

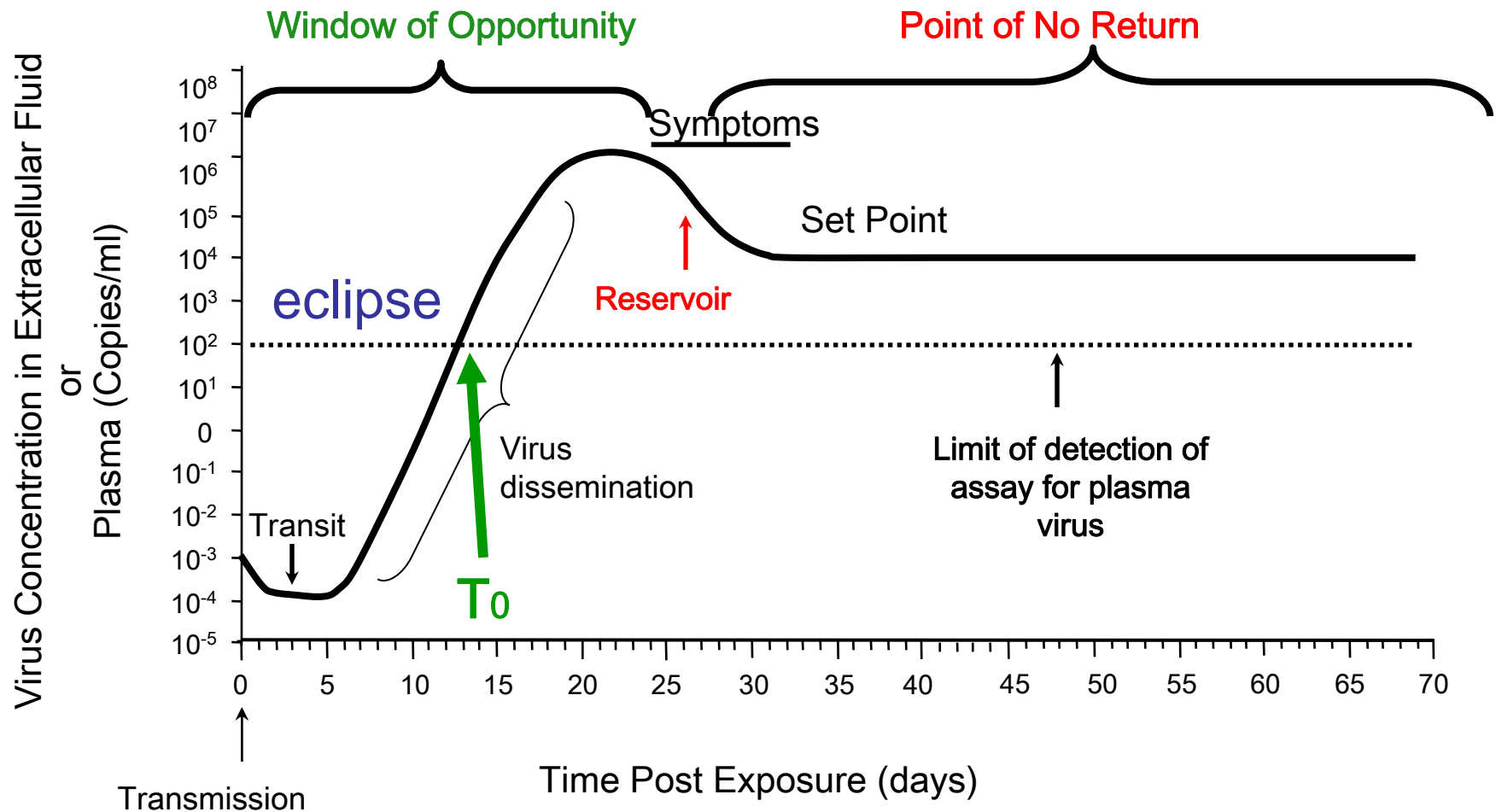
# Lack of highly poly-functional epitope-specific CD8+ memory T cell responses during spontaneous control of viremia: CHAVI 001 study

**AIDS Vaccine 2008**  
Cape Town, 13-16 October

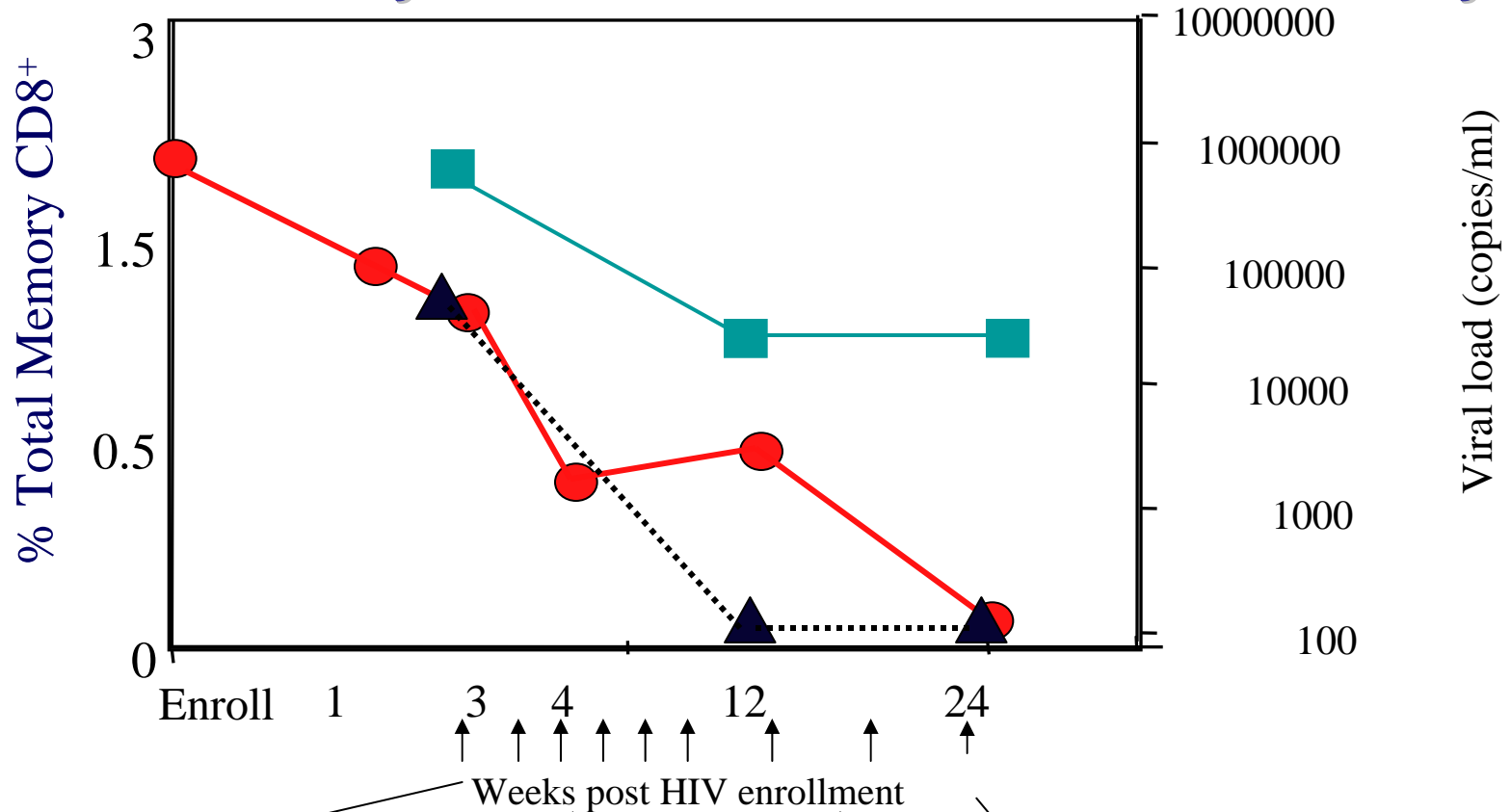
Guido Ferrari  
Duke University Medical Center



# Acute HIV-1 Infection



# CHAVI 001 Study: Course of Viremia and T Cell Study



Screening: Seronegative/NAT positive  
Full length HIV sequence

6 months: Full T cell epitope map on autologous peptides (ELISpot)

Peptides based on autologous sequence

Intervening full length sequences

● Virus load

■ p24 specific CD8 T cells

▲ Nef specific CD8 T cells

Sequential analysis of Wdel responses to mapped and mutating epitopes: ELISpot and ICS  
 IAGSEIQEQIGWMTSN  
 WYHTQGYFPDWQNYTPG



# CHAVI 001 Study: Virus Load and Time Points

## Summary

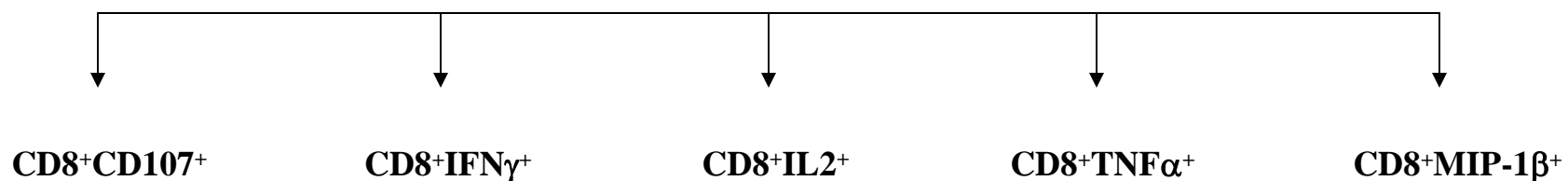
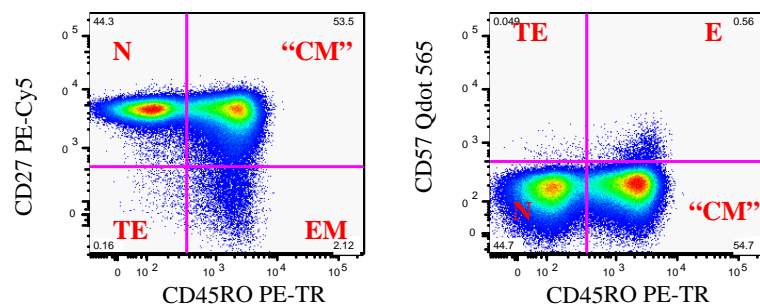
Patient #	HAART	Enrollment	Virus Load (copies/ml) at Week ICS assay				
			1	3	4	12	24
700-01-00-40	No	298,026	MV	MV	<b>89,156</b>	<b>17,587</b>	<b>29,453</b>
700-01-00-77	No	144,145	37,560	<b>17,907</b>	MV	<b>3,073</b>	<b>1,680</b>
700-01-00-58	No	394,649	MV	56,739	<b>1,908</b>	<b>2,168</b>	<b>205</b>
701-07-00-27	Yes	194,744	<b>3,687</b>	<b>1,804</b>	1,836	<b>400</b>	50
701-01-00-43	Yes	5,532	MV	1,250	380	<b>50</b>	50
701-01-00-55	Yes	31,513,812	<b>22,826,172</b>	<b>37,783</b>	31,699	<b>1,670</b>	50
700-01-00-81	Yes	<b>3,746</b>	<b>104</b>	50	50	<b>50</b>	50
700-01-01-06	Yes	>750,000	<b>14,538,865</b>	<b>33,884</b>	26,468	<b>50</b>	107

# CHAVI 001 Study: Week 24 Epitope Mapping Results

Patient #	Stimulation	HIV Antigen	Sequence	Peptide#	SFU/10 <sup>6</sup> cells
700-01-00-40 HLA type A*3101,*0201;B*4402,*4001;C*0302	Individual	RT	ORQIRSI SERILSTYLER	03899	208
	Individual	env	LFSYHRLRDLLLIVTRIV	00620	183
	Individual	env	IEVQRACRAILHIPRRR	00629	103
	Individual	gag	KELYPLASLRSLFGNDPS	00442	93
	Individual	pol	VKTIHTDNGSNFTSTTVK	00515	88
	Individual	gag	IVKCFNCGKEGHIARNCR	00049	73
	Individual	vif	DCFSESAIRKAILGRIVS	03819	68
	700-01-00-77 HLA type A*0205;B*5301,*5701;C*0401	Individual	gag	IAGSTSTLQEQVGMWTSN	003386
Individual		env	SGEDWNKTLSHVVDKLR	003304	313
Individual		env	TTTVPWNVSWSNKSLNEI	003335	243
Gag7 Pool		gag	HIVWASRELERFAVNPSL	003377	130
Gag7 Pool		gag	LGLNKIVRMYSPTSILDI	000415	53
Gag7 Pool		gag	LERFAVNPSLLETSEGCR	003378	83
Gag7 Pool		gag	FYKTLRAEQASQEVKNWVM	000419	83
Gag7 Pool		gag	PFRDYVDRFYKTLRAEQ	000418	52
Gag7 Pool		gag	GOMVHQAI SPRTLNAWVK	000018	113
Gag7 Pool		gag	GKKQYKLRHIVWASRELE	001988	112
Nef3 Pool		nef	QVPRPMTYKAALDLSHF	003411	62
Nef3 Pool		nef	FDSRLAQHVAREIHPEF	003423	40
Nef3 Pool		nef	YKAALDLSHFLKEGGLE	001563	60
Pool ELISPOT+		pol	KISTESIVWGRTPKFR	003464	120
Pool ELISPOT+		env	RAVLNIPTRIROGLERL	003359	92
Pool ELISPOT+		env	GCSGRVICTTTVPWNVSW	003334	82
Pool ELISPOT+		env	VAEGTDRVIEELQRAWRA	003357	60
Pool ELISPOT+		RT	DEDLKTVRLIKRLYQSN	003487	88
Pool ELISPOT+		pol	KQLTEAVQKISTESIVW	003463	52
Pool ELISPOT+		pol	LKKIIGQVRDQAEHLKTA	000171	40
Pool ELISPOT+		vpu	RLLDRIIDRAEDSGNESE	003514	40
700-01-00-58 HLA type A*0101,*2301;B*1402,*5701;C*0802	Individual	gag	IAGSTSTLQEQIGWMTSN	003646	170
	Individual	gag	GOMVHQAI SPRTLNAWVK	000018	75
	Individual	nef	WVYHTQGYFPDQWQNYTPG	000308	65
	Individual	gag	GSKKYKLRHIVWASRELE	003635	35
	Individual	gag	PPESFRFGEEKTAPVQK	003653	15
701-01-00-27 HLA type A*6802,*0201;B*5301,*5101;Cw*0402/01	Individual	nef	YFPDQWQNYT	000790	332
	Individual	pol	VPLDKDFRKYTAFTIPSI	000467	90
	Individual	pol	WEAWWTEYWOATWIPEWE	000490	60
	Individual	nef	WVYHTQGYFDQWQNYTPG	000308	55
	Individual	pol	KLPIQKETWEAWWTEYWQ	000489	32
701-01-00-43	Individual	No epitopes mapped at week 24			
HLA type A*2301,*3301;B*0702,*0701; C*0702,*1601					
701-01-00-55 HLA type A*6801,*0201;B*3501,*0801; C*0401,*0701	Individual	gag	EIYKRWII	000812	245
	Individual	env	RIROGLERALL	000631	70
	Individual	pol	KAGYVTDGRQKVVSLTD	000495	43
	Individual	gag	NNPPIPVGEIYKRWIIILG	000413	20
700-01-00-81	Individual	gag	GKKKYKLRHIVWASRELE	000390	10
HLA type A*1101,*2401;B*3501,*3502;C*0401					
700-01-01-06 HLA type A*1101,*2401;B*3501,*3502;C*0401	Individual	vpr	GPOREPYNEWTLELLEEL	000367	183
	Individual	vif	WRKKWYSTQVCPCLADQL	000692	110
	Individual	pol	KILEPFRKQNPDIIVIQY	000469	87
	Individual	nef	QVLRMTYX	000736	40

# 12 Color ICS Memory/Functional Markers Gating Strategy

CD8<sup>+</sup>

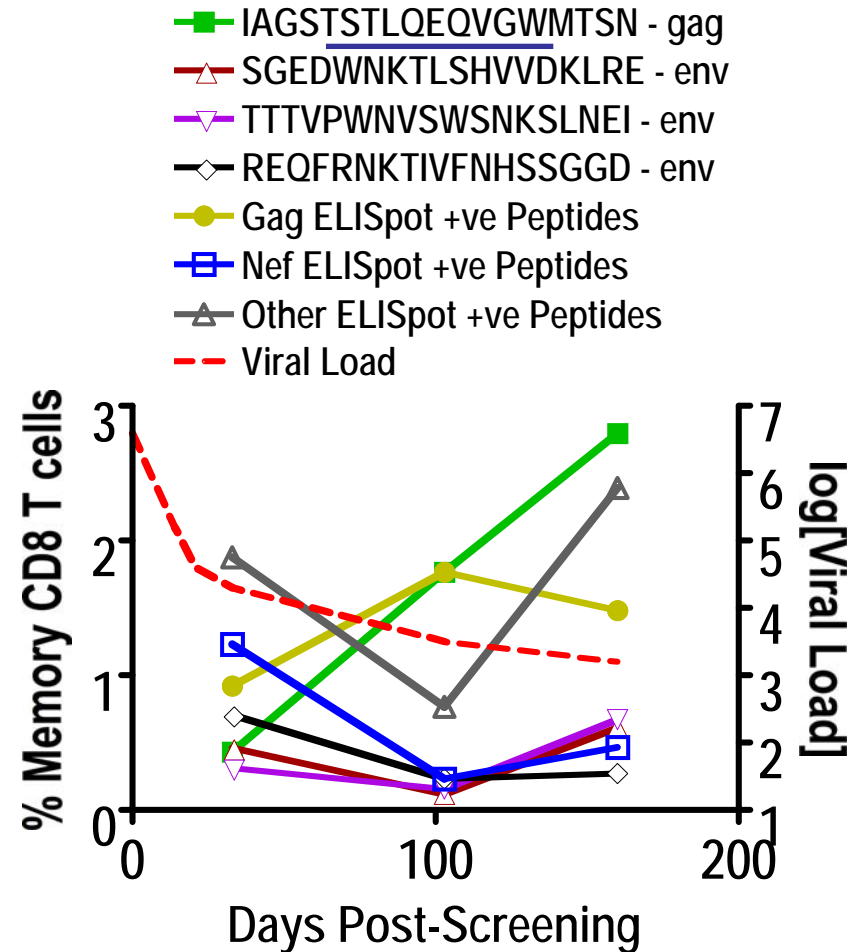
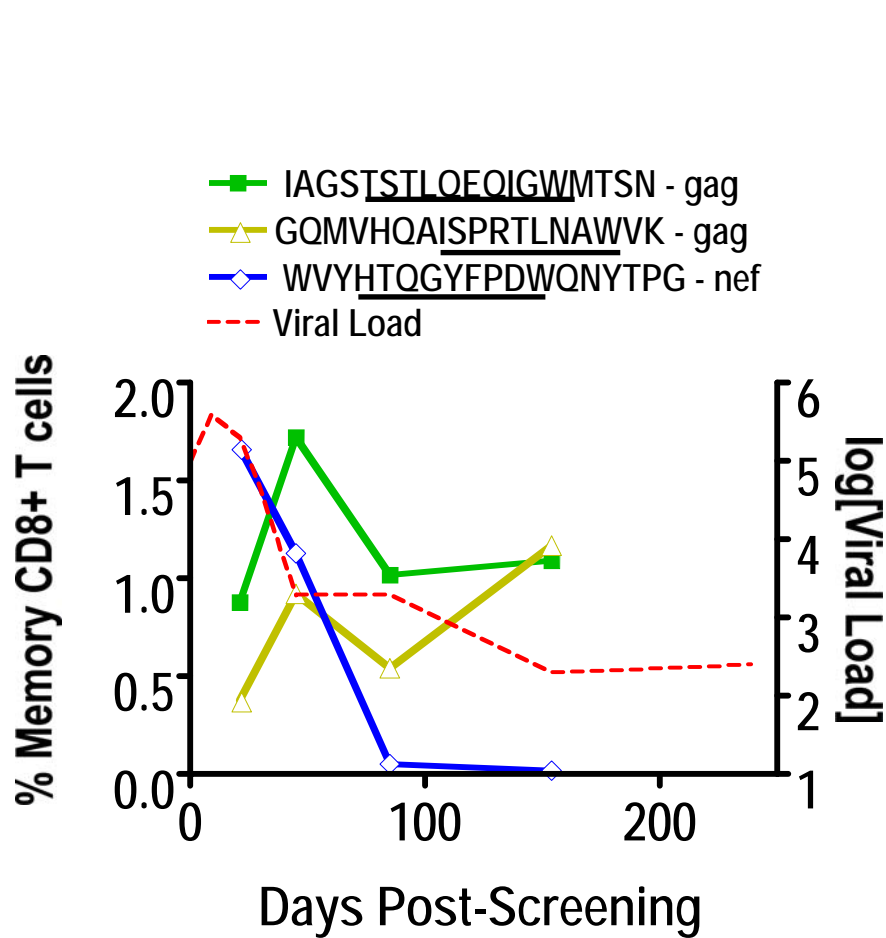


**Total M**  
**E and TE**  
**CM and EM**

**Boolean Gates**

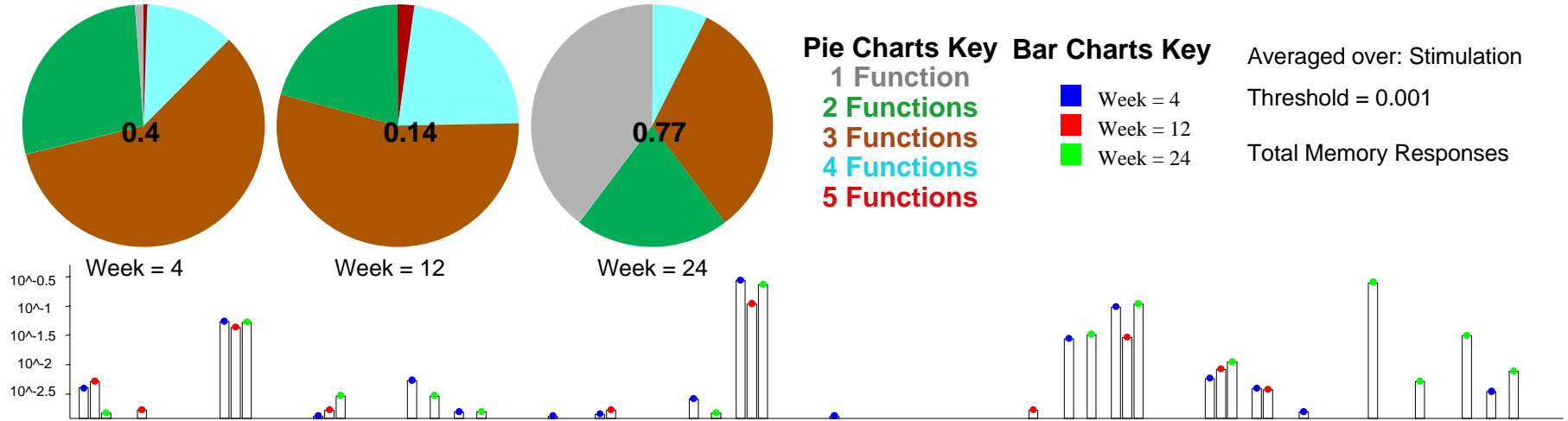
CD107a	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IFNγ	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	
IL2	+	+	+	+	-	-	-	-	+	+	+	+	-	-	-	-	-	+	+	+	+	-	-	-	-	-	+	+	+	+	+	+	+	+	-	-
MIP1b	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	-
TNFα	+	-	+	-	+	-	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+

# Kinetics of Epitope Recognition in Controllers CH58 and CH77

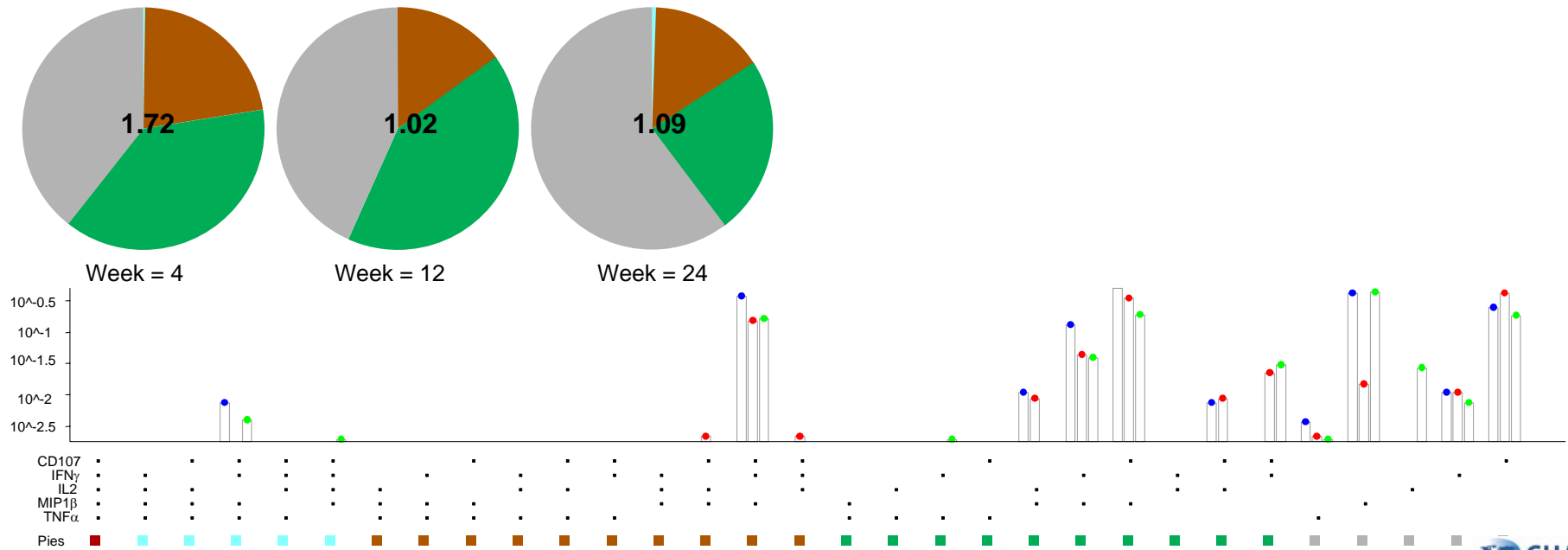


# Frequency and Functionality of Immunodominant Responses

CH40 (w/o HAART & Non-Controller) Epi 3899 RT: QRQIRISERILSTYLE (208 SFC/10<sup>6</sup> Wk 24)



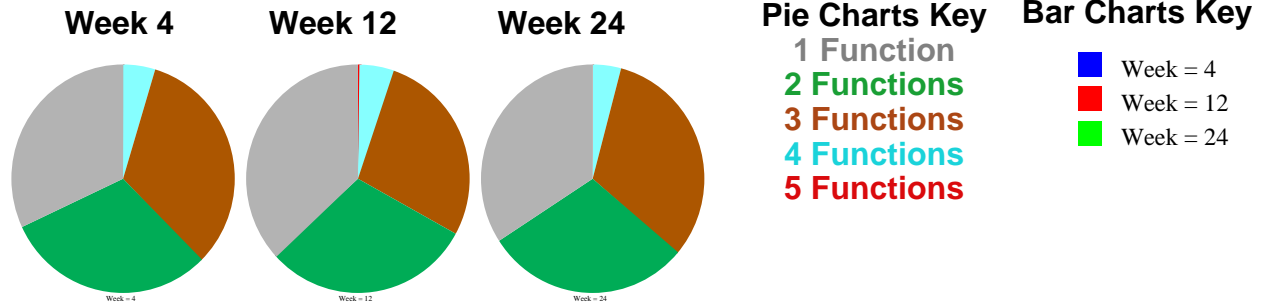
CH58(w/o HAART & Controller) Epi 3646 Gag: IAGSTSTLQEIQGWMTSN (170 SFC/10<sup>6</sup> Wk 24)



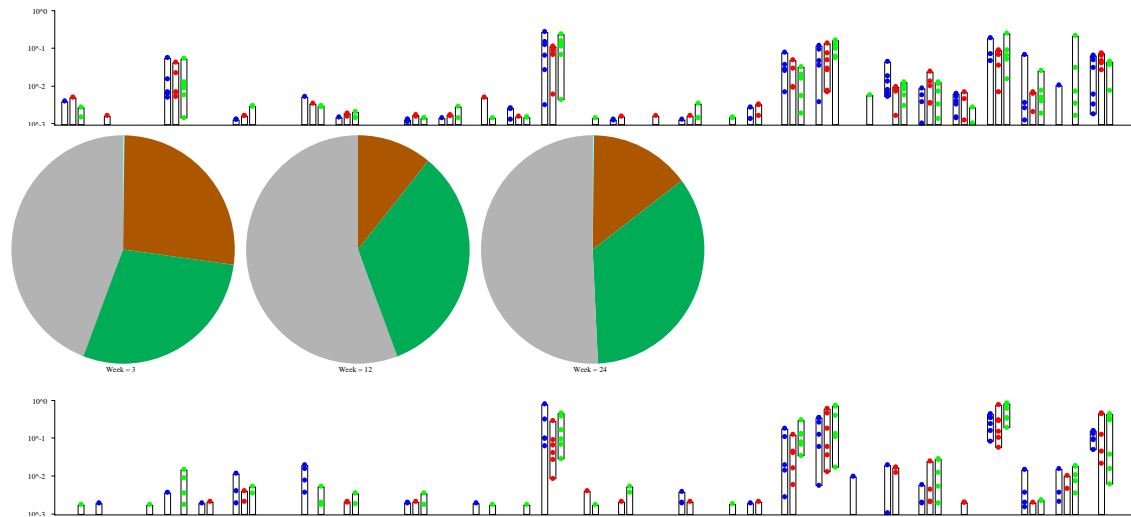


# Mapped Epitopes: Flavor of Total CD8+ Functions w/o HAART

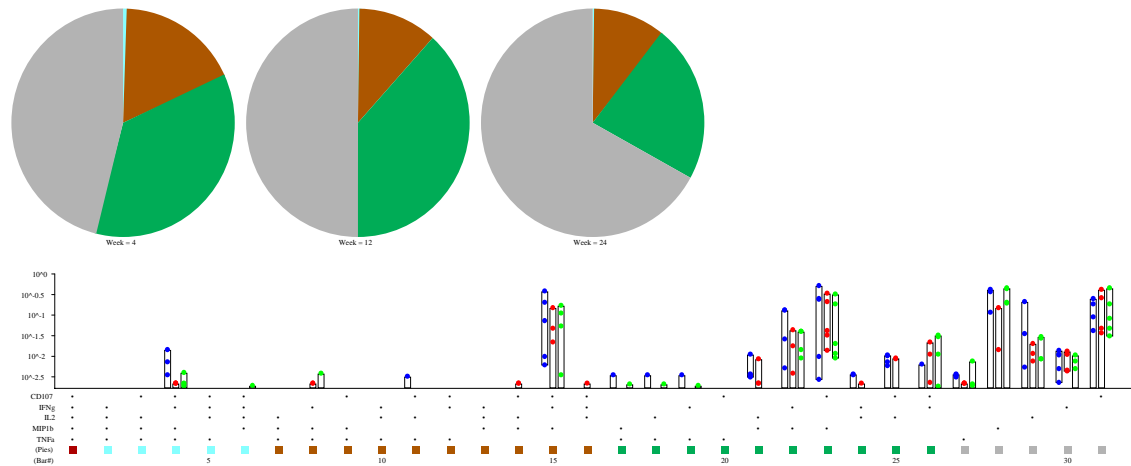
**CH40**  
Non Controller



**CH77**  
Controller

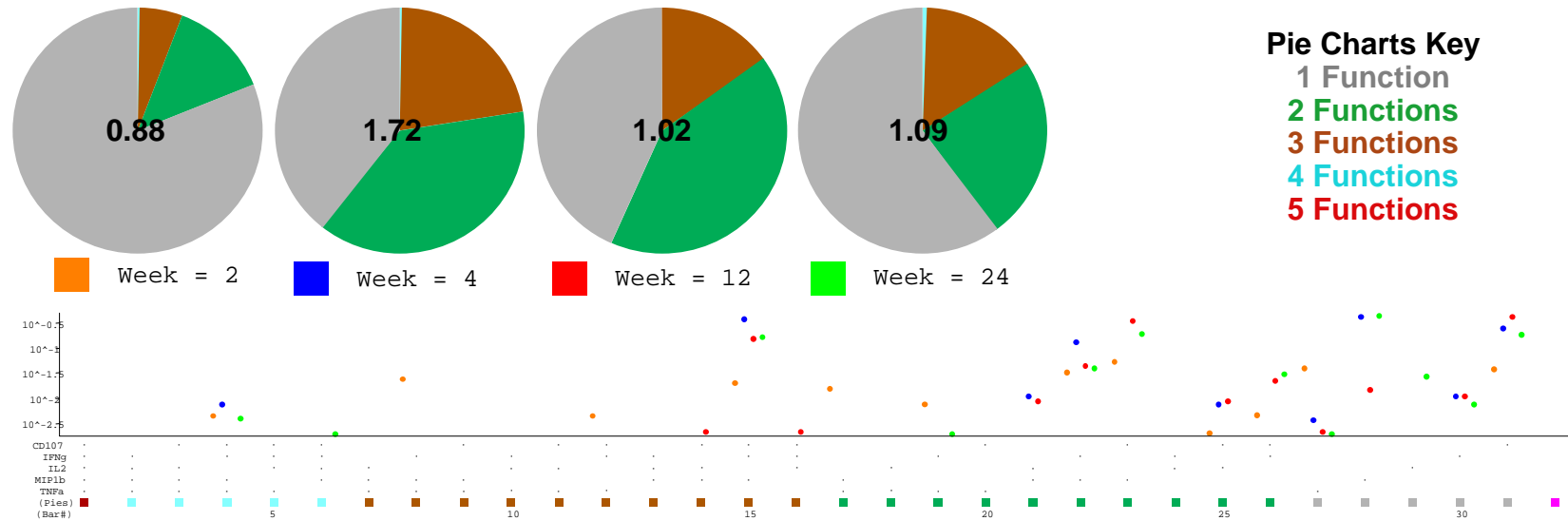


**CH58**  
Controller

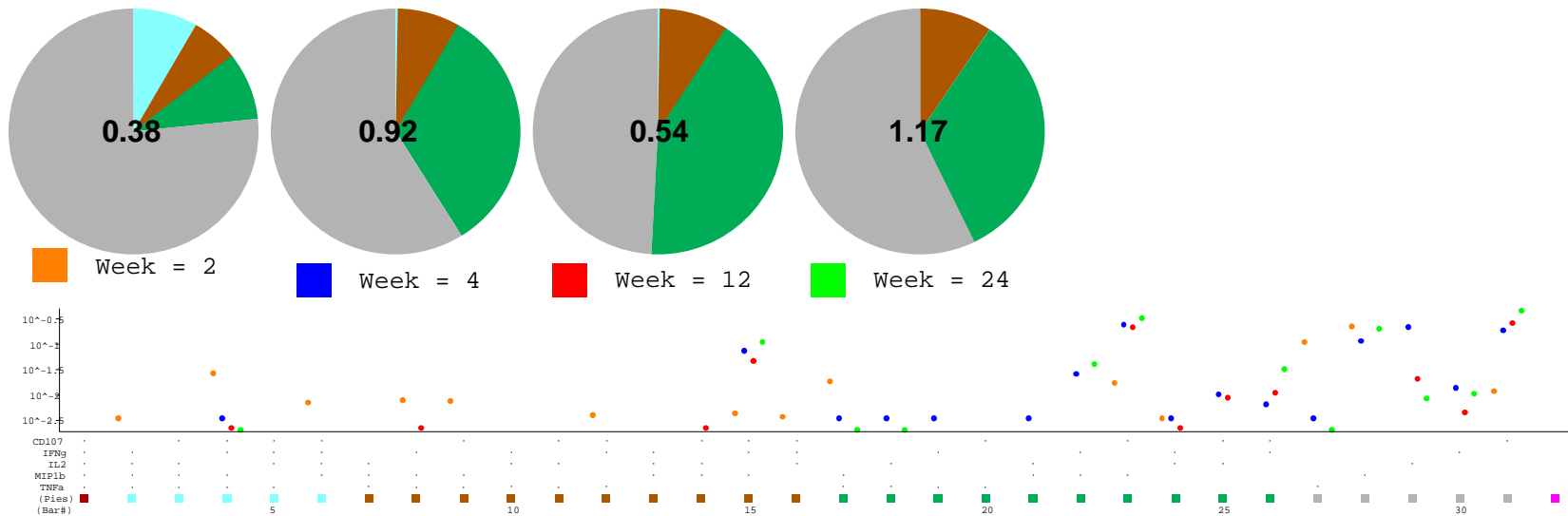


# Subject CH58: Longitudinal Responses to Dominant and Subdominant Epitopes

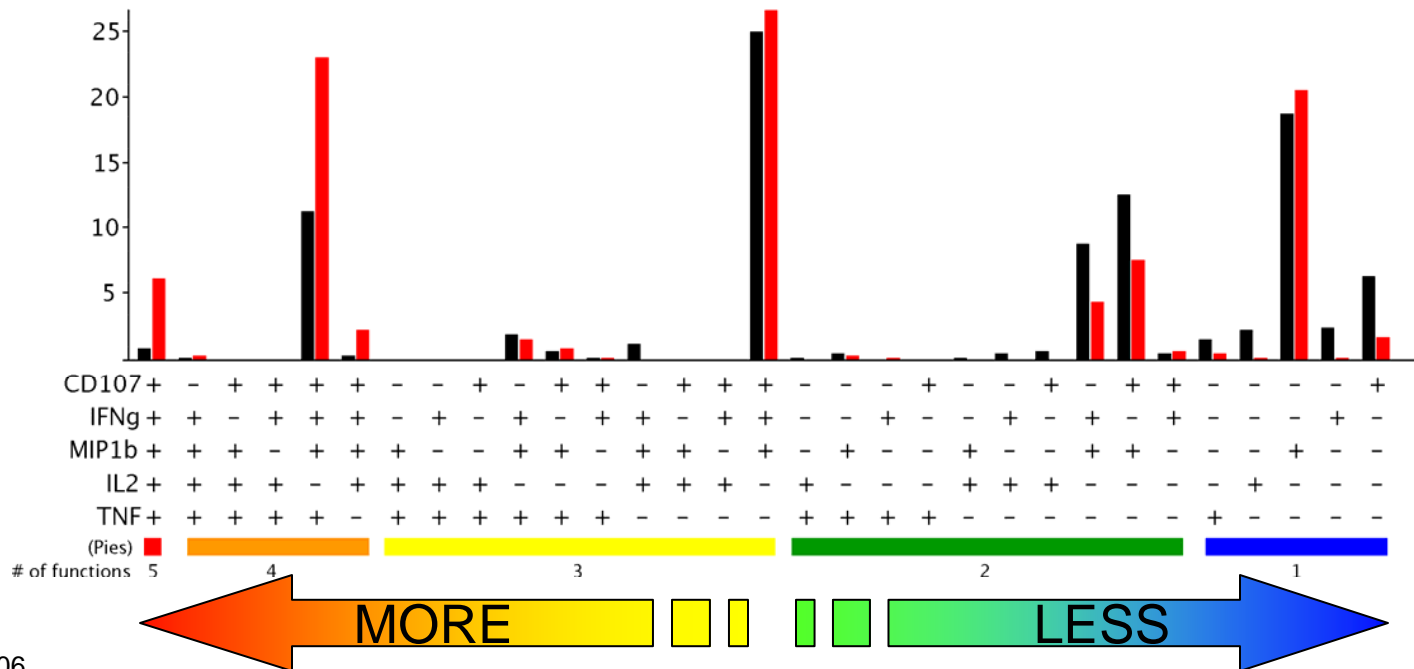
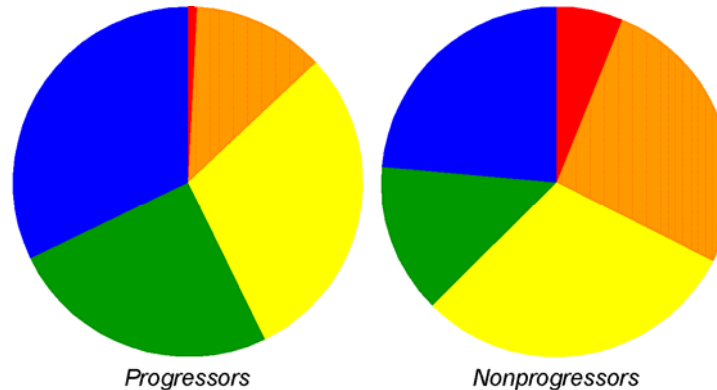
**Week 2-24 10058 Epi 3646 Gag: IAGSTSTLQEQIGWMTSN (170 SFC/10<sup>6</sup> Wk 24)**



**Week 2-24 10058 Epi 0018 Gag: GQMVHQAI SPRTLNAWVK (75 SFC/10<sup>6</sup> Wk 24)**



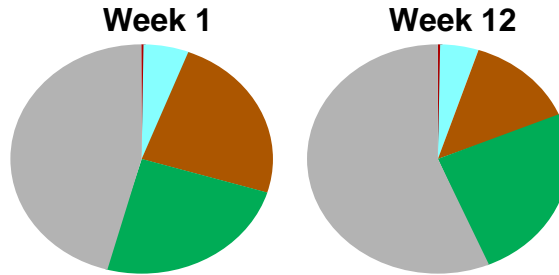
# HIV-specific CD8+ T cells in chronic HIV infection



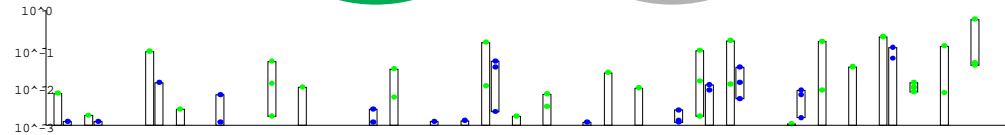
# Mapped Epitopes: Flavor of Total CD8+ Functions w/ HAART

## CH55

VL 1,670 c/ml @ Week 12

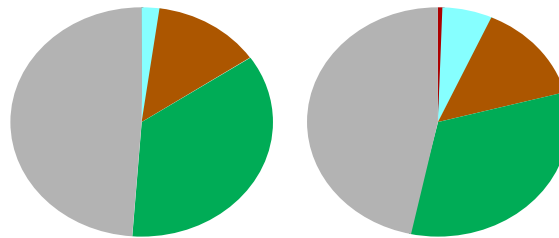


**Pie Charts Key**  
 1 Function  
 2 Functions  
 3 Functions  
 4 Functions  
 5 Functions

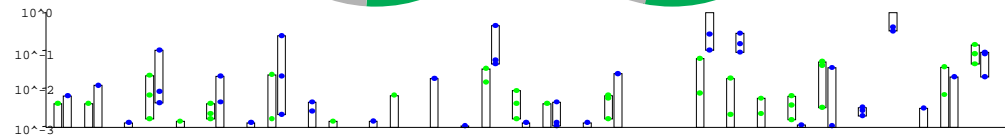


## CH27

VL 408 c/ml @ Week 12

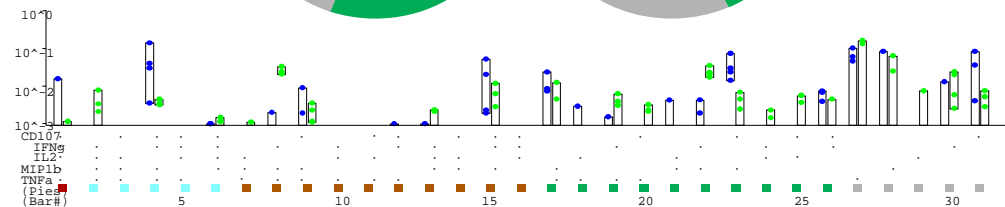
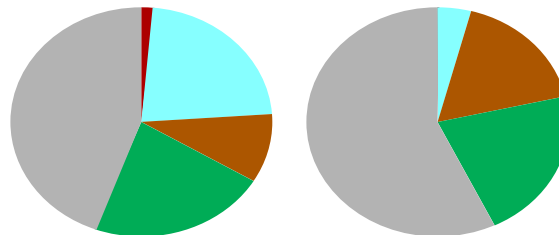


**Bar Charts Key**  
 ■ Week = 1  
 ■ Week = 12

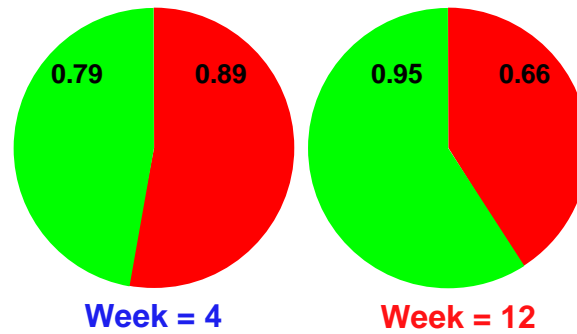
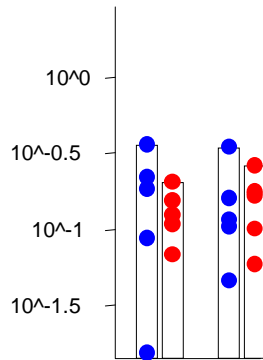


## CH06

VL 50 c/ml @ Week 12

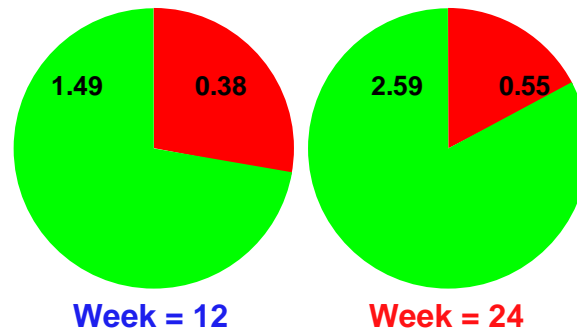
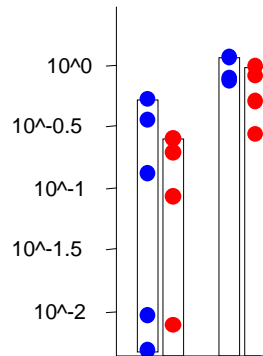


# IFN- $\gamma$ +/- Total CD8<sup>+</sup> Memory Poly-functional Responses and Virus Load

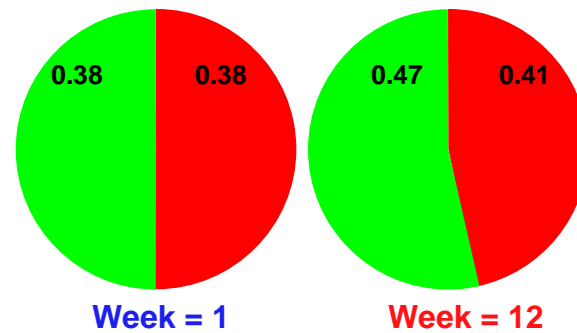
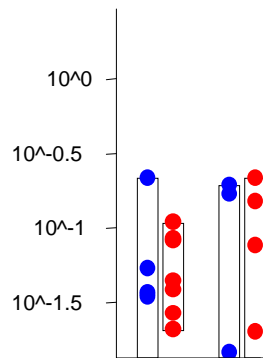


IFN- $\gamma$  Poly-functional  
Pie Charts Key  
IFN- $\gamma$  Pos  
IFN- $\gamma$  Neg

**CH40**  
Non Controller w/o HAART



**CH58**  
Controller w/o HAART

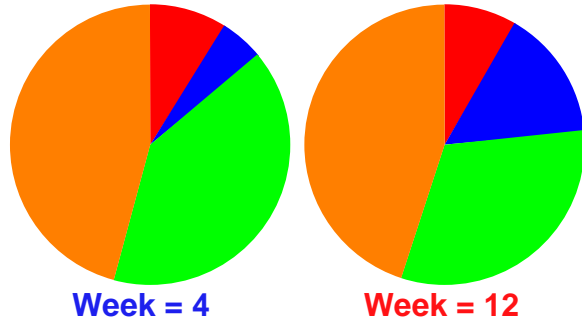
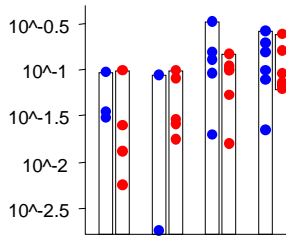


**CH06**  
Controller w HAART

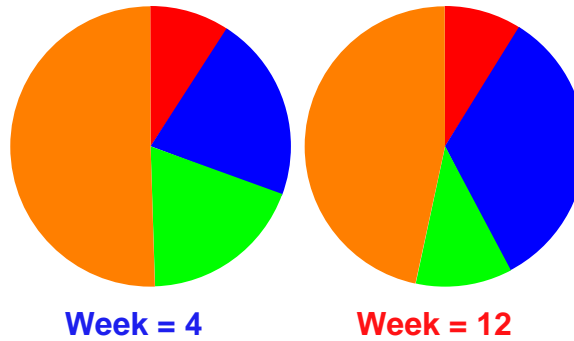
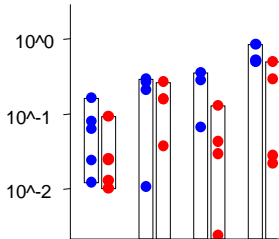
IFN $\gamma$  •  
Pies ■ ■

# IFN- $\gamma$ +/- Poly-functional Responses in Effector & Memory (CD57+/-) Subsets

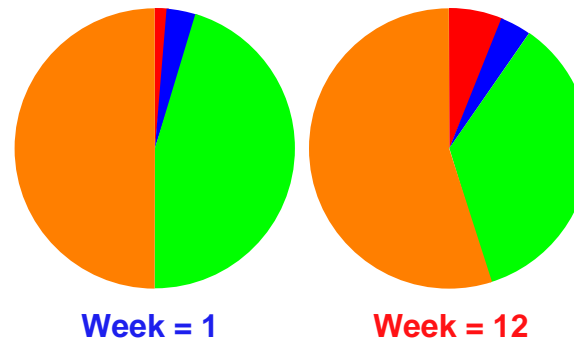
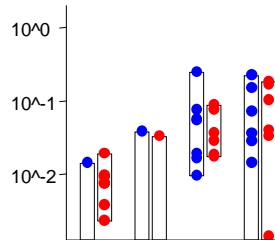
**Poly-functional Pie Charts Key**  
**IFN- $\gamma$ + Effector** (Red)  
**IFN- $\gamma$ - Effector** (Blue)  
**IFN- $\gamma$  + Memory** (Green)  
**IFN- $\gamma$ - Memory** (Orange)



**CH40**  
 Non Controller w/o HAART



**CH58**  
 Controller w/o HAART

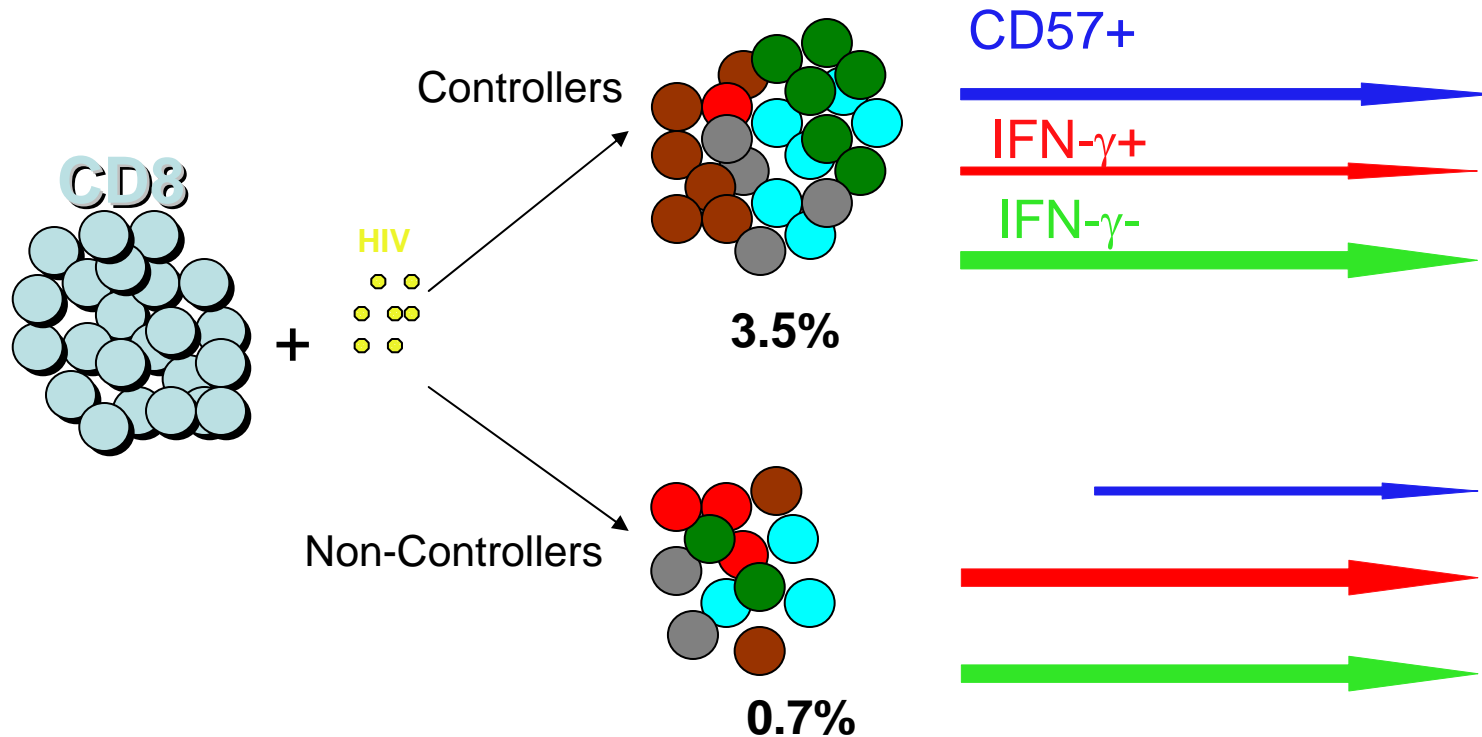


**CH06**  
 Controller w HAART

IFN $\gamma$   
 57  
 Pies    ■    ■    ■    ■

# Consequences of HIV infection

27+RO+ Memory



1. Lack of highly polyfunctional subsets in controller during acute infection (Low IL-2 and TNF- $\alpha$  subsets).
2. Mechanisms for control related to expansion of Effector subsets during AHI?
3. Could early responses in controllers better select for virus with reduced fitness?

# ACKNOWLEDGMENTS: CHAVI 001 T CELL STUDIES

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National Institute of Allergy and Infectious Diseases

