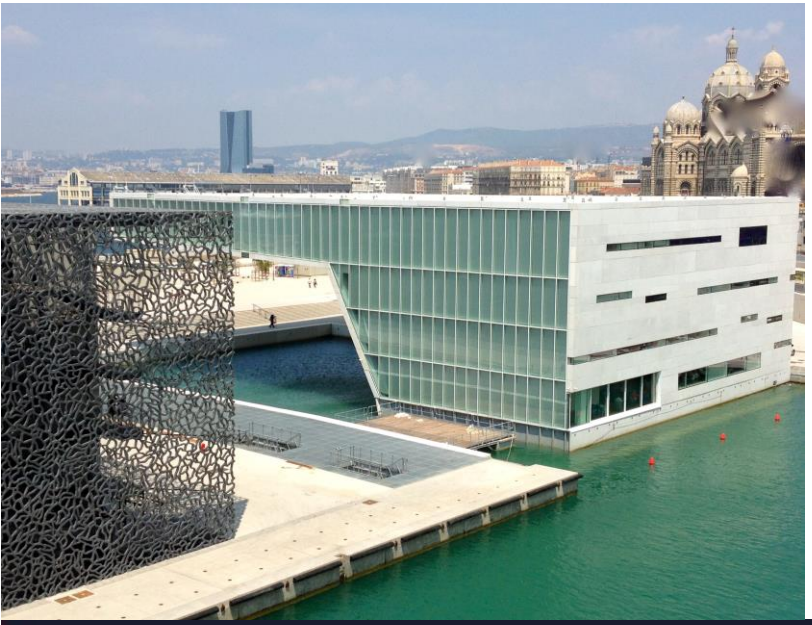
HIV CURE on trial: hype or hope?



Biological challenges of HIV

Dr I Poizot- Martin

CHU Sainte- Marguerite

Assistance Publique- Hôpitaux de Marseille

isabelle.poizot@mail.ap-hm.fr

2014 icshcid PARC CHANOT Marseille - FRANCE 21-23 MAY/MAI 2014

Conflits d'Intérêt

- Board d'experts:

Viiv Health care, Bristol Myers Squibb, MSD

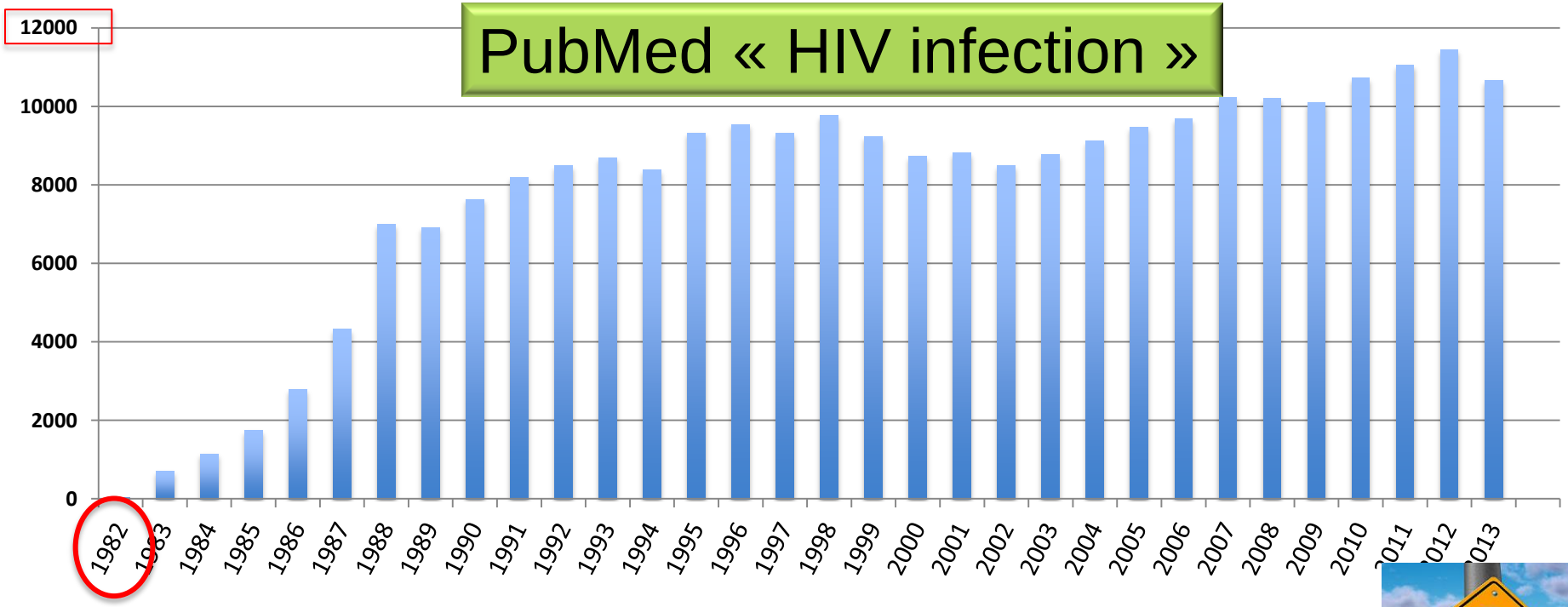
- Invitation Congrès:

Viiv Health care, Bristol Myers Squibb, Janssen

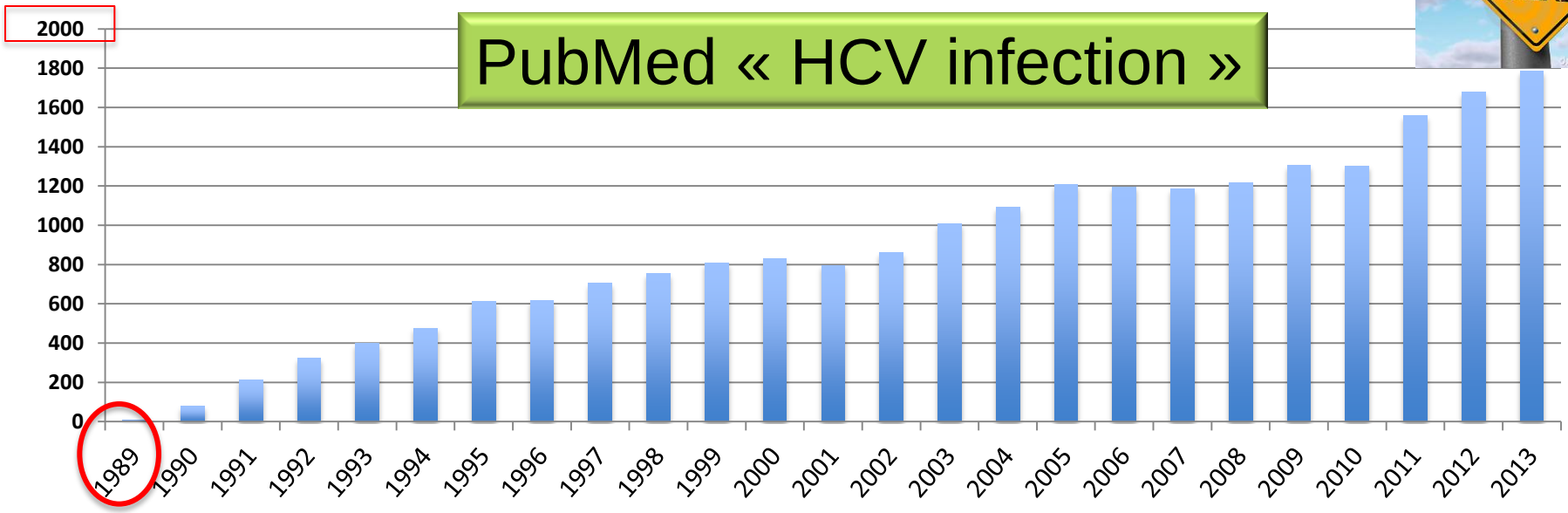
- Participation à des symposium Modérateur/Intervenant:

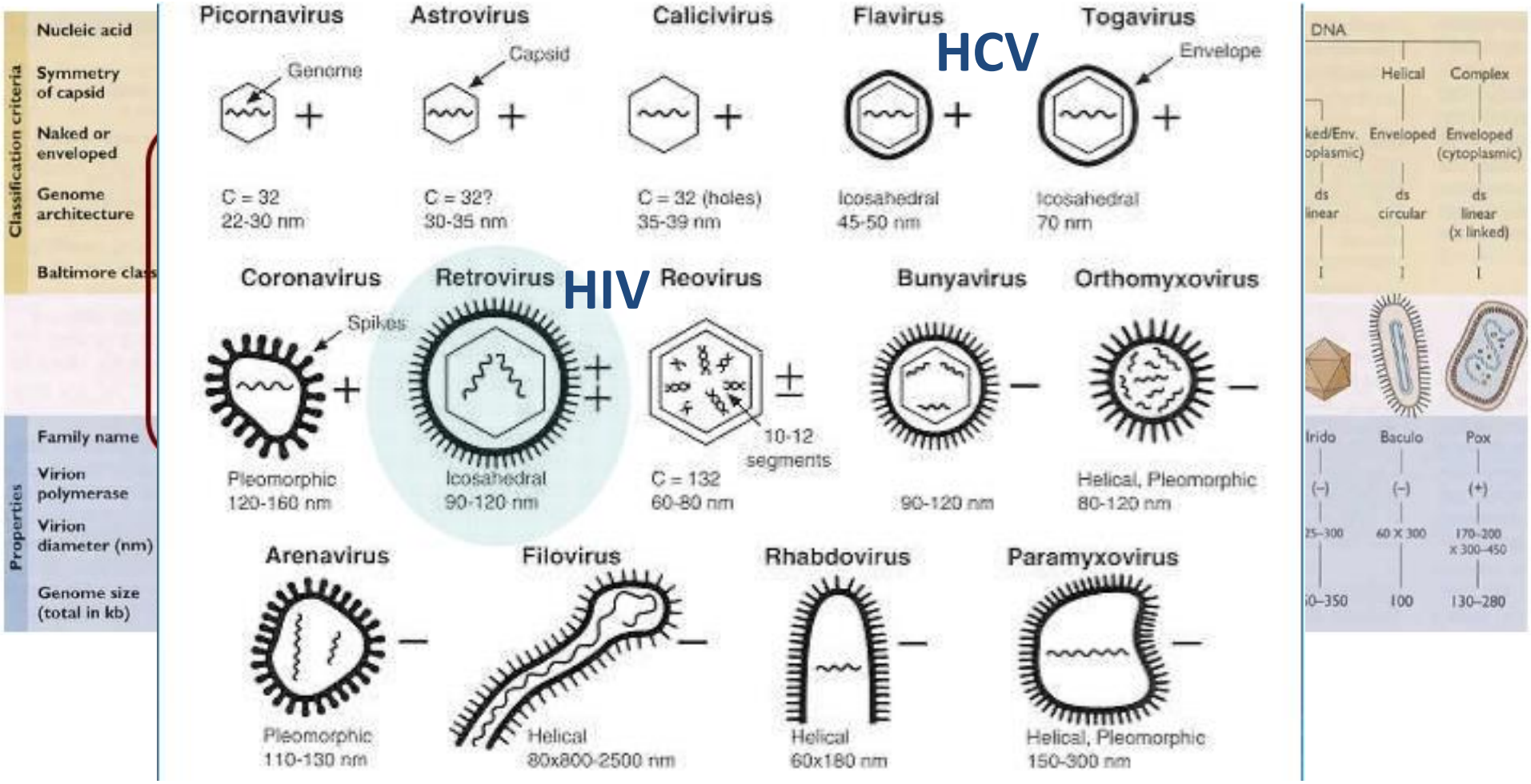
Viiv Health care, Bristol Myers Squibb, Gilead, MSD

PubMed « HIV infection »

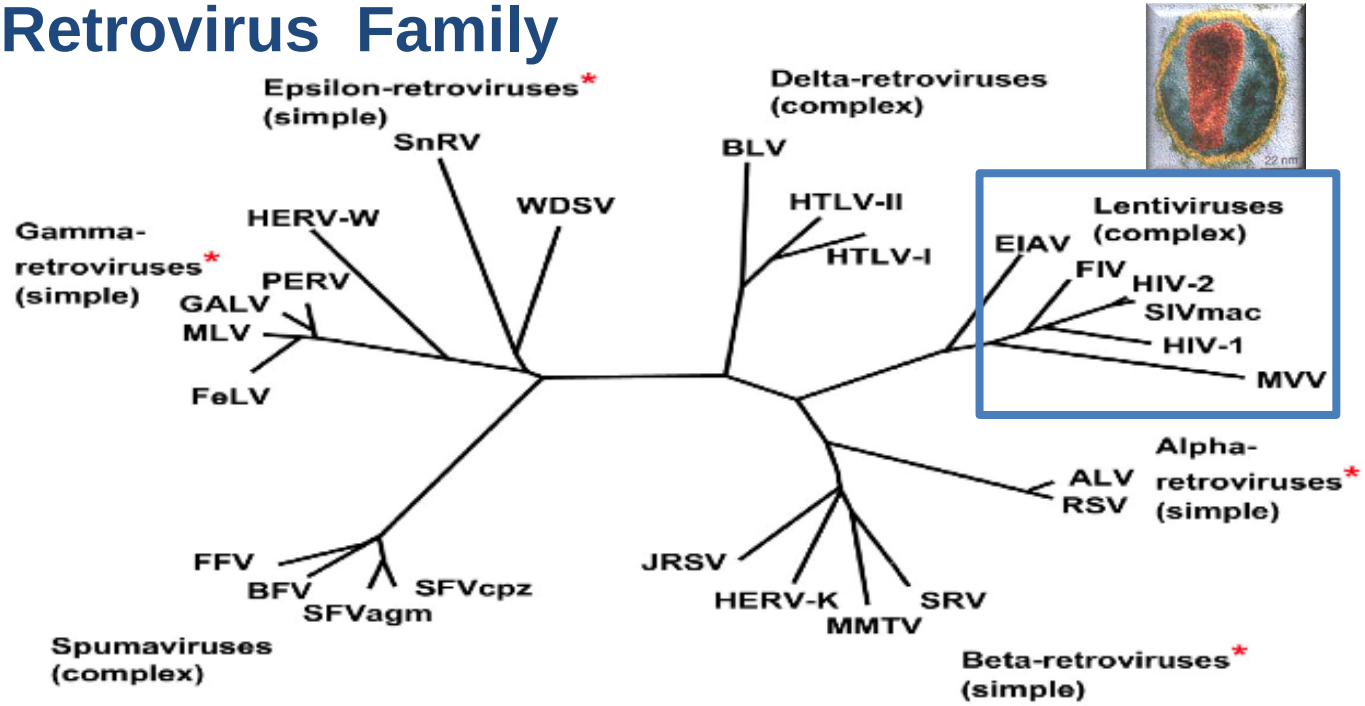


PubMed « HCV infection »




Classification criteria
Nucleic acid
Symmetry of capsid
Naked or enveloped
Genome architecture
Baltimore class
Properties
Family name
Virion polymerase
Virion diameter (nm)
Genome size (total in kb)
Picornavirus
Genome
C = 32
22-30 nm
Astrovirus
Capsid
C = 32?
30-35 nm
Calicivirus
C = 32 (holes)
35-39 nm
Flavirus
HCV
Icosahedral
45-50 nm
Togavirus
Envelope
Icosahedral
70 nm
Coronavirus
Spikes
Pleomorphic
120-160 nm
Retrovirus
HIV
Icosahedral
90-120 nm
Reovirus
10-12 segments
C = 132
60-80 nm
Bunyavirus
90-120 nm
Orthomyxovirus
Helical, Pleomorphic
80-120 nm
Arenavirus
Pleomorphic
110-130 nm
Filovirus
Helical
80x800-2500 nm
Rhabdovirus
Helical
60x180 nm
Paramyxovirus
Helical, Pleomorphic
150-300 nm
DNA
Helical
Complex
Enveloped
Enveloped (cytoplasmic)
ds linear
ds circular
ds linear (x linked)
Irido
Baculo
Pox
(–)
(–)
(+)
60 X 300
170-200 x 300-450
100
130-280

Retrovirus Family



Flaviviridae Family

- **Hepacivirus: HCV**
- **Flavivirus:**

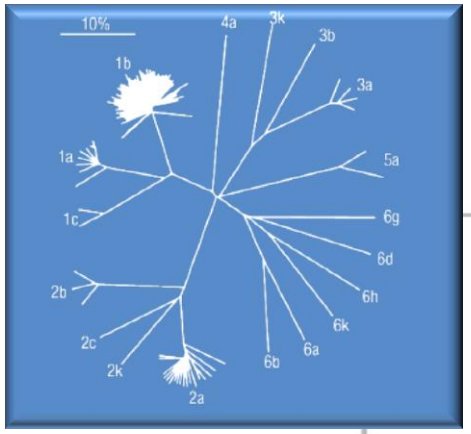
Yellow fever virus
Dengue fever virus
West Nile virus
Tick-borne encephalitis virus

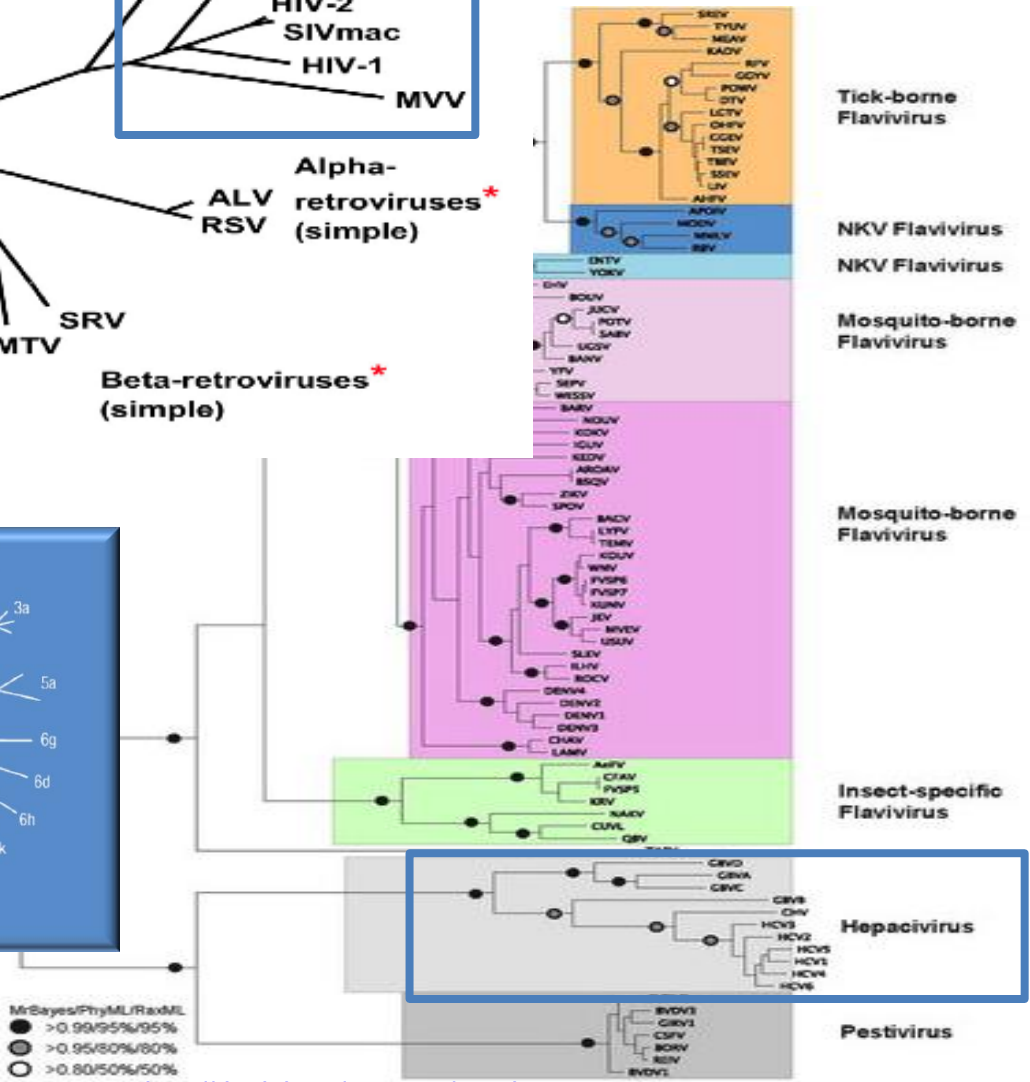
- **Pestivirus:**

Bovine viral diarrhea virus
Classical swine fever virus
Border disease virus

- **Unclassified Flaviviridae:**

Hepatitis GB, GB viruses





Vlachakis D et al. *PeerJ 1:e74* http://dx.doi.org/10.7717/peerj.74

VIH ≠ VHC

High genetic diversity

- **Groupe M** *(Major)* — 7 sous-types A B C D E F G
  - Sous-types non recombinants (« purs ») :
    A B C D F G H J K
  - Sous - sous-types : F1 F2
  - Formes recombinantes circulantes (CRF) :

Nom	Souche de réf.	Sous-types
CRF01_AE	CM240	A, E
CRF02_AG	IbNG	A, G
CRF03_AB	Kal153	A, B
CRF04_cpx	94CY032	A, G, H, K, U
CRF05_DF	VI1310	D, F
CRF06_cpx	BFP90	A, G, J, K
CRF07_BC	CN54	B', C

Nom	Souche de réf.	Sous-types
CRF08_BC	GX-6F	B', C
CRF09_?	p2911	non publié
CRF10_CD	TZBF061	C, D
CRF11_cpx	GR17	A, CRF01, G, J
CRF12_BF	ARMA159	B, F
CRF13_cpx	Non connue	A, E, G, J, U
CRF14_BG	X397	B, G

- **Groupe N** *(Non-M non-O)*
- **Groupe O** *(Outlier)*

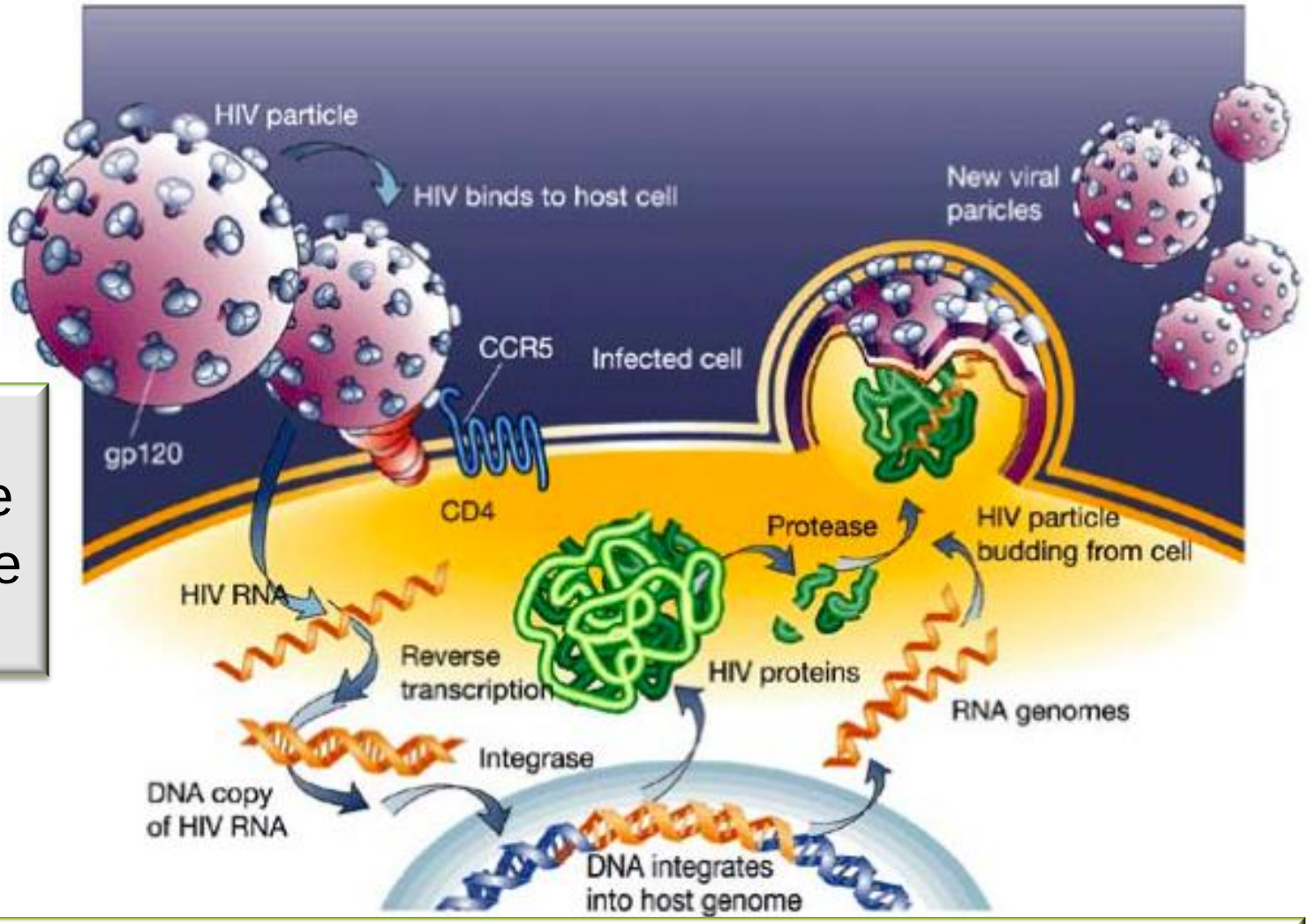
} Très rares isolats
Grande diversité génétique

McCutchan FE. AIDS. 2000, 14(suppl3) : S14-31.

VIH ≠ VHC

HIV lifecycle is more complex: Integration and latency

Integration: Viral genome persists in the infected cell

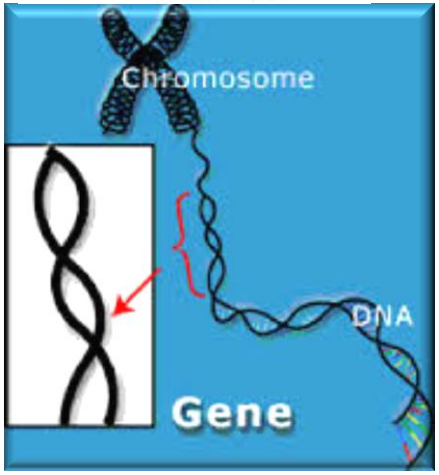


But don't forget, despite the lack of integration of HCV in the infected cell, some viral proteins may be involved in the progression to HCC (proteins C and NS5A or NS3 protease)

VIH ≠ VHC

HIV lifecycle is more complex: Integration and latency

*Basically **HIV was thought to integrate itself randomly** within our **DNA in those areas that are actively being transcribed** (at the time of integration) rather than in areas that are condensed and surrounded by histone proteins, around which our DNA is "stored…"*



The sites of HIV-1 integration in the human genome determines basal transcriptional activity and response to Tat transactivation

A Jordan et al, EMBO Journal, 2001; 20, 1728-1738

Open access, freely available online PLOS BIOLOGY

Retroviral DNA Integration: ASLV, HIV, and MLV Show Distinct Target Site Preferences

2004; 2:1127-1137

Rick S. Mitchell[1☯], Brett F. Beitzel[1☯], Astrid R. W. Schroder[2], Paul Shinn[3], Huaming Chen[3], Charles C. Berry[4], Joseph R. Ecker[3], Frederic D. Bushman[1*]

Chromosomal regions rich in expressed genes were favored for HIV integration

HIV Integration: not randomly …

Proliferation of Cells With HIV Integrated Into Regulatory Genes Is a Mechanism of Persistence *Abstract 138*

Thor A. Wagner[1,2], Sherry McLaughlin[1,2], Kavita Garg[3], Hannah Huang[2], Sheila Styrchak[2], James I. Mullins[1], Lisa M. Frenkel[1,2]

[1]University of Washington, Seattle, WA, United States, [2]Seattle Children's Hospital, Seattle, WA, United States, [3]Fred Hutchinson Cancer Research Center, Seattle, WA, United States

The Role of HIV Integration Sites in Extensive Clonal Expansion of Infected Cells in Patients *Abstract LB 407*

Frank Maldarelli[1], Xiaolin Wu[2], Mary Kearney[1], Ling Su[2], Wei Shao[3], Shawn Hill[1], Francesco Simonetti[1], Jon Spindler[1], John Coffin[4], **Stephen H. Hughes**[1]

[1]HIV Drug Resistance Program, NIH, Frederick, MD, United States, [2]Leidos, Inc, Frederick, MD, United States, [3]ISP/Advanced Biomedical Computing Center, Leidos, Inc., Frederick, MD, United States, [4]Department of Molecular Biology and Microbiology, Tufts University School of Medicine, Boston, MA, United States

• **Multiple identical HIV integration sites** were detected **within each individual**; these replicates accounted for **39.6%** (213/538) of integration sites (…). **Infected clones persisted in patients for at least 11 years.**

• The integration site recovered most frequently (32 times) was in **MDC1, which has a known role in cell cycle arrest and apoptosis**(….)The only gene with HIV integrated into multiple sites and in multiple (2 of 3) participants was **BACH2, recently identified as a tumor suppressor.**

• (…)Integrations in the same orientation in a specific intron of **two different genes (MKL2 and BACH2)**, both these genes have been linked to the **control of cell growth and human cancers**

HIV persistence: at least two mechanisms...

- ***If some infected cells still produce new HIVs that infect virgin cells***, refilling the pool (particularly in tissue that drugs have difficulty reaching), ***more importantly, the infected cells make copies of themselves: a cloning process known as homeostatic proliferation***
- *Furthermore, HIV integration into specific sites in the human chromosome may* ***modify gene function, allowing proliferation and prolonged persistence of specific infected cells****.*

CANCER GENES HELP HIV PERSIST, COMPLICATING CURE EFFORTS
J Cohen, Science 14 March 2014: Vol. 343 no. 6176 pp. 1188

VIH
≠
VHC

HIV latency …

• **Many viruses, especially the human herpesviruses**, can **remain in host cells throughout life without causing disease**. They may be reactivated by immunosuppression or others phenomenom, however, and cause disease.

• **Individual *components of the nucleus of the host cells interact with virus to maintain genome "silent" in specific nuclear compartments during viral latency***. This interaction is probably part of the antiviral response of the nucleus to infection and could be one of the barriers to raise during viral reactivation leading to disease onset

HSV-1 genome subnuclear positioning and associations with host-cell PML-NBs and centromeres regulate LAT locus transcription during latency in neurons.
F. Catez, *PLoS Pathogens (2012), 8(8):e1002852*

VIH
≠
VHC

Mechanisms of HIV latency

- ***Mechanisms*** *underlying establishment and maintenance of HIV latency are* ***complex…***
- *Although most* ***proviruses integrate in transcriptionally active genomic regions****, in most of cases* ***these proviruses remained repressed****…*

Transcriptional control of HIV latency: Cellular signaling pathways, epigenetics, happenstance and the hope for a cure

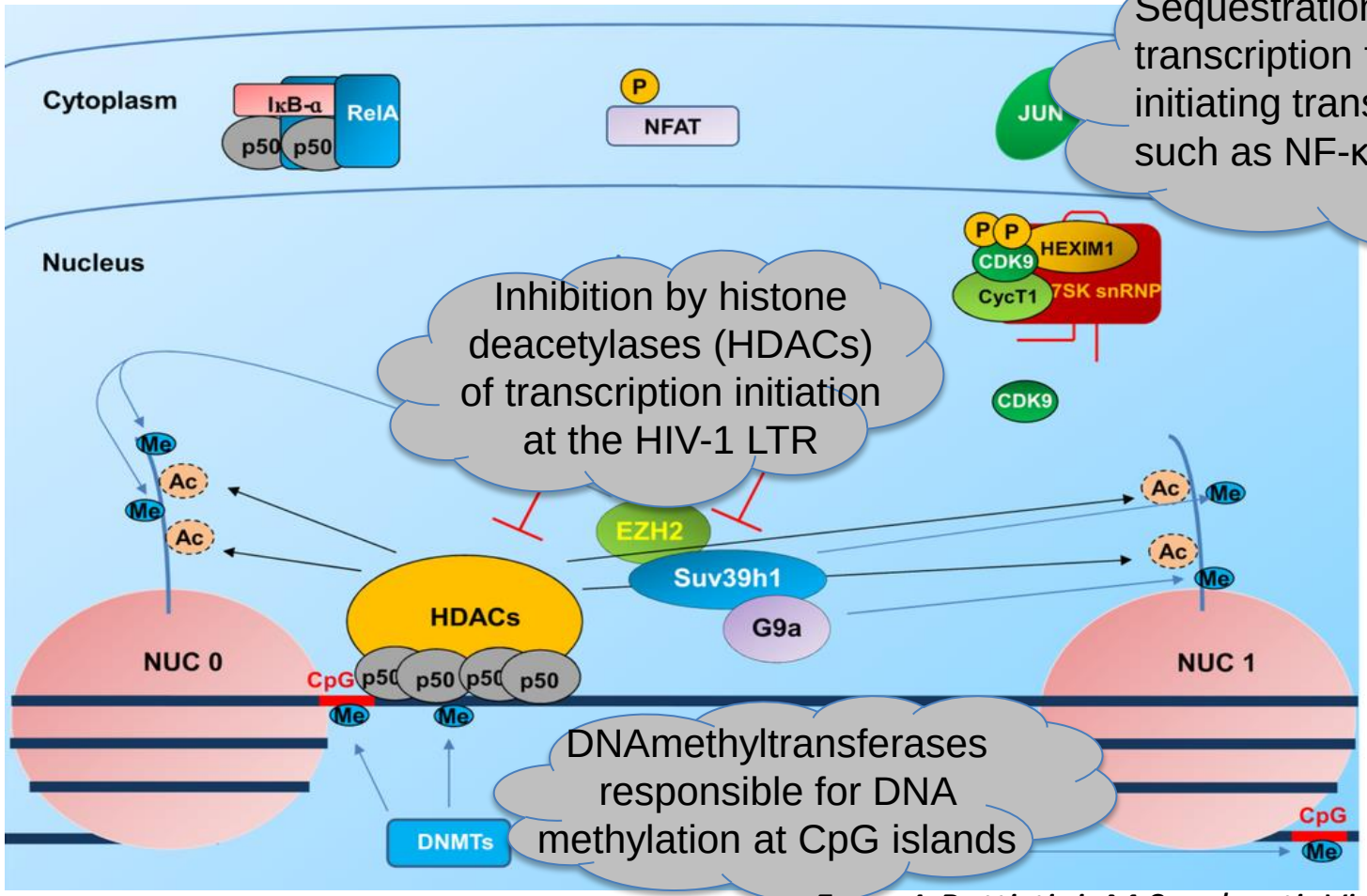
Uri Mbonye, Jonathan Karn* Virology 454-455 (2014) 328–339

HIV-1 Latency: An Update of Molecular Mechanisms and Therapeutic Strategies *Viruses* **2014**, *6*, 1715-1758;

Angela Battistini * and Marco Sgarbanti

VIH
≠
VHC

Mechanisms of HIV latency: multiple and complex



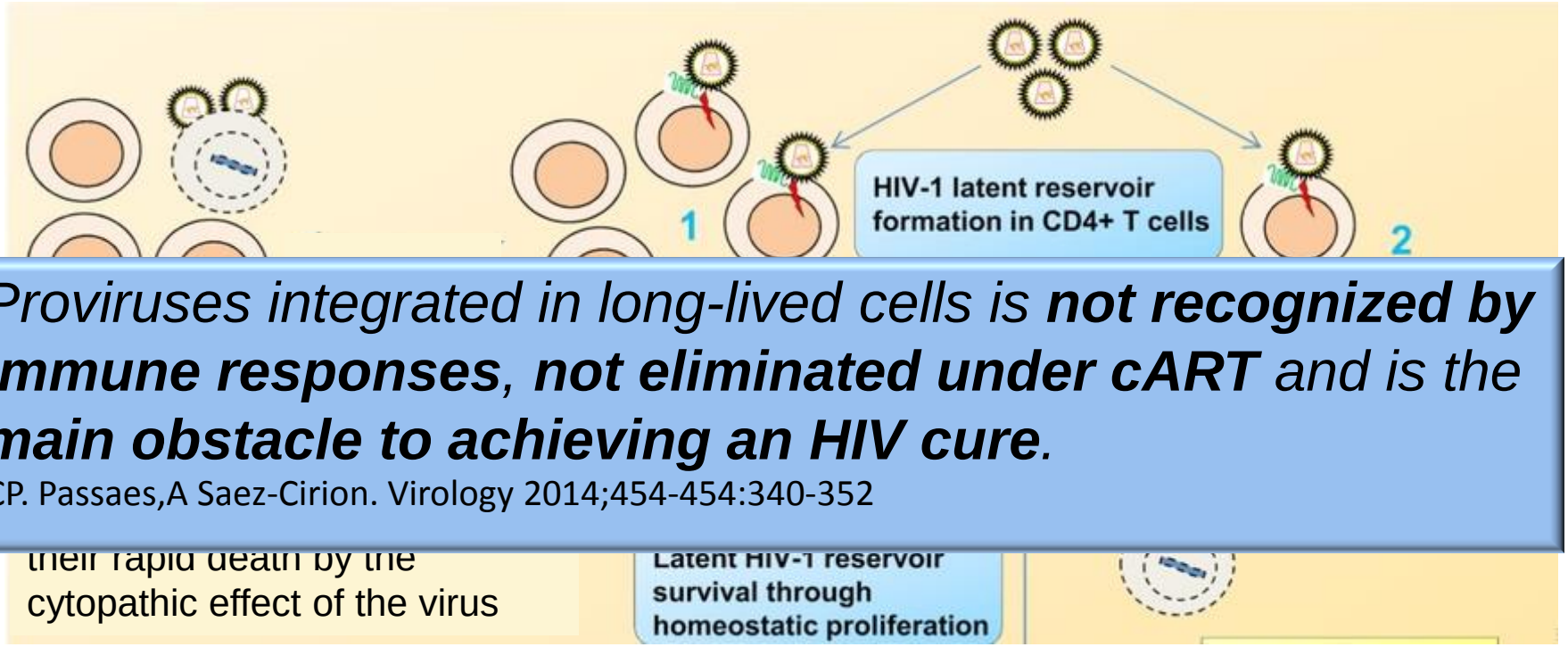
Sequestration in the cytoplasm of transcription factors responsible for initiating transcription at the LTR, such as NF-κB, NFAT and cJun

Inhibition by histone deacetylases (HDACs) of transcription initiation at the HIV-1 LTR

DNAmethyltransferases responsible for DNA methylation at CpG islands

From A Battistini, M Sgarbanti, Viruses 2014;6:1715-1758

Establishment of post-integration latency



Proviruses integrated in long-lived cells is ***not recognized by immune responses***, ***not eliminated under cART*** *and is the* ***main obstacle to achieving an HIV cure****.*

CP. Passaes,A Saez-Cirion. Virology 2014;454-454:340-352

1. A **minority of activated CD4+ T cells becomes infected just as they are undergoing the transition from an activated to a resting-memory** state where the provirus becomes silent

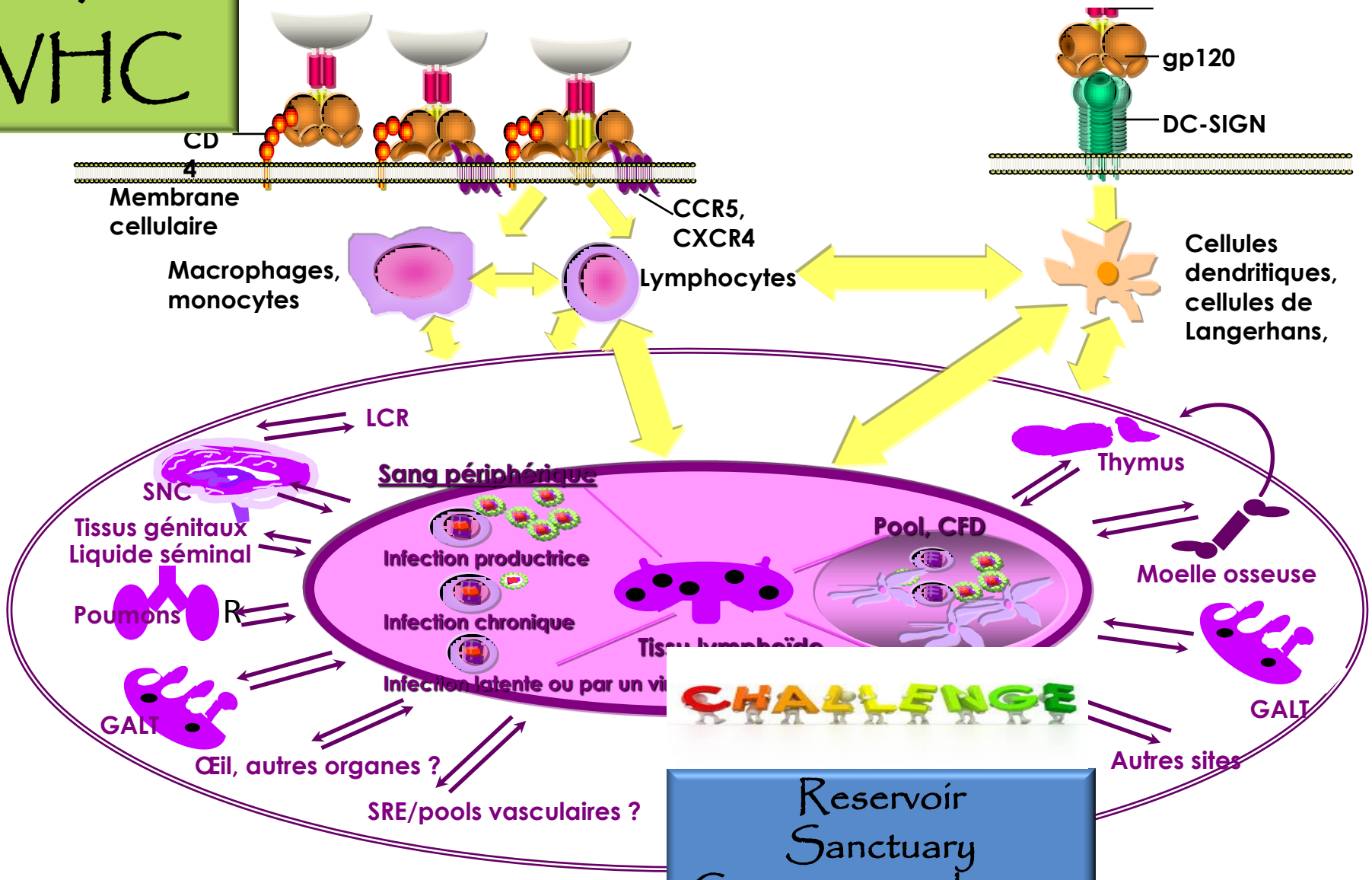
2. **Latent infection may arise from direct infection of resting CD4+ T cells**

3. The established latent reservoir in the **T CD4+ resting memory compartment then survives through homeostatic proliferation**

From A Battistini, M Sgarbanti, Viruses 2014;6:1715-1758

VIH ≠ VHC

HIV lifecycle not confined in cytoplasm of one type of cell …

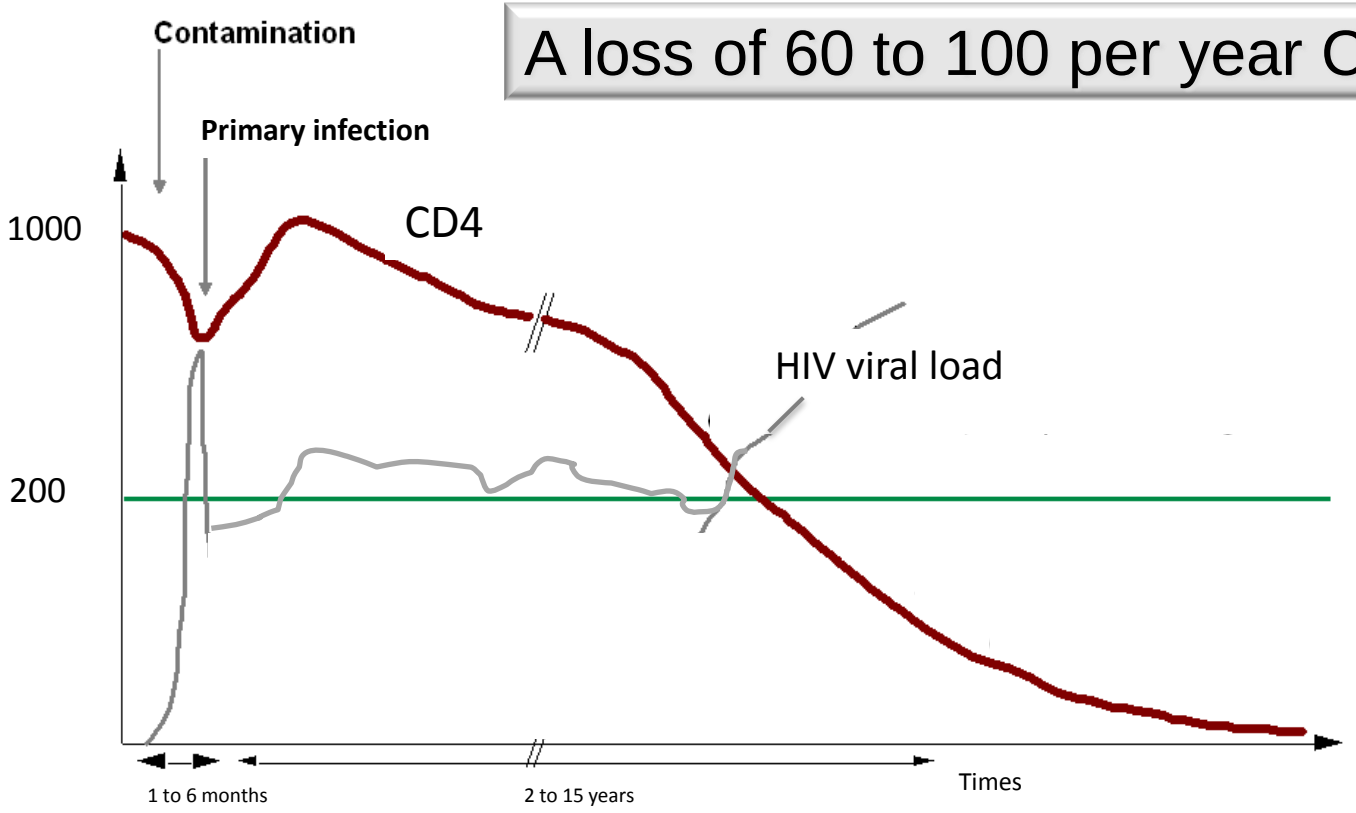


D'après Cavert W *et al*. Science. 1998, 280(5 371) : 1865-6. Geijtenbee Infect Dis. 2002, 39 : 91-7.

VIH ≠ VHC

Impact on immune system: A gradual establishment of Immune Deficiency

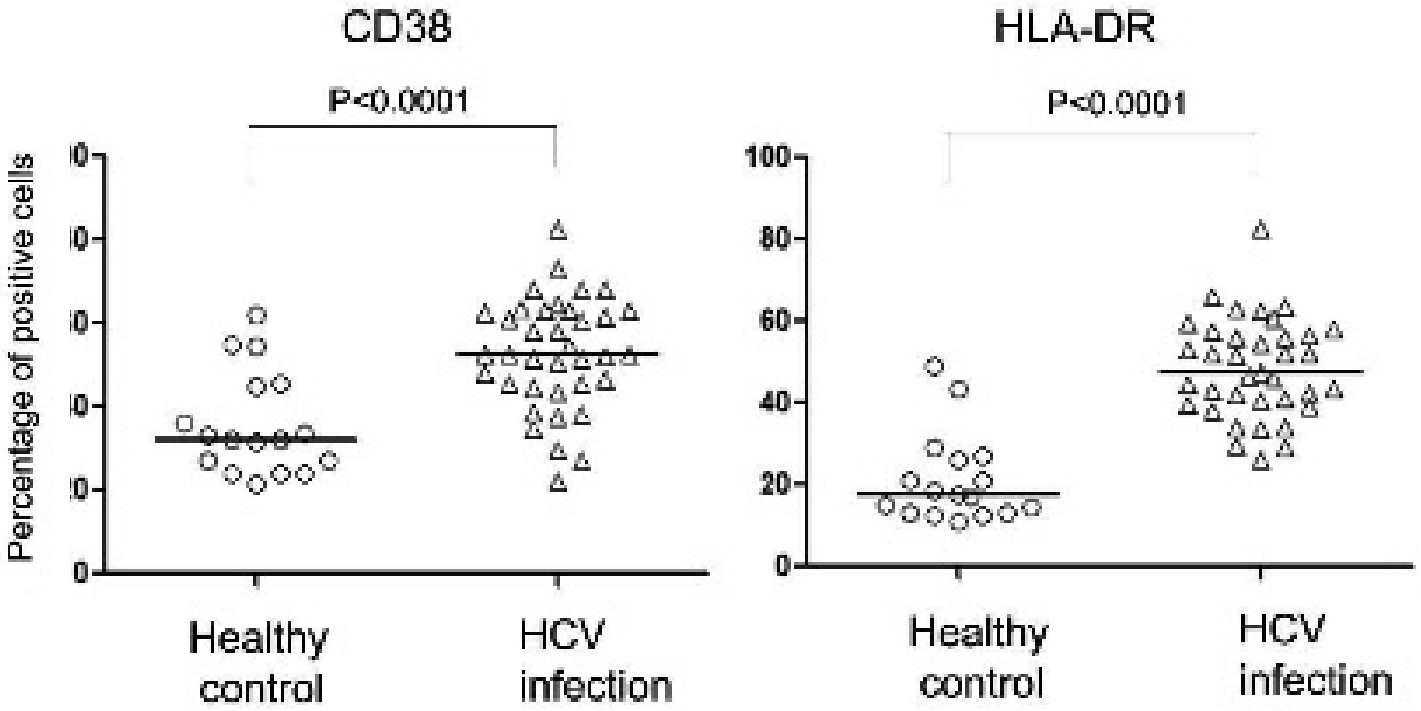
A loss of 60 to 100 per year CD4



VIH ≃ VHC

Impact on immune system: Immune activation and chronic inflammation as in all chronic infection

Chronic HCV infection induces CD8⁺ T cell activation and impaired balance of T cell-homeostasis



CD38, HLA-DR on total CD8+ T cells in HCV-infected patients.

Shen *et al. Virology Journal* 2010, **7**:310

HIV and Inflammation: Mechanisms and Consequences

Curr HIV/AIDS Rep (2012) 9:139-147

Peter W. Hunt

HIV Replication

Mortality

Microbial Translocation

Persistent Immune Activation

Chronic viral infections

Cardio Vascular Disease

Type II diabetes

Thrombo embolic Disease

Cancer

Morbidities

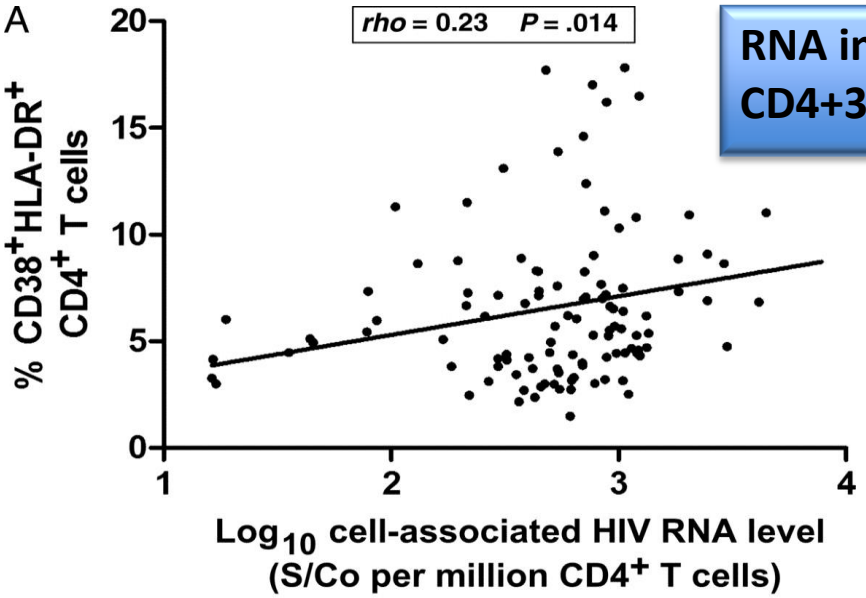
Neurocognitive Dysfunction

Fraitly

Multiple End-Organ Disease

Correlation between Immune activation and viral persistence/reservoir ?

Cell-based measures of viral persistence are modestly associated with immune activation.



RNA intra/
CD4+38+DR+

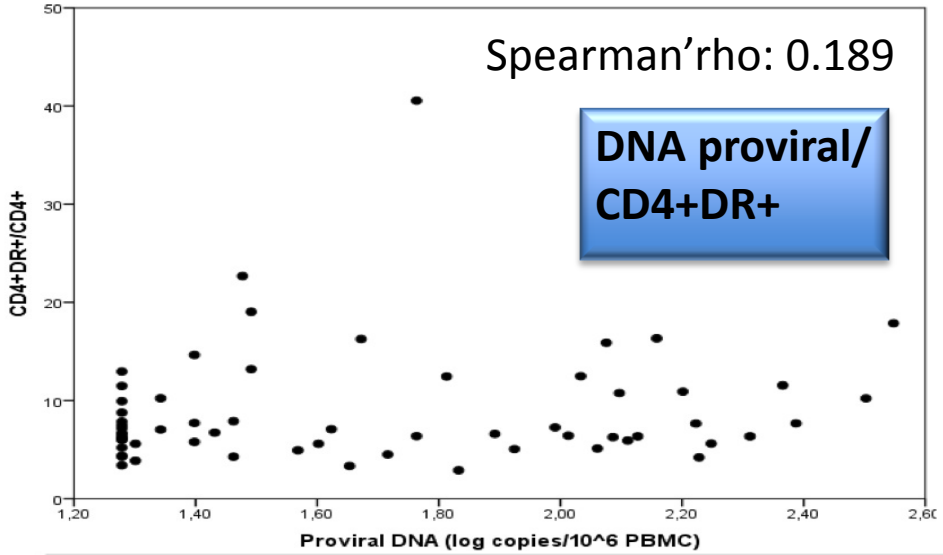
The Journal of Infectious Diseases

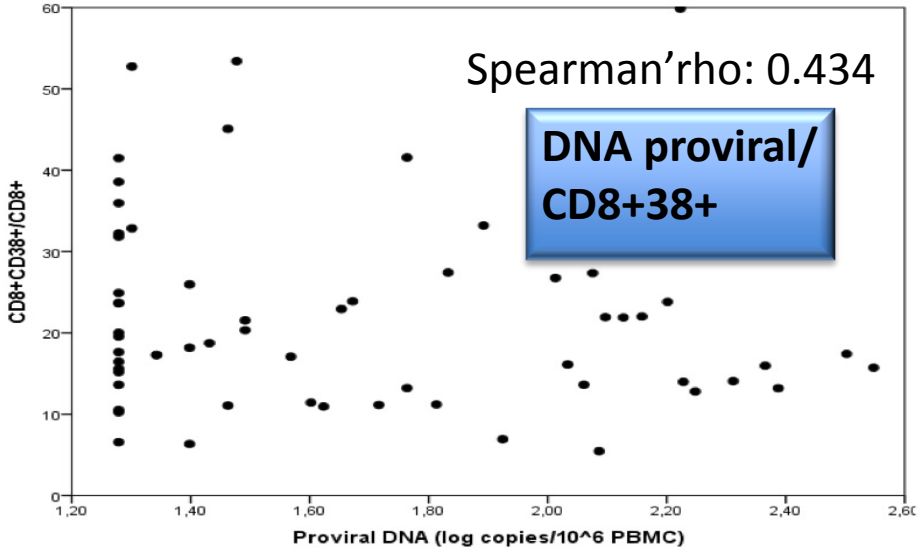
Hatano H et al.
J Infect Dis. 2013;208:50-56

Lack of correlation between the size of HIV proviral DNA reservoir and the level of immune activation in HIV-infected patients with a sustained undetectable HIV viral load for 10 years

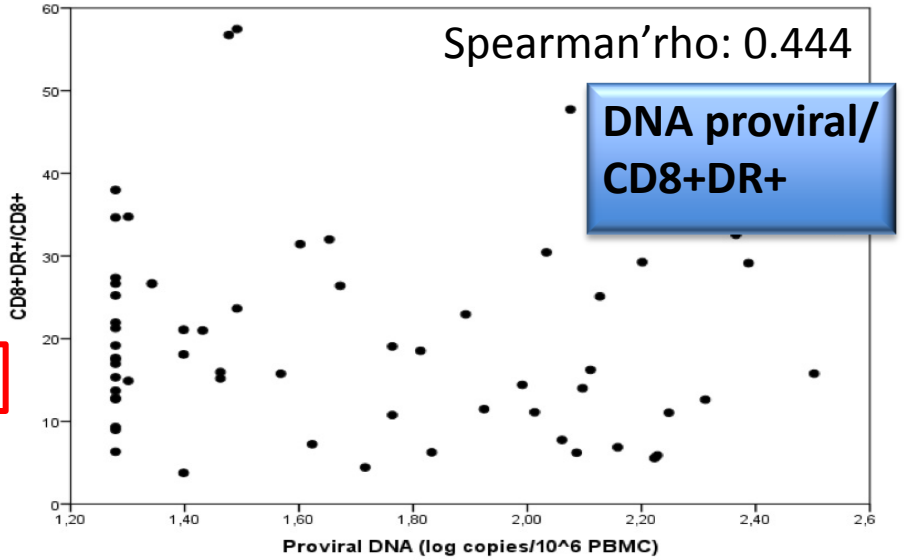
Journal of Clinical Virology 57 (2013) 351–355

Isabelle Poizot-Martin[a,*], Olivia Faucher[a], Véronique Obry-Roguet[a], Corinne Nicolino-Brunet[b], Sylvie Ronot-Bregigeon[a], Françoise Dignat-George[b], Catherine Tamalet[c]





Markers	Non-blippers ($n=27$) % [IQR]	Blippers ($n=35$) % [IQR]	p
$CD4^+45RA^+62L^+/CD4^+$	41.8 [29.3–51.1]	39 [32.8–50.1]	0.723
$CD4^+CD28^+/CD4^+$	95.96 [88.45–99.93]	96.61 [93.60–98.89]	0.584
$CD4^+DR^+/CD4^+$	6.42 [5.06–8.77]	6.42 [5.06–8.77]	0.265
$CD8^+DR^+/CD8^+$	15.1 [9.31–21.27]	21.08 [14.42–30.44]	0.036
$CD8^+CD38^+/CD8^+$	15.72 [11.06–27.42]	21.53 [16.11–27.34]	0.095
IC HIV-DNA	29 [IQR: 19–84]	40 [IQR: 20–125]	NS
< 20 cp/10^6M	40.7%	20%	0.074

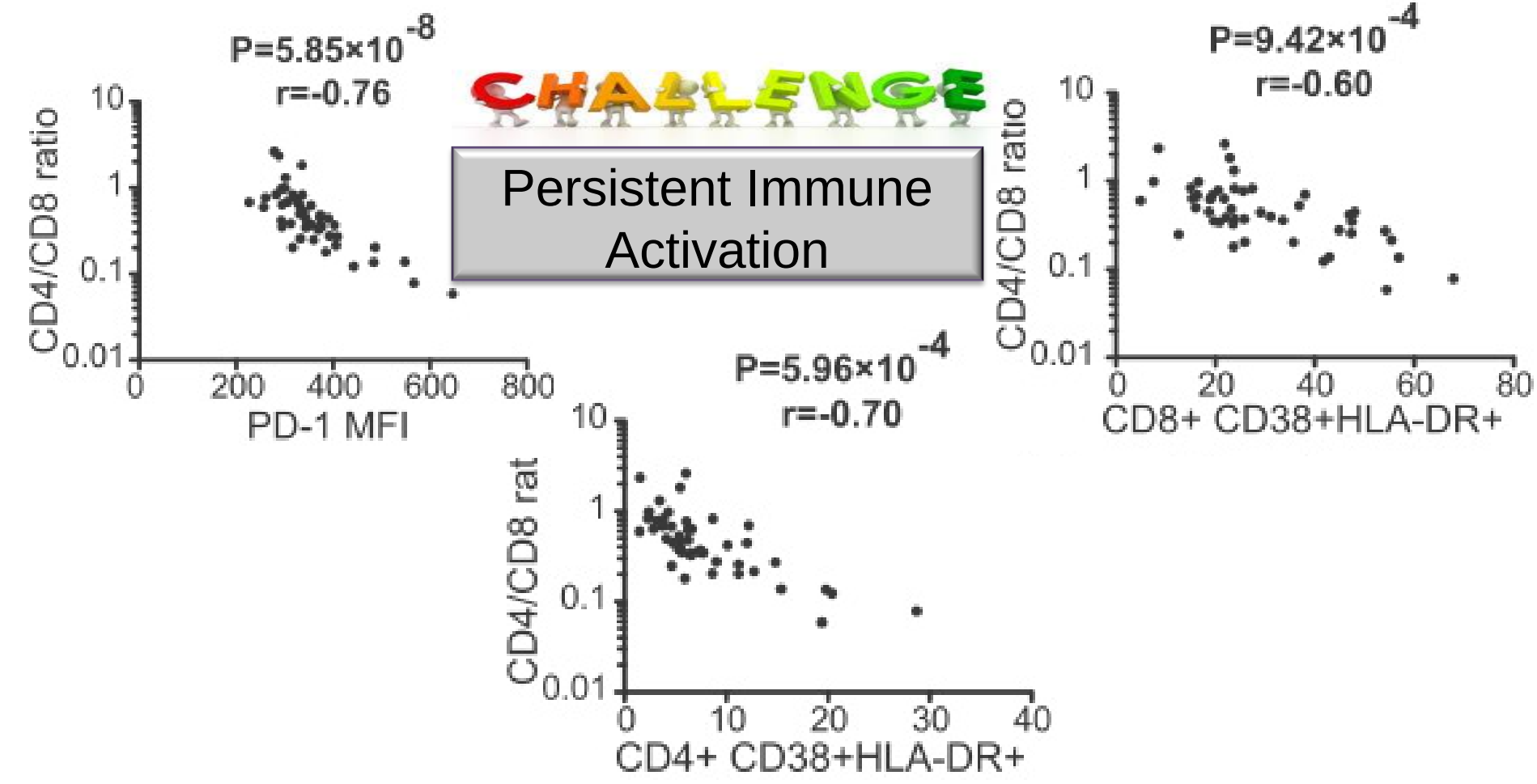


Multiparametric Bioinformatics Distinguish the CD4/CD8 Ratio as a Suitable Laboratory Predictor of Combined T Cell Pathogenesis in HIV Infection

The Journal of Immunology, 2014, 192: 2099–2108.

Marcus Buggert,* Juliet Frederiksen,† Kajsa Noyan,* Jenny Svärd,‡ Babilonia Barqasho,* Anders Sönnerborg,*,‡ Ole Lund,† Piotr Nowak,*,‡ and Annika C. Karlsson*

CD4/CD8 ratio correlation with T cell pathological changes

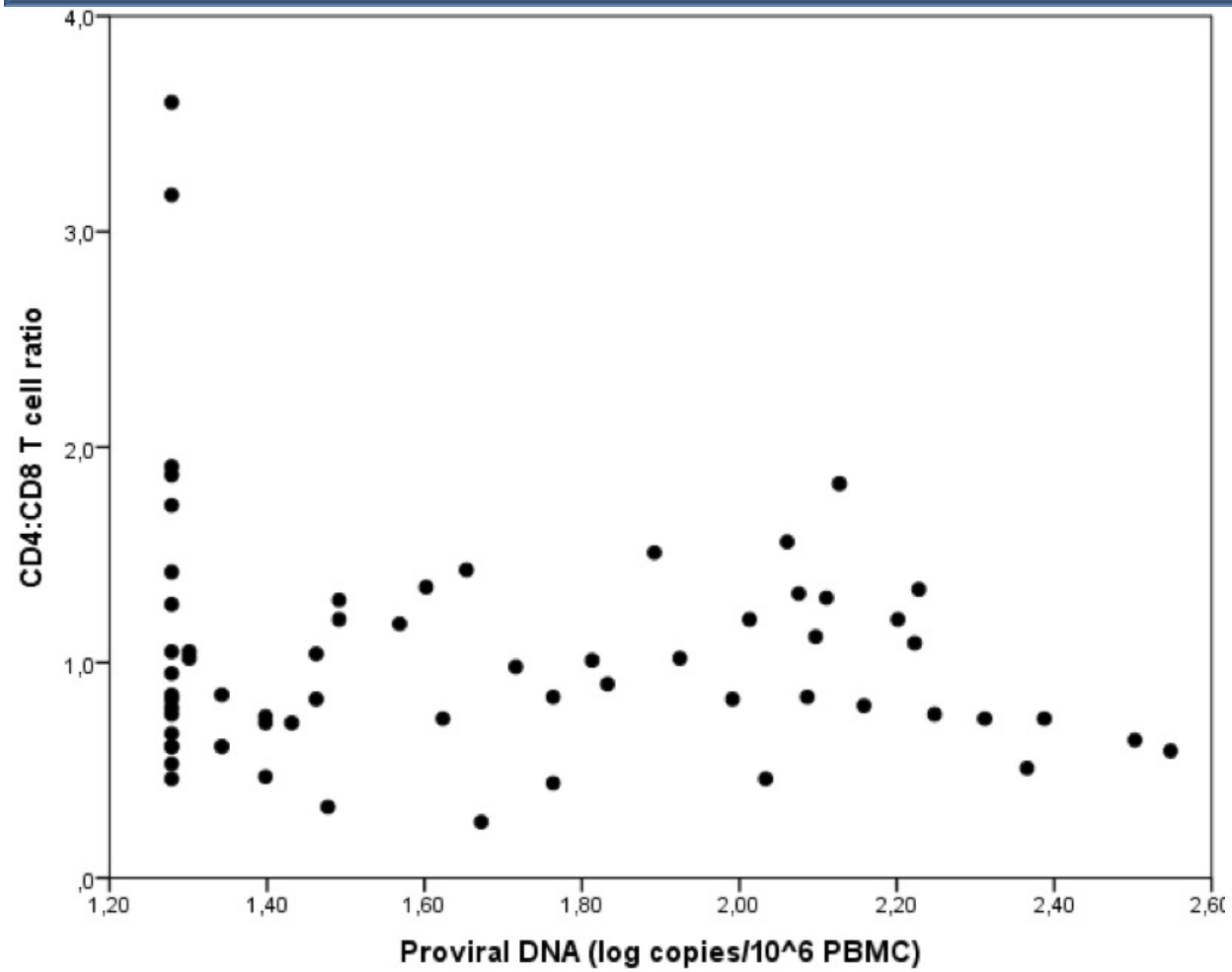


Lack of correlation between the size of HIV proviral DNA reservoir and the level of immune activation in HIV-infected patients with a sustained undetectable HIV viral load for 10 years

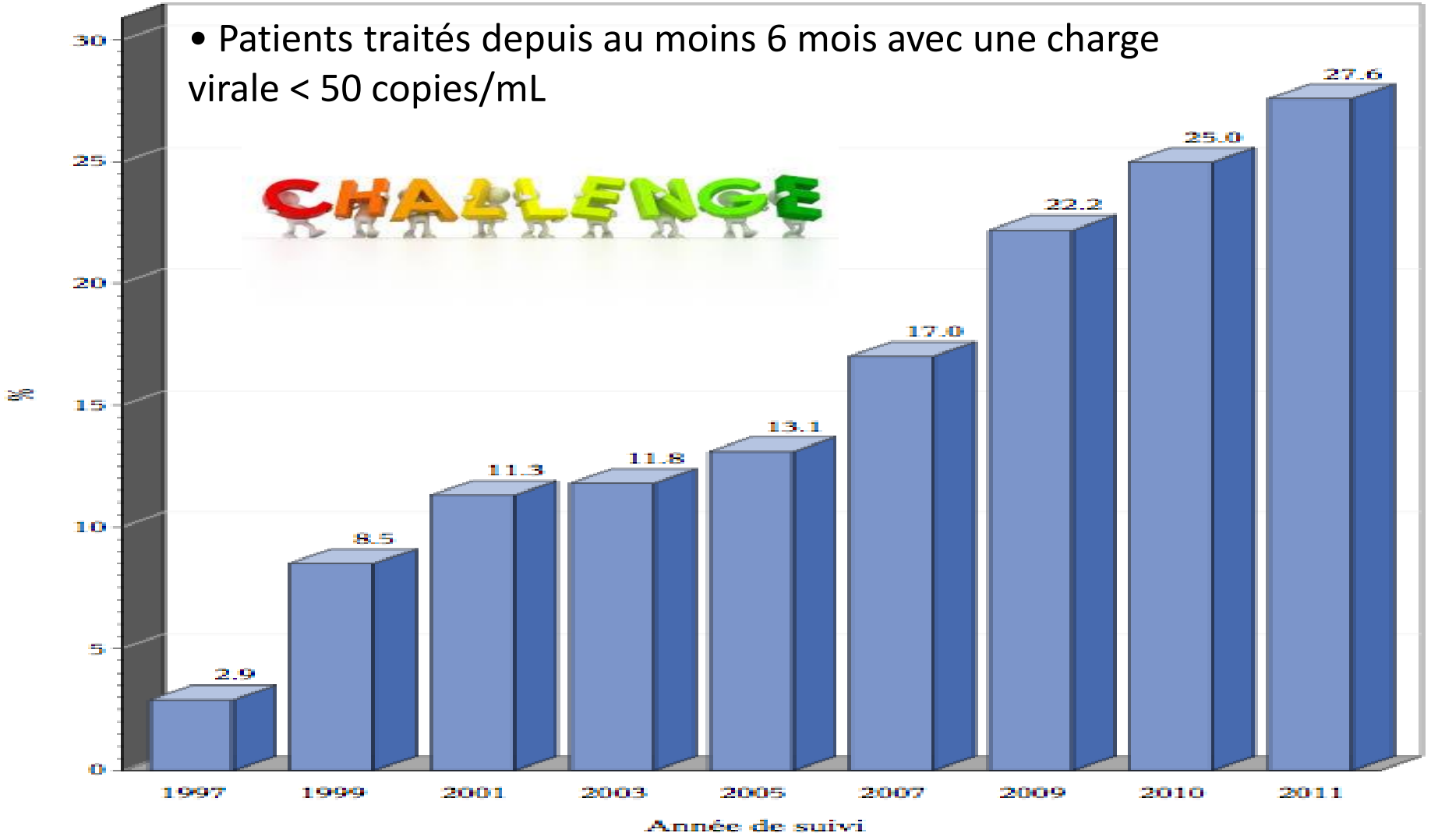
Journal of Clinical Virology 57 (2013) 351–355

Isabelle Poizot-Martin[a,*], Olivia Faucher[a], Véronique Obry-Roguet[a], Corinne Nicolino-Brunet[b], Sylvie Ronot-Bregigeon[a], Françoise Dignat-George[b], Catherine Tamalet[c]

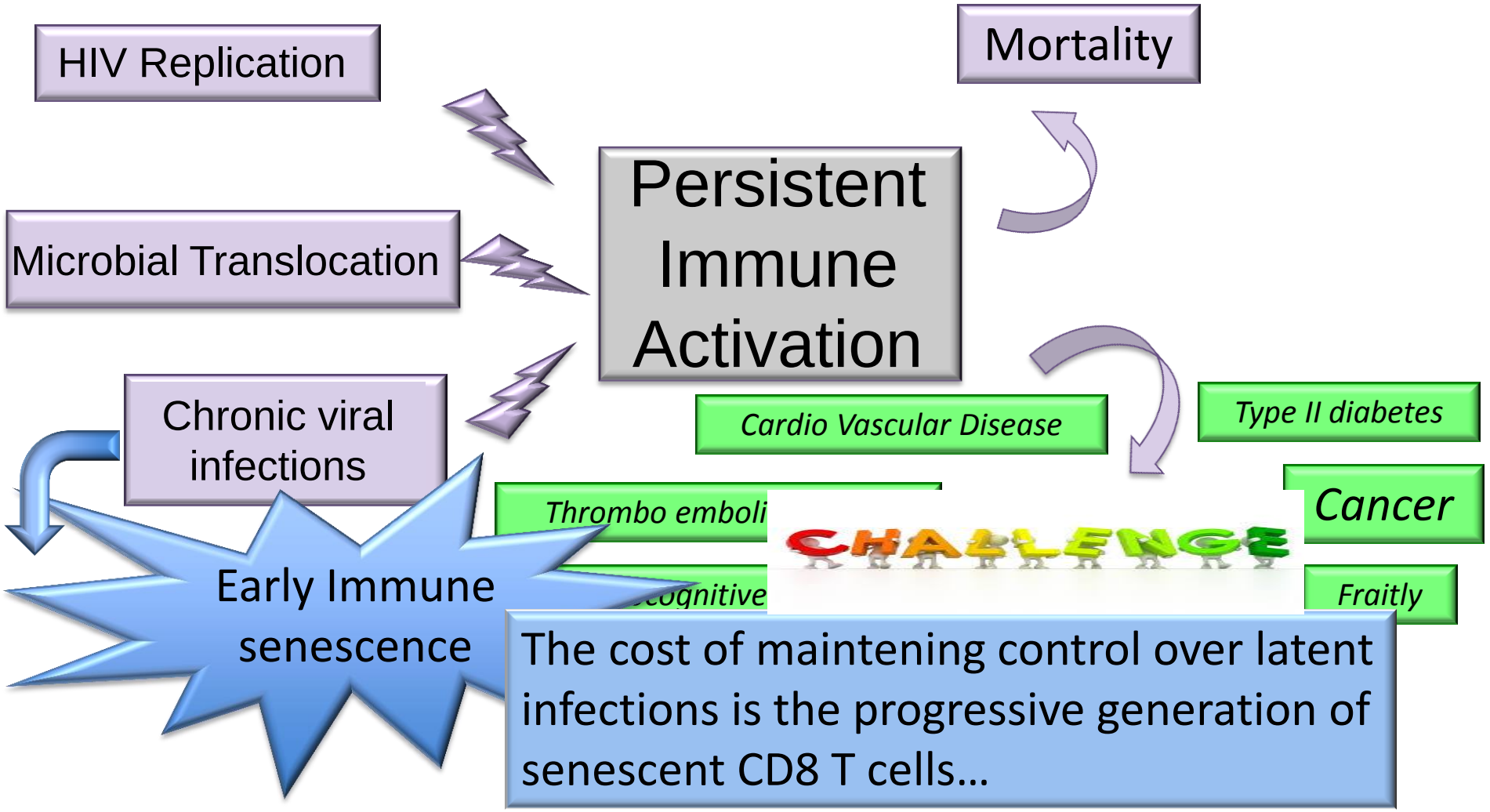
But CD4/CD8 ratio is not correlated with reservoir



Ratio CD4/CD8 > 1 in less than 30% of ART treated patients



Immunosenescence: the cost of maintening control over latent infections

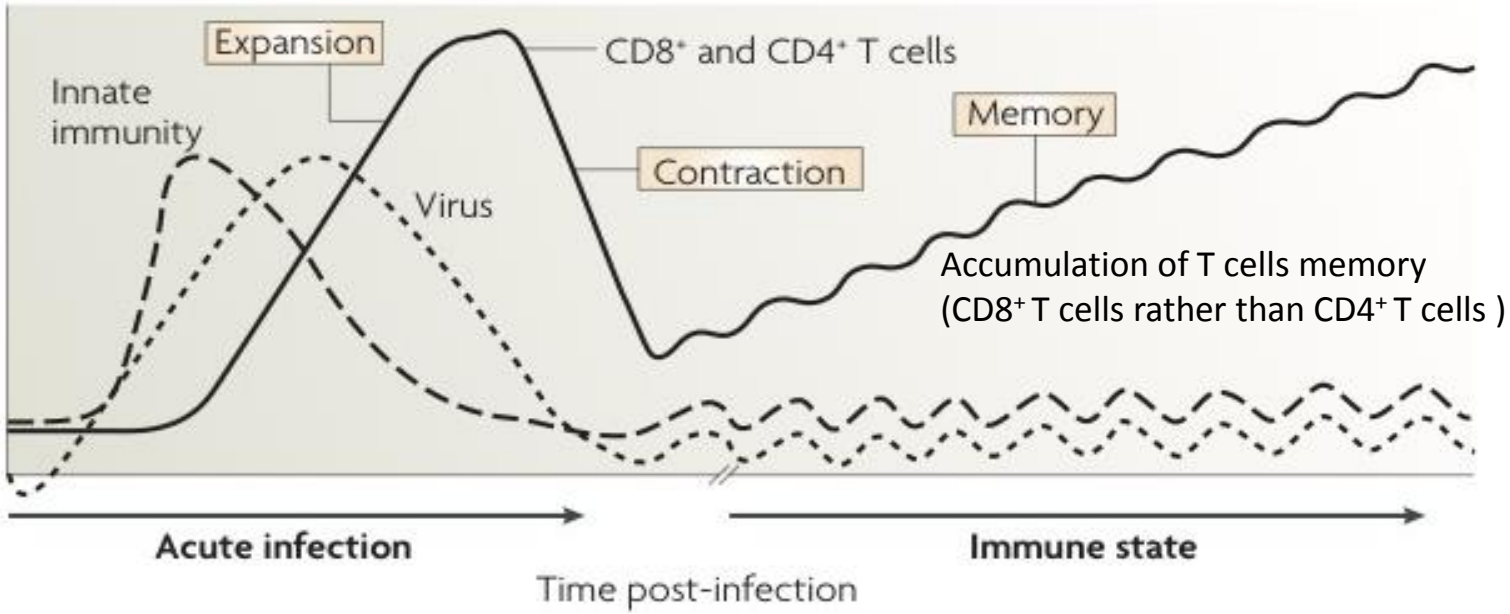


nature REVIEWS IMMUNOLOGY

Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections

J Nikolich-Zugich Nature Rev Immunol 2008; 8:512-522)

• Latent persistent pathogens (HSV, CMV) determine the extent of age associated immune deficiency ?

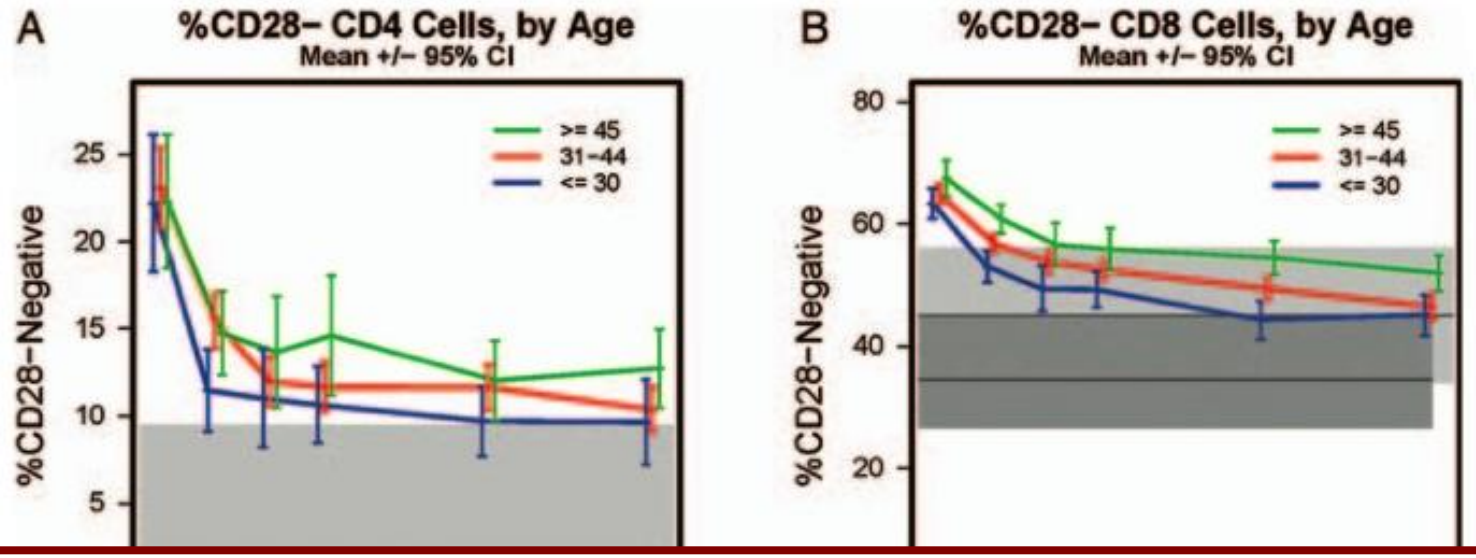


• During chronic infection (such as HIV, HCV) immune cells (including T cells) are constantly and systematically stimulated.**This persistent immune activation lead to a premature immunosenescence** and an exhaustion of immune resources.

V Appay et al. J Exp Gerontol 2007; 42: 432-437

CD28-Negative $CD4^+$ and $CD8^+$ T Cells in Antiretroviral Therapy–Naive HIV-Infected Adults Enrolled in Adult Clinical Trials Group Studies

N= 1291 HIV infected treatment naive adults from 5 ACTG ART Studies and the ALLERT cohort vs 48 HIV negative adults (HIV negative control study 18-30;45-66y)



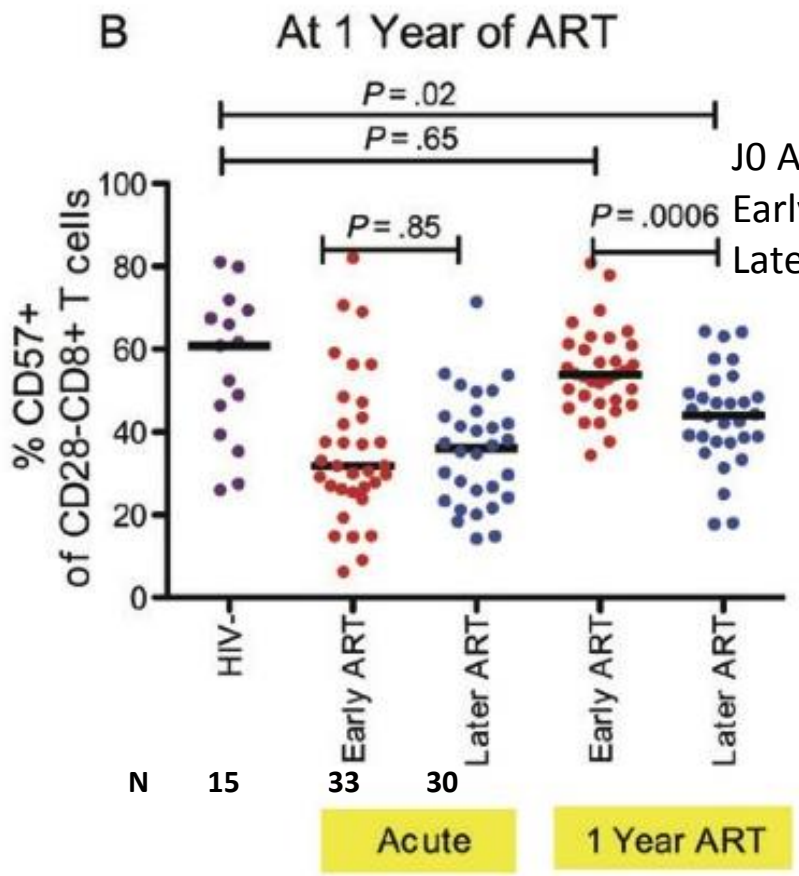
The apoptose resistance of the $CD28^-$ $CD8^+$ T cells leads to
- an accumulation of memory T cell pool: **ratio CD4:CD8 <1**
- an **excessive production of proinflammatory mediators such as TNFα, IL1β and IL6**

Tassiopoulos K et al J Infect Dis. 2012; 205:1730-8

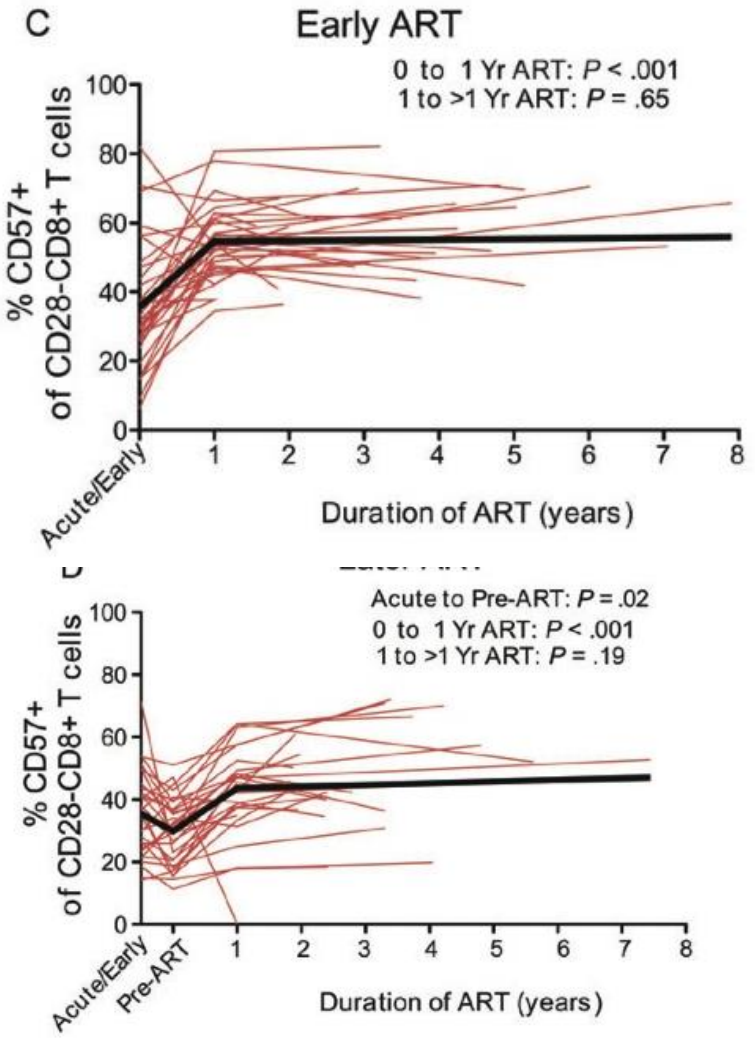
Low Proportions of CD28⁻ CD8⁺ T cells Expressing CD57 Can Be Reversed by Early ART Initiation and Predict Mortality in Treated HIV Infection

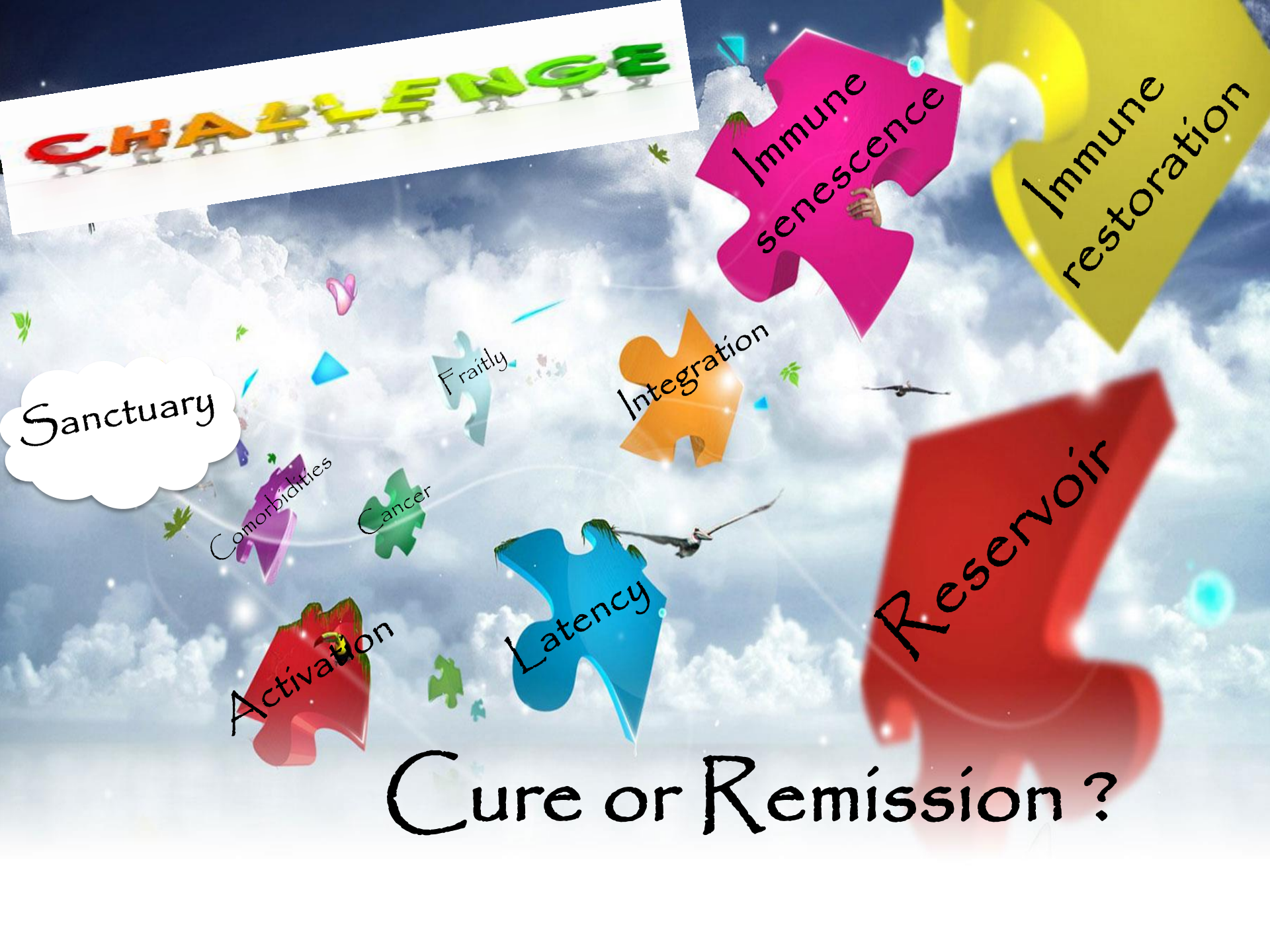
Sulggi A. Lee,[1] Elizabeth Sinclair,[1] Vivek Jain,[1] Yong Huang,[1] Lorrie Epling,[1] Mark Van Natta,[2] Curtis L. Meinert,[2] Jeffrey N. Martin,[1] Joseph M. McCune,[1] Steven G. Deeks,[1] Michael M. Lederman,[3] Frederick M. Hecht,[1] and Peter W. Hunt[1]

Journal of Infectious Diseases Advance Access published March 21, 2014



J0 ARV:
Early < 6 months
Later ⩾ 2 years




CHALLENGE
Immune senescence
Immune restoration
Sanctuary
Frailty
Integration
Comorbidities
Cancer
Reservoir
Activation
Latency
Cure or Remission ?