Semplificazione della terapia ARV

Paestum

13-15 maggio 2004

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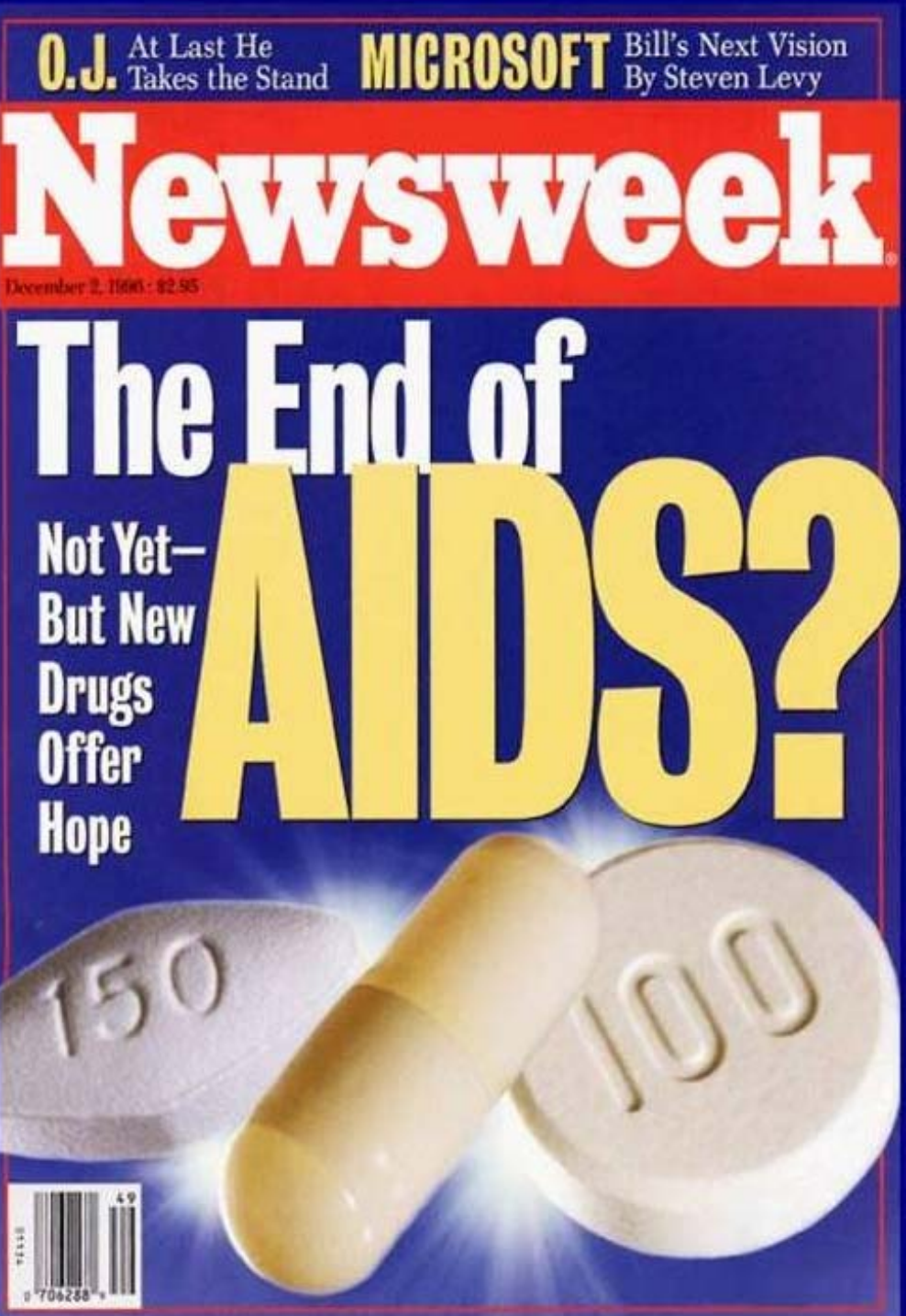


Infezione cronica che necessita di terapia "cronica"

Perché semplificare la terapia?

Tossicità

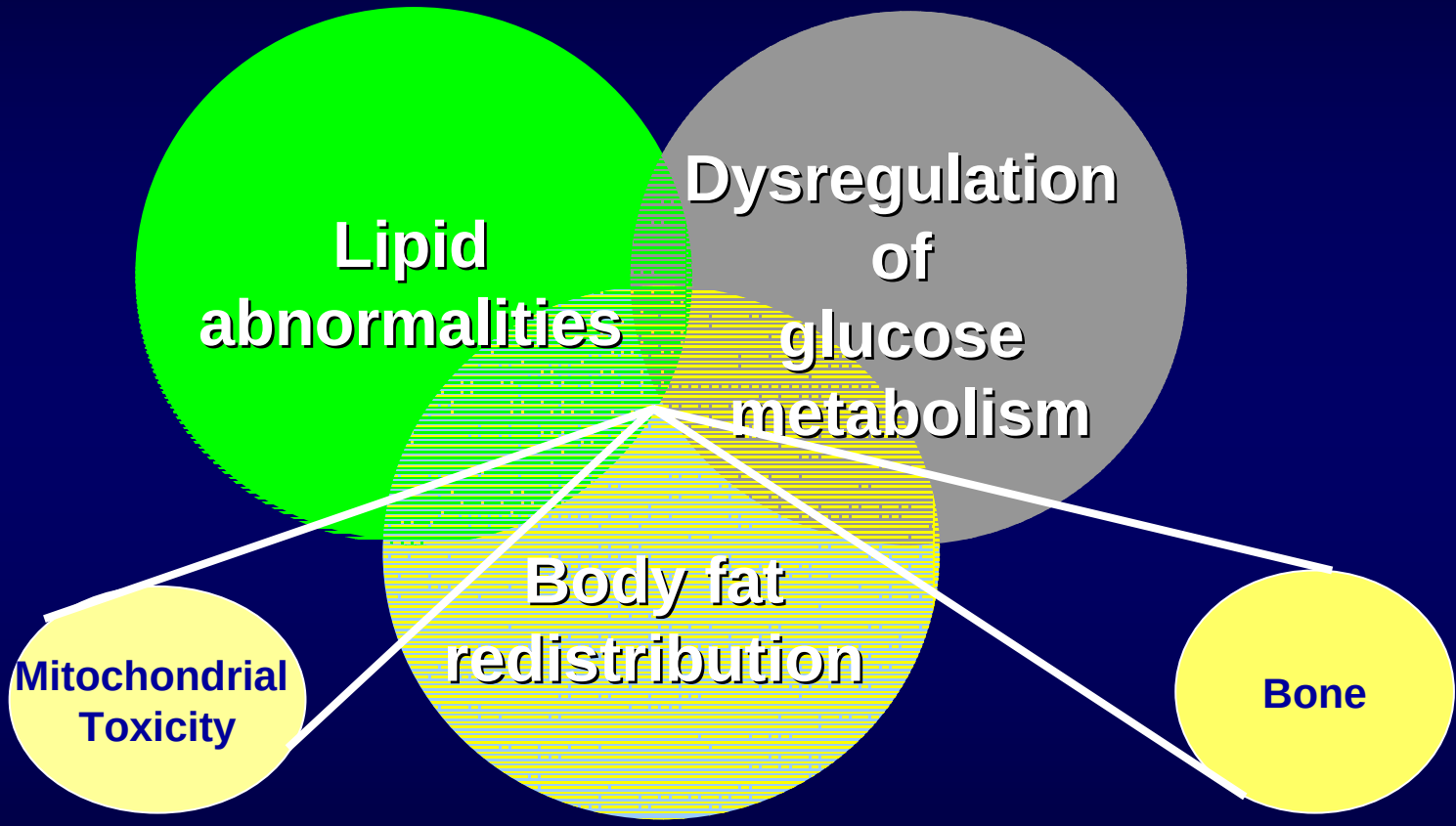
Aderenza

Effetti collaterali

Indicazione del medico

Richiesta del paziente

Metabolic Complications



- One syndrome or several?
- One etiology or multifactorial?

Managing toxicity

- Proactive approach
  - Symptom control
  - Individualisation
- Lipodystrophy
  - Choice of nucleosides
  - Switching / cosmetic approaches
- Hyperlipidemia
  - Manage other risk factors
  - Switching strategies

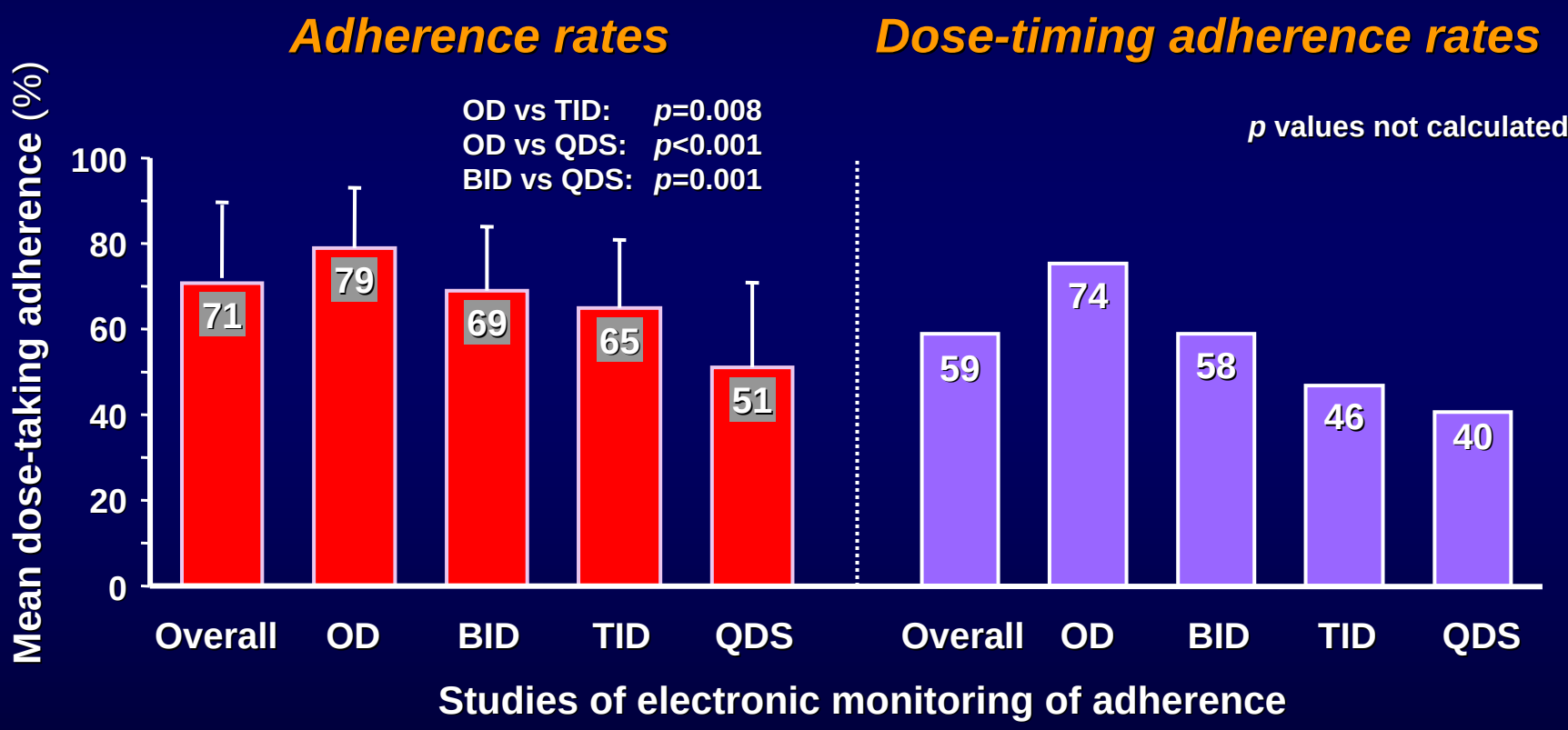
Improving Adherence

- Adherence behaviour is difficult to change
- Regimens can be changed to ease adherence
  - —reducing pill burden
  - —reducing dietary restrictions
  - —once-daily therapy
  - —better pharmacokinetics
  - —simplification

Impact of dose frequency upon adherence

Analysis of 76 studies of electronic monitoring of adherence

(Meta-analysis of different diseases: hypertension, diabetes,etc)



Adapted from: Claxton AJ *et al*. *Clin Ther* 2001; 23: 1296–1310

Once-a-Day therapy for HIV infection: a controlled, randomized study in antiretroviral-naive HIV-1 infected patients.

OD regimen
EFV+ddI+3TC

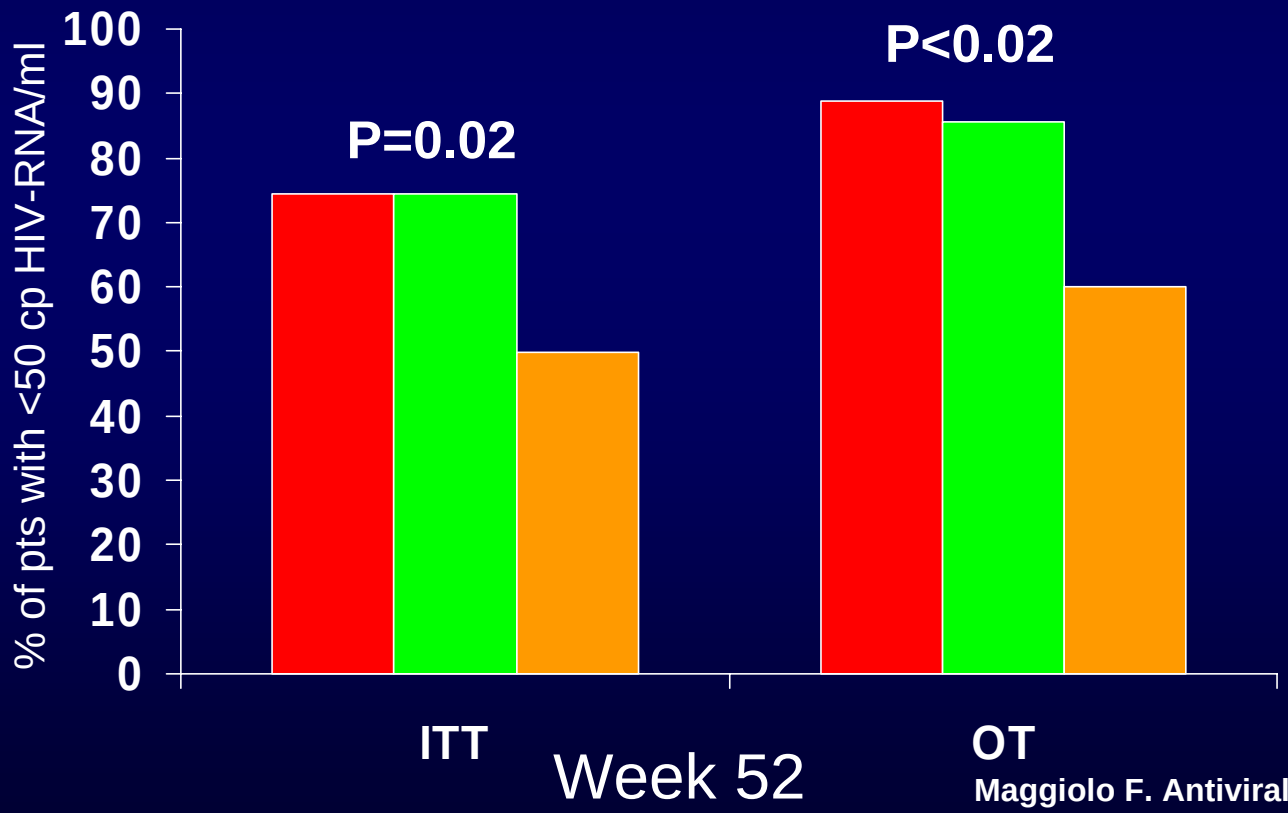
n. 34 naive pts

Bid-Low pill burden
EFV+ZDV+3TC

n. 34 naive pts

Bid-High pill burden
NFV+ZDV+3TC

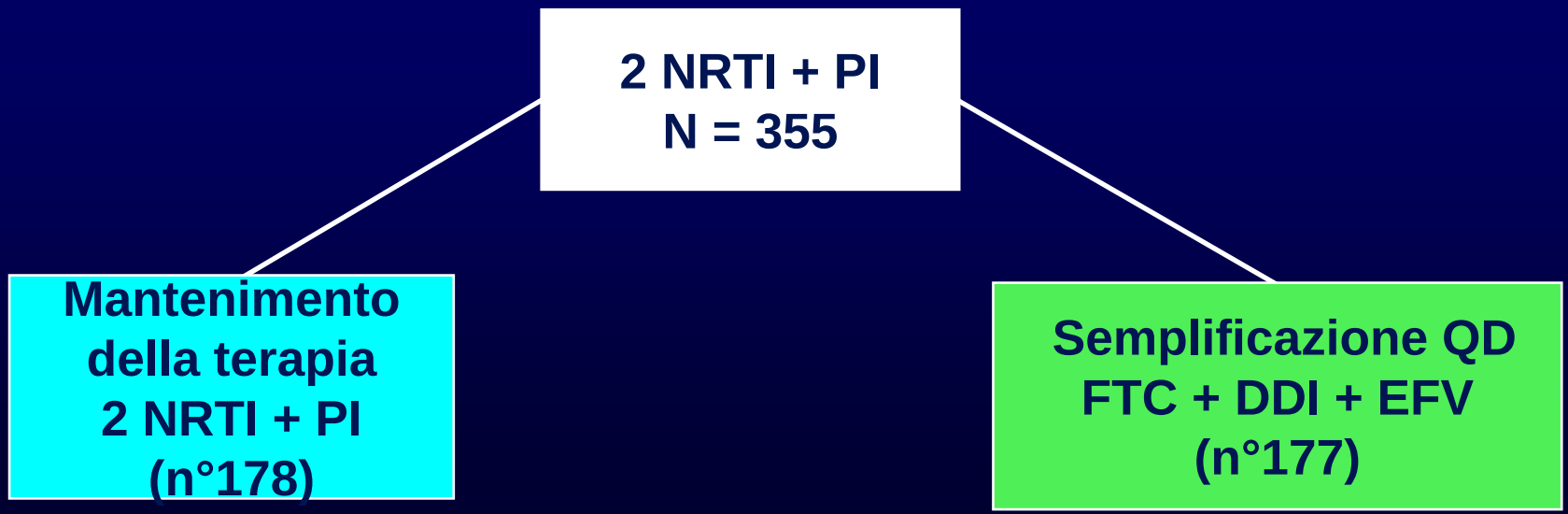
n. 34 naive pts



Maggiolo F. Antiviral Therapy, 8:339,2003

Emtricitabine, didanosine and efavirenz once-daily versus continued PI-based HAART in HIV-infected adults with undetectable HIV RNA 48-week results of a prospective randomized multicenter trial (ALIZE - ANRS 099)

JM Molina, 2nd IAS Conference on HIV Pathogenesis and Treatment Abstract 37



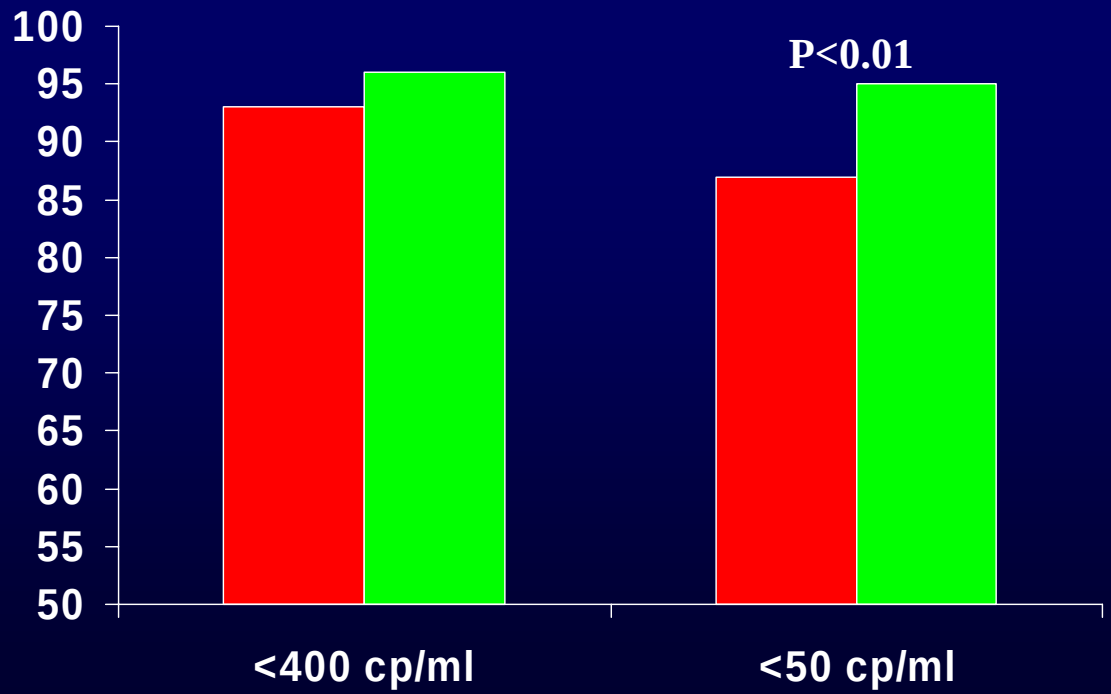
ALIZE-ARNS 99 (JM. Molina, Paris, France abs.37)

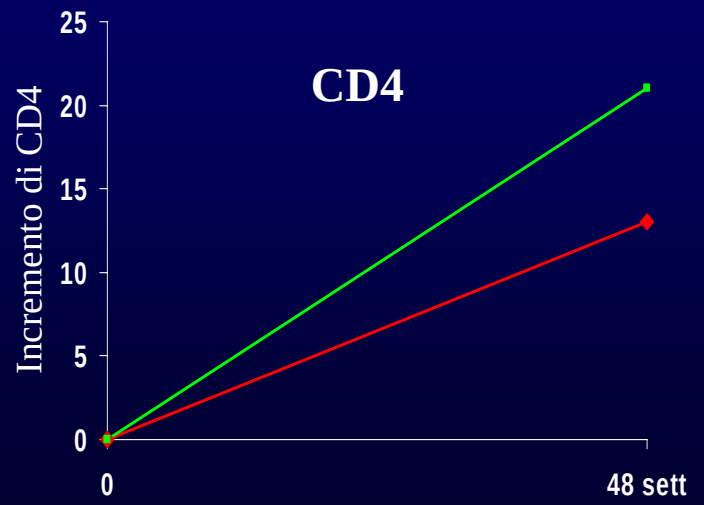
Studio finalizzato a valutare l'efficacia di terapia di semplificazione once-daily

355 pazienti in trattamento con HAART-PI e con < 50 cp HIV-RNA/ml

- Continuano la terapia
- ddI+EFV+Emtricitabina (FTC)

Risultati a 48 settimane "as treated"



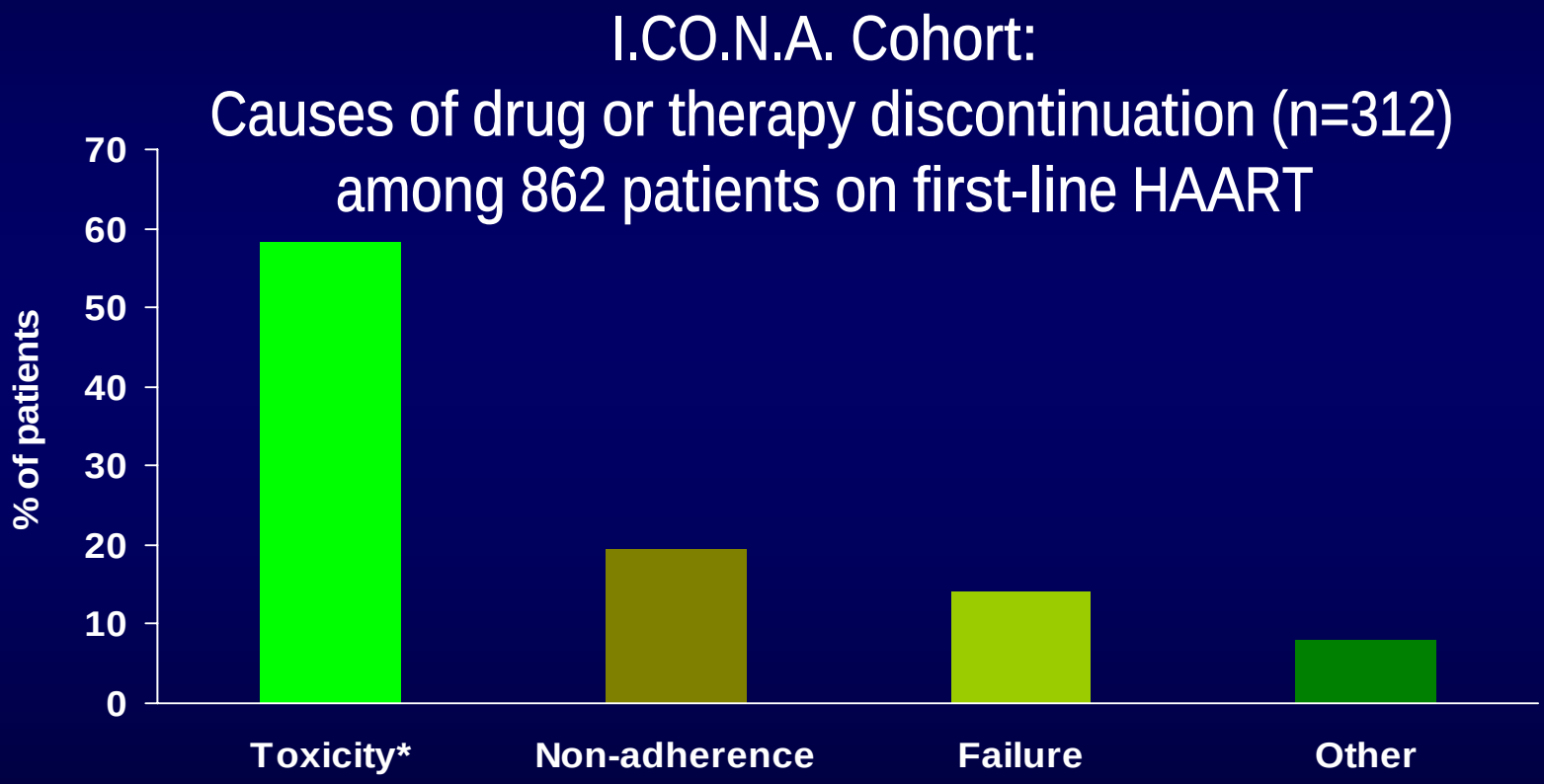


HIV OD agents approved or in development

Approved OD agents	*Approved agents under OD evaluation*	*Investigational agents*
Efavirenz	Nevirapine	Atazanavir*
Didanosine	Boosted PIs	T-1249
Tenofovir	Abacavir	FOS-amprenavir
Stavudine PRC		Emtricitabine (FTC)*
3TC		
Boosted PI		
SQV 1600/RTV 100		
APV 1200/RTV 200		
FosAPV 1400/RTv 200		

* approved in US

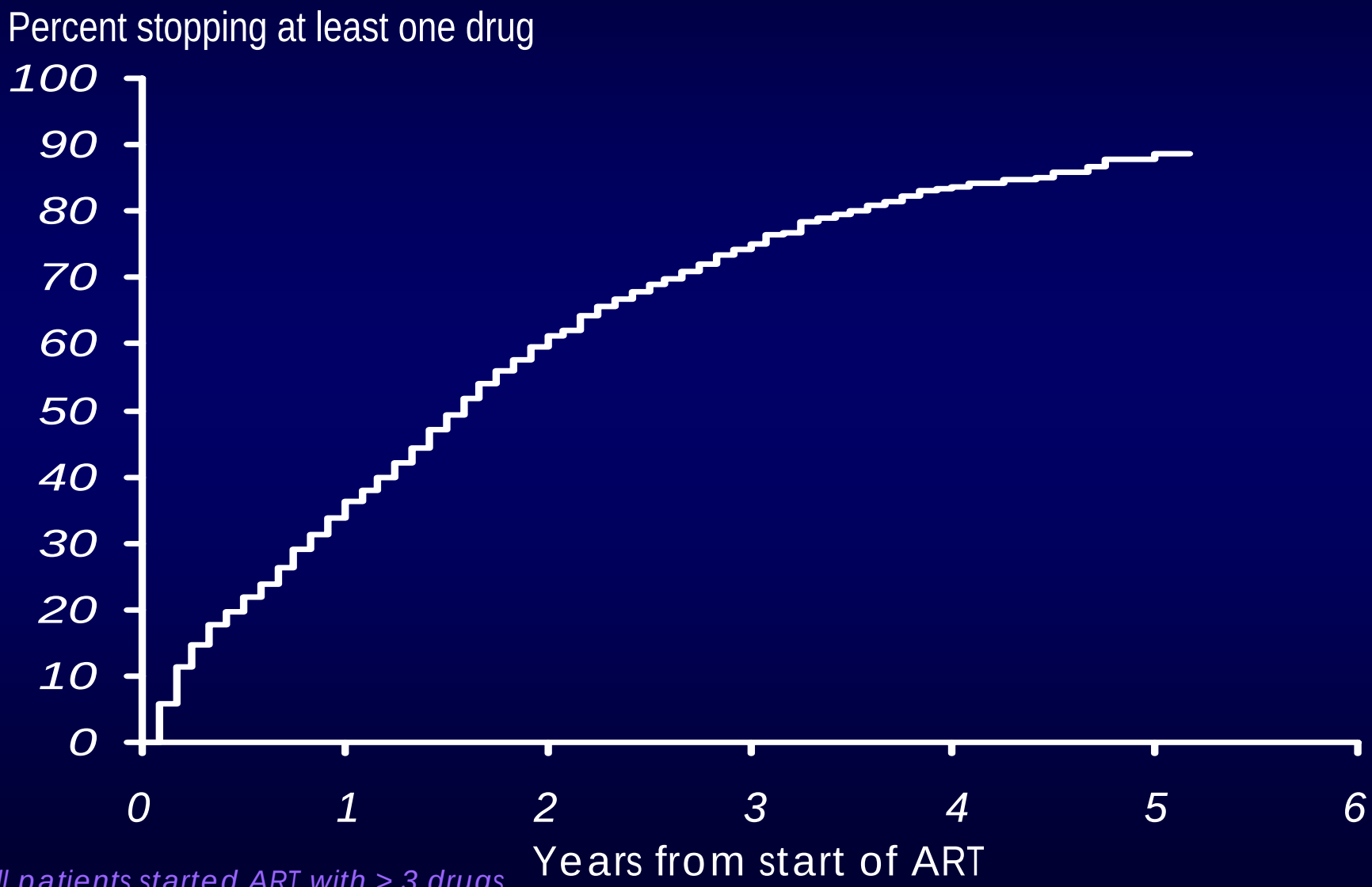
Drug Toxicity and Nonadherence Are More Common Reasons for Discontinuing ART than Therapeutic Failure



* Toxicity is itself a major cause of non-adherence.

Stopping or switching drugs in initial ART regimen

EuroSIDA: n = 1540 people starting ART



All patients started ART with ≥ 3 drugs

March 2003 EuroSIDA

Come semplificare la terapia

- 2 NRTIs + PI/rtv
- 2NRTI + NNRTI
- 2NRTI + NRTI
- STI

Semplificazione nel paziente plurifallito

Interruzione PI

Significant Improvement in Lipid Levels Upon Substitution of Protease Inhibitor Therapy with Efavirenz in HIV-infected Children

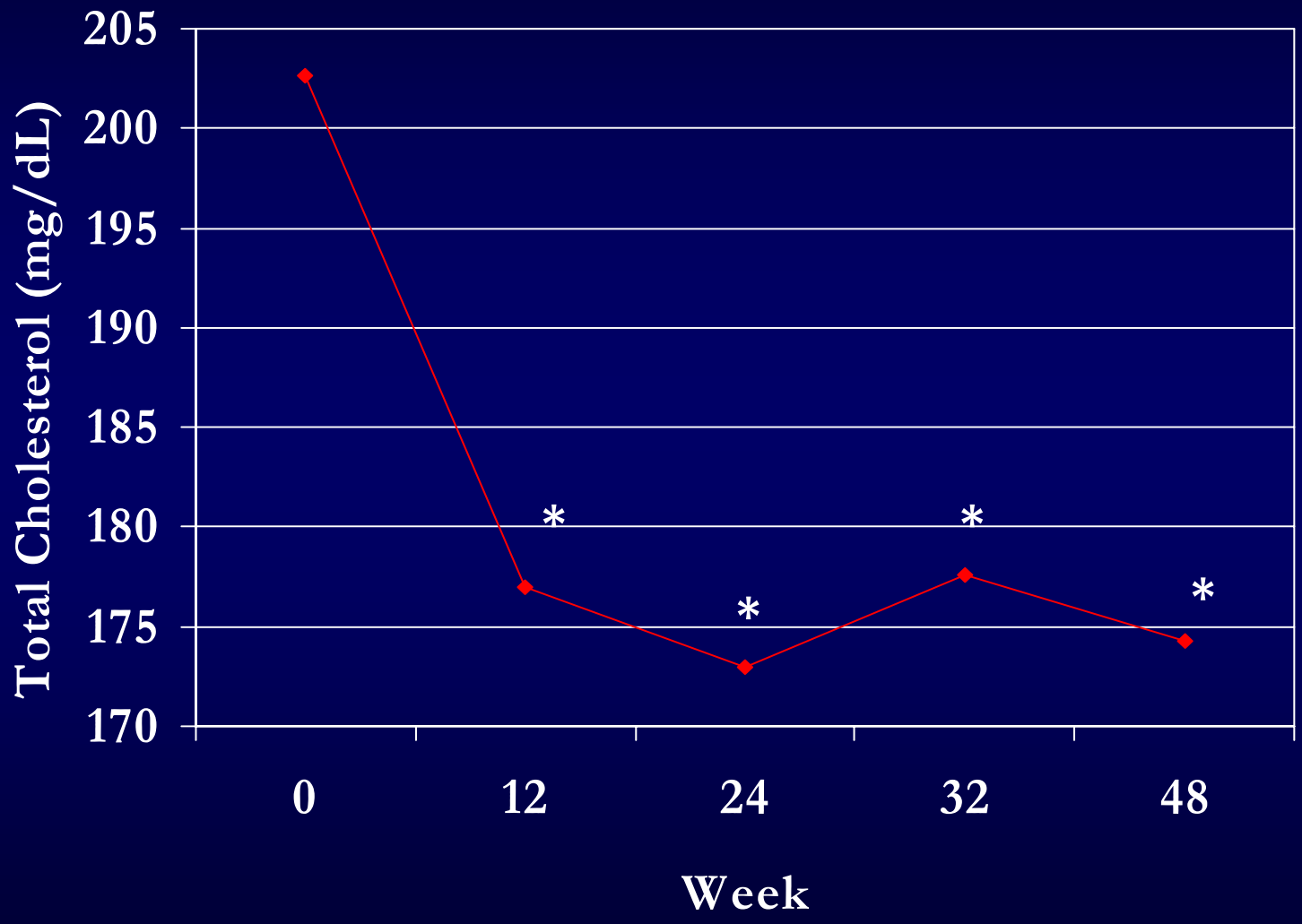
Grace McComsey[1,2], Nasreen Bhumbra[3], Jen-Fue Maa[4], Mobeen Rathore[5], and Ana Alvarez[5]

Rainbow Babies and Children's Hospital[1], Center for AIDS Research, Case Western Reserve University, Cleveland, OH, USA[2]; Medical College of Ohio, Toledo, Ohio, USA[3]; Bristol-Myers Squibb, NJ, USA[4]; and University of Florida Health Science Center, Jacksonville, FL, USA[5]

Inclusion Criteria

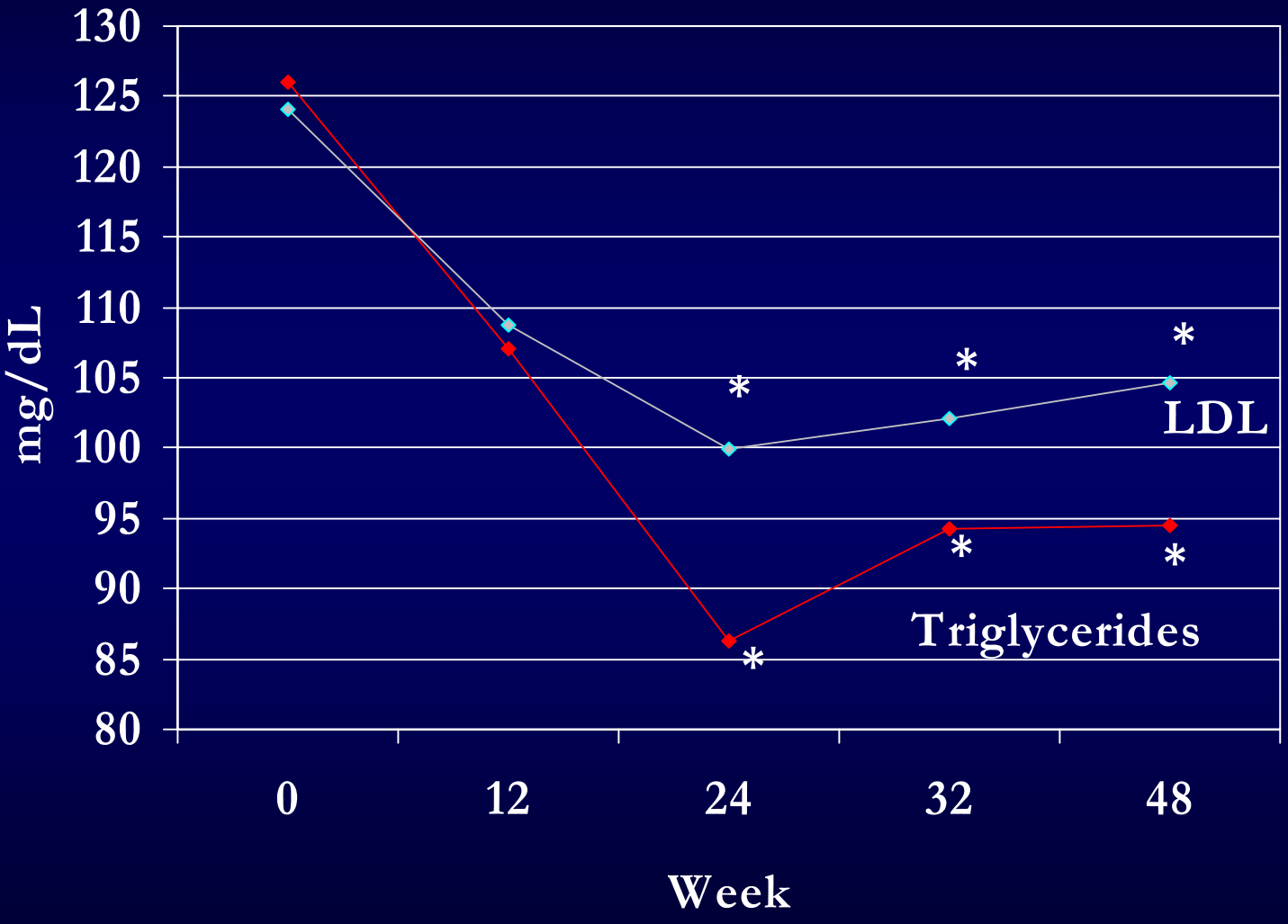
- Age 1-18 years
- Stable PI-containing regimen for > 6 months
- HIV RNA < 400 cps/mL for > 4 months
- Naïve to NNRTI
- Informed consent

Mean Total Cholesterol



* P < 0.05 change from baseline

Mean Fasting Triglycerides and LDL-C



* P< 0.05 change from baseline

Mean HDL-C

No statistical significance for change from baseline

Meta-analysis of randomized controlled trials of simplified versus continued protease inhibitor-based antiretroviral therapy in HIV-1-infected patients

Heiner C. Bucher[a], Andreas Kofler[a], Reto Nüesch[b], James Young[c], Manuel Battegay[c] and Milos Opravil[d]

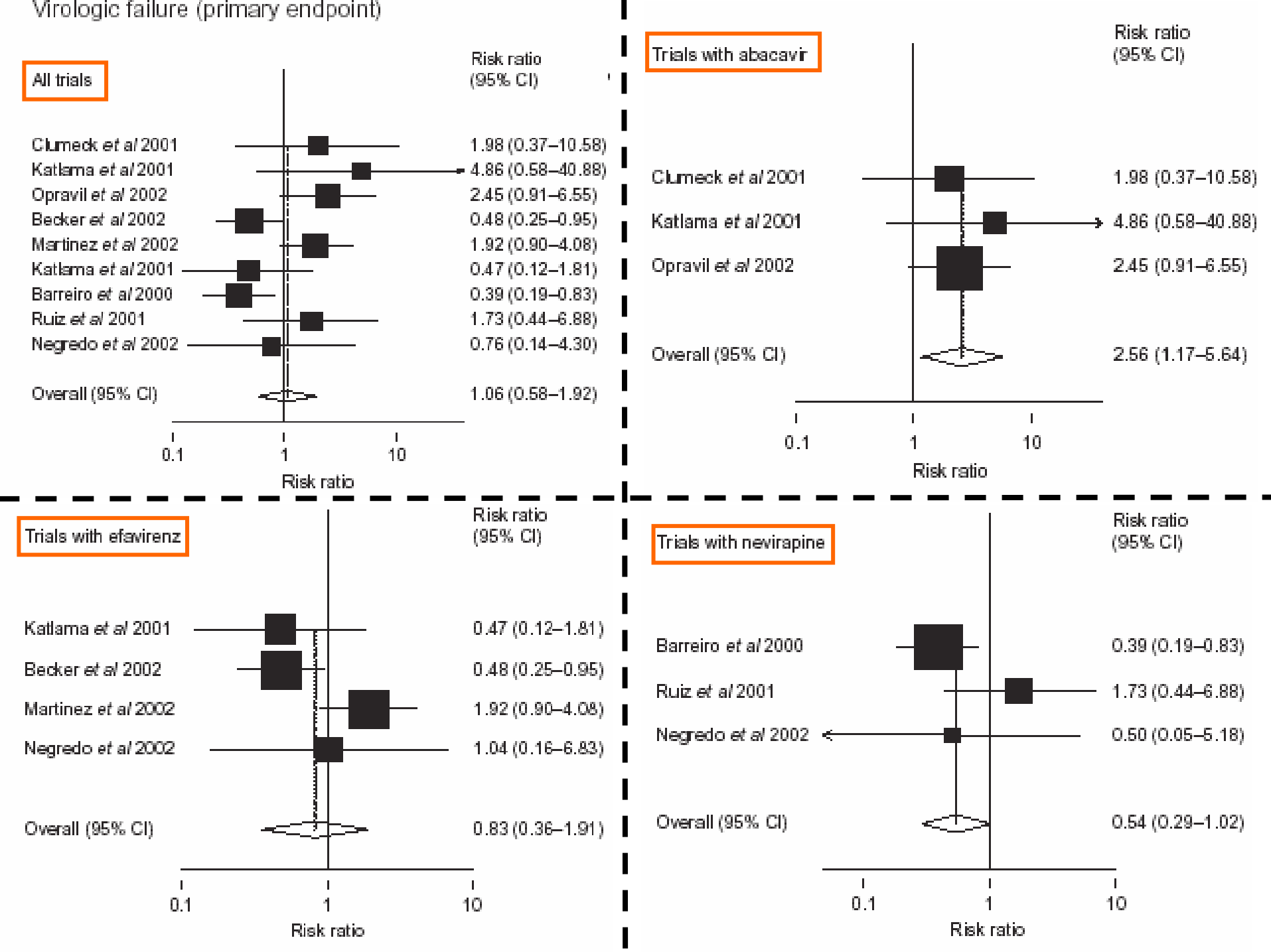
Objective: To evaluate the efficacy and safety of simplified maintenance therapy (SMT) compared with continued protease inhibitor (PI) therapy.

Design: Meta-analysis of nine randomized controlled trials in which 833 patients were switched to SMT (abacavir, efavirenz or nevirapine) and 616 continued PI, assessing virologic failure (primary outcome), discontinuation of therapy for reasons other than virologic failure, CD4 cell count, total plasma cholesterol and triglycerides.

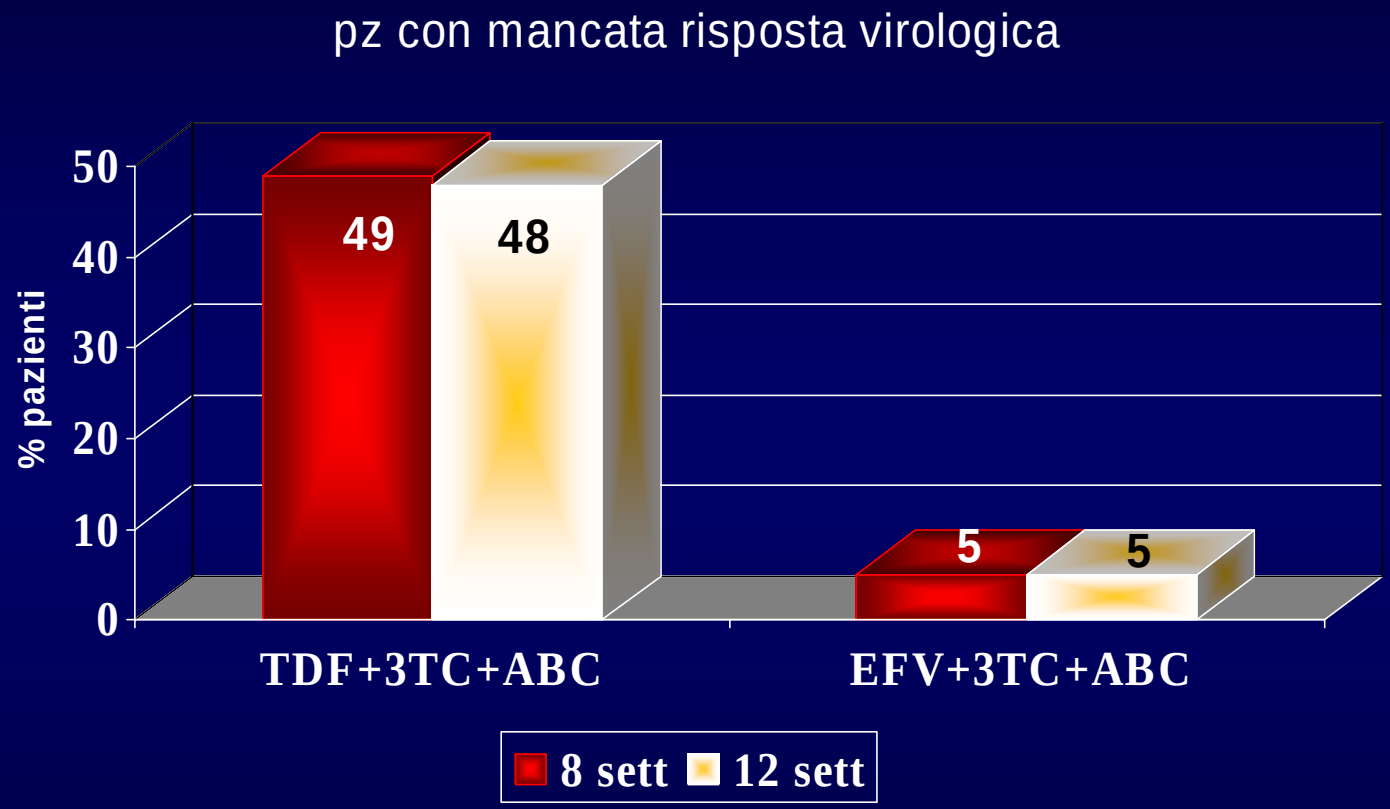
Results: The risk ratio for virologic failure for SMT compared to continued PI was 1.06 [95% confidence interval (CI) 0.58–1.92; test for homogeneity $P = 0.01$] for SMT, 2.56, (95% CI, 1.17–5.64) for abacavir, 0.83 (95% CI, 0.36–1.91) for efavirenz and 0.54 (95% CI, 0.29–1.02) for nevirapine. The risk ratio for premature discontinuation of therapy with SMT was 0.61 (95% CI, 0.48–0.77; test for homogeneity $P < 0.10$). The difference in absolute mean cholesterol for SMT compared to continued PI was −0.15 mmol/l, (95% CI, −0.40 to 0.09; test for homogeneity $P < 0.01$) for SMT, −0.51 mmol/l (95% CI, −0.70 to −0.33) for abacavir, 0.22 mmol/l (95% CI, 0 to 0.43) for efavirenz and −0.19 mmol/l (95% CI, −0.48 to 0.09) for nevirapine.

Conclusions: Current evidence suggests that SMT with abacavir rather than continued PI increases the risk of virologic failure, this increased risk may be confined to patients with prior mono or dual therapy with reverse transcriptase inhibitors. There is not enough evidence on whether SMT with efavirenz and nevirapine influences the risk of virologic failure. SMT with any of the three drugs reduces the risk of discontinuation of therapy, and SMT with abacavir reduces plasma cholesterol.

AIDS 2003, **17**:2451–2459

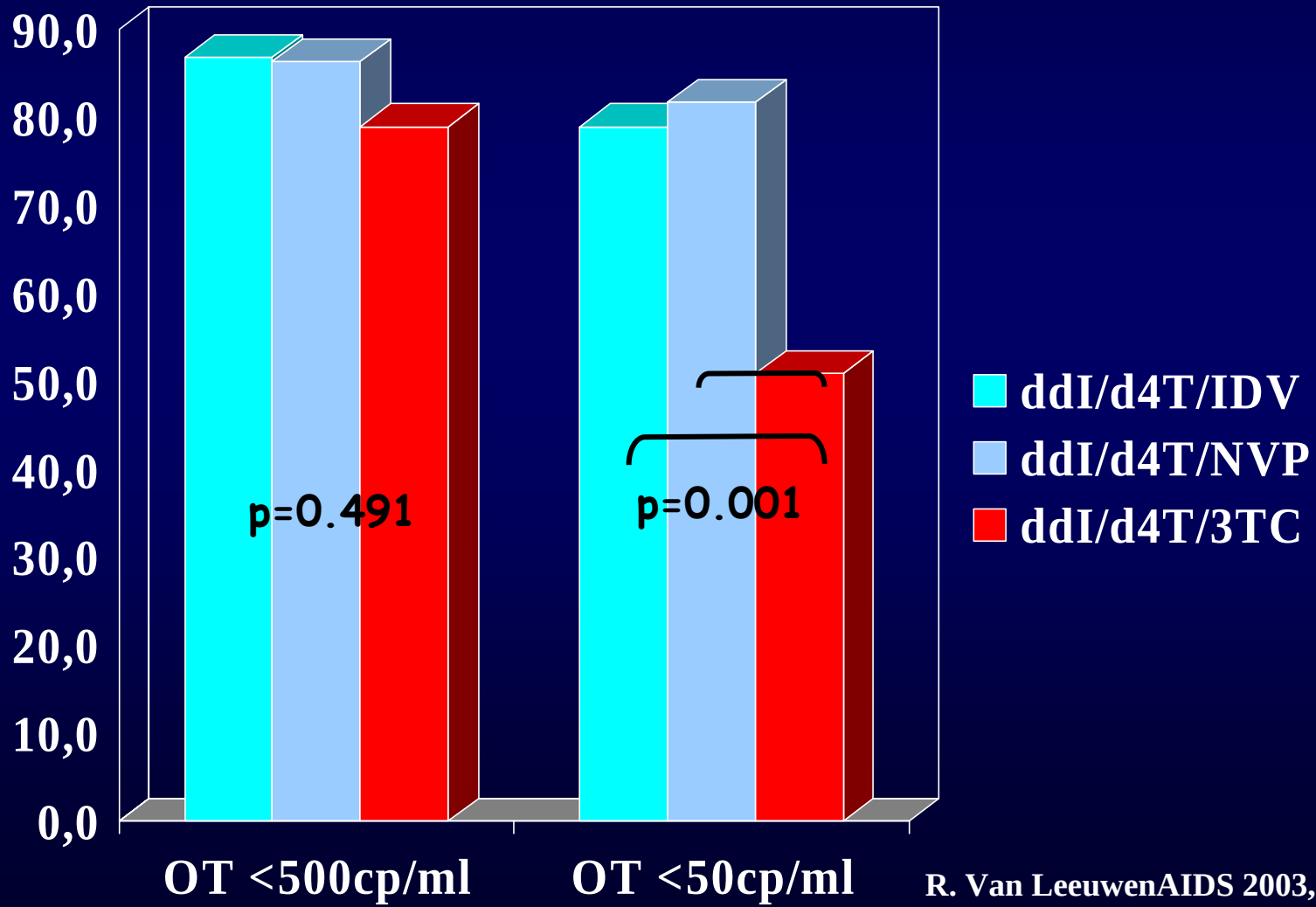

Virologic failure (primary endpoint)
All trials
Risk ratio (95% CI)
Clumeck et al 2001
Katlama et al 2001
Opravil et al 2002
Becker et al 2002
Martinez et al 2002
Katlama et al 2001
Barreiro et al 2000
Ruiz et al 2001
Negredo et al 2002
Overall (95% CI)
1.98 (0.37–10.58)
4.86 (0.58–40.88)
2.45 (0.91–6.55)
0.48 (0.25–0.95)
1.92 (0.90–4.08)
0.47 (0.12–1.81)
0.39 (0.19–0.83)
1.73 (0.44–6.88)
0.76 (0.14–4.30)
1.06 (0.58–1.92)
0.1
1
10
Risk ratio
Trials with abacavir
Risk ratio (95% CI)
Clumeck et al 2001
Katlama et al 2001
Opravil et al 2002
Overall (95% CI)
1.98 (0.37–10.58)
4.86 (0.58–40.88)
2.45 (0.91–6.55)
2.56 (1.17–5.64)
0.1
1
10
Risk ratio
Trials with efavirenz
Risk ratio (95% CI)
Katlama et al 2001
Becker et al 2002
Martinez et al 2002
Negredo et al 2002
Overall (95% CI)
0.47 (0.12–1.81)
0.48 (0.25–0.95)
1.92 (0.90–4.08)
1.04 (0.16–6.83)
0.83 (0.36–1.91)
0.1
1
10
Risk ratio
Trials with nevirapine
Risk ratio (95% CI)
Barreiro et al 2000
Ruiz et al 2001
Negredo et al 2002
Overall (95% CI)
0.39 (0.19–0.83)
1.73 (0.44–6.88)
0.50 (0.05–5.18)
0.54 (0.29–1.02)
0.1
1
10
Risk ratio

Studio ESS30009 Early virologic failure in a pilot study evaluating once-daily treatment with ABC/3TC/TDF (Farthing, IAS Paris, 2003, abs.43)



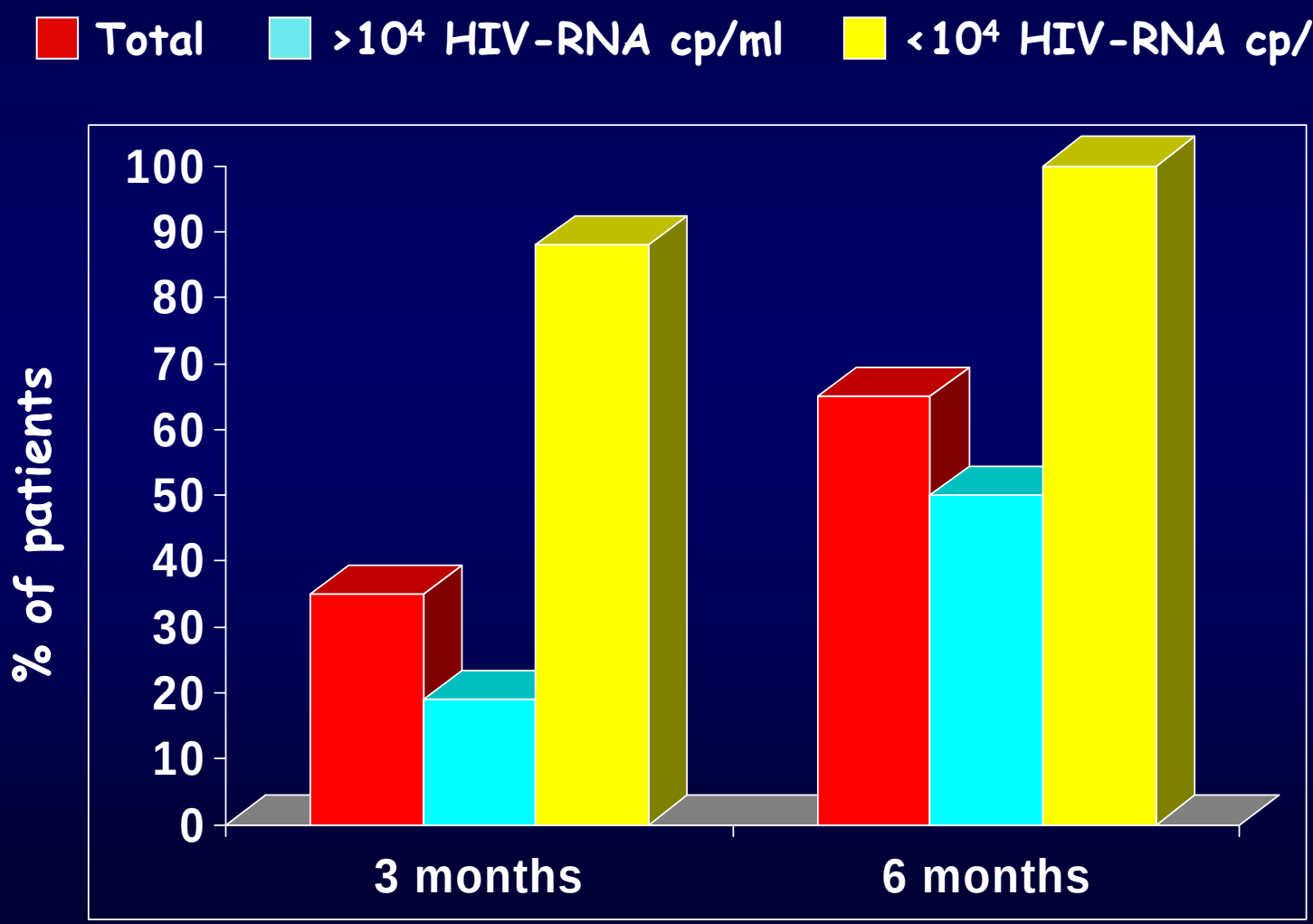
- **La valutazione genotipica degli isolati virali di 14 paz. con mancata risposta che assumevano il regime con TDF ha evidenziato che tutti i 14 isolati presentavano la mutazione M184V**
- **8 dei 14 isolati (57%) avevano anche la mutazione K65R**

A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1 infected patients (week 96)



R. Van LeeuwenAIDS 2003, 17:987-999

Low genetic barrier to resistance is a possible cause of early virologic failures in once-daily regimen of abacavir, lamivudine and tenofovir: the Tonus study



Landman R, CROI 2004 Abs 52

La terapia di semplificazione

Il miglioramento dell'aderenza non può essere fatto a discapito della potenza della terapia

Esistono parametri prognostici di successo alla terapia di semplificazione ?

Esiste la possibilità di utilizzare un regime monoclasse nella semplificazione ?

A Randomized Trial of Simplified Maintenance Therapy with Abacavir, Lamivudine, and Zidovudine in Human Immunodeficiency Virus Infection

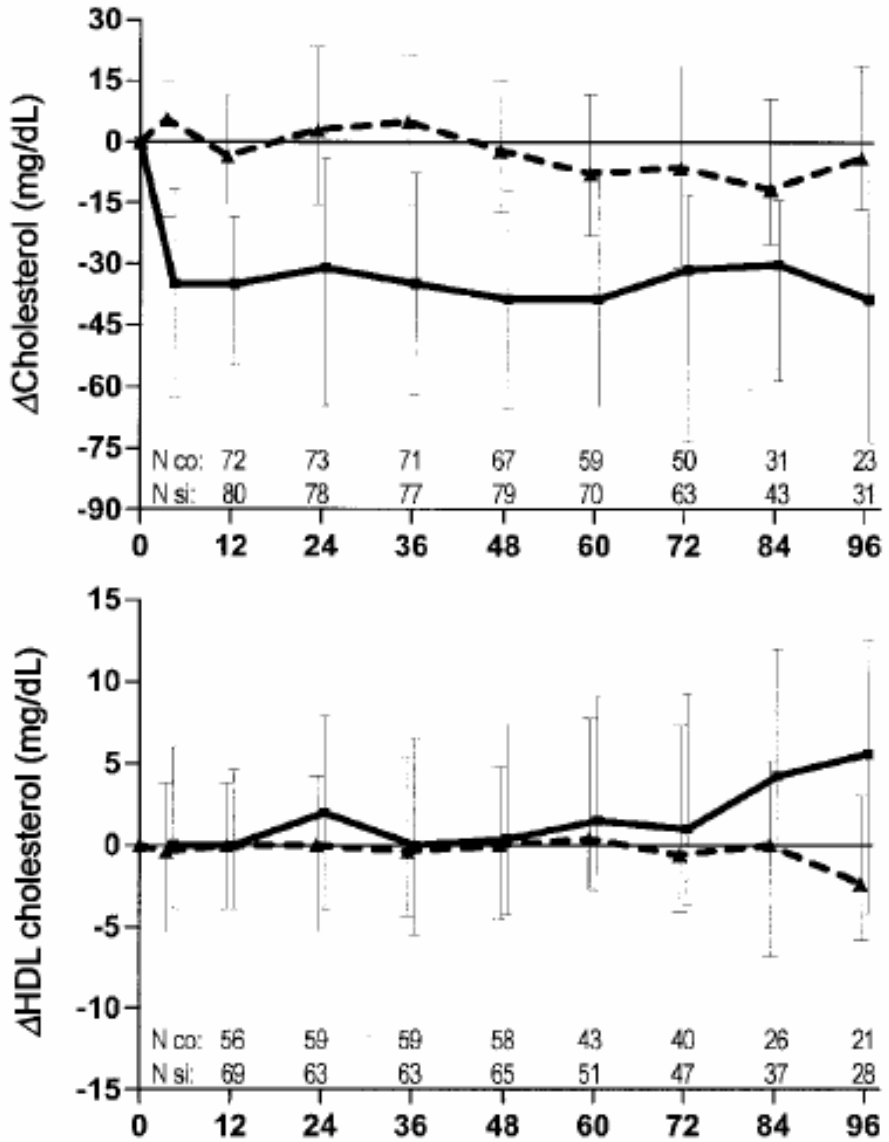
Milos Opravil,[1] Bernard Hirschel,[3] Adriano Lazzarin,[9] Hansjakob Furrer,[4] Jean-Philippe Chave,[5] Sabine Yerly,[3] Leslie R. Bisset,[2] Marek Fischer,[1] Pietro Vernazza,[6] Enos Bernasconi,[7] Manuel Battegay,[8] Bruno Ledergerber,[1] Huldrych Günthard,[1] Colin Howe,[10] Rainer Weber,[1] and Luc Perrin,[3] for the Swiss HIV Cohort Study[a]

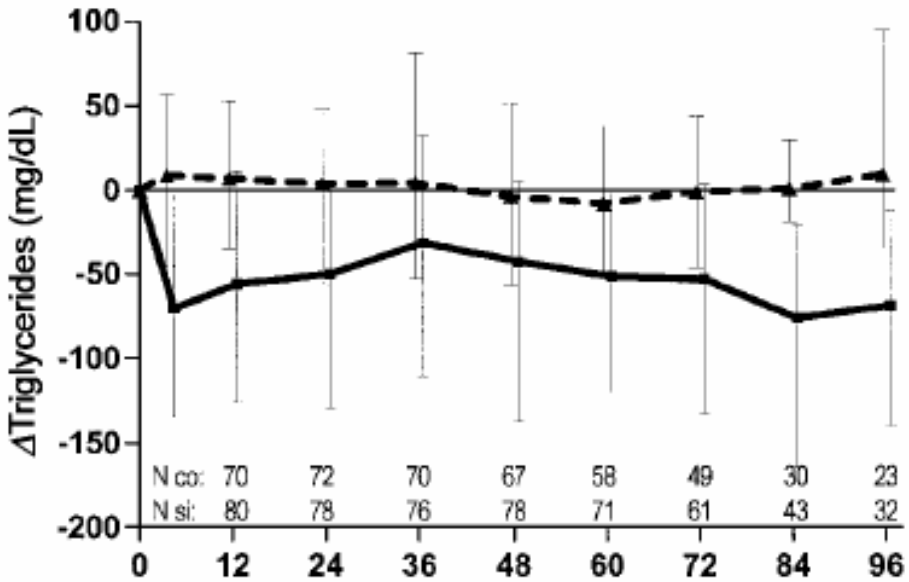
Divisions of [1]Infectious Diseases and [2]Clinical Immunology, University Hospital, Zurich, [3]Division of Infectious Diseases, University Hospital, Geneva, [4]Division of Infectious Diseases, University Hospital, Bern, [5]Infectious Diseases Practice, Lausanne, [6]Division of Infectious Diseases, Cantonal Hospital, St. Gallen, [7]Division of Infectious Diseases, Cantonal Hospital, Lugano, and [8]Department of Medicine, University Hospital, Basel, Switzerland; [9]Clinic of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy; [10]GlaxoSmithKline, Greenford, United Kingdom

This randomized study evaluated the efficacy and tolerability of continued treatment with protease inhibitor plus nucleoside-analogue combination regimens ($n = 79$) or a change to the simplified regimen of abacavir-lamivudine-zidovudine ($n = 84$) in patients with suppressed human immunodeficiency virus type 1 (HIV-1) RNA for ≥6 months who did not have the reverse transcriptase 215 mutation. After a median follow-up of 84 weeks, virologic failure was 6% in the continuation and 15% in the simplified group ($P = .081$). Previous zidovudine monotherapy or dual therapy and archived reverse transcriptase resistance mutations in HIV-1 DNA at baseline were significant predictors of failure. Study treatment was discontinued because of adverse events in 20% of the continuation and 7% of the simplified group ($P = .021$). Simplification to abacavir-lamivudine-zidovudine significantly decreased nonfasting cholesterol and triglyceride levels; however, this switch strategy carries a risk of virologic failure when treatment history or resistance testing suggest the presence of archived resistance mutations to the simplified regimen.

J Infect Dis. 2002 May 1;185(9):1251-60.

A Randomized Trial of Simplified Maintenance Therapy with Abacavir, Lamivudine, and Zidovudine in Human Immunodeficiency Virus Infection





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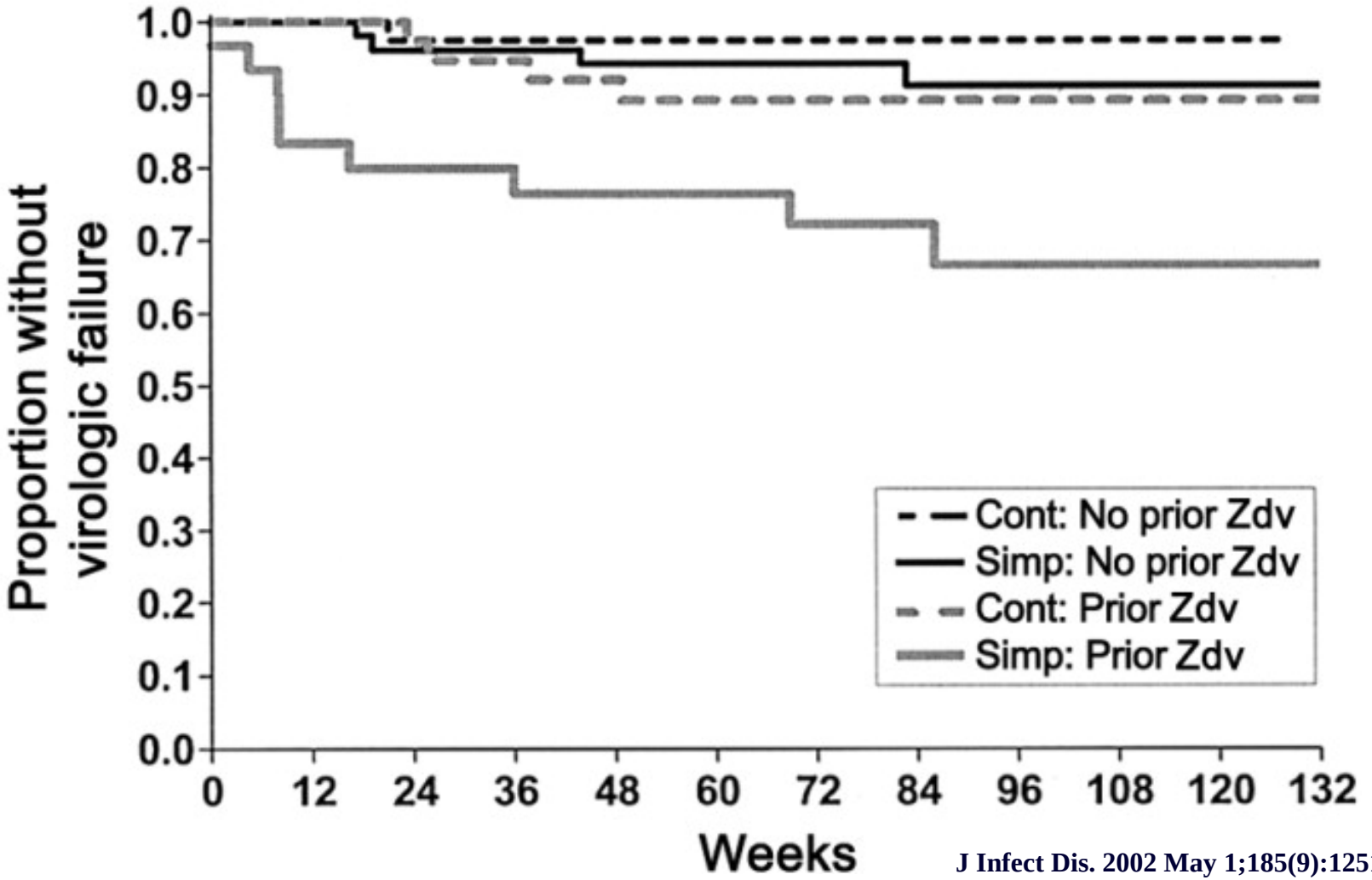
A Randomized Trial of Simplified Maintenance Therapy with Abacavir, Lamivudine, and Zidovudine in Human Immunodeficiency Virus Infection



J Infect Dis. 2002 May 1;185(9):1251-60.

Difference between HIV drug resistance detected in plasma and PBMCs at codon of PR gene

Andreoni J Clin Microb, 2003

Codon	N° samples with mutant at codon (%)	N° samples with different resistance pattern	Cohen K
10I	20 (31)	0	1.00
30N	1 (1)	1	**n.a.**
36I	22 (34)	2	**0.86**
46I/L	16 (25)	2	**0.83**
63P	20 (31)	10	0.32
71T/V	26 (40)	2	**0.87**
82A/F	20 (31)	4	0.71
84V	3 (4)	1	0.65
90M	13 (20)	1	**0.90**

Difference between HIV drug resistance detected in plasma and PBMCs at codon of RT gene

Andreoni J Clin Microb, 2003

Codon	N° samples with mutant at codon (%)	N° samples with different resistance pattern	Cohen K
41L	26 (40)	4	**0.74**
70R	9 (14)	1	**0.87**
74V	4 (6)	0	**1.00**
103N	23 (36)	3	**0.81**
108I	10 (15)	0	**1.00**
118I	12 (18)	2	**0.79**
151M	4 (6)	0	**1.00**
181C	6 (9)	0	**1.00**
184V	34 (53)	6	**0.62**
215F/Y	35 (54)	3	**0.81**

Characteristics of 32 patients failing HAART according to the agreement of primary resistant mutations in plasma and PBMCs

Andreoni J Clin Microb, 2003

	Genotypic plasma-PBMCs analysis			
	Discordant (n.8)	Concordant (n.24)	OR (IC 95%)	p
Time on ART months	80±31	50±29	0.23 (0.05-0.87)	0.03
CD4 pre-ART, cells/μl	179±114	186±172	0.78 (0.23-2.65)	0.69
HIV-RNA pre-ART	5.96±5.89	5.55±5.57	0.55 (0.18-1.67)	0.29
CD4 at genotype, cells/μl	263±225	276±229	1.77 (0.56-5.52)	0.33
HIV-RNA at genotype	5.16±5.33	5.48±5.93	1.00 (0.35-2.85)	1.00
N° of drugs used	6.4±1.8	5.2±1.8	0.68 (0.41-1.13)	0.14
PI exposure	8 (100%)	19 (82%)		
Subtype nonB isolates	3 (37%)	5 (21%)	0.33 (0.05-2.36)	0.27

Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy

Soo Aleman[a], Karin Söderbärg[b], Ubaldo Visco-Comandini[c], Gisela Sitbon[b] and Anders Sönnerborg[a,d]

Objective To study the appearance of drug-induced mutations at low viraemia in treated HIV-1-infected patients.

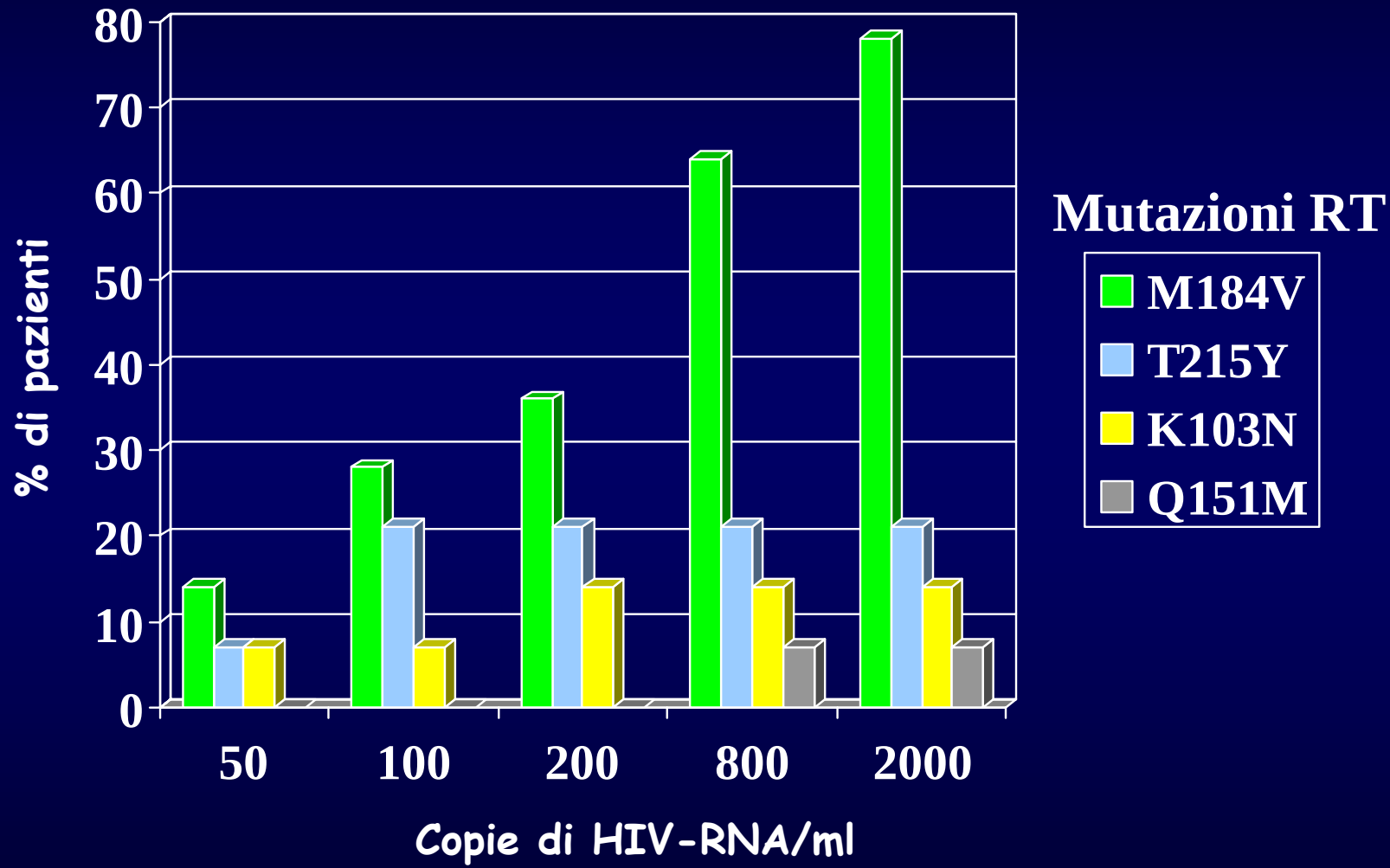
Design and methods Fourteen patients, who received their first (n = 5), second (n = 7) or third (n = 2) line antiretroviral combination therapy, developed a persistent low-grade viraemia after an initial decrease of the viral load (VL) to less than 500 copies/ml. The amount of HIV-1 RNA (n = 71) and reverse transcriptase (RT)/protease sequences (n = 56) were determined in longitudinally obtained plasma samples during a mean period of 16.6 months.

Results In the vast majority (93%) of patients, new primary resistance mutations were found in the RT and/or protease genes at virological failure at a median VL of 500 and 200 copies/ml, respectively. Drug-experienced patients developed mutations at a lower VL than naive patients. In one previously protease inhibitor-naive patient, primary RT and protease mutations were detected, although the VL was less than 50 copies/ml. A serial accumulation of drug resistance mutations was seen despite the VL increase being mostly modest, reaching a median of 1450 copies/ml at the end of the study, and the CD4 T cell counts continued to increase. One patient still had a VL of 300 copies/ml after 28 months, despite the presence of the multidrug-resistance Q151M mutation.

Conclusion Low viraemia after virological treatment failure can select for virus with several new drug resistance mutations, despite a concomitant increase in CD4 T cell counts. This serial accumulation of mutations is likely to exhaust future drug options

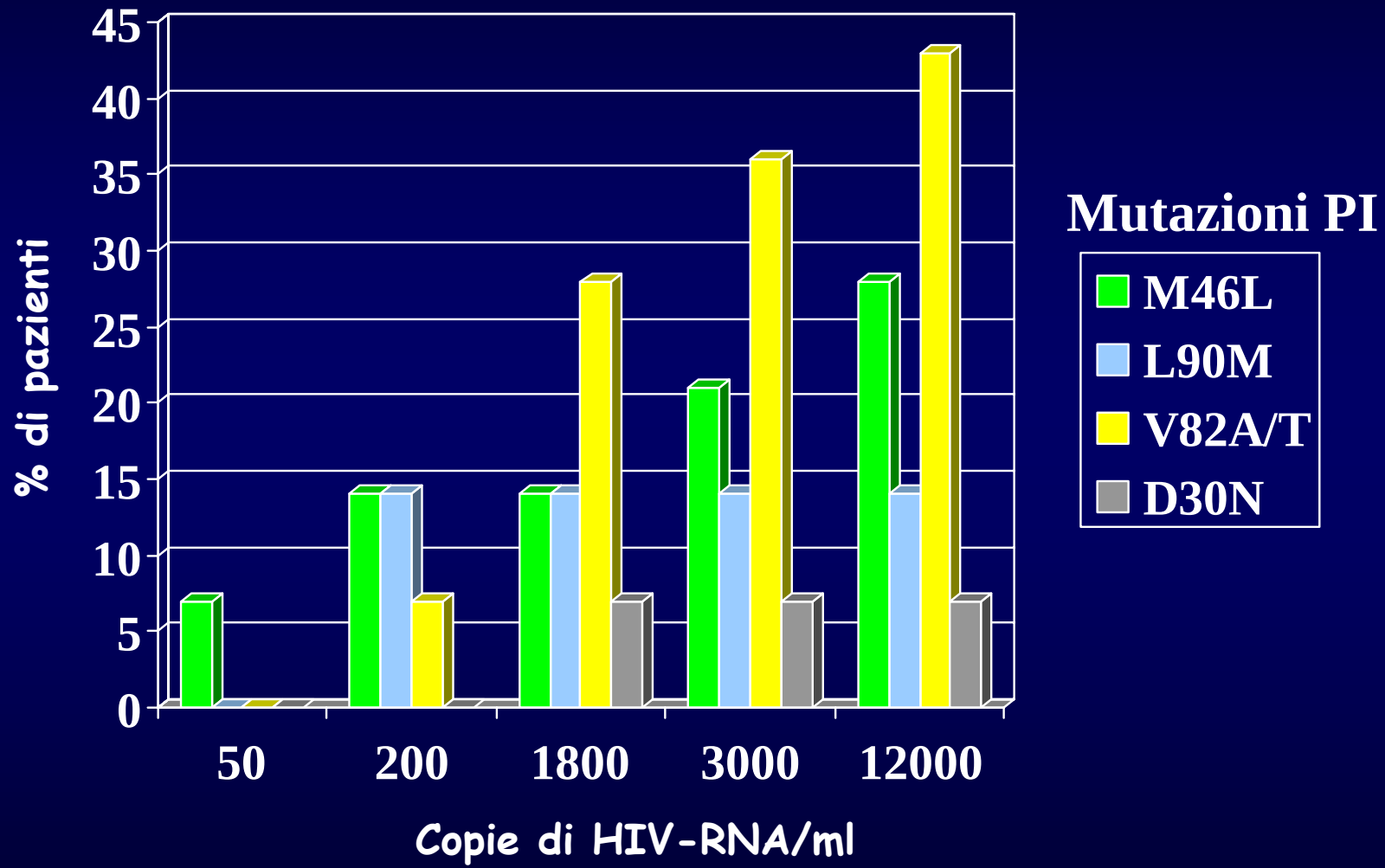
AIDS 2002, **16**:1039–1044

Sviluppo di resistenza in 14 pazienti in HAART in fallimento dopo aver raggiunto livelli di viremia non rilevabili

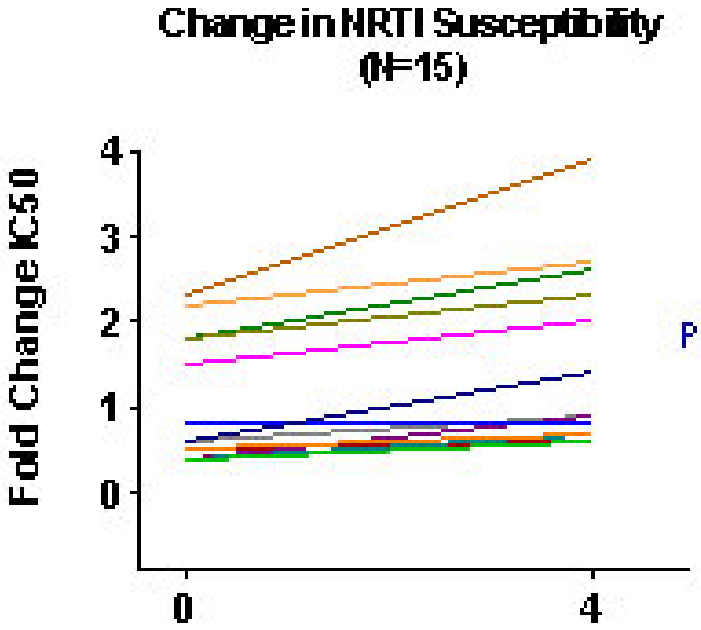


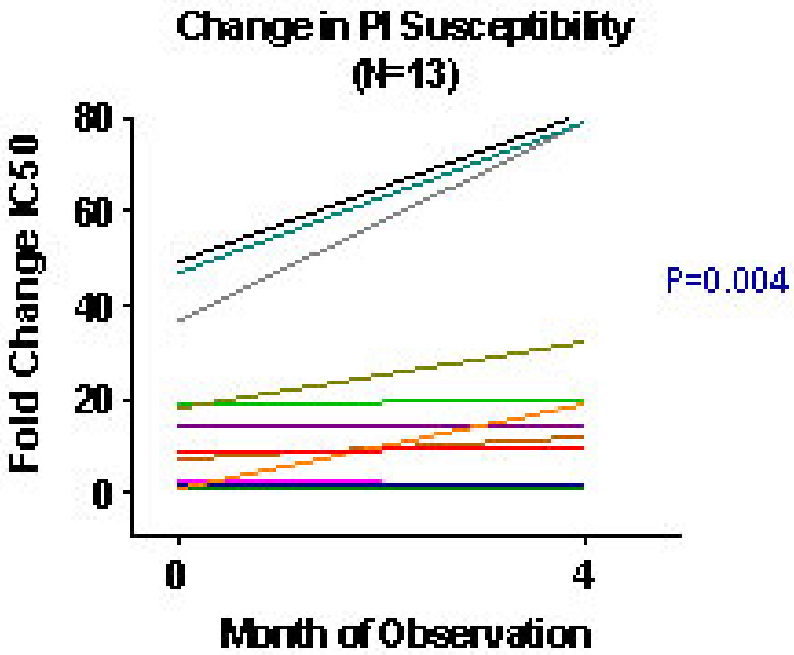
Aleman AIDS 2002

Sviluppo di resistenza in 14 pazienti in HAART in fallimento dopo aver raggiunto livelli di viremia non rilevabili



Aleman AIDS 2002





Drug-Resistance Emergence in Treated Patients with Ongoing Viral Replication

SCOPE cohort

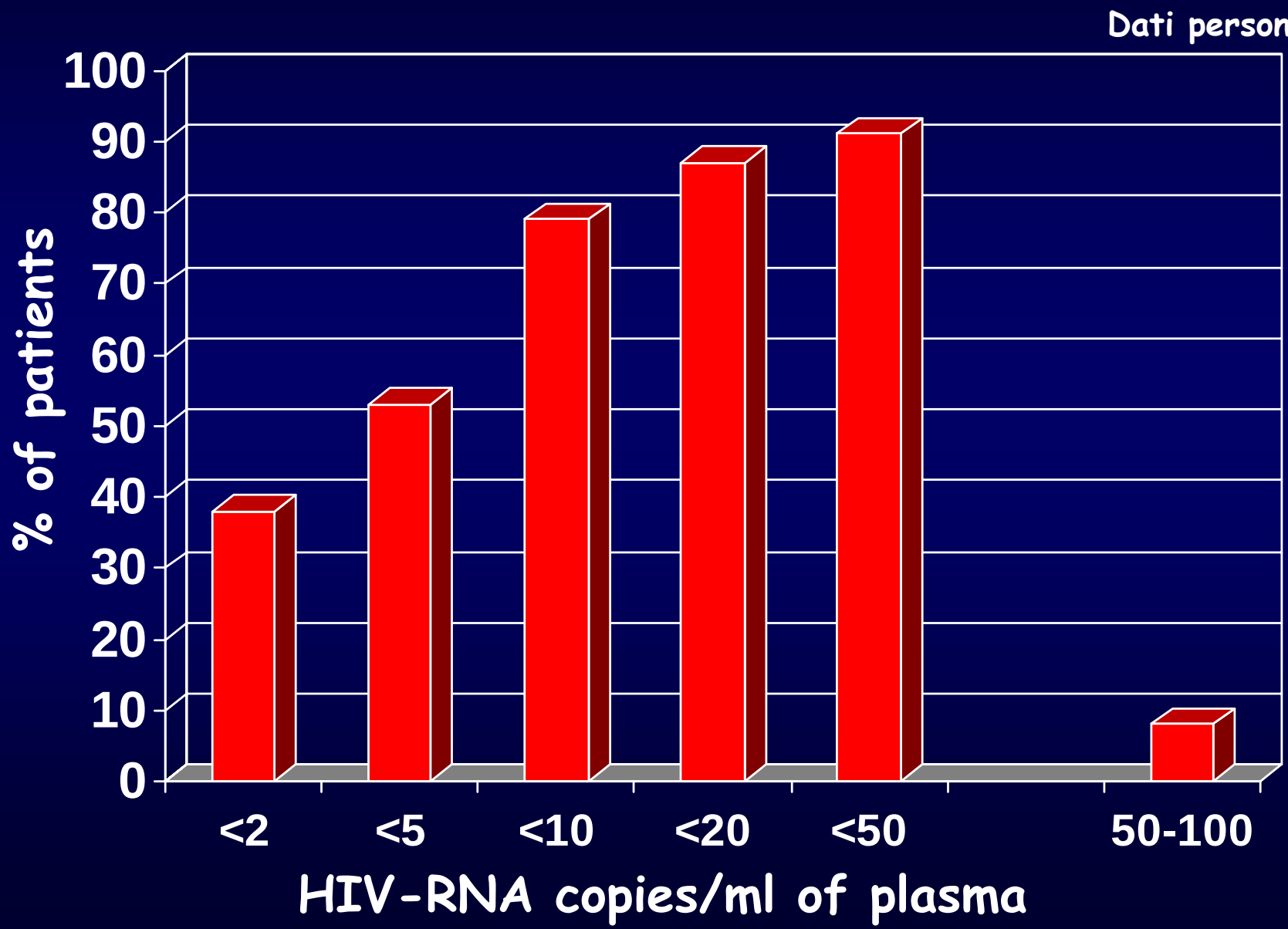
Change in drug susceptibility over consecutive study visits in treated patients who entered with a viral load of 50-1000 copies/mL and who had detectable viremia at second four-month visit

What is the threshold?

CROI 2003

ALSO: Duval and Brun-Vezinet, Abstract 609

Detection of viral load by ultrasensitive method in 50 patients with <50 HIV-RNA copies/ml



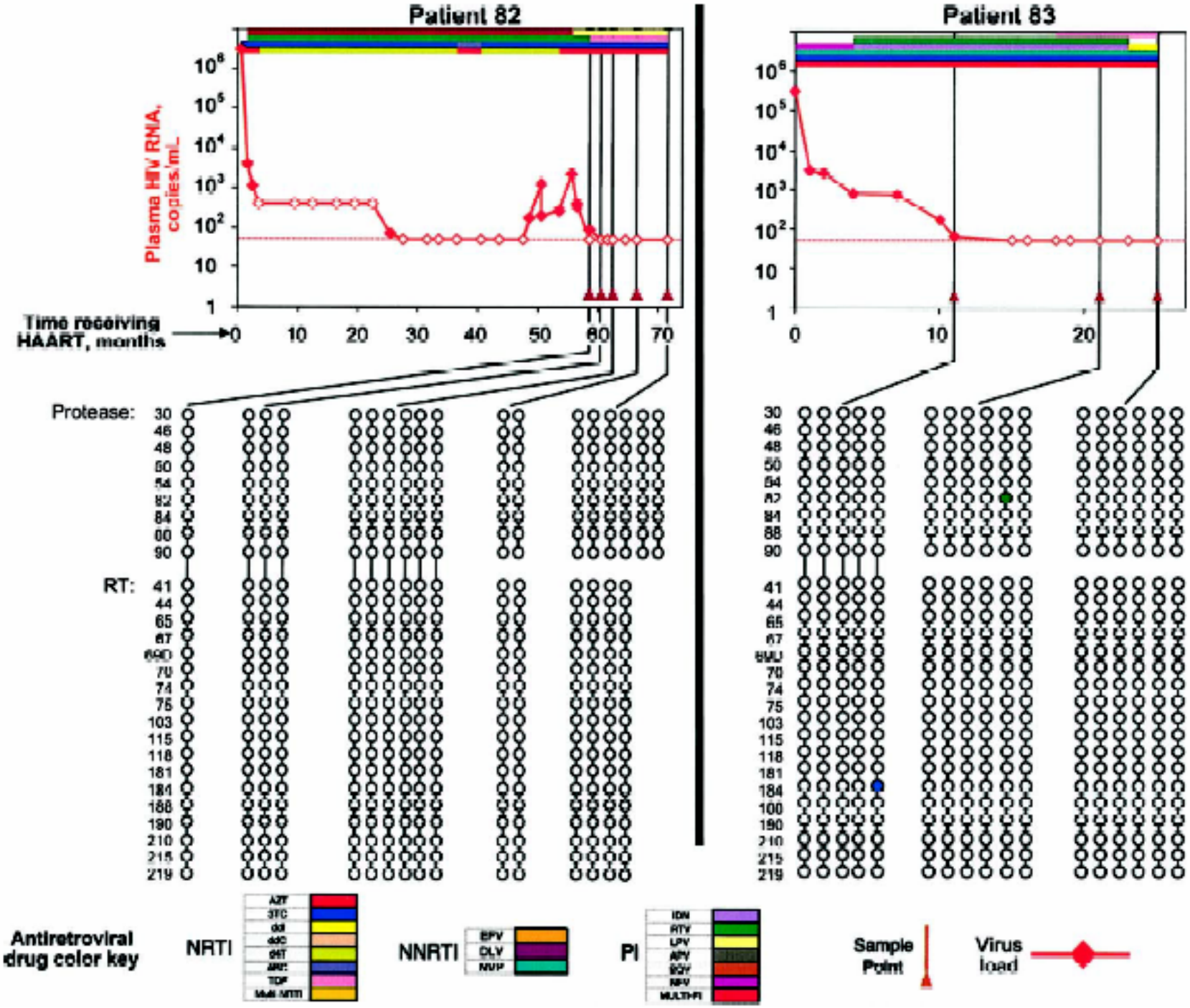
Genotypic Analysis of HIV-1 Drug Resistance at the Limit of Detection: Virus Production without Evolution in Treated Adults with Undetectable HIV Loads

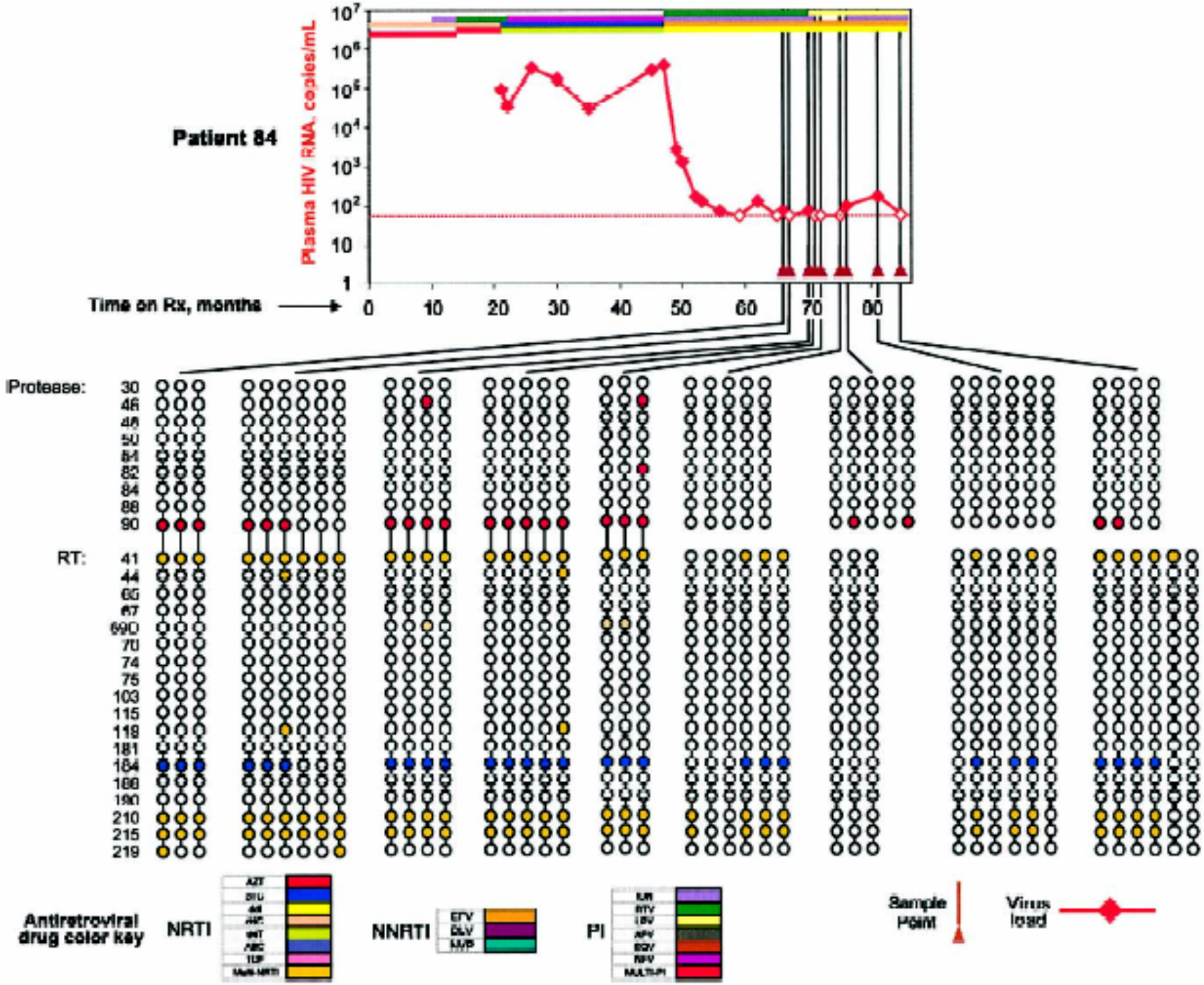
Tara L. Kieffer,[1] Mariel M. Finucane,[1] Richard E. Nettles,[1] Thomas C. Quinn,[1,5] Karl W. Broman,[4] Stuart C. Ray,[1] Deborah Persaud,[2] and Robert F. Siliciano[1,3]

Departments of [1]Medicine and [2]Pediatrics and [3]Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, and [4]Department of Biostatistics, Johns Hopkins University School of Public Health, Baltimore, and [5]National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Human immunodeficiency virus (HIV) production continues in patients receiving highly active antiretroviral therapy (HAART) with undetectable (<50 copies/mL) virus loads. Our initial cross-sectional study showed that this viremia is composed of viruses that lack new resistance mutations to the HAART regimen. Here we describe a longitudinal, clonal genotypic analysis of plasma virus loads in treated adults who had undetectable virus loads. We document a continuous production of virus in 8 HIV-1–infected adults who maintained suppression of viremia for up to 15 months. Using analytical approaches for distinguishing selected resistance mutations from nonselected mutations and polymerase chain reaction errors, we detected no evolution of resistance in the reverse-transcriptase and protease genes. Sporadic resistance mutations were detected in some viral clones that were not selected for subsequently. Thus, in some patients, HAART suppresses replication to a level that does not allow the evolution of drug resistance over a time frame of years.

The Journal of Infectious Diseases 2004; 189:1452–65


Patient 82
Patient 83
Plasma HIV RNA, copies/mL
Time receiving HAART, months
Protease:
RT:
Antiretroviral drug color key
NRTI
NNRTI
PI
Sample Point
Virus load


Patient 84
Plasma HIV RNA, copies/mL
10^7
10^6
10^5
10^4
10^3
10^2
10
1
Time on Rx, months
0
10
20
30
40
50
60
70
80
Protease:
30
46
48
50
54
82
84
88
90
RT:
41
44
65
67
69D
70
74
75
103
115
118
181
184
188
190
210
215
219
Antiretroviral drug color key
NRTI
AZT
3TC
d4T
ddC
ddI
ABC
TDF
Multi-NRTI
NNRTI
ETV
EFV
NVP
PI
IDV
RTV
LPV
APV
FPV
SQV
NFV
MULTI-PI
Sample Point
Virus load

The role of PBMC genotyping in predicting the emergence of resistance mutations during treatment interruption

- 136 patients
- Mutations at any time during STI: 39/136 (28.7%)
- M184V: 9.4% of all 3TC treated pts
- K103N: 7.9% of all NNRTIs treated pts
- T215Y: 2.9% of all NRTIs treated pts
- L90M: 10.3% of all SQV or NFV treated pts

Palmisano L, 2nd European HIV Drug Workshop, Rome 2004

The role of PBMC genotyping in predicting the emergence of resistance mutations during treatment interruption

Failure to therapy reinstitution:

- 33.3% pts with mutations
- 12.4% pts without mutations

Presence of mutations in PBMC at baseline:

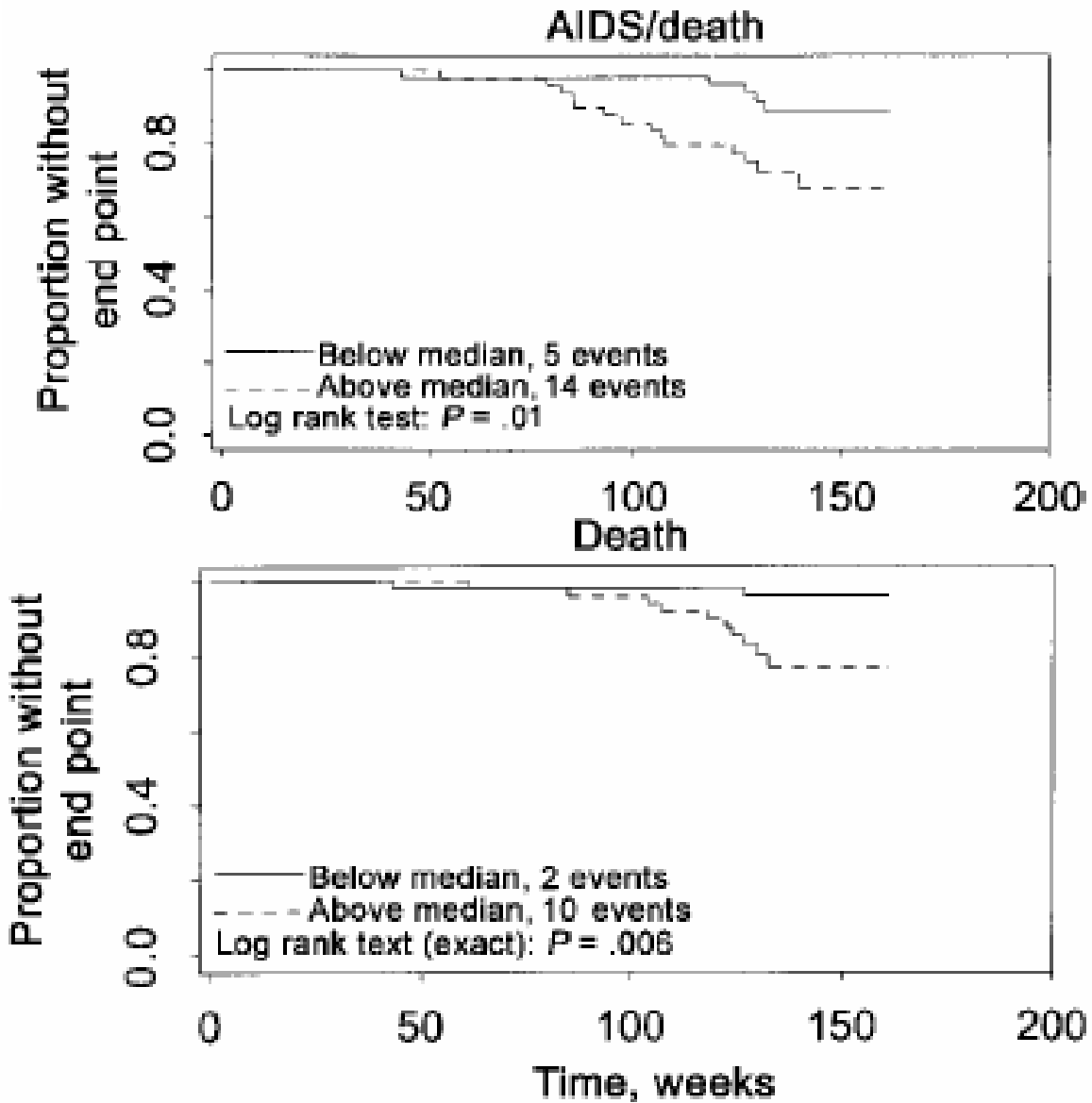
40.7% of pts developing mutations during STI

4.5% of pts non developing mutations during STI

Patients with mutations in proviral DNA may be not candidates to STI

Palmisano L, 2nd European HIV Drug Workshop, Rome 2004

Prognostic Value of Baseline Human Immunodeficiency Virus Type 1 DNA Measurement for Disease Progression in Patients Receiving Nucleoside Therapy

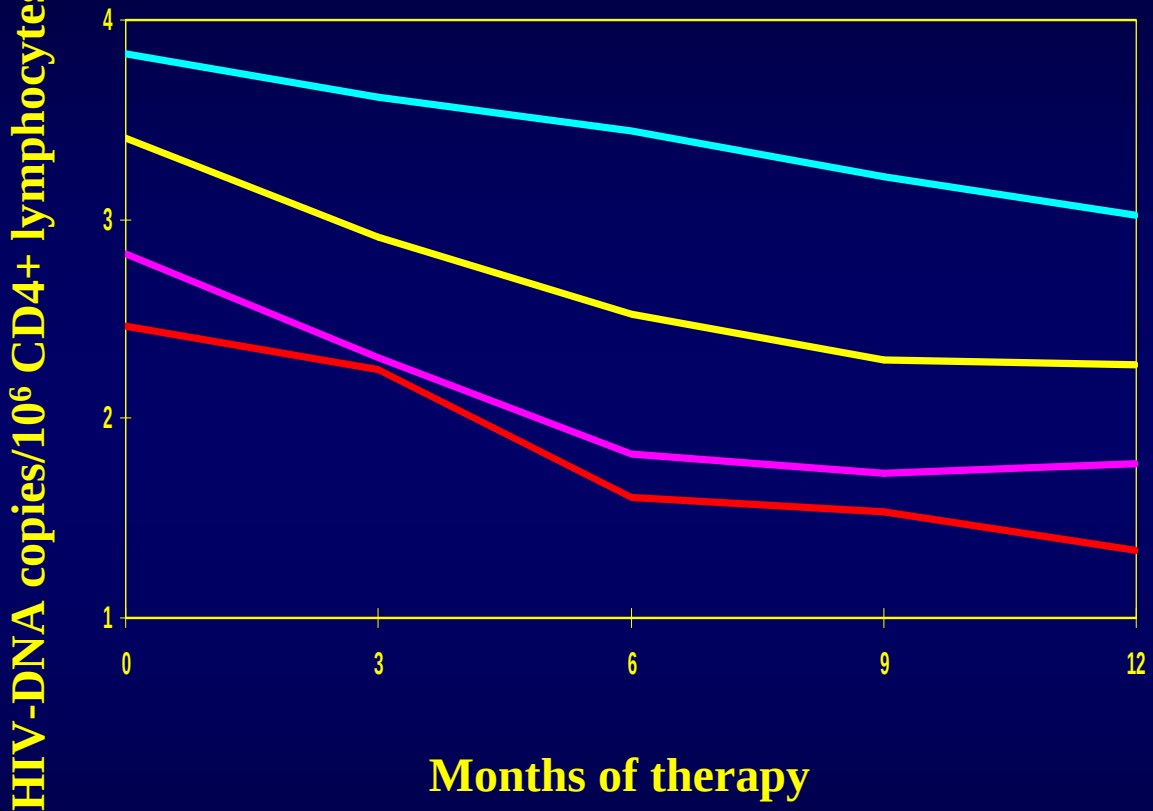


Median DNA: 2.08 log copies/ml

Tierney C, JID 2003; 187:144-8

CELLULAR PROVIRAL HIV-DNA DURING HAART IN EARLY ASYMPTOMATIC INFECTION

Patients with viral load <50 copies/ml

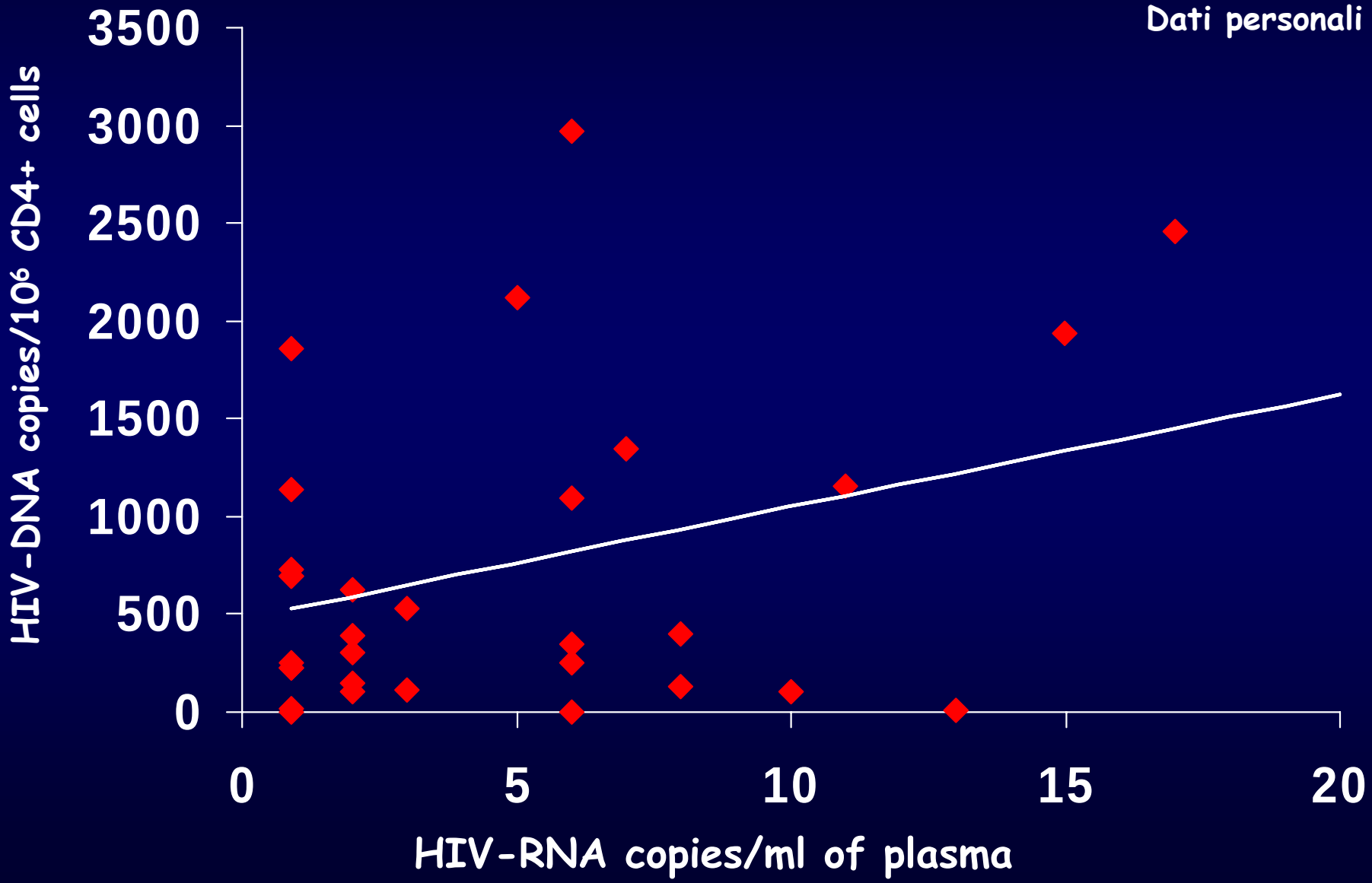


	HIV-DNA $t_{1/2}$ (weeks)	Infectious virus n° patients/total
Base line values	41.1	3/5
	28.7	5/9
	30.6	4/9
	28.1	4/11

- 5 subjects HIV-RNA >5000 CD4 <300
- 9 subjects HIV-RNA >5000 CD4 500-300
- 9 subjects HIV-RNA >5000 CD4 >500
- 11 subjects HIV-RNA <5000 CD4 >500

Andreoni AIDS, 2000,14:23-9

Plasma HIV-RNA and HIV-DNA copies number in patients with viral load <20 copies/ml



MAJOR ARTICLE

The Journal of Infectious Diseases 2003; 187:38–46

Predictive Value of Provirus Load and DNA Human Immunodeficiency Virus Genotype for Successful Abacavir-Based Simplified Therapy

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Departments of [1]Virology and [2]Internal Medicine and Infectious Diseases, Bordeaux University Hospital, Bordeaux, France

Of 75 human immunodeficiency virus (HIV) type 1–infected patients successfully responding to 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus 1 protease inhibitor (PI), 55 started a simplified abacavir (ABC)–based triple NRTI regimen. Influences of DNA load and DNA reverse-transcriptase (RT) mutations on virological responses were assessed at month 6 after initiation of therapy. Baseline heterogeneity was observed: peripheral blood mononuclear cell (PBMC) genotyping showed 31% RT mutations with 1–5 NRTI-related mutations, 78% protease mutations had 1–5 PI-related mutations; and HIV-1–DNA levels were 1.8–3.5 $\log_{10}$ copies/10^6 PBMC. Outcomes for 49 patients on a regimen of 2 NRTIs plus ABC were as follows: 22 successes, 10 blips ("blip" defined as intermittent plasma HIV-1 RNA levels between 50 and 100 copies/mL and a return to an undetectable level), and 17 failures, whereas, for patients continuing on a regimen of 2 NRTIs plus 1 PI, there were 19 successes and 1 blip. Previous treatment regimens, baseline provirus level, and PBMC genotype predicted virological outcome.

Table 3. Abilities of baseline virological parameters to predict virological outcome after switching from 2 nonnucleoside reverse-transcriptase inhibitors (NRTIs) plus 1 protease inhibitor (PI) to 2 NRTIs plus abacavir (ABC).

				Statistical analyses					
				Univariate		Multivariate			
	Virologic outcome in ABC group (n = 49)			Success, failure, blip	Success vs. failure	Success vs. failure + blip		Success vs. failure	
Parameters	Success (n = 22)	Failure (n = 17)	Blip (n = 10)	P[a]	P[a]	OR (95% CI)	P[a]	OR (95% CI)	P[a]
Sex, M:F	3:19	3:14	1:9	1.00	1.00	0.99 (0.1–8.4)	1	1.1 (0.09–14.2)	.93
Age in years[b]	40 [36, 46]	42 [39, 49]	45 [42, 54]	.42	.45	0.99 (0.1–8.4)	.8	1.00 (0.91–1.10)	.98
Baseline CD4$^+$ cell count, cells/μL[b]	522 [339, 740]	578 [331, 686]	393 [325, 616]	.42	.65				
Baseline DNA proviral load[b]	2.2 [2.0, 2.6]	2.8 [2.4, 3.2]	2.9 [2.3, 3.1]	.0012	.0023	0.1 (0.02–0.5)	.006	0.1 (0.03– 0.90)	.03
Duration of virus suppression, months[b]	36 [29, 40]	38 [28, 44]		.88	.68				
Treatment history[c]									
1 Previous ART regimen	18 (82)	8 (47)	6 (60)	.06[d]	.04	3.25 (0.6–16.3)	.1	3.2 (.5– 19.37)	.2
≤3 Previous drugs	15 (68)	8 (47)	4 (40)	.28[e]	.21				
Previous monotherapy and/or dual therapy	1 (4.5)	6 (35.3)	2 (20)	.04	.03				
Baseline PBMC DNA sequences									
RT mutations/sequence[f]	0.21 (0–2)	1.2 (0–5)	0.5 (0–3)	.03	.0087				
ABC-resistance mutations[c]				.06[g]	.04	0.19 (0.0–1.1)	.06	0.1 (0.02–0.95)	.04
WT mutations	18 (82)	8 (47)	8 (80)						
1–3	4 (18)	7 (41)	2 (20)						
4–5	0	2 (12)	0						
PR mutations/sequence[f]	1.3 (0–5)	2.1 (0–8)	1.5 (0–4)	.23	.095				
WT or 1 secondary mutation[c]	14 (64)	6 (35)	7 (70)	.12[g]	.11				
1 Primary or 2–8 mutations[c]	8 (36)	11 (65)	3 (30)						
RT + PR mutations[f]	1.5 (0–5)	3.3 (0–8)	2 (1–5)	.01	.003				