hiv&aids +asrh 2025

Dreams of a Cure: Challenges and Hopes in Overcoming HIV-1 Persistence

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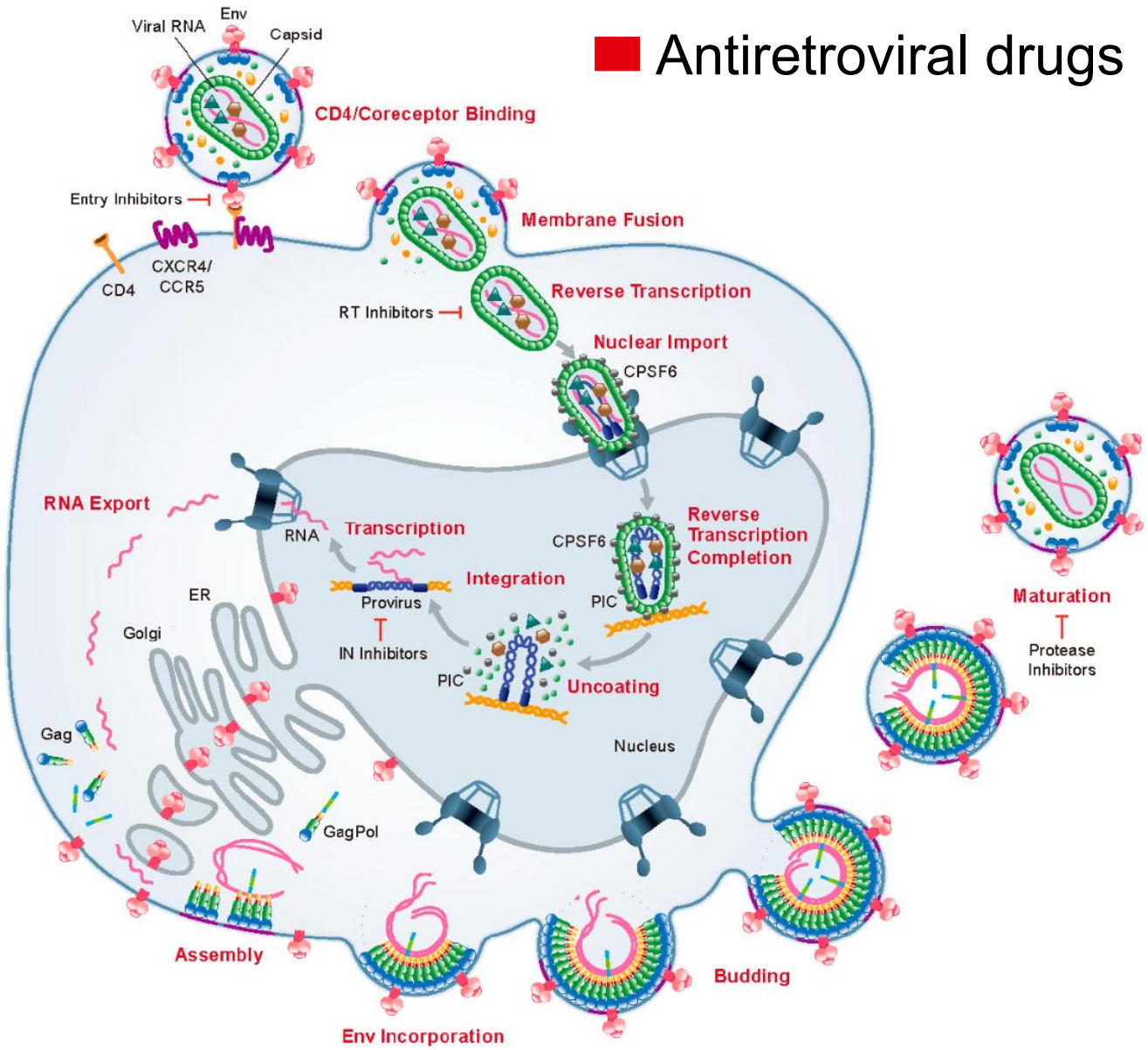
I have received honoraria from Gilead to present at scientific conferences

ART is incredibly effective, why we need a cure?

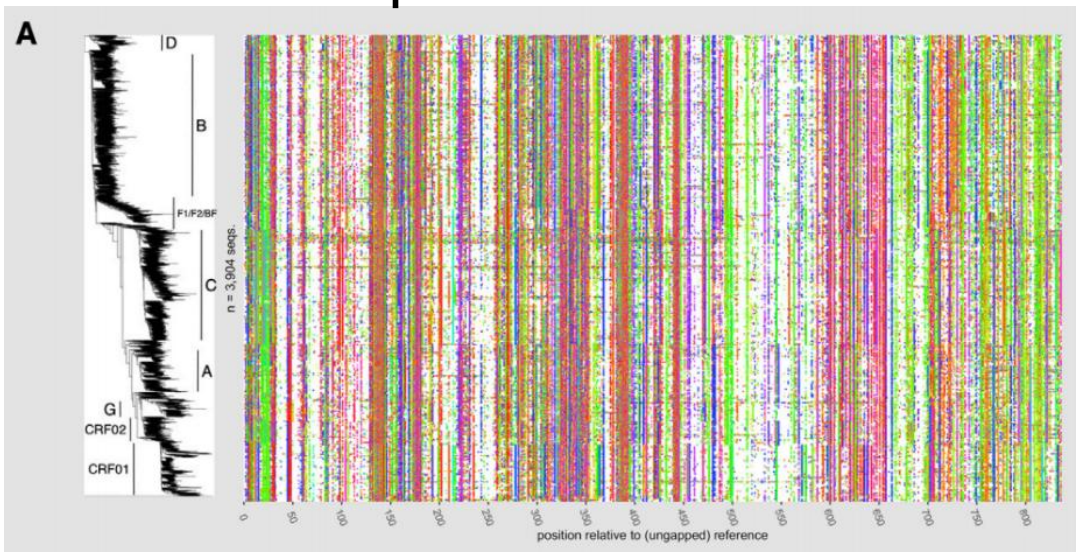
- To end the HIV epidemic, we need new prevention and therapeutic options
- HIV is still deadly (630,000 died in 2022)
- The cost of ART is unsustainable (19 billion USD by 2030)
- HIV-related stigma remains
- HIV is a driver of other diseases
- HIV research leads biomedical advances in other fields

HIV is a formidable challenge

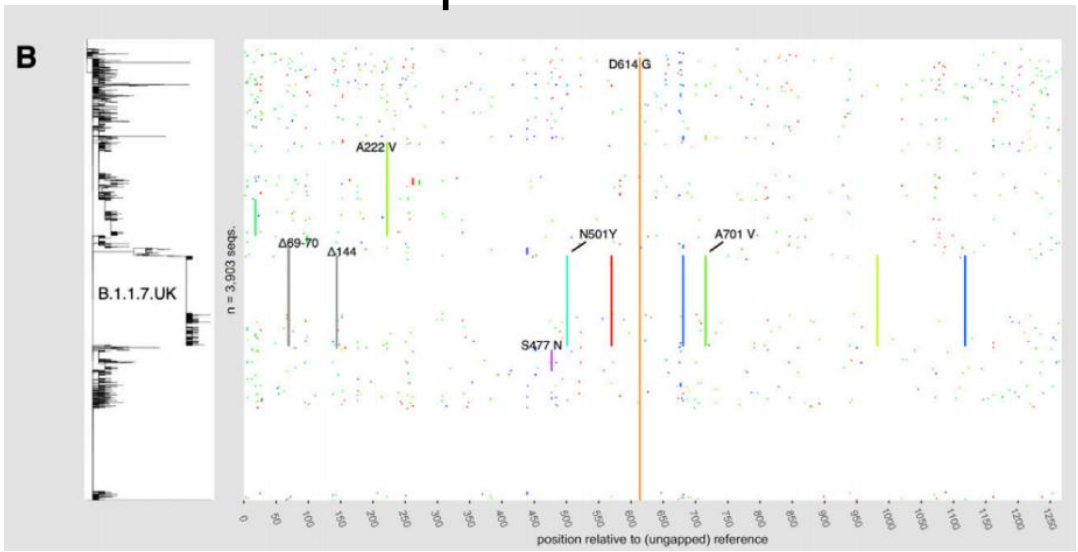


Kleinpeter and Freed, Viruses 2019

HIV-1 Envelope

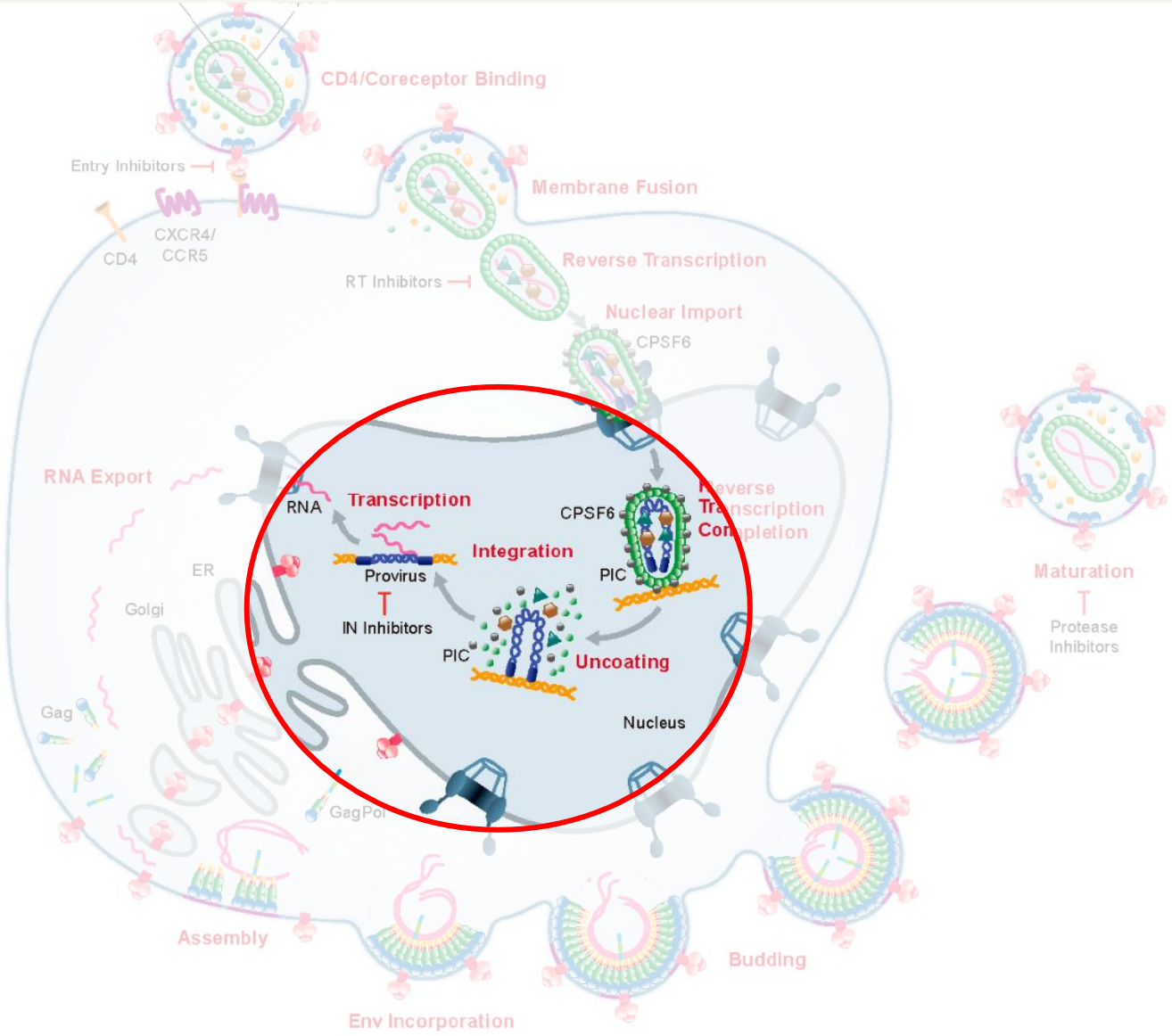


SARS-CoV-2 spike



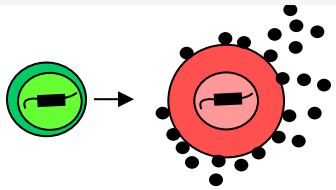
Fisher et al., CHM 2021

HIV is a formidable challenge



Kleinpeter and Freed, Viruses 2019

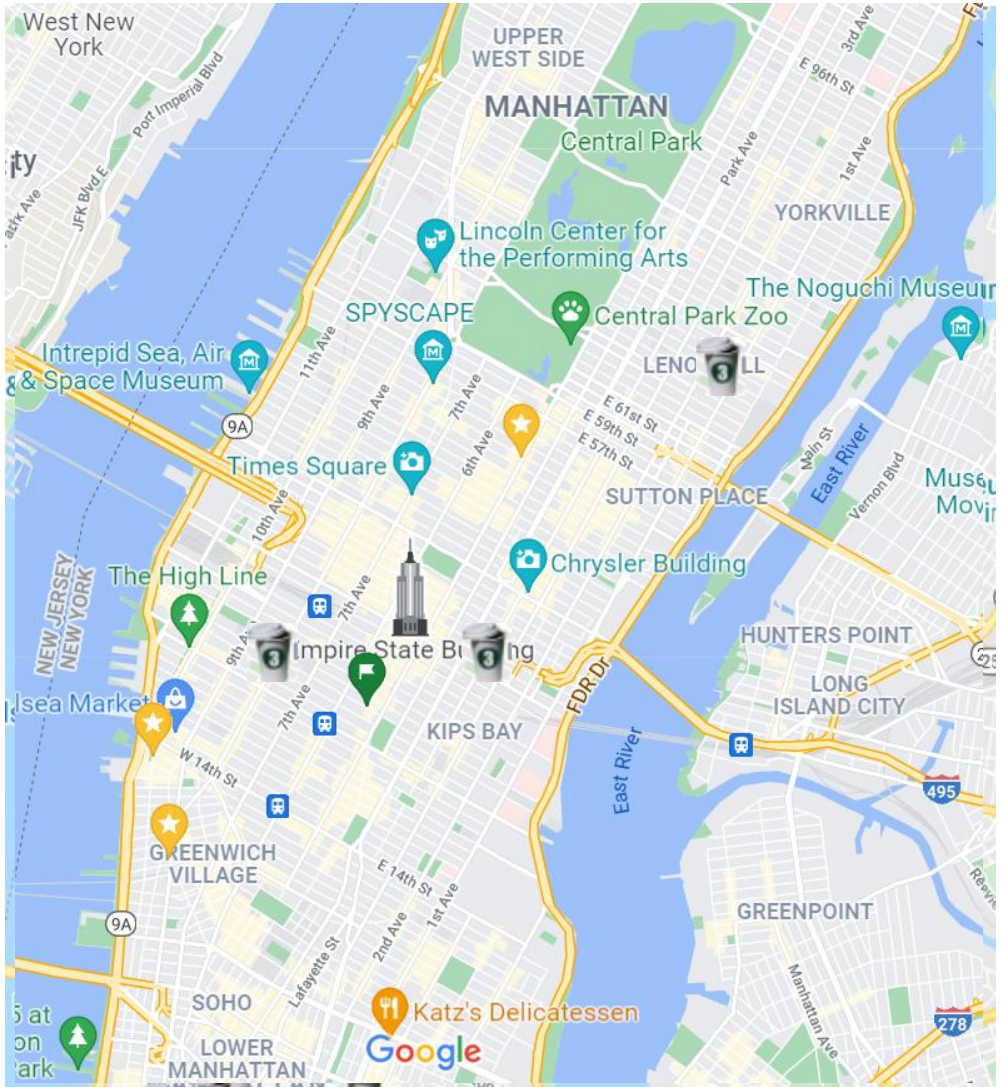
The HIV reservoir is an elusive target



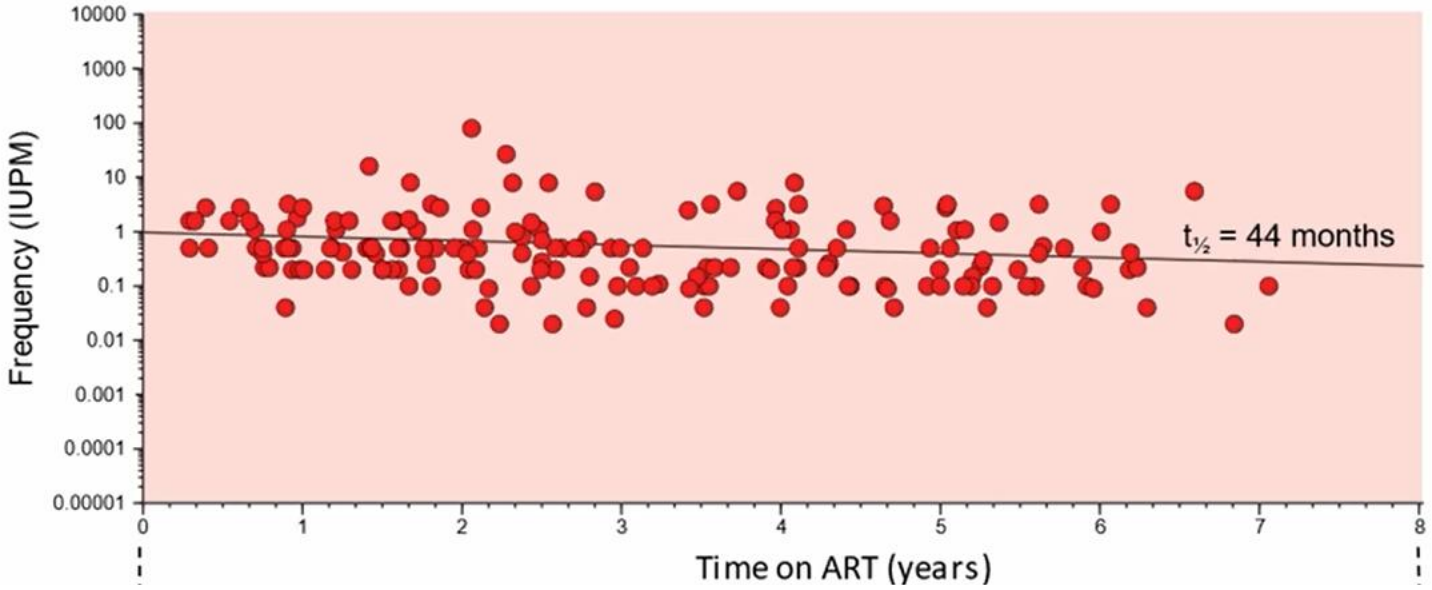
res·er·voir

/ˈrezərˌvwär/

“a supply or source of something”



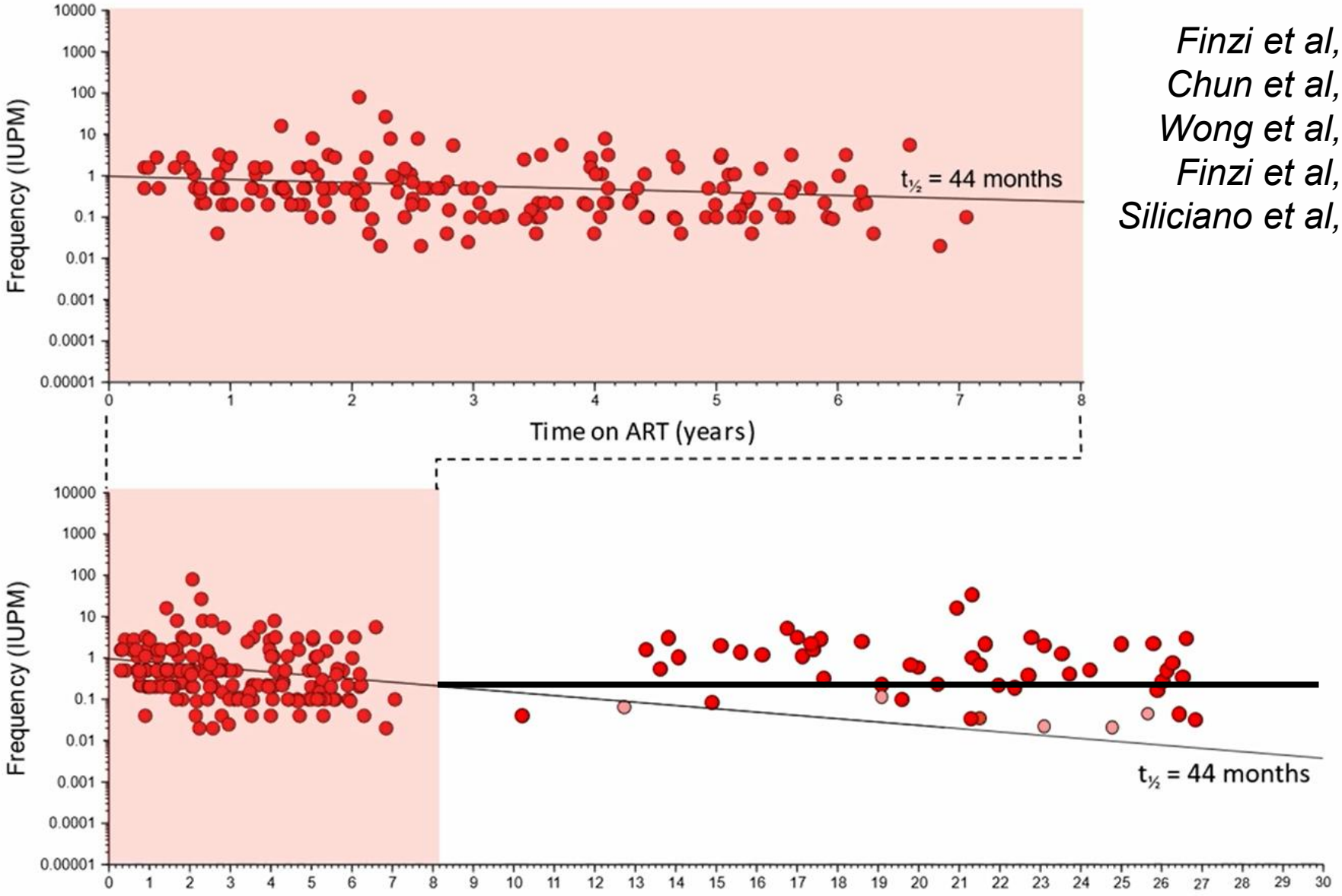
Lack of reservoir decay after 20+ years of ART



Finzi et al, 1997
Chun et al, 1997
Wong et al, 1997
Finzi et al, 1999
Siliciano et al, 2003

Janet Siliciano, CROI2023
McMyn et al, JCI 2023

Lack of reservoir decay after 20+ years of ART



Finzi et al, 1997
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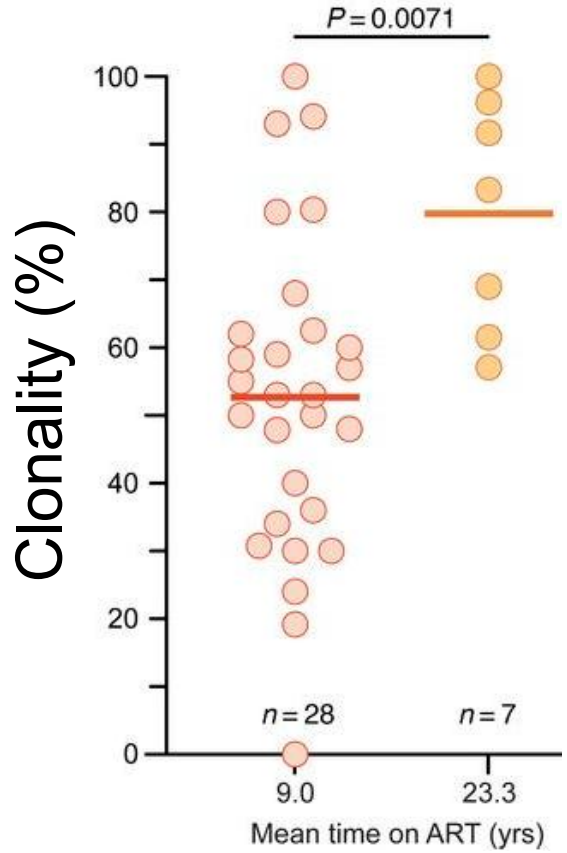
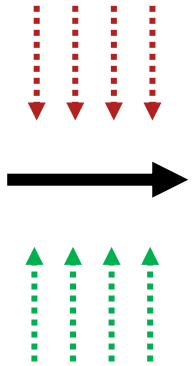


Janet Siliciano, CROI2023
McMyn et al, JCI 2023

Infected cells become progressively more clonal

Acute infection *in vivo* or *in vitro*

Initial distribution



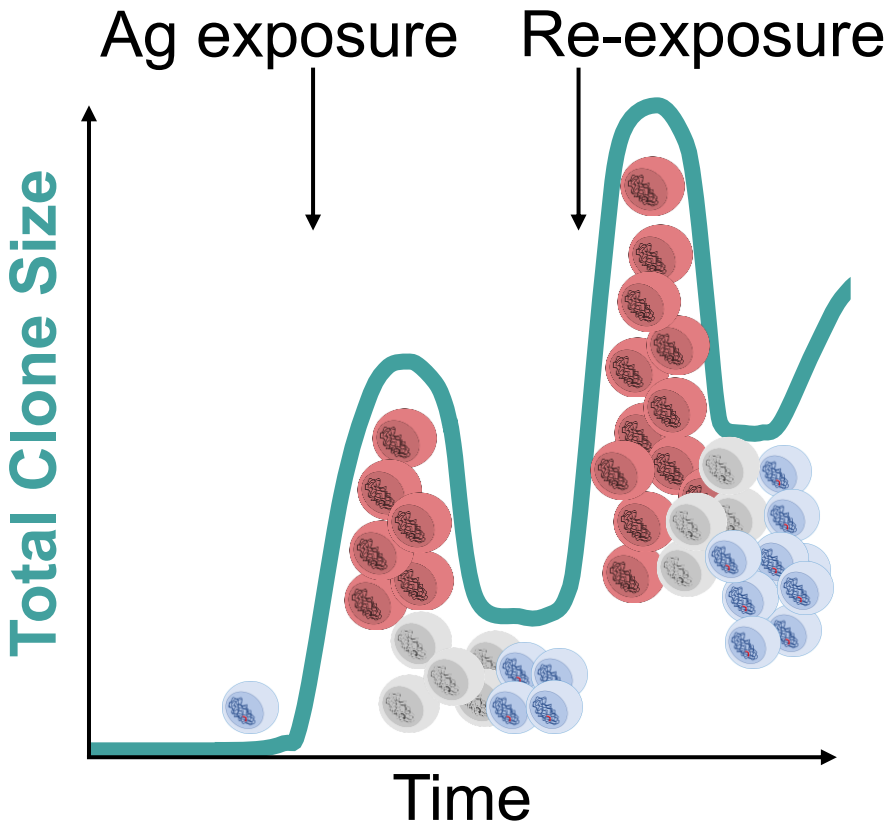
Long-term ART

Result of selection:
-Negative (immune clearance)
-Positive (clonal selection)

Coffin and Hughes, 2021

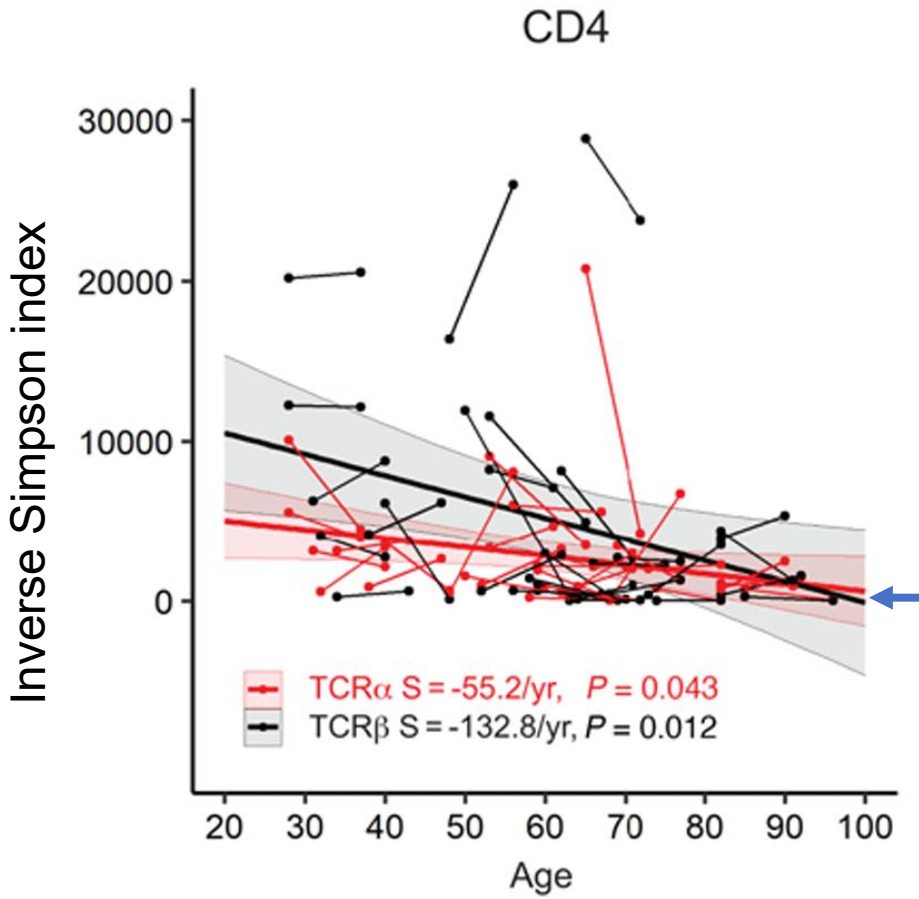
HIV persists in those cells deemed to survive

Clonal selection



Simonetti, JCI, 2021
Dragoni, JCI, 2023
Moskovjlevic, Immunity, 2024

Long-term memory

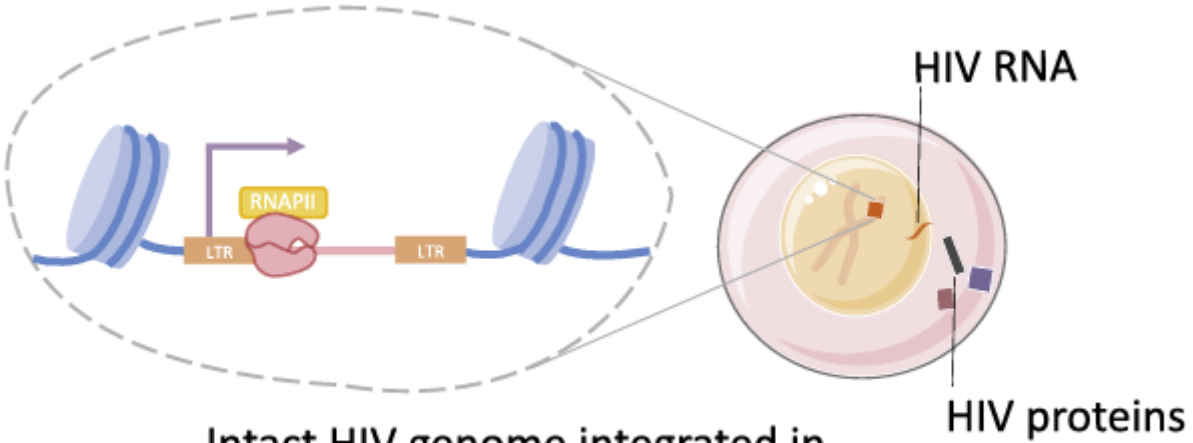


Increased clonality with age

Sun, JCI, 2022

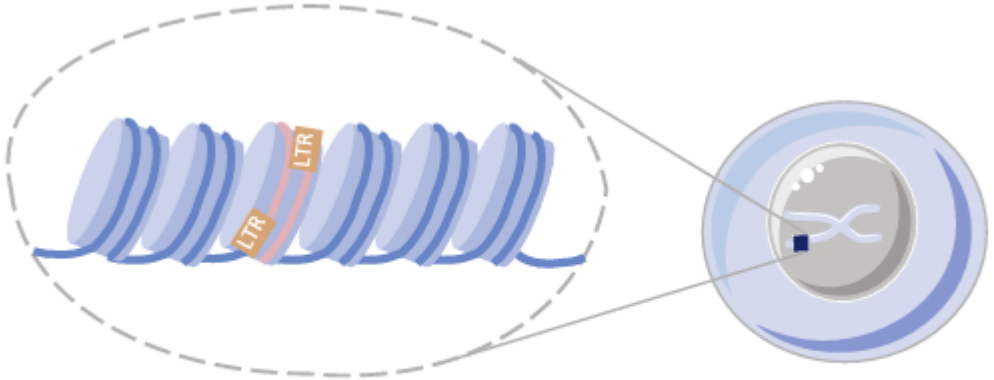
Progressive shift of reservoir features suggests selection

Early ART



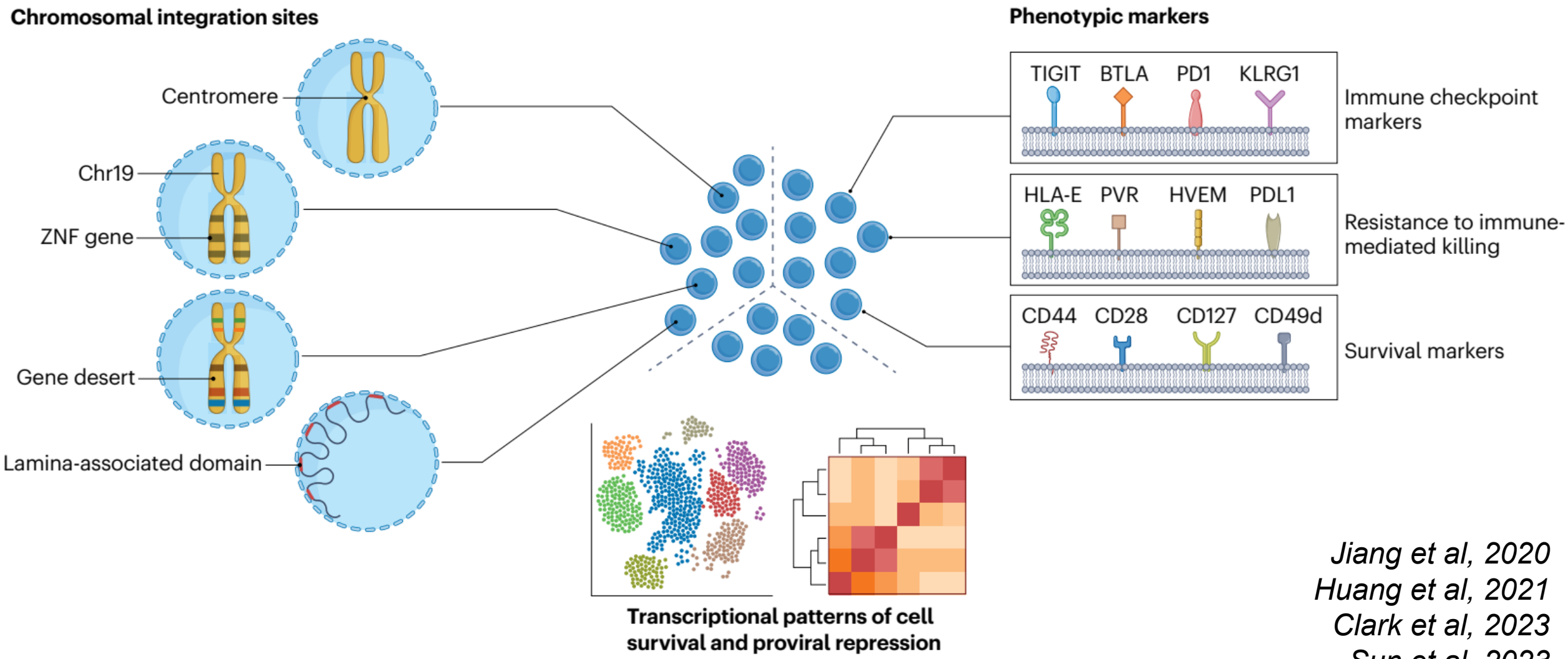
Intact HIV genome integrated in
active/accessible genomic regions

20+ years or ART or Elite Control



Intact HIV genome integrated in
repressed/non-accessible genomic regions

Progressive shift of reservoir features suggests selection



Jiang et al, 2020
Huang et al, 2021
Clark et al, 2023
Sun et al, 2023
Lian et al, 2023
Dragoni et al, 2023
Armani-Tourret et al, 2025

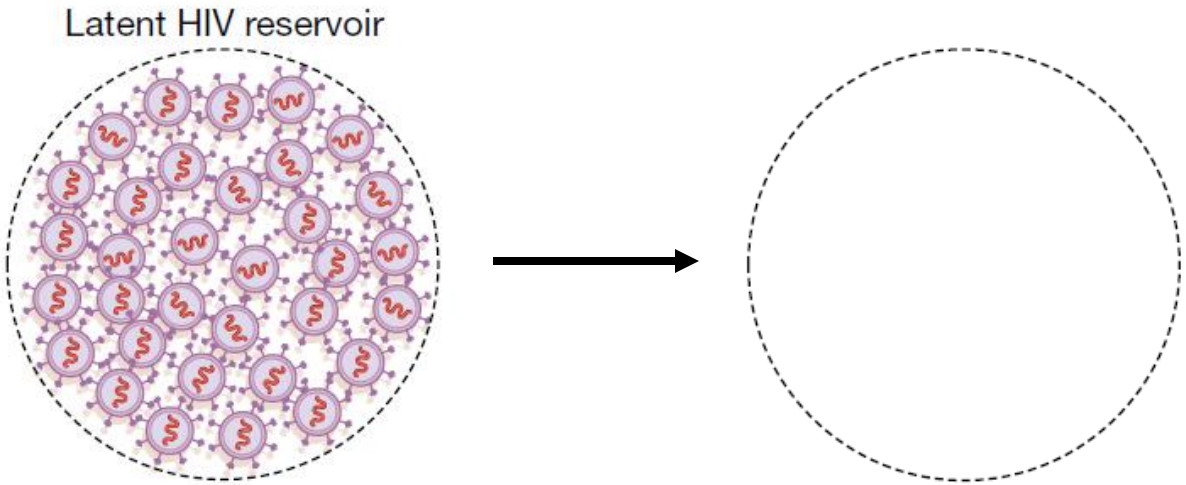
These feature are unique to cells with *intact proviruses*!

The reservoir is stable yet subjected to ***immune erosion***

This is good news, reflection of ongoing HIV-host interaction that we could target with therapeutics

Strategies for ART-free HIV remission

Eradication model



Hematopoietic cell transplant with CCR5 deletion

- >99.99% of the reservoir is eliminated by: conditioning regimen, chemoradiation, donor engraftment, graft versus host disease, recipient cell turnover
- Donor cells are protected by the CCR5 deletion

Ndung'u et al., Nature 2019

Hsu et al., Cell 2023

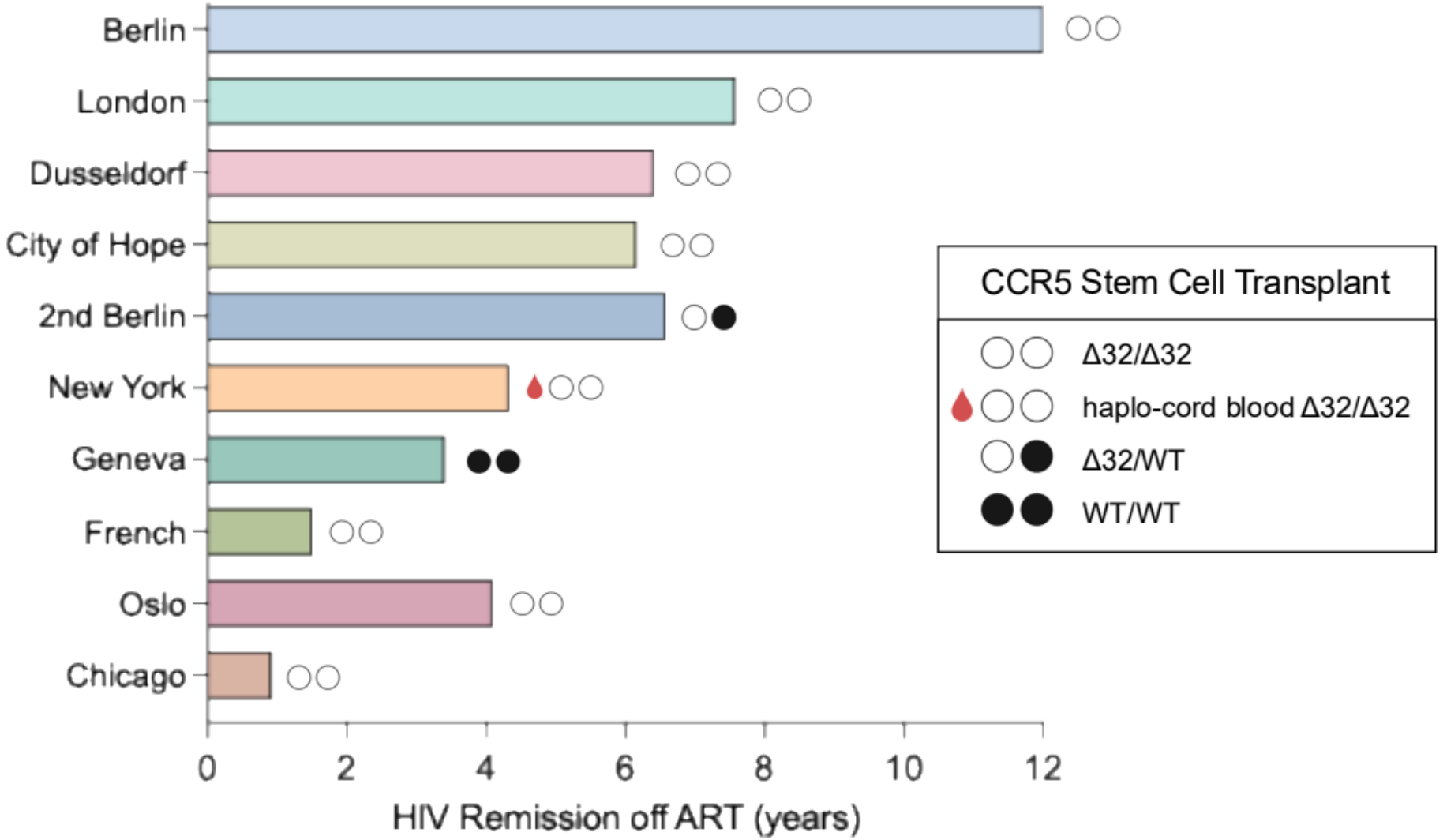
Learning from a few (but mighty) cases of HIV cure

Chemo + TBI
BM 10/10 HLA match

Tim Brown, 2009

Chemo
BM 9/10 HLA match

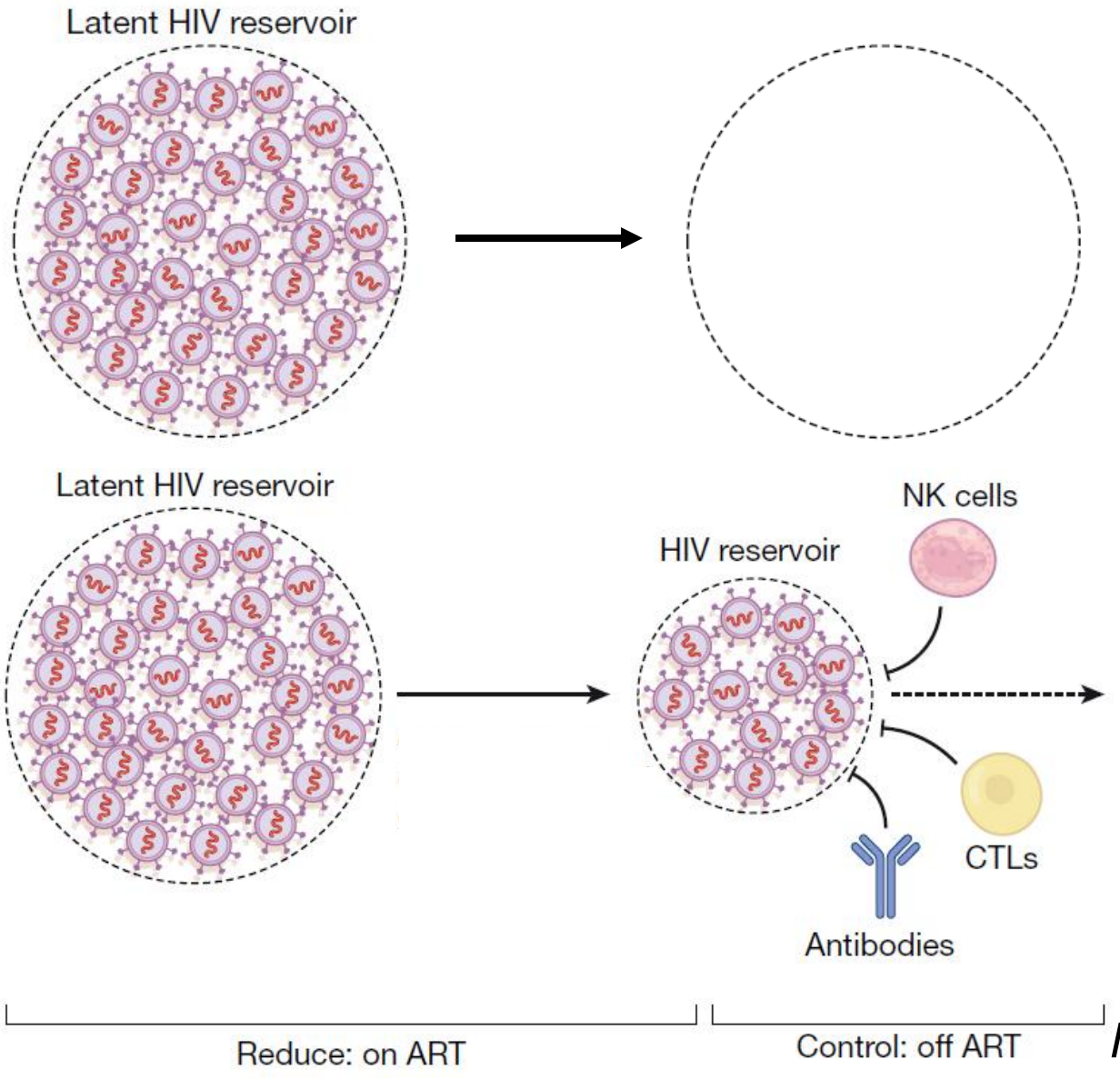
Adam Castillejo, 2019



Strategies to achieve ART-free remission

Eradication model

Remission model



Ndung'u et al., Nature 2019

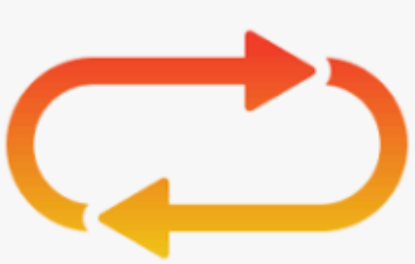
Reservoir elimination in Exceptional Elite Controllers

Loreen Willenberg, 2020

Esperanza Patient, 2021

HIV can be detected, but only from **defective** proviruses

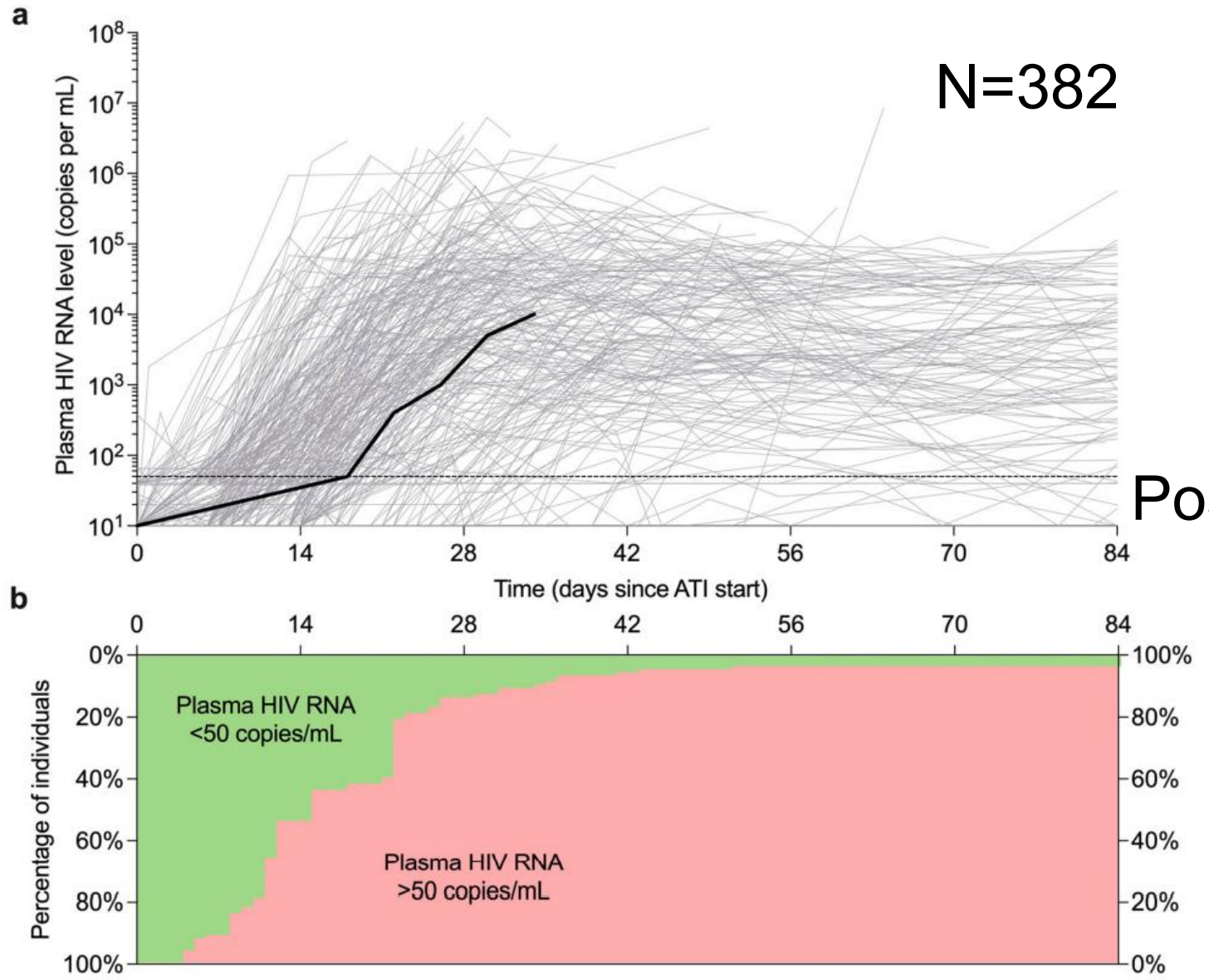
Less fit virus



Strong immune pressure

Jiang Nature, 2020; Turk, Annals Int Med, 2021
Salgado Med, 2024

Time to viral rebound is ~14-28 days in most PWH



N=382

Post-treatment control ~4%

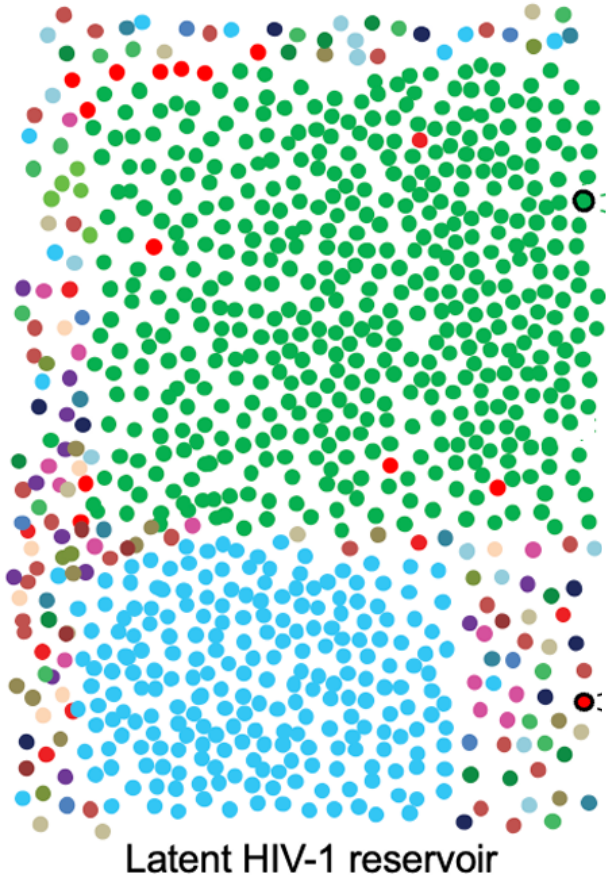
Treated <6mo -> 6%

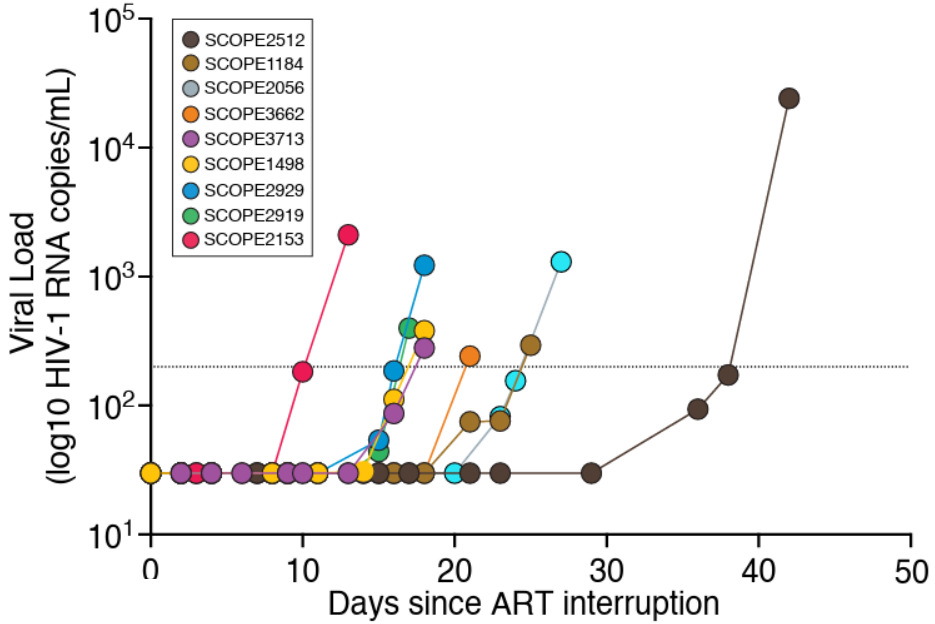
Treated >6mo -> 1%

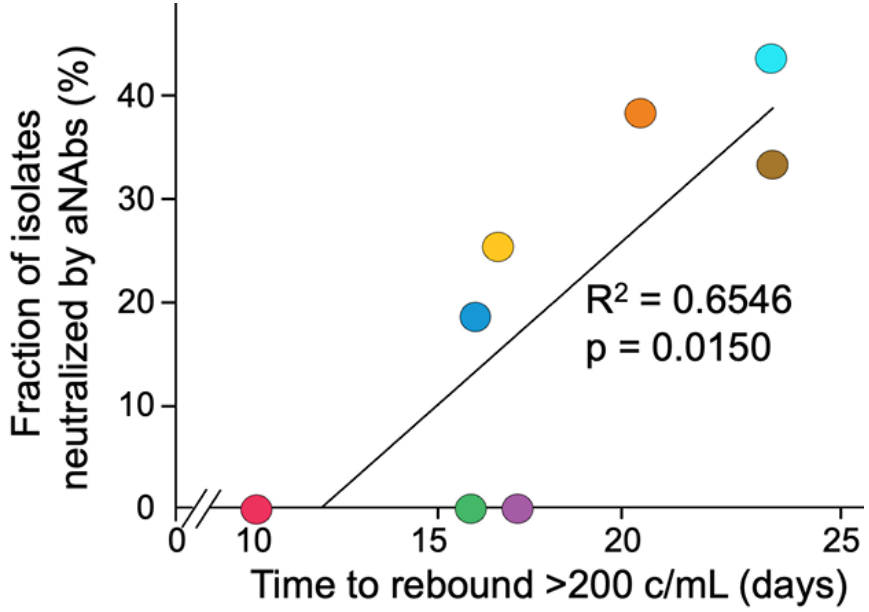
Gunst et al., Nat Comm 2025

Viral rebound is a selection process

Autologous neutralizing antibodies (ANAbs)
persist on ART and shape rebound dynamics



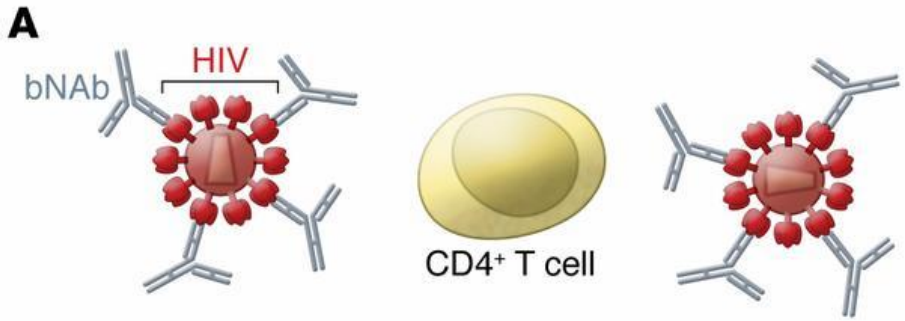




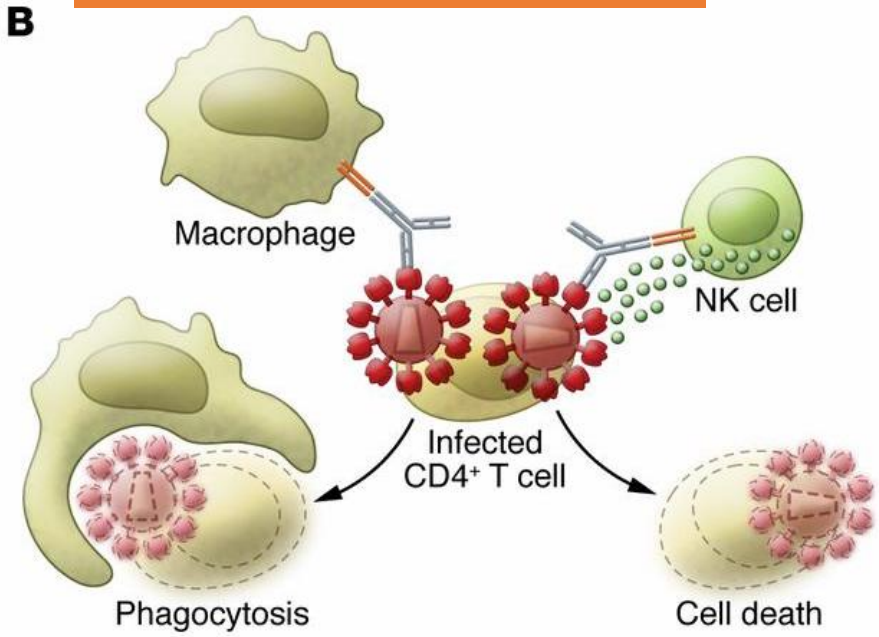
Garcia, CROI 2024 and 2025

HIV Broadly Neutralizing Antibodies as immune modulators

Block new infections

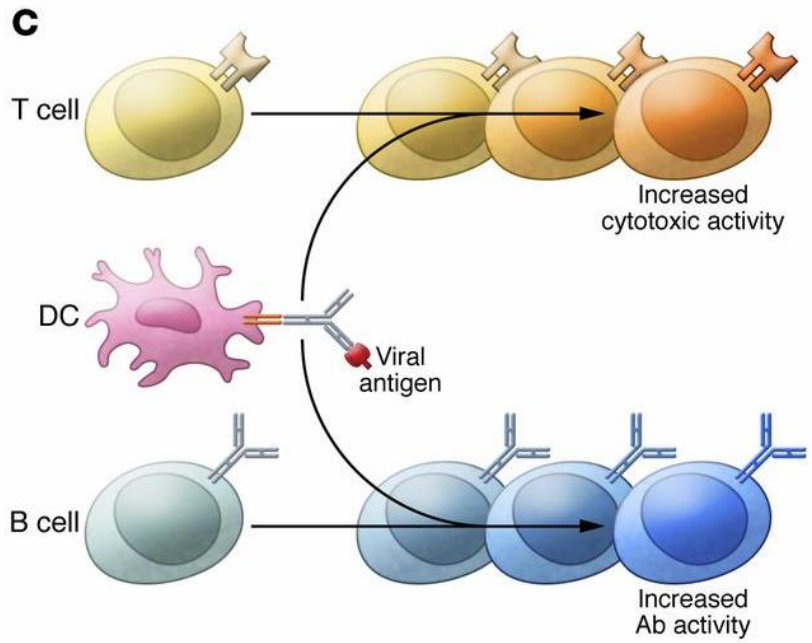


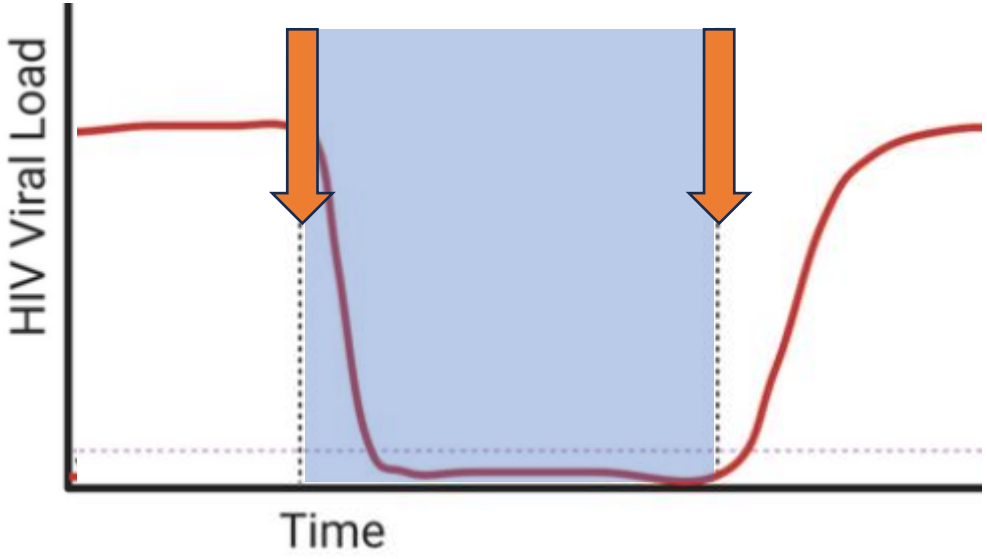
Mediate clearance



Halper-Stromberg, JCI, 2016

Enhance HIV-specific responses





bNABs in hyperacutely HIV-treated African women

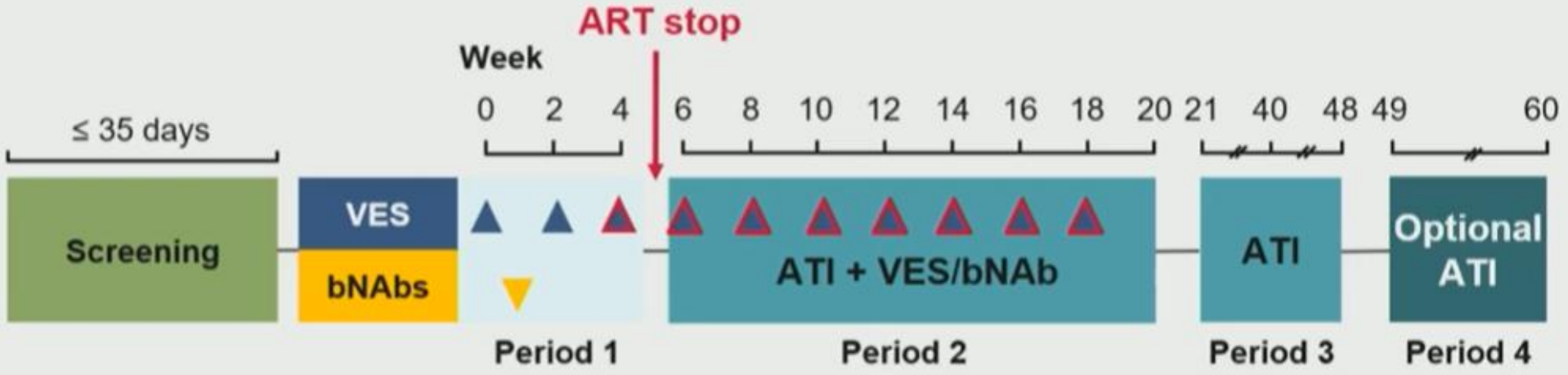
Ndung'u, CROI 2025

CROI
Conference on Retroviruses and Opportunistic Infections

Most women were treated during Fiebig I (FRESH cohort)

Inclusion criteria

- Females from FRESH cohort
- Virally suppressed on ART > 12 months
- Sensitive to at least 1 of the 2 bNAbs
- CD4+ T-cell count ≥ 500 cells/μL

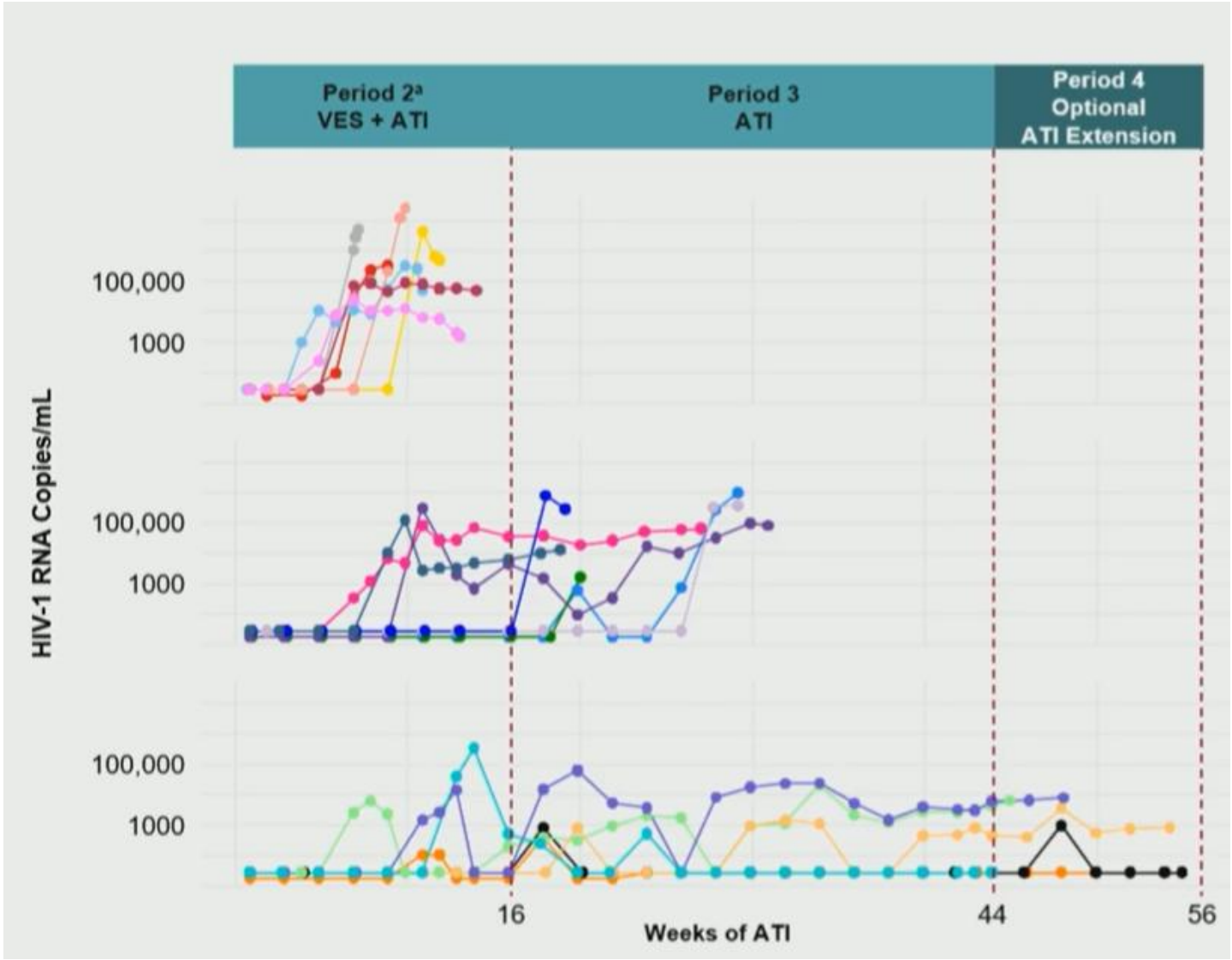


▲ VES (oral) ▲ Possible VES dose escalation[a] from 6 to 8 mg ▼ bNAbs: VRC07-523LS + CAP256V2LS (NIH) (20 mg/kg IV each bNAb)

bNABs in hyperacutely HIV-treated African women

Ndung'u, CROI 2025

CROI
Conference on Retroviruses and Opportunistic Infections



7/20 (35%)

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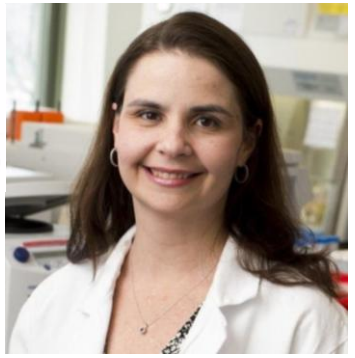
6/20 (30%)

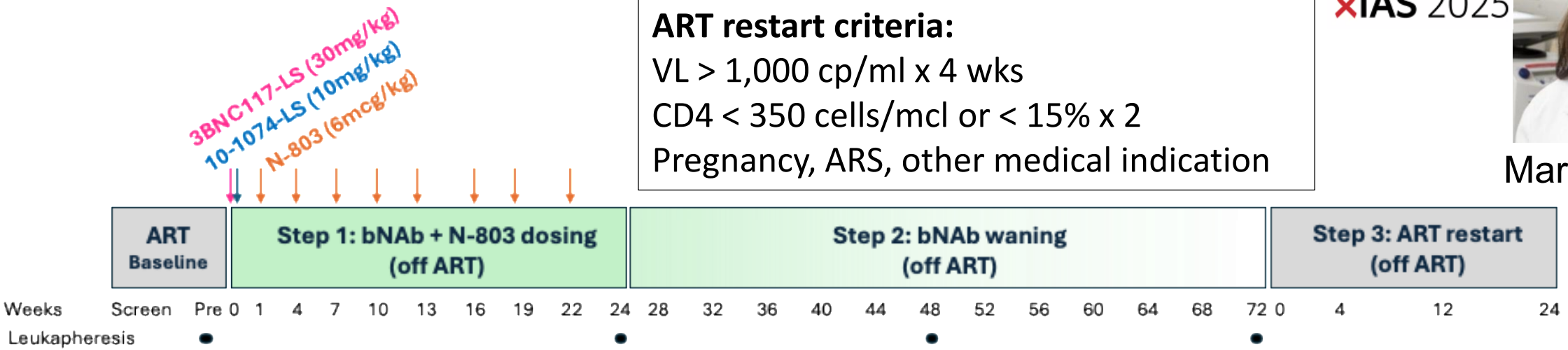
4/20 (20%)
>1.5 years
off ART

2 LS-bNAbs in ATI in people treated during **chronic** HIV

IAS 2025



Marina Caskey



ART restart criteria:
VL > 1,000 cp/ml x 4 wks
CD4 < 350 cells/mcl or < 15% x 2
Pregnancy, ARS, other medical indication

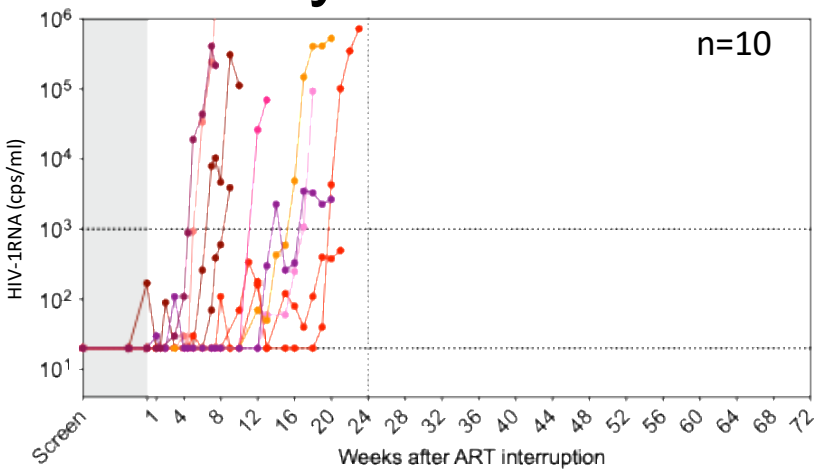
Study Population (n=28):
- 18 to 70 yrs
- Current CD4 > 450
- CD4 nadir > 200
- On ART w/ VL < LLOQ x > 1yr

- bNAb resistance testing not part of eligibility

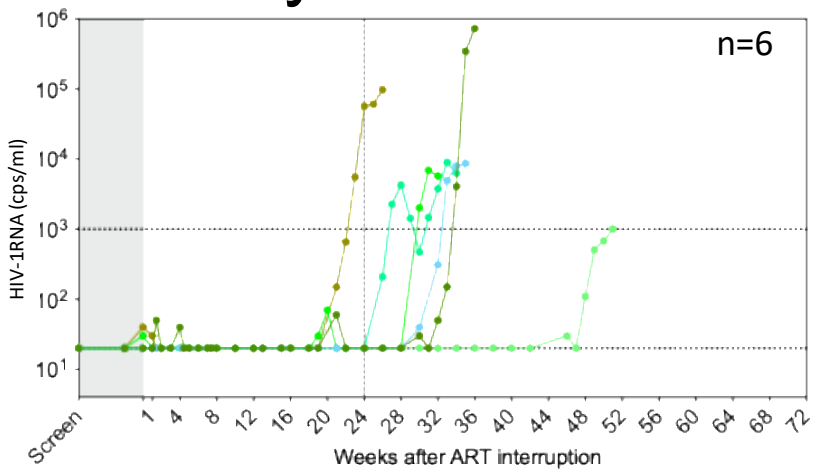
Primary Objectives:
- **Safety**
- ***Viral suppression by two bNAbs (wk 24)***:
  % of rebound (VL > 200 cps/ml x 2 wks)
- ***Viral control (off bNAbs)***:
  % participants who do not meet ART restart criteria by
  - wks 60 or 72 or
  - 12 wks after bNAb levels < 10 mcg/ml

Three patterns of viral rebound

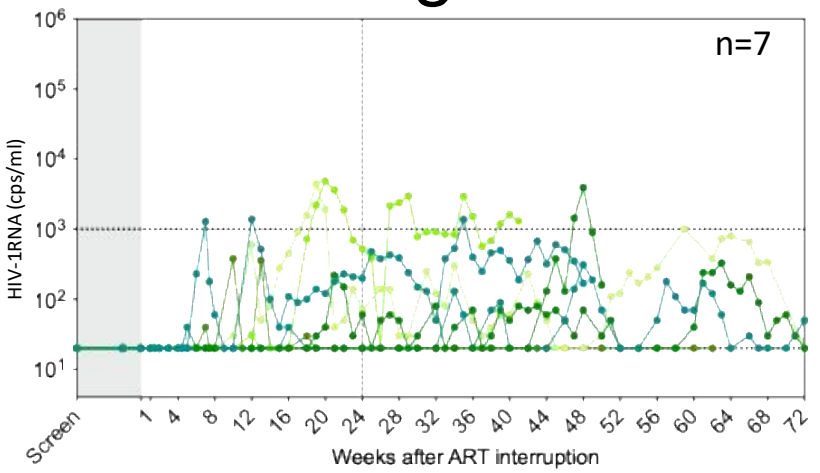
Early rebound:



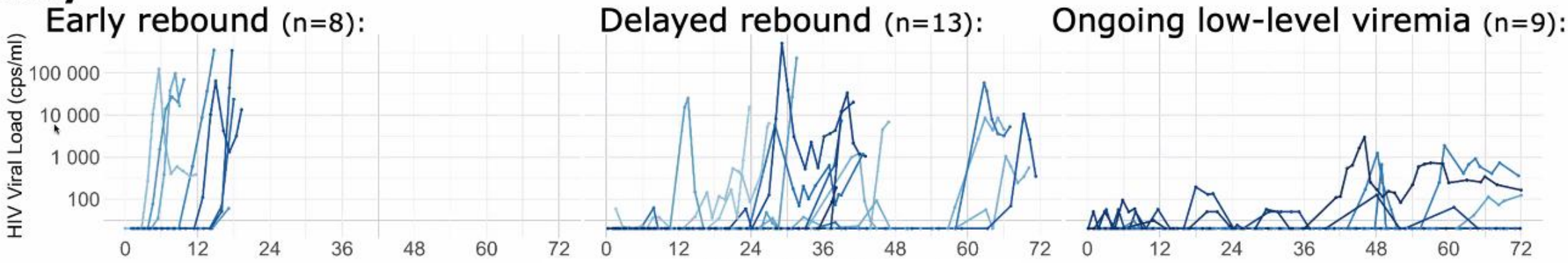
Delayed rebound:



Fluctuating viremia:

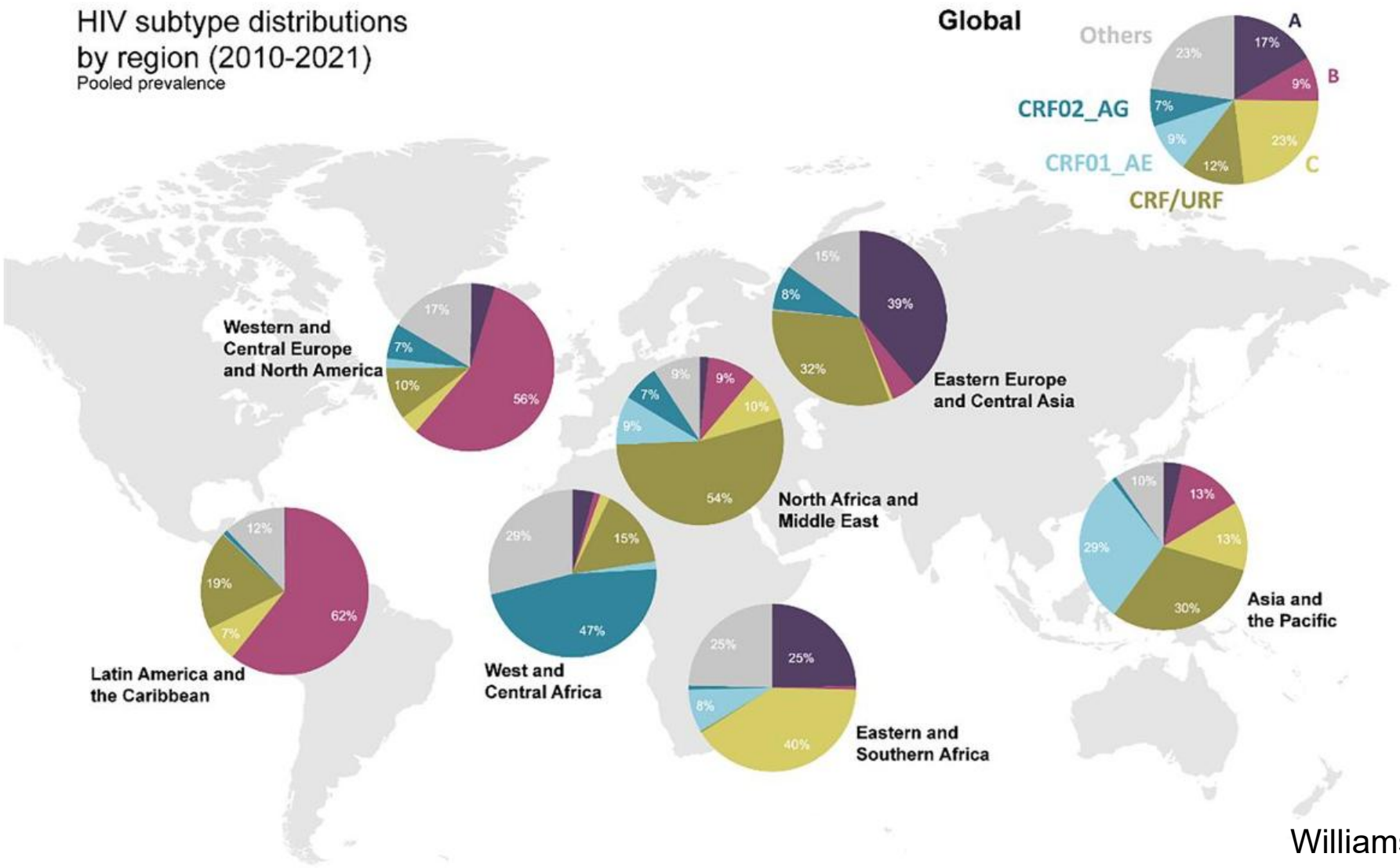


RIO study



Fiddler, CROI 2025

Costs and HIV-1 diversity hinder scalability of cure strategies

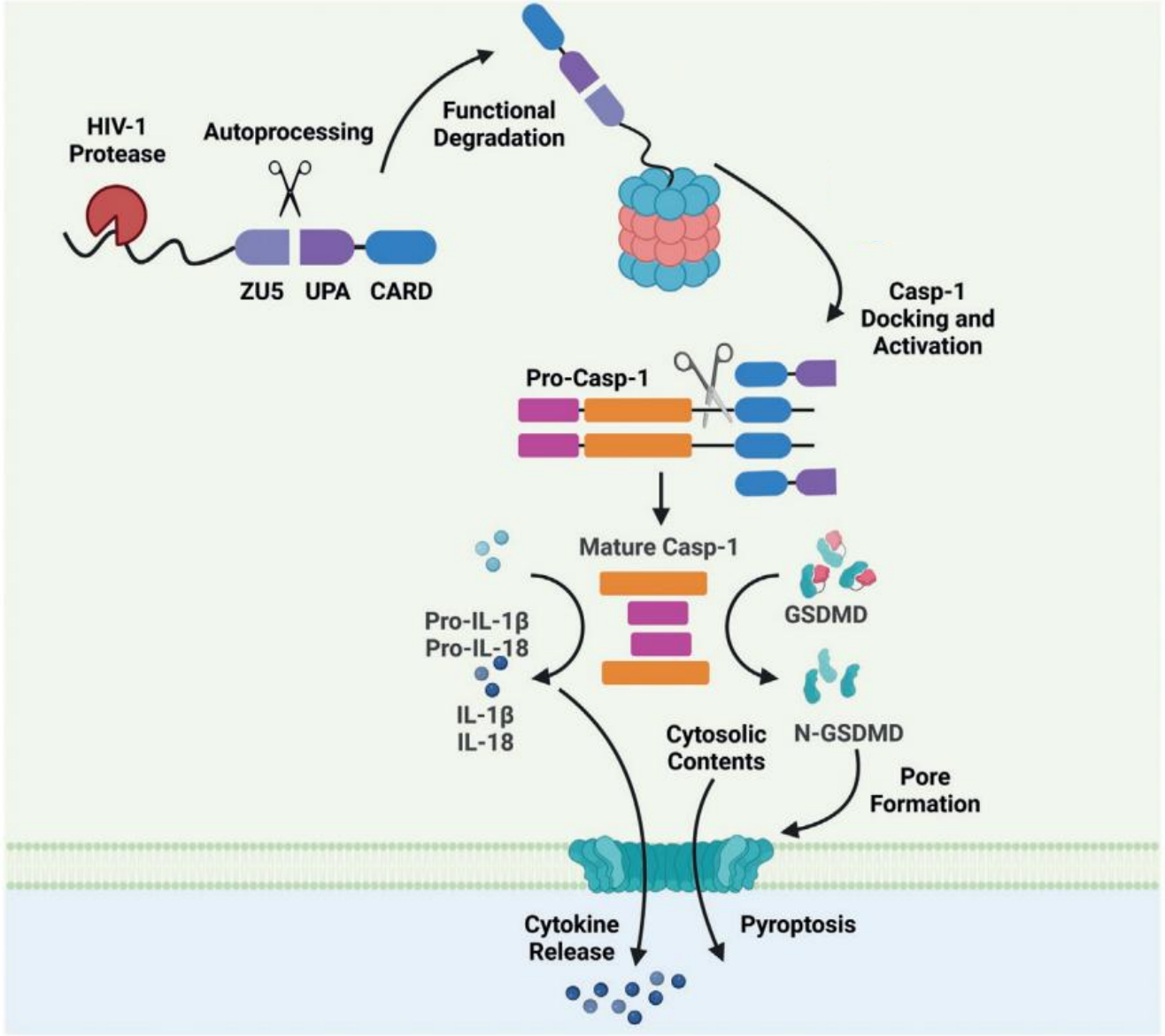


Williams et al., JID, 2021

What if we targeted ***function***, rather than sequence?

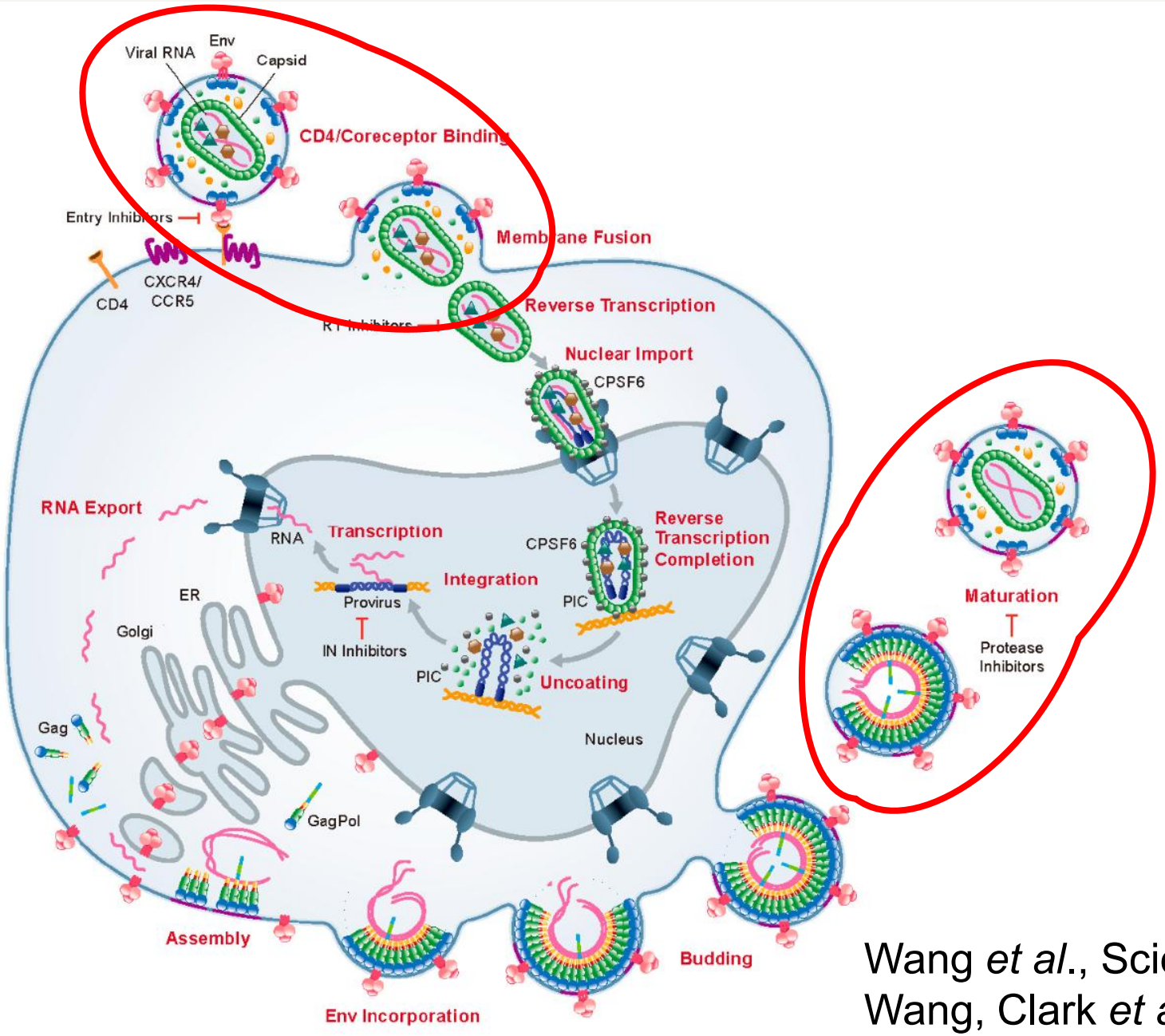
The CARD8 inflammasome senses HIV protease activity

Caspase recruitment domain-containing protein 8 (CARD8)

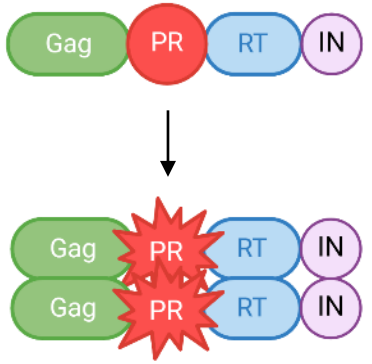


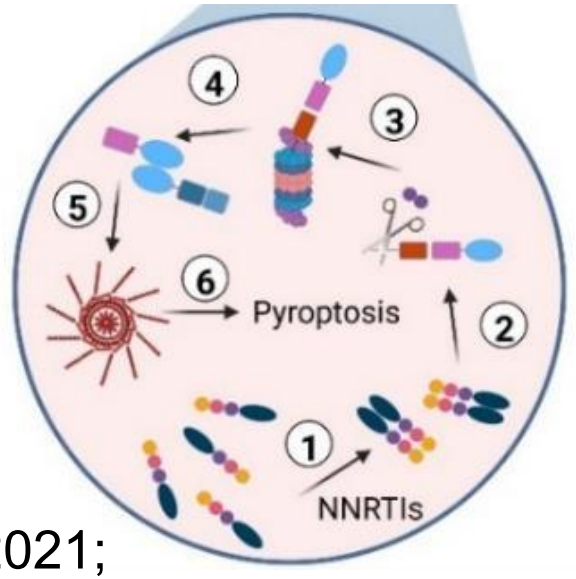
Wang *et al*., Science 2021;
Kulsuptrakul *et al*., elife 2023;
Clark *et al*., Adv in Immunology 2023

HIV Protease is active only after viral budding



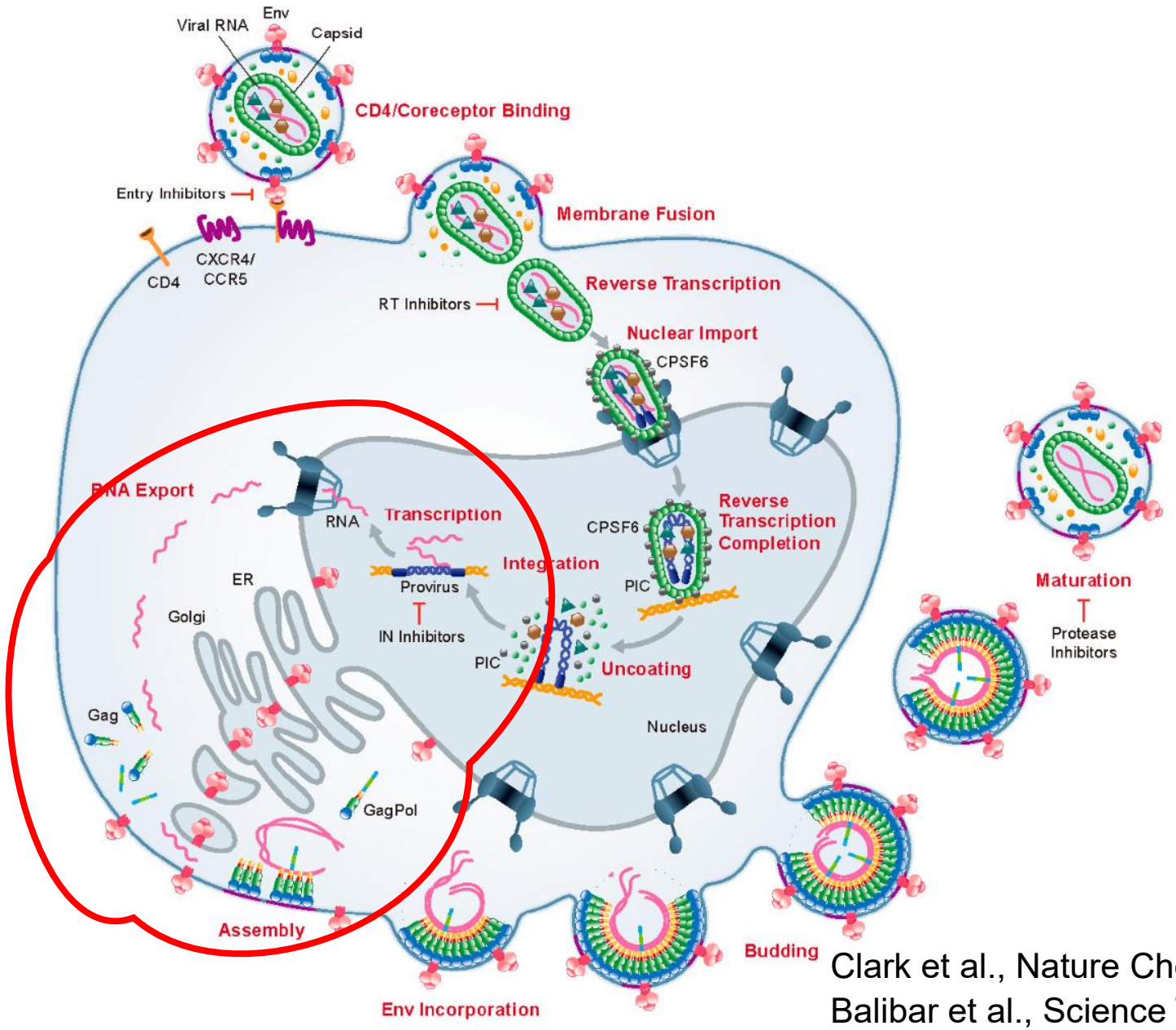
HIV-1 Gag-Pol polyprotein dimerization is required for HIV-1 protease activity

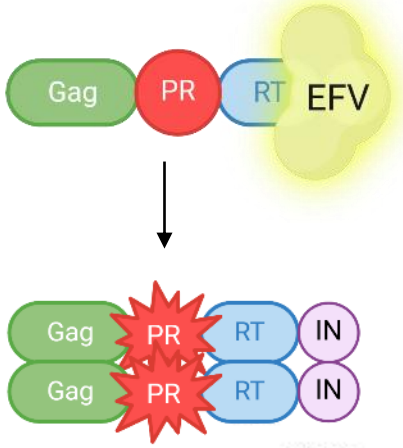


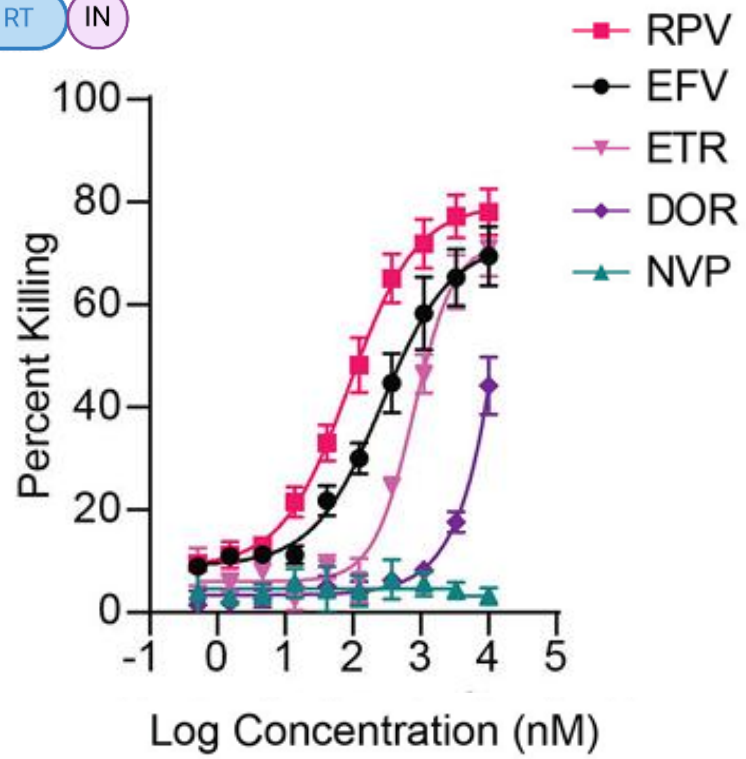


Wang *et al*., Science 2021;
Wang, Clark *et al*., Cell 2024

Some NNRTIs activate protease via Gag-Pol dimerization

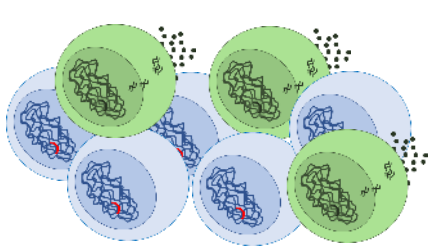


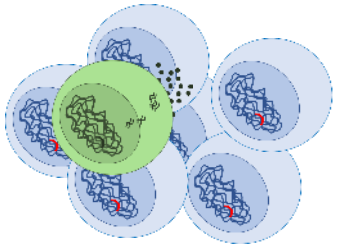


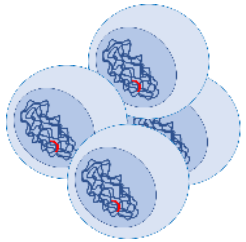


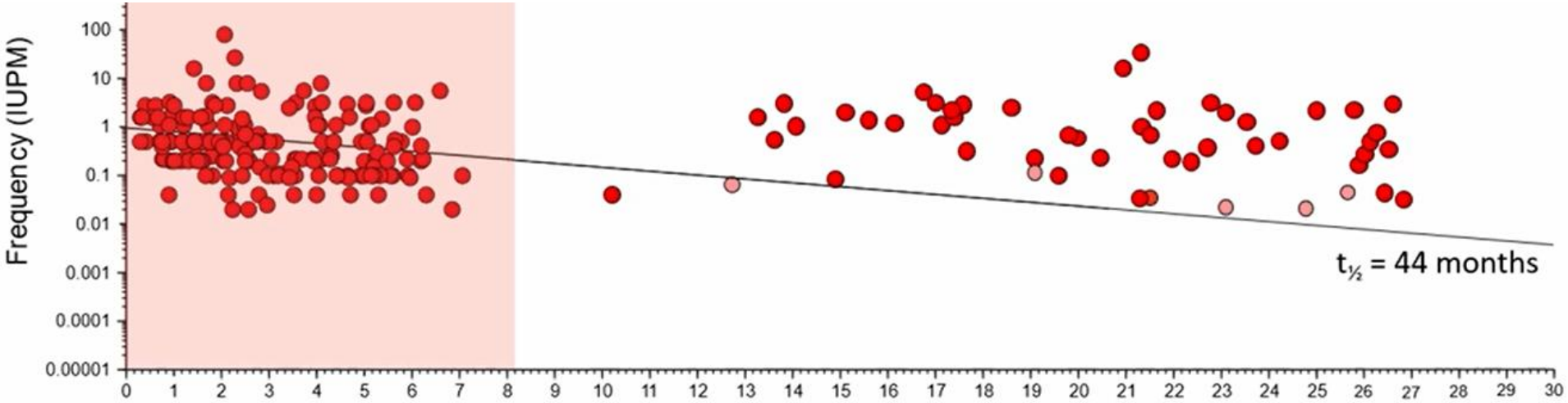
Clark et al., Nature Chemical Biology 2022
Balibar et al., Science Trans Med 2022

Can we accelerate reservoir decay and selection?



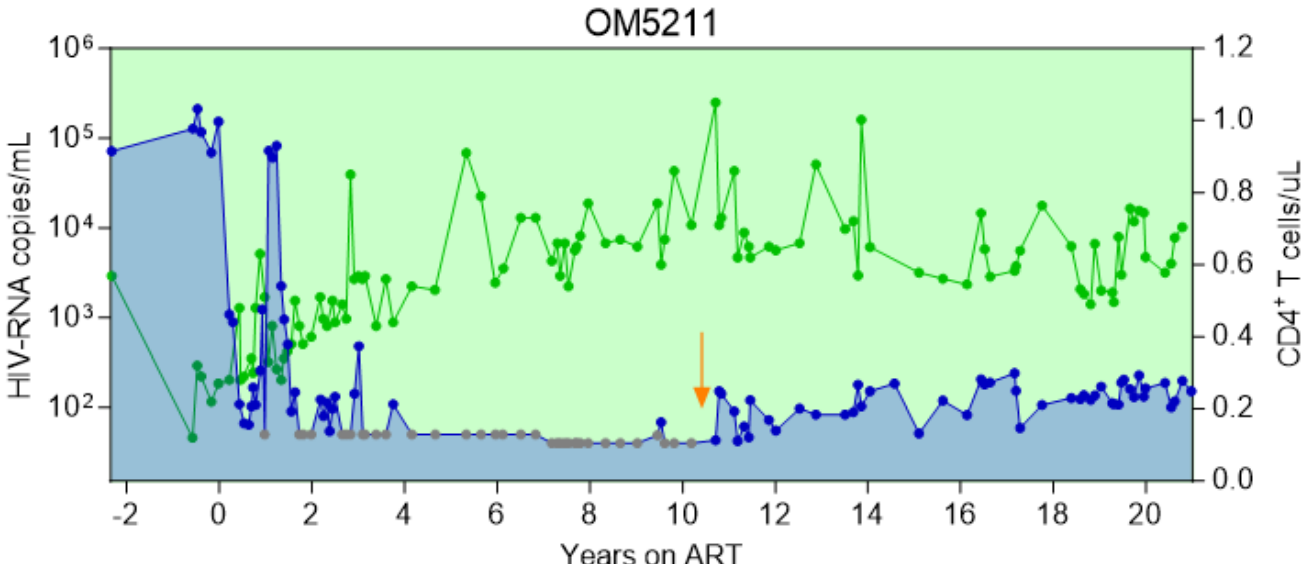




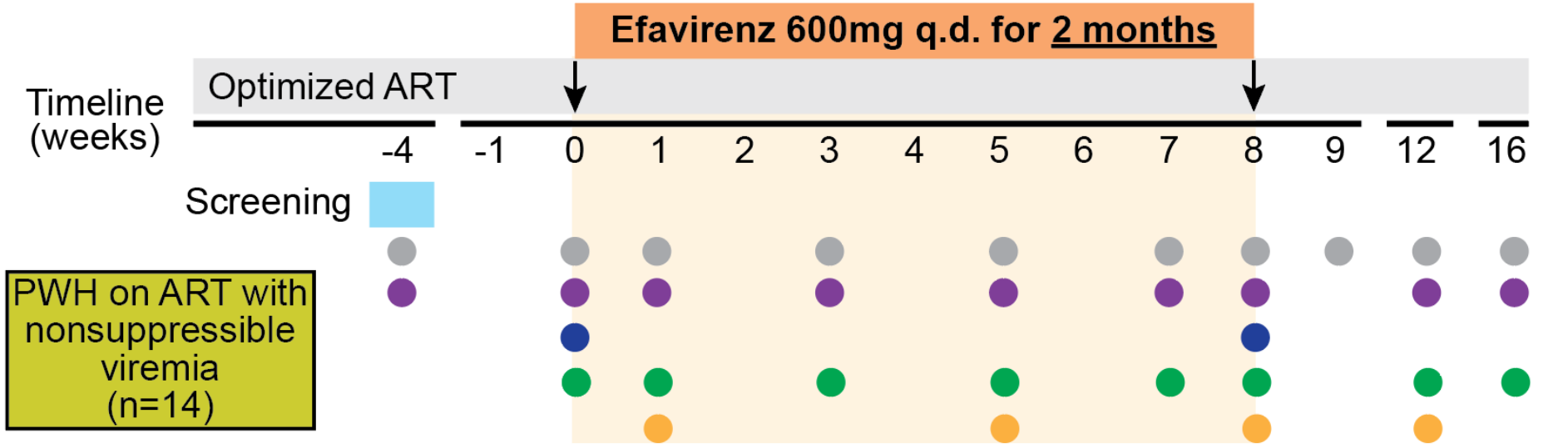


Jiang et al, 2020
Huang et al, 2021
Clark et al, 2023
Sun et al, 2023
Lian et al, 2023
McMyn et al, 2023

Reducing residual viremia with NNRTIs: a pilot trial



ONTARIO HIV TREATMENT NETWORK



Conclusions

- Cases of HIV cure show us that it is possible, but approaches based on transplant are too risky and not scalable

- Inducing HIV control by targeting multiple arms of the immune system seems the most achievable approach towards ART-free remission

- We are starting to see a signal that we can induce viral control

For any intervention that leads to HIV remission to reshape the course of the epidemic, these strategies needs to be studied and delivered to those communities that would benefit the most

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“Those who lose Dreaming are lost”

Art by Arone Meeks,
PATSIN, Positive Aboriginal and Torres Strait Islander Network

hiv&aids +asrh 2025

Thank you!

Jepp,
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