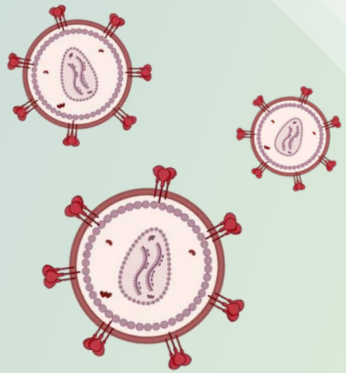
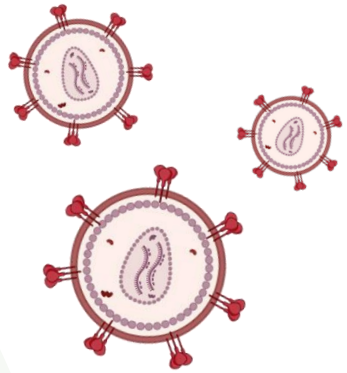
HIV CURE Research Center





13the Breach meeting

27th of November 2025

Update on projects about HIV cure in Belgium

Linos Vandekerckhove, MD, PhD

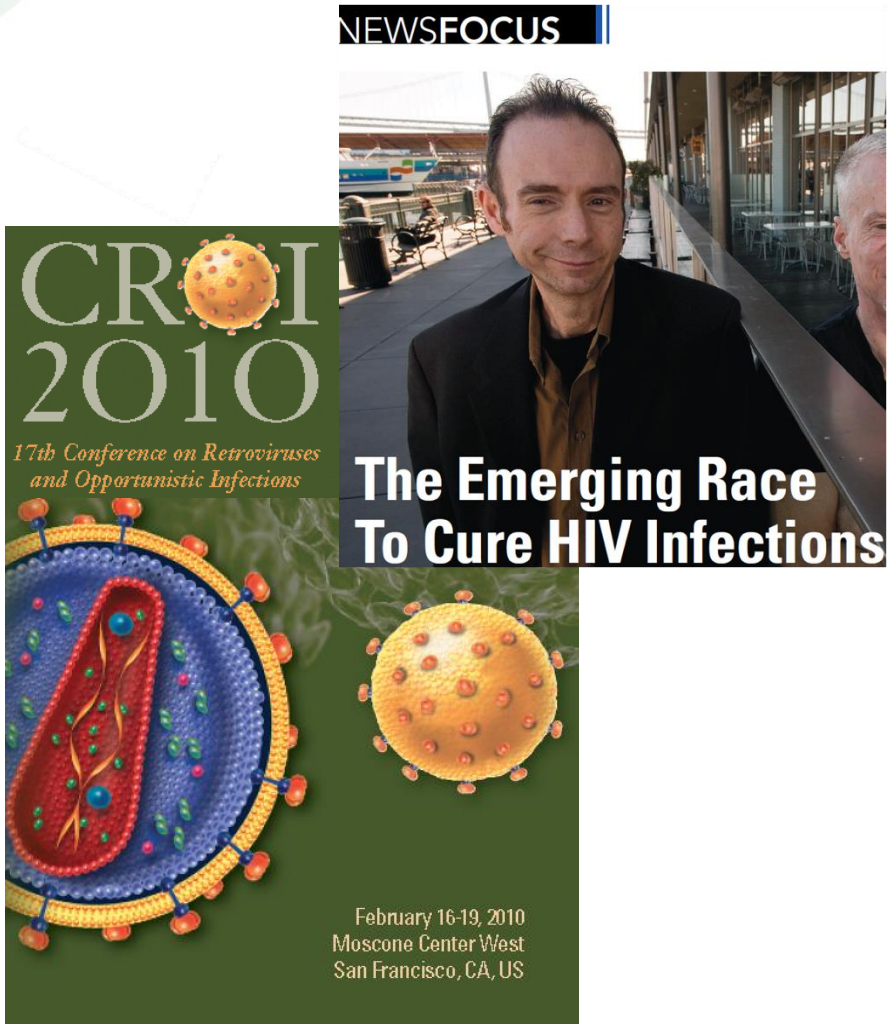
Professor in Internal Medicine and Infectious Diseases Ghent University, Belgium

Laboratory Director HIV Cure Research Center, Ghent University

Conflicts of interest statement

Disclosure: consulting or advisor fees for Abbvie, Shionogi, Gilead Sciences and Viiv Healthcare

Looking back -”early days” in HIV cure research



Meeting Coverage > CROI

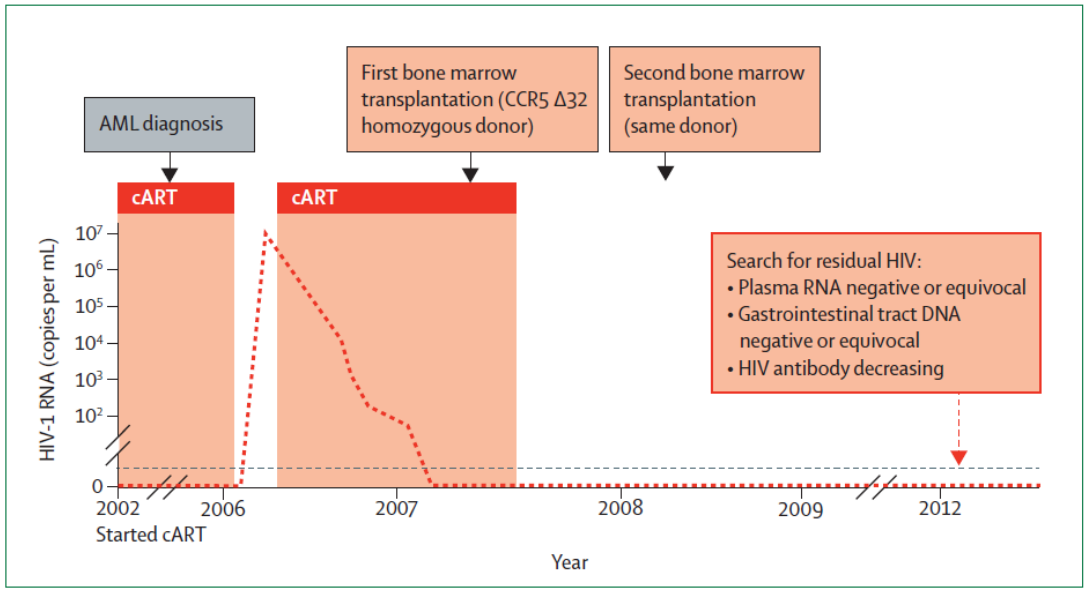
CROI: Fauci Sets High Goals for HIV Research

by Michael Smith, North American Correspondent, MedPage Today February 17, 2010

Hütter et al. 2009 NEJM; Cohen 2010 Science; Fauci 2010 CROI

HSCT can cure HIV but is not safe or scalable

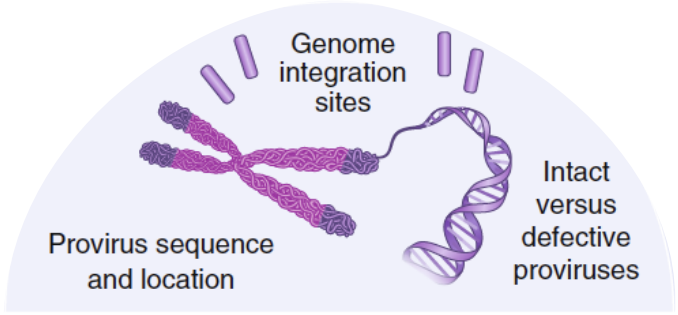
- At least 7 cases of HIV cure following hematological stem cell transplantion (HSCT) among people with HIV and hematological cancers … and more cases will follow*
- "HSCT" is too risky (~20% mortality) to be used more broadly
- However, these cases are important proof-of-principle that HIV can be cured



Hütter et al. 2009 NEJM; Kent et al. 2013 Lancet ID

The HIV reservoir is the main barrier to cure

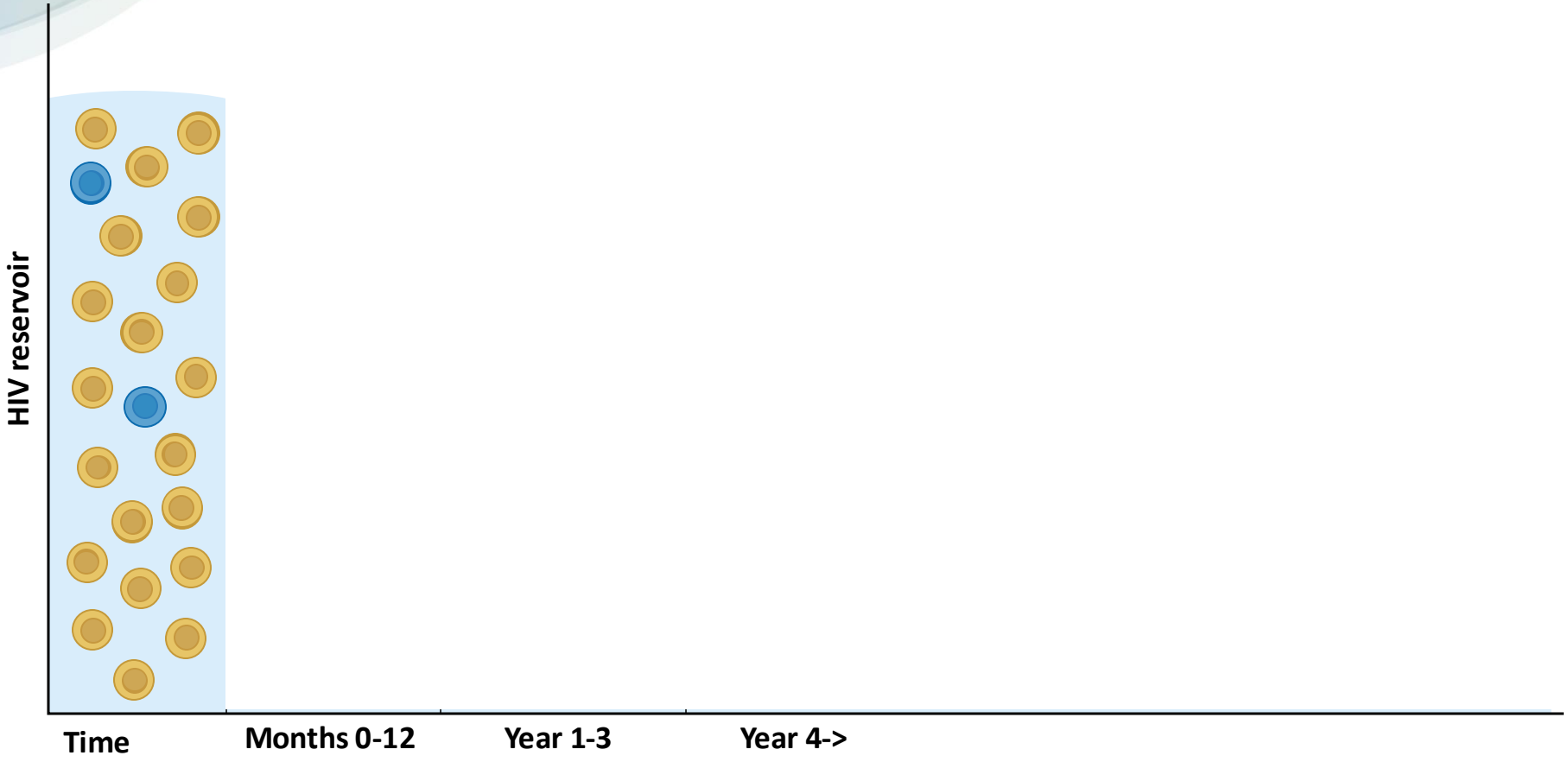
HIV integrates into human DNA and can be found through-out the body



Landscape of the HIV reservoir

Deeks et al. 2021 Nat Med

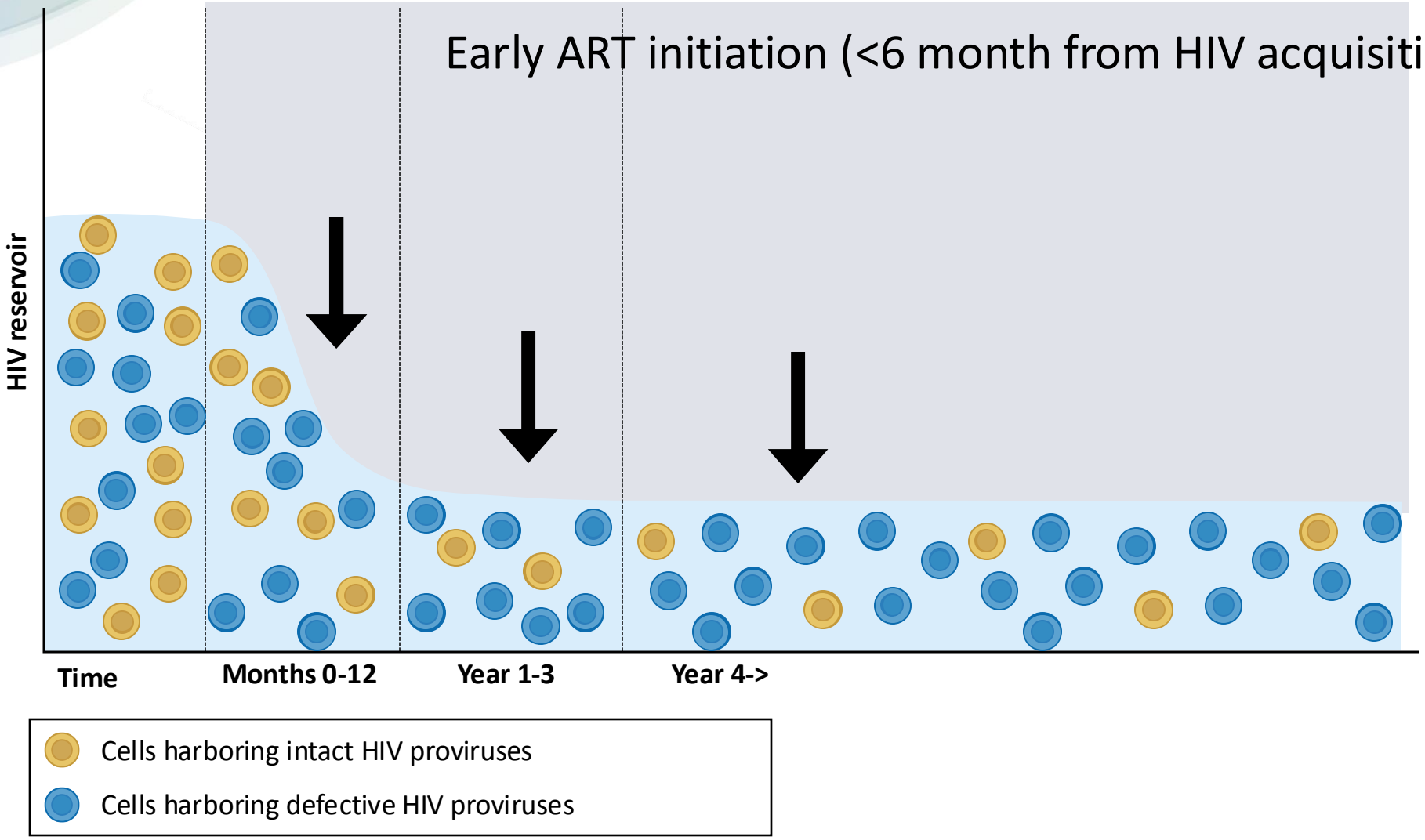
ART reduces the HIV reservoir



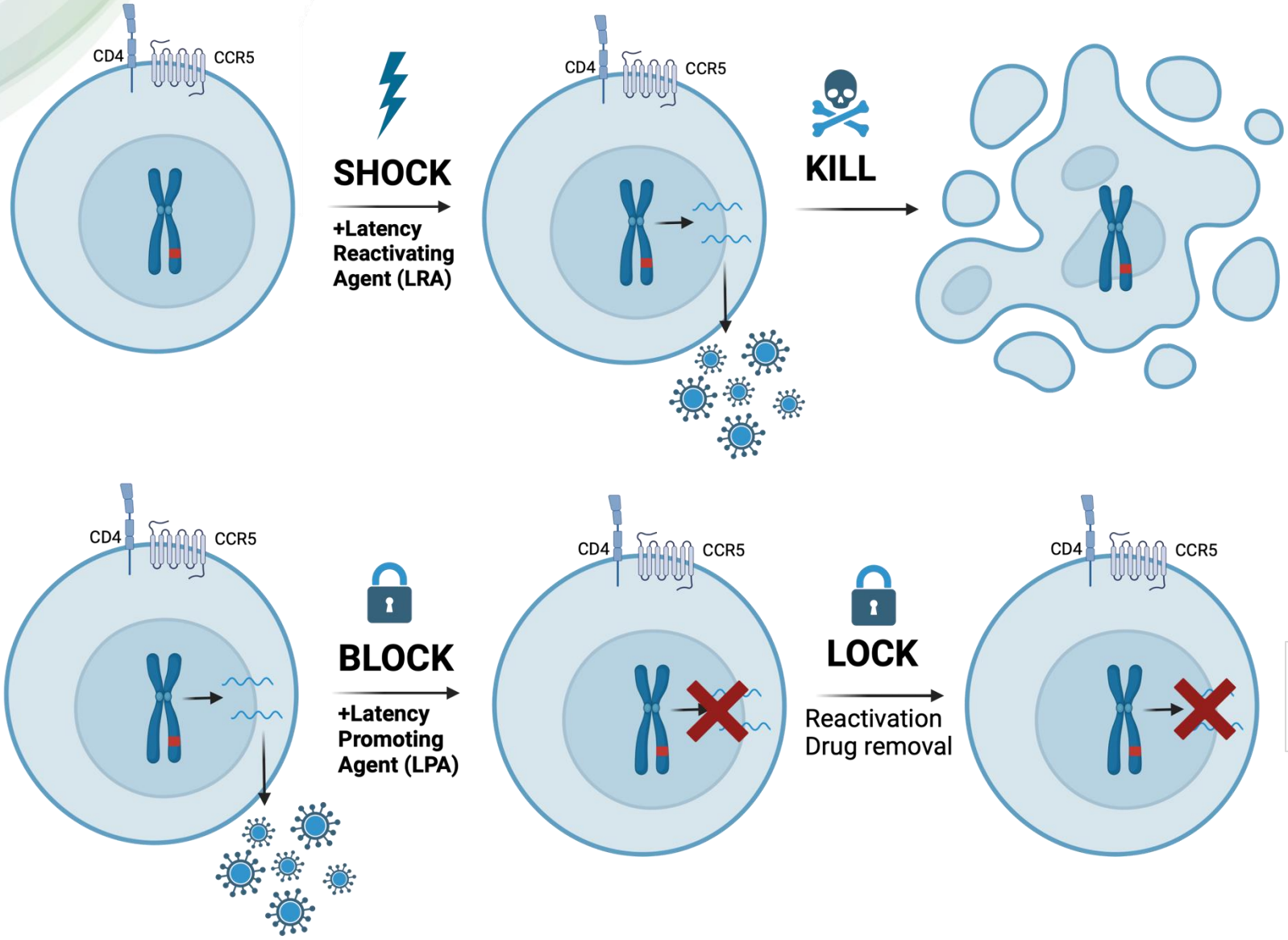
- After 4-7 years on ART, the size of the HIV reservoir is more or less stable
- Most HIV DNA is 'defective' but may still be expressed and might be a source of low-grade inflammation
- The lifespan of resting CD4+ memory T cells is years
- Homeostatic proliferation of T cells is a major driver of HIV persistence

Figure adapted from Armani-Tourret et al. 2024 Nat Rev Micro

Early ART limits the reservoir but does not cure



How to cure HIV infection?



LATENCY REACTIVATING AGENTS (LRAs)

LATENCY PROMOTING AGENTS (LPAs)

Translational evidence for a block-and-lock cure

Elite controllers

→HIV infected patients who control viral replication without ART

→0.5 % of HIV population

Post-treatment controllers

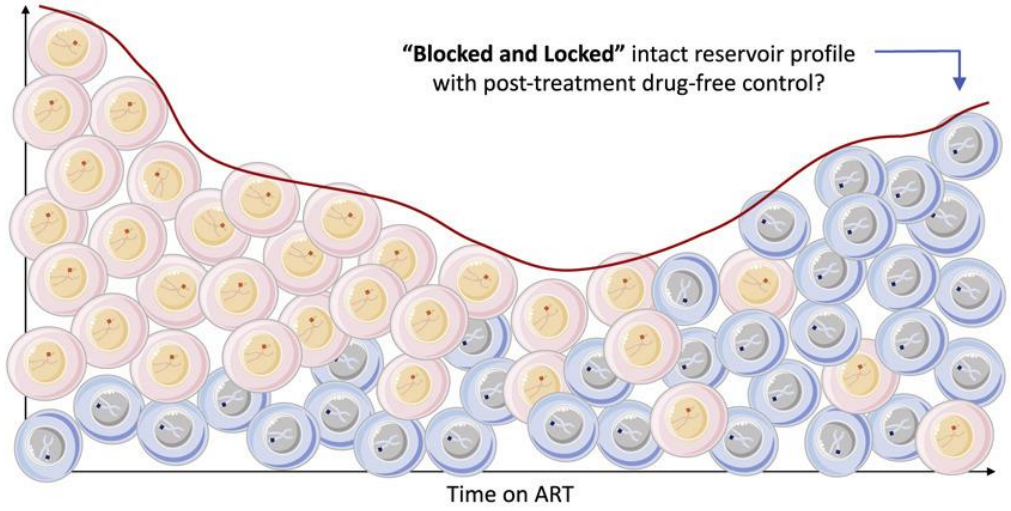
→long-term ART treated individuals who control viral replication after treatment-interruption

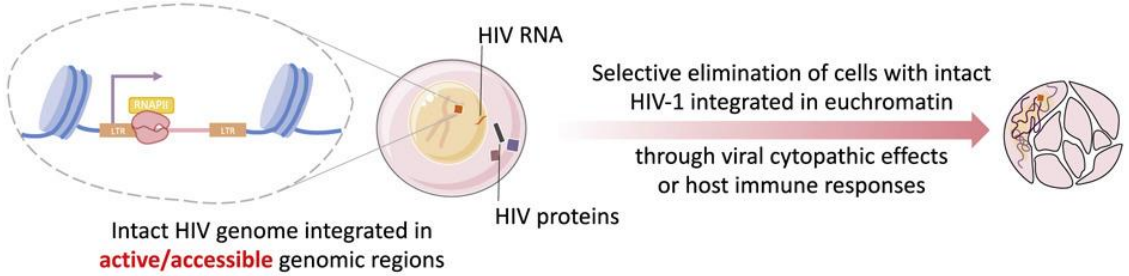
→viral reservoir characterized by large clones of intact proviruses integrated in heterochromatin regions

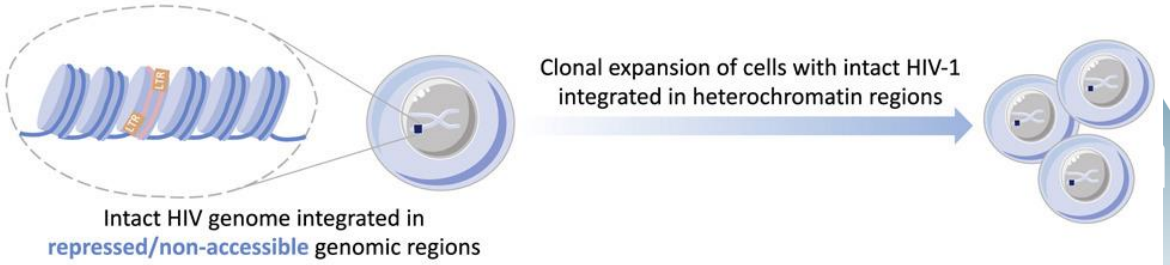
→Positive selection of deep latent provirus over time

*Jiang *et al.*, *Nature*, 2020.

*Einkauf *et al.*, *J Clin Invest*, 2019.

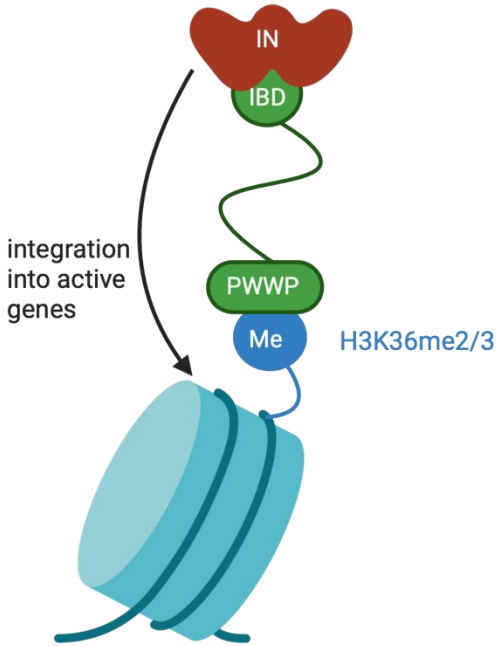


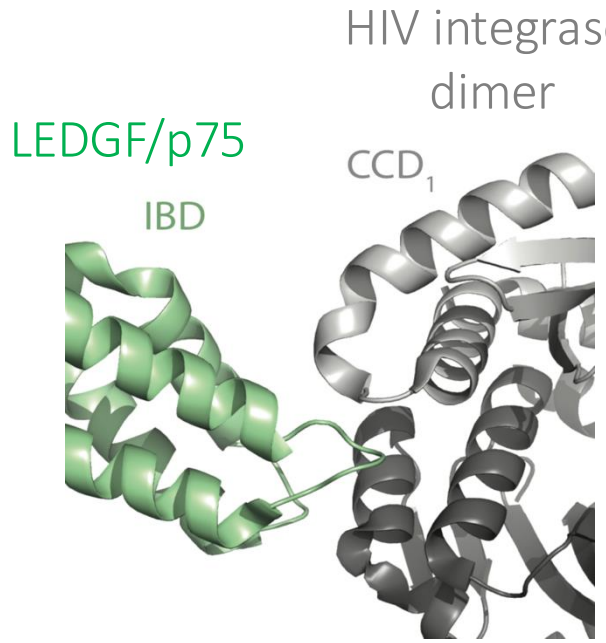




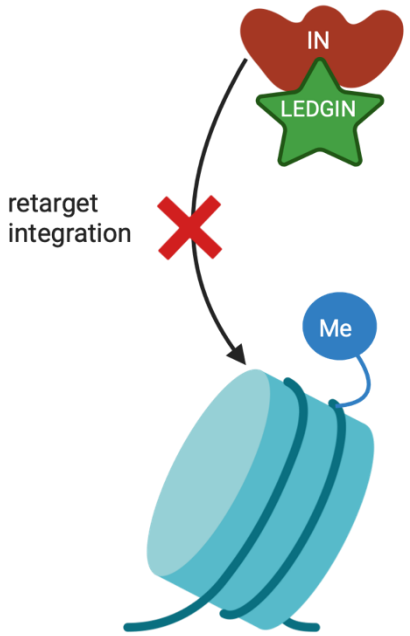
*Lian *et al.*, *Cell Host Microb*, 2022.

LEDGINs as a functional block-and-lock cure strategy





Christ *et al., Nat. Chem Biol.,* 2010.



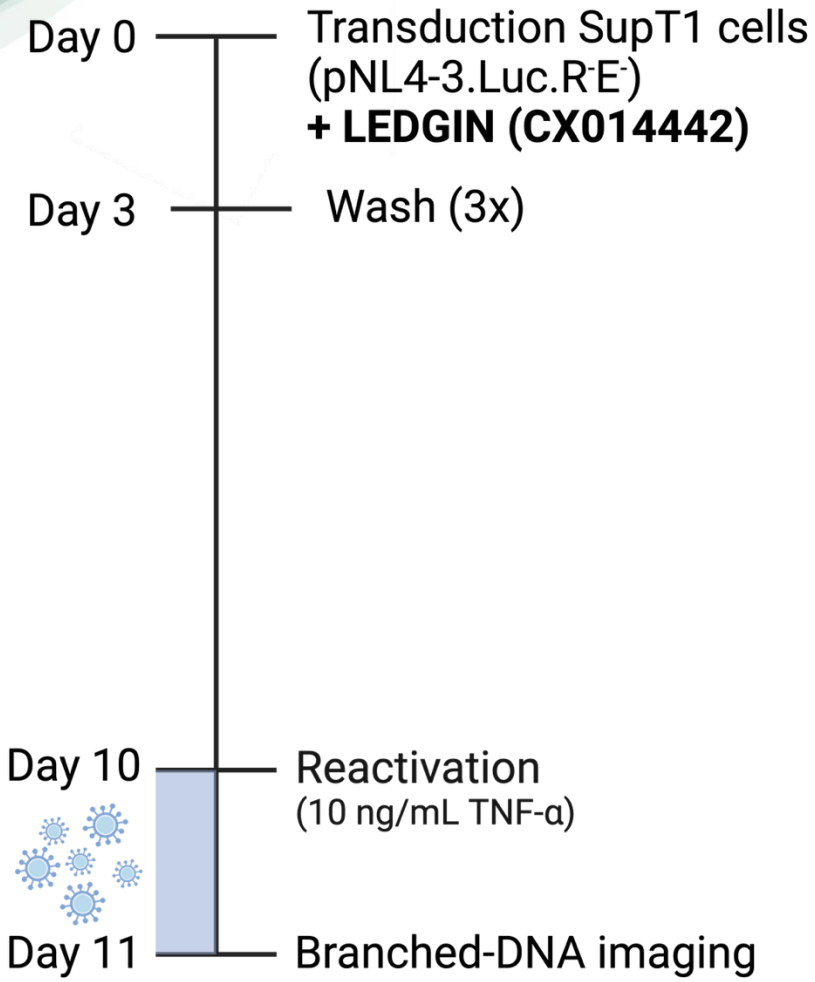
LEDGF/p75 mediates integration into active genes

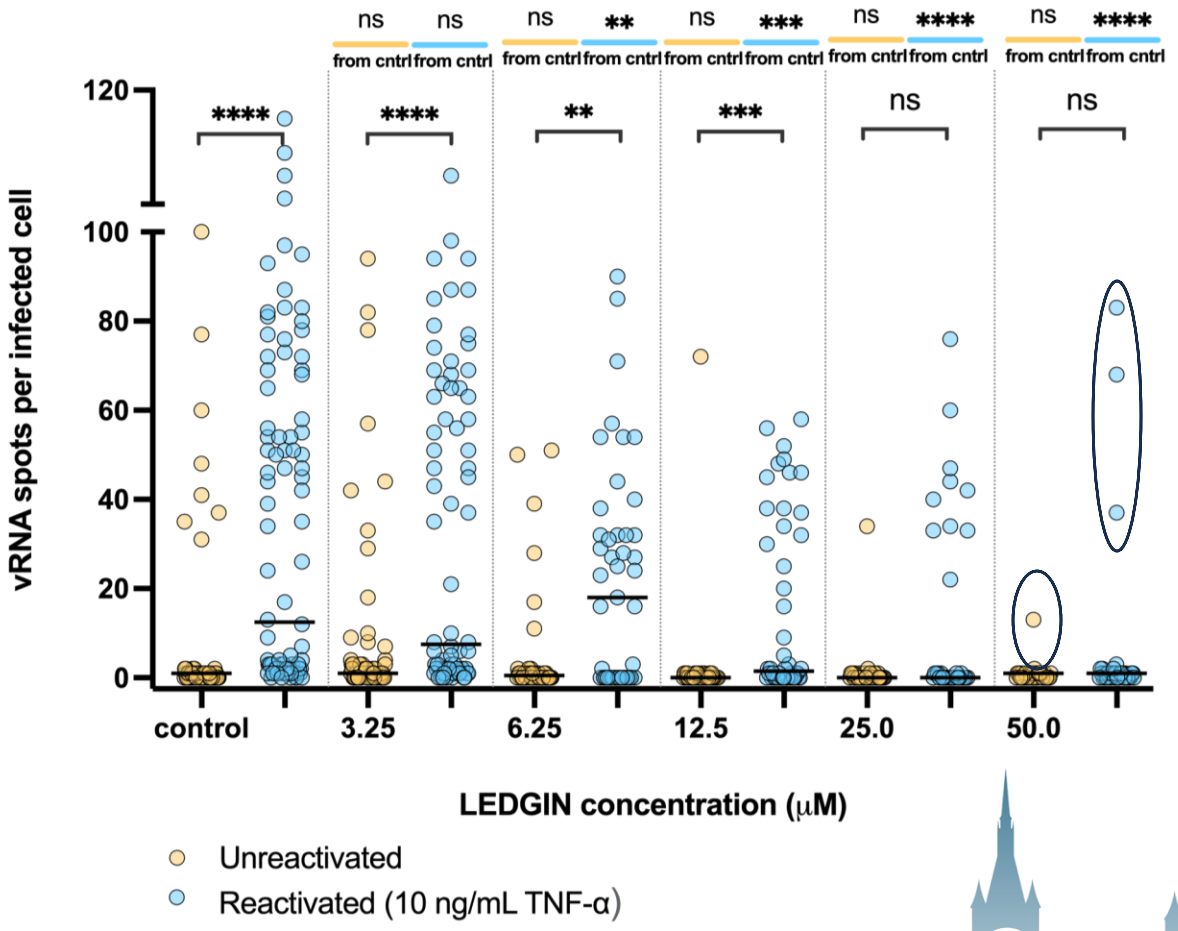
Inhibitors of LEDGF/p75-IN interaction:
LEDGINs

- ✔ Retarget integration
- ✔ Reduce HIV transcription
- ✔ Reduce HIV reactivation

*Christ *et al., Nat Chem Biol,* 2010.
*Vranckx *et al., EBioMedicine*, 2016 .
*Vansant *et al., Retrovirology*, 2019.
*Debyser *et al., Viruses*, 2019.
*Vansant *et al., NAR*, 2020.
*Bruggemans *et al., Antimicrob Agents Chemother*, 2021.
*Janssens *et al*., *mBio*, 2022.

LEDGINs in a block-and-lock cure

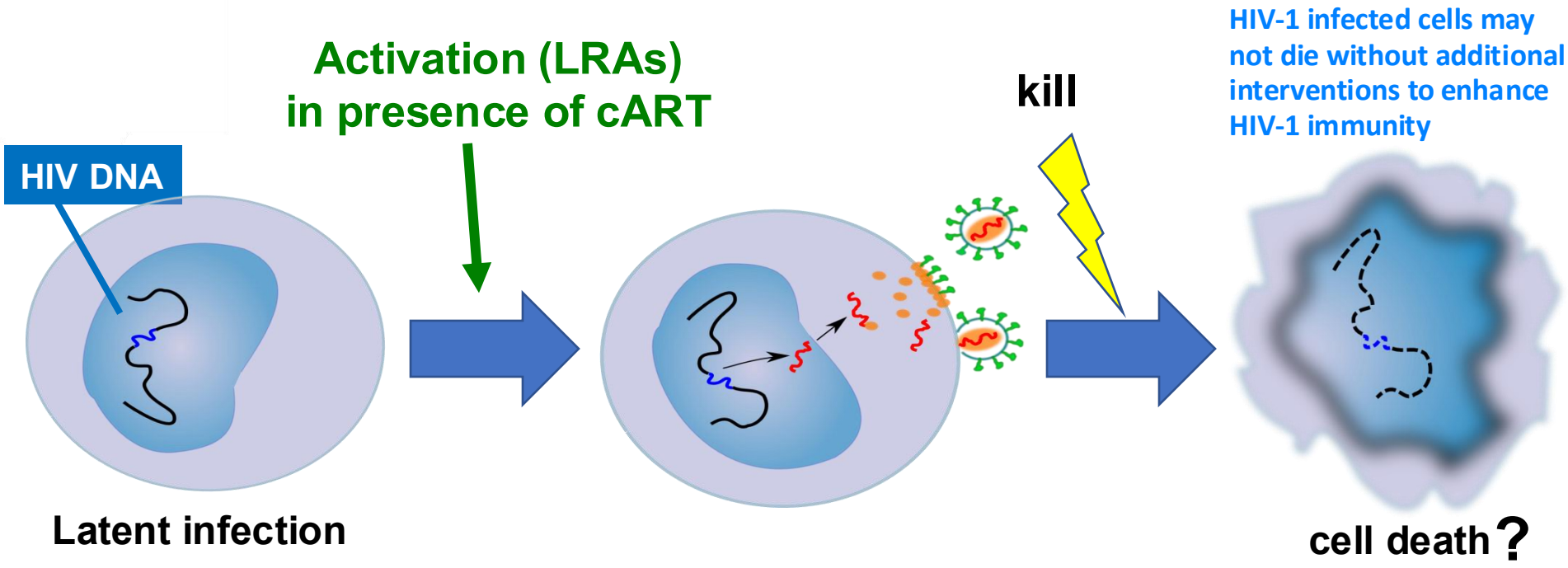




*dot= number of vRNA spots per infected cell
*line= median

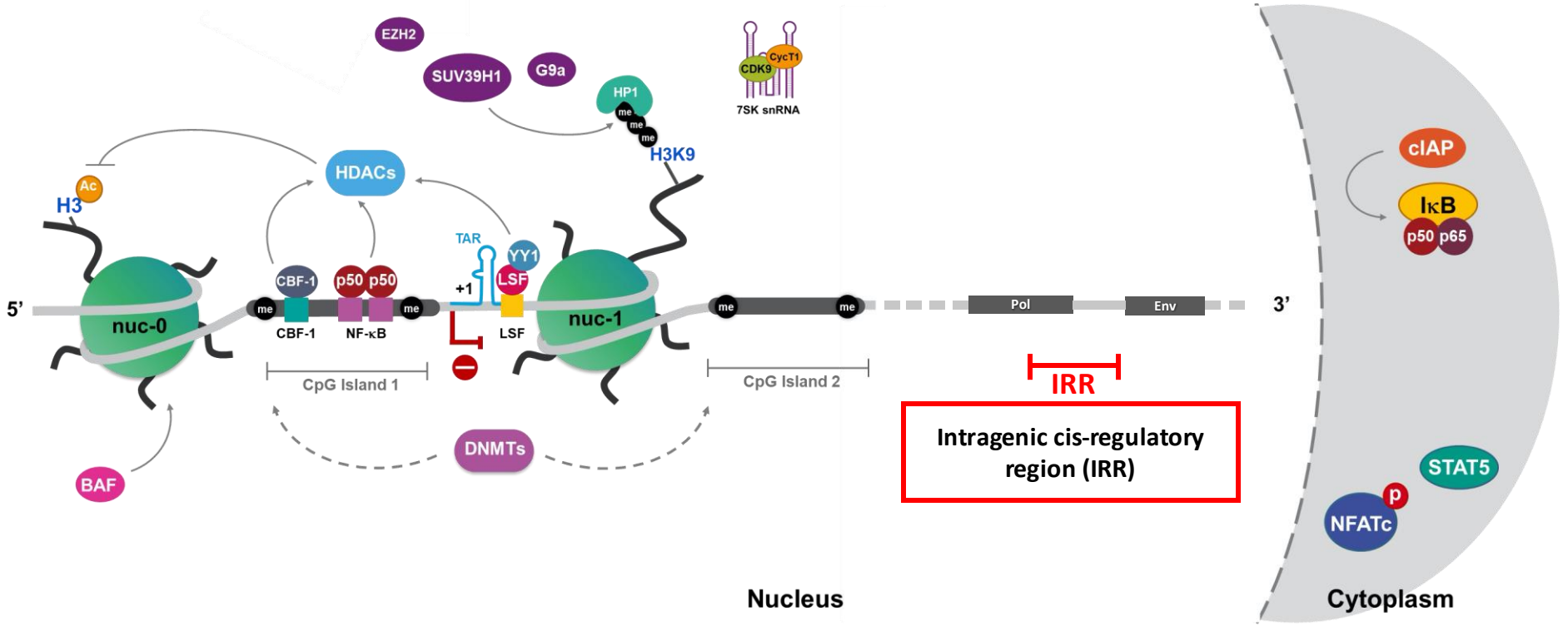
*Janssens *et al.*, *mBio*, 2022.

The « shock-and-kill » strategy is the most explored approach to reduce the size of the latent HIV reservoirs



The “shock and kill” strategy involves reactivating latent HIV-1 proviruses using LRAs, inducing viral protein expression, and exposing latently-infected cells for immune clearance.

Heterogeneity and multiplicity of the molecular mechanisms involved in HIV-1 post-integration latency



Epigenetic blocks

- DNA methylation
- Nucleosme positioning
- Histone PTMs (methylation, deacetylation)

Transcription initiation blocks

- Poor availability of positively acting TFs
- Abundance of negatively acting TFs

Transcription elongation blocks

- Negative elongation F
- Absence of Tat
- Sequestration of active P-TEFb

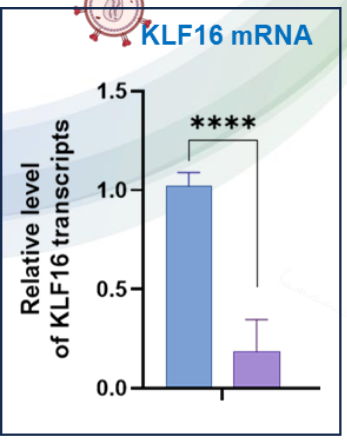
Post-transcriptional blocks

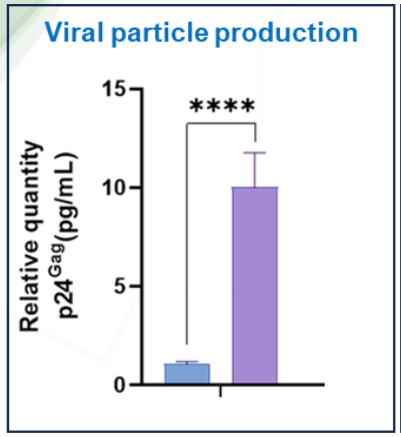
- Blocks to splicing
- Block to export
- Inhibitory miRNAs
- Translation blocks

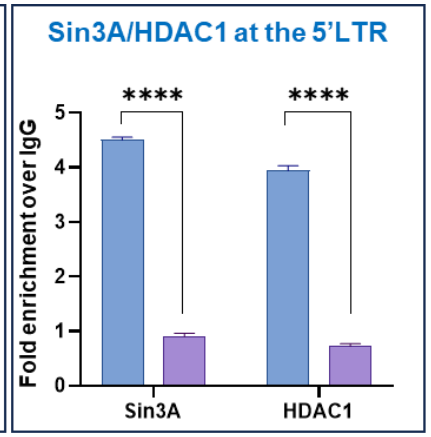
Studying the mechanisms that drive HIV into latency is critical for targeted HIV cure efforts aiming at either reactivating or blocking viral expression.

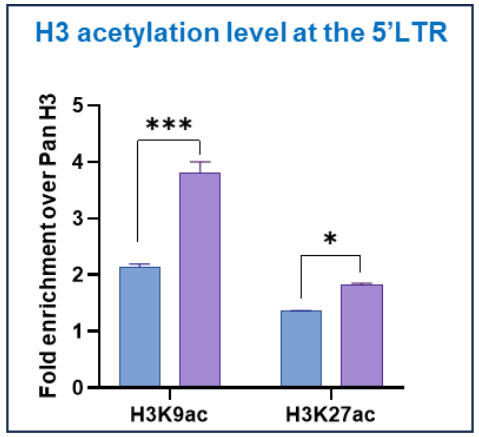
(A. Ait Ammar *et al.,* Front. Microbiol 2020; R. Verdikt *et al.,* Vaccines 2021; A. Rodari *et al.*, Annu. Rev. Virol. 2021 ; A.Kula *et al.*, Semin. Immunol. 2021)

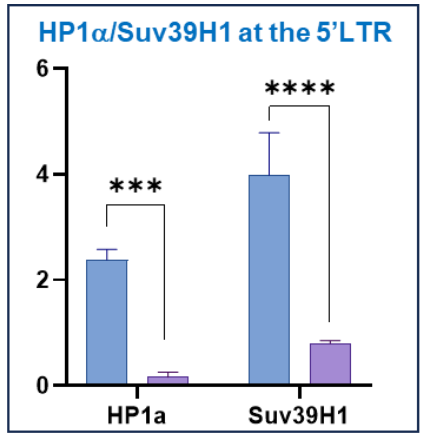
KLF16 is a novel epigenetic repressor of HIV-1 gene expression

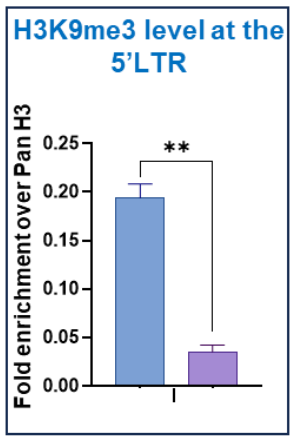








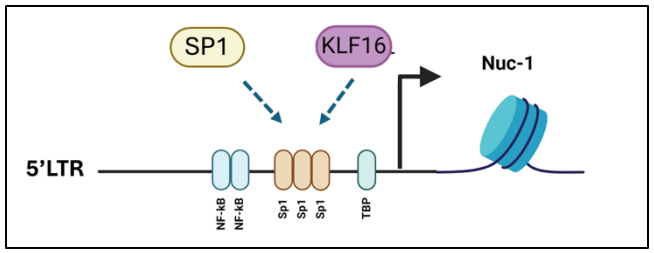


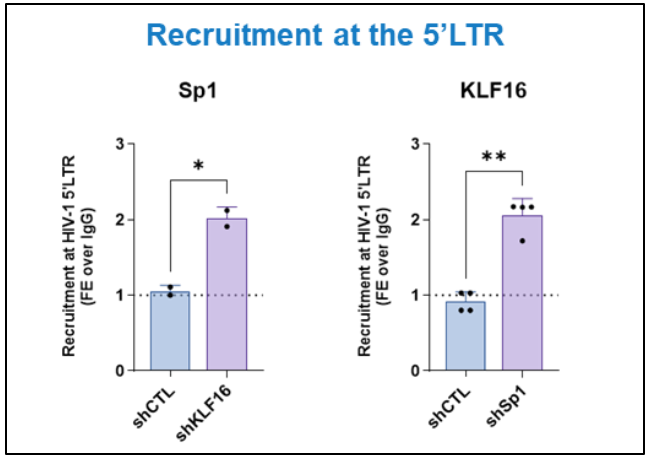


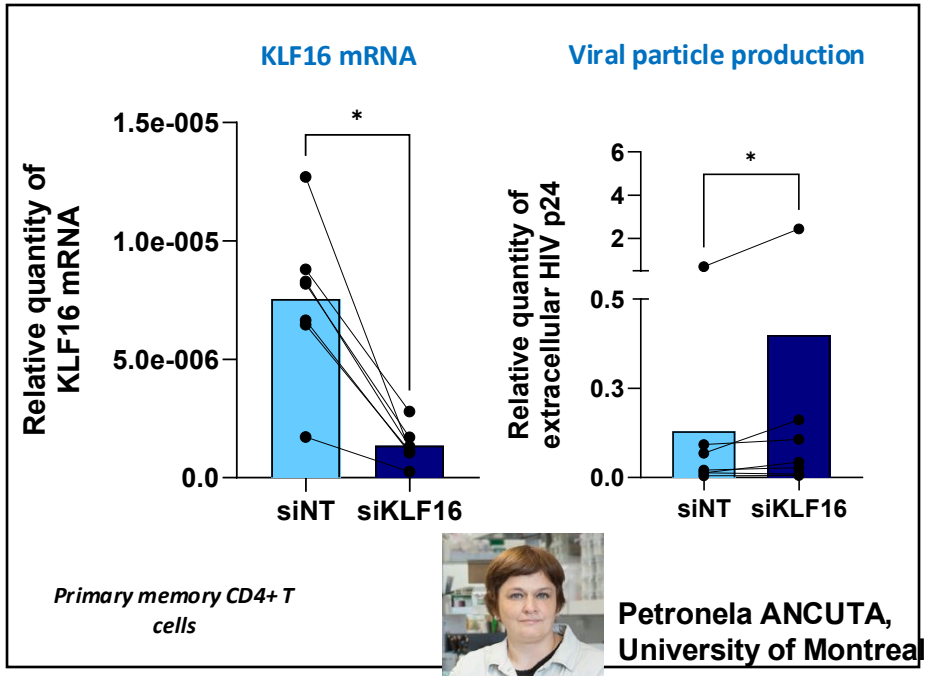
Jurkat HIVGKO

sh-CTL
sh-KLF16

KLF16 ↓ HIV-1 ↑ Sin3A/HDAC1 ↓ H3K9ac + H3K27ac ↑ HP1α/Suv39H1 ↓ H3K9me3 ↓

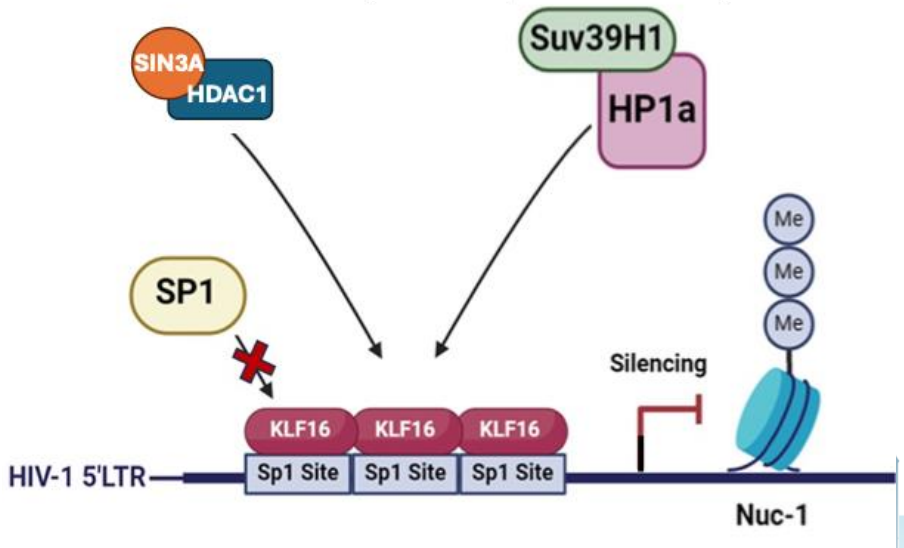






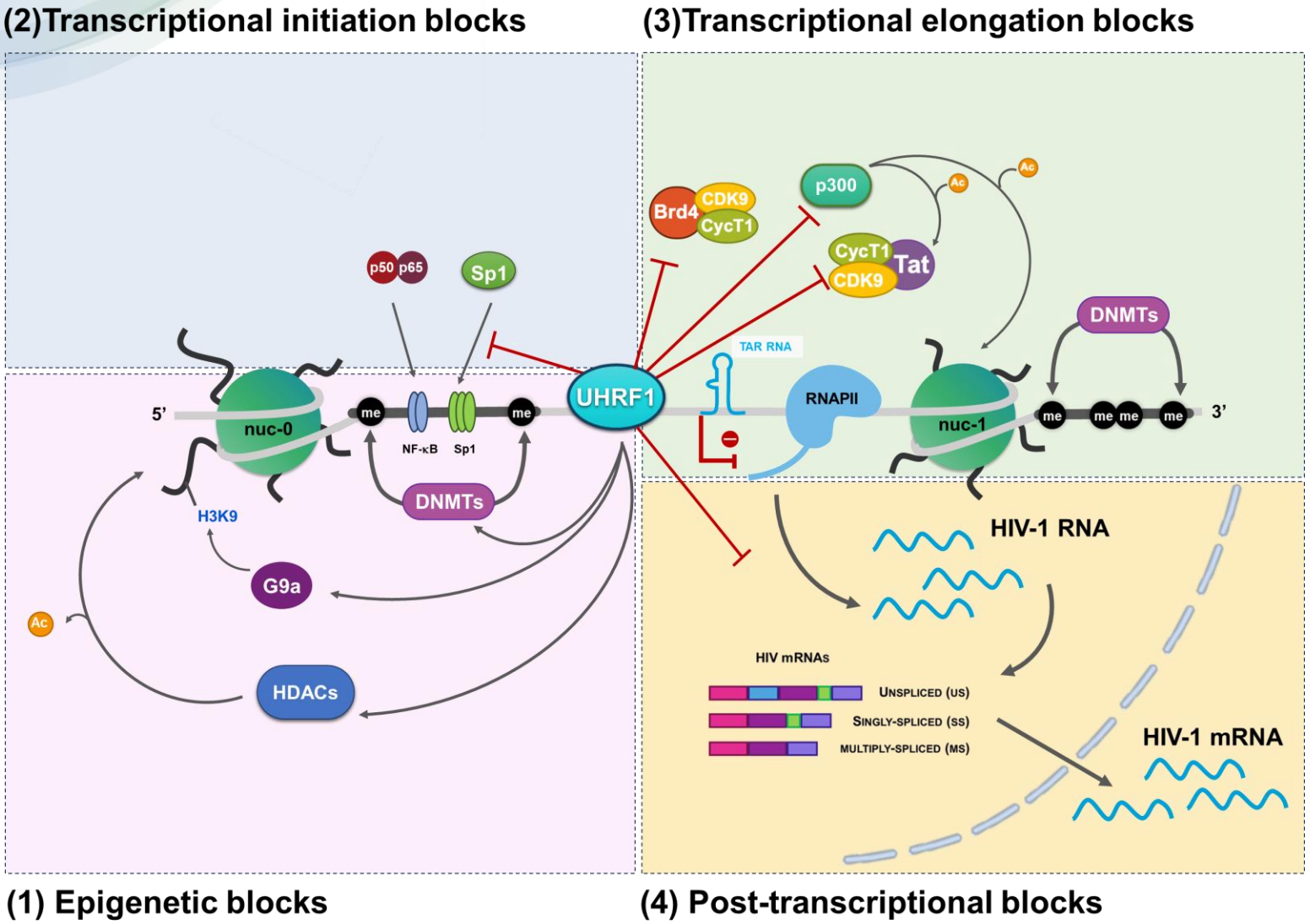
Primary memory CD4+ T cells

Petronela ANCUTA, University of Montreal



(M. Santangelo, M. Bendoumou, A. Dutilleul, P. Ancuta and C. Van Lint, unpublished data)

UHRF1 REGULATES MULTIPLE LAYERS OF HIV-1 GENE EXPRESSION, FROM EPIGENETICS TO POST-TRANSCRIPTIONAL EVENTS

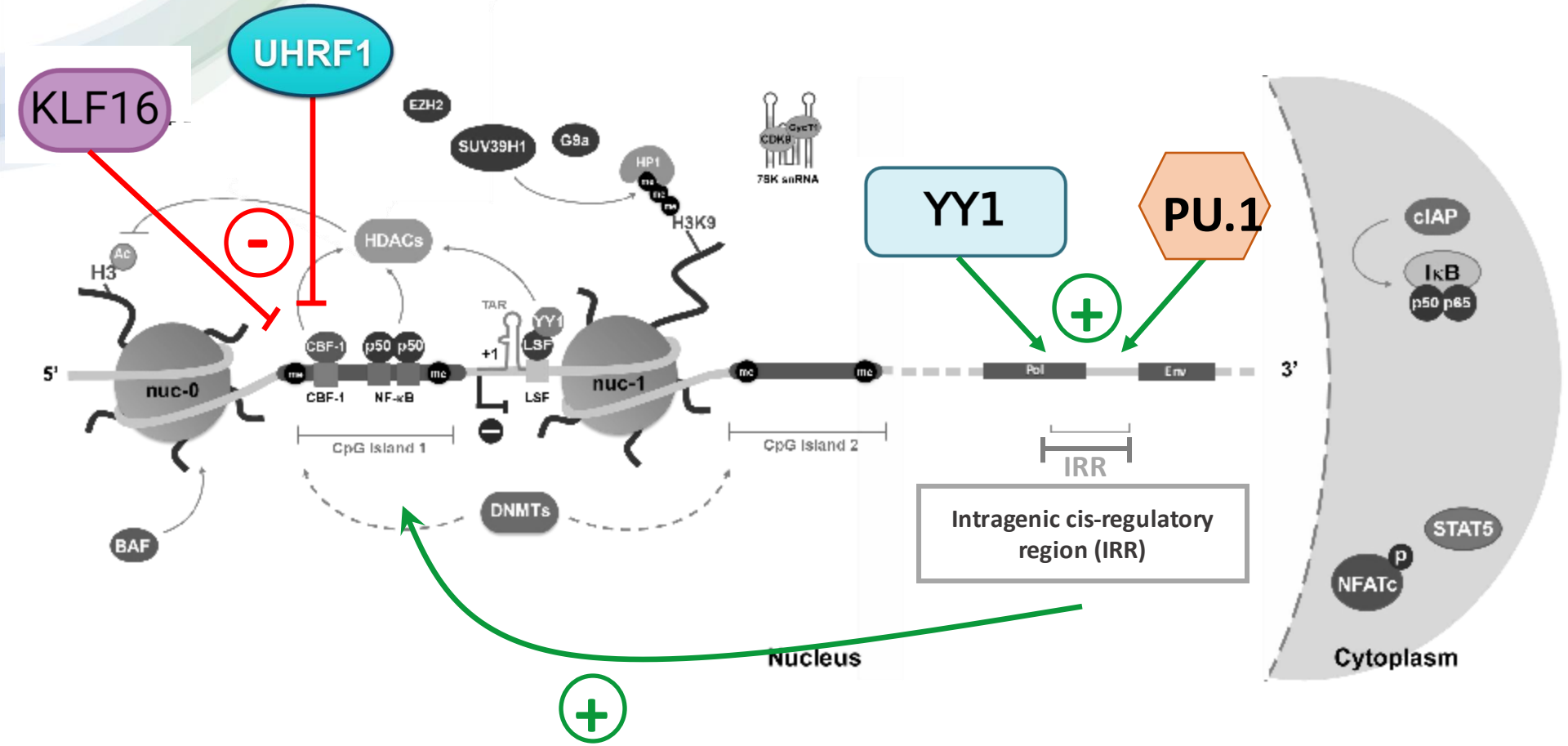


UHRF1 appears to be an important regulator of HIV-1 gene expression by acting on several transcriptional checkpoints: at the epigenetic level, at the transcriptional elongation levels pre- and post-Tat expression, and at the post-transcription level. This poses UHRF1 as an attractive therapeutic target.

Maryam Bendoumou
Poster

M. Bendoumou and C. Van Lint, unpublished data

Take home message



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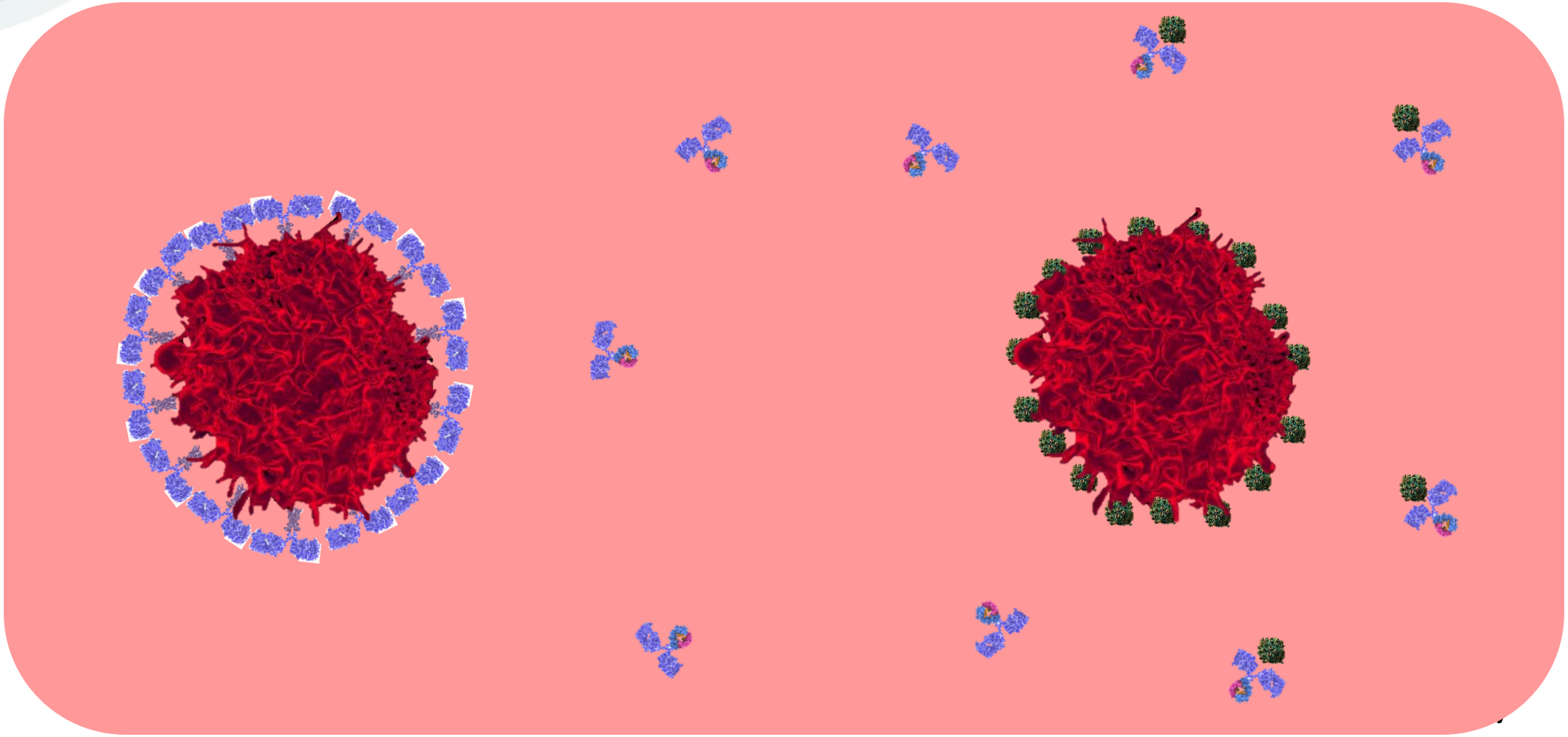
- Block to export
- Inhibitory miRNAs
- Translation blocks

Our molecular approaches thus identified several cellular factors as new epigenetic regulators of HIV-1 gene expression not only binding to the 5'LTR such as KLF16 and UHRF1, but also binding to the IRR such as PU.1 and YY1. The list of these factors is still growing although HIV transcription has been studied for over 35 years. Understand the molecular mechanisms of HIV-1 gene expression could tremendously contribute to the development of the "shock-and-kill" strategy and of the "block-and-lock" strategy since these factors constitute new drug targets.

Hybrid CAR-T cell project



Hybrid CAR-T cell project

🔍 Main research question

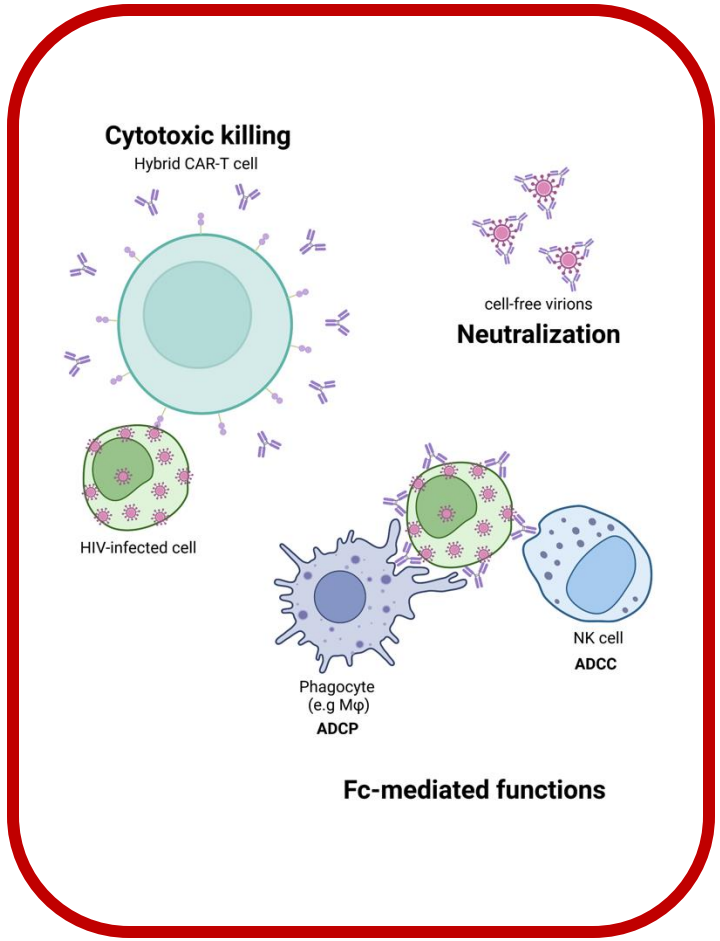
Can Hybrid CAR-T cells contribute to a functional cure?

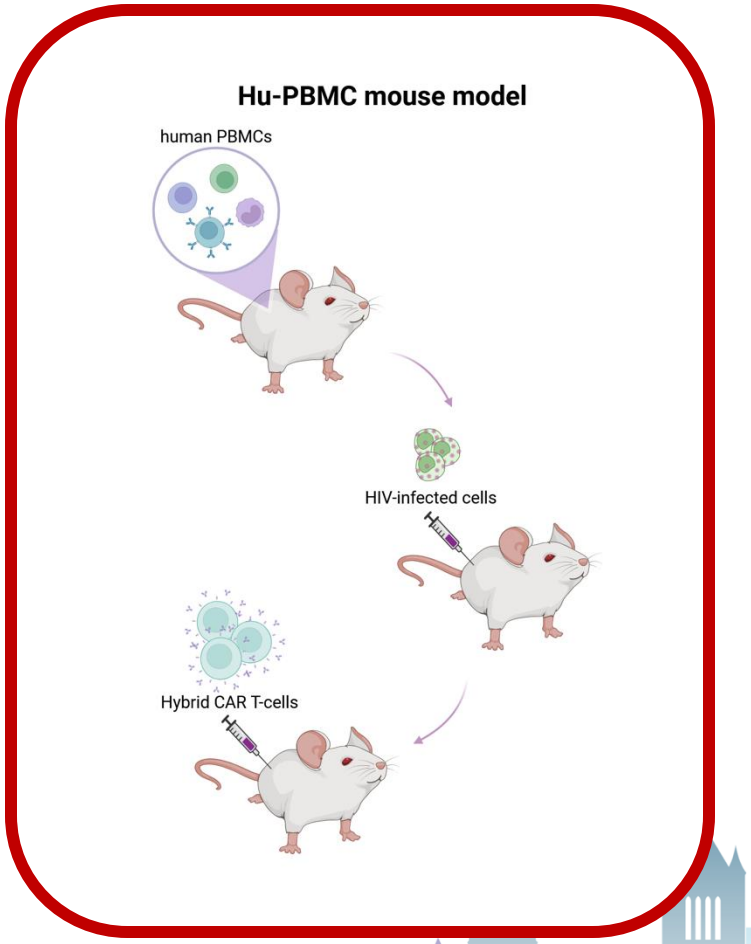
🔬 Key findings

- Cytotoxic killing of HIV-infected cells *in vitro*
- bNAb secretion and neutralization of HIV virions *in vitro*
- Initiation of Fc-effector functions
- Reduction of HIV plasma viremia *in vivo*
- bNAb detection *in vivo*

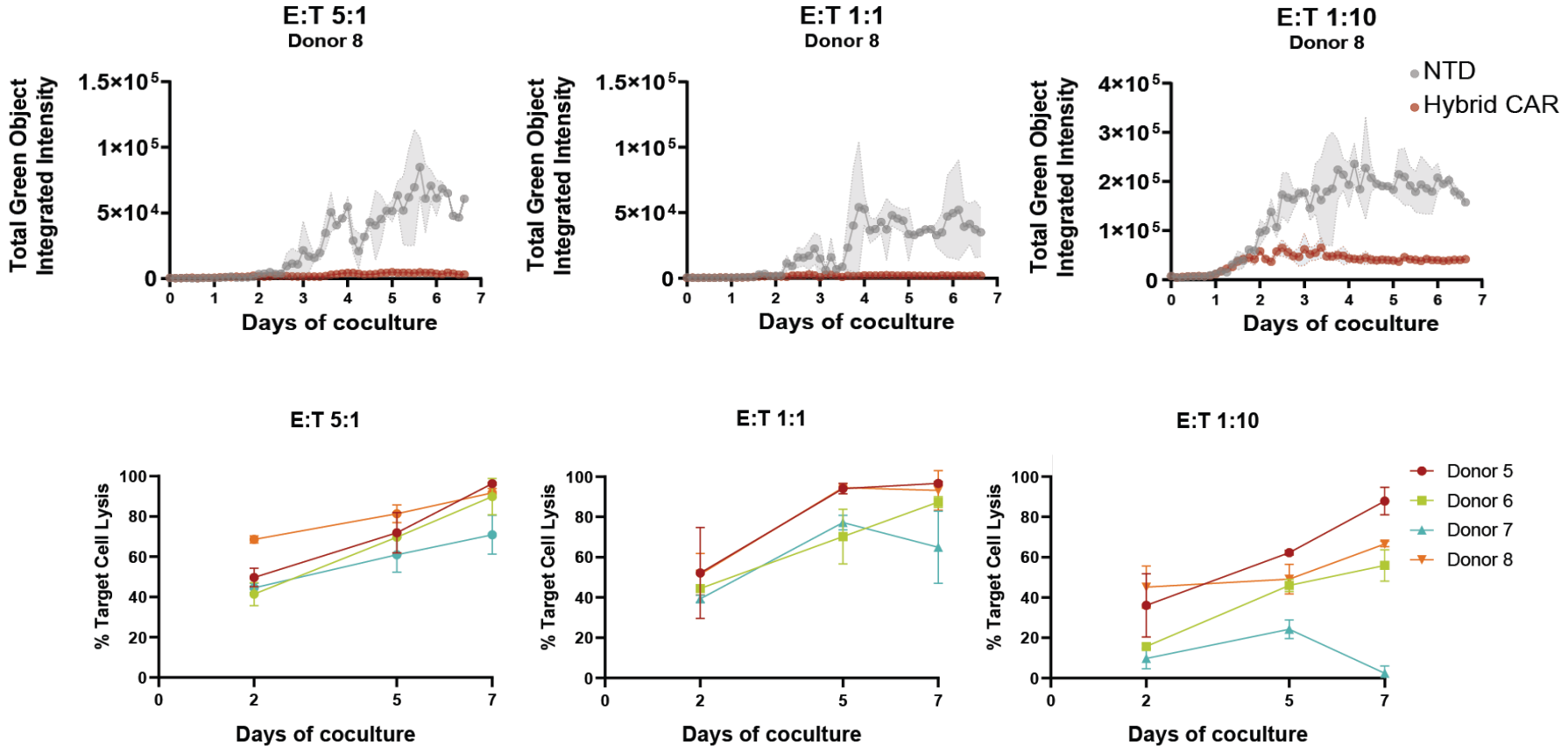
🌍 Why is it important

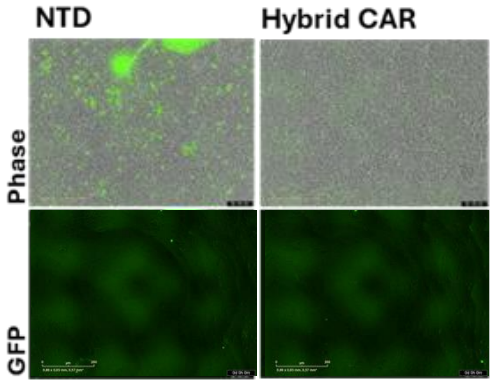
- Targets virus & infected cells simultaneously
- Bridges adaptive & innate immunity
- Highly adaptable





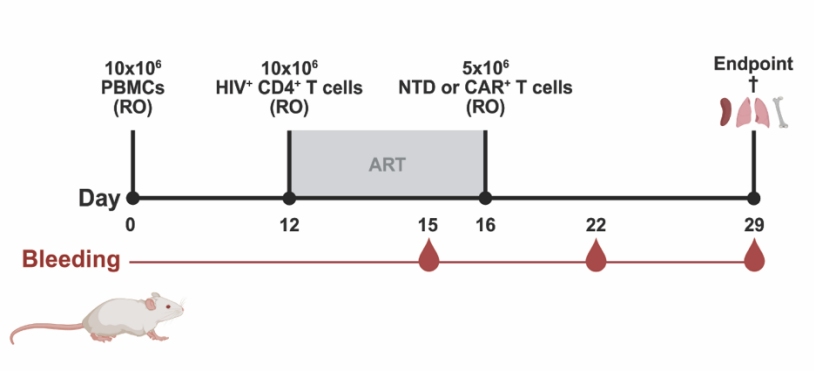
Hybrid CAR-T cells kill autologous HIV-infected CD4+ T cells

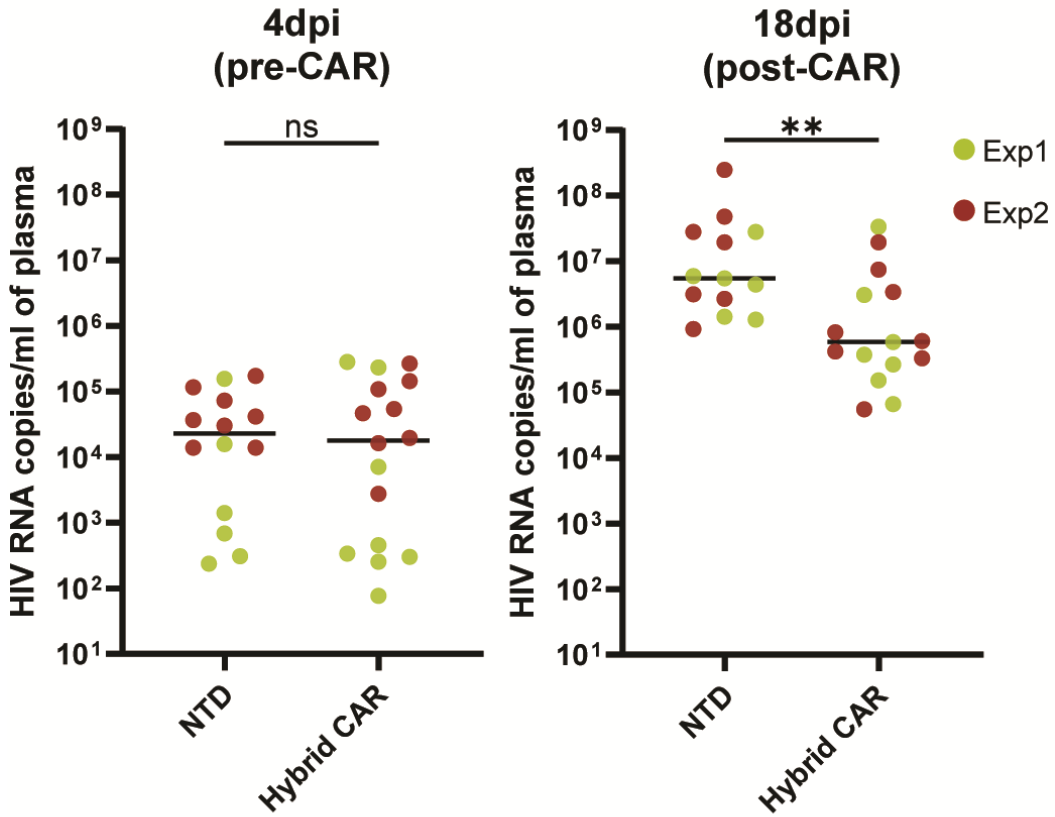




5:1
Day 1→7

Hybrid CAR-T cell-treated mice have lower plasma viremia





Grateful thanks to

RIO study participants, family, partners and friends

The RIO leadership team, funders

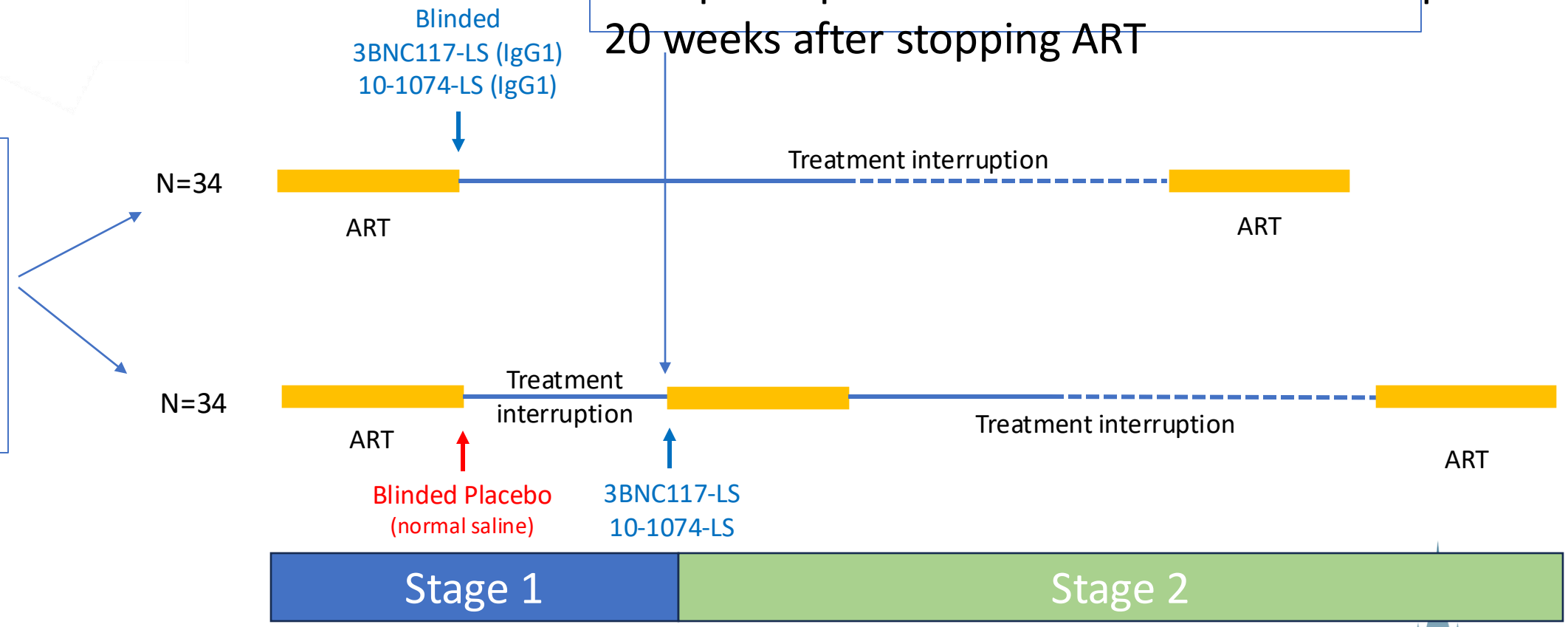
CHERUB

Collaborative HIV Eradication of Reservoirs: UK BRC

RIO study design

PRIMARY ENDPOINT
% of participants with HIV viral load <50 copies RNA/m
20 weeks after stopping ART

Double blind random allocation 1:1 bNAb sensitive



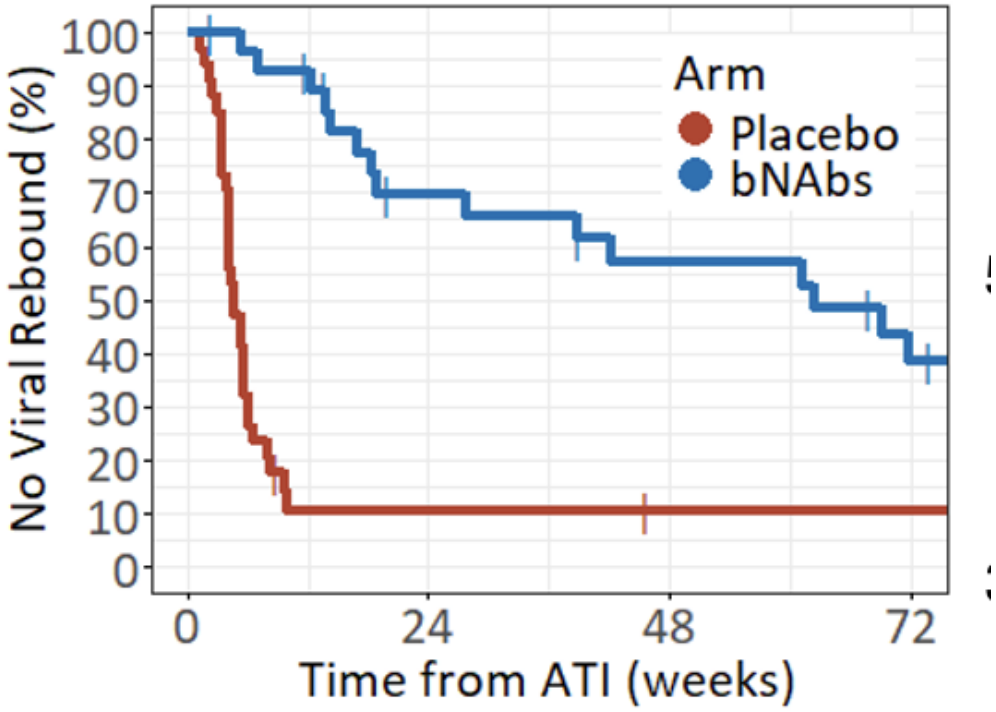
Endpoints

Primary: Time to viral rebound by week 20 by study arm

Secondary/exploratory: Immunological markers c/w the vaccinal effect, HIV proviral DNA, quality of life, adverse events

Viral rebound by study arm to week 72 after 2 doses

Hazard ratio: 0.24, 95% CI (0.13, 0.44)



bNAbs:

- 57% not rebounded week 48
  - 95% CI (0.41, 0.8)
- 39% not rebounded week 72
  - 95% CI (0.23, 0.65)

Placebo:

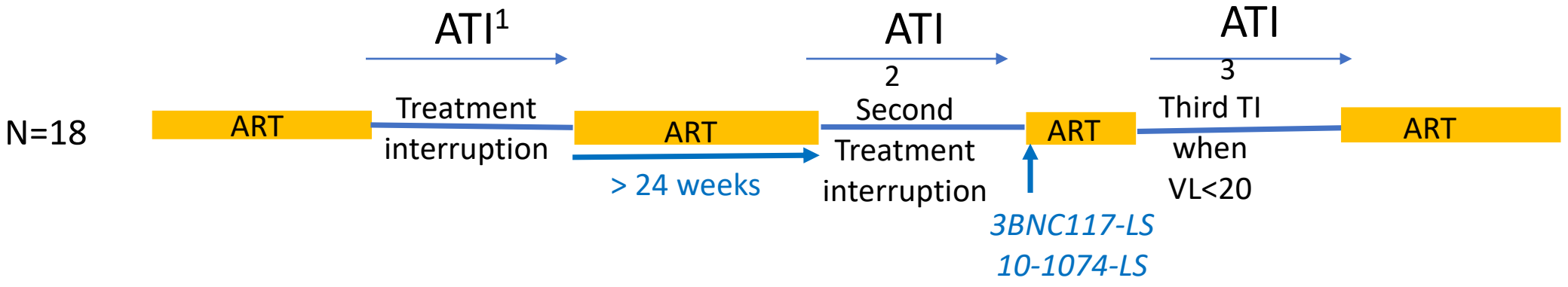
2/34 (6%) not rebounded

Number of participants

	0	24	48	72
bNAbs	34	20	13	8
placebo	34	3	2	2

EU2Cure ARM C RIO

Design RIO arm C



Primary endpoint time to VL rebound between ATI^2 vs ATI^1