

# T Cell Escape in Subjects with Acute HIV-1 Infection

Michael K.P. Liu

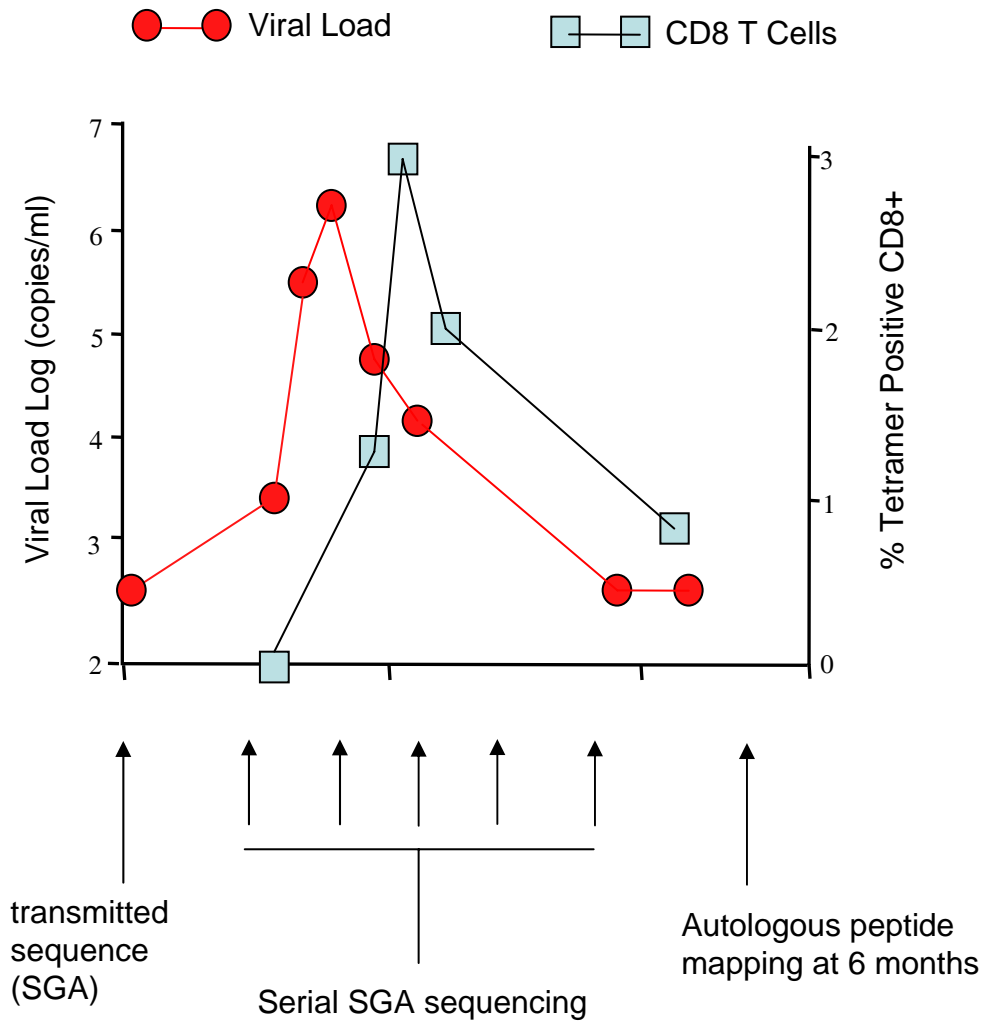


## T cells in HIV-1 infection

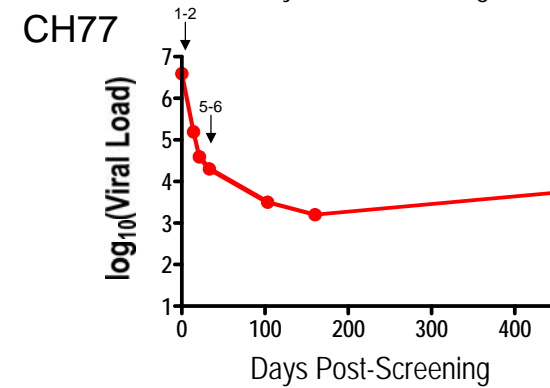
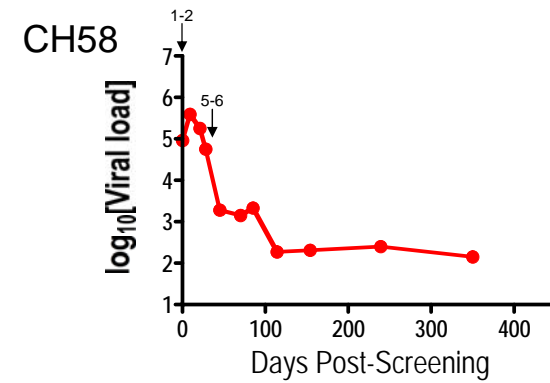
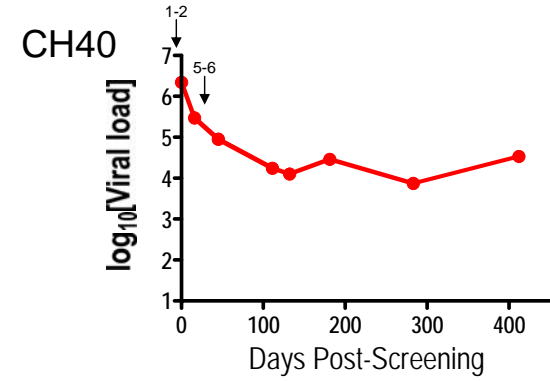
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- HIV-1-specific CD8 T cells are first detectable around peak viraemia in acute HIV-1 infection
- Increase in primary CD8 T cells coincides with initial decline in viraemia suggesting role in acute viral control
- some HLA alleles (e.g. B\*5701) associated with lower viral setpoint and delay to progression to AIDS
- HIV-1 T cell vaccines
  - in macaque challenge models show some protection- mostly using vaccine antigens that are homologous to challenge strain
  - in both macaque and human studies T cell vaccine efficacy could be compromised by virus variability

# Approach

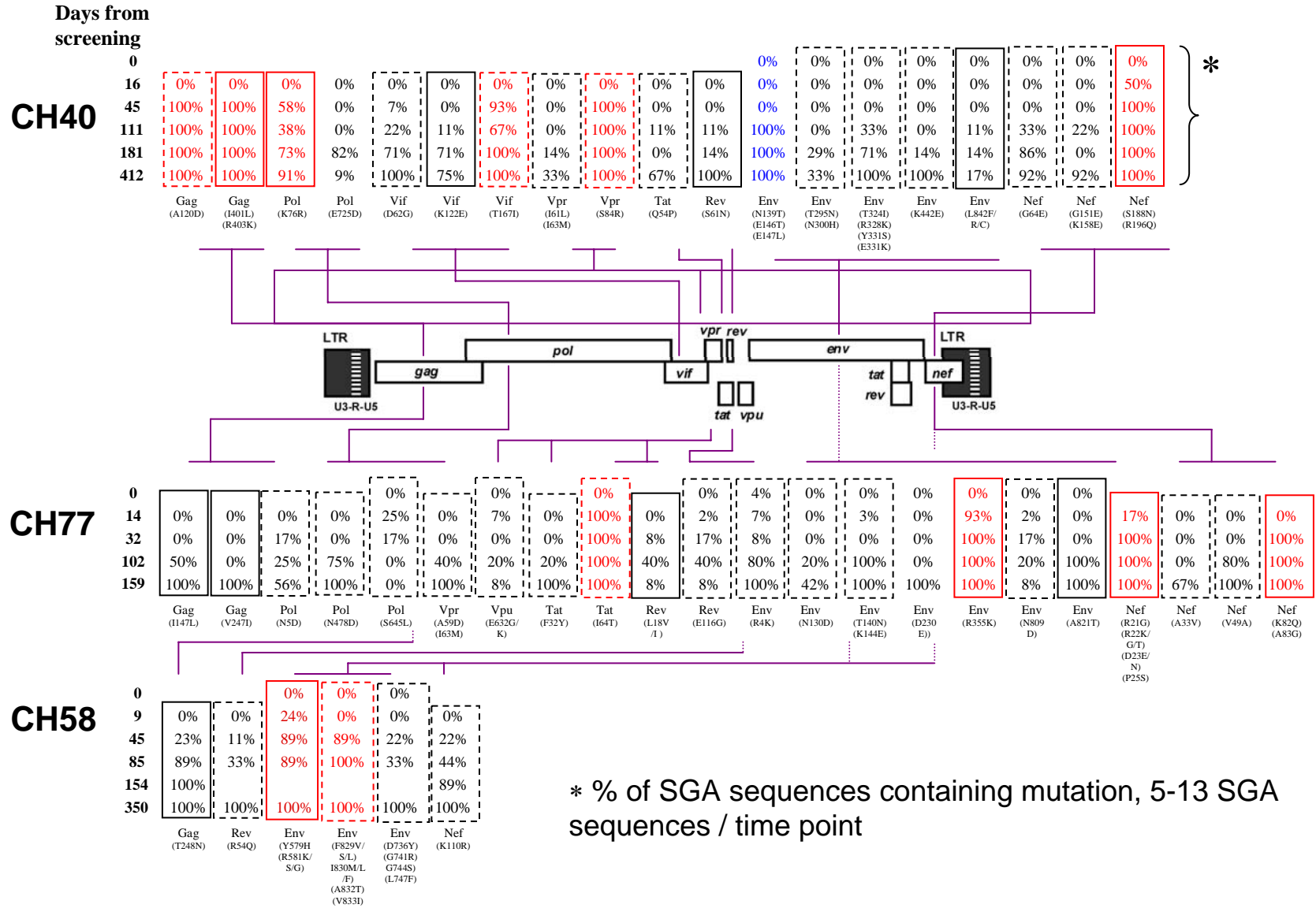


Patients



— Viral Load       $n_1 - n_2$  Fiebig Stage

# Numerous non-synonymous substitutions become fixed within months of HIV-1 infection....

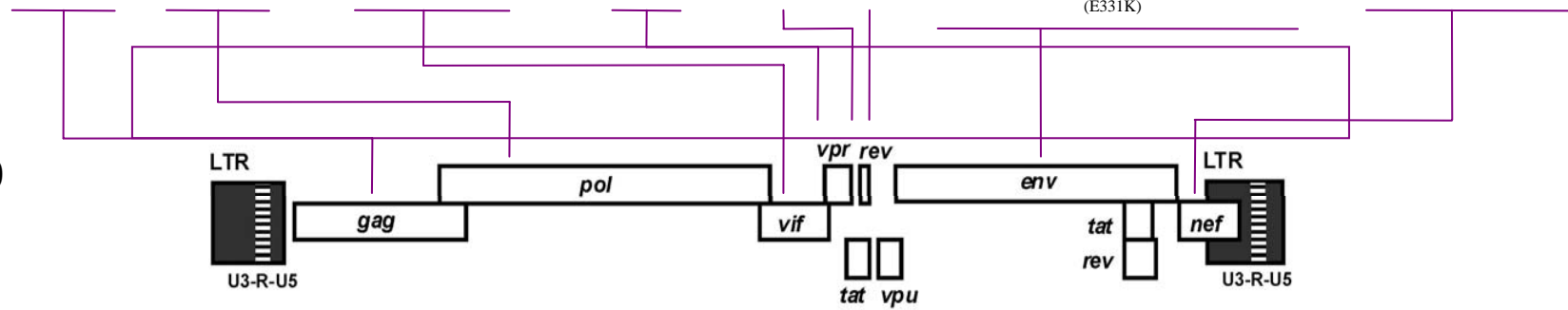


Numerous non-synonymous substitutions become fixed within months of HIV-1 infection....

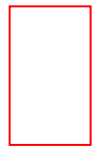
Days from screening

0												0%	0%	0%	0%	0%	0%	0%	0%
16	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	50%
45	100%	100%	58%	0%	7%	0%	93%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%
111	100%	100%	38%	0%	22%	11%	67%	0%	100%	11%	11%	100%	0%	33%	0%	11%	33%	22%	100%
181	100%	100%	73%	82%	71%	71%	100%	14%	100%	0%	14%	100%	29%	71%	14%	14%	86%	0%	100%
412	100%	100%	91%	9%	100%	75%	100%	33%	100%	67%	100%	100%	33%	100%	100%	17%	92%	92%	100%
	Gag (A120D)	Gag (I401L) (R403K)	Pol (K76R)	Pol (E725D)	Vif (D62G)	Vif (K122E)	Vif (T167I)	Vpr (I61L) (I63M)	Vpr (S84R)	Tat (Q54P)	Rev (S61N)	Env (N139T) (E146T) (E147L)	Env (T295N) (N300H)	Env (T324I) (R328K) (Y331S) (E331K)	Env (K442E)	Env (L842F) (R/C)	Nef (G64E)	Nef (G151E) (K158E)	Nef (S188N) (R196Q)

CH40



% of SGA sequences containing mutation, 5-13 SGA sequences / time point

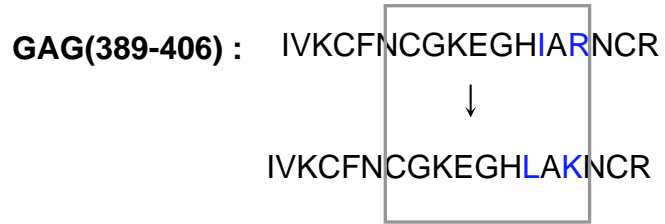
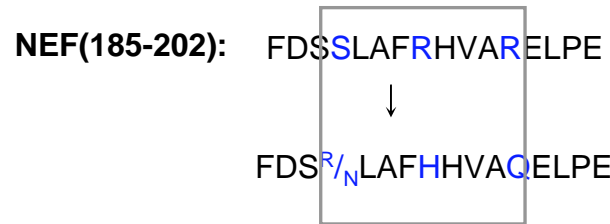


confirmed T cell responses



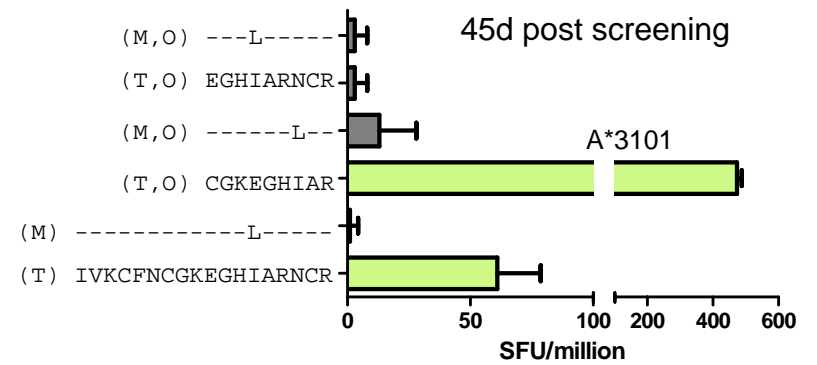
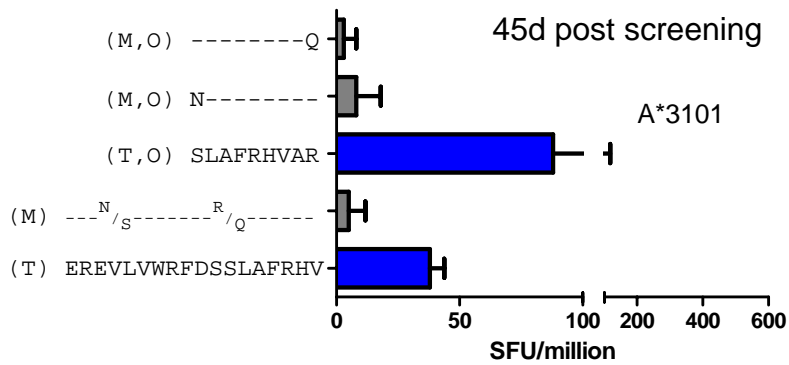
unconfirmed T cell responses, contain CTL epitopes/motifs

## Patient CH40: Primary T cells select virus escapes within weeks of infection. Complete fixation observed within 2 weeks



WEEK	DAYS	%WILD	%MUTANT
SCR	0	100	0
ENROL	+16	50	50
3	+45	0	100
12	+111	0	100
24	+181	0	100
60	+412	0	100

WEEK	DAYS	%WILD	%MUTANT
<b>SCR</b>	<b>0</b>		
<b>ENROL</b>	<b>+16</b>	<b>100</b>	<b>0</b>
<b>3</b>	<b>+45</b>	<b>0</b>	<b>100</b>
<b>12</b>	<b>+111</b>	<b>0</b>	<b>100</b>
<b>24</b>	<b>+181</b>	<b>0</b>	<b>100</b>
<b>60</b>	<b>+412</b>	<b>100</b>	<b>100</b>



## Very early and rapid escapes in patient CH40

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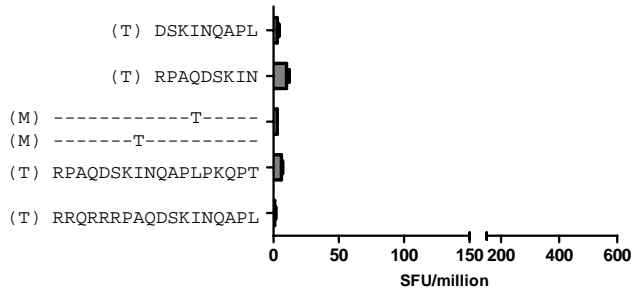
- Earlier and more rapid than previous studies for HIV-1
- Similar rapidity to escape selection by nevirapine (RT inhibitor)
- Suggest primary CD8 T cell responses have potent antiviral effects but rendered useless by escape

# Patient CH77

## TAT(57-74):

RPAQDSKINQAPLPKQPT  
 ↓  
 RPAQDSKINQAPLPKQPT

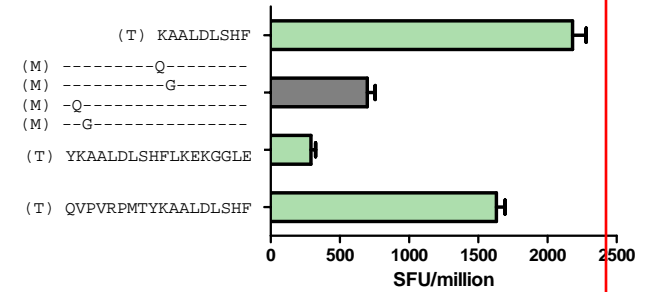
WEEK	DAYS	%WILD	%MUTANT
SCR	0	100	0
ENROL	+14	0	100
3	+82	0	100
12	+162	0	100
26	+198	0	100



## NEF(73-90):

QVPVRPMTYKAALDLSHF  
 ↓  
 QVPVRPMTYQGALDLSHF

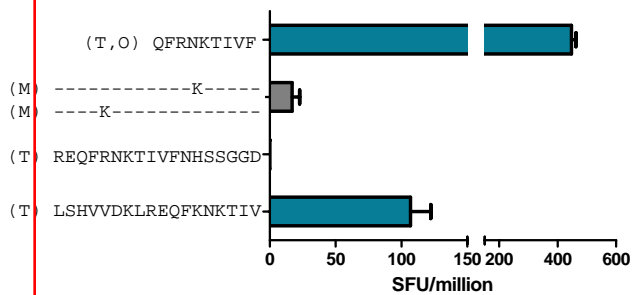
WEEK	DAYS	%WILD	%MUTANT
SCR	0	0	0
ENROL	+14	0	0
3	+82	0	100
12	+162	0	100
26	+198	0	100



## ENV(350-368):

REQFRNYTIVFNHSSGGD  
 ↓  
 KEQFKNYTIVFNHSSGGD

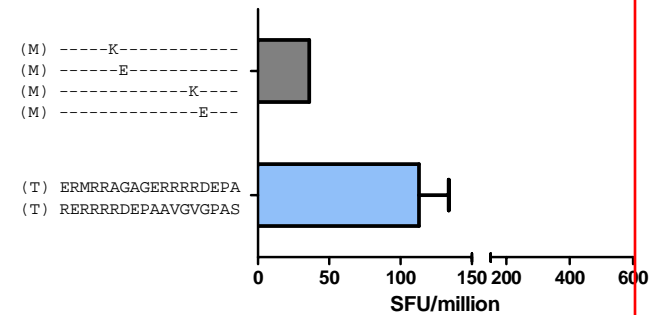
WEEK	DAYS	%WILD	%MUTANT
SCR	0	100	0
ENROL	+14	7	93
3	+82	0	100
12	+162	0	100
26	+198	0	100



## NEF(17-34):

RERRRRDEPAAVGVGPAS  
 ↓  
 RERRRRKEEPAAVGVGPAS

WEEK	DAYS	%WILD	%MUTANT
SCR	0	0	0
ENROL	+14	0	17
3	+82	0	100
12	+162	0	100
26	+198	0	100





...multiple T cell  
escape mutants  
occur in individual  
viruses in acute  
HIV-1 infection

Patient CH77 SGA sequences

DAY	SGA SEQUENCE CLONE	ENV(250-270)	NEF(17-34)	NEF(80-94)
0	TRANSMITTED SEQ	SHVVDKLREQ <b>FR</b> NKTIIVFNH	RERRRRDE <b>P</b> AAVGVGPAS	<b>KA</b> ALDLSHFLKEK
14	CH77_WGA_B3	.....K.....	.....	.....
	CH77_WGA_C7	.....K.....	.....	.....
	CH77_WGA_C9	.....K.....	.....	.....
	CH77_WGA_C4	.....K.....	.....	.....
	CH77_WGA_D5	...G.....K.....	.....	.....
	CH77_WGA_C3	.....K.....	.....	.....
32	CH77_WK03_3_B1	.....K.....	...G.....	Q.....
	CH77_WK03_3_D1	.....K.....	.....S.....	.....I.....
	CH77_WK03_3_D2	.....K.....	.....E.....	Q.....
	CH77_WK03_3_D3	.....K.....	.....K.....	Q.....
	CH77_WK03_3_TB1	.....K.....	.....K.....	Q.....
	CH77_WK03_3_TB2	.....K.....	.....E.....	T.....
	CH77_WK03_3_TB4	.....K.....	.....S.....	...H.....
	CH77_WK03_3_TB5	.....K.....	.....N.....	Q.....
	CH77_WK03_3_TB6	.....K.....	..GA.ERR..	Q.....
	CH77_WK03_3_TB7	.....K.....	.....K.....	Q.....
	CH77_WK03_3_TB8	.....K.....	.....E.....	T.....
	CH77_WK03_3_TC1	.....K.....	.....N.....	Q.....
102	CH77_WK12_3_E1	.Y.....K.....	.....N.....	Q.....
	CH77_WK12_3_TA1	.....K.....	.....K.....	Q.....
	CH77_WK12_3_TA2	.....K.....	.....T.....	Q.....
	CH77_WK12_3_TB1	.....K.....	.....G.....	.G.....
	CH77_WK12_3_TB2	.....K.....	.....G.....	.G.....
159	CH77_WK24_3_TA1	.....K.....	K.....E.....	.G.....#..
	CH77_WK24_3_TA2	...N.....K.....	.....G.....T..	Q.....
	CH77_WK24_3_TA3	.....K.....	.....G.....	Q.....
	CH77_WK24_3_TA4	.....K.....	.....N.....S..	Q.....
	CH77_WK24_3_TA6	...N.....K.....	.....E.....	.G.....
	CH77_WK24_3_TB1	...N.....K.....	.....G.....	Q.....#..
	CH77_WK24_3_TB2	N.....K.....	.....T.....	Q.....
	CH77_WK24_3_TB3	...N.....K.....	.....K.....V..	Q.....
	CH77_WK24_3_TB4	.....K.....	.....K.....V..	Q.....
	CH77_WK24_3_TB5	G.....K.....	.....T.....	.G.....
	CH77_WK24_3_TB6	...N.....K.....	.....E.....V..	.G.....
	CH77_WK24_3_TB7	...N.....K.....	.....G.....	.G.....

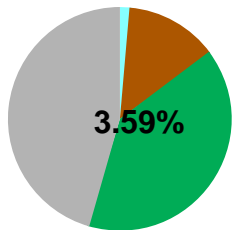
**Patient CH58: Virus control at setpoint despite early escape from primary T cells - conserved B\*5701 restricted epitopes**

ENV(576-596)

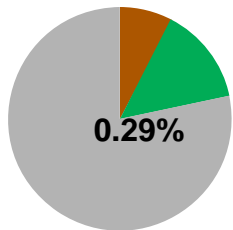
Days from screening

0 LQARVLALERYLRDQQLGIW 100%  
 9 -----H----- 18%

% cytokine production by CD8 memory T cells 21 days following screening...



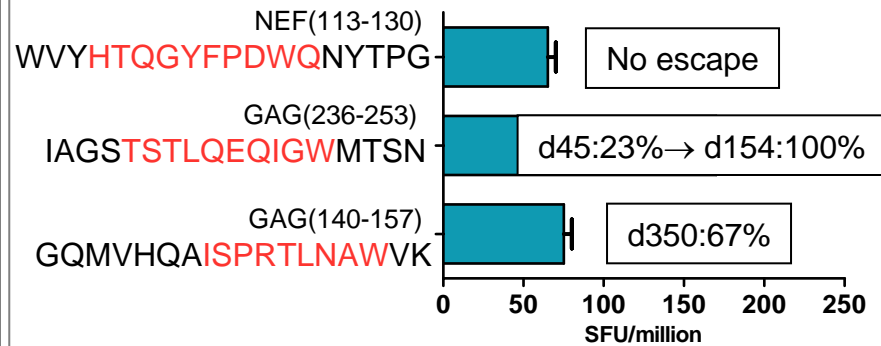
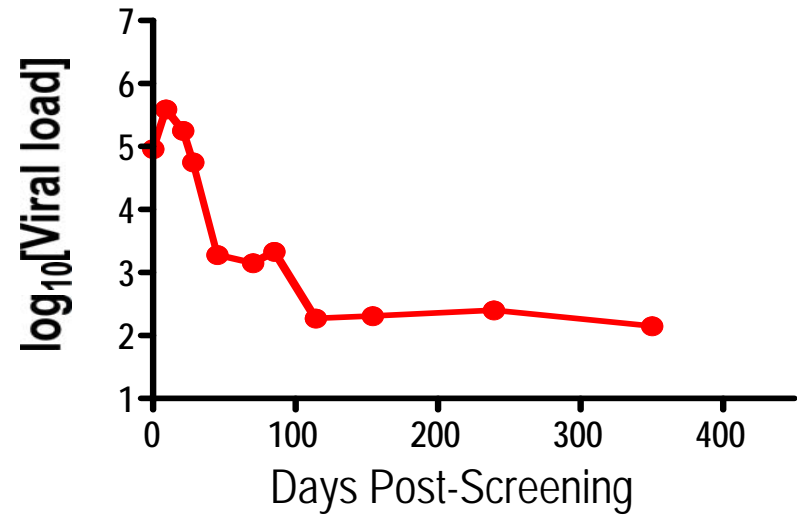
LQARVLALERYLRDQQLGIW



-----H-----

Colour indicates number cytokines produced  
 grey:1, green: 2, brown: 3, aqua:4, red:5

G. Ferrari



Red text = B\*5701 epitopes

## Summary

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- Primary T cells can select virus escape mutants within weeks of infection
- Some primary T cells are potent - driving fixation of mutants within 2 weeks
- Two or more escape mutants can be selected at the same time
- Multiple T cell escapes during primary infection > 50% of responses
- BUT some epitopes are conserved or escape more slowly - possibly with fitness costs e.g. HLA B57 and 27 restricted responses

# ACKNOWLEDGMENTS: AHI T CELL STUDIES

## T CELL CORE

**Nilu Goonetilleke**  
**Andrew McMichael**  
Stephen Moore  
Rachel Tanner  
Kati Digleria & Zhanru Yu  
Tim Rostron  
Suzanne Campion  
Victoria Bourne  
Tumena Corrah  
Al Leslie (Oxford, UK)

**Guido Ferrari**  
**Christine Marking**  
**Kent Weinhold** (Duke, US)

Mandla Mlotshwa  
Patti Kay  
Clive Gray (NICD, S.Africa)

**Emma Turnbull**  
**Seph Borrow** (Oxford, UK)

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**Brandon Keele**  
**Beatrice Hahn**  
**George Shaw** (UAB, US)

Jennifer Kirchner  
Chunlai Jiang  
Feng Gao (Duke, US)

Florette Treurnicht  
Carolyn Williamson (UCT, S. Africa)

## SCHARP

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**Cheryl DeBoer**  
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**Sravani Cheeti**  
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Grand Challenges  
in Global Health