NUOVI SCHEMI TERAPEUTICI: MENO DI TRE…MA IN SICUREZZA!

Cristina Mussini

Roma, 17 Marzo 2011

RAZIONALE PER STRATEGIE NRTI SPARING: PRO

1. **Revertire o evitare tossicità:**
   - Mitocondriale (neuropatia periferica);
   - Lipoatrofia, resistenza insulinica;
   - Rene, osso, apparato cardiovascolare.

2. "**Risparmiare" questi farmaci per futuri regimi**

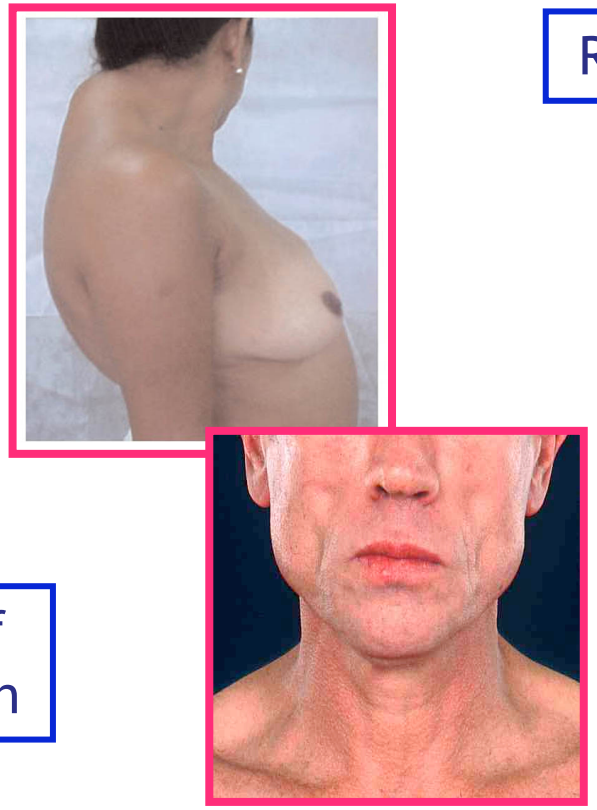
3. **Ridurre particolari interazioni farmacologiche** (es: ribavirina)

COMPLICANZE A LUNGO TERMINE DELLA HAART

Dyslipidaemia/CHD

Renal dysfunction

Insulin Resistence/
Diabetes



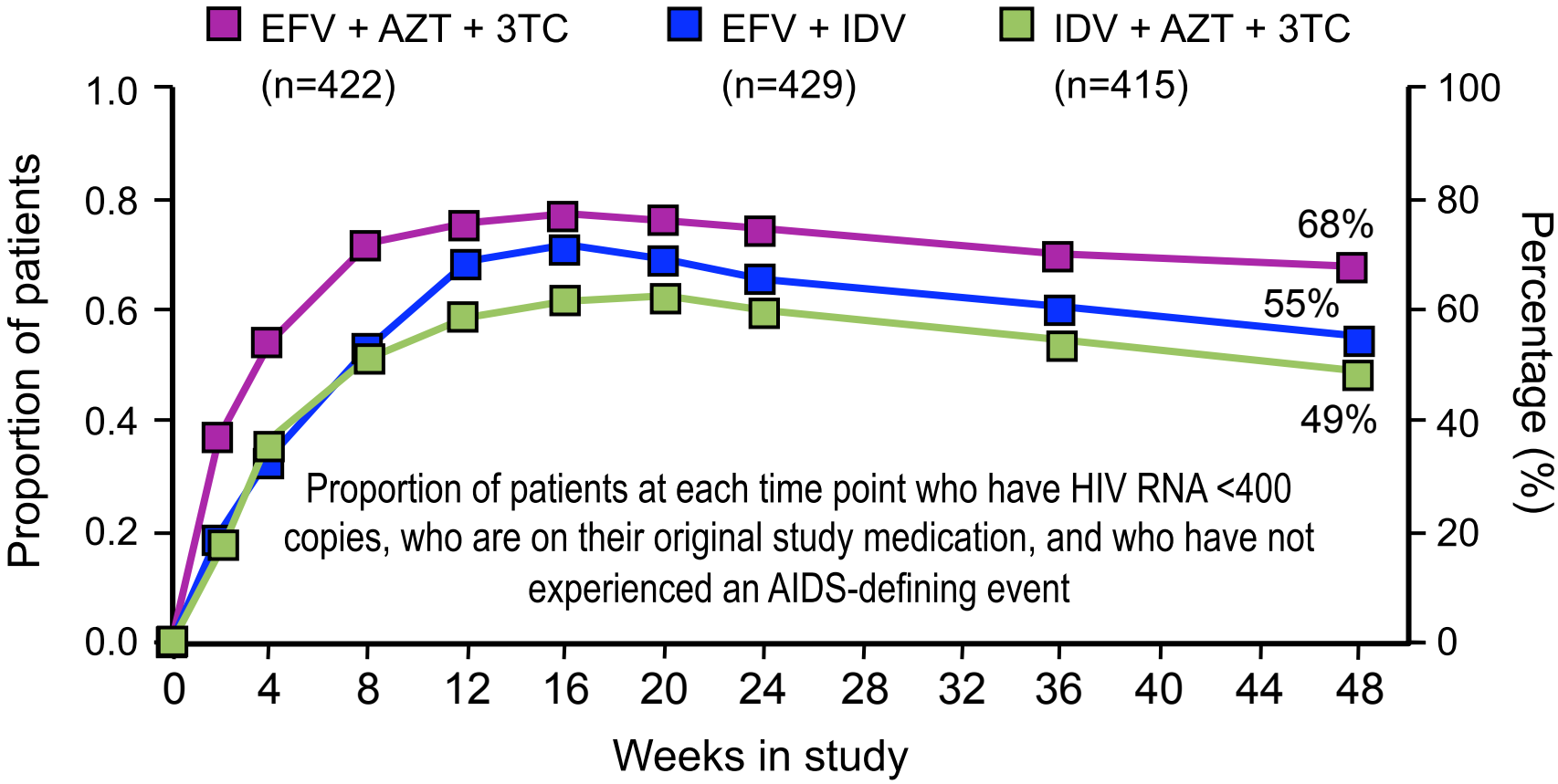
Abnormalities of
Body Composition

Osteoporosis/
Fractures

RAZIONALE PER STRATEGIE NRTI SPARING: CONTRO

1. I regimi NRTI-based sono lo Standard of Care in tutte le linee guida;
2. Non c'è un beneficio provato vs. regimi NRTI-based;
3. Problemi di potenza:
   - IP/r monoterapia;
   - Elevate cariche virali.
4. Specifiche tossicità:
   - Lipidi: IP/ NNRTI.
5. Dipendono dal ritonavir quindi interazioni farmacologiche;
6. Più elevato rischio di resistenza?
7. Regimi BID (due volte al dì);
8. Mancanza di penetrazione in alcuni compartimenti.

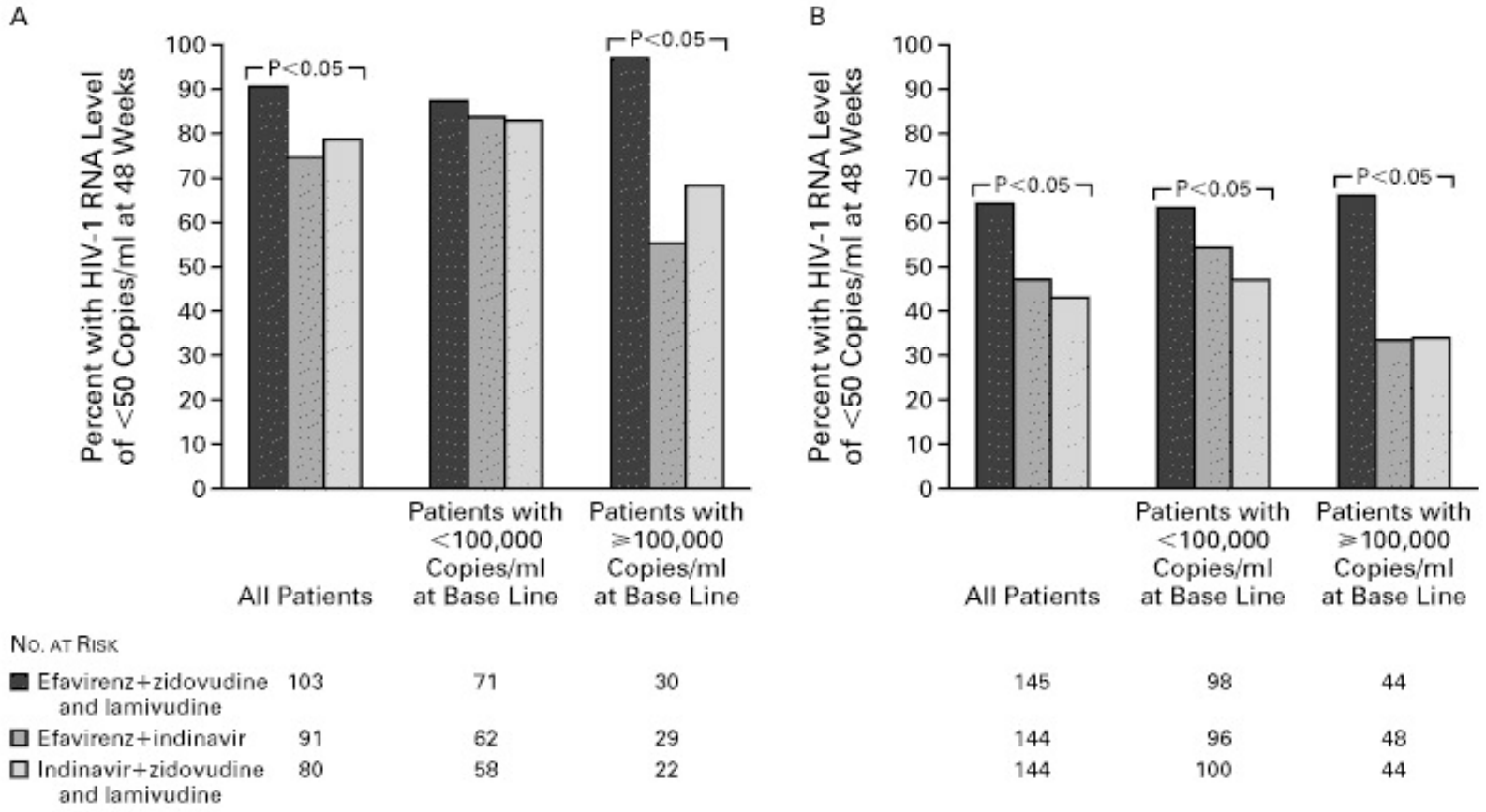
IL PRIMO STUDIO NRTI SPARING È STATO LO 266-006: RISPOSTA VIROLOGICA (ITT)



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 et al NEJM 1999

PAZIENTI CON VIREMIA <50 COPIE/ML ALLA SETTIMANA 48 STRATIFICATI PER VIREMIA AL BASALE

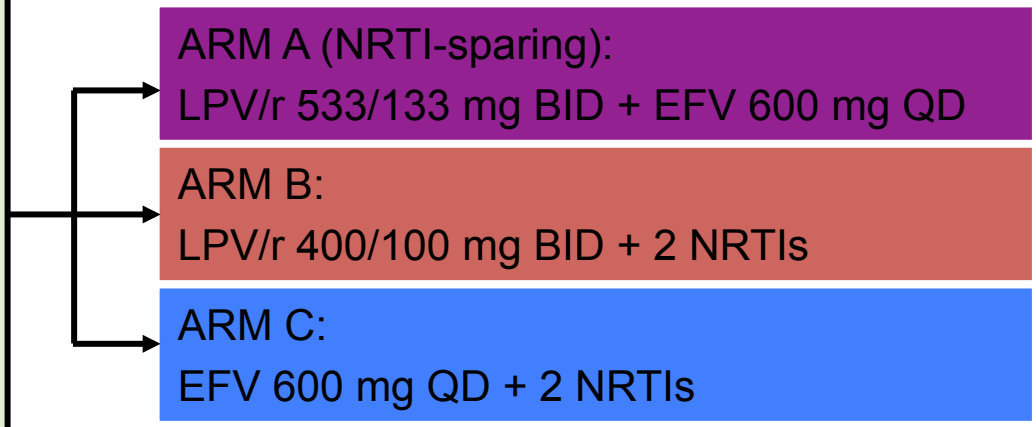


No. at Risk						
Efavirenz+zidovudine and lamivudine	103	71	30	145	98	44
Efavirenz+indinavir	91	62	29	144	96	48
Indinavir+zidovudine and lamivudine	80	58	22	144	100	44

Staszewski et al NEJM 1999

STUDIO ACTG 5142: DISEGNO

- 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



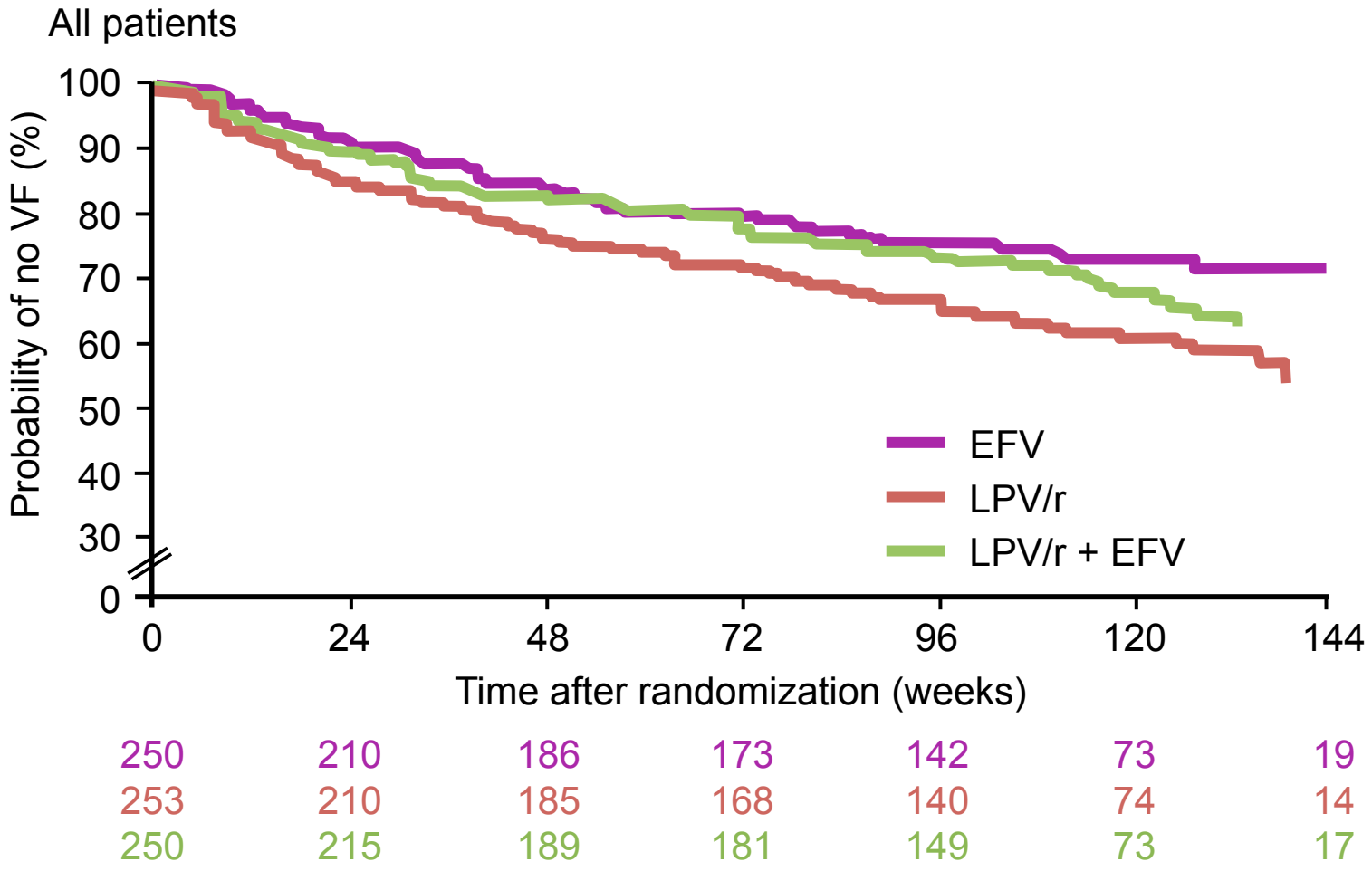
- **LPV/r given as soft gel capsules**
- **2 NRTIs included 3TC (300 mg QD or 150 mg BID) + investigator selection of AZT 300 mg BID or d4T XR[a] 100 mg QD[b] or TDF 300 mg QD**
- **3TC dosed:**
  - **150 mg BID with AZT**
  - **300 mg QD with d4T XR or TDF**

[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

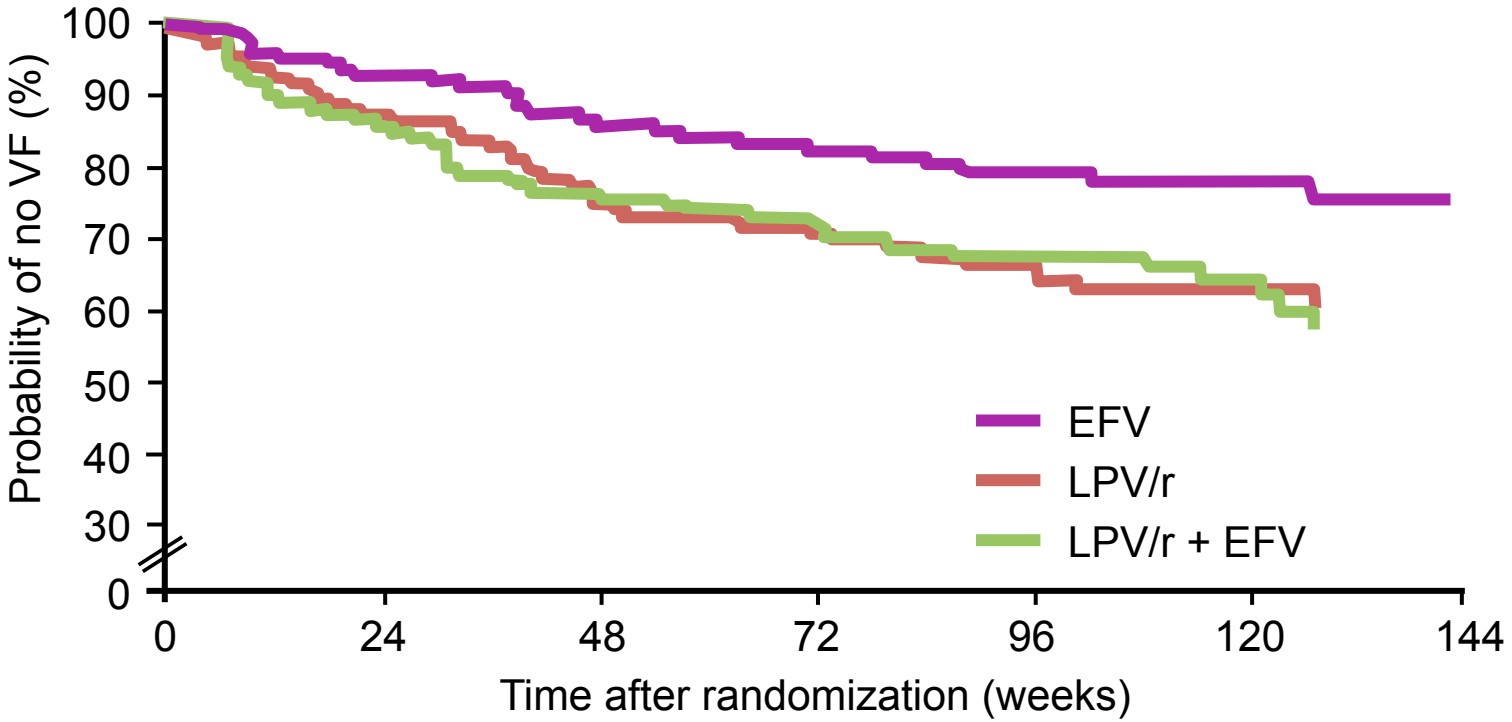
Riddler S et al. N Engl J Med 2008;358(20):2095−2106

ACTG 5142: REGIME NRTI-SPARING AVEVA UN' EFFICACIA SIMILE A EFV (time to VF: > 200 cp/ml at week 32)



Adapted from Riddler SA et al. N Engl J Med 2008;358::2095−2106

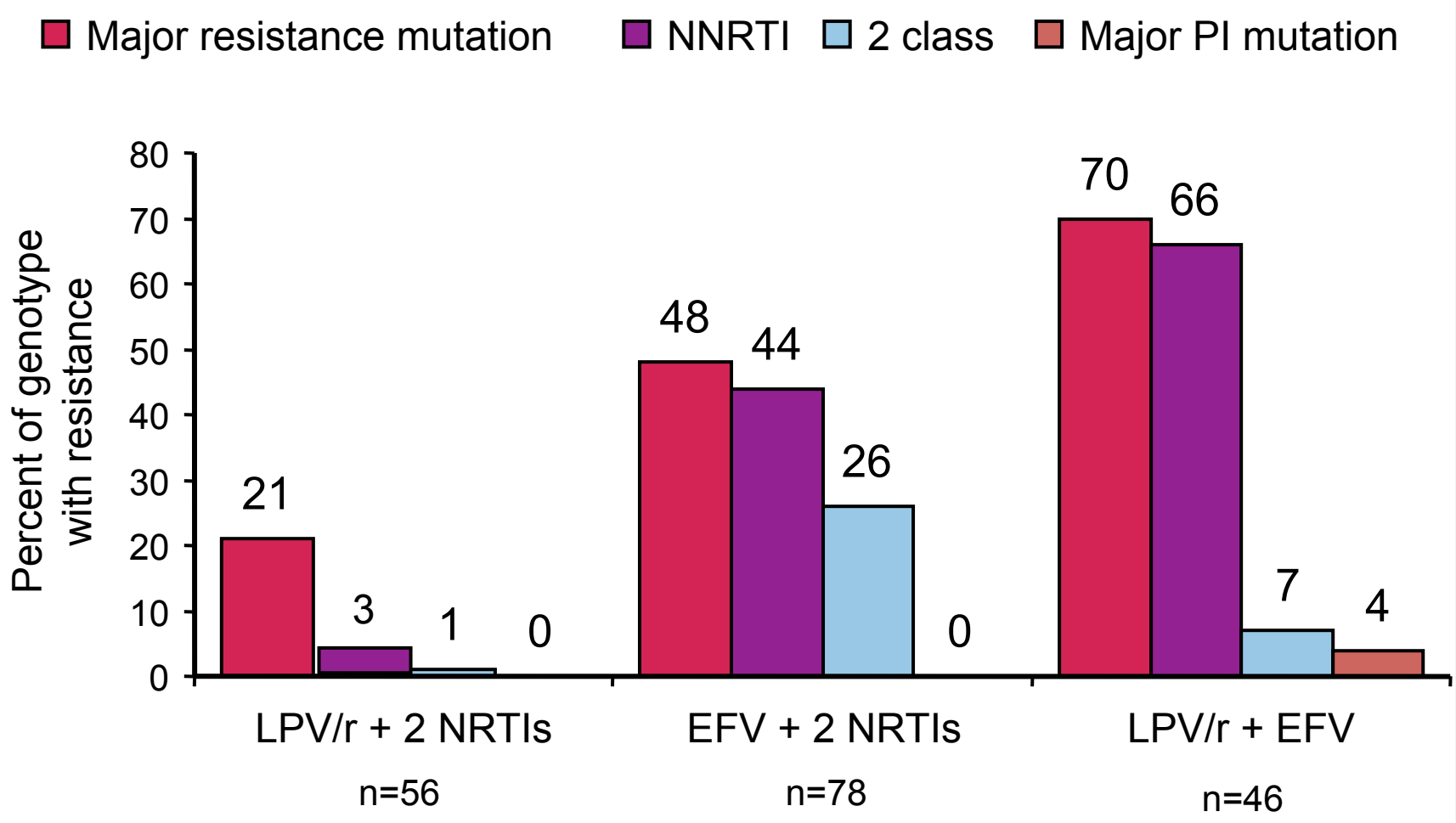
CARICA VIRALE AL BASALE ≥100 000 COPIE/ML: NRTI-SPARING & LPV/R+NRTI ERANO MENO EFFICACI DI EFV



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

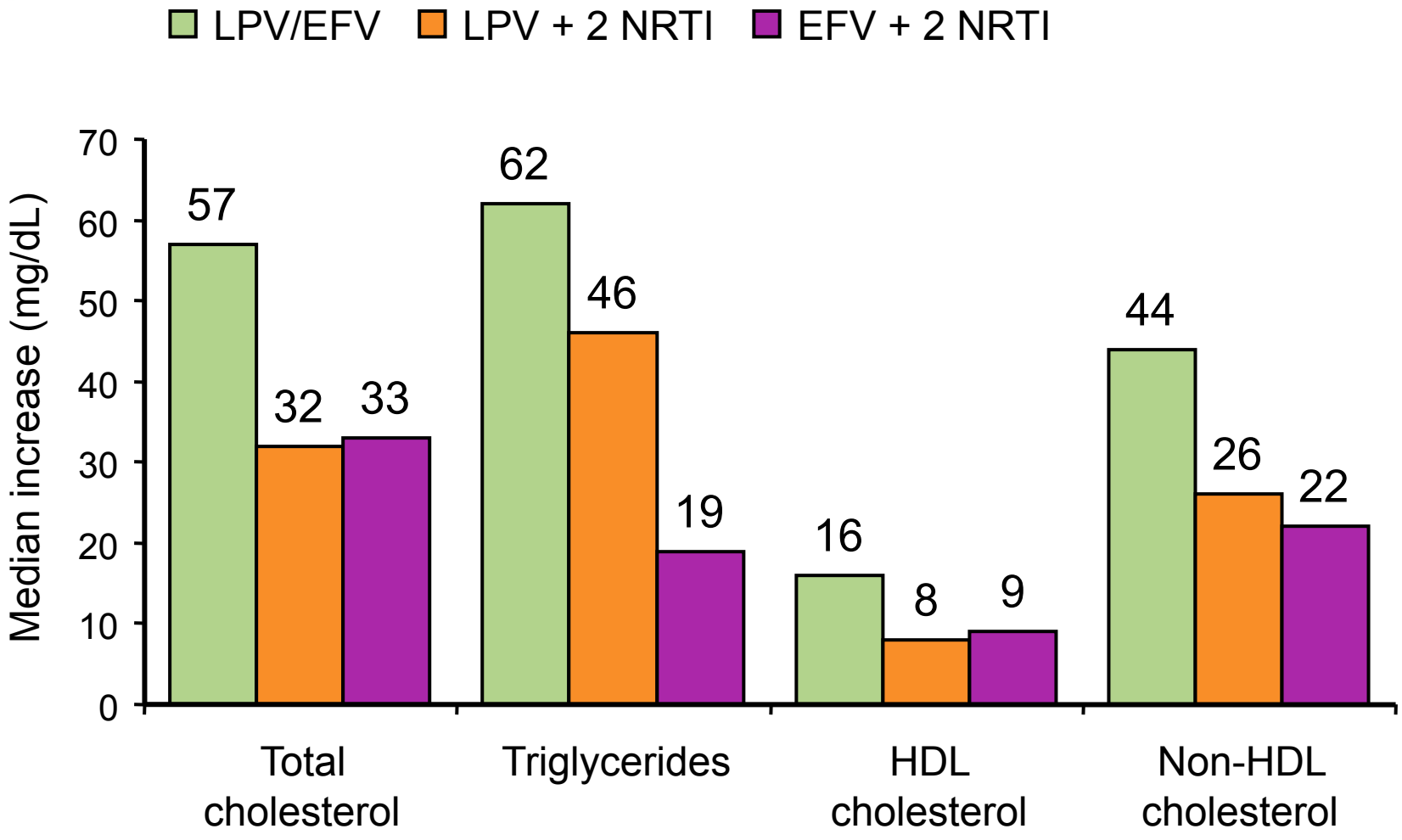
Adapted from Riddler SA et al. N Engl J Med 2008;358::2095−2106

ACTG 5142: FALLIMENTO VIROLOGICO E SVILUPPO DI RESISTENZA



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

ACTG 5142:DATI METABOLICI



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

NNRTI + PI : TAKE HOME MESSAGES

- E' l'approccio più studiato;

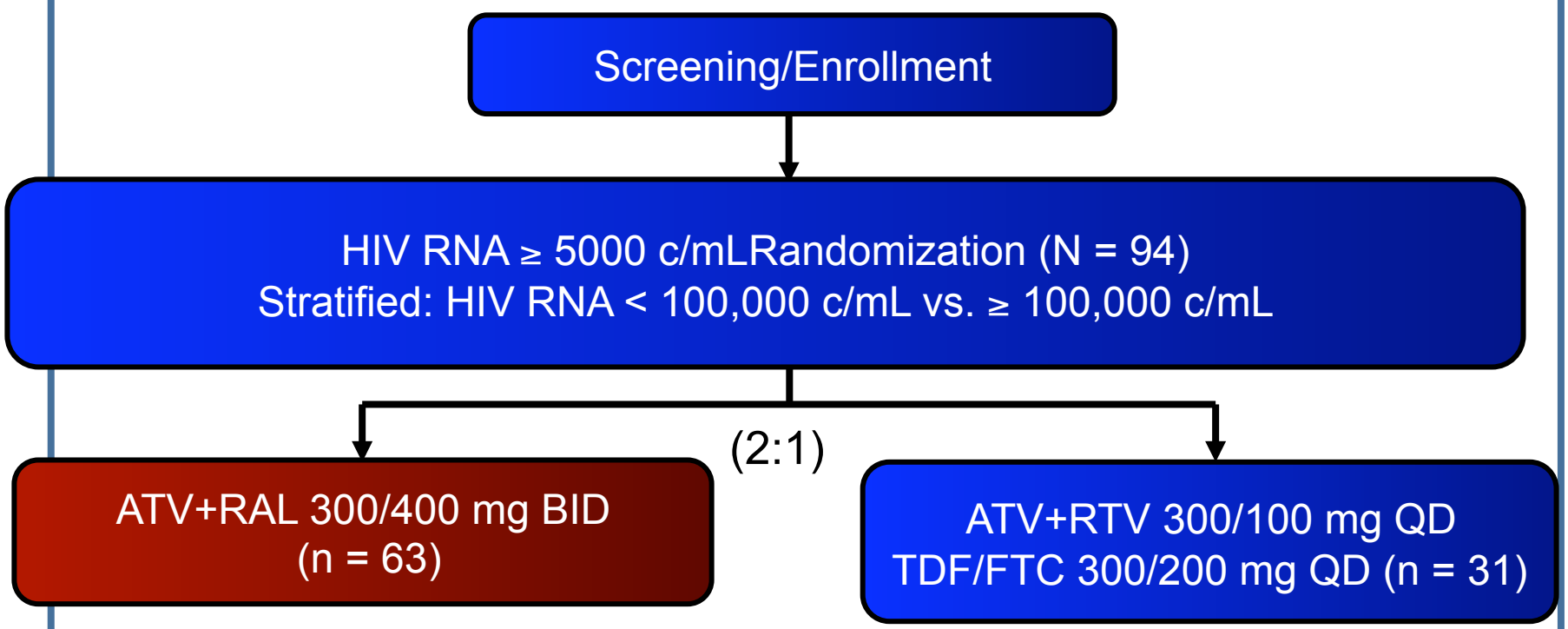
- Problemi:
  - ✓Efficacia a elevata viremia;
  - ✓Sicurezza soprattutto per i lipidi;
  - ✓Impatto sullo sviluppo di resistenze;
  - ✓Interazioni farmacologiche.

REGIMI NRTI SPARING CON LE NUOVE CLASSI

Studi clinici in corso:

- IP/r + inibitori dell'integrasi;
- IP/r + antagonisti del CCR5.

STUDIO SPARTAN: DISEGNO



Primary endpoint:

- Determine the proportion of patients with HIV RNA < 50 c/mL at week 24

Secondary endpoints:

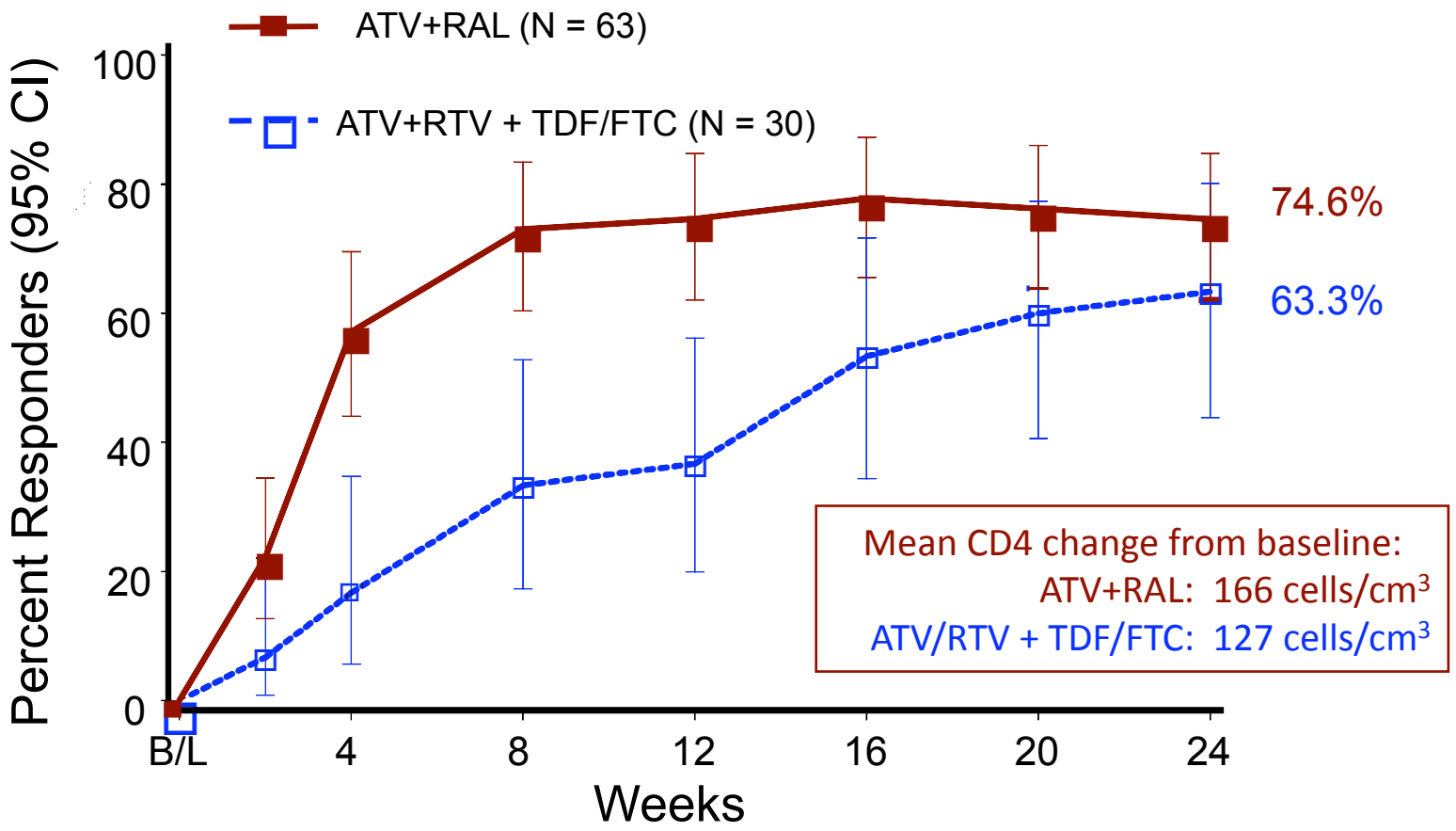
- Change from baseline in CD4 cell counts at weeks 24, 48 & 96
- Safety through weeks 24, 48 & 96
- Assess pharmacokinetics of ATV+RAL experimental regimen

MJ Kozal IAC July 22, 2010: SPARTAN: THLBB204

SPARTAN: DATI DEMOGRAFICI

	ATV+RAL	ATV+RTV+TDF/FTC
Median Age (years)	40.0	40.5
Male n/N (%)	55/63 (87.3)	28/30 (93.3)
Race n/N (%)		
White	54/63 (85.7)	23/30 (76.7)
African American	8/63 (12.7)	6/30 (20.0)
Asian	0	1/30 (3.3)
Other	1/63 (1.6)	0
Mean BL HIV RNA $\log_{10}$ c/mL	**4.9 (0.07)**	**4.9 (0.12)**
Baseline HIV RNA < 100,000	29/63 (46.0)	17/30 (56.7)
Baseline HIV RNA ≥ 100,000	34/63 (54.0)	13/30 (43.3)
Mean CD4 cells/mm^3 (SE)	**256 (14.7)**	**261 (24.6)**

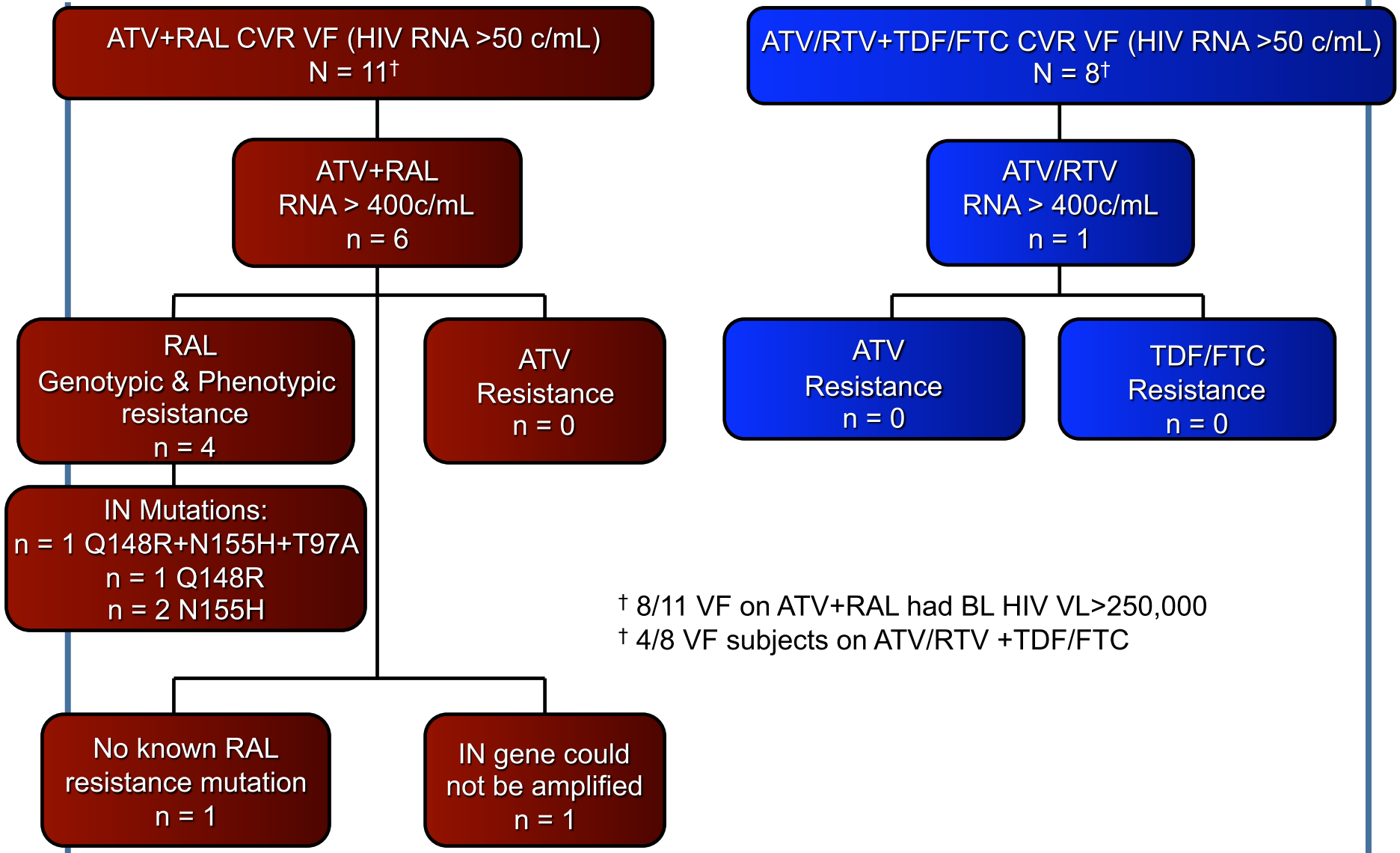
SPARTAN: RESPONSE RATE (HIV RNA < 50 CP/ML) THROUGH WEEK 24-CVR (NC = F)



CVR (NC = F) is a modified intent-to-treat analysis of confirmed virologic response where non-completers equal failure.
Responders are:

- Subjects who achieve and maintain confirmed response (2 consecutive on-treatment HIV RNA < 50 cp/mL) through the visit week without intervening virologic rebound or discontinuation
- Subjects who achieve resuppression (i.e., confirmed response after virologic rebound) at the visit week.

SPARTAN: RESISTANCE THROUGH WEEK 24



† 8/11 VF on ATV+RAL had BL HIV VL>250,000
† 4/8 VF subjects on ATV/RTV +TDF/FTC

SPARTAN: SAFETY THROUGH WEEK 24

	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)

ATV + RAL: TAKE HOME MESSAGES

L’associazione raltegravir + ATV ha evidenziato alcuni limiti:

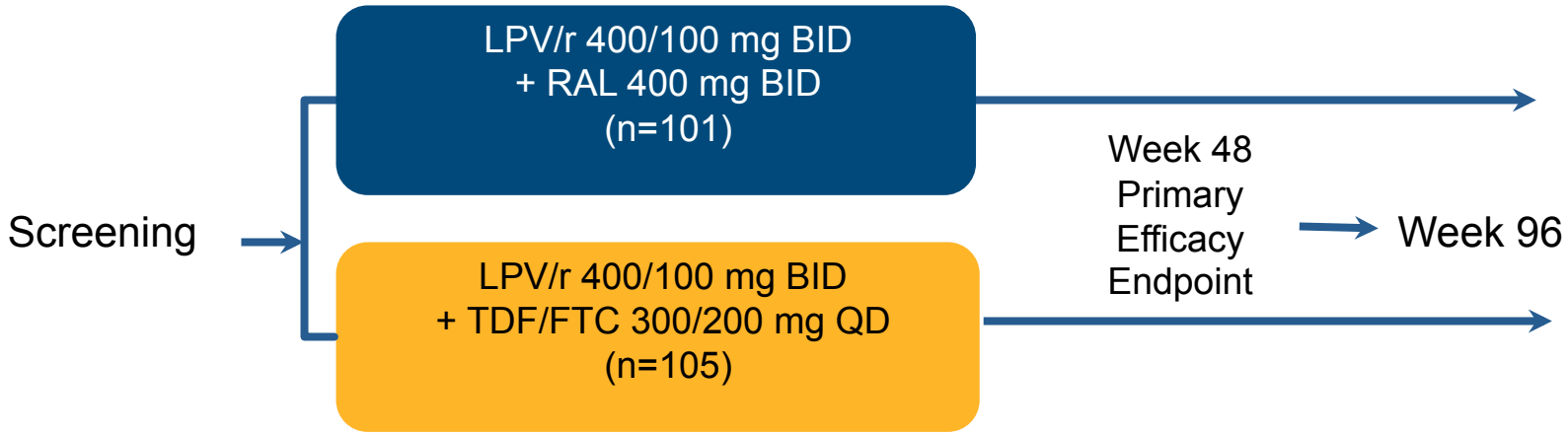
1) Esiste un’interazione farmacologica tra le 2 molecole, pertanto non è ancora chiaro quale possa essere il + corretto dosaggio di raltegravir;

2) Il rischio maggiore è quello di un’elevata bilirubinemia.

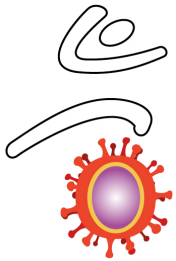
STUDIO PROGRESS: LPV/R + RAL *VS.* LPV/R + TDF/FTC IN PAZIENTI NAÏVE. DISEGNO

Inclusion Criteria for PROGRESS (M10-336)

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



•Primary endpoint: plasma HIV-1 RNA <40 copies/mL at week 48 (FDA ITT TLOVR);
•Non-inferiority assessed by 95% CI for the difference ([LPV/r + RAL] – [LPV/r + TDF/FTC]) using a -20% threshold;
•If non-inferiority with respect to the -20% margin was demonstrated, then non-inferiority with respect to a -12% margin was to be evaluated.

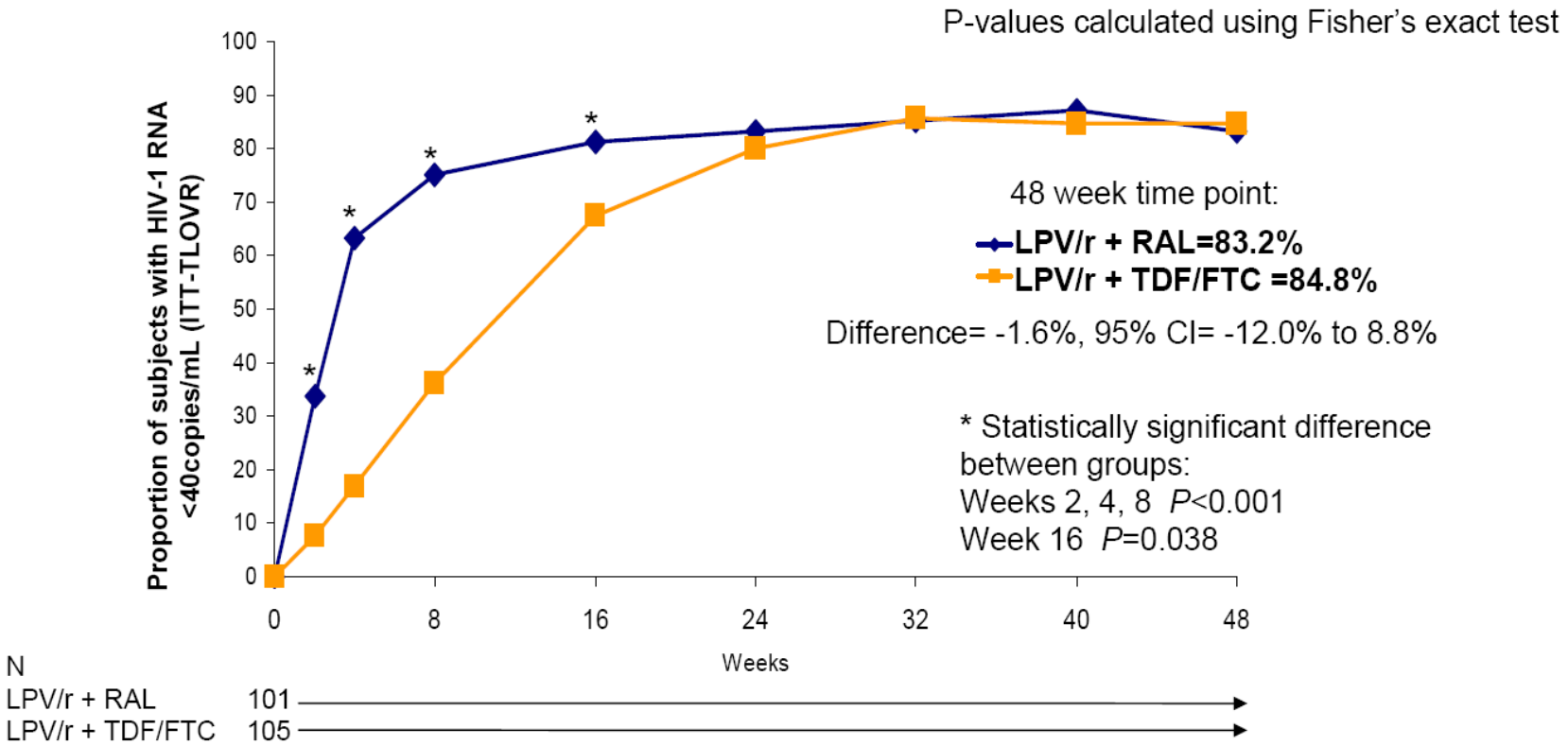


PROGRESS: BASELINE DEMOGRAPHICS AND HIV DISEASE CHARACTERISTICS

Variable	LPV/r + RAL (N=101)	LPV/ + TDF/FTC (N=105)	Total (N=206)
Males, n (%)	88 (87.1)	86 (81.9)	174 (84.5)
White, n (%)	74 (73.3)	81 (77.1)	155 (75.2)
Black, n (%) Other, n (%)	22 (21.8) 5 (4.9)	22 (21.0) 2 (1.9)	44 (21.4) 7 (3.4)
Mean age ± SD, years	39.8 ± 9.9	39.4 ± 11.2	39.6 ± 10.6
Mean BL HIV-1 RNA, log_{10} copies/mL (range)†	**4.24** (2.0-6.0)	**4.25** (2.7 – 6.0)	**4.25** (2.0 – 6.0)
Mean BL CD4, cells/μL (range)	289.3 (5 – 668)	**297.6** (5 – 743)	**293.5** (5 – 743)

Reynes et al. IAS Vienna 2010

PROGRESS - PRIMARY EFFICACY ENDPOINT AT WEEK 48: PROPORZIONE DI SOGGETTI CHE RISPONDONO (FDA ITT TLOVR)



LPV/r + RAL was non-inferior to LPV/r + TDF/FTC in treatment-naïve subjects at 48 weeks

PROGRESS - PROPORZIONE DI SOGGETTI CON HIV-RNA<40 COPIE/ML ALLA SETTIMANA 48

	LPV/r + RAL N=101 n/N(%)	LPV/r + TDF/FTC N=105 n/N(%)	Difference [95% CI]	*P*-value
FDA ITT TLOVR	84/101 (83.2)	89/105 (84.8)	-1.6% [-12.0%, 8.8%]	0.850
ITT NC=F	82/101 (81.2)	90/105 (85.7)	-4.5% [-15.1%, 5.9%]	0.454
ITT M=F	82/101 (81.2)	90/105 (85.7)	-4.5% [-15.1%, 5.9%]	0.454
ITT LOCF	85/101 (84.2)	93/105 (88.6)	-5.4% [-15.2%, 4.4%]	0.418
OD	82/97 (84.5)	90/96 (93.8)	-9.3% [-18.9%, -0.3%]	0.062

***P*-values calculated using Fisher's exact test**

PROGRESS - EMERGENZA DI RESISTENZE*

7 subjects (4 LPV/r + RAL and 3 LPV/r + TDF/FTC) met the protocol-defined criteria for resistance testing:
- N155H mutation detected in 1 LPV/r + RAL subject;
- M184V mutation detected in 1 LPV/r + TDF/FTC subject.

Study Drug	Number of subjects with new mutations	
	LPV/r + RAL	LPV/r + TDF/FTC
LPV	0/4	0/3
RAL †	1/3	N/A
TDF	0/4	0/3
FTC	0/4	1/3

*LPV-associated mutations: Major: V32I, I47V/A, L76V, V82A/F/T/S. Minor: L10F/I/R/V, K20M/R, L24I, L33F, M46I/L, I50V, F53L, I54/V/L/A/M/T/S, L63P, A71V/T, G73S, I84V, or L90M
RAL-associated mutations: Y143R/H/C, Q148H/K/R, or N155H
TDF-associated mutations: K65R or K70E
FTC-associated mutations: K65R or M184V/I
† 1 RAL sample not available for testing after meeting protocol-defined criteria
N/A-not applicable

PROGRESS - PERCENTUALE DI SOGGETTI CON EVENTI AVVERSI MODERATI O SEVERI*

	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)
Any Adverse Event	28 (27.7)	29 (27.6)
Diarrhea	8 (7.9)	14 (13.3)
Hypercholesterolemia	8 (7.9)	5 (4.8)
Hypertriglyceridemia	6 (5.9)	2 (1.9)
Hyperlipidemia	3 (3.0)	1 (1.0)
Blood triglycerides increased	3 (3.0)	1 (1.0)
Alanine aminotransferase increased	2 (2.0)	1 (1.0)

PROGRESS - NUMERO E % DI SOGGETTI CON ANOMALIE DI LABORATORIO >DI GRADO 3*

	LPV/r + RAL (N=101) n (%)	LPV/r + TDF/FTC (N=105) n (%)
SGPT/ALT >5X ULN, n (%)	3 (3.0)	1 (1.0)
SGOT/AST >5X ULN	5 (5.0)	1 (1.0)
CPK >4X ULN †	13 (12.9)	4 (3.8)
Calcium <1.75 mmol/L		
Cholesterol >7.77 mmol/L	2 (2.0)	0
Triglycerides >8.475 mmol/L	16 (15.8)	14 (13.5)
Calculated creatinine	10 (9.9)	5 (4.8)
clearance <50 mL/min	1 (1.0)	4 (3.8)
Lipase >2X ULN	4 (4.0)	7 (6.7)

LPV/r + RAL: TAKE HOME MESSAGES

L'associazione tra lopinavir/r e raltegravir ha evidenziato:

1) Un più veloce abbattimento della carica virale, come in tutte le associazioni comprendenti raltegravir;

2) Un inaspettato peggior profilo lipidico dei pazienti in duplice rispetto a quelli in triplice;

3) Come la potenza dell'IP, in caso di scarsa aderenza, non riesca a "proteggere" completamente raltegravir e quindi come si possano sviluppare resistenze.

Poster #551
Session 107

CROI 2011 BOSTON FEB 27-MAR 2, 2011

ACTG AIDS CLINICAL TRIALS GROUP

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

Table 1: BASELINE CHARACTERISTICS (N=112)		
Age (years)	Median (Q1, Q3)	36 (27, 45)
Sex	Male	98 (88%)
Race	White	49 (44%)
CD4 cell count (cells/mm^3)	< 200 200--< 350 ≥350	40 (36%) 32 (29%) 40 (36%)
HIV-1 RNA (copies/mL)	≤100,000 >100,000	63 (56%) 49 (44%)
HIV-1 Resistance Mutations	NNRTI Only NRTI Only PI Only NNRTI + NRTI NNRTI + NRTI + PI	9 (8%) 8 (7%) 2 (2%) 1 (1%) 1 (1%)

VIROLOGIC FAILURE

By week 24: 17 subjects (11 failed to suppress, 6 rebounded)

Cumulative week 24 proportion of VF= 16%, 95% CI [10%, 24%]

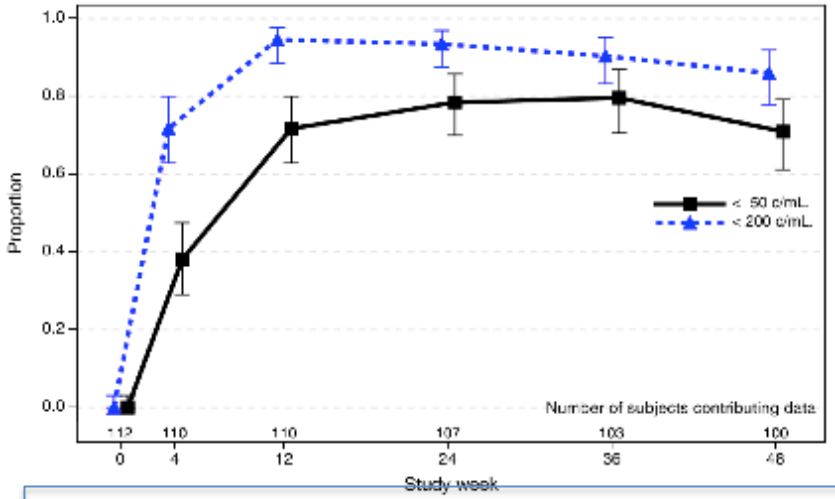
By week 48: 28 subjects (11 additional rebounds)

Cumulative week 48 proportion of VF= 26%, 95% CI [19%, 36%]

Adjusting for age and sex, VF was associated with:

- higher (>100,000 vs. ≤ 100,000 c/mL) BL VL (HR 3.76, 95% CI [1.52, 9.31],
- lower BL CD4 (0.77 per 100 cells/mm^3 increase, [0.61, 0.98], p=0.037)

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



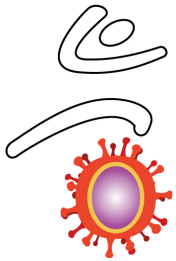
Week	Proportion (95% CI)	
	< 200 c/mL.	< 50 c/mL.
24	93% (87%, 97%)	79% (70%, 86%)
48	86% (78%, 92%)	71% (61%, 79%)

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

Table 2: SUBJECTS WITH INTEGRASE MUTATIONS AT VIROLOGIC FAILURE *

Baseline HIV RNA** copies/mL	Integrase Mutations at Virologic Failure	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 subjects. Samples for 3 could not be amplified.
**All HIV RNA > 100,000 copies/mL



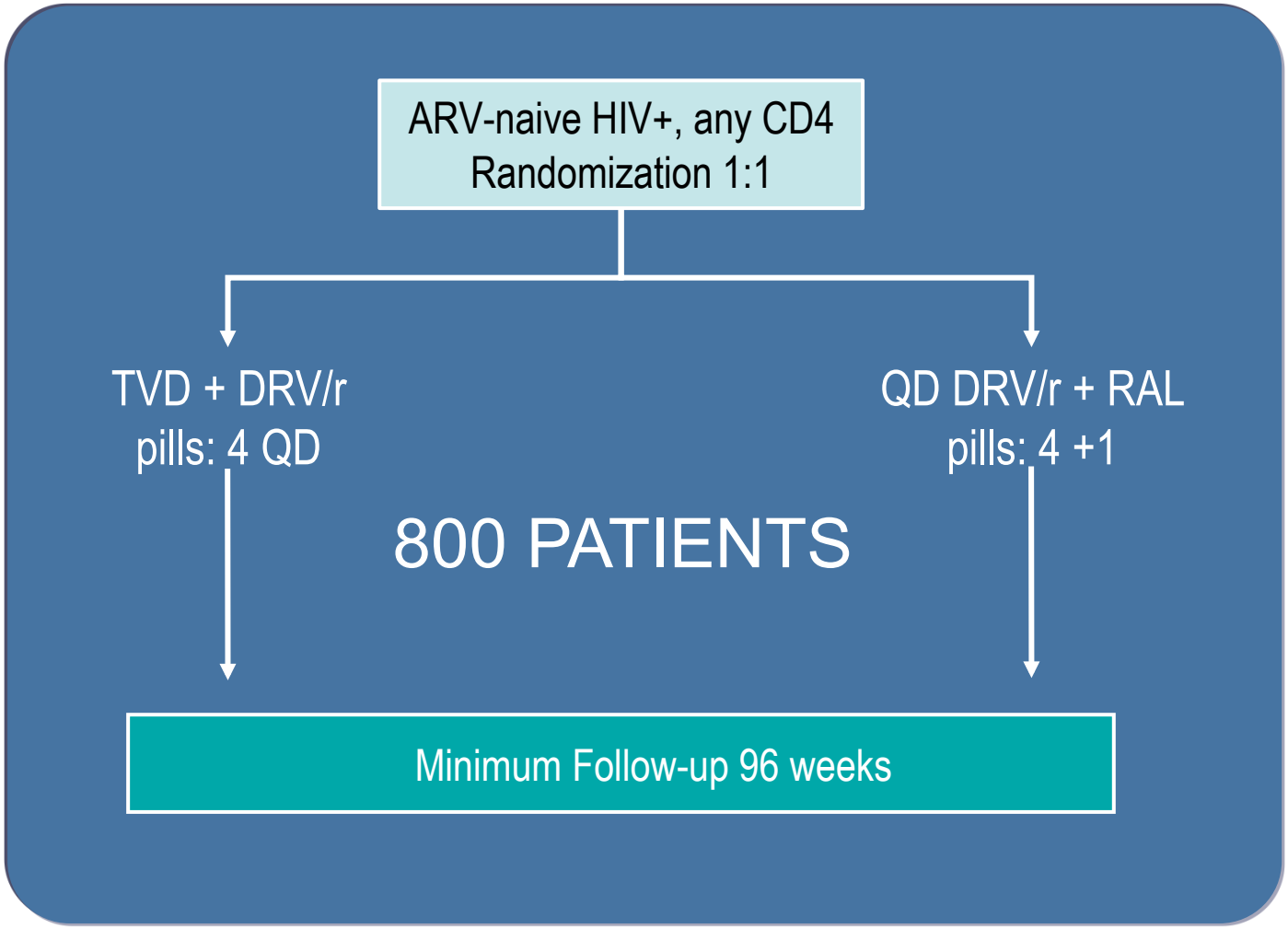
SAFETY AND TOLERABILITY

- 22 Subjects had ≥ Grade 3 adverse events
  - 5 possibly study treatment related, none definitely/probably related
  - 3 subjects changed or discontinued study treatment due to AEs
  - Median increases in fasting HDL, LDL, total cholesterol and triglycerides at week 48 were 9, 17, 30 and 23 mg/dL ($p < 0.001$, except triglycerides $p=0.006$)

CONCLUSIONS

- Darunavir/ritonavir plus raltegravir was effective and well tolerated in treatment-naive patients
- Subjects with baseline HIV-1 RNA >100,000 copies/mL experienced more virologic failure and integrase resistance.

NEAT PROTOCOL 001 / ANRS 143



March 3rd, 2011

Dear NEAT001/ANRS 143 investigator,

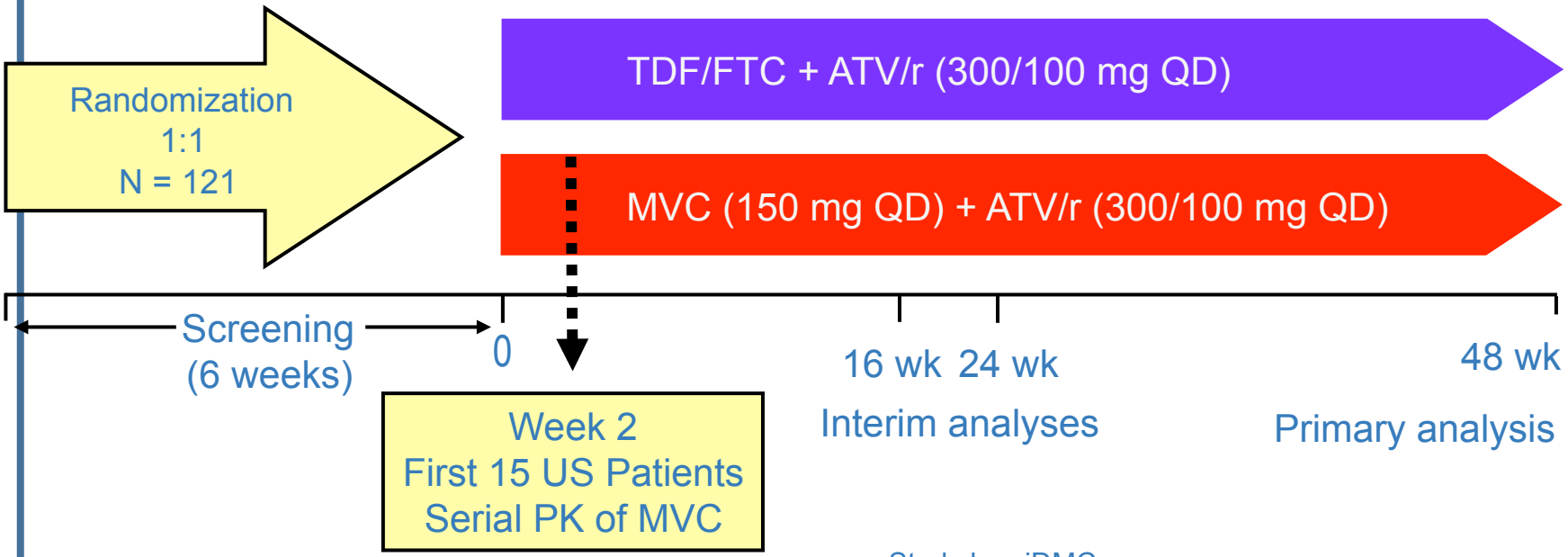
- ACTG A5262
  - study results are from a single-arm non-comparative study
  - most « virologic failures » have viral load between 50 and 200 copies/mL
  - virologic failure was found to be associated with high viral load and/or low CD4 count at baseline.
  - the low rate of resistance suggests that most failures were linked to non-adherence
- NEAT001/ANRS 143
  - enrolment should be continued and completed as soon as possible to obtain comparative results and final results planned end 2013
  - An early review of the data will be performed by the IDMC in July 2011

TAKE HOME MESSAGES: RAL + DRV/r

Al momento i dati sull'associazione raltegravir + darunavir/r sono conflittuali, quindi bisognerà aspettare i risultati dello studio NEAT che, a differenza dell'ACTG 5262, è uno studio randomizzato e con più pazienti.

MVC+ATV/r: DISEGNO DELLO STUDIO

In aperto, 48 settimane, di fase 2b



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

* Sparse PK sampling on all patients at Weeks 2 (non-PK substudy), 12 and 24.

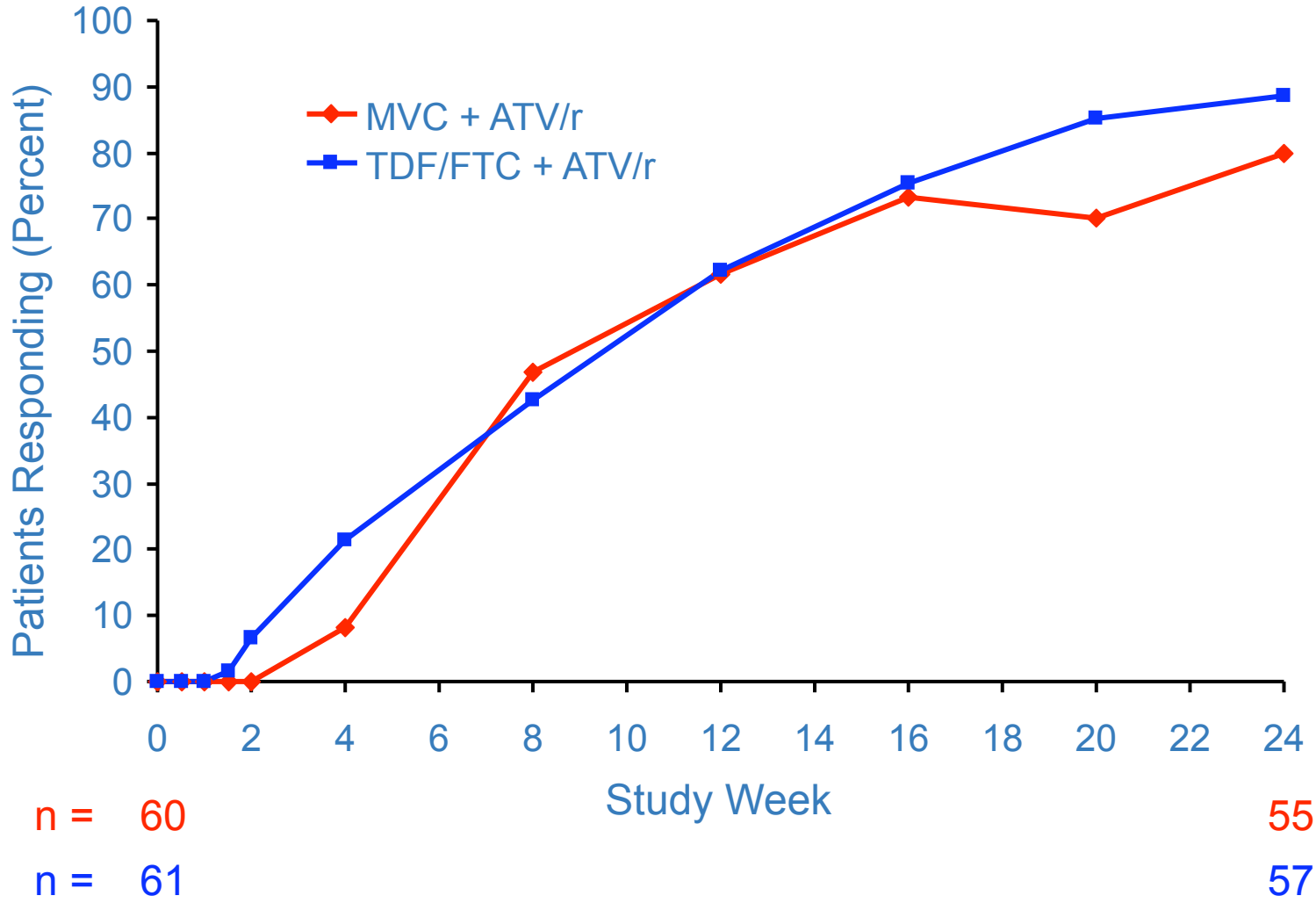
Mills A et al. IAC 2010. Abstract THLBB203

MVC+ATV/r: CARATTERISTICHE AL BASALE

	MVC + ATV/r n=60	TDF/FTC + ATV/r n=61
Mean Age, years (range)	38.3 (21 – 61)	35.3 (18 – 68)
Male, n (%)	56 (93.3)	52 (85.2)
Median $CD4^+$ count, cells/mm^3 (range)	344 (160 – 744)	358 (110 – 902)
Mean HIV-1 RNA, log_{10} copies/mL (range)	4.6 (3.4-5.9)	4.7 (3.3-5.9)
Patients with HIV-1 RNA >100,000 copies/mL (%)	27%	36%

Mills A et al. IAC 2010. Abstract THLBB203

MVC+ATV/r: HIV-1 RNA < 50 COPIES/ML ALLA SETTIMANA 24



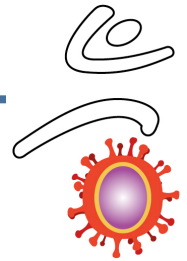
Mills A et al. IAC 2010. Abstract THLBB203

MVC + ATV/R: TAKE HOME MESSAGES

La sostituzione del backbone nucleosidico con maraviroc, oltre che possibile solo in soggetti infettati con virus R5, sembra essere apparentemente meno efficace della triplice terapia standard in associazione con ATV/r.

NUOVI REGIMI NRTI-SPARING: TAKE HOME MESSAGES

- Pochi dati fino ad oggi.
- Interesse anche nei confronti di regimi RTV-sparing.
- Problemi:
  - ✓Interazioni farmacologiche;
  - ✓Efficacia in pazienti con elevate viremie;
  - ✓Sicurezza: soprattutto lipidi/bilirubina;
  - ✓Emergenza di resistenza.



INIBITORI DELLE PROTEASI CON MENO NUCLEOSIDICI

STUDIO ATLAS - ATV/r + 3TC: DISEGNO

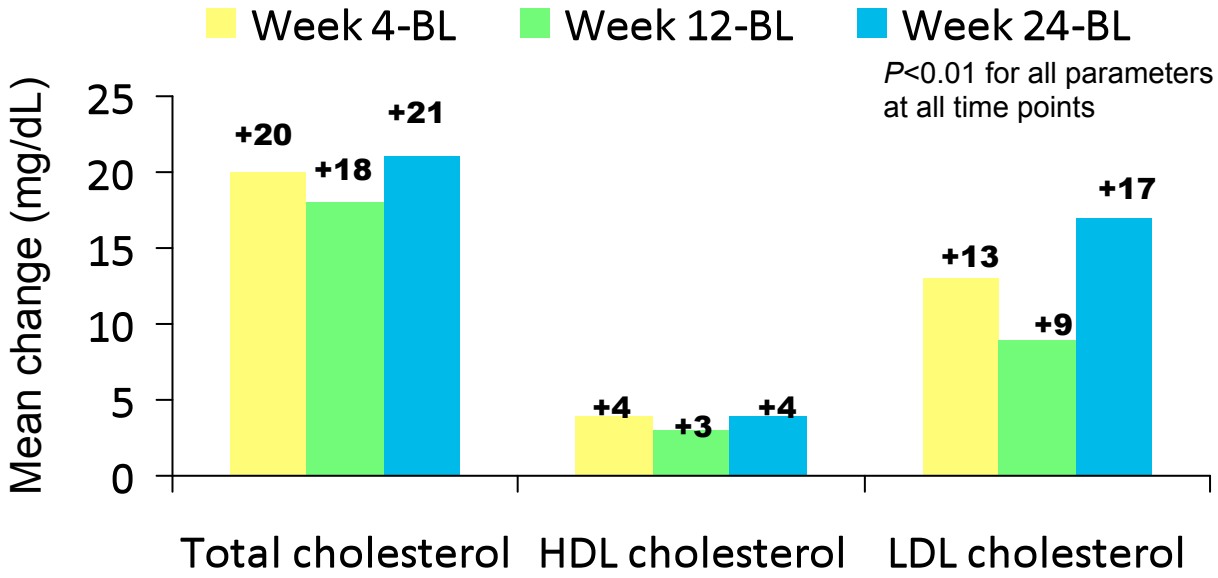
- **Single-arm, Pilot Simplification Study (N=40)**
- **Inclusion criteria:**
  - Patients on ATV/r + 2 NRTIs ≥3 months (97.5% on TDF)
  - HIV-RNA <50 copies/mL >3 months
  - CD4 >200 cells/mm^3 ≥6 months
- **Exclusion criteria:**
  - History consistent with possible resistance to 3TC or atazanavir
  - Proton pump inhibitor use
  - HBsAg positive

Caratteristiche al basale	
Age (median, years)	45
Male sex	57.5%
Injecting drug users	22.5%
HCV co-infection	20%
Time (median, years) from starting last cART regimen	2.6
CD4 cells count (median, cells/mm^3)	598

De Luca A, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. THLBB207

STUDIO ATLAS: RISULTATI A 48 SETTIMANE

- Virologic Results: All maintained HIV RNA <50 copies/mL, without blips
- Lipid Changes Through Week 24:



- Week 24 Renal Outcomes: Creatinine decrease of 0.08 (P<0.001); GFR increase 6 ml/min by MDRD (P<0.001)

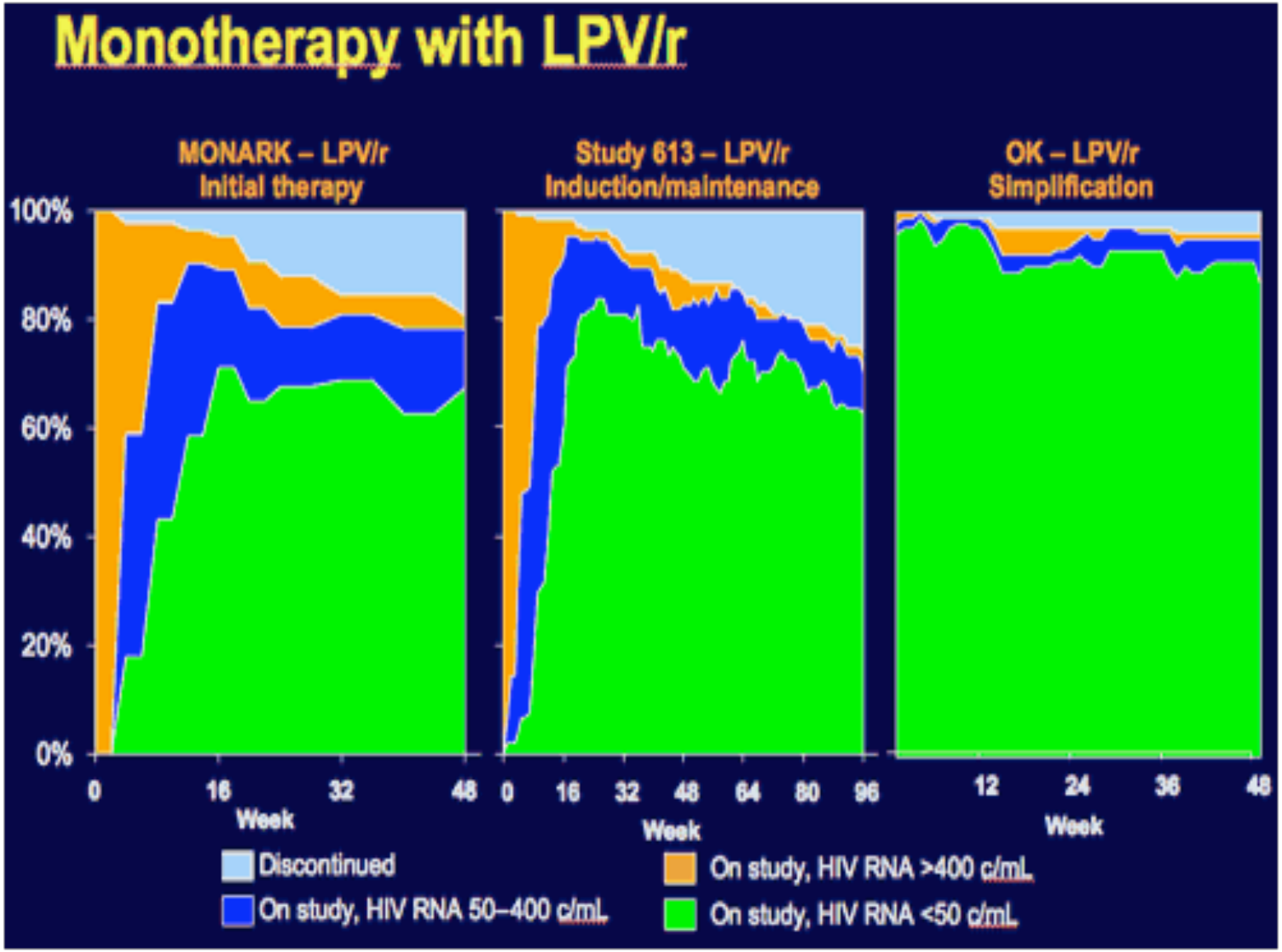
Conclusione: se a 48 settimane si confermano i risultati, si andrà in fase III

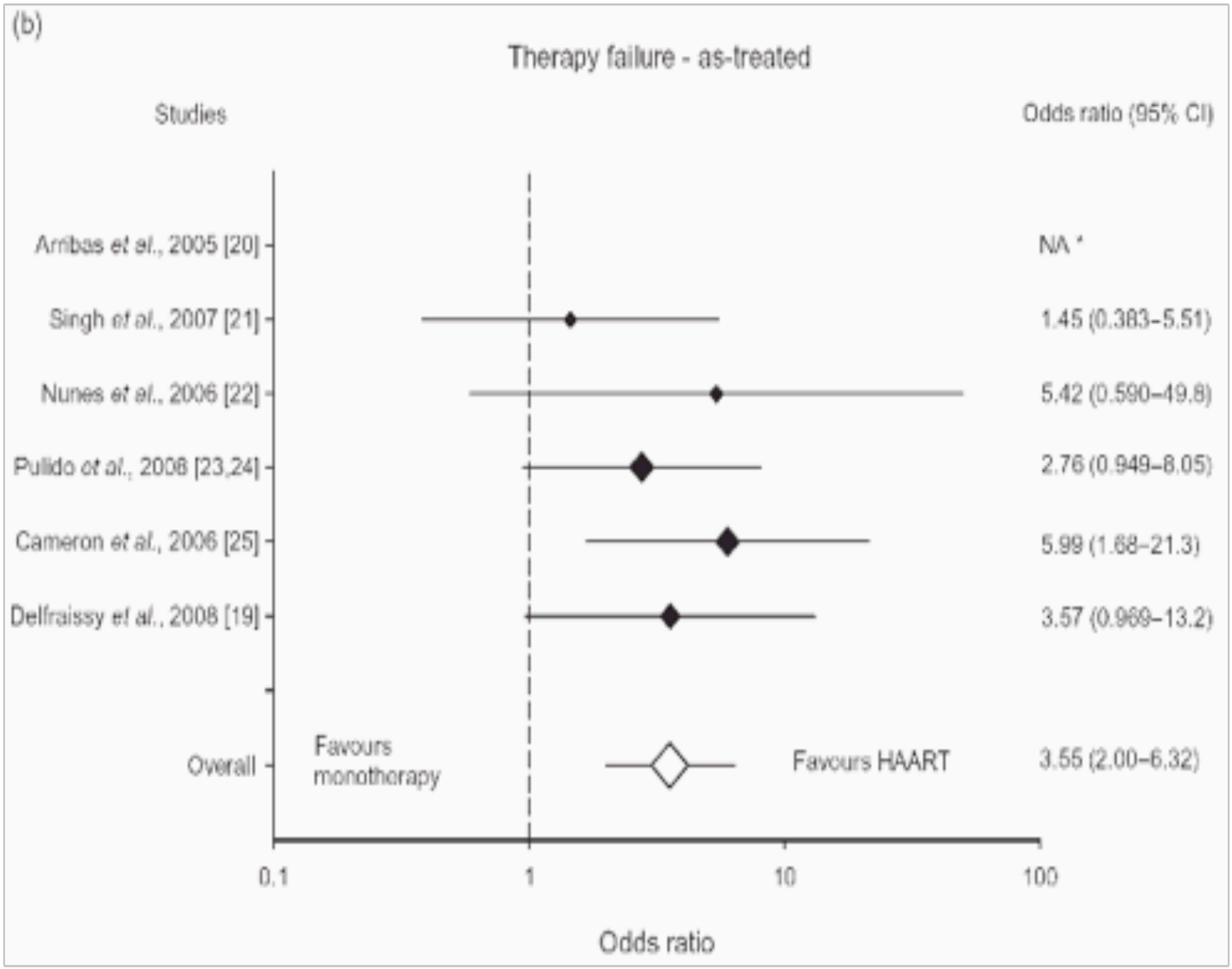
De Luca A, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. THLBB207

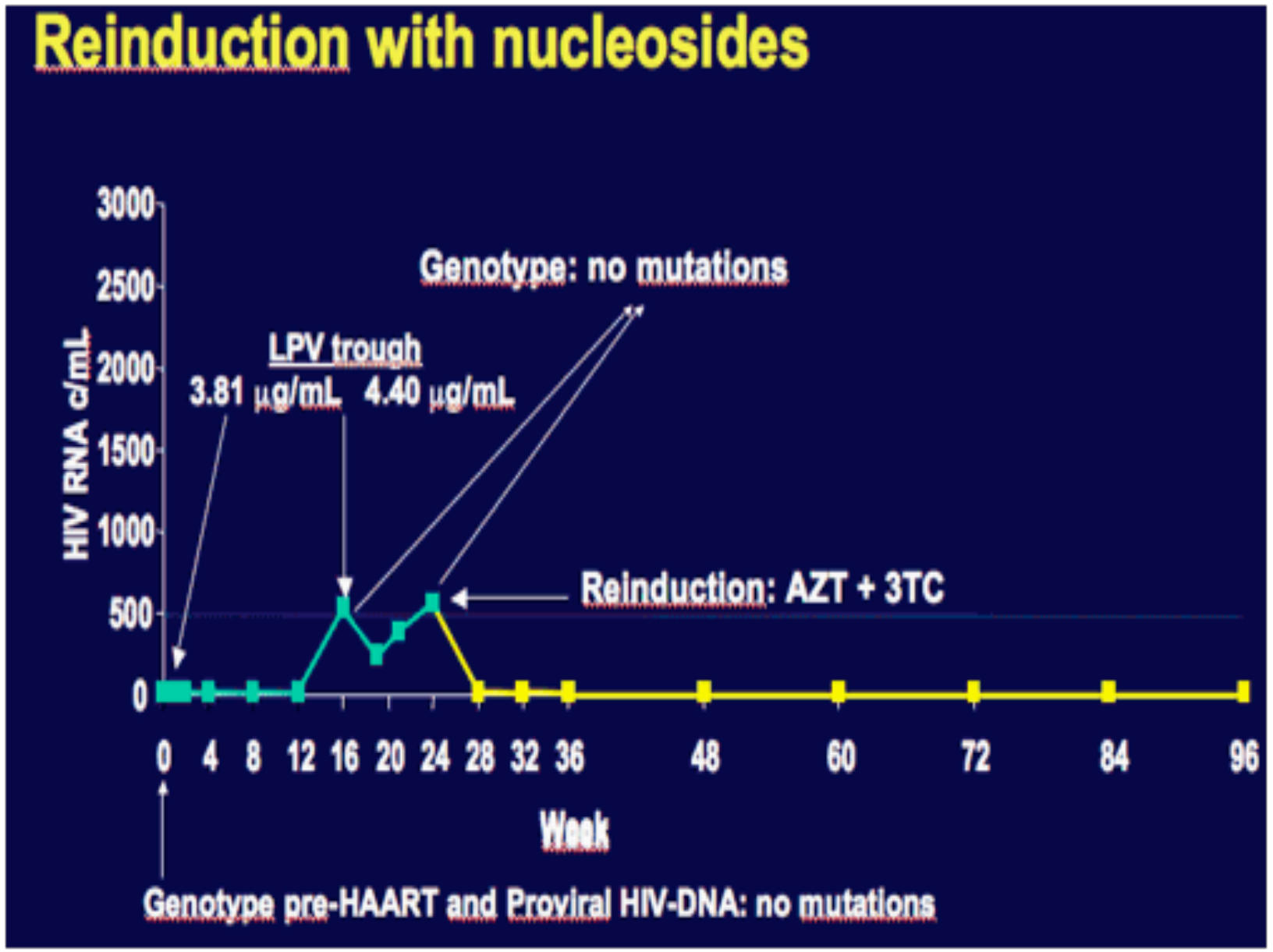
ATV/r + 3TC: TAKE HOME MESSAGE

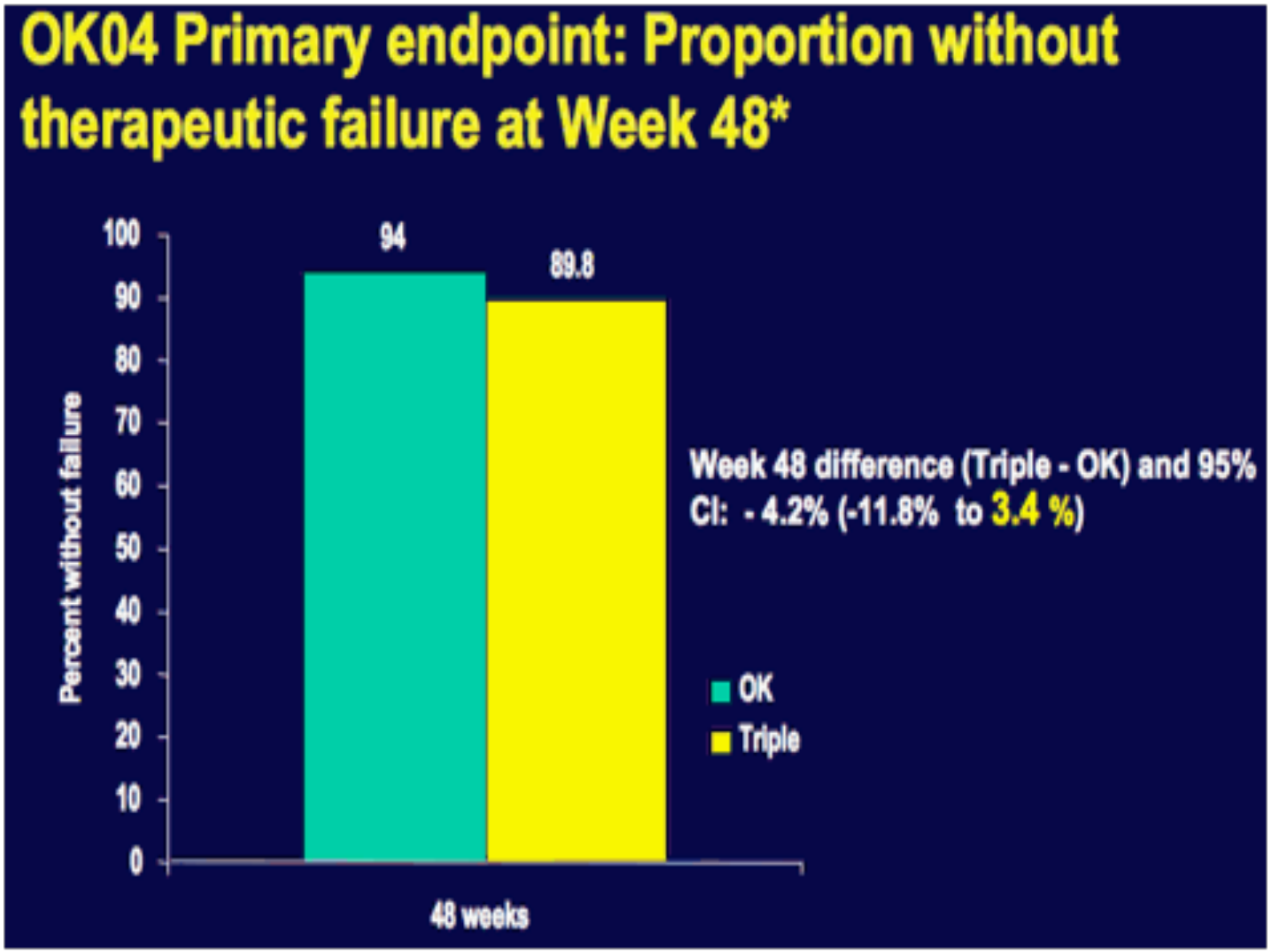
La deintensificazione con un solo nucleosidico al posto di 2, in associazione ad atazanavir/r, in semplificazione e in soggetti a viremia soppressa, sembra mantenere intatta l'efficacia virologica.

INIBITORI DELLE PROTEASI IN MONOTERAPIA


Monotherapy with LPV/r
MONARK – LPV/r
Initial therapy
Study 613 – LPV/r
Induction/maintenance
OK – LPV/r
Simplification
100%
80%
60%
40%
20%
0%
0
16
32
48
0
16
32
48
64
80
96
12
24
36
48
Week
Week
Week
Discontinued
On study, HIV RNA 50–400 c/mL
On study, HIV RNA >400 c/mL
On study, HIV RNA <50 c/mL


(b)
Therapy failure - as-treated
Studies
Odds ratio (95% CI)
Arribas et al., 2005 [20]
NA *
Singh et al., 2007 [21]
1.45 (0.383–5.51)
Nunes et al., 2006 [22]
5.42 (0.590–49.8)
Pulido et al., 2008 [23,24]
2.76 (0.949–8.05)
Cameron et al., 2006 [25]
5.99 (1.68–21.3)
Delfraissy et al., 2008 [19]
3.57 (0.969–13.2)
Overall
3.55 (2.00–6.32)
Favours monotherapy
Favours HAART
0.1
1
10
100
Odds ratio

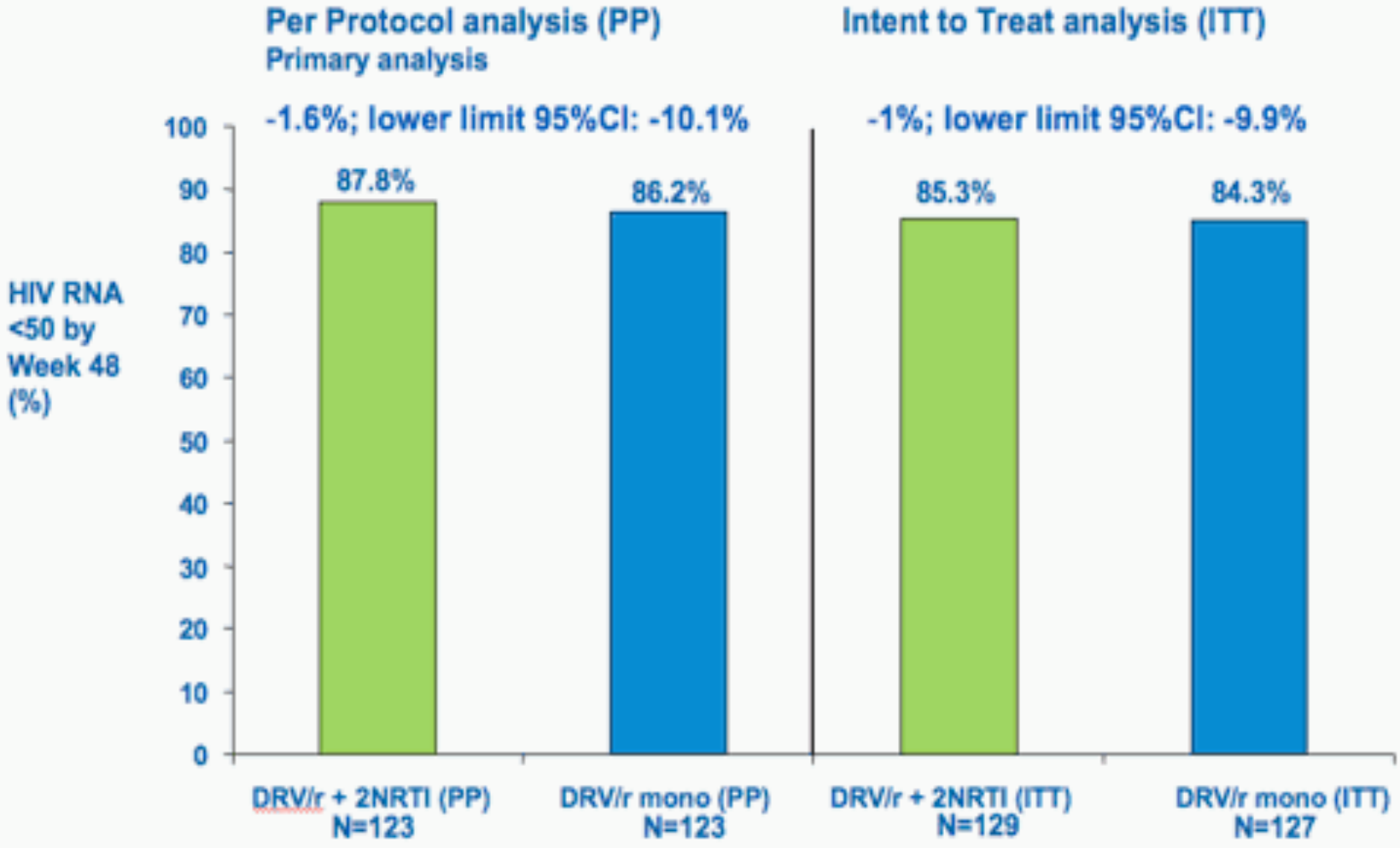

Reinduction with nucleosides
HIV RNA c/mL
3000
2500
2000
1500
1000
500
0
Genotype: no mutations
LPV trough
3.81 µg/mL
4.40 µg/mL
Reinduction: AZT + 3TC
0 4 8 12 16 20 24 28 32 36 48 60 72 84 96
Week
Genotype pre-HAART and Proviral HIV-DNA: no mutations


OK04 Primary endpoint: Proportion without therapeutic failure at Week 48*
Percent without failure
100
90
80
70
60
50
40
30
20
10
0
94
89.8
48 weeks
Week 48 difference (Triple - OK) and 95% CI: - 4.2% (-11.8% to 3.4 %)
OK
Triple

LPV/r: TAKE HOME MESSAGE

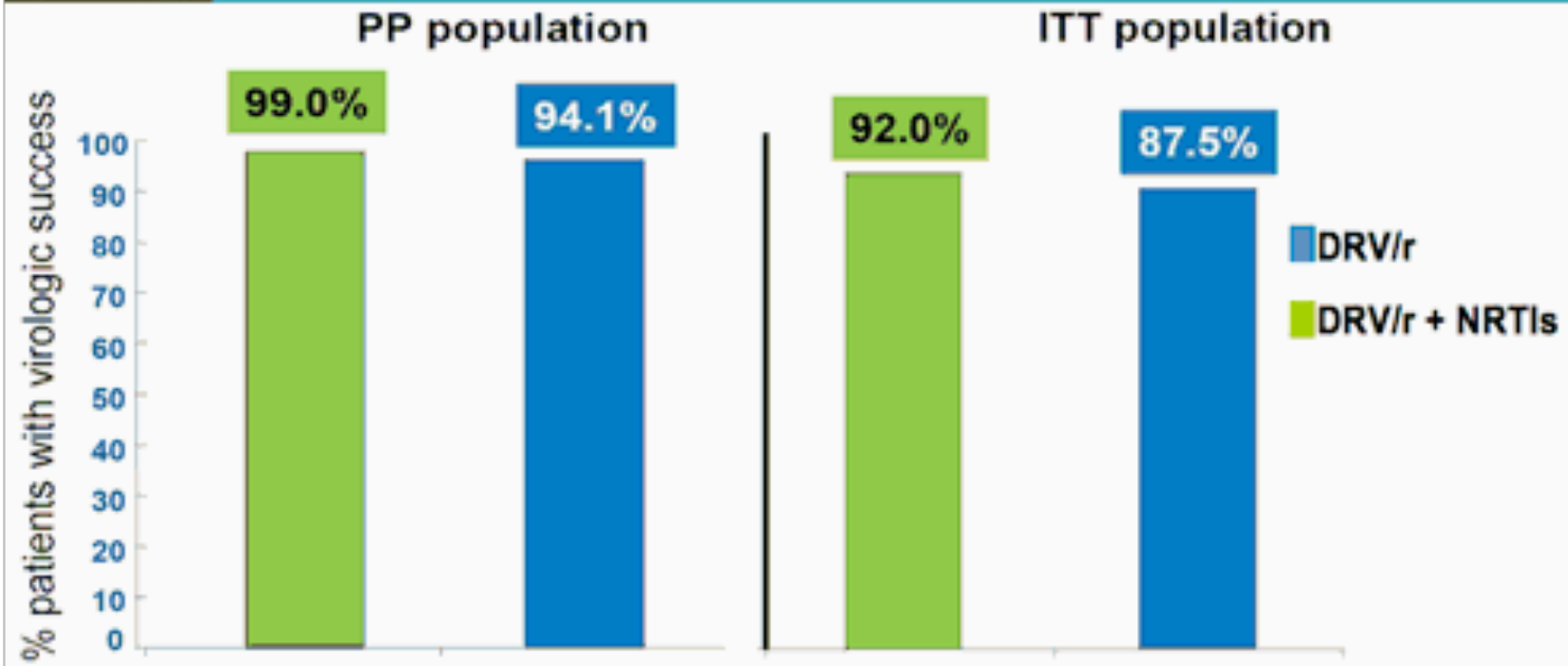
La semplificazione con monoterapia con lopinavir/r è stata quella più studiata e, soprattutto, grazie all'accorgimento di reintrodurre i nucleosidici al minimo blip viremico, ha anche ottenuto buoni risultati di efficacia, anche se non del tutto sovrapponibili alla triplice terapia.

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



J. Arribas et al, AIDS (in press)

MONOI Primary Endpoint W48



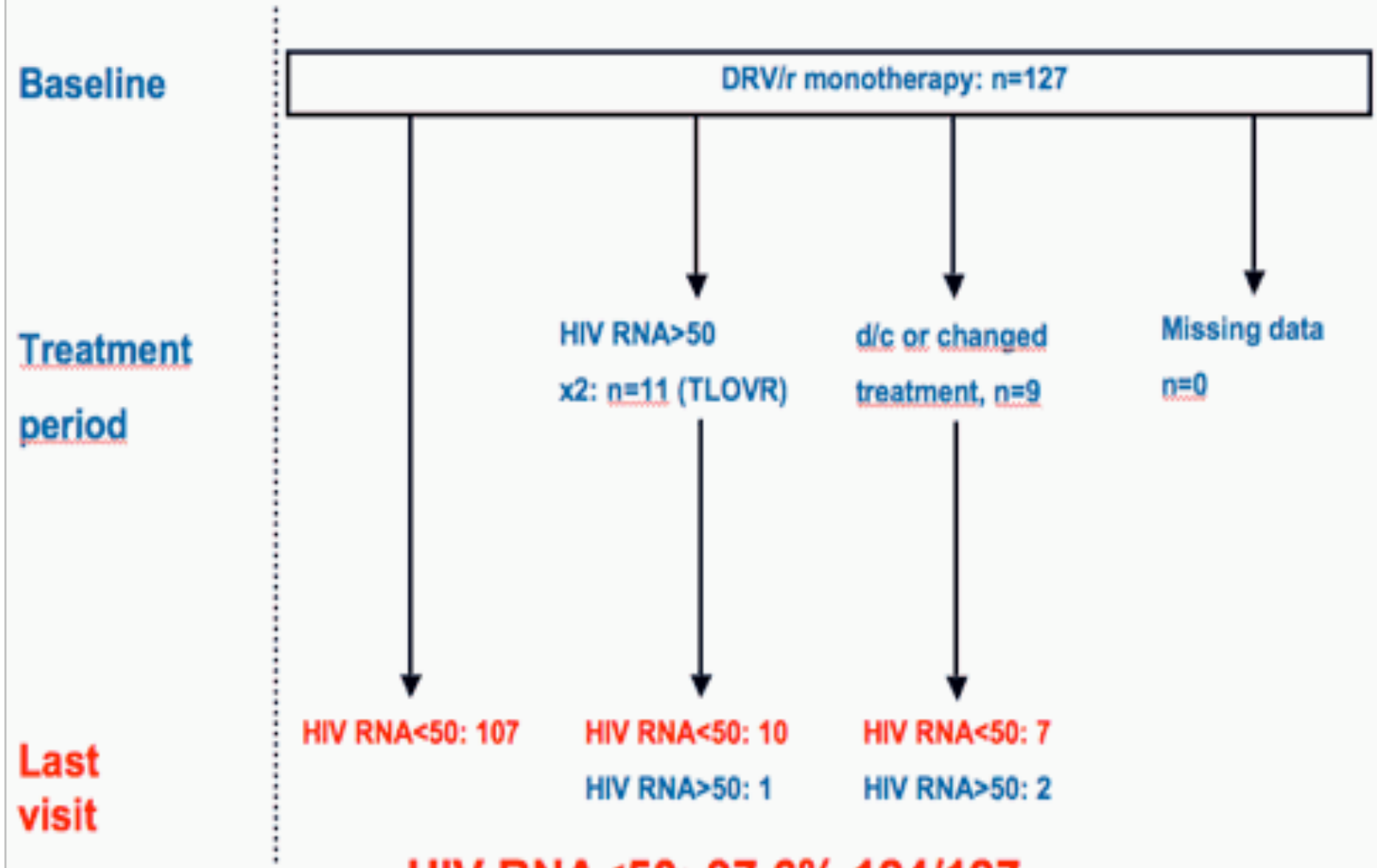
Response	Difference (Lower limit CI)
Rx success (PP, n=204))	- 4.9% (- 9%)
Rx success (ITT, n=225)	- 4.5% (-11%)

-9% > -10% → mono DRV/r non inferior to DRV/r + 2 NRTIs

-11% < -10% → failure to demonstrate non-inferiority

Katlama C et al, IAS Conference, Cape Town, SA, 21 July 2009, WELBB102

MONET: Patient outcomes in DRV/r monotherapy (ITT)



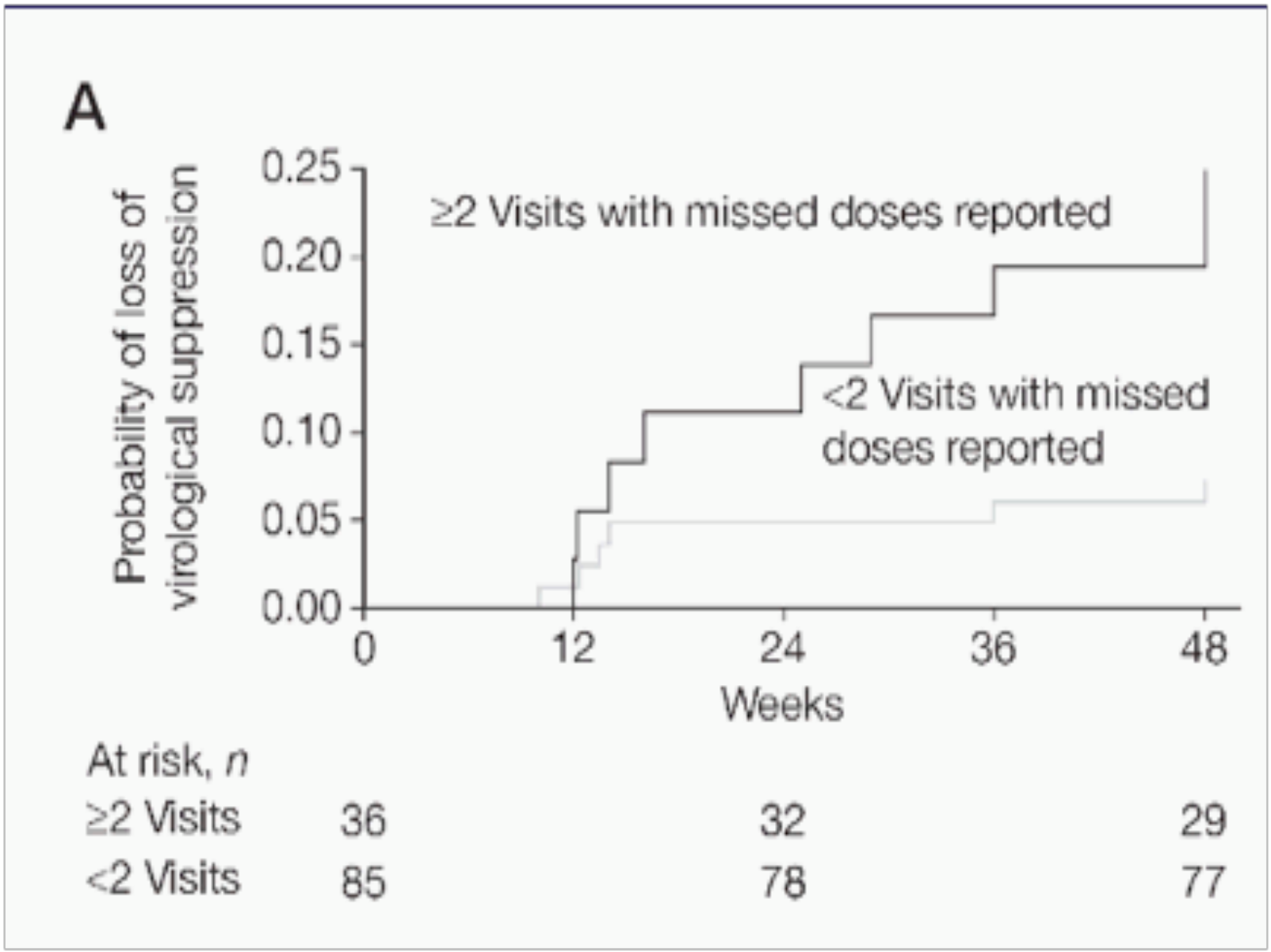
HIV RNA<50: 97.6% 124/127

J. Arribas et al, AIDS (in press)

PI resistance incidence 0.51 per 100 patients years (95% CI: 0,06 -1,82)

	OK (n = 100)	Triple (n = 98)
Genotyping Population*	16 (16%)	4 (4%)
Number of samples	29	9
Patients with isolates with major PI mutations	2 (2%) [10F, 46I, 82A/V] [54V, 77I, 82A]	2 (2%) [54V, 63P, 71V, 82A]

* All patients with HIV-1 RNA > 500 copies/mL analyzed (blips > 500 copies/mL included)


A
Probability of loss of virological suppression
0.25
0.20
0.15
0.10
0.05
0.00
≥2 Visits with missed doses reported
<2 Visits with missed doses reported
0
12
24
36
48
Weeks
At risk, n
≥2 Visits 36 32 29
<2 Visits 85 78 77

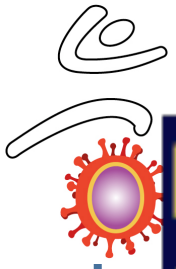
MONOI Serious Adverse events

Number of events	DRV/r + 2 NRTIs n=15	DRV/r n=14
Infections	2	2
Psychiatric events	1	0
CNS disorders	1	3*
Cardiovascular	2	1
Cancer	0	3
Lipodystrophy	0	1
Surgery	6	3
GI disorders	1	0
Hepatic transaminases increase	1	1
CPK	1	0

*one HIV encephalitis and one neurological symptoms possibly related to HIV, both possibly related to study treatments

HIV RNA CSF:580 cp/ml and 330 cp/ml

Katlama C et al, IAS Conference, Cape Town, SA, 21 July 2009, WELBB102



HIV-related Meningoencephalitis in Patients with Optimally Suppressed Plasma HIV RNA Receiving Stable ART

- We identified 10 patients who had experienced acute or sub-acute neurological symptoms (...).
- Patients had been on a stable ART for a median of 14 months (10 to 32)
- their neurological episode occurred in a context of plasma HIV RNA <500 copies/mL, including 7 with plasma viral load <50 copies/mL.

Grade 1-4 Nervous System Adverse Events MONET

	DRV/r + 2NRTI N=129	DRV/r N=127
Total	21 (16.3%)	20 (15.7%)
Areflexia	1	0
Burning sensation	1	0
Carotid artery stenosis	0	1
Disturbance in attention	1	0
Dizziness	3	1
Dysgeusia	1	1
Headache	9	10
Hypoasthaesia	1	2
Intracranial hypotension	0	1
Nervous system disorder	1	0
Parasthaesia	0	2
Post herpetic neuralgia	0	1
Radiculitis	2	0
Sciatica	1	0
Syncope	0	2
Tremor	1	0
Trigeminal neuralgia	0	1

Arribas JR et al. AIDS (in press)

DRV/r: TAKE HOME MESSAGE

La semplificazione con darunavir/r in monoterapia ha ottenuto i migliori risultati (sempre con la reintroduzione dei nucleosidici alla comparsa del minimo blip viremico).

Tuttavia ha evidenziato per prima il possibile escape del virus nel sistema nervoso centrale, che rimane a tutt'oggi un grande punto interrogativo rispetto a questa strategia terapeutica nel suo complesso.

E' inoltre richiesta, da parte del paziente, un'aderenza molto serrata per prevenire lo sviluppo di resistenze genotipiche.

STUDIO OREY - ATV/r: DISEGNO

No history of previous virologic failure

HIV-1, on ATV/RTV + 2 NRTIs ≥8 weeks

Virologic suppression (HIV-RNA <50 c/mL) ≥24 weeks[a]

Study entry

Discontinue NRTIs

ATV/r monotherapy[b]
300 mg/100 mg once daily

n=61

12- and 24-week interim analyses (DSMB)

48-week primary analysis

96-week final analysis

[a] Single blips allowed.

[b] Those subjects who prematurely discontinued monotherapy prior to completion of the study continued to be followed according to the schedule of events.

EACS 2009, Pulido F, et al

STUDIO OREY - ATV/r: RISULTATI

	Number of Subjects/ Evaluable (%)
Maintained suppression <400 copies/mL	48/61 (79%)
Maintained suppression <50 copies/mL	40/60[a] (67%)
Virological rebound ≥400 copies/mL[b]	7/61 (12%)
Virological rebound ≥50 copies/mL	16/60[a] (27%)
Triple therapy resumed with HIV RNA 50-400 copies/mL[c]	2/61 (3%)
Discontinued study	
– Adverse event	1/61 (2%)
– Pregnancy	1/61 (2%)
– Lost to follow-up	1/61 (2%)
– Protocol major deviation (history of virologic failure to PIs)	1/61 (2%)

Seven subjects resumed triple therapy before Week 48 and 2 at Week 48 (and continued being followed in the study). All these 7 subjects reinduced before Week 48 remained resuppressed below 400 copies/mL by Week 48 and all but one also below 50 copies/mL.

EACS 2009, Pulido F, et al

ATV/r: TAKE HOME MESSAGE

La semplificazione con atazanavir/r in monoterapia non ha ottenuto, almeno da questi dati preliminari, buoni risultati virologici. Pertanto, al momento, la strategia migliore sembra essere quella dello studio ATLAS che propone atazanavir/r + 3TC.

IP/r: TAKE HOME MESSAGE

I dati in nostro possesso mostrano una migliore efficacia della triplice terapia rispetto a questa strategia.

Si sono effettuati quasi sempre di studi di switch.

Vi sono possibili importanti problemi di “escape virologico” nel sistema nervoso centrale e problematiche di maggior tossicità lipidica.

DISCUSSIONE GENERALE

Cosa pensano i pazienti di queste strategie?

Abbiamo sufficienti dati per dire che “meno farmaci” sono meglio di 3?

Quasi tutti i regimi “alternativi” proposti sono BID: sarà un po’ come tornare indietro?

Vi vengono proposte queste nuove strategie e/o siete voi a ricercarle? Perché?