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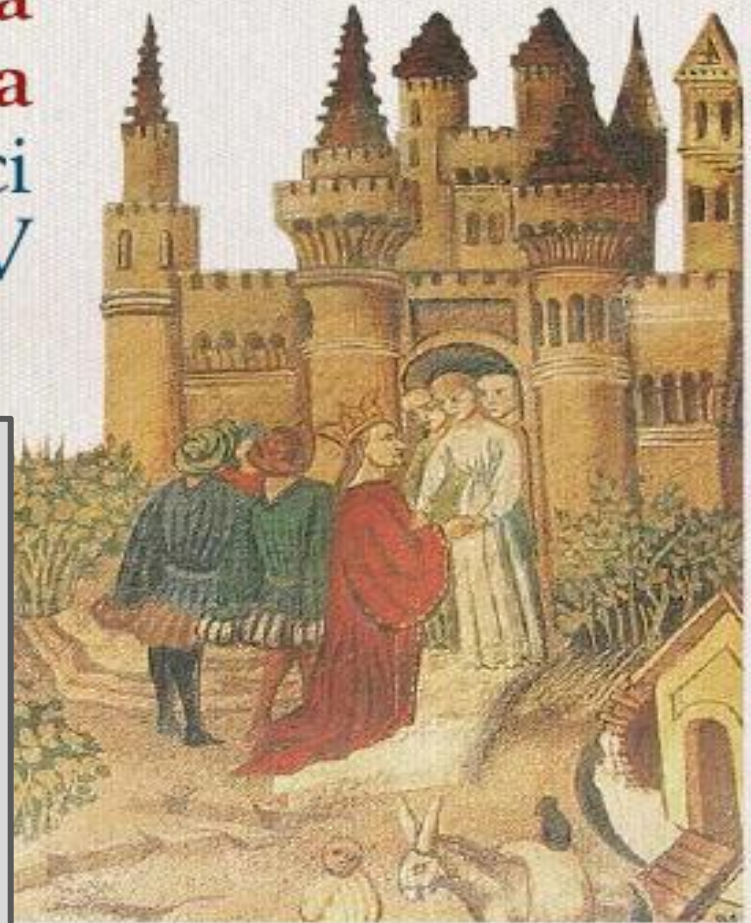
**SIMIT**  
Società Italiana  
di Malattie Infettive  
e Tropicali

# 1° Workshop La Scuola Medica Salernitana i Virus Epatitici e l'HIV

16-17 Marzo 2016

Lloyd's Baia Hotel, Vietri sul Mare (SA)

Via Enrico de Marinis, 2



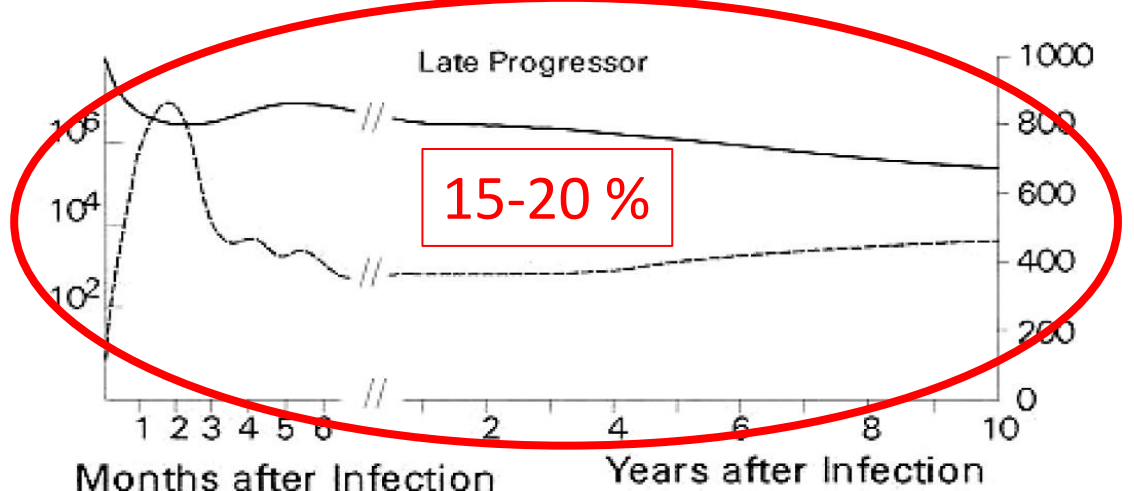
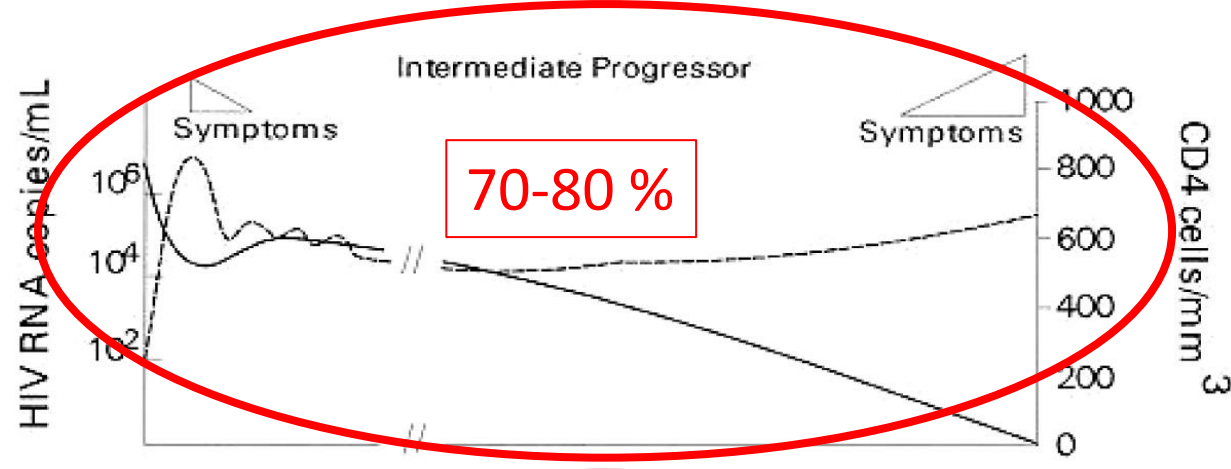
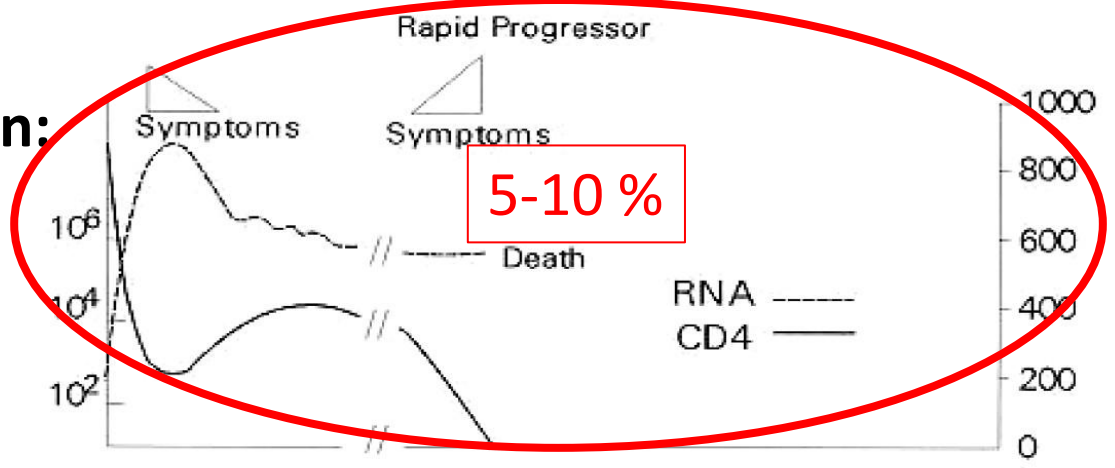
**La terapia nel naive: il  
problema dei pazienti  
gravemente immunodepressi e  
alto viremici**

Loredana Sarmati

CODICE ECM ID 148758

# Predictors of disease progression in HIV infection: a review

Langford SE et al,  
AIDS Research and Therapy, 2007



# Progressione dell'infezione da HIV

- Immunological Factors
- Virological factors

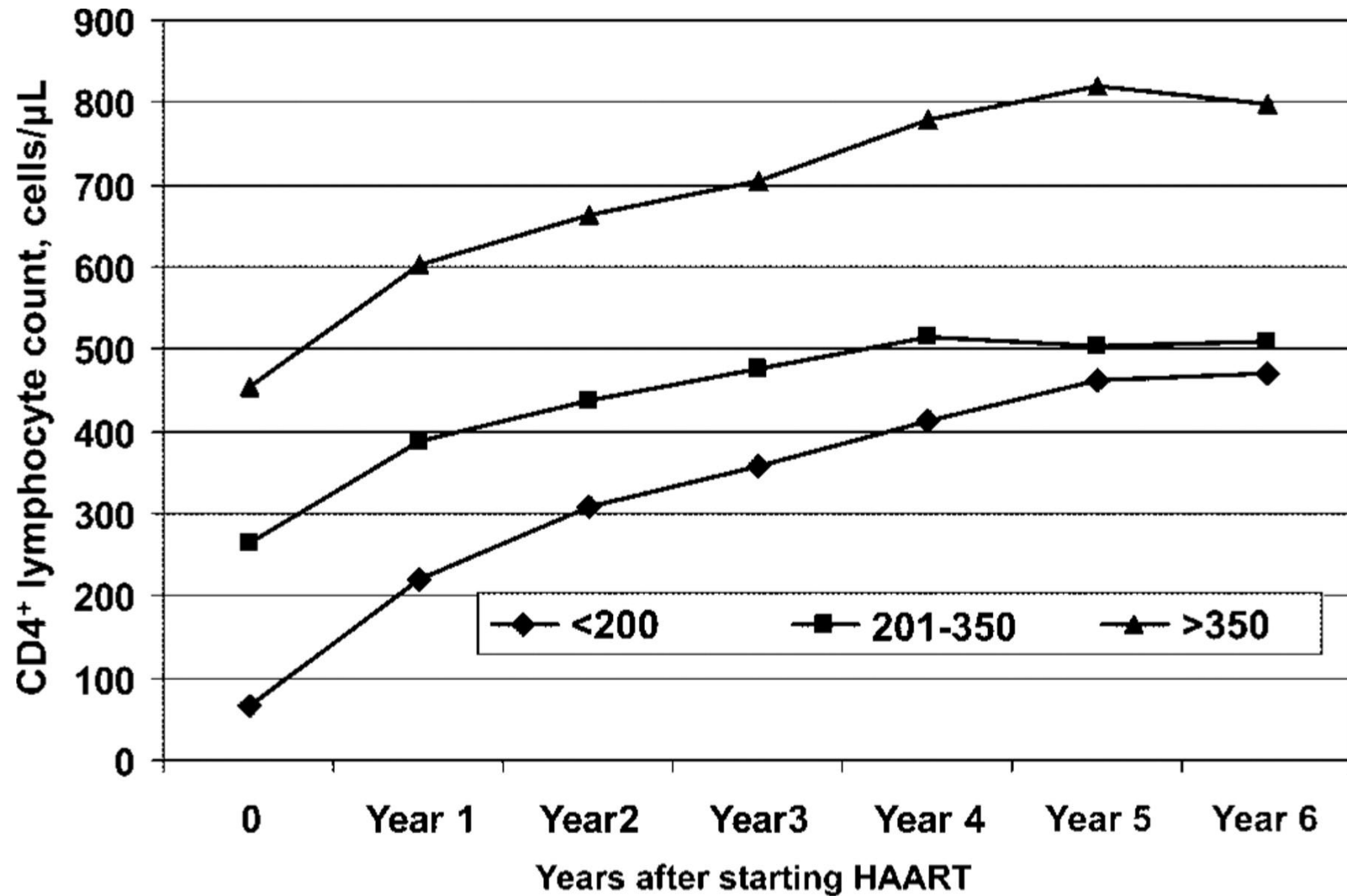
# Predicted 6 month risk of AIDS according to age, current CD4+ cell count and viral load, based on a Poisson regression mode (Cascade 3226 ART-naive)

Age	Viral load (copies/mL)		Predicted risk (%) at current CD4 count ( $\times 10^6$ cells/L)							
	50	100	150	200	250	300	350	400	450	500
<b>25 years</b>										
3000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
10 000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
30 000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
100 000	18.4	10.4	6.7	4.4	3.2	2.4	1.8	1.4	1.1	0.8
300 000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
<b>35 years</b>										
3000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
10 000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
30 000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
100 000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
300 000	30.8	18.0	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
<b>45 years</b>										
3000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
10 000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
30 000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
100 000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
300 000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
<b>55 years</b>										
3000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
10 000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
30 000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
100 000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
300 000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4

<2%, risk 2–9.9%, risk 10–19.9%, risk  $\geq 20\%$

This table is reproduced from Table 4 in [10]

Median CD4+ lymphocyte count over time, stratified by baseline CD4+ cell count (<200, 201–350, or >350 cells/ $\mu$ L).

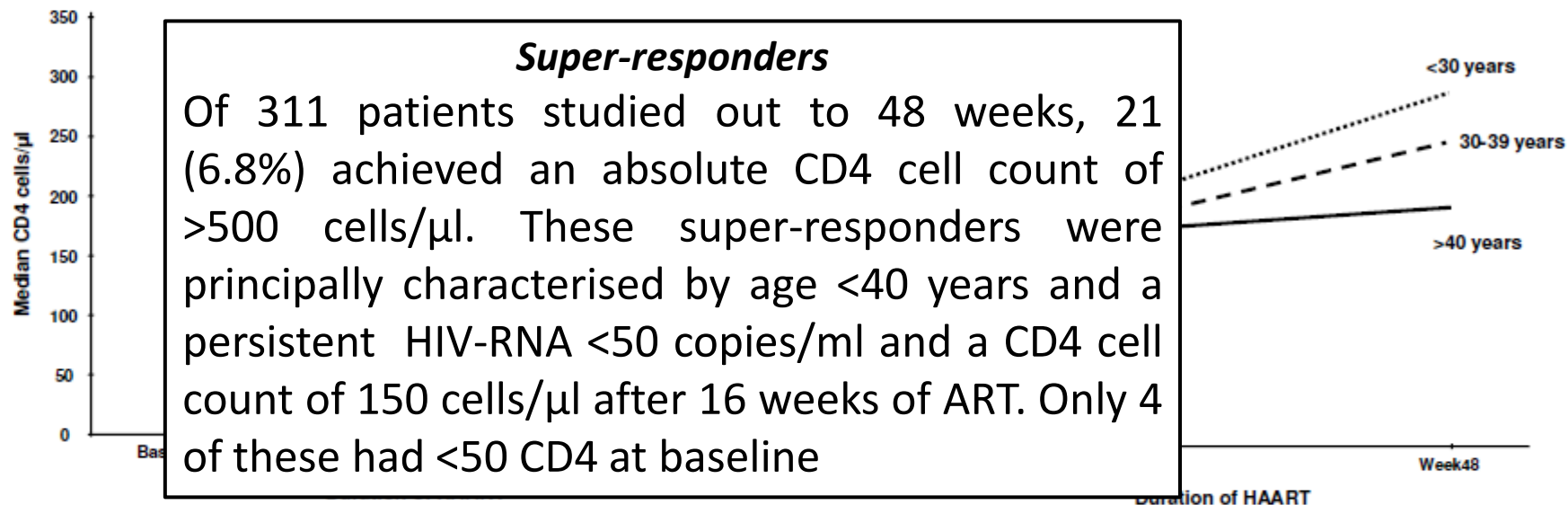


John Hopkins Clinical Cohort, follow up 11 years post ART. 665 pts followed for 6 years (VL<400)



# CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa

Stephen D Lawn<sup>\*1,2</sup>, Landon Myer<sup>3,4</sup>, Linda-Gail Bekker<sup>1</sup> and Robin Wood<sup>1</sup>



Baseline CD4 cell count (cells/μl)	Phase 1 (0-16 weeks)	Phase 2 (16-48 weeks)
≥150	21.9 (9.3, 42.9)	5.1 (-3.0, 15.5)
100-149	24.5 (13.4, 44.2)	5.3 (-2.1, 13.5)
50-99	26.0 (11.4, 42.9)	6.8 (-0.2, 14.6)
<50	26.0 (17.8, 40.8)	9.9 (2.3, 21.3)

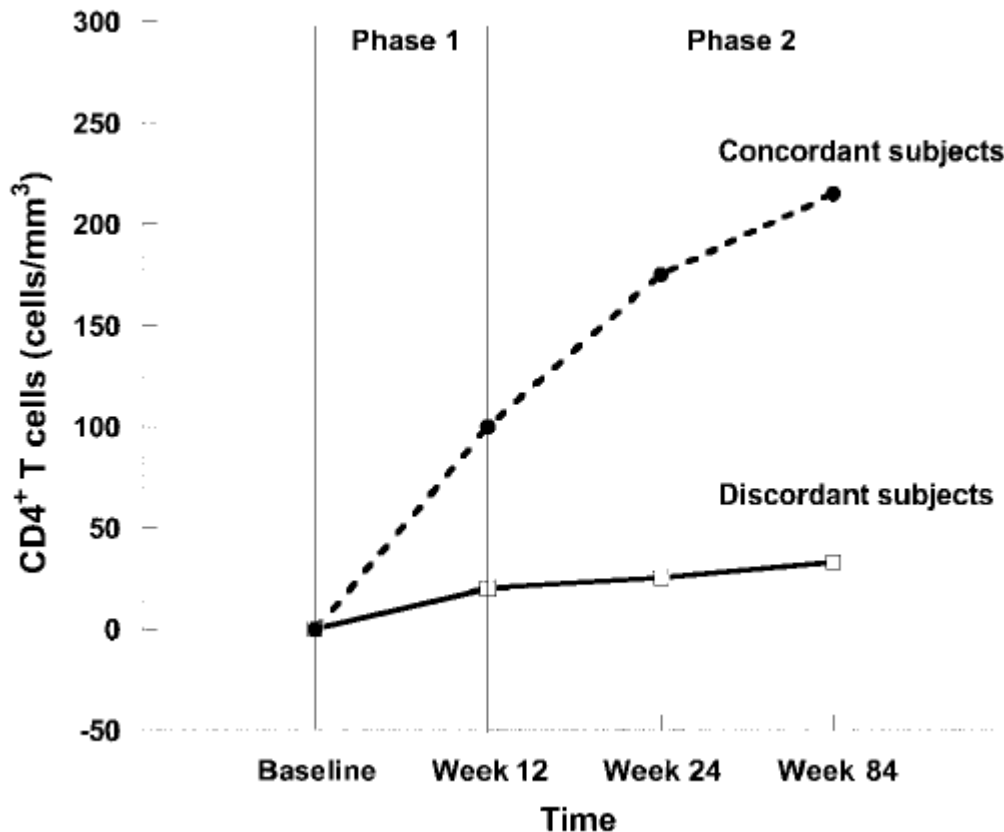
Patient age (years)	Phase 1 (0-16 weeks)	Phase 2 (16-48 weeks)
<30	26.8 (12.7, 43.3)	8.4 (1.1, 20.4)
30-39	24.8 (11.8, 43.0)	6.6 (-1.2, 16.9)
≥40	23.3 (13.1, 38.0)	4.8 (-1.4, 10.6) <sup>†</sup>

CD4 recovery in 596 patients ART-comencing

# Determinants of CD4<sup>+</sup> T Cell Recovery during Suppressive Antiretroviral Therapy: Association of Immune Activation, T Cell Maturation Markers, and Cellular HIV-1 DNA

Goicoechea M et al JID 2006

116 HIV-infected subjects <50 copies/mL on ART. Measurements of T cell immunophenotypes before and during ART. After 48 weeks of ART, On the basis of increases in the CD4<sup>+</sup> T cell count, 68 concordant (increase 100 CD4), 48 discordant (not increase)



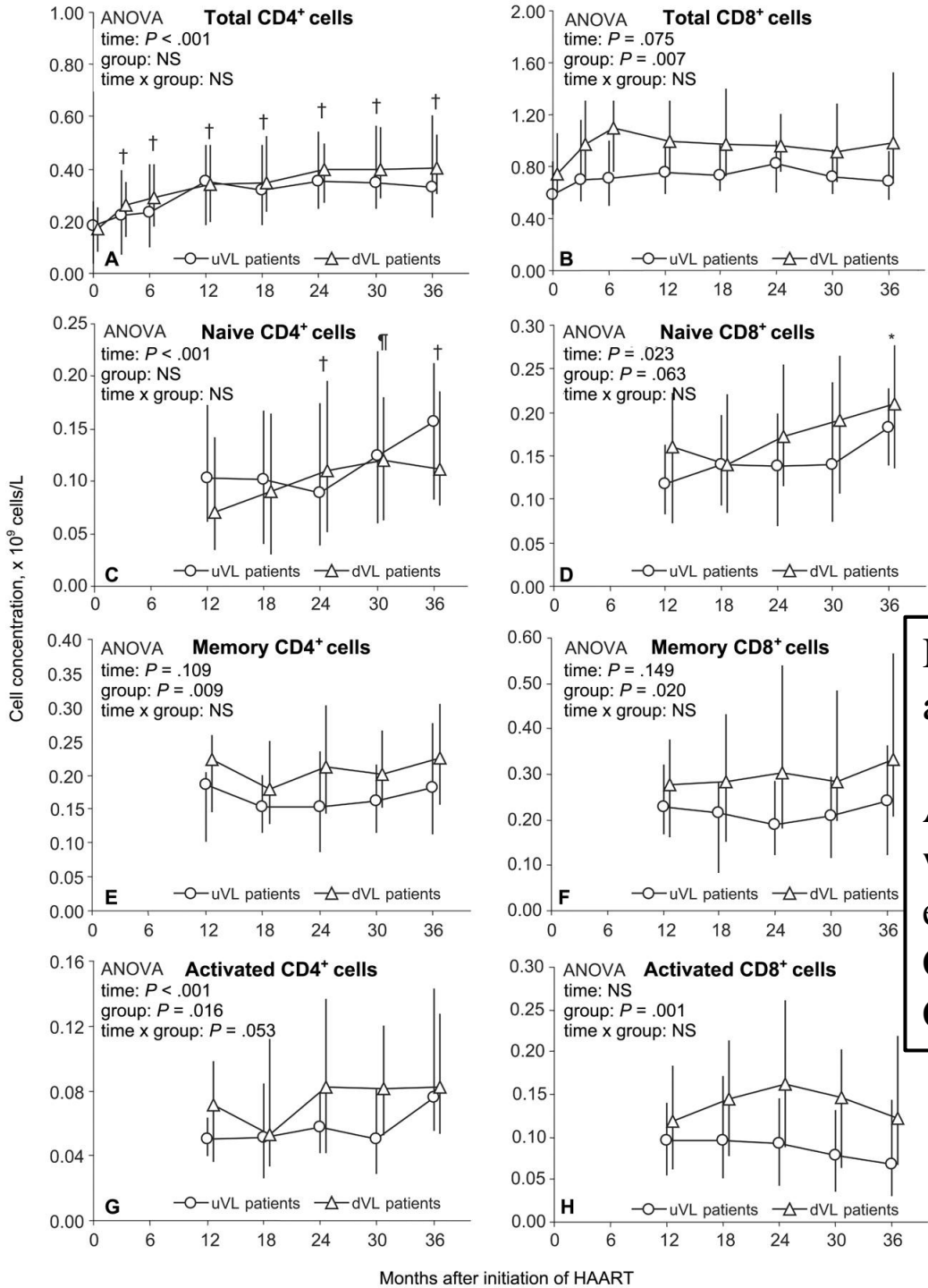
- ❖ Higher CD4<sup>+</sup> and CD8<sup>+</sup> T cell activation at baseline predictive of lower CD4<sup>+</sup> T cell increases during ART.
- ❖ At virus control, CD8<sup>+</sup> T cell activation decreased to similar levels in both groups, but the % of activated CD4<sup>+</sup> T cells remained higher in individuals with limited immune restoration.

101 pts followed prospectively post-ART, 48 VL<20, 68 VL>20  
 ART initiation (A) , 36 (B) and 12–36 months after (C-H)

**Concentrations of CD4 cells, CD8 cells, and various T cell subsets in patients stratified according to plasma HIV RNA level during the study period.**

Sisse R. Ostrowski et al. J Infect Dis. 2005;191:348-357

Higher VL associated with CD8 activation and reduced CD4 gain  
 A higher proviral DNA level was associated with increases in CD4<sup>+</sup>CD45RA<sup>-</sup>CD28<sup>-</sup> effector cells and reductions in naive CD4<sup>+</sup>CD45RA<sup>+</sup>CD62L<sup>+</sup> and CD8<sup>+</sup>CD45RA<sup>+</sup>CD62L<sup>+</sup> cells ( $P < .05$ )

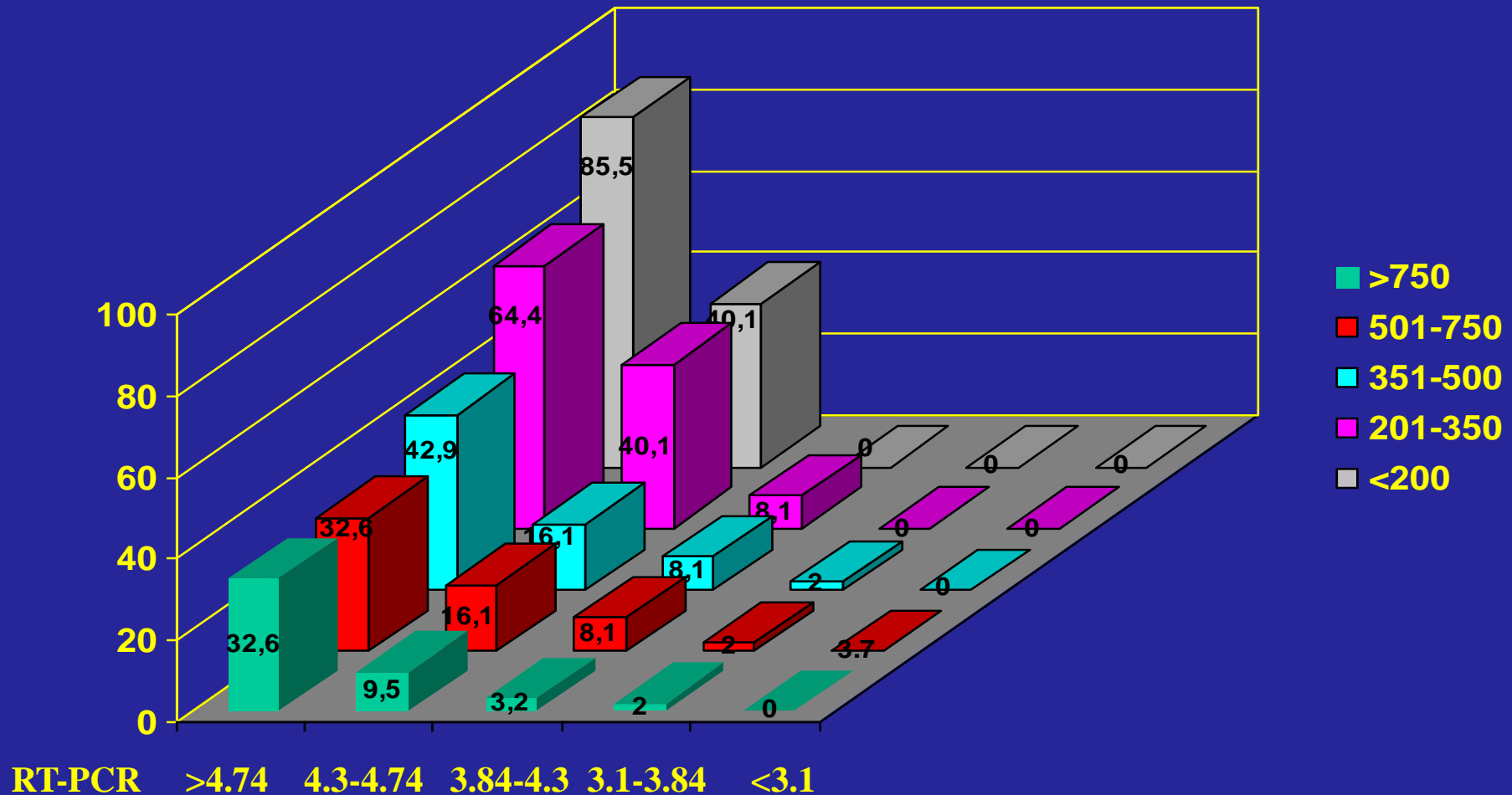




# Progressione dell'infezione da HIV

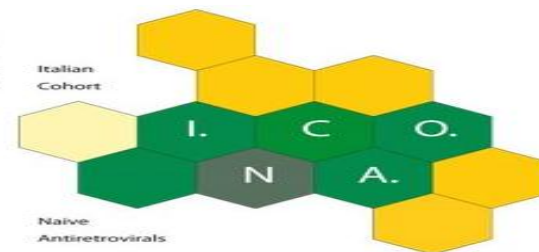
- Immunological Factors
- Virological factors

# Likelihood of developing AIDS within 3 years

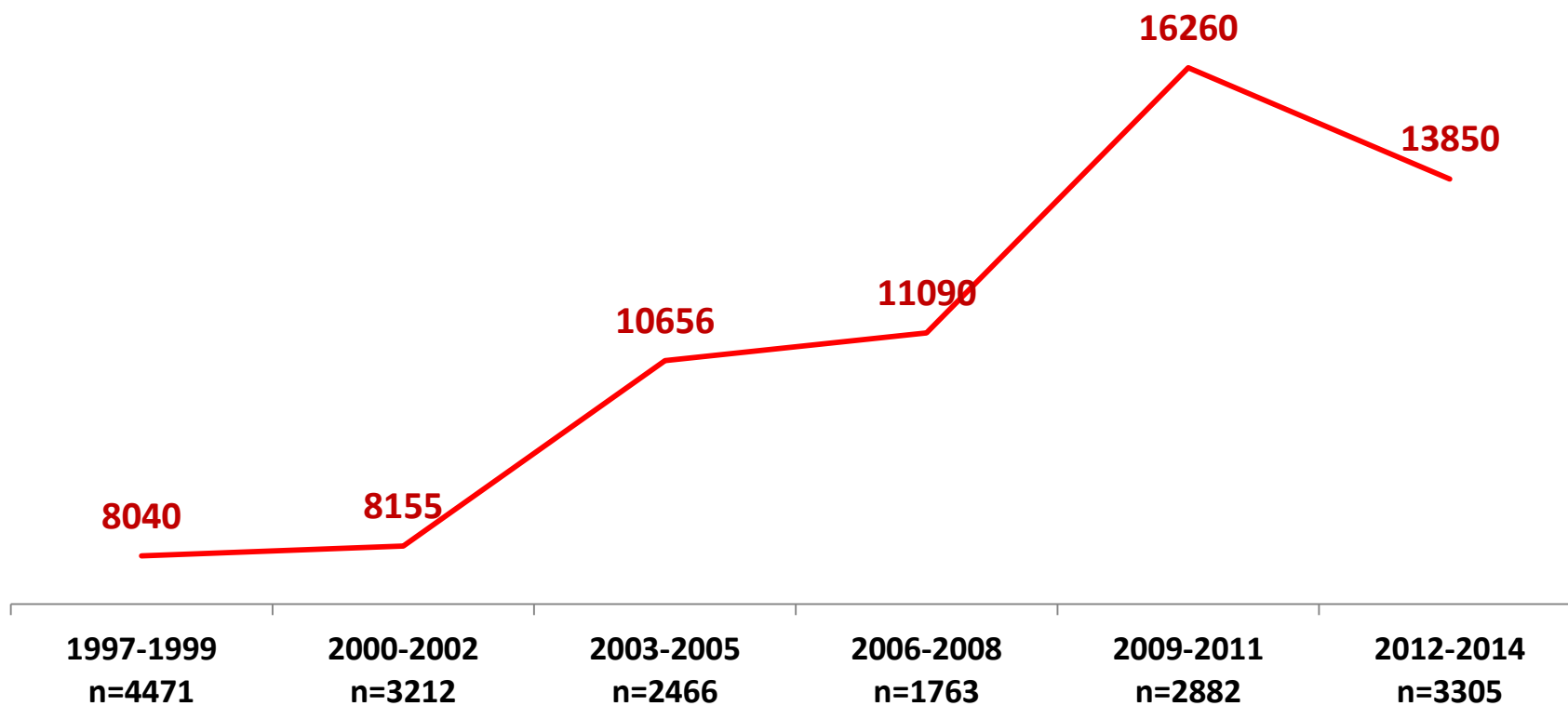


HIV-RNA log copies/ml

MMWR 1998. Mellors JW 1997



## Median HIV-RNA copies/ml per calendar period in naive patients (log<sub>10</sub> scale)



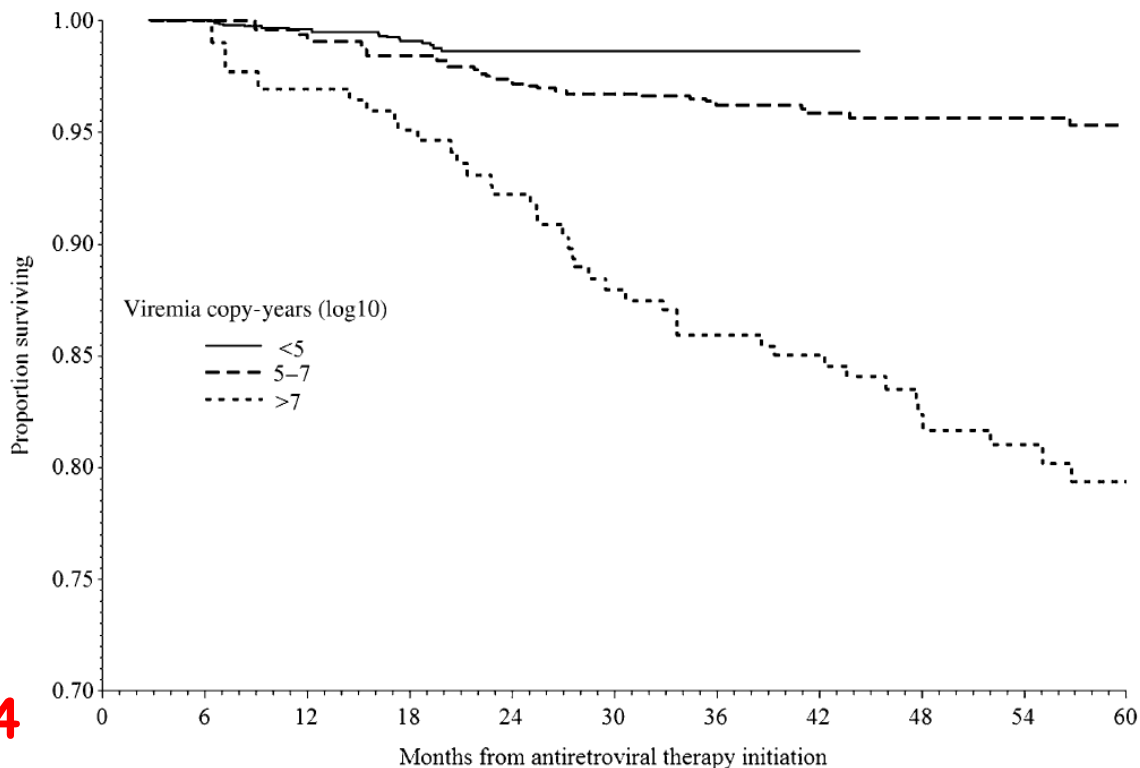


# Viremia Copy-Years Predicts Mortality Among Treatment-Naive HIV-Infected Patients Initiating Antiretroviral Therapy

Mugavero M.J.  
2011;53(9):927–935

**Cumulative plasma HIV burden, demonstrated prognostic value for all-cause mortality among 2027 HIV-infected patients following ART**

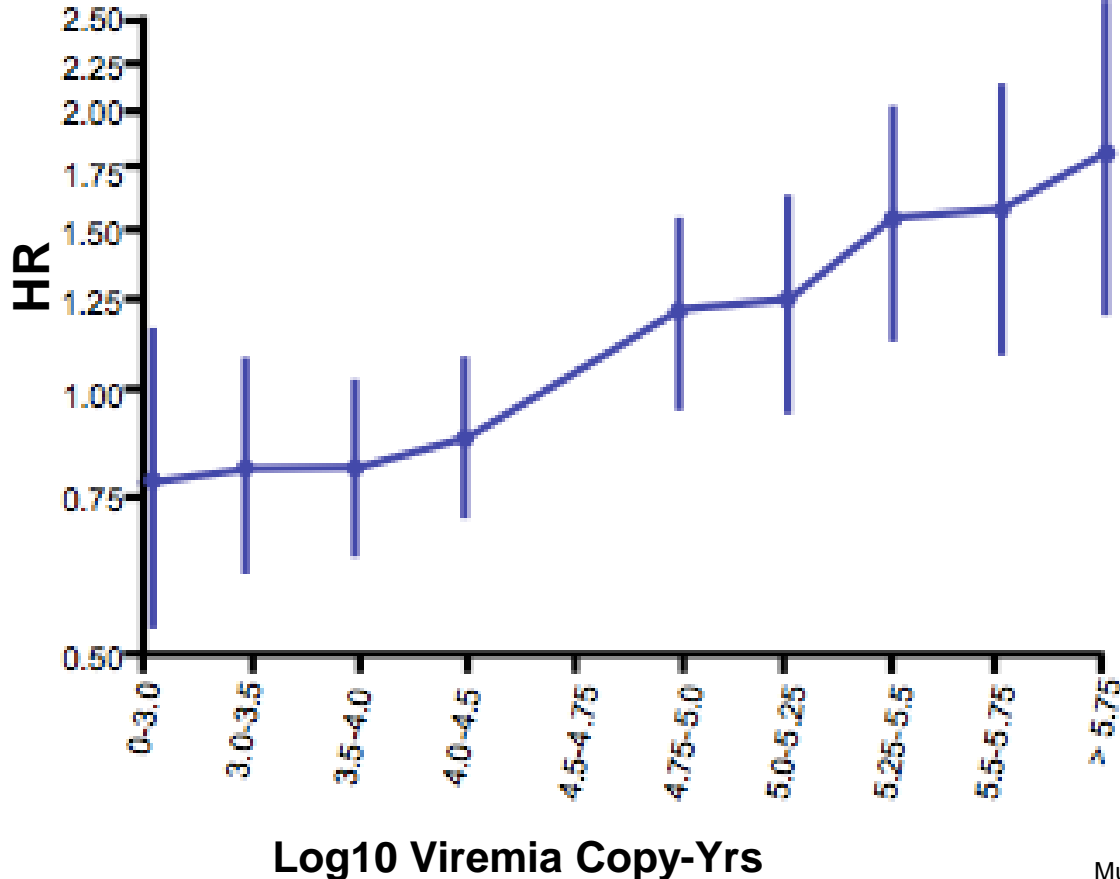
**(viral load values prior to 24 weeks of ART initiation were excluded)**



Viremia copy-years (log <sub>10</sub> )	Number at risk									
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
<5	1692	1414	1105	317	79	18	2			
5-7	245	289	332	833	851	727	606	509	414	316
>7	90	135	181	192	183	169	152	132	122	108

# Cumulative Viral Load Predicts Mortality in ART-Treated Patients

Hazard of All-Cause Mortality  
by Viremia Copy-Yrs Deciles  
(Controlling for Cross-sectional VL)



- Estimated cumulative VL (viremia copy-yrs) assessed in 33,563 pts at 17 sites of ART Cohort Collaboration
- After adjusting for age, sex, risk group, BL and time-related VL, and cohort, viremia copy-yrs stratum predicted
  - All-cause mortality
  - AIDS-related mortality





# Fatal and nonfatal AIDS and non-AIDS events in HIV-1-positive individuals with high CD4 cell counts according to viral load strata

Joanne Reekie<sup>a</sup>, Jose M. Gatell<sup>b</sup>, Israel Yust<sup>c</sup>, Elzbieta Bakowska<sup>d</sup>,  
Aza Rakhmanova<sup>e</sup>, Marcelo Losso<sup>f</sup>, Maksym Krasnov<sup>g</sup>,  
Patrick Francioli<sup>h</sup>, Justyna D. Kowalska<sup>i</sup>, Amanda Mocroft<sup>a</sup>, for  
EuroSIDA in EuroCoord

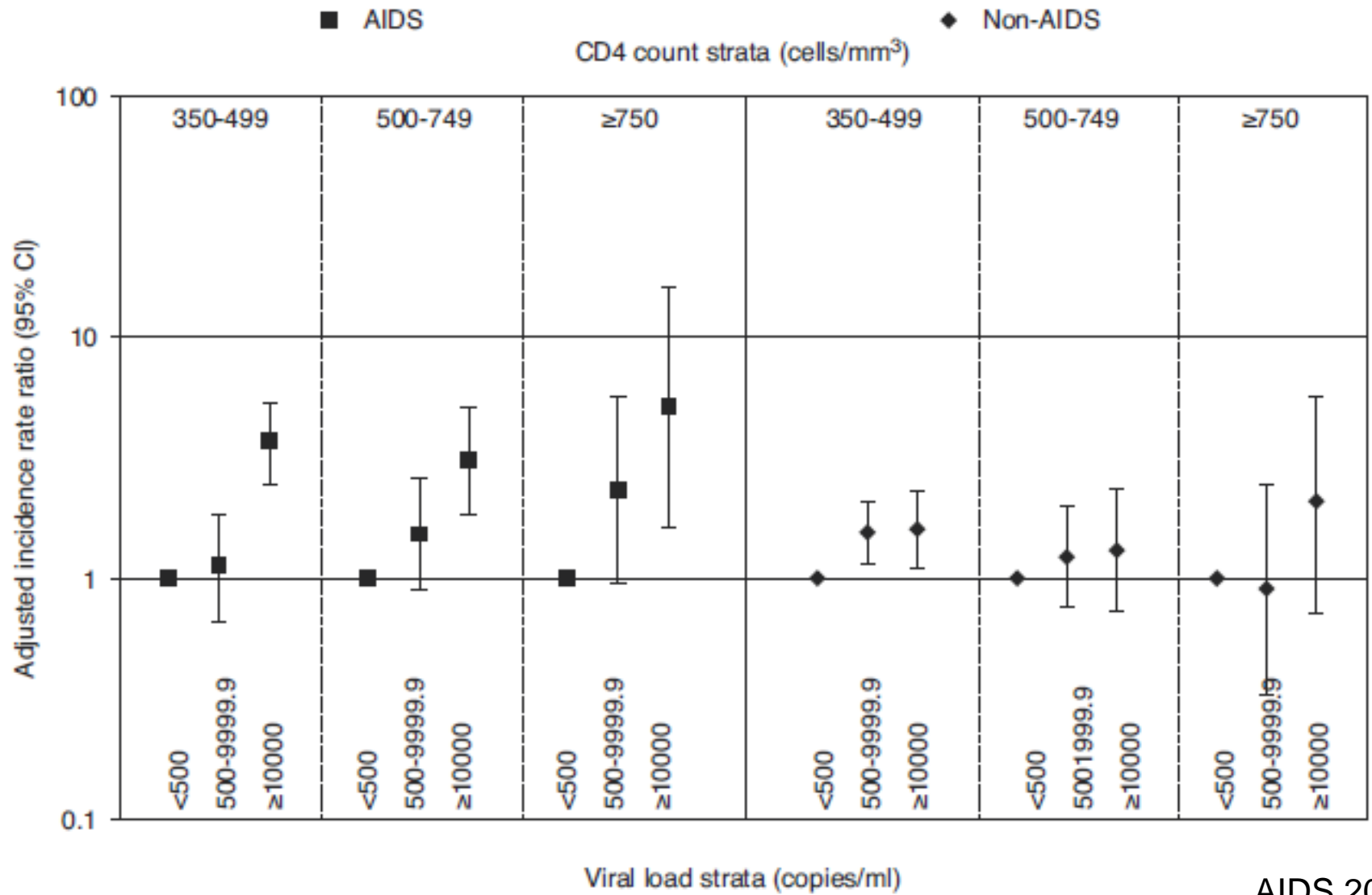
AIDS 2011, 25:2259–2268

This study compared the incidence of fatal and nonfatal AIDS and non-AIDS events during 51732 person-years of follow-up with a CD4 cell count more than 350 cells/ml among viral load strata: low (<500 copies/ml), intermediate (500–9999.9 copies/ml) and high (10000 copies/ml).



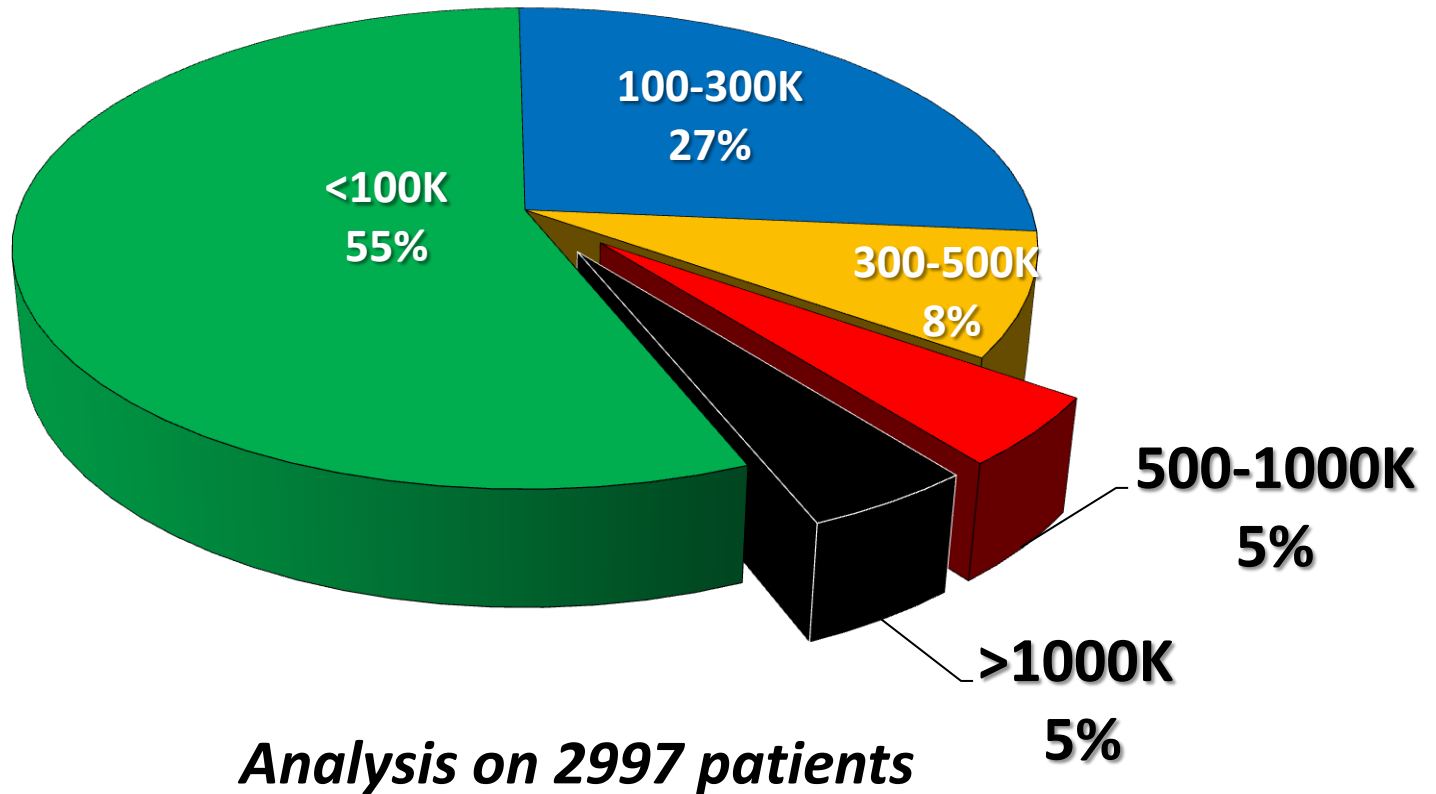
J Reekie

# Adjusted incidence rate ratios for AIDS and non-AIDS events by viral load strata stratified by current CD4 cell count.

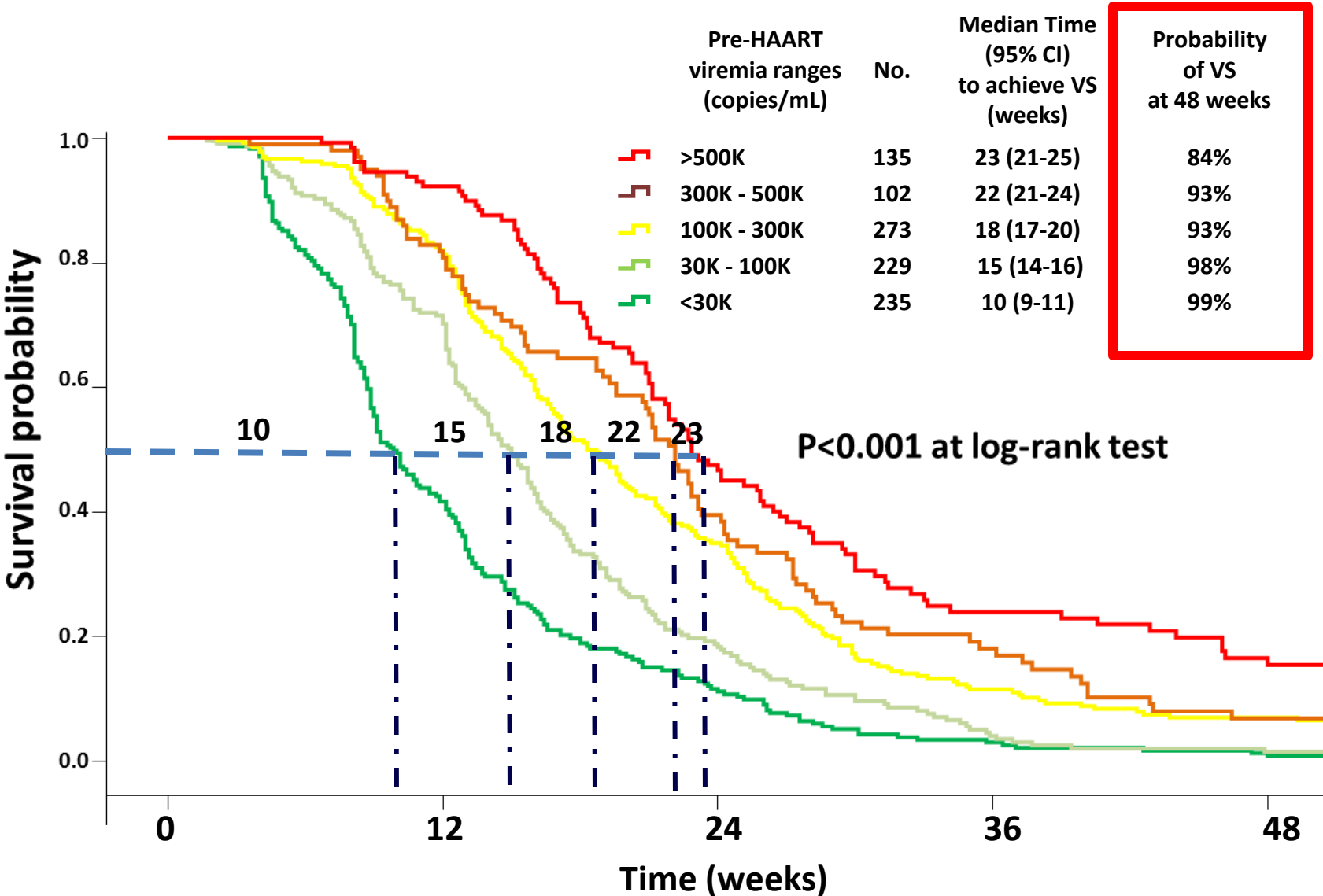




# Pre-HAART viremia (copies/mL)



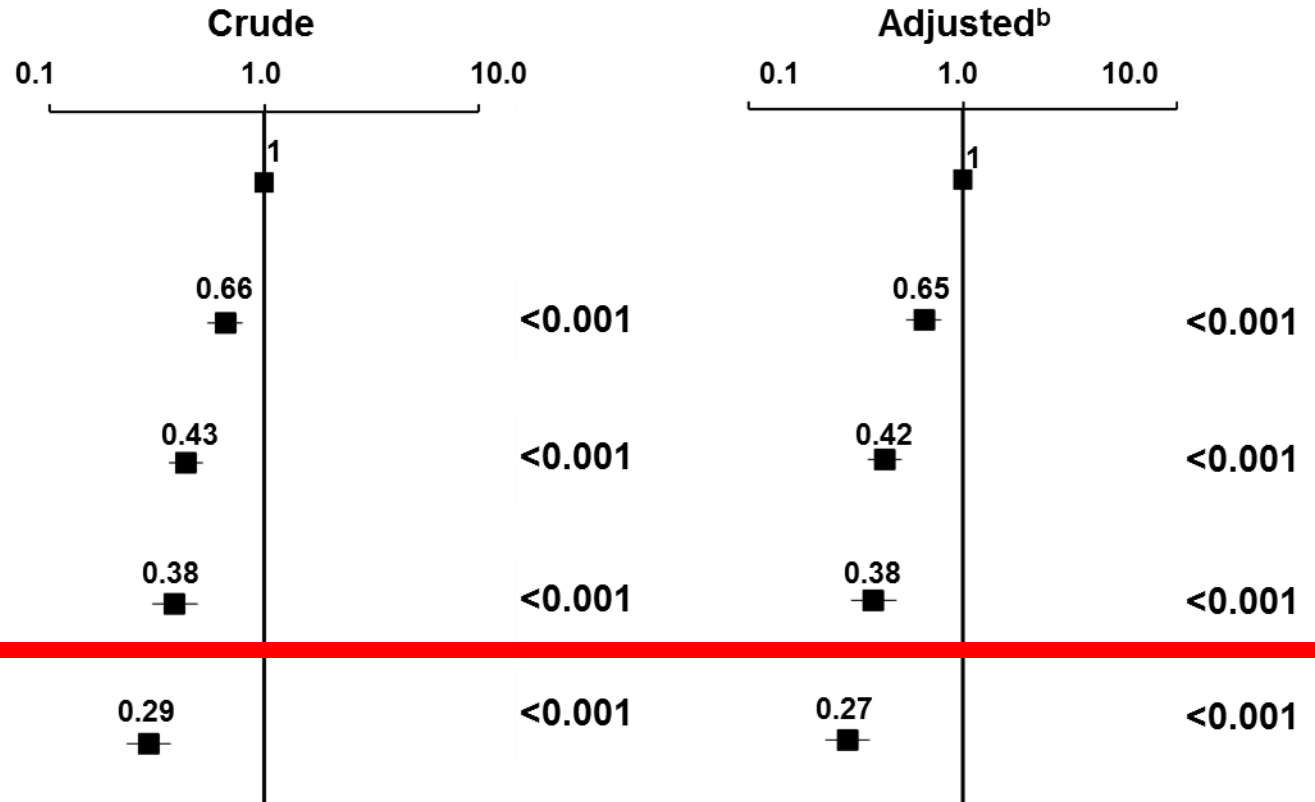
# The time to achieve virological undetectability and the rate of success at 48 weeks are pre-HAART viremia dependent



Patients having **pre-HAART viremia >500K copies/mL** have the lowest relative hazard to achieve virological success in comparison to other ones, also after adjusting for gender, age, pre-HAART CD4 cell count, transmitted drug resistance, calendar year and third drug administered (PI/r vs. NNRTI)

**Relative Hazard to achieve HIV-RNA <50 copies/mL**

Baseline HIV-RNA ranges

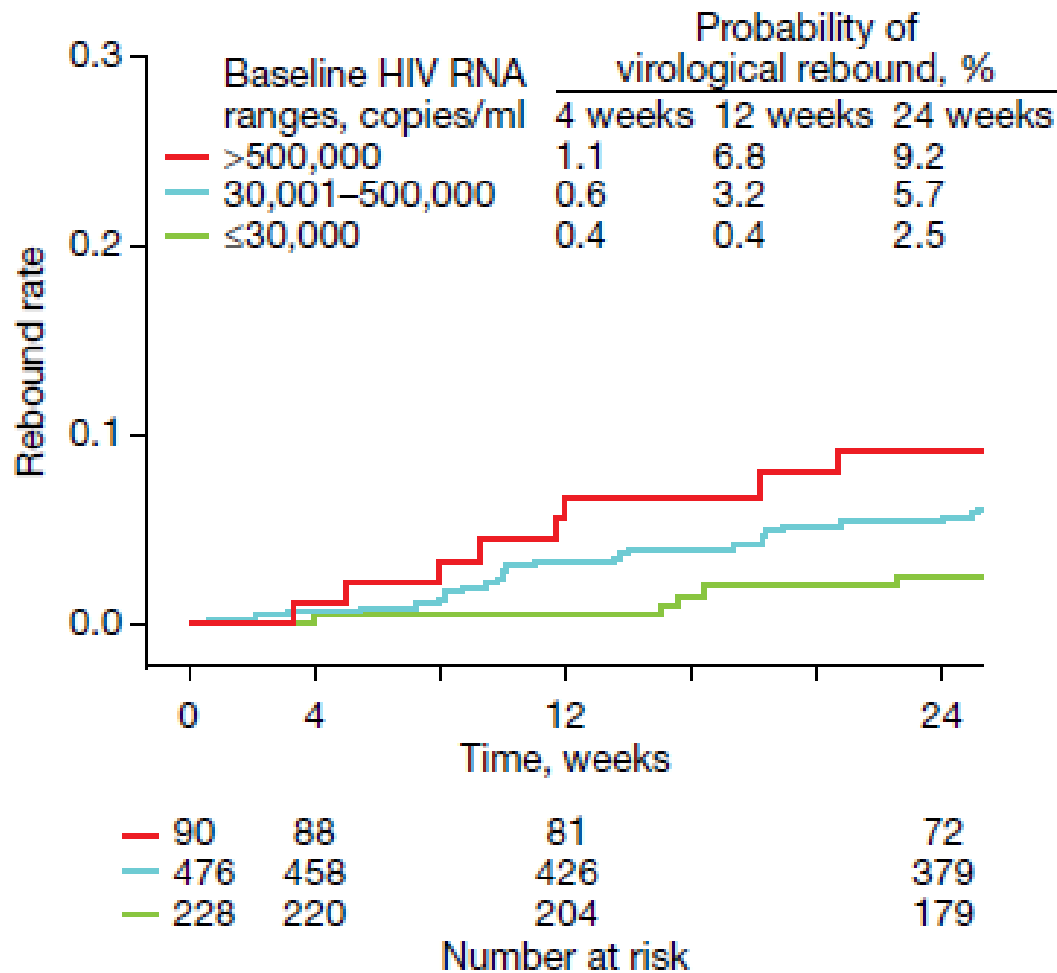


<sup>a</sup> Reference range.

<sup>b</sup> Adjusted for: gender, age, pre-HAART CD4 cell count, transmitted drug resistance, calendar year, third drug (PI vs. NNRTI).



# Patients having pre-HAART viremia >500K copies/ml showed the high probability of virological rebound (VL>50 copies) by 4 years from achievement of virological suppression



$P=0.050$  at log-rank test. The analysis was performed on 794 patients by on-treatment approach. \*As two consecutive viral load measurements >50 copies/ml after achieving undetectability.

***The level of residual viremia positively correlates with the risk of virological failure during HAART***

- **Increased Risk of Virologic Rebound in Patients on Antiviral Therapy with a Detectable HIV Load <48 Copies/mL**

*Henrich et al., Plos Pathogens 2012*

- **HIV DNA loads, plasma residual viraemia and risk of virological rebound in heavily treated, virologically suppressed HIV-infected patients**

*Gianotti et al., CMI 2015*

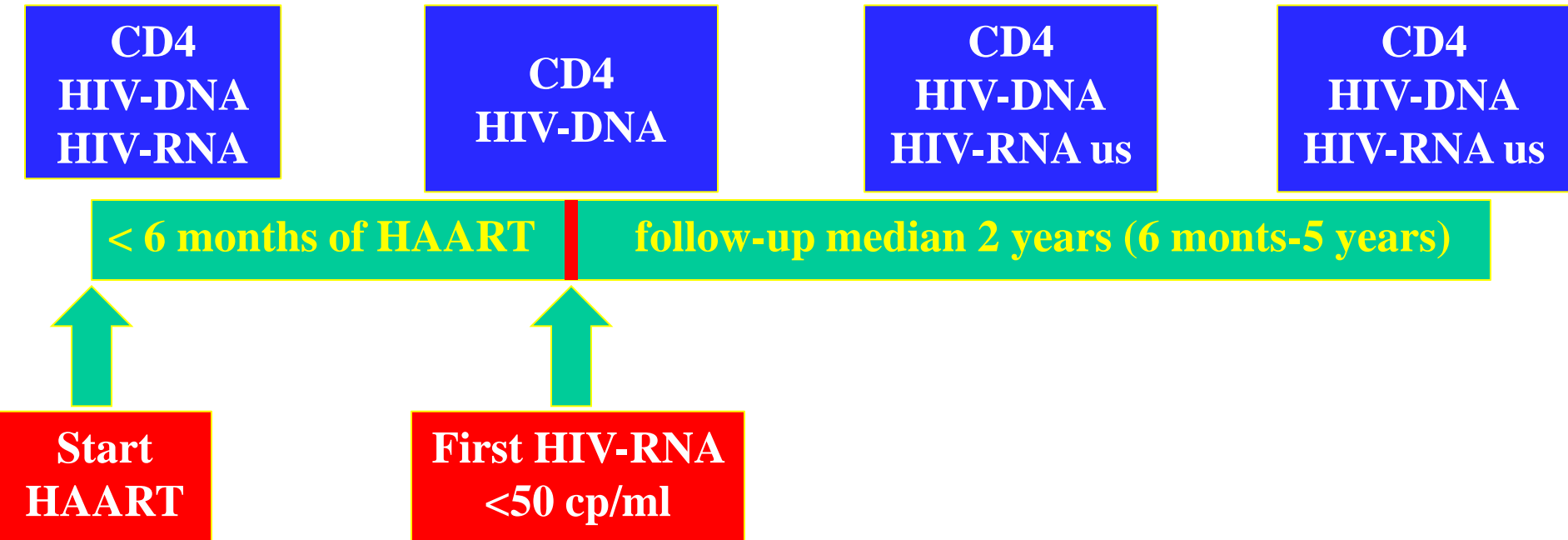
- **Ultrasensitive Assessment of Residual Low-Level HIV Viremia in HAART-Treated Patients and Risk of Virological Failure**

*Maggiolo et al. JAIDS 2012*

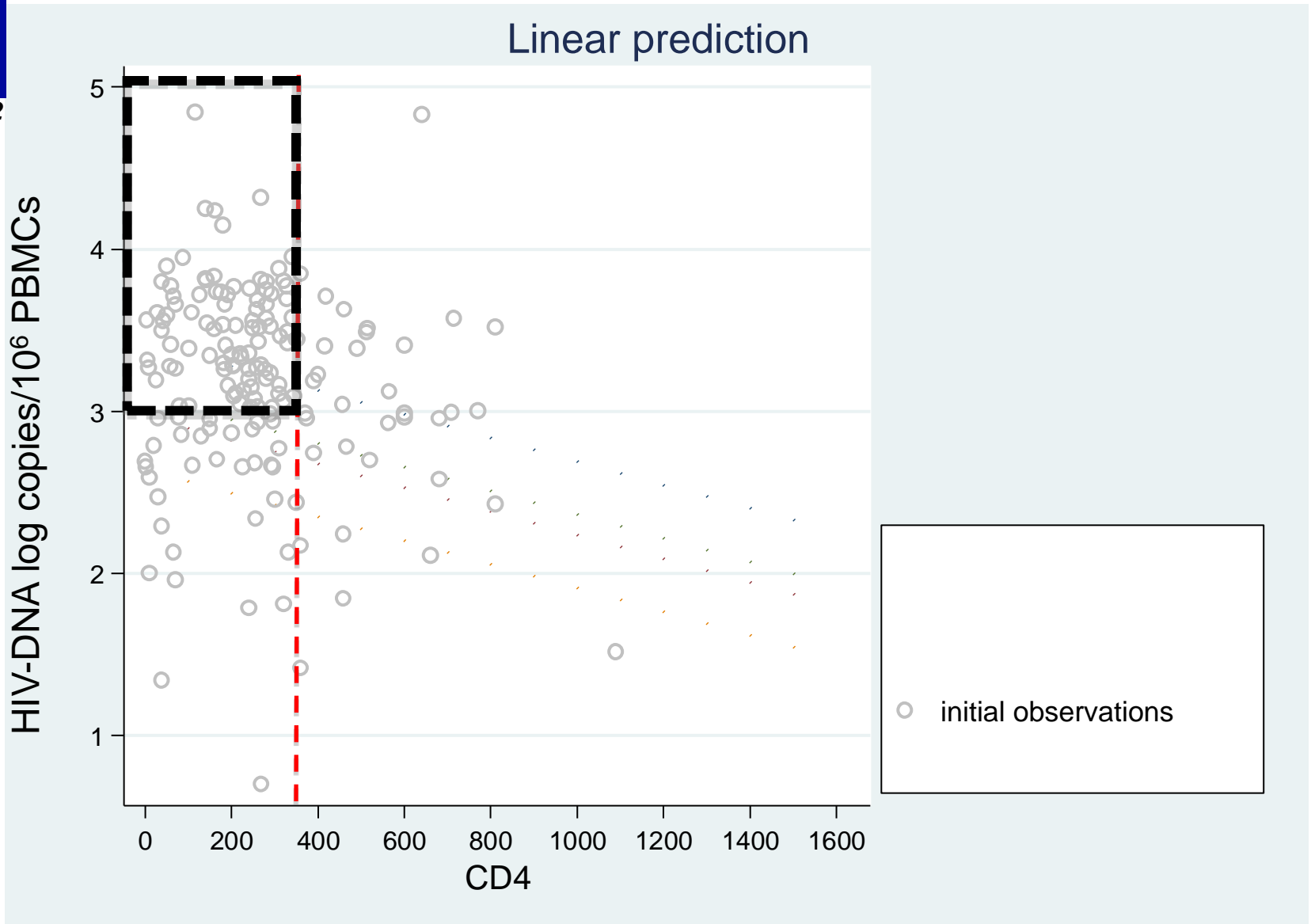
# Baseline Cellular HIV DNA Load Predicts HIV DNA Decline and Residual HIV Plasma Levels during Effective Antiretroviral Therapy

Saverio Giuseppe Parisi,<sup>a</sup> Samantha Andreis,<sup>a</sup> Carlo Mengoli,<sup>a</sup> Renzo Scaggiante,<sup>b</sup> Roberto Ferretto,<sup>c</sup> Vinicio Manfrin,<sup>d</sup> Mario Cruciani,<sup>e</sup> Mario Giobbia,<sup>f</sup> Caterina Boldrin,<sup>a</sup> Monica Basso,<sup>a</sup> Massimo Andreoni,<sup>g</sup> Giorgio Palù,<sup>a</sup> and Loredana Sarmati<sup>g</sup>

**180** ART-naïve patients achieved virological suppression <50 copies/ml with their first line therapy within 6 mo, and maintained always undetectable plasma viremia, with no more than one viral blip.



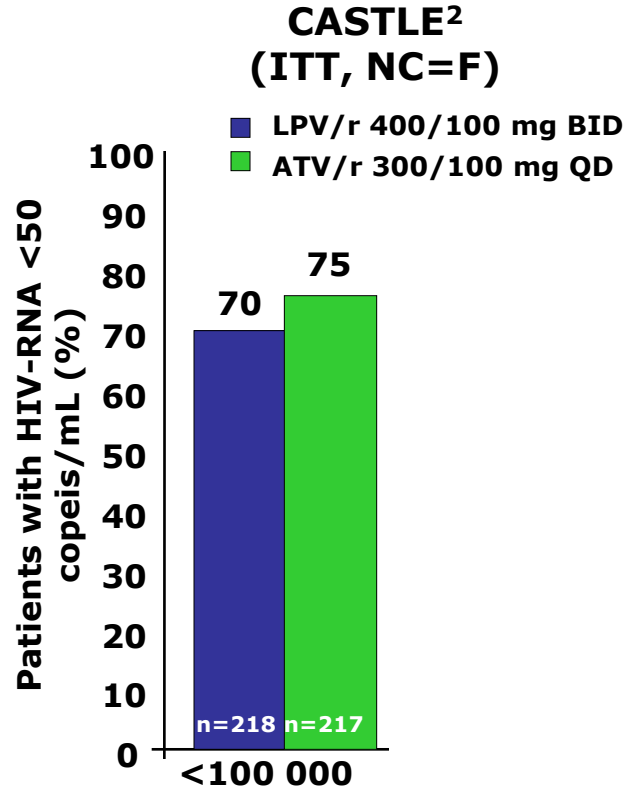
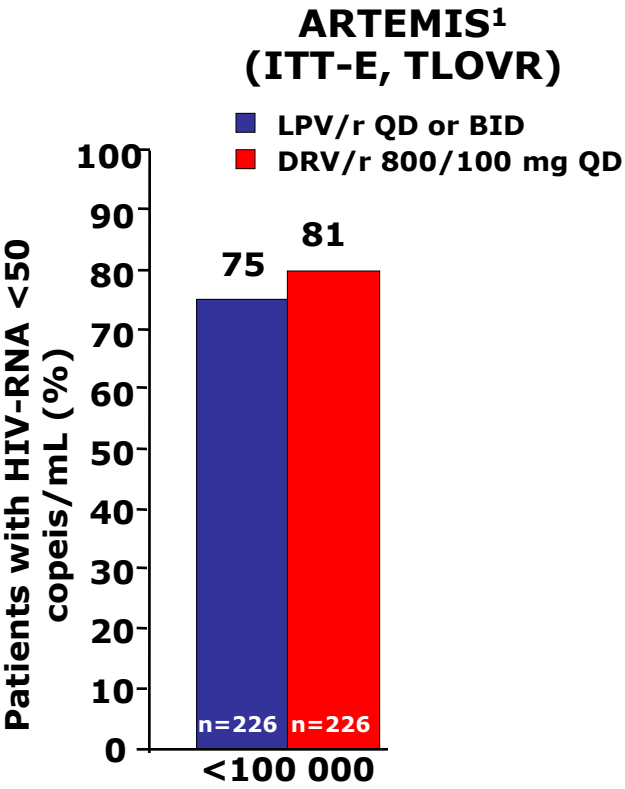
# STRICT CORRELATION BETWEEN CD4 NADIR E HIV-DNA LEVEL



Time 0 = after 6 months of ART;

Time 1= follow up

# Boosted PIs in ARV-naïve: The challenge of high viral load (96 weeks)



Baseline HIV RNA (copies/mL)

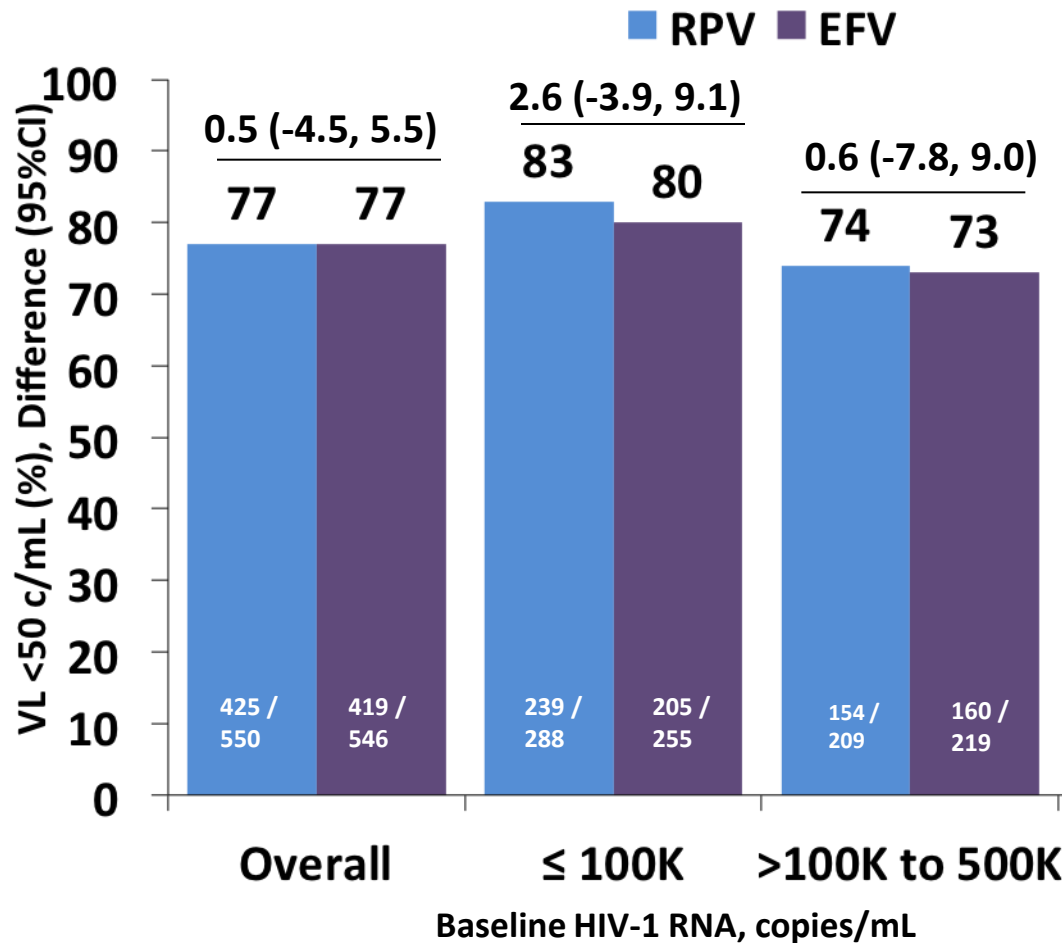
ITT, intent to treat; ITT-E, intent to treat, exposed; TLOVR, time to loss of virological response; VL, viral load; NC=F, non-completer = failure

1. Mills A, et al. 48th ICAAC. Washington DC, Oct 25–28, 2008, Abstract H-1250c;  
2. Molina JM, et al. 48th ICAAC. Washington, DC, Oct 25–28, 2008, Abstract H-1250d



# Pooled ECHO and THRIVE: Wk 96 FTC/TDF Dataset

## VL <50 c/mL by Baseline Viral Load (Snapshot)



RPV+FTC/TDF was non-inferior to EFV+FTC/TDF in the overall analysis and in baseline viral load strata of ≤ 100,000 and 100,001-500,000 copies/mL by Snapshot analysis

# QDMRK – HIV RNA < 50 copies/mL at Week 48 by Subgroup (NC=F)

	Response				Difference % (95% CI)
	RAL QD		RAL BID		
	n/N	%	n/N	%	
<b>Baseline HIV RNA (copies/mL)</b>					
> 100,000 copies/mL	113/152	74.3	128/152	84.2	-9.9 (-19.0, -0.8)
≤ 100,000 copies/mL	205/230	89.1	215/234	91.9	-2.7 (-8.3, 2.7)
<b>Baseline CD4 (cells/mm<sup>3</sup>)</b>					
≤ 200 cells/mm <sup>3</sup>	63/89	70.8	80/99	80.8	-10.0 (-22.3, 2.2)
> 200 cells/mm <sup>3</sup>	254/292	87.0	262/286	91.6	-4.6 (-9.8, 0.4)



## Short communication

# No advantage of quadruple- or triple-class antiretroviral therapy as initial treatment in patients with very high viraemia

*Marlous L Grijzen<sup>1\*</sup>, Rebecca Holman<sup>2</sup>, Luuk Gras<sup>2</sup>, Ferdinand WNM Wit<sup>3</sup>, Andy IM Hoepelman<sup>4</sup>, Guido E van den Berk<sup>5</sup>, Frank de Wolf<sup>2</sup>, Jan M Prins<sup>1</sup>, the ATHENA National Observational Cohort Study*

<sup>1</sup>Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, University of Amsterdam, Center for Infection and Immunity Amsterdam, Amsterdam, the Netherlands

<sup>2</sup>HIV Monitoring Foundation, Amsterdam, the Netherlands

<sup>3</sup>Department of Global Health, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands

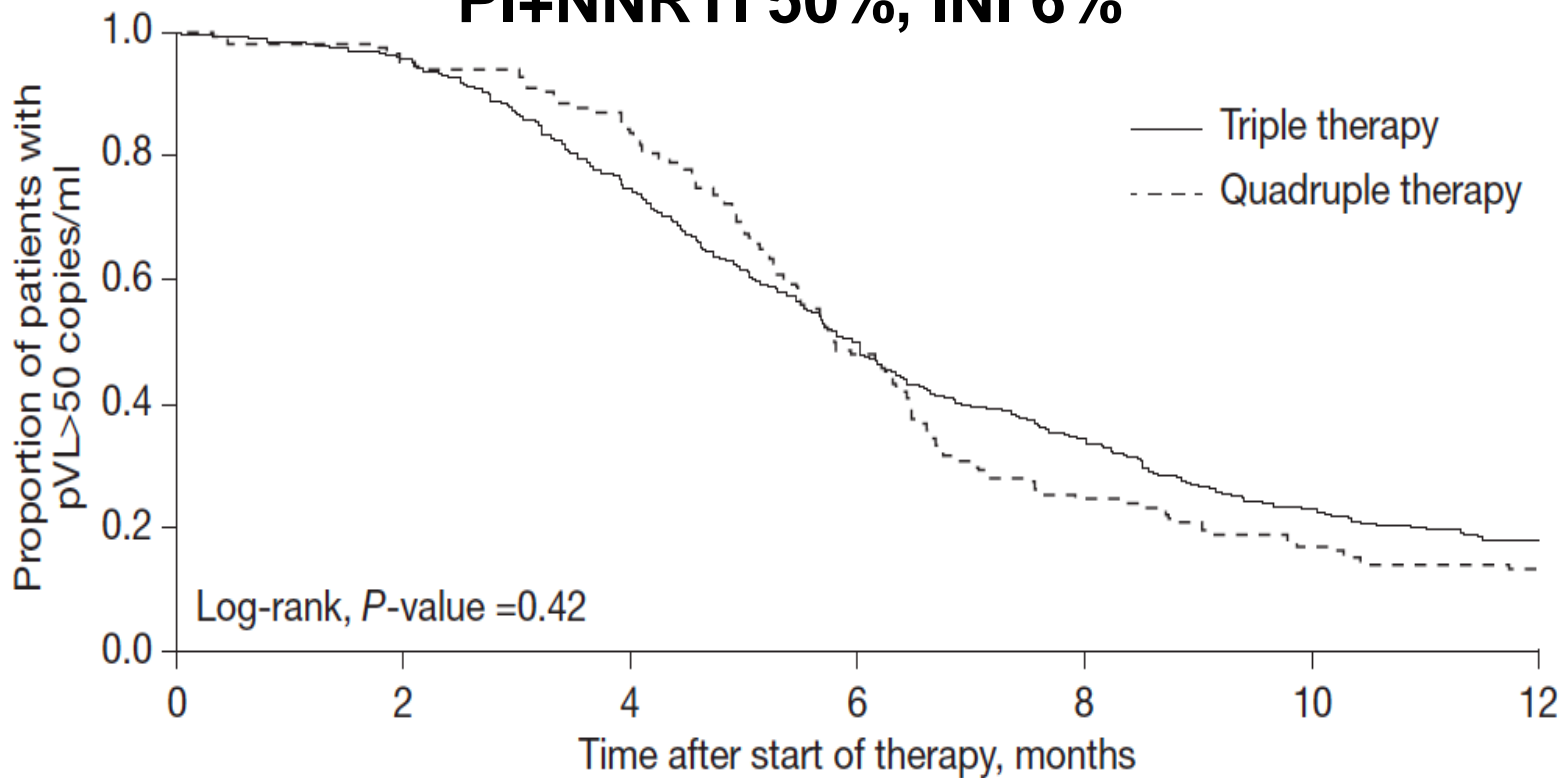
<sup>4</sup>Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, the Netherlands

<sup>5</sup>Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands

**Inclusion criteria: Treatment naive patients, HIV-RNA >500.000cp/ml, initiation of quadruple or triple therapy between 2001 and 2011**



# Quad regimen including: NNRTI 18%, PI/r 25%, PI+NNRTI 50%, INI 6%



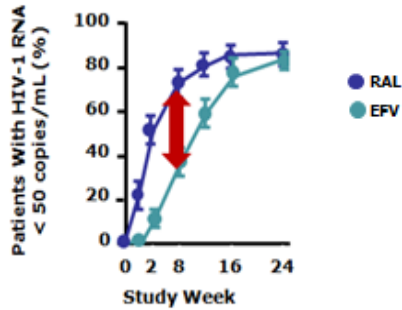
Patients remaining, <i>n</i>	0	2	4	6	8	10	12
Triple	548	516	398	254	167	106	79
Quadruple	125	118	103	57	29	19	14

22 (18%) pts on quadruple and 63(12%) on triple interrupted the treatment because drug toxicity (p=0.06).

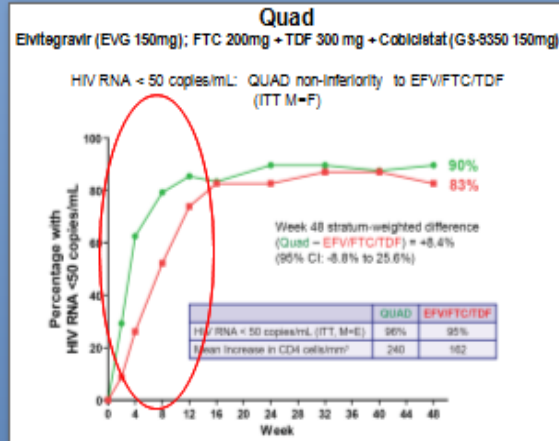
In the adjusted Cox analysis quadruple was not associated with time to viral suppression.

# Alte viremie

## STARTMRK: Does early viral decay predict long-term virologic control?

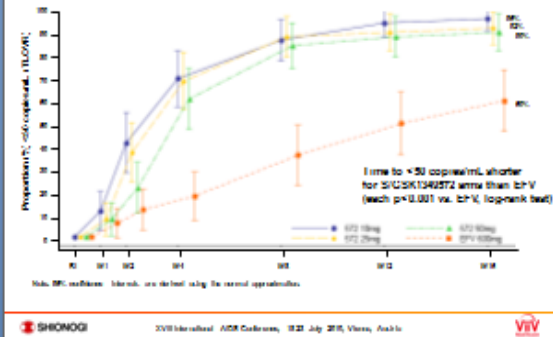


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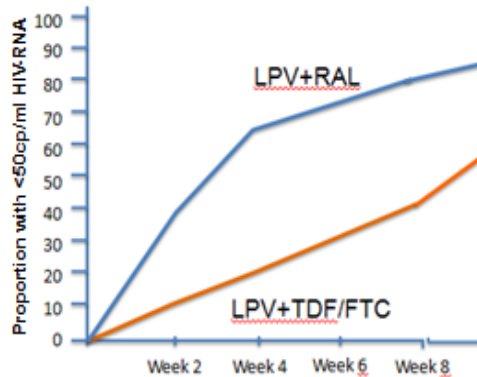
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## Rapid and Robust Antiviral Activity: Dolutegravir



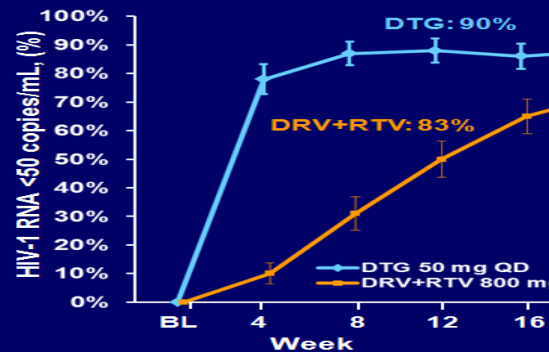
48

## PROGRESS STUDY



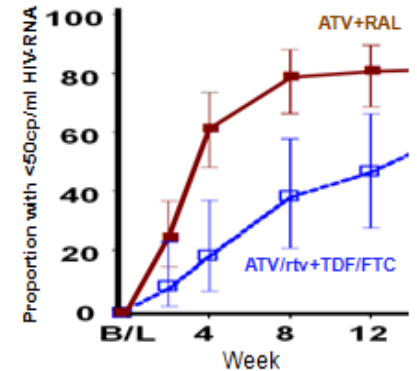
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## FLAMINGO



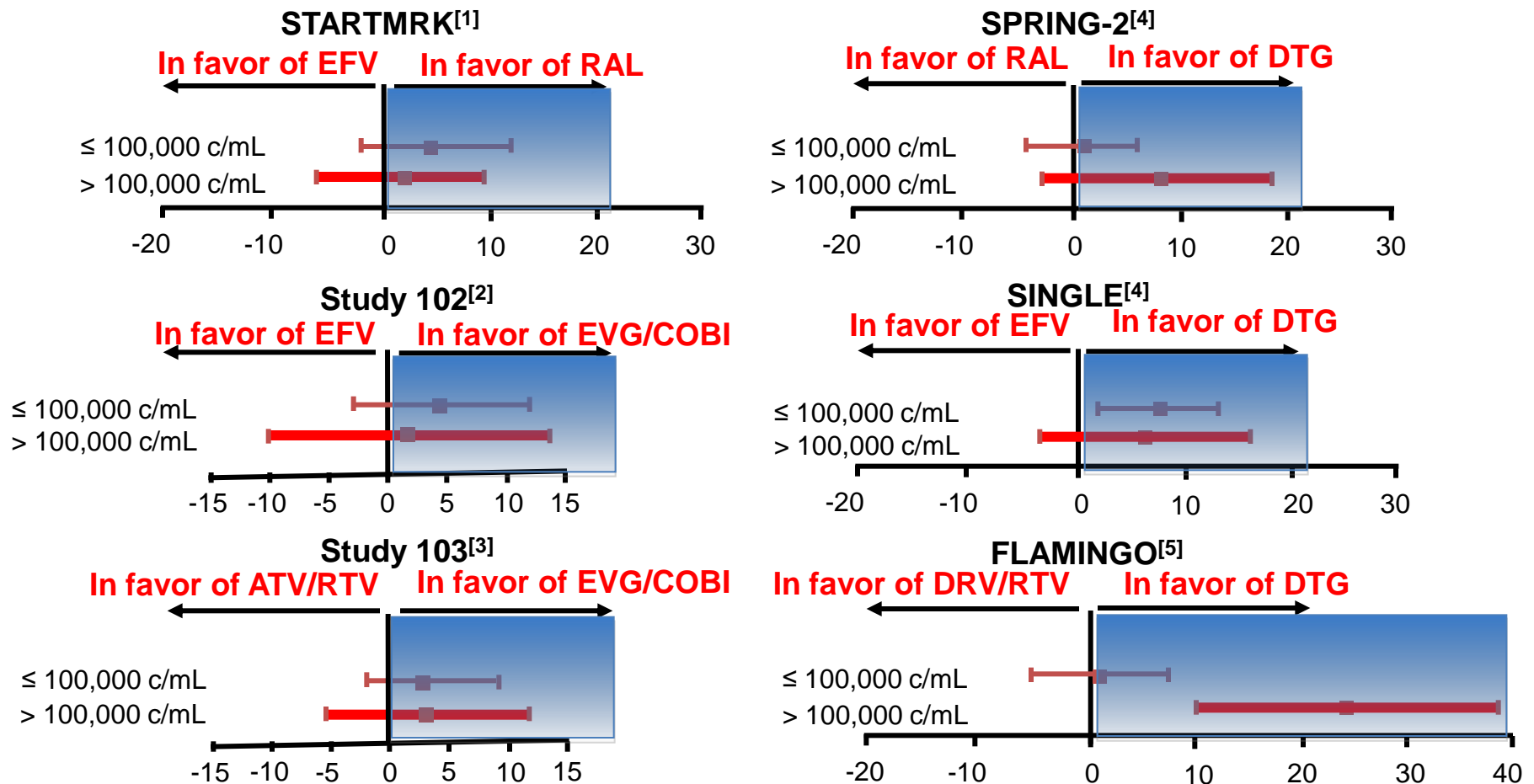
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## SPARTAN STUDY



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# Virologic Suppression at Wk 48 by Baseline HIV-1 RNA



1. Lennox J, et al. Lancet. 2009;374:796-806. 2. Sax PE, et al. Lancet. 2012;379:2439-2448. 3. DeJesus E, et al. Lancet. 2012;379:2429-2438. 4. Brinson C, et al. CROI 2013. Abstract 554. 5. Feinberg J, et al. ICAAC 2013. Abstract H1464a.\

# Impact of baseline viral Load and Time to Viral Suppression on Virologic Rebound according to first-line ART

## **SPEED Study**

Lydie Khatchatourian, Matthieu Hanf, Thomas Jovelin, Nolwenn Hall, Véronique Joly, Eric Cua, Pierre Delobel, Tristan Ferry, Christine Katlama, Antoine Cheret, François Raffi, Clotilde Allavena, and Dat' AIDS Study Group



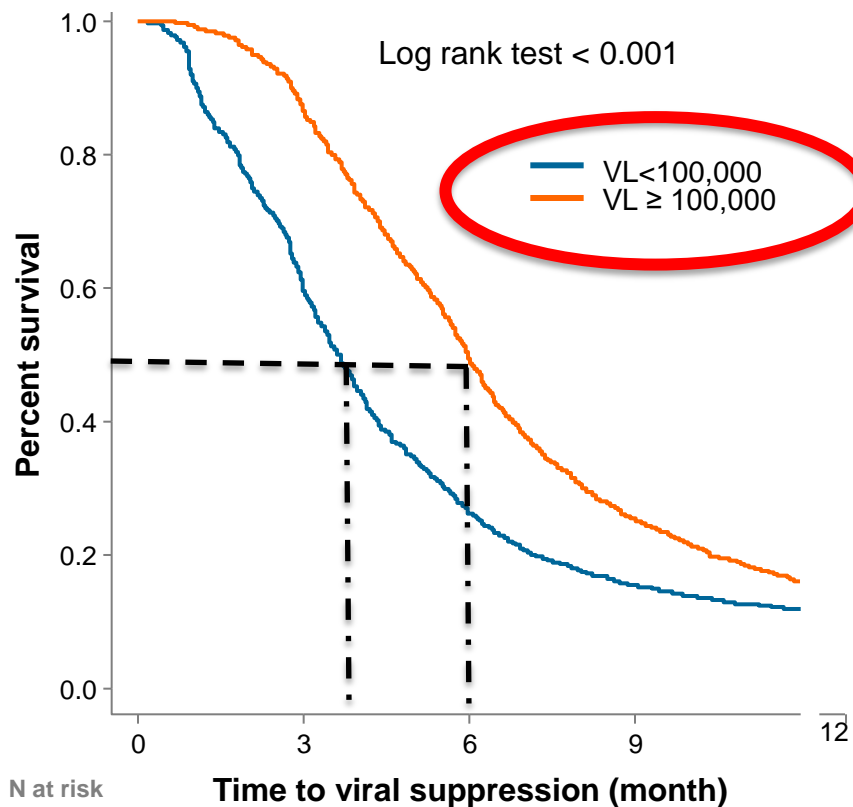
**42,000-person group of people in care for HIV  
7592 (91%) reached a viral load below 50 copies**



# Time to observed viral **suppression** according to baseline VL and to regimen class

## *Time to viral suppression according to baseline VL*

N=8351

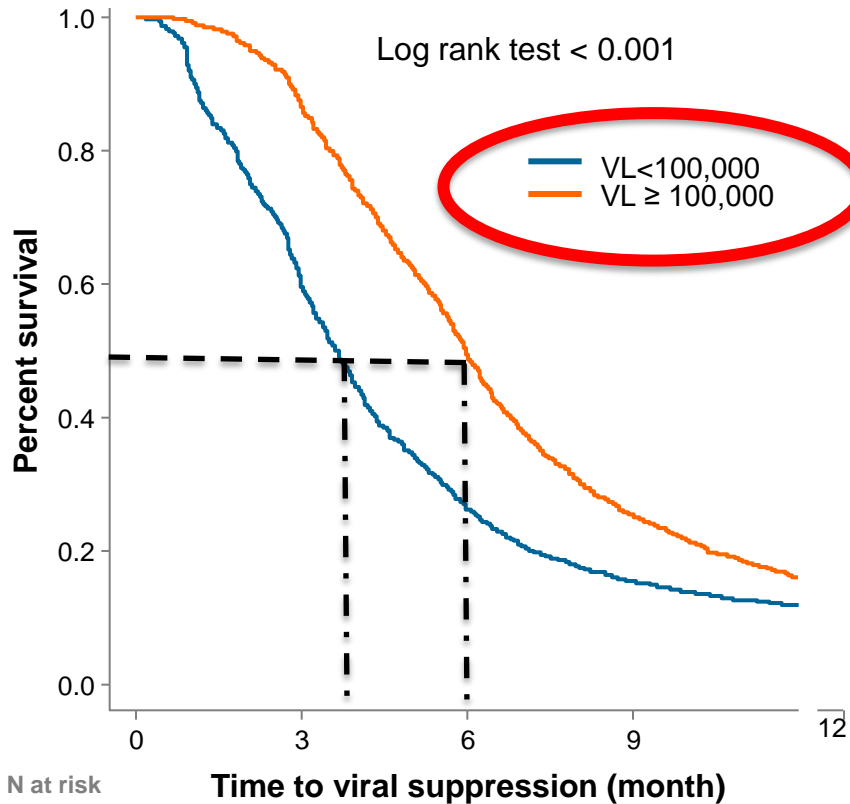


	0	3	6	9	12
VL < 100,000	5135	2959	1280	730	530
VL ≥ 100,000	3216	2664	1477	732	442



# Time to observed viral **suppression** according to baseline VL and to regimen class

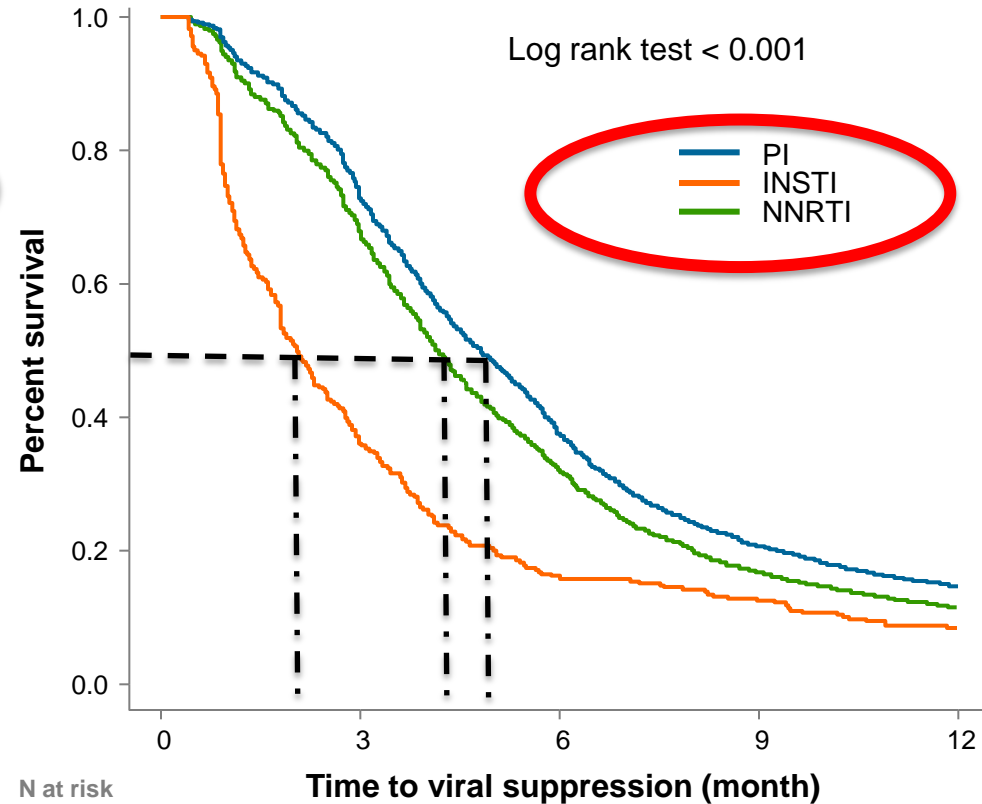
**Time to viral suppression according to baseline VL**



VL < 100,000	2959	1280	730	530
5135	2664	1477	732	442
VL ≥ 100,000	3216			






N=8351

**Time to viral suppression according to regimen class**



PI	4088	2049	1086	729
5828	131	57	42	26
INSTI	377			
377	1404	651	334	217
NNRTI	2146			

# Risk of viral **suppression** (multivariate Cox model)

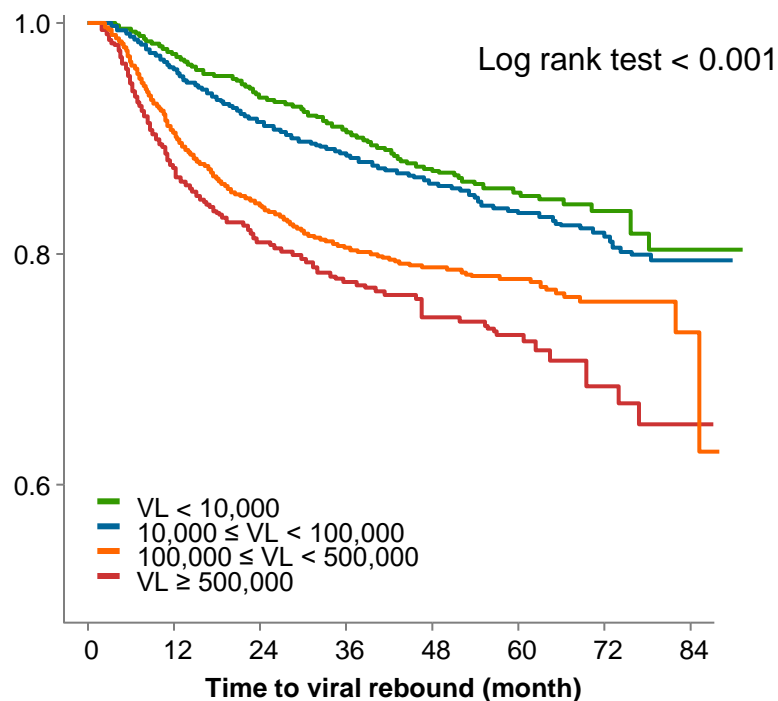
Variables		All patients N=8351		
		HR	95% CI	P
<b>Age</b> (ref: < 40 years)	≥ 40 years	1.01	0.95 - 1.05	0.999
 <b>Sex</b> (ref: Female)	Male	<b>0.89</b>	<b>0.83 - 0.94</b>	<b>&lt;0.001</b>
 <b>Exposure</b> (ref: hetero.)	MSM	<b>1.19</b>	<b>1.12 - 1.26</b>	<b>&lt;0.001</b>
	Other/unknown	0.96	0.89 - 1.04	0.334
<b>HBV or HBC Co-Infection</b> (ref: No)	Yes	0.98	0.91 - 1.05	0.522
 <b>AIDS status at baseline</b> (ref: A)	B	0.95	0.88 - 1.03	0.242
	C	<b>0.81</b>	<b>0.76 - 0.87</b>	<b>&lt;0.001</b>
 <b>Regimen class</b> (ref: PI)	NNRTI	<b>1.12</b>	<b>1.06 - 1.18</b>	<b>&lt;0.001</b>
	INSTI	<b>1.92</b>	<b>1.72 - 2.14</b>	<b>&lt;0.001</b>
<b>Backbone</b> (ref: TDF+ FTC)	ABC + 3TC	1.03	0.97 - 1.10	0.307
	AZT + 3TC	0.94	0.85 - 1.03	0.189
	Other	0.9	0.75 - 1.08	0.267
<b>CD4 count</b> (ref: <500 cells/mm <sup>3</sup> )	≥ 500 cells/mm <sup>3</sup>	0.99	0.93 - 1.06	0.726
 <b>Viral load</b> (ref: < 100,000 copies/ml)	≥ 100,000 c/ml	<b>0.67</b>	<b>0.64 - 0.71</b>	<b>&lt;0.001</b>

# Risk of virologic rebound according to baseline viral load and time to viral suppression

- 990 (13.0%) patients experienced virologic rebound ( CV > 50 copies/ml X2)
  - Median [IQR] follow-up time from cART initiation : 41.2 [23.8,61.5] months

N=7592

## Time to virologic rebound according to baseline viral load



N at risk

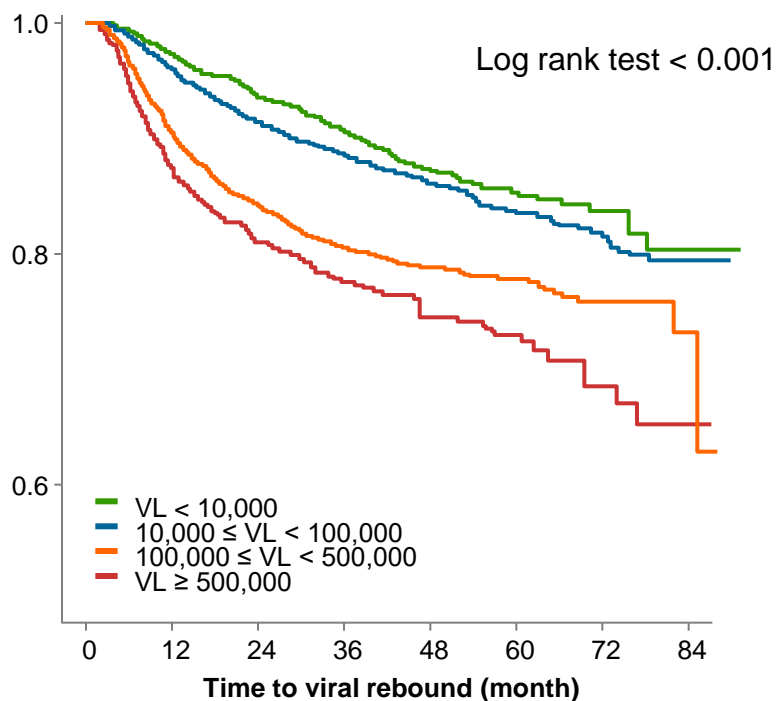
VL < 10,000	1556	1283	996	715	503	302	131	34
10,000-100,000	3189	2562	1931	1362	873	519	241	46
100,000-500,000	2036	1514	1125	784	516	315	132	12
VL > 500,000	8141	555	390	292	189	110	55	2

# Risk of virologic rebound according to baseline viral load and time to viral suppression

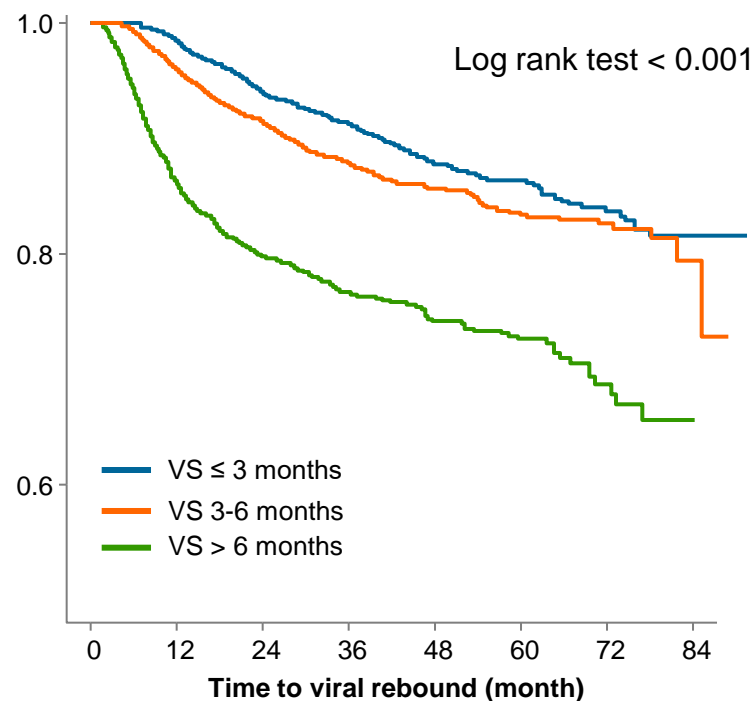
- 990 (13.0%) patients experienced virologic rebound ( CV > 50 copies/ml X2)
  - Median [IQR] follow-up time from cART initiation : 41.2 [23.8,61.5] months

N=7592

Time to virologic rebound according to **baseline viral load**



Time to virologic rebound according to **time to viral suppression**



N at risk

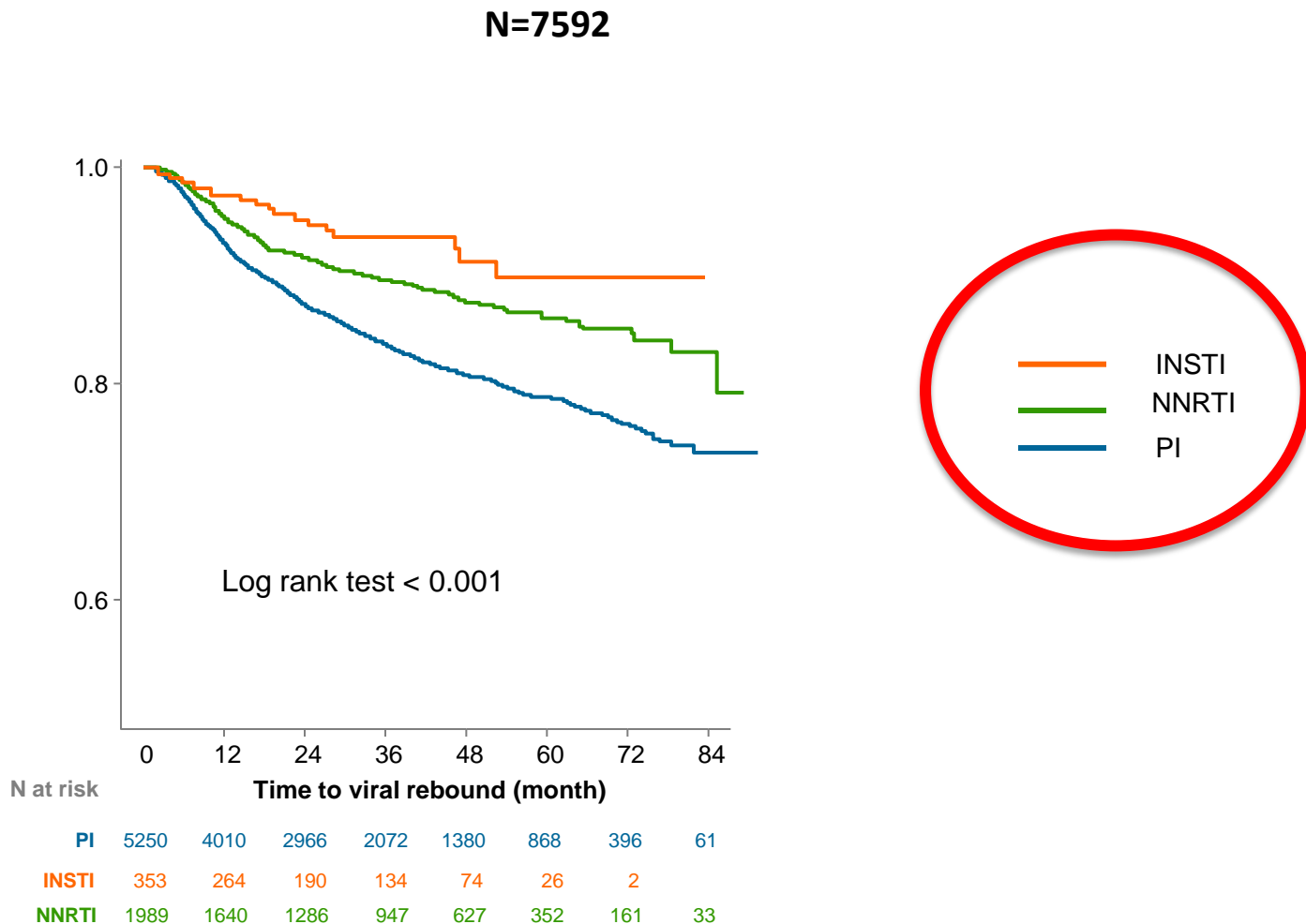
	0	12	24	36	48	60	72	84
VL < 10,000	1556	1283	996	715	503	302	131	34
10,000-100,000	3189	2562	1931	1362	873	519	241	46
100,000-500,000	2036	1514	1125	784	516	315	132	12
VL > 500,000	8141	555	390	292	189	110	55	2

N at risk

	0	12	24	36	48	60	72	84
VS ≤ 3 months	2454	2096	1663	1227	841	547	274	70
VS 3-6 months	2772	2219	1669	1167	780	444	197	24
VS > 6 months	2366	1599	1110	759	460	255	88	35

# Risk of virologic rebound according to regimen class

990 (13.0%) patients experienced virologic rebound ( CV > 50 copies/ml X2)



# Conclusioni

- Pazienti con CD4+ <200 alla diagnosi hanno minori probabilità di un reale recupero immunologico
- Le alte cariche di HIV alla diagnosi sono correlate a un ritardo nella risposta alla terapia e una maggior rischio di *viral rebound*
- In pazienti in *advanced infection* la terapia con classi farmacologiche ad alta potenza facilita il raggiungimento dell'undetectability ed è protettivo sul rebound virologico