SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

FEMI

XXXI Congreso Nacional de la Sociedad Española de Medicina Interna

OVIEDO
17-20 Noviembre 2010

Auditorio-Palacio de Congresos
"Príncipe Felipe"

II Congreso Ibérico de Medicina Interna

VII Congreso de la Sociedad Asturiana de Medicina Interna

Monoterapia en el tratamiento de la infección por el virus de la inmunodeficiencia humana

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www.idipaz.es

Conflicto de intereses

- Advisory fees, speaker fees and grant support: Tibotec, Janssen, Abbott, BMS, Gilead, MSD
- Advisory fees, speaker fees: Viiv

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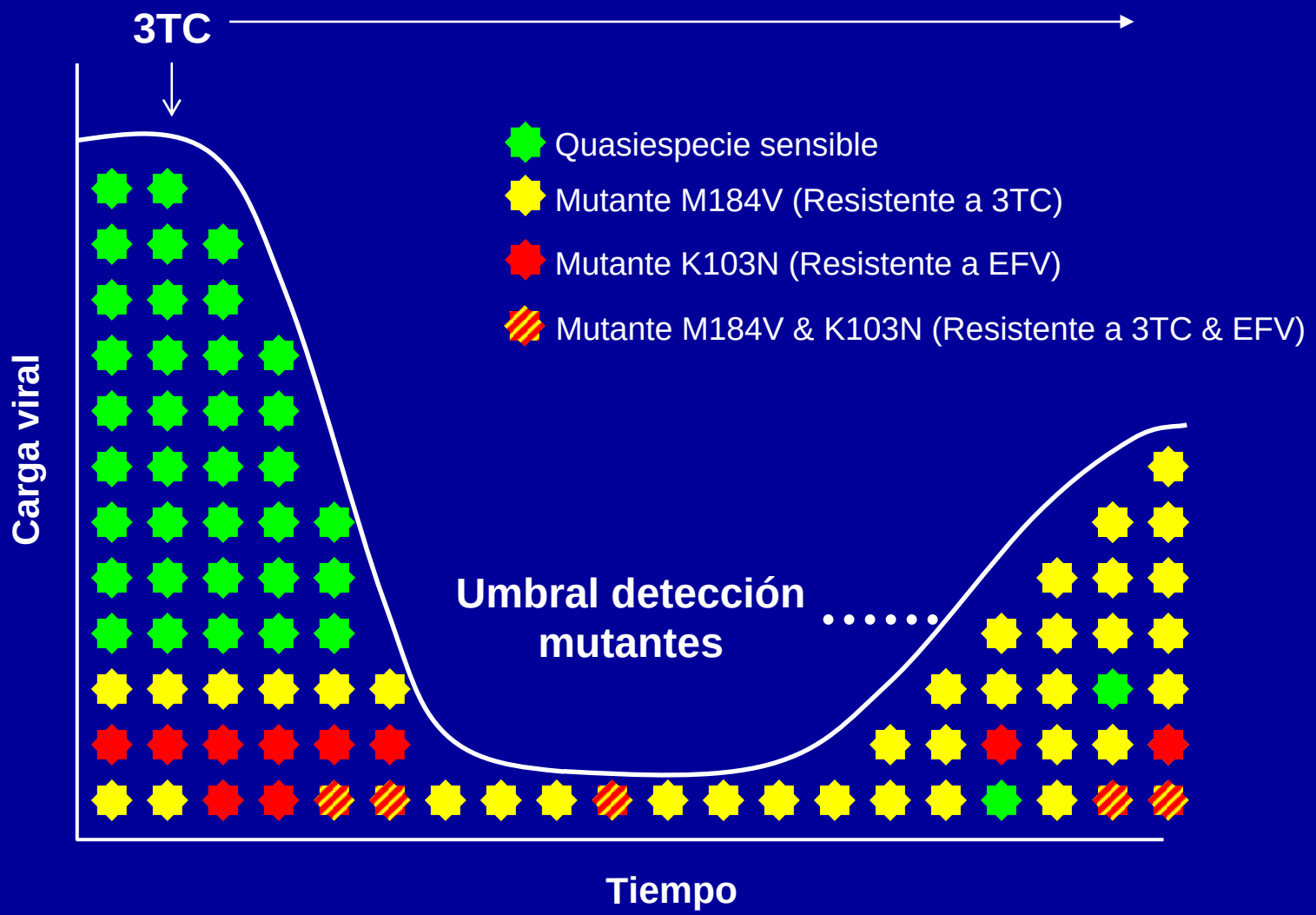
Tenth International Congress on Drug Therapy in HIV Infection
7-11 November 2010 Glasgow, UK

Tenth International Congress on
Drug Therapy in HIV Infection
7–11 NOVEMBER
2010
GLASGOW, UK

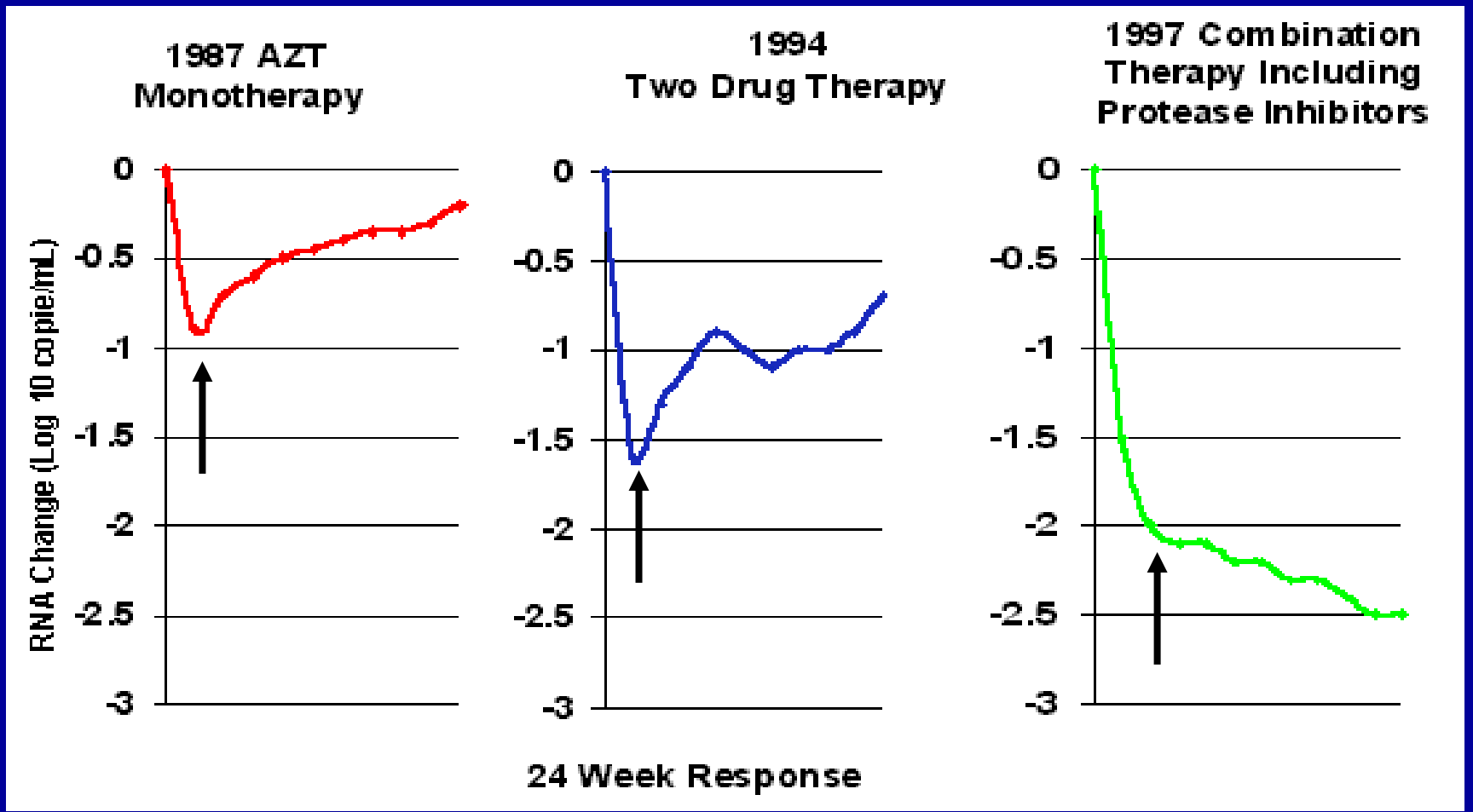
TUESDAY 9 NOVEMBER | Top of page

08.30–10.05	**Plenary and Oral Papers** **Treatment Strategies**
	Chairs: Manuel Battegay (Switzerland) *Abdel Babiker (UK)*
08.30–08.50	The state of PI monotherapy and NRTI-sparing therapy (Jose Arribas, Spain)
08.50–09.05	Ritonavir-boosted protease inhibitor monotherapy is 6% less effective than combination antiretroviral therapy in a meta-analysis (Wouter Bierman, The Netherlands)
09.05–09.20	Low-level viraemia during treatment with darunavir/r monotherapy versus DRV/r + 2NRTIs in the MONET trial (Nathan Clumeck, Belgium)
09.20–09.35	Virological findings from the SARA trial: boosted PI monotherapy as maintenance second-line ART in Africa (David Yirrell, UK)

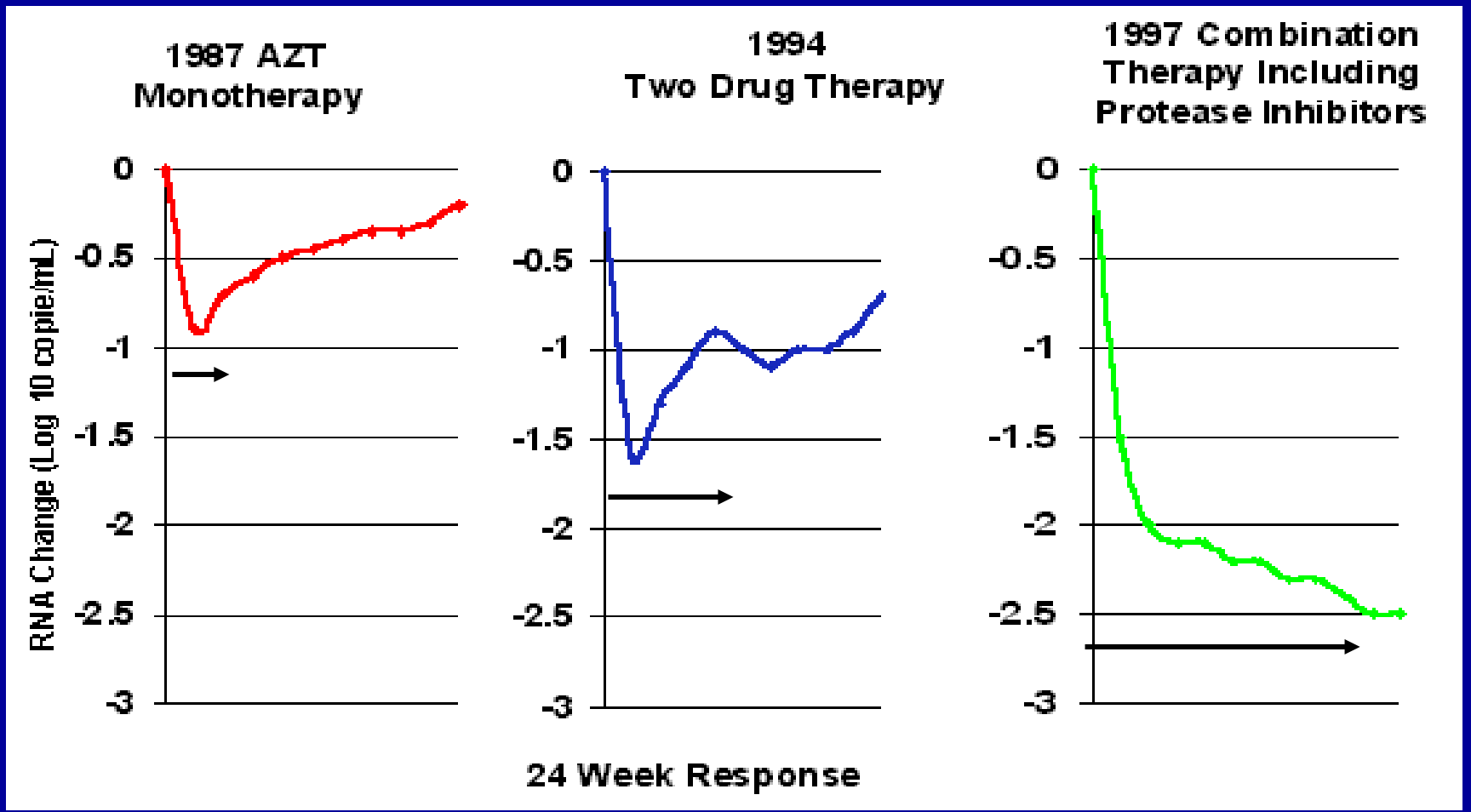
Selección de quasiespecie resistente



¿Por qué usamos triple?
POTENCIA



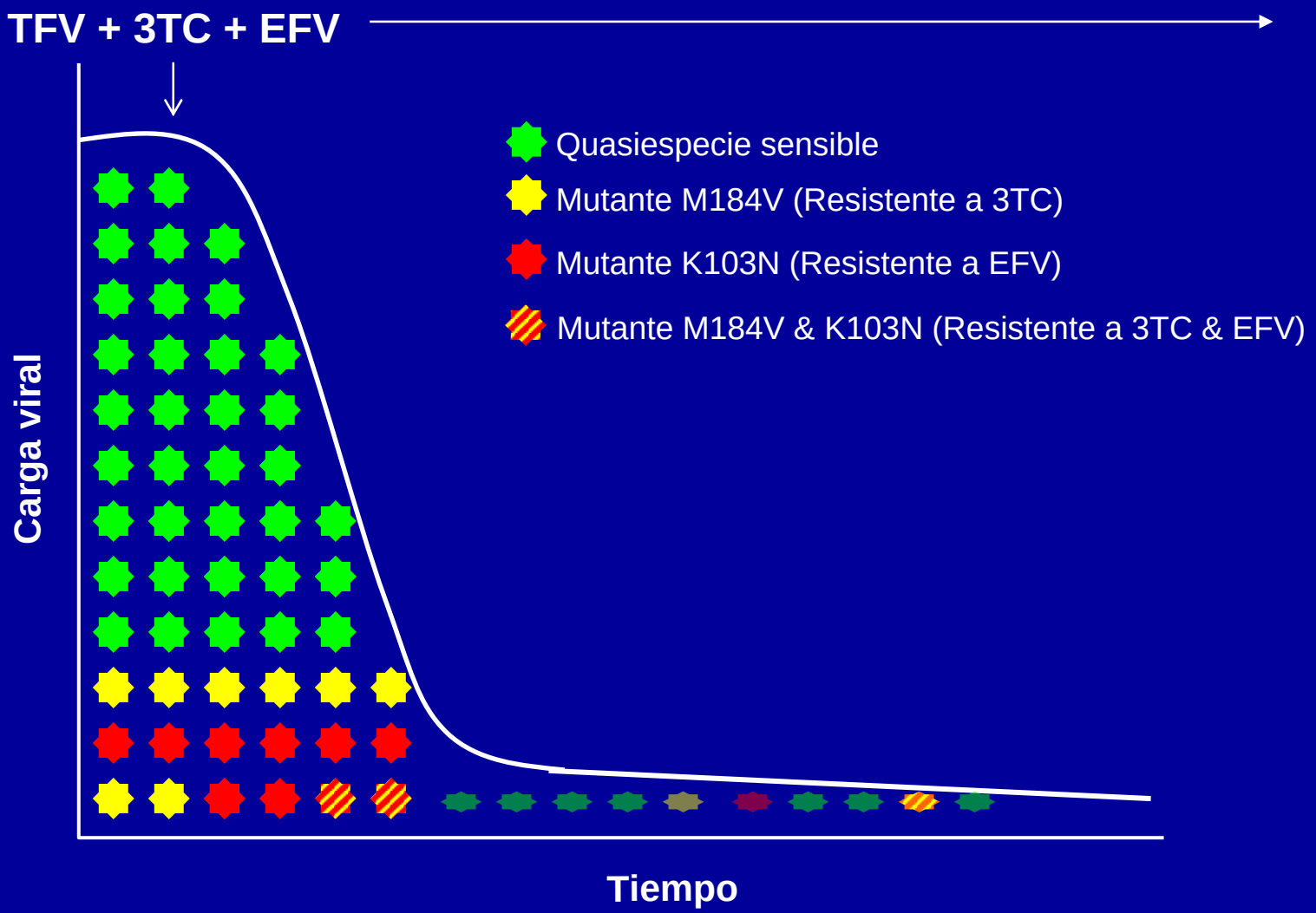
¿Por qué usamos triple?
DURABILIDAD

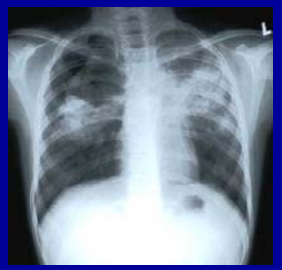


GUIAS GESIDA (Actualización Enero 2010))

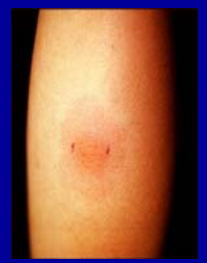
	PAUTAS		
	Un fármaco de la columna A + un fármaco de la columna B + un fármaco de la columna C		
PAUTAS PREFERENTES	A	B	C
	Tenofovir (TDF) Abacavir (ABC)	Emtricitabina (FTC) Lamivudina (3TC)	Efavirenz Nevirapina Atazanavir/r QD Darunavir/r QD Fosamprenavir/r BID Lopinavir/r QD ó BID Saquinavir/r BID Raltegravir

TARGA


TFV + 3TC + EFV
Quasiespecie sensible
Mutante M184V (Resistente a 3TC)
Mutante K103N (Resistente a EFV)
Mutante M184V & K103N (Resistente a 3TC & EFV)
Carga viral
Tiempo



Probabiliad de mutantes

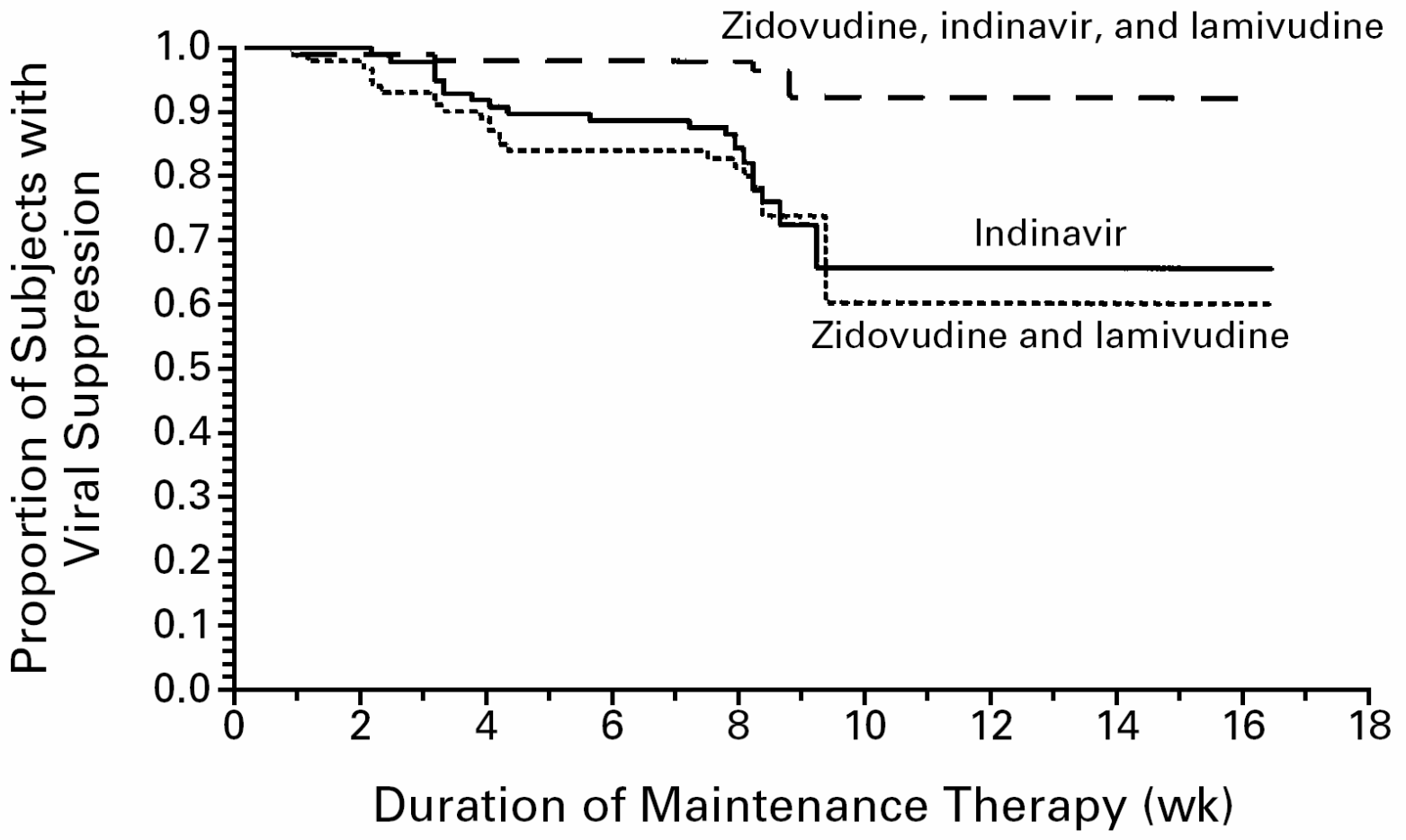


CARGA BACILAR

FARMACOS

4 2 1

ACTG-343



N Engl J Med 1998;339:1261-8.

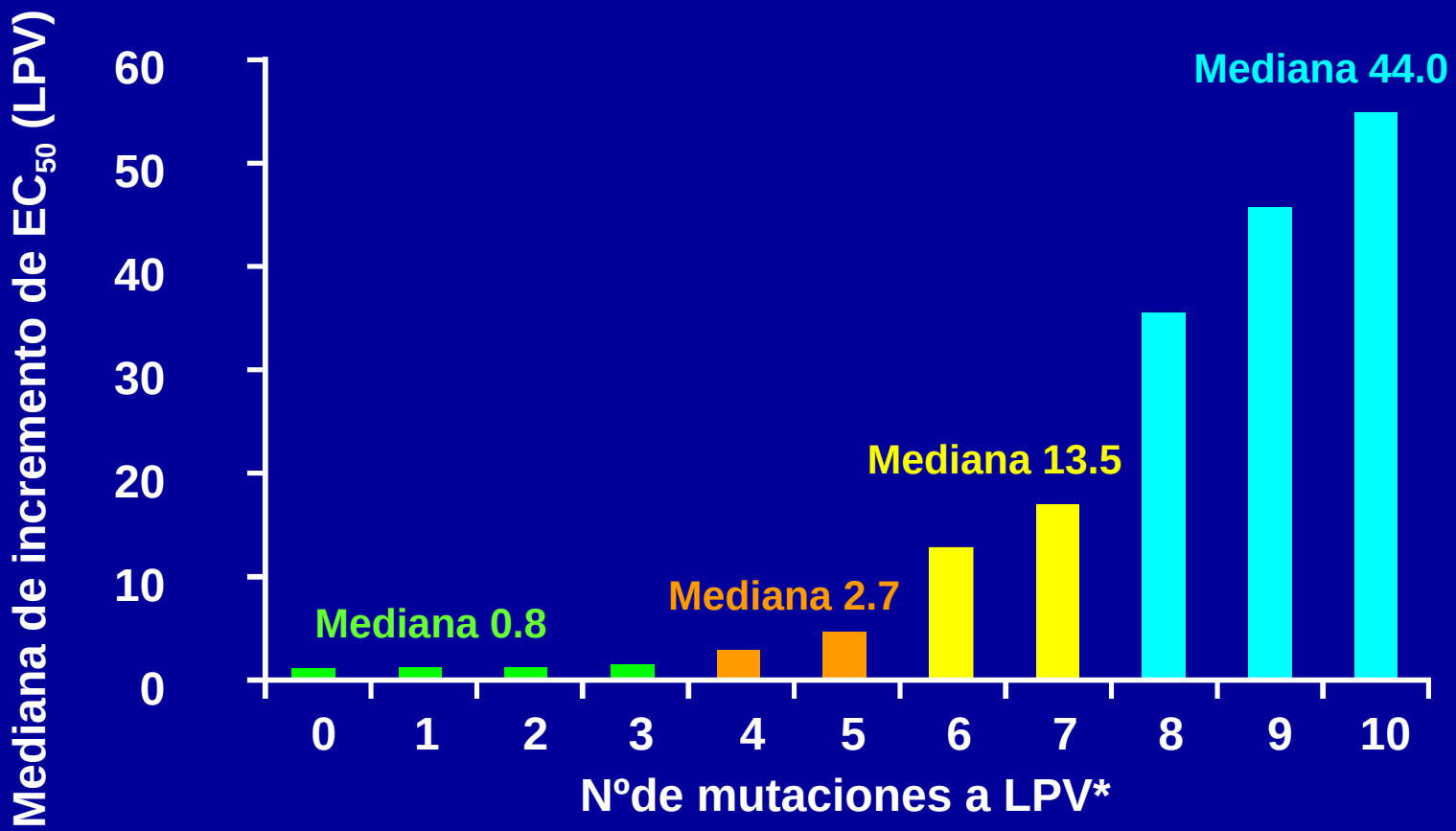
The NEW ENGLAND JOURNAL of MEDICINE

LOPINAVIR–RITONAVIR VERSUS NELFINAVIR FOR THE INITIAL TREATMENT OF HIV INFECTION

SHARON WALMSLEY, M.D., BARRY BERNSTEIN, M.D., MARTIN KING, PH.D., JOSÉ ARRIBAS, M.D., GILDON BEALL, M.D., PETER RUANE, M.D., MARGARET JOHNSON, M.D., DAVID JOHNSON, M.D., RICHARD LALONDE, M.D., ANTHONY JAPOUR, M.D., SCOTT BRUN, M.D., AND EUGENE SUN, M.D., FOR THE M98-863 STUDY TEAM*

N Engl J Med 2002; 346:2039-2046June 27, 2002

La susceptibilidad a LPV disminuye con la acumulación de mutaciones



*** De las 11 mutaciones seleccionadas que se asociaron con susceptibilidad reduacida a LPV (en las posiciones 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 y 90 de los aminoacidos de la proteasa)**

OK Study design

- HIV RNA <50 cop/mL for > 6 months
- No history of virological failure while taking a PI
- Receiving LPV/r for + 2 NRTIs > 1 month

LPV/r 400/100 mg BID
No NRTIs (“Only Kaletra-OK”) arm
(*n*=21)

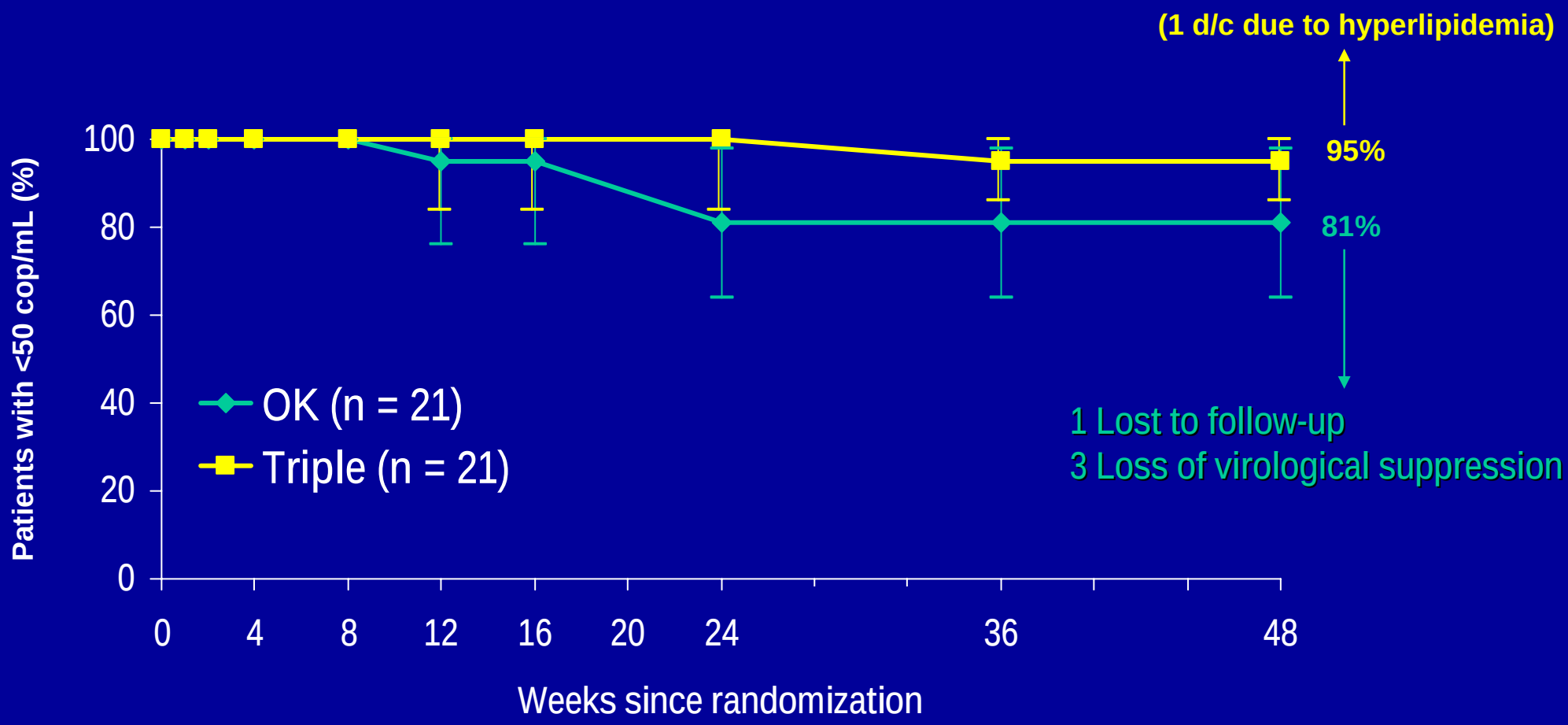
LPV/r 400/100 mg BID
+ 2 NRTIs (“Triple”) arm
(*n*=21)

96 wks

Definition of loss of virological suppression per protocol analysis (ITT-MD = F)

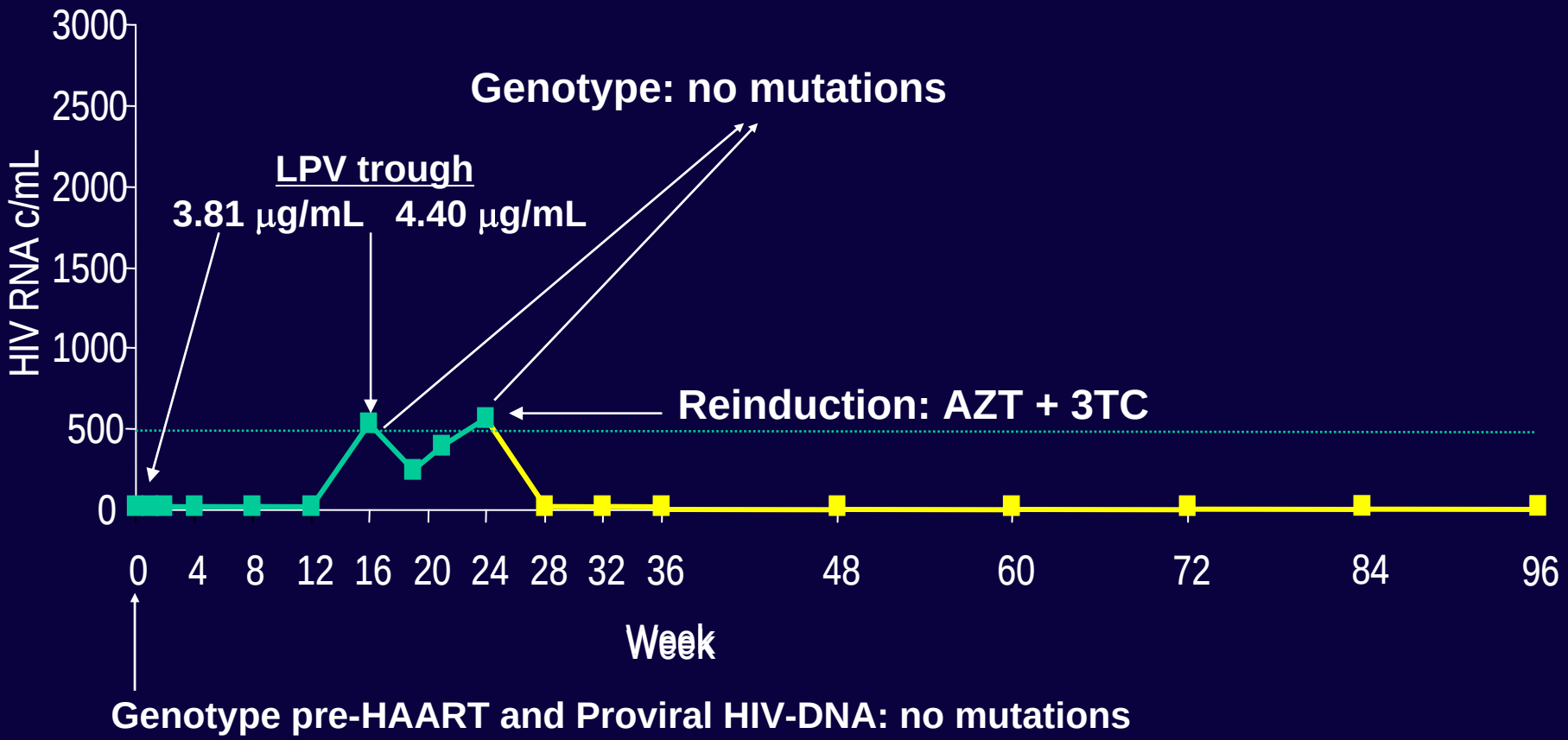
- 2 viral loads >500 cop/mL 2 weeks apart OR
- Change of randomized therapy OR
- Treatment discontinuation OR
- Lost to follow up.

HIV-RNA <50 copies/mL (ITT, MD = F) by treatment arm



Arribas JR, Pulido F et al. JAIDS 2005;40:280–287

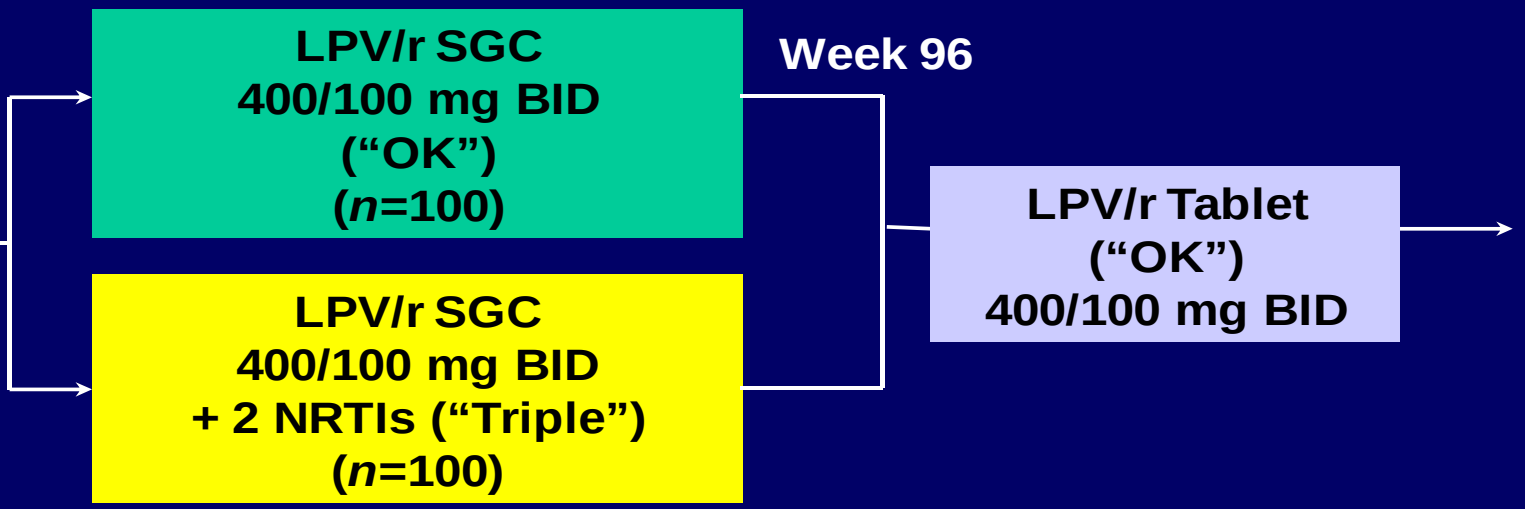
Reinduction with nucleosides



Arribas JR. JAIDS 2005;40:280-287

OK04 trial design

- HIV-1 RNA < 50 c/mL for > 6 months
- No history of virological failure while taking a PI
- Receiving LPV/r for + 2 NRTIs > 1 month



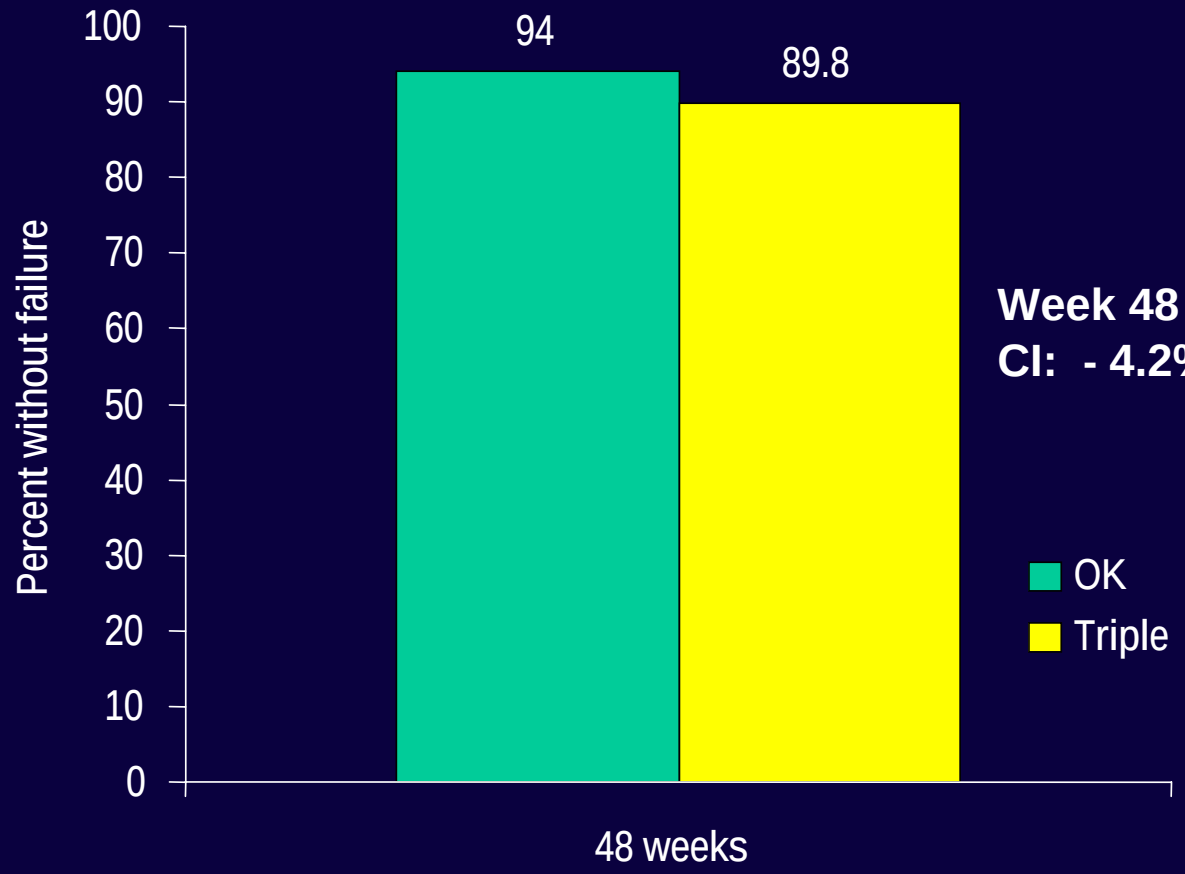
Visits: Screening, Baseline, Week 4 and 12, then every 12 weeks up to Week 96

Primary endpoint: Therapeutic failure at 48 weeks

- **2 viral loads > 500 c/mL 2 weeks apart* (without virological re-suppression after reinduction with NRTI in the OK arm)** OR
- Change of randomized therapy for reasons different from re-induction OR
- Treatment discontinuation OR
- Lost to follow-up

* OR decrease in HIV-1 RNA < 1 log 4 weeks after intensification OR failure to reach HIV-1 RNA < 50 c/mL 16 weeks after intensification

OK04 Primary endpoint: Proportion without therapeutic failure at Week 48*

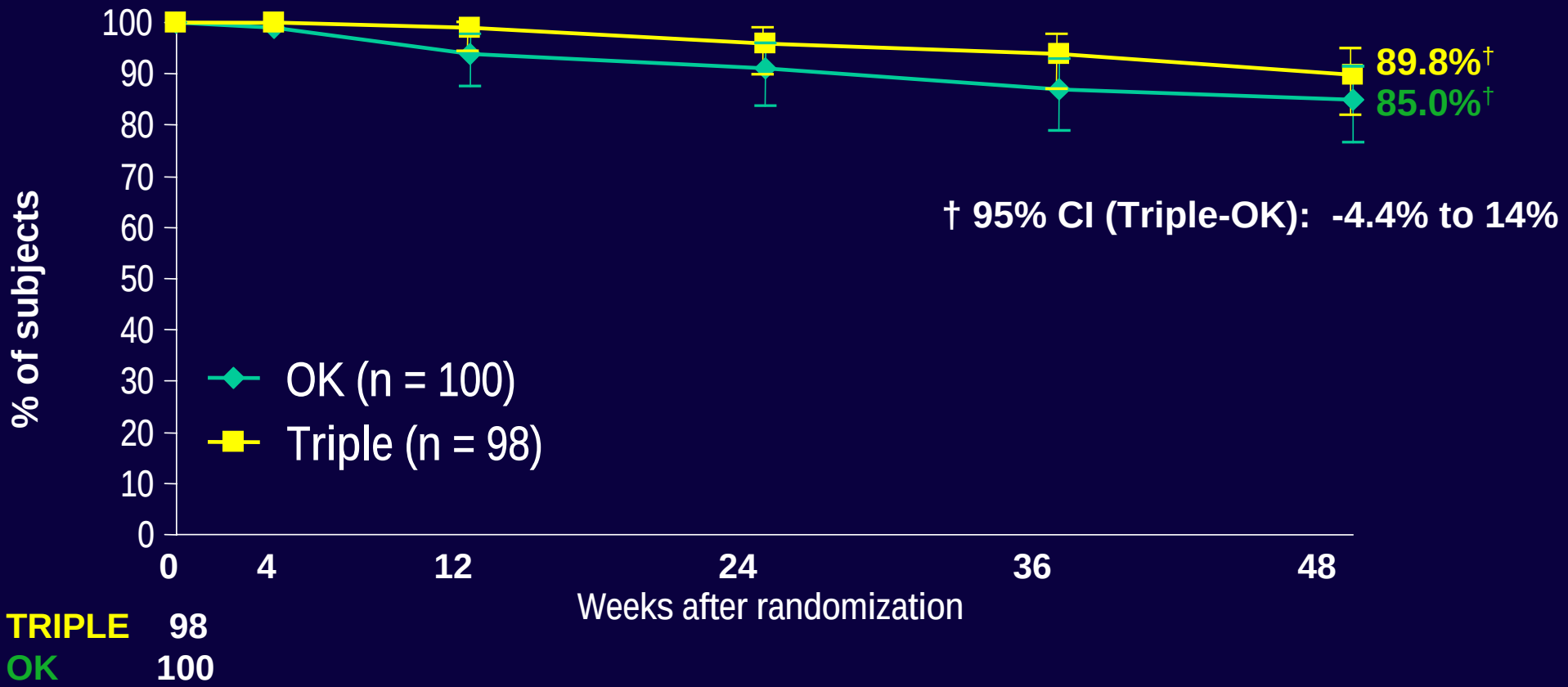


Week 48 difference (Triple - OK) and 95% CI: - 4.2% (-11.8% to 3.4 %)

Pulido F et al. AIDS. 2008 Jan 11;22(2):F1-9.

HIV-1 RNA < 50 copies/mL

(ITT M = F, Reinduction = F)*



† 95% CI (Triple-OK): -4.4% to 14%

TRIPLE	98
OK	100

*For this analysis, patients with confirmed virological rebound (> 50 c/mL) are considered as failures without taking in account whether viral load become resuppressed after resuming baseline nucleosides

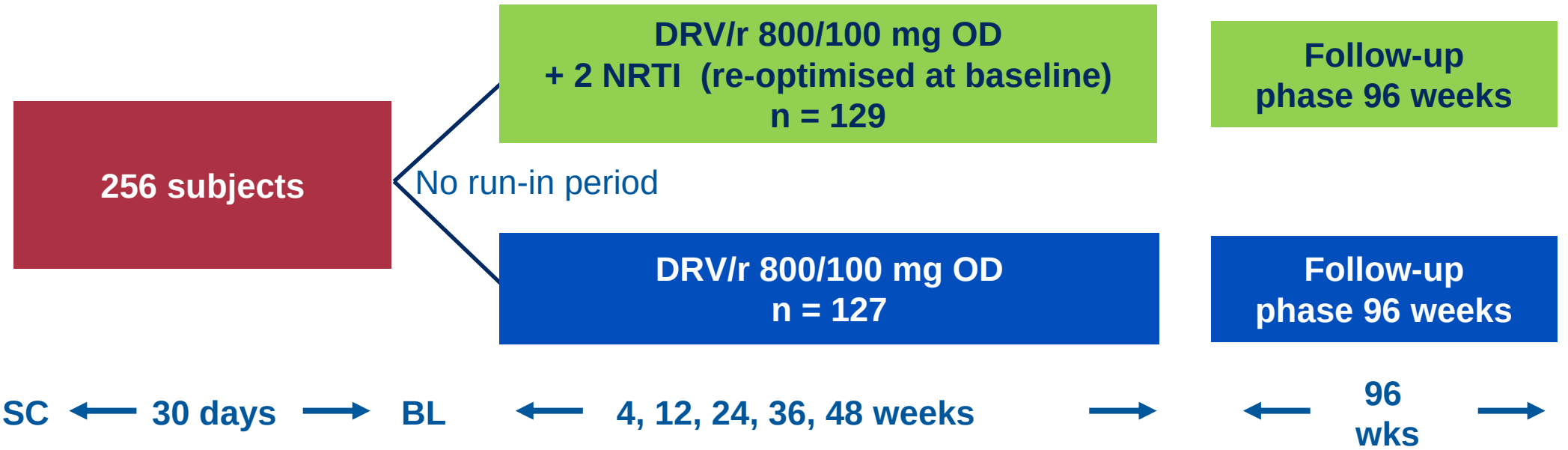
BOOSTED PI MONOTHERAPY

Scenario	Trial	PI
Naïve	IMANI I, II MONARK	LPV/r
Induction-Maint	MO-613	
Simplification	OK pilot OK04 KALMO IMANI III	
	ACTG-5201	ATV/r
	ATARITMO	
	Karlström et al	
	OREY	
	MONOI	DRV/r
	MONET	

XV WAC 2004 MoOrB1057. 4th IAS 2007 WEPEB034. J Infect Dis. 2008 15;198:234. JAIDS 2005;40:280–287. AIDS. 2008;11:F1-9. XVI IAC 2006; #TUAB0102. EACS 2009 PS4/5 .J Infect Dis. 2009 15;199:866. AIDS 2007; 21:1309–1315. JAIDS 2007;44:417. EACS 2009 PS4/6. 5th IAS 2009 AIDS 2009 (in press)

MONET - Trial Design

- Taking 2 NRTI + either NNRTI or boosted PI at screening (stratified)
- No prior use of darunavir (DRV)
- HIV RNA <50 copies/mL for at least 6 months,
- No history of virological failure



Primary Endpoint: HIV RNA< 50 at week 48 (TLOVR). Per Protocol, Switch = Failure

- 2 consecutive HIV RNA > 50 copies/mL (Roche Amplicor HIV-1 Monitor assay 1.5)
- Stopping DRV/r
- Starting NRTIs in the monotherapy arm
- Stopping NRTIs in the triple therapy arm (switches in NRTIs were permitted at any time).

J. Arribas et al, IAS Conference, Cape Town, SA, 21 July 2009, TUAB106-LB

MONET: Outcome of HIV RNA elevations in DRV/r arm (15 patients)

Patient (HCV)	HIV RNA blips
BE000213 (HCV-)	140, 133
BE000305 (HCV-)	59, 214
DE002503 (ACUTE)	132, 139
DE015601 (HCV-)	539, 862
ES000110 (HCV+)	810, 605
ES000302 (HCV+)	40500, 628
ES001703 (HCV-)	158, 140
GB003002 (ACUTE)	106, 268
GB004002 (HCV+)	722, 157
PL000503 (HCV+)	288, 3880
PL000520 (HCV+)	779, 267
ES001704 (HCV+)	134, 79
GB002203 (ACUTE)	51, 80
DK000214 (HCV-)	215, 427
ES000307 (HCV+)	154, 100

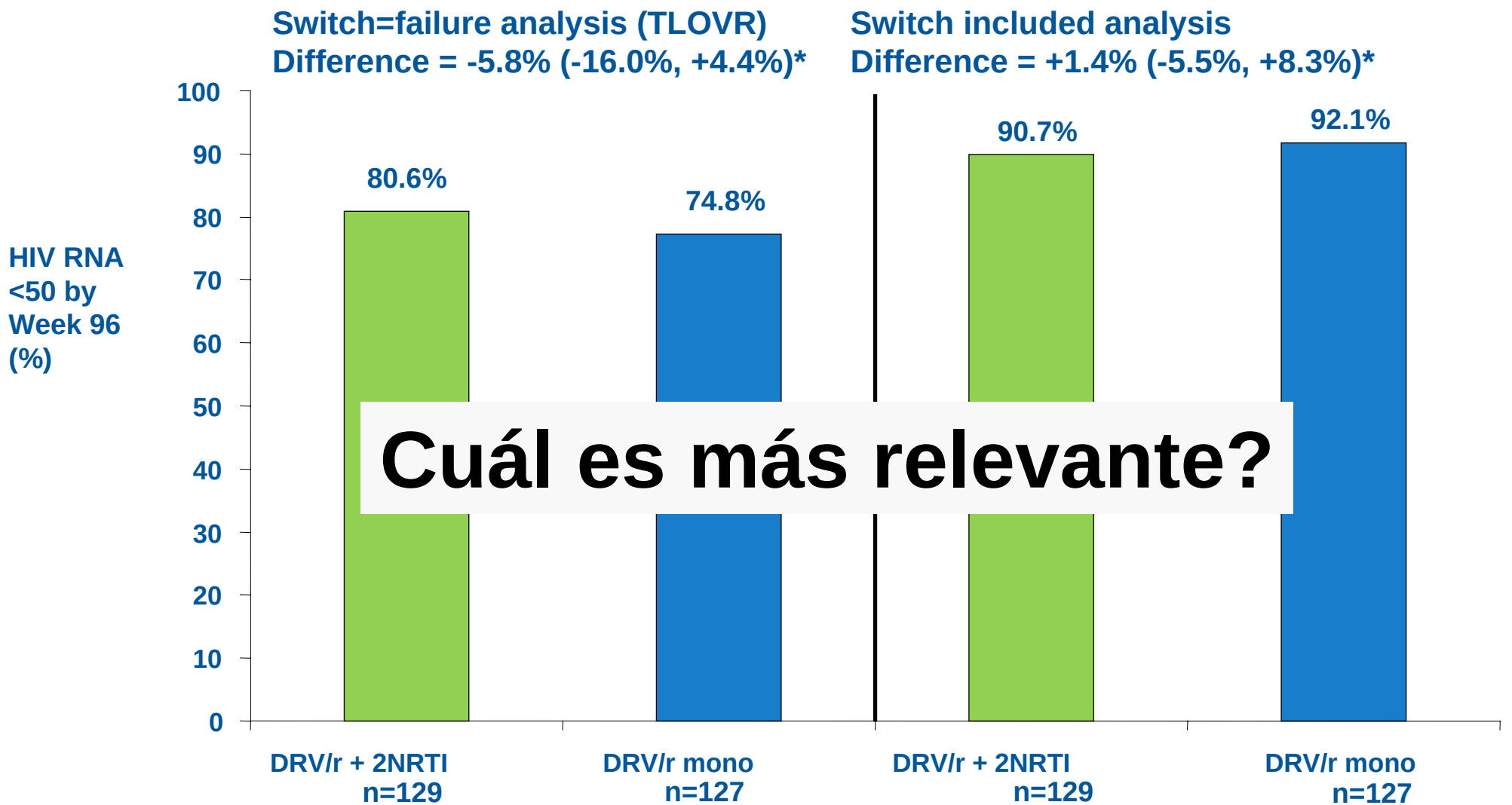
Data on file

MONET: Outcome of HIV RNA elevations in DRV/r arm (15 patients)

Patient (HCV)	HIV RNA blips	Changed ARV / comments*	Last HIV RNA
BE000213 (HCV-)	140, 133	None / sinusitis	<50 (wk 96)
BE000305 (HCV-)	59, 214	ZDV/3TC/NVP	<50 (wk 128)
DE002503 (ACUTE)	132, 139	LPV/r mono	<50 (wk 96)
DE015601 (HCV-)	539, 862	TDF/FTC/EFV	<50 (wk 96)
ES000110 (HCV+)	810, 605	TDF/FTC/DRV/r	<50 (wk 96)
ES000302 (HCV+)	40500, 628	None (stopped Rx)	<50 (wk 112)
ES001703 (HCV-)	158, 140	ABC/3TC/DRV/r	<50 (wk 96)
GB003002 (ACUTE)	106, 268	TDF/FTC/DRV/r	231 (wk 116)
GB004002 (HCV+)	722, 157	TDF/FTC/DRV/r	<50 (wk 96)
PL000503 (HCV+)	288, 3880	TDF/FTC/DRV/r	<50 (wk 112)
PL000520 (HCV+)	779, 267	ABC/3TC/DRV/r	<50 (wk 112)
ES001704 (HCV+)	134, 79	None	108 (wk 96)
GB002203 (ACUTE)	51, 80	None	<50 (wk 112)
DK000214 (HCV-)	215, 427	None	158 (wk 112)
ES000307 (HCV+)	154, 100	None	100 (current)

Data on file

MONET: HIV RNA <50 copies/mL at Week 96, TLOVR, Switch=failur (ITT population)



* 95% confidence intervals from univariate analysis

Rieger et al. WAC July 2010, Vienna [abstr TBLBB209]

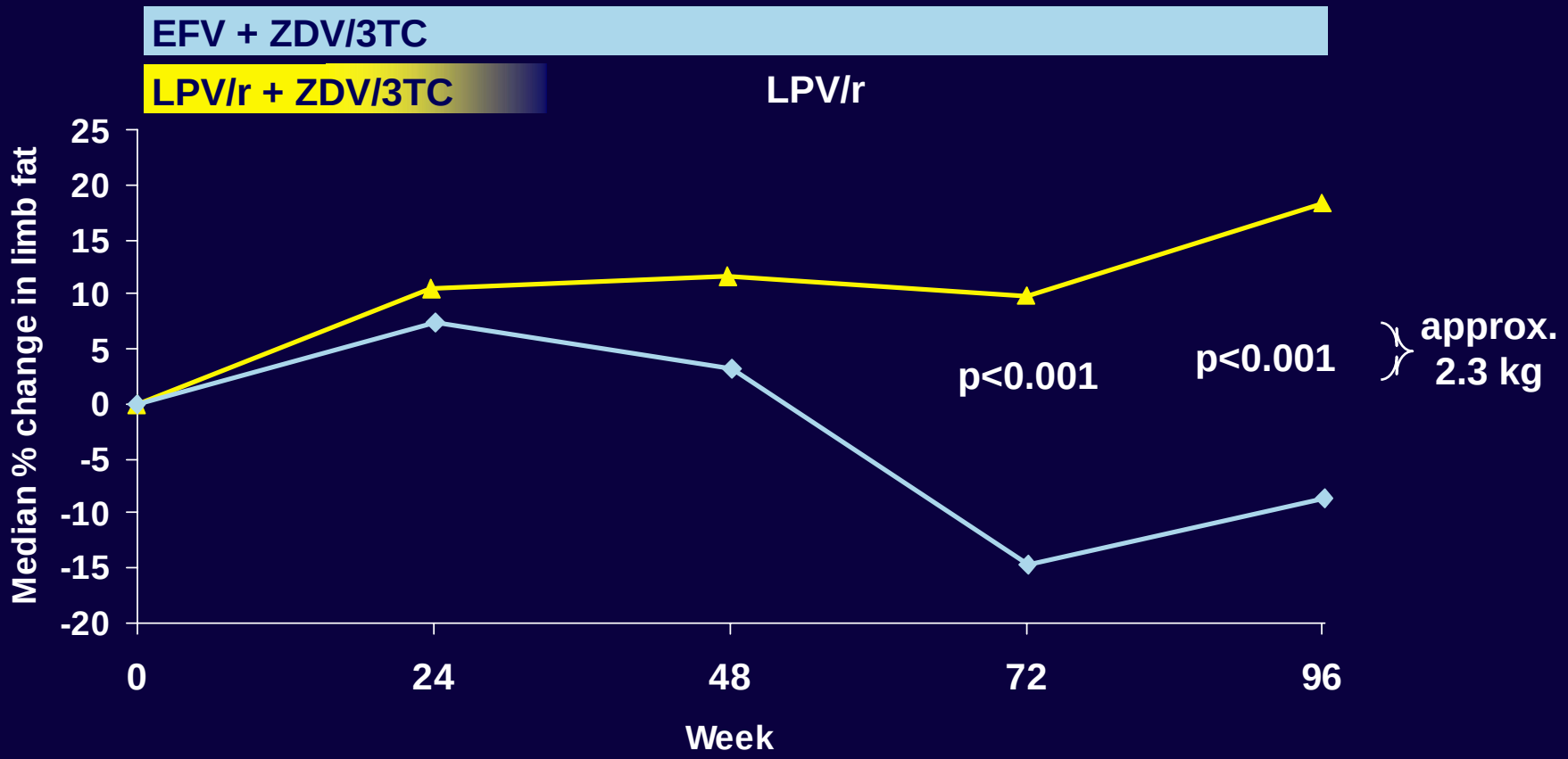
MONET: Major IAS-USA Genotypic mutations when HIV RNA >50 copies/mL

Genotypic results	DRV/r + 2NRTI N=129	DRV/r N=127
Number of genotypes performed (RNA >50 copies/mL)	55	91
Patients with at least 1 successful genotype	21	27
Patients with genotype(s) showing no primary PI or DRV mutations, M184V or NRTI mutations	**20/21 (95.2%)**	**26/27 (96.3%)**
NRTI mutations	1	0
M184V	1	0
Primary IAS-USA PI mutations	1	1
DRV mutations	0	1

Only 1 patient per arm had any evidence of mutations of resistance

Pulido F el al HIV 10. Abstract P131.

Significant Difference in Change in Limb Fat

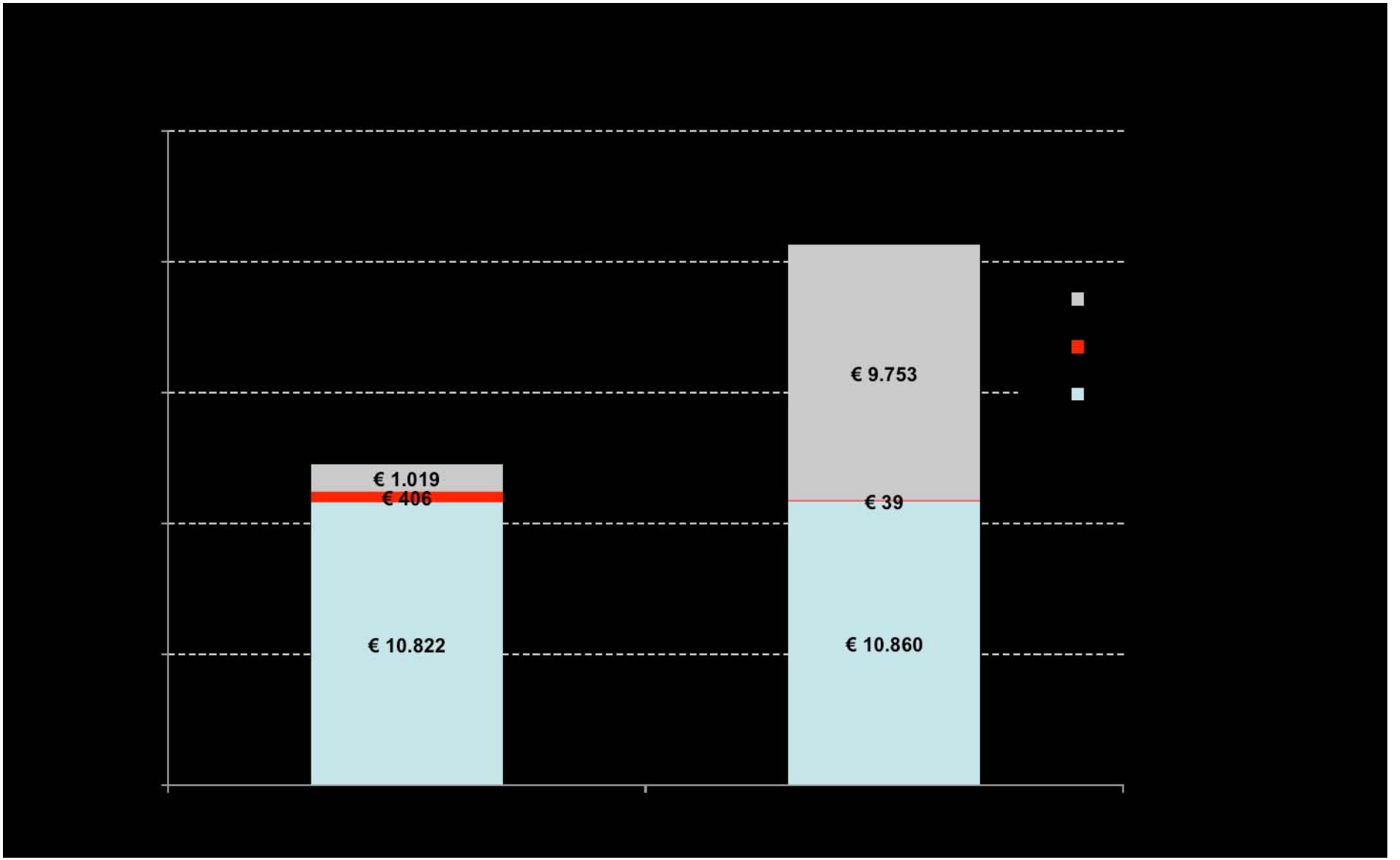


LPV/r: N=97	90	89	79	74
EFV: N=45	41	36	32	32

Cameron DW *et al., 14th CROI*, Los Angeles, February 2007, Oral#44LB

M03-613

Two-year Spanish Costs of antiretrovirals in the MONET trial



CONTRAS	PROS
Menos eficaz que la triple	Pequeña diferencia. Dependiente de IP?. Fracaso “reversible”.
↑ Viremia de bajo nivel	Reversible tras reinducción con nucs
↑ Riesgo de resistencias	Muy pequeño incremento. Dependiente de IP?. No compromete el resto de la familia. Preserva otras opciones de tto.
Se necesita una adherencia más alta	Fracaso “reversible”. Es fácil y seguro identificar a los pacientes que necesitan NUCS
Durabilidad incierta	Buenos resultados a dos años
Eficacia en reservorios (SNC, genital)?	Se necesita más investigación (también para la TARGA triple)
Beneficios no demostrados	Menos lipoatrofia?. Coste beneficio
Estudios pequeños	>1000 pacientes han recibido monoterapia en ensayos publicados

The state of PI Monotherapy (Guidelines)

GUIDELINES	COMMENTS
GESIDA[1]	En pacientes, sin historia de fracaso previo a IP, con CVP indetectable al menos 6 meses y signos o síntomas de toxicidad por los AN **es posible la simplificación** a DRV/r o LPV/r en monoterapia
EACS[2]	PI/r monotherapy with bid LPV/r, or qd DRV/r, **might represent an option** in patients with intolerance to NRTI or for treatment simplification.
IAS[3]	Therefore, PI/r monotherapy is not recommended, **except in exceptional circumstances** when other drugs cannot be considered for reasons of toxicity/tolerability.
DHHS[4]	In aggregate, boosted-PI monotherapy as initial or as simplification treatment has been somewhat less effective in achieving complete virologic suppression and avoiding resistance. Therefore, this strategy **cannot be recommended** currently.

1. Disponible en: http://www.gesida.seimc.org/pcientifica/fuentes/DcyRc/gesidadcyrc2010_DocconsensoTARGESIDA-PNS-verimp.pdf
2. Clumeck N et al. Available at: http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf
3. Thompson MA, et al. JAMA 2010;304(3):321-333;
4. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009.

Agradecimientos

- Unidad VIH del Servicio de Medicina Interna del Hospital La Paz : Juan González-García, Ignacio Bernardino, Marisa Montes, Miriam Estebanez, Ignacio Pérez-Valero, Jose Francisco Zamora, Jose Mª Peña, Juan Miguel Castro, Raquel Martin, Blanca Arribas
- Unidad VIH del Servicio de Medicina Interna del Hospital 12 de Octubre HIV Unit: Federico Pulido