hiv&ai
+asrh
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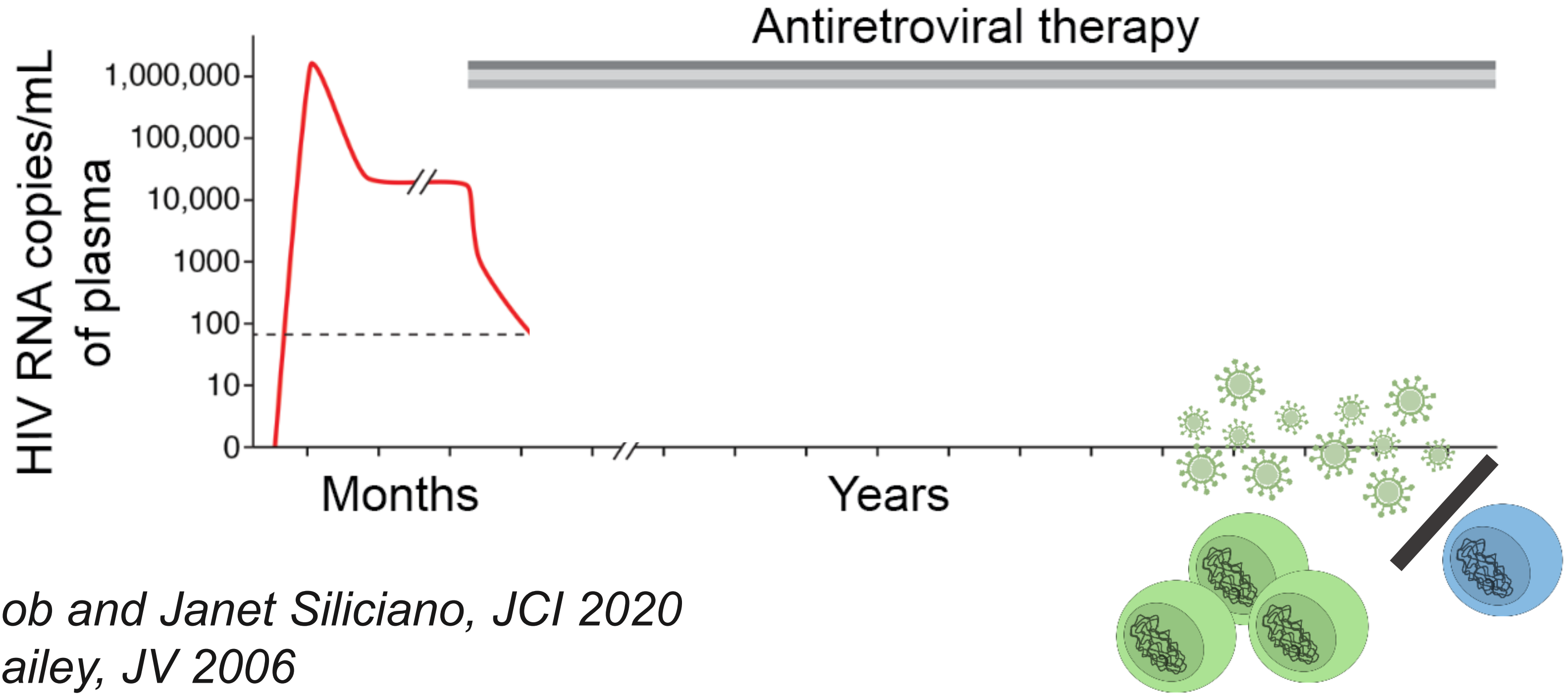
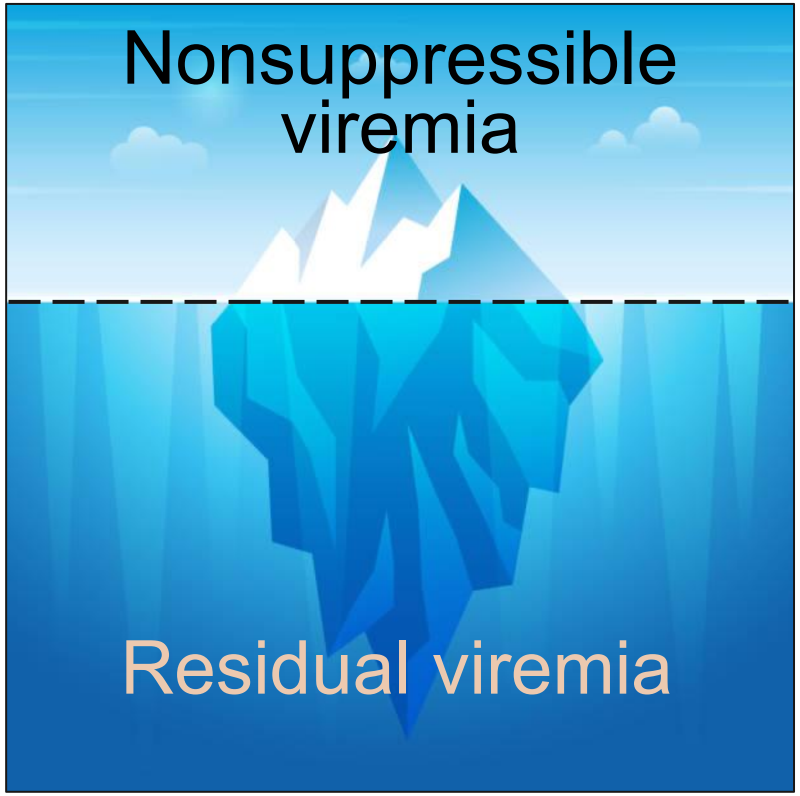
5'Leader-defective proviruses are a common source of persistent viremia despite effective ART

Francesco R. Simonetti, M.D. Ph.D.
Assistant Professor
Division of Infectious Diseases
Johns Hopkins University

I have received honoraria from Gilead to present at scientific conferences

Persistent viremia complicates HIV clinical care

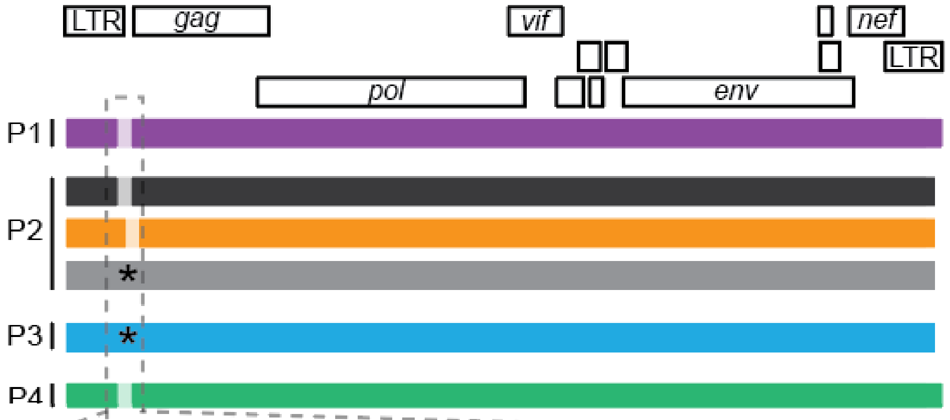


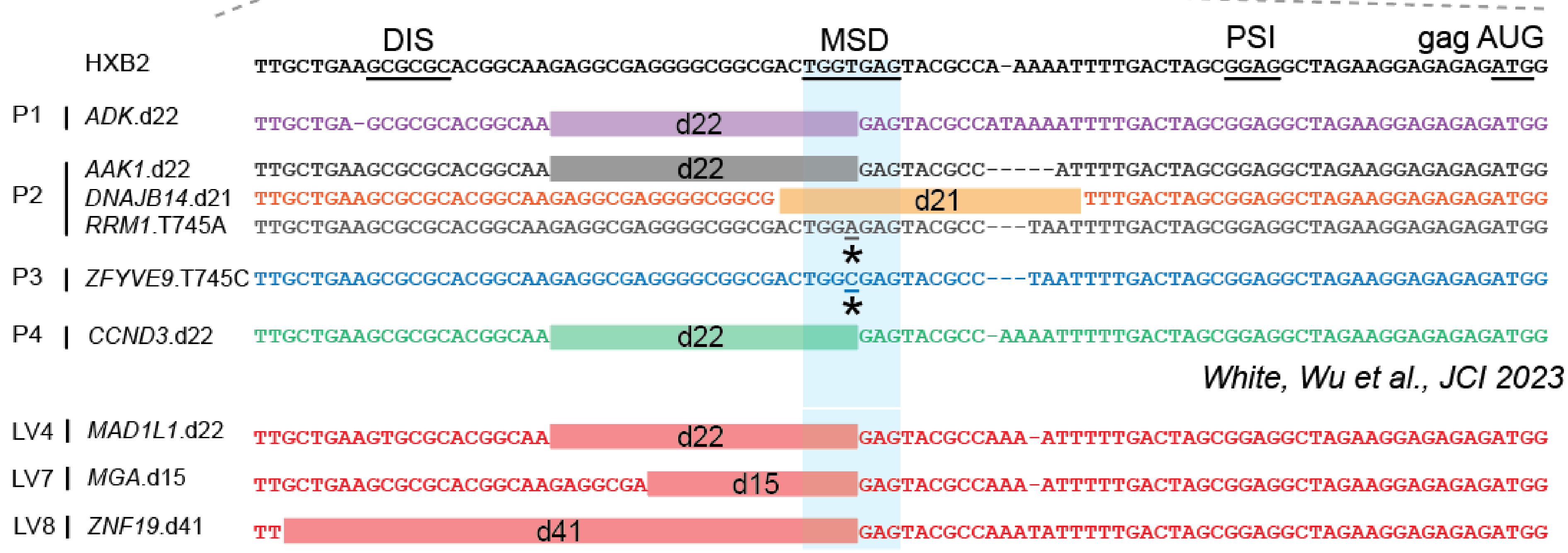


Bob and Janet Siliciano, JCI 2020
Bailey, JV 2006
Simonetti, PNAS 2016
Halvas, JCI 2020

Determining virus and host drivers of persistent viremia can improve clinical care and our understanding of HIV persistence

Proviruses with 5'Leader Defects can cause NSV





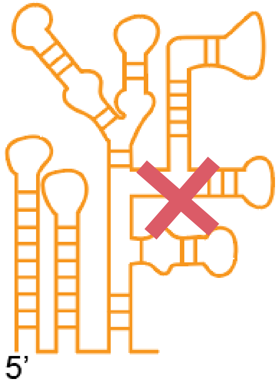
	HXB2	TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCA-AAAATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
P1	*ADK*.d22	TTGCTGA-GCGCGCACGGCAA d22 GAGTACGCCATAAAATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
P2	*AAK1*.d22	TTGCTGAAGCGCGCACGGCAA d22 GAGTACGCC-----ATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
	DNAJB14.d21	TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCG d21 TTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
	RRM1.T745A	TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGAGAGTACGCC---TAATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
P3	*ZFYVE9*.T745C	TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGCGAGTACGCC---TAATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
P4	*CCND3*.d22	TTGCTGAAGCGCGCACGGCAA d22 GAGTACGCC-AAAATTTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG

White, Wu et al., JCI 2023

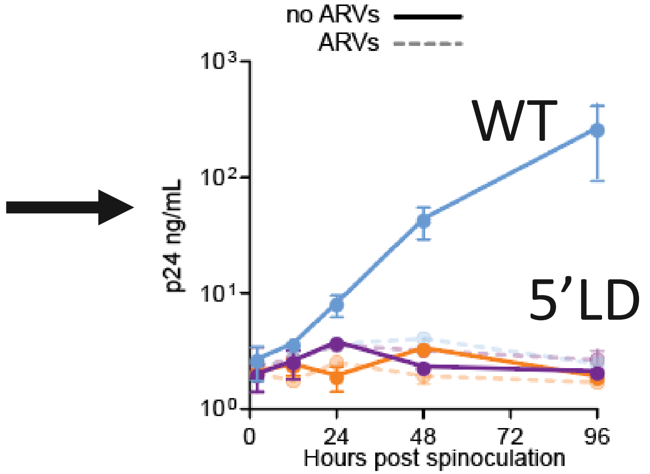
LV4	*MAD1L1*.d22	TTGCTGAAGTGCGCACGGCAA d22 GAGTACGCCAAA-ATTTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
LV7	*MGA*.d15	TTGCTGAAGCGCGCACGGCAAGAGGCGA d15 GAGTACGCCAAA-ATTTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG
LV8	*ZNF19*.d41	TT d41 GAGTACGCCAAATATTTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGG

Mohammadi et al., Nature Med 2023

HIV-1 5'-Leader

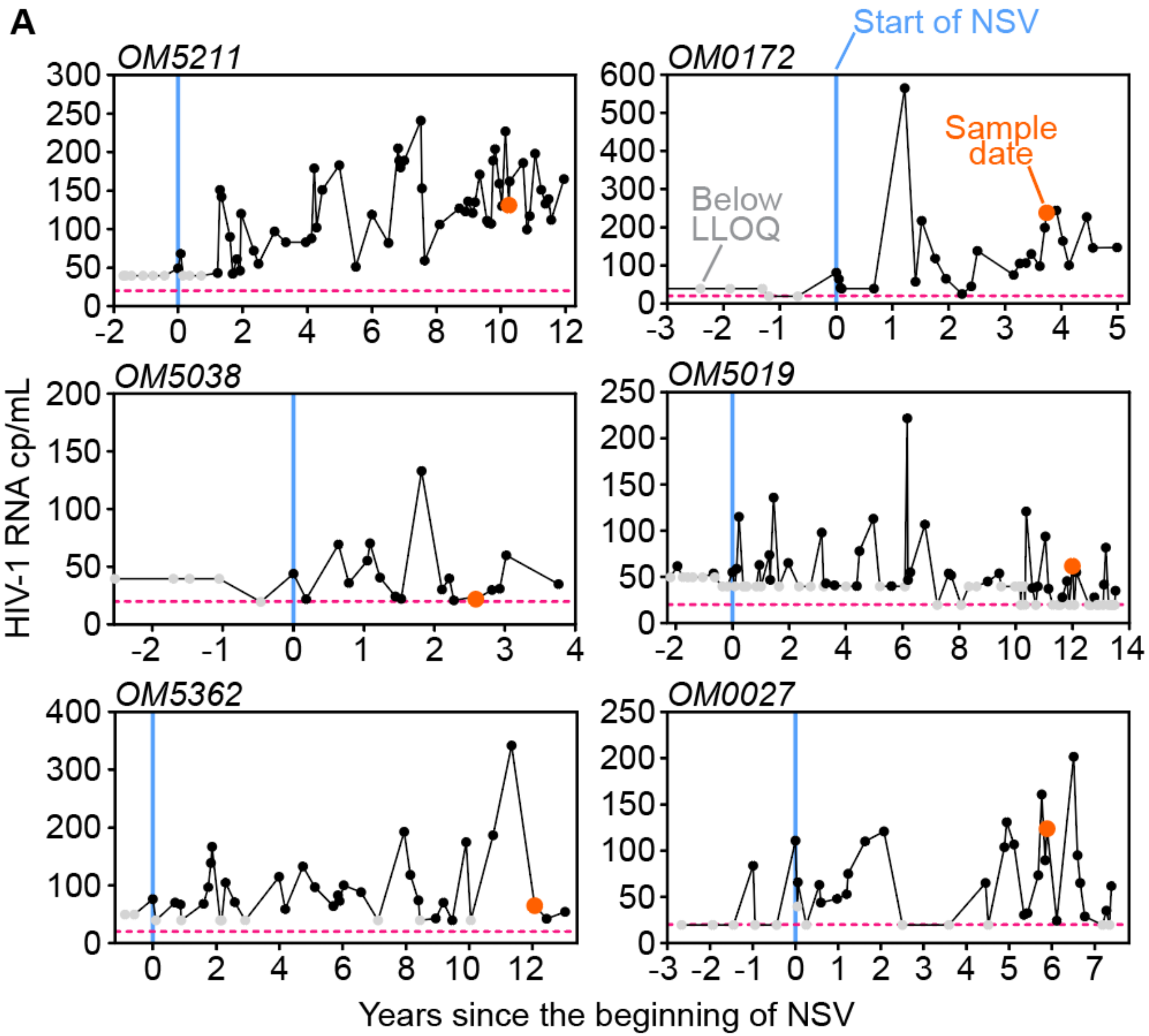


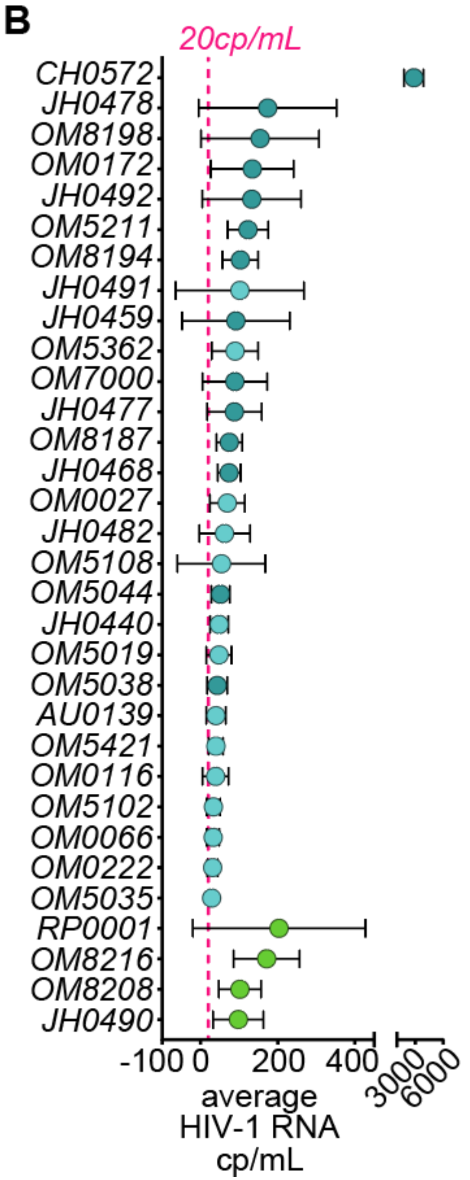
Non-infectious



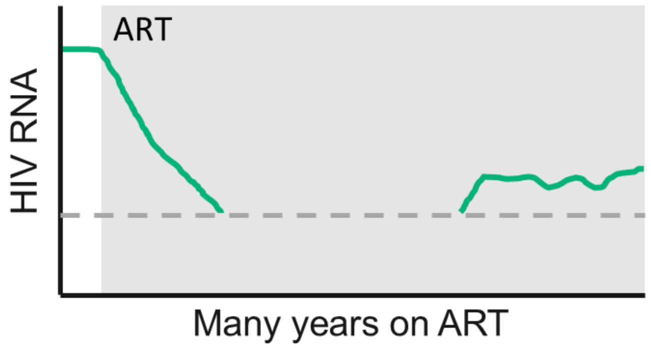
To which extent do 5’L defects contribute to NSV?

We studied **32 people on ART** with persistent (or intermittent) viremia >20 cp/mL

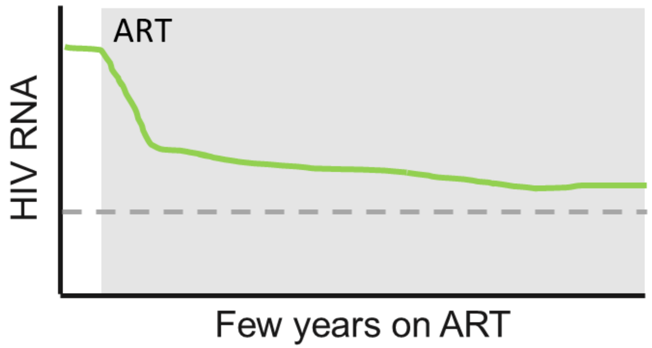




NSV type
● Persistent
● Intermittent
● Short-term ART



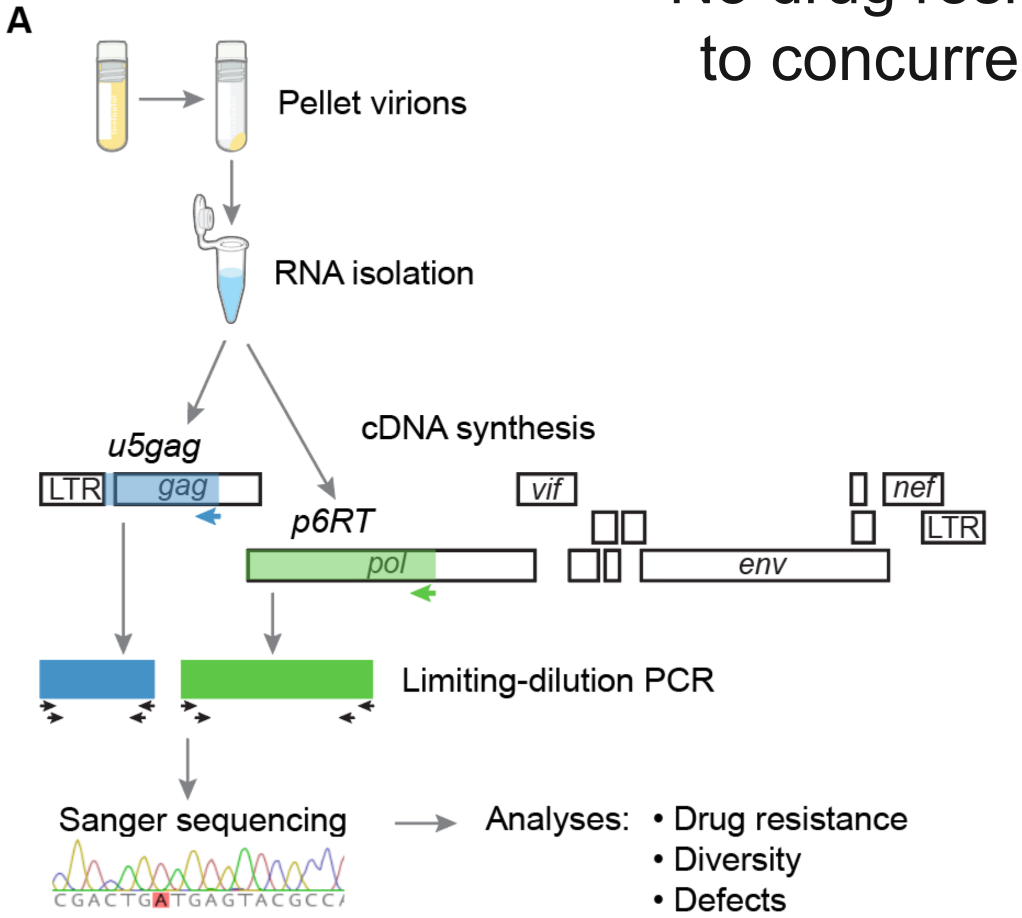
Many years on ART



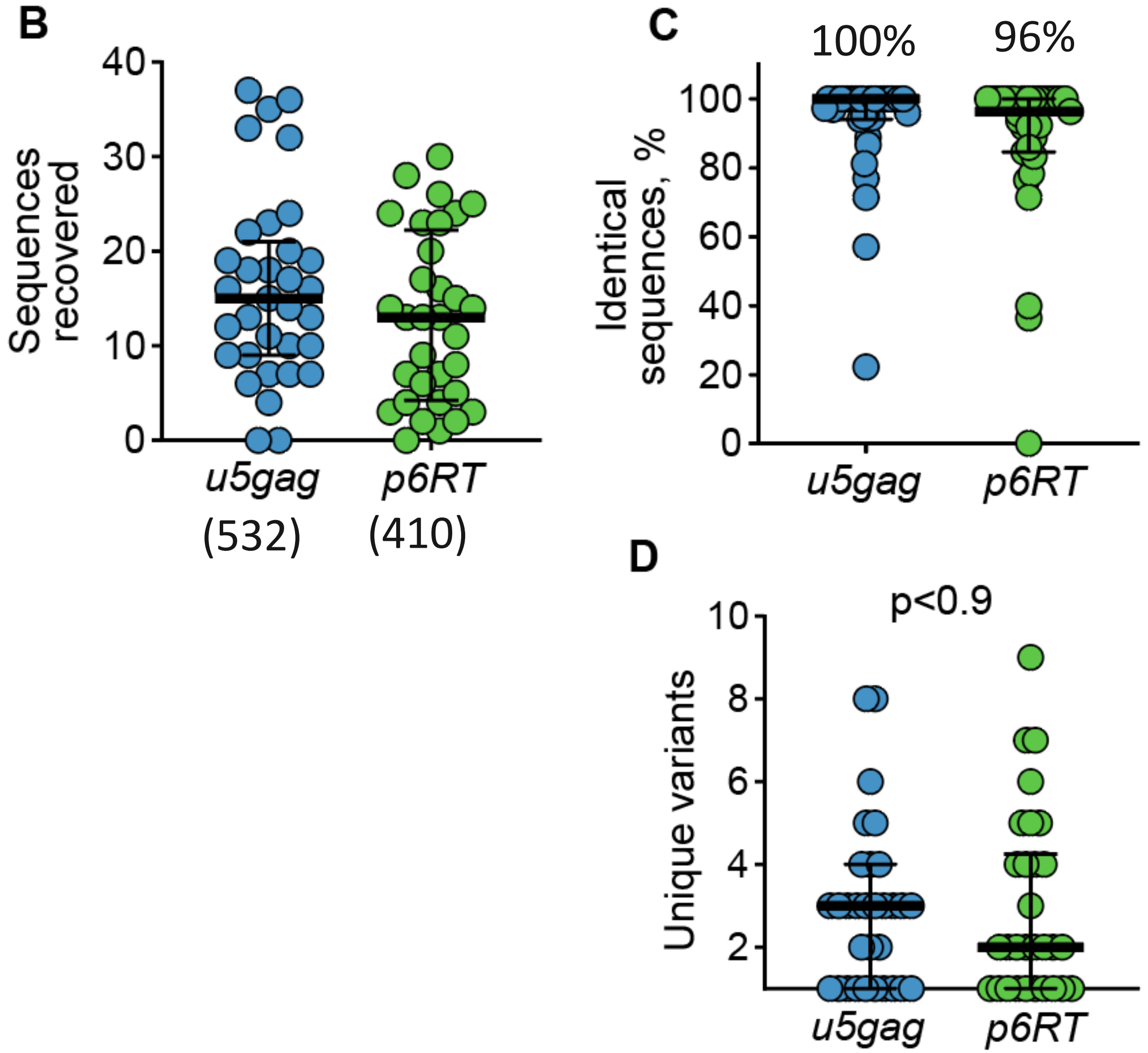
Few years on ART

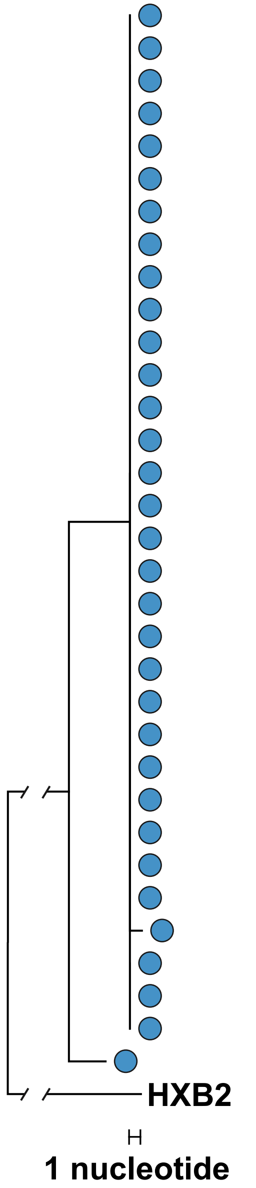
HIV-1 variants contributing to NSV are highly clonal

No drug resistance mutations detected
to concurrent PIs, NRTIs, or NNRTIs

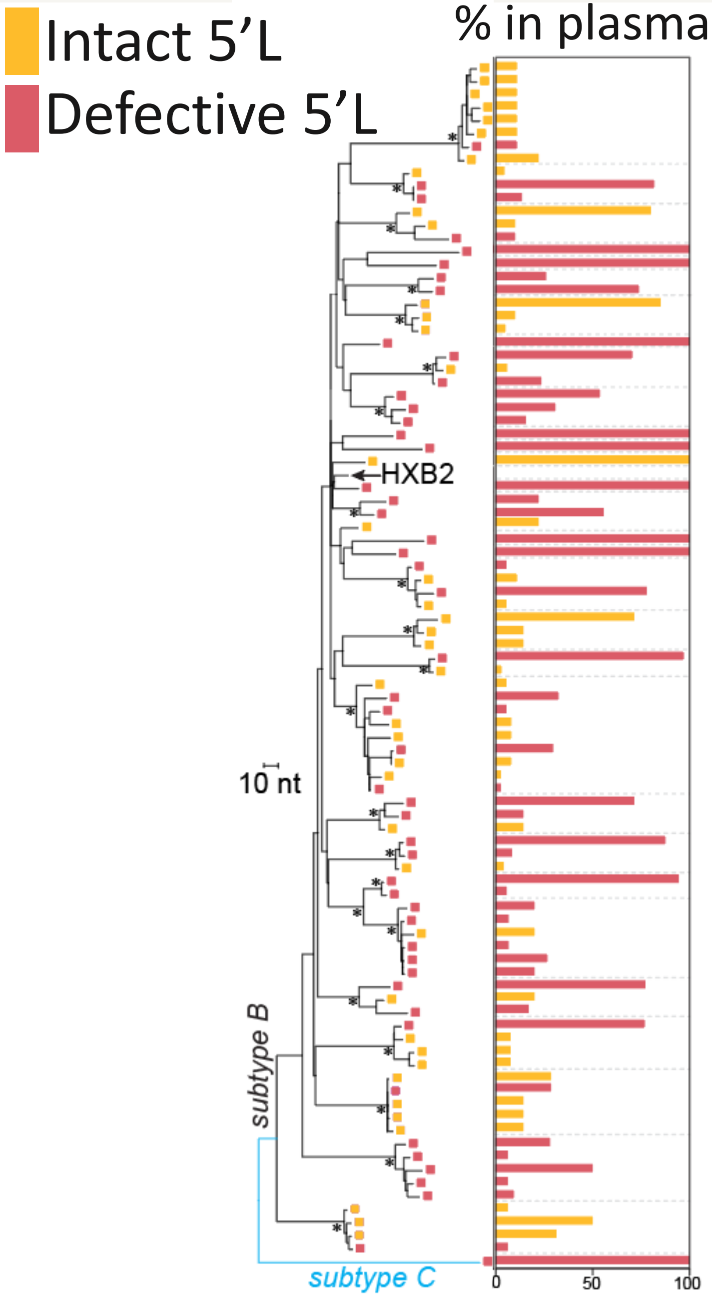


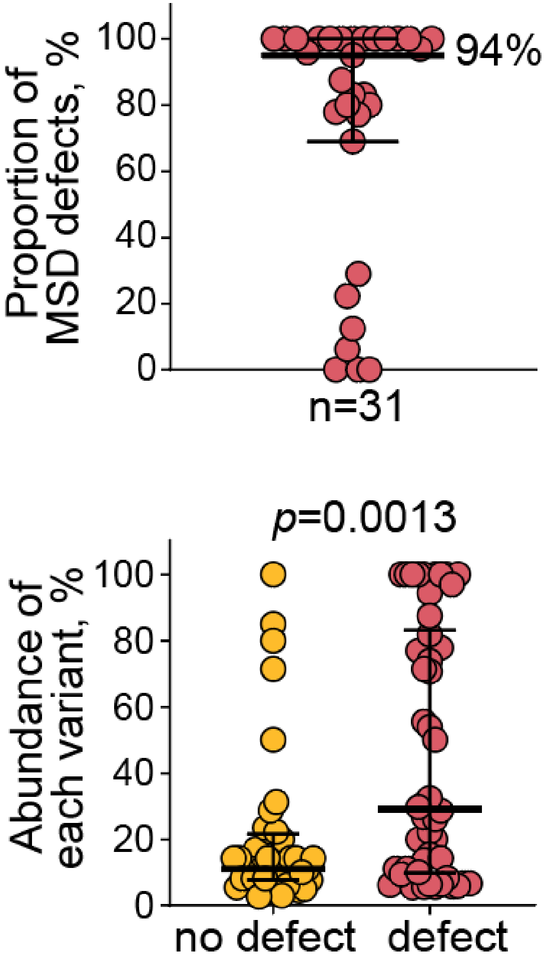
31/32
participants

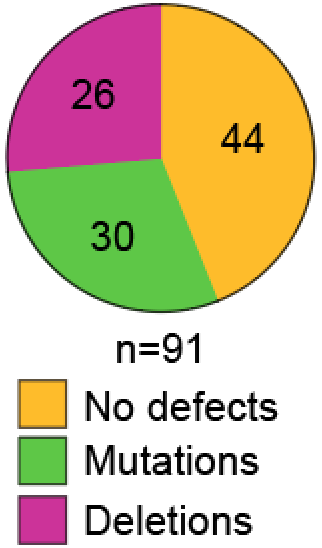


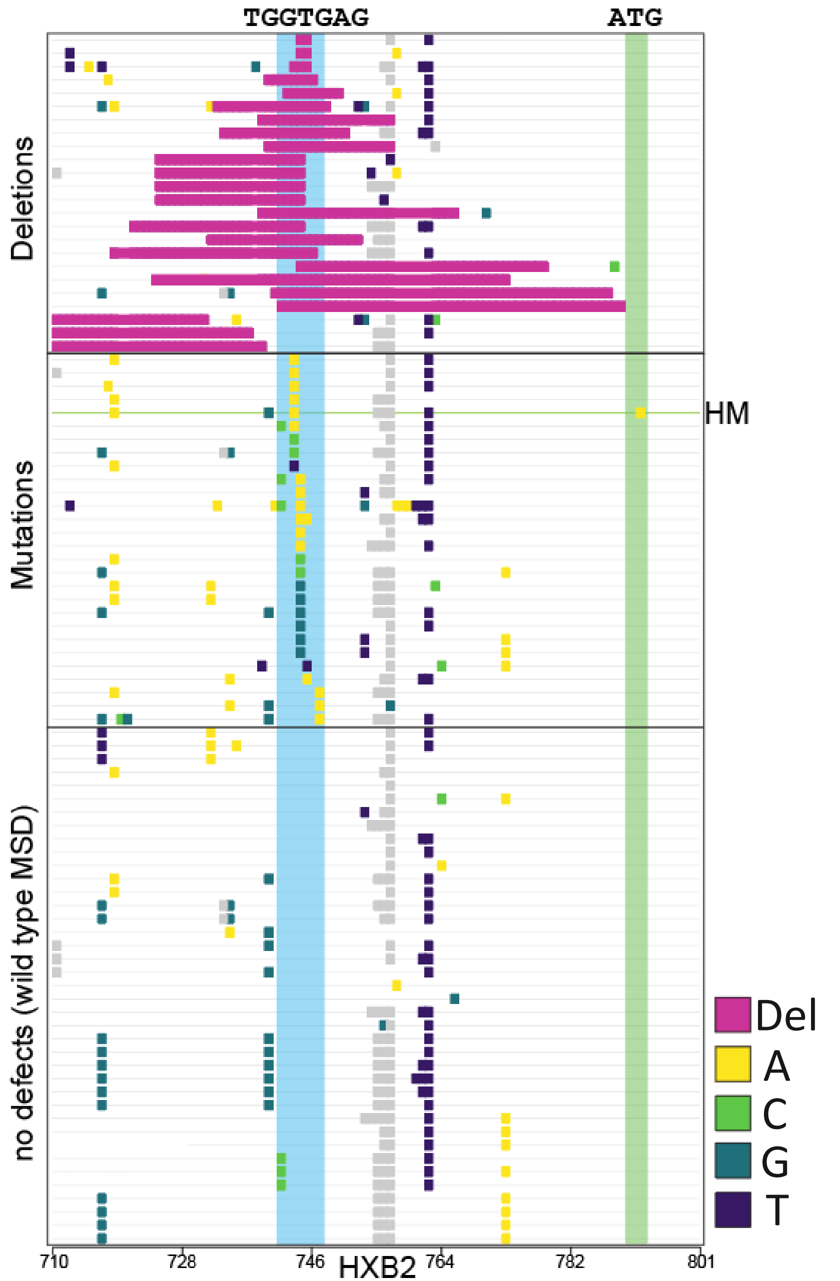


>90% of virus in plasma has 5'Leader defects



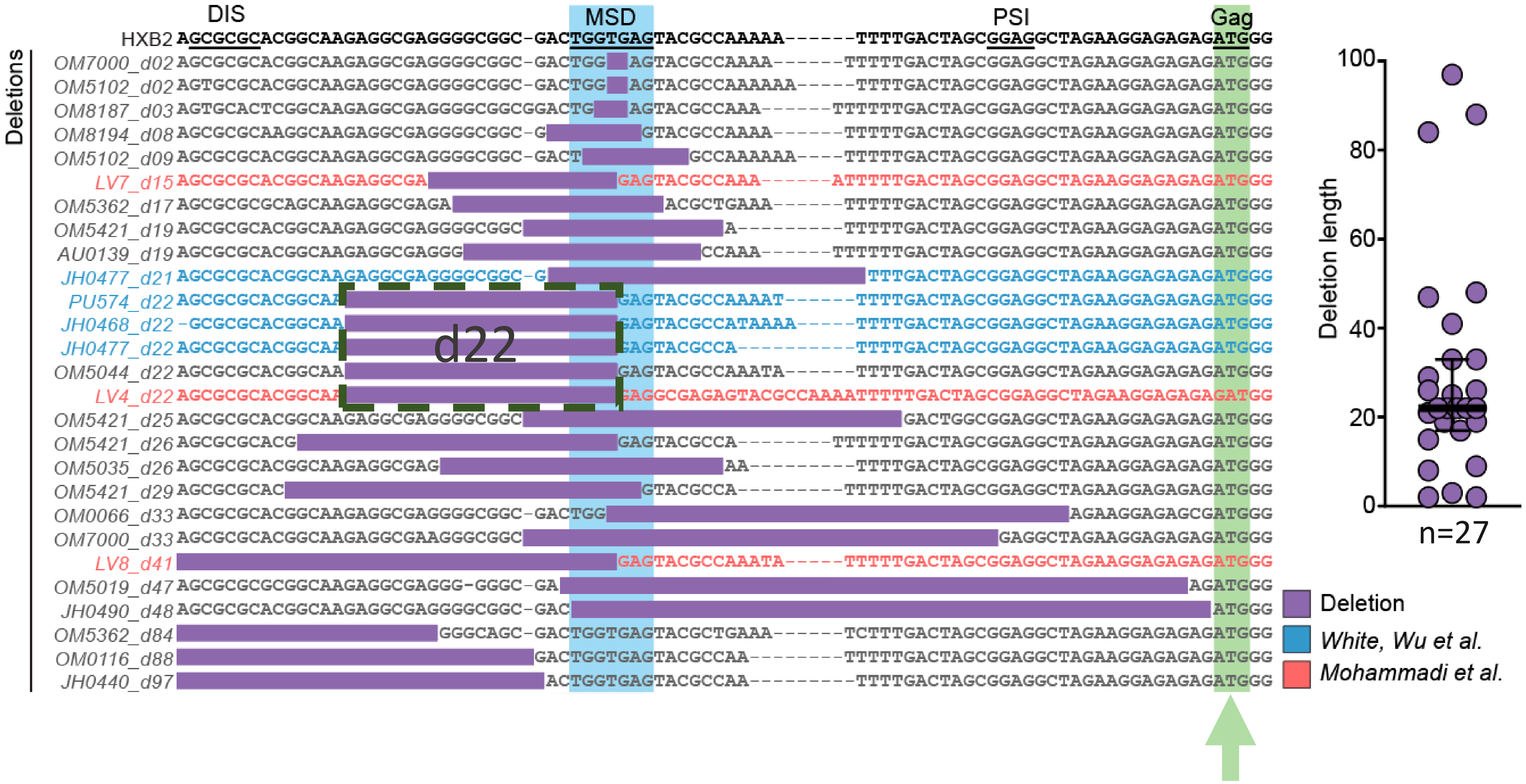




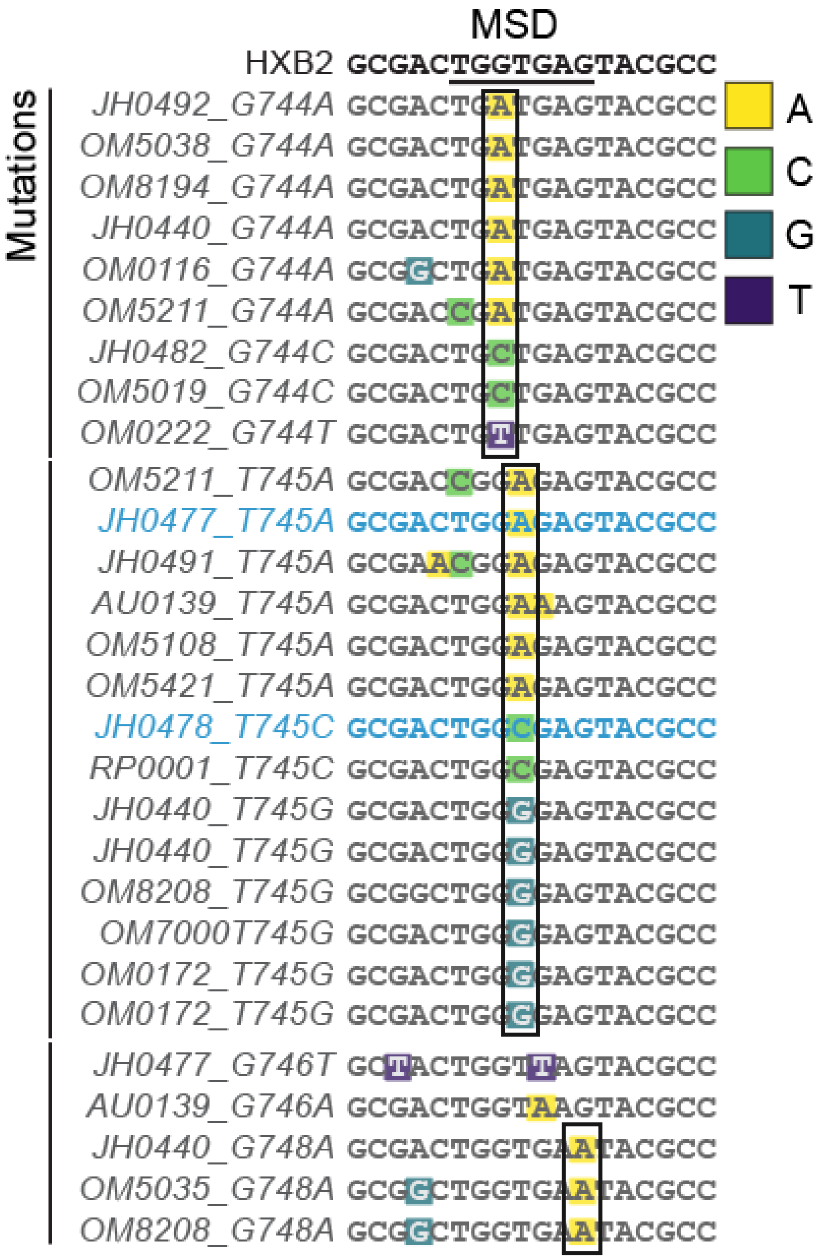


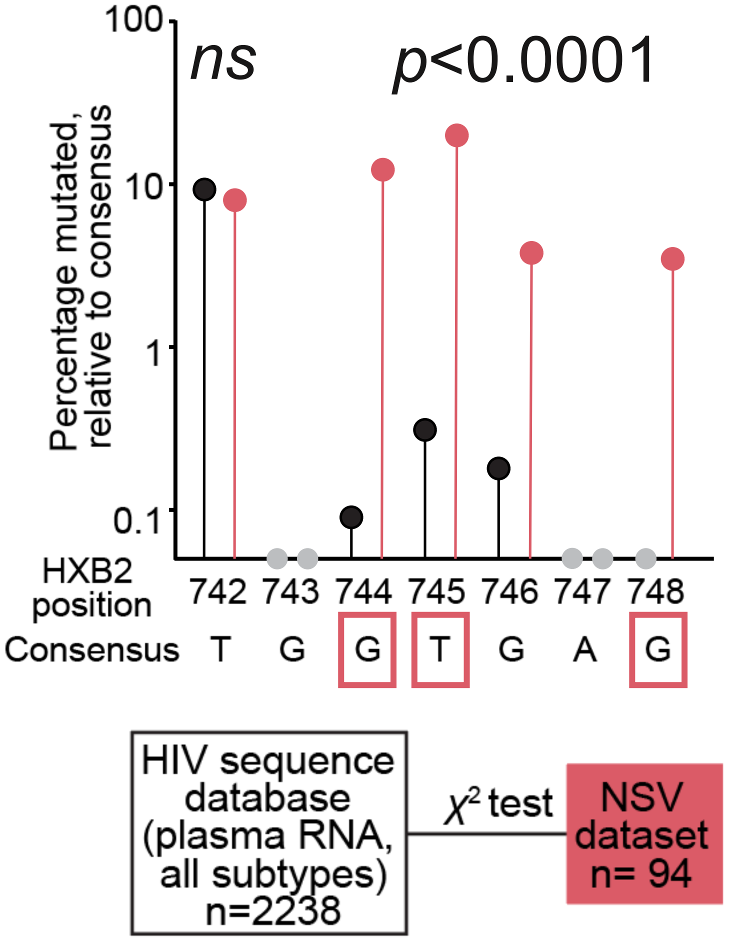
Box, et al., in preparation

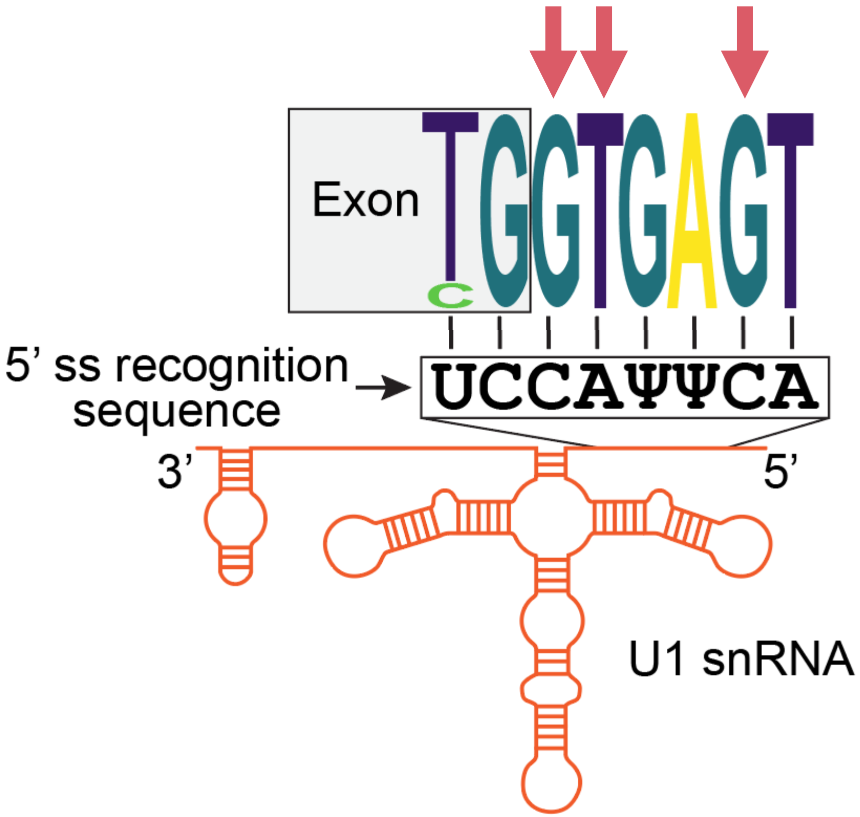
Deletions involve the Major Splicing Donor



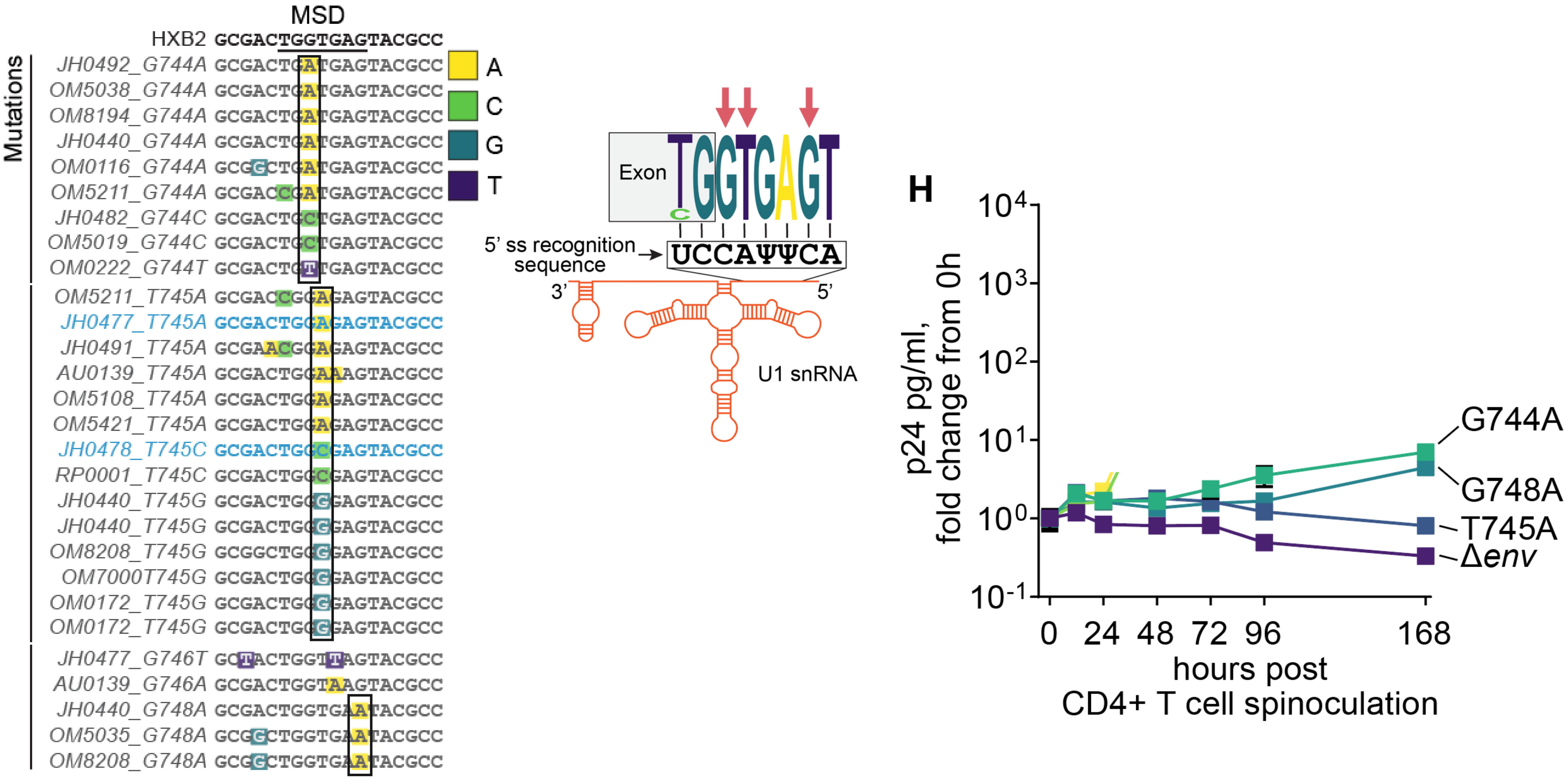
Specific MSD mutations are enriched in NSV



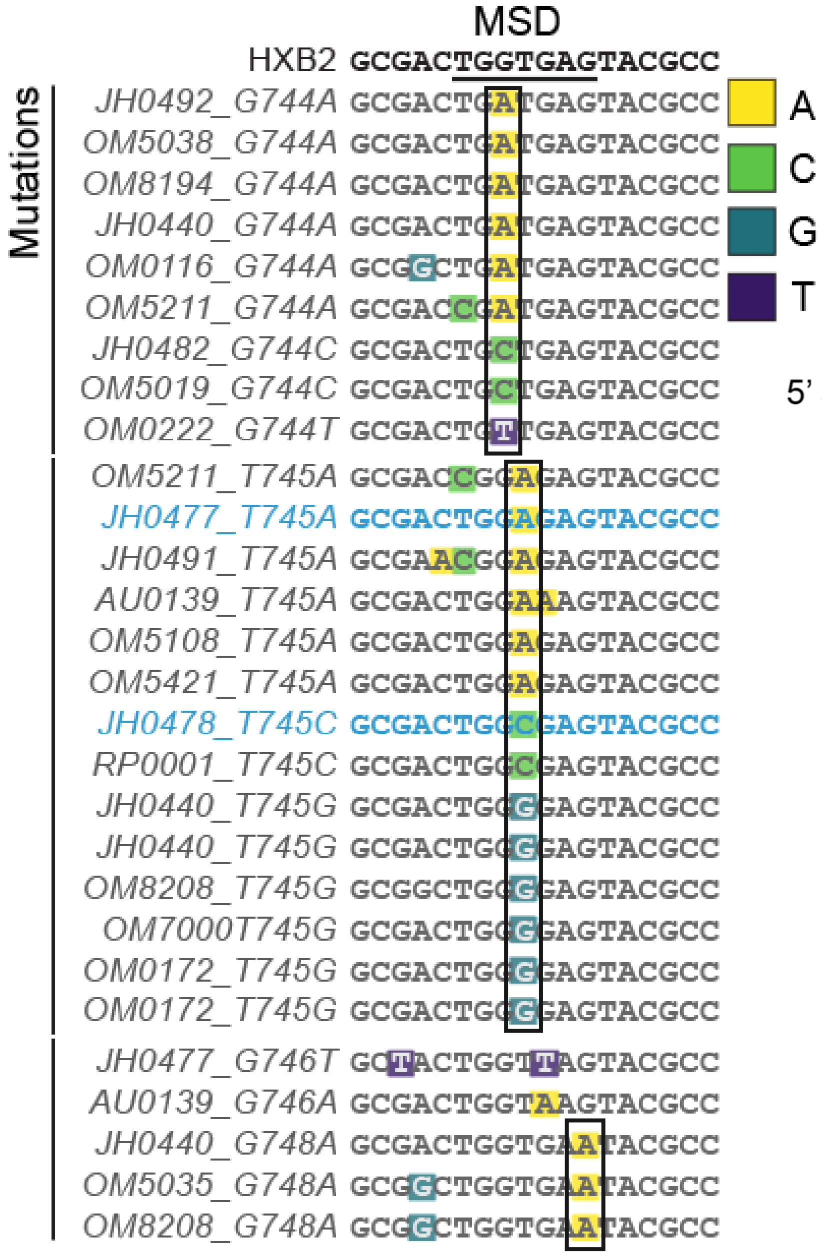


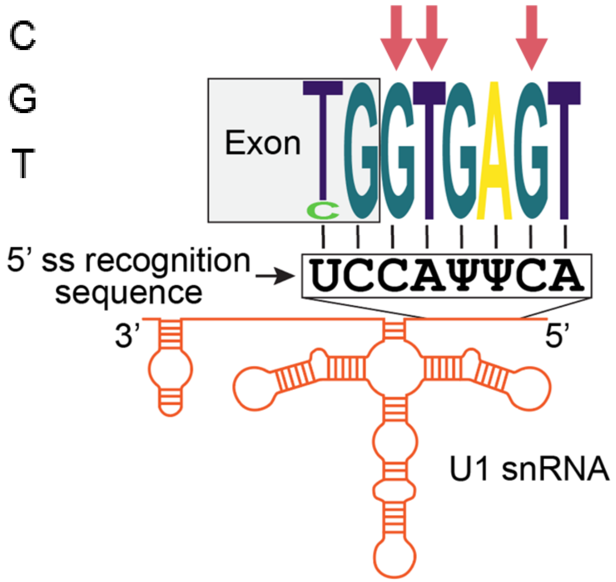


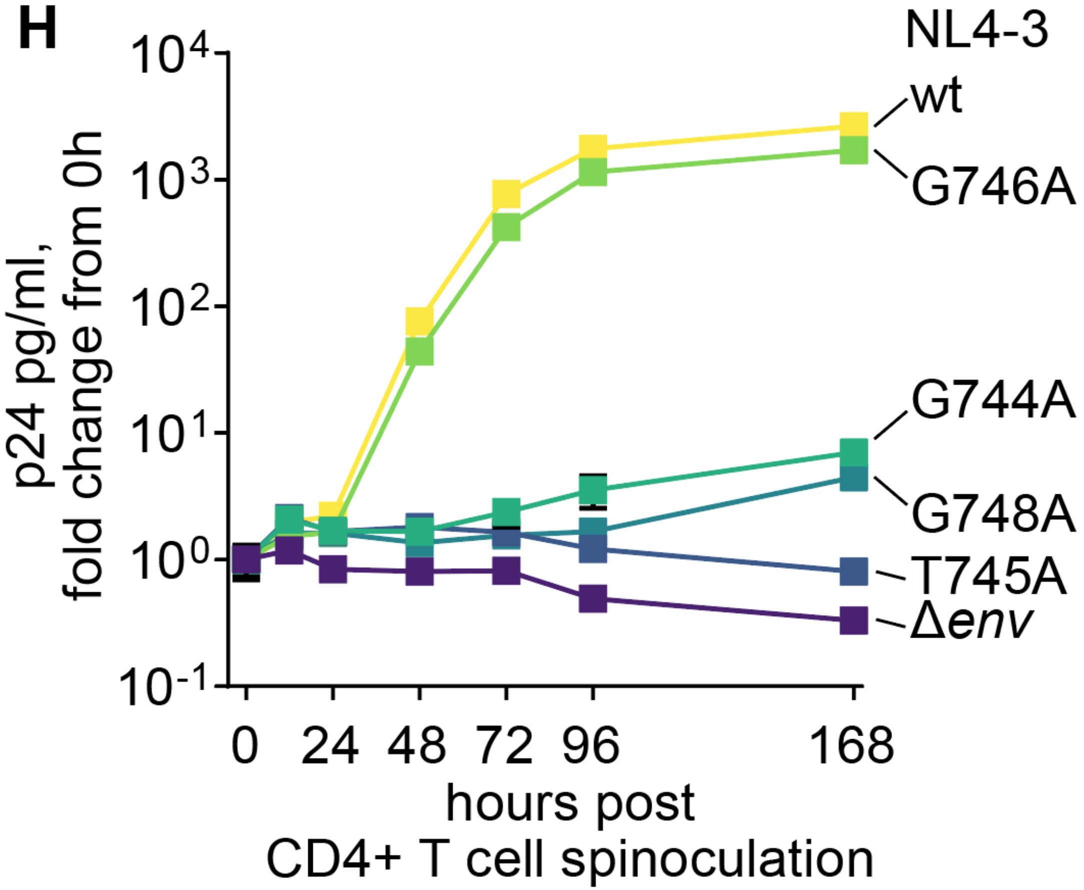
Mutations affect RNA binding to splicing machinery



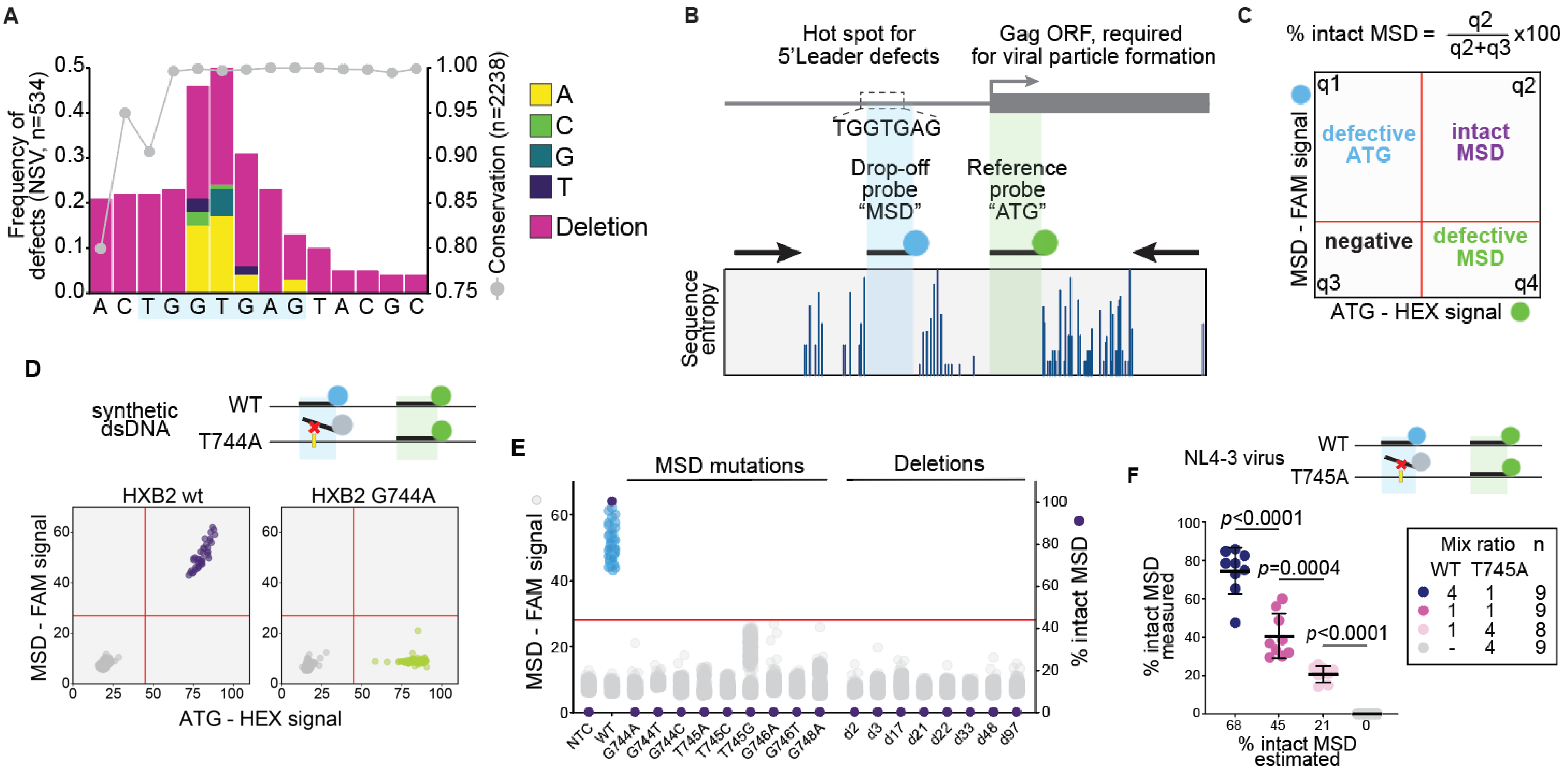
Mutations affect RNA binding to splicing machinery



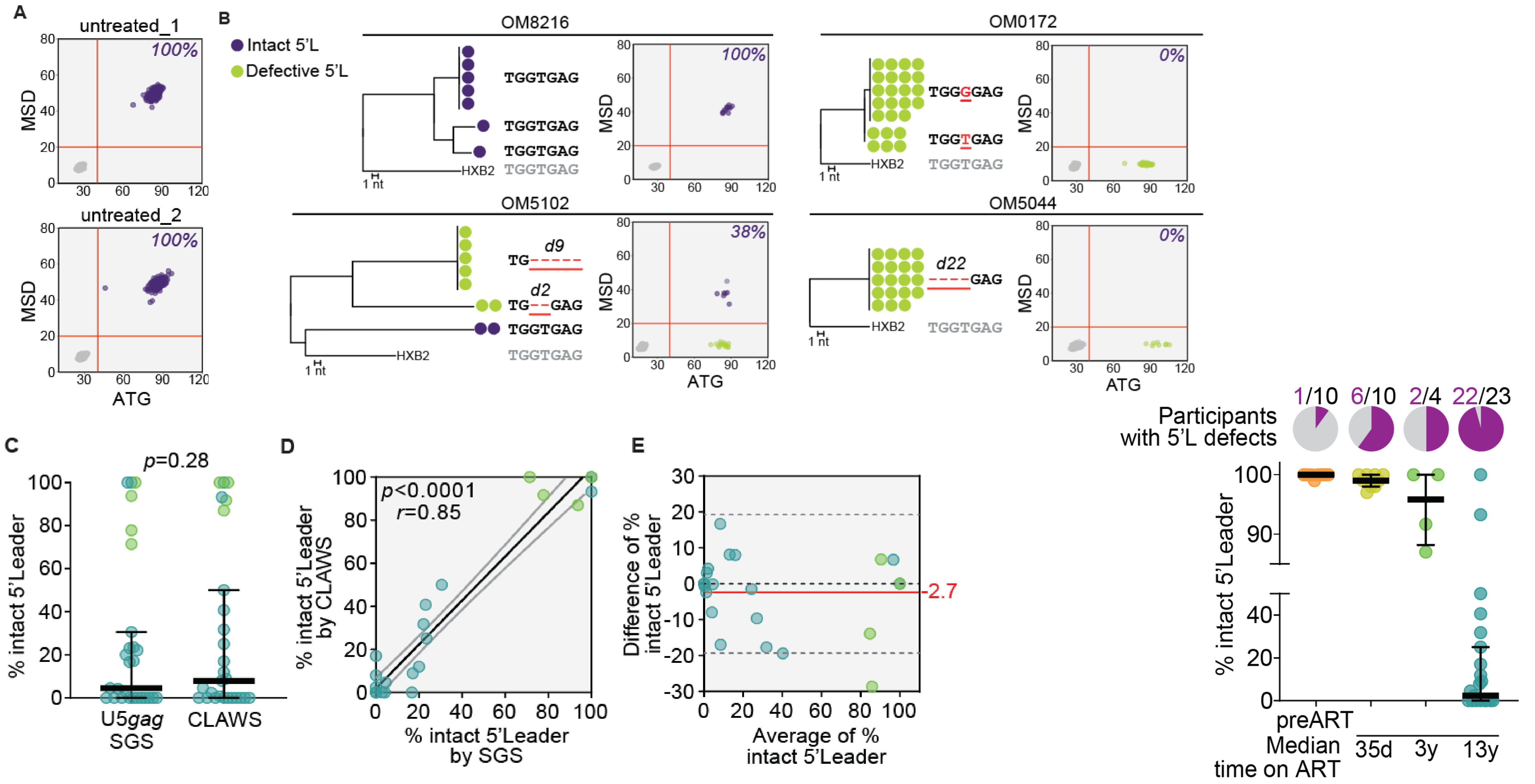




Capturing 5'**L** **A**nomalies **W**ithout **S**equencing



CLAWS strongly correlates with 5’L sequencing



Conclusions

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

Proviruses with **small defects in the 5’Leader region** are a common cause detectable viremia, complicating ART management.

These defects result in **non-infectious virus**, due to inefficient HIV splicing

→ **differential selection pressure** compared to intact proviruses?

→These results allow a ***better clinical interpretation of detectable viral load***

→Sequencing data informed the design of a ***simpler, targeted assay*** that can distinguish intact from defective viral RNA

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Study Participants

WUSTL
Liang Shan
Priya Pal
Marilia Pinzone

W.W. SMITH
CHARITABLE TRUST

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