Early Stages of the HIV Reservoir Seeding

Nicolas Chomont, PhD

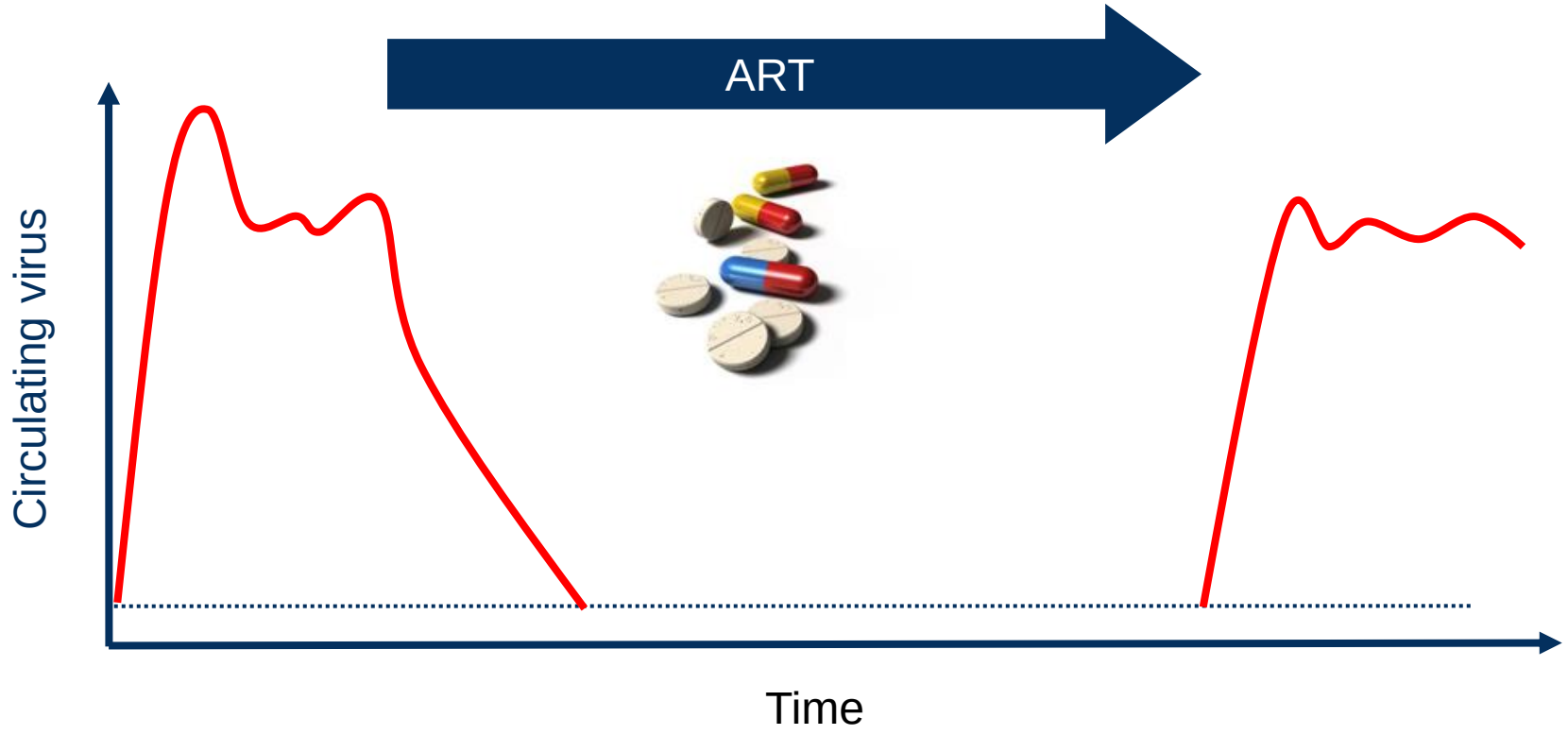
Hot Topics in HIV

Barcelona • October 24th, 2024

Université de Montréal

CRCHUM
CENTRE DE RECHERCHE

ART does not eradicate HIV



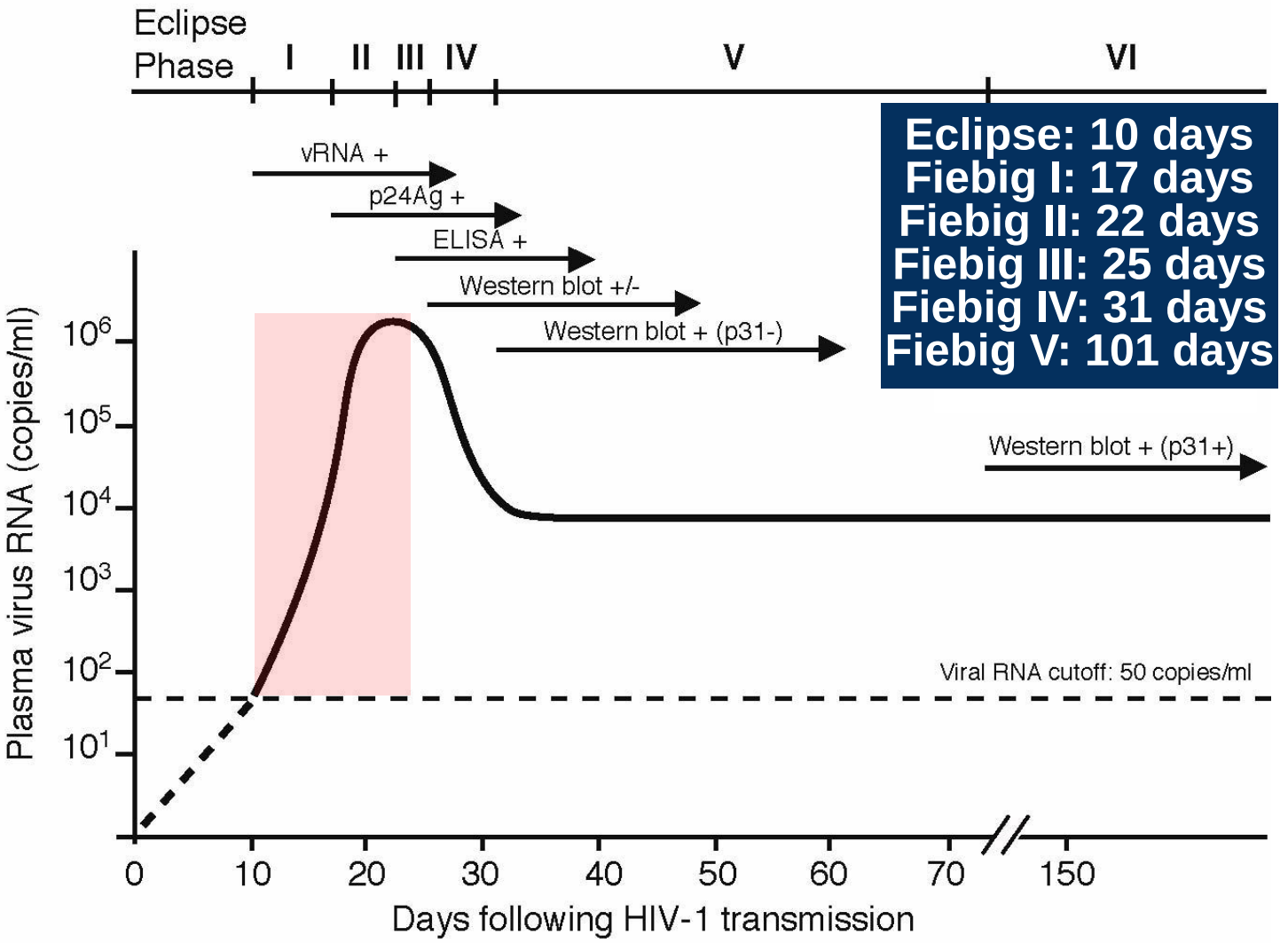
- HIV persists during ART

Establishment of HIV reservoirs

- When does HIV establish a persistent reservoir during acute infection?
- In non-human primate studies, SIV rapidly establishes a small pool of latently infected cells in peripheral blood and lymphoid tissues
- However, studies in humans are limited (for obvious reasons!)

MC Strain JID 2005; Ananworanich AIDS 2014; L Leyre STM 2019; CJ Miller JVI 2005; ZQ Zhang PNAS 2004; Whitney Nature 2014

Stages of acute HIV infection

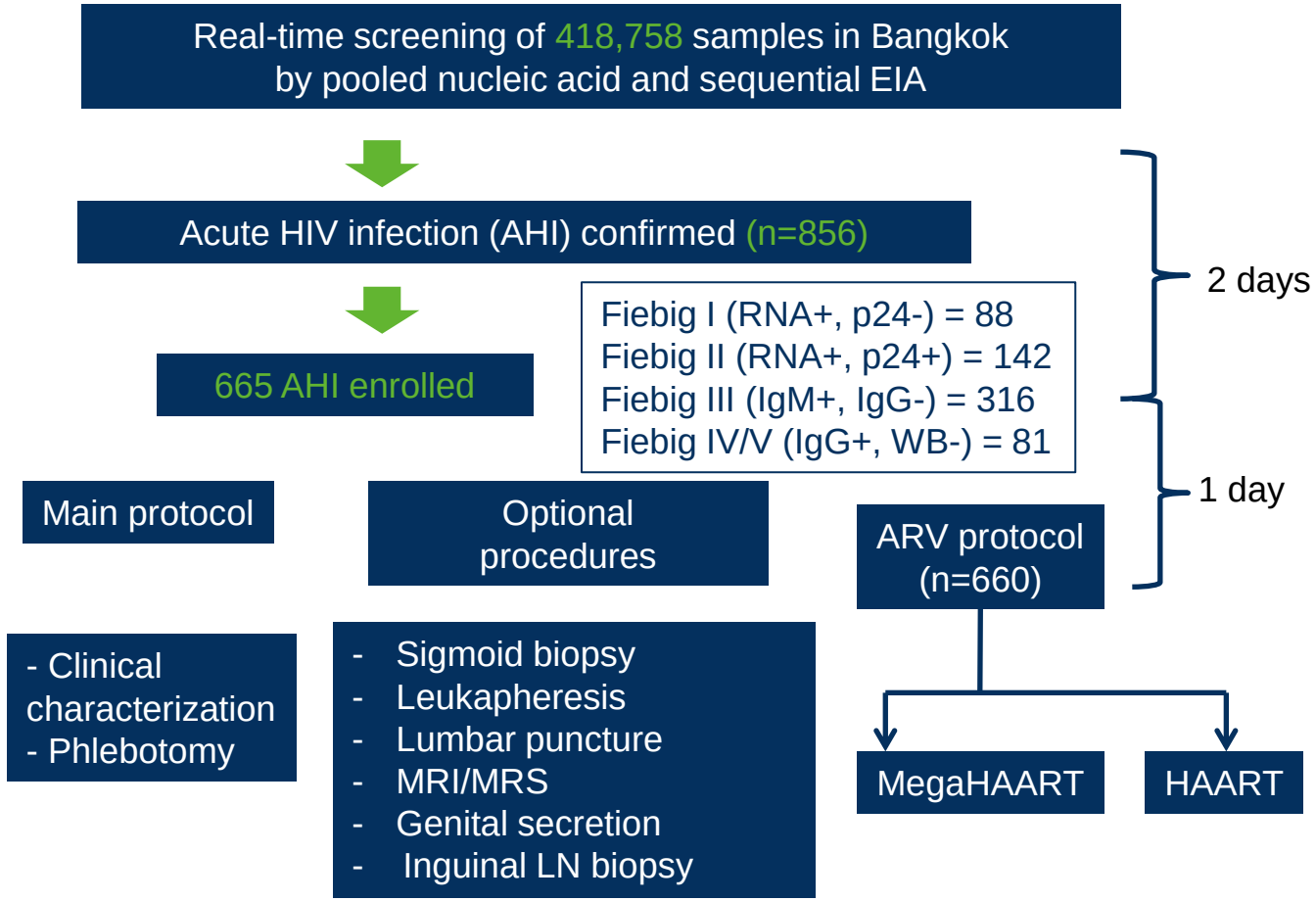


Fiebig/Busch et al., AIDS 2003
Cohen/Hecht et al. JID 2010

RV254 study design - MHRP and Thai Red Cross

J. Ananworanich

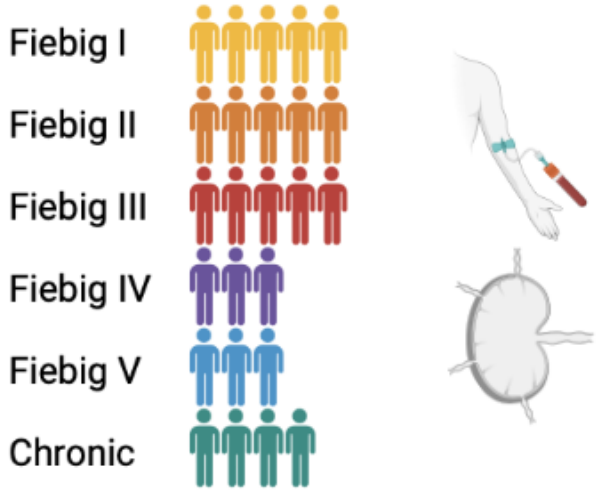
L. Trautmann



Updated from J Ananworanich, Retrovirology 2013
www.clinicaltrials.gov 00796146

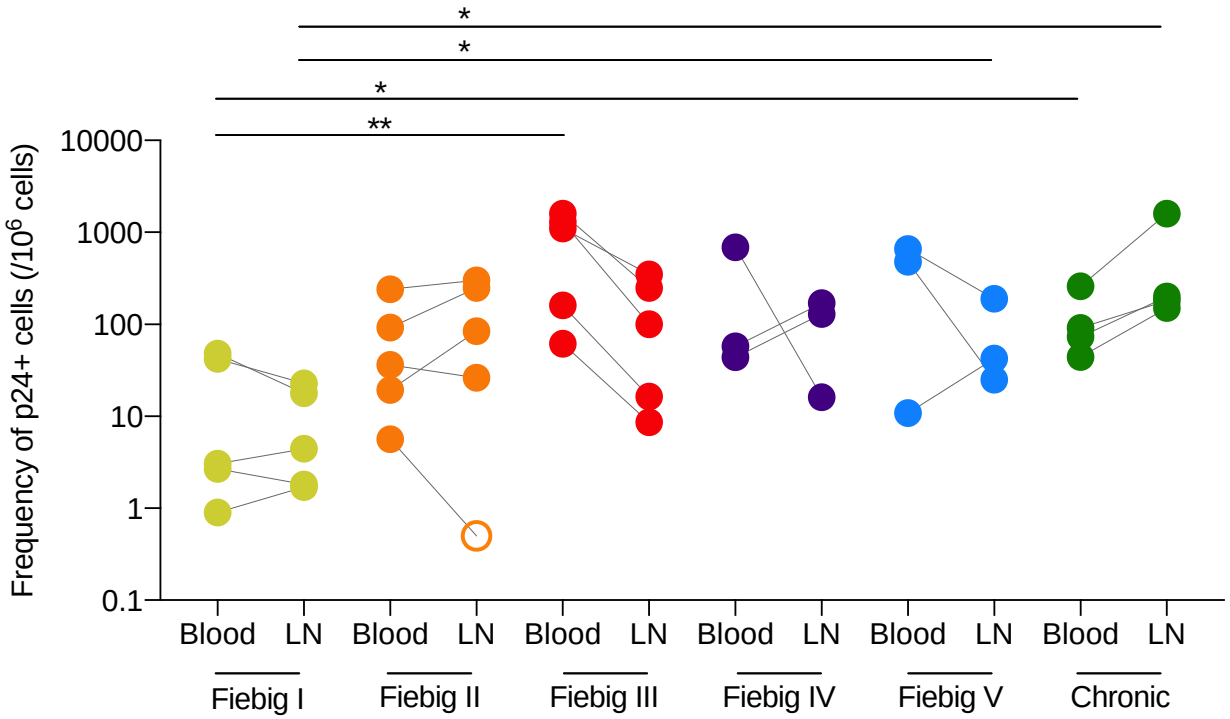
What are the early targets of HIV during acute infection?

25 Thai participants
(RV254/SEARCH010)



Gantner et al. Immunity 2023

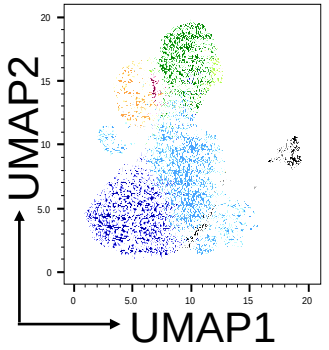
p24+ cells are detected since the earliest stage of acute infection



n=25

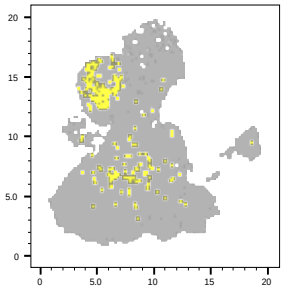
- Frequencies of p24+ cells gradually increase with time of infection (up to 1/1000 cells)
- No clear difference in the frequencies of p24+ cells between blood and lymph nodes

Phenotype of productively infected cells



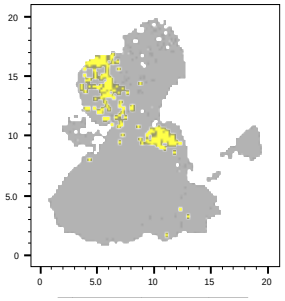
Fiebig I
n=4

Blood



n=209 p24+ cells

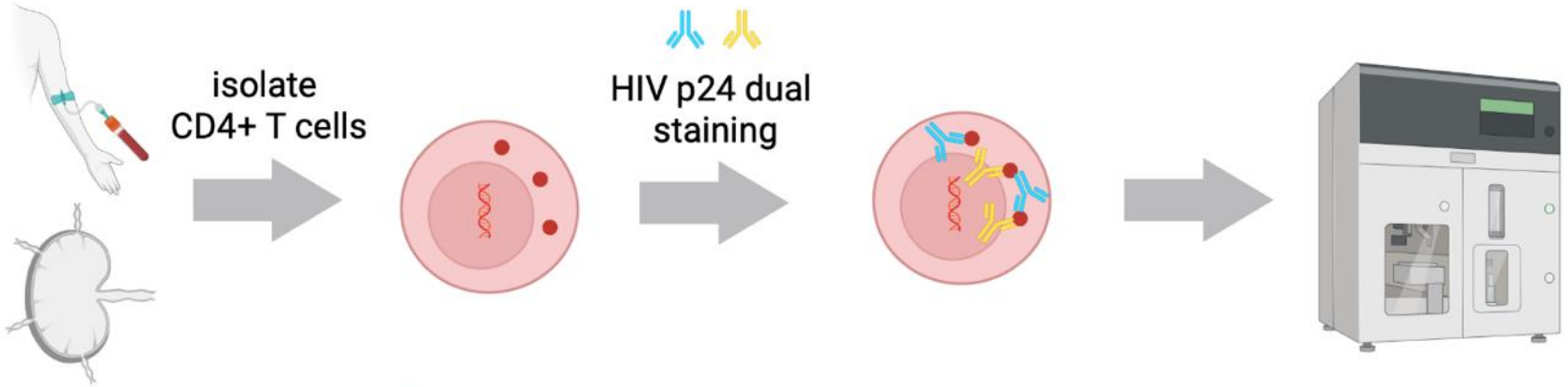
Lymph node



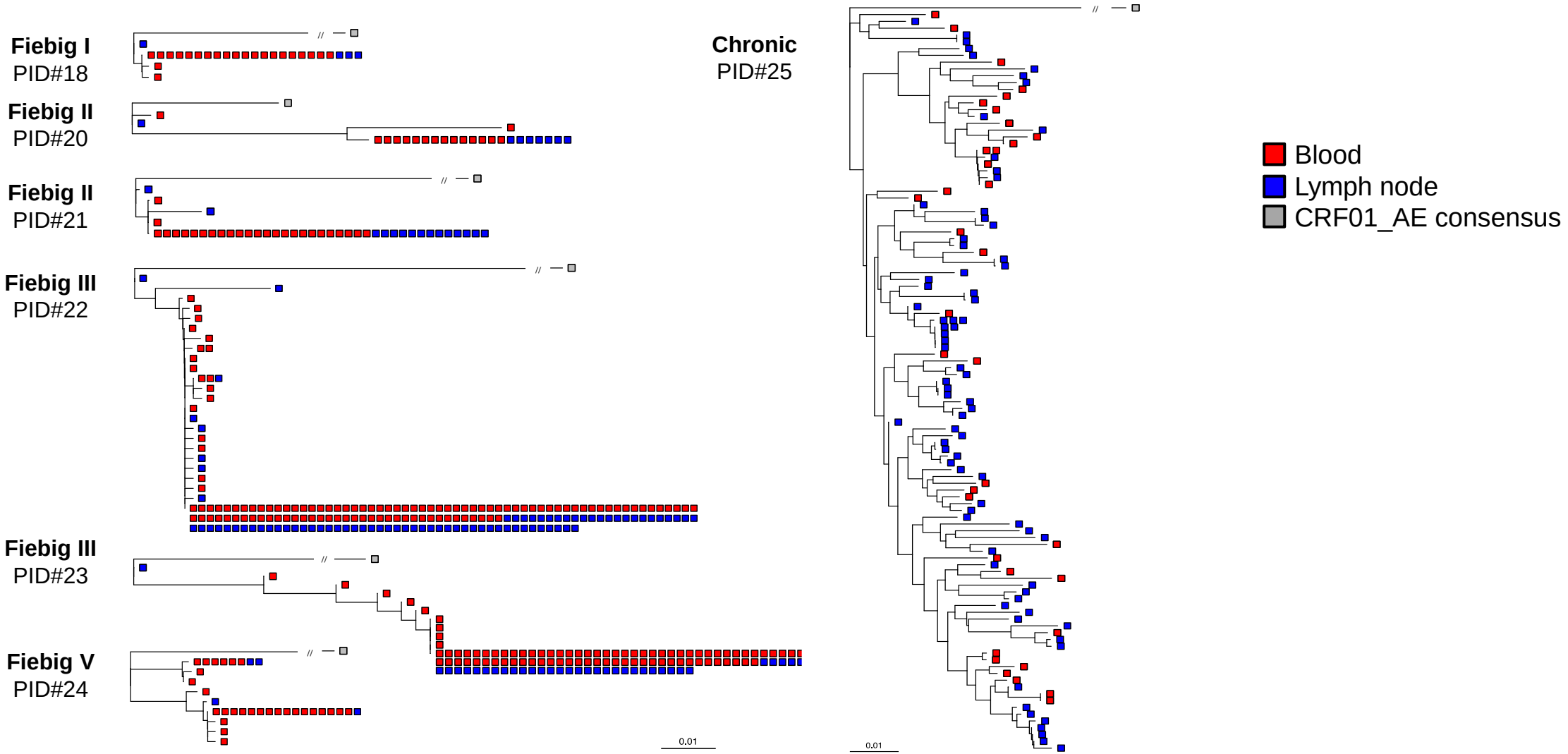
n=210 p24+ cells

- The phenotype of infected cells changes over time and varies between blood and lymph nodes

How diverse are the virus and the infected cells during acute infection?

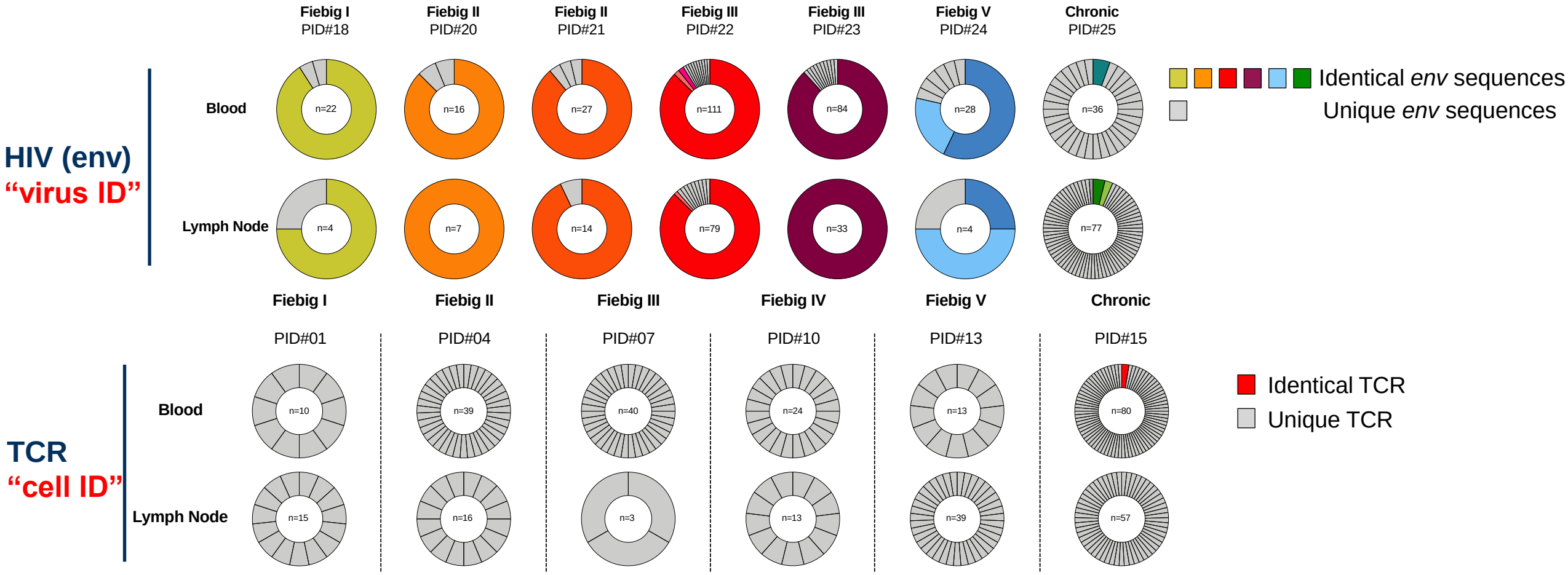


HIV diversity (*env*)



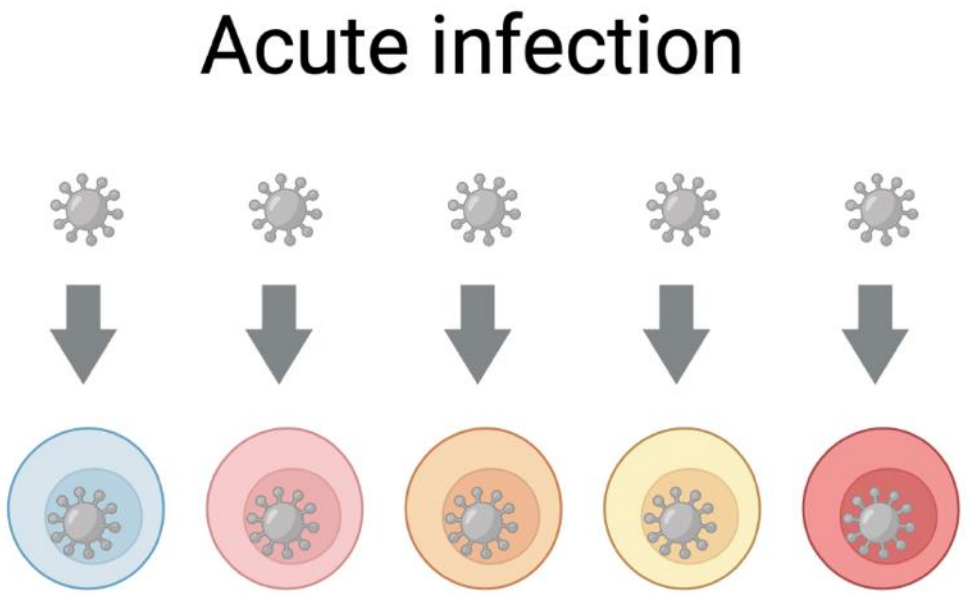
- Limited proviral diversity during acute infection. Major variants are often shared between blood and lymph node

HIV and TCR sequencing



- During acute infection, productively infected CD4+ T cells carry identical genomes but belong to different T cell clones

Proposed model



- During acute infection, similar variants target individual T cells from distinct clones
- During chronic infection, HIV quasispecies are more diverse, and the proliferation of infected clones contributes to viral dissemination

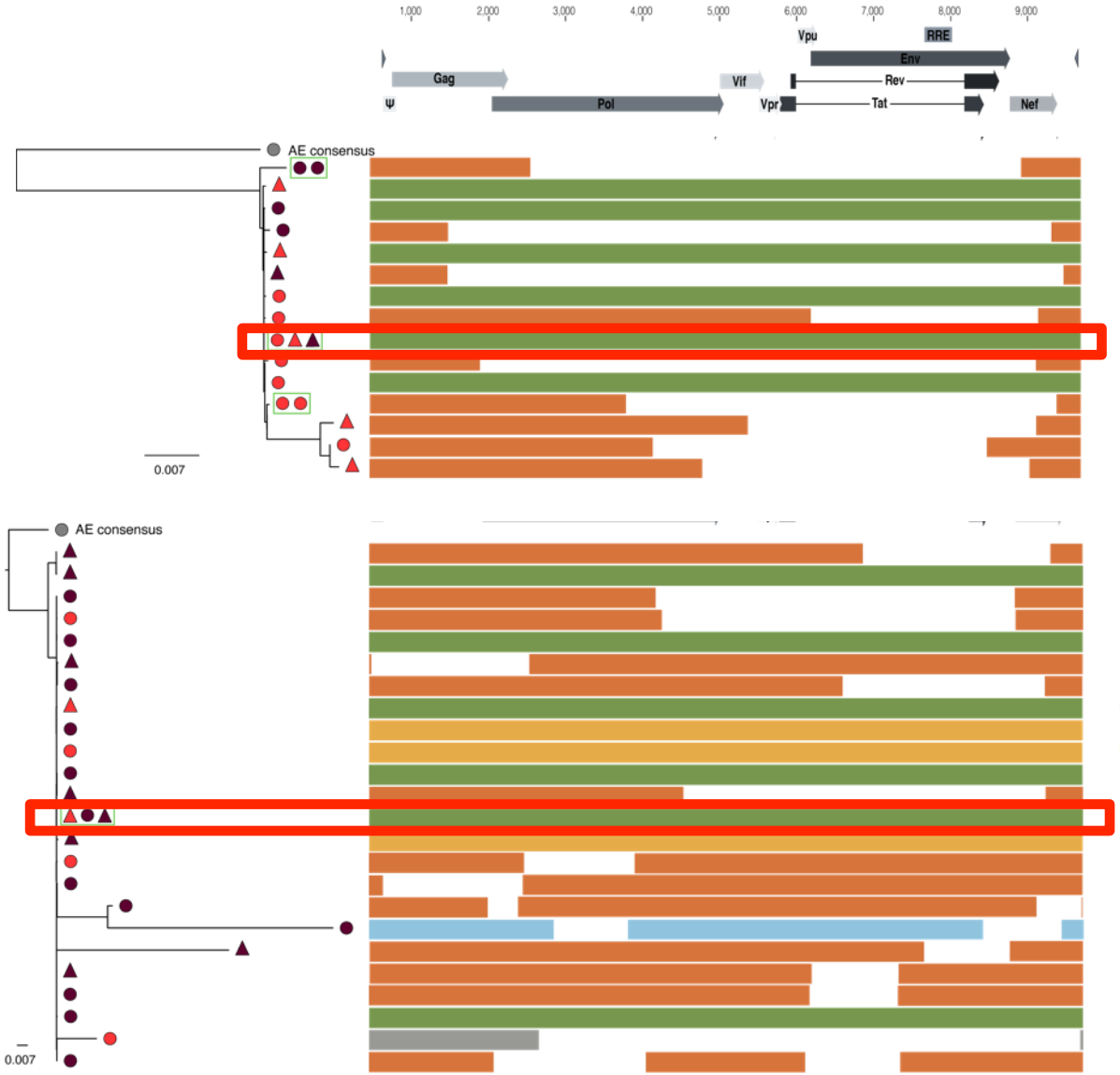
When is the persistent reservoir seeded?

Gantner et al. Immunity 2023

HIV genomes in early treated people

PID#30

PID#13

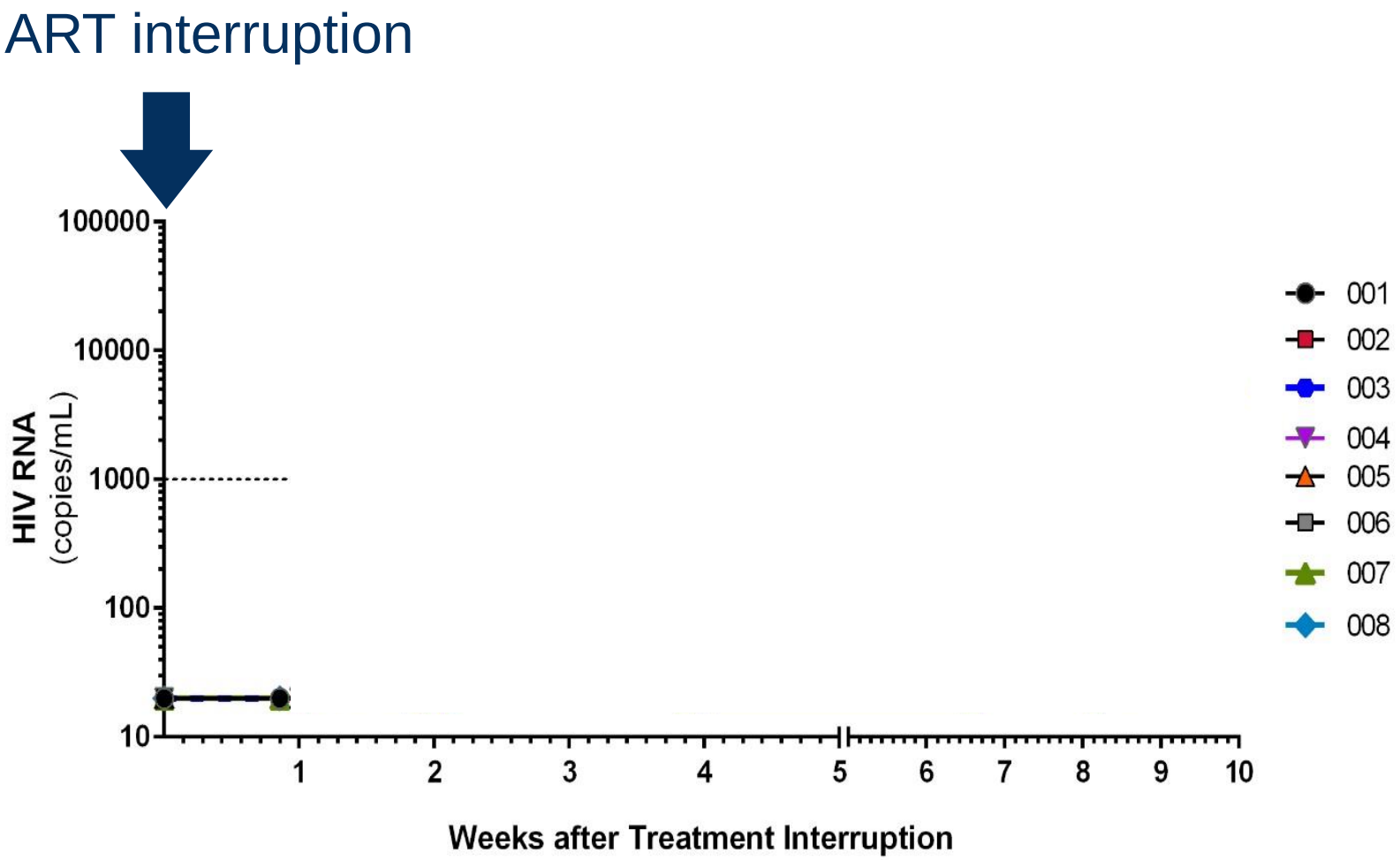


Intact
Inversion
Hypermutations
Large deletion
Stop codons

W0
W96
Non productive
Non induced
Identical sequence

- Intact proviruses are archived during acute infection and can persist on ART

ART interruption in Fiebig I participants (RV411)



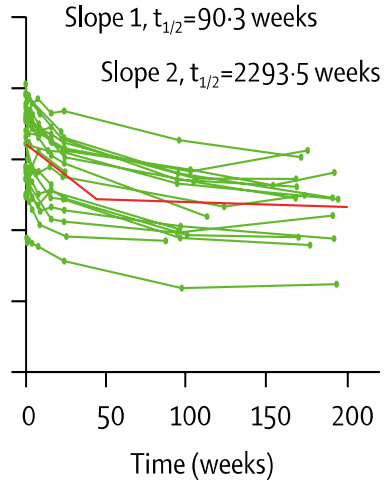
- Very early ART is not enough to clear the reservoir and prevent viral rebound

Colby et al. Nat Medicine 2018

Half life of the reservoir: Early ART in Peru

ART initiation during

Chronic
206 days (196–220)



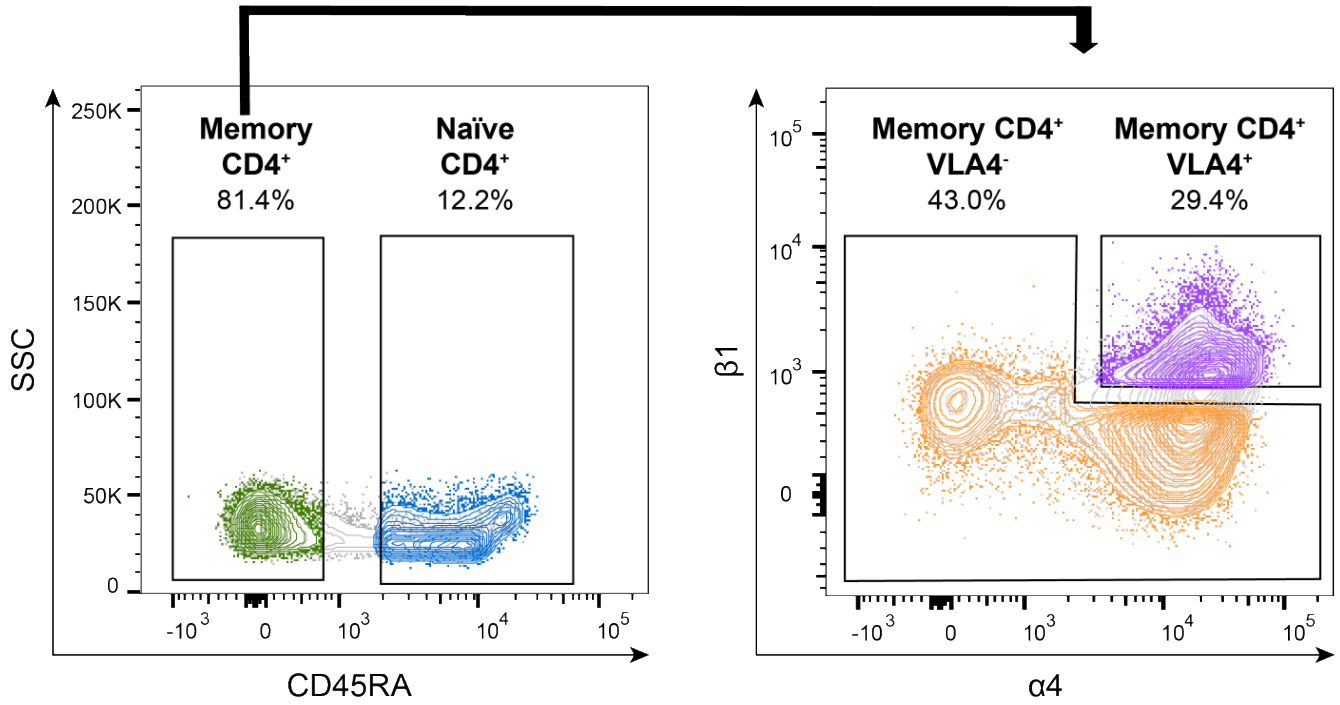
- Early ART limits the size of the pool of infected cells and is associated with a faster decay of HIV reservoir markers

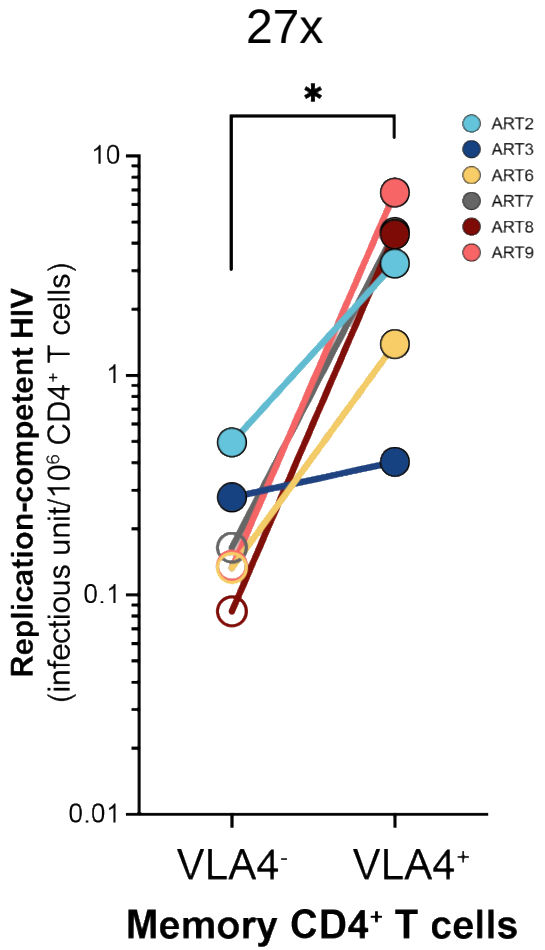
Massanella et al. Lancet Microbe 2021

In which cells does HIV hide?

- The establishment of the reservoir seems unavoidable, even with very early ART
- We need to better characterise these cells that persist after prolonged therapy to eliminate them

VLA-4 is a marker of the inducible, replication-competent reservoir

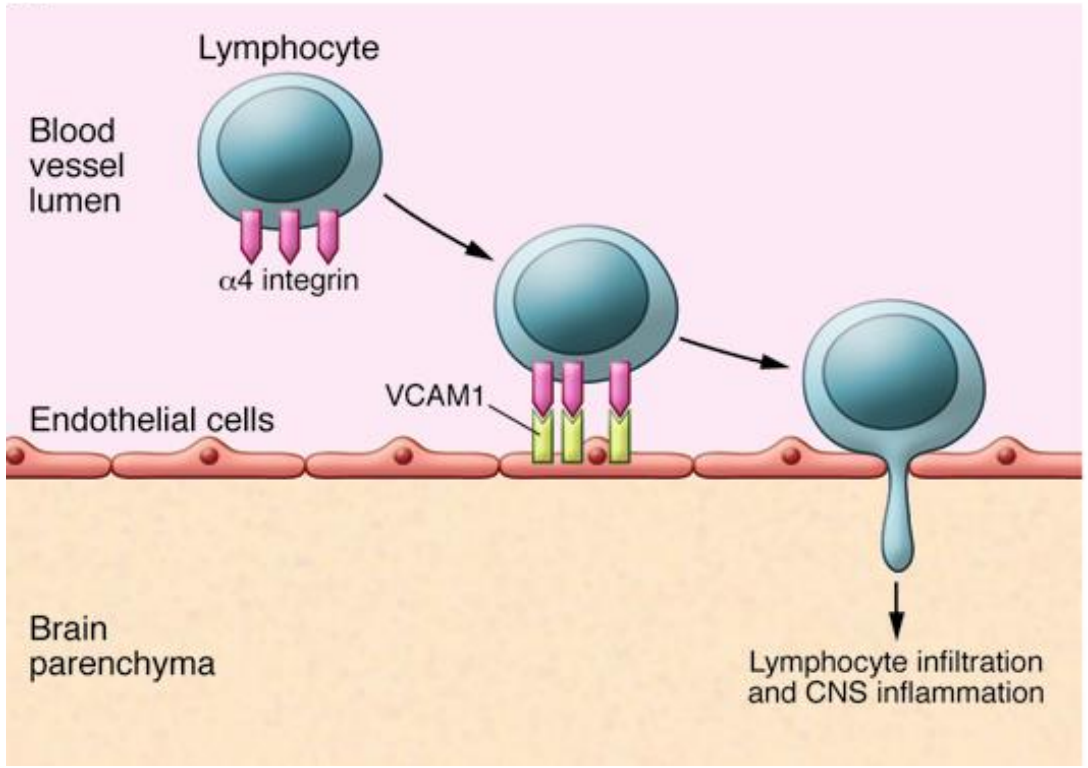


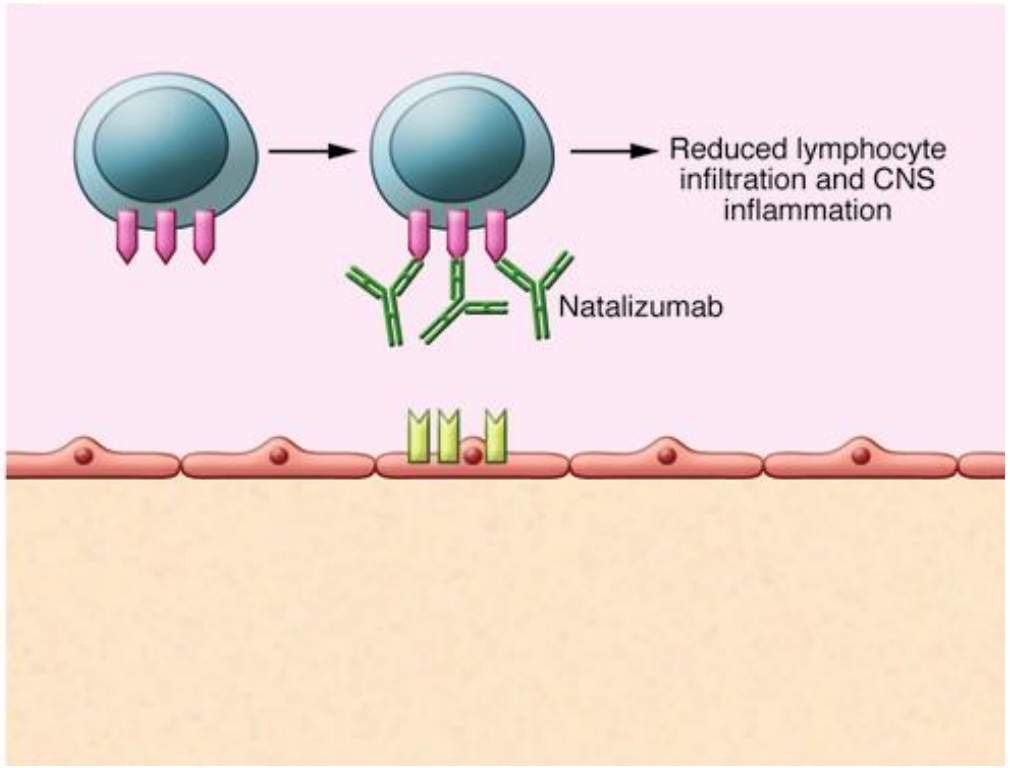


- Memory VLA-4 expressing cells are highly enriched in replication-competent HIV

Dufour et al. Nat Comm 2023

A therapeutic avenue to target reservoirs?





- Natalizumab is a humanized monoclonal antibody targeting VLA-4 and approved for multiple sclerosis and Crohn's disease
- However, it increases the risk of progressive multifocal leukoencephalopathy (PML), making it an unlikely therapeutic candidate in PWH
- Novel generations of VLA-4 antagonists such as the recently approved α4 antagonist carotegrast methyl could be tested in animal models (Dhillon et al., Drugs 2022)

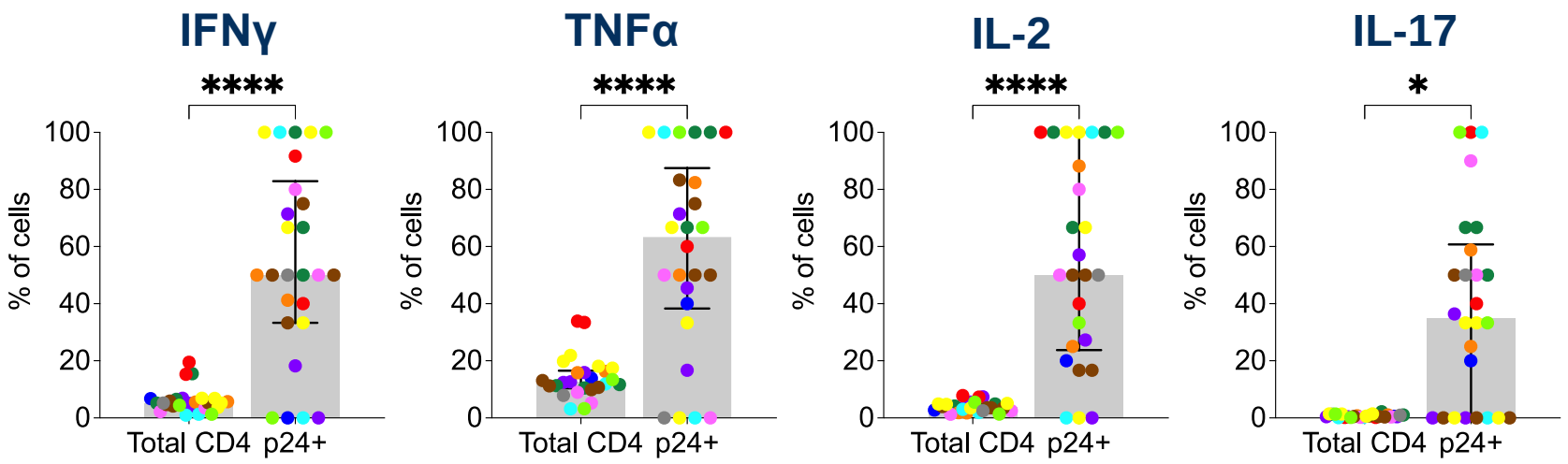
Participants

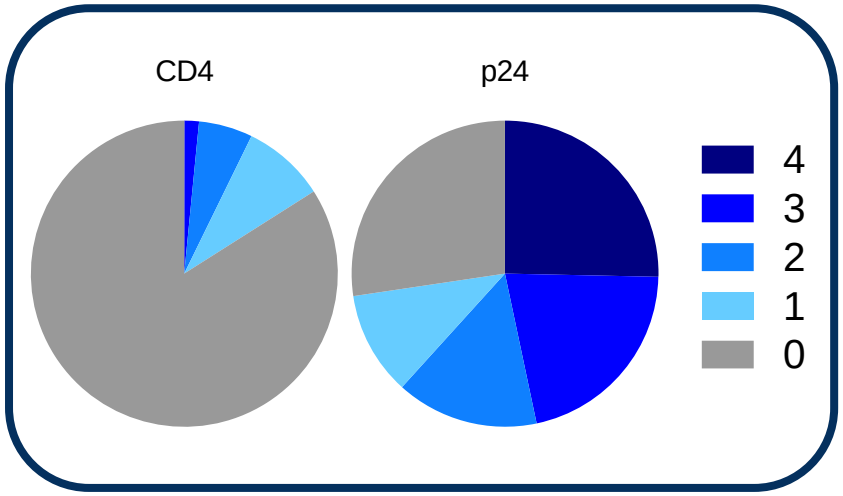
- **11 PWH**
- **all males, 35-60 yo**
- **2-4 time points per participant**
- **4-25 years on ART**

Hélène Roux, in preparation

Cytokines

Each colour is a participant
Each ● is a time-point

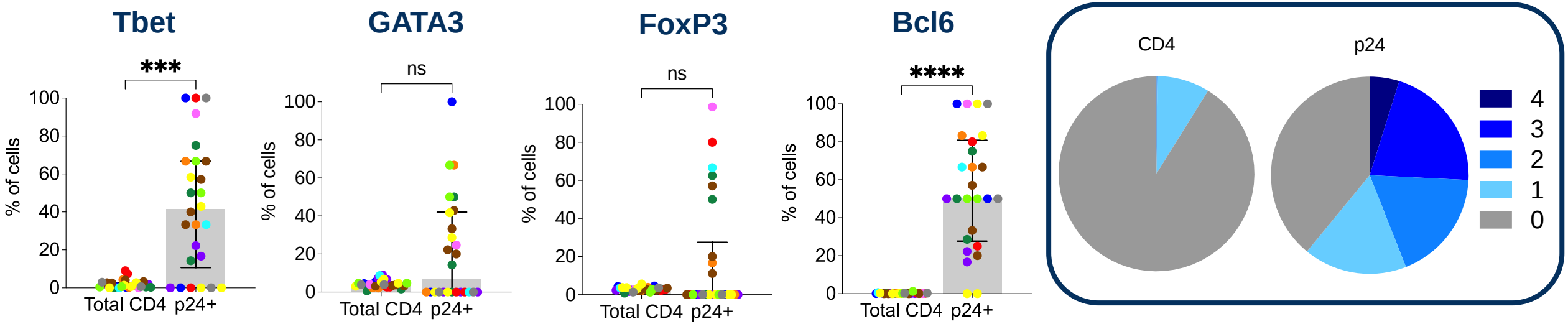




- p24+ cells express cytokines more frequently than uninfected cells
- They also often express several cytokines simultaneously

Transcription factors

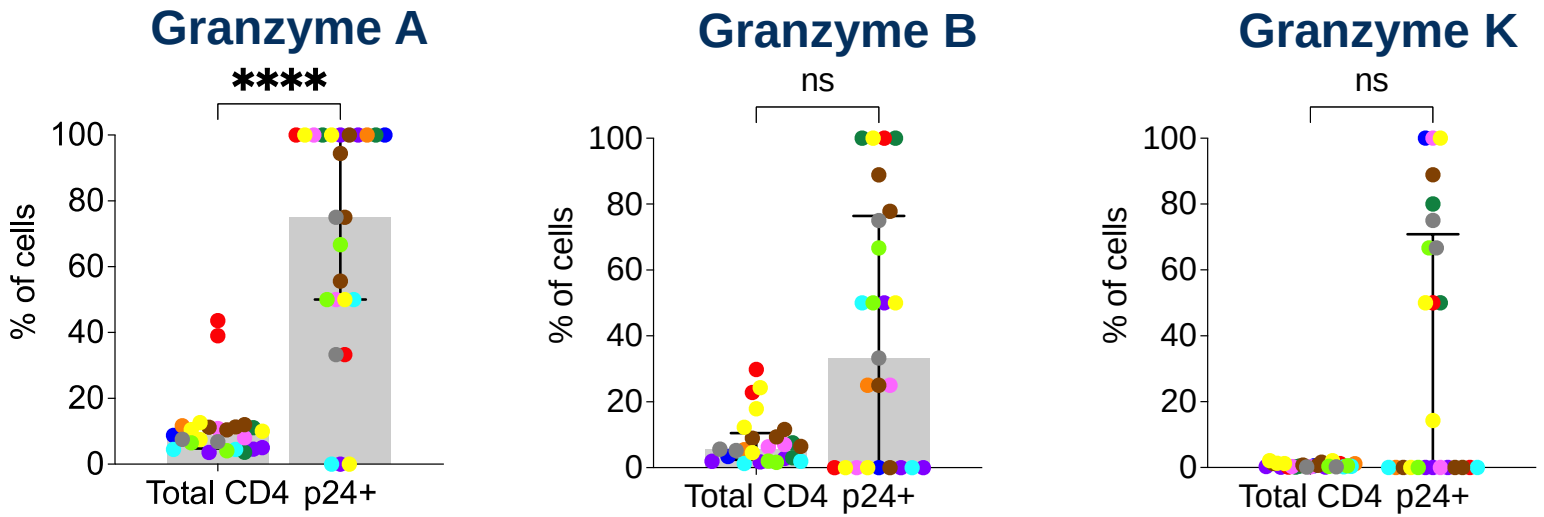
Each colour is a participant
Each ● is a time-point

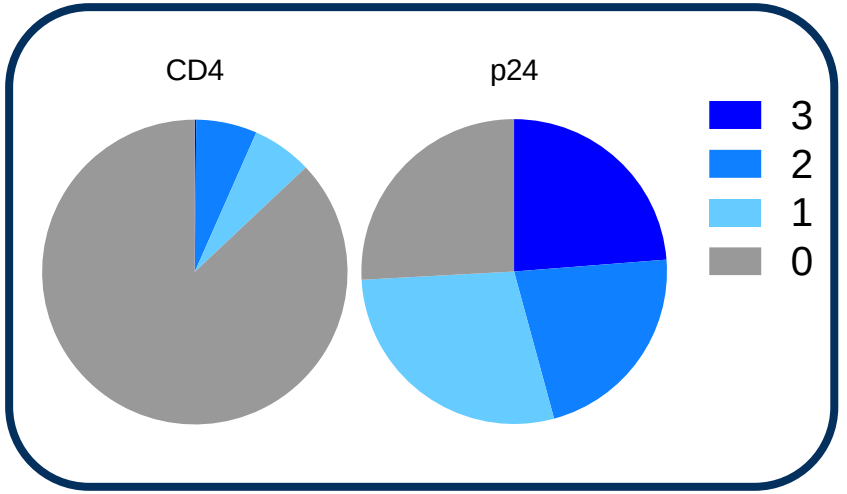


- p24+ cells express Tbet and Bcl6 more frequently and also tend to express higher levels of FoxP3 and GATA3 than p24- cells
- Surprisingly, they express several of these markers simultaneously

Cytotoxicity

Each colour is a participant
Each ● is a time-point

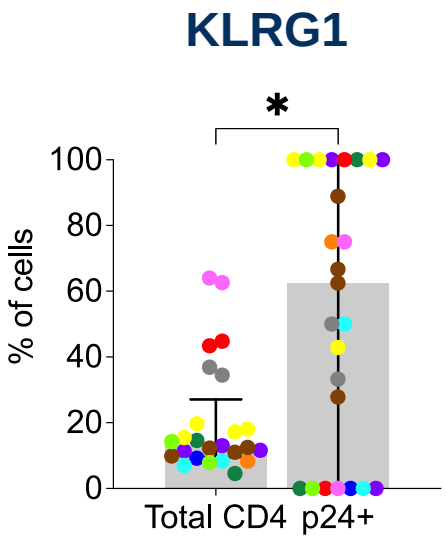


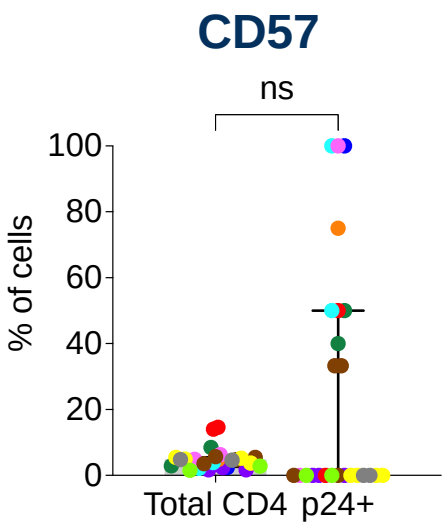


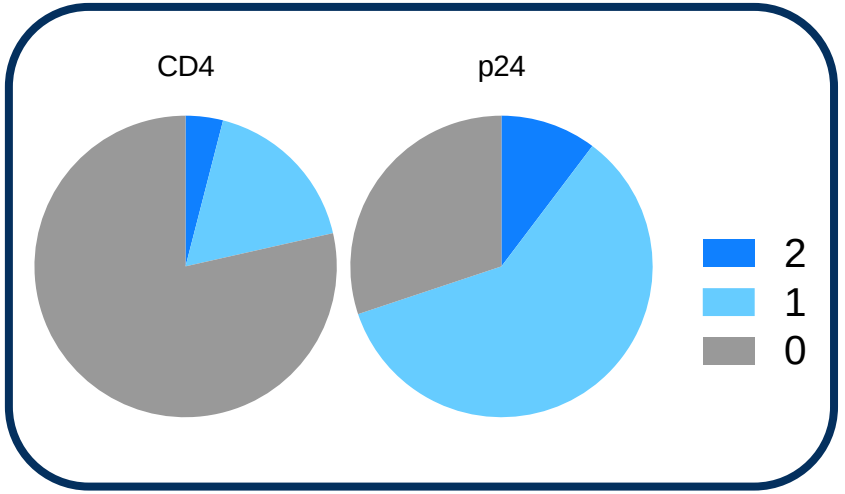
- p24+ cells express granzyme A more frequently than uninfected cells
- They also express several granzymes simultaneously

Senescence

Each colour is a participant
Each ● is a time-point



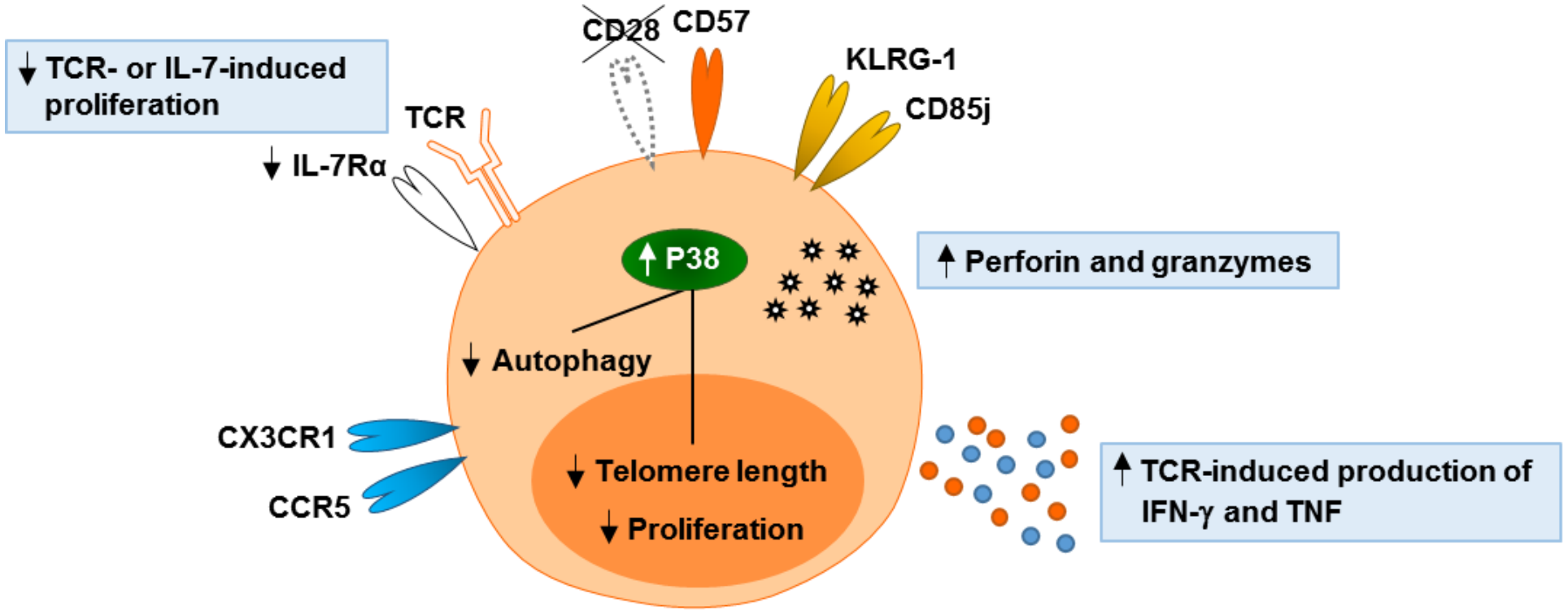




- p24+ cells express KLRG1 more frequently than uninfected cells

Summary

- p24+ cells express multiple cytokines and transcription factors, as well as granzyme and KLRG1 (and immune checkpoint and bcl-2, not shown)
- This signature is reminiscent of senescent T cells



http://liid.kaist.ac.kr/research/research2/

Targeting reservoir cells using senolytic drugs

CURRENT OPINION **Senotherapeutics for HIV and aging**

Matthew A. Szaniawski and Adam M. Spivak

A. Spivak

J. Alcami

M. Coyras

Table 1. Investigational senotherapeutics

Drug	Senotherapeutic behavior	Mechanism(s) of action	Clinical status	Tested in HIV-1 infection?	References
Dasatinib	Senolytic	Broadly active TKI	FDA approved for CML	Yes	[143▪,178,179]
Fisetin	Senolytic	PI3K/AKT/mTOR antagonist	Experimental	No	[140]
Quercetin	Senolytic	PI3K antagonist	Experimental	No	[136▪▪,143▪]
Fenofibrate	Senolytic	PPARα agonist	FDA approved for hyperlipidemia	Yes	[122,123]
Navitoclax (ABT-263)	Senolytic	BCL-2 antagonist	Experimental	No	[121,146▪]
A1331852	Senolytic	BCL-XL antagonist	Experimental	No	[141]
A1155463	Senolytic	BCL-XL antagonist	Experimental	No	[141]
Venetoclax (ABT-199)	Senolytic	BCL-2 antagonist	FDA approved for CLL	Yes	[150,151]
Piperlongumine	Senolytic	GSTP1 antagonist	Experimental	No	[124,125]
Tanespimycin (17-AAG)	Senolytic	HSP90 inhibitor	Experimental	Yes	[126–128]
Radicilol	Senolytic	HSP90 inhibitor	Experimental	No	[129]
Geldanamycin	Senolytic	HSP90 inhibitor	Experimental	Yes	[129,130]
FOXO4-related peptide	Senolytic	FOXO4 antagonist	Experimental	No	[131]
UBX0101	Senolytic	MDM2/p53 antagonist	Experimental	No	[132]
Panobinostat	Senolytic	HDAC inhibitor	FDA approved for multiple myeloma	Yes	[172,173]
Metformin	Senolytic/ senomorphic	AMPK agonist and glycerophosphate dehydrogenase (mGPD) inhibitor	FDA approved for T2DM	No	[138]
NBD peptide	Senomorphic	IKK inhibitor	Experimental	No	[133]
Rapamycin	Senomorphic	mTOR inhibitor	FDA approved for immune suppression	Yes	[158,159]
Everolimus	Senomorphic	mTOR inhibitor	FDA approved for immune suppression	Yes	[158]
Ruxolitinib	Senomorphic	JAK1/JAK2 inhibitor	FDA approved for myeloproliferative diseases	Yes	[162,164]
KU-60019	Senomorphic	ATM kinase inhibitor	Experimental	No	[134]
Mmu-miR-291a-3p	Senomorphic	TGFRB2 antagonist	Experimental	No	[135]

Szaniawski & Spivak, Curr Op HIV/AIDS 2020

Targeting reservoir cells using senolytic drugs

NCT05780073 Recruiting

Safety and Impact of **Dasatinib** on Viral Persistence and Inflammation in People With **HIV** Under Antiretroviral Treatment

Conditions

HIV Infection Primary

Locations

Badalona, Barcelona, Spain

Beatriz Mothe Pujadas

NCT05527418 Recruiting

Safety, Tolerance and Antiretroviral Activity of **Dasatinib**: a Pilot Clinical Trial in Patients With Recent HIV-1 Infection

Conditions

Recent HIV-1 Infection

Locations

Barcelona, Spain

https://clinicaltrials.gov

Conclusions

- Genetically intact genomes are rapidly archived in the reservoir and persist on ART
- The reservoir decays faster in people who received ART early
- These cells present very peculiar characteristics (VLA-4), including a senescent-like phenotype, suggesting that senolytic drugs may reduce the HIV reservoir

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The study participants!

www.chomontlab.com