Facing the challenge of the HIV patient in the near future / co-morbidities

A. The HIV infected individual

B. The pandemic

C. In summary….

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CARMEN

Facing the challenge of the HIV patient in the near future / co-morbidities

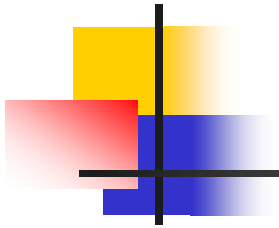
A. The HIV infected individual

Achieving an Undetectable Plasma Viral Load

and

What else beyond that ?

Undetectable Plasma Viral Load and beyond ..



1. Undetectable plasma VL
2. HIV eradication or at least functional cure
3. Residual HIV replication (ART intensification)
4. Reduction of reservoirs
5. Detection below 50, blips & low level viremia
6. Accelerate & increase CD4 response
7. Avoid mid-long term "toxic actives"
8. Salvage therapy in case of failure
9. In summary…

Hospital Clinic. Barcelona, June 2013. N=4500

Fig

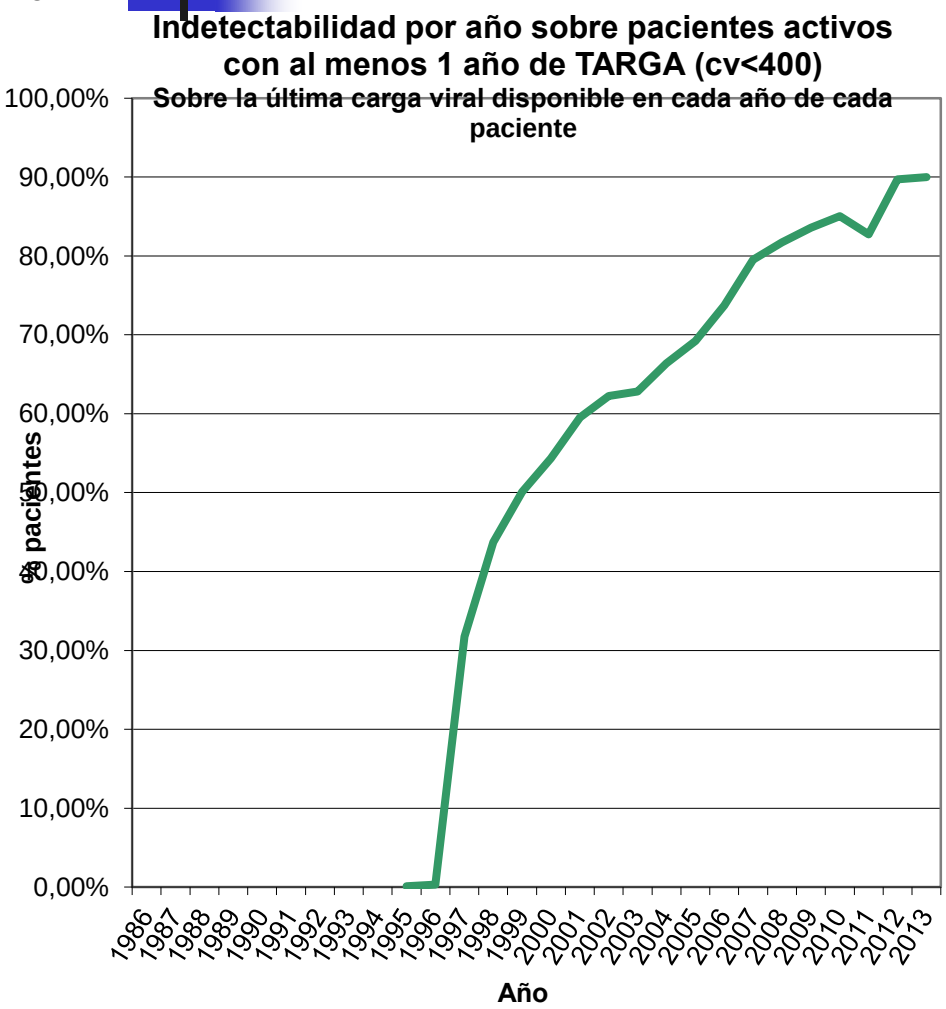
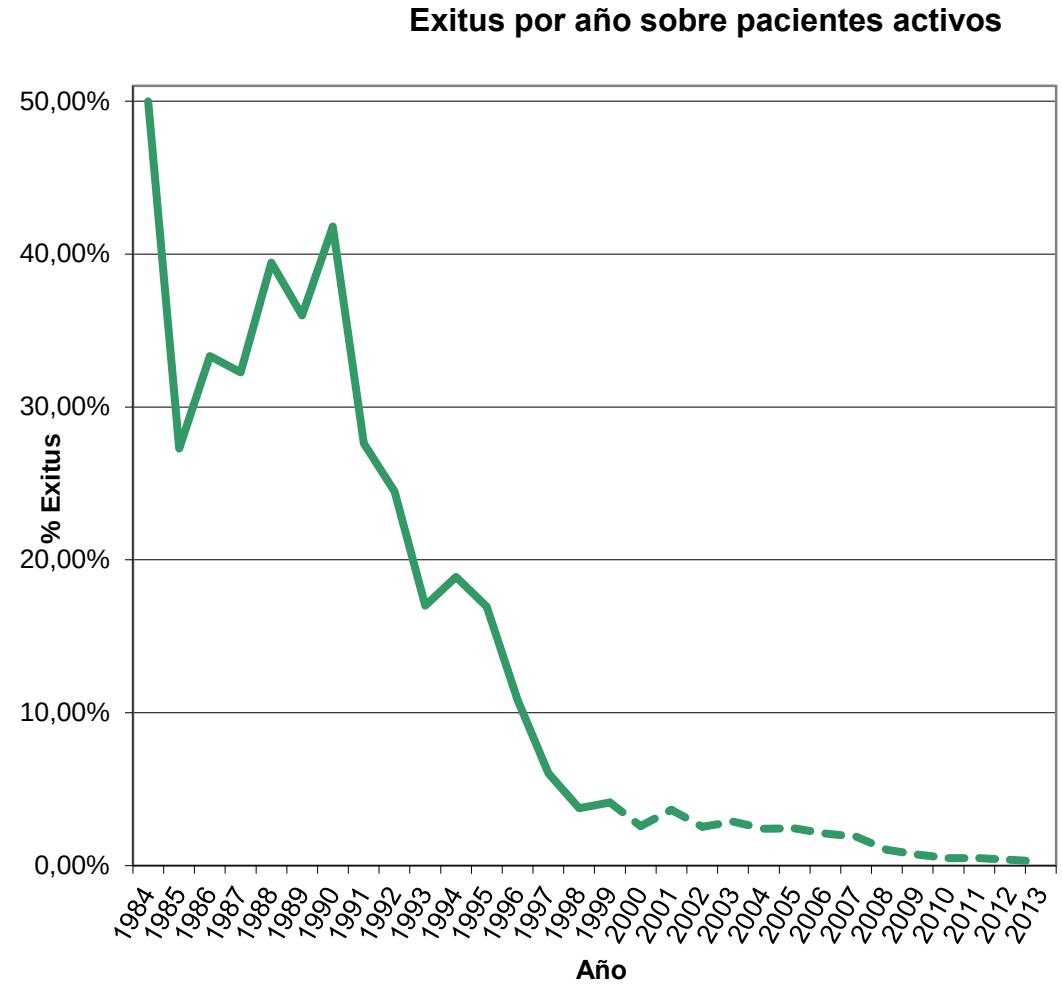
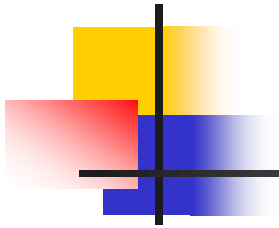


Fig.




How old is old enough … ?



Initial ART, year 2013

Early: viral replication is bad irrespective of CD4 count (350, 500 ??).

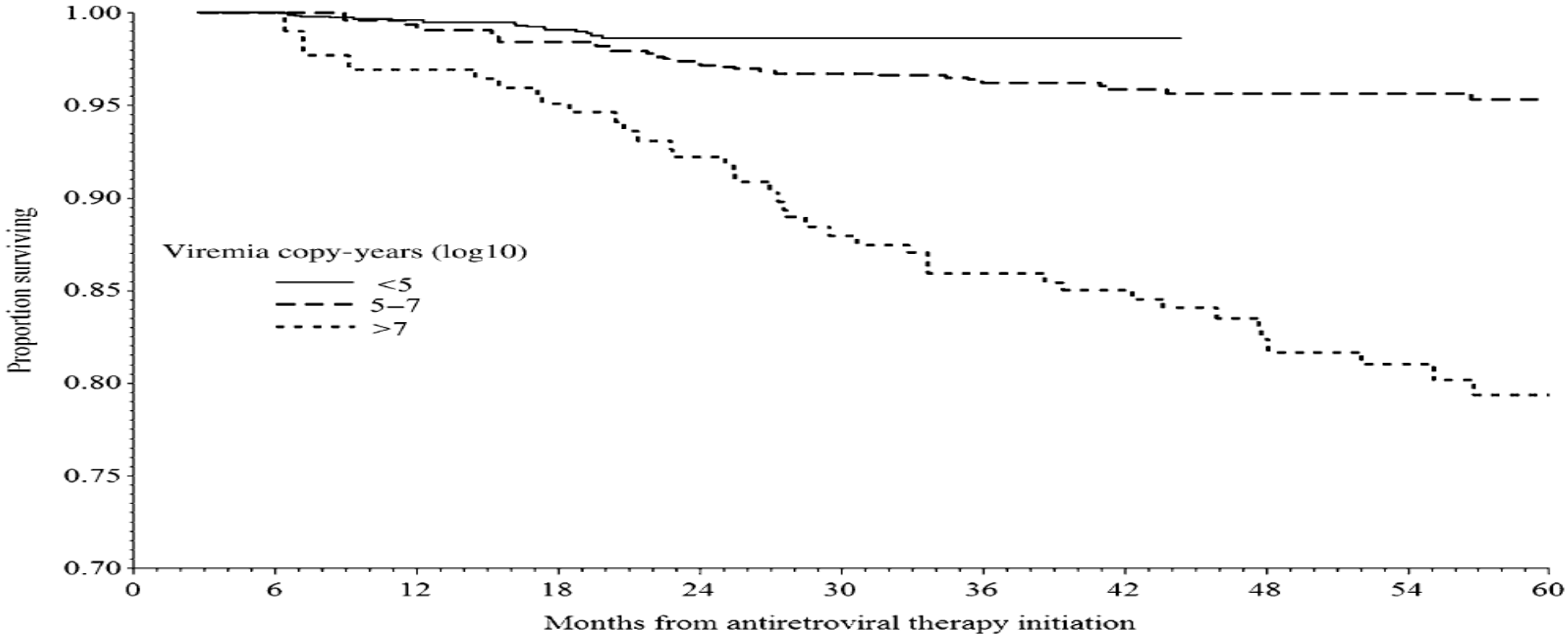
Hard: >=90% response

What: Old vs. new paradigms

Viremia Copy-Years Predicts Mortality Among Treatment-Naive HIV-Infected Patients Initiating Antiretroviral Therapy

Clin Infect Dis, 2011

Michael J. Mugavero,[1,a] Sonia Napravnik,[2,3,a] Stephen R. Cole,[3] Joseph J. Eron,[2,3] Bryan Lau,[4] Heidi M. Crane,[5] Mari M. Kitahata,[5] James H. Willig,[1] Richard D. Moore,[6] Steven G. Deeks,[7] Michael S. Saag,[1] and on behalf of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort Study



Viremia copy-years (log_{10})	Number at risk									
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
<5	1692	1414	1105	317	79	18	2			
5–7	245	289	332	833	851	727	606	509	414	316
>7	90	135	181	192	183	169	152	132	122	108

Initial ART, year 2013

Early: viral replication is bad irrespective of CD4 count (350, 500 ??).

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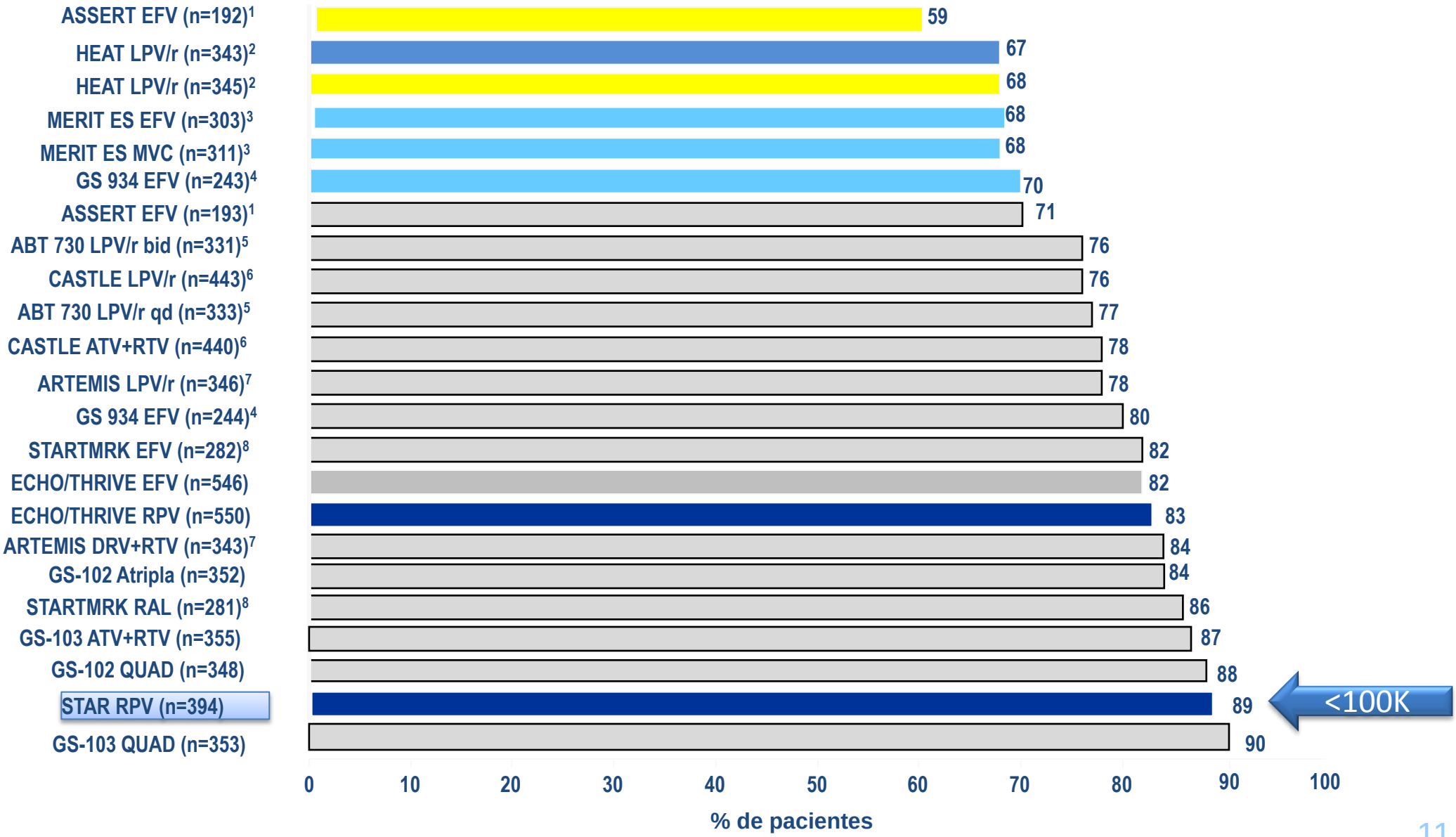
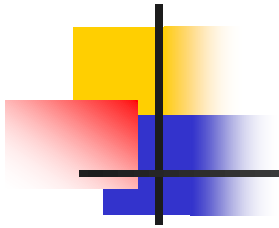
What: Old vs. new paradigms

Eviplera: Tasas de respuesta virológica entre las más altas registradas en estudios previos en pacientes naïve



Fuente: **Stephan** C, Hill A, Sawyer W, van Delft Y, et al. HIV Med. 2012 Nov 22. [Epub ahead of print]ºº



Initial ART, year 2013

Early: viral replication is bad irrespective of CD4 count (350, 500 ??).

Hard: >=90% response

What: Old vs. new paradigms

Recommended 1st line Regimen	EACS (10/2013)	DHHS (2/2013)	IAS (07/2012)
TDF/FTC/EFV	Preferred	Preferred	Recommended
TDF/FTC-DRV/r	Preferred	Preferred	Recommended
TDF/FTC-ATV/r	Preferred	Preferred	Recommended
TDF/FTC-RAL	Preferred	Preferred	Recommended
ABC/3TC-EFV	Preferred	Alternative	Alternative
ABC/3TC-(ATV/r or DRV/r)	Preferred	Alternative	Alternative
TD			ternative
AB			ternative
AB			No
ABC/3TC-RAL	No	Alternative	Alternative
TDF/FTC-NVP	Alternative	Alternative	
TDF/FTC/COBI/EVG	No	Alternative	
TDF/FTC/RPV ABC/3TC-RPV	Preferred	Alternative	
2 NRTI-MVC	Alternative	No	Alternative

2 NRTIs + 3rd Drug

Guidelines: What to start with?

	EACS[1]	DHHS[2]	IAS[3]
EFV[a]	✓	✓	✓
ATV/r	✓[c]	✓	✓
DRV/r	✓	✓	✓
RAL	✓	✓	✓
LPV/r	✓[c]	●[c]	●
MVC	●	✗	●
NVP[b]	●	●	✗
RPV	✗	●	✗
SQV/r	●[c]	✗	✗

✓ Recommended/preferred

● Alternative

✗ Not recommended/not mentioned as alternative

a. EFV not recommended in pregnant women or women without reliable/consistent contraception
b. NVP should not be used in women with >250 CD4 cells/mm^3 and men with >400 CD4 cells/mm^3
c. Preferred for pregnant women.

RAL	>	EFV	STARMRK
	?	ATA/r	ARDENT
	?	DRV/r	ARDENT

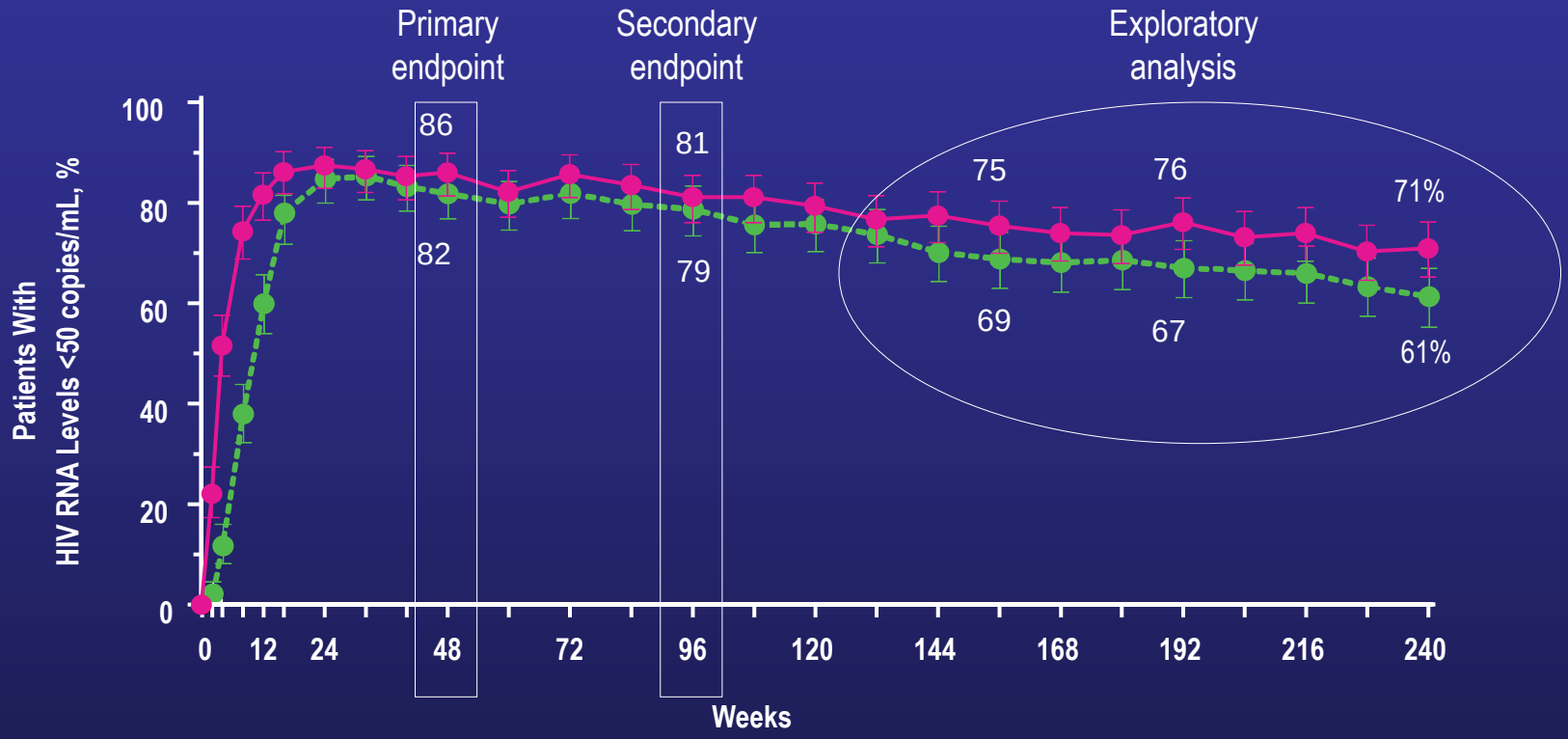
EVG	=	EFV	GS-102
	=	ATA/r	GS-103

DTG	=	RAL	Spring 2
	>	EFV	Single
	>	DRV/r	Flamingo

Almost no interactions (RAL & DTG)
Neutral lipid profile
Very quick response
Very good overall tolerance
Higher genetic barrier (DTG)

Percentage of Patients Achieving HIV RNA <50 Copies/mL (95% CI) Over Time

NC = F approach

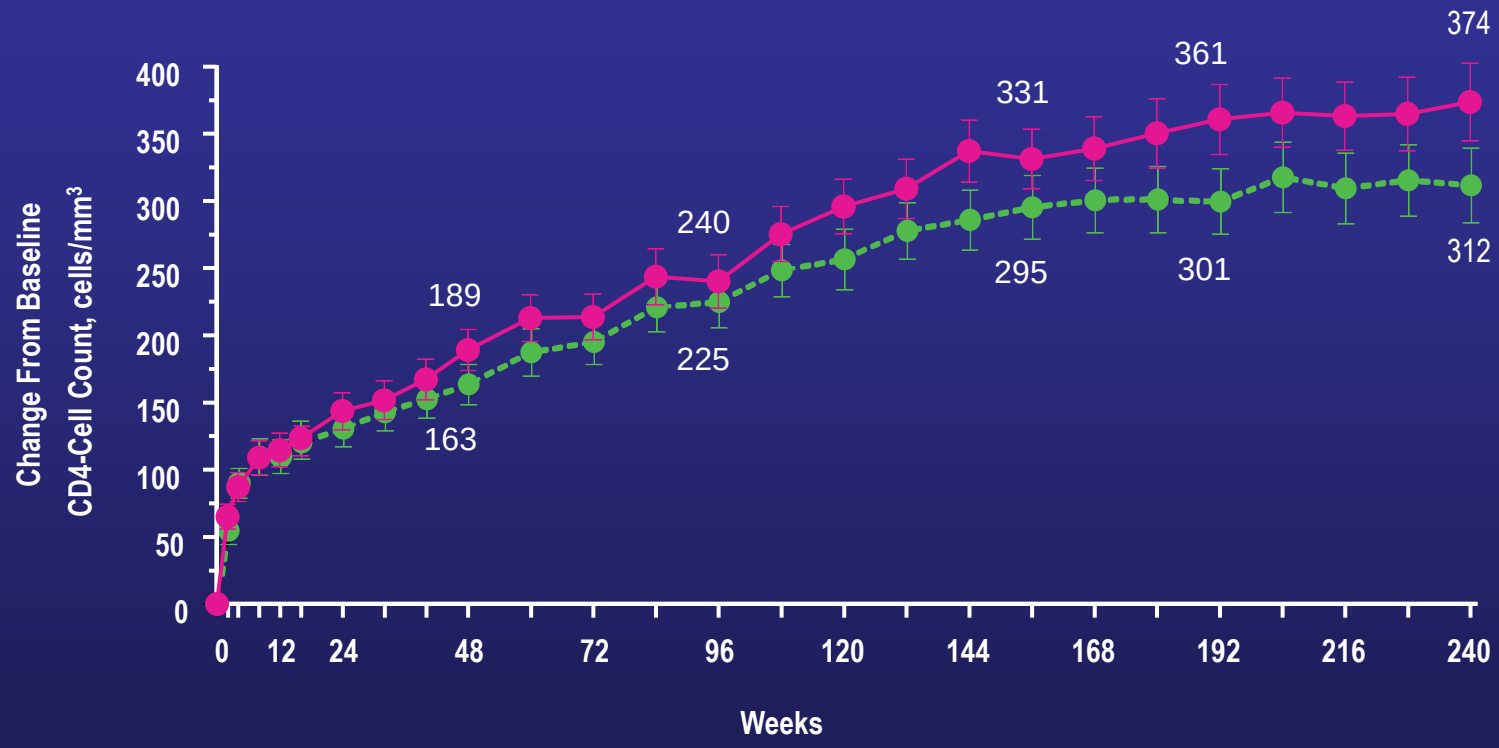


Number of Contributing Patients

Raltegravir 400 mg BID	281	278	279	280	281	281	277	280	281	281	277	279
Efavirenz 600 mg QHS	282	282	282	281	282	282	281	281	282	282	282	279

BID = twice daily; CI = confidence interval; F = failure; NC = noncompleter; QHS = once every night.

Change From Baseline in CD4-Cell Count (95% CI) Over Time



Number of Contributing Patients

Raltegravir 400 mg BID	281	272	266	258	255	250	240	235	231	235	227	222
Efavirenz 600 mg QHS	281	268	266	251	252	243	234	228	224	220	218	212

BID = twice daily; CI = confidence interval; QHS = once every night.

Resistance Frequency by Treatment Group

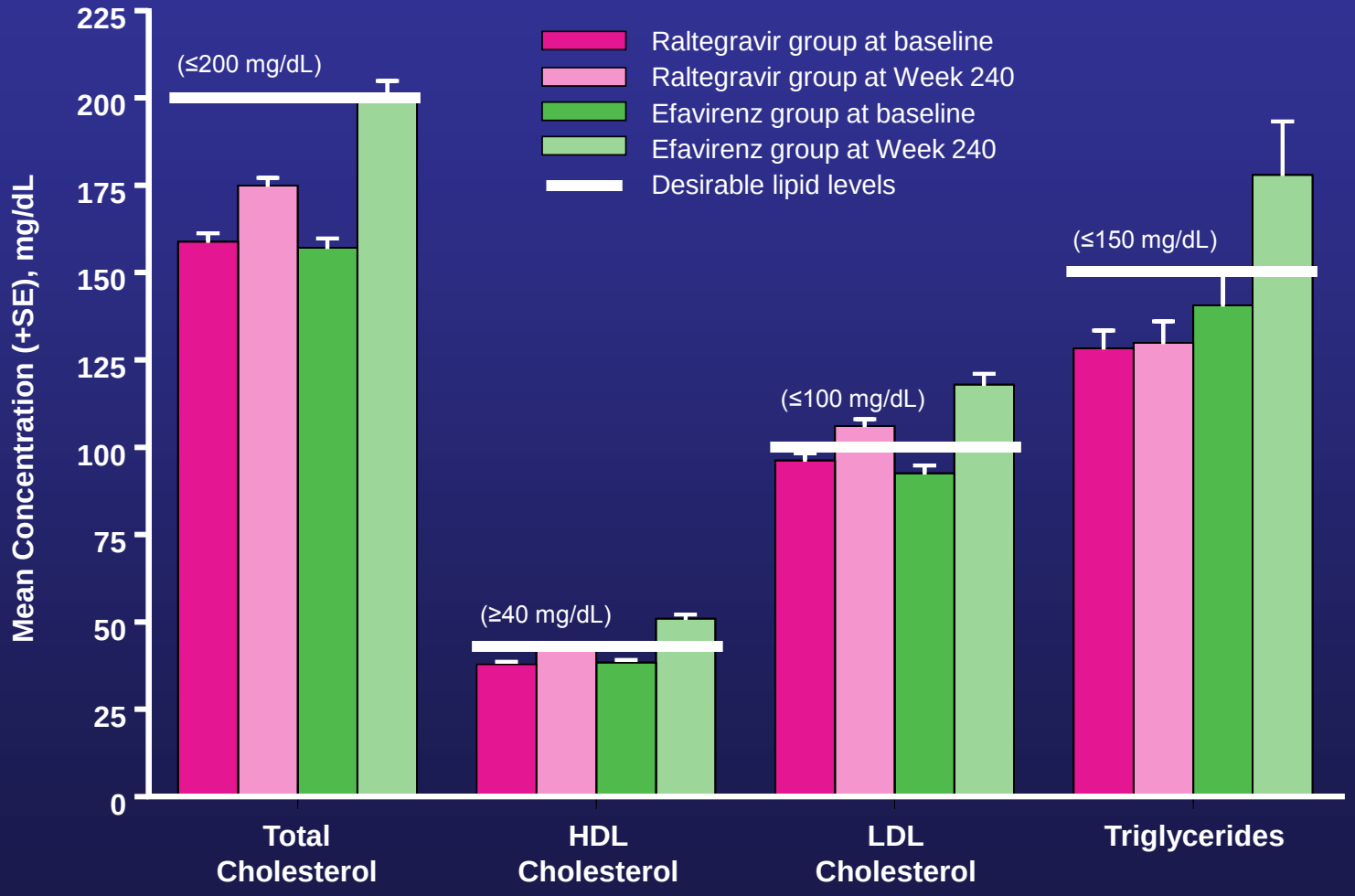
	RAL Group (n = 281)	EFV Group (n = 282)
Virologic failure, n (%) (confirmed vRNA level ≥50 copies/mL)	55 (19.6)	59 (20.9)
Resistance data available, n (%) (vRNA level >400 copies/mL)	23 (8.2)	20 (7.1)
RAL or EFV resistance alone, n	1	7
RAL or EFV resistance and NRTI resistance, n	3	3
NRTI resistance alone, n	3	2

EFV = efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; vRNA = viral RNA.

Adverse Event Summary

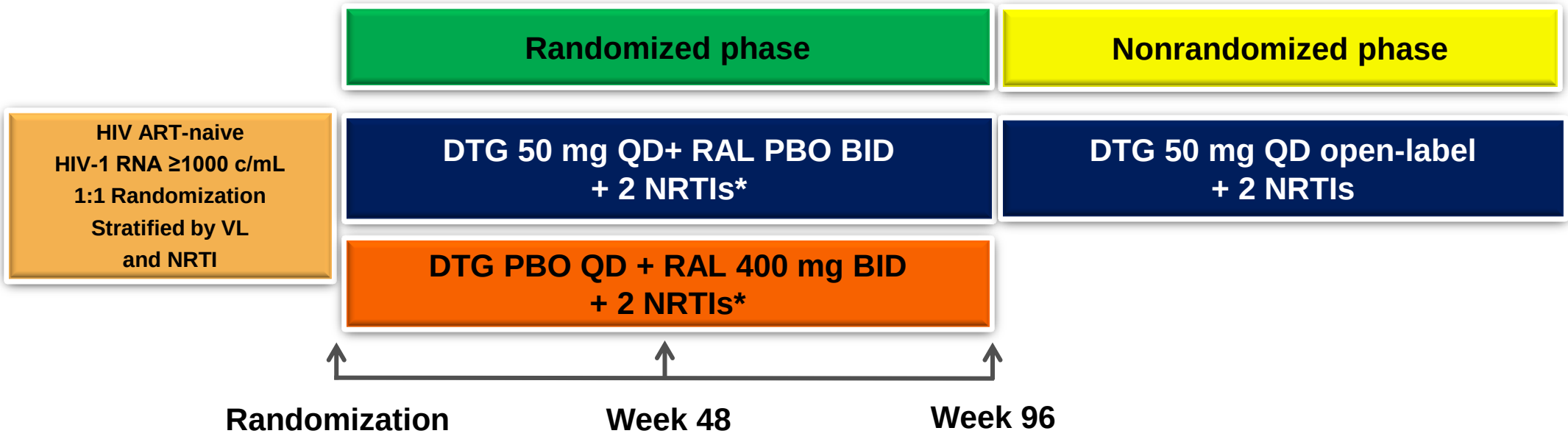
Patients	RAL Group (n = 281) n (%)	EFV Group (n = 282) n (%)	Difference (RAL – EFV) % (95% CI)	*P* value
With ≥1 AEs	271 (96.4)	276 (97.9)	–1.4 (–4.6, 1.5)	0.325
With no AEs	10 (3.6)	6 (2.1)	1.4 (–1.5, 4.6)	0.325
With drug-related AEs	146 (52.0)	226 (80.1)	–28.2 (–35.5, –20.6)	<0.001
With serious AEs	57 (20.3)	57 (20.2)	0.1 (–6.6, 6.7)	1.000
With serious drug-related AEs	8 (2.8)	7 (2.5)	0.4 (–2.6, 3.3)	0.801
Who died	5 (1.8)	5 (1.8)	0.0 (–2.5, 2.6)	1.000
D/C due to AEs	14 (5.0)	25 (8.9)	–3.9 (–8.3, 0.3)	0.096
D/C due to drug-related AEs	3 (1.1)	14 (5.0)	–3.9 (–7.2, –1.2)	NPS
D/C due to serious AEs	11 (3.9)	10 (3.5)	0.4 (–3.0, 3.8)	NPS
D/C due to serious drug-related AEs	1 (0.4)	2 (0.7)	–0.4 (–2.2, 1.3)	NPS

Fasting Lipid Levels at Baseline and Week 240 Compared With NCEP Goals[a]



[a]Taken from the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Final Report. NIH Publication No. 02-5215 September 2002.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program; SE = standard error.

SPRING-2 (ING113086) Study Design



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

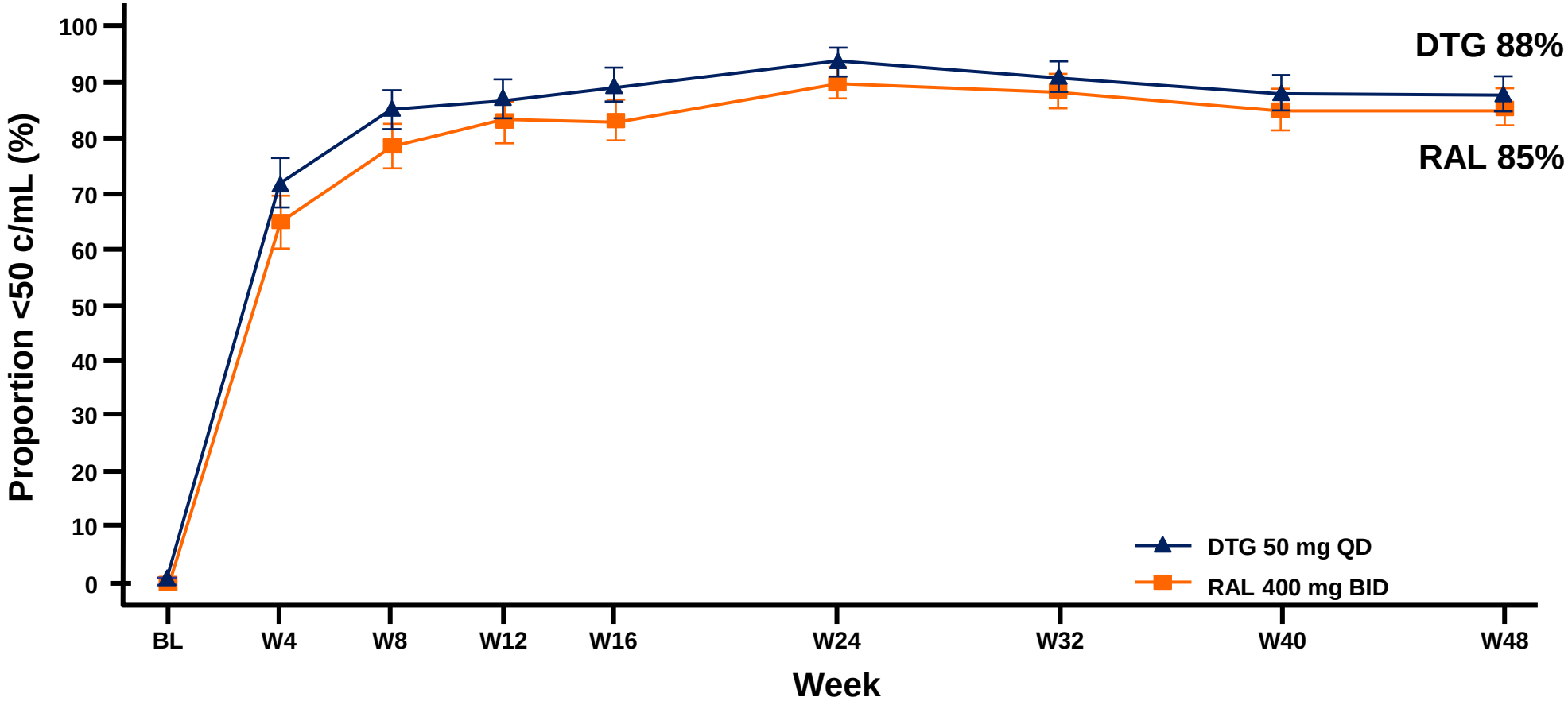
Phase III, randomized, double-blind, double-placebo, multicenter, parallel-group, non-inferiority study, ART-naive patients

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%

Lancet 2013; 381: 735–43

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)

Protocol-Defined Virologic Failure (PDVF): Genotype

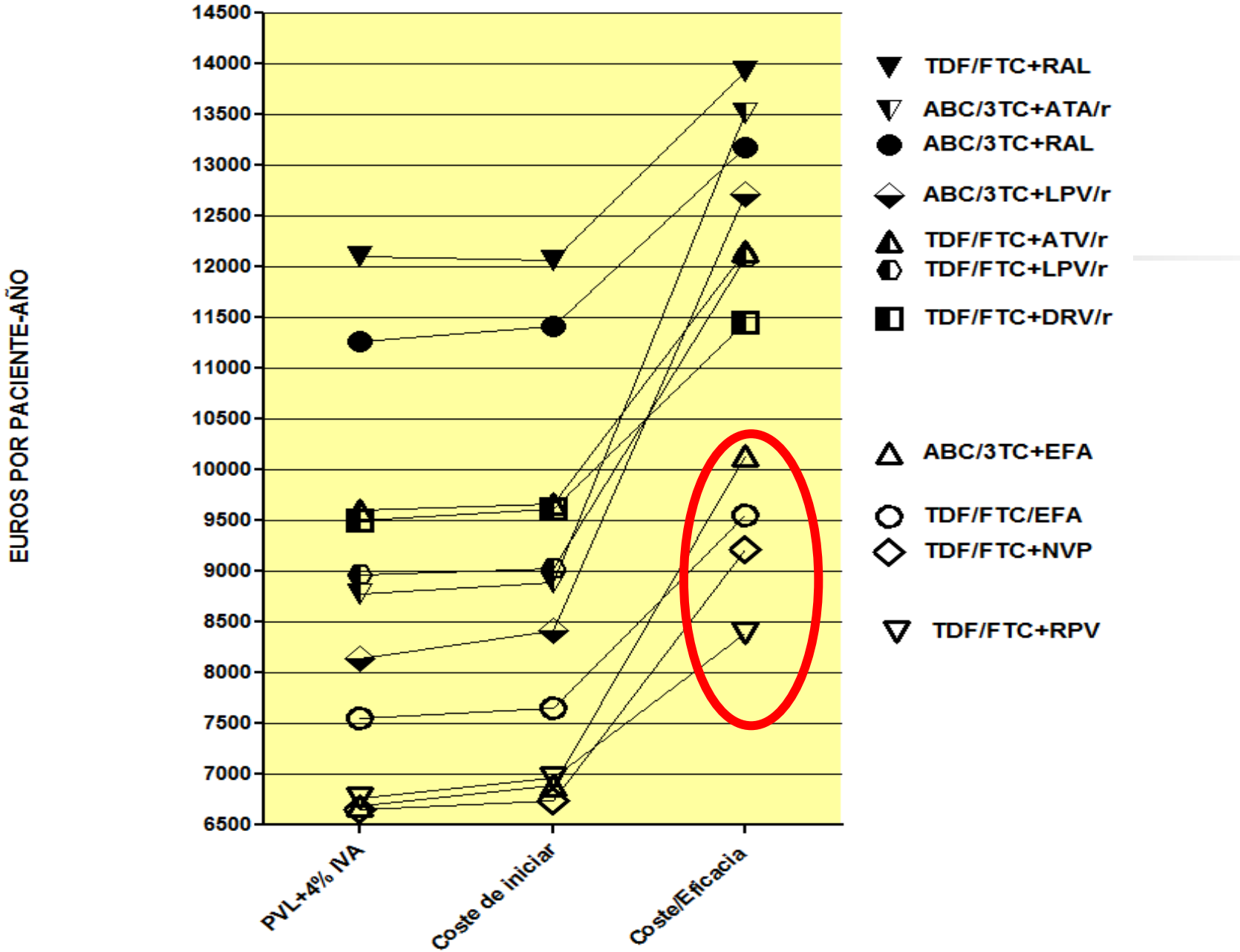
- **Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected through Week 48**

	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]**

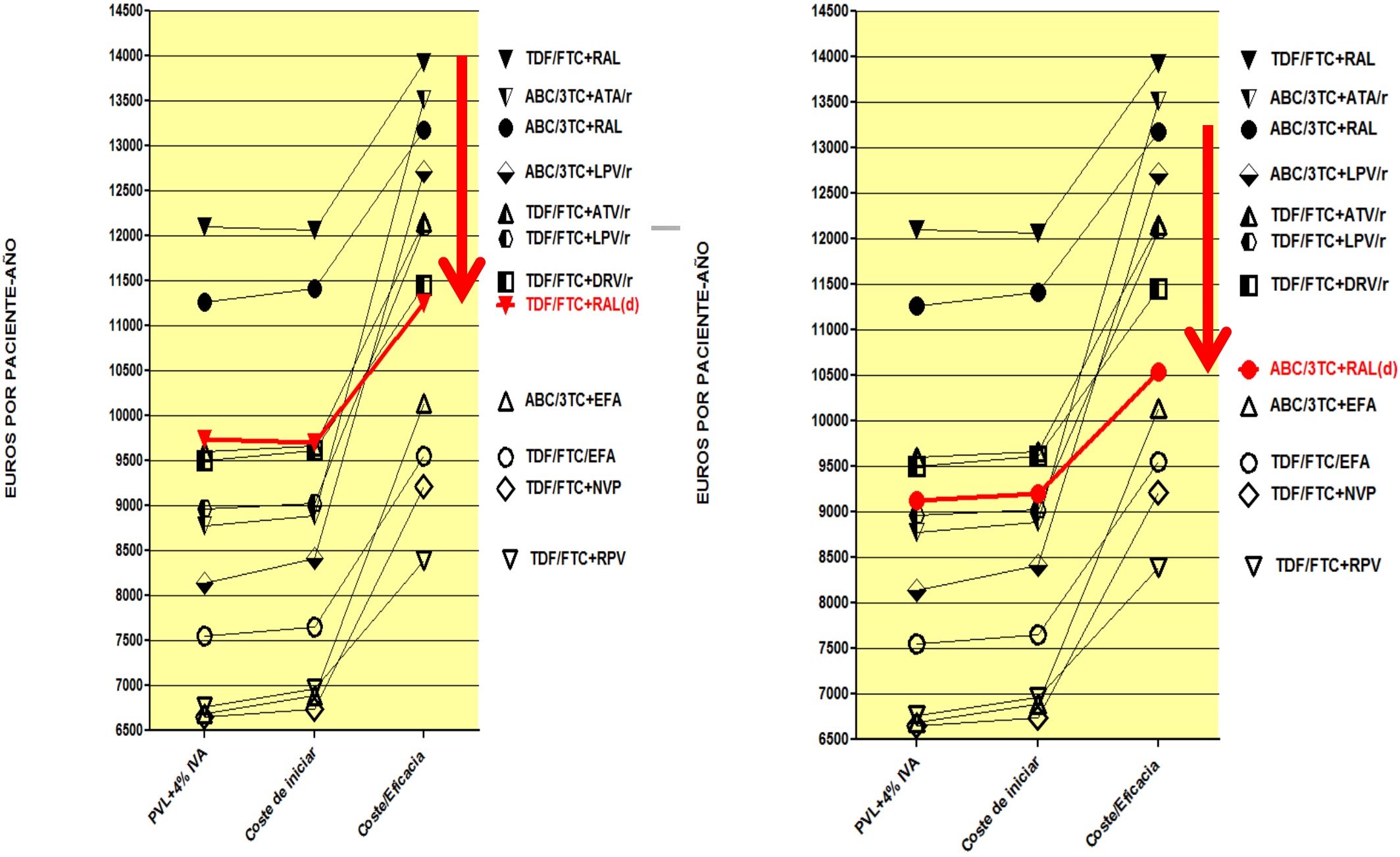
Mutations by subject in the RAL 400 mg BID arm:

[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)

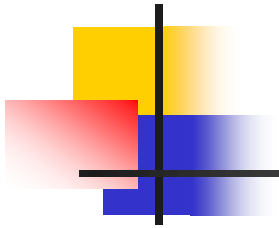


Blasco, Gatell et al. EIMC 2013



Blasco, Gatell et al. EIMC 2013

Undetectable Plasma Viral Load and beyond ..



1. Undetectable plasma VL
2. HIV eradication or at least functional cure
3. Residual HIV replication (ART intensification)
4. Reduction of reservoirs
5. Detection below 50, blips & low level viremia
6. Accelerate & increase CD4 response
7. **Avoid mid-long term "toxic actives"**
8. Salvage therapy in case of failure
9. In summary…

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

Toxic actives

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

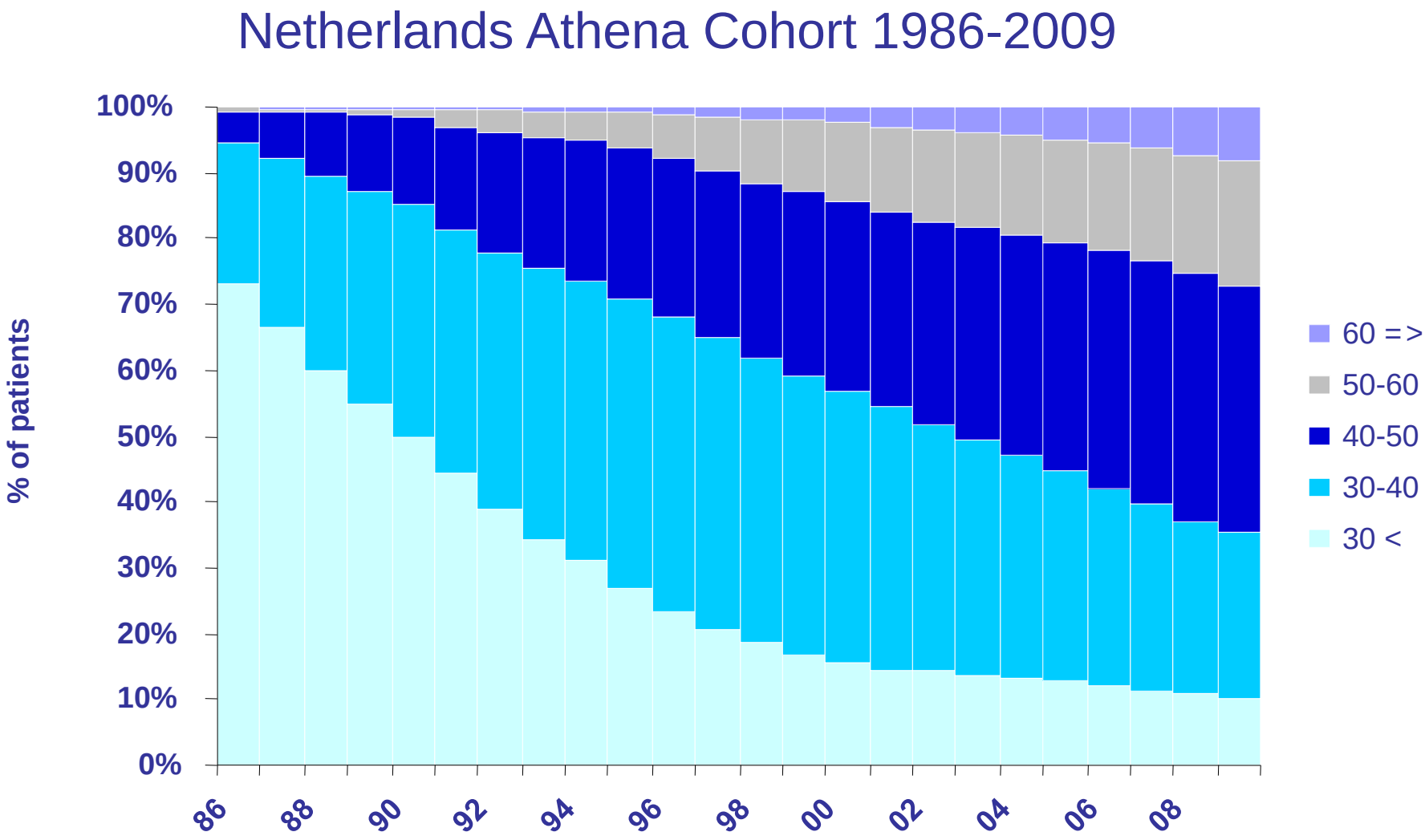
Undetectable Plasma Viral Load and beyond ..

7. Avoid mid-long term "toxic actives"

- >90% of treated patients
- long life ART

- apparently healthy, but getting older
  maybe with accelerated aging

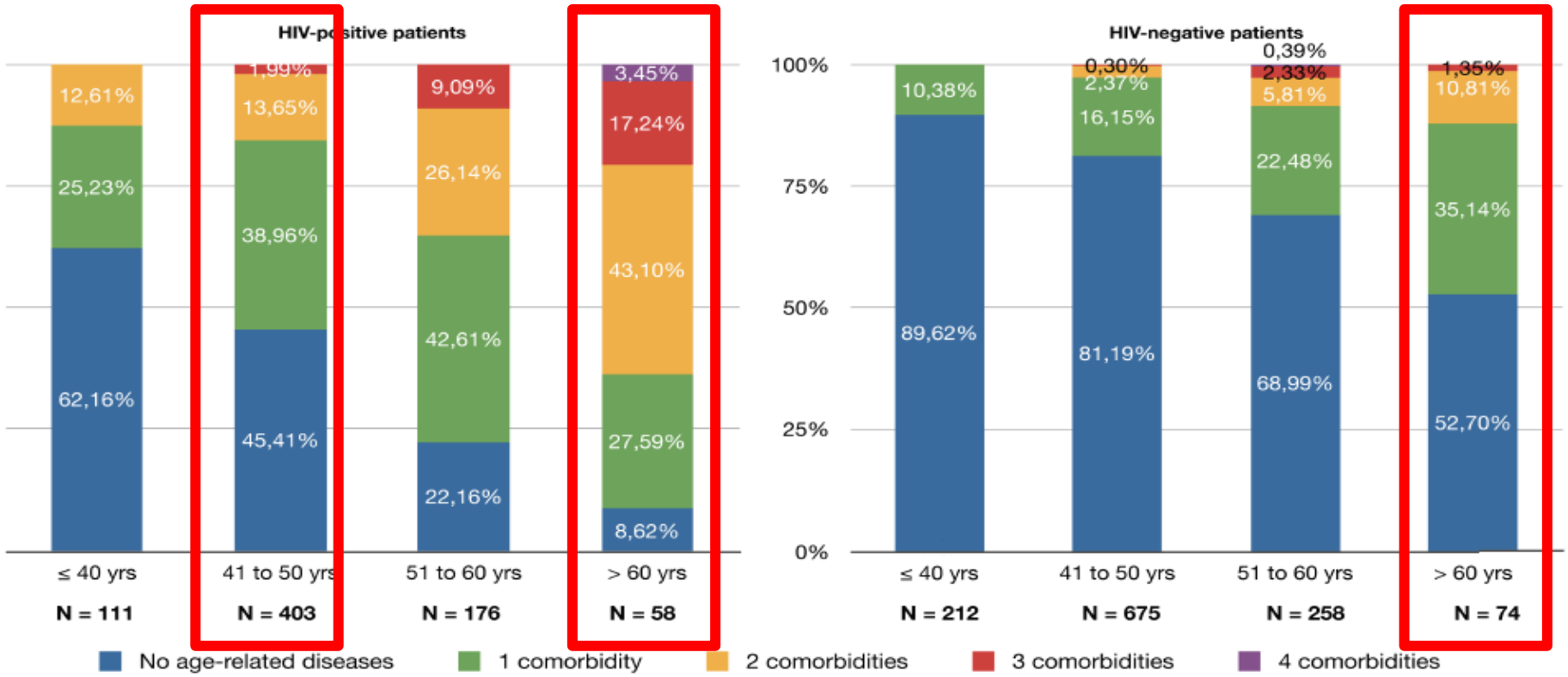
Increasing proportion of older persons in The Netherlands



Slide courtesy of Peter Reiss

Co-morbidities are more common with increasing age but occur earlier in HIV

Co-mobidities prevalence in cases and controls, stratified by age categories.



The following co-morbidities were analysed: Hypertension, Type 2 Diabetes, Cardiovascular Disease and Osteoporosis.

Co-morbidities prevalence was higher in cases than controls in all age strata (all p-values <0.001).

Co-morbidities prevalence in cases aged 41-50 was similar to that in controls aged >60 (p=0.282).

Guaraldi G et al. Clin Infect Dis 2011;53:1120–6

Undetectable Plasma Viral Load and beyond ..

Non-AIDS defining co-morbidities:

1. cART mid-long term toxicities (lipids, kidney, bone)
2. Cardiovascular events
3. Liver disease (HBV, HCV)
4. HAND
5. HIV nephropathy
6. Malignancies

   virus related: EBV, HBV, HVC, HPV
   other : lung cancer ?

7. STD´s

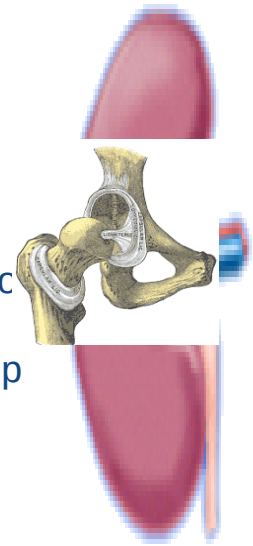
Emerging co-morbidities in HIV+: HIV+ ~10-15 years older than HIV-

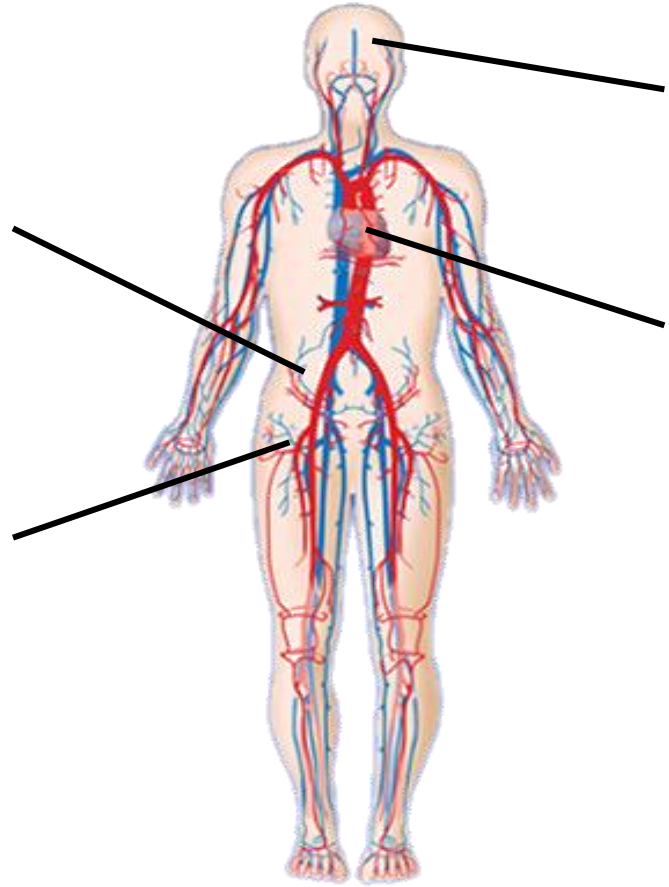
Renal dysfunction

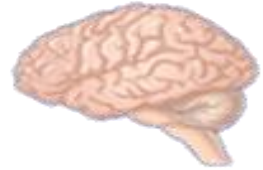
30% of HIV+ patients have abnormal kidney function[1]

Reduced bone mineral density

Increased prevalence of osteoporosis or osteopenia in spine, hip or forearm:
63% of HIV+ patients[2]

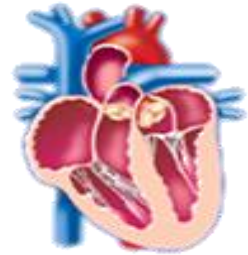






Neurocognitive dysfunction

Neurological impairment present in ≥50% HIV+ patients[3]



Cardiovascular disease

75% increase in risk of acute MI[4]

Cancer

Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal[5]

Frailty

Increased frailty phenotype if HIV infected 3-14x; Associated with CD4 count

1. Gupta SK *et al. Clin Infect Dis* 2005;**40**:1559–85.
2. Brown TT *et al. J Clin Endocrinol Metab* 2004;**89**(3):1200–06.
3. Clifford DB. *Top HIV Med* 2008;**16**(2):94–98.
4. Triant VA *et al. J Clin Endocrinol Metab* 2007;**92**:2506–12.
5. Patel P *et al. Ann Intern Med* 2008;**148**:728–36.

Results – Myocardial Infarction

Premature aging?

	N	# of events	Mean age
HIV-	56,456	286	**55.3**
HIV+	27,988	231	**55.3**

0.0 years crude difference

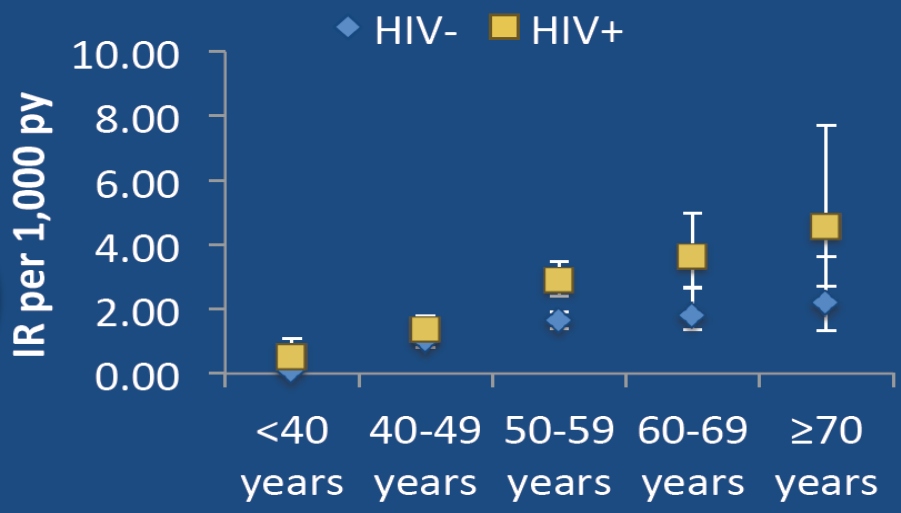
Adjusted mean difference in age:
-0.04 (-0.62, 0.54) years

No difference in age at diagnosis by HIV status

Greater risk?

	IR per 1,000 py	95% CI	aIRR	95% CI
HIV-	1.31	(1.17, 1.47)	1.00	
HIV+	2.18	(1.92, 2.48)	1.81	(1.49, 2.20)

An 81% increase in the rate in HIV+ compared to HIV-



Linear regression models to estimate the mean difference in age at diagnosis and Poisson regression models to estimate incidence rate ratios (aIRR) were adjusted for age, race, sex, body mass index, alcohol use, cigarette smoking, hepatitis C infection, anemia, diabetes, hyperlipidemia, lipid-lowering medications, hypertension, anti-hypertension medications, and statin use.

Undetectable Plasma Viral Load and beyond ..

Management of Non-AIDS defining co-morbidities:

1. Early & long term control of HIV replication (plasma)
2. Achieve highest possible current CD4 count (early diagnosis and treatment of HIV
3. Select/switch cART to minimize kidney, bone and lipid abnormalities and (in some patients) to achieve better CSF penetration
4. Control of traditional cardiovascular risk factors (smoking, ..)
5. Treatment of HBV and HCV
6. Screening/early diagnosis of malignancies
   virus related: EBV, HBV, HVC, HPV
   other : lung cancer ?
7. Early diagnosis and treatmet of STD´s

Grind House: Killer Burgers. Sweet Auburn Vurb Market, Atlanta (GA).

Switching strategies in suppressed patients usually consist on:

In the past and now:

Replacing thymidine by non thymidine analogs

Replacing T20 by raltegravir

Replacing PI/r by abacavir,efavirenz or nevirapine (NEFA)

rilpivirine (SPIRIT)

atazanvir/r (ATAZIP)

raltegravir (SWITCHMRK, SPIRAL)

elvitegravir/cobi

dolutegravir

maraviroc (MARCH)

Replacing efavirenz by rilpivirine

But also ……

Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study

Esteban Martinez[a,*], María Larrousse[a,*], Josep M. Llibre[b], Felix Gutierrez[c], Maria Saumoy[d], Antonio Antela[e], Hernando Knobel[f], Javier Murillas[g], Juan Berenguer[h], Judit Pich[a], Ignacio Pérez[a], José M. Gatell[a], for the SPIRAL Study Group

Background: Switching to raltegravir in selected patients treated with ritonavir-boosted protease inhibitors may result in similar efficacy and lower plasma lipids.

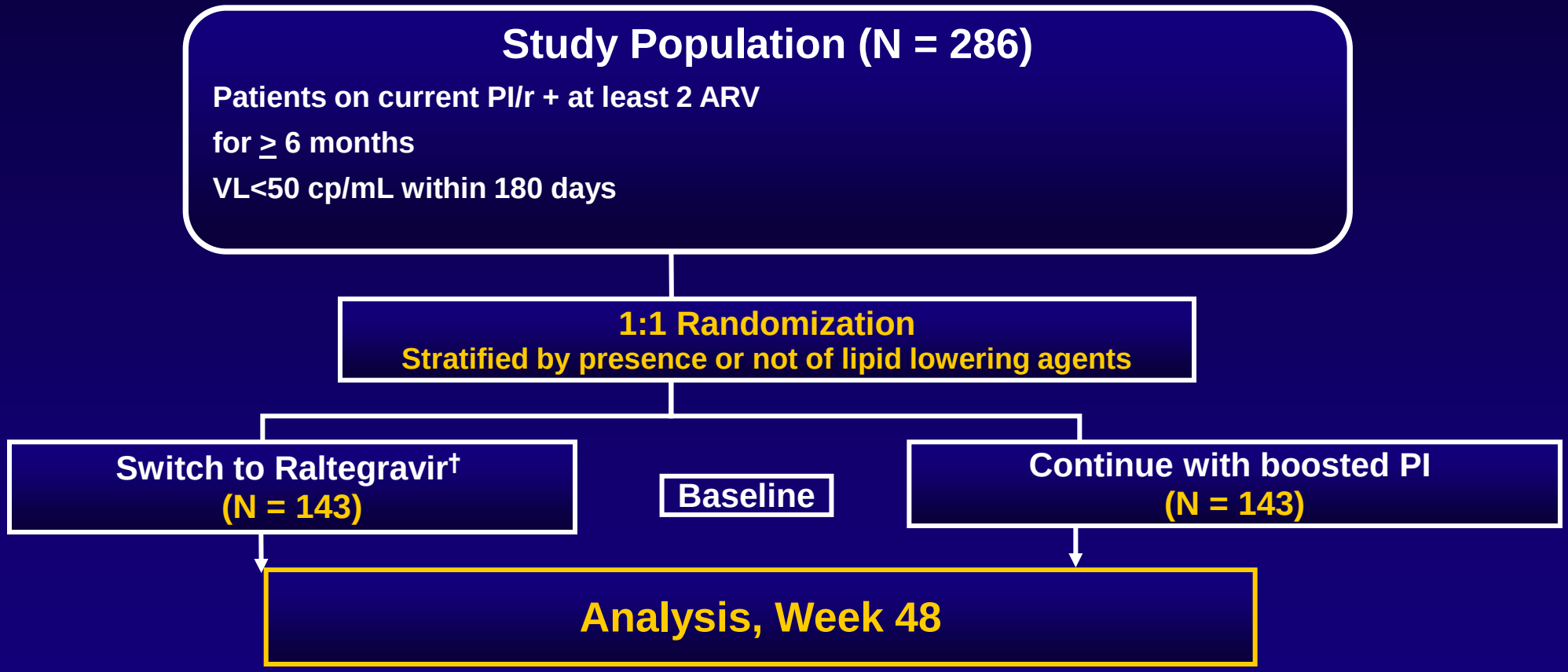
Methods: SPIRAL is a 48-week multicentre, open-label trial in which HIV-infected adults with less than 50 copies/ml of plasma HIV RNA for at least the previous 6 months on ritonavir-boosted protease inhibitor-based therapy were randomized (1 : 1) to switch from the ritonavir-boosted protease inhibitor to raltegravir or to continue on ritonavir-boosted protease inhibitor-based therapy. Primary endpoint was the proportion of patients free of treatment failure (noncompleter = failure) at 48 weeks. SPIRAL study was powered to show noninferior efficacy of raltegravir-based therapy with a margin of −12.5%.

Results: Two hundred and seventy-three patients assigned to switch to raltegravir ($n = 139$) or to continue ritonavir-boosted protease inhibitor ($n = 134$) were included in the efficacy analysis. At 48 weeks, 89.2% (raltegravir-based therapy) and 86.6% (ritonavir-boosted protease inhibitor-based therapy) of the patients remained free of treatment failure [difference 2.6%; 95% confidence interval (CI) −5.2 to 10.6]. A total of 96.9% (raltegravir-based therapy) and 95.1% (ritonavir-boosted protease inhibitor-based therapy) of the patients remained free of virological failure (difference 1.8%; 95% CI −3.5 to 7.5). Switching to raltegravir was associated with significant decreases in plasma lipids and total-to-HDL cholesterol ratio relative to continuing ritonavir-boosted protease inhibitor. Severe adverse events and study drug discontinuations due to any adverse event occurred in 4 and 2% of the patients in each group.

Conclusion: In patients with sustained virological suppression on ritonavir-boosted protease inhibitor-based therapy, switching from ritonavir-boosted protease inhibitor to raltegravir demonstrated noninferior efficacy and resulted in a better lipid profile at 48 weeks than continuing ritonavir-boosted protease inhibitor.

AIDS 2010, **24**:1697–1707

Study Design

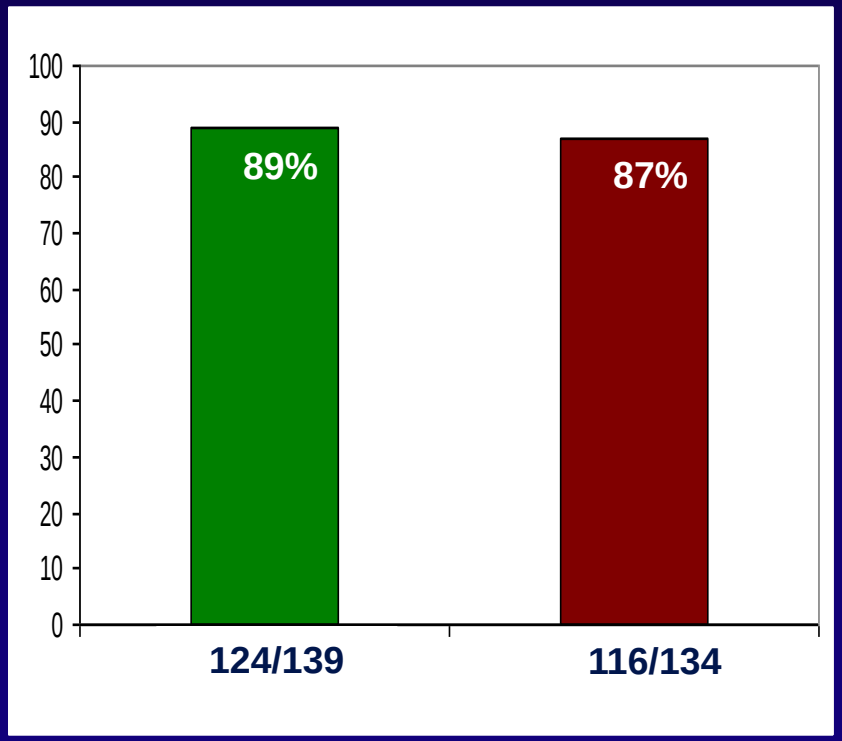


* Raltegravir 400mg BID (maintaining other antiretrovirals unchanged).

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

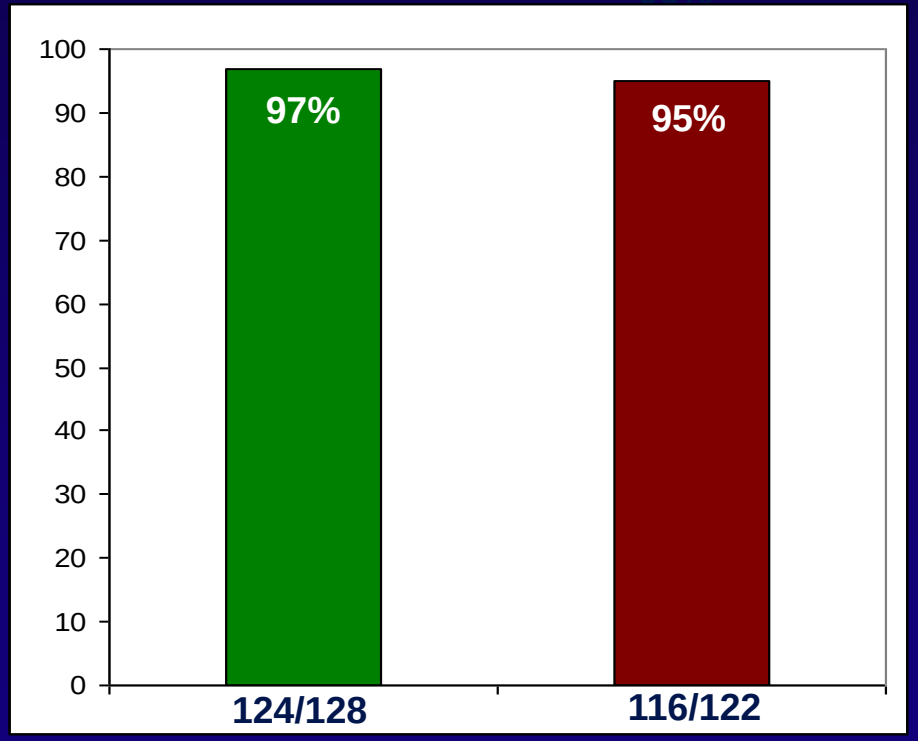
Free of Treatment Failure (ITT, S=F)

RALTEGRAVIR PI/r



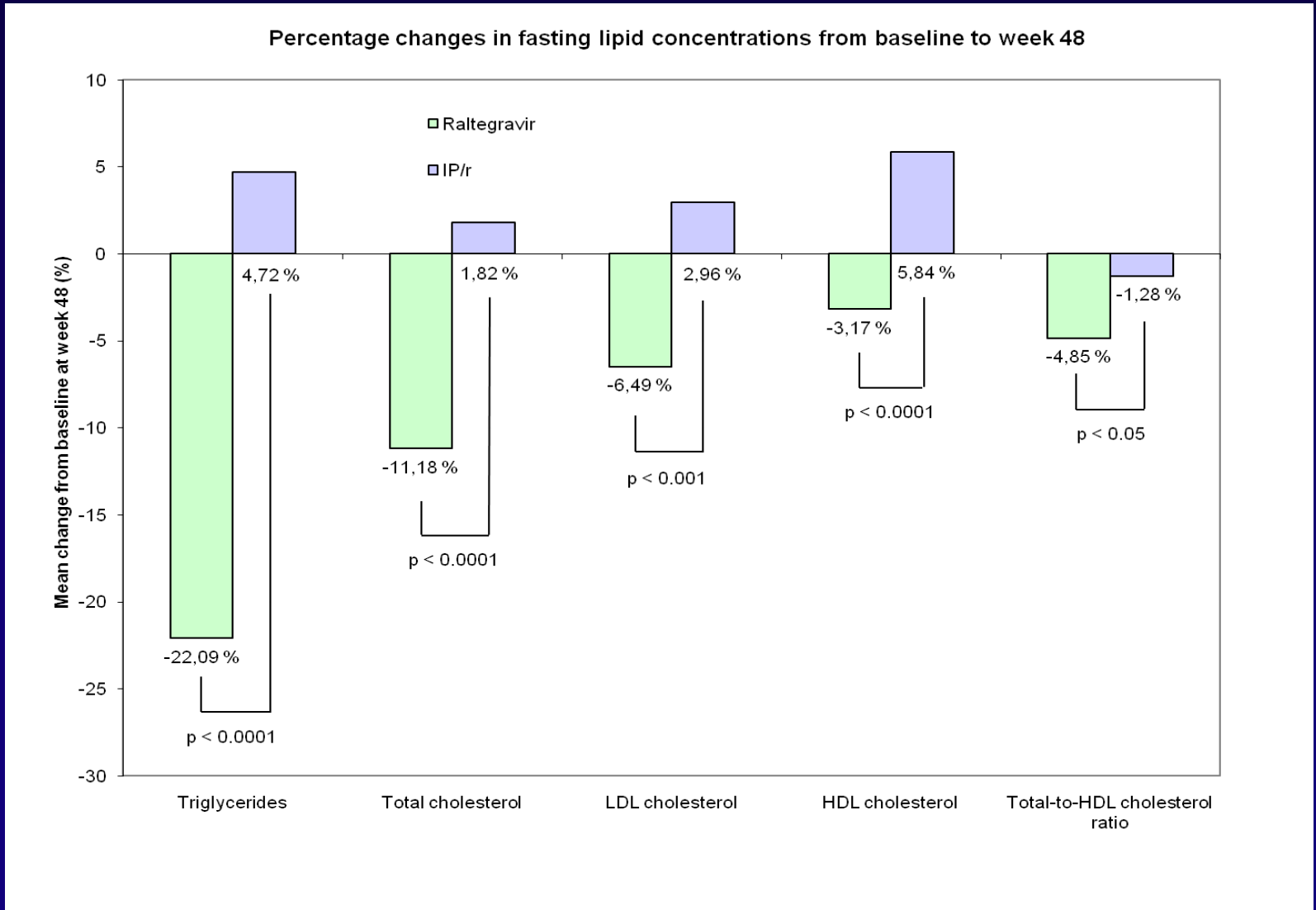
Difference Estimate (95% CI) 2.6% (–5.2%, 10.6%)

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



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

LIPIDS. Change in mean Fasting Lipid Parameters through Week 48



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LDL subclasses and lipoprotein-phospholipase A2 activity in suppressed HIV-infected patients switching to raltegravir: Spiral substudy

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Lipoprotein-associated phospholipase A2

ABSTRACT

Objective: To analyze the effect of switching the ritonavir-boosted protease inhibitor (PI/r) in a stable combined antiretroviral therapy (cART) regimen to raltegravir on low-density lipoprotein (LDL) particles, and lipoprotein-associated phospholipase A2 (Lp-PLA2).
Design: Substudy of a multicenter randomized trial that compared the efficacy of switching a PI/r to raltegravir-based cART in stable HIV-infected patients.
Methods: LDL size and phenotype (by gel-gradient electrophoresis), Lp-PLA2 (by 2-thio-PAF [Cayman]), proprotein convertase subtilisin/kexin type 9 (PCSK9) (by ELISA), and standard lipid parameters were measured at baseline and week 48.
Results: Eighty-one (PI/r $n = 41$ and raltegravir $n = 40$) patients were evaluated. No differences in baseline demographic and metabolic variables between arms were found except in apolipoprotein (Apo) B ($p = 0.042$). At week 48, total cholesterol (TC) ($p < 0.001$), LDL-c ($p = 0.023$), non-high density lipoprotein cholesterol non-high-density lipoprotein cholesterol (non-HDL-c) ($p < 0.001$), TC/HDL ($p = 0.026$), triglyceride ($p < 0.001$), Apo B ($p < 0.001$), Apo A-I ($p = 0.004$) and Lp (a) ($p = 0.005$) decreased in raltegravir arm compared to PI/r arm. At week 48, a shift from LDL phenotype B to the less atherogenic phenotype A was observed only in raltegravir arm ($p < 0.001$). LDL size increased (PI/r 2.1 nm, $p = 0.019$; raltegravir 3.8 nm, $p = 0.001$) and cholesterol content in small and dense LDL subfractions (LDL 4,5,6) decreased (PI/r $p = 0.007$, raltegravir $p = 0.006$) at week 48 in both arms. Total Lp-PLA2 activity (PI/r $p = 0.037$ and raltegravir $p = 0.051$) and PCSK9 plasma concentration decreased in both arms (PI/r $p = 0.034$ and raltegravir $p < 0.001$).
Conclusions: Switching a PI/r to a raltegravir-based cART in virologically suppressed HIV-infected patients was associated with an overall improvement in lipid profile, including a shift to a less atherogenic LDL phenotype.

Changes of cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir

Esteban Martinez[a], Polyana M. D'Ibuquerque[a], Josep M. Llibre[b], Felix Gutierrez[c], Daniel Podzamczer[d], Antonio Antela[e], Juan Berenguer[f], Pere Domingo[g], Xabier Moreno[a], Ignacio Perez[a], Judit Pich[a] and Jose M Gatell[a] for the SPIRAL Trial Group

Background: Switching from boosted protease inhibitors (PI/r) to raltegravir (RAL) results in a better plasma lipid profile than continuing PI/r. Whether this strategy affects plasma biomarkers associated with atherosclerosis is unknown.

Methods: We assessed 48-week changes in fasting lipids and several biomarkers including serum hsCRP, MCP-1, osteoprotegerin, IL-6, IL-10, TNF-α, ICAM-1, VCAM-1, E- and P-selectin, adiponectin, insulin, and D-dimer in otherwise healthy, virologically suppressed HIV-infected patients treated with PI/r who randomly switched from PI/r to RAL or continued with PI/r in the SPIRAL trial. Biomarkers and lipids at baseline and 48 weeks, and biomarker and lipid changes between both study arms were compared. Correlations between changes in biomarkers and changes in lipids were also evaluated.

Results: Of 273 patients initiating study drugs in the SPIRAL trial, 233 (119 RAL, 114 PI/r) remained on allocated therapy for 48 weeks and had sera available for the purpose of this sub-study. Triglycerides (−28%, $p < 0.0001$), total (−14%, $p < 0.0001$), LDL (−9%, $p = 0.0069$), and HDL (−10%, $p = 0.0017$) cholesterol decreased in RAL relative to PI/r group. Among biomarkers, hsCRP (−40%, $p < 0.0001$), MCP-1 (−20%, $p = 0.0003$), osteoprotegerin (−13%, $p = 0.0024$), IL-6 (−46%, $p < 0.0001$), TNF-α (−27%, $p = 0.0011$), insulin (−26%, $p < 0.0001$), and D-dimer (−8%, $p = 0.0187$) decreased in RAL relative to PI/r group, while IL-10 (+1%, $p = 0.7773$), ICAM-1 (−6%, $p = 0.1255$), VCAM-1(0%, $p = 0.8671$), E-selectin (−9%, $p = 0.2174$), P-selectin (−6%, $p = 0.3865$), and adiponectin (+8%, $p = 0.2028$) remained unchanged. Biomarkers and lipids changes at 48 weeks were weakly correlated.

Conclusions: Switching from PI/r to RAL induced significant changes in several cardiovascular biomarkers that were not completely explained by lipid changes.

AIDS 2012, **26**:000–000

Body composition changes after switching from protease inhibitors to raltegravir: SPIRAL-LIP substu

Adrian Curran[a], Esteban Martinez[b], Maria Saumoy[c], Luis del Rio[d], Manuel Crespo[a], Maria Larrousse[b], Daniel Podzamczer[c], Joaquin Burgos[a], Montse Lonca[b], Pere Domingo[e], Jose Maria Gatell[b] and Esteban Ribera[a]

Objective: To compare 48-week changes in body fat distribution and bone mineral density (BMD) between patients switching from a ritonavir-boosted protease inhibitor (PI/r) to raltegravir (RAL) and patients continuing with PI/r.

Design: Substudy of the prospective, randomized, open-label, multicenter SPIRAL study.

Methods: Patients were randomized (1 : 1) to continue with the PI/r-based regimen or switch to RAL, maintaining the rest of the treatment unchanged. Dual-energy X-ray absorptiometry and computed tomography scans were performed at baseline and after 48 weeks to measure body fat and bone composition, analyzing intragroup and intergroup differences.

Results: Eighty-six patients were included and 74 patients (39 RAL, 35 PI/r) completed the substudy. Significant increases in median [interquartile range (IQR)] visceral adipose tissue (VAT) [20.7 (−2.4 to 45.6) cm^2, $P = 0.002$] and total adipose tissue (TAT) [21.4 (−1.3 to 55.4) cm^2, $P = 0.013$] were seen within the PI/r group. No significant changes in body fat were seen with RAL or between treatment groups. Regarding bone composition, total BMD [0.01 (0 to 0.02) g/cm^2, $P = 0.002$], total hip BMD [0.01 (0 to 0.03) g/cm^2, $P = 0.015$] and total hip T score [0.12 (−0.05 to 0.21) SD, $P = 0.004$] significantly increased with RAL, with no significant changes within the PI/r group. Differences between treatment groups were significant in femoral neck BMD [0.01 (−0.02 to 0.02) g/cm^2, $P = 0.032$] and T score [0.01 (−0.18 to 0.18) SD, $P = 0.016$].

Conclusion: Although there were no significant changes in body fat between groups, maintaining a PI/r-based regimen was associated with a significant increase in VAT and TAT. Switching to RAL led to a significant increase in femoral neck BMD when comparing between groups.

AIDS 2012, **26**:475–481

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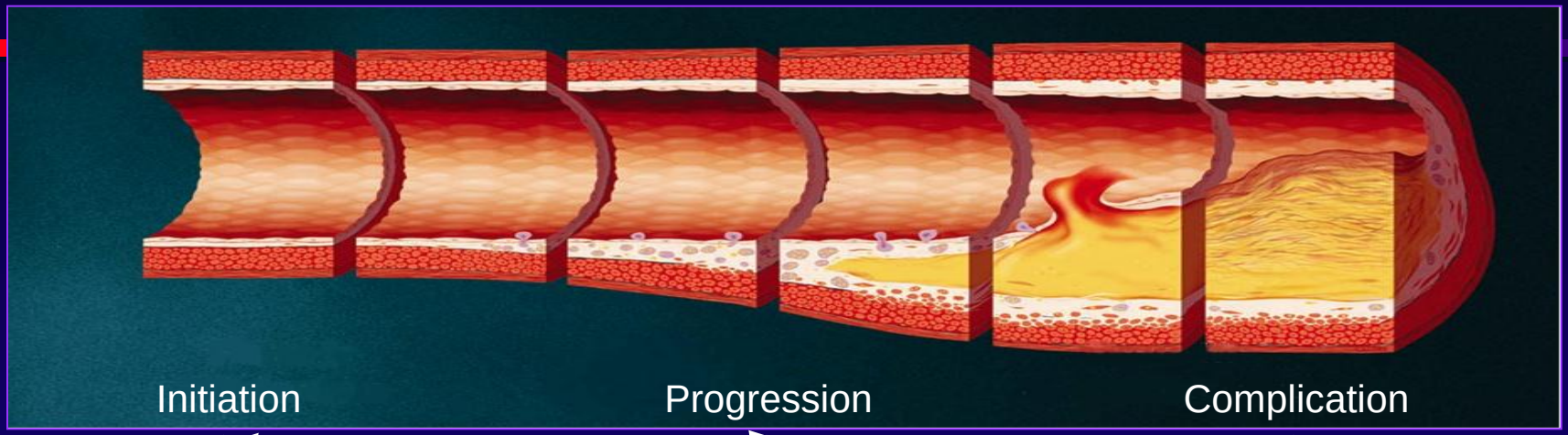
Abacavir/Lamivudine versus Tenofovir/Emtricitabine in Virologically Suppressed Patients Switching from Ritonavir-Boosted Protease Inhibitors to Raltegravir

Esteban Martínez, Polyana M. d'Albuquerque, Ignacio Pérez, Judit Pich, and José M. Gatell

Abstract

There are few clinical data on the combination abacavir/lamivudine plus raltegravir. We compared the outcomes of patients from the SPIRAL trial receiving either abacavir/lamivudine or tenofovir/emtricitabine at baseline who had taken at least one dose of either raltegravir or ritonavir-boosted protease inhibitors. For the purpose of this analysis, treatment failure was defined as virological failure (confirmed HIV-1 RNA ≥50 copies/ml) or discontinuation of abacavir/lamivudine or tenofovir/emtricitabine because of adverse events, consent withdrawal, or lost to follow-up. There were 143 (72.59%) patients with tenofovir/emtricitabine and 54 (27.41%) with abacavir/lamivudine. In the raltegravir group, there were three (11.11%) treatment failures with abacavir/lamivudine and eight (10.96%) with tenofovir/emtricitabine (estimated difference 0.15%; 95% CI −17.90 to 11.6). In the ritonavir-boosted protease inhibitor group, there were four (14.81%) treatment failures with abacavir/lamivudine and 12 (17.14%) with tenofovir/emtricitabine (estimated difference −2.33%; 95% CI −16.10 to 16.70). Triglycerides decreased and HDL cholesterol increased through the study more pronouncedly with abacavir/lamivudine than with tenofovir/emtricitabine and differences in the total-to-HDL cholesterol ratio between both combinations of nucleoside reverse transcriptase inhibitors (NRTIs) tended to be higher in the raltegravir group, although differences at 48 weeks were not significant. While no patient discontinued abacavir/lamivudine due to adverse events, four (2.80%) patients (all in the ritonavir-boosted protease inhibitor group) discontinued tenofovir/emtricitabine because of adverse events ($p = 0.2744$). The results of this analysis do not suggest that outcomes of abacavir/lamivudine are worse than those of tenofovir/emtricitabine when combined with raltegravir in virologically suppressed HIV-infected adults.

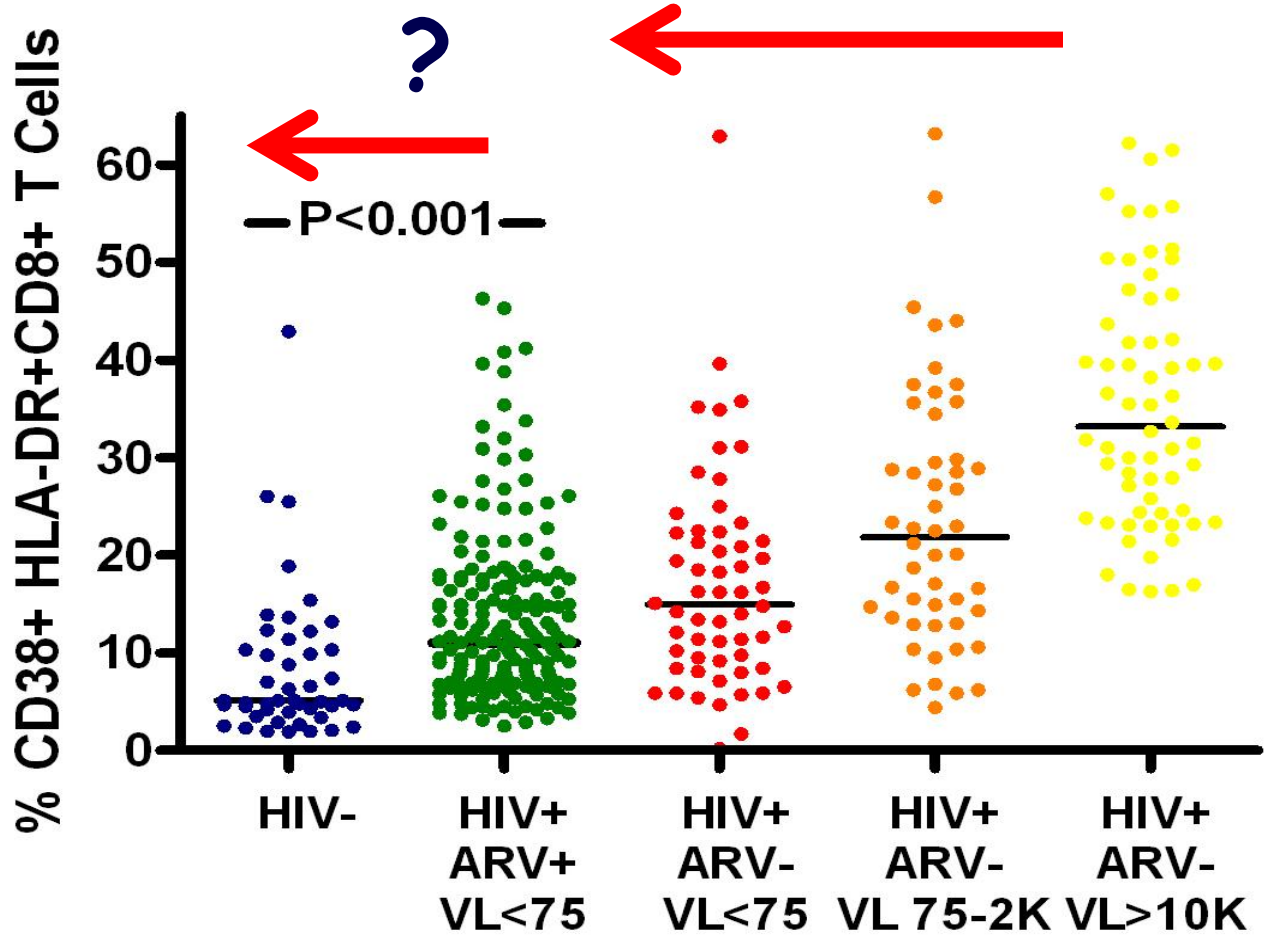
Chronic inflamation
Immuneactivation/senescence



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**

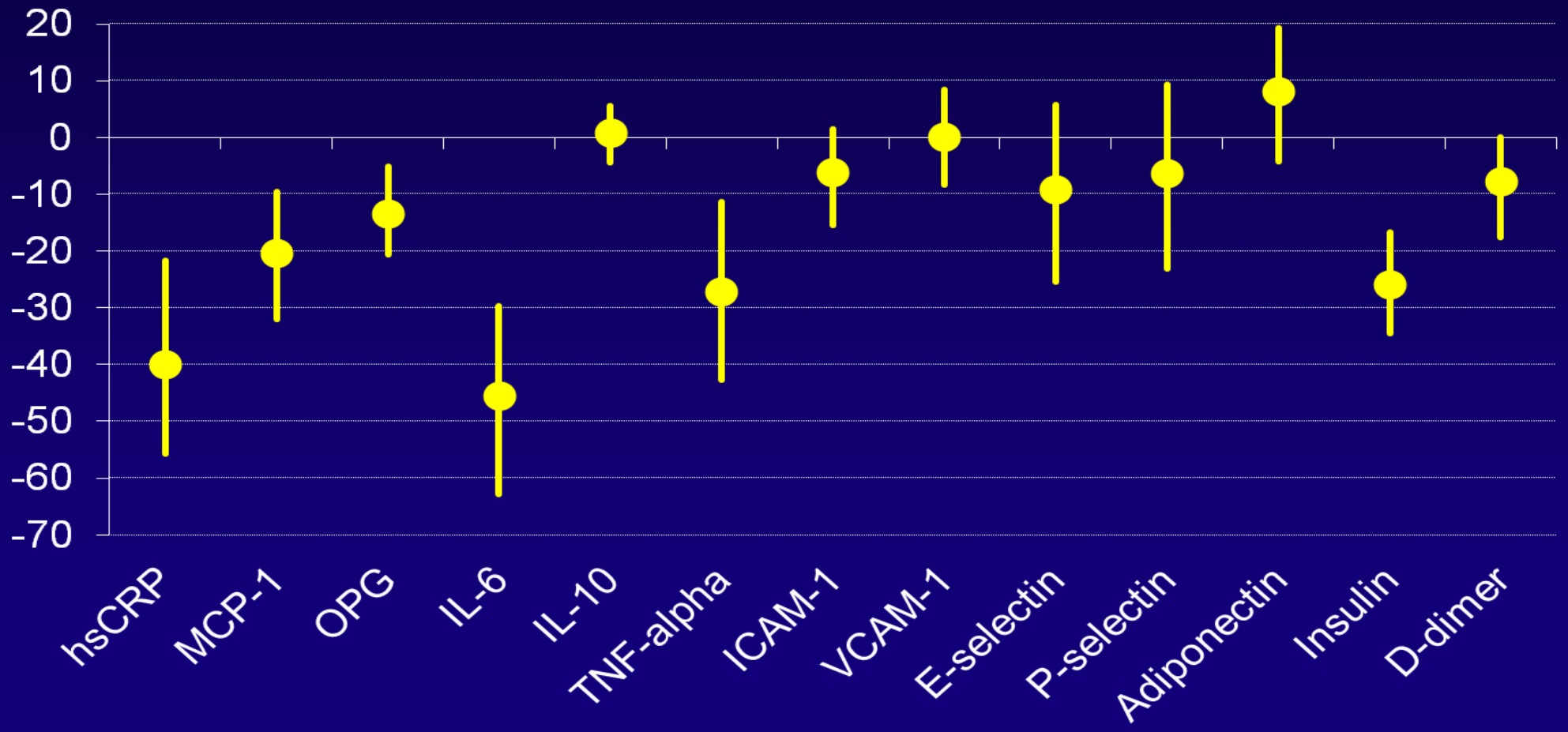
CD38+HLA-DR+CD8 T cells
CD28-CD57+ CD8 T cells, resit. to apoptosis, shortened telomers

….. but ART-suppressed Patients Have Persistently Abnormal T Cell Activation ……



Hunt et al, JID, 2003 and 2008

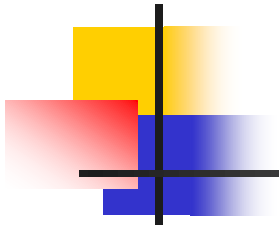
Biomarkers: Median difference of percent change RAL minus PI/r (95% CI)



Conclusions

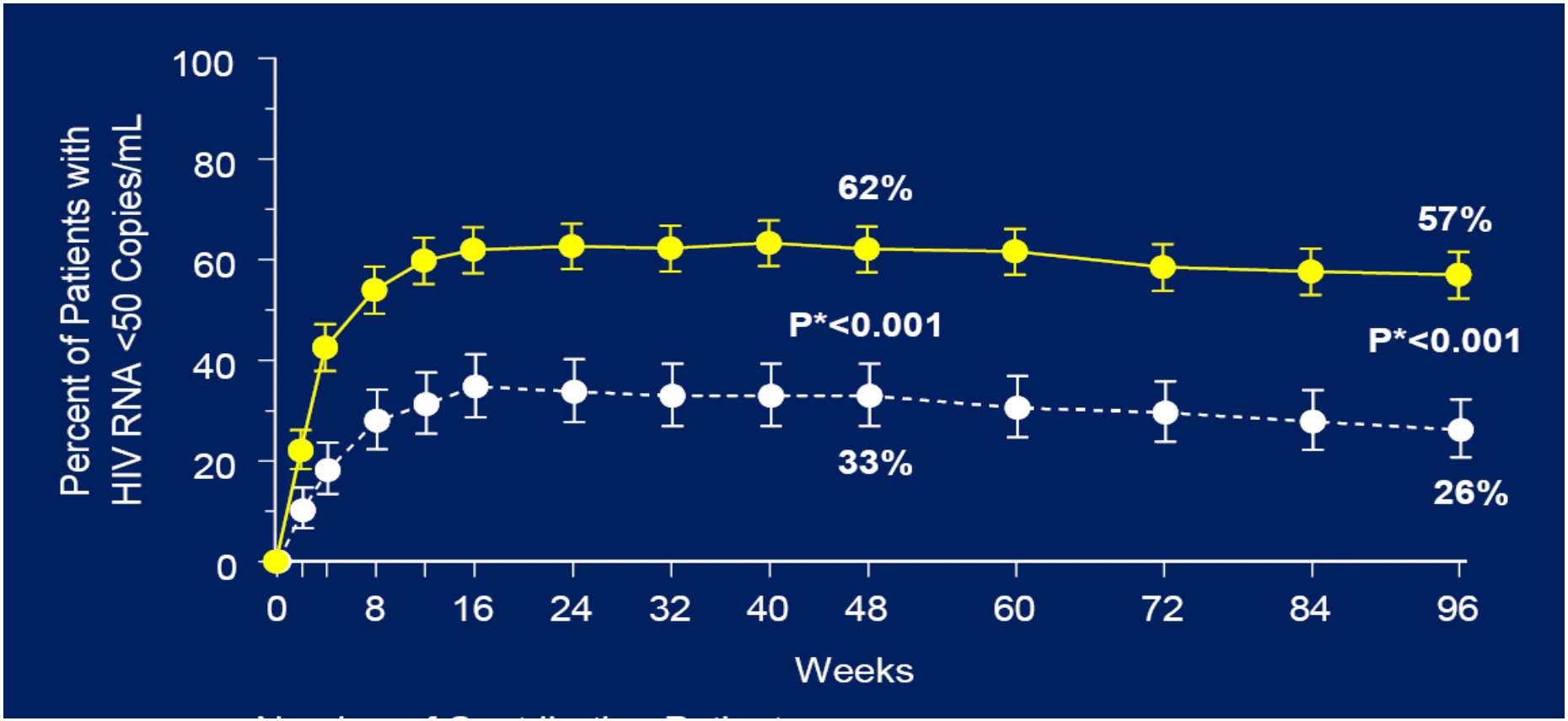
- Switching from PI/r to RAL in SPIRAL study led significant changes in several cardiovascular biomarkers associated with inflammation, insulin resistance and hypercoagulability, although not in those associated with endothelial dysfuntion.
- There were few and weak significant correlations between changes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

Undetectable Plasma Viral Load and beyond ..



1. Undetectable plasma VL
2. HIV eradication or at least functional cure
3. Residual HIV replication (ART intensification)
4. Reduction of reservoirs
5. Detection below 50, blips & low level viremia
6. Accelerate & increase CD4 response
7. Avoid mid-long term "toxic actives"
8. Salvage therapy in case of failure
9. In summary…

BENCHMRK: Percent of patients achieving HIV RNA <50 copies/mL (NC=F Approach)



Facing the challenge of the HIV patient in the near future / co-morbidities

A. The HIV infected individual

B. The pandemic

C. In summary….

Facing the challenge of the HIV patient in the near future / co-morbidities

B. The pandemic

Towards an AIDS free generation ….
in 2050 …… ?

Antiretroviral prophylaxis: a defining moment in HIV control

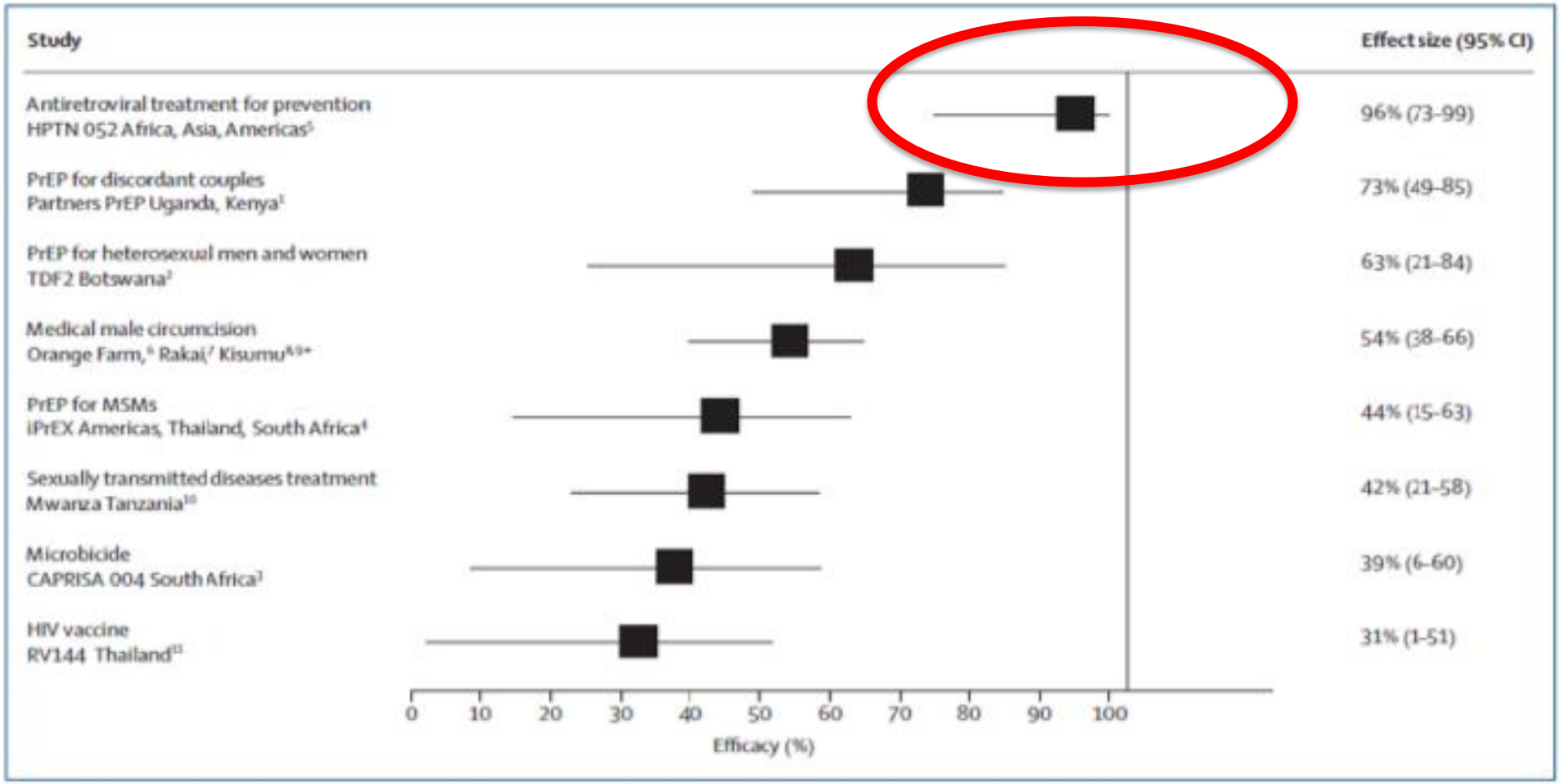
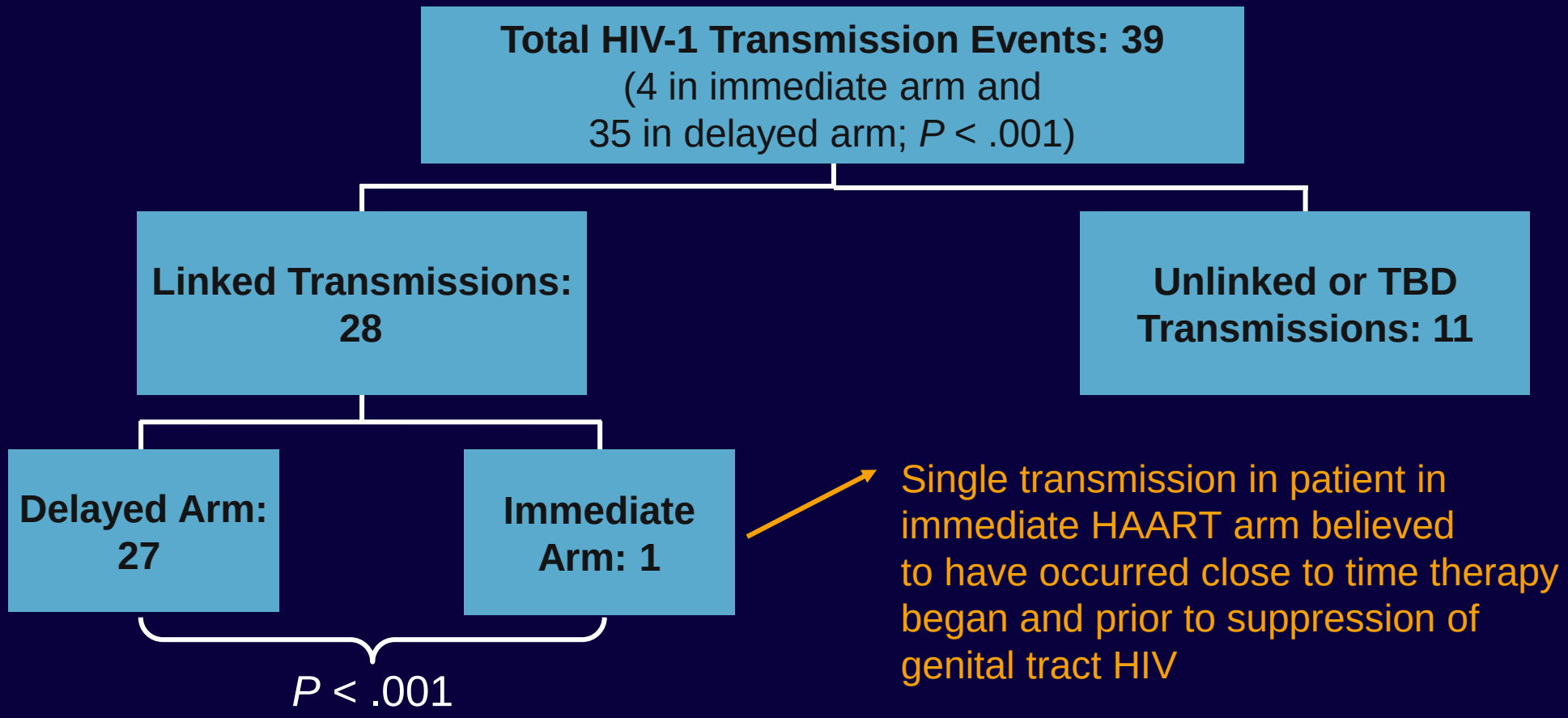


Figure: **HIV prevention technologies shown to be effective in reducing HIV incidence in randomised controlled trials[1–11]**
PrEP=Pre-exposure prophylaxis. *Meta-analysis of circumcision trials.

Published Online
July 15, 2011
DOI:10.1016/S0140-6736(11)61136-7

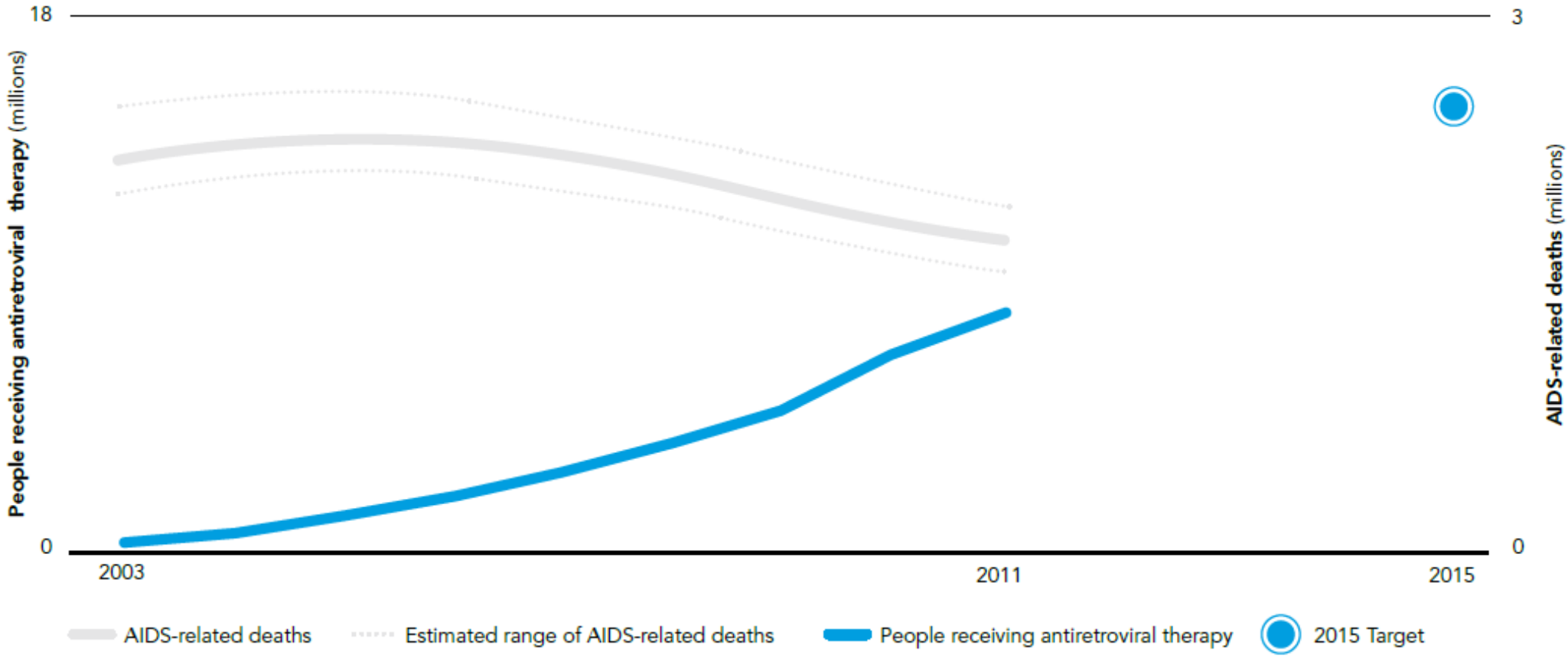
HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples



Cohen MS, et al. N Engl J Med. 2011;365:493-505.

UNAIDS, June 2012

People receiving antiretroviral therapy versus the 2015 target and the number of AIDS-related deaths, low- and middle-income countries, 2003–2011



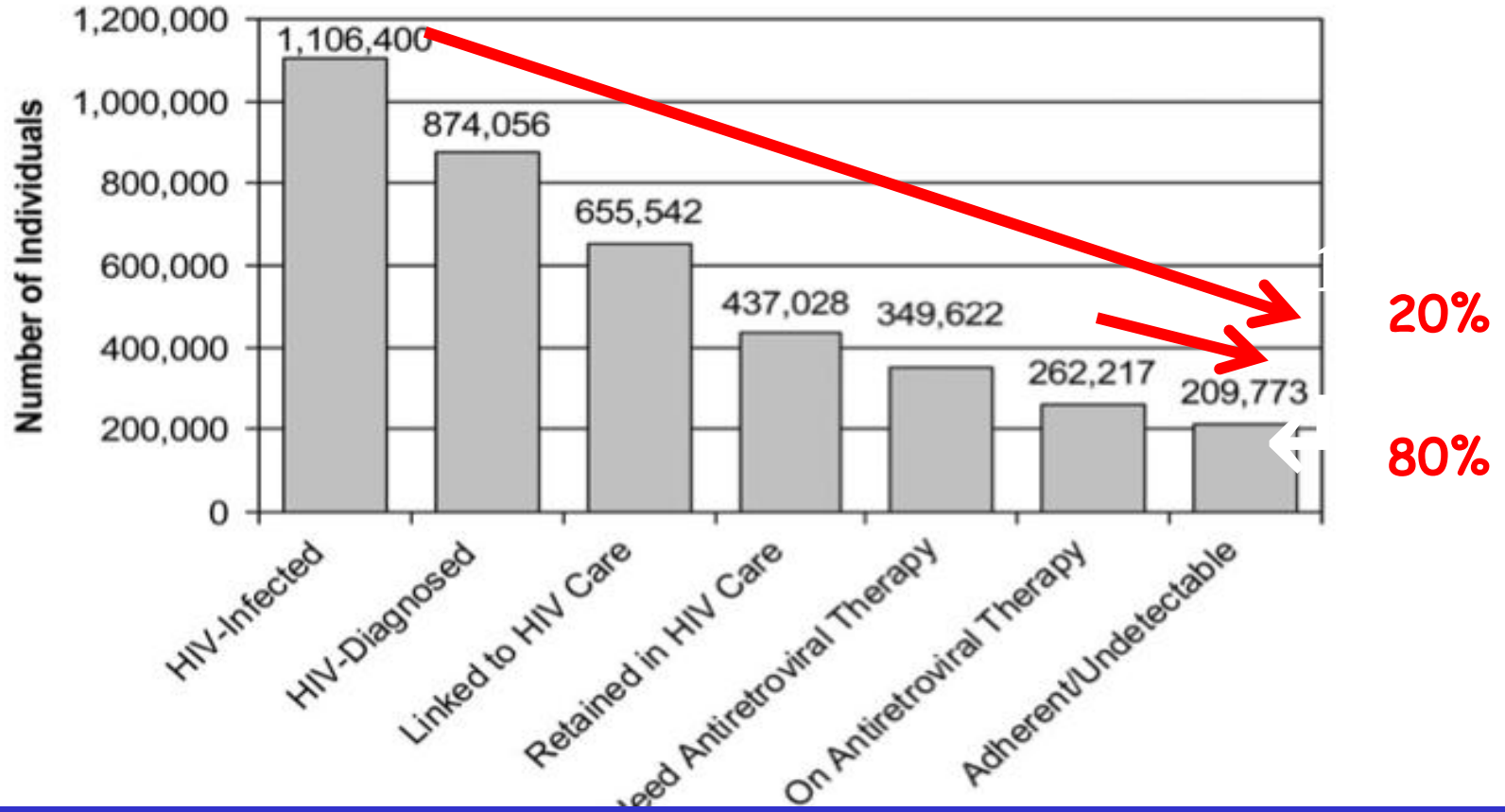
REVIEW ARTICLE HIV/AIDS

The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection

Edward M. Gardner,[1,3] Margaret P. McLees,[1,3] John F. Steiner,[2] Carlos del Rio,[4,5] and William J. Burman[1,3]

[1]Denver Public Health and [2]Kaiser Permanente Colorado, Denver, [3]University of Colorado Denver, Aurora, Colorado, and [4]Rollins School of Public Health of Emory University, and [5]Emory Center for AIDS Research, Atlanta, Georgia

(See the editorial commentary by Lange, on pages 801–802.)



Facing the challenge of the HIV patient in the near future / co-morbidities

A. The HIV infected individual

B. The pandemic

C. In summary….

In summary….

For HIV infected individuals …

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

- Achieving an sustaining an undetectable plasma VL is mandatory. II´s like Raltegravir have an important role

- Objectives beyond undetectable plasma viral load should be considered

- 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 (PI/r to raltegravir) have been successfully tested going as far as PI/r monotherapy

In summary….

For the AIDS pandemic

- Ultimate goal is an AIDS free generation in 2050…..?

- A combination of preventive strategies will be required including:

  Classical prevention approaches
  More testing and more treating
  Likely PrEP (intermittent ?) in selected settings
  Possibly a preventative vaccine (even one only partially effective)

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