UNSW AUSTRALIA

Kirby Institute Symposium

Kirby Institute

Global Challenges in Infectious Disease

17th July 2014 - Sydney

How host response to HIV can make the difference?

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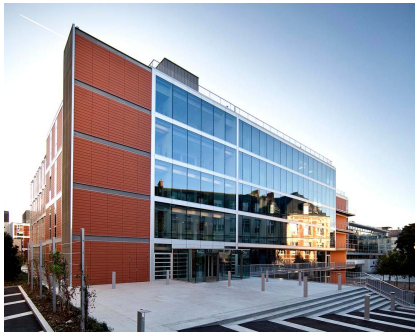


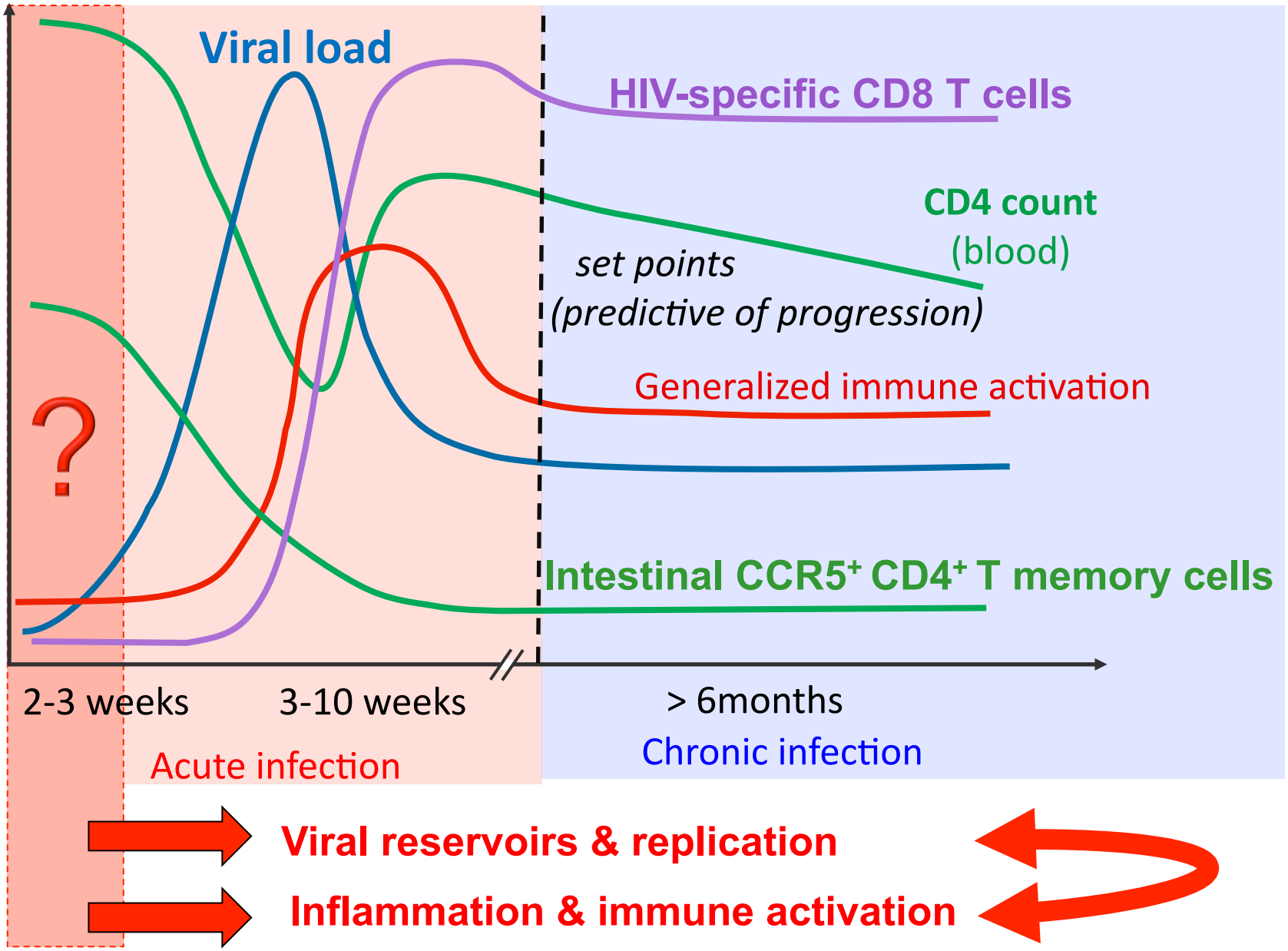
International AIDS Society
Stronger Together Against HIV

Institut Pasteur

AIDS 2014 20th International AIDS Conference Melbourne, Australia July 20-25, 2014 WWW.AIDS2014.ORG
STEPPING UP THE PACE

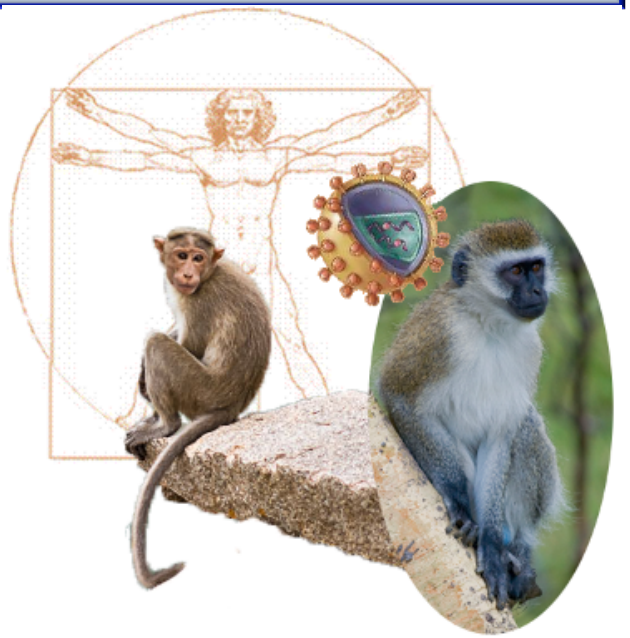
Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Early events during acute HIV infection



Models of protection against HIV/SIV pathogenesis

Control of HIV infection



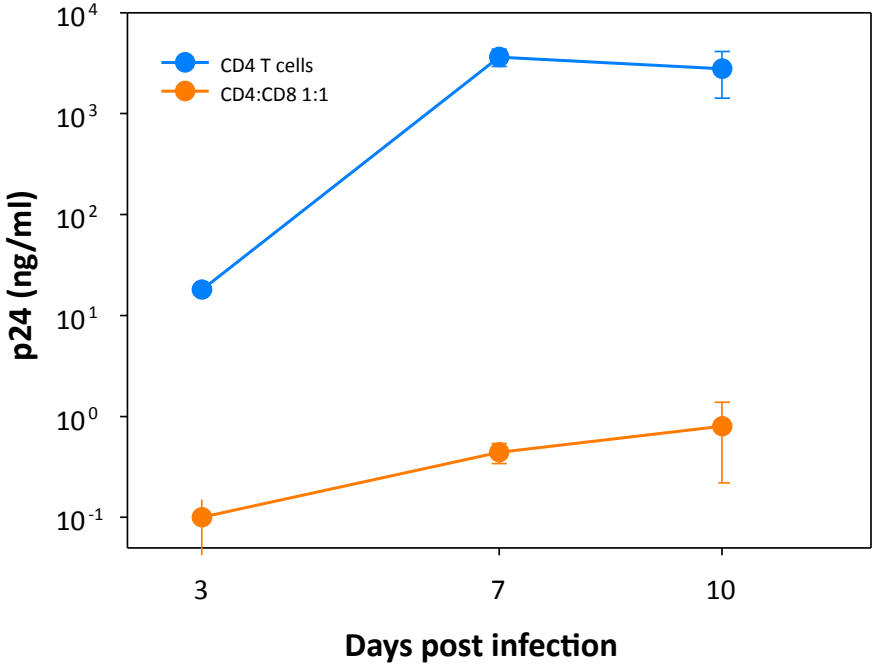
HIV controllers (HIC)
~0.5% of HIV+ individuals, cART naive infected for >5 years

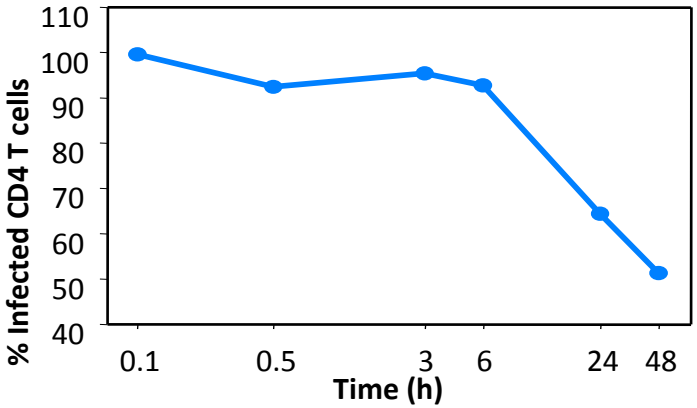
Post treatment controllers (PTC): Visconti cohort *(5-15% of early treated HIV+ individuals)*

Control of abnormal immune activation

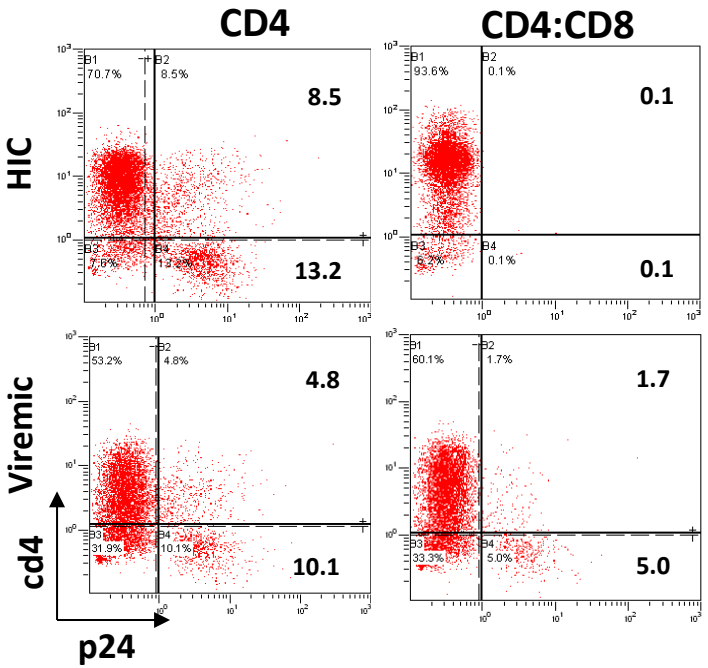
Non pathogenic SIV infection
African Green Monkeys (AGM)

Non stimulated CD8 T cells from HIC have strong HIV (cytotoxic) suppressive capacity





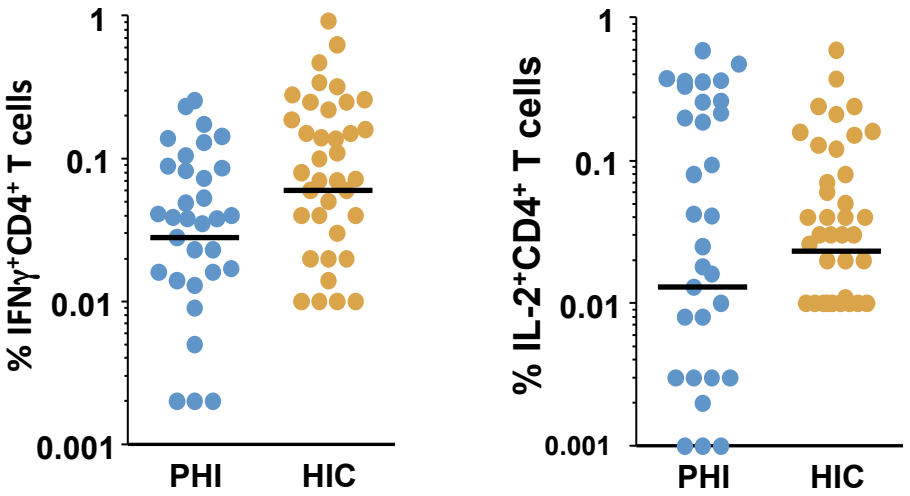
Saez-Cirion et al, PNAS 2007; Nature Protocols 2010

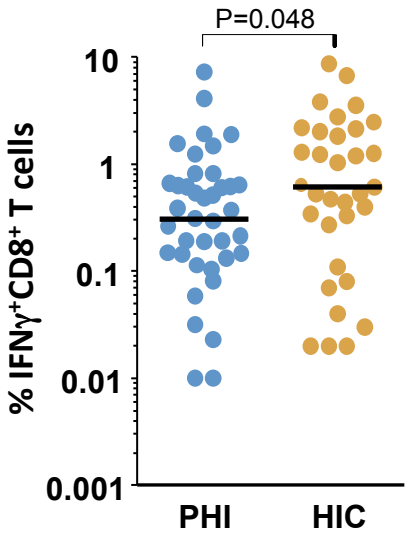


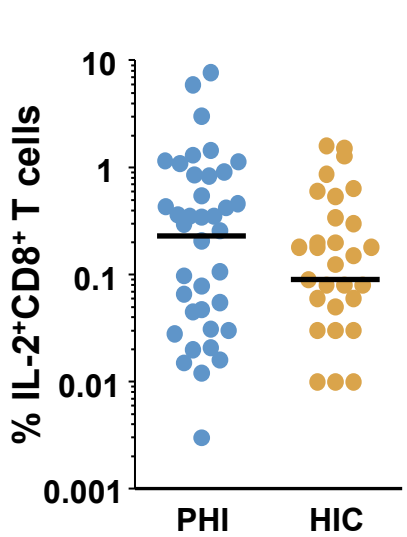
- **HIV-specific CD8+ T cells from LTNP exhibit greater upregulation of cytotoxic mediators**
  – *Migueles, et al. Immunity 2008*

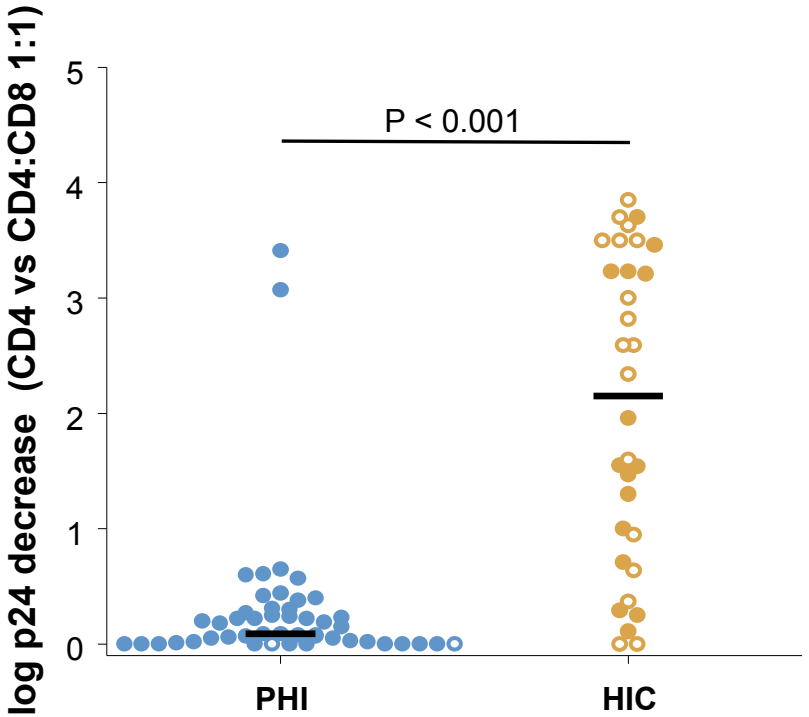
- **HIV-specific CD8 T cells from Elite Controllers Rapidly Upregulate Perforin**
  – *Hersperger, et al. PLoS Pathogens 2010*

Strong CD8+ T cell capacity to suppress HIV-1 is usually absent in PHI







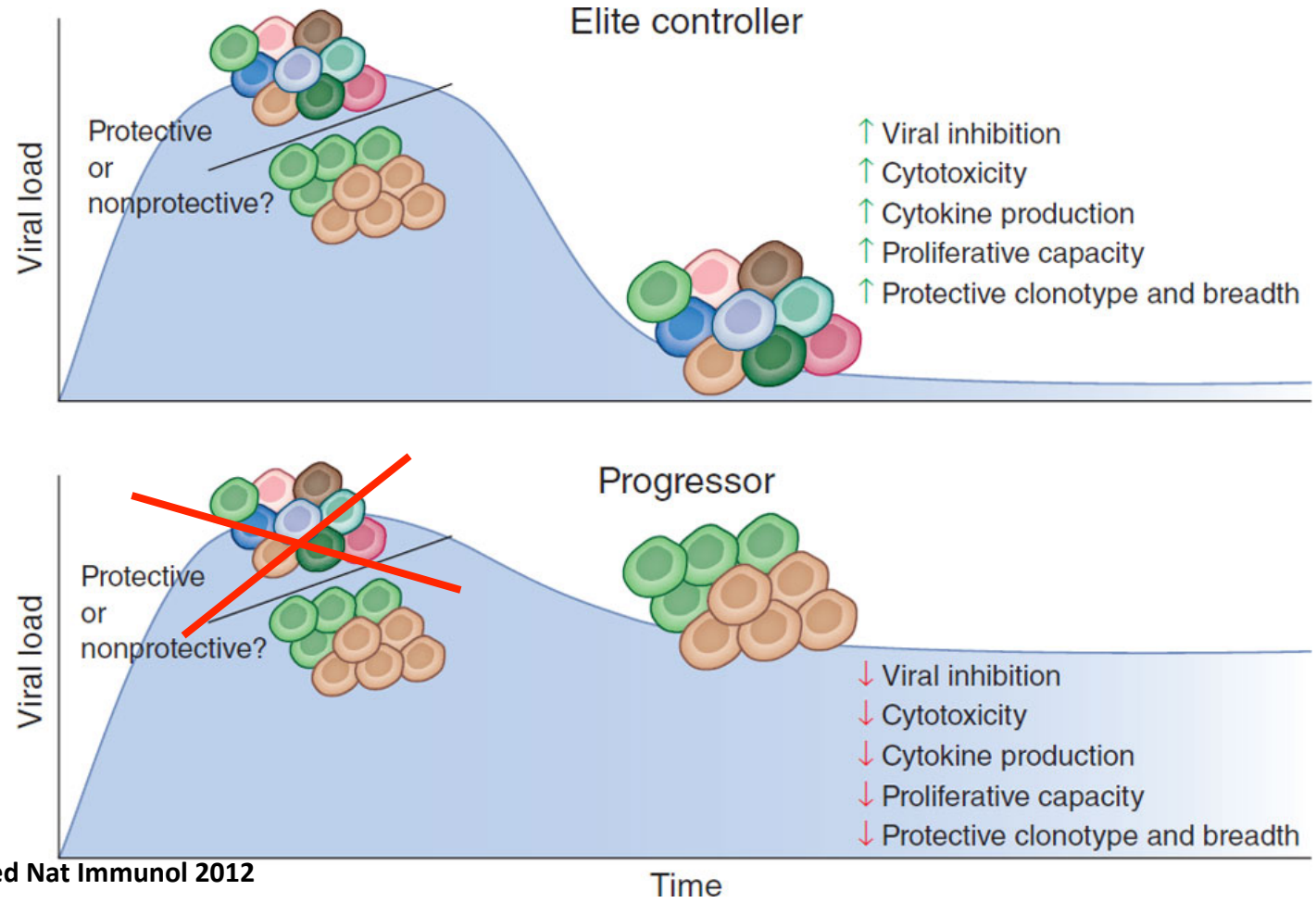


50 patients in PHI (median 35 days p.i.)

Median drop of -0.94 log HIV-1 RNA copies/ml within 7 days

Lecuroux et al PLoS One, 2013

The higher HIV-suppressive capacity of CD8+ T-cells from HIC is likely related to intrinsic characteristics of their cells

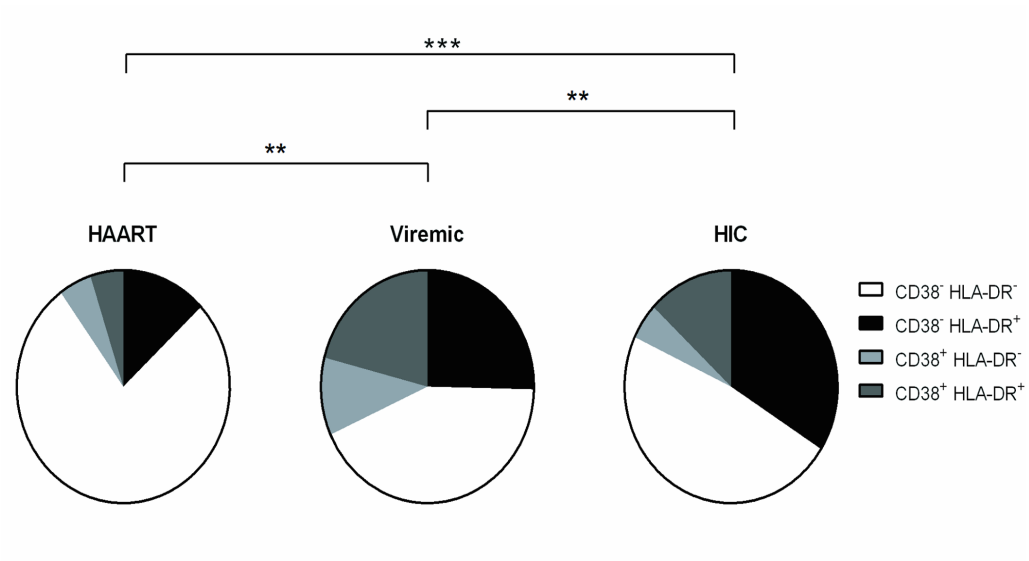


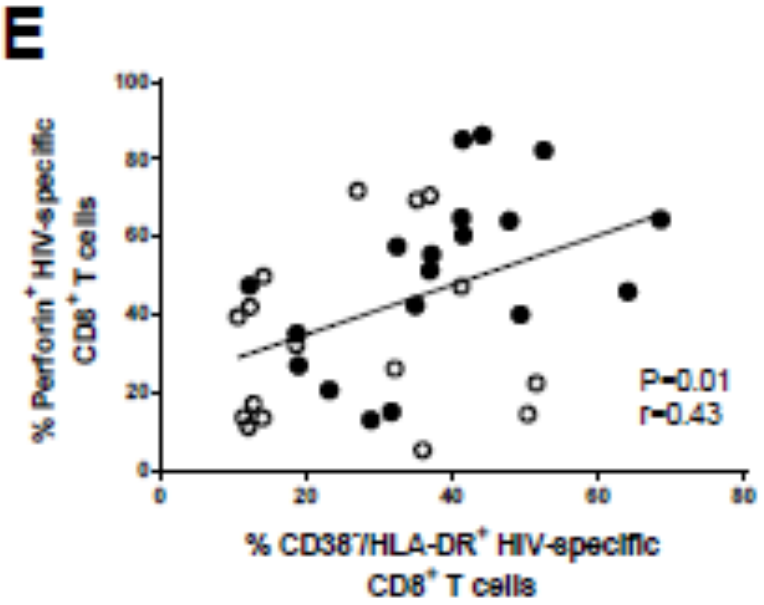
Feinberg and Ahmed Nat Immunol 2012

High functional avidity–Almeida*, et al. JEM 2007*

MHC and TCR plasticity–Ladell et al Immunity 2013; Chen et al Nat Immunol 2012; Pereyra et al Science 2010; Bailey et al JEM 2006

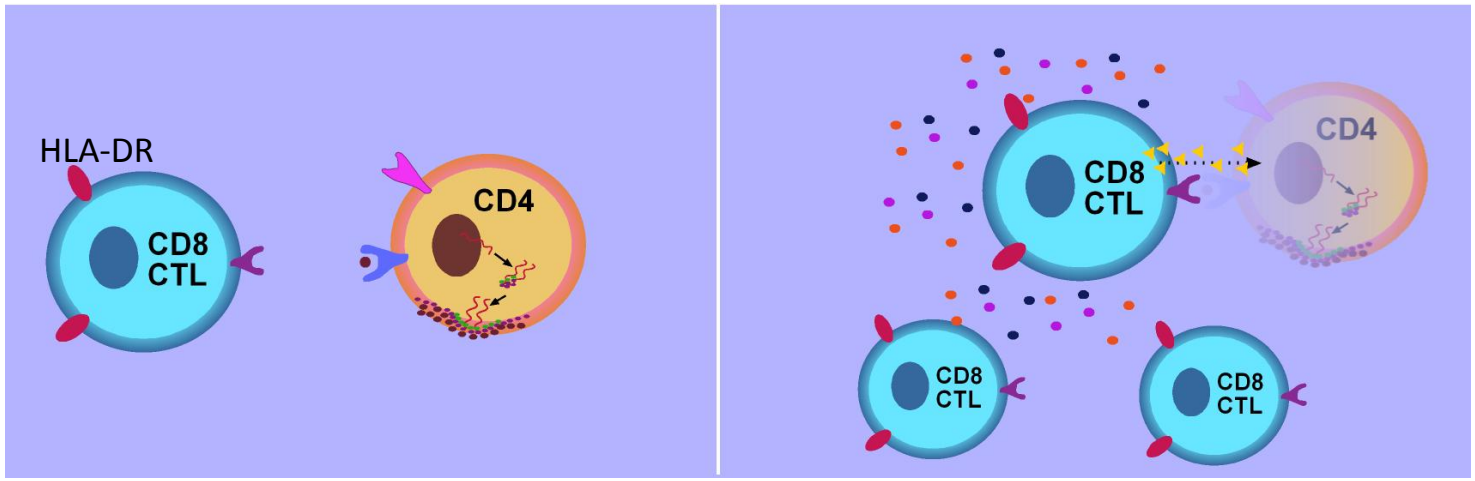
CD8+ T cell mediated HIV suppression is associated to a peculiar activation phenotype (DR+CD38-)



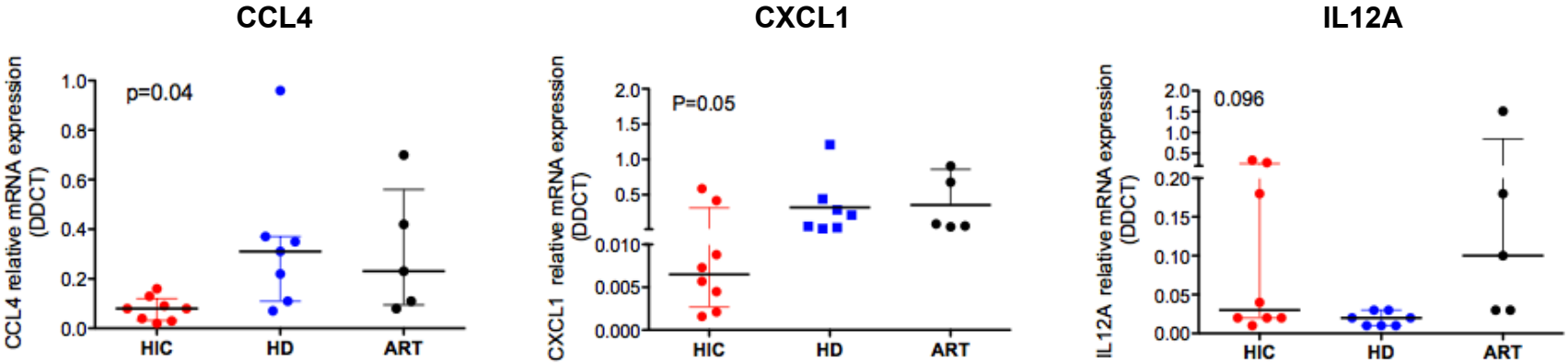


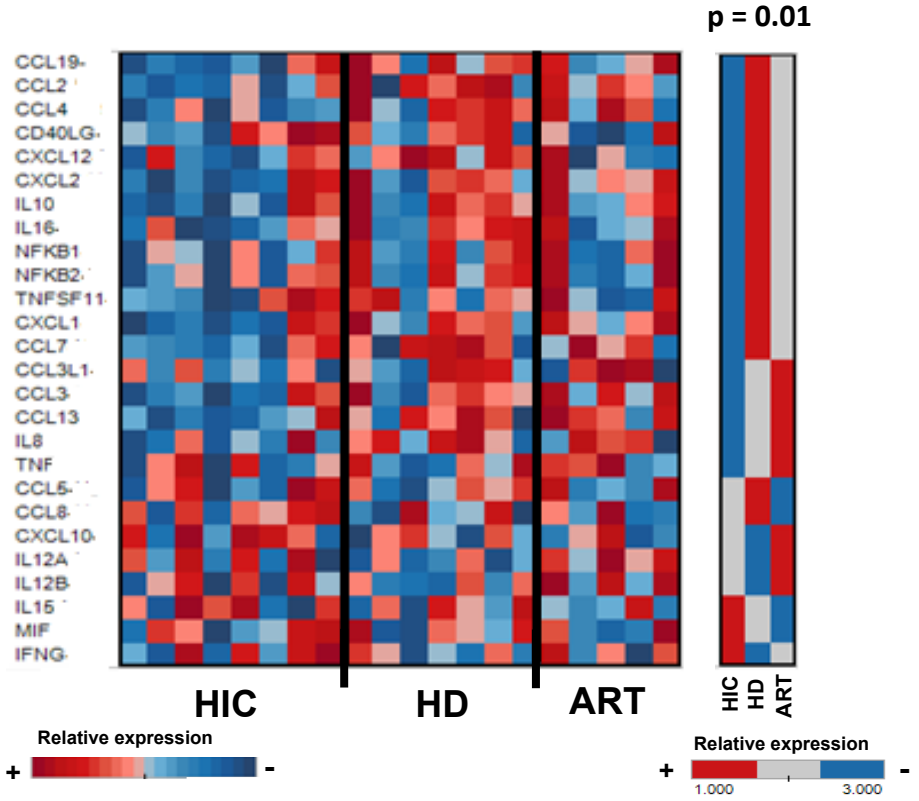
Hua et al, PlosOne 2014

HLA-DR+/CD38- phenotype ⟶ **Proliferation… and effector function?**



Circulating mDC from HIC: non inflammatory profile



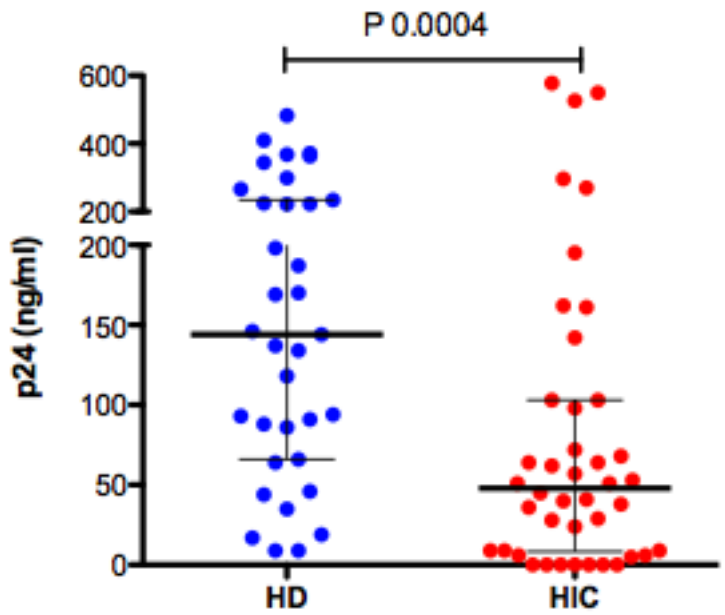


Hamimi et al, in preparation

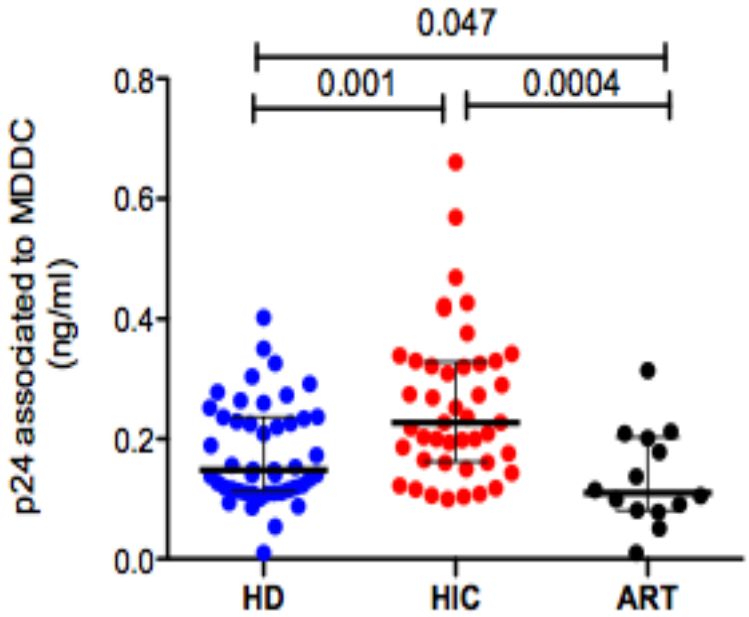
MDDC from HIC: resistant to infection but highly efficient in capture of viral particles

Monocytes isolation (CD14+) → GM-SCF + IL4, 6-7Days → MDDC

HIV-1 susceptibility



HIV-1 capture



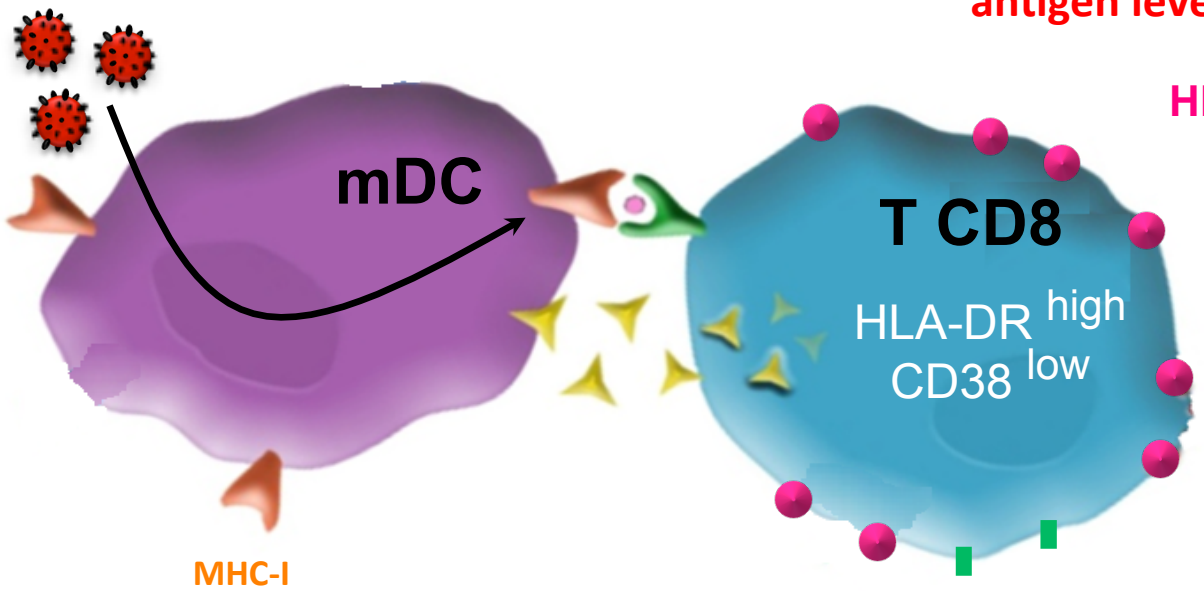
No enhanced capture of small antigens or antigen processing.

Hamimi et al, unpublished

Role of mDC from HIC in the priming of CD8+ T cells

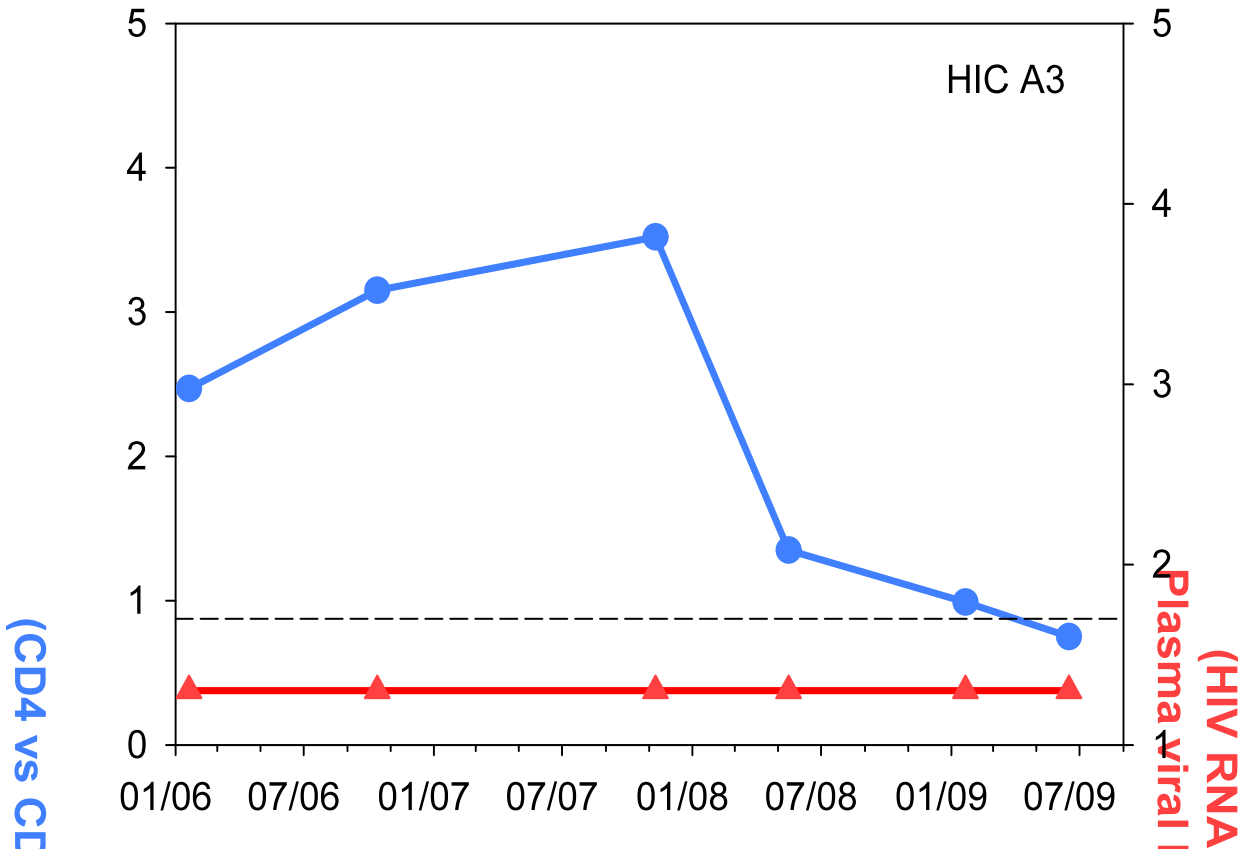
mDC reduced HIV-1-susceptibility → Preserved mDC functions?

Enhanced HIV capture → Efficient induction of CD8+ T cell responses despite low antigen levels?



Non-inflammatory transcriptional profile → Low inflammatory context…

CD8+T cell responses wane over time in some HICs while maintaining perfect control of infection



No antigenic stimulation? Highly reactive memory T cells?

CONCLUSIONS

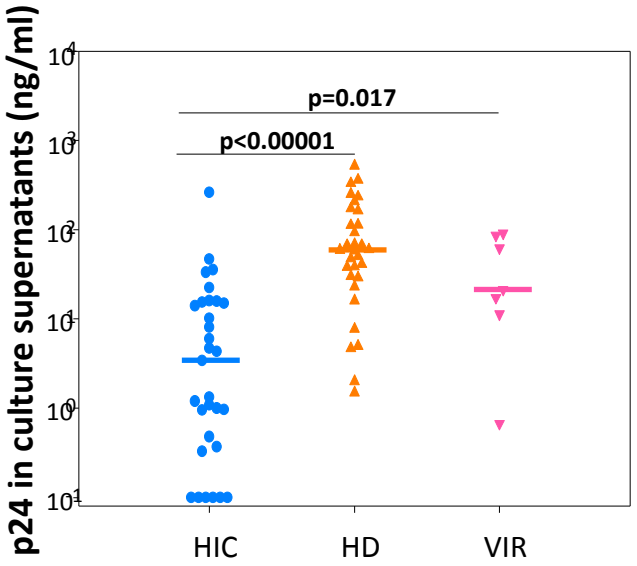
- **A robust efficient CD8+ T cell response is likely important for establishing natural control of infection, but this effector response may be no longer required (contraction) once control at particular low levels has been achieved.**

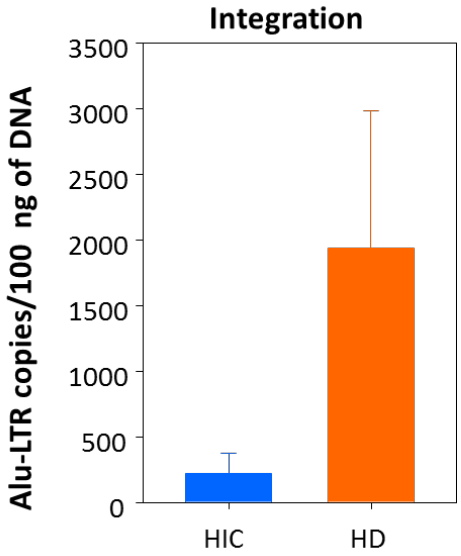
- **Controllers are characterized by a very early control and extremely low reservoirs**

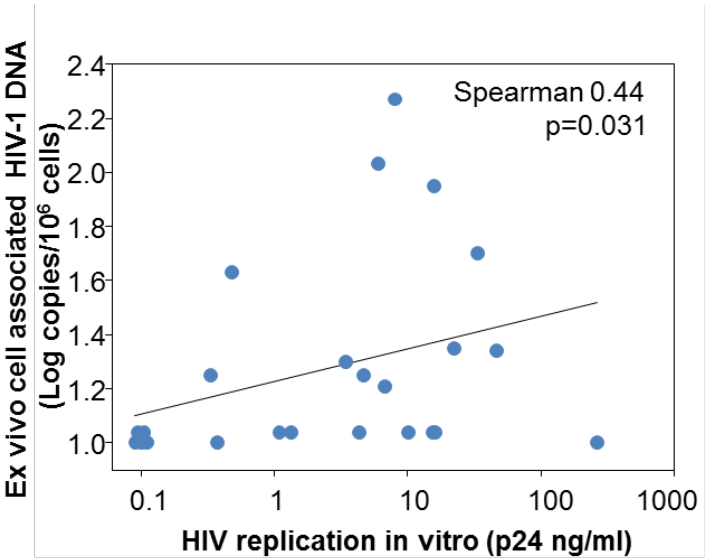
Additional innate mechanisms of control?

Intrinsic cell resistance may contribute to limit the size of HIV reservoir in HIC

CD4+ T cells and macrophages from HIC have reduced susceptibility to HIV-1 infection



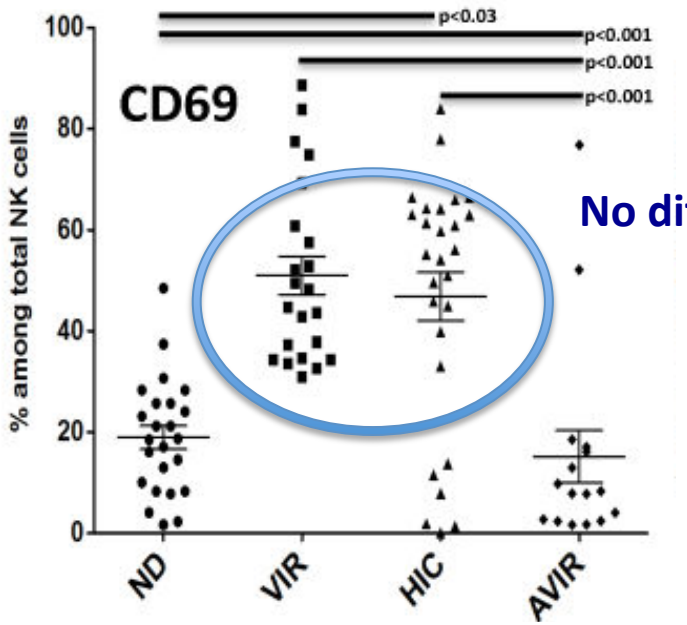




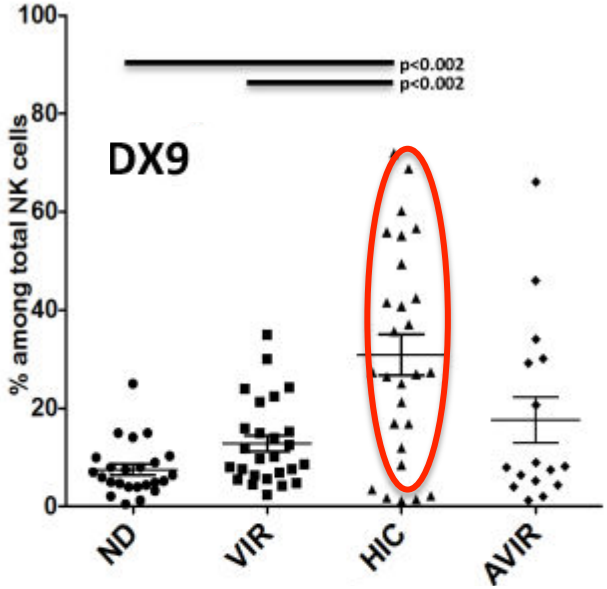
Sáez-Cirión et al Blood 2011

See also Chen et al JCI 2011, Buzon et al JVI 2011; Graf et al PLoS Path 2011

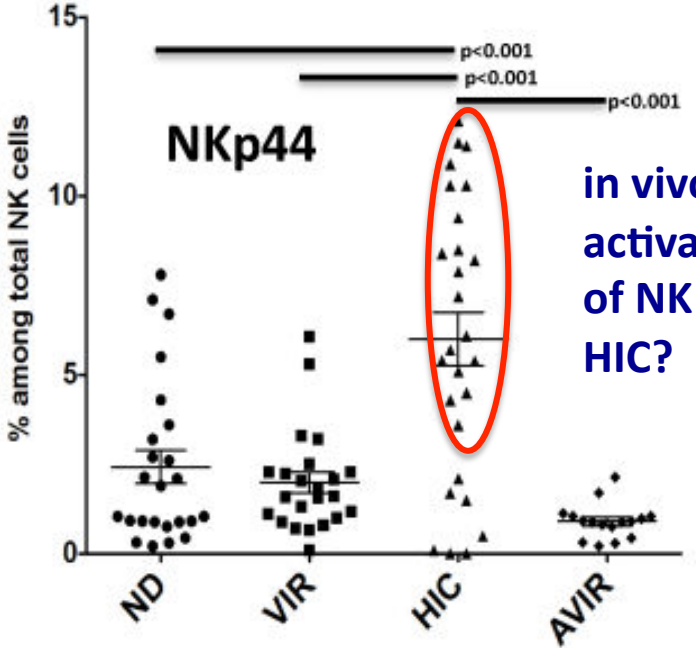
Phenotypic and functional features of NK cell activation suggest a role of NK cells in viral control in HIC



No difference



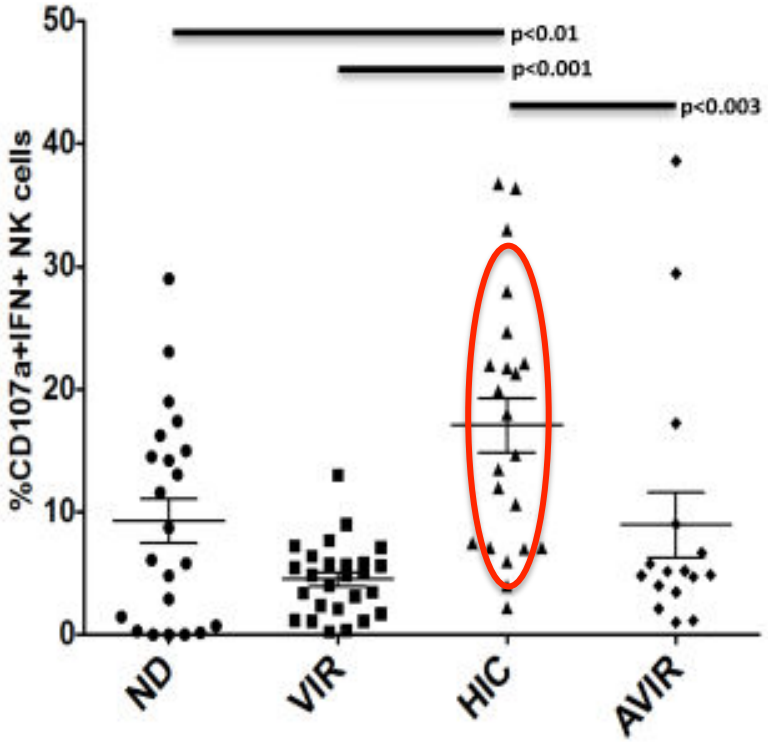
Association with ADCC

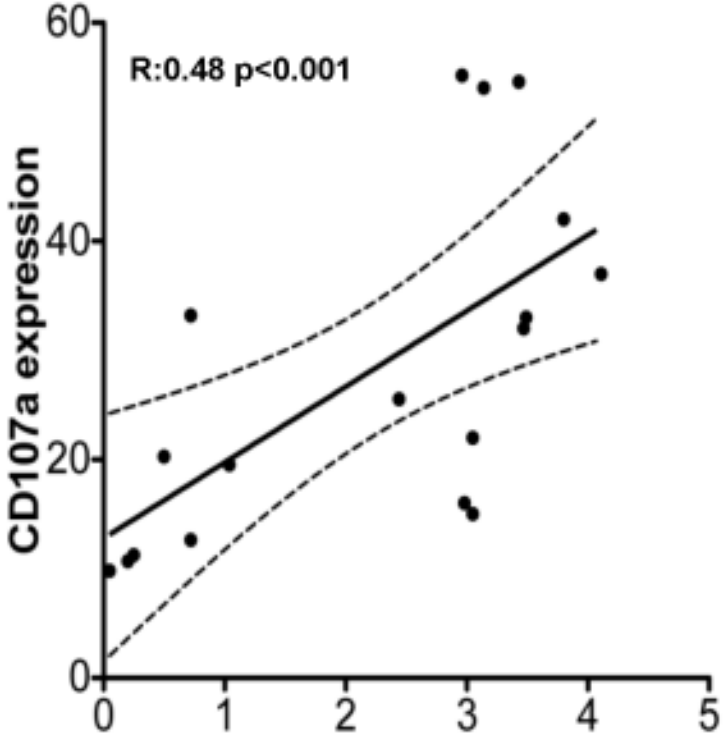


in vivo activation state of NK cells from HIC?

Didier C, Scott-Algara D et al for the ANRS EP36 HIV Controllers Study Group. Submitted

The correlation with CD8+ T cell suppressive capacity may underlie cooperation between innate and adaptive immunity in viral control.





Suppression of HIV replication by CD8+ T cell

Didier C, Scott-Algara D et al for the ANRS EP36 HIV Controllers Study Group. Submitted

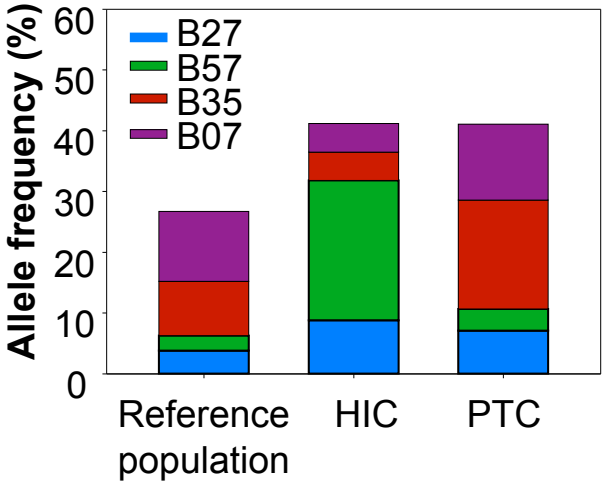
Early treatment initiation allows long-term virological remission in some patients

14 patients (ANRS VISCONTI study)
Therapy started within 10 weeks following infection

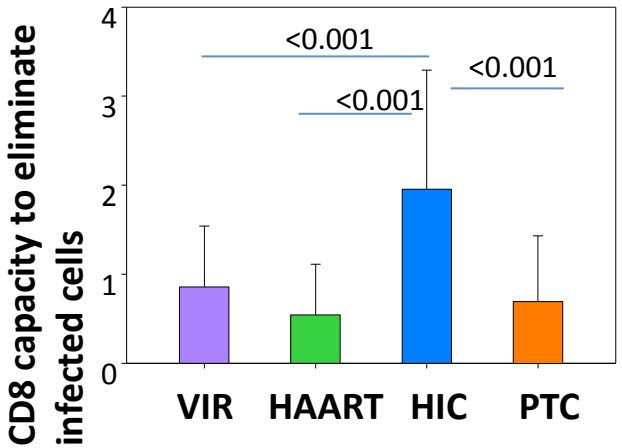
3 years on therapy, then stop and since then:

> 9 years of viral control without treatment

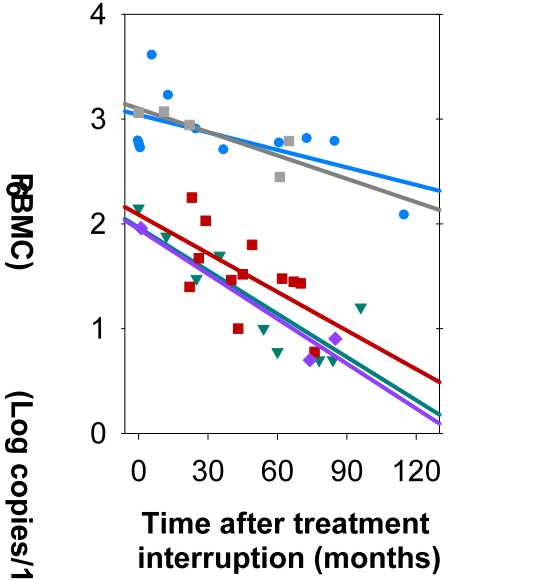
Unlike natural controllers, PTC Have rather unfavorable MHC



Control in PTC is independent of strong CD8 T cell responses



PTC : weak HIV reservoirs which further decrease in some cases



Saez-Cirion et al PLoS Path 2013

HIC vs PTC

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

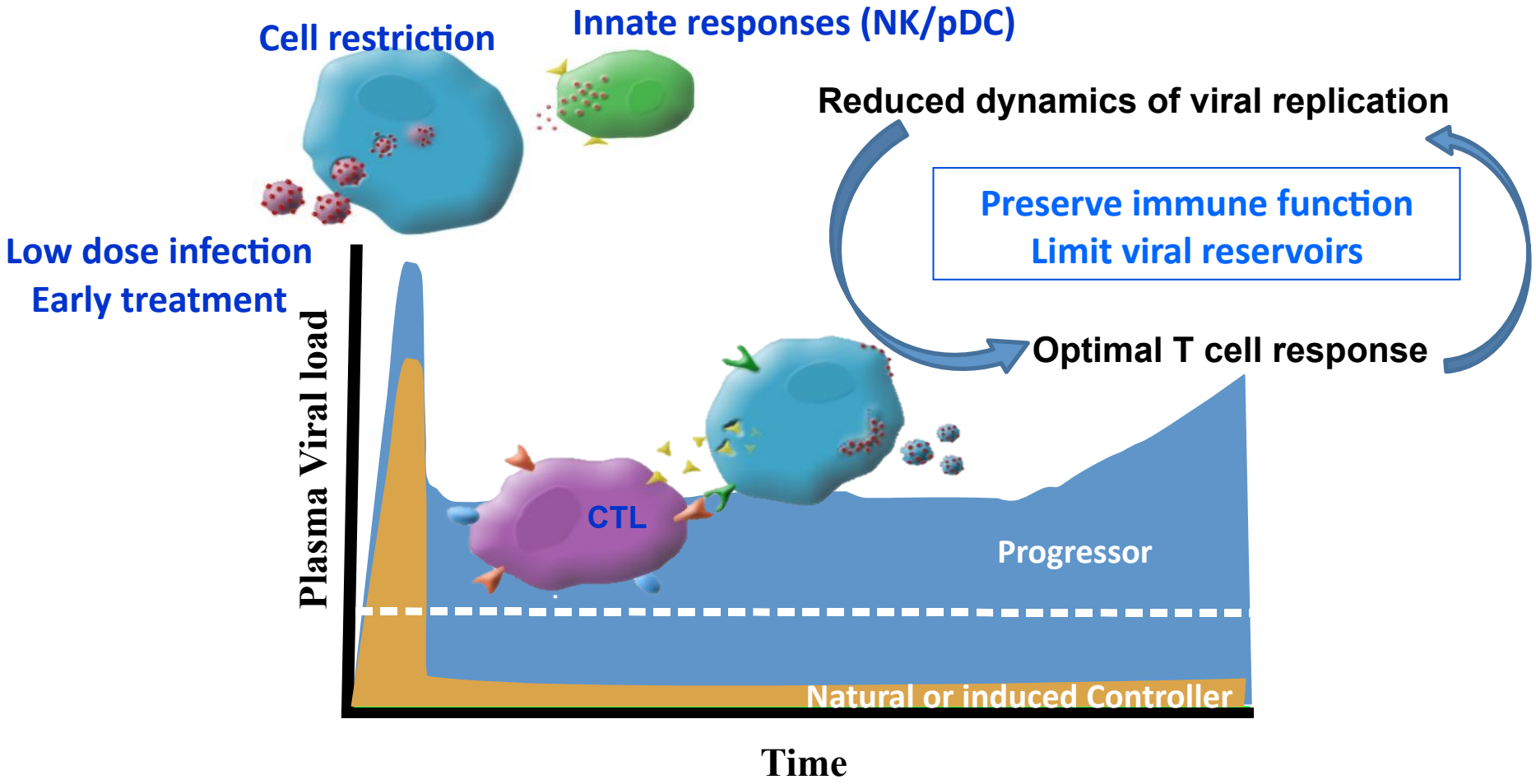
57% PTC carry **one HLA-class I** allele associated with **high viral loads**

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

Long-term control of infection



Pancino and Saez-Cirion. Immunological Reviews. 2013

Models of protection against HIV/SIV pathogenesis

Control of HIV infection

- HIV controllers (HIC)
  ~0.5% of HIV+ individuals, cART naive infected for >5 years
- Post treatment controllers (PTC): Visconti cohort *(5-15% of early treated HIV+ individuals)*

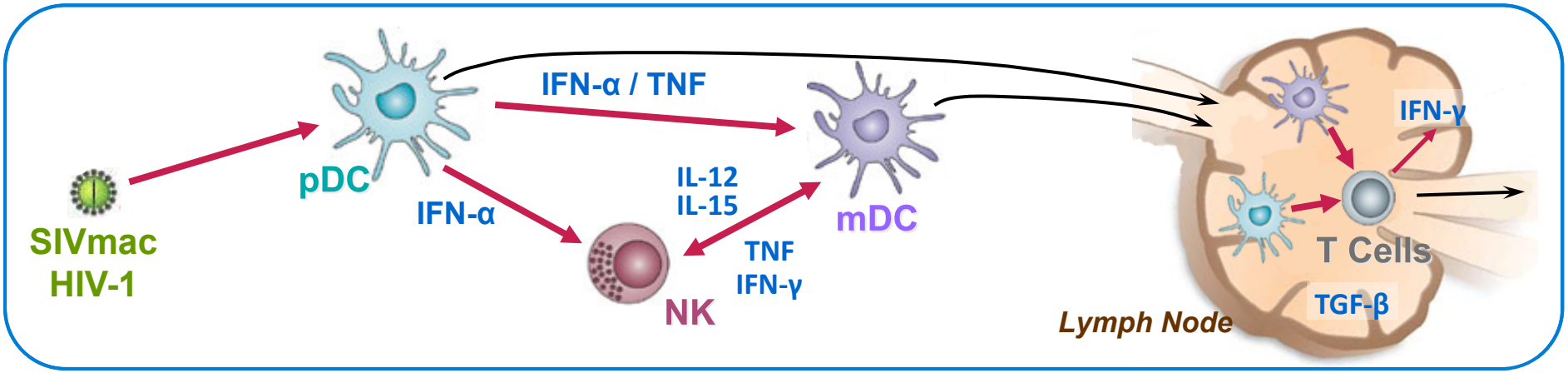
Control of abnormal immune activation

- **Non pathogenic SIV infection**
  African Green Monkeys (AGM)

How AGMs control immune activation ?

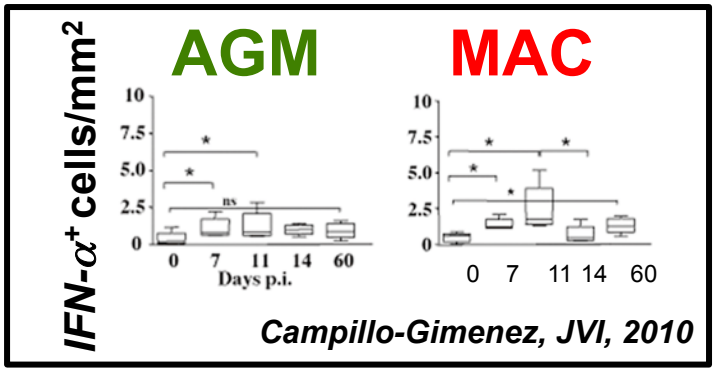
	SIVsmm, SIVagm	HIV-1, SIVmac
High plasma viremia	✓	✓
LN viral load	-	✓
Chronic T cell activation	-	✓
AIDS	-	✓

HYPOTHESIS: Innate immune responses regulation



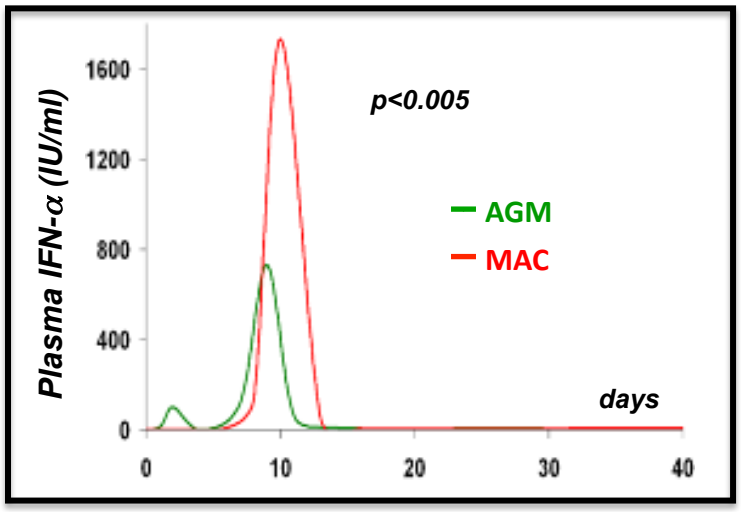
Weak and transient inflammation during acute SIVagm infection including lower levels of IFN-α

Lymph Node

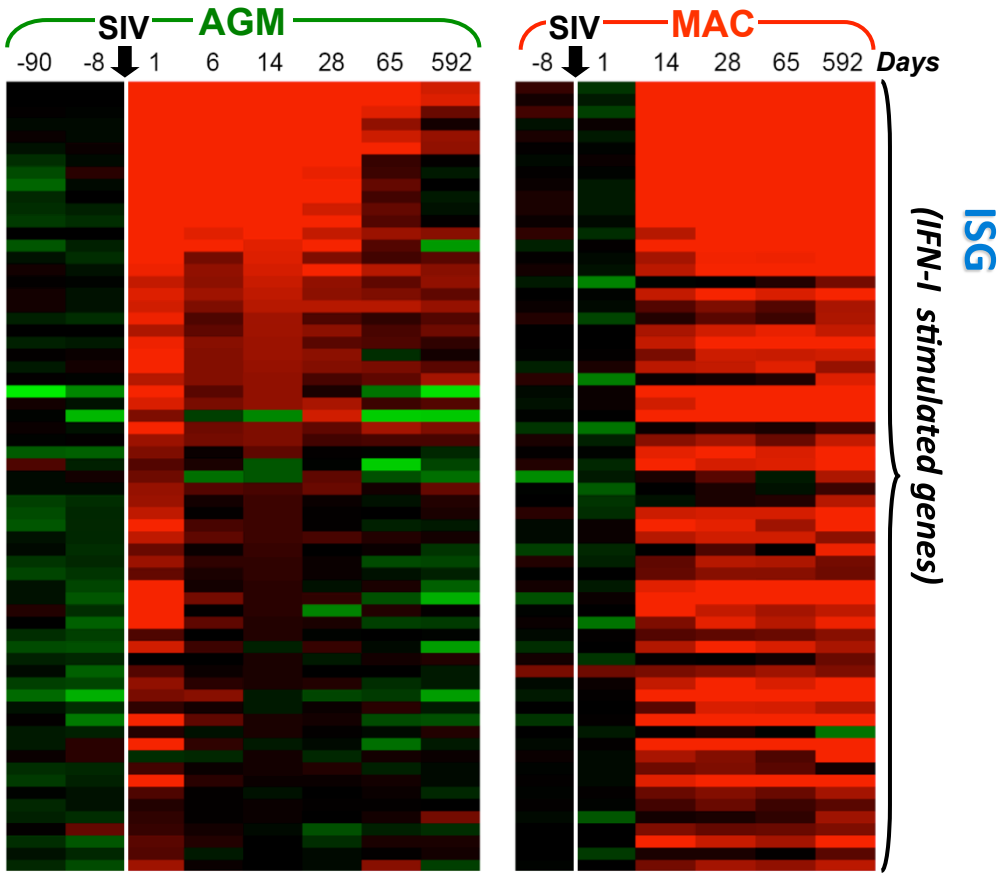


Campillo-Gimenez, JVI, 2010

Plasma



Microarrays on lymph node CD4+ :



Diop O et al, JVI 2008
Jacquelin et al, JCI, 2009

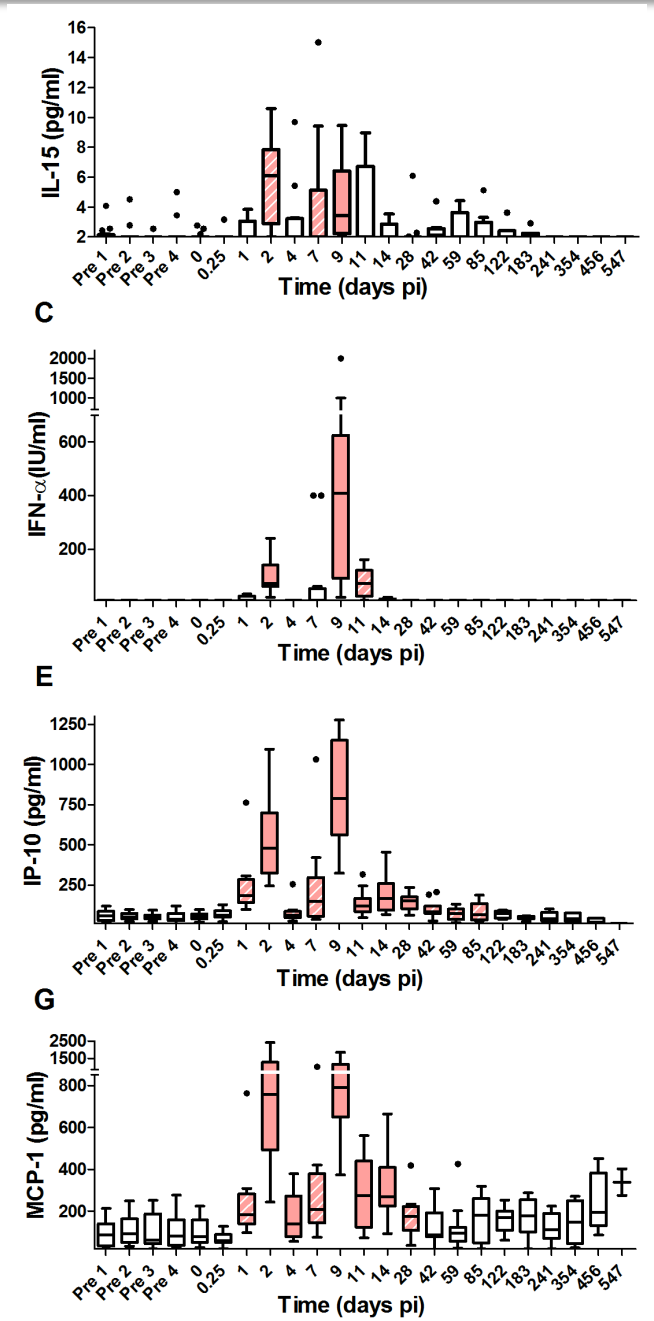
OBJECTIVES

➔ **Are the differences observed in IFN-α production involved in the attenuated immune activation ?**

- What will happen if we increase the IFN-α levels during the acute infection ?

➔ **Assess if innate immune cells (NK) are involve in the control mechanism in AGMs**

Robust induction of early cytokines in AGM/SIVagm infection



Jacquelin B et al, Plos Path, 2014

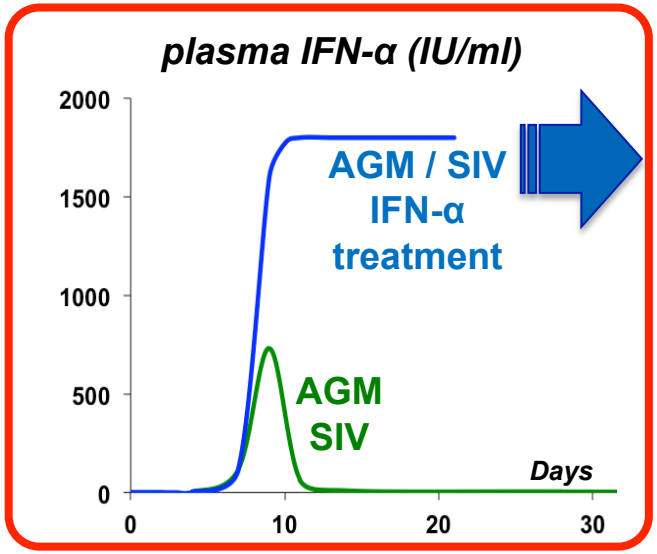
Marker	AGM	MAC
IL-15	++	+++
IFN-α	++	+++
IP-10	+++	+++
MCP-1	+++	++
IFN-γ	+	++
IL-18	+	+++
TNF-α	-	+
IL-8	-	+++
sTrail	-	+++
Il-6	-	+
IL-12	+	+
MIP-1α	-	++
MIP-1β	-	++
TGF-β	+	+++
IL-10	-	+

Order of appearance in HIV-1 and SIVmac (peak level)

How AGMs resolve the IFN-I associated inflammation?

Objectives

Is there a link between the lower levels of IFN-α in vivo, the lack of sustained ISG expression and the lack of T cell activation in AGMs ?



Outcome ?

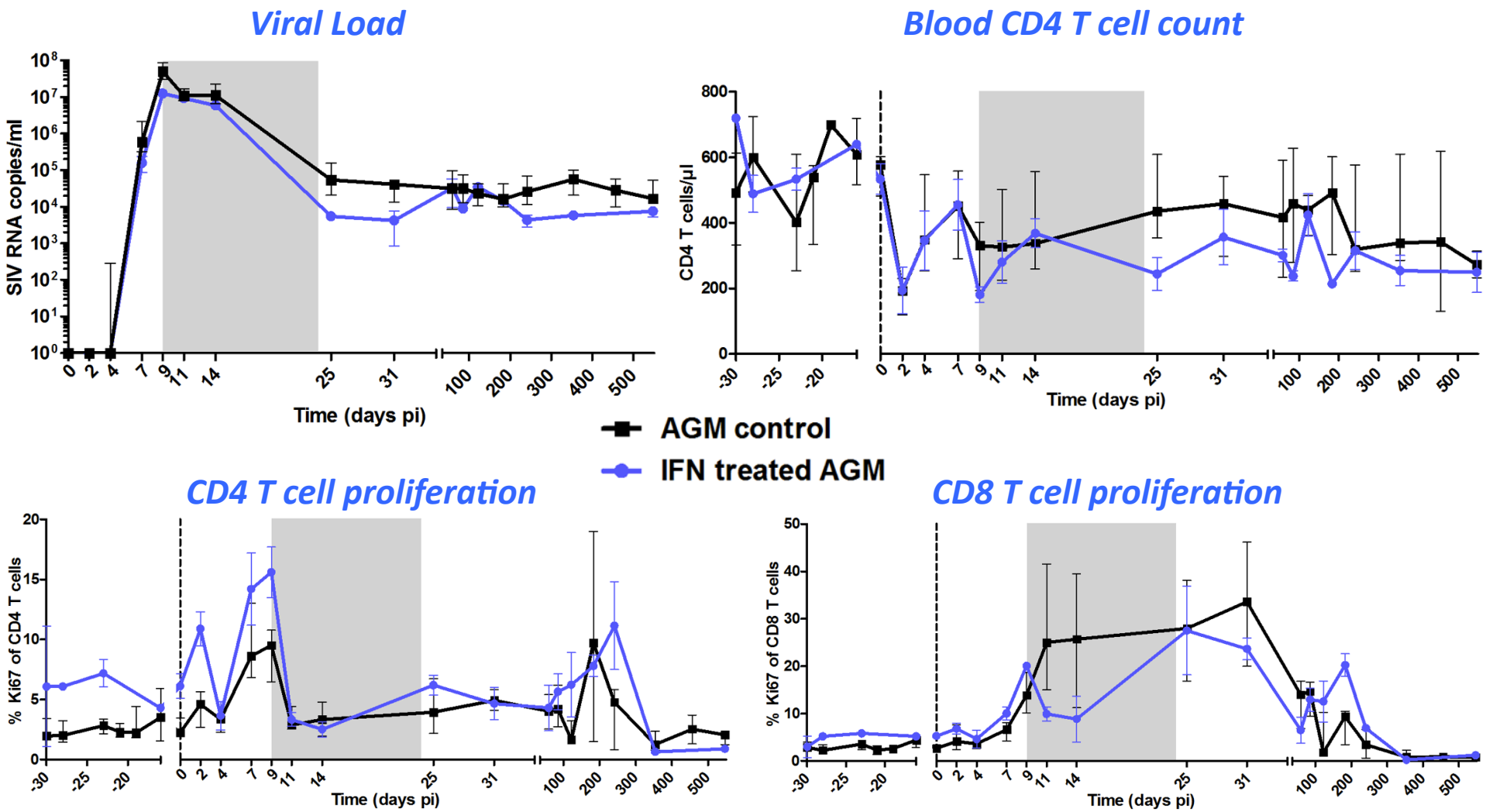
Treat AGMs with high doses of IFN-α during acute infection starting from the day of the peak

⇨ **2 AGM injected daily s.c. with r-mamu-IFN-α (day 9 to 24 post-infection, 5.10^5IU, with 10% increase every 2 days)**

⇨ **6 untreated AGM**

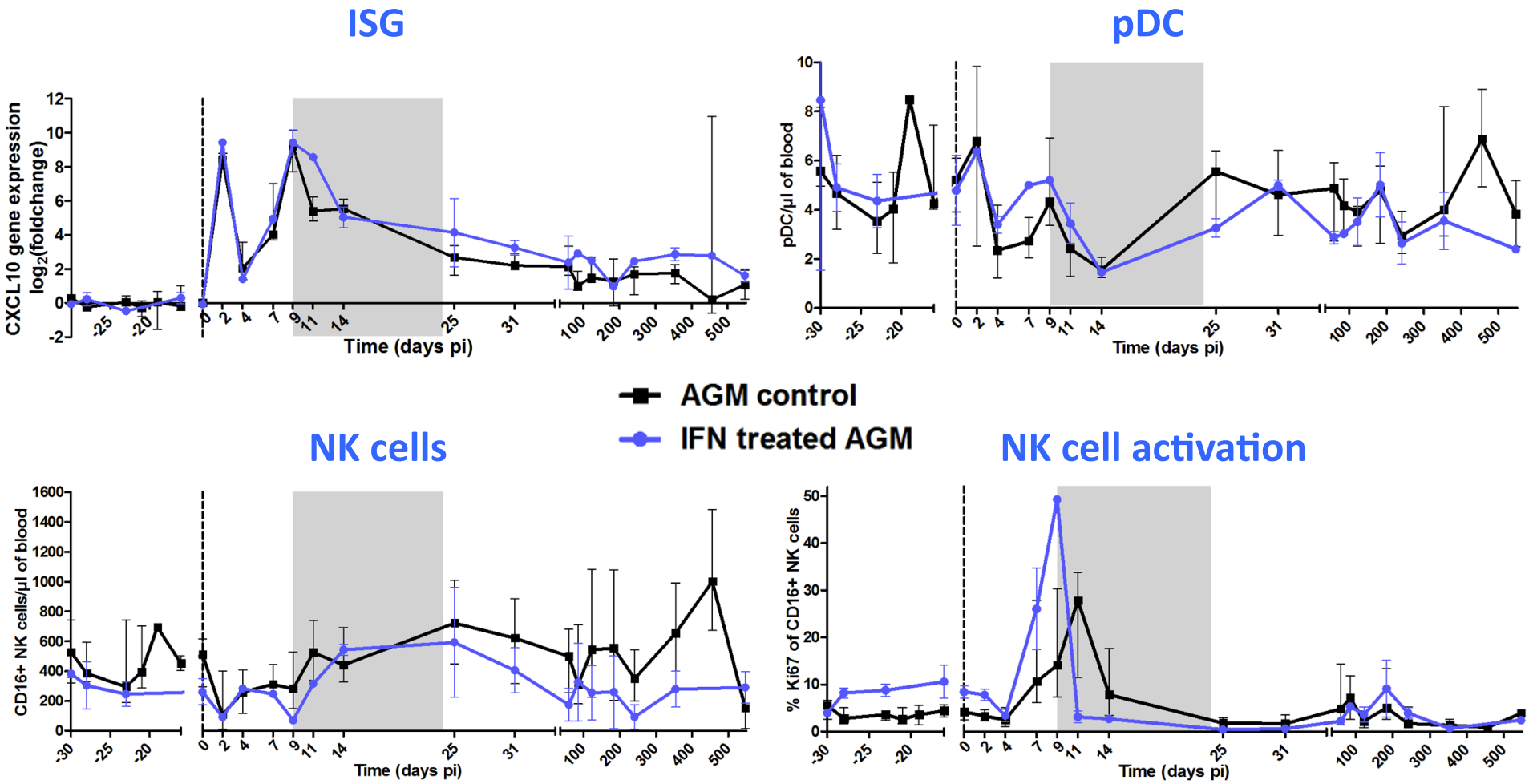
ISG expression (mRNA, plasma proteins)
T cell activation, viremia, $CD4^+$ T cell counts
NK cell activation, DC maturation, inflammatory mediators (plasma)

Follow-up of disease progression markers



⇨ High dose of IFN-α in acute infection has no sustained major effect on VL, CD4 T cell count or T cell proliferation

Does high IFN-α dose in acute SIVagm infection have an impact on ISG levels or innate immune cells ?

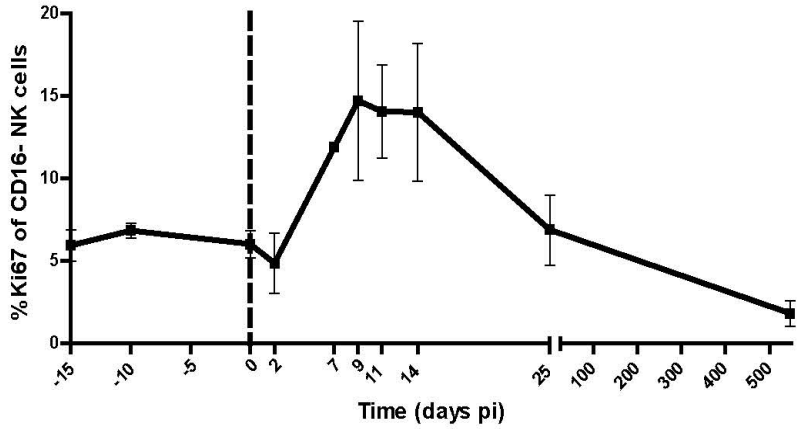


⇨ IFN-α administration does not induce persistent ISG expression

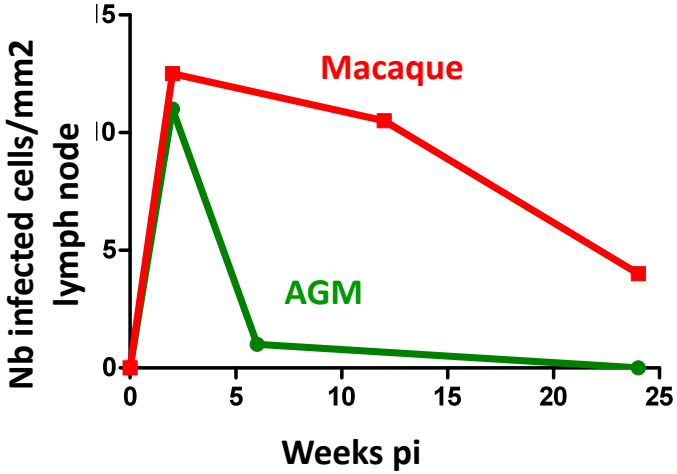
⇨ IFN-α injection does not affect innate cell profiles

Strong activation and proliferation of NK cells during acute SIVagm infection

Lymph nodes



* p<0.01



Correlation

	IFN-α		IL-15	
	Rs	**p-value**	**Rs**	**p-value**
CD69%	0.39	p<0.0001	0.25	p=0.009
Ki-67%	0.24	p=0.008	0.28	p=0.003

Jacquelin B et al, Plos Path, 2014

Is NK cytotoxic activity responsible for the control of SIVagm replication in lymph node?

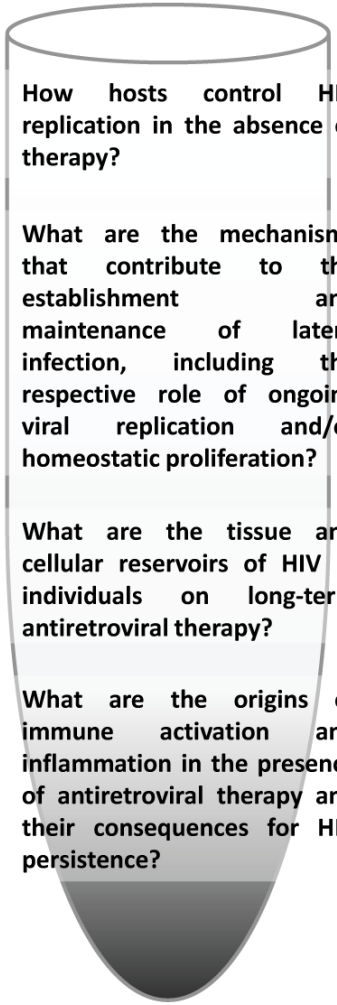
Conclusions

➔ Only early cytokines are strongly induced. The control of IA in AGM seems to be triggered earlier than previously considered

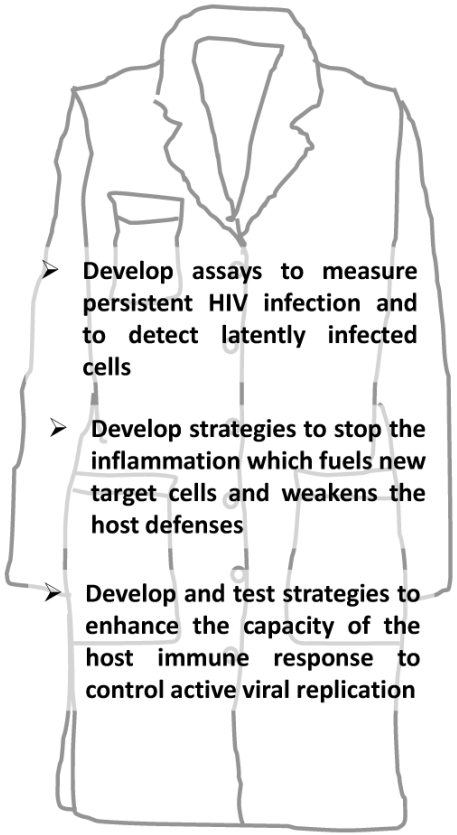
➔AGM are still able to control immune activation in the presence of high levels of IFN-α during acute infection

➔NK cells are activated early on

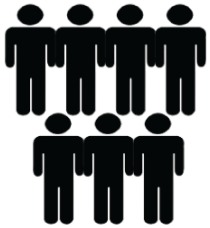
BASIC RESEARCH ⟷ **TRANSLATIONAL RESEARCH** → **CLINICAL RESEARCH** → **CLINICAL CARE**



- How hosts control HIV replication in the absence of therapy?
- What are the mechanisms that contribute to the establishment and maintenance of latent infection, including the respective role of ongoing viral replication and/or homeostatic proliferation?
- What are the tissue and cellular reservoirs of HIV in individuals on long-term antiretroviral therapy?
- What are the origins of immune activation and inflammation in the presence of antiretroviral therapy and their consequences for HIV persistence?



- Develop assays to measure persistent HIV infection and to detect latently infected cells
- Develop strategies to stop the inflammation which fuels new target cells and weakens the host defenses
- Develop and test strategies to enhance the capacity of the host immune response to control active viral replication

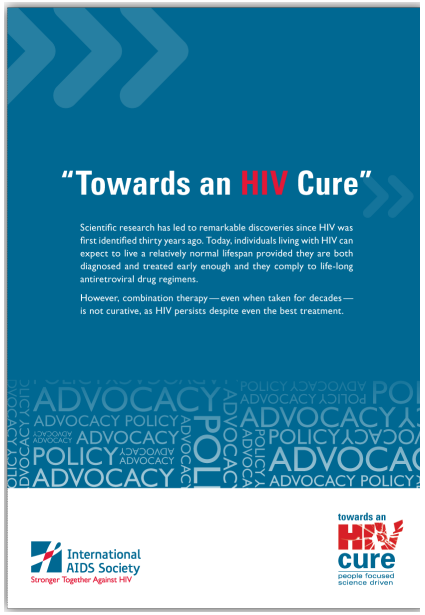


- Develop and test therapeutic agents or immunological strategies to safely eliminate latent infection or control viral reservoirs in animal models and in individuals on antiretroviral therapy

HIV CURE

HIV Remission

A combined and integrated scientific strategy….



Saez-Cirion A, Jacquelin B, Barré-Sinoussi F, Müller-Trutwin M. Philos Trans R Soc Lond B Biol Sci. 2014 May 12

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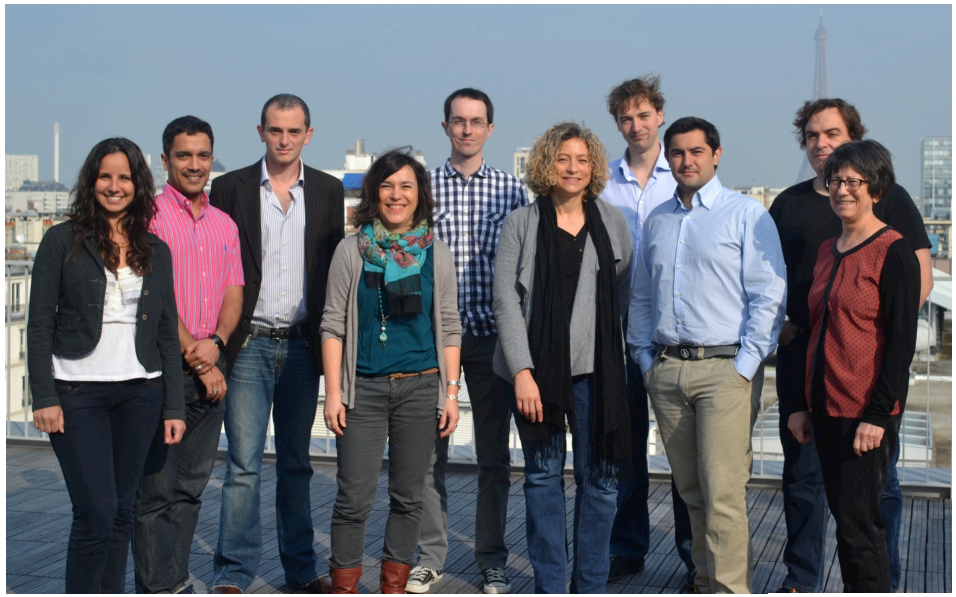
Daniel Scott-Algara's teams



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