UPDATE ON THERAPEUTIC TRIALS: 2012

1. Natural history of HIV-1 infection
2. cART in 2012. Achievements & limitations
3. Therapeutic vaccines against HIV
4. Final considerations

Jose M Gatell
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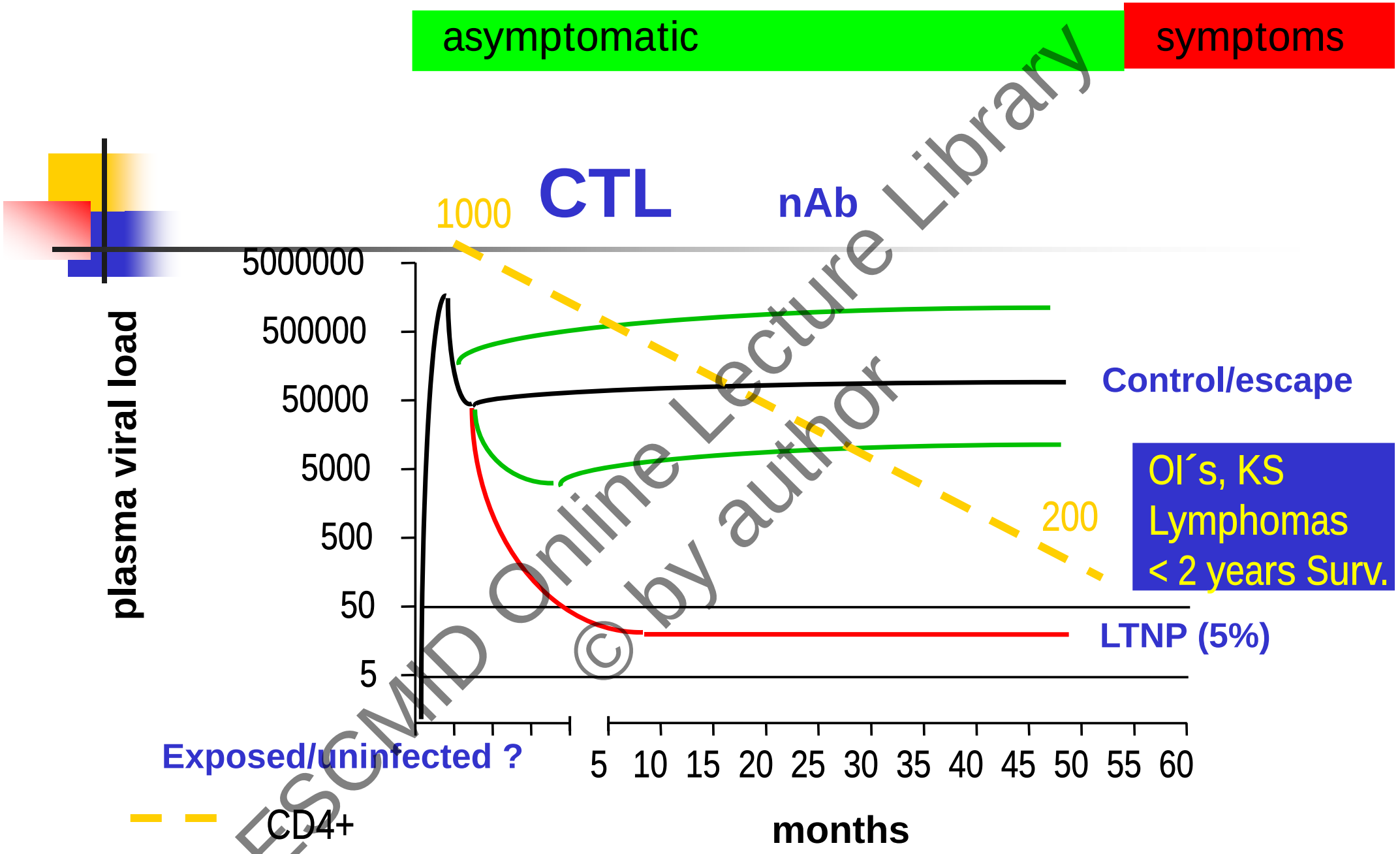

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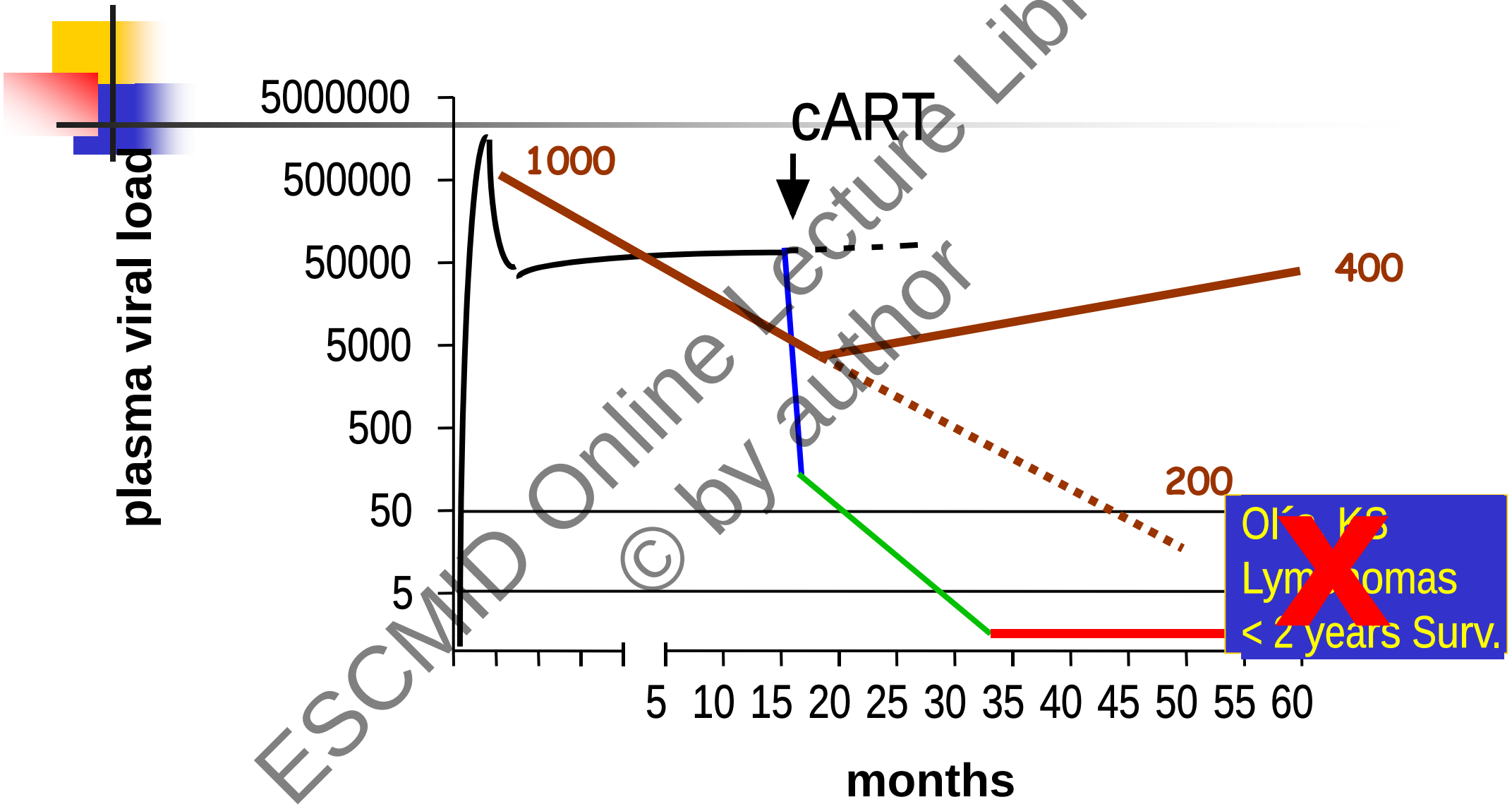
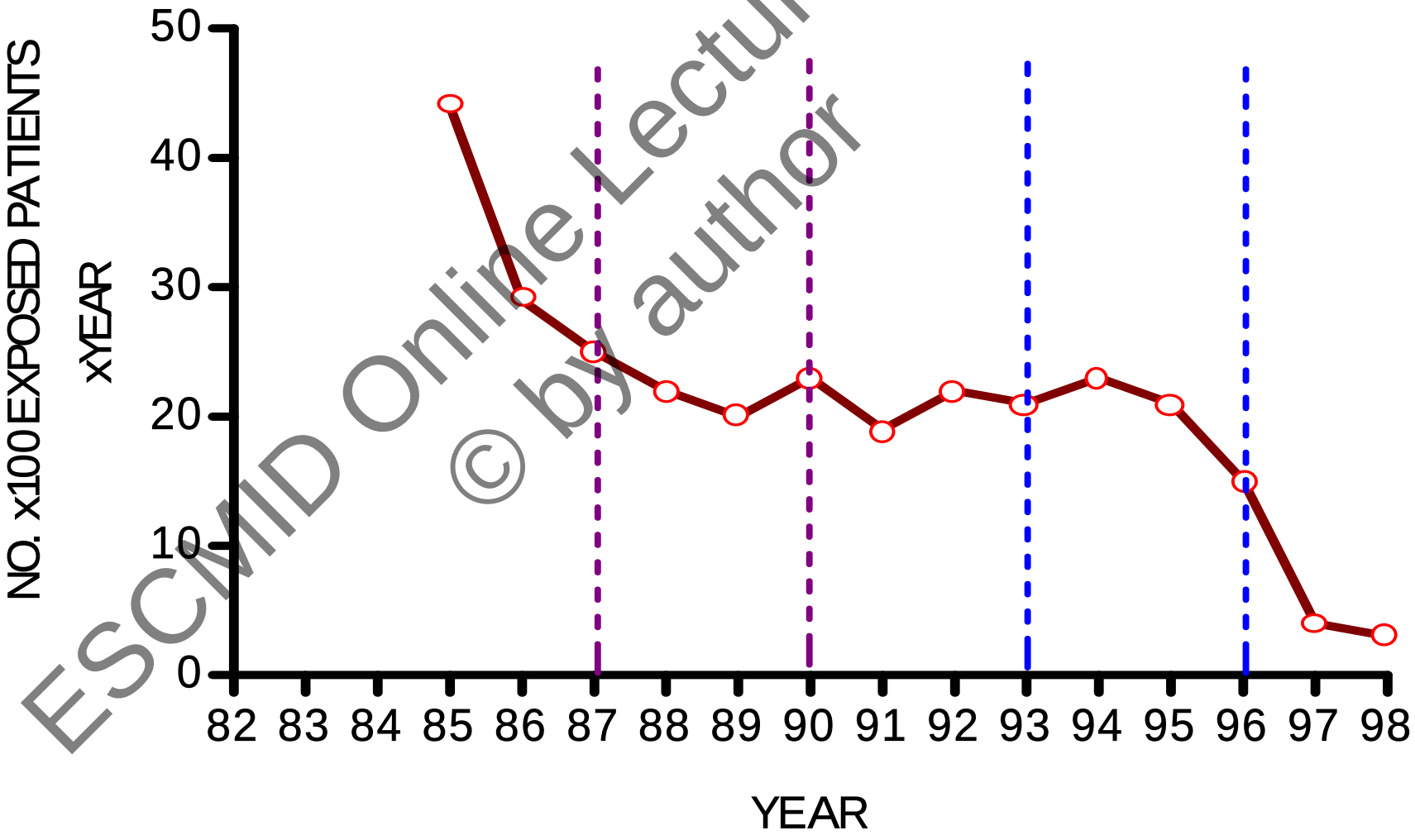
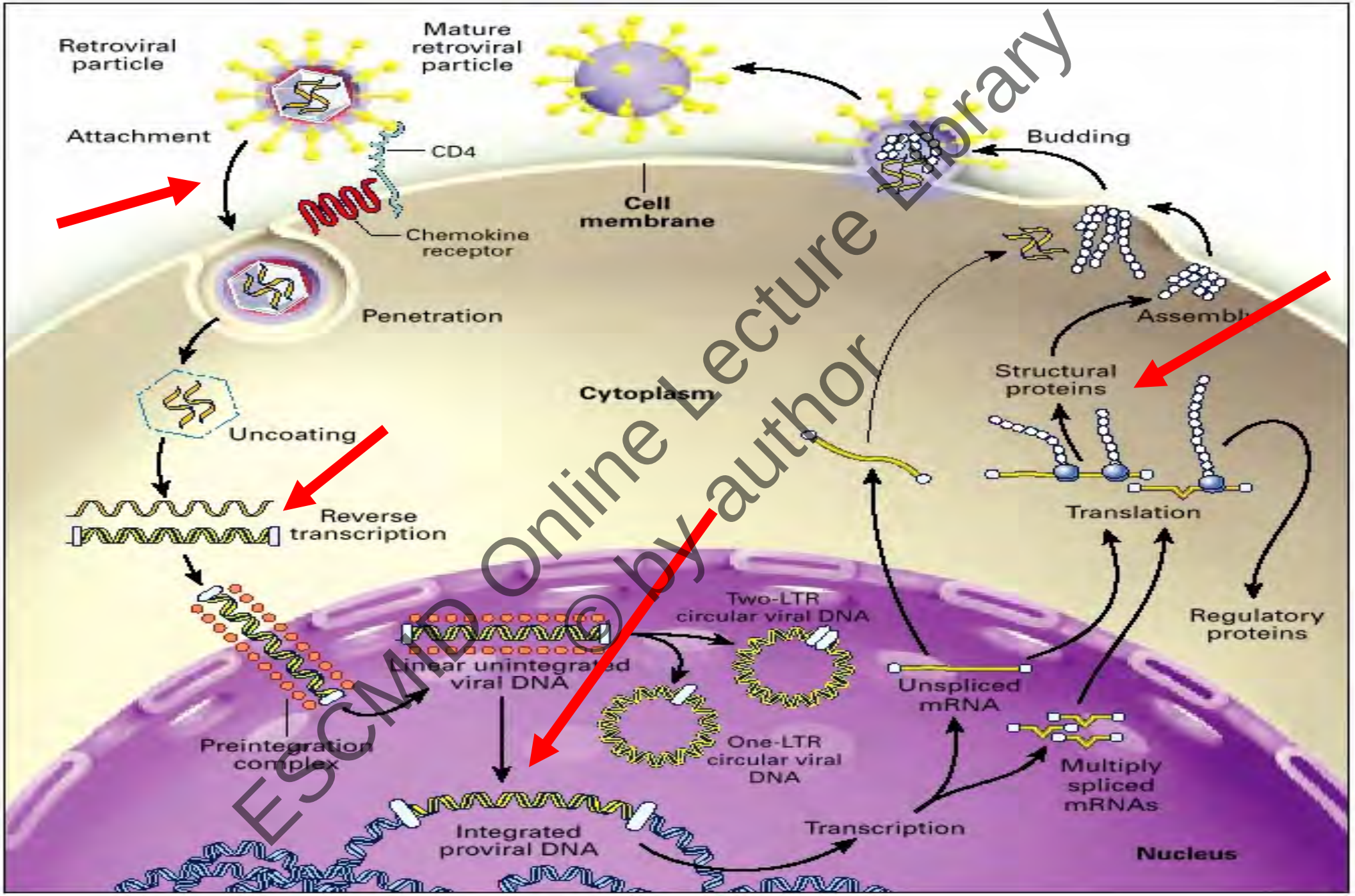
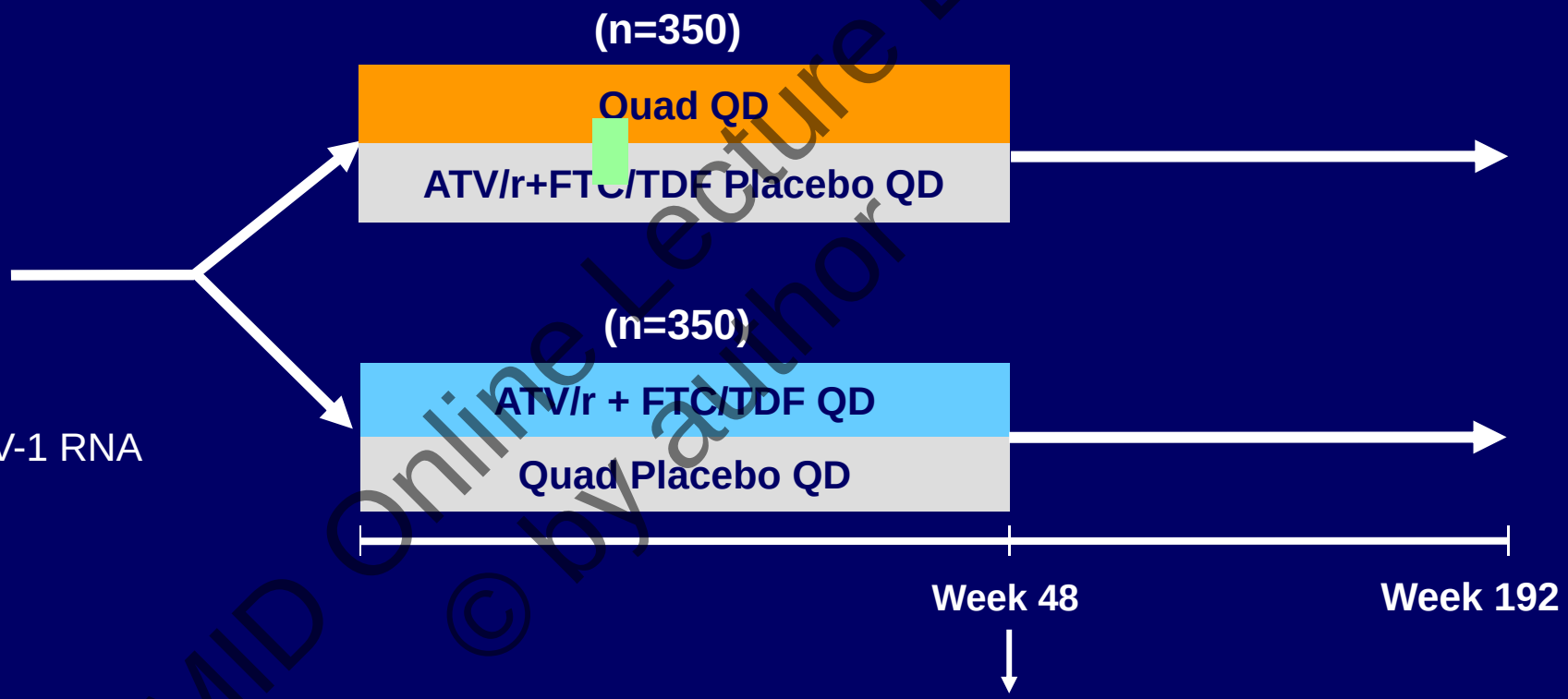


OI's IN AIDS. CHEMOPROPHYLAXIS THE ERA OF HAART
MORTALITY. HOSPITAL CLINIC. BARCELONA





Study Design
236-0103



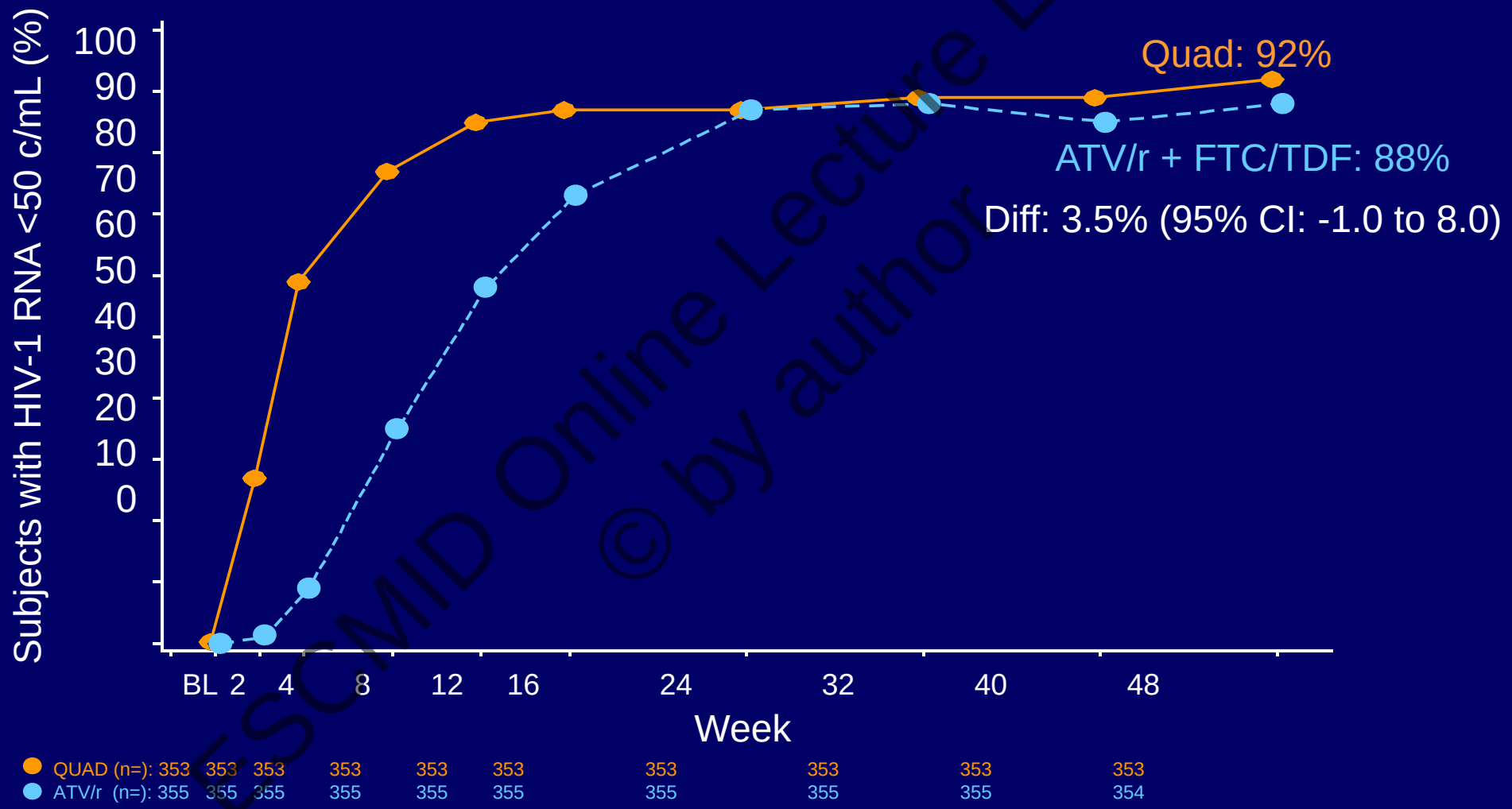
Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48

- **FDA snapshot analysis, 12% non-inferiority margin**
- **HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5**

Conducted in parallel with Study 236-0102 comparing Quad to EFV/FTC/TDF

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

HIV-1 RNA < 50 c/mL through Week 48 (M=F)
236-0103



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

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

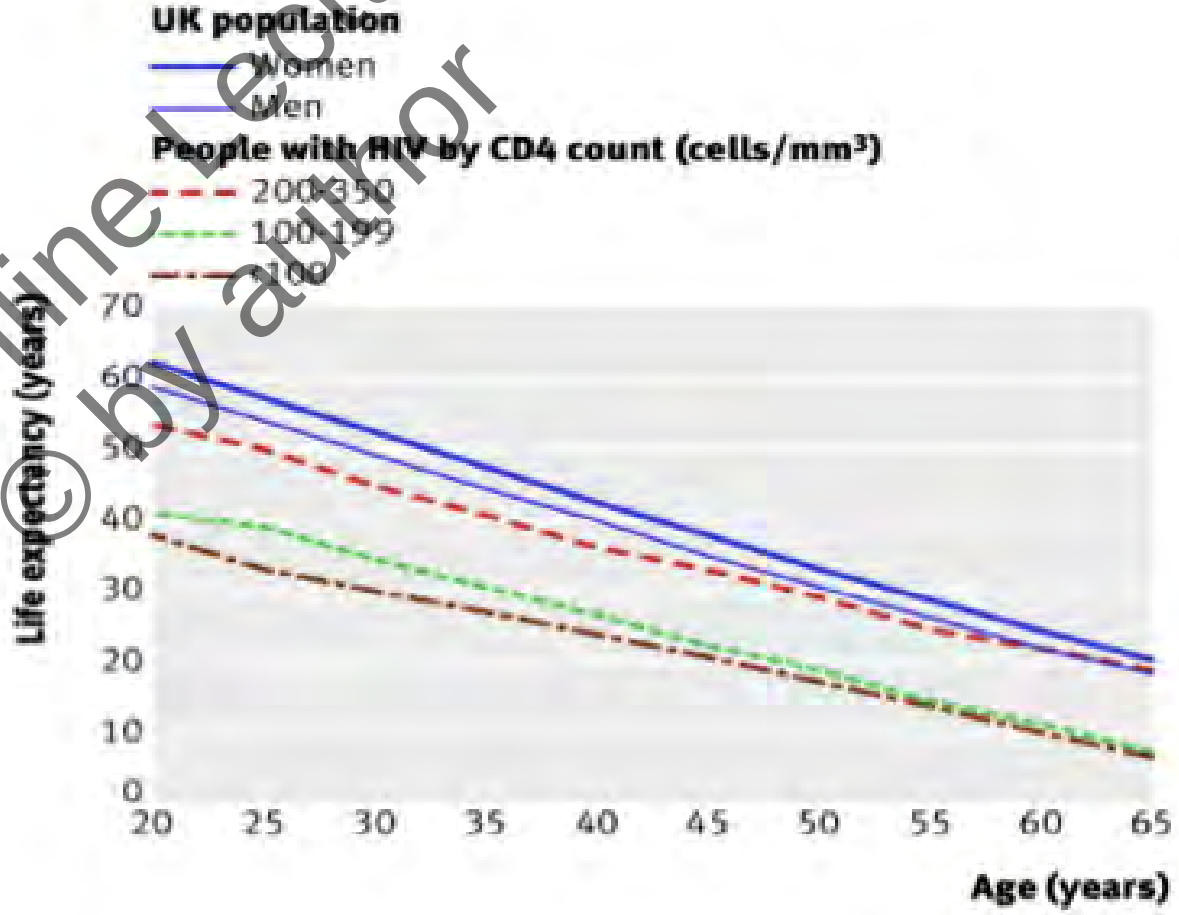
	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Subjects Analyzed for Resistance[a], n (%)	12 (3)	8 (2)
Subjects with Resistance to ARV Regimen, n (%)	5 (1)	0
Any Primary Integrase-R, n	4	-
E92Q	1	-
T66I	1	-
Q148R	2	-
N155H	2	-
Any Primary PI-R, n	-	0
Any Primary NRTI-R, n	4	0
M184V/I	4	
K65R	1	

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.

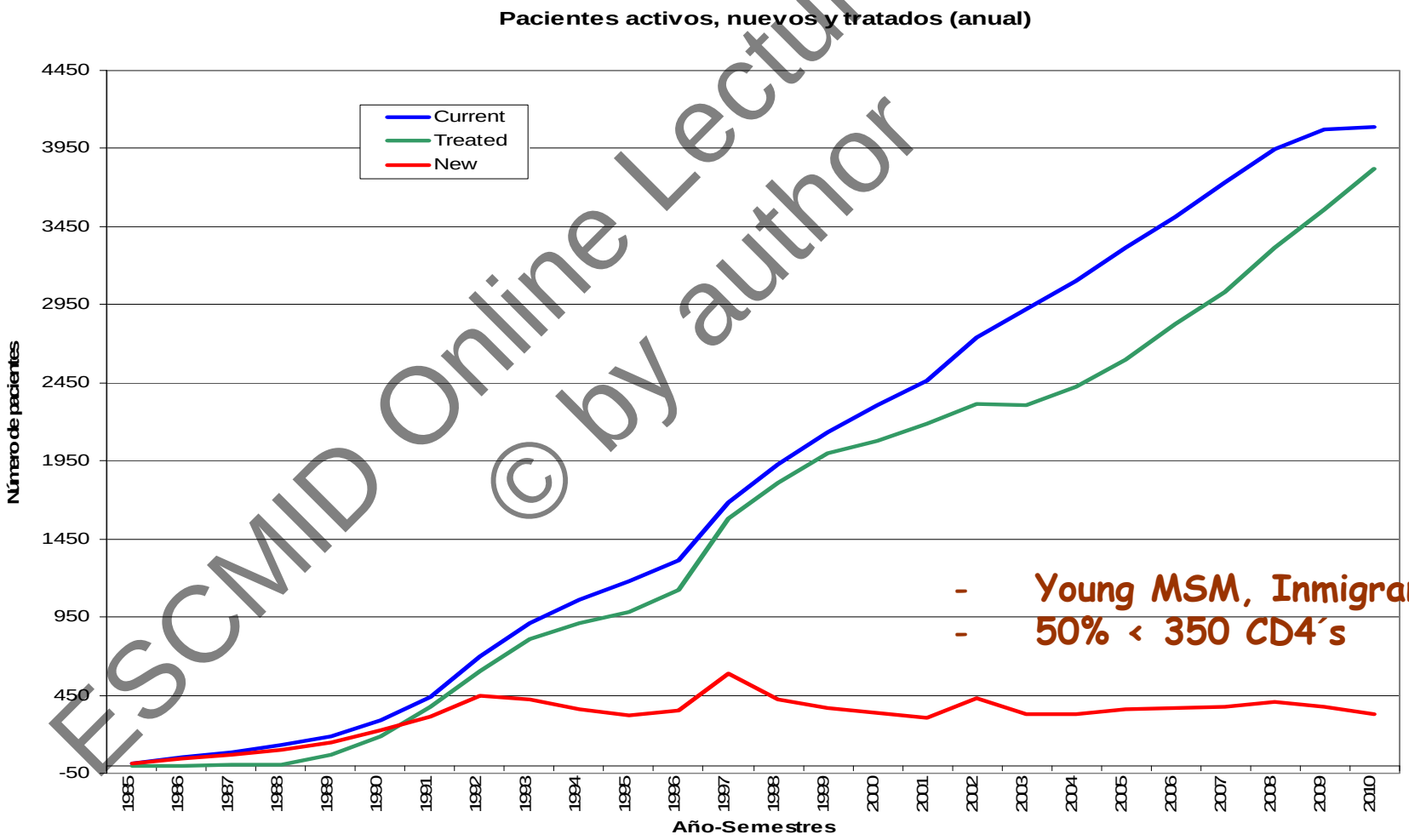
Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study

Life expectancy from age 20-65 of people who started antiretroviral therapy in 2000-8 by CD4 cell count group at start of antiretroviral therapy compared with that of UK population (2000-6 women and men)



BMJ 2011;343:d6016 doi: 10.1136/bmj.d6016

- Very low mortality
- Getting older (> 50% more than 50 years old)
- More than 80% undetectable VL



- Young MSM, Inmigrants
- 50% < 350 CD4´s

UPDATE ON THERAPEUTIC TRIALS: 2012

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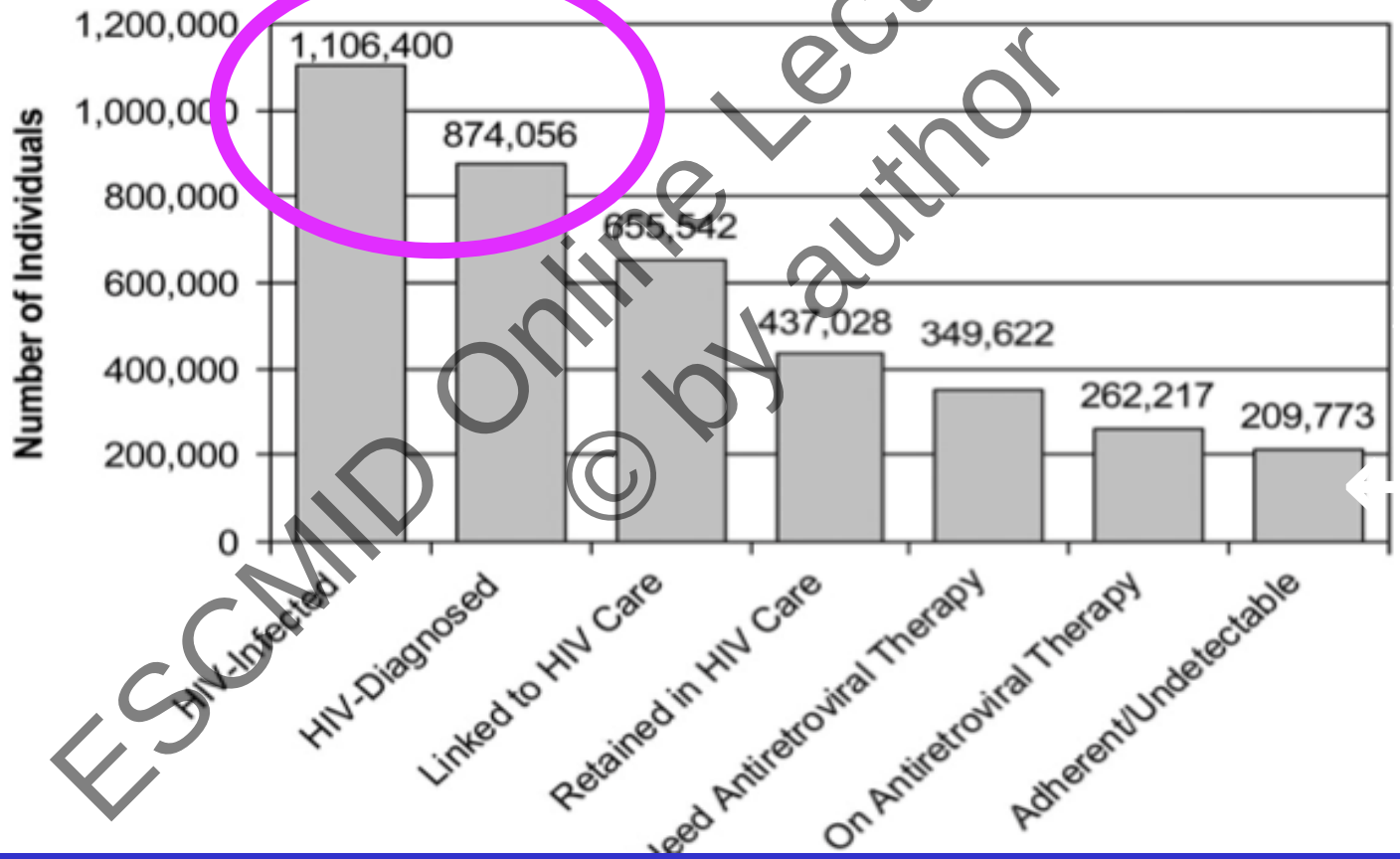
REVIEW ARTICLE HIV/AIDS

The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection

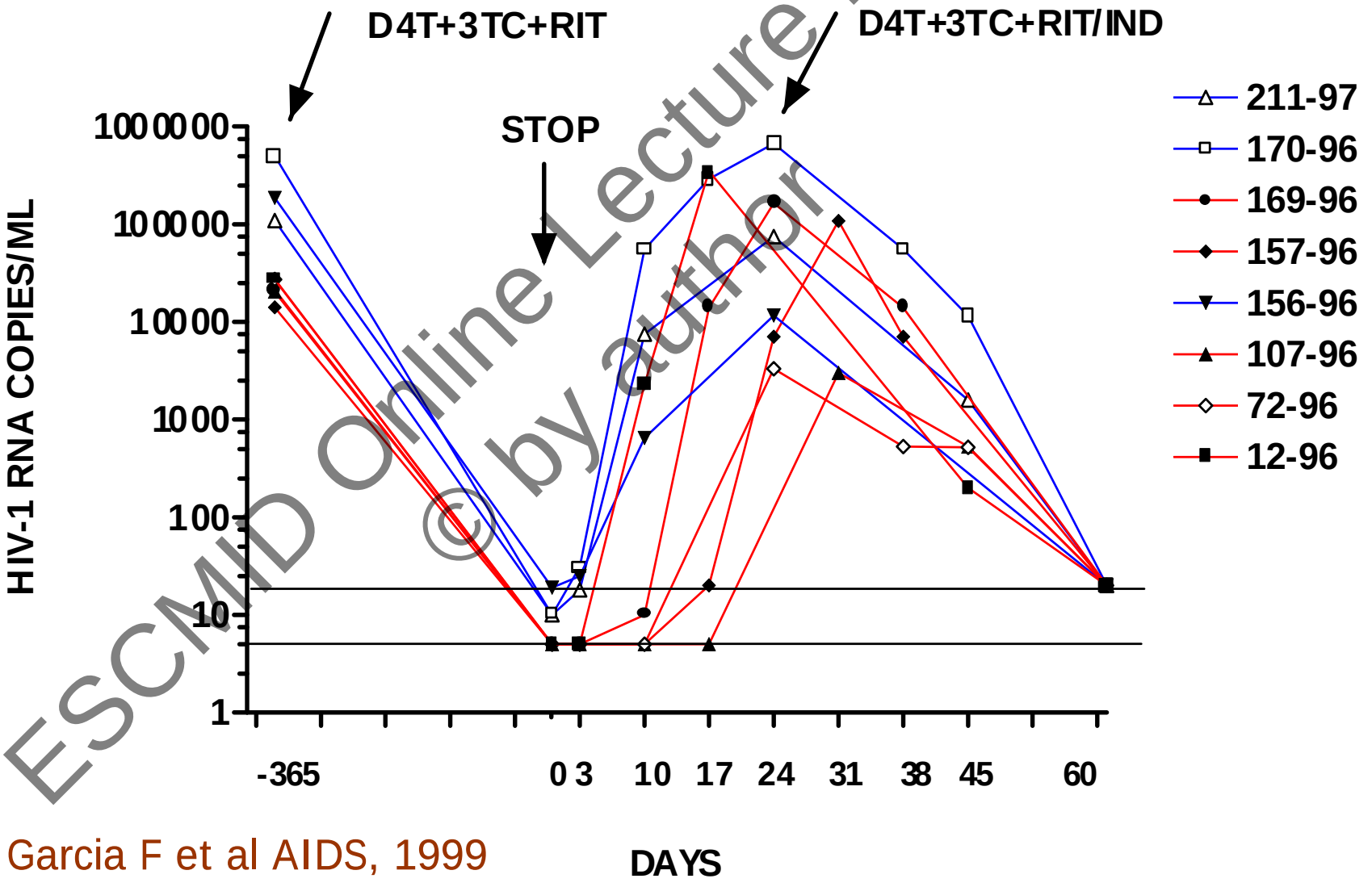
Edward M. Gardner,[1,3] Margaret P. McLees,[1,3] John F. Steiner,[2] Carlos del Rio,[4,5] and William J. Burman[1,3]

[1]Denver Public Health and [2]Kaiser Permanente Colorado, Denver, [3]University of Colorado Denver, Aurora, Colorado, and [4]Rollins School of Public Health of Emory University, and [5]Emory Center for AIDS Research, Atlanta, Georgia

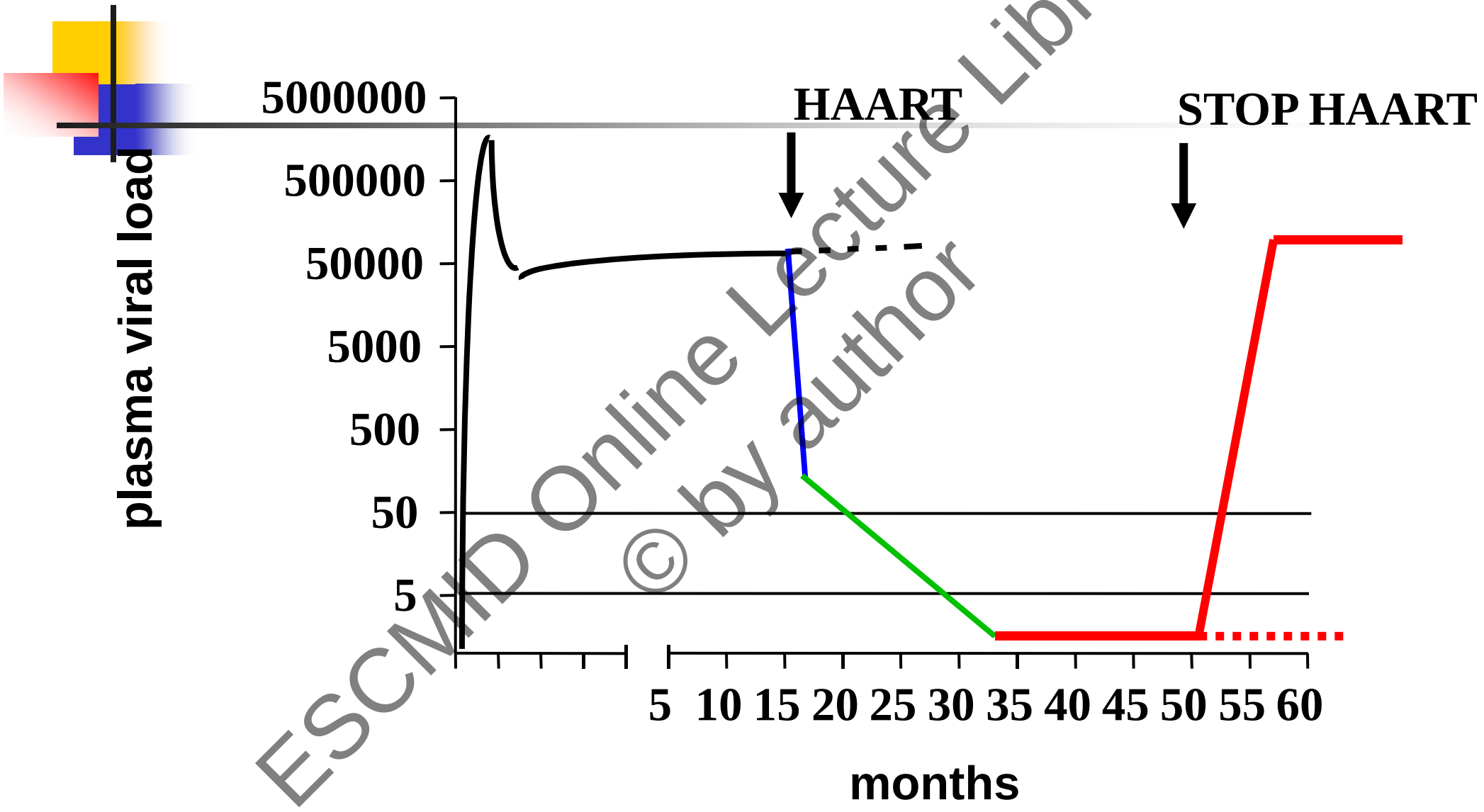
(See the editorial commentary by Lange, on pages 801–802.)



SPANISH EARTH-1 STUDY (CD4>500 AND VL >10000).
STOP THERPAY AFTER 1 YEAR OF D4T+3TC+RIT/IND AND VL<20



Garcia F et al AIDS, 1999



UPDATE ON THERAPEUTIC TRIALS: 2012

Despite apparent complete response to cART….

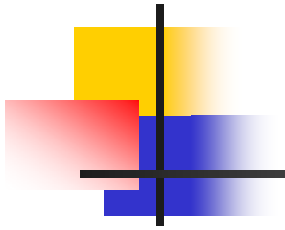
Persistence of viral reservoirs

- Possible residual replication
- Latent infection
- Anatomic compartments

And the consequences are

- Chronic inflamation and immune activation
- Reduced life expectancy (10-15 years)

UPDATE ON THERAPEUTIC TRIALS: 2012



What can we do ……

Improve cART

Intensification. Improve PK/PD

Achieve prolonged remission without cART or even a functional cure

Therapeutic vaccines. Gene therapy

HIV-1 eradication

Selective activation of latent infection while on cART and maybe after stimulating cytholytic T cell response with an immunogen or a therapeutic vaccine

UPDATE ON THERAPEUTIC TRIALS: 2012

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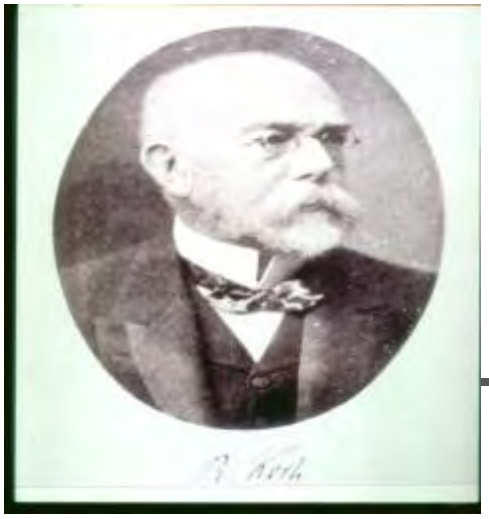
The immune system is not able to "contain" VL rebound even after a long term successful suppressive ART

Conversely, the aim of an immunogen or a therapeutic vaccine should be to avoid VL rebound after interruption of ART



Wild type

I Res.

R Res.

Z Res.

I

I

I+R+P

THERAPEUTIC VACCINE AGAINST HERPES ZOSTER

Vaccines againts rabies, tetanus and difteria are therapeutic

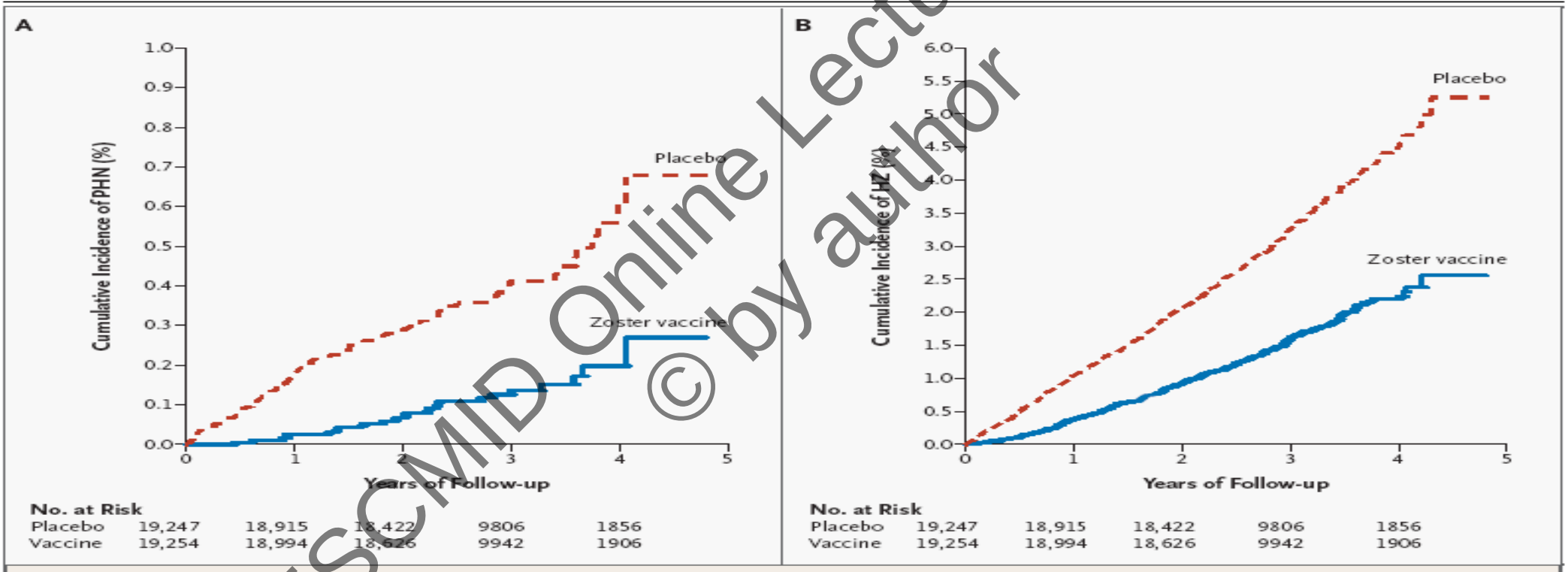


Figure 2. Kaplan–Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population.

Incidence rates of postherpetic neuralgia (PHN) and herpes zoster (HZ) were significantly lower in the vaccine group than in the placebo group ($P<0.001$, by a stratified log-rank test that pooled the results of the log-rank test from the two age groups). Cumulative incidence, expressed as a percentage of the subjects at risk, is the probability of the development of the disease during the period from 30 days after vaccination to the follow-up time.

VACCINES AGAINST HIV-AIDS: 2011

Therapeutic vaccines against HIV infection

Felipe García, Agathe León, Josep M Gatell, Montserrat Plana, Teresa Gallart
Hospital Clinic-HIVACAT, IDIBAPS, University of Barcelona. Barcelona. Spain

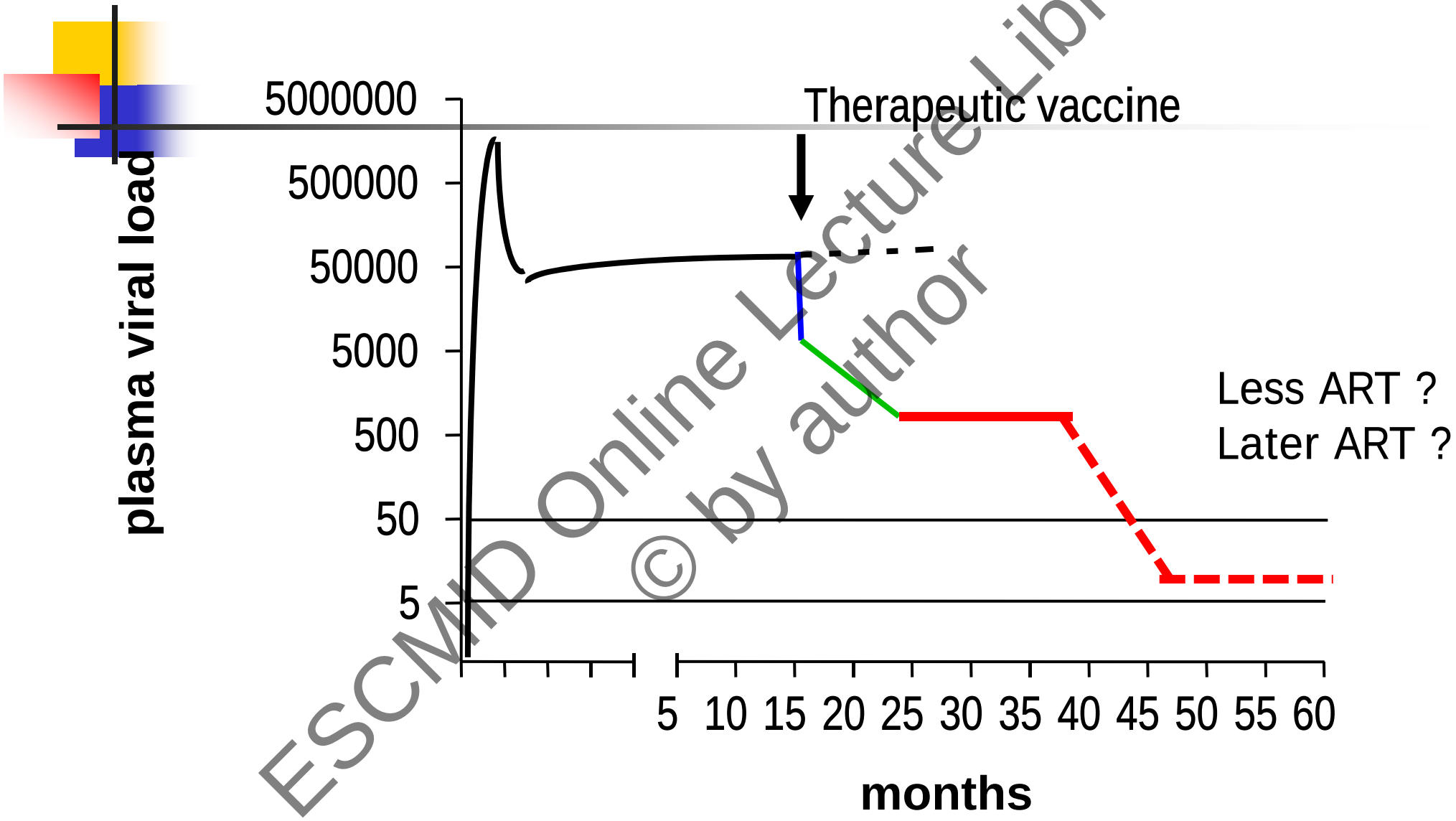
Correspondence to: Dr. Felipe García, Infectious Diseases Unit, Hospital Clínic, Villarroel, 170, 08036 Barcelona, Spain. Phone: 34932275586, FAX: 34934514438, E-mail: fgarcia@clinic.ub.es;

Acknowledgments: This study was partially supported by grants: FIS PS09/01297, TRA-094, EC10-153, FIS PI10/02984, SAF2006-26667-E, RIS*, HIVACAT**, ORVACS***. Dr Felipe García was recipient of a Research Grant from IDIBAPS****, Barcelona, Spain. Dr. M Plana was supported by contract FIS 03/0072 from the Fundació Privada Clínic per a la Recerca Biomèdica in collaboration with the Spanish Health Department

VACCINES AGAINST HIV-AIDS: 2011

Modalities of therapeutic vaccines tested in clinical trials

-Whole inactivated virus:	1
-Subunit vaccines:	4
-Vaccines using DNA as vector:	4
-Viral vector vaccines:	12
-Dendritic cells based vaccines:	2



Lu et al Nat Med 2003

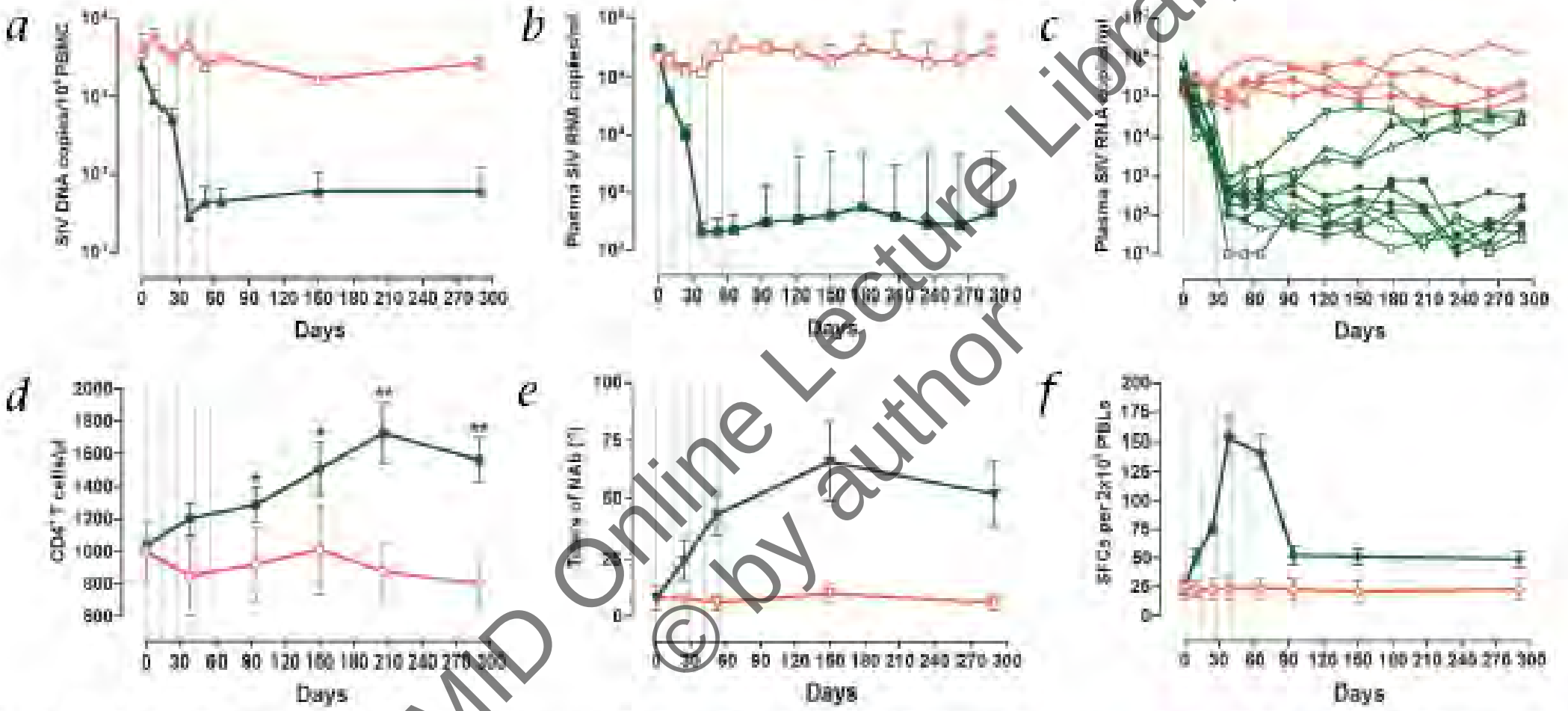


Fig. 2 Virologic and immunologic monitoring in immunized and non-immunized macaques. *a*, PBMC SIV DNA per million cells (geometric mean ± s.e.m) in immunized (▲) and non-immunized (△) macaques. *b*, Plasma SIV RNA (geometric mean ± s.e.m.) in immunized (■) and non-immunized (□) macaques. *c*, Plasma SIV RNA concentrations in immunized animals (■, monkey no. 1; ▲, no. 2; ▼, no. 3; ◆, no. 4; ●, no. 5; □, no. 6; △, no. 7; ▽, no. 8; ◇, monkey no. 9; and ○, 10) and non-immunized animals (×, monkey no. 11; +, no. 12; *, no. 13; and ■, no. 14). *d*, $CD4^+$ T-cell count (mean ± s.e.m) in immunized (●) and non-immunized (○) macaques. *e*, Neutralizing antibody (NAb) titers (mean ± s.e.m.) in immunized (▼) and non-immunized (▽) macaques. *f*, SIV-specific spot-forming cells (SFCs) frequency (mean ± s.e.m) in immunized (◆) and non-immunized (◇) macaques. Vertical dotted lines indicate the time points of immunization. *P value < 0.05; **P value < 0.01.

A Phase I Double Blind Placebo-Controlled Randomized Study of a Therapeutic Vaccine Using Autologous Dendritic Cells (DCs) Loaded with Autologous HIV-1 in Untreated Patients with Asymptomatic Chronic HIV Infection (CHI) with CD4 T Cells Above 450/Mm3.

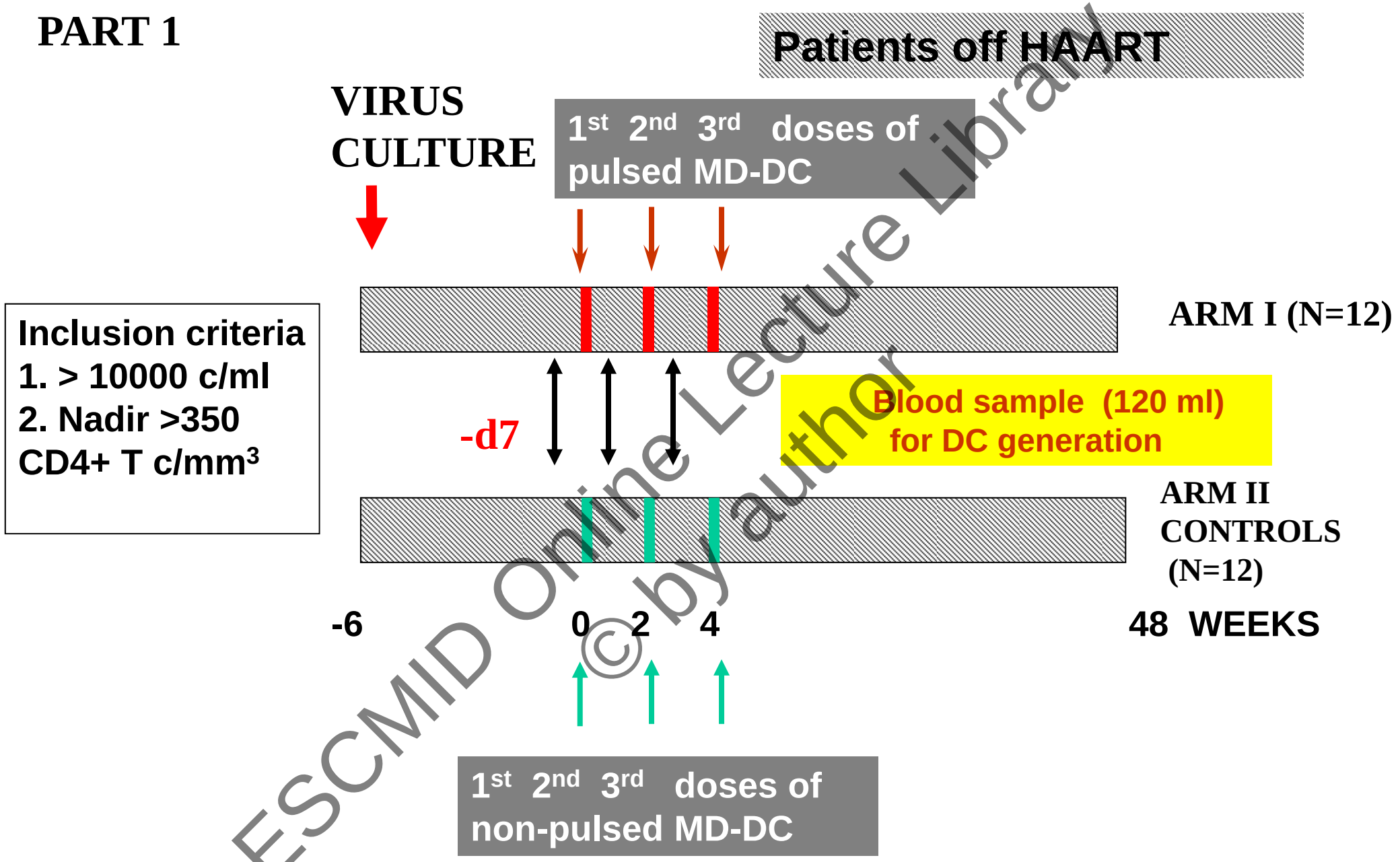
Montserrat Plana1, Felipe García*1, Nuria Climent1, Cristina Gil1, Brigitte Autran2, L. Assoumou3, Dominique Costagliola3, Bonaventura Clotet4, Josep M Gatell1, Teresa Gallart1

for DCV2/MANON07-ORVACS study group.

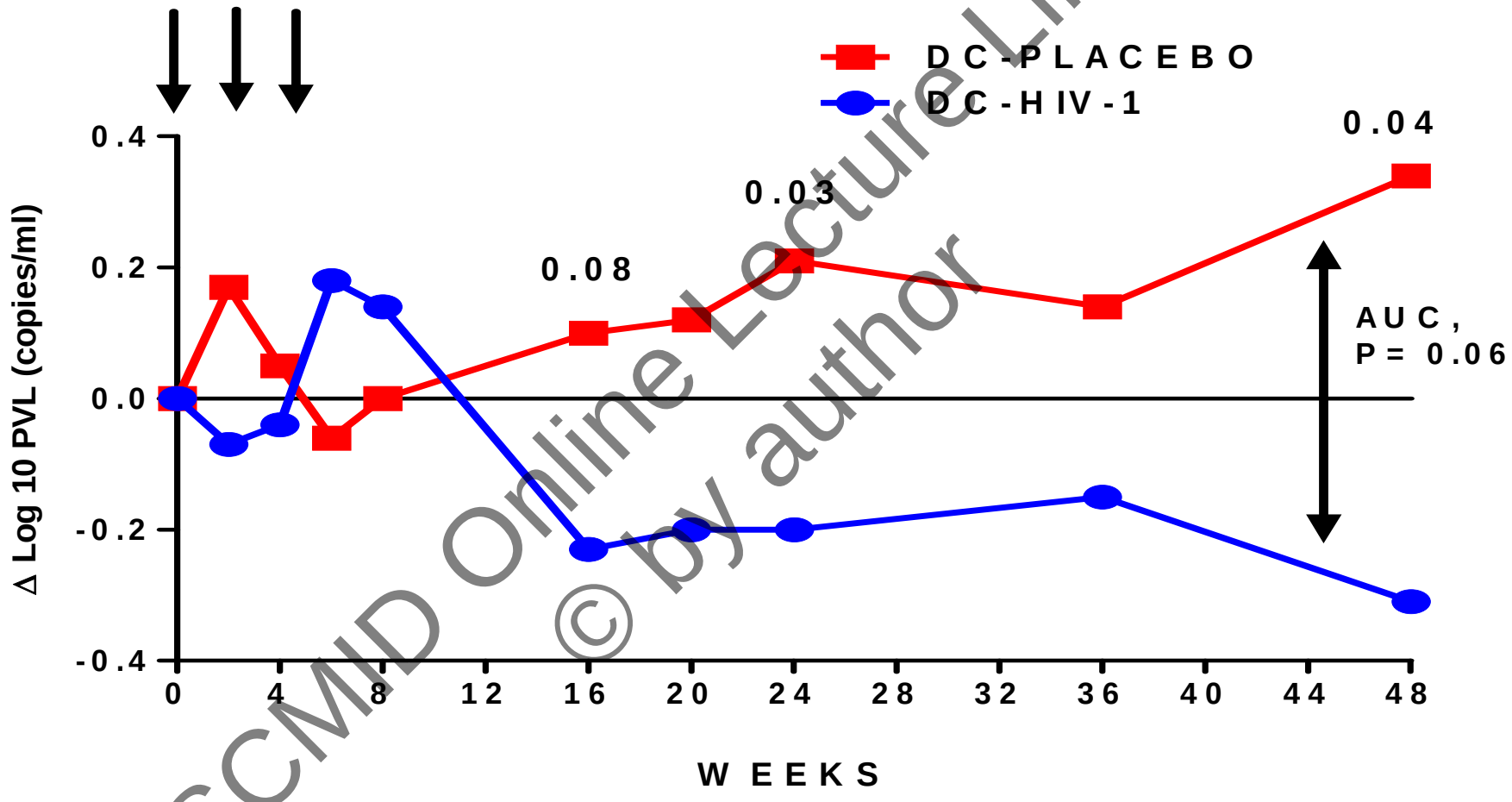
1Hospital Clinic-IDIBAPS-HIVACAT, University of Barcelona. Barcelona.Spain ;
2INSERM UMR-S 945 - Université Paris VI Pierre et Marie Curie. Hôpital Pitié-Salpêtrière, Paris ;
3U943-INSERM et Université Pierre et Marie Curie Epidemiologie, France ;
4 Hospital Germans Trias i Pujol, IRSICAIXA-HIVACAT, Badalona, Spain.

Garcia F et al JID, 2011

PART 1



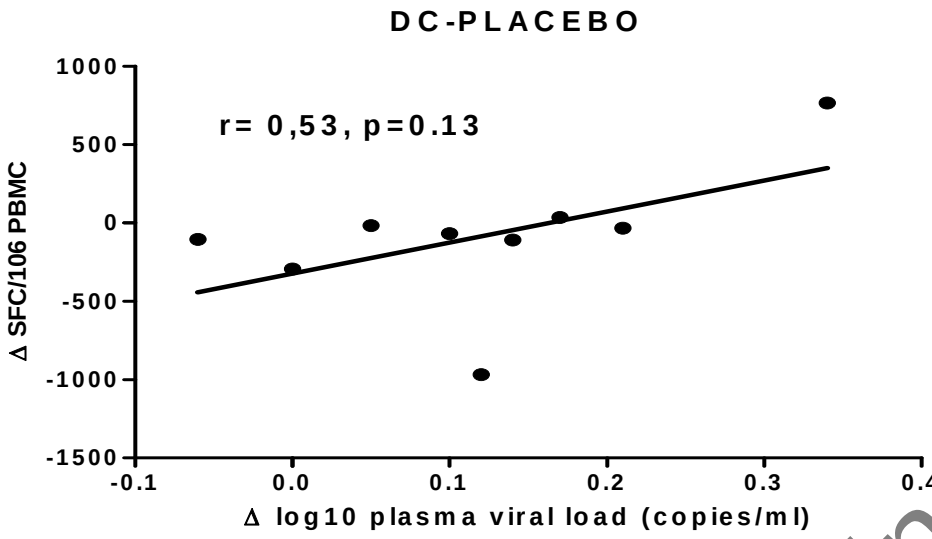
VIRAL LOAD RESPONSES

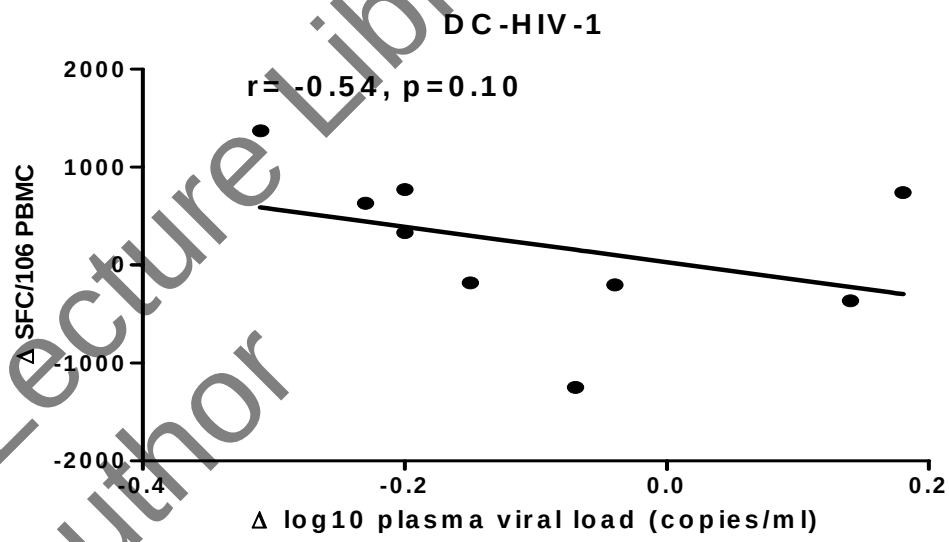


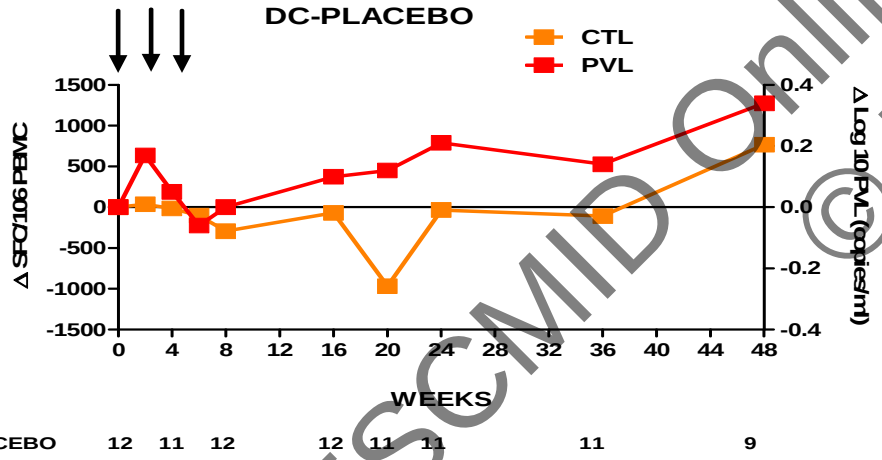
DC-PLACEBO	12	12	12		12	11	11			11		9
DC-HIV-1	10	10	10		10	8	8			8		7

IT WAS OBSERVED A MODEST DECREASE OF VL IN VACCINATED PATIENTS

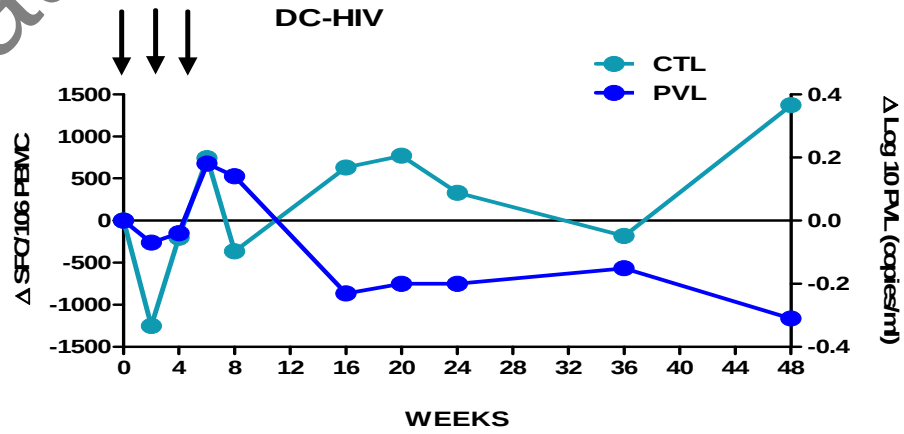
VIRAL LOAD-HIV SPECIFIC T CELL RESPONSES





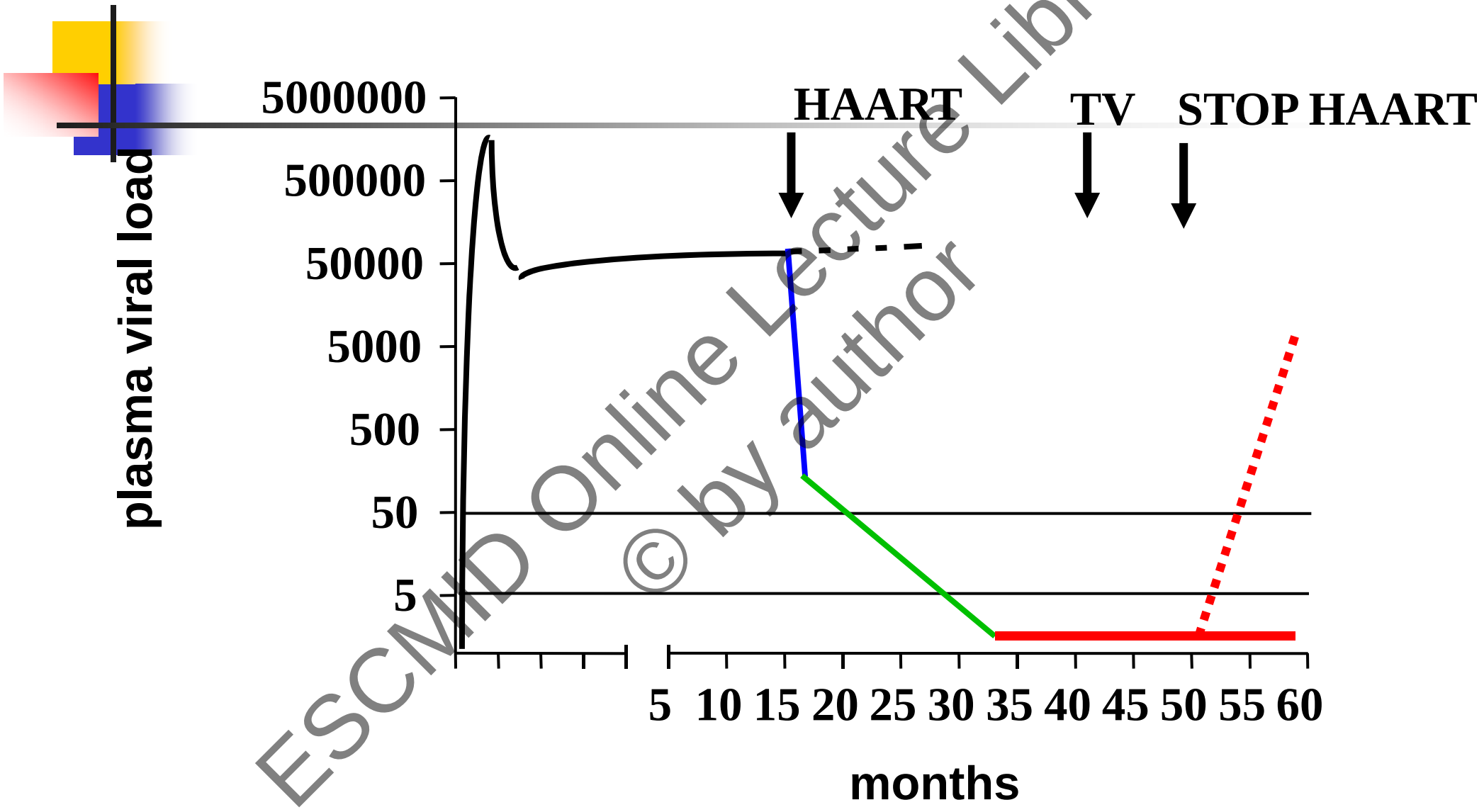


PLACEBO 12 11 12 12 11 11 11 9



VACCINE 10 10 10 10 7 8 8 7

VL CORRELATED INVERSELY WITH HIV SPECIFIC T CELL RESPONSES IN VACCINATED PATIENTS



Therapeutic Immunization with Dendritic Cells Loaded with Heat-Inactivated Autologous HIV-1 in Patients with Chronic HIV-1 Infection

Felipe García,[1] Merylene Lejeune,[2] Nuria Climent,[2] Cristina Gil,[3] José Alcamí,[8] Vanessa Morente,[4] Llucia Alós,[4] Alba Ruiz,[5] Javier Setoain,[5] Emilio Fumero,[1] Pedro Castro,[1] Anna López,[2] Anna Cruceta,[1] Carlos Pìera,[5] Eric Florence,[1] Arturo Pereira,[6] Agnes Libois,[1] Nuria González,[8] Meritxell Guilá,[3] Miguel Caballero,[7] Francisco Lomeña,[5] Joan Joseph,[1] José M Miró,[1] Tomás Pumarola,[3] Montserrat Plana,[2] José M Gatell,[1] and Teresa Gallart[2]

Received 29 September 2004; accepted 3 December 2004; electronically published 11 April 2005.

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The Journal of Infectious Diseases 2005; 191:1680–5

0022-1899/2005/19110-0014$15.00

ORVACS
MANON 03 STUDY

HAART PLUS THERAPEUTIC VACCINE WITH AUTOLOGOUS MONOCYTE-DERIVED DENDRITIC CELLS (DC) LOADED WITH INACTIVATED AUTOLOGOUS HIV-1

CD4>500 cells/microL
PVL>5000 copies/ml

PVL<20

HAART

STOP-1

HAART

STOP-2

-w246

-w90

-w78

s.c. DC injections

w30

Non-Pulsed DC

Pulsed DC (4x10^6 virions/vaccine)

CASES N=12

w0 6w 12w 18w 24w

PLASMAPHERESIS

-d8 -d8 -d8 -d8 -d8

Blood sample (60-80 ml) for DC generation

PVL<20

CONTROLS N=6*

HAART

*2 lost for follow-up

HAART

DCV-1 study

Figure 3A

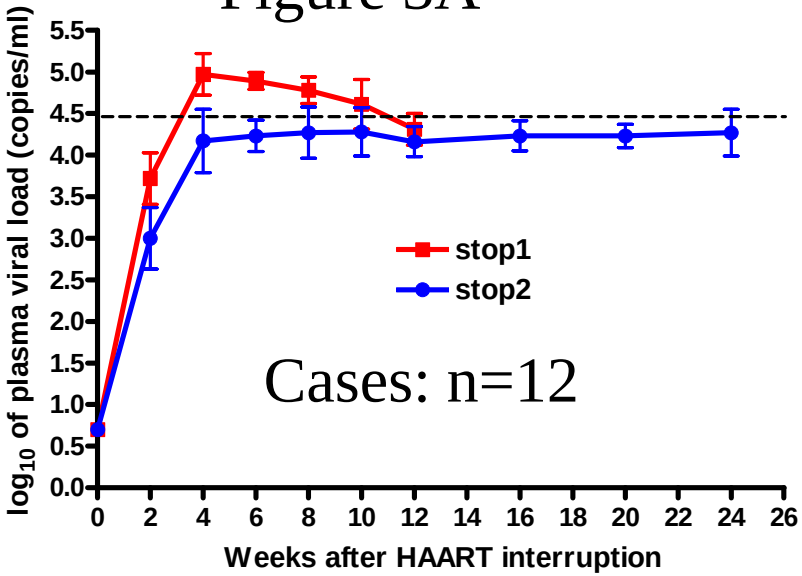


Figure 3B

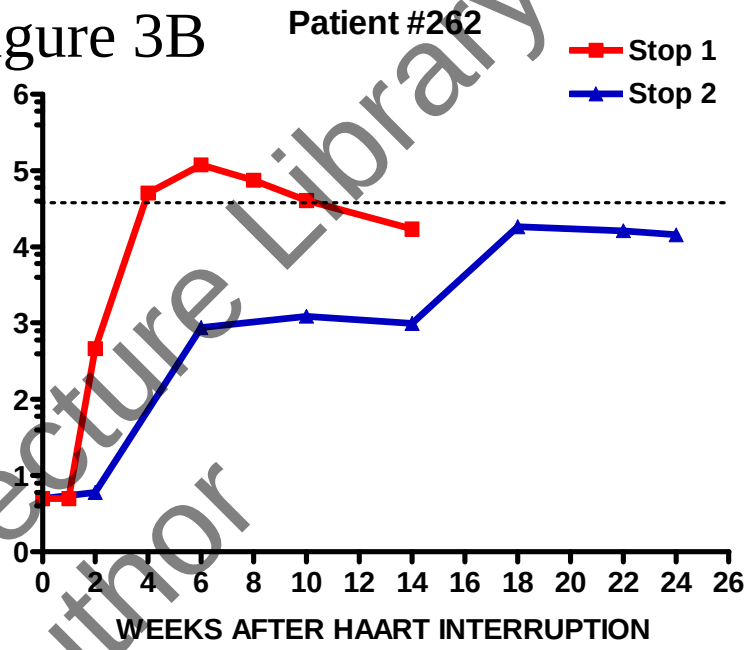


Figure 3C

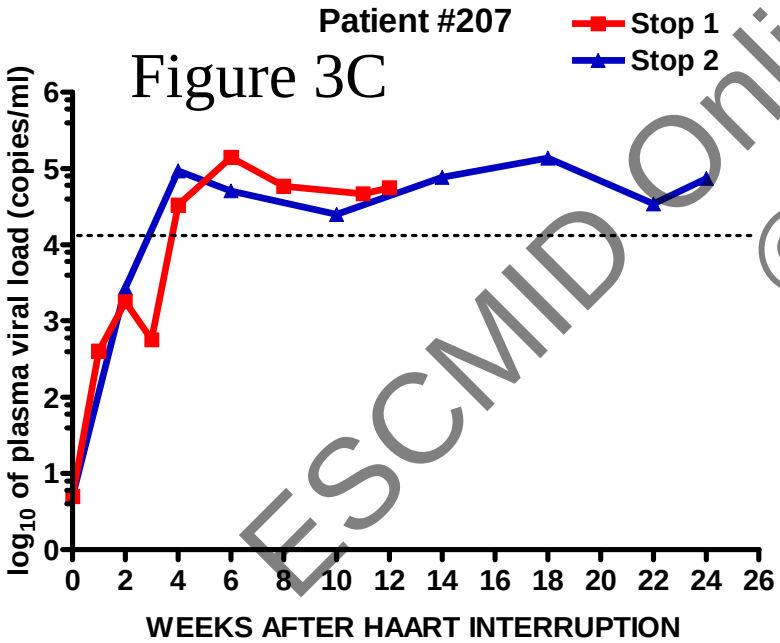
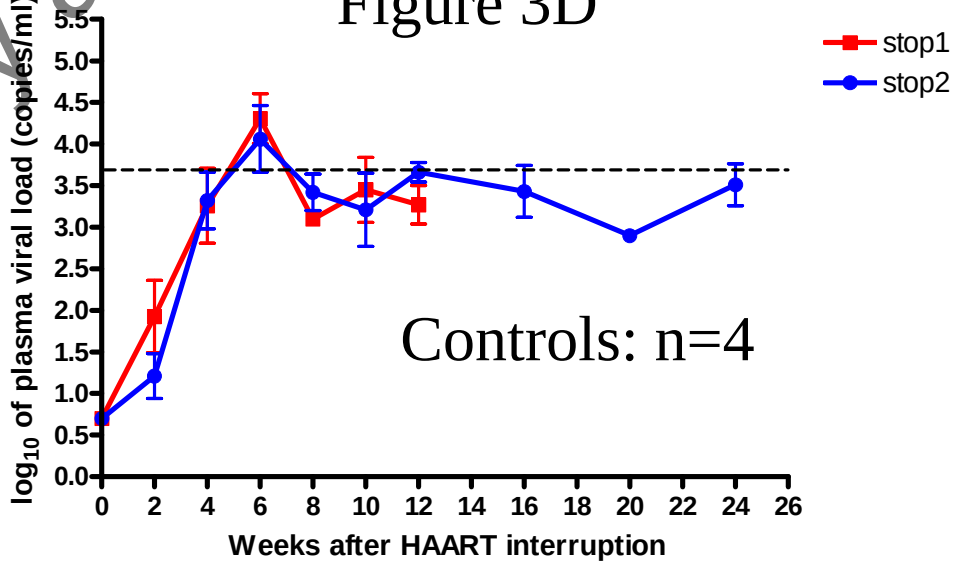


Figure 3D



Results: Primary end-point

-Δ VL >=0.5 log

Controls	0 / 4
P-DC vaccine	4* / 12

(*) 0.9; 0.5; 0.7; 0.8

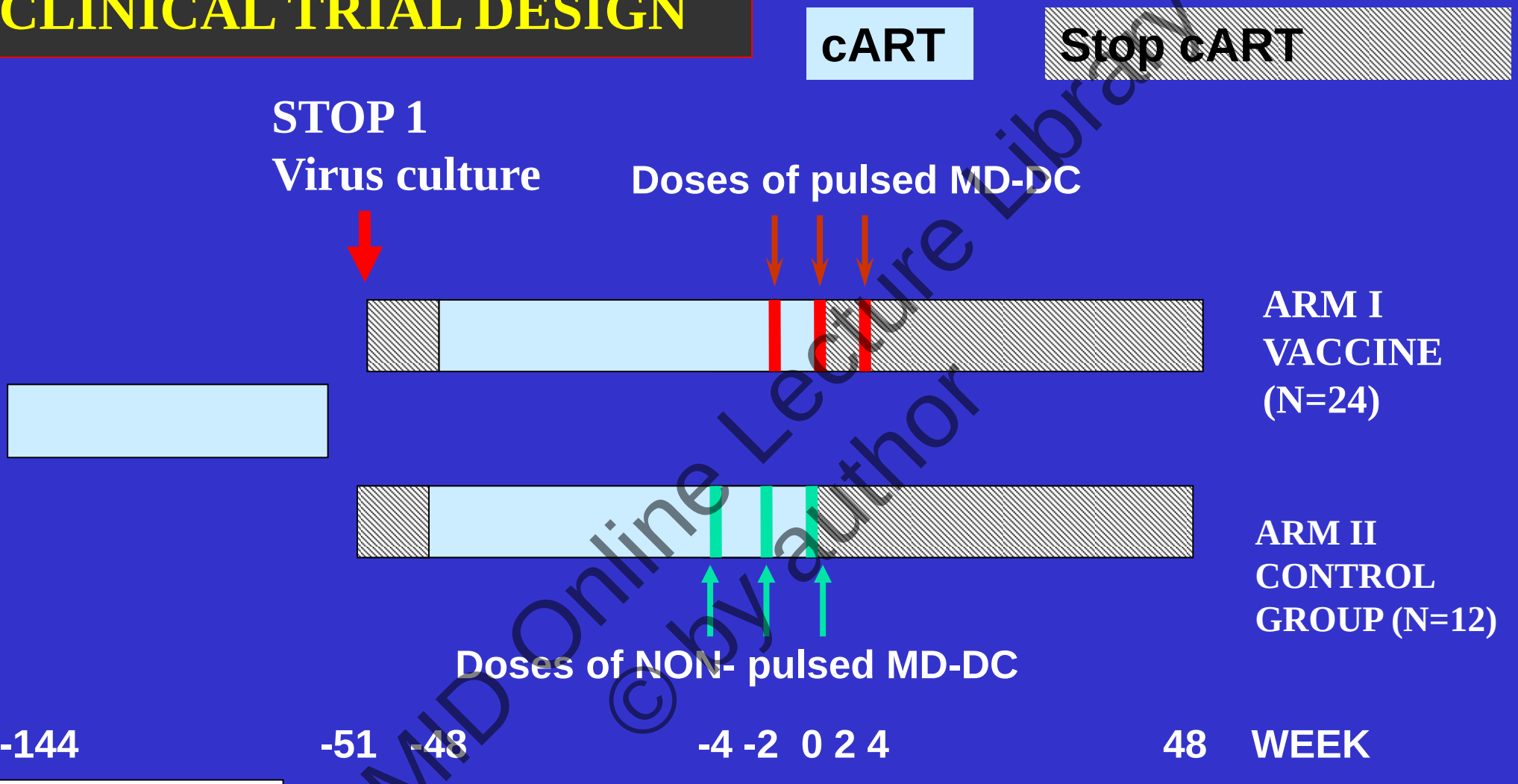
Significant Decrease of Viral Load (VL) with a Therapeutic Dendritic Cell (DC)- Based Vaccine in Patients with Chronic HIV-1 Infection (CHI) receiving Antiretroviral Therapy: A Phase I/II Blinded Randomized Placebo-Controlled Study

Felipe García*1, Nuria Climent1, Cristina Gil1, Agathe León1, Brigitte Autran2, Jeff Lifson3, Bonaventura Clotet4, Josep M Gatell1, Montserrat Plana1, Teresa Gallart1 for DCV2/MANON07-ORVACS study group. Clinical trial.gov NCT00402142

1Hospital Clinic-IDIBAPS, HIVACAT, University of Barcelona. Barcelona.Spain
2INSERM UMR-S 945 - Université Paris VI Pierre et Marie Curie. Hôpital Pitié-Salpêtrière, Paris, France
3 AIDS and Cancer Virus Program, SAIC-Frederick, Inc., NCI-Frederick, Frederick, MD 21702, USA.
4 Hospital Germans Trias i Pujol, IRSICAIXA-HIVACAT, Badalona, Spain.

Garcia et al CROI 2012. submitted for publication

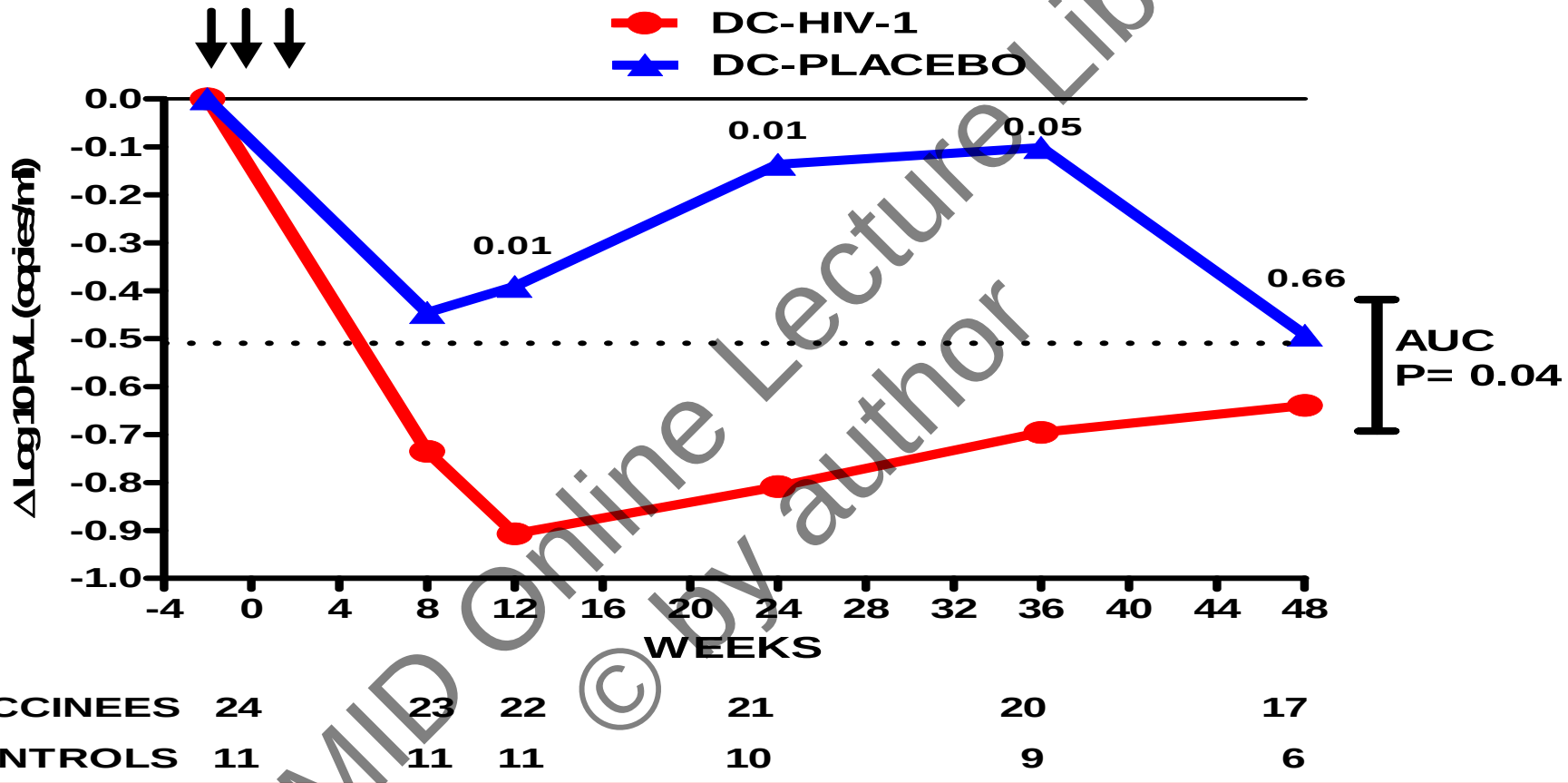
CLINICAL TRIAL DESIGN



Inclusion criteria

1. <20 copies/ml
2. Nadir >350 C CD4+ T c/mm^3

VIRAL LOAD RESPONSES



ΔVL SET-POINT IN DC-HIV: -1 log w12 and maintained > 0.5 log 1 year
ΔVL SET-POINT IN DC-placebo: < 0.5 log in all time points

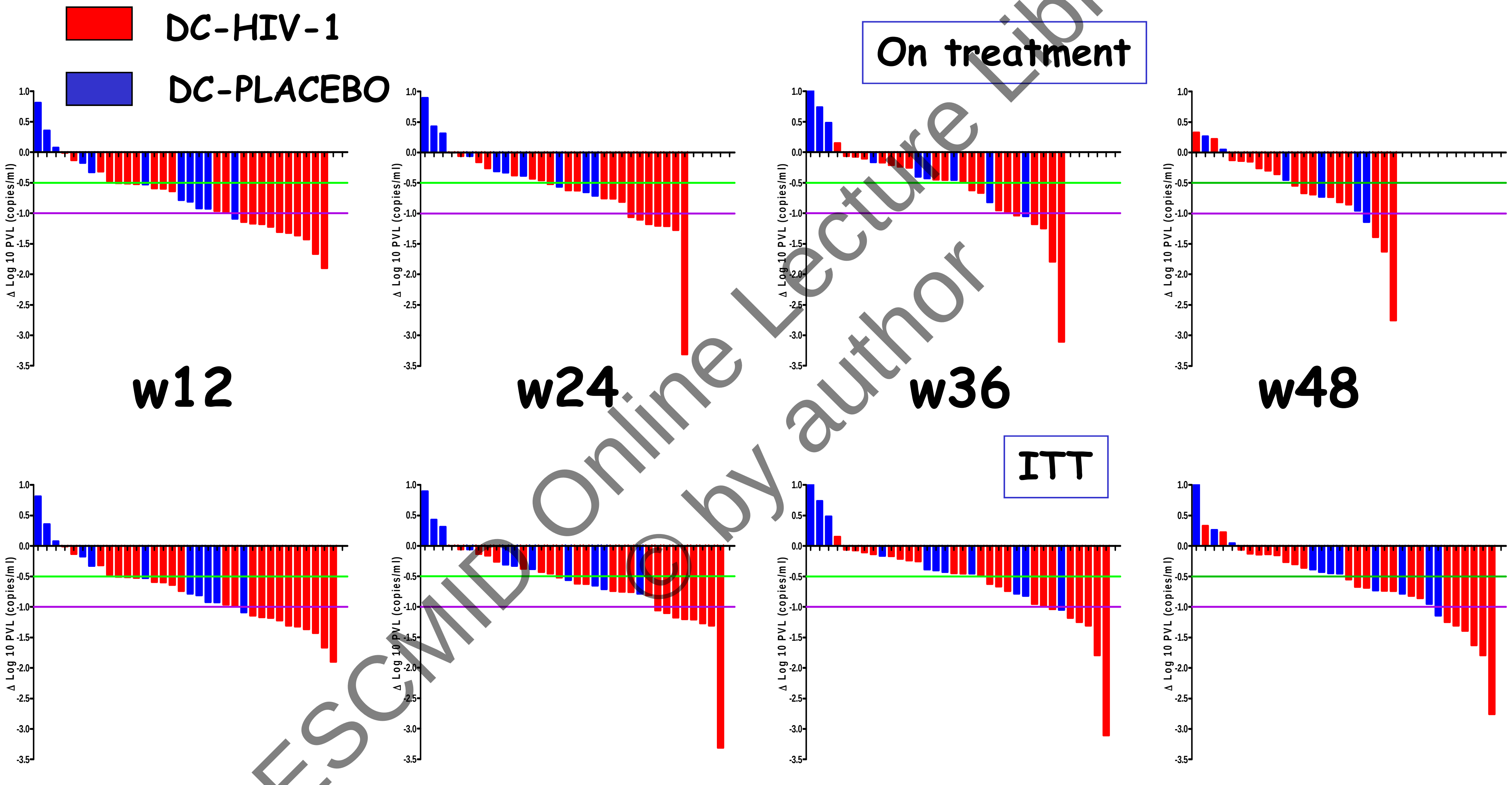
IT WAS OBSERVED A SIGNIFICANT DECREASE OF VL IN VACCINATED PATIENTS

VIRAL LOAD RESPONSES

- Δ VL >=0.5 log	W12	W24	W36	W48
DC-PLACEBO	6 / 11	3/10	2/9	3/6
DC-HIV-1	19 / 22	14/20	10/20	9/17
P	0.08	0.05	0.23	0.9

- Δ VL >=1 log	W12	W24	W36	W48
DC-PLACEBO	1 / 11	0/10	1/9	1/6
DC-HIV-1	12 / 22	7/20	6/20	3/17
P	0.02	0.03	0.37	0.9

VIRAL LOAD RESPONSES



-Δ VL >=0.5 log: green line; - Δ VL >=1 log: purple line

CONCLUSIONS

- Therapeutic vaccination was **feasible, safe and well tolerated.**
- A consistent and significant **decrease in VL (1 log)** was observed in vaccine recipients and was correlated with an increase in **CD4 T cell count.**
- **86%** of vaccinated patients had a significant **lower set point VL** when compared to baseline and this was maintained in **52%** of patients at week 48

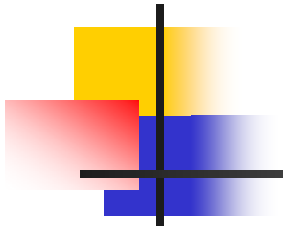
Figure 5. Pre-ART vs. Week 12 of STI Log Change in Viral Load

- Routy et al.

UPDATE ON THERAPEUTIC TRIALS: 2012

1. Natural history of HIV-1 infection
2. cART in 2012. Achievements & limitations
3. Therapeutic vaccines against HIV
4. **Final considerations**

UPDATE ON THERAPEUTIC TRIALS: 2012



4. Final considerations

A therapeutic vaccine againts HIV-1 may be feasible and viable.

Two or more immunogens may need to be combined to obtain strong and presistent cytholytic T cell response

Selective activation (vorinostat, valproic acid, disulfiram) of latent infection may also be needed

HIVACAT

Projecte de Recerca de la Vacuna de la Sida

Codirecció

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Recerca d'una vacuna

8 línies de recerca,
més de 60 investigadors

Infectious Diseases & AIDS Units. Hospital Clinic. Barcelona. Spain