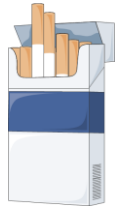


# IHIV infection and chronic inflammation

## Behavior

Smoking

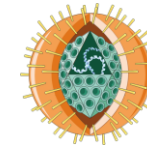


Drugs

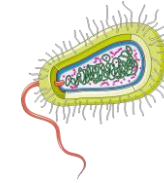


## Co-infections

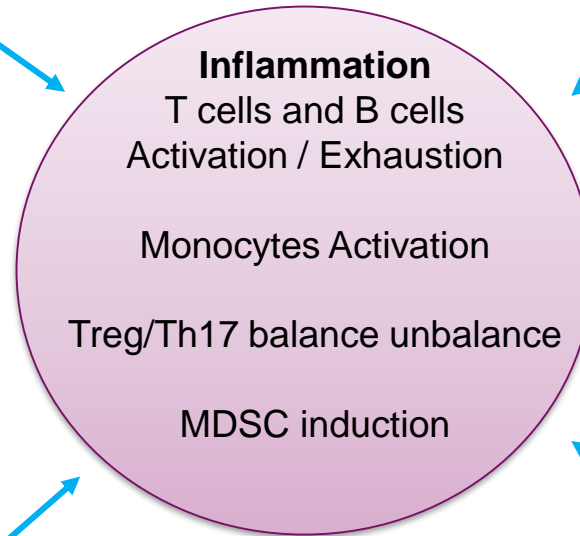
CMV  
Hepatitis



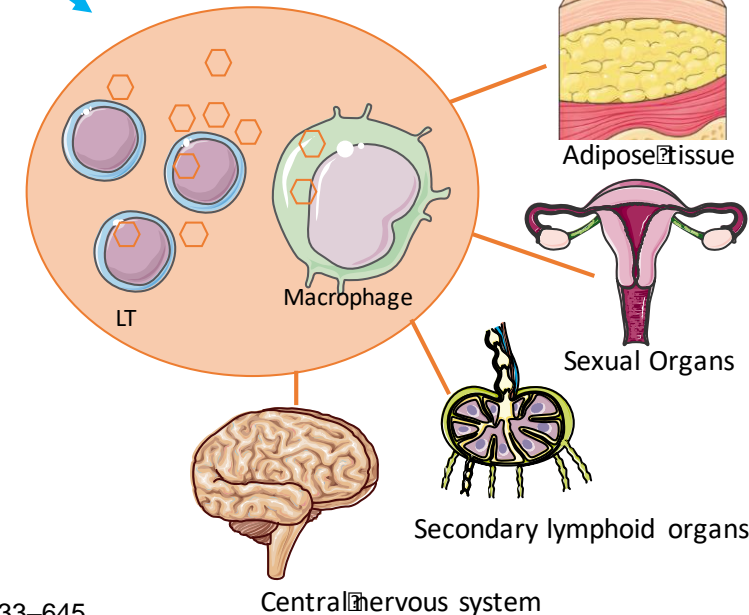
MtB



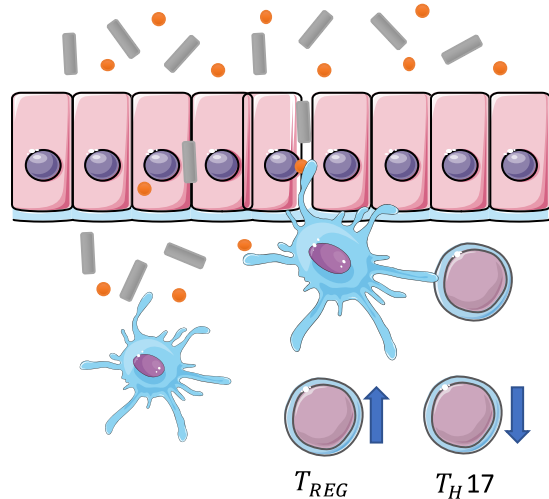
Plasmodium



Residual replication  
Pharmacologic sanctuaries



## Microbial translocation



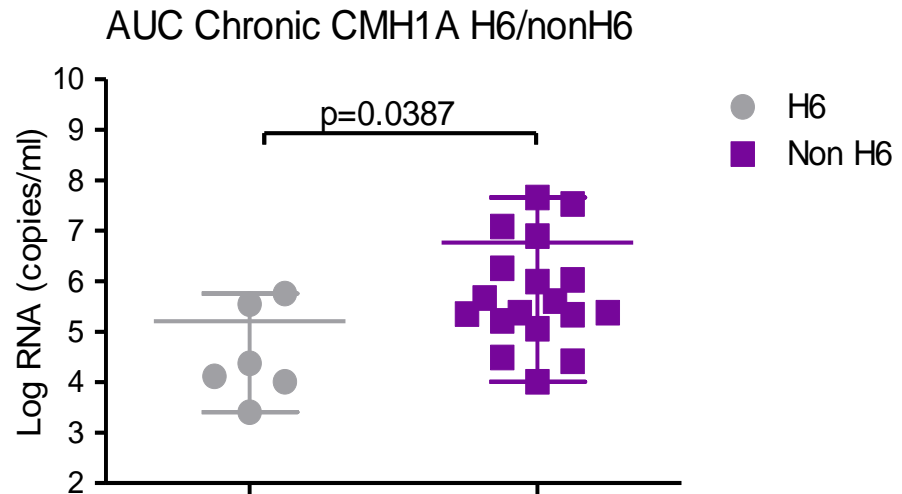
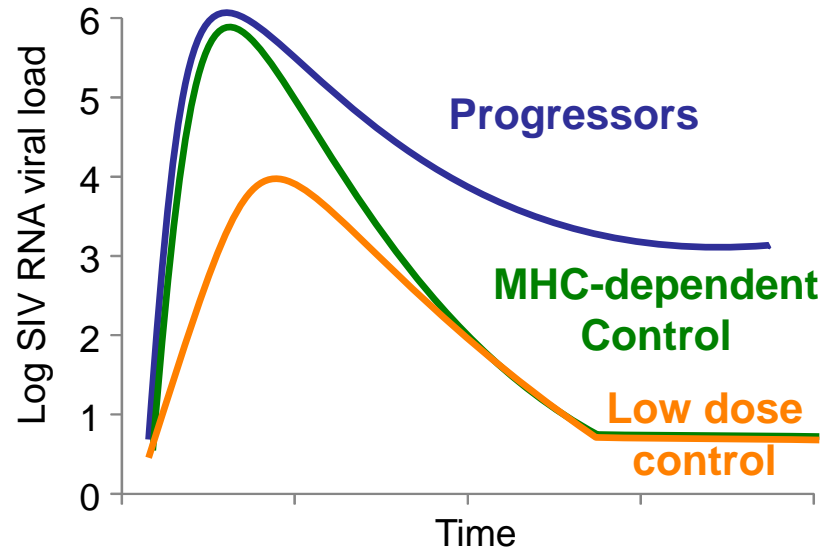
# Non-Human Primate models of HIV infection & AIDS



Asian  
Species

Cynomolgus Mac  
SIVmac251

↓  
AIDS

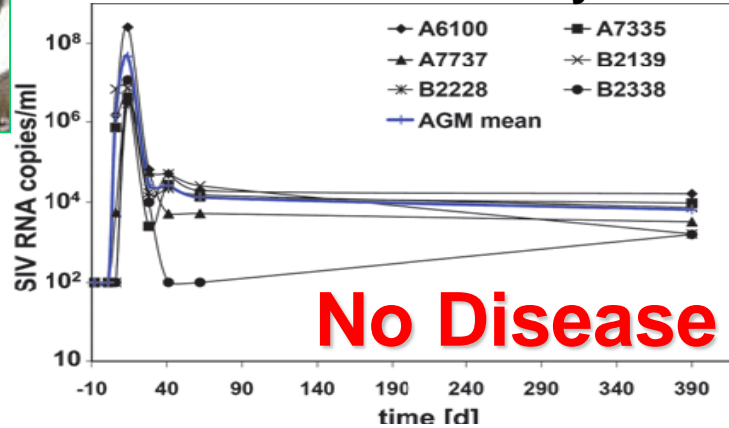


(Aarninck *et al* 2011)

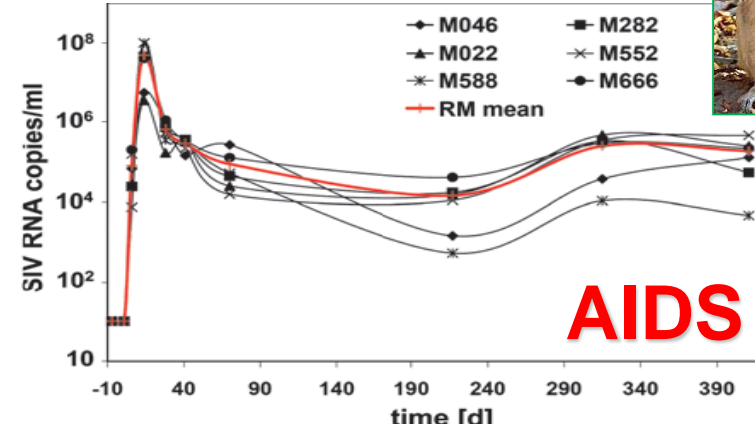
# Nonpathogenic SIV infection of ADM induces a strong but rapidly controlled type I IFN response



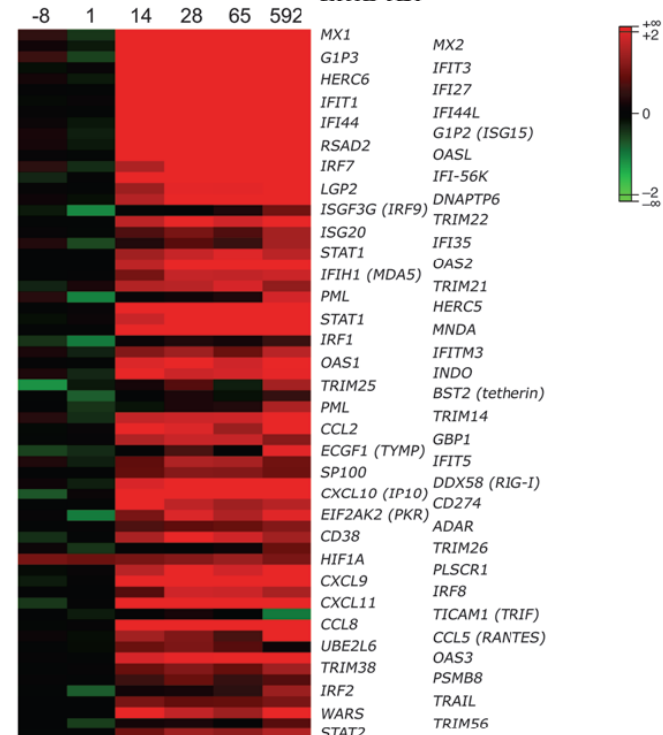
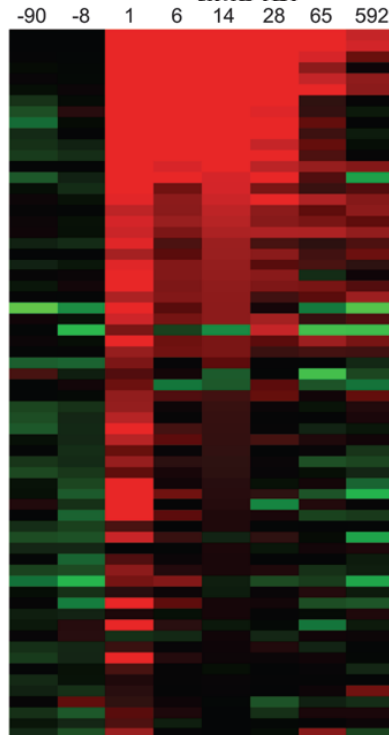
## African Green Monkeys



## Rhesus Macaques



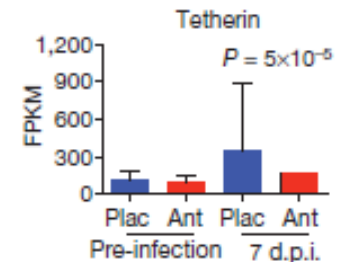
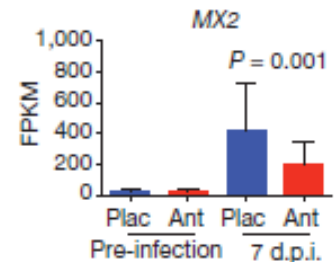
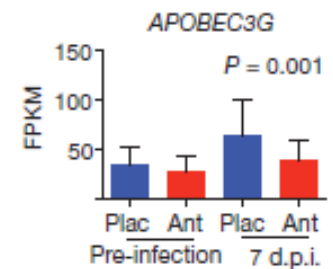
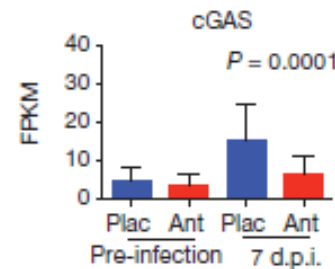
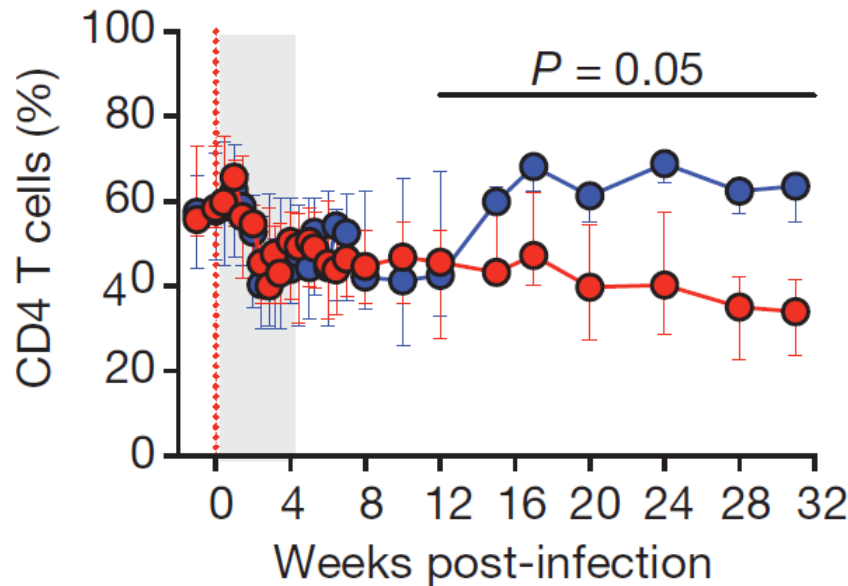
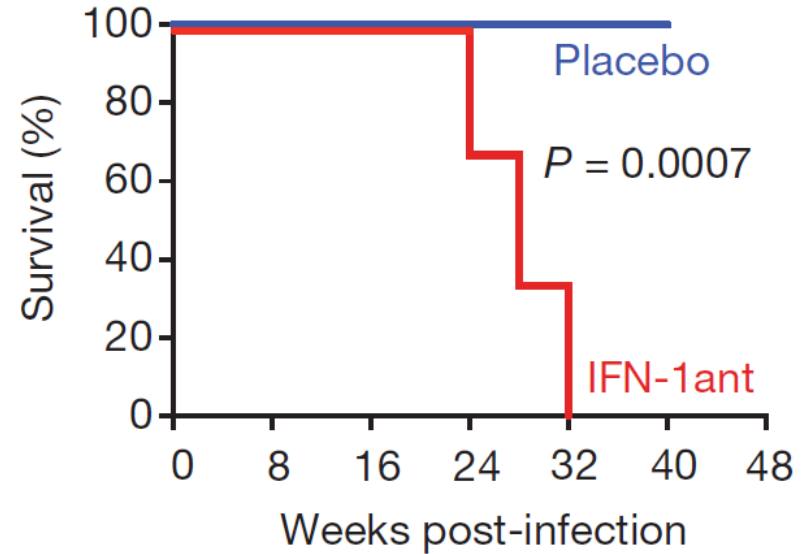
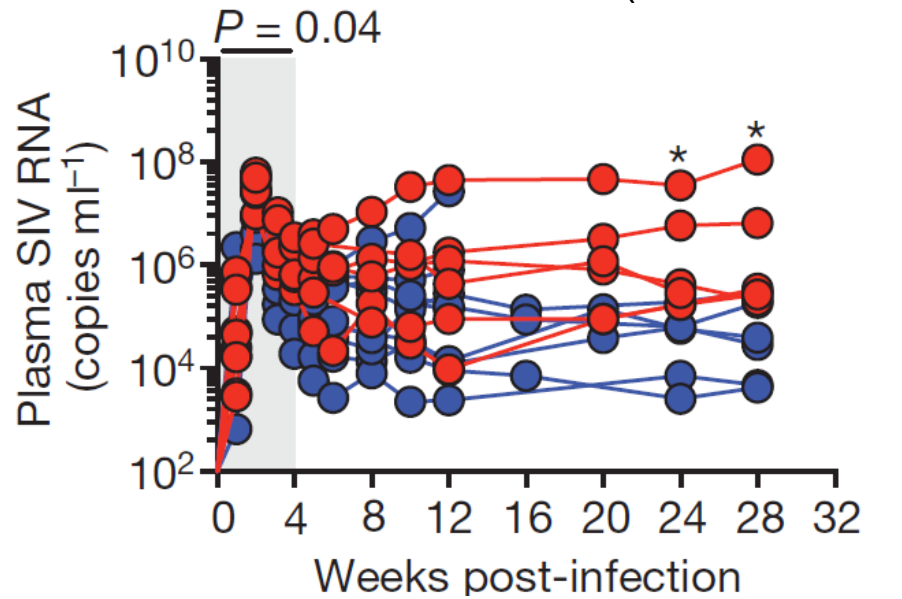
### Gene Expression Profile in Lymph Nodes





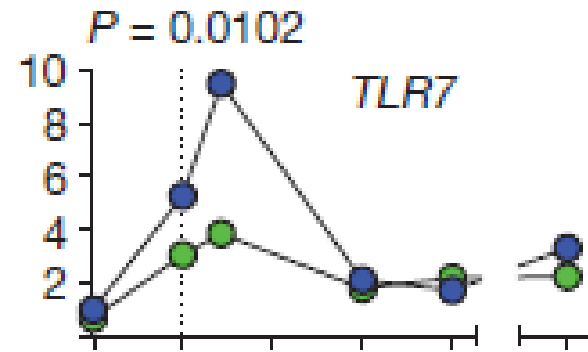
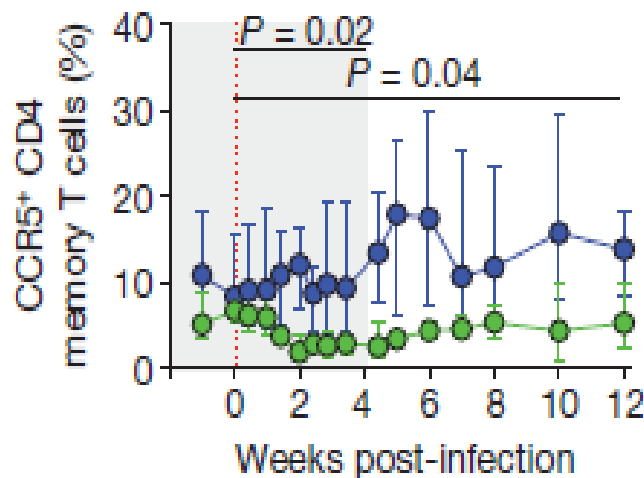
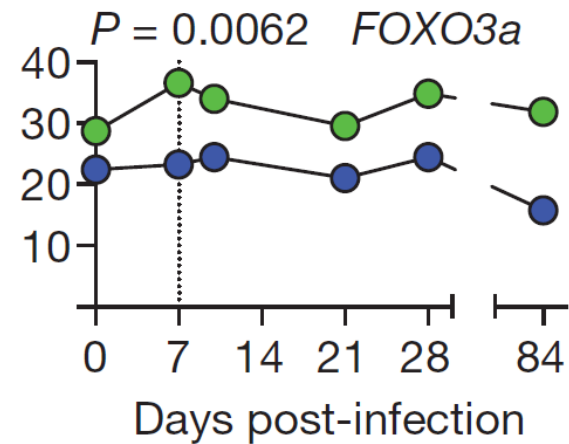
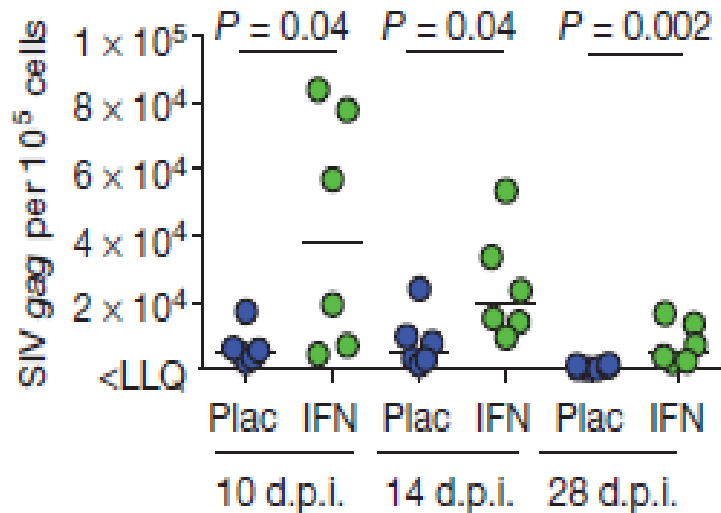
# Early IFN-I blockade accelerates progression of SIV infection

(Sandler N *et al*, Nature 2014)

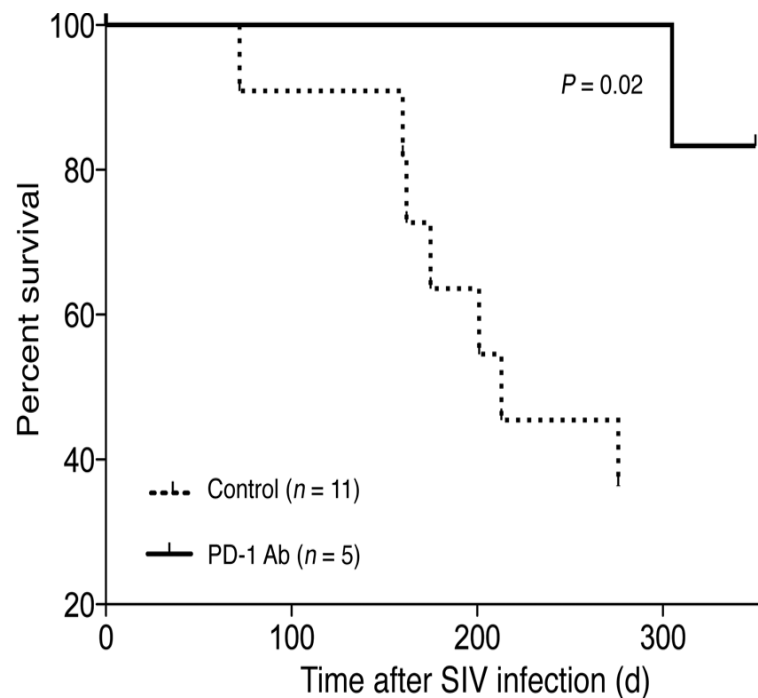
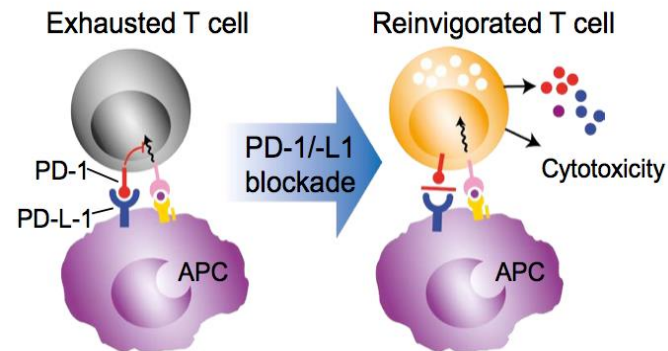
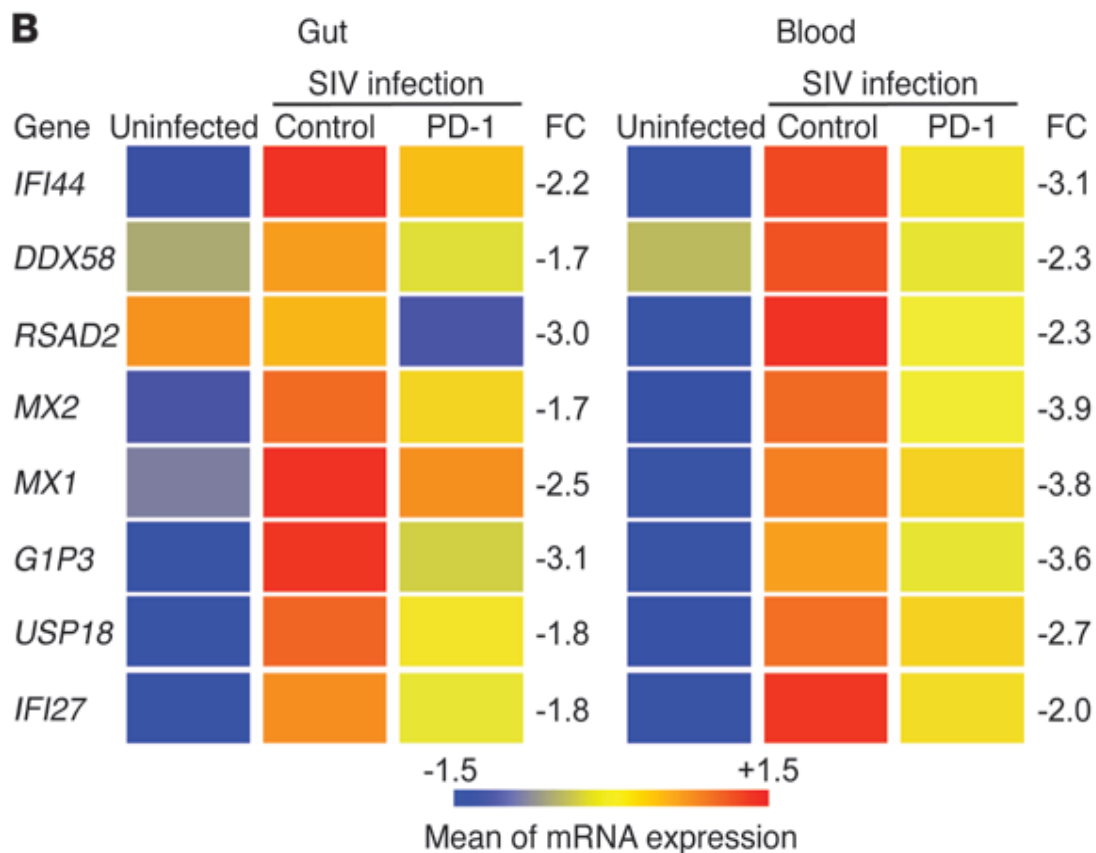


# Continued IFN-1 2α treatment resulted in an IFN-desensitized state

(Sandler N *et al*, Nature 2014)

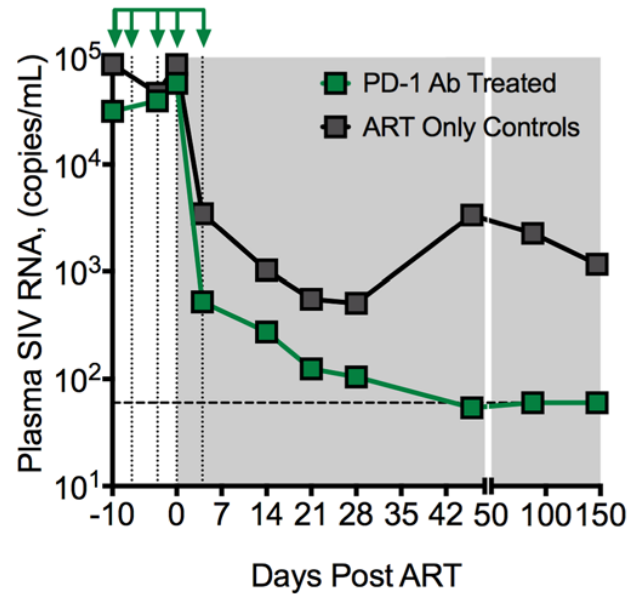
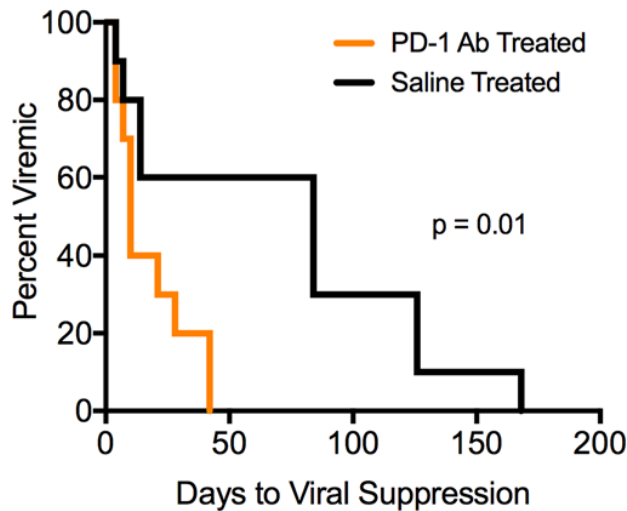
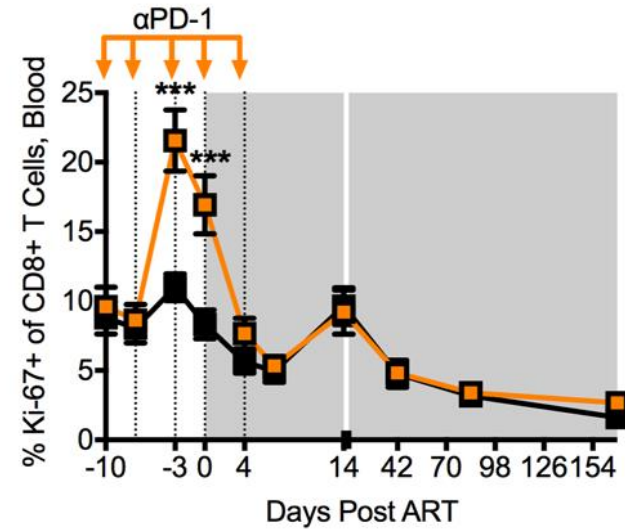
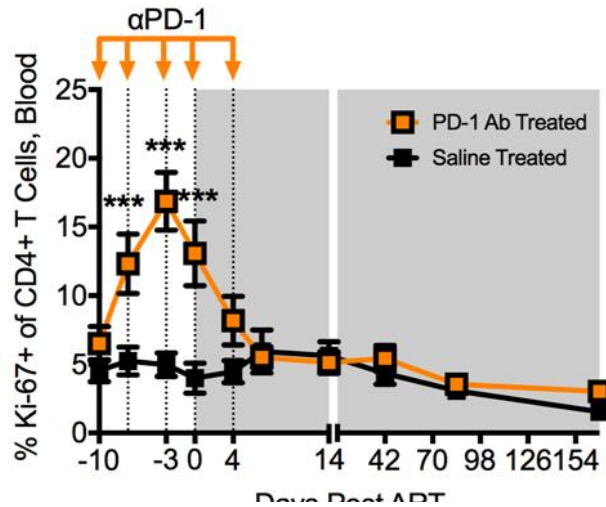


# PD-1 blockade downregulates type I IFN responses in SIV infection

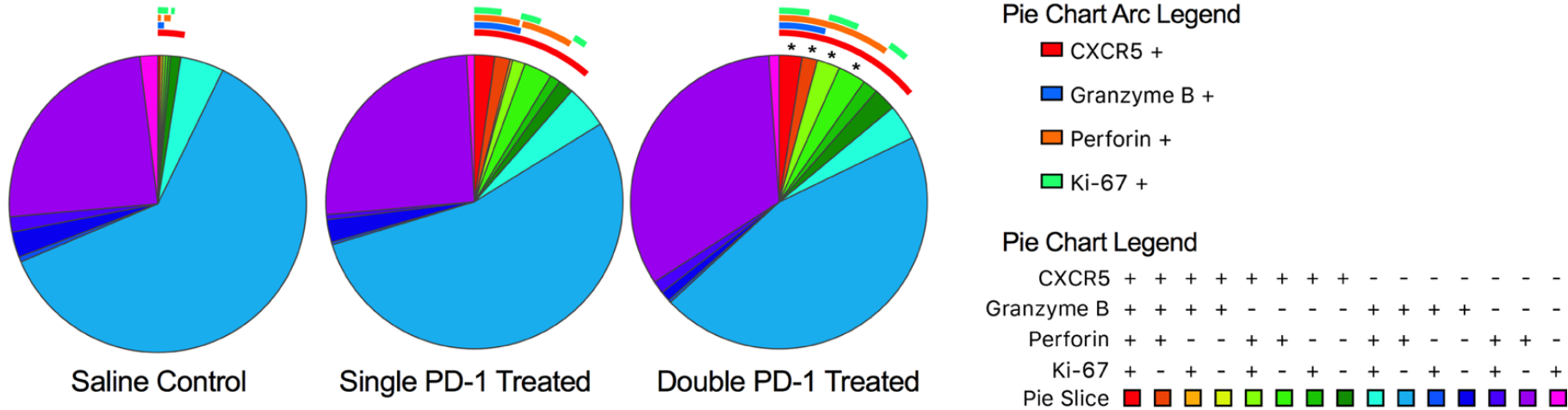


Shetty *et al*, JCI 2012

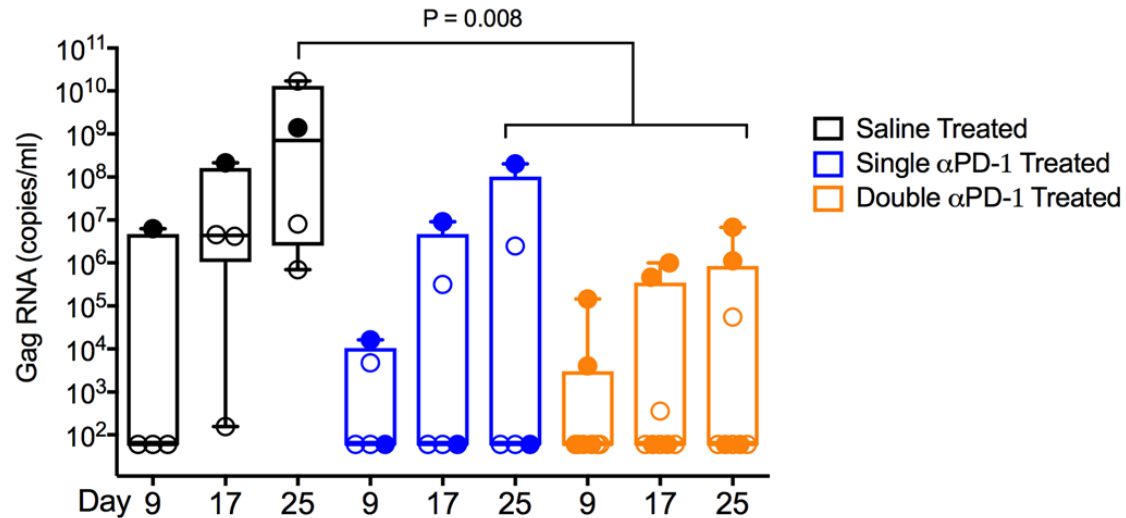
# PD-1 blockade-prior to ART-improved T cell functionality in SIV+ macaques



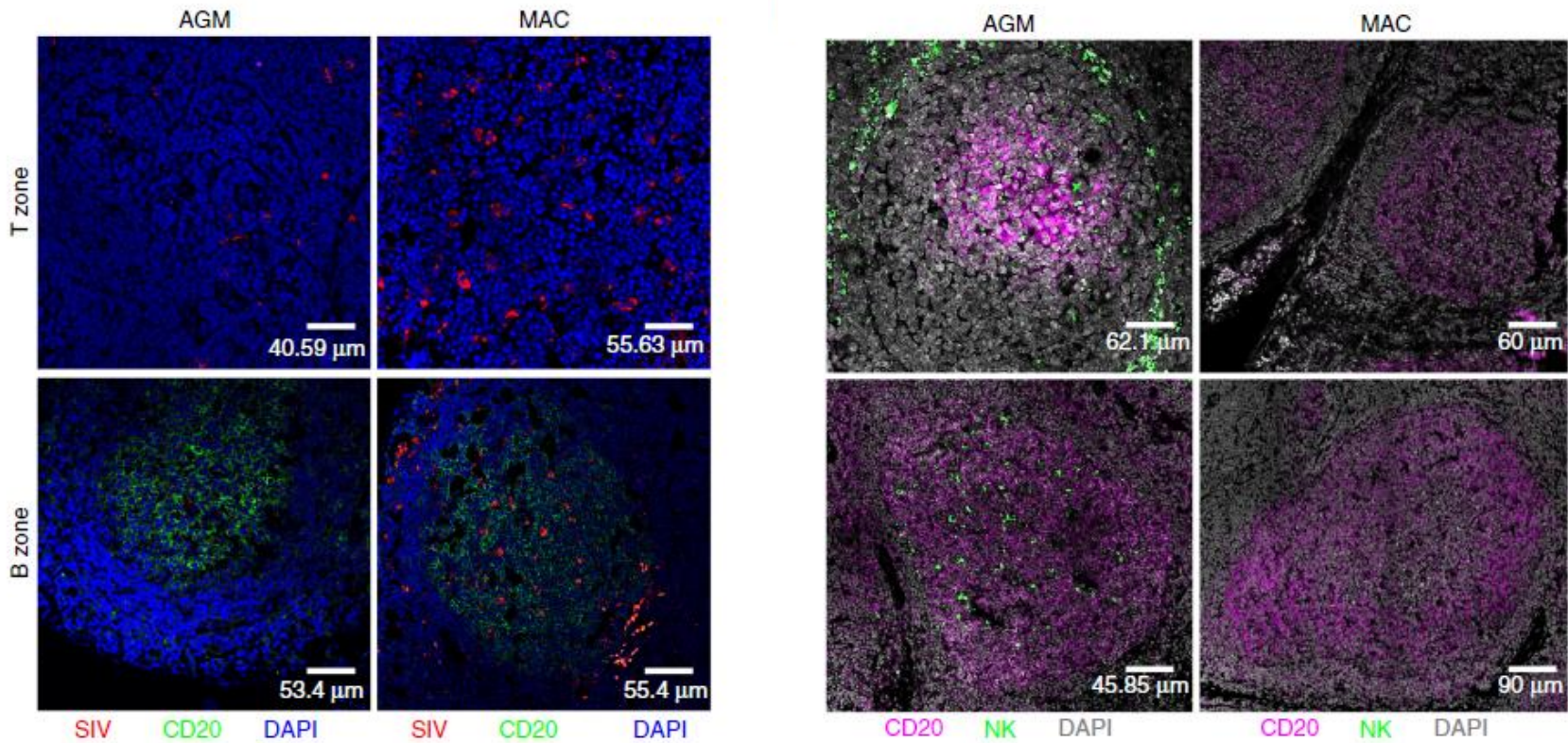
# Enhanced viral control in PD-1 Ab-treated animals after ART interruption



**C**

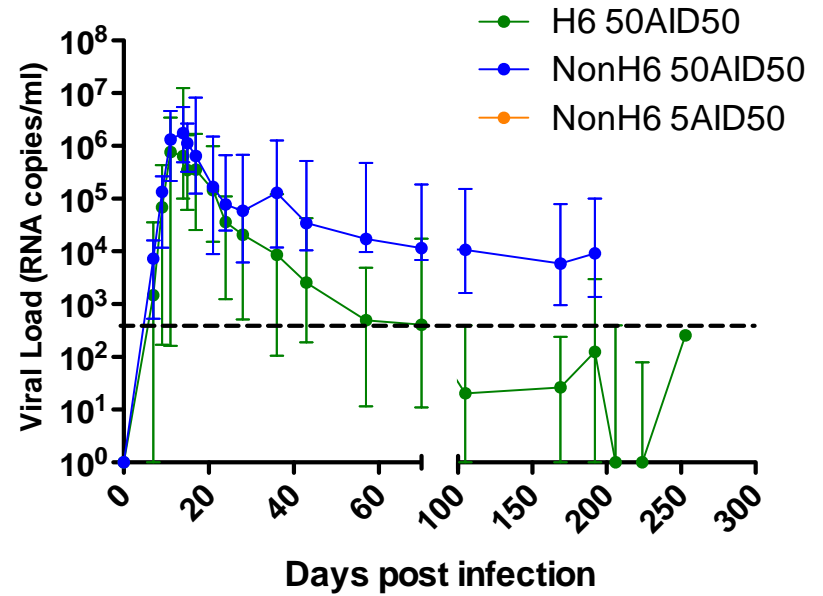
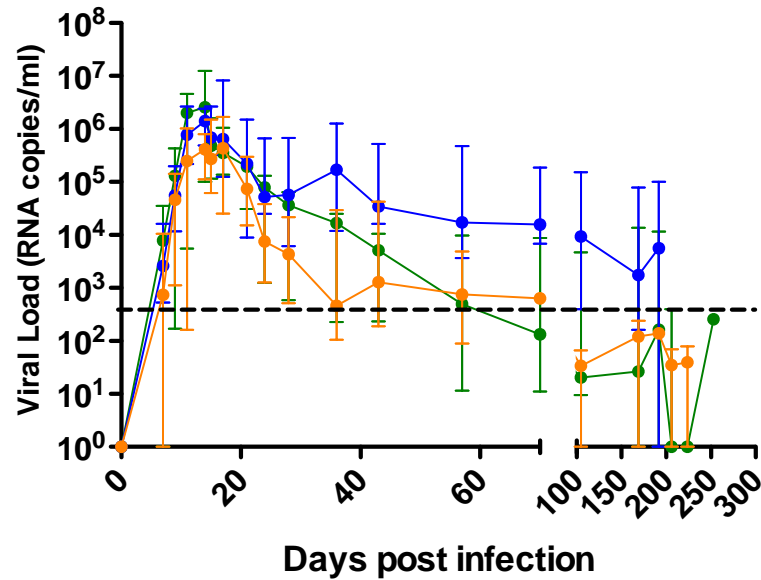


# NK cells and control of SIV replication in lymph node follicles

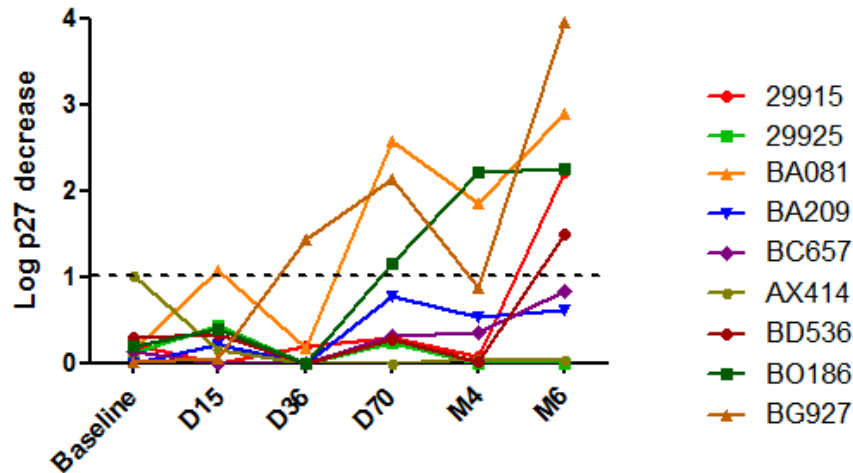


- NK cells capable to acquire CXCR5 expression and migrate into follicles
- Membrane-bound presentation of IL-15 by follicular dendritic cells
- CXCR5<sup>+</sup>NK cells express high levels of FcγR and cytotoxic markers

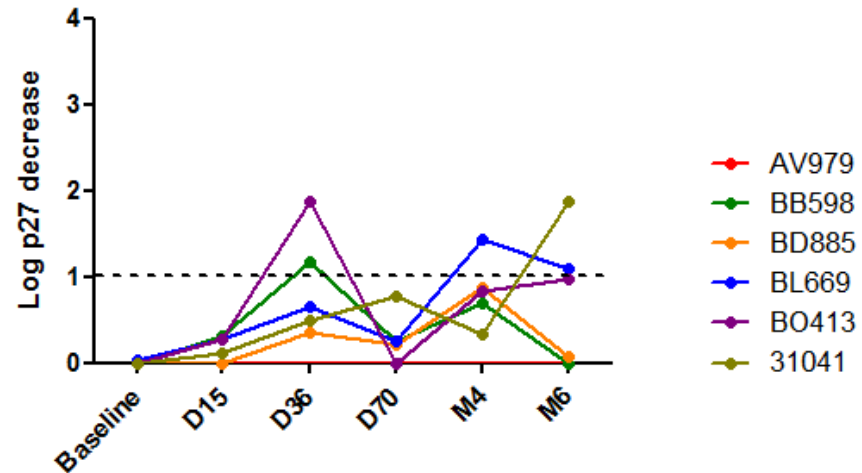
# CD8+ T cells ex vivo to control infection of autologous CD4+ T cells



## CONTROLLERS

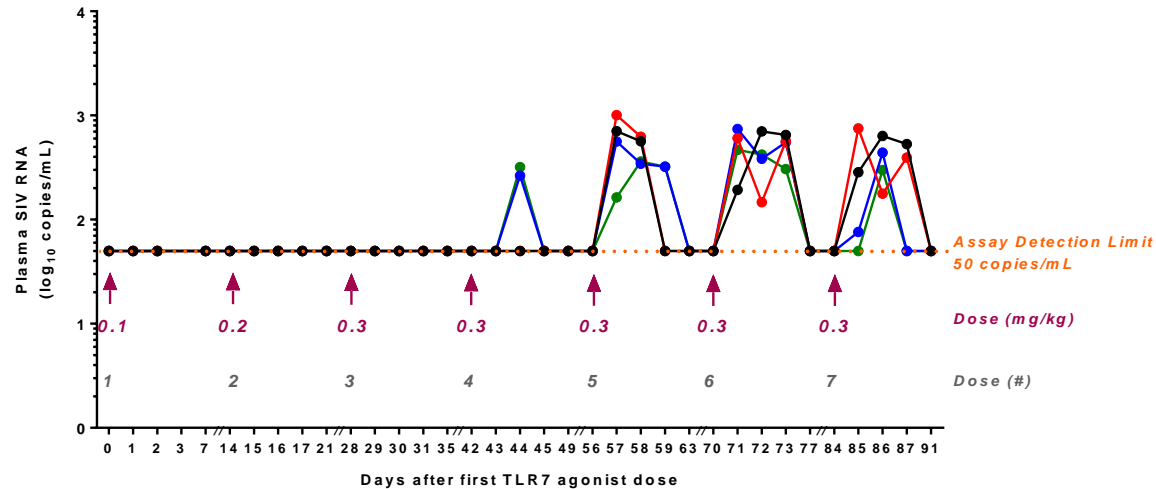


## NON CONTROLLERS

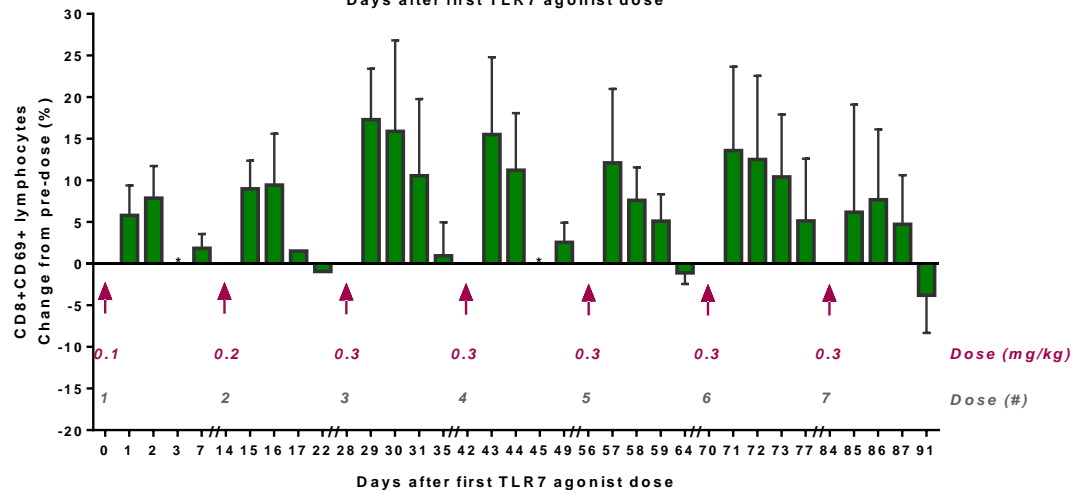


# TLR7 agonist administration in SIV infected macaques

Plasma SIV RNA



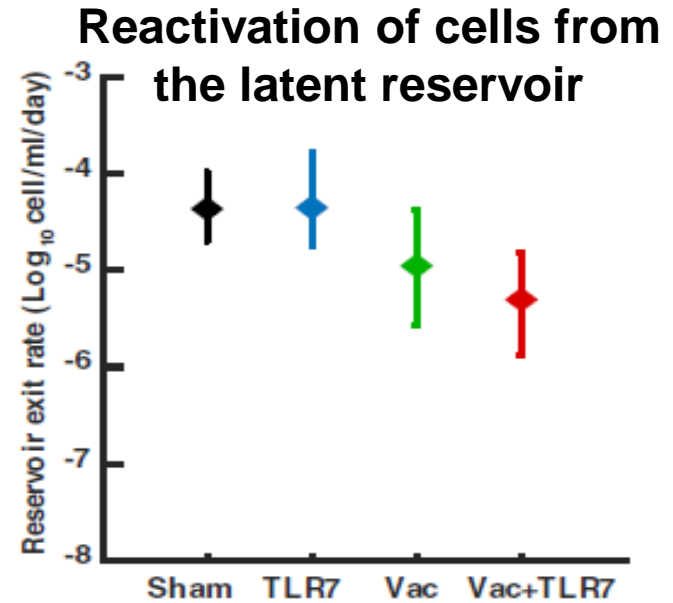
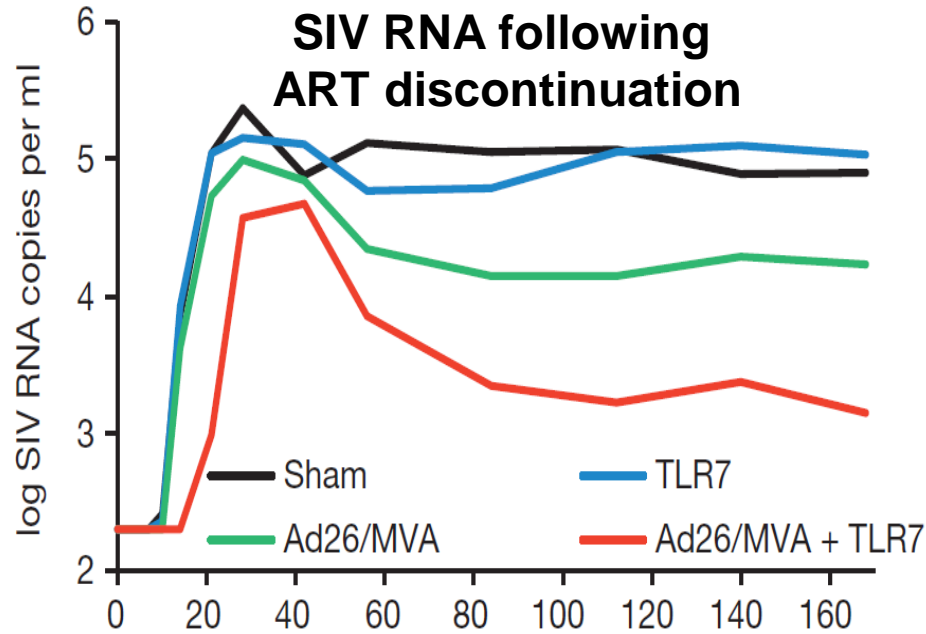
CD8+ T cell activation



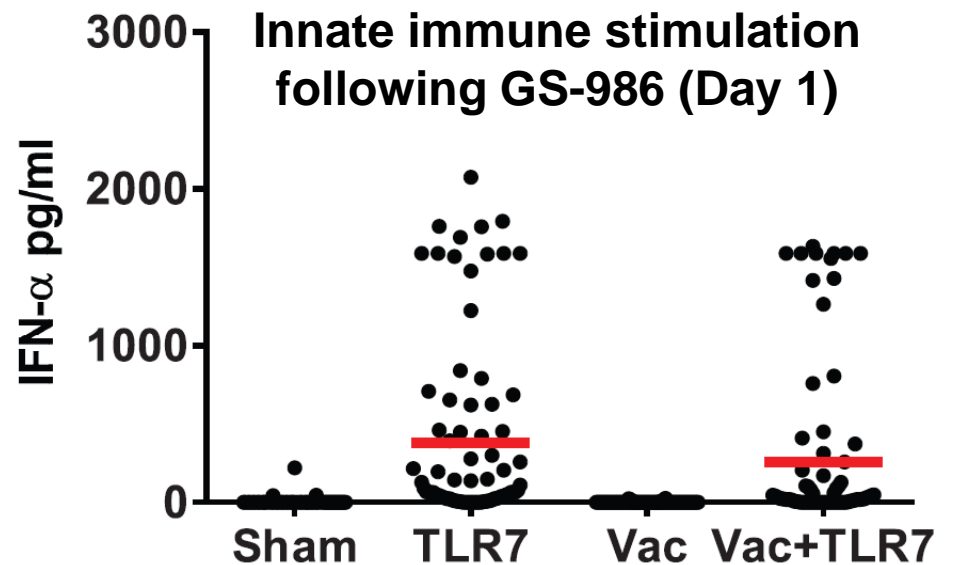
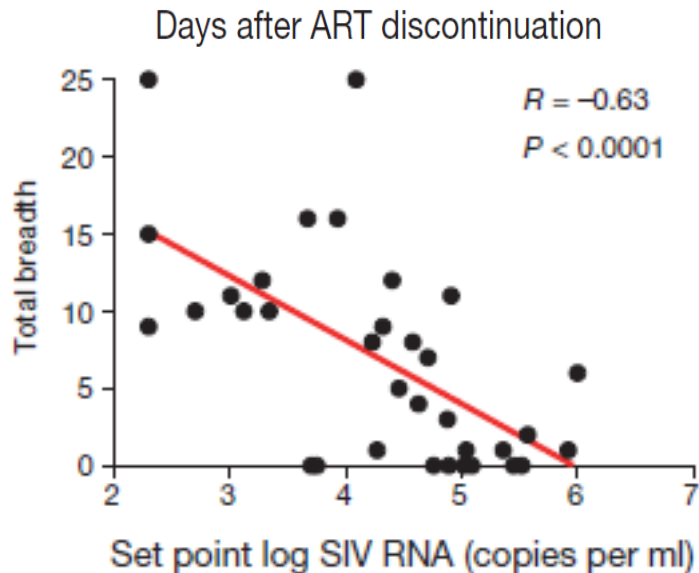
➤ TLR7 agonist induces viral production and increases CD8+ T cell activation

# Effect of Ad26/MVA therapeutic vaccination with TLR7 stimulation

(Borducchi E *et al*, Nature 2016)



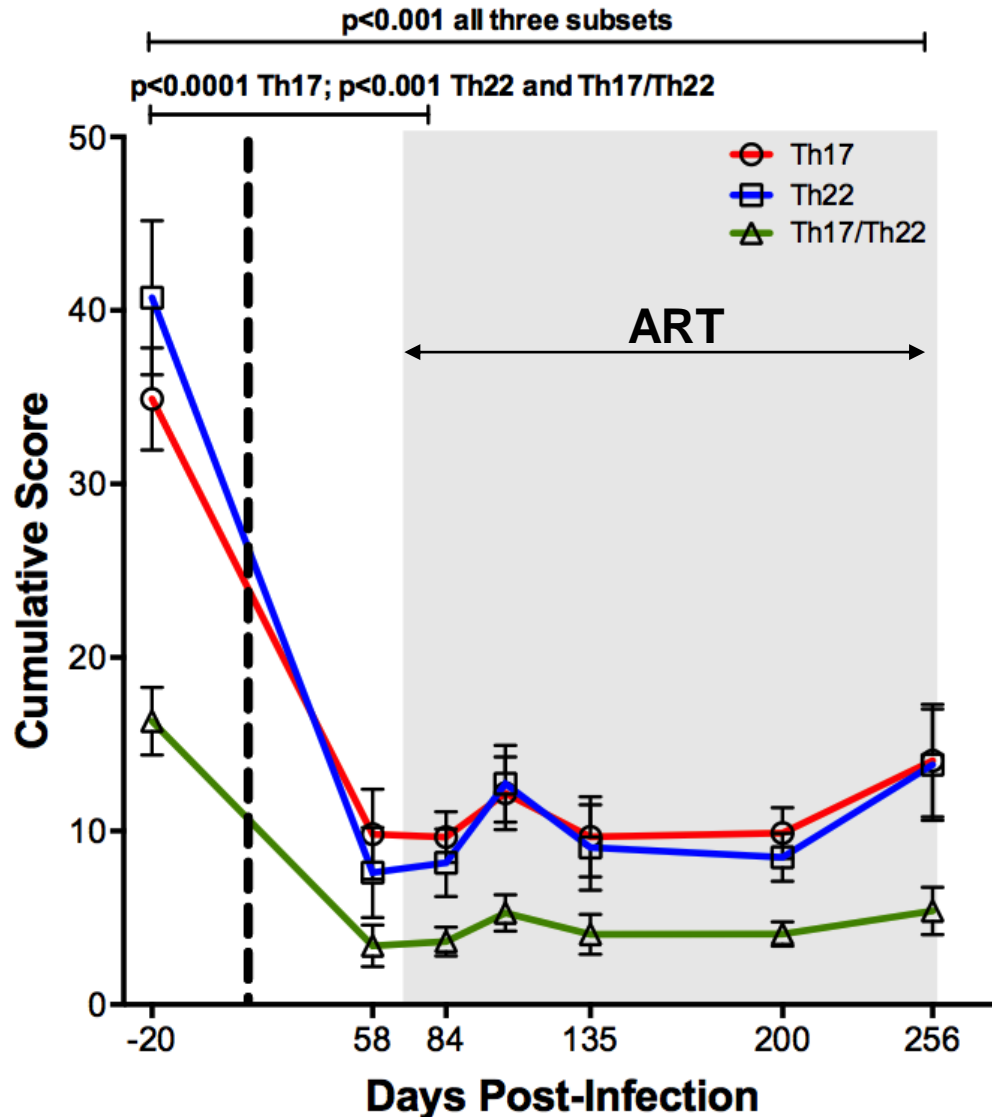
Cellular immune breadth



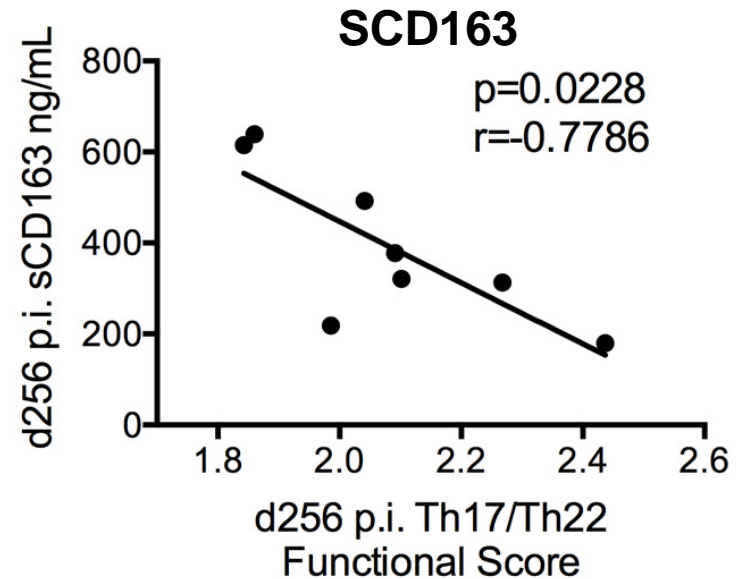
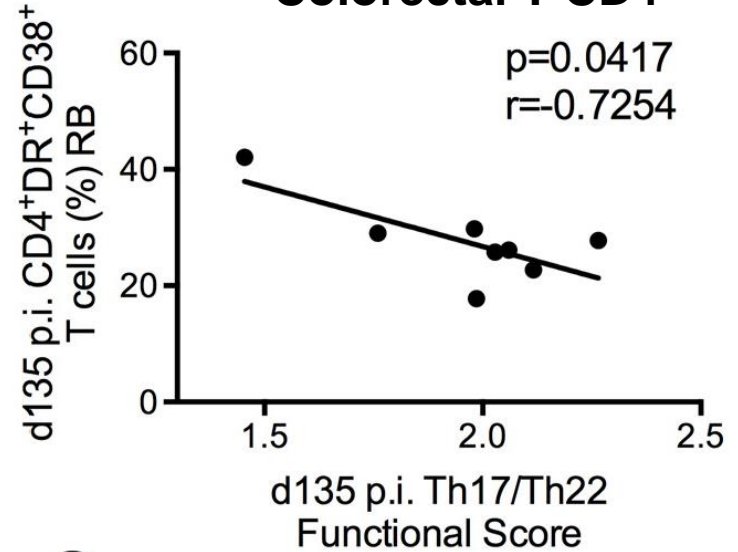
# Intestinal IL-17 and IL-22 – Inflammation & SIV Persistence

(Ryan E *et al*, PLOS Path 2016)

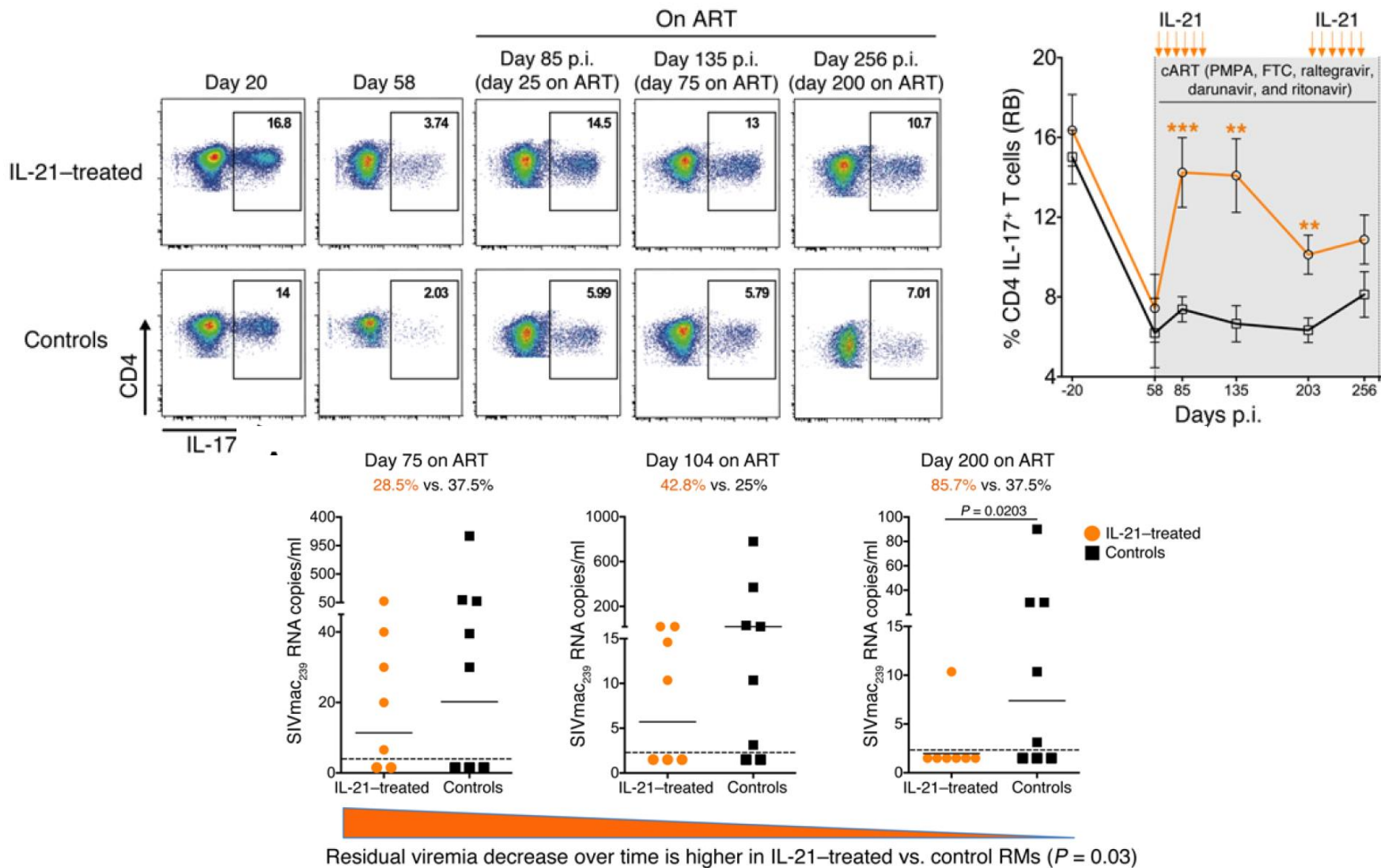
## Combined subset levels and function Rectal biopsies



## Colorectal T CD4



# Interleukin-21 combined with ART reduces inflammation & viral reservoir in SIV-infected macaques



# Large internal collaborative programs



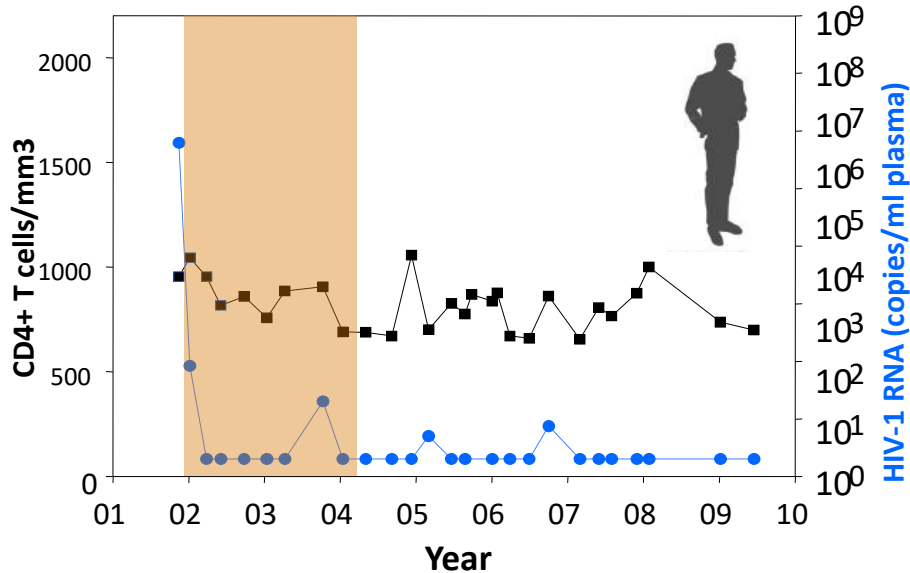
## MSDAVENIR

Améliorer la Vie Ensemble  
par l'Innovation et la Recherche



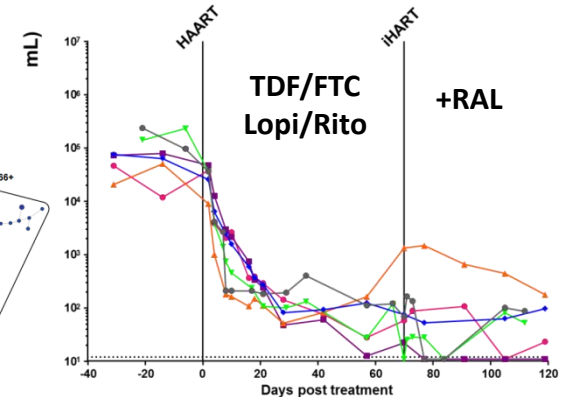
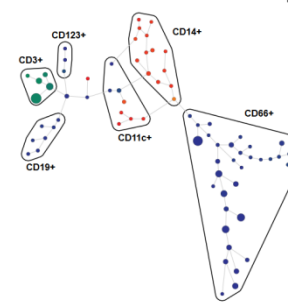
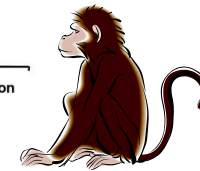
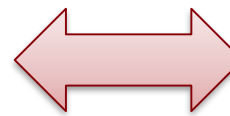
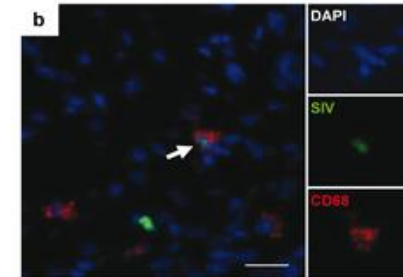
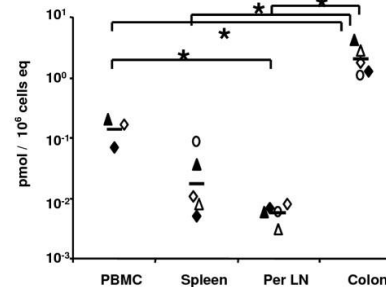
## VISCONTI & pVISCONTI programs

### Post-treatment controllers (PTC)



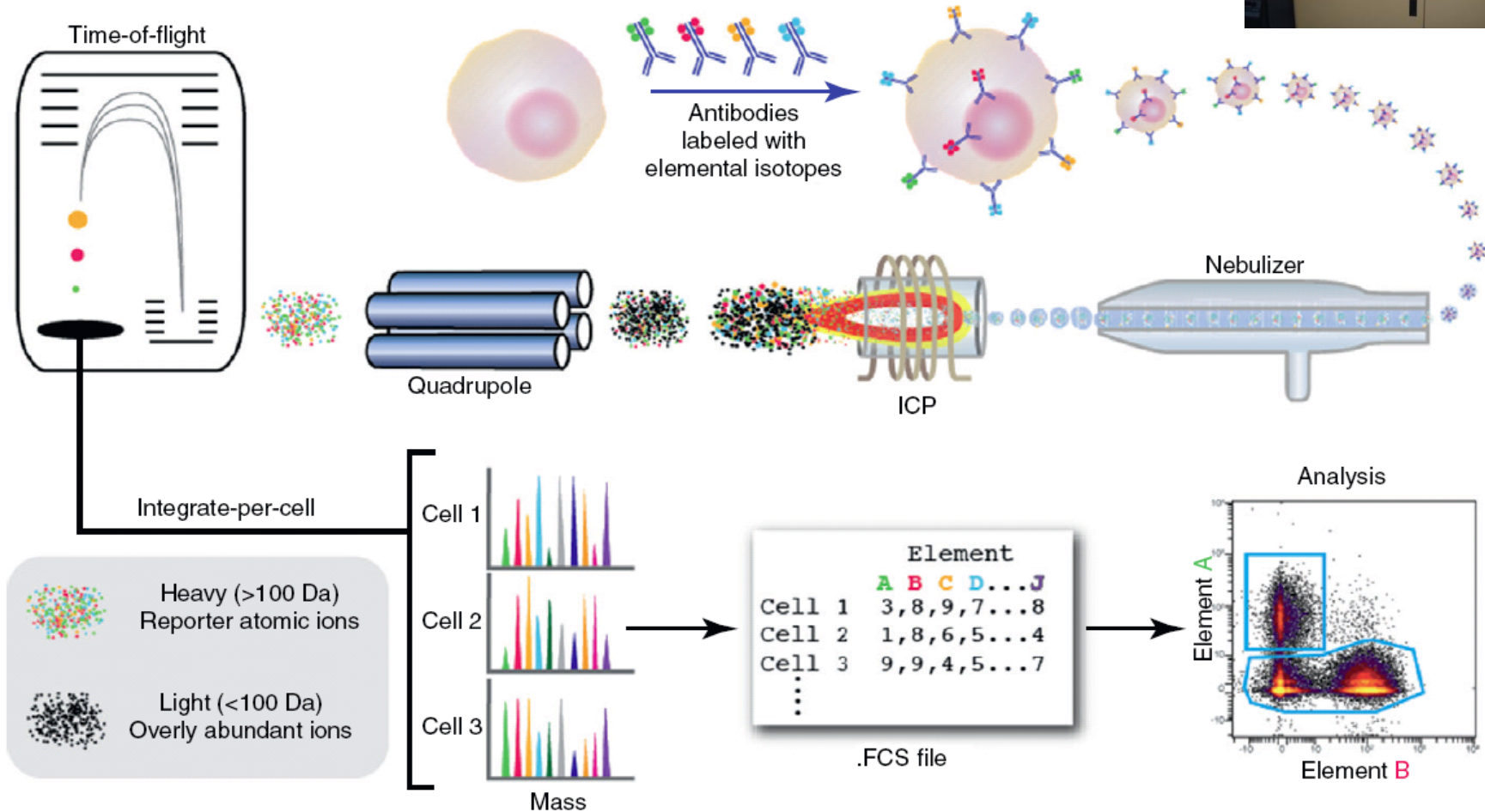
**ANRS EP47 VISCONTI. 14 patients**  
Months on cART : **36.5** (12-92)  
Months post-cART: **89** (48-115)

(a) 3TC tissue concentrations



# Cytometry by time of flight (CyTOF)

- Metal tags instead of fluorescent tags : 130 distinct tags in theory
- Detection of tags by mass spectrometry



# Cytometry by time of flight (CyTOF) & integrated pipeline analysis

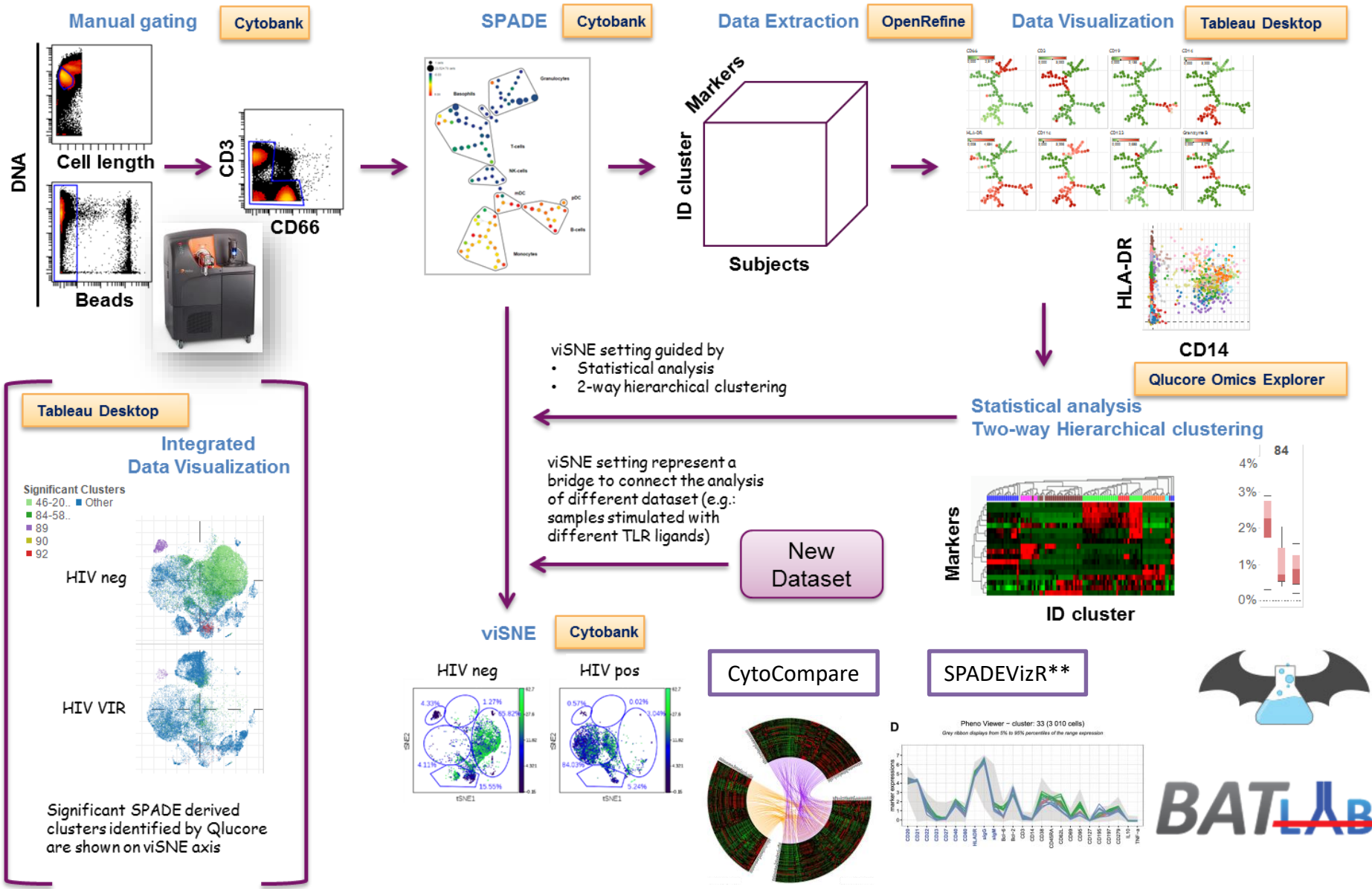
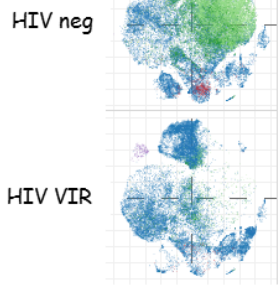


Tableau Desktop

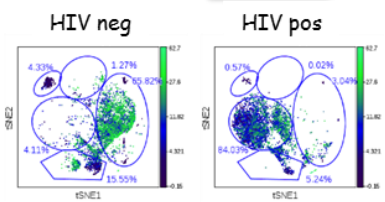
Integrated Data Visualization

- Significant Clusters
- 46-20.. Other
  - 84-58..
  - 89
  - 90
  - 92

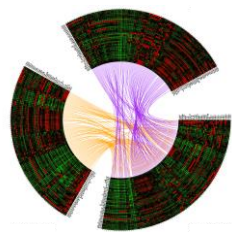


Significant SPADE derived clusters identified by Glucore are shown on viSNE axis

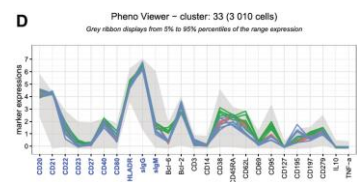
viSNE (Cytobank)



CytoCompare



SPADEvizR\*\*

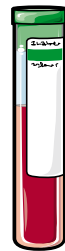


BATLAB

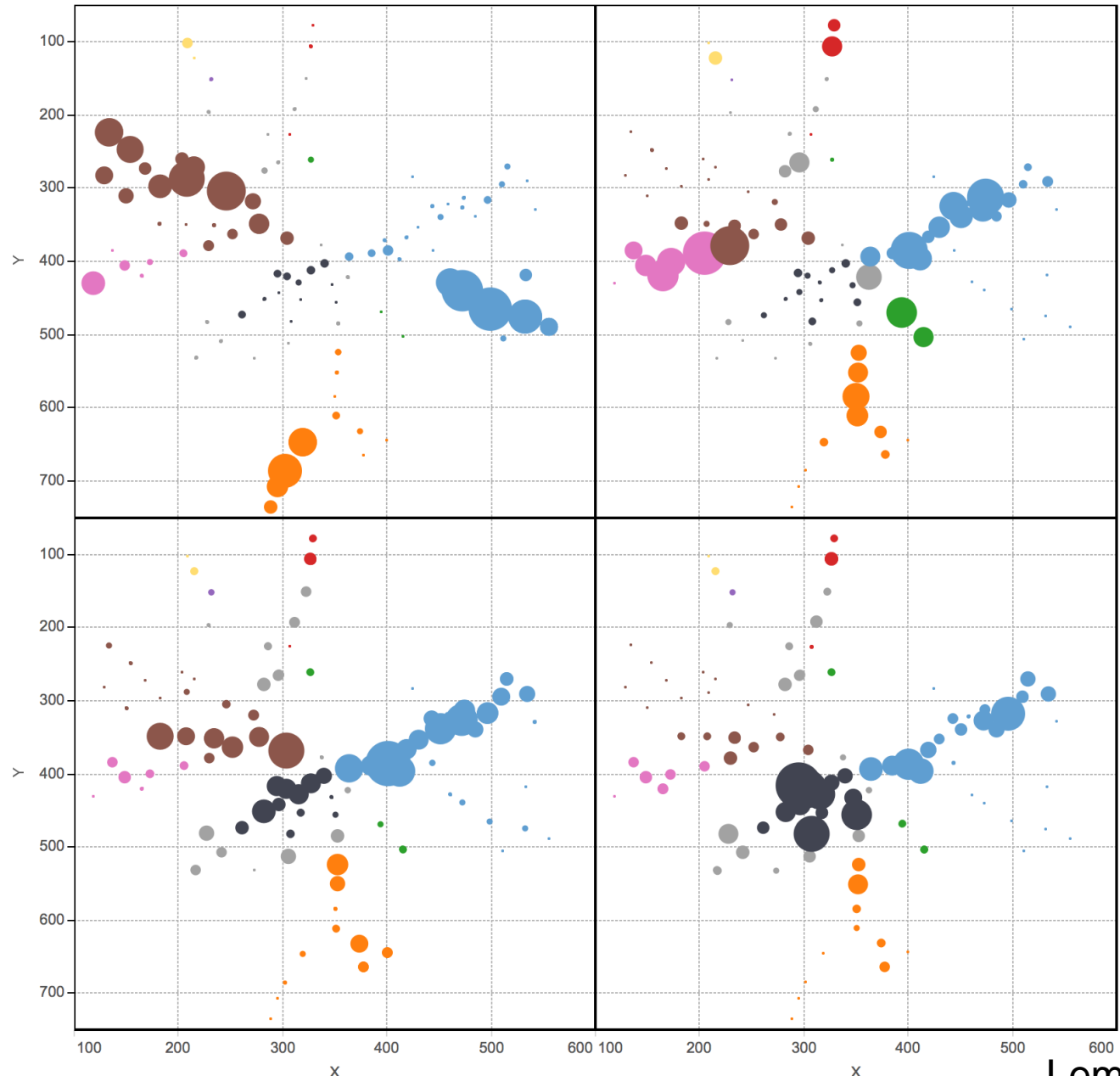
# Cluster analysis : Myeloid cells during late chronic SIV infection

SIV-N=3

SIV+ N=2



Blood

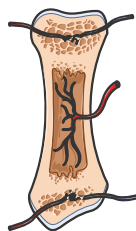


Cell populations

- Neutrophils
- T lymphocytes
- B lymphocytes
- CD45 -
- NK cells
- Monocytes
- cDC
- Basophils
- pDC
- Undetermine

Percentage of parent

- 0,00
- 5,00
- 10,00
- 14,57

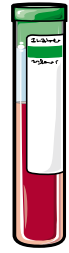


Bone marrow

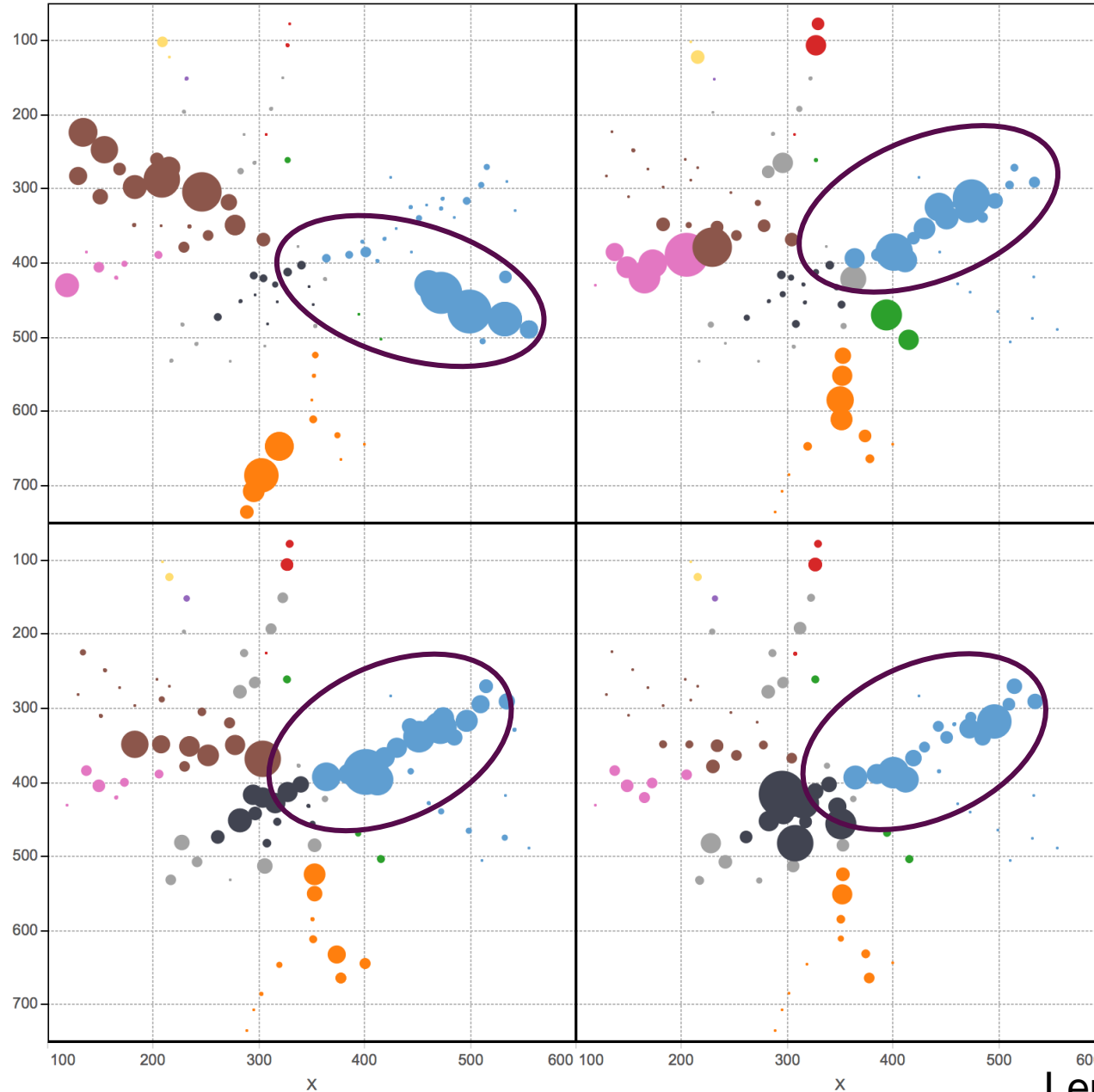
# Cluster analysis : Myeloid cells during late chronic SIV infection

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Blood

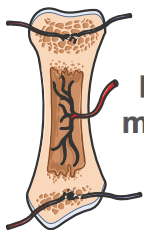


Cell populations

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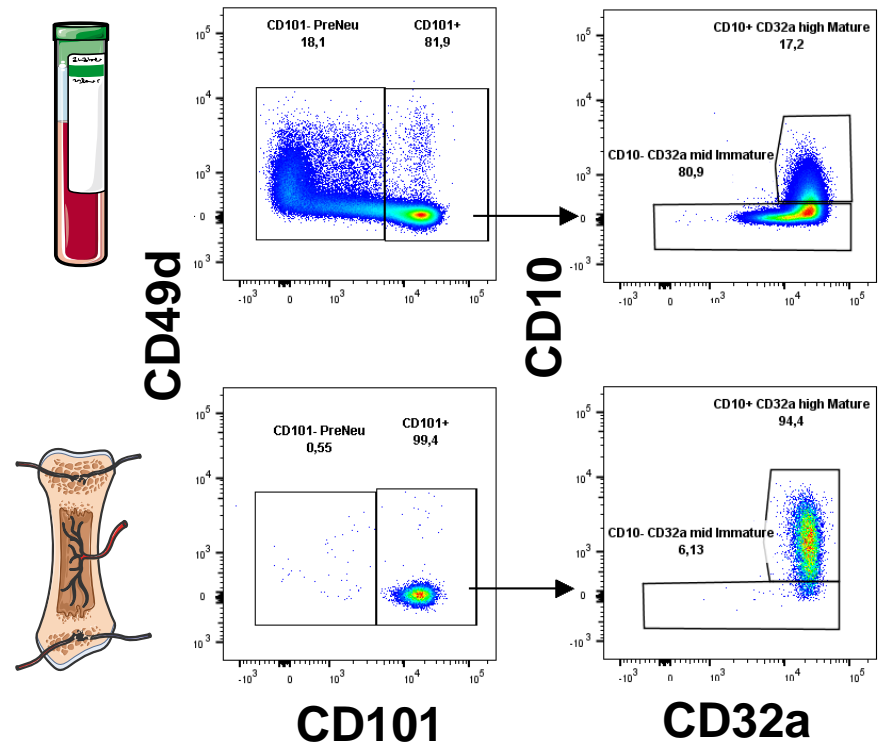
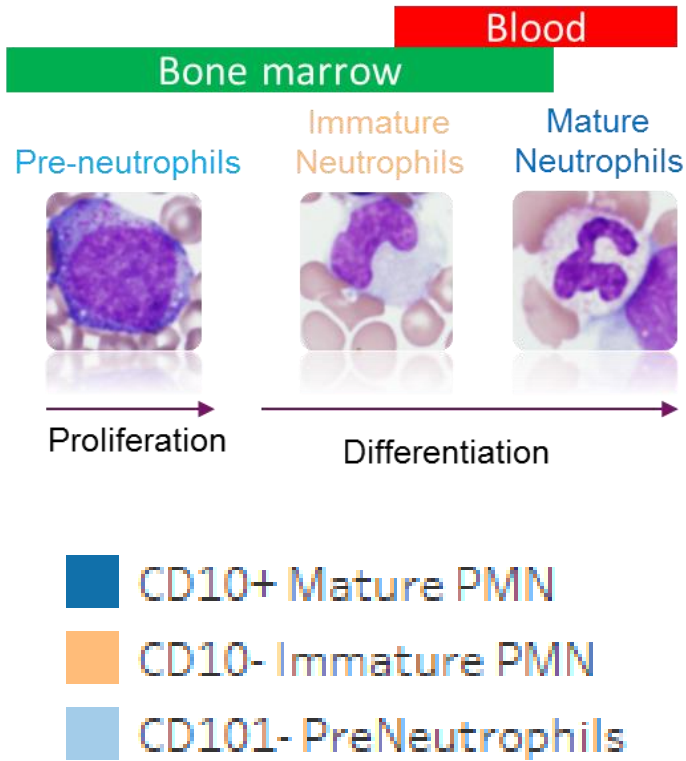
Percentage of parent

- 0,00
- 5,00
- 10,00
- 14,57



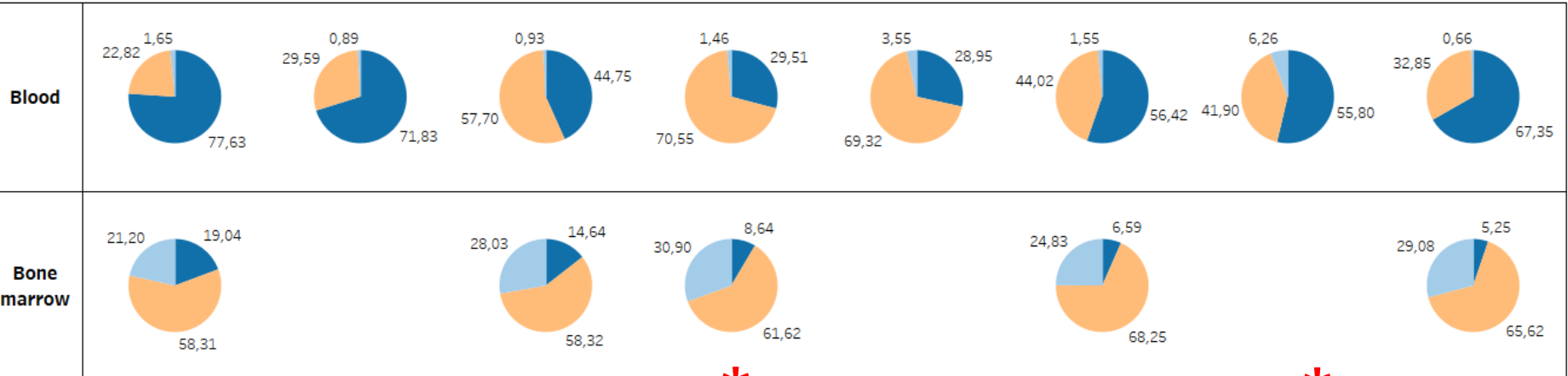
Bone marrow

# Impact of SIV infection on PMN maturation



Days post-infection

0      3      7      10      14      28      42      83



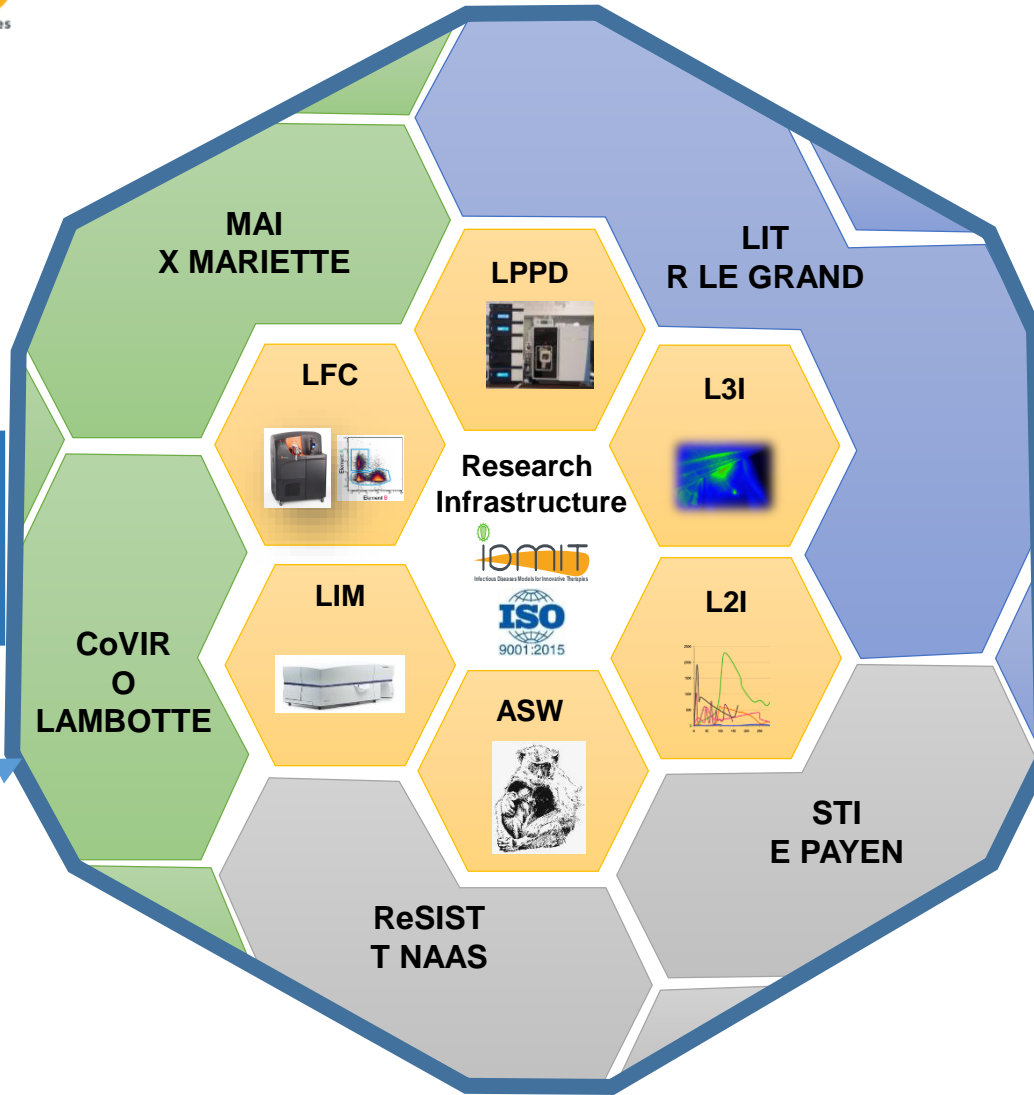
\*

\*


Lemaitre J, PhD

Friedman test, Dunn's multiple comparison

**UMR1184**



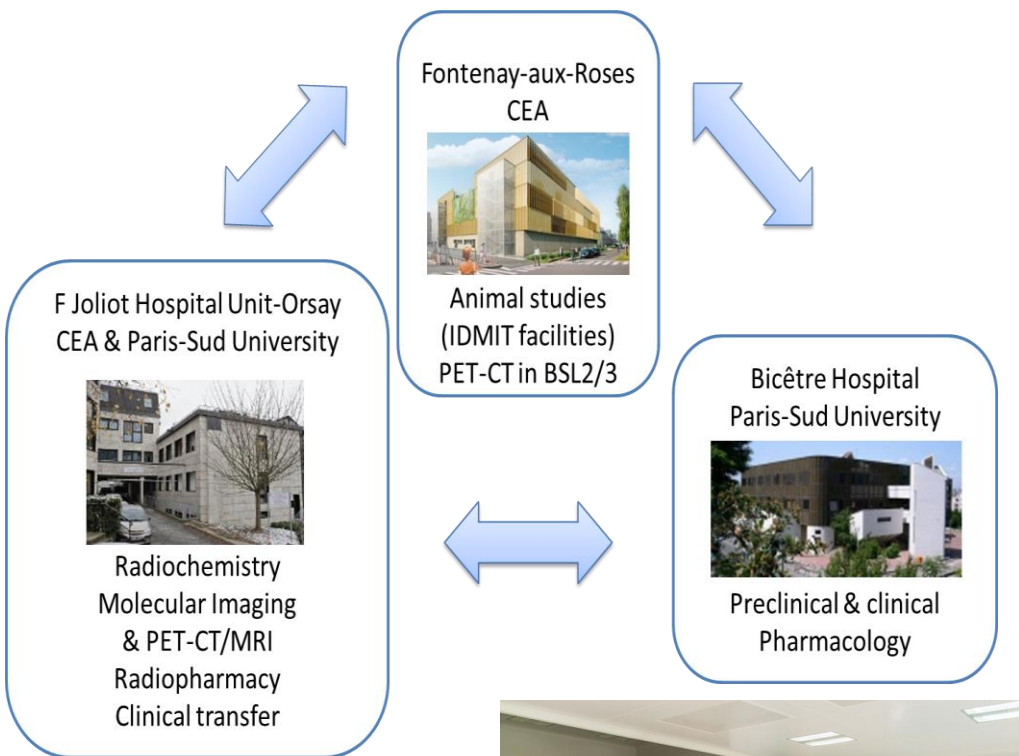
**Modèles Précliniques**



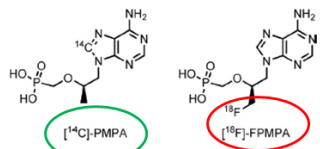
**Cohortes nationales**



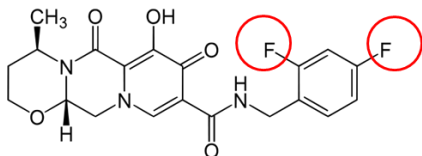
# In vivo imaging of anti-HIV drugs bio-distribution



## Tenofovir-<sup>18</sup>F

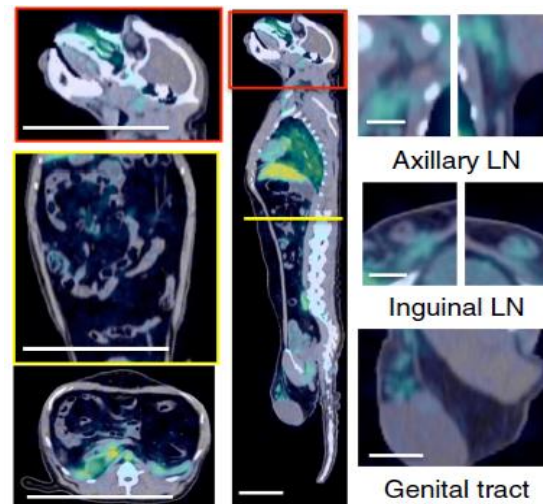


## Dolutegravir

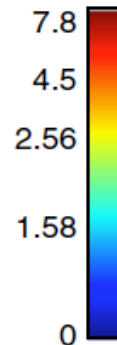
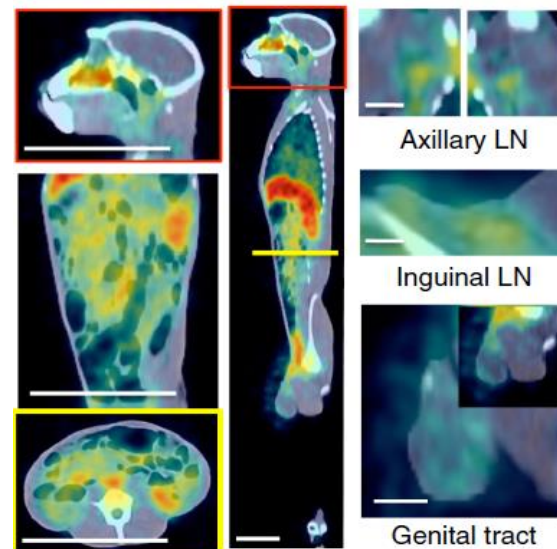


## Visualizing SIV replication PET-TDM

Control Animal



Infected Animal



# Thanks for your attention



## Roger Le Grand

Delphine Desjardins  
Anne-Sophie Beignon  
Elisabeth Menu  
Frédéric Martinon  
Mariangela Cavarelli  
Nathalie Bosquet  
Vanessa Contreras  
Pierre Roques  
Pauline Maisonnasse  
Candie Joly  
Jean-Louis Palgen  
Ernesto Marcos

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Benoit Favier  
Christine Bourgeois  
Bruno Vaslin  
Nicolas Noel

## Antonio Cosma

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Nicolas Tchitckek  
Quentin Jauhault  
Mario Gomez

## Catherine Chapon

Sabine Tricot  
Naya Sylla  
Sophie Luccantoni

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Christophe Joubert  
Benoit Delache  
Sebastien Langlois  
Jean-Marie Robert

