



**CLONALLY EXPANDED HIV-1 PROVIRUSES WITH
5'-LEADER DEFECTS CAN GIVE RISE TO
NONSUPPRESSIBLE RESIDUAL VIREMIA
AND COMPLICATE ART MANAGEMENT**

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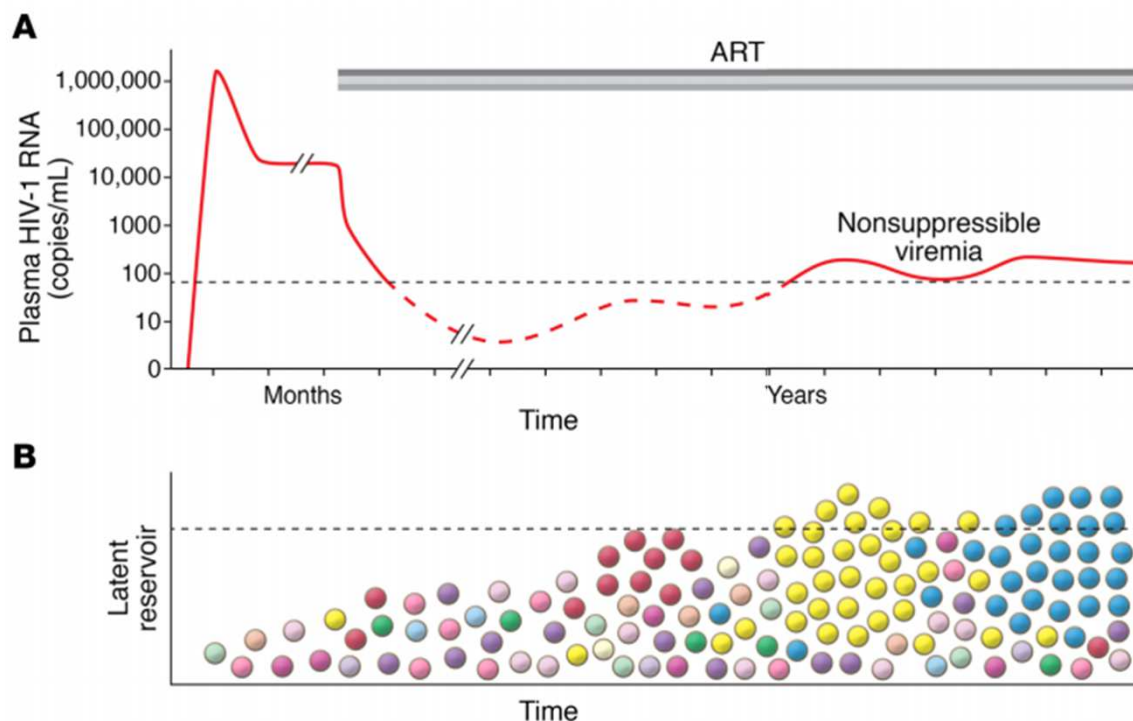


Takahiko Hayashi,
Emitting Blue, 2013

I HAVE NO CONFLICTS OF INTEREST

www.hiv-persistence.com

Some people on ART experience nonsuppressible residual viremia (NSV)



Typical features of “Replicones”:

- Drug sensitive
- Can be recovered by outgrowth assay → infectious
- They are relatively large ($>10^7$)
- Represent a small % of total infected cells ($\sim 1\%$)

Simonetti et al, PNAS 2016

Halvas et al, JCI 2020

Janet and Robert Siliciano, JCI 2020

If residual viremia is a reflection of reservoir persistence (**always present**),
why only some people experience NSV (**rare**)?

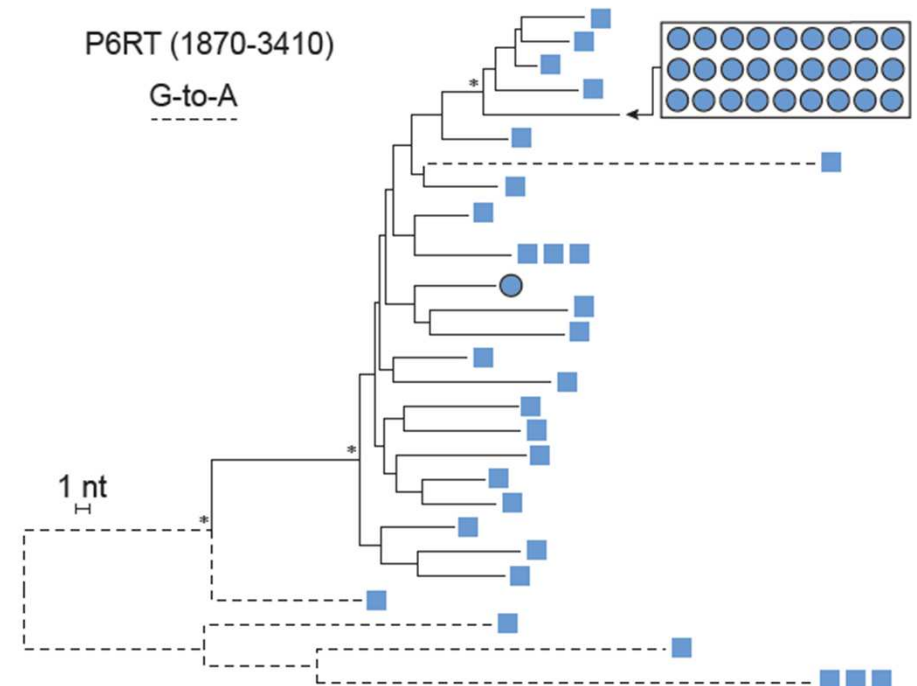
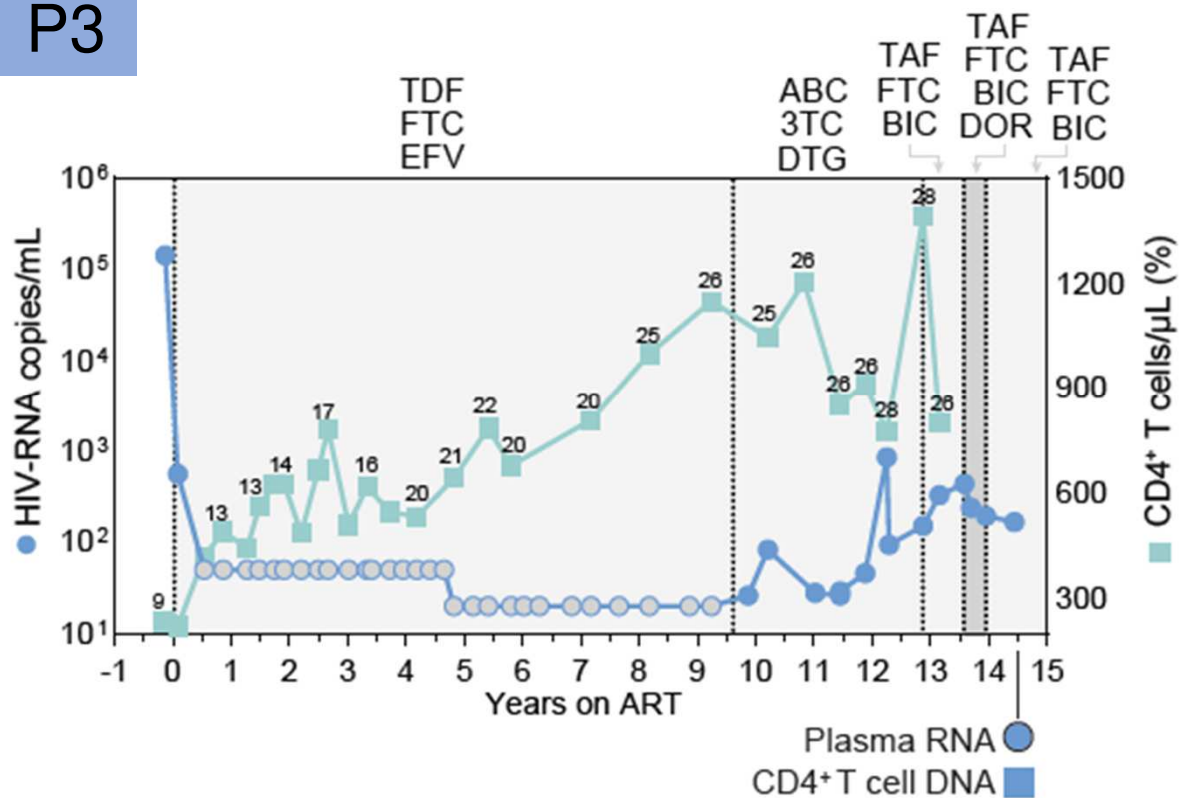
Participant Characteristics

Characteristics	P1	P2	P3	P4	Median ^d
Sex	Male	Male	Female	Male	
Age (y)	63	60	58	60	60
Race	African American	Caucasian/White	African American	Caucasian/White	
Years since diagnosis	30	31	15	32	31
Years on ART	7.8	26.4	14.5	27	20
CD4 ⁺ T cell count nadir (cells/mm ³)	454	197	221	na	
CD4 ⁺ T cell count, last (cells/mm ³)	828	793	803	610	798
HIV-1 RNA, setpoint (copies/mL)	8771	na ^c	141667	na	
HIV-1 RNA, last (copies/mL) ^a	58	20	167	3400	113
Years with detectable viremia	5	11	5	5	5
ART regimen, last ^b	TAF,FTC,BIC	TAF,FTC,BIC,FTR	TAF,FTC,BIC	TAF, FTC, BIC, DOR, MVC	
Infectious units per million (QVOA)	<0.06	15 (10-21)	na	na	
Intact proviruses/10 ⁶ CD4 ⁺ T cells (IPDA)	3.5	311	161	58	110
HLA-B	53:01, 57:03	44:02	44:03	44:03, 57:02	

Supplementary Table S1. Participant characteristics. a, measured with limit of detection of 20 copies/mL; b, TAF tenofovir alafenamide fumarate, FTC emtricitabine, BIC bictegravir, FTR fostemsavir, DOR doravirine, MVC maraviroc; c, not available. d, median values were calculated when available for all 4 participants.

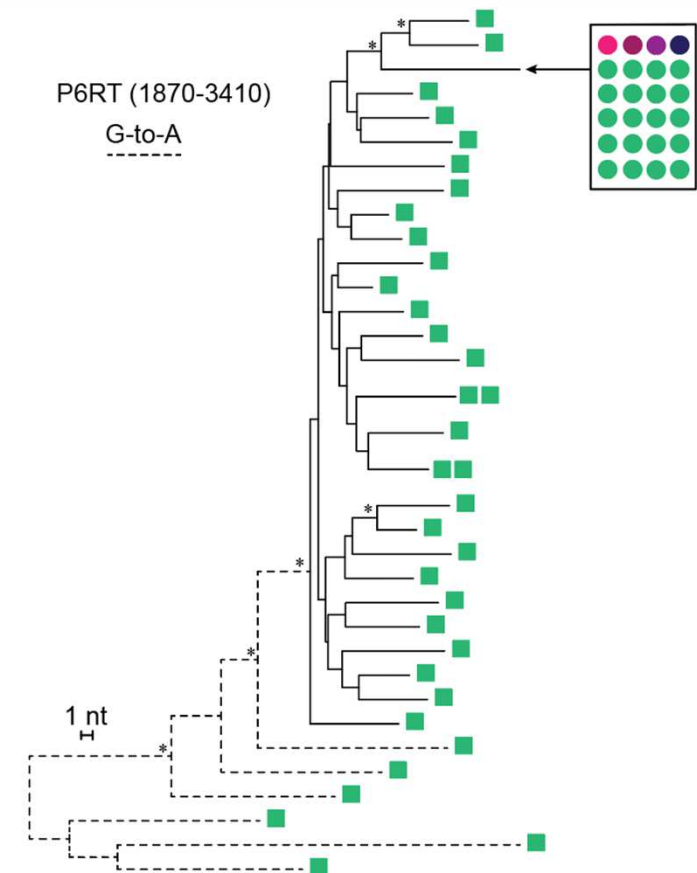
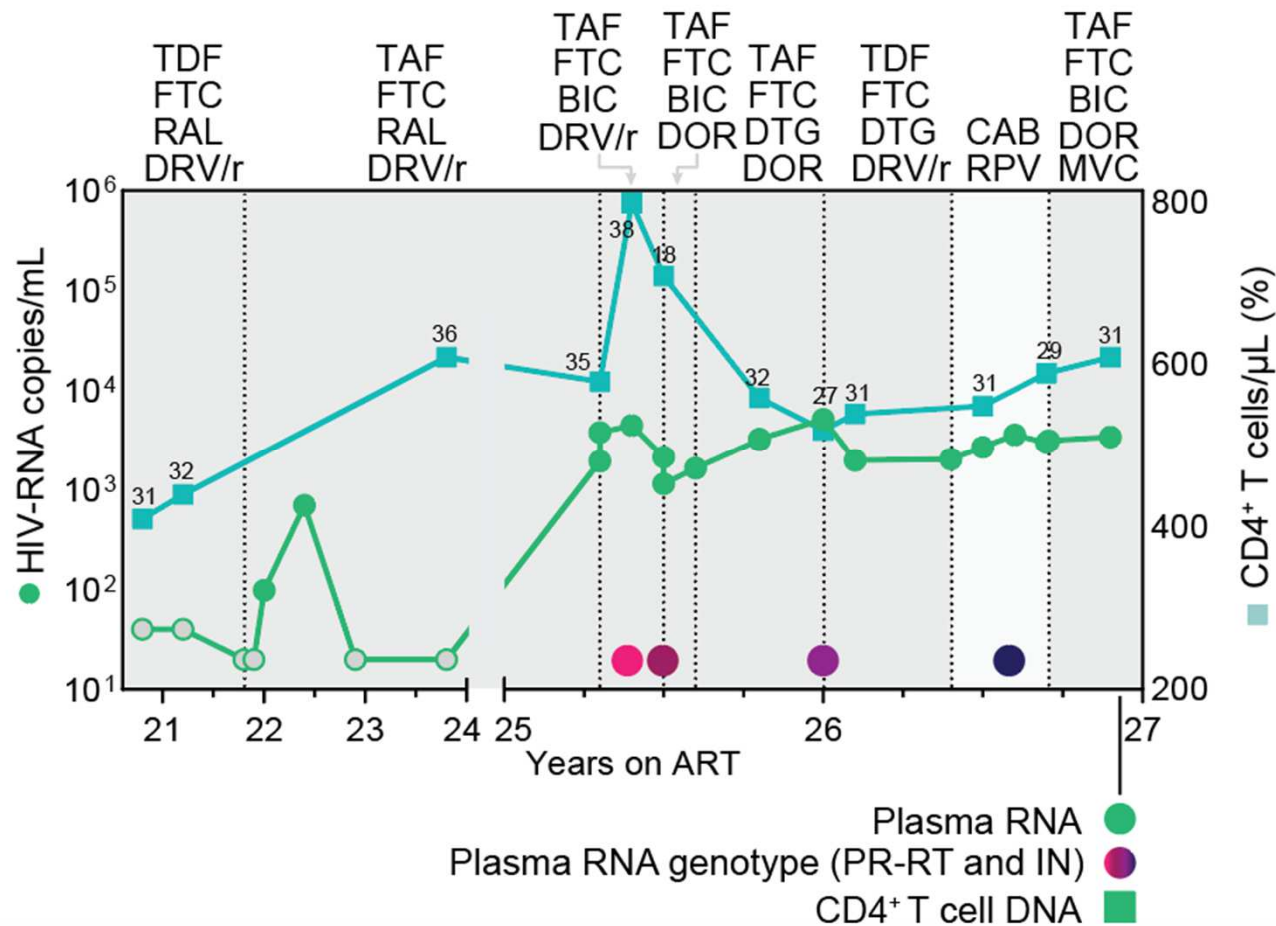
NSV is caused by a single, rare, drug-sensitive variant

P3

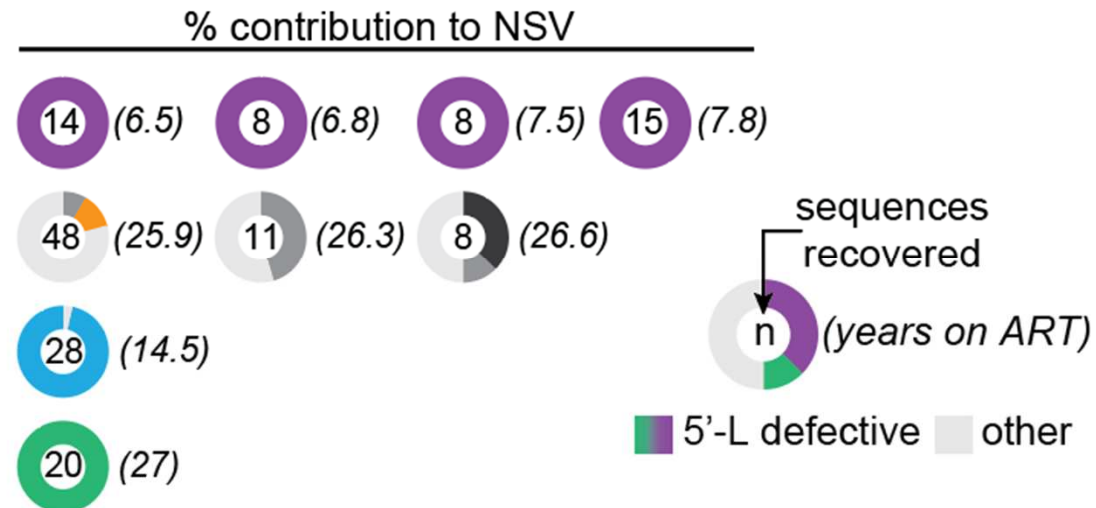
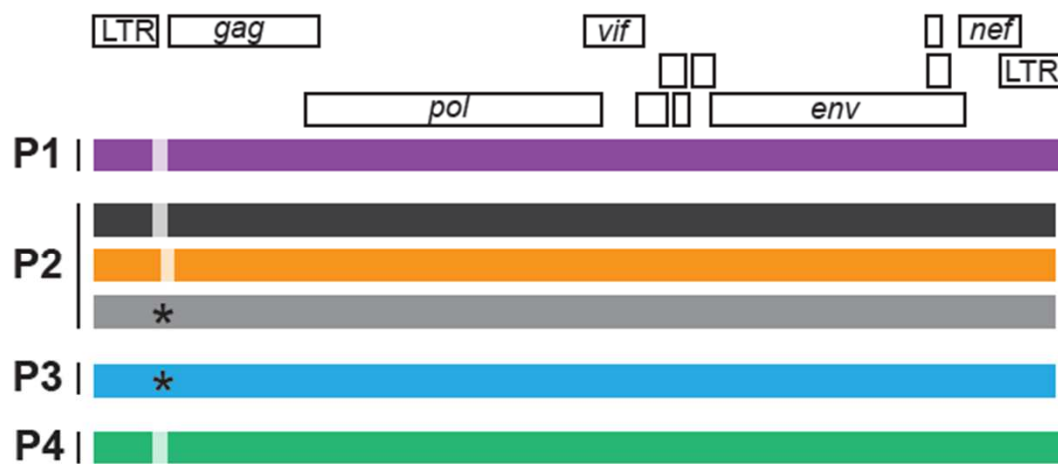


>10³ copies/mL of HIV RNA caused by a single drug-sensitive variant

P4



Provirus cause of NSV show defects in the 5'-Leader



White, Wu et al., under review

Ho et al, 2013

Pollack et al, 2017

Bruner et al, 2016

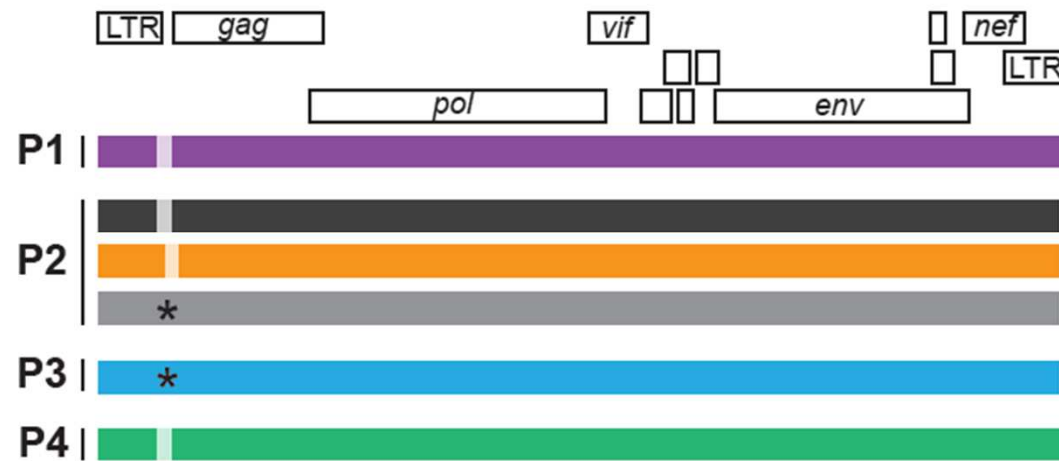
Imamichi et al, 2020

Hiener et al, 2017

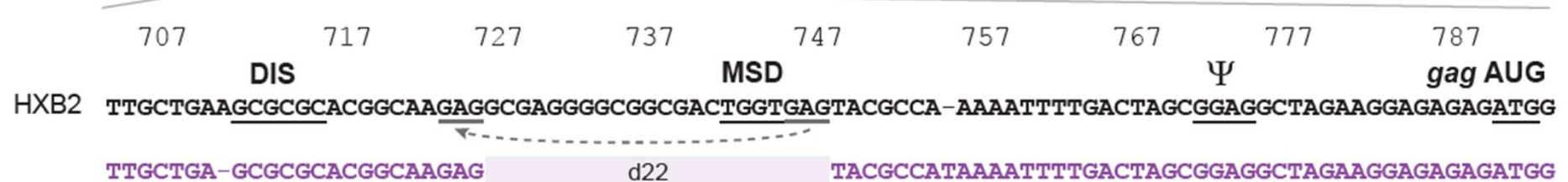
Cole et al, 2021

Provirus cause of NSV show defects in the 5'-Leader

A

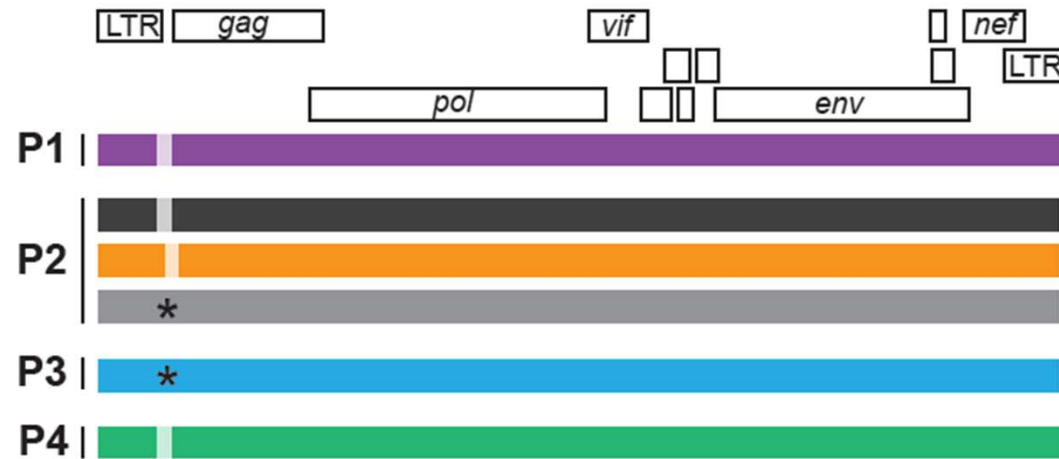


B

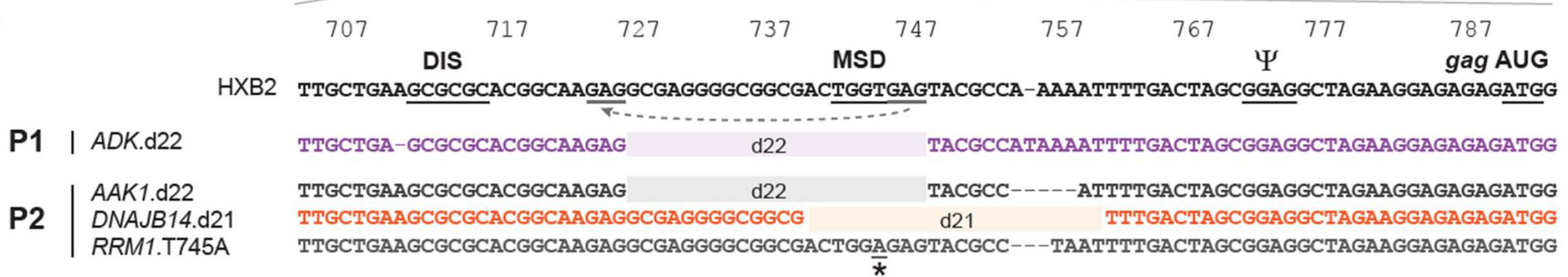


Proviruses cause of NSV show defects in the 5'-Leader

A

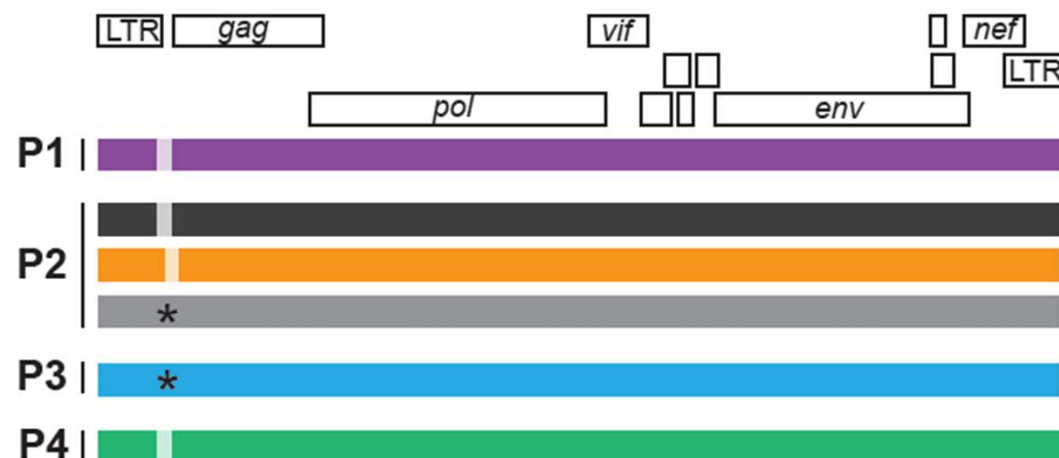


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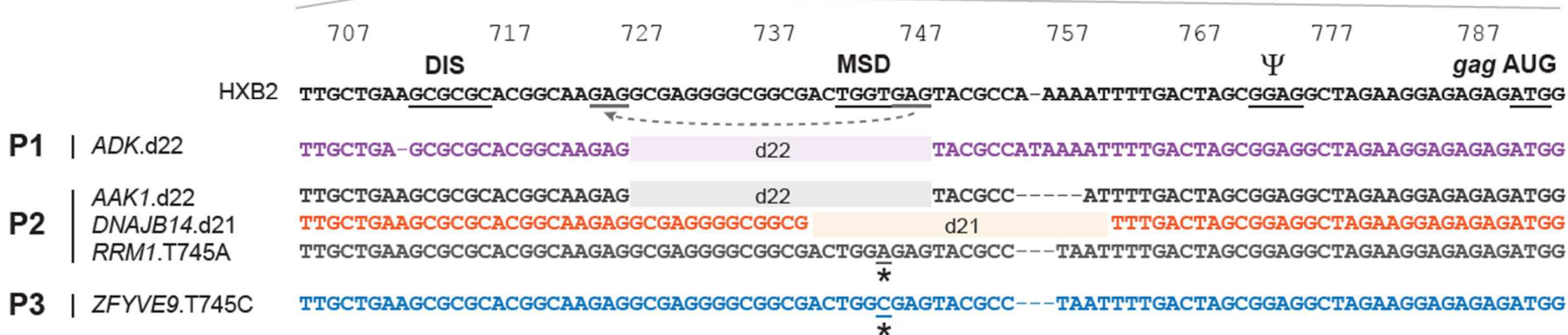


Provirus cause of NSV show defects in the 5'-Leader

A

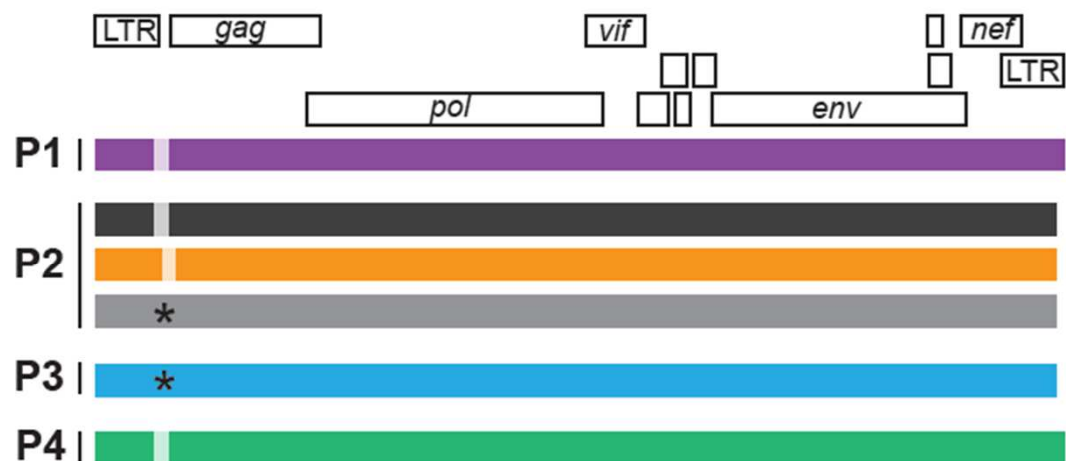


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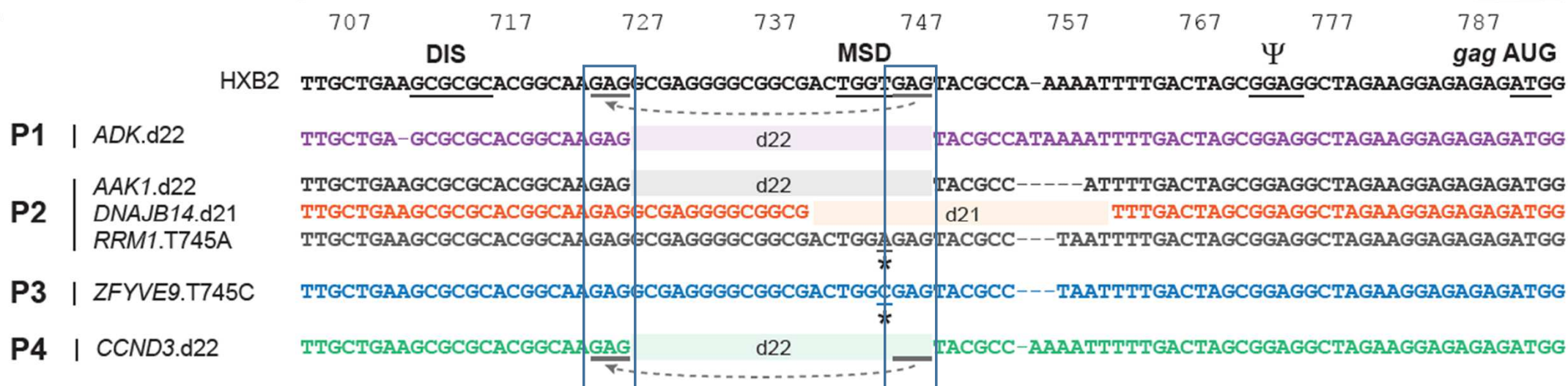


Provirus cause of NSV show defects in the 5'-Leader

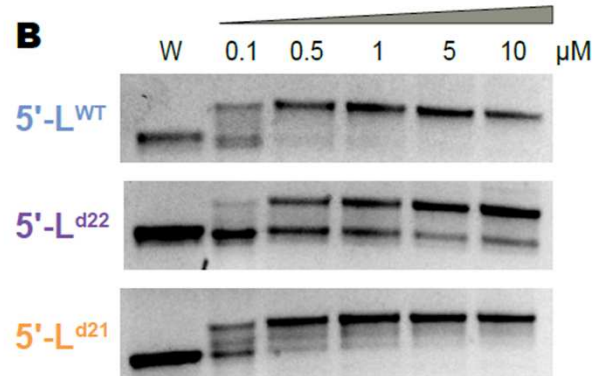
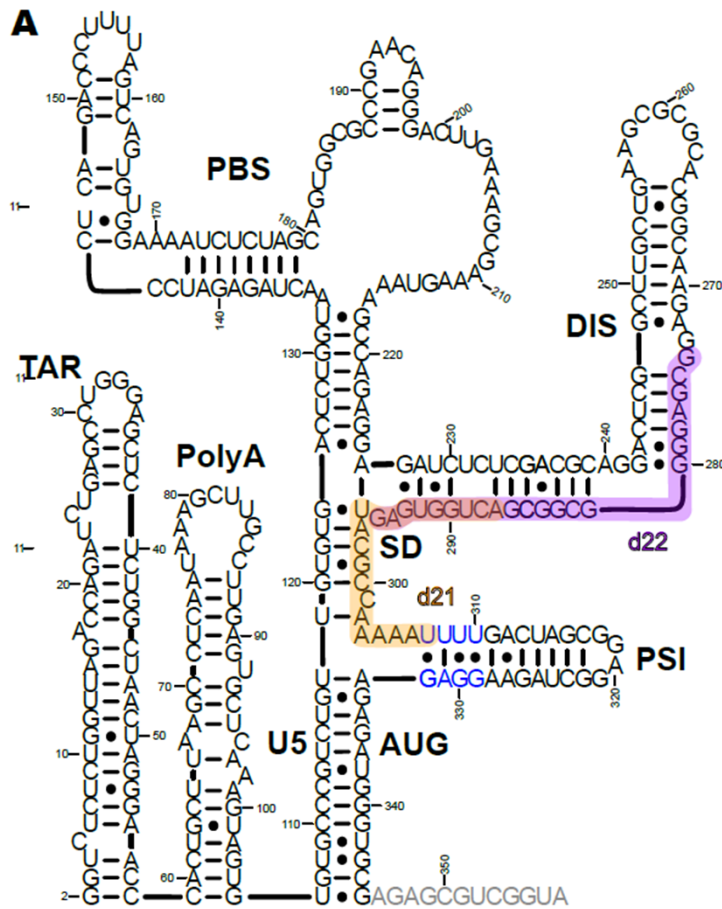
A



B



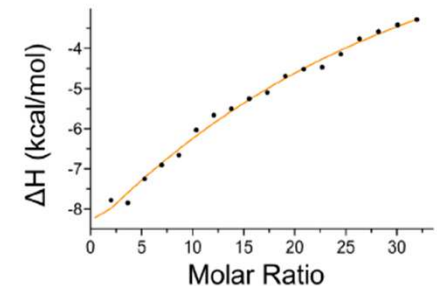
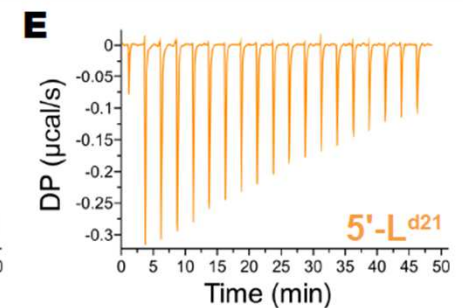
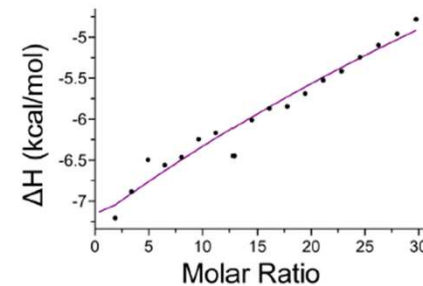
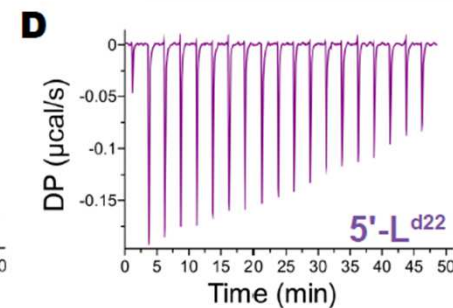
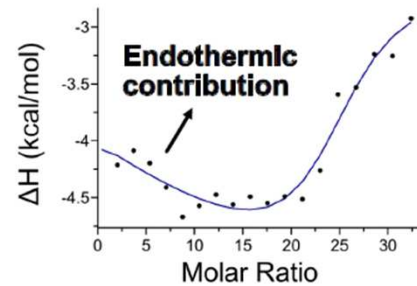
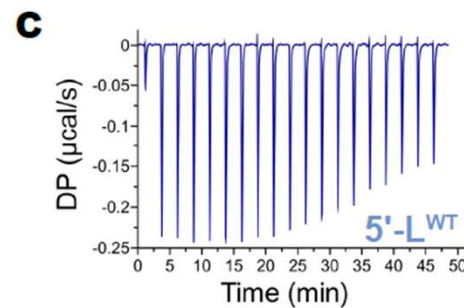
5'-L deletions only partially affect dimerization and Gag binding properties



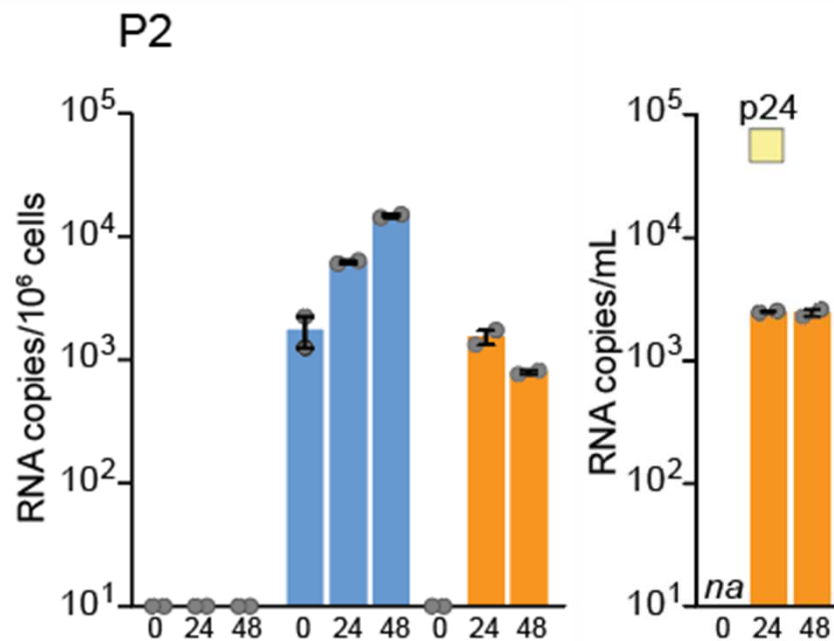
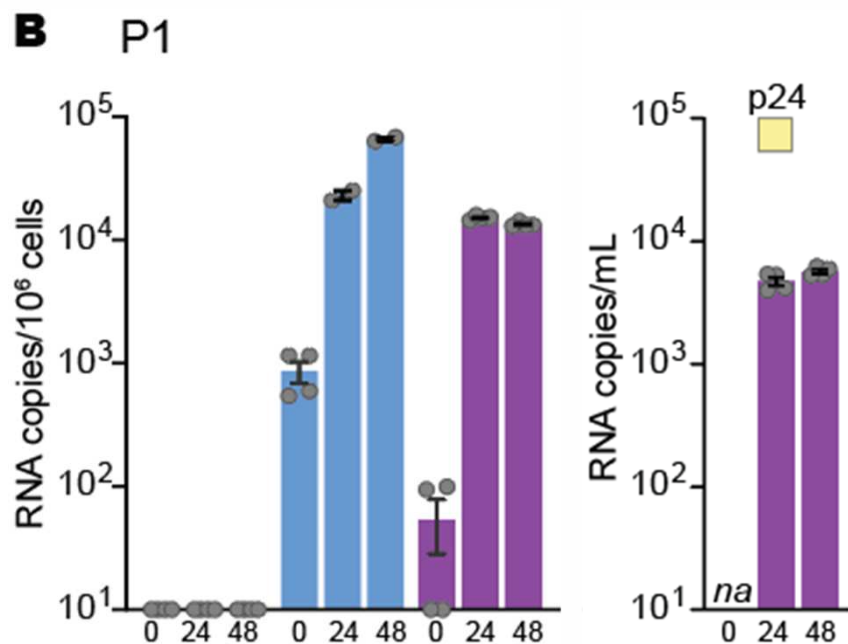
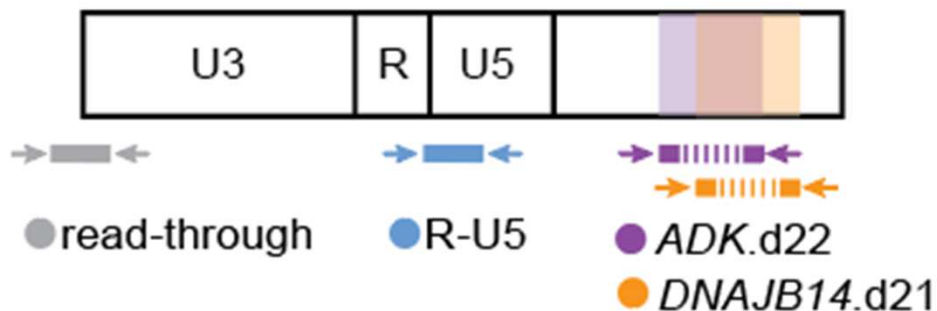
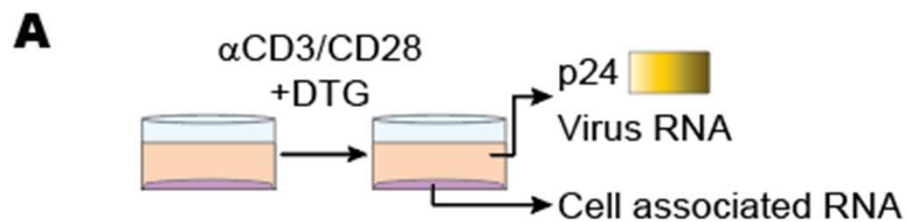
Mike Summers



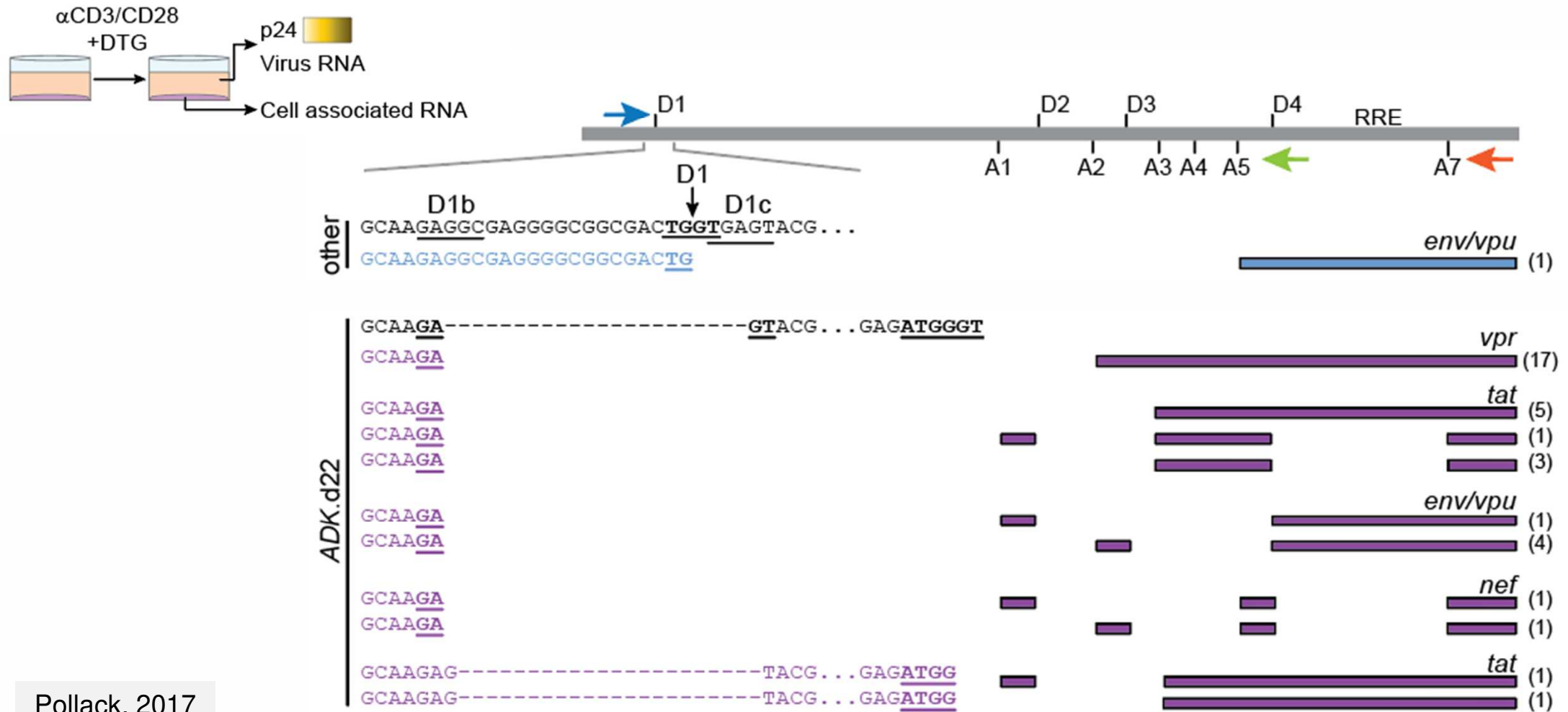
Saif Yasin



5'-L defective proviruses are inducible ex vivo upon T cell activation



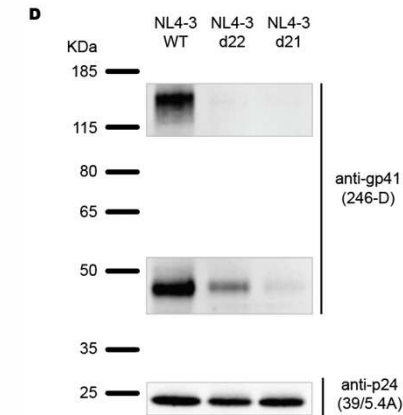
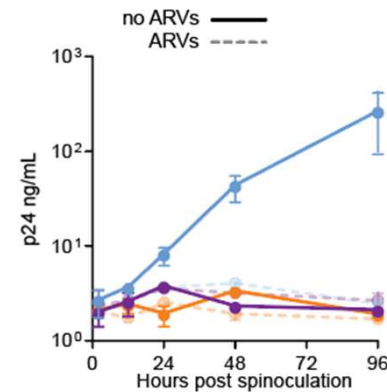
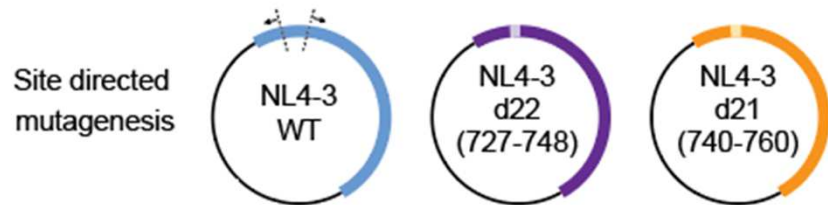
5'-L defective proviruses are inducible ex vivo upon T cell activation



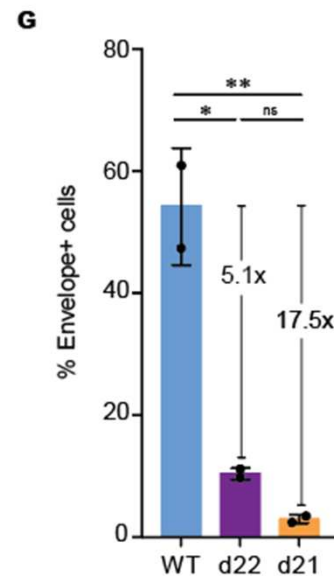
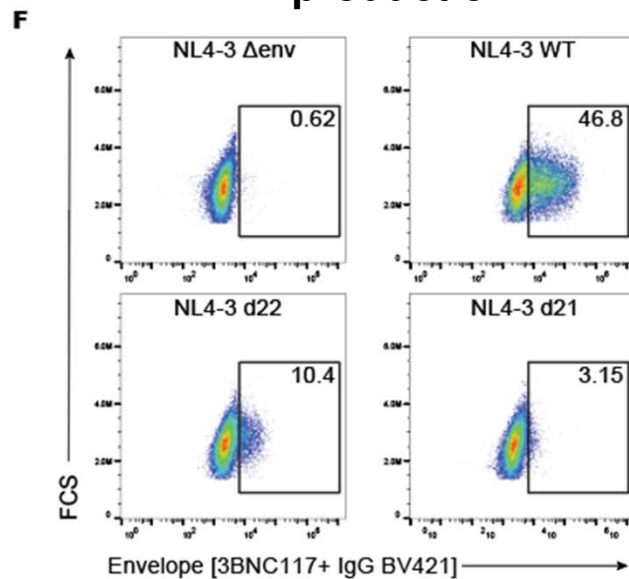
Pollack, 2017

Cole, 2021

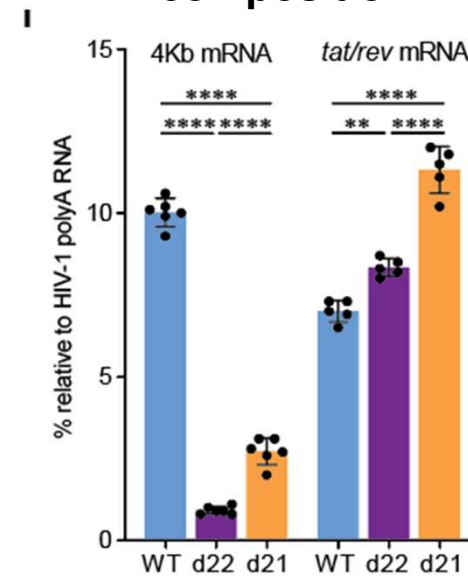
5'-L defects result in non-infectious virus with low Envelope expression



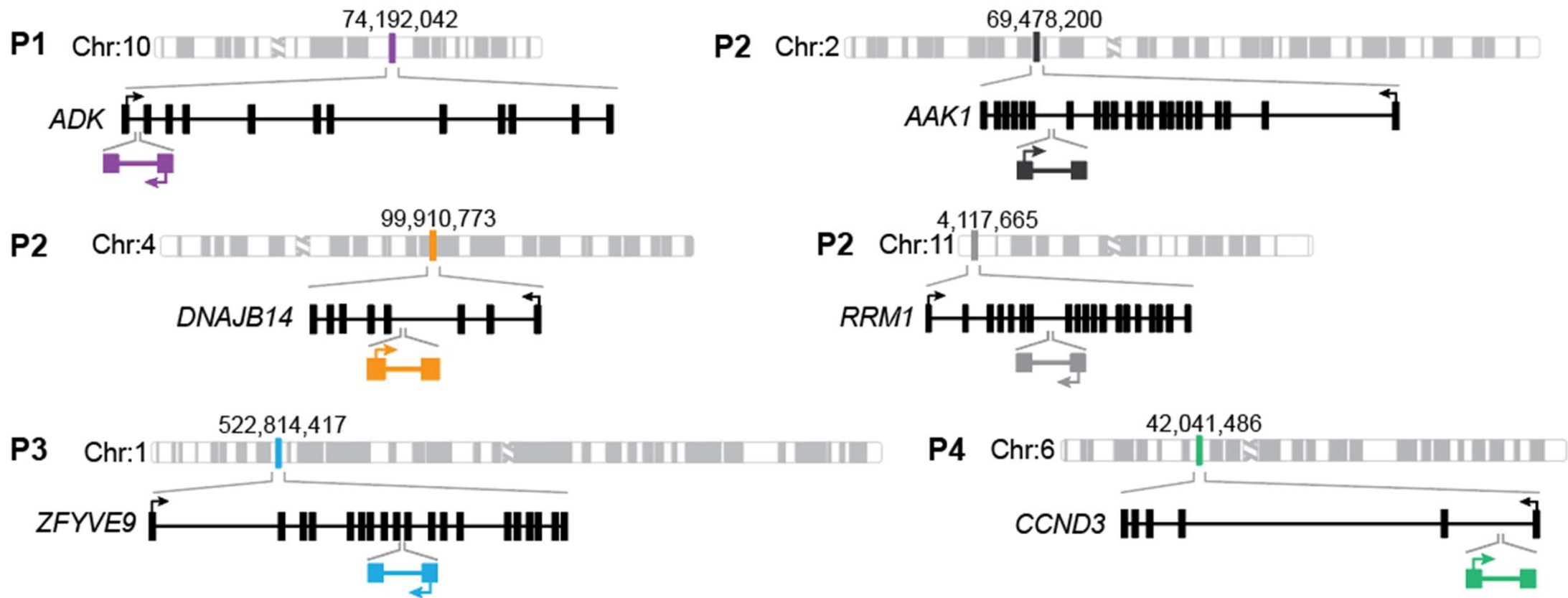
Reduced Envelope production



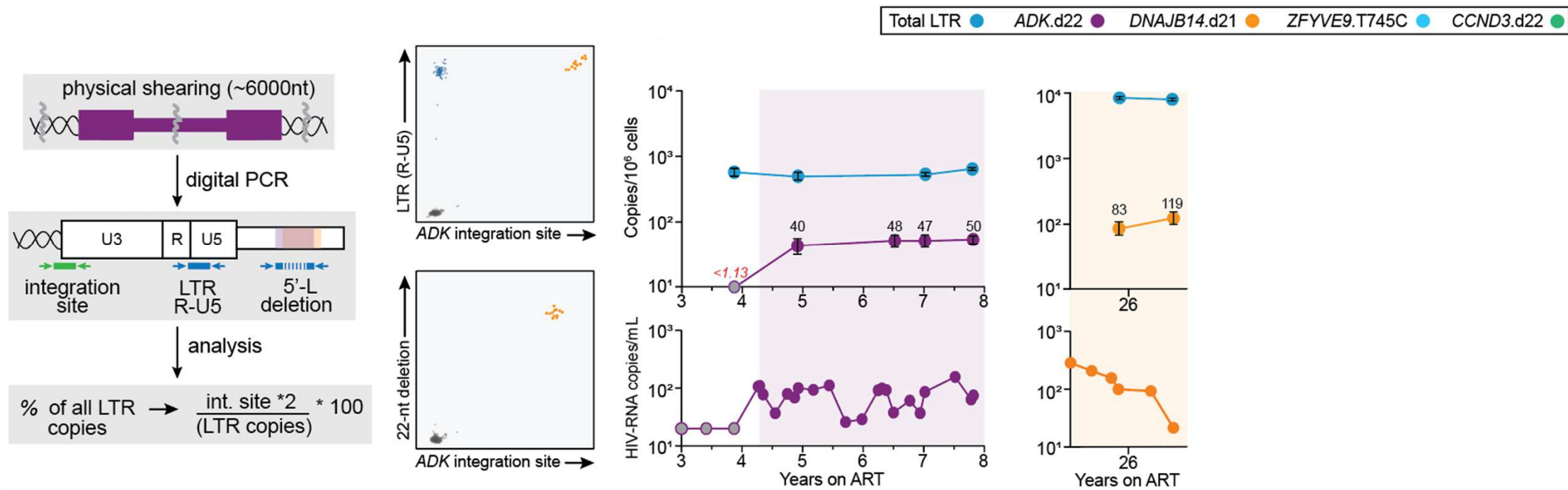
Disrupted spliceosome composition



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

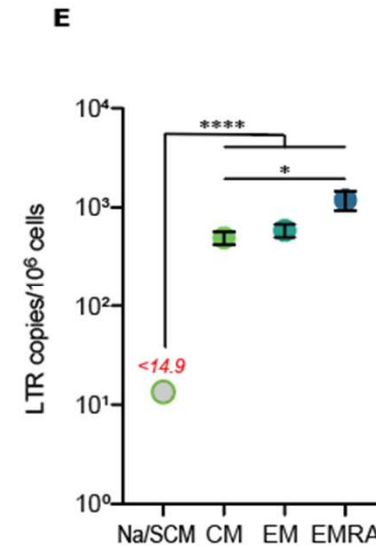
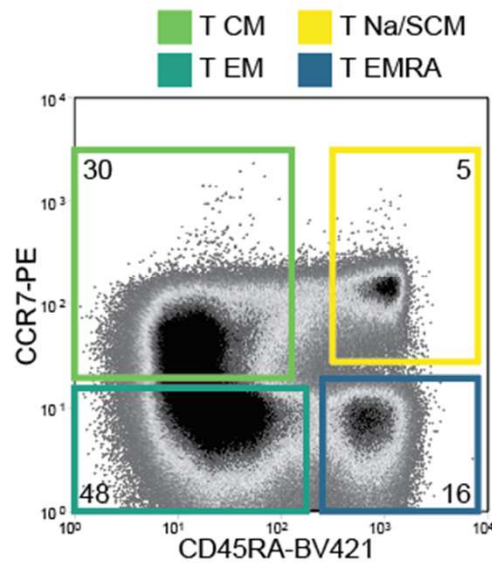


Clones expanded around onset of NSV and are stable over time

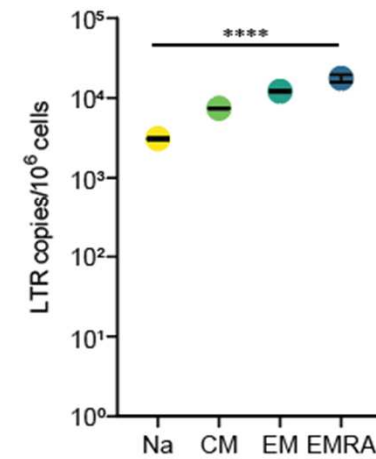
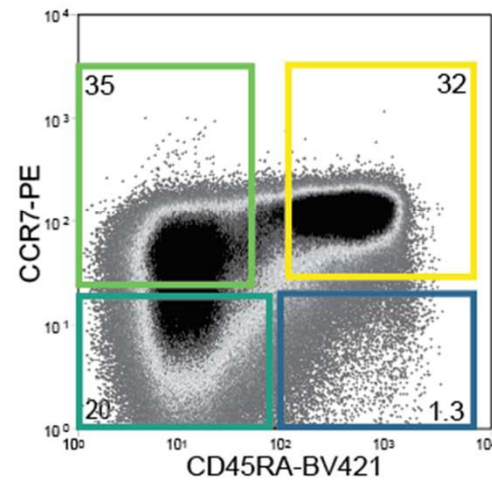


Clones cause of NSV are siloed in Effector Memory cells

P1



P2





COMMUNITY SUMMARY

Key question What causes viremia that cannot be fully suppressed by ART?

Key finding Proviruses with [small defects in the 5'-Leader region](#) can also cause detectable viremia, up to thousands of copies per ml, complicating ART management.

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 are stable over time thanks to frequent cell division.

Next steps How common is this phenomenon? What drives the constant virus production from specific infected cells cause of residual viremia?
How can we get rid of them?

Thank you All !!!

Study Participants

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Jiayi Duan

Fengting Wu

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Rebecca Veenhuis

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Alison L. Hill
Andrei Gheorghe

BSPH Sorting Core

Hao Zhang

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Jerald Cherian
Natasha Chida
Joyce Jones
Christin Kilcrease
Patricia Barditch-Crovo

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Saif Yasin

Montreal

Sebastien Poulin
Frederic Chano
Cecile Tremblay

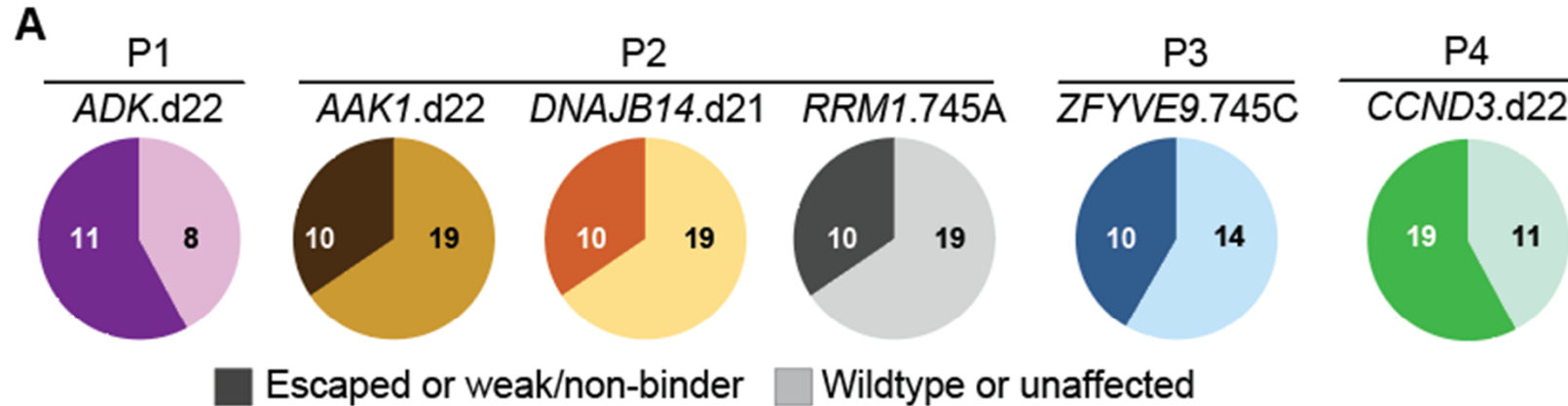


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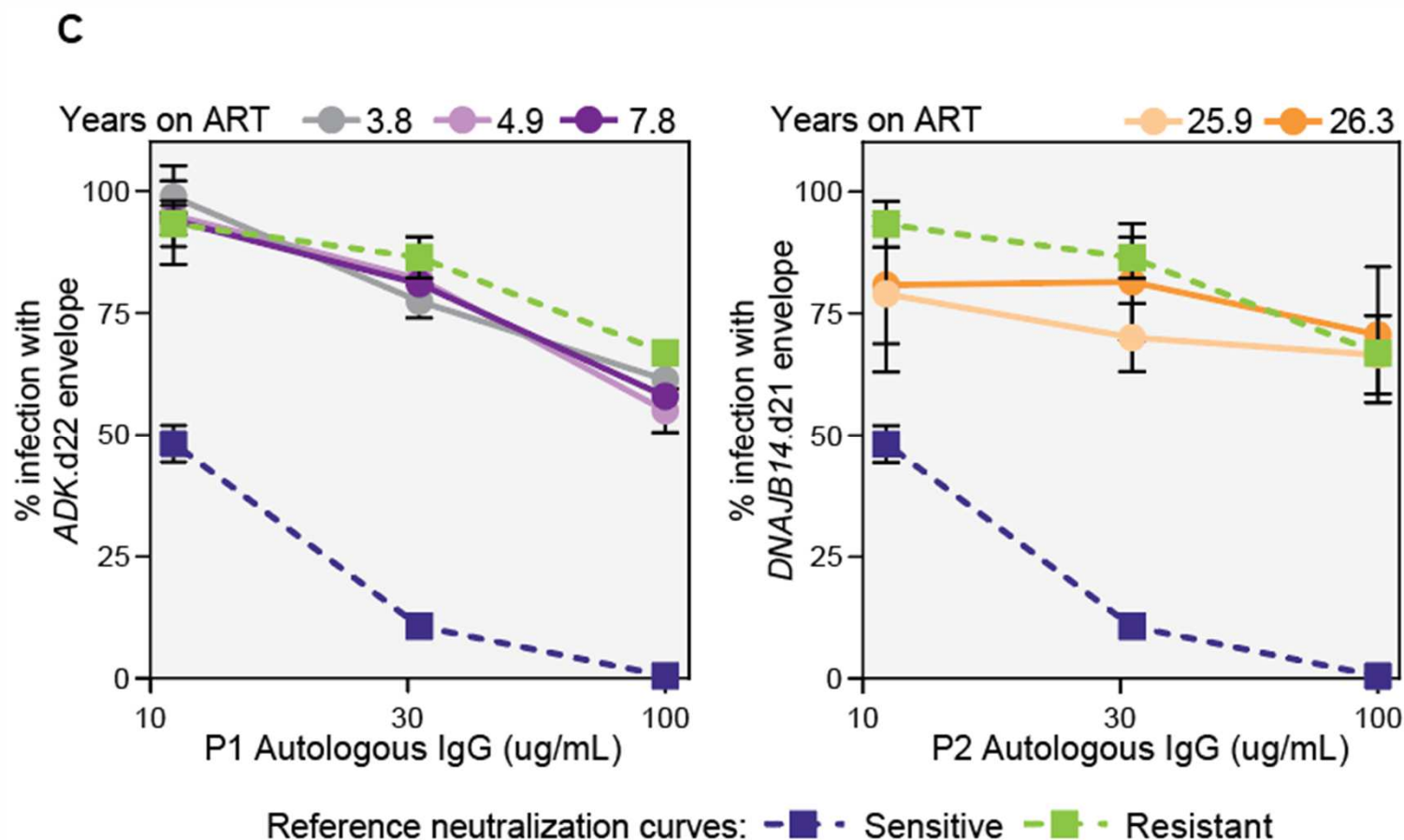


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Provirus cause of NSV may elude CTL and antibody immune pressure

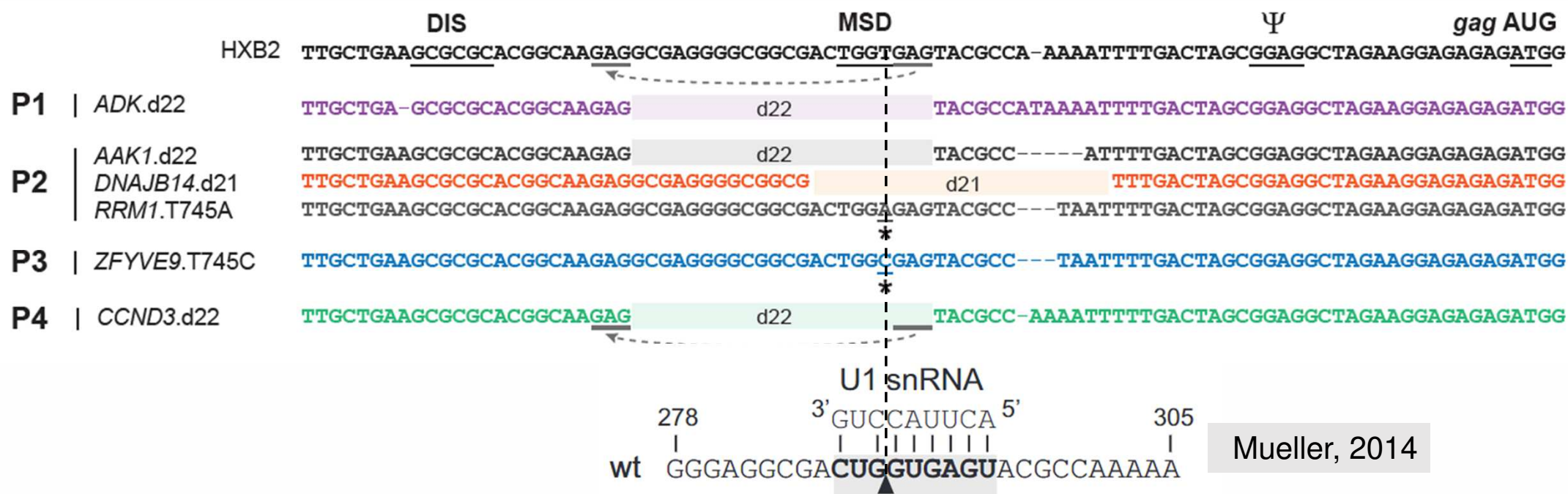


Provirus cause of NSV may elude CTL and antibody immune pressure

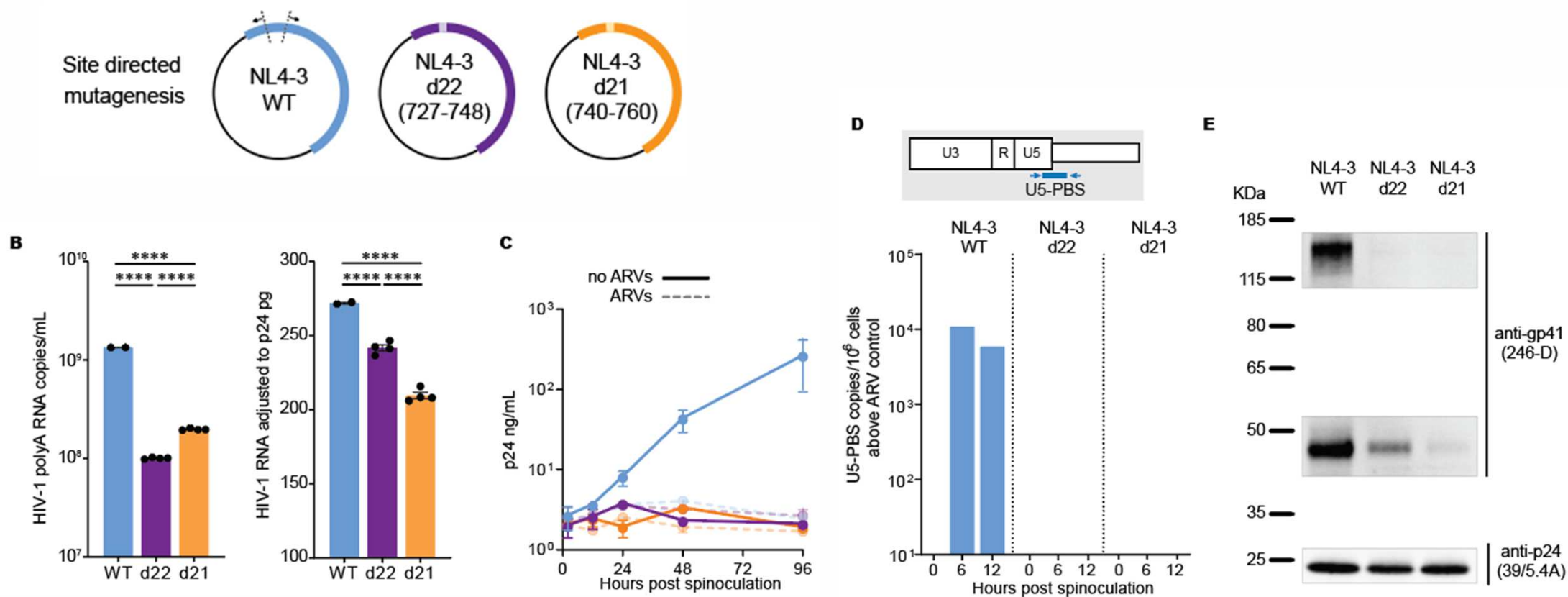


However, given the small number of virus-producing cells required to cause NSV at any given time, immune escape may not be necessary if proliferation outpaces immune clearance.

Defects in the 5' Leader involve the major splicing donor site



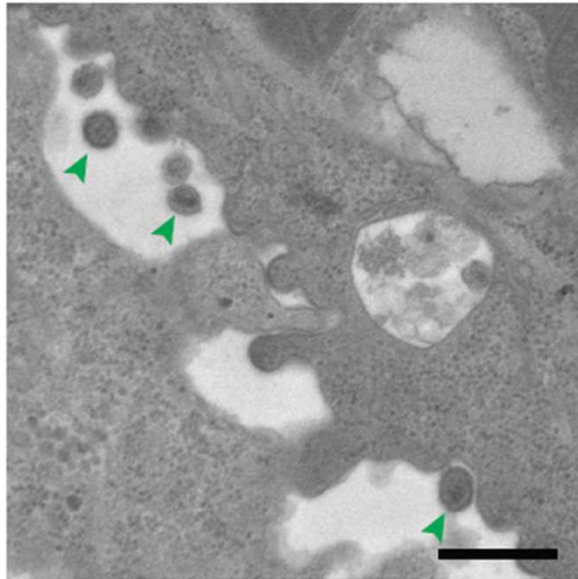
Small 5' leader deletions lead to noninfectious viral particles



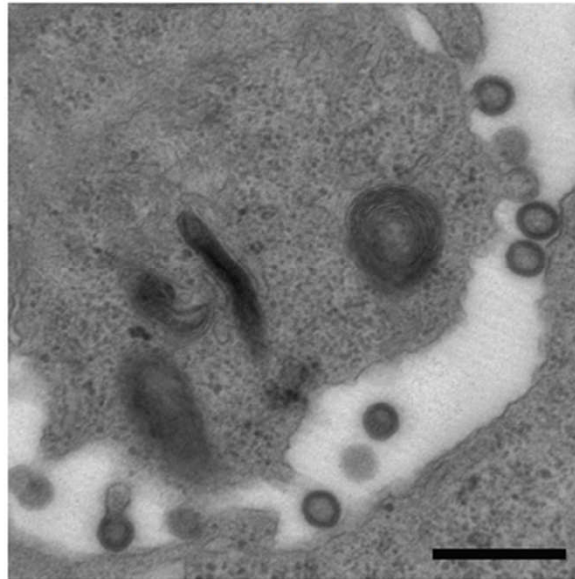
293 cells transfected with 5'L defective vector produce virions

A

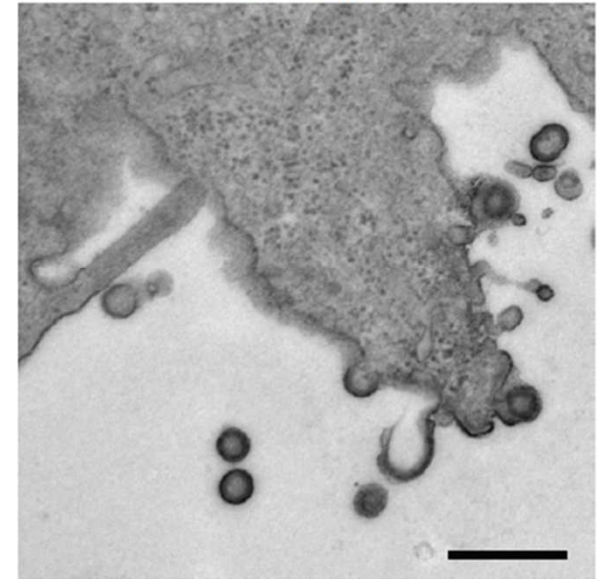
Wild type NL4-3



NL4-3 d22



NL4-3 d21



In Memoriam of Giulio Maria Corbelli

