Monoterapia y biterapia de la infección VIH, ¿cuándo?, ¿con que?¿con que grado de evidencia

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Disclosures

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

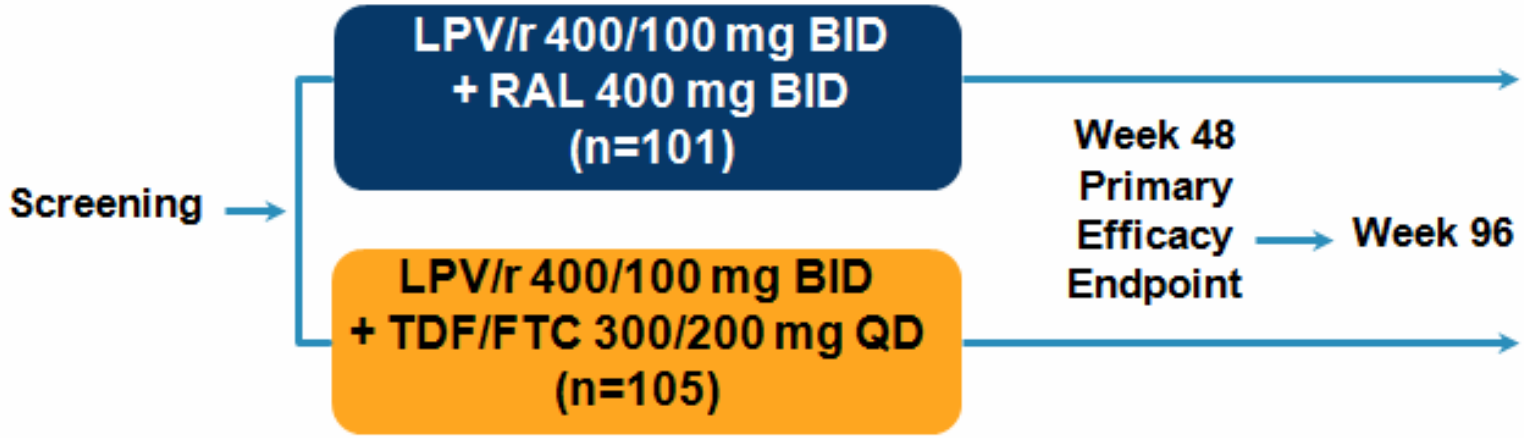
RATIONALE FOR NUCS-SPARING REGIMENS

- Toxicity of current nucleosides (short and long term)
  - Cardiovascular?
  - Renal
  - Bone
  - CNS?
  - Limb fat
  - Cost

LPV/r + RAL *vs.* LPV/r + TDF/FTC in Treatment-Naive Subjects: PROGRESS Study Design*

Inclusion Criteria for PROGRESS (M10-336)

- HIV-1 infection
- ARV-naïve
- Plasma HIV-1 RNA >1000 copies/mL
- Any CD4$^+$ T-cell count

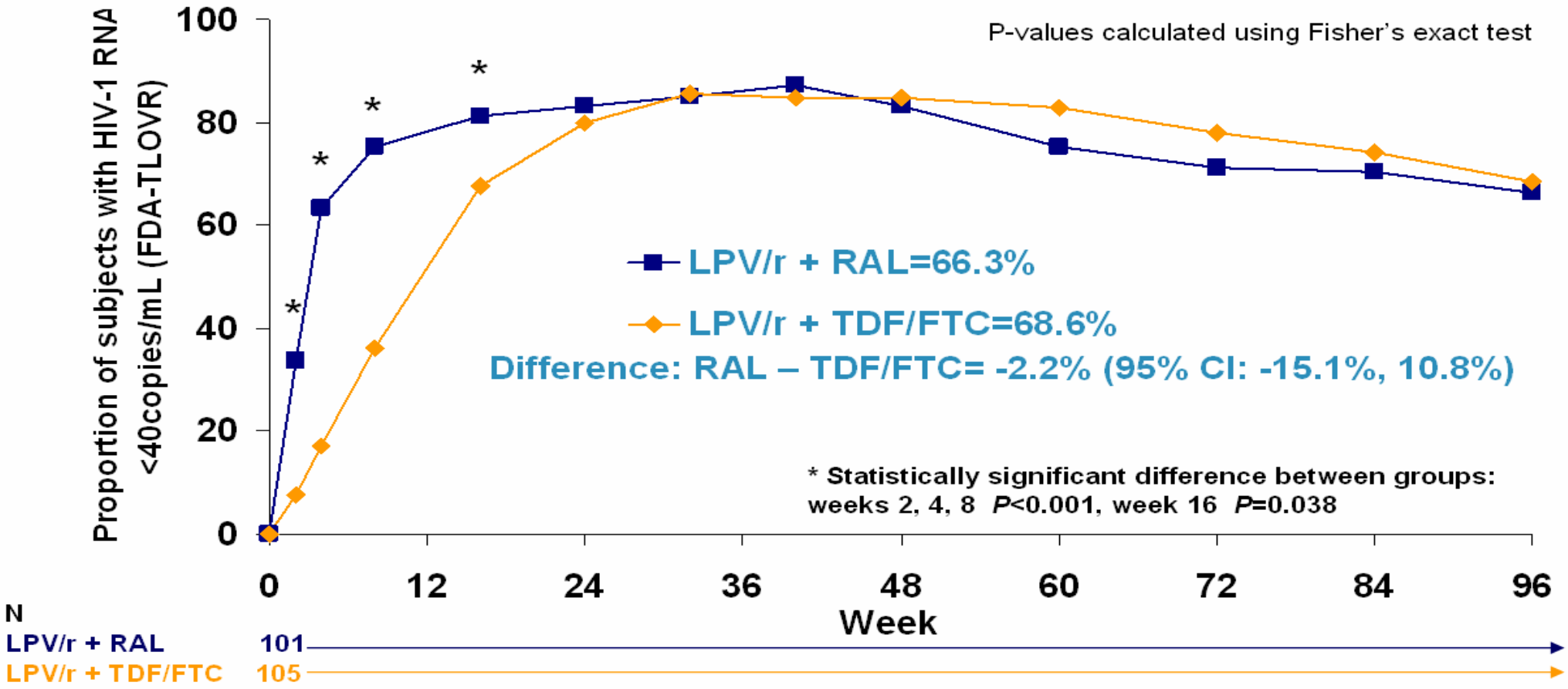


Met Primary Endpoint of Noninferiority

- Primary endpoint: plasma HIV-1 RNA <40 copies/mL at week 48 (FDA-TLOVR)
- FDA-TLOVR week 48: LPV/r + RAL=83.2%, LPV/r + TDF/FTC=84.8%
- *P*=0.850, difference -1.6%, 95% exact confidence interval (CI) -12.0%, 8.8%
- Safety and tolerability were similar at week 48

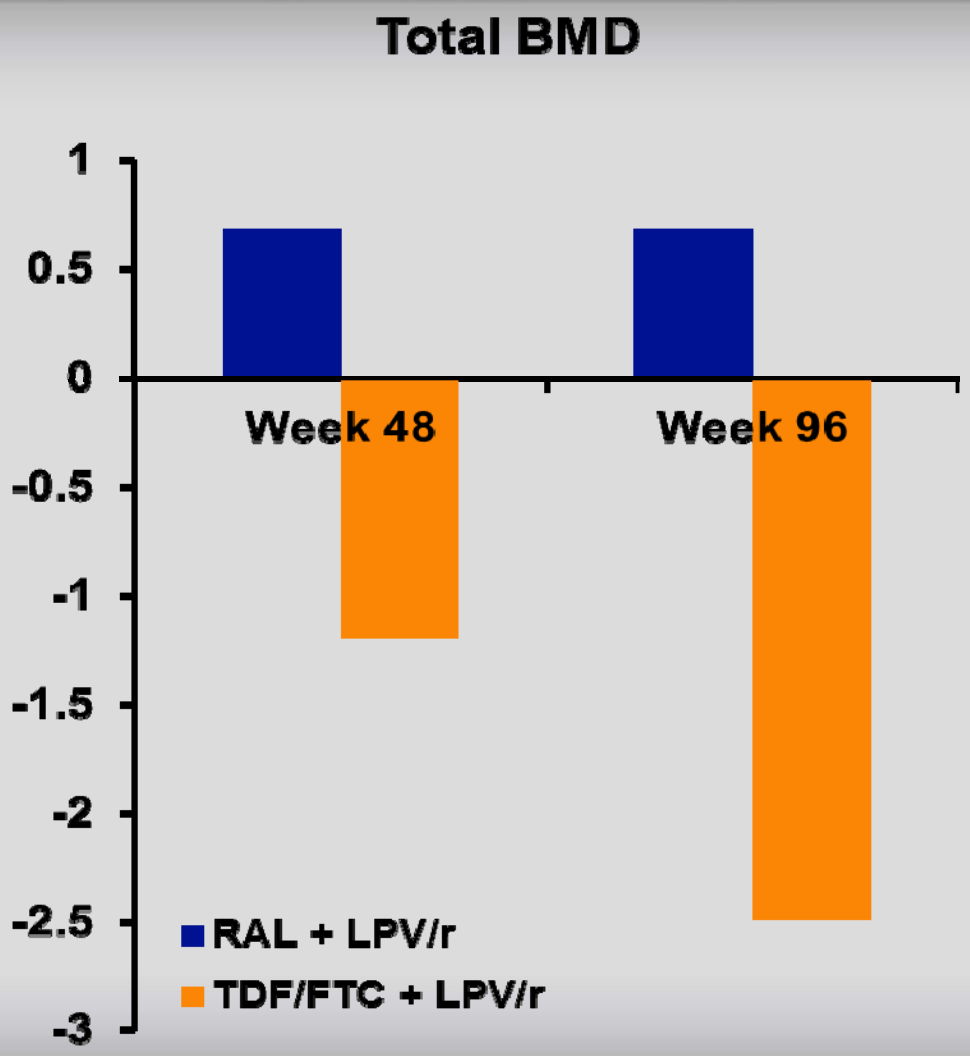
* 3 subjects were randomized but not dosed

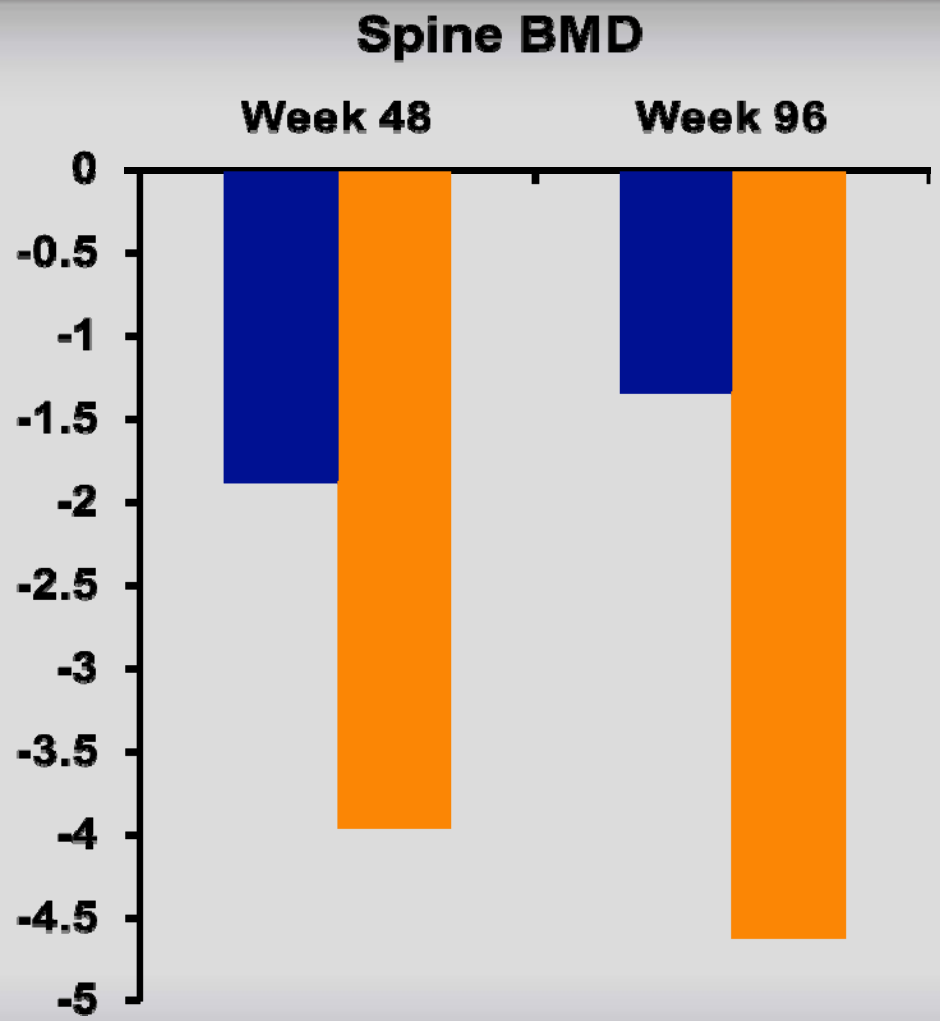
Proportion of Subjects Responding at Week 96 (FDA-TLOVR)



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

Progress: BMD Changes by LPV/r + RAL or TDF/FTC





Qaqish R, et al. 6th IAS; Rome, Italy; July 17-20, 2011. Abst. TULBPE021.

ACTG 5262
Study Design

Single arm study of DRV/r (800/100 mg) QD + RAL (400 mg BID) (N=112)		
Age (years)	Median (Q1,Q3)	36 (27, 45)
Sex	Male	98 (88%)
Race	White	49 (44%)
CD4 cell count (cells/mm^3)	<200	40 (36%)
	200<350	32 (29%)
	≥350	40 (36%)
HIV-1 RNA (copies/mL)	≤100,000	63 (56%)
	≥100,000	49 (44%)

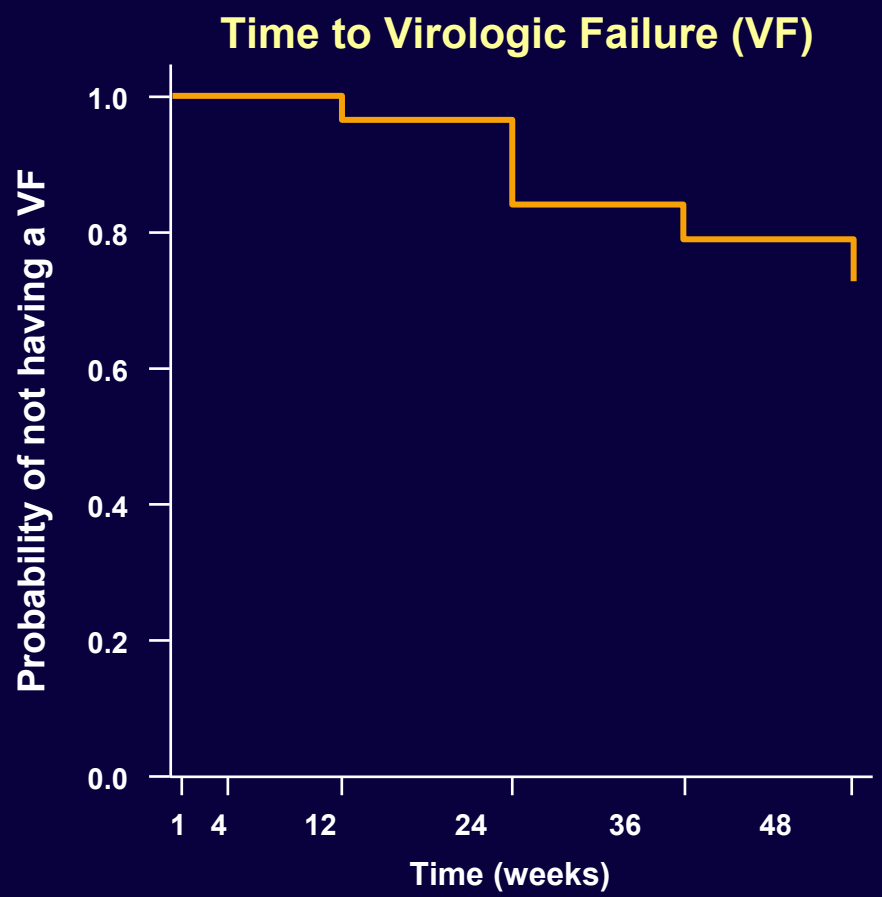
Primary Endpoint:

•Virologic failure prior to or at week 24. Proportion Of Subjects With HIV-1 RNA <200 and <50 copies/mL (ITT analysis, missing/off study= ignored

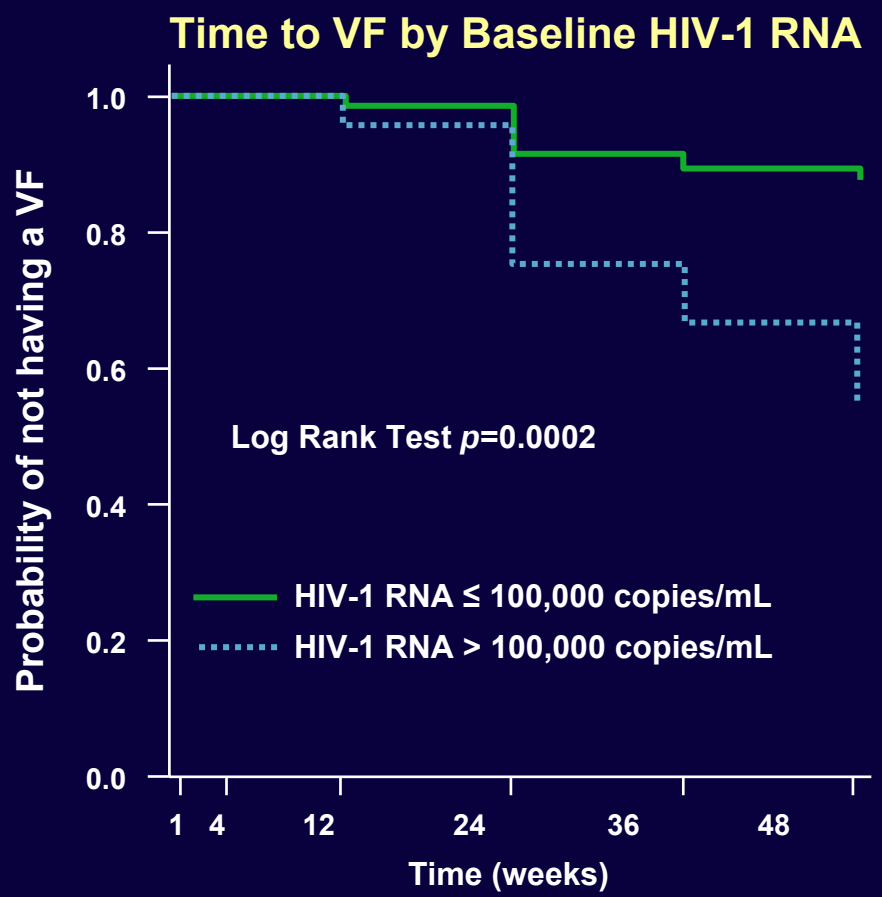
Taiwo B, et al. CROI 2010. Boston. #551.

ACTG 5262

Time to Virologic Failure (ITT approach)



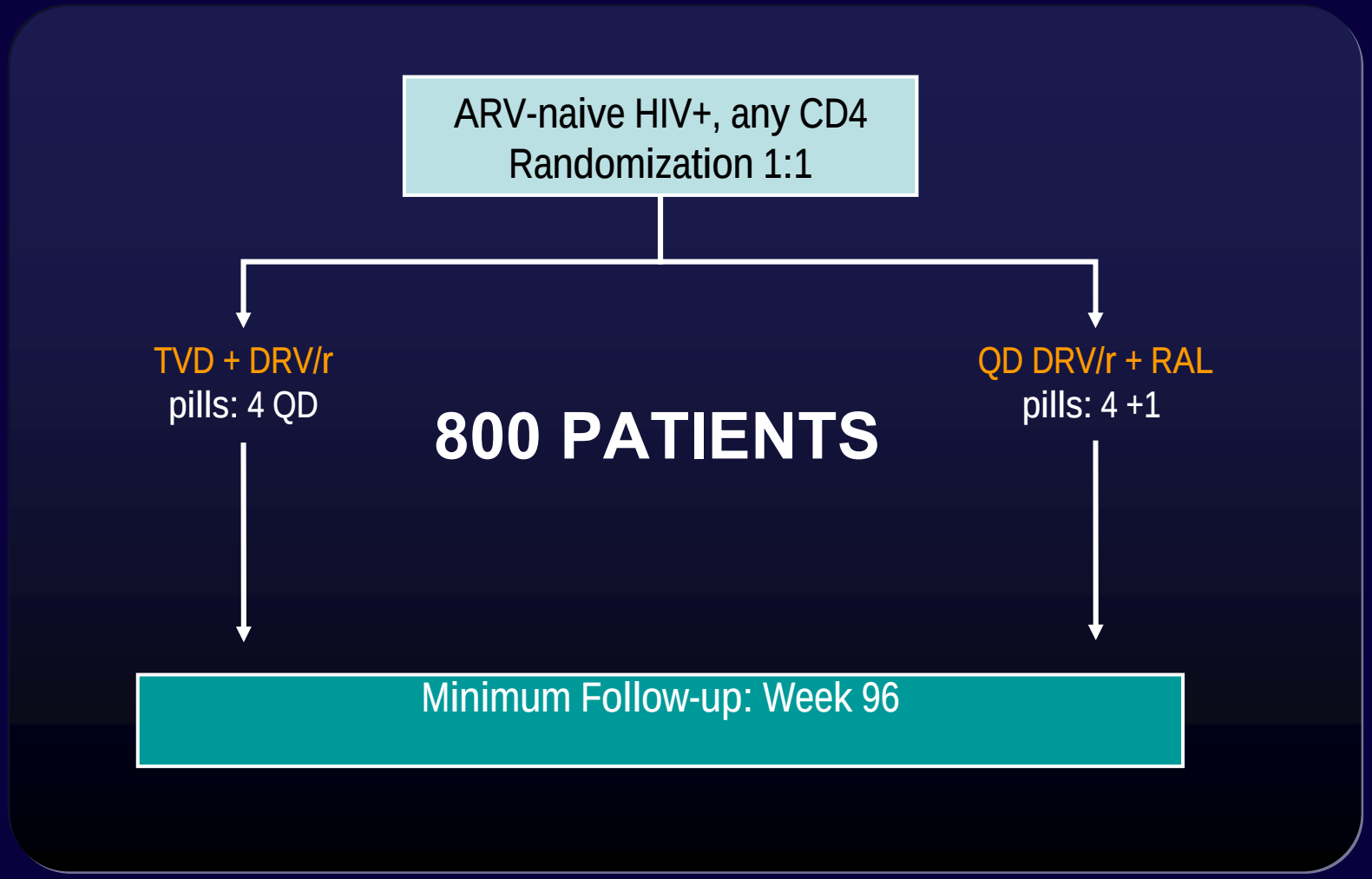
n with VF:	0	0	3	14	5	6
n at risk:	112	111	110	105	89	81



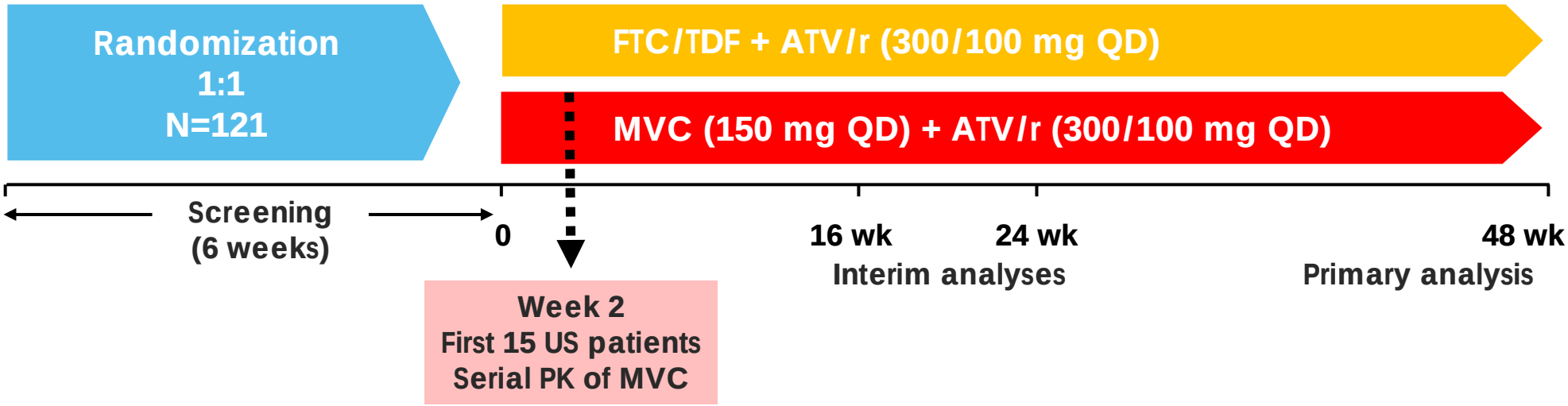
HIV-1 RNA ≤ 100,000 copies/mL						
n with VF:	0	0	1	4	1	1
n at risk:	63	63	62	59	54	50
HIV-1 RNA > 100,000 copies/mL						
n with VF:	0	0	2	10	4	5
n at risk:	40	45	45	45	39	31

Taiwo B, et al. CROI 2010. Boston. #551.

NEAT Protocol 001 / ANRS 143



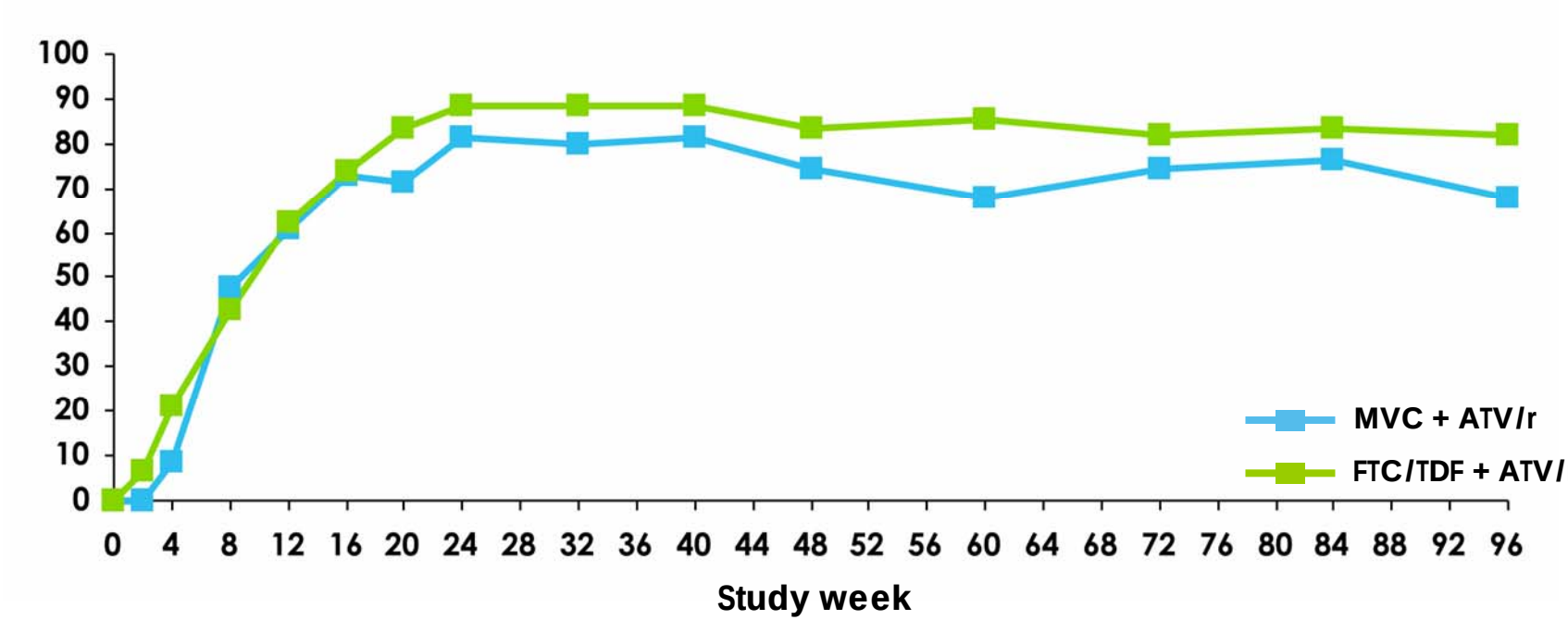
Study design
Open-label, 48-week Phase 2b pilot study



- **Patient eligibility criteria**
  - R5 HIV (ESTA) at screening
  - ≥16 years of age
  - HIV-1 RNA ≥1000 copies/mL
  - CD4 ≥100 cells/mm^3
  - No evidence of resistance to ATV/r, TDF, or FTC
  - Study has iDMC
  - Ongoing study: USA, Spain, Germany
  - Extended to 96 weeks
  - Study is not powered to show a treatment difference and no formal comparative statistics will be performed

Portsmouth,Set al. 6th IAS; Rome, Italy; July 17-20, 2011. Abst. TUAB0103

HIV-1 RNA <50 copies/mL over time



n=	59	48	44	40
	61	54	51	50

Intent-to-treat. Non-completer=failure.

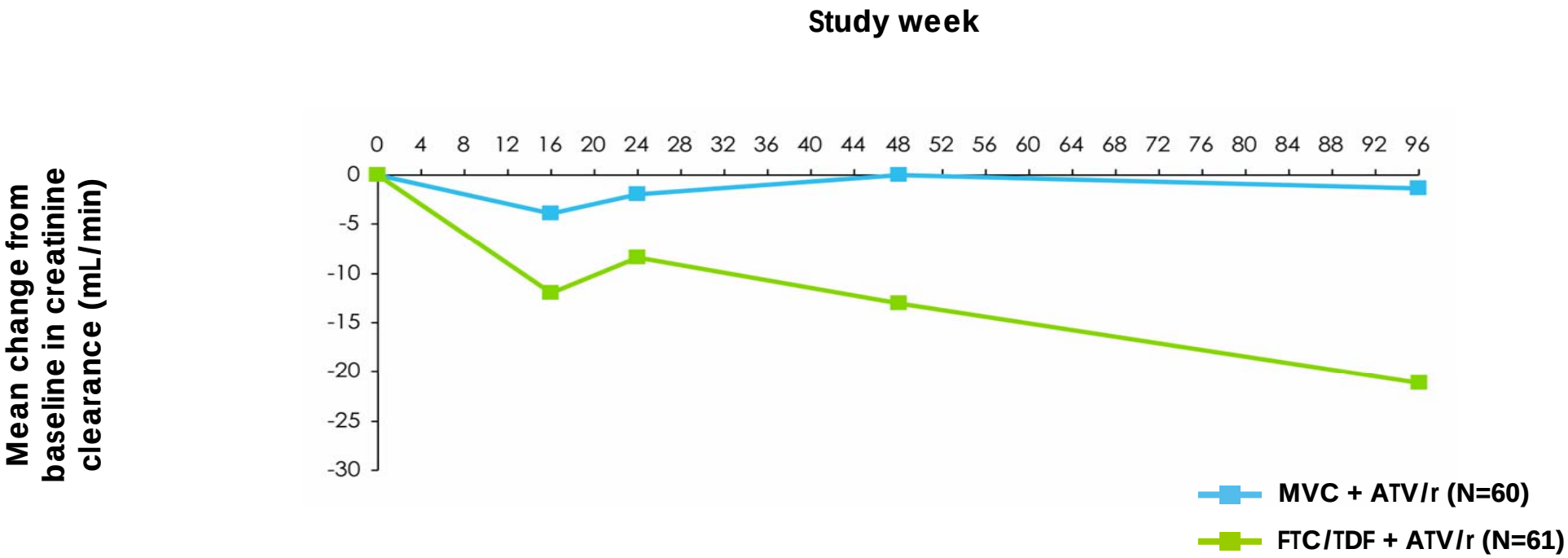
No genotypic or phenotypic resistance was observed through Week 96

Change in tropism	Development of relevant resistance mutations				Susceptibility to drug retained	
	MVC	ATV	TDF	FTC	MVC	FTC/TDF
0	0	0	0	0	7	4

- 7 patients in the MVC arm and 4 patients in the FTC/TDF arm were identified for virologic analyses[a]

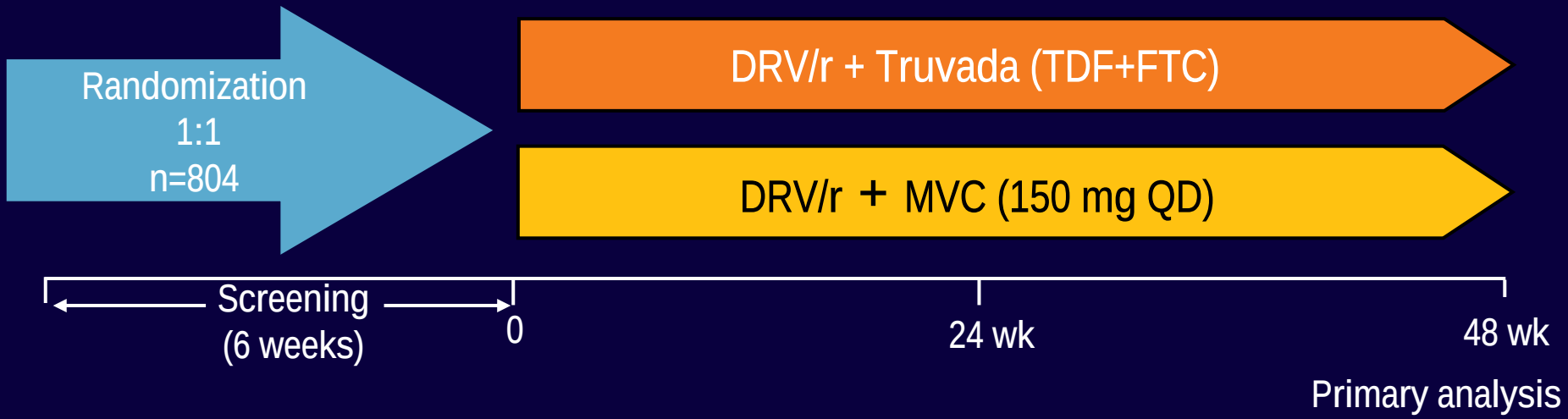
[a]Patients who discontinued from the study early with sufficient VL (≥500 copies/mL). Assays (ESTA, Monogram GenoSeq and/or PhenoSenseGT) performed at screening/baseline and at the last on-treatment time point were available

Creatinine clearance over time



Study A4001095

Double blind placebo controlled
Primary endpoint: Proportions < 50 copies/mL at week 48*



*** Study is powered to show a treatment difference and comparative statistics will be performed.**

Patient eligibility criteria:

- ≥ 16 years of age
- Treatment naive
- R5 HIV-1 infection
- HIV-1 RNA ≥ 1000 copies/mL
- CD4 ≥ 100 cells/mm^3
- No evidence of resistance to ATV/r, TDF, or FTC

AIDS 2012 | XIX INTERNATIONAL AIDS CONFERENCE JULY 22 - 27 WASHINGTON DC USA

Conclusions: MVC/DRV/r 150/800/100 mg once-daily was well-tolerated and effective, but VF occurred in 3/4 patients with baseline VL > 100,000 c/ml. These findings should be evaluated with caution in larger randomized studies.

Abstract

TUPE099 - Pos

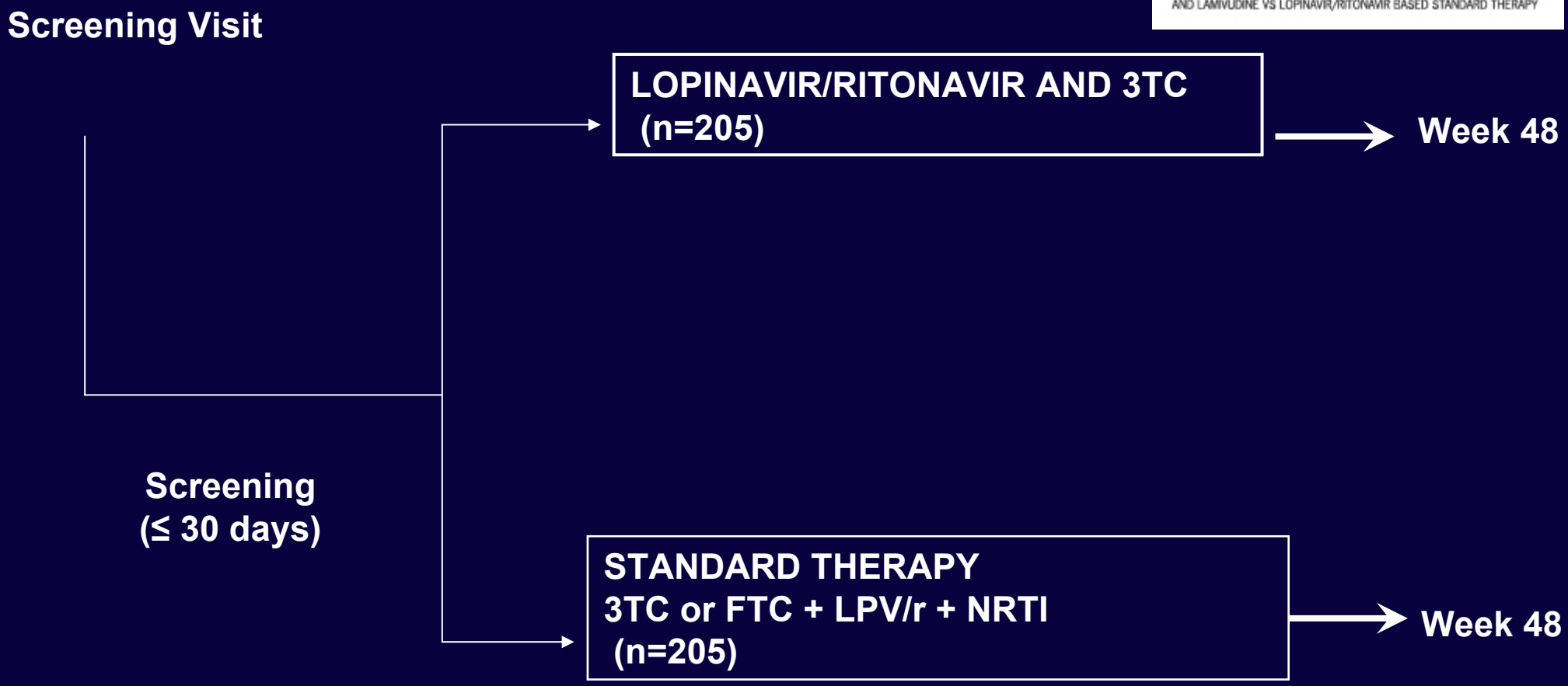
Week 48 resul -naive patients infected with R5-tropic HIV-1

B. Taiwo[1], S. Swindells[2], B. Berzins[1], E. Acosta[3], P. Ryscavage[1], J. Lalezari[4], J. Castro[5], O. Adeyemi[6], B. Yip[1], M. Rathert[1], D. Kuritzkes[7], J. Eron[8], MIDAS Study Team

Investigational Plan. Gardel Study

Study Design Schematic

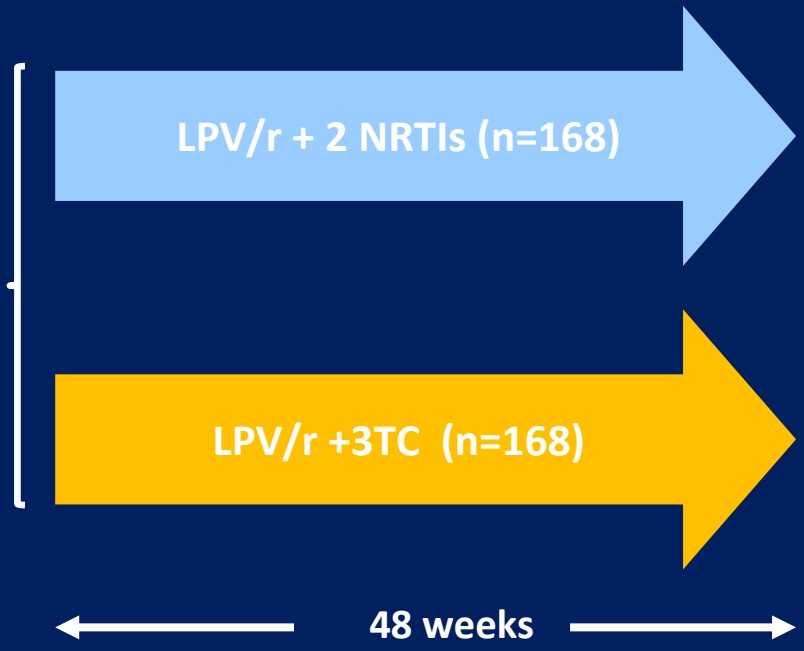
GARDEL
GLOBAL ARV DESIGN ENCOMPASSING LOPINAVIR/RITONAVIR AND LAMIVUDINE VS LOPINAVIR/RITONAVIR BASED STANDARD THERAPY



OLE STUDY

Inclusion criteria:

- Stable HAART (1yr)
  - 2 NRTIs + LPV/r
  - HIV RNA < 50 (6M))
-



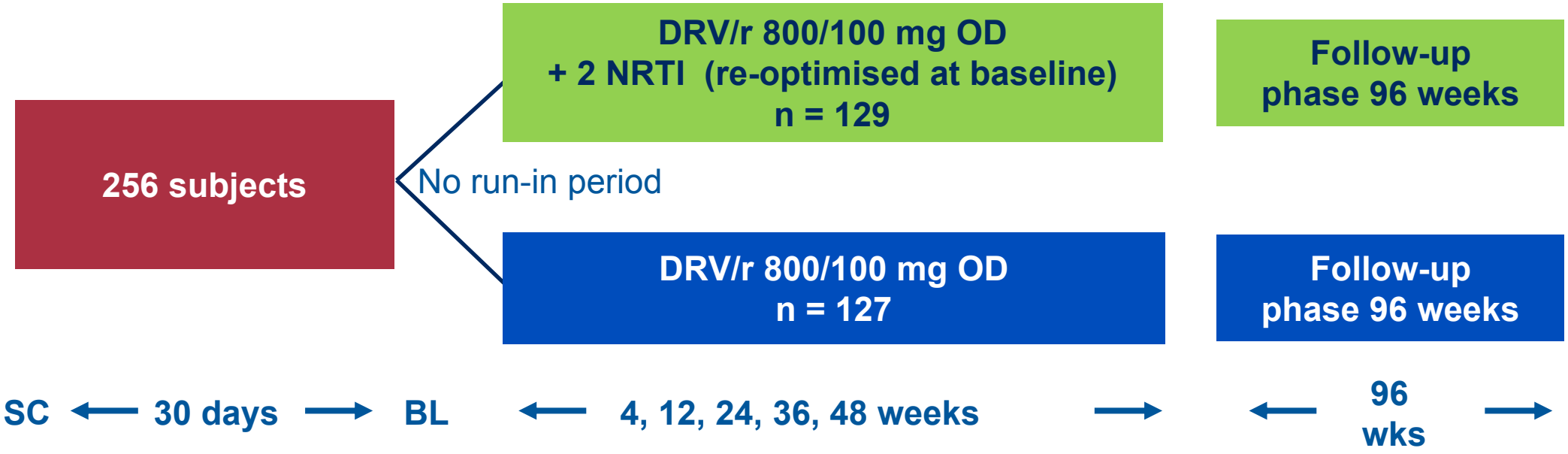
The state of PI Monotherapy (Guidelines)

GUIDELINES	COMMENTS
EACS[1]	PI/r monotherapy with bid LPV/r, or qd DRV/r, might represent an option in patients with intolerance to NRTI or for treatment simplification.
IAS[2]	Ritonavir-boosted protease inhibitor monotherapy is associated with an increased risk of virologic failure and is not recommended when other options are available
DHHS[3]	In aggregate, boosted-PI monotherapy as initial or as simplification treatment has been somewhat less effective in achieving complete virologic suppression and avoiding resistance. Therefore, this strategy cannot be recommended outside of a clinical trial.

1. http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EACSGuidelines-v6.1-English-Nov2012.pdf
2. Thompson MA, et al. JAMA 2012; 308:387–402.
3. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

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

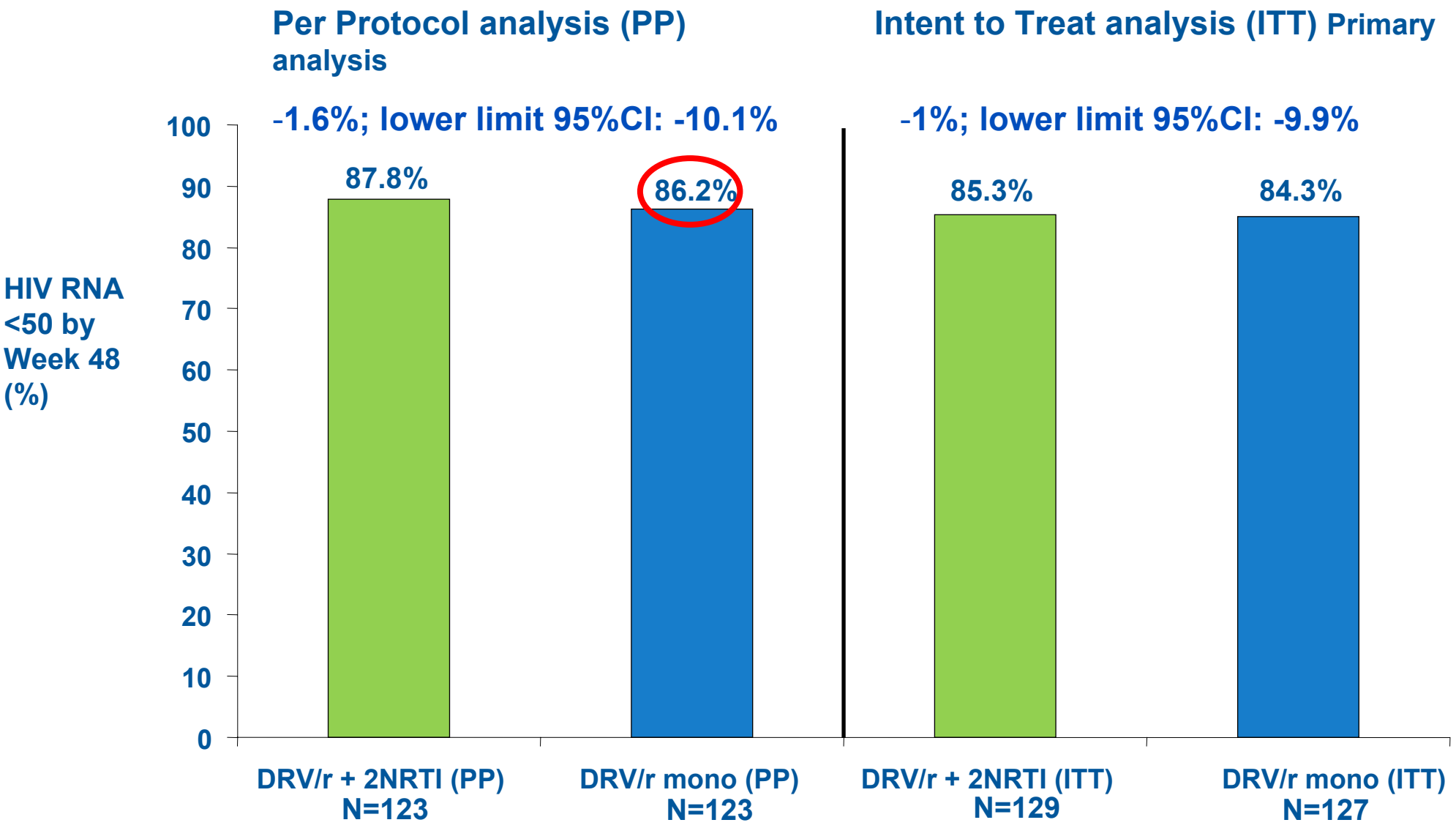


Primary Endpoint: HIV RNA< 50 at week 48 (TLOVR). Per Protocol, Switch = Failure

- 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).

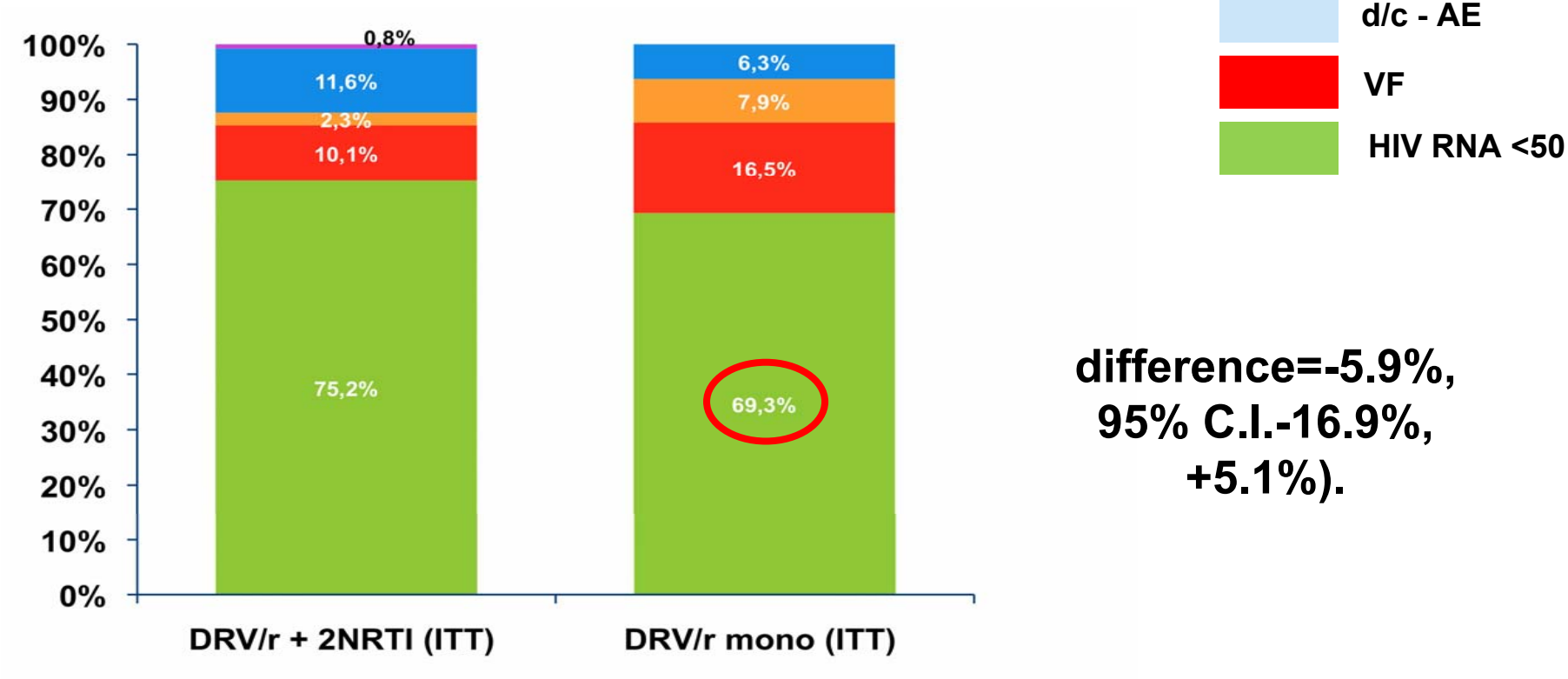
J. Arribas et al, IAS Conference, Cape Town, SA, 21 July 2009, TUAB106-LB

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



J. Arribas et al, AIDS 2010

MONET Week 144 analysis:
HIV RNA, TLOVR, ITT Population Switch=failure



difference=-5.9%, 95% C.I.-16.9%, +5.1%).

Arribas JR et al. HIV Med (in press)

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

MONET Week 144 analysis: Outcome of HIV RNA elevations in DRV/r arm (21 patients)

Patient	HIV RNA blips	Changed ARV / comments	Last HIV RNA
1	140, 133	None / sinusitis	<50 (wk 144)
2	59, 214	ZDV/3TC/NVP	<50 (wk 144)
3	53,160	TDF/FTC/DRV/r	<50 (wk 144)
4	132, 139	LPV/r mono	<50 (wk 144) - local
5	539, 862	TDF/FTC/EFV	<50 (wk 128) - local
6	75, 111	TDF/FTC/RAL	<50 (wk 144) - local
7	215, 56	None / Poor adherence	50 (wk 144)
8	810, 605	TDF/FTC/DRV/r	<50 (wk 144)
9	40500, 628	None (stopped Rx)	<50 (wk 144)
10	154, 100	None	<50 (wk 144)
11	158, 60	ABC/3TC/DRV/r	<50 (wk 144)
12	134, 79	None / Viral infection	<50 (wk128)
13	585, 69	None	69 (wk 144)
14	151,97	None / Poor adherence	<50 (wk 144)
15	51, 80	None	<50 (wk 96)
16	114, 106	TDF/FTC/DRV/r	231 (wk 112)
17	722, 157	TDF/FTC/DRV/r	<50 (wk 96), 82 (wk 144?)
18	398, 288	TDF/FTC/DRV/r / Infection	<50 (wk 144)
19	156, 6530	None	<50 (wk 144)
20	779, 267	ABC/3TC/DRV/r / Infection	<50 (wk 144)
21	164, 114	None	<50 (wk 144)

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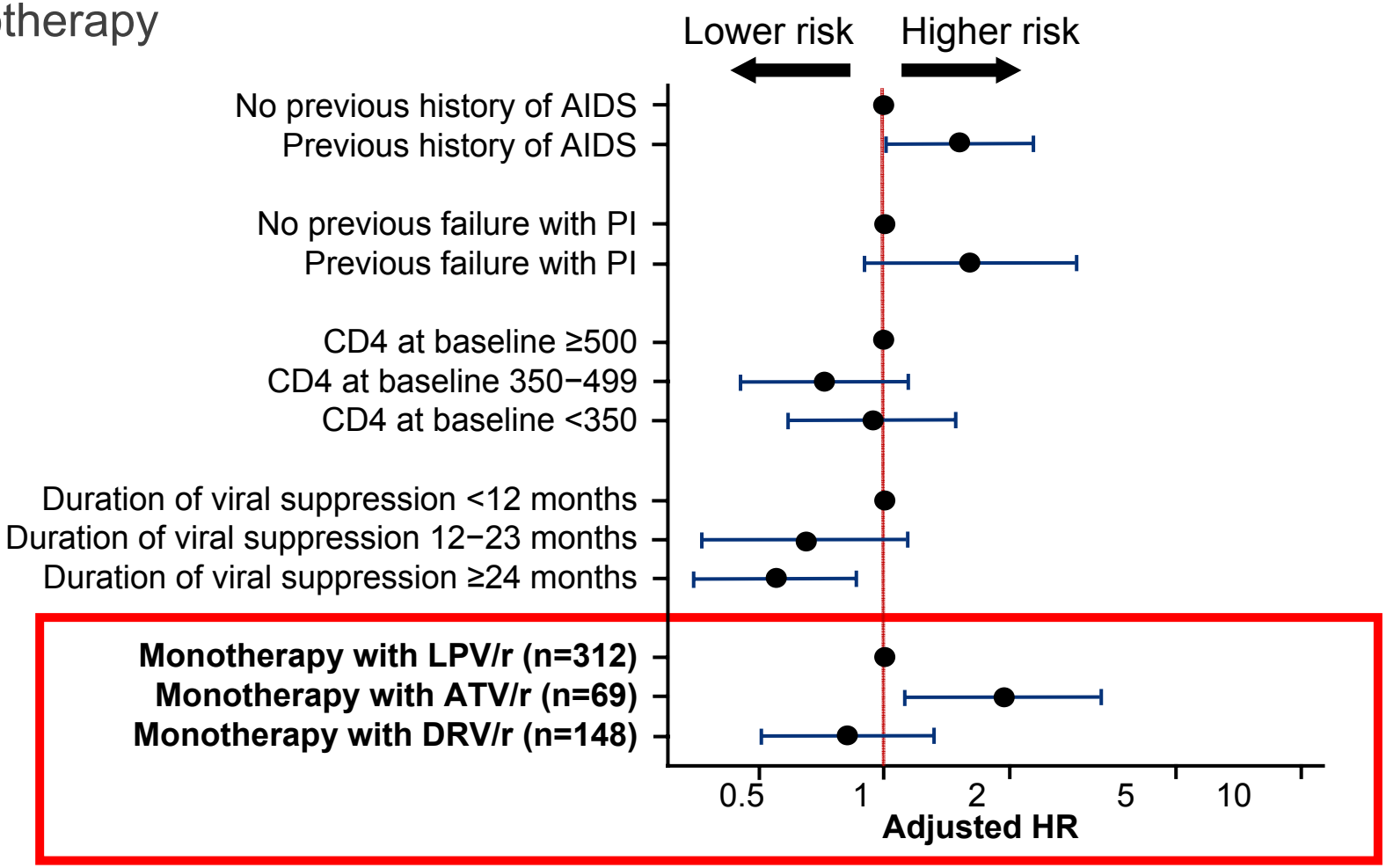
Observational study: PI/r monotherapy in routine clinical practice

- Predictors of virological failure among 529 experimented individuals receiving PI/r monotherapy



HR=hazard ratio, estimated using a Cox proportional hazards model and adjusted for age, sex and exposure group, and migration from sub-Saharan Africa

Guiguet M, et al. AIDS Epub 12 June 2012. doi:10.1097/QAD.0b013e32835646e0

MONOI: Predictors of Response

All Patients (Week 96)	Multivariate Analysis	
Variables Associated with Rebound by W96	OR (95%CI)	*P*
Randomized Group (Monotherapy vs. HAART)	4.81 (1.91, 13.7)	0.002
HIV-1 DNA at D 0 (per 1 $\log_{10}$ copies/10^8 cells increase)	1.97 (1.10, 3.57)	0.02
Duration of Prior ART (per 5 years decrease)	2.11 (1.23, 3.8)	0.009
Patients Randomized in the DRV/r Monotherapy ARM		
Variables Associated with Rebound by W48		
Baseline US HIV-RNA(< 1 copy/mL vs. others)	0.24 (0.05, 0.86)	0.042
HIV-RNA at D0 (blip vs. < 50 copies/mL)	10.0 (1.63, 62,7)	0.025
Variables Associated with Rebound by W96	OR (95%CI)	*P*
Difficulty in Adherence (< 100% vs. 100% adherence)	3.84 (1.29, 12.49)	0.02
Duration of prior ART (per 5 years decrease)	2.93 (1.43, 6.66)	0.006
HIV-1 DNA at D 0 (per 1 $\log_{10}$ copies/10^8 cells increase)	2.66 (1.11, 7.48)	0.04

- So good candidates should :
  - Have strictly undetectable viral load (HIV-1 RNA < 50 copies/ml) at the time of monotherapy beginning, and even below 50 copies/mL
  - Be fully adherent and even more adherent than for a triple therapy
  - Be treated with ART for a long time before switching to monotherapy

Marcelin AG, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 534.

PROLONGED TREATMENT WITH BOOSTED PROTEASE INHIBITOR MONOTHERAPY IS NOT ASSOCIATED WITH A HIGHER RATE OF NEUROCOGNITIVE IMPAIRMENT THAN TRIPLE DRUG ANTIRETROVIRAL THERAPY

Pérez-Valero I, González-Baeza A, Estébanez M, Montes-Ramírez ML, Bayón C, Pulido F, Cambrón I, Bernardino JI, Zamora FX, Monge S, Gaya F, Lagarde M, González-García J, Rubio R, Hernando A, Arnalich F, Arribas JR

Abstract # O333

IdiPAZ www.idipaz.es

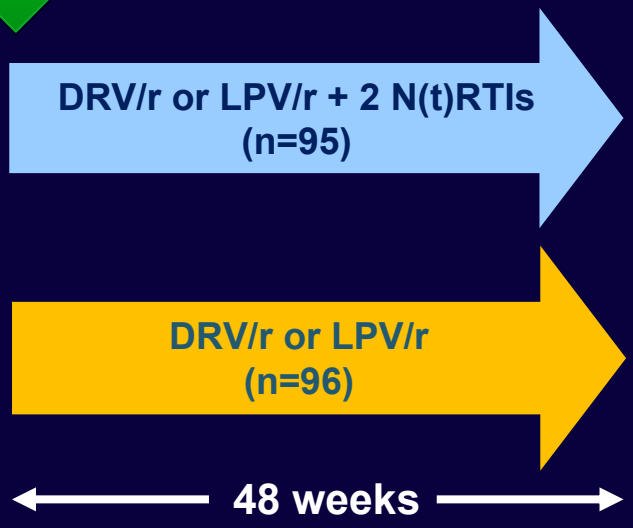
i+12 Instituto de Investigación Hospital 12 de Octubre

11 International Congress on Drug Therapy in HIV Infection

Study Design

Cross-sectional 4/11-6/12

- HIV+ patients receiving:
  - ✓ 2 N(t)RTIs + LPV/r or DRV/r
  - ✓ LPV/r or DRV/r alone
- HIV-RNA <50 (≥ 1yr)*
- Patients with confounders excluded



Objectives

- Prevalence of NCI**
- Is MT a risk factor for NCI?
- CSF Viral escape
- Biomarkers of NCI
- Evolution of NCI (48 wks)

Procedures (baseline & 48 week)

- Neurocognitive assessment
- Blood tests
- CSF & MRI (only if neurocognitively impaired)

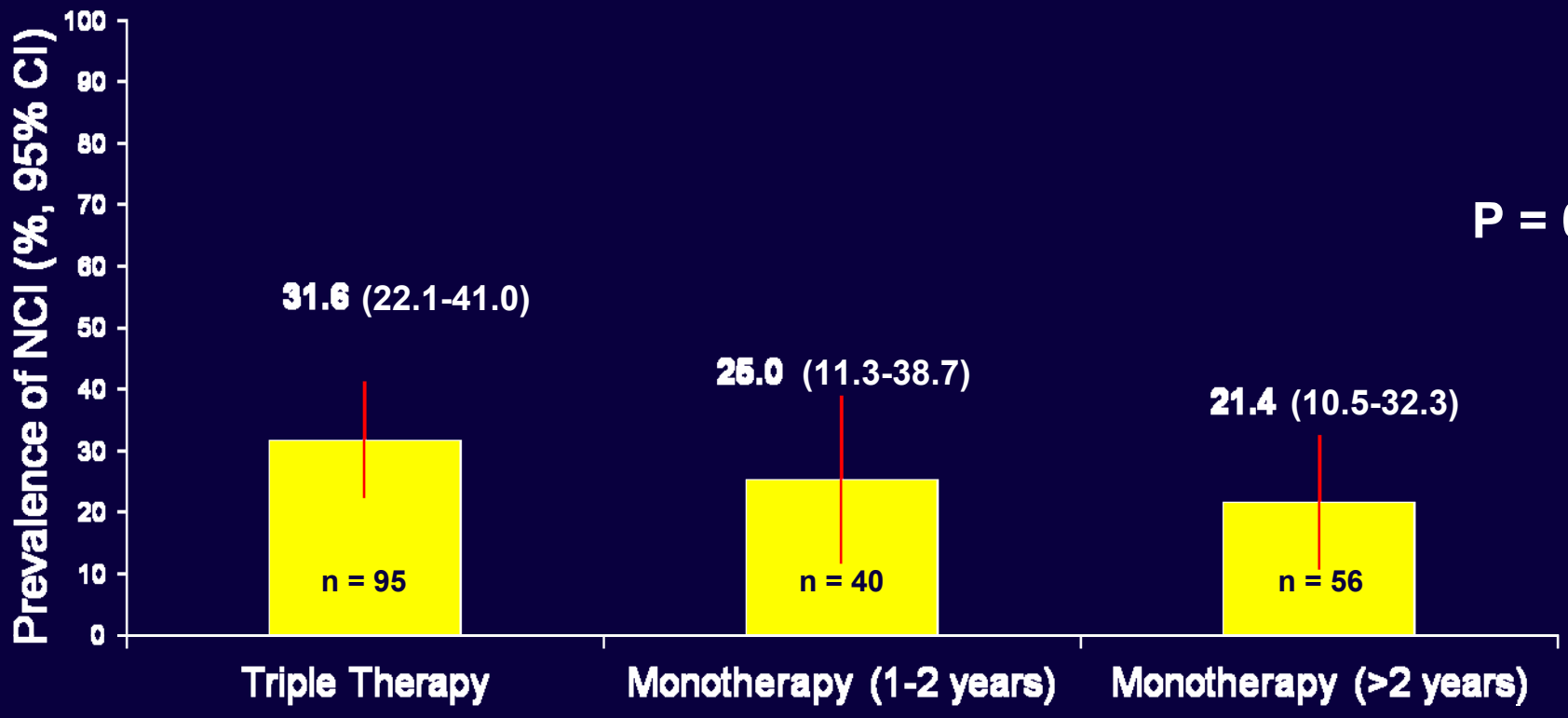
*Single blip allowed
**Neurocognitive Impairment

Antiretroviral Therapy

	Triple Therapy N = 95	MT (1-2 years) N = 40	MT (>2 years) N = 56	p < 0.05
Years of antiretroviral therapy. Median (IQR)				
Total	10.7 (4.8-15.7)	14.9 (11.0-16.6)	13.4 (10.0-15.0)	MT1, MT2 vs TT
Triple Therapy	10.7 (4.8-15.7)	13.2 (9.5-15.4)	9.9 (5.2-11.7)	MT1 vs MT2
Monotherapy	NA	1.5 (1.2-1.8)	3.0 (2.6-4.9)	MT1 vs MT2
Current protease inhibitor. N (%)				MT1 vs TT, MT2
Darunavir/ritonavir	25 (26.3)	24 (60.0)	19 (33.9)	
Lopinavir/ritonavir	70 (73.7)	16 (40.0)	37 (66.1)	
Adherence level < 100%. N (%)	25 (27.8)	7 (18.0)	11 (19.6)	
CPE score*. Median (IQR)	7 (7-7)	3 (3-3)	3 (3-3)	Not applicable

*Letendre et al. 17th Conference of Retroviruses and Opportunistic infections. San Francisco, 2010. Abstract 172

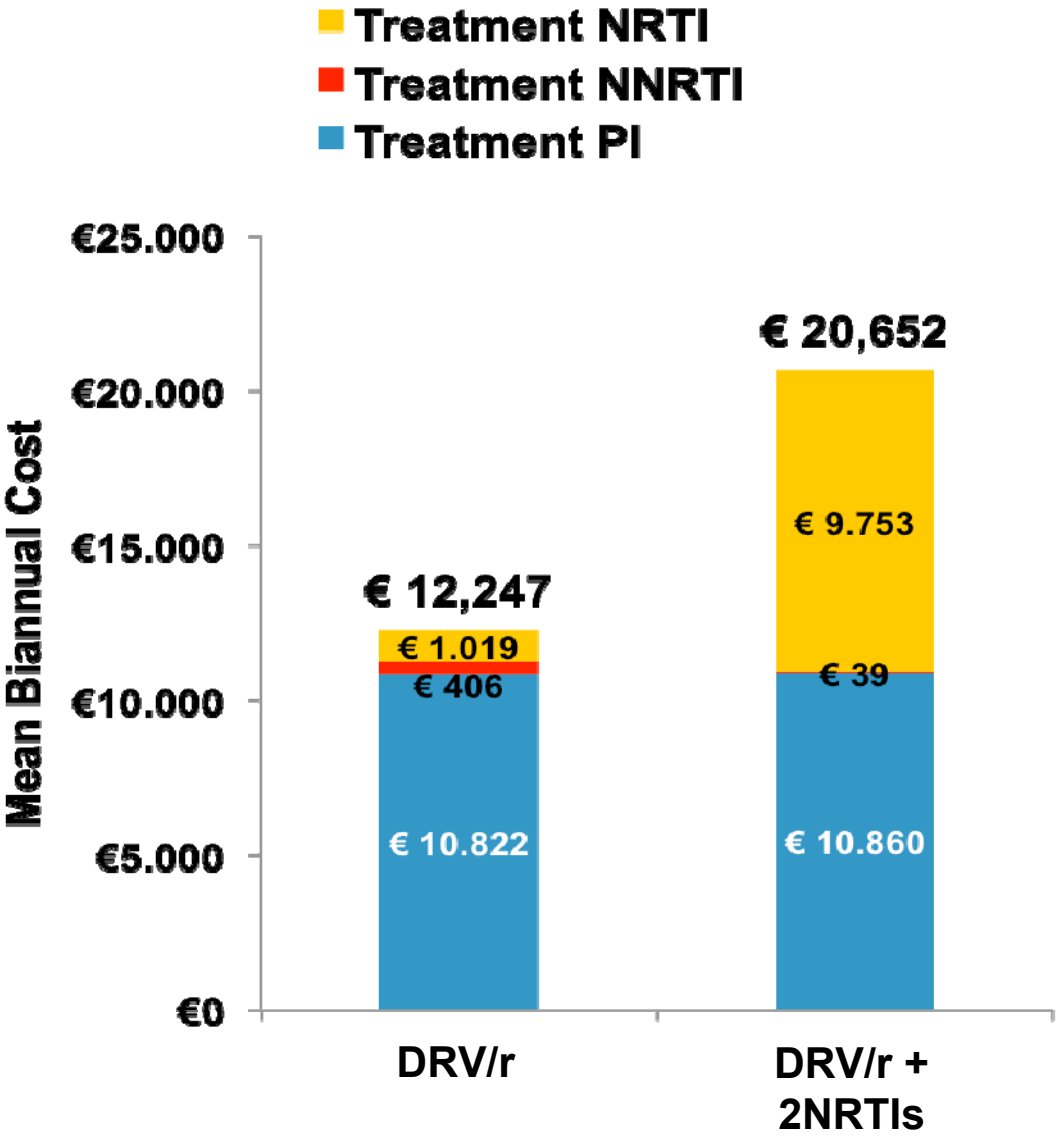
Prevalence of Neurocognitive Impairment



P = 0.38

All asymptomatic/mild by self report

Two-year Spanish costs of antiretrovirals in MONET – all patients



- **Acquisition cost** – the cost of DRV/r monotherapy is 21% lower than standard 2NRTI + NNRTI treament, and 33% lower than 2NRTI + PI treatment
- **Cost per response** – Cost per patient with HIV RNA <50 copies/mL at 96 weeks is lower for DRV/r monotherapy
  - A higher number of patients can be treated for a fixed budget
- **Budget Impact** – if a country such as Spain switched all patients with HIV RNA <50 and no prior virologic failure, to DRV/r monotherapy,
  there is the potential to save over **46 million Euros per two years** in antiretroviral treatment costs

Arribas J, et al; HIV10, 2010; Abstract P235.

Monoterapia y biterapia de la infección VIH, ¿cuándo?, ¿con que?¿con que grado de evidencia

- ~~There is active research in trying to find mono and dual~~ therapies for HIV infection.
  - Avoiding long-term toxicity of nucleosides. Increase treatment options
- Dual nuc-sparing therapy in naïve. Still more data needed
  - Preliminary data support efficacy of some combinations but doubts still persist (High viral loads) in naïve Proving less toxicity would require more follow-up
  - CNS protection?
  - 3TC/FTC?
- Monotherapy in suppressed.
  - Viable alternative for selected patients?