6th Infectivology Today®

L'infettivologia del 3 millennio: AIDS ed altro

VI Convegno Nazionale

15- 16 -17 maggio 2014

Centro Congressi Hotel Ariston
Paestum (SA)

6th Infectivology Today®

La deintensificazione terapeutica in HIV: Razionale e vantaggi della mono e della dual-therapy

Paestum (Sa) 15- 16 -17 maggio 2014

Diego Ripamonti ,
Malattie Infettive, Bergamo

HIV treament paradigm

The end of AIDS: HIV infection as a chronic disease

Steven G Deeks, Sharon R Lewin, Diane V Havlir

The success of antiretroviral therapy has led some people to now ask whether the end of AIDS is possible. For patients who are motivated to take therapy and who have access to lifelong treatment, AIDS-related illnesses are no longer the primary threat, but a new set of HIV-associated complications have emerged, resulting in a novel chronic disease that for many will span several decades of life. Treatment does not fully restore immune health; as a result, several inflammation-associated or immunodeficiency complications such as cardiovascular disease and cancer are increasing in importance. Cumulative toxic effects from exposure to antiretroviral drugs for decades can cause clinically-relevant metabolic disturbances and end-organ damage. Concerns are growing that the multimorbidity associated with HIV disease could affect healthy ageing and overwhelm some health-care systems, particularly those in resource-limited regions that have yet to develop a chronic care model fully. In view of the problems inherent in the treatment and care for patients with a chronic disease that might persist for several decades, a global effort to identify a cure is now underway.

Lancet 2013; 382: 1525–33

Published Online
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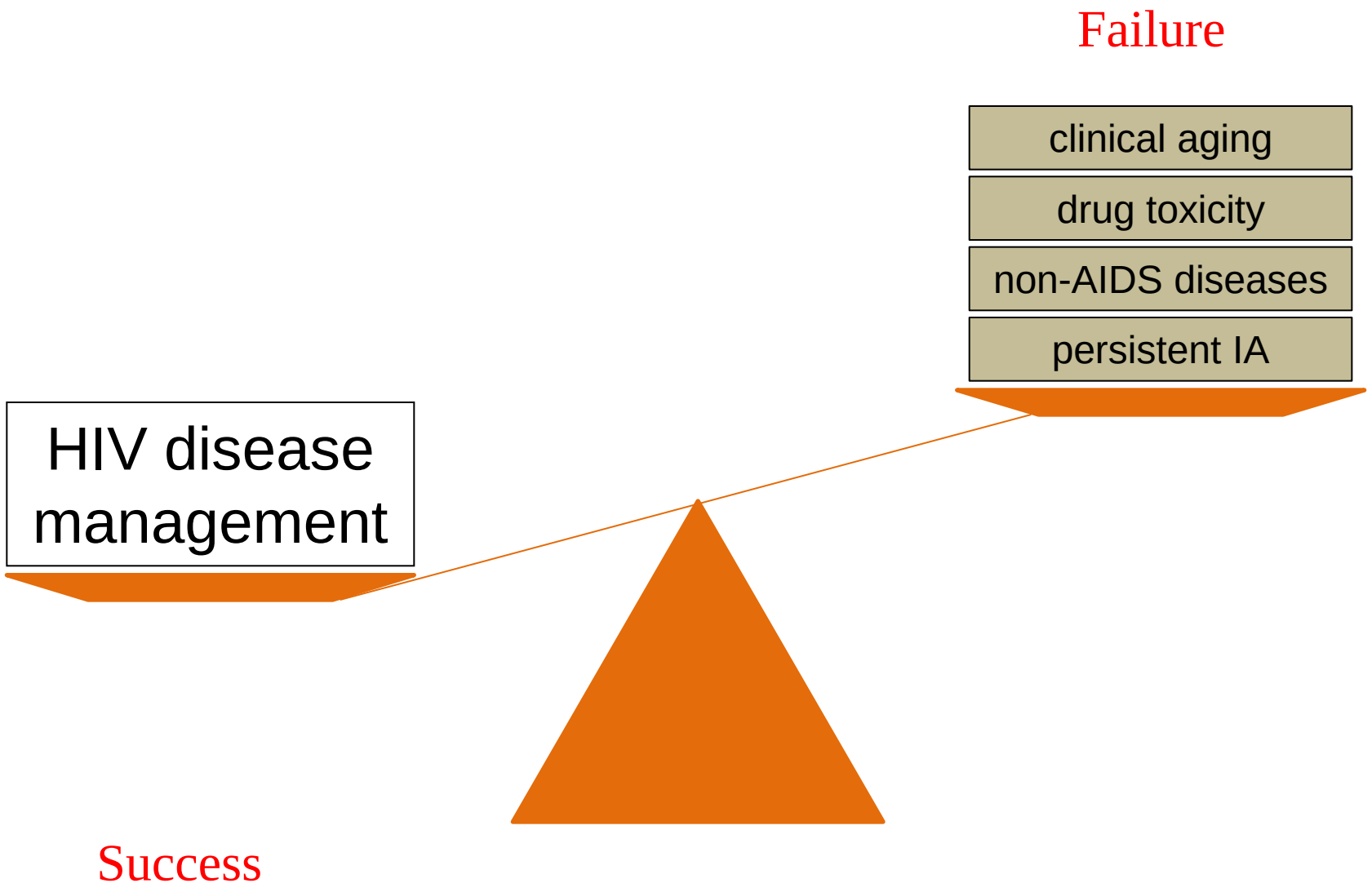
Department of Medicine, University of California, San Francisco, CA, USA (Prof S G Deeks MD, Prof D V Havlir MD); **Department of Infectious Diseases, Monash University and Alfred Hospital, Melbourne, VIC, Australia**

Deeks SG et al. Lancet, November 2013

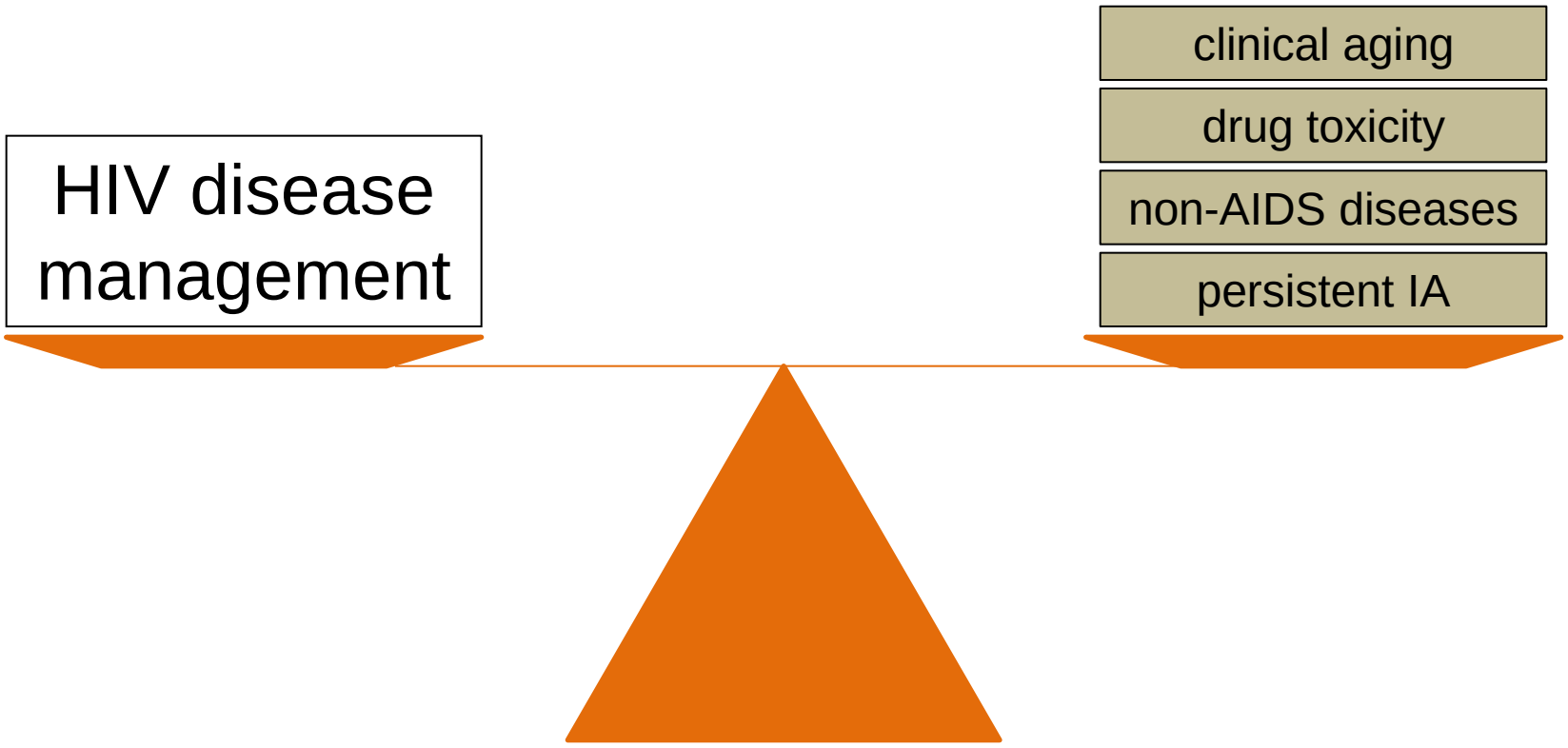
The burden of HIV disease



Deeks S et al. Lancet 2013; 382:1525-33

The burden of HIV disease

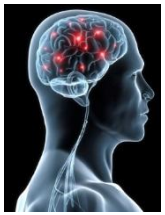
Failure



Success

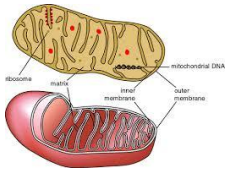
Deeks S et al. Lancet 2013; 382:1525-33

lipodistrofia



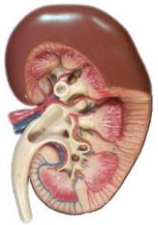
SNC

mtDNA

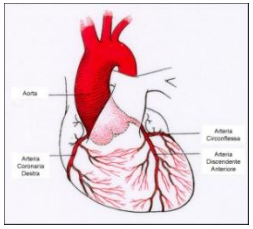


HAART Toxicity

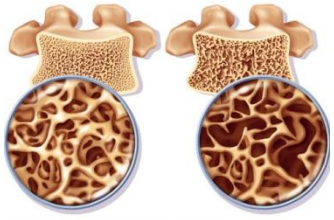
rene



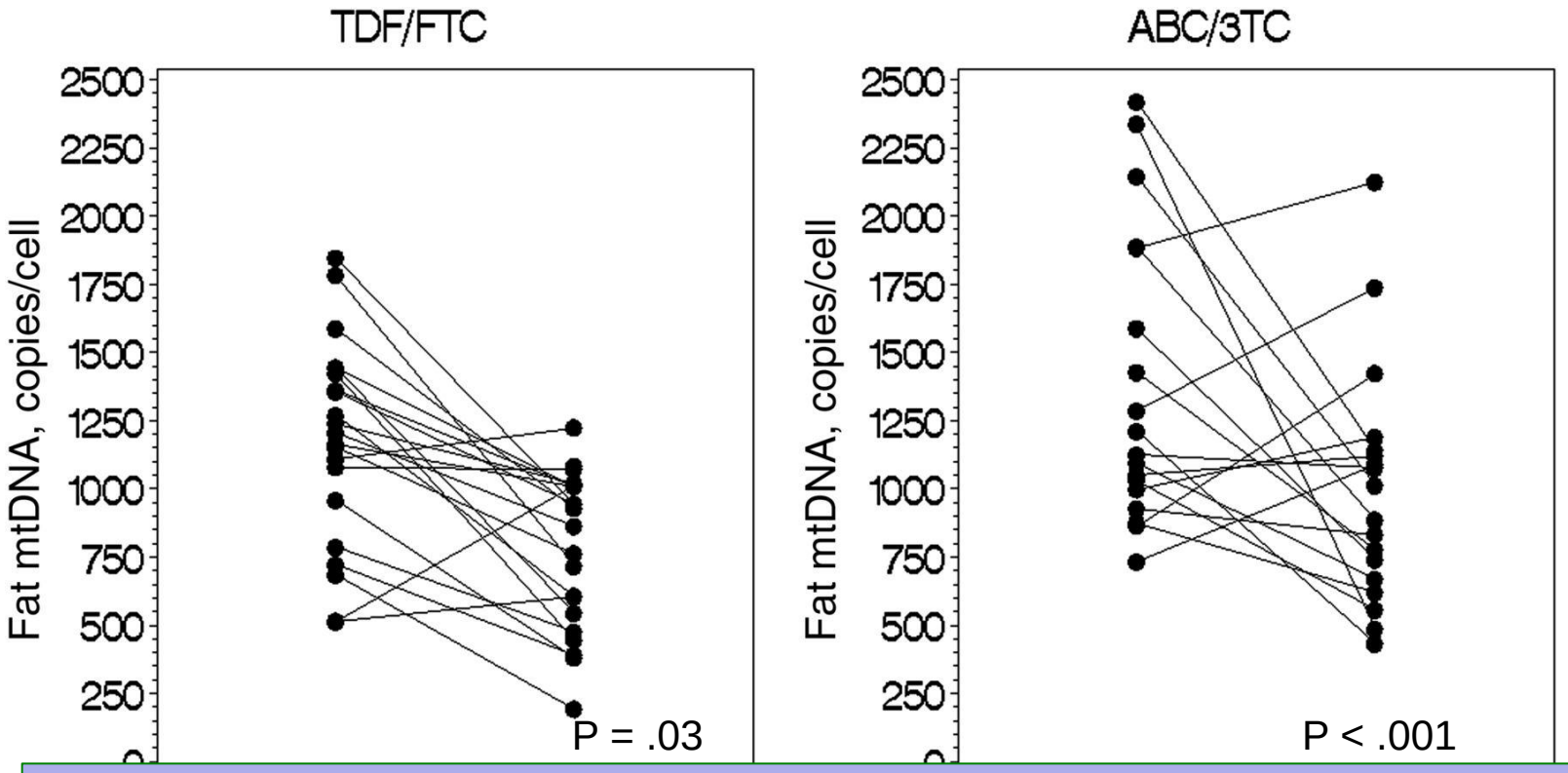
cardiovascolare



osso



Changes in Fat Mitochondrial DNA and Function by type of NRTIs (A5224s study): 39 paired samples



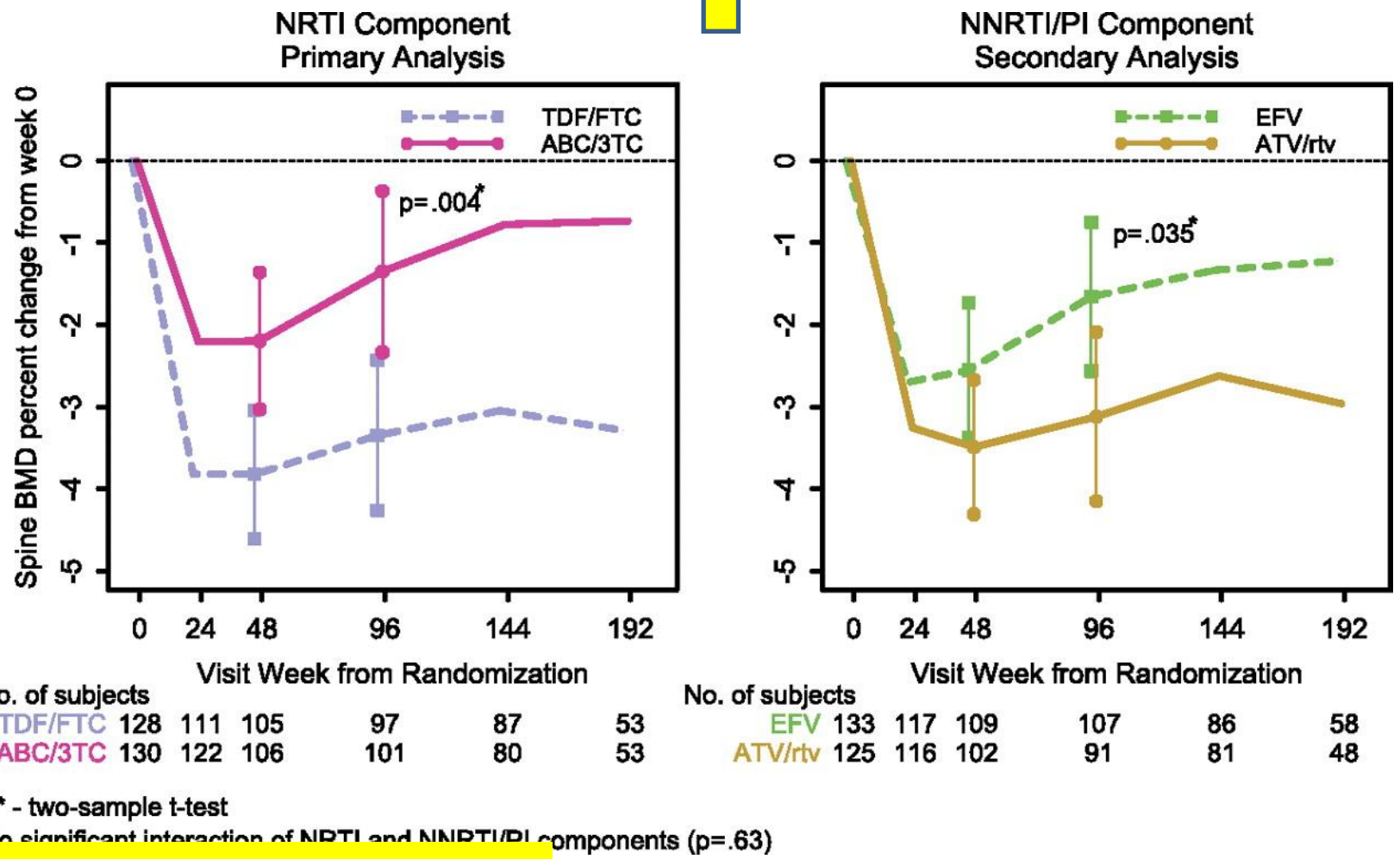
In addition, in subjects treated with TDF/FTC (but not ABC/3TC), there was evidence of mitochondrial respiratory chain dysfunction.

Median change in mtDNA over 2 years: -340 and -400 copies (p=0.57)

McComsey GA, et al. J Infect Dis 2013;207:604–11

ACTG A5224s Study, 269 pts, DXA scans

Mean percentage change in lumbar spine BMD by ITT analysis.

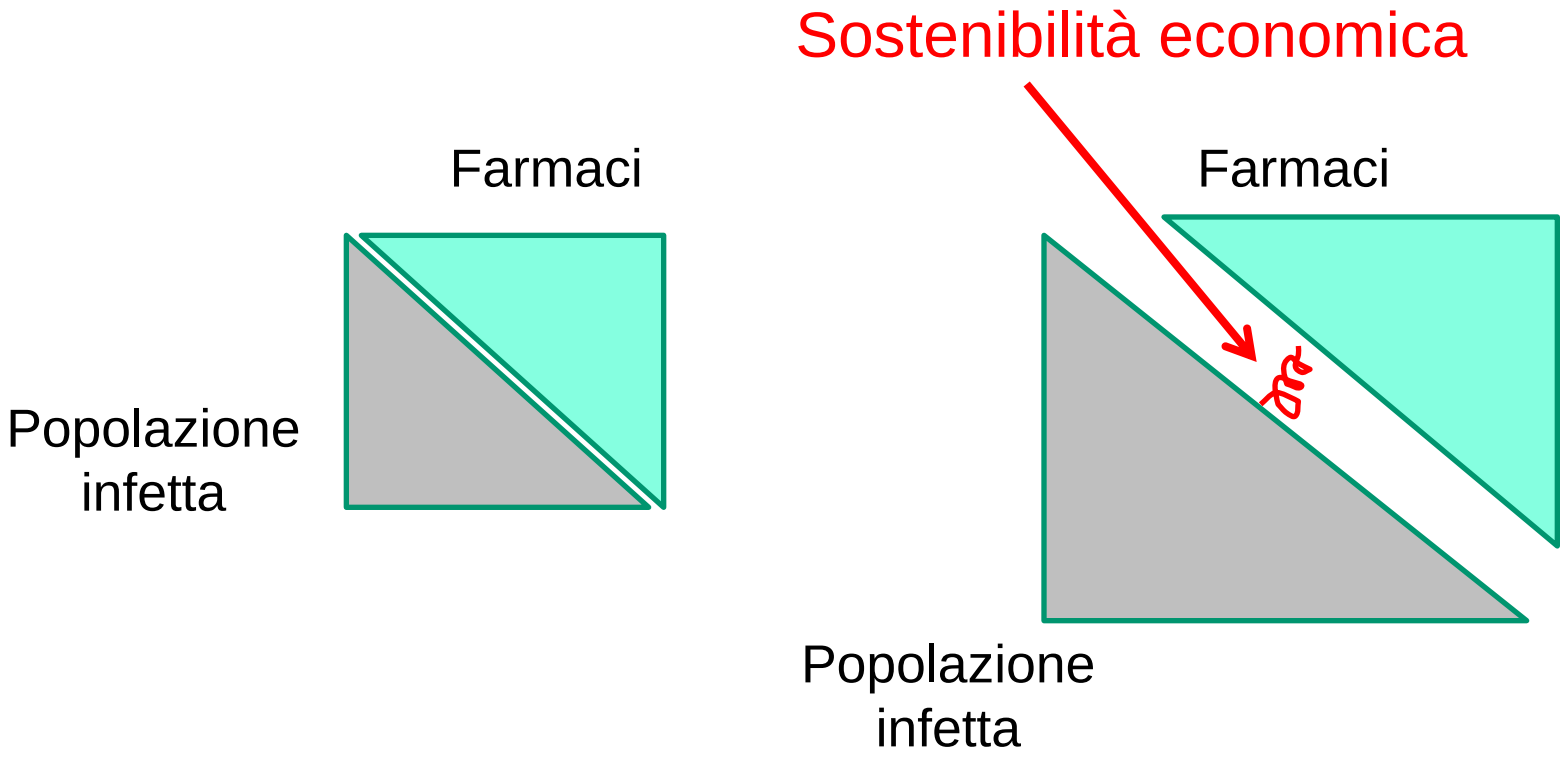


Regimi con minore tossicità

McComsey G A et al. J Infect Dis. 2011;203:1791-1801

Antiretroviral treatment French guidelines 2013: economics influencing science

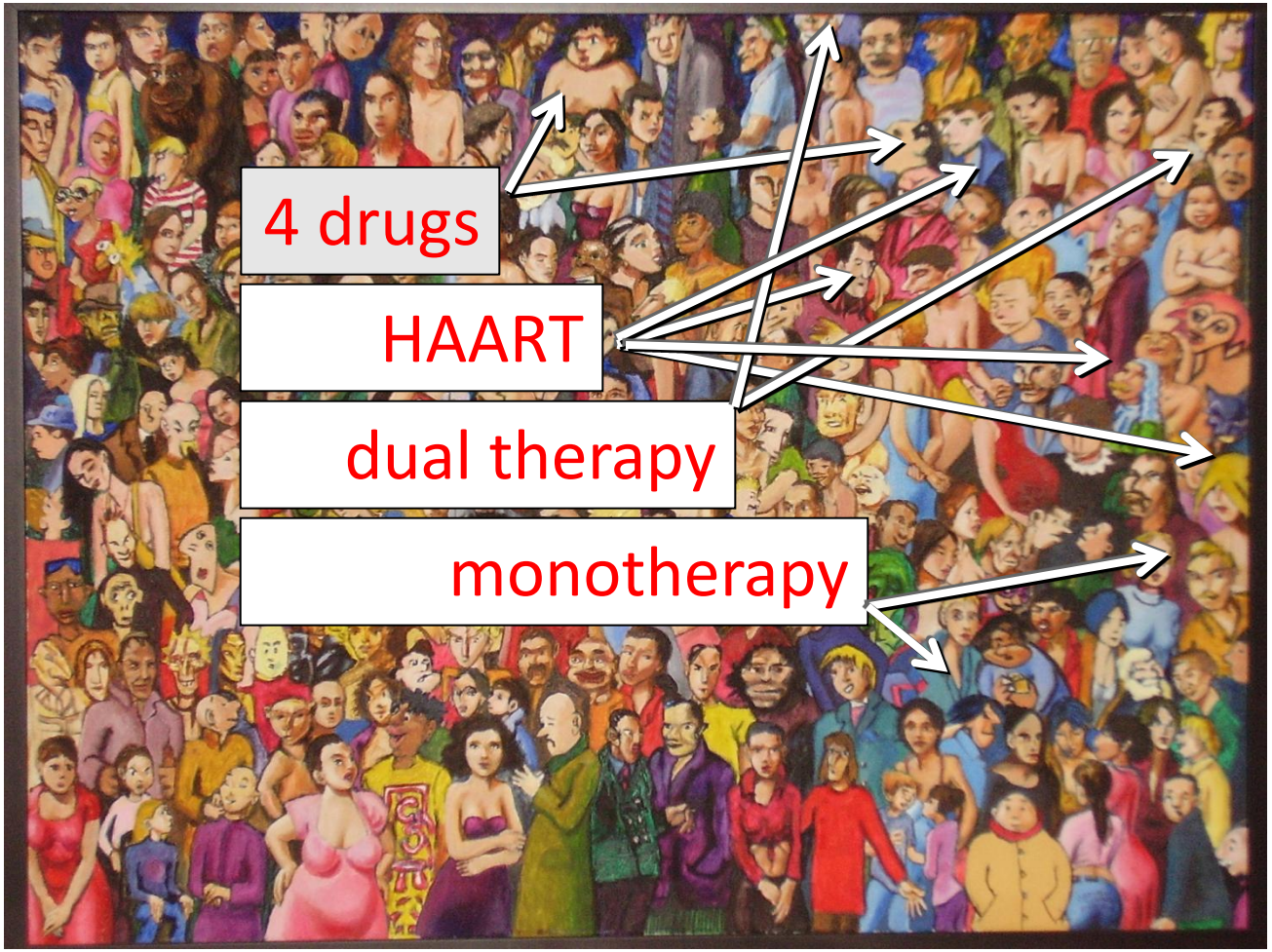
F. Raffi[1]* and J. Reynes[2]



regimi meno costosi

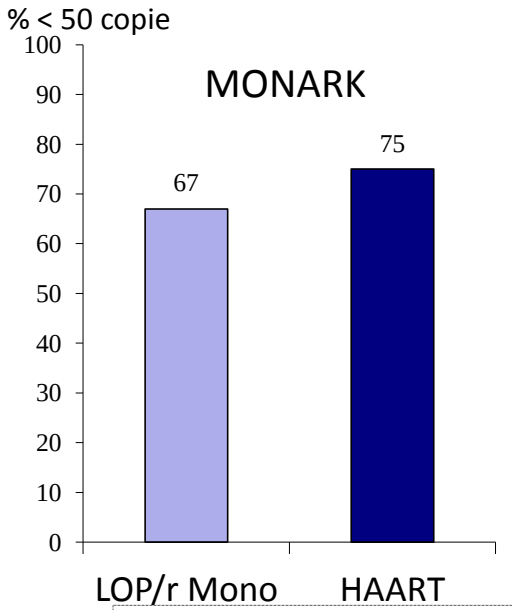
Raffi F, Reynes J. JAC 2014;69:1158-61.

Minore tossicità + Minor costo → Strategie alternative → Personalised HIV medicine



Is HAART de-intensification possible?

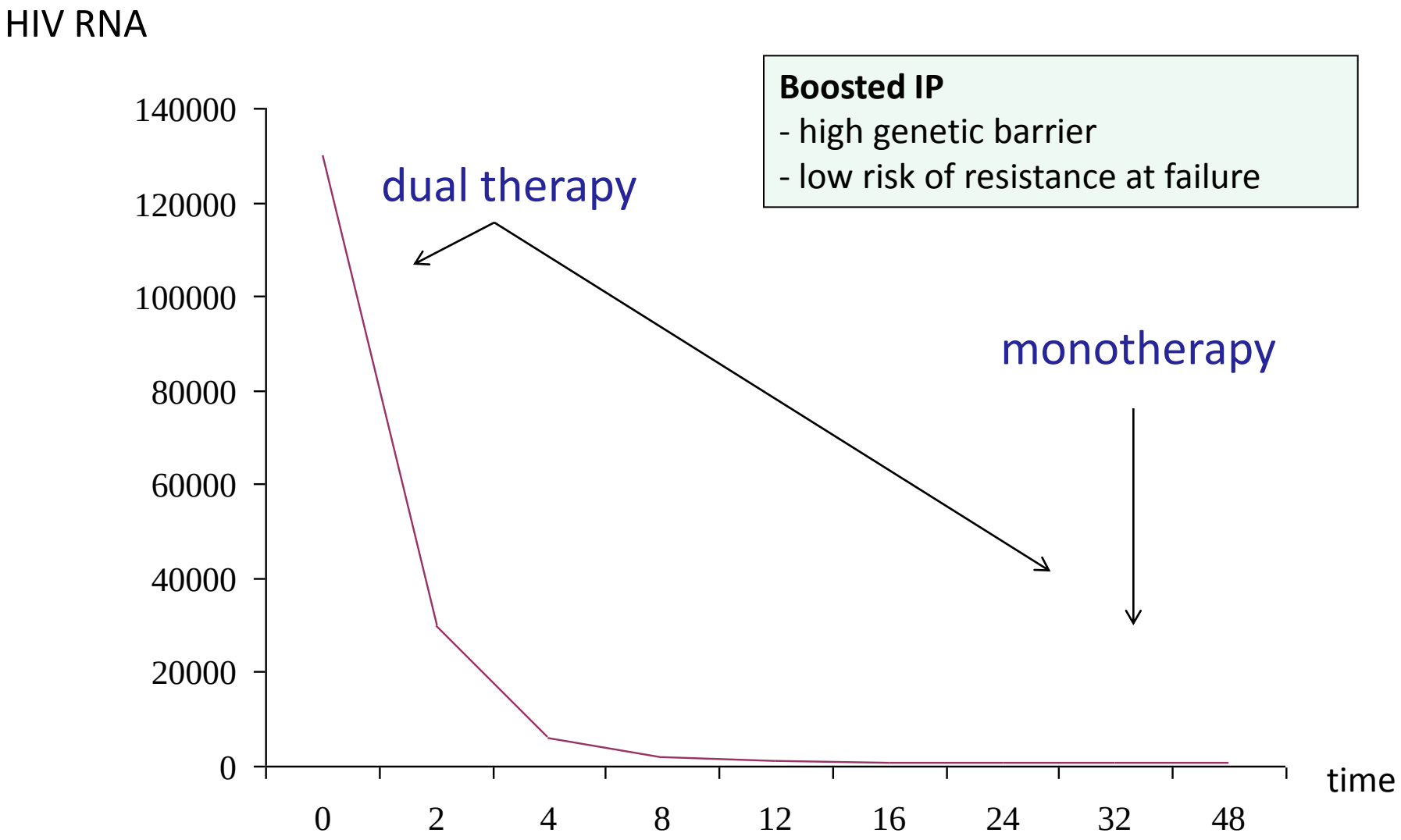
- PI monotherapy in naive: Monark study
- Dual therapy in heavily treated patients
- “Functional” monotherapy in experienced pts



83 versus **53** pts
v.l. < 10^5; CD4 > 100 cells
48 weeks, < 50 copies

Meynard JL et al JAC 2010

- Viremic and aviremic pts are different settings
- New agents and new combinations


HIV RNA
Boosted IP
- high genetic barrier
- low risk of resistance at failure
dual therapy
monotherapy
140000
120000
100000
80000
60000
40000
20000
0
0
2
4
8
12
16
24
32
48
time

DUAL THERAPY

Any combination?

1. Genetic barrier of the regimen
2. Antiviral potency of single agents
3. Drug-to-drug interactions
4. Toxicity profile
5. PK simmetry
6. Forgiveness of the regimen
7. Penetration into compartments
8. Convenience

DUAL regimens

LOP/r		DRV/r		
PROGRESS	**GARDEL**	**NEAT**	**MODERN**	**GUSTA**
206 pts naive Abbott	**416 pts** naive international	**800 pts** naive European	**804 pts** naive ViiV	**330 pts** switch Italy
LOP/r +TDF/FTC LOP/r + **RAL**	LOP/r +2NRTIs LOP + **3TC** bid	DRV/r + TDF/FTC DRV/r + **RAL**	DRV/r + TDF/FTC DRV/r + **MRV** od 150mg	DRV/r + TDF/FTC DRV/r + **MRV** od 300mg
96 weeks	48 weeks	96 weeks	48 weeks	48 weeks
completed	completed	completed	stop	ongoing

GARDEL

GLOBAL ARV DESIGN ENCOMPASSING LOPINAVIR/RITONAVIR AND LAMIVUDINE VS LOPINAVIR/RITONAVIR BASED STANDARD THERAPY

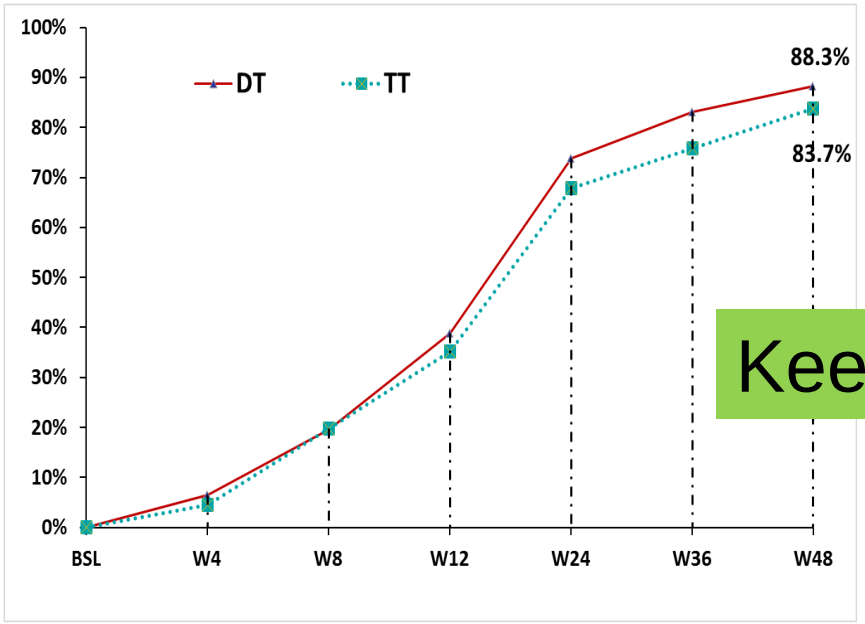
Phase III, randomized, international , controlled, open-label study

(Argentina, Chile, Mexico, Peru, Spain, US.)

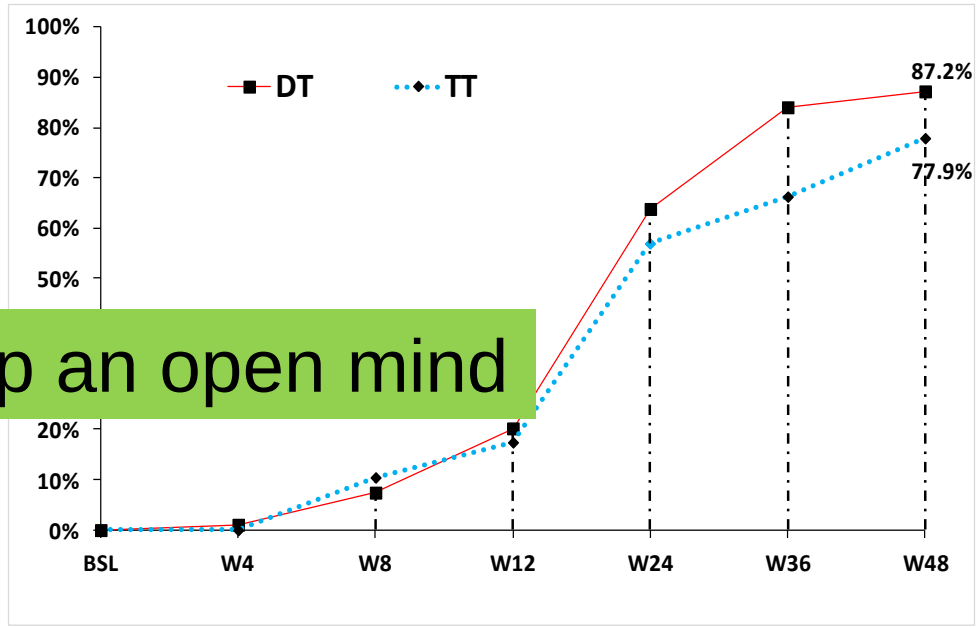
DT: LPV/r 400/100mg BID + 3TC 150 mg BID (n=217)

TT: LPV/r 400/100mg BID + (3TC or FTC) + (NRTI) (n=209)

Viral load <50 copies/mL at week 48 (ITTe)



Viral load <50 copies/mL at week 48 (ITTe), baseline VL > 100.000 copies/mL



Keep an open mind

Primary endpoint : % of patients with HIV-1 RNA< 50 copies/mL in an ITT-exposed analysis at 48 weeks (FDA-snapshot algorithm).*

HIV RNA >10^5 c/ml = 43%

CD4 < 200 c/mmc = 19%

NRTIs (%)

ABC/3TC: 9.5

TDF/FTC: 36

ZDV/3TC: 54

M184V mutations: 2 in dual arm

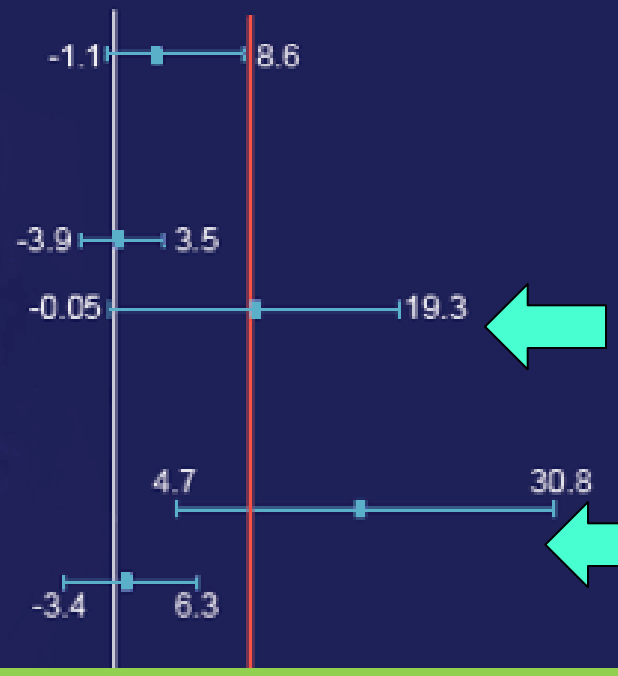
Cahn P et al. EACS 2013

CROI 2014

NEAT 001/ANRS 143

Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r



		RAL + DRV/r	TDF/FTC + DRV/r
Overall	n = 805	17.4 %	13.7 %
Baseline HIV-1 RNA			
< 100,000 c/ml	n = 530	7 %	7 %
≥ 100,000 c/ml	n = 275	36 %	27 %
			p = 0.09*
Baseline CD4+			
< 200/mm³	n = 123	39.0 %	21.3 %
≥ 200/mm³	n = 682	13.6 %	12.2 %
			p = 0.02*

NRTI-based regimens are robust!

Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* Test for homogeneity

CD4 gain at wk 96 = 267 vs 266 c/mmc

Virological failure during follow-up and resistance data

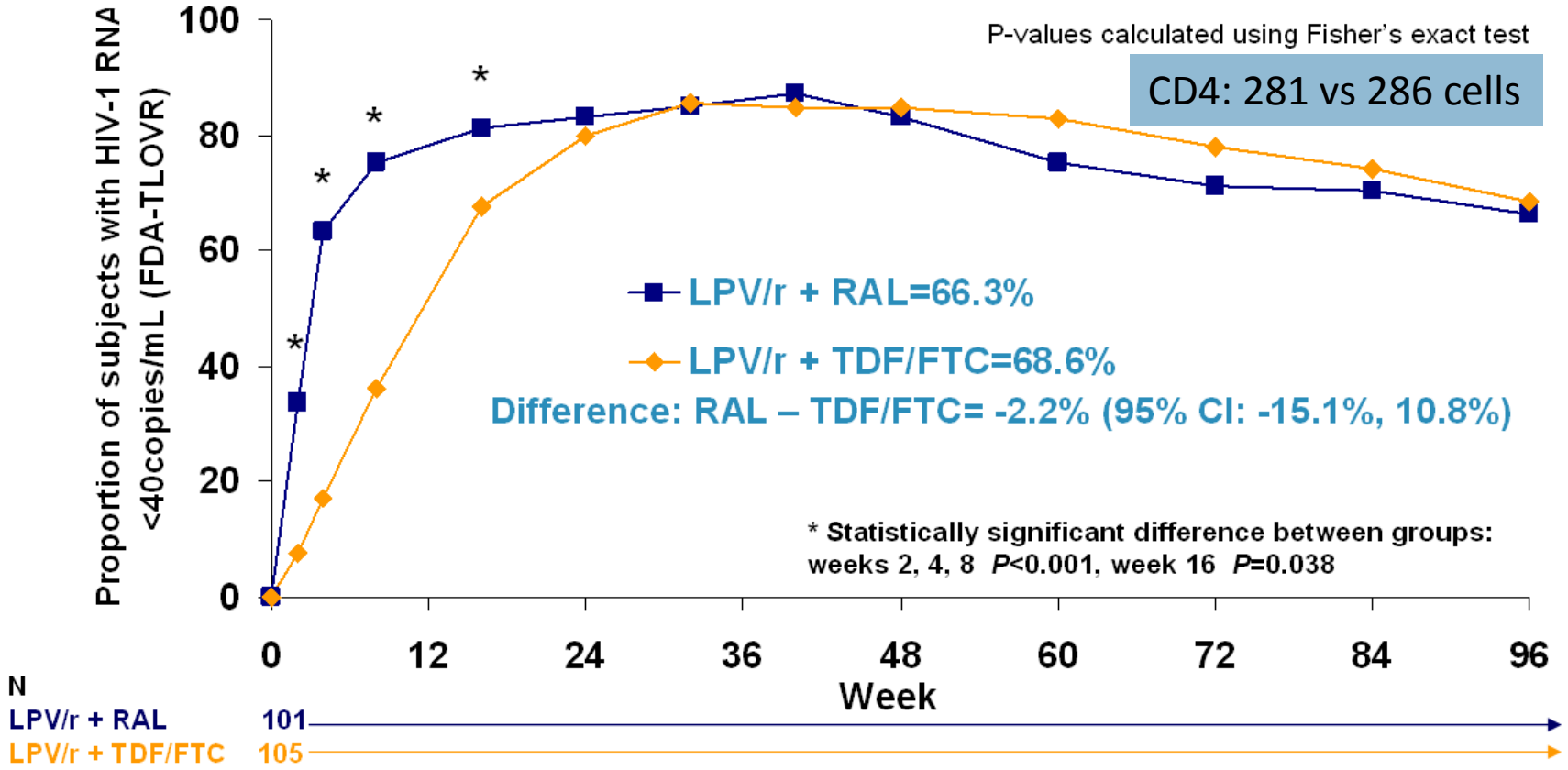
	RAL + DRV/r n=401	TDF/FTC + DRV/r n=404
Protocol-defined virological failure (PDVF), n	66	52
Number of PDVF who met criteria for genotype testing (HIV RNA > 500 copies/ml at or after W32)	33	9
Number of patients with single unconfirmed value of HIV RNA > 500 copies/ml at or after W32 (meeting criteria for genotype testing)	3	6
Genotype done, n	28/36	13/15
Major resistance mutations, n	5	0
NRTI	1 (K65R)	0
PI	0	0
INI	5 (N155H)*	-

* 1 additional patient with T97A

Protocol-defined virological failure change of any component of the initial randomised regimen before W32 because of confirmed insufficient virological response, defined as HIV-1 RNA reduction < 1 $\log_{10}$ copies/ml by W18 or HIV-1 RNA ≥ 400 copies/ml at W24 ; failure to achieve virological response by W32 (confirmed HIV-1 RNA ≥ 50 copies/ml at W32) ; confirmed HIV-1 RNA ≥ 50 copies/ml at any time after W32

According to the protocol, genotypic testing was carried out by local laboratories when patients had a single VL > 500 copies/ml at or after W32.

PROGRESS: proportion of subjects responding at week 96 (FDA-TLOVR)



Week 96 FDA-TLOVR response for subjects with BL plasma HIV-1 RNA ≥100,000 copies/mL:
LPV/r + RAL= 6/15, LPV/r + TDF/FTC= 10/19

MODERN study

Re: **Data Monitoring Committee Recommendation to Terminate ViiV Healthcare Study A4001095 (MODERN); A Multicenter, Randomized, Double-Blind, Comparative Trial of Maraviroc + Darunavir/Ritonavir versus Emtricitabine/Tenofovir + Darunavir/Ritonavir for the Treatment of Antiretroviral-Naïve HIV-infected patients with CCR5-Tropic HIV-1**

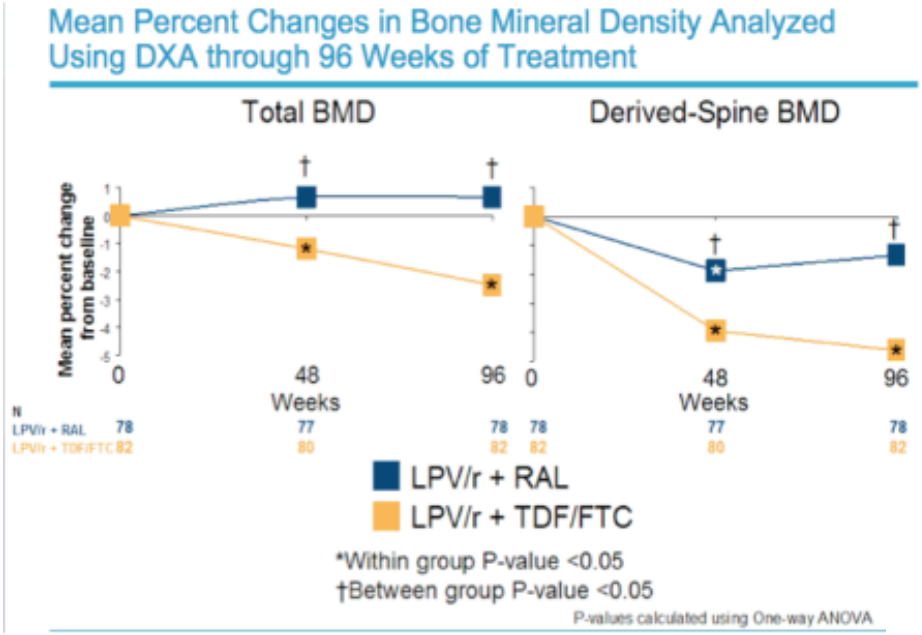
The analysis showed that the percentage of subjects with HIV-1 RNA <50 copies/mL at week 48 was approximately **72% and 83% for MVC and TDF/FTC**, respectively. Response on the MVC arm was statistically significantly lower than the TDF/FTC arm, with the lower bound of the 95% confidence interval (CI) being lower than the non-inferiority margin of -10% (the 95% CI for MVC versus TDF/FTC: −17.7% to −6.1%).

Do not assume potency!
drug-to-drug interactions?

The differences in **of both baseline viral load and th** on, there were 38 subjects on the MVC arm versus 13 subjects on the TDF/FTC arm who met the protocol defined confirmed **treatment failure criteria**.

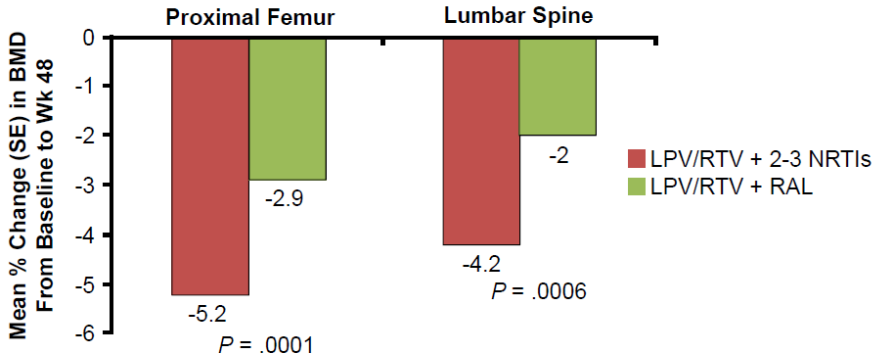
Which benefit for NRTI-sparing regimens?

PROGRESS study



In 210 participants,
DEXA scans at T0 and T48 wk

SECOND-LINE: Greater Mean BMD Loss With NRTI-Based Regimen at Wk 48



- No significant difference in frequency of new osteopenia, osteoporosis
- Greater decline in lumbar spine BMD associated with lower BMI, no TDF before study, and TDF initiation on study

Martin A, et al AIDS 2013;27:2403–11

… if we just stop TDF?

ATLAS study

ATV/r +3TC 300mg

*40 pts, 97.5% discontinued TDF.

Table 3. Changes in bone composition, bone metabolism biomarkers and body fat distribution after 48 weeks

	Baseline value	Change after 48 weeks	Percentage change in BMD after 48 weeks	*P* value
Weight, kg	74 (15)	0 (4)	—	0.965
BMI, kg/m^2	25 (4)	0 (1)	—	0.990
Bone composition				
total BMD, g/cm^2	1.03 (0.09)	+0.03 (0.06)	+2.04 (5.7)	**0.026**
total Z-score	−0.60 (0.92)	+0.25 (0.65)	—	**0.028**
femoral neck BMD, g/cm^2	0.79 (0.14)	+0.01 (0.28)	+0.75 (3.5)	0.262
femoral neck Z-score	−0.32 (1.02)	+0.14 (0.24)	—	**0.002**
total hip BMD, g/cm^2	0.92 (0.14)	0 (0.07)	+0.02 (6.8)	0.864
total hip Z-score	−0.16 (0.96)	+0.10 (0.31)	—	0.055
L2–L4 column BMD, g/cm^2	0.99 (0.17)	+0.01 (0.03)	+0.91 (0.9)	0.064
L2–L4 column Z-score	−0.59 (1.53)	+0.18 (0.46)	—	**0.022**
Bone metabolism biomarkers				
vitamin D, ng/mL	27.20 (8.25)	−3.68 (9.51)	—	**0.024**
PTH, pg/mL	53.71 (17.31)	−3.54 (18.13)	—	0.243
osteocalcin, ng/mL	34.07 (13.05)	−12.76 (14.81)	—	**<0.001**
Body fat distribution				
total fat, g	21488 (8014)	−327 (2)	—	0.307
limb fat, g	8451 (3114)	−33 (793)	—	0.804
trunk fat, g	12001 (5409)	−378 (1542)	—	0.150
limb/trunk fat ratio	1.10 (0.30)	+0.03 (0.09)	—	**0.027**

Total BMD + 2.04 %

Femoral neck

Lumbar spine

Di Giambenedetto et al. JAC 2013;68:1364-72

ATLAS study

ATV/r +3TC 300mg

*40 pts, 97.5% discontinued TDF.

Table 2. Changes in CD4 cell count, blood lipids, bilirubin and renal function after 48 weeks (on-treatment analysis)

	Baseline	Week 48	Mean change after 48 weeks	*P* value
Immunological parameters				
CD4 cell count, cells/mm^3	630 (190)	669 (232)	+36 (159)	0.179
Lipid parameters				
total cholesterol, mg/dL	188 (37)	204 (47)	+17 (27)	**0.001**
HDL cholesterol, mg/dL	45 (11)	50 (12)	+6 (8)	**<0.001**
LDL cholesterol, mg/dL	109 (25)	116 (36)	+8 (24)	0.052
total cholesterol/ HDL cholesterol	4.4 (1.3)	4.3 (1.4)	−0.16 (0.9)	0.287
HDL cholesterol/ LDL cholesterol	0.4 (0.2)	0.5 (0.2)	+0.04 (0.1)	0.086
triglycerides, mg/dL	185 (137)	196 (131)	+8 (116)	0.668
Bilirubin				
total bilirubin, mg/dL	2.6 (0.9)	2.8 (1.4)	+0.1 (1.4)	0.657
unconjugated bilirubin, mg/dL	2.2 (0.8)	2.4 (1.3)	+0.18 (1,3)	0.402
Renal function				
estimated GFR, mL/min/1.73 m^2	70 (13)	77 (17)	+7.3 (11.6)	**<0.001**

TC +17 mg/dl

HDL-C +6 mg/dl

eGFR +7.3 mL/min

Di Giambenedetto et al. JAC 2013;68:1364-72

… and PI-sparing dual regimen?

+ NVP

(Montrucchio et al. ICAAR 2013)

RAL

+ MRV

(Katlama C et al. JAC 2014
Nozza S et al. JAC 2014)

+ ETR

(Calin R et al. IAS 2013
Monteiro P et al. JAC 2014)

MRV 300mg bid + RAL 400mg bid

Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study

Switch study in 44 aviremic (median time: 5.2 years),
nadir CD4: > 100 [median 210 (150-270)] cells,
R5 tropic virus on HIV-DNA, with lypodistrophy.
VF in **5/44** patients (11.4%, CI: 3.8–24.6) < 24 weeks
Resistance to RAL (F121Y, Y143C, N155H) in 3/5 patients
and switch from R5 to X4 tropic virus in 2/5 patients.

69:1648

Una coppia non è necessariamente solida!!!

Viral rebound after switch to maraviroc/raltegravir dual therapy in highly experienced and virologically suppressed patients with HIV-1 infection

Switch study in 26 aviremic , but extensively experienced pts
R5 tropic virus on HIV-DNA.
VF in **9/26** (35%) < 24 weeks.
Resistance to RAL (Y143C, N155H) in 5/9 patients

Nozza S. et al. JAC 2014;69:1436

ETR 200mg BID + RAL 400mg BID

- Observational, single centre.
- Switch study in **91 aviremic**, median F-up: 11.5 months (4.6 – 22.7)
- Follow up: 65 pts (month 6), 48 pts (month 12).
- PP analysis: **98.2**% (6 mos) and **92.3** % (12 mos) had HIV RNA < 50 copies

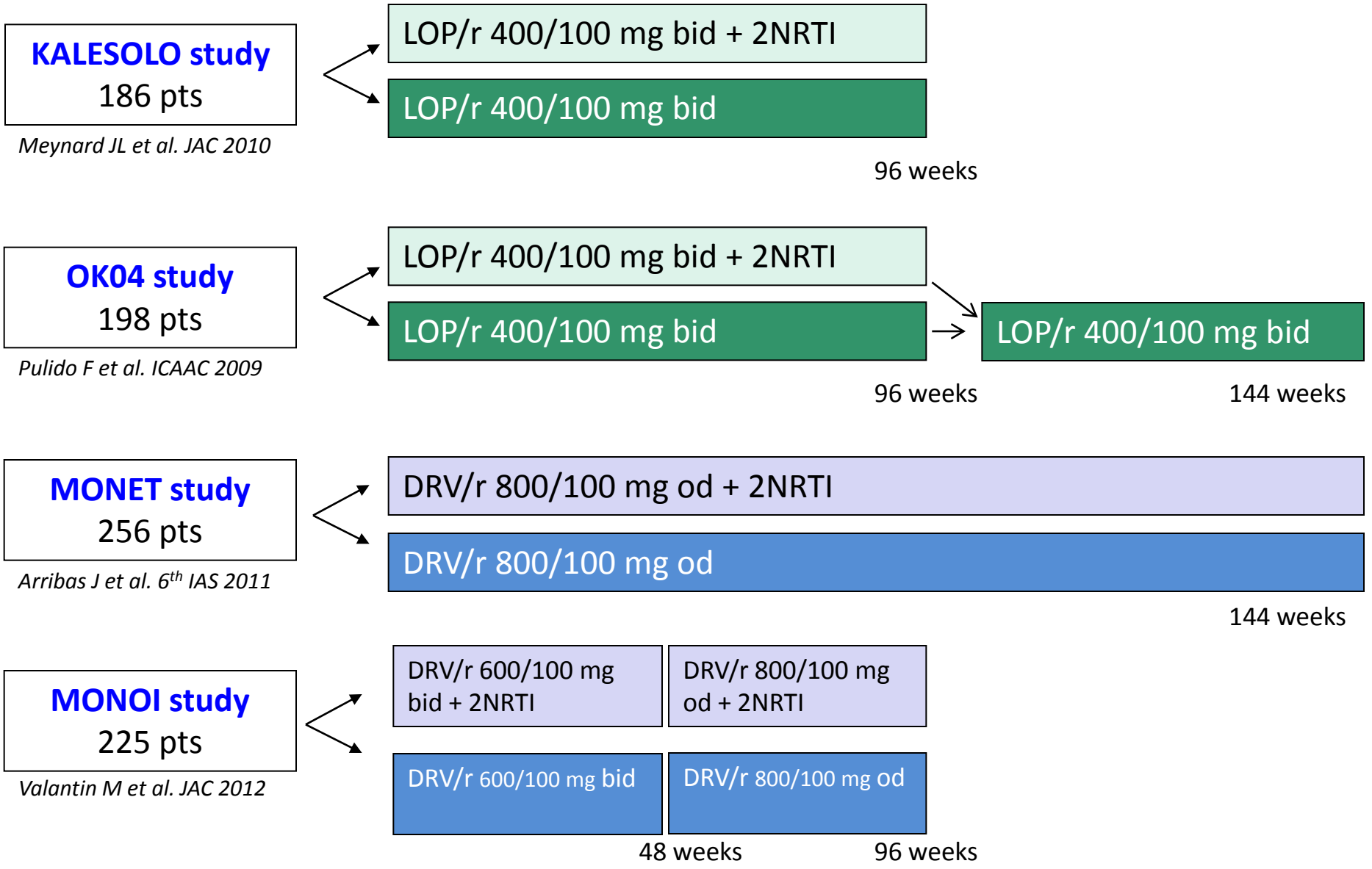
VF in **3** patients

Pts	Previous NNRTI	Previous NNRTI mutation	Genotype at failure	Time since switch (months)
1	yes	V179I	-	<6
2	yes		72I	6-12
3	yes	K103N, Y181C,	225H, 181C, **155H**	6-12

Calin R et al. IAS 2013; P WEPE516

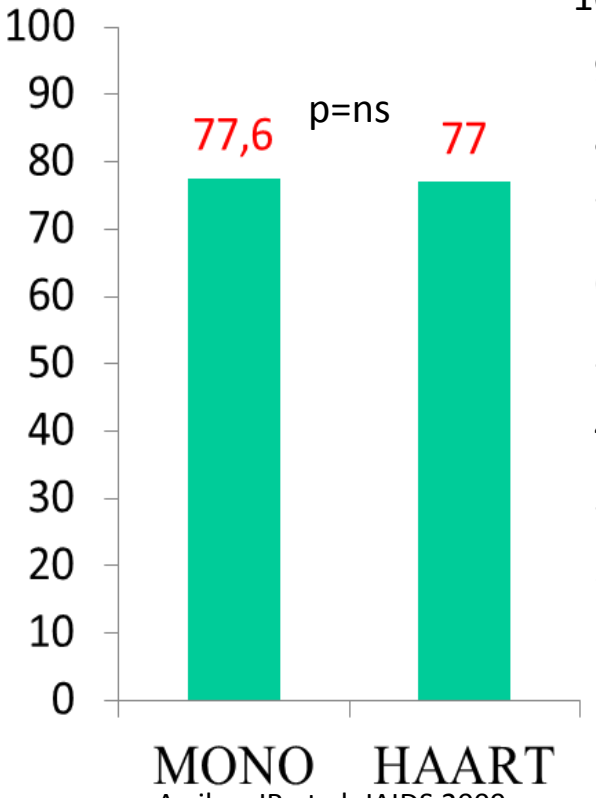
PI MONOTHERAPY
(maximal de-intensification)

Efficacy and durability for boosted PI monotherapy



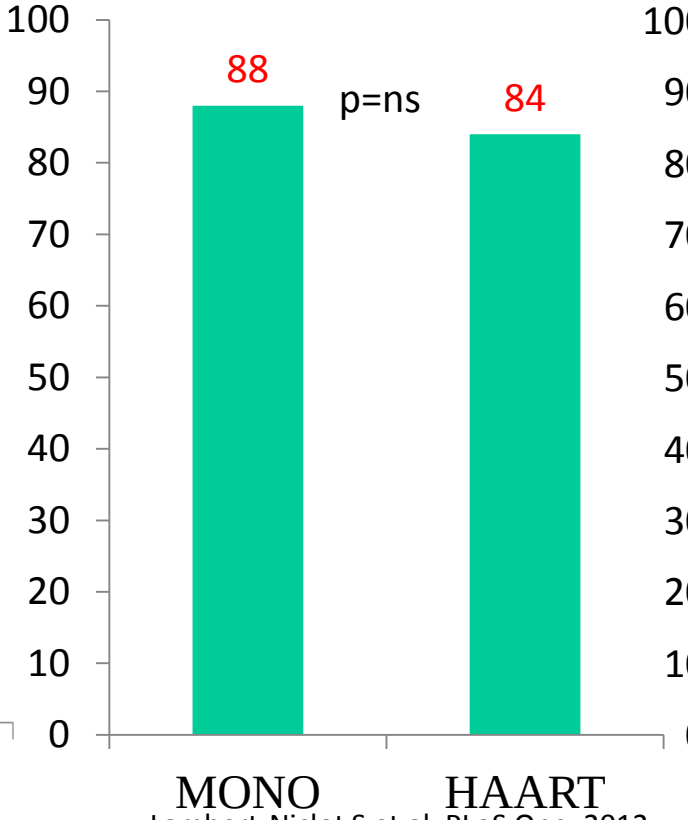
PI/r monotherapy trials: virological efficacy

OK04 study (96 wks)
198 patients
LOP/r bid vs HAART
HIV RNA < 50 copies/ml
Analysis: ITT, M=F, R=F



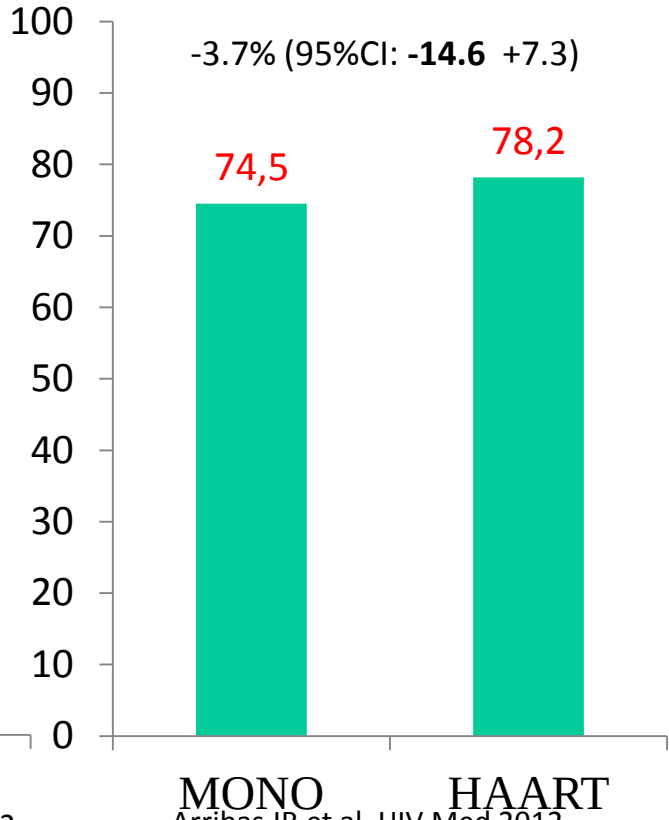
Arribas JR et al. JAIDS 2009

MONOI (96 wks)
225 patients
DRV/r vs HAART
HIV RNA < 50 copies/ml
Analysis: ITT, withdrew consent=F, M=F



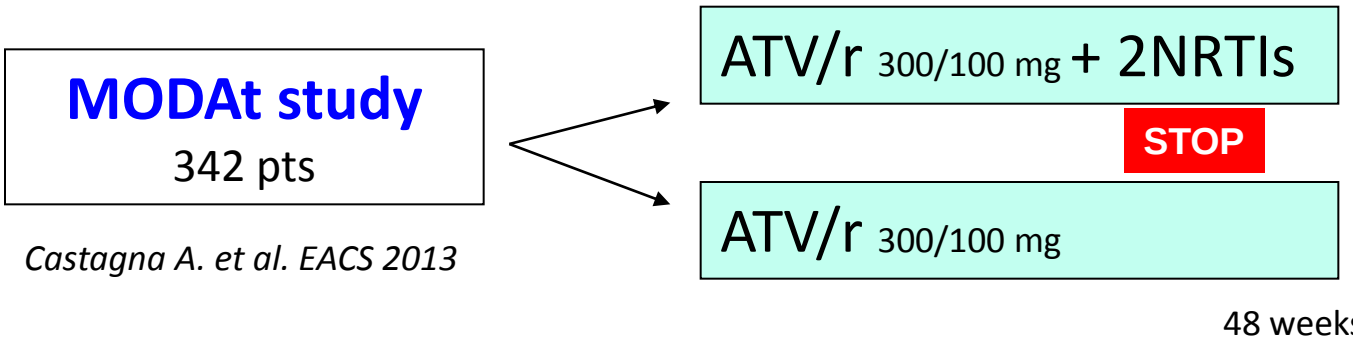
Lambert-Niclot S et al. PLoS One. 2012

MONET (144 wks)
256 patients
DRV/r od vs HAART
HIV RNA < 50 copies/ml
Analysis: PP, M=F

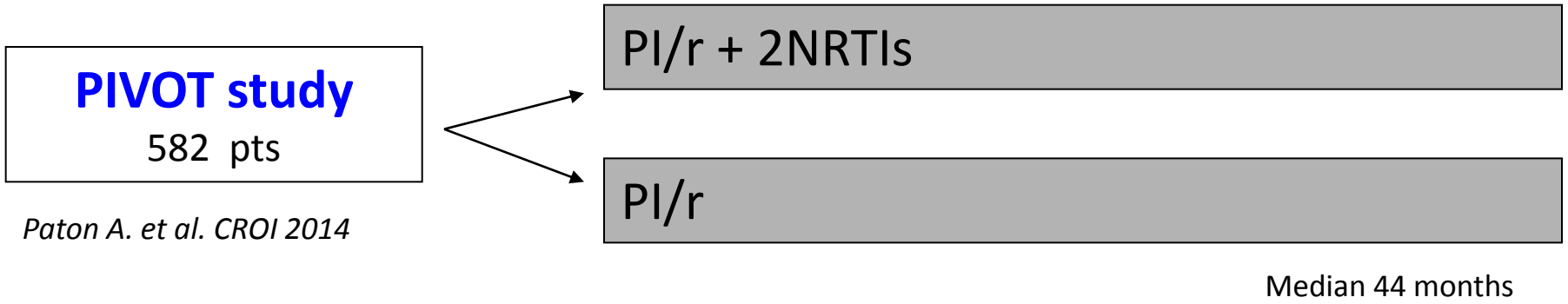


Arribas JR et al. HIV Med 2012

Efficacy and durability for boosted PI monotherapy



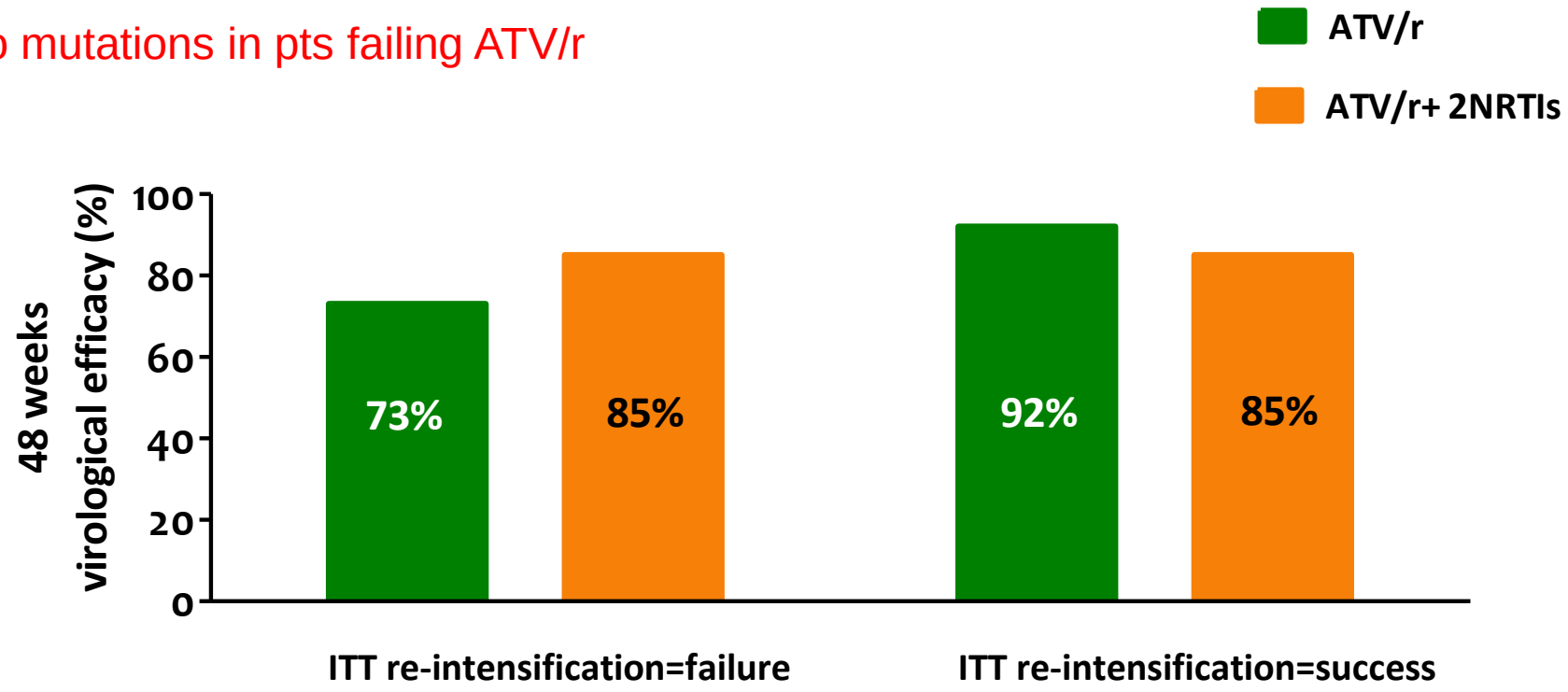
Castagna A. et al. EACS 2013



Paton A. et al. CROI 2014

MODAt 48 weeks virological efficacy

No mutations in pts failing ATV/r

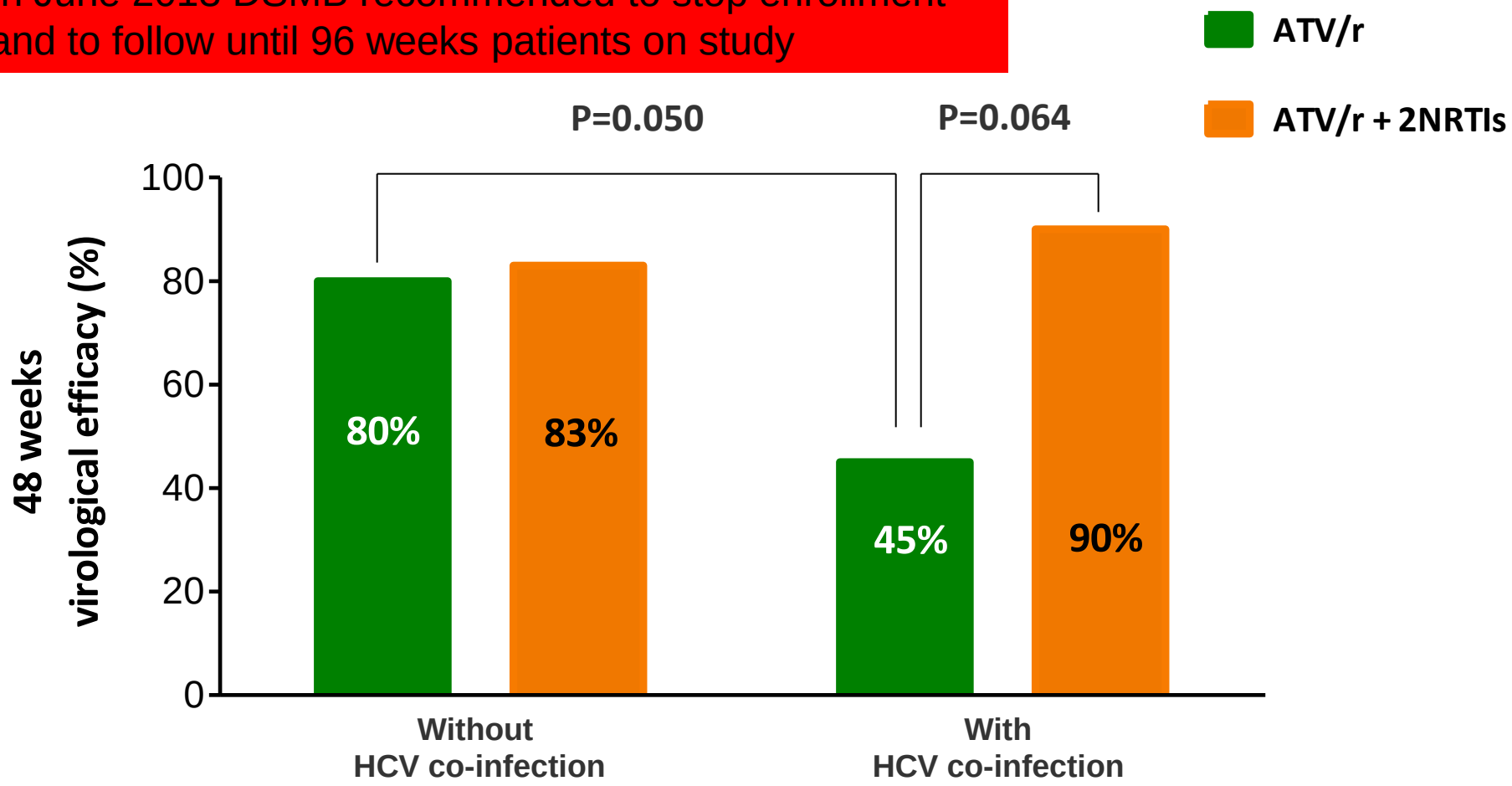


Difference (95% CI):	**-12.1% (-27.8% to 3.6%)**	**7.5% (-4.7% to 19.8%)**
BL CD4+ (cells/ µL)	**599 (457-774)**	**570 (417-735)**
48 weeks CD4+ change (cells/µL)	**50 (-21/+131)**	**33 (-34/+136)**

Castagna A. et al, EACS 2013

MODAt Virological efficacy according to HCV co-infection

on June 2013 DSMB recommended to stop enrollment and to follow until 96 weeks patients on study



Castagna A. et al, EACS 2013

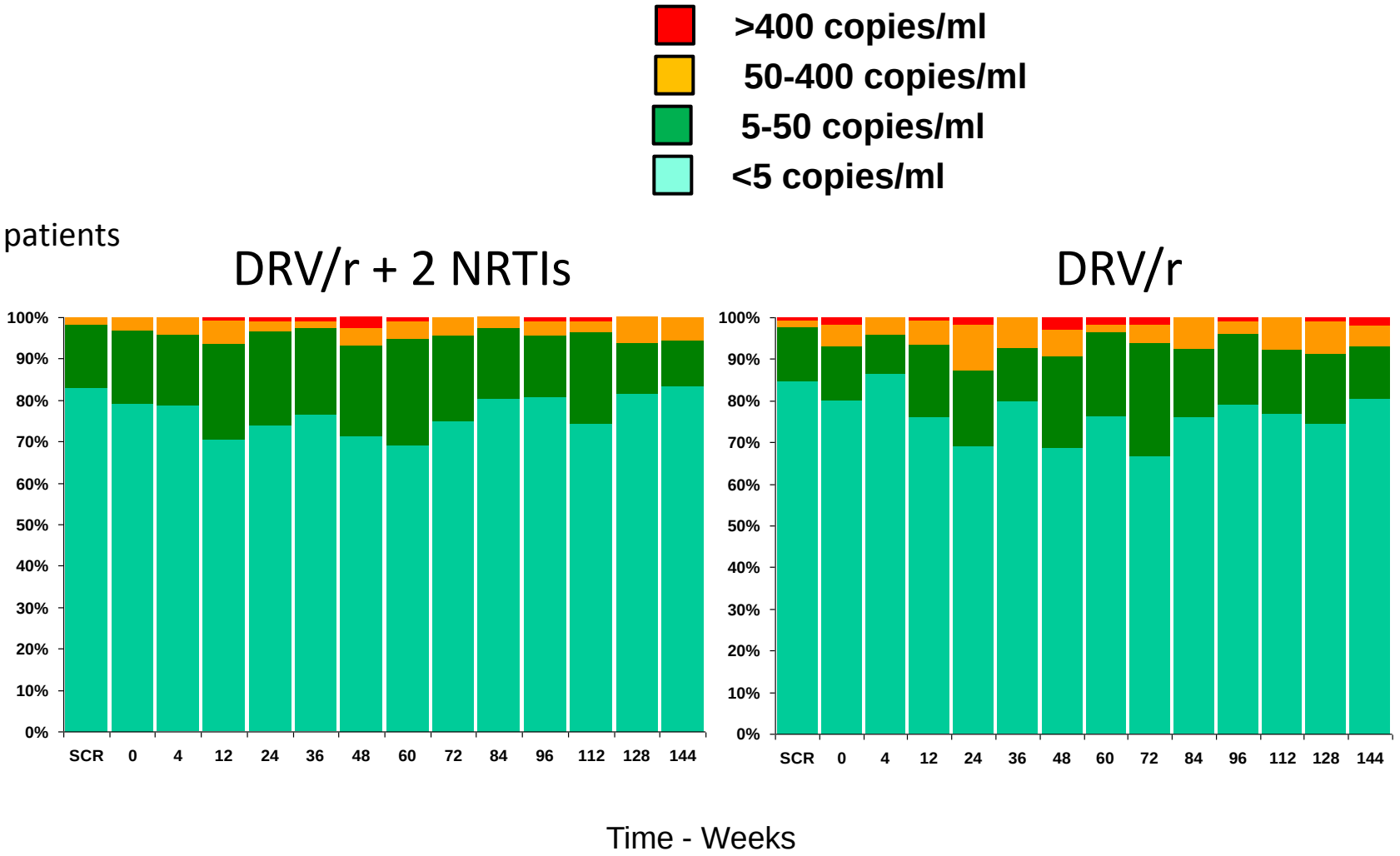
PIVOT Trial (44 UK HIV centres)

	PI/r + 2NRTIs 291 pts	PI/r 296 pts	Difference (95%CI)	P value
VL > 50 copies n (%)	8 (3.2)	95 (35)	31.8 (24.6 to 39)	<0.001
Loss of future options (by 36 mos)	2 (0.7)	6 (2.1)	1.4 (-0.4 to 3.4)	0.15
Loss of future options n (%) (by the end of trial)	4 (1.8%)	6 (2.1%)	0.2% (-2.5 to 2.6)	0.85
CD4 change (SE)	+91 (9)	+108 (9)	+17 (-10 to +43)	0.21
Serious AE n(%)	8 (2.8)	15 (5.1)	2.3	0.15
Grade 3-4 AEs	159 (55%)	137 (46%)	-8.4% (-16.4 to 0.3)	0.043
Neuro-cognitive Function mean change	+0.15	+0.50	-0.01 (-0.11 to +0.09)	0.86

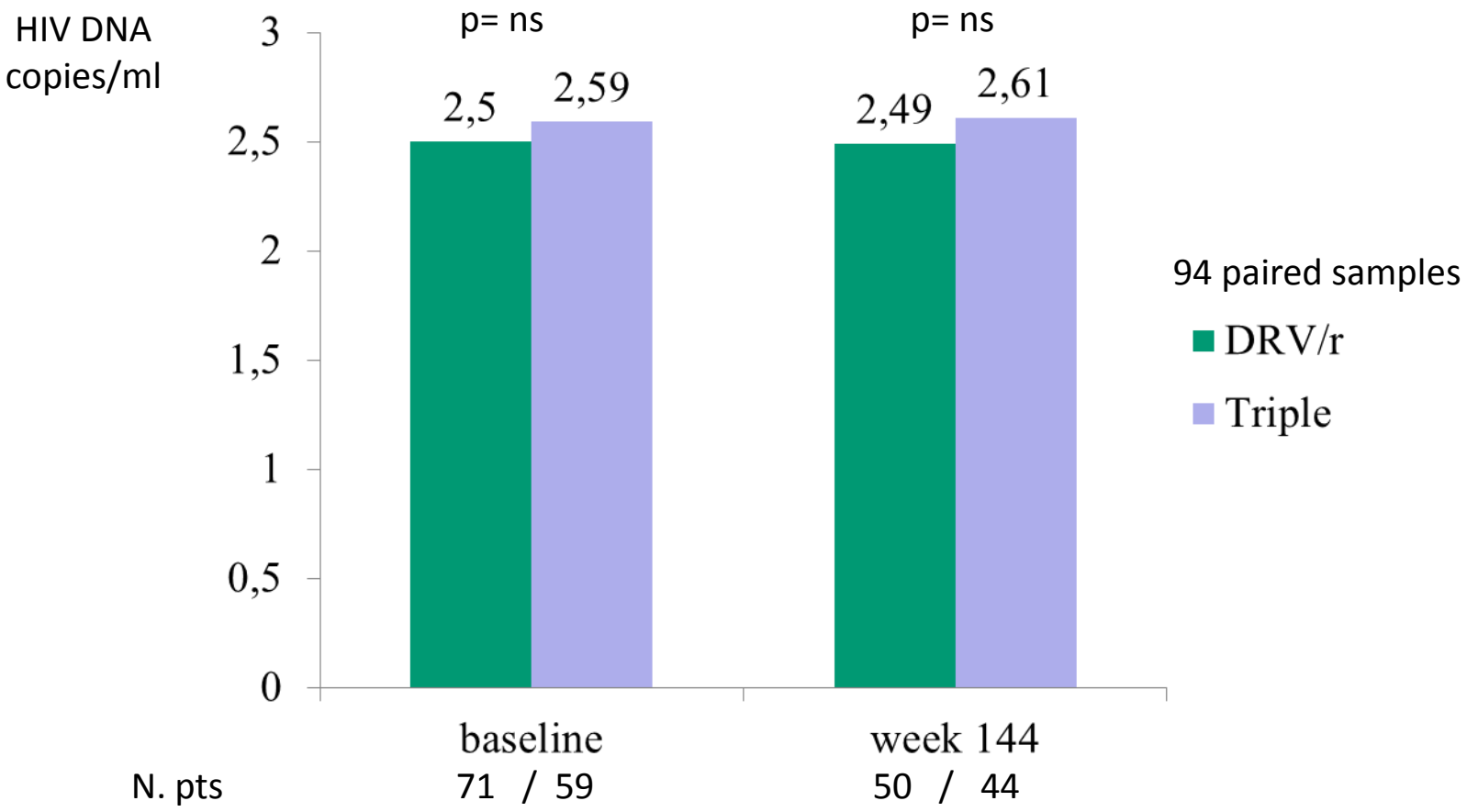
Median follow up: 44 months

Paton N et al. CROI 2014; Abs 550LB

MONET Week 144 analysis: HIV RNA <5 versus time on DRV/r monotherapy (observed data analysis)



MONET study: HIV-1 DNA change by treatment group from baseline to 144 wks



Mean change from baseline (Log copies/10^6 PBMC)	-0.05 / +0.03	p= ns

Geretti AM et al. HIV Clin Trials 2013;14:45-50

Risks of monotherapy compared to HAART

	Resistance mutations at failure			Immune recovery	salvage
Study (N of pts) Follow-up	**Primary PI mutations**	**secondary PI mutations**	**mutations in gag gene**	**mean CD4 count increase**	**Efficacy of reinduction**
OK04 [1] (100 vs 98) 96 weeks	2 vs 2	3.0 vs 3.5 (in 15 patients)	No difference	+71 vs +41	83% (10/12)
MONOI [2] (112 vs 113) 96 weeks	1 vs 0	1/9 patients	No difference	+70 vs +39	100% (5/5)
MONET [3] (127 vs 126) 144 weeks	1 vs 1	No difference	Not done	+95 vs +99	85% (6/7)

§ non statisticamente significativo;
° mutazione V11I, già presente 7 anni prima;
For all comparisons: mono vs triple arm

1. Arribas J. JAIDS 2009; 2. Valantin M. JAC 2012; 3. Arribas J. HIV Med 2012

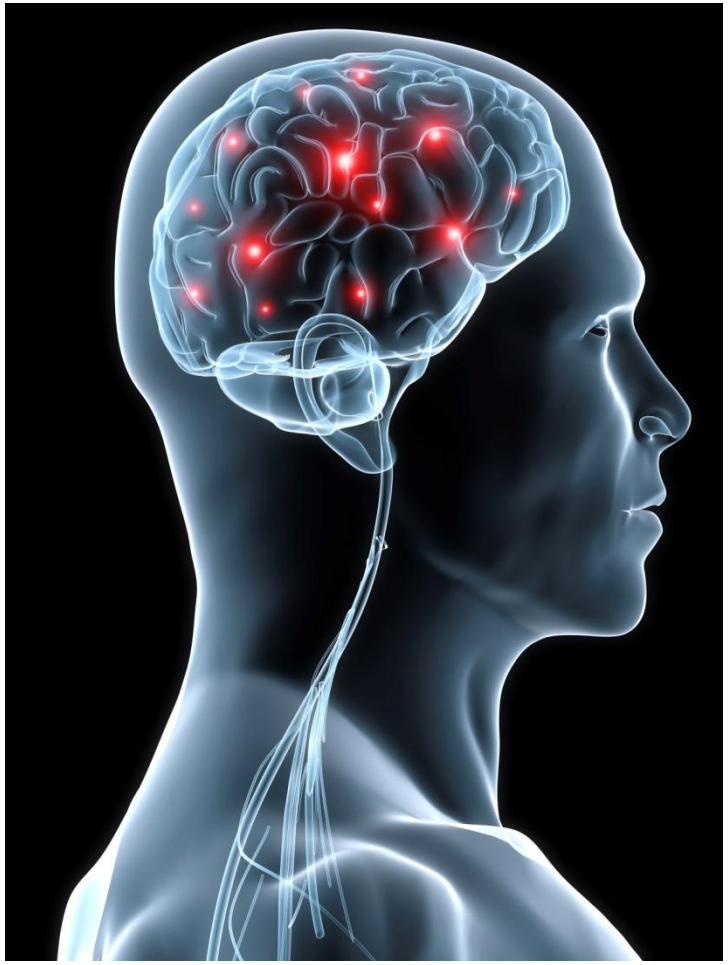
Which patients can qualify for PI mono?

1. Switch strategy in virologically suppressed patients (PI- or NNRTI-based Rx)
2. Nadir CD4+ count > 100 c/mm^3 [1-3] or HIV-1 RNA <10^5 c/mL[4]
3. No need of NRTIs (HIV-related encephalopathy. HBV coinfection …)
4. Patients with optimal adherence
5. Long (?) history for suppression
6. No history of PI failure
7. Patients able to tolerate low-dose RTV
8. HCV coinfection (?)

A large proportion of selected patients can be treated with PI mono (~70-75% after 3 years are still suppressed in RCTs)

1. Pulido F et al. Antivir Ther. 2009;14:195-201.
2. Campo R et al. CROI 2007. Abstract 514 .
3. Gutmann C et al. AIDS. AIDS. 2010;24:2347-2354
4. Katlama C et al. AIDS. 2010 ;24:2365-2374.

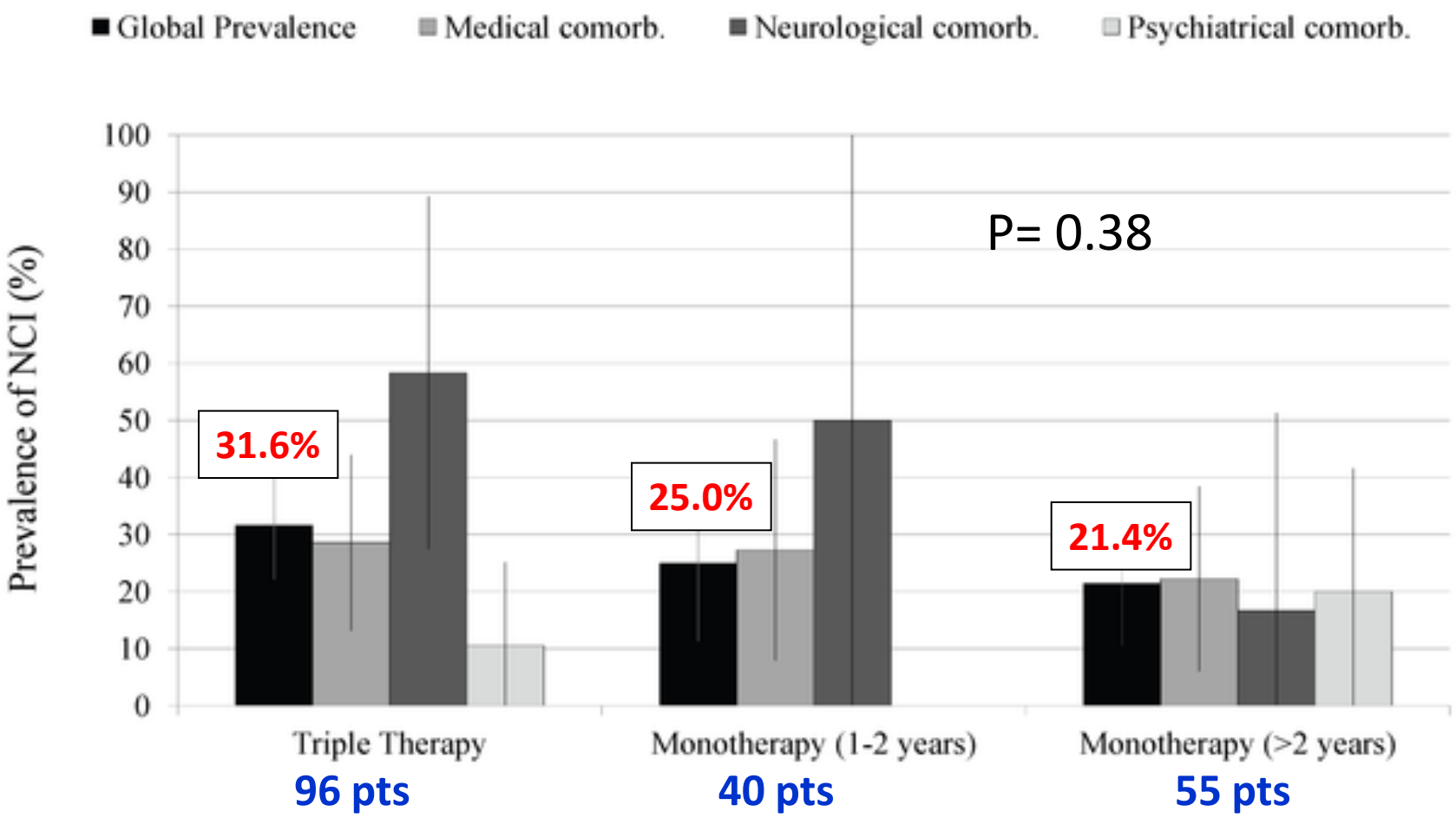
PI monotherapy and the brain



- PROTEA and PIVOT trials ongoing

NCI n patients treated with PI monotherapy compared to triple regimens

Observational, cross sectional, DRV/r or LOPV/r monotherapy vs triple, 191 pts



Pérez-Valero I, et al PLoS ONE 2013 8(7): e69493

Summary

NRTI-based regimens:
Restano lo standard di riferimento nei pazienti naive.

NRTI-sparing regimens (Dual):
Opzione possibile in pazienti naive (NEAT 01, Gardel).
Solitamente regimi PI-based.
Attenzione alle dosi ed alla combinazioni.
Minor tossicità rispetto ai TDF-based regimens (BMD, renal).
Di solito regimi più costosi della NRTI-based HAART.

Monoterapia
Solo con PI boosted
Solo in strategia di switch in pazienti selezionati
Meno costosi di altri regimi

GRAZIE

Deintensification strategies

	DUAL	PI MONO
Treatment Paradigm	Combination regimen	single drug
Settings	viremic, failing or switch	switch
Options	NRTI- sparing	NRTI- sparing
	RTV- and PI-sparing **?**	NO
Drug exposure	higher	minimal
Risks	higher risk of resistance mutations at failure	marginal risk
Control in different compartments	potentially more	potentially less
Costs	± expensive	cheaper
Randomized Clinical Trials	Progress, Earnest NEAT 001, Gardel	4 RCTs, up to 144 weeks

How PI monotherapy compares to HAART?

Can a «single drug» regimen suppress plasma HIV RNA?

Which price at virological failure?

Which risks for intermittent viremia

Durability? CD4 count evolution?

How many patients can benefit?

How to select patients?

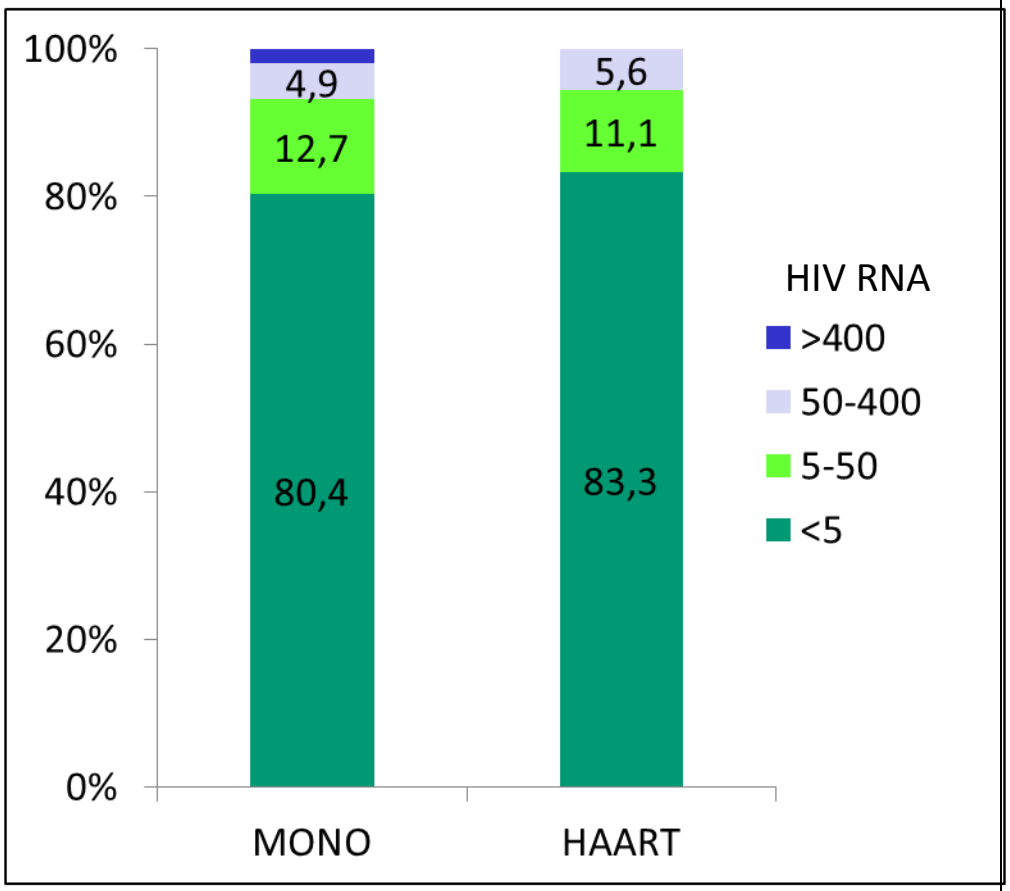
Which effect on HIV DNA reduction and evolution?

Can HIV be controlled in compartments other than plasma?

Low level viremia in monotherapy arms

MONET (144 weeks)

Observed data analysis

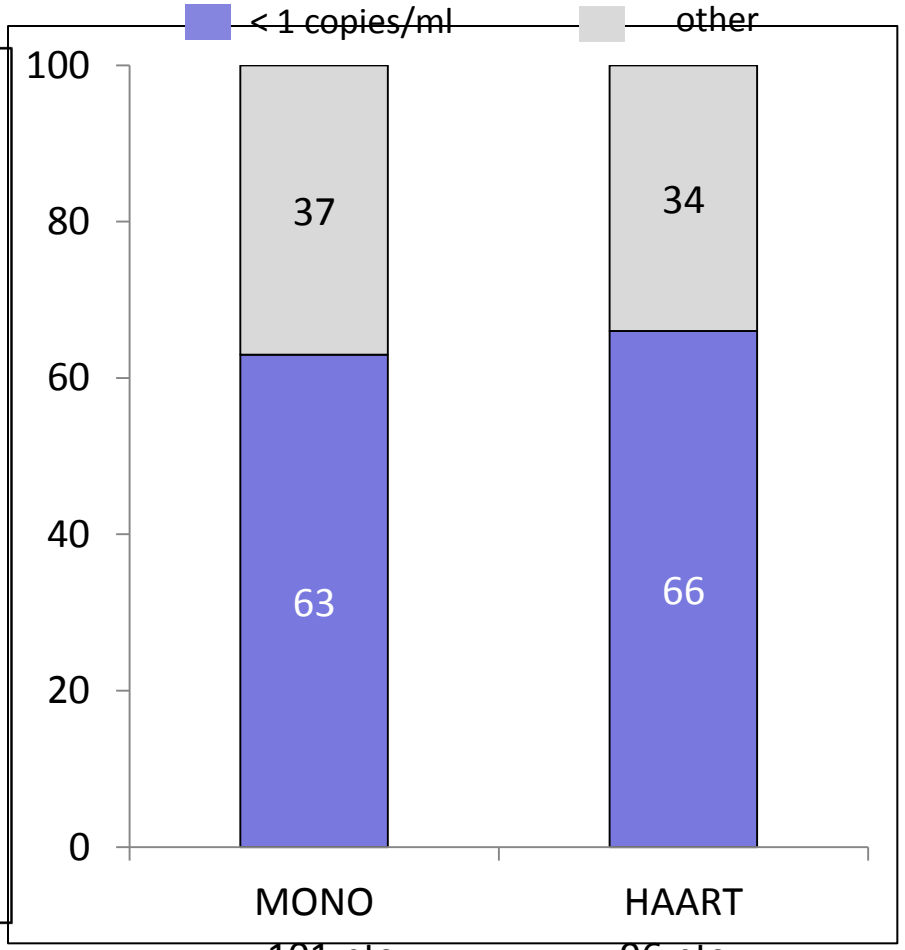


102 pts 108 pts

Data on file, Janssen

MONOI (48 weeks)

Observed data analysis



101 pts 96 pts

Lambert-Niclot S et al. JID 2011

Risk factors for HIV RNA > 50 copies/ml

monotherapy arms in randomized trials

Study	Multivariate analysis Risk factors	OR, 95%CI	P value
OK + OK04 [1] 121 pts, 144 weeks	- > 2 missed visits - Haemogobin (per 1 g/dl increase) - Nadir CD4 (>100 vs > 100 cells)	6.30 (2.0 - 19.6) 0.68 (0.5 - 0.92) 4.1 (1.30 - 13.5)	<0.002 <0.013 <0.02
MONOI [2] 256 pts, 96 weeks	- Adherence (<100% or 100%) - HAART duration (5 ys decrease) - HIV DNA at D0 (1 Log increase)	3.84 (1.29 - 12.49) 2.93 (1.43 - 6.66) 2.66 (1.11 - 7.48)	<0.02 <0.006 <0.04
MONET [3] 225 pts, 144 weeks	- HCV coinfection	4.5 (2.06 - 9.17)	<0.0001

1. Pulido F et al. Antiv Ther 2009;14:195-201
2. Lambert-Niclot S et al. JID 2011;204:1211-16
3. Rieger et al. WAC July 2010, Vienna [abstr TBLBB209]

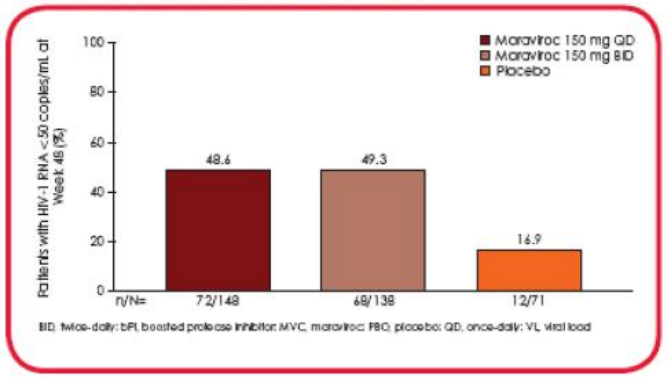
BACK UP

Efficacy of maraviroc administered once-daily or twice-daily with boosted protease inhibitors to treatment-experienced patients

Jayvant.Heera@pfizer.com

S Taylor,[1] J Arribas,[2] C-F Perno,[3] R Burnside,[4] L McFadyen,[5] D Hardy,[6] H-J Stellbrink,[7] DA Cooper,[8] J-M Molina,[9] E van der Ryst,[5] J Heera,[4] H Valdez[10]

Figure 5. A similar percentage of patients who received MVC QD or BID with a bPI achieved a VL <50 copies/mL at Week 48 when classified by use of a single bPI

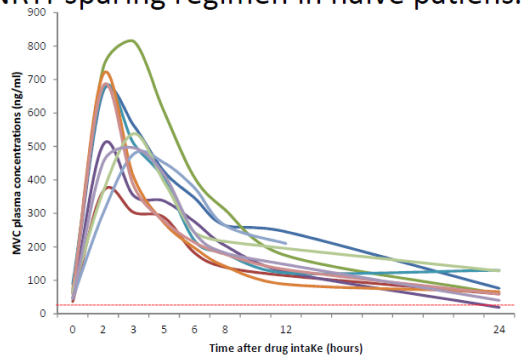


Conclusions

- In combination with a bPI (except TPV/r and FPV/r), comparable efficacy was demonstrated with MVC 150 mg QD and MVC 150 mg BID compared with placebo.
- Similarly, greater efficacy was maintained on MVC QD and BID compared with placebo in patients:
  - with high screening VL or low baseline CD4 count
  - receiving ≥1 other fully active drug
  - receiving a single bPI, or treated with a single bPI for the first time, or wi
- Exposure-response m administration was a
  - MVC concent were not foun after accounti of quantificati
- MVC administered Q that may offer patien their regimen to QD c

IAS 2011

Pharmacokinetics of Maraviroc administered at **150 mg QD** in association with Lopinavir/Ritonavir as a part of a novel NRTI-sparing regimen in naïve patiens.



- *Substudy of the VEMAN Study: 10 subjects, all of them achieved the targeted C_{avg} (> 75 ng/ml) for near maximal virological efficacy according to exposure-response analysis of MERIT study.*
- Moreover, PK profile was comparable to the previously reported for MVC 150 mg QD associated with ATV/RTV.

Calcagno A et al...

itted)

Lower Maraviroc Plasma Levels in Combination with Darunavir than with Other Protease Inhibitors Was Associated to Virological Failure - 24 Week Analysis of the MITOX Study

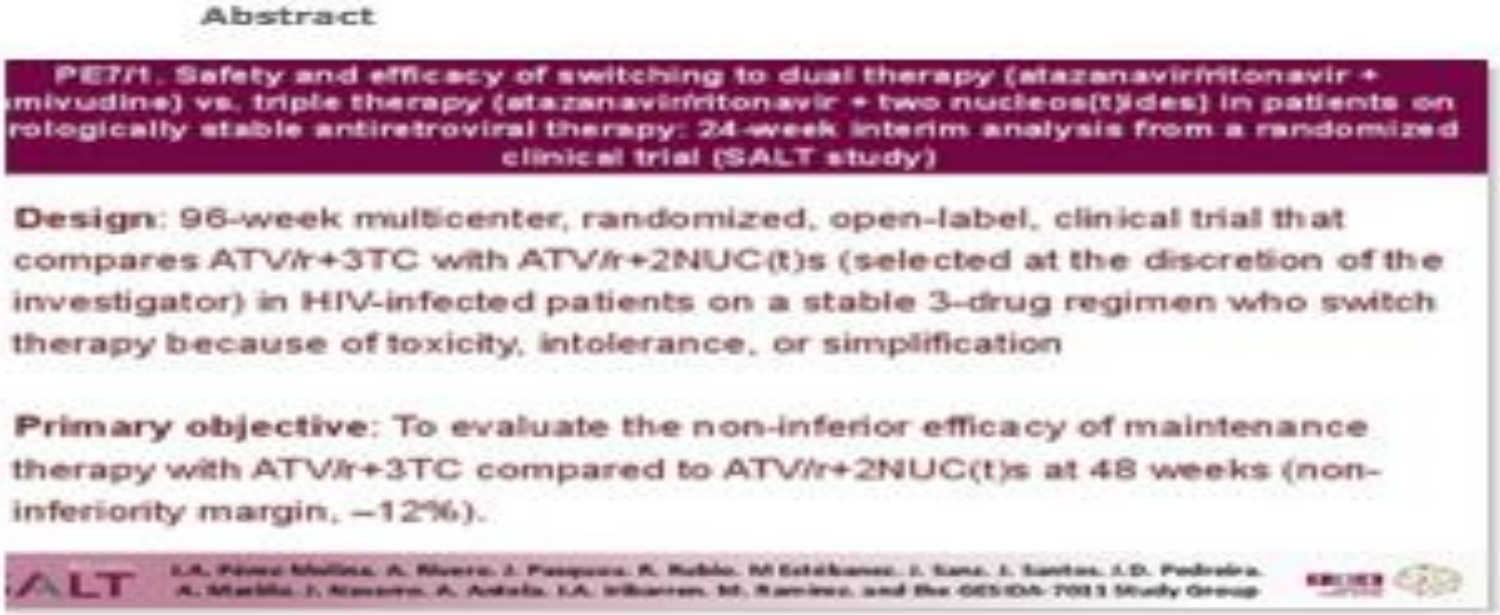
Obemeier et al. EACS 2013, Brussels. Poster PE10/15

- 80 HIV-infected pts with undetectable HIV plasma load <50 copies/mL and receiving two NRTI + PI/r were randomized either to continue ART or to switch to MVC 150 mg + PI/r regimen.
- Failure at week 24 (6 in MVC arm vs 2) was caused frequently by insufficient MVC levels,
- The most frequently used combination, DRV/r qd + MVC, was associated with lower plasma levels of MVC and may have been caused **by insufficient boosting due to lower RTV levels**. DRV/r+MVC regimen should be monitored by therapeutic drug monitoring.

MVC 300 mg bd +TVD (n=12)					MVC 300 mg OD +DRV/r (n=27)					MVC 150 mg OD +DRV/r (n=15)				
	Peak	Time (h)	Trough	Time (h)		Peak	Time (h)	Trough	Time (h)		Peak	Time (h)	Trough	Time (h)
Median	**384**	2	**48**	13	Median	**773**	2	**70**	24	Median	-	-	**50**	24
Mean	**546**	2	**48**	13	Mean	**698**	2	**95**	24	Mean	-	-	**65**	22
IQR 1st	340	2	38	12	IQR 1st	395	2	48	24	IQR 1st	-	-	39	24
IQR 3rd	743	3	66	14	IQR 3rd	982	2	102	25	IQR 3rd	-	-	56	24

Okoli, JAC 2012

SALT: 24 weeks interim analysis – No virological failures



Abstract

PE7/1. Safety and efficacy of switching to dual therapy (atazanavir/ritonavir + mivudine) vs. triple therapy (atazanavir/ritonavir + two nucleos(t)ides) in patients on rologically stable antiretroviral therapy: 24-week interim analysis from a randomized clinical trial (SALT study)

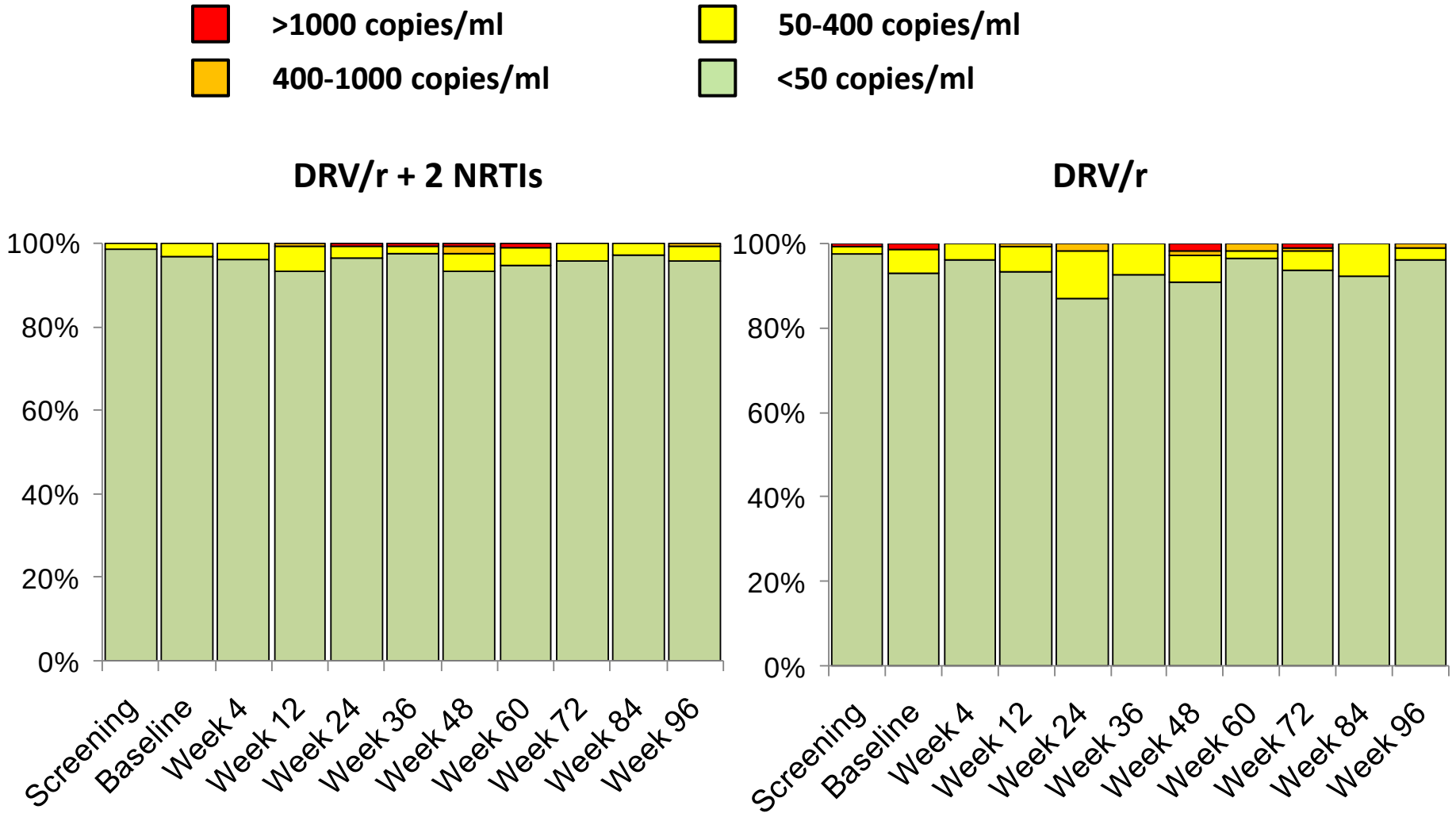
Design: 96-week multicenter, randomized, open-label, clinical trial that compares ATV/r+3TC with ATV/r+2NUC(t)s (selected at the discretion of the investigator) in HIV-infected patients on a stable 3-drug regimen who switch therapy because of toxicity, intolerance, or simplification

Primary objective: To evaluate the non-inferior efficacy of maintenance therapy with ATV/r+3TC compared to ATV/r+2NUC(t)s at 48 weeks (non-inferiority margin, −12%).

SALT

CONS	PROS
Less efficacious than triple	Small difference. PI dependent?. "Reversible" failure.
↑ Low level viremia	Reversible after nuc reinduction
Increased risk of resistance	Very small increase. PI dependent?. Do not compromise the rest of the class. Preserves other treatment options.
Higher adherence needed	"Reversible" failure. Identifying patients needing NUCS easy and safe.
Durability uncertain	3 years results encouraging.
Efficacy in reservoirs (CNS, genital)?	More research needed (also for triple drug therapy)
Benefits not proven	Less lipoatrophy?. Clear cost benefit.
Small studies	>1000 patients received monotherapy in published clinical trials

MONET 96-week: low-level viremia with DRV/r monotherapy



Clumeck N, et al. HIV10, 2010. Abstract O-19

MONET: DRV/r MT does not increase IL-6 or hs-CRP levels

- Levels of the inflammatory markers, interleukin-6 (IL-6) and C-reactive protein (CRP), are elevated in HIV-infection.
- High levels of IL-6 (>3 pg/mL) and CRP (>5 mg/L) have been associated with more rapid progression to AIDS and death[1]

Marker	DRV/r + 2 NRTIs	DRV/r monotherapy
IL-6 >3 pg/mL	20/65 (31%)	15/64 (23%)
hs-CRP > 5 mg/L	8/80 (10%)	9/75 (12%)

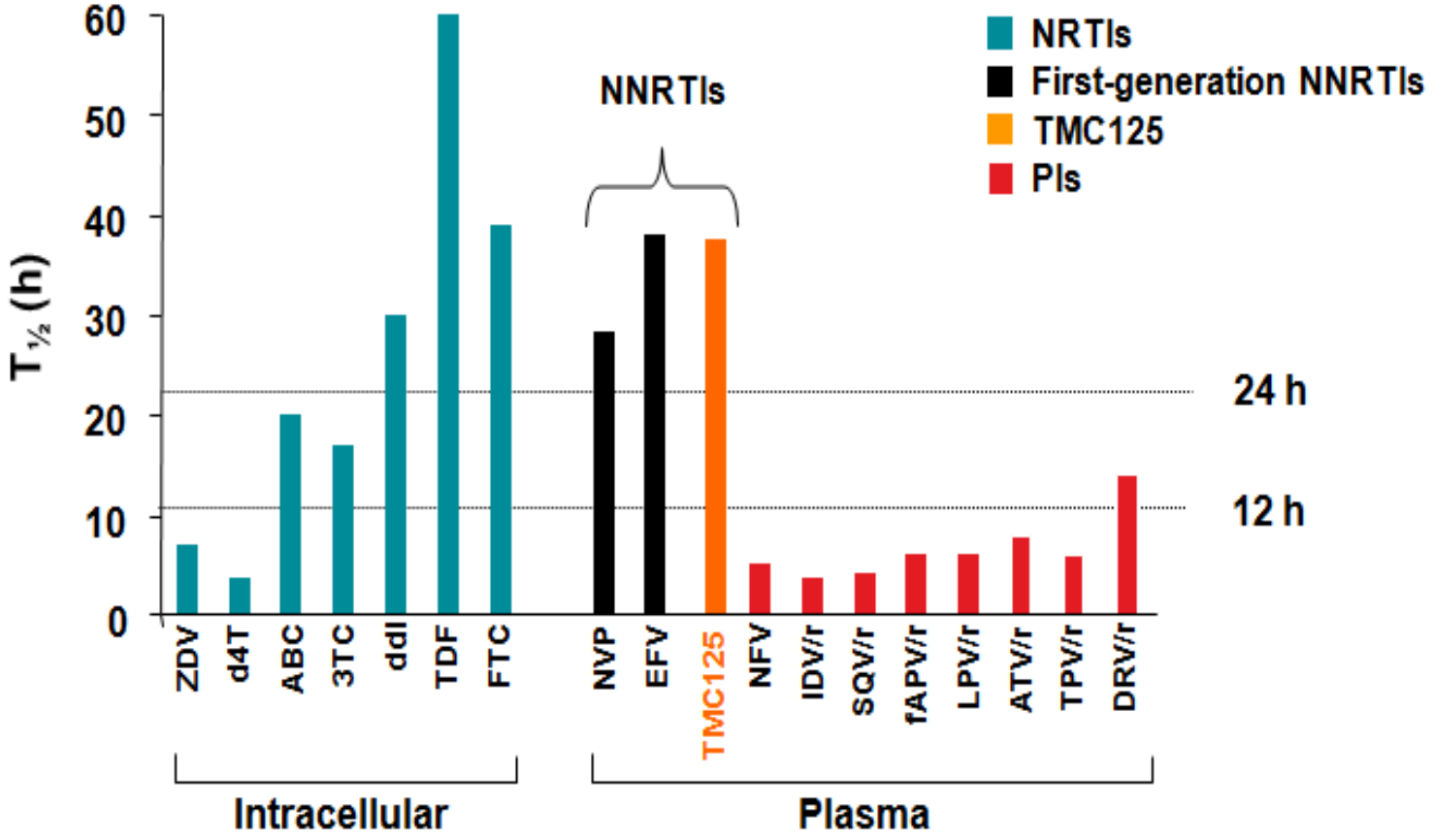
p=n.s. for both comparisons, chi-square test

- There was no difference between the treatment arms in IL-6 or hs-CRP levels at the Week 144 visit

1. Rodger A, et al. JID 2009, 200: 973-983.

Arribas JR, et al. EACS, Belgrade, Serbia, October 2011. Abstract PS 10/2.

Half-life of antiretrovirals

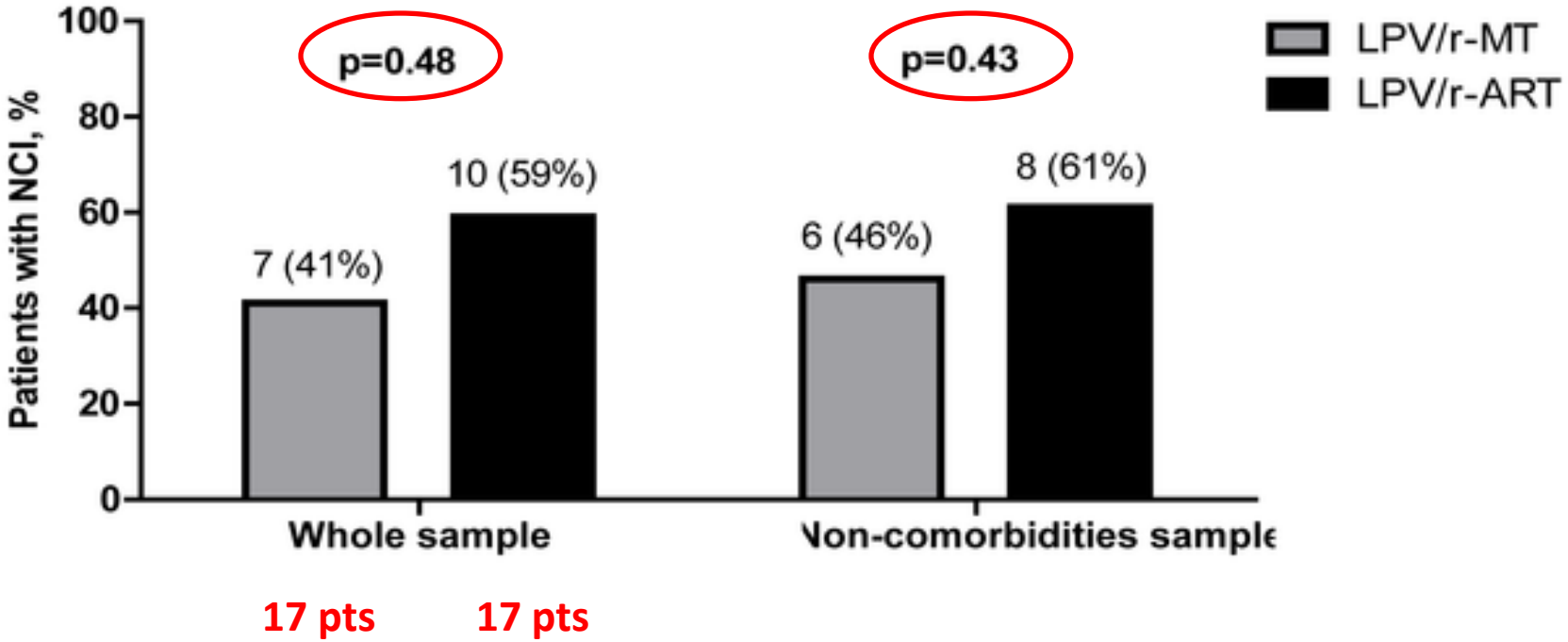


1. Moore KH, et al. AIDS 1999;13:2239-50.
2. Kewn S, et al. Antimicrob Agents Chemother 2002;46:135-43.
3. Hawkins T, et al. 5th IWCPHT, 2004. Abstract 2.4.
4. Product SmPCs.
5. Tibotec, data on file.

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.

Neurocognitive impairment and virological efficacy in monotherapy compared to HAART

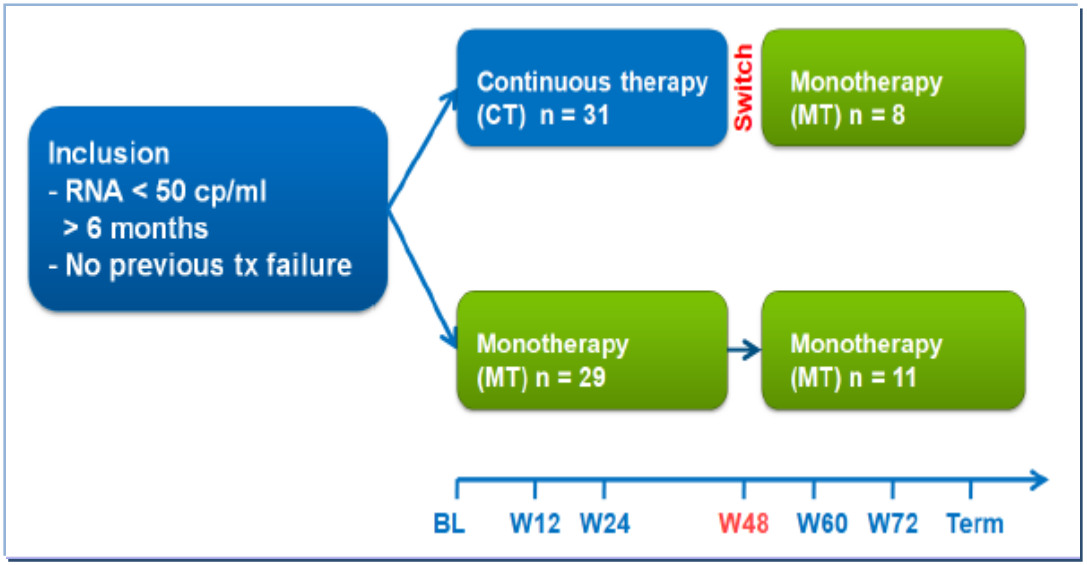
Observational, cross sectional, LOPV/r monotherapy vs triple (> 96wks), 34 pts



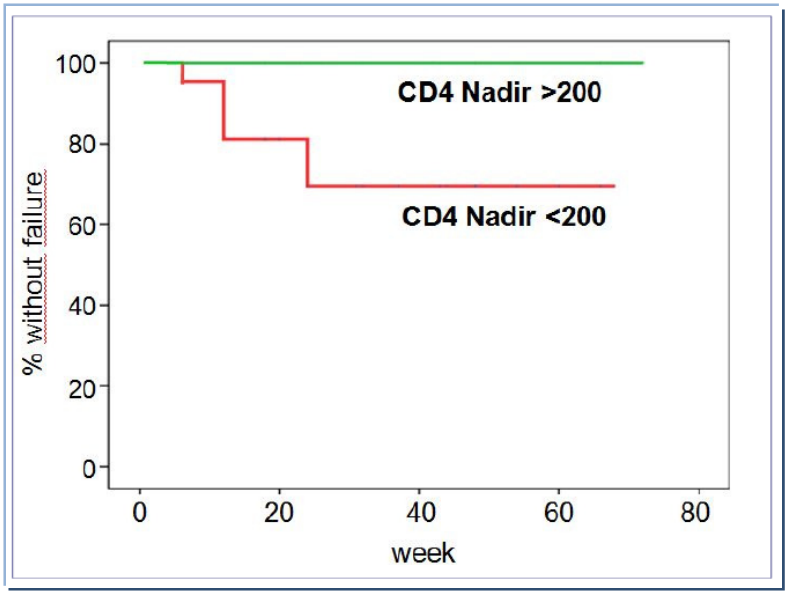
CSF HIV RNA: (< 1 copy/ml)	**82.4** *versus* **94.1%** p= 0.6

Santos JR, et al PLoS ONE 2013;8:e70201

LPV/r monotherapy



Tab. 1 Baseline Characteristics		CT n = 31	MT n = 29
Pretreatment (%)	PI	74	73
	NNRTI	23	24
	Triple N	3	3
CD 4 Nadir	absolute	160	160
	%	12	12
CD 4 Baseline	absolute	517	519
	%	28	29
Gender (%)	female	23	34
	male	77	66
Age (years)		44	44
HIV RNA setpoint (log)		4.8	4.8
Follow up (weeks)		48	48
Length of therapy until baseline (years)		3.9	3.9



Gutman Ch et al. CROI 2009; Abs 189

Tab 2: Characteristics of the six failing patients

ID	Weeks on MT	Pre-Study Therapy	VL Blood	VL CSF	CD4 Nadir (abs.)	CD4 Nadir (%)	LPV/r ng/ml (percentile)
101	12	ATV/r + 2N	4.3 log	5.1 log	57	13	87 (<1)
108	12	LPV/r + 2N	2.7 log	3.1 log	5	1	6777 (50)
126	12	LPV/r + 2N	4.1 log	5.0 log	149	26	6388 (25-50)
302	24	EFV + 2N	3.0 log	4.1 log	7	3	6438 (50)
303	6	LPV/r + 2N	5.0 log	Refused	54	2	4661 (25)
713	24	EFV + 2N	3.0 log	3.7 log	160	5	< LoD

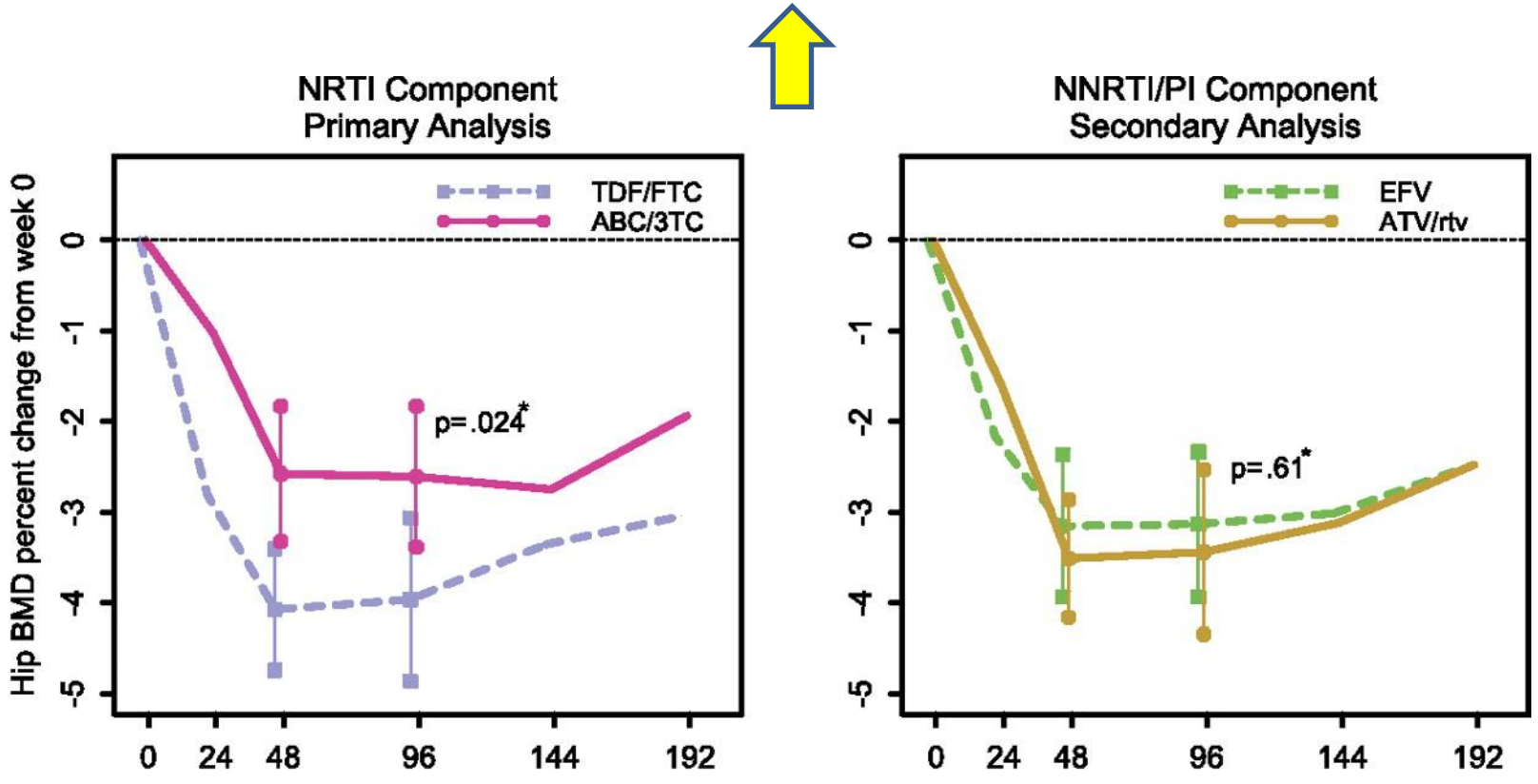
CONCLUSION

- Monotherapy failure appears to occur in the first 6 months after switch to mono-maintenance.
- No development of drug resistance was detected in patients failing monotherapy.
- LPV/r monotherapy results in suboptimal HIV RNA suppression in the CSF compartment in approx. 10% of cases.
- A high failure rate of monotherapy was associated with low nadir CD 4 count.

Gutman Ch et al. CROI 2009; Abs 189

ACTG A5224s Study, 269 pts, DXA scans

Mean percentage change in hip BMD by ITT analysis.



* - two-sample t-test

No significant interaction of NRTI and NNRTI/PI components (p=.69)

McComsey G A et al. J Infect Dis. 2011;203:1791-1801

Lopinavir Monotherapy and CSF Replication in IMANI

Table 3: Plasma viral load, CD4+ and week of LP

Subject	Weeks of LPV/r	Pre-treatment plasma CD4+ cells/mm^3	Plasma CD4+ cells/mm^3 at time of LP	Plasma copies/ml (bDNA)	CSF HIV RNA copies/mL
003	48	228	449	< 75	< 50
004	48	482	546	< 75	< 50
010	48	204	646	< 75	< 50
016	48	308	471	< 75	< 50
017	48	257	515	< 75	< 50
031	32	530	599	< 75	< 50
032 (Sample 9/06)	36	171	348	< 75	251
032 (Sample 1/07)	48	- -	399	< 75	747
036	32	272	458	< 75	< 50
037	32	143	265	< 75	< 50
041	32	516	371	< 75	< 50
044	24	186	769	< 75	< 50

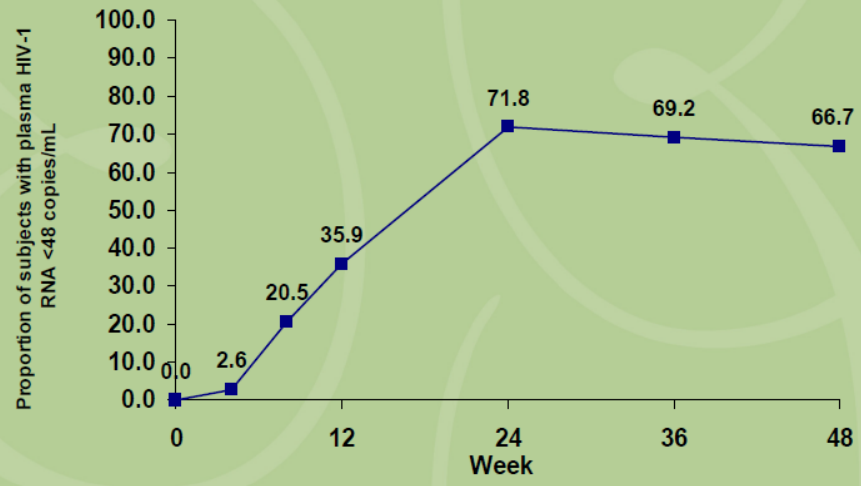
- significance of these data?
- Few data comparing CSF VL on triple therapy vs monotherapy

Yeh R, et al. CROI 2007. Abstract 381.

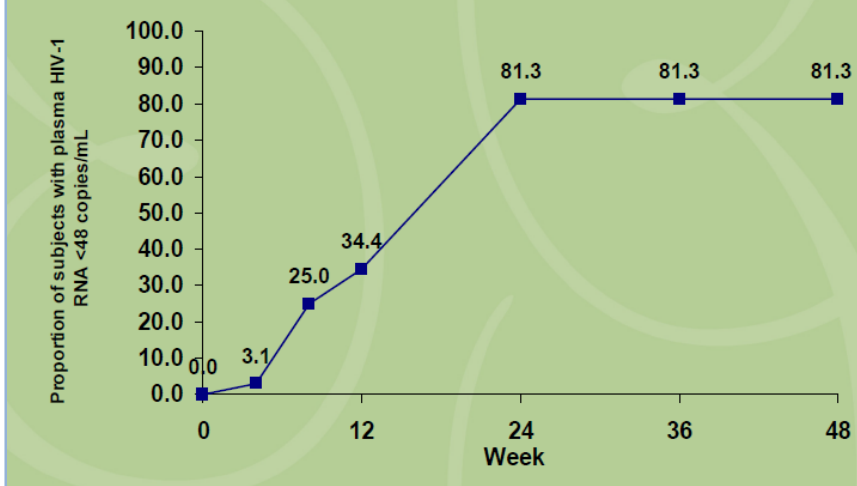
A Pilot Study: Lopinavir/ritonavir Plus Lamivudine as Dual Agents in Antiretroviral Naïve, HIV-Infected Subjects (The LOREDA Study)

Single arm, phase IV study
39 naive pts
CD4 > 50 cells
HIV RNA : > 5000 c/ml

Virologic Responders through Week 48 (ITT)



Virologic Responders through Week 48 (AT)



Among 3 subjects with available genotypes:
Primary PI resistance = 0 mutations
M184V mutation = 3/3.

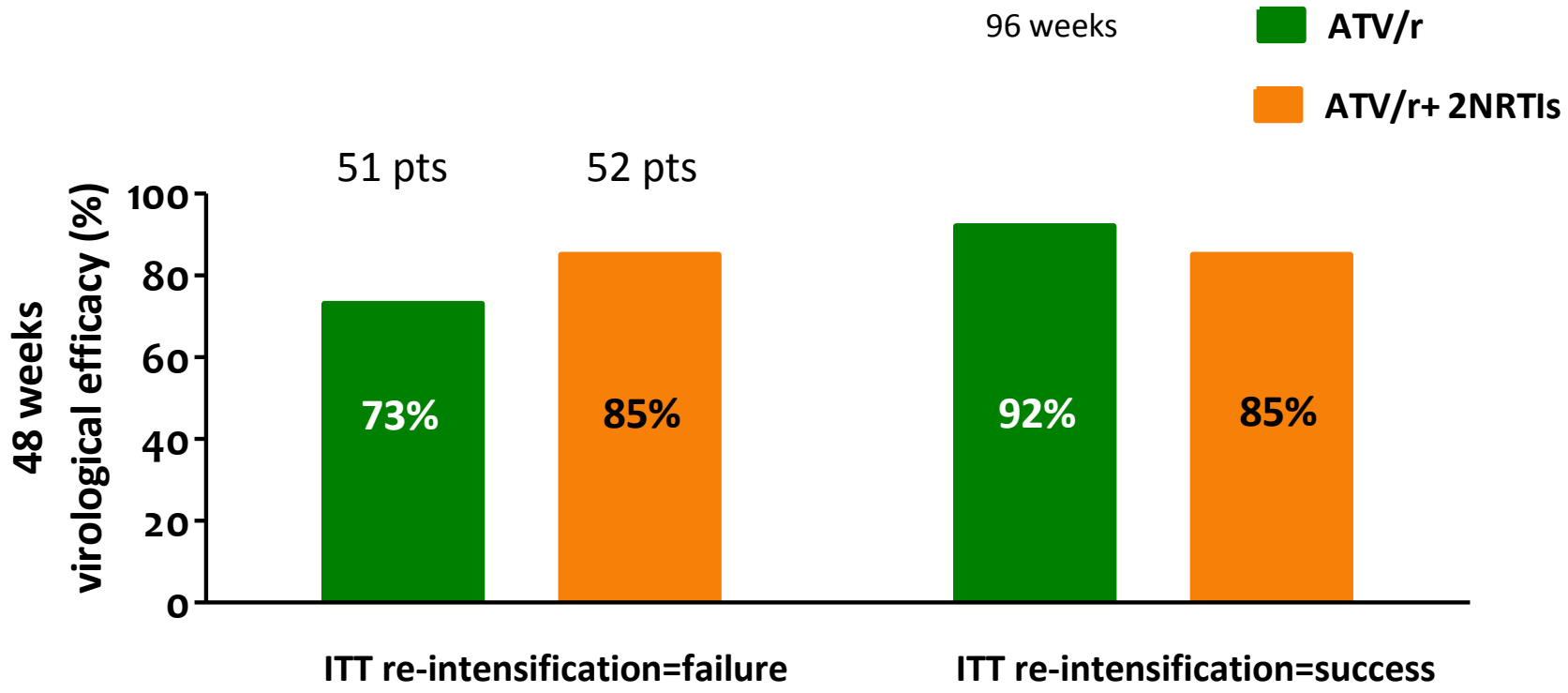
Andrade R et al. IAS 2011, Rome

Efficacy and durability for boosted PI monotherapy

MODAt study
342 pts on ATV/r

→ ATV/r 300/100 mg + 2NRTI
→ ATV/r 300/100 mg

96 weeks



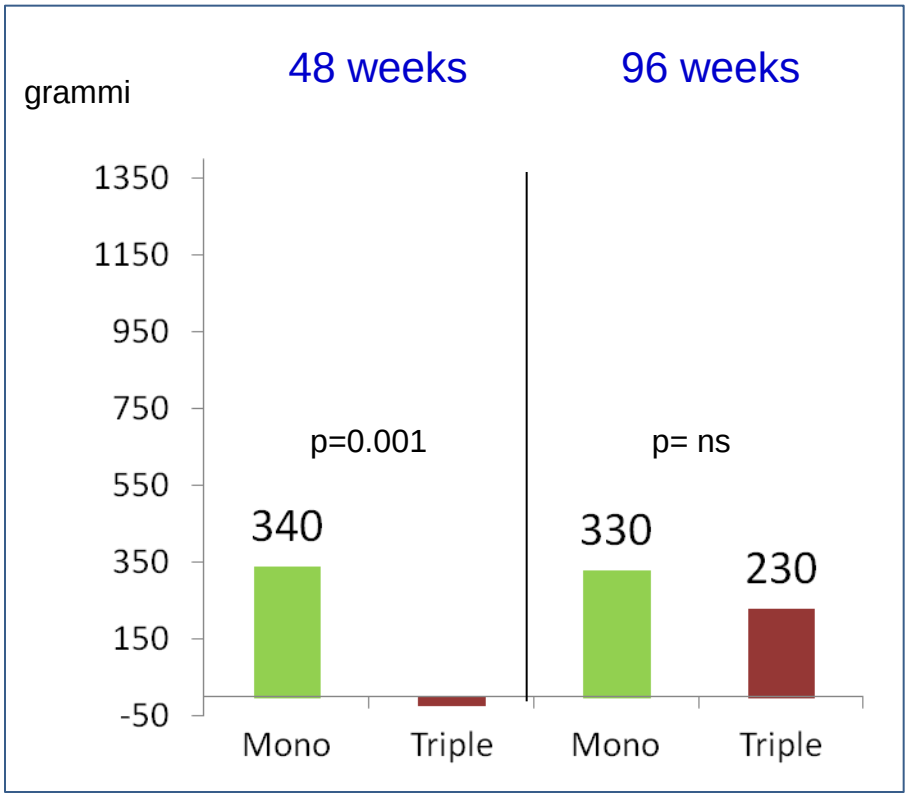
Difference (95% CI): -12.1% (-27.8% to 3.6%) 7.5% (-4.7% to 19.8%)

No mutations in pts failing ATV/r

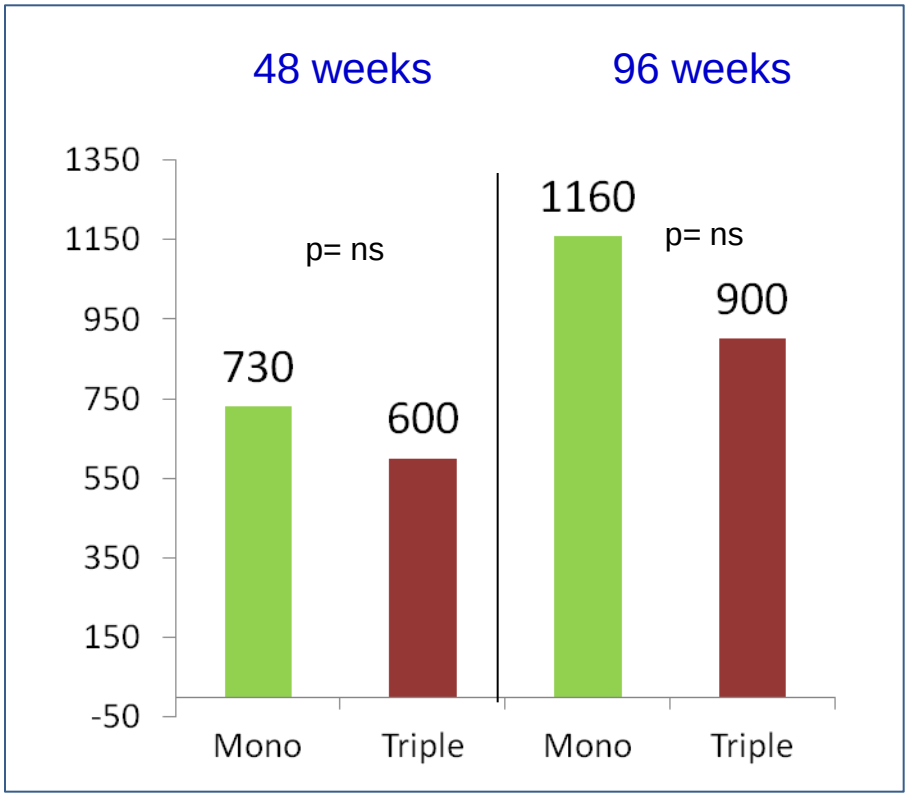
Castagna A et al. EACS 2013

Body fat distribution in patients on DRV/r monotherapy vs DRV/r+ 2NRTIs: the **MONOI**-ANRS136 Substudy.

Median limb fat increase



Median trunk fat increase



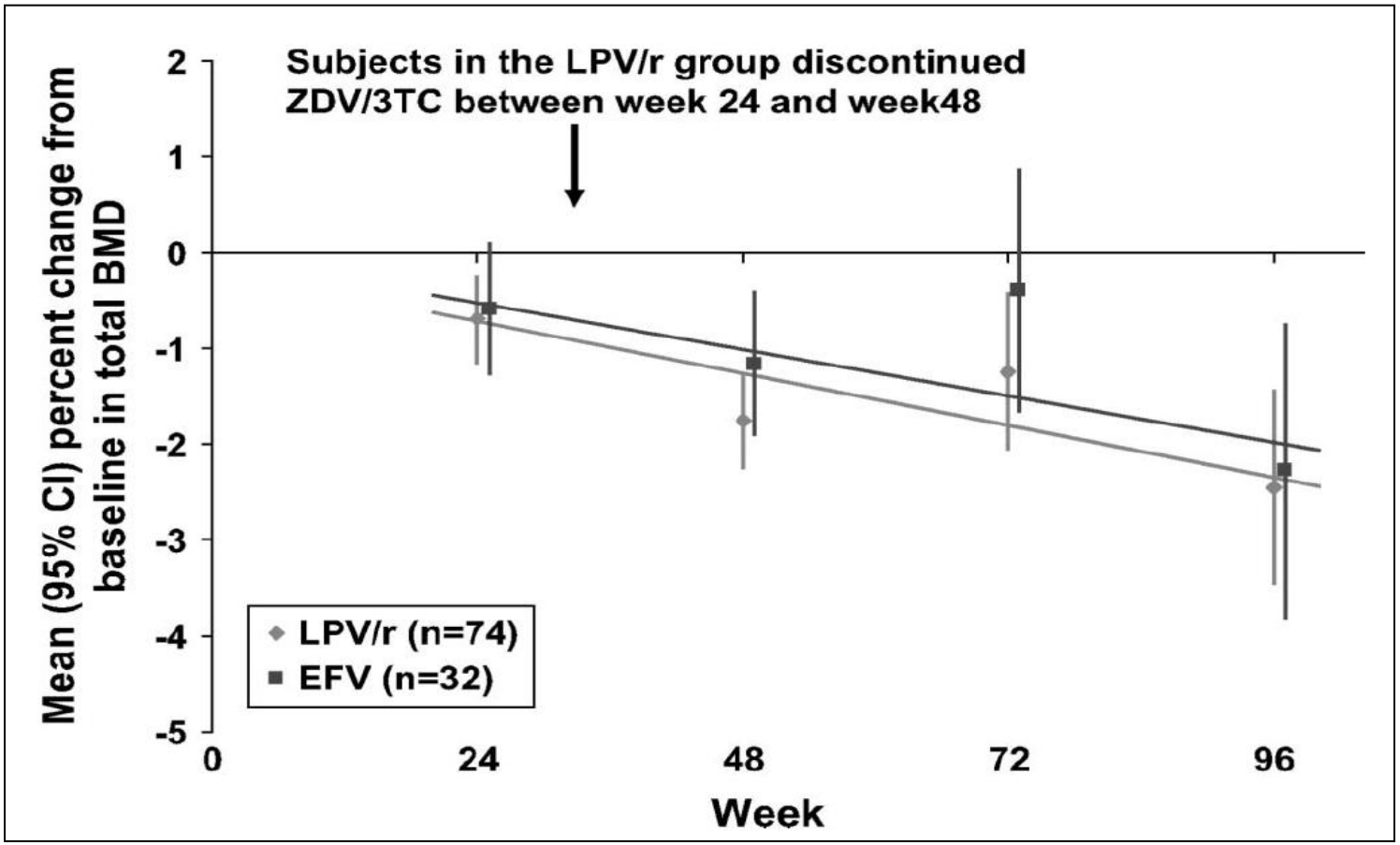
Mono 67 patients

Triple 74 patients

Valantin M et al. HIV Med. 2012; Mar 14

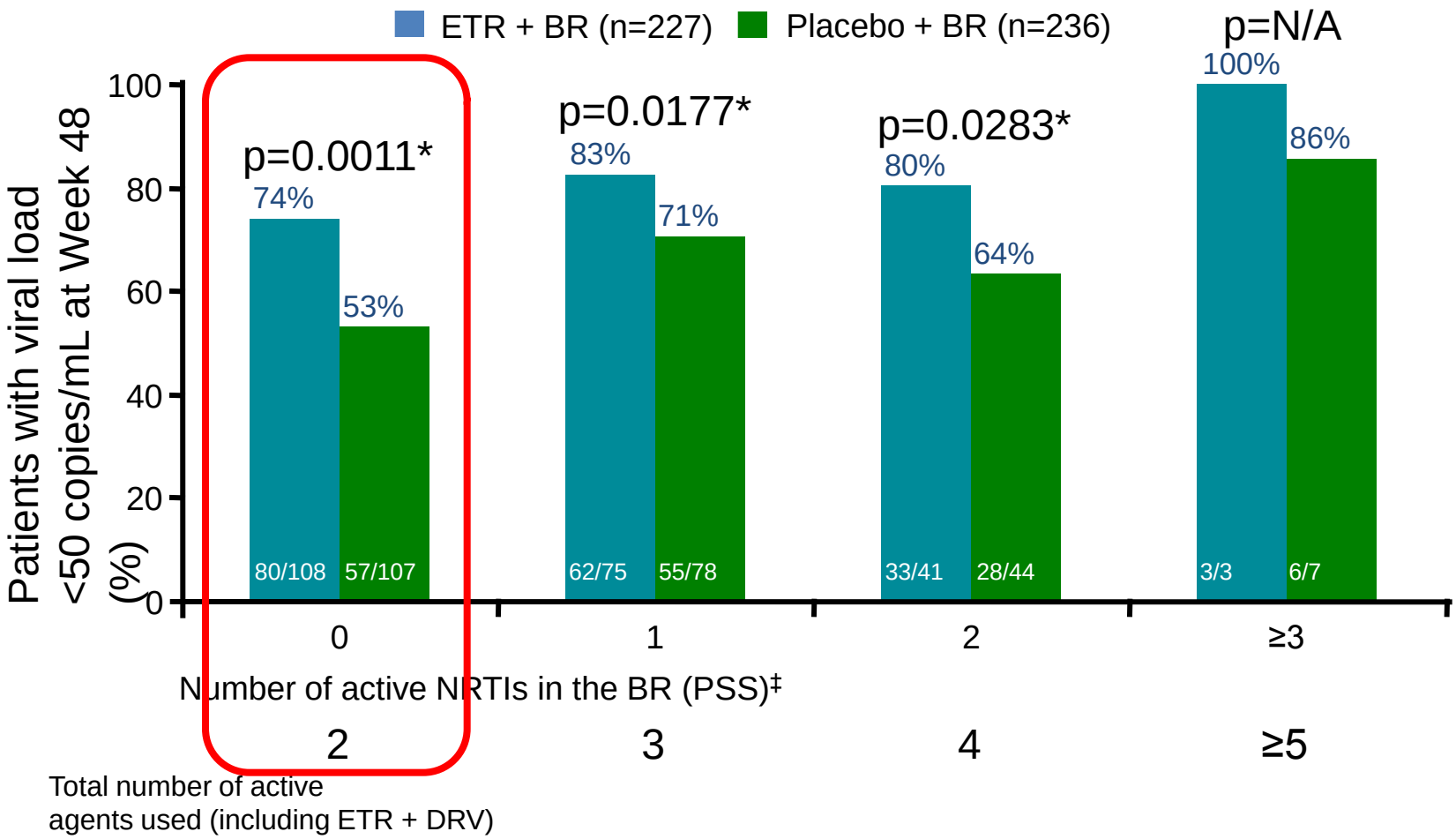
M03-613: Changes in Bone Mineral Density from baseline to week 96

DEXA scans: baseline, every 24 weeks through Wk 96 (n = 106)



Brown TT, et al. JADIS. 2009;51:554-561

DUET: Virological response at Week 48 (TLOVR) with fully active ETR and fully active DRV



Fully active ETR = patients with ETR FC ≤3; DRV = patients with DRV FC ≤10; ETR and DRV were not included in the PSS calculation; Analysis excludes patients who discontinued for reasons other than VF; *Logistic regression; ‡According to Antivirogram®

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