



**GHENT  
UNIVERSITY**

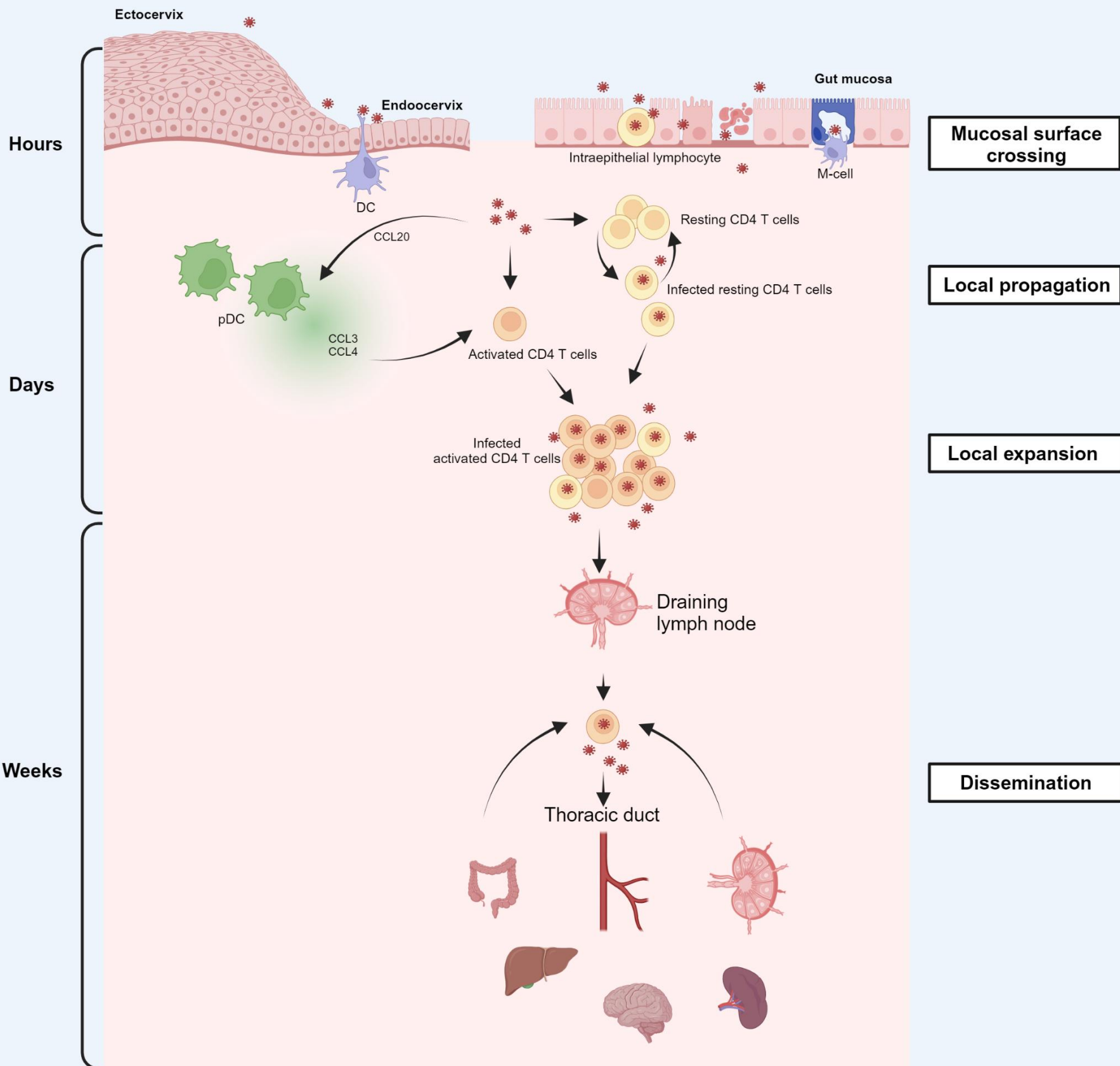
# EARLY TREATMENT & POST-TREATMENT HIV CONTROL

LESSONS LEARNED FROM VISCONTI

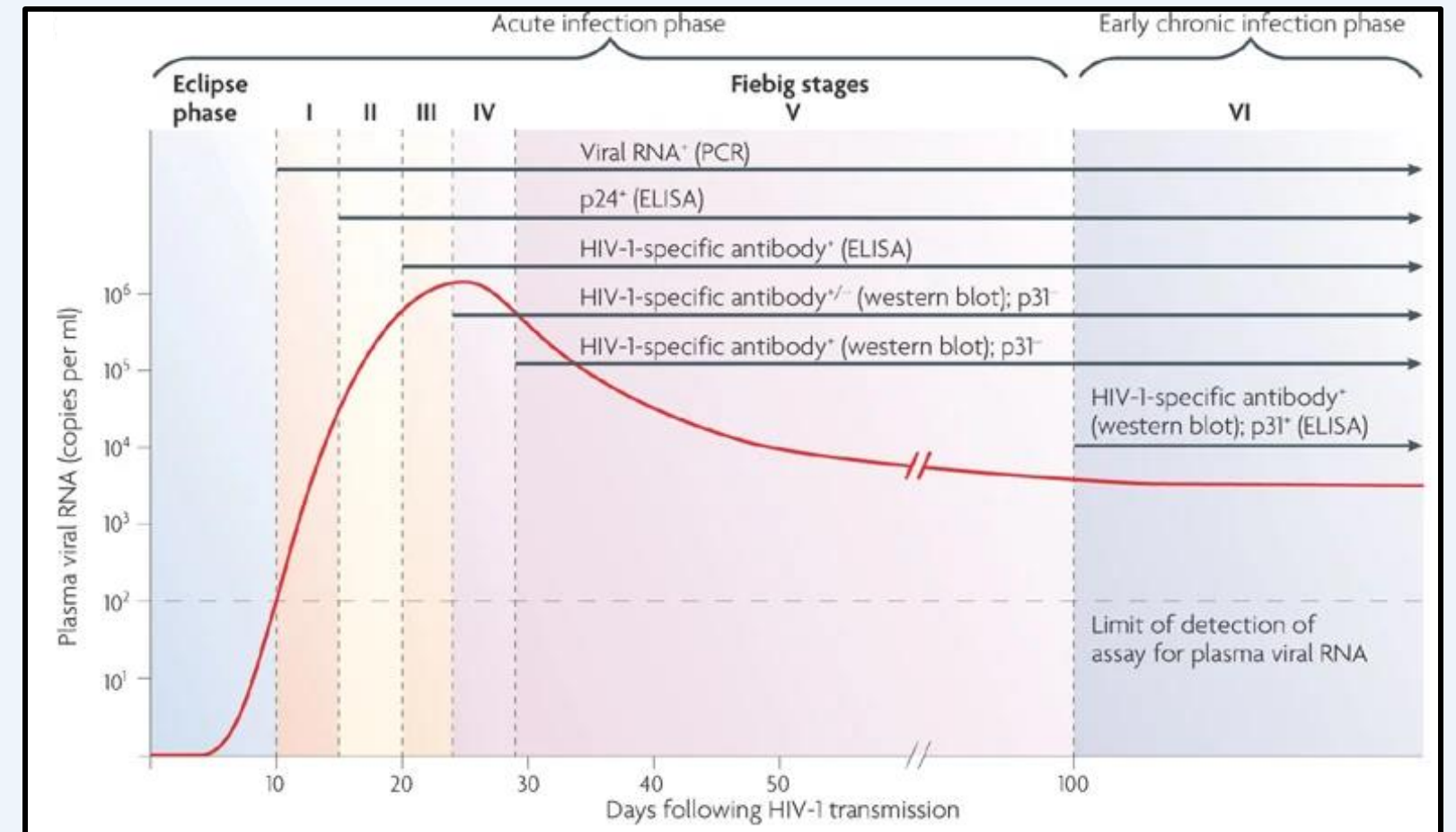
# ACUTE HIV INFECTION

INSIGHTS FROM THE EARLIEST EVENTS

# EARLIEST EVENTS



## Fiebig stages



McMichael *et al.* Nature rev. Immunology 2010

# EXTREMELY EARLY RESERVOIR ESTABLISHMENT

1

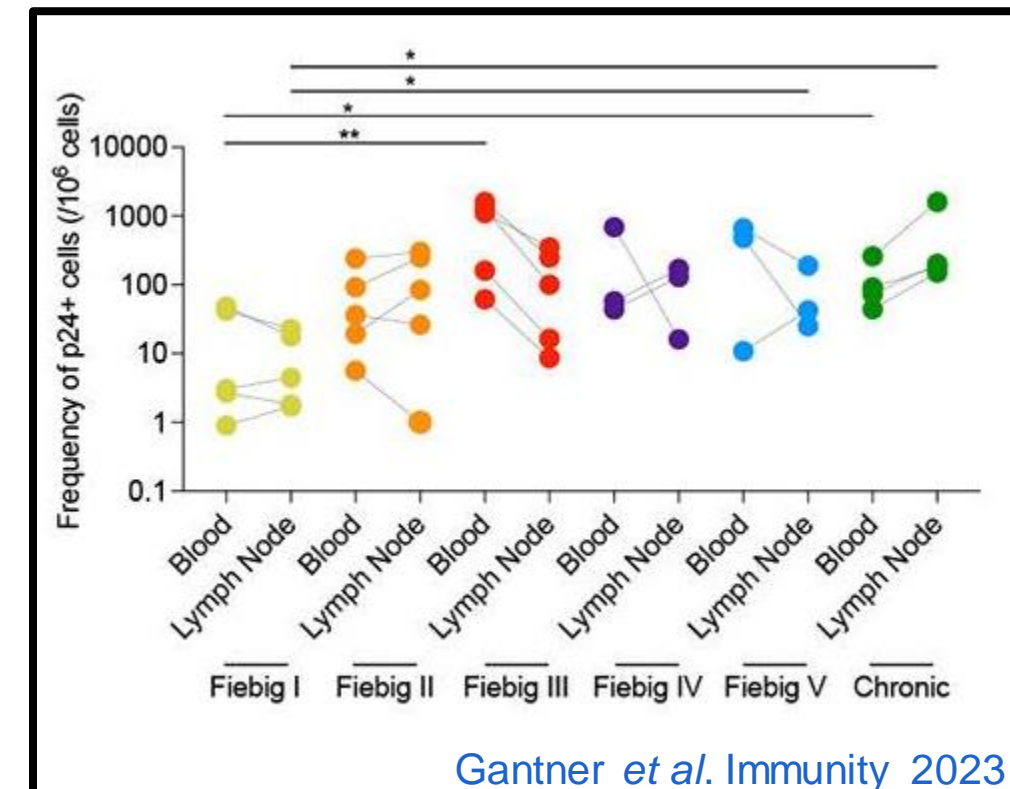
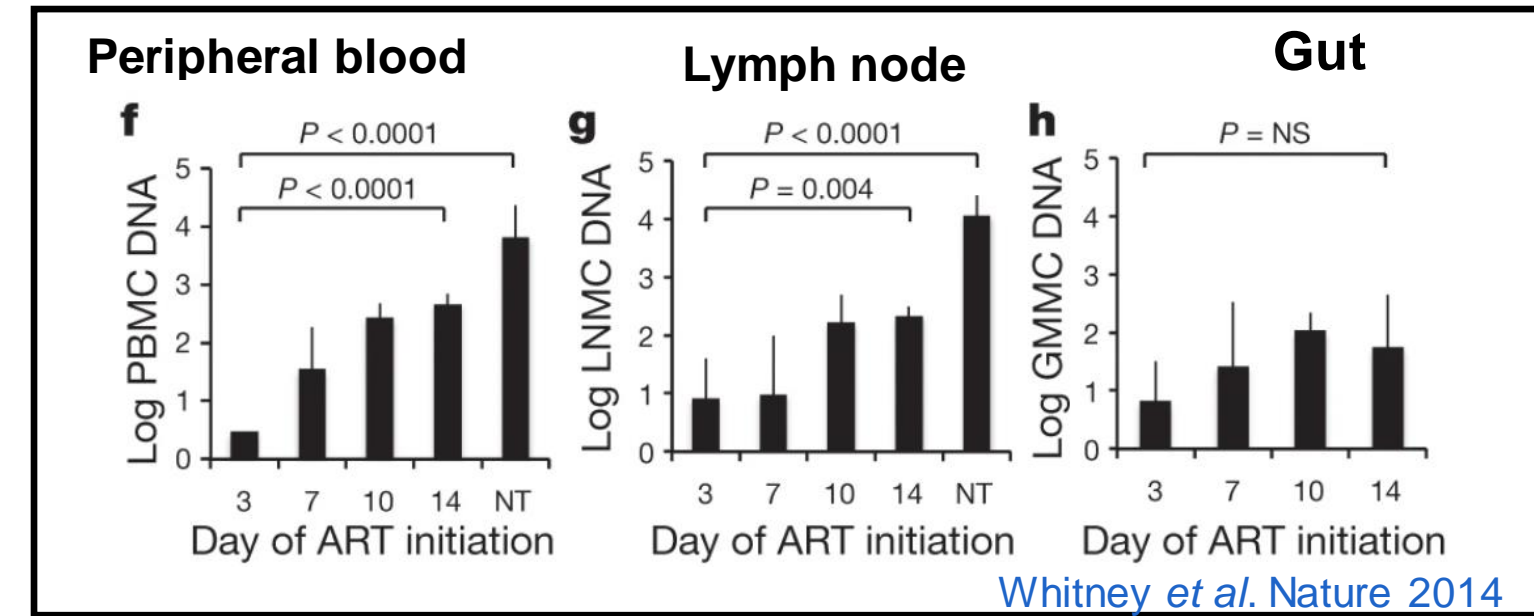
Non human primate models

2

Perinatal infection cohorts

3

Acute HIV infection cohorts



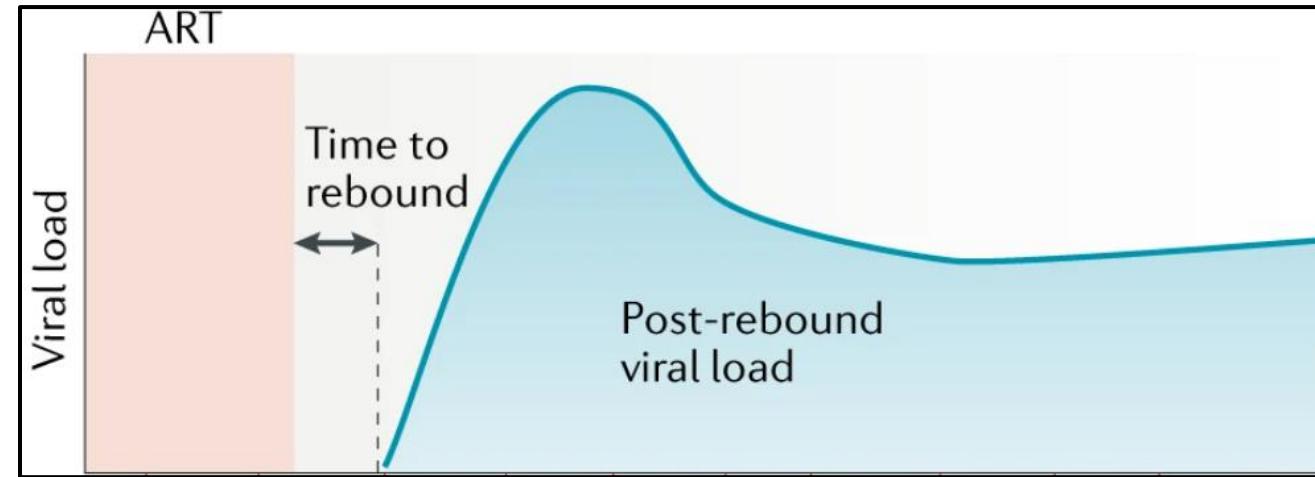
# POST-TREATMENT HIV CONTROL

BEYOND VISCONTI

# IN SEARCH FOR LONG-TERM HIV REMISSION

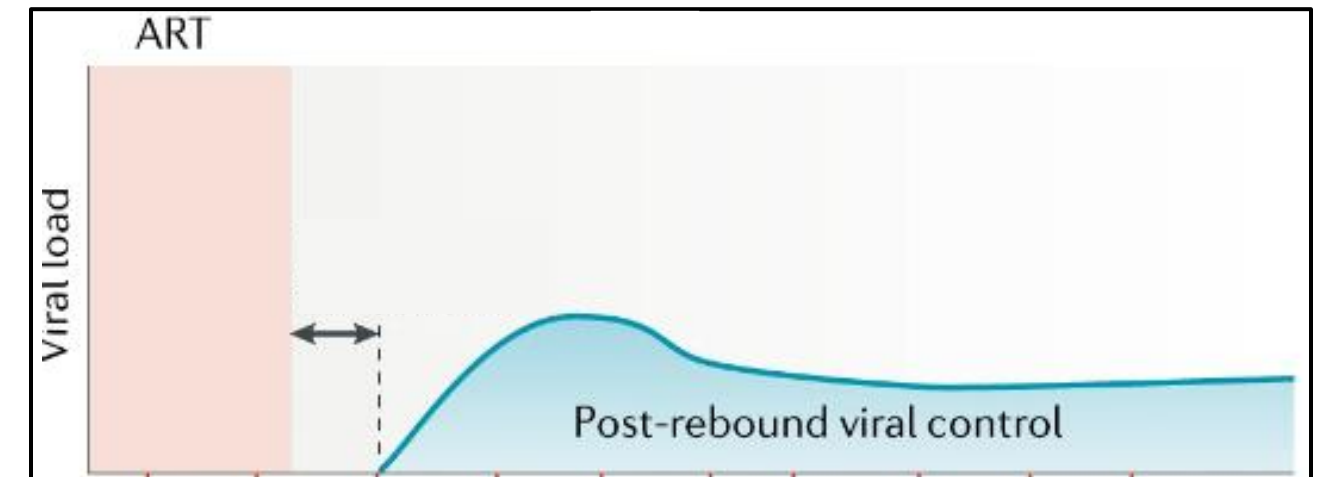
## No control

- || Time to rebound 2-4 weeks



## Post-treatment control

- || Control of viremia after ART interruption



## Elite control

- || Protective HLA-B alleles
- || High frequency of HIV-specific CD8 T cells

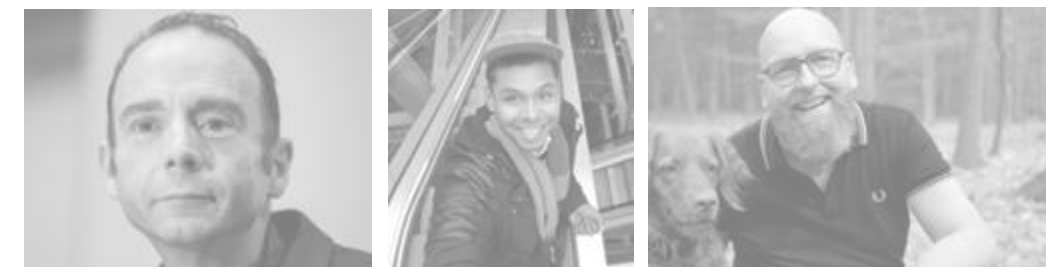
Large majority

5-15 %

<1%

6

## HIV Cure



# VISCONTI COHORT

> PLoS Pathog. 2013 Mar;9(3):e1003211. doi: 10.1371/journal.ppat.1003211. Epub 2013 Mar 14.

## Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study

Asier Sáez-Cirión<sup>1</sup>, Charline Bacchus, Laurent Hocqueloux, Véronique Avettand-Fenoel, Isabelle Girault, Camille Lecuroux, Valerie Potard, Pierre Versmisse, Adeline Melard, Thierry Prazuck, Benjamin Descours, Julien Guergnon, Jean-Paul Viard, Faroudy Boufassa, Olivier Lambotte, Cécile Goujard, Laurence Meyer, Dominique Costagliola, Alain Venet, Gianfranco Pancino, Brigitte Autran, Christine Rouzioux; ANRS VISCONTI Study Group

Affiliations + expand

PMID: 23516360 PMCID: PMC3597518 DOI: 10.1371/journal.ppat.1003211



## 14 PTC

ART initiation within 10 weeks of primary HIV infection

Frequently symptomatic  
ARS

Peak VL  
CD4 T cell count  
≈  
non-controllers

Lack of protective  
HLA-B alleles  
↔  
EC



# CHAMP STUDY

> J Infect Dis. 2018 Nov 5;218(12):1954-1963. doi: 10.1093/infdis/jiy479.

## The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies

Golnaz Namazi<sup>1</sup>, Jesse M Fajnzylber<sup>1</sup>, Evgenia Aga<sup>2</sup>, Ronald J Bosch<sup>2</sup>, Edward P Acosta<sup>3</sup>, Radwa Sharaf<sup>1</sup>, Wendy Hartogensis<sup>4</sup>, Jeffrey M Jacobson<sup>5</sup>, Elizabeth Connick<sup>6</sup>, Paul Volberding<sup>4</sup>, Daniel Skiest<sup>7</sup>, David Margolis<sup>8</sup>, Michael C Sneller<sup>9</sup>, Susan J Little<sup>10</sup>, Sara Gianella<sup>10</sup>, Davey M Smith<sup>10</sup>, Daniel R Kuritzkes<sup>1</sup>, Roy M Gulick<sup>11</sup>, John W Mellors<sup>12</sup>, Vikram Mehraj<sup>13</sup>, Rajesh T Gandhi<sup>14</sup>, Ronald Mitsuyasu<sup>15</sup>, Robert T Schooley<sup>10</sup>, Keith Henry<sup>16</sup>, Pablo Tebas<sup>17</sup>, Steven G Deeks<sup>4</sup>, Tae-Wook Chun<sup>9</sup>, Ann C Collier<sup>18</sup>, Jean-Pierre Routy<sup>13</sup>, Frederick M Hecht<sup>4</sup>, Bruce D Walker<sup>19</sup>, Jonathan Z Li<sup>1</sup>

Affiliations + expand

PMID: 30085241 PMID: PMC6217727 DOI: 10.1093/infdis/jiy479



## 67 PTC

14 clinical trials, >700 participants

Early infection: n= 38 (13%)  
Chronic infection: n=25 (4%)

Slightly lower pre-ART VL  
than noncontrollers

Durability of control:  
median 89 weeks

# CHAMP STUDY

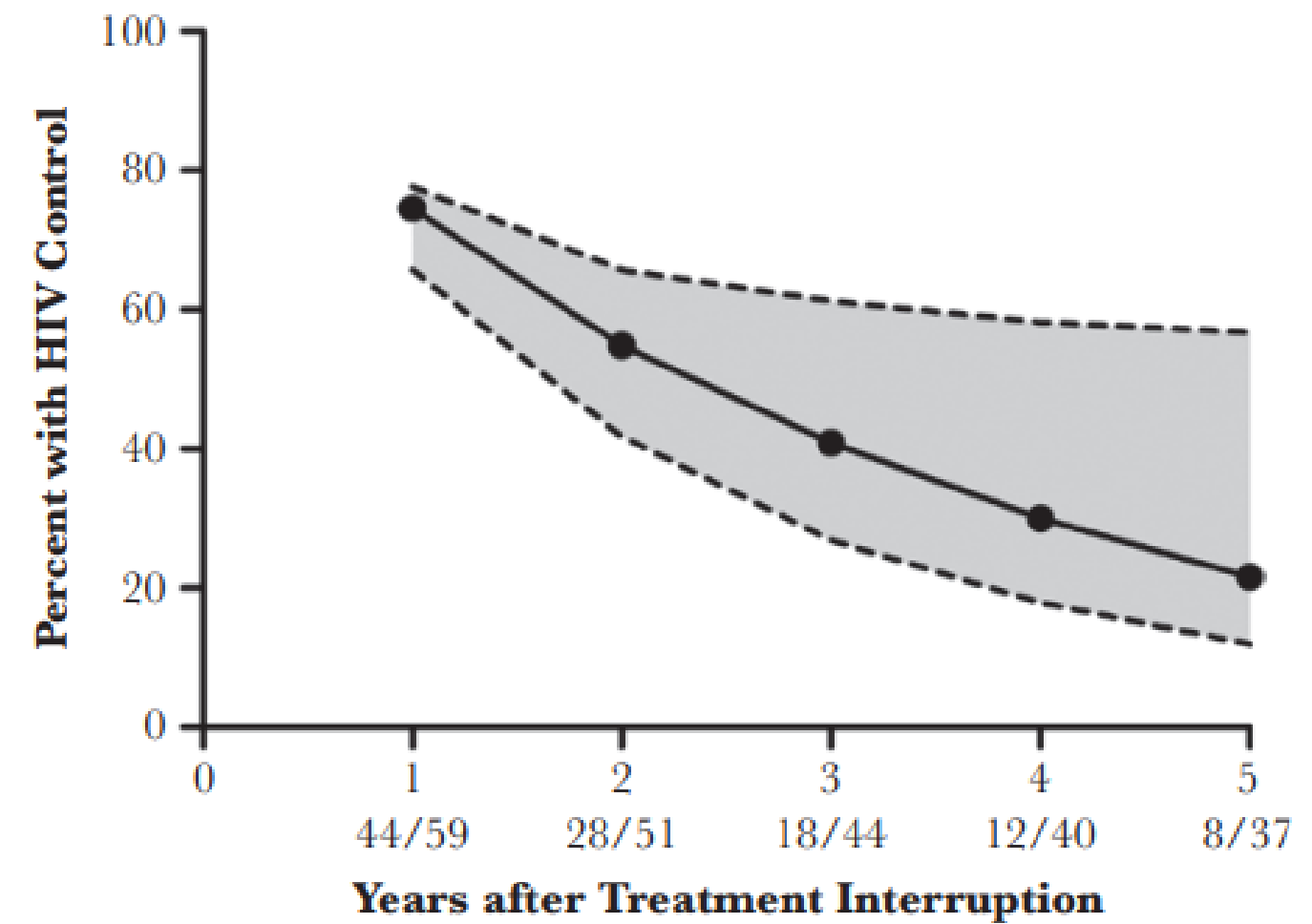
> J Infect Dis. 2018 Nov 5;218(12):1954-1963. doi: 10.1093/infdis/jiy479.

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Affiliations + expand

PMID: 30085241 PMCID: PMC6217727 DOI: 10.1093/infdis/jiy479



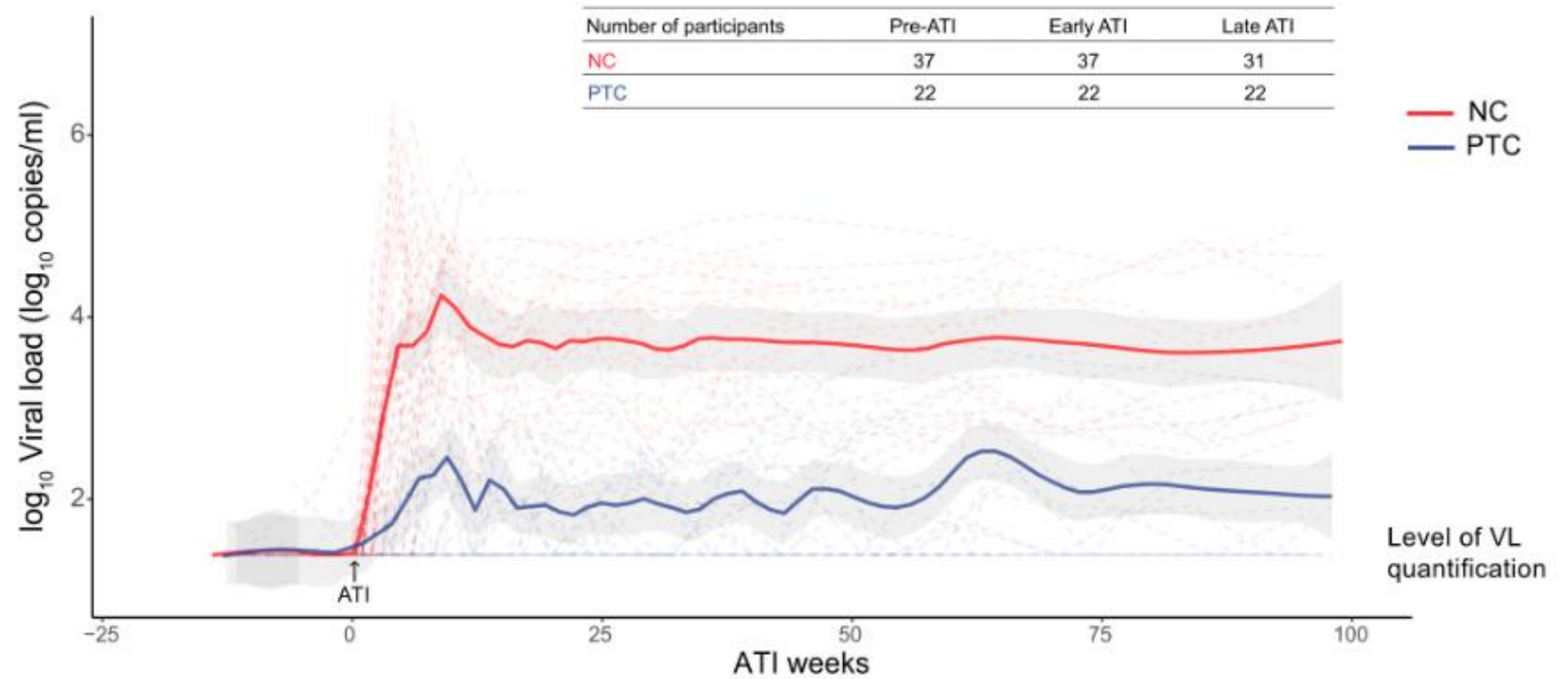
Namazi *et al.* J Infect Dis. 2018

Early infection: n= 38 (13%)  
Chronic infection: n=25 (4%)

Slightly lower pre-ART VL  
than noncontrollers

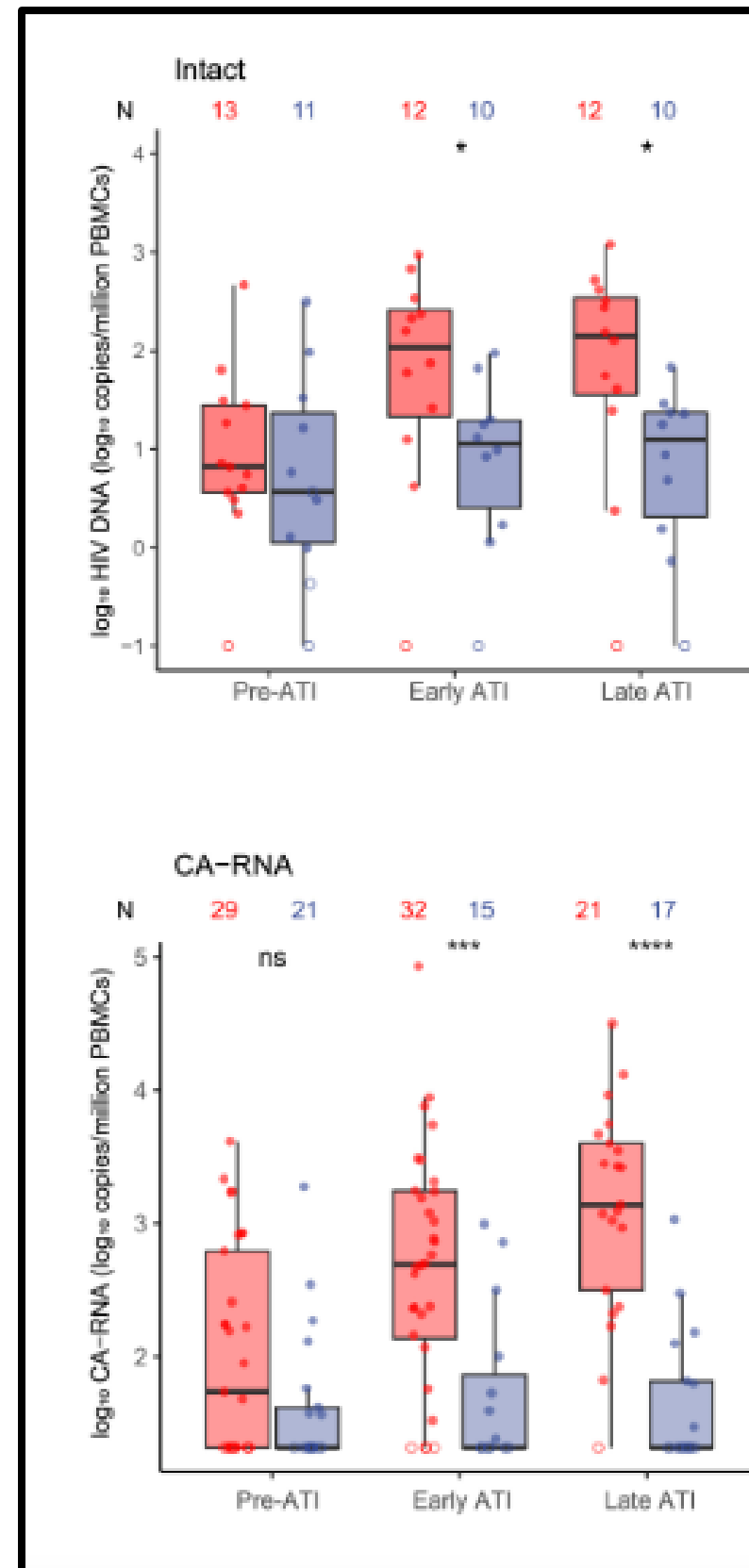
Durability of control:  
median 89 weeks

# What are the immunological and virological features of PTC?



Etemad *et al.* PNAS. 2023

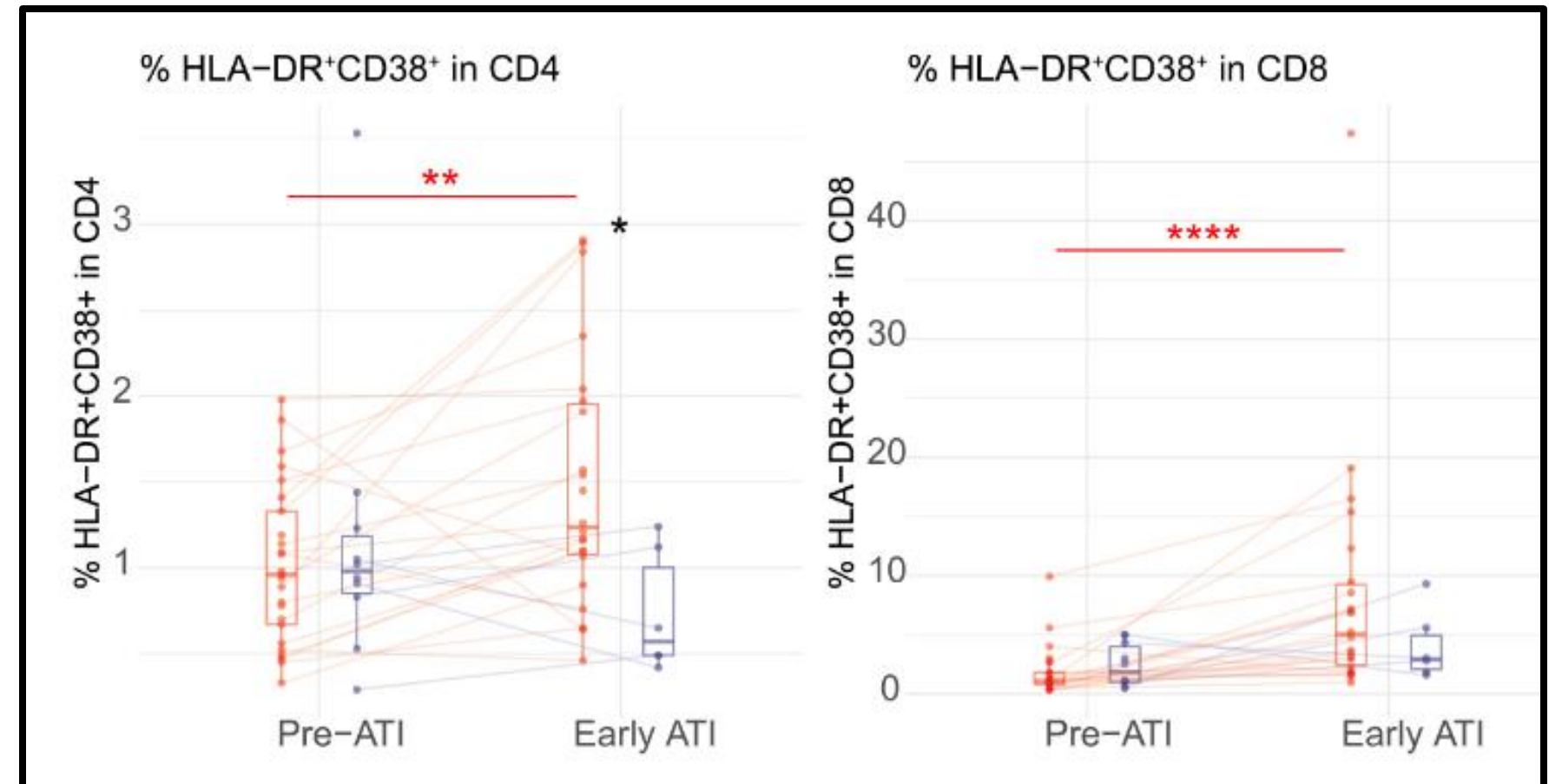
# Stable HIV reservoir



NC  
PTC

Stable HIV reservoir

Low activation of  
CD4 & CD8 T cells



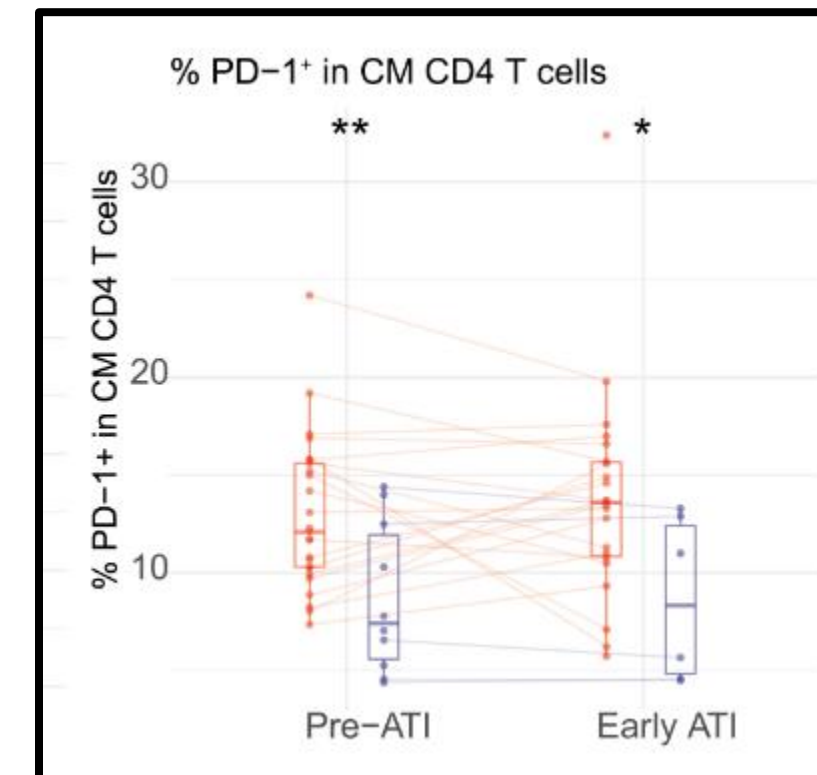
NC

PTC

Stable HIV reservoir

Low exhaustion of  
CD4 T cells

Low activation of  
CD4 & CD8 T cells



NC

PTC

Stable HIV reservoir

Low exhaustion of  
CD4 T cells

Low activation of  
CD4 & CD8 T cells

- Robust responses of:**
- || **Gag-specific CD4 T cells**
  - || **NK cells**

# pVISCONTI STUDY

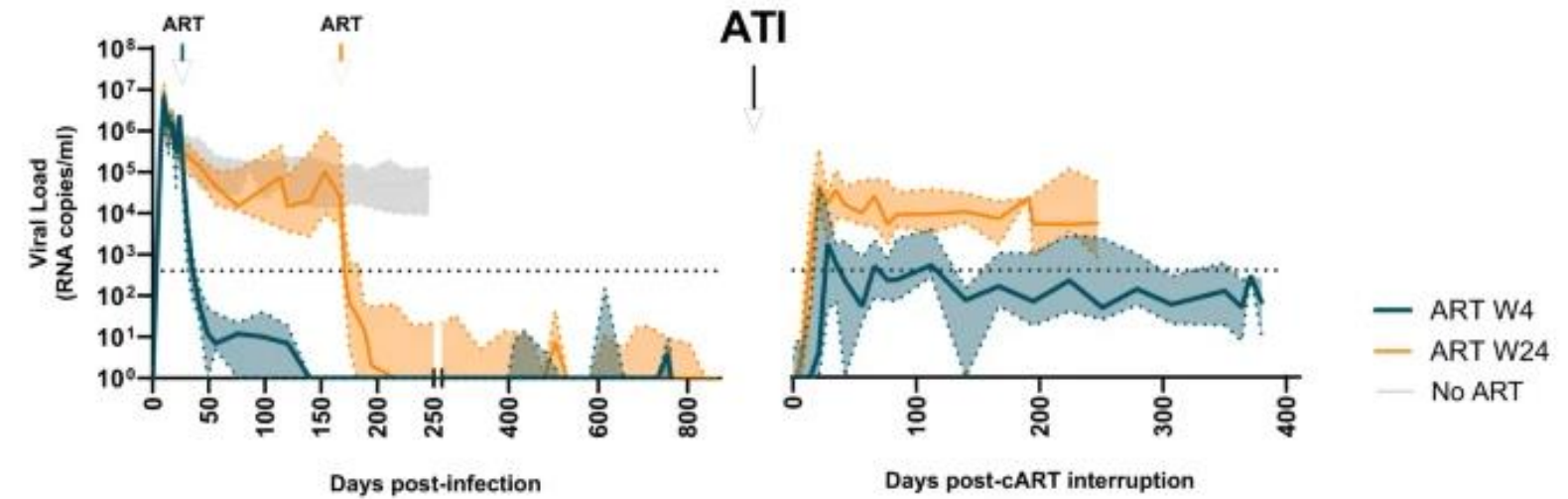
> Nat Commun. 2024 Jan 11;15(1):178. doi: 10.1038/s41467-023-44389-3.

## Early antiretroviral therapy favors post-treatment SIV control associated with the expansion of enhanced memory CD8<sup>+</sup> T-cells

Caroline Passaes<sup>1,2</sup>, Delphine Desjardins<sup>3</sup>, Anaïs Chapel<sup>4,5</sup>, Valérie Monceaux<sup>4,5</sup>, Julien Lemaître<sup>3</sup>, Adeline Mélard<sup>6</sup>, Federico Perdomo-Celis<sup>5</sup>, Cyril Planchais<sup>7</sup>, Maël Gourvès<sup>4</sup>, Nastasia Dimant<sup>3</sup>, Annie David<sup>5</sup>, Nathalie Dereuddre-Bosquet<sup>3</sup>, Aurélie Barrail-Tran<sup>3,8</sup>, Hélène Gouget<sup>3</sup>, Céline Guillaume<sup>3</sup>, Francis Relouzat<sup>3</sup>, Olivier Lambotte<sup>3,9</sup>, Jérémie Guedj<sup>10</sup>, Michaela Müller-Trutwin<sup>5</sup>, Hugo Mouquet<sup>7</sup>, Christine Rouzioux<sup>11</sup>, Véronique Avettand-Fenoël<sup>6,12</sup>, Roger Le Grand<sup>#3</sup>, Asier Sáez-Cirión<sup>#13,14</sup>



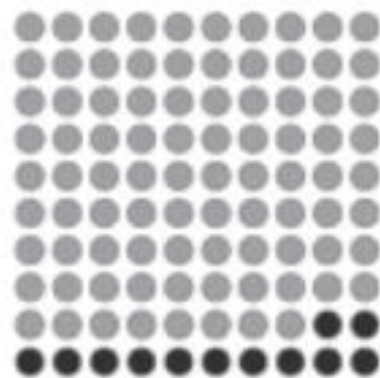
Non-human primate study



No ART

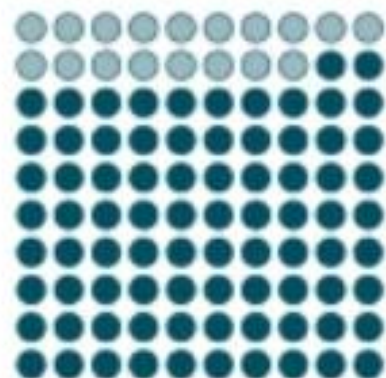
ART W4

ART W24



Total=17

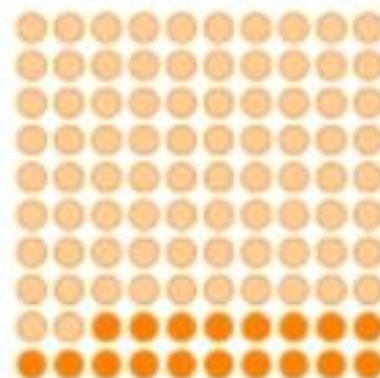
■ Spontaneous control (11.76%)



Total=11

■ 81.8% PTC

9/11

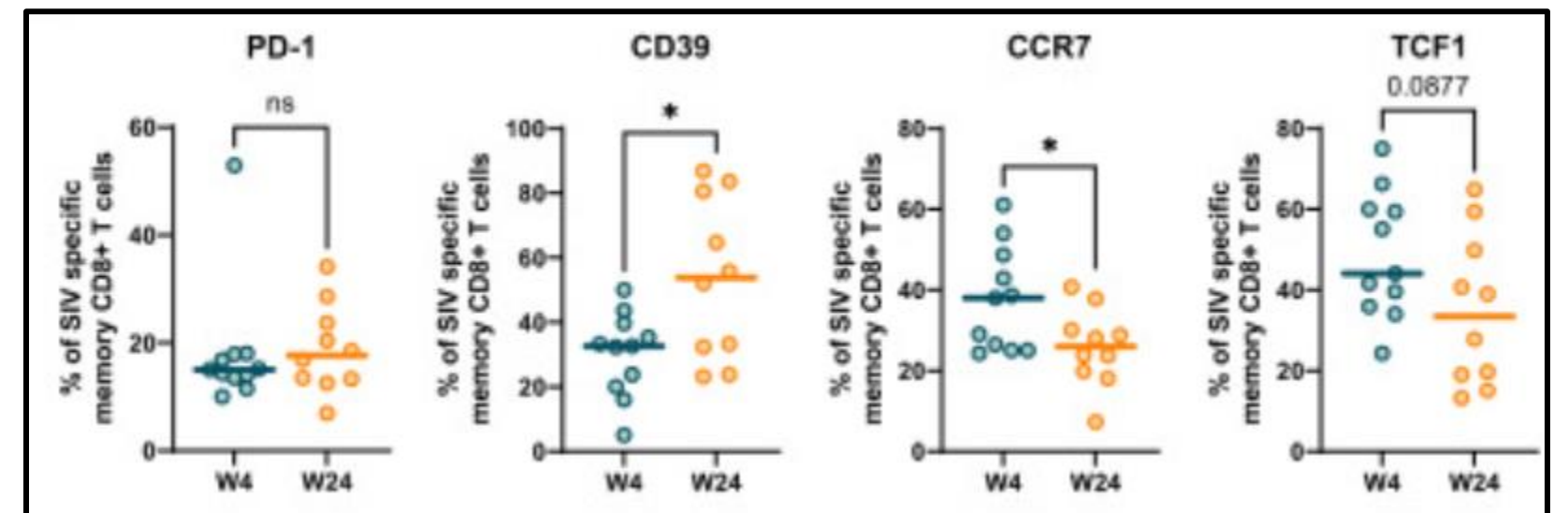


Total=11

■ 18.1% PTC

2/11

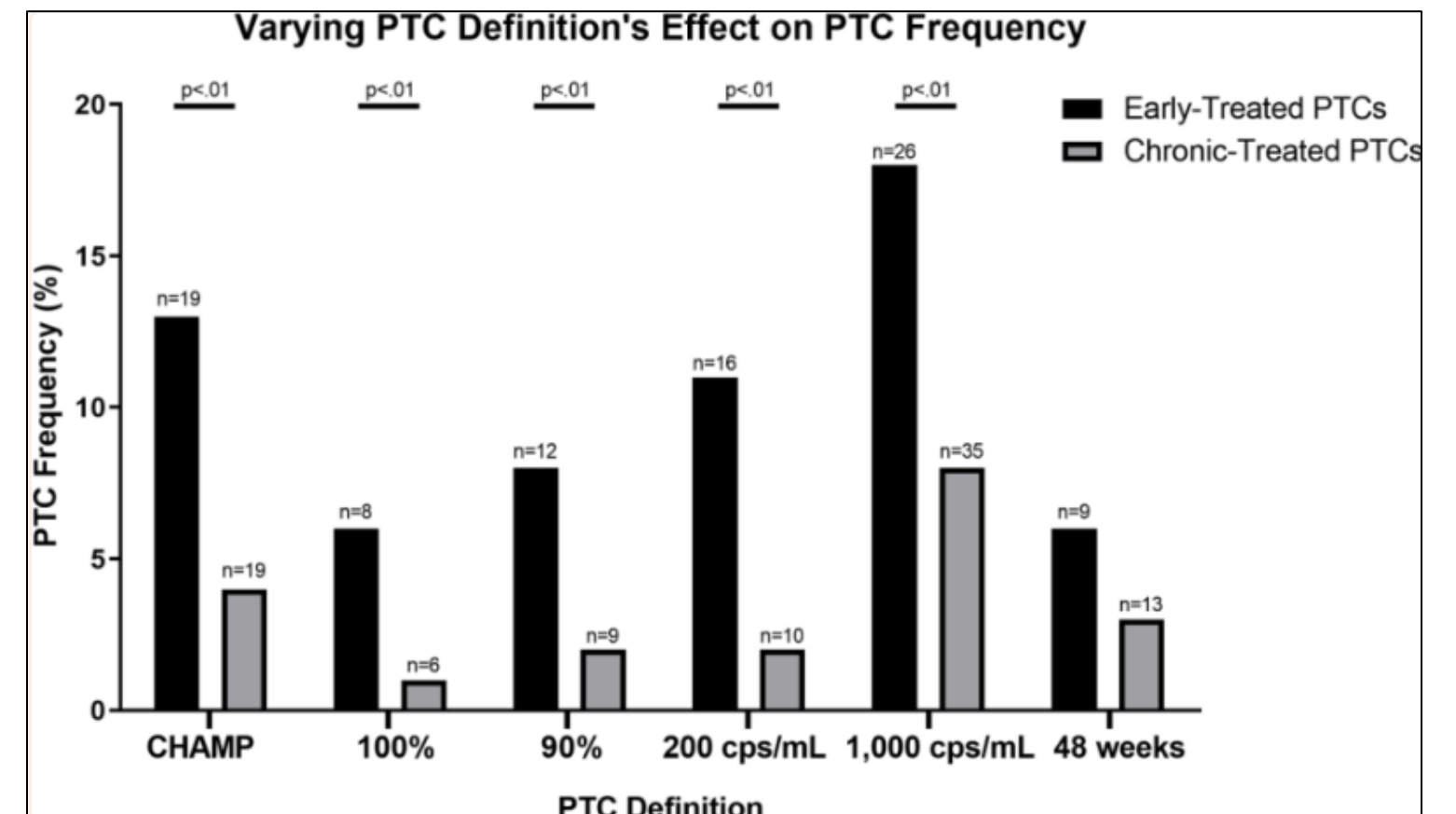
Expansion of SIV-specific CD8<sup>+</sup> T cells with long-lived and stem-like traits after early ART





# DIFFICULTIES IN STUDYING PTC

- || Barriers towards ATI
- || Few trials involving ATI
- || Within ATI studies:
  - || Small sample sizes
  - || Low frequency of PTC
  - || Variable ART restart



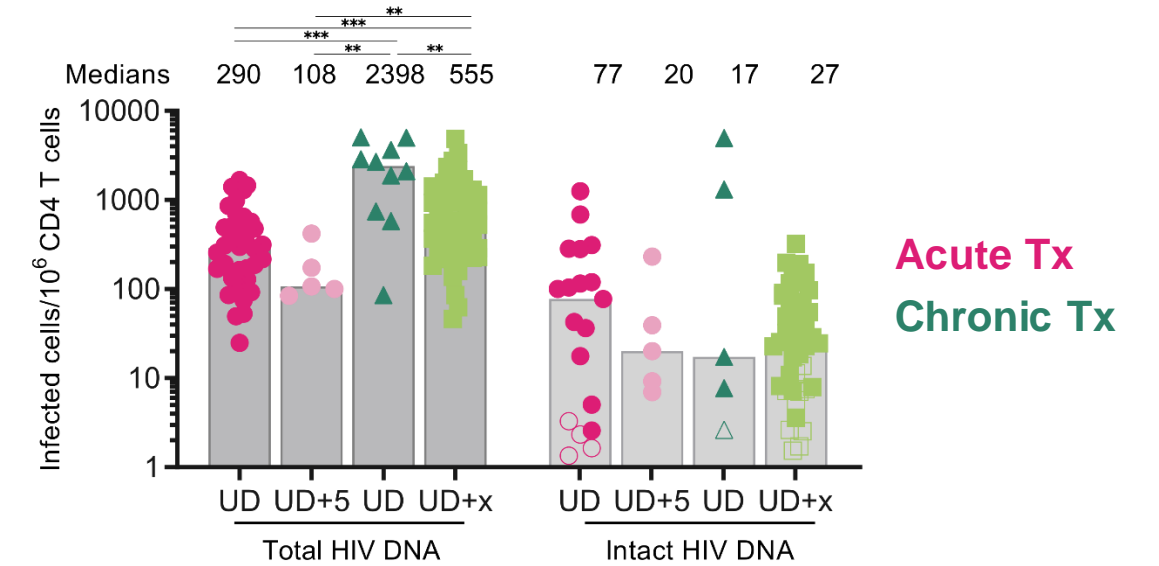
# ART INITIATION DURING AHI

BENEFITS ON MULTIPLE LEVELS

# EARLY ART & VIRAL RESERVOIR

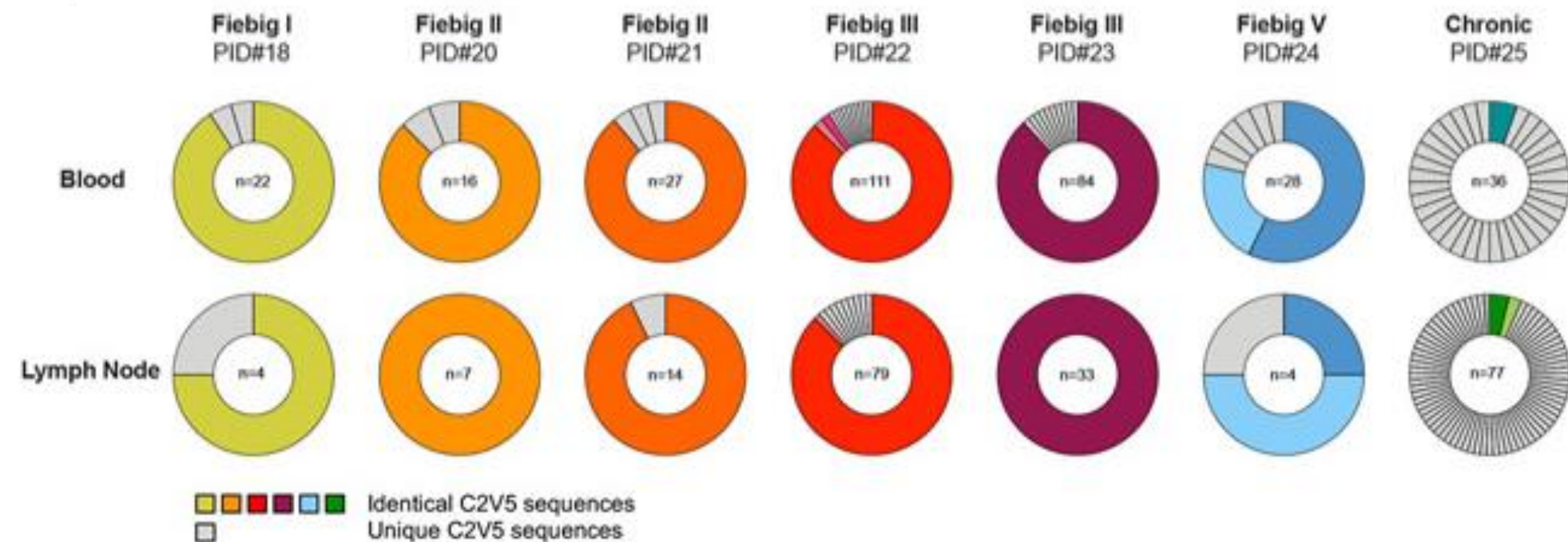
## || Limited viral reservoirs

- || Blood
- || Gut
- || LN



Struyve *et al.* ACS cohort unpublished data

## || Limited viral diversity



Gantner *et al.* Immunity 2023

# EARLY ART & CD4 T CELLS

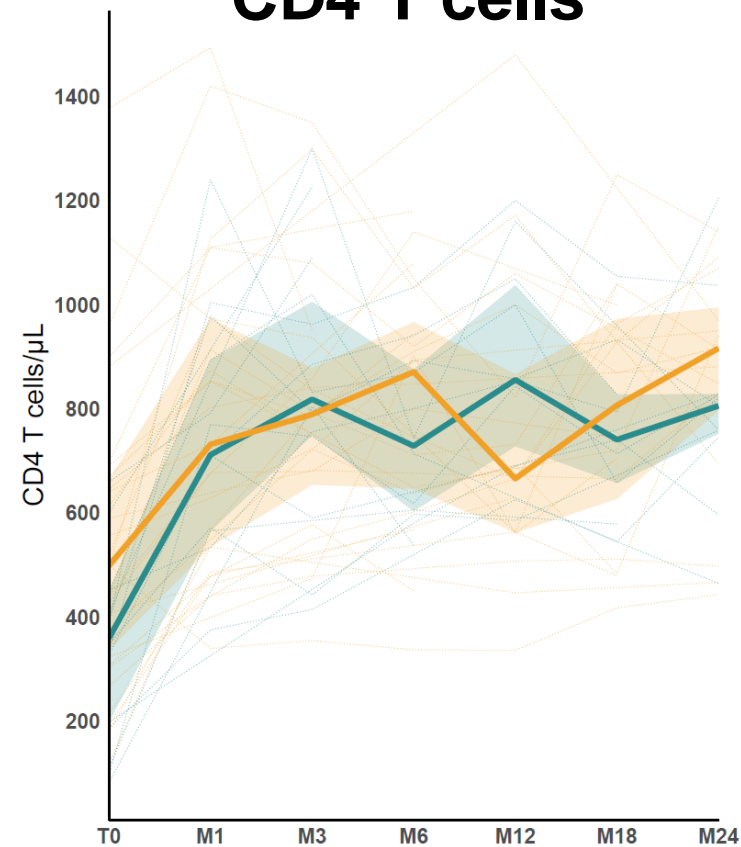
## Peripheral Blood

|| Rapid recovery

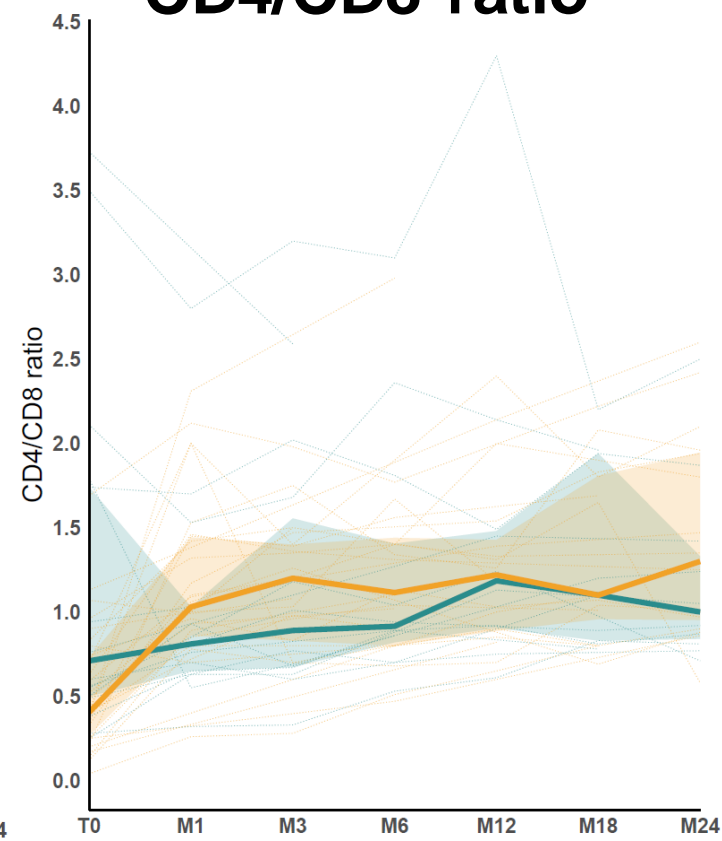
## Lymphoid tissues

|| Incomplete recovery

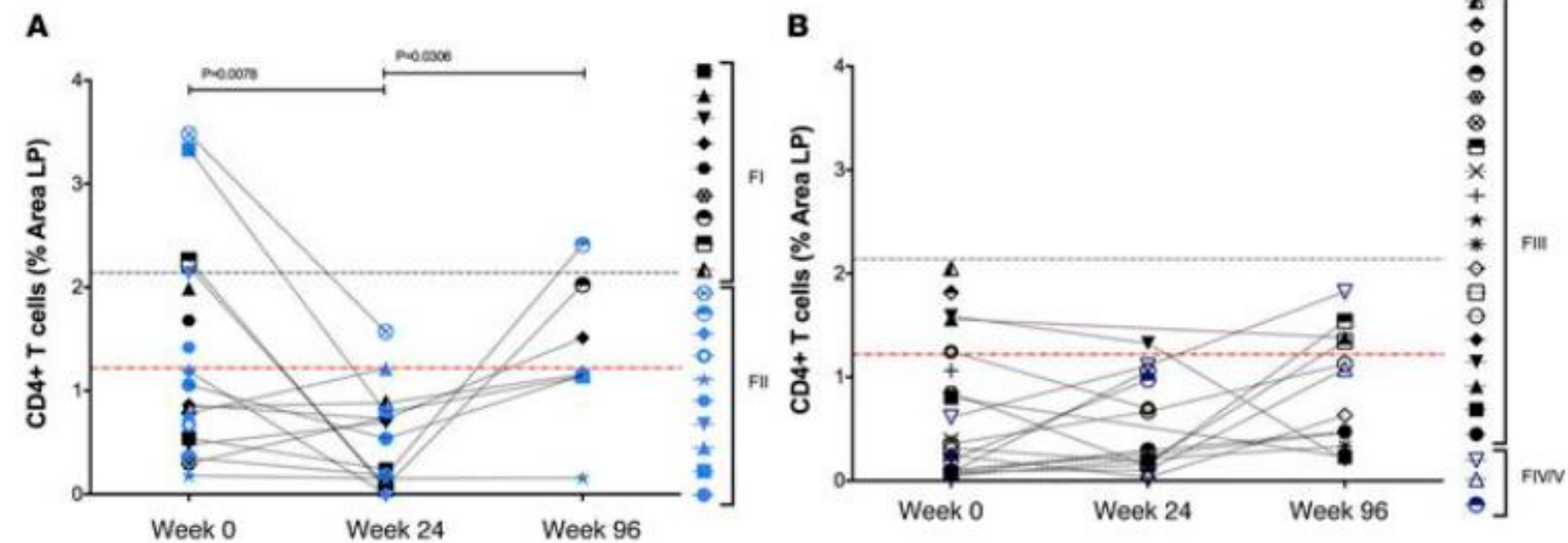
### CD4 T cells



### CD4/CD8 ratio



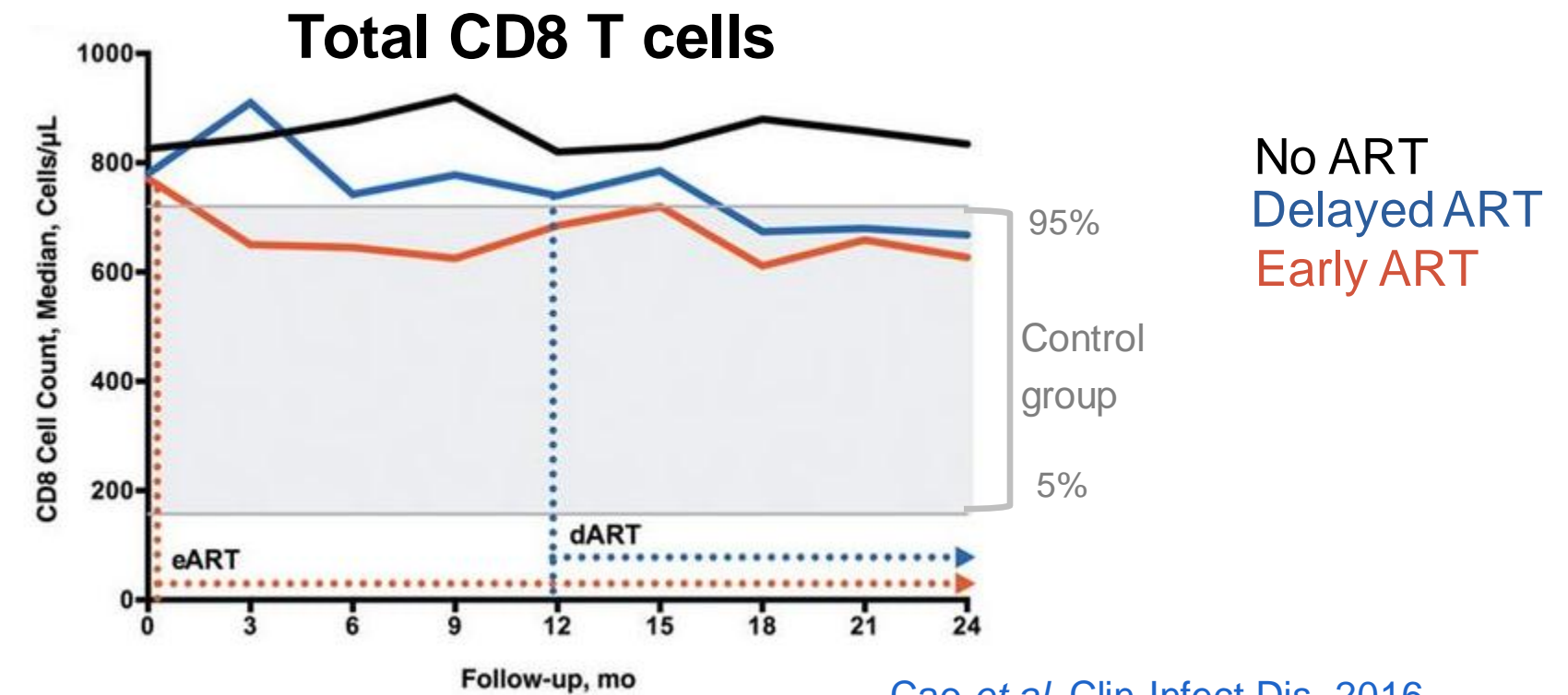
### CD4 T cells in LP (gut)



# EARLY ART & CD8 T CELL RESPONSES

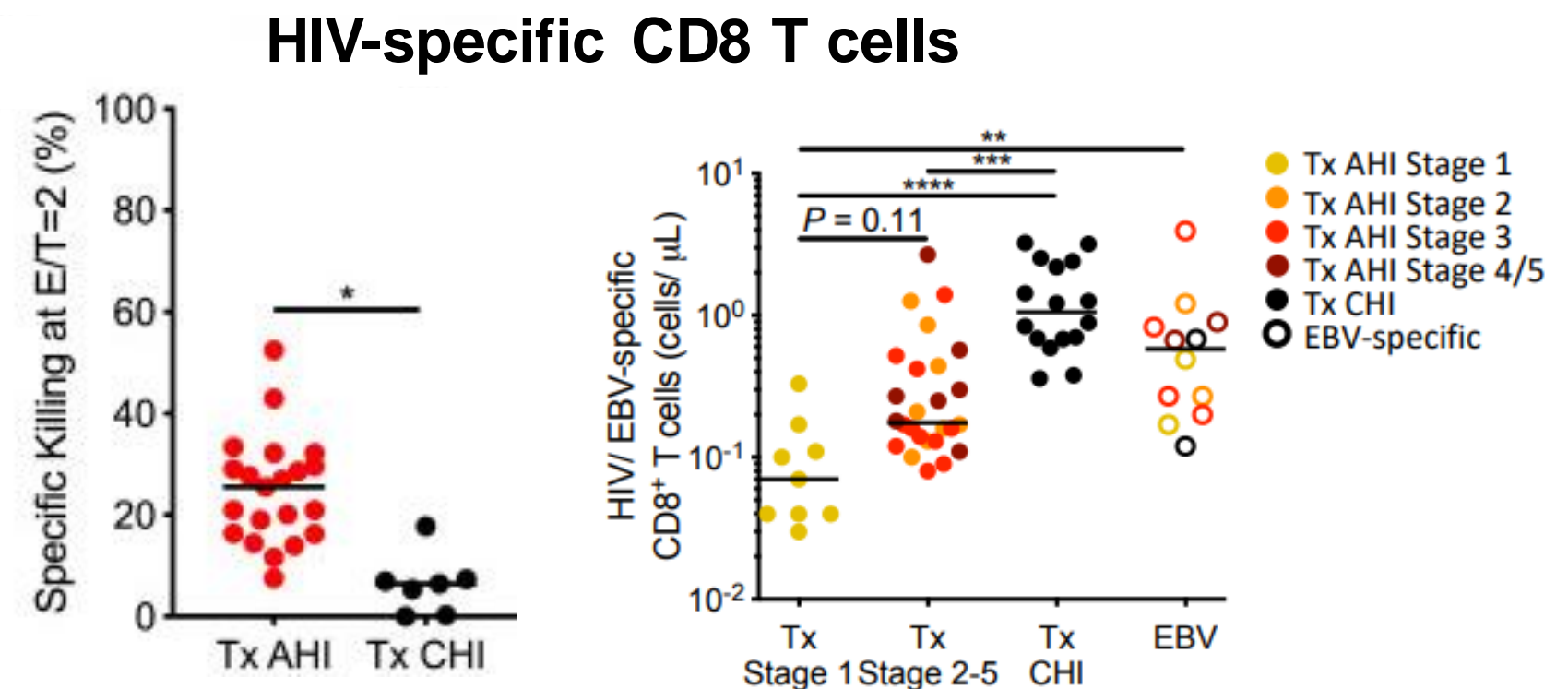
## || CD8 T cells

- || Normalized CD8 counts
- || Decreased activation state



## || HIV specific CD8 T cells

- || Preservation of functionality
- || Low frequency!

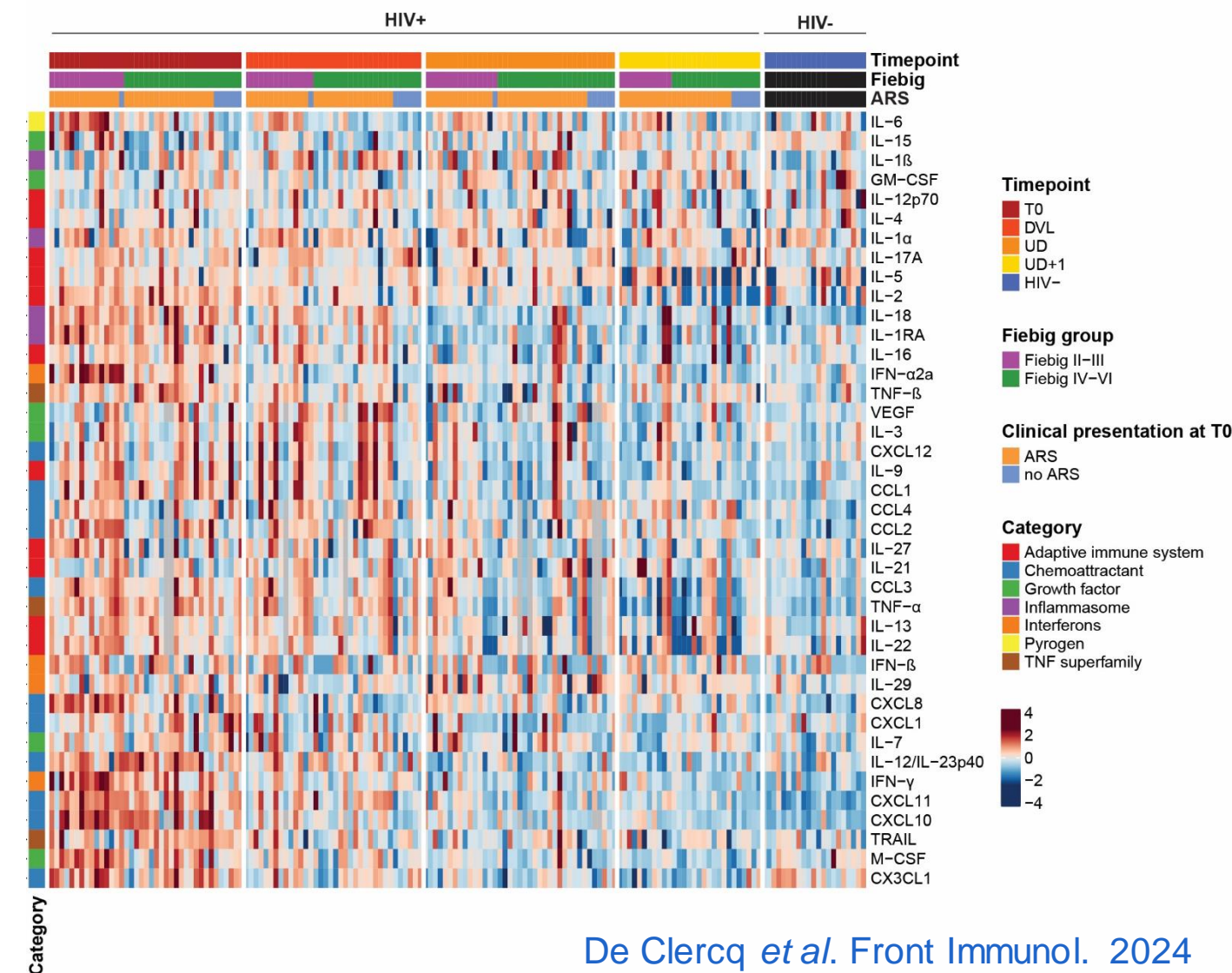


# EARLY ART & HUMORAL IMMUNITY

- || Preservation **functional resting memory B-cells** and **Tfh cells**
- || Impact on the development **HIV-specific antibodies**
  - || Delayed seroconversion
  - || Seroreversion

# EARLY ART & INFLAMMATION

- || **Reduced, not normalized** systemic inflammation



# DOES EARLY ART SUFFICE?

IMPLICATIONS FOR HIV CURE

# BENEFITS FOR CURE

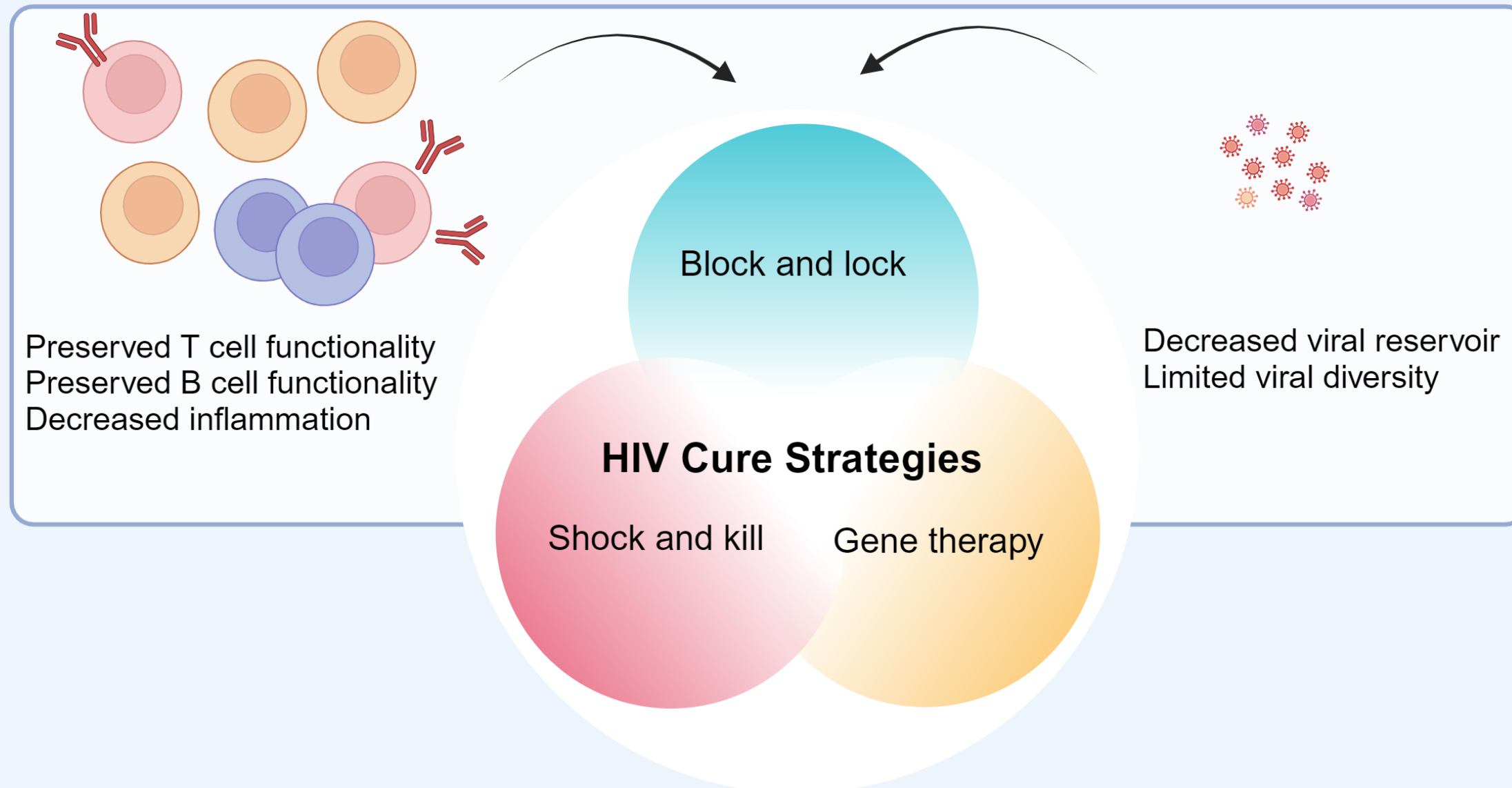
Immune system

Viral reservoir

Late ART



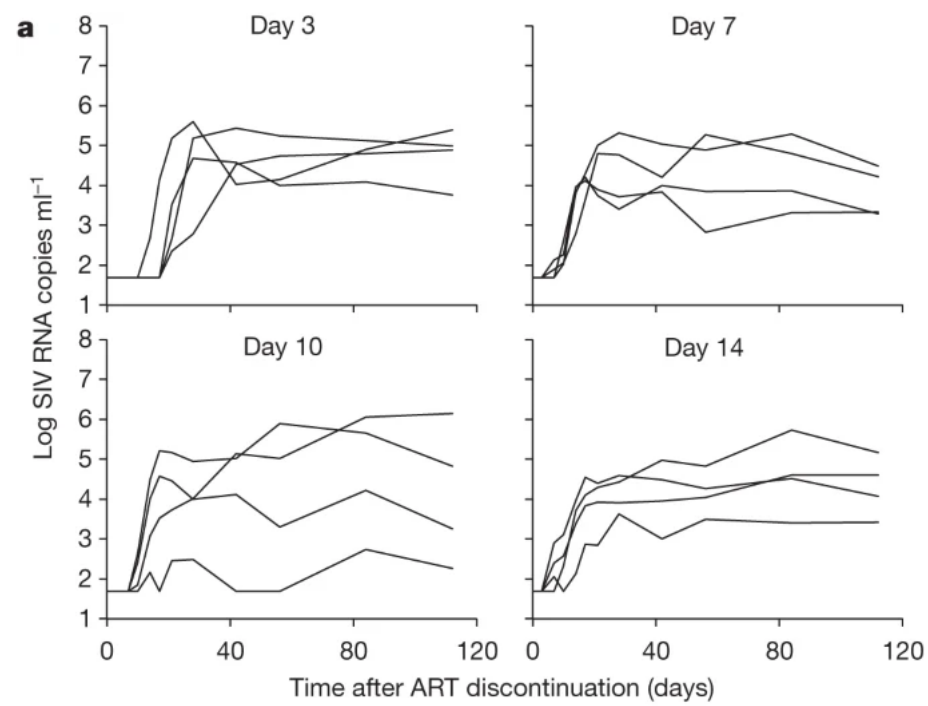
Early ART





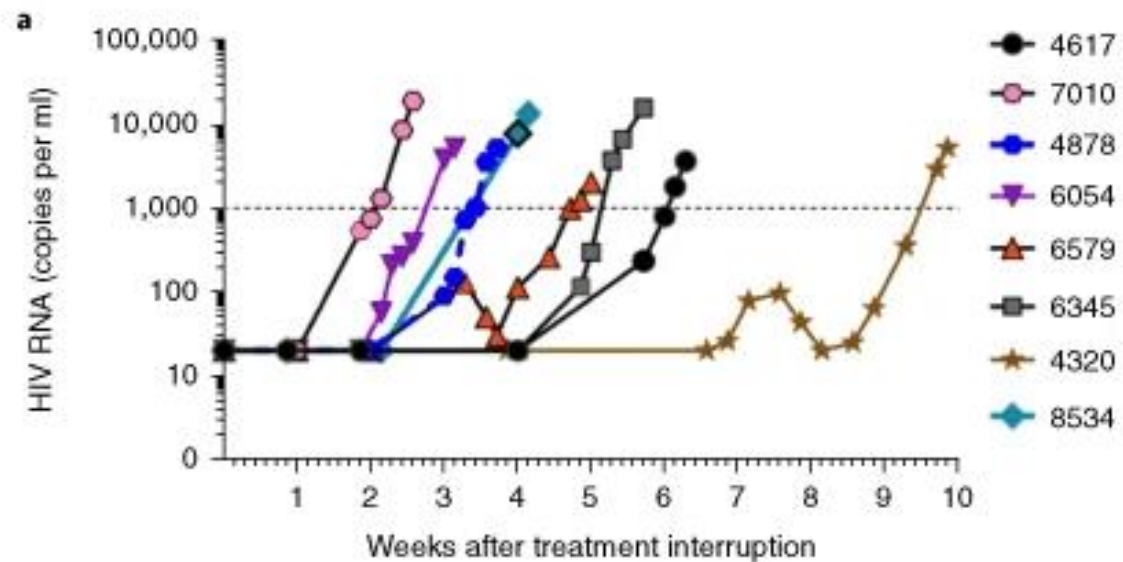
# CAN EARLY BE TOO EARLY?

## NHP model

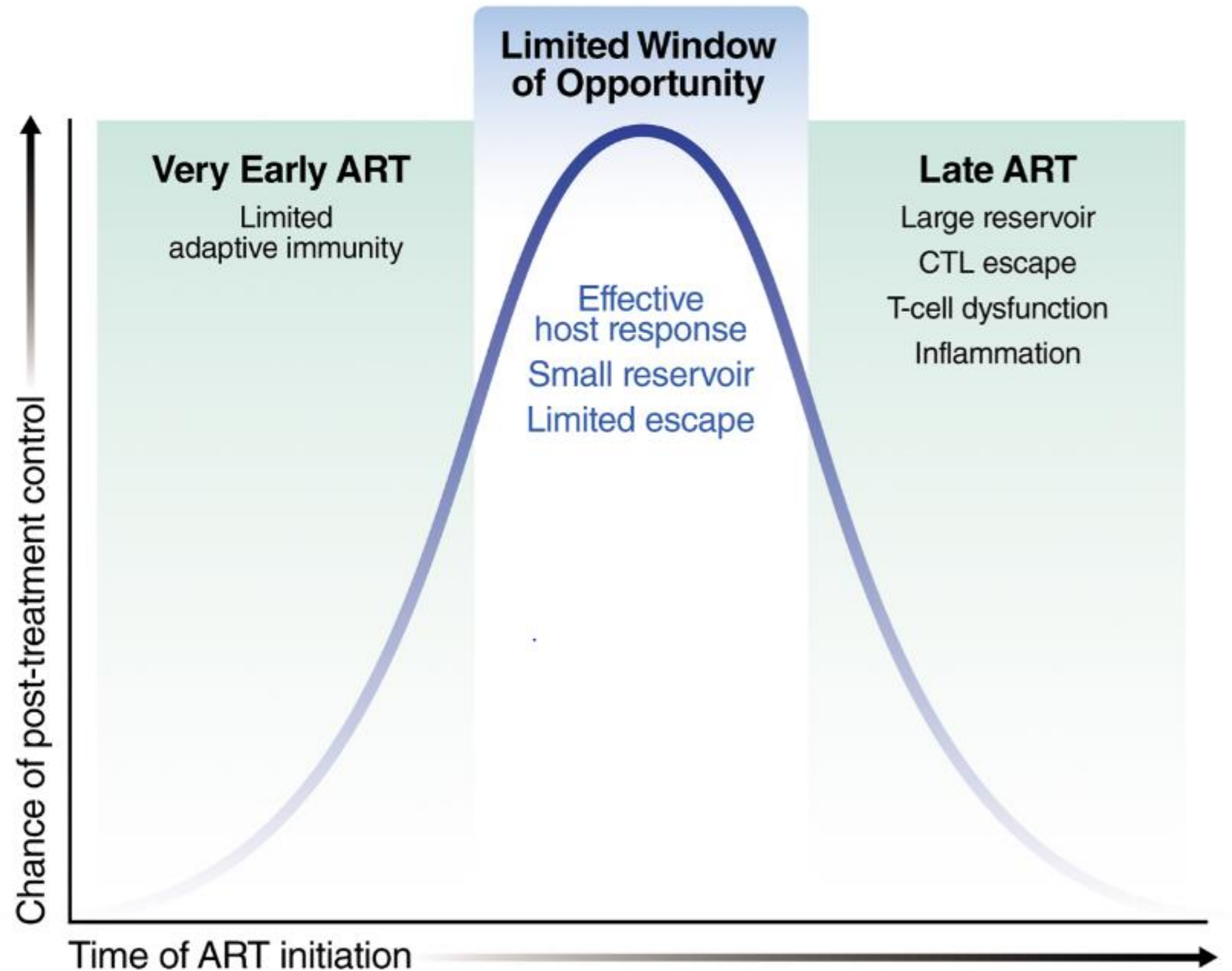


Whitney *et al.* Nature 2014

## Acute HIV cohort: Fiebig I



Colby *et al.* Nat Med 2018



Goulder *et al.* PLoS Pathog. 2018

# HARNESSING THE BENEFITS OF EARLY ART IN CURE TRIALS

## RV397

Clinical Trial > Lancet HIV. 2019 May;6(5):e297-e306. doi: 10.1016/S2352-3018(19)30053-0.

Epub 2019 Apr 15.

**Safety and efficacy of VRC01 broadly neutralising antibodies in adults with acutely treated HIV (RV397): a phase 2, randomised, double-blind, placebo-controlled trial**

Trevor A Crowell<sup>1</sup>, Donn J Colby<sup>2</sup>, Suteeraporn Pinyakorn<sup>3</sup>, Carlo Sacdalan<sup>2</sup>, Amélie Pagliuzza<sup>4</sup>,

NIH U.S. National Library of Medicine

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**ClinicalTrials.gov**

Home > Search Results > Study Record Detail

**Safety and Efficacy of Neutralizing Antibodies and Vaccination for Induction of HIV Remission (RV582)**

Condition or disease ⓘ	Intervention/treatment ⓘ
HIV-1-infection	Biological: VRC07-523LS Biological: PGDM1400LS Biological: N-803 Biological: Ad26.Mos4.HIV Biological: MVA-BN-HIV Biological: A244d11 gp120 Biological: ALFQ Combination Product: Antiretroviral Therapy (ART)

## eCLEAR

Clinical Trial > Nat Med. 2022 Nov;28(11):2424-2435. doi: 10.1038/s41591-022-02023-7.

Epub 2022 Oct 17.

**Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial**

Jesper D Gunst<sup>1 2</sup>, Marie H Pahun<sup>1 2</sup>, Miriam Rosás-Umbert<sup>1 2</sup>, I-Na Lu<sup>3</sup>, Thomas Benfield<sup>4</sup>,

## RIO

> Trials. 2022 Apr 5;23(1):263. doi: 10.1186/s13063-022-06151-w.

**The RIO trial: rationale, design, and the role of community involvement in a randomised placebo-controlled trial of antiretroviral therapy plus dual long-acting HIV-specific broadly neutralising antibodies (bNAbs) in participants diagnosed with recent HIV infection-study protocol for a two-stage randomised phase II trial**

Ming Jie Lee<sup>1</sup>, Simon Collins<sup>2</sup>, Daphne Babalis<sup>3</sup>, Nicholas Johnson<sup>3</sup>, Emanuela Falaschetti<sup>3</sup>,

# CONCLUSIONS

& FURTHER THOUGHTS

# KEY MESSAGES & COMMUNITY CONCLUSIONS

- || Multiple benefits of starting ART during acute HIV infection
  - || HIV reservoir
  - || Immune system
- || Post treatment control of HIV is rare
  - || More common in early treated PLWH
- || Rapid diagnosis, rapid ART initiation!



# FURTHER THOUGHTS

- || PTC show distinct immunovirological features
  - || Can we predict successful control based on this?
- || Achievement vs. maintenance of viral control
  - mediated by different factors?
- || Early treated individuals: ideal candidates for future cure trials

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