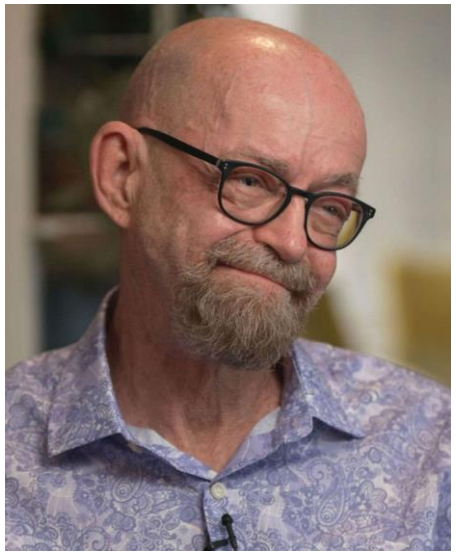
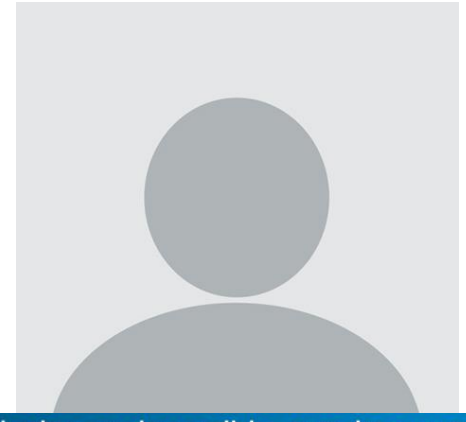
What does cure mean and why is a cure difficult ?
24 May 2024

Linos Vandekerckhove, MD
Professor of Medicine
Division Infectious Diseases, and Internal Medicine
Ghent University Hospital
Ghent University, Flanders, Belgium

BILL & MELINDA GATES foundation
fwo
NIH
GHENT UNIVERSITY



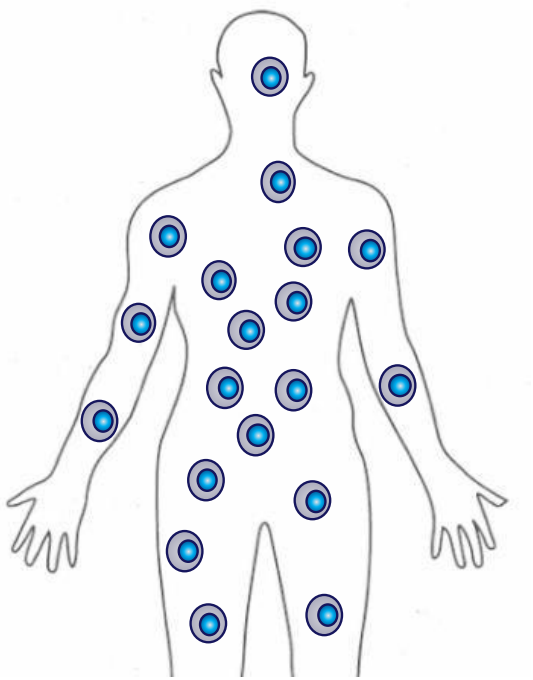


HIV-1 remission and possible cure in a woman after haplo-cord blood transplant

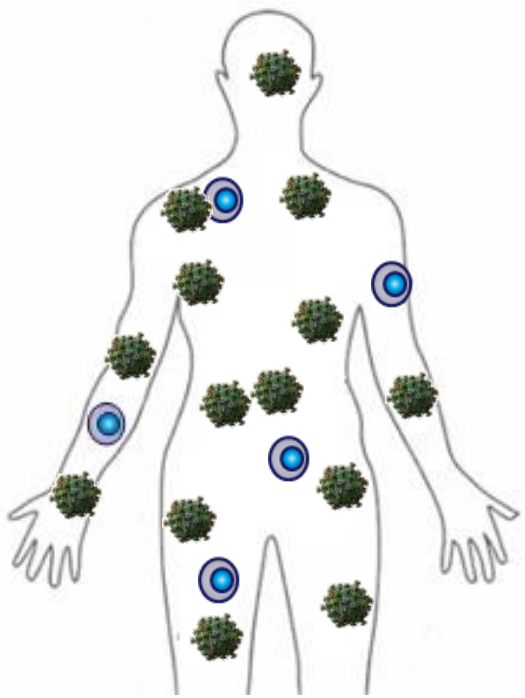
Jingmei Hsu [18] • Koen Van Besien • Marshall J. Glesby • ... Deborah Persaud [16] • Yvonne Bryson [16] • the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1107 Team •

What does infection mean?

Non-infected individual

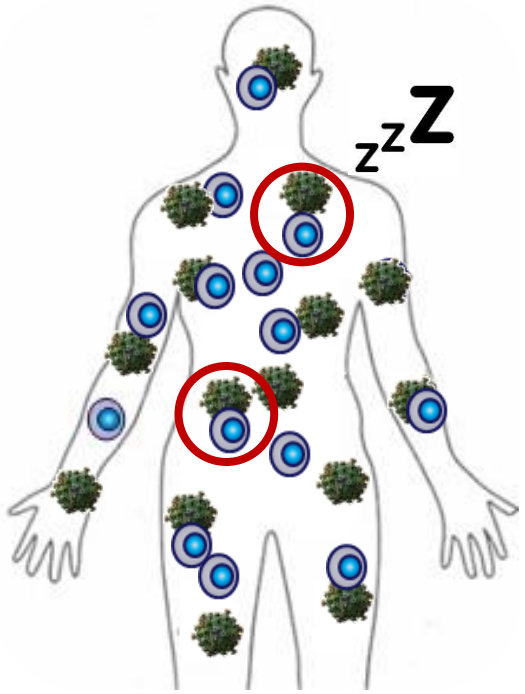


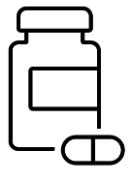
HIV infection



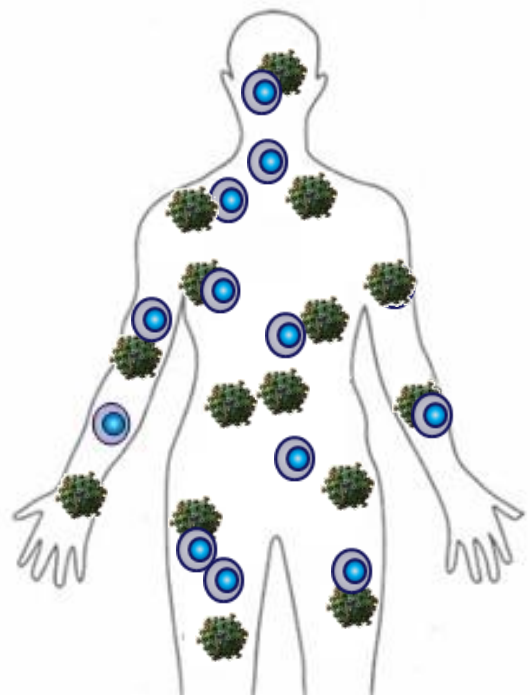
AIDS

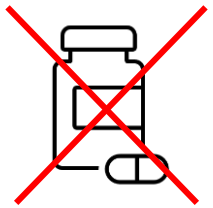
HIV therapy (ART)





Treatment interruption

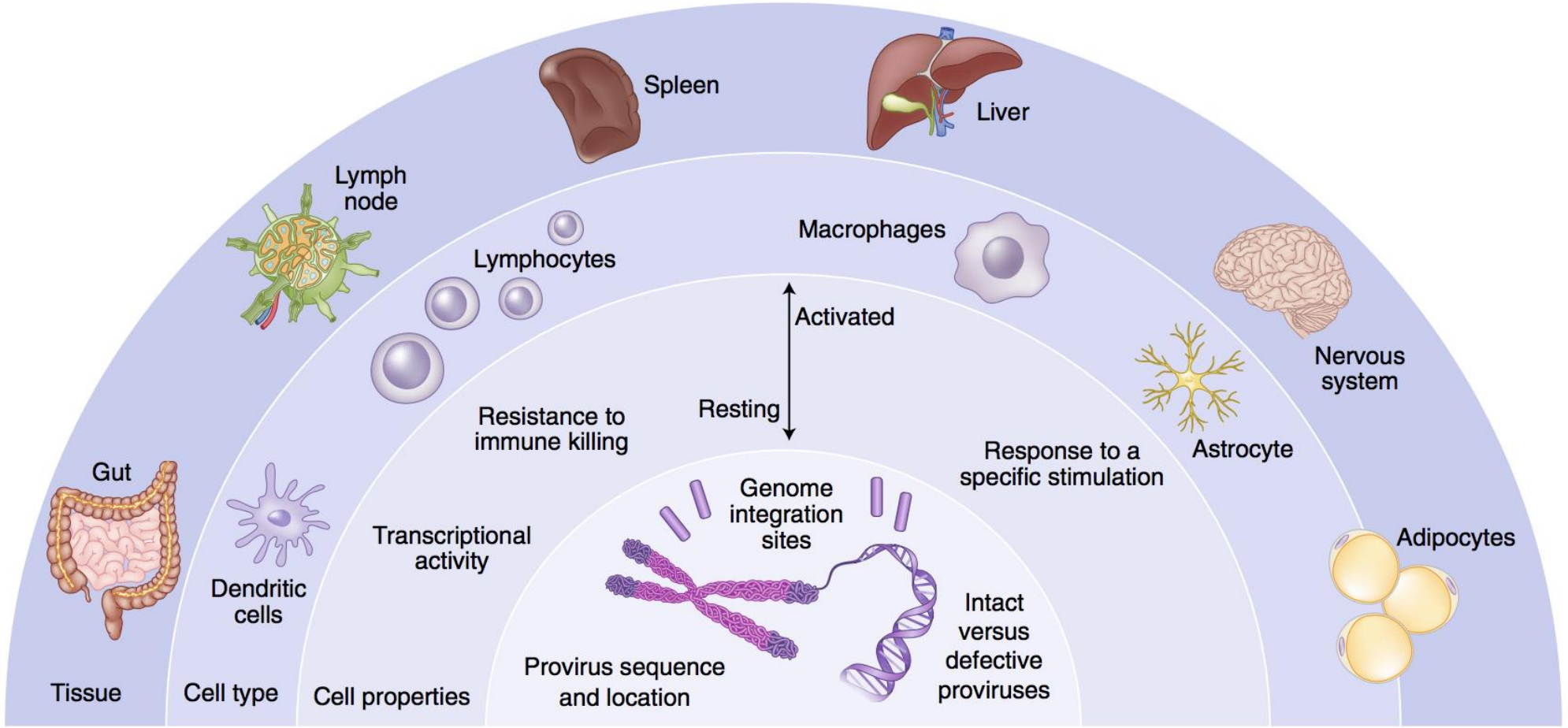




CD4 T cells

HIV

Multidimensional nature of the HIV reservoir.



Landscape of the HIV reservoir

S. Deeks, *Nature Med 2021*

nature medicine

The HIV anatomical reservoir

Defining total-body AIDS-virus burden with implications for curative strategies

Jacob D Estes[1], Cissy Kityo[2], Francis Ssali[2], Louise Swainson[3], Krystelle Nganou Makamdop[4], Gregory Q Del Prete[1], Steven G Deeks[5], Paul A Luciw[6], Jeffrey G Chipman[7], Gregory J Beilman[7], Torfi Hoskuldsson[7], Alexander Khoruts[8], Jodi Anderson[8], Claire Deleage[1], Jacob Jasurda[8], Thomas E Schmidt[8], Michael Hafertepe[8], Samuel P Callisto[8], Hope Pearson[8], Thomas Reimann[8], Jared Schuster[8], Jordan Schoephoerster[8], Peter Southern[9], Katherine Perkey[9], Liang Shang[9], Stephen W Wietgrefe[9], Courtney V Fletcher[10], Jeffrey D Lifson[1], Daniel C Douek[4], Joseph M McCune[3], Ashley T Haase[9] & Timothy W Schacker[8]

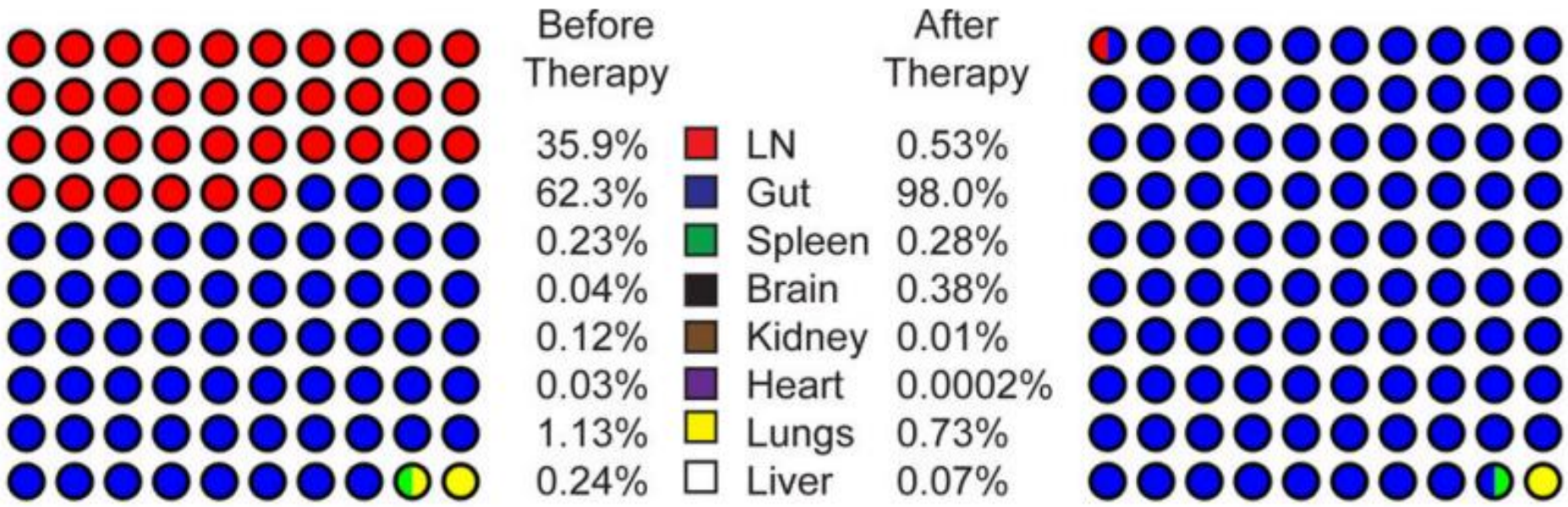
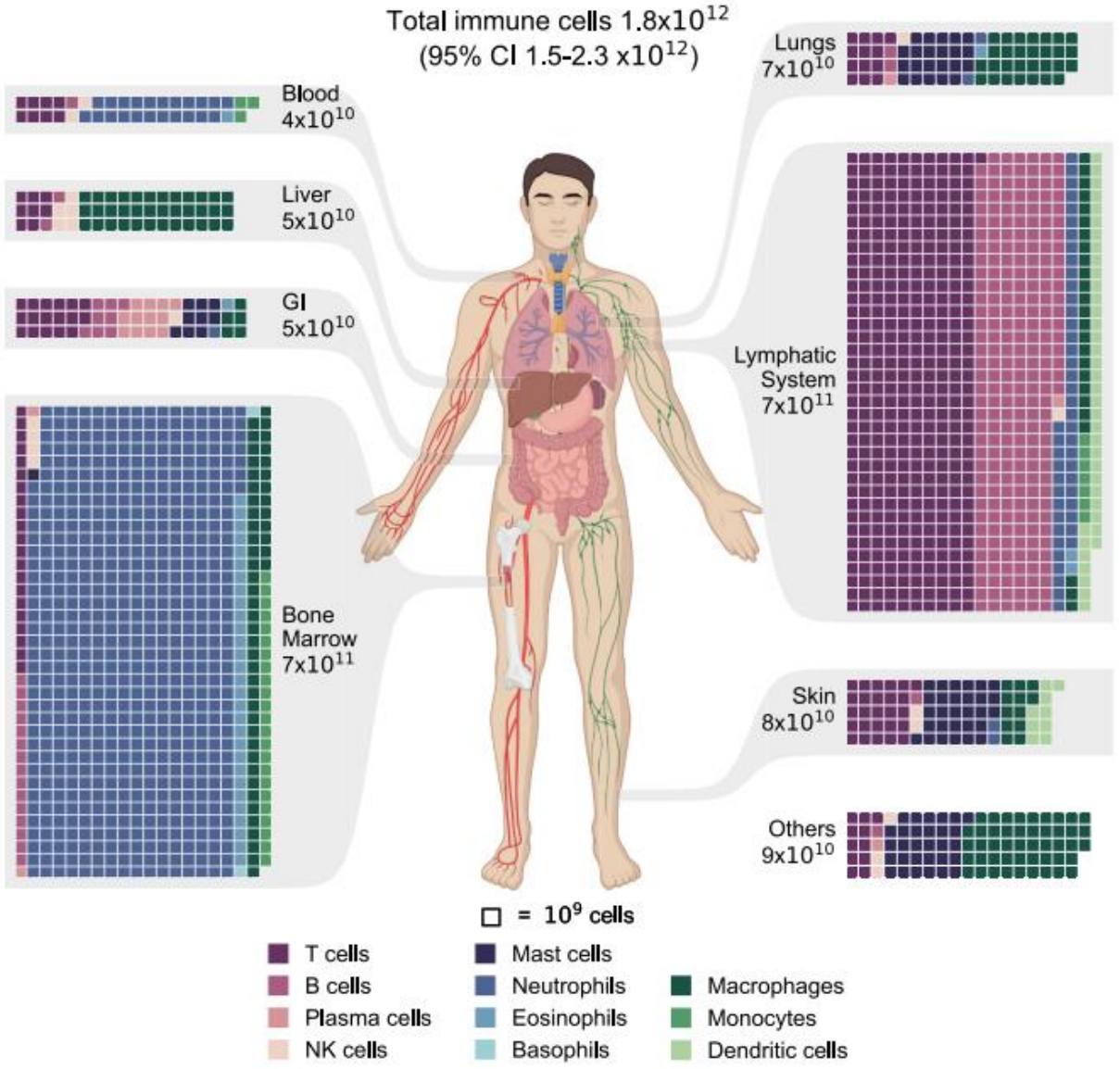


Figure 1.
Graphical representation of proportion of vRNA+ cells in each organ system before and during suppressive ART.

The HIV reservoir



PNAS RESEARCH ARTICLE | SYSTEMS BIOLOGY OPEN ACCESS

The total mass, number, and distribution of immune cells in the human body

Yoav Navon[a], Idan Milo[c], Nofar Azulay[c], Leeat Keren[c], Shai Fuchs[d], Danny Ben-Zvi[e], Elad Noor[a],

f Washington, Seattle, WA; received May 21, 2023; accepted September 11, 2023

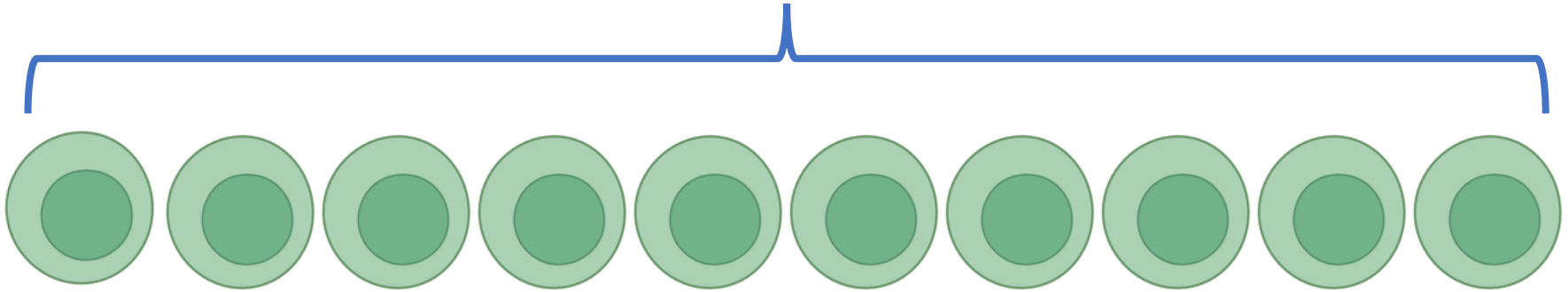
The HIV target cells

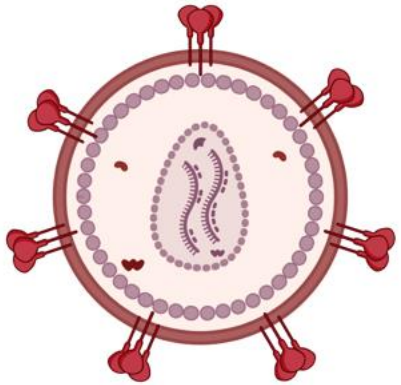
PNAS RESEARCH ARTICLE | SYSTEMS BIOLOGY OPEN ACCESS

The total mass, number, and distribution of immune cells in the human body

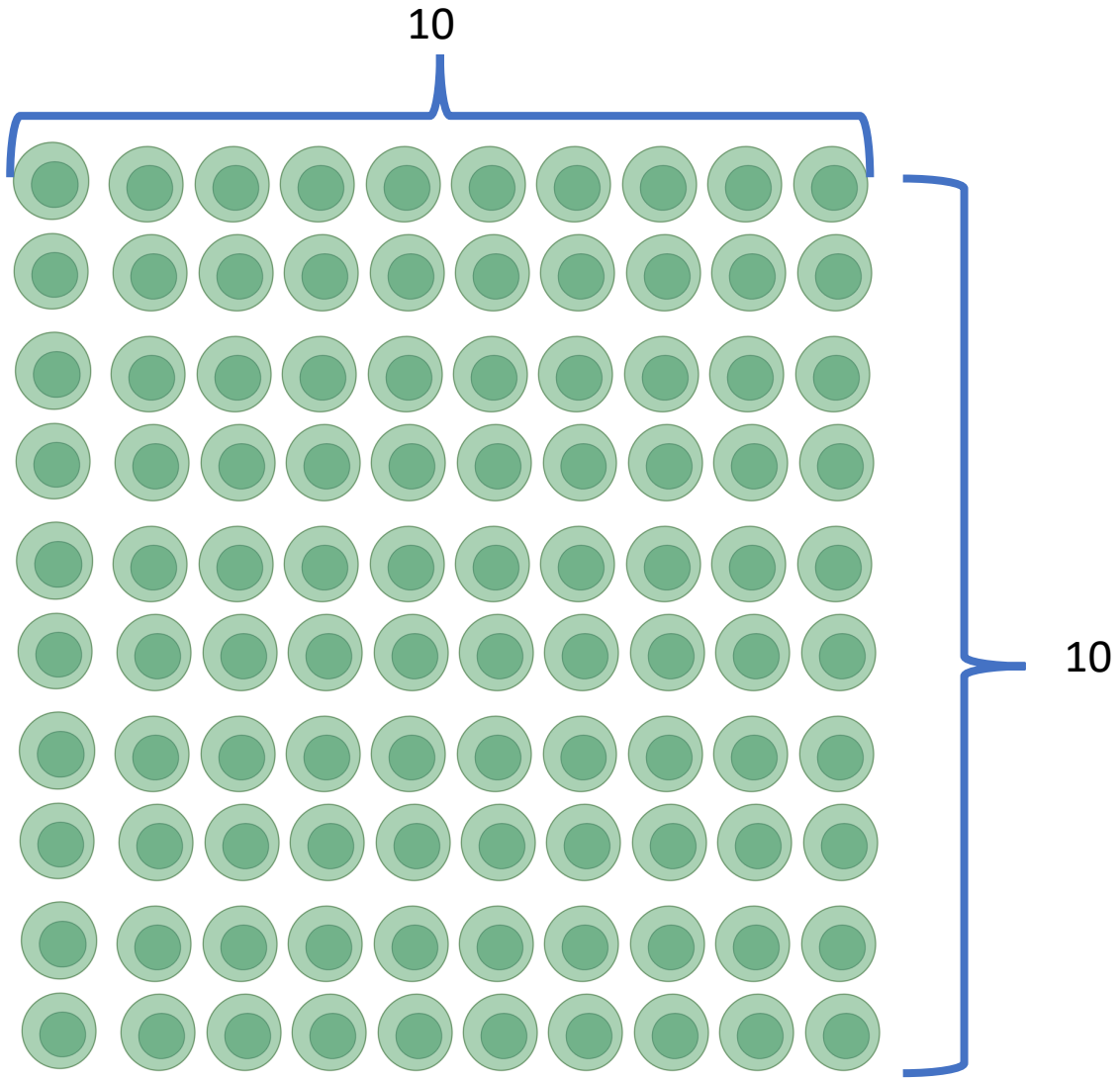
Ron Sender[a], Yarden Weiss[b], Yoav Navon[a], Idan Milo[c], Nofar Azulay[c], Leeat Keren[c], Shai Fuchs[d], Danny Ben-Zvi[e], Elad Noor[a], and Ron Milo[a,1]

Edited by David Baker, University of Washington, Seattle, WA; received May 21, 2023; accepted September 11, 2023

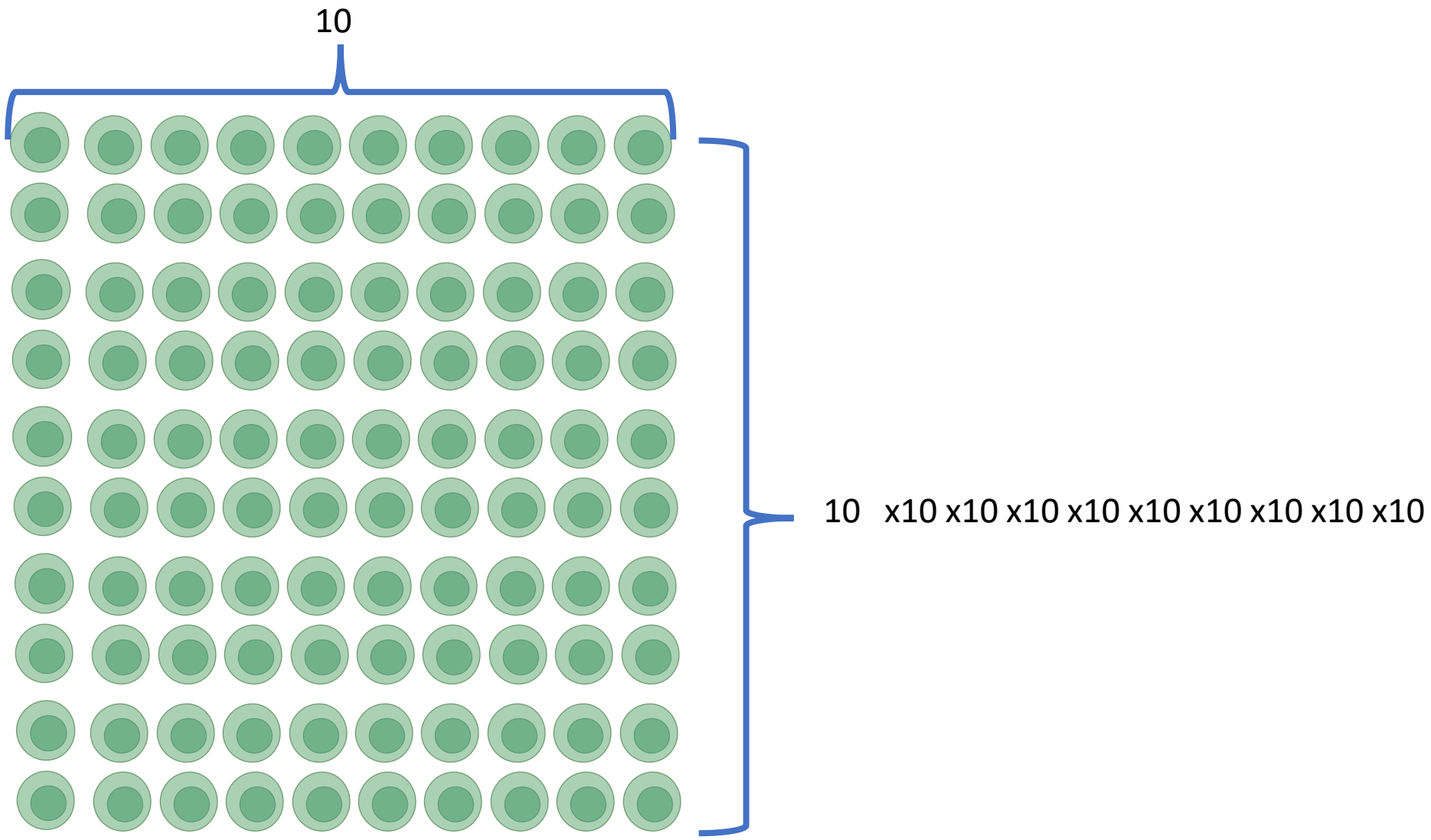




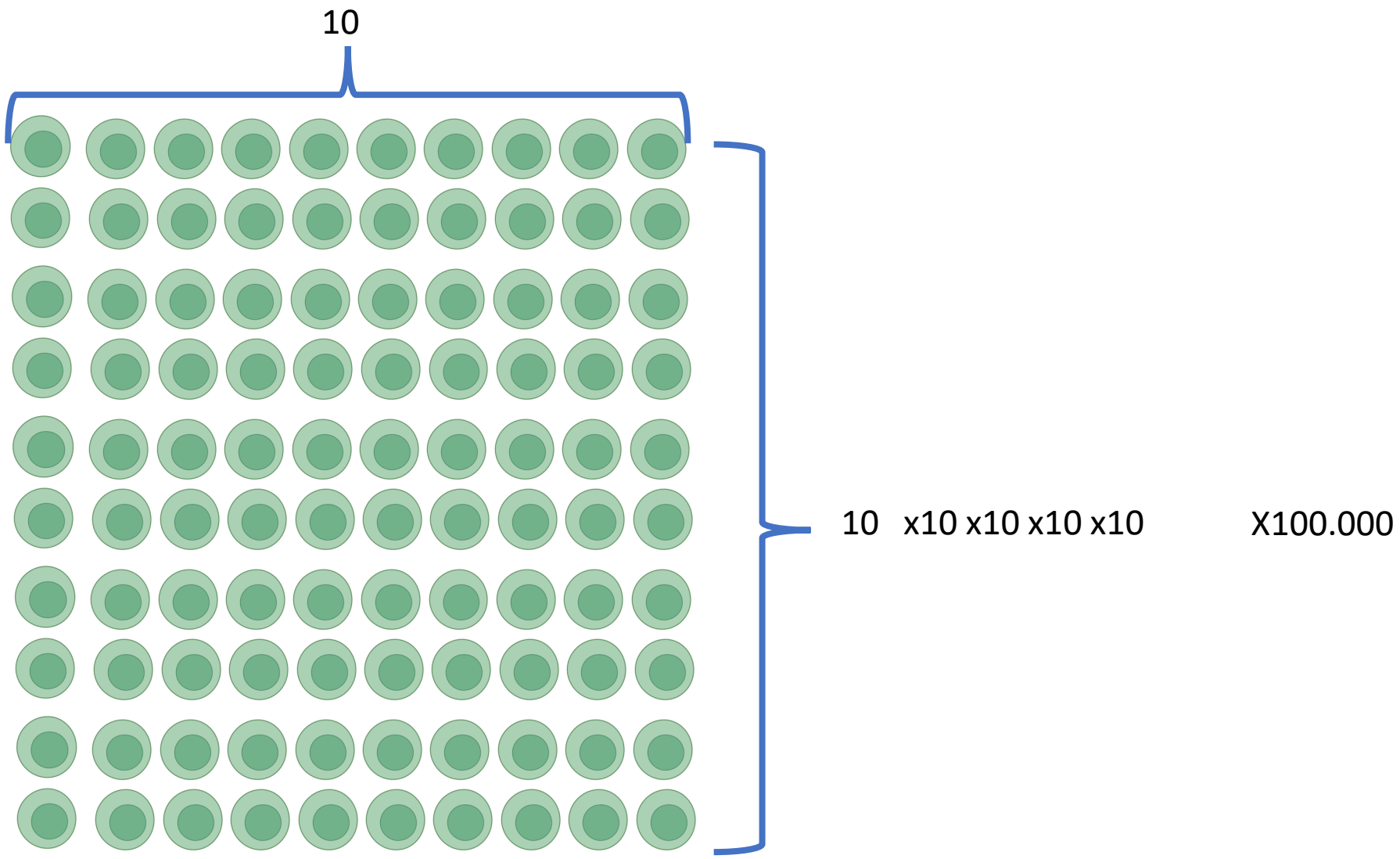
The HIV target cells



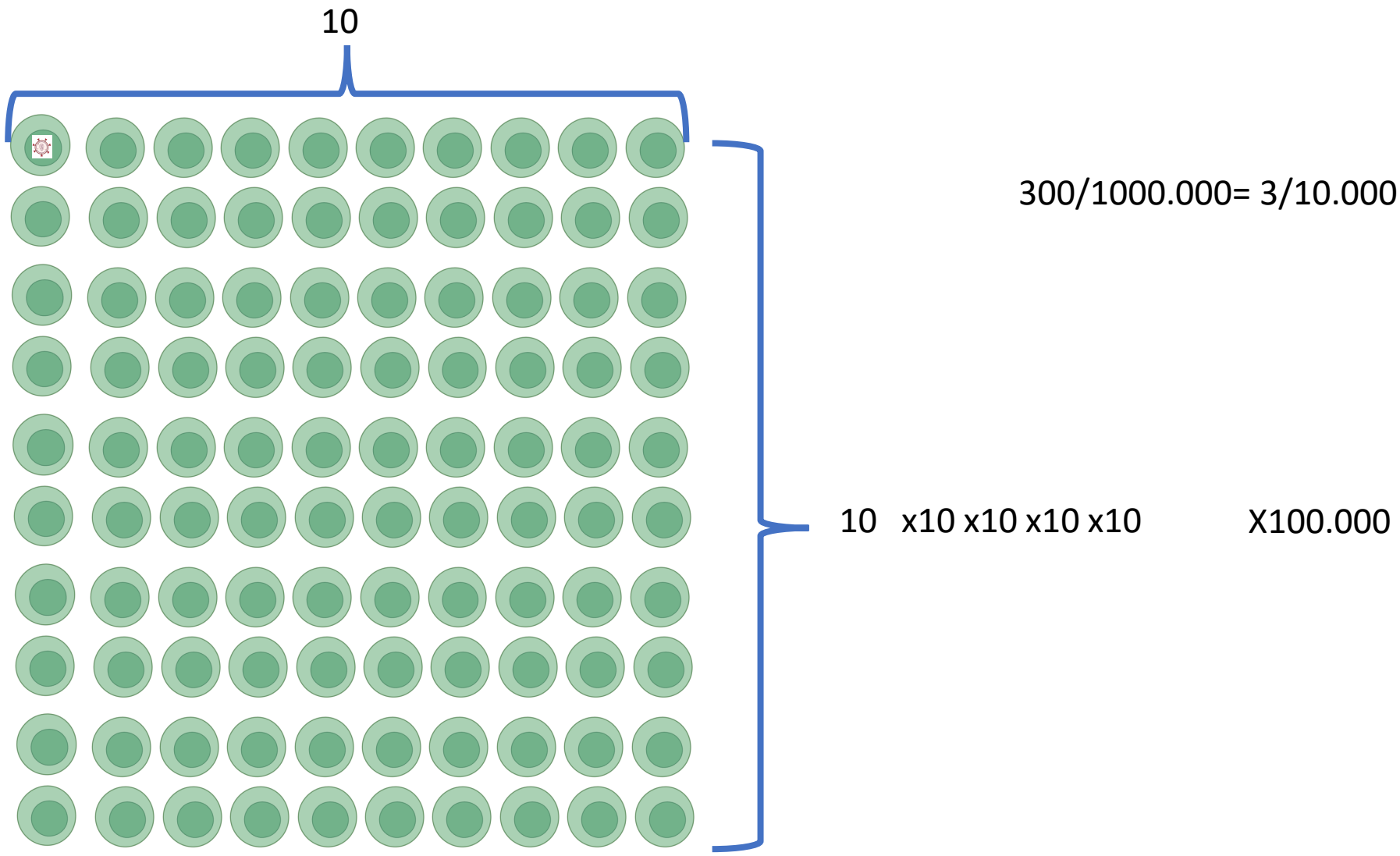
The HIV target cells



The HIV target cells

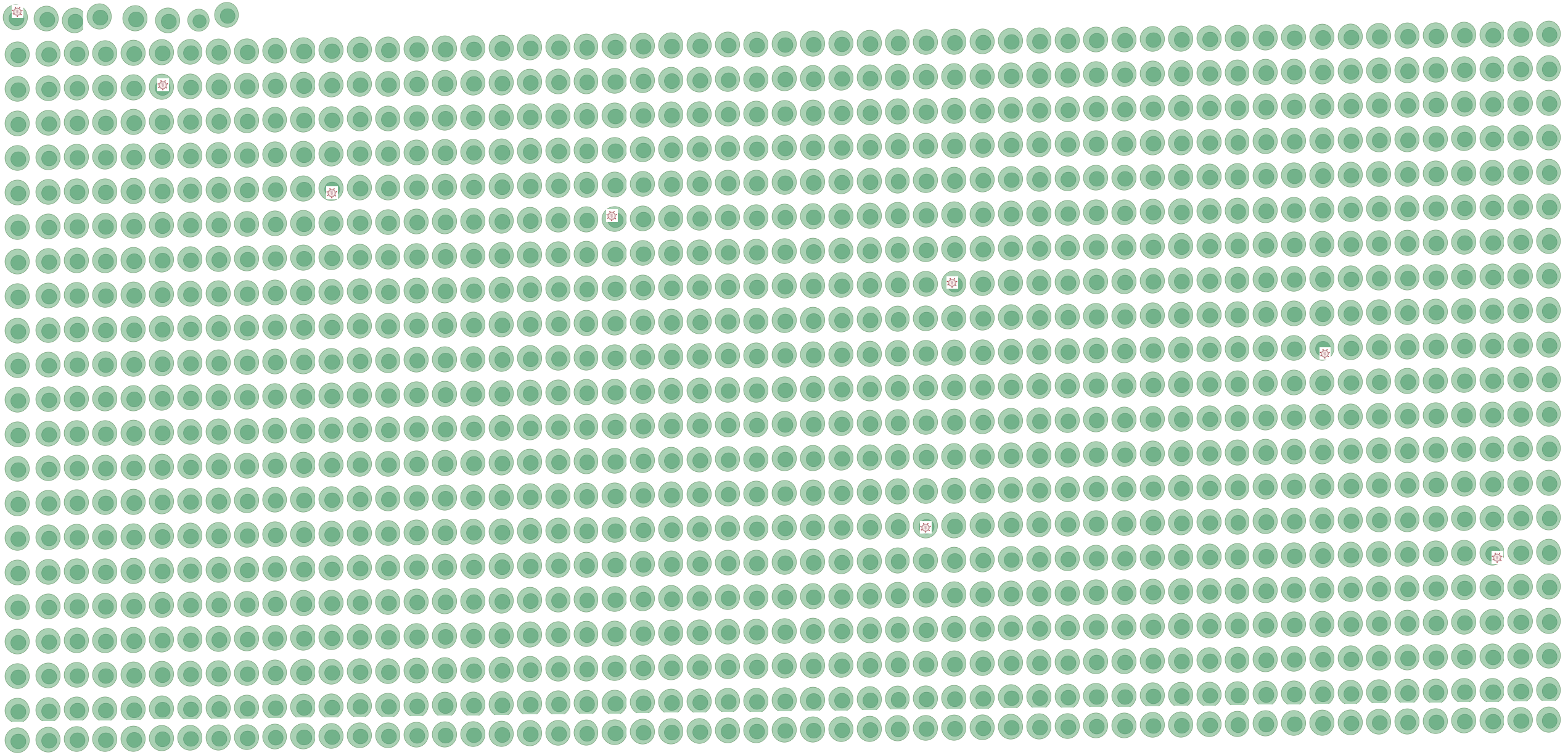


The HIV cellular reservoir

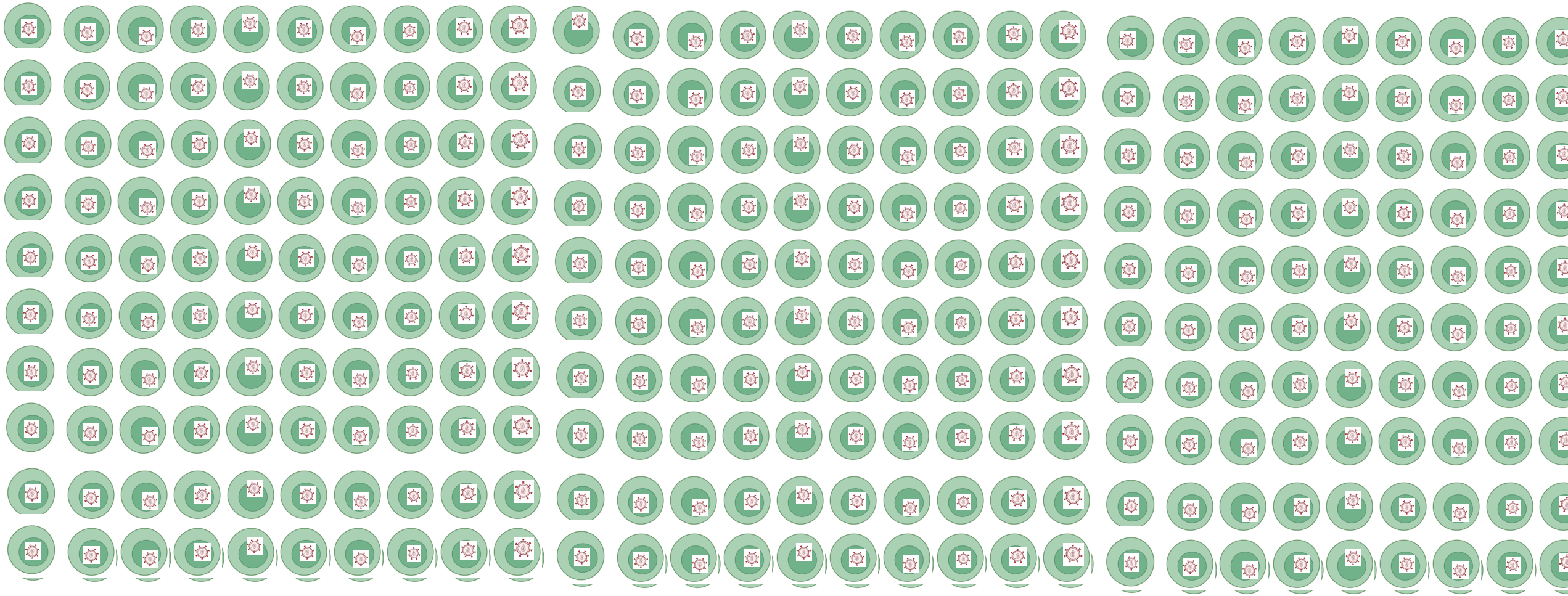


300/1000.000= 3/10.000

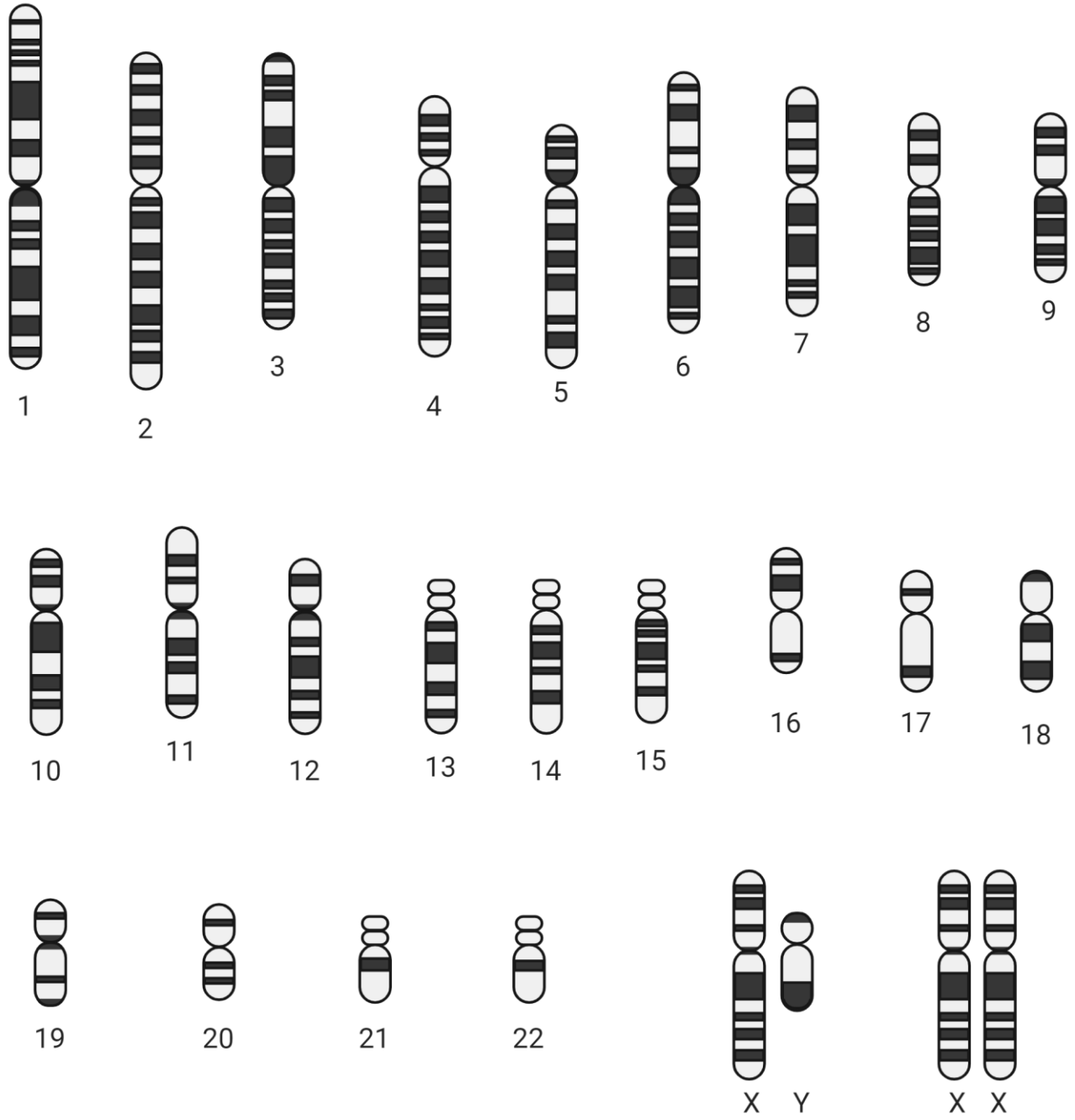
The HIV cellular reservoir



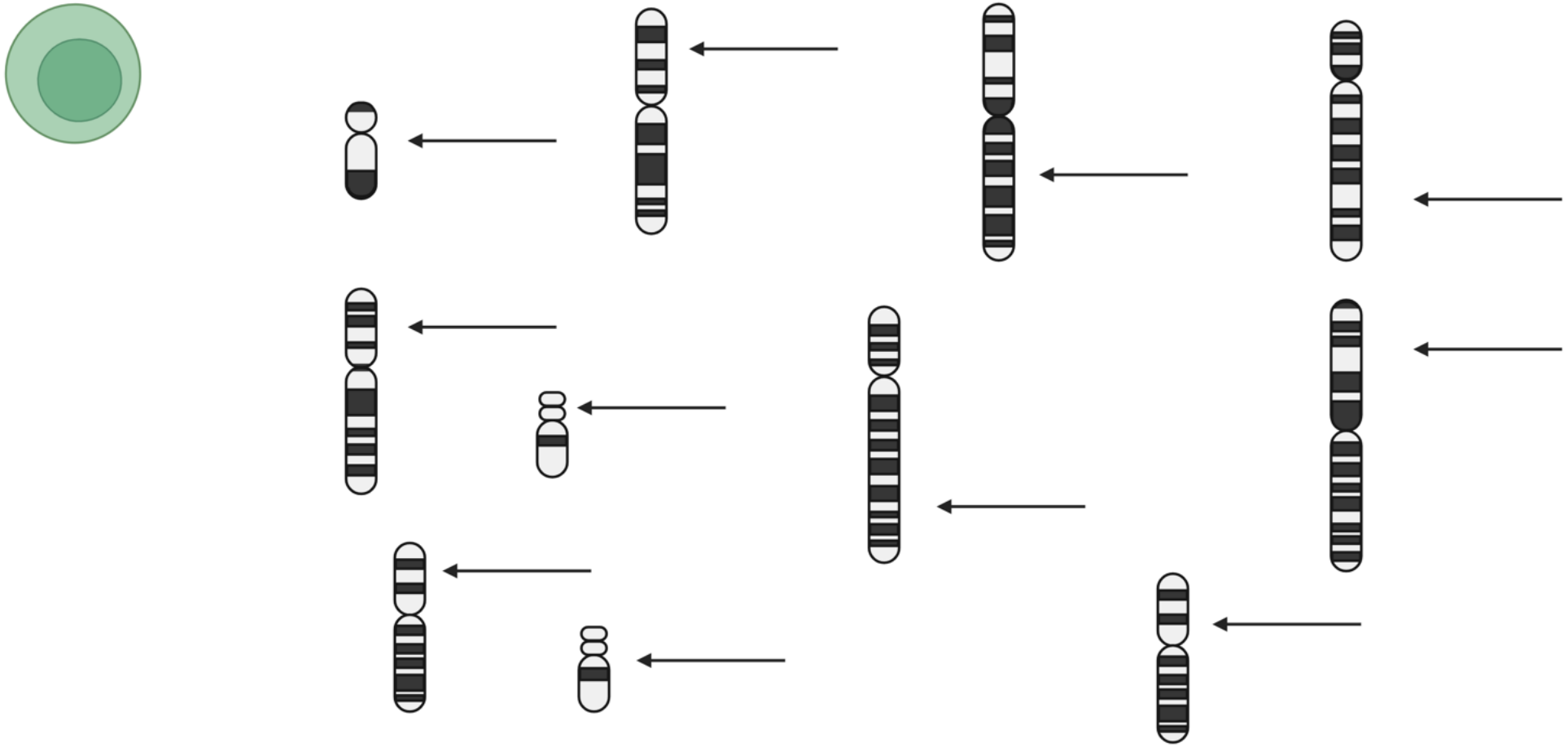
Are all cells infected with HIV identical?



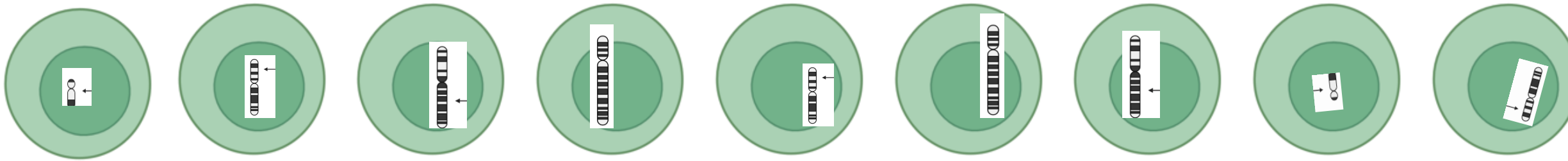
How does the HIV landing ground looks like? ?



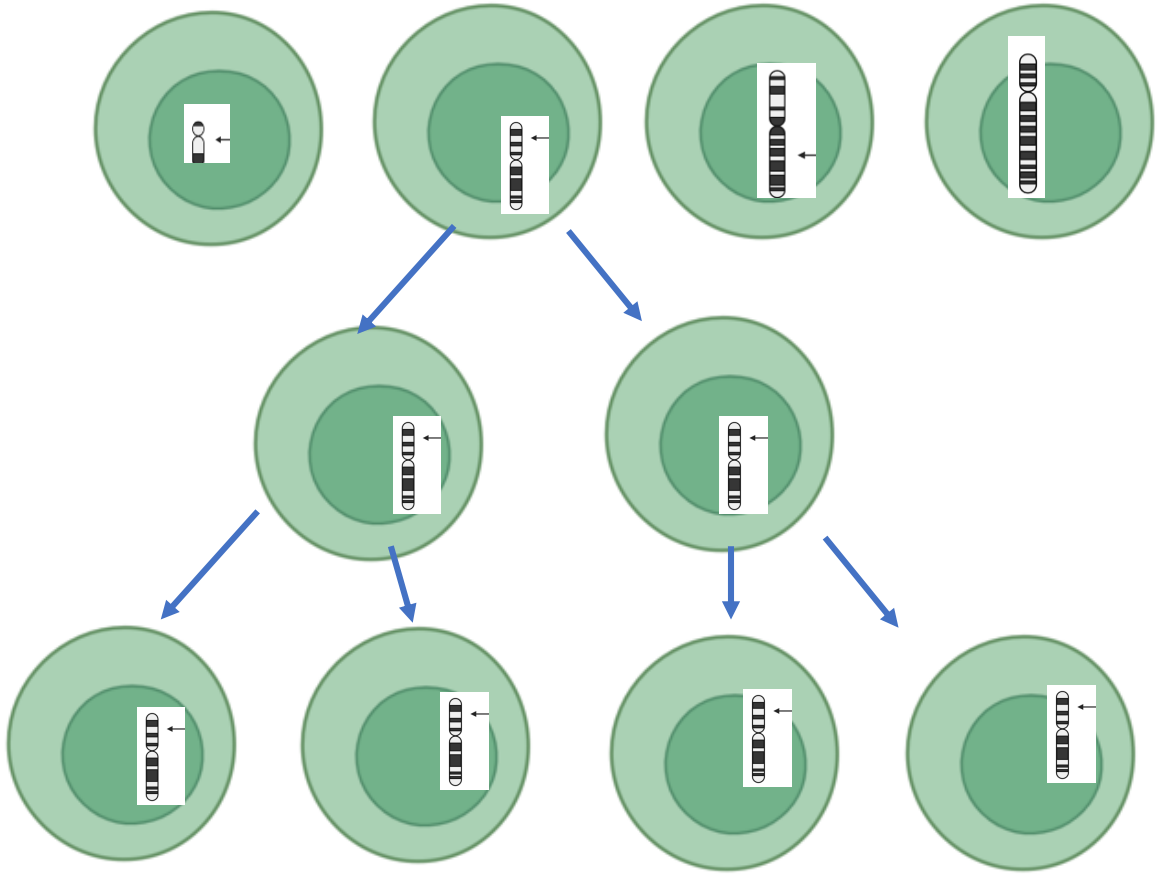
The HIV cellular reservoir



All infected cells have HIV virus in a different position in the beginning of an infection

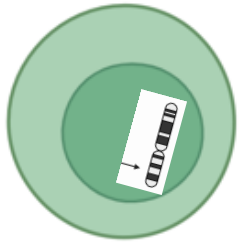


All infected cells have HIV virus in a different position in the beginning of an infection



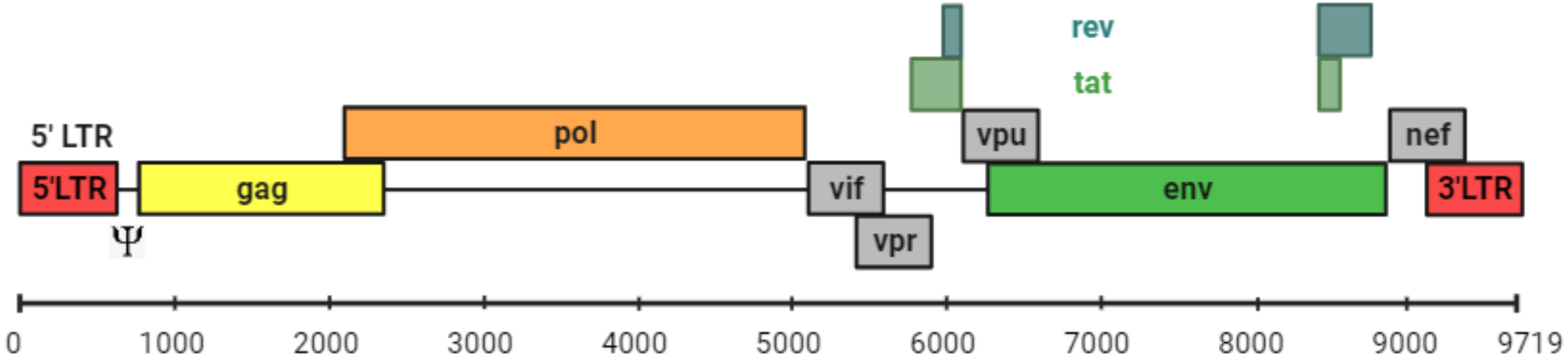
Infected cells can start deviding, making copies of themself

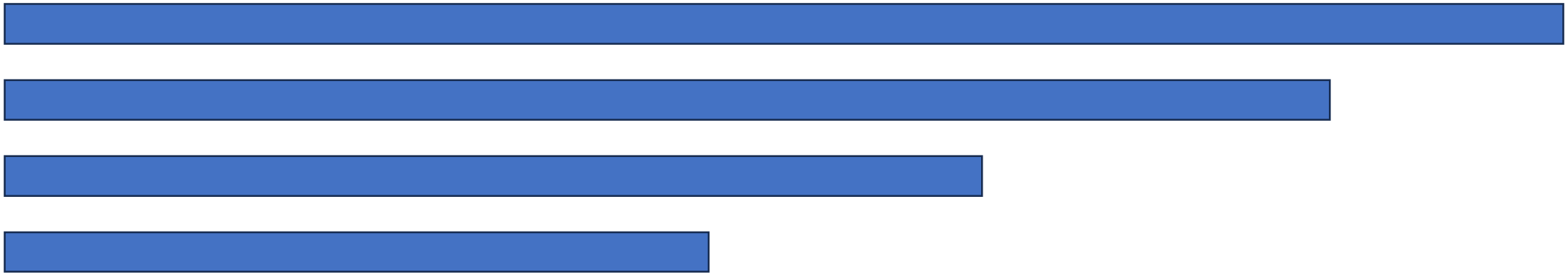
Understanding the layers of complexity of the viral reservoir



- The number of targetcells (mainly CD4+ T cells)is very high
- CD4 Tcells are present in many organs
- The number of infected cells is low
- Infections occur in different positions in the chromosomes
- Infected cells can devide to maintain the reservoir

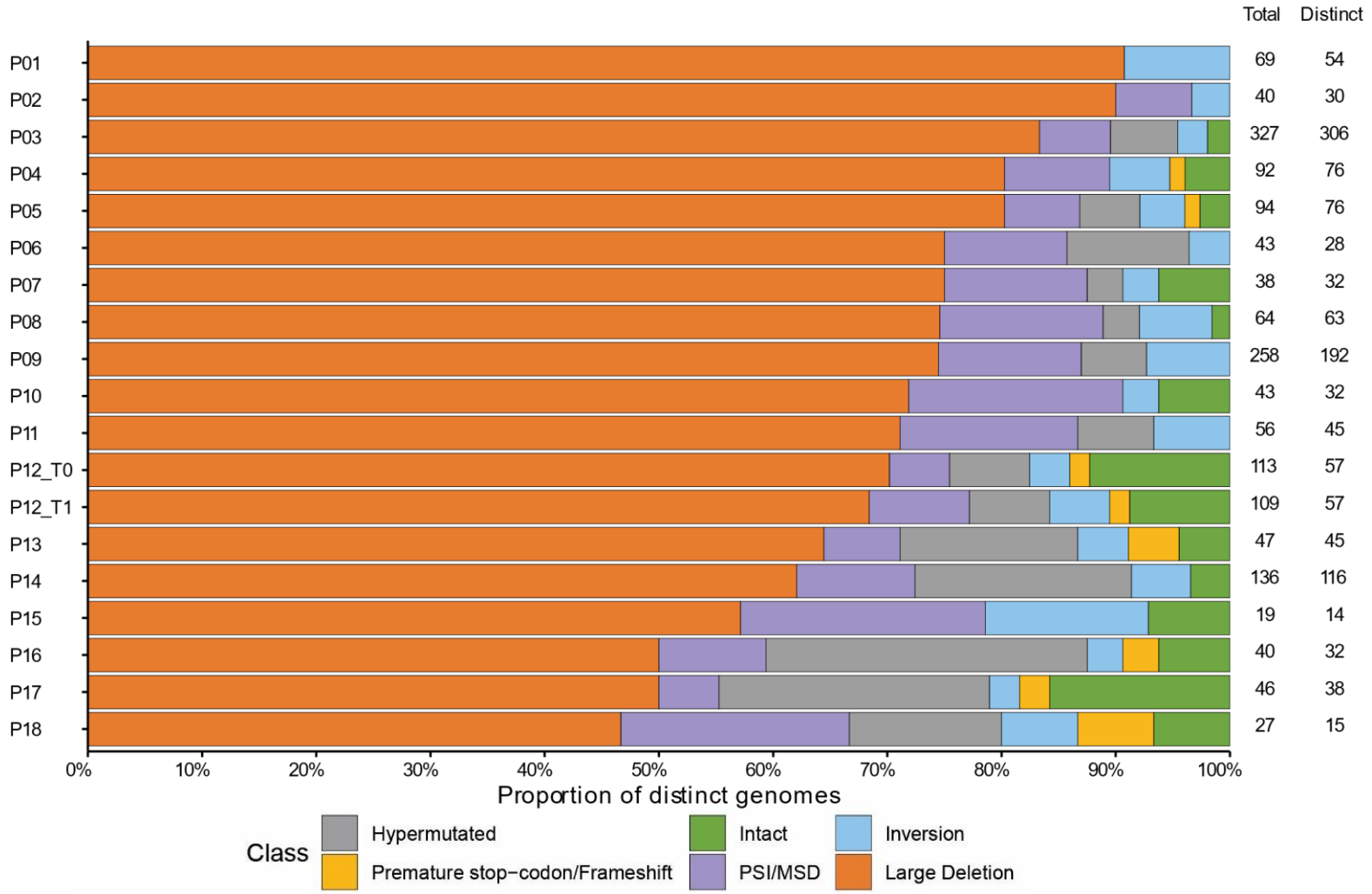
Additional layers of complexity of the viral reservoir



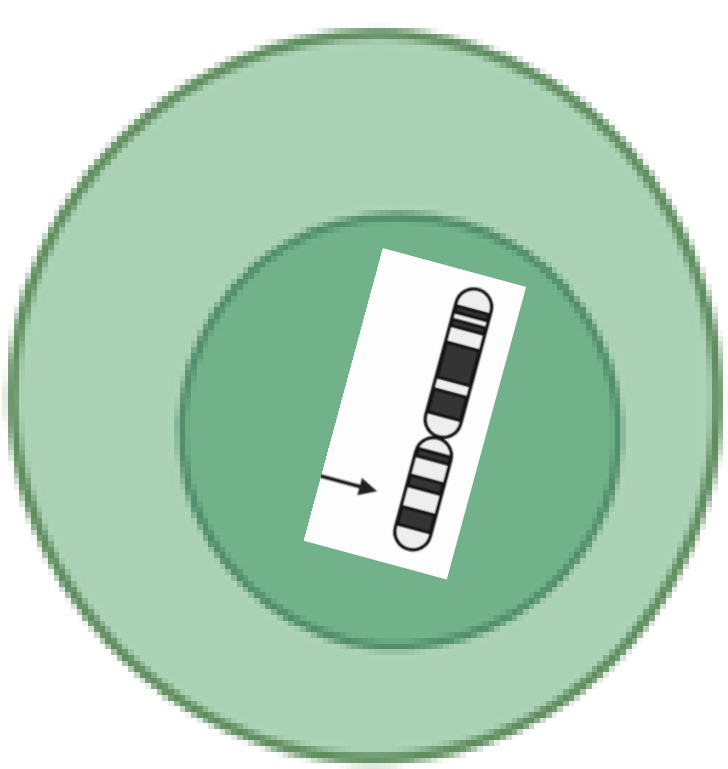


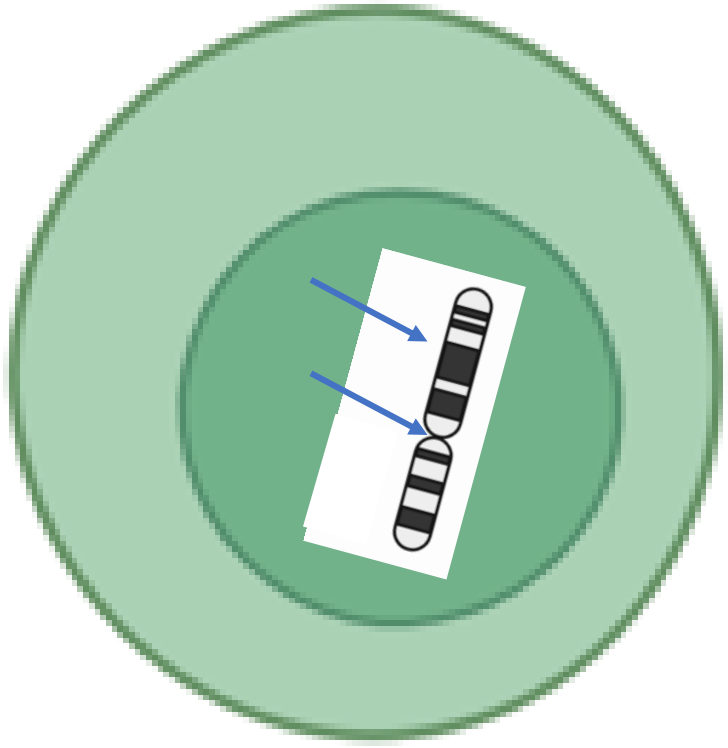
95% of the integrated viruses are not intact

- Cohort of 18 chronic PLWH on ART
- 1661 total proviral genomes
  - 1308 distinct

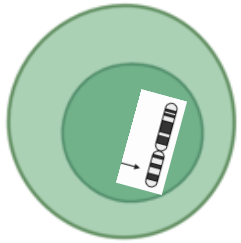


The position of the integration in the chromosome is important for potential generation of new viral particles



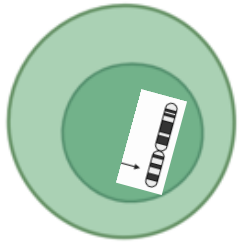


Understanding the layers of complexity of the viral reservoir



- The number of targetcells (mainly CD4+ T cells)is very high
- CD4 Tcells are present in many organs
- The number of infected cells is low
- Infections occur in different positions in the chromosomes
- Infected cells can divide to maintain the reservoir

Understanding the layers of complexity of the viral reservoir

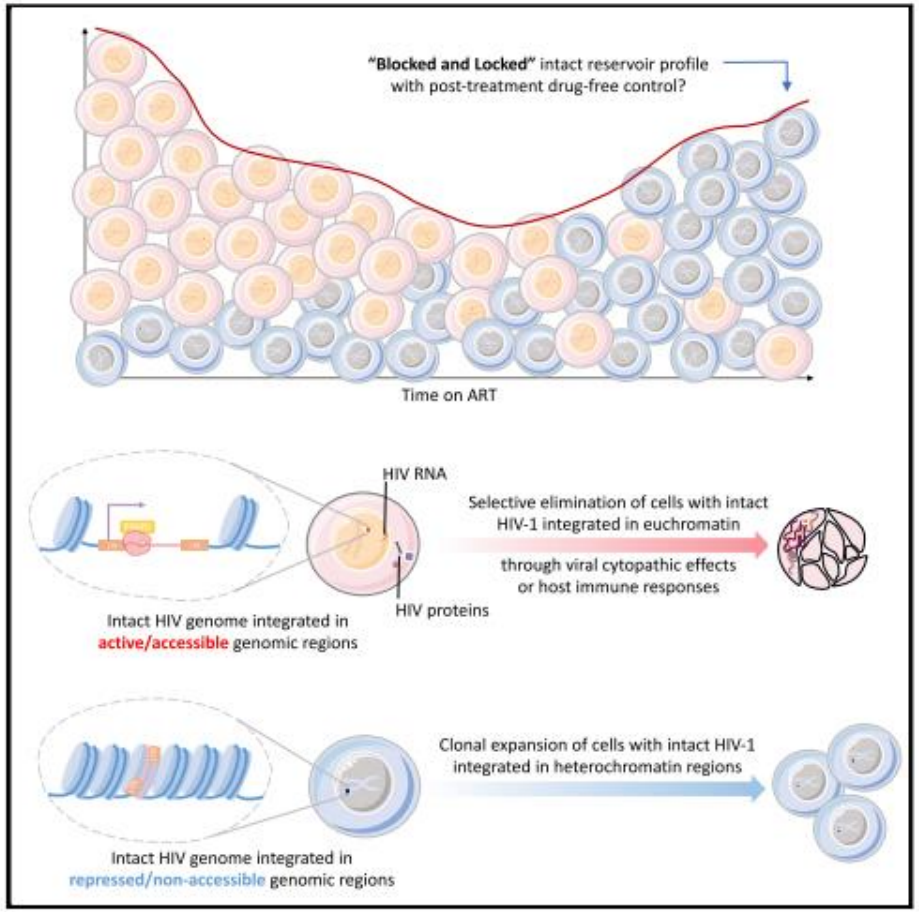


- The number of targetcells (mainly CD4+ T cells)is very high
- CD4 T cells are present in many organs
- The number of infected cells is low
- Infections occur in different positions in the chromosomes
- Infected cells can divide to maintain the reservoir
- Not all cells harbor an intact virus, only 5%
- Not all virus can be easy reactivated

Cell Host & Microbe

Progressive transformation of the HIV-1 reservoir cell profile over two decades of antiviral therapy

Graphical abstract



Authors

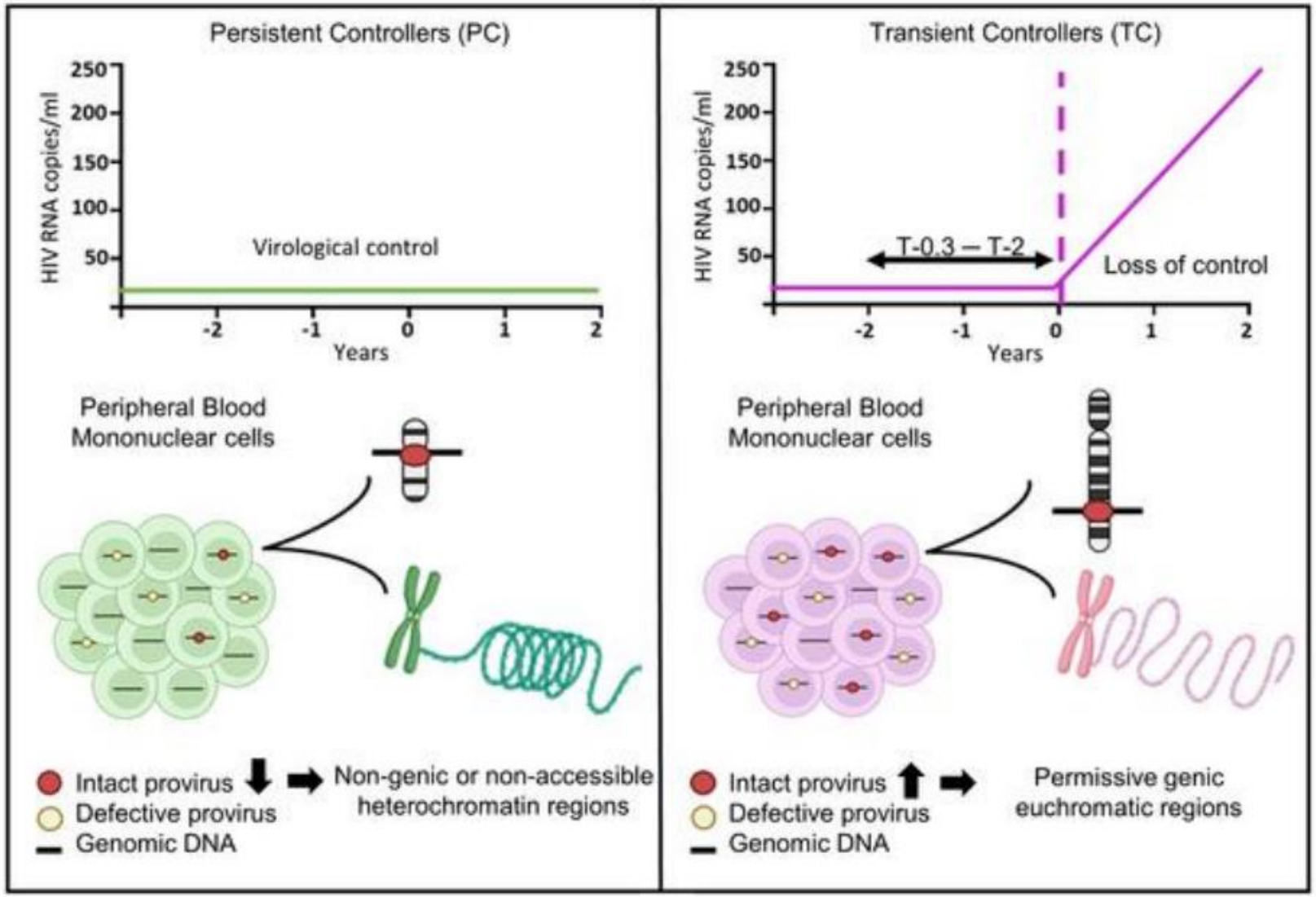
Xiaodong Lian, Kyra W. Seiger, Elizabeth M. Parsons, ..., Steven G. Deeks, Xu G. Yu, Mathias Lichterfeld

Correspondence

mlichterfeld@partners.org

In brief

Lian et al. show that following two decades of continuous antiretroviral therapy, the integration site profile of intact HIV-1 proviruses is heavily biased toward heterochromatin locations, likely as a result of immune selection mechanisms; such proviruses are less transcriptionally active and, possibly, less rebound competent.



Carmen Gasca-Capote, JCI 2024

nature medicine

Article

https://doi.org/10.1038/s41591-022-02023-7

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

Received: 15 March 2022

Accepted: 22 August 2022

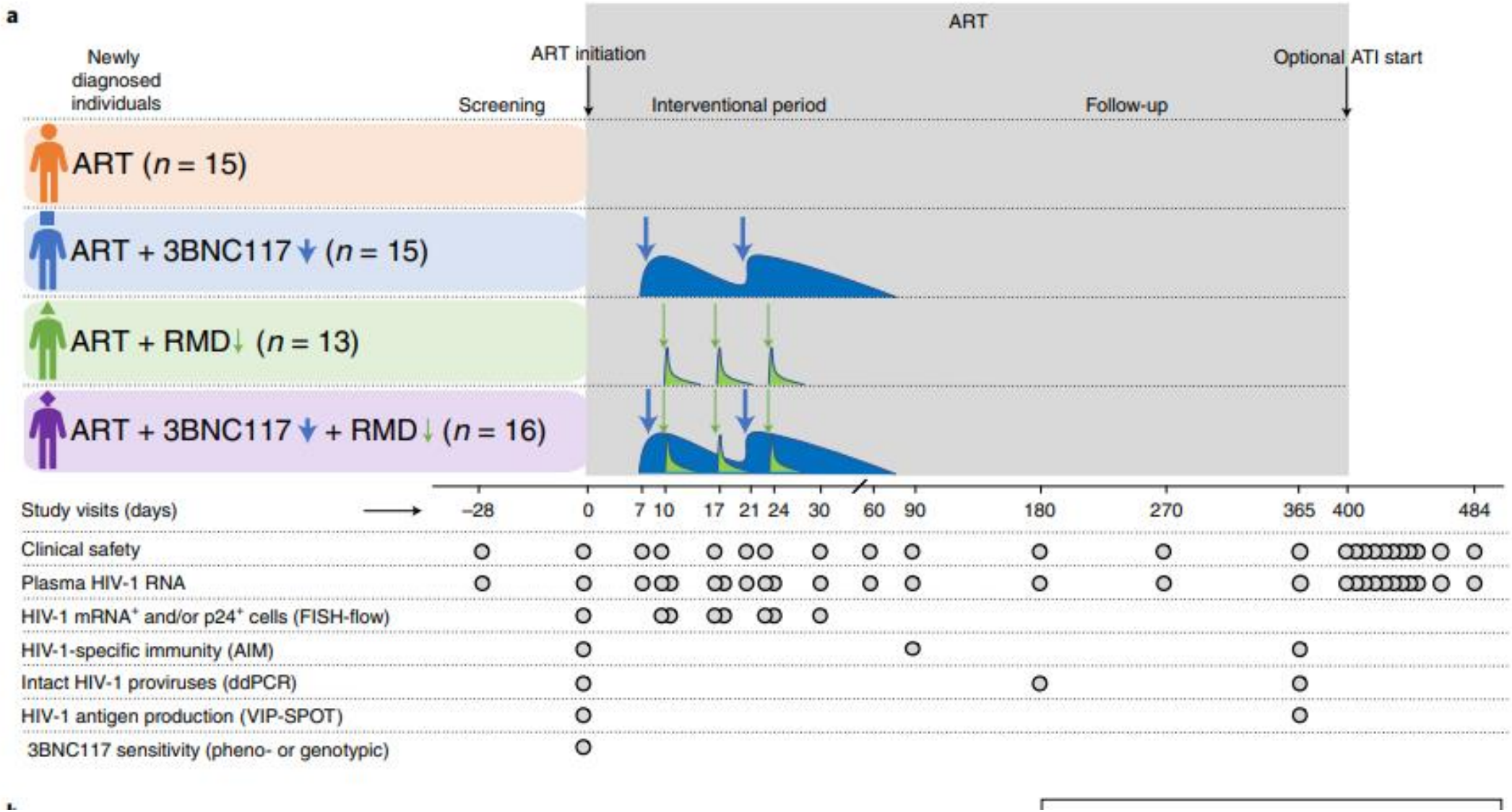
Published online: 17 October 2022

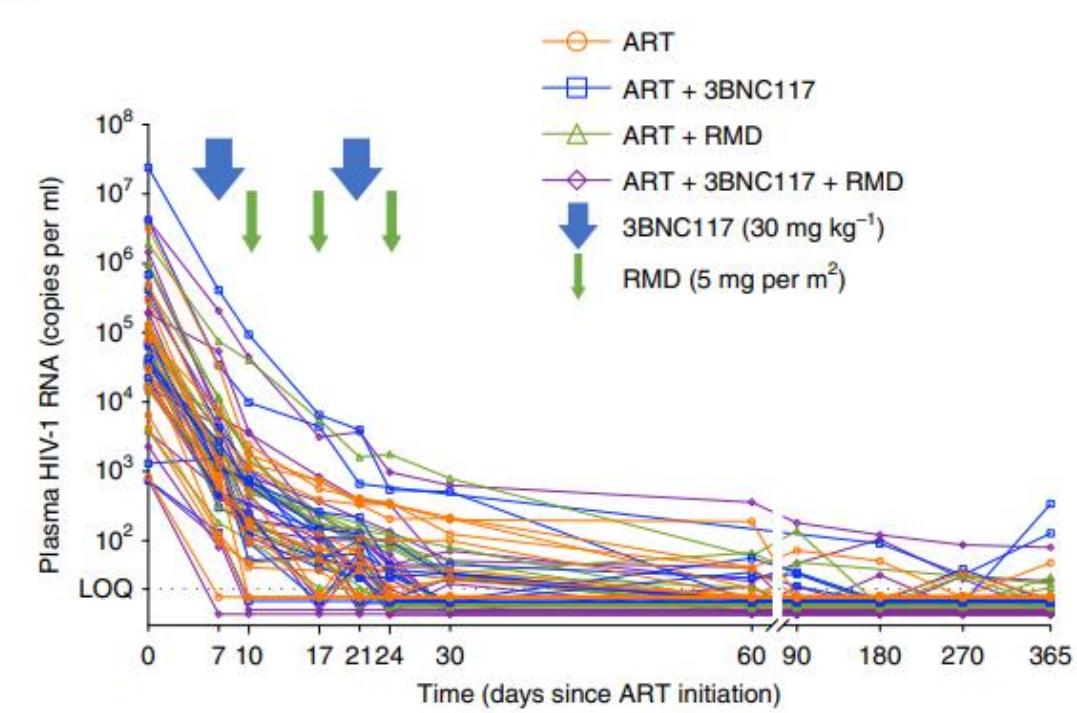
Check for updates

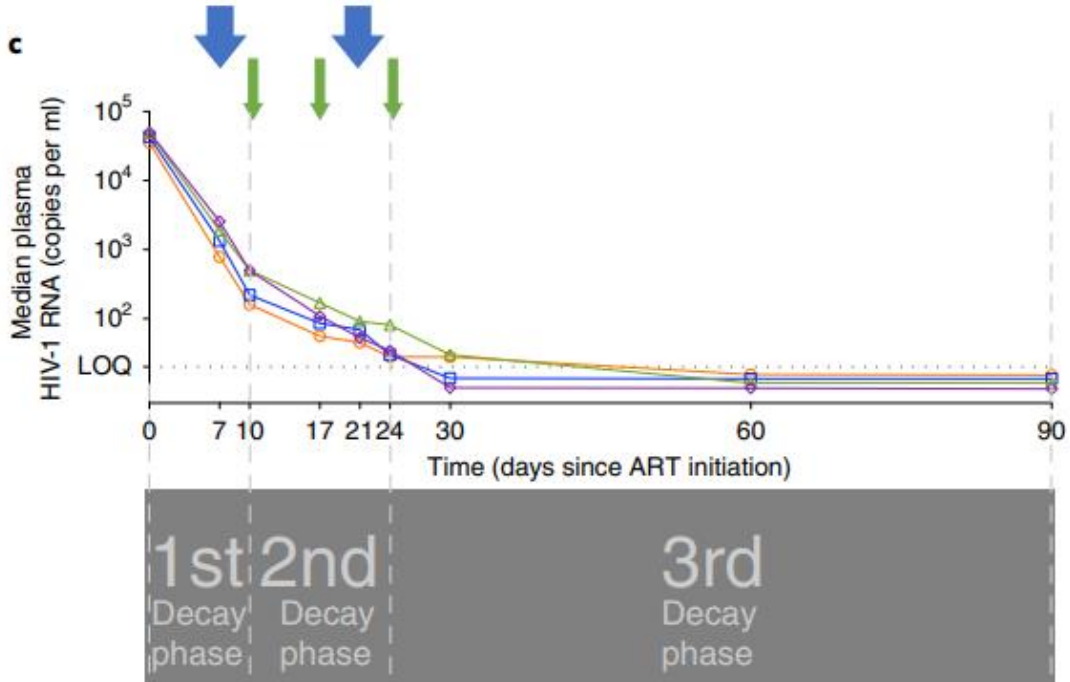
A list of authors and their affiliations appears at the end of the paper

Attempts to reduce the human immunodeficiency virus type 1 (HIV-1) reservoir and induce antiretroviral therapy (ART)-free virologic control have largely been unsuccessful. In this phase 1b/2a, open-label, randomized controlled trial using a four-group factorial design, we investigated whether early intervention in newly diagnosed people with HIV-1 with a monoclonal anti-HIV-1 antibody with a CD4-binding site, 3BNC117, followed by a histone deacetylase inhibitor, romidepsin, shortly after ART initiation altered the course of HIV-1 infection (NCT03041012). The trial was undertaken in five hospitals in Denmark and two hospitals in the United Kingdom. The coprimary endpoints were analysis of initial virus decay kinetics and changes in the frequency of $CD4^+$ T cells containing intact HIV-1 provirus from baseline to day 365. Secondary endpoints included changes in the frequency of infected $CD4^+$ T cells and virus-specific $CD8^+$ T cell immunity from baseline to day 365, pre-ART plasma HIV-1 3BNC117 sensitivity, safety

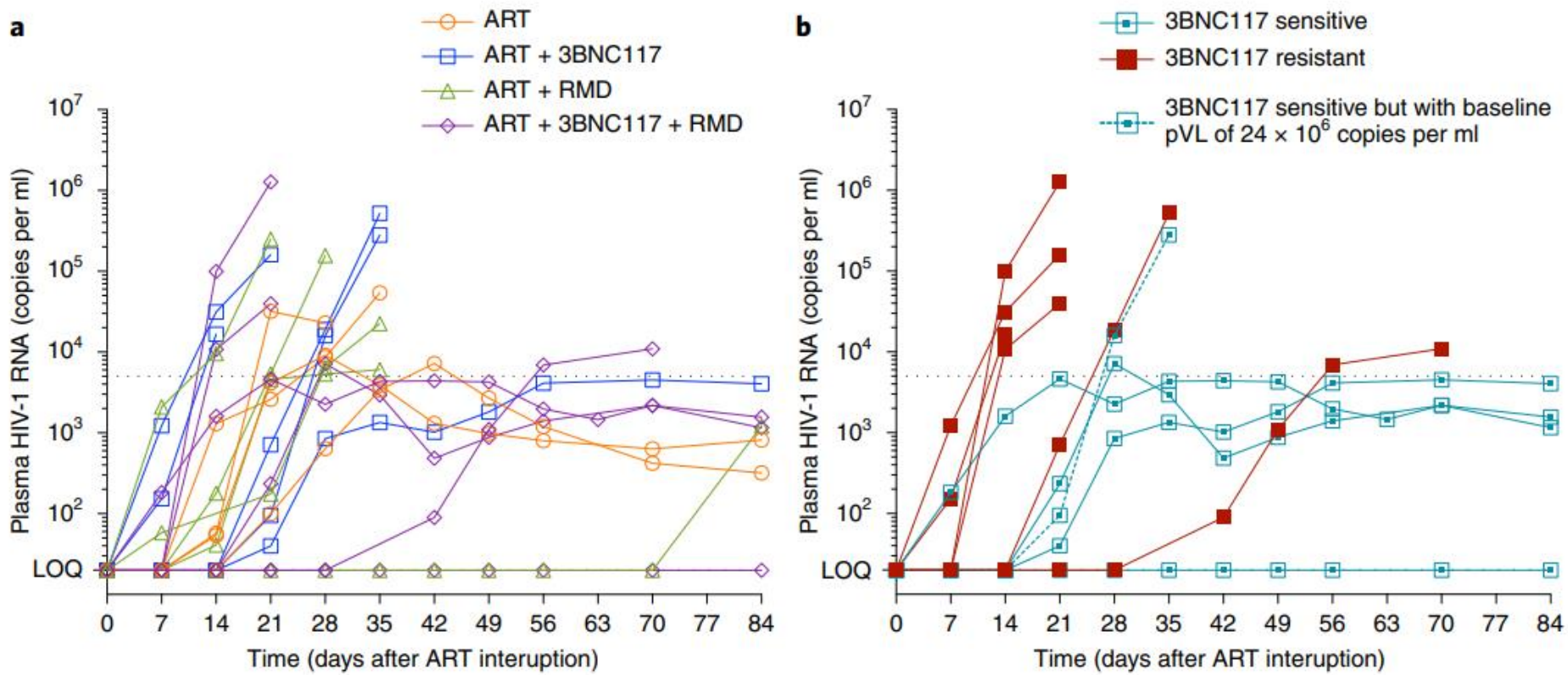
https://doi.org/10.1038/s41591-022-02023-7




ART
ART + 3BNC117
ART + RMD
ART + 3BNC117 + RMD
3BNC117 (30 mg kg^{-1})
RMD (5 mg per m^2)
Plasma HIV-1 RNA (copies per ml)
10^8
10^7
10^6
10^5
10^4
10^3
10^2
LOQ
0 7 10 17 21 24 30 60 90 180 270 365
Time (days since ART initiation)


c
Median plasma HIV-1 RNA (copies per ml)
10^5
10^4
10^3
10^2
LOQ
0 7 10 17 21 24 30 60 90
Time (days since ART initiation)
1st Decay phase
2nd Decay phase
3rd Decay phase

https://doi.org/10.1038/s41591-022-02023-7



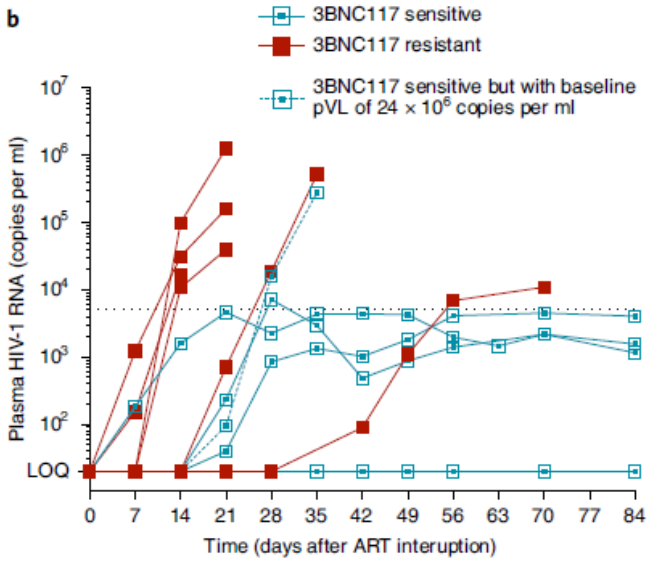
ID127

ID 127: <u>Only subtype B with leuka</u>

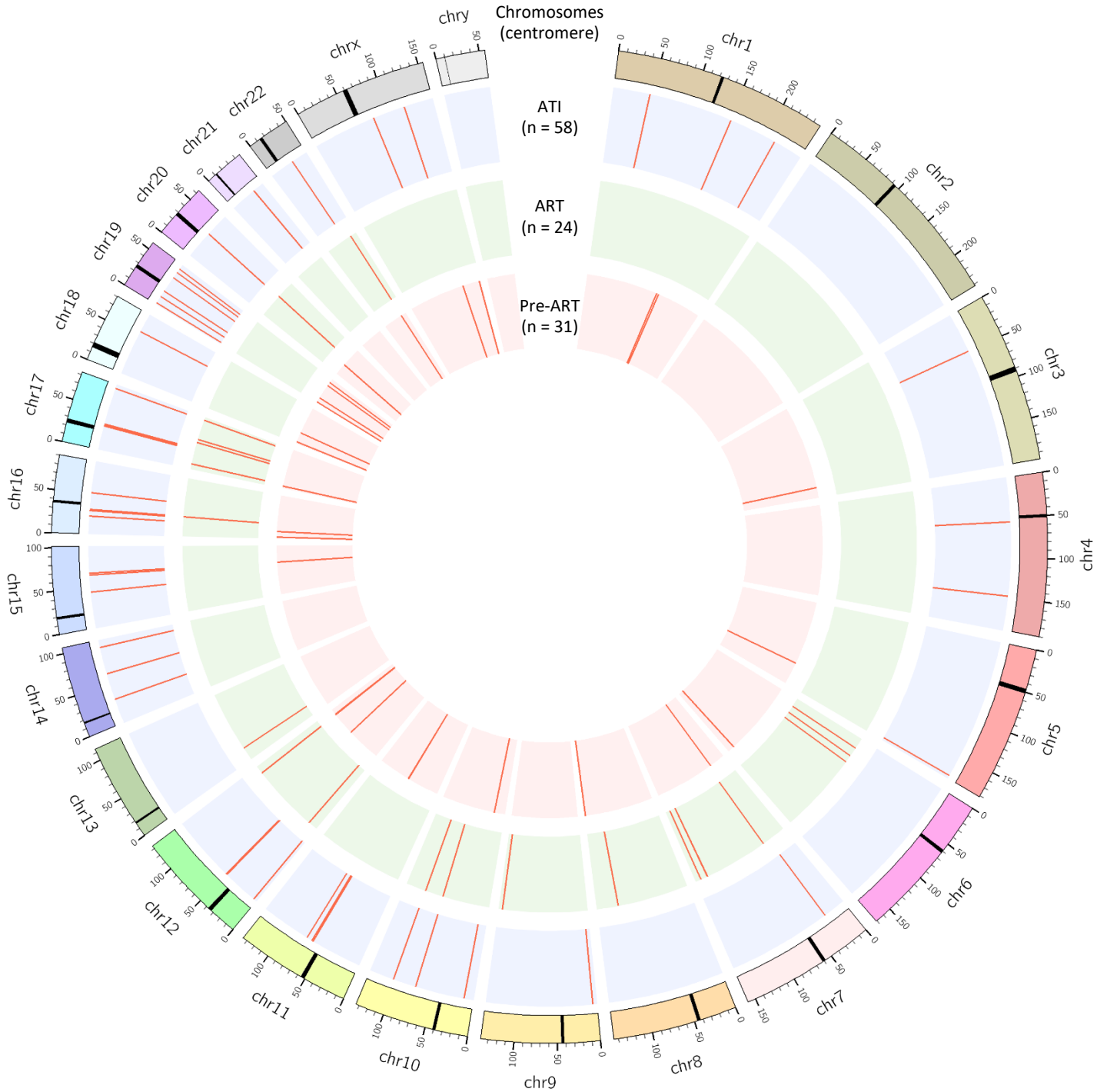
- Clinic
  - Acute treated (0-3 months from infection)
  - ART + Romidepsin + 3BNC117
  - ATI: viremic after 7 days, controls < 5.000 until day 84 (end of study)
- Paraclinic
  - Total HIV DNA (day 365): 2756 copies/10^6 CD4 T cells

V25 – ATI end

- 151 days into ATI
- Viral load: 7630 copies/mL
- Leukapheresis: 50 mio PBMCs



GHENT UNIVERSITY


Chromosomes
(centromere)
ATI
(n = 58)
ART
(n = 24)
Pre-ART
(n = 31)
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
chr10
chr11
chr12
chr13
chr14
chr15
chr16
chr17
chr18
chr19
chr20
chr21
chr22
chrx
chry

What does cure mean and why is a cure difficult ?

- The viral reservoir has many layers of complexity that evolve over time
- Does cure mean an elimination of all intact viruses (in remission)
- Does cure mean an elimination of all viruses
- Does cure mean an elimination of all intact viruses in active genes

BILL & MELINDA GATES foundation
fwo
NIH
GHENT UNIVERSITY

Community slide

- The viral reservoir has many layers of complexity that evolves over time
- Cure approaches need to take into account the complexity of the reservoir to generate long term safety data

BILL & MELINDA GATES foundation
fwo
NIH
GHENT UNIVERSITY

Hartelijk dank aan all PLWH die deelnemen aan deze studies

BILL & MELINDA GATES foundation

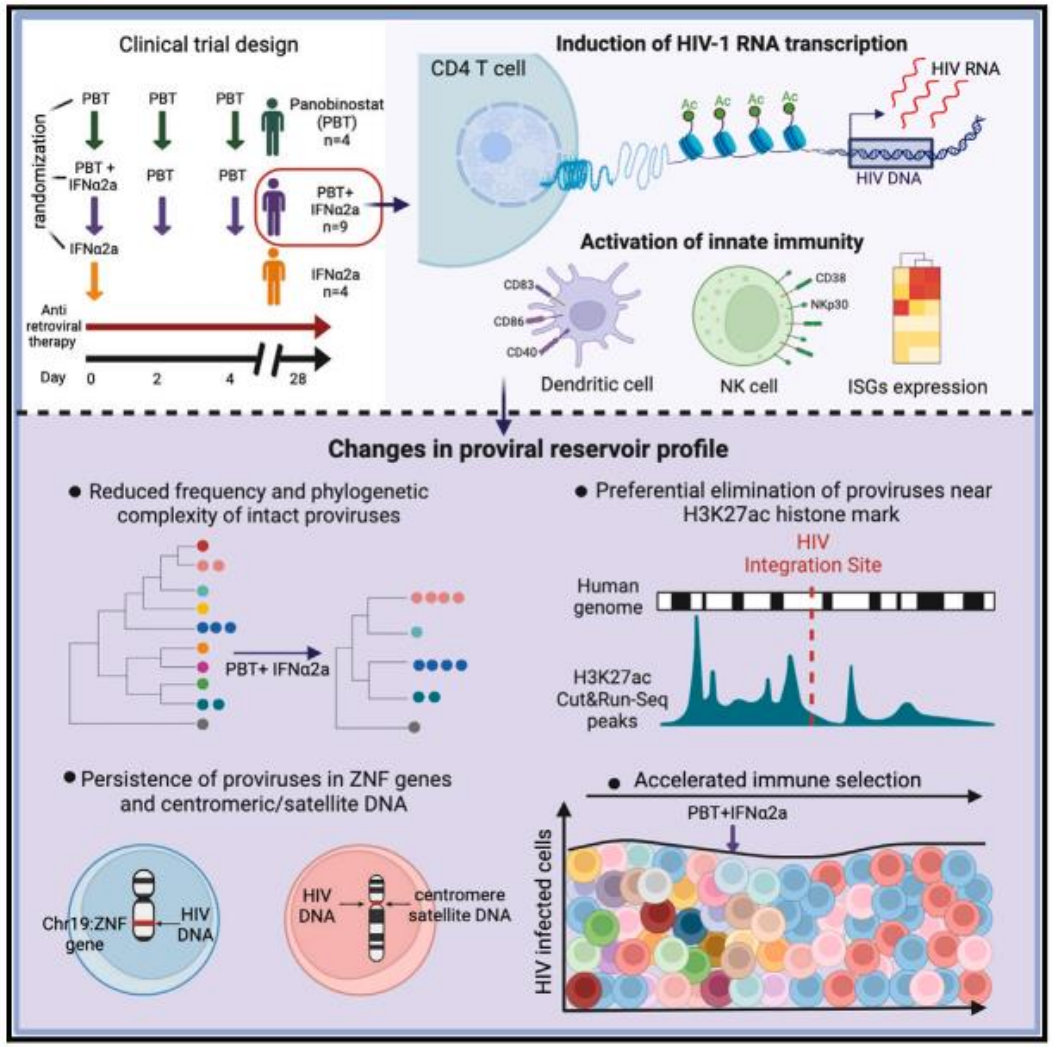
fwo

NIH

GHENT UNIVERSITY

Selection of epigenetically privileged HIV-1 proviruses during treatment with panobinostat and interferon-α2a

Graphical abstract



Authors

Marie Armani-Tourret, Ce Gao, Ciputra Adijaya Hartana, ..., Xu G. Yu, Daniel R. Kuritzkes, Mathias Lichterfeld

Correspondence

mlichterfeld@mgh.harvard.edu

In brief

In a human clinical trial, combined treatment with the histone deacetylase inhibitor panobinostat and pegylated interferon-α2a increased the immunological vulnerability of HIV-1 reservoir cells and amplified naturally occurring immune selection pressure against HIV-1 proviruses integrated in permissive chromatin locations.