Nuevos fármacos en el tratamiento del VIH:
-Rilpivirina
-Dolutegravir
-Elvitegravir-Cobicistat

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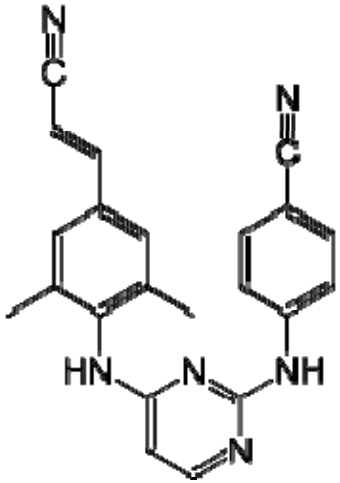
Madrid, 9 de mayo de 2013

CONFLICTOS DE INTERESES:

- JANSSEN
- GILEAD

RILPIVIRINA (RPV)



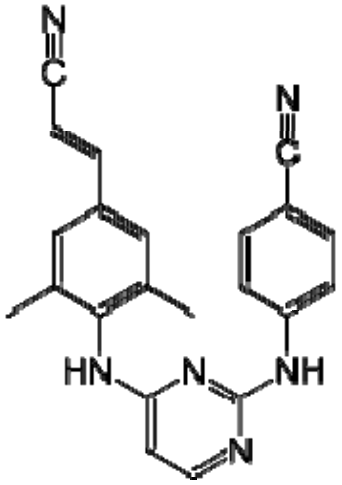
1) Generalidades

2) Naïve
(ECHO y THRIVE, STAR)

3) Pretratado
(SPIRIT y GS-111)

RILPIVIRINA (RPV)

1) Generalidades



2) Naïve
(ECHO y THRIVE, STAR)

3) Pretratado
(SPIRIT y GS-111)

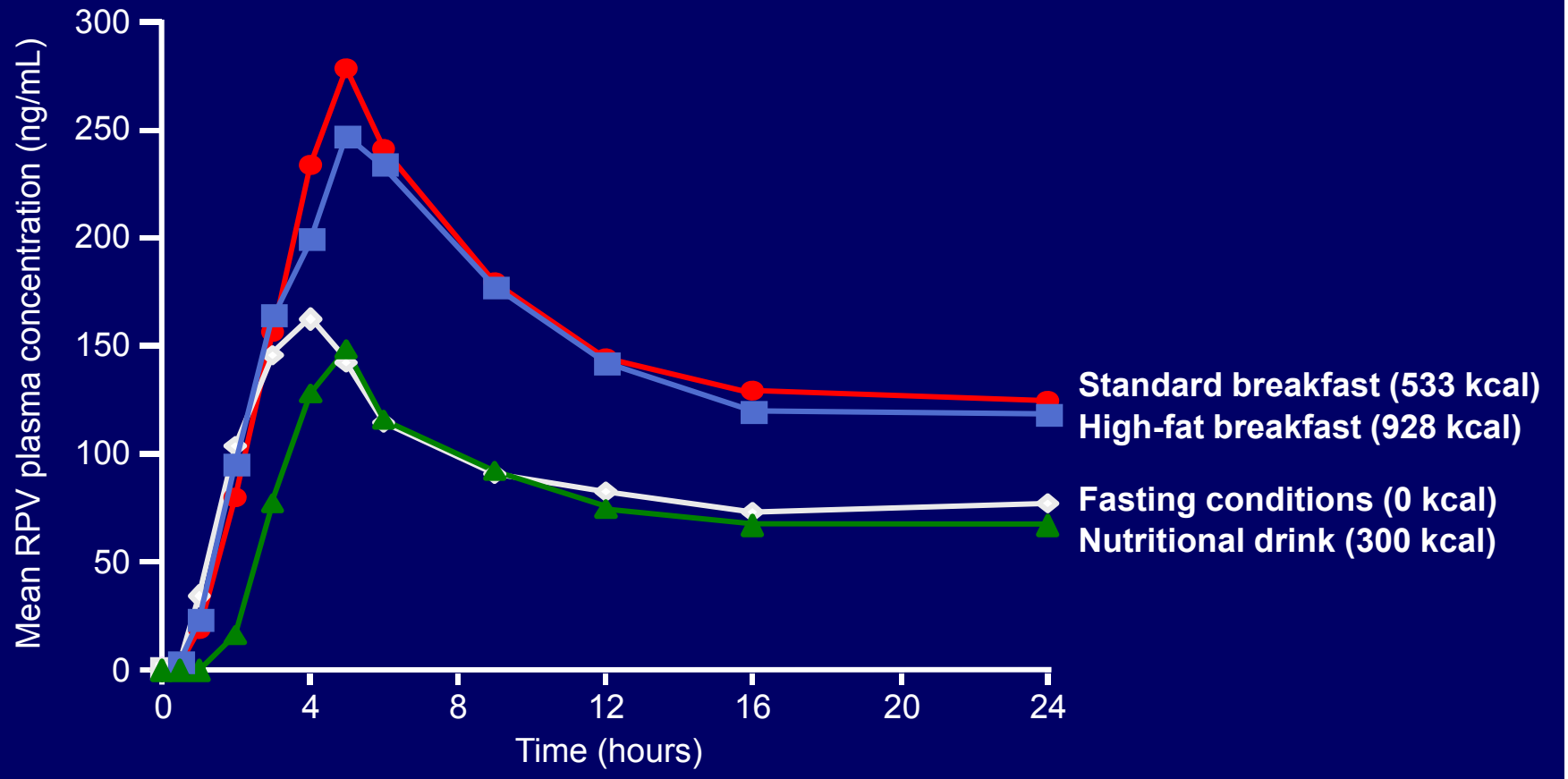
RPV Background

Rilpivirine (RPV) is a new NNRTI with the following attributes:

- Anti-HIV-1 activity, EC_{50}=0.3ng/mL[1]
- No teratogenicity in preclinical studies[2]
- Half-life of ~ 45 hours[3]
- Food increases RPV's bioavailability by approximately 60%
  - RPV should be taken with a meal[4]
- No significant drug interaction with TDF[5] or FTC[6]
- >99.7% protein-bound *in vitro*[7]
- Metabolised primarily via the CYP3A pathway[8]

1. Azijn H, et al. AAC 2010;54:718–27
2. Desmidt M, et al. EACS 2009. Cologne, Germany. #PE7.1/4
3. Eviplera® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate). Summary of Proeuct Characteristics. November 2011
4. Crauwels H, et al. IWCPHT 2008. New Orleans, LA. #P32
5. Hoetelmans R, et al. IAS 2005. Rio de Janeiro, Brazil. #WePe3.3C15
6. Mathias A, et al. IAC 2010. Vienna, Italy. #LBPE17
7. Janssen PA, et al. J Med Chem 2005;48:1901–9
8. Lachau-Durand S, et al. EACS 2009. Cologne, Germany. #PE7.1/3

Effect of Food Type on Mean RPV PK Profile



Taking RPV with food increases RPV exposure by 57% compared to fasting. RPV AUC was similar when administered after a high-fat or standard breakfast.

Crauwels HM, et al. IWCPHT 2008. New Orleans, LA. #P32

GS-264-112: Food Effect Study

Effect of food on the PK of RPV/FTC/TDF-STR

Single dose, cross-over study design evaluating food effect (light and standard) meals

RPV Concentration –Time Curve

Food Effect on RPV AUC and Cmax [GMR (90%CI)]

RPV PK Parameter	Light Meal vs. Fasting	Standard Meal vs. Fasting	Light Meal vs. Standard Meal
AUC_{inf}	109 (92.2, 129)	116 (98.6, 137)	93.8 (79.2, 111)
C_{max}	134 (111, 163)	126 (105, 153)	106 (87.6, 129)

- Relative to fasting conditions, RPV and TFV exposures were modestly higher following light meal or standard meal
- RPV exposures were narrowly outside the lack of effect bounds (80-125%) at 79.2% for the light meal versus standard meal comparison

It is recommended that the RPV/FTC/TDF STR be administered with food.

Effect of food on RPV exposure is smaller for the RPV/FTC/TDF -STR vs. RPV single agent (fasting vs. fed: ↓12-16% vs. ↓43%)

AUC: area under concentration-time curve; Cmax: maximum concentration; GMR: geometric mean ratio

Ramanathan, et al. HIV-11 2012; Glasgow. P068

Rilpivirine & Methadone Drug Interaction: No Initial Dosage Adjustment Needed

- Open-label, single-sequence, drug-drug interaction trial of RPV 25mg qd and methadone (individualized stable doses) 60-100mg qd
  - 13 healthy subjects, Male 100%, White 77%, Asian 15%, Black 8%
- PK parameters in presence and absence of RPV – LSM ratio (90%CI)

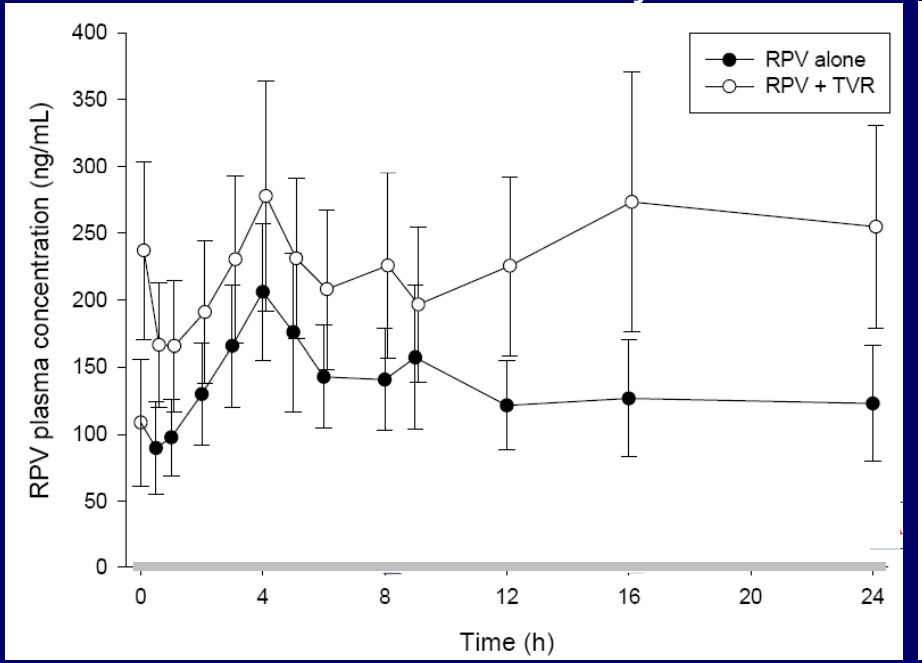
Parameter LSM (90% CI)	C_{min}	C_{max}	AUC_{24h}
R-methadone	0.78 (0.67-0.91)	0.86 (0.78-0.95)	0.84 (0.74-0.95)
S-methadone	0.79 (0.67-0.92)	0.87 (0.78-0.97)	0.84 (0.74-0.96)

- During co-administration with RPV, no clinically relevant changes in the pharmacodynamic assessments of methadone withdrawal signs and symptoms were observed
- No adjustment of the methadone dosage is required when initiating co-administration with RPV 25 mg QD
  - However, clinical monitoring for methadone withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients

Crauwels HM, et al. IAC 2010; Vienna. WEPE0089

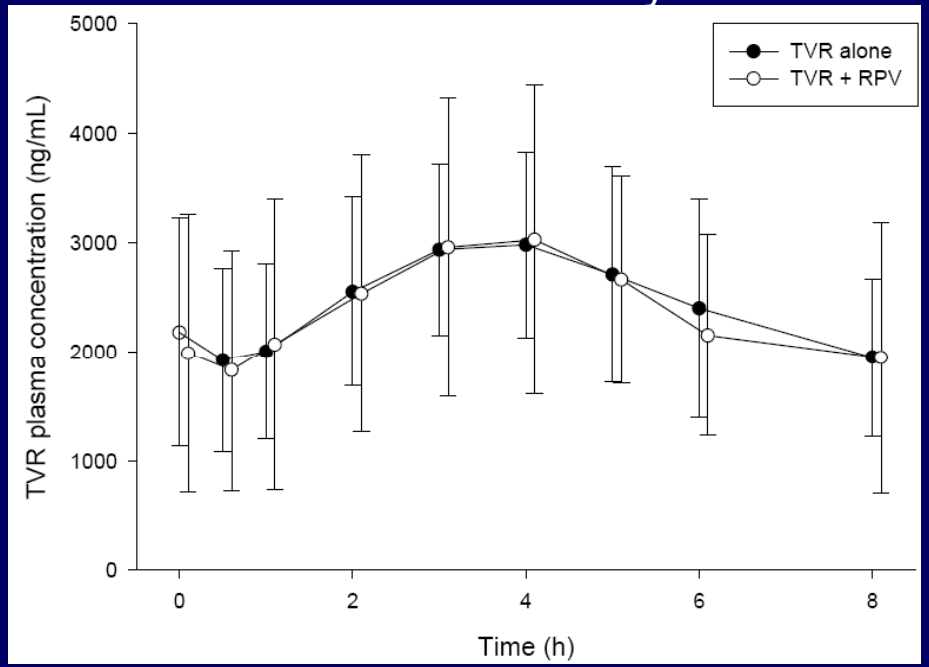
Rilpivirina - Telaprevir

Concentración de RPV con y sin TPV



AUC ↑ 78%
Cmax ↑ 49%

Concentración de TPV con y sin RPV



AUC ↓ 5%
Cmax ↓ 3%

El incremento de exposición a RPV no se considera clínicamente relevante por lo que NO se considera ajuste de dosis cuando se co-administra con telaprevir

Kakuda T et al. 13th International HIV Clinical Pharmacology Workshop. Barcelona, Spain, 2012. Oral 18

Drug Interaction: RPV and Boceprevir

No Dosage Adjustment Needed

- Healthy volunteers PK study of 20 subjects assessed changes in exposure to both RPV and BOC when co administered for 11 days

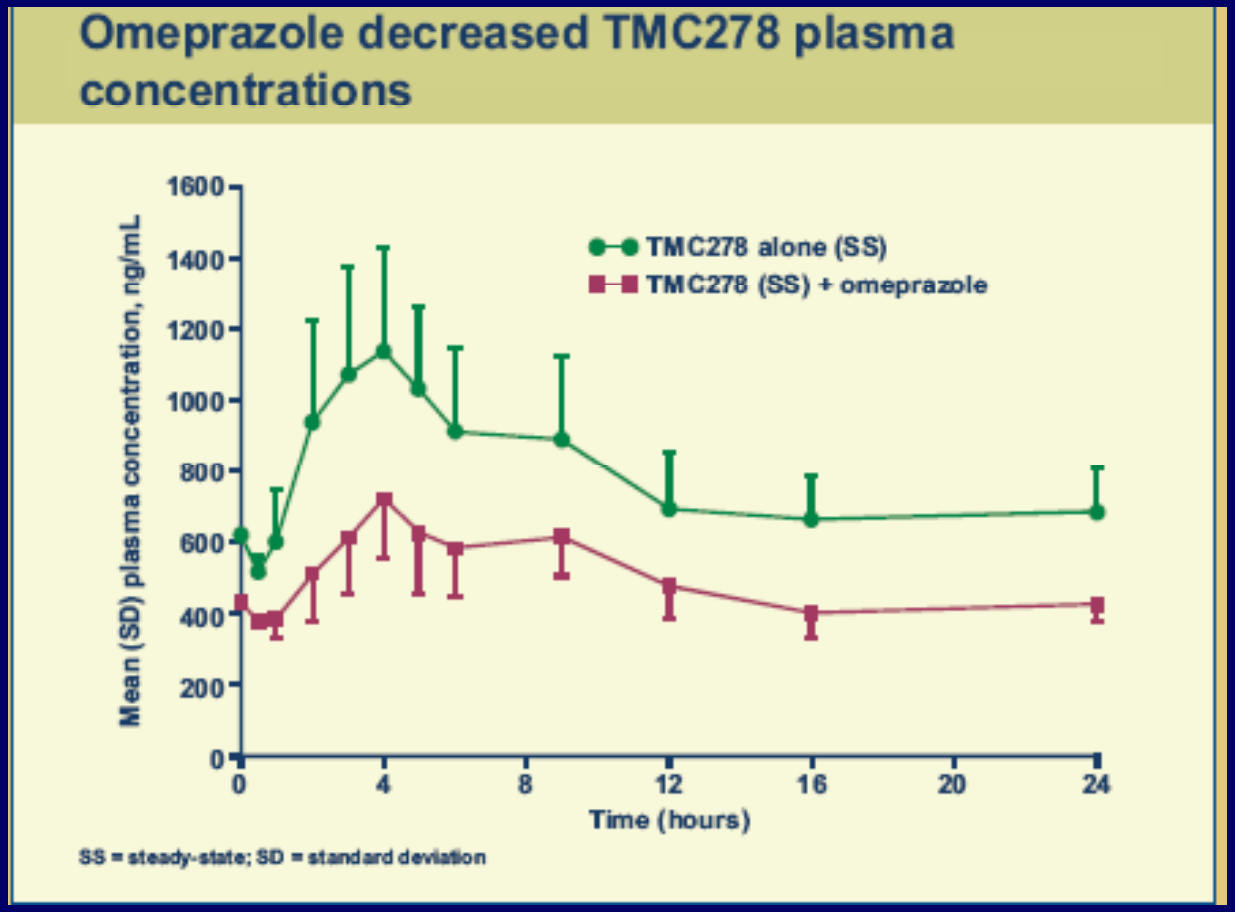
Parameter	Boceprevir	Rilpivirine
Cmin, ng/mL	↑ **4%**	↑ **51%**
Cmax, ng/mL	↓ **2%**	↑ **15%**
AUC, ng.hr/mL	↓ **6%**	↑ **39%**

- RPV exposure was increased by BOC but no effect of RPV on BOC PK
- Finding consistent with CYP3A inhibition by BOC inhibiting RPV metabolism

- Increase in RPV exposure not clinically significant and NO dose adjustment recommended

Rhee EG, et al. CROI 2013; Atlanta, GA. #537

Interacciones medicamentosas: Rilpivirina y Omeprazol

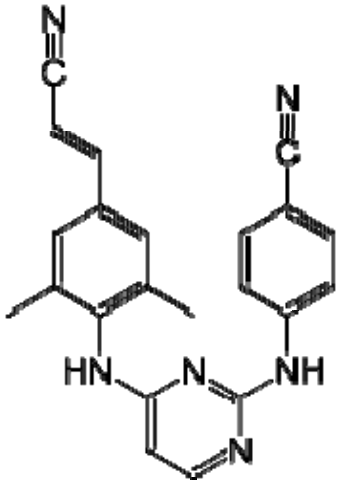


RPV interacciona con los IBP

H2-antagonistas se pueden utilizar si se toman 12 horas antes o 4 horas después de TMC278

Crauwels HM, 9th International Congress on Drug Therapy in HIV Infection, Glasgow, November 2008.

RILPIVIRINA (RPV)

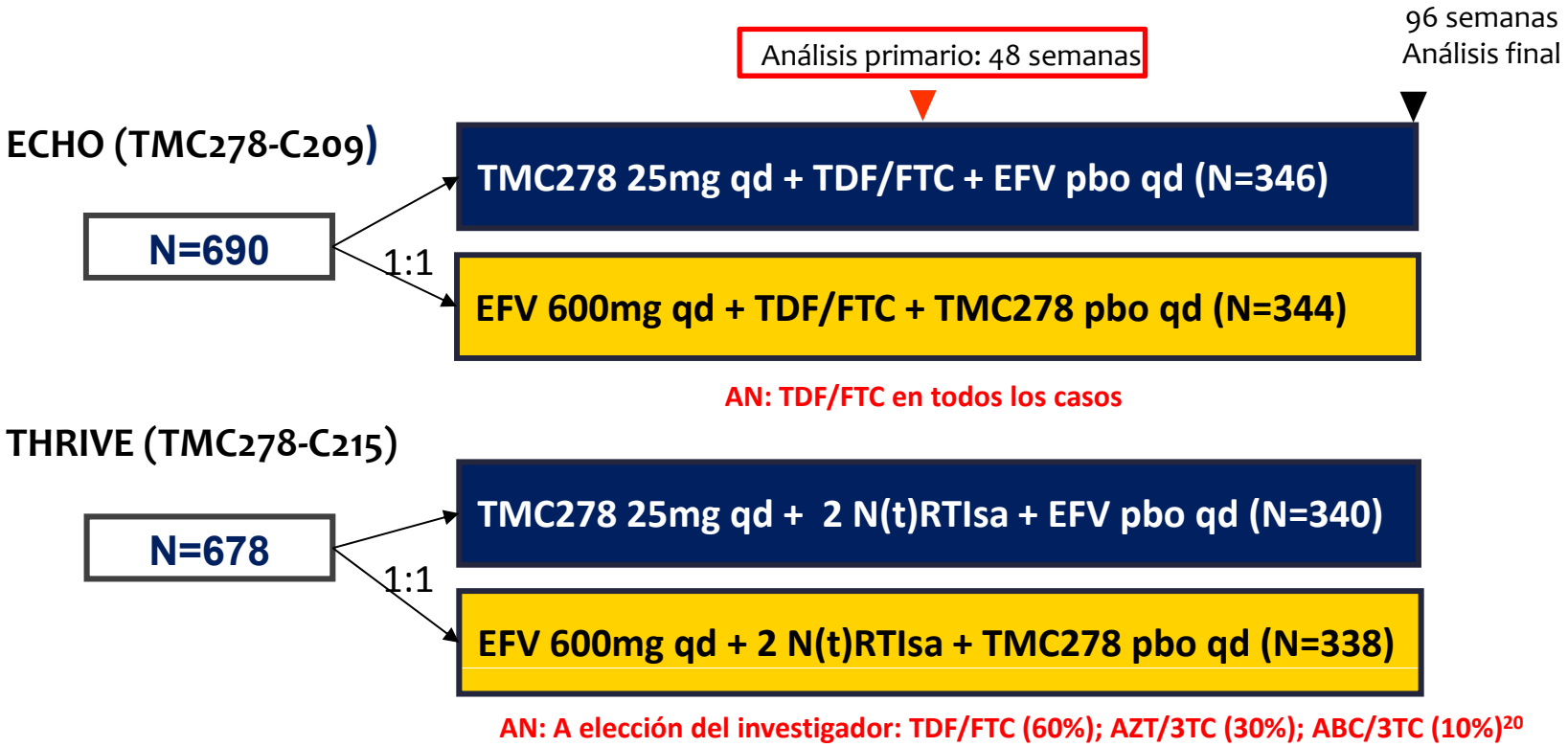


1) **Generalidades**

2) **Naïve**
(ECHO y THRIVE, STAR)

3) **Pretratado**
(SPIRIT y GS-111)

Estudios ECHO & THRIVE: Diseño



- **Objetivo primario:** demostrar la no-inferioridad (margen 12%) de RPV vs EFV por respuesta virológica confirmada (CV<50 copias/ml, ITT-TLOVR) a las 48 semanas. Análisis conjunto planeado a priori.
- **Criterios de inclusión:** naïve, CV≥5000 copias/ml; sin RAMs a NN, sensibilidad a los ITIAN.

20. Orkin C, Cohen C, Molina JM, et al. Pooled week 96 efficacy, resistance and safety results from the double-blind, randomised, phase III trials comparing rilpivirine (RPV, TMC278) versus efavirenz (EFV) in treatment-naïve, HIV-1-infected adults. 18th BHIVA, 2012. Poster P184. 18.Cohen C, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trail. The Lancet 2011;378:229-337.

Análisis conjunto ECHO & THRIVE:
Características basales

Table 1. Demographics and baseline characteristics.

Baseline parameter	RPV N=686	EFV N=682
Female, %	24	24
Male, %	76	76
Median age, years (range)	36 (18–78)	36 (19–69)
Race, %		
Caucasian	61	60
Black	24	23
Asian	11	14
Other races/not stated	3	3
Median $\log_{10}$ viral load, copies/mL (range)	5 (2–7)	5 (3–7)
Baseline viral load copies/mL, % >100,000 copies/mL*	46	52
Median CD4 cell count, cells/mm^3 (range)	249 (1–888)	260 (1–1,137)
Hepatitis B or C co-infection, %	7	9

*Median baseline viral load, copies/mL (interquartile range [IQR]) in patients with baseline viral load >100,000 copies/mL was RPV 235,000 (152,000–443,000 copies/mL) vs EFV 236,000 (150,000–460,000 copies/mL), and in patients with baseline viral load ≤100,000 copies/mL it was RPV 37,000 (18,000–59,000 copies/mL) vs EFV 34,000 (16,000–62,000 copies/mL)

Análisis conjunto ECHO & THRIVE:
CV<50 copias/mL a las 48 semanas (ITT-TLOVR)

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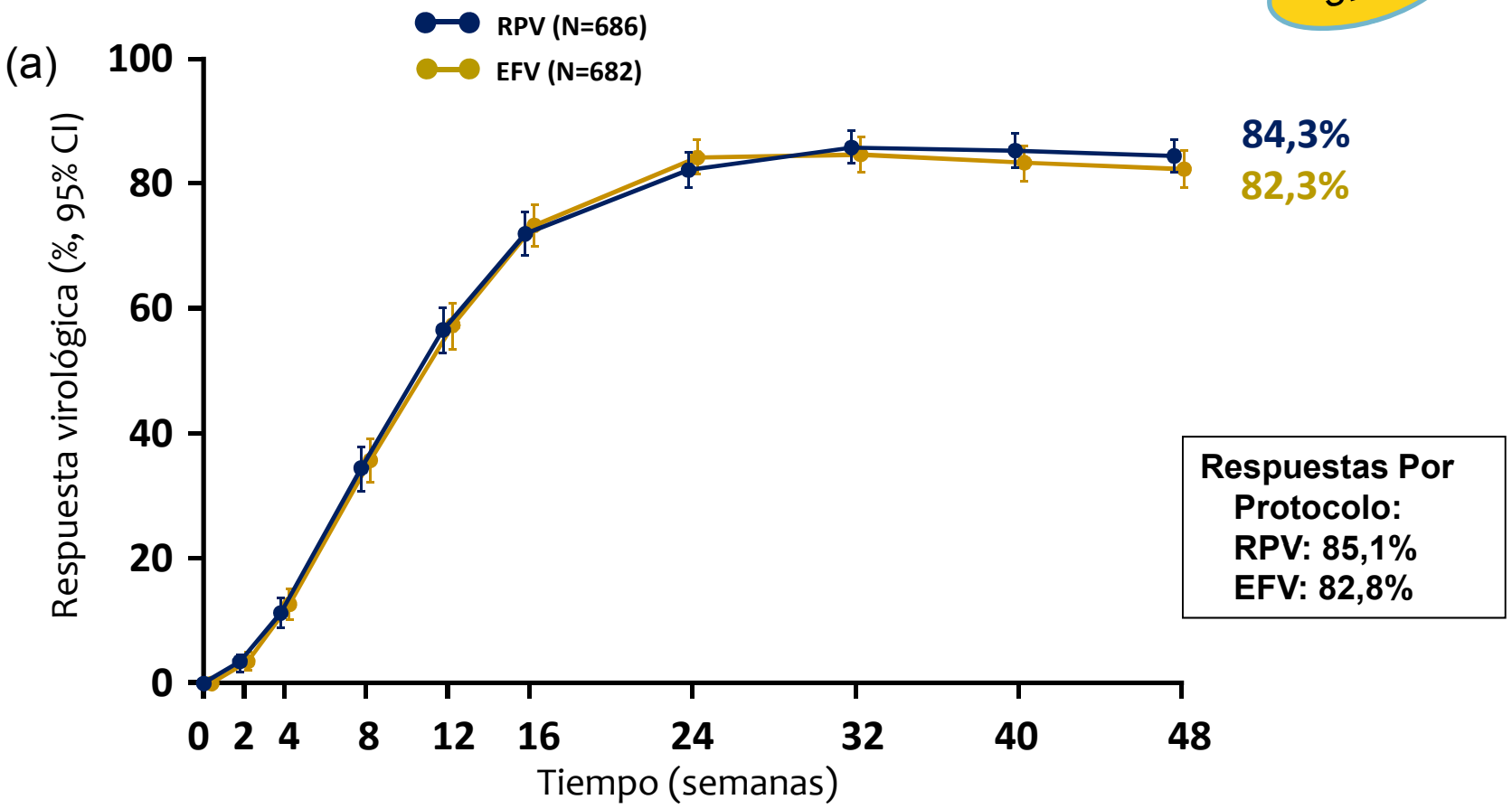

RPV demostró la **no-inferioridad** frente a EFV
(diferencia = **2,0%**, IC95% **-2,0% a 6,0%**)

Análisis conjunto de los ECHO&THRIVE:

Cambio en el recuento de CD4 basal

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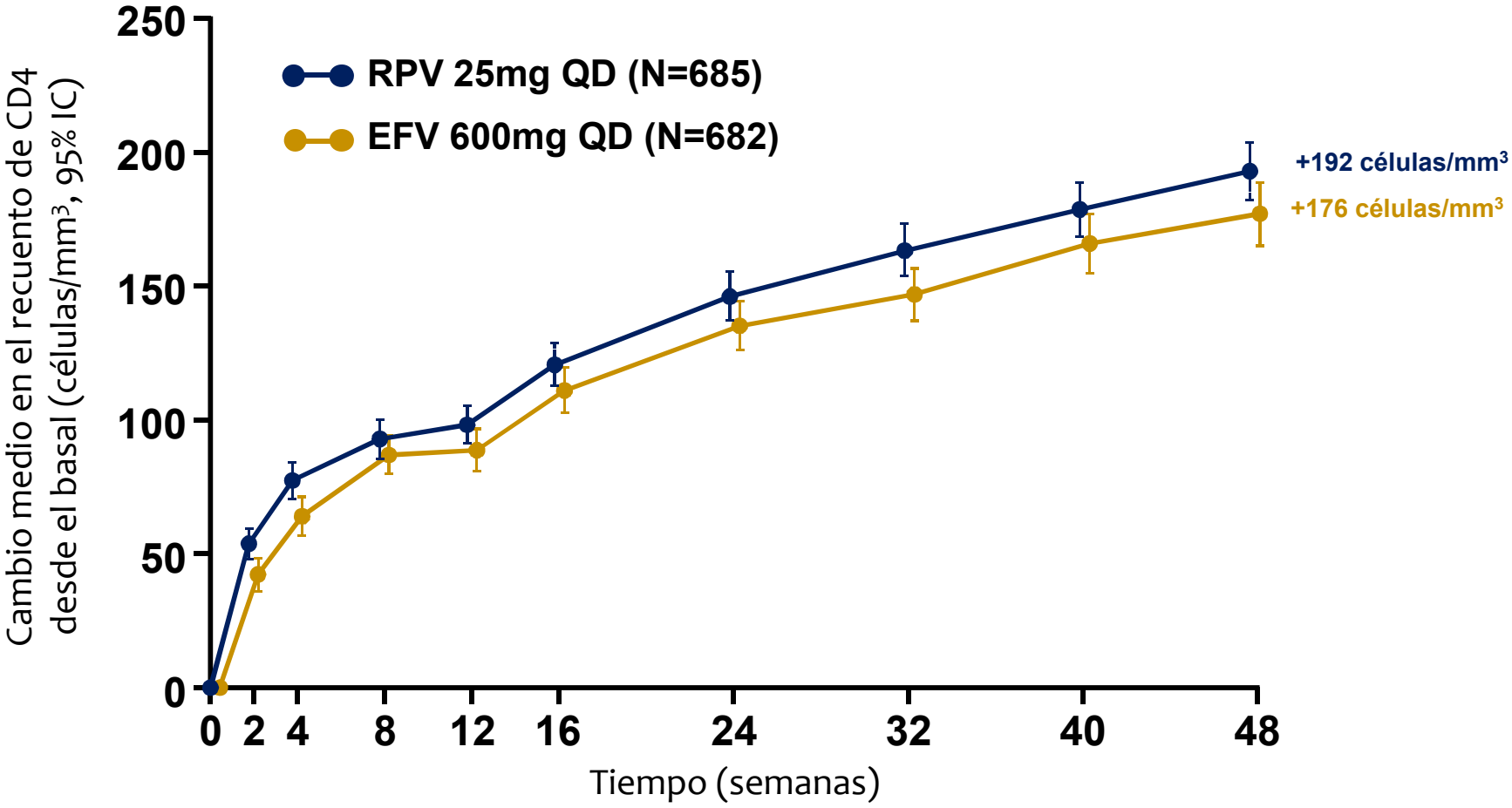

Análisis conjunto ECHO & THRIVE:
CV <50 copias/mL a la semana 96 (ITT-TLOVR)

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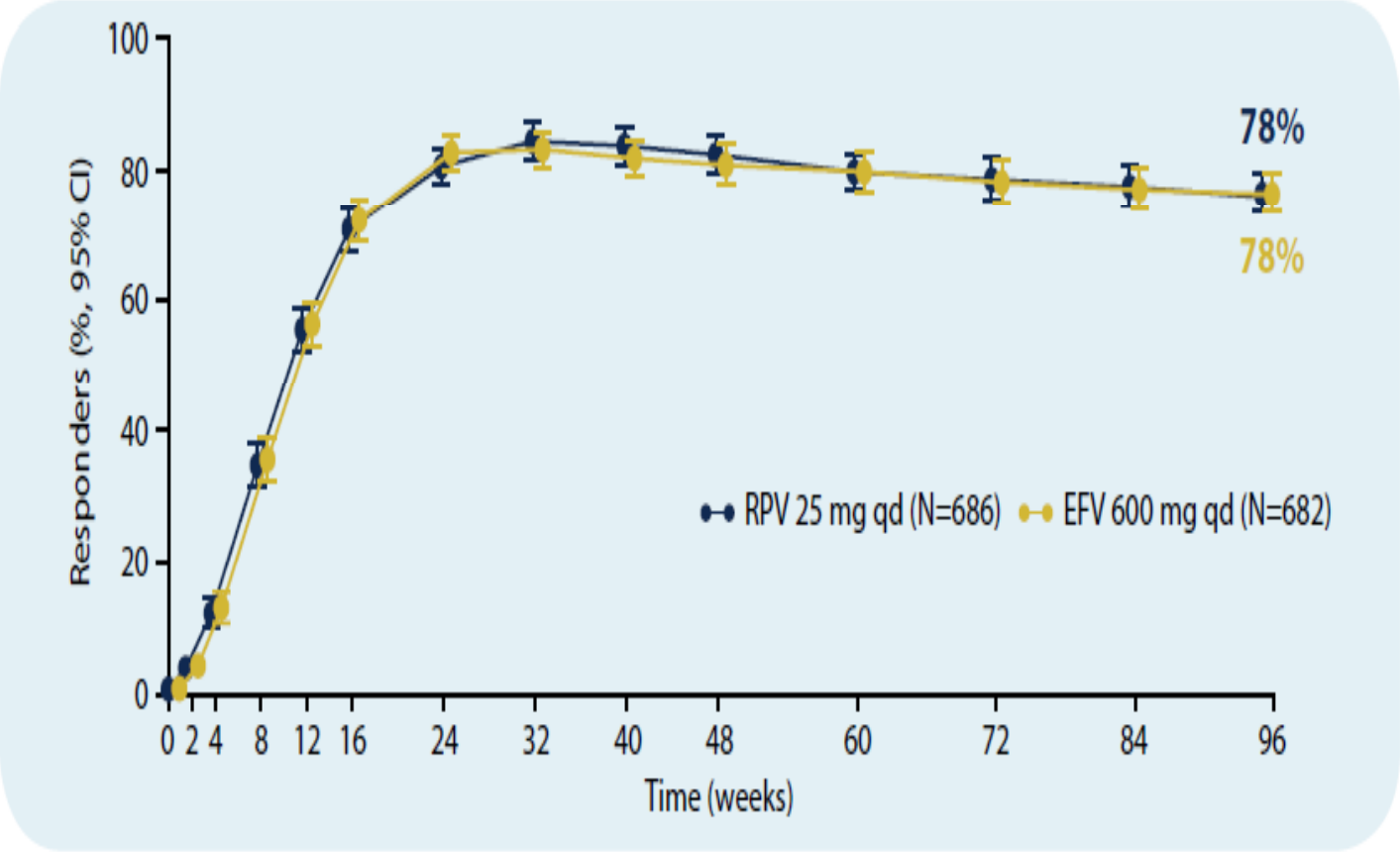

Se observaron **tasas de respuesta similares (78%)** tanto para RPV como EFV

1 Cohen C, et al. XVIIIth IAC 2010; Abstract THLBB206
2 Cohen C, et al. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Italy, 2011. Poster TULBPE032

ECHO & THRIVE: Diferencia en las tasas de respuesta a las 96 semanas (ITT-TLOVR)

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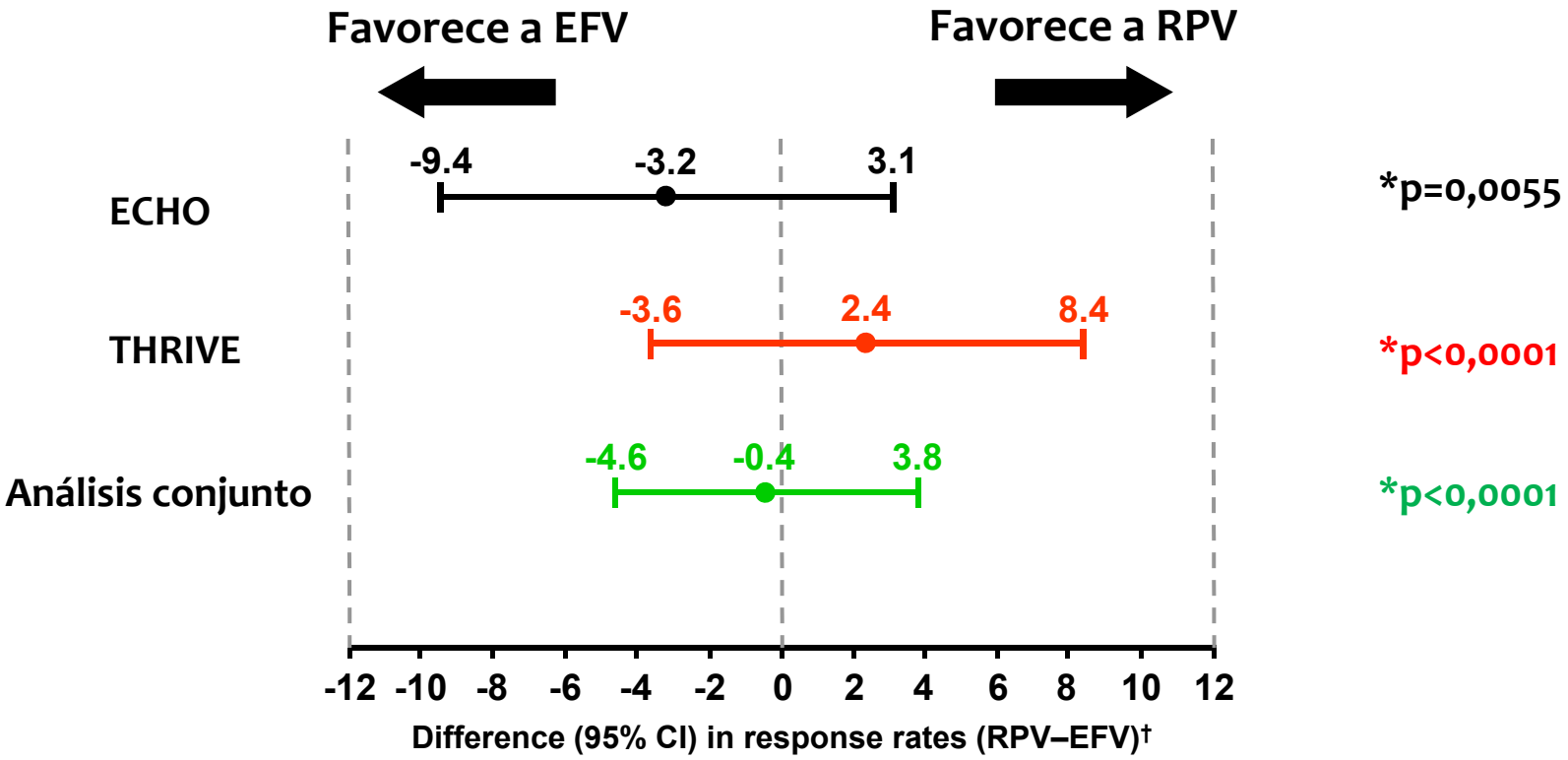

*Valor p para la no-inferioridad con un margen del 12%; †Estimación por regresión logística ajustada por los factores de estratificación

RPV mostró **tasas similares** de respuesta a EFV a las 96 semanas

22. Orkin C, Cohen C, Molina JM, et al. Pooled Week 96 efficacy, resistance and safety results from the double-blind, randomised, Phase III trials comparing rilpivirine (RPV, TMC278) versus efavirenz (EFV) in treatment-naïve, HIV-1-infected adults. 18th BHIVA. Poster P184.

ECHO & THRIVE:

Eficacia en pacientes adultos naïve con CV≤100.000 copias/ml

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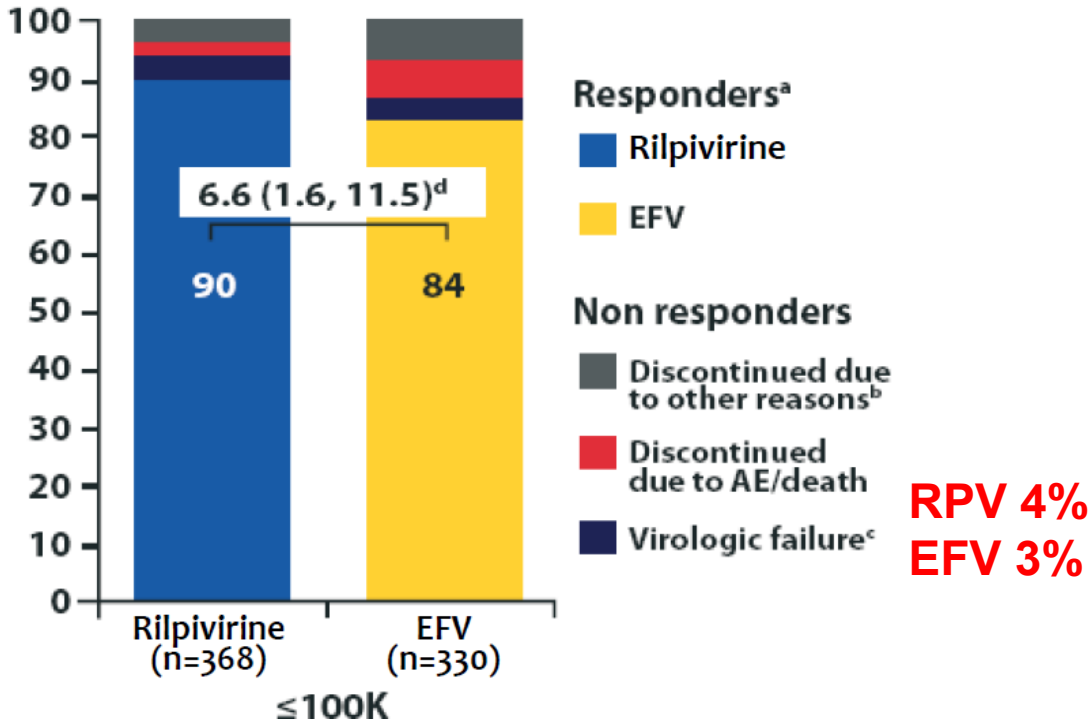

RPV 4%
EFV 3%

La tasa de FV fue **baja y similar en ambos brazos** en el análisis conjunto con CV≤100.000 copias/ml a las 48 semanas[28]

26. Molina JM, Clumeck N, Orkin C, et al. Rilpivirine efficacy, virology and safety in antiretroviral treatment-naïve patients with baseline viral load≤100.000 HIV-1 RNA copies/ml: ECHO and THRIVE 96-week pooled dataset. 11th CROI 2012. Poster P270. 28. Cohen C, Molina JM, Jayaweera D, et al. Relationship between combination of baseline viral load and CD4 cell count, and Week 48 or 96 responses to rilpivirine (RPV) or efavirenz (EFV) in treatment-naïve HIV-1-infected adults: pooled analysis from the Phase III ECHO and THRIVE trials. 19th CROI, Seattle, WA, USA, March 5–8 2012. Poster nº 626

ECHO & THRIVE:
CV<50 copias/mL según AN acompañantes (ITT-TLOVR)

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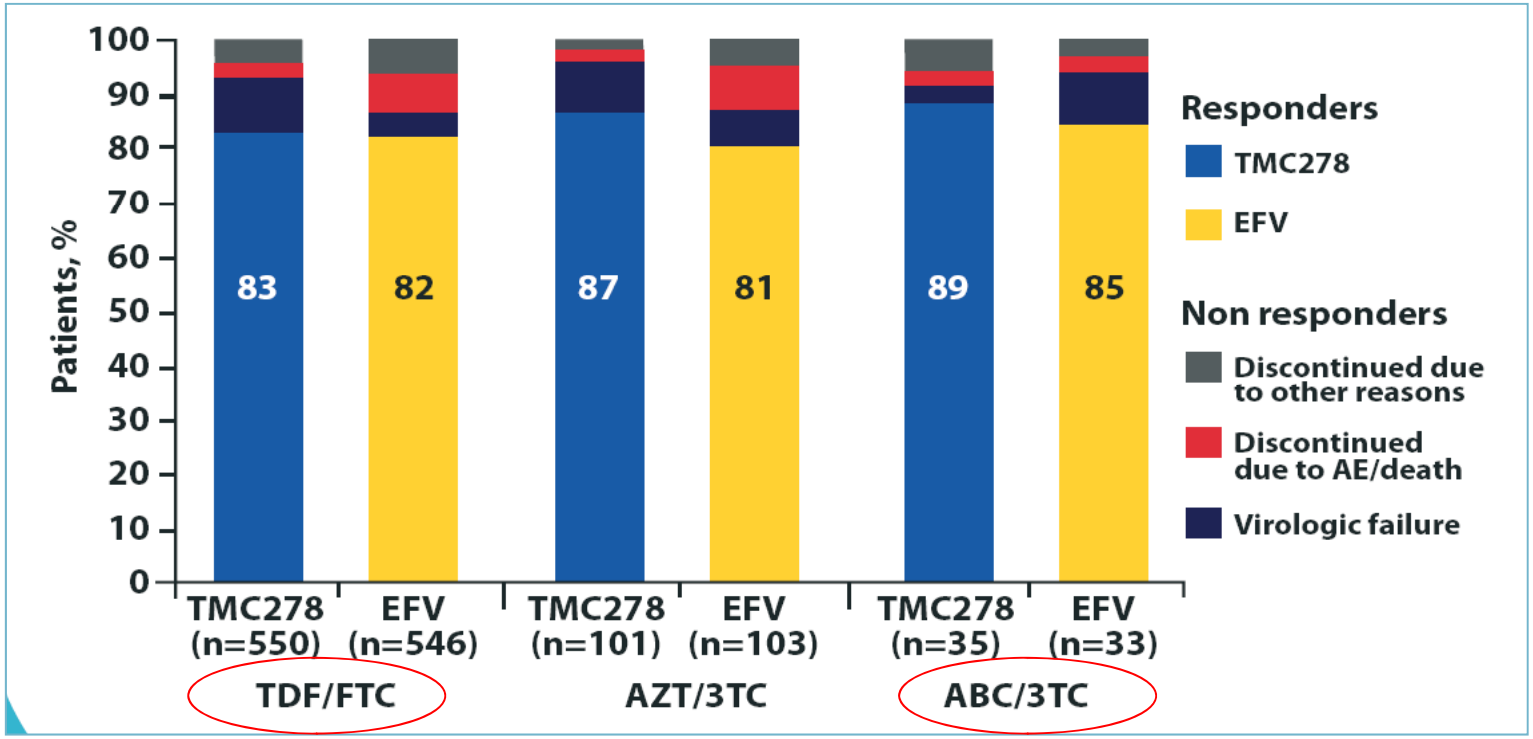


La respuesta fue similar para todos los **AN acompañantes**

24.Cohen C, Molina JM, Cahn P. et al. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomized, phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected Patients. ACTHIV Denver 2011. Poster TPOI-3.

ECHO & THRIVE:
Eficacia según la adherencia (ITT-TLOVR)

s.48

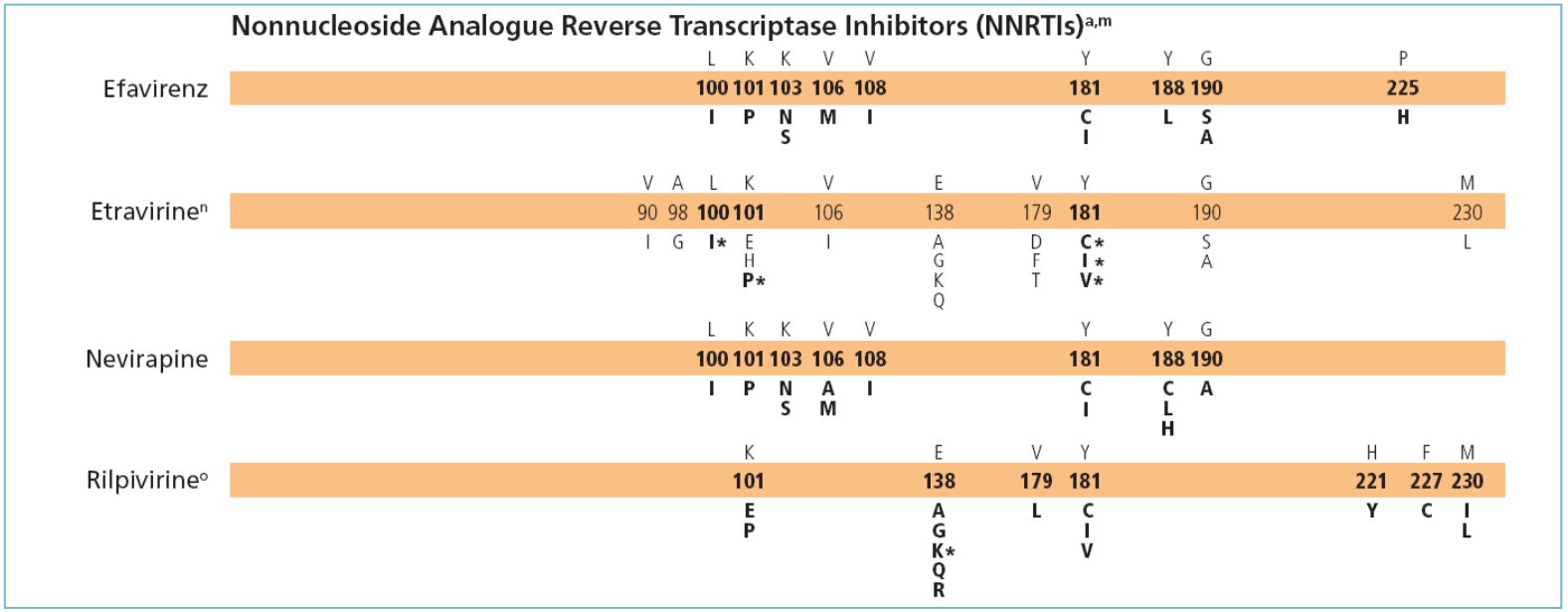
	Virologic response (VR)			
M-MASRI adherence	TMC278[b]		EFV[b]	
	n	VR	n	VR
>95%	547	88%	492	88%
>90–95%	45	78%	56	75%
≤90%	35	51%	39	59%

Las mala adherencia se tradujo en **menor eficacia** para ambos brazos

24.Cohen C, Molina JM, Cahn P. et al. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomized, phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected Patients. ACTHIV Denver 2011. Poster TPOI-3.

Resistencias

- Se han descrito 15 mutaciones que reducen la sensiblidad de Rilpivirina[30]:



- La mutación K103N por sí sola, no compromete la eficacia de Rilpivirina[32]

30. Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. JAIDS 2012;59(1):39-46.31. Johnson VA, Calvez V, Günthard HF, et al. 2011 Update of the drug resistance mutations in HIV-1. Topics in Antiviral Medicine 2011;19(4):156-64. 32. Fernández-Montero J, Vispo E, Anta L, et al. Rilpivirine: a next-generation non-nucleoside analogue for the treatment of HIV infection. Expert Opinion Pharmacother 2012;13(7):1007-1014.
Para mayor información sobre resistencias, consulte la ficha técnica de rilpivirina.

Resistencias

TABLE 1. Incidence of VF by Baseline VL in the ITT Population (Including All Data Until the Last Patient Reached 48 Weeks of Treatment) and Distribution of the RAMs Among the VFs with Genotypic Data at Time of Failure

	RPV Patients			EFV Patients		
	BL VL ≤100,000 copies/mL	BL VL >100,000 copies/mL	All	BL VL ≤100,000 copies/mL	BL VL >100,000 copies/mL	All
VFs, n/N (%)						
All	19/368 (5)	53/318 (17)	72/686 (10)	16/330 (5)	23/352 (7)	39/682 (6)
Rebounders*	9/368 (2)	20/318 (6)	29/686 (4)	12/330 (4)	8/352 (2)	20/682 (3)
Never suppressed†	10/368 (3)	33/318 (10)	43/686 (6)	4/330 (1)	15/352 (4)	19/682 (3)
B subtype‡	13/245 (5)	42/240 (18)	55/485 (11)	13/220 (6)	15/242 (6)	28/462 (6)
Subtype non-B	6/123 (5)	11/78 (14)	17/201 (8)	3/110 (3)	8/110 (7)	11/220 (5)
VFs with, n/N (%)	RPV VFs with genotypic data			EFV VFs with genotypic data		
No N(t)RTI and/or NNRTI RAMs	8/16 (50)	10/46 (22)	18/62 (29)	6/12 (50)	6/16 (38)	12/28 (43)
Any NNRTI RAM	6/16 (38)	33/46 (72)	39/62 (63)	5/12 (42)	10/16 (63)	15/28 (54)
Any N(t)RTI RAM	7/16 (44)	35/46 (76)	42/62 (68)	2/12 (17)	7/16 (44)	9/28 (32)
Any N(t)RTI and/or NNRTI RAM	8/16 (50)	36/46 (79)	44/62 (71)	6/12 (50)	10/16 (63)	16/28 (57)
Any N(t)RTI and NNRTI RAM	5/16 (31)	32/46 (70)	37/62 (60)	1/12 (8)	7/16 (44)	8/28 (29)

*First achieved 2 consecutive VL values <50 copies per milliliter followed by VL value(s) ≥50 copies per milliliter.
†Never achieving <50 copies per milliliter and with a VL increase ≥0.5 $\log_{10}$ copies per milliliter above nadir.
‡Proportion of B subtype at baseline was 71% in the RPV group and 68% in the EFV group.
BL, baseline.

A la semana 48 hubo un 10% de pacientes con FV del brazo de RPV y un 6% del brazo de EFV

30. Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. JAIDS 2012;59(1):39-46

FV y Resistencias
En pacientes con CV≤100.000 copias/ml

Table 3. Incidence of VF_{res} and emergence of RAMs at time of failure for patients with baseline viral load ≤ 100 000 copies/ml in the pooled ECHO/THRIVE population.

	RPV	EFV
VF_{res} patients, *n/N* (%)	19/368 (5)[c]	16/330 (5)
VF_{res} patients with paired baseline/endpoint genotypic data, *N'*	16	12
VF_{res} patients with ≥1 treatment-emergent NNRTI RAM[a] and/or N(t)RTI RAM[b], n (%)	8/16 (50)[c]	6/12 (50)
VF_{res} patients with >1 treatment-emergent NNRTI RAM[a], *n* (%)	6/16 (38)[c]	5/12 (42)
E138K	5 (83)	0
K101E	2 (33)	1 (20)
V90I	1 (17)	0
L100I	1 (17)	0
V179I	1 (17)	0
K103N	0	5 (100)
VF_{res} patients with ≥1 treatment-emergent N(t)RTI RAM[b], *n* (%)	7/16 (44)[c]	2/12 (17)
M184I	6 (86)	0
M184V	2 (29)	2 (100)

[a]Based on extended list of 48 RAMs [17].
[b]IAS-USA [19].
[c]Not statistically significant versus efavirenz (EFV) (Fisher's Exact test, post-hoc analysis); RPV, rilpivirine; VF_{res}, virological failure for the virology analyses; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; N(t)RTI, nucleotide reverse transcriptase inhibitor; N, number of patients in each treatment group; N', number of evaluable patients in each treatment group; n, number of observations.

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- En pacientes con **CV≤100.000 copias/ml**, la tasa de FV fue **similar (5%) en ambos brazos**.
- En ambos grupos, la tasa de mutaciones aparecidas al FV fue menor en pacientes con CV basal ≤100.000 copias/ml[30]

29. Molina JM, Clumeck N, Redant K, et al. Rilpivirine versus efavirenz in HIV-1 patients with baseline viral load ≤100.000 copies/ml: week 48 phase III analysis. AIDS 2013:27;[ahead of print] 30. Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virological failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. JAIDS 2012;59(1):39-46.

En resumen (E&T) …

- RPV demostró una eficacia no-inferior a EFV en los estudios ECHO & THRIVE.
- En pacientes adultos naïve con CV≤100.000 copias/ml RPV demostró una respuesta virológica mayor, y un mayor incremento del recuento de CD4.
- RPV demostró una eficacia similar a EFV con cualquier AN de base.

E&T: Resumen de Seguridad

s.96

Table 5. AE summary.*

	RPV N=686			EFV N=682			
Median treatment duration, weeks		**104**			**104**		**All p value RPV vs EFV**
Incidence, n (%)	**All***	**Up to Week 48†**	**Week 48 to 96†**	**All***	**Up to Week 48†**	**Week 48 to 96†**	
Any serious AE	65 (9)	45 (7)	20 (3)	71 (10)	52 (8)	19 (3)	
Grade 2–4 AE at least possibly related to treatment	116 (17)	99 (14)	14 (2)	226 (33)	206 (30)	26 (4)	<0.0001§
Discontinuations due to AEs‡	28 (4)	21 (3)	5 (1)	58 (9)	47 (7)	7 (1)	
Most common AEs of interest¶							
Any neurological AE	119 (17)	111 (16)	3 (<1)	259 (38)	255 (37)	2 (<1)	<0.0001§
Dizziness	55 (8)	54 (8)	1 (<1)	182 (27)	182 (27)	1 (<1)	<0.0001§
Any psychiatric AE	107 (16)	95 (14)	5 (1)	166 (24)	149 (22)	9 (1)	<0.0001§
Abnormal dreams/nightmares	57 (8)	53 (8)	1 (<1)	90 (13)	86 (13)	2 (<1)	0.0039§
Rash (any type)	29 (4)	27 (4)	3 (<1)	103 (15)	102 (15)	0	<0.0001§

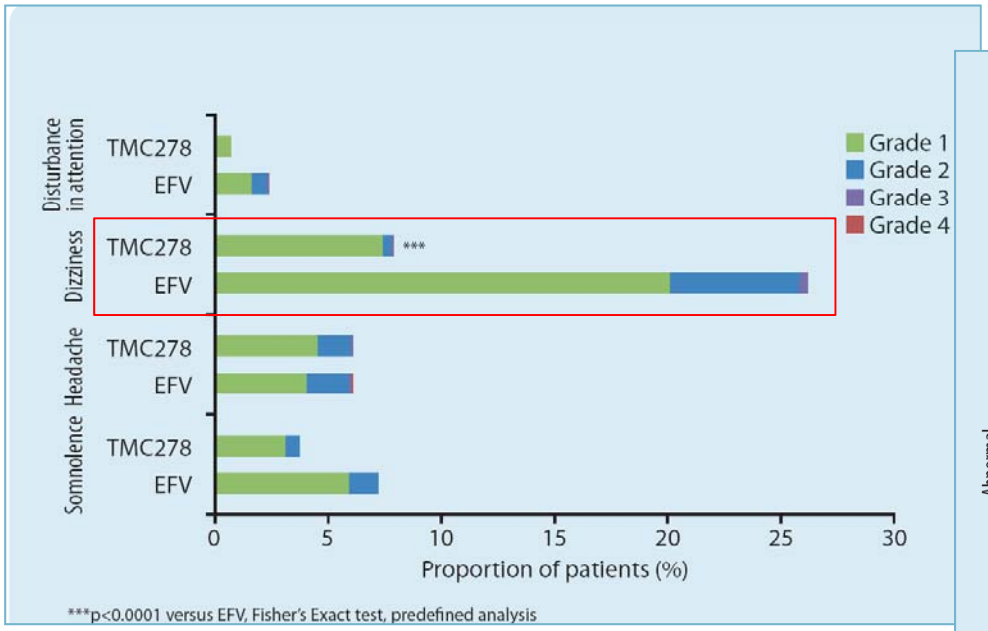
*Analysis performed using all available data, including beyond Week 96; †Patients were counted more than once in the Week 0–48 and Week 48–96 periods, and data after Week 96 are not included in the Week 48–96 period; ‡The most common AEs leading to discontinuation were rash (RPV: 1 [0.1%]; EFV: 8 [1.2%]) and depression (RPV: 3 [0.4%]; EFV: 4 [0.6%]); §Fisher's Exact test, preplanned analysis for these AEs; ¶Well-described AEs associated with current NNRTIs at least possibly related to treatment and observed in ≥10% of patients in either group (all grades)

RPV tuvo una **tasa menor de EAs** de grado 2-4 relacionados con el tratamiento, exantema (cualquier grado), mareo, sueños anormales, discontinuaciones debidas a EAs y menores alteraciones lipídicas de grado 2-4 que EFV.

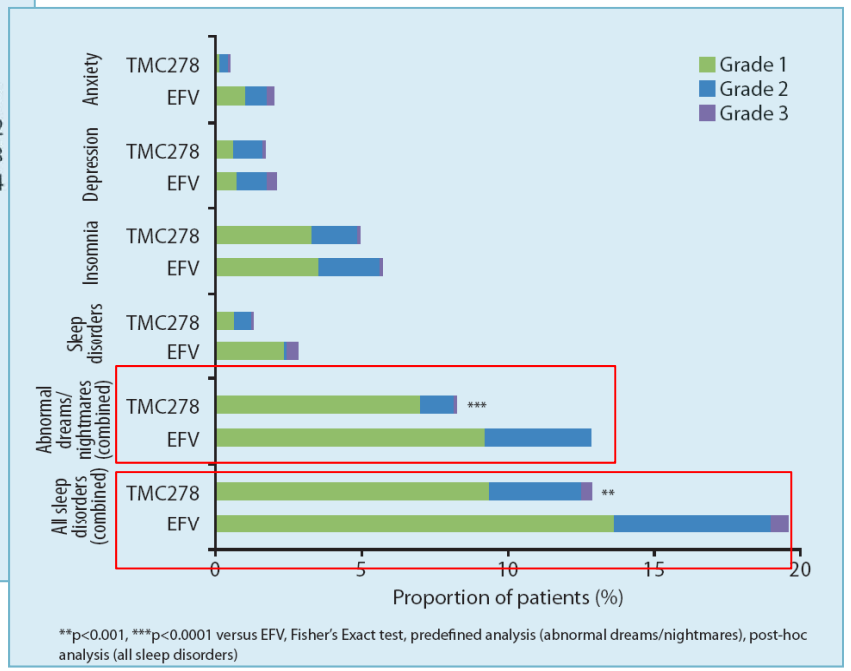
E&T: Tolerabilidad neuropsiquiátrica

s.48

Incidencia de EAs Neurológicos



Incidencia de EAs Psiquiátricos



RPV se asoció con **menos EA neurológicos y psiquiátricos** que EFV a las 48s:

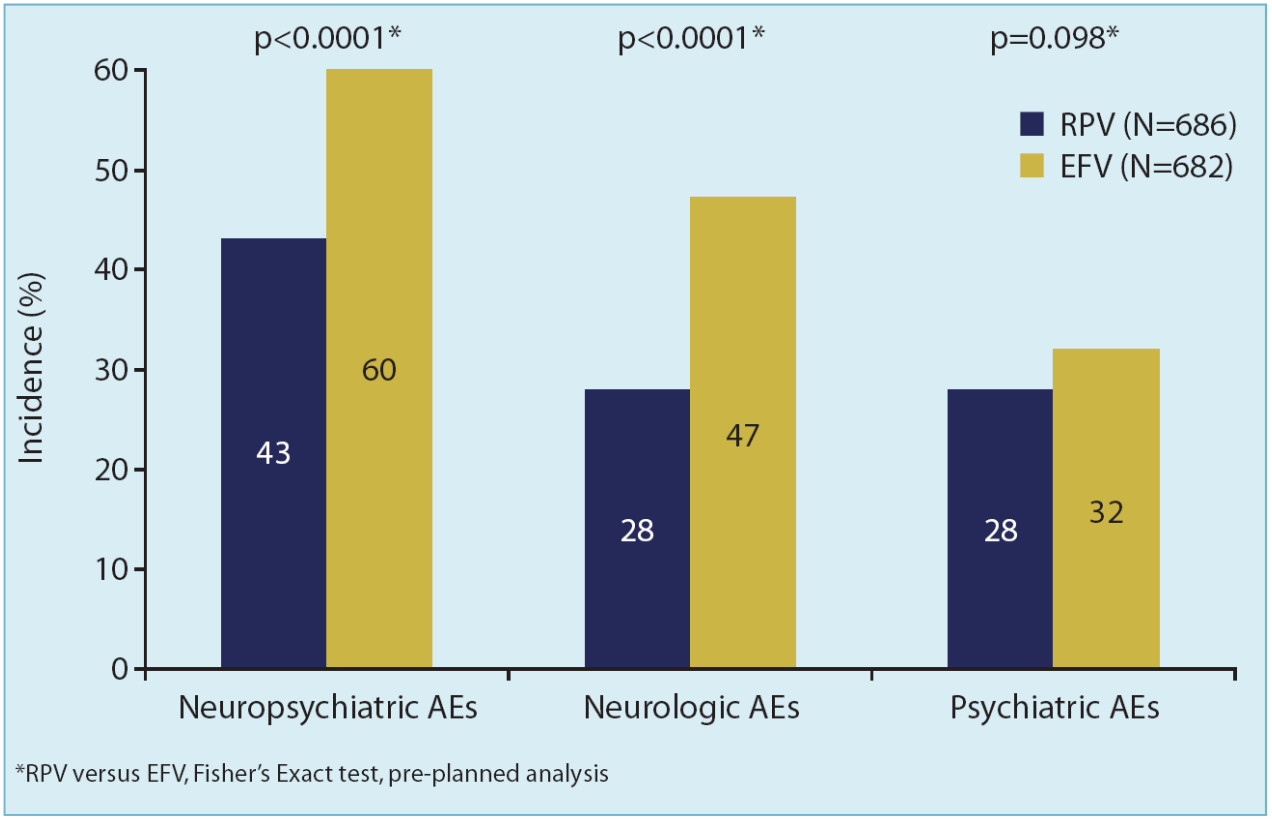
- En particular, el **mareo y sueños anormales** ocurrieron con una frecuencia significativamente menor con RPV que con EFV[21]

21. Mills A, Clotet B, Fisher M, et al. Neurologic and psychiatric safety profile of TMC278 compared with efavirenz in treatment-naive, HIV-1-infected patients: pooled analysis from the randomized, double-blind, phase III ECHO and THRIVE trials at 48 weeks. 20th CAHR Toronto, 2011. Poster P100. 22. Mills A, Antinori A, Clotet B,e t al. Neurological and psychiatric tolerability of rilpivirine (TMC278) vs. Efavirenz in treatment-naïve, HIV-1-infected patients at 48 weeks. HIV Med. 2013: [en prensa]. Para mayor información sobre seguridad, consulte la ficha técnica de rilpivirina.

E&T: Tolerabilidad neuropsiquiátrica

s.96

Incidencias de EAs neuropsiquiátricos de interés a lo largo de 96 semanas



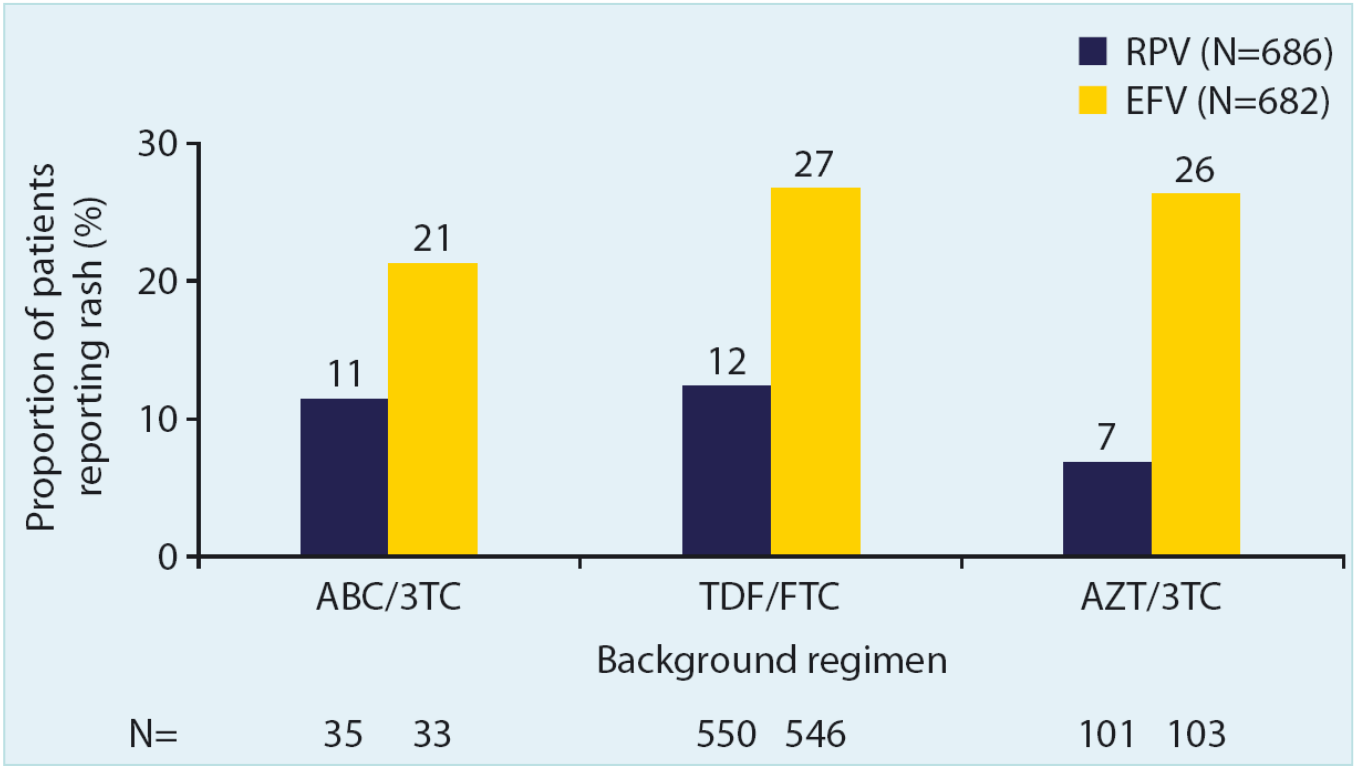
A las 96 semanas, RPV **se asoció significativamente con una menor incidencia de EAs neurológicos y psiquiátricos** de interés posiblemente relacionados con el fármaco

23. Arribas J, Sension M, Fätkenheuer G, et al. Neuropsychiatric events over 96 weeks of treatment with rilpivirine or efavirenz in the phase III ECHO and THRIVE studies. 5th International Symposium on Neuropsychiatry & HIV, Barcelona 2012. Para mayor información sobre seguridad, consulte la ficha técnica de rilpivirina.

E&T: Tolerabilidad cutánea

s.96

Incidencia de exantema (cualquier tipo y causa) según tratamiento y régimen de base



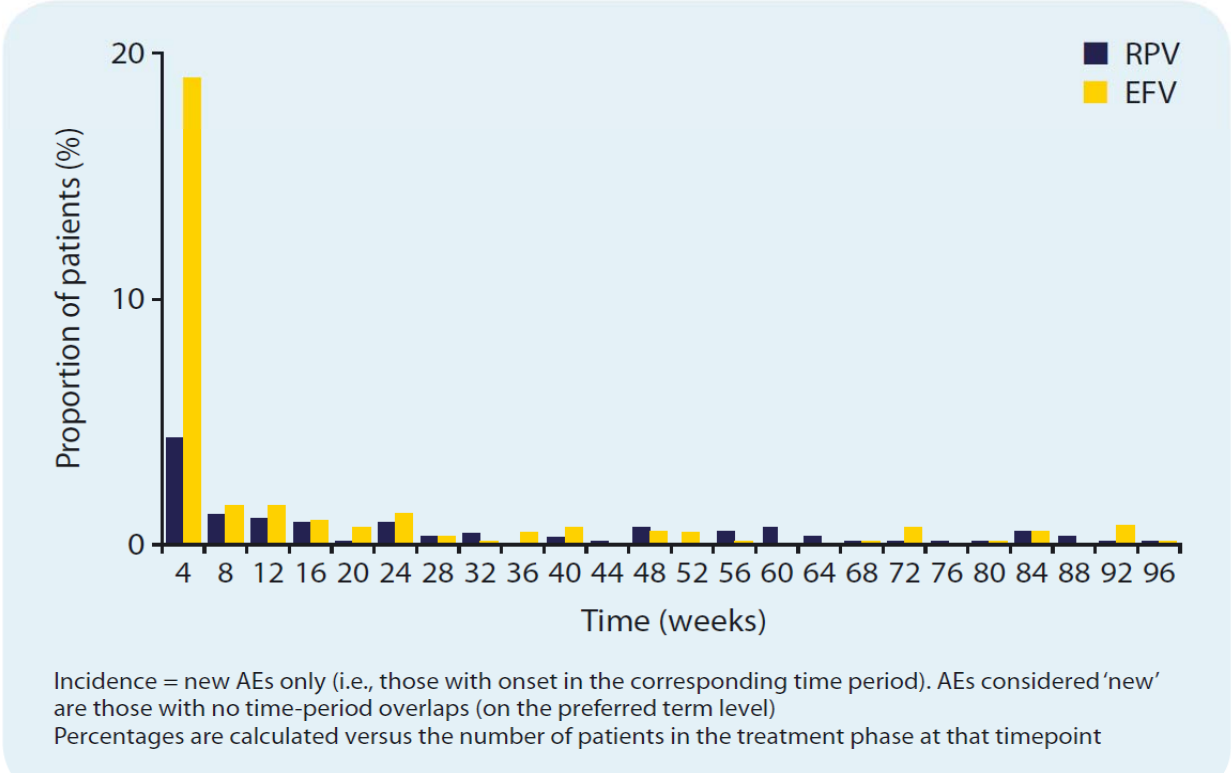
A la semana 96 hubo una **incidencia numéricamente inferior de exantema y menos discontinuaciones** en todos los subgrupos analizados en la rama de RPV en comparación con EFV.

26. Orkin C, Arribas J, Hodder S. Incidence of rash in the 96-week analysis of the pooled, phase III, randomised, double-blind ECHO and THRIVE trials. 18th BHIVA, Birmingham 2012. Poster P123. Para mayor información sobre seguridad, consulte la ficha técnica de rilpivirina.

E&T: Tolerabilidad cutánea

s.96

Incidencia de exantema a lo largo del tiempo



Incidence = new AEs only (i.e., those with onset in the corresponding time period). AEs considered 'new' are those with no time-period overlaps (on the preferred term level)
Percentages are calculated versus the number of patients in the treatment phase at that timepoint

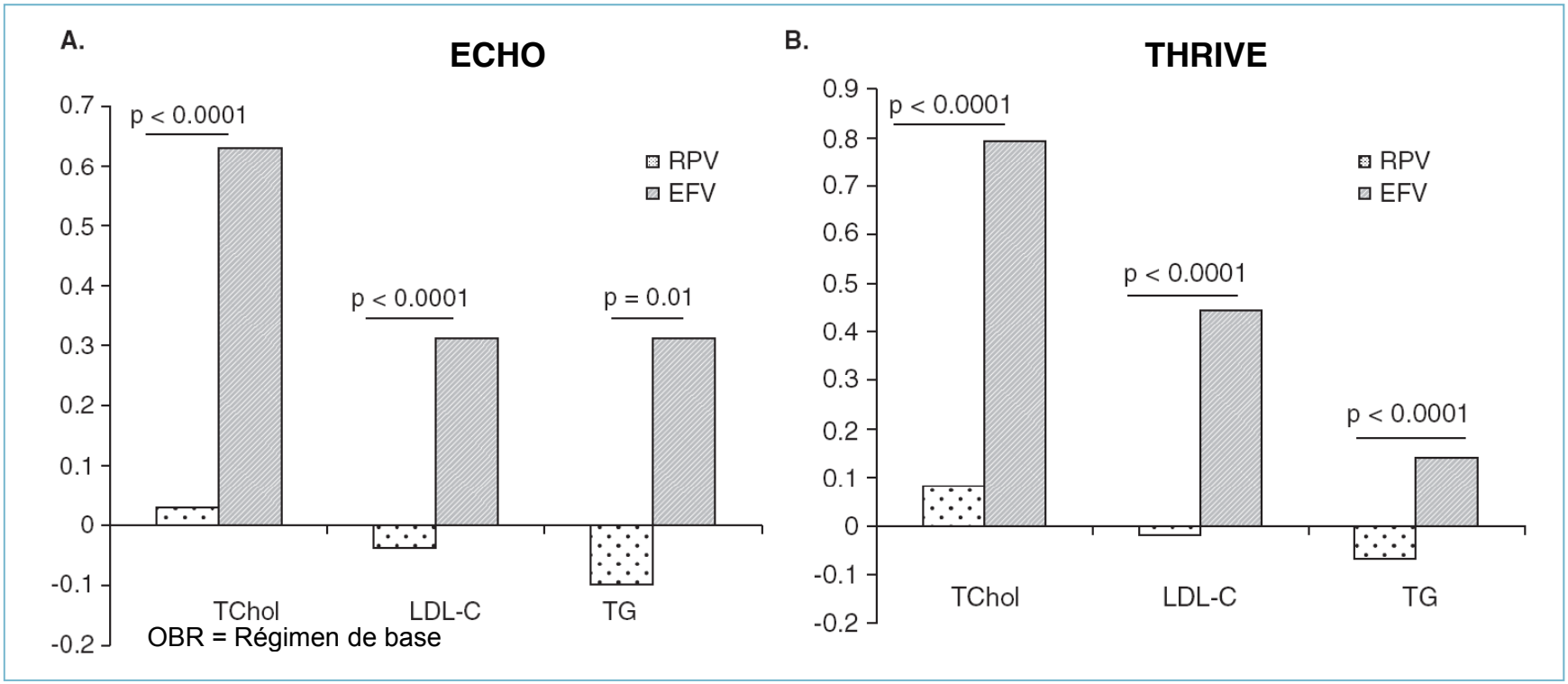
La incidencia de exantema fue mayor en las 4 primeras semanas, con una **incidencia mucho menor en el brazo de RPV** que en el de EFV.

26. Orkin C, Arribas J, Hodder S. Incidence of rash in the 96-week analysis of the pooled, phase III, randomised, double-blind ECHO and THRIVE trials. 18th BHIVA, Birmingham 2012. Poster P123. Para mayor información sobre seguridad, consulte la ficha técnica de rilpivirina.

E&T: Tolerabilidad lipídica

s.48

Cambio en los parámetros lipídicos desde el basal a la semana 48[27]



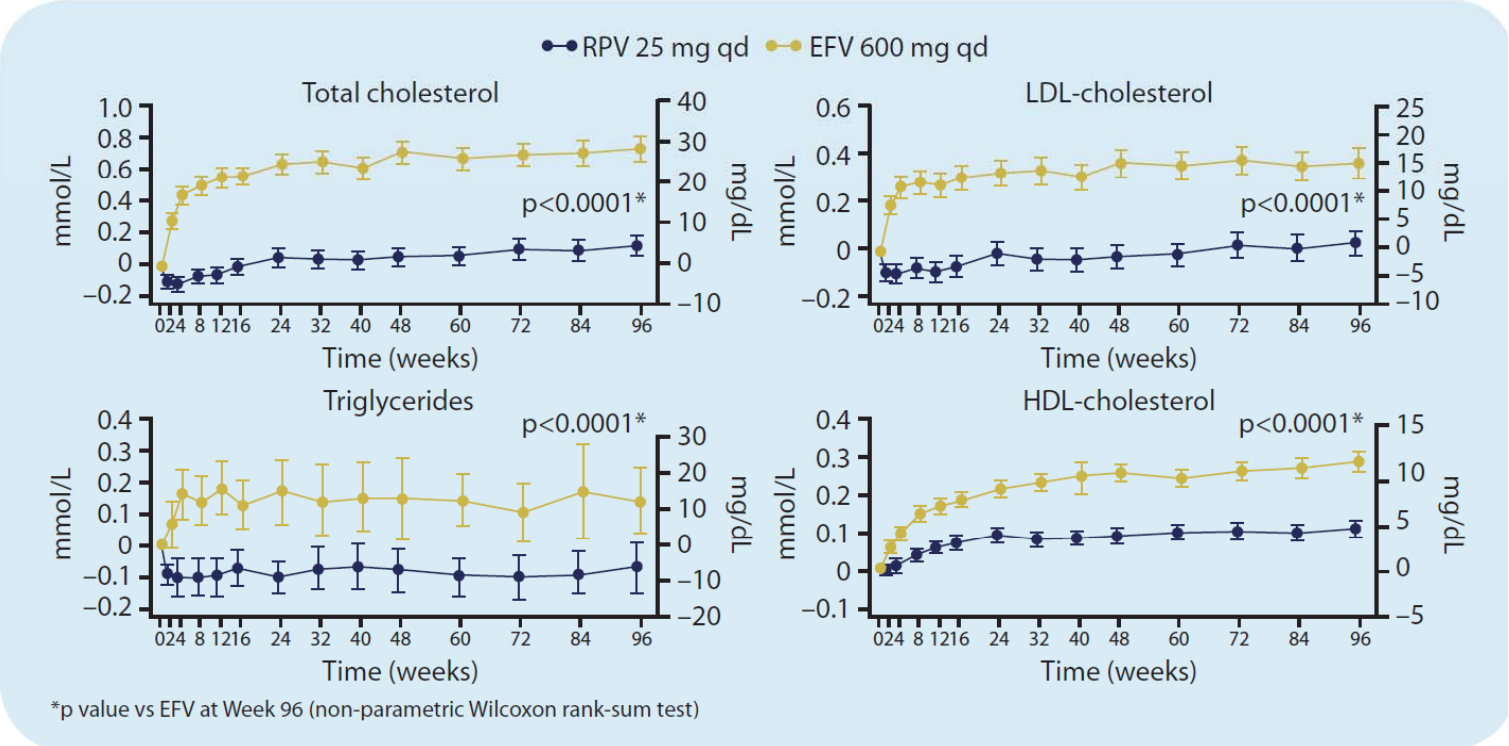
Las alteraciones lipídicas emergentes al tratamiento ocurrieron con una **mayor incidencia en la rama de EFV** que en la de RPV[30]

27. Fernández-Montero J, Vispo E , Anta L, et al. Rilpivirine: a next-generation non-nucleoside analogue for the treatment of HIV infection. Expert Opinion 201213(7):1007-1014.30. Arribas J, Andrade-Villanueva J, Bellos N, et al. Lipid profiles of TMC278 and efavirenz in treatment-naïve, HIV-1-infected patients: pooled week 48 data from the randomized, double-blind, phase III ECHO and THRIVE trials. 18th CROI, Boston 2011. Poster O-304. Para mayor información sobre seguridad, consulte la ficha técnica de rilpivriina.

E&T: Tolerabilidad lipídica

s.96

Cambio medio (IC 95%) desde el basal en los parámetros lipídicos



RPV mostró **una incidencia significativamente menor de alteraciones lipídicas** de **grado 2-4** que EFV

9.Orkin C, Cohen C, Molina JM, et al. Pooled week 96 efficacy, resistance and safety results from the double-blind, randomised, phase III trials comparing rilpivirine (RPV, TMC278) versus efavirenz (EFV) in treatment_naïve, HIV-1-infected adults. 18th BHIVA Birmingham 2012. Poster P184.

Para mayor información sobre seguridad, consulte la ficha técnica de rilpivirina.

En resumen (E&T)…

- RPV se asocia, en general, a menos EA comparado con EFV en los estudios ECHO y THRIVE:
  - Neuro-psiquiátricos: RPV se asoció con menos EA psiquiátricos y neurológicos a las 48 semanas.
  - Lipídicos: RPV se asoció a cambios medios significativamente inferiores de los parámetros lipídicos.
  - Cutáneos: la incidencia de exantema posiblemente relacionado con la medicación fue significativamente inferior con RPV.

STaR Study: Single-Tablet Regimen Emtricitabine/Rilpivirine/Tenofovir DF is Non-Inferior to Efavirenz/Emtricitabine/Tenofovir DF in ART-Naïve Adults

Week 48 Results

José R Arribas, Daniel Podzamczer, Calvin Cohen, Jan van Lunzen, Mark Bloch, Edmund Wilkins, Hui Wang, Danielle Porter, Todd Fralich, Pedro Ferrer, María L Álvarez

Fourth National Congress of GESIDA-SEIMC

Toledo, Spain

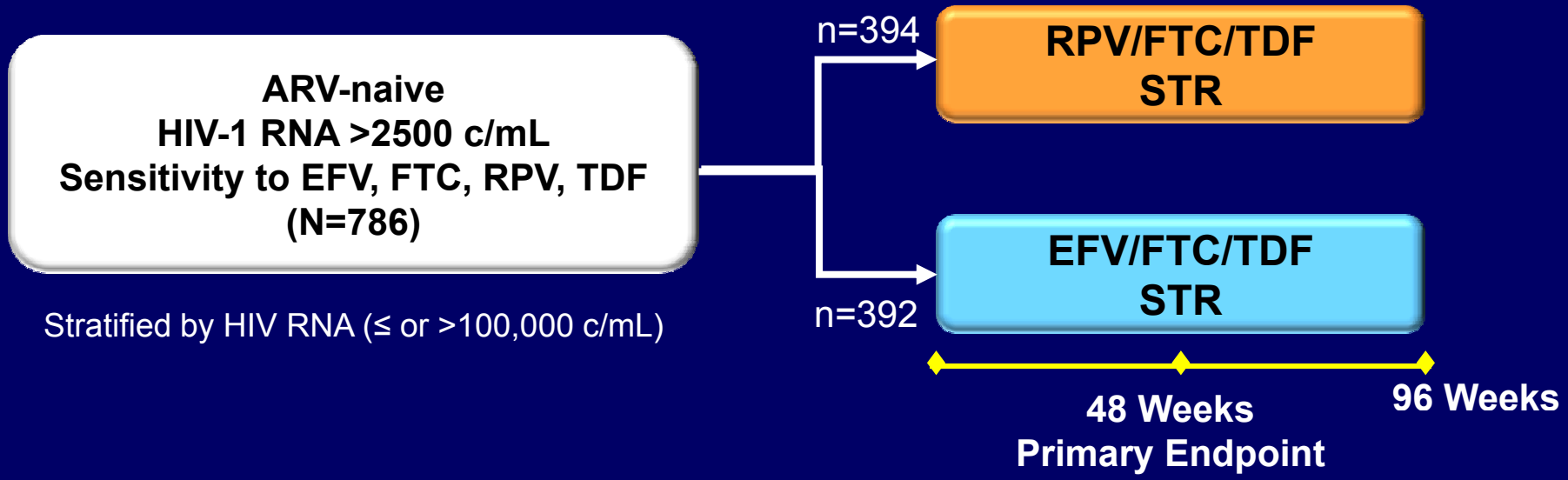
29 November 2012

Clinical trial number: GS-US-264-0110

Clinical Trials.gov: NCT01309243

STaR
Study Design

Multicenter, international, randomized, open-label, Phase 3b, 96-week study



Primary endpoint: Efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot analysis); non-inferiority margin of 12%

Secondary endpoints: Safety and efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 96 (FDA Snapshot analysis)
Change in CD4 cell count at Weeks 48 and 96
Genotype/phenotype resistance at time of virologic failure

STaR

Baseline Demographics and Characteristics

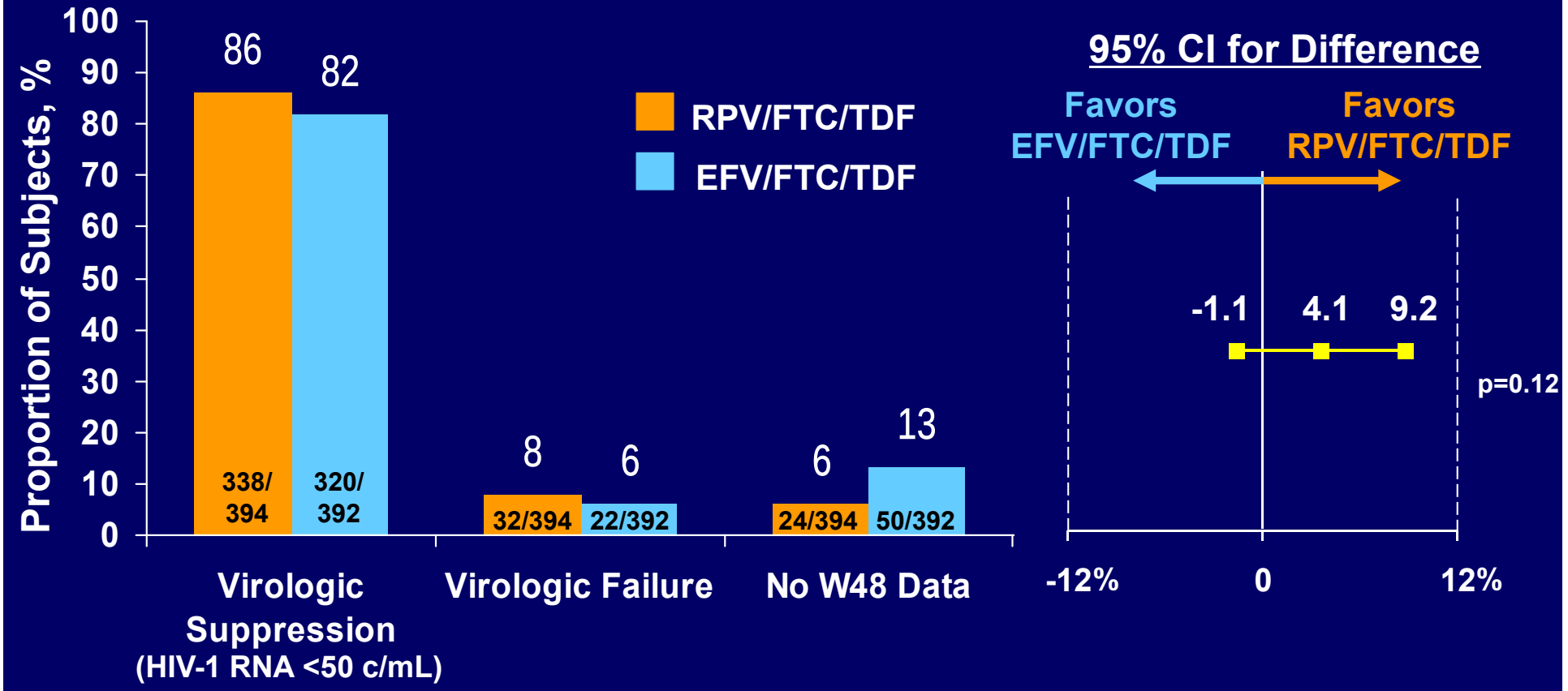
	RPV/FTC/TDF	EFV/FTC/TDF
Median age, years (IQR)	37 (29, 45)	35 (28, 45)
Male	93%	93%
White race	68%	67%
Black race	25%	24%
Latino ethnicity	15%	19%
Mean CD4 cell count, cells/mm^3 (SD)	396 (180)	385 (187)
HIV-1 RNA, log10 c/mL, mean (SD)	4.8 (0.7)	4.8 (0.6)
≤100,000 c/mL, n (%)	260 (66%)	250 (64%)
>100,000 to ≤500,000 c/mL, n (%)	98 (25%)	117 (30%)
>500,000 c/mL, n (%)	36 (9%)	25 (6%)

Research sites include Australia, Austria, Belgium, Canada, France, Germany, Italy, Portugal, Spain, Switzerland, United Kingdom, United States and Puerto Rico

STaR

Virologic Suppression and CD4 Change at Week 48
FDA Snapshot Analysis – ITT Population

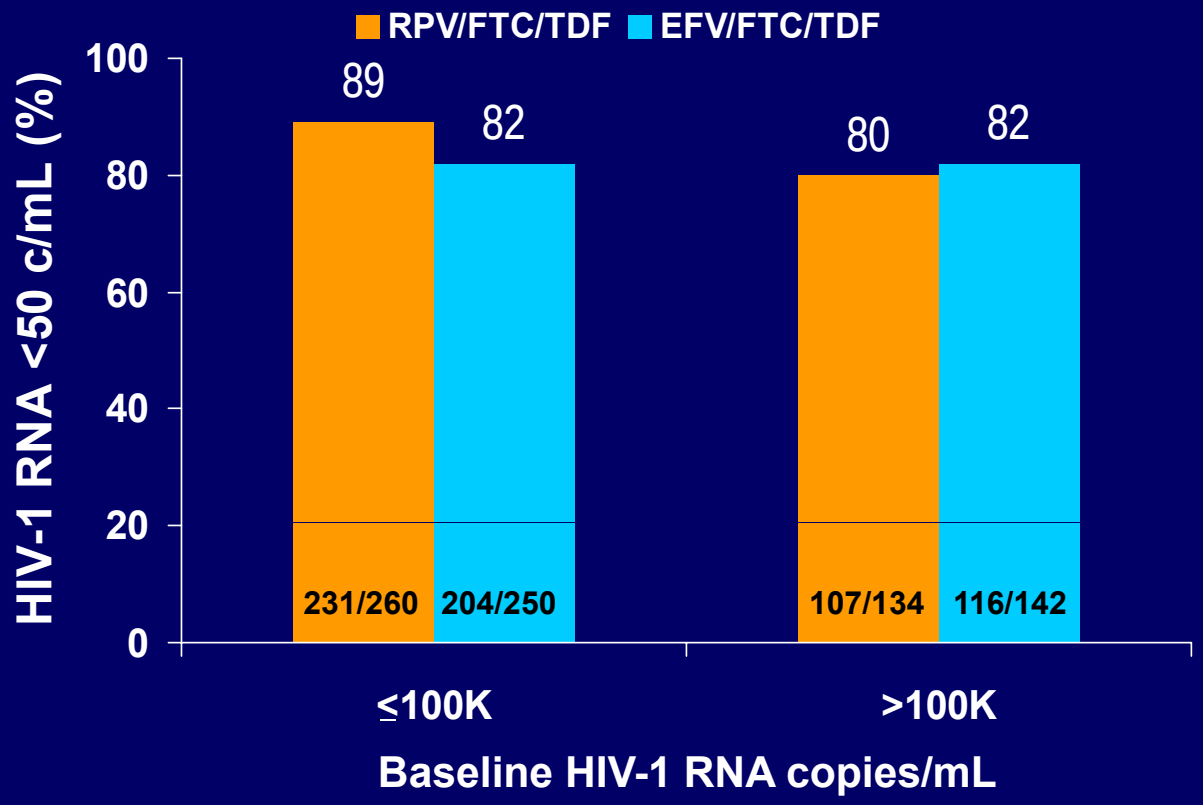
RPV/FTC/TDF is non-inferior to EFV/FTC/TDF

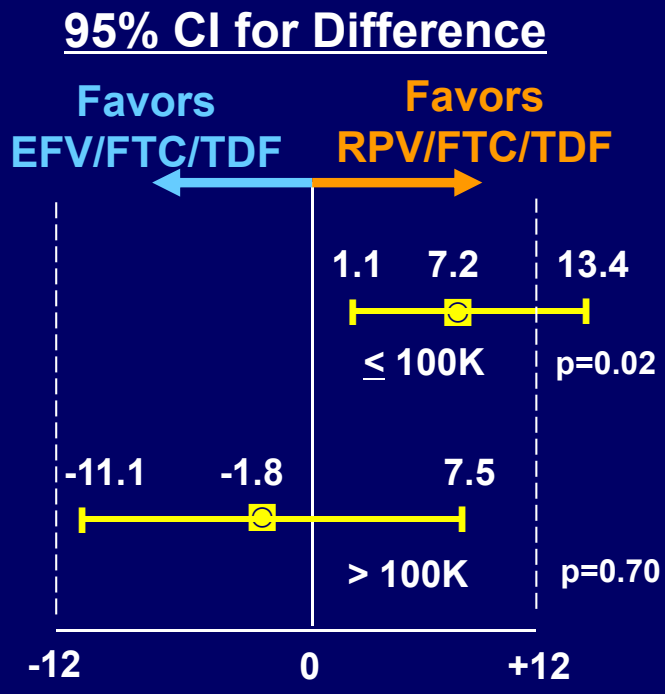


CD4 count change (cells/mm³): RPV/FTC/TDF +200 vs EFV/FTC/TDF +191 (p=0.34)

STaR

Virologic Suppression at Week 48 FDA Snapshot Analysis by Baseline HIV-1 RNA Stratified by 100,000 c/mL

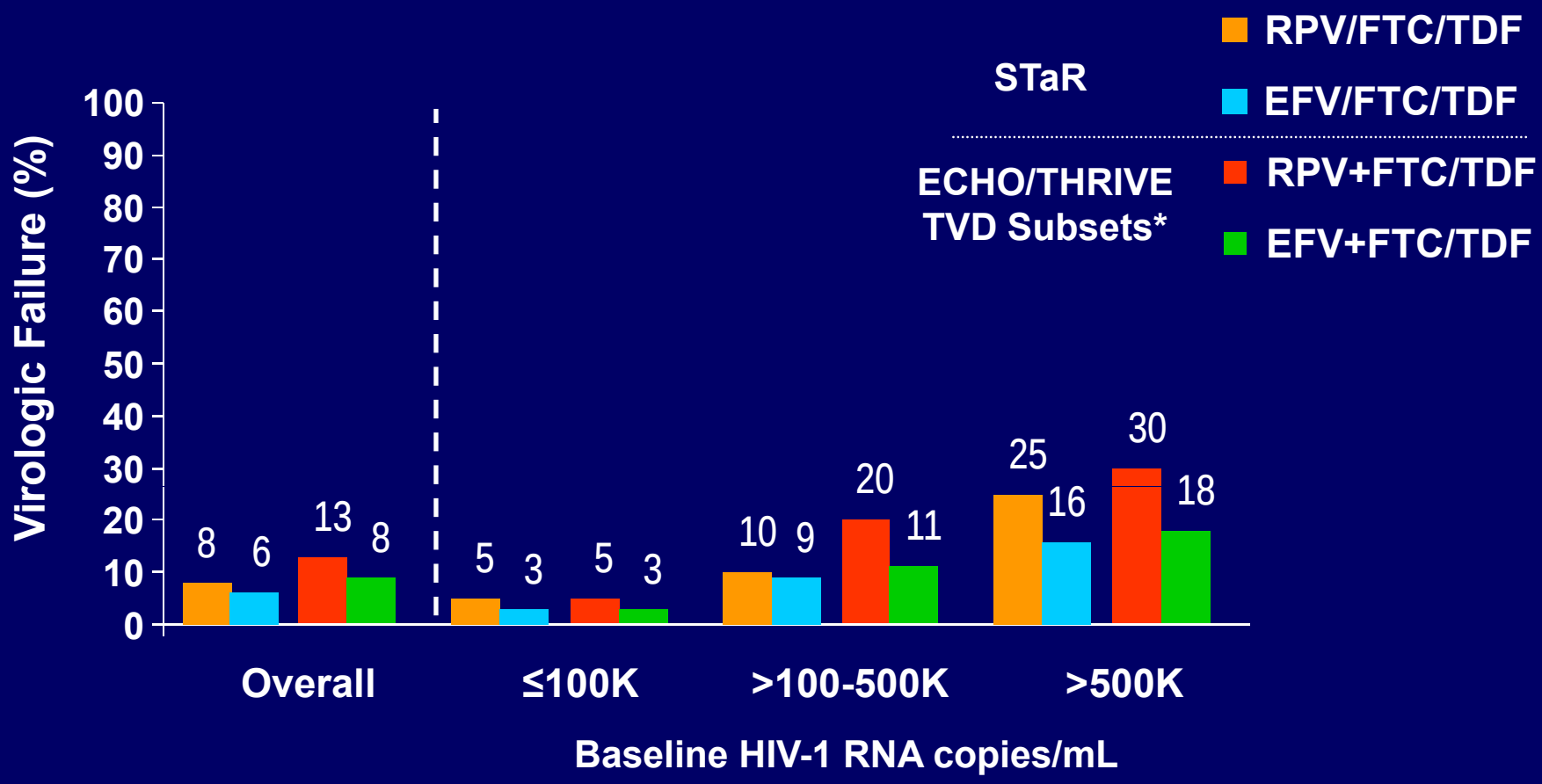




RPV/FTC/TDF compared to EFV/FTC/TDF
Superior for subjects with baseline HIV-1 RNA ≤100,000 c/mL
Non-inferior for subjects with baseline HIV-1 RNA >100,000 c/mL

STaR & ECHO/THRIVE

Virologic Failure at Week 48 per FDA Snapshot Overall and by Baseline HIV-1 RNA



ECHO/THRIVE: Two Phase III double-blinded, double dummy, mulitcenter 96 week studies in treatment-naïve HIV-1 infected subjects randomized to receive either RPV (25mg) or EFV (600mg) in combination with 2 NRTIs (ECHO, FTC/TDF; THRIVE, Investigator's choice [FTC/TDF, n=406; 3TC/AZT, n=204; 3TC/ABC, n=68]). In the pooled TVD subset analysis (N=1096), RPV+TVD was non-inferior to EFV+TVD (HIV-1 RNA <50 c/mL [83%, 81%])

*COMPLERA Prescribing Information. Gilead Sciences Inc. 2011.

STaR

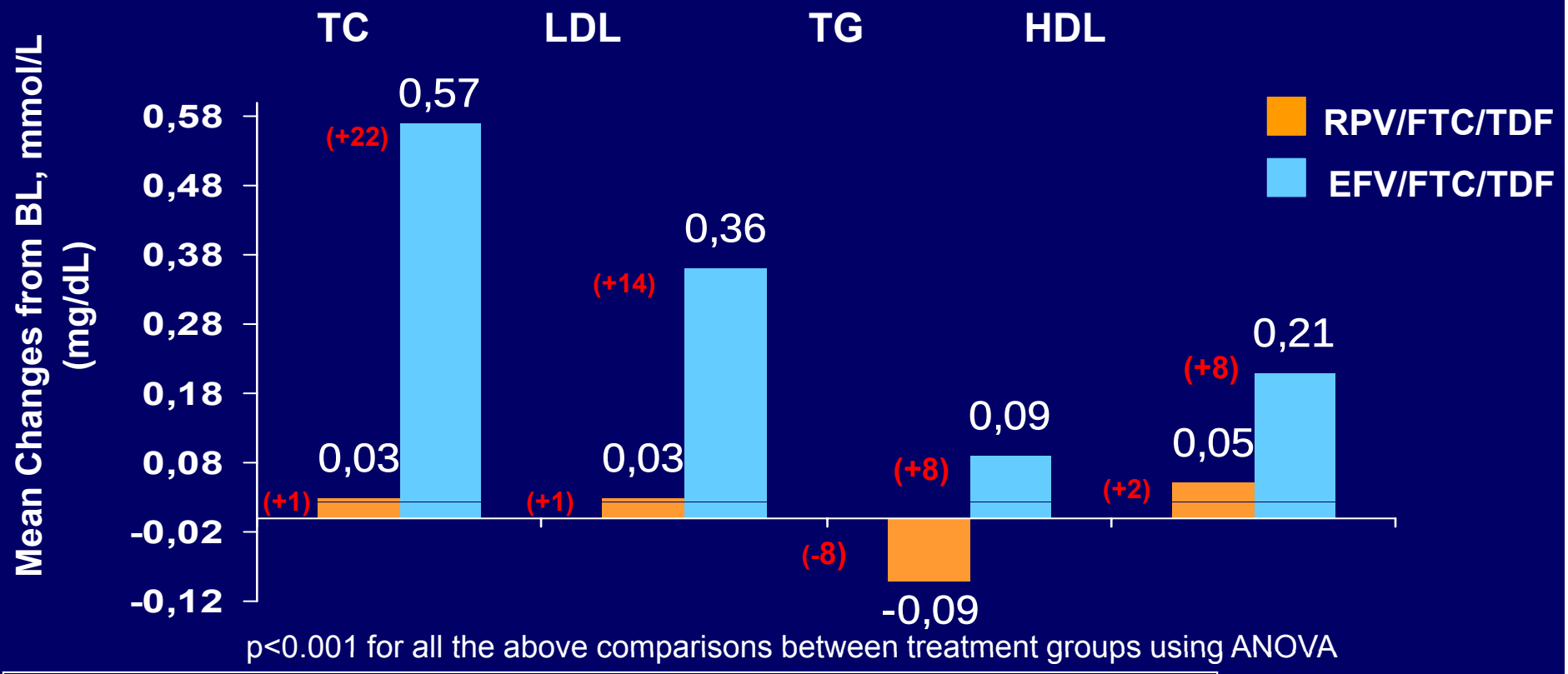
Adverse Events Leading to Discontinuation of Study Drug Through Week 48

	RPV/FTC/TDF (n=394)	EFV/FTC/TDF (n=392)	
Discontinuations* Due to Adverse Event (AE), n (%)	**10 (2.5%)**	**34 (8.7%)**	**P<0.001**
AE leading to discontinuation in >1 subject in either arm			
Nervous System Events			
Dizziness	**0**	**5 (1.3%)**	
Abnormal Dreams or Nightmare	**0**	**6 (1.5%)**	
Insomnia	**1 (0.3%)**	**3 (0.8%)**	
Psychiatric Disorders			
Depression, Anxiety or Depressed Mood	**0**	**9 (2.3%)**	
Suicidal Ideation	**0**	**2 (0.5%)**	
GI, General, Skin Disorders			
Diarrhea	**0**	**2 (0.5%)**	
Fatigue	**0**	**2 (0.5%)**	
Pyrexia	**0**	**2 (0.5%)**	
Toxic Skin Eruption	**0**	**2 (0.5%)**	

*per safety population

STaR

Changes from Baseline Through Week 48 in Fasting Lipids



p<0.001 for all the above comparisons between treatment groups using ANOVA

Mean Baseline Values, mmol/L								
	4.24	4.22	2.69	2.66	1.37	1.46	1.14	1.14

Change in TC:HDL at Week 48 was -0.2 in both arms

TC - total cholesterol, LDL - low-density lipoprotein, TG - triglycerides, HDL - high-density lipoprotein

En resumen (STAR)…

- Globalmente RPV/TDF/FTC demostró la no inferioridad frente a EFV/FTC/TDF en semana 48 (supresión virológica):
  - ✓Superior cuando HIV-1 RNA ≤100,000 copias/mL
  - ✓No inferior cuando HIV-1 RNA >100,000 copias/mL
- RPV/FTC/TDF se tolera significativamente mejor que EFV/FTC/TDF:
  - ✓Menos EA relacionados con SNC y Psiquiátricos.
  - ✓Menor número de discontinuaciones por EA.

A drug from column A should be combined with the drugs listed in column B (**)

A	B	Remarks
NNRTI	**NRTI**	
• EFV (i) • RPV (ii)	ABC/3TC (vii) or TDF/FTC	• TDF/FTC co-formulated • ABC/3TC co-formulated • EFV/TDF/FTC co-formulated • RPV/TDF/FTC co-formulated
• NVP (iii)	TDF/FTC	• TDF/FTC co-formulated
Ritonavir-boosted PI		
• ATV/r (iv) • DRV/r (iv) • LPV/r (v)	ABC/3TC (vii) or TDF/FTC	• ATV/r: 300/100 mg qd • DRV/r: 800/100 mg qd • LPV/r: 400/100 mg bid or 800/200 mg qd
ITI		
• RAL	TDF/FTC	• RAL: 400 mg bid

* Only drugs currently licensed for initiation of therapy by the European EMA are taken into consideration.

** Generic HIV drugs are becoming more available and can be used as long as they replace the same drug and do not break recommended fixed dose combinations.

i EFV: not recommended to be initiated in pregnant women or women with no reliable and consistent contraception; continuation is possible if already started before pregnancy; not active on HIV-2 and HIV-1 group O.

ii RPV: only if VL < 100 000 c/mL; PPI contraindicated, H2 antagonists to be taken 12h before or 4h after RPV.

iii NVP: Use with extreme caution in women with CD4 > 250 and men with CD4 > 400 µL and only if benefits outweigh the risk; not active on HIV-2 and HIV-1 group O.

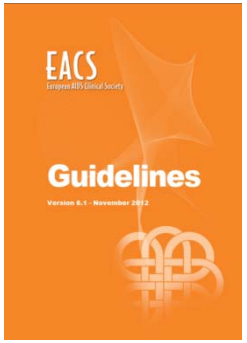
iv Castle study (LPV/r vs. ATV/r) has shown better tolerability of ATV/r and Artemis study (LPV/r vs. DRV/r) better efficacy and greater tolerability of DRV/r.

v ACTG 5142 randomised study showed lower virological efficacy of LPV/r vs. EFV while no PI mutations were seen in the LPV/r plus two nucleoside failures. However, PI mutations were seen on LPV/r + EFV.

vi Unlicensed in Europe for naive patients.

vii ABC contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in patients with a high CVD risk and/or patients with a VL > than 100,000 c/mL.

viii Only if unavailability or intolerance to other recommended NRTIs.



Combinaciones preferentes de tratamiento antirretroviral de inicio (GESIDA y PNS 2013)

3er Fármaco	Pauta‡	Ensayos clínicos que la sustentan
ITINN	*TDF/FTC/EFV[1,2,3]	STARTMRK, ACTG 5202, GS-US-236-0102, GILEAD 934, SINGLE
	~~ABC/3TC+EFV[1,2,4,5]~~	ACTG 5202, CNA30024
	TDF/FTC/RPV[2,3,5,7]	ECHO, THRIVE, STAR
	TDF/FTC+NVP[2,3,6]	ARTEN, VERXVE
IP/r	*TDF/FTC+ATV/r [3,7]	CASTLE, ACTG 5202, ARTEN, GS-US-236-0103 GS-US-216-0114
	*TDF/FTC+DRV/r[3]	ARTEMIS
	TDF/FTC+LPV/r[3,8]	ARTEMIS, ABT-730, CASTLE, GEMINI, HEAT, PROGRESS
	ABC/3TC+ATV/r[4,5,7]	ACTG 5202
	ABC/3TC+LPV/r[5,8]	KLEAN, HEAT
InInt	*TDF/FTC+RAL[3]	STARTMRK, QDMRK, SPRING2
	ABC/3TC+RAL[4]	SPRING 2

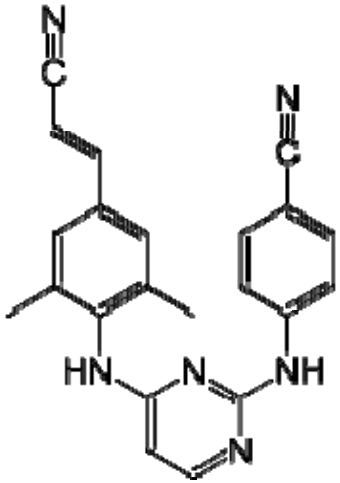
† Ordenado por tercer fármaco. Se recomienda el uso de preparados que combinen fármacos a dosis fijas. No existe en la actualidad suficiente información que permita considerar como equivalentes terapéuticos a FTC y 3TC, por lo que el uso de uno u otro fármaco en los regímenes seleccionados depende fundamentalmente de la experiencia disponible en su uso conjunto con los otros fármacos de la combinación.

‡ Los comentarios reflejan aspectos que se deben considerar en la elección de régimen, pero no pretenden ser una guía exhaustiva de las precauciones a tomar en el uso de los fármacos. Para mayor información se recomienda revisar el texto del documento así como las fichas técnicas de los fármacos. * Solo estas pautas han sido consideradas como preferentes por la totalidad del panel de expertos.

En otro apartado de estas guías se tratan aspectos de precio y de costes de los diferentes regímenes terapéuticos. Simultáneamente con las guías se publica un artículo en el que se hace un análisis formal de coste/eficacia de las pautas recomendadas como preferentes

1 Evitar en mujeres que planean quedarse embarazadas y en pacientes con alteraciones neuropsiquiátricas no estabilizadas. Usar con precaución en pacientes que realicen tareas peligrosas si presentan síntomas de somnolencia, mareos y/o trastornos de la concentración.
2 Es preciso realizar previamente un estudio genotípico que descarte mutaciones de resistencia a ITINN.
3 Usar TDF con precaución en pacientes con factores de riesgo para insuficiencia renal. Contraindicado si FG <30 ml/min. El uso combinado de IP/r y TDF incrementa particularmente el riesgo de nefrotoxicidad de éste.
4 Es preciso realizar previamente determinación de HLA-B*5701. No utilizar si HLA-B*5701 positivo.
5 Mayor riesgo de fracaso virológico que con TDF/FTC/EFV en pacientes con CVP >100.000 copias/ml
6 No iniciar en mujeres con CD4 >250 células/µL ni en varones con CD4 > 400 células/µL.
7 Evitar si se utilizan inhibidores de la bomba de protones.
8 Evitar en pacientes con hiperlipidemia y/o riesgo cardiovascular elevado.

RILPIVIRINA (RPV)



1) **Generalidades**

2) **Naïve**
(ECHO y THRIVE, STAR)

3) **Pretratado**
(SPIRIT y GS-111)

GS 111
Diseño del estudio

Ensayo clínico fase 2b, abierto, multicéntrico, 48sem de seguimiento de cambio de ATP a Eviplera en pacientes estables, controlados virológicamente

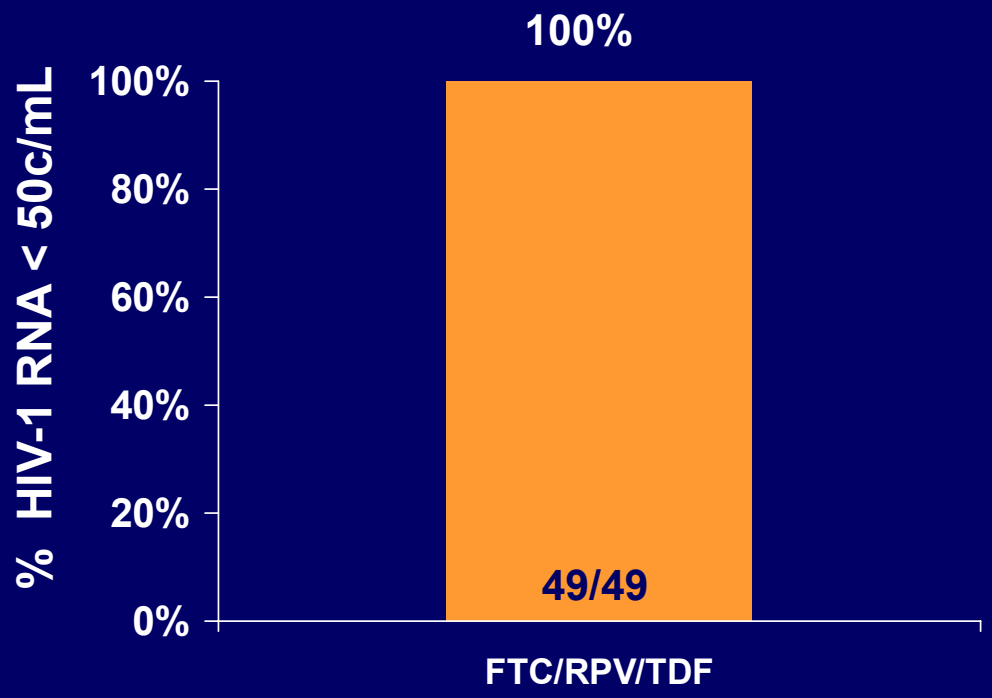
Estable con EFV/FTC/TDF x ≥ 3 meses
-Deseo de cambiar por problemas de tolerancia
-CV <50 c/ml ≥ 8sem
-No resistencia genotípica
-eGFR ≥ 50ml/min
N=50

Endpoint primario: % de pacientes con CV<50 c/ml a **Sem 12** tras el cambio
Análisis FDA Snapshot, población ITT

Endpoints secundarios: Seguridad de FTC/RPV/TDF a 24 y 48 sem
CV <50 c/ml a Sem 24 y48
Farmacocinética de RPV tras el cambio

Cohen C, et al. EACS 2011. Belgrade, Serbia. Oral #LBPS10/4

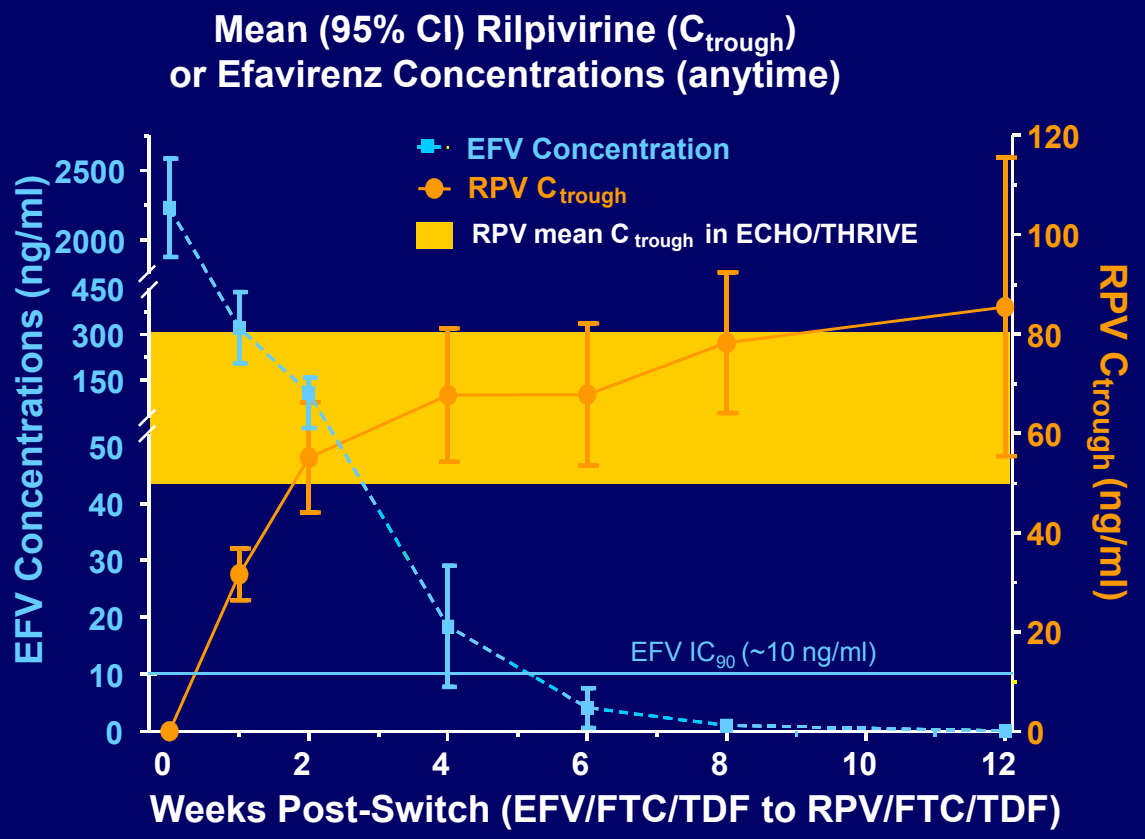
GS 111
CV <50 copias/ml a Sem 12 (Análisis FDA Snapshot– Población ITT)



- 1 paciente retiró el consentimiento antes de iniciar tratamiento

Cohen C, et al. EACS 2011. Belgrade, Serbia. Oral LB #PS10/4

GS 111
Farmacocinética de RPV tras el cambio desde EFV



- C_{valle} media de EFV por encima de la IC_{90} (~10 ng/ml*) hasta ~4 sem
- Ningún paciente con concentraciones de RPV por debajo del límite de detección
- C_{valle} media de RPV alcanza el rango de referencia en 2 sem

Week	RPV C_{trough} Mean (%CV), ng/ml
2	52 (47)
4-12	66 (51) - 84 (76)

*protein-binding adjusted; Corbett JW, et al. J Med. Chem 2000:43;2019-2030

Adapted from Cohen C, et al. EACS 2011; Belgrade, Serbia. Oral #PS10/4

GS 111

Seguridad

- Ningún paciente tuvo EA que condicionaran discontinuación del tratamiento
- EA relacionados con el tratamiento
  - Grado 1 en dos o más pacientes
    - Náuseas (n = 2)
    - Insomnio (n = 2)
    - Flatulencia (n = 2)
  - Grado 2
    - Astenia (n = 1)
    - Aumento de bilirrubina (n = 1)
  - Grados 3 o 4 - ninguno

Cohen C, et al. EACS 2011. Belgrade, Serbia. Oral LB #PS10/4

En resumen (GS111)…

- En semana 12 todos los pacientes mantenían supresión virológica tras el cambio de EFV/FTC/TDF a RPV/TDF/FTC.
- Los efectos inductores transitorios de EFV sobre el metabolismo de RPV no parecen ser clínicamente relevantes en pacientes con supresión viral.
- RPV/TDF/FTC fue bien tolerado y no se presentaron EA que condicionaran la retirada del fármaco a lo largo de esas primeras 12 semanas.

SPIRIT: Switching to Emtricitabine/Rilpivirine/Tenofovir DF Single-Tablet Regimen from Boosted Protease Inhibitor Maintains HIV Suppression through Week 48

Juan Berenguer, Bonaventura Clotet, Josep M Gatell, Santiago Moreno, Martin Fisher, Brian Gazzard, Jan van Lunzen, Hui Wang, Danielle Porter, Todd Fralich, Pedro Ferrer, María L Álvarez

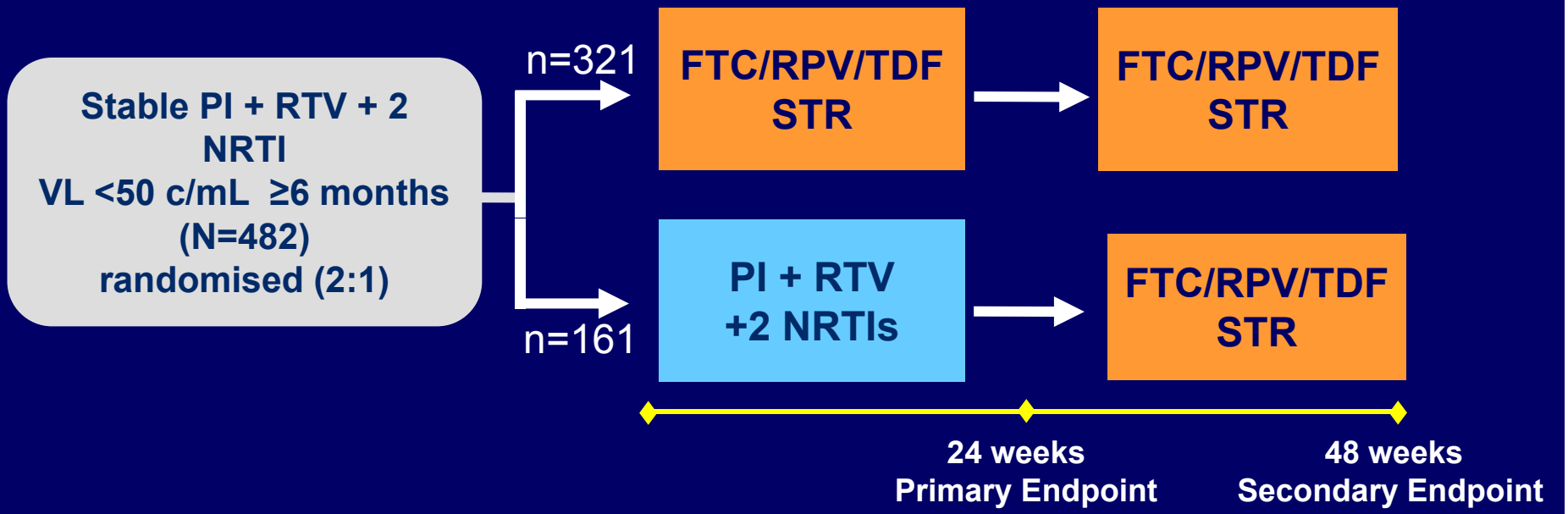
Fourth National Congress of GESIDA-SEIMC
Toledo, Spain
28 November 2012
GS-US-264-0106 NCT01252940

GS 106

SPIRIT: Study Design

Switching boosted PI to Rilpivirine In-combination with Truvada as an STR

multicentre, international, randomised, open-label, Phase 3b, 48-week study



Primary Endpoint: Non-inferiority to PI+RTV+2 NRTIs HIV RNA <50 c/mL at **24 weeks**

Secondary Endpoints: Change in fasting lipid parameters at 24 and 48 weeks
Undetectable viral load (<50 c/mL) at 48 weeks

Adherence and PROs: VAS Adherence Questionnaire, HIVSI, HIVTSQ

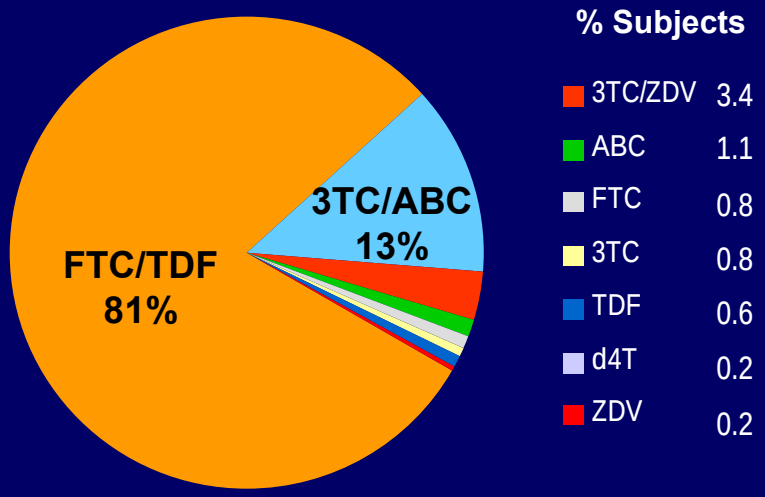
Fully enrolled

Data on file. Gilead Sciences, Inc

SPIRIT

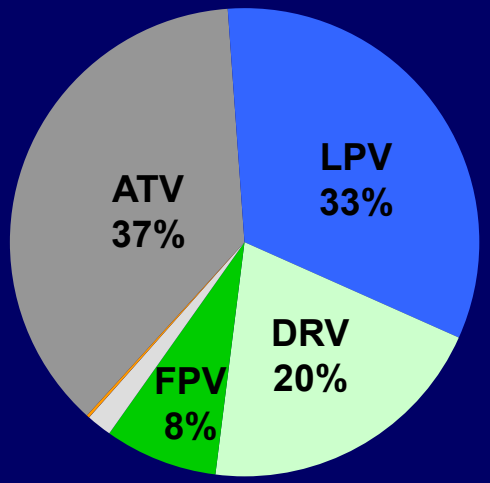
Antiretroviral Therapy at Screening

NRTI



% Subjects	
3TC/ZDV	3.4
ABC	1.1
FTC	0.8
3TC	0.8
TDF	0.6
d4T	0.2
ZDV	0.2

RTV-boosted PI†



% Subjects	
SQV	1.7
APV	0.2

3TC: lamivudine; d4T: stavudine; ABC: abacavir; APV: amprenavir; ATV: atazanavir; DRV: darunavir; FPV: fosamprenavir; FTC: emtricitabine; LPV: lopinavir; RTV: ritonarvir; SQV: saquinavir; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine

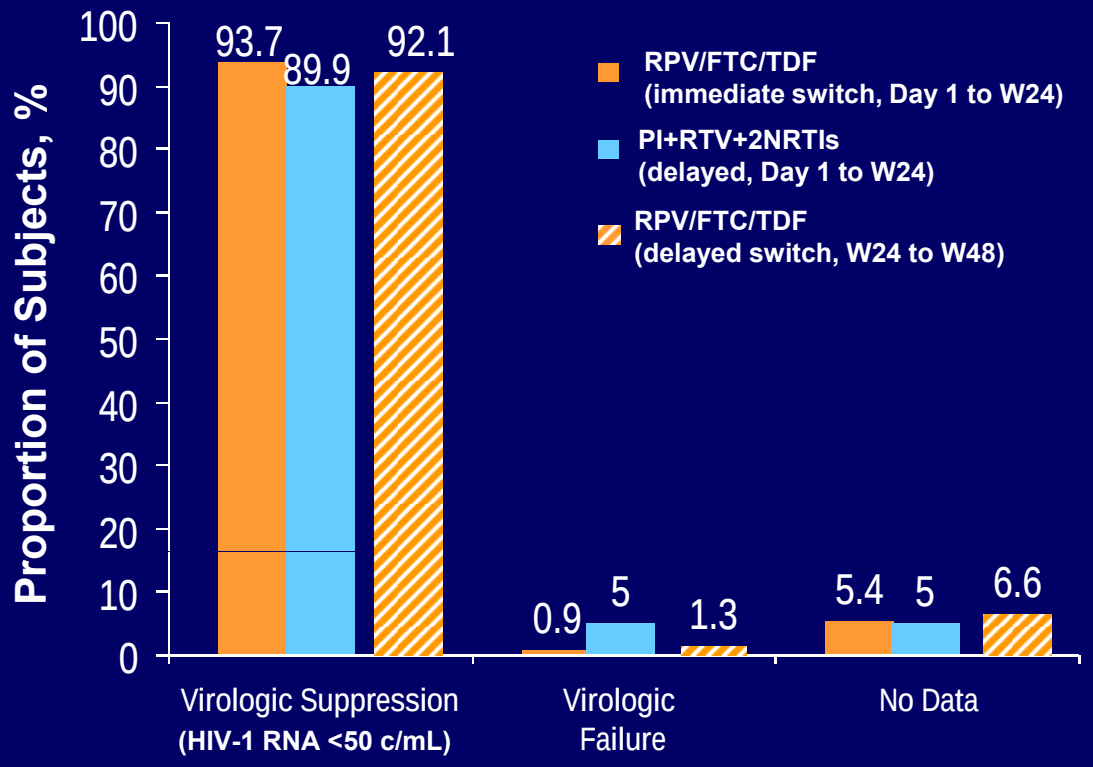
† Includes all treated participants. 2 subjects enrolled on EFV/FTC/TDF instead of a boosted PI (protocol violation)

SPIRIT

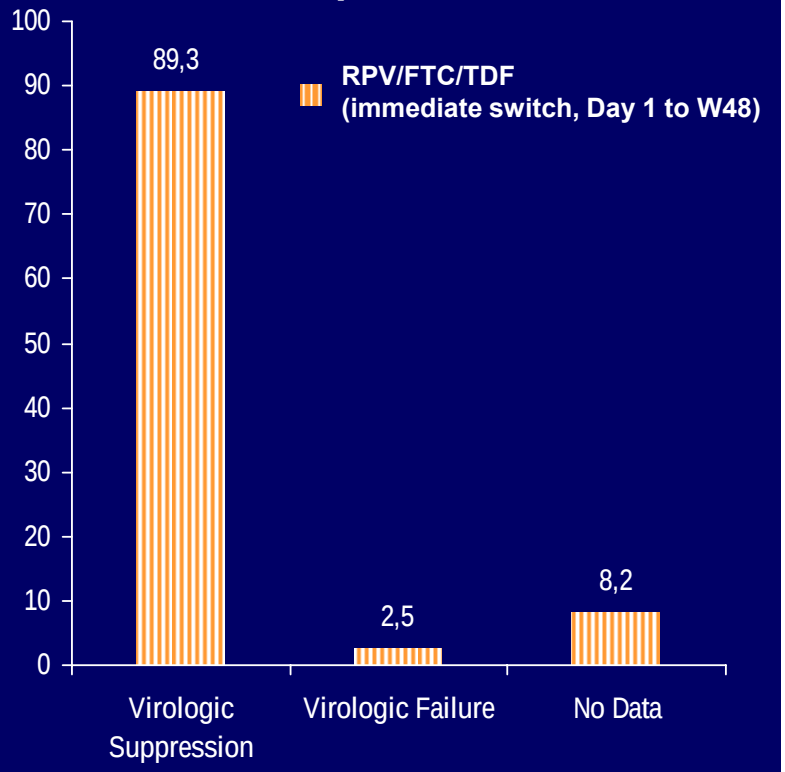
Virologic Suppression at Weeks 24 and 48 FDA Snapshot Analysis – ITT Population

Switching to RPV/FTC/TDF was non-inferior* to remaining on PI+RTV+2NRTIs for 24 weeks (delta 3.8, CI [-1.6, 9.1]). Similar rates of virologic suppression were also seen with 48 weeks of treatment with RPV/FTC/TDF

FDA Snapshot at 24 Weeks



FDA Snapshot at 48 Weeks



CD4 count change (cells/mm^3): Week 24, RPV/FTC/TDF immediate switch +20, PI+RTV+2NRTIs +32 (p=0.28), RPV/FTC/TDF delayed switch -7. Week 48, RPV/FTC/TDF immediate switch +10

SPIRIT
Grade 3 or 4 Adverse Events and Laboratory Abnormalities

	RPV/FTC/TDF N = 317 (Immediate switch, at W48)	PI+RTV +2NRTIs N = 159 (at W24)	RPV/FTC/TDF N = 152 (Delayed switch, at W24)
Grade 3 or 4 Adverse Events	**18 (5.7%)**	**11 (6.9%)**	**12* (7.9%)**
Grade 3 or 4 Laboratory Abnormalities	**28† (8.8%)**	**18‡ (11.3%)**	**23§ (15.2%)**

Adverse events and laboratory abnormalities occurring in ≥1% of subjects:

*creatine kinase increase

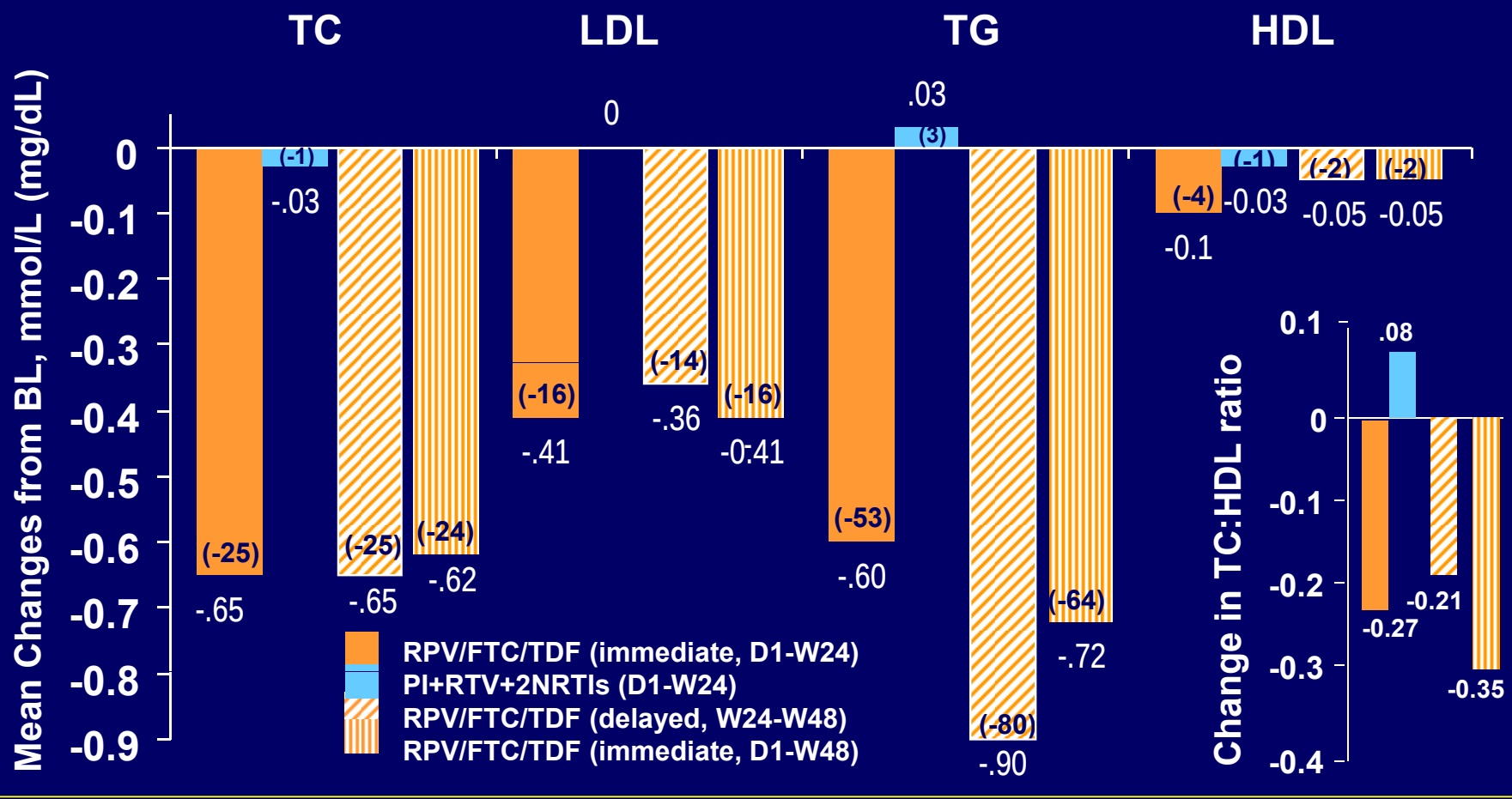
†ALT, AST, creatine kinase, hematuria

‡AST, bilirubin, creatine kinase, triglycerides

§ ALT, AST, creatine kinase, glycosuria

SPIRIT

Changes from Baseline in Fasting Lipids



Switching to RPV/FTC/TDF resulted in improvement in fasting lipids, including TC, LDL, TGs, and TC:HDL ratio at Week 24 and maintained through Week 48

TC - total cholesterol, LDL - low-density lipoprotein, TG - triglycerides, HDL - high-density lipoprotein

En resumen (SPIRIT)…

- En semana 24 el cambio a RPV/FTC/TDF demostró ser no inferiorior a continuar con IP/r + 2NRTIs (93,7% vs. 89,9%).
- Menor tasa de fallo virológico en los que cambian a RPV/FTC/TDF (0,9%) comparado con los que continúan con IP/r +2NRTIs (5,0%) en semana 24.
- El desarrollo de resistencias fue infrecuente en los que cambiaron a RPV/FTC/TDF.
- El cambio a RPV/FTC/TDF resultó en una mejora de los lípidos (CT, cLDL, TG y CT/cHDL) en semana 24 que se mantiene en semana 48.

DOLUTEGRAVIR

1) Generalidades

2) Naïve

(Single y Spring-2)

3) Pretratado

(Sailing y Viking-3)

DOLUTEGRAVIR

1) Generalidades

2) Naïve (Single y Spring-2)

3) Pretratado (Sailing y Viking-3)

DTG Clinical Attributes & Pharmacologic Basis for Differentiation

Clinical Efficacy

- ***Superiority demonstrated against ATRIPLA AND RALTEGRAVIR***
- Active across HIV clades and subtypes

Activity against INI-resistance

- ***Limited cross-resistance with RAL and EVG in vitro***
- ***69% of INI-R suppressed in VIKING-3 (despite weak OBR)***

Barrier to resistance

- ***Unlike RAL or EVG, single mutation s not associated with high-level resistance***
- ***Trough concentrations above target 3-4days after last dose***
- ***No INI or NRTI mutations in Ph3 naïve studies***

Dolutegravir

Clinical Pharmacology

Favorable PK profile

- ***Low mg, QD dosing , unboosted***
- ***Consistent PK (low CV%)***
- ***Few significant drug interactions***
- ***No food or pH effect***

Preclinical Safety Assessment

- Negative genotoxicity and carcinogenicity studies
- Negative pre/postnatal and reprotox studies
- Projected pregnancy Category B

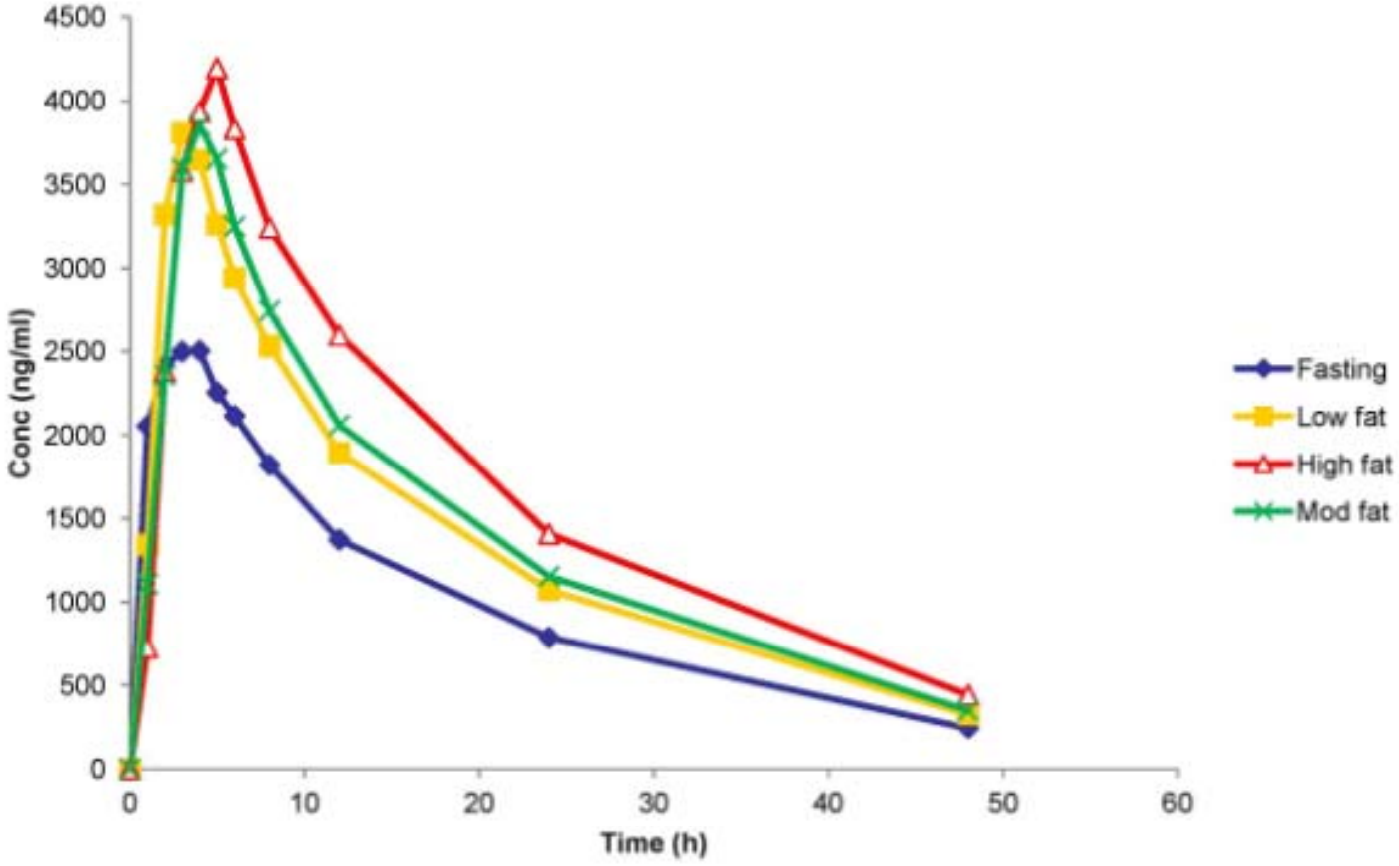
Clinical Safety

- ***Tolerability improved vs. Atripla, comparable to RAL***
- No signature toxicity requiring monitoring beyond SOC
- Lipid neutral
- Negative TQT study

Chem Dev / Pharm Dev

- Simple, small, low mg tablet formulation
- *FDC opportunity*
- Robust CMC package, 24 month shelf life

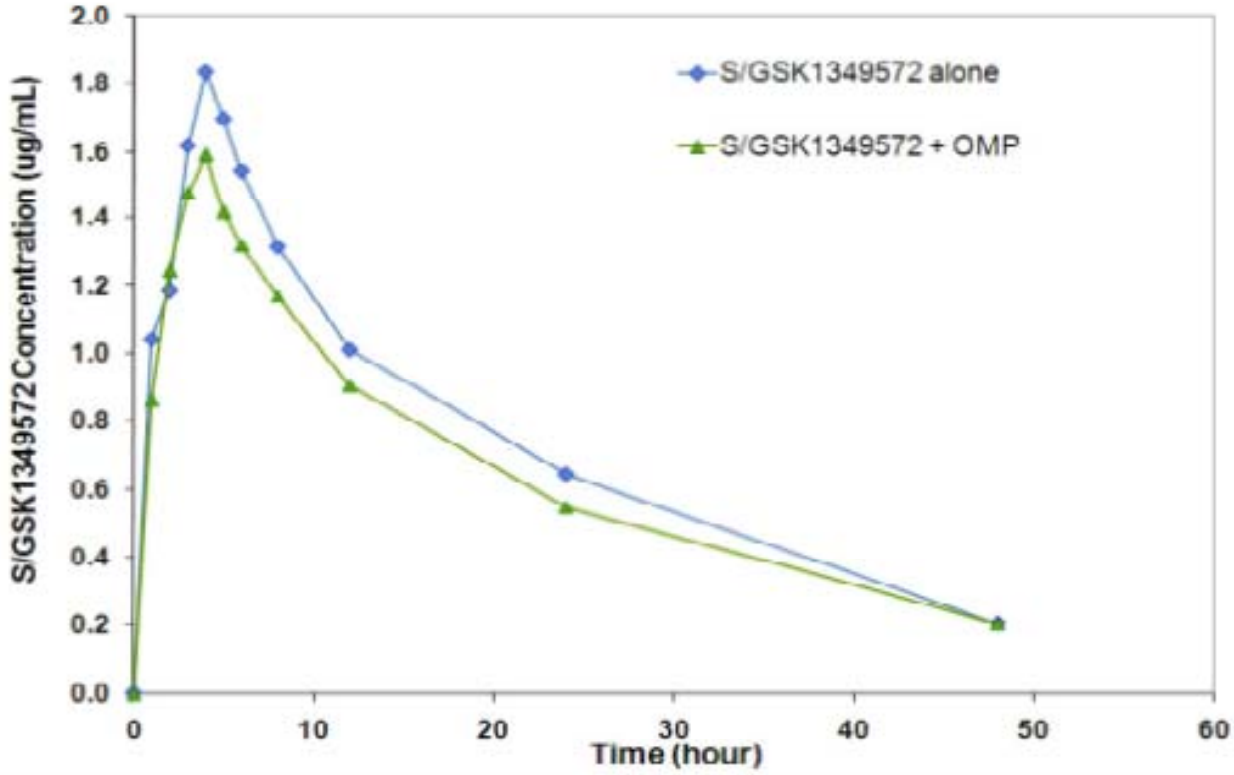
Efecto de los alimentos en Dolutegravir dosis de 50 mg



Dolutegravir puede tomarse con o sin alimentos.

Johannes, C., et al Expert Opinion Investig. Drugs (2011) April 2011. 20;4.537-548.

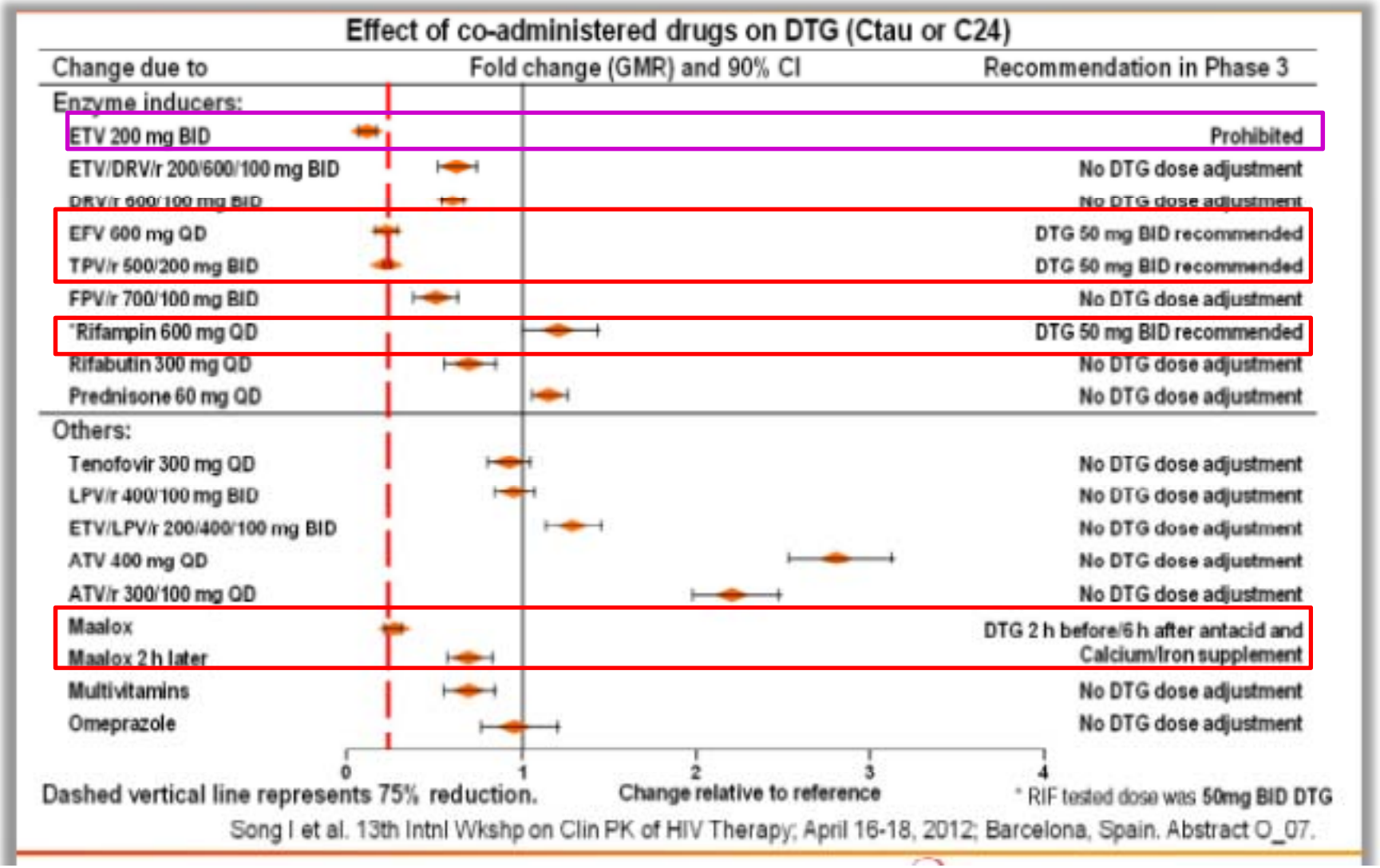
Los inhibidores de la bomba de protones (omeprazol) no tienen efecto en el PK de Dolutegravir



Dolutegravir puede ser co-administrado con IBP o antagonistas H2 sin ajuste de dosis

Ref: Patel P, et al, 2010 ICAAC.

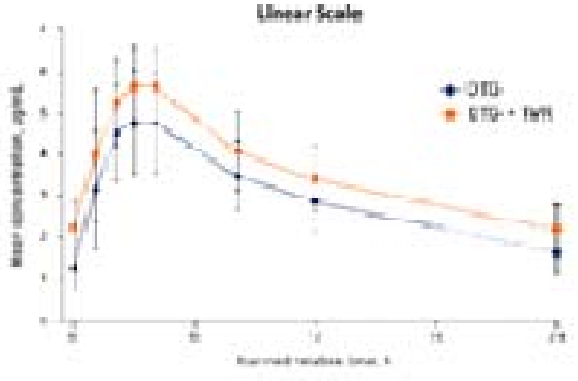
Resumen de los efectos de los fármacos administrados conjuntamente en DTG



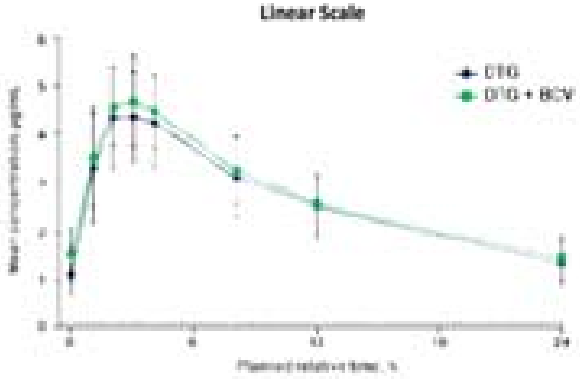
INTERACCIÓN DTG CON INH. PROTEASA DEL VHC

14th International Workshop on Clinical Pharmacology of HIV Therapy, April 22-24, 2013, Amsterdam

The Effect of Telaprevir on DTG



The Effect of Boceprevir on DTG



DTG SE PUEDE ADMINISTRAR JUNTO CON BCV Y TPV SIN NECESIDAD DE AJUSTE POSOLÓGICO

DOLUTEGRAVIR

1) Generalidades

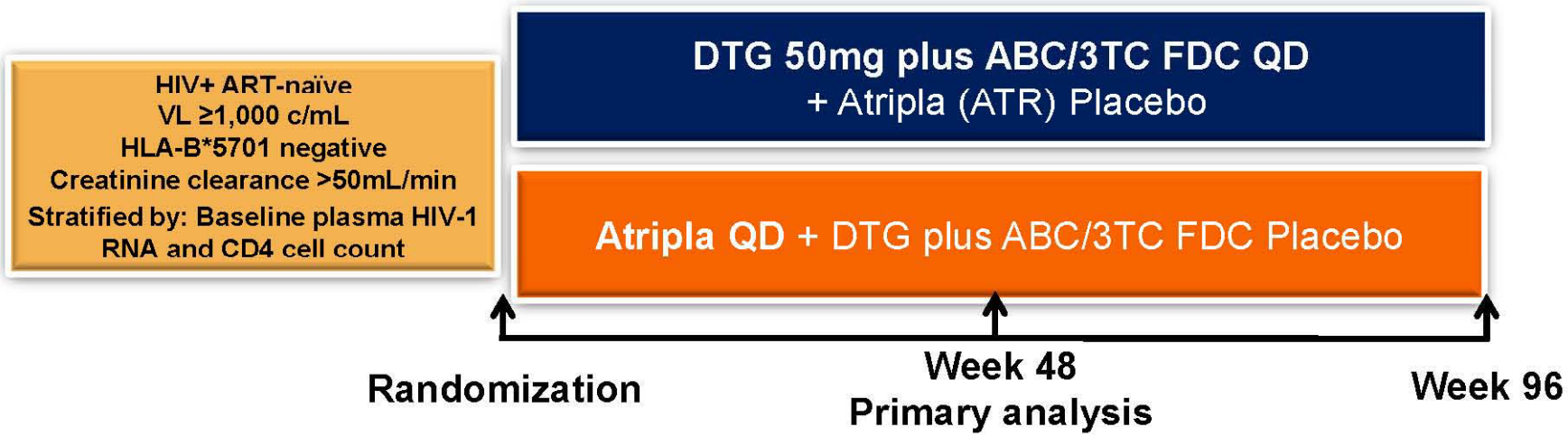
2) Naïve

(Single y Spring-2)

3) Pretratado

(Sailing y Viking-3)

Study Design



Primary endpoint:
Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis, -10% non-inferiority margin with pre-specified tests for superiority

Secondary endpoints:
Tolerability, long-term safety, immunologic, health outcome and viral resistance

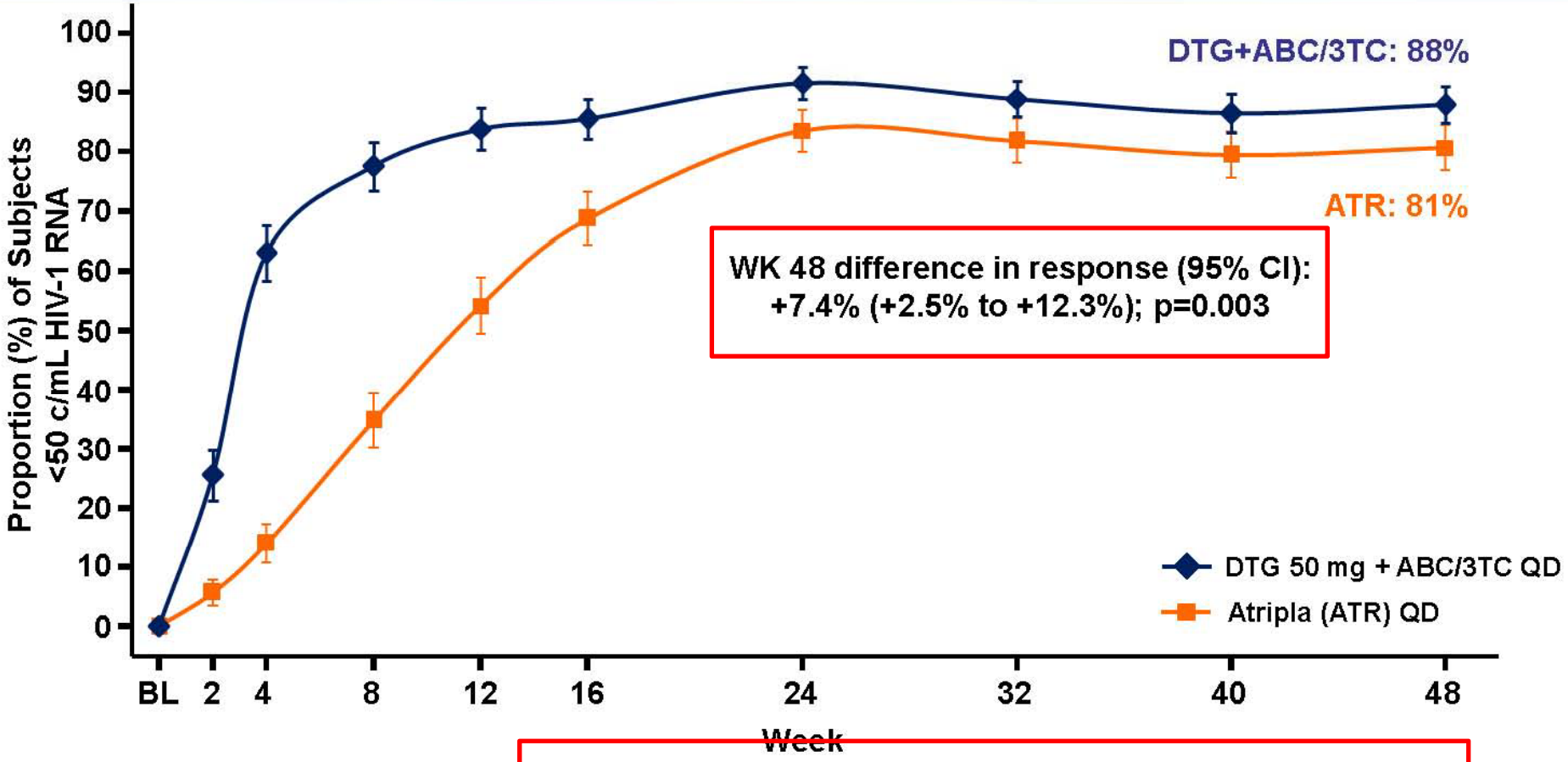
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Baseline Characteristics

	DTG 50mg+ABC/3TC QD (N=414)	Atripla QD (N=419)	Total (N=833)
Age (years), median	36	35	35
Female (%)	16%	15%	16%
African American / African Heritage	24%	24%	24%
CDC class C (%)	4%	4%	4%
HIV-1 RNA (log10 c/mL), median	4.67	4.70	4.68
>100,000	32%	31%	32%
CD4+ (cells/mm^3) median	335	339	338
<200	14%	14%	14%
200 to <350	39%	38%	39%
350 to <500	32%	31%	31%
≥500	15%	17%	16%

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)



- DTG 50mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Snapshot of Primary Outcome at Week 48 by Strata

	DTG 50 mg +ABC/3TC QD (N=414) (%)	Atripla QD (N=419) (%)	Difference in Proportion (95% CI) (DTG - ATR)
	Number of Responders/ Total Assessed		
Baseline Plasma HIV-1 RNA			
≤100,000 c/mL	253/280 (90)	238/288 (83)	7.7 (2.1, 13.3)
>100,000 c/mL	111/134 (83)	100/131 (76)	6.5 (-3.2, 16.2)
			p=0.831*
CD4 Cell Count			
>200 cells/mm^3	319/357 (89)	290/357 (81)	8.1 (3.0, 13.3)
≤200 cells/mm^3	45/57 (79)	48/62 (77)	1.5 (-13.3, 16.4)
			p=0.414*

*Test for homogeneity: p value confirms that there is no evidence of heterogeneity in treatment difference across the baseline stratification factors

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Virology: Resistance

	DTG 50mg +ABC/3TC QD (N=414)	Atripla QD (N=419)
Subjects with PDVF	**18 (4%)**	**17 (4%)**
PDVF genotypic population	**11**	**9**
PDVF Genotypic (RT Results at Baseline and PDVF)	**9**	**9**
NRTI tmt-emergent major mutations	0	1(K65R)
NNRTI tmt-emergent major mutations	0	4 (K101E, K103N, G190A)*
PDVF Genotypic (IN Results at Baseline and PDVF)	**7**	**7**
INI-r tmt-emergent major substitution	0**	0

* n=1 with K101E, n=1 with K103N, n=1 with G190A and n=1 with K103N+G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Select Adverse Events

	DTG 50mg +ABC/3TC QD (N=414) (%)	Atripla QD (N=419) (%)
Subjects with events leading to withdrawal	**10 (2)**	**42 (10)***
Serious Drug-Related – Any Event	**1 (<1)****	**8 (2)^**
Fatal AEs	**0**	**2(<1)¥**

*Atripla: Most commonly reported events were CNS, gastrointestinal and rash

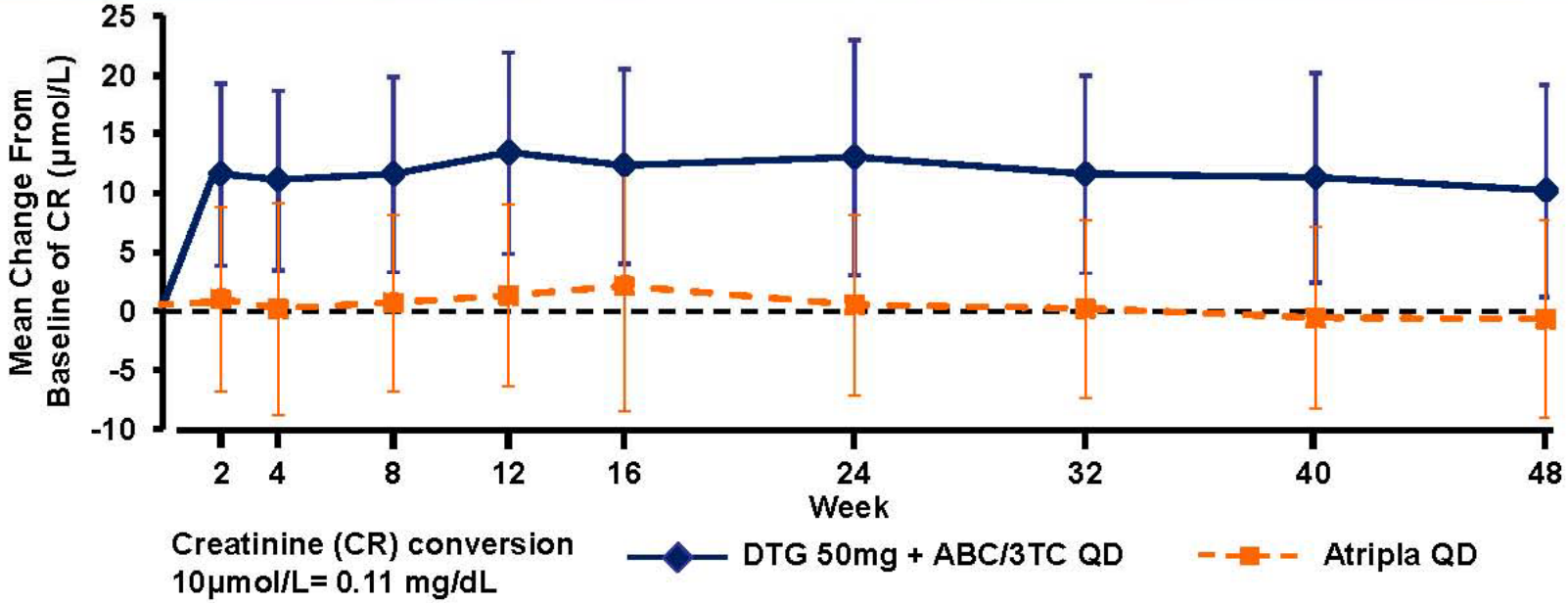
**DTG+ABC/3TC: 1 drug hypersensitivity

^ Atripla: 4 psychiatric, 2 drug hypersensitivity, 1 cerebral vascular accident, 1 renal failure

¥ Deaths: n=1 primary cause of death judged unrelated to study drug but complicated by renal failure judged possibly related to ATR, n=1 not related to ATR (pneumonia).

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Renal Safety



	DTG 50 mg+ABC/3TC QD	Atripla QD
Urine albumin/creatinine		
Median change (IQR) from baseline (mg/mmol CR) to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

- **Small increase in creatinine due to blockade of Cr secretion[1]**
- **DTG does not affect actual glomerular filtration rate (GFR)[1]**

1. Koteff, J. et al. Br J Clin Pharmacol. In press; 2012 Aug.

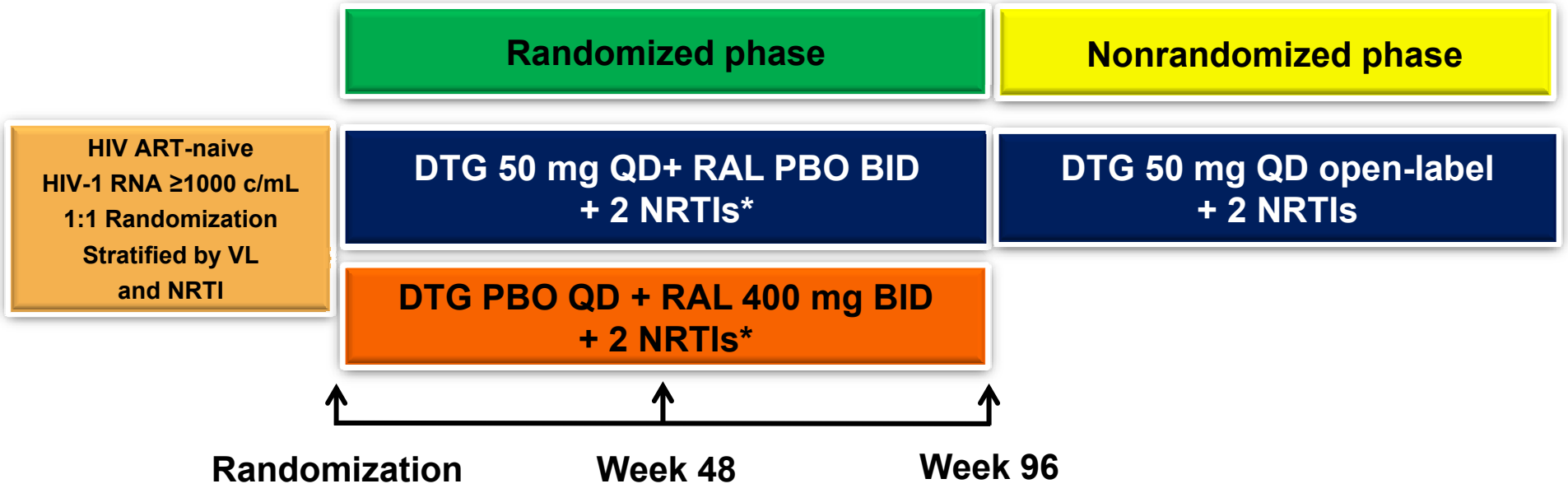
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

En resumen (SINGLE)…

- DTG 50mg + ABC/3TC es superior a EFV/TDF/FTC (supresión virológica -<50 c/mL-, snapshot) en semana 48.
- DTG 50mg + ABC/3TC tiene un perfil de seguridad favorable vs. EFV/TDF/FTC
  - ✓ Menor tasa de EA de SNC y Piel.
  - ✓ Menor tasa de discontinuación por EA.
  - ✓ Menor alteración de enzimas hepáticos.
- No se detectaron mutaciones de resistencia emergentes a INI ni a NRTI.

SPRING-2 (ING113086) Study Design

- Phase III, randomized, double-blind, double-placebo, multicenter, parallel-group, non-inferiority study, ART-naive patients
- All arms include 2 NRTI backbone given once daily (ABC/3TC or TDF/FTC)
- Primary endpoint: % <50 c/mL at 48 weeks (“snapshot”) , non-inferiority margin 10%

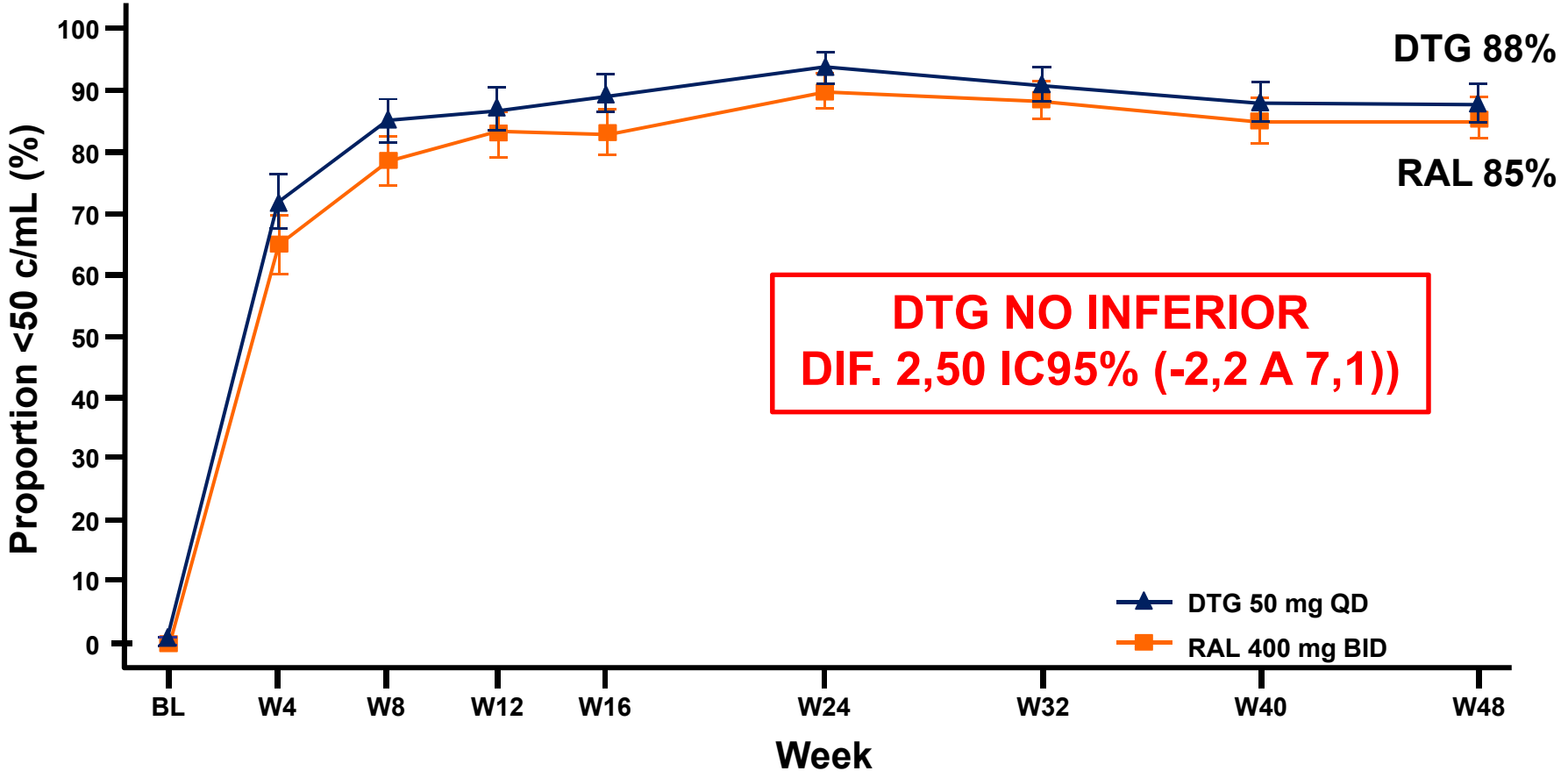


*Investigator’s selection ABC/3TC or TDF/FTC

Baseline Characteristics

		DTG 50 mg QD n=411	RAL 400 mg BID n=411
Age	Median (y)	37	35
Gender	Male	85%	86%
Race	White	84%	86%
	African American/African heritage	12%	9%
	Other	4%	5%
Baseline HIV-1 RNA	Median (log_{10} c/mL)	4.52	4.58
	>100,000 c/mL	28%	28%
Baseline $CD4^+$	Median (cells/mm^3)	359	362
	<200 cells/mm^3	13%	12%
Hepatitis coinfection	HBV	2%	2%
	HCV	10%	9%
Investigator-selected dual NRTIs	TDF/FTC	59%	60%
	ABC/3TC	41%	40%

Virologic Success Over Time



	Median (IQR) Change From Baseline CD4⁺ Cell Count (cells/mm³)					
	W4		W24		W48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

Treatment Differences (95% CI) at Week 48 by Strata

	DTG 50 mg QD n=411	RAL 400 mg BID n=411	Difference in Proportion (95% CI) (DTG - RAL)
	Number of Responders/Total Assessed		
Baseline Plasma HIV-1 RNA			
≤100,000 c/mL	267 / 297 (90%)	264 / 295 (89%)	**0.4 (-4.5, 5.3)**
>100,000 c/mL	94 / 114 (82%)	87 / 116 (75%)	**7.5 (-3.1, 18.0)**
			p= 0.236*
Background Dual NRTI			
ABC/3TC	145 / 169 (86%)	142 / 164 (87%)	**-0.8 (-8.2, 6.6)**
TDF/FTC	216 / 242 (89%)	209 / 247 (85%)	**4.6 (-1.3, 10.6)**
			p=0.264*

*Test for homogeneity

Protocol-Defined Virologic Failure (PDVF): Genotype

- **Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected through Week 48**

	DTG 50 mg QD n=411	RAL 400 mg BID n=411
Subjects with PDVF	**20 (5%)**	**28 (7%)**
IN genotypic results at BL and time of PDVF	8	18
INI-r mutations	**0**	**1/18 (6%)[a]**
PR/RT genotypic results at BL and time of PDVF	12	19
NRTI-r mutations	**0**	**4/19 (21%)[a,b,c,d]**

Mutations by subject in the RAL 400 mg BID arm:

[a] T97T/A, E138E/D, V151V/I, N155H + A62A/V, K65K/R, K70K/E, M184V

[b, c, d] A62A/V (n=1), M184M/I (n=1), M184M/V (n=1)

Select Summary of Adverse Events

	DTG 50 mg QD n=411 n (%)	RAL 400 mg BID n=411 n (%)
Grade 2-4 Drug-Related Events	**24 (6)**	**27 (7)**
Grade 3	**2***	**5*****
Grade 4	**2****	**0**
Serious Adverse Events	**29 (7)**	**31 (8)**
Drug related	**3**	**5**
	Arrhythmia, hypersensitivity, hepatitis	**Convulsion (2), Aphasia, hypersensitivity/hepatitis#, diarrhea**
AEs Leading to Withdrawal	**10 (2)**	**7 (2)**
Events with >1 subject		
Acute Hepatitis C	**2 (<1)**	**0**
ALT increased	**2 (<1)**	**1 (<1)**
AST increased	**1 (<1)**	**1 (<1)**
Nausea	**1 (<1)**	**1 (<1)**

* Grade 3: headache, dizziness, feeling abnormal, arrhythmia
** Grade 4: Drug hypersensitivity with associated ALT/AST/ALP/BilT/LFT, hepatitis
*** Grade 3: nausea, abdominal pain, aphasia, drug eruption, fatigue, ALT increased, CPK increased, lipase increased, decreased appetite
#One subject with cytolytic hepatitis, hypersensitivity, influenza, lymphadenitis viral

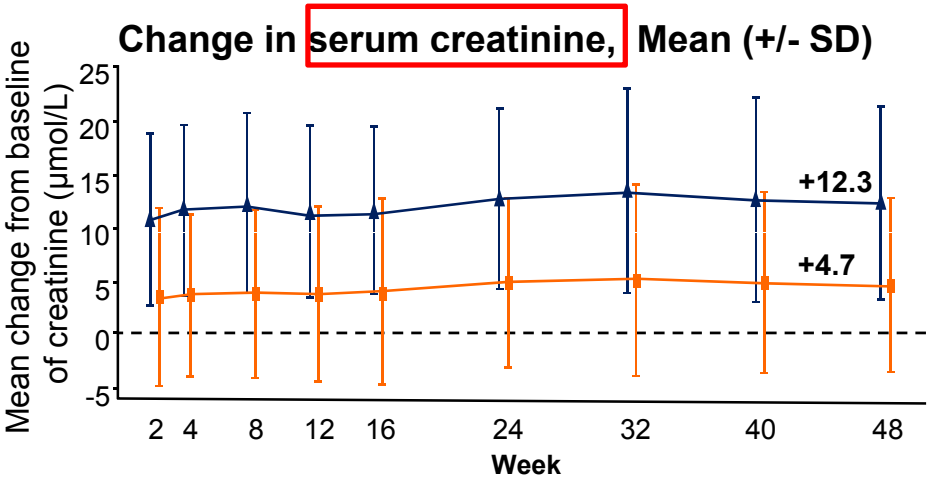
Laboratory Results

Maximum Post-Baseline Emergent Toxicity Grade 3 – 4	DTG 50 mg QD N=411 n (%)	RAL 400 mg BID N=411 n (%)
Creatine Phosphokinase (CPK)	20 (5)	14 (3)
Aspartate Aminotransferase (AST)	11 (3)	9 (2)
Alanine Amino Transferase (ALT)	9 (2)	7 (2)
Lipase	7 (2)	14 (3)
Total Bilirubin	2 (<1)	1 (<1)
Creatinine	0	0

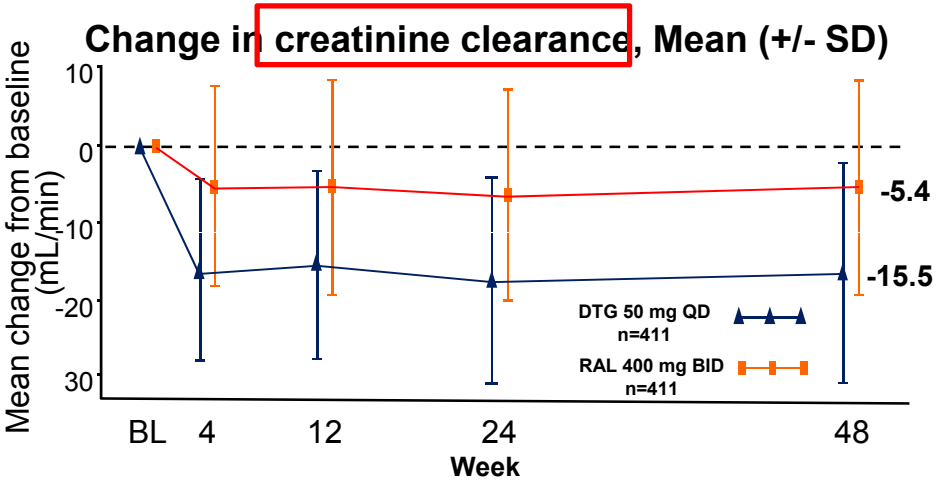
- **Minimal changes from baseline to week 48 in total cholesterol and triglycerides in both arms**
  - Total cholesterol median (IQR): DTG +3.9 mg/dL (-10.8, +21.3); RAL +7.7 mg/dL (-8.9, +23.6)
  - Triglycerides median (IQR): DTG +0.9 mg/dL (-23.9, +24.8); RAL +6.2 mg/dL (-19.5, +34.5)

Renal Safety

- No withdrawals due to renal events
- Small increase in creatinine due to blockade of Cr secretion[1]
- DTG does not affect actual glomerular filtration rate (GFR)[1]



Baseline (µmol/L): DTG: 74.7 vs. RAL: 75.2



Baseline (ml/min): DTG: 125 vs. RAL: 128

		DTG 50 mg QD	RAL 400 mg BID
Creatinine			
Maximum emergent toxicity	Grade 1/2	10 (2%) / 1 (<1%)	7 (2%) / 0
Urine albumin/creatinine			
Median change (IQR) from baseline (mg/mmol CR)	Week 48	0.00 (-0.30, 0.20)	0.00 (-0.20, 0.20)

[1] Koteff J et al, 51st ICAAC, Sept 2011.

En resumen (SPRING-2)…

- DTG es no inferior a RAL (95% CI: -2.2% +7.1%).

- Perfil de seguridad comparable entre DTG y RAL:
  - ✓ Similar tasa de EA y alteraciones de parámetros de laboratorio.
  - ✓ No discontinuaciones prematuras por eventos renales.

- No se detectaron mutaciones de resistencia a INI ni a NRTI con DTG.

DOLUTEGRAVIR

1) Generalidades

2) Naïve

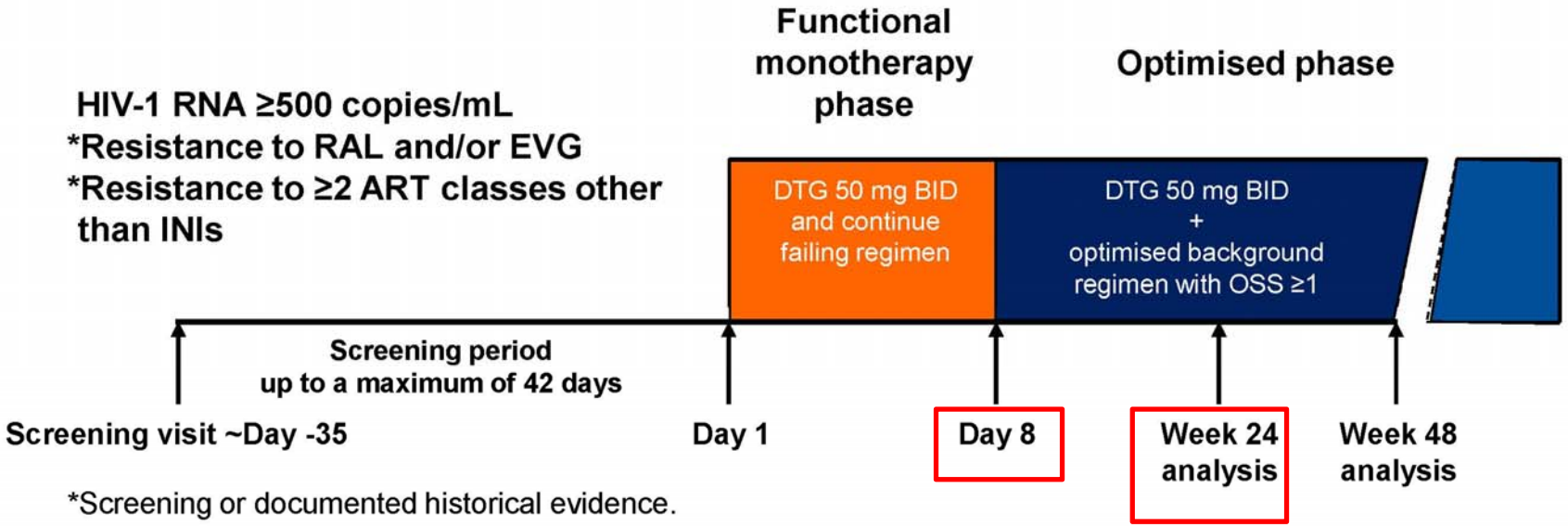
(Single y Spring-2)

3) Pretratado

(Sailing y Viking-3)

Study Design

VIKING-3



*Screening or documented historical evidence.

Var. Ppal: Eficacia virológica

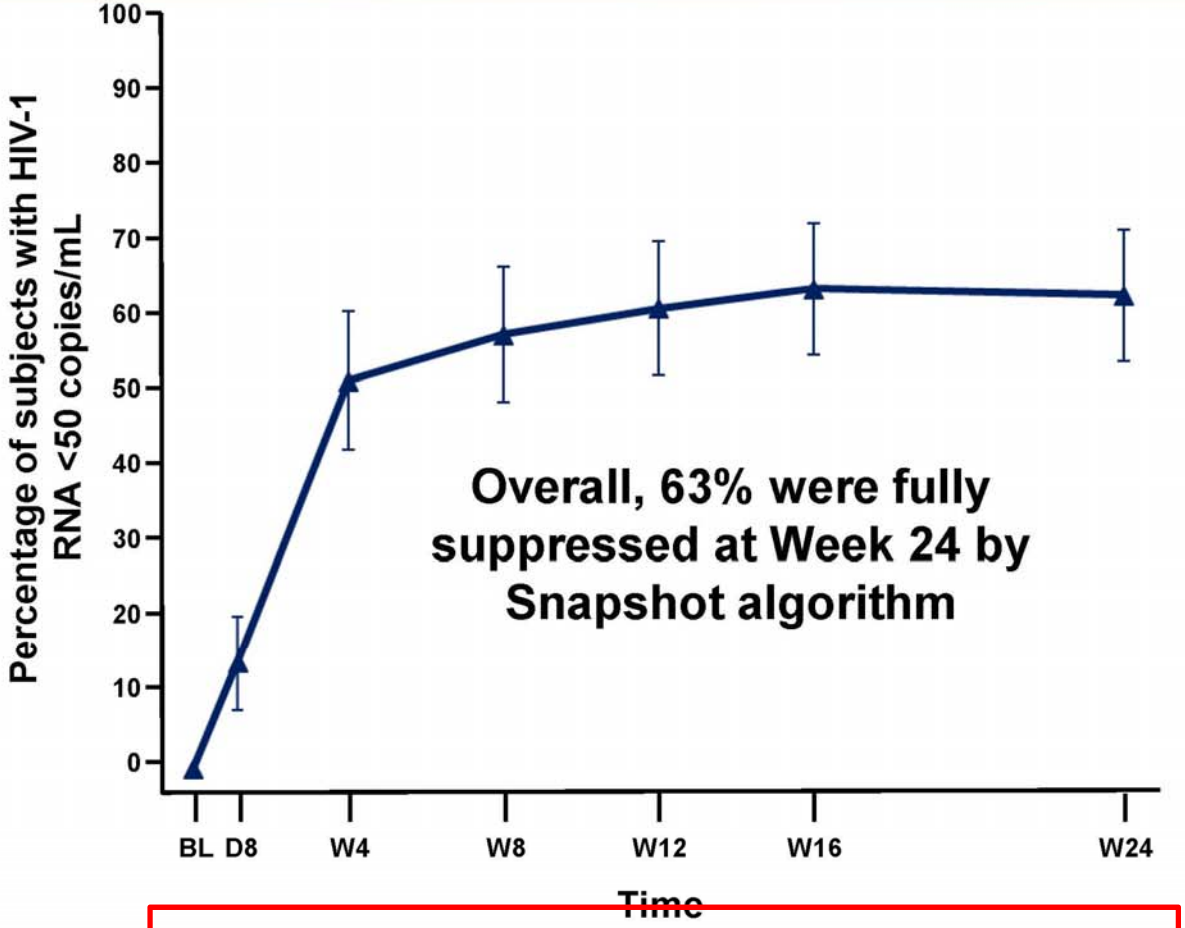
OSS (overall susceptibility score) determined by Monogram Biosciences

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Day 8 and Week 24 Efficacy Endpoints

VIKING-3

- Day 8 change from BL: -1.43 $\log_{10}$ copies/mL, *P*<0.001
  - 95% CI, -1.52 to -1.34 (ITT-E, N=183)
- Week 24 by Snapshot (MSDF): 72/114 (63%) <50 copies/mL
  - 37/114 (32%) were virologic non-responders
    - 6/114 (5%) changed OBR
  - Only 5/114 (4%) were non-responders for discontinuation due to AEs



Week 24 population (N=114) was those subjects who had opportunity to reach Week 24 at time of data cut-off

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Week 24 Response by Mutation Category and OBR Overall Susceptibility Score (OSS)

VIKING-3

	HIV-1 RNA <50 copies/mL at Week 24 (Snapshot) (N=101)			
Derived IN mutation group*	OSS=0	OSS=1	OSS≥2	Total
No Q148,** n (%)	2/2 (100)	24/29 (83)	31/41 (76)	57 (79)
Q148 + 1,† n (%)	2/2 (100)	3/7 (43)	4/11 (36)	9 (45)
Q148 +≥ 2,† n (%)	1/2 (50)	0/7 (0)	0	1 (11)

* Virus from the ≥2 primary mutations group was re-categorized to the Q148+ or No Q148 groups as appropriate
**143, 155, 66, 92, historical resistance evidence only. †G140A/C/S, E138A/K/T, L74I

- **In multivariate analyses of baseline factors on Week 24 response rates, the presence of Q148 + ≥2 mutations and increasing DTG FC were highly correlated with fewer subjects achieving <50 copies/mL (*P*≤0.001)**

- **Increasing OBR activity score did not impact response**
  - **In patients with OSS=1, the most common active ARVs were TDF, T20, MVC and ETR**
  - **Overall, only 23% (28/114) received a PI/r as the fully active ARV in OBR**
  - **In most cases, the 2nd and 3rd active ARV was an NRTI**

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

En resumen (VIKING-3)…

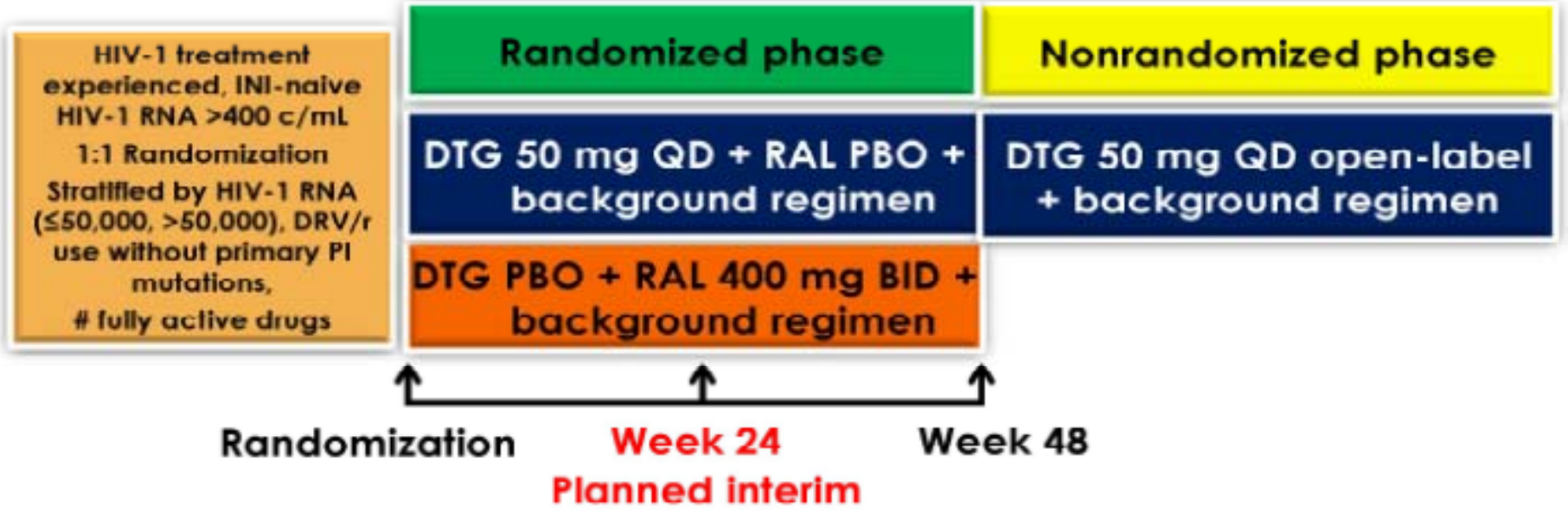
- DTG fue altamente efectivo en pacientes con resistencias múltiles (RAL, EVG, etc.).

- Las respuestas se asociaron más bien con el Genotipo Basal de IN pero NO con la mejora del OSS del OBR.

- DTG 50 mg BID tuvo un bajo grado de discontinuación debido a EA en pacientes altamente pretratados.

SAILING (ING111762) Study Design

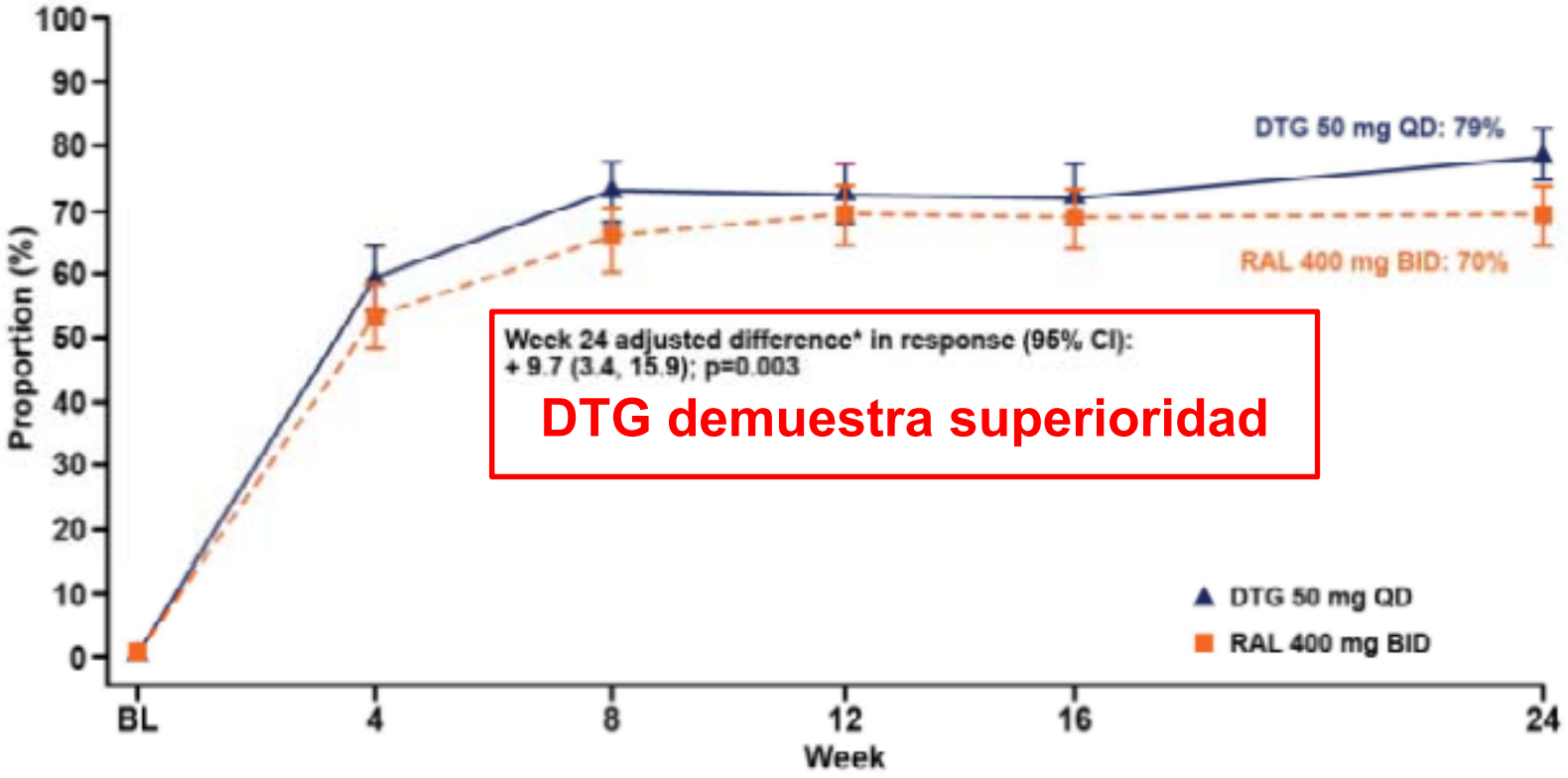
- Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study of integrase inhibitor-naïve, ART-experienced patients with at least 2 class resistance
- All arms include investigator selected background regimen*
- Primary endpoint: % <50 c/mL at 48 weeks ("snapshot") , non-inferiority margin 12%



*Investigator selected background regimen consisting of one fully active single agent plus no more than one second single agent which may or may not be active.

Pozniak et al. 20th CROI. 3-7 March, 2013 Atlanta, GA . Abstract L-1003.

Virologic Success Over Time (HIV-1 RNA <50 c/mL)



Mean (SD) Change From Baseline CD4⁺ Cell Count (cells/mm³) – Observed Case

	W4		W12		W24	
DTG 50 mg QD	59	(114)	82	(105)	114	(135)
RAL 400 mg BID	56	(98)	80	(112)	106	(116)

Additional Efficacy Analysis (Snapshot, mITT-E)

	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
HIV-1 RNA <50 c/mL	281 (79%)	252 (70%)
Virologic nonresponder[a]	53 (15%)	86 (24%)
No virologic data at Week 24[b]	20 (6%)	23 (6%)
Per protocol, HIV-1 RNA <50 c/mL	263/323 (81%)	245/339 (72%)
95% Confidence interval	9.3 (3.0, 15.7)	
Response <50 c/mL by Baseline HIV-1 RNA	n/N (%)	n/N (%)
≤50,000 c/mL	207/249 (83%)	195/254 (77%)
>50,000 c/mL	74/105 (70%)	57/107 (53%)
Response <50 c/mL by Baseline CD4+		
<200 cells/mm^3	128/173 (74%)	115/184 (63%)
≥200 cells/mm^3	153/181 (85%)	137/177 (77%)
Response <50 c/mL by background regimen phenotypic susceptibility score[c]		
<2	83/105 (79%)	67/94 (71%)
2	198/249 (80%)	185/267 (69%)
Use of DRV without primary PI mutations		
Yes	57/71 (80%)	63/78 (81%)
No	224/283 (79%)	189/283 (67%)

[a] HIV-1 RNA not <50 c/mL in window; discontinued for lack of efficacy; discontinued for other reason while not <50 c/mL; change in ART.

[b] Discontinued due to AE, death or for other reasons unrelated to safety; missing data but still on study.

[c] PSS=0 (n=11); PSS=3 (n=2).

Pozniak et al. CROI 2013; Atlanta, GA. Poster #179LB.

Failure with Genotypic and/or Phenotypic Evidence of INI Resistance

SAILING

Treatment	Subjects with INI Resistance / Total Assessed	Adjusted Difference in Proportion (95% CI) (DTG – RAL)	P-Value
DTG 50 mg QD	2 / 354 (0.6%)*		
RAL 400 mg BID	10 / 361 (2.8%)	-2.3% (-4.2%, -0.4%)	0.016

- Two subjects on the DTG arm had integrase substitutions at position 263 (R263K or R263R/K); FC for each to both DTG and RAL was <2.

- RAL-associated substitutions included Y143, Q148, and/or N155 conferring high level phenotypic resistance to RAL (consistent with previous RAL studies).***(FC 0 to >20 (max) (7of 10 were >20)

There was a statistically significant difference in favor of DTG for the proportion of subjects harboring virus with evidence of INI Resistance by Week 24.

Select Summary of Adverse Events and Laboratory Abnormalities

	DTG 50 mg QD (n=357)	RAL 400 mg BID (n=362)
Drug-related AEs (≥3% in either arm)	**73 (20%)**	**85 (23%)**
Diarrhea	30 (8%)	22 (6%)
Nausea	12 (3%)	16 (4%)
Vomiting	7 (2%)	11 (3%)
Fatigue	4 (1%)	10 (3%)
Serious—any event	**28 (8%)**	**41 (11%)**
Serious drug-related—any event	**2 (<1%)***	**4 (1%)^**
Fatal AEs	**0**	**2 (<1%)¥**
Select Grade 3-4 laboratory abnormalities		
Creatine phosphokinase (CPK)	7 (1)	4 (<1)
Alanine aminotransferase (ALT)	9 (3)	6 (2)
Lipase	4 (1)	7 (2)
Total bilirubin**	19 (5)	12 (3)
Creatinine	0	1 (<1)

* DTG: 1 Hepatotoxicity, 1 Myositis & Renal failure acute

^ RAL: 1 Oral mucosal blistering & Rash pruritic, 1 Pancreatitis, 1 Hepatitis, 1 Suicidal ideation

¥ 1 Adenocarcinoma, 1 Acute hepatic and Renal failure.

**17/19 subjects on the DTG arm, and 10/12 on the RAL arm were receiving atazanavir or atazanvir/ritonavir.

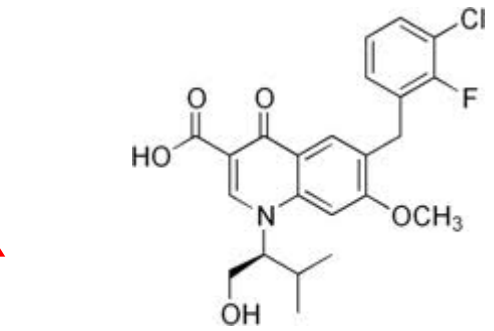
Minimal changes from Baseline to Week 24 in total cholesterol and triglycerides in both arms.

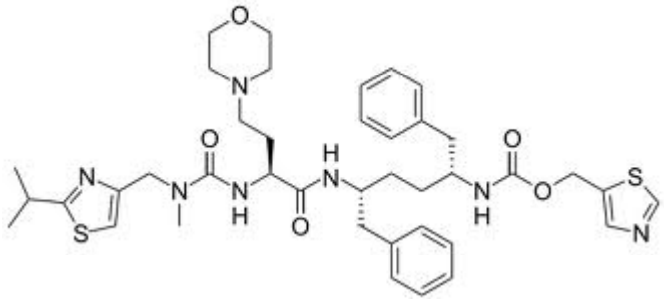
En resumen (SAILING)…

- En semana 24, DTG 50 mg QD demostró superioridad a RAL 400 mg BID.
- La proporción de sujetos con resistencia a INI fue menor en el brazo de DTG.
- DTG 50 mg QD se toleró bien en general (con una amplia variedad de OBR).

ELVITEGRAVIR COBICISTAT

1) Generalidades
2) Naïve (GS-102 y GS-103)
3) Pretratado (GS-145)



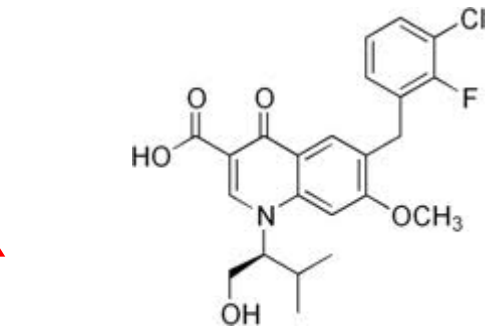


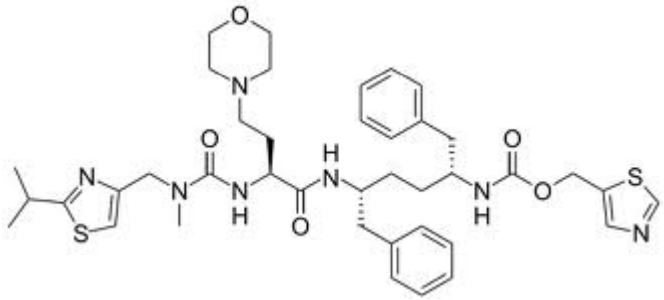
ELVITEGRAVIR COBICISTAT

1) Generalidades

2) Naïve (GS-102 y GS-103)

3) Pretratado (GS-145)





Dolutegravir: Comparativa con Raltegravir y Elvitegravir

	Raltegravir	Elvitegravir	Dolutegravir
In vitro Potency	33nM=15.9 ng/mL (PA-IC95)	45 ng/mL (PA-IC95)	64 ng/mL (PA-IC90)
Clinical Dose	400mg BID	150mg QD boosted	50mg QD (INI-naïve) 50mg BID (Ral-resistant)
T1/2	~9hr	~9hr	~15hr
PK variability	High	Low to moderate when boosted	Low to moderate
Food Effect	No food restriction	Dosed with meal	No food restriction
Protein binding	Moderate: 83%	High: 99.4%	High: 99.5-99.7%
Metabolism and Excretion	UGT1A1	CYP3A (major) UGT1A1 (minor)	UGT1A1 (major) CYP3A (minor)
PK/PD relationship	No	Yes, C_{trough}-driven efficacy	Yes, C_{trough}-driven efficacy
DDI Profile	Manageable; dose adjustment with rifampin	Manageable; dose adjustment with LPV/r, ATV/r, Maraviroc	Manageable; contraindicated with etravirin alone
Effect on QT	No	unknown	No

ELVITEGRAVIR COBICISTAT

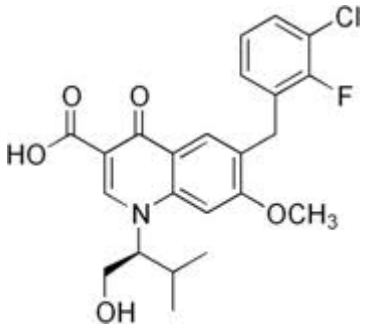
1) Generalidades

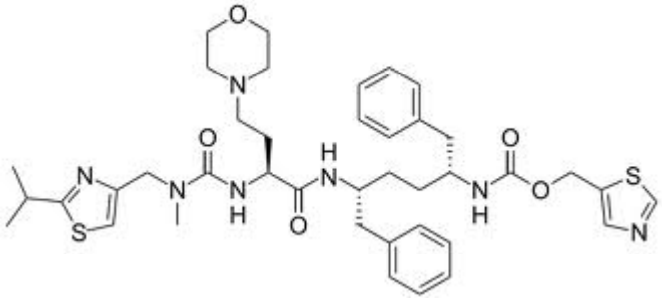
2) Naïve

(GS-102 y GS-103)

3) Pretratado

(GS-145)





Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF (STB) Has Durable Efficacy and Differentiated Safety Compared to Efavirenz/Emtricitabine/Tenofovir DF (ATR) in Treatment-naïve HIV-1 Infected Patients: Week 96 Results

A Zolopa[1], JE Gallant[2], C Cohen[3], P Sax[4], E DeJesus[5], A Mills[6], D Wohl[7], HC Liu[8], MS Rhee[8], J Szwarcberg[8],

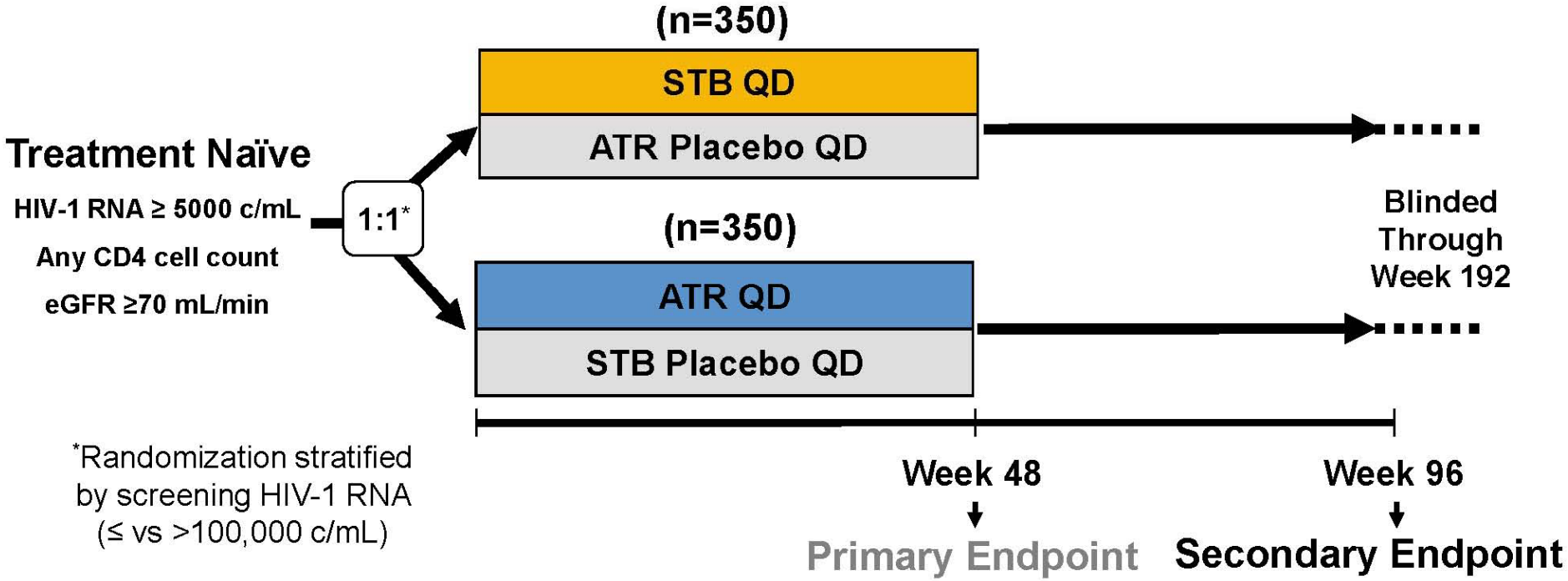
[1]Stanford University, Palo Alto, CA, US; [2]Johns Hopkins School of Medicine, Baltimore, MD, US; [3]Community Research Initiative of New England, Boston, MA, US; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]Orlando Immunology Center, Orlando, FL, US; [6]Anthony Mills MD, Inc., Los Angeles, CA, US; [7]University of North Carolina, Chapel Hill, NC, US; [8]Gilead Sciences, Foster City, CA, US

Eleventh International Congress on Drug Therapy in HIV Infection
11-15 November, 2012, Glasgow, UK
Poster and Presentation # O424A

Study Design

Study 102

Randomized, double-blind, double dummy, active-controlled study



HIV-1 RNA < 50 c/mL by snapshot analysis (ITT)

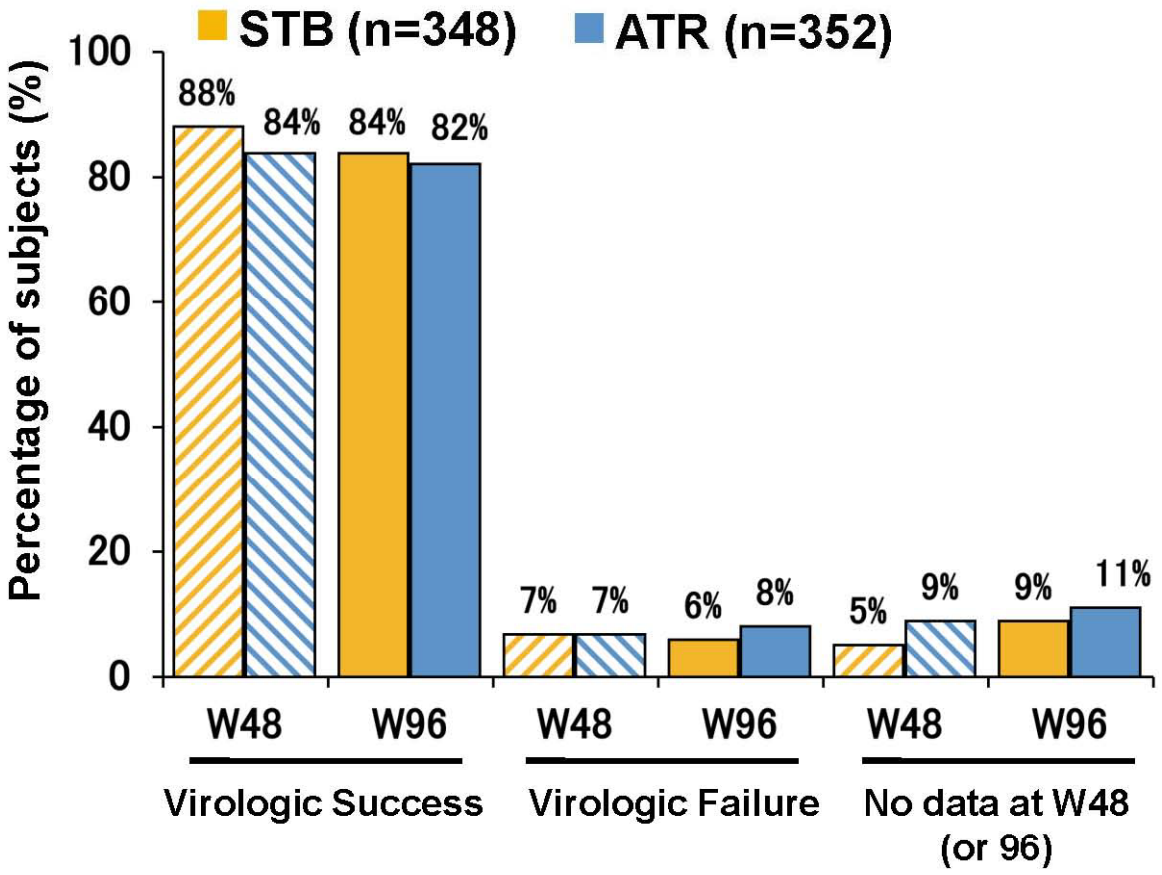
Non-inferiority margin -12%

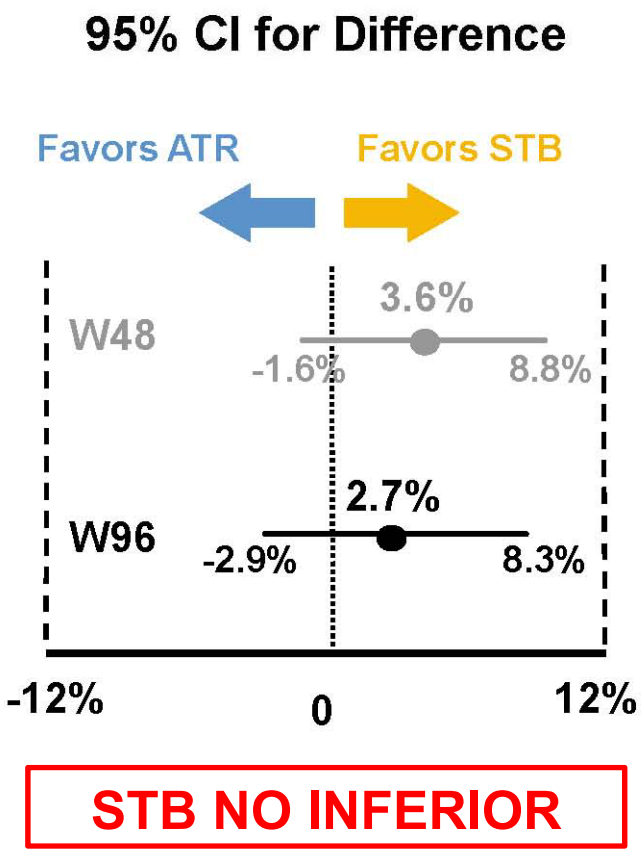
Conducted in parallel with Study 103 comparing STB to ATV/r + TVD

(Poster # O424B)

Efficacy Endpoint: HIV-1 RNA <50 c/mL

Study 102 – Primary (Week 48) and Secondary (Week 96)

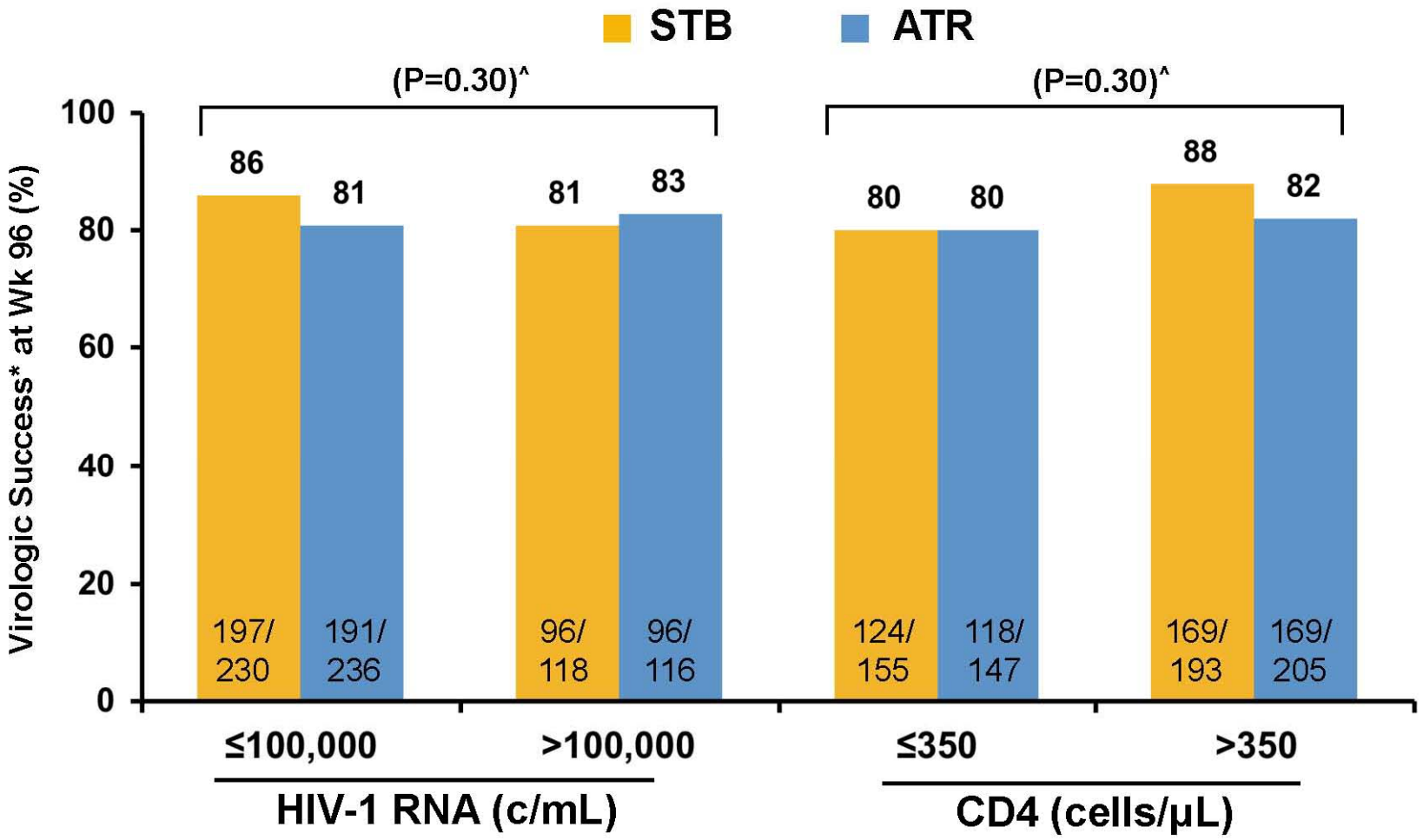




STB NO INFERIOR

Efficacy by Baseline HIV-1 RNA and CD4 Subgroups

Study 102 – Week 96



*Virologic success (HIV-1 RNA <50 copies/mL) as defined by FDA Snapshot algorithm

^P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup

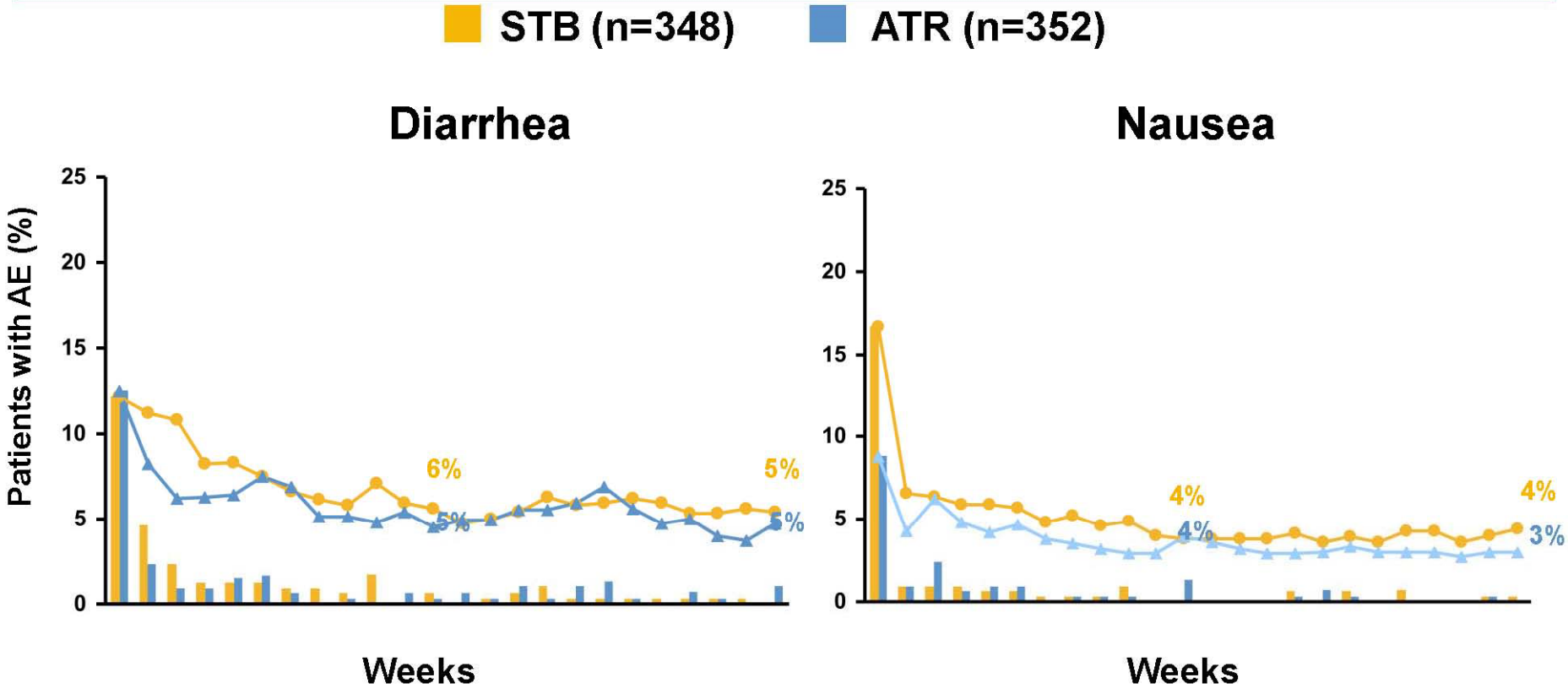
Integrase, NNRTI, NRTI Resistance Through Week 96

Study 102 – Week 48 and 96

		STB (n=348)			ATR (n=352)	
		W48	W96		W48	W96
Emergent Resistance, n (%)		8 (2%)	+2 (+1%)		8 (2%)	+2 (+1%)
Primary INSTI-R or NNRTI-R, n (%)		7 (2%)	+2 (+1%)		8 (2%)	+2 (+1%)
	E92Q	7	0	K103N	7	+2
	N155H	1	+2	K101E/K	3	0
	Q148R	1	0	M230L	2	0
				Y188F/H/L	1	+1
				G190A/S	1	0
Primary NRTI-R, n (%)		8 (2%)	+2 (+1%)		2 (1%)	+1 (+0.3%)
	M184V/I	8	+2	M184V/I	2	+1
	K65R	3	+1	K65R	2	+1

Incidence and Prevalence of Common Gastrointestinal AEs

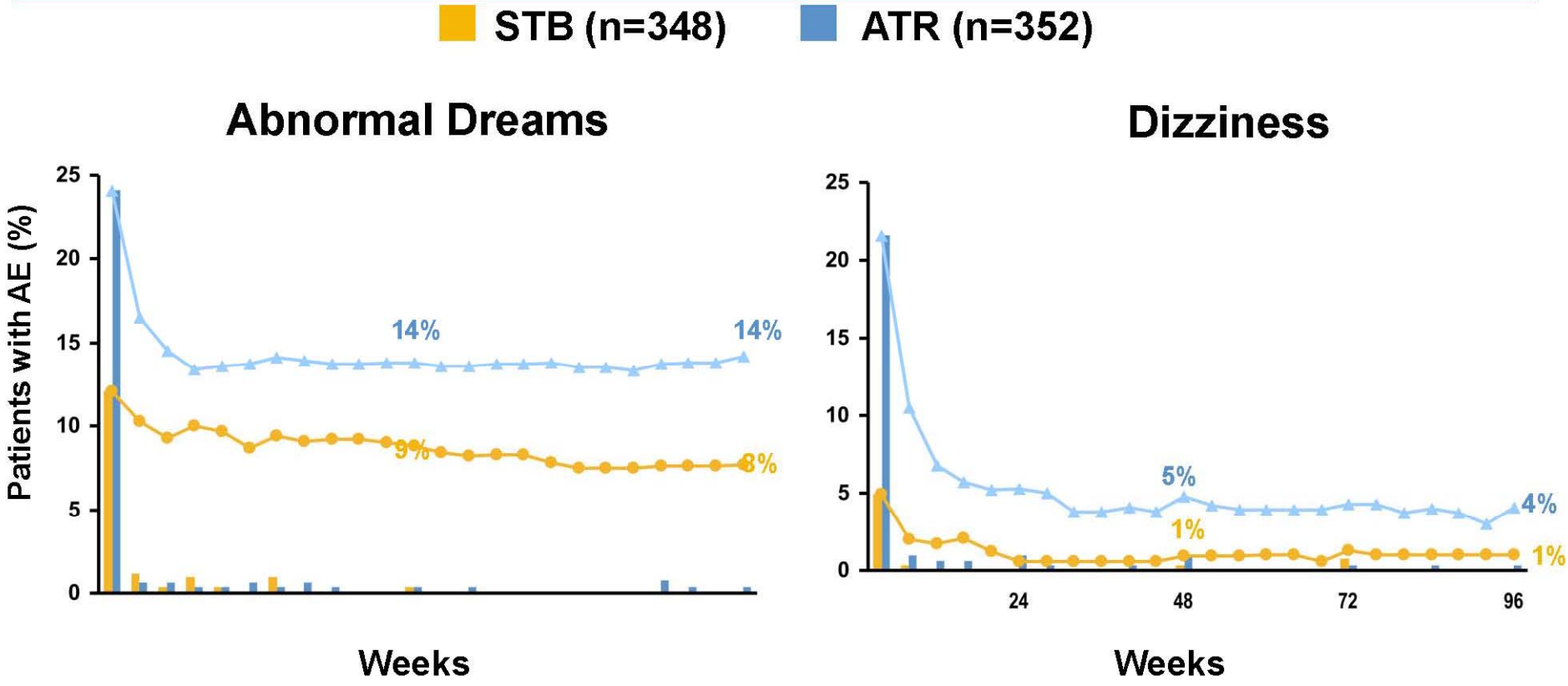
Study 102 – Week 96



Bar (incidence): patients with new onset AEs at each 4-week window
Line (prevalence): patients with ongoing events in the window

Incidence and Prevalence of Common Neuropsychiatric AEs

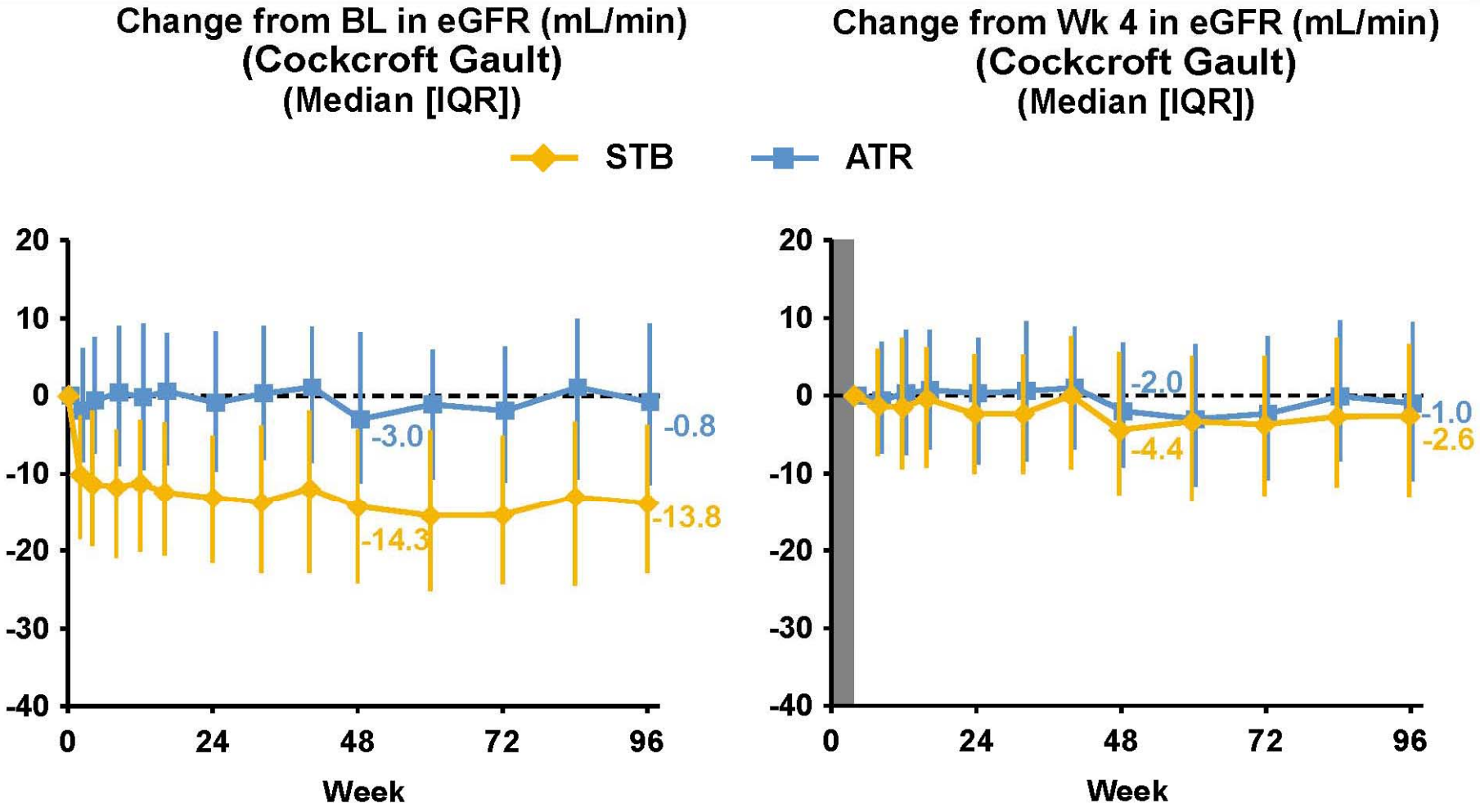
Study 102 – Week 96



Bar (incidence): patients with new onset AEs at each 4-week window
Line (prevalence): patients with ongoing events in the window

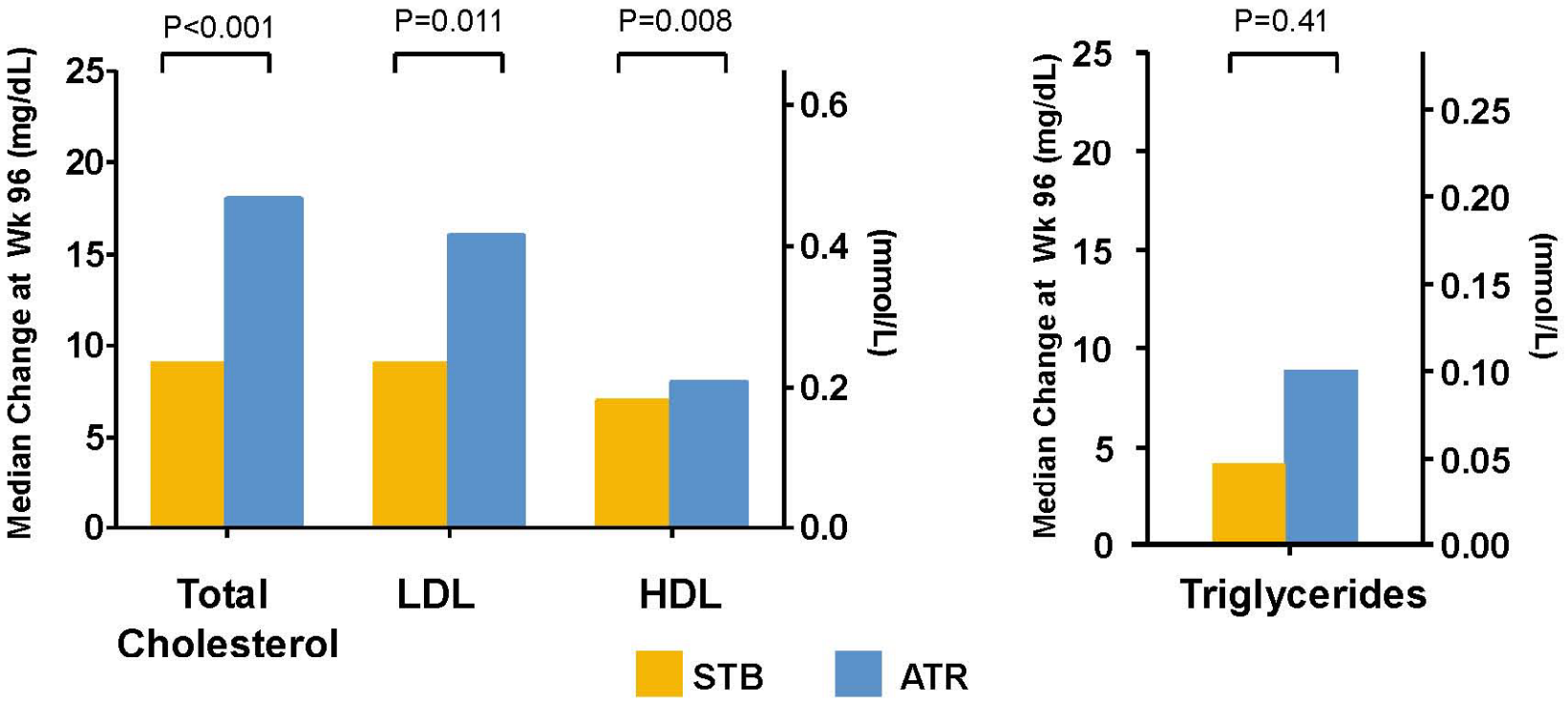
Changes in eGFR from Baseline and from Week 4

Study 102 – Week 96



Change from Baseline in Fasting Lipids at Week 96

Study 102 – Week 96



No difference in change in TC to HDL ratio at Week 48 or 96

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF (STB) Has Durable Efficacy and Differentiated Safety Compared to Atazanavir Boosted by Ritonavir Plus Emtricitabine/Tenofovir DF in Treatment-naïve HIV-1 Infected Patients: Week 96 Results

JK Rockstroh[1], E DeJesus[2], K Henry[3], J-M Molina[4], J Gathe[5], X Wei[6], M Fordyce[6], MS Rhee[6], J Szwarcberg[6]

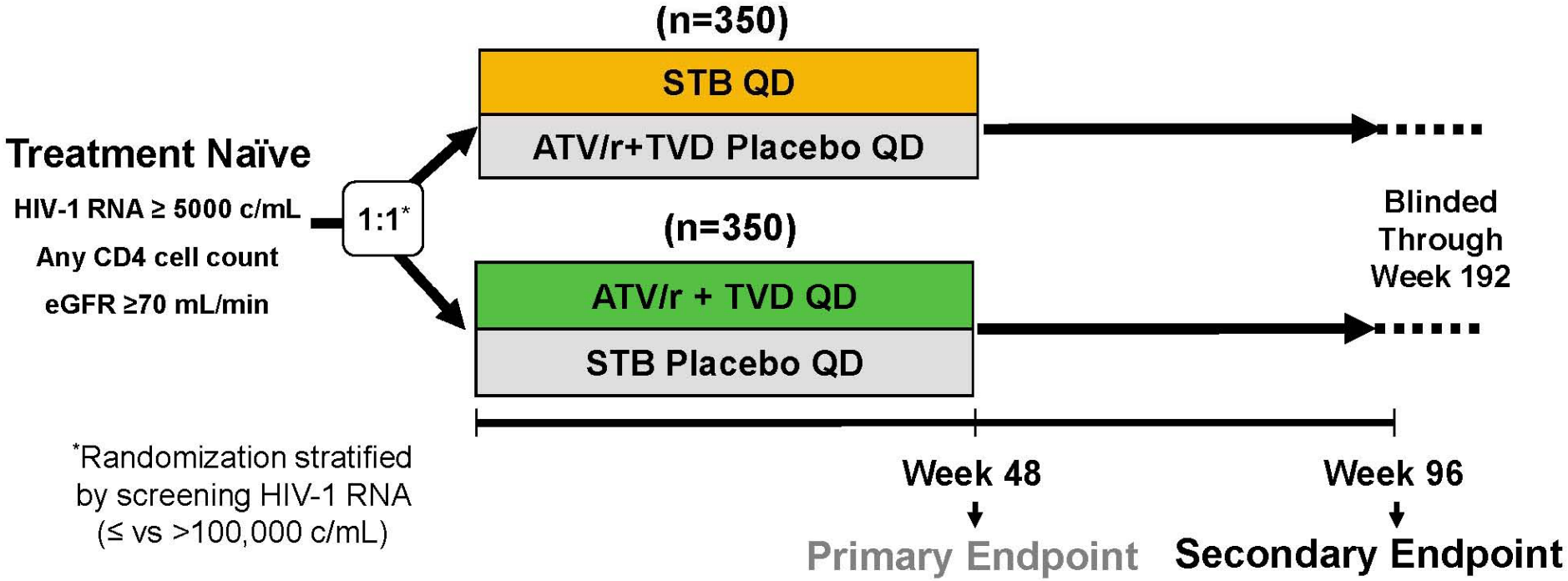
[1]University of Bonn, Bonn, Germany, [2]Orlando Immunology Center, Orlando, FL, US, [3]Hennepin County Medical Center, Minneapolis, MN, US, [4]Saint Louis Hospital, Paris, France, [5]Therapeutic Concepts P.A., Houston, TX, US, [6]Gilead Sciences, Foster City, CA, US

Eleventh International Congress on Drug Therapy in HIV Infection
11-15 November, 2012, Glasgow, UK
Poster and Presentation # O424B

Study Design

Study 103

Randomized, double-blind, double dummy, active-controlled, international study



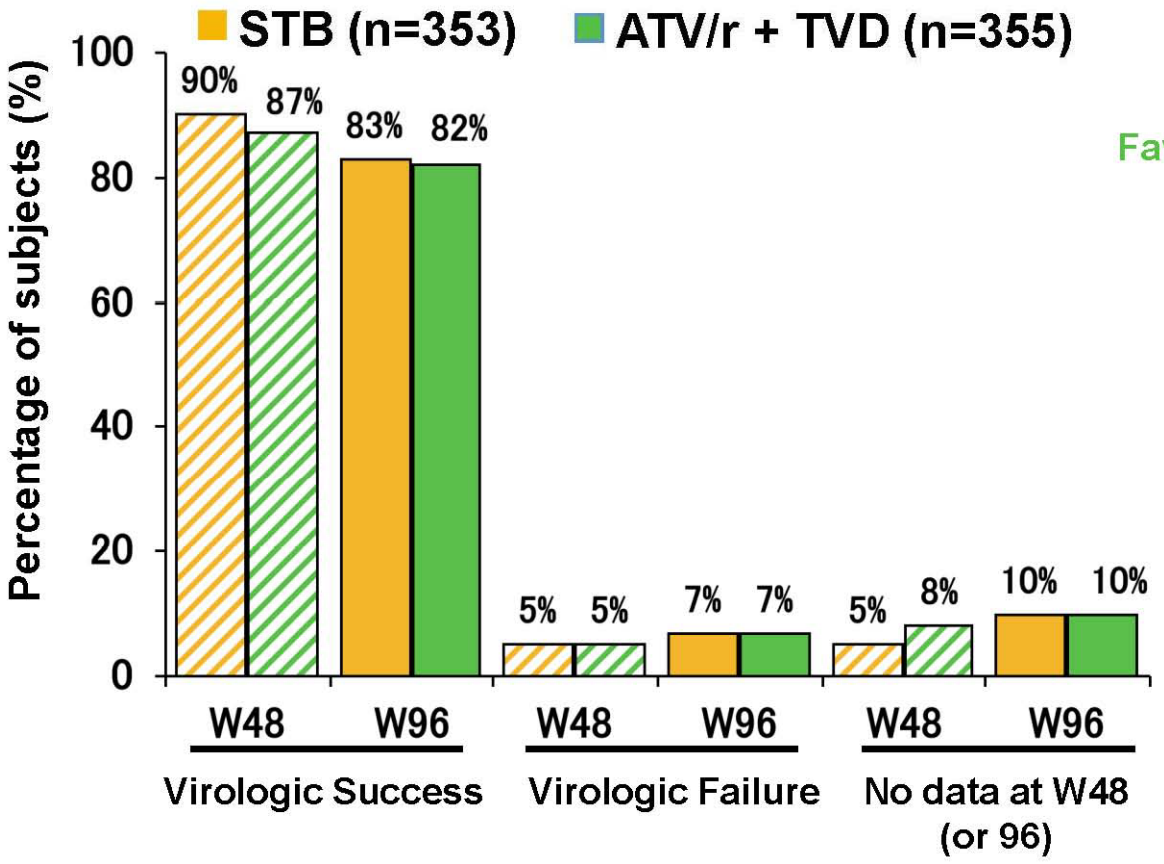
HIV-1 RNA < 50 c/mL by snapshot analysis (ITT)
Non-inferiority margin -12%

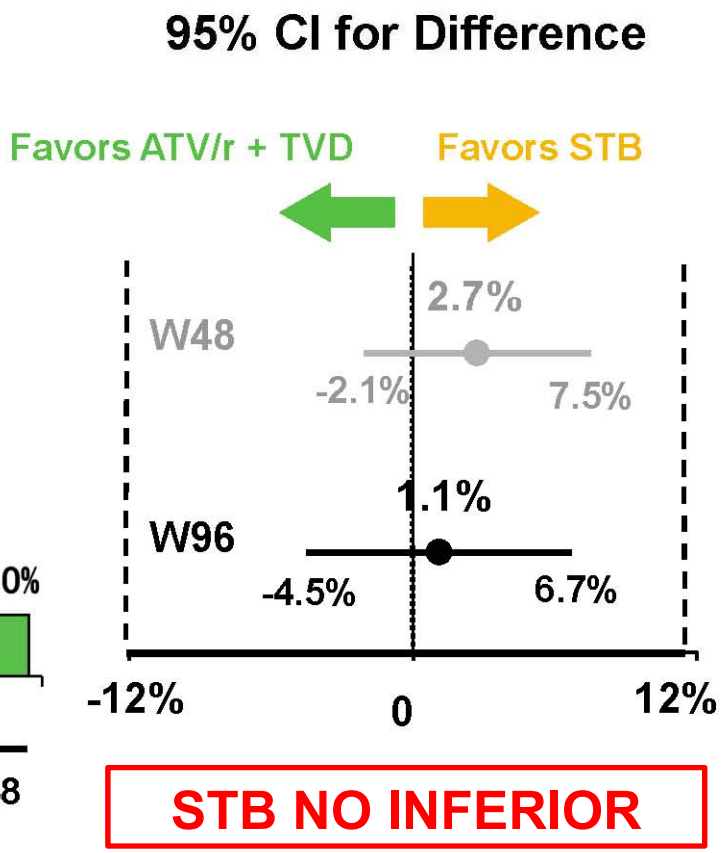
Conducted in parallel with Study 102 comparing STB to ATR

(Poster # O424A)

Efficacy Endpoint: HIV-1 RNA <50 c/mL

Study 103 – Primary (Week 48) and Secondary (Week 96)

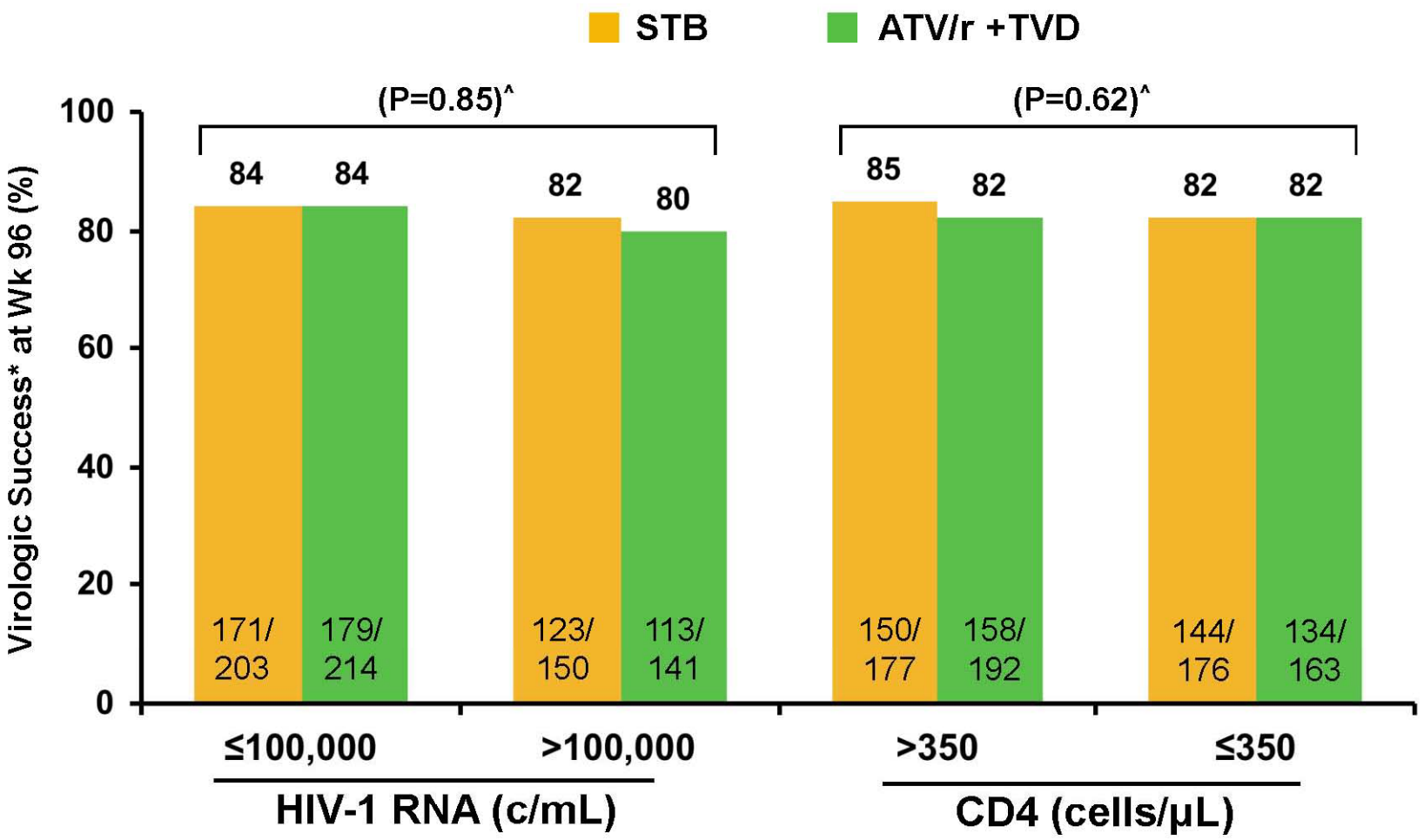




STB NO INFERIOR

Efficacy by Baseline HIV-1 RNA and CD4 Subgroups

Study 103 – Week 96



*Virologic success (HIV-1 RNA <50 copies/mL) as defined by FDA Snapshot algorithm

^P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup

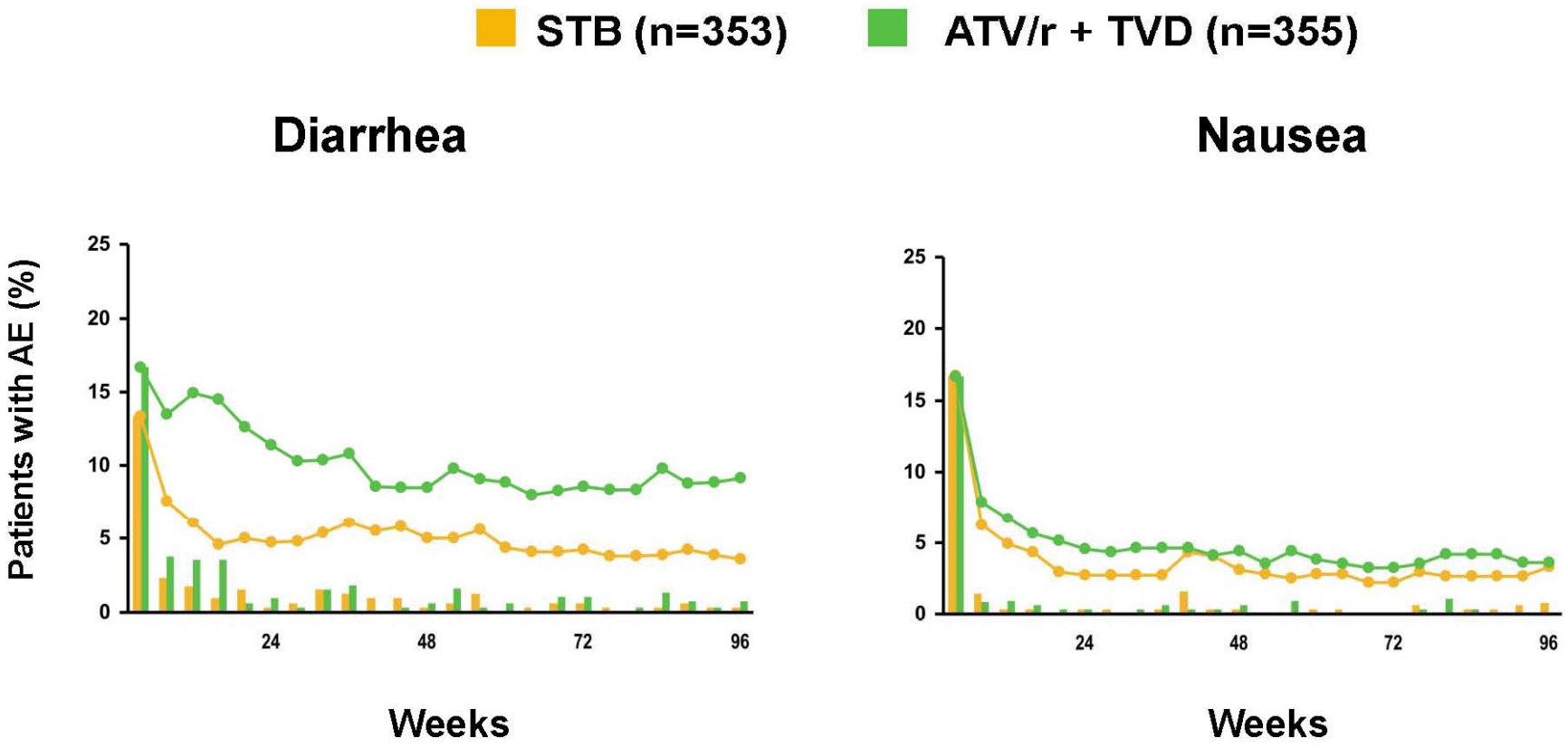
Integrase, PI, NRTI Resistance Through Week 96

Study 103 – Week 48 and 96

		STB (n=353)			ATV/r + TVD (n=355)	
		W48	W96		W48	W96
Emergent Resistance, n (%)		5 (1%)	+1 (+0.3%)		0	0
Primary INSTI-R or PI-R, n (%)		4 (1%)	+1 (+0.3%)		0	0
	E92Q	1	+1	I50L	0	0
	N155H	2	0	I84V	0	0
	Q148R	2	0	N88S	0	0
	T66I	1	0			
Primary NRTI-R, n (%)		4 (1%)	+1 (+0%)		0	0
	M184V/I	4	+1	M184V/I	0	0
	K65R	1	0	K65R	0	0

Incidence and Prevalence of Common Gastrointestinal AEs

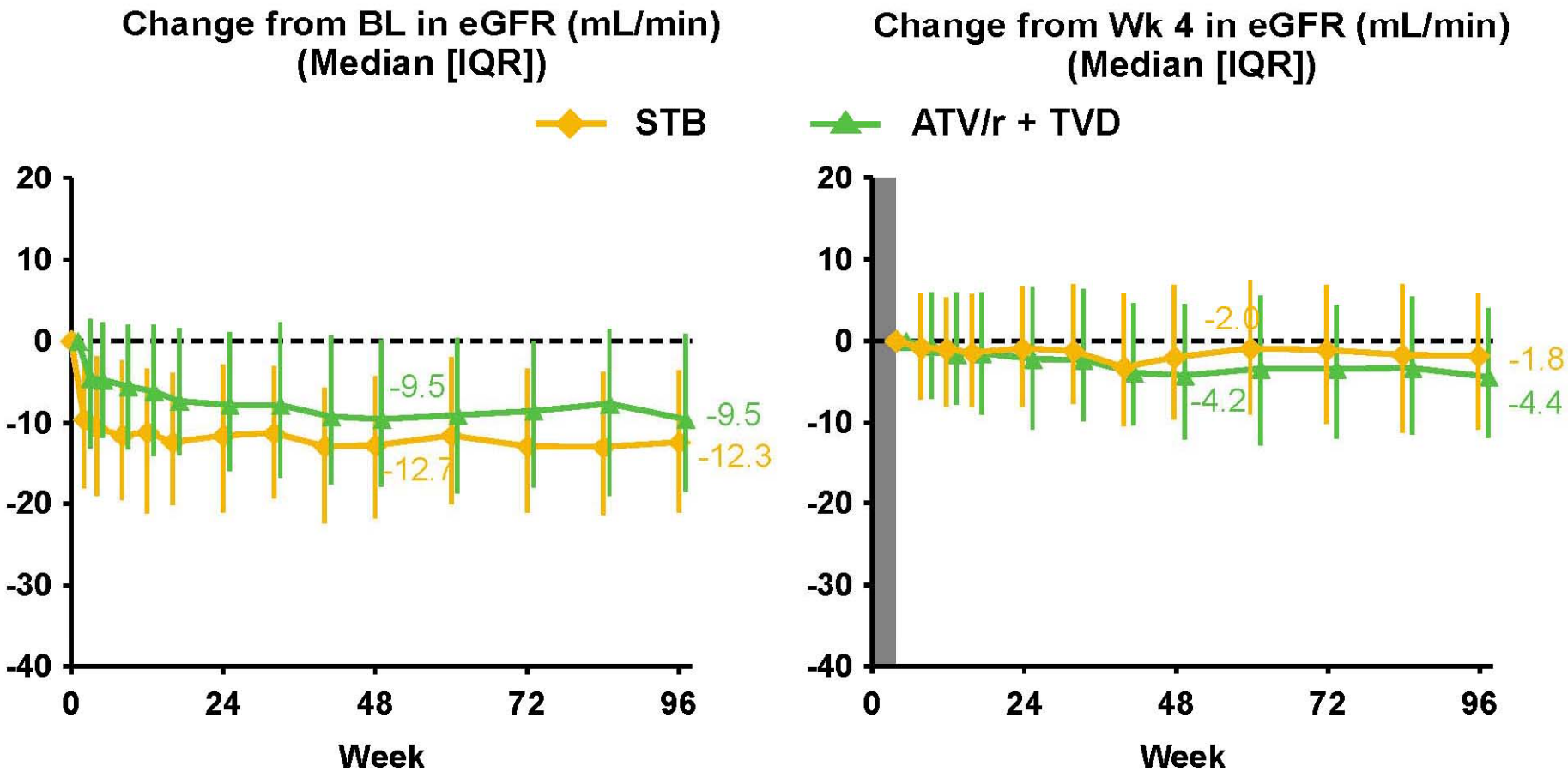
Study 103 – Week 96



Bar (incidence): patients with new onset AEs at each 4-week window
Line (prevalence): patients with ongoing events in the window

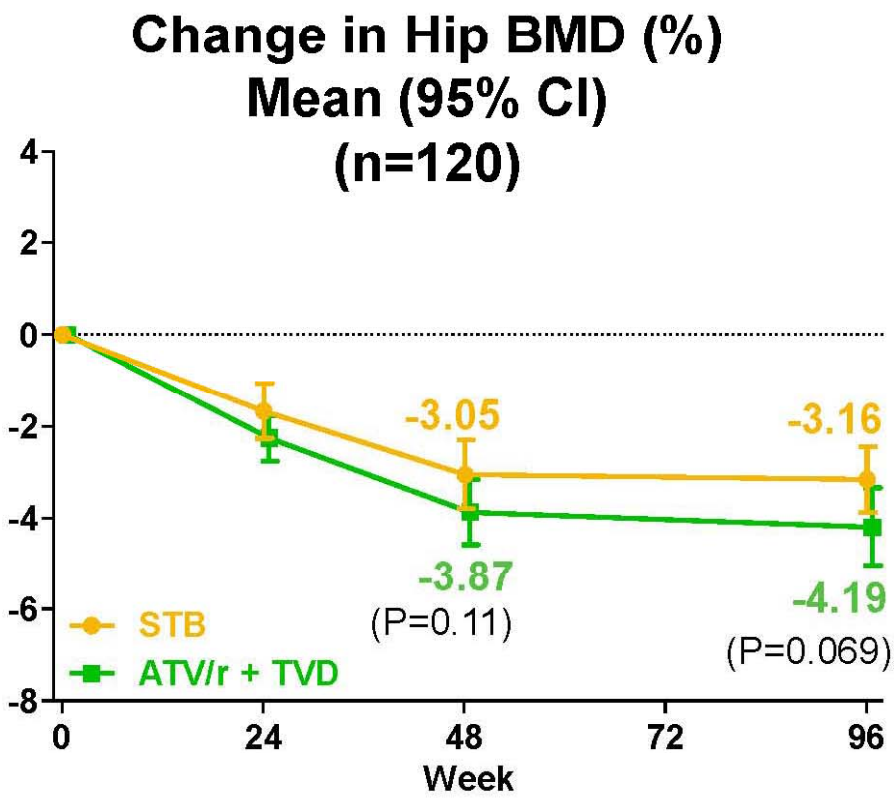
Changes in eGFR from Baseline and from Week 4

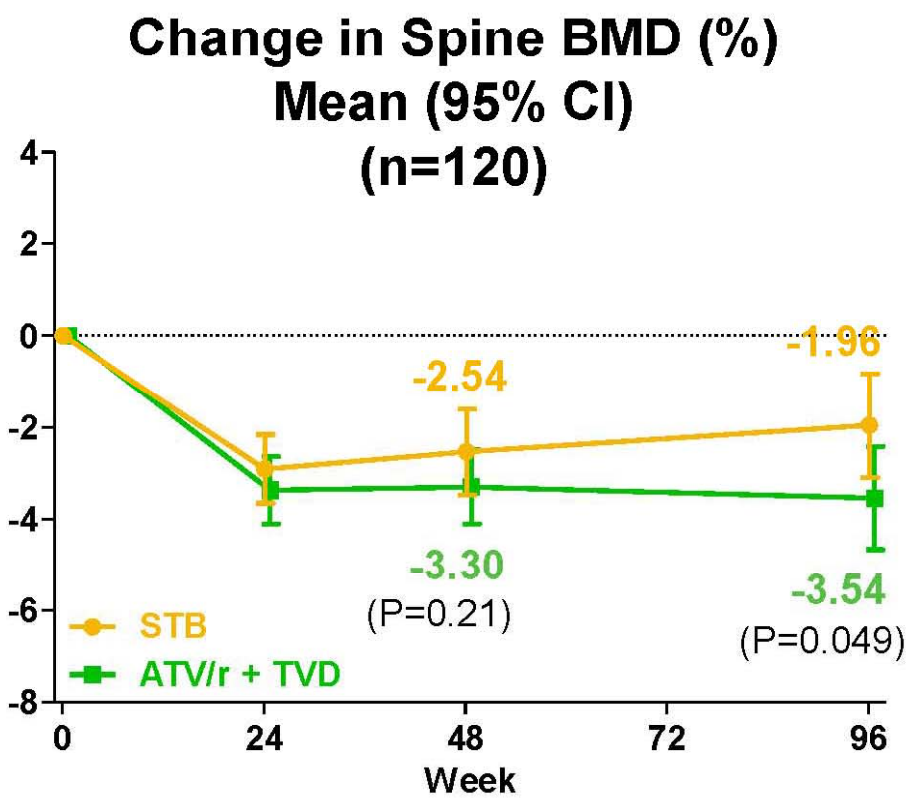
Study 103 – Week 96



Changes in Bone Mineral Density

Study 103 – Week 96





	STB (n=353)		ATV/r + TVD (n=355)	
	W48	W96	W48	W96
Fracture events, (n)	3 (1%)	+1 (+0.3%)	6 (2%)	+8 (+2%)

En resumen (GS-102 y 103)…

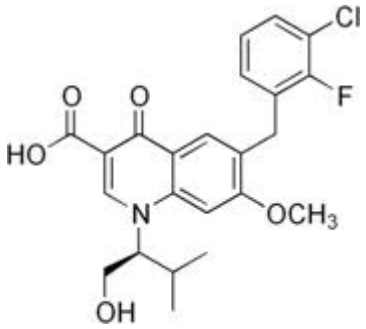
- EVG/COBI/FTC/TDF presenta una eficacia robusta en semana 96, comparable a a EFV/FTC/TDF y ATV + RTV + FTC/TDF (incluido el análisis de subgrupos).

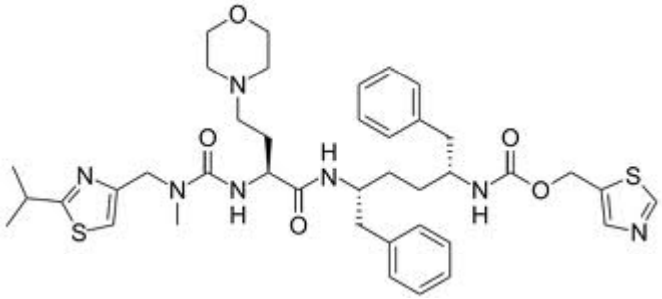
- EVG/COBI/FTC/TDF se asoció con una menor tasa de resistencias en semana 96 comparado con semana 48 (0,4% vs. 1,9% = 2,3%).

- EVG/COBI/FTC/TDF fue bien tolerado (en semana 96 no hubo nuevos casos de tubulopatía ni aumento de creatinina -comparado con semana 48-).

ELVITEGRAVIR COBICISTAT

1) Generalidades
2) Naïve
(GS-102 y GS-103)
3) Pretratado
(GS-145)





GS 145: EVG QD vs. RAL BID – Week 96

Study Design

‡

International, randomized, double blinded, 96-week, non-inferiority study of EVG QD vs. RAL BID in ARV-experienced patients

ARV-experienced (≥ 6mos) with >2 ARV class resistance and/or 2 ARV class experience ≥ 6 mos

HIV RNA >1,000 c/mL

(N = 702)

- **EVG QD & Placebo BID** + **PI + RTV based OBR**
- **RAL BID & Placebo QD** + **PI + RTV based OBR**

Stratification by:
- HIV RNA (> and <100,000 c/mL)
- 2nd Agent

96 weeks
Blinded Treatment Phase

Optimized background regimen (OBR):
2nd Agent: fully active PI+RTV
3rd Agent: NRTI, ETR, MVC, T-20
If M184V/I, may add 3TC or FTC

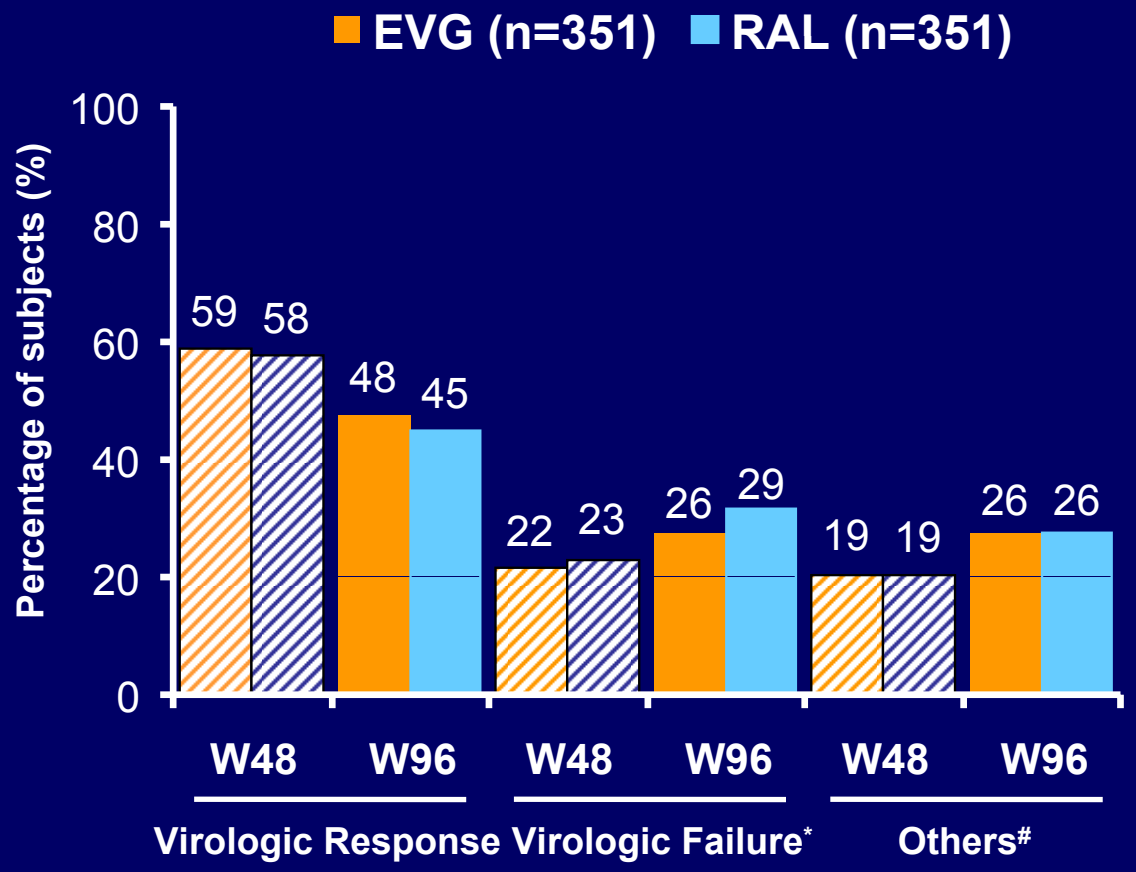
Primary Endpoint: **Non-inferiority (10% margin) of EVG QD to RAL BID by TLOVR analysis HIV-1 RNA <50 copies/mL at 48 weeks**

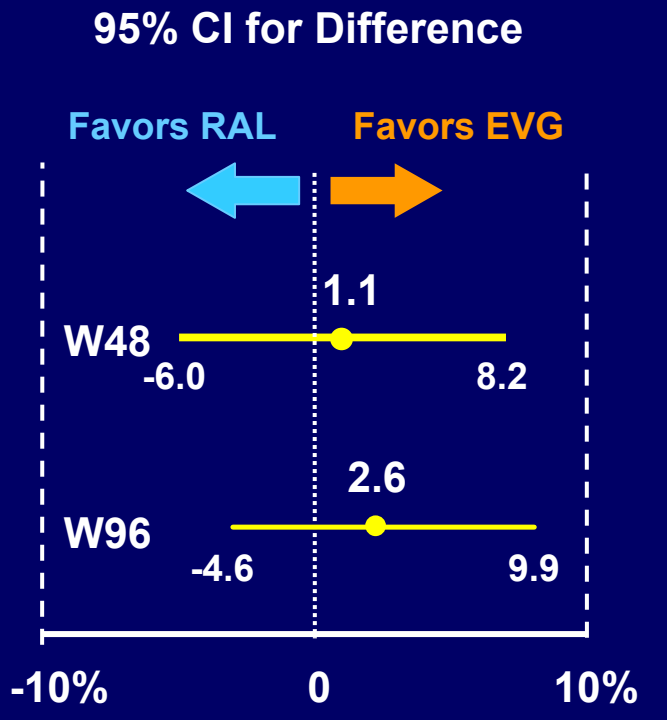
Adapted from Molina JM et al. Lancet Infect Dis. 2012; 12: 27-35.
Elion R, et al. IAC 2012; Washington, DC. Oral TUAB0105

‡

GS 145: EVG QD vs. RAL BID – Week 96

Efficacy Endpoint: HIV-1 RNA <50 c/mL (ITT, TLOVR)





Once-daily EVG was comparable to twice-daily RAL at Week 96

* Virologic failure includes never suppressed, rebound, switch of background regimen, and discontinuation due to lack of efficacy

\# Others include death, discontinuation due to AE, investigator's discretion, lost to follow up, pregnancy, protocol violation, subject non-compliance, withdrawal of consent.

Elion R, et al. IAC 2012; Washington, DC. Oral TUAB0105

GS 145: EVG QD vs. RAL BID – Week 96

Treatment Emergent Resistance

	EVG (n=351)	RAL (n=351)
Resistance analysis population*, n	87 (25%)	93 (26%)
Any Primary Integrase RAM, n	23 (7%)	26 (7%)
Any NRTI RAM, n	9 (3%)	12 (3%)
Any Primary PI RAM, n	5 (1%)	5 (1%)
Any Primary NNRTI RAM, n	12 (3%)	8 (2%)

* Subjects with either 1) suboptimal virologic response (HIV-1 RNA ≥50 c/mL and <1 $\log_{10}$ below baseline at Wk 8 and confirmed at the subsequent visit), virologic rebound (2 consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving <50, or >1 $\log_{10}$ increase from nadir), or 2) had HIV-1 RNA ≥400 c/mL at their last visit.

Elion R, et al. IAC 2012; Washington, DC. Oral TUAB0105
Margot NA, et al. ibid. TUPE050

RAM: resistance associated mutations

GS 145: EVG QD vs. RAL BID – Week 96

AEs Leading to Study Drug Discontinuation and Grade 3 to 4 Laboratory Abnormalities

‡

Adverse Events (AE)

AEs*	EVG (n=354)	RAL (n=358)
Any AE leading to DC at Week 96	3%	4%
Liver-related AEs†	0.8%	1.7%
Lung cancer	0.6%	0.3%
Nausea	0.6%	0
Vomiting	0.6%	0
Rash	0	0.6%

*AEs leading to DC in >1 subject in either group

† Liver-related AEs include hepatitis cholestatic, hepatitis C, hepatitis, hepatitis acute, hepatic enzymes increased, transaminase increased, GGT increased, and chronic hepatic failure

Grade 3-4 laboratory abnormalities‡

	EVG (n=354)	RAL (n=358)
Any Grade 3-4 lab. abnormality	37%	42%
Total bilirubin	6%	9%
AST#	2%	6%
ALT#	2%	5%
GGT#	3%	7%
Amylase	6%	6%
Creatine kinase	6%	4%
Total Cholesterol	5%	5%
Hematuria	6%	7%

‡ ≥5% in either group. # P≤0.05

AST: aspartate aminotransferase
ALT: alanine aminotransferase
GGT: gamma-glutamyl transferase

En resumen (GS-145)…

- EVG QD TIENE TASAS DE SUPRESIÓN VIROLÓGICA COMPARABLES A RAL BID EN PACIENTES CON IP/r + 3er AGENTE.

- LA TASA DE RESISTENCIAS FUE SIMILAR CON EVG QD (7%) QUE CON RAL BID (7%).

- AMBOS REGÍMENES SE TOLERARON CORRECTAMENTE.

¡Gracias!