

The Role of Early T Cell Responses in Subjects with Acute HIV-1 Infection

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CHAVI 001: T cell Study

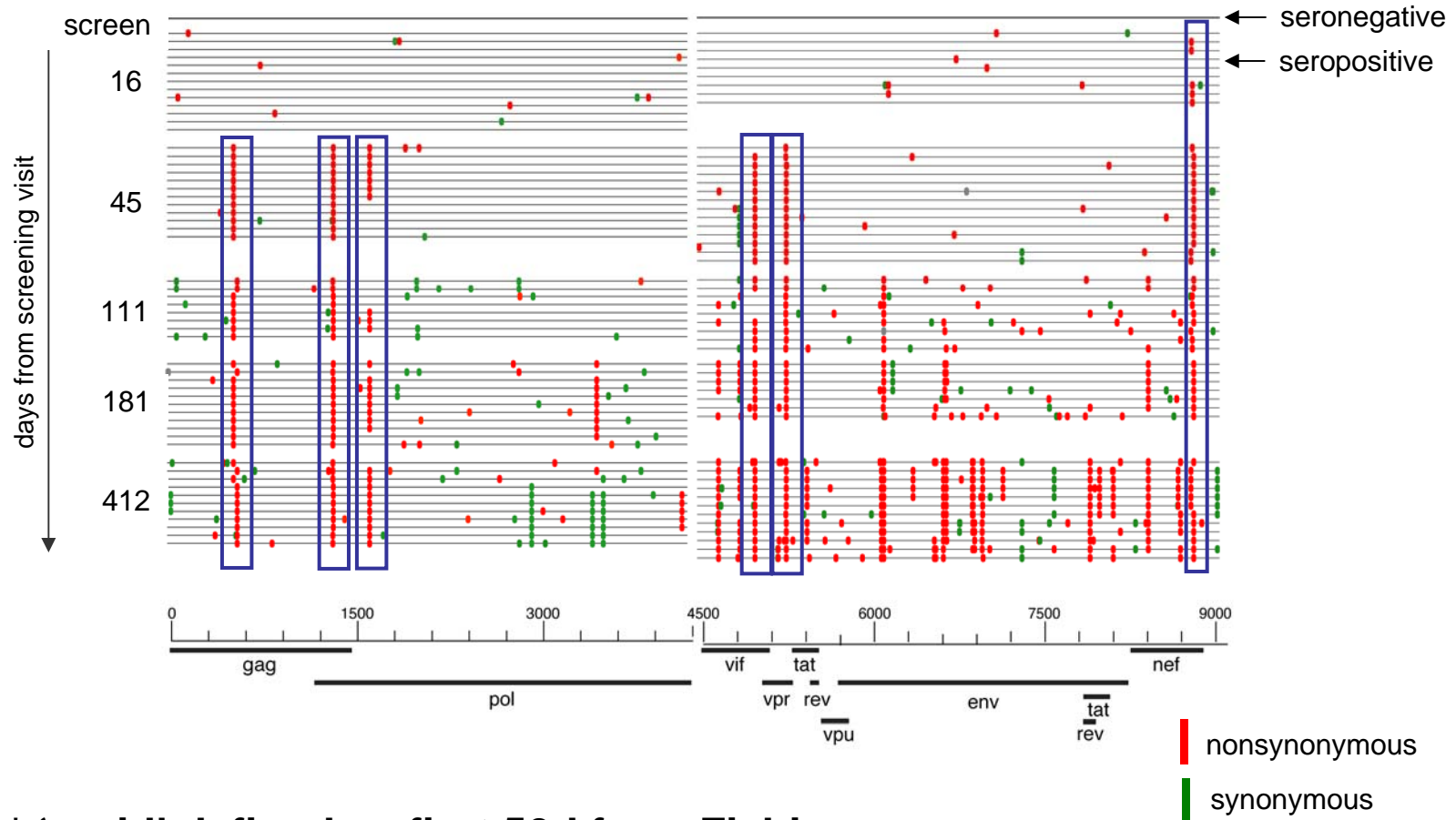
- Nature of T cell responses during acute HIV-1 infection
 - Control/escape of viral replication \Rightarrow viral set point
- Unique Features of CHAVI 001
 - Very early acute samples - PCR positive & antibody negative
 - Mapping using autologous viral sequences
 - Extensive phenotyping of HIV-1 specific T cell responses
 - \Rightarrow Evolution of T cell responses, T cell kinetics
 - Viral Evolution
 - Mathematical Modelling

T cells during HIV-1 infection

- HIV-1-specific CD8 T cells have been first detected around and just prior to the peak of viraemia in acute HIV-1 infection (Borrow 1994, Koup 1994, Wilson 2000).
- Increase in primary CD8 T cells is coincident with initial decline in viraemia suggesting role in acute viral control.
- some HLA alleles (eg B*5701) associated with lower viral setpoint and delay to progression to AIDS (Fellay 2007, Carrington 2003).
- CD8+ depletion studies in macaques showed a loss of control against SIV.

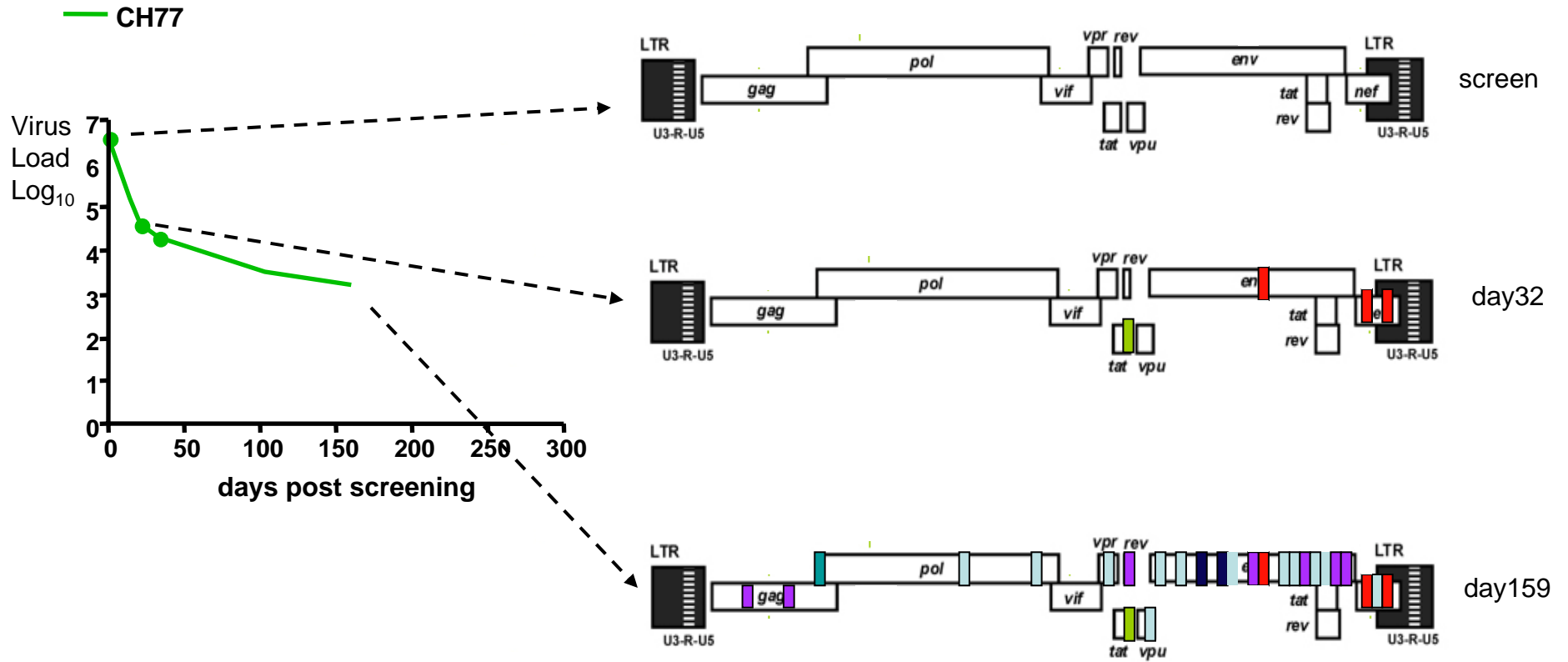
Detection of 'rapid' virus escape 16 days post-screening around seroconversion

Patient CH40



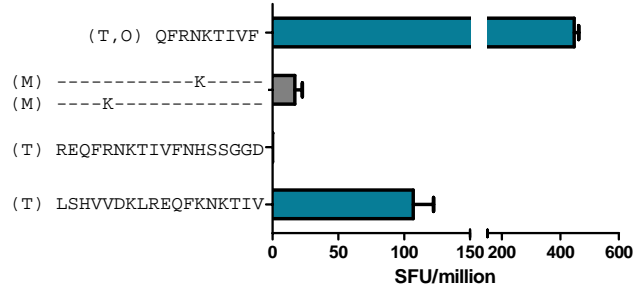
*** 'rapid' defined as first 50d from Fiebig I-II as viral load is still declining**

Selection of mutations in HIV during the first 180 days



CH77 - 3 Full T cell Escapes Within 32 days

ENV(350-368):



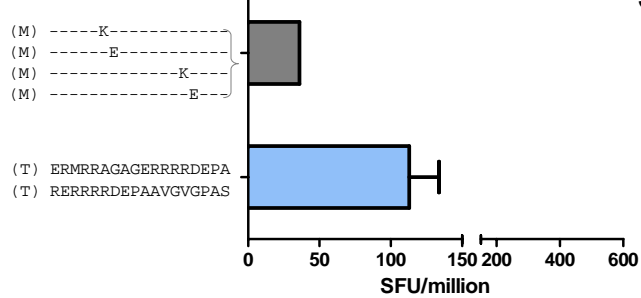
0 TRANSMITTED SEQ

SHVVDKLRQFRNKTIIV NH RERRRRDEPAAVGVGPAS KAALDLSHF LKEK

14

CH77_WGA_B3K.....
CH77_WGA_C7K.....
CH77_WGA_C9K.....
CH77_WGA_C4K.....
CH77_WGA_D5	...G.....K.....
CH77_WGA_C3K.....

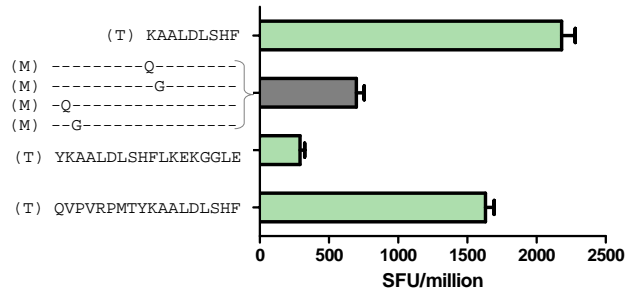
NEF(17-34):



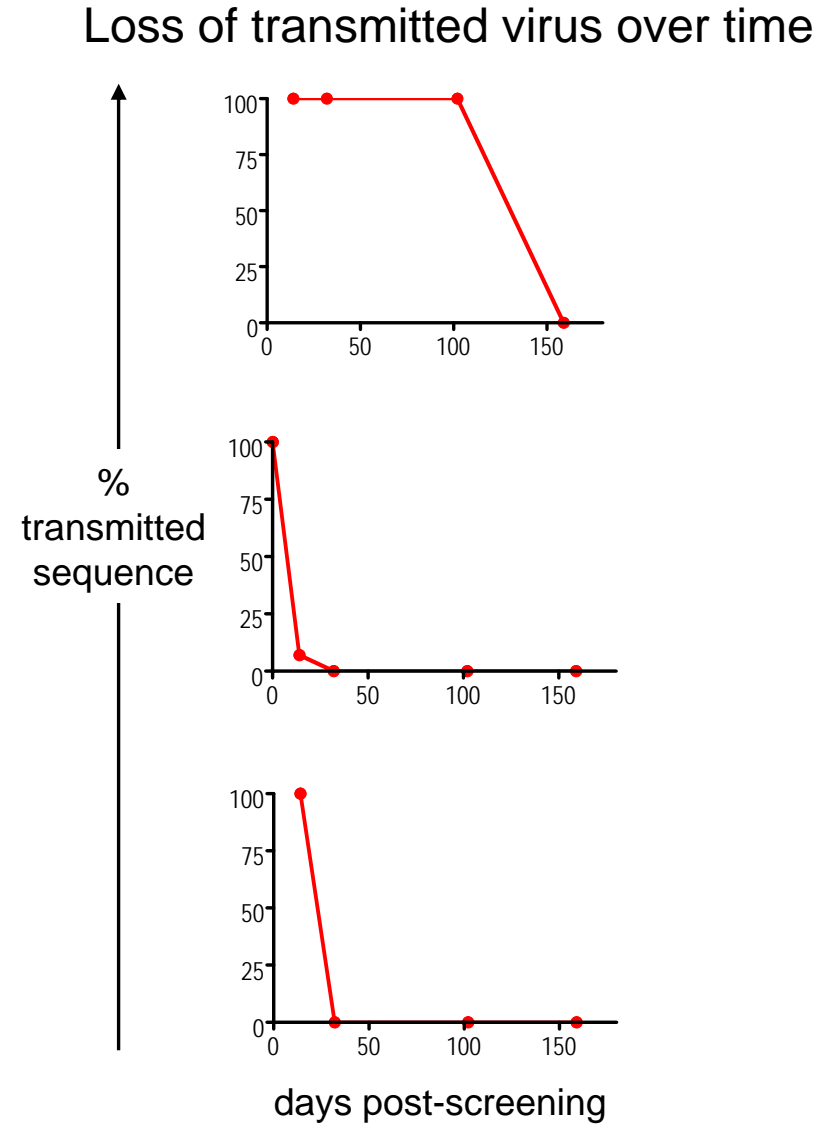
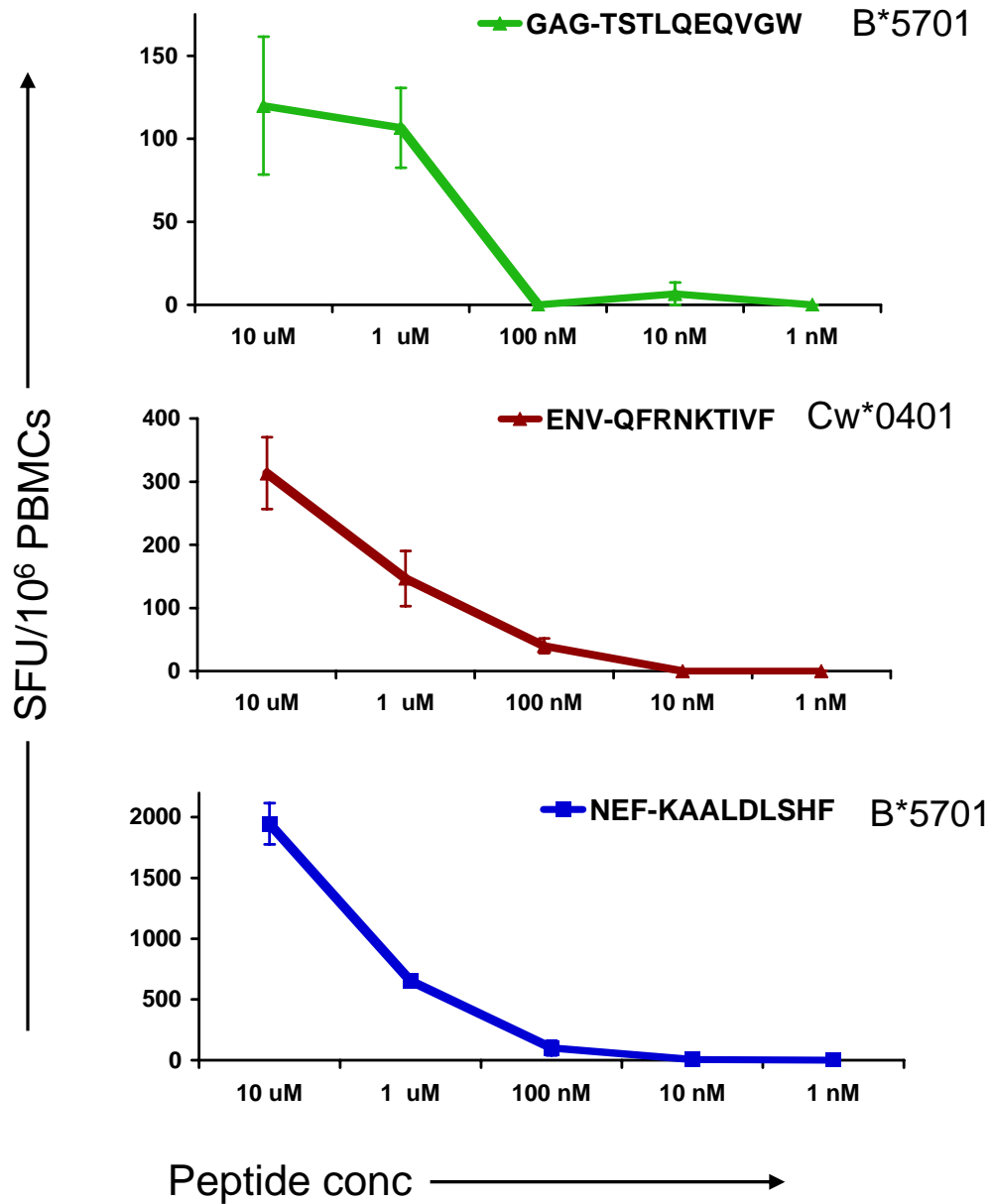
32

CH77_WK03_3_B1K.....	...G.....	Q.....
CH77_WK03_3_D1K.....S.....I.....
CH77_WK03_3_D2K.....E.....	Q.....
CH77_WK03_3_D3K.....K.....	Q.....
CH77_WK03_3_TB1K.....K.....	Q.....
CH77_WK03_3_TB2K.....E.....	T.....
CH77_WK03_3_TB4K.....S.....	...H.....
CH77_WK03_3_TB5K.....N.....	Q.....
CH77_WK03_3_TB6K.....	..GA.ERR..	Q.....
CH77_WK03_3_TB7K.....K.....	Q.....
CH77_WK03_3_TB8K.....E.....	T.....
CH77_WK03_3_TC1K.....N.....	Q.....

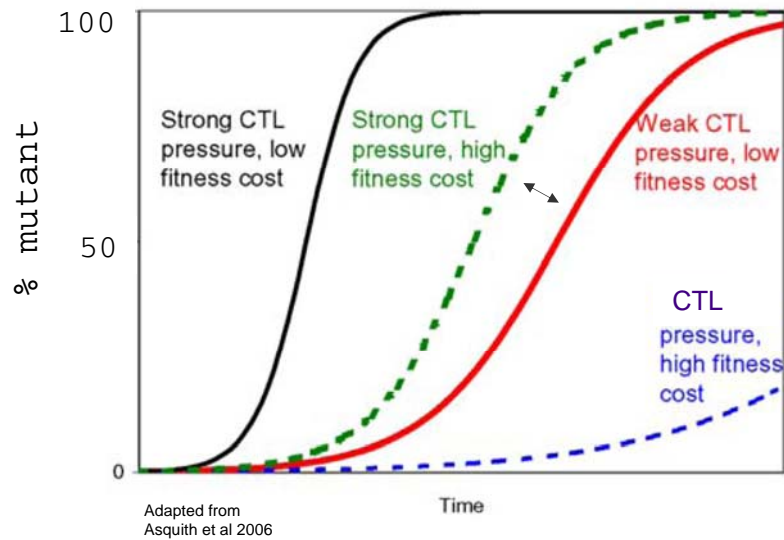
NEF(73-90):



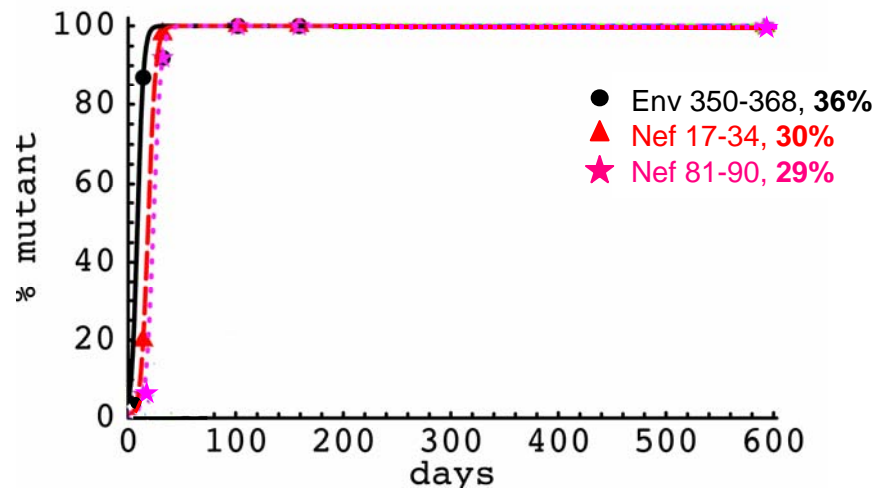
Peptide avidity in CH77



First T cells contribute to decrease in acute viremia



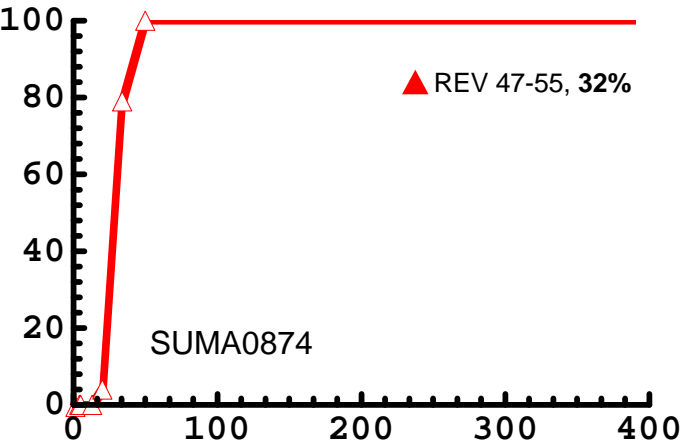
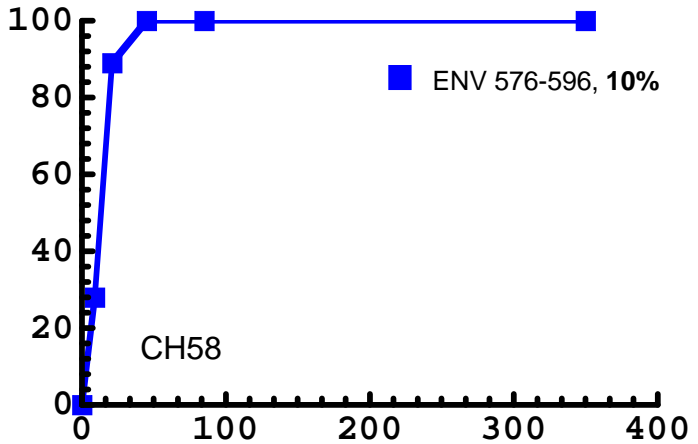
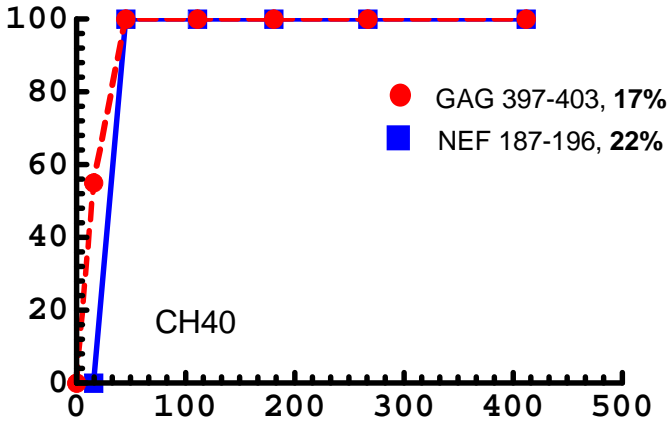
* Previous estimates from early/chronic infection using bulk sequencing estimated 4% Asquith et al 2006



Patient CH77

% = rate of killing per day of productively infected cells by T cell against its target epitope

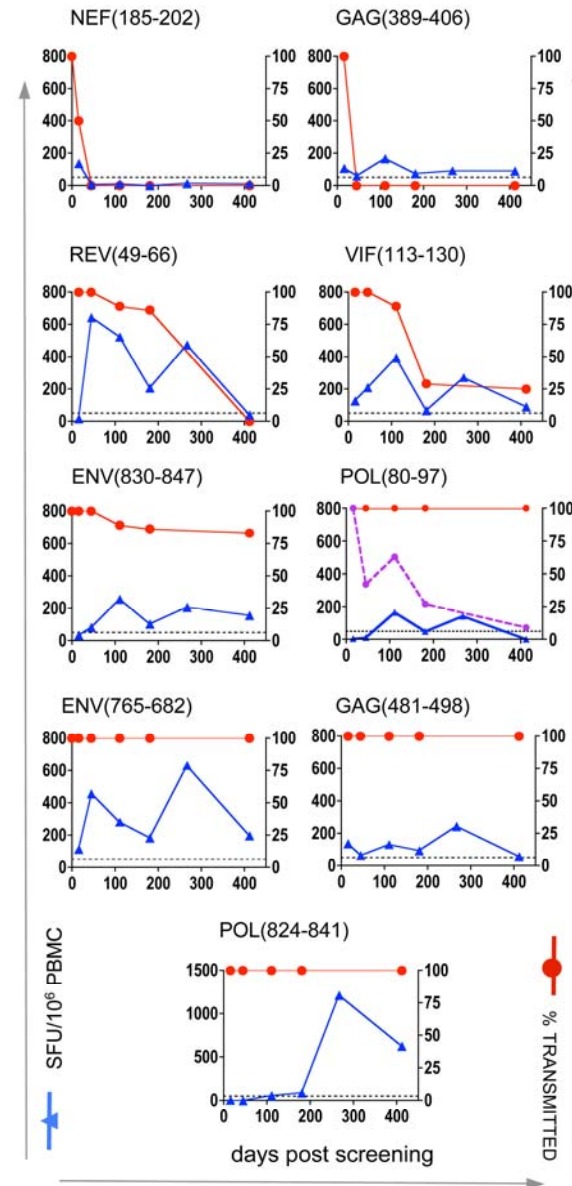
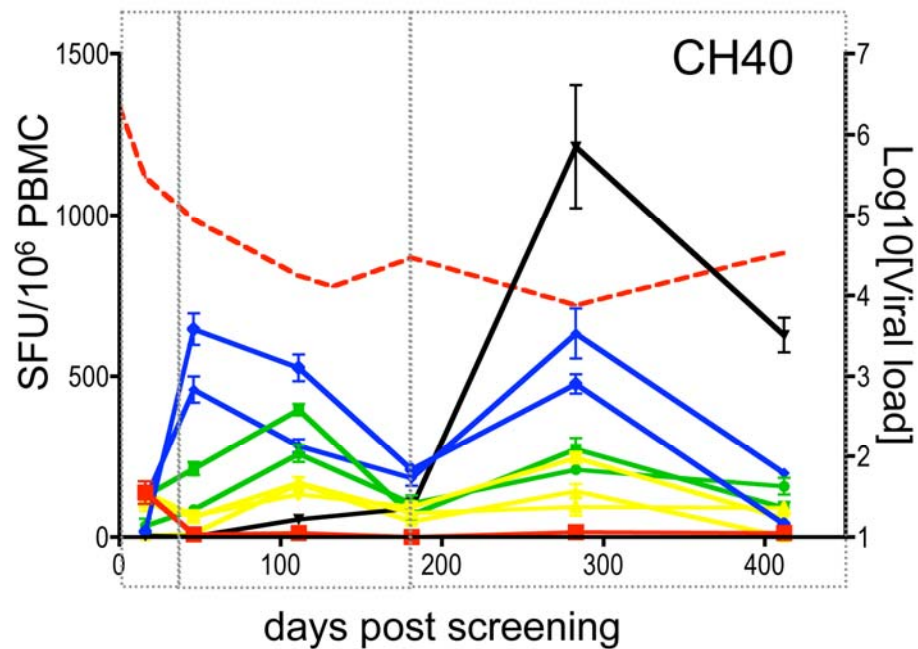
Early rapid escape from T cells observed in 3 other patients



% = rate of killing per day of productively infected cells by T cell against its target epitope

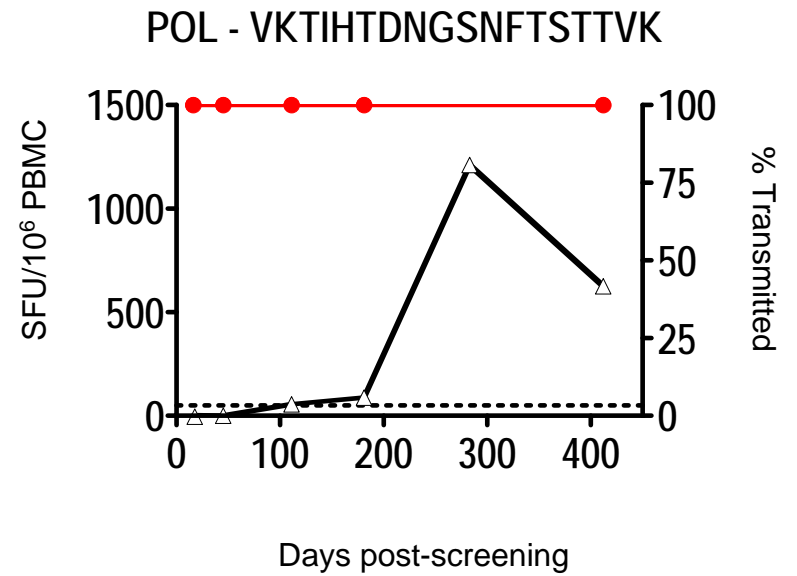
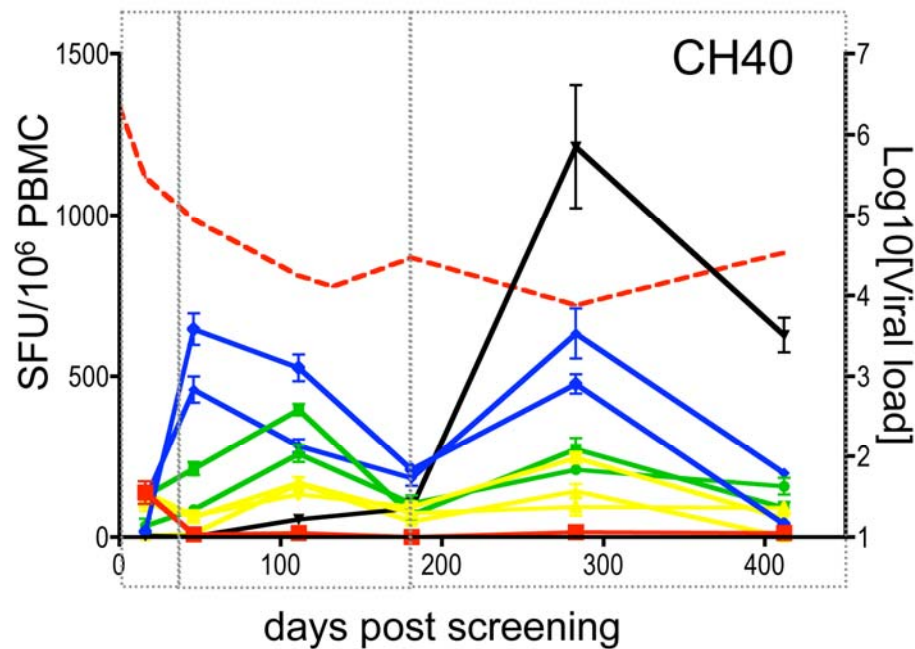
T cell kinetics

- the T cell response broadens over time - competition for targets between T cells
- virus escape occurs at different rates in acute HIV-1 infection - conserved epitopes
- vaccine strategies are aiming to induce T cell breadth possibly focusing on conserved epitopes

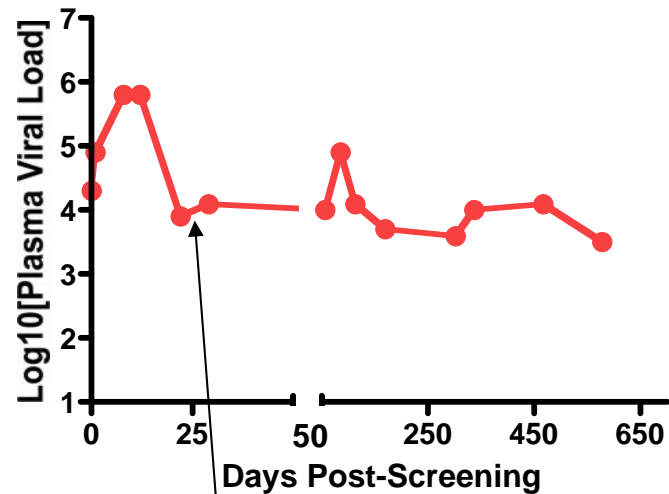


T cell kinetics

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More patients with early and rapid escape – CH159



Escape in rev from likely T cell epitope
GRPTEPVPFQLPPLERLC (62 SFU/10⁶
at day 29)

Days	SGA	
0	GRPTEPVPFQLPPLERLC	8/8
8	-----	11/11
12	-----	12/12
22	-----	4/6
29	--S-----	1/6
	-----S-----	1/6
29	--S-----	1/7
	-----S-----	2/7
	-----L-----	4/7
56	-----	1/13
	--S-----	4/13
	--H-----	4/13
	--L-----	1/13
	-----L-----	1/13
	-----L-----	2/13
85	--S-----	9/10
	--H-----	1/10

*Detected at day 8 at 0.04% with PASS

- A further 4/5 patients also appear to have early and rapid escape

Summary

- evidence of the early and rapid virus escape from T cells in 4 patients
 - from low avidity T cells
 - ongoing studies suggest more (4/5);
- mathematical modelling suggests that these first T cells play a role in controlling viraemia early in acute infection;
- T cell responses broaden over time.

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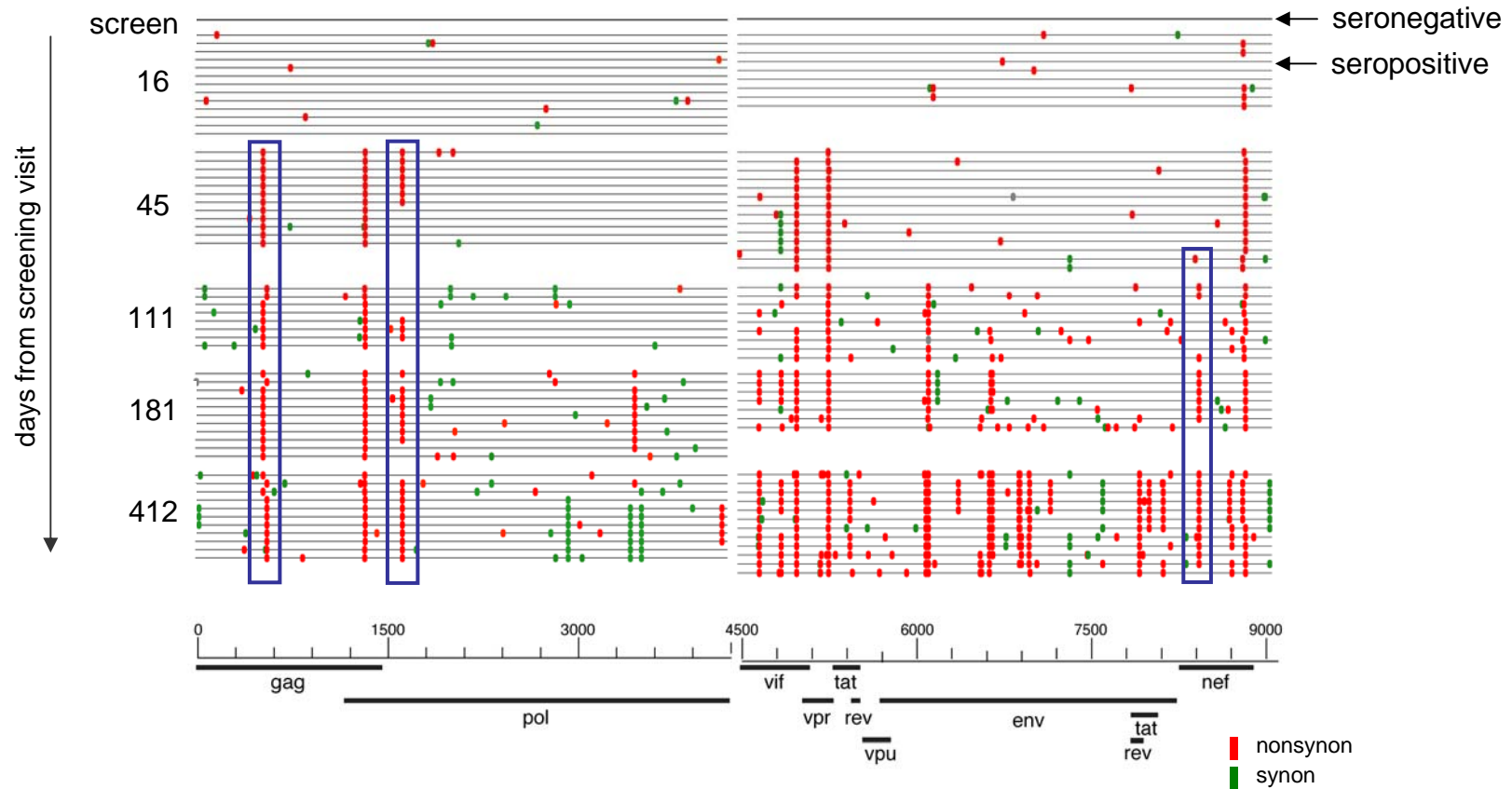


National Institute of Allergy and Infectious Diseases



Unexplained virus mutations?

Patient CH40



- some mutations not explained by T cells/Nabs/reversions
- presence of cryptic epitopes?

No!

Mathematical Modelling

$$f(t) = \frac{f_0}{(f_0 + (1 - f_0)e^{-kt})}$$

$f(t)$ = frequency of an escape variant in a population

k = rate of escape

- rate of escape = rate of escape variant that replaces the wild-type;
- balance between efficiency of the evasion from the CTL clones killing the wild-type virus and the fitness cost of the mutations
 - if no virus fitness costs, the rate of escape = rate of CTL killing of the wild-type virus as the escape variant is not killed (\therefore growth advantage = killing rate);
- Assumption: each epitope is independent and is targeted by an independent CTL response;
escape variant is present at $t=0$ at frequency f_0 ;