Triple terapia antirretroviral en 2019

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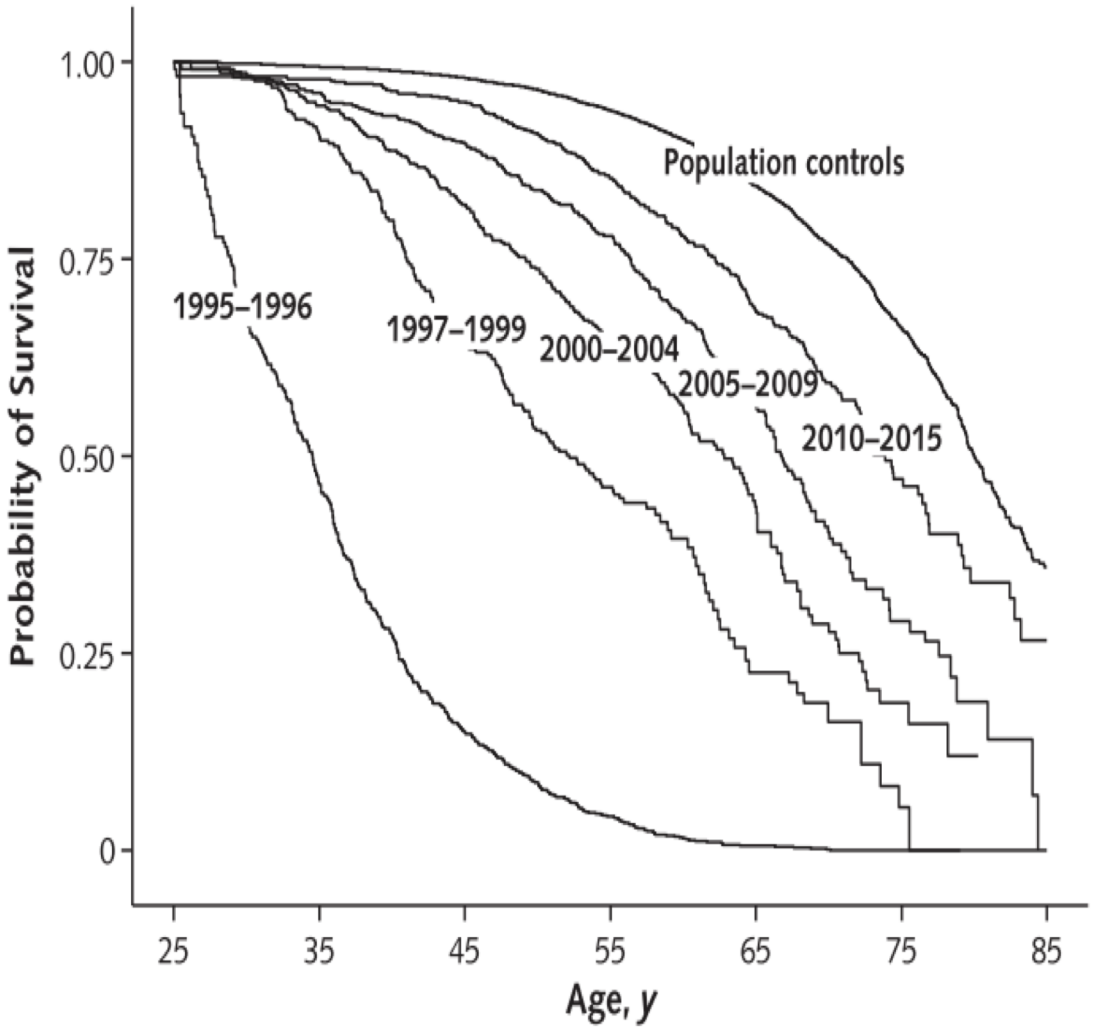
19 octubre 2019

Complejo Hospitalario Universitario de Pontevedra

Triple terapia antirretroviral

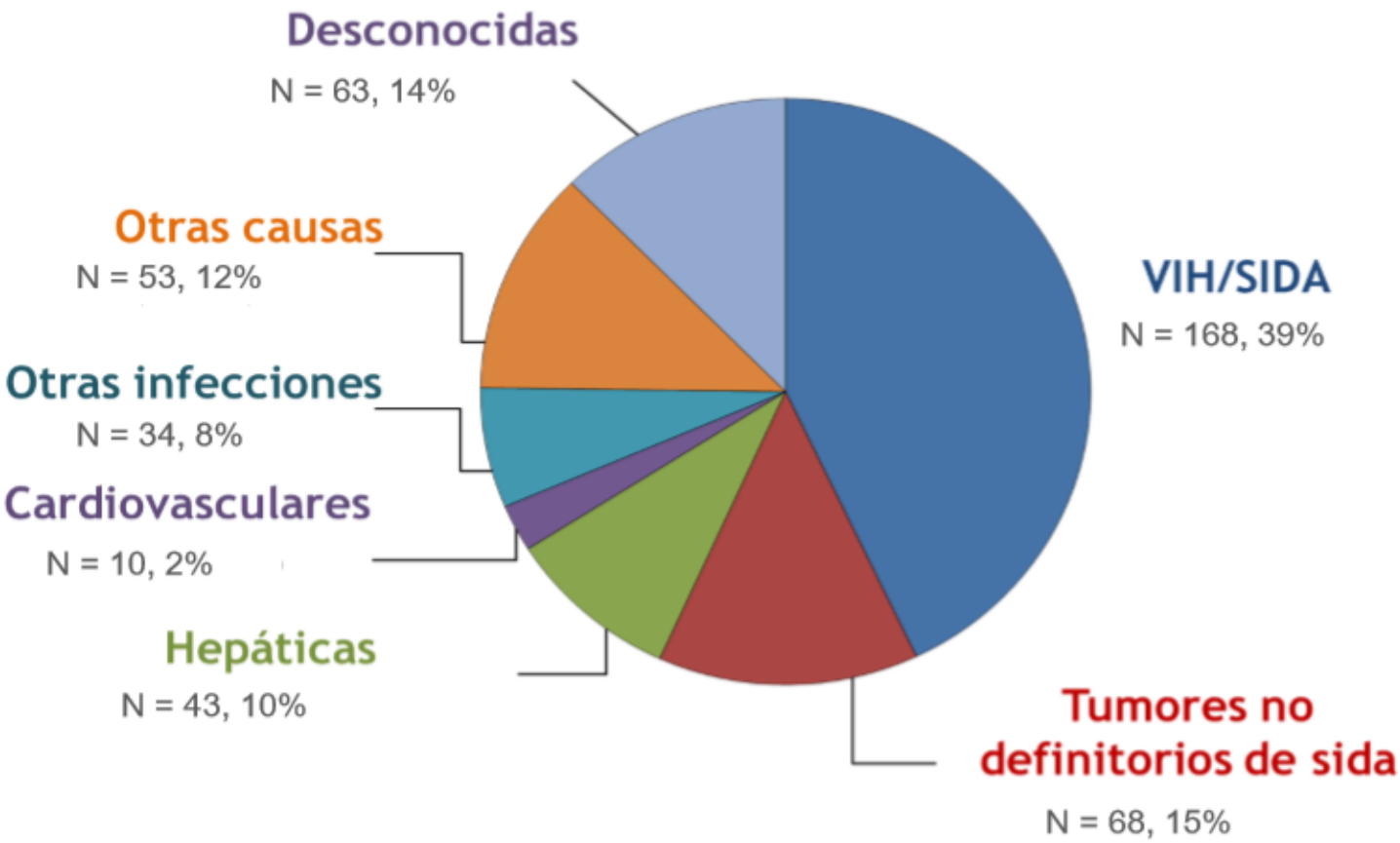
- **La infección por VIH en la actualidad**
  - Objetivos y evolución de la epidemia con la terapia antirretroviral
- **Eficacia**
- **Seguridad**
- **Barrera genética**
- **Impacto de la M184V/I**
- **Inflamación**
- **Conclusiones**

Higher survival in HIV-infected persons since the introduction of HAART (3DR)



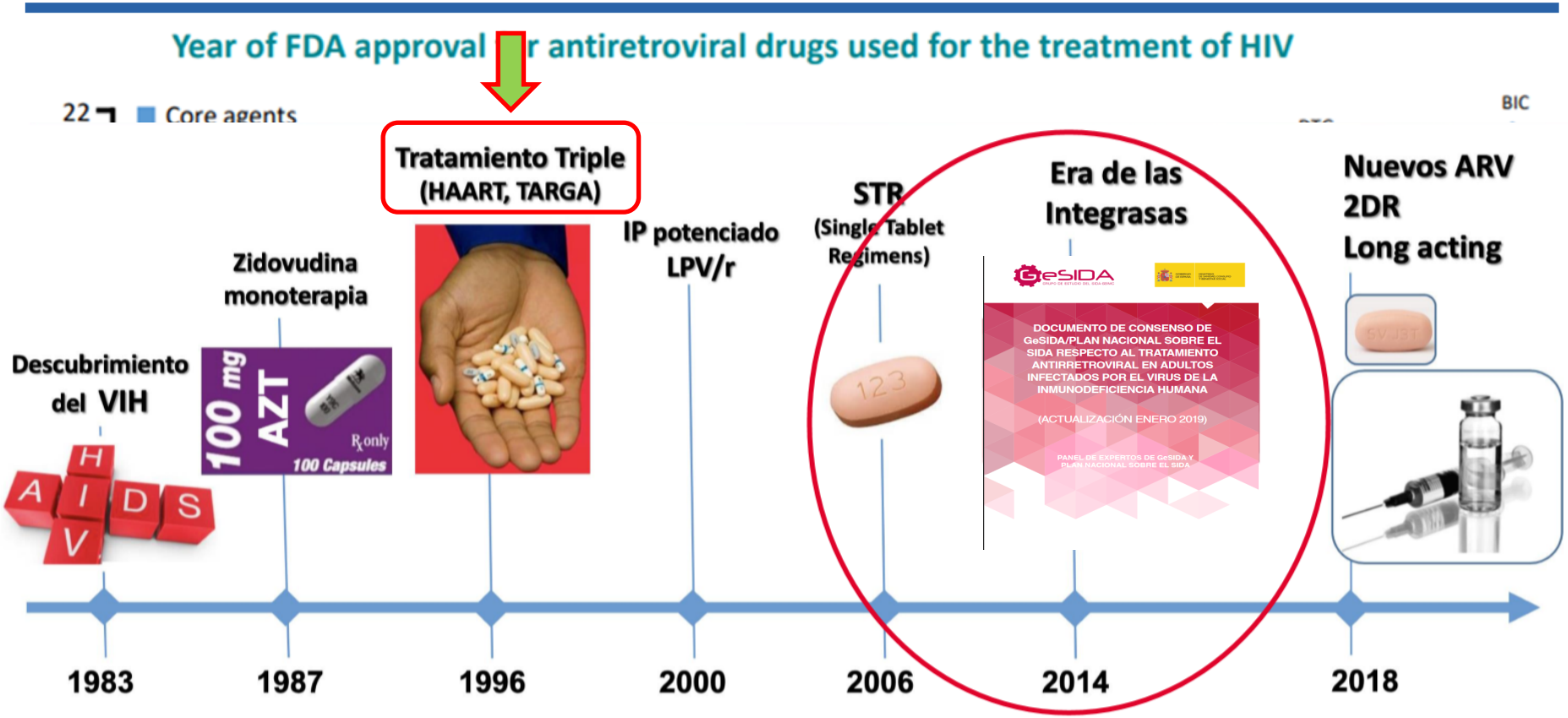
Lohse & Obels. Annals Intern Med 2016

Distribución de las causas de muerte. CoRIS 2004-2015



Alejos B, et al. Congreso GESIDA 2017 #O-09

Evolución del tratamiento antirretroviral



Adaptado de: David Back. Virology Education 2017. http://regist2.virology-education.com/2017/2GlobalHCF/05_Back.pdf (acceso noviembre 2017)

*No longer marketed in the USA; See slide notes for abbreviations.

DHHS. https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/58/fda-approved-hiv-medicines. Accessed February 2018.

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Objetivos del tratamiento antirretroviral

- **Supresión mantenida de forma indefinida** de la carga viral plasmática del RNA-VIH por debajo del nivel establecido en los ensayos clínicos – FDA Guidance[1]
- **La supresión máxima y duradera de la supresión viral plasmática** previene la selección de mutaciones de resistencia, preserva e incluso favorece la la reconstitución inmune (recuento de CD4) que se traduce en beneficios clínicos sustanciales – DHHS Guidelines[2]

1. DHHS & FDA CDER. *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. November* 2015. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128
2. DHHS. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 2017*. Available at: *http://aidsinfo.nih.gov/guidelines*

Estudios en pacientes Naïve: **EFICACIA**

Table 2. Main results with contemporary STR in registrational studies in drug-naive HIV-infected patients

Drugs	Study	Number	Efficacy* (%)	Virological failure (%)	Discontinuation due to SAEs (%)
DRV/c/TAF/FTC	AMBER[18]	362	91.4	4.4	1.9
EVG/c/TAF/FTC	GS-104/111[23]	866	92	0.8	0.9
DTG/ABC/3TC	SINGLE[24]	414	88	5	2
DTG/ABC/3TC	GS-1489[25]	315	93	2.5	1.3
BIC/TAF/FTC	GS1489	314	92.4	1	0
DTG/TAF/FTC	GS-1490[26]	325	93	2.5	<1
BIC/TAF/FTC	GS1490	320	89.4	4	1.6

STR: single-tablet regimen, DRV: darunavir, c: cobicistat, TF: tenofovir alafenamide, FTC: emtricitabine, VG: elvitegravir, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudine, BIC: bictegravir, SAEs: serious adverse events, *Plasma HIV-RNA <50 copies/mL at week 48, intent-to-treat analysis

AIDS Rev. 2018;20:141-149

Estudios en pacientes Naïve: **EFICACIA SOSTENIDA**

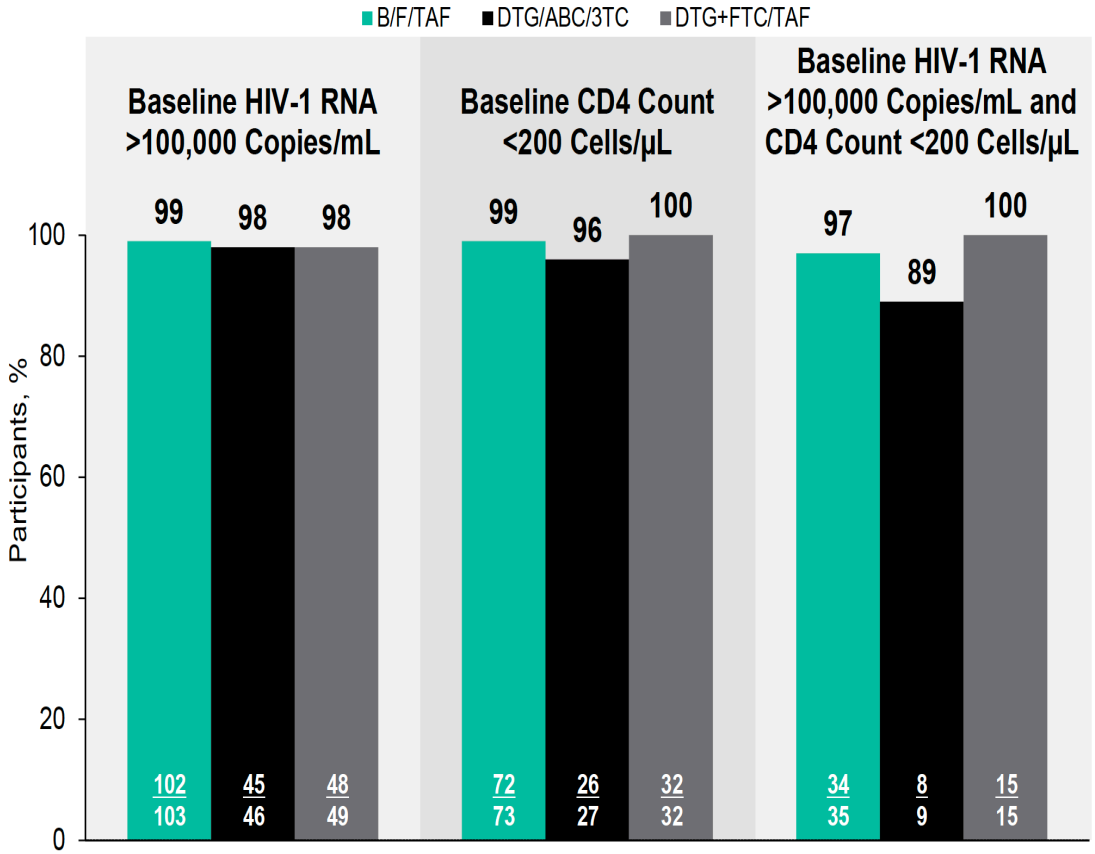
ENSAYO CLÍNICO	F/U, SEMANAS	TAR
SPRING-2[1]	96	**DTG + 2 NRTIs (n = 411)** ---- RAL + 2 NRTIs (n = 411)
SINGLE[2]	144	**DTG + ABC/3TC (n = 414)** ---- EFV/TDF/FTC (n = 419)
FLAMINGO[3]	96	**DTG + 2 NRTIs (n = 242)** ---- DRV/RTV + 2 NRTIs (n = 242)
GS-102[4]	144	**EVG/COBI/TDF/FTC** (n = 348) ---- EFV/TDF/FTC (n = 352)
GS-103[5]	144	**EVG/COBI/TDF/FTC** (n = 353) ---- ATV/RTV + TDF/FTC (n = 355)
GS 104/111	144	EVG/COB/TDF/FTC ---- **EVG/COB/TAF/FTC**
ACTG 5257	144	TDF/FTC/ATZ/RIT ---- TDF/FTC/DRV/RIT ---- **RAL/TDF/FTC**
GS 1489[8]	96	**BIC/TAF/FTC** ---- DTG/3TC/ABC
GS 1490[8]	96	**BIC/TAF/FTC** ---- DTG + TAF/FTC
AMBER[9]	96	**DRV/COBI /TAF/FTC** ---- Control ARM

1. Raffi F, et al. Lancet Infect Dis. 2013;13:927-935. 2. Walmsley S, et al. J Acquir Immune Defic Syndr. 2015;70:515-519. 3. Molina JM, et al. Lancet HIV. 2015;2:e127-e136. 4. Wohl DA, et al. J Acquir Immune Defic Syndr. 2014;65:e118-e120. 5. Clumeck N, et al. J Acquir Immune Defic Syndr. 2014;65:e121-e124. 6. Fulcher JA, et al. CROI 2017. Abstract 500LB. 8 Gupta S, et al. CROI 2019. Seattle, WA. Poster 502. 9. Lathouwers E, et al. HIV Glasgow 2018. Abstract P294

Pooled 1489 & 1490 studies: B/F/TAF versus DTG-containing triple therapy in ART-naïve adults

HIV-1 RNA <50 copies/mL at Week 48: per-protocol analysis

Includes all participants who had on-treatment HIV-1 RNA in the Week 48 window or who discontinued due to lack of efficacy
Excludes participants from the FAS who violated entry criteria due to genotype or prohibited medication, or adherence to study medication
<2.5th percentile

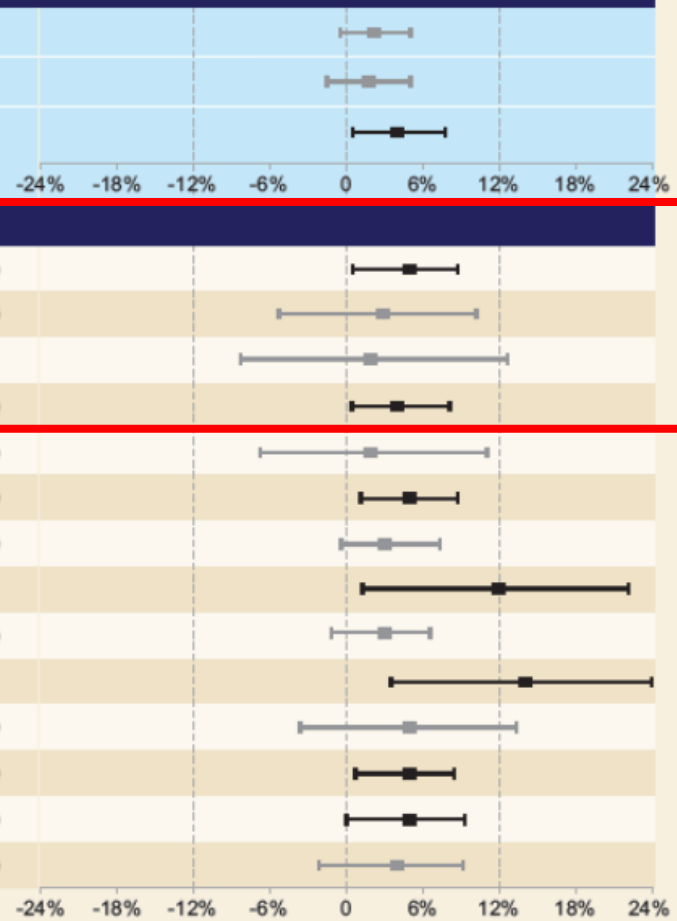


3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; DTG, dolutegravir; F, emtricitabine; TAF; tenofovir alafenamide; TFV, tenofovir

Podzamczer D et al. *IAS* AIDS 2018; PEB148: 1-14

GS-US-104/111: Difference in Virologic outcome, 144 w

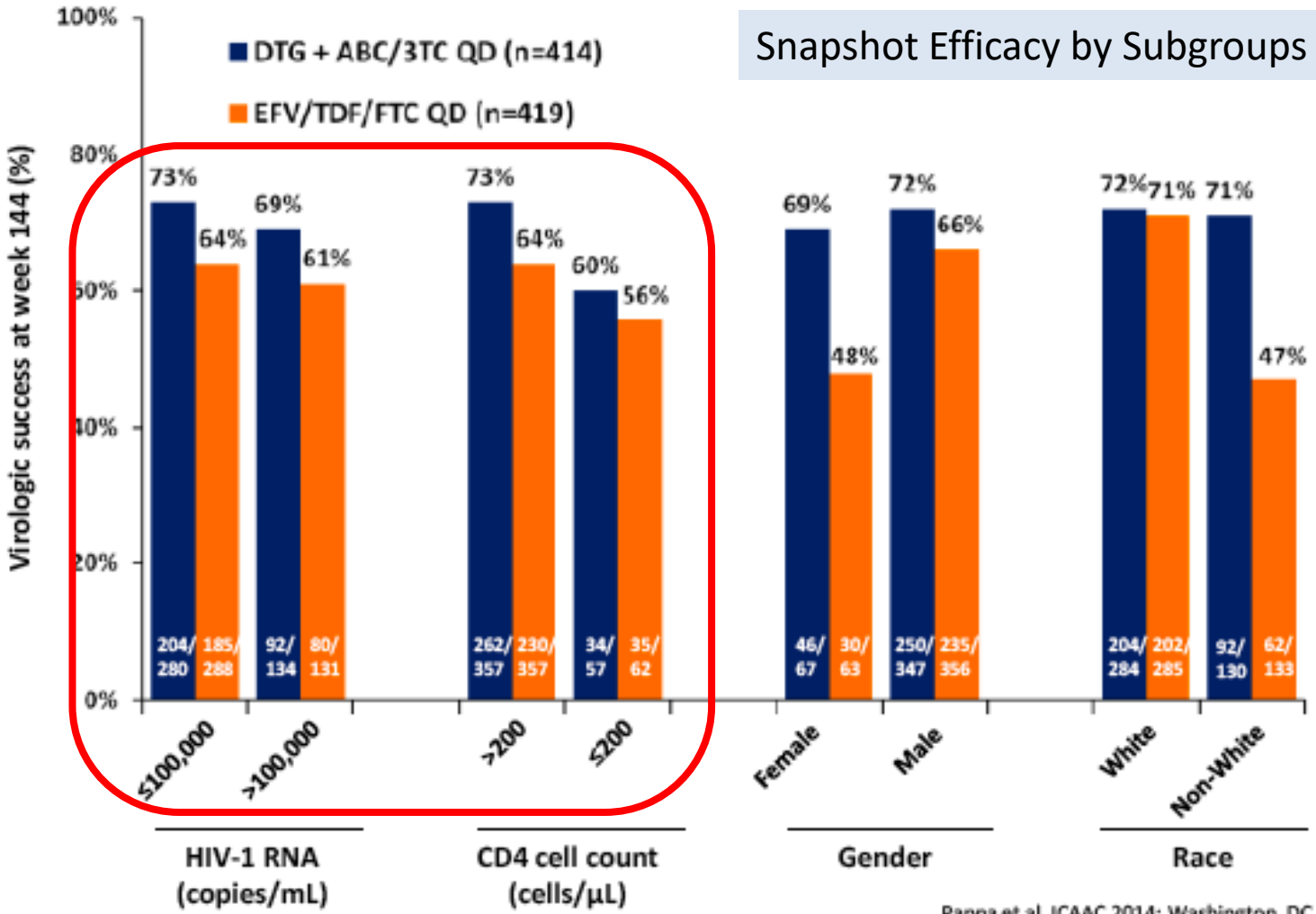
		% (n/n) of Participants		Difference (95% CI)
		E/C/F/TAF n=866	E/C/F/TDF n=867	E/C/F/TDF ← → E/C/F/TAF
Overall*				
Week 48		92	90	
Week 98		87	85	
Week 144*		84	80	
Prespecified Subgroups at Week 144				
Baseline HIV-1 RNA	≤100,000 c/mL*	85 (567/670)	80 (537/672)	
	>100,000 c/mL	83 (162/196)	81 (157/195)	
Baseline CD4 count	<200 cells/µL	83 (93/112)	80 (94/117)	
	≥200 cells/µL*	84 (635/753)	80 (600/750)	
Study drug adherence	<95%	72 (152/211)	71 (142/200)	
	≥95%*	89 (577/651)	84 (553/661)	
Age	<50 yrs	83 (647/777)	80 (602/753)	
	≥50 yrs*	92 (82/89)	81 (92/114)	
Sex	Male	84 (616/733)	82 (603/740)	
	Female*	85 (113/133)	72 (91/127)	
Race	Black	75 (168/223)	71 (152/213)	
	Nonblack*	87 (561/643)	83 (542/654)	
Region	US*	84 (447/532)	80 (423/532)	
	Non-US	84 (282/334)	81 (271/335)	



*Statistically superior. c, copies.

Arribas JR, et al. CROI 2017. Poster #453

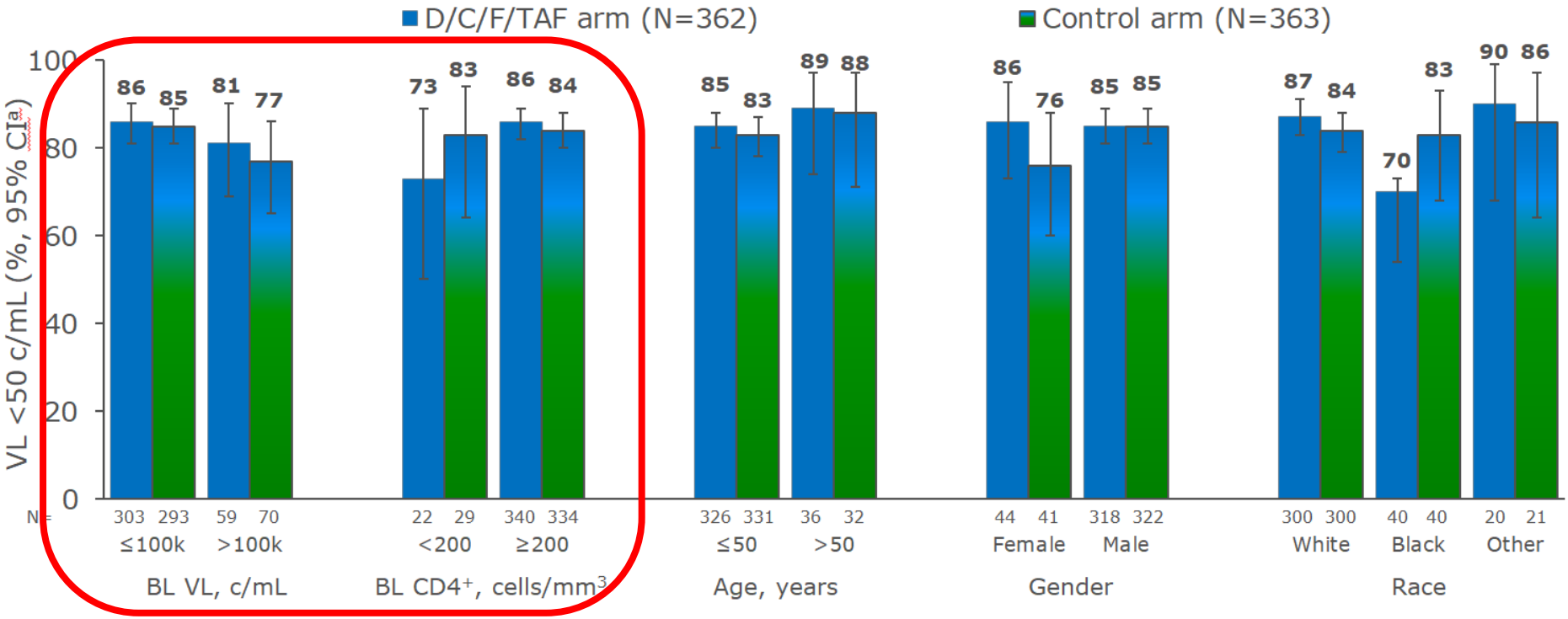
SINGLE study (ING-114167): 144-Week Results



Pappa et al. ICAAC 2014; Washington, DC. H-647a.

AMBER study: Week 96 results

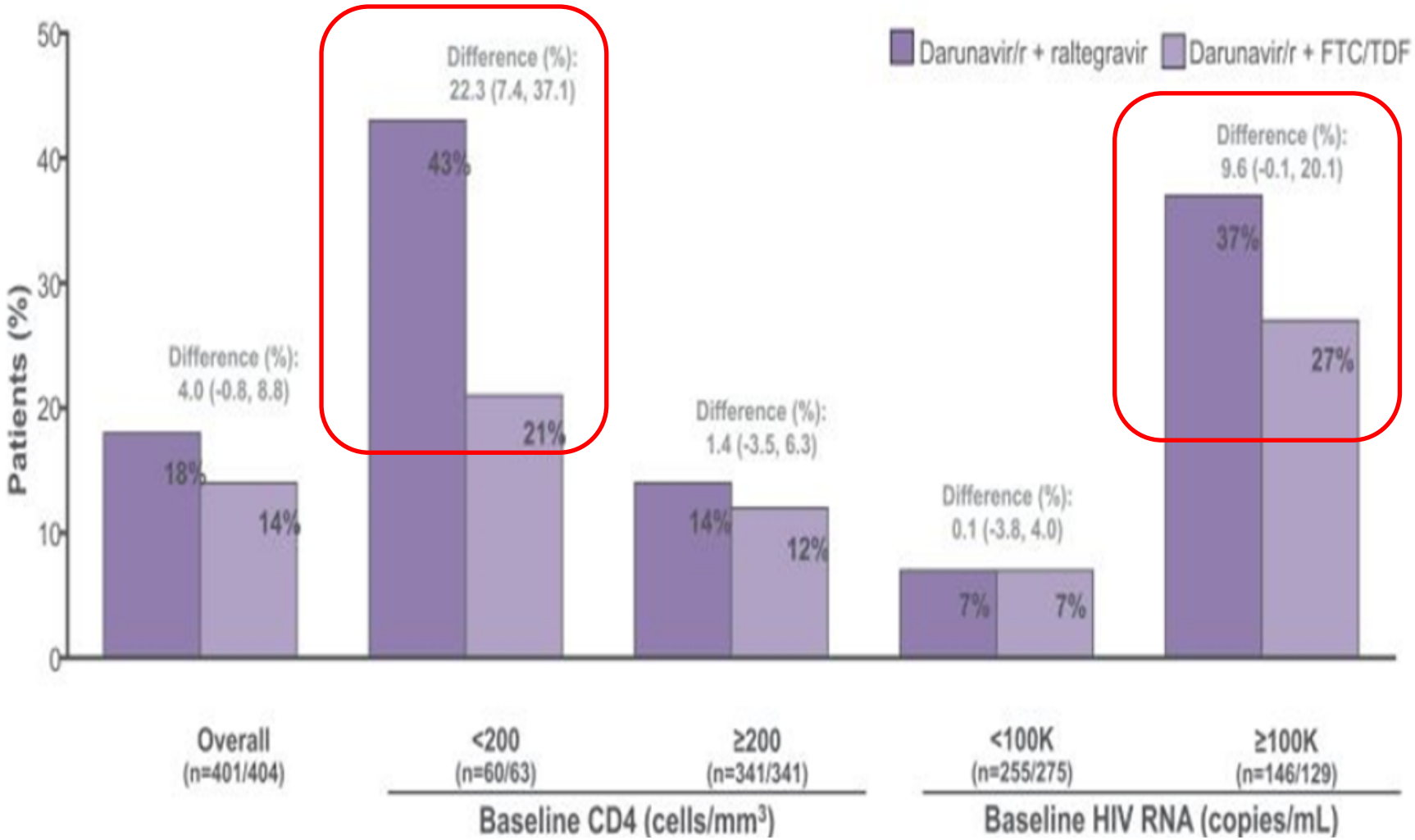
Efficacy and safety of the once-daily, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen in antiretroviral treatment-naïve adults: Snapshot VL <50 c/mL at Week 96 by Subgroups (ITT)



ITT, intent-to-treat; BL, baseline; VL, viral load; [a]Two-sided Exact Clopper-Pearson 95% confidence interval (CI)

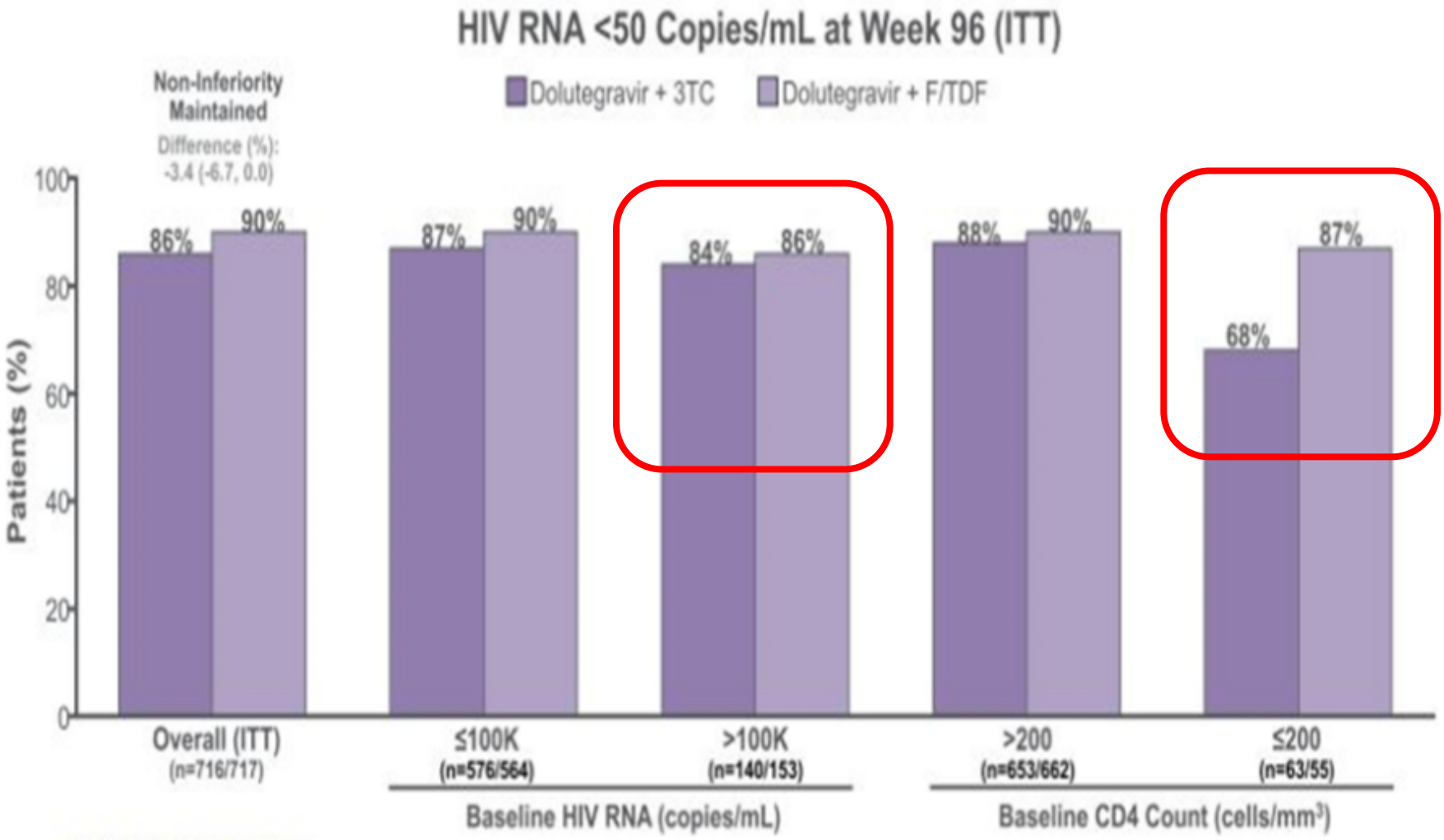
Lathouwers E, et al. HIV Glasgow 2018. Abstract P294

NEAT-001: DRV/r + RAL vs. DRV/r + TDF/FTC en PLWH naïve



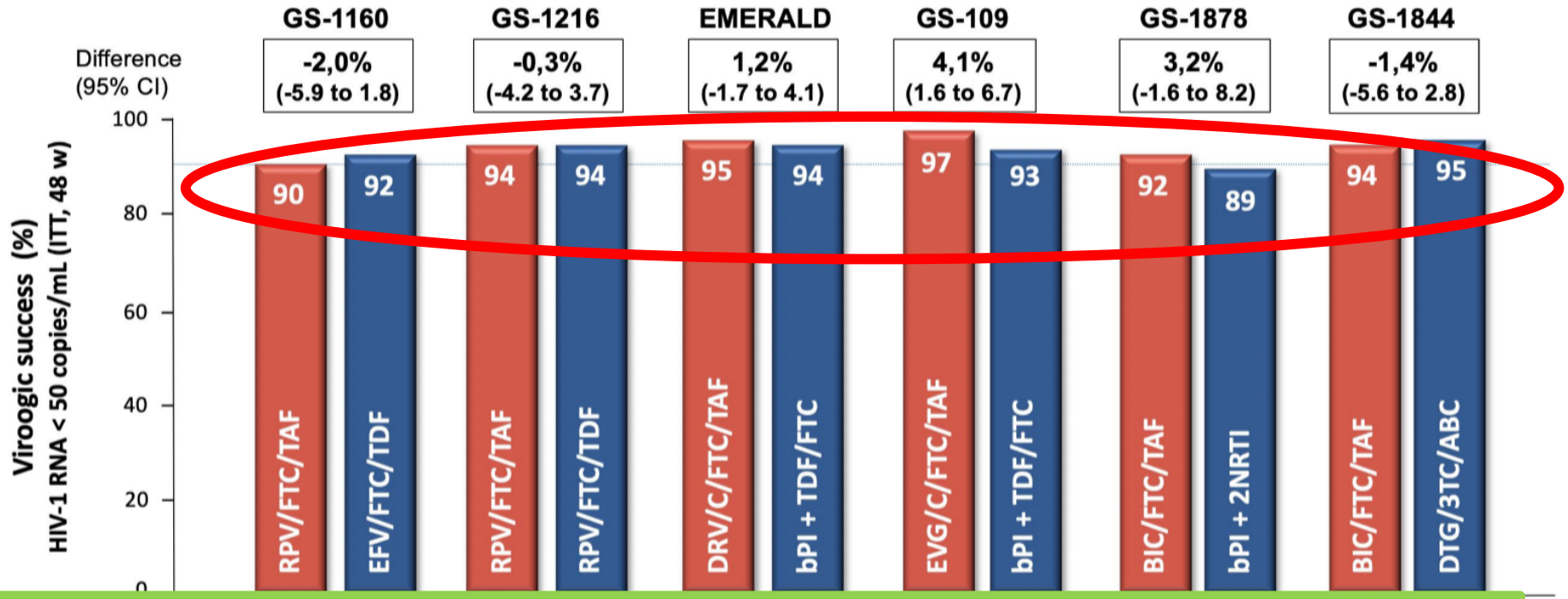
Raffi et al. Lancet 2014; 384: 1942-1954

Gemini 1-2 Studies: Virologic Outcomen at week 96



Cahn P. et al. J Inf AIDS Soc. 2019. 22(suppl 5). 103. Abstract WEAB0404LB

Estudios en pretratados: **EFICACIA / SEGURIDAD**



N	438	437	316	313	763	378	959	477	290	287	282	281
Virologica Failure, %	1.1	0.9	0.6	0	0.8	0.5	1.0	1.3	1.7	1.7	1.1	0.4
Discontinuation due to Adverse Events, %	2.5	1.8	1.3	1.0	1.4	1.3	0.9	2.5	0.7	0.3	2.1	0.7

Switch Continue previous triple therapy

DeJesus E. Lancet HIV 2017;4:e205-13; Orkin C. Lancet HIV 2017;4: e195-204; Orkin C. Lancet HIV 2018;5:e23-e34; Mills A. Lancet Infect Dis 2016; 16:43-52; Daar ES. Lancet HIV 2018;5:e347-56; Molina JM. Lancet HIV 2018;5:e357-65.

VACH Cohort Spain: Virologic Failure and Toxicity 2-Drug Combinations vs Triple Therapy

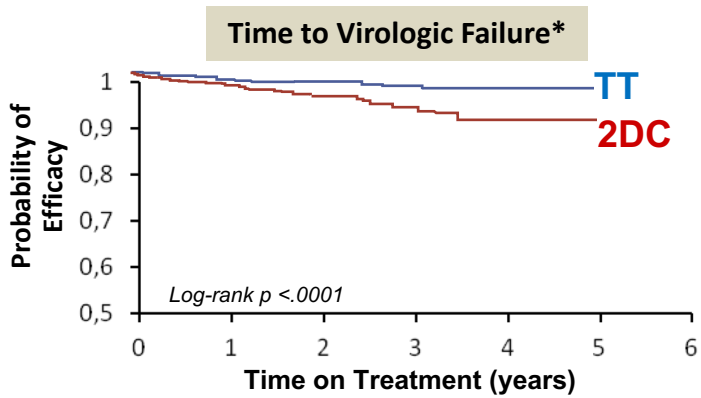
Retrospective analysis of large cohort (n= 9243) to compare real-world persistence, efficacy, and toxicity of DTG and PI containing 2DC (n=1872) vs. INSTI TT (n=7371) in ART experienced patients (2012-2016)

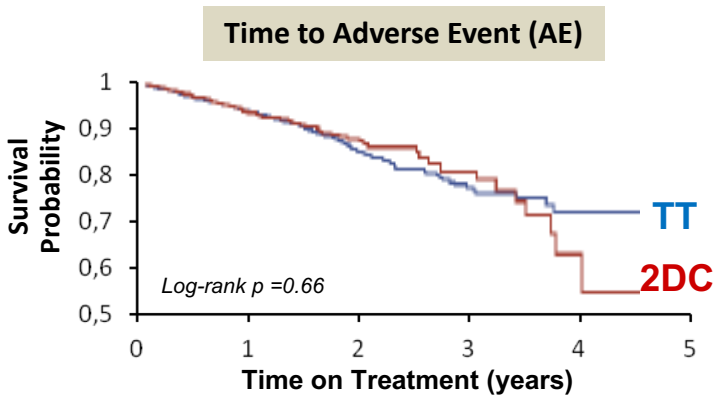
Risk of Virologic Failure

- Significantly higher with 2DC vs TT
- 2-fold higher overall and 3-fold higher with DTG (both $p < 0.0001$)

Risk of Toxicity (Intolerance or AEs)

- No differences was observed after controlling for demographic and clinical characteristics
- Overall (p=0.16) and DTG analyses (p=0.99)





"In this analysis of 9262 recent patient-regimens, probability of remaining free of virological failure were significantly higher in patients on INSTI-based TT compared to DTG and/or PI/r containing Dual Therapy, with no trade-offs in toxicity."

* Kaplan-Meier curves and Cox proportional hazard models controlled for demographics, comorbidities, viral load, CD4, number of previous regimens, CD4 nadir and years on antiretroviral therapy – all at patient-regimen initiation

Teira R, et. al. EACS 2017. Milan, Italy. PE9/33

Poster: 442

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EFICACIA EN VIDA REAL DE LA SIMPLIFICACIÓN EN PACIENTES VIH+ CON CARGA VIRAL SUPRIMIDA DE UNA PAUTA BASADA EN TRES ANTIRRETROVIRALES A DOLUTEGRAVIR-LAMIVUDINA.

Ignacio Pérez-Valero, Rosa De Miguel, Víctor Hontañón, Rafael Micán, Carmen Busca, José Ignacio Bernardino, María Luisa Montes, Victoria Moreno, Eulalia Valencia, Luz Martin-Carbonero, Juan Julián González García

Hospital Universitario La Paz, Madrid, Spain,

METODOS

Diseño: Estudio observacional prospectivo abierto diseñado para valorar la eficacia y seguridad en vida real del cambio a DTG + 3TC en pacientes con carga viral suprimida (<50 cop/mL)

Sujetos: Pacientes VIH+ en seguimiento en el Hospital U. La Paz. El seguimiento de los pacientes se censuró a 31 de enero de 2019.

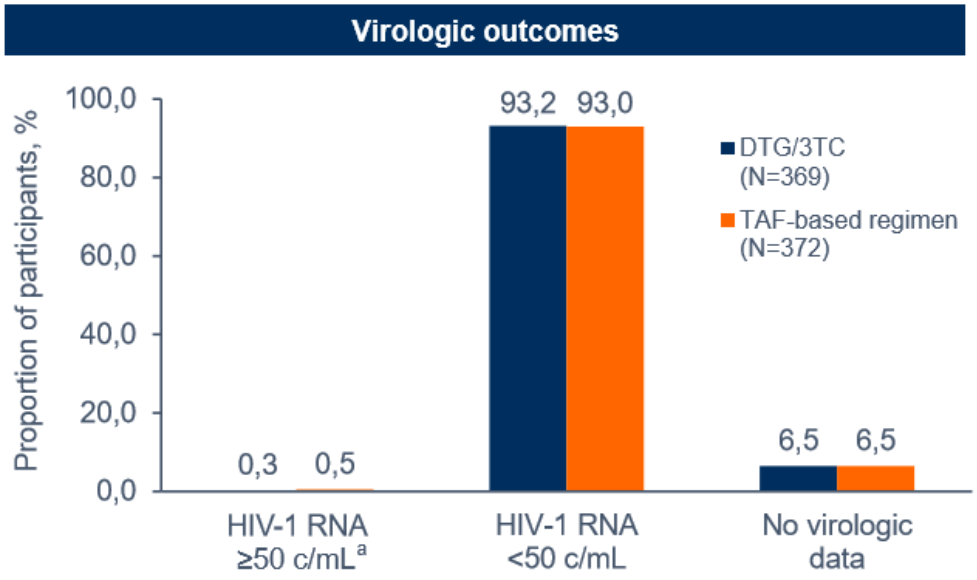
Criterios de selección:

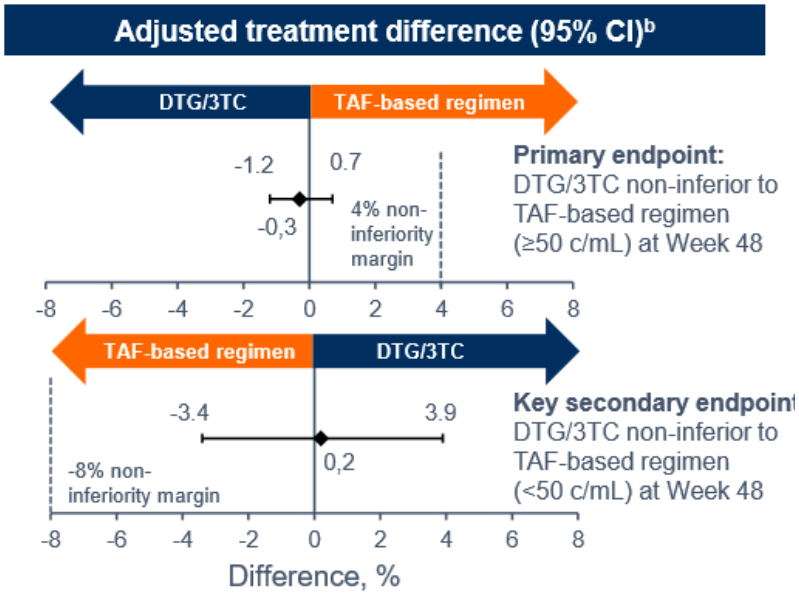
- Pacientes adultos infectados crónicamente de VIH-1 con carga viral suprimida.
- Cambio a DTG + 3TC por cualquier motivo y desde cualquier pauta previa.
- Seguimiento tras el cambio de al menos 24 semanas (se admiten pacientes con un seguimiento inferior que fueron pérdidas de seguimiento o cambiaron el TAR por cualquier causa antes de la semana 24).

CONCLUSIONES

- **En nuestro centro, el cambio a DTG + 3TC en condiciones de práctica clínica habitual demostró ser efectivo en la mayoría de los pacientes y se asoció con una mejoría de los niveles de colesterol total y LDL.**
- **Sin embargo, debido a la alta tasa de fallos terapéuticos observada y sobre todo al desarrollo en un paciente previamente sensible de la mutación M184V durante un fallo virológico relacionado con la aparición de un efecto adverso neuro-psiquiatrico, consideramos que el uso de esta estrategia en pacientes pretratados debe realizarse con cautela.**

SWITCHING TO DTG/3TC FIXED-DOSE COMBINATION (FDC) IS NON-INFERIOR TO CONTINUING A TAF-BASED REGIMEN IN MAINTAINING VIROLOGIC SUPPRESSION THROUGH 48 WEEKS (TANGO STUDY)





- In the per-protocol population, 0/352 participants in the DTG/3TC group and 2/358 participants in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.6; 95% CI, −1.3 to 0.2)[b]

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline third agent class.

van Wyk et al. IAS 2019; Mexico City, Mexico. Slides WEAB0403LB.

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Estudios en pacientes Naïve: **SEGURIDAD**

Table 2. Main results with contemporary STR in registrational studies in drug-naive HIV-infected patients

Drugs	Study	Number	Efficacy* (%)	Virological failure (%)	Discontinuation due to SAEs (%)
DRV/c/TAF/FTC	AMBER[18]	362	91.4	4.4	1.9
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BIC/TAF/FTC	GS1490	320	89.4	4	1.6

STR: single-tablet regimen, DRV: darunavir, c: cobicistat, TF: tenofovir alafenamide, FTC: emtricitabine, VG: elvitegravir, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudine, BIC: bictegravir, SAEs: serious adverse events, *Plasma HIV-RNA <50 copies/mL at week 48, intent-to-treat analysis

AIDS Rev. 2018;20:141-149

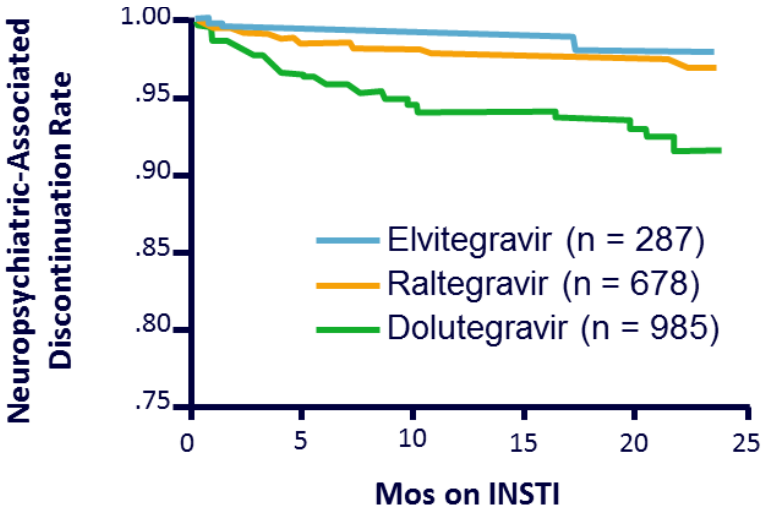
El TAR puede incrementar el riesgo de comorbilidades

FÁRMACO ANTIRRETROVIRAL	RIESGO POTENCIAL
Tenofovir sidoproxil fumarato (TDF)	Hueso y riñón
Tenofovir alafenamida (TAF)	?
Abacavir	Riesgo cardiovascular
Efavirenz	Efectos sobre SNC: suicidabilidad
Inhibidores de la proteasa potenciados	- Interacciones - Riesgo cardiovascular (excepto atazanavir)
Atazanavir	Ictericia
Ritonavir y cobicistat	Interacciones con otros fármacos
Dolutegravir	Insomnio
INHIBIDORES DE LA INTEGRASA	**Ganancia de peso**

Discontinuación por EAs sobre el SNC con DTG

- Estudio restrospectivo para evaluar causas de interrupción del TAR en dos clínicas de Alemania
- Pacientes VIH (N = 1704) iniciando TAR basado en ITI (N = 1950) January 2007 - April 2016

Razón de la discontinuación	Dolutegravir (n = 985)	Elvitegravir (n = 287)
Any AE, n (%)	67 (6.8)	27 (9.4)
Neuropsychiatric AE,* n (%)	49 (5.0)	3 (1.0)
▪ Insomnio/sleep disturbances	36 (3.7)	2 (0.7)
▪ Poor concentration/slow thinking	8 (0.8)	0 (0)
▪ Dizziness	13 (1.3)	1 (0.3)
▪ Headache/paresthesia	16 (1.6)	1 (0.3)
▪ Depression	7 (0.7)	0 (0)



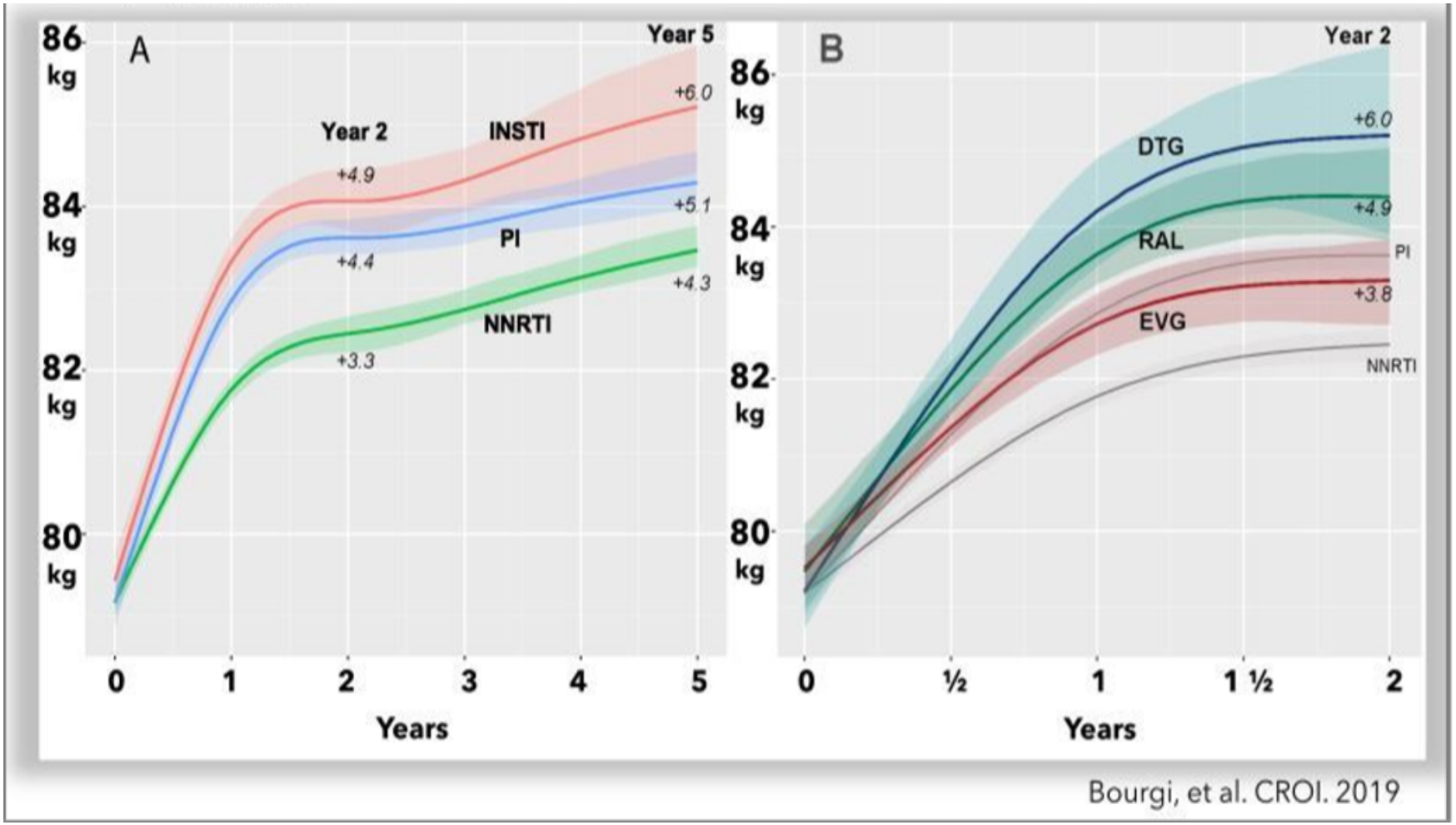
Factores de riesgo

Factor de riesgo o factor para discontinuación por trastorno neuropsiquiátrico	RH (95% CI)	*P* Value
Sexo (femenino vs hombre)	2.64 (1.23-5.65)	.0122
Edad (> 60 vs < 60 yrs)	2.86 (1.42-5.77)	.0033
Abacavir en asociación inicial (si o no)	2.42 (1.38-4.24)	.002
Período de iniciación (2016 vs 2014-2015)	11.36 (4.31-9.41)	< .0001

Sabranski M, et al. HIV Glasgow 2016. Abstract O214.

INSTI y ganancia de peso

INST-based ART has been implicated in greater weitht gain than other regimens in PLWH



INSTI: otras implicaciones metabólicas

Conclusions – Future Directions

- Initiating INSTI- or PI- vs. NNRTI-based regimens may confer increased risk of DM, though risk is heterogeneous among INSTIs
- Mediation analyses, direct vs. indirect effects of ART on incident DM to determine if elevated risk observed in these analyses attributable partially to weight gain

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Barrera genética: resistencias al fracaso virológico

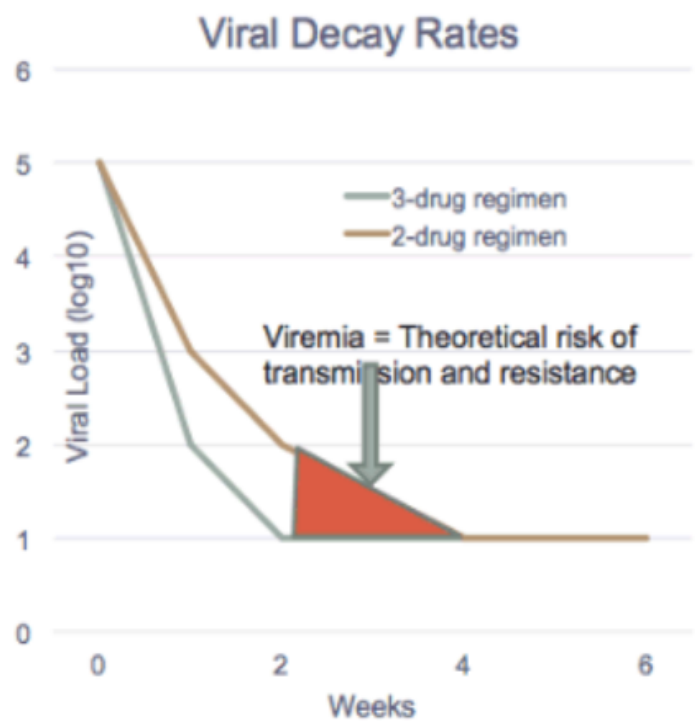
ENSAYO CLÍNICO	F/U, SEMANAS	TAR	FALLO VIROLÓGICO, n (%)	MUTACIONES PRIMARIAS EMERGENTES A ITI, n
SPRING-2[1]	96	**DTG + 2 NRTIs (n = 411)**	22 (5)	**0**
		RAL + 2 NRTIs (n = 411)	29 (7)	1 (INSTI), 4 (NRTI)
SINGLE[2]	144	**DTG + ABC/3TC (n = 414)**	39 (9)	**0**
		EFV/TDF/FTC (n = 419)	33 (8)	1 (NRTI), 6 (NNRTI)
FLAMINGO[3]	96	**DTG + 2 NRTIs (n = 242)**	2 (< 1)	**0**
		DRV/RTV + 2 NRTIs (n = 242)	4 (2)	**0**
GS-102[4]	144	**EVG/COBI/TDF/FTC (n = 348)**	NR (7)	9 (INSTI), 10 (NRTI)
		EFV/TDF/FTC (n = 352)	NR (10)	14 (NRTI)
GS-103[5]	144	**EVG/COBI/TDF/FTC (n = 353)**	NR (8)	8 (INSTI), 8 (NRTI)
		ATV/RTV + TDF/FTC (n = 355)	NR (7)	2 (NRTI)
GS 104/111	144	EVG/COB/TDF/FTC	NR (12)	7 (II+ITI), 4 (ITI)I, 1 (II)
		EVG/COB/TAF/FTC	NR (12)	8 (II+ITI), 4 (ITI)
ACTG 5257	144	TDF/FTC/ATZ/RIT	NR (18)	9 (ITI)
		TDF/FTC/DRV/RIT	NR (4)	**0**
		RAL/TDF/FTC	NR (9)	10 (II+ITI), 7 (ITI), 1 (II)
GS 1489[8]	96	**BIC + TAF +FTC**	1	**0**
GS 1490[8]	96	**BIC + TAF+FTC**	4	**0**
AMBER[9]	96	**DRV/COBI/TAF/FTCdr**	4.4	**0**

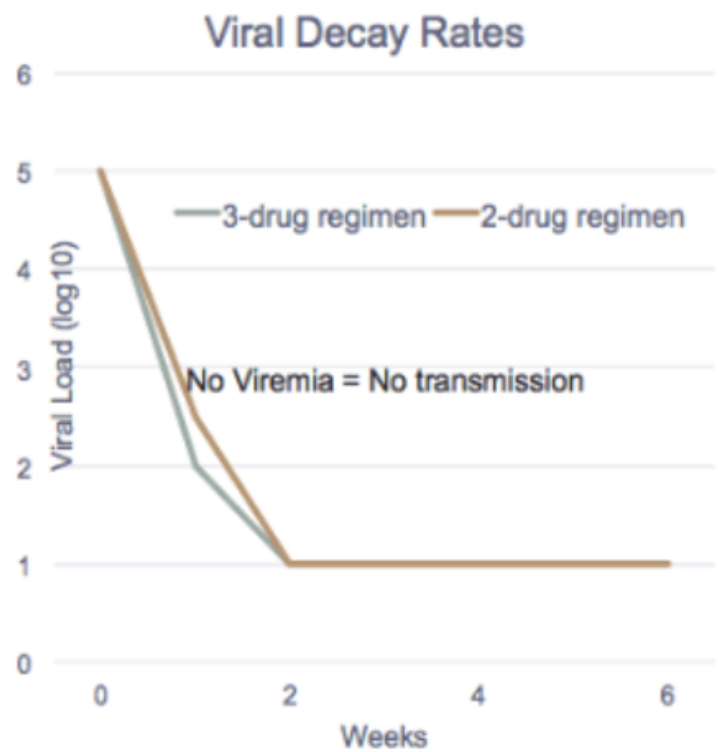
1. Raffi F, et al. Lancet Infect Dis. 2013;13:927-935. 2. Walmsley S, et al. J Acquir Immune Defic Syndr. 2015;70:515-519. 3. Molina JM, et al. Lancet HIV. 2015;2:e127-e136. 4. Wohl DA, et al. J Acquir Immune Defic Syndr. 2014;65:e118-e120. 5. Clumeck N, et al. J Acquir Immune Defic Syndr. 2014;65:e121-e124. 6. Fulcher JA, et al. CROI 2017. Abstract 500LB. 8 Gupta S, et al. CROI 2019. Seattle, WA. Poster 502. 9 Lathouwers E, et al. HIV Glasgow 2018. Abstract P294

Descenso de viremia con DTG + 3TC vs. terapia triple

Se estima que la prevalencia global en España de resistencias primarias en los genes de la transcriptasa inversa y la proteasa es del 7,9%.

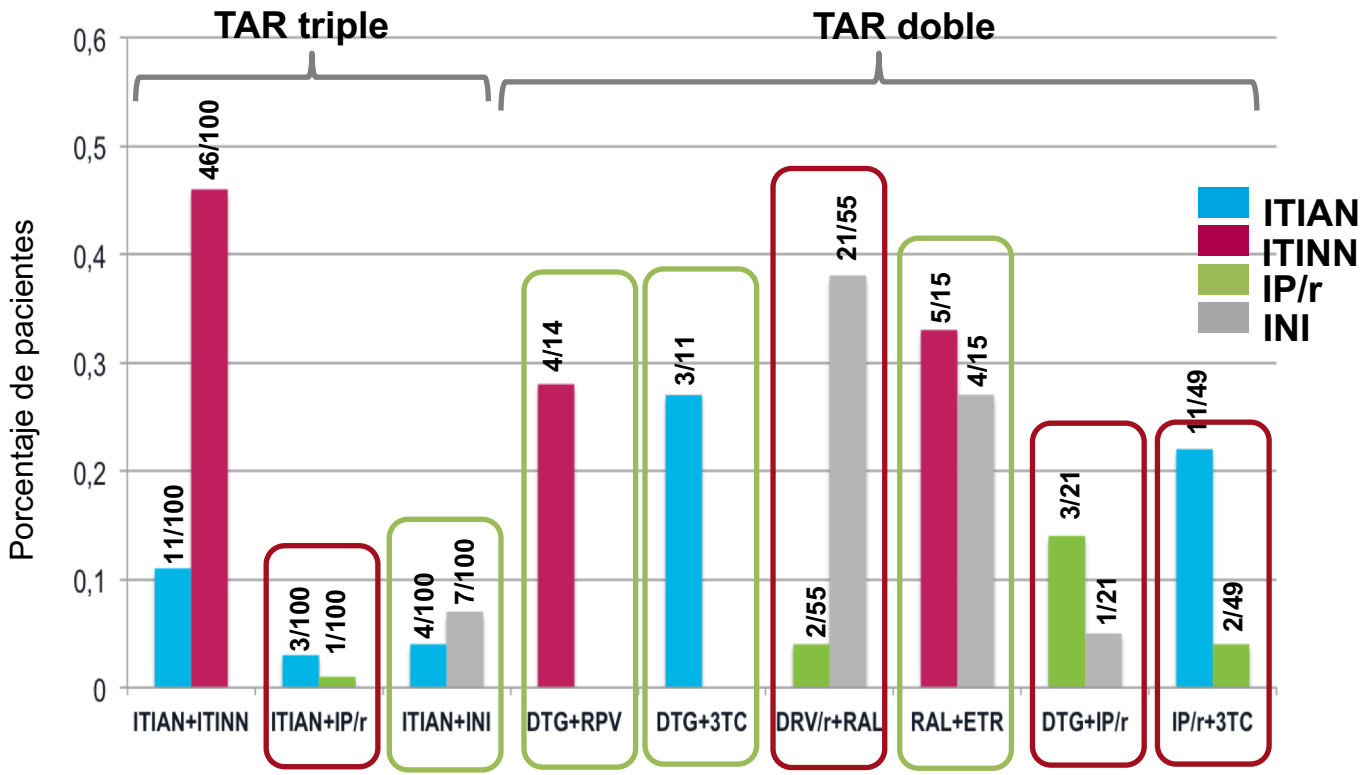
Viral dynamics may influence the risk of viral transmission or selection of resistant variants





Taiwo et al. CID 2018

Resistencia en el momento del fallo virológico, según las clases de ARV y el régimen de terapia triple o doble



- **En TAR triple:**
  - Gran protección de los IP/r a los ITIAN
  - No desarrollo de resistencia a DTG
- **En TAR doble:**
  - DTG no siempre protege a RPV o 3TC
  - DRV/r o ATV/r no siempre protegen a 3TC

…en términos generales, en los pacientes con fallo virológico, el TAR doble genera mayor número de mutaciones de resistencia que el TAR triple.

Calvez V, et al. 16th EACS. Milan, October 25-27, 2017. PS1/4.

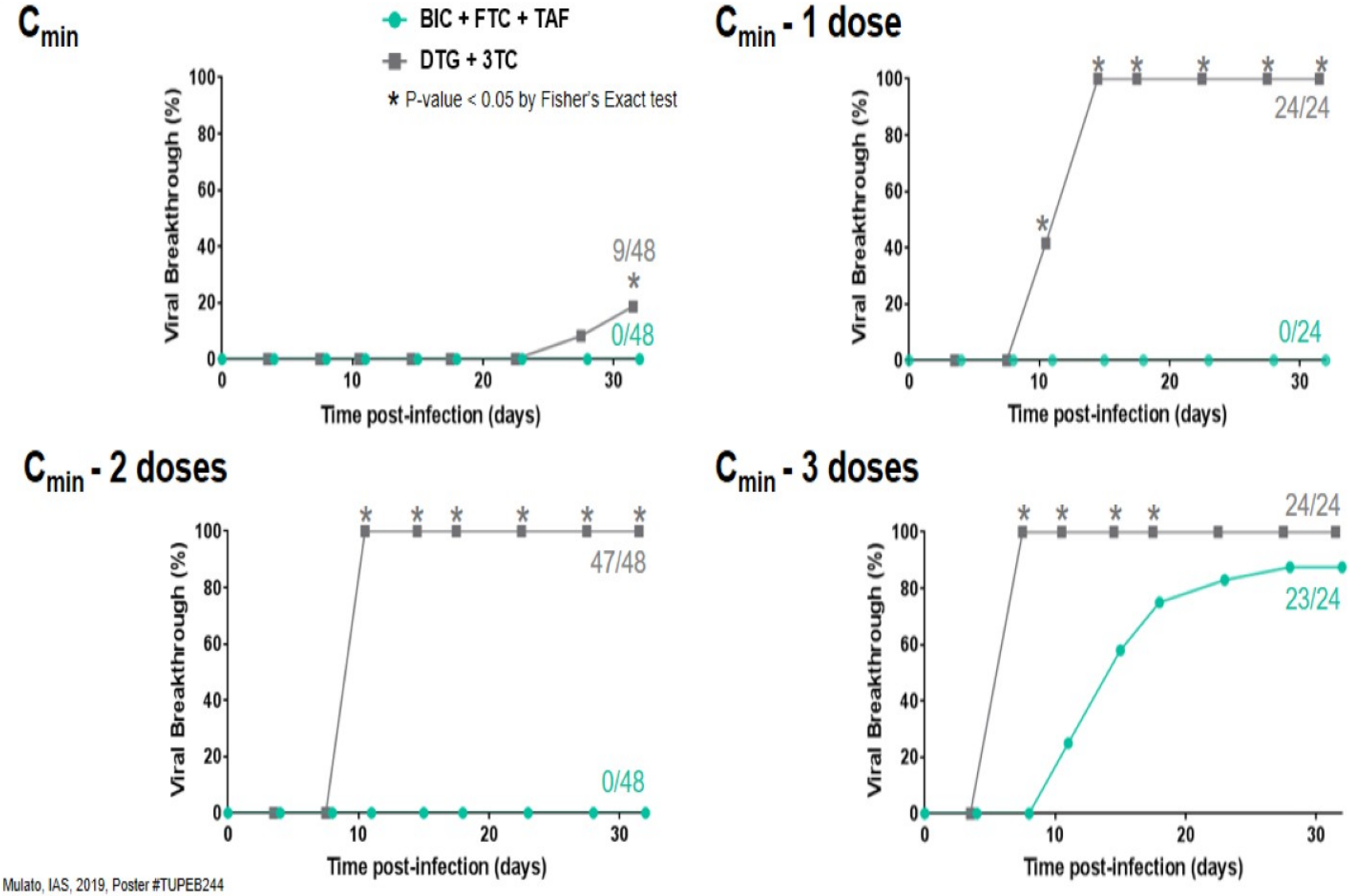
Forgiveness of Antiretroviral Regimens: *In Vitro* HIV-1 Viral Breakthrough with 2-Drug versus 3-Drug Regimens Simulating Variable Adherence to Treatment

Andrew Mulato, Rima Acosta, Stephen R. Yant, Tomas Cihlar, and Kirsten White

Gilead Sciences, Inc., Foster City, CA, USA

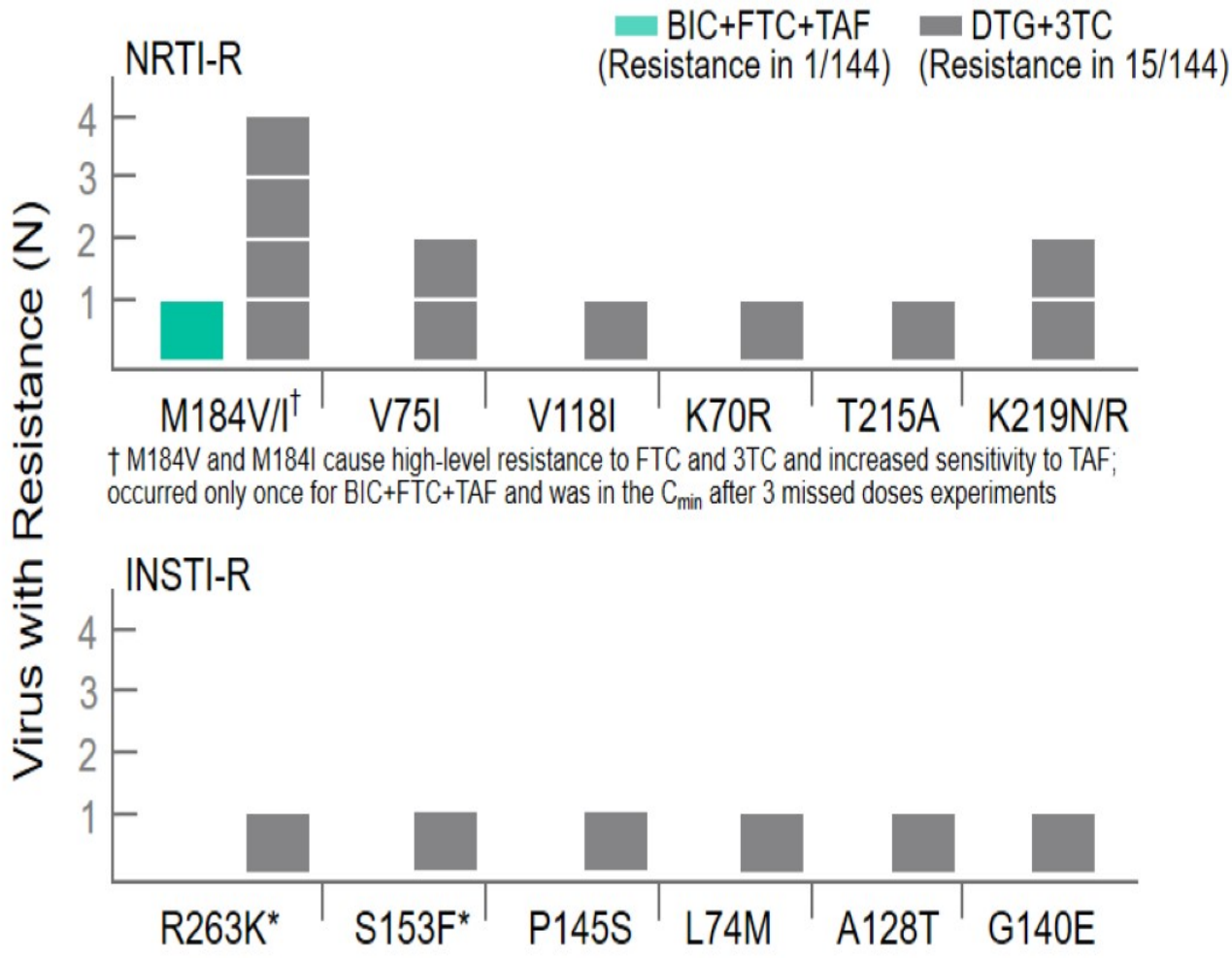
Presented at: The 10th IAS Conference on HIV Science (IAS 2019)
July 21-24, 2019, Mexico City, Mexico
Poster: TUPEB244

Time to Viral Breakthrough: C_{min} and After Missing 1-3 Consecutive Dosis (N=144)



Mulato, IAS, 2019, Poster #TUPEB244

Resistance in Breakthrough Viruses at C_{min} and After Missing 1-3 Consecutive Dosis



*R263K and S153F have been previously selected by DTG and cause reduced susceptibility to DTG
The well with R263K in IN also had T215A and K219R present.

Mulato, IAS, 2019, Poster #TUPEB244

Triple terapia antirretroviral

- La infección por VIH en la actualidad
  - Objetivos y evolución de la epidemia con la terapia antirretroviral
- Eficacia
- Seguridad
- Barrera genética
- **Impacto de la M184V/I**
- Inflamación
- Conclusiones

Study 1878: B/F/TAF vs Boosted PI + 2 NRTIs in Virologically Suppressed Adults

Analyses of Baseline M184V/I & B/F/TAF Efficacy at W48

Pre-existing unrecognized M184V/I*

- En pacientes que no tenían sospechas de la M184V/I o cepa salvaje M184M por genotipo histórico

0%
(0/141)‡

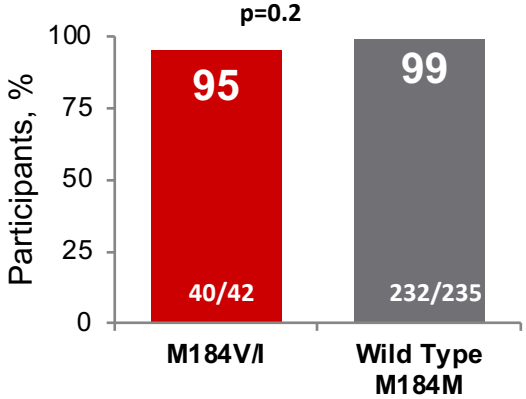
15%
(42/277)

Hubo niveles inesperadamente altos de M184V/I preexistente identificados en genotipado proviral

Efficacy

- B/F/TAF maintained high levels of suppression, regardless of M184V/I presence †
- No treatment-emergent resistance

HIV RNA < 50c/ml at W48 or last visit



B/F/TAF may be an effective treatment for suppressed adults with or without M184V/I

B/F/TAF is indicated for patients with no known substitutions associated with resistance to the individual components.

* Baseline M184V/I resistance was an exclusion criteria and no prior switch with VF
† Virologic failure occurred in 2 B/F/TAF participants at W8 and W12 with no treatment-emergent resistance; both poorly adherent with pre-existing M184V/I
‡ 149 participants were enrolled in the B/F/TAF arm with no M184V/I suspected based on treatment history alone as no historical genotype was available
* Blip: single HIV-1 RNA value ≥50 c/mL

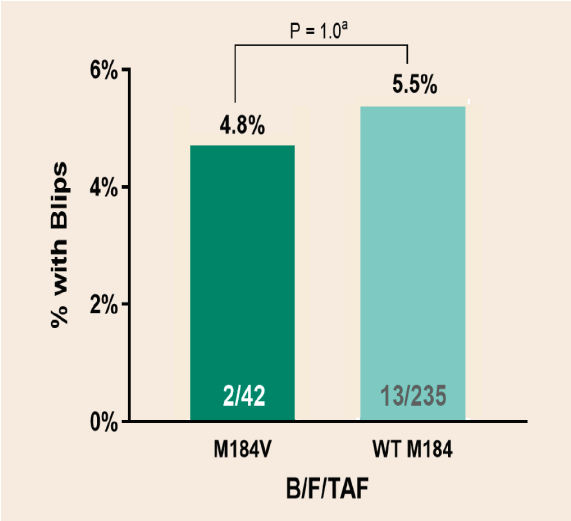
Andreatta K, et al. HIV Drug Therapy 2018, Glasgow, UK. Poster 298

Study 1878: B/F/TAF vs Boosted PI + 2 NRTIs

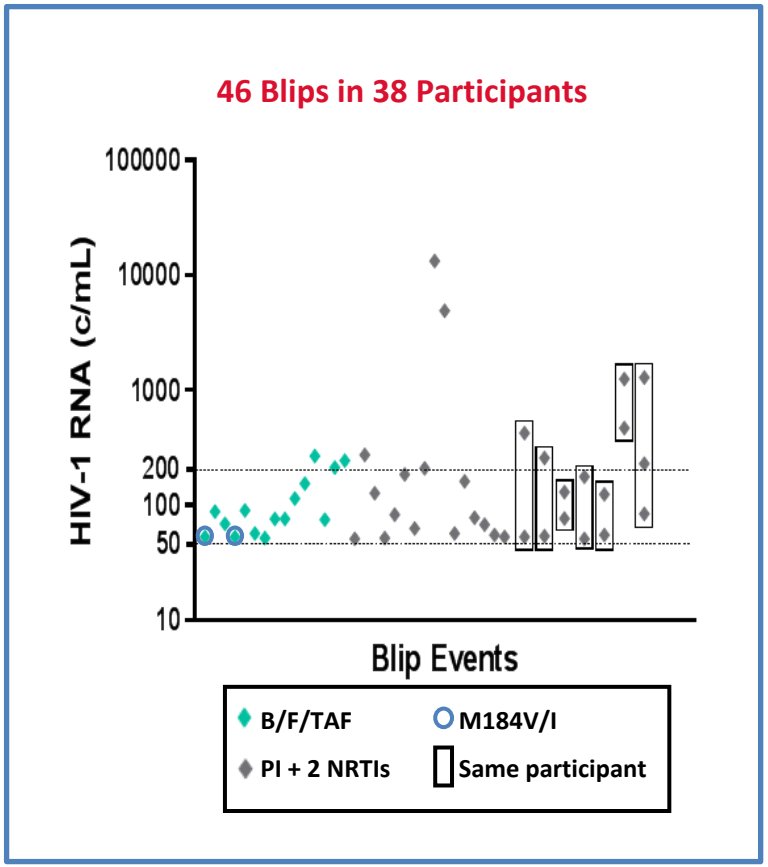
Analyses of Baseline M184V/I and Blips at Week 48

Blips*

- Blips occurred in similar proportion of B/F/TAF participants with or without M184V/I



- **Significantly fewer blip events with B/F/TAF** vs boosted PI regimen
  - 15 vs 31, p=0.03
  - Only 2/42 B/F/TAF participants with M184V/I had a blip



* Blip: single HIV-1 RNA value ≥50 c/mL

Andreatta K, et al. HIV Drug Therapy 2018, Glasgow, UK. Poster 298

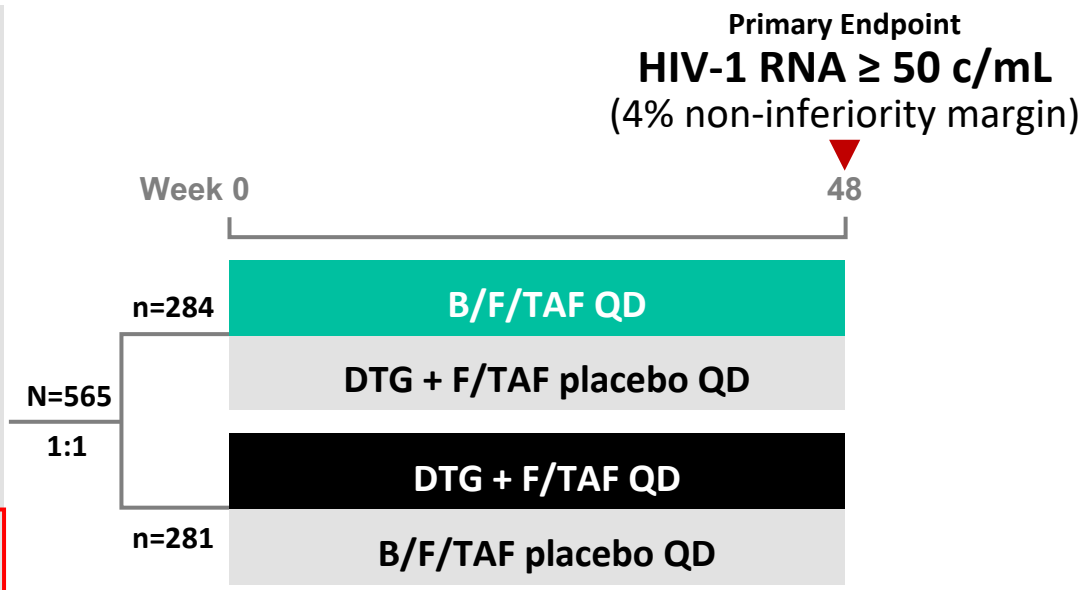
GS-US-380-4030 Study.

Switch to DTG or BIC + F/TAF w/wo prior resistance

- **Phase 3, randomized, double-blind, multicenter, active-controlled study**

Adults with HIV on DTG + F/TAF or F/TDF

- HIV-1 RNA < 50 c/mL for
  - ≥ 3 months if no NRTI resistance
  - ≥ 6 months if NRTI resistance is known or suspected
- Any NRTI, NNRTI, or PI resistance was allowed
- No documented INSTI resistance or confirmed virologic failure on an INSTI-containing regimen



Randomization stratified by:

- F/TAF vs F/TDF at baseline
- Documented or suspected history of NRTI resistance

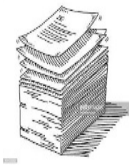
Acosta, IAS, 2019, Poster #MOPEB241

GS-US-380-4030 Study.

Pre-Existing NRTI Resistance

Category	NRTI Resistance Mutation	At Stratification[a] N=565	Final[a] N=565	B/F/TAF[a] n=284	DTG + F/TAF[a] n=281
1	K65R/E/N or ≥ 3 TAMs[b], n (%)	15 (3%)	30 (5%)	16 (6%)	14 (5%)
2	Other NRTI Resistance, n (%)	63 (11%)	108 (19%)	55 (19%)	53 (19%)
3	No NRTI Mutation, n (%)	487 (86%)	427 (76%)	213 (75%)	214 (76%)

Historical Genotype
HIV-1 RNA ≥ 400 c/mL



50% (285/565)

+

Proviral DNA
HIV-1 RNA < 50 c/mL

69% (391/565)

=

Any Genotypic Data

83% (470/565)

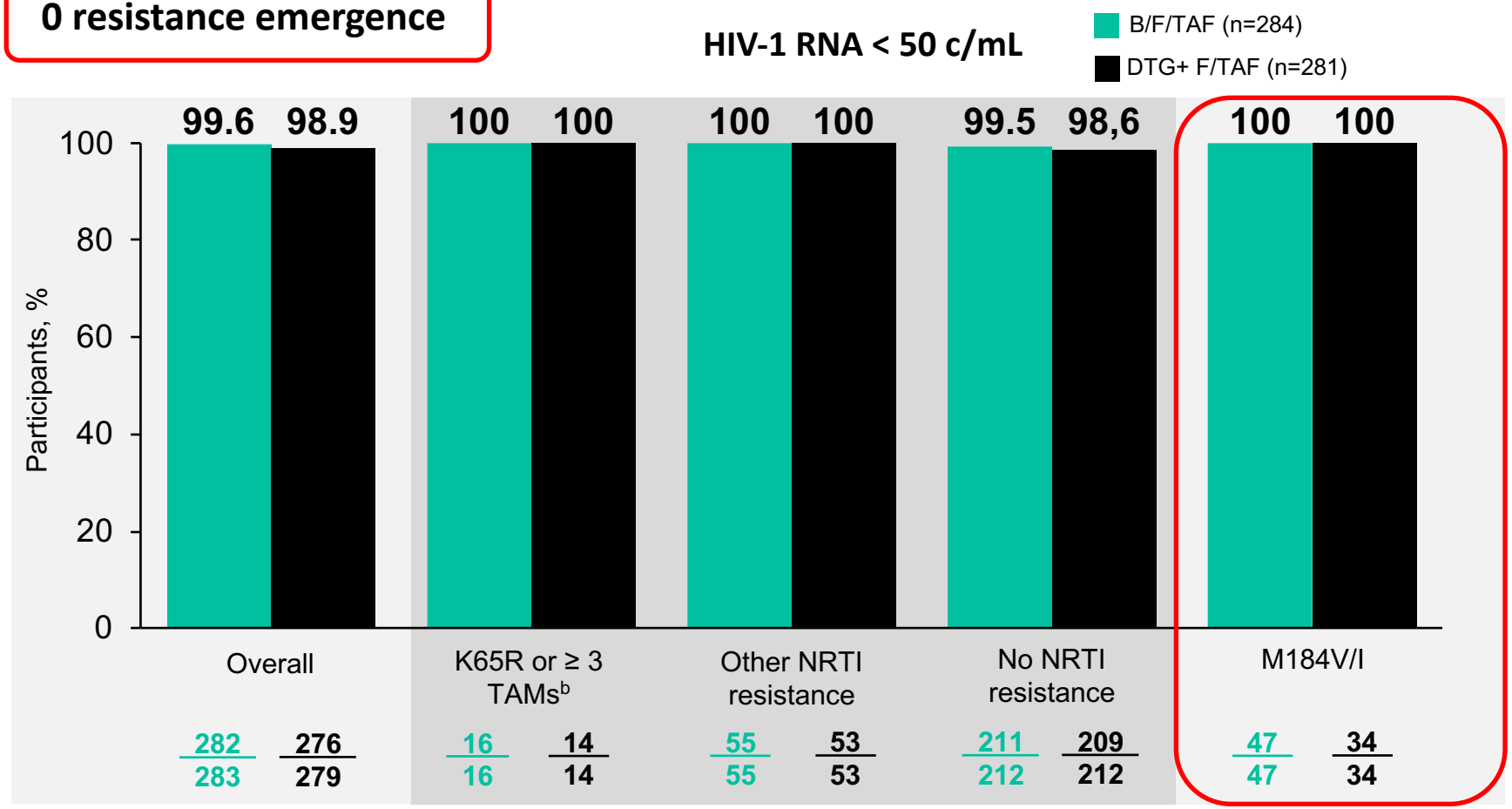
a. 20 participants stratified to categories 1 or 2 based on investigator suspected NRTI resistance (19 participants category 2, and 1 participant category 1) which were not confirmed by historical genotype or proviral DNA genotype.
b. Includes K65R/E/N, or 3 or more thymidine analogue mutations (TAMs) that include M41L or L210W, or T69 insertions.

Acosta, IAS, 2019, Poster #MOPEB241

Virologic Outcome by the LOCF Method, NRTI Resistance Categories

GS-US-380-4030 Study.

0 resistance emergence

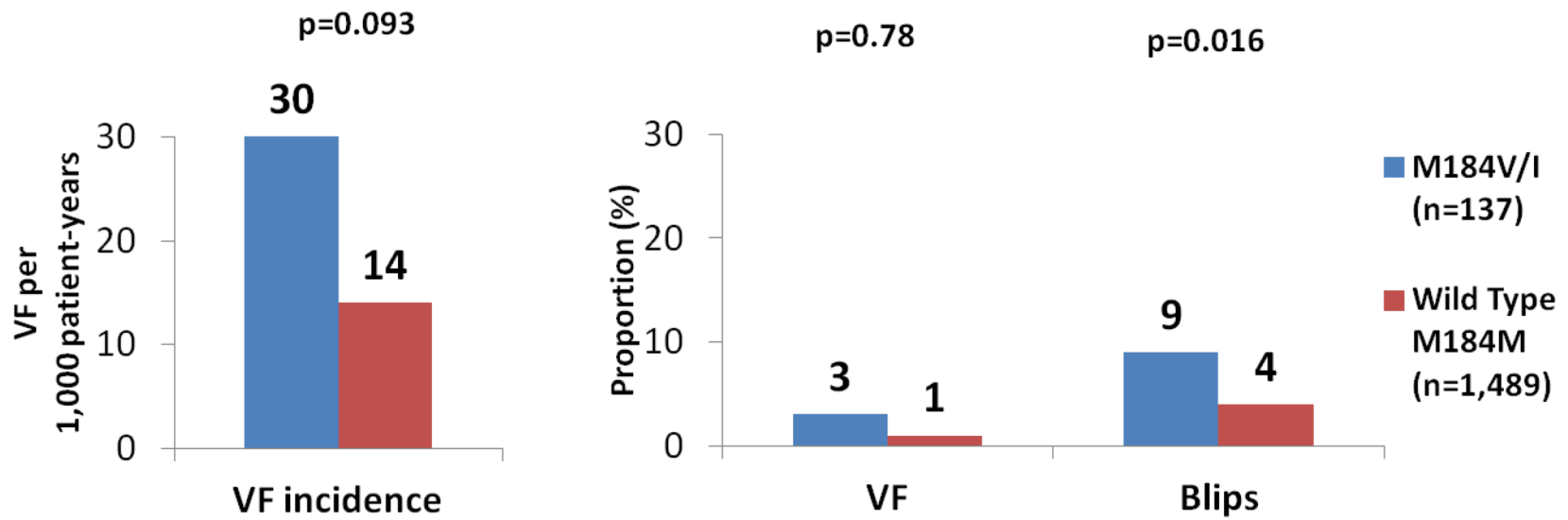


a. The LOCF outcome analysis did not include 3 participants (1 B/F/TAF; 2 DTG + F/TAF) who had no on-treatment post-baseline data.
b. Includes K65R/E/N, or 3 or more TAMs that include M41L or L210W, or T69 insertions.

Acosta, IAS, 2019, Poster #MOPEB241

Impacto de M184V/I en la eficacia de DTG en pacientes virológicamente suprimidos

Evaluación del efecto de M184V/I en 1626 pacientes virologicamente suprimidos cambiando a DTG/ABC/3TC con genotipo disponible seguido del primer fallo virológico (VF) con blips pre-VF documentados en 5 cohortes europeas: ARCA, ICONA, ANRS CO3, ATHENA, SHCS



- Solo 21 pacientes tuvieron un fallo virológico definido por protocolo durante el estudio (1.29%),

Las tasas de VF y la incidencia de blips fueron numericamente más altas con M184V/I (both p=NS)

Olearo F, et al. HIV Drug Therapy 2018, Glasgow, UK, Oral 214

Poster: 442

Ignacio Perez-Valero | Pº Castellana 261 | Madrid 28034, Spain | +34917277099 | Ignacio.perez@salud.madrid.org

EFICACIA EN VIDA REAL DE LA SIMPLIFICACIÓN EN PACIENTES VIH+ CON CARGA VIRAL SUPRIMIDA DE UNA PAUTA BASADA EN TRES ANTIRRETROVIRALES A DOLUTEGRAVIR-LAMIVUDINA.

Ignacio Pérez-Valero, Rosa De Miguel, Víctor Hontañón, Rafael Micán, Carmen Busca, José Ignacio Bernardino, María Luisa Montes, Victoria Moreno, Eulalia Valencia, Luz Martin-Carbonero, Juan Julián González García

Hospital Universitario La Paz, Madrid, Spain,

METODOS

Diseño: Estudio observacional prospectivo abierto diseñado para valorar la eficacia y seguridad en vida real del cambio a DTG + 3TC en pacientes con carga viral suprimida (<50 cop/mL)

Sujetos: Pacientes VIH+ en seguimiento en el Hospital U. La Paz. El seguimiento de los pacientes se censuró a 31 de enero de 2019.

Criterios de selección:

- Pacientes adultos infectados crónicamente de VIH-1 con carga viral suprimida.
- Cambio a DTG + 3TC por cualquier motivo y desde cualquier pauta previa.
- Seguimiento tras el cambio de al menos 24 semanas (se admiten pacientes con un seguimiento inferior que fueron pérdidas de seguimiento o cambiaron el TAR por cualquier causa antes de la semana 24).

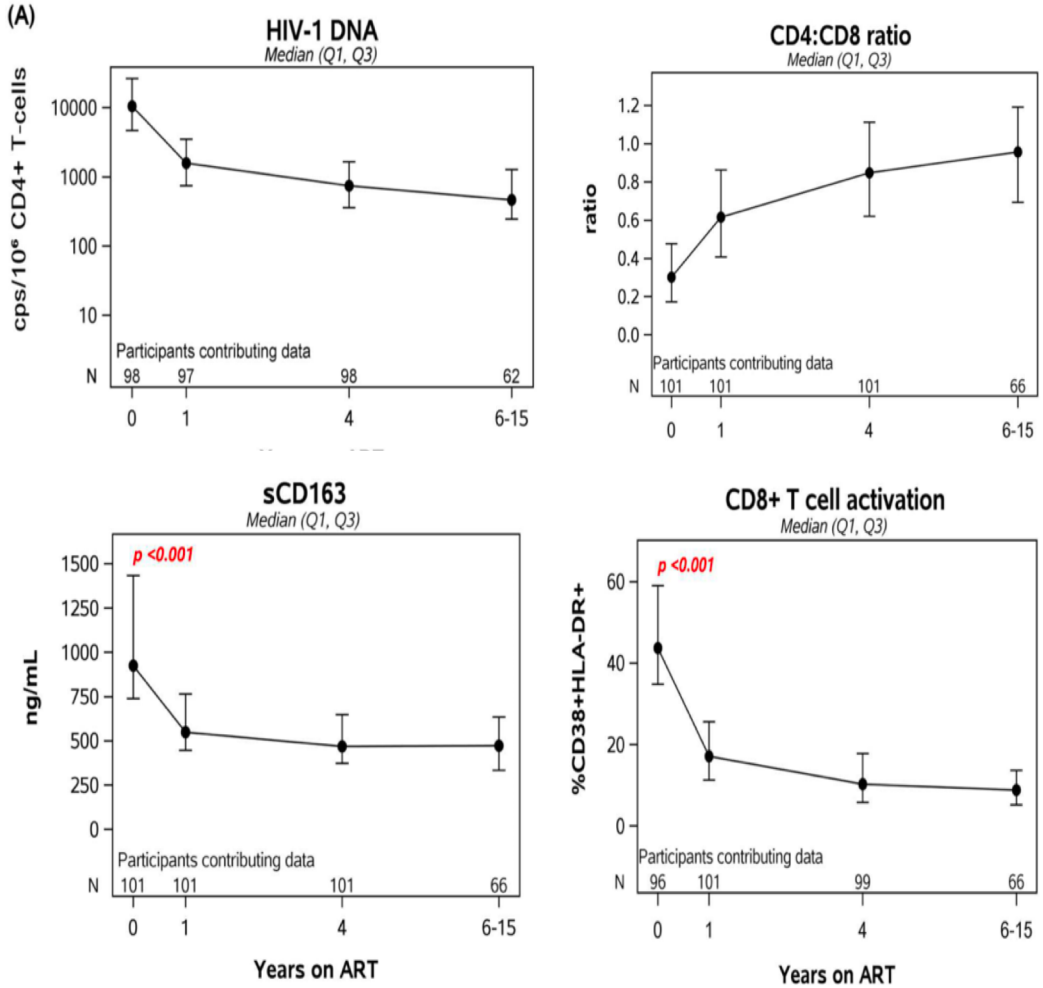
CONCLUSIONES

- **En nuestro centro, el cambio a DTG + 3TC en condiciones de práctica clínica habitual demostró ser efectivo en la mayoría de los pacientes y se asoció con una mejoría de los niveles de colesterol total y LDL.**
- **Sin embargo, debido a la alta tasa de fallos terapéuticos observada y sobre todo al desarrollo en un paciente previamente sensible de la mutación M184V durante un fallo virológico relacionado con la aparición de un efecto adverso neuro-psiquiatrico, consideramos que el uso de esta estrategia en pacientes pretratados debe realizarse con cautela.**

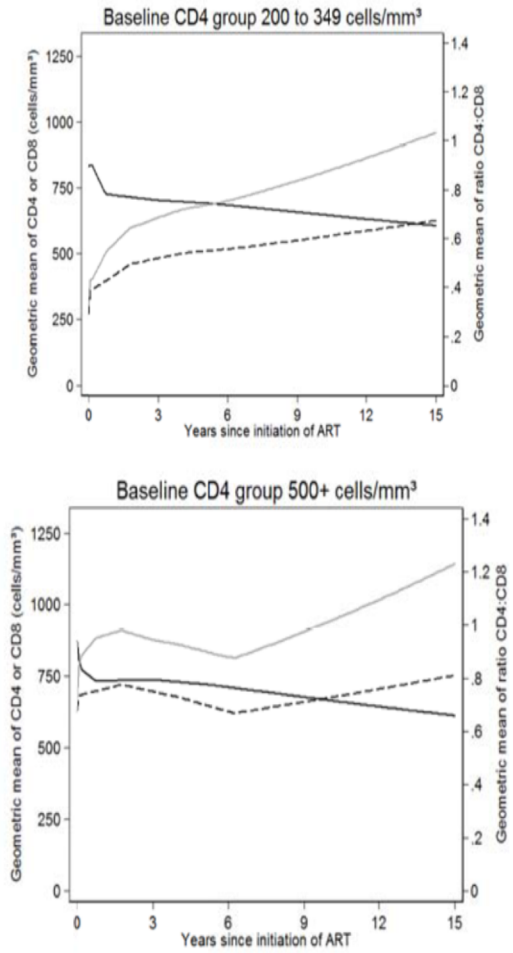
Triple terapia antirretroviral

- La infección por VIH en la actualidad
  - Objetivos y evolución de la epidemia con la terapia antirretroviral
- Eficacia
- Seguridad
- Barrera genética
- Impacto de la M184V/I
- **Inflamación**
- Conclusiones

Most Biomarkers Improve Slowly During Long-Term Triple ART, especially if ART is Initiated Early



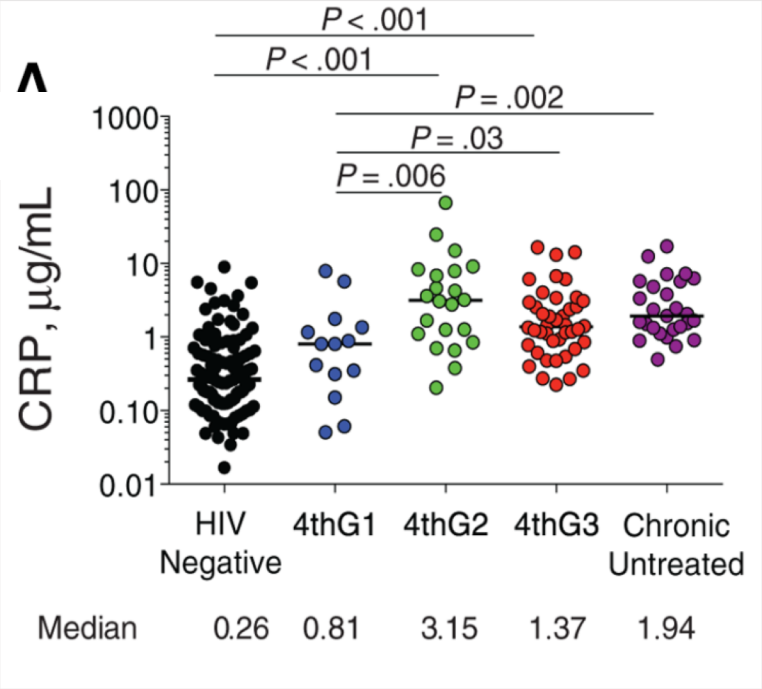
Gandhi. Plos Pathogens 2017



Hughes. AIDS 2018

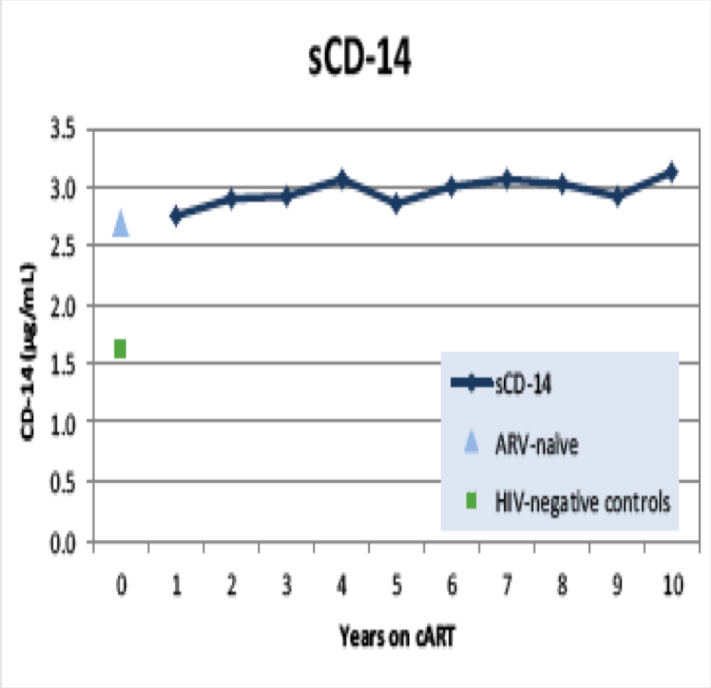
Very Early ART or Long-Term ART Improves but do not Normalize Inflammatory Markers

Inflammation Persists Despite Early Initiation of ART in Acute HIV Infection



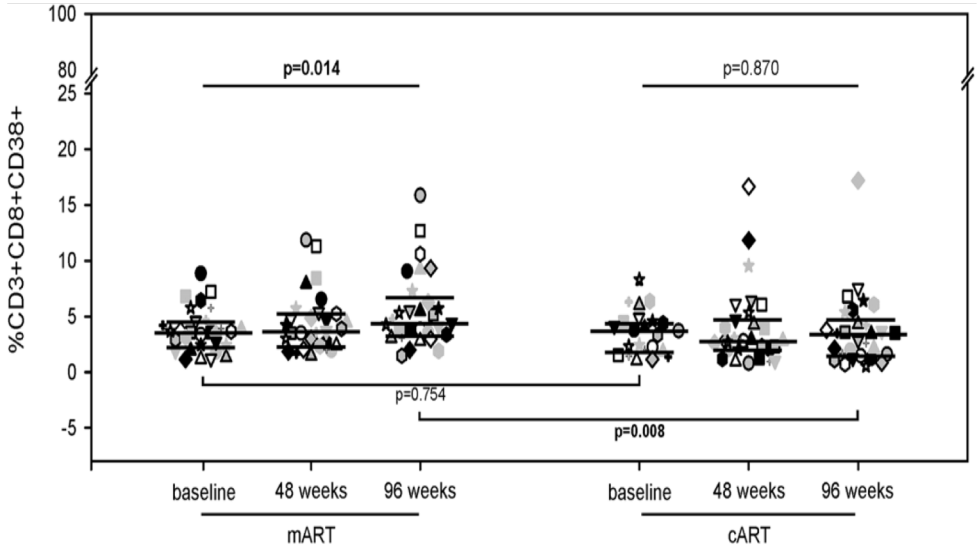
Sereti. CID 2017

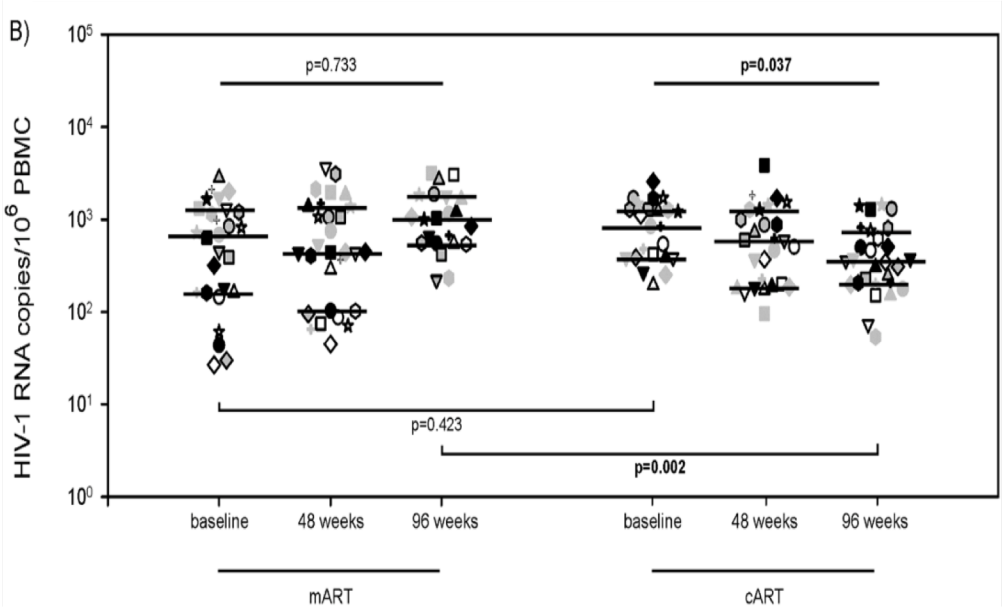
Inflammatory Biomarkers Decline but Do Not Normalize after 10 Years of cART



Lichtenstein. CROI 2015

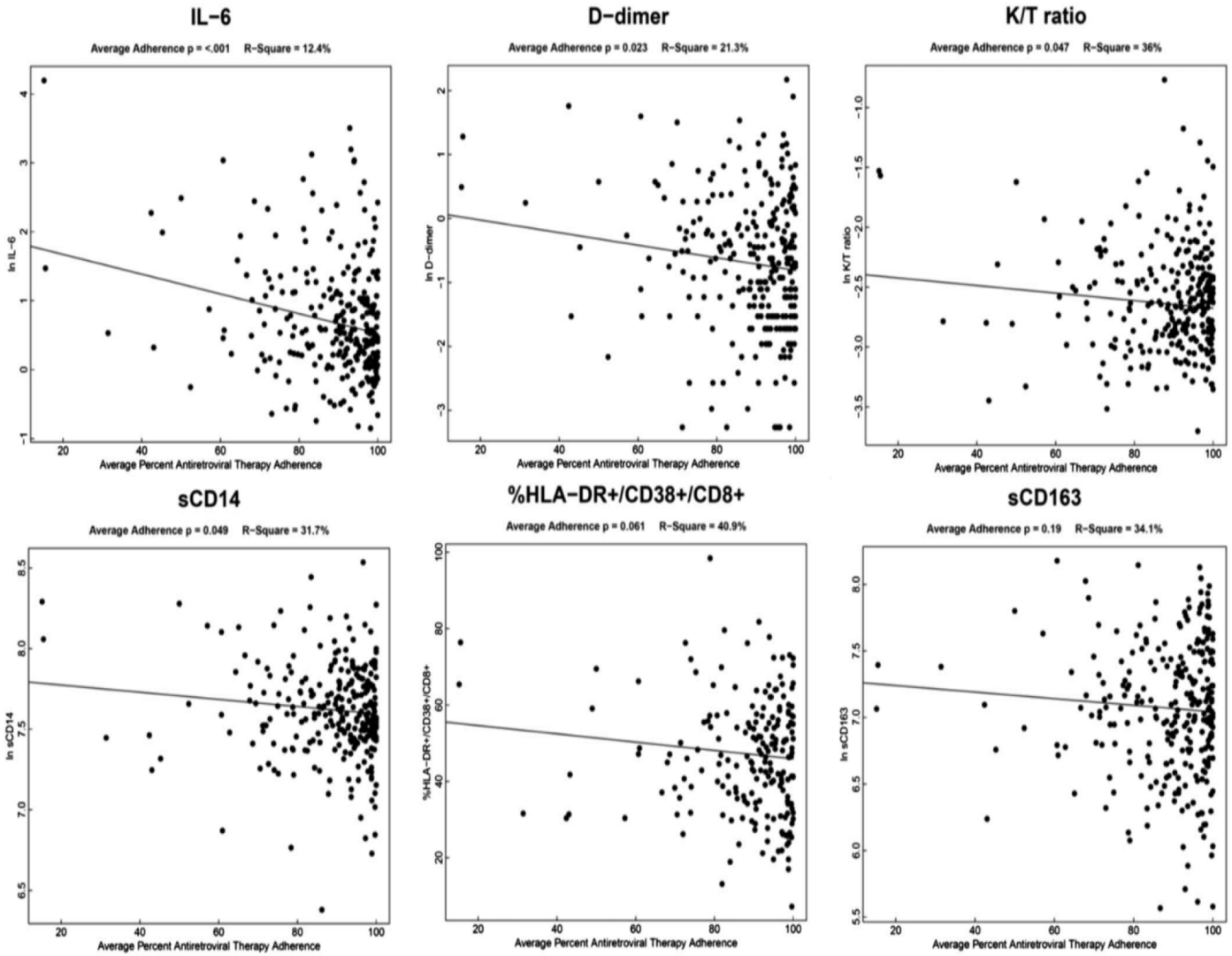
Immune Activation
mART-treated and cART-treated patients





Petrara. PLoS One 2017

Suboptimal cART Adherence is Associated with Higher Levels of Inflammation Despite HIV Suppression

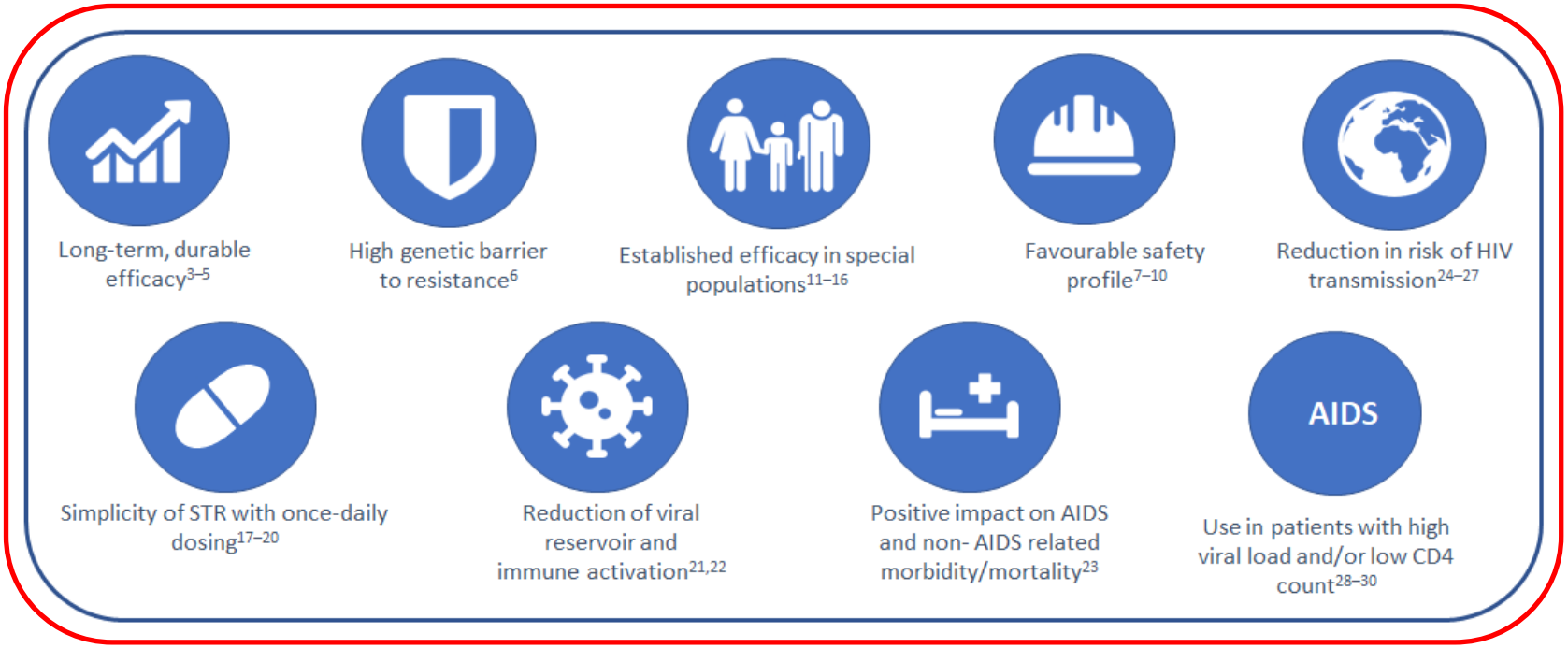


Castillo-Mancilla. JAIDS 2018

En conclusión.....

PROS DE LA TERAPIA ANTIRRETROVIRAL TRIPLE
Años de experiencia en EECC y estudios observacionales
Excelente eficacia y duradera
Tolerabilidad / Seguridad
Barrera genética: Menor FV y mayor barrera a la resistencia
Protege frente a la mutación M184V
↓ Síndrome inflamatorio
Posología STR
Algunos regímenes apropiados para "inicio rápido“del TAR
Actividad contra el VHB en pacientes coinfectados
De elección en embarazo

CONTRAS DE LA TERAPIA ANTIRRETROVIRAL TRIPLE
Coste ------ ¿ Toxicidad?



DHHS[1]	IAS-USA[2]	GESIDA[3]
▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/TAF o TDF ▪ RAL + FTC/TAF or TDF	▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/TAF	▪ BIC/FTC/TAF ▪ DTG/ABC/3TC ▪ DTG + FTC/TAF ▪ RAL + FTC/TAF

*Single-tablet regimens.

- Las recomendaciones pueden diferir en función del ARN-VIH basal, el recuento de células CD4+, la tasa de filtrado glomerular (CrCl, eGFR), el HLA-B*5701 status, el HBsAg status, osteoporosis status y el estado o el deseo de gestación.
- Los datos son insuficientes o limitados para las mujeres en edad fértil que no utilizan métodos anticonceptivos

1. DHHS ART Oct 2019 https://aidsinfo.nih.gov/guidelines on 10/16/2019 . 2. Saag. JAMA. 2018;320:379. 3. Gesida 2019

Gracias