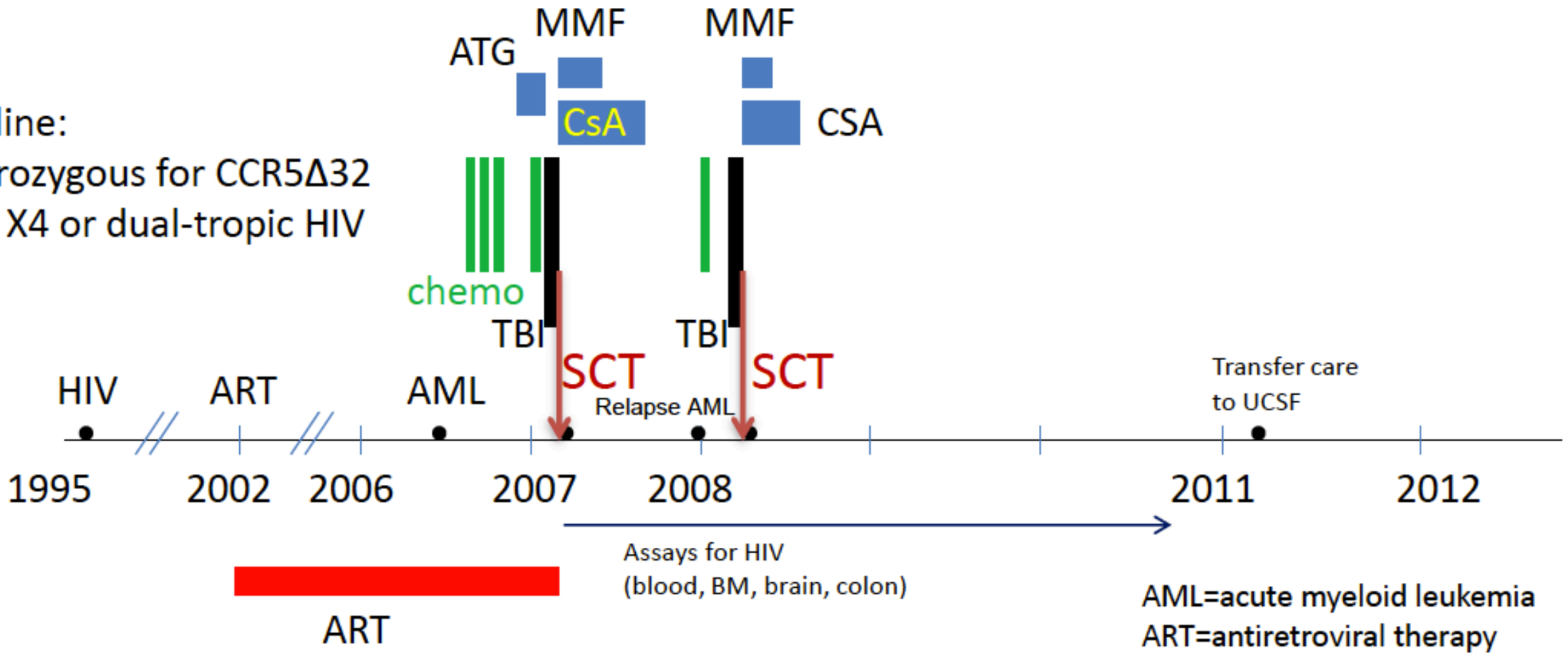
HIV Persistence, Eradication and Cure: Role of the CNS

Ron Ellis
UCSD HIV Neurobehavioral Research Center
University of California, San Diego

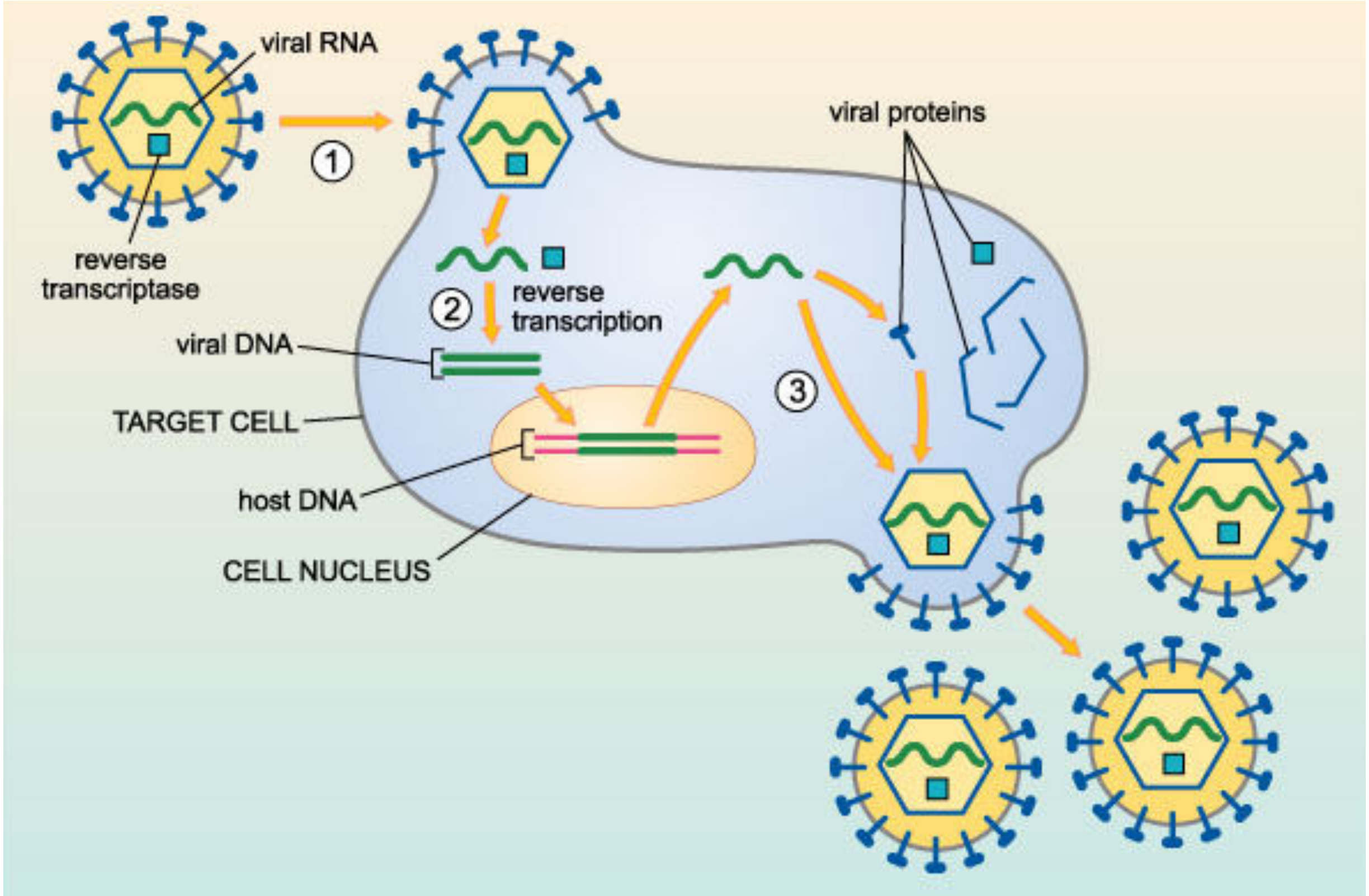
Background: the Berlin Patient

Baseline:
Heterozygous for CCR5Δ32
2.9% X4 or dual-tropic HIV

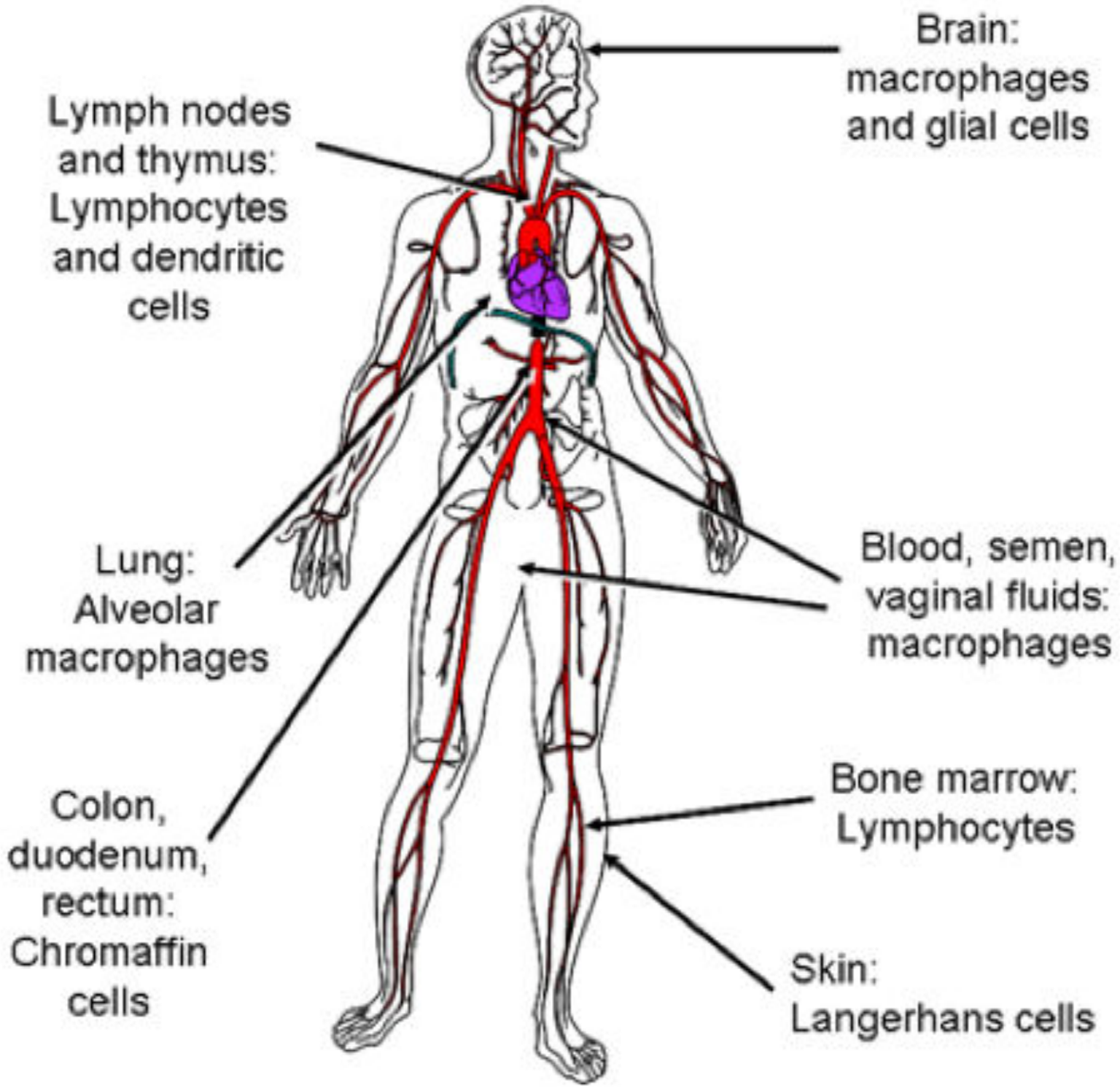


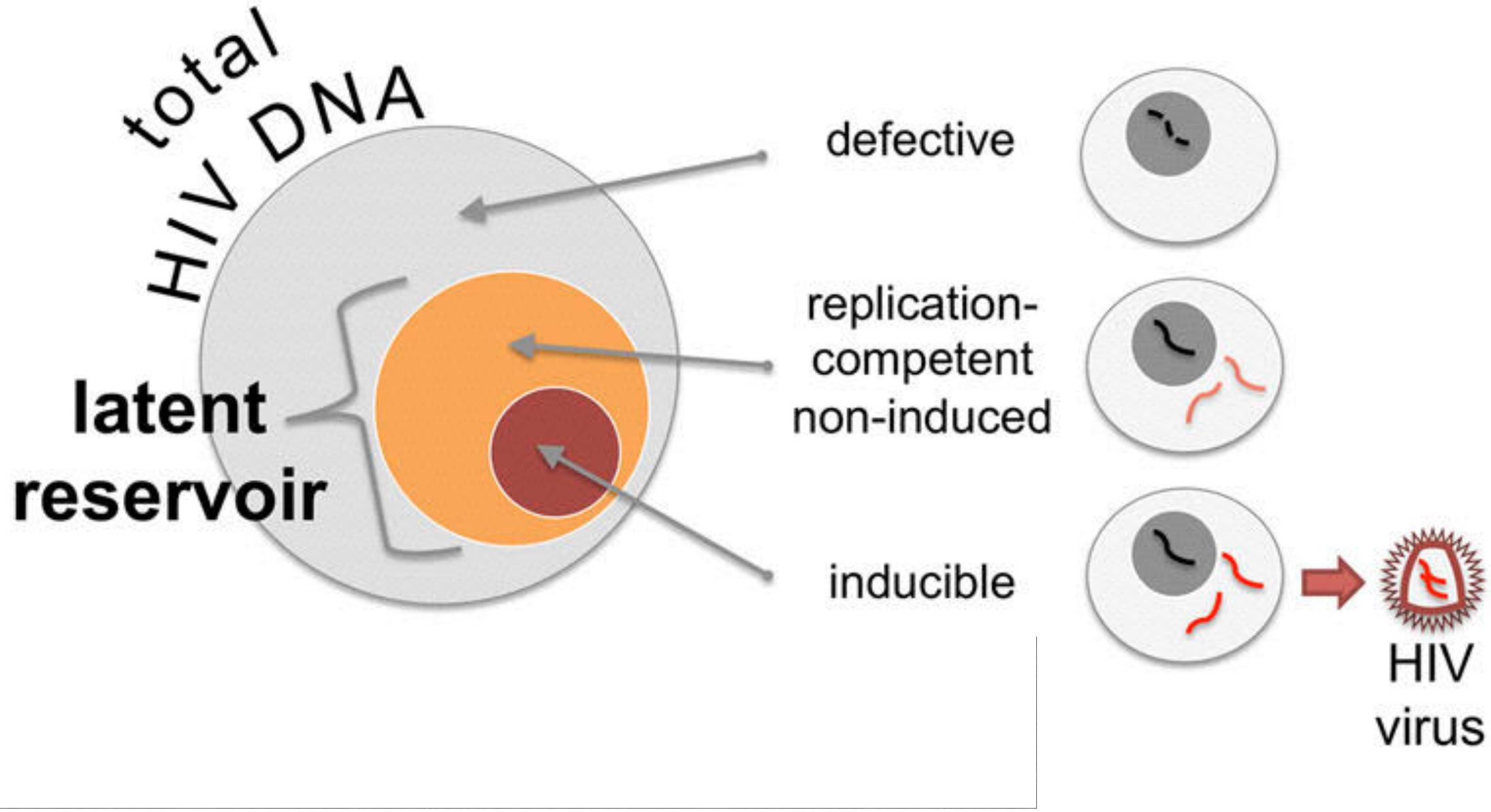
Hütter et al NEJM 2009

AML=acute myeloid leukemia
ART=antiretroviral therapy
ATG=antithymocyte globulin
BM=bone marrow
CsA=cyclosporine A
LN=lymph node
LP=lumbar puncture
MMF=mycophenolate mofetil
SCT=stem-cell transplant
TBI=total body irradiation


viral RNA
reverse transcriptase
1
viral proteins
2
reverse transcription
viral DNA
3
TARGET CELL
host DNA
CELL NUCLEUS

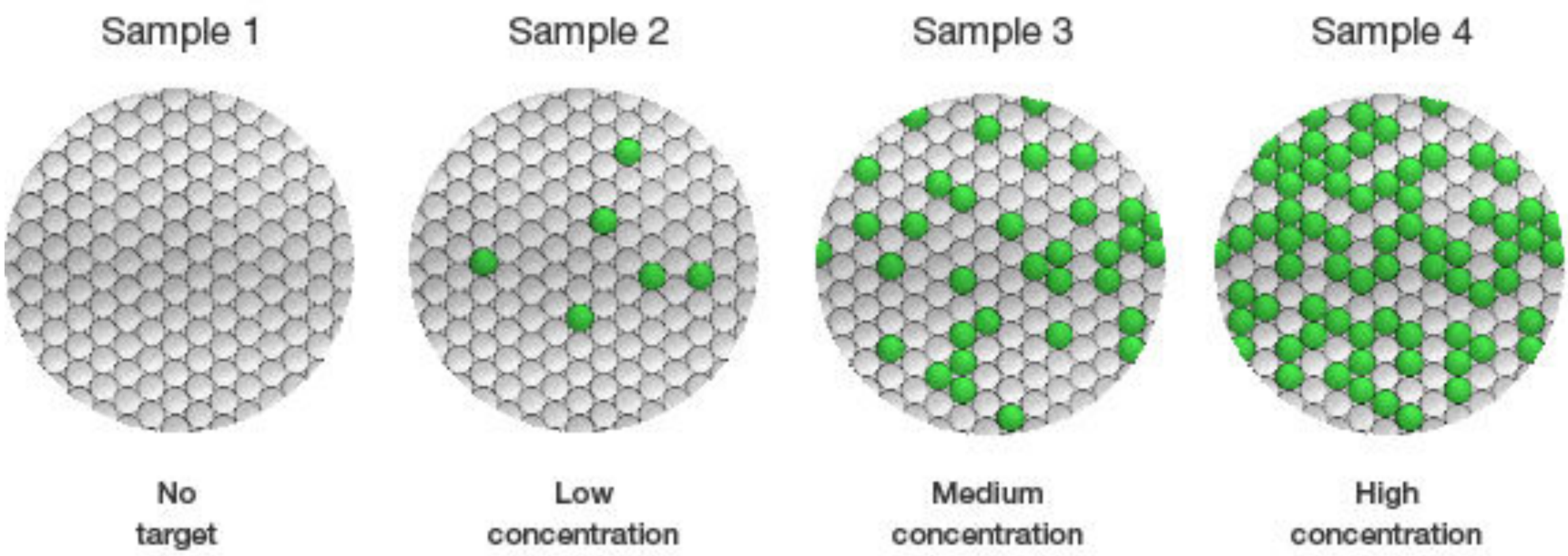
Reservoir sites





Cockerham and Deeks, 2014

Droplet digital PCR (ddPCR)

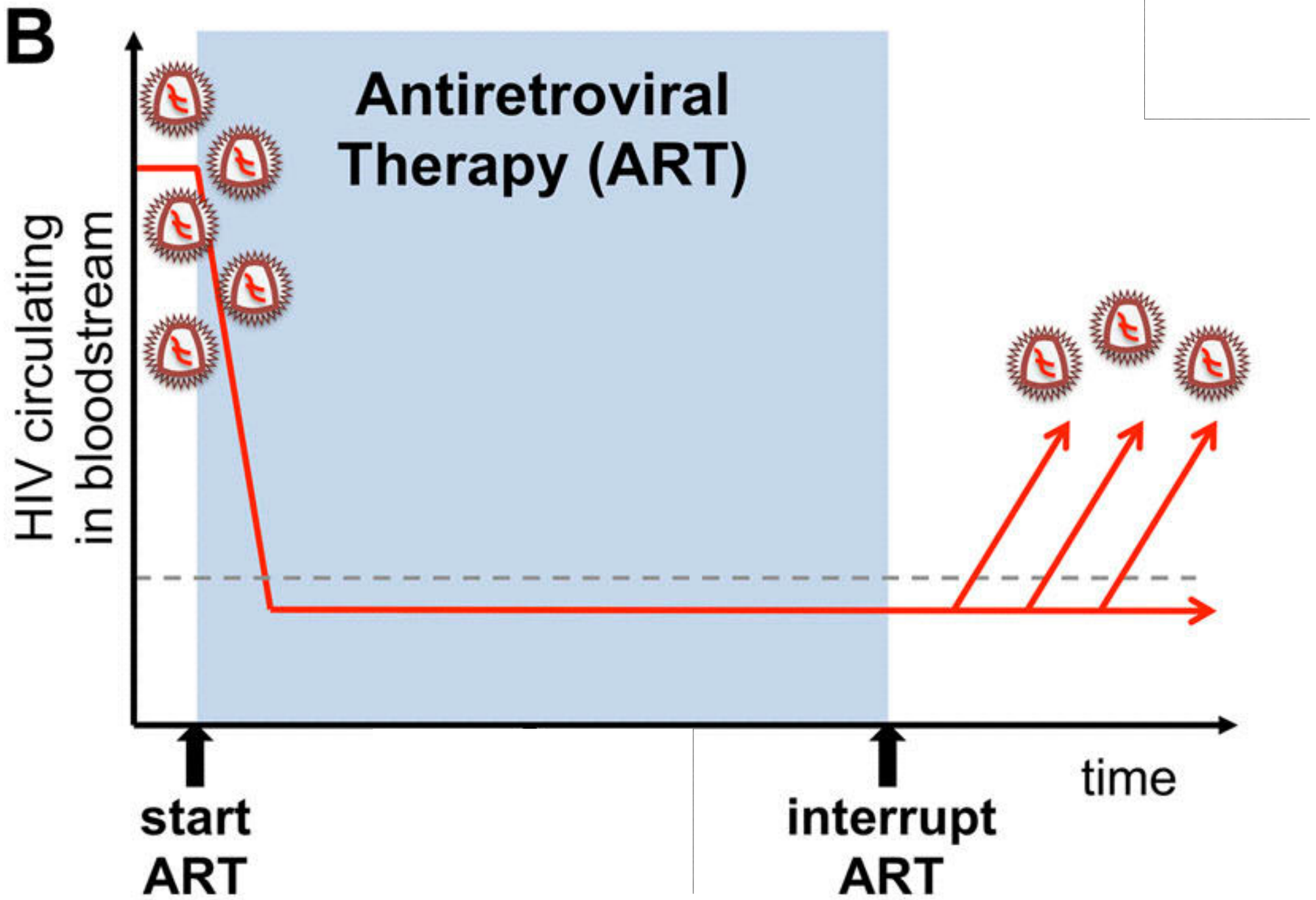


Pilot study Detecting HIV DNA in Brain in suppressed individuals

	Antemortem Plasma and CSF HIV RNA	Postmortem Brain HIV DNA
Brain tissue samples N=15	Detectable N=11	Detectable 10/11
	Undetectable N=4	Detectable 3/4

Replication Competence of HIV DNA from Brain Tissue

- Extract Brain HIV DNA, amplify and dilute
- Barcode and screen for full-length (FL) sequences
- Ligate FL (N=~30/sample) HIV DNA into SMRTbell (™) library complexes
- Consensus sequence FL HIV DNA
- Clone remaining intact FL HIV DNA into expression vectors
- Demonstrate infection of CD4+ T-cell and evaluate replication kinetics



Cockerham and Deeks, 2014

Probing the HIV Reservoir: Cure/Eradication Interventions

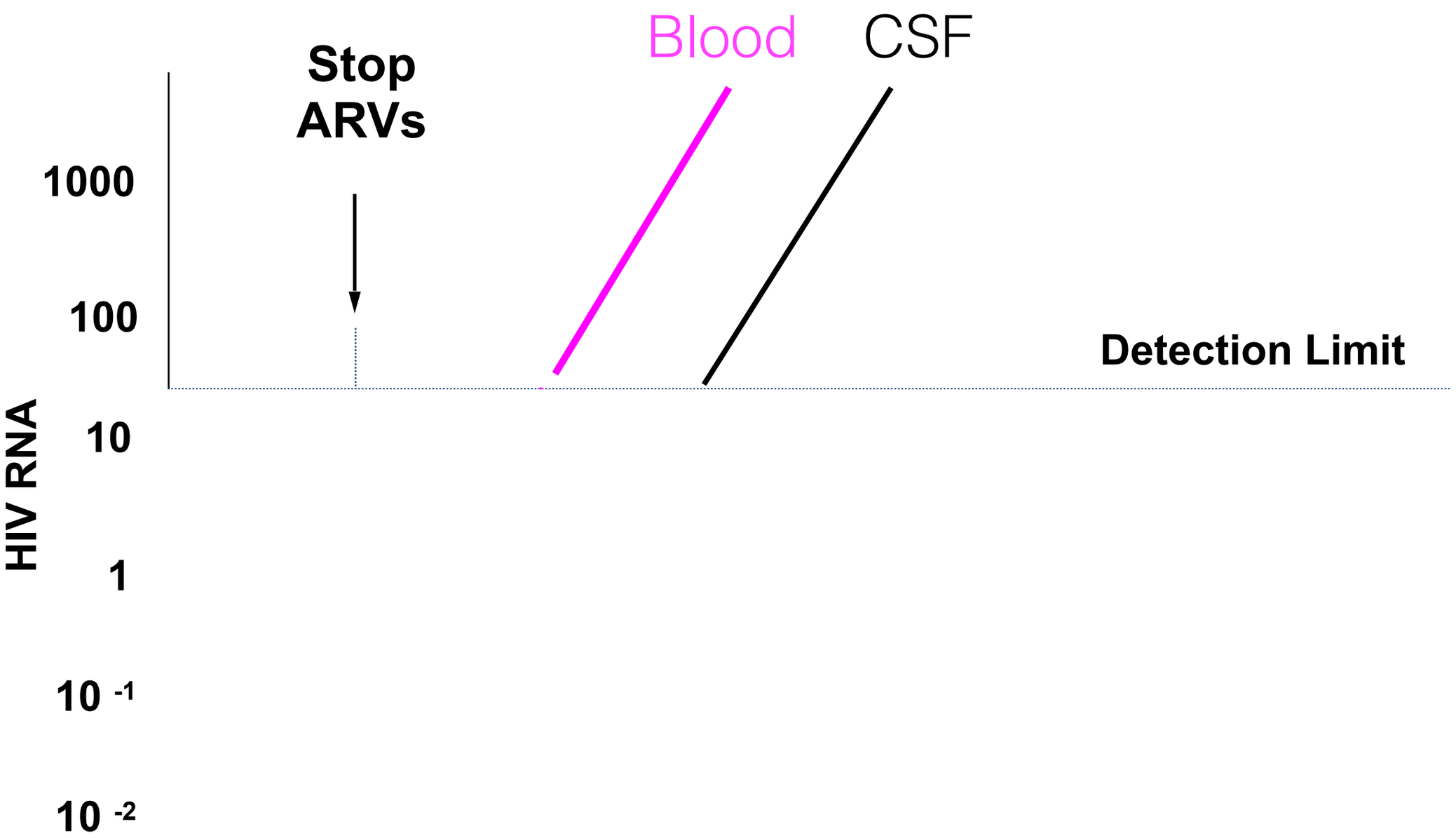
- HDAC inhibitors: vorinostat, panobinostat
- VRC01 – [A5342] (Impact of VRC01 on HIV Persistence)
- Romidepsin –[A5315] (Romidepsin to Awaken HIV)
- Anti-PD-L1 Antibody – [A5326] (Anti-PD-L1 Antibody in HIV-1)
- Sirolimus – [A5337] (Sirolimus Study)
- TLR7 Agonists and BNAb for HIV

VISCOUNT Cohort: Functional Cure of HIV?

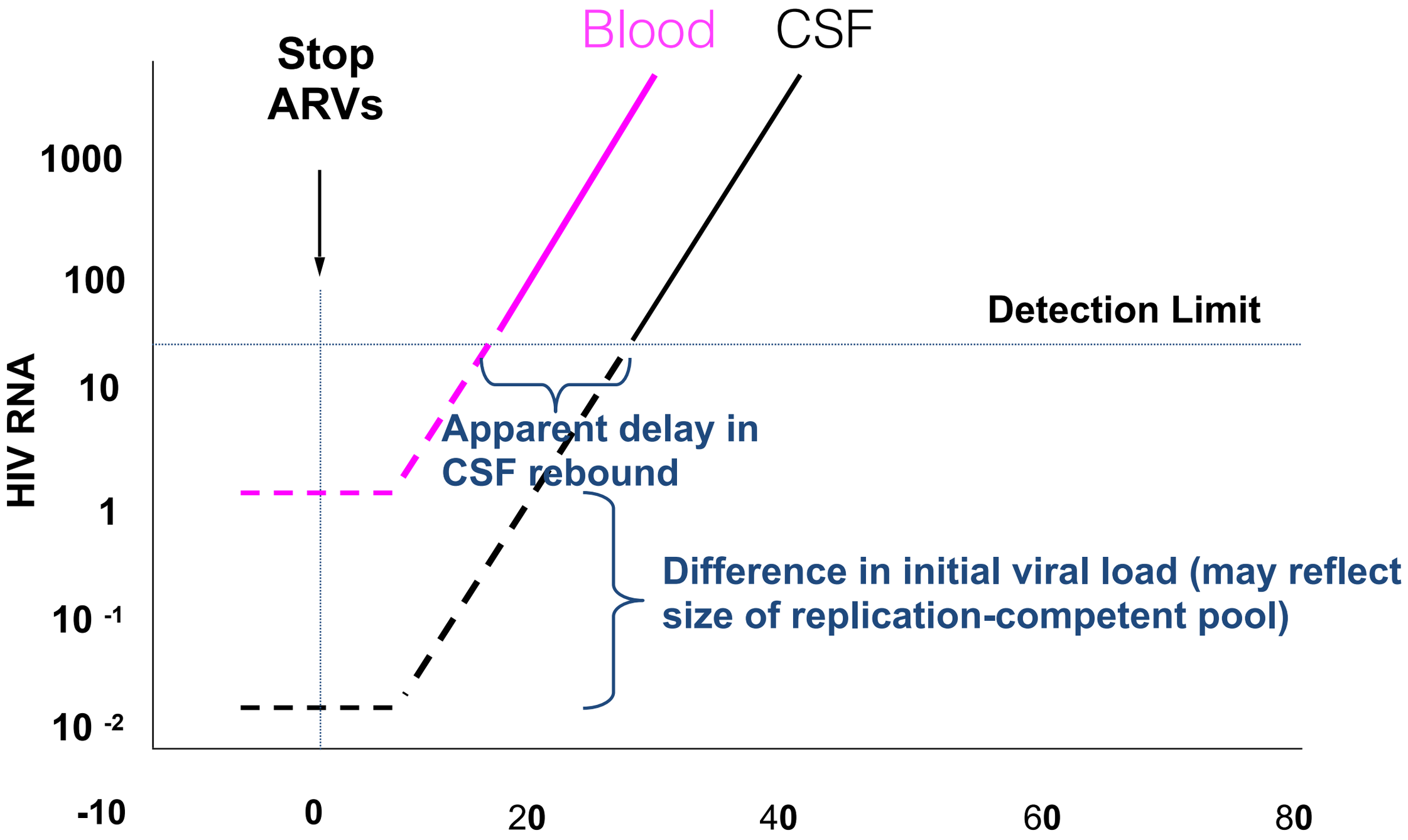
- 756 French adults started ARVs within 6 months of infection (1997 -2011), stayed on ART >1 year
- 70 subsequently interrupted ART, serial plasma VL assessed
- 56 had viral rebound
- 14 no viral rebound – all treated within 2 mos of infection

Saez-Cirion et al., PLoS Pathogens 2013

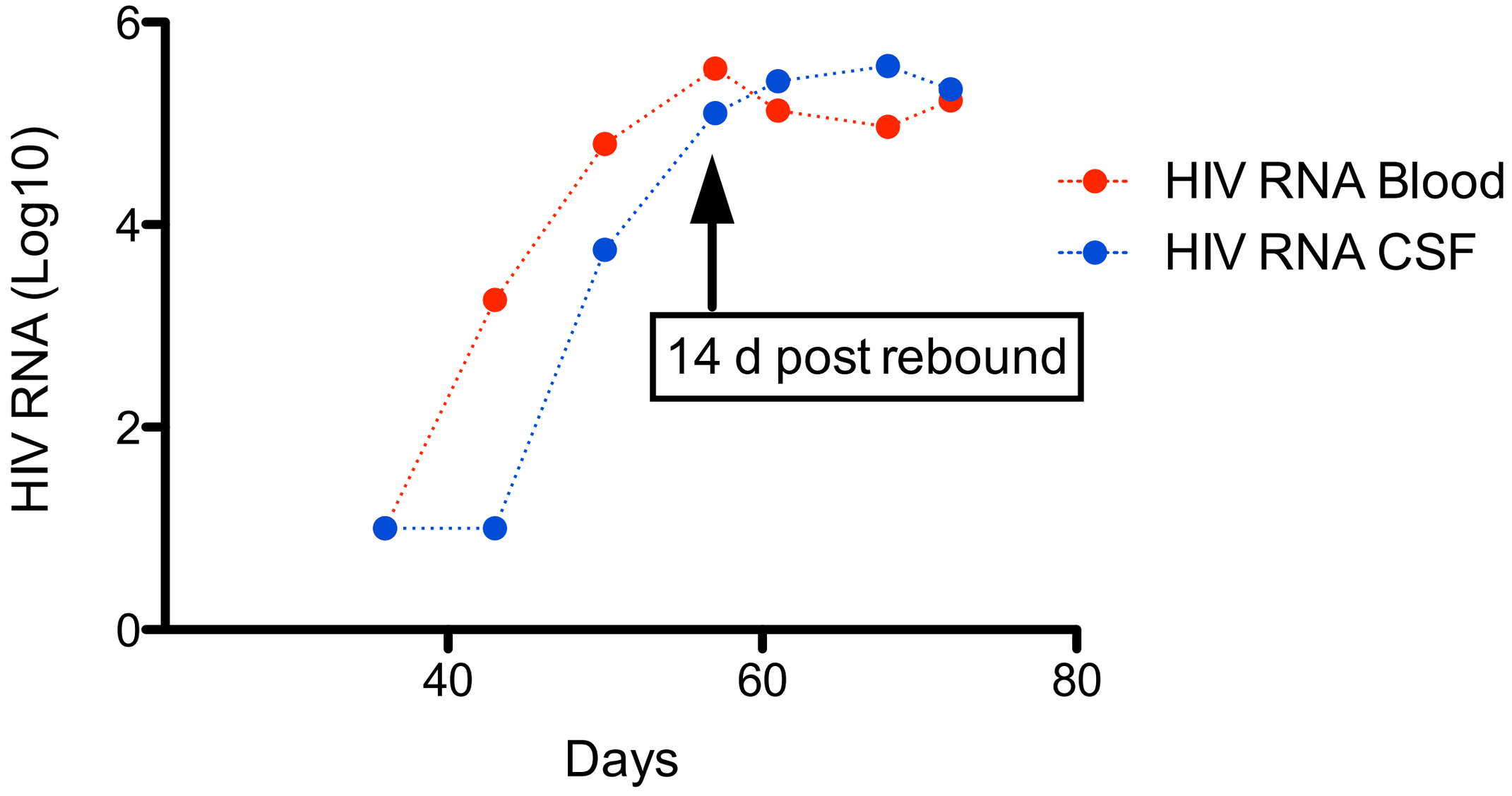
Difference in Initial Viral Load



Difference in Initial Viral Load



Viral Rebound dynamics

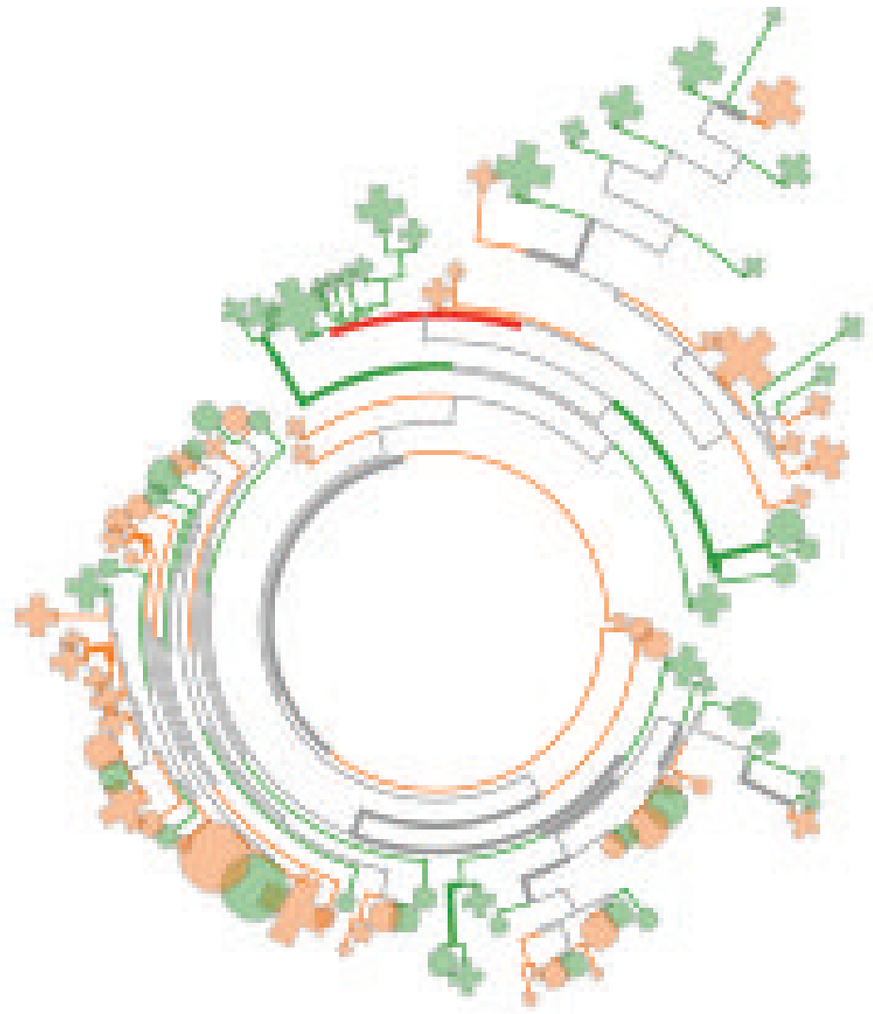


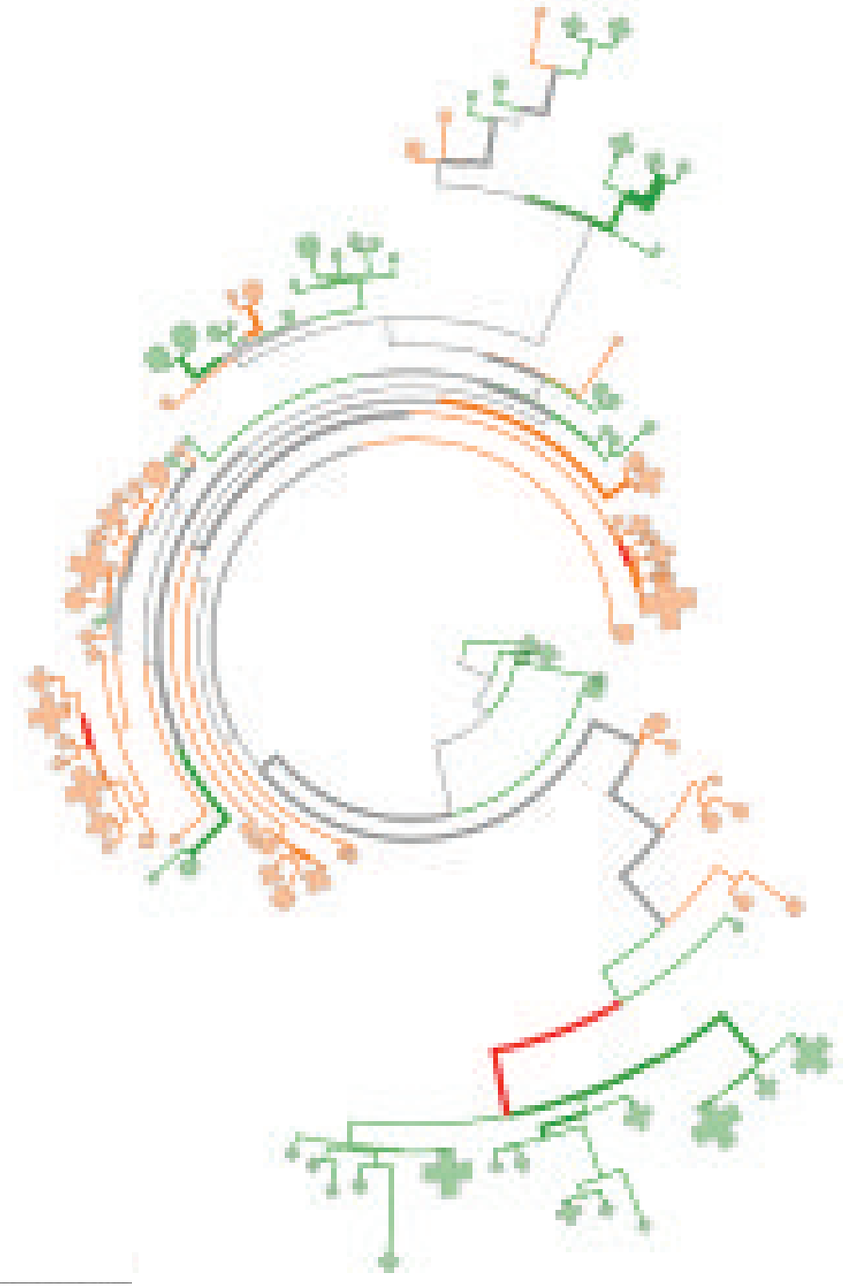
Approach

- 14 subjects interrupting ART
- 1-3 timepoints selected for each subject
- Sequencing: Roche 454 FLX Titanium platform
- HIV-1 env (C2-V3), gag (p24), and pol (partial RT)
  - cell-free HIV RNA (blood and CSF)
  - HIV DNA from CSF and blood cells

58213 rt

CA149 rt



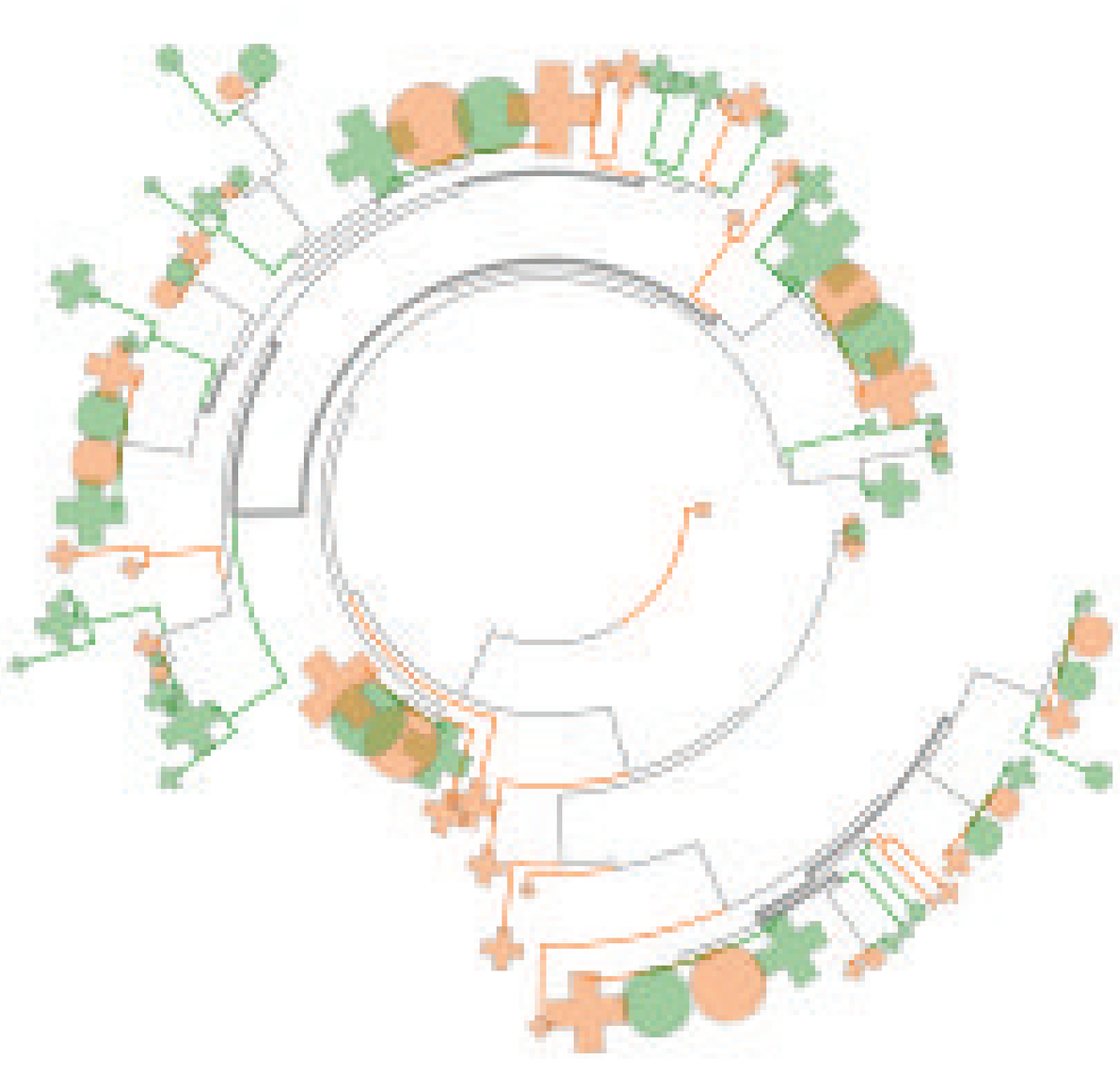


Blood plasma + CSF

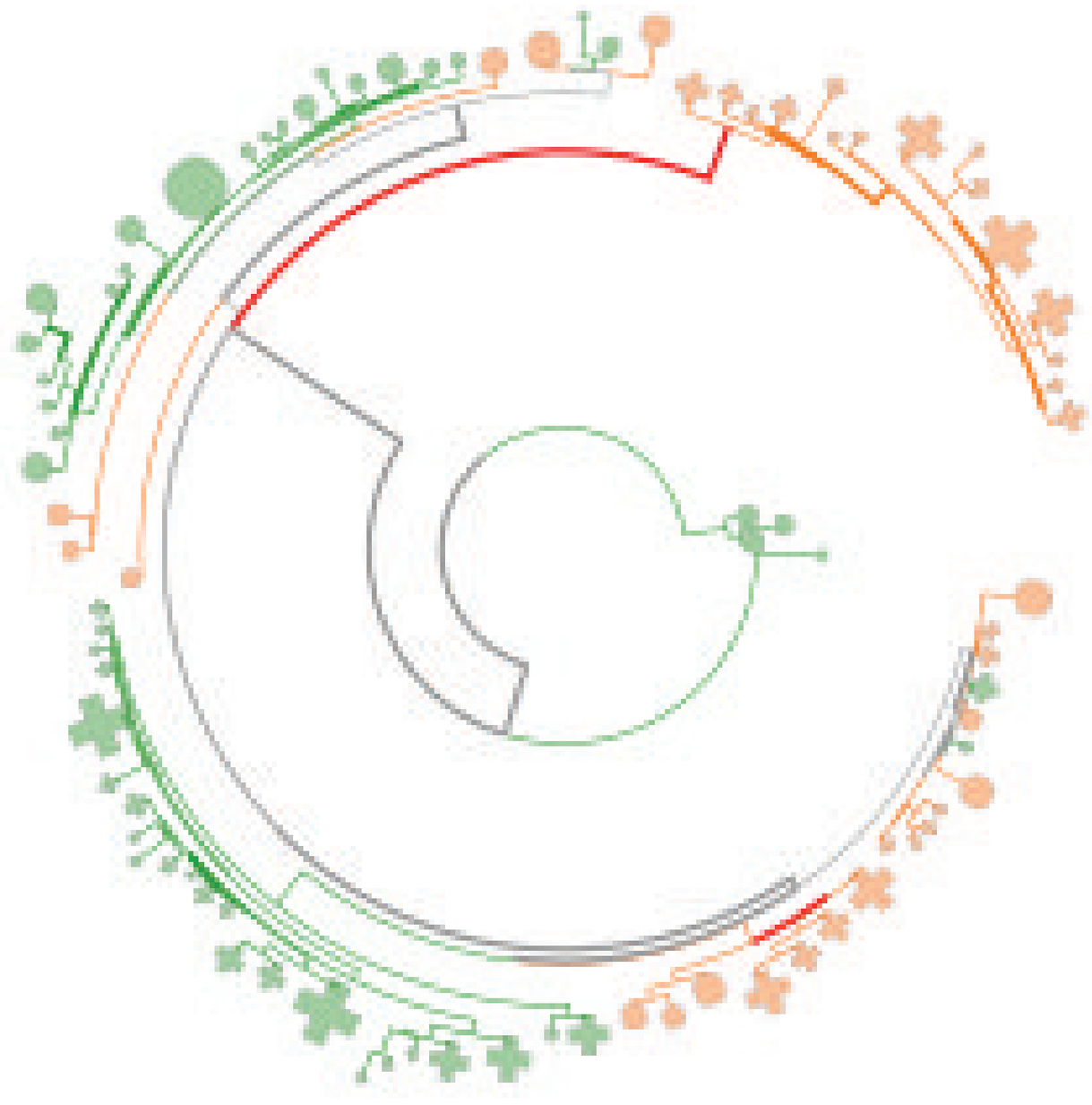
TP1 TP2 TP3

Abundance

26742 gag



24273 env



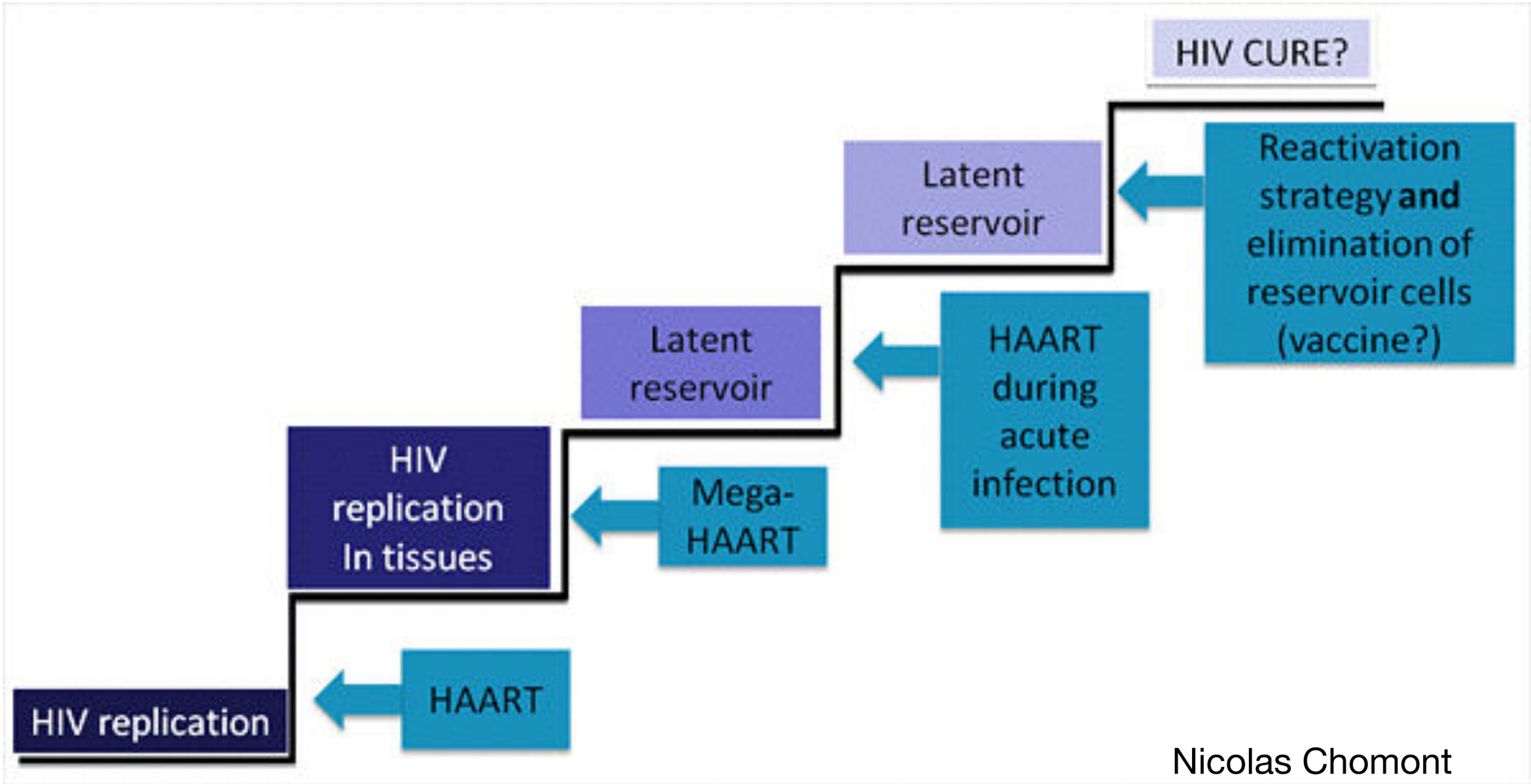
Summary

- 13/14 participants showed compartmentalization between HIV RNA in CSF and blood after ART interruption (Fst)
    - Compartmentalization present even when sampled within 2 weeks from HIV RNA rebound
        - Sequences unique to CSF found in 13/14 cases
- Additional compartmentalized viral populations emerged later in 3 pts
- Only one pt maintained genetically mixed populations for the entire study follow-up

Unanswered Questions

- What is the size and distribution of the HIV DNA population in the brain in patients who achieve durable virologic suppression with ART
- What fraction is replication competent?
- Can early ART initiation minimize the HIV DNA reservoir in the CNS, reducing the barrier to eradication?
- Do HIV DNA populations in the brain increase through clonal expansion?

A long, uphill journey



Nicolas Chomont