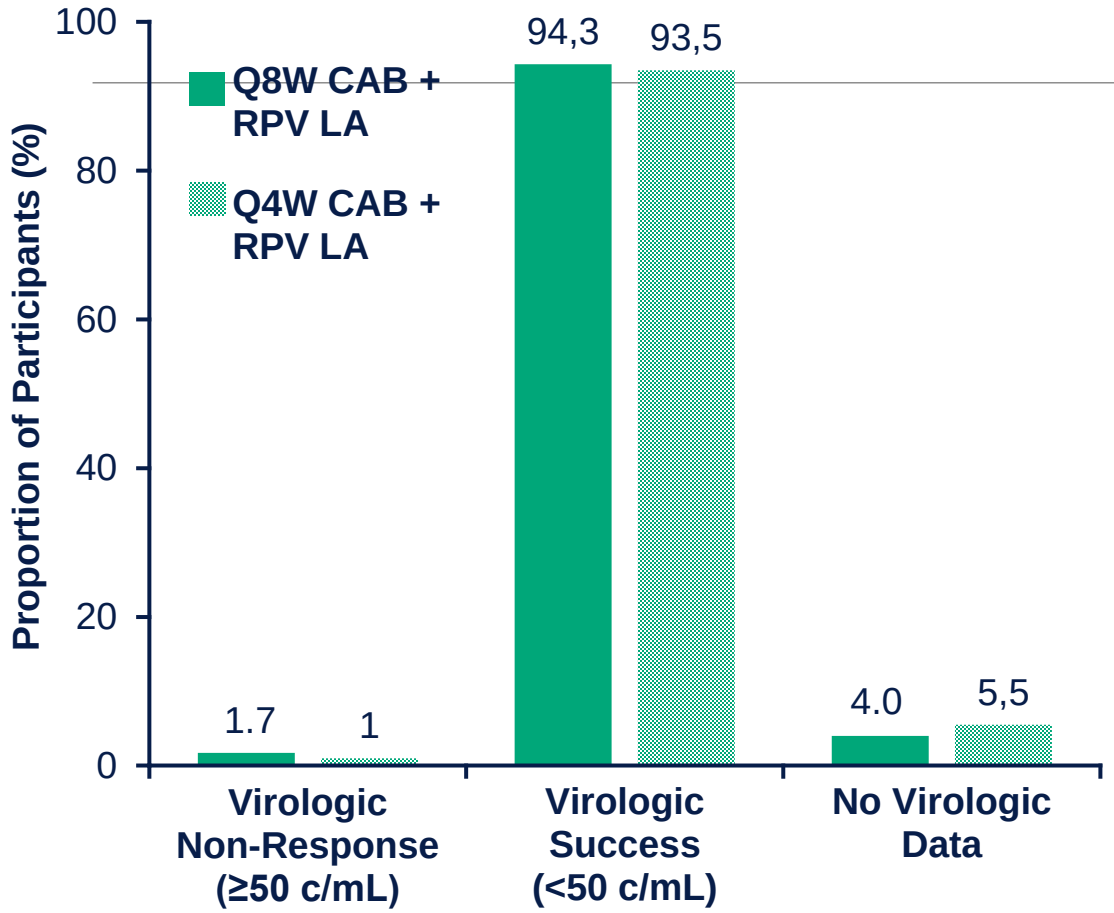
Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study

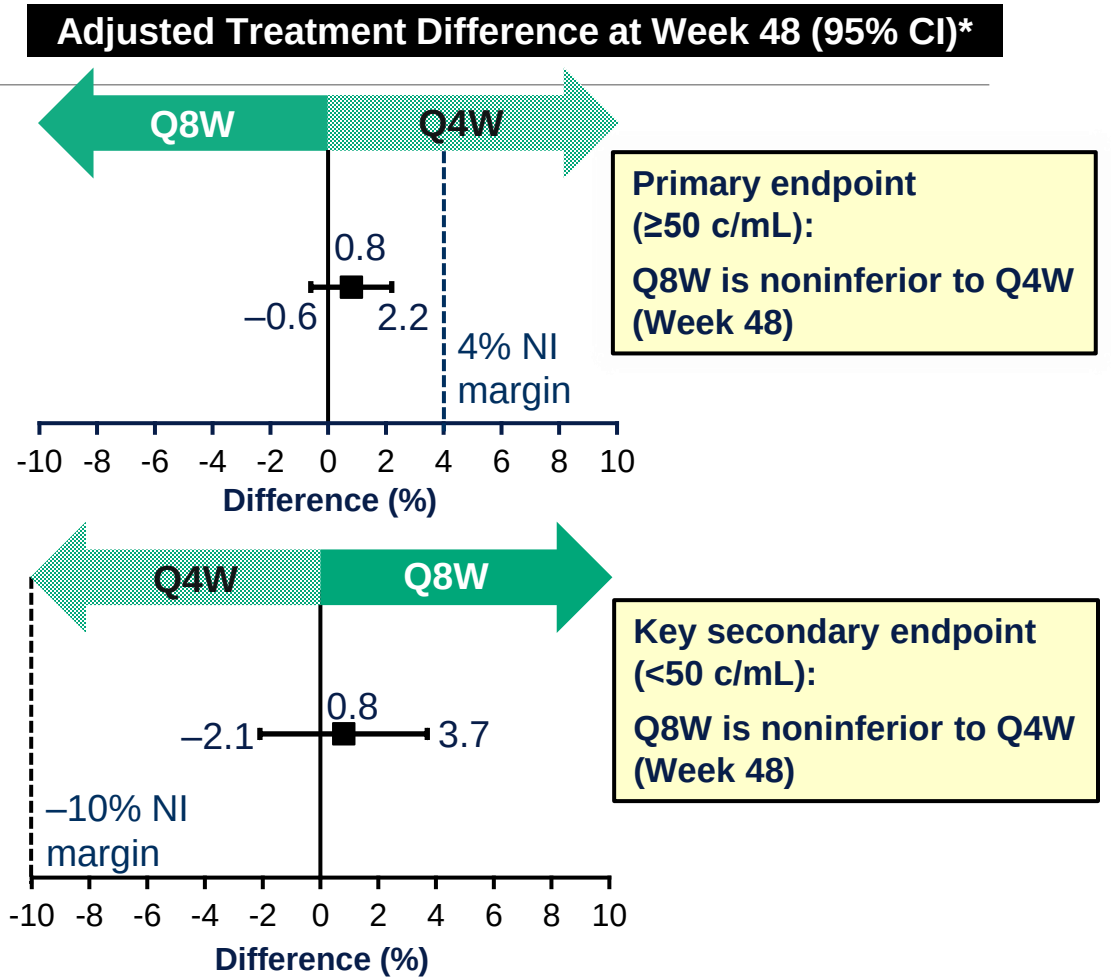


*Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA <50 c/mL at screening. †SOC participants not transitioning from the ATLAS study were to be on uninterrupted current regimen (either the 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- to 12-month window and one within 6 months prior to screening, was required. Participants were excluded if they had a history of virologic failure; evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) from prior genotype assay results. ‡Intent-to-treat exposed population. §1149 participants were screened, and 1049 participants were randomized. 4 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-week long-term follow-up if randomized regimen is not yet locally approved and commercially available. ¶Participants on oral lead-in treatment attended a Week 4 visit to assess tolerability. In participants in the Q4W arm who had an oral lead-in, the first LA dose was CAB 600 mg + RPV 900 mg.

ART, antiretroviral therapy; CAB, cabotegravir; IM, intramuscular; INSTI, integrase strand transfer inhibitor; ITT-E, intent-to-treat exposed; LA, long-acting; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care; Wk, week.

ATLAS-2M Virologic Snapshot Outcomes at Week 48 for ITT-E: Noninferiority Achieved for Primary and Secondary Endpoints





Participant numbers: n=522 Q8; n=523 Q4; CAB, cabotegravir; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; LA, long-acting; NI, noninferiority; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.

*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).

Overton et al. CROI 2020; Boston, MA. Presentation 3334.

ATLAS-2M Snapshot Outcomes at Week 48 (ITT-E Population)

Snapshot outcome, ITT-E, n (%)	Q8W (n=522)	Q4W (n=523)
HIV-1 RNA <50 c/mL at Week 48	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL at Week 48	9 (1.7)	5 (1.0)
Data in window not <50 c/mL	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reasons while not <50 c/mL	0	1 (0.2)
No virologic data	21 (4.0)	29 (5.5)
Discontinued for AE or death	9 (1.7)*	13 (2.5)†
Discontinued for other reasons	12 (2.3)‡	16 (3.1)§

*Discontinuations for AEs (event level) include Q8W: Injection site pain (n=2), injection site abscess, injection site discomfort, skin lesion, fatigue, acute hepatitis B, asthenia, presyncope, pancreatitis acute, headache, rash maculo-papular (all n=1). †Q4W: injection site pain (n=11), abnormal dreams (n=2), injection site swelling (n=2), hyperhidrosis (n=2), fatigue (n=2), injection site nodule, influenza, headache, acute hepatitis B, dizziness, glioblastoma, allergic reaction, transaminase increase, depression, chills, insomnia, myalgia, nausea, presyncope, pyrexia, sleep disorder, disturbance in attention (all n=1). ‡Q8W: Withdrawal by participant (n=4), investigator decision (n=4), lost to follow-up (n=2), protocol deviation (n=1), lack of efficacy (n=1). §Q4W: Withdrawal by participant (n=12), protocol-specified withdrawal criteria met (pregnancy) (n=3), protocol deviation (n=1).

AE, adverse event; ITT-E, intent-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

ATLAS-2M: Summary of Confirmed Virologic Failures

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs Observed at Failure	CVFs with IN RAMs*	IN RAMs Observed at Failure
Q8W	522	8 (1.5)	6/8	K101E, E138E/K, E138A, Y188L	5/8	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

- *Post hoc* baseline PBMC HIV-1 DNA results for Q8W arm:
  - 5/8 CVFs had pre-existing major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1/8 CVFs had a pre-existing major IN RAM (G140G/R)
  - 5/8 CVFs had L74I polymorphism (3 subtype A or A1, 1 subtype C, 1 complex subtype)
- 9/10 CVFs re-suppressed on fully active oral HAART (1/10 non-compliance on PI-based ART)
  - All CVFs retained phenotypic sensitivity to dolutegravir
- Factors contributing to CVF (e.g. baseline resistance and drug concentrations) are being further evaluated
  - PBMC HIV-1 DNA analysis underway across Phase 3 program

*For those with observed RAMs at failure: 6/6 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >2.5); CVF definition: 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. †Or mixture

ART, antiretroviral therapy; CVF, confirmed virologic failure; HAART, highly active antiretroviral therapy; IN, integrase; PBMC, peripheral blood mononuclear cell; PI, protease inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

ATLAS-2M Safety and Tolerability Was Similar Between Q8W and Q4W Dosing Arms: AEs Excluding ISRs

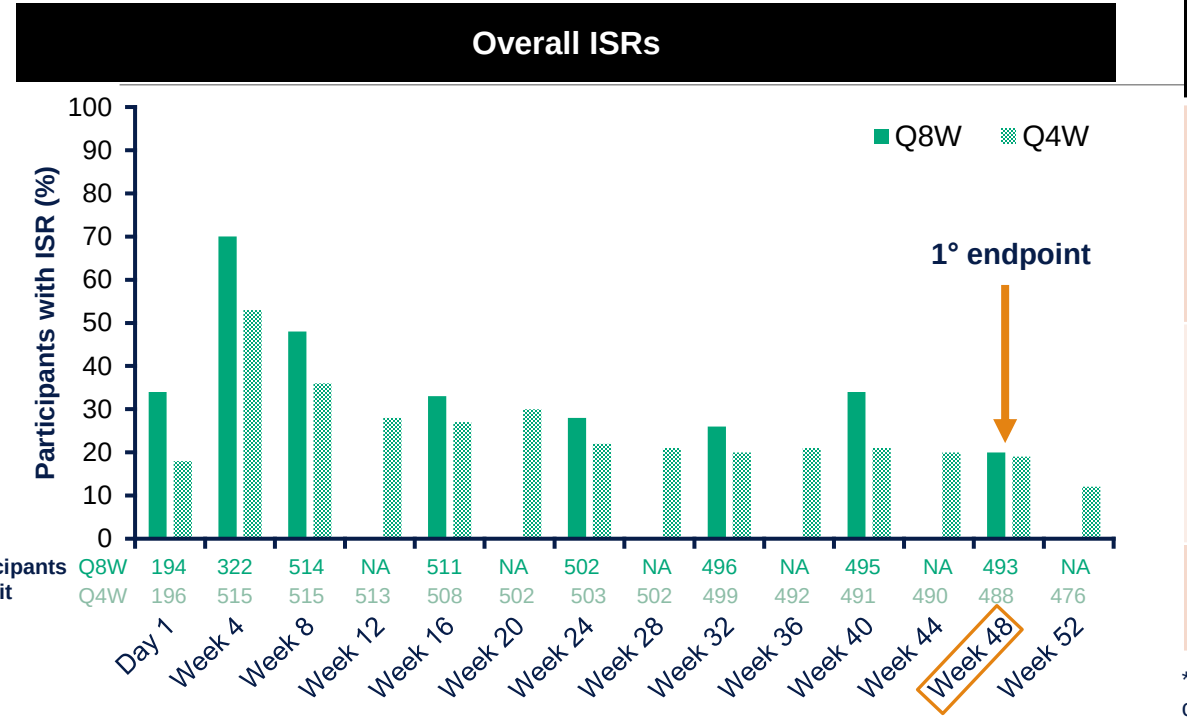
	Q8W (n=522) n (%)	Q4W (n=523) n (%)
Any AE	403 (77)	441 (84)
Drug-related AEs	109 (21)	125 (24)
Any Grade ≥3	29 (6)	30 (6)
Drug-related Grade ≥3	4 (<1)	5 (<1)
AEs leading to withdrawal	8 (2)	10 (2)
Drug-related AEs leading to withdrawal	5 (<1)	8 (2)
Any SAE	26 (5)	19 (4)
Drug-related SAEs*	2 (<1)	1 (<1)
Fatal SAEs†	1 (<1)	0
Drug-related fatal SAEs	0	0

*Drug-related SAEs were presyncope and acute pancreatitis in the Q8W group and allergic reaction in the Q4W group. †The fatal SAE was sepsis. The death was not considered related to study drug. A further participant died during screening (did not receive study drug).

- AEs were similar between the Q8W and Q4W dosing arms
- Overall, 96% of drug-related AEs were Grade 1–2
- Drug-related AEs led to withdrawal in 5 participants in the Q8W arm and 8 in the Q4W arm

AE, adverse event; ISR, injection site reaction; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event.

ATLAS-2M Injection Site Reactions



Note: Day 1 only included participants with prior CAB + RPV exposure due to the oral lead-in phase.

Outcome, n (%), ITT-E	Q8W (n=522)	Q4W (n=523)
Number of injections	8470	15,711
Number of ISR events (events/injections)*	2507 (30)	3152 (20)
Grade ≥3 – severe†	43 (<1)	48 (<1)
Injection site reactions‡		
Pain	2014 (24)	2567 (16)
Nodule	113 (1)	204 (1)
Discomfort	92 (1)	110 (1)
Withdrawals due to injection-related reasons, participant n (%)§	6 (1)	11 (2)

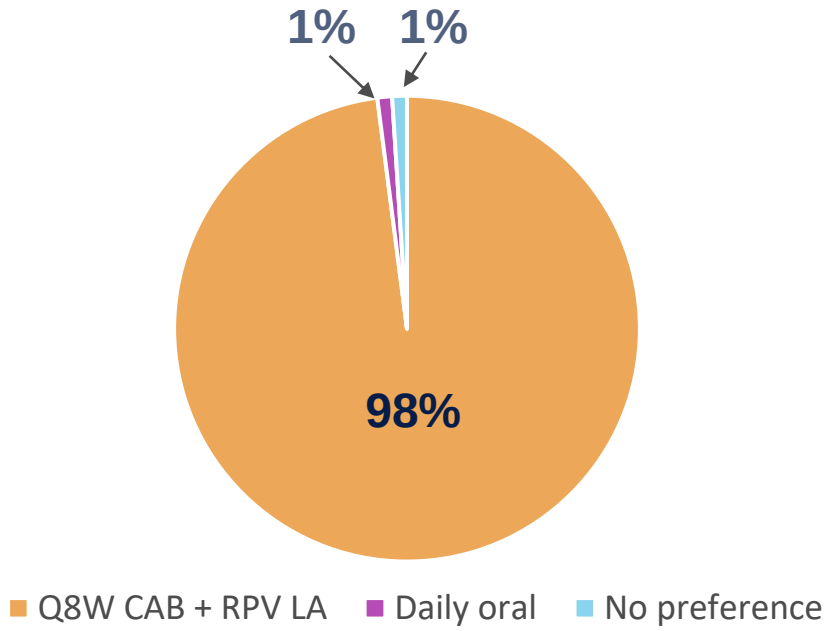
*All event-level ISR percentages are calculated from the total number of injections. Note: A single injection could result in more than one ISR. †There were no Grade 4 or Grade 5 ISRs. ‡ISRs occurring in >1% of injections in either the Q4W or Q8W arms are shown. §Q8W: 5 participants had an ISR leading to withdrawal and 1 participant withdrew consent from the study due to injection intolerability; Q4W: 5 participants had an ISR leading to withdrawal and 6 participants withdrew consent from the study due to injection intolerability.

- 24,181 injections were administered in total
  - <2% of participants discontinued due to injection-related reasons
- The majority (98%, 5568/5659) of ISRs were Grade 1–2, with a median duration of 3 days in both arms

AE, adverse event; ISR, injection site reaction; ITT-E, intent-to-treat exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

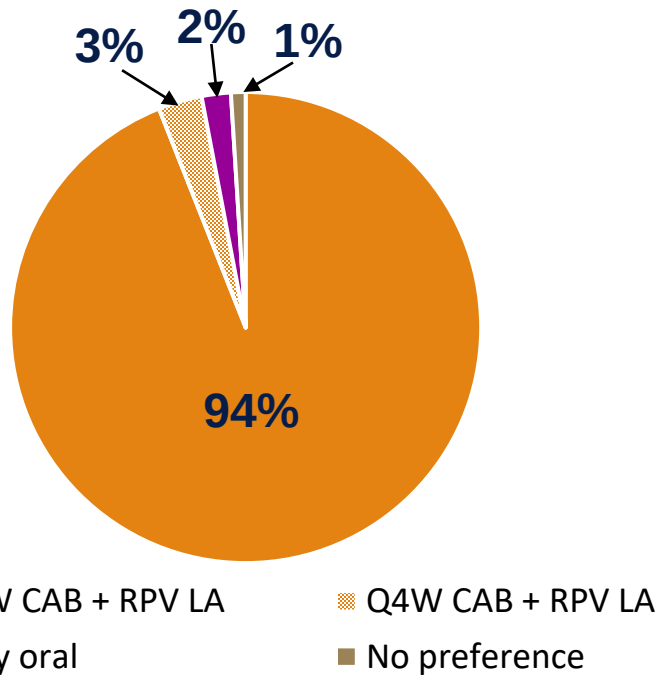
ATLAS-2M: Majority of Participants Preferred Q8W Dosing

Participants in Q8W arm from SOC (no prior Q4W experience)*



*306 participants responded to the preference question.

Participants in Q8W arm with prior Q4W experience in ATLAS†



†191 participants responded to the preference question.

Daily oral therapy refers to CAB + RPV oral therapy that was received during the oral lead-in period for either this study or the ATLAS study.

Percentages are calculated out of those participants with recorded response to the preference.

CAB, cabotegravir; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SOC, standard of care.

ATLAS-2M Week 48 Conclusions

Q8W dosing of CAB + RPV LA was highly efficacious and noninferior to Q4W dosing

- Virologic non-response (≥50 c/mL) was infrequent and similar between the two arms
- Virologic suppression was maintained in 94.3% and 93.5% of those in the Q8W and Q4W arms, respectively
- The rate of confirmed virologic failure was low overall (1%)

CAB + RPV LA was well tolerated with a comparable safety profile between arms

- ISRs were mostly Grade 1–2 (98%) with a median duration of 3 days

98% of participants preferred Q8W dosing of CAB + RPV LA treatment over oral therapy, and Q8W dosing was preferred by 94% of participants with prior Q4W experience

CAB + RPV LA, dosed every 2 months, is an innovative and effective treatment for maintenance of virologic suppression in people living with HIV

CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks.

What do patients want?

- ISR reported in 28.6% of all injections in FLAIR of which <1% led to treatment withdrawal
- High satisfaction rates with LA therapy reported across studies
- 98% of participants in ATLAS 2M preferred CAB + RPV LA over oral therapy

- 94% of the ATLAS 2M participants who had been on Q4 week dosing in ATLAS preferred Q8 week dosing

PLOS ONE

RESEARCH ARTICLE

Experiences with long acting injectable ART: A qualitative study among PLHIV participating in a Phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain

Deanna Kerrigan[1☯*], Andrea Mantsios[1☯], Miguel Gorgolas[2], Maria-Luisa Montes[3], Federico Pulido[4], Cynthia Brinson[5], Jerome deVente[6], Gary J. Richmond[7], Sarah W. Beckham[1‡], Paige Hammond[1‡], David Margolis[8], Miranda Murray[9]

PLOS ONE

RESEARCH ARTICLE

"A dream come true": Perspectives on long-acting injectable antiretroviral therapy among female sex workers living with HIV from the Dominican Republic and Tanzania

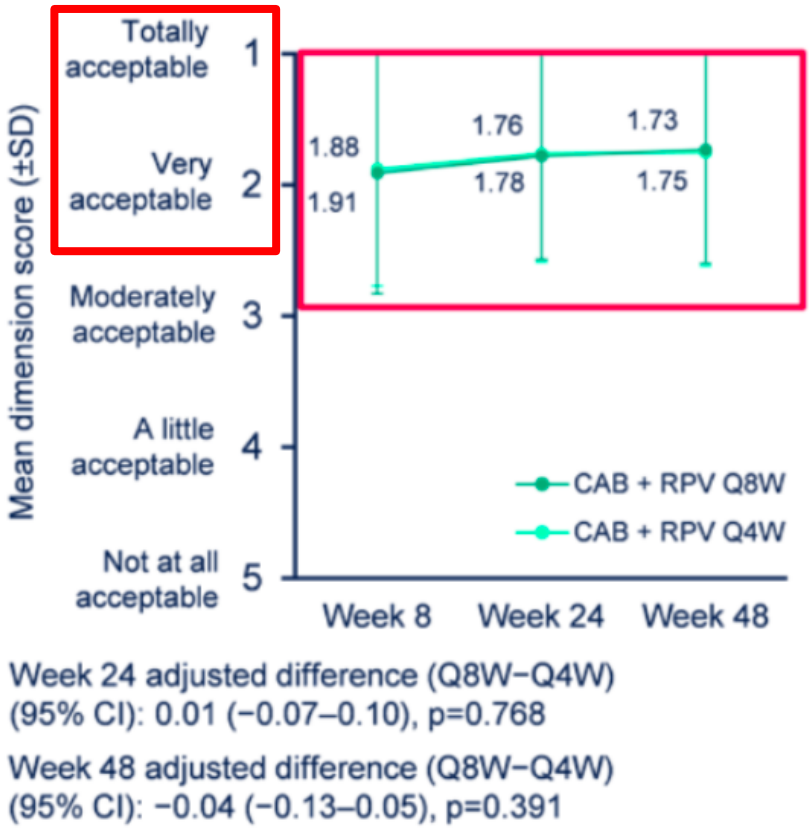
Deanna Kerrigan[1☯*], Tahilin Sanchez Karver[2☯], Ohvia Muraleetharan[3‡], Virginia Savage[4‡], Jessie Mbwambo[5], Yeycy Donastorg[6], Samuel Likindikoki[5], Martha Perez[6], Hoisex Gomez[6], Andrea Mantsios[7], Miranda Murray[8], S. Wilson Beckham[2], Wendy Davis[1], Noya Galai[2,9], Clare Barrington[4]

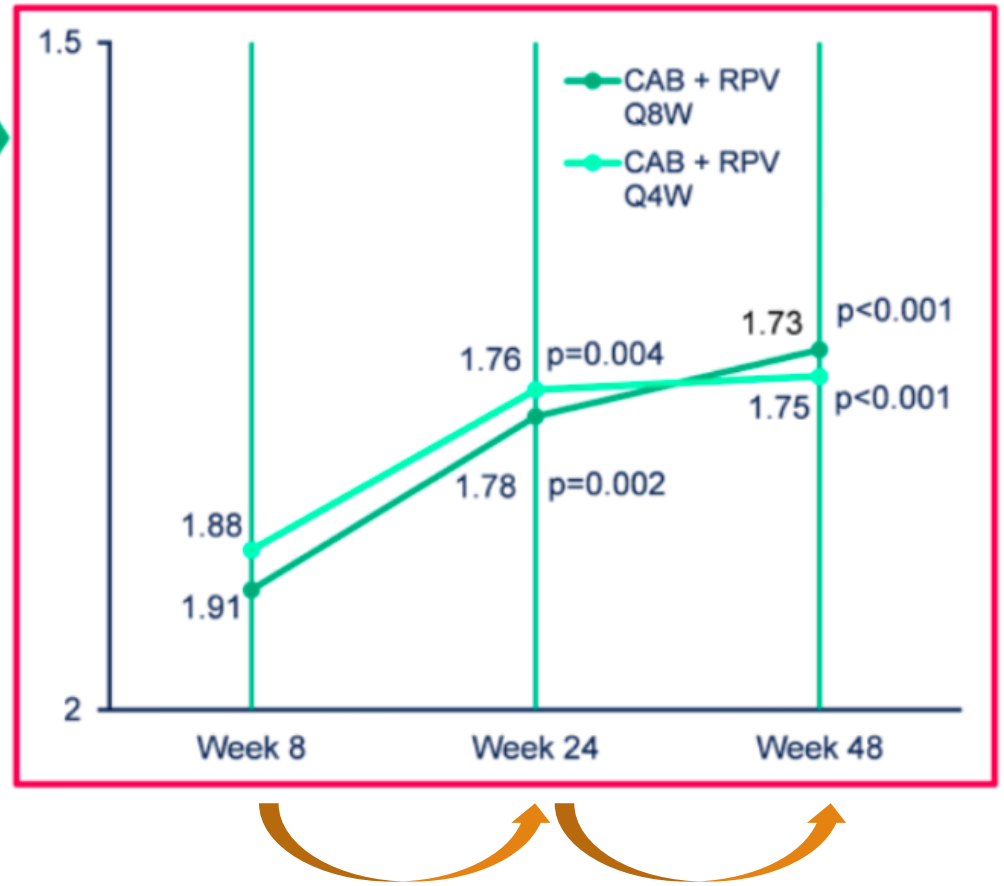
Crystal

Patient-Reported Outcomes Through Week 48 of ATLAS-2M: A Study of Long-Acting Cabotegravir and Rilpivirine Administered Every Four or Eight Weeks

V Chounta, ET Overton, A Mills, S Swindells, PD Benn, S Vanveggel, R van Solingen-Ristea, Y Wang, KJ Hudson, M Shaefer, DA Margolis, K Smith, W Spreen

Resultados: ACEPTACIÓN en el ISR (PIN)



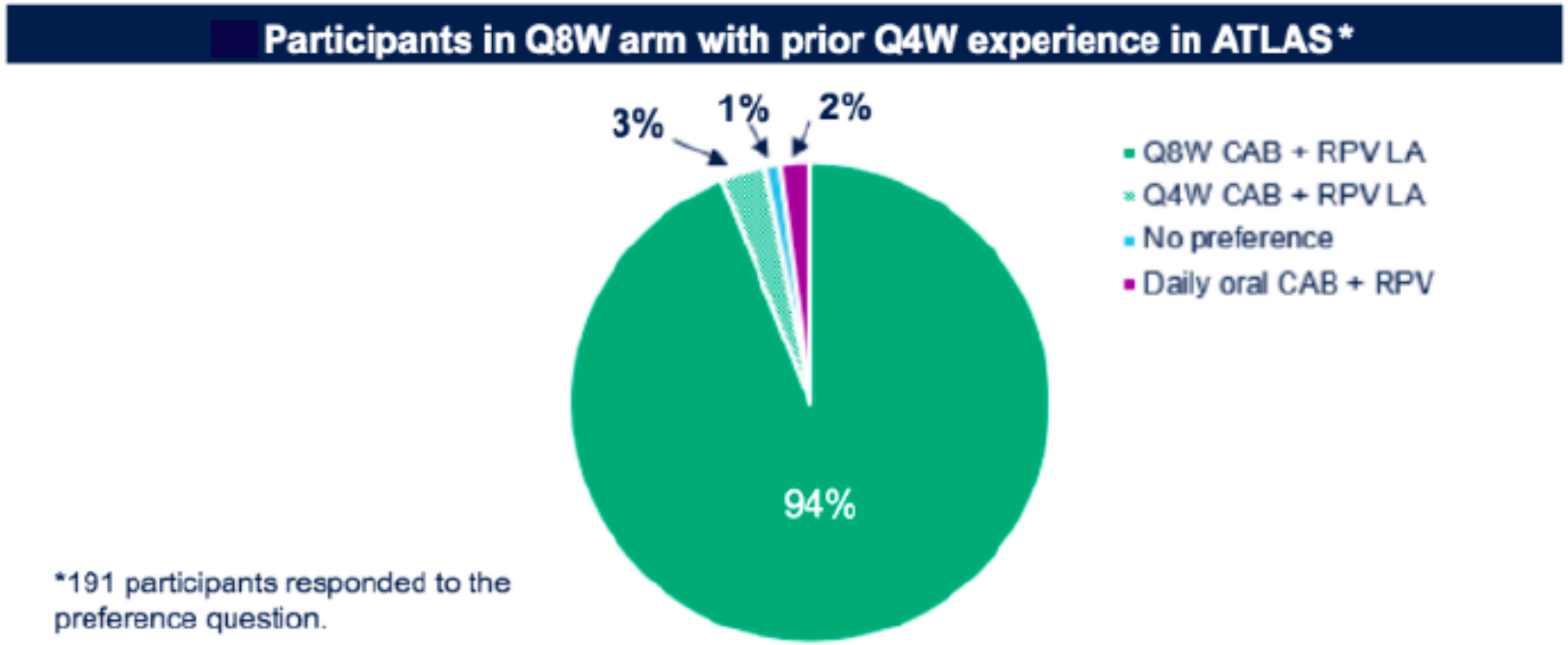


PRO, Patient Reported Outcomes; LA, long-acting; CAB, cabotegravir; RPV, rilpivirine; ISRs, injection-site reactions; Q8W, once every 8 weeks; Q4W, once every 4 weeks.

Aumenta la aceptación

Resultados: PREFERENCIAS- I

Preferencias en el Tratamiento LA en el grupo de administración Q8W



- Entre los participantes del grupo Q8W con exposición previa a CAB + RPV, el 94% (n = 179/191) prefirió la dosis de CAB + RPV Q8W frente a Q4W (3% [n = 6/191]) o la dosis oral diaria (2% [n = 4/191])

PRO, Patient Reported Outcomes; LA, long-acting; CAB, cabotegravir; RPV, rilpivirine; Q8W, once every 8 weeks; Q4W, once every 4 weeks.

ATLAS 2M Wk 48 PRO: Conclusiones

- CAB + RPV LA se asoció con altos niveles de satisfacción y aceptación con el tratamiento independientemente de si habían estado expuestos o no previamente a CAB + RPV LA

- De aquellos sin experiencia previa de CAB + RPV LA, la satisfacción y la aceptación al tratamiento con LA, en comparación con el tratamiento oral diario previo, aumentaron sustancialmente tanto ambos brazos Q8W y Q4W
- Para los participantes que hicieron la transición desde el grupo Q4W del estudio ATLAS, se mantuvieron altos niveles de satisfacción con el tratamiento después de más de 96 semanas con CAB + RPV LA
- La gran mayoría de los participantes prefirieron la dosificación Q8W y Q4W sobre la dosificación oral diaria, y la gran mayoría prefirió la pauta de Q8W versus la pauta Q4W

PRO, Patient Reported Outcomes; LA, long-acting; CAB, cabotegravir; RPV, rilpivirine; Q8W, once every 8 weeks; Q4W, once every 4 weeks;

Feasibility of implementing long-acting injectable anti-retroviral therapy to treat HIV: a survey of health providers from the 13 countries participating in the ATLAS 2-M trial

Deanna Kerrigan, Miranda Murray, Tahilin Sanchez Karver, Andrea Mantsios, Nicki Walters, Krischan Hudson, Emma Kaplan-Lewis, Federico Pulido, AC Bassa, David Margolis, Noya Galai

Skin cells at 20x magnification

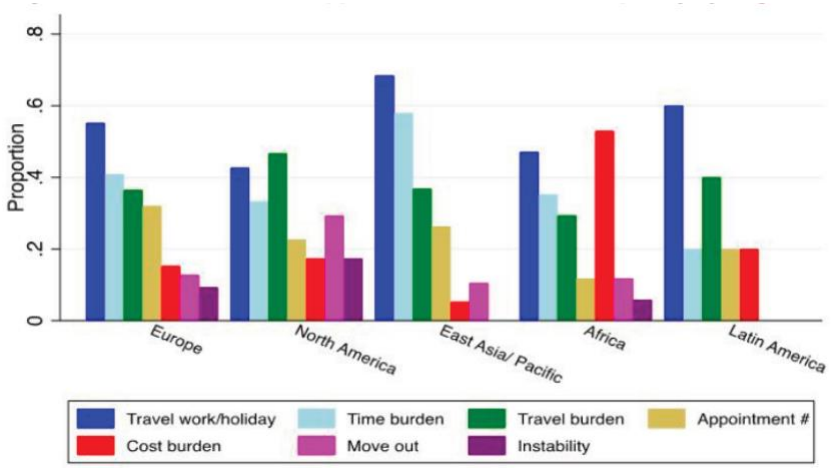
Resultados

Table 1. Characteristics of Participating Clinical Care Providers (N=293)

Variable	N	%
Provider characteristics		
Region		
Europe	179	61.1
North America	68	23.2
Asia/Pacific	18	6.1
Africa	16	5.5
Latin America	12	4.1
Role in clinic		
Physician	172	58.7
Nurse/PA	72	24.6
Pharmacist	11	3.8
Research staff	38	13.0
Prior trial involvement		
1-2 clinical trials	155	52.9
3+ clinical trials	138	47.1
Injection experience		
Yes	121	43.1
No	160	56.9

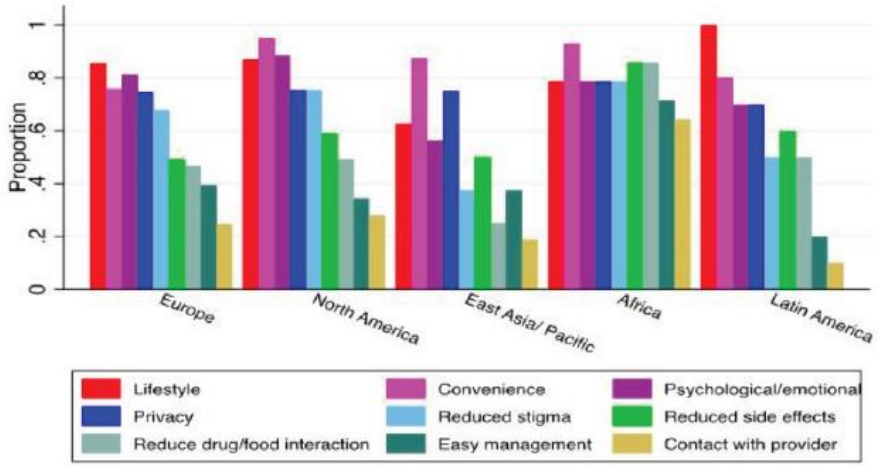
Resultados: feasibility

Barreras del Long Acting



- Barreras principals: la falta de adherencia a las visitas: tiempo empleado en el viaje, tiempo empleado en la visita, barreras logísticas
- Coste: Barrera reportada en Africa

Beneficios del Long Acting



- Beneficios: Privacidad, estilo de vida, Comodidad

Resultados: Preocupaciones del clínico (cont.)

	N (293)	%
Patients not returning to clinic on time for injection appointments	224	79.7
Risk of resistance for patients not adherent to injections	195	69.4
Patients moving out of the area	182	64.8
Patients switching to a different provider	154	54.8
Drug interactions and comorbidities (e.g. TB, HCV)	138	49.1
Taking a patient off CAB LA + RP LA and switching to oral ART	120	42.7
The oral lead-in phase before starting injections	68	24.2

- Focalizado en la adherencia a los horarios de inyección:
  - Pacientes que no regresan a la cita prevista para la inyeccion (80%)
  - Riesgo de Resistencia debido a la falta de adherencia a la cita para la inyección (69%)
  - Miedo de que los pacientes se muden (65%)

Conclusiones

- Los resultados del estudio sugieren un éxito en la implentación del LA
- Las barreras logísticas y las preocupaciones de los clínicos se centran en la pérdida de adherencia a las vistas
- Hay por tanto retos logísticos que superar para conseguir beneficios en el tratamiento de los pacientes
- La privacidad se informó como un beneficio en la mayoría de las regiones.
- En Europa los beneficios otorgados al long acting son sobre todo la conveniencia y aquellos de carga emocional

Otros long acting

Additional Longer-Acting Investigational Agents (Phase II/III)

Agent	MoA	Phase	Implications
3BNC117[1,2]	Anti-CD4 receptor mAb	II	▪ Studies ongoing in treatment-experienced and naive pts
TMC278 LA[3]	LA injectable RPV (IM)	II	▪ Potential as long-acting injectable (Q8W)
UB-421[4]	Anti-CD4 receptor mAb	II	▪ Studied as possible ART alternative for maintenance therapy in suppressed pts
VRC01[5,6]	Anti-CD4 receptor mAb	II	▪ Phase II PrEP and treatment trials ongoing

1. Caskey M, et al. Nature. 2015;522:487-491. 2. ClinicalTrials.gov. NCT03041012. 3. Bekker L-G, et al. CROI 2017. Abstract 421LB. 4. Wang C-Y, et al. CROI 2017. Abstract 450LB. 5. ClinicalTrials.gov. NCT02716675. 6. ClinicalTrials.gov. NCT02568215.

Slide credit: clinicaloptions.com

P011: First-in-Class NRTTI Islatravir + Doravirine vs DOR/3TC/TDF in Treatment-Naive Adults

International, randomized, double-blind phase IIb trial

ART-naive patients ≥ 18 yrs of age with HIV-1 RNA ≥ 1000 copies/mL, CD4+ cell count ≥ 200 cells/mm^3, no ARV drug resistance, no active HCV or HBV coinfection (N = 121)

Stratified by HIV-1 RNA ≤ vs > 100,000 c/mL

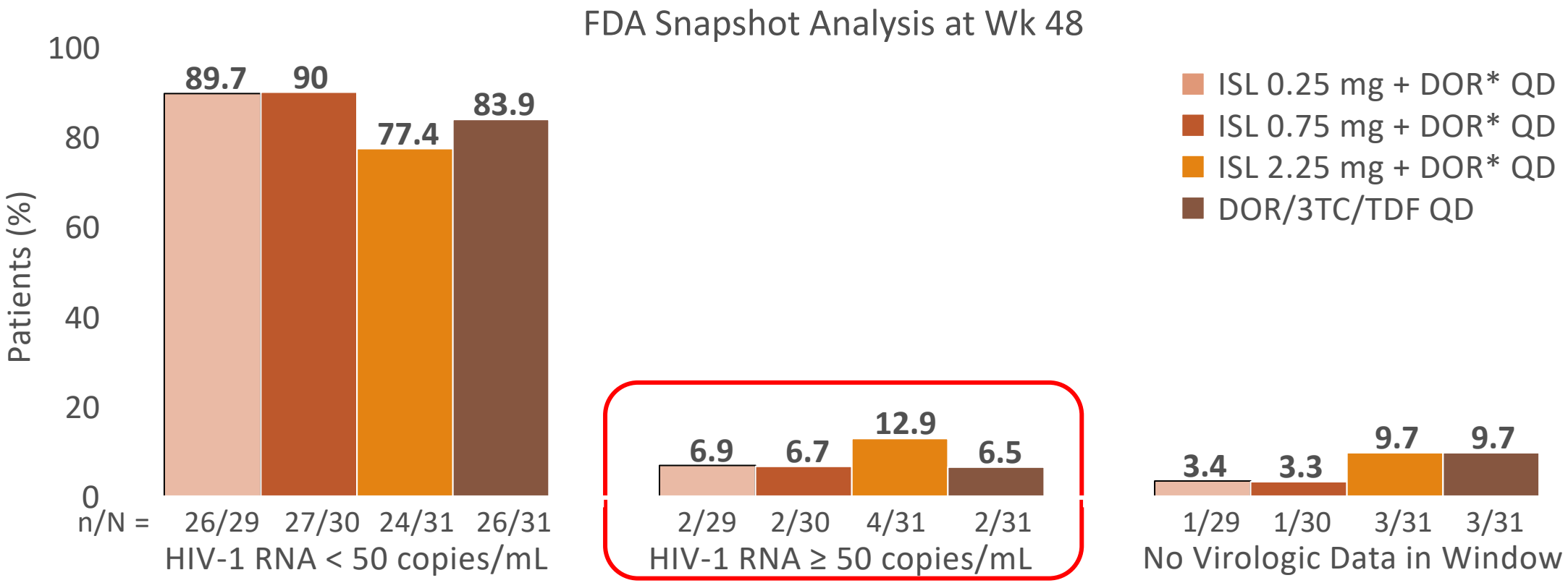
	Wk 24	***Wk 48 Current Analysis***	***Wk 192***
ISL 0.25 mg QD + DOR QD + 3TC QD* + DOR/3TC/TDF placebo (n = 29)		**ISL 0.25 mg QD** + DOR QD (n = 29)	
ISL 0.75 mg QD + DOR QD + 3TC QD* + DOR/3TC/TDF placebo (n = 30)		**ISL 0.75 mg QD + DOR QD** (n = 30)	
ISL 2.25 mg QD + DOR QD + 3TC QD* + DOR/3TC/TDF placebo (n = 31)		**ISL 2.25 mg QD + DOR QD** (n = 31)	
DOR/3TC/TDF + ISL/DOR/3TC placebo (n = 31)		**DOR/3TC/TDF** (n = 31)	

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

DeJesus. AIDS 2020. Abstr OAB0305.

Slide credit: clinicaloptions.com

P011 Study: ISL + DOR vs DOR/3TC/TDF in Treatment-Naive Adults



*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during the Wk 24-48 period of the study.

P011: Protocol Defined Virologic Failure at Wk 48

HIV-1 RNA levels at second assessment were < 80 copies/mL in all patients with PDVF; no patient met criteria for resistance testing (HIV-1 RNA > 400 copies/mL)

No evidence that PDVF was associated with drug pharmacokinetics

	ISL (0.25 mg) + DOR* QD	ISL (0.75 mg) + DOR* QD	ISL (2.25 mg) + DOR* QD	DOR/3TC/TDF QD
	N=29	N=30	N=31	N=31
Protocol Defined Virologic Failure				
Non responder, n (%)	0 (0)	0 (0)	1 (3.2)	0 (0)
Rebounder with HIV-1 RNA >50 copies/mL, n (%)	2 (6.9)	2 (6.7)	0 (0)	1 (3.2)
Rebounder with HIV-1 RNA >200 copies/mL, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Details on participants with HIV-1 RNA ≥ 50 copies/mL not classified as PDVF				
Early Discontinuation, n (%)	0 (0)	0 (0)	3 (9.7)	1 (3.2)
Reasons for Early Discontinuation			2 lost to follow-up, 1 participant withdrawal	1 protocol violation for exclusionary criteria

Orkin. AIDS 2020. Abstr OAB0302.

Islatravir + Doravirine: Adverse Events Through Wk 48

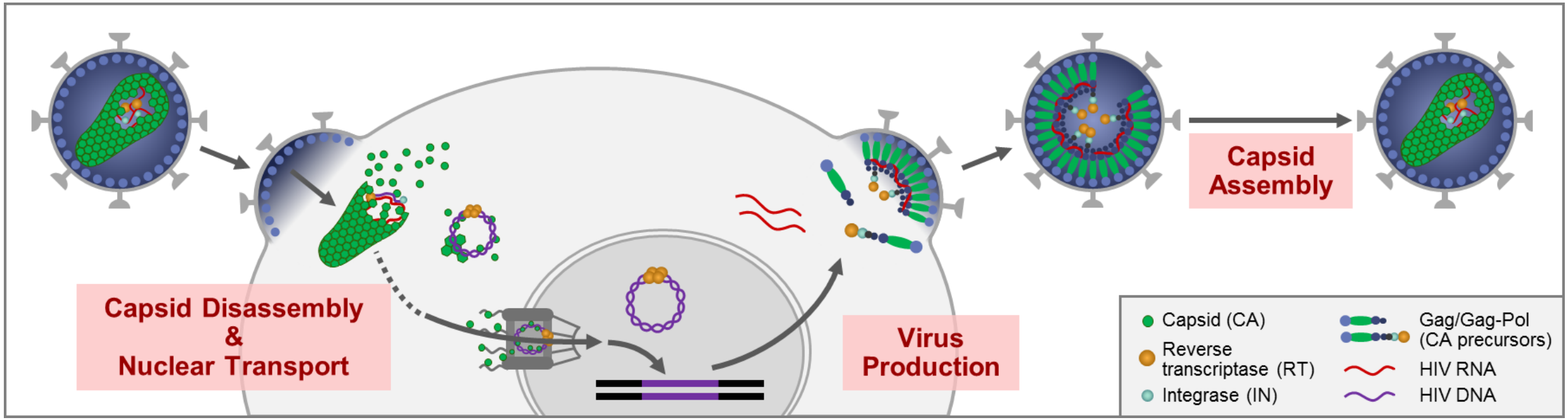
	ISL 0.25 mg + DOR* QD	ISL 0.75 mg + DOR* QD	ISL 2.25 mg + DOR* QD	Combined ISL Groups	DOR/3TC/TDF QD
Number (%) of Participants	N=29	N=30	N=31	N=90	N=31
with ≥1 AE	21 (72.4)	26 (86.7)	19 (61.3)	66 (73.3)	24 (77.4)
with drug-related AE	0 (0.0)	3 (10.0)	4 (12.9)	7 (7.8)	6 (19.4)
with serious AE	1 (3.4)	2 (6.7)	0 (0.0)	3 (3.3)	2 (6.5)
discontinued due to AE	0 (0.0)	0 (0.0)	2 (7.4)	2 (2.2)	1 (3.2)
with moderate or severe AE	7 (24.1)	13 (43.3)	12 (38.7)	32 (35.6)	15 (48.4)

*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.

Majority of diarrhea, headache events were mild, transient, and not related to study drug

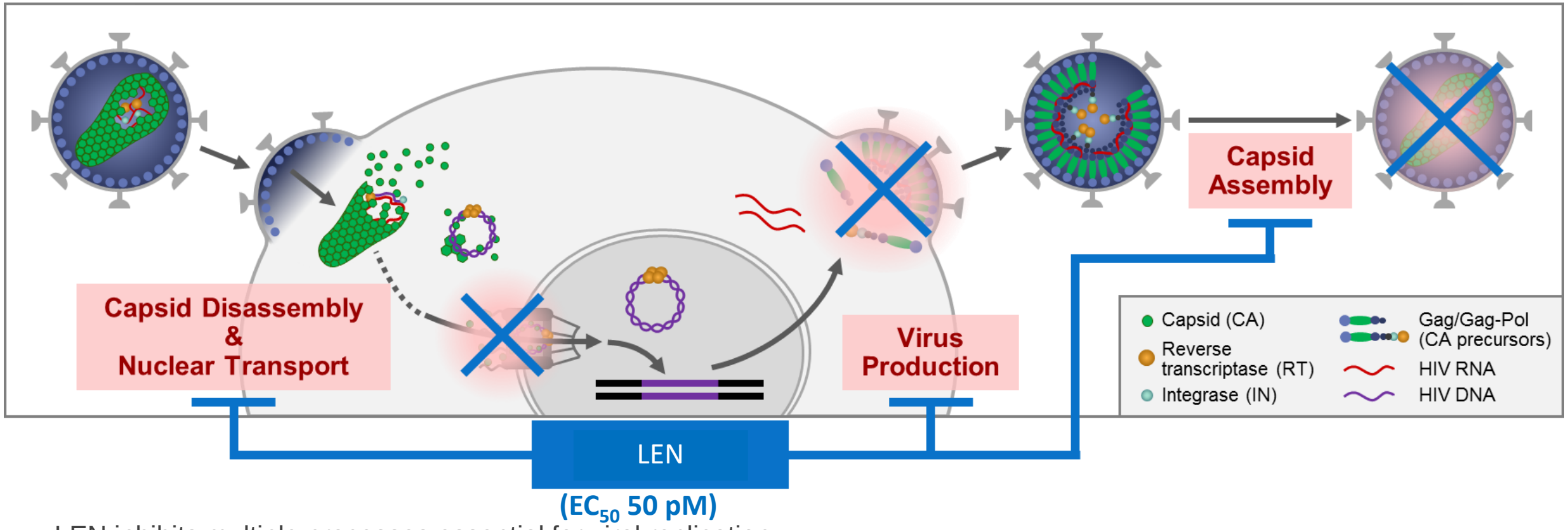
Elevated creatinine kinase was most common laboratory abnormality; no dose-related trends; 9 of 10 cases associated with physical exertion and all resolved

Lenacapavir: First-in-Class HIV Capsid Inhibitor



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

Lenacapavir: First-in-Class HIV Capsid Inhibitor



LEN inhibits multiple processes essential for viral replication

LEN modulates the stability and/or transport of capsid complexes

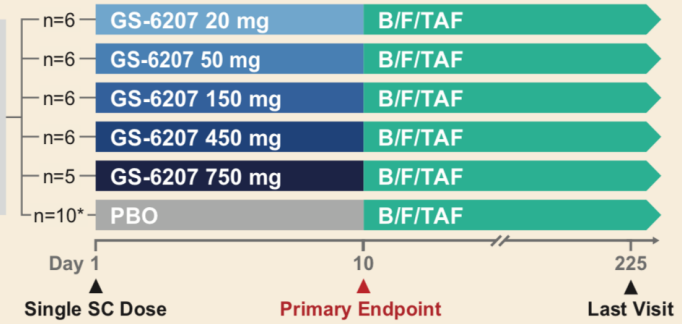
EC50, half-maximum effective concentration; Gag, group-specific antigen; Pol, polymerase.

Dose-dependent Antiviral Activity of Subcutaneous, Long-acting GS-6207 (Phase 1b)[1]

Study Design

Key inclusion criteria:

- HIV-1 RNA 5000–400,000 copies/mL
- CD4+ cell count >200 cells/mm³
- Naïve to CA and IN inhibitors
- Experienced off ARV medications ≥12 months

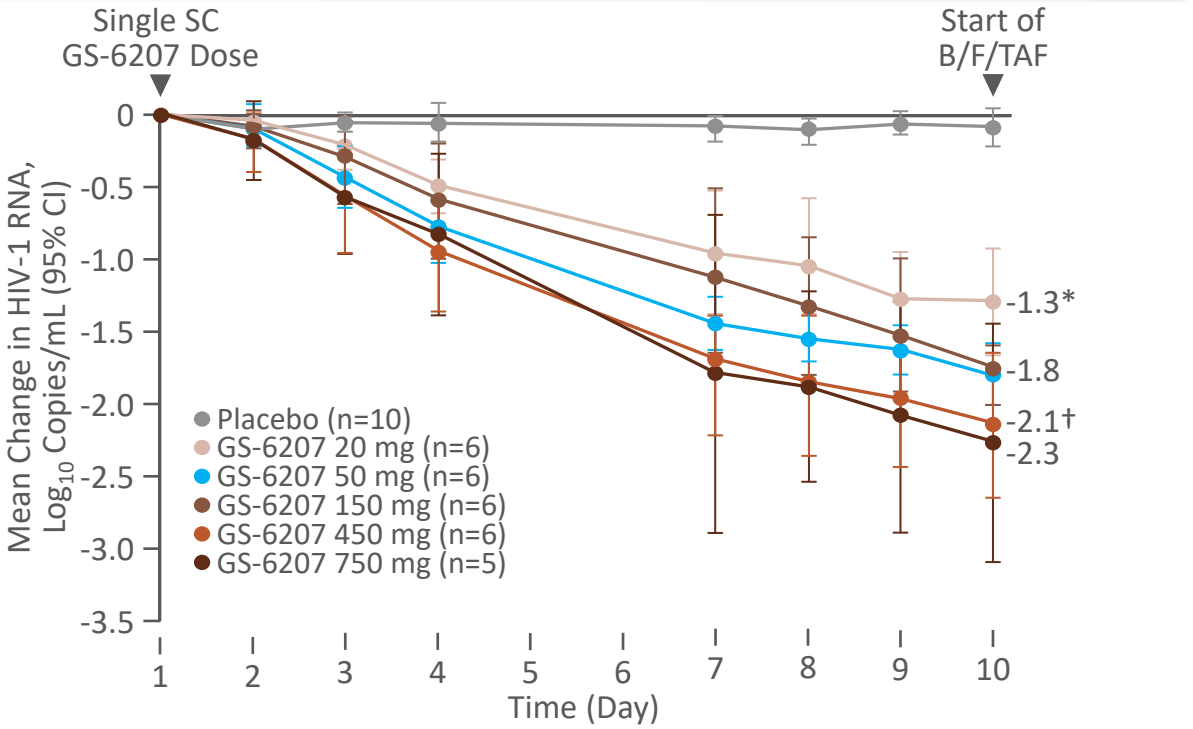


*The 10 participants receiving placebo (PBO) consisted of 2 from each dose cohort; participants were randomized to receive either active treatment (n=6, except n=5 for 750-mg cohort) or PBO (n=2). ARV, antiretroviral; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation-4.

Other Findings

Site-directed mutagenesis → GAG mutations had no effect on potency of GS-6207

GS-6207 oral tablets can be administered without regard to food[3]



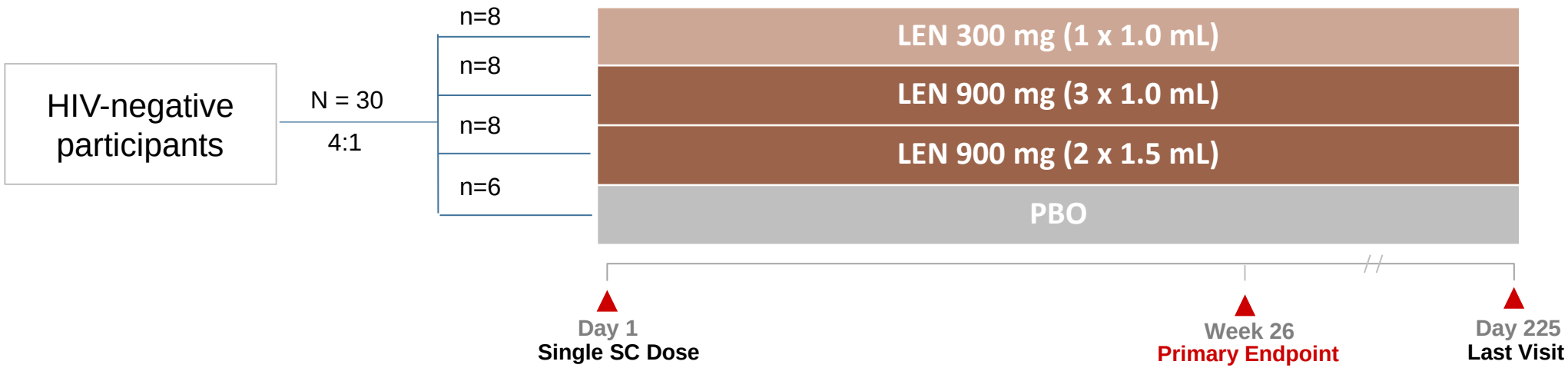
* Change (mean) on Day 10 in 20-mg cohort was -1.3 log_{10} copies/mL, while maximal change (mean) through Day 10 was -1.4 log_{10} copies/mL;
† Change (mean) on Day 10 in 450-mg cohort was -2.1 log_{10} copies/mL, while maximal change (mean) through Day 10 was -2.2 log_{10} copies/mL

These results support further clinical evaluation of GS-6207 as a long-acting antiretroviral agent, and of oral GS-6207 for use in PLWH.

Adapted from: 1. Daar E, et al. Presented at CROI 2020; Poster #469; 2. Margot NA, et al. Presented at CROI 2020; Poster #529; and 3. Begley R, et al. Presented at CROI 2020; Poster #470.

Study DesignGS-US-200-4538: Lenacapavir Safety and PK in Healthy Volunteers

Phase 1, blinded, placebo-controlled, randomized, single ascending dose study in healthy volunteers (N=30)



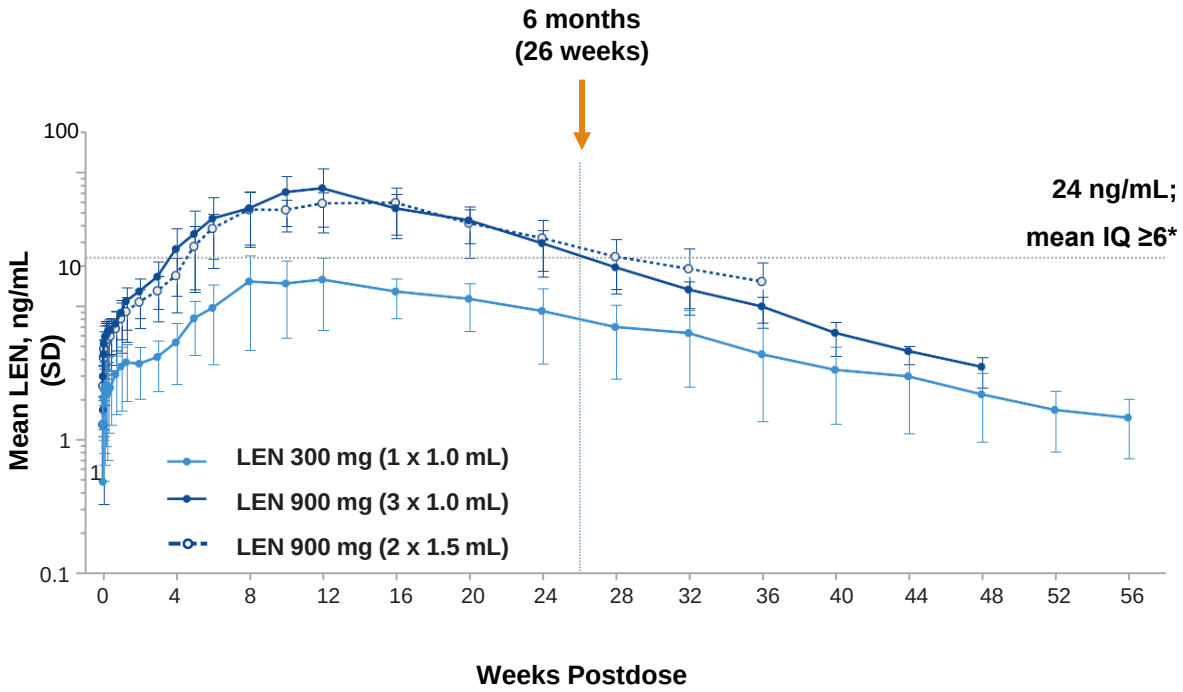
Primary Objective

- To assess the safety, tolerability, and PK of escalating single doses of subcutaneous LEN

Begley R, et al. AIDS 2020. PEB0265

Lenacapavir PK Study: PK & Safety of SC LEN

Mean (SD) LEN Single Dose Plasma Concentration-Time Profiles



- Single SC doses of up to 900 mg LEN were generally safe and well tolerated
  - No serious or Grade 2, 3, or 4 AEs related to study drug†
  - No AEs leading to discontinuation
  - ISRs were common (80%) and all mild
- Target concentrations sustained for ≥6 months after single 900 mg dose
  - Slow release necessitates oral PK loading dose prior to first injection

Preliminary PK and safety data support continued clinical development of long-acting SC LEN in conjunction with an oral LEN loading dose

ISRs, injection site reactions. IQ: Ratio of LEN plasma concentration/EC_{95} *paEC$_{95}$ =1.16 ng/mL (macrophages), 2.32 ng/mL (CD4+ T cells), and 3.87 ng/mL (MT-4 cells)
†One participant had Grade 3 AEs of abscess (also serious AE), cellulitis, and MRSA infection, none of which were related to LEN

Begley R, et al. AIDS 2020. PEB0265

Lenacapavir PK Study: PK & Safety of SC LEN

AEs Occurring in ≥ 5 Patients, n (%)	LEN 300 mg or PBO, 1 x 1.0 mL (n = 10)	LEN 900 mg or PBO, 3 x 1.0 mL (n = 10)	LEN 900 mg or PBO, 2 x 1.5 mL (n = 10)	Total LEN or PBO (n = 30)
Injection-site induration	3 (30)	8 (80)	10 (100)	21 (70)
Injection-site pain	0	6 (60)	8 (80)	14 (47)
Injection-site erythema	1 (10)	5 (50)	4 (40)	10 (33)
Headache	3 (30)	4 (40)	3 (30)	10 (33)
Injection-site swelling	0	4 (40)	4 (40)	8 (27)
Injection-site nodule	2 (20)	3 (30)	0	5 (17)

ISRs occurred in 80% of patients; all grade 1 severity, most resolved within days

No patient experienced grade 2, 3, or 4 AEs

Grade 3/4 laboratory abnormalities occurred in 7 (23%) patients; none was of clinical relevance

No discontinuations due to AEs

Nuevos tratamientos en investigación

Agent	Class	Development Stage	Parenteral long acting formulation	Targeting MDR population	Two-Drug Approach
Fostemsavir	Attachment inhibitor	FDA approved	✗	✔	✗
Islatravir (MK-8591)	Nucleoside reverse transcriptase translocation inhibitor	Phase 2/3	✔	✔	✔
Lenacapavir (GS-6207)	Capsid Inhibitor	Phase 2/3	✔	✔	✔
Cabotegravir plus rilpivirine LA	Integrase inhibitor + NNRTI	FDA resubmission	✔	✗	✔
(e.g., VRC07-523 LS,10-1074, SAR441236)	Broadly neutralizing antibodies	Phase 1/2	✔	✗	✔
Leronlimab (PRO 140)	Humanized monoclonal antibody against CCR5	FDA partial submission	✗/✔	✔	✗

¿perspectivas terapéuticas?

- De qué punto partimos
- Qué hay disponible
- Qué nos gustaría tener

Gracias por su atención