Nuevas estrategias en el tratamiento del paciente VIH

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Esquema

- **Introducción (necesidad)**

- **Pacientes naïve (Inicio de tratamiento)**

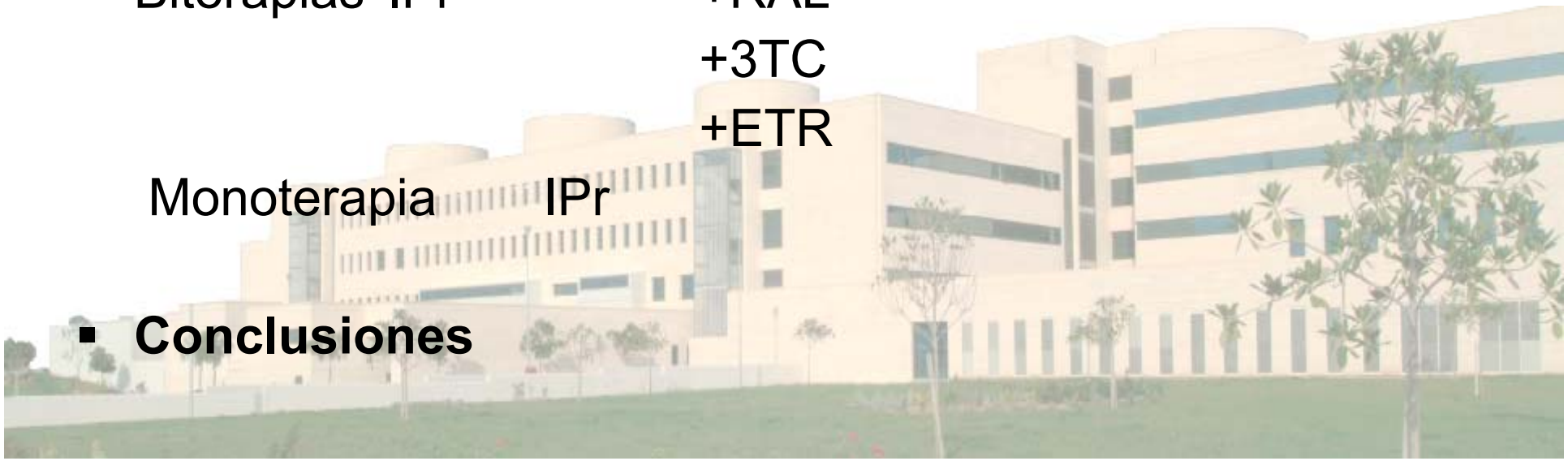
  Biterapias IPr +MVC
  + RAL
  + 3TC

- **Pacientes pretratados**

  Biterapias IPr +RAL
  +3TC
  +ETR

  Monoterapia IPr

- **Conclusiones**

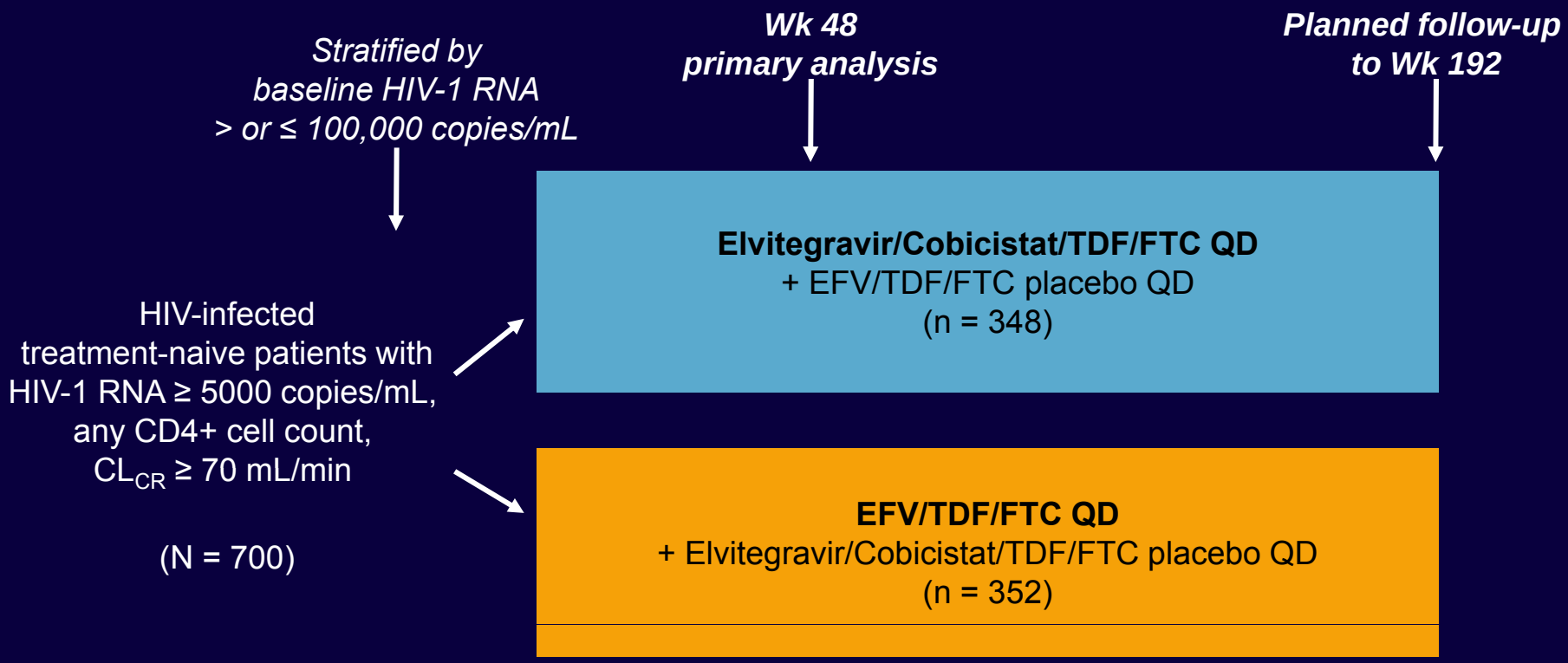


Nuevas estrategias vs Triple terapia (podemos mejorar?)

- Eficacia virológica
- Resistencias
- Tolerancia (toxicidad a corto plazo)
- Toxicidad a largo plazo
- Conveniencia
- Coste

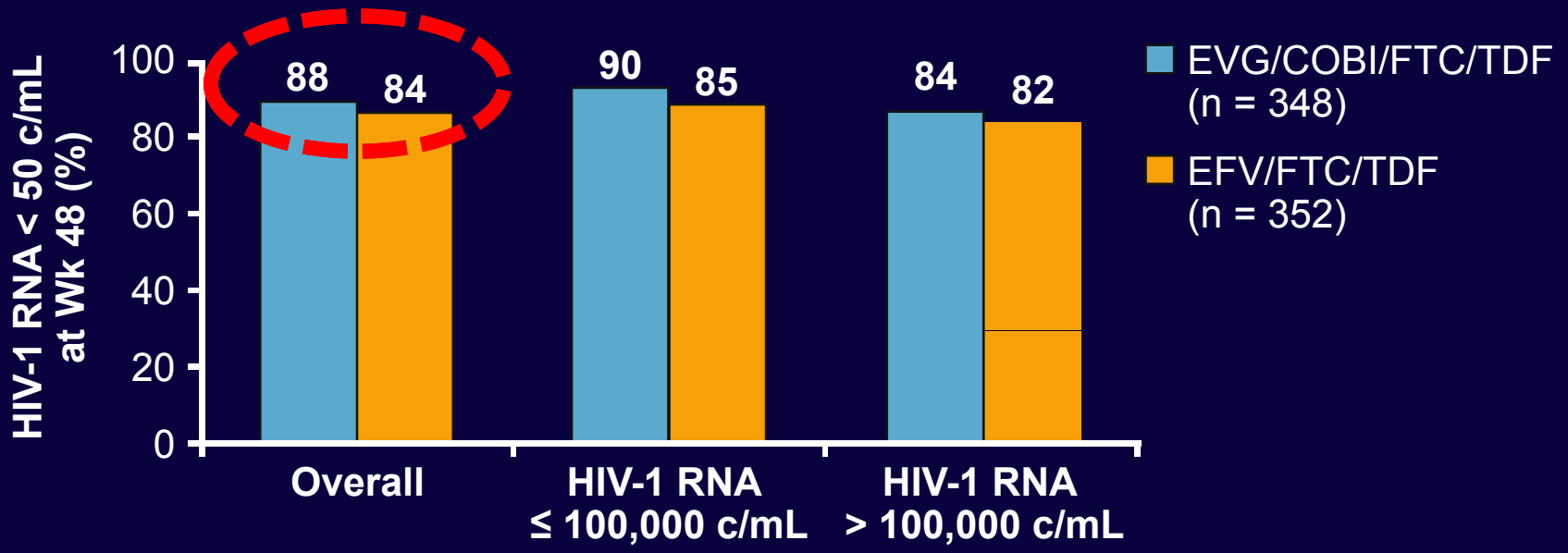
Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC in Treatment-Naive Patients

- Multicenter, randomized, double-blinded, active-controlled phase III study



Sax P, et al. CROI 2012. Abstract 101.

Elvitegravir/Cobicistat Regimen Noninferior to EFV Regimen at Wk 48

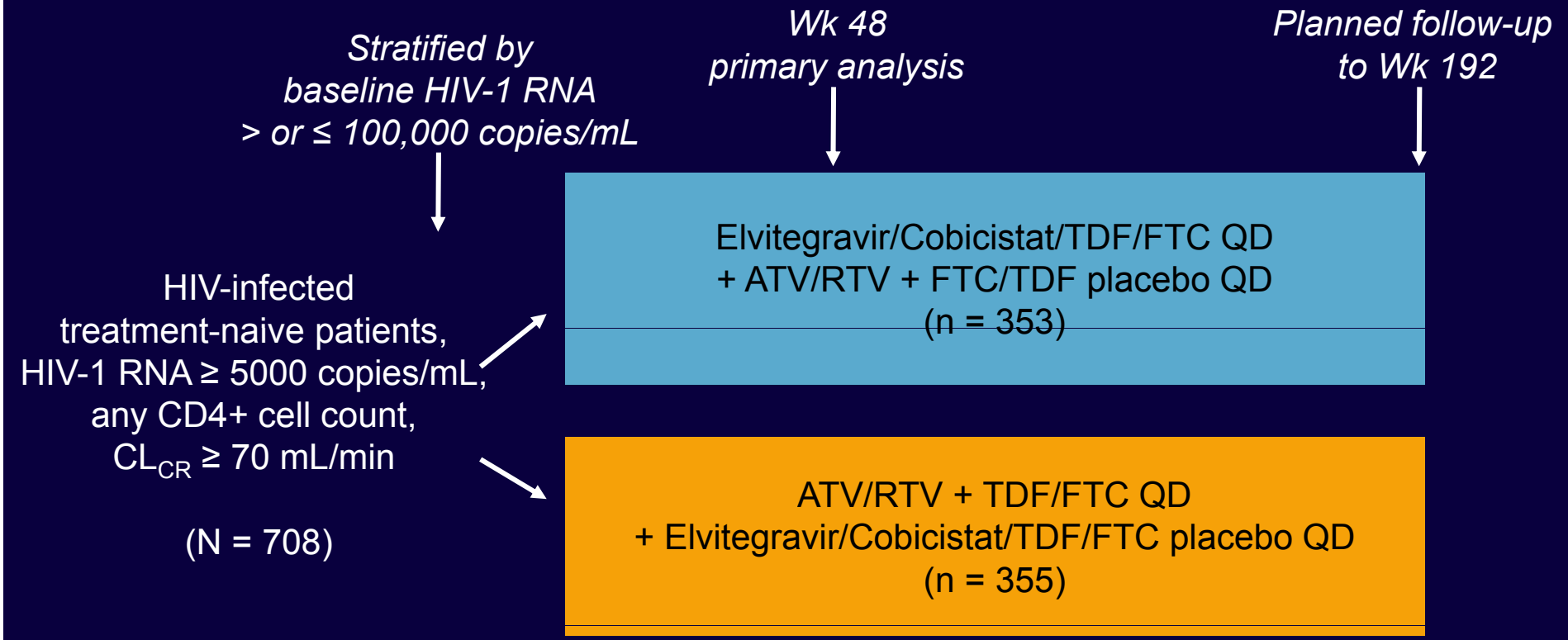


- Greater CD4+ count increase with EVG/COBI vs EFV: 239 vs 206 cells/mm^3 (*P* = .009)
- Among pts with confirmed virologic failure or rebound, resistance detected in 8/14 pts in EVG/COBI arm vs 8/17 patients in EFV arm
  - Primary integrase mutations and primary NNRTI mutations observed in 7 and 8 patients in EVG/COBI and EFV arms, respectively
  - All 8 pts in EVG/COBI arm had M184V/I mutation vs 2 pts in EFV arm; 3 and 2 had K65R, respectively

Sax P, et al. CROI 2012. Abstract 101.

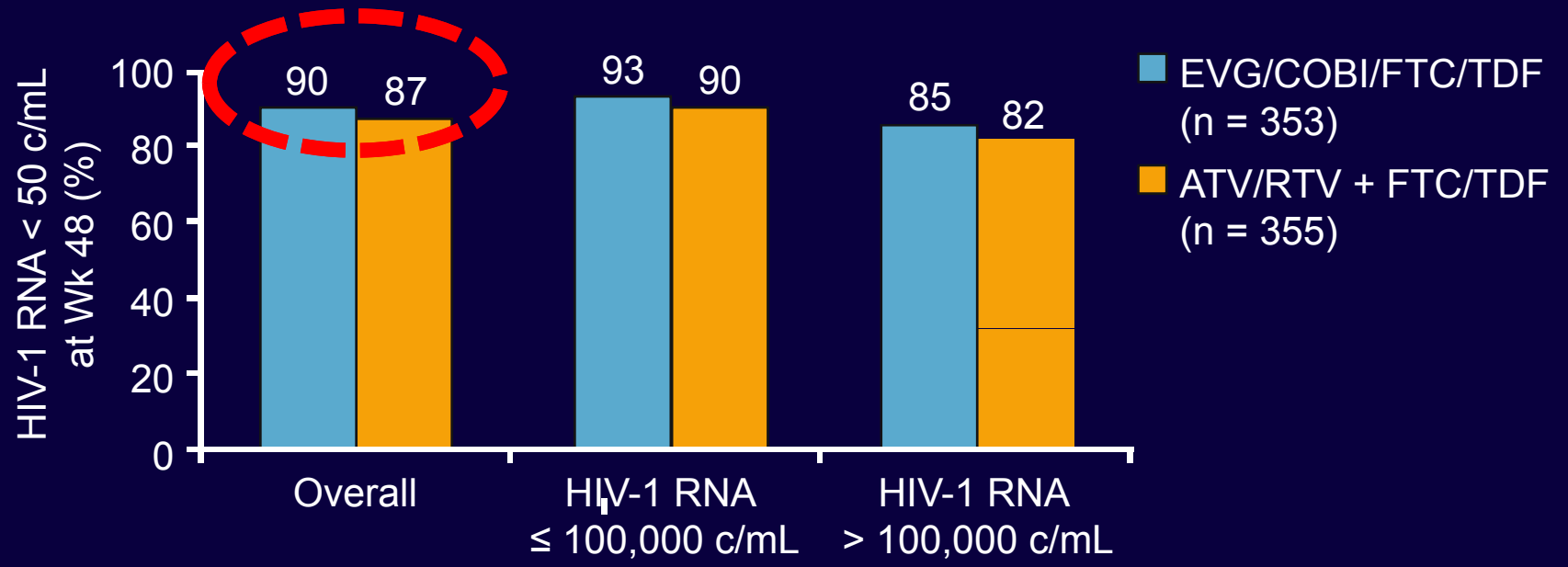
Elvitegravir/Cobicistat/TDF/FTC vs ATV/RTV + TDF/FTC in Tx-Naive Patients

- Multicenter, randomized, double-blinded, active-controlled phase III study



DeJesus E, et al. CROI 2012. Abstract 627.

Elvitegravir/Cobicistat Regimen Noninferior to ATV/RTV Regimen at Wk 48



- Similar CD4+ cell count increases in both study arms at Wk 48
- Among pts with confirmed virologic failure or rebound, resistance detected in 5/12 pts in EVG/COBI arm vs 0/8 pts in ATV/RTV arm
  - 4/5 pts in EVG/COBI arm had M184V/I mutation; 4 had primary integrase mutations

DeJesus E, et al. CROI 2012. Abstract 627.

Nuevas estrategias vs Triple terapia (podemos mejorar?)

- Eficacia virológica (difícil)
- Resistencias
- Tolerancia (toxicidad a corto plazo)
- Toxicidad a largo plazo
- Conveniencia
- Coste

Study 236-0102
Integrase & NNRTI Resistance Through Week 48

	Quad (n=348)	EFV/FTC/TDF (n=352)
Subjects Analyzed for Resistance*, n (%)	14 (4)	17 (5)
Subjects with Resistance to ARV Regimen, n (%)	8 (2)	8 (2)
Any Primary Integrase-R, n	7	
E92Q	7	
T66I	1	
Q148R	1	
N155H	1	
Any Primary NNRTI-R, n		8
K103N		7
V108I		1
Y188L		1
G190A		1
Any Primary NRTI-R, n	8	2
M184V/I	8	2
K65R	3	2

Con fármacos de baja barrera genética!!!!

*Subjects who experienced either suboptimal virologic response (two consecutive visits with HIV-1 RNA ≥50 c/mL and <1 log10 below baseline after Week 8), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 log10 increase from nadir), or had HIV-1 RNA ≥400 c/mL at their last visit.

236-0103
Integrase, PI, NRTI Resistance Through Week 48

	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Subjects Analyzed for Resistance[a], n (%)	12 (3)	8 (2)
Subjects with Resistance to ARV Regimen, n (%)	5 (1)	0
Any Primary Integrase-R, n	4	-
E92Q	1	-
T66I	1	-
Q148R	2	-
N155H	2	-
Any Primary PI-R, n	-	0
Any Primary NRTI-R, n	4	0
M184V/I	4	
K65R	1	

a. Subjects who experienced either suboptimal virologic response (two consecutive visits with HIV-1 RNA ≥50 c/mL and <1 $\log_{10}$ below baseline after Week 8), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 $\log_{10}$ increase from nadir), or had HIV-1 RNA ≥400 c/mL at their last visit.

DeJesus E, et al., CROI 2012; Seattle. Poster 627.

Nuevas estrategias vs Triple terapia (podemos mejorar?)

- Eficacia virológica (dificilmente)
- Resistencias (posible, impacto en clínica?)
- Tolerancia (tox. corto plazo)
- Toxicidad a largo plazo
- Conveniencia
- Coste

Study 102: Adverse Events

	Quad (n=348)	EFV/FTC/TDF (n=352)
Discontinuations Due to AE	4%	5%
AE leading to discontinuation in >1 subject (%)		
Rash and Drug Hypersensitivity	0	1.4%
Renal Abnormalities	1.4%	0
Depression	0.3%	0.9%
Abnormal Dreams	0	0.6%
Fatigue	0.3%	0.3%
Paranoia	0.3%	0.3%

Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC in Treatment-Naive Patients

Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

236-0103
Summary of Adverse Events (AE)

	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Grade 3 or 4 AE	13%	14%
Drug-related AE	45%	57%
SAE	7%	9%
Drug-related SAE	1%	1%
AE leading to DC of study drug	4%	5%
Death, (n)	0	1% (3)[a]

[a]Causes of death included septic shock, Pneumocystis jiroveci pneumonia, and cardiopulmonary arrest after overdose of recreational drugs.

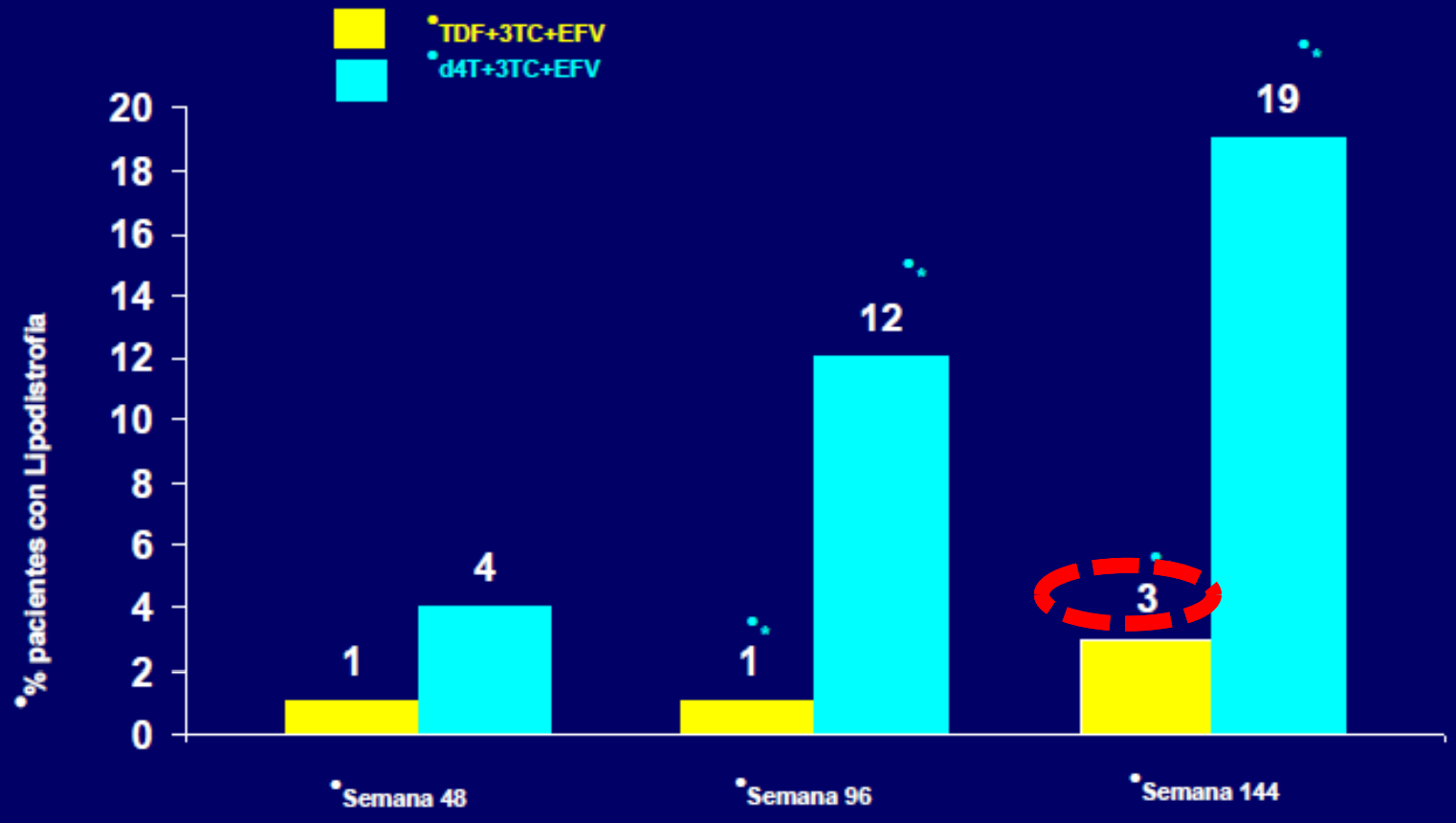
Elvitegravir/Cobicistat/TDF/FTC vs ATV/RTV + TDF/FTC in Tx-Naive Patients

*DeJesus E, et al., CROI 2012; Seattle. Poster 627.

Nuevas estrategias vs Triple terapia (podemos mejorar?)

- Eficacia virológica (dificilmente)
- Resistencias (posible, impacto en clínica?)
- Tolerancia (tox. corto plazo) (aspectos concretos algún fco)
- Toxicidad a largo plazo
- Conveniencia
- Coste

Study 903
Patients (%) with Lipodistrophy



+ Definidas por el investigador

* p < 0.001

Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial.

Gallant JE. *JAMA*. 2004;292:191-201.

Sub-study ACTG 5224
Subjects (%) with fat loss in limbs ≥10% y ≥20%
(ITT analysis, main outcome)

Fat loss (%) in limbs in weeks 0-96	TDF/FTC +EFV (n=56)	TDF/FTC +ATV/r (n=45)	ABC/3TC +EFV (n=53)	ABC/3TC +ATV/r (n=49)	Total (n=203)
≥ 10% Principal	14,3% (6,4%, 25,3%)	15,6% (7,0%, 28,6%)	18,9% (9,4%, 31,6%)	16,3% (7,5%, 28,8%)	16,3% (11,8%, 22,0%)
≥ 20% Post hoc	8,9%	0%	3,8%	6,1%	4,9%

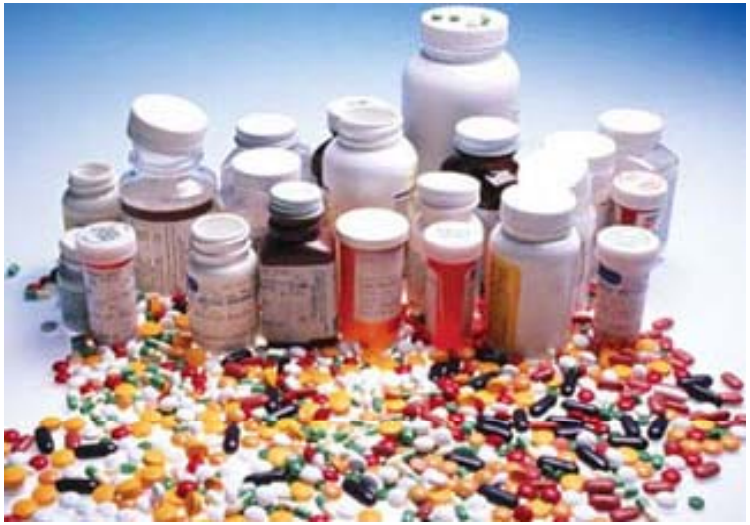
McComsey G, Kitch D, Darr E, et al. Bone and limb fat outcomes of ACTG 5224s, a substudy of ACTG A5202: a prospective, randomized, partially blinded phase III trial of abacavir/3TC or tenofovir/FTC with efavirenz or atazanavir/ritonavir for initial treatment of HIV-1 infection. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16-19 February 2010, San Francisco, U.S. Abstract 106 LB.

• McComsey. et al. 17ª conferencia CROI, San Francisco, CA, 2010, presentación 106LB

Nuevas estrategias vs Triple terapia (podemos mejorar?)

- Eficacia virológica (dificilmente)
- Resistencias (posible, impacto en clínica?)
- Tolerancia (tox. corto plazo) (aspectos concretos algún fco)
- Toxicidad a largo plazo (mejoras en lipidos, tox. renal, ósea)
- Conveniencia
- Coste

Conveniencia



Nuevas estrategias vs Triple terapia (podemos mejorar?)

- Eficacia virológica (dificilmente)
- Resistencias (posible, impacto en clínica?)
- Tolerancia (tox. corto plazo) (aspectos concretos algún fco)
- Toxicidad a largo plazo (mejoras en lipidos, tox. renal, ósea)
- Conveniencia (single tablet regimen STR)
- Coste (cómo único argumento?, no siempre favorable)

Esquema

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  +MVC
  +3TC

- **Pacientes pretratados**
  Monoterapia IPr
  Biterapias IPr +RAL
  +3TC
  +ETR

- **Conclusiones**

Inicio de tratamiento
IPr + RAL

- LPVr + RAL (PROGRESS)
- ATVr + RAL (SPARTAN)
- DRVr + RAL (ACTG5262)

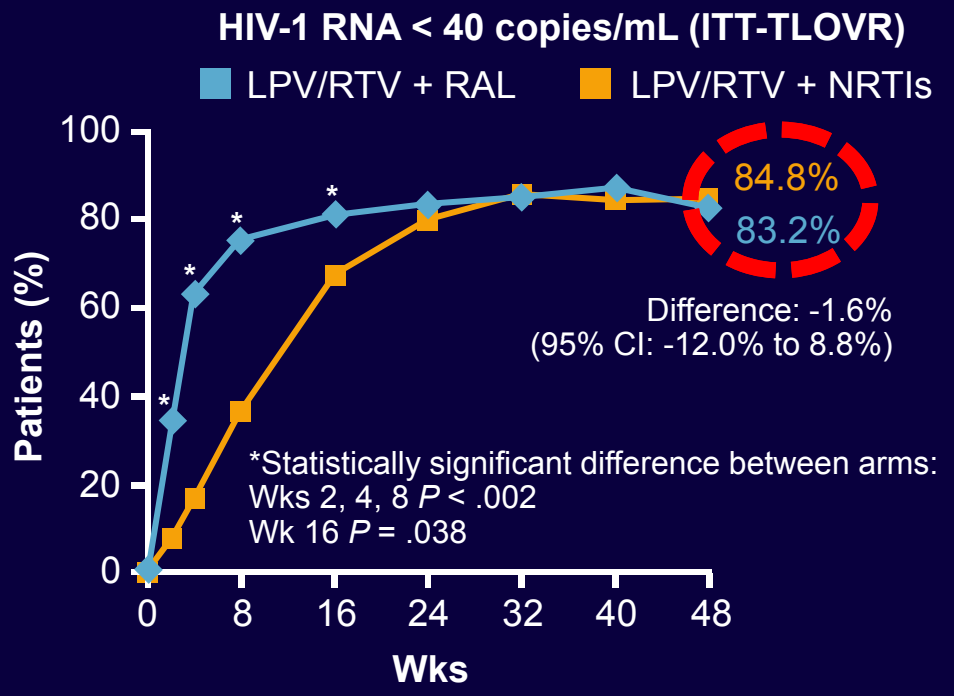
(RADAR)

(ANRS143)

PROGRESS: LPV/RTV + RAL vs LPV/RTV + TDF/FTC in Treatment-Naive Patients

- Randomized, open-label, multicenter phase III trial in treatment-naive patients with HIV-1 RNA > 1000 copies/mL
  - LPV/RTV 400 mg BID + RAL 400 mg BID (n = 101) vs
  - LPV/RTV 400 mg BID + TDF/FTC 300/200 mg QD (n = 105)
- Relatively low mean baseline HIV-1 RNA
  - 4.25 $\log_{10}$ copies/mL

20.000 cop/mL!!!

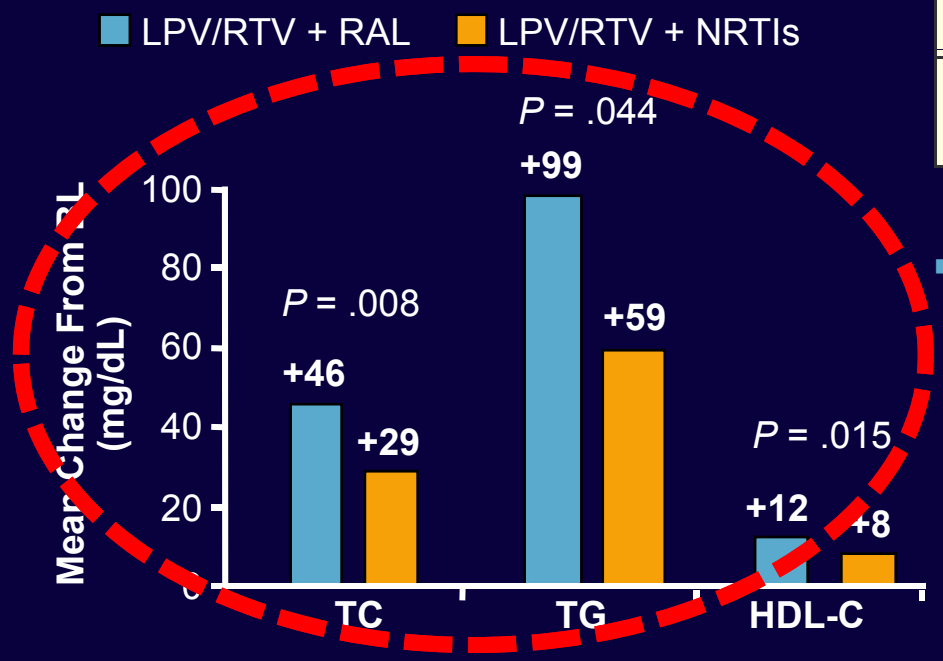


- Similar CD4+ cell count gain at Wk 48
  - LPV/RTV + RAL: 215 cells/mm³
  - LPV/RTV + NRTIs: 245 cells/mm³

Reynes J, et al. AIDS 2010. Abstract MOAB0101.

PROGRESS: Lipids and Adverse Events at Wk 48

- Mean increases in TC, TG, and HDL-C from BL to Wk 48 significantly greater in RAL arm vs NRTI arm



Resistance Development at VF	LPV/RTV + RAL	LPV/RTV + NRTIs
Met criteria for resistance testing	4	3
▪ INSTI mutation (N155H)	1	0
▪ NRTI mutations (M184V)	0	1

- Grade 3/4 laboratory events did not differ between arms, except higher risk of CPK > 4 x ULN in RAL arm
  - 12.9% vs 3.8% (*P* = .023)

Reynes J, et al. AIDS 2010. Abstract MOAB0101.

Inicio de tratamiento
IPr + RAL

- LPVr + RAL (PROGRESS)

Eficacia en CV altas?
Tox: Perfil lipídico
Conveniencia

Coste >3.000/año tri NN >800/año triple IPr

- ATVr + RAL (SPARTAN)
- DRVr + RAL (ACTG5262)

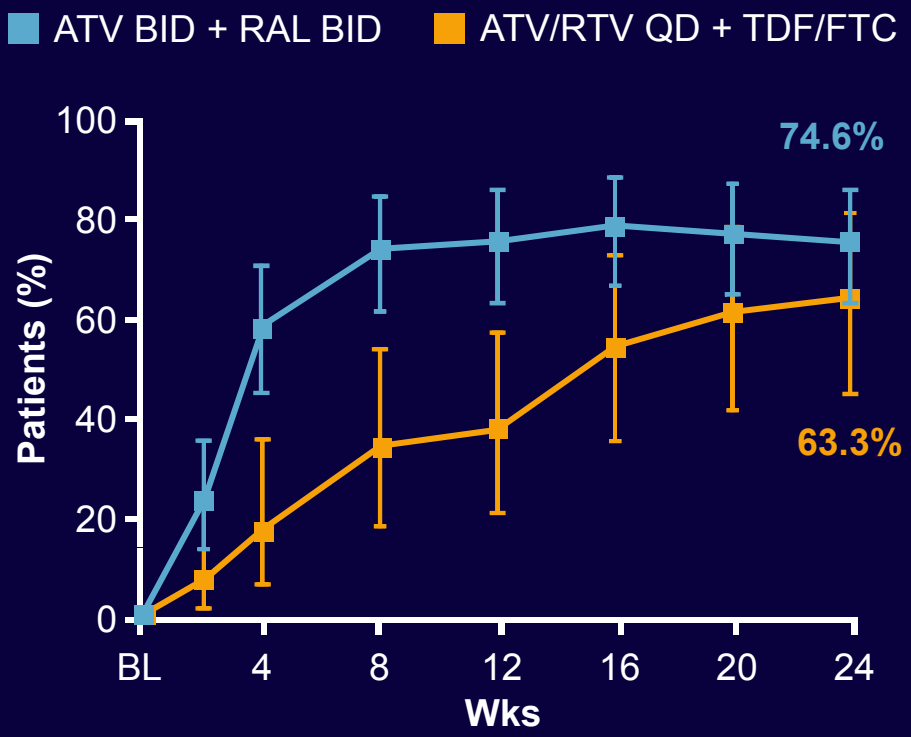
(RADAR)

(ANRS143)

SPARTAN: Pilot Study of ATV + RAL vs ATV/RTV + TDF/FTC in Naive Pts

- Randomized, noncomparative, open-label, multicenter pilot study in treatment-naive patients with HIV-1 RNA ≥ 5000 copies/mL
  - ATV 300 mg BID + RAL 400 mg BID (n = 63) vs
  - ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD (n = 31)
- Mean BL HIV-1 RNA: 4.9 $\log_{10}$ copies/mL

Primary Endpoint: HIV-1 RNA < 50 copies/mL Through Wk 24 (CVR*, NC = F)



*CVR = modified ITT.

Kozal MJ, et al. AIDS 2010. Abstract THLBB204. Graphic used with permission.

SPARTAN: Wk 24 Results

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		
▪ N155H	2	NA
▪ Q148R	1	NA
▪ Q148R + N155H + T97A	1	NA
Phenotypic RAL resistance without genotypic evidence of resistance	1	NA
ATV resistance	0	0
TDF/FTC resistance	NA	0

- No significant changes in fasting lipids observed in either arm during study period
- Trial terminated at Wk 24 due to resistance data and grade 4 bilirubin abnormalities (21%) with experimental regimen vs control arm (0%)

*Criteria for resistance testing:
- HIV-1 RNA ≥ 400 copies/mL at or after Wk 24
- Rebound to HIV-1 RNA ≥ 400 any time during the study
- Discontinued before achieving HIV-1 RNA < 50 copies/mL after Wk 8 with last HIV RNA ≥ 400 copies/mL

Kozal MJ, et al. AIDS 2010. Abstract THLBB204.

Inicio de tratamiento
IPr + RAL

- LPVr + RAL (PROGRESS)

  Eficacia en CV altas
  Tox: Perfil lipídico
  Conveniencia

  Coste >3.000/año tri NN 800/año triple IPr

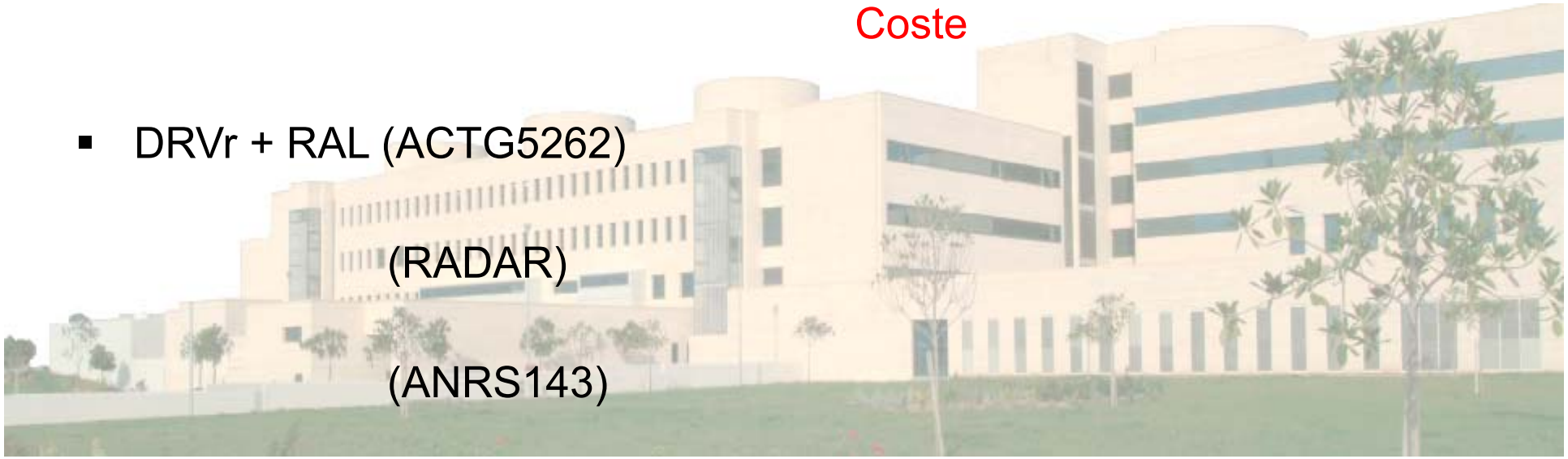
- ATVr + RAL (SPARTAN)

  Eficacia, Resistencia
  Tox: hiperbilirrubinemia
  Conveniencia
  Coste

- DRVr + RAL (ACTG5262)

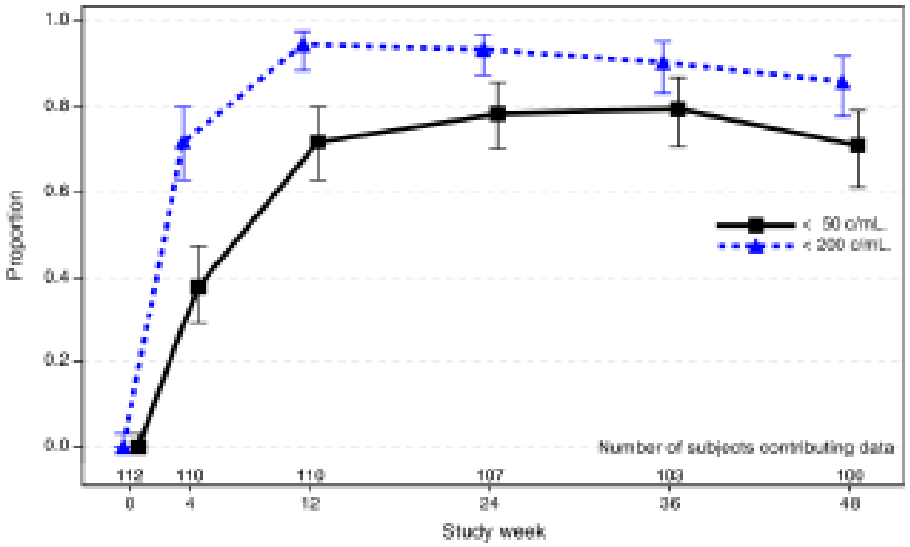
  (RADAR)

  (ANRS143)



Results from a Single Arm Study of Darunavir/Ritonavir Plus Raltegravir in Treatment-Naïve HIV-1-Infected Patients (ACTG A5262)

Figure 2: PROPORTION OF SUBJECTS WITH HIV-1 RNA < 200 and < 50 copies/mL (ITT analysis, missing/off study=ignored)



Week	Proportion (95% CI)	
	< 200 c/mL.	< 50 c/mL.
24	93% (87%, 97%)	79% (70%, 86%)
48	86% (78%, 92%)	71% (61%, 79%)

Artemis 48 sem: 84%

13/28 (46%) of virologic failures had confirmatory HIV-1 RNA 51-200 copies/mL

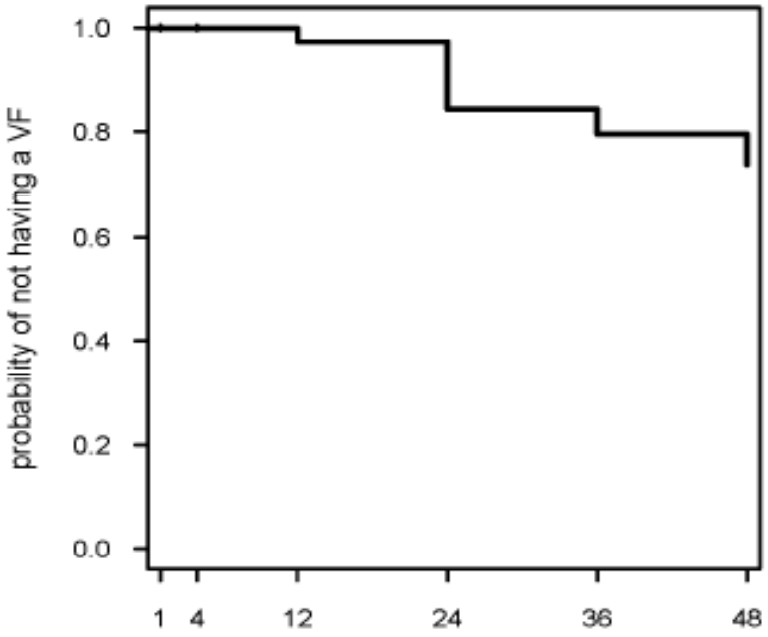
Babafemi Taiwo*[1], Summer Zheng[2], Sebastien Gallien[3], Roy Matining[2], Daniel Kuritzkes[3], Cara Wilson[4], Baiba Berzins[1], Edward Acosta[5], Peter Kim[6], Joseph Eron[7], and ACTG A5262 Team

[1]Northwestern Univ., Chicago, IL, US [2]Harvard Sch. of Publ. Hlth., Boston, MA, US [3]Brigham and Women's Hosp. Harvard Med. Sch., Boston, MA, US [4]Univ. of Colorado, Denver, CO, US [5]Univ. of Alabama at Birmingham, US [6]NIAID, NIH, Bethesda, MD, US and [7]Univ. of North Carolina at Chapel Hill, US

Results from a Single Arm Study of Darunavir/Ritonavir Plus Raltegravir in Treatment-Naïve HIV-1-Infected Patients (ACTG A5262)

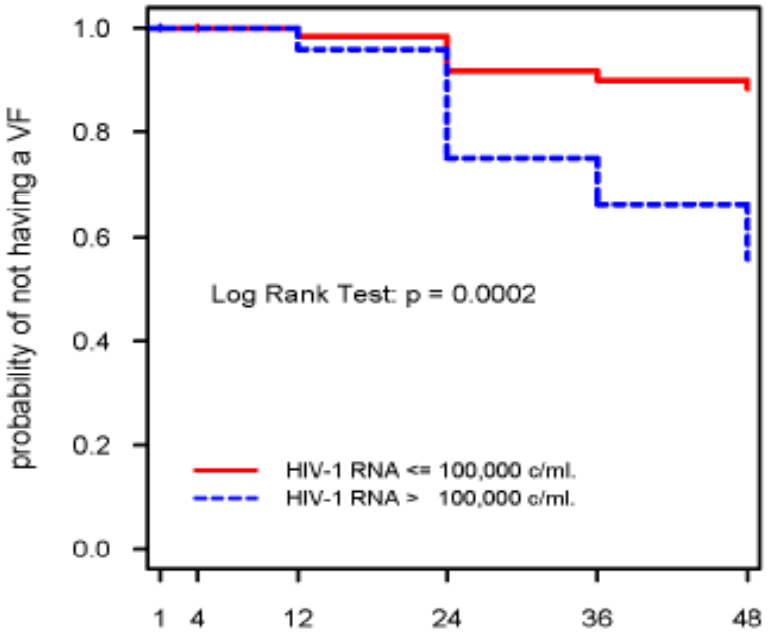
Figure 1: TIME TO VIROLOGIC FAILURE (ITT Approach)

A: Time to Virologic Failure (VF)



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

B: Time to VF by Baseline HIV-1 RNA



HIV-1 RNA <= 100,000 c/ml.:						
n with VF:	0	0	1	4	1	1
n at risk:	63	63	62	59	54	50
HIV-1 RNA > 100,000 c/ml.:						
n with VF:	0	0	2	10	4	5
n at risk:	49	48	48	46	35	31

Inicio de tratamiento
IPr + RAL

- LPVr + RAL (PROGRESS)

  Eficacia en CV altas
  Tox: Perfil lipídico
  Conveniencia

  Coste >3.000/año tri NN 800/año triple IPr

- ATVr + RAL (SPARTAN)

  Resistencia
  Tox: hiperbilirrubinemia
  Conveniencia
  Coste

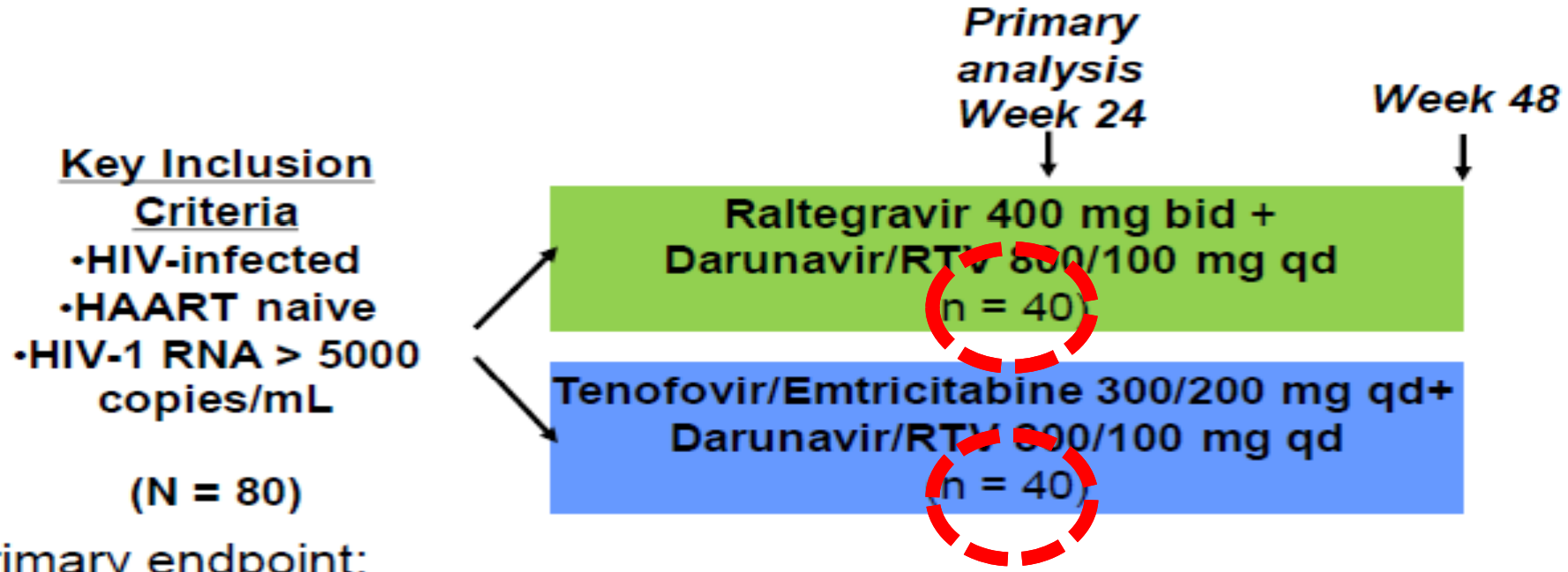
- DRVr + RAL (ACTG5262)

  Eficacia (un solo brazo)(CV altas)
  Conveniencia
  Coste

  (RADAR)

  (ANRS143)

RADAR Study: RAltegravir + DARunavir/Ritonavir has similar safety and antiviral efficacy as Tenofovir/Emtricitabine + Darunavir/Ritonavir in ARV-naive patients



Primary endpoint:

- Proportion of patients with HIV RNA < 50 c/mL at week 24

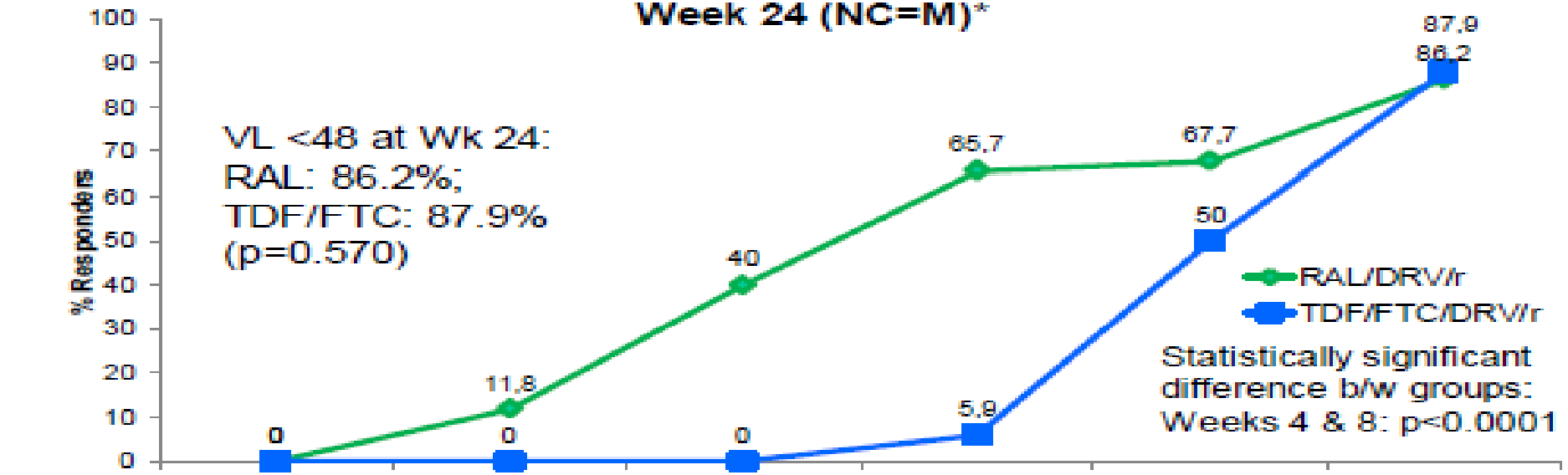
Secondary endpoints:

- Change from baseline in CD4 cell counts at weeks 24 & 48
- Proportion of patients with HIV RNA < 50 c/mL at week 48
- Safety through weeks 24 & 48: Lipid profile, insulin resistance, bone density and body fat changes

Bedimo R, et al. IAS 2011. Abstract MOPE214.

Baseline Characteristics	RAL (n=39)	TDF/FTC (n=40)	Total (n=79)
Median Age (years)	44.5	39.0	41.5
Male/Female	36/4	38/2	74/6
Race (AA/Whites/Hisp.)	18/11/11	20/9/11	38/20/22
Log_{10} HIV RNA (c/mL)	4.62	4.80	4.72
Median CD4 (Cells/mm^3)	297	227	261

Proportion of Patients with HIV RNA<48 c/mL Through Week 24 (NC=M)*



N (obs)	B/L	Wk 2	Wk 4	Wk 8	Wk 16	Wk 24
RAL	39	34	35	35	31	29
TDF/FTC	40	36	37	34	32	33

*Non complete = missing

- VL <400 c/mL at Wk 24: RAL: 93.1%; TDF/FTC: 100% (p=0.215)
- Log_{10} VL Change at Wk 24: RAL: -2.77; TDF/FTC: -3.05 (p=0.17)

Bedimo R, et al. IAS 2011. Abstract MOPE214.

Inicio de tratamiento
IPr + RAL

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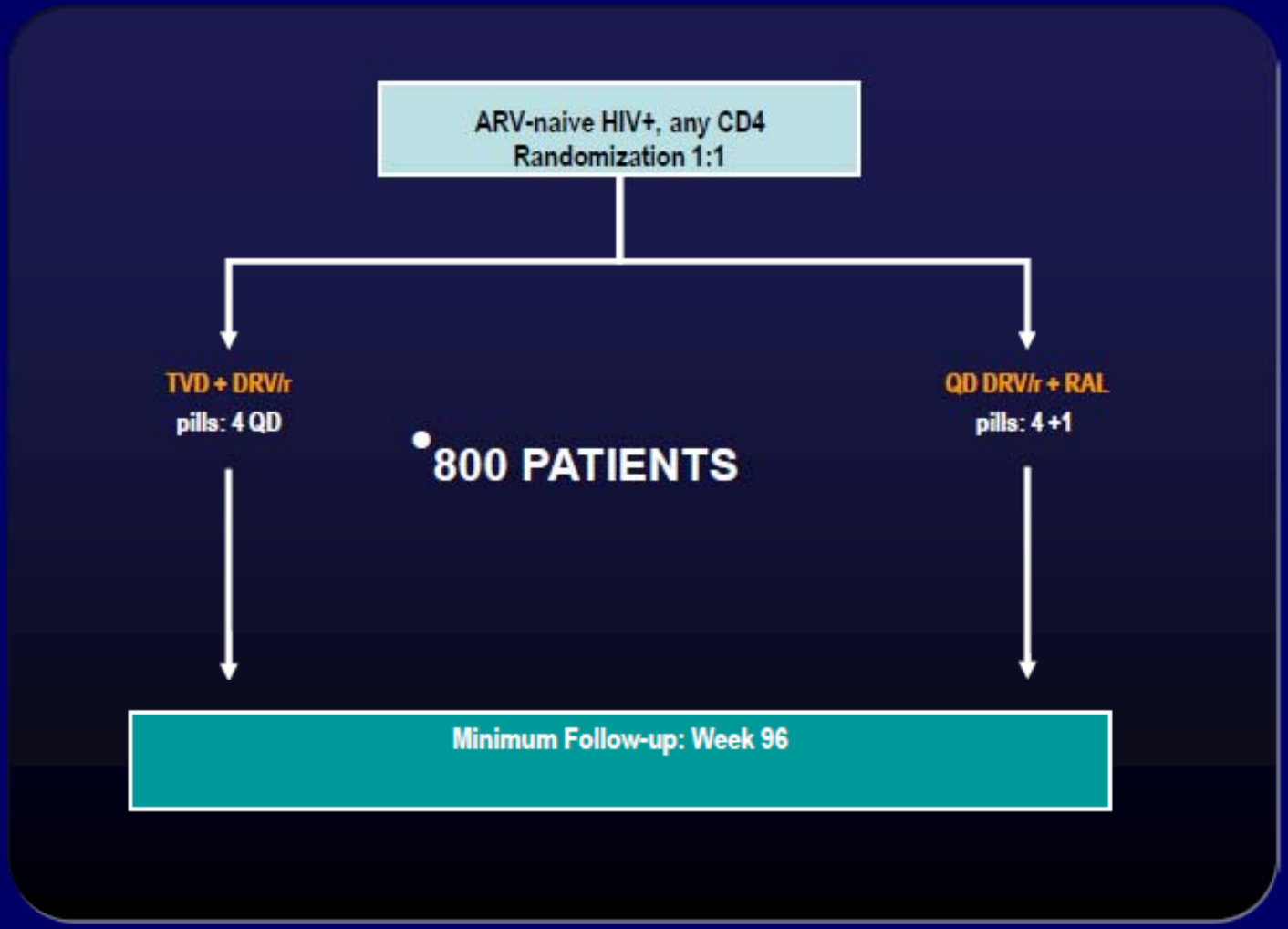
  - Eficacia en CV altas
  - Tox: Perfil lipídico
  - Conveniencia
  - Coste >3.000/año tri NN 800/año triple IPr
- ATVr + RAL (SPARTAN)
  - Resistencia
  - Tox: hiperbilirrubinemia
  - Conveniencia
  - Coste
- DRVr + RAL (ACTG5262)
  - Eficacia (un solo brazo)(CV altas)
  - Conveniencia
  - Coste

(RADAR)
- n=40 por rama
- Conveniencia
- Coste

(ANRS143)

NEAT Protocol 001 / ANRS 143



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  - Coste
- DRVr + RAL (ACTG5262)
  - Eficacia (un solo brazo)(CV altas)
  - Conveniencia
  - Coste
- (RADAR)
  - n=40 por rama
  - Conveniencia
  - Coste
- (ANRS143)
  - Sin datos publicados***

Esquema

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  +MVC
  +3TC

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  Monoterapia IPr
  Biterapias IPr +RAL
  +3TC
  +ETR

- **Conclusiones**

Inicio de tratamiento
IPr + MVC

- LPVr + MVC (VEMAN)
- ATVr + MVC (A4001078)
- DRVr + MVC (A4001095)

IAS 2011

CDB325

Maraviroc 150 mg QD plus lopinavir/ritonavir, a NRTIs-sparing regimen for naïve patients: preliminary 48-weeks results.

S. Nozza[1], L. Galli[1], A. Antinori[2], M. Di Pietro[3], C. Tommasi[2], M. Zaccarelli[2], R. Fezza[2], S. Bonora[4], G. Tambussi[1], A. Lazzarin[1], VEMAN Study Group.

[1]San Raffaele Scientific Institute, Milan, Italy.

[2]IRCCS INMI Spallanzani, Rome, Italy.

[3]S.M. Annunziata, Florence, Italy.

[4]University of Turin, Italy.

IAS 2011

Background

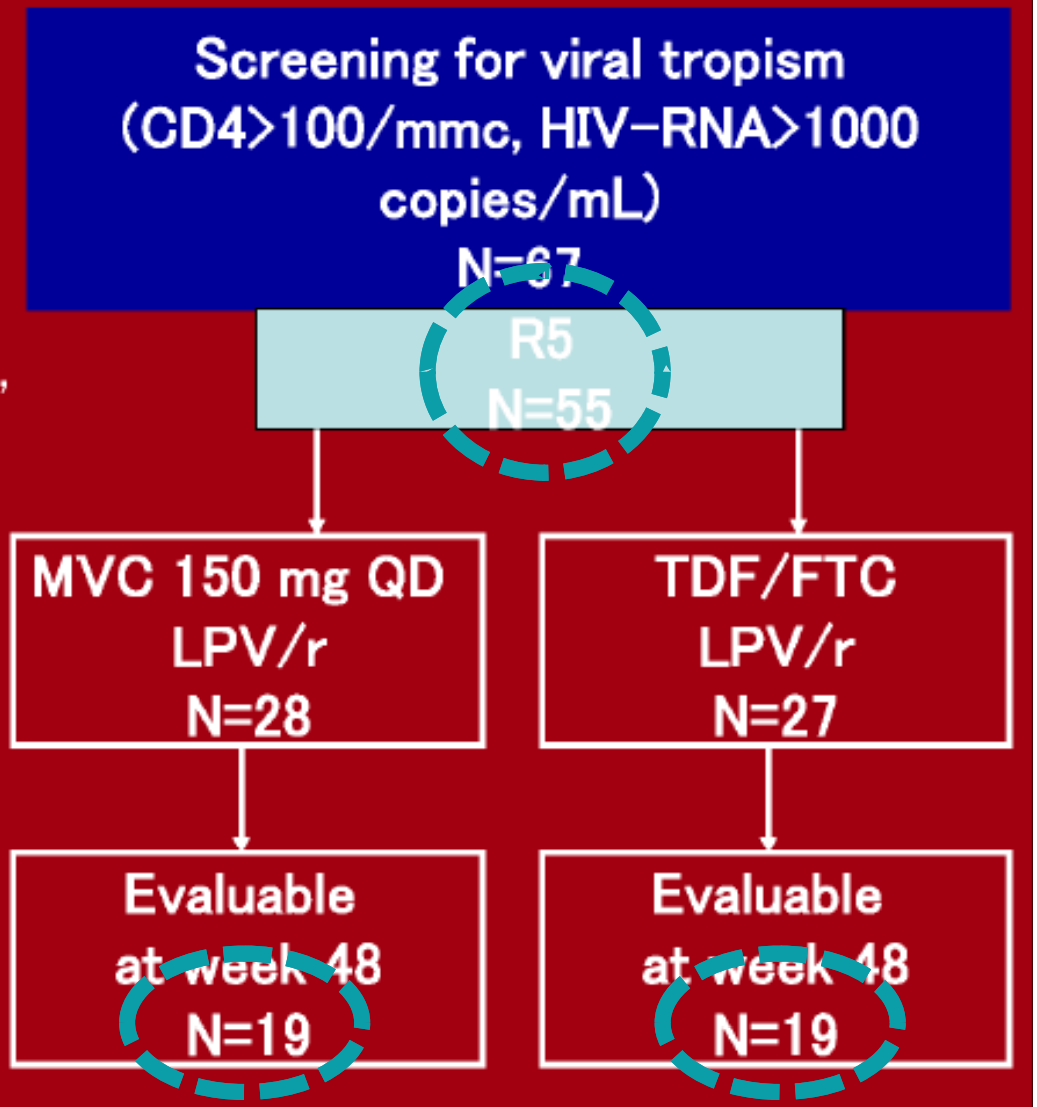
- Some data of novel strategies with antiretroviral naive HIV-infected patients are now available.
- Pharmacokinetic profile of Maraviroc with PI is favourable, so we could administer it at dosage of 150 mg QD.
- Study A4001078 (MVC 150 mg QD plus atazanavir/ritonavir) demonstrated 90% of virological efficacy at week 24.
- The aim of this study was to evaluate 48 weeks efficacy and safety of once daily MVC 150 mg plus LPV/r versus TDF/FTC plus LPV/r.

Nozza S, et al. 6th IAS Conf. CDB325

IAS 2011

Methods

- Multicentric, prospective study.
- Patients were assessed at screening, baseline, week 4, 8, 12, 24, 36 and 48 (or study discontinuation).
- ANOVA for repeated measures (statistical significance of the time and/or therapy group were evaluated according to Greenhouse–Geisser probabilities).



Nozza S, et al. 6th IAS Conf. CDB325

IAS 2011

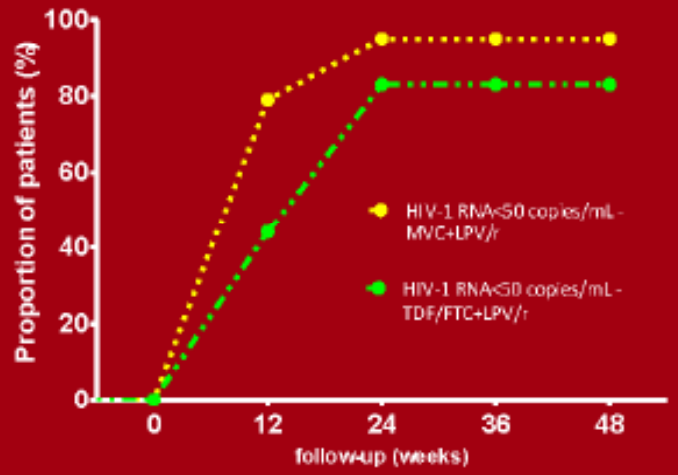
Baseline characteristics

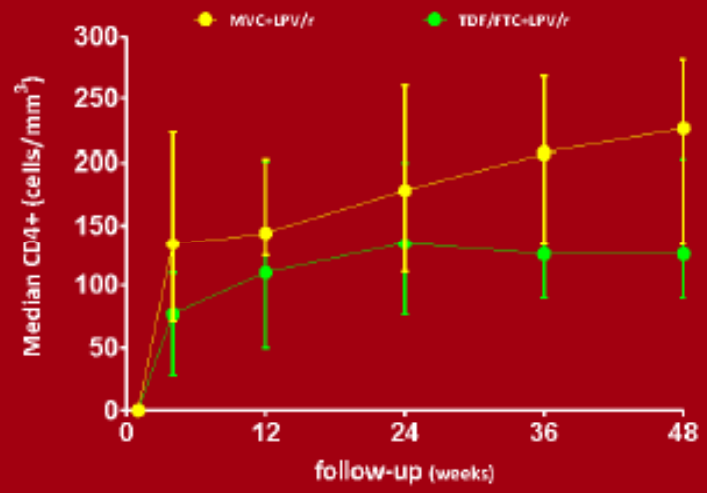
	OVERALL (N=38)	MVC+LPV/r (N= 19)	TDF/FTC+LPV/r (N = 19)	p value
Age (years)	39.5 (33.2–44.0)	38.5 (32.1–44.0)	40.1 (33.2–47.0)	0.793
Male sex	37 (97%)	19 (100%)	18 (95%)	1.000
HIV risk factor				
▪ MSM	31 (82%)	13 (68%)	18 (95%)	0.089
▪ Other	7 (18%)	5 (32%)	1 (5%)	
Duration of HIV-infection (years)	2.7 (1.0–5.3)	2.5 (0.6– 7.2)	3.0 (1.0–4.8)	0.579
CD4 nadir (cells/ mm^3)	271 (248–350)	265 (248–335)	290 (246–380)	0.797
CD4 cell count (cells/ mm^3)	286 (261–376)	273 (250–359)	301 (262–381)	0.456
CD4%	[illegible]	[illegible]	20.5 (14.6–23.8)	0.781
HIV-RNA (log_{10} copies/mL)	4.37 (3.9–4.7)	4.38 (4.1–4.8)	4.09 (3.7 –4.6)	0.231

Nozza S, et al. 6th IAS Conf. CDB325

IAS 2011

Results





- Three patients in TDF/FTC arm interrupted therapy due to dhiarrea.
- Metabolic profile in terms of cholesterol (total, HDL and LDL), trygliceride, glucose and insulin was stable.

Nozza S, et al. 6th IAS Conf. CDB325

IAS 2011

Conclusion

- Virological response with this NRTIs sparing regimen is comparable to conventional therapy.
- Patients in MVC group reached undectable viral load more rapidly: at week 12 83% subjects had HIV-RNA<50 copies/ml
- CD4 recovery with this regimen resulted to be greater than standard therapy, with an increase of 226 cells/mm^3.
- MVC+LPV/r and TDF/FTC+LPV/r were well tollerated with a stable metabolic profile.
- Longer follow up and more patients are needed to evaluate long term efficacy and toxicity.

Nozza S, et al. 6th IAS Conf. CDB325

Inicio de tratamiento
IPr + MVC

- LPVr + MVC (VEMAN)

N aprox.= 20 por rama

Eficacia CV altas?

Conveniencia

Coste >1.500/año vs triple NN, < 600 vs triple IPr

- ATVr + MVC (A4001078)

- DRVr + MVC (A4001095)

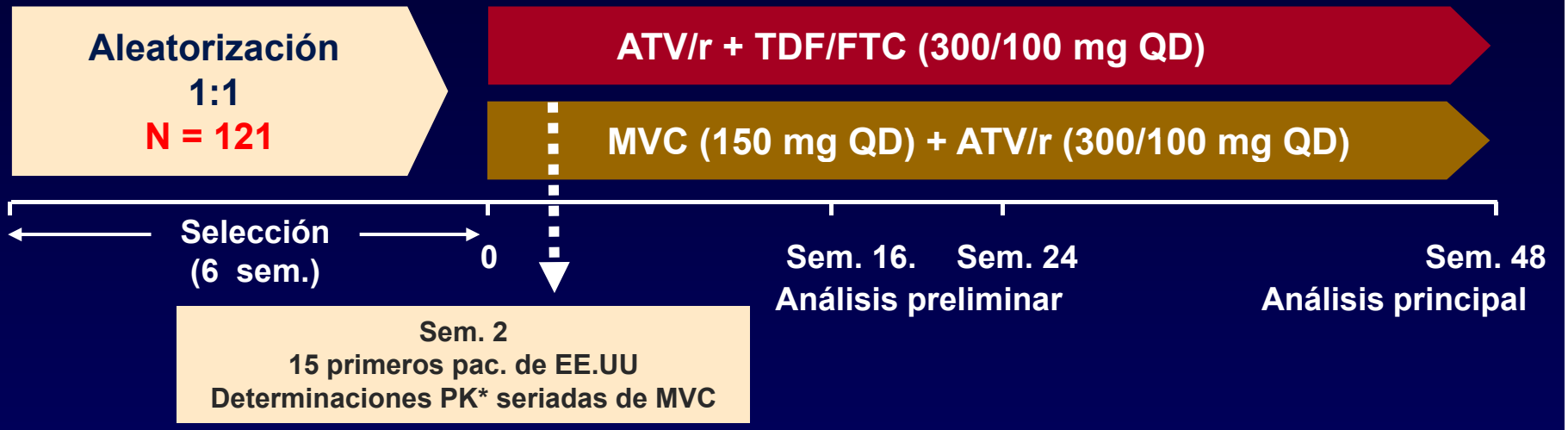
MVC QD + ATV/r frente a ATV/r +TDF/FTC – Diseño del estudio A4001078

IAS 2011

Mills A, et al

Presentación TUAB0103

- Estudio piloto de fase IIb y diseño abierto de 48 semanas



- **Criterios de elegibilidad de los pacientes**
  - VIH R5 (ESTA) en la selección
  - Edad ≥ 16 años
  - ARN-VIH-1 ≥ 1000 copias/mL
  - CD4 ≥ 100 células/mm^3
  - Sin evidencias de resistencia a ATV/r, TDF o FTC

- Comité interno de monitorización
- Estudio en curso: EE.UU., España y Alemania
- Ampliación a 96 semanas
- Sin potencia para mostrar una diferencia del tratamiento y no se realizarán valoraciones estadísticas formales

*Extracción de muestras para determinaciones PK en todos los pacientes en la sem. 2 (subestudio no PK), 12 y 24 (Vourvahis. Abstract 37 IWCPHIV, 2010)

MVC QD + ATV/r frente a ATV/r + TDF/FTC - Características basales

IAS 2011

Mills A, et al

Presentación TUAB0103

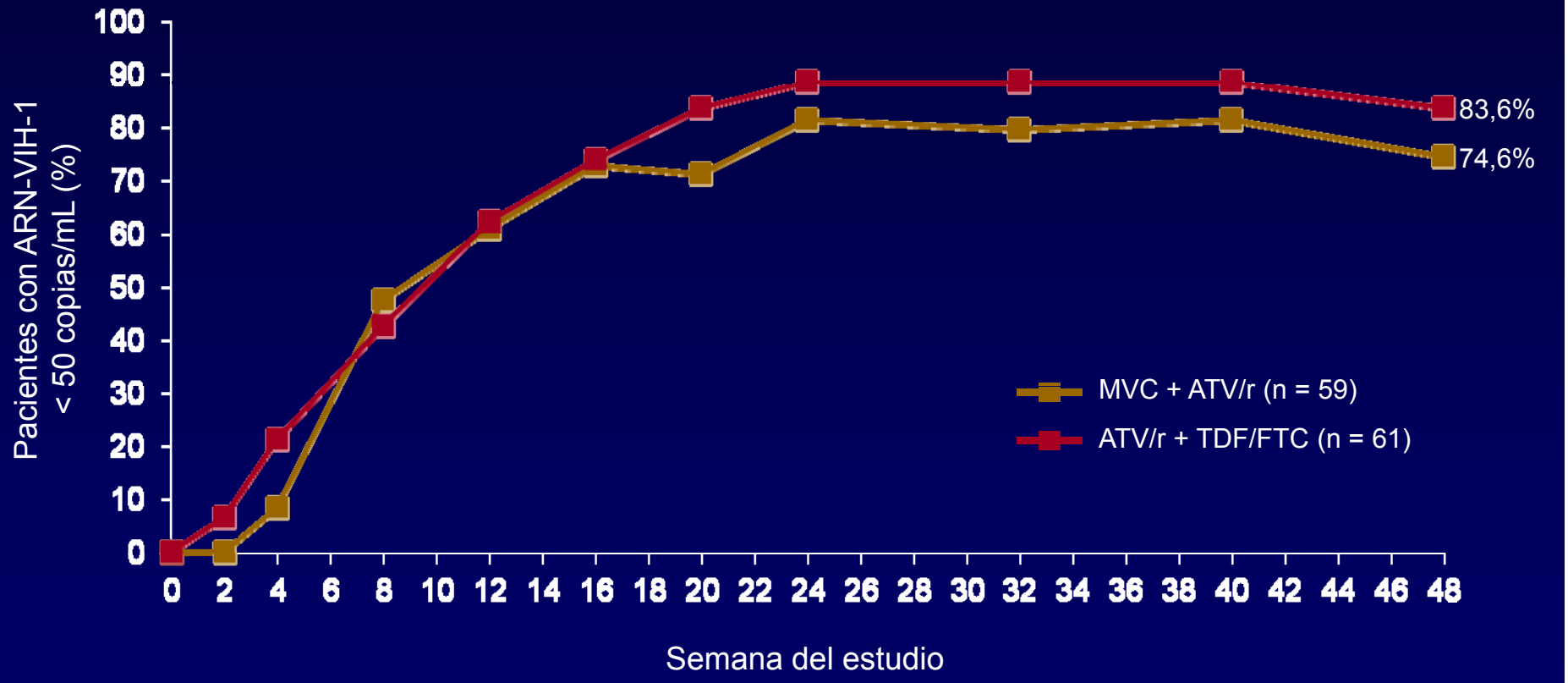
	MVC + ATV/r n = 60	FTC/TDF + ATV/r n = 61
Media de edad, años (rango)	38,3 (21–61)	35,3 (18–68)
Hombres, n (%)	56 (93,3)	52 (85,2)
Etnia, n (%)		
Blanca	45 (75,0)	46 (75,4)
Negra	13 (21,7)	11 (18,0)
Asiática	0	3 (4,9)
Otra	2 (3,3)	1 (1,6)
Mediana del recuento $CD4^+$, células/mm^3 (rango)	344 (160–744)	358 (110–902)
Niveles medios ARN-VIH-1, log_{10} copias/mL (rango)	4,6 (3,4–5,9)	4.7 (3,3–5,9)
ARN-VIH-1 ≥ 100.000 copias/mL, n (%)	16 (27)	22 (36)

MVC QD + ATV/r frente a ATV/r + TDF/FTC - ARN-VIH-1 < 50 copias/mL en la semana 48

IAS 2011

Mills A, et al

Presentación TUAB0103



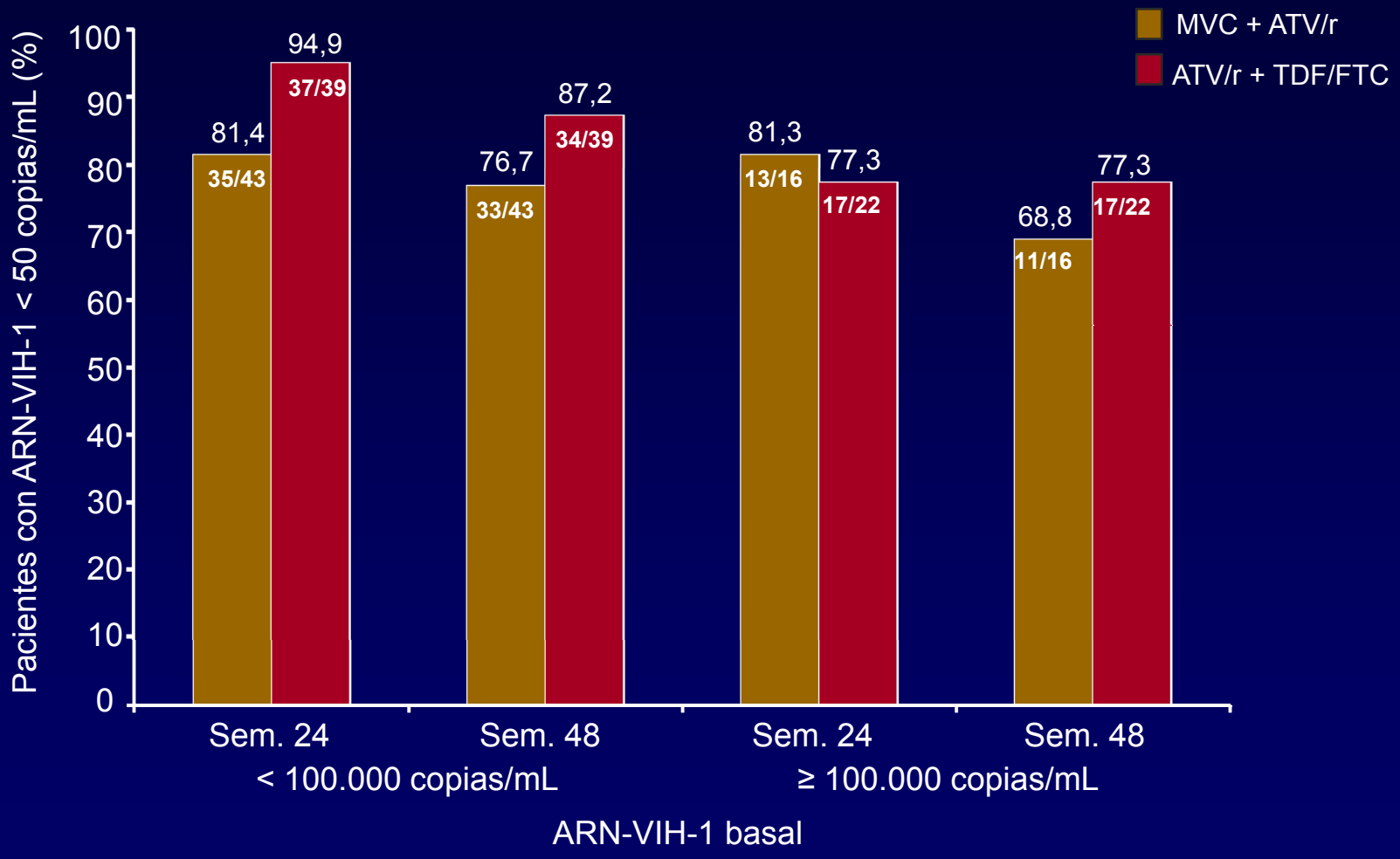
Intención de tratar. Datos perdidos = fracaso

MVC QD + ATV/r frente a ATV/r + TDF/FTC - ARN-VIH-1 < 50 copias/mL según la carga viral

IAS 2011

Mills A, et al

Presentación TUAB0103



Intención de tratar. Datos perdidos = fracaso

Inicio de tratamiento
IPr + MVC

- LPVr + MVC (VEMAN)

  N aprox.= 20 por rama

  Eficacia CV altas?

  Conveniencia

  Coste >1.500/año vs triple NN, < 600 vs triple IPr

- ATVr + MVC (A4001078)

  N=60 sin pot. estadística

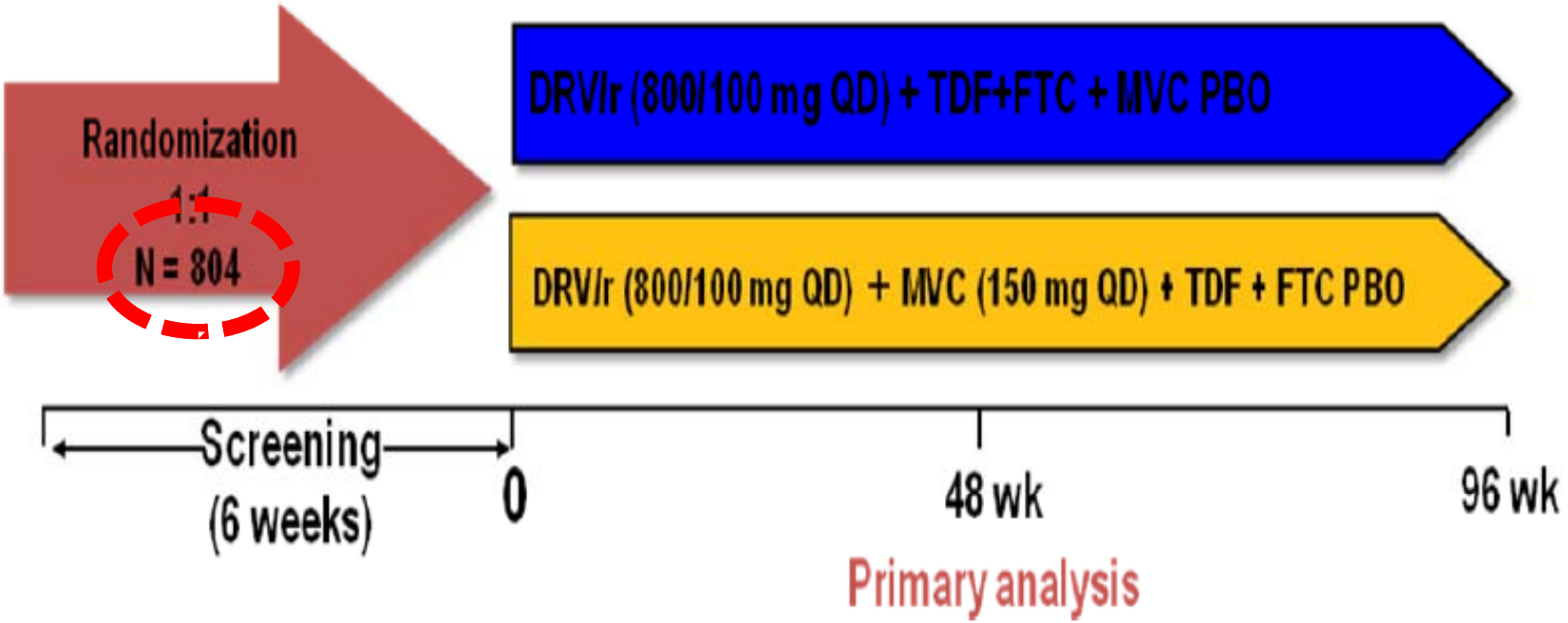
  Conveniencia

  Coste

- DRVr + MVC (A4001095)

Estudio1095 para la autorización de Maraviroc QD con IPs potenciados en pacientes naïves

Estudio multicéntrico, aleatorizado, doble ciego, comparativo entre Maraviroc + Darunavir/ritonavir vs. Tenofovir/Emtricitabina + Darunavir/ritonavir en el tratamiento de pacientes naïve VIH-1 con tropismo CCR5



La previsión del inicio del estudio es para Septiembre 2011

Inicio de tratamiento
IPr + MVC

- LPVr + MVC (VEMAN)

  N aprox.= 20 por rama

  Eficacia CV altas?

  Conveniencia

  Coste >1.500/año vs triple NN, < 600 vs triple IPr

- ATVr + MVC (A4001078)

  N=60 sin pot. estadística

  Conveniencia

  Coste

- DRVr + MVC (A4001095)

  Sin datos publicados***

Esquema

- **Introducción (necesidad)**

- **Pacientes naïve (Inicio de tratamiento)**

  Biterapias IPr +RAL
  +MVC
  +3TC

- **Pacientes pretratados**

  Monoterapia IPr
  Biterapias IPr +RAL
  +3TC
  +ETR

- **Conclusiones**

Investigational Plan. Gardel Study

NAÏVE

Screening Visit

LOPINAVIR/RITONAVIR AND 3TC
(n=205)

→ Week 48

Pendiente resultados...

Coste <2300 vs triple NN < 4000 vs triple IPr

Screening
(≤ 30 days)

STANDARD THERAPY
3TC or FTC + LPV/r + NRTI
(n=205)

→ Week 48

Esquema

- Introducción (necesidad)
- Pacientes naïve (Inicio de tratamiento)

  Biterapias IPr +RAL
  +MVC
  +3TC

- **Pacientes pretratados**

  Biterapias IPr +RAL
  +3TC
  +ETR

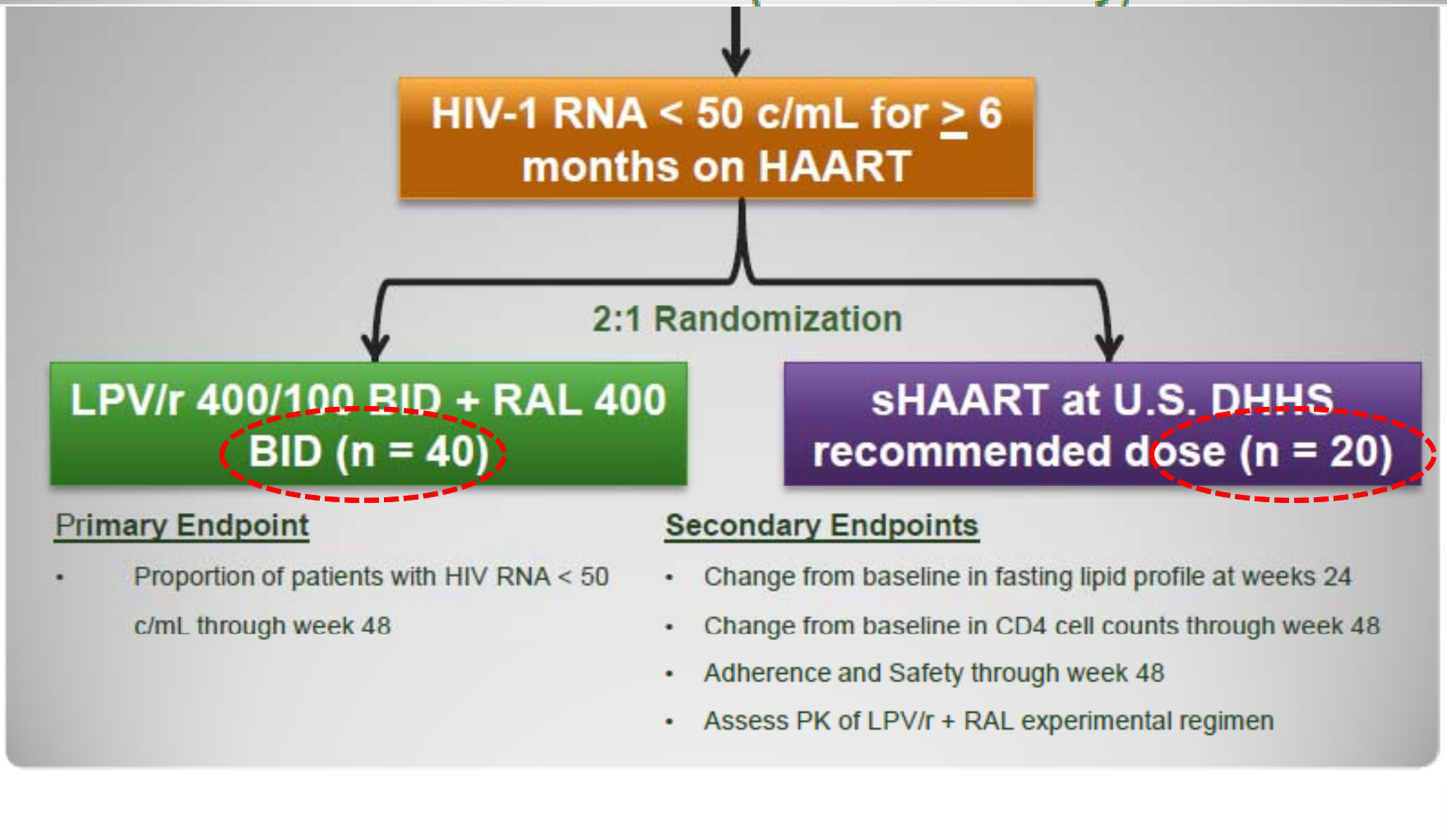
  Monoterapia IPr

- Conclusiones

Pacientes pretratados suprimidos
IPr + RAL

- LPVr + RAL (KITE)
- ATVr + RAL (BATAR)
- DRVr + RAL (SPARE)

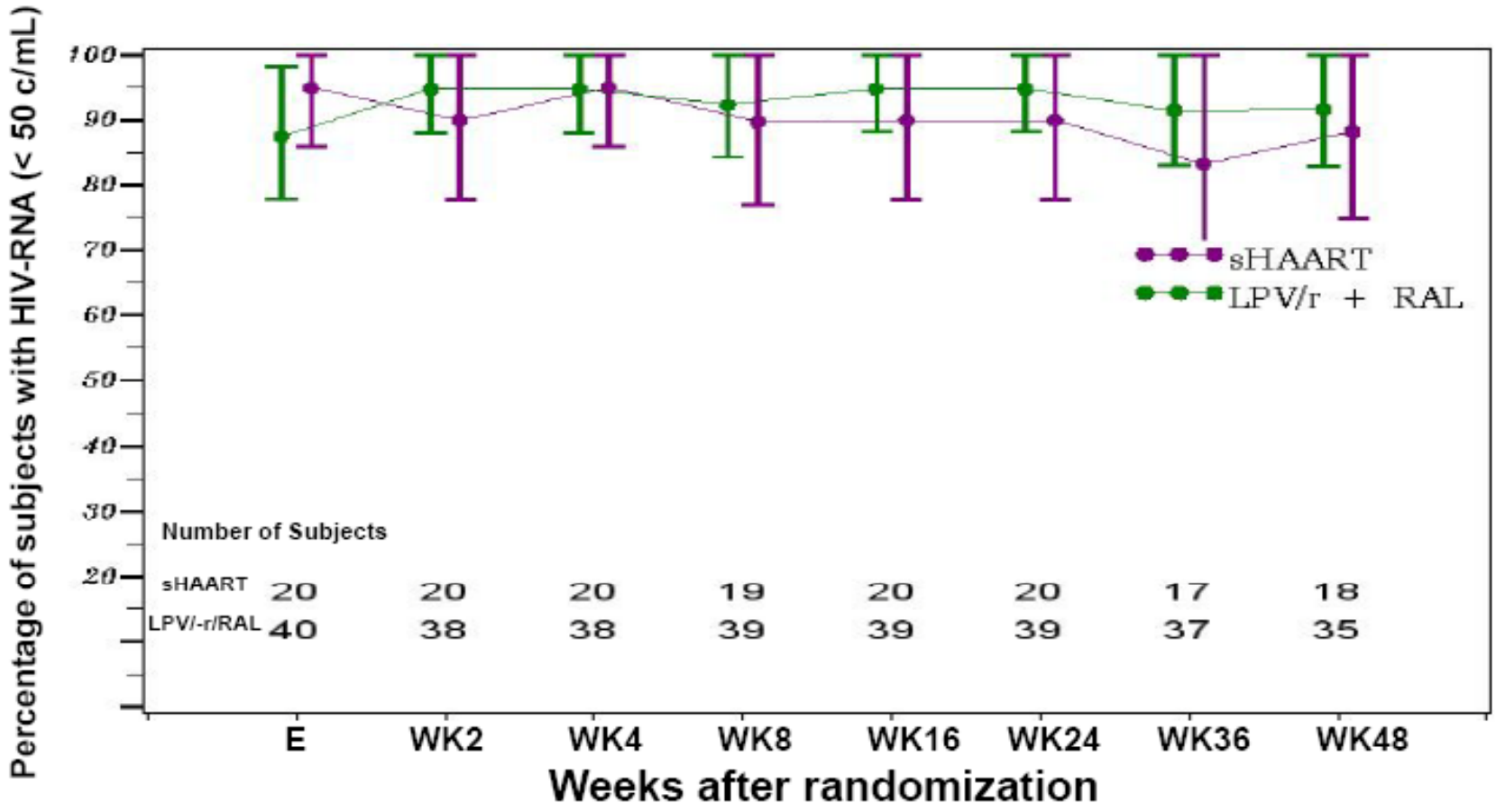
Switching Antiretroviral Therapy to a Reverse Transcriptase Inhibitor Sparing Combination of Lopinavir/Ritonavir and Raltegravir in Virologically Suppressed HIV-infected Patients is Safe and Well Tolerated (The KITE Study)



Ofotokun[1,2], A.N. Sheth[1], K.A. Easley[2,3], N. Shenvi[3], M. Rivas[1], K. White[4], M. Eaton[1,2], C. Del Rio[1,2,5], J.L. Lennox[1,2]

Emory CFAR

Virologic Response Rate (HIV RNA < 50 c/mL) Through Week 48



At 48 week, 92% (95% CI: 83% - 100%) of LPV-r/RAL arm and 88% (95% CI: 75% - 100%) of sHAART-arm had HIV-RNA < 50 c/mL (p = 0.70).

Ofotokun[1,2], A.N. Sheth[1], K.A. Easley[2,3], N. Shenvi[3], M. Rivas[1], K. White[4], M. Eaton[1,2], C. Del Rio[1,2,5], J.L. Lennox[1,2]

Emory CFAR

Summary Statistics For Secondary Outcomes by Treatment Group Adjusting for Baseline Characteristics using Analysis of Covariance

‡Outcomes	Treatment	n	Adjusted Mean ± SEM*	Difference Between Means (95% CI)	p†
Total Cholesterol (mg/dl)	• LPV-r/RAL	35	194 ± 4	-22 (-37,-7)	0.004
	• sHAART	19	172 ± 6		
Triglycerides (mg/dl)	• LPV-r/RAL	35	238 ± 20	-105 (-173,-37)	0.003
	• sHAART	19	133 ± 27		
HDL cholesterol (mg/dl)	• LPV-r/RAL	35	51 ± 3	- 4 (-13,6)	0.45
	• sHAART	19	47 ± 4		
LDL cholesterol (mg/dl)	• LPV-r/RAL	35	121 ± 6	-13 (-32,6)	0.17
	• sHAART	19	108± 8		
Creatinine clearance (ml/min)	• LPV-r/RAL	33	106 ± 4	10 (-5,24)	0.18
	• sHAART	18	116 ± 6		
CD4 T-cell counts (cells/µl)	• LPV-r/RAL	35	535 ± 23	39 (-43,120)	0.35
	• sHAART	17	574 ± 33		

- Changes in plasma total cholesterol and triglyceride were statistically significantly higher in the LPV-r/RAL.
- Incidence of lipid lowering agent use at week 48 was not different between study arms.

Ofotokun[1,2], A.N. Sheth[1], K.A. Easley[2,3], N. Shenvi[3], M. Rivas[1], K. White[4], M. Eaton[1,2], C. Del Rio[1,2,5], J.L. Lennox[1,2]

Pacientes pretratados suprimidos
IPr + RAL

- LPVr + RAL (KITE)

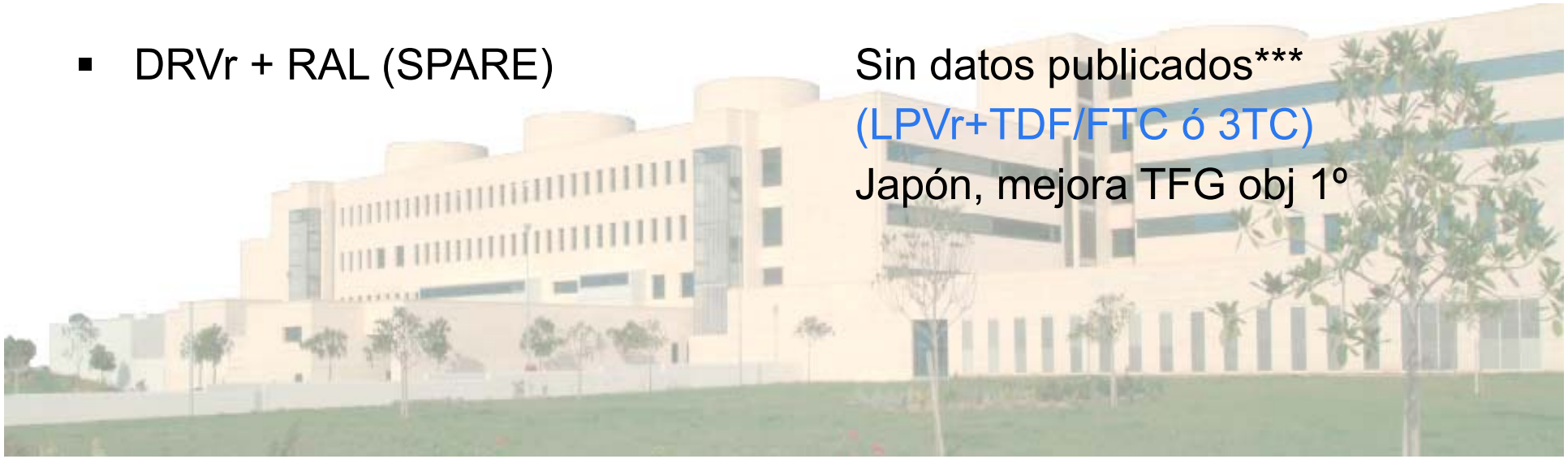
  n pacientes
  Tox: perfil lipídico
  Conveniencia (BID, 6p)
  Coste >3.000/año tri NN >800/año triple IPr

- ATVr (ATV) + RAL (BATAR)

  Sin datos publicados***
  (ATVr+TDF/FTC)

- DRVr + RAL (SPARE)

  Sin datos publicados***
  (LPVr+TDF/FTC ó 3TC)
  Japón, mejora TFG obj 1º



Pacientes pretratados suprimidos
IPr + 3TC

- LPVr + 3TC (OLÉ) — Sin resultados publicados***
- ATVr + 3TC (ATLAS)

(SALT)

ATLAS: Study Design

- **Pilot study (40 patients)**
  - Prospective, **single-arm**, single center, 48 weeks
  - Safety and tolerability
  - Maximum allowed failure rate (VL > 50 copies/mL): 12.5%
  - Enrollment June 2009–May 2010

Inclusion Criteria	Exclusion Criteria
• Patients on ATV/r + 2NRTI for ≥ 3 months • HIV-RNA < 50 copies/mL for ≥ 3 months • CD4 > 200 cells/mm^3 for ≥ 6 months	• Previous VF of 3TC or PI-containing regimen or exposure to mono-dual NRTI • VF with other regimens but a GRT with any RAM to 3TC or ATV • Proton pump inhibitors co-administration • HBs Ag positive • Pregnancy

- At baseline simplification to ATV/r 300/100 mg QD + 3TC 300 mg QD
- Follow-up visits at 4, 12, 24, 36 and 48 weeks
- At each visit: chemistry, CD4 and HIV-RNA, TDM, self-reported adherence (VAS)
- At baseline and 48 weeks: self-reported symptoms, QoL, neurocognitive assessment, bone density (DXA), fat distribution (DXA, liposound), carotid IMT and endothelial function (brachial FMD)

ATLAS Week 48: Efficacy

- 38 patients reached week 48
- Median CD4 change was +33 cells/µl

	n (%)
Treatment failures	5 (13.2)
Death (brain haemorrhage)	1 (2.6)
Re-inductions with 2NRTI (1 pregnancy and 1 inadequate ATV concentration)	2 (5.3)
VF (both without resistance mutations, undetectable plasma ATV, both successfully reinduced)	2 (5.3)

Eficacia 86,8%

- Six severe adverse events were recorded (4 renal colic, 1 hypertensive crisis, 1 brain haemorrhage)
- Adherence was stable (mean 83.7% at baseline; 82.9% at 48 wks; $p = 0.85$)
- Significant improvements were observed in total physical ($p = 0.002$) and mental health scores ($p < 0.001$) but not self-reported symptom score ($p = 0.34$)
- No change in neurocognitive performance was observed

Pacientes pretratados suprimidos
IPr + 3TC

- LPVr + 3TC (OLÉ) — Sin resultados publicados***
- ATVr + 3TC (ATLAS) — n=40, Un solo brazo
  Eficacia 86,8%?
  Coste <2300 vs triple NN < 4000 vs triple IPr

(SALT)

ATV/r + 3TC en pretratados

Simplification to Atazanavir/Ritonavir + Lamivudine as Maintenance Therapy (SALT)

This study is currently recruiting participants

Verified by Fundacion SEIMC-GESIDA, March 2011

First Received: March 1, 2011 Last Updated: March 2, 2011 History of Changes

Sponsor:	Fundacion SEIMC-GESIDA
Collaborator:	Bristol-Myers Squibb
Information provided by:	Fundacion SEIMC-GESIDA
ClinicalTrials.gov Identifier:	NCT01307488

ATV/r + 3TC en pretratados

Purpose

A switch to a regimen consisting of ATV/RTV 300/100 mg QD + 3TC 300 mg QD in **HIV**-1 infected subjects in their first antiretroviral regimen and who are virologically suppressed on a regimen which consists of 2 NRTIs + any 3rd agent, is non-inferior to continue or switch to ATV/RTV 300/100 mg QD + 2 optimized NRTIs for maintenance of virological suppression.

Condition	Intervention	Phase
HIV Infection	Drug: Ritonavir boosted Atazanavir + Lamivudine Drug: Ritonavir boosted Atazanavir + 2 NRTIs	Phase IV

Study Type: Interventional

Study Design: Allocation: Randomized
Control: Active Control
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Estimated Enrollment: 325

Pacientes pretratados suprimidos
IPr + 3TC

- LPVr + 3TC (OLÉ) — Pendiente resultados***
- ATVr + 3TC (ATLAS) — n=40, Un solo brazo
  Eficacia 86,8%?
  Coste <2300 vs triple NN < 4000 vs triple IPr
- (SALT) — Pendiente resultados***

Pacientes pretratados suprimidos
IPr + ETR

- DRVr + ETR (INROADS)

Pendiente resultados***

Coste >2.000/año vs triple NN =vs triple IPr

INROADS, Abbreviated Title: Intelence aNd PRezista Once A Day Study

This study is currently recruiting participants.

Verified by Tibotec, Inc, October 2010

First Received: September 9, 2010 Last Updated: October 21, 2010 History of Changes

Sponsor:	Tibotec, Inc
Collaborator:	Tibotec Therapeutics Clinical Affairs, a Division of Centocor Ortho Biotech Clinical Affairs, LLC
Information provided by:	Tibotec, Inc
ClinicalTrials.gov Identifier:	NCT01199939

Fase II, un solo brazo, abierto, multicéntrico

United States
Puerto Rico

Objetivo : Eficacia del tº **etravirina (ETR) 400mg y DRV/r 800/100mg QD** medida como porcentaje de pacientes con una **CV<50 copias/mL a las 48 semanas, en pacientes en primeras líneas de tratamiento.**

n	50
Fecha estimada de comienzo de tº:	May 2010
Fecha estimada de finalización:	January 2012 (julio 2012)

http://www.clinicaltrials.org

Esquema

- **Introducción (necesidad)**
- **Pacientes naïve (Inicio de tratamiento)**

  Biterapias IPr +RAL

  +MVC

  +3TC

- **Pacientes pretratados**

  Biterapias IPr +RAL

  +3TC

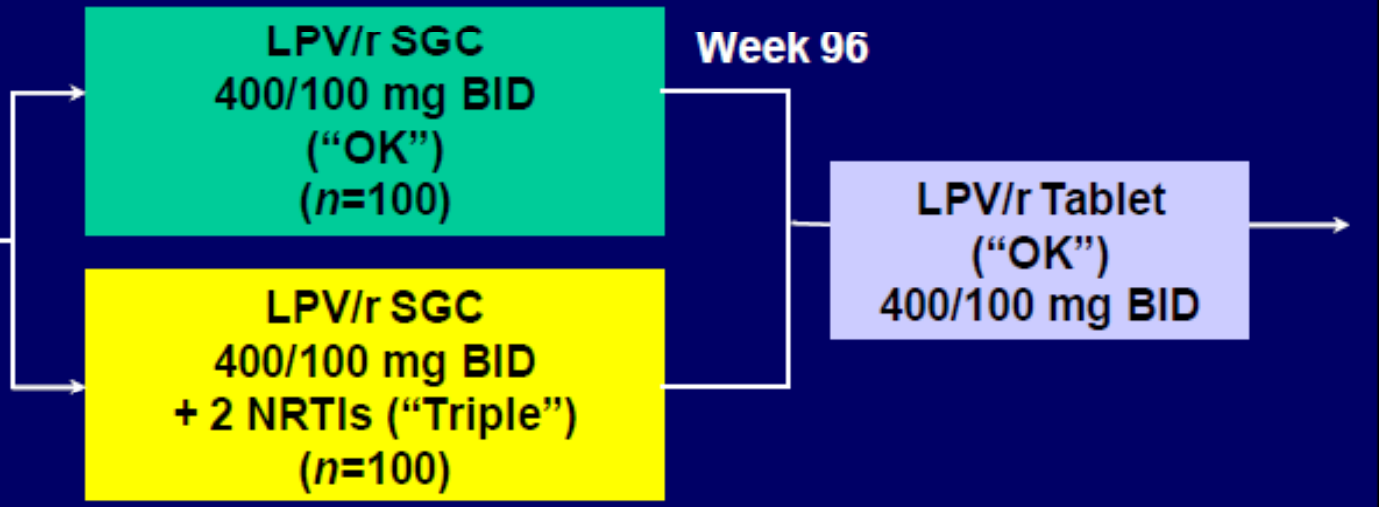
  +ETR

  Monoterapia IPr

- **Conclusiones**

LPV/r Monotherapy
OK04 trial design

- HIV-1 RNA < 50 c/mL for > 6 months
- No history of virological failure while taking a PI
- Receiving LPV/r for + 2 NRTIs > 1 month



Visits: Screening, Baseline, Week 4 and 12, then every 12 weeks up to Week 96

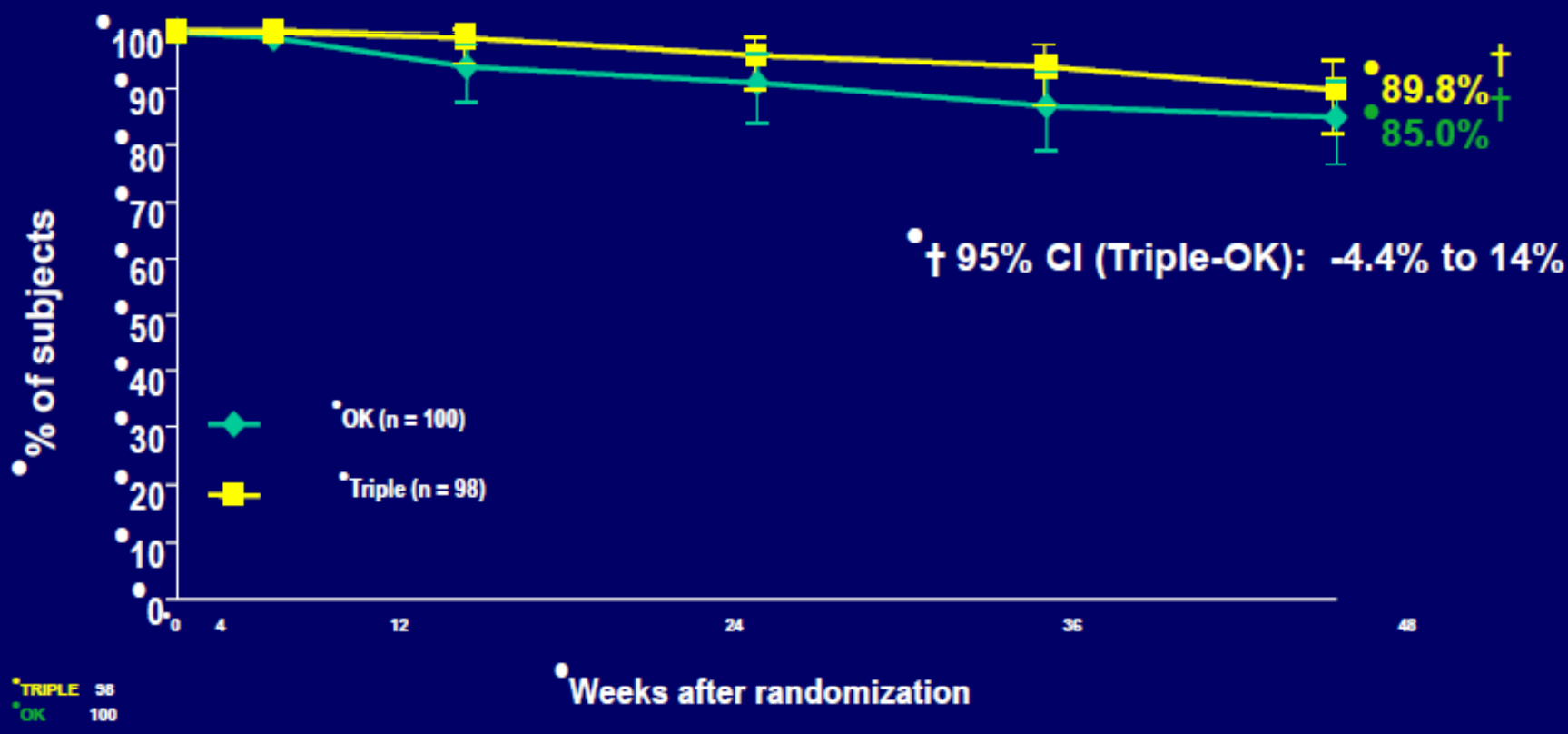
Primary endpoint: Therapeutic failure at 48 weeks

- **2 viral loads > 500 c/mL 2 weeks apart* (without virological re-suppression after reinduction with NRTI in the OK arm)** OR
- Change of randomized therapy for reasons different from re-induction OR
- Treatment discontinuation OR
- Lost to follow-up

* OR decrease in HIV-1 RNA < 1 log 4 weeks after intensification OR failure to reach HIV-1 RNA < 50 c/mL 16 weeks after intensification

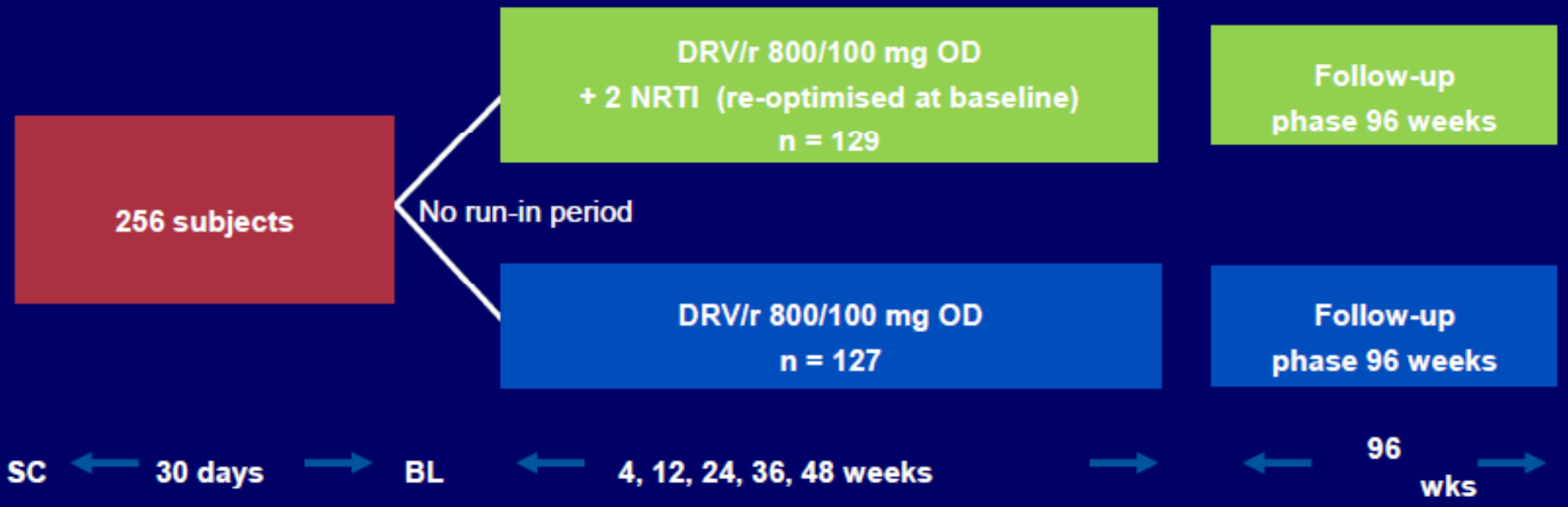
HIV-1 RNA < 50 copies/mL

(ITT M = F, Reinduction = F)*



*For this analysis, patients with confirmed virological rebound (> 50 c/mL) are considered as failures without taking in account whether viral load become resuppressed after resuming baseline nucleosides

DRV/r Monotherapy
MONET - Trial Design



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)

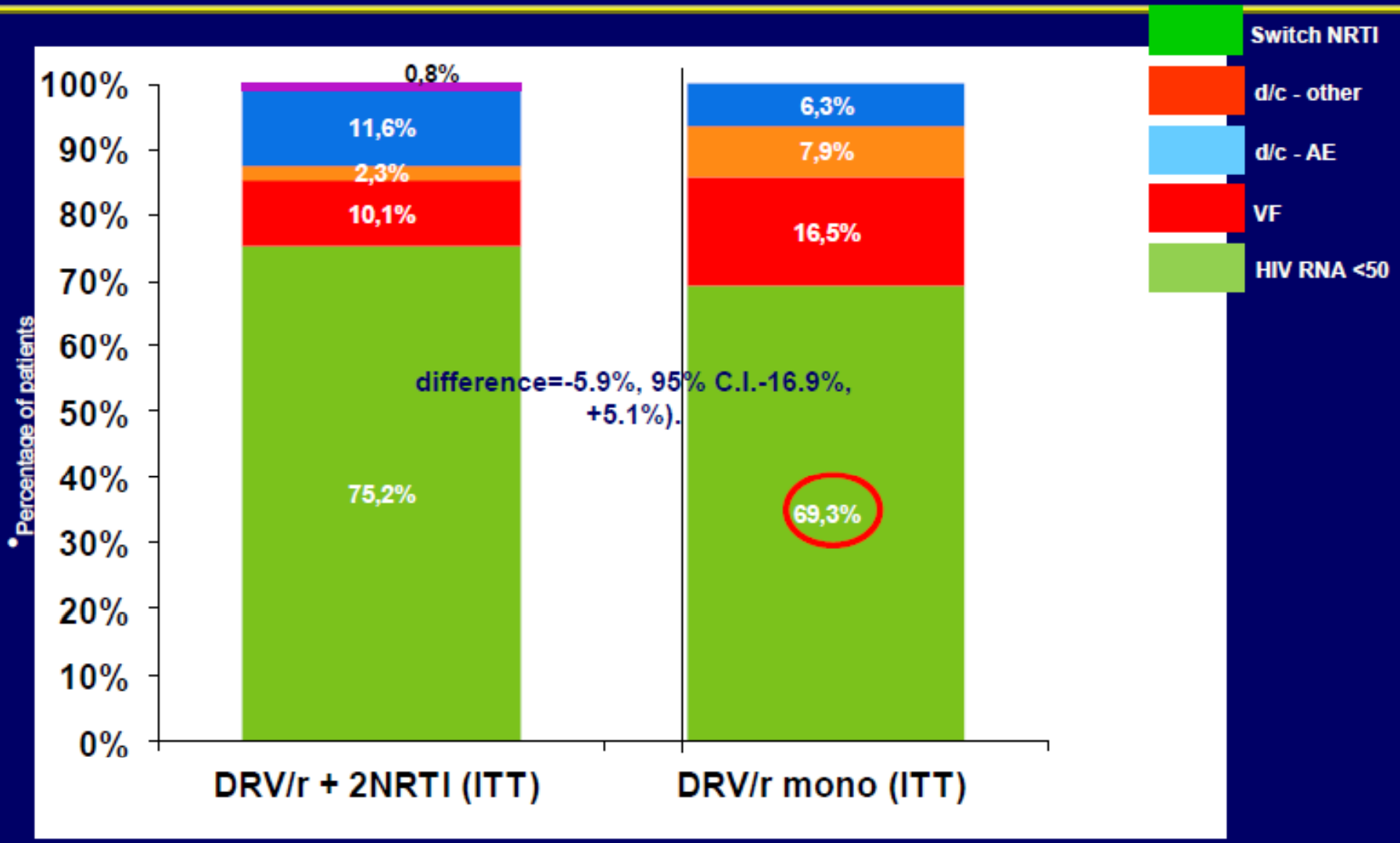
Stopping DRV/r

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, TUA8106-LB

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



Methods

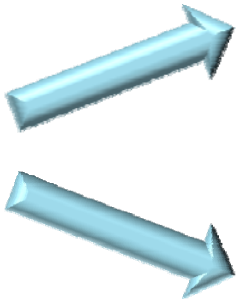
Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in the long term management of HIV infection

- multicentre study across UK
- over 40 sites
- open label, randomised study

Study ongoing; fully recruited as of Autumn 2010
Total number recruited 587

Eligible subjects:

- **Receiving combination ART for at least 24 weeks with a regimen comprising 2 NRTIs and either an NNRTI or a PI**
- **Plasma VL <50 copies/mL at screening and for at least 24 *weeks* prior to screening**
- **CD4+ count >100 cells/uL at screening.**



Protease inhibitor monotherapy

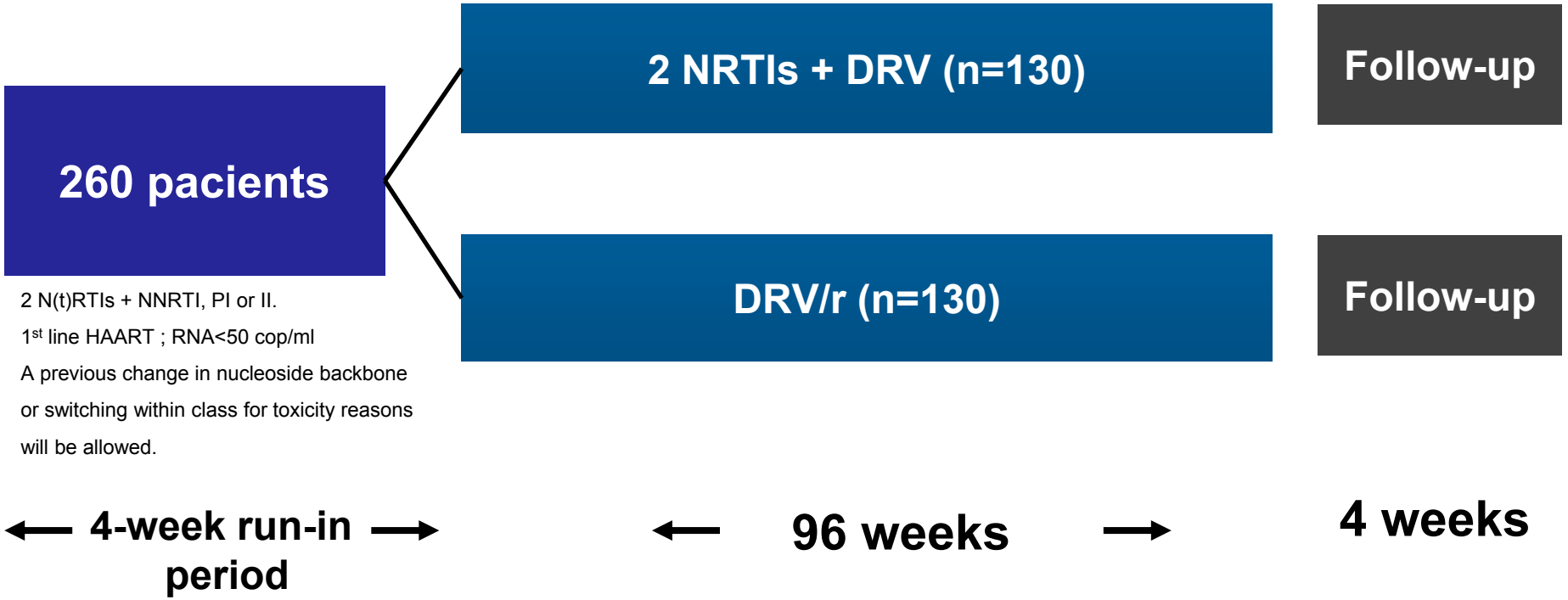
Ongoing triple therapy

Primary Outcome Measures:

- Loss of future drug options [Time Frame: Up to 5 years] [Designated as safety issue: No]

  The first occurrence of intermediate to high level resistance to any one or more of the standard antiretroviral drugs (limited to licensed drugs in contemporary use) to which the patient's virus was considered to be sensitive at trial entry (i.e. excluding drug resistance that was known to be present on previous resistance testing).

PROTEA



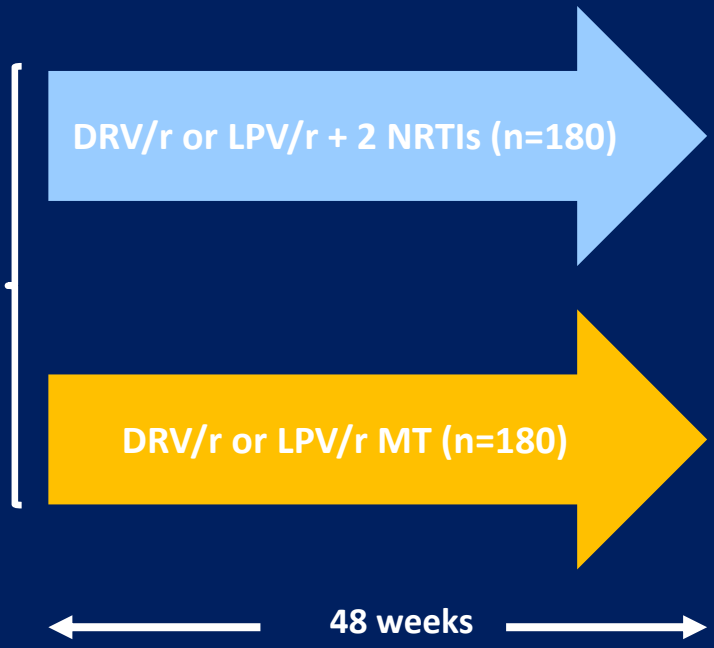
Primary endpoint: The primary objective is to demonstrate non-inferiority in terms of the percentage of subjects RNA<50 copies/mL after 48 weeks of follow-up after switching to DRV/r monotherapy vs triple therapy containing DRV/r (FDA Snapshot method).

Secondary endpoints: To evaluate the correlation of plasma HIV-1 RNA, **cerebrospinal fluid (CSF) HIV-1 RNA, and neurocognitive function** of DRV/r monotherapy vs triple therapy containing DRV/r at Week 48. To evaluate and compare change in neurocognitive function of DRV/r monotherapy vs triple therapy containing DRV/r over 48 and 96 weeks.

Picasso study

Inclusion criteria:

- Stable HAART (1yr)
  - 2 NRTIs + PI*
  - PI* MT
- HIV RNA < 50 (1yr)
- Pts. w. cofounders excl**.



End points (MT vs. TT):

- Prevalence of HAND
- Evolution of NP
- % Viral escape
- Risk factors for HAND (MT)
- Neurological markers
- Neuro-image (MRI)

Basal and follow up visit procedures:

- Clinical evaluation, neurocognitive testing (NPZ-7), blood
- LP & MRI (only patients with neurocognitive impairment)
- NP evaluators are blind for HAART regimen

* DRV/r or LPV/r

** (neurological or psychiatric illness, drug or alcohol abuse, unable to be tested)

Documento de consenso de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana
(Actualización enero 2012)

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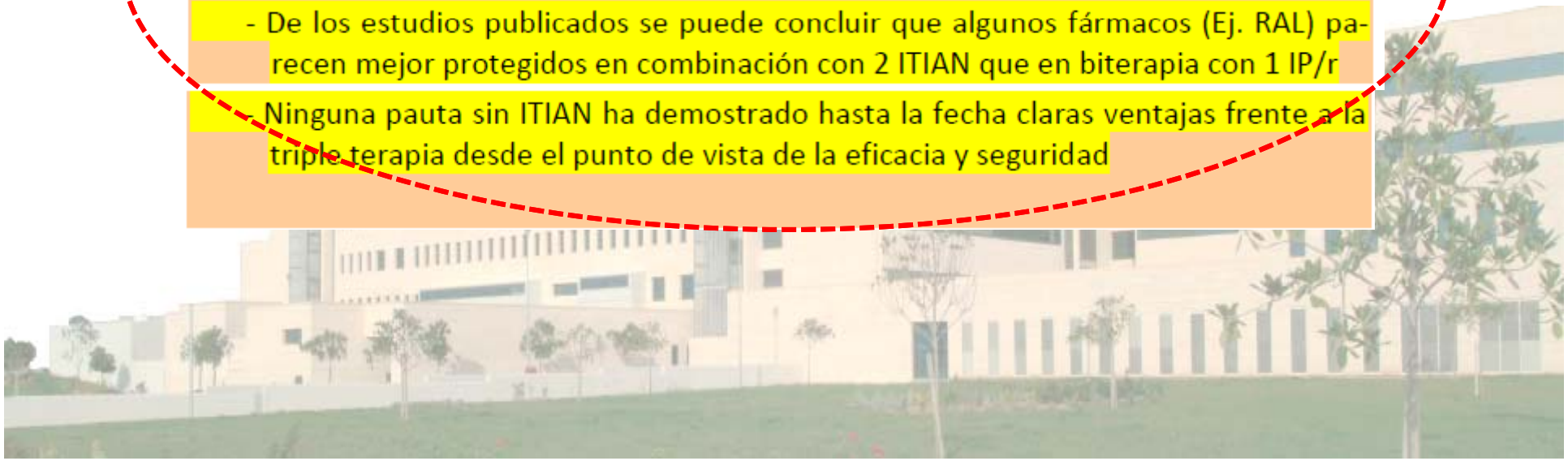
4.8. Pautas libres de análogos de nucleósidos

Recomendaciones

- La monoterapia con un IP/r no se recomienda como primer tratamiento
- No se deben usar pautas libres de ITIAN para el TAR de inicio **(A-III)**. Esta recomendación se base en los siguientes puntos:
  - La necesidad de TAR de inicio sin ITIAN es ahora menos acuciante que en el pasado dado que los ITIAN de elección actuales (FTC/TDF, 3TC/ABC) son más eficaces y seguros que los usados previamente
  - De los estudios publicados se puede concluir que algunos fármacos (Ej. RAL) parecen mejor protegidos en combinación con 2 ITIAN que en biterapia con 1 IP/r
  - Ninguna pauta sin ITIAN ha demostrado hasta la fecha claras ventajas frente a la triple terapia desde el punto de vista de la eficacia y seguridad



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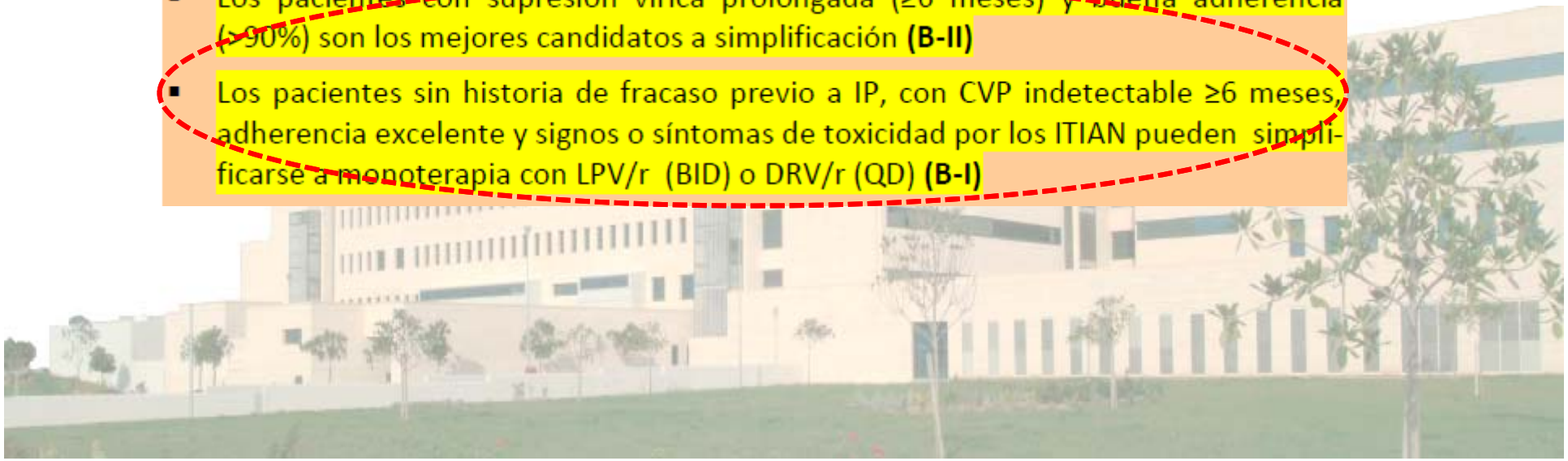
5.1. SIMPLIFICACION

Recomendaciones

- Es importante seleccionar muy bien los pacientes a los que se debe simplificar y la estrategia a seguir. La simplificación no se puede realizar a costa de la pérdida de eficacia virológica. Sólo se puede plantear una simplificación si no ha existido fracaso previo o si se utilizan fármacos plenamente activos para mantener el éxito virológico **(A-I)**
- Los pacientes con supresión vírica prolongada (≥6 meses) y buena adherencia (>90%) son los mejores candidatos a simplificación **(B-II)**
- Los pacientes sin historia de fracaso previo a IP, con CVP indetectable ≥6 meses, adherencia excelente y signos o síntomas de toxicidad por los ITIAN pueden simplificarse a monoterapia con LPV/r (BID) o DRV/r (QD) **(B-I)**



NUEVAS ESTRATEGIAS EN TRIPLE TERAPIA
(SINGLE TABLET REGIMENS)

ITINN

- RPV/FTC/TDF

I.INT

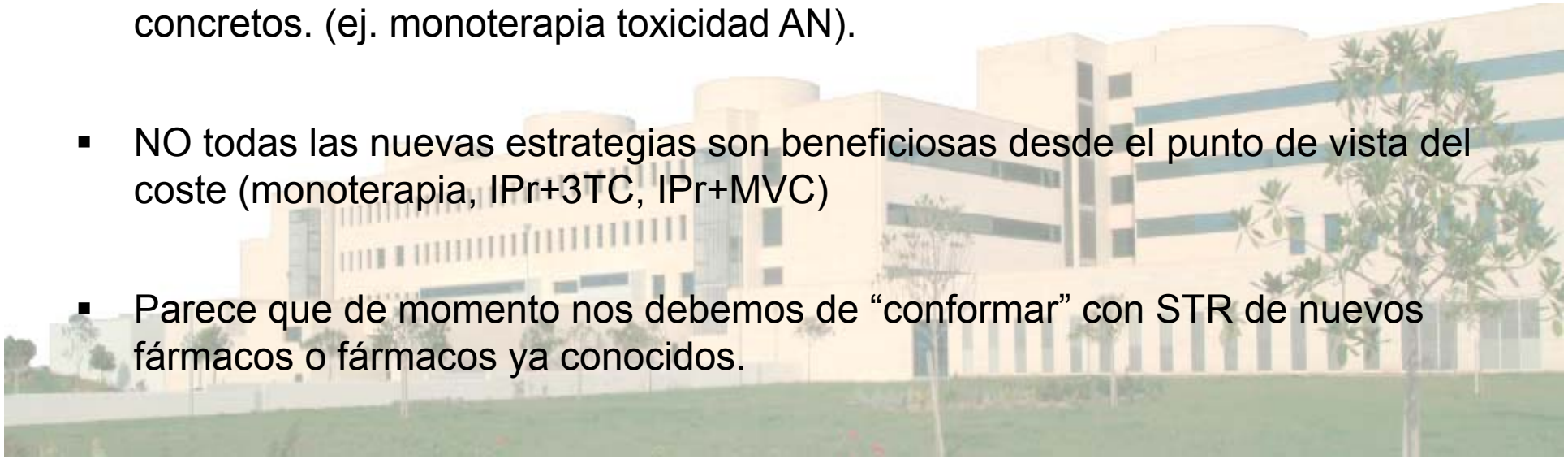
- ELV/COBI/FTC/TDF
- DOLU/ABC/3TC

IPr

- DARU/COBI/FTC/PRO-TDF

Conclusiones

- La terapia TRIPLE es difícilmente mejorable.
- Ninguna de las NUEVAS ESTRATEGIAS mejora a la triple terapia en todos sus aspectos.
- INICIO de tratamiento: se necesitan resultados más contundentes en estudios con potencia suficiente para incorporarlos de rutina a la práctica clínica (guias)
- En pacientes PRETRATADOS, hay muchos estudios en marcha, de momento deberían utilizarse como estrategias individuales en pacientes con problemas concretos. (ej. monoterapia toxicidad AN).
- NO todas las nuevas estrategias son beneficiosas desde el punto de vista del coste (monoterapia, IPr+3TC, IPr+MVC)
- Parece que de momento nos debemos de “conformar” con STR de nuevos fármacos o fármacos ya conocidos.



GRACIAS!!!!!