HOT TOPICS IN HIV

Vaccines, immune recovery and eradication

24th October, 2024
Hub Social – Fundació Bofill, Barcelona

Learning from Persistent Viremia: Mechanisms and Implications for Clinical Care and HIV-1 Cure

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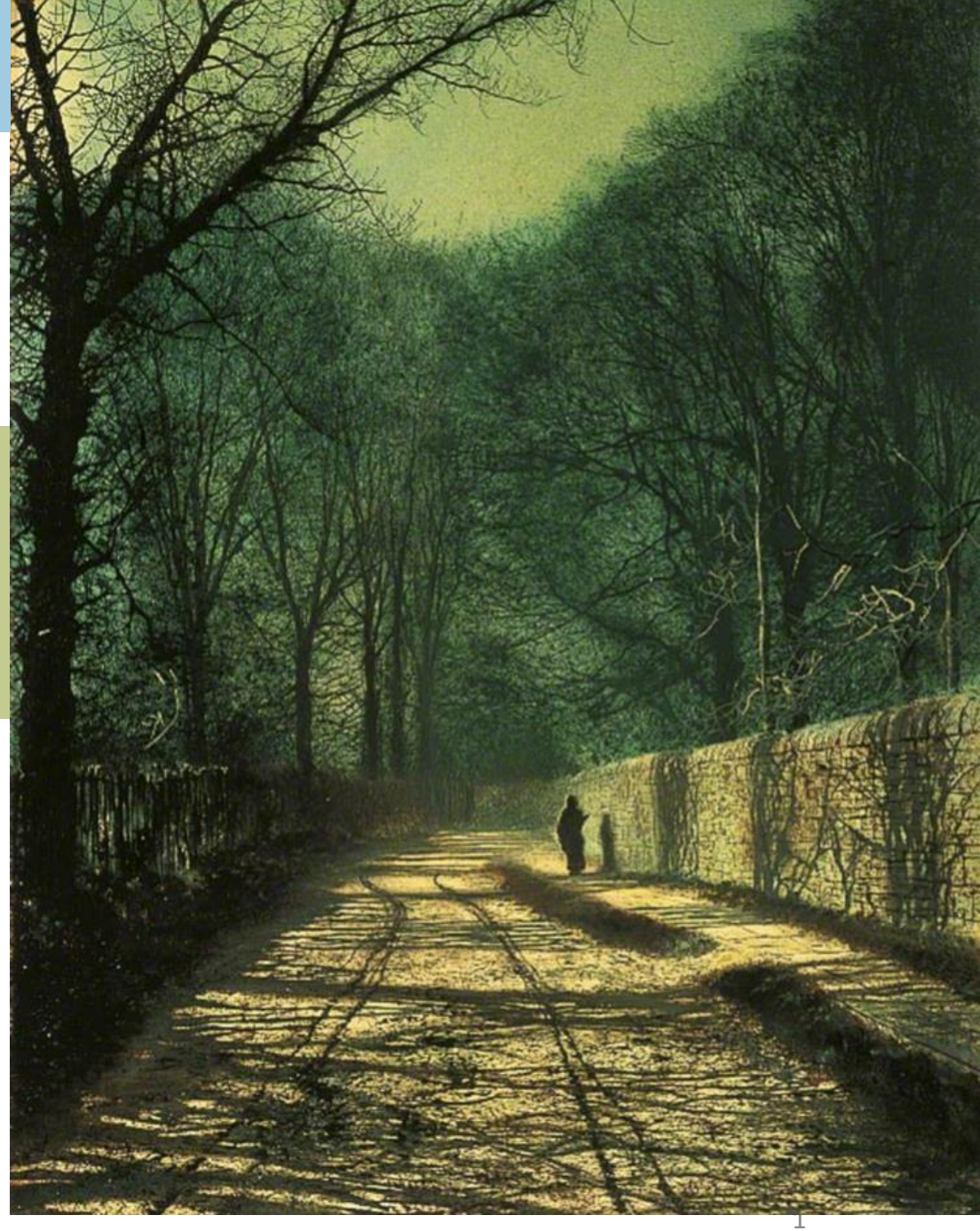
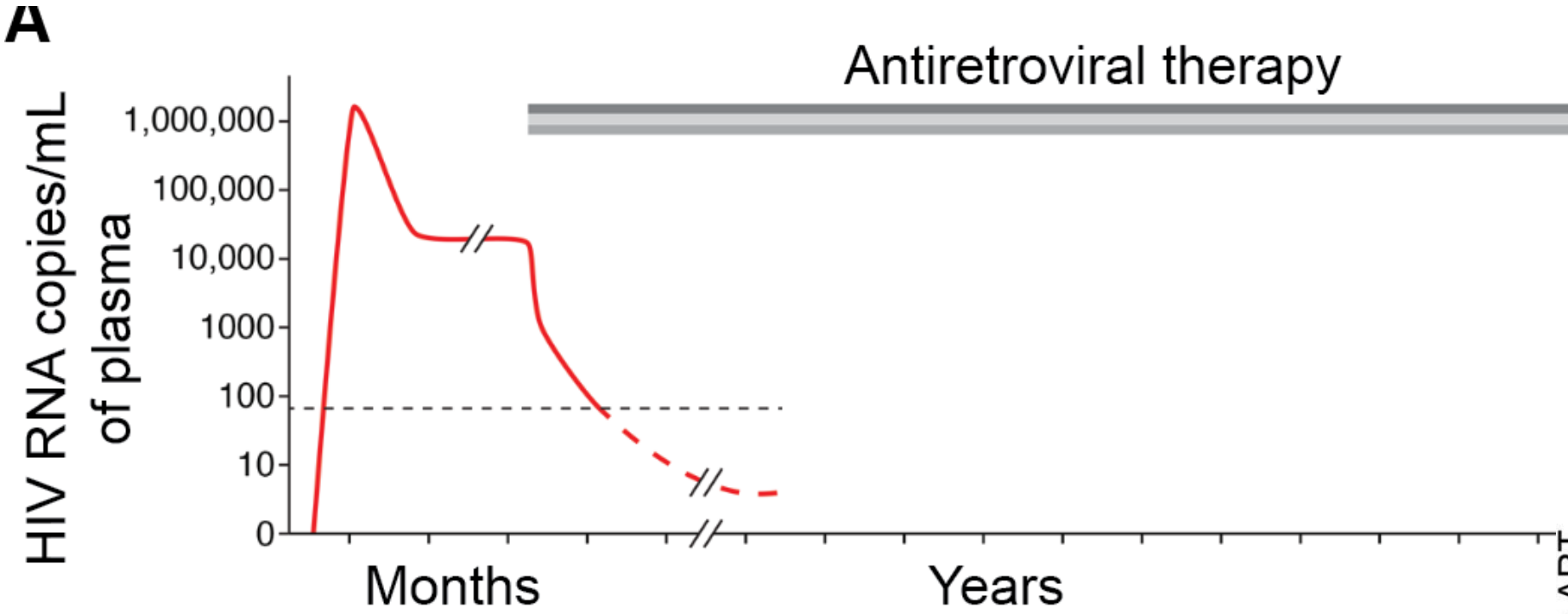


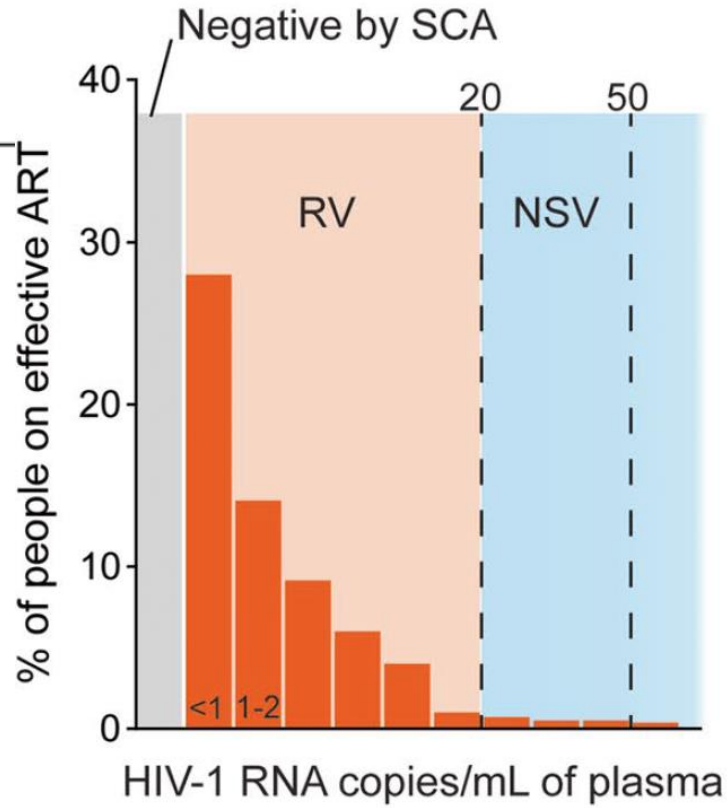
John Grimshaw, *Tree shadows on the park wall*

HIV-1 RNA in plasma can persist during effective ART

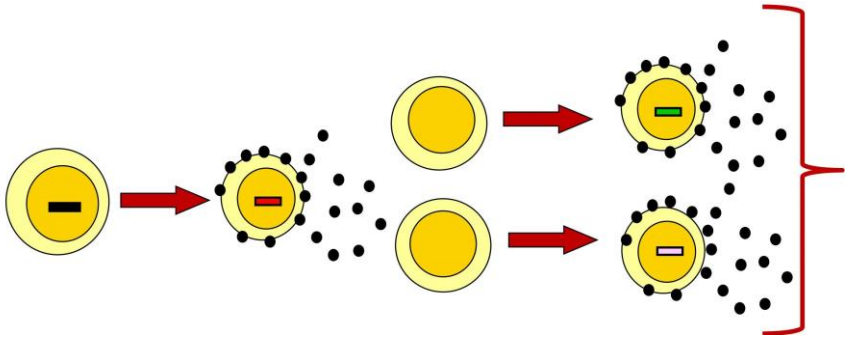


The time a virion survives in blood is very short (~1 hour)

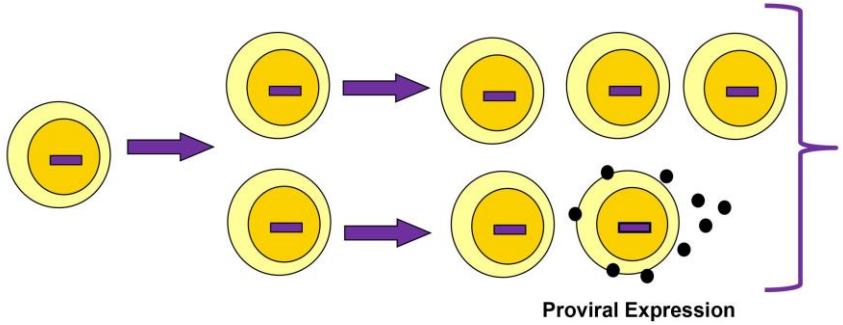
The time an HIV-producing cell survives is also very short



Viral replication *versus* viral expression



Productive cycles of viral replication



Proviral expression

Causes	Outcome	Management
-Sub-optimal adherence -Drug to drug interactions -Poor absorption -Drug resistance	-Viral evolution -Selection for drug resistance -Virological failure	-Adherence counselling -Assess drug interactions -Therapeutic drug monitoring -Genotyping →**<u>Optimize regimen</u>**

Jacobs et al., Front. Microbiol. 2019
Li et al., AIDS 2021
Richman, AIDS 2021

Studying persistent viremia on ART is important

It is a challenging clinical scenario

- It may be associated with virological failure and drug resistance
- It complicates ART management
- Raises concerns regarding risk for transmission
- It could contribute to immune activation and inflammation
- Most clinicians are not aware of the mechanisms causing NSV

It provides an opportunity to better understand HIV-1 persistence

- Its underlying mechanisms likely play a role in all people on ART
- Discoveries about viremia can be relevant for HIV-1 remission research

There is a dire need for awareness (and guidelines) on NSV

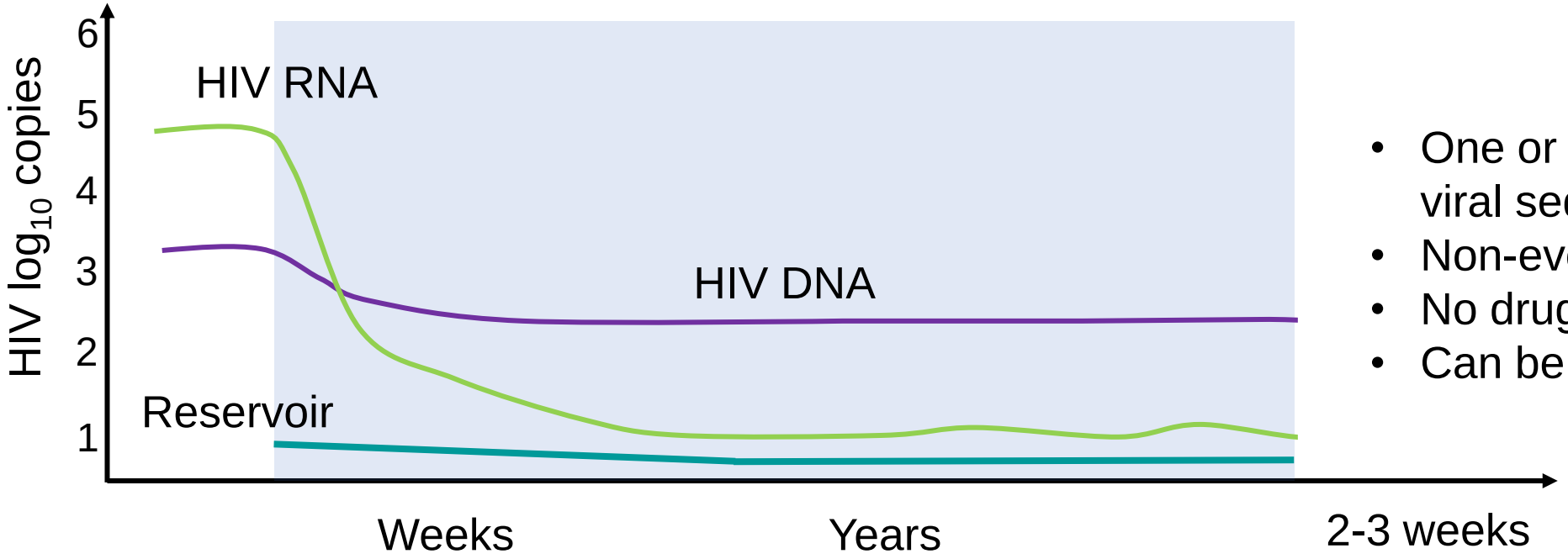
Person in care

What is wrong with me?
Worry
Guilt
Trust issues
Frustration

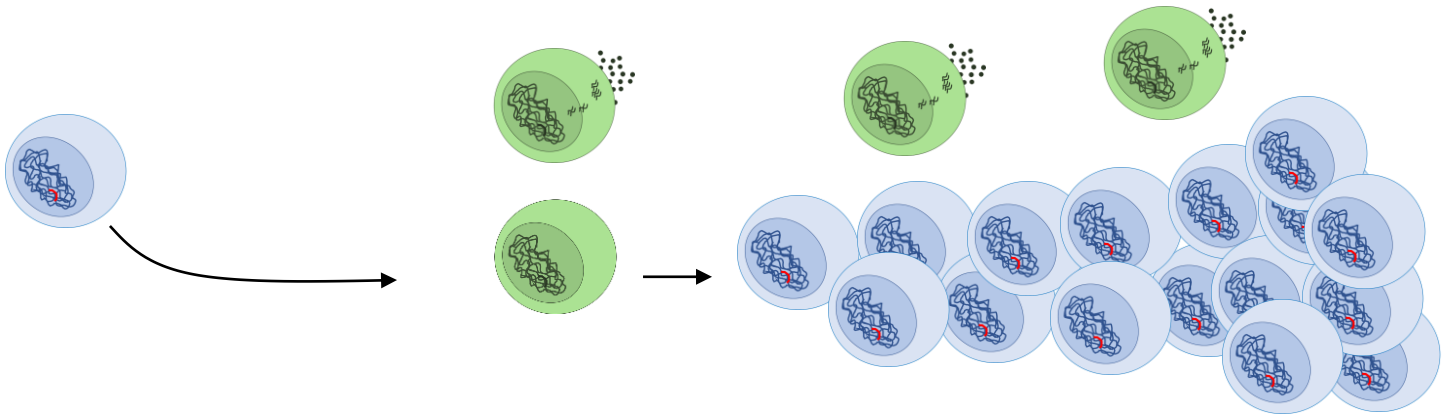
Care provider

Questioning adherence
Trust issues
What am I doing wrong?
Guilt
Frustration

HIV-1 persists through the proliferation of CD4+ T cells

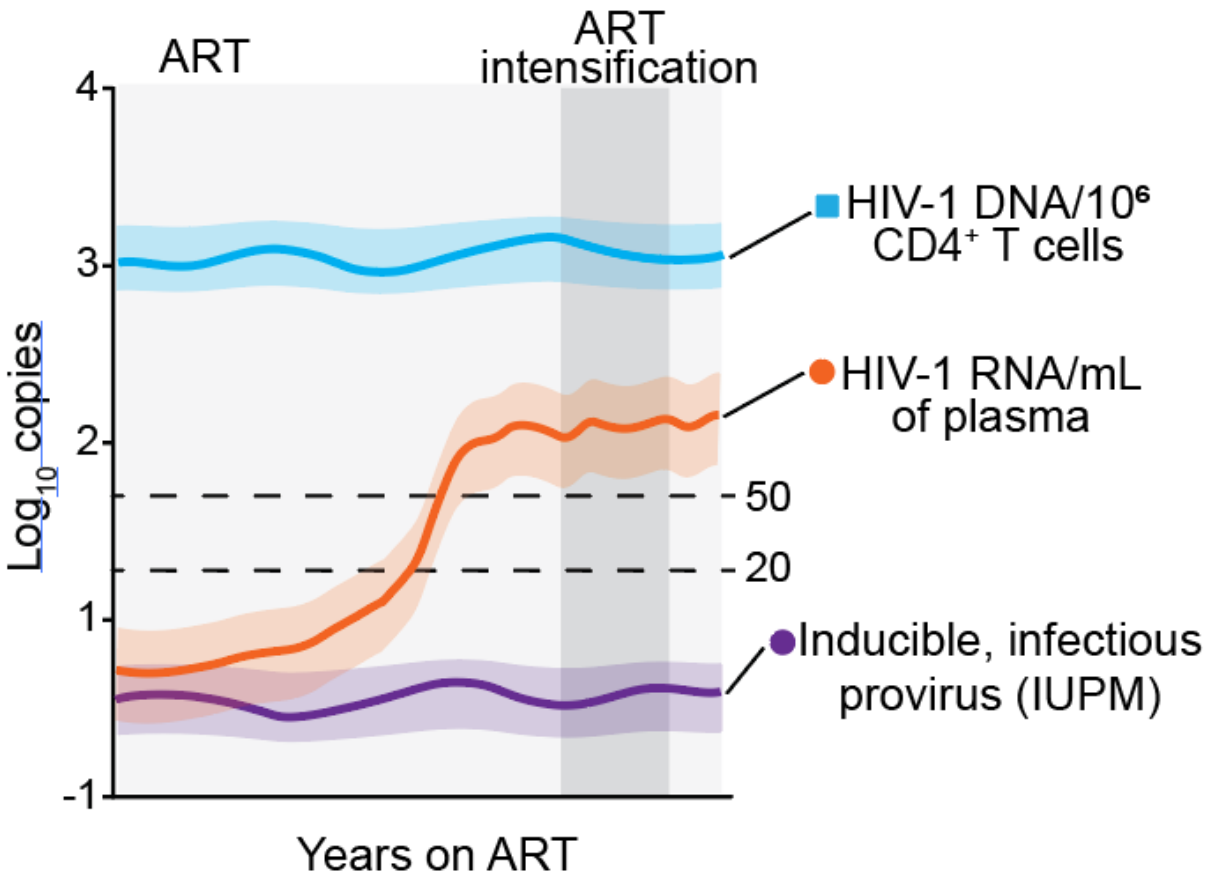


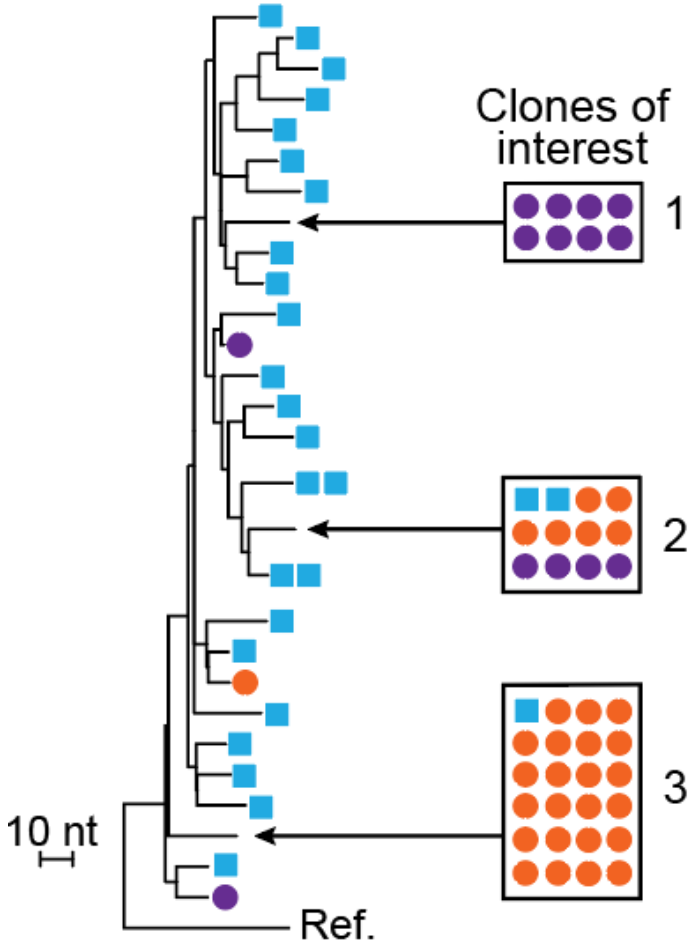
- One or more groups of identical viral sequences in plasma
- Non-evolving over time on ART
- No drug resistance
- Can be replication-competent



Proliferation of infected clones

HIV-1 persists through the proliferation of CD4+ T cells

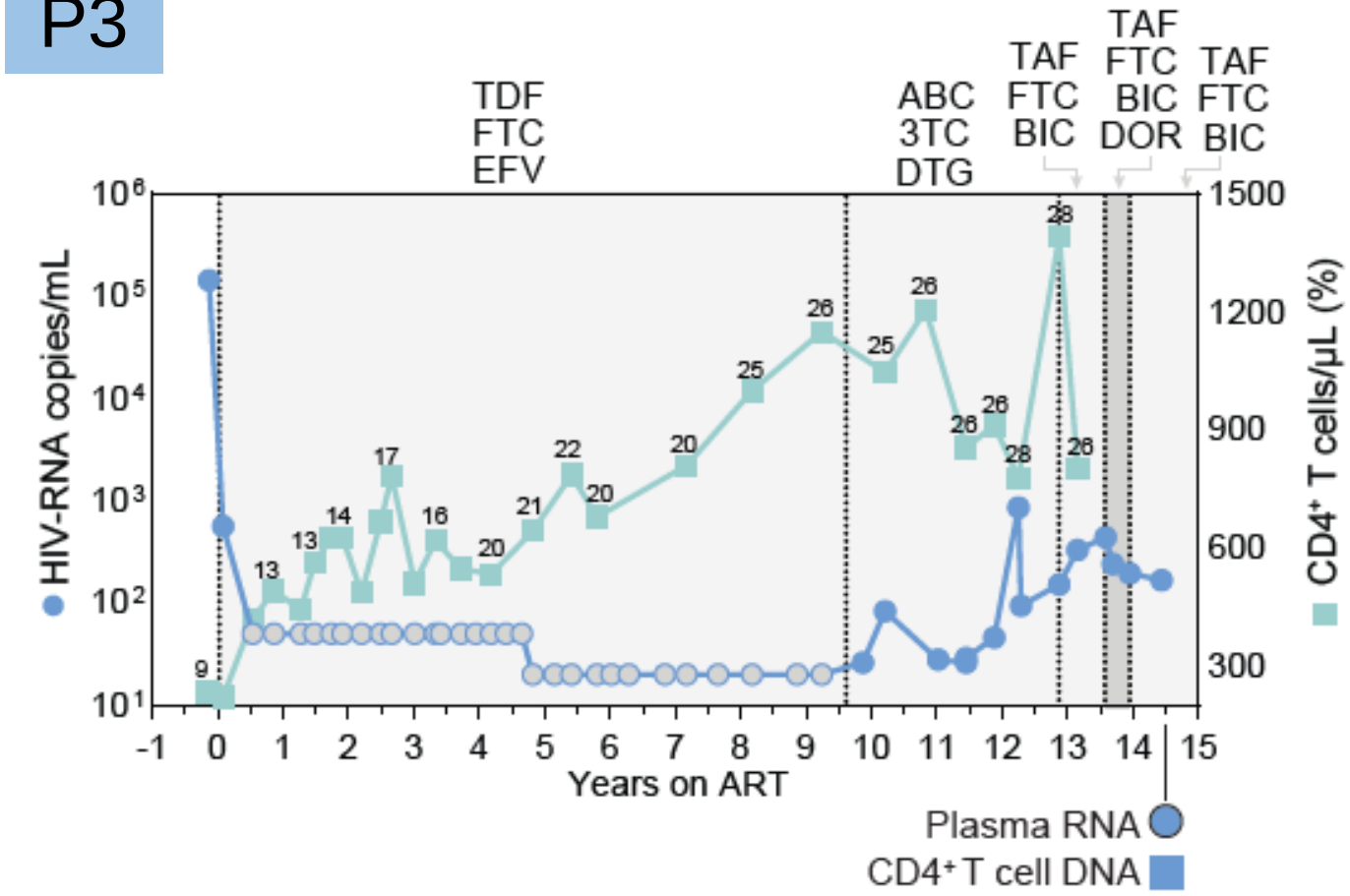


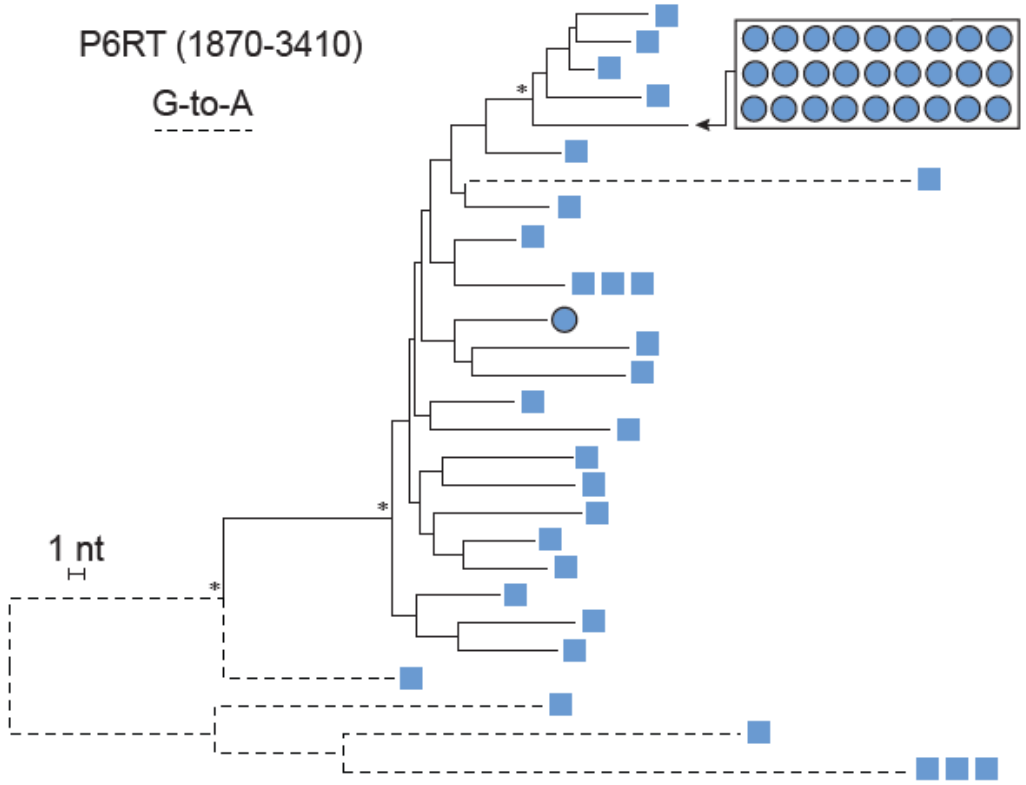


Wu and Simonetti,
Current HIV/AIDS Reports 2023

A case of NSV caused by a single, rare, drug-sensitive variant

P3



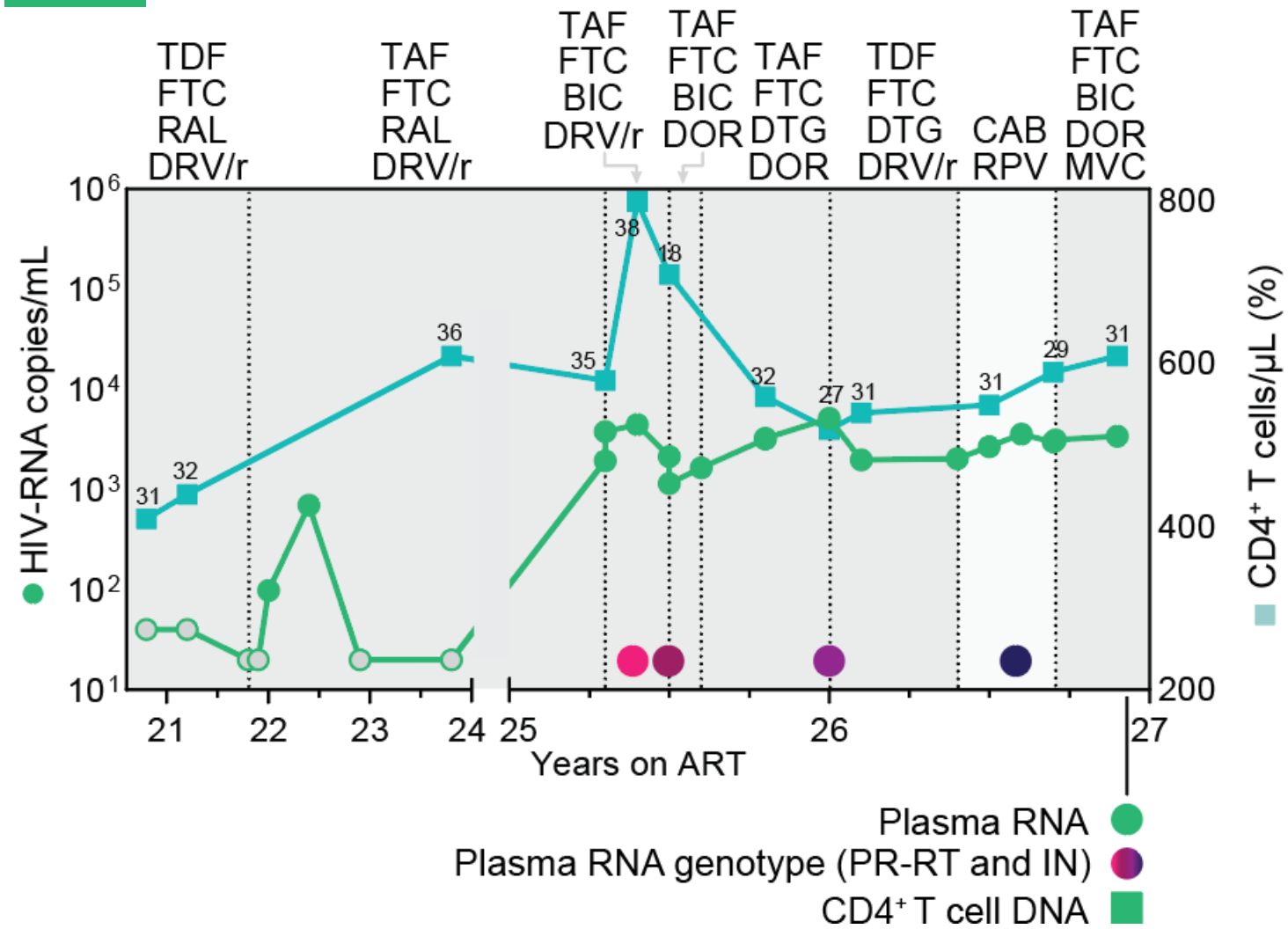


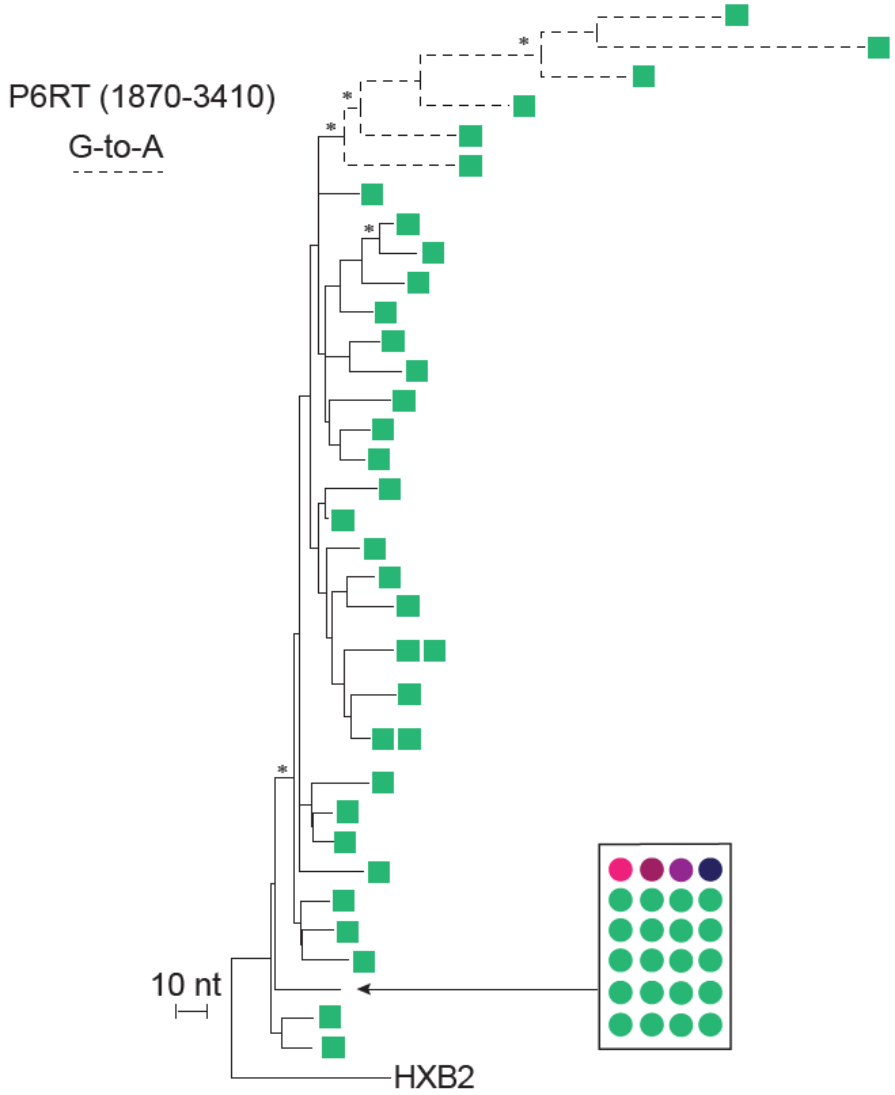
White, Wu, et al. JCI 2023

>10^3 copies/mL of HIV RNA caused by a single drug-sensitive variant

"LOW-LEVEL VIREMIA" → "NONSUPPRESSIBLE VIREMIA"

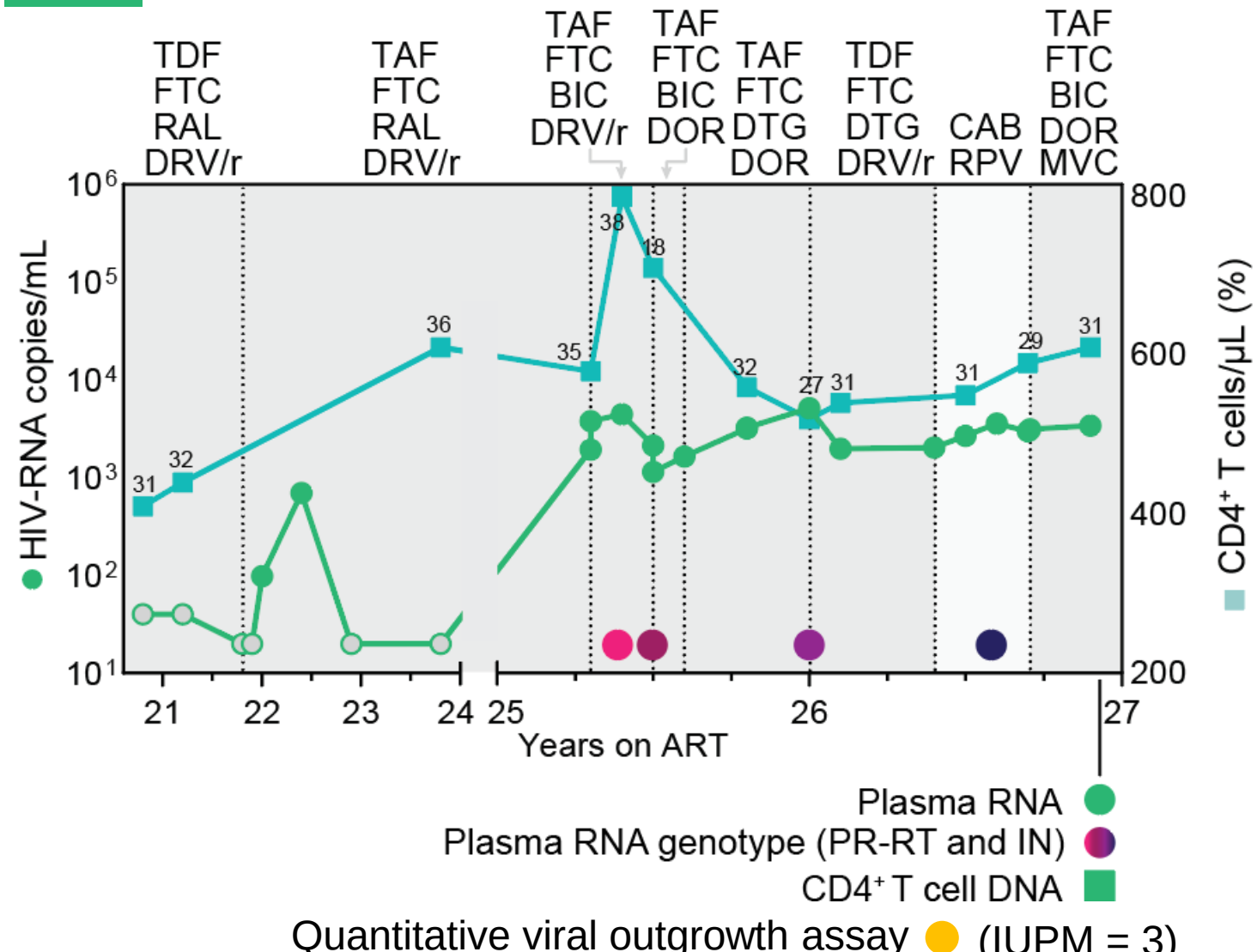
P4

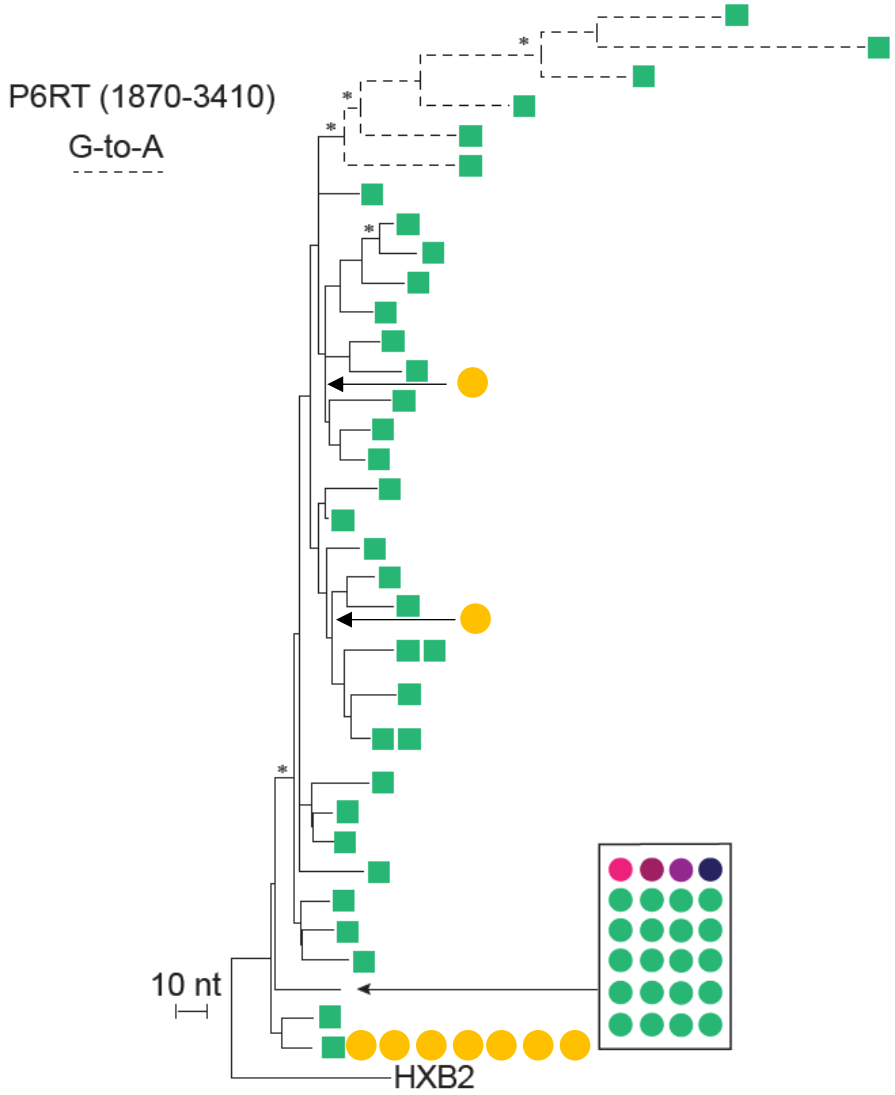




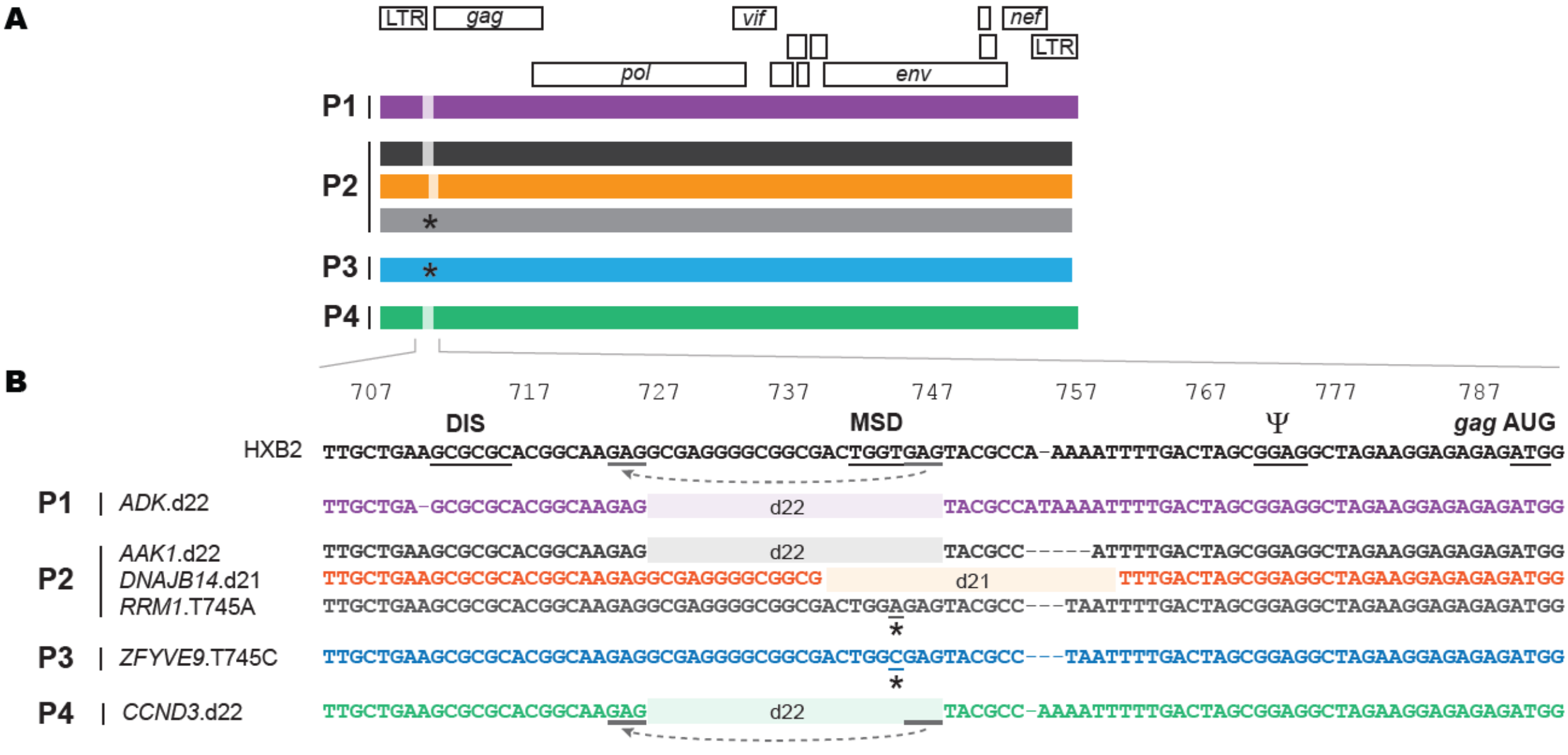
The virus causing NSV cannot be recovered by culture ex vivo

P4

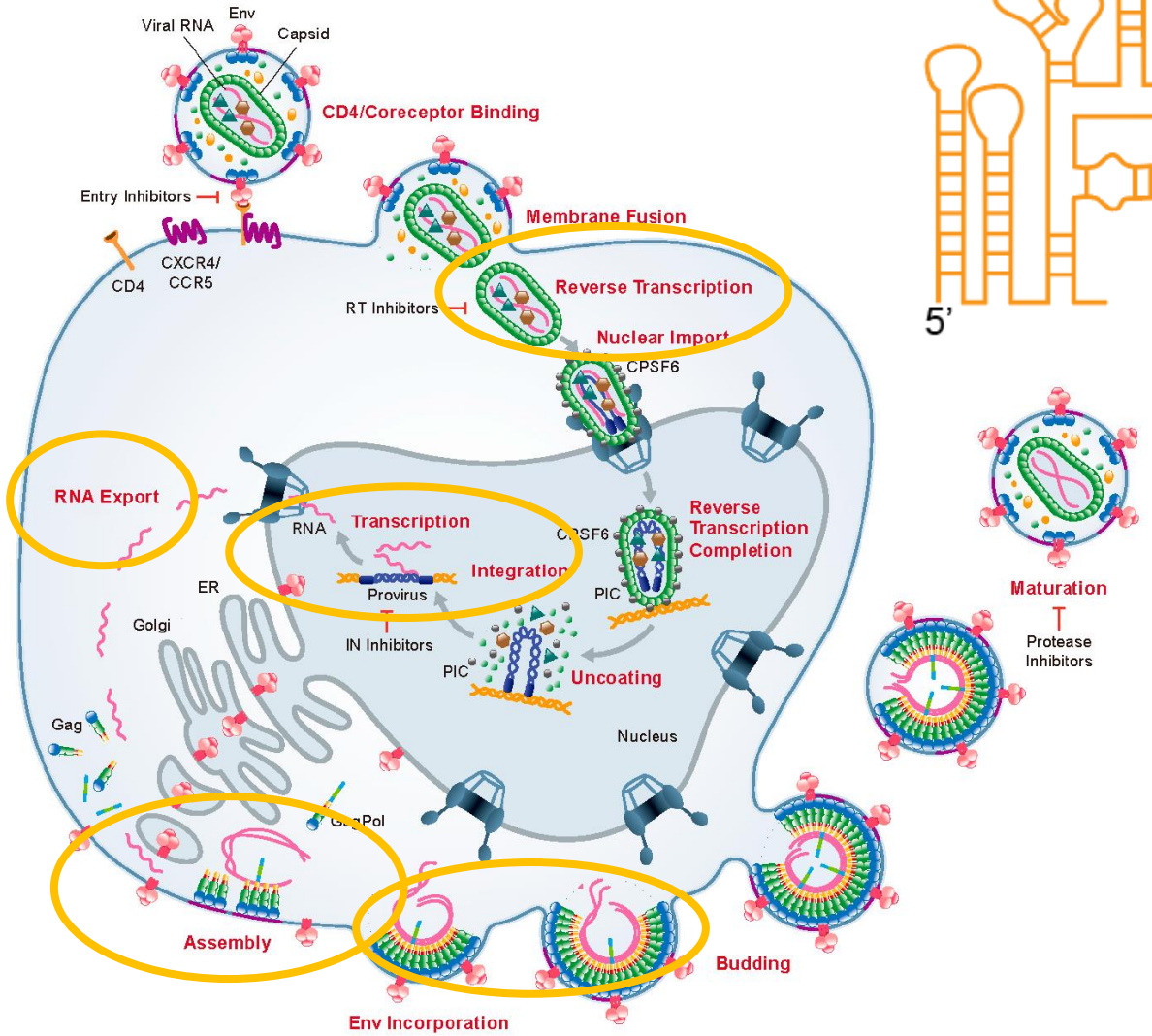


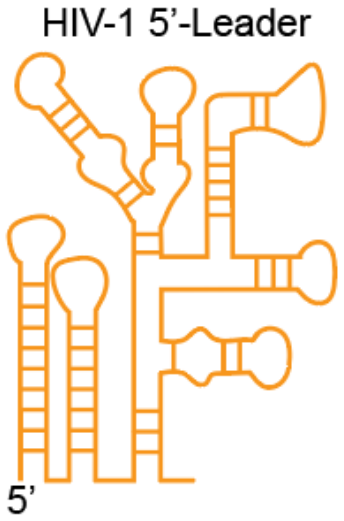


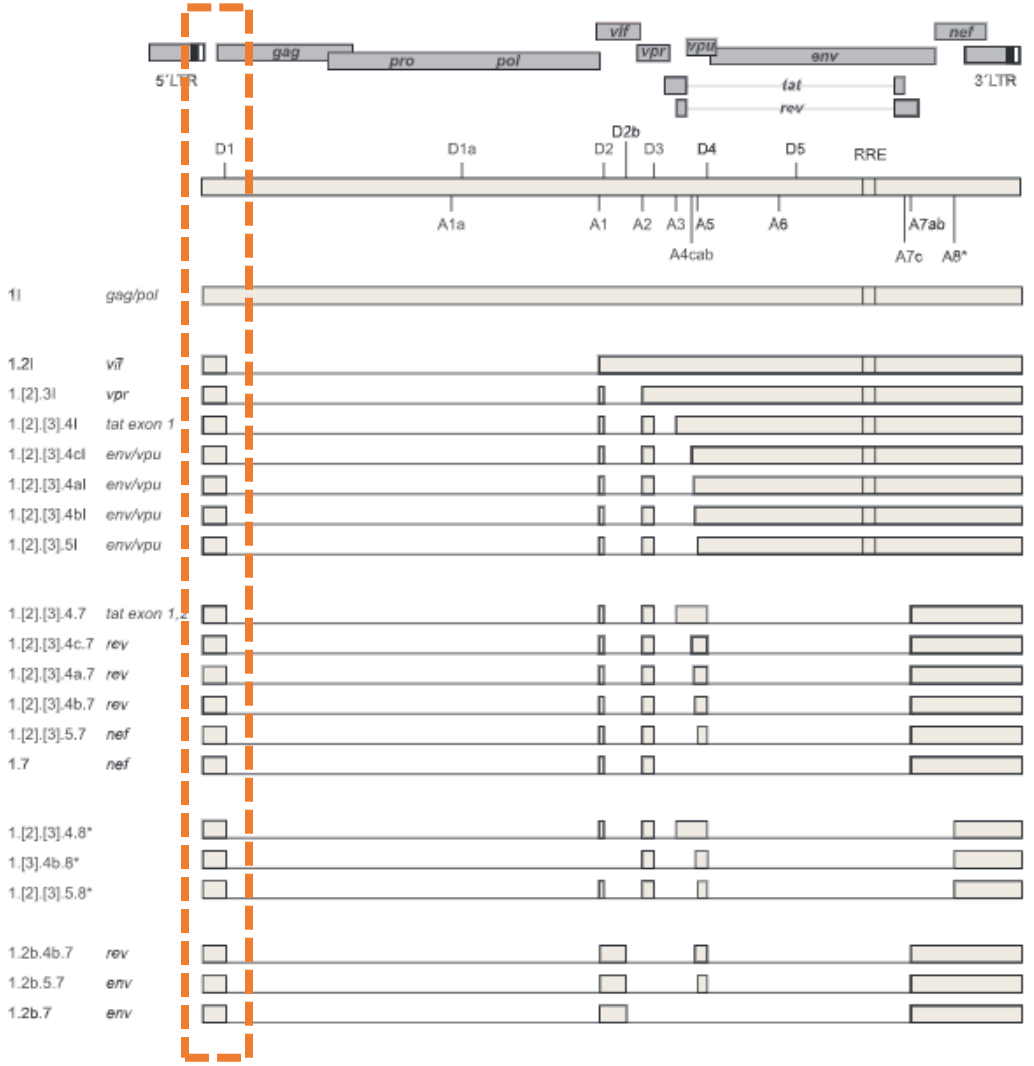
Proviruses cause of NSV can have defects in the 5’ leader



5’ Leader defects result in non-infectious viral particles

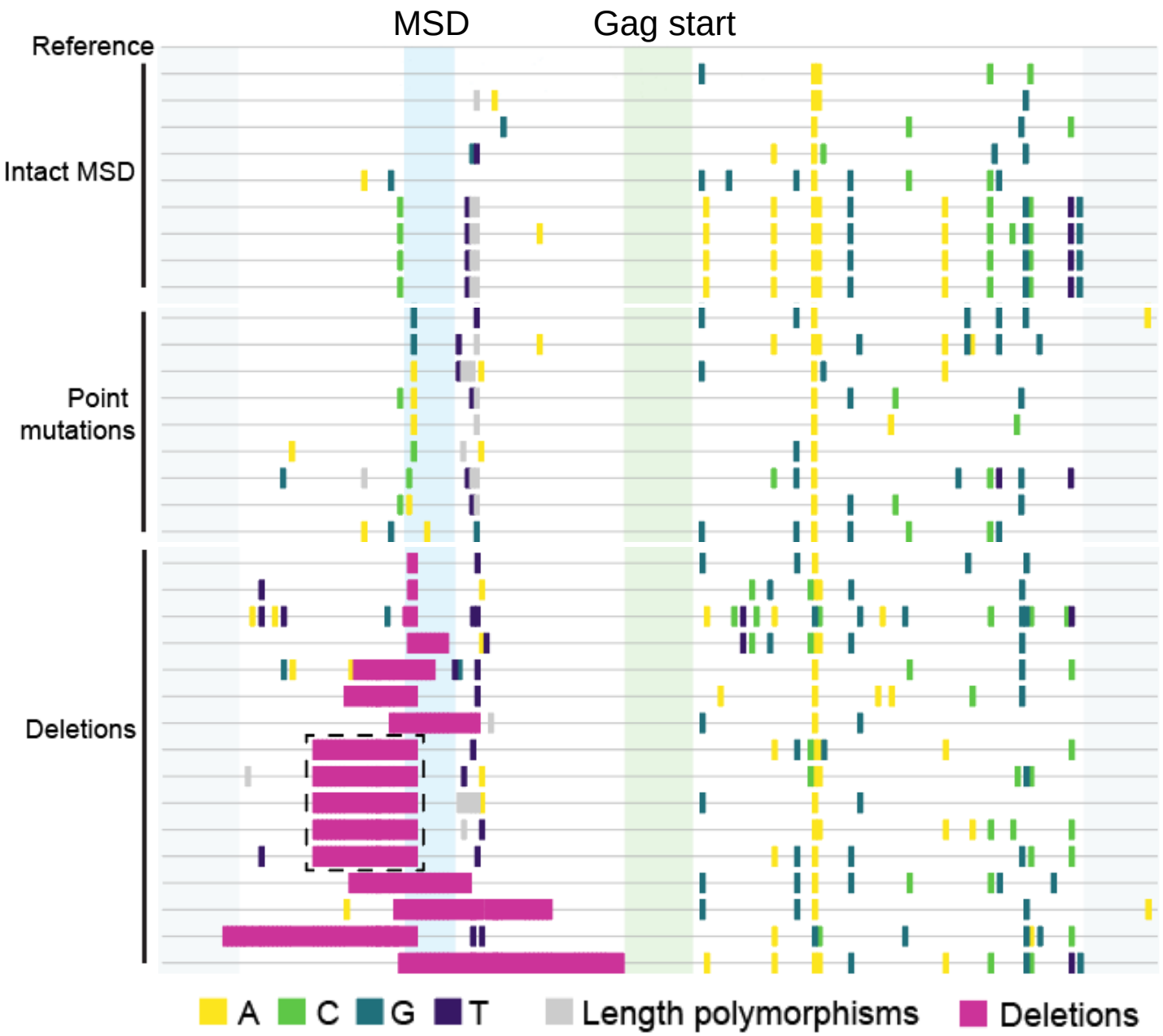






White, Wu, et al. JCI 2023 Mueller, 2014

5’Leader defects are common in plasma virus during long-term ART



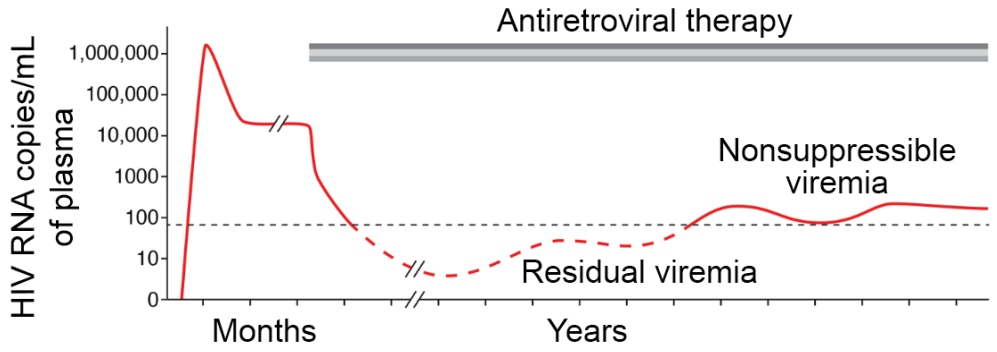
In a follow up study on 30 people with NSV, ~80% of viruses in plasma showed 5’-Leader defects

All subtypes
n=2238

Virus contributing to NSV
n=65

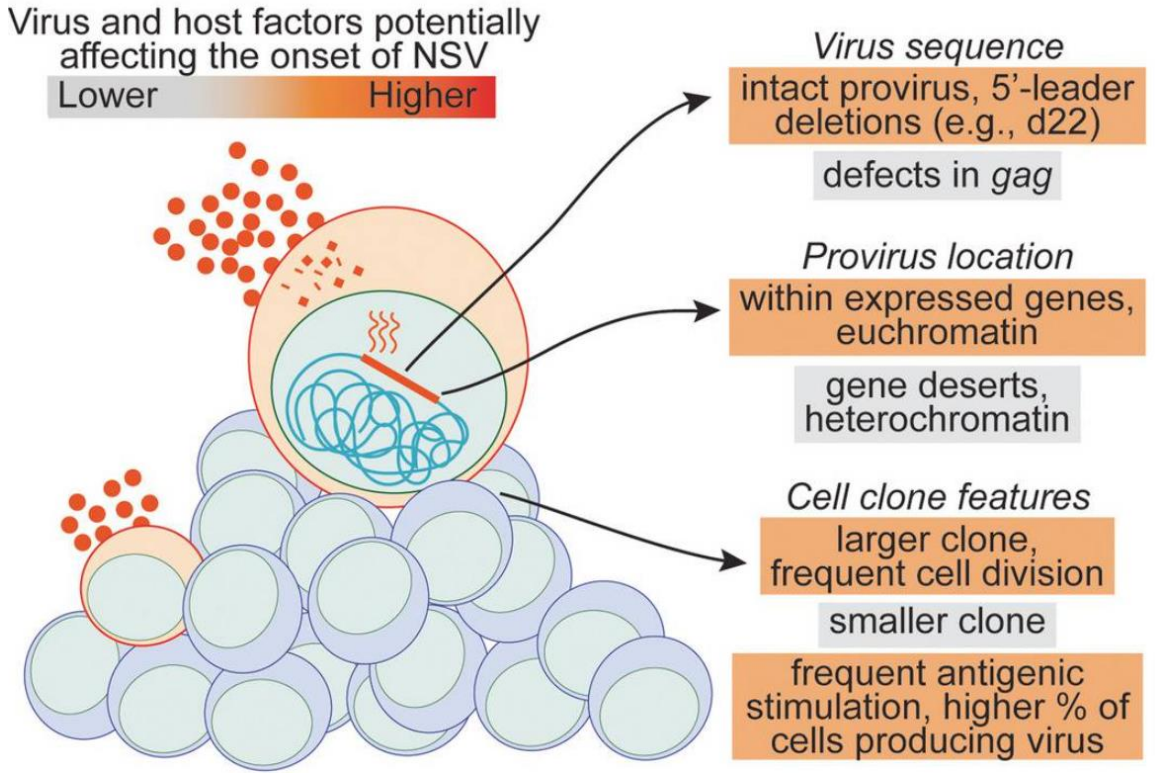
Open research questions

- NSV is relatively rare, but it is becoming **more common than in the past**, why?
  - longer time on ART?
  - older population?
  - changes in ART regimen?
  - better assays?



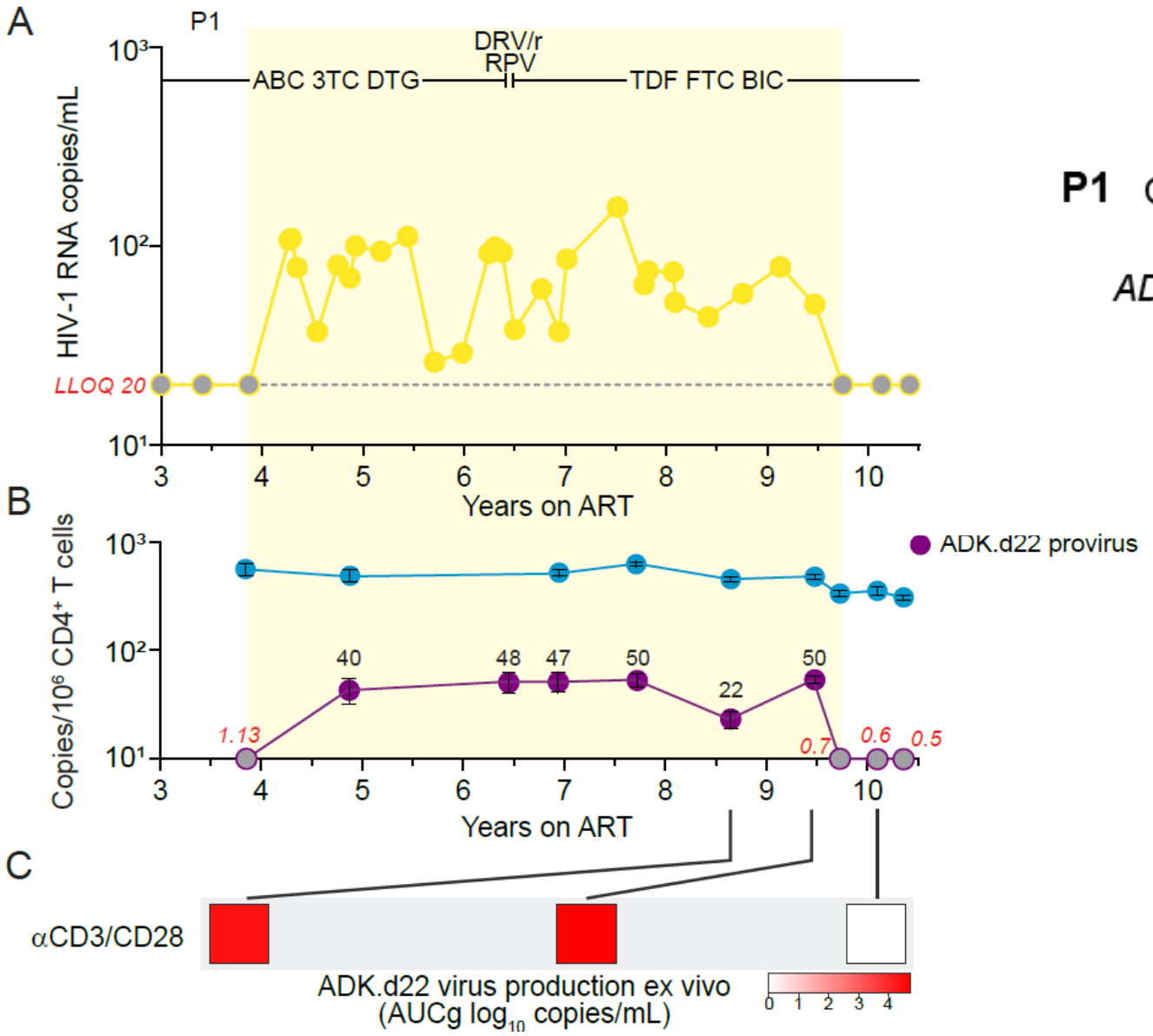
- What impact for **inflammation**?

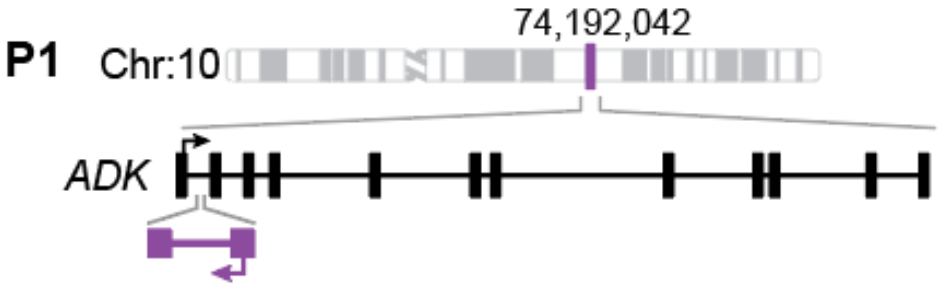
- **What does it take to develop NSV?**
  - The right provirus
  - In the right site of integration
  - In the right cell (clone size, persistence)
  - **Frequent stimulation**

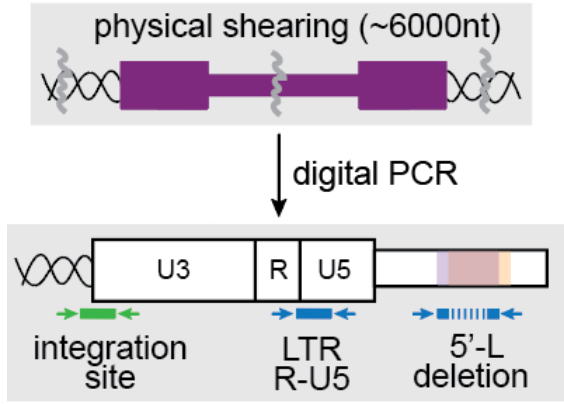


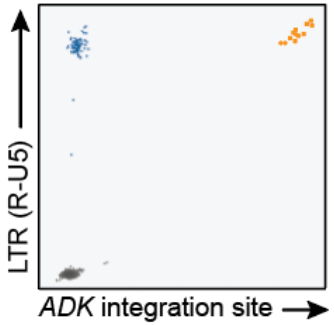
Halvas, et al. JCI 2020
White, Wu, et al. JCI 2023
Mohammadi et al., Nat Med 2023

Clonal expansion and contraction drive the onset and resolution of NSV



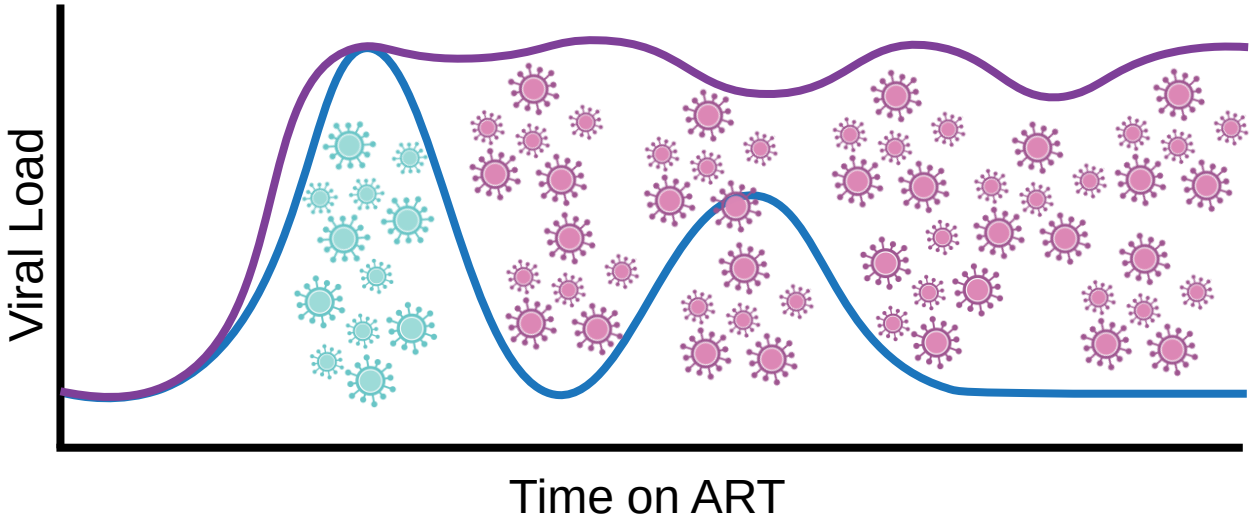


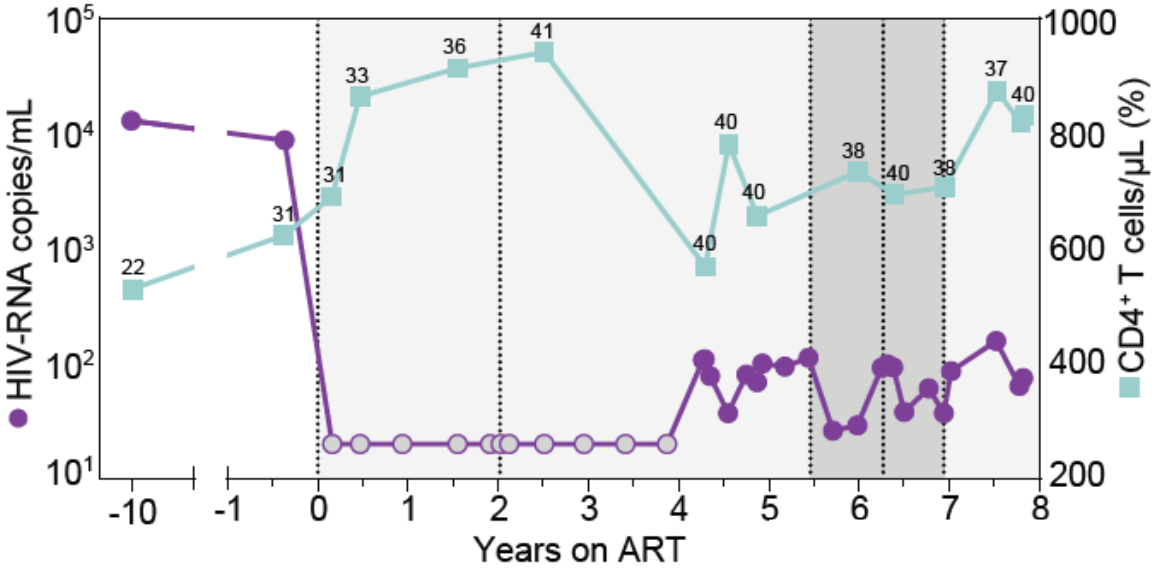




Wu, et al., in preparation

How can we explain years of persistent nonsuppressible viremia?



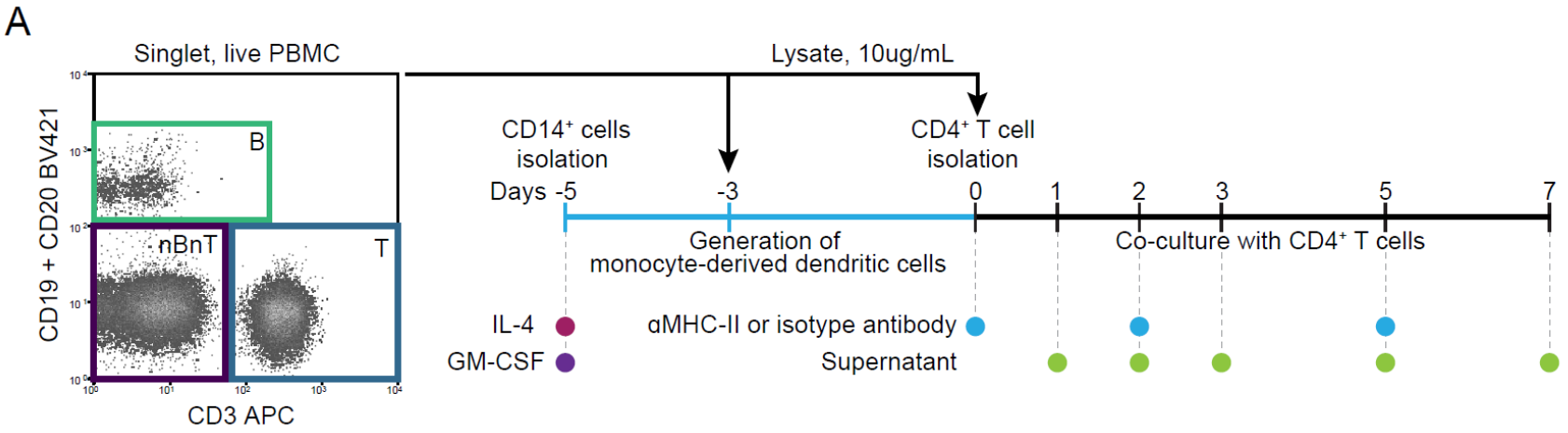


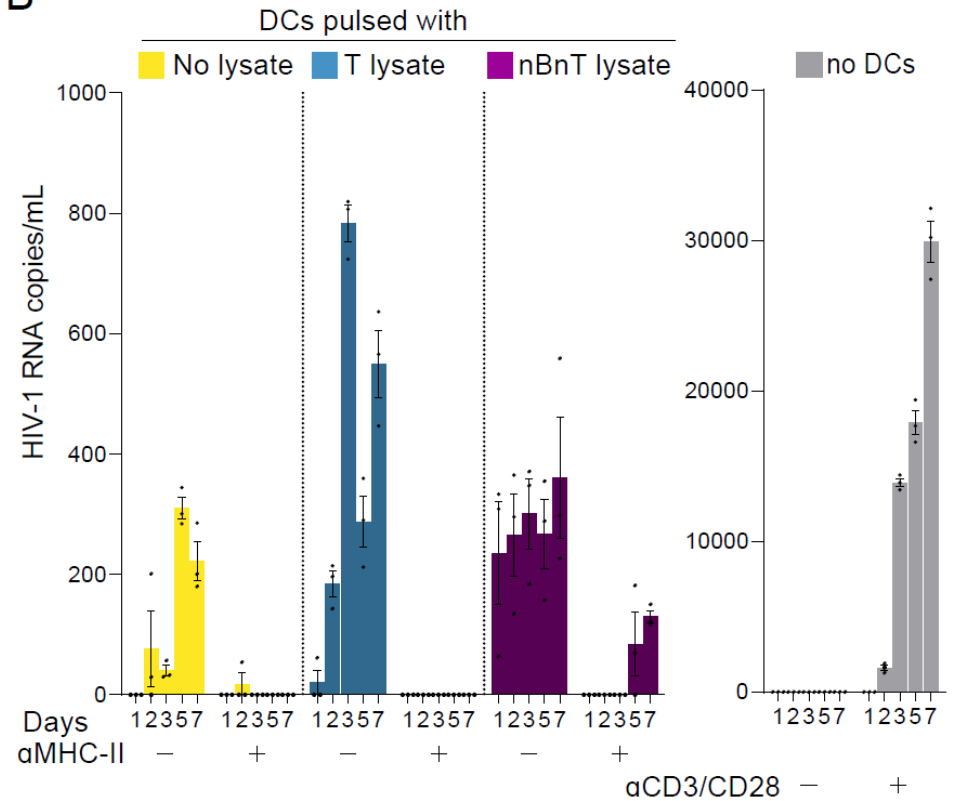
Constant virus production cannot be explained by the typical immune responses to a transient antigen

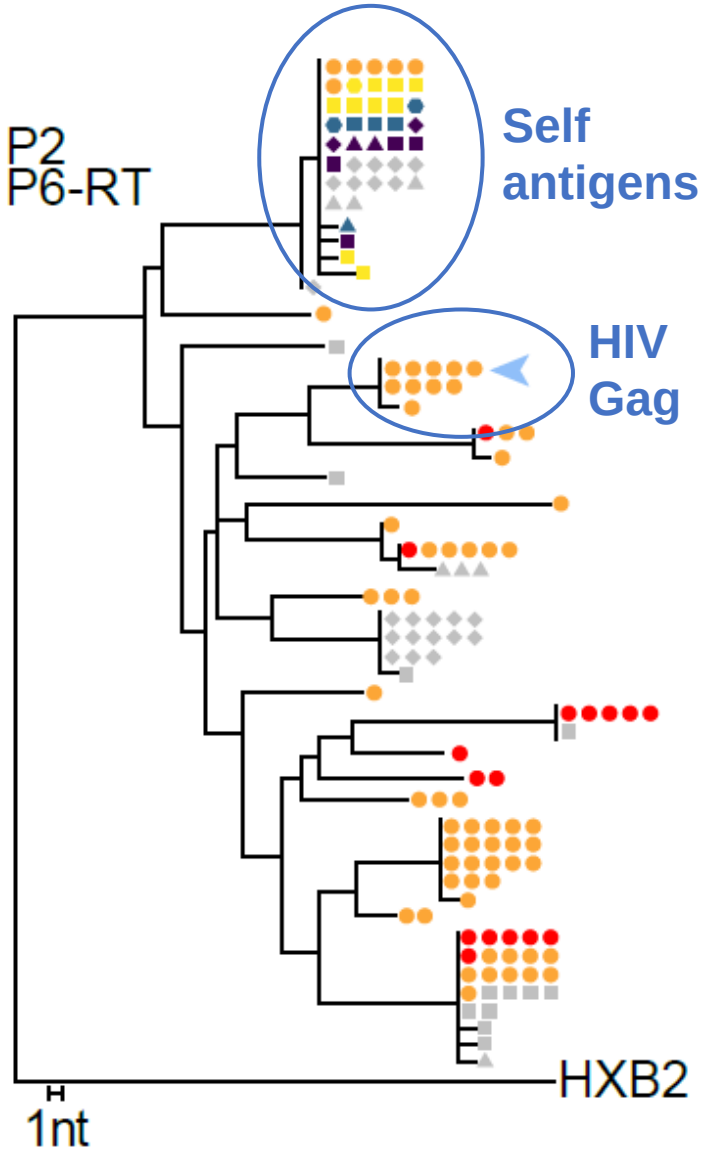
What makes these infected clones (always present) responsible for persistent non-suppressible viremia (relatively rare)?

Hypothesis: frequent antigenic stimulation, including **self-antigens**, can lead to spontaneous activation of infected CD4+ T cells and virus production

Virus production is induced by autologous cell stimulation ex vivo

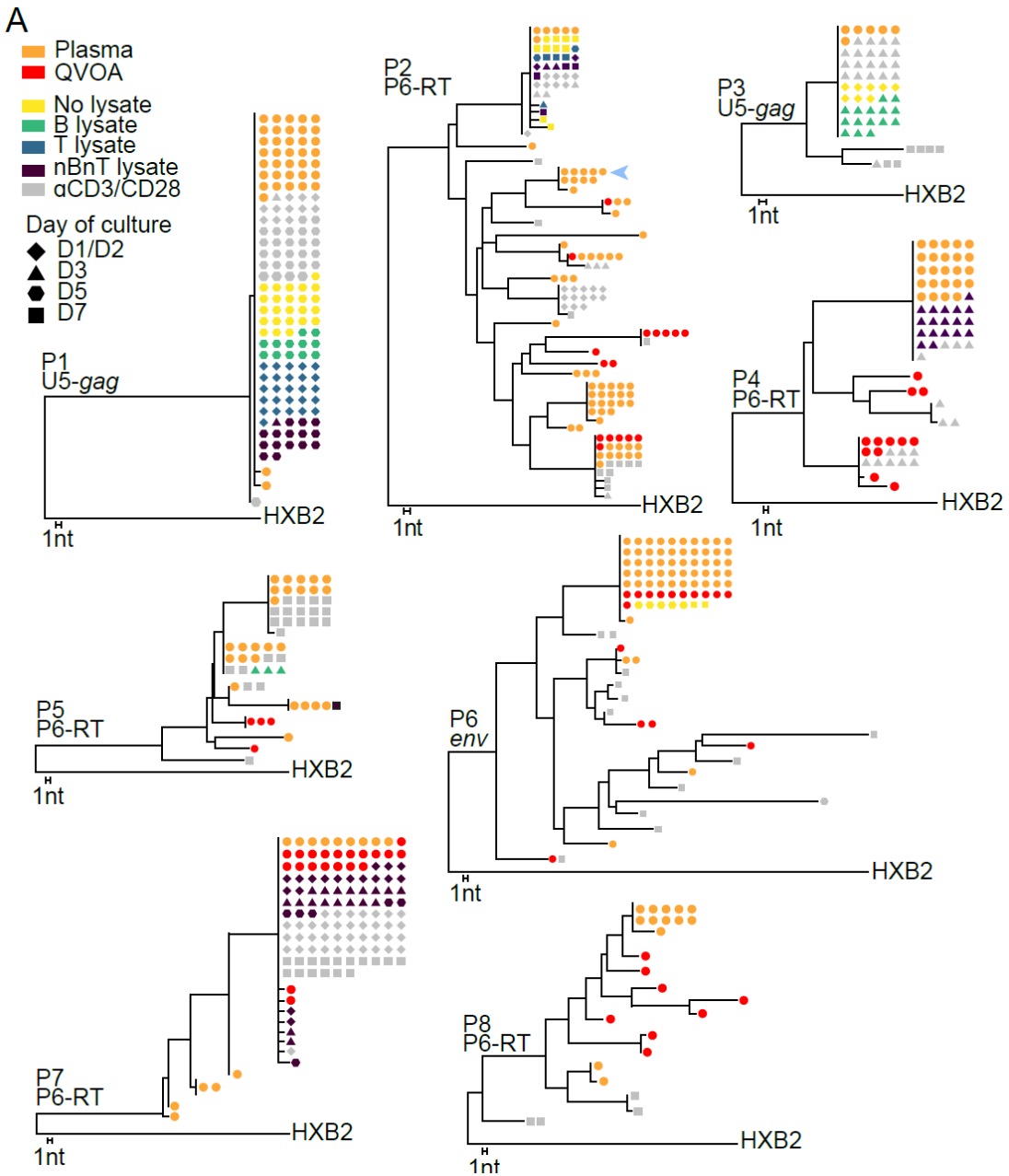


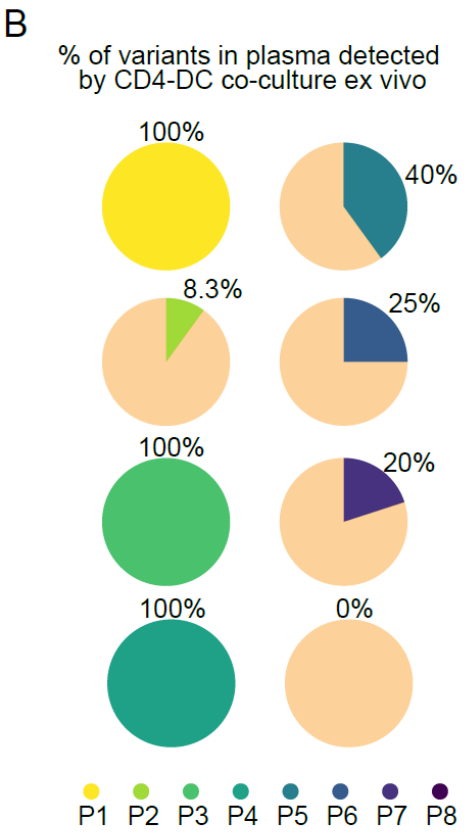


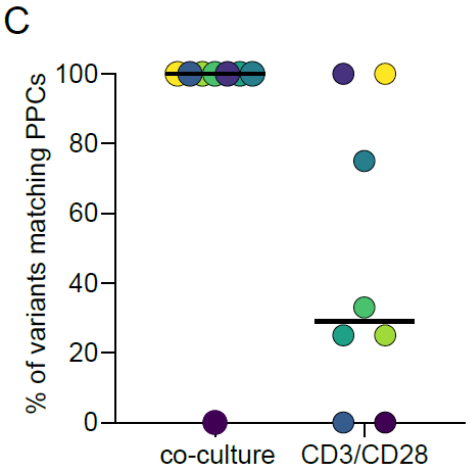


Wu, et al., in preparation

Autologous cell lysates lead to production of virus found in plasma







Wu, et al., in preparation

Conclusions

The new onset of persistent viremia despite no issues in adherence and drug efficacy is driven by **virus production from expanded infected clones**. Not replication.

Proviruses with **small defects in the 5'-Leader region** can also cause detectable viremia, up to thousands of copies per ml, complicating ART management and the interpretation of single-copy assays.

This type of defects result in **non-infectious virus**, in part due to low expression of the Envelope.

These proviruses are found in expanded CD4 T cell clones that can be stable over time thanks to frequent cell division.

CD4 **stimulation ex vivo with antigens, including autologous antigens**, results in latency reversal and production of viral particles from the same variants causing NSV.

What can we do about it, from a clinical perspective?

- **Increase awareness** of NSV and its different mechanisms among clinicians and communities

Non-suppressible viraemia during HIV-1 therapy: a challenge for clinicians

Andrés Esteban-Cantos, PhD * • Rocío Montejano, PhD * • Adriana Pinto-Martínez, MD • Javier Rodríguez-Centeno, PhD • Federico Pulido, PhD † • Prof José R Arribas, PhD † • Show footnotes

Published: April 08, 2024 • DOI: https://doi.org/10.1016/S2352-3018(24)00063-8 • Check for updates

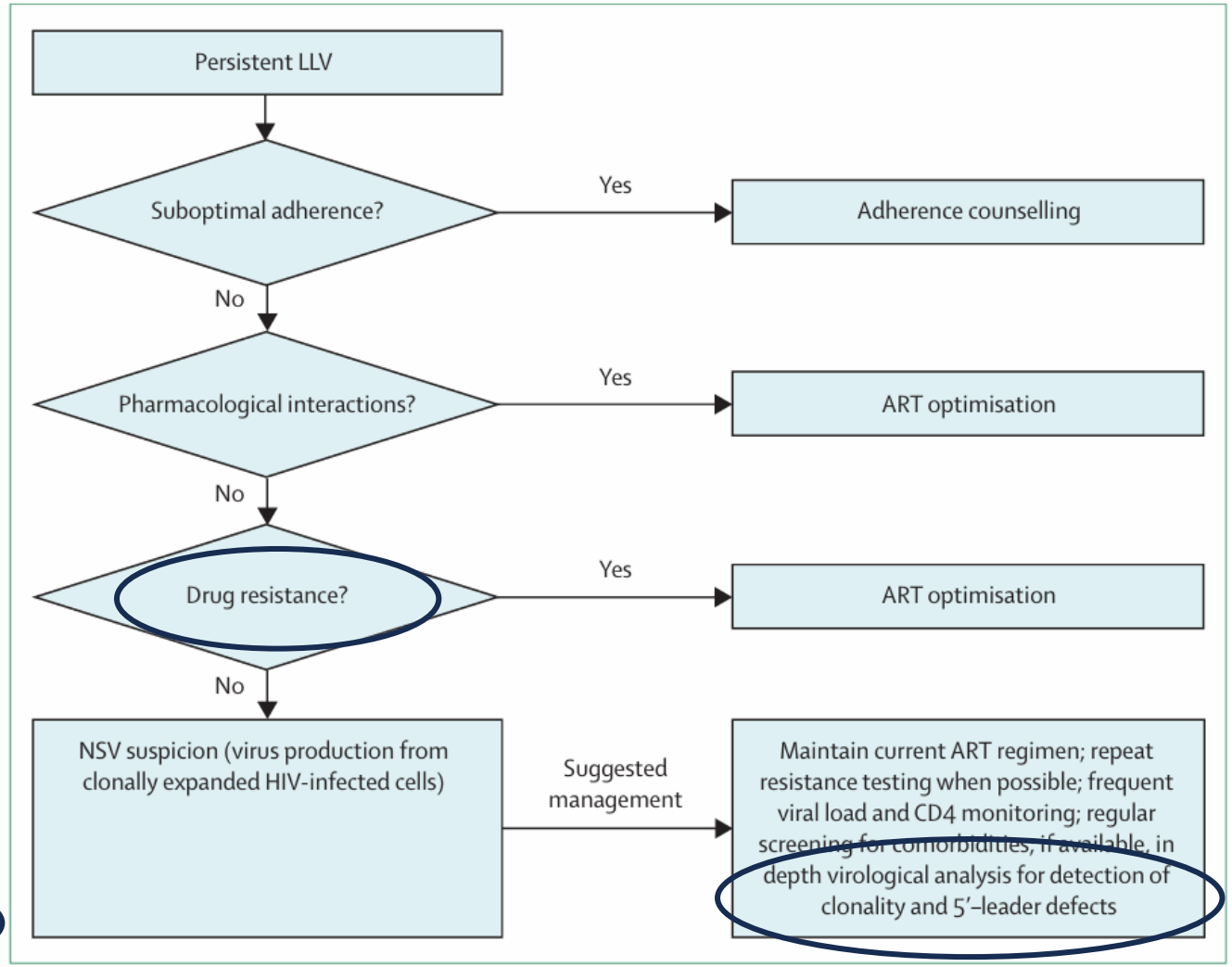
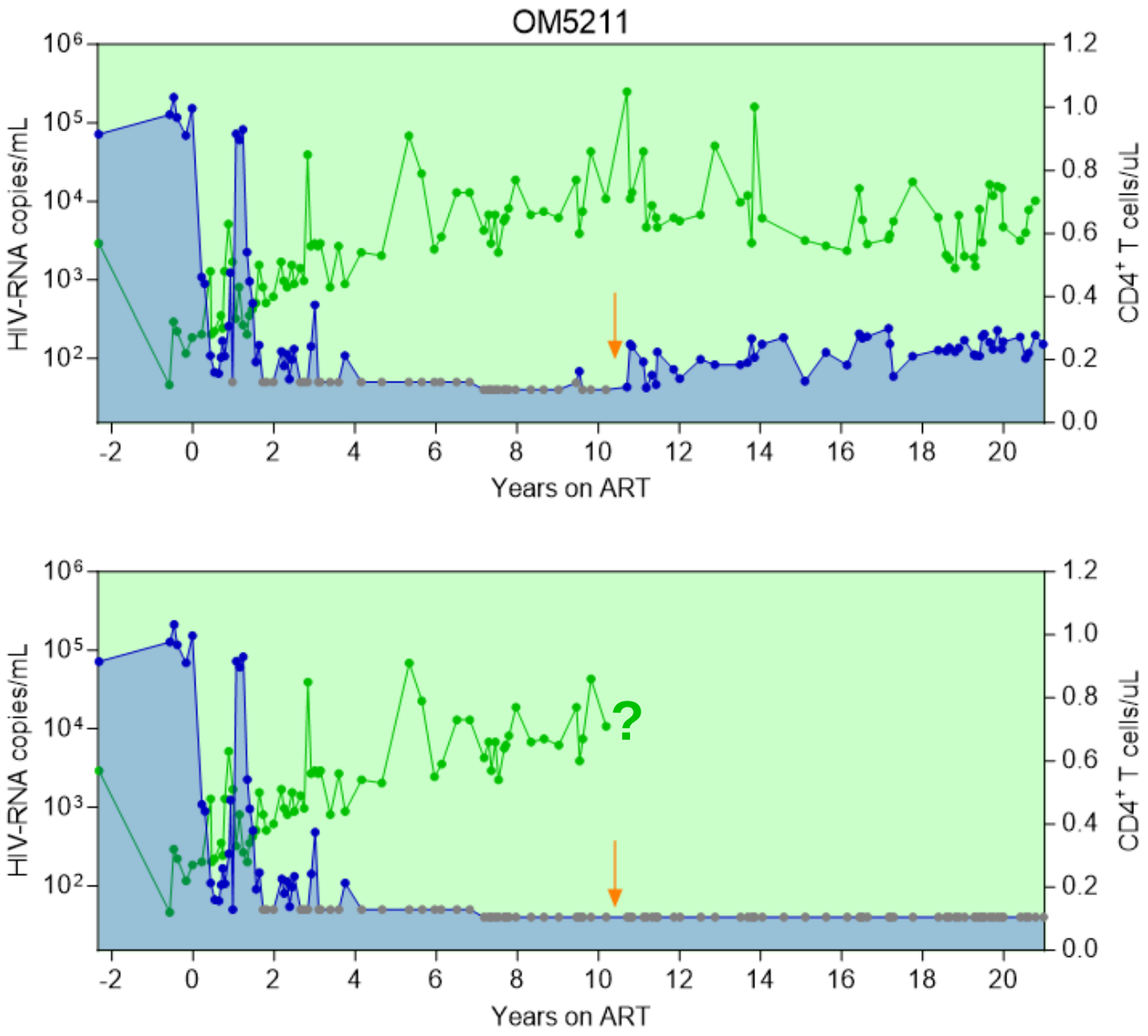


Figure: **Clinical management recommendations for patients with persistent LLV and suspected of NSV**
ART=antiretroviral therapy. LLV=low-level viremia. NSV=non-suppressible viremia.

Technology gaps

- Develop **ultrasensitive, clinically approved assays** to sequence virus in plasma can help rule out drug resistance, presence of 5'-Leader defects, and accumulation of evolution (or lack thereof)

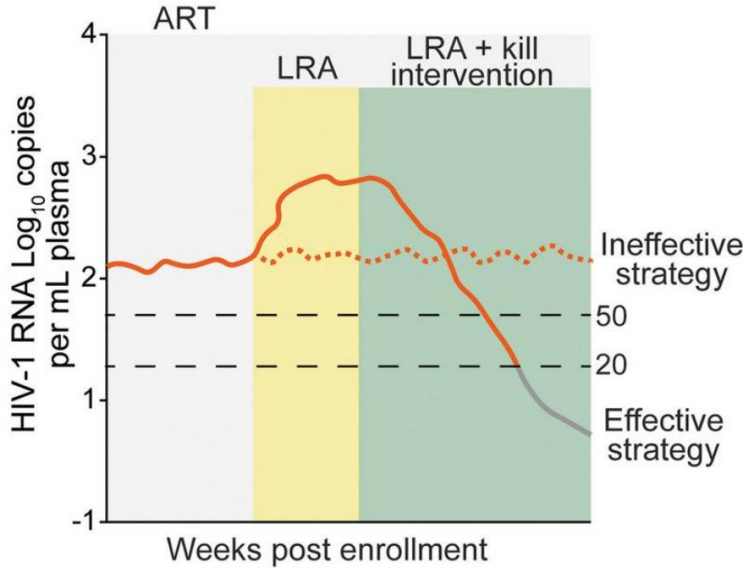
What can we do about it, from a research perspective?



- Which long-term impact on inflammation?
- Can the immune system sense intact and defective HIV RNA?

- What can we do to eliminate clones contributing to persistent viremia? CARD8 activating molecules, bNAbs, etc.?

- Can we resort to study participants with NSV to investigate the effect of such interventions?



This work happens thanks to many people

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Annie Chamberland

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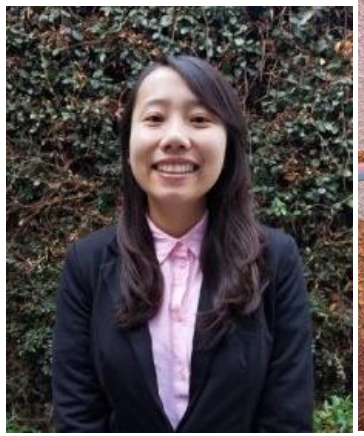

Fengting Wu, PhD, (Gilead Sciences)

Simonetti Lab dinner at Clavel, Baltimore, 2024

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JOHNS HOPKINS UNIVERSITY

NIH DIRECTOR'S EARLY INDEPENDENCE AWARD

DP5OD031834

NIH NIAID

R01AI176594

Study Participants

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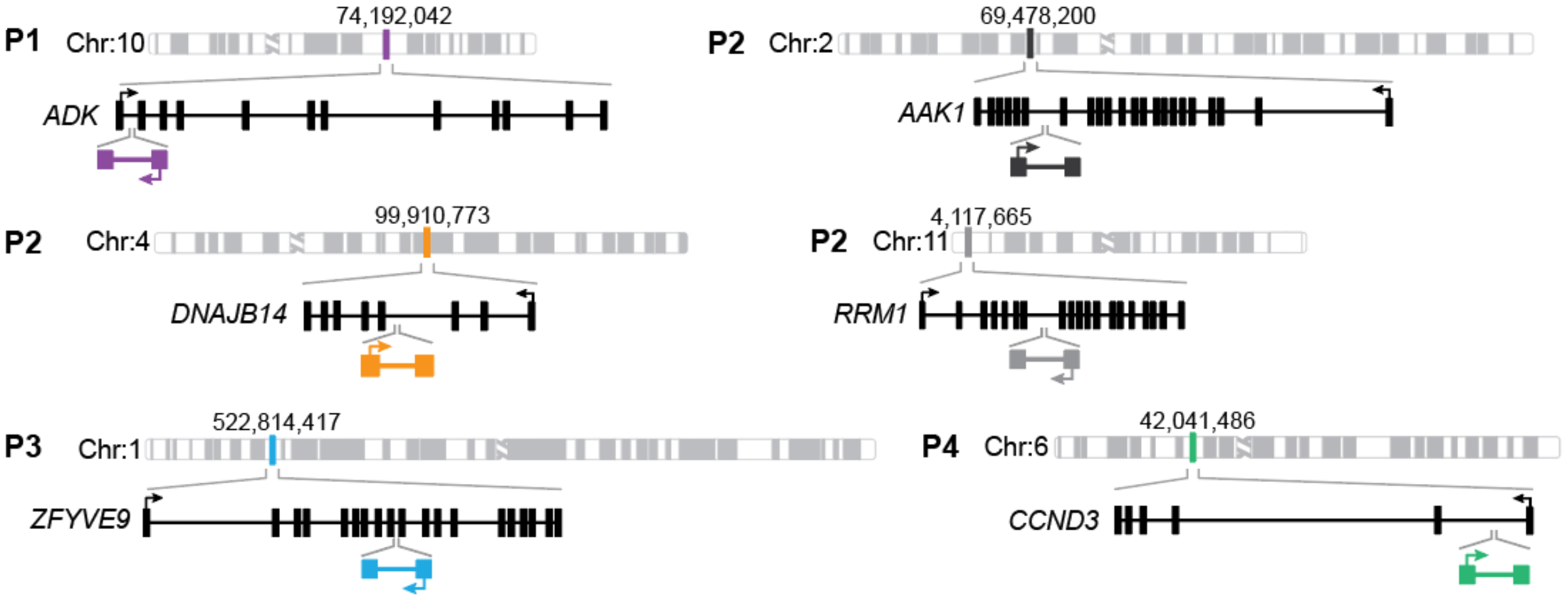
Thank you for the attention!

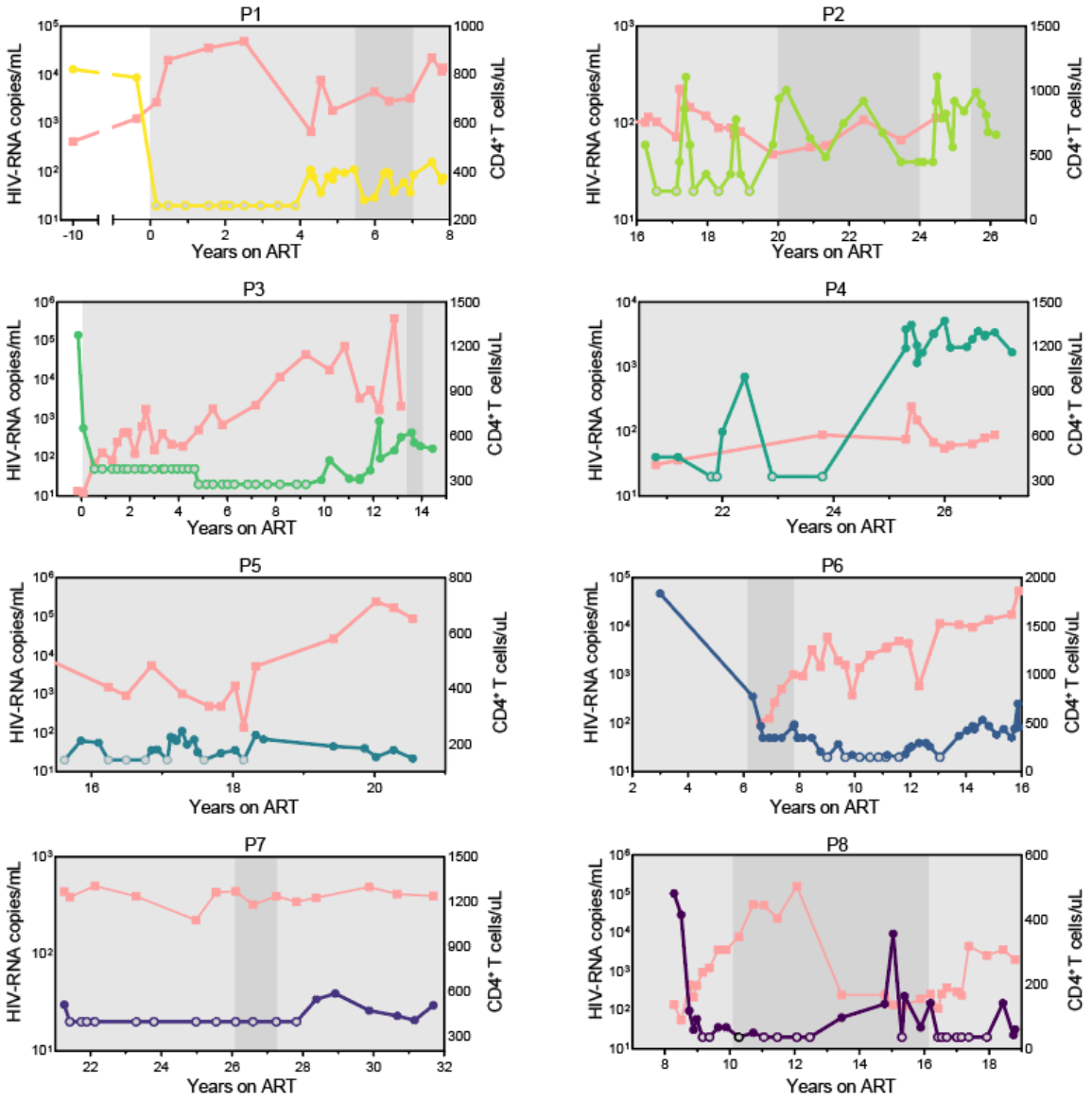
Jepp 2023

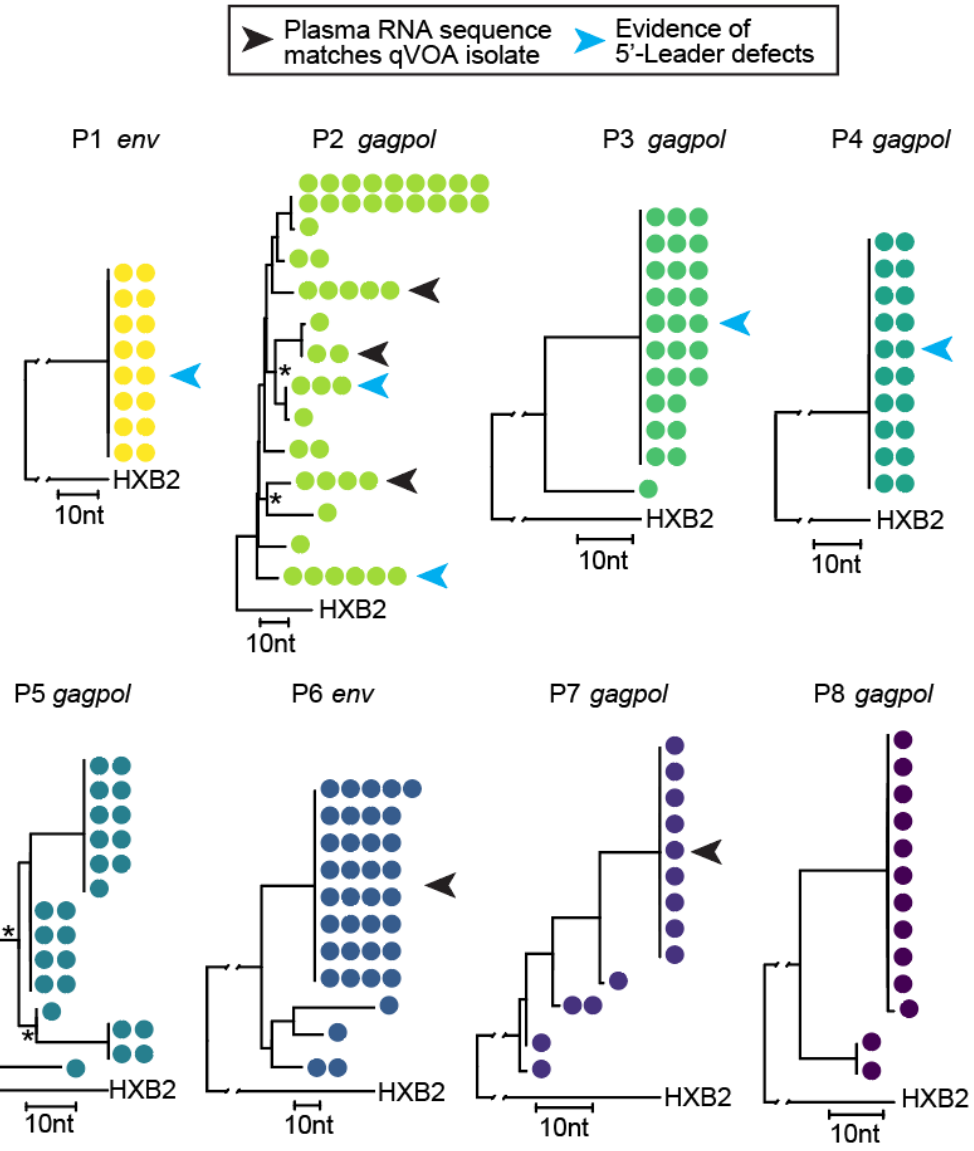
Jepp 2024

Proviruses cause of NSV are integrated into genes with variable expression in CD4$^+$ T cells, all in opposite orientation



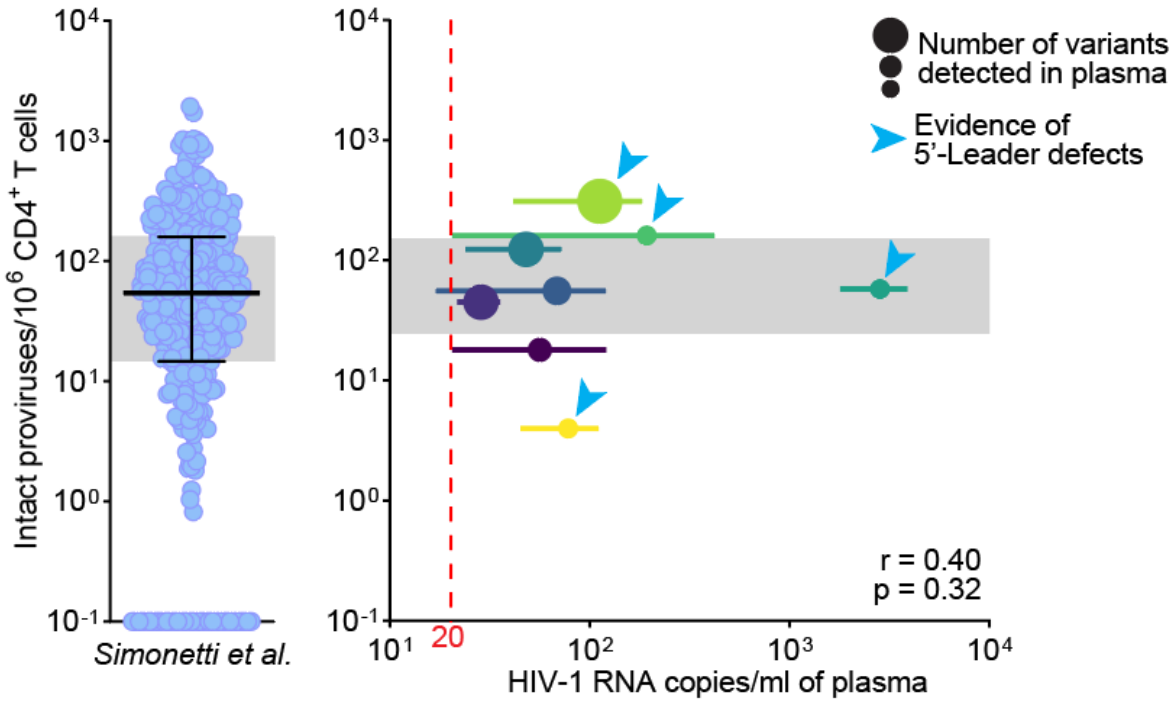
Reservoir size is not sufficient to explain the presence of NSV





Reservoir size is not sufficient to explain the presence of NSV

Characteristics	P1	P2	P3	P4	P5	P6	P7	P8	Median
Age (Years)	63	60	58	60	55	61	56	67	
Sex	M	M	F	M	M	F	M	M	
Race	AA	AA	AA	W	AA	W	AA	W	
HIV-1 RNA, last (copies/mL)	50.8	37.8	191	3400	40.5	129	29.5	31.6	45.65
Years on ART	9	26	15	27	18	23	31	14	23
Years since VL >20 copies/mL	5	10	6	5	5	5	3	10	5
Infectious units/million CD4+ (QVOA)	<0.06	15	na	3	1.9	2.1	7.8	1.6	2.55
Intact provirus/million CD4+ (IPDA)	4	311	161	58	124	56	45	18	58
Number of plasma clones	1	10	1	1	5	4	5	2	3

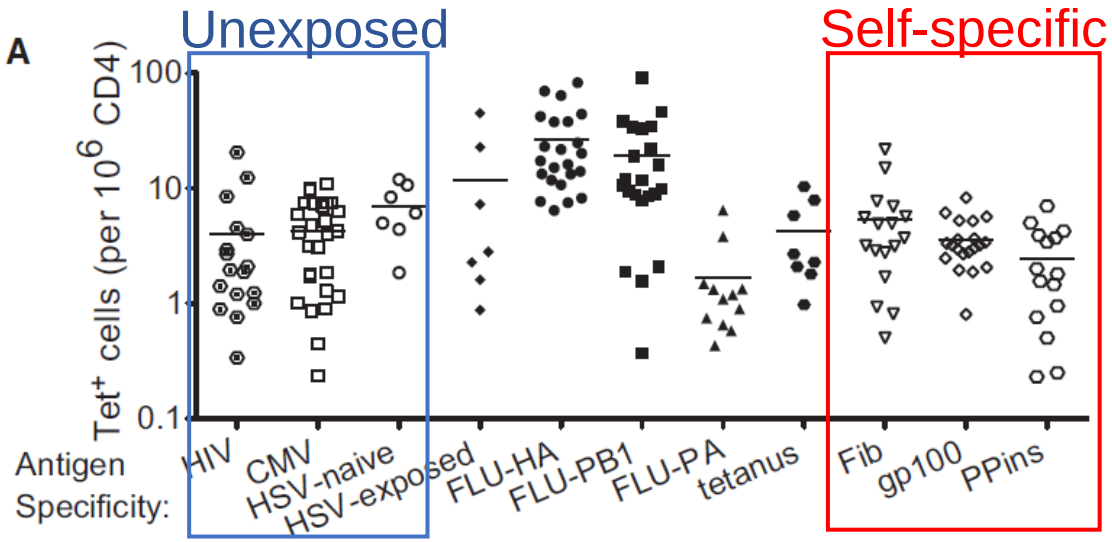


CD4+ T cells constantly scan self-peptides through MHC-II

Tissue	MHC class II
Lymphoid tissues	
T cells	+*
B cells	+++
Macrophages	++
Dendritic cells	+++
Epithelial cells of the thymus	+++

Janeway's Immunobiology (8th ed)

Self-specific cells have frequency of 1-10/M $CD4^+$



Su et al, Cell, 2013