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Can we live without nucleosides?

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19th Annual Conference of the
British HIV Association [BHIVA]

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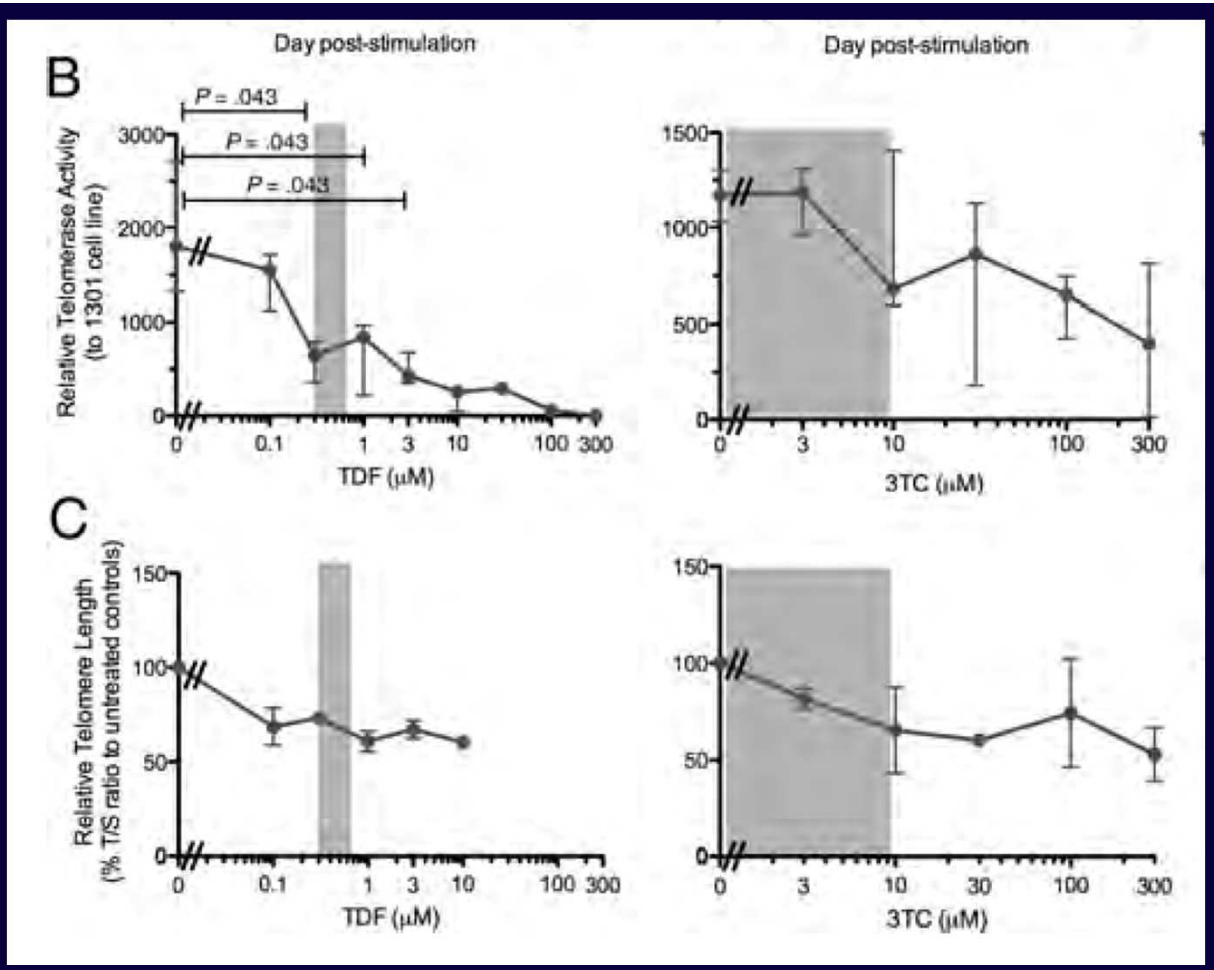
RATIONALE FOR NUCS-SPARING REGIMENS

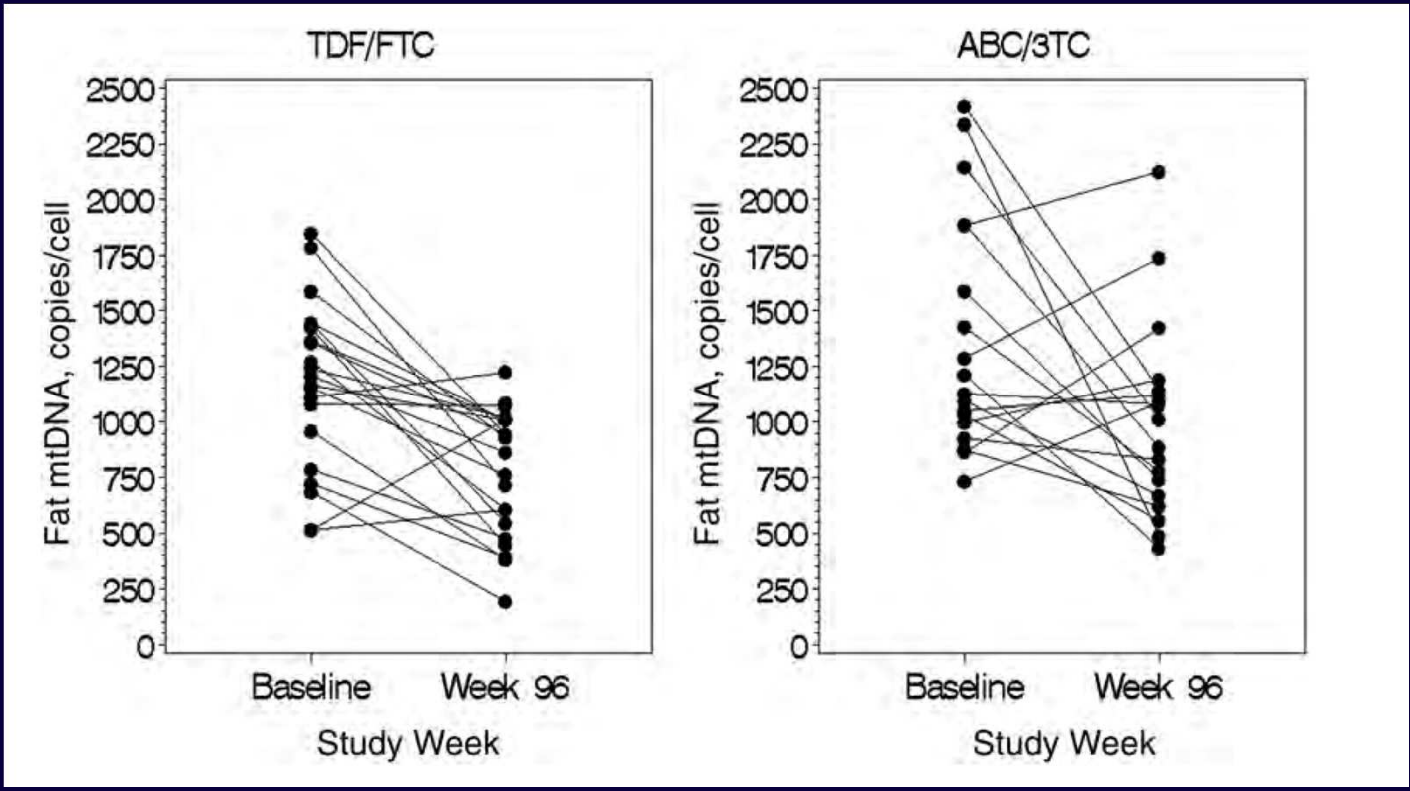
- Toxicity of current nucleosides (short and long term)
  - Cardiovascular?
  - Renal
  - Bone
  - CNS?
  - Limb fat
  - Cost

Inhibition of Telomerase Activity by Human Immunodeficiency Virus (HIV) Nucleos(t)ide Reverse Transcriptase Inhibitors: A Potential Factor Contributing to HIV-Associated Accelerated Aging



Leeansyah E Journal of Infectious Diseases 2013; 207:1157–1165.

Changes in Fat Mitochondrial DNA and Function in Subjects Randomized to Abacavir-Lamivudine or Tenofovir DF–Emtricitabine With Atazanavir-Ritonavir or Efavirenz: AIDS Clinical Trials Group Study A5224s, Substudy of A5202



McComsey GA et al Journal of Infectious Diseases 2013; 207:604–611.

What to Start: Comparison of Guidelines

Regimen	EACS	DHHS	IAS	GESIDA
TDF/FTC	RAL	Recommended	Preferred	Recommended	Preferred

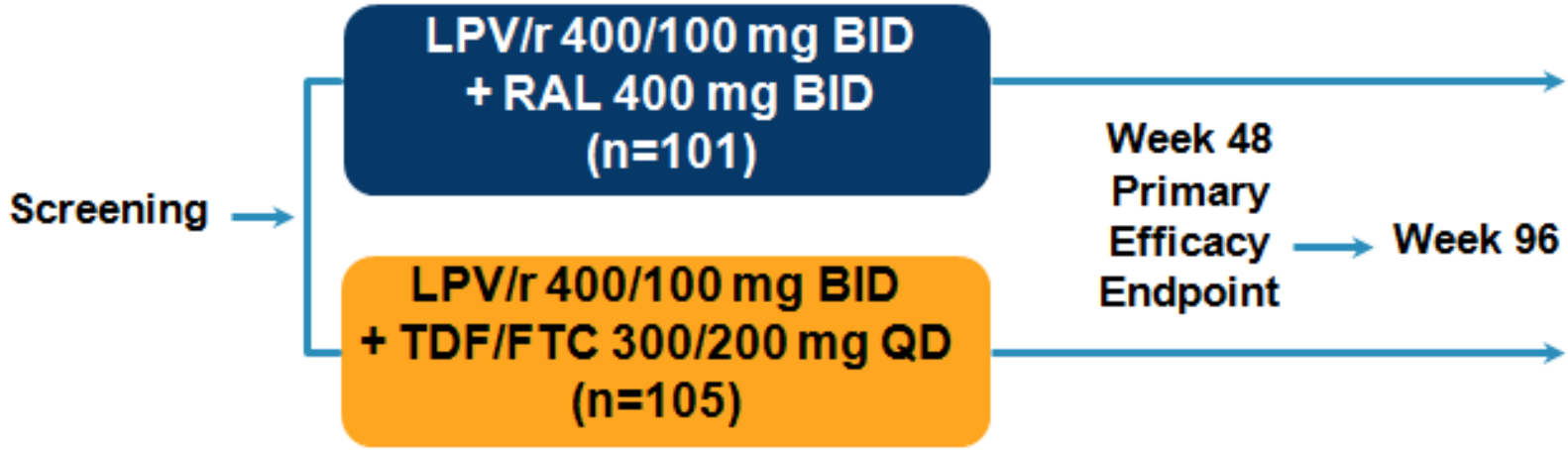
2 Nucs + 3rd Drug

Clumeck N et al. Available at http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf (November 2012)
Available at http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
Thompson MA, et al. JAMA 2012; 308:387–402.
Available at http://www.gesida-seimc.org/pcientifica/fuentes/DcyRc/gesidadcyrc2013-TAR-adulto.pdf (Enero 2013)
Availabel at http://www.aidsportugal.com/Modules/WebC_Docs/GetDocument.aspx?DocumentId=2828

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

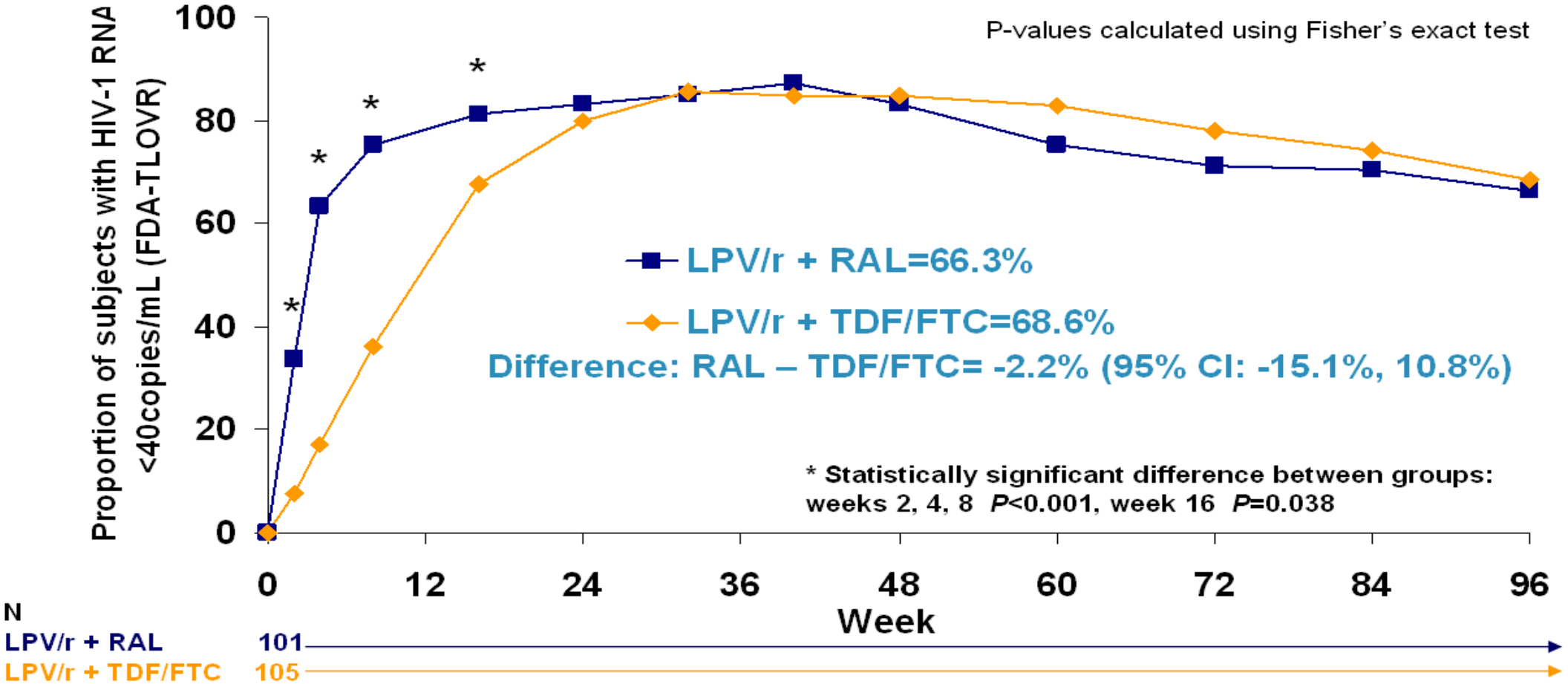


Met Primary Endpoint of Noninferiority

- 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)



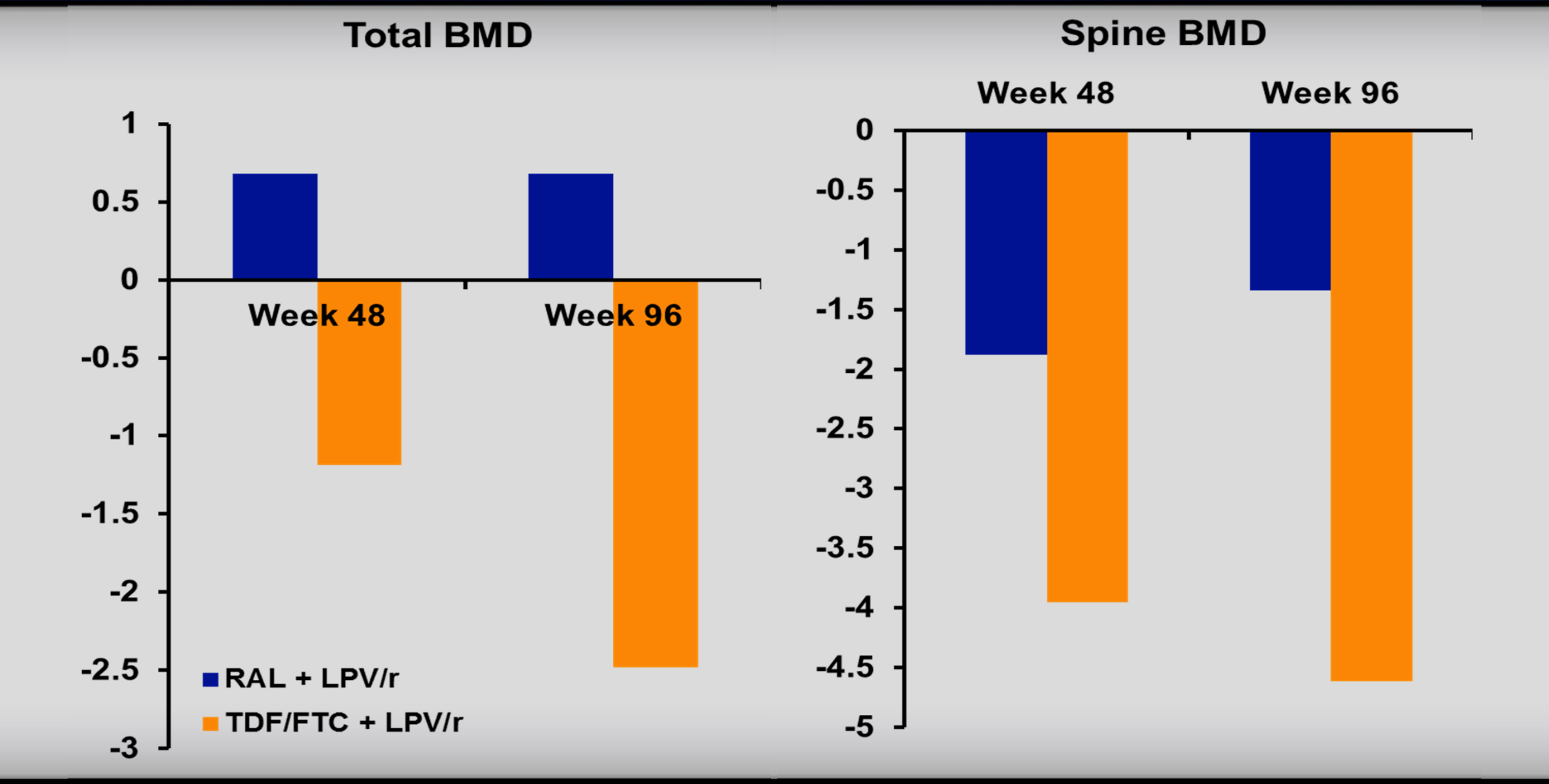
Week 96 FDA-TLOVR response for subjects with BL plasma HIV-1 RNA ≥100,000 copies/mL:
LPV/r + RAL= 6/15, LPV/r + TDF/FTC= 10/19

Mean change in Lipid Levels at Week 96

Variable		LPV/r + RAL N=82	LPV/r + TDF/FTC N=90
LDL:HDL ratio	Baseline	2.64	2.57
	Week 96	2.60	2.51
	Mean change	-0.04	-0.06
HDL mmol/L	Baseline	0.99	1.07
	Week 96	1.33	1.33
	Mean change	+0.35	+0.26
LDL mmol/L	Baseline	2.53	2.61
	Week 96	3.24	3.15
	Mean change	+0.72	+0.54
Total Cholesterol mmol/L	Baseline	4.25	4.40
	Week 96	5.36	5.20
	Mean change	+1.11	+0.81
Triglycerides mmol/L	Baseline	1.43	1.40
	Week 96	2.53	2.25
	Mean change	+1.10	+0.85

P>0.05 for difference between treatment groups in mean change at all time points using one-way ANOVA

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%)

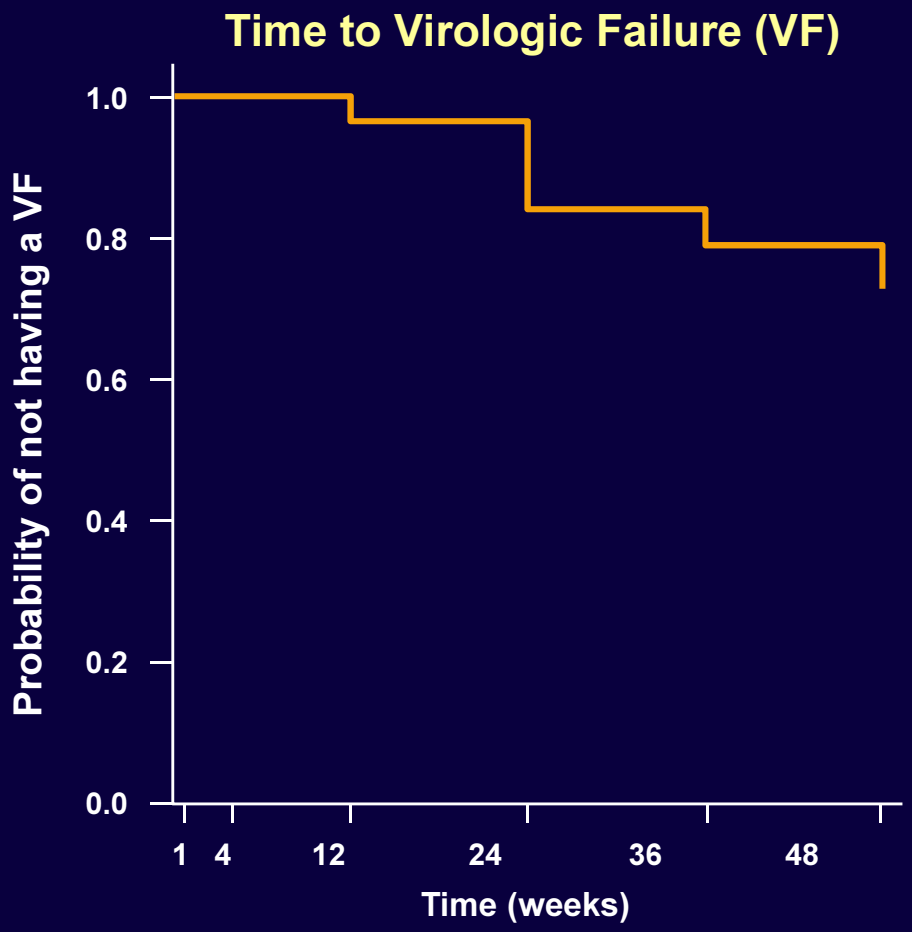
Primary Endpoint:

•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

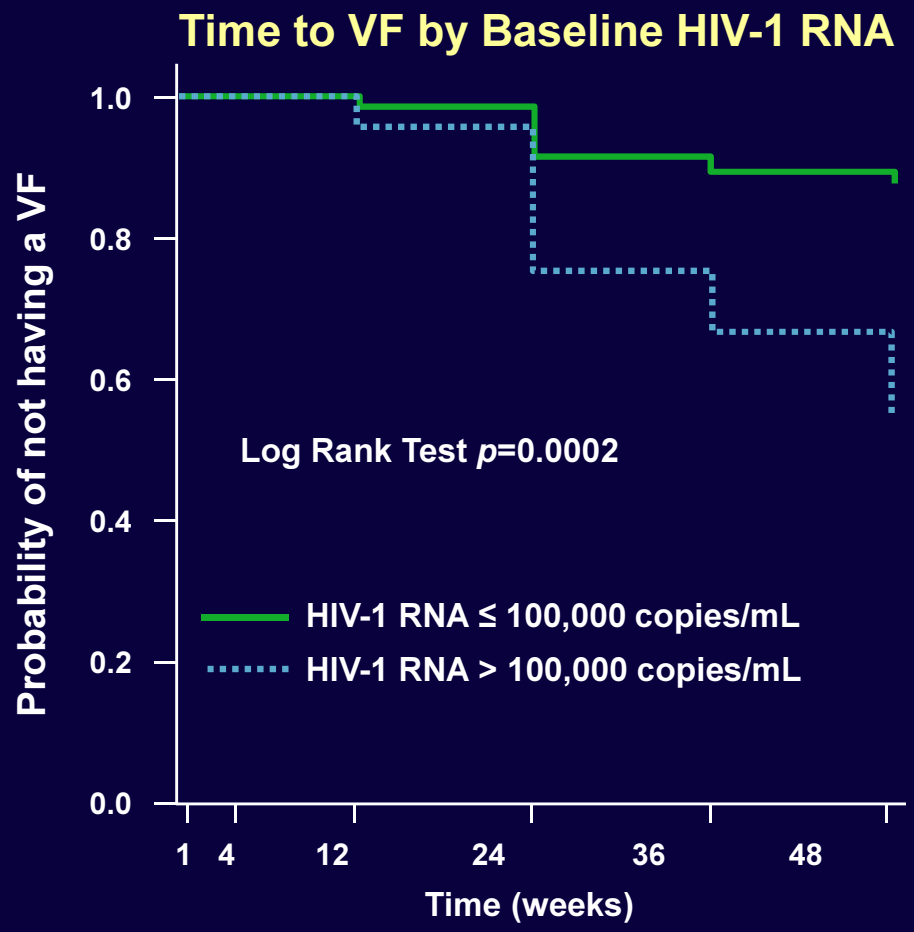
Taiwo B, et al. CROI 2010. Boston. #551.

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.

ACTG 5262

Integrase Mutations at Virologic Failure*

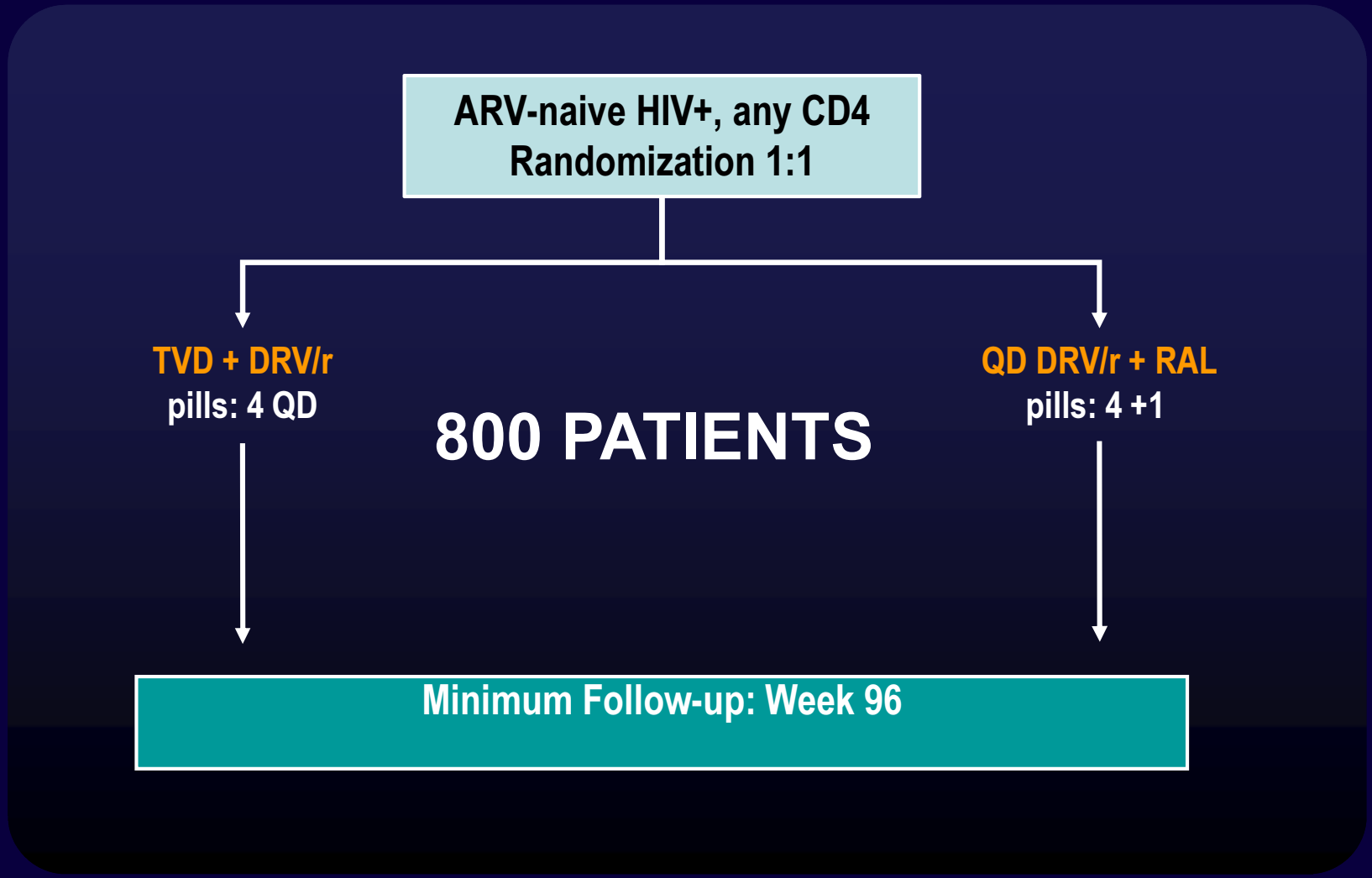
Baseline HIV RNA** (copies/mL)	Integrase Mutations at VF	Baseline Mutations
911,043	N155H	
246,270	N155H/N	
184,212	Q148K/Q, N155H/N	
230,627	Q148Q/R, N155H/N	
147,076	N155H/N	M41L

* Tested 25/28 VF subject. Samples for 3 could not be amplified.
** All HIV RNA > 100,000 copies/mL.

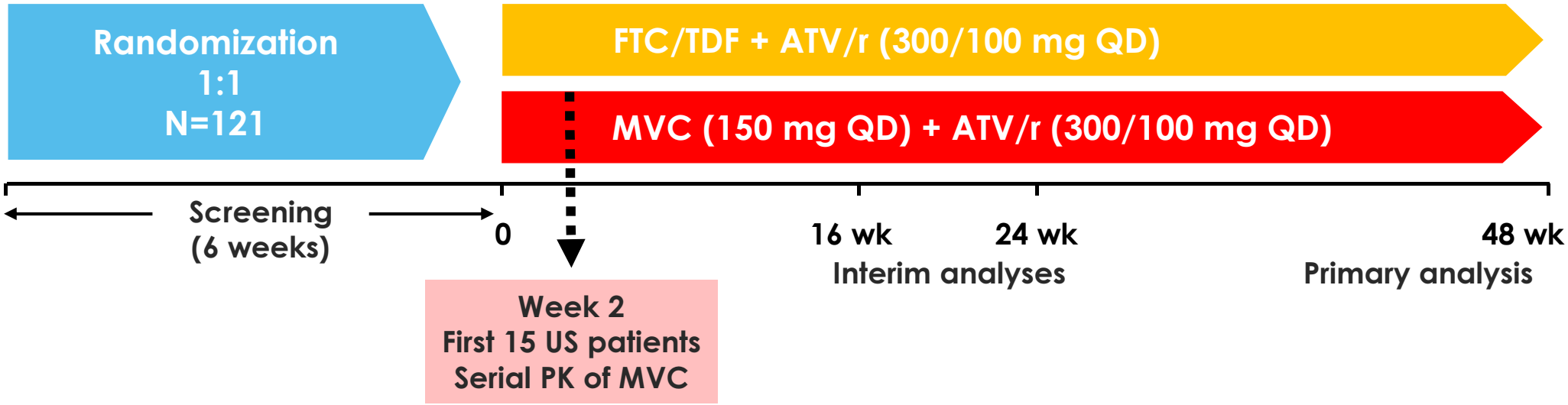
ACTG 5262 5/112 = 4.5%
STARTMRK 4/280 = 1.4%

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

NEAT Protocol 001 / ANRS 143



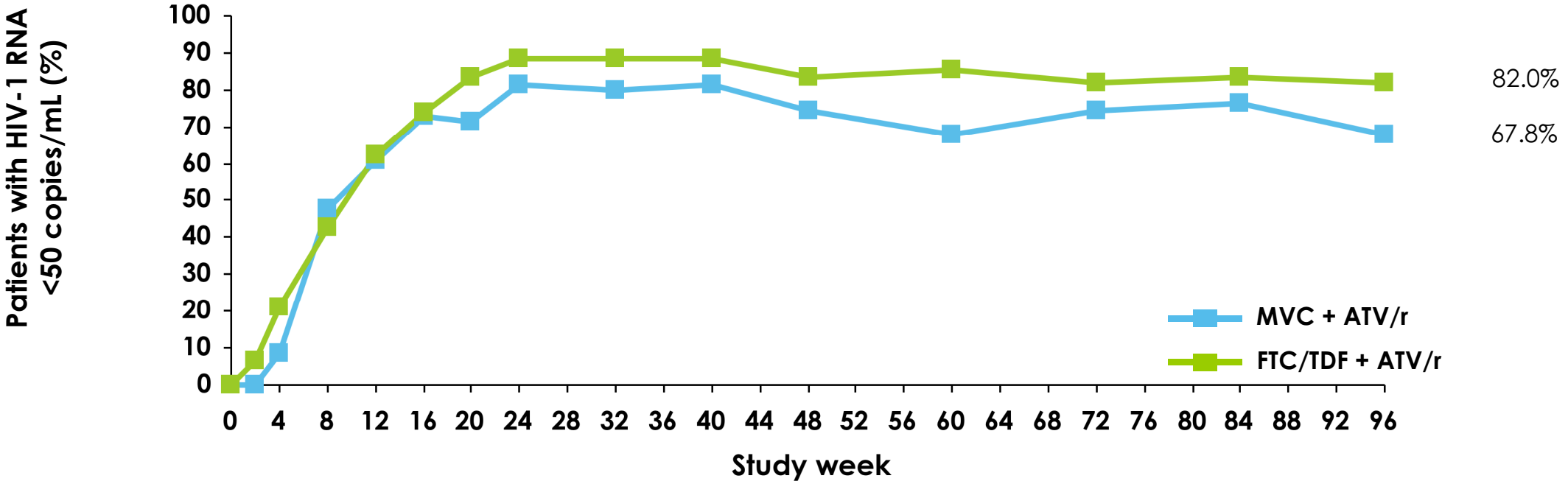
Study design
Open-label, 48-week Phase 2b pilot study



- **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.

Subjects with detectable viremia at week 96

	HIV-1 RNA, copies/mL					
	Baseline	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**
MVC + ATV/r						
A	<100,000	**<50**	**<50**	**<50**	**<50**	7670
B	<100,000	**<50**	**<50**	135	66	73
C	<100,000	**<50**	**<50**	**<50**	**<50**	54
D[a]	<100,000	57	70	**<50**	*Missed visit*	81
E	≥100,000	81	102	145	**<50**	109
F	<100,000	167	99	**<50**	53	93
G	<100,000	87	**<50**	231	463	222
H[b]	<100,000	51	**<50**	137	**<50**	1200
FTC/TDF+ATV/r						
I	<100,000	**<50**	**<50**	**<50**	**<50**	77

[a] Ran out of medication and missed visits
[b] Missed dosing due to vomiting

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

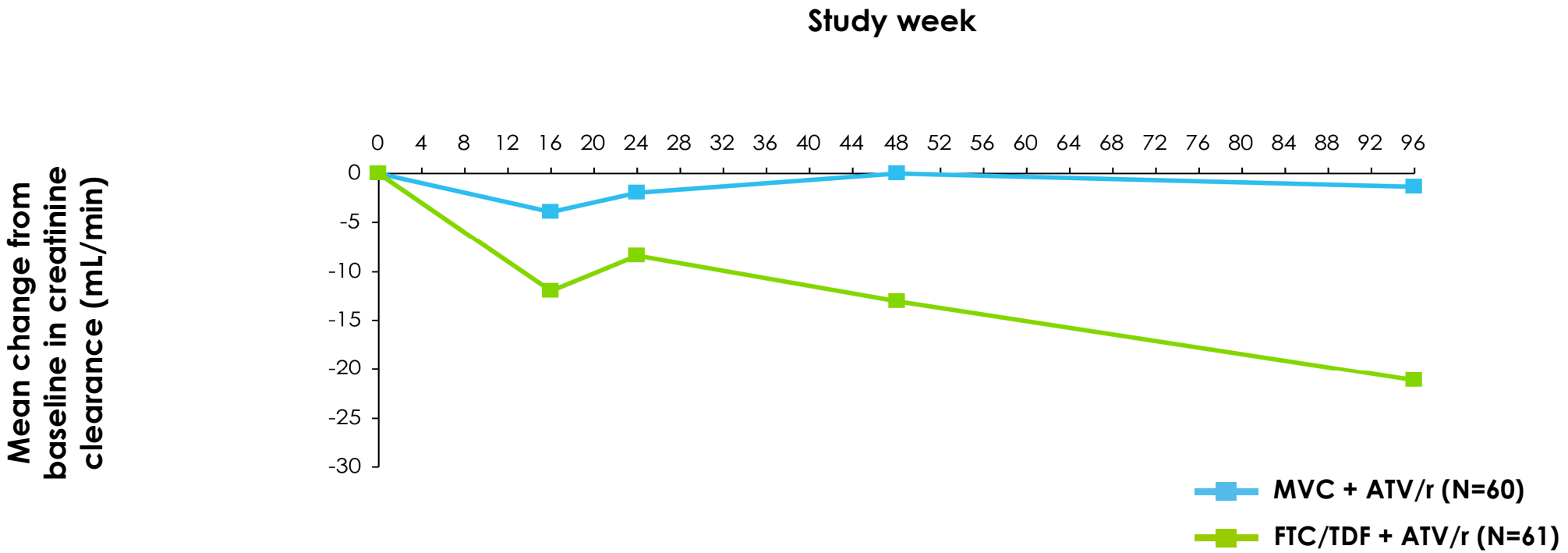
Safety

	MVC + ATV/r n=60	FTC/TDF + ATV/r n=61
Any AE, n (%)	58 (96.7)	61 (100.0)
Serious AE, n (%)	13 (21.7)	11 (18.0)
Grade 3 or 4 AE, n (%)	32 (53.3)	20 (32.8)
Discontinued due to AE, n (%)	2 (3.3)	0
Hyperbilirubinemia, n (%)		
AE-related	18 (30.0)	16 (26.2)
Grade 3 or 4 AE related	10 (16.7)	8 (13.1)
Grade 3 or 4 laboratory*	42 (70.0)	34 (55.7)
Jaundice, n (%)		
AE-related	10 (16.7)	6 (9.8)
Grade 3 or 4 AE related	5 (8.3)	1 (1.6)

AE, adverse event
*According to AIDS Clinical Trial Group classification

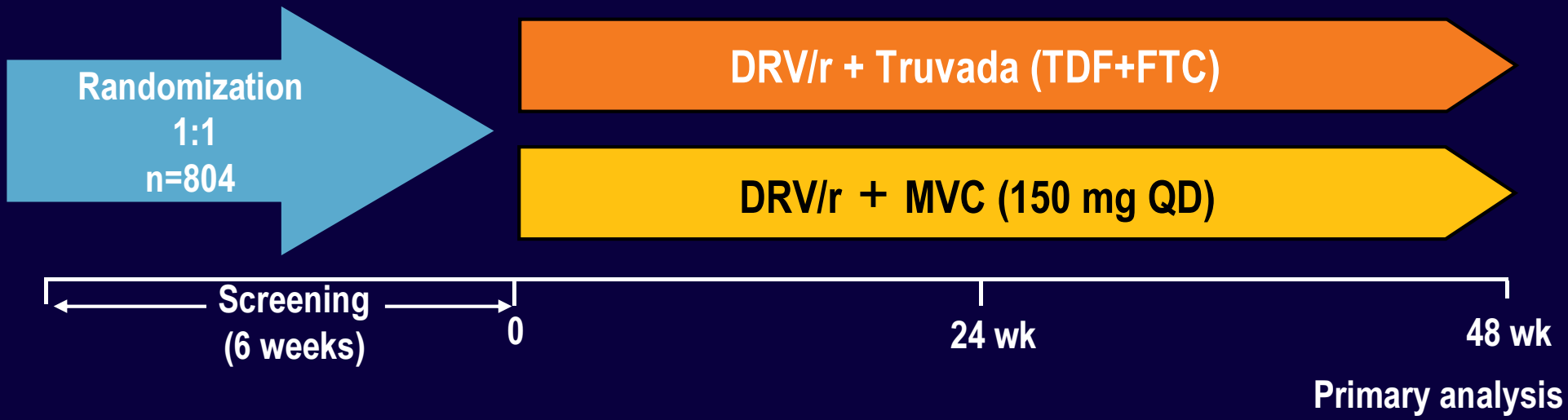
- The most frequently reported (≥20%) all causality adverse events (AE) in the MVC + ATV/r treatment group were: hyperbilirubinemia (n=18; 30.0%); diarrhea (n=15; 25.0%); and ocular icterus (n=13; 21.7%) in the MVC +ATV/r arm, and hyperbilirubinemia (n=16; 26.2%), nausea (n=16; 26.2%) and diarrhea (n=14; 23.0%) in the FTC/TDF arm

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

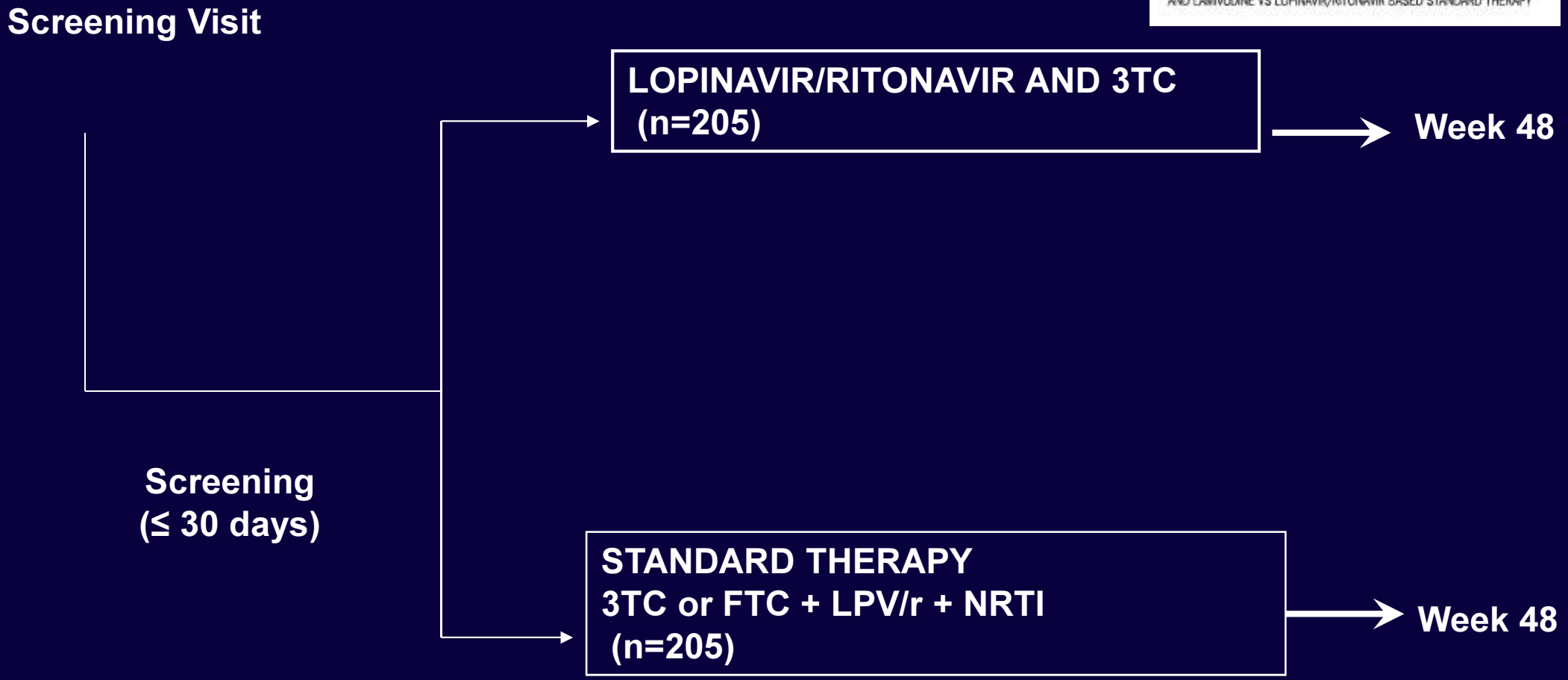
Week 48 resul -naive patients infected with R5-tropic HIV-1

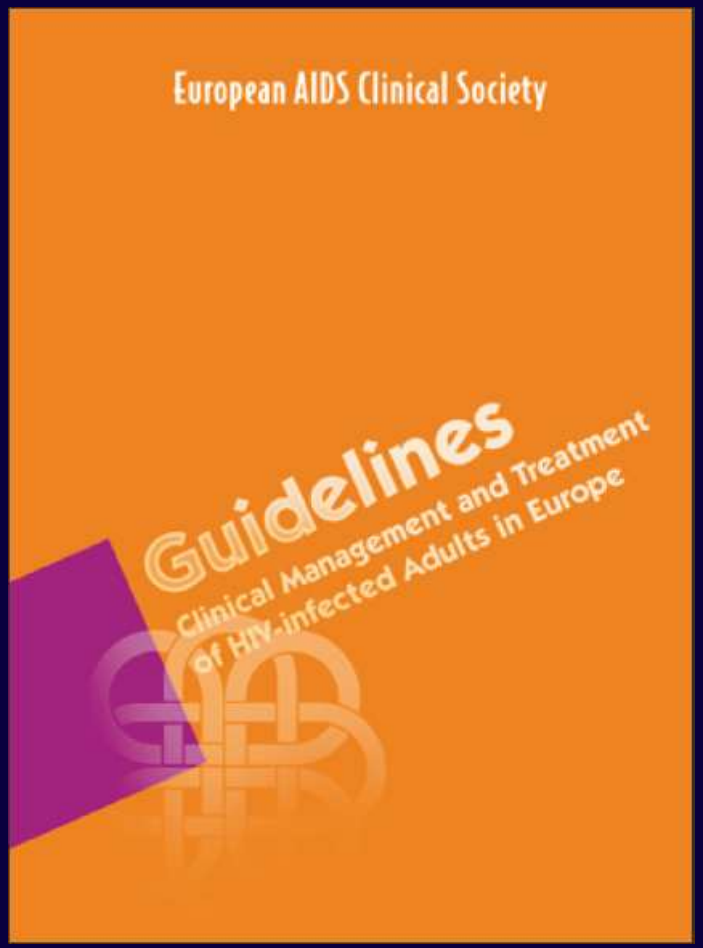
B. Taiwo[1], S. Swindells[2], B. Berzins[1], E. Acosta[3], P. Ryscavage[1], J. Lalezari[4], J. Castro[5], O. Adeyemi[6], B. Yip[1], M. Rathert[1], D. Kuritzkes[7], J. Eron[8], MIDAS Study Team

Investigational Plan. Gardel Study

Study Design Schematic

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





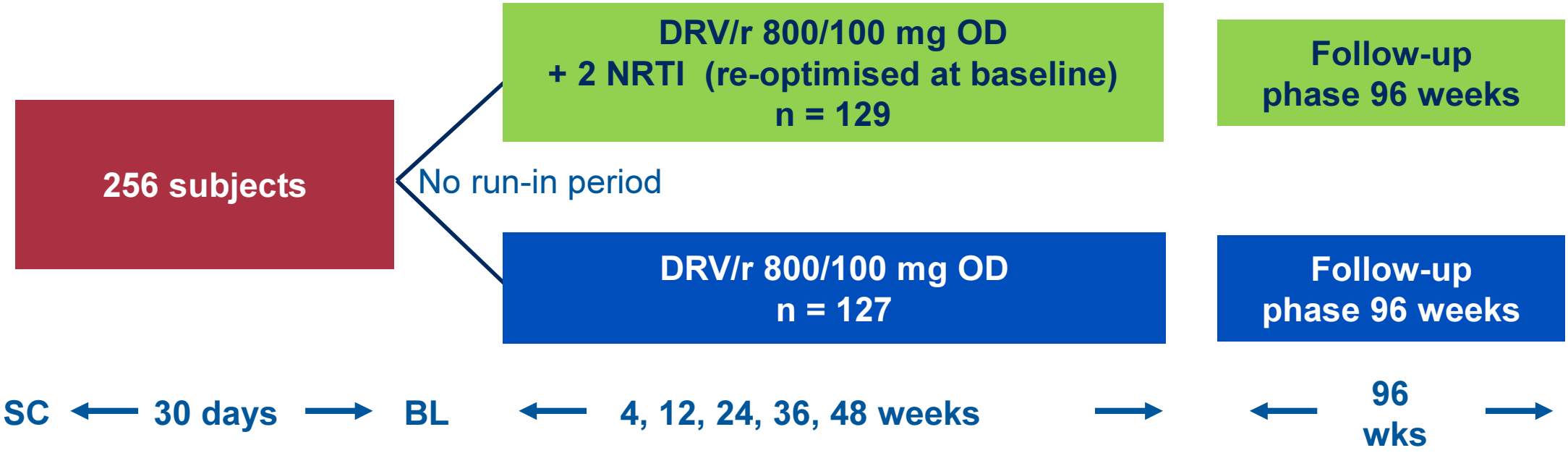
CLINICAL MANAGEMENT AND TREATMENT OF HIV INFECTED ADULTS IN EUROPE

Switch strategies for virologically suppressed patients
(confirmed plasma viral load < 50 c/ml)

Clumeck N et al. Available at http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf (November 2012)

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

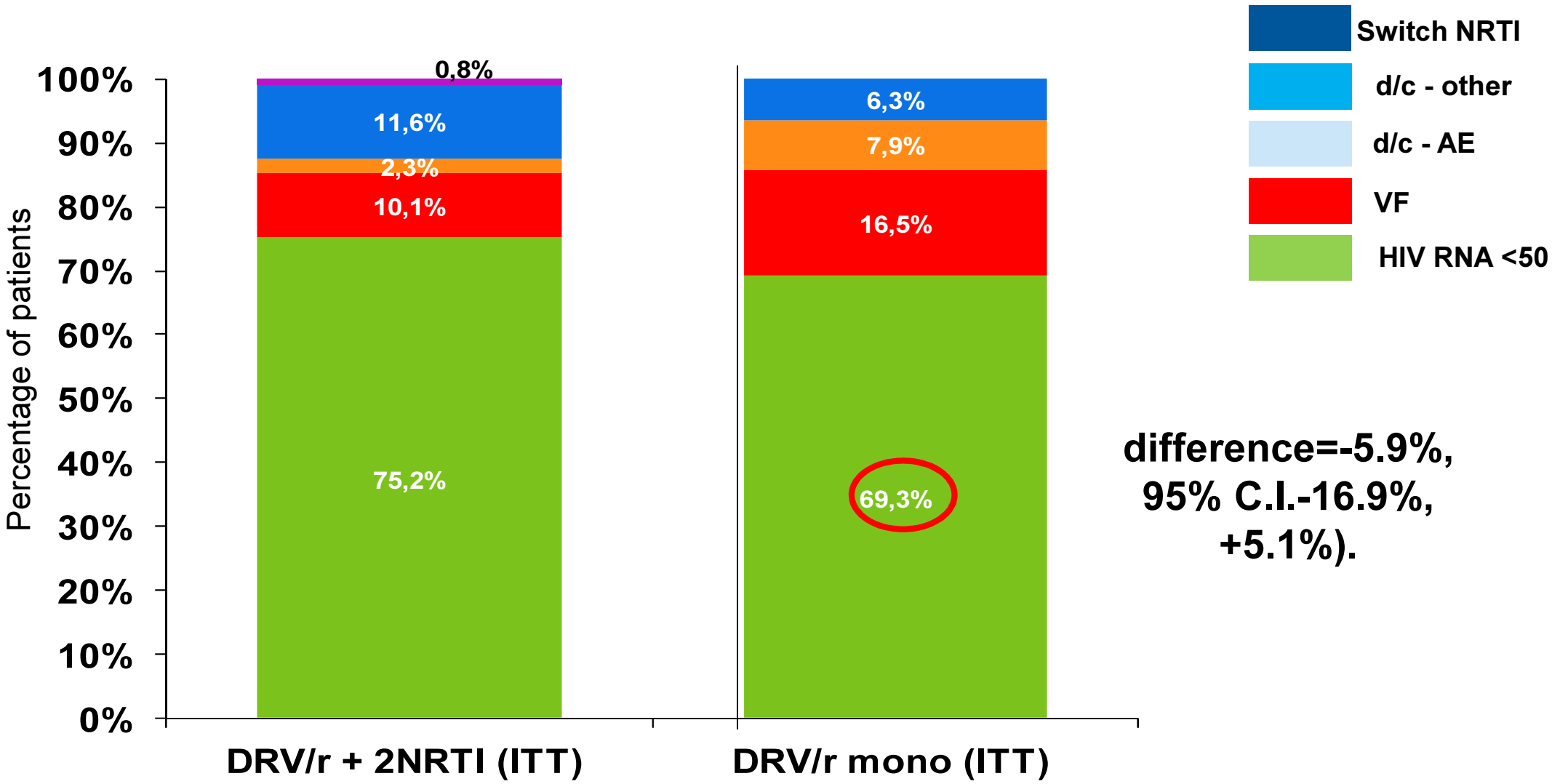


Primary Endpoint: HIV RNA< 50 at week 48 (TLOVR). Per Protocol, Switch = Failure

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



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

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

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

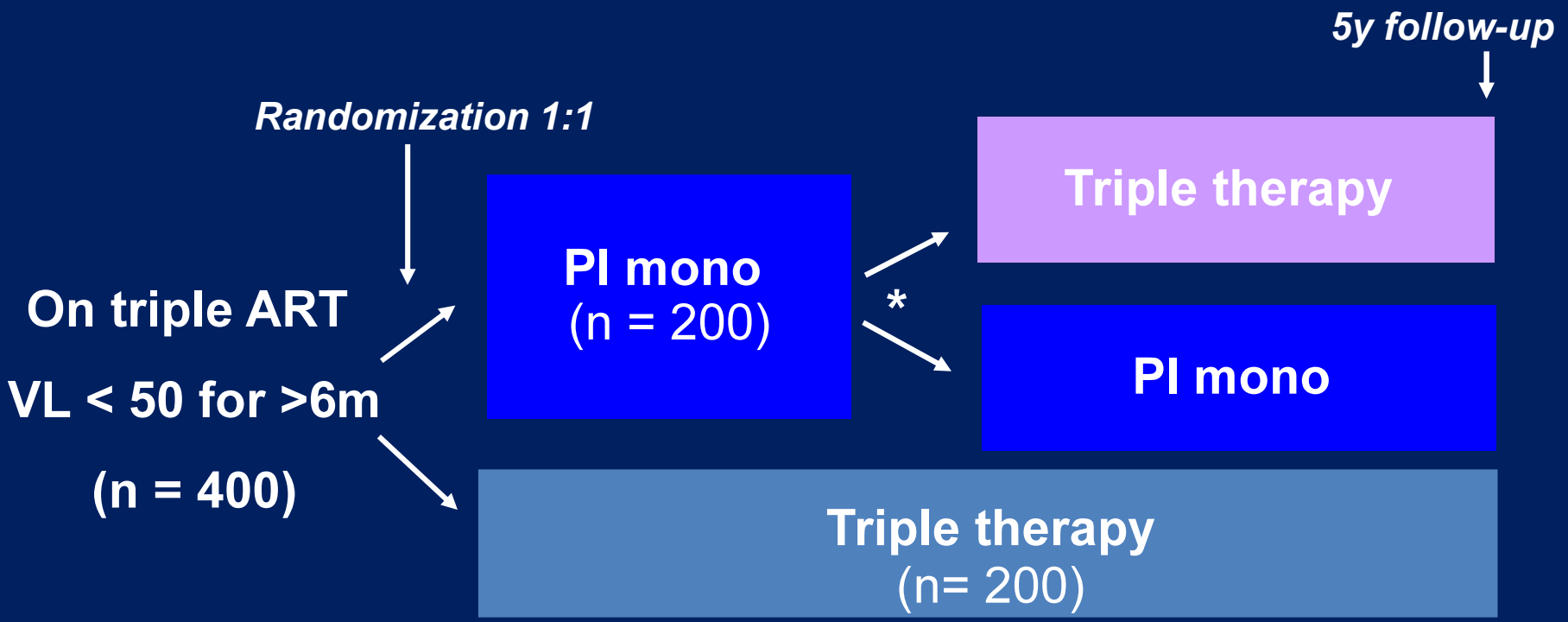
	Patient	HIV RNA blips	Changed ARV / comments	Last HIV RNA
11	1	140, 133	None / sinusitis	<50 (wk 144)
	2	59, 214	ZDV/3TC/NVP	<50 (wk 144)
7	3	53,160	TDF/FTC/DRV/r	<50 (wk 144)
	4	132, 139	LPV/r mono	<50 (wk 144) - local
	5	539, 862	TDF/FTC/EFV	<50 (wk 128) - local
3	6	75, 111	TDF/FTC/RAL	<50 (wk 144) - 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)

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

PIVOT trial: Design and primary end-point

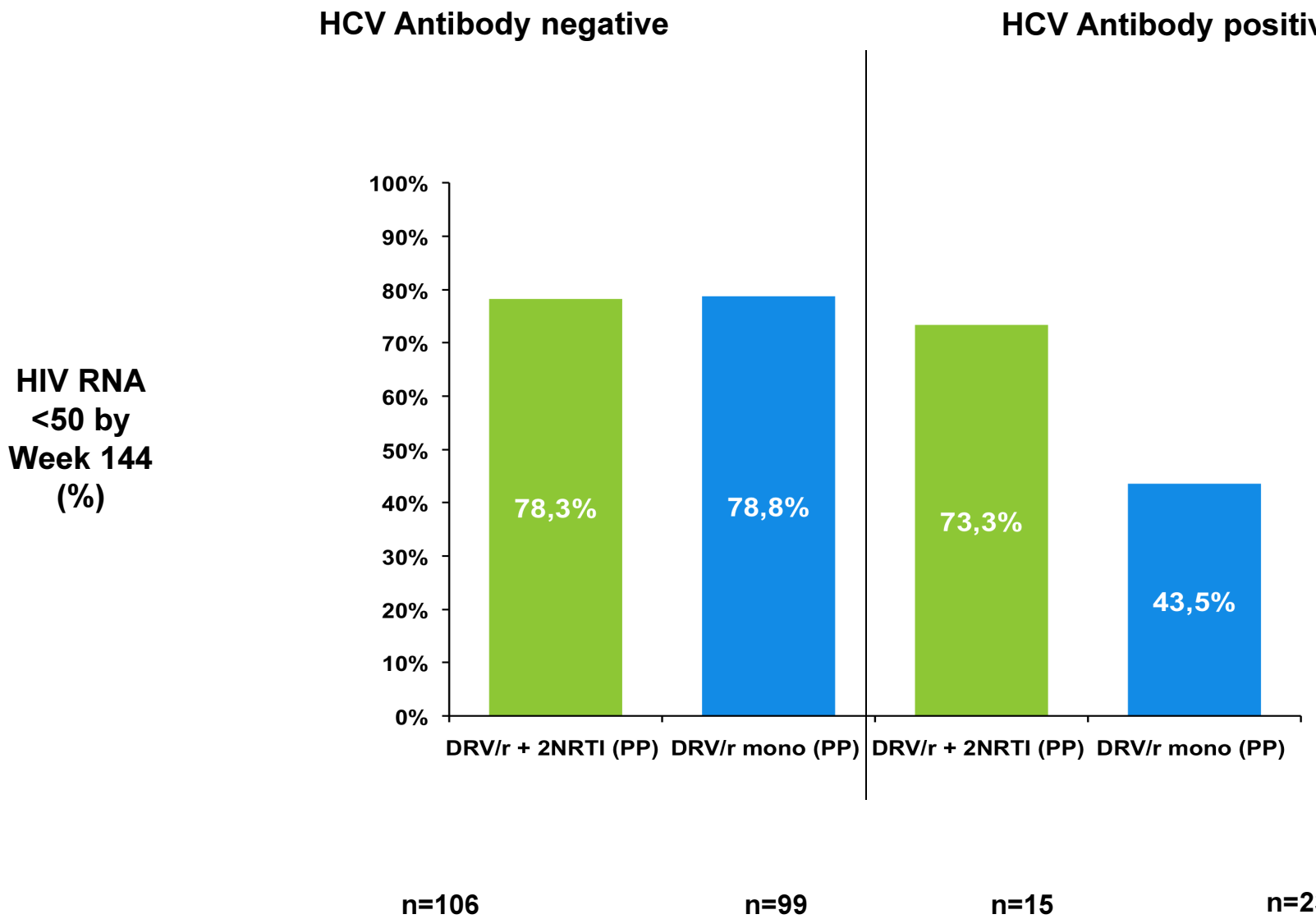


*Patients return to triple therapy if VL >50 copies X 2 tests

- **Primary end-point: Loss of future drug options (apparition of high level resistance to any antiretroviral drug).**

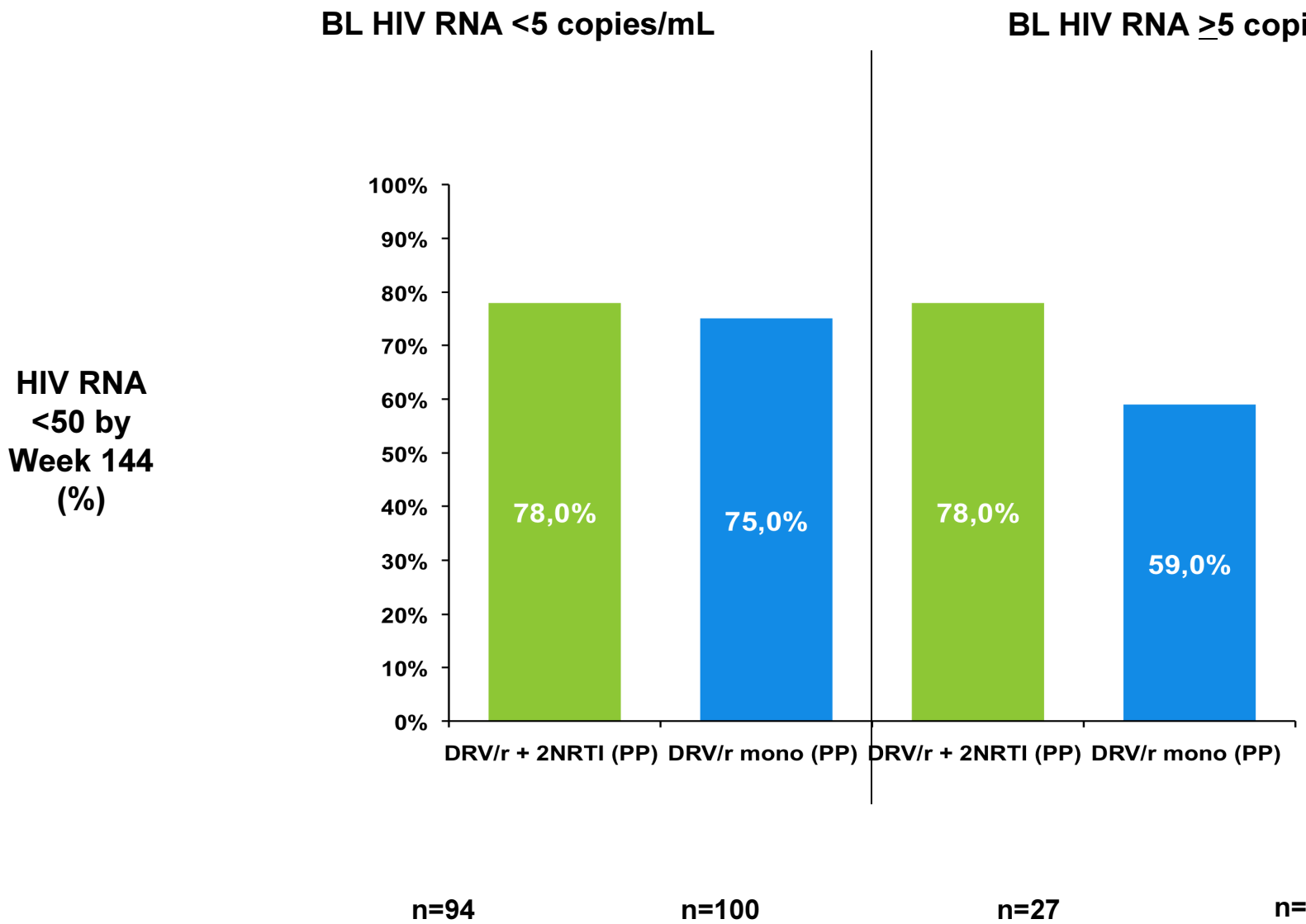
Available at: clinicaltrials.gov/ct2/show/NCT01230580

HIV RNA <50 copies/mL at Week 144
by HCV serology at baseline (PP, TLOVR, Switch=Failure)



Ref: Arribas et al, HIV Medicine 2012, 13:398-405

HIV RNA <50 copies/mL at Week 144
by baseline HIV RNA (Per Protocol, TLOVR, Switch=Failure)



Ref: Arribas et al, HIV Medicine 2012, 13:398-405

Multivariate predictors of treament failure
Endpoint – HIV RNA <50 copies/mL by Week 144

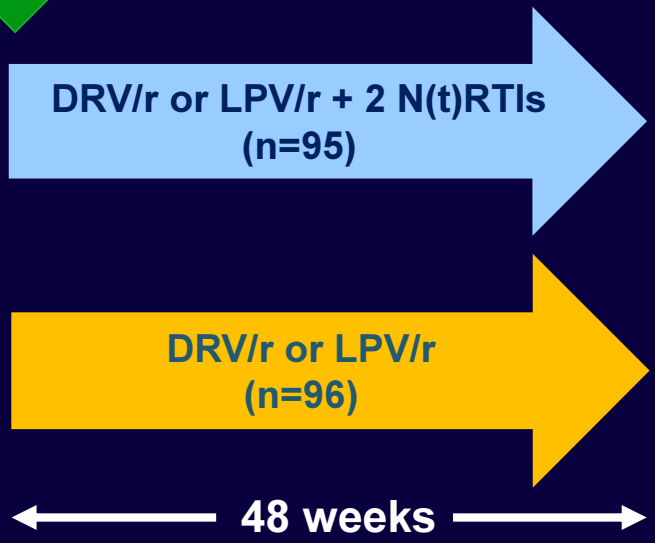
Analysis / predictors	Odds Ratio (95% CI)	p value
ITT TLOVR Switch=Failure analysis:		
Hepatitis C Antibody positive	2.44 (1.20 – 5.00)	p=0.008
Age (per 1 year older)	0.96 (0.93 - 1.00)	p=0.042
ITT Switch Included analysis:		
BL HIV RNA >5 copies/mL	2.78 (1.28 – 6.01)	p=0.009
Virological Failures only analysis:		
BL HIV RNA >5 copies/mL	2.71 (1.21 – 6.08)	p=0.016
Hepatitis C Antibody positive	2.77 (1.18 – 6.67)	p=0.020

Other predictors: baseline CD4 count, CD4 nadir, Prior PI use, weight, sex were not significant in any of the analyses.

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)

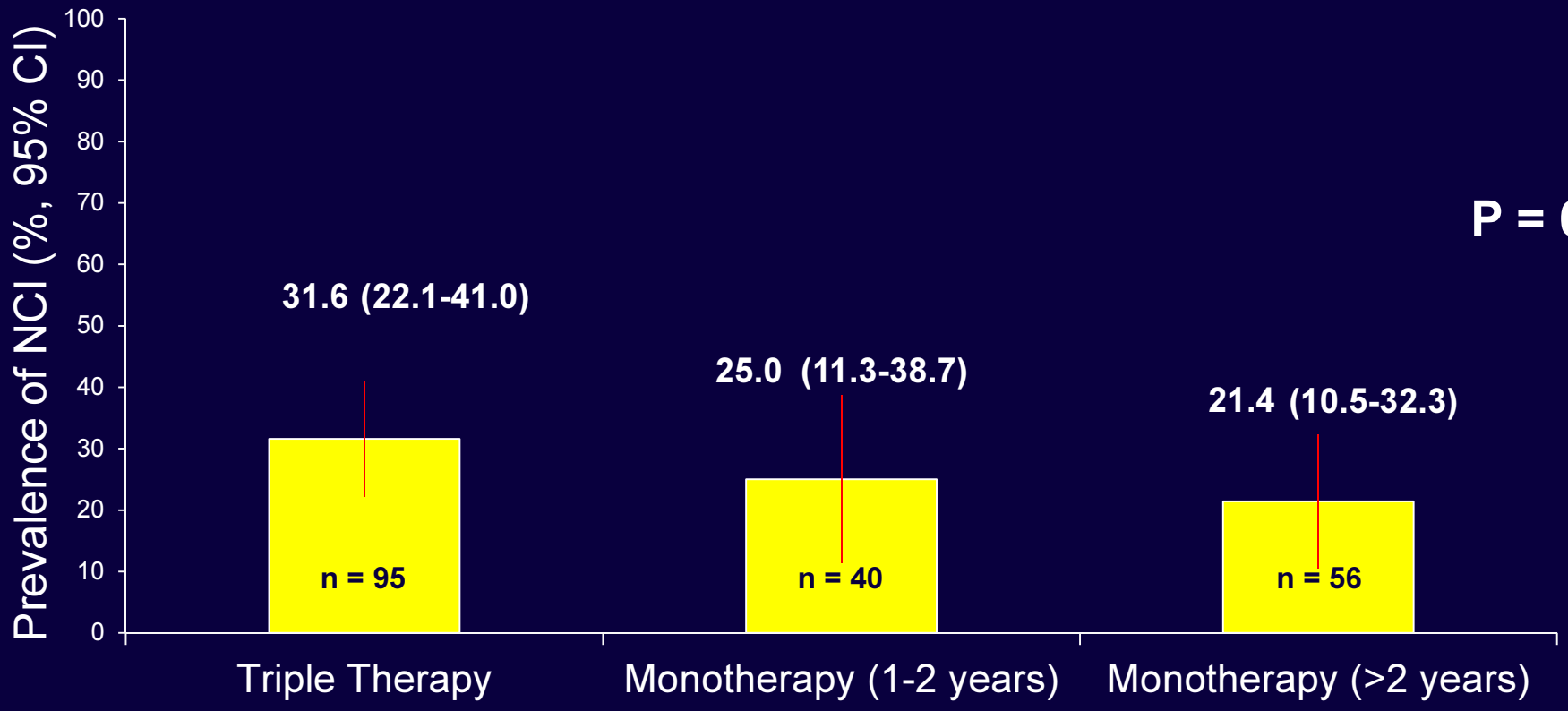
*Single blip allowed
**Neurocognitive Impairment

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

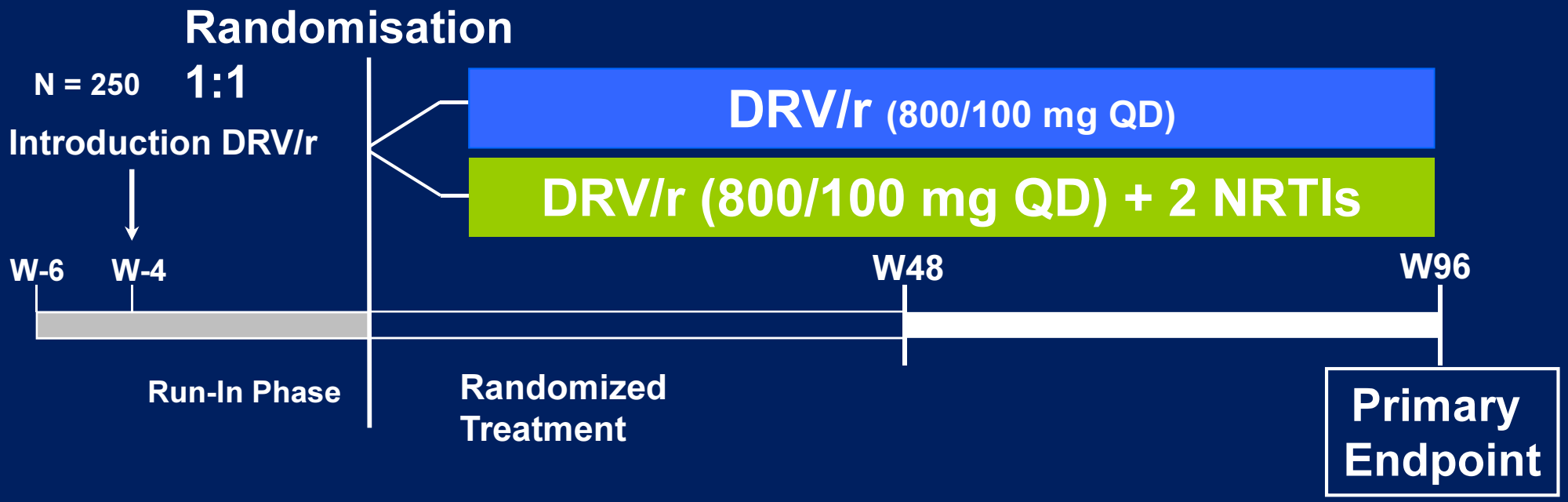


P = 0.38

All asymptomatic/mild by self report

PROTEA Study: Design and primary end-point

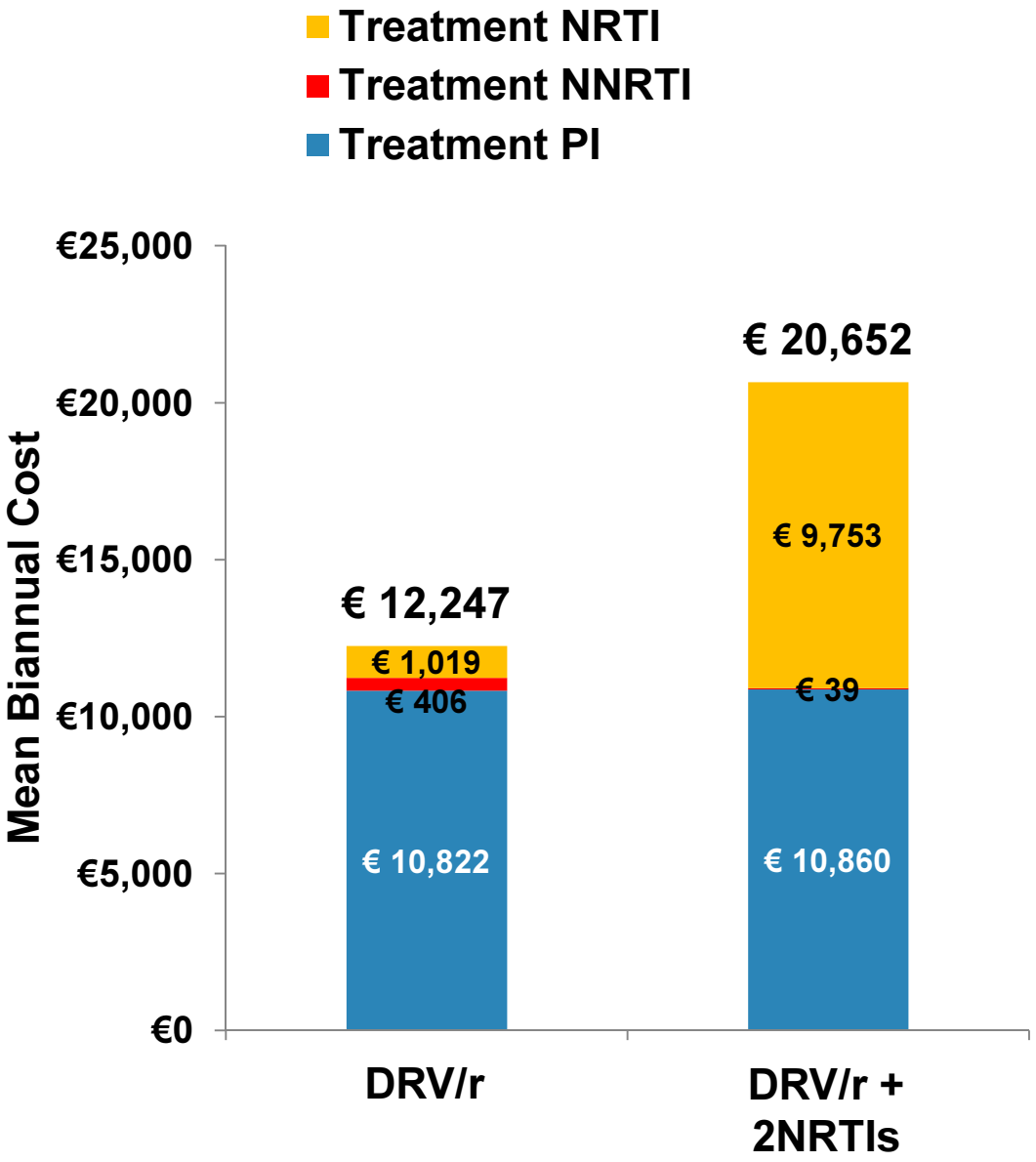
- **Multicenter open label randomized study**



- Primary end-point: Percentage of patients with HIV-RNA in plasma <50 cp/mL after 48 weeks of follow-up after switching to DRV MT vs. triple therapy containing DRV/r.

Available at: clinicaltrials.gov/ct2/show/NCT01448707

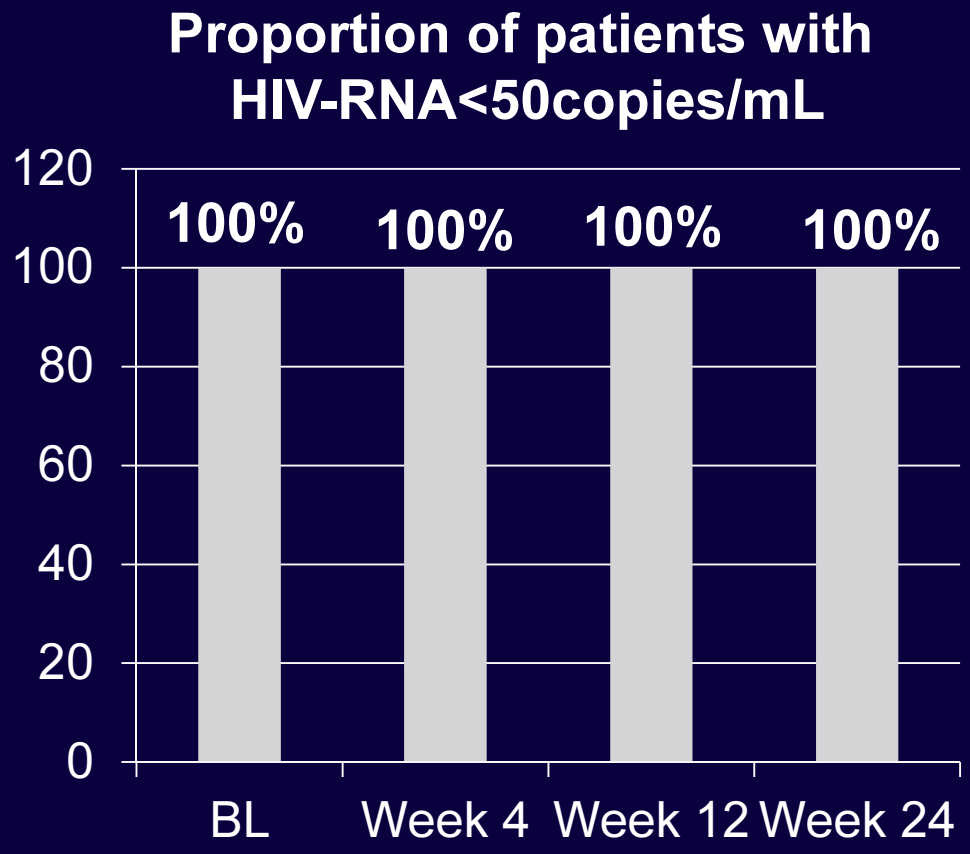
Two-year Spanish costs of antiretrovirals in MONET – all patients



- **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.

Atazanavir/ritonavir + lamivudine for maintenance of suppression



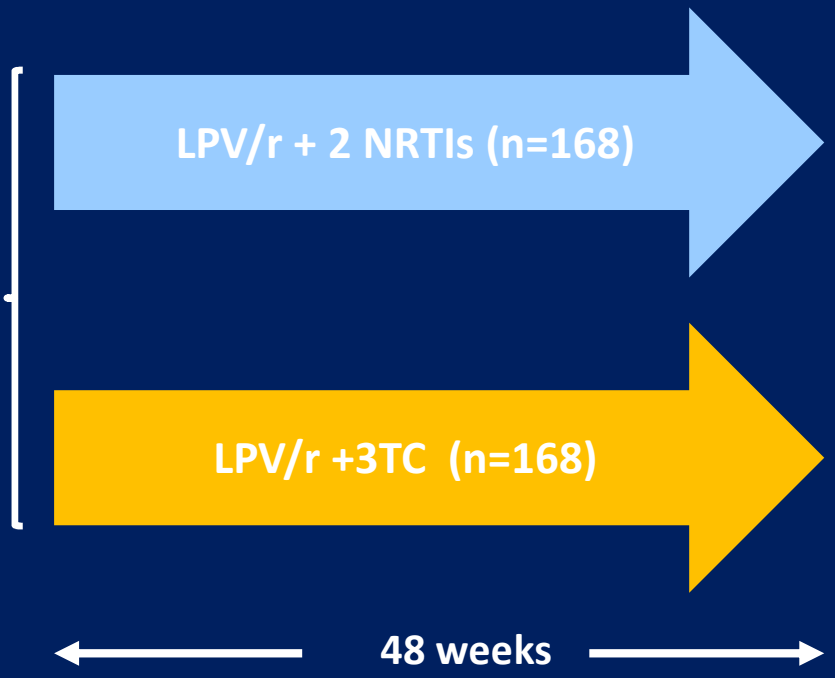
48 WEEKS: 86.8%

Di Giambenedetto. Journal of Antimicrobial Chemotherapy Published Online First: 30 January 2013. doi:10.1093/jac/dkt007

OLE STUDY

Inclusion criteria:

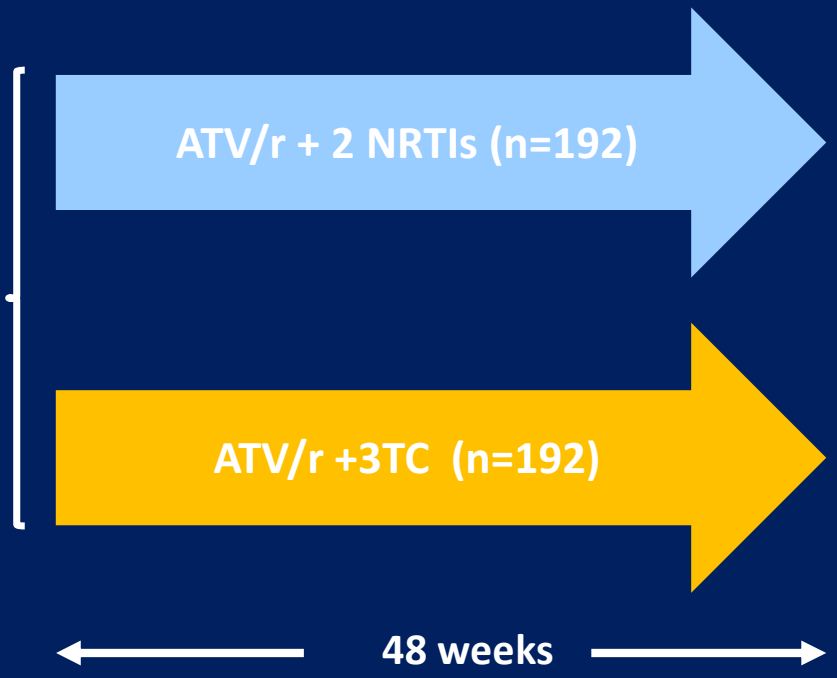
- Stable HAART (1yr)
  - 2 NRTIs + LPV/r
  - HIV RNA < 50 (6M))
-



SALT STUDY

Inclusion criteria:

- **Stable HAART (1yr)**
  - **HIV RNA < 50 (6M))**
-



SECOND-LINE: LPV/r with 2-3 N(t)RTI or RAL in Subjects Failing First-Line NNRTI/2 N(t)RTI ART

- Inclusion Criteria:
  - Received first-line ART comprising an NNRTI + 2 N(t)RTIs for ≥24 weeks with no change within 12 weeks prior to screening
  - Virological failure as defined by two consecutive (≥7 days apart) plasma HIV RNA results >500 copies/mL
  - No previous use of HIV integrase and protease inhibitors
- Nucs:
  - TDF + FTC/3TC: 46%
  - AZT + FTC/3TC: 18%
  - Of 492 participants with baseline GRT:
    - 89% had ≥1 N(t)RTI resistance mutation
    - 60% had M184V plus one or more additional N(t)RTI mutations

Genotypic antiretroviral testing (GART) prior to randomization was optional

Boyd M, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 180LB.

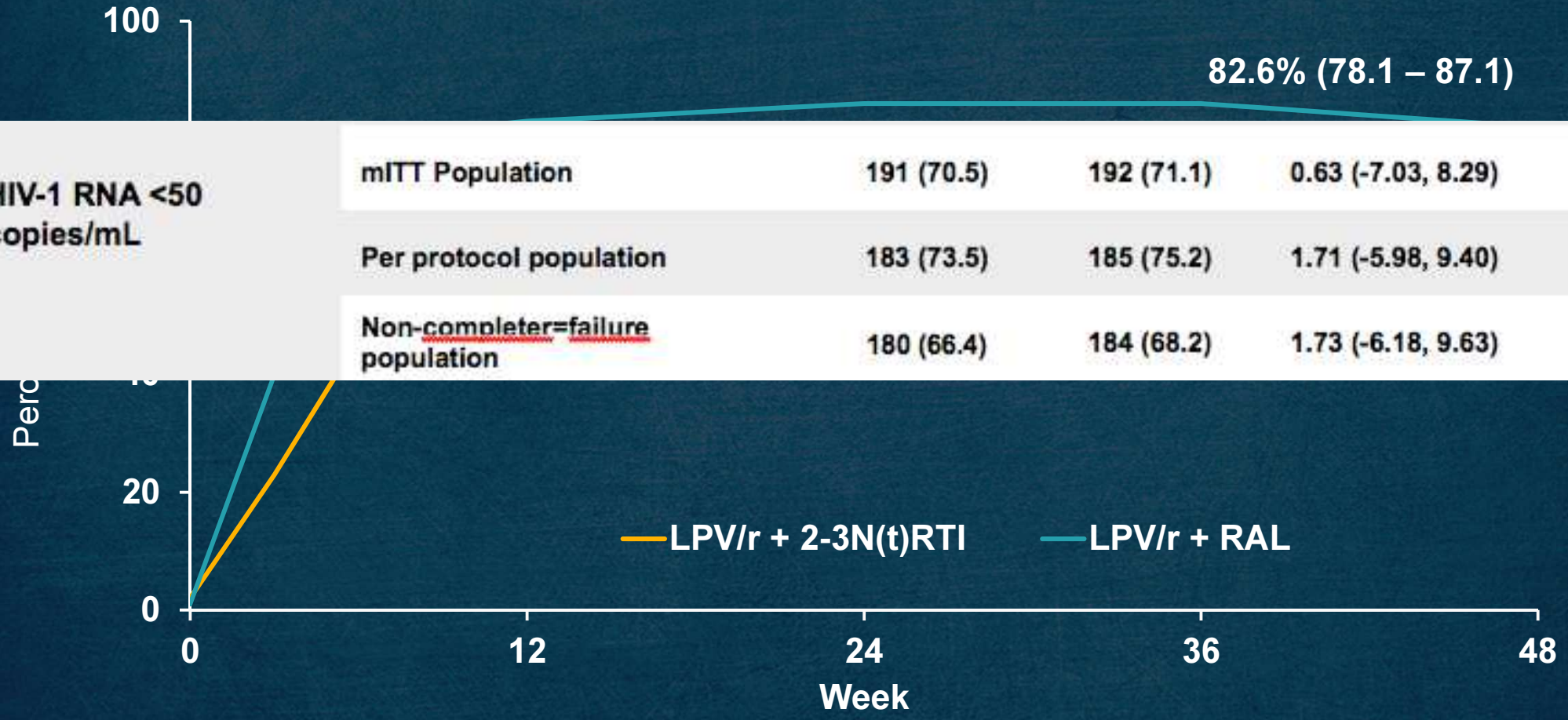
Second-line Study: Baseline Characteristics

	LPV/r + 2-3 N(t)RTI (n=271)	LPV/r + RAL (n=270)	Total (n=541)
Age, years	38.5 (32.9 - 44.6)	38.4(31.9 - 44.4)	38.5 (32.4 - 44.4)
Sex, male	156 (57.6)	142 (52.6)	298 (55.1)
Ethnicity			
Caucasian	18 (6.6)	23 (8.5)	41 (7.6)
Asian	117(43.2)	112 (41.5)	229 (42.3)
Hispanic	38 (14.0)	37 (13.7)	75 (13.9)
African	98 (36.2)	97 (35.9)	195 (36.0)
Unknown	0	1 (0.4)	1 (0.2)
Mode of transmission			
Homosexual / bisexual contact	35 (12.9)	35 (13.0)	70 (12.9)
Heterosexual contact	200 (73.8)	194 (71.9)	394 (72.8)
Injecting drug use	0	6 (2.2)	6 (1.1)
Blood / blood product recipient	6 (2.2)	7 (2.6)	13 (2.4)
Other	30 (11.1)	28 (10.4)	58 (10.7)
Estimated duration of infection, yrs	5.8 (3.4 - 8.6)	6.1 (3.7 - 8.9)	6.0 (3.6 - 8.7)
Duration of first antiretroviral Regimen (NNRTI + 2N(t)RTIs), yrs	3.3 (1.8 - 5.4)	3.5 (2.0 - 5.7)	3.5 (1.9 - 5.5)
Hepatitis C antibody, positive	14 (5.2)	13 (4.8)	27 (5.0)
HIV disease stage			
Asymptomatic- stage A	99 (36.5)	95 (35.2)	194 (35.9)
Symptomatic- stage B	46 (17.0)	47 (17.4)	93 (17.2)
AIDS- stage C	126 (46.5)	128 (47.4)	254 (47.0)
Log_{10} HIV-RNA (copies/mL)	4.3 (3.7 - 4.9)	4.2 (3.6 - 4.8)	4.3 (3.7 - 4.9)
Plasma HIV-RNA (copies/mL)			
<1000	25 (9.2)	25 (9.3)	50 (9.2)
1000 to <10,000	86 (31.7)	75 (27.7)	161 (29.8)
10,000 to <100,000	105 (38.7)	117 (43.3)	222 (41.0)
≥100,000	55 (20.3)	53 (19.6)	108 (20.0)
CD4 (cells/µL)	189.0 (80.0 - 289.0)	190.0 (104.0 - 307.0)	190.0 (95.0 - 293.0)
CD4 (cells/µL)			
<100	78 (28.8)	61 (22.6)	139 (25.7)
100 to <200	61 (22.5)	78 (28.9)	139 (25.7)
200 to <350	97 (35.8)	79 (29.3)	176 (32.5)
≥350	35(12.9)	52 (19.3)	87(16.1)

Boyd M, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 180LB.

Second-line Study: Results

HIV RNA <200 copies/mL (ITT)



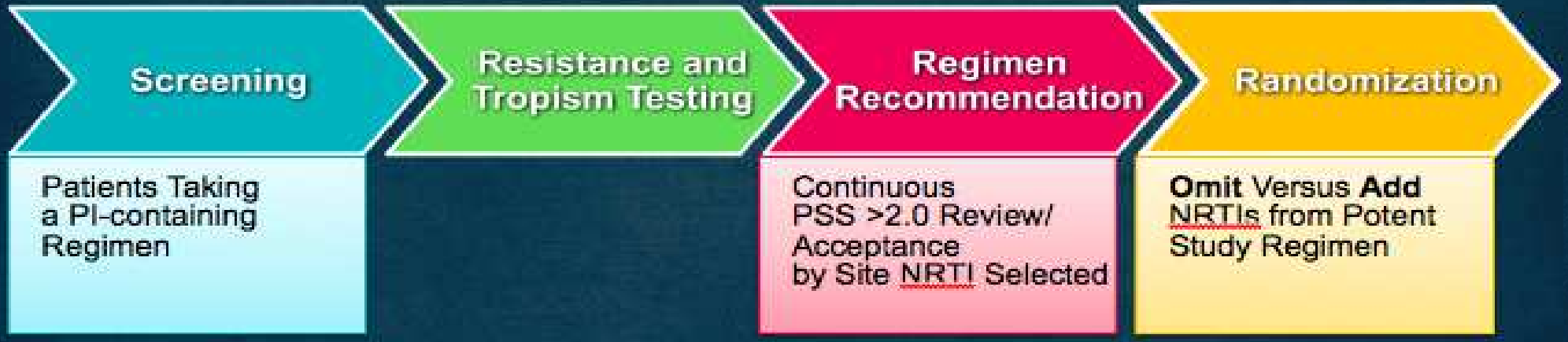
HIV-1 RNA <50 copies/mL				
mITT Population	191 (70.5)	192 (71.1)	0.63 (-7.03, 8.29)	0.87
Per protocol population	183 (73.5)	185 (75.2)	1.71 (-5.98, 9.40)	0.66
Non-completer=failure population	180 (66.4)	184 (68.2)	1.73 (-6.18, 9.63)	0.67

Boyd M, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 180LB.

OPTIONS Study: Omitting vs. Adding NRTI in Treatment-experienced Subjects Failing a PI Regimen

- Major Inclusion Criteria:
  - Failing current PI-based ARV regimen
  - Prior NRTI and NNRTI resistance and/or experience
  - Plasma HIV-1 RNA ≥1,000 copies/mL

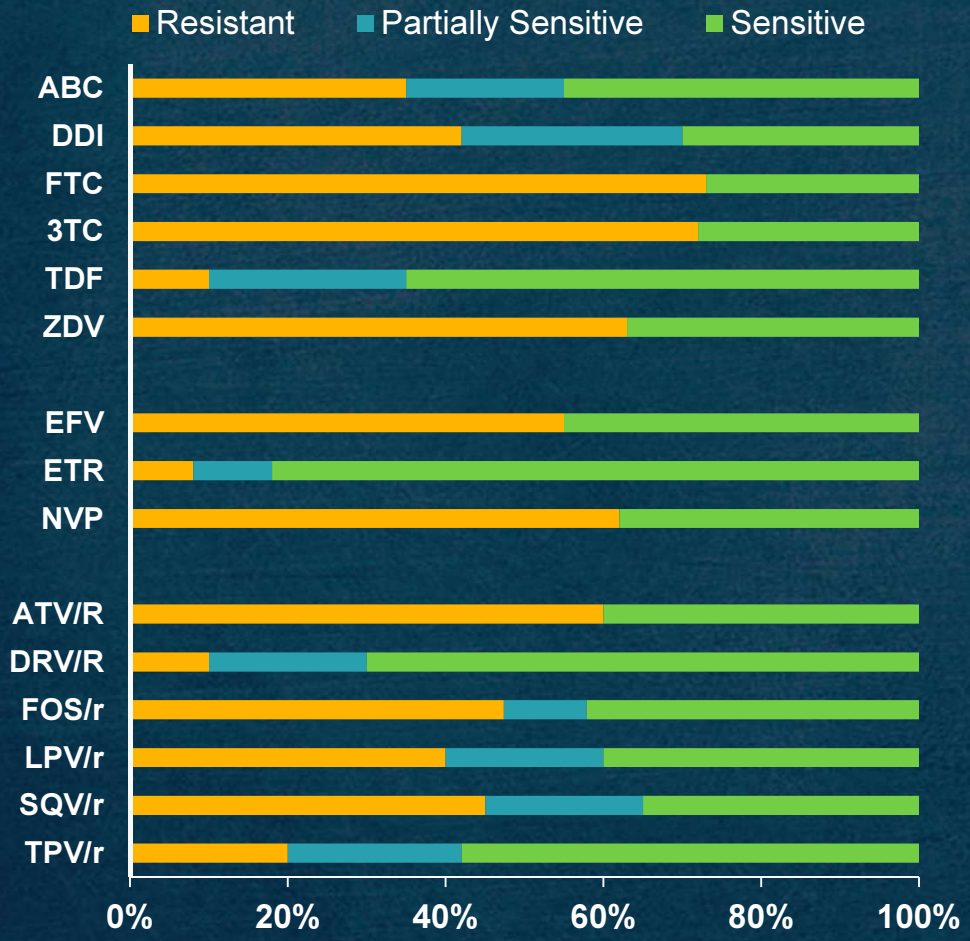
Enrollment Period
Feb 2008-May 2011



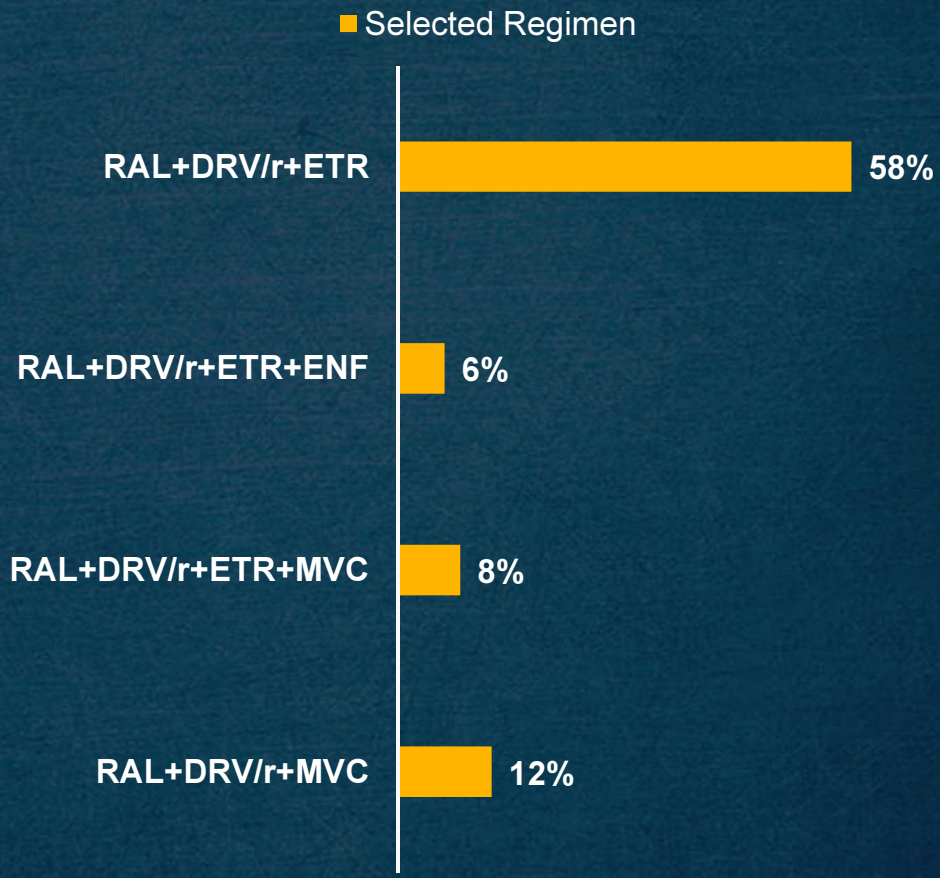
Tashima K, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 153LB.

OPTIONS Study: Resistance and Selected Regimens

Drug Susceptibility at Screen (% of N = 413)



Top Four #1 Ranked Regimens N=413



Tashima K, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 153LB.

OPTIONS Study: Results

A5241 Baseline Characteristics	Omit NRTIs N= 179	Add NRTIs N=181	Log rank *P*=value [95% CI of difference between arms]
Outcomes through 48 weeks: n(%)			
Primary efficacy endpoint	53 (30%)	48 (26%)	[-6.1, 12.5]
Any confirmed **VF**	44 (25%)	45 (25%)	[-9.4, 8.7]
Any discontinuation of NRTI assignment	19 (8%)	10 (6%)	[1.7, 9.0]
Week 48 plasma HIV RNA <200 copies/mL	76% (125/165)	77% (130/160)	-
Week 48 plasma HIV RNA <50 copies/mL	64% (106/165)	66% (112/169)	-
Median CD4 increase from baseline to week 48, cells/mm^3	90 (n=163)	106 (n= 166)	0.11 (Wilcoxon Rank Sum Test)
Premature study discontinuation	11 (6%)	5 (3%)	0.13
Primary safety endpoint	67 (38%)	65 (35%)	0.93
Any ≥ grade 3 signs/symptoms	35 (20%)	48 (26%)	0.15
Any ≥ grade 3 lab abnormalities	39 (24%)	27 (15%)	0.09
First of new AIDS event or death	5 (3%)	12 (7%)	0.09
Death following treatment initiation	0 (0%)	6 (3%)	0.01

Tashima K, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 153LB.

Can we live without nucleosides?

- NAÏVE
  - THE JURY IS STILL OUT
- SWITCH
  - PROBABLY WE CAN
- SALVAGE.
  - YES WE CAN