HIV Post-Treatment Control: Insights On Remission from a Unique European Cohort

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This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

Disclosures

- Speaker fees from MSD, ViiV Healthcare, Janssen, Gilead
- Research grants from MSDAvenir and ViiV Healthcare to ANRS RHIVIERA consortium

Learning Objectives

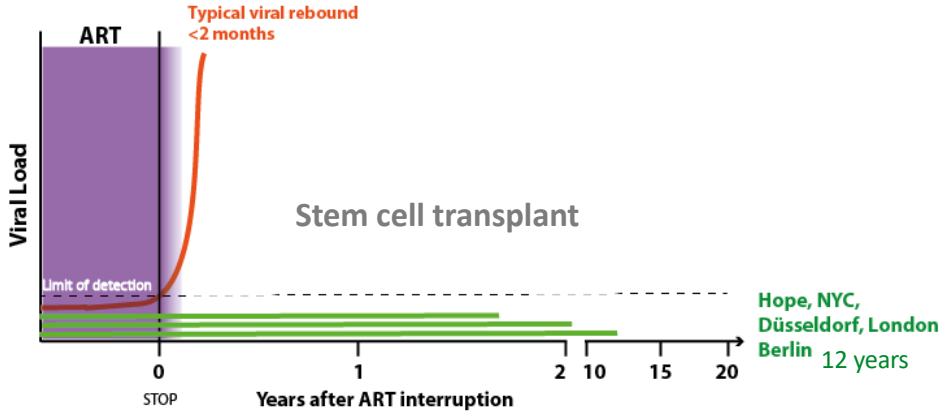
1. Be aware of markers that may help predict who among people on ART may have better chances to control viremia if ART is discontinued for any reason.

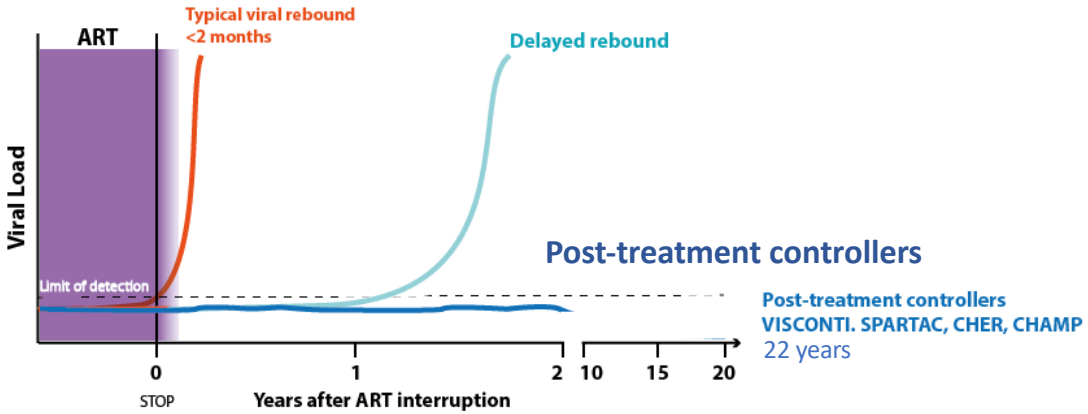
2. Understand the viral and host factors that have been associated with post-treatment control, as well as the immune mechanisms mobilized during acute infection vs treatment interruption.

3. Know the difference between HIV remission and HIV cure.

4. Understand how post-treatment controllers are different (or are not) from other cases of durable remission or potential HIV cure.

Living with HIV but without ART: HIV remission and HIV cure





HIV Cure

Complete elimination of infected cells

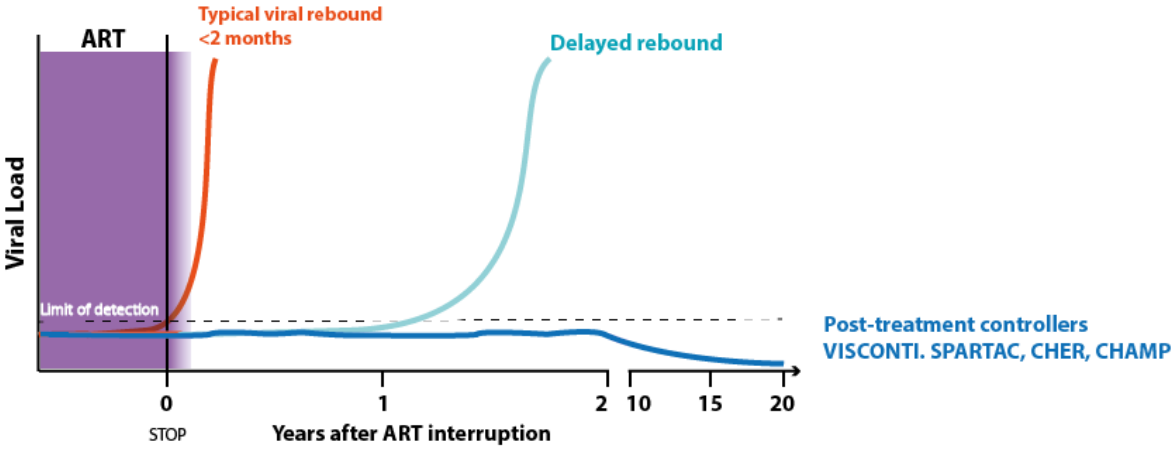
Permanent

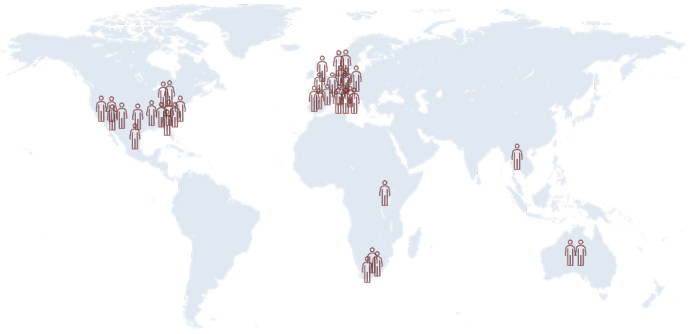
HIV Remission

The virus may persist at low levels but remains undetectable, controlled by host mechanism

May be transient

HIV remission: learning from the few exceptions





ANRS VISCONTI study

31 PTC (9 women)
HIV diagnosed (mean) : June 2001

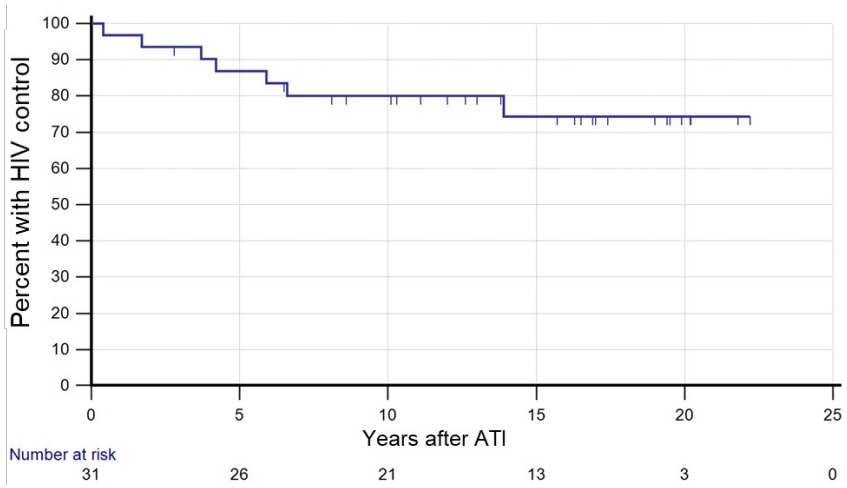
73% symptomatic PHI
Viremia at ART initiation : **5.1** [4.6-5.8] Log RNA
Multiple ARV strategies
Time on ART : **3.8y** [2.3-6.1]
Age at ART discontinuation: 38y [33-45]

Time off ART : **13.1y** [8.2-16.1] max >23y
Age at last follow-up : 53 y [42-60] – max. 82y

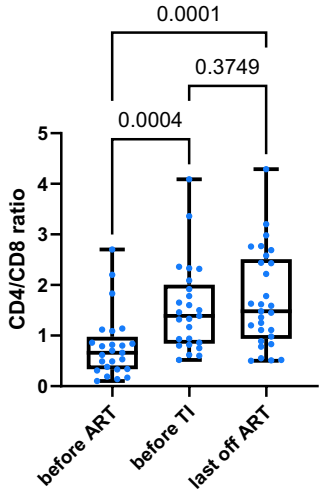
7 PTC have resumed cART

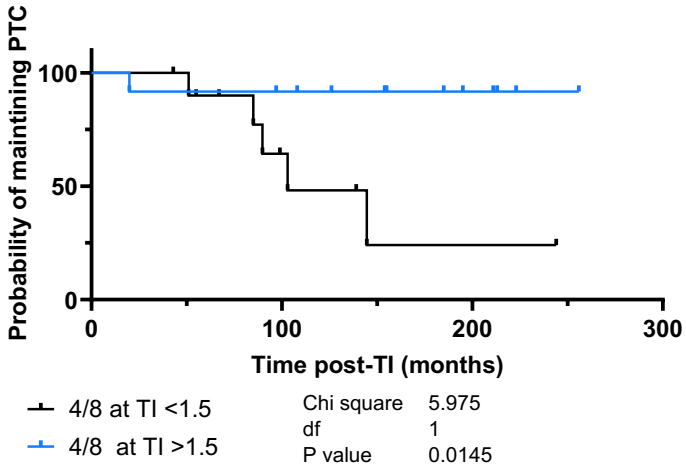
Post-treatment controllers: a durable phenotype

Over a decade of HIV remission in most PTCs



The importance of immune reconstitution under ART

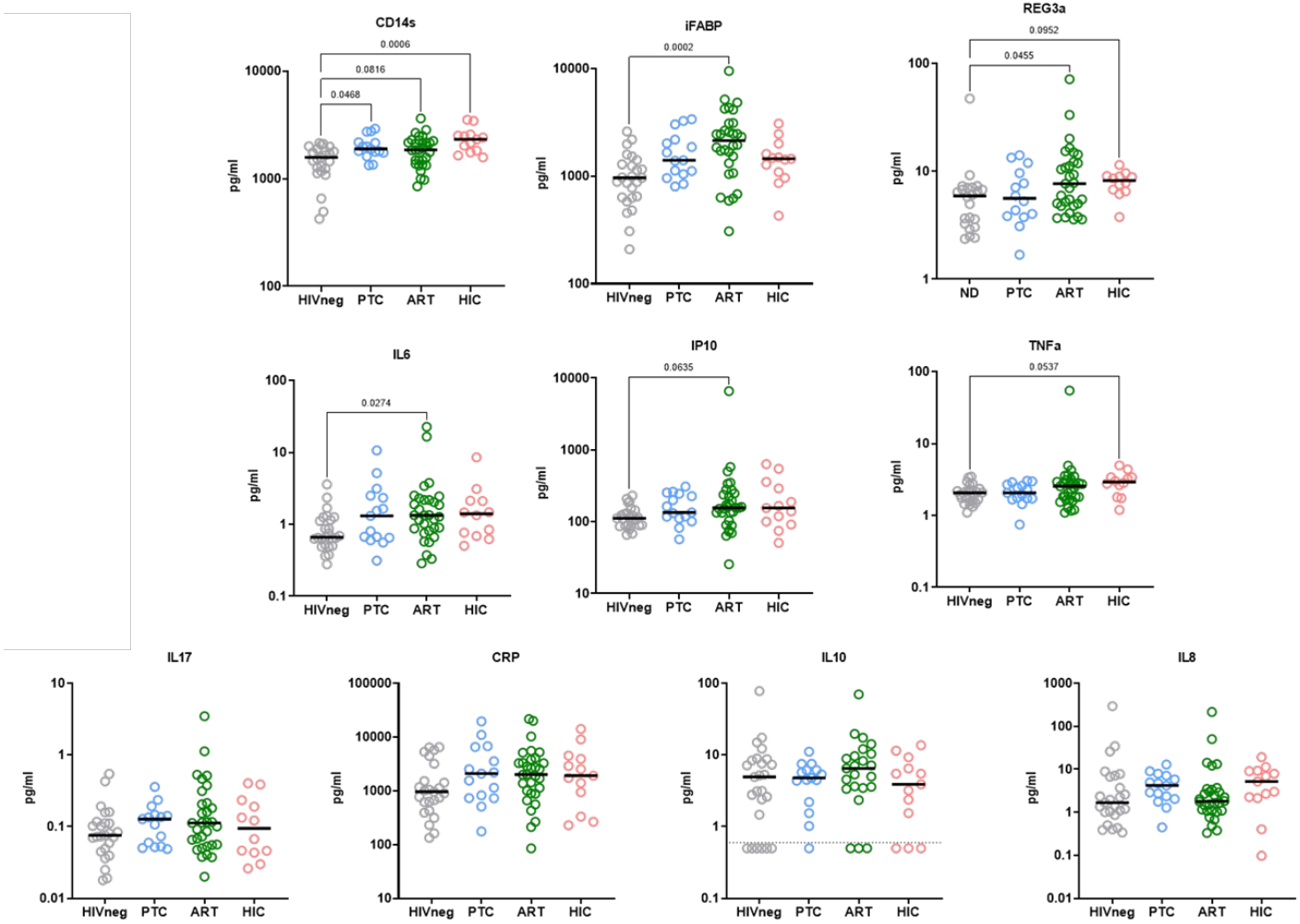




VISCONTI study unpublished

See also Martin et al AIDS 2017

Inflammation markers in PTCs close to levels found in general population



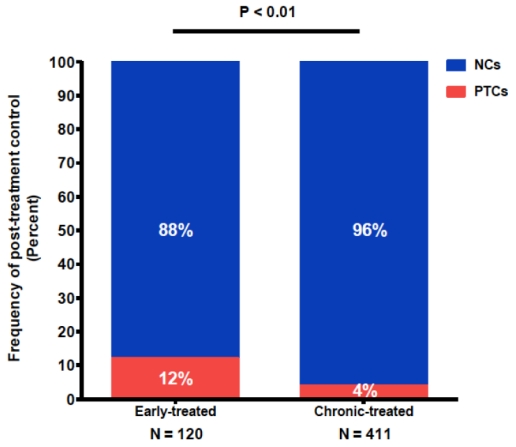
Early ART as starting point towards post-treatment control?

Initiation of treatment during primary infection favors control after ART interruption (VISCONTI)

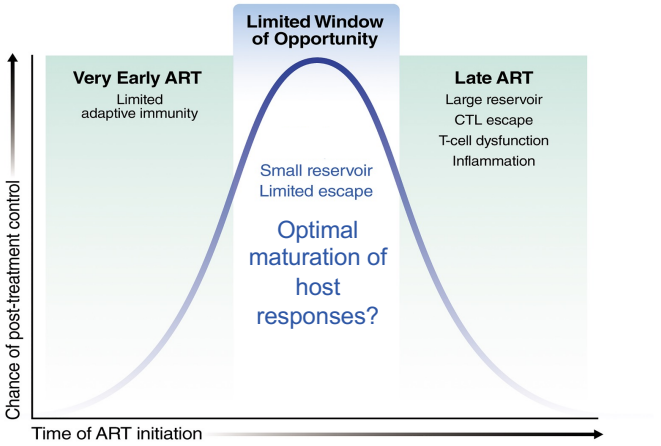
Hocqueloux et al AIDS 2010; Sáez-Cirión PLoS Path 2013; Frange et al Lancet HIV 2016

Advantage of early ART initiation has been proposed in other independent studies:
PRIMO: 8.5% PTC 1y after ART interruption among early treated
CASCADE: 8.2% PTC 1y after ART interruption among early treated
SPARTAC : 7.6% PTC 1y after ART interruption among early treated
OPTIPRIM: 6.5%PTC 1y after ART interruption among early treated
CHAMP: 13% PTC among early ART versus 4% among ART in chronic infection

Lodi et al Arch Intern Med 2012; Goujard et al Ant Ther 2012; Cheret et al JAC 2015; Namazi et al JID 2018; Gossez et al AIDS 2019



Is there a window of opportunity for ART initiation?

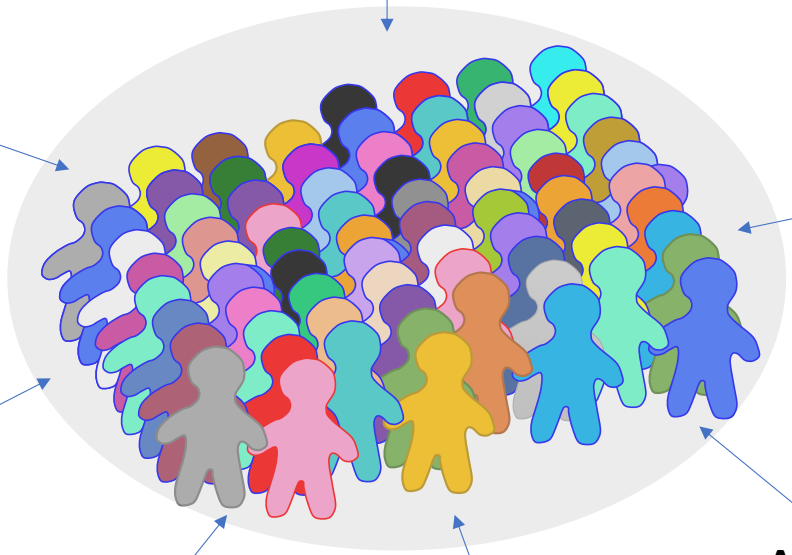


Adapted from Goulder and Deeks, PLoS Path 2018

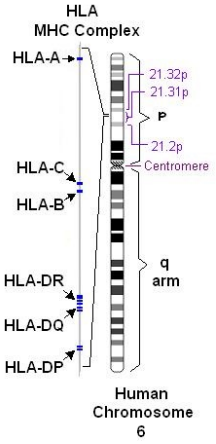
All the same… but all different in response to viral infections

Viral factors

Environmental factors
lifestyle



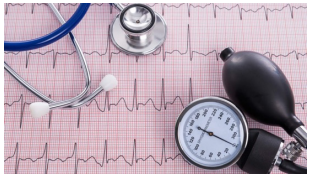
Immunogenetics



Sex

Age

Underlying conditions

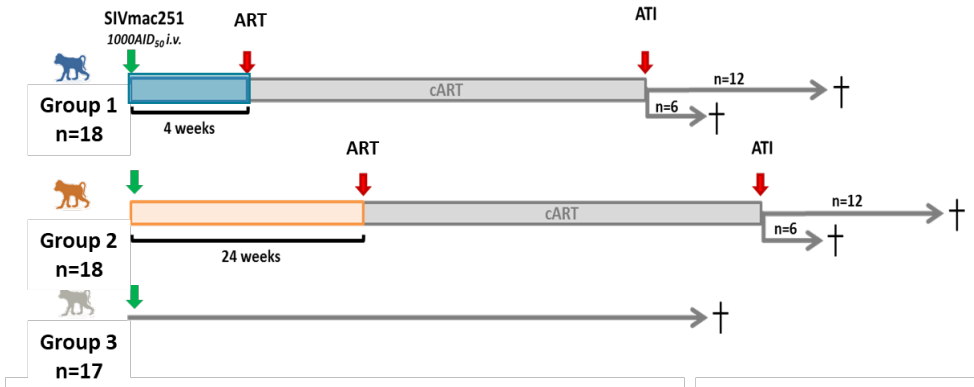


Antiretroviral regimens
(composition, delay)

The pVISCONTI study: Non-human primate (NHP) model of-post treatment SIV control:

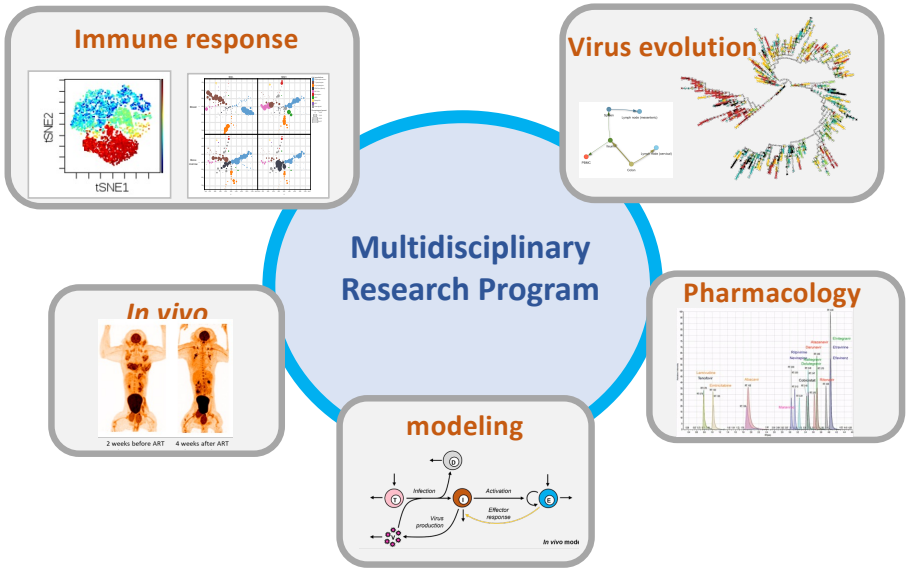
p(rimate)VISCONTI:
Impact of early (d28) vs late (M6) initiation of prolongued ART on the outcome after treatment interruption

Cynomolgus macaques from Mauritius, SIVmac251



cART regimen: TDF (5.1 mg/kg) + FTC (40 mg/kg) + DTG (2.5 mg/kg)
Route of administration: subcutaneous

cART duration = 24 months
Post-ATI follow-up = 12 months

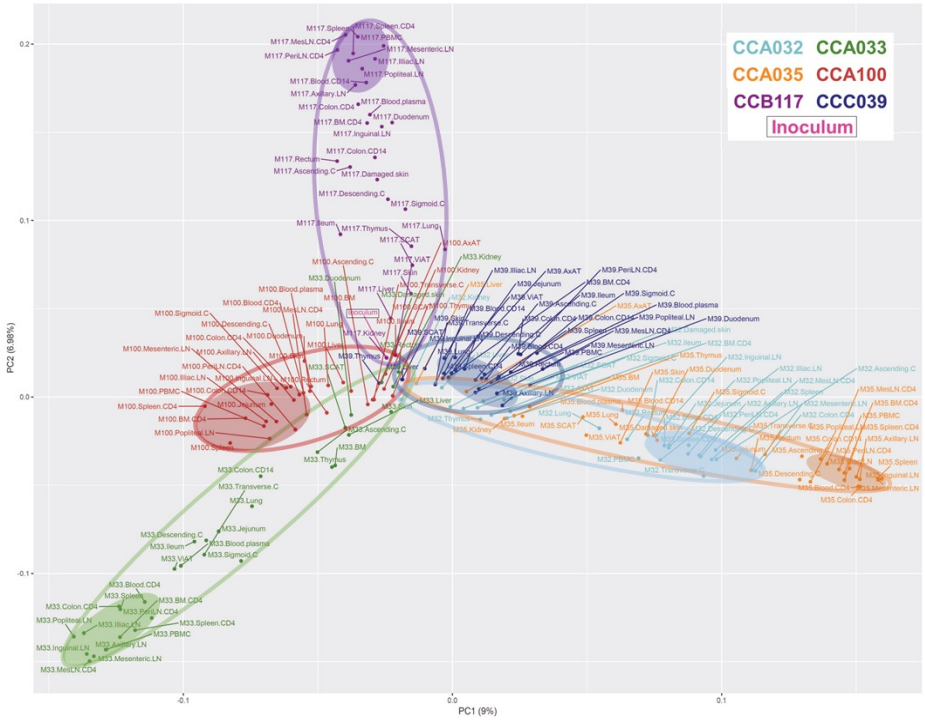


MHC H6 haplotype associated with natural control was excluded

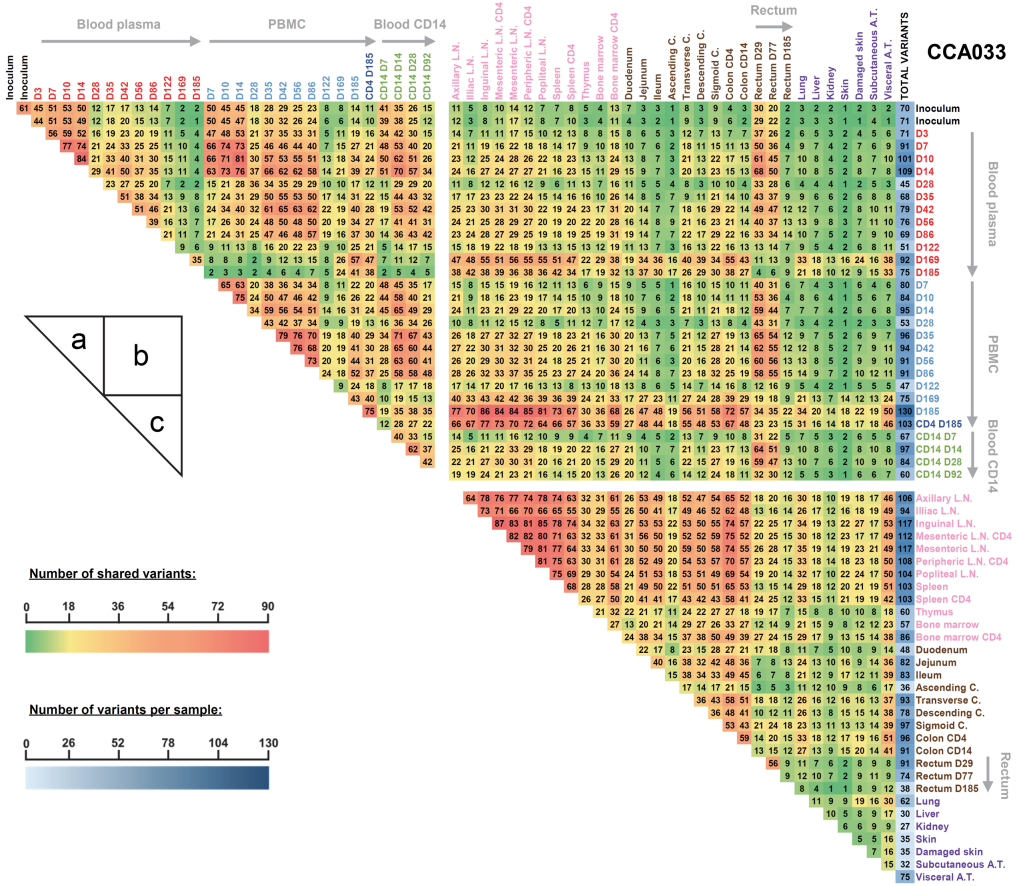
Passaes et al Nat Com (accepted)

Drastic evolution of viral diversity 6 months after infection

Viral quasispecies in different tissues from six macaques at 6 months post infection

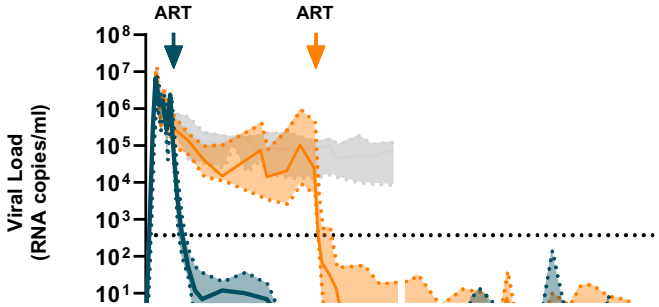


Dynamics of viral evolution in one individual

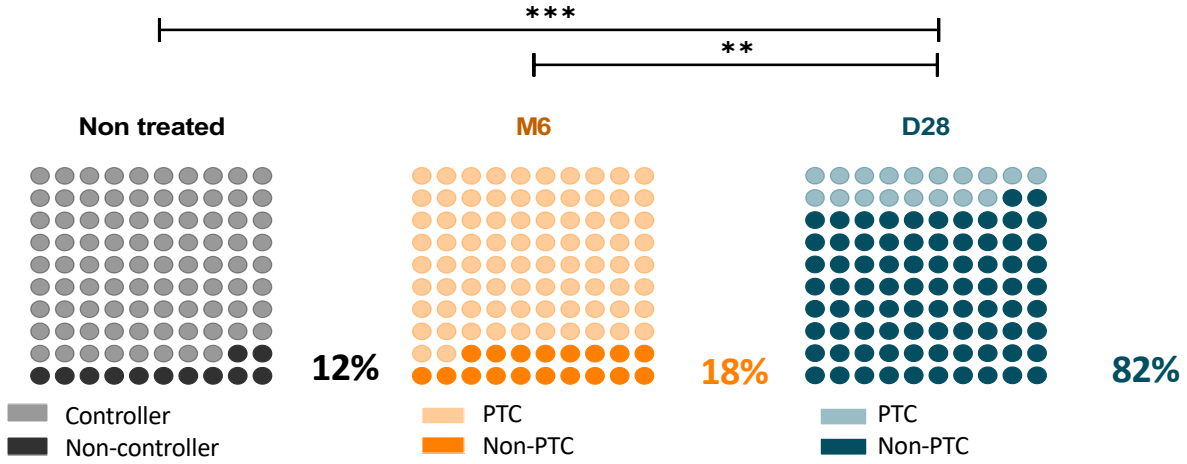


Millet, Avettand-Fenoel. Unpublished

Early antiretroviral treatment favored a delayed viral rebound and lower viral setpoint post-ATI



Higher rate of post-treatment controllers (VL<400 copies) among early treated macaques, at the end of the study



Passaes et al Nat Com (accepted)

Which are the mechanisms associated with post-treatment control?

Viral rebound

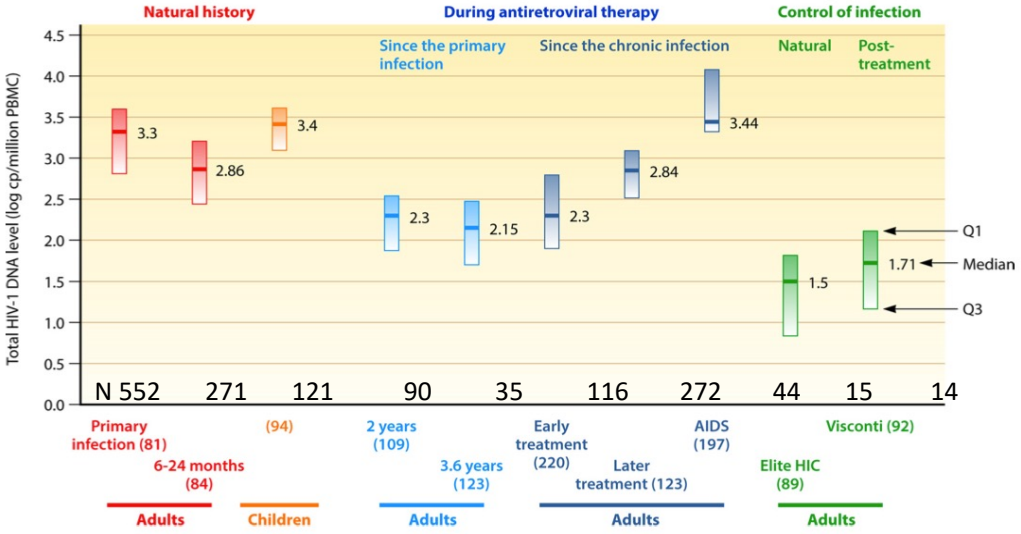
Limited reservoirs?

Host barriers?

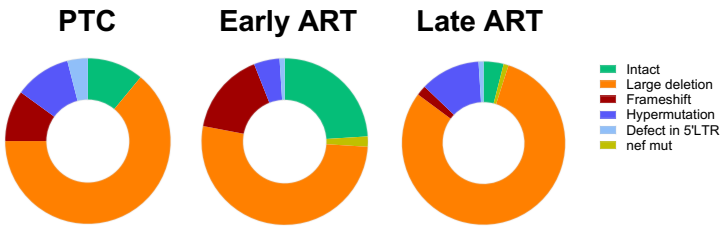
Post-treatment control

Low frequency of infected cells… but carrying infectious viruses

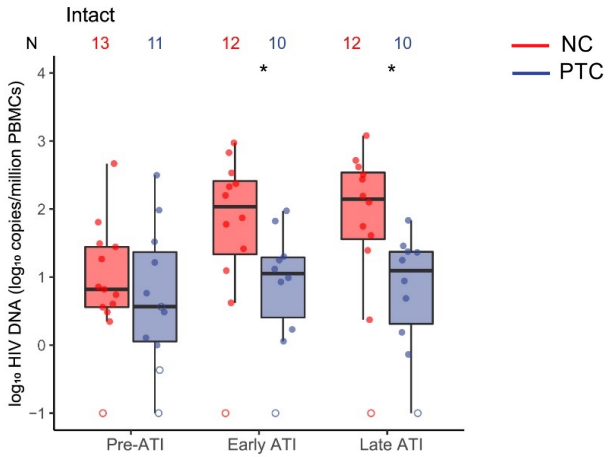
Low levels of cell-associated HIV DNA



Presence of intact and reactivable proviruses at inclusion



Number of intact proviruses at ATI does not explain PTC

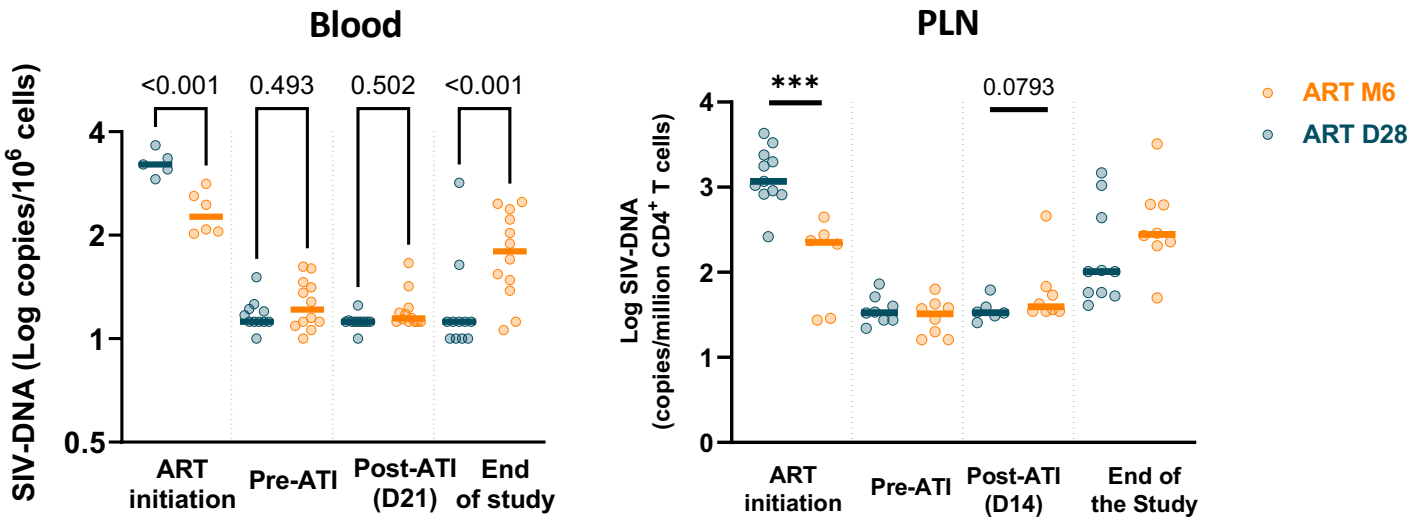


Virus is controlled by host mechanisms!!

Saez-Cirion et al. PLoS Pathog. 2013; Avettand-Fènoël et al. Clin Microbiol Rev. 2016; Trémeaux et al. Microbiol Spectr. 2023; Etemand et al PNAS 2023

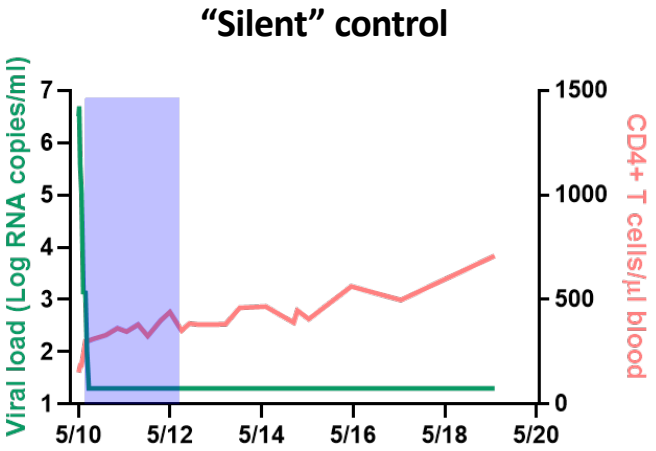
Similar SIV-DNA levels in PTC and non PTC at ART interruption

Cell-associated SIV DNA

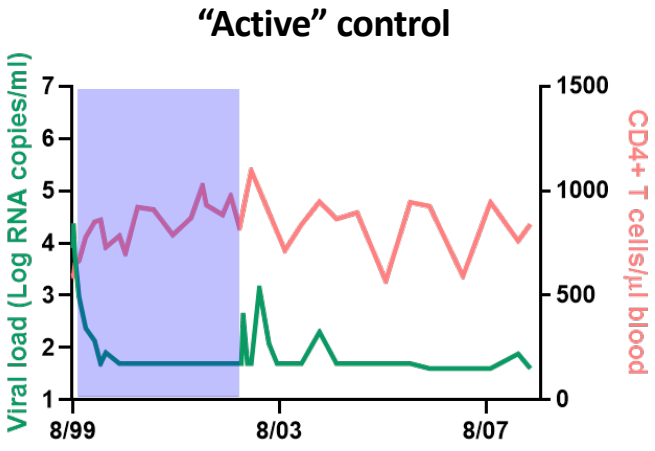


Passaes et al submitted

Silent vs active post-treatment control



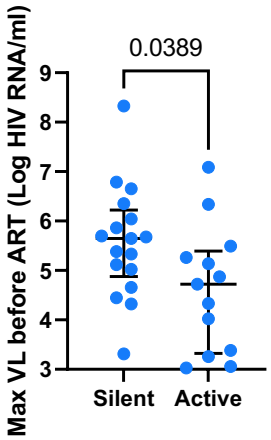
18 PTC in iVISCONTI



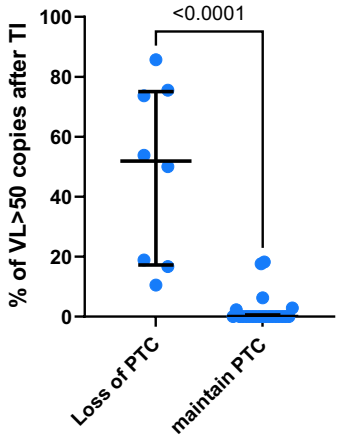
12 PTC in iVISCONTI

Clinical observations informing on durable post-treatment control

Reverting an unfavorable situation



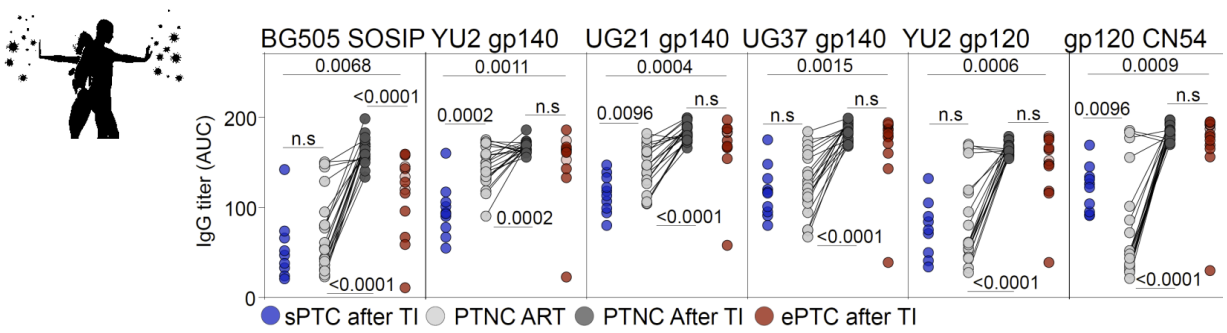
Transient viremia, not generally good for permanent control



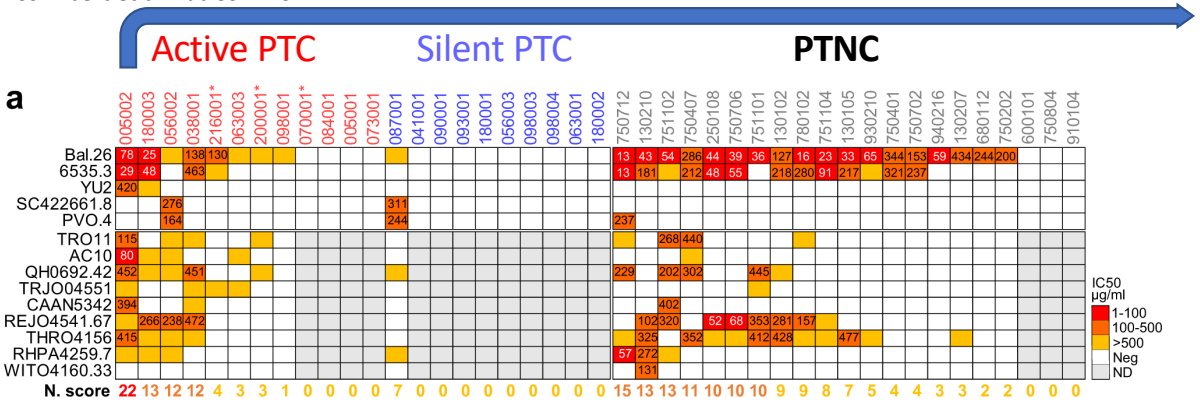
Monceaux et al Unpublished

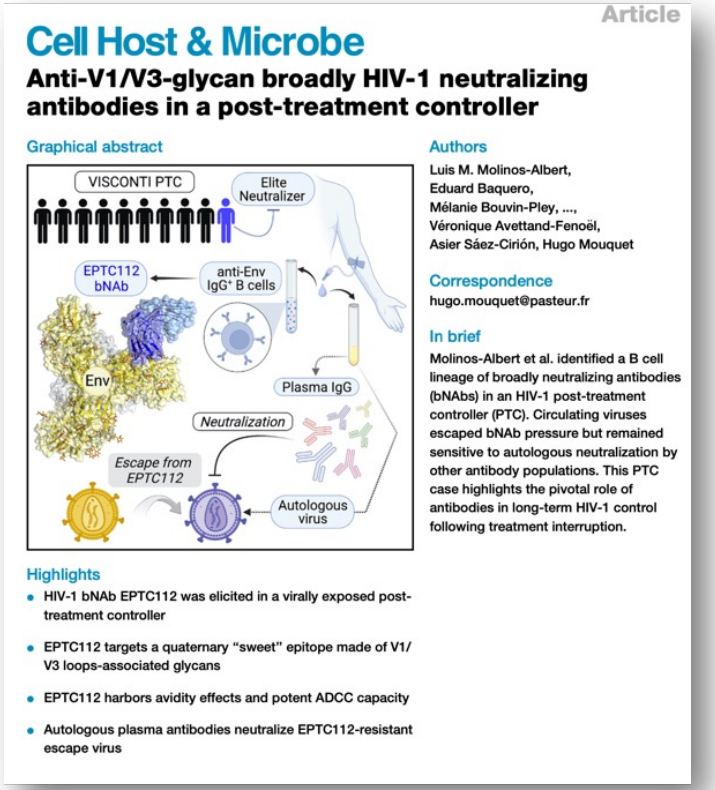
Antibody titers: retracing the history of antigen exposure in PTC

Higher antibody responses associated with PTC with episodes of viremia



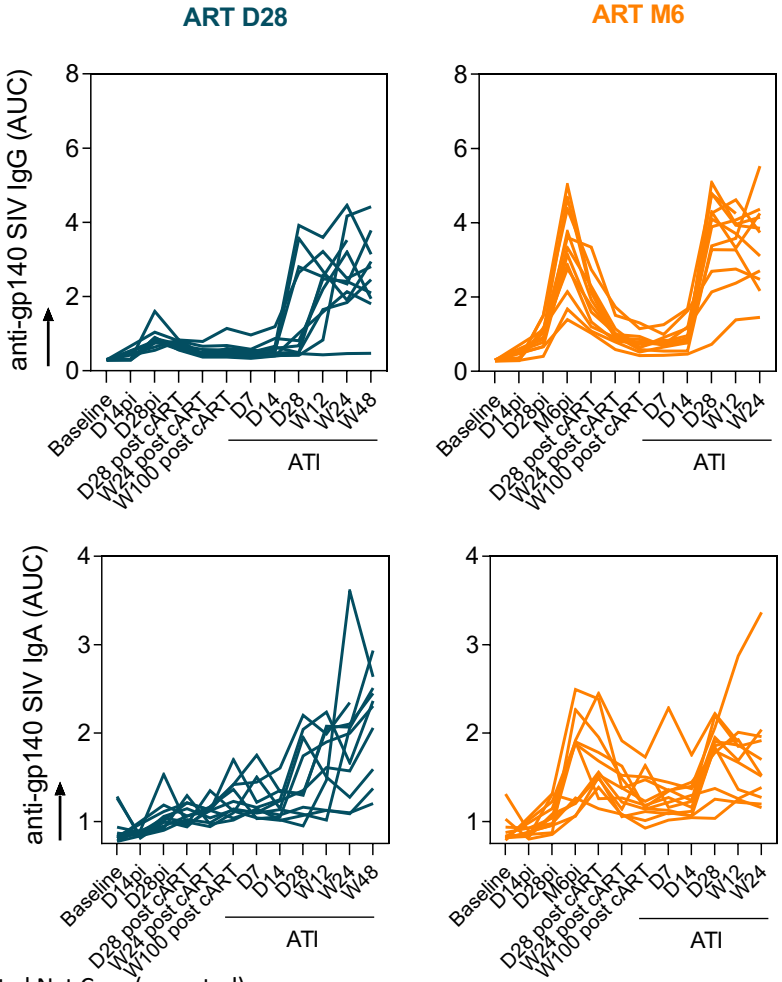
Molinos-Albert et al Nat Com 2022



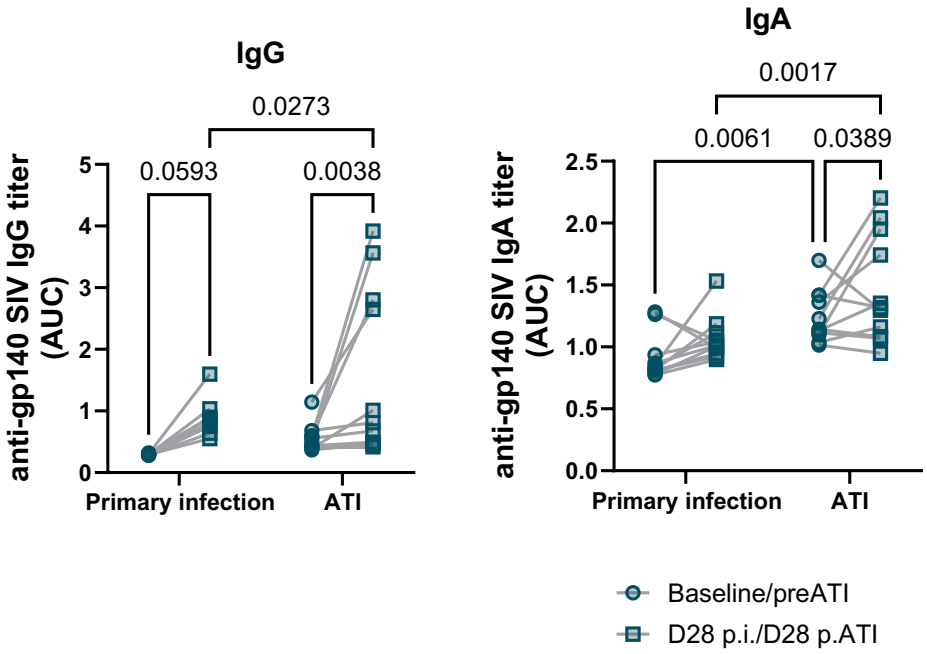


Autologous neutralizing antibodies increase with early ART and shape viral rebound after ATI. *Esmaelizadeh et al Science Trans Med 2023*

Early vs delayed treatment: changes in the dynamics of humoral response



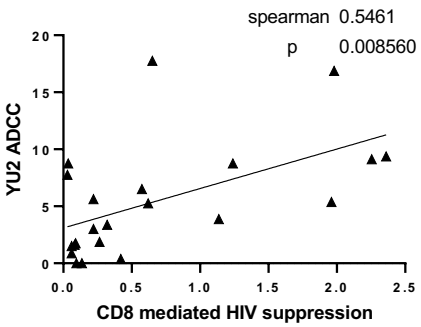
Faster antibody response towards viral rebound

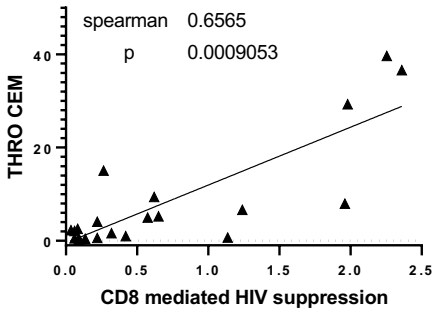


Passaes et al Nat Com (accepted)

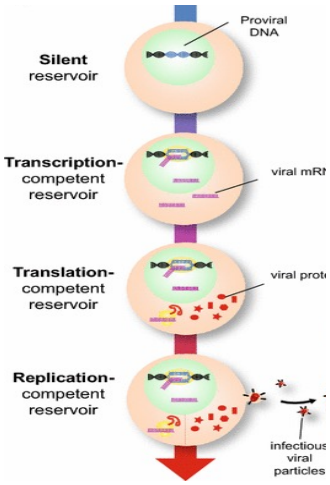
Transient antigen exposure may drive expansion of efficient immune responses after ART interruption in some PTC

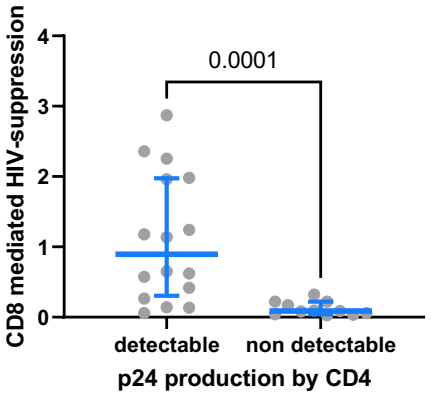
Correlation between antibody activities and CD8+ T cell suppression capacity in PTC





Enhanced antiviral activity of CD8+ T cells in PTCs with detectable antigen production by CD4+ T cells





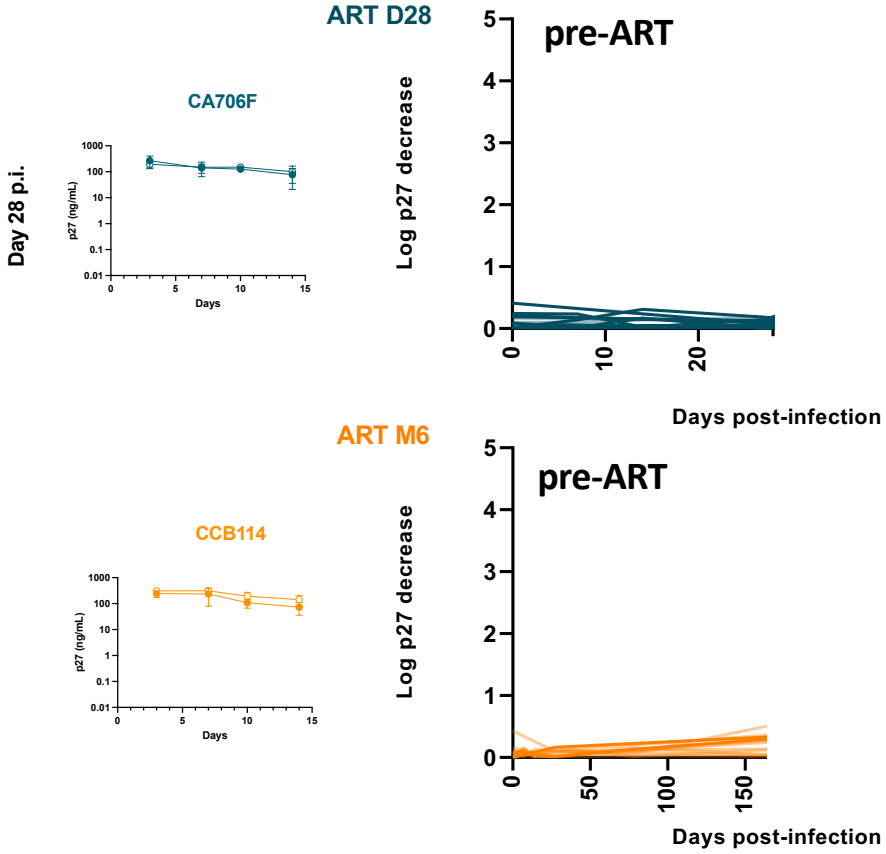
Virtuous circle driving active control

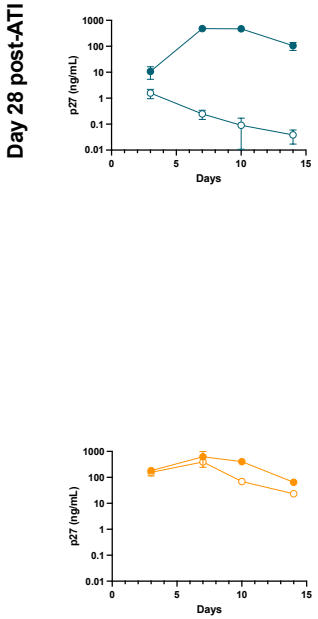
Pool of HIV-specific cells protected/matured thanks to early ART?

Monceaux et al Unpublished

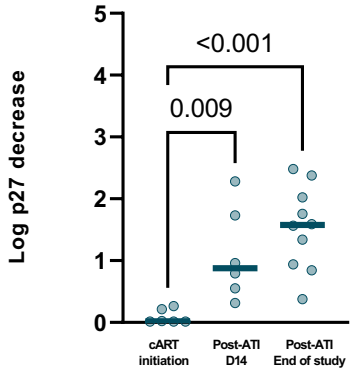
Early ART initiation promotes a more efficient SIV-specific CD8+ T cell response

Superior SIV-suppressive activity of CD8+ T cells expanded against rebounding virus than against virus in primary infection





Enhanced antiviral activity of CD8+ T cells in PLN

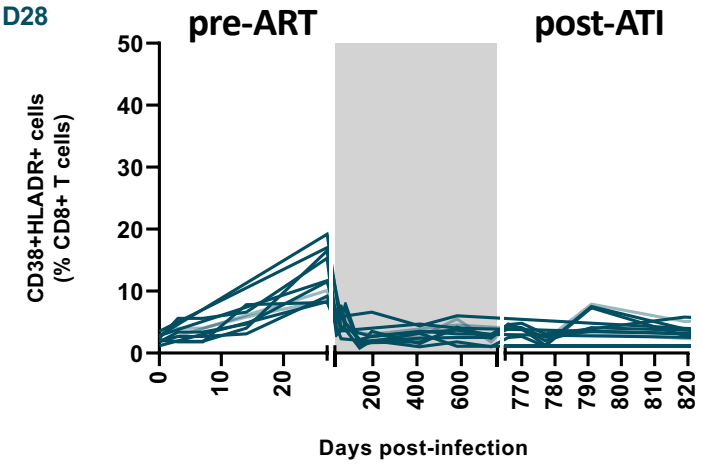


Early ART appears to favor the maturation of CD8+ T cell response

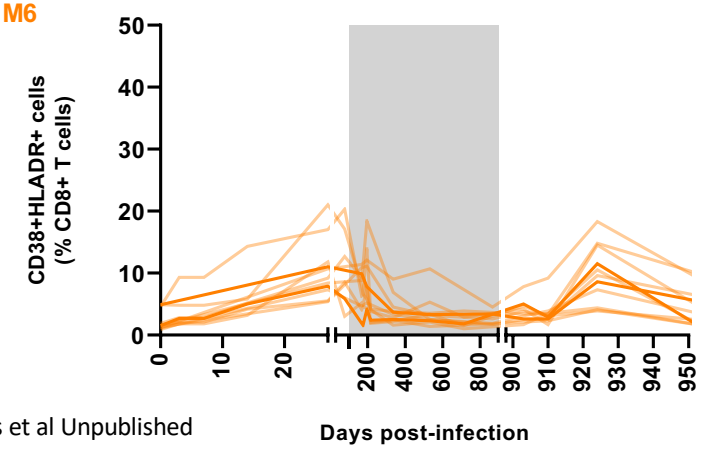
Passaes et al Unpublished

CD8+ T cell response after early ART: restricted activation

ART D28

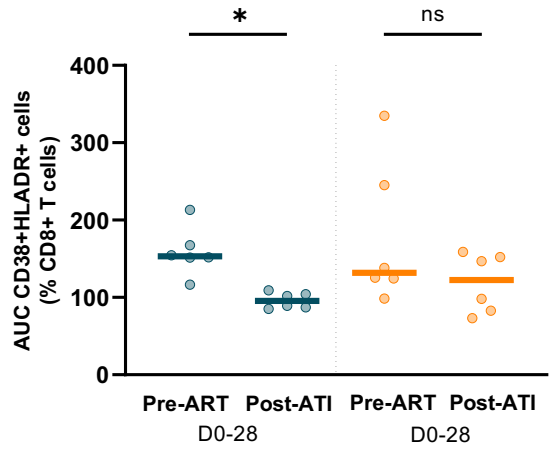


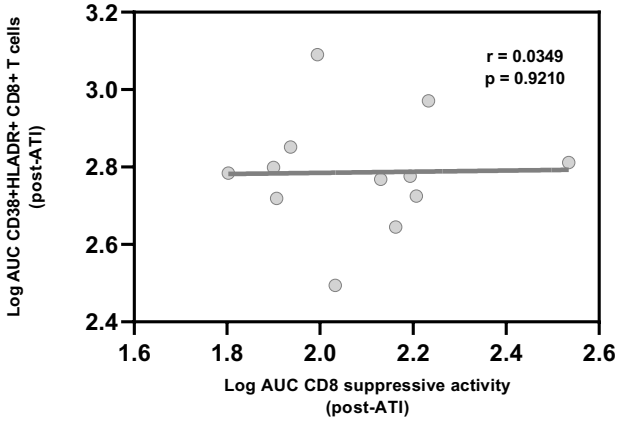
ART M6



Passaes et al Unpublished

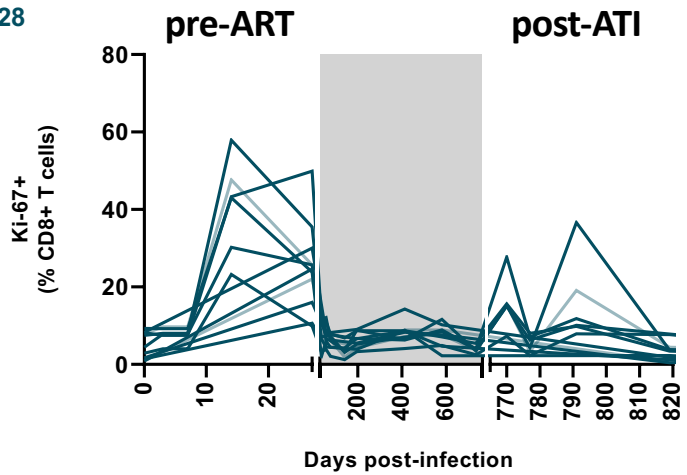
Lower activation levels on CD8 T cells after ATI in early ART group



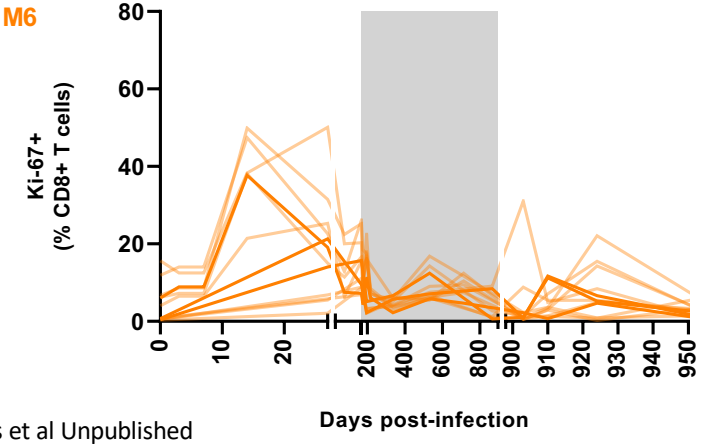


CD8+ T cell response after early ART: proliferation correlated with SIV suppressive activity

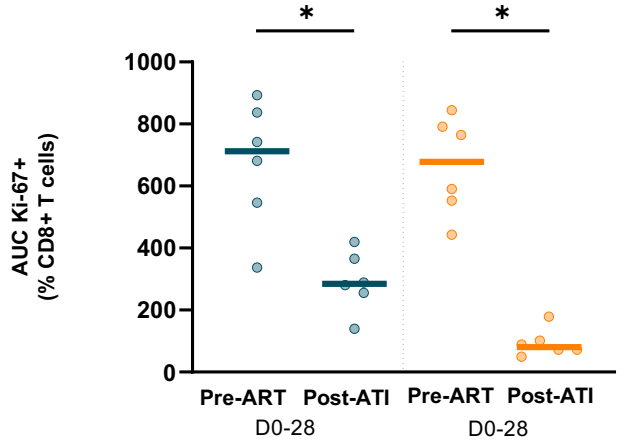
ART D28

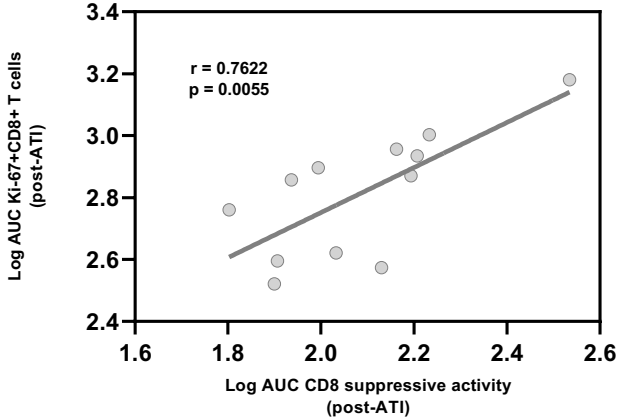


ART M6



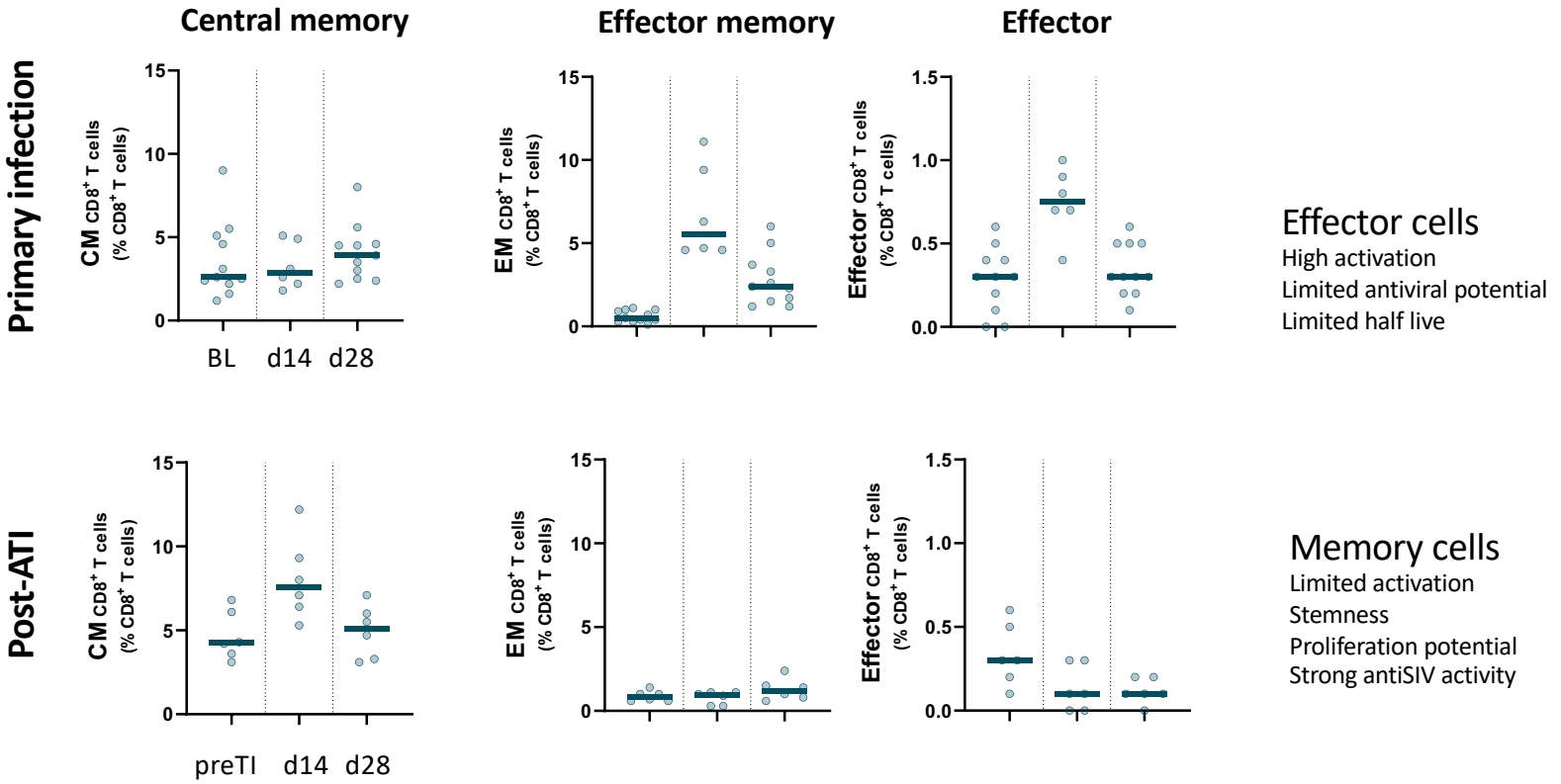
More robust proliferation of CD8 T cells after ATI in early ART group





Passaes et al Unpublished

Different expansion of CD8+ T cell subpopulations during primary infection and after treatment interruption



Effector cells
High activation
Limited antiviral potential
Limited half live

Memory cells
Limited activation
Stemness
Proliferation potential
Strong antiSIV activity

CD8+ T cell response after ATI seems to be driven by expansion of early memory populations

Passaes et al Unpublished

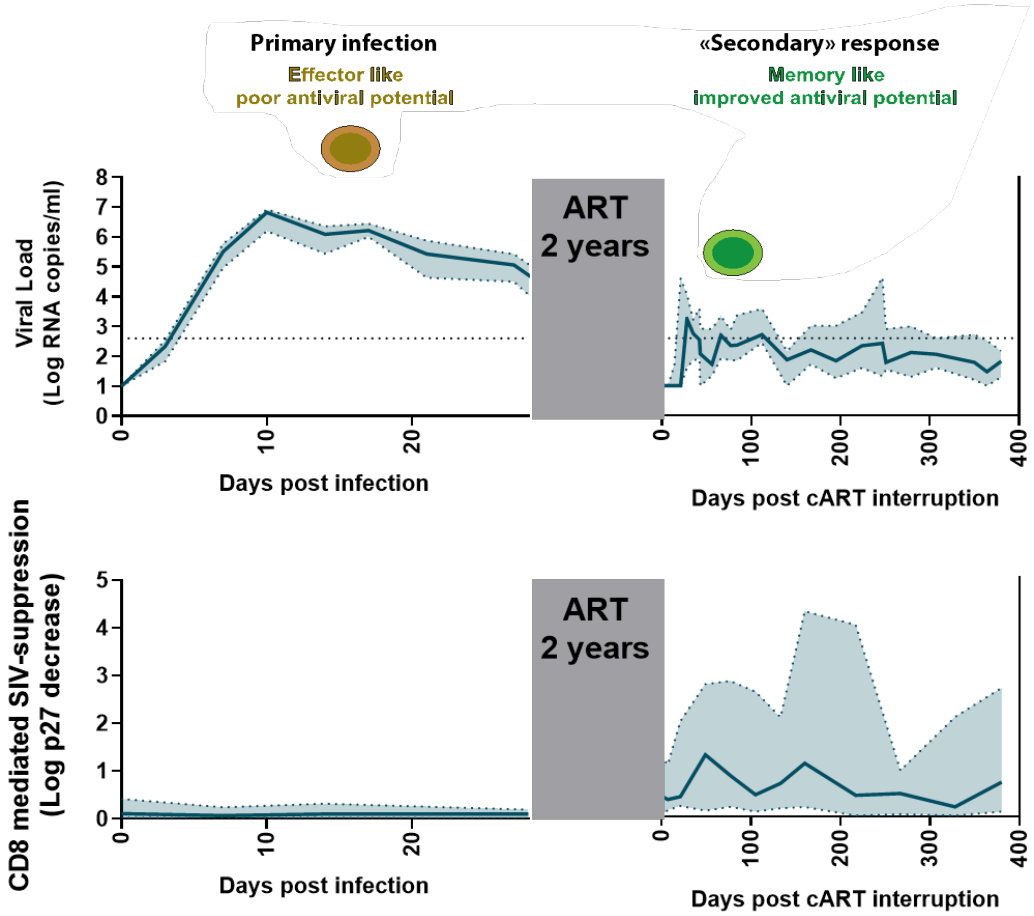
Summary-I

Early ART initiation (week 4) favored delayed viral rebound and lower viral load set point post-ATI
A higher frequency of PTC was observed among the early treated animals

Poor antiviral capacity of SIV-specific CD8+ T cells developed during primary infection

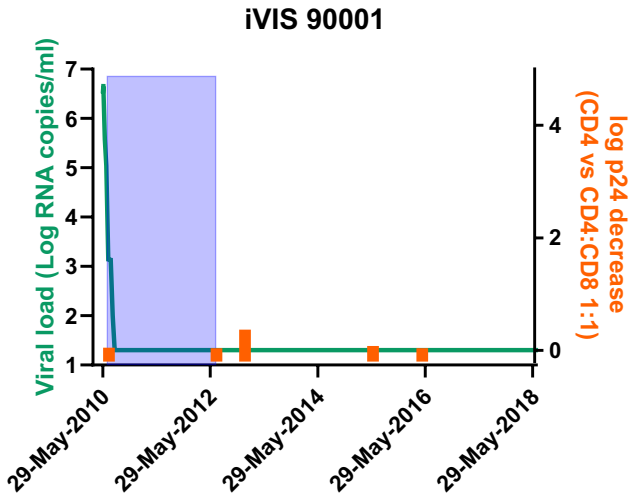
CD8+ T cell response after TI is characterized by expansion of early memory populations and limited activation

Prolonged early ART favors the development of a robust “secondary” SIV-specific CD8+ T-cell response, in blood and lymphoid tissues, that may contribute to counteract viral rebound after TI

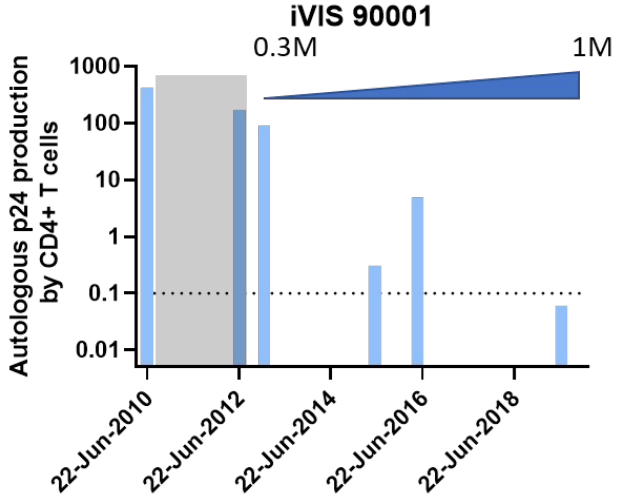


Shrinking translation competent reservoir despite silent control?

CD8 T cell antiviral activity

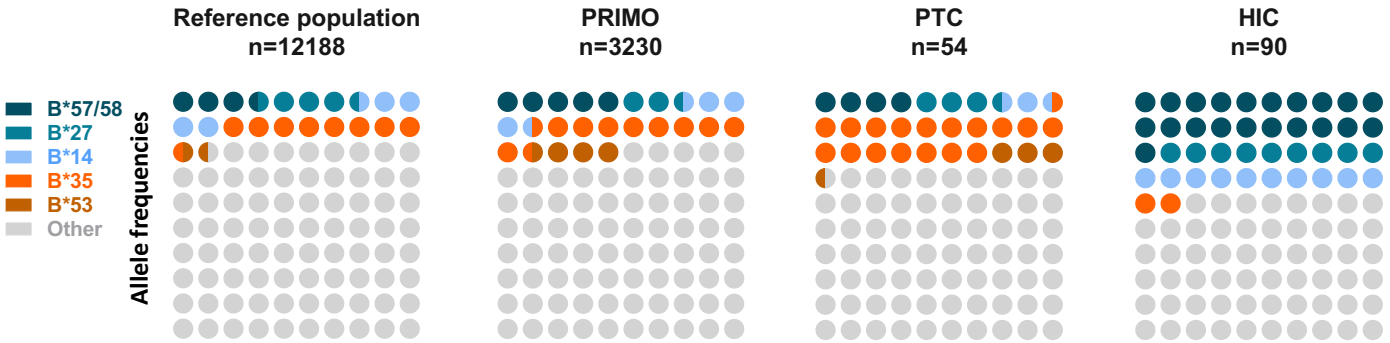


p24 production by CD4 T cells



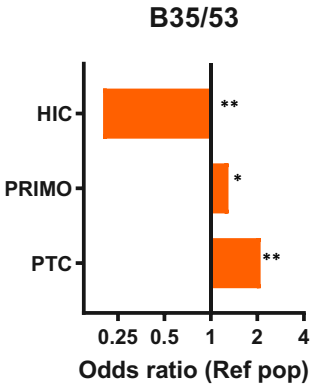
Monceaux et al Unpublished

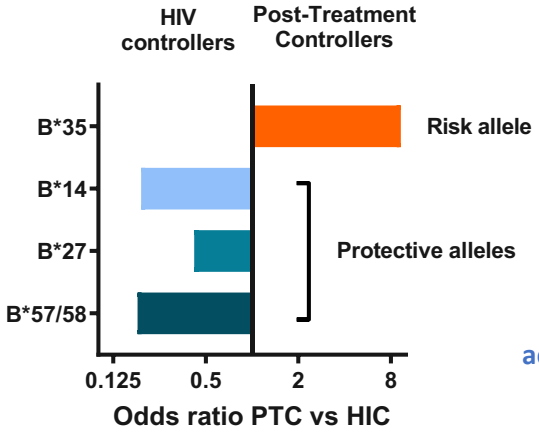
The HLA-B*35 paradox: unfavorable HLA alleles highly frequent among PTC



HLA-B*35 associated with rapid progression to AIDS without ART

New international PTCs
2 PTC: 1 B35
1 PTC: 1 B35

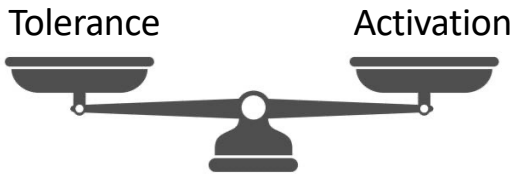


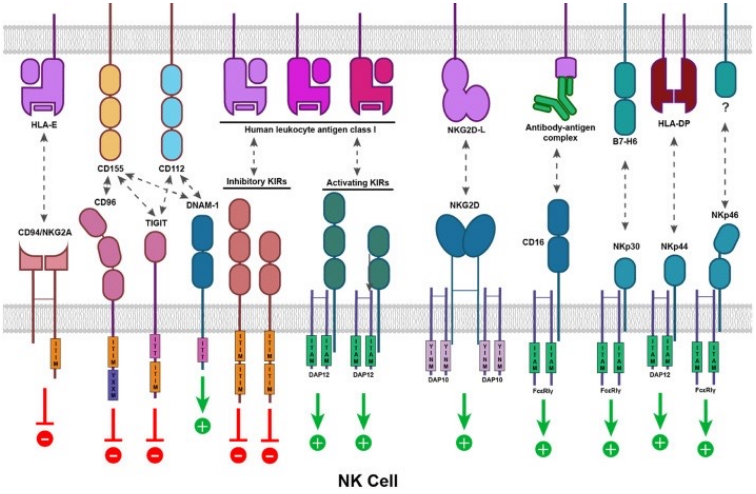


Different paths to control:
achieving control ≠ maintaining control

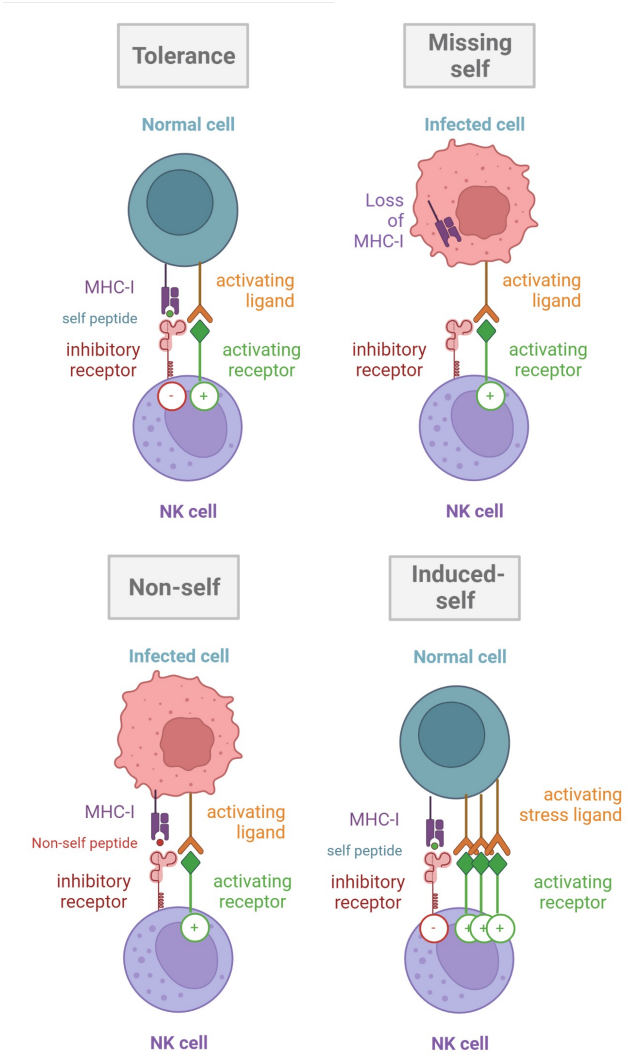
NK cell function

regulated by a complex combination of activating and inhibitory signals

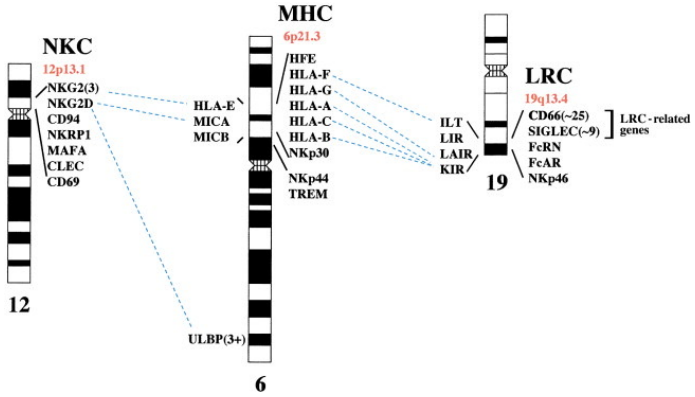


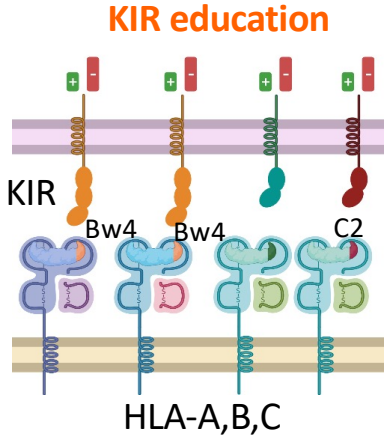


Xie et al eBioMedicine 2020



Genetic traits in PTCs suggest KIR-educated NK cells associated with post-treatment control

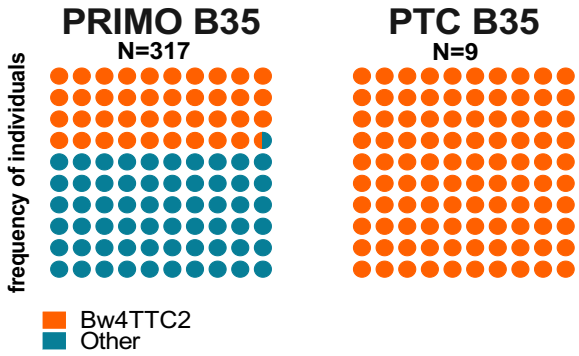


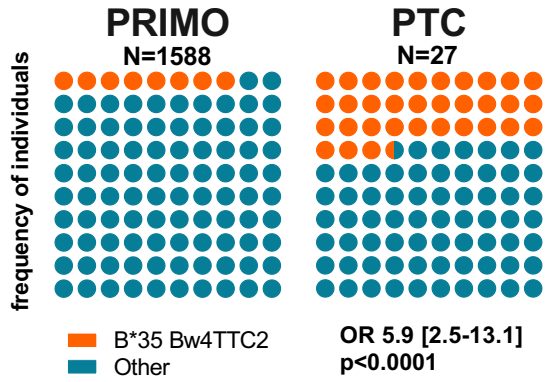


HLA-B*35+ Bw4TTC2 enriched in PTC from VISCONTI

Bw4TTC2

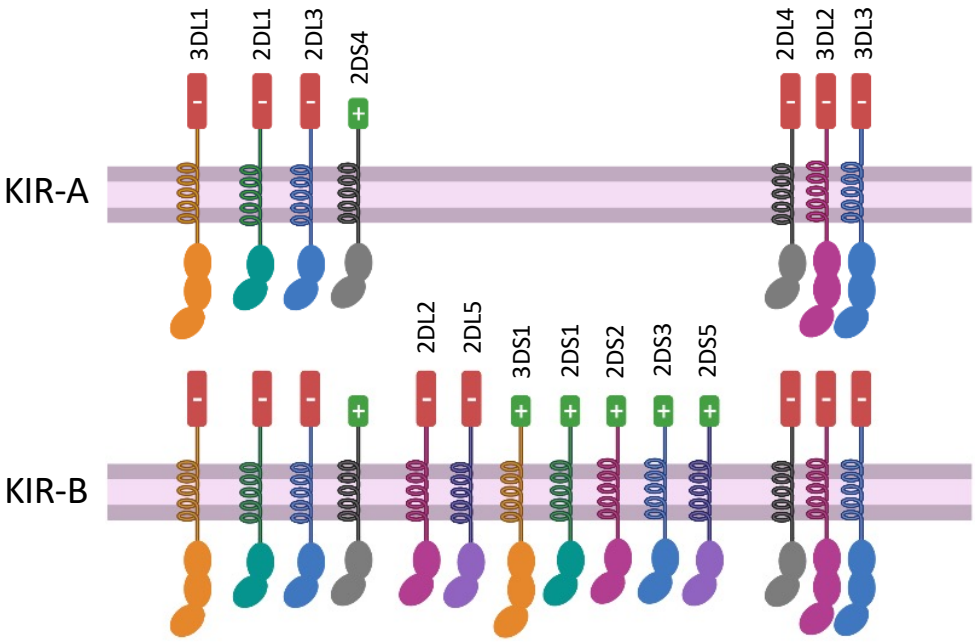
↑Bw4 ↓HLA-E ↑C2

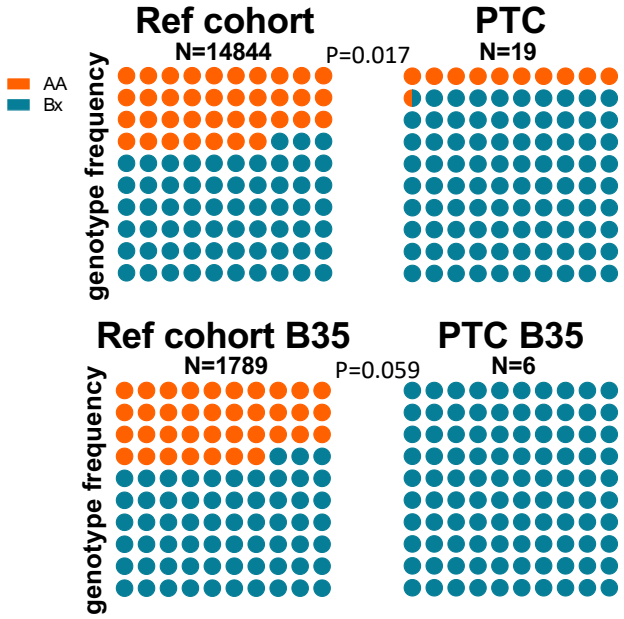




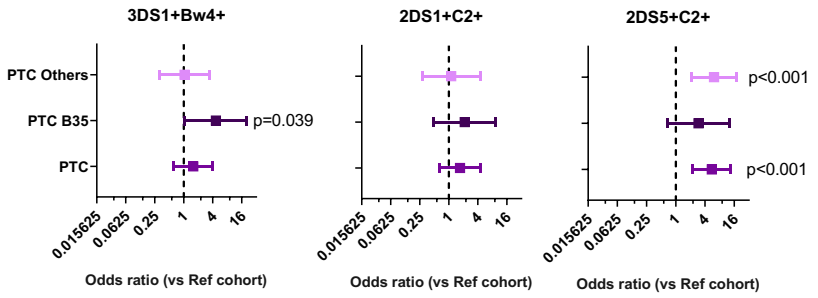
Chapel, Essat et al submitted

Genotypes with high KIR B content are frequent among B35 PTCs





PTCs have complementary KIR repertoires for the cognate HLA-ligands abundantly present in these persons

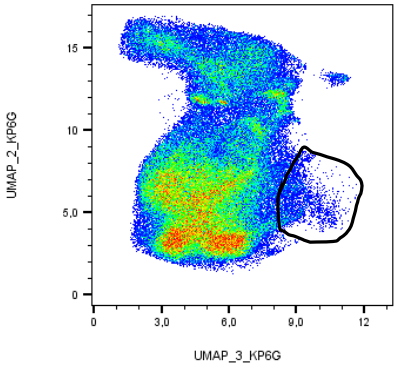


Reference cohort: Hanson PLoS Gen 2020

Essat et al submitted

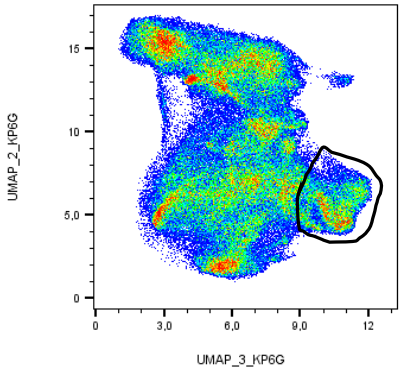
More frequent presence in PTC of NK cells with cytotoxic potential expressing the KIR receptor for Bw4

ART



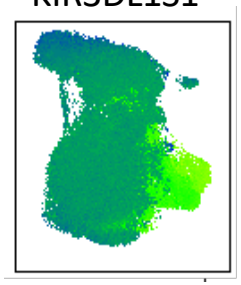
n = 8

PTC



n = 15

KIR3DL1S1



Genetic and phenotypic analyses suggest an important role of NK cells in post-treatment control

Which is the precise function of these cells?

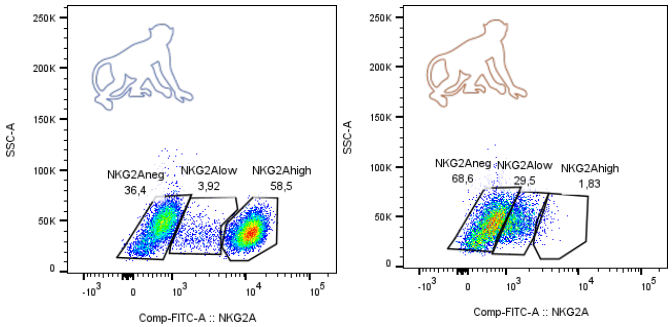
Caveat: analyses performed in a quiescent situation

Chapel, Essat et al submitted

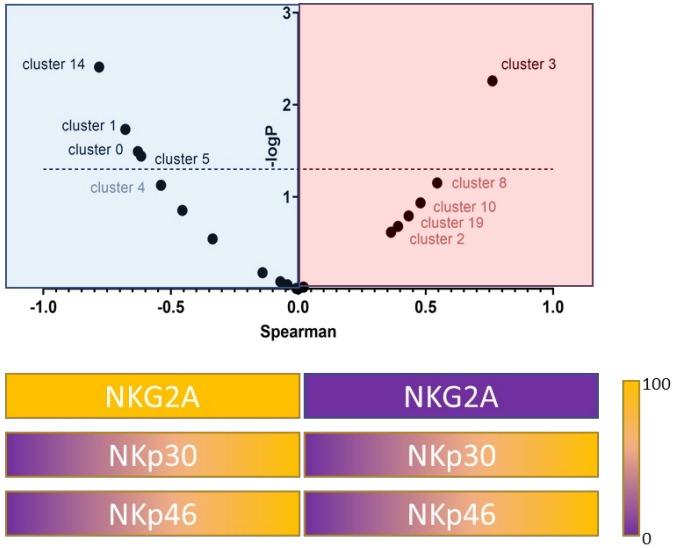
Constitutive characteristics and delay to treatment impact the capacity of NK cells to control viremia

Chapel, Romero-Martin unpublished

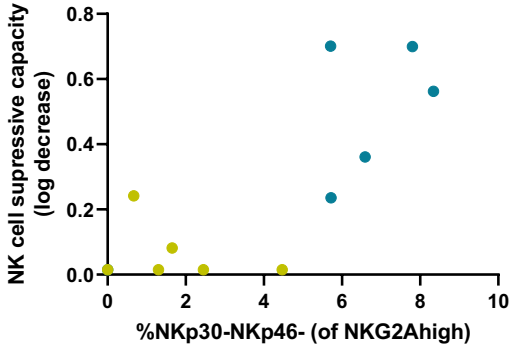
Distinct NKG2A levels at baseline



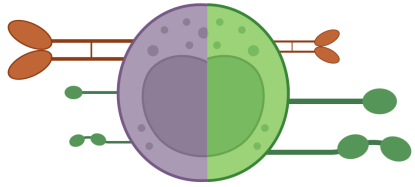
Correlation with viremia after ART interruption



Correlation with NK cell antiviral activity and PTC



Negative correlation with viremia:
during primary infection
during ART interruption
Enhanced antiviral activity
Expanded with early treatment



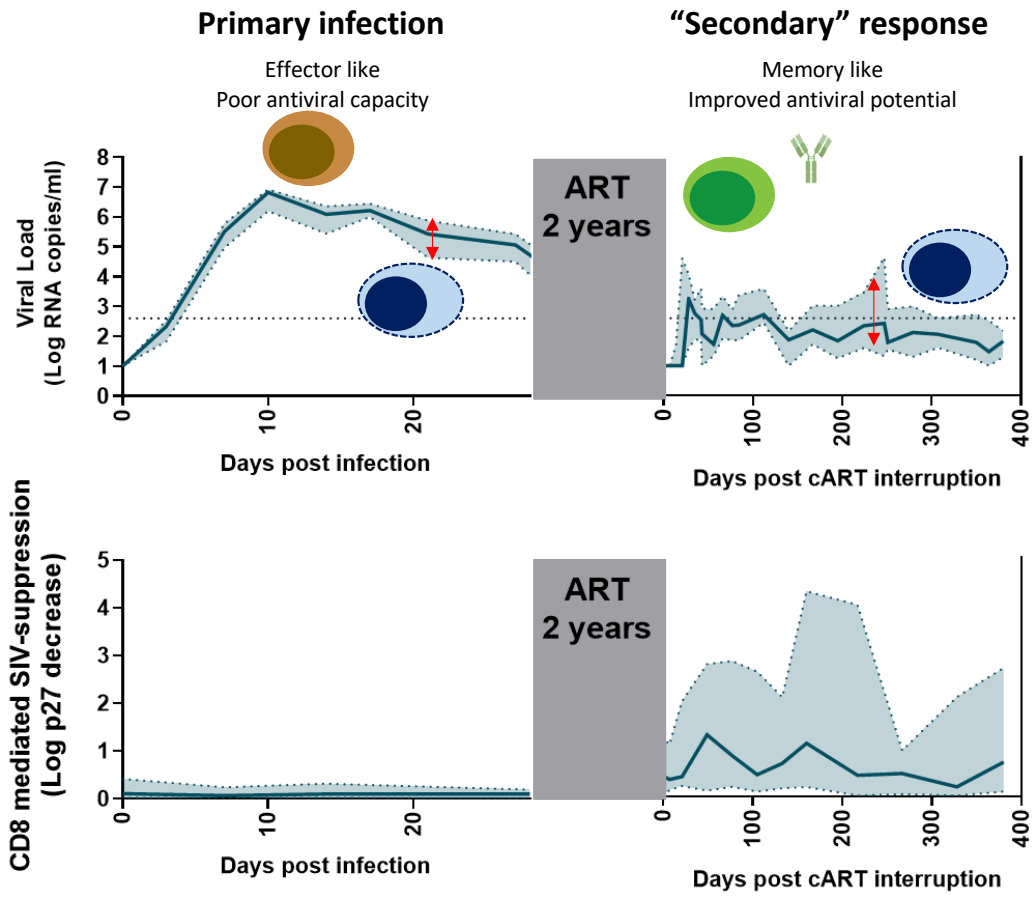
NKG2A^{+}NKp30^{-}NKp46^{-} NKG2A^{-}NKp30^{+}NKp46^{+}

Positive correlation with viremia:
during ART interruption
Accumulation in tissues before ART initiation
Limited antiviral capacity

Summary II

- Viral remission in PTC is often associated with “silent” control after treatment interruption. Limited capacity to maintain durable control if episodes of viremia >400 copies occur.
- Tight post-treatment control is associated with weak adaptive responses.
- Frequency of HIV carrying cells appears to progressively decrease in some PTCs despited presence of intact HIV genomes
- HLA-B35 alleles are enriched among PTC and associated with better control after interruption of early treatment
- Post-treatment HIV control associated with selection of particular HLA genotypes pointing to an important role of KIR-educated NK cells in suppressing viremia

Early ART favors the development of a robust “secondary” response against the rebounding virus

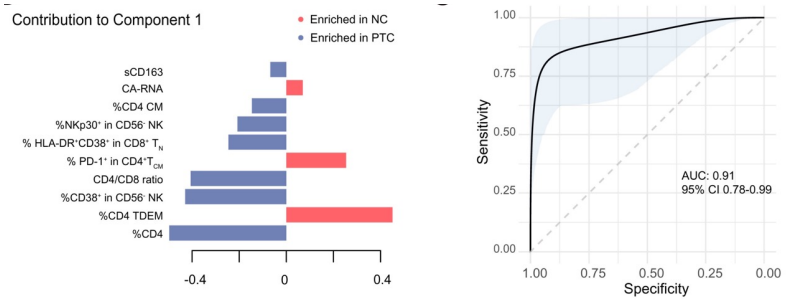


Constitutive characteristics of NK cells (related to immunogenetic factors?) may influence viremia during primary infection and after ART interruption (effect lost if delayed treatment)

Can we predict post-treatment control of HIV infection?

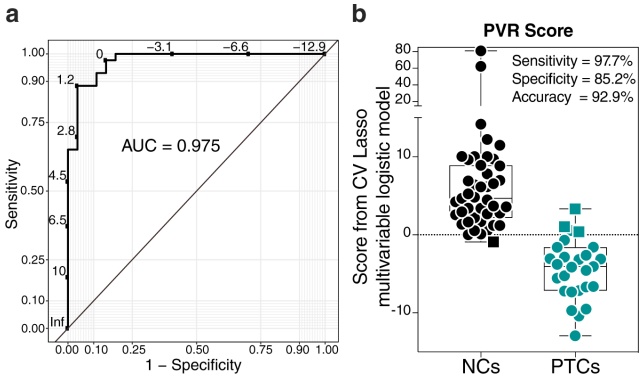
Early ART initiation
Low levels of viral DNA
High CD4:CD8 ratio

Viro-immunological markers associated with post-treatment control of HIV



Etemad et al, PNAS 2023

Non-invasive plasma glycomic and metabolic biomarkers of post-treatment control of HIV



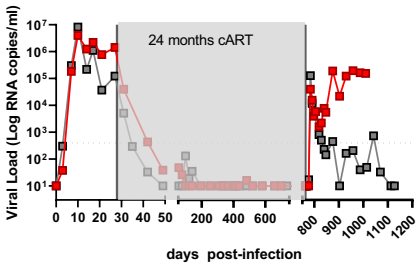
Giron et al, Nat Com 2021

What can we learn from VISCONTI and pVISCONTI studies?

Post-treatment controllers

~6% of early treated?

Post-treatment SIV controllers



NK cells associated with post-treatment control

Early ART initiation favors post-treatment control

→ ANRS RHIVIERA01

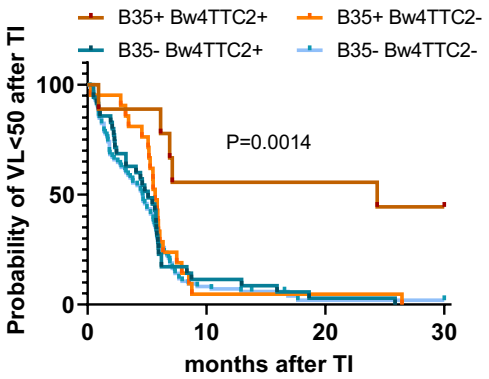
Role of bNAbs on post-treatment control

Need to boost CD8+ T cell memory

→ ANRS RHIVIERA02

175 RHIVIERA 01: Validation of immunogenetic fingerprint associated with durable post-treatment control

ANRS PRIMO cohort, 150 HLA typed participants all treated at PHI (30-45 days p.i.) who later discontinued ART



Essat et al, submitted

ANRS 175 RHIVIERA 01: HLA-B*35/53 and Bw4TTC2 among early treated individuals

Pilot open label phase 2 trial, “proof of concept”, one arm, multicenter

HLA typing of 2200 participants ANRS PRIMO cohort

B35/53 Bw4TTC2

69 candidates

Analytical treatment interruption

Viral rebound: rapid ART reinitiation

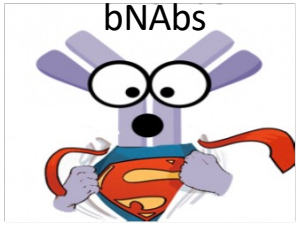
Viral control: continuous monitoring VISCONTI

Clinical Protocol	Feasibility enquiry	CPP	ansm	First inclusion
✓	✓	✓	✓	✓

April 2023

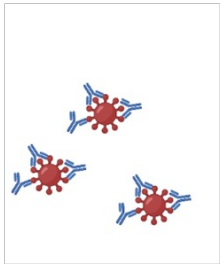
176 RHIVIERA02: Potential for HIV remission of ART and broadly neutralizing antibodies delivered during primary HIV-1 infection

Collab: Michel Nussenzweig, Rockefeller University

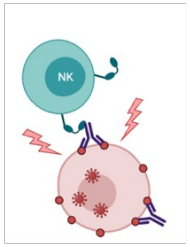


Specific activity
No major secondary effects
Long-lasting: >6 months
Antiviral activity clinically proven
Multiple potential activities

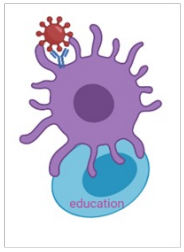
Block the virus



Facilitate the elimination of infected cells



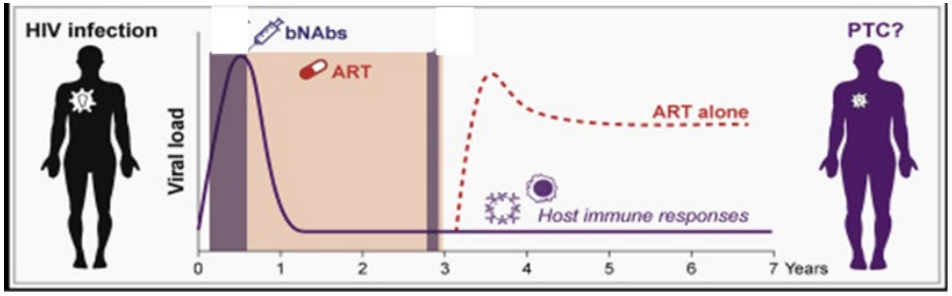
"vaccinal" effect



Combine the effects of ART and bNAbs during primary infection to facilitate the elimination of infected cells and the development of immune responses

ANRS 176 RHIVIERA 02: primo-bNAbs

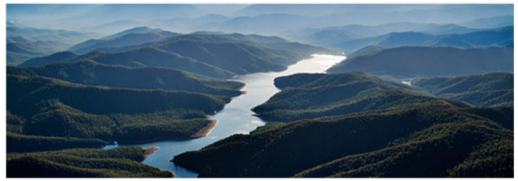
Randomized, phase II placebo-controlled
Impact of ART + dual long-acting HIV-specific bNAbs (3BNC117-LS & 10-1074-LS) on post-treatment HIV control



Implementation stage:

Clinical Protocol	Feasibility enquiry	CPP	ansm	First inclusion
✓	✓	✓	✓	January 2024

Our current knowledge and tools do not allow us to measure the reservoir and to prove eradication



Hidden viral reservoirs might be at the origin of viral rebound

From remission to… cure?

Some people with natural and post-treatment control consistently maintain undetectable viremia for decades

No detectable residual viral replication

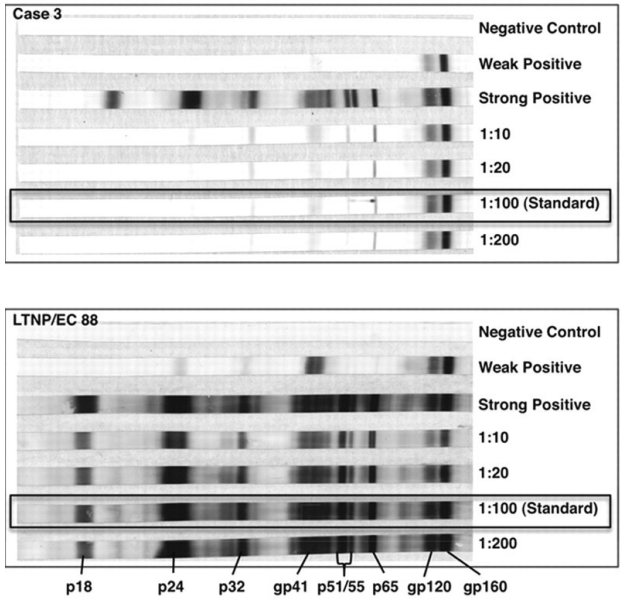
No (or very limited) evidence of viral evolution

Extremely low, and defective, viral DNA reservoir

No changes in CD4+ T cell levels

Quiescent immune responses

Weakly reactive immunoblots



Mendoza et al Blood 2012; Canouï et al Open Forum Inf Dis 2017; Casado et al Sci Rep 2020; Jiang et al Nature 2020; Turk et al Ann Intern Med 2022

Sáez-Cirión et al unpublished

Adapted from Martínez-Picado Towards HIV Cure symposium IAS AIDS2022

How far are these persons of being considered cured?

Acknowledgements

All the persons with HIV participating to our studies

INSTITUT PASTEUR

Viral Reservoirs and Immune control

ANRS CO21 CODEX
ANRS CO6 "PRIMO"
CHU Bicetre
Olivier Lambotte
Nicolas Noel
Cecile Goujard

INSERM U1018
Laurence Meyer
Sylvie Orr
Faroudy Boufassa
Asma Essat
Samia Hendou
Azeb Tadesse

VISCONTI
CHU Orleans
Laurent Hocqueloux
Thierry Prazuck

Institut Cochin
Véronique Avettand-Fenoel,
Antoine Millet
Christine Rouzioux,
Pauline Trémeaux
Adeline Mélard

NHP, IDMIT center
Roger Le Grand
Bruno Vaslin
Delphine Desjardins
Naya Sylla
Nastasia Dimant
Nathalie Bosquet
Catherine Chapon
Aurélie Barrail-Tran
Julien Lemaitre
Mariangela Cavarelli
Thibaut Gele
Thibaut Naninck
Quantin Pascal
Animal care workers

Institut Pasteur
Michaela Müller-Trutwin
Béatrice Jacquelin
Nicolas Huot
Caroline Petitdemange
Marie Lazzerini
Aurélio Ortiz

Hugo Mouquet
Luis Molinos-Albert
Valérie Lorin
Cyril Planchais

CHU St Louis
Sophie Caillat-Zucman
Kahina Amokrane

IAME UMR1137
Jeremie Guedj
Vincent Madelain

Indian Institute of Science
Narendra Dixit
Vemparala Bharadwaj

TrT-5 CHV
Hugues Fischer

Clinical follow-up
Laurence Weiss, Patrick Miailhes, Sophie Pailhes, Sophie Matheron, David Zucman, Jean-Paul Viard, Corinne Merle de Boever, Caroline Lascoux-Combes, Corinne Jadand, Laurent Cotte, Bernard Cardon, Alain Lafeuillade, Jürgen Rockstroh, Franco Maggiolo, Pierre Delobel and many others involved in our studies

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