NRTI-sparing regimes
For whom? Which one?

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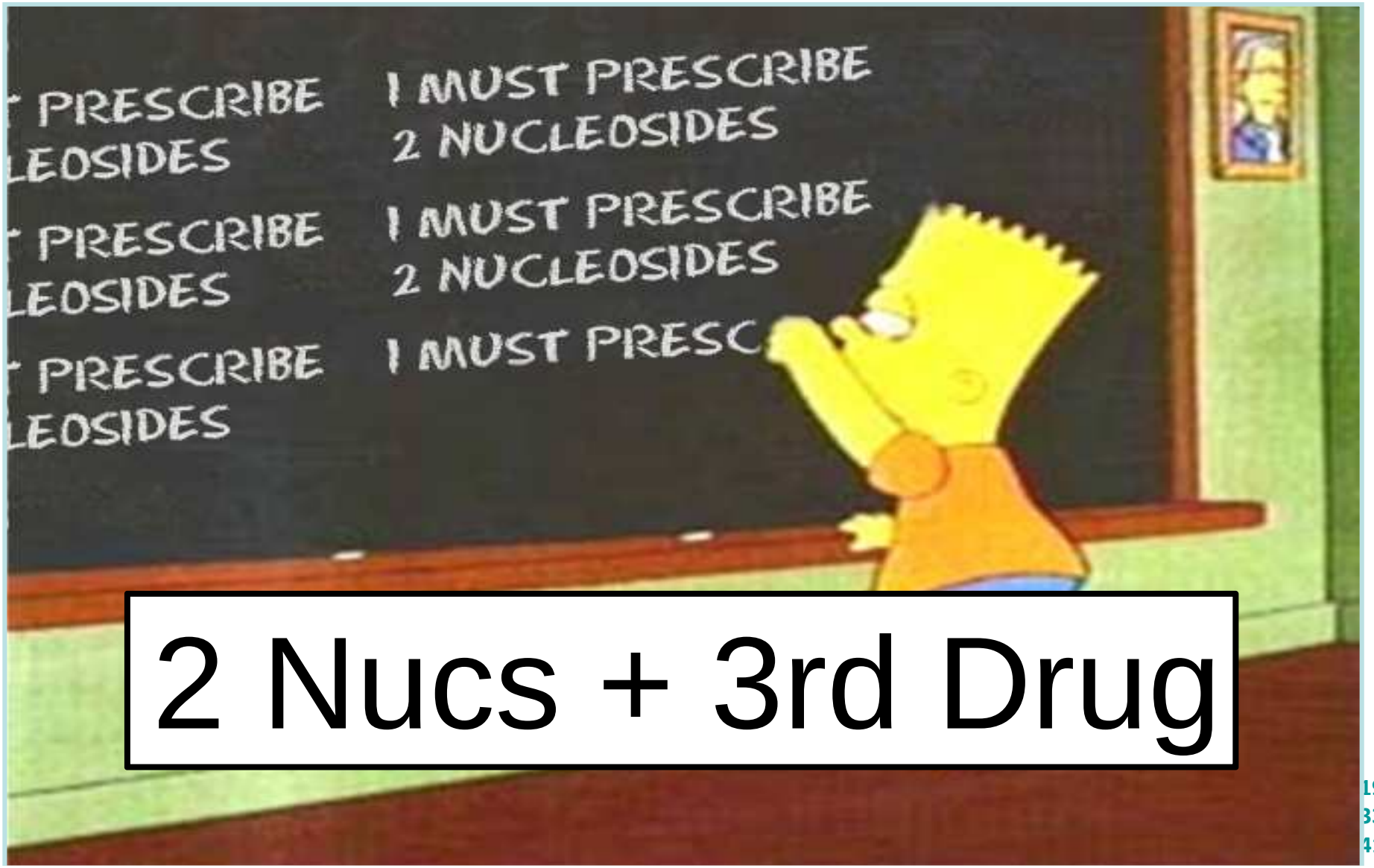
What to Start: Comparison of Guidelines

Arribas1



Diapositiva 2

Arribas1 I have added recent DHHS recomendations. References need to be updated
Jose R Arribas; 01/11/2011

Do we need NRTI-free regimes?

- **NRTI toxicity**
  - **Old thymidine NRTI**
    - **Mitochondrial toxicities**
  - **New toxicities**
    - **Bone**
    - **Kidney**
    - **CVR and ABC**
- **NRTI uselessness**
  - **Resistance**

NRTI drawbacks

ART considerations	TDF/FTC	ABC/3TC
*High baseline viral load[1,2]	Recommended	Caution
High CVR[1,2]	Recommended	Caution
Kidney dysfunction[1,2]	Caution	Recommended
Low BMD[1,2]	Caution	Recommended
Positive HLAB*5701[1,2]	Recommended	Avoid

1.EACS Guidelines Octubre 2013 http://www.europeanaidsclinicalsociety.org/
2. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. (Last updated February 12, 2013; last reviewed February 12, 2013)

Lamivudine (3TC) / Emtricitabine (FTC)

- **Good tolerability. Toxicity exceedingly rare.**
- **Low genetic barrier: complete resistance with one mutation (M184V/I).**
  - First virological failure
  - Transmitted resistance
- **Formerly used for decreasing viral fitness when there were not other available treatment options even with resistance.**
- **Current goal: suppressive ART for every patient.**

NRTI-sparing regimes

- Naïve patients
  - Protease inhibitor +
    - EFV
    - RAL
    - MVC
- Switching
  - LPV/r + EFV (ACTG 5116)
  - IP+ NVP o EFV (ANRS108)
  - LPV/r + RAL (KITE)
  - DRV/r + RAL, MVC or ETR
  - ETR + RAL
- Salvage therapy?

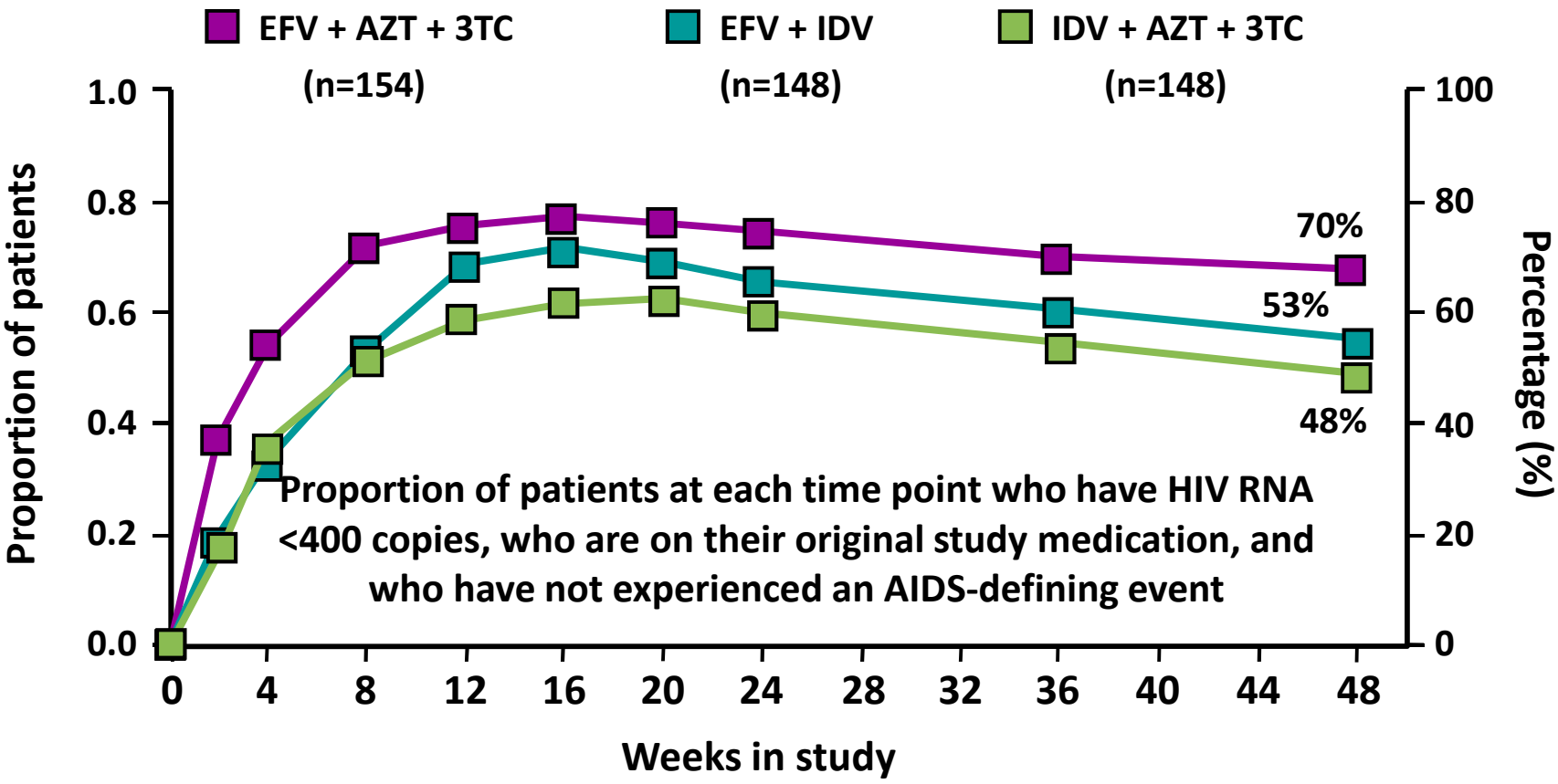
Naïve patients

ARVs in NRTI sparing regimes

Study	Drugs	Comparator
DMP-006[1]	IDV + EFV	EFV+AZT/3TC vs IDV AZT/3TC
ACTG5142[2]	LPV/r + EFV	EFV+2AN vs LPV/r+ 2AN
PROGRESS[3]	LPV/r + RAL	LPV/r + TDF/FTC
CCTG589[4]	LPV/r + RAL	EFV + TDF/FTC
SPARTAN[5]	ATV + RAL	ATV/r + TDF/FTC
A4001078[6]	ATV/r + MVC	ATV/r + TDF/FTC
ACTG5262[7]	DRV/r + RAL	----------
RADAR[8]	DRV/r + RAL	DRV/r + TDF/FTC

[1] Staszewski S, et al. NEJM 1999;341:1865-73 [2] Riddler S, et al. NEJM 2008;358:2095-106
[3] Reynes J, et al. AIDS Res Hum Retro 2012;28 [4] Bowman V, et al. IAS 2011, CDB336
[5] Portsmouth S, et al. IAS 2011 Abstract TUAB0103 [6] Mills A, et al. IAS 2012 Abstract TUAB0102
[7] Taiwo B, et al. AIDS 2011;25:2113-22 [8] Bedimo R, et al. IAS 2011 Abstract MOPE214

DMP 266-006



There was no significant difference in mean CD4 cell count among the treatment groups; the overall mean increase was approximately 200 cells/mm^3 at 48 weeks among patients who continued on study regimens.

Staszewski S, et al. N Engl J Med. 1999;341:1865-73

ACTG 5142: study design

- Randomised, multicentre, open-label, 96-week trial
- n=753
- ARV naïve
- HIV RNA ≥2000 copies/mL
- Any CD4 count
- Stratified at randomisation:
  - HIV-1 RNA ≥100 000 copies/mL
  - Hepatitis B/C infection
  - NRTI selection

ARM A (NRTI-sparing):
LPV/r 533/133 mg BID + EFV 600 mg QD

ARM B:
LPV/r 400/100 mg BID + 2 NRTIs

ARM C:
EFV 600 mg QD + 2 NRTIs

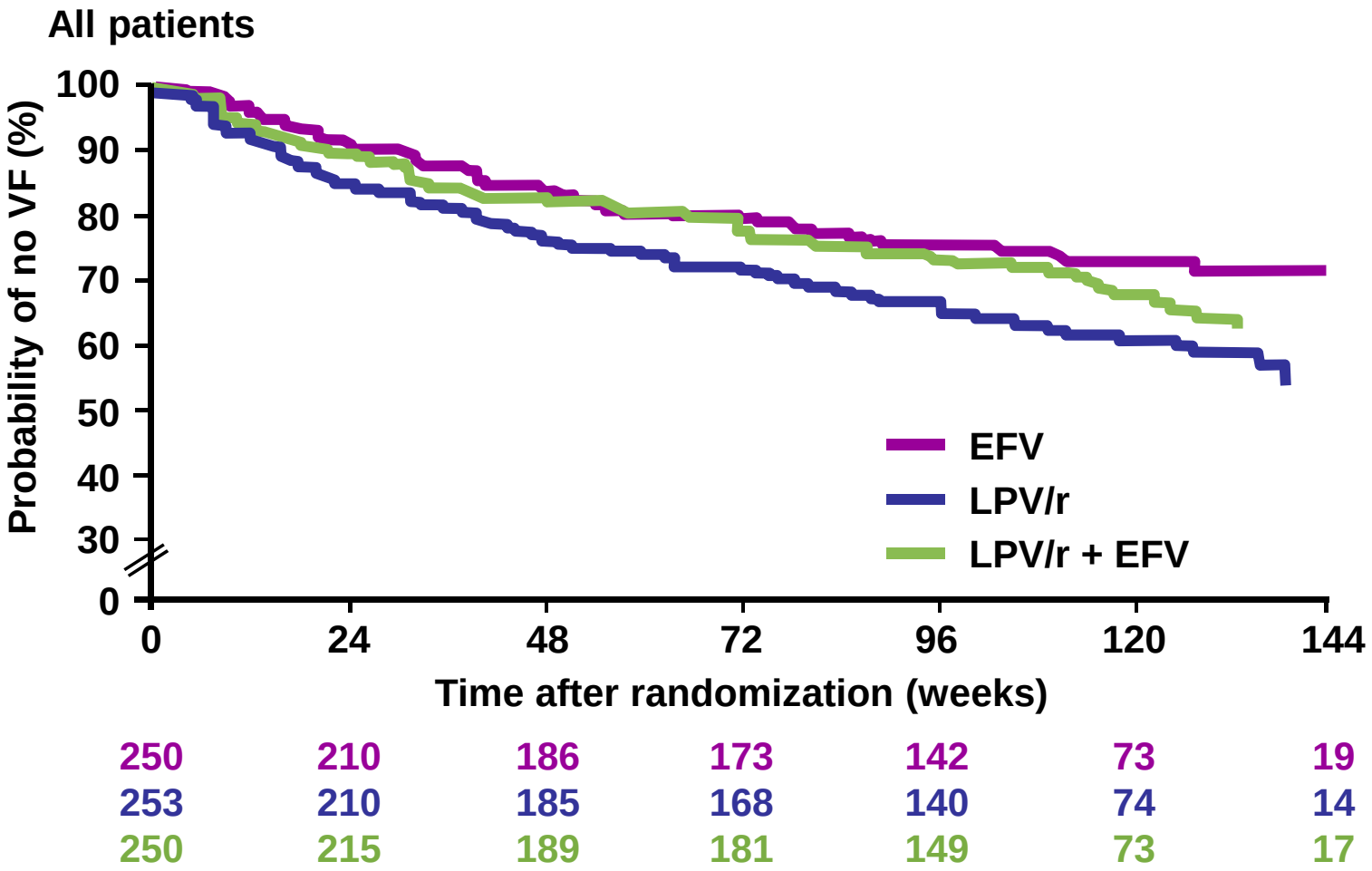
- LPV/r given as soft gel capsules
- 2 NRTIs included 3TC (300 mg QD or 150 mg BID) + investigator selection of AZT 300 mg BID or d4T XR[a] 100 mg QD[b] or TDF 300 mg QD
- 3TC dosed:
  - 150 mg BID with AZT
  - 300 mg QD with d4T XR or TDF

[a] d4T XR is an experimental formulation of stavudine that is not commercially available

[b] d4T XR dose was 75 mg QD in patients who weighed <60 kg

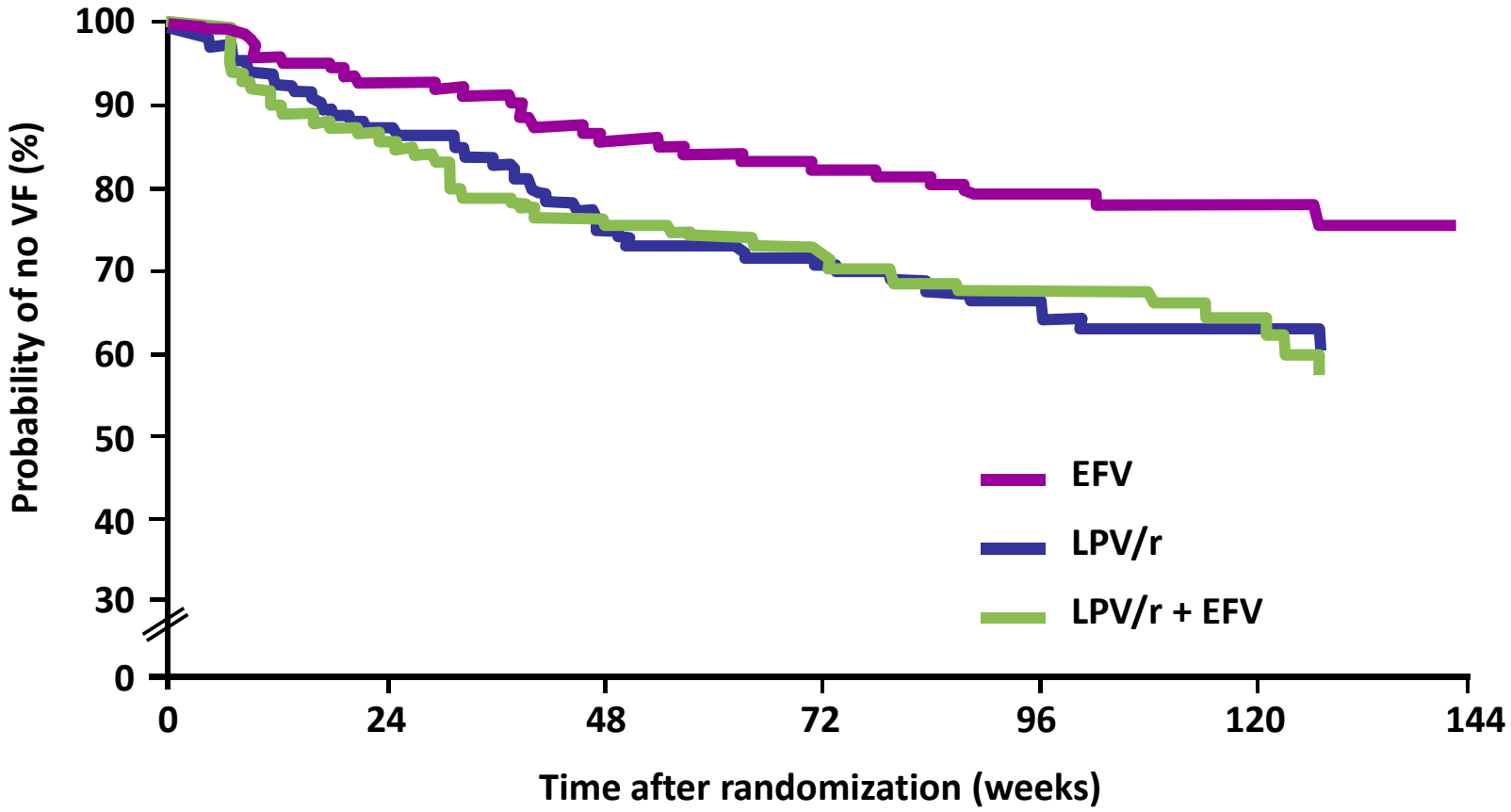
Adaptado de Riddler S et al. N Engl J Med 2008;358:2095–2106

ACTG 5142: Overall efficacy



Adaptado de Riddler SA et al. N Engl J Med 2008;358::2095–2106

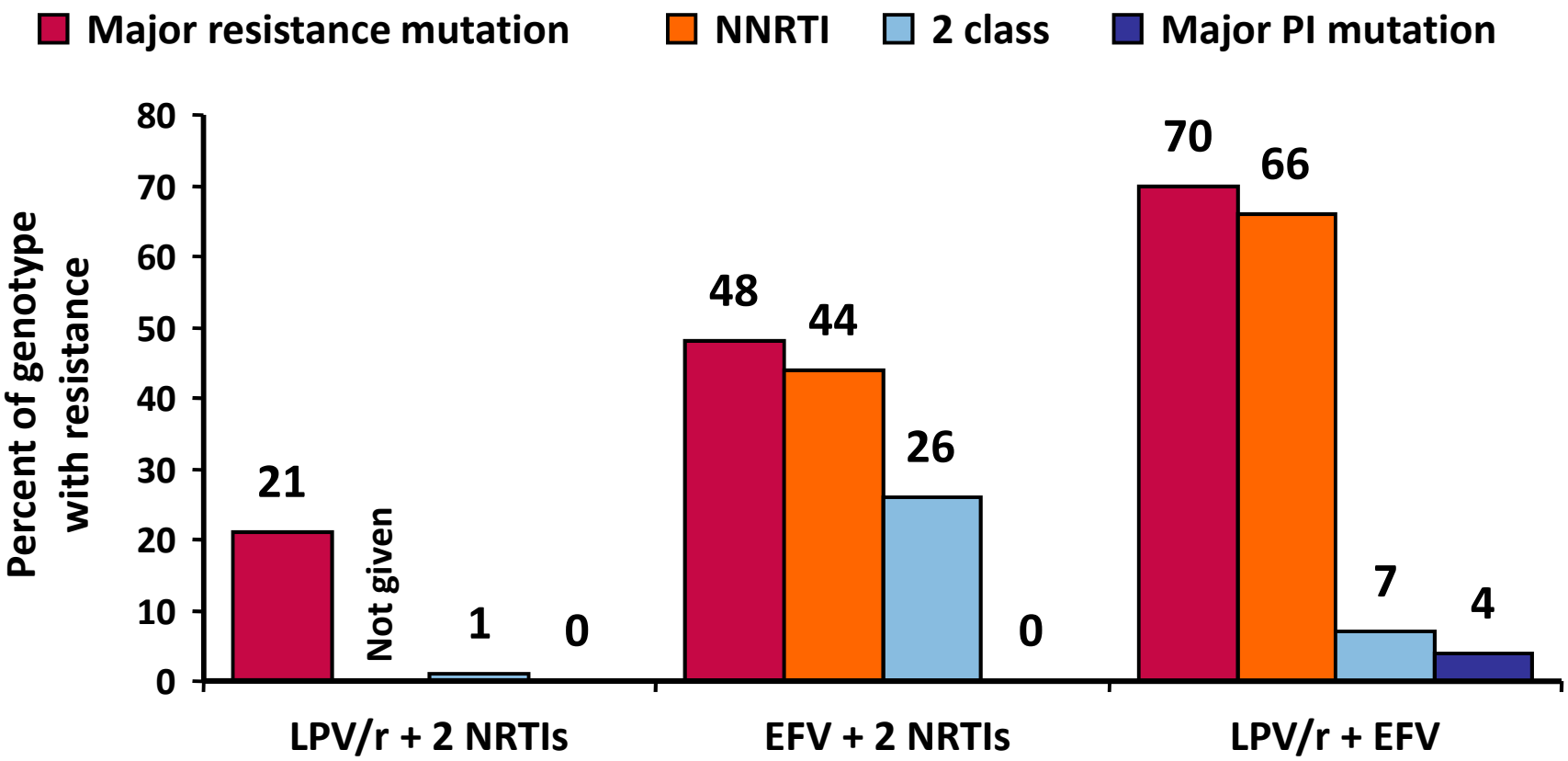
ACTG 5142: efficacy baselineVL > 5 logs



121	108	96	90	76	40	11
123	105	90	81	67	32	6
122	102	86	81	66	35	9

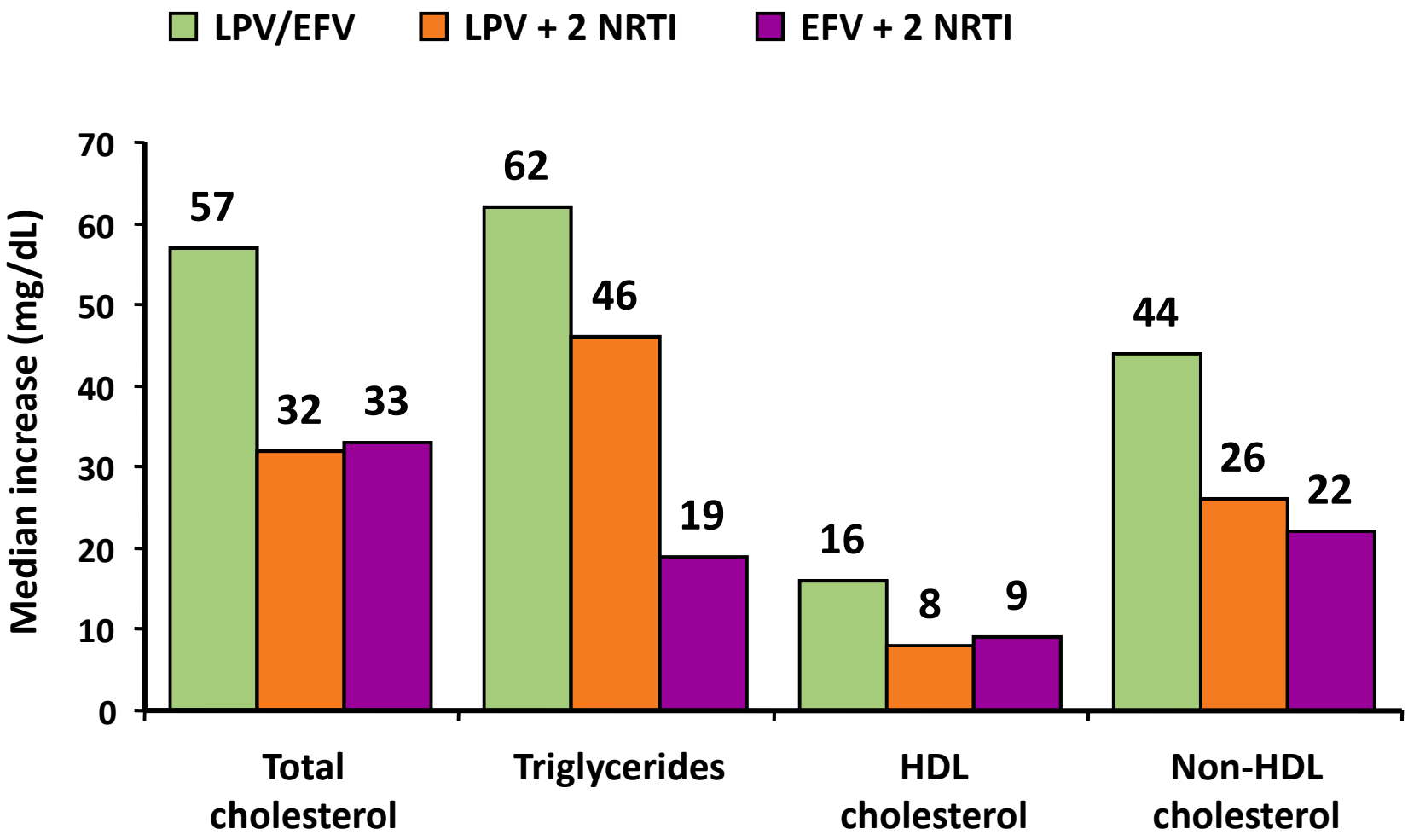
Adaptado de Riddler SA et al. N Engl J Med 2008;358::2095–2106

ACTG 5142: resistance



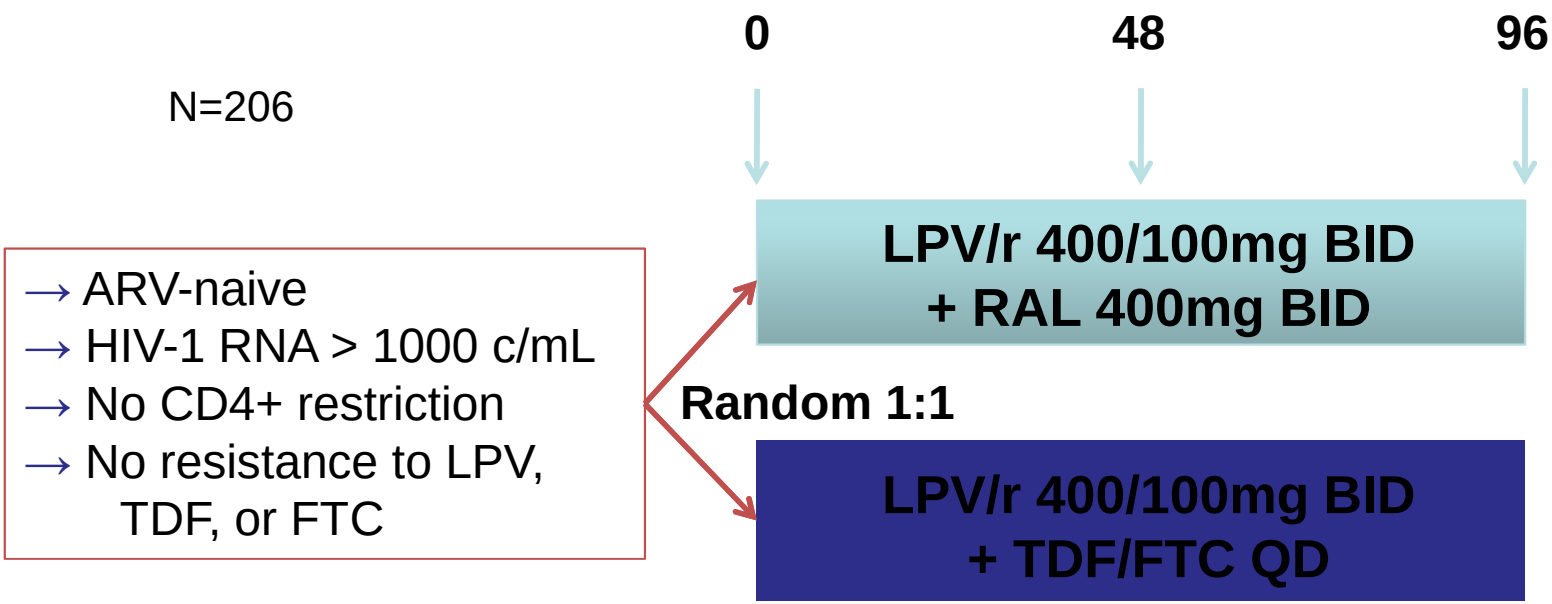
Haubrich *et al.* XVI International HIV Drug Resistance Workshop; June 12–16, 2007; Barbados. Abstract 57

ACTG 5142: toxicity



Haubrich *et al.* 14th CROI; February 25–28, 2007; Los Angeles, CA. Abstract 38

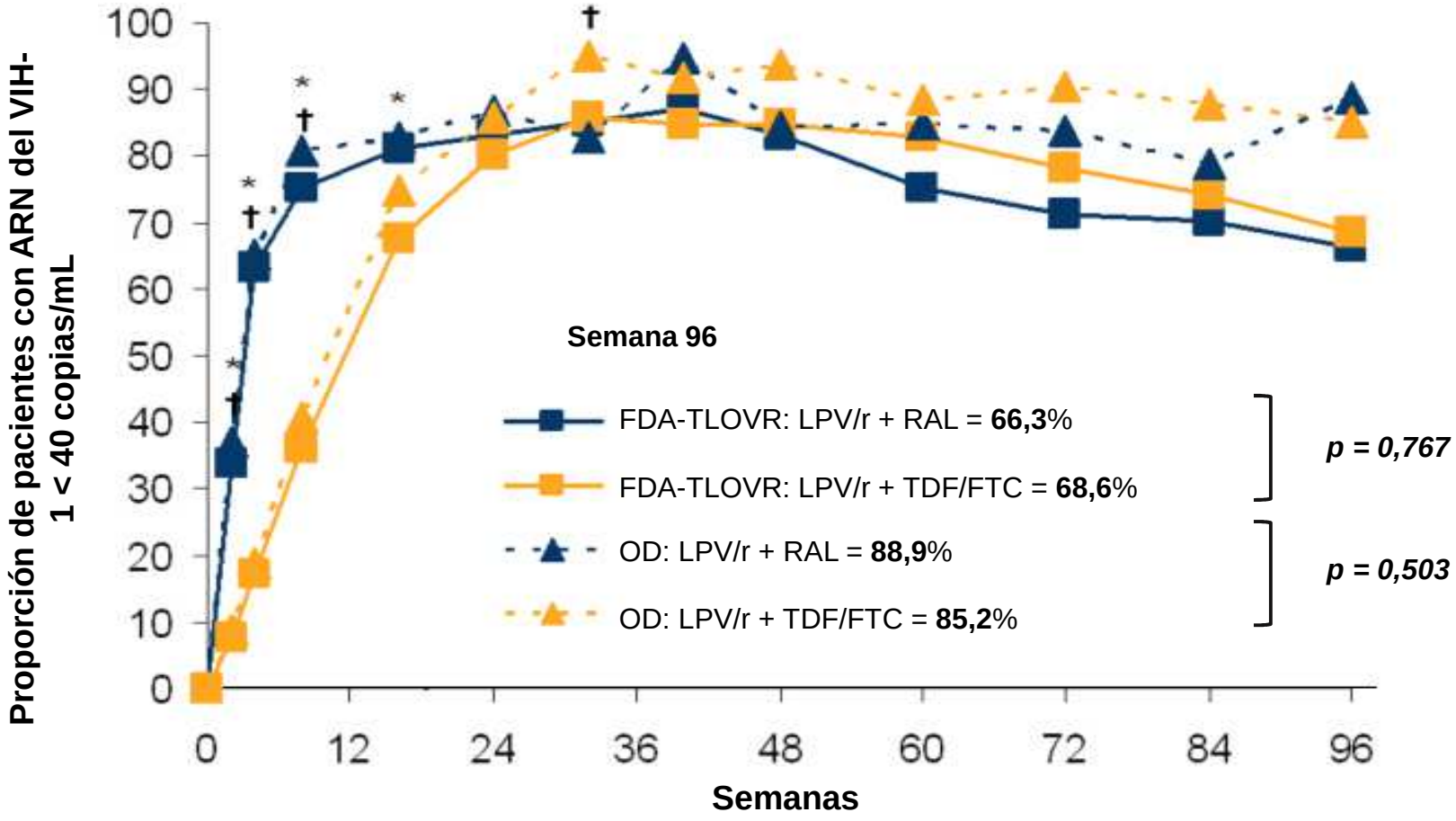
PROGRESS: LPV/r + RAL vs. TDF/FTC
Study design



- Virologic efficacy: proportion of subjects with plasma HIV-1 RNA below the limit of quantification (40 copies/ml) using the FDA-TLOVR algorithm.
- Full body DXA scans were performed at baseline, week 48, and week 96.

Reynes J, et al. AIDS Res Human Retroviruses 2012;28 (ahead of print)

PROGRESS: efficacy

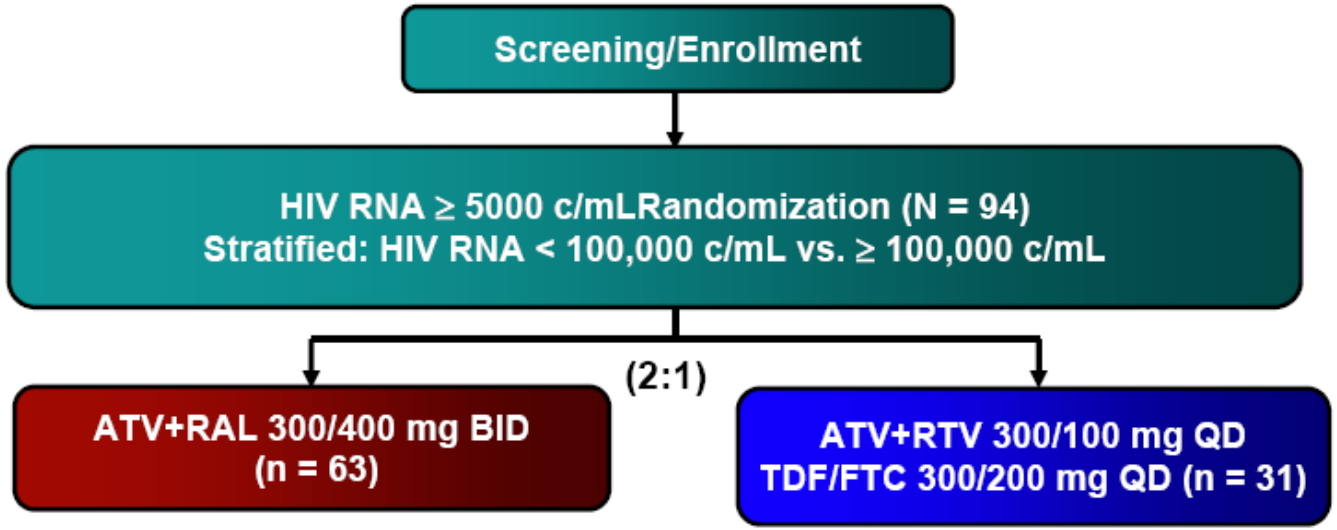


Diferencia estadísticamente significativa entre los grupos:
***** FDA-TLOVR: semanas 2, 4, 8 *P<0,001*; semana 16 *P=0,038*
† OD: semanas 2, 4, 8 *P<0,001*; semana 32 *P=0,011*

Reynes J, et al. AIDS Res Human Retroviruses 2012

SPARTAN: ATV + RAL vs ATV/r + TDF/FTC
Study design

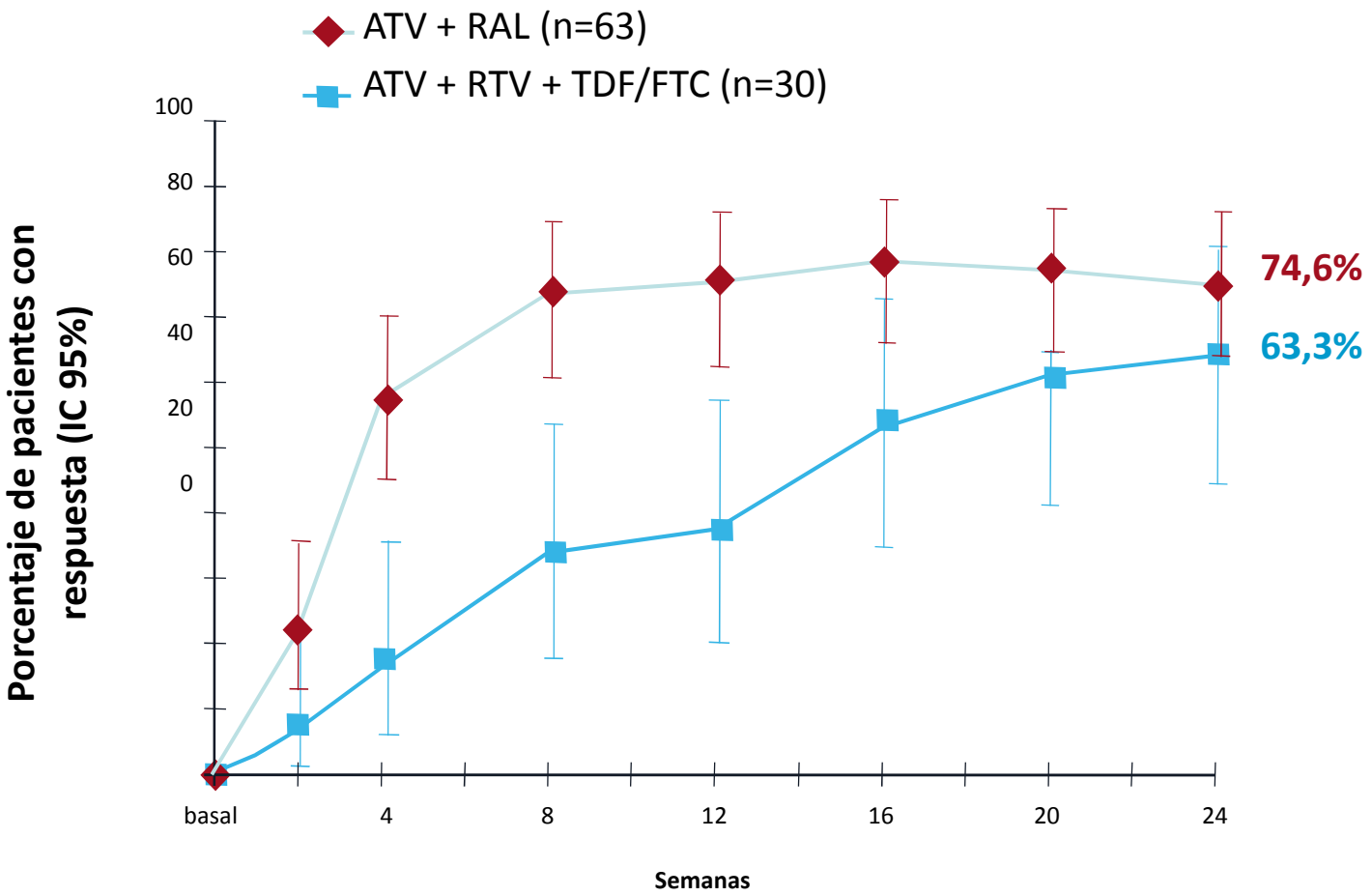
- Estudio piloto, abierto, aleatorizado (2:1), no comparativo y multicéntrico en pacientes *naive* con CV ≥ 5.000 copias/mL.



- Enpoint Primario: % pacientes con CV<50 c/mL a las 24 semanas

Kozal MJ, et al. IAS, Viena, Julio 2010. Abstract THLBB204.

SPARTAN: efficacy at 24 w.



Incremento de CD4: ATV+RAL: 166 cél/cm^3 ATV/RTV + TDF/FTC: 127 cél/cm^3

Kozal MJ, et al. IAS, Viena, Julio 2010. Abstract THLBB204.

SPARTAN: adverse events

Adverse events	Number of Patients	
	ATV+RAL	ATV+RTV +TDF/FTC
AEs leading to DC*	4/63 (6.3%)	0
Grade 2-4 treatment-related AEs†	19/63 (30.2%)	10/30 (33.3%)
Grade 3-4 AEs	16/63 (25.4%)	6/30 (20.0%)
Grade 3-4 total bilirubin abnormalities	38/63 (60.3%)	14/30 (46.7%)
Grade 4 total bilirubin abnormalities	13/63 (20.6%)	0
PR mean change from BL‡ msec (SE)§	17.6 (2.10)	4.9 (2.25)
QRS mean change from BL msec (SE)§	8.9 (1.02)	3.6 (1.97)

*Included arrhythmia-1, jaundice-1, jaundice and ocular icterus-1, Lung cancer-1

†Grade 2-4 treatment-related AE hyperbilirubinemia occurred in 19% (12/63) of subjects on ATV+RAL and 16.7% (5/30) on ATV/RTV+TVD

§ The worst value in the visit window was used

Kozal MJ, et al. IAS, Viena, Julio 2010. Abstract THLBB204.

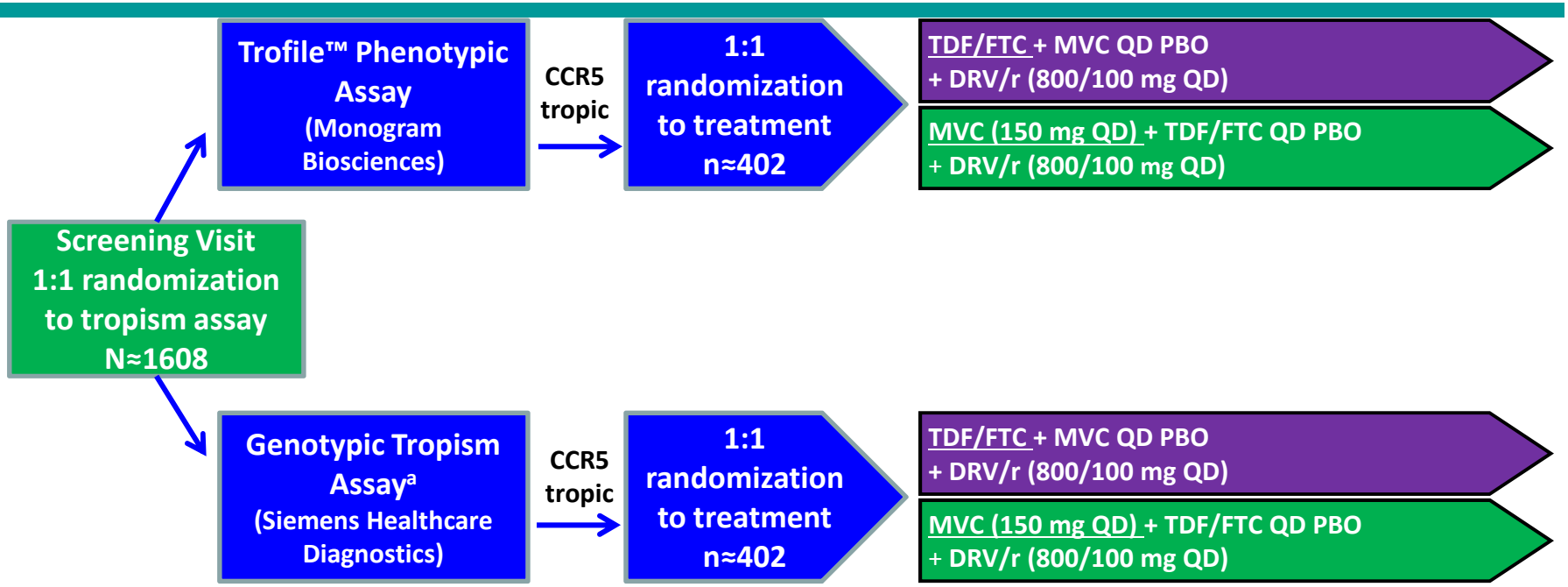
SPARTAN: resistance

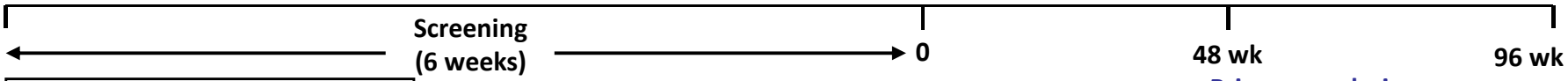
Resistance Through Wk 24, n	ATV + RAL (n = 63)	ATV/RTV + TDF/FTC (n = 30)
Virologic failure (HIV-1 RNA > 50 copies/mL)	11	8
▪ BL HIV-1 RNA > 250,000 copies/mL	8	4
Evaluable for resistance testing* (HIV-1 RNA > 400 copies/mL)	6	1
Genotypic and phenotypic RAL resistance	4	–
▪ N155H	2	–
▪ Q148R	1	–
▪ Q148R + N155H + T97A	1	–
Phenotypic RAL resistance without genotypic evidence of resistance	1	–
ATV resistance	0	0
TDF/FTC resistance	–	0

- Buena eficacia virológica de ATV + RAL.
- No se observaron cambios significativos en el perfil lipídico en ningún brazo del estudio.
- **La compañía anuncia que decide terminar el estudio prematuramente por los casos detectados de resistencia a RAL (6%, 67% de los fallos virológicos testados) e hiperbilirrubi- nemia grado 4 (21% vs 0%).**

Kozal MJ, et al. IAS, Viena, Julio 2010. Abstract THLBB204.

MODERN: MVC+DRV/r QD vs. DRV/r+TDF/FTC: Study design





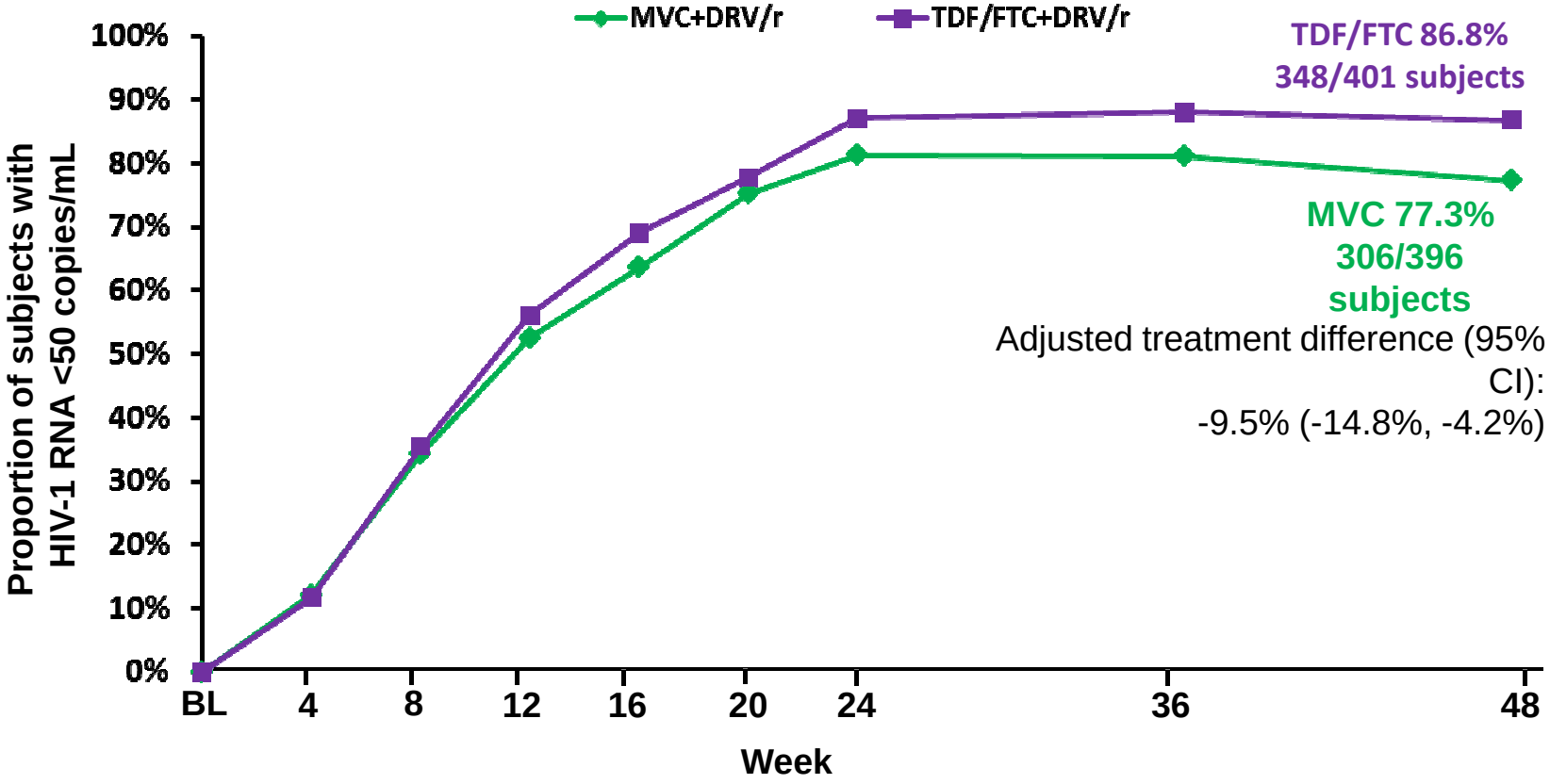
Eligibility Criteria
- Antiretroviral treatment naive
- Plasma HIV-1 ≥ 1000 c/mL
- CD4 ≥ 100 cells/mm^3
- No evidence of resistance to DRV, TDF, FTC
- ≥ 18 years of age

- Phase 3, randomized, double-blind
- Primary endpoint: proportion of subjects with HIV-1 RNA <50 c/mL at wk 48 (MSDF)[b] by FDA snapshot algorithm
- Non-inferiority study (NI margin of 10% between treatment groups)
- 195 sites in 22 countries
- Study was terminated on 04 Oct 2013 upon recommendation of IDMC

[a]Siemens HIV-1 Coreceptor Tropism Assay is for research use only.
[b]MSDF: Missing, Switch, Discontinuation = Failure.

Stellbrink et al. IAC 2014; Melbourne, Australia. Abstract TUAB0101.

MODERN: efficacy

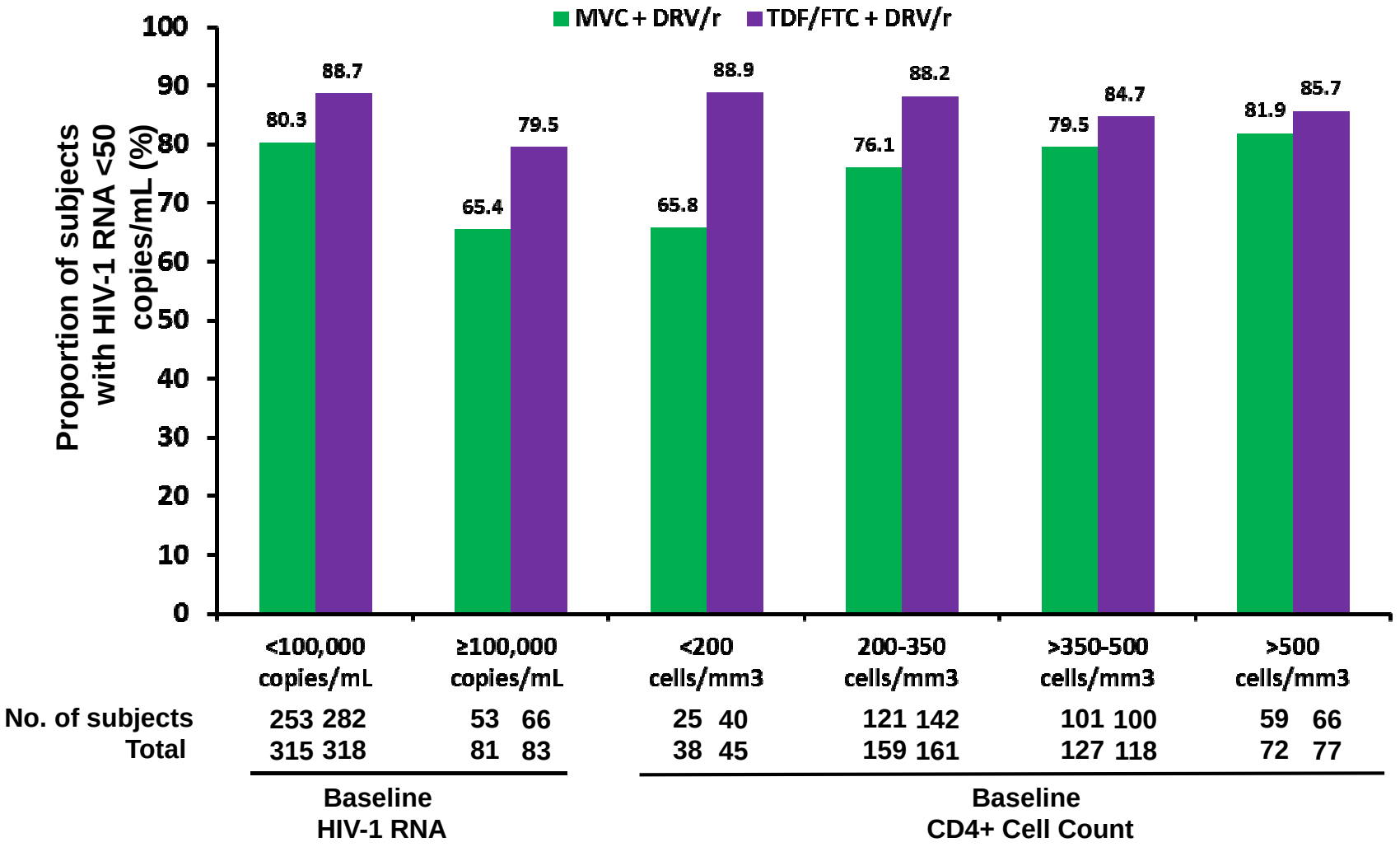


Mean CD4+ cell count changes at Week 48 (mean ± SD, cells/mm³)

MVC + DRV/r	195.3 ± 175.7
TDF/FTC + DRV/r	193.9 ± 175.7

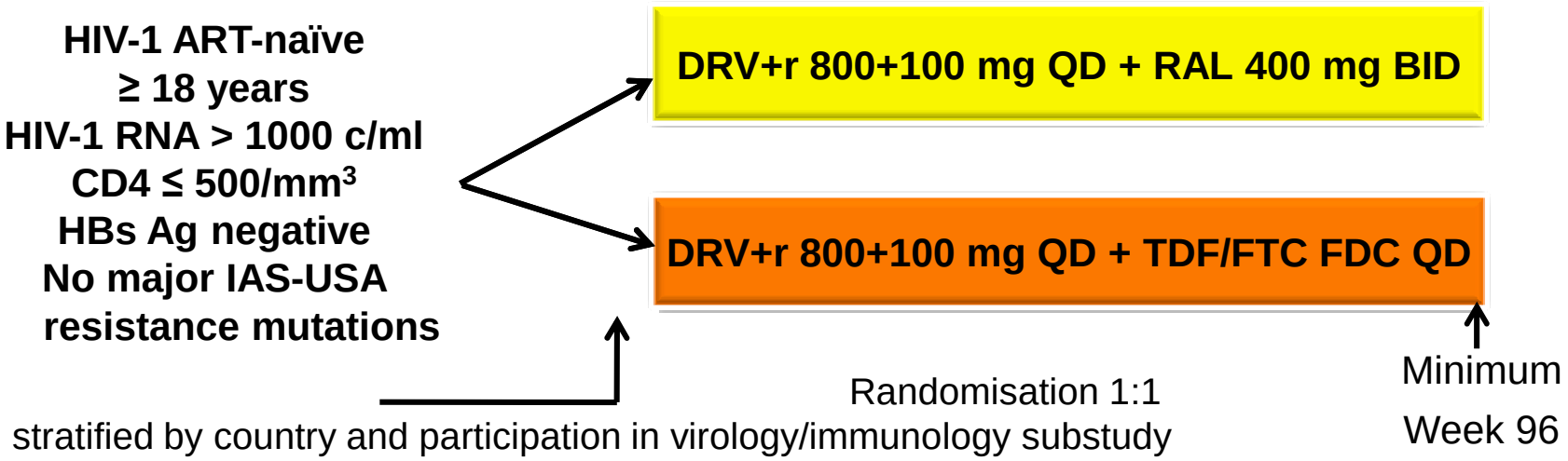
Stellbrink et al. IAC 2014; Melbourne, Australia. Abstract TUAB0101.

MODERN: efficacy by subgroups



Stellbrink et al. IAC 2014; Melbourne, Australia. Abstract TUAB0101.

NEAT 001: Study design



Raffi F, et al. Lancet 2014

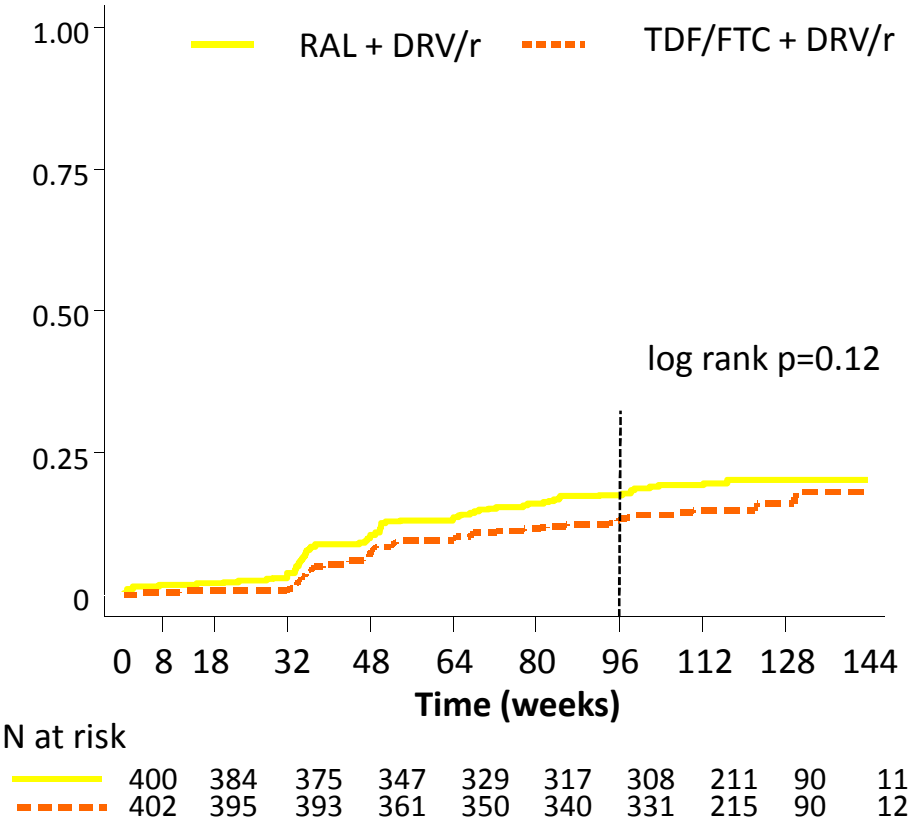
NEAT 001: primary endpoint

Primary endpoint

	RAL + DRV/r	TDF/FTC + DRV/r
N	401	404
N with primary endpoint	76 (19%)	61 (15%)
V1. Regimen change for insufficient response		
< 1 log_{10} c/ml HIV RNA reduction W18*	1	0
HIV RNA ≥ 400 c/ml W24*	1	0
V2. HIV RNA ≥ 50 c/ml at W32*	27	28
V3. HIV RNA ≥ 50 c/ml after W32*	32	22
C1. Death	3	1
C2. AIDS event	5	3
C3. SNAIDS event	7	7

** confirmed by a subsequent measurement*

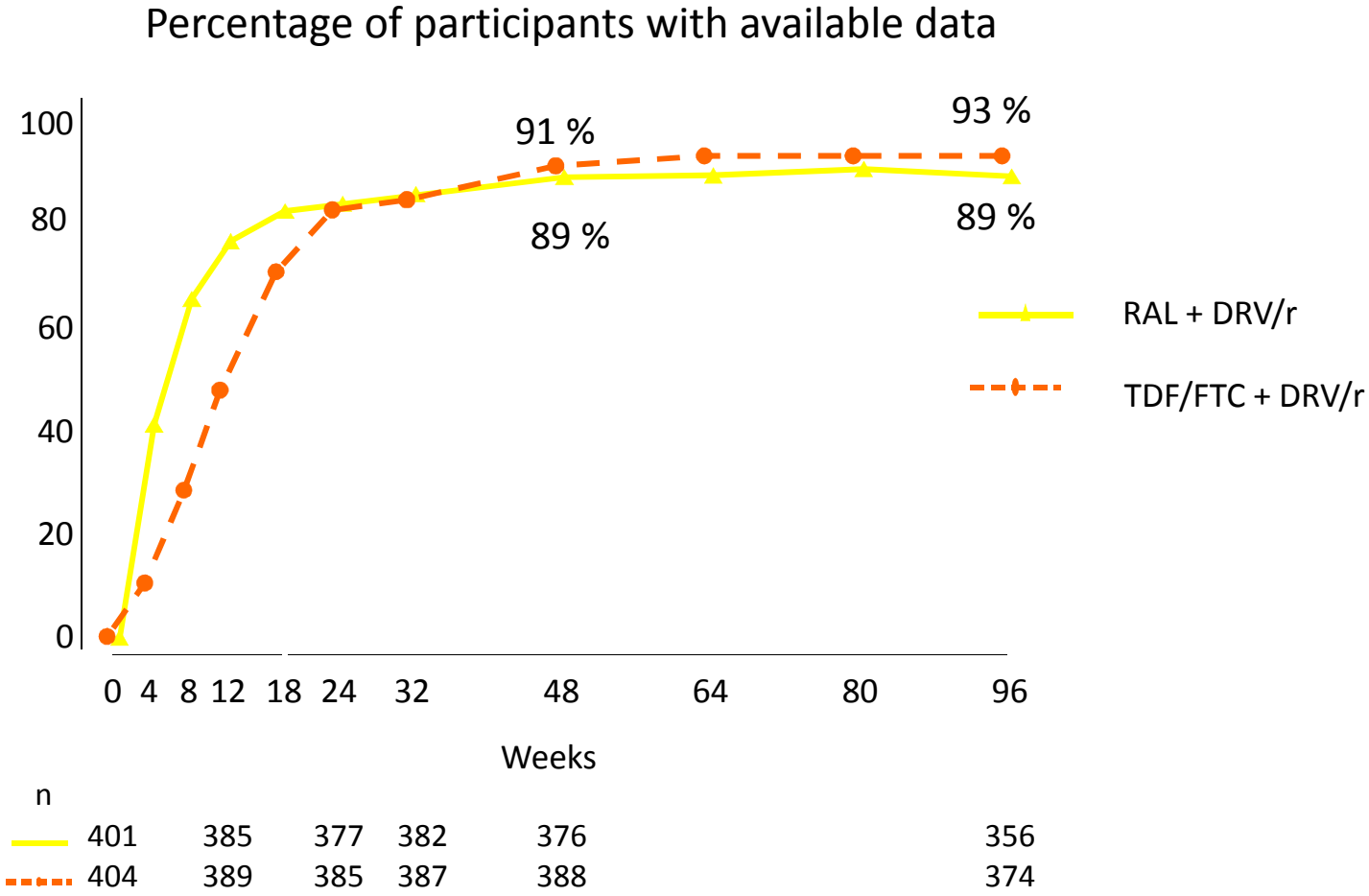
Probability of reaching primary endpoint



Estimated proportion reaching primary endpoint at W96
RAL: 17.4% vs TDF/FTC: 13.7%
Adjusted difference: 3.7% (95% CI: -1.1, 8.6%)

Raffi F, et al. Lancet 2014

NEAT 001: VL < 50 copies/ml

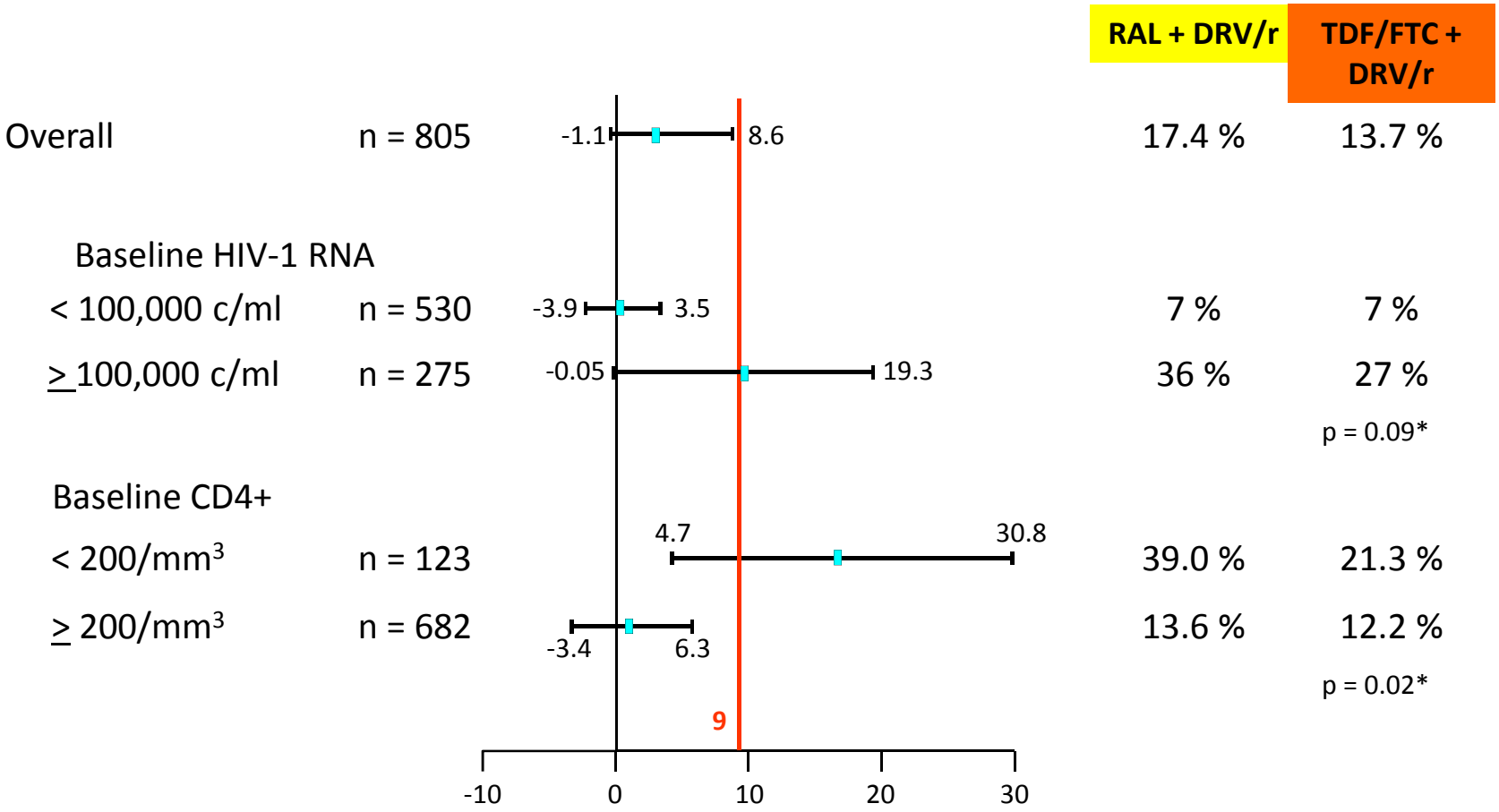


	Mean (95% CI) Change From Baseline CD4⁺ Cell Count (cells/mm³)								
					W48			W96	
RAL + DRV/r					+ 197	(184, 210)		+ 267	(250, 285)
TDF/FTC + DRV/r					+ 193	(180, 206)		+ 266	(249, 283)

Rabi F, et al. Lancet 2014

Neat 001: subgroups

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



* Test for homogeneity

Raffi F, et al. Lancet 2014

Switching

Switching studies to NRTI-sparing regimes

- No big randomized studies
- Small retrospective observational studies
- Regimes studied:
  - LPV/r + EFV (ACTG 5116)
  - IP+ NVP o EFV (ANRS108)
  - New ARV:
  - LPV/r + RAL (KITE)
  - DRV/r + RAL, MVC or ETR
  - **ETR + RAL**

ACTG 5116

ACTG388
naïve

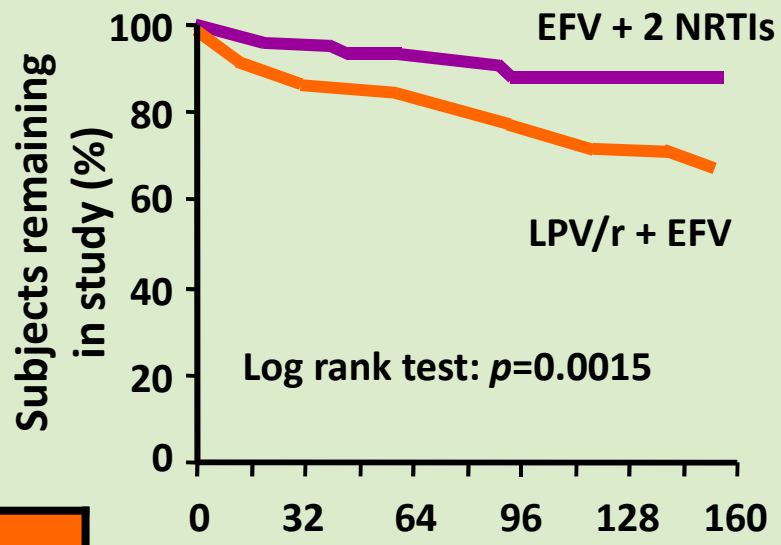
- 2 AN + IDV
- 2 AN+IDV+NFV
- 2AN+IDV+EFV

→

ACTG 5116
Switch

- 2 NRTI+EFV (n=118)
- LPV/r+EFV (n=118)

Time to virologic failure or toxicity related discontinuation

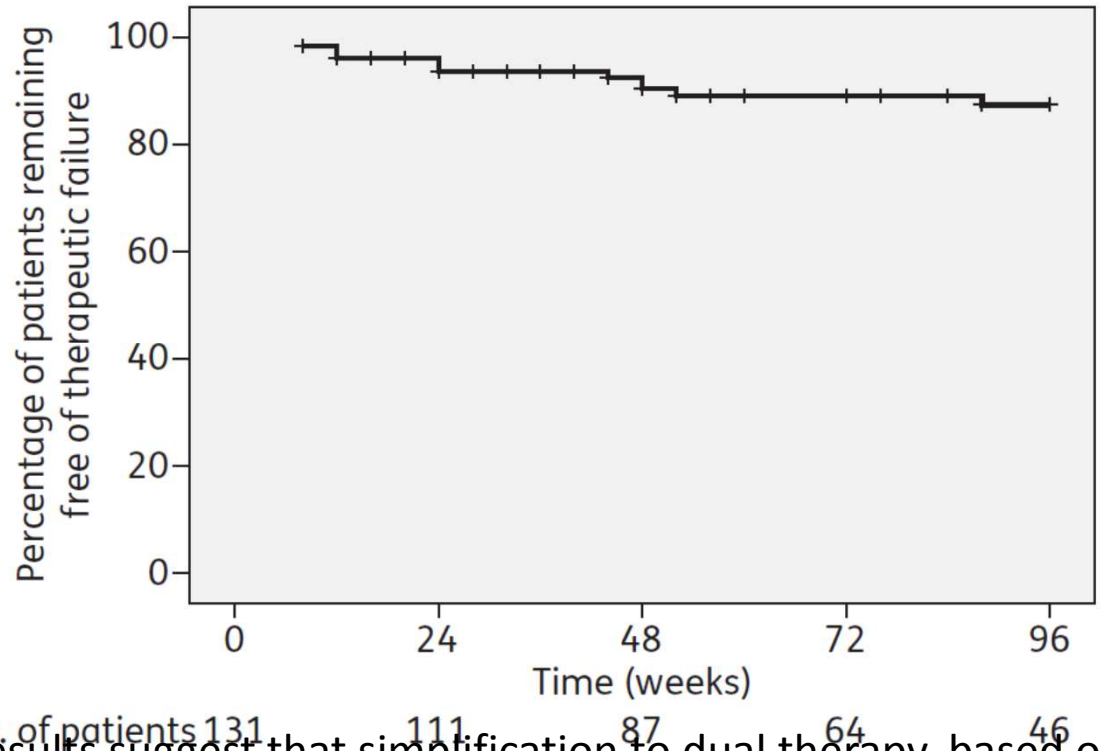


Discontinuations	EFV + 2 NRTIs (n=118)	LPV/r + EFV (n=118)	*P*
Virological failure	7	14	0.088
Toxicity	6	20	0.002
Total D/C	13	34	<0.001

Fischl M, et al. AIDS 2007

DRV/r + ETR

Más frecuentes: DRV/r + RAL o ETR



90%

- Our results suggest that simplification to dual therapy, based on a PI/r, might be an alternative in treatment-experienced patients.

- This option may be particularly attractive for patients in whom convenience, tolerance or the safety profile are a concern. Preserving further therapeutic options and a reduction of treatment costs might be additional advantages.

BITERAPIA DRV/r + ETR
CARACTERÍSTICAS BASALES

- 86 pacientes

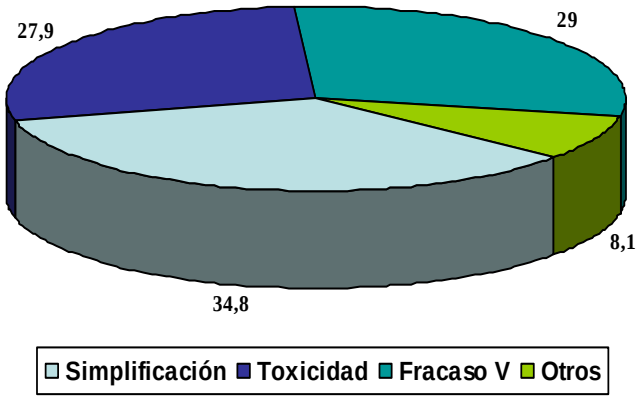
Características basales (antes del cambio a DRV/r + ETR)

Edad, años, mediana (IQR)	**47 (43.5-53)**
Varones (%)	**75.5**
Vía transmisión (%)	
HMSX	**37.2**
HTSX	**27.9**
UDVP	**32.5**
Tiempo medio desde el Dx, años (IQR)	**17 (13.5-21)**
Estadio CDC C (%)	**51**
CD4 nadir, cel/mm3, mediana (IQR)	**114 (40-210)**
CV VIH cenit, log, mediana (IQR)	**5.39 (5-5.68)**
Coinfección VHC (%)	**40.6**

DRV/r+ETR: Motivos cambio a biterapia

- Motivo de cambio a DRV/r + ETR, n(%)

- **Simplificación** **30 (34.8)**
- **Fracaso virológico** **25 (29)**
- **Toxicidad** **24 (27.9)**
  - **Renal** **7**
  - **Metabólica** **5**
  - **GI** **4**
  - **Ósea** **3**
  - **Otras** **5**
- **Otros** **7 (8.1)**



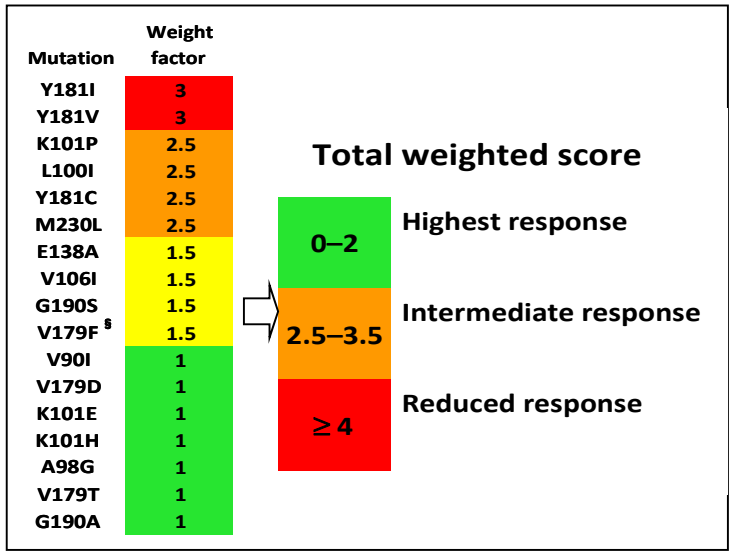
- Biterapia QD: n=71 (82.5%)

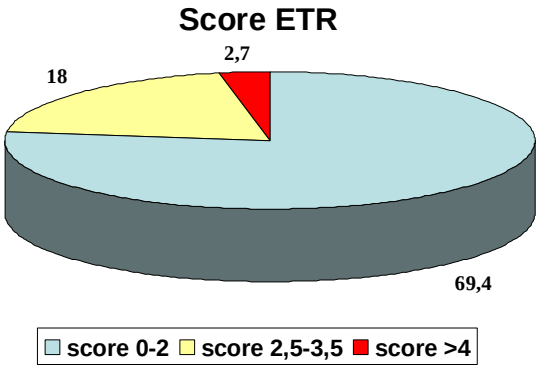
BITERAPIA DRV/r + ETR
CARACTERÍSTICAS BASALES

Prevalencia mutaciones basales

Fracasos virológicos previos, n (%)	**72 (83.7)**	
• **No mutaciones**		**7 (9.7)**
• **Resistencias a ITIAN**	**65 (90.2)**	
• **Resistencias a ITINN**	**49 (68)**	
• **Resistencias primarias a IP**		**27 (37.5)**

Mutaciones específicas a fármacos de la biterapia n (%)	
• **Mutaciones ETR**	**23 (31.9)**
• **Score ETR**	
–0-2 (respuesta alta)	50 (69.4)
–2.5-3.5 (resp intermedia)	13 (18)
–≥ 4 (respuesta reducida)	2 (2.7)
• **Muts DRV**	**13 (18)**
• **Resistencias a ETR + DRV**	**4 (5.5)**
–1 mut DRV, score ETR 0-2	1
–1 mut DRV, score ETR 2.5-3.5	1
–2 mut DRV, score ETR 2.5-3.5	2





BITERAPIA DRV/r + ETR
CARACTERÍSTICAS BASALES

Características basales (antes del cambio a DRV/r + ETR)

Tiempo carga viral VIH < 50, meses, media (rango)	**16.2 (0-102)**
CD4+ basal, cel/mm3, mediana (IQR)	**385.5 (249.7-622)**
CV VIH basal, logs, mediana (IQR)	***1.27 (1.27-3.72)***
Pacientes con CV indetectable (%)	***58.1***
Nº pautas previas, mediana (IQR)	***7 (4-9.7)***
Pautas previas al cambio a biterapia (%)	
2 ITIAN + 1 IP/r	***29***
2 ITIAN + 1 ITINAN	***22***
DRV/r + ETR + algún otro fármaco	***25.5***
Otras	***23.2***

BITERAPIA DRV/r + ETR
Resultados a 48 semanas

		BASAL	MES 12	P
CD4+, cel/mm3, mediana (IQR)		385.5 (249.7-622.5)	486 (340-730)	**0.001**
Carga viral, logs, mediana (IQR)		1.27 (1.27-3.72)	1.27 (1.27-1.53)	
Pacientes con CV indetectable, n (%)		50 (58.1)	74 (86)	**< 0.0001 ***
Perfil Hepático	**GOT**	26 (21-43)	24 (19-34)	0.393
	GPT	32 (18-49)	24 (16-38)	0.713
	GGT	33 (23-83)	31.5 (22-59.2)	0.819
Perfil Lipídico	**CT**	187.7 (147-220)	193 (165.6-226)	0.298
	HDL	40.3 (34-47.4)	42 (34.6-52.1)	**0.033**
	LDL	110.6 (85.2-147.8)	116 (86.8-145.7)	0.561
	TG	132.7 (102.6-194)	153 (114-220)	0.653
Glucosa		90 (84.6-99)	93 (86-100.8)	0.640
Creatinina		0.91 (0.83-1.06)	0.91 (0.81-1.08)	0.348

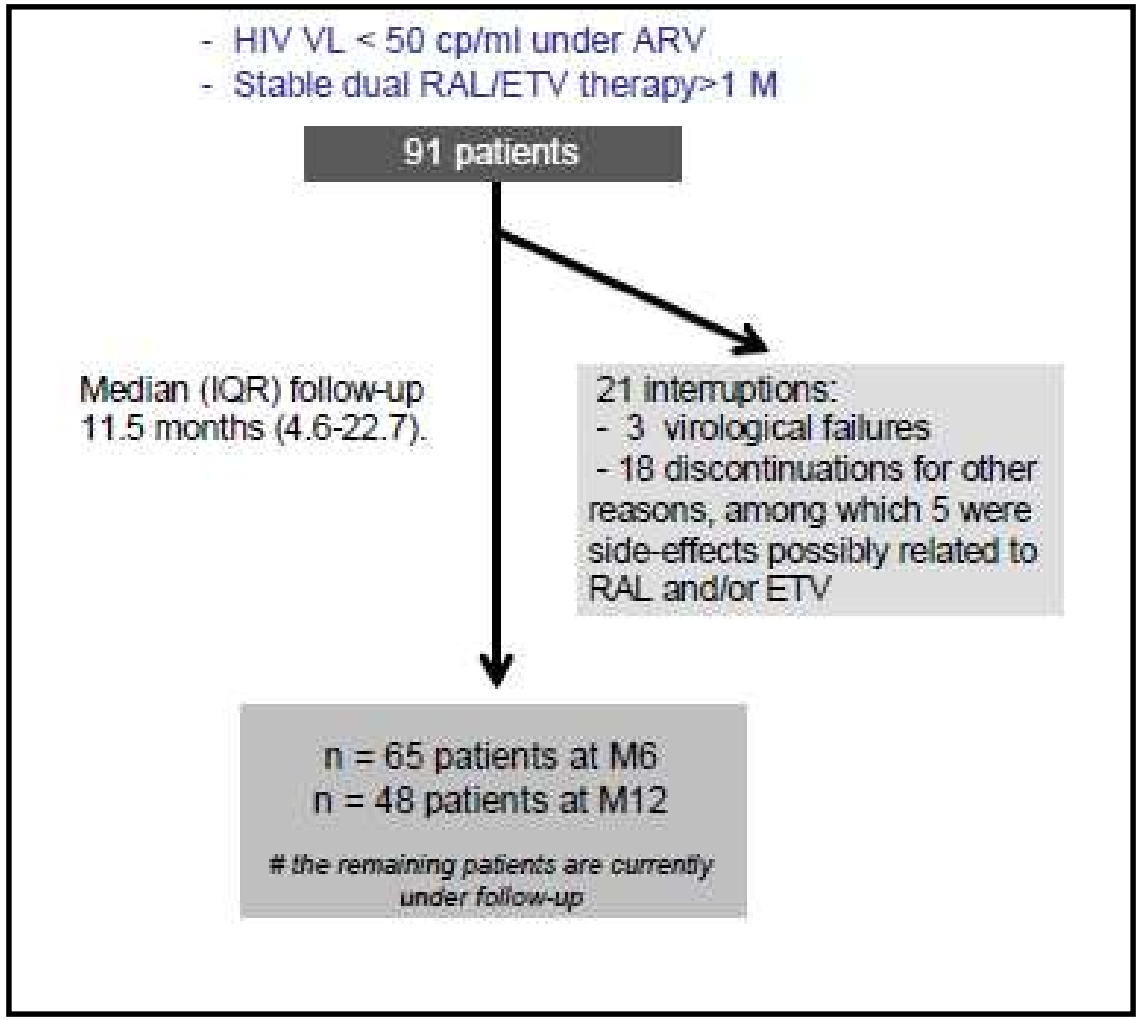
* **CV mes 12 < CV basal**: 45.3%, **CV mes 12 = CV basal**: 40.7%, **CV mes 12 > CV basal**: 14%

BITERAPIA DRV/r + ETR
Variables asociadas con CV mes 12 < 50 cop/ml

- **Variables asociadas con CV mes 12 indetectable:**
  - **Carga viral basal indetectable** **p < 0.0001**
  - **CD4 basales altos (≥ 500 vs < 500 cel/mm3)** **p = 0.014**

- **Variables no relacionadas con CV mes 12 indetectable:**
  - **CD4 nadir** **p = 0.786**
  - **CV cenit** **p = 0.459**
  - **Estadío CDC** **p = 0.889**
  - **Coinfección VHC** **p = 0.364**
  - **Mutaciones primarias IP** **p = 0.293**
  - **Mutaciones específicas DRV** **p = 0.457**
  - **Score ETR** **p = 0.585**

RAL + ETR: the french experience



RAL + ETR: the french experience

	Virological success (per-protocole)*	Virological failures
M0-M6 (n=65)	98 % (55/56, 95% CI : 90.5-99.6)	n = 1
M6-M12 (n=48)	92 % (36/39, 95% CI : 79.6-97.3)	n = 2

* In per-protocole analysis were included only patients that did not discontinue dual therapy for other reasons than virological failure

Description of 3 cases of virologic failure under RAL/ETV treatment

	Previous NNRTI exposure	Previous replication under NNRTI (>200 cp/ml)	Previous RAL exposure	Cumulative genotype before switch (NNRTI&II)	Genotype at the time of failure	VL D0	VL M1	VL M3	VL M6	VL M12	VL at discontinuation
1	+	-	-	V179I	-	<20	<20	ND**	90		38
2	+	+	-	-	V72I	37	ND	69			51
3	+	+	-	K103N, Y181C	P225H, Y181C, N155H	<40	ND	ND	2653	7679	7679

**ND = not done

- One patient had pre-existing mutations conferring resistance to ETR (K103N and Y181C). One other harbored a single mutation impacting, but not compromising, ETR activity (V179I).
- Virological failure was followed by acquired RAL (N155H) resistance (in red in table).

RAL + ETR: HCP experience

Reasons	n (%)
Drug interaction only	3 (12%)
Toxicity	
Gastrointestinal symptoms	1 (4%)
Lipodystrophy	1 (48%)
Renal impairment	3 (12%)
Neuropsychiatric symptoms	3 (12%)
Combination of causes	
Gastrointestinal symptoms and drug interaction	1 (4%)
Gastrointestinal symptoms and lipodystrophy	7 (28%)
Lipids abnormalities and lipodystrophy	6 (24%)

Therapeutic efficacy	ITT - **84.0%** (21/25) (95% CI 65.3%–93.6%)
	PP - **91.3%** (21/23) (95% CI 73.2%–97.6%)

Immunological response	↑ 114 cells/mm3 in CD4+ T cell (IQR 217, -4; 21 patients, P=0.075)
	↓ -232 cells/mm3 in CD8+ T cell (IQR 26, -323; 23 patients; P=0.020)
	↑ 0.14 in the T4/T8 ratio (IQR 0.37, 0.06; 19 patients, P=0.001)

Monteiro P, et al. JAC 2014

Salvage therapy

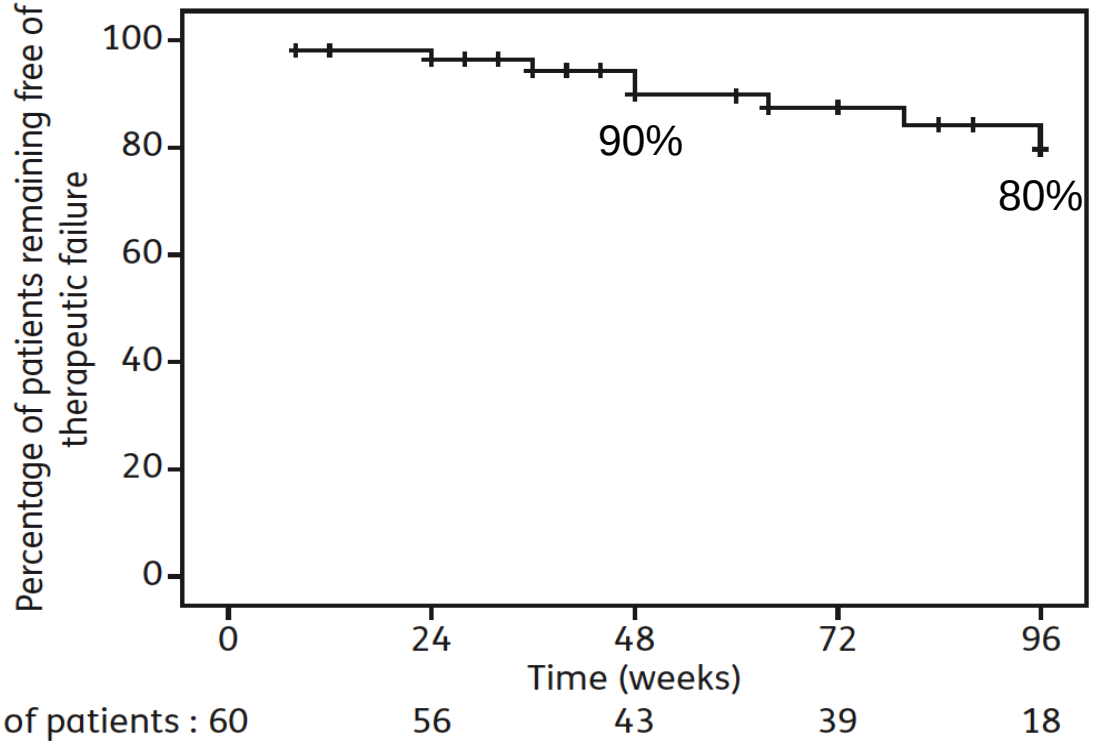
Salvage ?

- **Efficacy demonstrated for salvage in the absence of active NRTI (DUET).**
- **Very scarce data in this setting.**
- **Could be an option for selected patients (High CD4 count, low VL, …)**

  – **Burgos J, et al. J Antimicrob Chemother 2012;67:1453–58.**

DRV + ETR

CD4 cell count (cells/mm^3), median (IQR)	380 (232–613)
HIV RNA (log_{10} copies/mL), median (IQR)	3.04 (2.5–4)



Our results suggest that a dual-therapy rescue regimen including a PI/r is convenient, well tolerated and potent enough to achieve persistent viral suppression in selected pre-treated patients with low viral load and few PI resistance mutations.

Burgos J, et al. JAC 2012

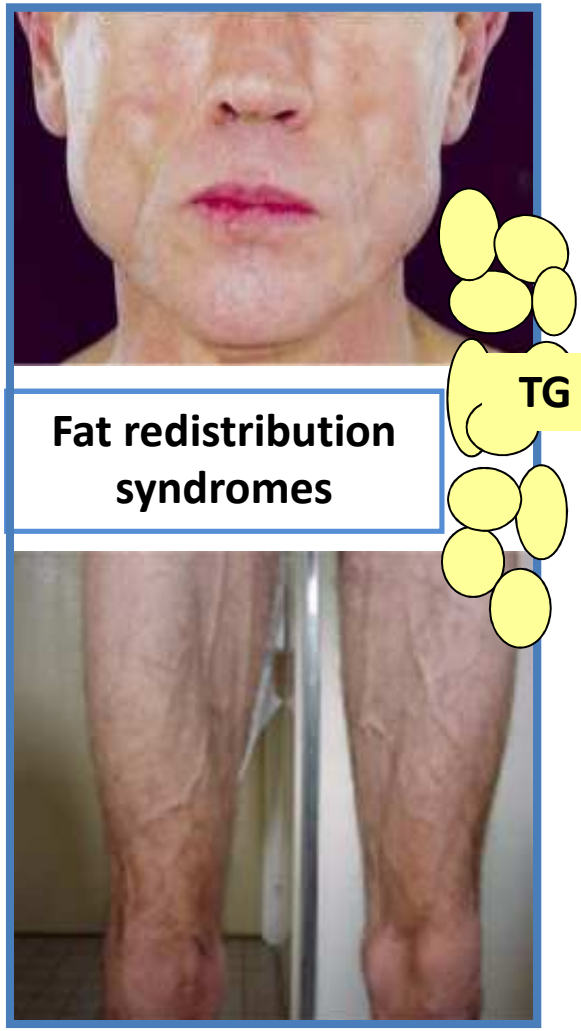
Future scenarios

- ***Naive*:**
  - **Hard to foresee for ART start**
  - Exception: transmitted resistance
- ***Switching*: most probable scenario**
  - **ART switch for NRTI toxicity (TAF?)**
  - Simplification of triple therapies coming from early salvage therapies with long undetectable VL
- **Early salvage?**
- **Drugs for future scenarios:** rilpivirina, dolutegravir…

Conclusions

- **NRTI-sparing regimes may be useful for:**
  - **Simplification**
  - **NRTI toxicity**
  - **Early salvage therapy**
- **Provided that drugs used retain full activity**

The old mitochondrial toxicity



Fat redistribution syndromes

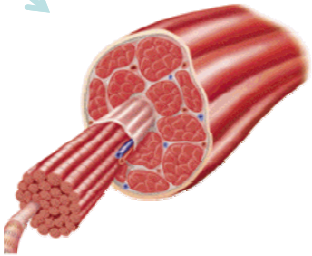
TG

Free fatty acids

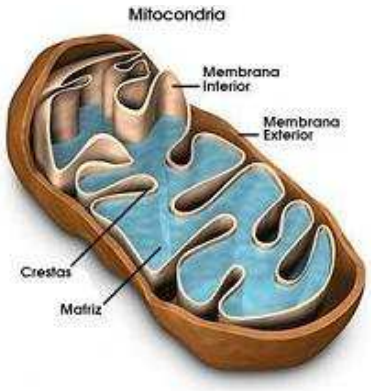
↑ VLDL

↑Steatosis

β Cell dysfunction



Disturbed glucose homeostasis



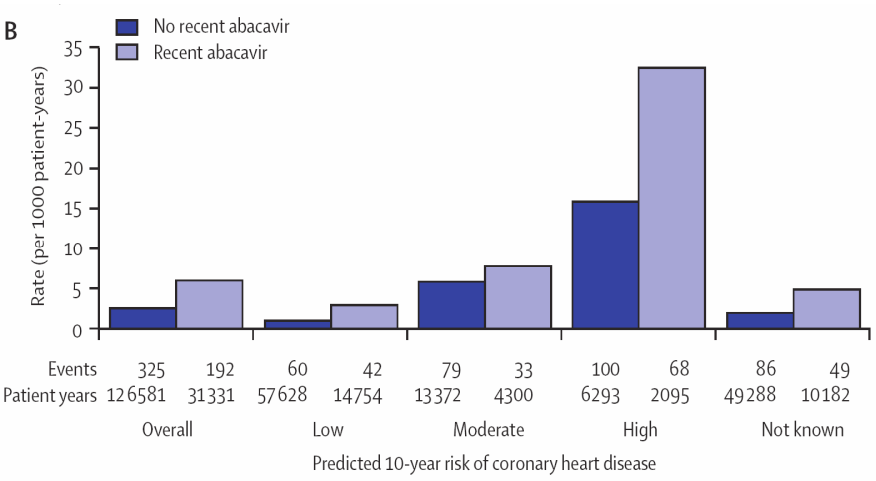
Cardiovascular risk

- Lactacidosis
- Pancreatitis?
- Polyneuritis
- Anemia macro?

Van Wijk JP, et al. JCEM 2005

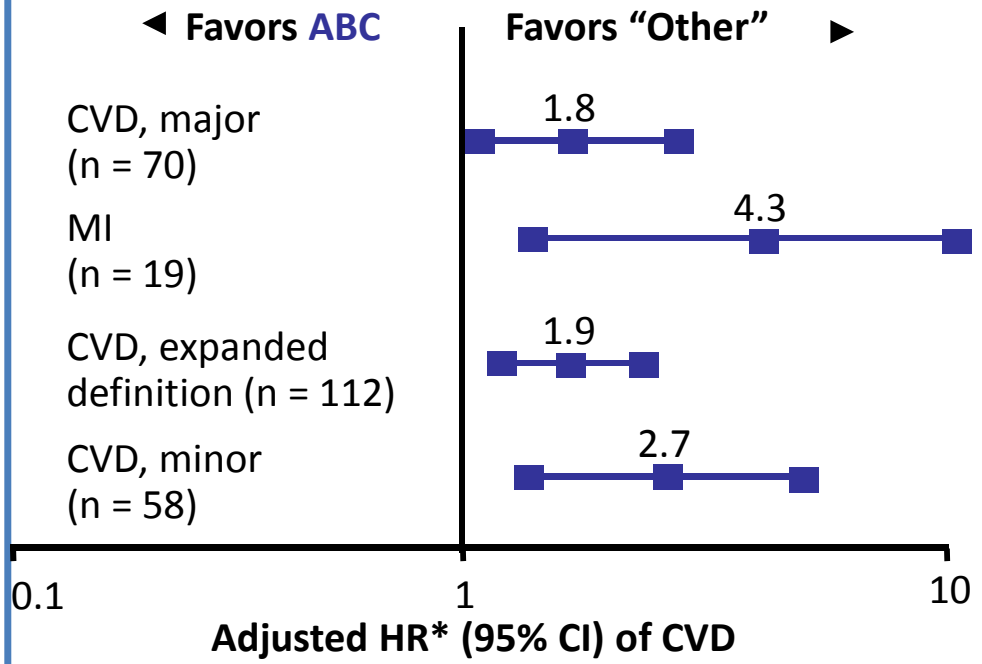
ABC and cardiovascular risk?

DAD



Abacavir	
Cumulative exposure (per year)	1·01 (0·93–1·09); p=0·80
Any recent exposure	1·90 (1·47–2·45); p=0·0001

SMART



DAD Study Group. Lancet 2008

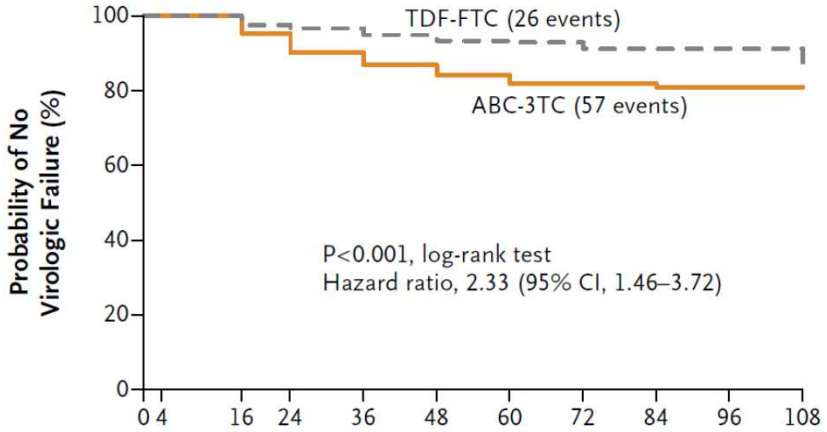
SMART Group. AIDS 2008

ABC vs. TDF

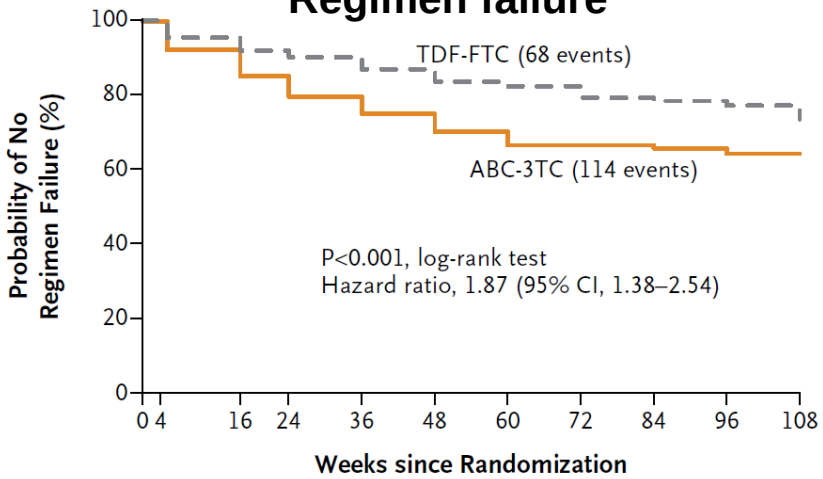
ACTG 5202

Baseline VL > 100000 c/mL

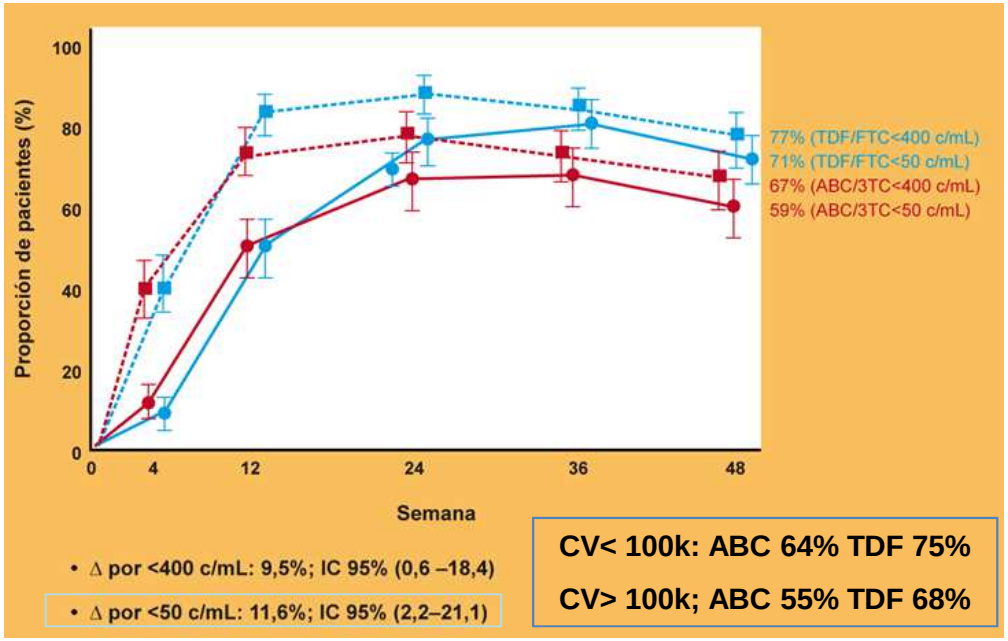
Virologic failure



Regimen failure



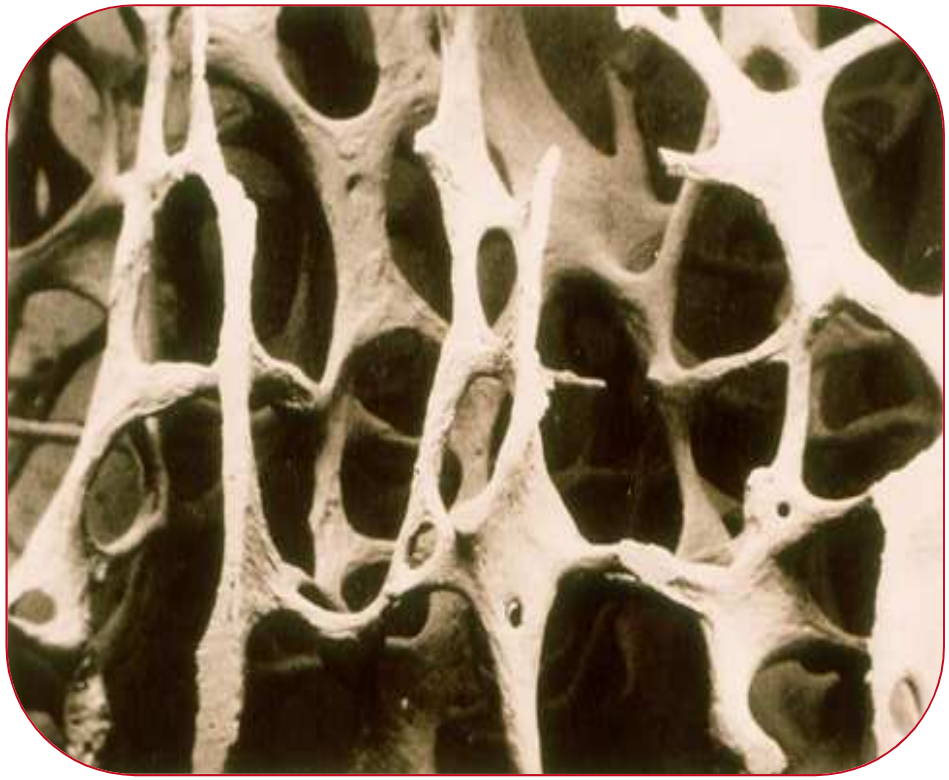
Assert

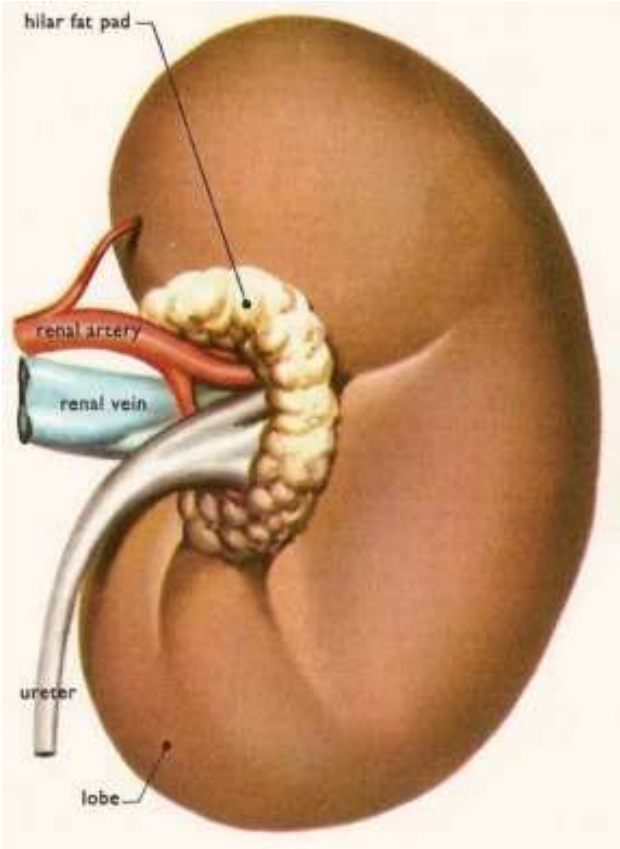


- Less efficacy of ABC with:
  - ✓ High baseline VL
  - ✓ in NNRTI-based regimes

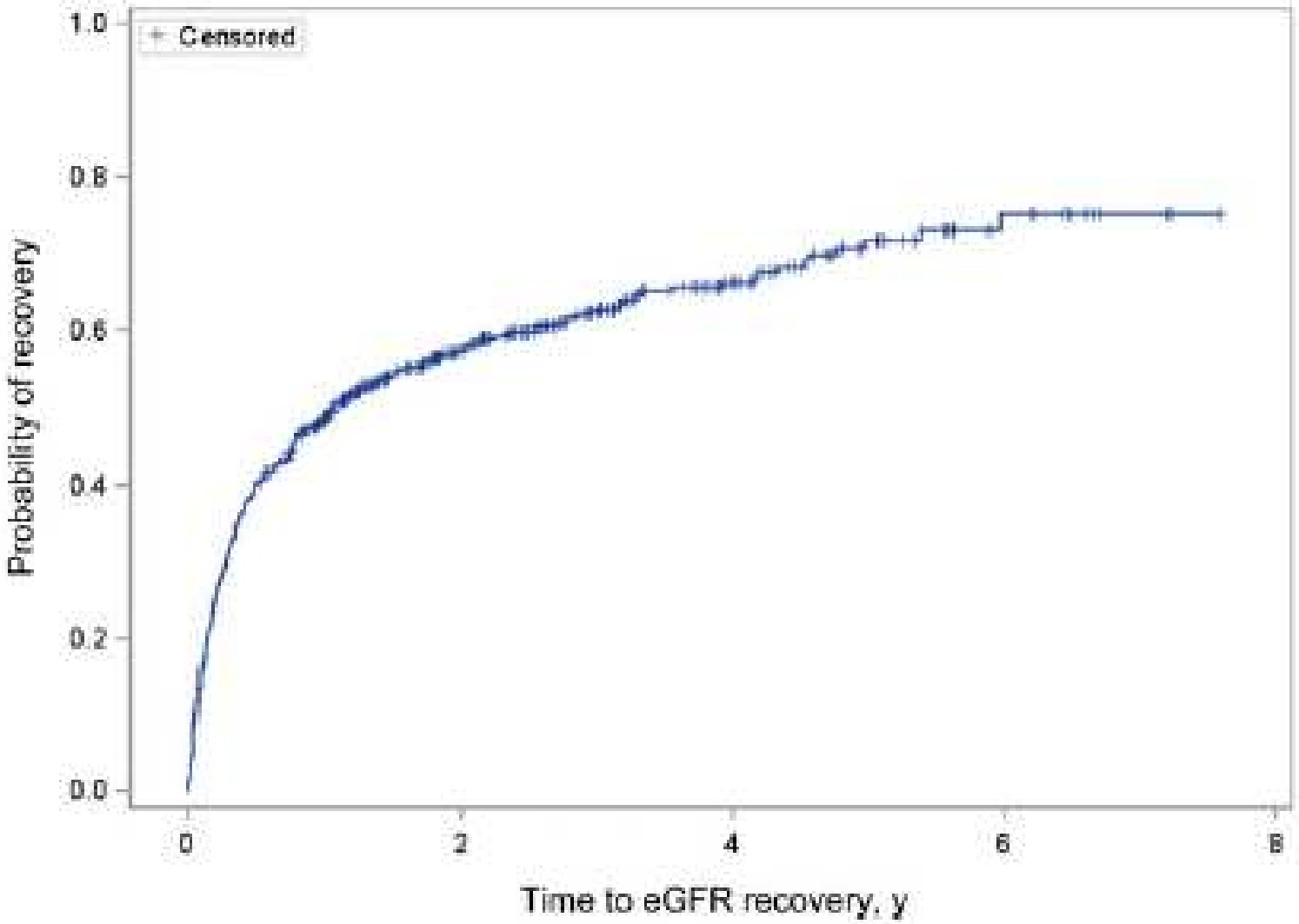
Sax PE, et al. J Infect Dis 2011
Sax PE, et al. N Engl J Med 2009

The targets of TDF toxicity





Cumulative proportion of individuals discontinuing TDF therapy following a decline in eGFR that experienced eGFR recovery



Number under follow up	
Discontinuation	601
6 months	601
1 year	287
2 years	169
5 years	27

Jose S et al. JID 2014