Strategie a lungo termine della terapia antiretrovirale

Napoli 17 ottobre 2014

Clinical Infectious Diseases

HIV/AIDS MAJOR ARTICLE

Influence of Geographical Origin and Ethnicity on Mortality in Patients on Antiretroviral Therapy in Canada, Europe, and the United States

Background. Our objective was to assess differences in all-cause mortality, as well as AIDS and non-AIDS death rates, among patients started on antiretroviral therapy (ART) according to their geographical origin and ethnicity/race in Europe, Canada, and the United States.

Methods. This was a collaboration of 19 cohort studies of human immunodeficiency virus–positive subjects who have initiated ART (ART Cohort Collaboration) between 1998 and 2009. Adjusted mortality hazard ratios (AHRs) were estimated using Cox regression. A competing risk framework was used to estimate adjusted subdistribution hazard ratios for AIDS and non-AIDS mortality.

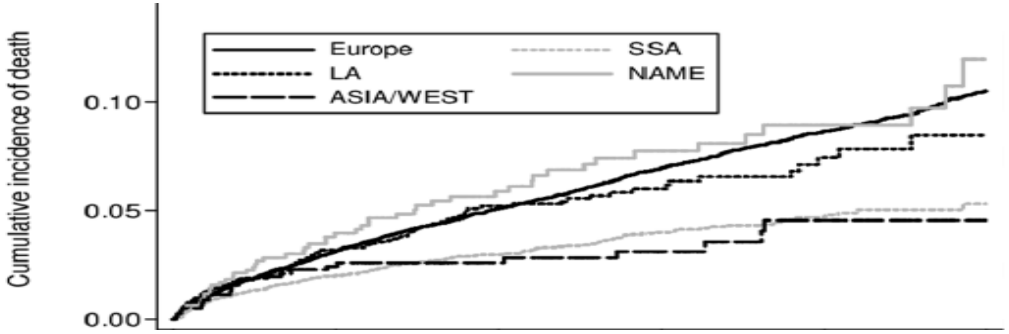
Results. Of 46 648 European patients, 16.3% were from sub-Saharan Africa (SSA), 5.1% Caribbean and Latin America, 1.6% North Africa and Middle East, and 1.7% Asia/West; of 1371 patients from Canada, 14.9% were First Nations and 22.4% migrants, and of 7742 patients from North America, 55.5% were African American and 6.6% Hispanic. Migrants from SSA (AHR, 0.79; 95% confidence interval [CI], .68–.92) and Asia/West (AHR, 0.62; 95% CI, .41–.92) had lower mortality than Europeans; these differences appeared mainly attributable to lower non-AIDS mortality. Compared with white Canadians, mortality in Canadian First Nations people (AHR, 1.48; 95% CI, .96–2.29) was higher, both for AIDS and non-AIDS mortality rates. Among US patients, when compared with whites, African Americans had higher AIDS and non-AIDS mortality, and hazard ratios for all-cause mortality increased with time on ART.

Conclusions. The lower mortality observed in migrants suggests "healthy migrant" effects, whereas the higher mortality in First Nations people and African Americans in North America suggests social inequality gaps.

J del Amo et al., CID 2013

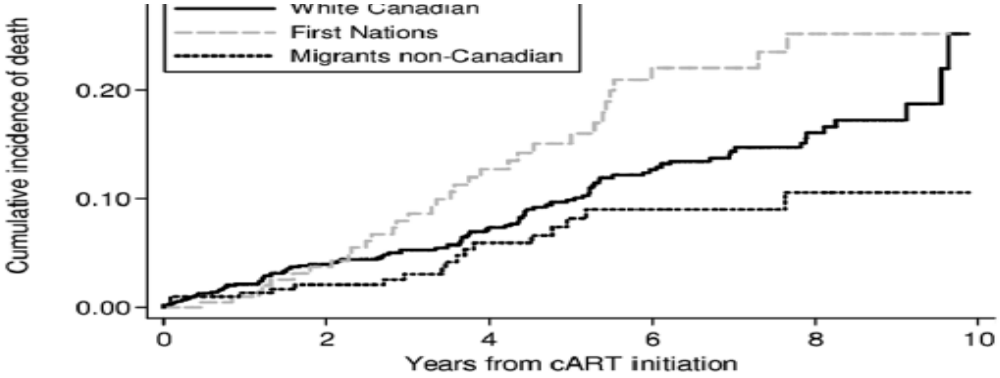
Cumulative incidence of death from antiretroviral initiation according to geographical origin and race/ethnicity

Europe
46,648 subjects

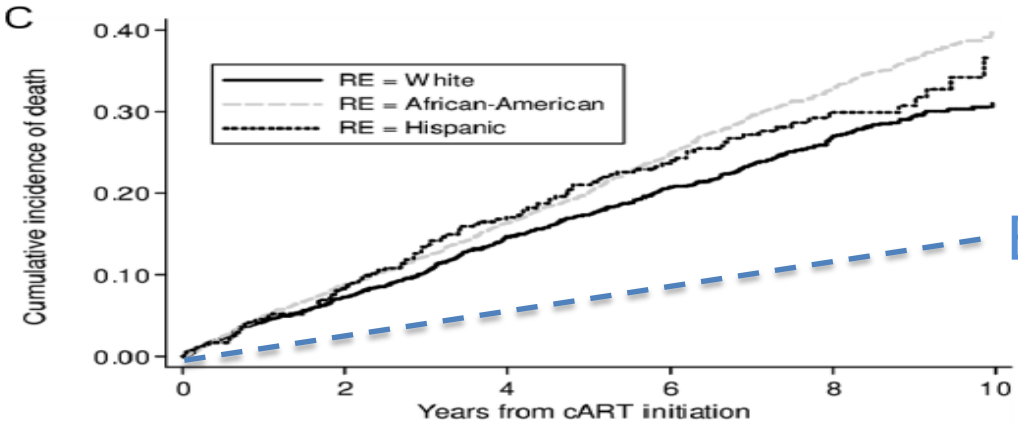


the lowest mortality rate was observed in Europe

Canada
1,371 subjects



USA
7,742 subjects



del Amo et al., CID 2013

In Europe, migrants from Sub-Saharan Africa and Asia/West had lower mortality than Europeans

Origin or Ethnicity/Race	Person-Years of Follow-up	AIDS Related[a] No. of Deaths	AIDS Related[a] Rate (95% CI)	Non-AIDS Related[b] No. of Deaths	Non-AIDS Related[b] Rate (95% CI)
Europe					
EUROPE	170 705	681	4.0 (3.7–4.3)	1101	6.4 (6.1–6.8)
SSA	32 046	109	3.4 (2.8–4.1)	80	2.5 (2.0–3.1)
LA	9002	44	4.9 (3.6–6.6)	40	4.4 (3.3–6.1)
NAME	3709	17	4.6 (2.8–7.4)	25	6.7 (4.6–10.0)
ASIA/WEST	3685	11	3.0 (1.7–5.4)	11	3.0 (1.7–5.4)
Canada			x 2,4		x 1,5
White Canadian	4256	41	9.6 (7.1–13.1)	42	9.9 (7.3–13.4)
First Nations	983	12	12.2 (6.9–12.5)	20	20.3 (13.1–31.5)
Migrants	1339	8	6.0 (3.0–11.9)	8	6.0 (3.0–11.9)
United States			x 4,9		x 2,4
White	14 161	277	19.6 (17.4–22.0)	225	15.9 (13.9–18.1)
African American	21 273	574	27.0 (24.9–29.3)	402	18.9 (17.1–20.8)
Hispanic	2551	65	25.5 (20.0–32.5)	42	16.5 (12.2–22.3)

Abbreviations: CI, confidence interval; LA, Caribbean and South and Central America; NAME, Northern Africa and Middle East; SSA, sub-Saharan Africa; WEST, non-European Western countries.

[a] AIDS-related mortality: AIDS, AIDS infection, AIDS malignancy.

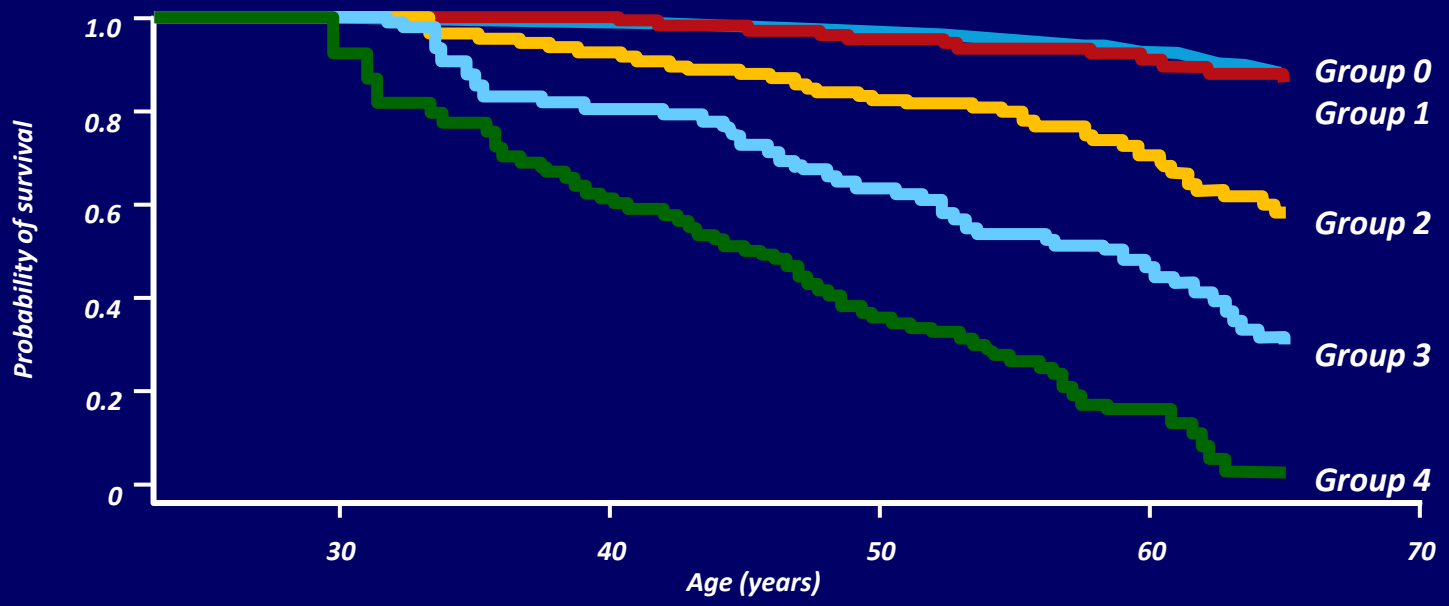
[b] Non-AIDS-related mortality: liver related (hepatitis, gastrointestinal bleeding, liver failure), cardiovascular (myocardial infarction/ischemic heart disease, stroke, lung embolus, heart/vascular), pulmonary (pulmonary hypertension, chronic obstructive pulmonary disease, respiratory), external cause (accident/violence, suicide), other (diabetes, pancreatitis, lactic acidosis, renal failure, hematological, psychiatric, central nervous system, digestive, skin/motor system, other).

J del Amo et al., CID 2013

‡

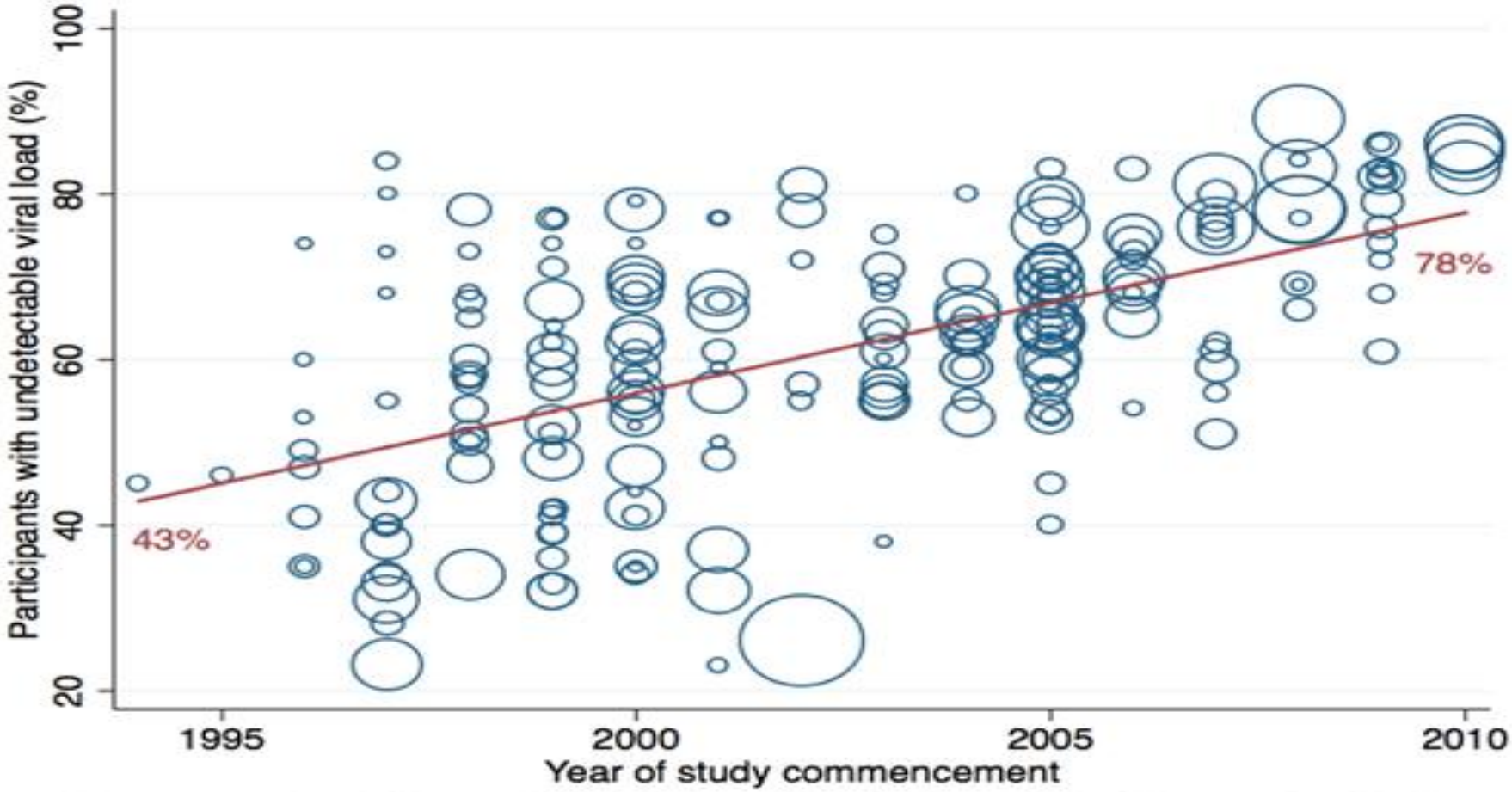
Danish HIV Cohort Study

Life Expectancy of HIV+ Persons vs General Population



Cumulative survival for HIV-infected patients starting HAART & persons from the general population				
Group 0	Population comparison			
Group 1	HIV +			
Group 2	HIV +	+ Risk factors		
Group 3	HIV +		+ Comorbidity	
Group 4	HIV +			+ alcohol / drug abuse

Obel N et al. PLoS ONE 2011;6(7):e22698



Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Efficacy (SD)	47% (14)	52% (17)	64% (7.1)	74% (8.5)	82% (6.7)

F. Lee, IAS 2013

ART Coverage: Low/Middle- and High-Income Countries

Country Ranking of % of HIV-Infected Patients on ART (Abbreviated Table)

Ranking	Country*	No. HIV-Infected	No. on ART	% on ART
1.	United Kingdom	98,400	65,928	67.0
2.	Botswana	340,000	212,083	62.4
3.	Denmark	6,500	4,029	62.0
4.	France	149,900	89,940	60.0
5.	Netherlands	25,000	14,817	59.0
6.	Rwanda	210,000	114,978	54.8
11.	British Columbia	11,700	5,975	51.1
13.	Cambodia	110,000	48,913	44.5
18.	Ethiopia	760,000	288,137	37.9
26.	Australia	33,000	11,523	35.0
30.	United States	1,148,200	375,461	32.7

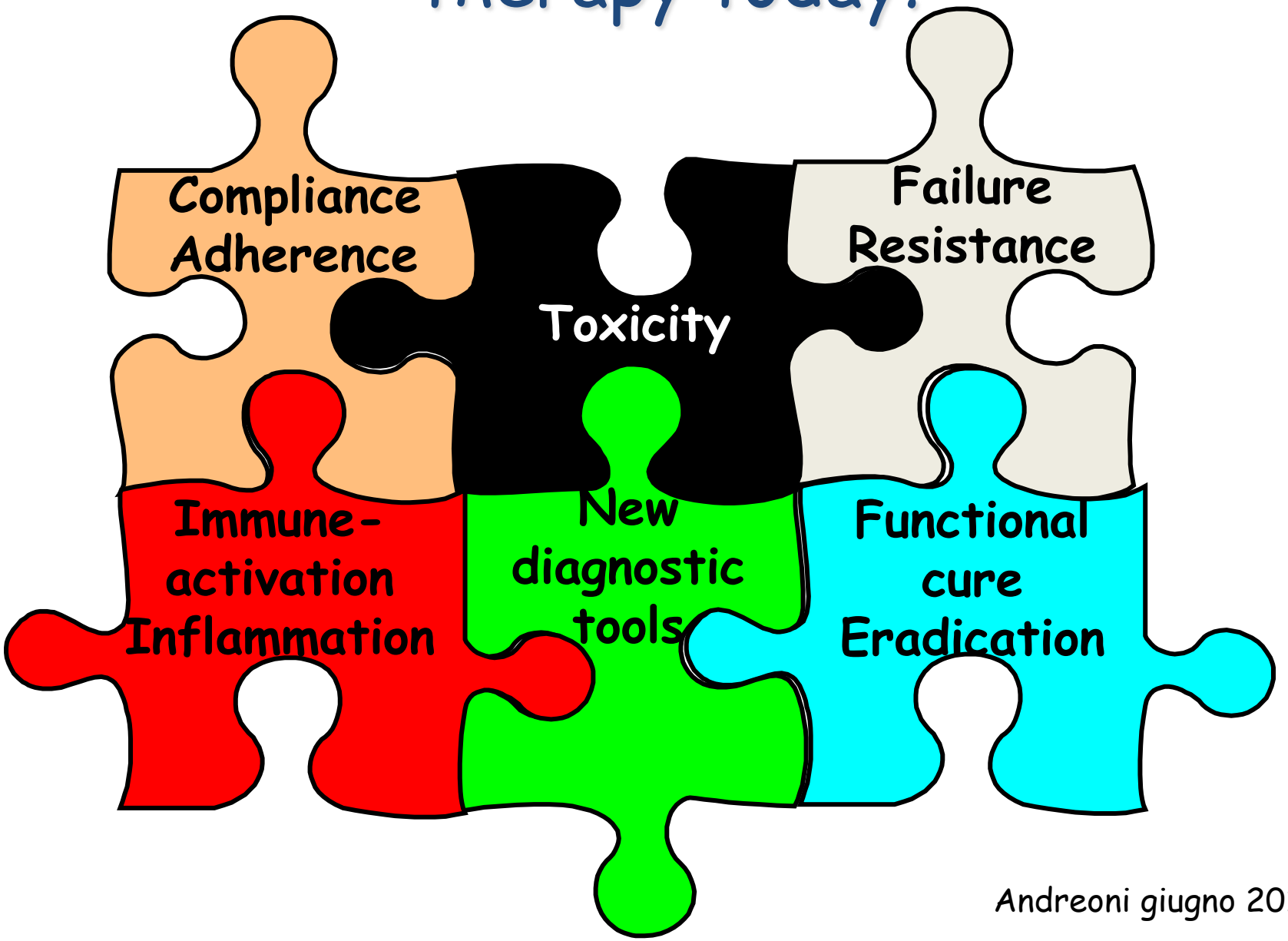
*High-income countries in red – ART coverage data extracted from published reports

- **If all 51 countries had 62% ART coverage (Botswana): 1.2 million (65%) new infections and 1 million (70%) of HIV related deaths in 2012 could have been avoided**
- **Some low income countries now have higher ART coverage than high income countries, e.g. the USA (33%, ranked 30th out of 58)**

Adapted from Hill A, et al. IAC 2014. Melbourne, Australia. #LBPE29


Sterilizing cure
Functional cure
Long-term treatment

What problems in the antiretroviral therapy today?



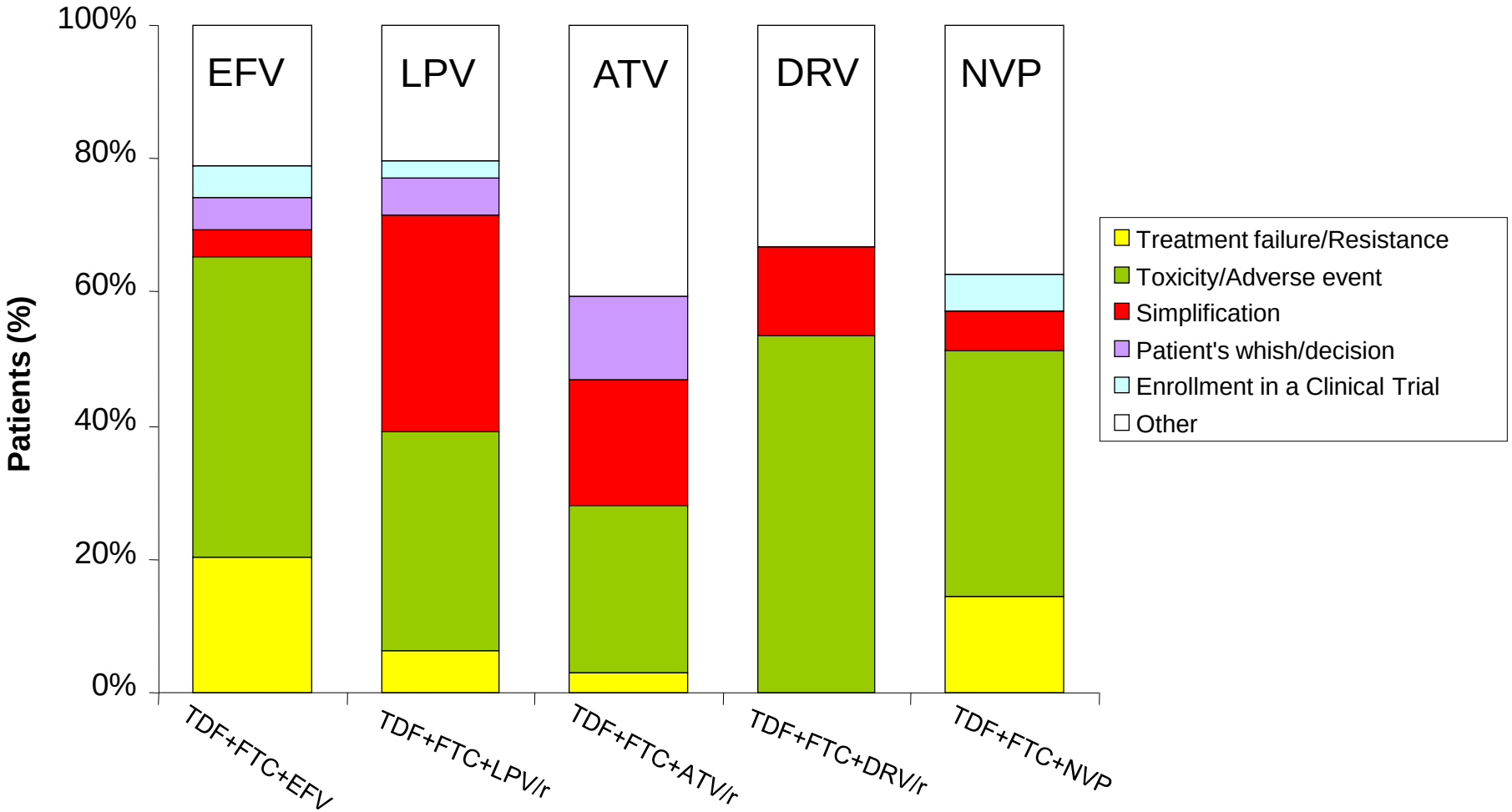
Andreoni giugno 2014

We need new drugs and/or new strategies?

Problems in Chronic HIV Treatment

Toxicity remains a major reason for first-line cART change

Persistence of first line ART in the Spanish prospective HIV cohort CoRIS

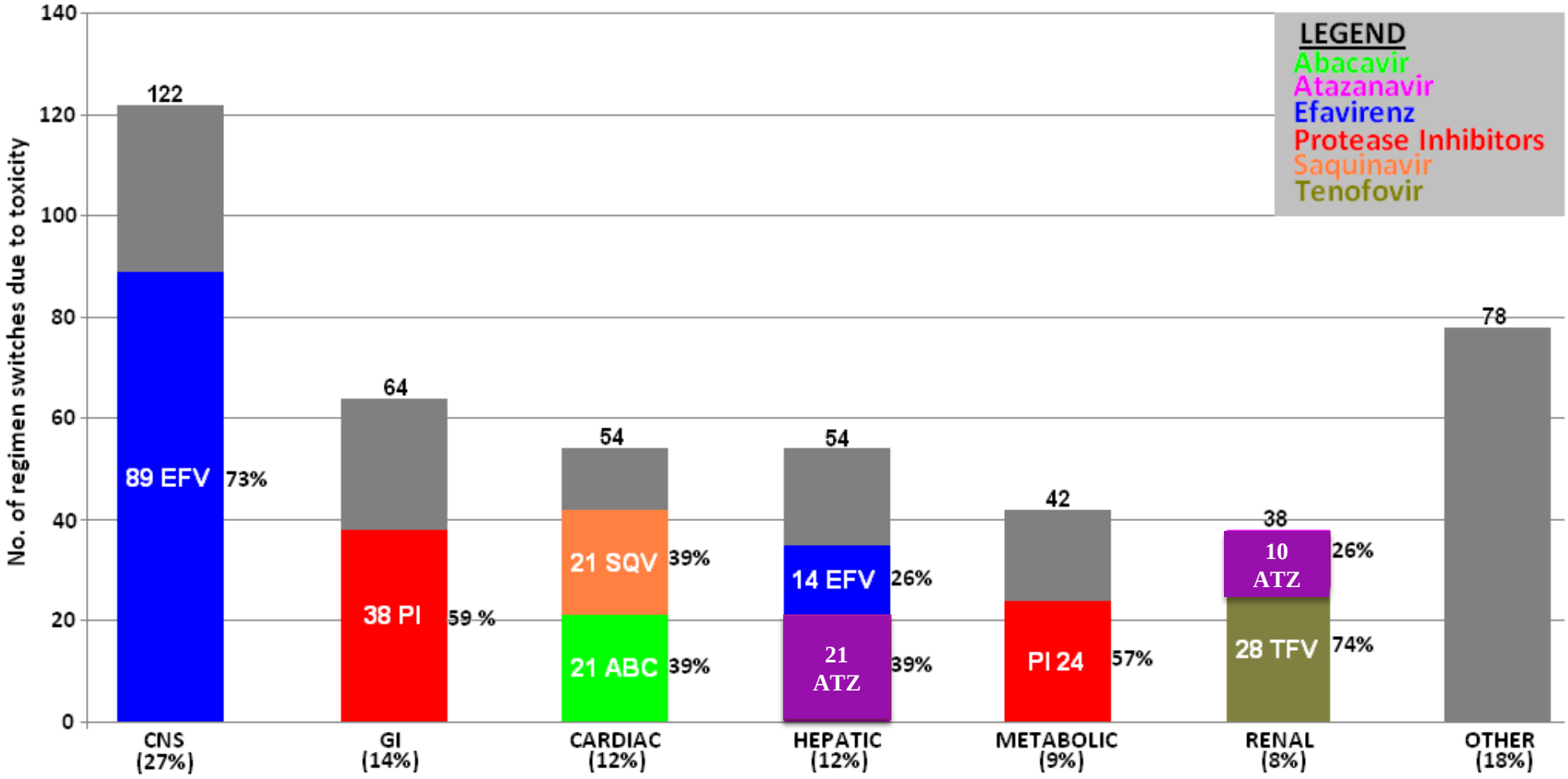


Jarrin I et al. 13th EACS Conference, Belgrado 2011

Major toxicities of most common drugs are the reasons for ART switch

Chelsea and Westminster Cohort

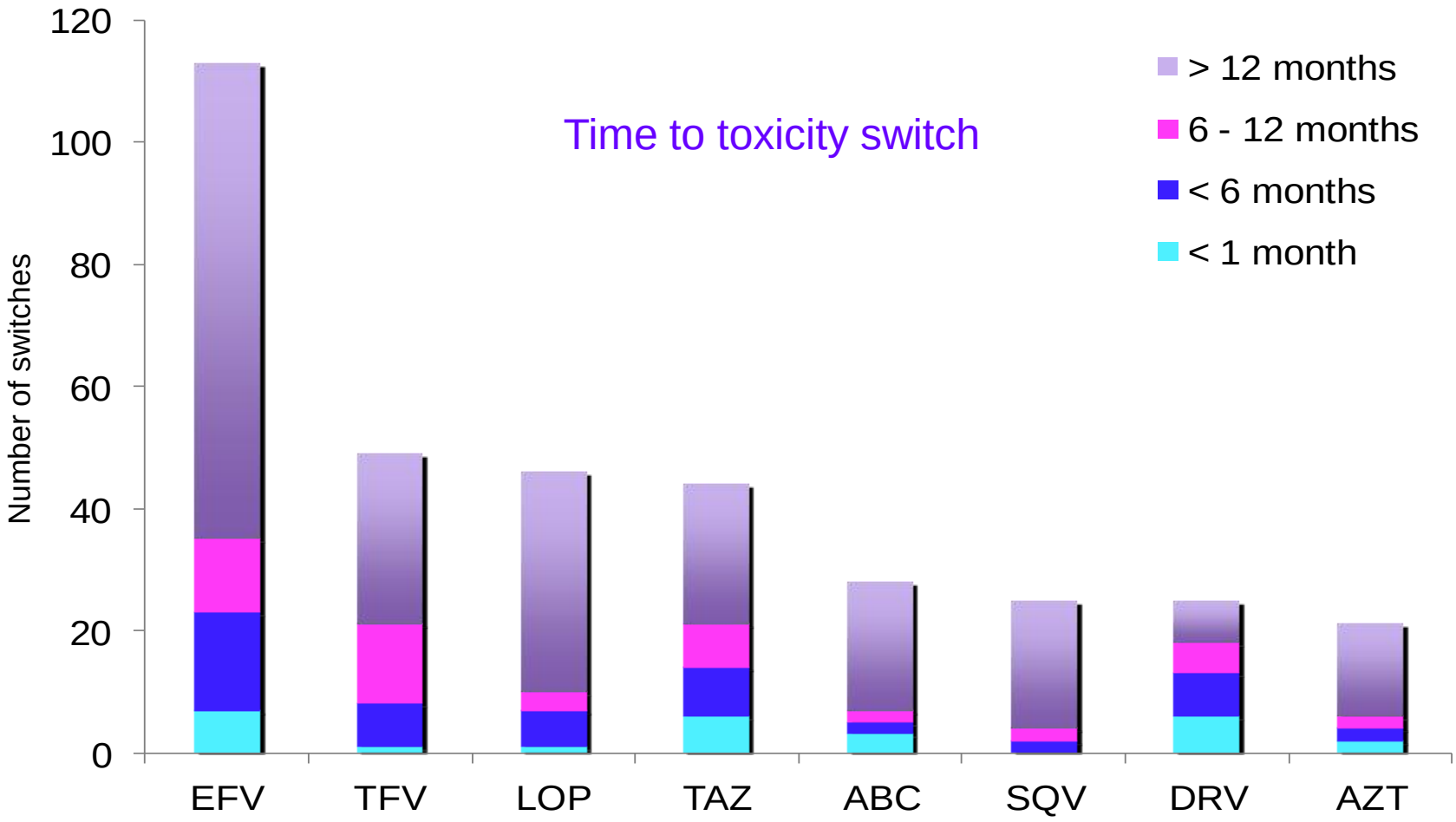
452 switches due to toxicity/perceived toxicity



Boyle A et al. Why do patients switch therapy? 18th Annual Conference BHIVA, April 2012

Time to toxicity switch not neccesarily short

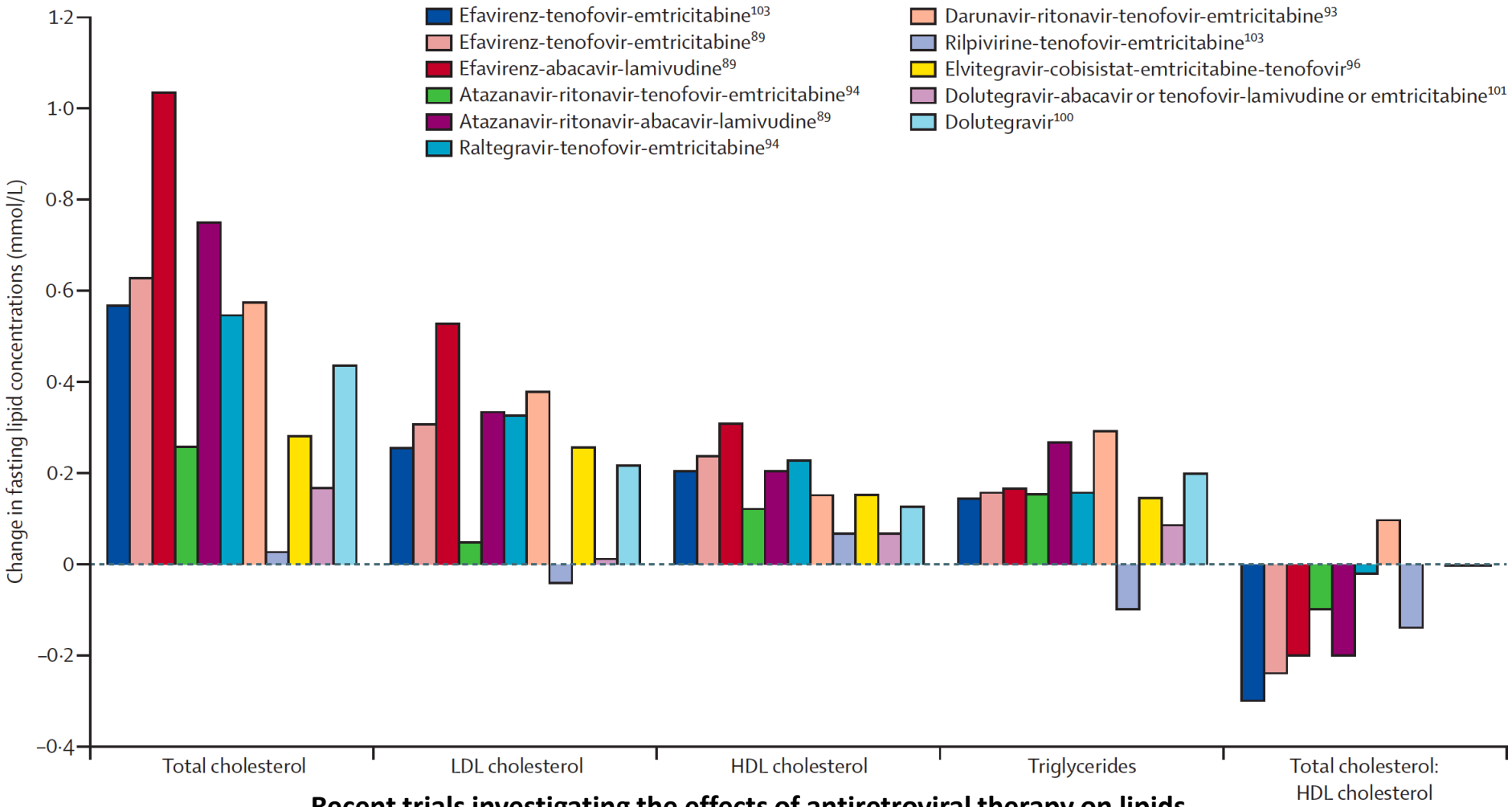
Chelsea and Westminster Cohort



Boyle A et al. Why do patients switch therapy? 18th Annual Conference BHIVA, April 2012

Metabolic disease in HIV infection

Metabolic diseases probably develop at the intersection of traditional risk factors (such as obesity, tobacco use, and genetic predisposition) and HIV-specifi c and ART-specific contributors (including chronic inflammation and immune activation)



Recent trials investigating the effects of antiretroviral therapy on lipids

Lake JE & Currier JS. Lancet Infect Dis, 2013

Problems in Chronic HIV Treatment

New drugs

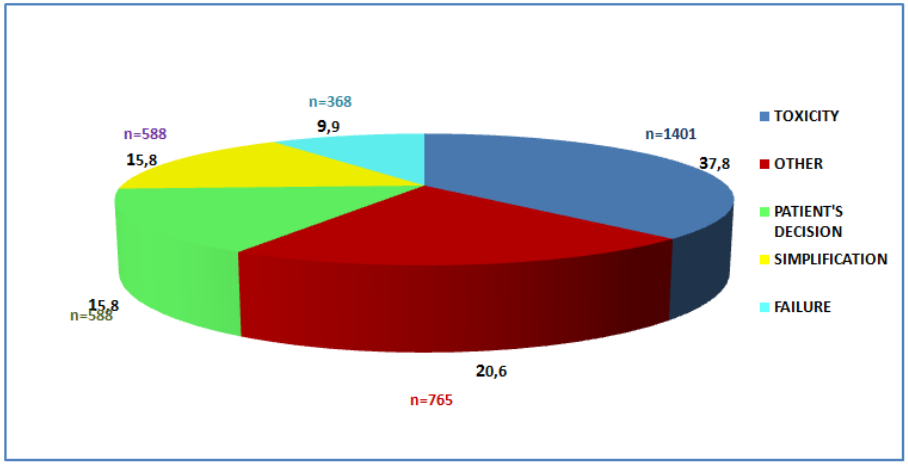
New Strategies

RPV, TAF, COB

Mono-Dual therapy

Fondazione Icona
Italian Cohort of Antiretroviral Naïve Patients

Distribution of reason for ever stopping the drugs included in the first regimen



Problems in Chronic HIV Treatment

New Strategies

STR

STR: Strategie per ogni fase della terapia

Naive

Switch per tossicità

NNRTI
Atripla/Eviplera

→

PI DRV/cob/FTC/7340

INI Stribild – DLT/ABC/3TC

PI
DRV/cob/FTC/7340

→

NNRTI Atripla

NNRTI Eviplera

INI Stribild – DLT/ABC/3TC

INI
Stribild

→

NNRTI Atripla

NNRTI Eviplera

PI DRV/cob/FTC/7340

INI DLT/ABC/3TC

Andreoni giugno 2014

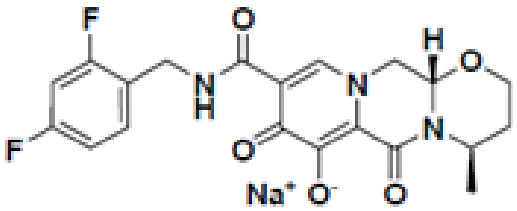
Problems in Chronic HIV Treatment

New Strategies → STR

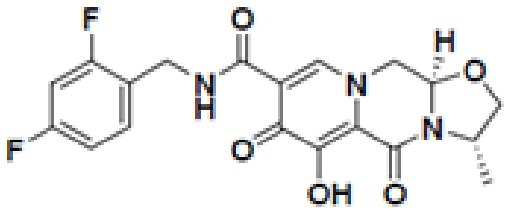
Long-acting drugs → Treatment Prophylaxis

GSK 1265744A

- **Analogue to Dolutegravir (DTG) with similar preclinical profile**



Dolutegravir (DTG)



GSK1265744 (744)

- **GSK744 is well-suited to long acting nanosuspension**

- **GSK 744 LAP 200 mg/mL formulation for IM or SC**
  - No cold chain storage requirements

  - **HIV PrEP: mono or combination ARV approach**

  - **HIV treatment: need for partner LA-ARV agent(s); ongoing clinical collaboration with Janssen long-acting NNRTI (rilpivirine)**

S/GSK1265744 Biochemical and Antiviral Characteristics

- **S/GSK744 shows potent antiviral activity and high plasma protein shift**

Compound	IC50 in PBMCs (nM)
S/GSK744	0.22
Dolutegravir	0.51
Raltegravir	2
Elvitegravir	2

- **S/GSK744 shows antiviral activity against a broad range of clinical isolates**

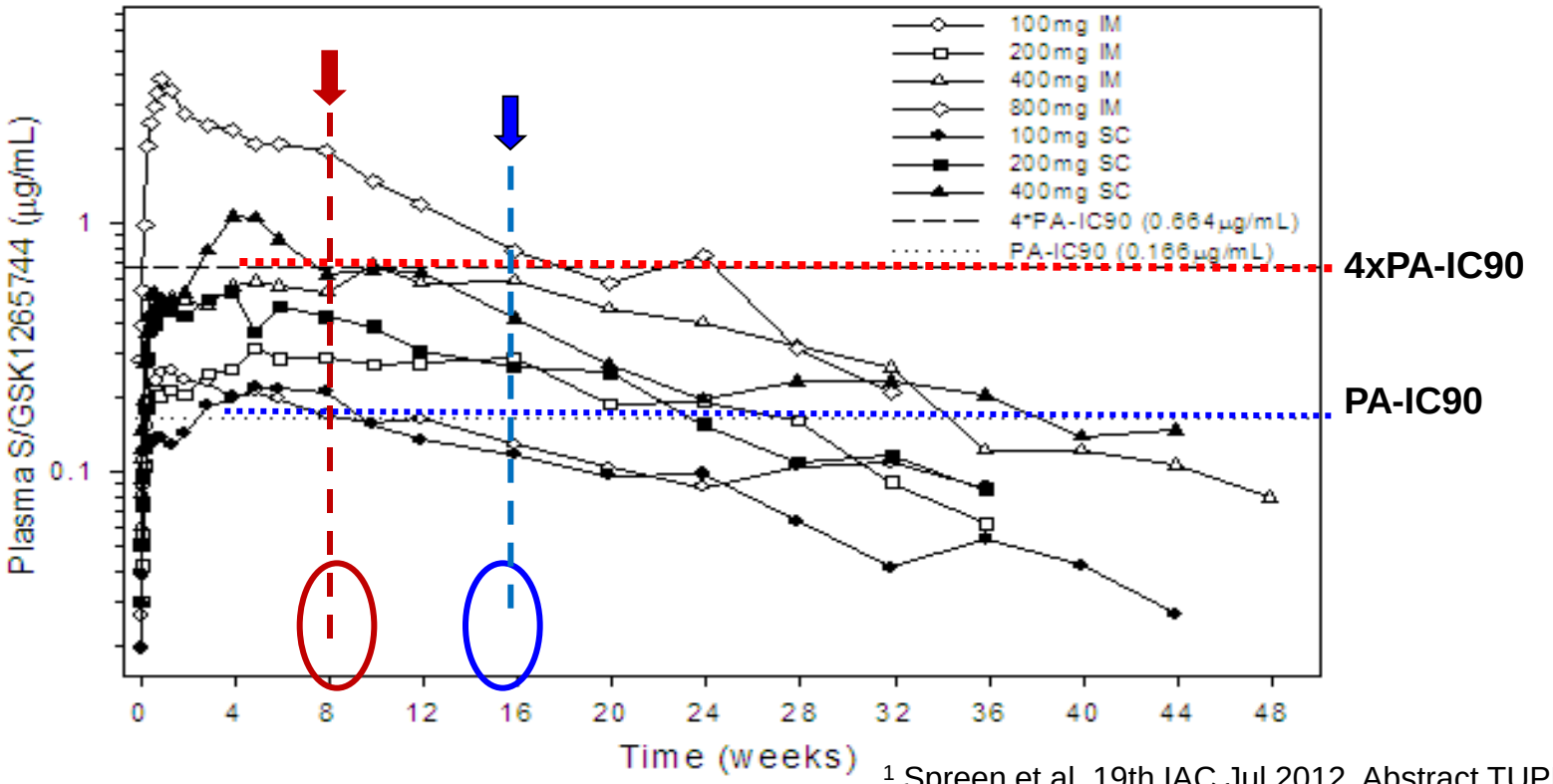
	N	Mean IC50 in PBMC (range) nM
HIV-1 subtypes (Group M: A, B, C, D, E, F, G; Group O)	28	0.18 (0.02-1.06)
HIV-2	4	0.12 (0.10-0.14)

Yoshinaga, T, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-550.

S/GSK1265744 Nanosuspension for Injection: a Potential Long-Acting Therapy for HIV Infection and PrEP

S/GSK744 LAP 200mg/mL formulation for IM or SC use

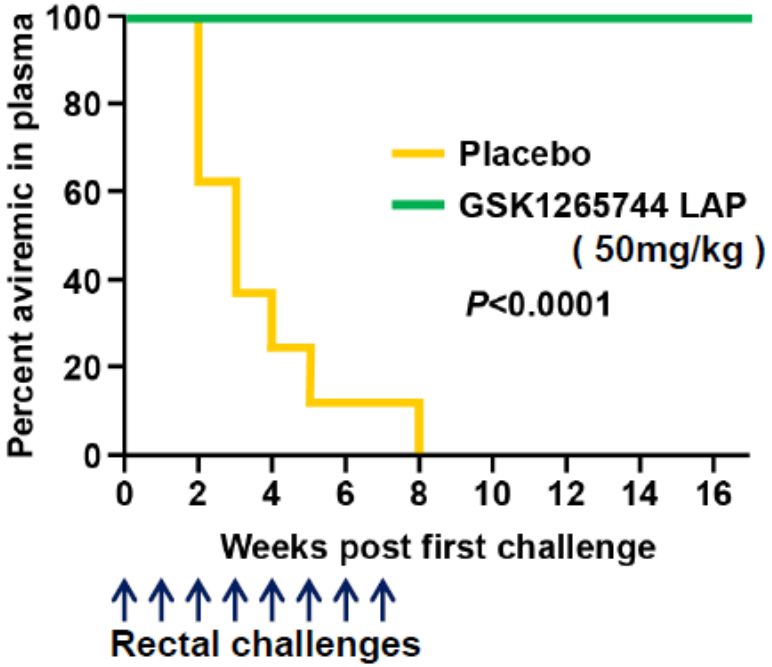
- Phase 1 single dose study of 100-800mg IM/SC
- Single dose S/GSK744 LAP injections in healthy subjects (n= 42) were generally well tolerated and produced apparent **plasma half-life range of 21-50 days**
- **Data support once-monthly to once-quarterly dosing**

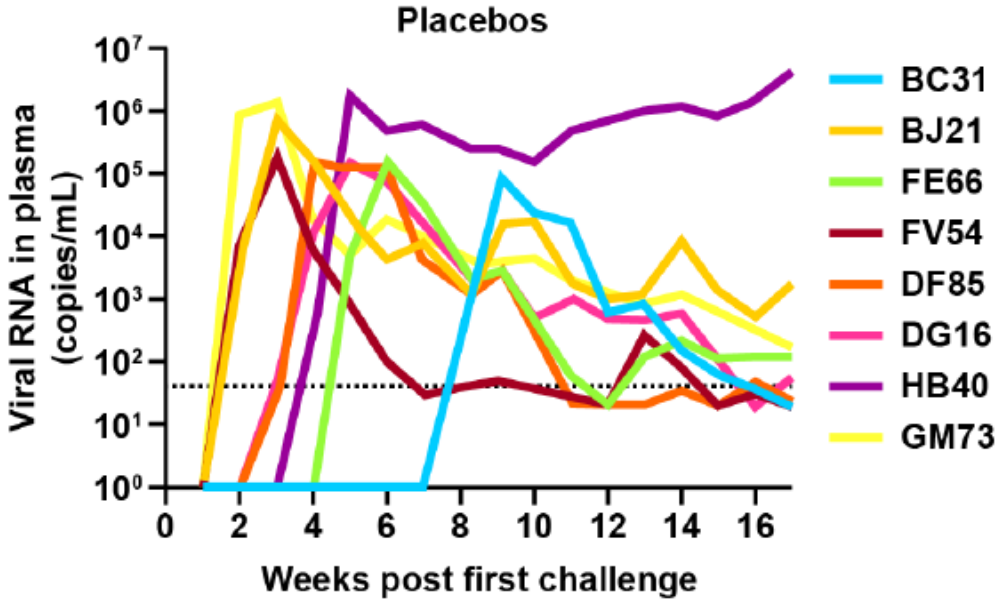


[1] Spreen et al. 19th IAC Jul 2012. Abstract TUPE040
Yoshinaga, T, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-550.

Long-acting Parenteral Formulation of GSK1265744 Protects Macaques against Repeated Intrarectal Challenges with SHIV

Chasity Andrews*[1], A Gettie[1], K Russell-Lodrigue[2], L Moss[3], H Mohri[1], W Spreen[3], C Cheng-Mayer[1], Z Hong[3], M Markowitz[1], and D Ho[1]





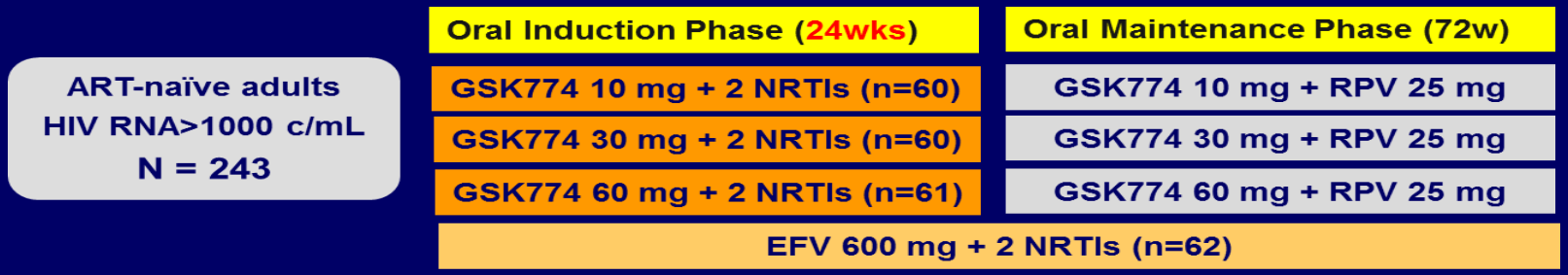
- Proviral DNA and virus-specific antibody responses
  - Not detected in any GSK1265744 LAP–treated macaque
  - Detected in all placebo-treated animals

CROI 2013, paper #24LB

GSK744 - LATTE Study

24-week interim analysis - Safety and Efficacy Results

Ongoing, Phase 2b, randomised, multicentre, partially blinded, dose ranging study to demonstrate the safety and efficacy of GSK-744 LA + RPV LA



Primary endpoint: Percentage of subjects with HIV-1 RNS <50 copies/mL at week 48 by FDA snapshot

- At Week 24, 87% of subjects in the GSK-744 10mg and 74% of subjects on EFV were virologically supressed (HIV-1 <50 copies/mL)
- Similar rates of graded laboratory abnormalities between all doses of GSK-744 and EFV
- Neuropsychiagtric AEs were more common with EFV compared with GSK-744
- Headache was more commonly seen with GSK-744 (21%) compared with EFV (11%)
- 4 subjects on GSK-774 and 8 subjects on EFV discontinued due to AEs
- No INI, NNRTI or NRTI mutations were detected through 24 wks

D. Margolis et al. EACS 2013. Brussels, Belgium. #PS7/1

* NRTI ABC/3TC or TDF/FTC

GSK 744 oral treatment in naive pts: LATTE study

Induction phase 24 wks

744 (10-30-60 mg) QD + 2 NRTI (n. 215 naive pts)

Maintenance phase 96 wks

744 (10-30-60 mg) QD + RPV 25 mg QD

Atripla

➢Successful two-drug regimen POC will trigger “LATTE-2” phase 2B study using long-acting injectable formulations (744+RPV) (first study using LA-ART in HIV infected population)

- 744 LAP 400 mg IM q28d: PK similar to 744 oral 30 mg QD
  RPV 900 mg IM q28d: PK similar to RPV oral 25 mg QD

Current Investigational Agents for HIV PrEP

	Mechanism	Main dosing route	Dosing frequency	Development stage
Maraviroc (MVC)	CCR5 antagonist	oral	once daily	Phase 2 enrolling
Rilpivirine (RPV)-LA*	NNRTI	injectable, IM	once monthly	Phase 1 pilot; Phase 2 planned
Dapivirine	NNRTI	ring	monthly	Phase 3 enrolling
Ibalizumab	CD4 attachment inhibitor	injectable, SC	once weekly	Phase 1 pilot
744-LAP*	integrase inhibitor	injectable, IM	once quarterly	Phase 1 pilot; Phase 2 planned

Gulick, R, et al. IAS 2013; Kuala Lumpur, Malaysia. Oral #MOBS020

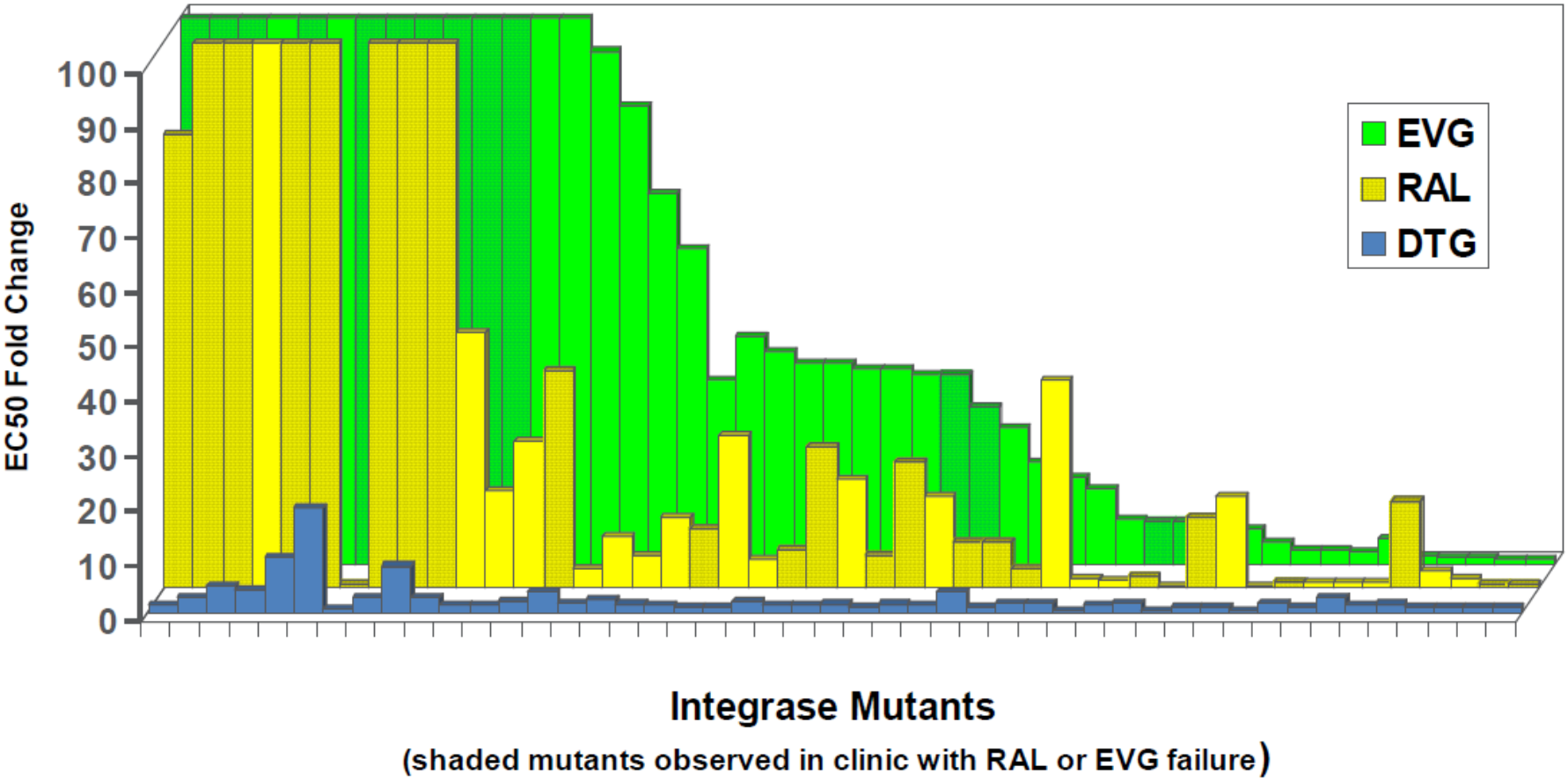
Problems in Chronic HIV Treatment

New drugs

DLT
GSK 1265744

FOLD CHANGE IN EC_{50} AGAINST MOLECULAR CLONES WITH INI SUBSTITUTION

In vitro, most RAL and EVG resistant strains remain susceptible to dolutegravir



Seki T, et al. CROI 2010, poster abstract J-122
Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21

Problems in Chronic HIV Treatment

New drugs

DLT
GSK 1265744

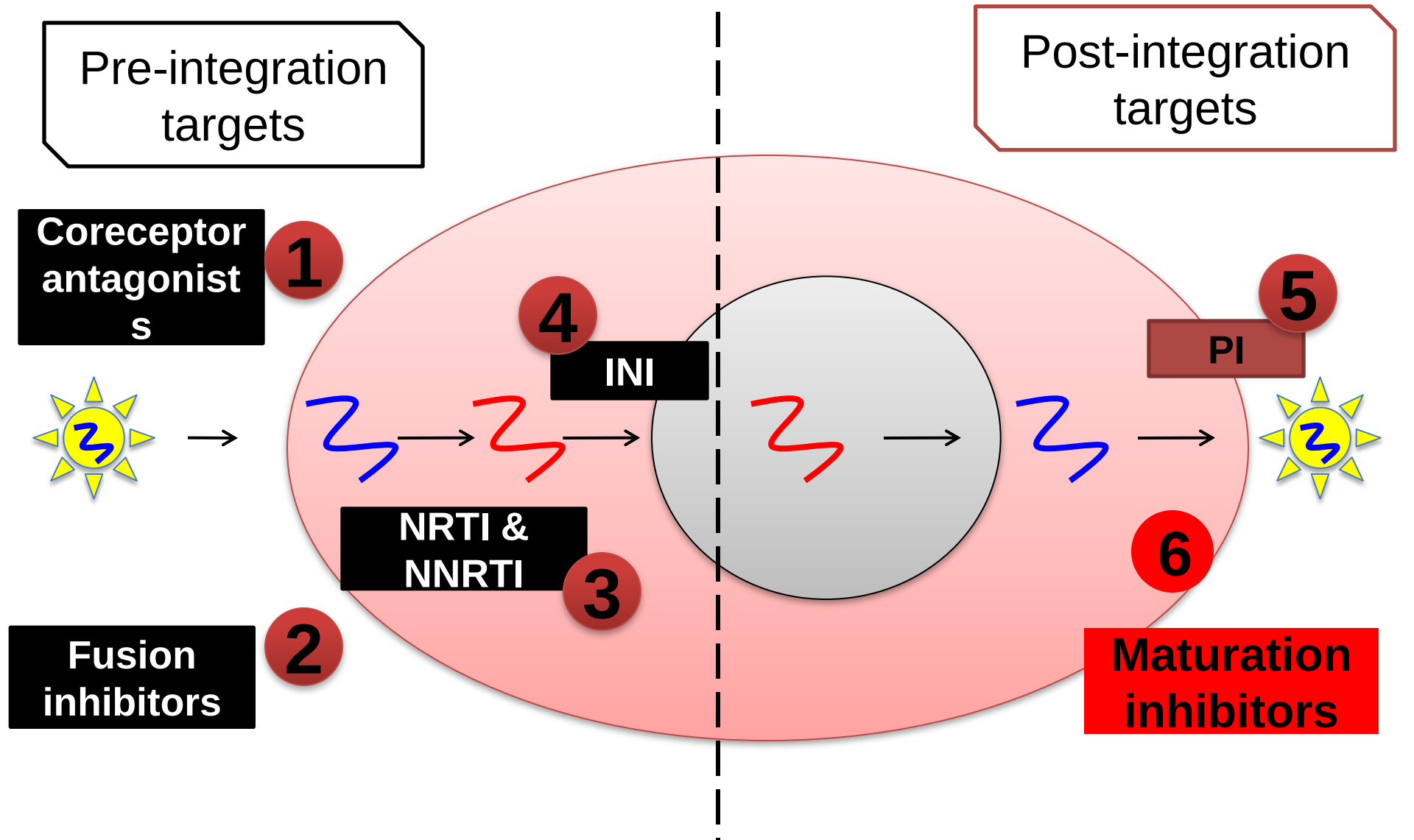
New Strategies

New synergistic regimens

Antiretroviral agents in clinical development

Drug class	Agent	Drug company
NRTI	BMS-986001 (ex Festinavir) Apricitabine (similar 3TC and FTC) GS-7340 (prodrug TFV)	Bristol-Myers-Squibb Avexa Gilead Sciences
NNRTI	Lersivirine (UK-453061) MK-1439	Pfizer MSD
PI	CTP-518 (deuterium-midifed ATV) TMC-310911	Concert Pharma TIBOTEC
Integrase inhibitors	GSK-1265744	GSK
CCR5 inhibitors	Cenicriviroc (TBR-652) (also CCR2 inhibitor)	Tobira Therapeutics
Entry inhibitors	BMS-663068 (prodrud of an attachment inhibitor) Ibalizumab (CD4 mab)	Bristol-Myers Squibb TaiMed Biologics
Maturation Inhibitors (Gag)	Bevirimat (MPC-4326) GSK2838232	Myriad Genetics GSK

Pre-integration and post-integration targets in HIV life cycle



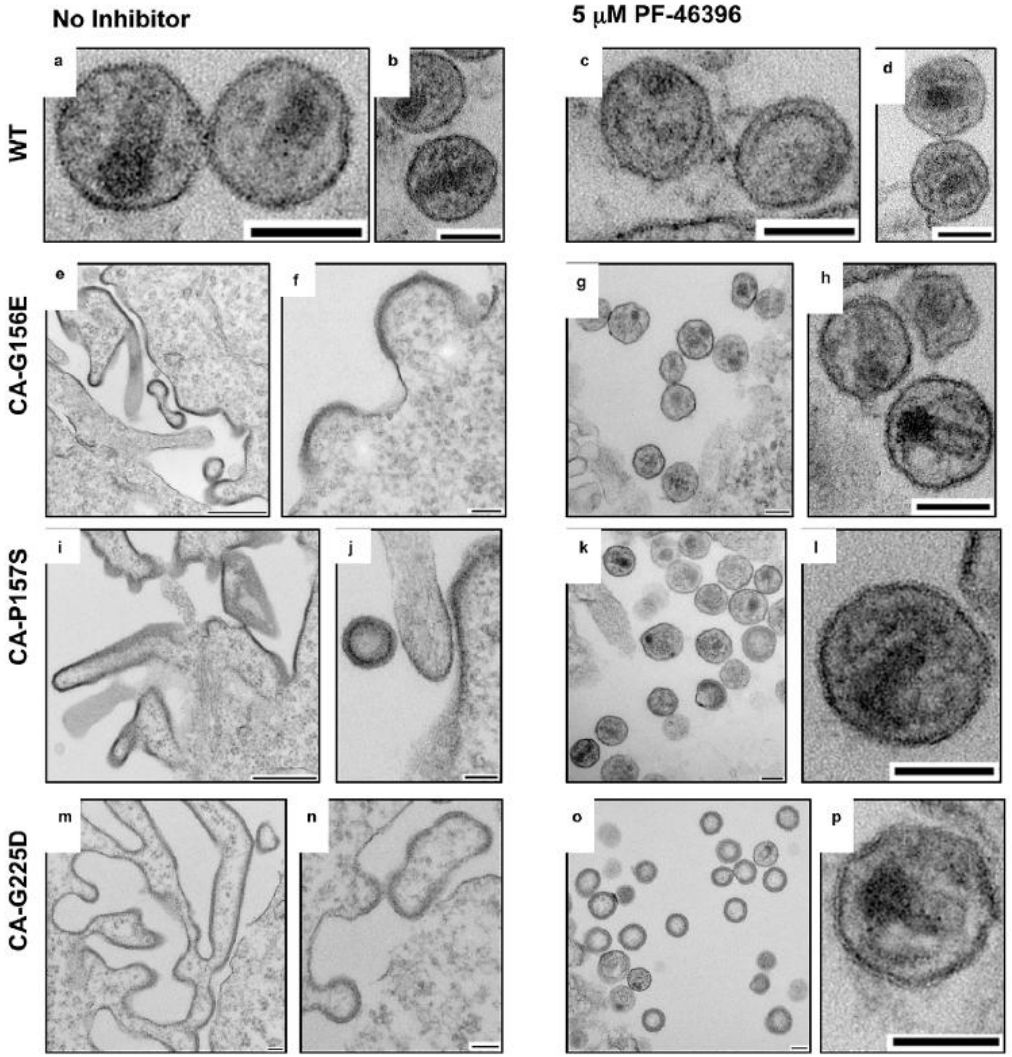
November 8, 2012

PLOS | PATHOGENS

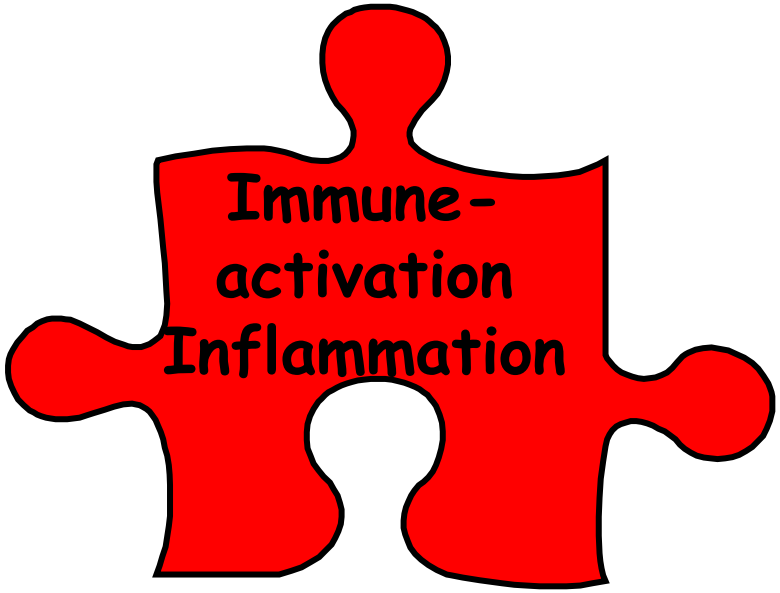
Structural and Functional Insights into the HIV-1 Maturation Inhibitor Binding Pocket

Kayoko Waki[1], Stewart R. Durell[2], Ferri Soheilian[3], Kunio Nagashima[3], Scott L. Butler[4¤], Eric O. Freed[1]*

The first-in-class HIV-1 maturation inhibitor dimethylsuccinyl betulinic acid [PA-457 or **bevirimat** (BVM)] blocks HIV-1 maturation by inhibiting the cleavage of the binding pocket in Gag.



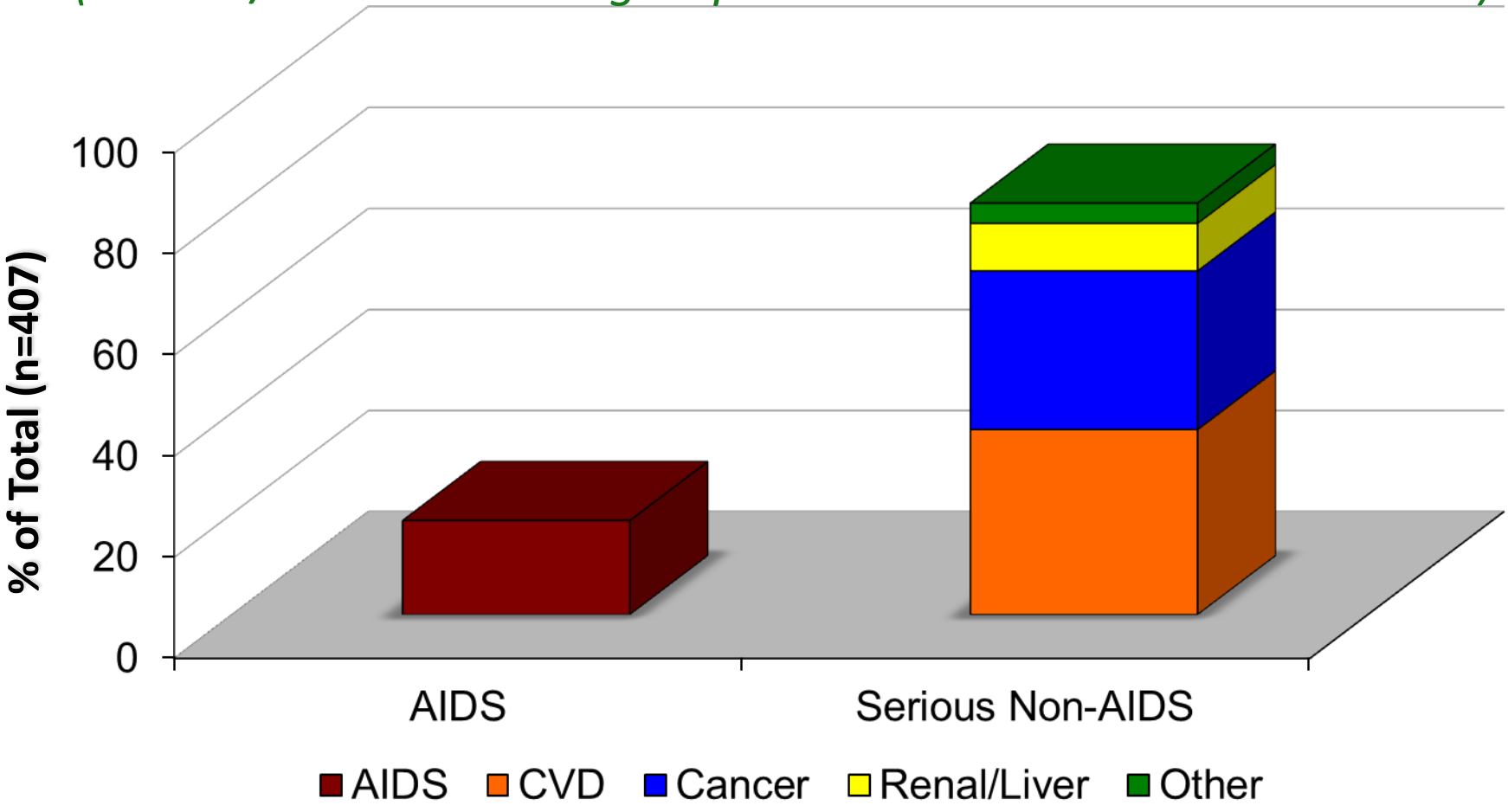
Problems in Chronic HIV Treatment



New Strategies

Events in ART-Treated Patients are largely Non-AIDS

(SMART/ESPRIT control groups: randomized to continuous ART)



INSIGHT SMART & ESPRIT Study Groups

AIDS 2010; 24(12):1877, NEJM 2006; 355:2283-2296 , Ann Int Med 2008; 149:289-299

OPEN ACCESS Freely available online October 2008 | Volume 5 | Issue 10 | e203 PLOS MEDICINE

Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

Lewis H. Kuller[1], Russell Tracy[2], Waldo Belloso[3], Stephane De Wit[4], Fraser Drummond[5], H. Clifford Lane[6], Bruno Ledergerber[7], Jens Lundgren[8], Jacqueline Neuhaus[9], Daniel Nixon[10], Nicholas I. Paton[11], James D. Neaton[9*], for the INSIGHT SMART Study Group

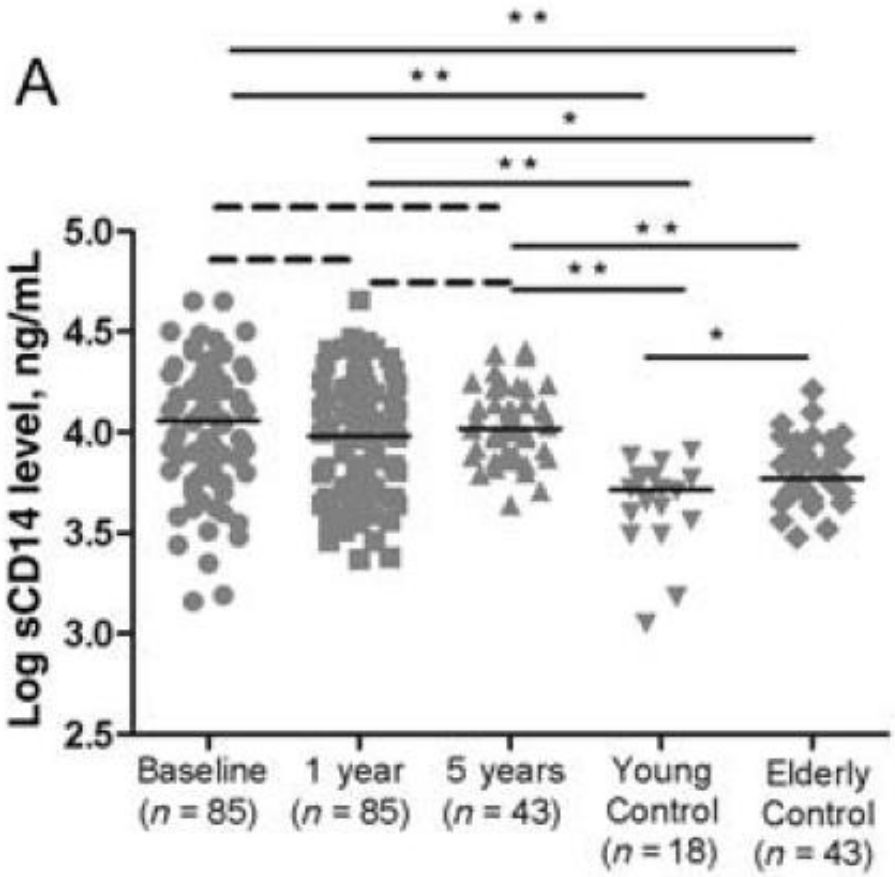
1 University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **2** University of Vermont, Burlington, Vermont, United States of America, **3** Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, **4** Saint-Pierre Hospital, Brussels, Belgium, **5** National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia, **6** National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, United States of America, **7** University Hospital, Zurich, Switzerland, **8** University of Copenhagen, Copenhagen, Denmark, **9** University of Minnesota, Minneapolis, Minnesota, United States of America, **10** Virginia Commonwealth University, Richmond, Virginia, United States of America, **11** Medical Research Council Clinical Trials Unit, London, United Kingdom

Biomarker and All-Cause Mortality Associations

Baseline Level	**OR ($4^{th}/1^{st}$ QRT) Univariate**	*P-value*
D-dimer	**12.4**	<0.0001
IL-6	**8.3**	<0.0001
hsCRP	**2.0**	0.05

G. Mendez-Lagares 4, 2013

Long-Term Suppressive Combined Antiretroviral Treatment Does Not Normalize the Serum Level of Soluble CD14

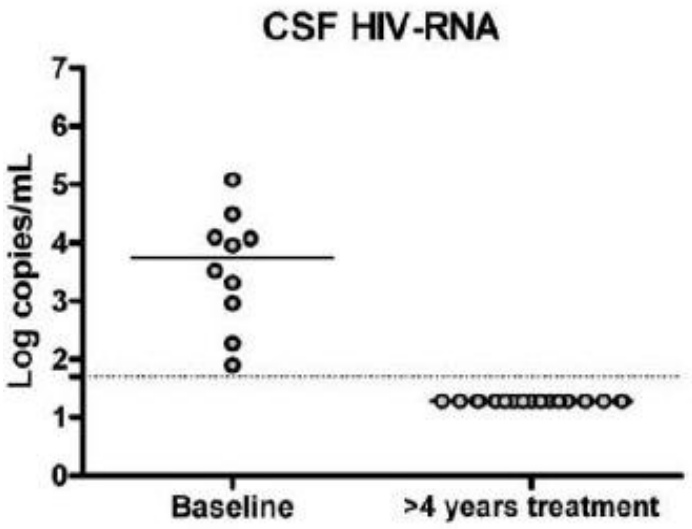


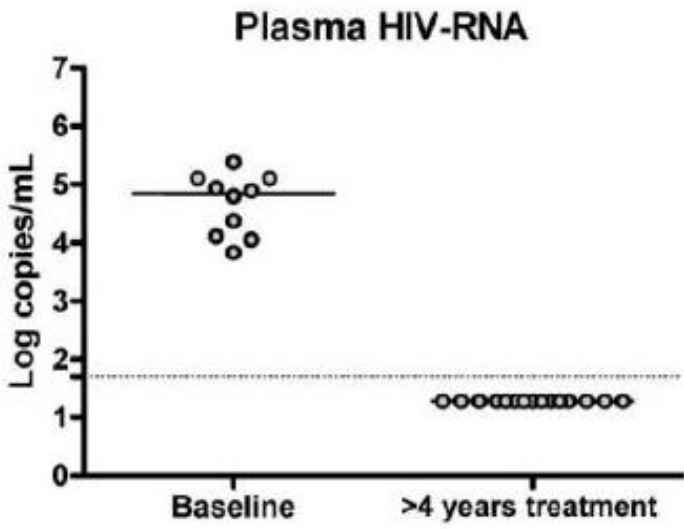
HIV-infected group displayed a significantly higher sCD14 level at baseline (ie, before cART initiation), 1 year and 5 years after cART initiation, compared with both control groups.

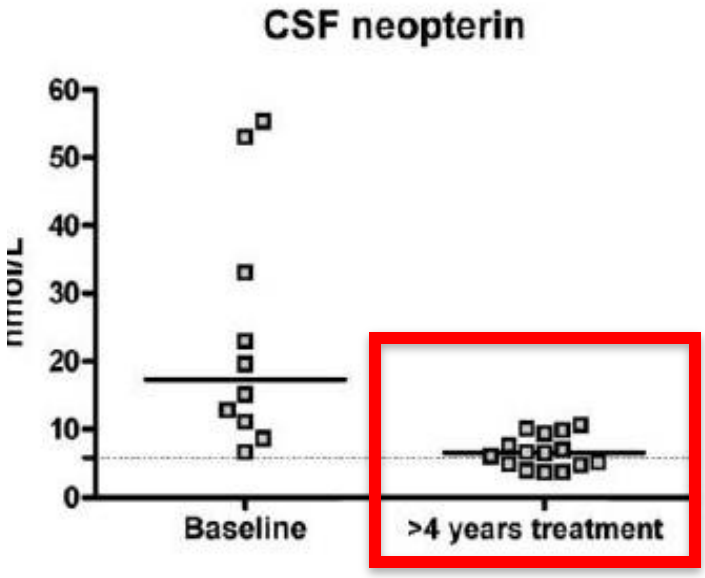
Immune activation of the central nervous system is still present after >4 years of effective HAART

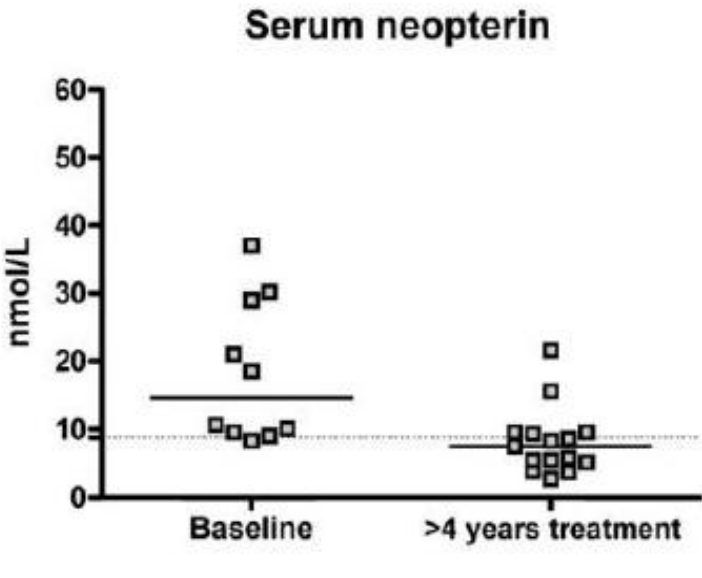
Even A JID 2007

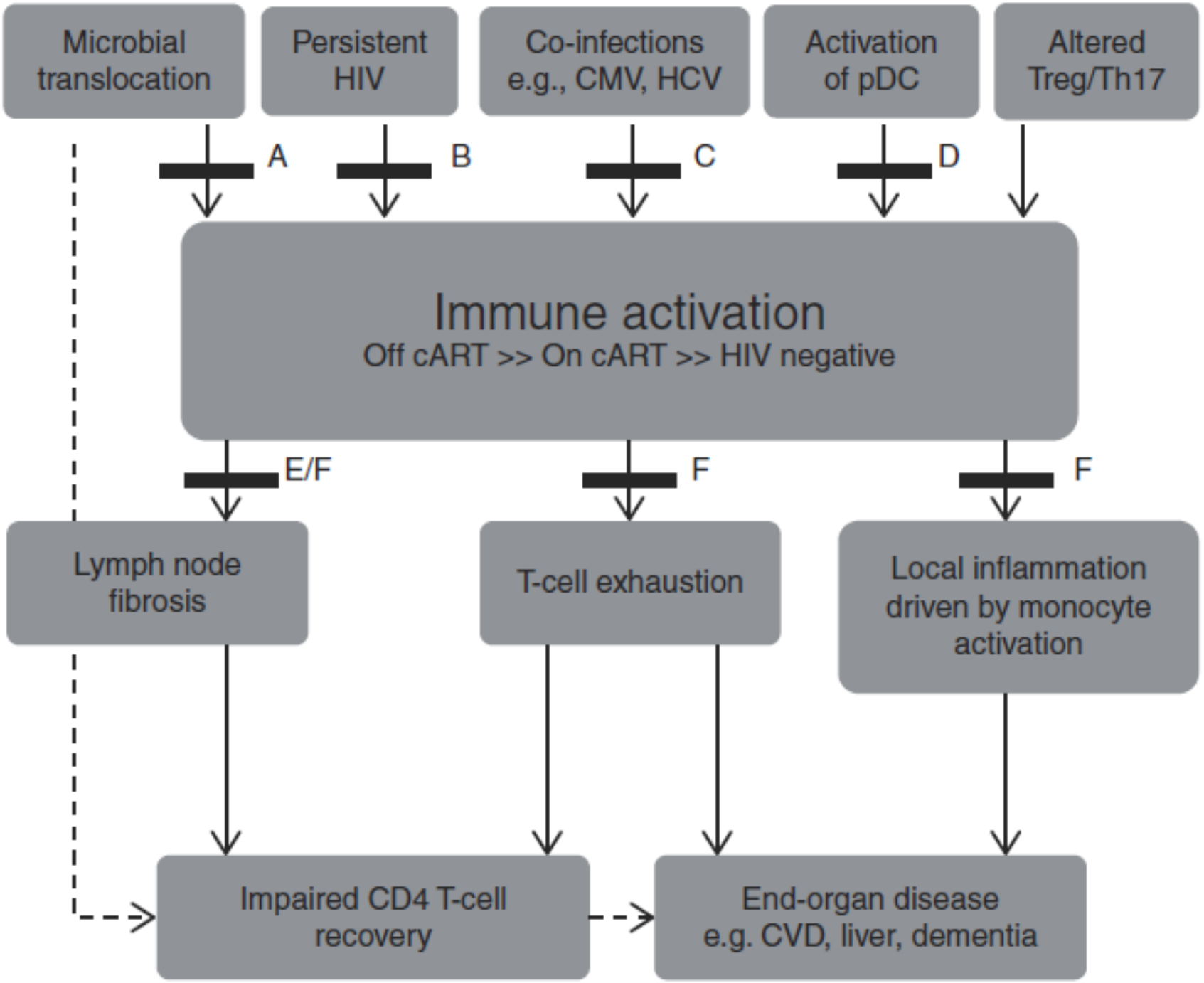
Neopterin levels in CSF decresed but were above normal value

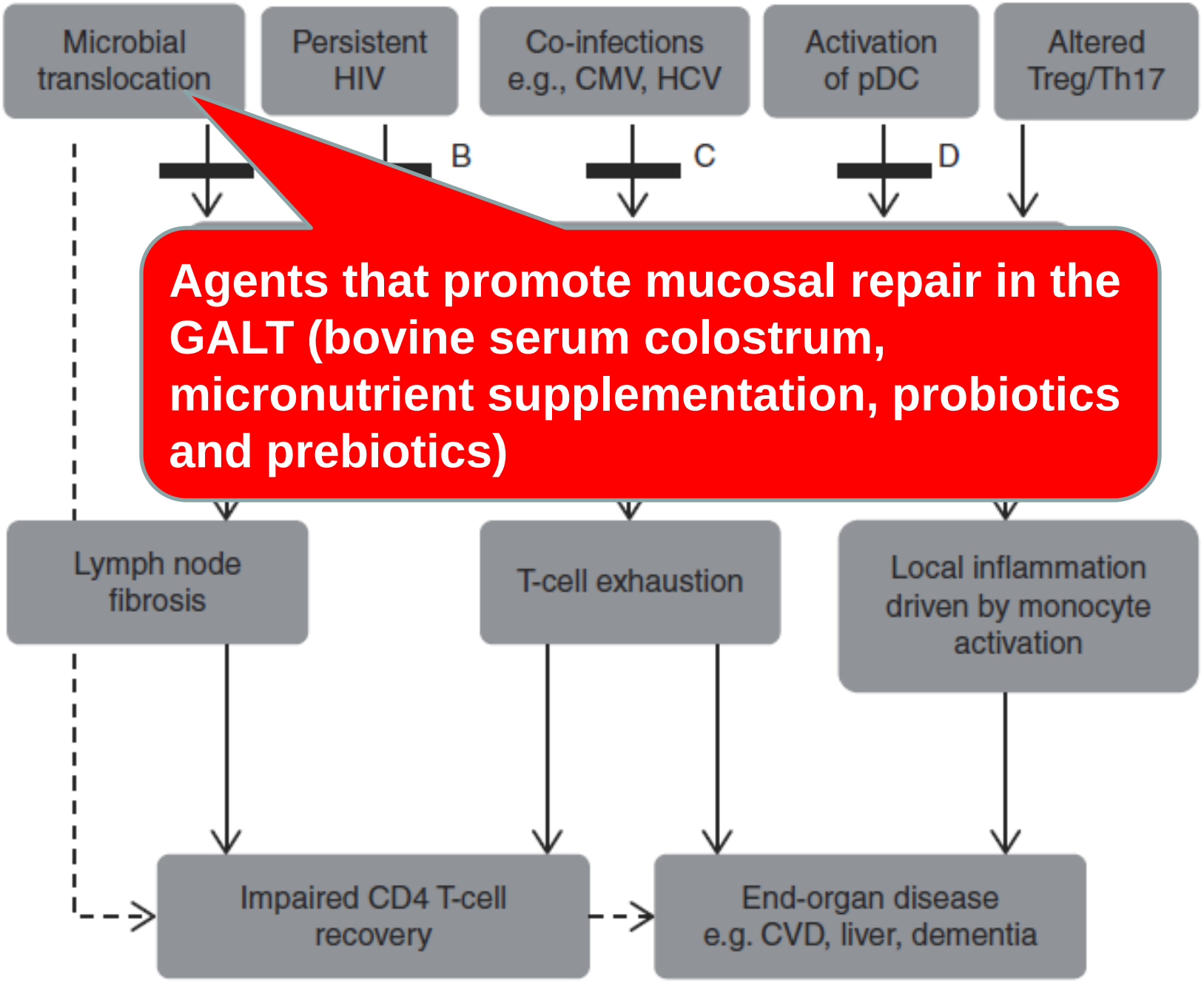


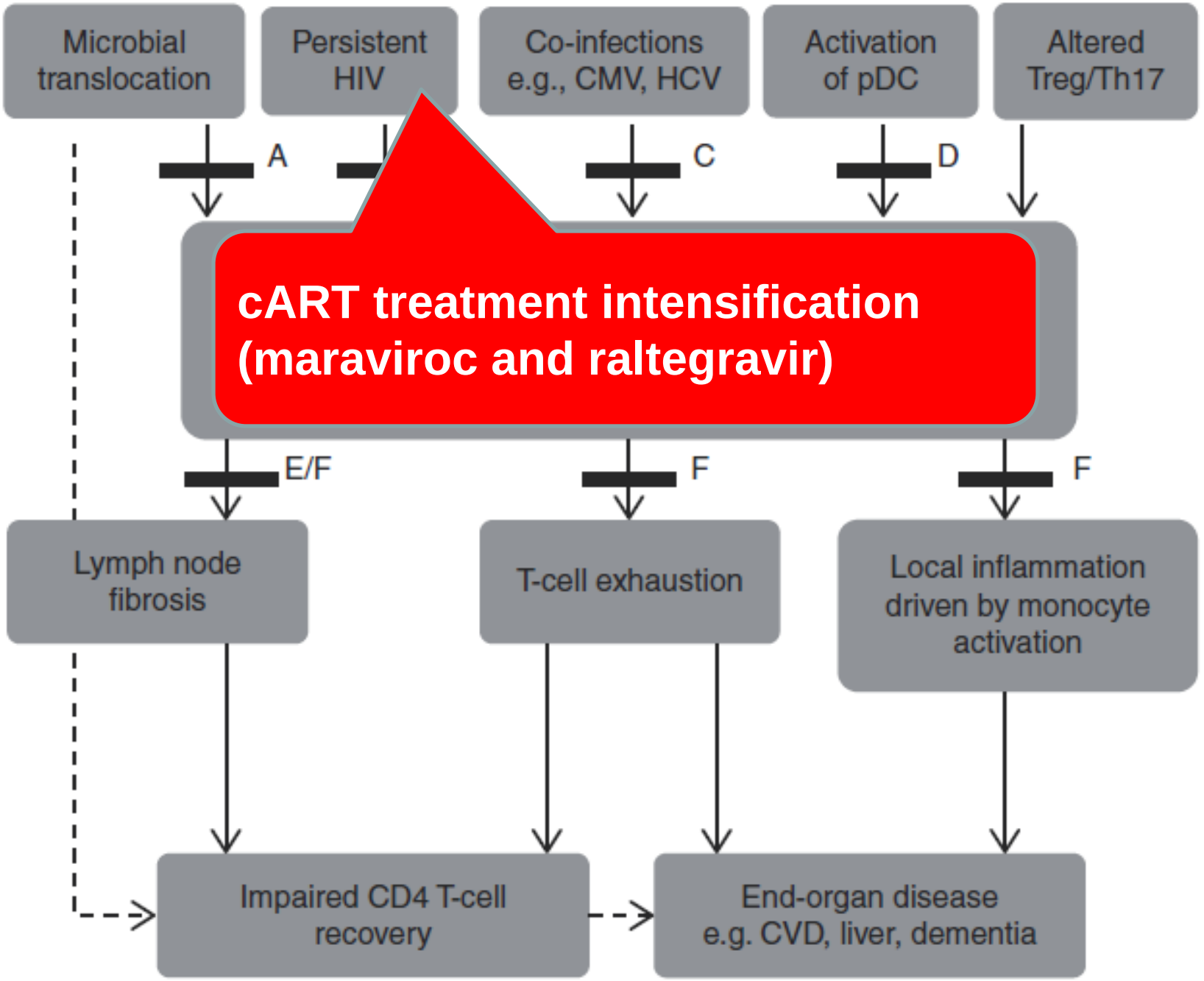







Microbial translocation
Persistent HIV
Co-infections e.g., CMV, HCV
Activation of pDC
Altered Treg/Th17
A
B
C
D
Immune activation
Off cART >> On cART >> HIV negative
E/F
F
F
Lymph node fibrosis
T-cell exhaustion
Local inflammation driven by monocyte activation
Impaired CD4 T-cell recovery
End-organ disease e.g. CVD, liver, dementia


Microbial translocation
Persistent HIV
Co-infections e.g., CMV, HCV
Activation of pDC
Altered Treg/Th17
B
C
D
Agents that promote mucosal repair in the GALT (bovine serum colostrum, micronutrient supplementation, probiotics and prebiotics)
Lymph node fibrosis
T-cell exhaustion
Local inflammation driven by monocyte activation
Impaired CD4 T-cell recovery
End-organ disease e.g. CVD, liver, dementia


Microbial translocation
Persistent HIV
Co-infections e.g., CMV, HCV
Activation of pDC
Altered Treg/Th17
A
C
D
cART treatment intensification (maraviroc and raltegravir)
E/F
F
F
Lymph node fibrosis
T-cell exhaustion
Local inflammation driven by monocyte activation
Impaired CD4 T-cell recovery
End-organ disease e.g. CVD, liver, dementia

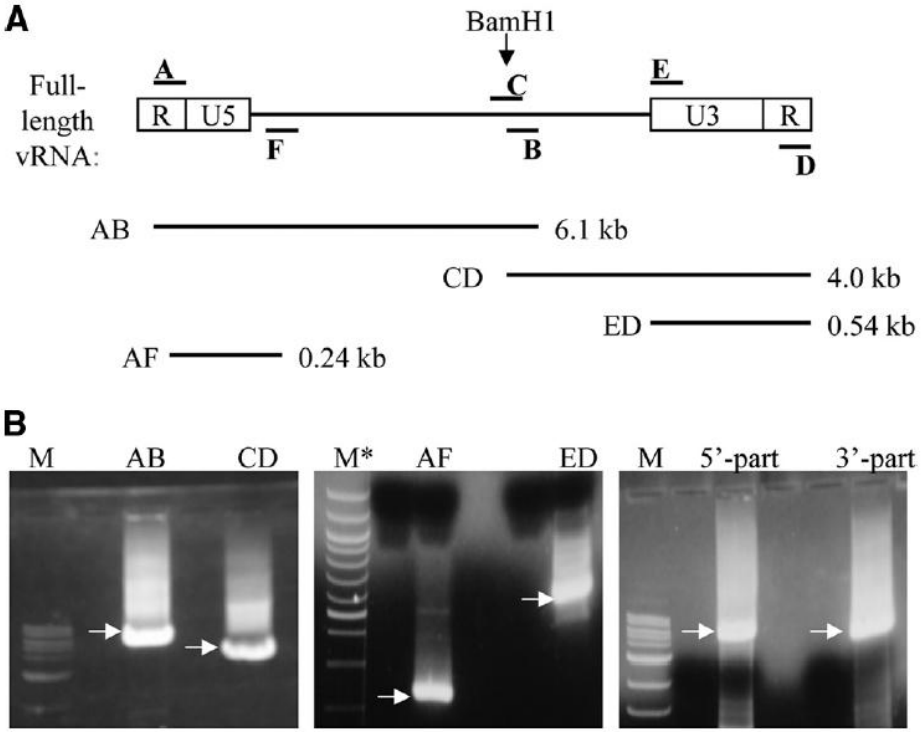
JOURNAL OF VIROLOGY, Aug. 2010, p. 8348–8352 Vol. 84, No. 16
0022-538X/10/$12.00 doi:10.1128/JVI.00362-10

Recovery of Replication-Competent Residual HIV-1 from Plasma of a Patient Receiving Prolonged, Suppressive Highly Active Antiretroviral Therapy▽

Gautam K. Sahu,[1]* Juan C. Sarria,[2] and Miles W. Cloyd[1]

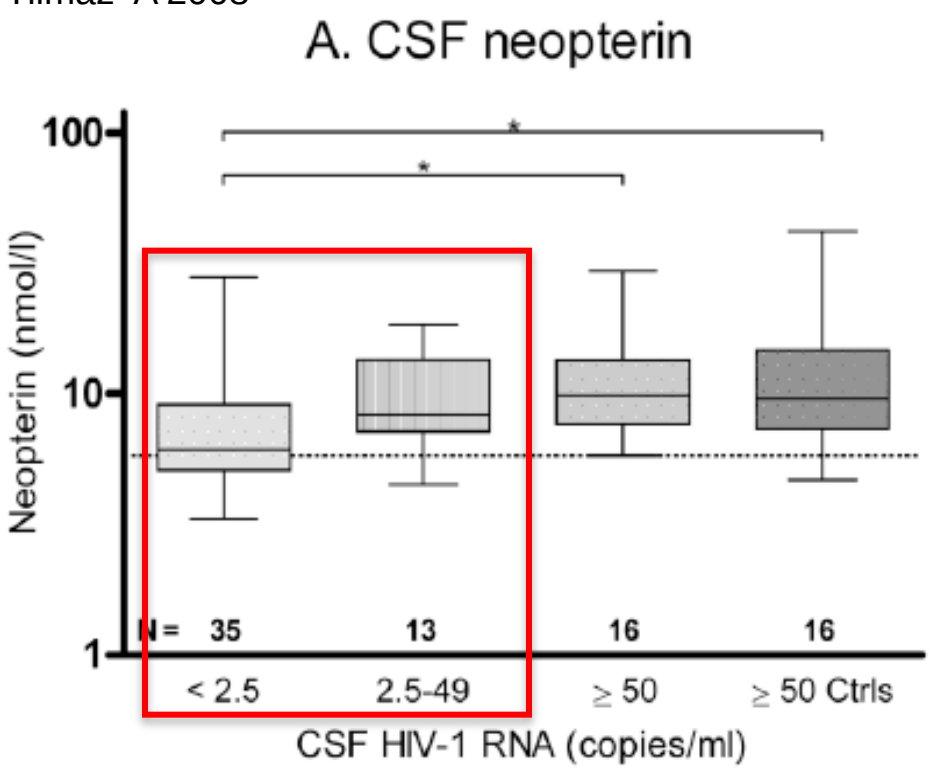
Residual viruses can initiate fresh cycles of infection and spread in host cells

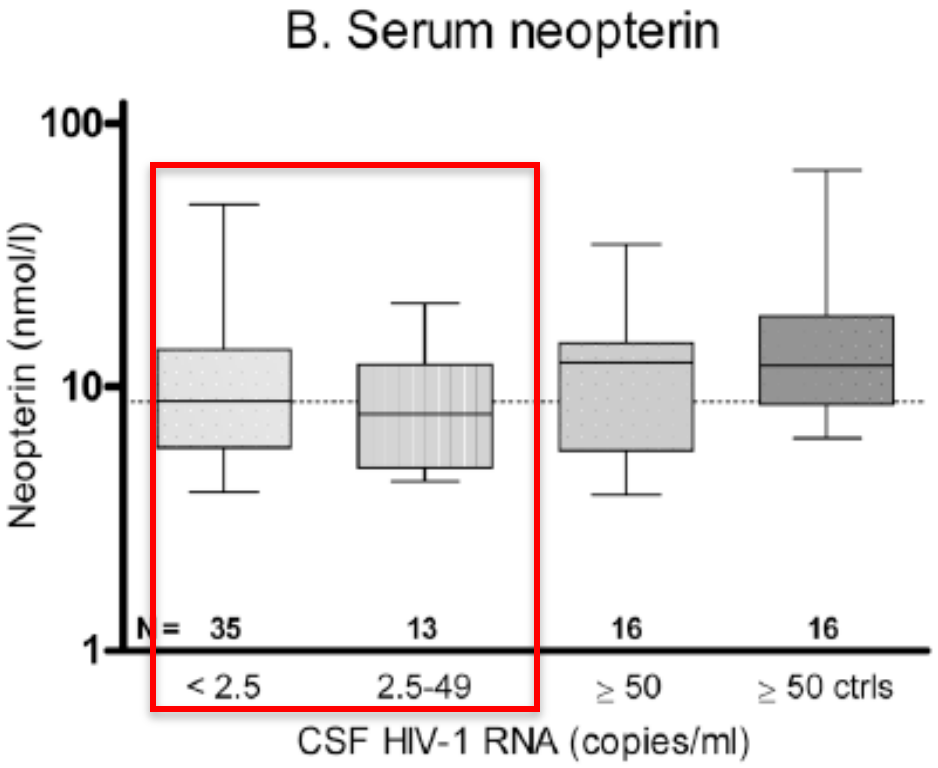
Cloning of the residual-virus genome



Persistent intrathecal immune activation in HIV-1-infected individuals on antiretroviral therapy

Yilmaz A 2008

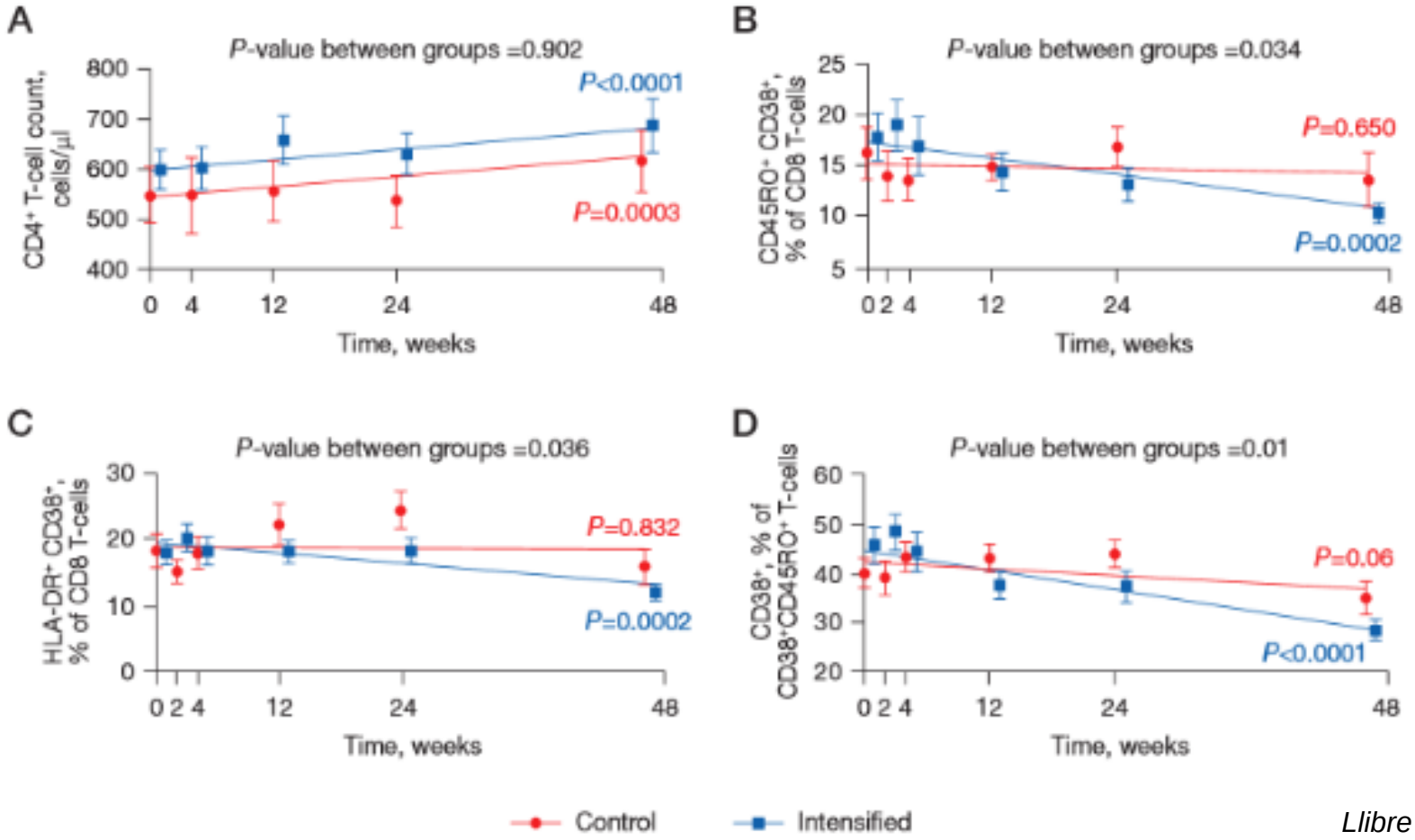




CSF and serum neopterin levels with different HIV-RNA levels during HAART

Treatment intensification with raltegravir in subjects with sustained HIV-1 viraemia suppression: a randomized 48-week study

Raltegravir intensification significantly reduced activation of $CD8^+$ T-cells at week 48 ($HLA\text{-}DR^+CD38^+$, P=0.005), especially in the memory compartment ($CD38^+$ of $CD8^+CD45R0^+$, P<0.001).



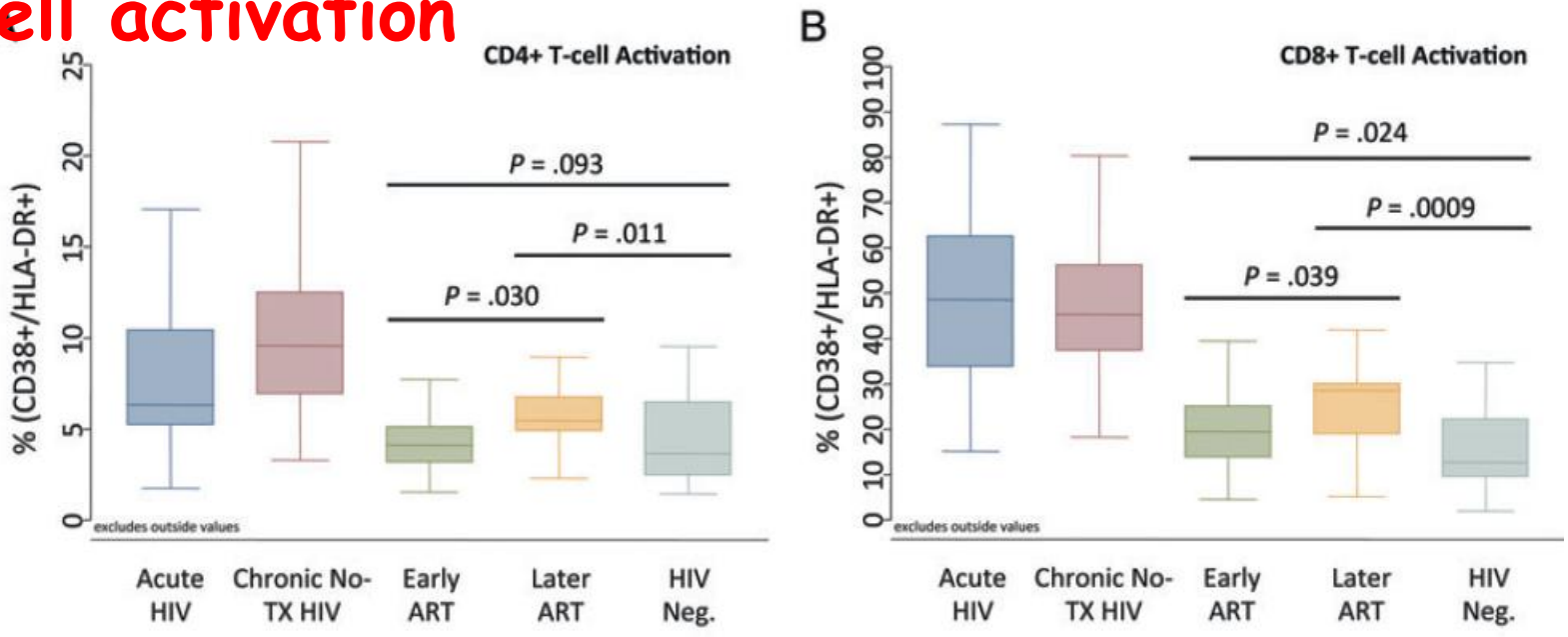
Llibre et al 2012

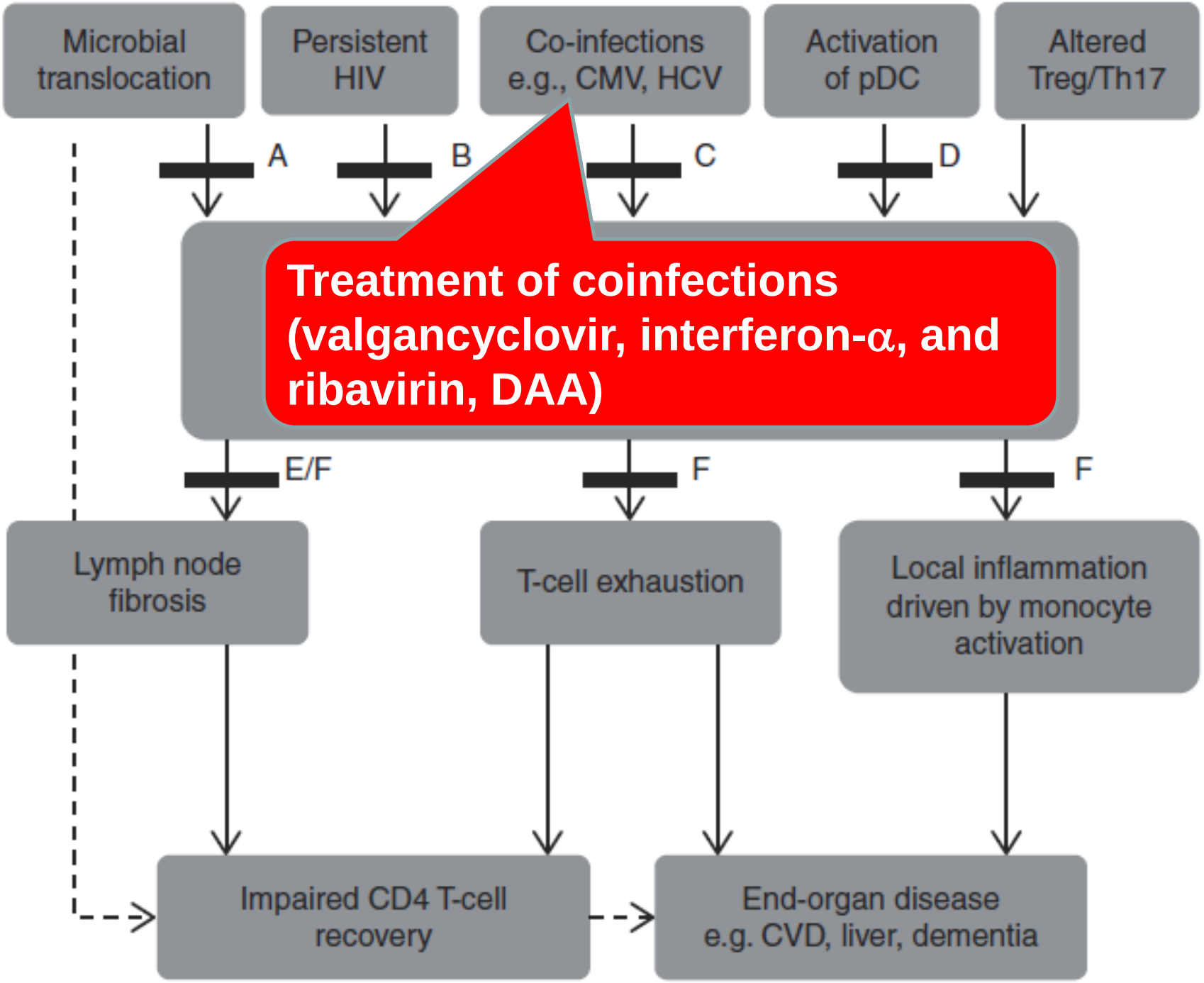
Antiretroviral Therapy Initiated Within 6 Months of HIV Infection Is Associated With Lower T-Cell Activation and Smaller HIV Reservoir Size

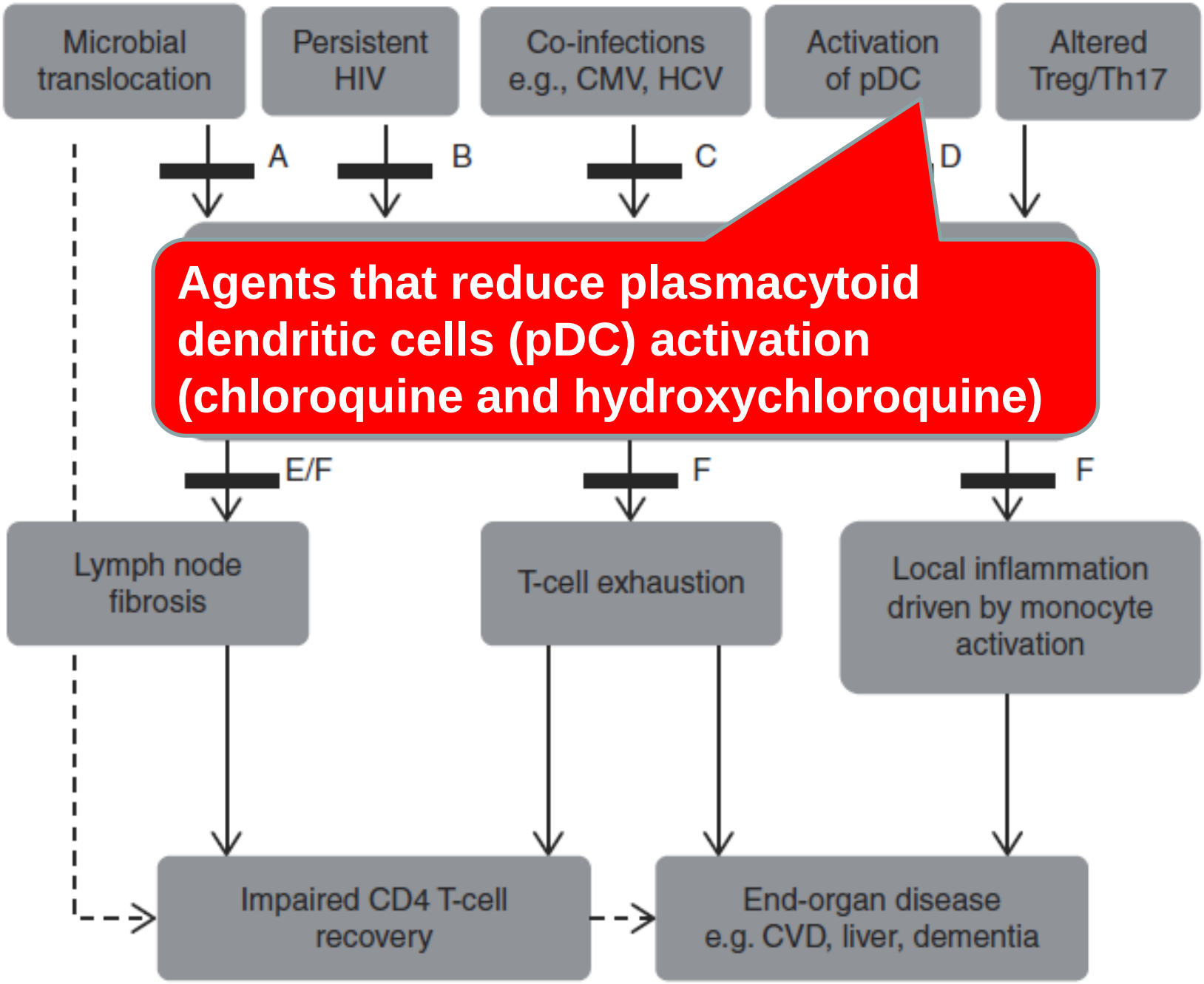
2013:208 (15 October) 1202

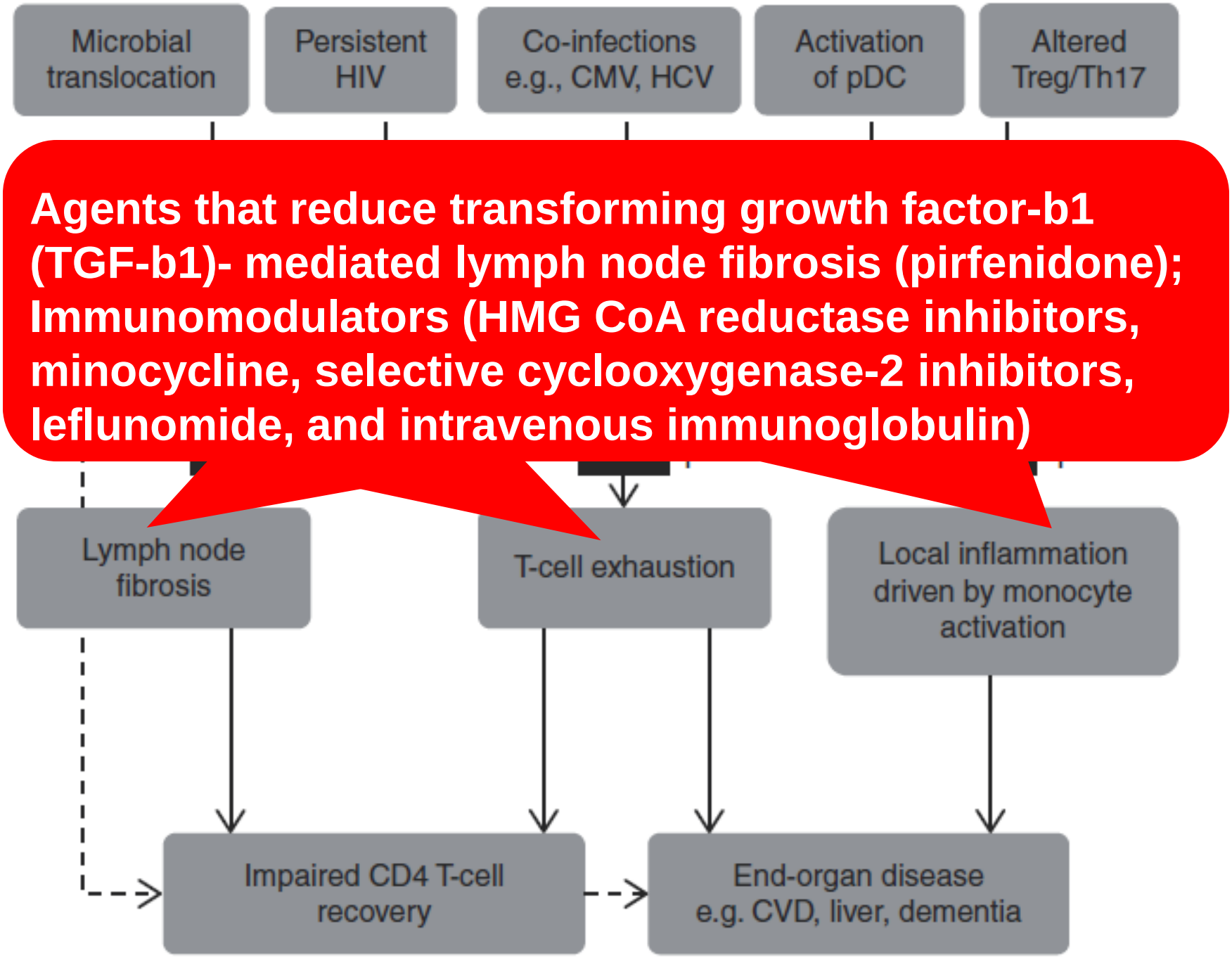
Vivek Jain,[1] Wendy Hartogensis,[1] Peter Bacchetti,[2] Peter W. Hunt,[1] Hiroyu Hatano,[1] Elizabeth Sinclair,[3] Lorrie Epling,[3] Tzong-Hae Lee,[4] Michael P. Busch,[4] Joseph M. McCune,[3] Christopher D. Pilcher,[1] Frederick M. Hecht,[1] and Steven G. Deeks[1]

ART initiation <6 months after infection is associated with lower levels of CD4+ and CD8+ T-cell activation

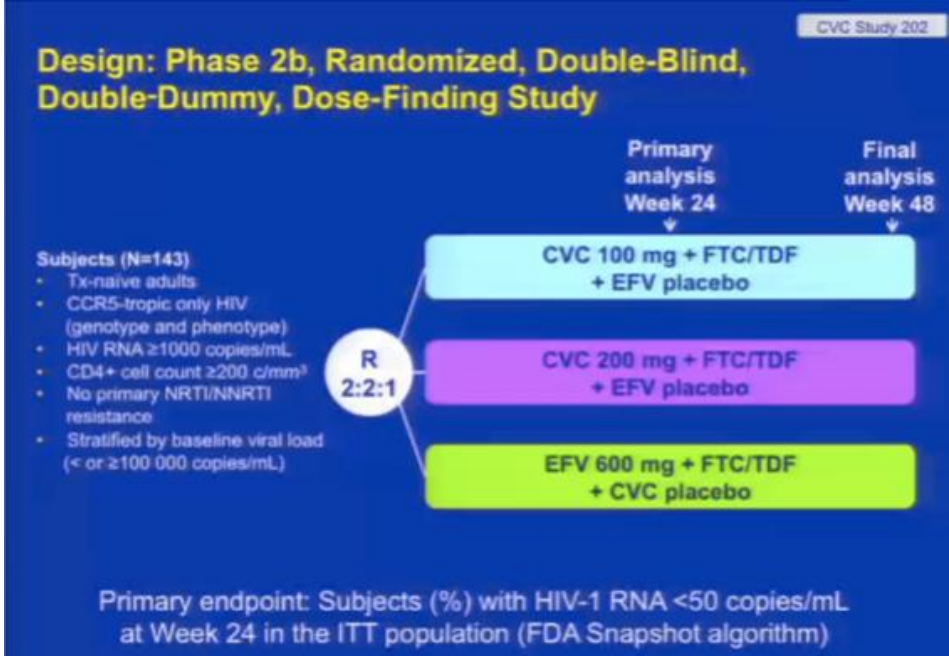


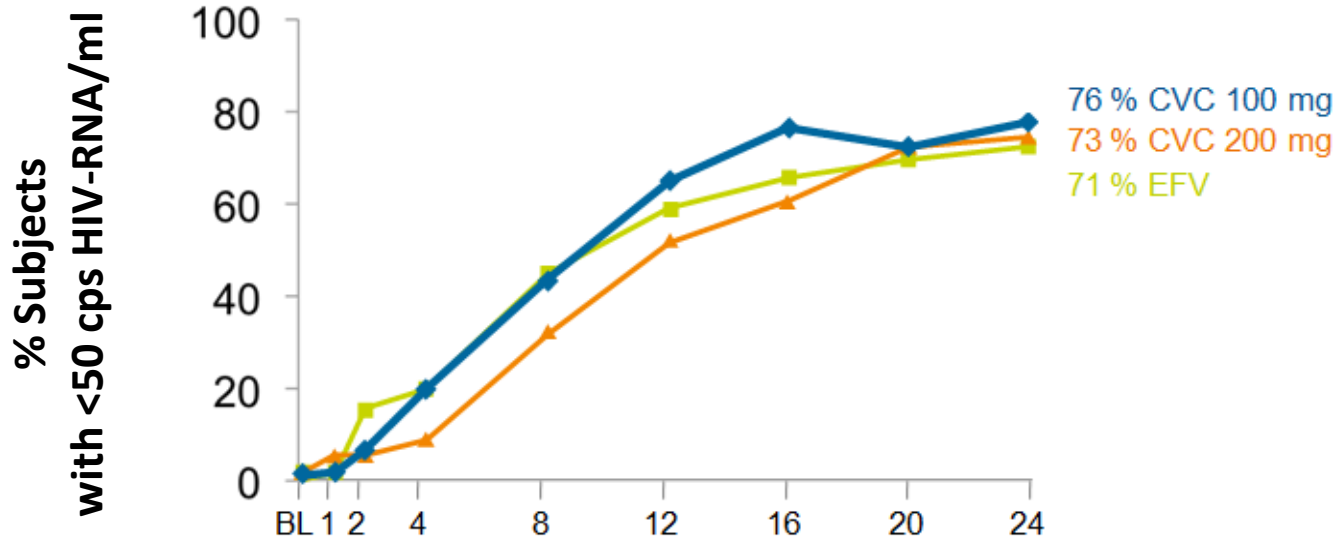

Microbial translocation
Persistent HIV
Co-infections e.g., CMV, HCV
Activation of pDC
Altered Treg/Th17
A
B
C
D
Treatment of coinfections (valgancyclovir, interferon-α, and ribavirin, DAA)
E/F
F
F
Lymph node fibrosis
T-cell exhaustion
Local inflammation driven by monocyte activation
Impaired CD4 T-cell recovery
End-organ disease e.g. CVD, liver, dementia


Microbial translocation
Persistent HIV
Co-infections e.g., CMV, HCV
Activation of pDC
Altered Treg/Th17
A
B
C
D
Agents that reduce plasmacytoid dendritic cells (pDC) activation (chloroquine and hydroxychloroquine)
E/F
F
F
Lymph node fibrosis
T-cell exhaustion
Local inflammation driven by monocyte activation
Impaired CD4 T-cell recovery
End-organ disease e.g. CVD, liver, dementia


Microbial translocation
Persistent HIV
Co-infections e.g., CMV, HCV
Activation of pDC
Altered Treg/Th17
Agents that reduce transforming growth factor-b1 (TGF-b1)- mediated lymph node fibrosis (pirfenidone); Immunomodulators (HMG CoA reductase inhibitors, minocycline, selective cyclooxygenase-2 inhibitors, leflunomide, and intravenous immunoglobulin)
Lymph node fibrosis
T-cell exhaustion
Local inflammation driven by monocyte activation
Impaired CD4 T-cell recovery
End-organ disease e.g. CVD, liver, dementia

Cenicriviroc vs EFV (both with TDF/FTC Phase 2 study

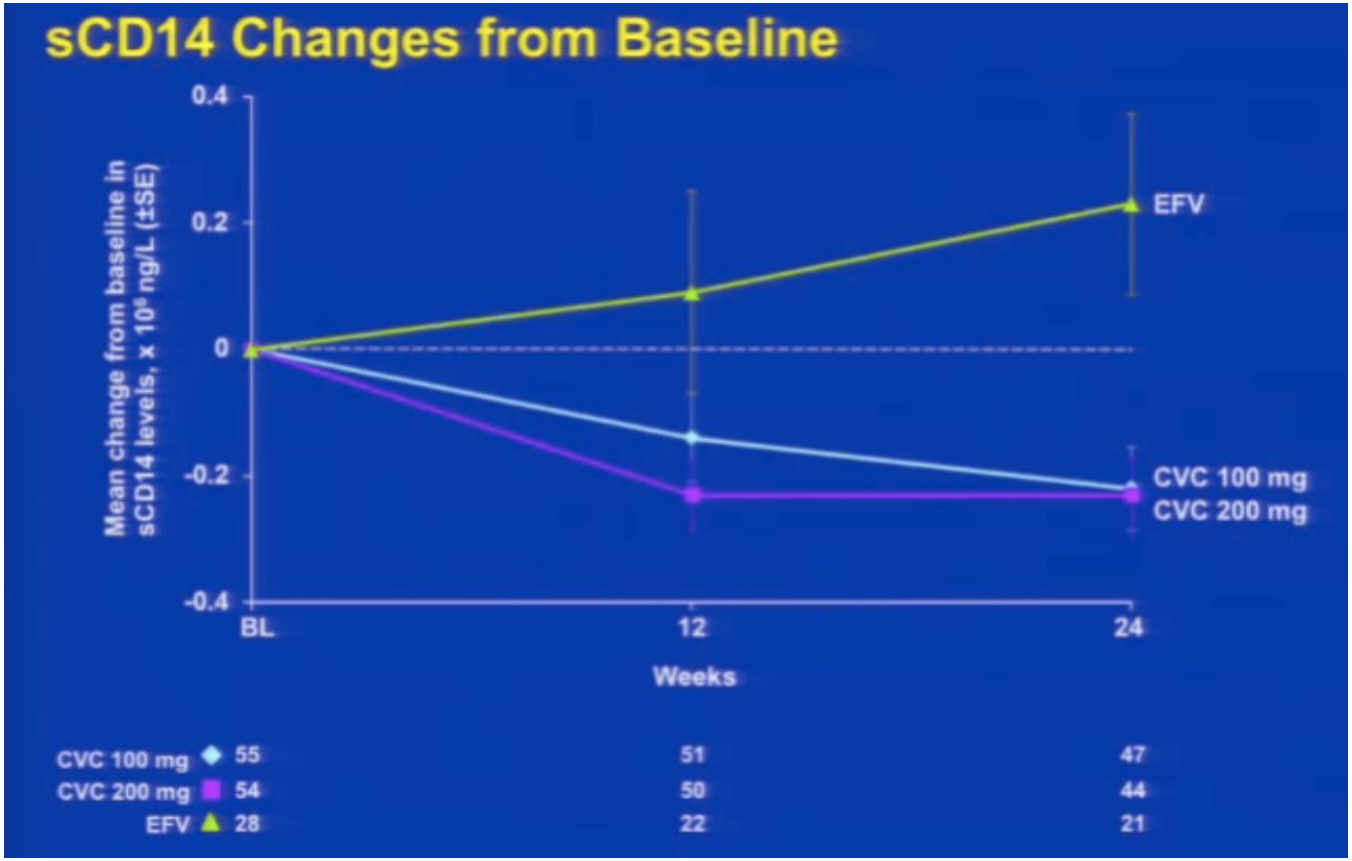




CVC 100 mg (n = 59)	0	3	11	25	37	44	42	45
CVC 200 mg (n = 56)	2	2	4	17	28	33	40	41
EFV (n = 28)	0	4	5	12	16	18	19	20

Cenicriviroc anti CCR5/CCR2

In the CVC groups lower level of soluble CD14 (marker of monocyte activation).



The activation of CCR2 on monocytes correlates with nephropathy, liver fibrosis, metabolic syndrome, cardiovascular disease

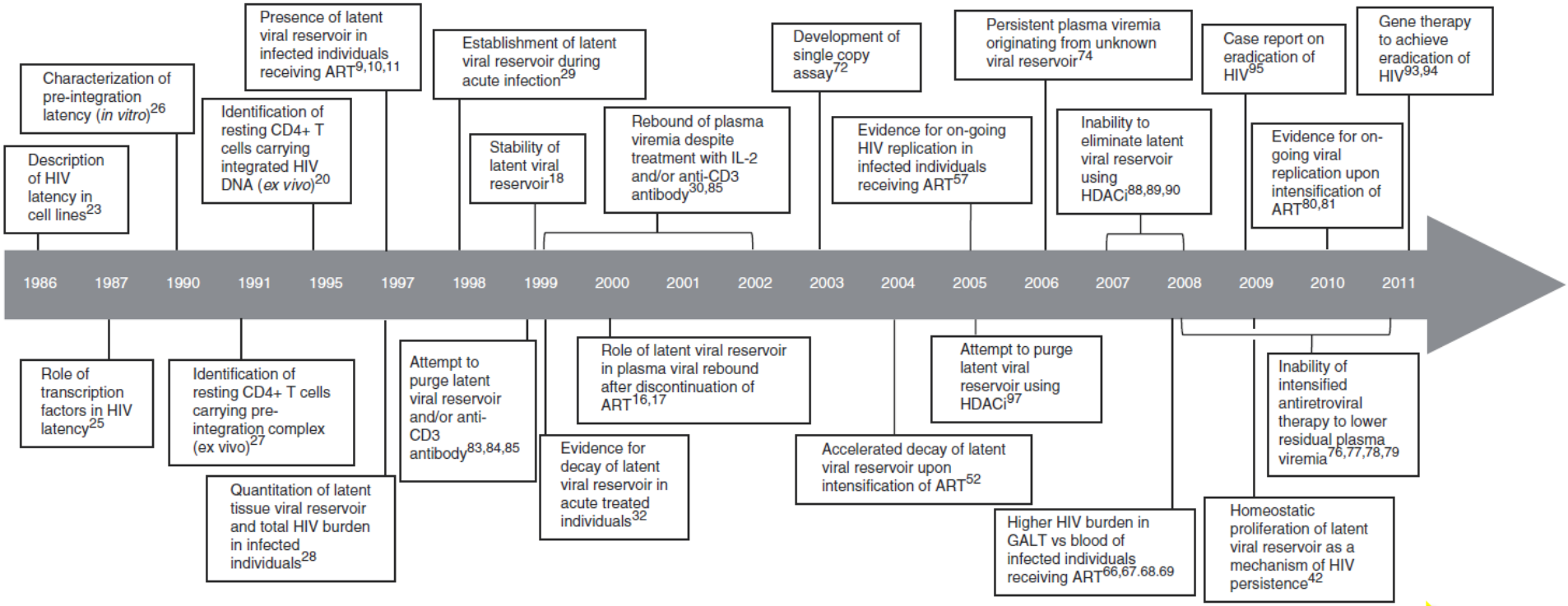
Problems in Chronic HIV Ttreatment

Diagnostica imunologica

Tabella 2 - Marcatori plasmatici di infiammazione/attivazione immune testati in studi caso-controllo e di coorte, relativo outcome clinico e referenze.

MARCATORE IMMUNOLOGICO	OUTCOME CLINICO	RACCOMANDAZIONE (FORZA/EVIDENZA)
Attivazione T-linfocitaria (CD4/CD45/CD8/CD38; CD8/CD38; CD8/CD38/HLA-DR) HIV-2: CD4/HLA-DR	Recupero CD4+, morte	[CII]
Neopterina, b2-microglobulina, PCR, IL-6, amiloide A e amiloide P, IgA, IL-10, sIL-2r, MCP-1, M-CSF, MMP-1, selectina-E, sICAM-1, TNF-a, TNF-b, TNF-R75	Mortalità per ogni causa	[CII]
Neopterina, b2-microglobulina, PCR, IL-6, amiloide A e amiloide P, IgA, IL-10, sIL-2r, MCP-1, M-CSF, MMP-2, GSH, APO-1/FAS, TNF-a, TNF-b, TNF-R75, TNF-R55	AIDS	[CII]
Neopterina, PCR, IL-6, sCD27, sCD40L, TNF-RI, TNF-RII, IFN-a, sCD14, LPS	AIDS o morte	[CII]
Mieloperossidasi, sCD14	Eventi cardiovascolari	[CII]

Highlights of research on basic and clinical aspects of HIV reservoirs conducted over the past two decades.



HIV-RNA HIV-DNA replication-competent virus

Tae-Wook Chun and Anthony S. Fauci. AIDS 2012, 26:*1261–1268*

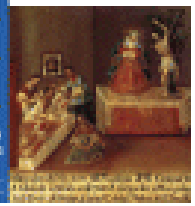
Diagnostica virologica

Recenti studi hanno evidenziato una correlazione tra la quantità di HIV-DNA provirale e la viremia residua in pazienti trattati con cART e in successo terapeutico [63]. I livelli al baseline di HIV-DNA sono anche associati al raggiungimento di livelli non rilevabili sia di HIV-RNA (viremia plasmatica) che di HIV-DNA in pazienti naïve che iniziavano un cART [64]. Infine, esiste una correlazione livelli di HIV-DNA e rischio di fallimento virologico in pazienti che hanno semplificato la terapia [65]. Mancano consistenti dati da studi longitudinali che permettano di considerare l'HIV-DNA un marcatore surrogato nella pratica clinica.

Tabella 13 – Determinazione quantitativa dell'HIV-DNA provirale e suo utilizzo nella pratica clinica.

IMPIEGO	RACCOMANDAZIONE (FORZA/EVIDENZA)
Il test per l'HIV-DNA provirale dovrebbe essere effettuato in laboratori specializzati.	[BII]
L'uso di tale marcatore può essere preso in considerazione in situazioni terapeutiche particolari (monitoraggio dell'efficacia del trattamento, valutazione del paziente candidato alla semplificazioni della terapia, ecc.).	[CIII]

Clinical Infectious Diseases



2010

Plasma HIV-1 RNA Detection Below 50 Copies/mL and Risk of Virologic Rebound in Patients Receiving Highly Active Antiretroviral Therapy

Tomas Doyle,[1,3] Colette Smith,[4] Paola Vitiello,[3] Valentina Cambiano,[4] Margaret Johnson,[2,5] Andrew Owen,[6] Andrew N. Phillips,[4] and Anna Maria Geretti[1,3,7]

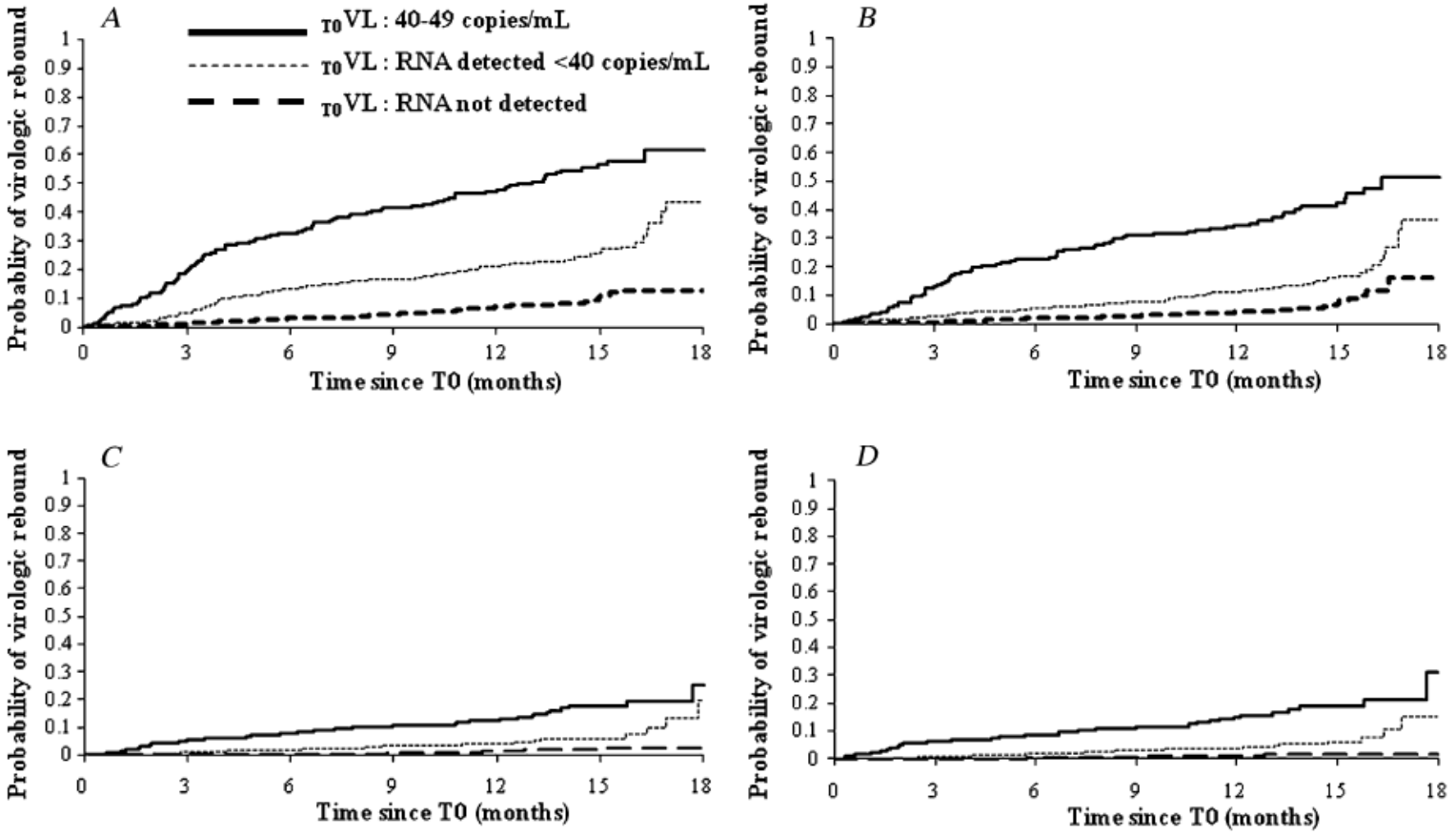


Figure 1. Time to virologic rebound according to the T0 viral load (VL) and 4 definitions (*A–D*) of rebound. *A*, Single viral load >50 copies/mL. *B*, confirmed or last available viral load >50 copies/mL. *C*, confirmed or last available viral load >400 copies/mL. *D*, confirmed or last available viral load >400 copies/mL or single viral load >400 copies/mL followed by a treatment change. Whole population (*A–C*); Royal Free Hospital population (*D*). $P < .0001$ for all analyses (log rank test). Abbreviation: T0, time zero (arbitrarily selected time point during highly active antiretroviral therapy).

Exploratory "Target Not Detected" analysis for efficacy of first-line ART (studies 102-103)

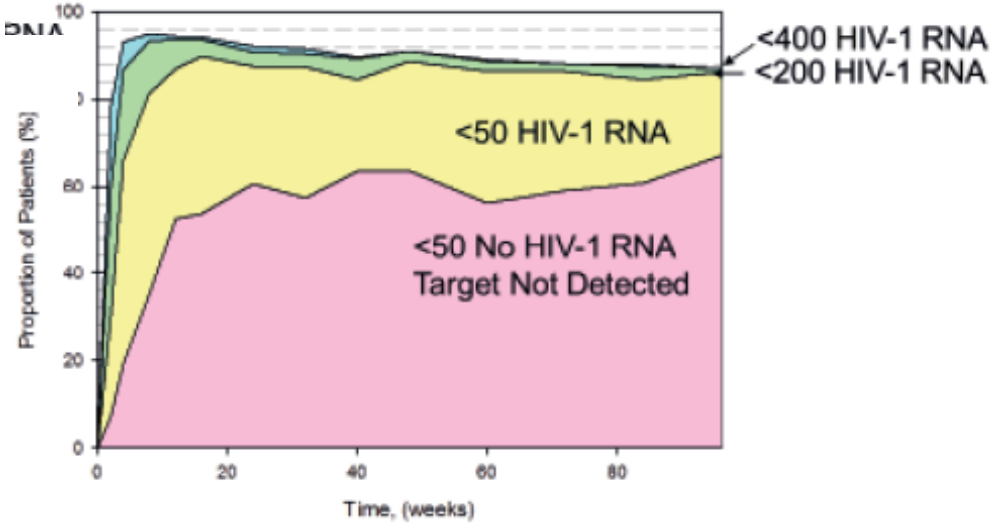
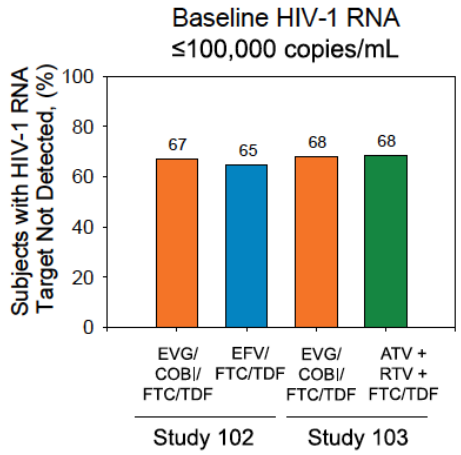


Figure 3. Frequency of HIV-1 RNA Target Not Detected at Week 144 by Baseline Viral Load (By Treatment Group)

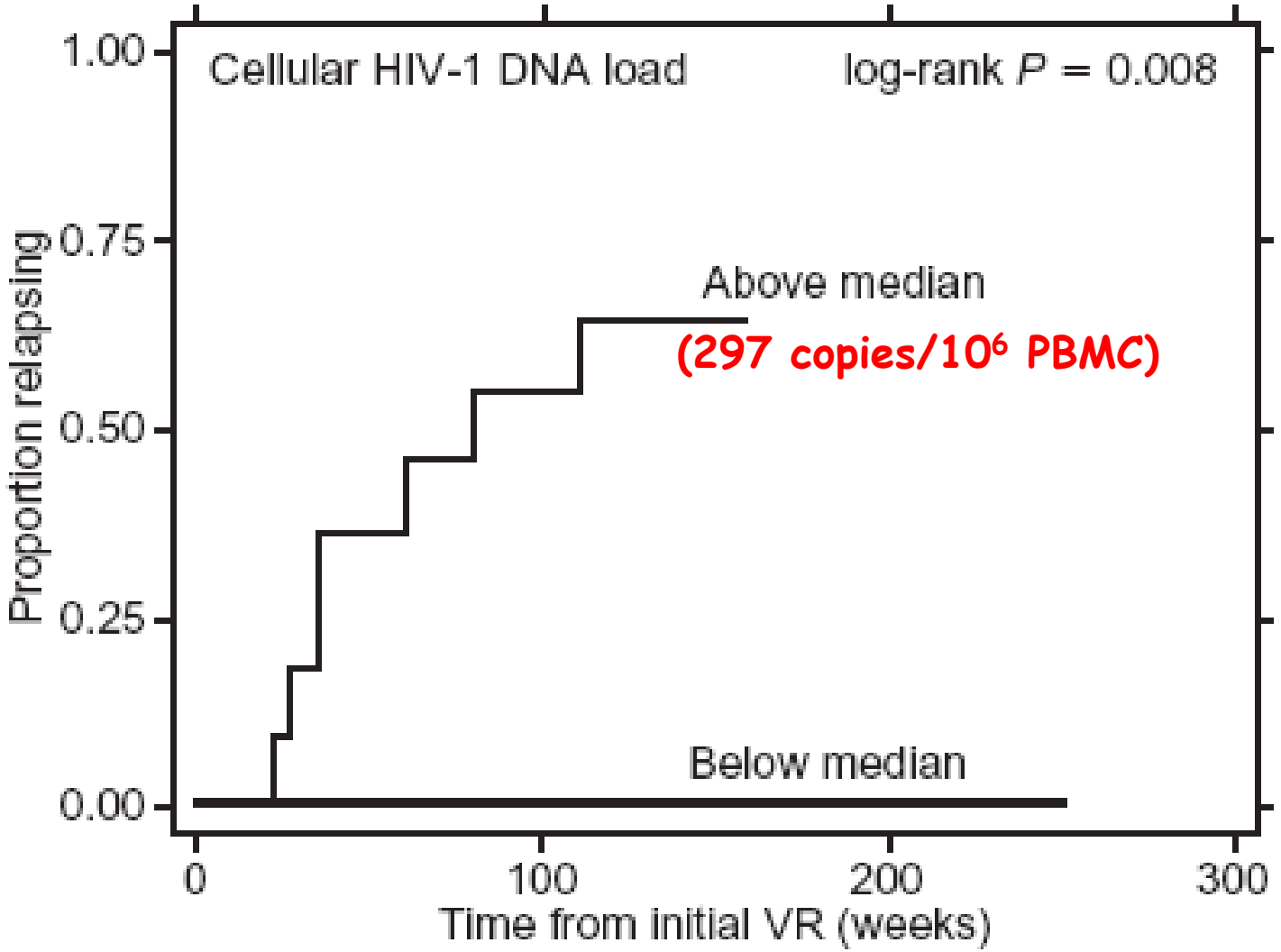


By Week 48 through Week 144, the proportion of subjects with HIV-1 RNA Target Not Detected was similar between treatment groups.

Achieving HIV-1 Target Not Detected was associated with lower HIV-1 RNA at baseline and drug adherence ≥ 95%.

White KL, et al. CROI 2014, Boston (MA). Abst.#546

Cellular HIV-1 DNA load predicts HIV-RNA rebound and the outcome of highly active antiretroviral therapy



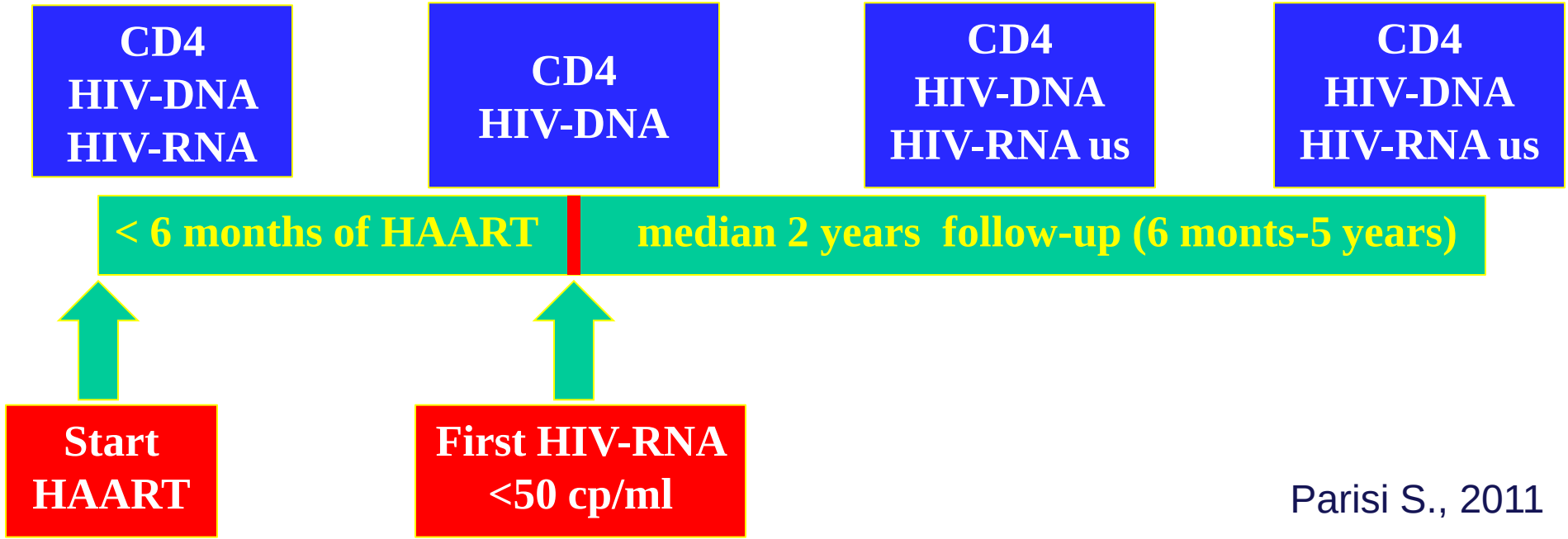
A. Hatzakis, AIDS 2004, 18:2261-2267

JCM
Journals.ASM.org

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

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

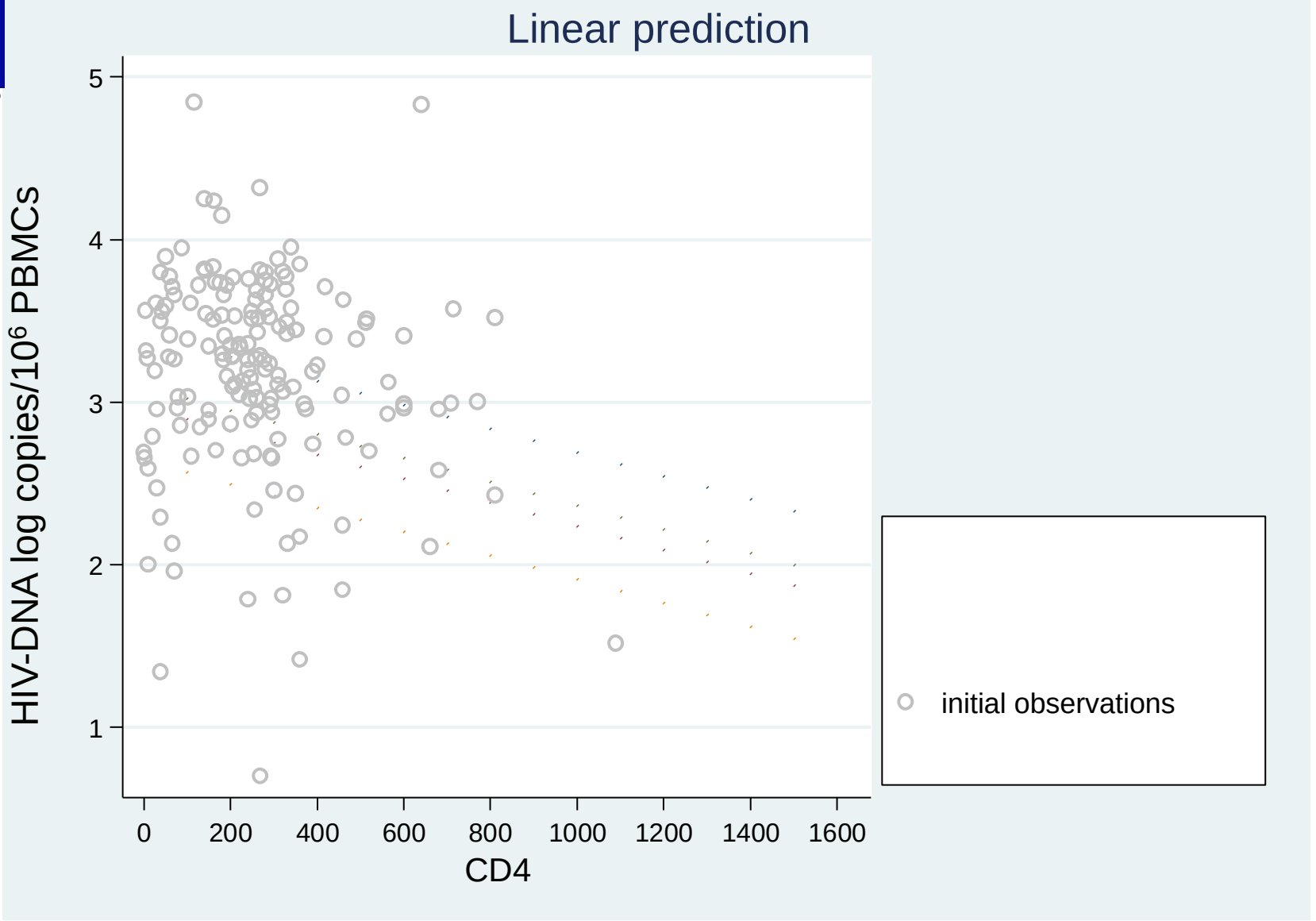
180 ART-naïve patients achieved virological suppression <50 copies/ml with their first line therapy within 6 mo, and maintained always undetectable plasma viremia, with no more than one viral blip.



Parisi S., 2011

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

Parisi S. 2012

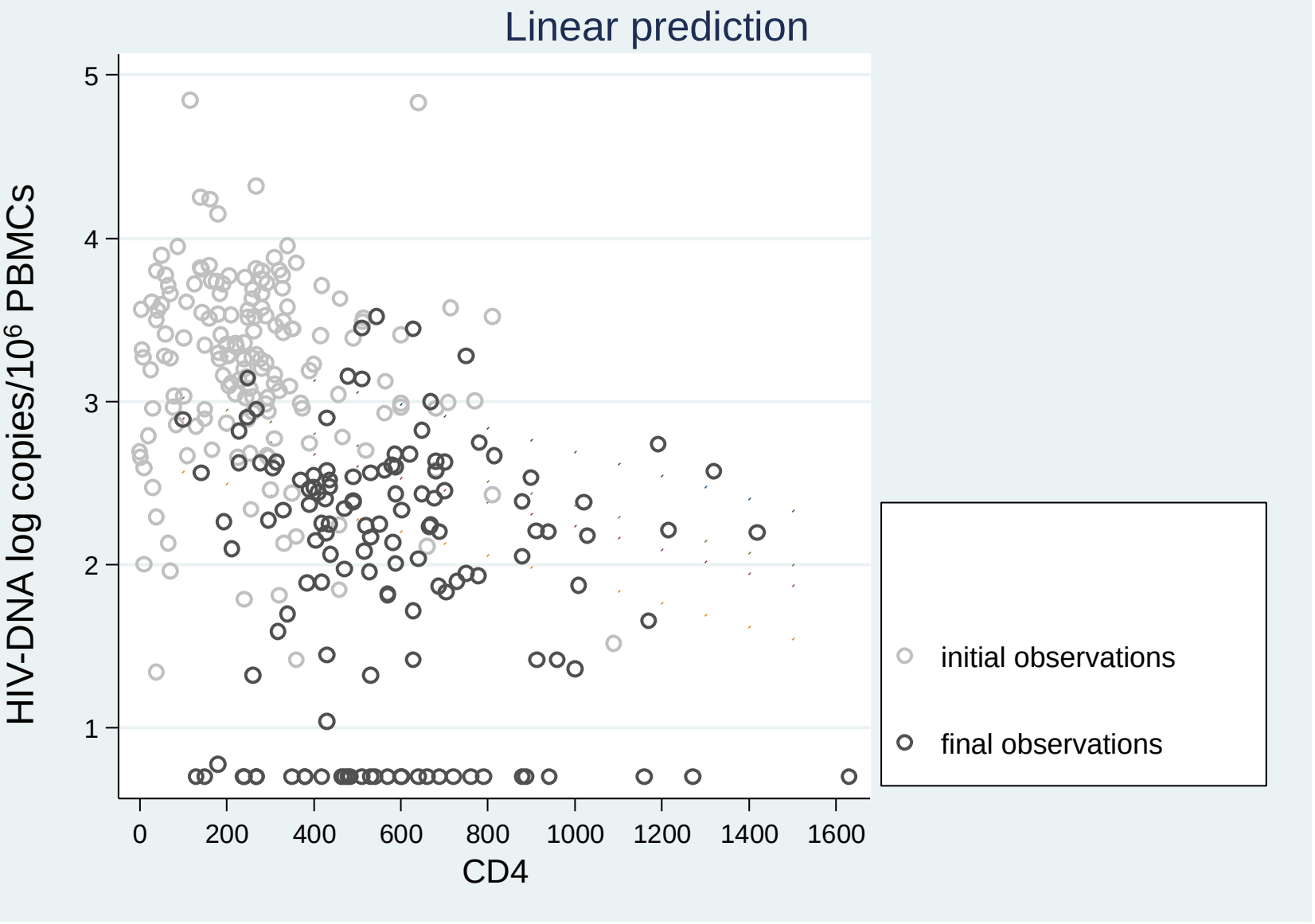


Time 0 = after 6 months of ART; Time 1= follow up

JOURNAL OF Clinical Microbiology JCM

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

Parisi S. 2012

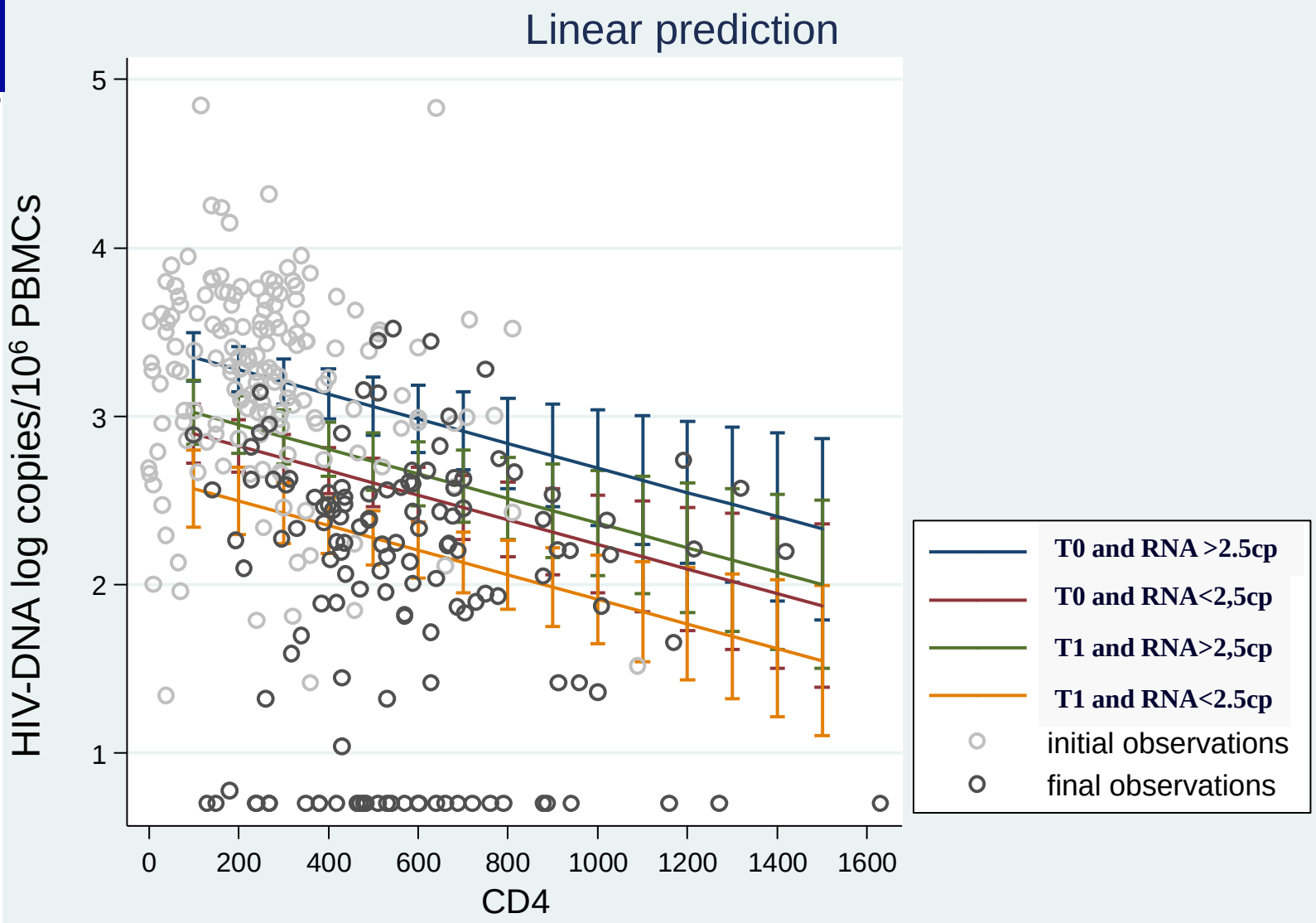


Time 0 = after 6 months of ART; Time 1= follow up

JOURNAL OF Clinical Microbiology JCM

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

Parisi S. 2012



Time 0 = after 6 months of ART; Time 1= follow up

Parisi 2012

In conclusion, early treatment facilitated the achievement of undetectable levels of plasma viremia and cellular HIV DNA and a better recovery of CD4 lymphocytes.

TABLE 1 Patient characteristics[a]

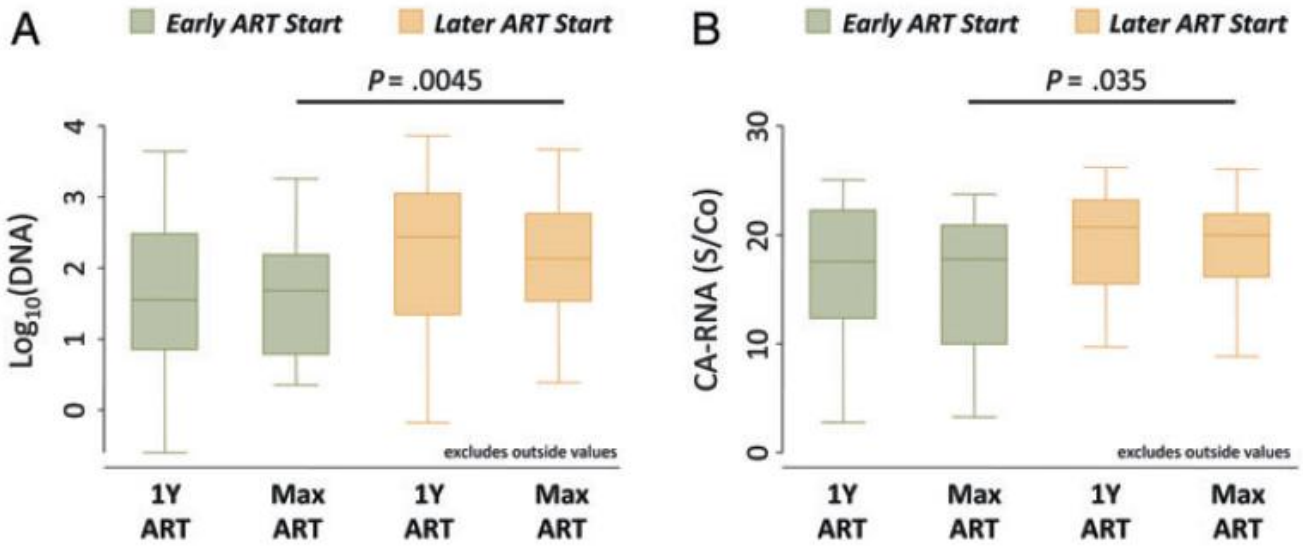
Parameter	Value for patient group			
	HIV RNA at <2.5 copies/ml	HIV RNA at 2.5–20 copies/ml	HIV RNA at 21–49 copies/ml	HIV RNA at 50–1,000 copies/ml
No. (%) of patients				
Total	73 (40.5)	49 (27.2)	25 (13.9)	31 (17.2)
Patients with primary infection	16 (22)	1 (2)	2 (8)	2 (6.4)
CD4 count (cells/mm^3)				
Baseline	296 (0–1,090)	240 (10–390)	181 (6–770)	230 (0–680)
Follow-up	571 (150–1,418)	490 (270–941)	436 (130–1,430)	520 (100–1,170)
% CD4 cells				
Baseline	16 (0–42)	14 (0–29)	11 (2–38)	17.5 (0–33)
Follow-up	30.7 (6–51)	28 (13–44)	22 (5–46)	30 (6–51)
Cellular HIV DNA level ($\log_{10}$ copies/10^6 PBMCs)				
Baseline	3.09 (1.34–4.84)	3.28 (1.78–3.94)	3.32 (1.96–3.80)	3.51 (2.69–4.82)
Follow-up	1.41 (<0.69–2.89)	2.40 (<0.69–3.52)	1.77 (<0.69–3.15)	2.38 (<0.695–1.91)
No. (%) of subjects reaching DNA level of <5 copies/10^6 PBMCs	27 (37)	7 (14.3)	3 (12)	2 (6.4)
No. (%) of subjects taking PIs	24 (33)	21 (42.8)	15 (60)	17 (54.8)
Length (yr) of follow-up	2 (0.5–5)	1 (0.5–4)	2 (0.5–4)	1 (0.5–5)

Antiretroviral Therapy Initiated Within 6 Months of HIV Infection Is Associated With Lower T-Cell Activation and Smaller HIV Reservoir Size

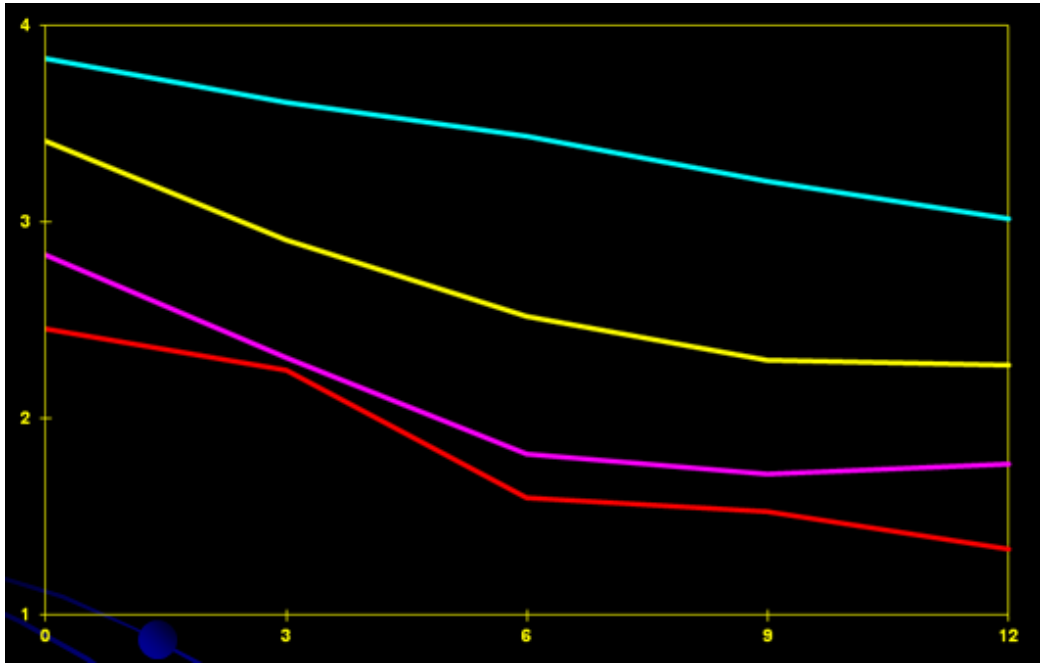
2013:208 (15 October) 1202-11

Vivek Jain,[1] Wendy Hartogensis,[1] Peter Bacchetti,[2] Peter W. Hunt,[1] Hiroyu Hatano,[1] Elizabeth Sinclair,[3] Lorrie Epling,[3] Tzong-Hae Lee,[4] Michael P. Busch,[4] Joseph M. McCune,[3] Christopher D. Pilcher,[1] Frederick M. Hecht,[1] and Steven G. Deeks[1]

ART initiation <6 months after infection is associated with lower levels HIV-DNA and cell-associated RNA levels



Cellular proviral HIV-DNA decline and viral isolation in naive subjects with <5000 copies/ml HIV-RNA and >500x10^6/l CD4 cells treated with highly active antiretroviral therapy



	HIV-DNA $t_{1/2}$ (weeks)	Infectious virus N°Patients/total
	41.1	3/5 (60%)
	28.7	5/9 (55%)
	30.6	4/9 (44%)
	28.1	4/11 (36%)

Base line values

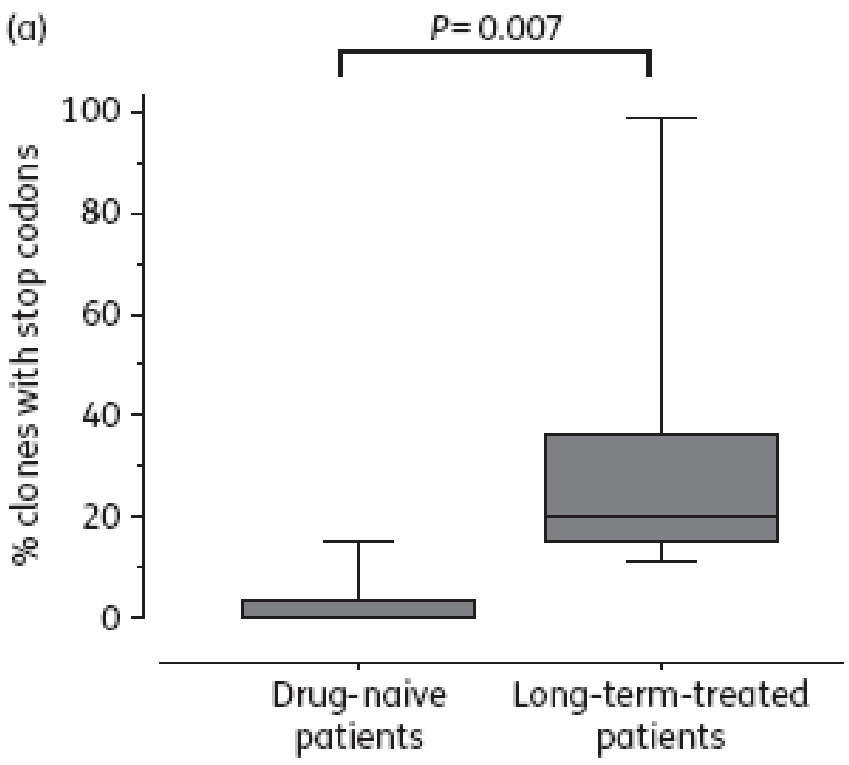
- 5 subjects HIV-RNA >5000 CD4 <300
- 9 subjects HIV-RNA >5000 CD4 300-500
- 9 subjects HIV-RNA >5000 CD4 >500
- 11 subjects HIV-RNA <5000 CD4 >500

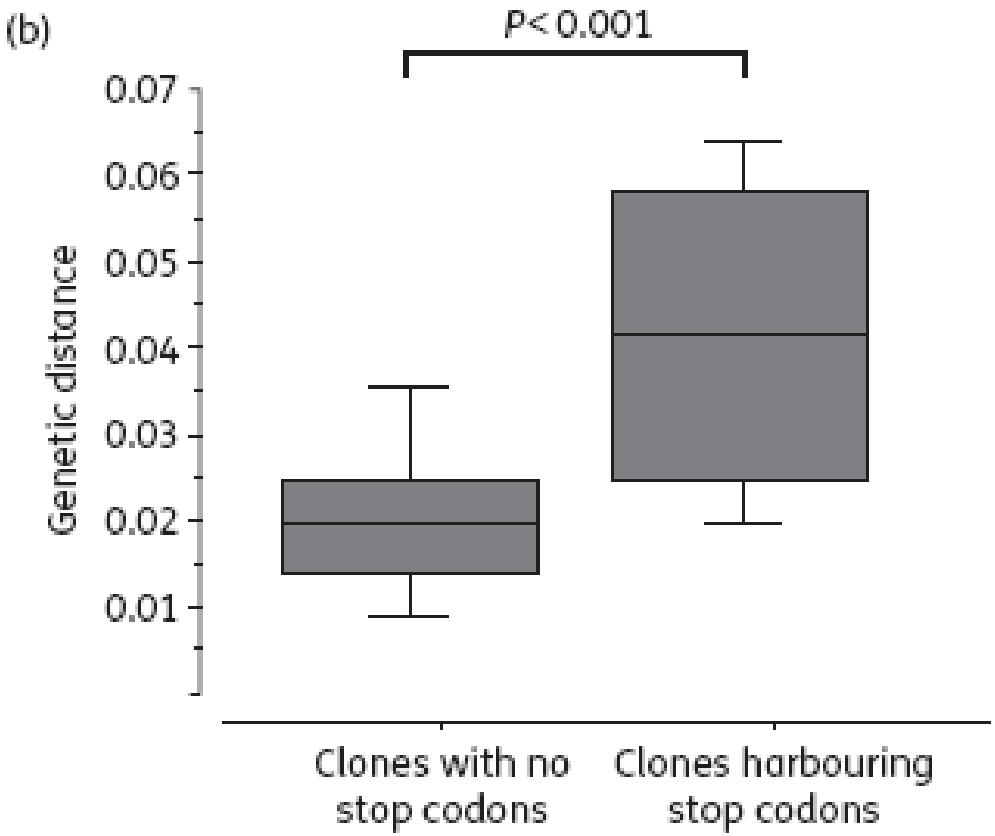
Andreoni M, 2000,14:23-29

2012

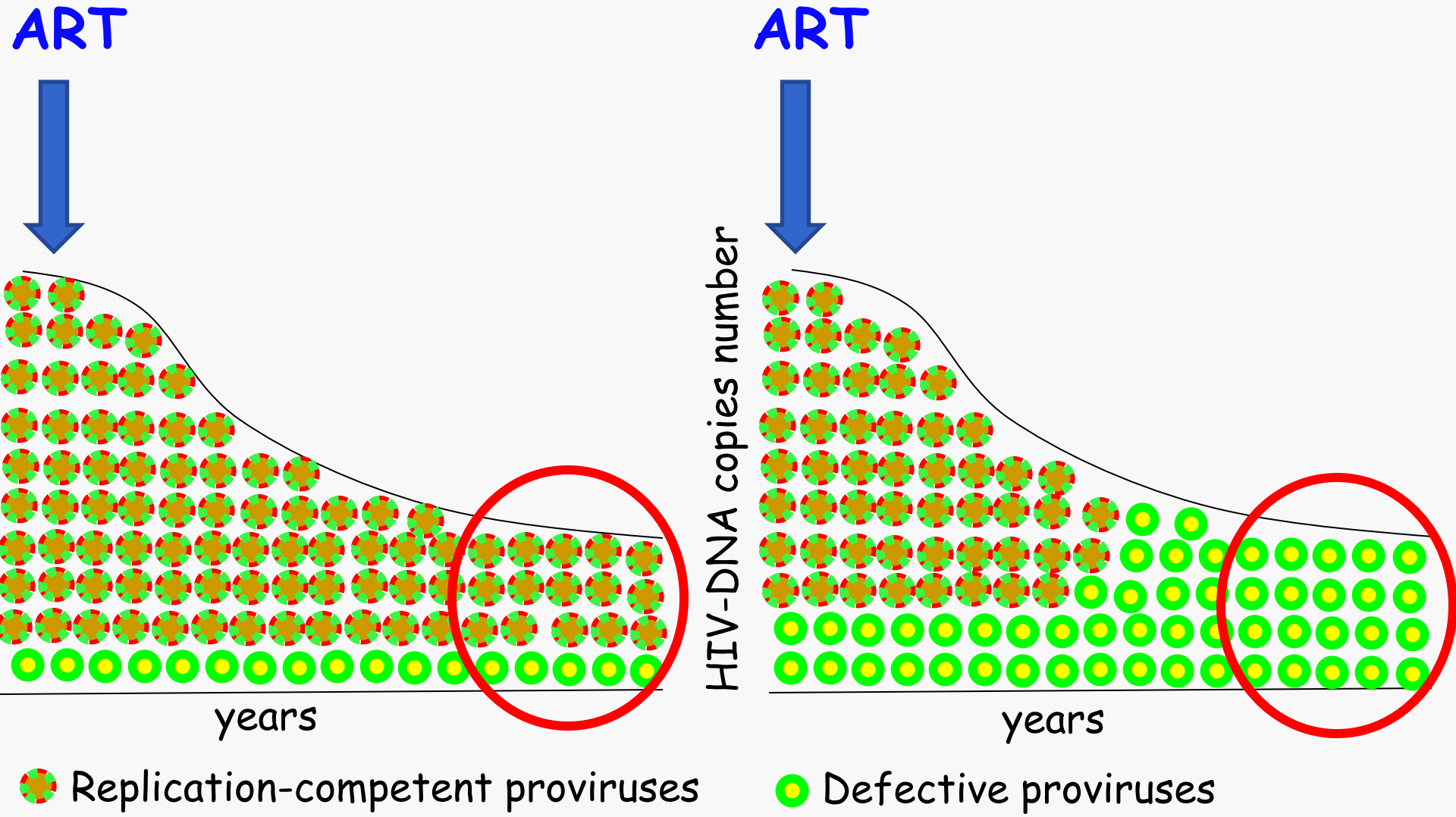
HIV-1 genome is often defective in PBMCs and rectal tissues after long-term HAART as a result of APOBEC3 editing and correlates with the size of reservoirs

Slim Fourati[1–3]*, Sidonie Lambert-Niclot[1–3], Cathia Soulie[1–3], Isabelle Malet[1–3], Marc Antoine Valantin[1,2,4], Benjamin Descours[1,5,6], Zaina Ait-Arkoub[1–3], Benoit Mory[7], Guislaine Carcelain[1,5,6], Christine Katlama[1,2,4], Vincent Calvez[1–3] and Anne Geneviève Marcelin[1–3]

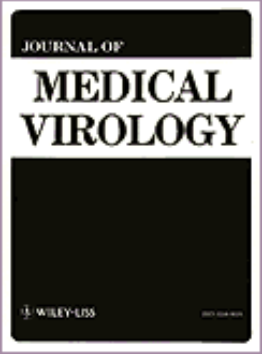




Patients with equal HIV-DNA copies number but different probability of plasma viremia rebound at cessation or simplification of ART



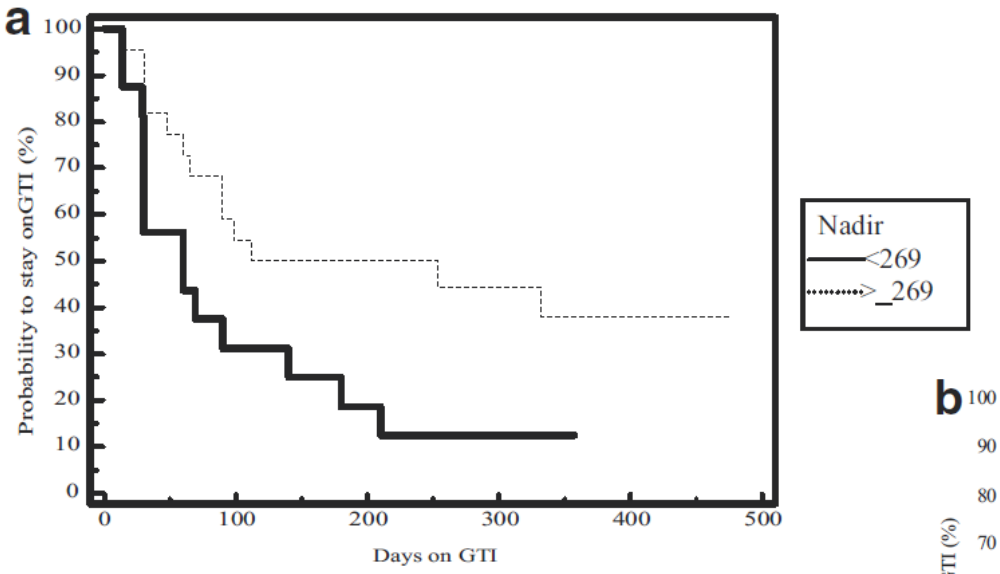
Andreoni 05 2013



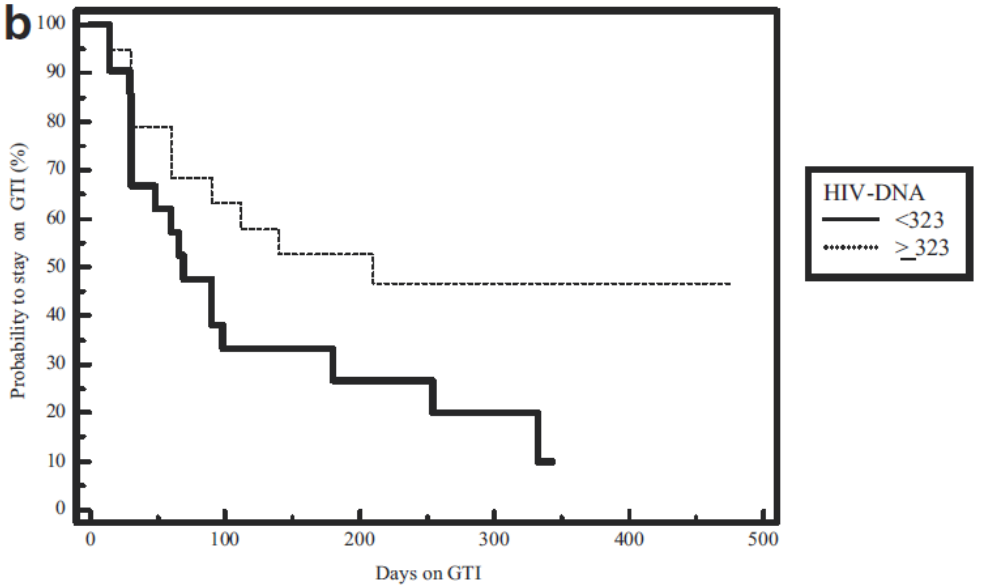
2009

Prognostic Factors of Long-Term CD4+ Count-Guided Interruption of Antiretroviral Treatment

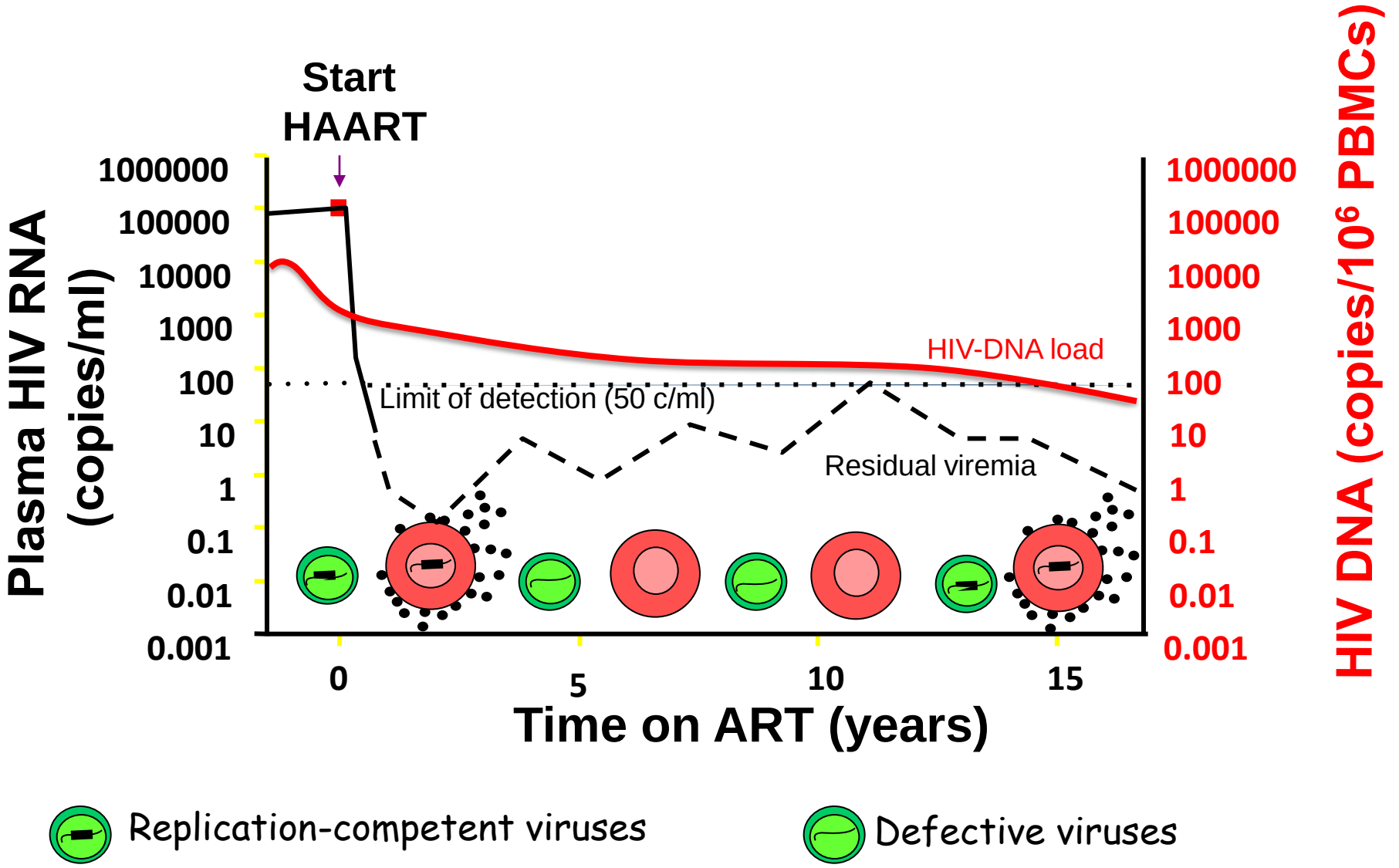
L. Sarmati,[1] C. Andreoni,[2] E. Nicastri,[3] C. Tommasi,[1] A. Buonomini,[1] G. D'Ettorre,[2] A. Corpolongo,[3] L. Dori,[1] M. Montano,[1] A. Volpi,[1] P. Narciso,[3] V. Vullo,[2] and M. Andreoni[1]*



15 Patients with more than 180 days of treatment interruption



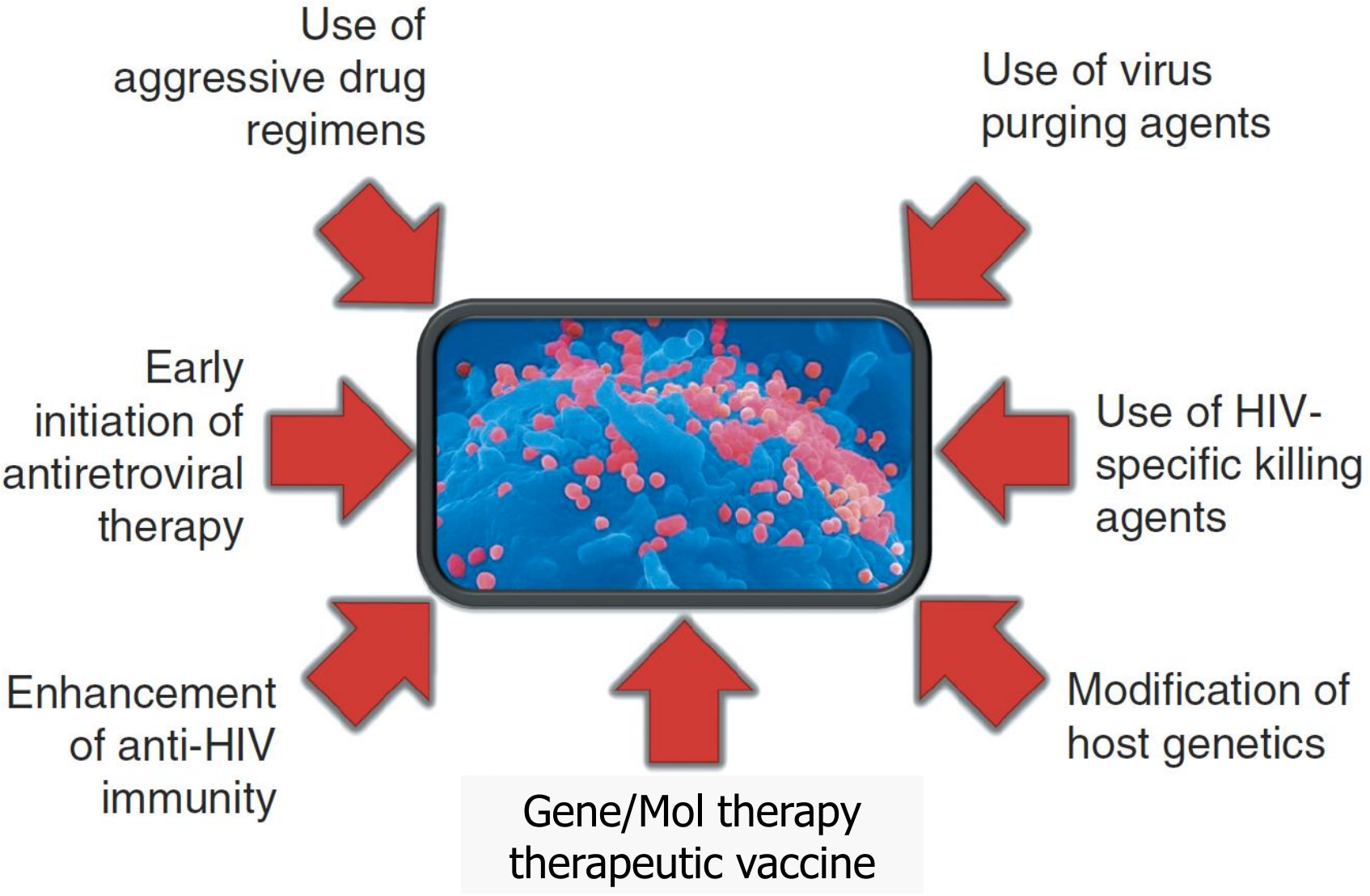
Months of current therapy p=0.01



Andreoni settembre 2014

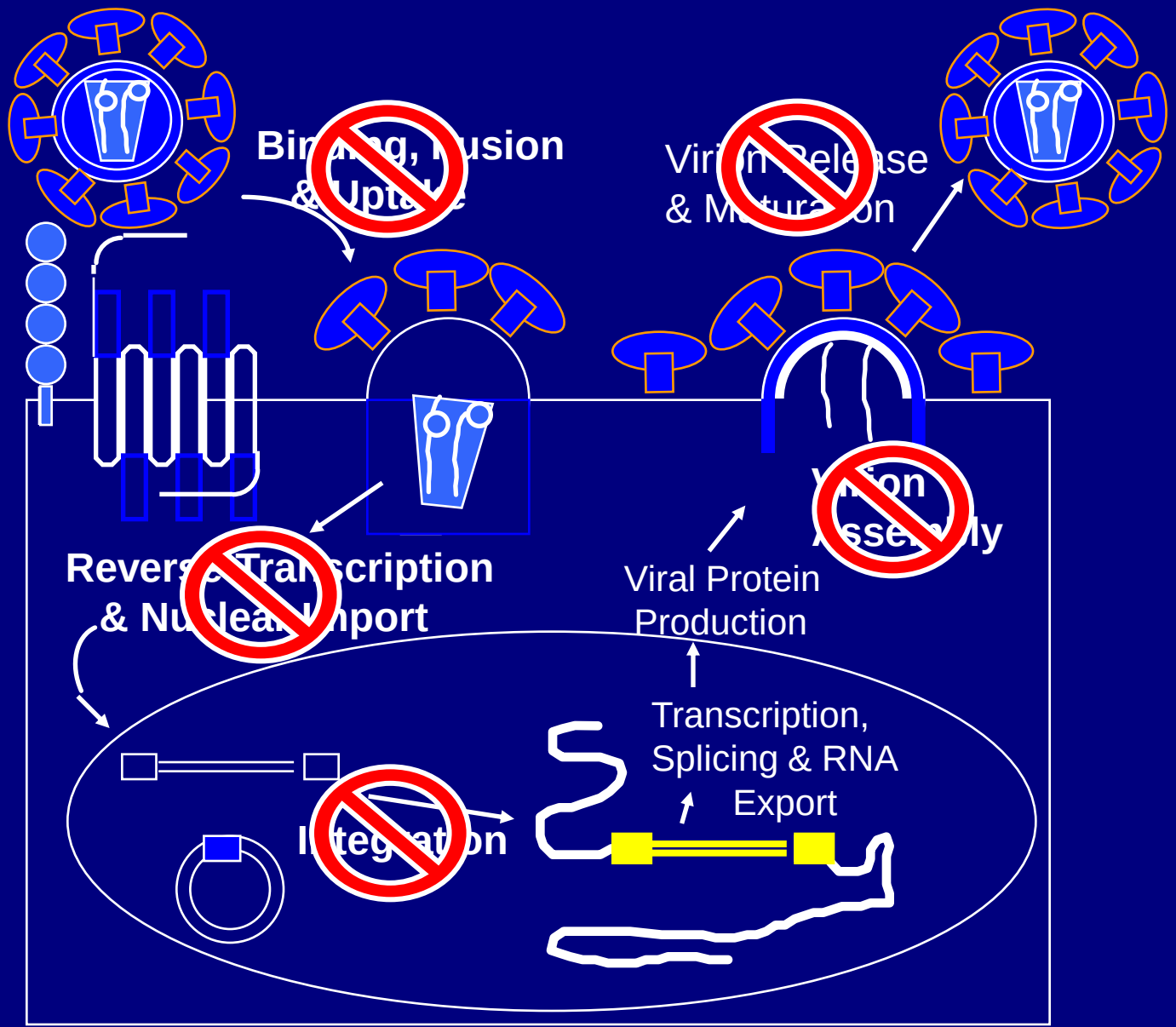
Problems in Chronic HIV Treatment

Potential strategies for eradicating HIV in infected individuals receiving ART



Tae-Wook Chun and Anthony S. Fauci. AIDS 2012, *Modified*

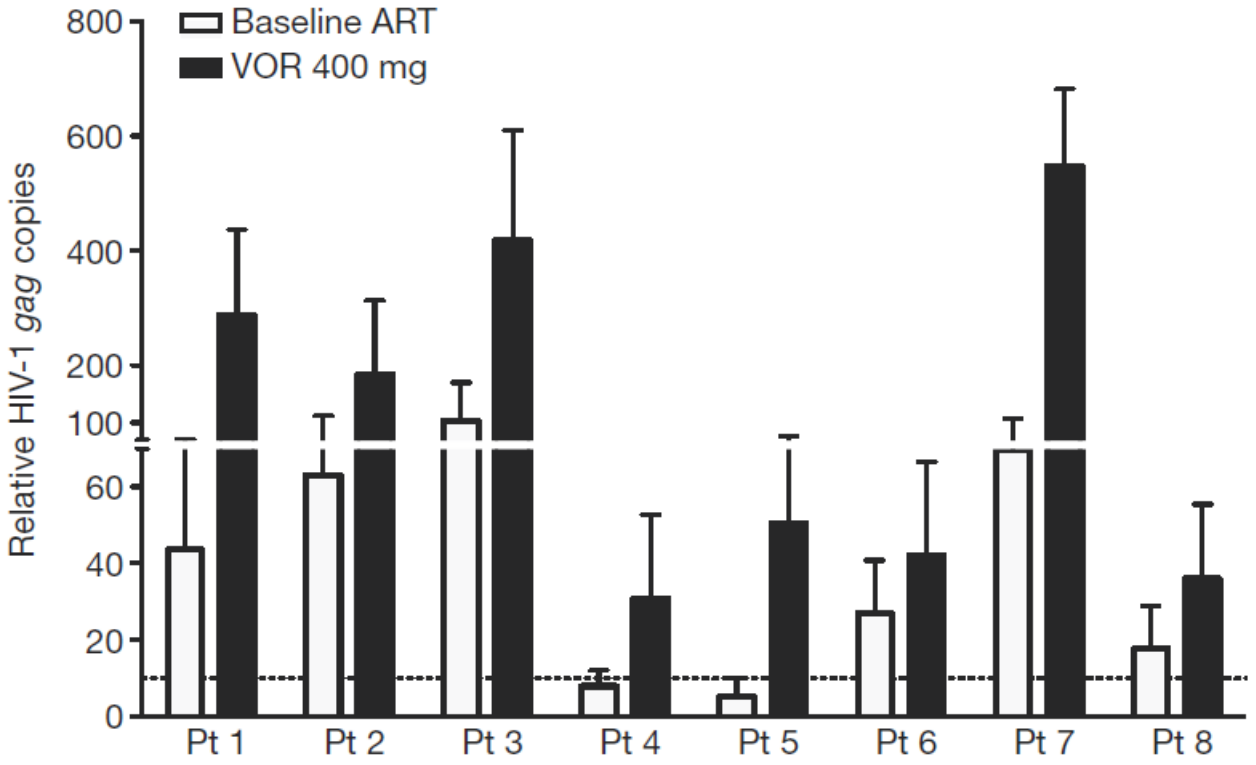
Many therapies for replicating HIV
None for persistent HIV genomes



Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

Archin N 2012

VOR induced an increase in HIV RNA expression in resting CD41 cells (mean increase, 4.8-fold).



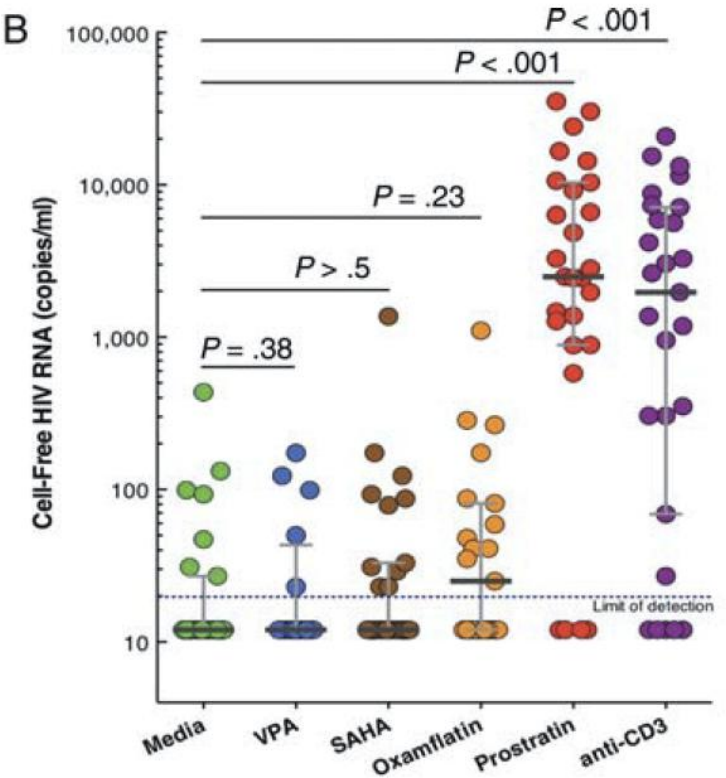
VOR upregulates HIV RNA expression. The relative HIV-1 RNA copy number measured in the resting CD41 T cells of eight HIV-positive patients with plasma HIV RNA BDL is shown on background ART and on ART following a single 400 mg oral dose of VOR. For each subject, the differences are significant ($P<0.01$).

Effect of Histone Deacetylase Inhibitors on HIV Production in Latently Infected, Resting CD4+ T Cells From Infected Individuals Receiving Effective Antiretroviral Therapy

Jana Blazkova, Tae-Wook Chun, Bietel W. Belay, Danielle Murray, J. Shawn Justement, Emily K. Funk, Amy Nelson, Claire W. Hallahan,Susan Moir, Paul A. Wender and Anthony S. Fauci

Effect of histone deacetylase inhibitors (HDACis; valproic acid [VPA], suberoylanilide hydroxamic acid [SAHA], or oxamflatin) and T-cell mitogens (prostratin or anti-CD3 antibody) on cellular activation and viral production in resting CD4+ T cells from aviremic individuals infected with HIV

HDAC is do not induce HIV production in the latent viral reservoir of aviremic individuals.



The Journal of Infectious Diseases 2012;206:765–9

Research article

IL-7 is a potent and proviral strain–specific inducer of latent HIV-1 cellular reservoirs of infected individuals on virally suppressive HAART

Feng-Xiang Wang,[1] Yan Xu,[1] Julie Sullivan,[1] Emily Souder,[1] Elias G. Argyris,[1] Edward A. Acheampong,[1] Jaime Fisher,[1] Maria Sierra,[2] Michael M. Thomson,[2] Rafael Najera,[2] Ian Frank,[3] Joseph Kulkosky,[1] Roger J. Pomerantz,[1] and Giuseppe Nunnari[1]

IL-7 could be combined with its ability to stimulate HIV-1 replication from resting CD4(+) T lymphocytes, in addition to other moieties, to potentially deplete HIV-1 reservoirs and lead to the rational design of immune-antiretroviral approaches.

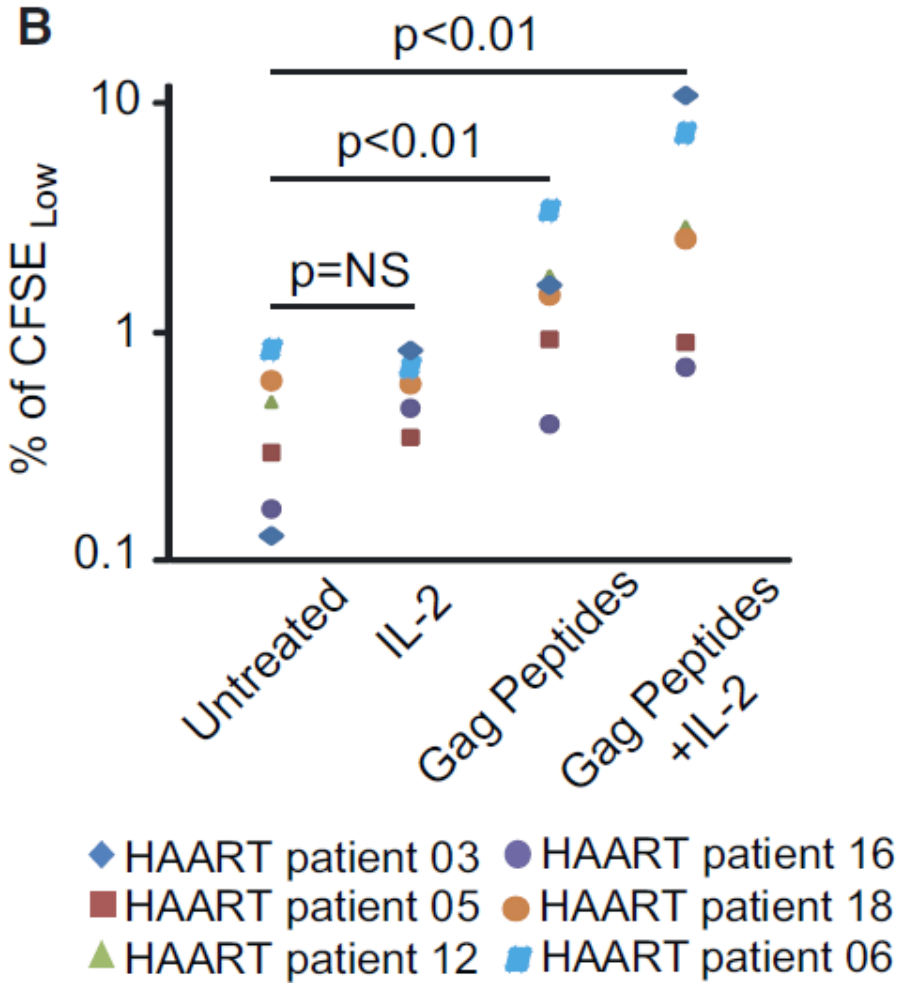
The Journal of Clinical Investigation http://www.jci.org Volume 115 Number 1 January 2005

Why are the clinical effects of HDAC inhibition not more impressive?
Why is persistent HIV so hard to treat?

- *Other viral reservoirs with persistent viral expression*
- *More potent HDAC inhibitors targeted to the HDACs most relevant for HIV latency*
- *More than one mechanism maintains latency; more than one mechanism must be attacked*

Shan L 2012

Stimulation of HIV-1-Specific Cytolytic T Lymphocytes Facilitates Elimination of Latent Viral Reservoir after Virus Reactivation



Prestimulation with Gag Peptides plus IL-2 Induces Proliferation of HIV-1-Specific CD8+ T Cells

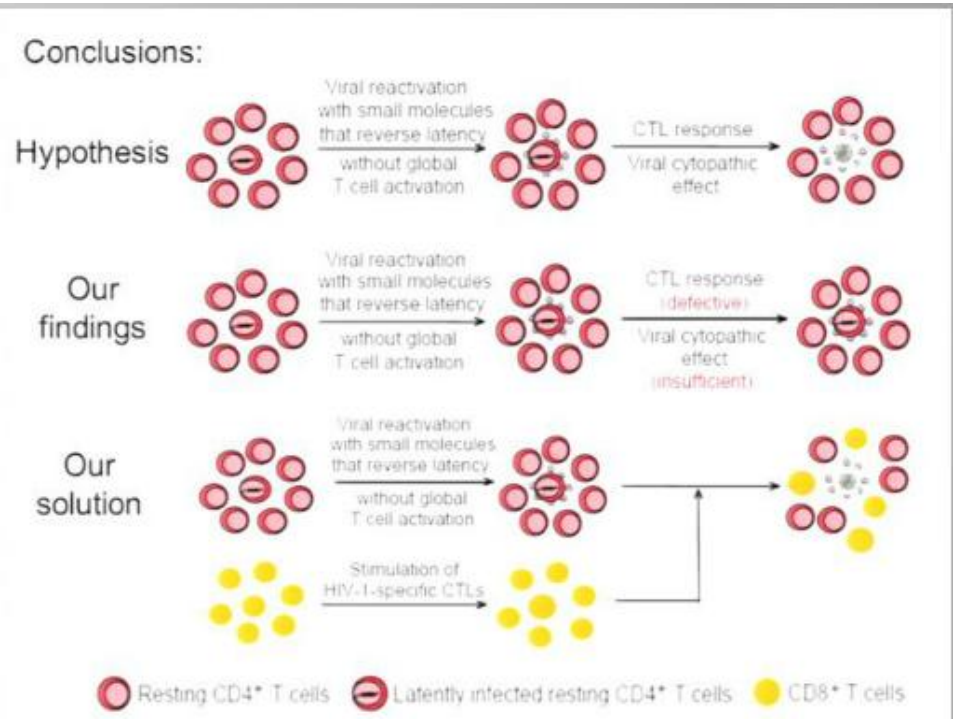
Stimulation of HIV-1-Specific Cytolytic T Lymphocytes Facilitates Elimination of Latent Viral Reservoir after Virus Reactivation

Liang Shan,[1,2] Kai Deng,[1] Neeta S. Shroff,[1] Christine M. Durand,[1] S. Alireza. Rabi,[1] Hung-Chih Yang,[3] Hao Zhang,[4] Joseph B. Margolick,[4] Joel N. Blankson,[1] and Robert F. Siliciano[1,5,*]

36, 2012

Antigen-specific stimulation of patient CTLs led to efficient killing of infected cells.

These results demonstrate that stimulating HIV-1-specific CTLs prior to reactivating latent HIV-1 may be essential for successful eradication efforts.



New strategies