

Infection à VIH : une rémission possible

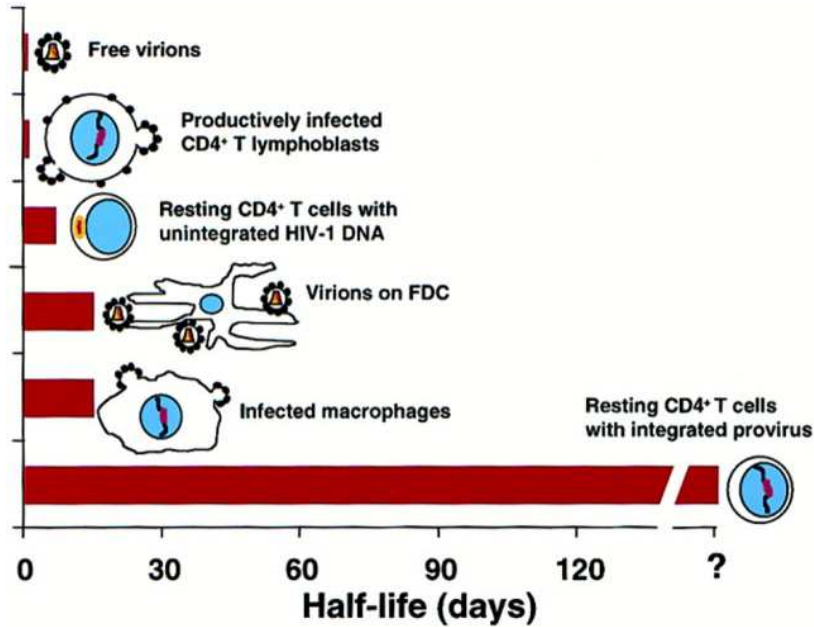


Asier Sáez-Cirión, PhD

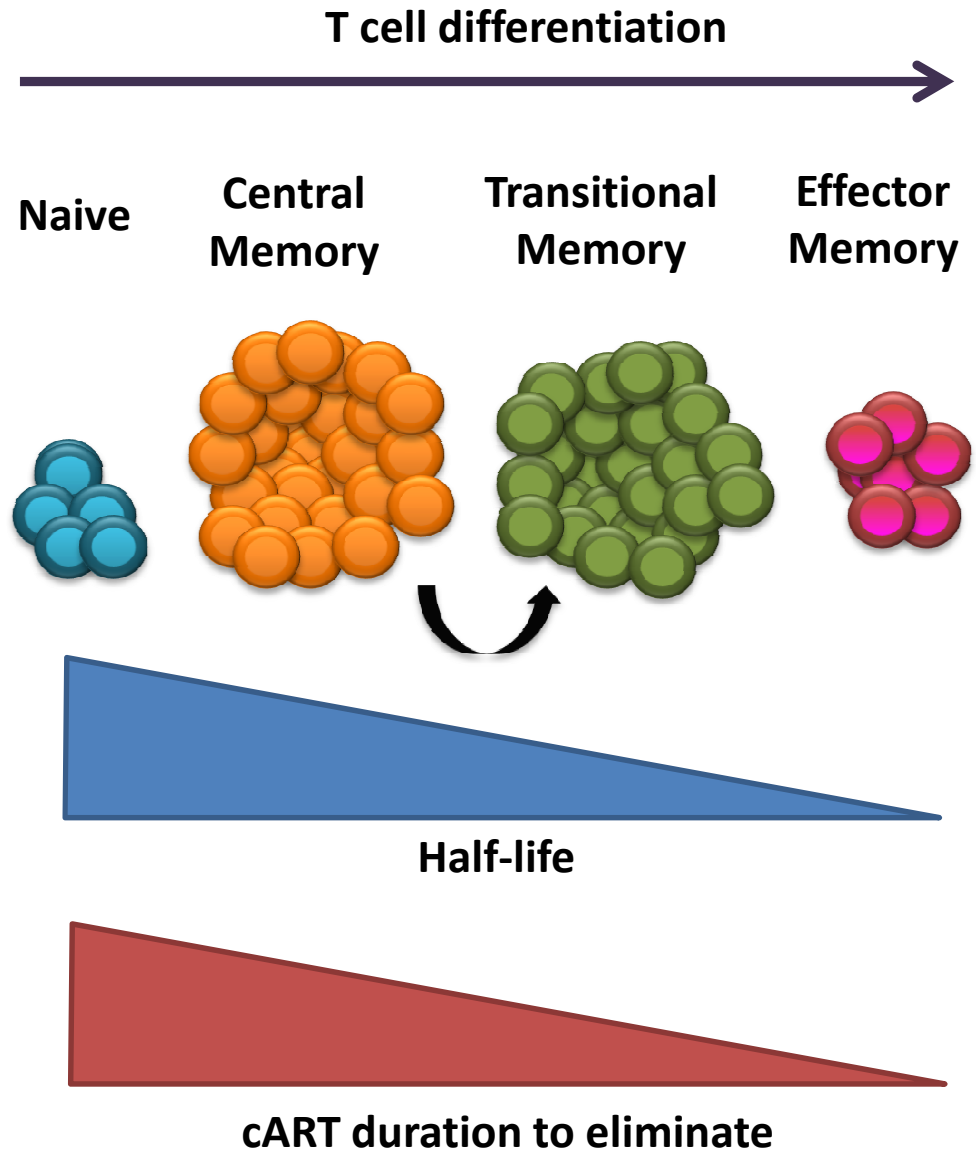
Unité de Régulation des Infections Rétrovirales
Institut Pasteur, Paris, France



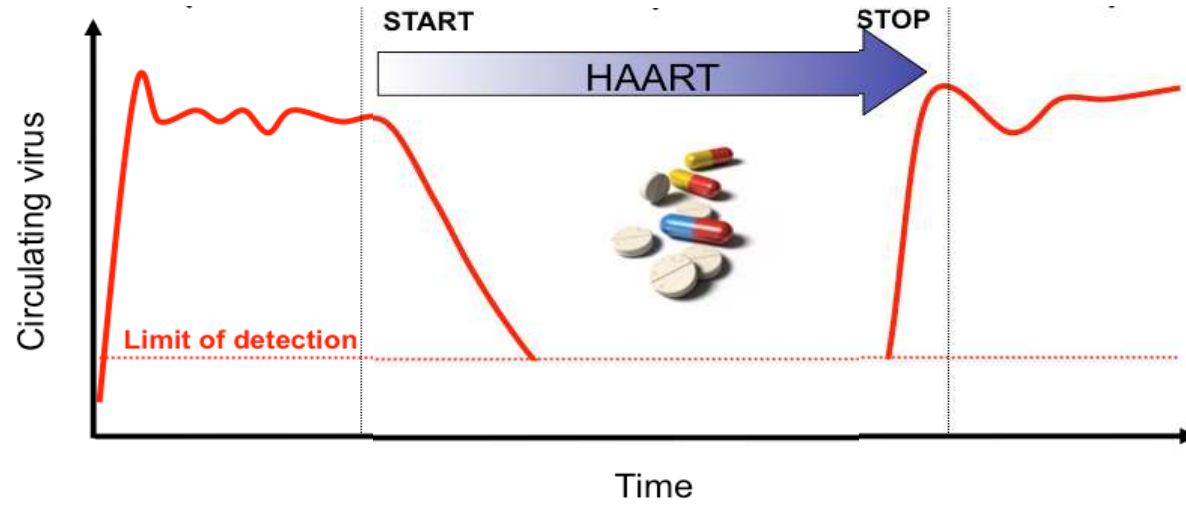
Viral reservoirs persist in HIV-infected individuals receiving cART



Finzi et al. Cells 1997



Viral replication resumes as soon as therapy is interrupted



Targeting viral reservoirs



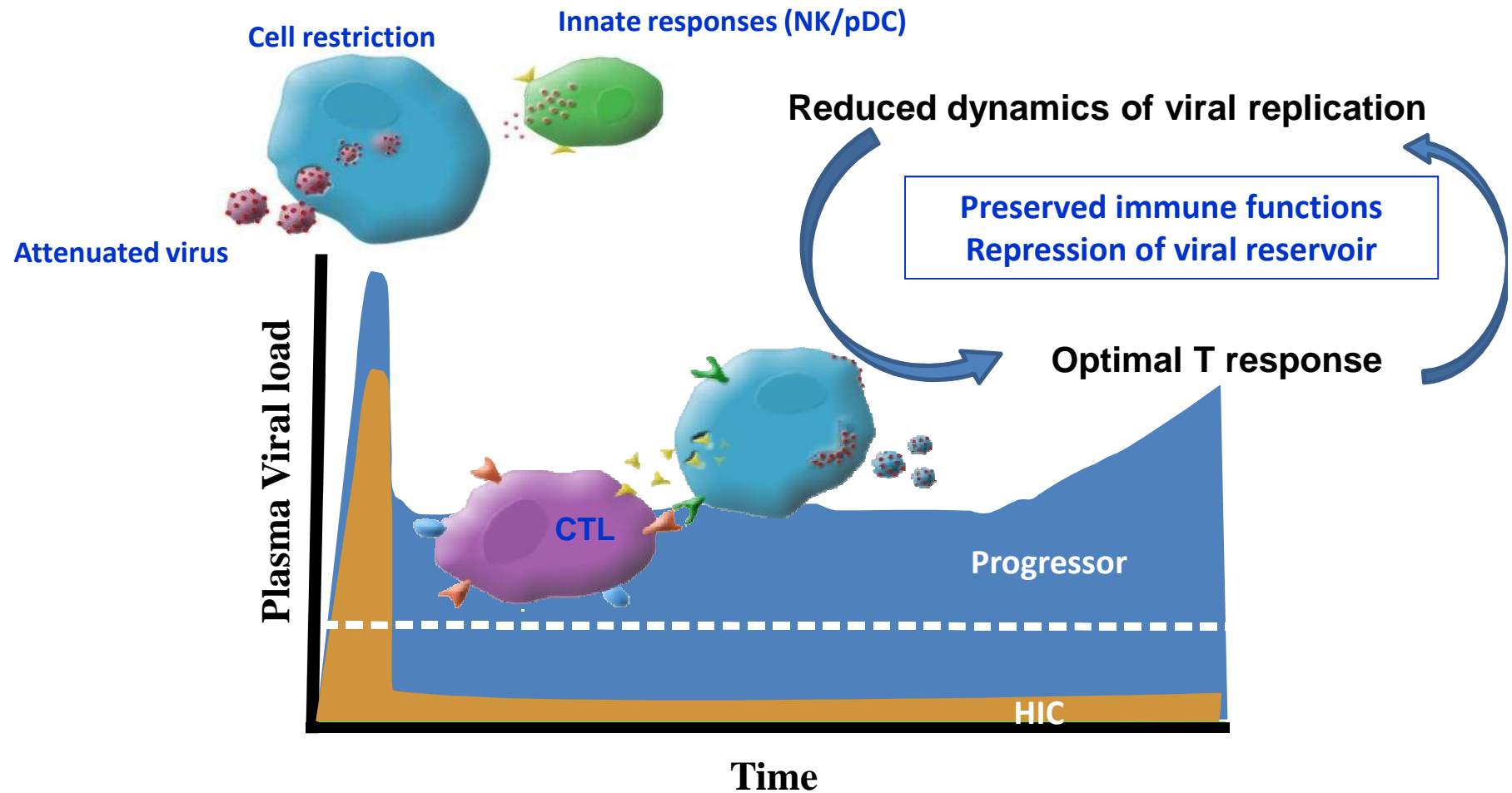
Draining → Eradication



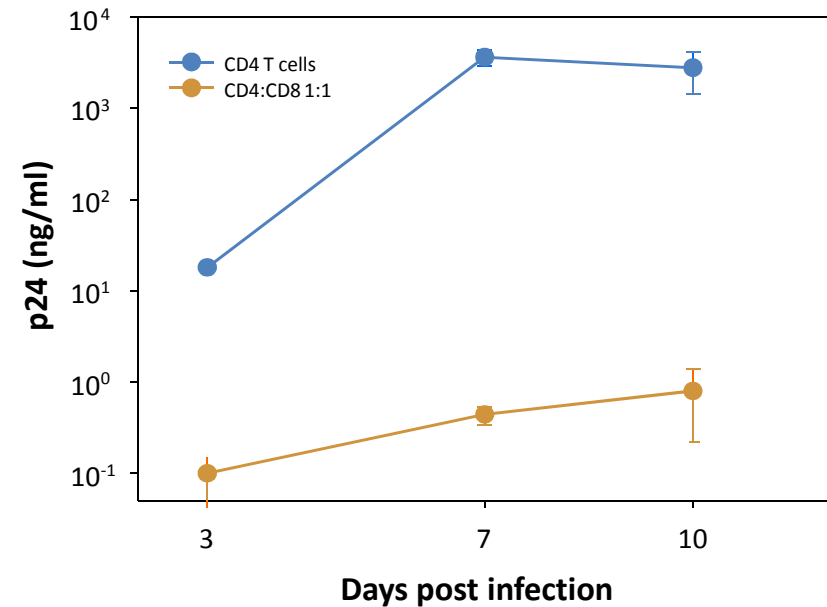
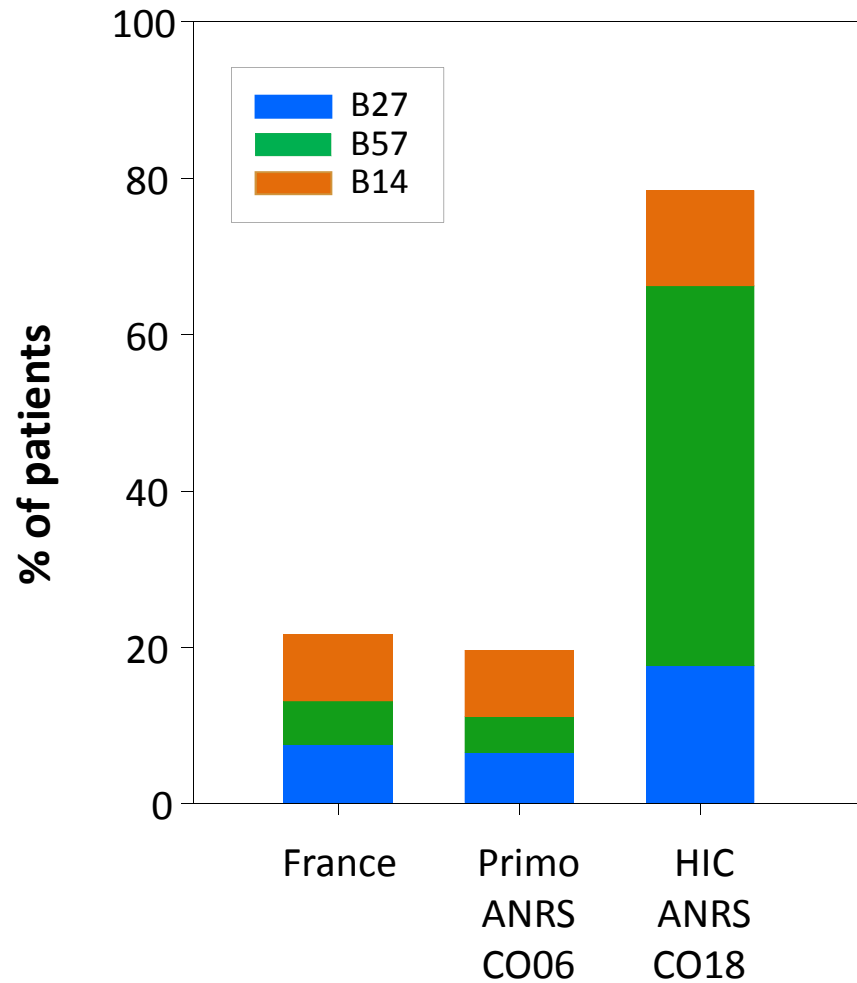
Limiting → Remission



HIV controllers (HIC): infected individuals spontaneously controlling HIV-1 infection



Favorable genetic background and Efficient CD8 T cell responses are associated with control



Saez-Cirion et al, PNAS 2007; Nature Protocols 2010

- **Greater and faster upregulation of cytotoxic mediators**
Migueles, et al. Immunity 2008; Hersperger, et al. PLoS Pathogens 2010
- **High functional avidity**—Almeida, et al. *JEM 2007*
- **MHC and TCR plasticity**—Chen et al *Nat Immunol 2012*; Pereyra et al *Science 2010*; Bailey et al *JEM 2006*

Is it possible to induce a HIV controller-like status?

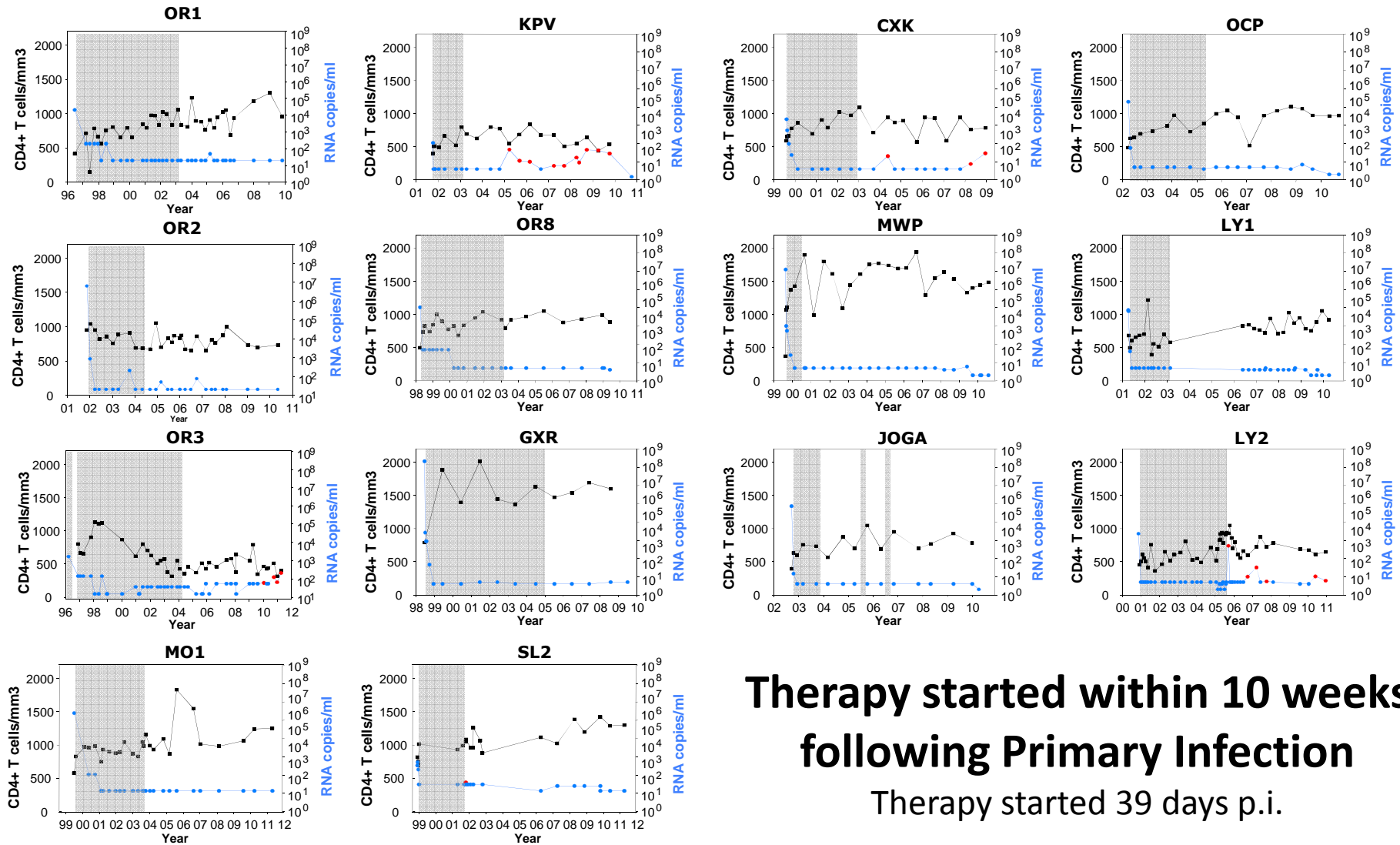


anRS)

VISCONTI Study

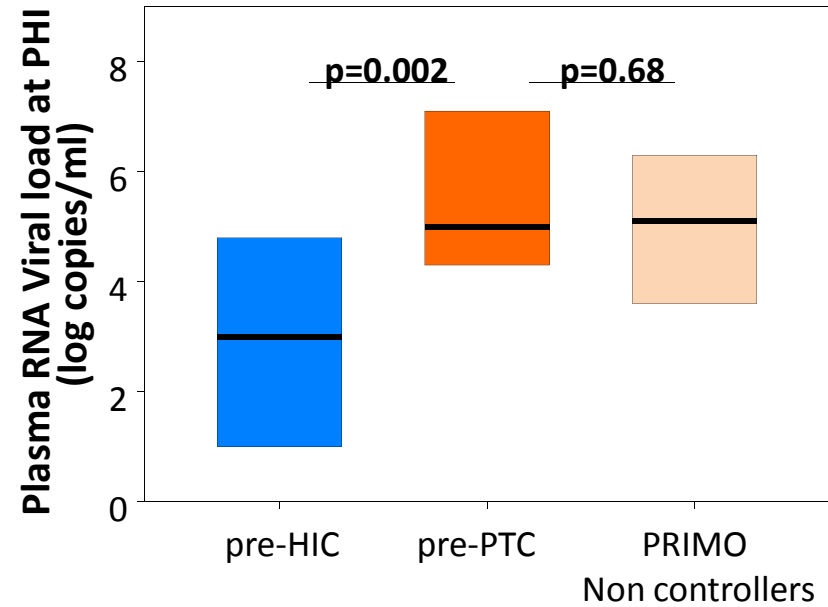
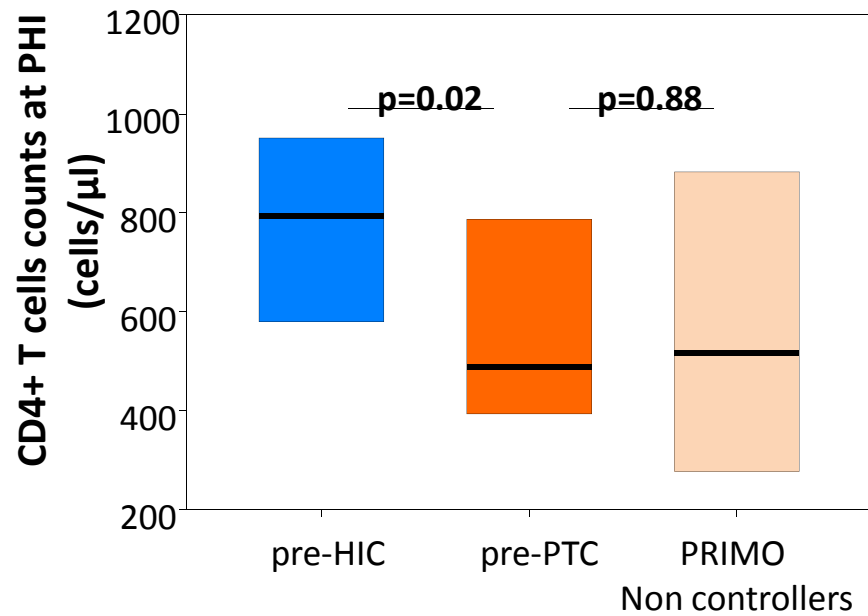
Virological and Immunological Studies in CONTrollers
after Treatment Interruption

ANRS VISCONTI : Post-Treatment Controllers (PTC)

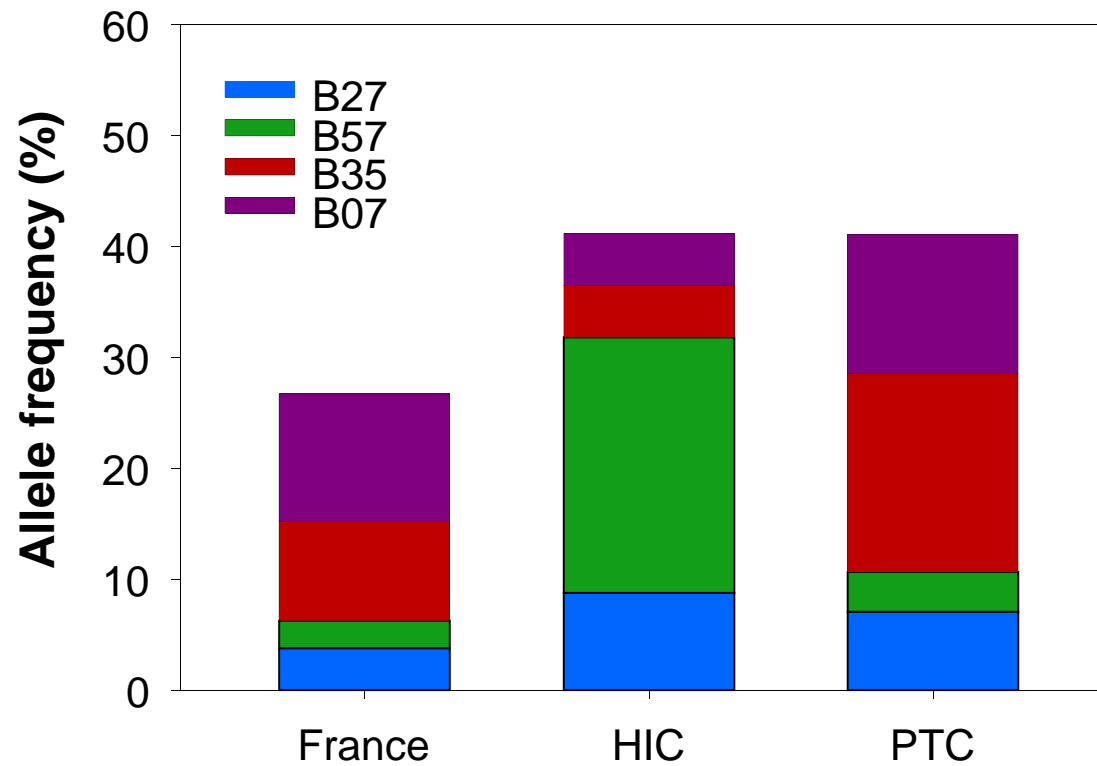


3 years on therapy followed by 7.5 years of control off therapy

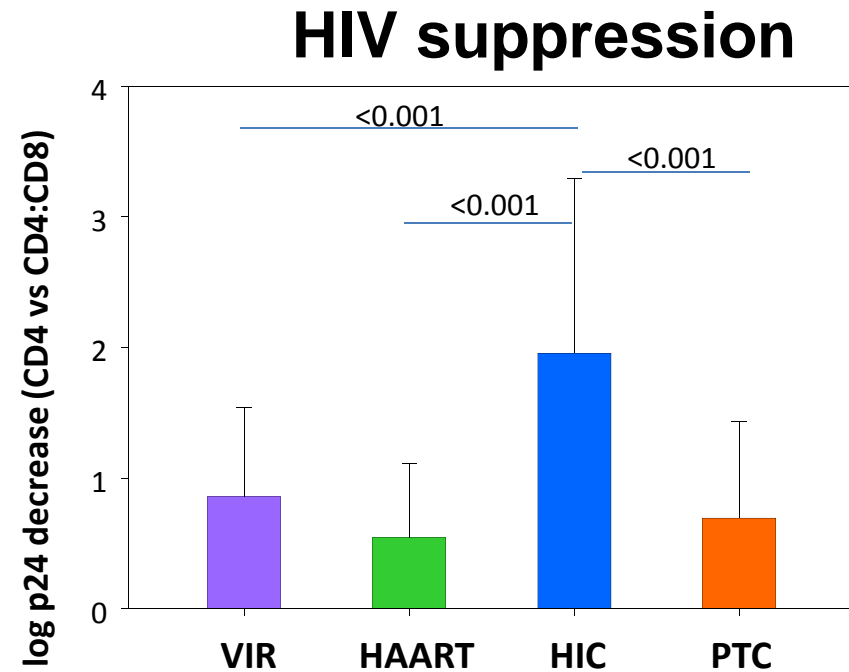
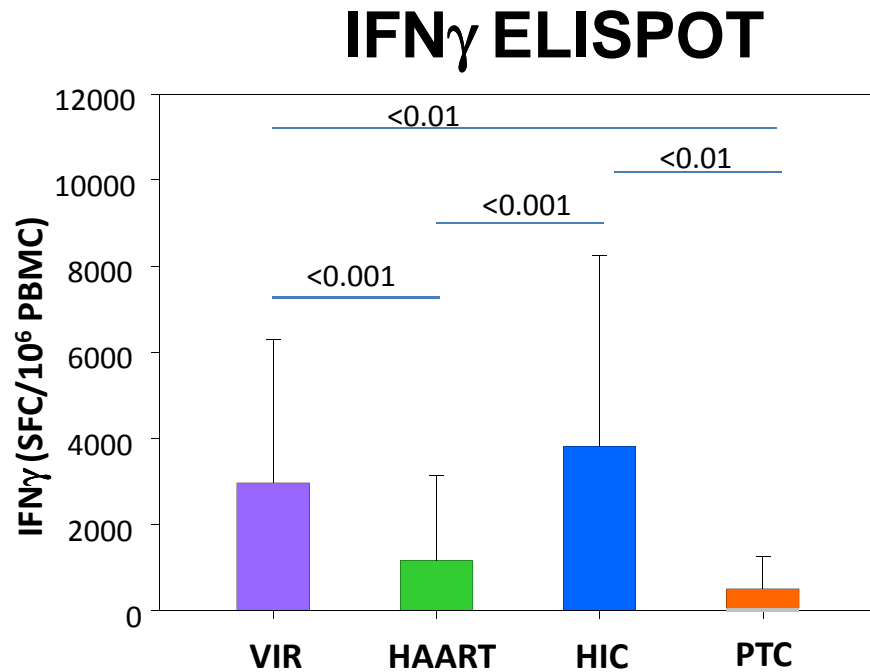
Post-treatment controllers have a tougher primary infection than HIV controllers



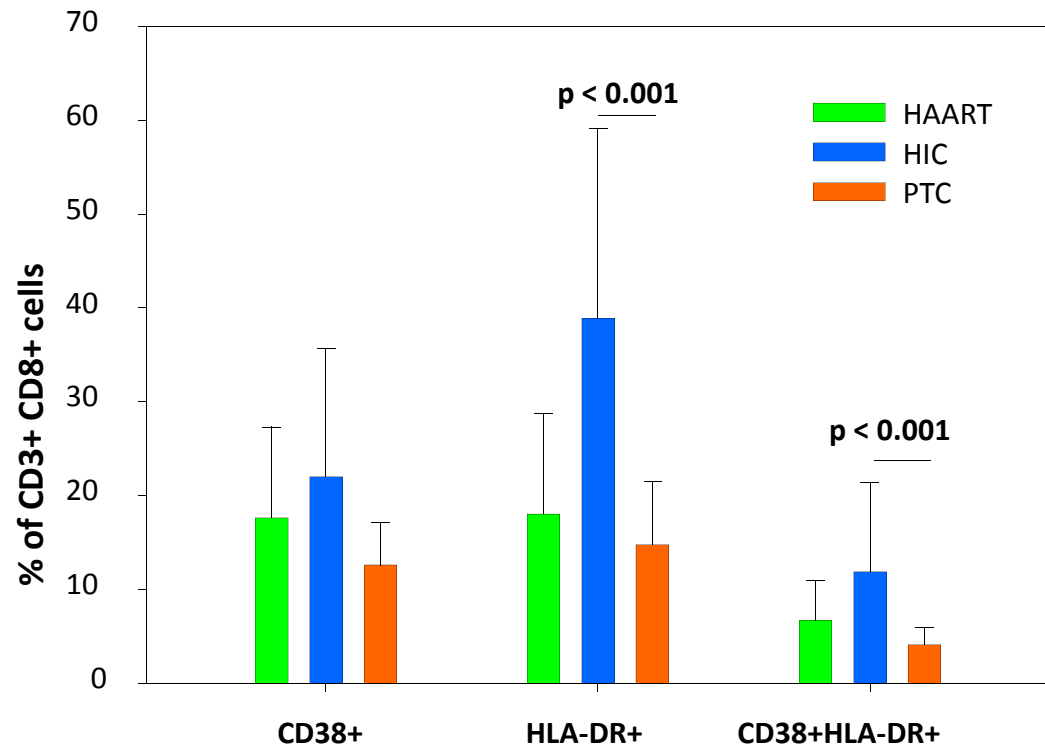
Post-treatment controllers don't have a favorable MHC background



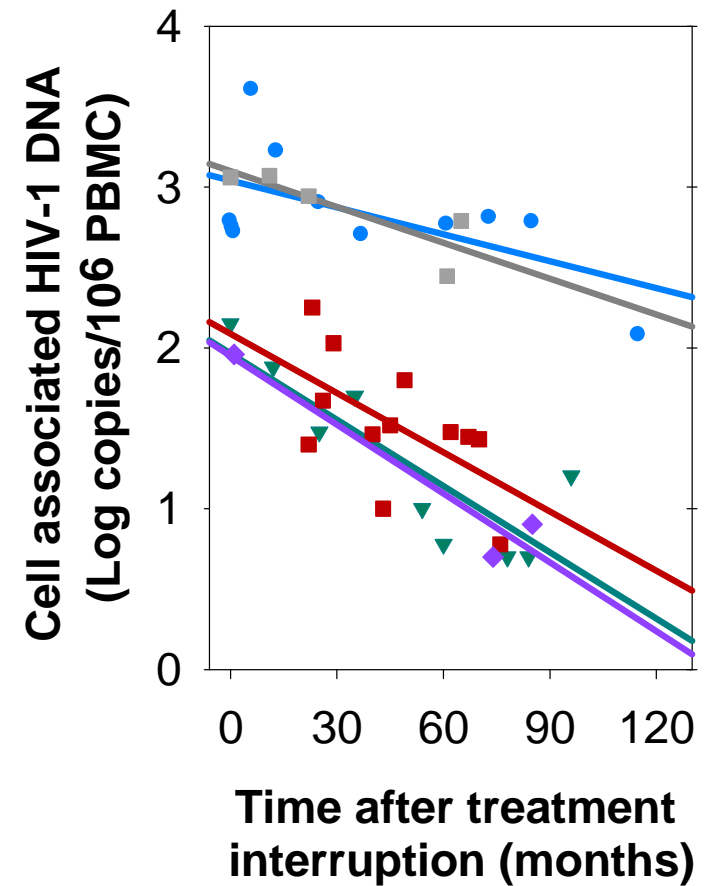
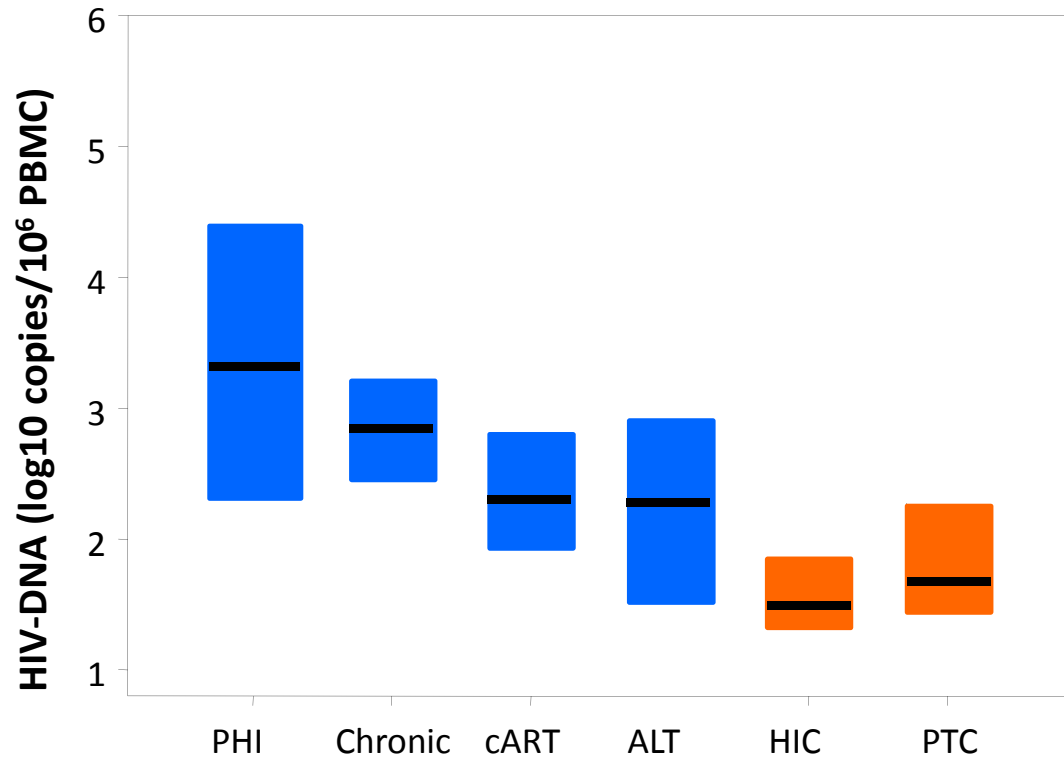
Post-treatment controllers have weak HIV-specific CD8+ T cell responses



Post-treatment controllers have weak levels of T cell activation

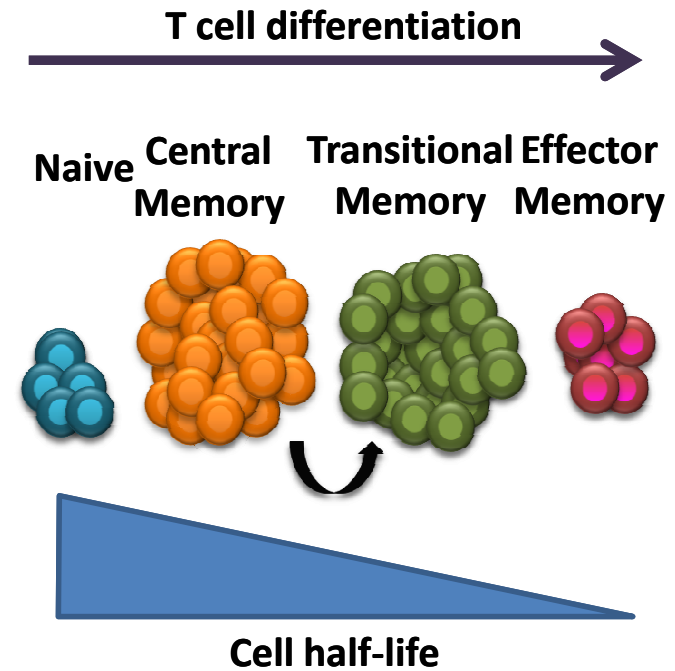
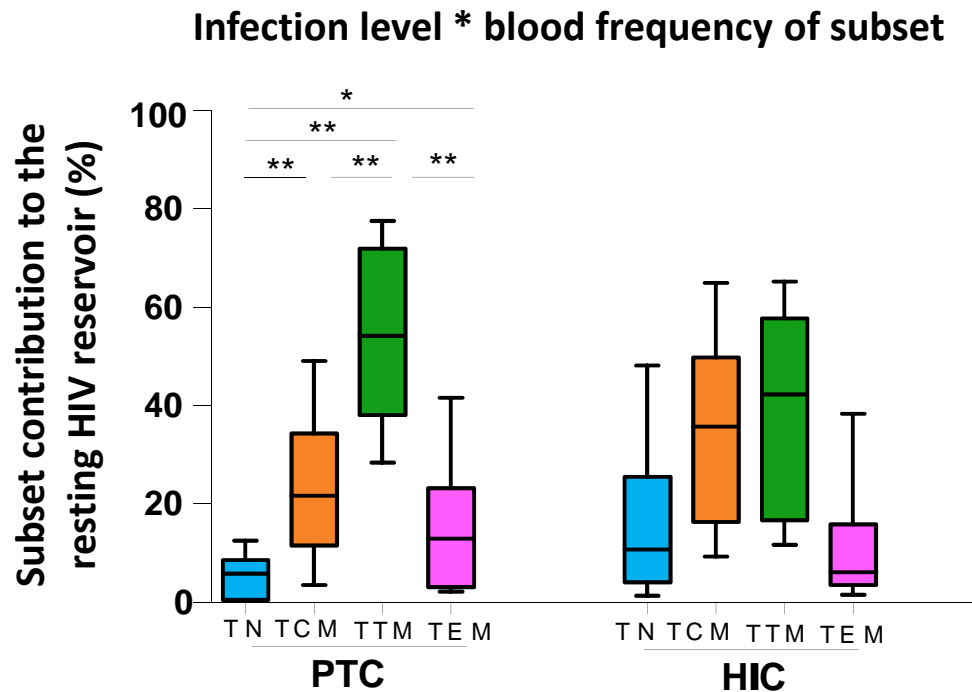


Post-treatment controllers have low levels of HIV-1 DNA in PBMC, which further decreased after treatment interruption in some cases



Skewed CD4 subsets distribution in PTC impacts the subsets contribution to the HIV reservoir

Resting CD4 Cell Subsets Contribution to the HIV reservoir



- A contribution to the HIV reservoir:
 - Major for TTM subset
 - Low for the TN and TCM subsets

A long-term treatment initiated during primary infection seems to increase the chances to control viremia

Natural control of infection: 81 HIC from **34 317 patients** followed-up: **0.24%**
Buffassa et al, PLoS One 2011

Early treatment induced control of infection:

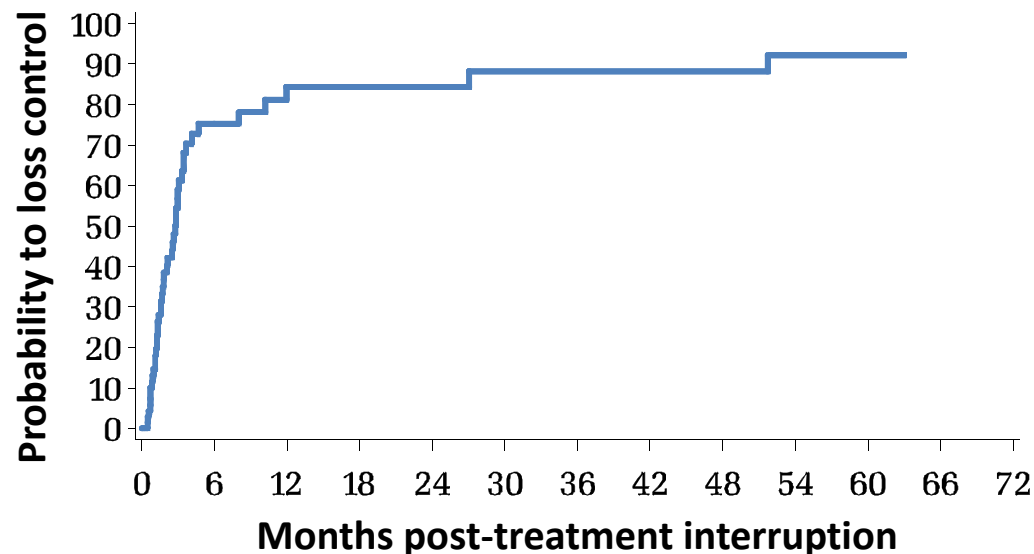
Hocqueloux et al AIDS 2010: N=32 patients, **15.6%** VL<50 at M24

Goujard et al Antivir Ther 2013: N=164 patients, **8.5%** VL<50 at M24

3538 patients included in the FHDH within 6 months of primary infection 1997-2011

756 patients treated within 6 months and at least for a year

74 patients with a viral load below <50 RNA copies/ml who stop



Probability to keep controlling infection at 24M (loss of control: 2VL>50 RNA copies/ml or 1VL>50 RNA copies/ml +cART) :
15.7% [6.5-28.5]

Saez-Cirion et al PLoS Path 2013

HIV controllers (HIC)

Asymptomatic primary infection, **low viral loads** and **high CD4** T cell counts in PHI

80% HIC carry one **protective HLA-class I** allele

Generally **strong HIV-specific T cell** responses with strong capacity to eliminate infected cells

Abnormal **high** levels of **T cell activation**

Estimated **frequency: 0.5%** of HIV infected patients

Post-Treatment Controllers (PTC)

Symptomatic primary infection, **high viral loads** and **low CD4** T cell counts in PHI

57% PTC carry one **HLA-class I** allele associated with **high viral loads**

Generally very **weak HIV-specific T cell** responses with poor capacity to eliminate infected cells

Low levels of **T cell activation**

Estimated **frequency: 5-15%** of HIV infected patients interrupting a >12 months-length treatment initiated in primary infection

Conclusions from the VISCONTI study

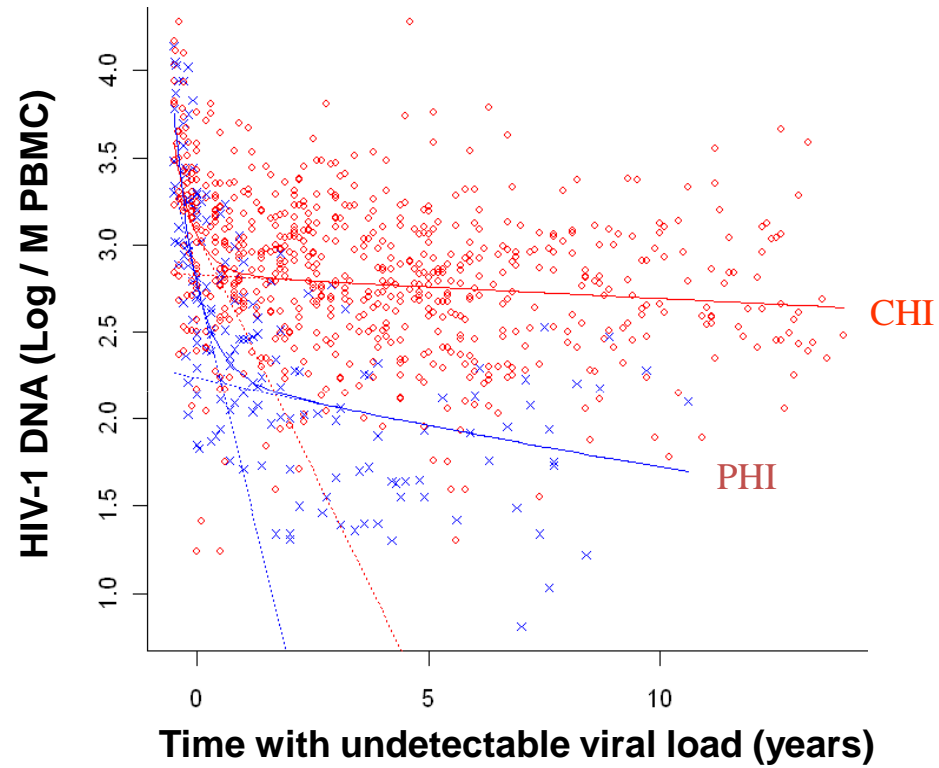
We have identified a group of HIV patients in virological remission, who are able to maintain a durable control of viral replication after treatment interruption.

Overall, these patients have a different HLA profile, lower frequency and quality of HIV-specific CD8+ T cell responses, and lower CD8+ T cell activation than “natural” HIV controllers.

Post-treatment controllers have a weak HIV reservoir in which there is a minor contribution of long-lived cells.

Post-treatment control Patients in the VISCONTI study was likely achieved through early and long-lasting therapeutic intervention.

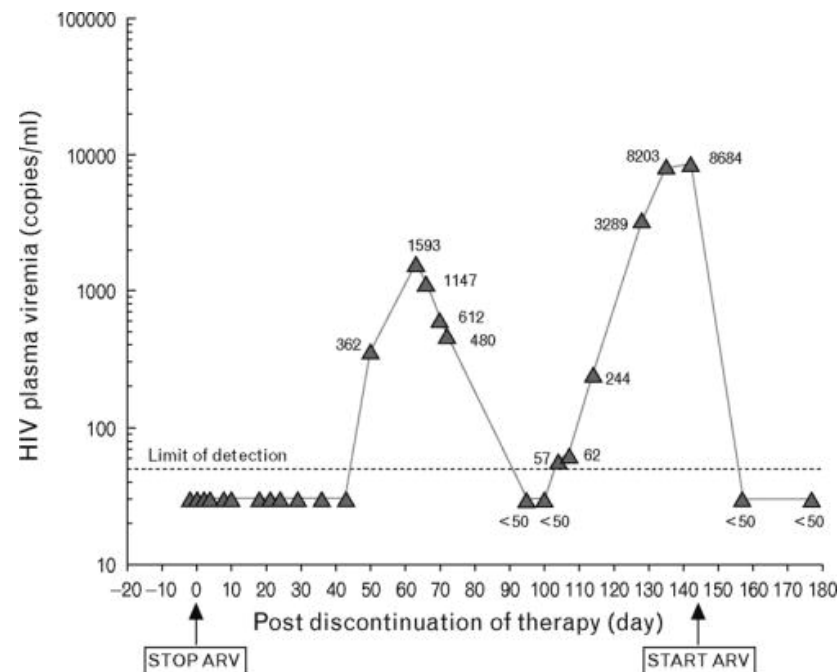
cART initiation during primary infection deeply impacts on HIV reservoirs



However, a weak HIV reservoir is not enough

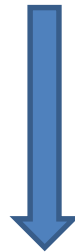
Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication

Tae-Wook Chun^a, J. Shawn Justement^a, Danielle Murray^a,
Claire W. Hallahan^a, Janine Maenza^b, Ann C. Collier^b,
Prameet M. Sheth^c, Rupert Kaul^c, Mario Ostrowski^c, Susan Moir^a,
Colin Kovacs^c and Anthony S. Fauci^a



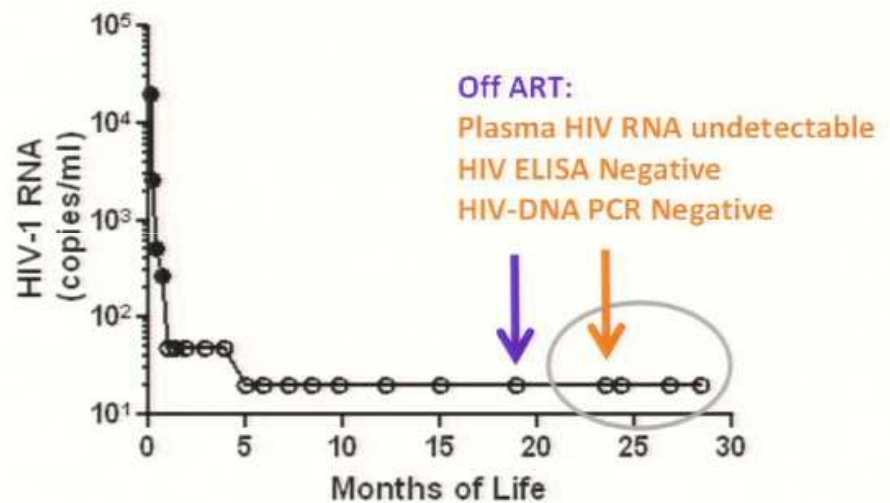
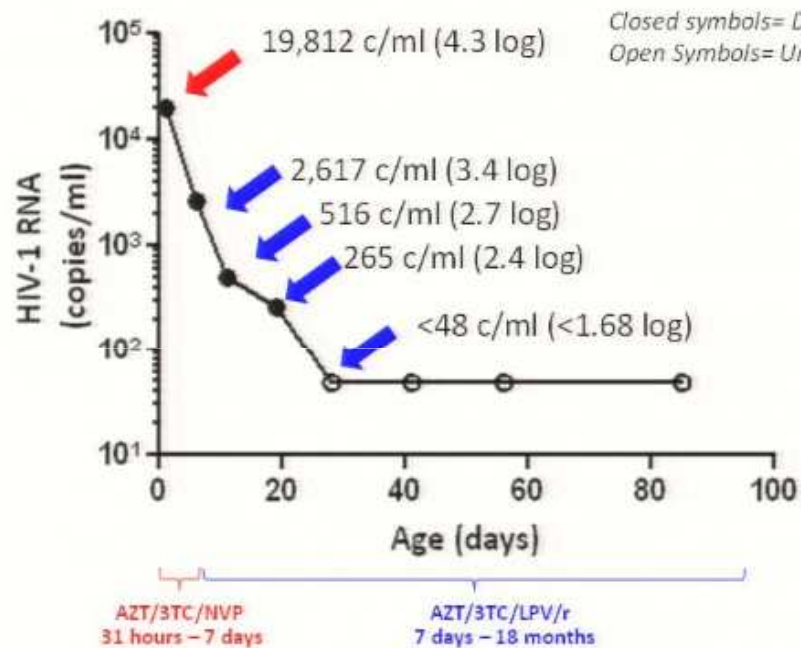
EARLY TREATMENT

Limiting the establishment of the viral reservoir
Limiting viral diversity
Reducing immune activation
Preserving and cooperating with immune responses



**Limiting the dynamics of viral replication in acute infection
may be crucial for spontaneous control of infection**

HIV remission in a 28-month old Perinatally-infected child (Mississippi Toddler)



Regimen #1: AZT/3TC/NVP (31 hours-7 days of life)
Regimen #2: AZT/3TC/LPV/ritonavir (7 days-18 months of life)

World-wide observations of post-treatment controllers



Remember: treatment interruption is not recommended outside structured protocols!!!

OBJECTIVES

- **To build an international cohort of Post Treatment Controllers in order to :**
 - Uncover mechanisms underlying viral control, i.e. HIV remission
 - Identify predictive markers associated with viral control after treatment interruption
- **Main Outcome:**

To identify patients in whom HAART could be safely interrupted

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Patients and clinicians who participate in the studies



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**ANRS CO6
 “PRIMO”**

**ANRS CO18
 “HIV controllers”**

**ANRS CO15
 “ALT”**

**FHDH
 “French Hospital
 Database on HIV”**