ART year 2012: When & how to switch cART in virologically suppressed patients

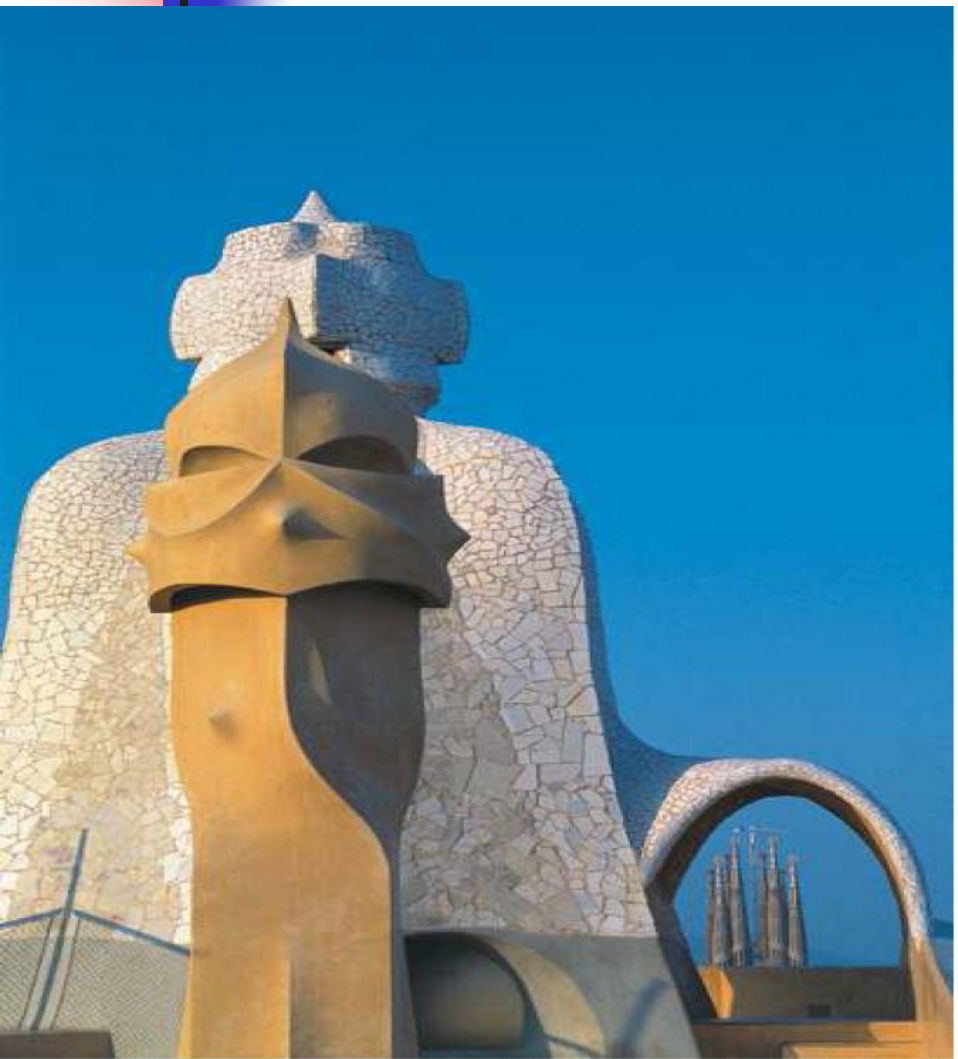
Jose M Gatell MD, PHD
Head, Infectious Diseases & AIDS Units. Hospital Clinic
Professor of Medicine. University of Barcelona
Barcelona, Spain
gatell0@attglobal.net
jmgatell@clinic.ub.es

José M Gatell MD, PhD

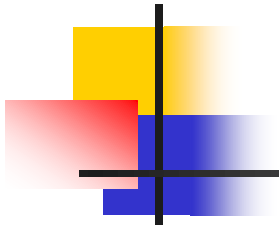
Hospital Clinic. University of Barcelona

gatell0@attglobal.net

Hospital Clínic – Facultad de Medicina (U.B.) Barcelona (España)

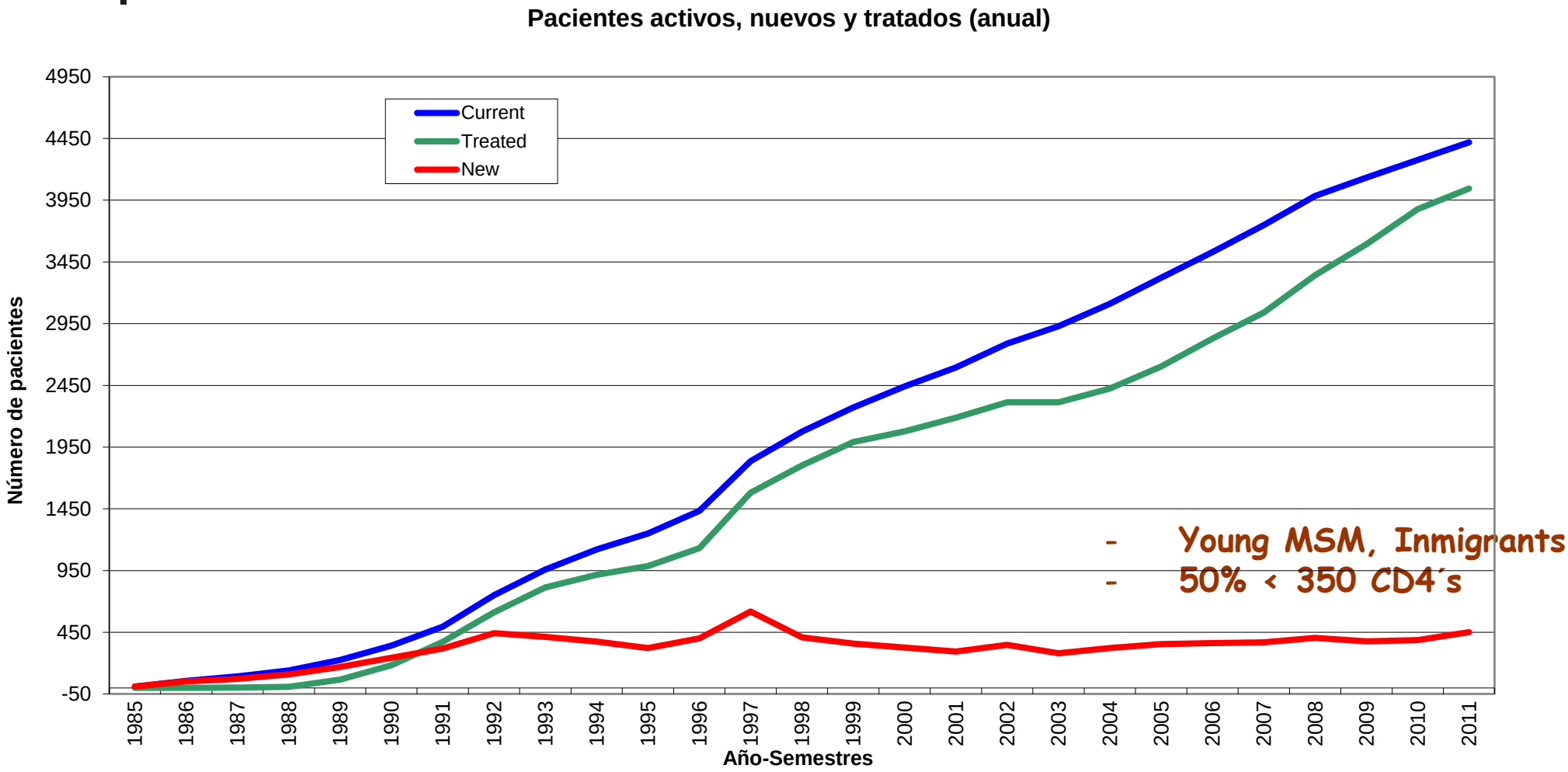


ART year 2012: When & how to switch cART in virologically suppressed patients



1. Current scenario
2. Objectives & limitations
3. Stable & suppressed patients
4. In summary…

- Very low mortality
- Getting older (> 50% more than 50 years old)
- More than 80% undetectable VL

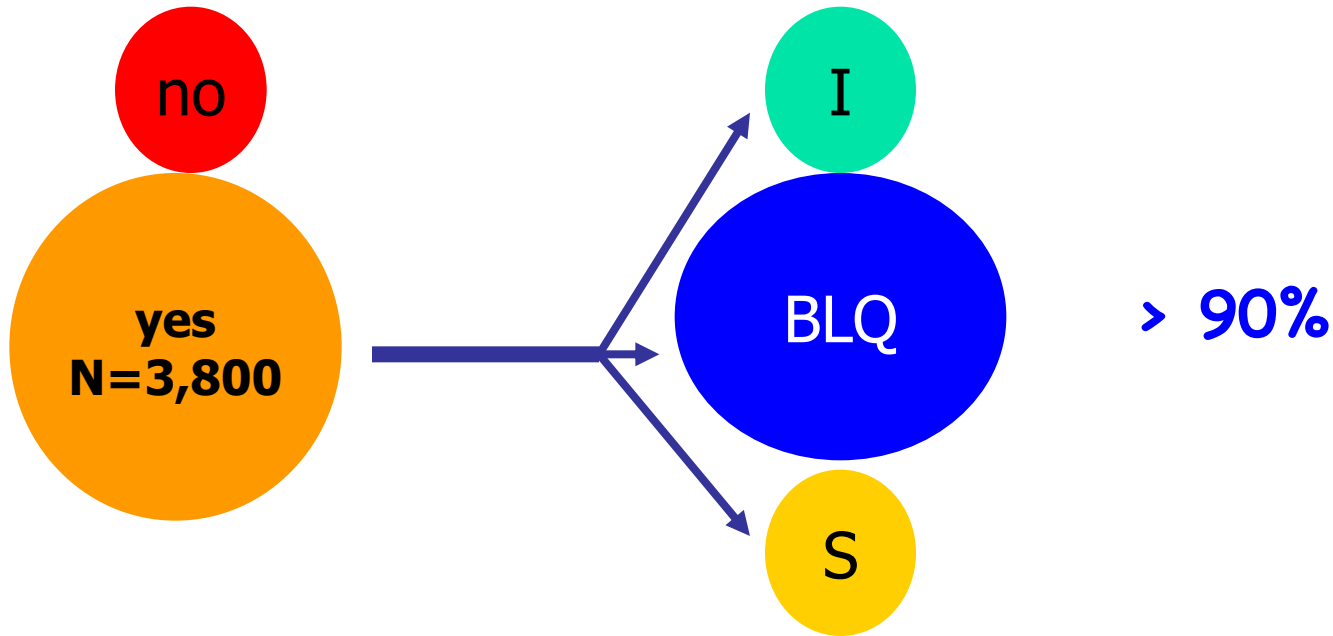


- Young MSM, Inmigrants
- 50% < 350 CD4´s

ART year 2012: When & how to switch cART in virologically suppressed patients

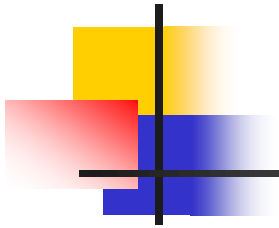
Treated

type of ART



Hospital Clinic.
Barcelona. Spain
Data on file, 2010

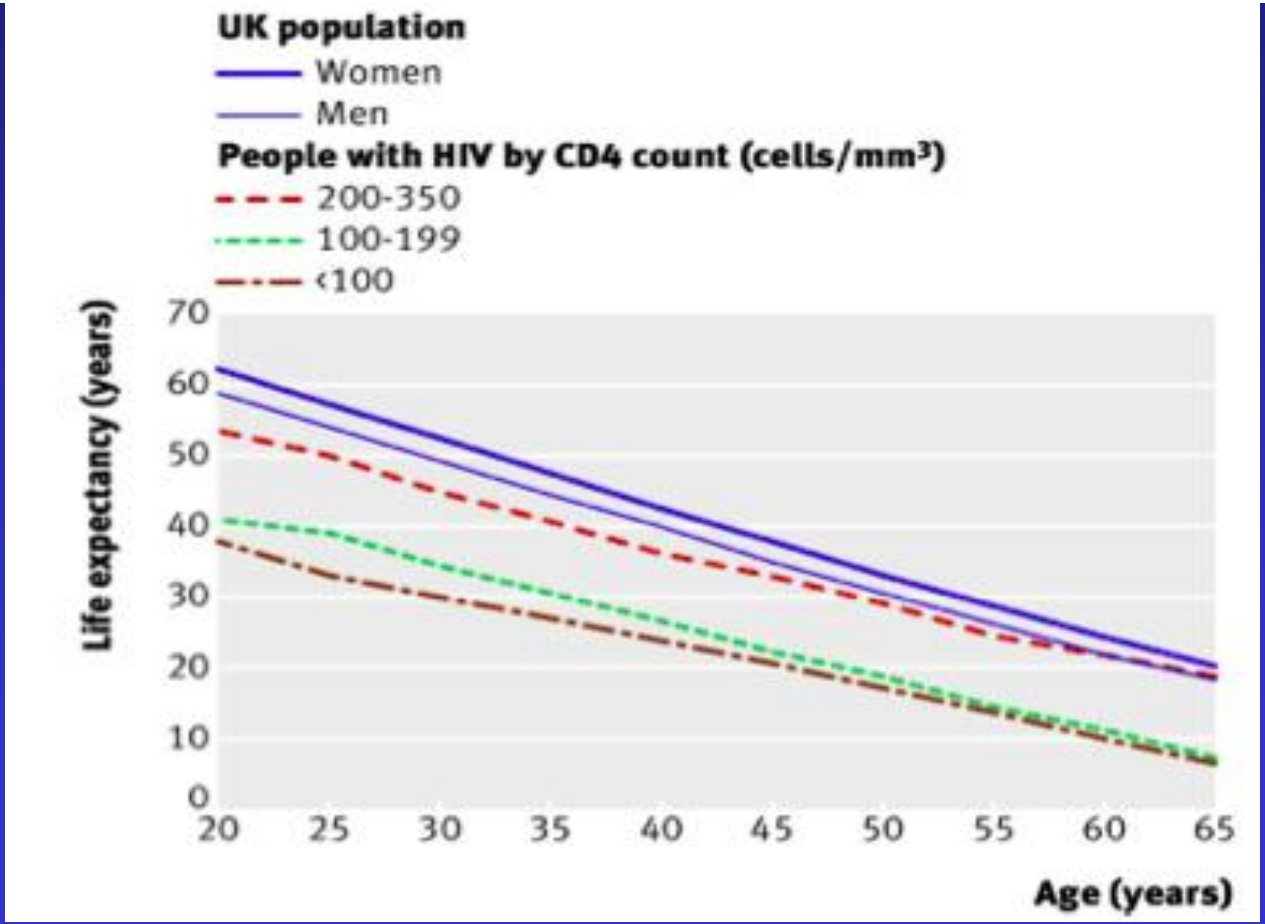
ART year 2012: When & how to switch cART in virologically suppressed patients



1. Current scenario
2. Objectives & limitations
3. Stable & suppressed patients
4. In summary…

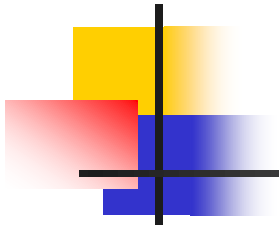
Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study

Life expectancy from age 20-65 of people who started antiretroviral therapy in 2000-8 by CD4 cell count group at start of antiretroviral therapy compared with that of UK population (2000-6 women and men)



BMJ 2011;343:d6016 doi: 10.1136/bmj.d6016

ART year 2012: When & how to switch cART in virologically suppressed patients



1. Current scenario
2. Objectives & limitations
3. Stable & suppressed patients
4. In summary…

ART year 2012: When & how to switch cART in virologically suppressed patients

4. Stable & suppressed patients

- >90% of treated patients
- apparently healthy

The issue of toxic actives !!!!!!

Lehman Brothers se declara en bancarrota

La quiebra del cuarto banco de inversión de EE UU confirma los temores sobre la estabilidad del mercado financiero del país

ELPAÍS.com / AGENCIAS - Madrid / Washington - 15/09/2008

Lehman Brothers, cuarto banco de inversión de Estados Unidos, se ha declarado hoy en quiebra tras 158 años de actividad ante el fracaso de las negociaciones con las dos entidades que en un principio se perfilaban como posibles compradores, Bank of America y el grupo británico Barclays. La iniciativa, que el banco justifica en la necesidad de proteger los activos del banco y maximizar su valor, aunque se consideraba ya inevitable, tendrá importantes consecuencias para el sistema financiero del país.

- Greenspan pide dinero público para evitar más víctimas
- Diez bancos crearán un fondo de 50.000 millones para luchar contra la crisis de crédito
- El Bank of America compra Merrill Lynch por 31.000 millones
- El Dow Jones pierde un 4,42 % en una jornada marcada por la quiebra de Lehman
- Obama urge al Congreso la aprobación de la reforma financiera este año
- De las hipotecas a la nacionalización

Lehman, que sobrevivió a guerras e incluso al crack de 1929 pero que no ha podido capear la tormenta de la crisis de crédito, ha anunciado su intención de acoger su holding al capítulo 11 del código de bancarrota de EEUU, iniciativa que no afectará ni a su división de gestión de activos ni a su filial Neuberger Berman.

La bancarrota de Lehman Brothers, que ha pasado a convertirse en el tercer banco de inversión que desaparece o cambia de manos en seis meses en EE UU, representa al mismo tiempo la quiebra más importante en EE UU desde 1990, cuando

Lehman Brothers, el cuarto banco de inversión de EEUU, se declara en quiebra

VIDEO - AGENCIA ATLAS - 15-09-2008

El banco inversor Lehman Brothers, la cuarta entidad bancaria de Estados Unidos, se ha declarado hoy en quiebra tras fracasar las negociaciones para su venta. El Bank of America ha decidido al final comprar Merrill Lynch y el Barclays, el otro potencial salvador en un principio, decidió no comprar Lehman, un banco creado en 1850. Tras las especulaciones sobre la posible intervención estatal, Alan

Toxic actives

ART year 2012: When & how to switch cART in virologically suppressed patients

Switching can be considered as long as virological suppression can be maintained

What are the toxicactives for our virologically suppressed patients ?

- Thymidine analogs
- Low grade clinical intolerance
- Lab. abnormalities (lipids, kidney function)
- T20 containing regimens
- Potential interactions
- Pregnancy desire
- Lack of convenience (no. pills, doses), adherence
- High cost

Optimal Candidates for Switching:

- Patients without a history of treatment failure or drug-resistant virus

- Prolonged viral suppression. Fully adherent patients

DHHS Guidelines, October 2011.

ART year 2012: When & how to switch cART in virologically suppressed patients

Switching strategies usually consist on:

Replacing thymidine by non thymidine analogs
Replacing T20 by raltegravir (EASIER)
Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)
atazanvir/r (SWAN, ATAZIP)
raltegravir (SWITCHMRK, SPIRAL)
elvitegravir/cobi
Replacing efavirenz by rilpivirine
Monotherapy with LOP/r or DRV/r (OKT4,MONET, MONOI)

EASIER study. De Castro et al CID, 2009

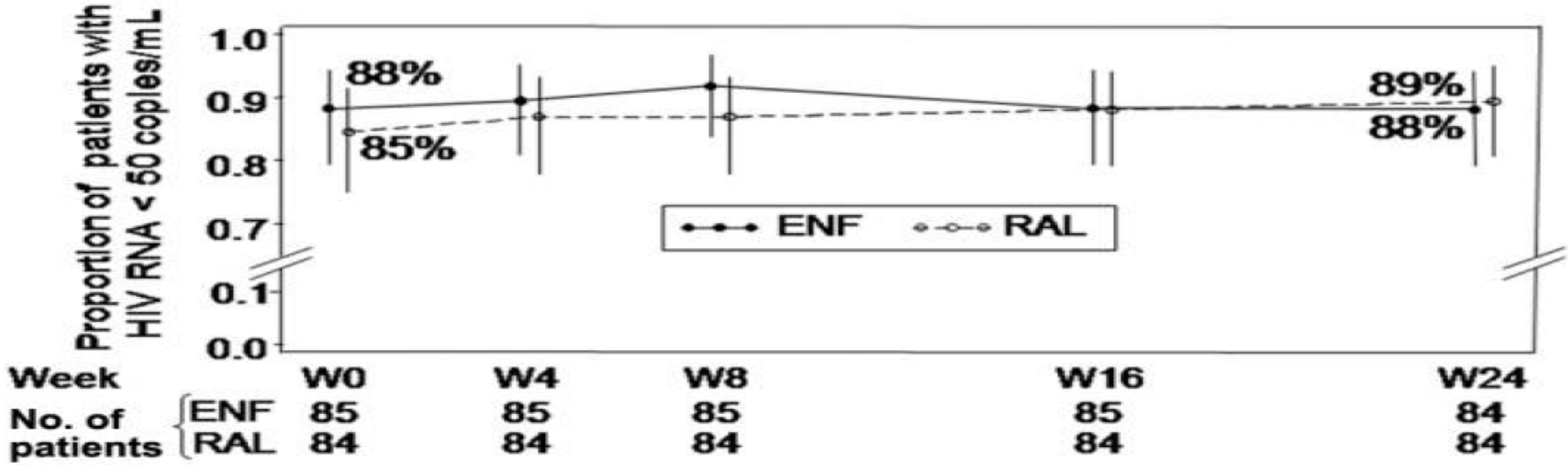


Figure 2. Proportion of patients (with 95% confidence intervals) with a plasma human immunodeficiency virus (HIV) RNA level <50 copies/mL over 24 weeks in the raltegravir (RAL) and enfuvirtide (ENF) arms of the EASIER ANRS 138 study (intention-to-treat analysis). Differences were not statistically significant ($P = .81$) at week 24.

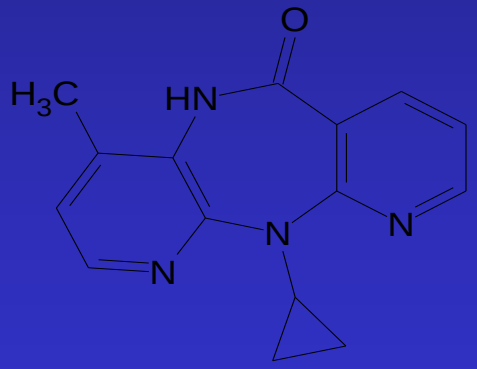
ART year 2012: When & how to switch cART in virologically suppressed patients

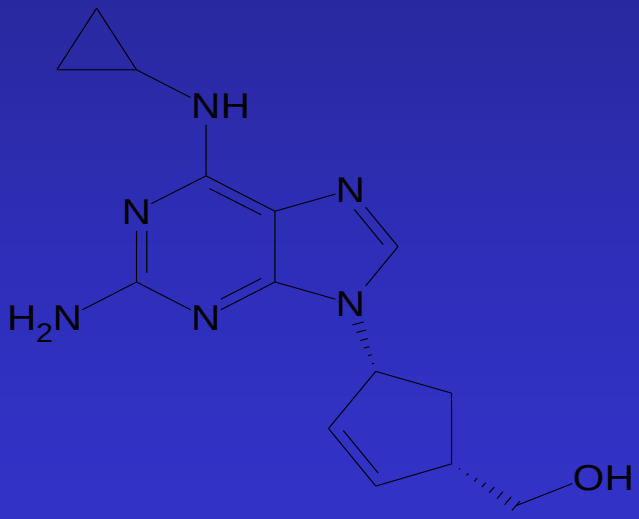
Switching strategies usually consist on:

Replacing thymidine by non thymidine analogs
Replacing T20 by raltegravir (EASIER)
Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)
atazanvir/r (SWAN, ATAZIP)
raltegravir (SWITCHMRK, SPIRAL)
Replacing efavirenz by rilpivirine
Monotherapy with LOP/r or DRV/r (OKT4,MONET, MONOI)

NEVIRAPINE, EFAVIRENZ, OR ABACAVIR FOR SIMPLIFICATION OF EFFECTIVE PROTEASE INHIBITOR-BASED ANTIRETROVIRAL THERAPY

(The **N**EV/**EF**A/**A**BA Study)



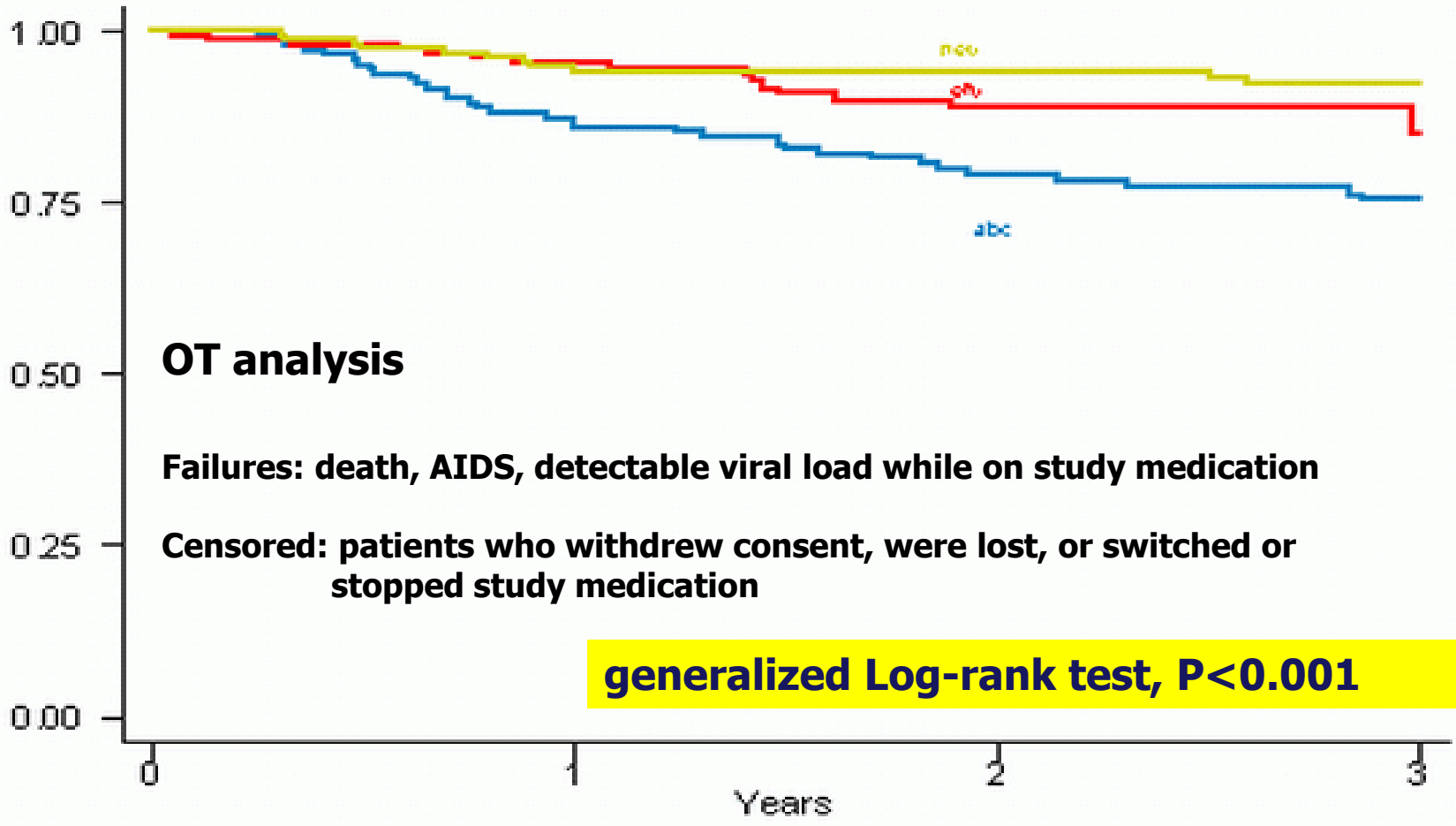


1 yr / 3 yr Martinez et al NEJM, 2003 /CROI, 2006

NEV/EFA/ABA Study

Proportion of non-failing patients

Martinez et al
NEJM 2003



OT analysis

Failures: death, AIDS, detectable viral load while on study medication

Censored: patients who withdrew consent, were lost, or switched or stopped study medication

generalized Log-rank test, P<0.001

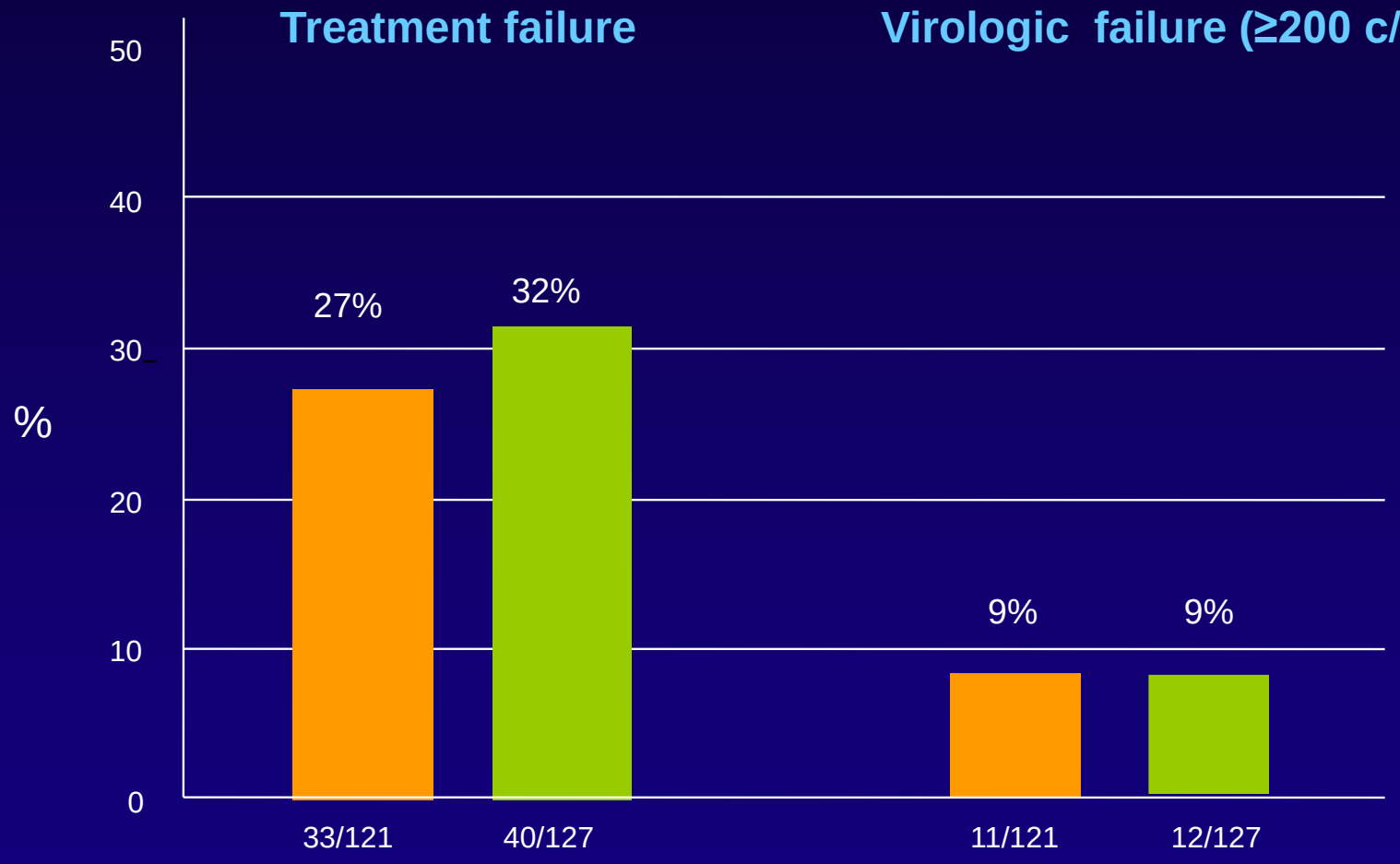
Nevirapine	155	144	109	54
Efavirenz	156	142	94	40
Abacavir	149	123	98	48

ART year 2012: When & how to switch cART in virologically suppressed patients

Switching strategies usually consist on:

Replacing thymidine by non thymidine analogs
Replacing T20 by raltegravir (EASIER)
Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)
atazanvir/r (SWAN, ATAZIP)
raltegravir (SWITCHMRK, SPIRAL)
Replacing efavirenz by rilpivirine
Monotherapy with LOP/r or DRV/r (OKT4,MONET, MONOI)

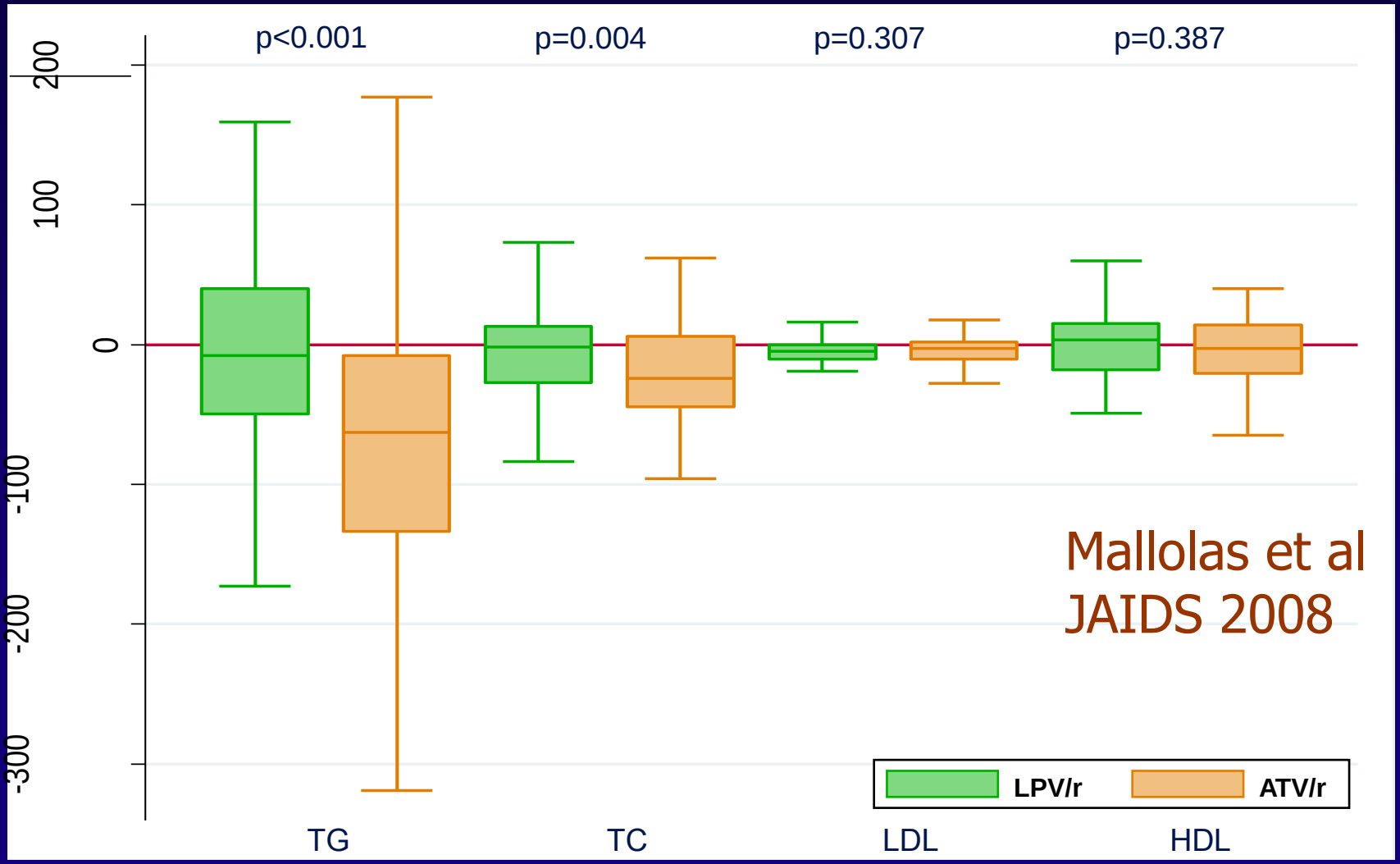
Treatment Failure and Virologic Failure (≥ 200 c/mL) through month 24



Mallolas et al JAIDS 2008

Difference Estimate (95% CI)	-4.2% (–15.6%, 7.1%)	–0.36% (–7.6%, 6.9%)

Change in median fasting plasma lipids at month 24



ART year 2012: When & how to switch cART in virologically suppressed patients

Switching strategies usually consist on:

Replacing thymidine by non thymidine analogs
Replacing T20 by raltegravir (EASIER)
Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)
atazanvir/r (SWAN, ATAZIP)
raltegravir (SWITCHMRK, SPIRAL)
Replacing efavirenz by rilpivirine
Monotherapy with LOP/r or DRV/r (OKT4,MONET, MONOI)

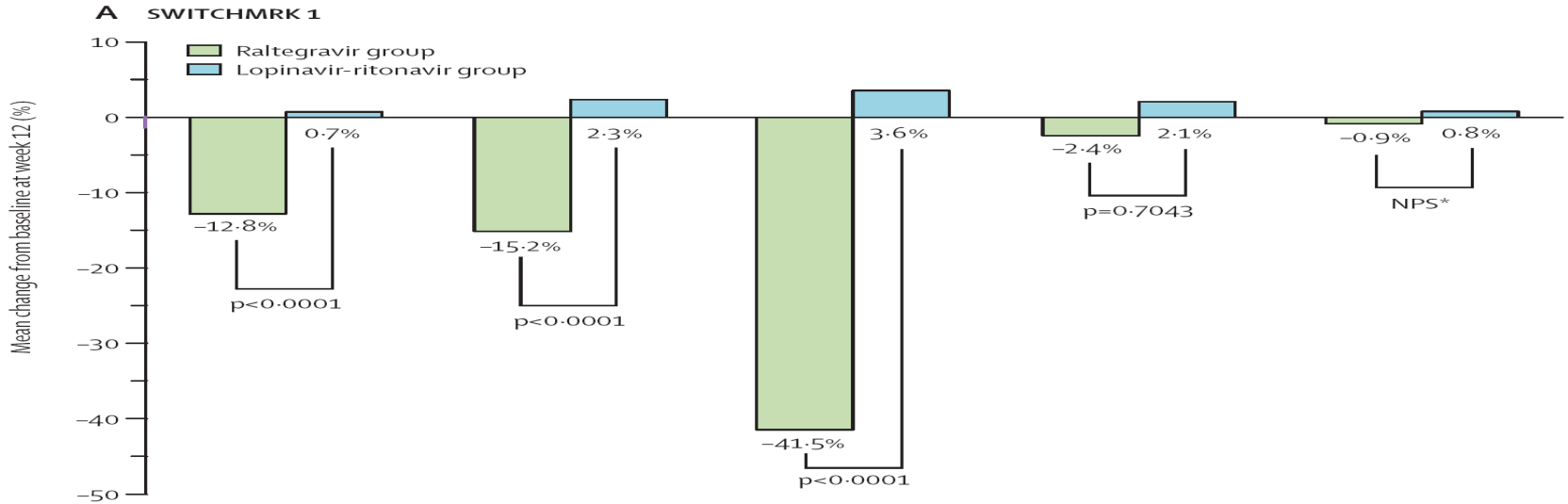
Lancet 2010

Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials

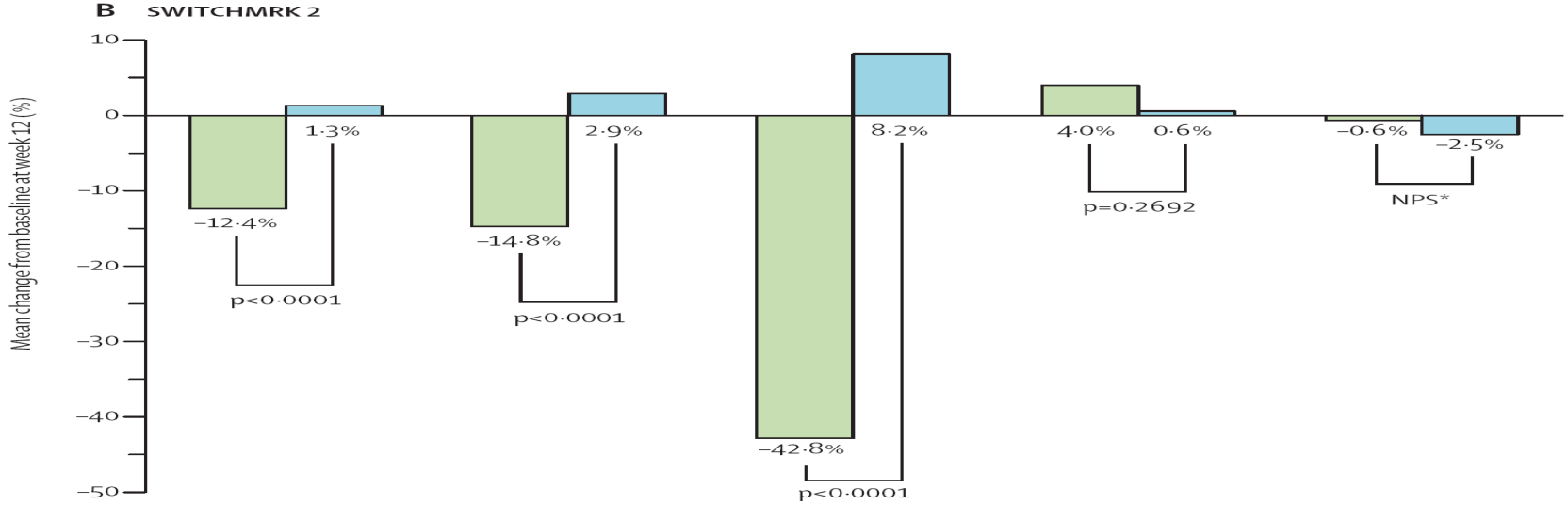
*Joseph J Eron, Benjamin Young, David A Cooper, Michael Youle, Edwin DeJesus, Jaime Andrade-Villanueva, Cassy Workman, Roberto Zajdenverg, Gerd Fätkenheuer, Daniel S Berger, Princy N Kumar, Anthony J Rodgers, Melissa A Shaughnessy, Monica L Walker, Richard J O Barnard, Michael D Miller, Mark J DiNubile, Bach-Yen Nguyen, Randi Leavitt, Xia Xu, Peter Sklar, for the SWITCHMRK 1 and 2 investigators**

Summary

Background To reduce lipid abnormalities and other side-effects associated with antiretroviral regimens containing lopinavir-ritonavir, patients might want to switch one or more components of their regimen. We compared substitution of raltegravir for lopinavir-ritonavir with continuation of lopinavir-ritonavir in HIV-infected patients with stable viral suppression on lopinavir-ritonavir-based combination therapy.

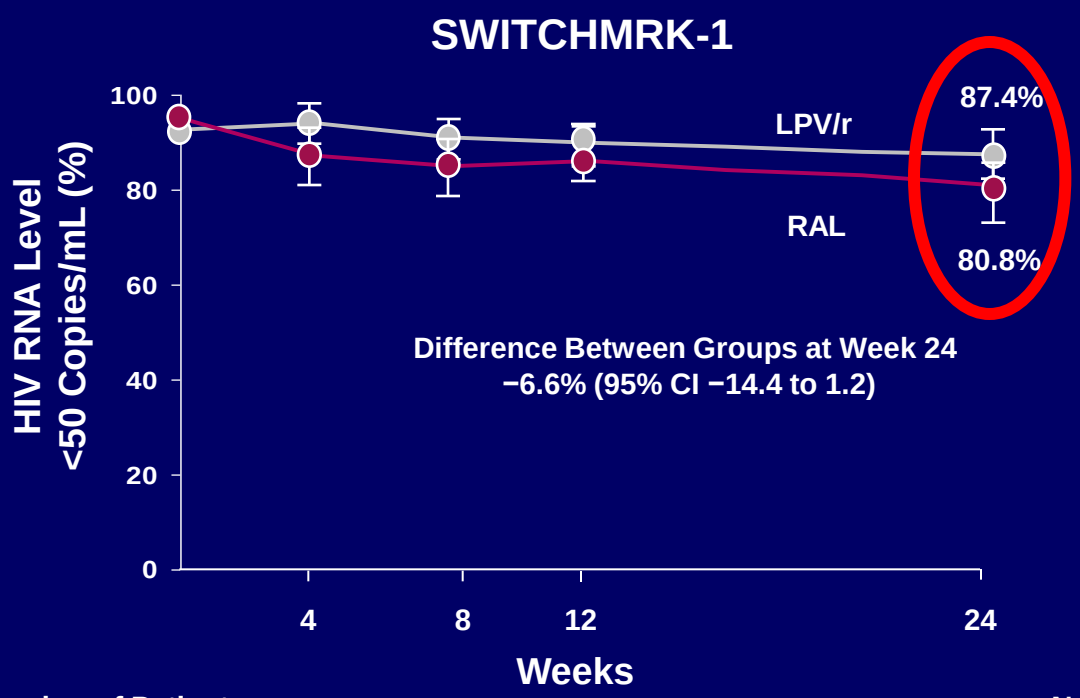


Mean concentration (SD) at baseline (mmol/L)	Total cholesterol	Non-HDL cholesterol	Triglycerides†	LDL cholesterol	HDL cholesterol
Raltegravir group	5·6 (1·3)	4·3 (1·3)	2·1 (1·5)	3·0 (1·0)	1·3 (0·4)
Lopinavir–ritonavir group	5·3 (1·4)	4·1 (1·4)	1·8 (1·3)	2·7 (0·9)	1·2 (0·4)
Mean concentration (SD) at week 12 (mmol/L)					
Raltegravir group	4·8 (1·0)	3·6 (1·0)	1·3 (0·8)	2·8 (0·9)	1·2 (0·4)
Lopinavir–ritonavir group	5·3 (1·4)	4·1 (1·4)	1·9 (1·6)	2·7 (0·9)	1·2 (0·3)

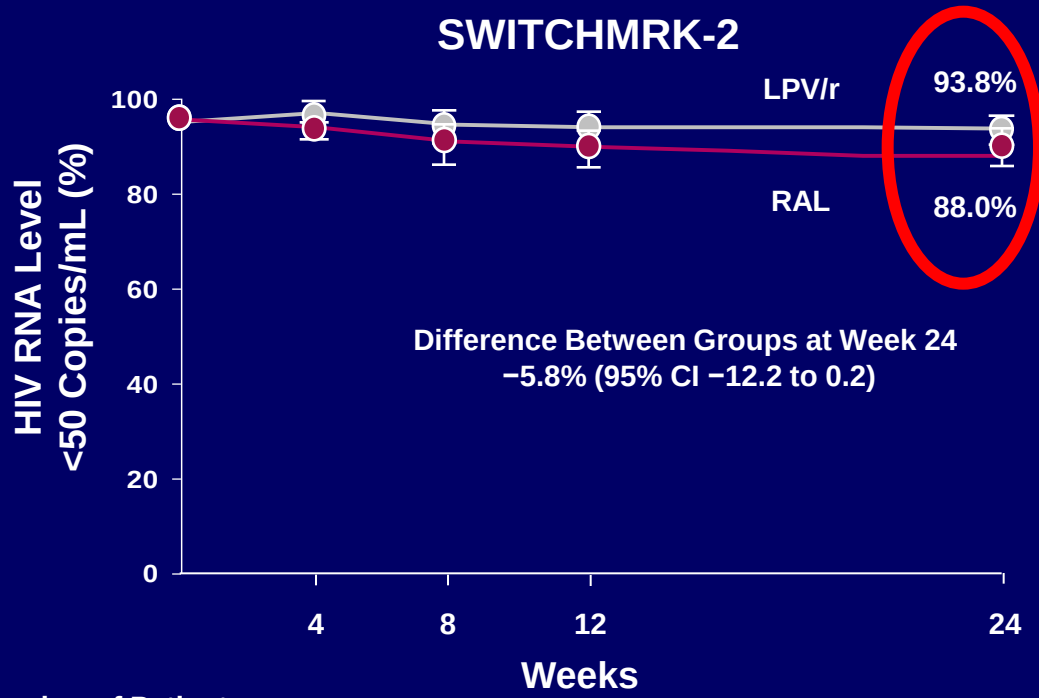


Mean concentration (SD) at baseline (mmol/L)	Total cholesterol	Non-HDL cholesterol	Triglycerides†	LDL cholesterol	HDL cholesterol
Raltegravir group	5·6 (1·8)	4·3 (1·9)	2·4 (1·8)	2·7 (1·1)	1·2 (0·3)
Lopinavir–ritonavir group	5·5 (1·1)	4·2 (1·1)	2·5 (1·8)	2·7 (0·8)	1·2 (0·3)
Mean concentration (SD) at week 12 (mmol/L)					
Raltegravir group	4·7 (1·3)	3·6 (1·3)	1·4 (0·8)	2·7 (1·1)	1·2 (0·3)
Lopinavir–ritonavir group	5·5 (1·2)	4·3 (1·2)	2·7 (2·1)	2·7 (0·8)	1·2 (0·3)

Efficacy at 24 Weeks: Proportion of Patients With Viral RNA <50 Copies/mL[a,b]



Number of Patients					
RAL group	174	166	169	173	172
LPV/r group	174	171	171	171	174

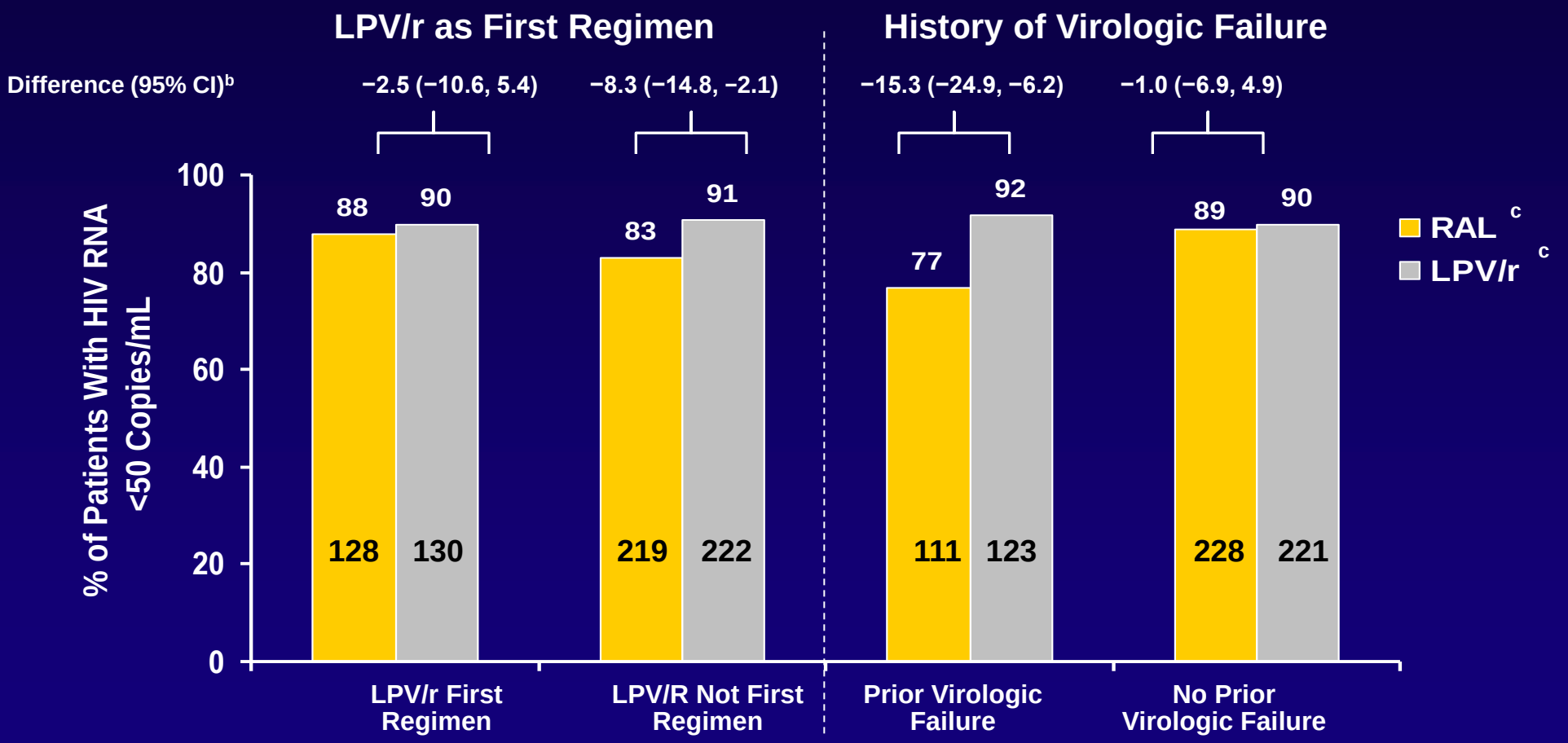


Number of Patients					
RAL group	176	176	176	176	175
LPV/r group	178	178	177	177	178

Studies were interrupted by the DSMB iiiii

CI = confidence interval; LPV/r = lopinavir/ritonavir; RAL = raltegravir.
[a]Error bars represent 95% confidence intervals.
[b]All patients who did not complete the study were regarded as failures.
Adapted with permission from Eron JJ et al. *Lancet*. 2010 Jan 13; [Epub ahead of print].

Efficacy at 24 Weeks: Subgroup Analysis – SWITCHMRK-1 and -2 Combined Data[1,a]



CI = confidence interval; LPV/r = lopinavir/ritonavir; RAL = raltegravir.
[a]All patients who did not complete the study were regarded as failures.
[b]Calculated by the method of Miettinen and Nurminen.
[c]Plus existing baseline regimen.
1. Eron JJ et al. *Lancet*. 2010 Jan 13; [Epub ahead of print].

An Open-label, Randomized, 48-Week Study to Assess the Safety, Tolerability and Activity of Raltegravir when Replacing the Ritonavir-boosted PI Component of HAART in HIV-Infected Individuals with Viral Load Suppression on a Ritonavir-Boosted PI Containing Regimen.

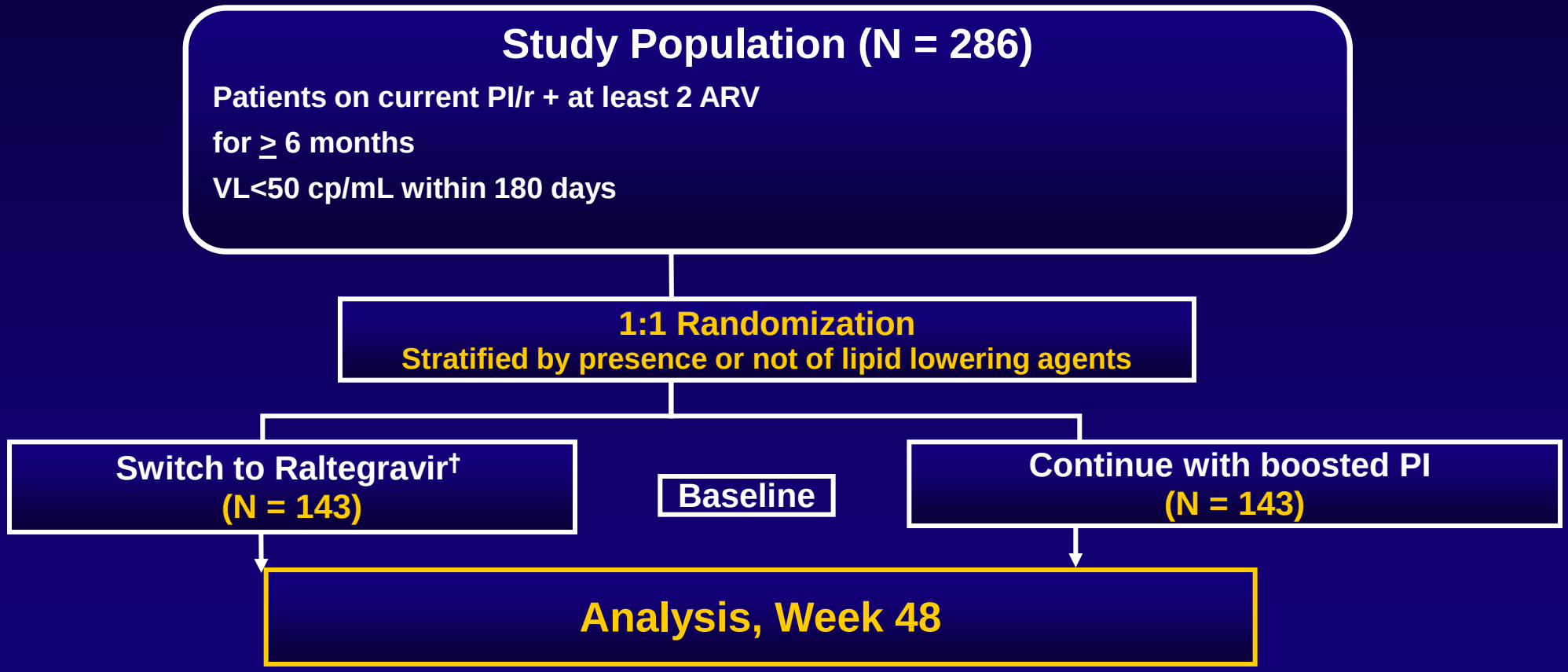
The SPIRAL Study

Martinez E.[1], Larrousse M.[1], Llibre J.M.[2], Gutierrez F.[3], Saumoy M.[4], Antela A.[5], Knobel H.[6], Pich J.[1], Perez I.[1], J. Murillas[7], J. Portilla[8], J. Berenguer[9], E. Ribera[10] and Gatell J.M.[1] , for the SPIRAL study group

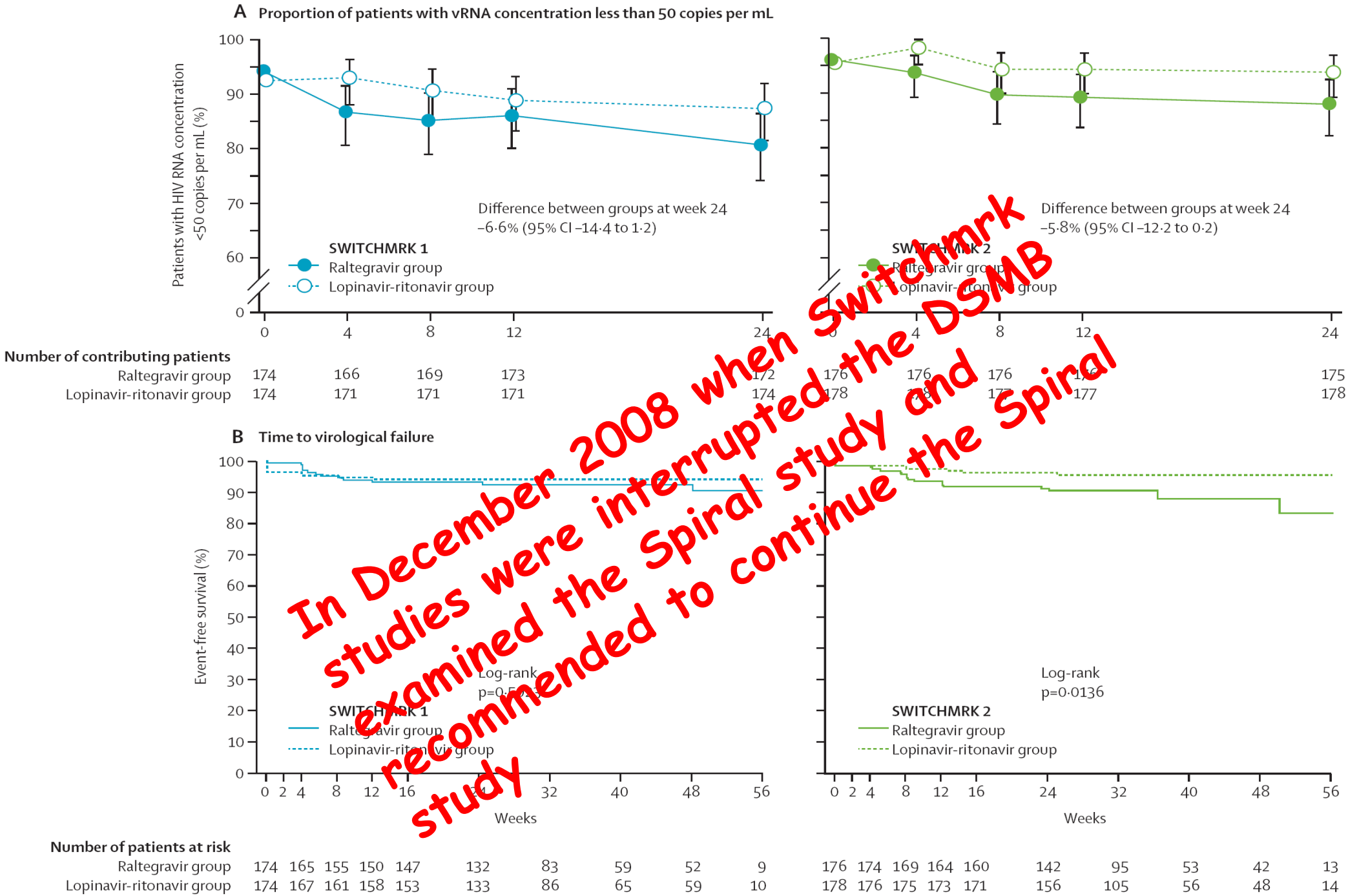
[1]Hospital Clínic, Barcelona, Spain; [2]Hospital Germans Trias i Pujol, Badalona, Spain; [3]Hospital General Universitario de Elche, Elche, Spain; [4]Hospital de Bellvitge, Hospitalet de Llobregat, Spain; [5]Hospital de Santiago, Santiago de Compostela, Spain; and [6]Hospital del Mar, Barcelona, Spain;[7]Hospital Son Dureta, Palma de Mallorca, Spain; [8]Hospital Univ. de Alicante, Alicante, Spain;[9]Hospital Gregorio Marañón, Madrid, Spain; [10]Hospital Vall d'Hebrón, Barcelona, Spain .

Martinez E et al . AIDS 2010

Study Design

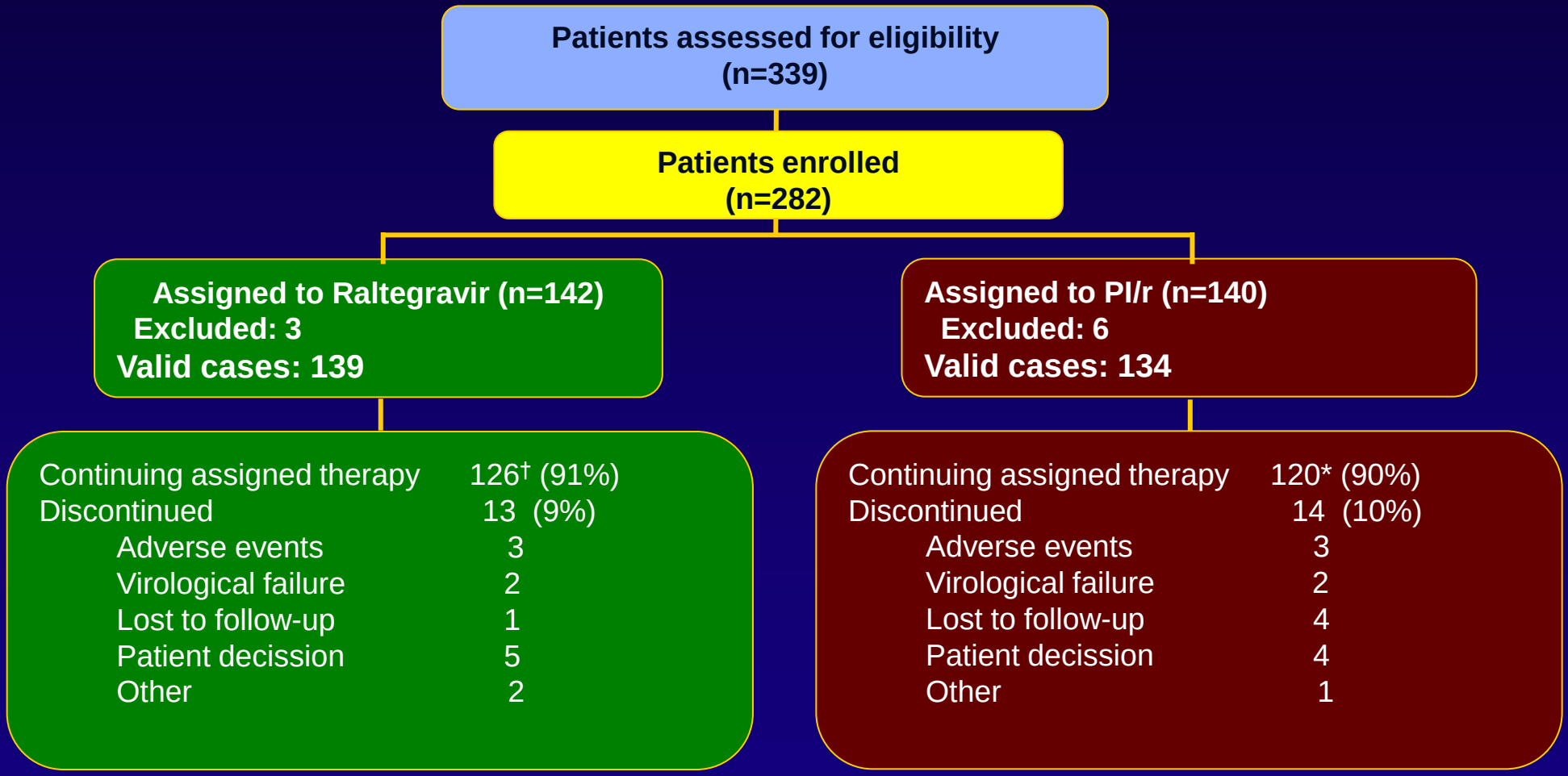


* Raltegravir 400mg BID (maintaining other antiretrovirals unchanged).



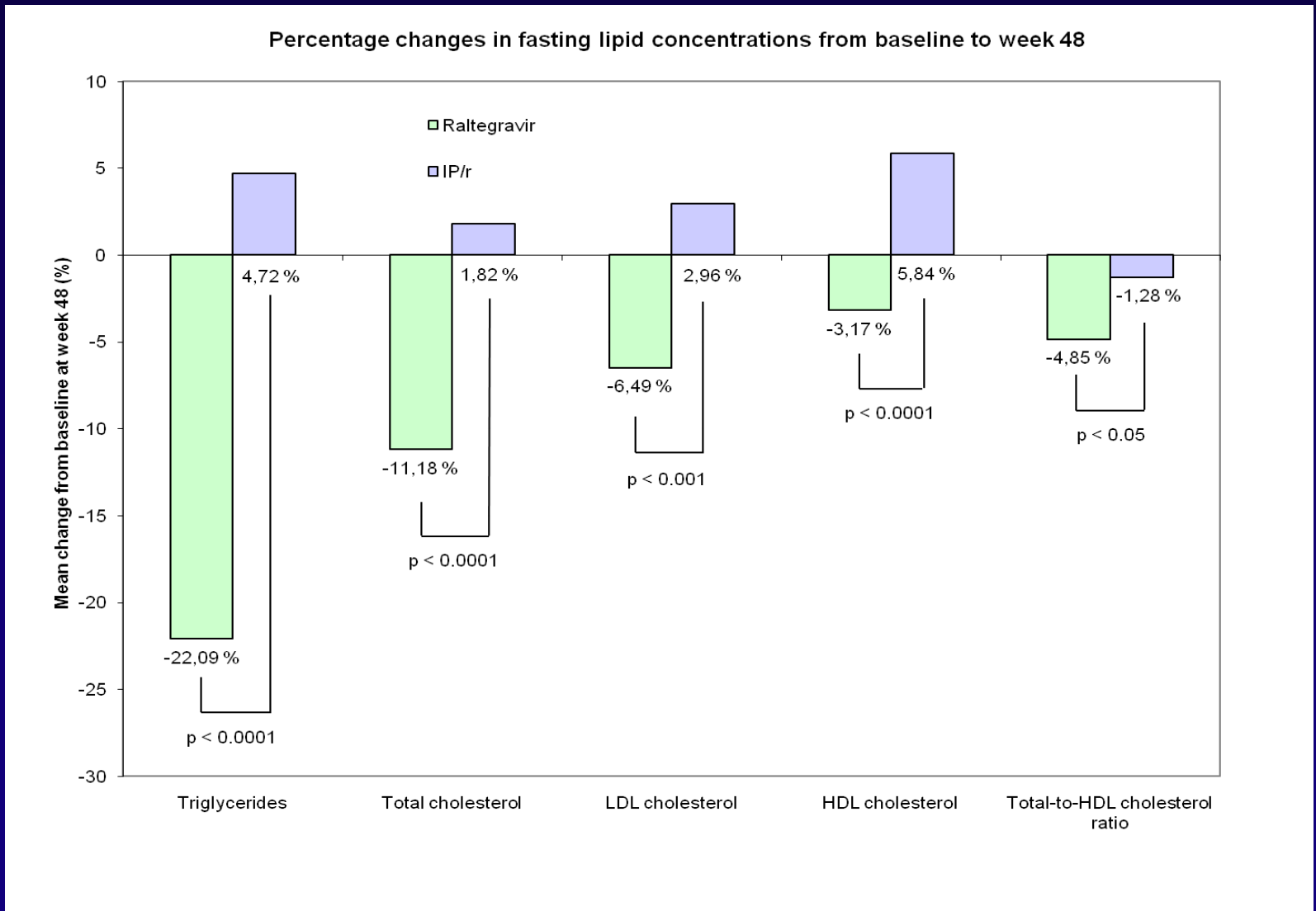
In December 2008 when Switchmrk studies were interrupted the DSMB examined the Spiral study and recommended to continue the Spiral study

Patient Disposition at week 48



† 2 subjects with virological failure
* 4 subjects with virological failure

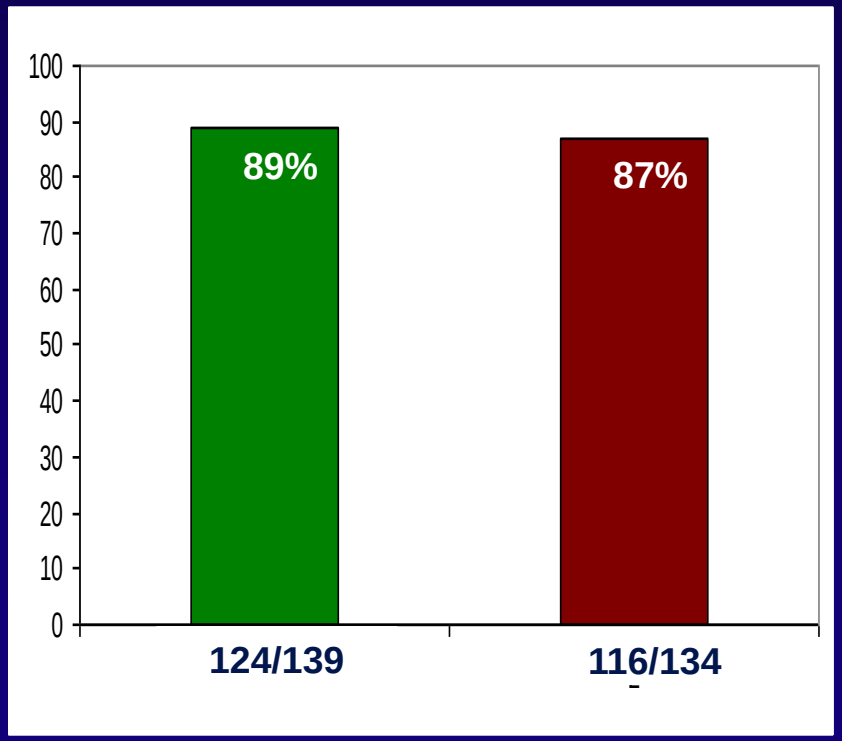
LIPIDS. Change in mean Fasting Lipid Parameters through Week 48



Patients free of Treatment Failure and Virologic Failure (≥ 50 cp/mL) through Week 48

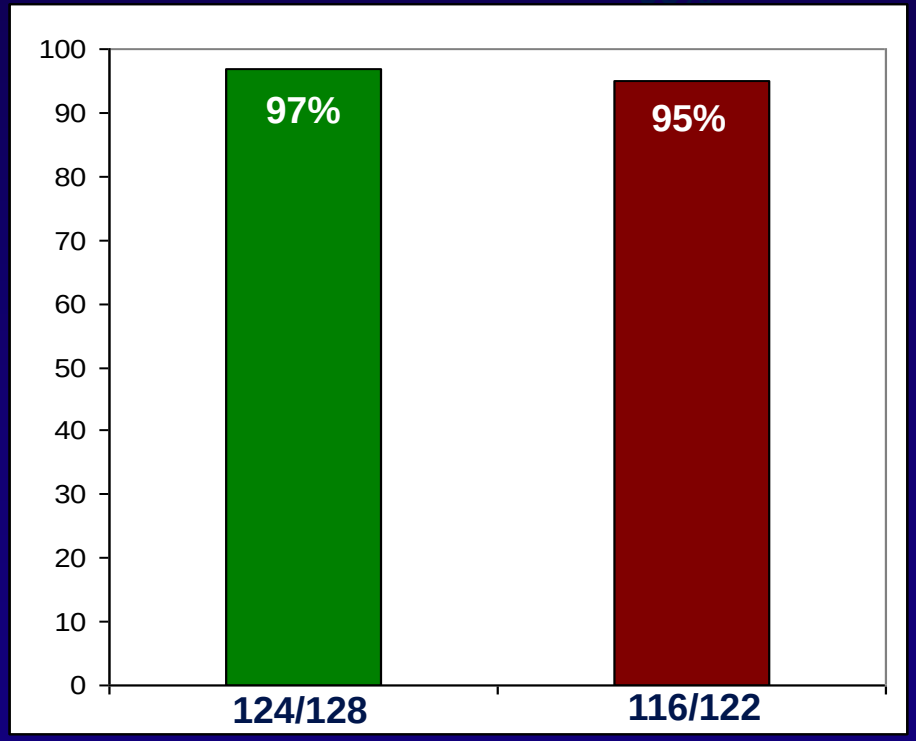
Free of Treatment Failure (ITT, S=F)

RALTEGRAVIR PI/r



Difference Estimate (95% CI) 2.6% (–5.2%, 10.6%)

Free of Virologic Failure (≥ 50 cp/mL) (OT)



Difference Estimate (95% CI) 1.8% (–3.5%, 7.5%)

Compared with SPIRAL, SWITCHMRK studies 1 & 2:

- Double blinded & Double dummy
- 24 weeks
- No need to confirm VL>50 for the main end point
- Different backbone of NRTI´s
- Substantially shorter median duration of virological suppression before entry
- Shorter minimum duration of virological suppression before entry
- All Lopinavir/r

Yet, response rate was very high in both arms in both studies. Probably among the highest ever seen in switching studies

Increased duration of viral suppression is associated with lower viral rebound rates in patients with previous treatment failures

Andrew A. Benzie[a], Loveleen K. Bansi[b], Caroline A. Sabin[b], Simon Portsmouth[a], Teresa Hill[a], Margaret Johnson[c], Richard Gilson[b], Philippa Easterbrook[d], Brian Gazzard[e], Martin Fisher[f], Chloe Orkin[g], David Dunn[h], Valerie Delpech[i], Graham P. Taylor[a], John C. Walsh[a], and Andrew N. Phillips[b] on behalf of the United Kingdom Collaborative HIV Cohort (CHIC) Study

AIDS, 2007

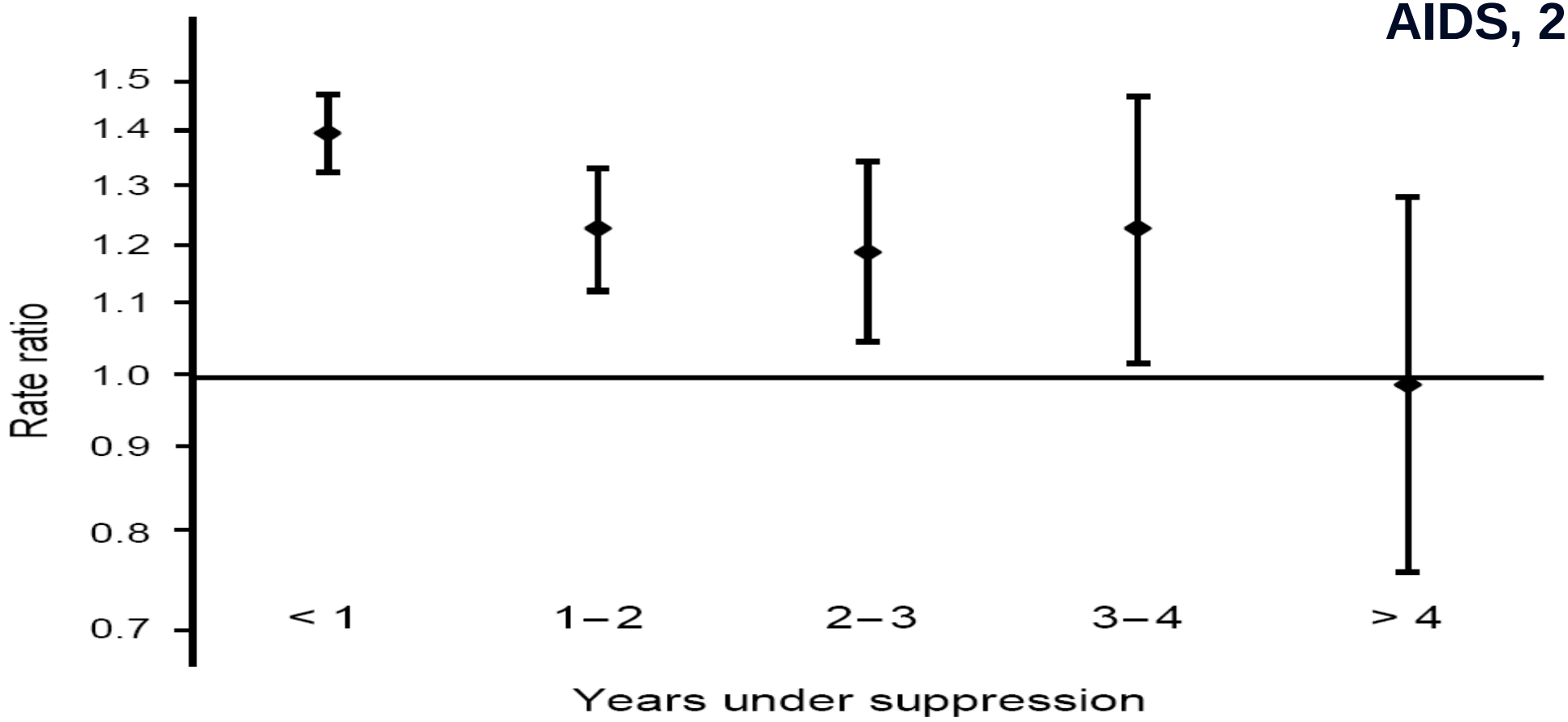


Fig. 2. Relative rate of viral rebound (95% confidence interval), per additional antiretroviral regimen failed.

Conclusions of SPIRAL study:

- In patients with sustained virological suppression on PI/r-based cART, switching from PI/r to raltegravir demonstrated non-inferior efficacy and resulted in a better lipid profile at 48 weeks than continuing PI/r.

Comprehensive Lipid Evaluation in Patients Switching from PI/r-based cART to a RAL-based cART: SPIRAL-MET Substudy

Maria Saumoy*[1], J Ordoñez[2], E Martinez[1], J Llibre[3], E Ribera[4], H Knobel[5], and D Podzamczer[1] .

[1]Hosp Univ de Bellvitge, Hosp de Llobregat, Spain; [2]Hosp de Sant Pau, Barcelona, Spain; [3]Hosp Germans Trias i Pujol, Badalona, Spain; [4]Hosp Vall d`Hebrón, Barcelona, Spain; and [5]Hosp del Mar, Barcelona, Spain

18th CROI, Boston 2011: abstract 820

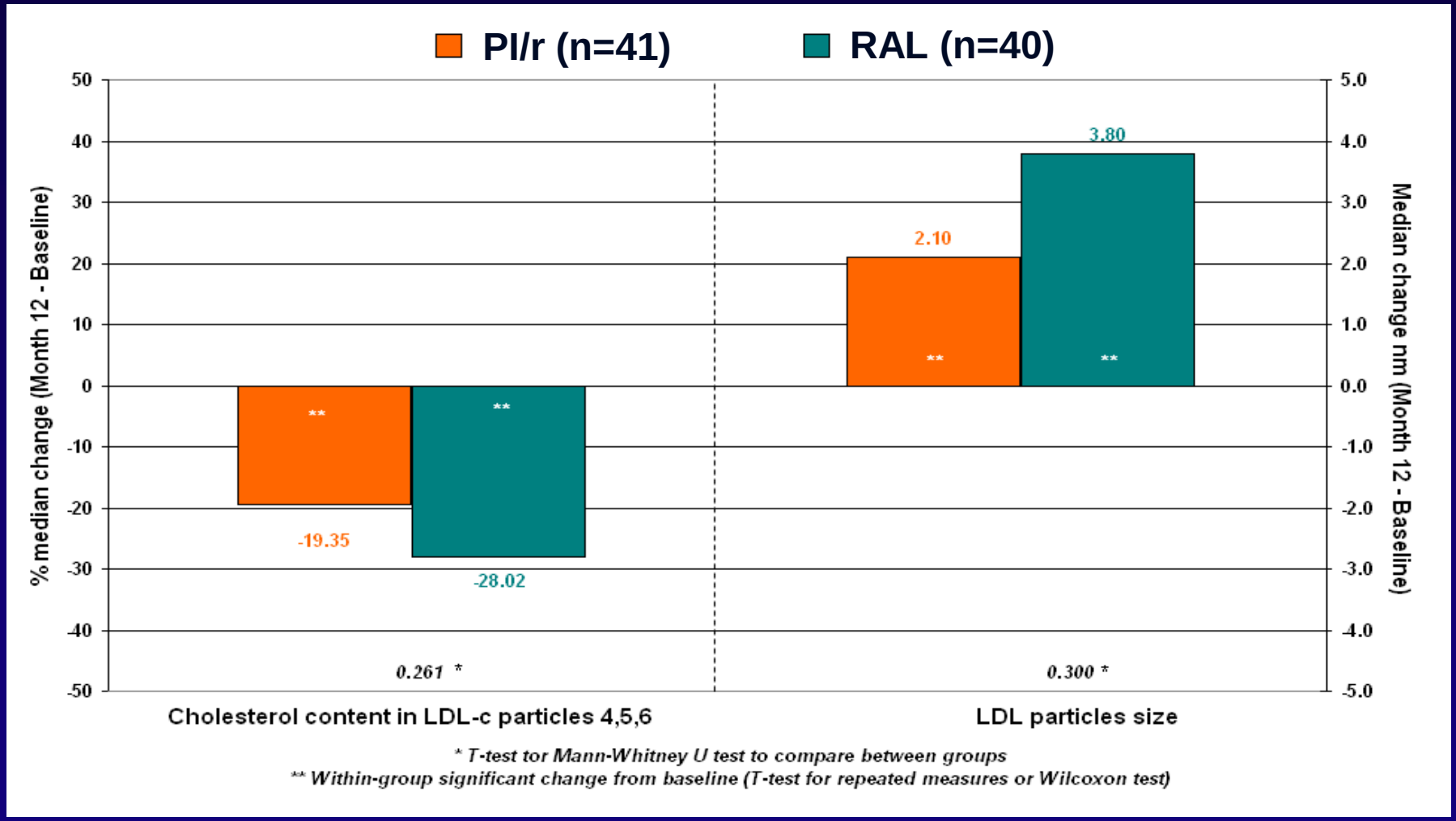
Changes in Body Composition after Switching from PI/r to RAL in Virologically Suppressed HIV-1^{+} Patients: SPIRAL-LIP Substudy

Adria Curran*[1], M Saumoy[2], E Martinez[3], M Larrousse[3], D Podzamczer[2], I Ocaña[1], M Lonca[3], J Gatell[3], E Ribera[1], and SPIRAL Study Group.

[1]Hosp Univ Vall d`Hebrón, Barcelona, Spain; [2]Hosp de Bellvitge, Barcelona, Spain; and [3]Hosp Clin, Barcelona, Spain

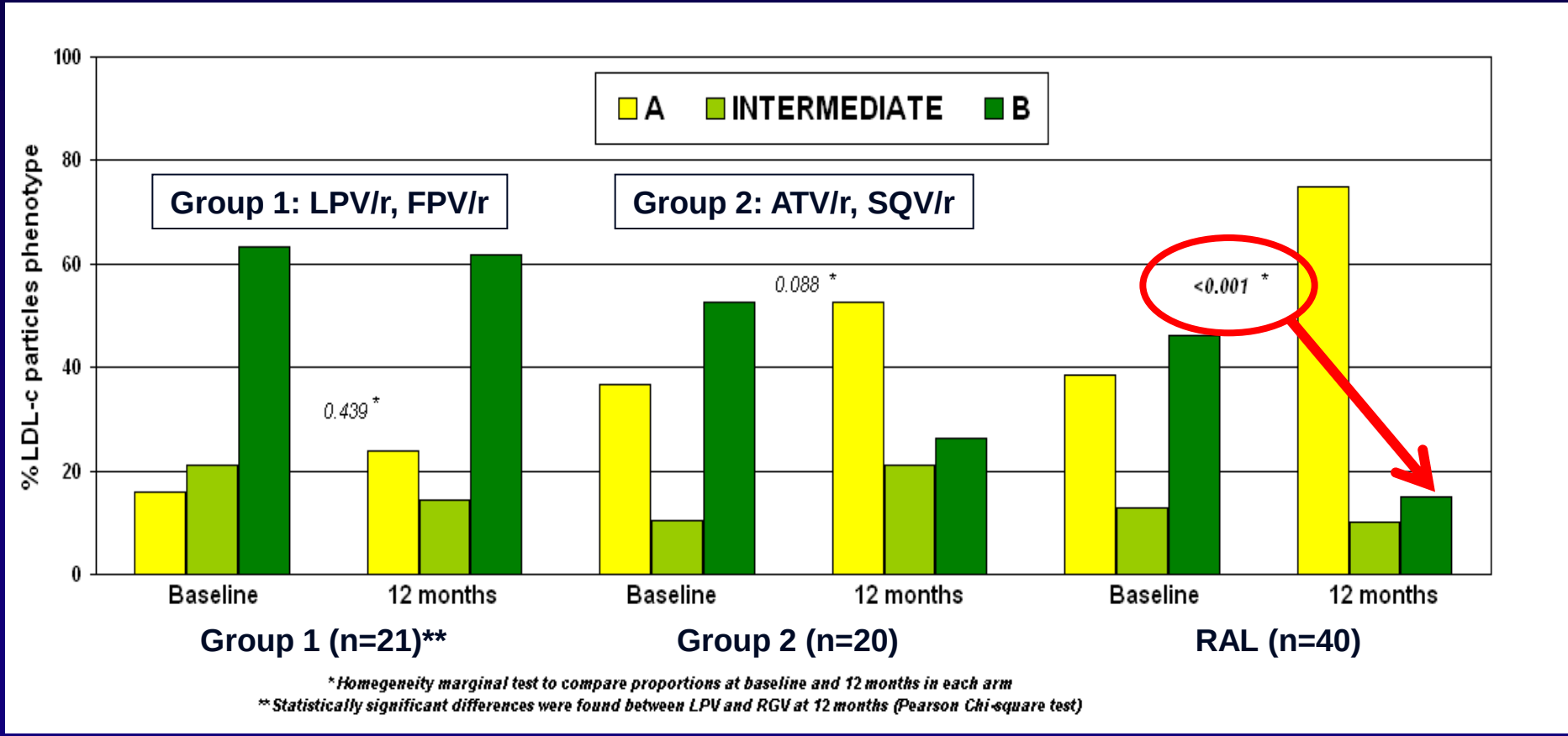
AIDS 2012

SPIRAL-MET: Median change in the cholesterol content transported by LDL particles 4-6 (smaller and denser) and in LDL size at month 12 according to therapy



LDL size and subfractions were measured by gel electrophoresis

SPIRAL-MET: Median changes in the percentage of LDL-c phenotype in RAL arm and PI arm stratified by PI/r used (group 1 vs group 2) at month 12



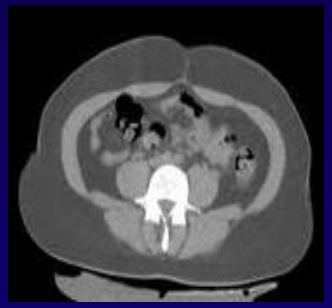
SPIRAL-MET: Conclusions

- Switching a PI/r-based to a RAL-based ART in otherwise stable, healthy HIV-infected patients was associated with an improvement in standard quantitative lipid parameters.

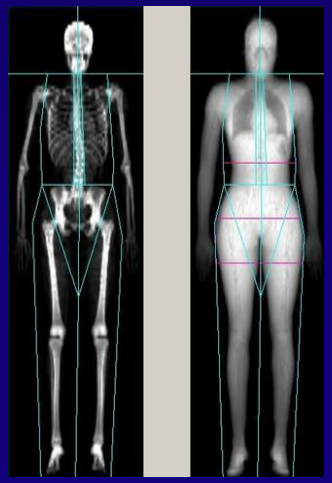
- There was shift to a less atherogenic LDL profile in the RAL arm:
  - ↓ cholesterol content
  - ↓ sdLDL particles
  - ↑ LDL size
  - ↑ less atherogenic LDL phenotype (phenotype A)

SPIRAL-LIP: Methods

BASELINE & 48 weeks



Computed Tomography (CT) scan (single cut at L4):
- Total fat
- Subcutaneous fat
- Visceral fat

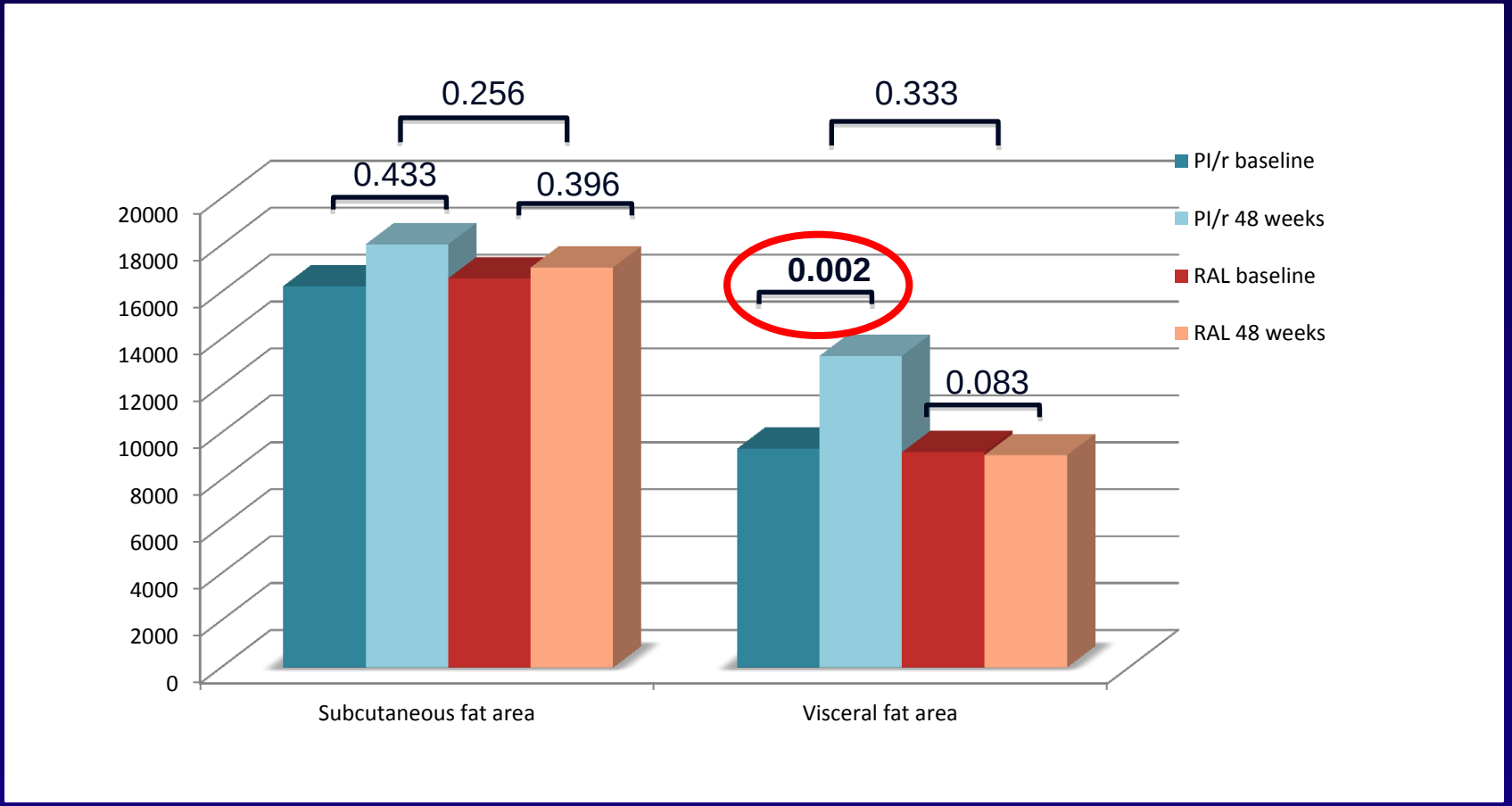


Dual X-ray Absorptiometry (DXA) scan:
- Body fat content (limbs, trunk, total fat)
- Total body, lumbar and femoral BMD and T-scores

SPIRAL-LIP: Fat change (CT scan)

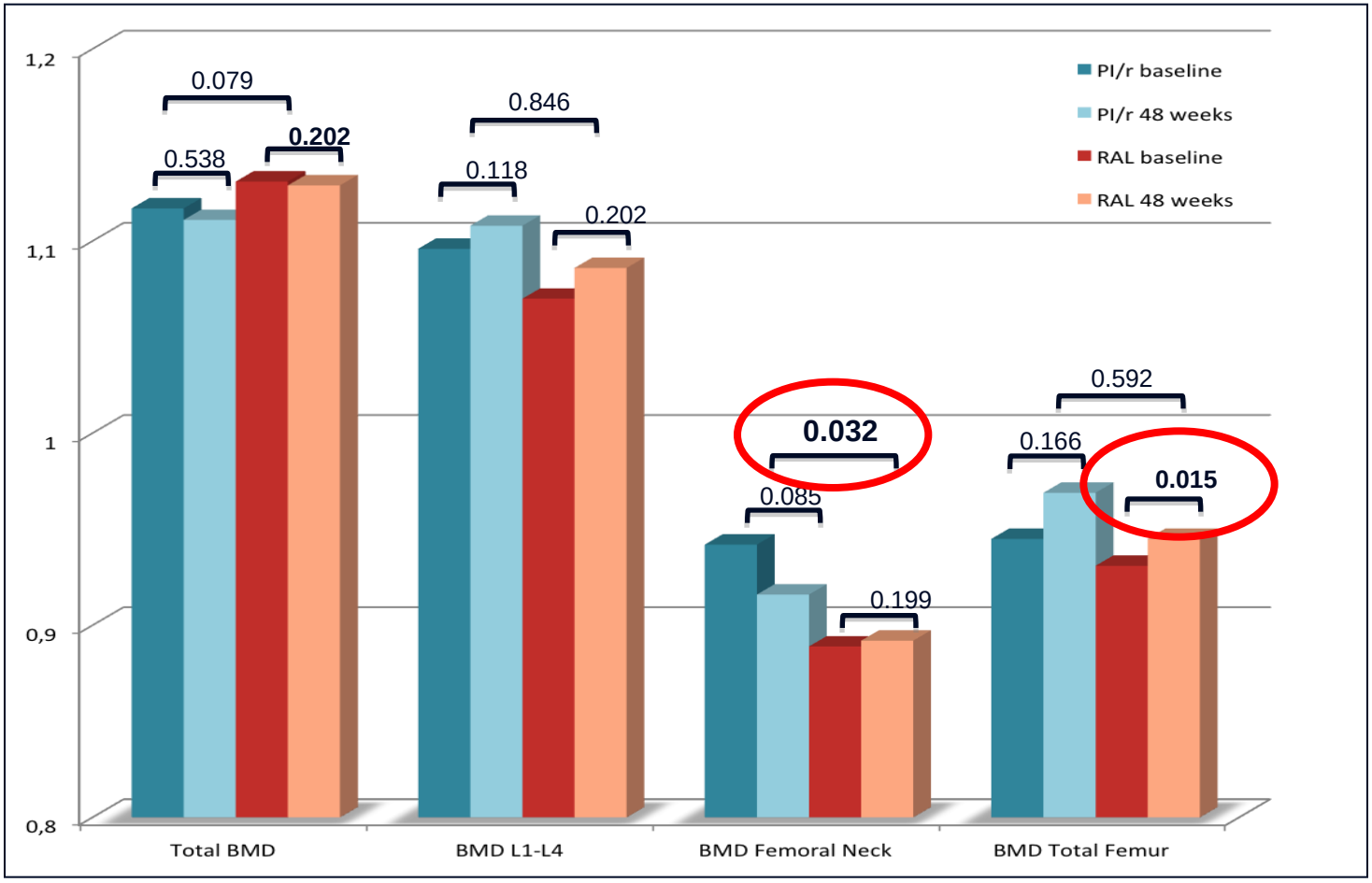
Body fat evolution measured by CT, single cut at L4

(results expressed as median, mm^2).



SPIRAL-LIP: BMD change (DXA scan)

Bone mineral density changes in total body, L1-L4, femoral neck and total femur area (expressed as g/cm²).



SPIRAL-LIP: Conclusions

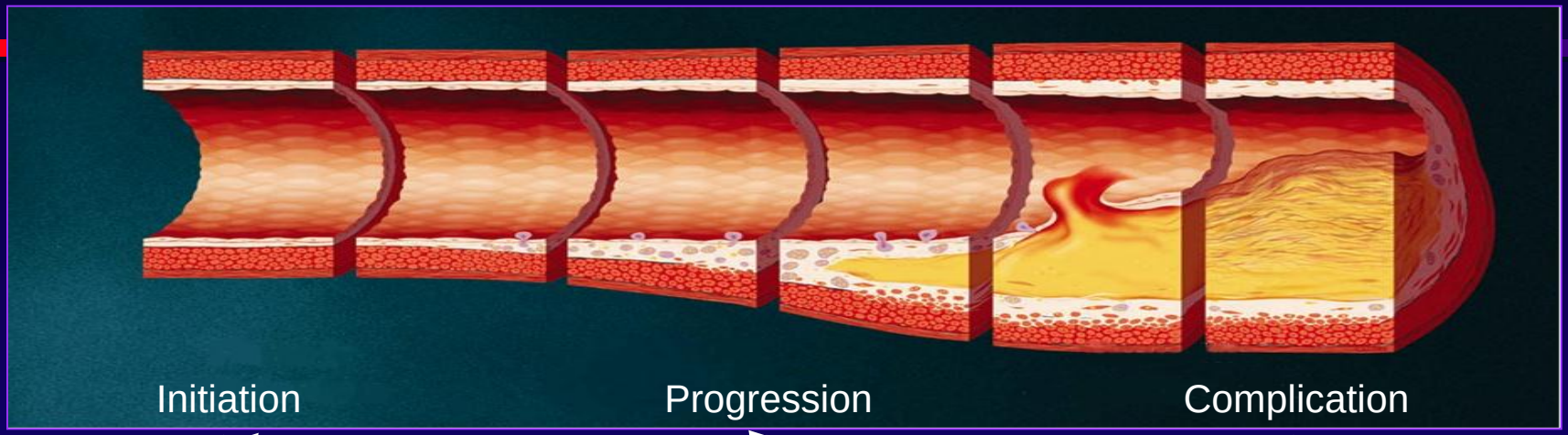
- VAT significantly increased in the PI/r arm after 48 weeks, whereas VAT changes in the RAL group were no significant. However, there were no between treatment arms differences in VAT. There were no significant changes within or between treatment arms in subcutaneous fat.
- Femoral neck (but no total femur) BMD and T-score experienced a significantly greater decrease in the PI/r arm after 48 weeks as compared with the RAL arm. There were no significant differences in lumbar spine BMD or T-score.

Changes in Cardiovascular Biomarkers in Subjects Switching from Ritonavir-Boosted Protease Inhibitors to Raltegravir: The SPIRAL Study.

E Martinez[1], P Monteiro[1], JM Llibre[2], F Gutierrez[3], D Podzamczer[4], A Antela[5], J Berenguer[6], I Perez[1], J Pich[1], JM Gatell[1], and the SPIRAL Study Group.

1 Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona;2 Germans Trias i Pujol University Hospital and Lluita contra la SIDA Foundation, Badalona; 3 Hospital General Universitario de Elche, Elche; 4 Hospital Universitari de Bellvitge, L`Hospitalet de Llobregat; 5 Complexo Hospitalario Universitario de Santiago, Santiago de Compostela; and 6 Hospital General Universitario Gregorio Marañón, Madrid, all in Spain.

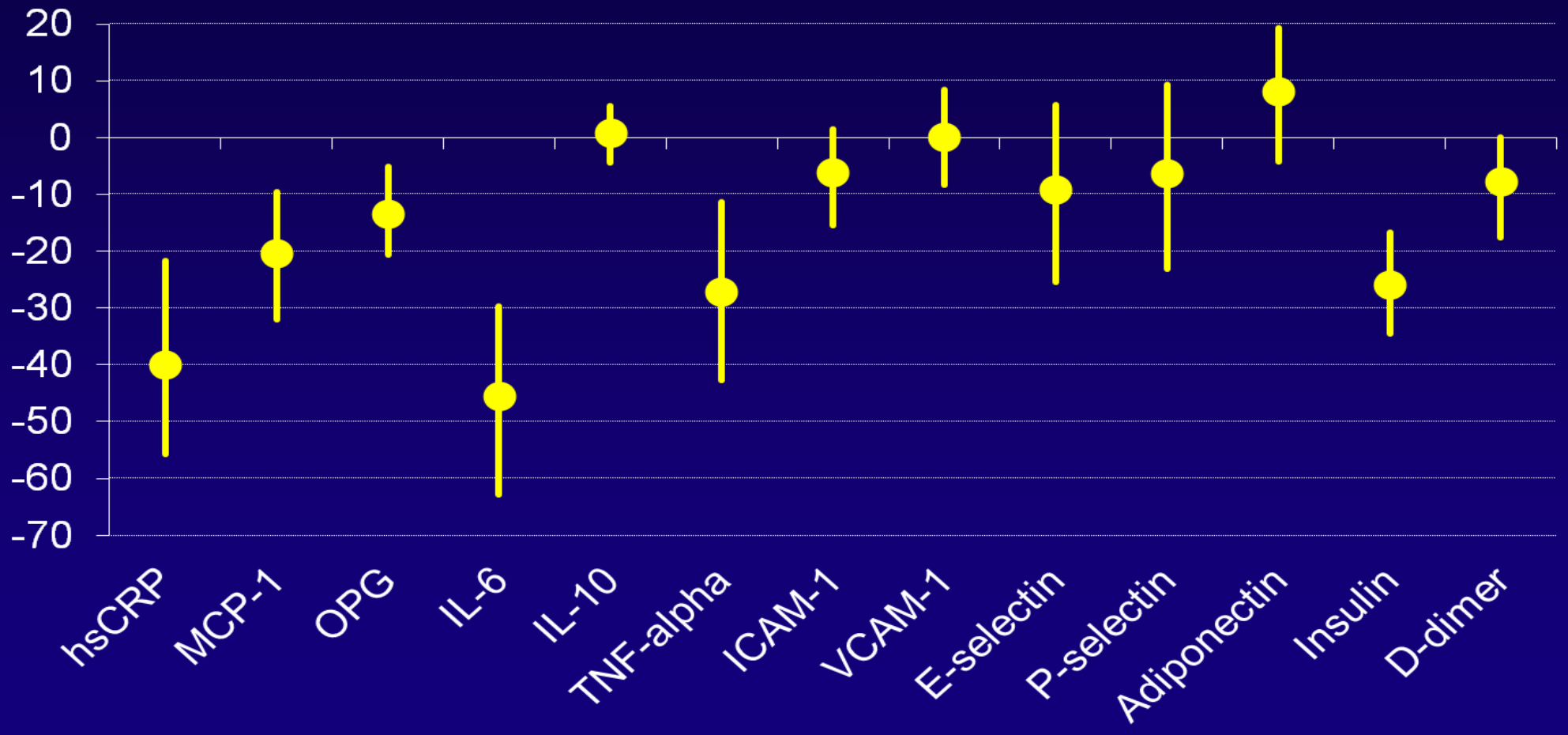
Biomarkers and lipids measured at baseline and 48 weeks



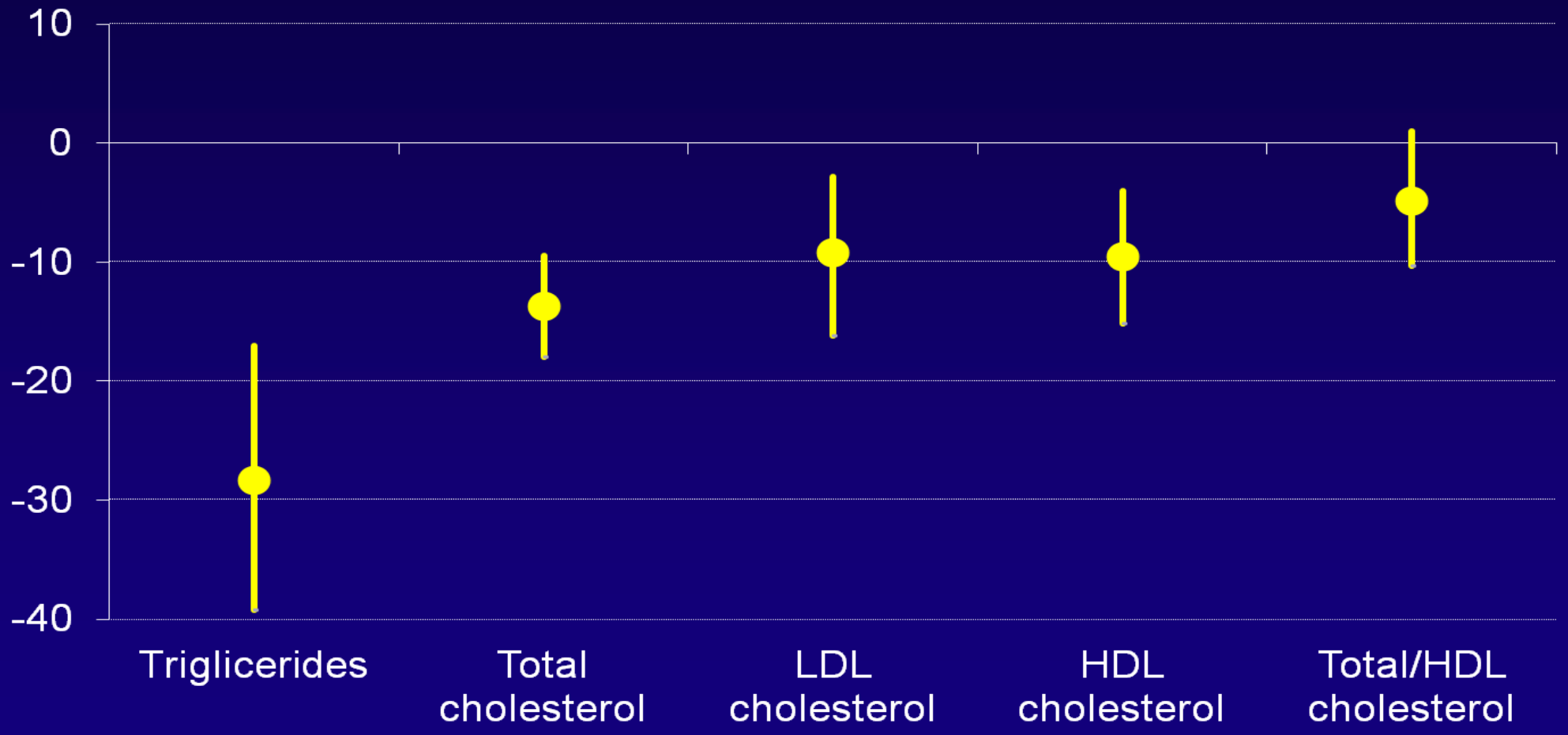
Inflammation	Endothelial dysfunction Insulin resistance	Hypercoagulability
hsCRP, MCP-1 OPG, IL-6 TNF-alpha, IL-10	**ICAM-1, VCAM-1 E-Selectin, P-Selectin Insulin, Adiponectin**	**D-dimer**

Lipids (fasting)	**Triglycerides, Total cholesterol, LDL cholesterol, HDL cholesterol**

Biomarkers: Median difference of percent change RAL minus PI/r (95% CI)



Lipids: Median difference of percent change RAL minus PI/r (95% CI)



Correlations between Δ biomarkers and Δ lipids

	ΔTriglycerides	ΔTotal cholesterol	ΔLDL cholesterol	ΔHDL cholesterol
ΔhsCRP	-	-	Spearman's rho 0.2415 (P=0.0016)	-
ΔMCP-1	-	Spearman's rho 0.1608 (P=0.0320)	-	Spearman's rho 0.1807 (P=0.0202)
ΔOPG	-	-	-	-
ΔIL-6	-	-	-	-
ΔIL-10	-	-	-	-
ΔTNF-alpha	-	-	-	-
ΔICAM-1	-	-	-	-
ΔVCAM-1	-	-	-	-
ΔE-selectin	-	-	-	-
ΔP-selectin	-	-	-	-
ΔAdiponectin	-	-	-	-
ΔInsulin	Spearman's rho 0.2842 (P=0.0001)	Spearman's rho 0.2125 (P=0.0040)	-	-
ΔD-dimer	-	-	-	-

Only correlations showing a P value <0.005 are shown

Conclusions

- Switching from PI/r to RAL in SPIRAL study led significant changes in several cardiovascular biomarkers associated with inflammation, insulin resistance and hypercoagulability, although not in those associated with endothelial dysfuntion.
- There were few and weak significant correlations between changes in lipids and changes in biomarkers suggesting that decreases in inflammation, insulin resistance, and hypercoagulability biomarkers were rather independent of lipid changes.

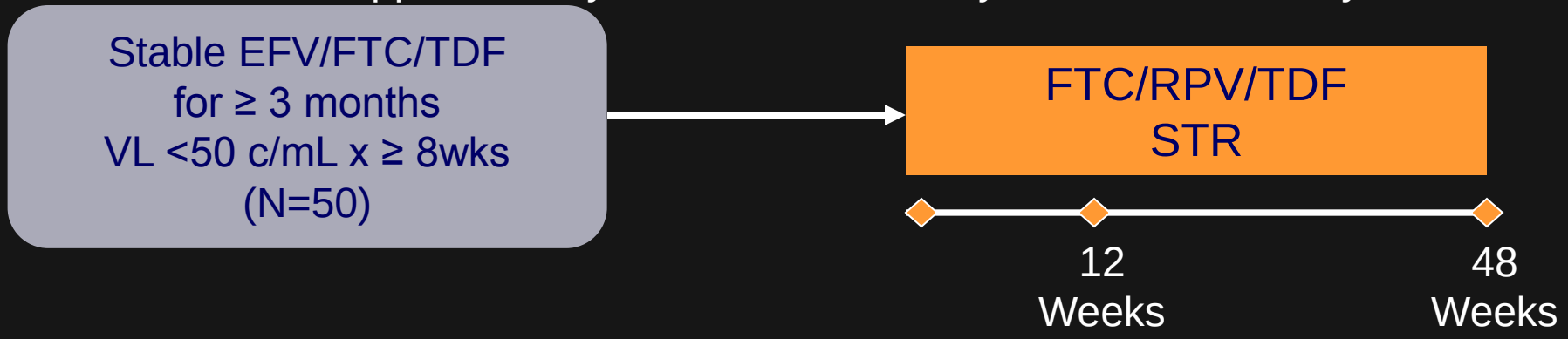
ART year 2012: When & how to switch cART in virologically suppressed patients

Switching strategies usually consist on:

Replacing thymidine by non thymidine analogs
Replacing T20 by raltegravir (EASIER)
Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)
atazanvir/r (SWAN, ATAZIP)
raltegravir (SWITCHMRK, SPIRAL)
Replacing efavirenz by rilpivirine
Monotherapy with LOP/r or DRV/r (OKT4,MONET, MONOI)

Switching EFV/TDF/FTC to RPV/TDF/FTC

Switching from EFV to RPV resulted in reduced RPV C_{min} up to 25% for approximately 4 weeks in a healthy volunteer PK study[4]



Primary endpoint: Percentage of subjects with HIV-1 RNA <50 c/mL at week 12 after switching
- ITT population Snapshot analysis

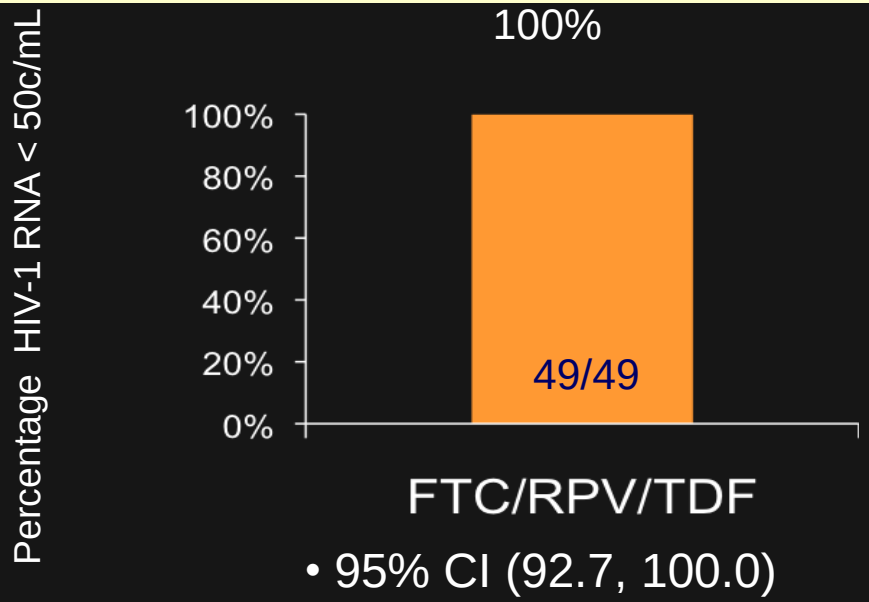
Secondary endpoints: Safety and tolerability of FTC/RPV/TDF over 24 & 48 weeks
HIV-1 RNA <50 c/mL at Week 24 and Week 48 after switching
Pharmacokinetics of RPV after switching from EFV

ITT = intent to treat

Mills A, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-974c.

Baseline Characteristics and Virologic Results

Baseline parameter	FTC/RPV/TDF N=49
Male, percentage	92
Median age, years	39
Race, percentage Caucasian	80
Median treatment duration prior to switch, years	2.5
Median CD4 cell count, cells/mm^3	653



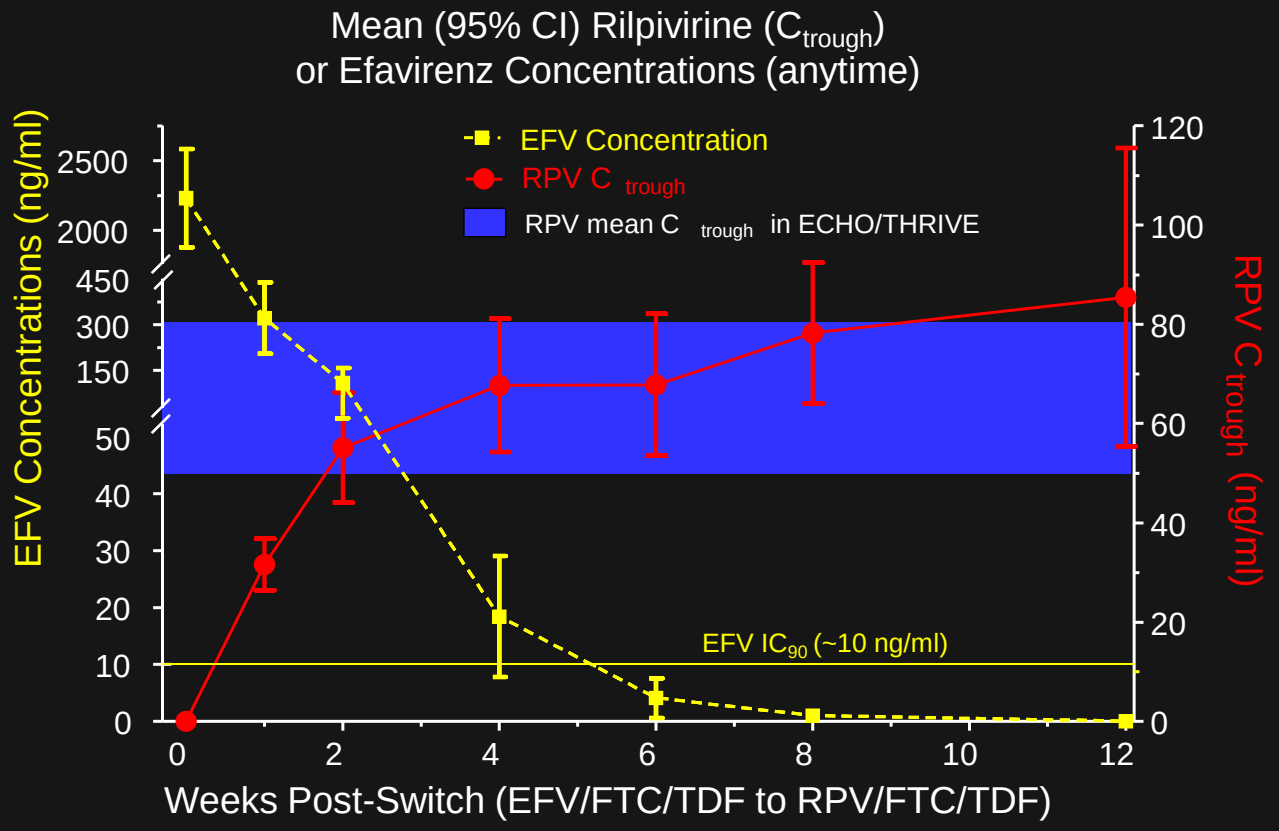
• 95% CI (92.7, 100.0)

- 50 subjects enrolled in the study
- 49 subjects dosed and completed the study through 12 weeks
  - One subject withdrew consent before dosing

- All subjects were virologically suppressed at the week 12 visit
- No subjects had events leading to study drug discontinuation

Mills A, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-974c.

Secondary Endpoint: RPV PK after Switching from EFV



- EFV mean C_{trough} above IC_{90} (~10 ng/ml*) up to ~4 weeks
- No subject had RPV below quantifiable levels at any visit
- RPV mean C_{trough} within historic range by 2 weeks

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

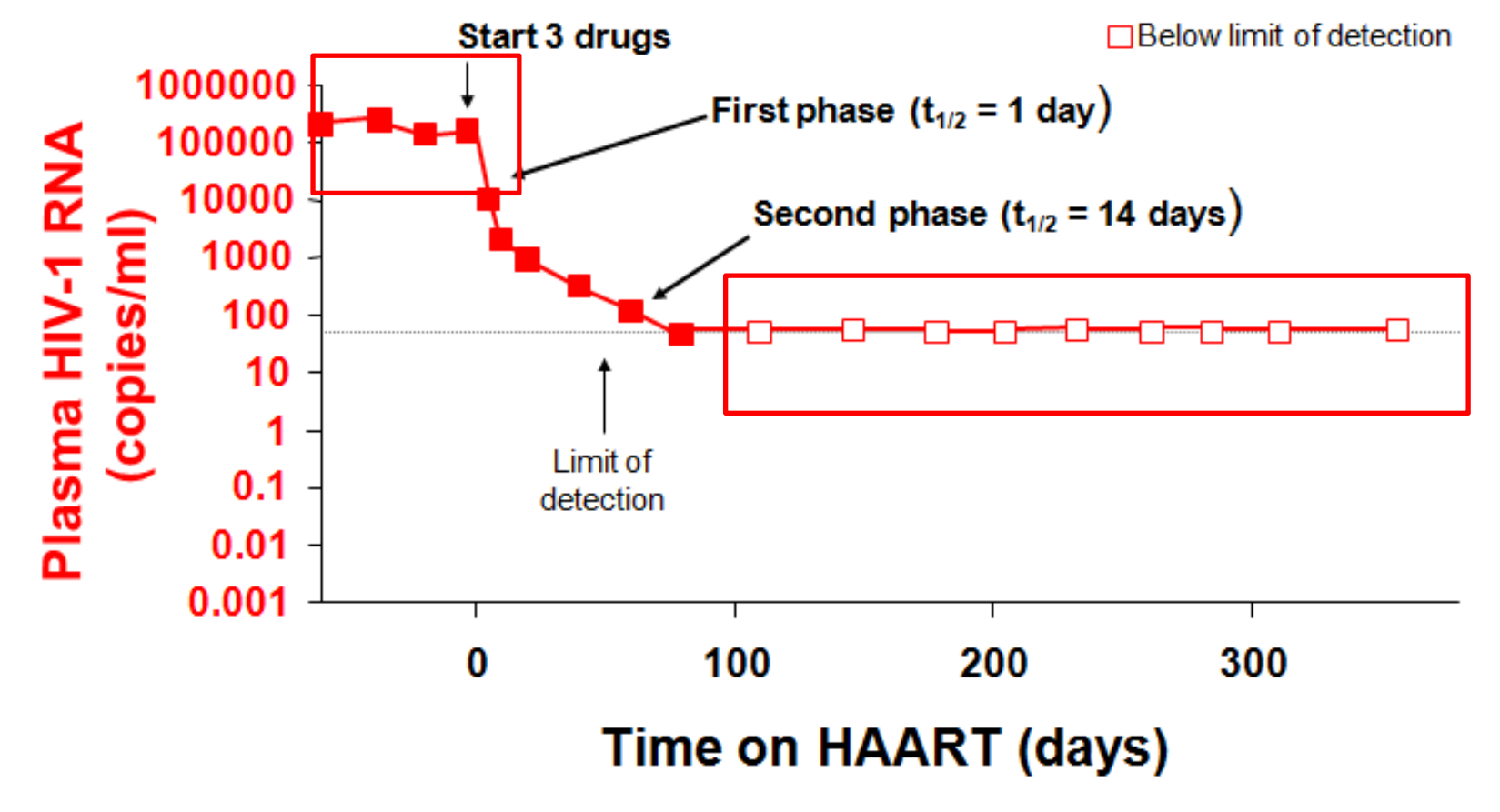
*protein-binding adjusted; Corbett JW, et al. J Med. Chem 2000:43;2019-2030

ART year 2012: When & how to switch cART in virologically suppressed patients

Switching strategies usually consist on:

Replacing thymidine by non thymidine analogs
Replacing T20 by raltegravir (EASIER)
Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)
atazanvir/r (SWAN, ATAZIP)
raltegravir (SWITCHMRK, SPIRAL)
Replacing efavirenz by rilpivirine
Monotherapy with LOP/r or DRV/r (OKT4,MONET, MONOI)

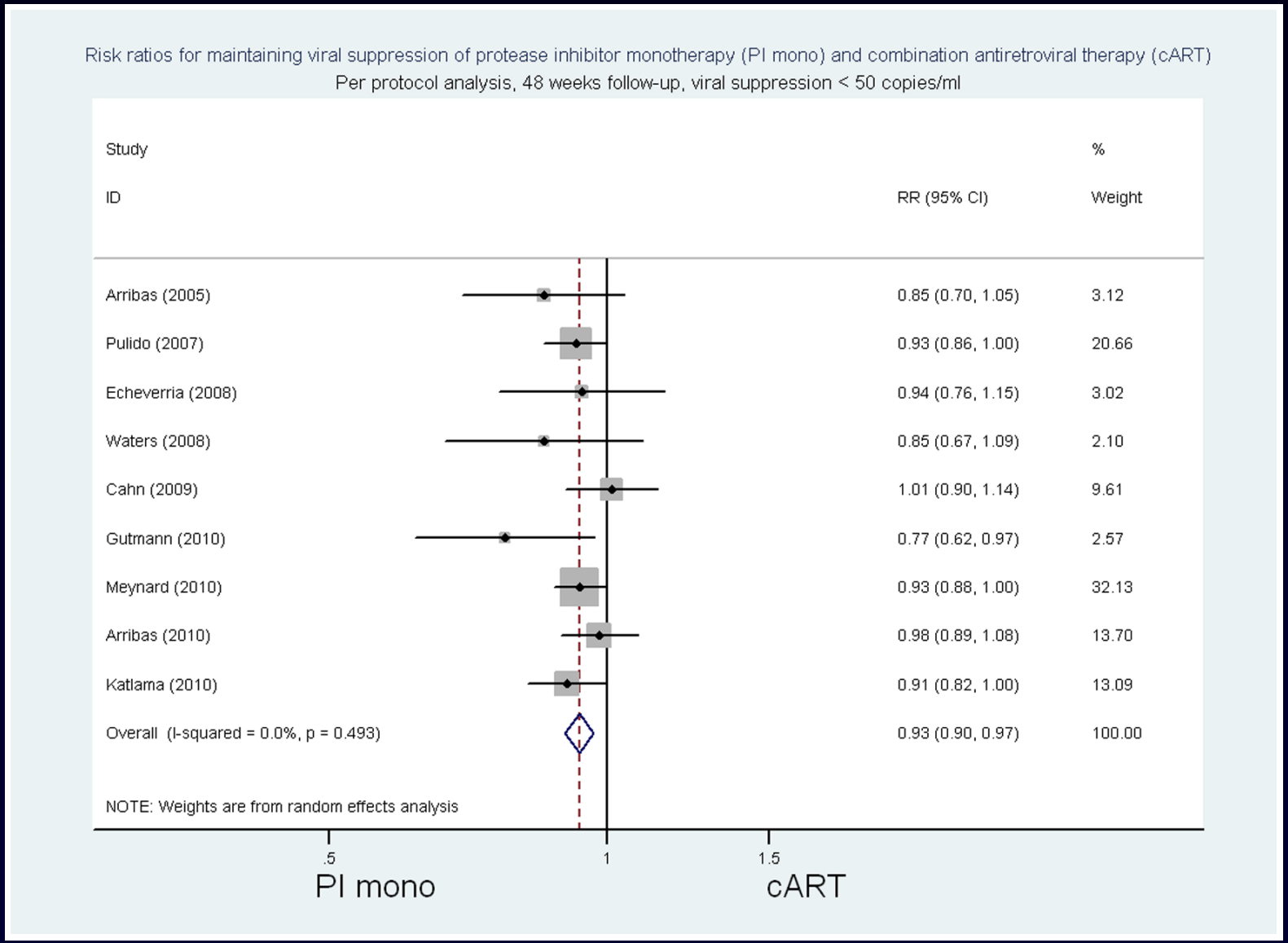
Dynamics of HIV-1 Replication in Patients on Antiretroviral Therapy



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	

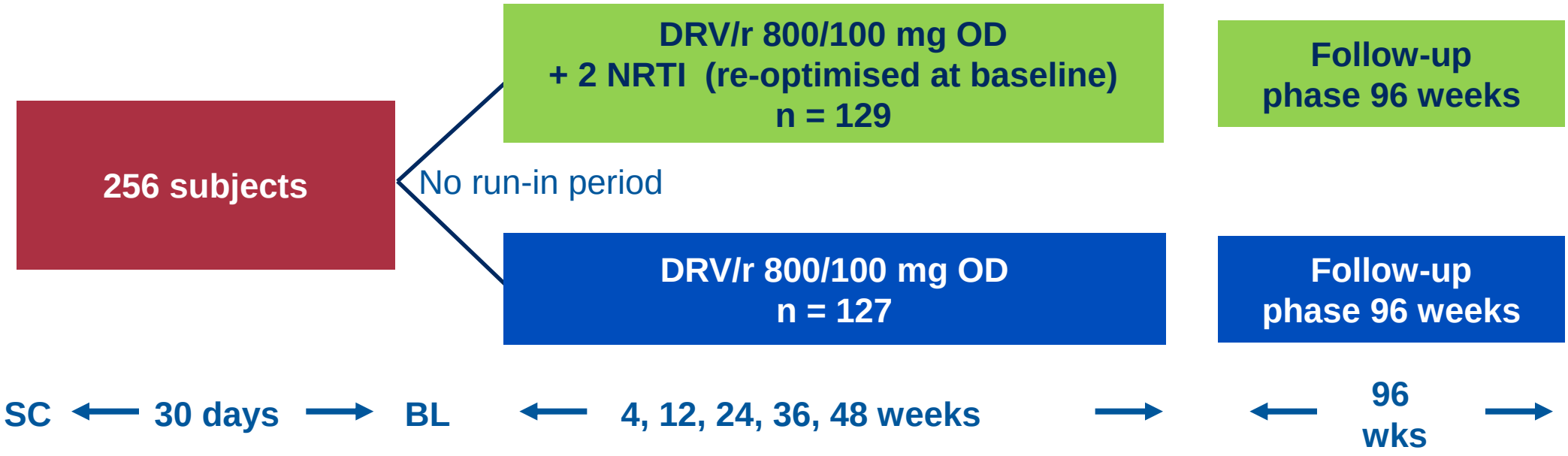
XV WAC 2004 MoOrB1057. 4th IAS 2007 WEPEB034. J Infect Dis. 2008 15;198:234. JAIDS 2005;40:280–287. AIDS. 2008;11:F1-9. XVI IAC 2006; #TUAB0102. EACS 2009 PS4/5 .J Infect Dis. 2009 15;199:866. AIDS 2007; 21:1309–1315. JAIDS 2007;44:417. EACS 2009 PS4/6. 5th IAS 2009 AIDS 2009 (in press)



Mathis S et al. PLoS ONE 6(7): e22003. doi:10.1371/journal.pone.0022003

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

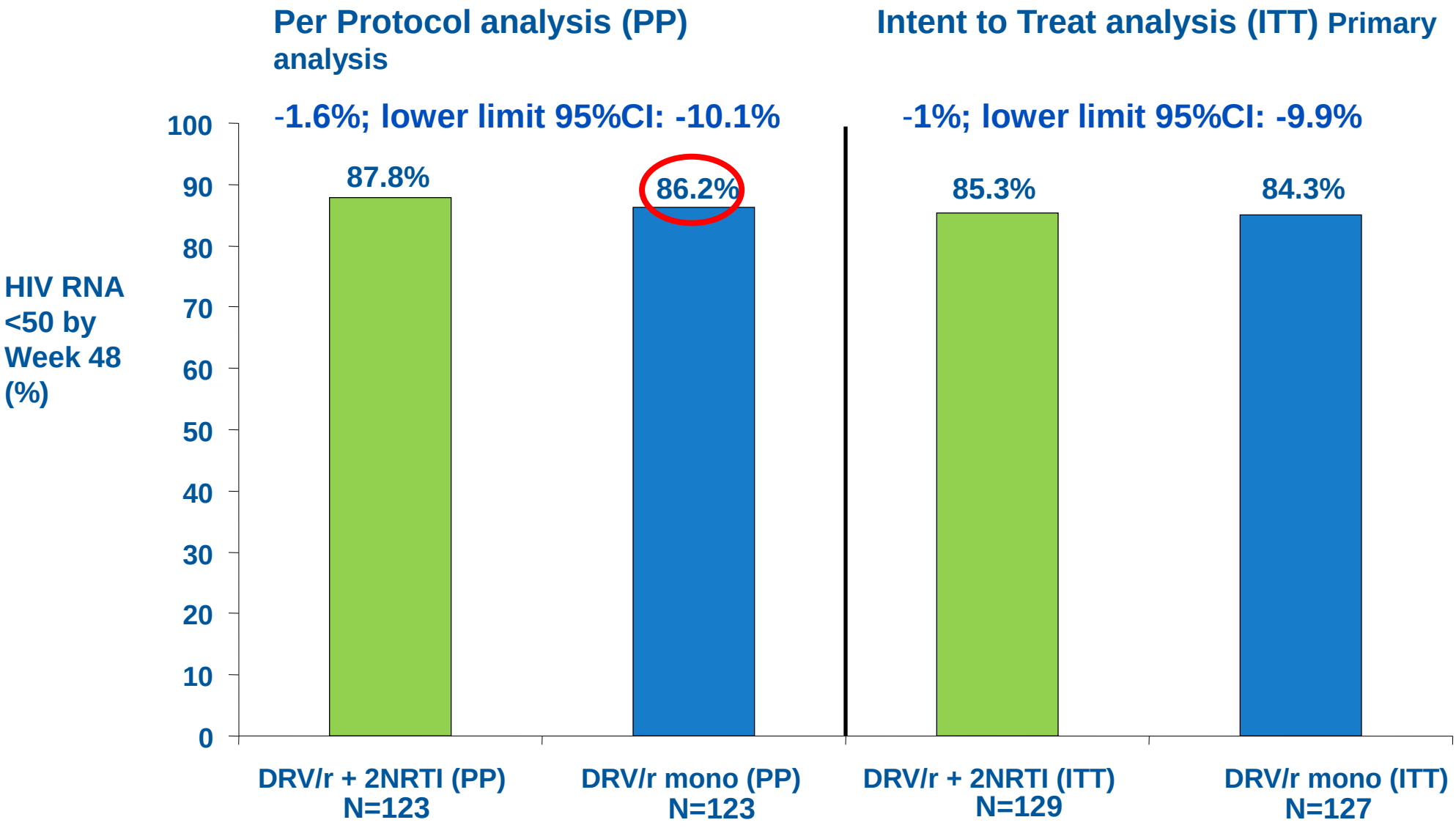


Primary Endpoint: HIV RNA< 50 at week 48 (TLOVR). Per Protocol, Switch = Failure

- 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: Primary Efficacy Analysis: HIV RNA <50 copies/mL at Week 48, TLOVR, S = F



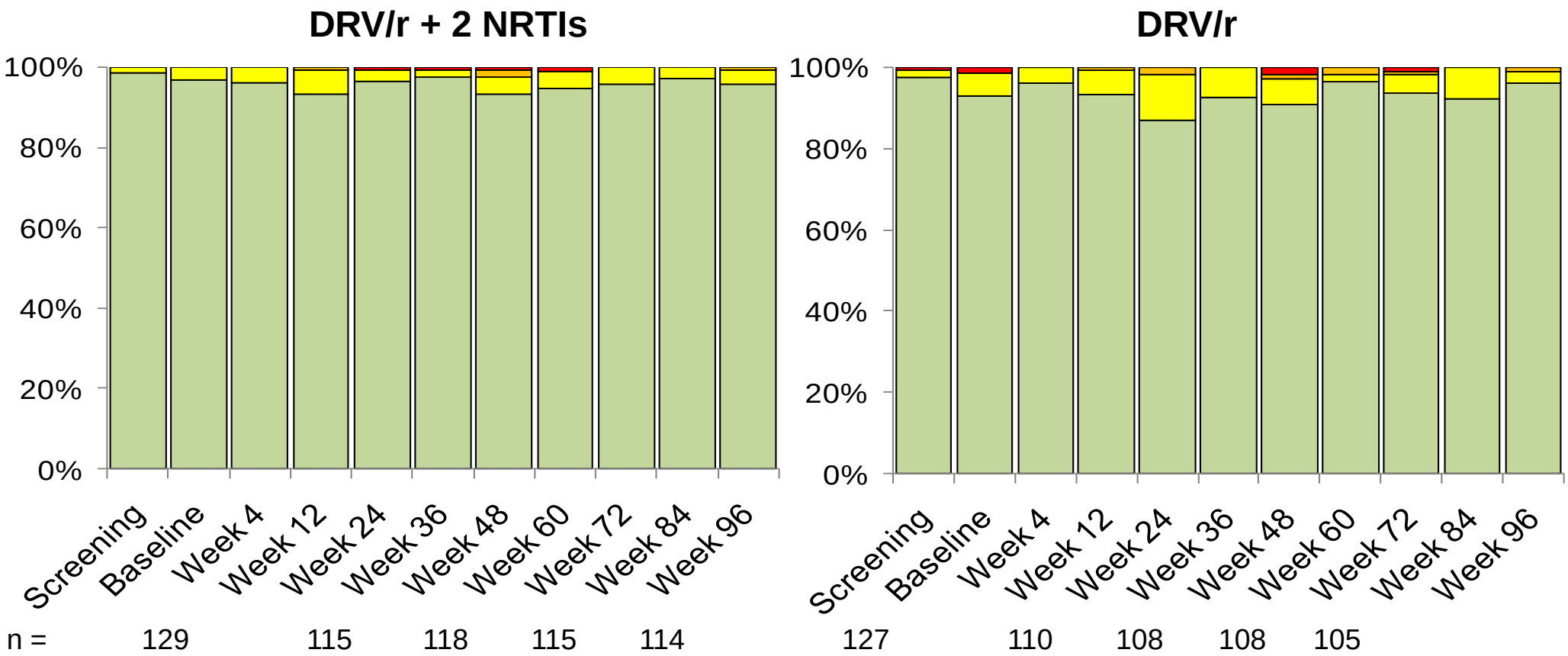
J. Arribas et al, AIDS 2010

MONET: HIV RNA by study visit (observed data)

HIV RNA>50 copies/mL in 47/1051 samples (4.5%)

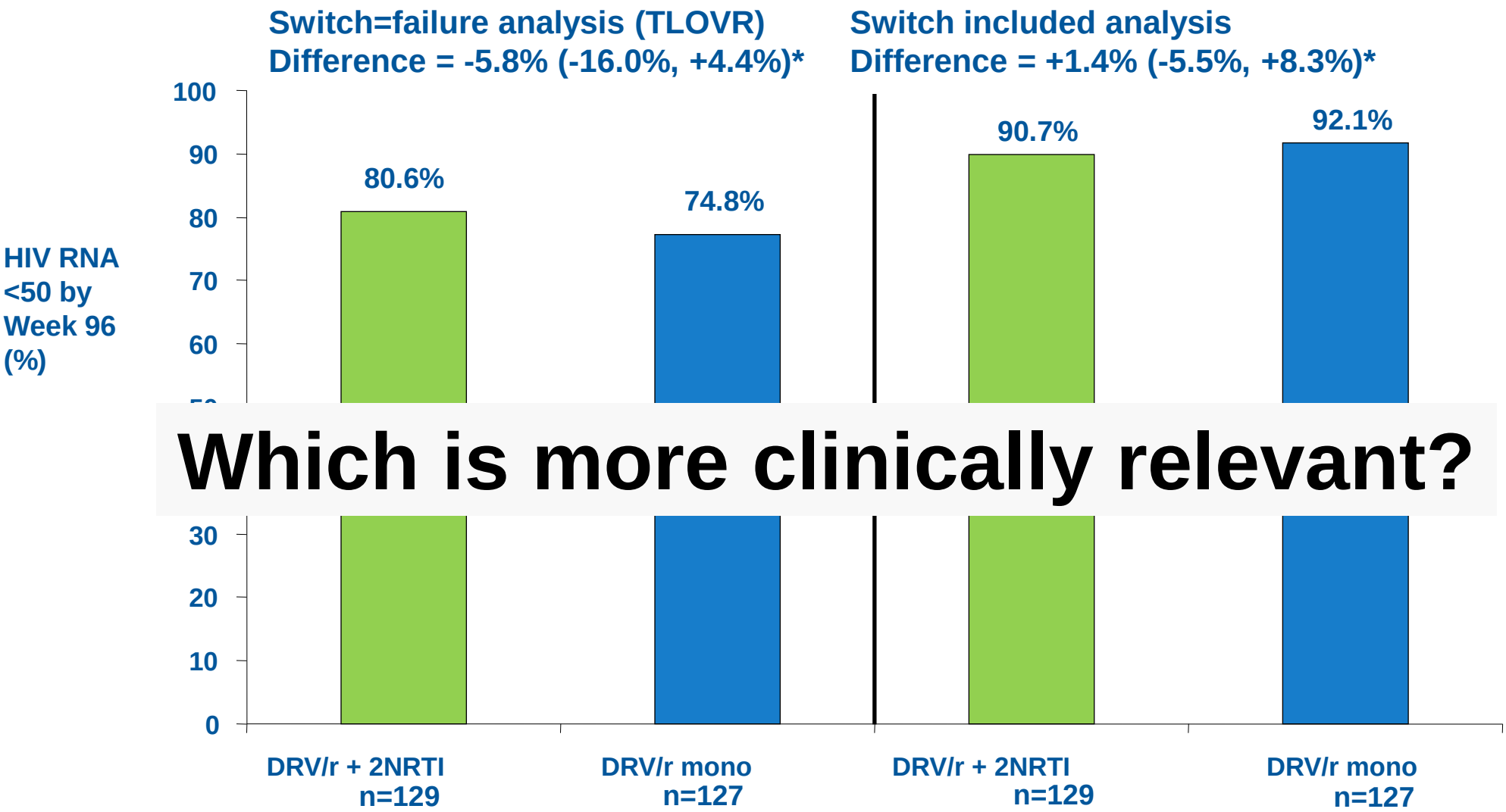
>1000 copies/ml
400-1000 copies/ml
50-400 copies/ml
<50 copies/ml

HIV RNA>50 copies/mL in 69/1009 samples (6.9%)



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

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



Which is more clinically relevant?

* 95% confidence intervals from univariate analysis

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

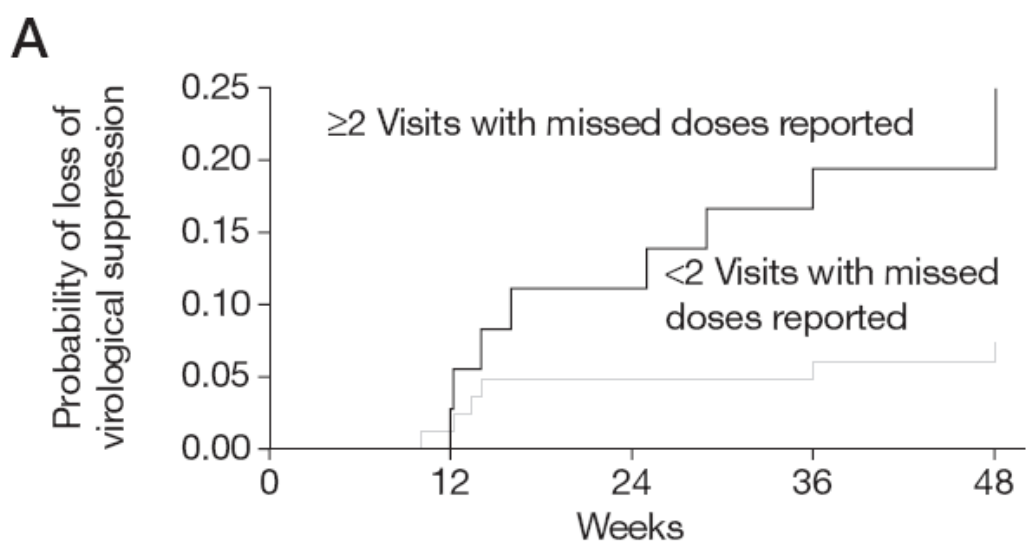
MONET Week 144 analysis: Major IAS-USA Genotypic mutations when HIV RNA >50 copies/mL

Genotypic results	DRV/r + 2NRTI N=129	DRV/r N=127
Number of patients with genotypes performed (RNA >50 copies/mL)	40	47
Patients with at least 1 successful genotype	23	31
Patients with genotype(s) showing no primary PI or DRV mutations, M184V or NRTI mutations	**22/23 (96%)**	**30/31 (97%)**
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 genotypic resistance

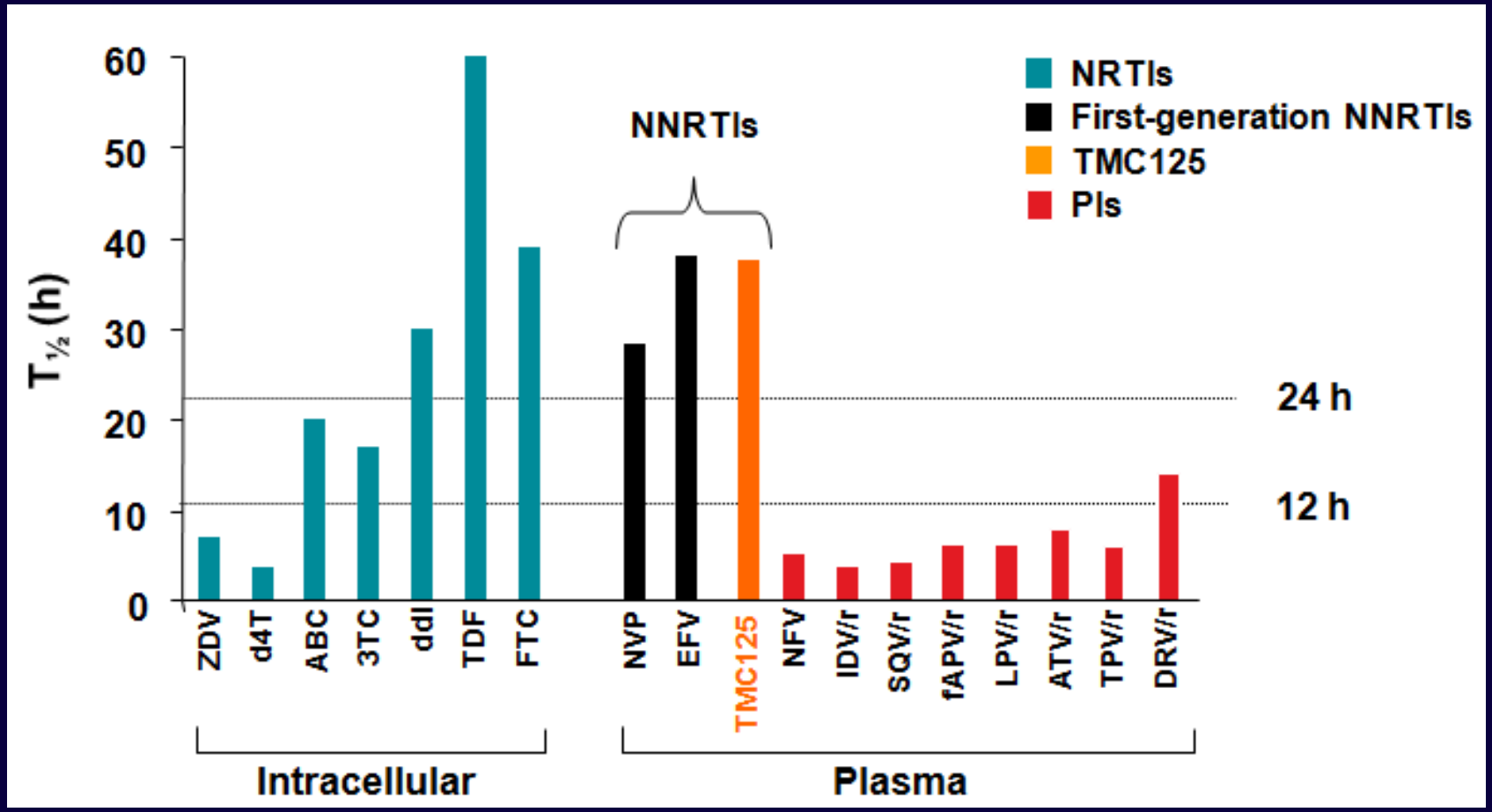
Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression.

Figure 2. Probability of loss of virological suppression after treatment simplification stratified by number of visits with reported missed doses and by nadir CD4+ T-cell count



Pulido P et al. Antivir Ther. 2009;14(2):195-201.

Half-life of antiretrovirals



1. Moore KH, et al. AIDS 1999;13:2239-50.
2. Kewn S, et al. Antimicrob Agents Chemother 2002;46:135-43.
3. Hawkins T, et al. 5th IWCPHT, 2004. Abstract 2.4.
4. Product SmPCs.
5. Tibotec, data on file.

OXFORD JOURNALS

Journal of Antimicrobial Chemotherapy

Journal of Antimicrobial Chemotherapy Advance Access published June 13, 2011

J Antimicrob Chemother
doi:10.1093/jac/dkr229

Protease inhibitor monotherapy and the CNS: peace of mind?

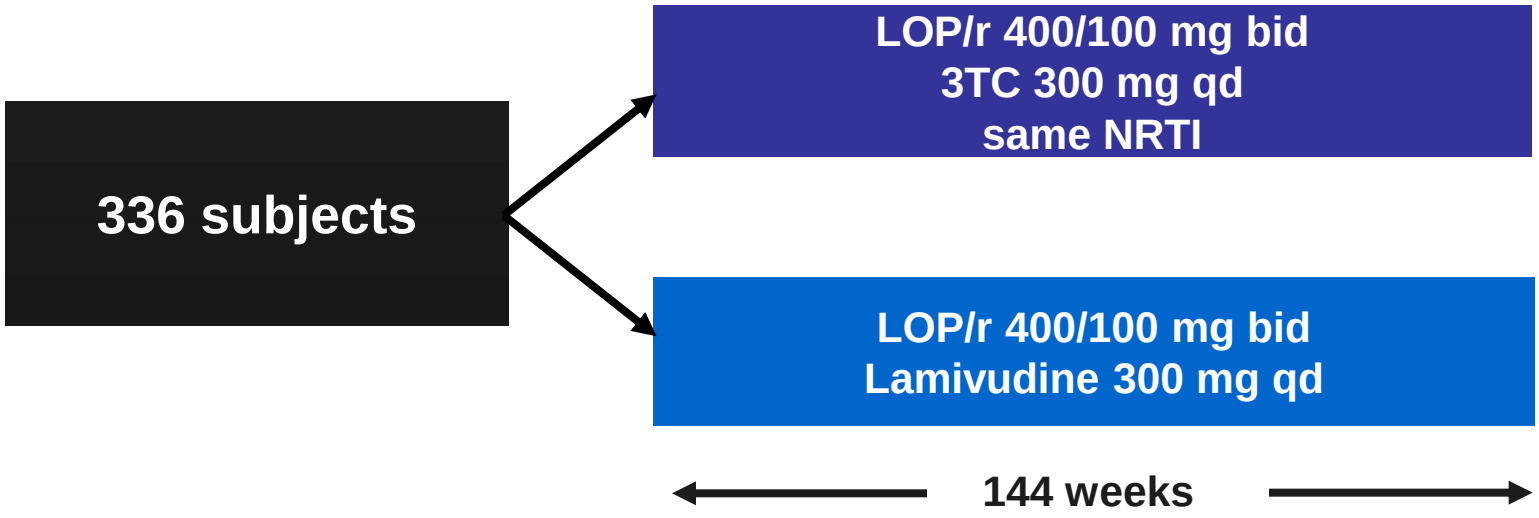
Ignacio Perez-Valero[1], Carmen Bayon[2], Irene Cambron[2], Alicia Gonzalez[1] and Jose R. Arribas[1]*

[1]Servicio de Medicina Interna, Unidad VIH, Hospital La Paz, IdiPAZ, Madrid, Spain; [2]Servicio de Psiquiatría, Hospital La Paz, IdiPAZ, Madrid, Spain

*Corresponding author. Consulta Medicina Interna 2, Hospital La Paz, Paseo de la Castellana 261, 28046, Madrid, Spain. Tel: +34-91-207-1676; Fax: +34-91-729-0033; E-mail: jrarribas.hulp@salud.madrid.org

OLE - Trial Design

- Inclusion: Taking Lop/r+3TC/FTC+1 NRTI for at least 2 months
- HIV RNA <50 copies/mL for at least 6 months
- No history of virological failure to PI, 3TC/FTC or known mutations

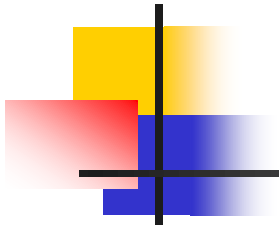


Primary Endpoint: failure at week 48 (ITT S or NC=F).

- **2 consecutive HIV RNA > 50 copies/mL .**

- **JR Arribas, JM Gatell y cols. SPAIN, FRANCE**

ART year 2012: When & how to switch cART in virologically suppressed patients



1. Current scenario
2. Objectives & limitations
3. Stable & suppressed patients
4. In summary…

In summary….

- Ultimate goal of ART is an ajusted life expectancy close to general population

- The situation of many stable & suppressed patients can be potentially improved (including lowering the costs) without increasing the risk of loosing the virological suppression if the candidates are well selected.

- Several strategies have been successfully tested going as far as PI/r monotherapy

Institut Clínic d'Infeccions i Immunologia
Infectious Diseases & AIDS Division

Clinical Group

JL Blanco
C Cáceres
P Callau
M Calvo
S Corral
F Etcheverri
E Fernández
JM Gatell
F García
M Larrousse
E Lazzari
A León
M Loncà
M Laguno
M López-Diéguez
J Mallolas
C Manzardo
D Martínez
E Martínez
M Martínez
C Mensa
A Milinkovic
JM Miró
A Moreno
I Pérez
L Zamora

External Colaborators

J Alcamí
B Autran
M Lederman
D Nixon
G Pantaleo
B Walker

Immunology Lab

C Alvarez
N Climent
R Fernández
T Gallart
A García
J Joseph
MJ Maleno
L Miralles
M Plana
C Rovira
S Sánchez
V Sánchez
N Saubí
S Varea
E Yuste

Clinical Trials Coordination

JA Arnaiz
X Carné
A Cruceta
J Pich
M Sarasa

S Varea

Virology Lab

M Arnedo
N Boulanger
T Escribá
C García
M García
C Gil
C Hurtado
S Lyonnais
A Merino
G Mirambeau
L Muñoz

CLÍNIC BARCELONA Hospital Universitari

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

RIS RD 06/0006 Red Española de Investigación en SIDA Spanish AIDS Research Network

HIVACAT


CARMEN