Early HIV-specific $CD8^+$ T cell responses in treated and untreated hyper acute HIV infection in the FRESH cohort

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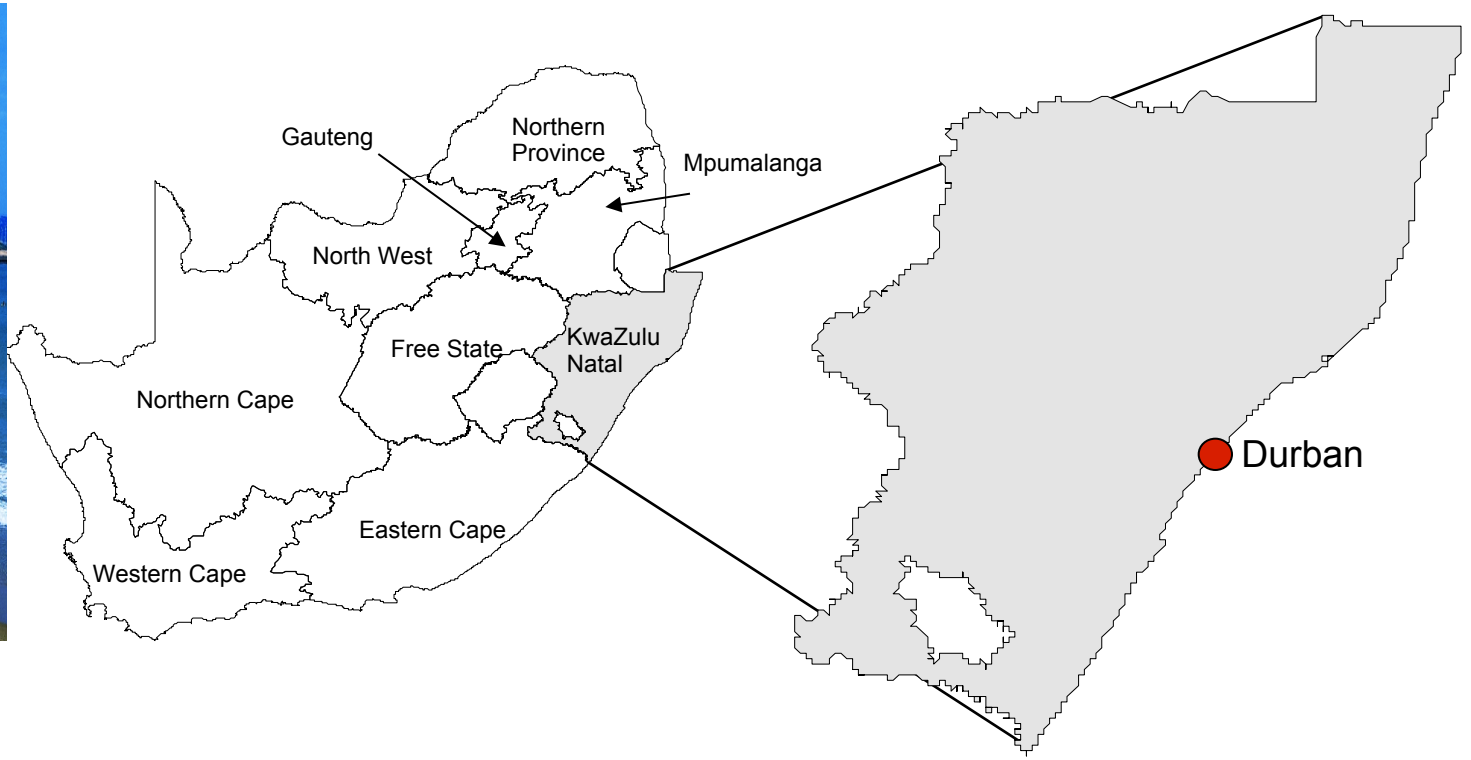
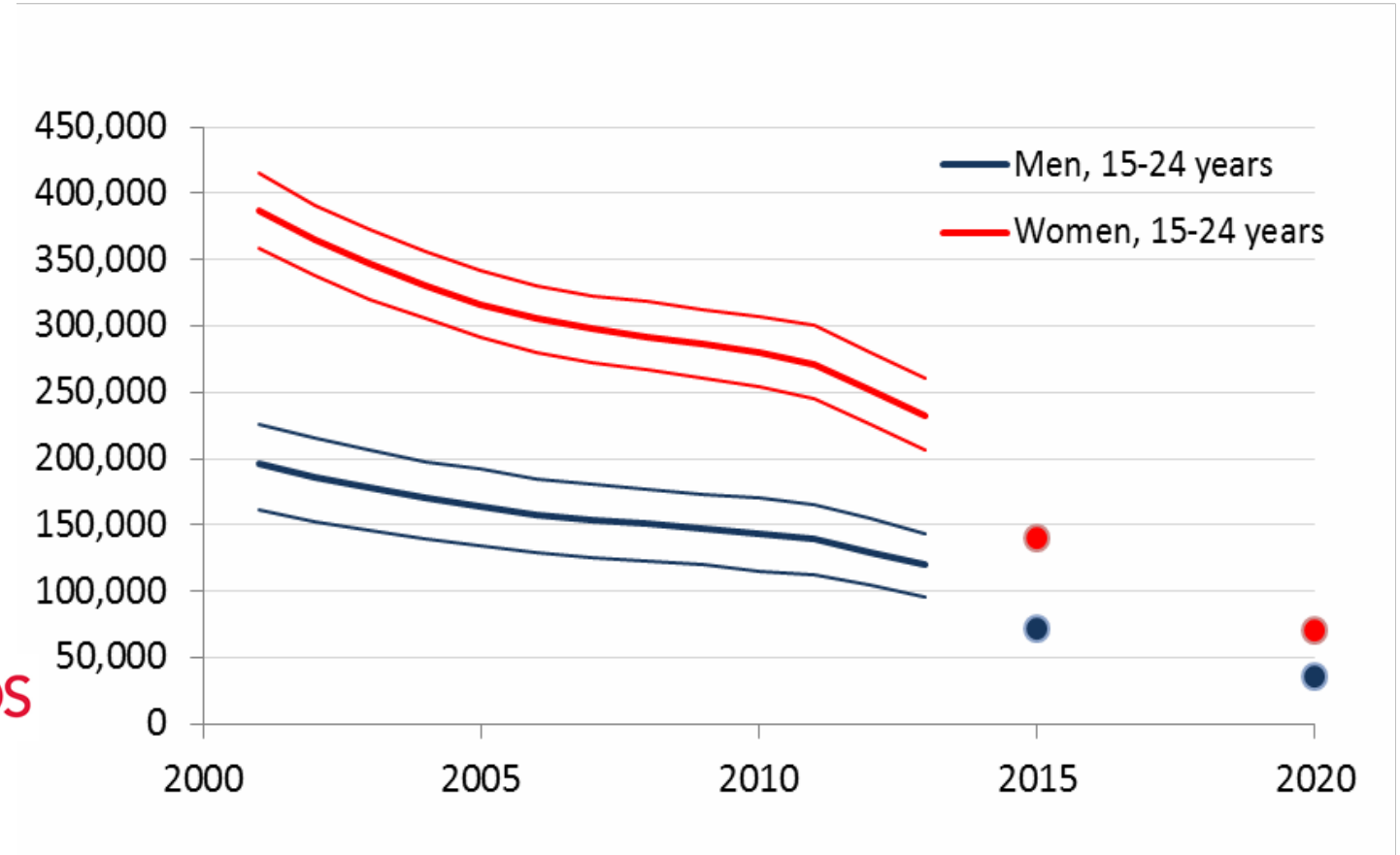
Outline

- HIV incidence in young women in KwaZulu-Natal and in sub-Saharan Africa
- The FRESH cohort- a unique cohort to address gaps in HIV prevention, pathogenesis and cure research
- Insights on early CD8 and CD4 T cell responses during untreated and treated hyperacute HIV infection
- Implications for HIV prevention and cure strategies in resource-limited settings

KwaZulu-Natal and Durban, South Africa

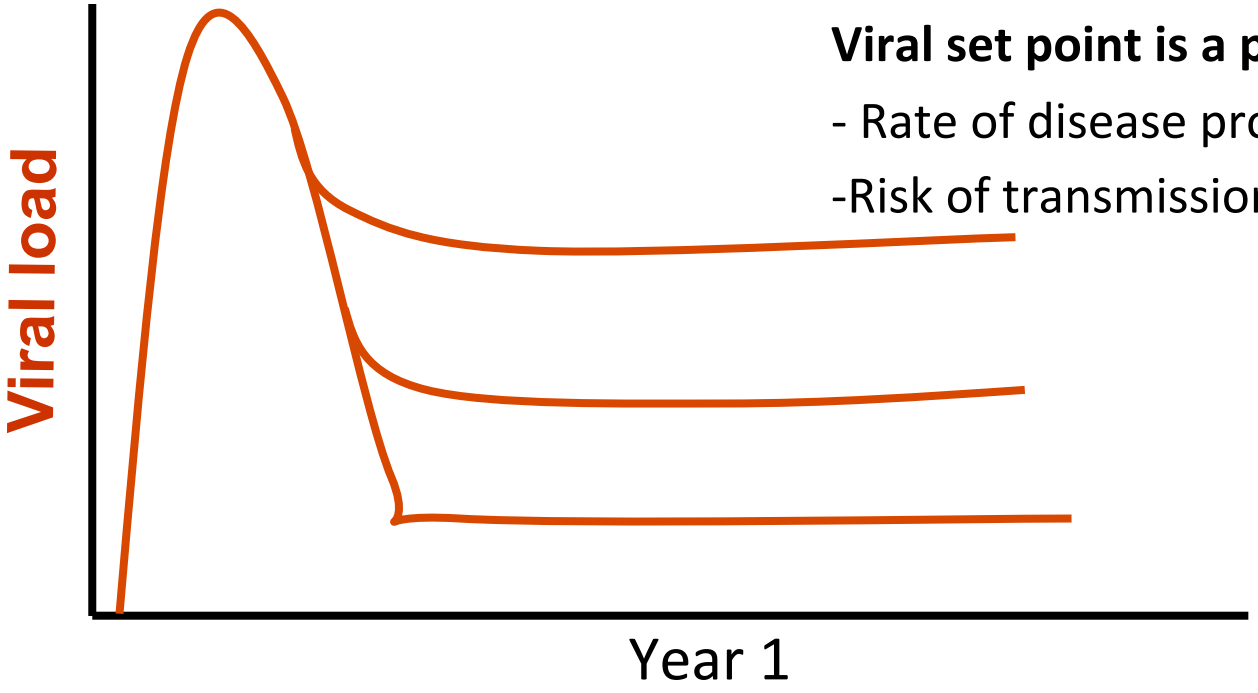


Eastern and southern Africa: high new HIV infections among young women aged 15-24 years



- There is a need to better understand the reasons for high incidence among young women
- Current strategies are suboptimal- new biomedical interventions such as vaccines are needed

Acute HIV-1 infection- what lessons can we learn?



Viral set point is a predictor for:

- Rate of disease progression

-Risk of transmission

Key questions:

- What behavioural, socioeconomic and biomedical factors are responsible for such high incidence among young women?
- What is the nature of the transmitted/founder virus?
- What do immune responses in acute HIV-1 infection look like and why do they ultimately fail in most cases?

FRESH study cohort

- **FRESH**: **F**emales **R**ising through **E**ducation, **S**upport and **H**ealth
- Recruit women 18 to 23 at very high risk of HIV infection
- **Objectives**

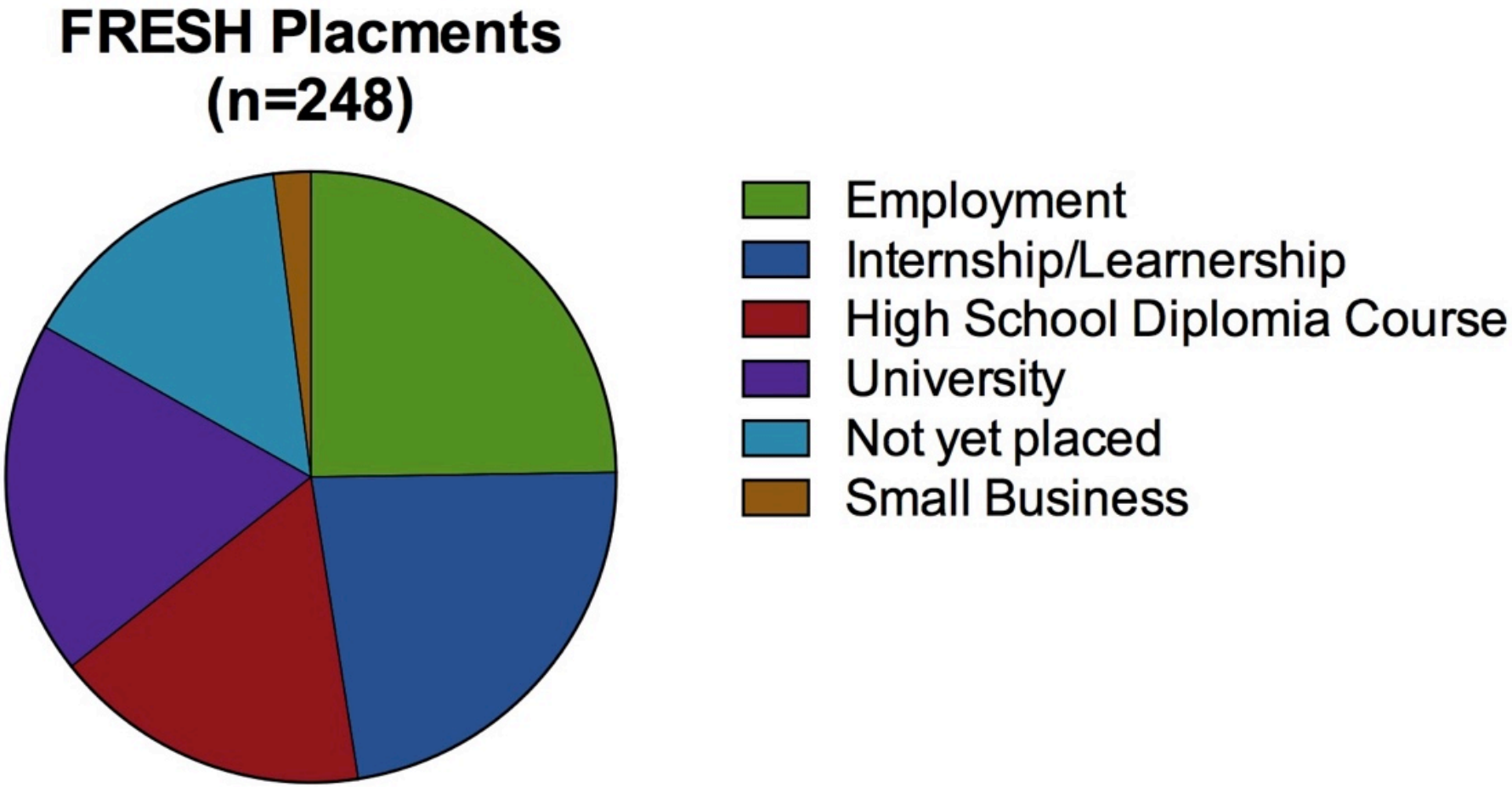
1. Provide an intensive empowerment, life-skills and job readiness curriculum.
2. Identify persons in the earliest stages of acute infection.
   - Study antiviral immune mechanisms

Study setup and sample collection

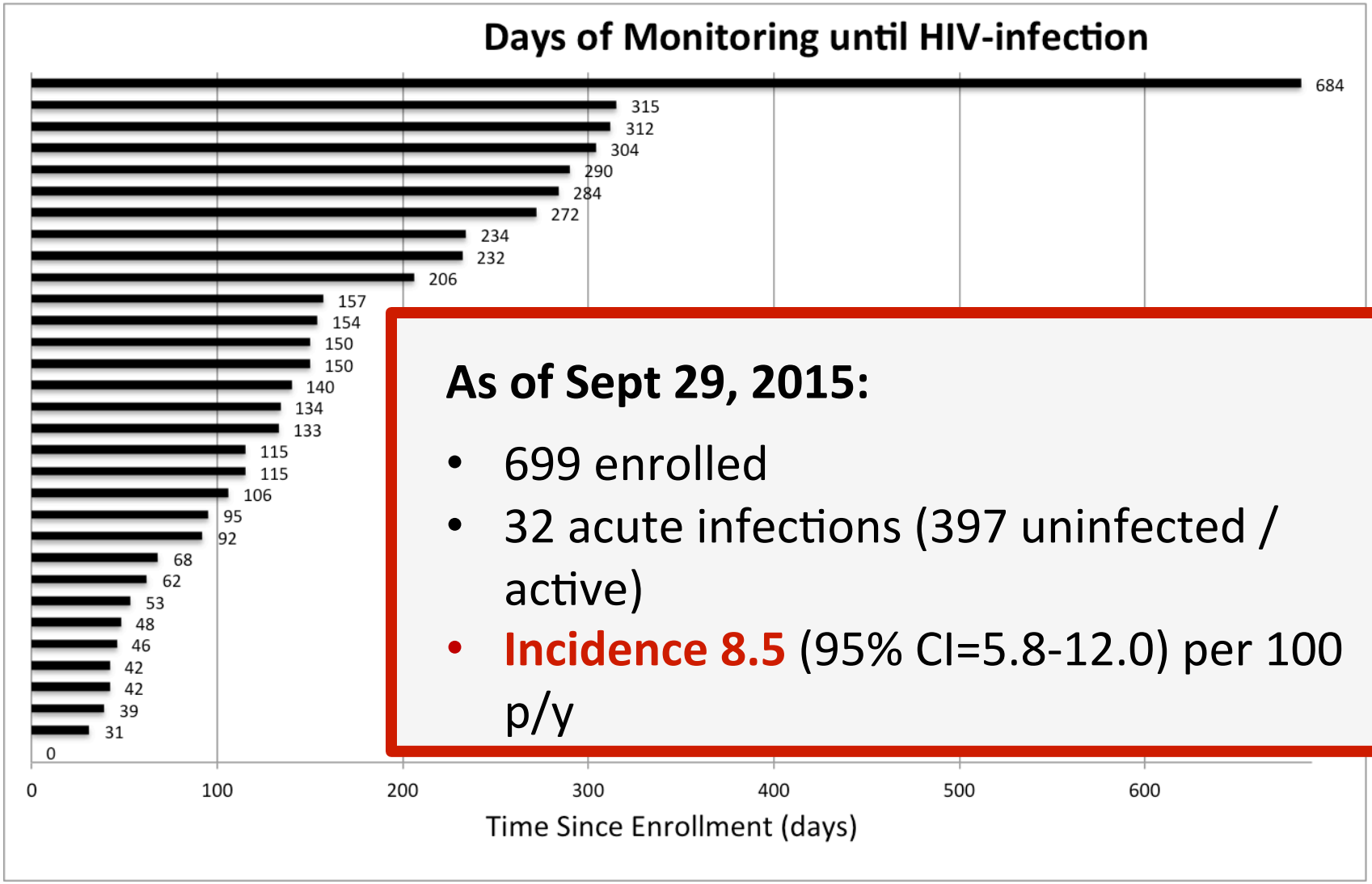
- Phase I: Surveillance
  - Twice weekly HIV RNA PCR testing via finger stick blood draws
  - Quarterly blood and mucosal sampling of the female genital tract
- Phase II: Acute Infection

WEEK	0	1	2	3	4	6	8	12	24	36	48	100	152
PBMC Plasma	X	X	X	X	X	X	X	X	X	X	X	X	X
SWABS CVL Cytobrush	X	X	X	X	X	X	X	X	X		X	X	X

Empowerment Program



Acute infections detected (N=32)

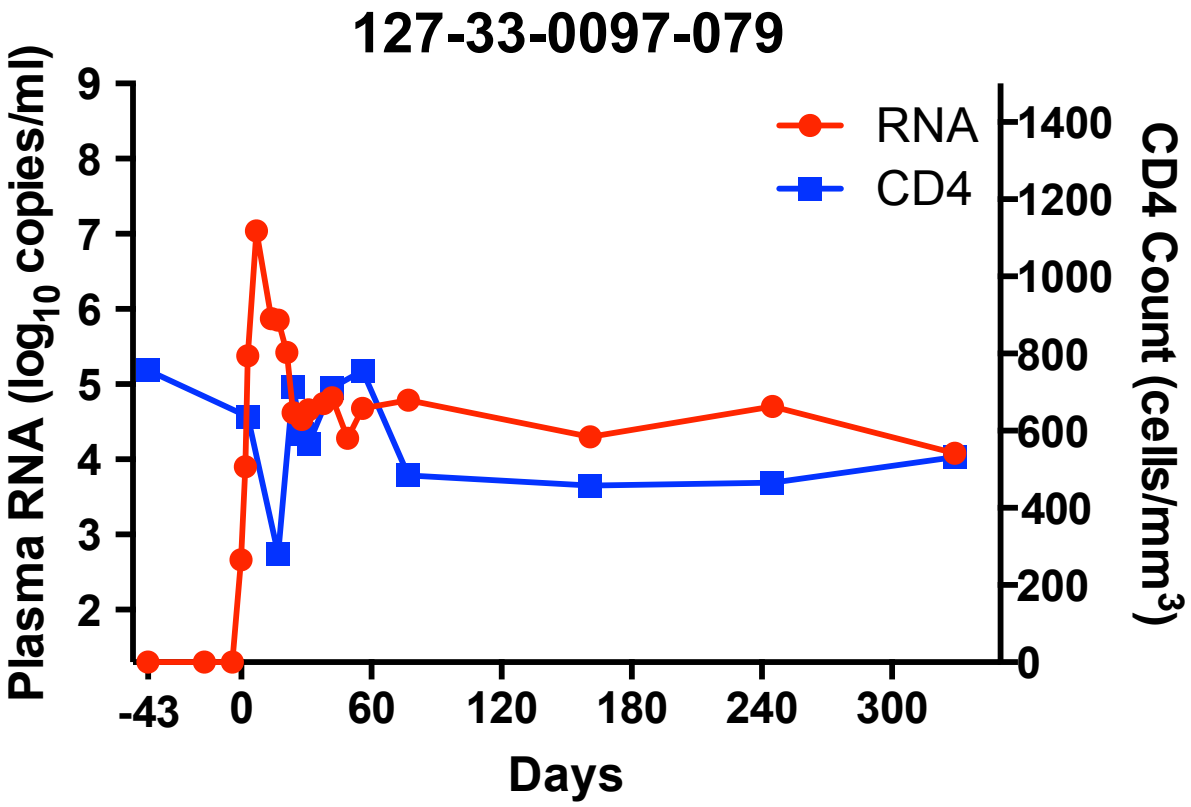


As of Sept 29, 2015:

- 699 enrolled
- 32 acute infections (397 uninfected / active)
- **Incidence 8.5** (95% CI=5.8-12.0) per 100 p/y

- Median: 124 days; range 0-684

Viral and cellular dynamics in hyperacute HIV infection



FRESH studies

- The FRESH study design allows us to address critical questions in:
- HIV prevention research-
- Risk factors for HIV acquisition (Anahtar et al, 2015, *Immunity*) (Byrne, Anahtar et al, *Lancet ID*, in press)
- Innate immune responses (Kløverpris et al, 2016, *Immunity*
- Early B cell responses
- **Early CD8 T cell responses (Ndhlovu et al, 2015, Immunity**

Dynamics of T cell responses in primary HIV infection: experimental approach

Study subjects- 12 FRESH seroconverters

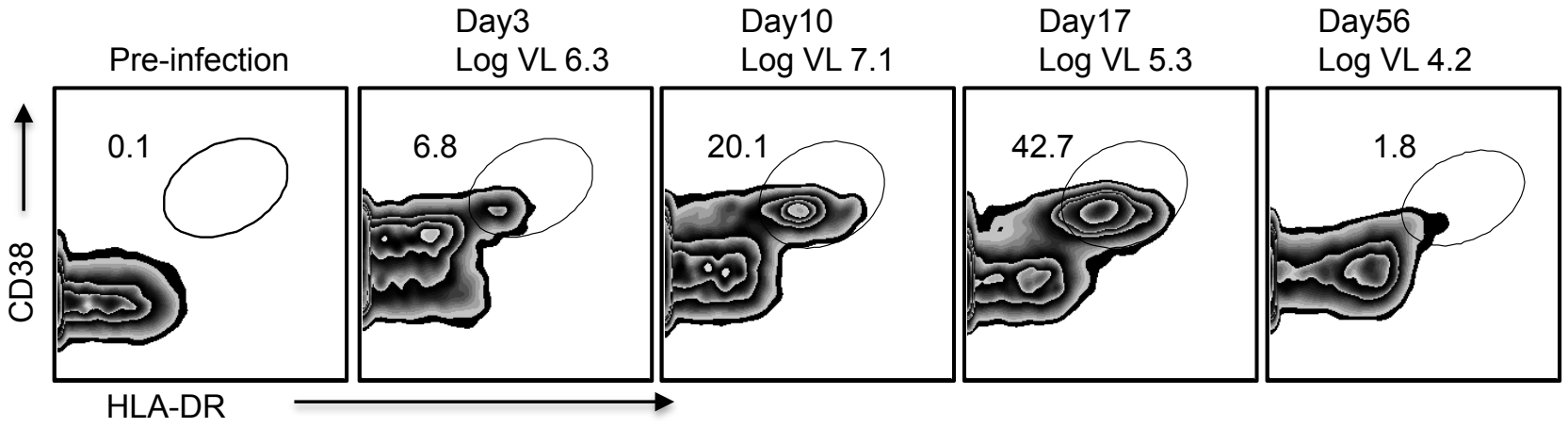
Longitudinal analysis of HIV induced T cell responses

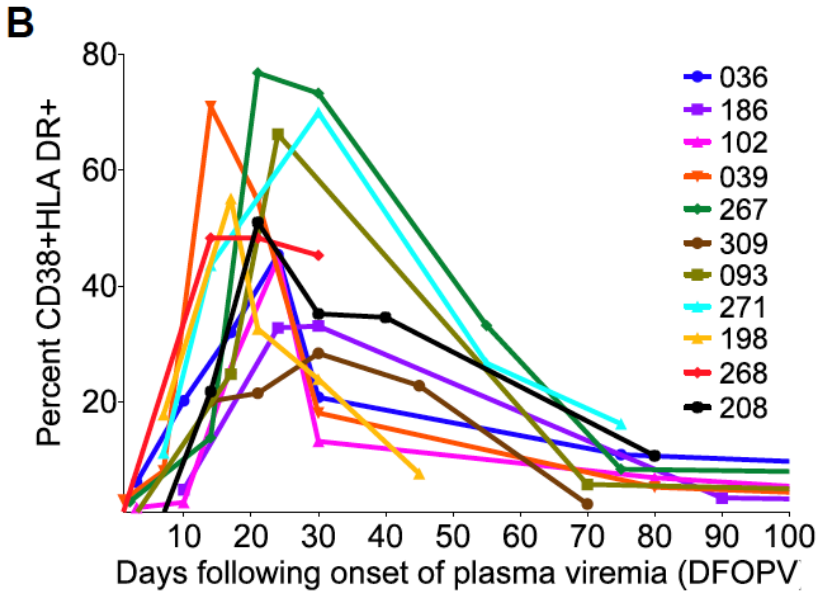
Recently activated T cells (CD38+, HLA-DR+)

Recently stimulated cycling T cells (Ki67+, Bcl-2 negative)

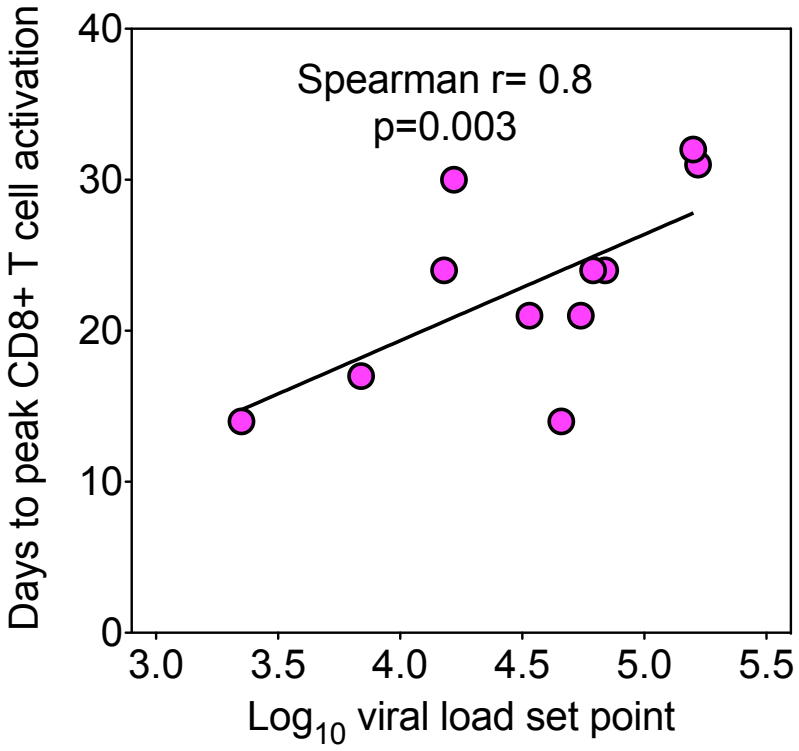
HIV antigen-specific T cells (Elispot, ICS and tetramer)

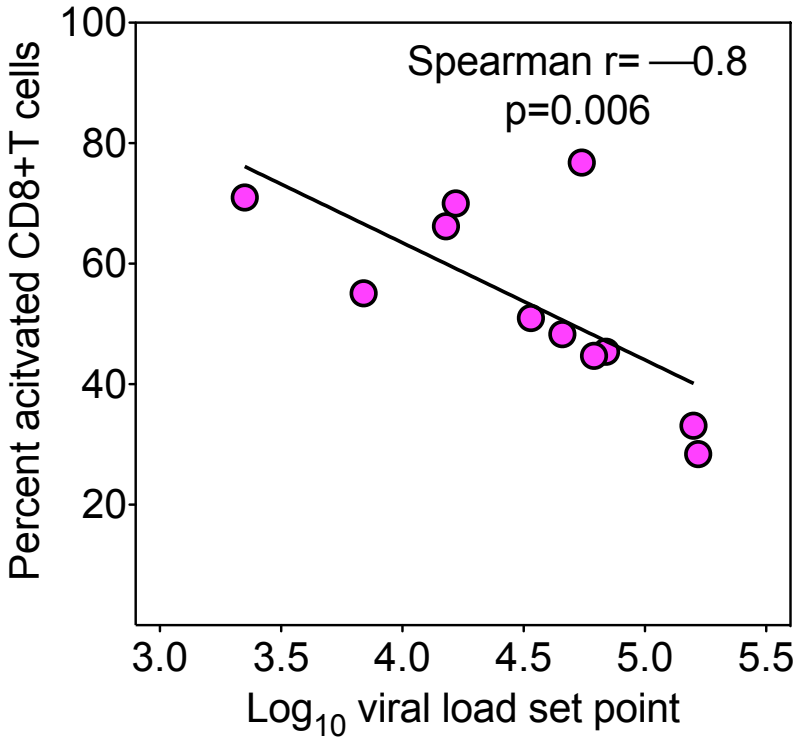
HIV infection induces massive activation (CD38+HLA-DR+) of CD8+ T cells



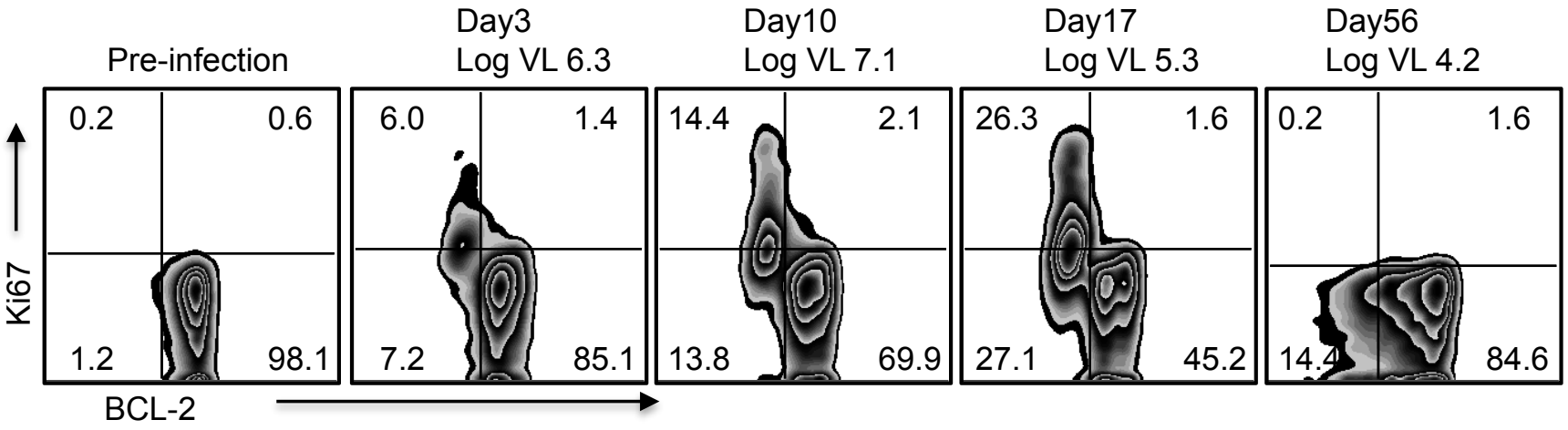


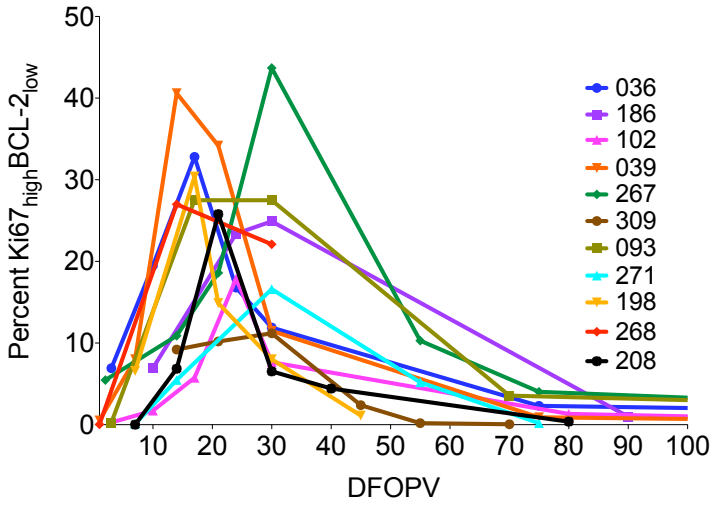
The timing and strength of the initial CD8+ T cell responses impact viral load set point

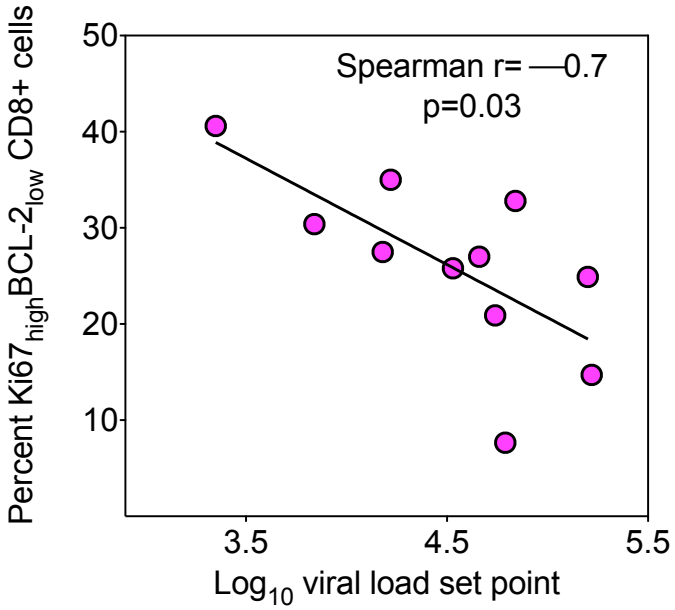




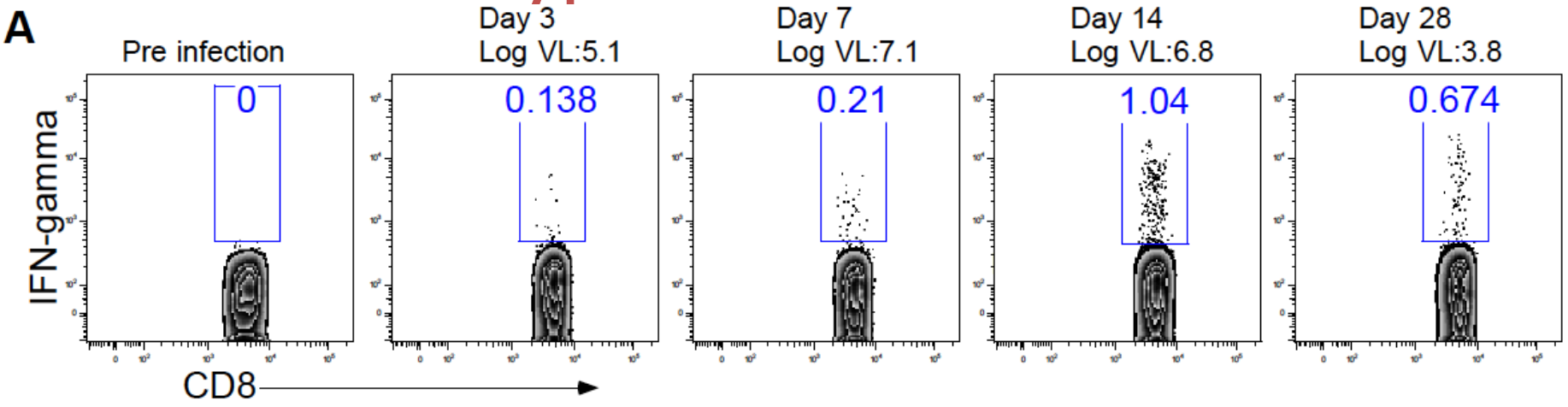
Hyperacute CD8+ T cells are highly proliferative and pro-apoptotic (Ki67+BCL2low)

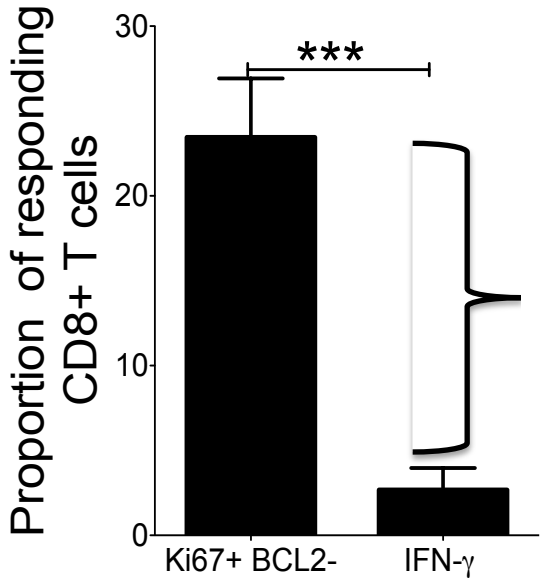






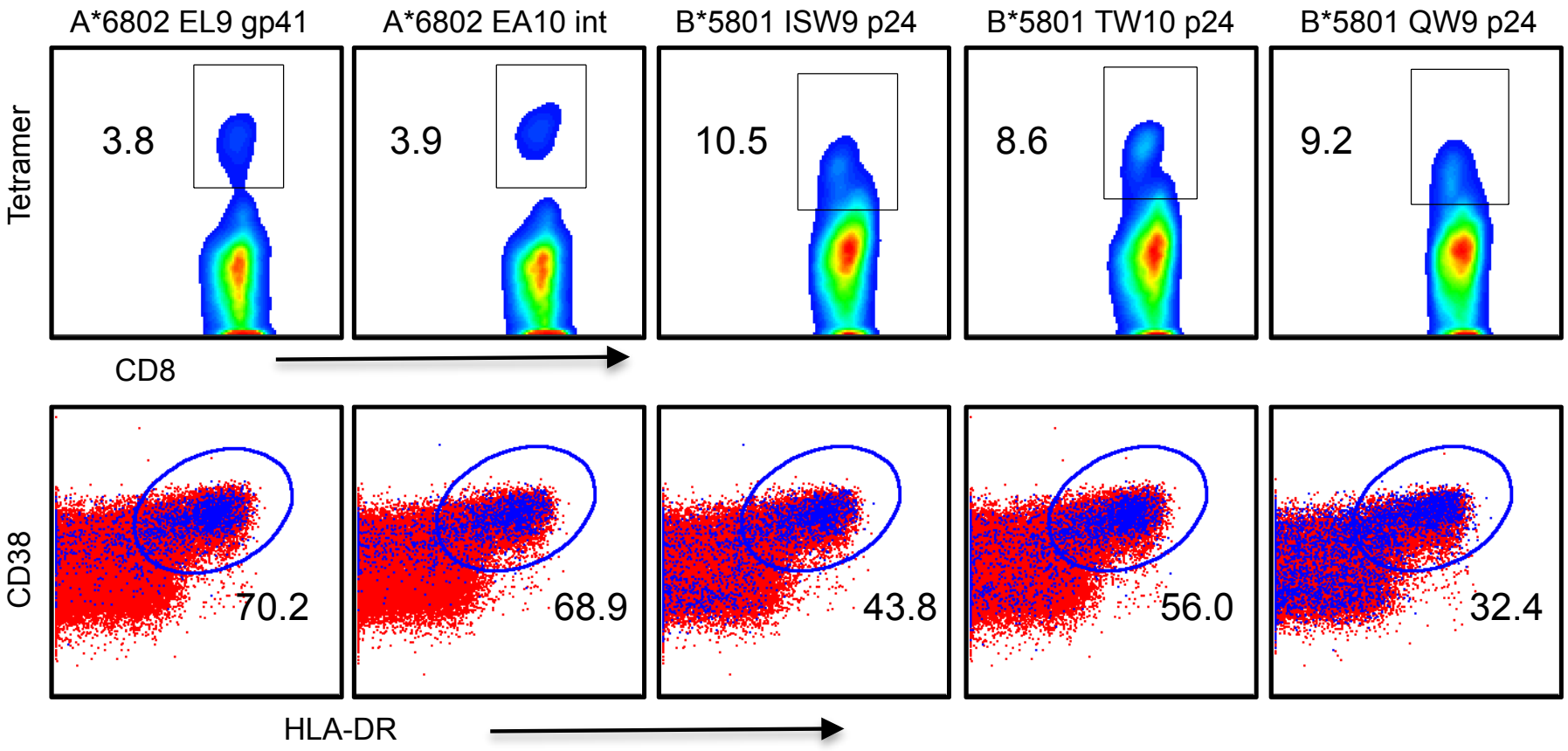
Paucity of IFN-γ production in hyperacute infection



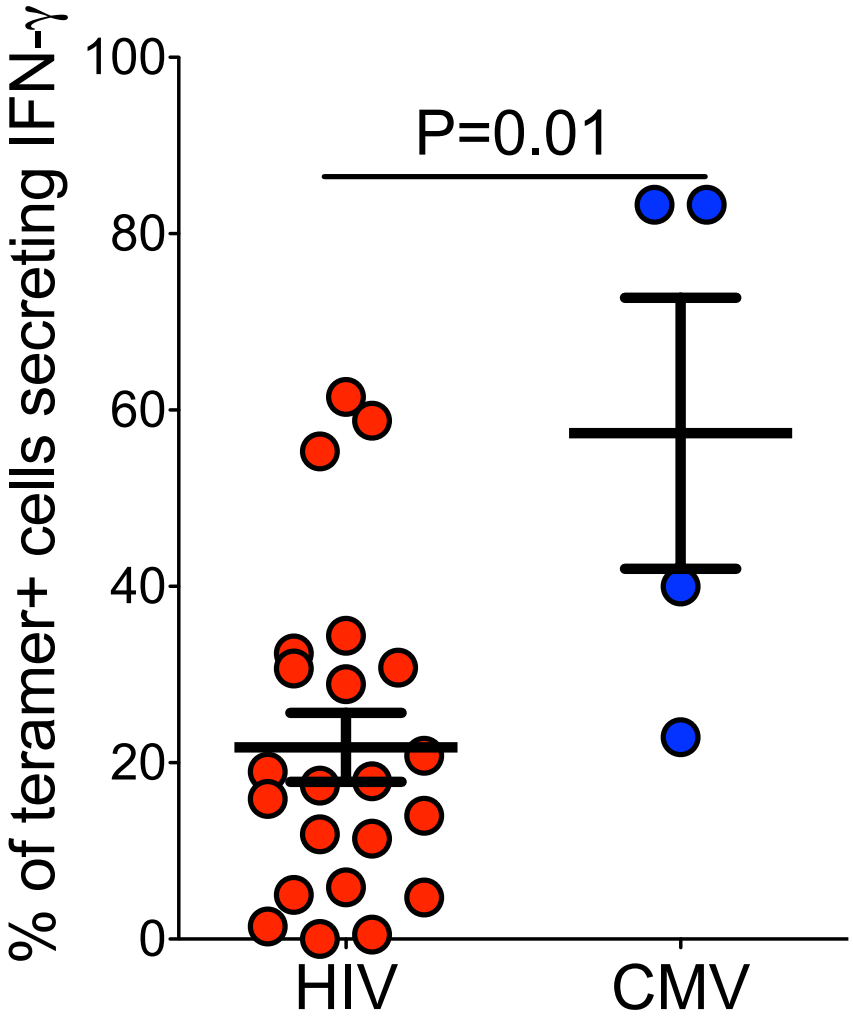


HIV-specific?

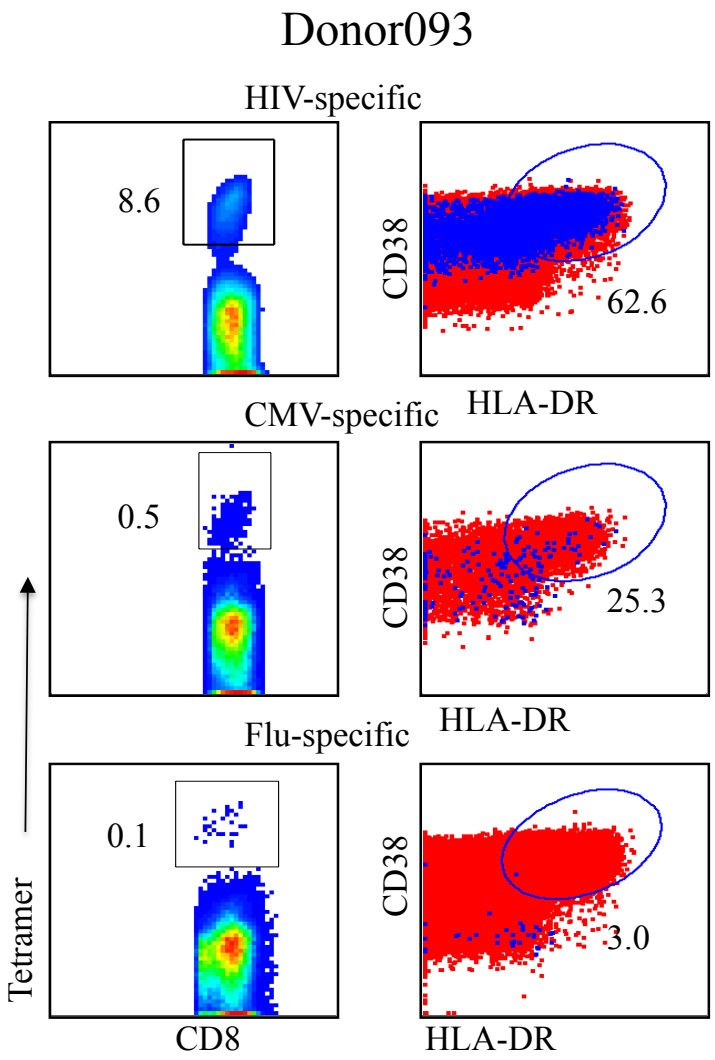
Tetramer staining CD8+ T cells at peak activation

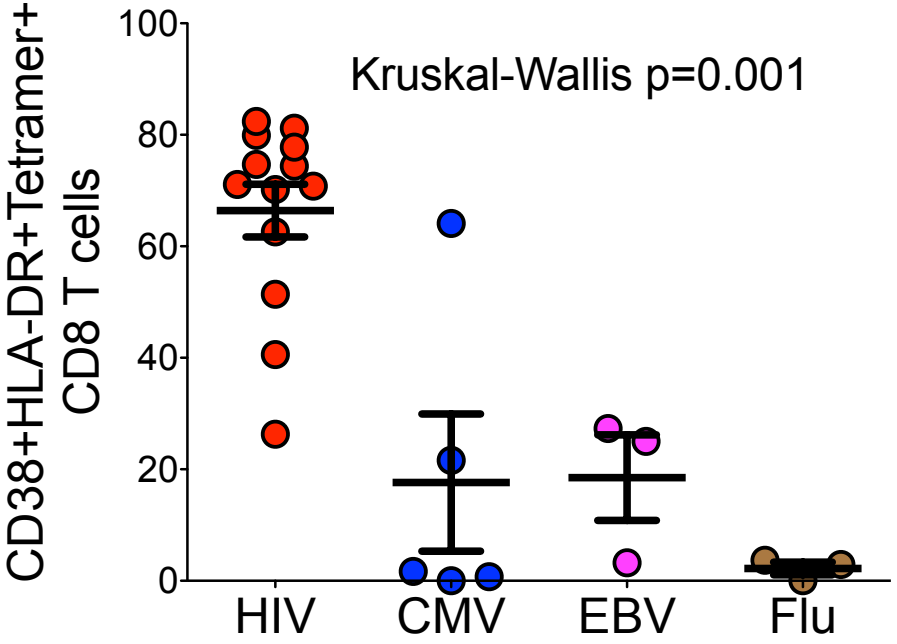


HIV specific CD8 T cells are defective in IFN-gamma secretion during acute HIV infection

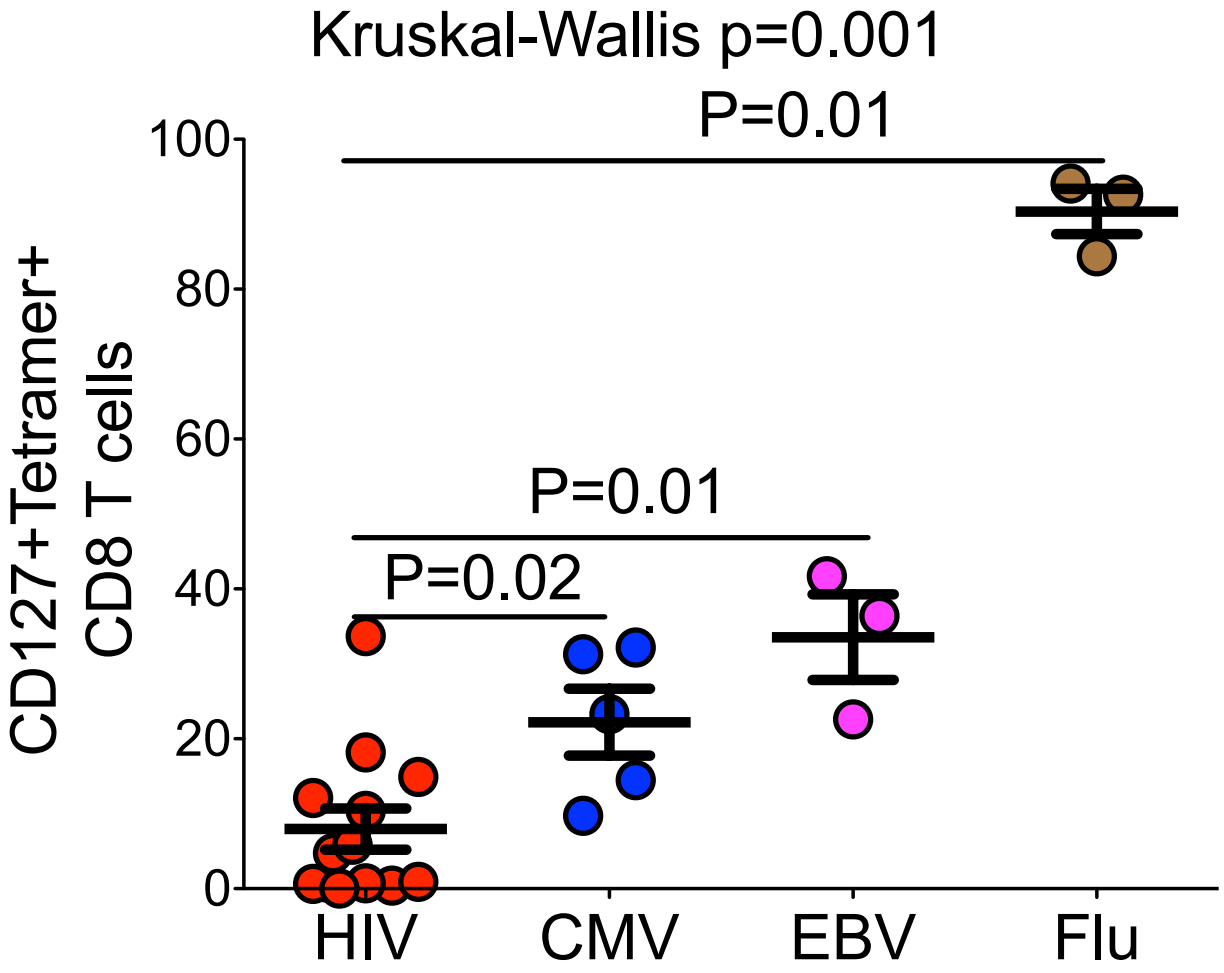


Assessment of bystander activation during hyperacute HIV infection

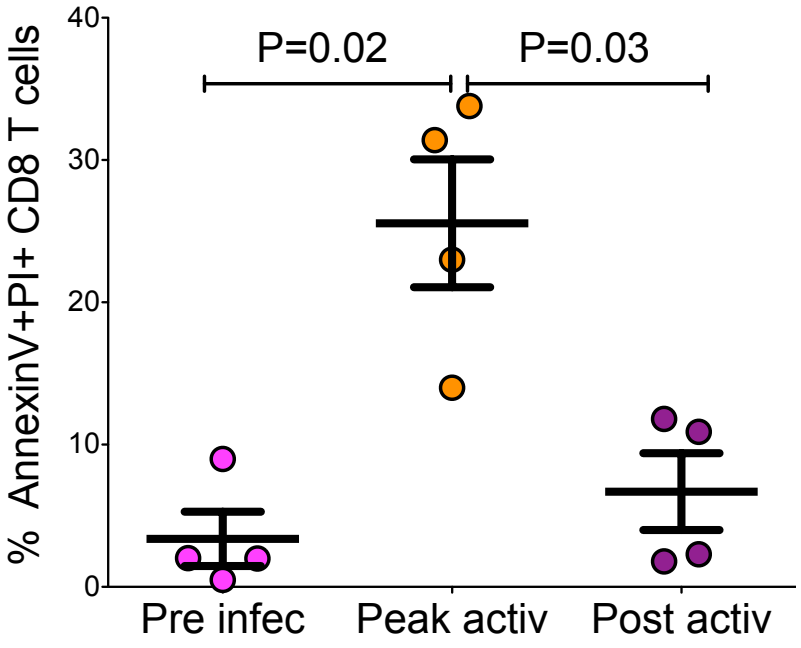


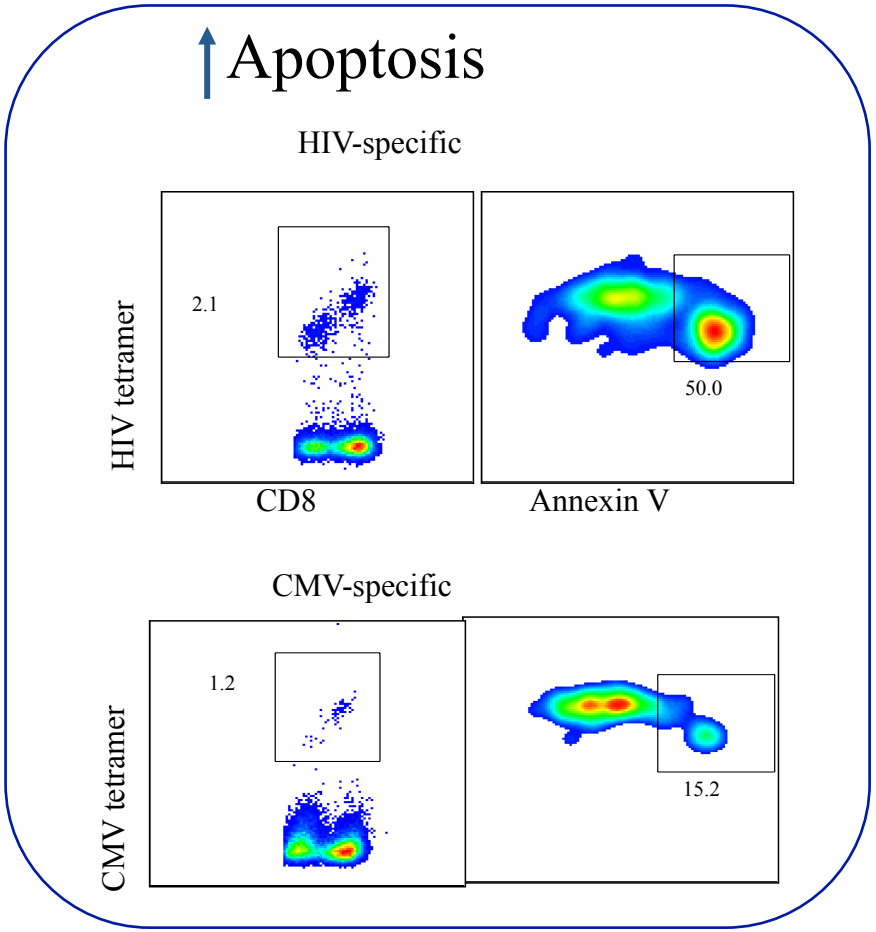


HIV-specific CD8 T cells fail to upregulate survival molecules during acute HIV infection



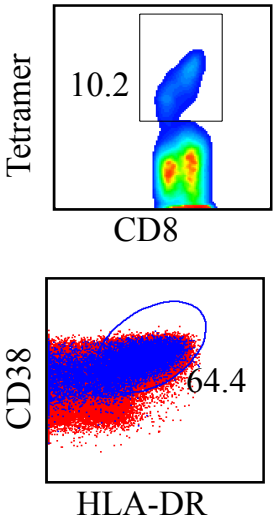
Marked apoptosis of HIV-specific CD8 T cells during hyperacute HIV infection



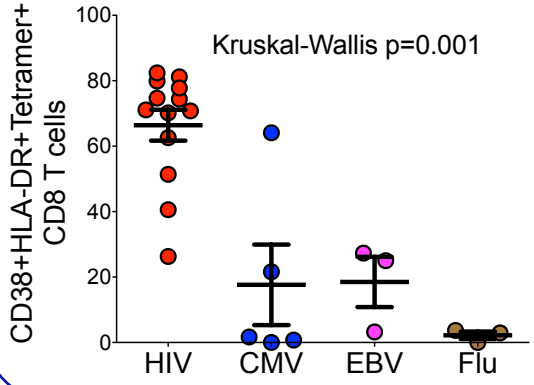


CD8 responses in hyperacute HIV Infection

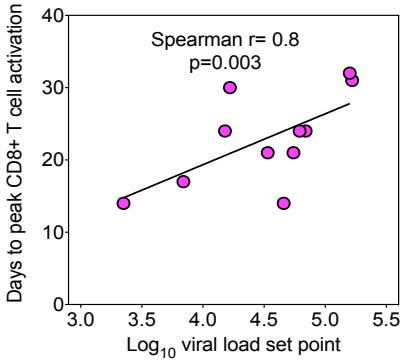
Activation

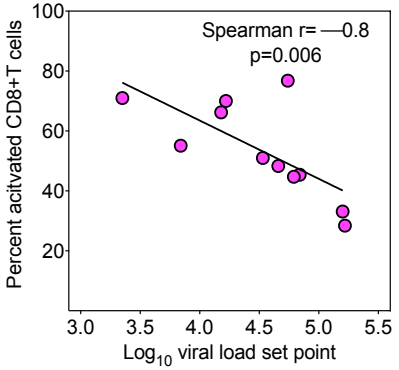


Bystander Activation

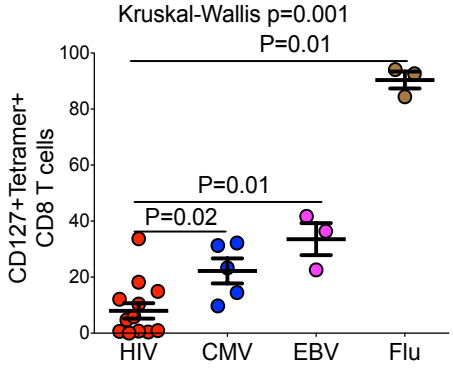


Impact on viral replication

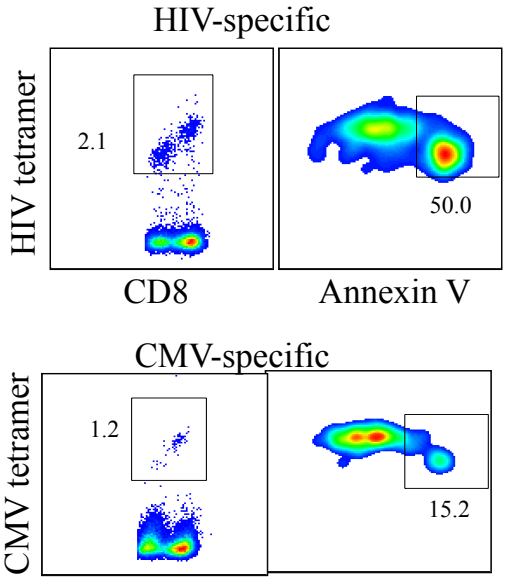




Poor survival



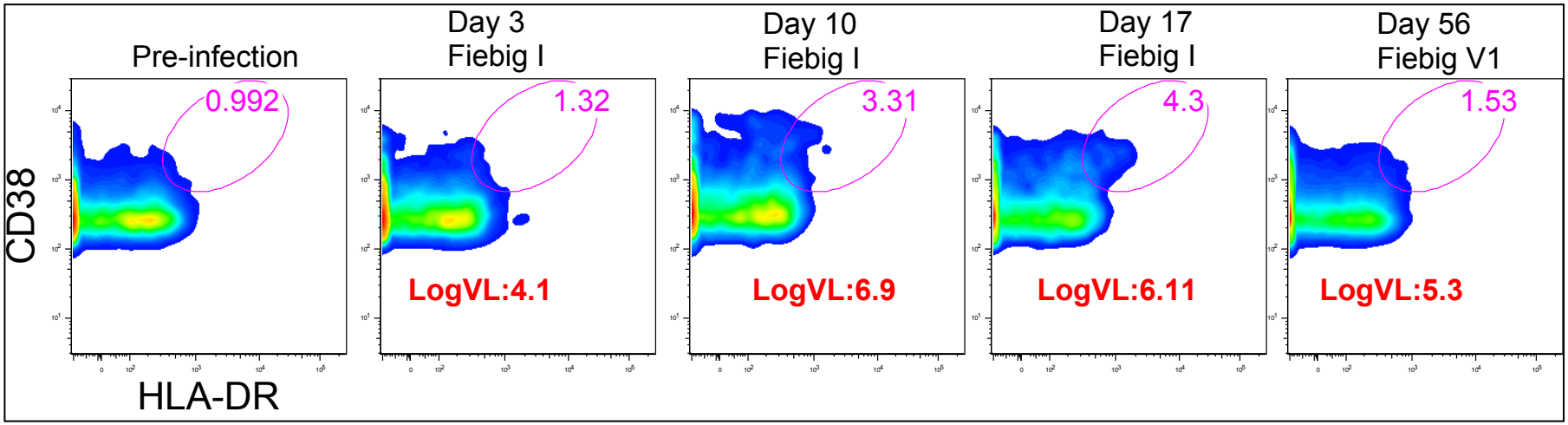
Apoptosis

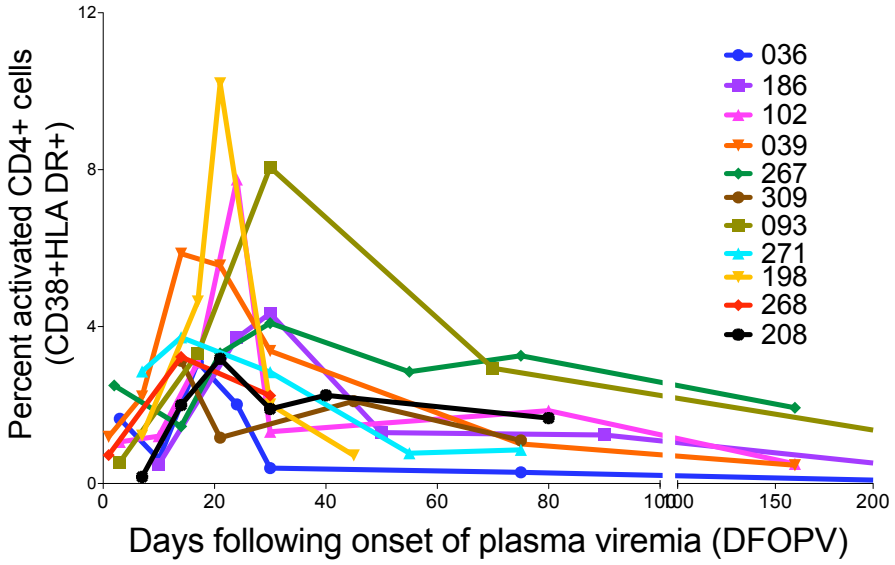


Ndhlovu et al Immunity 2015

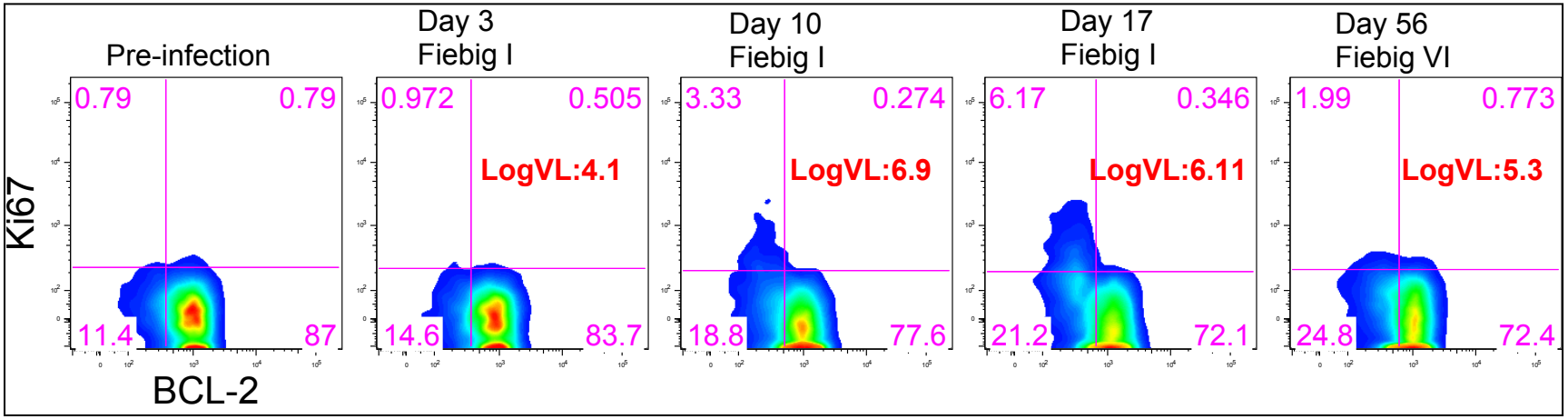
CD4 T cell responses in hyperacute HIV infection

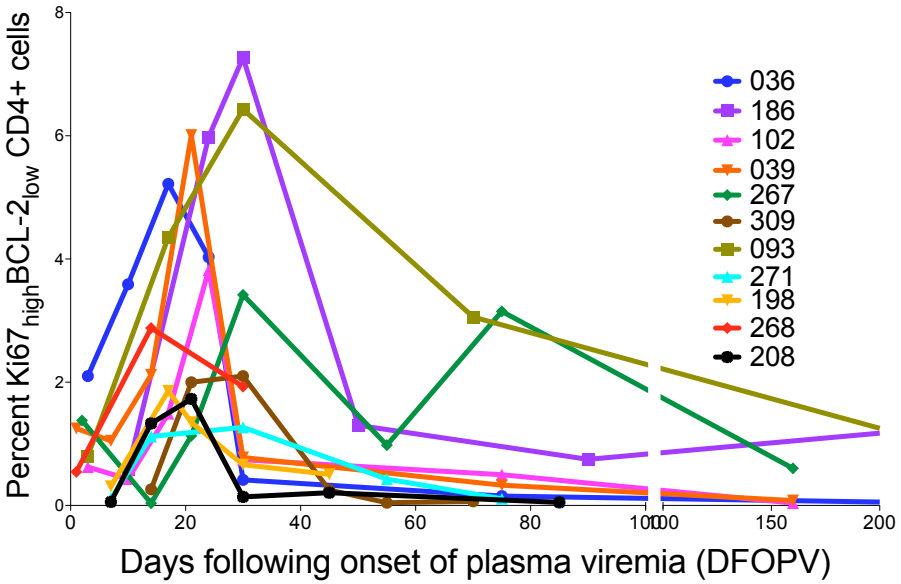
CD4+ T cell activation during acute HIV infection



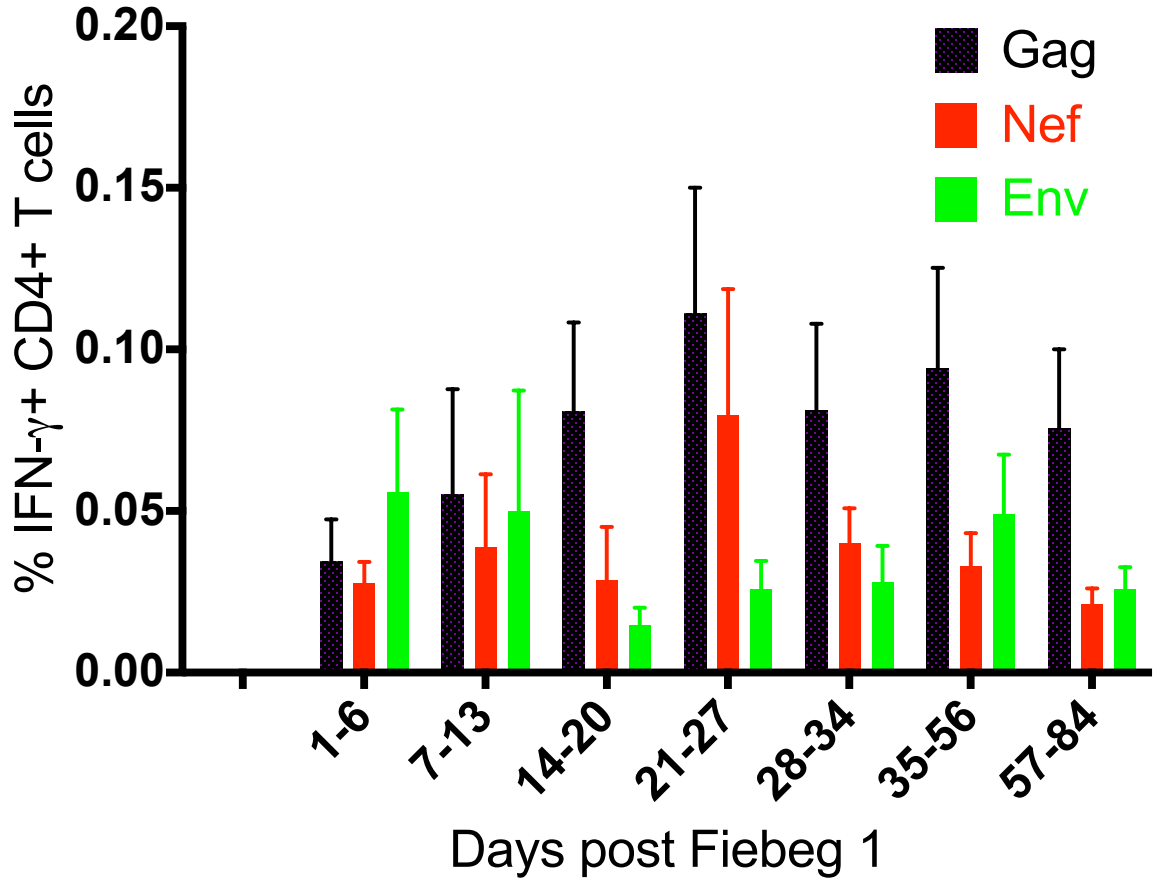


CD4+ T proliferation during hyperacute HIV infection

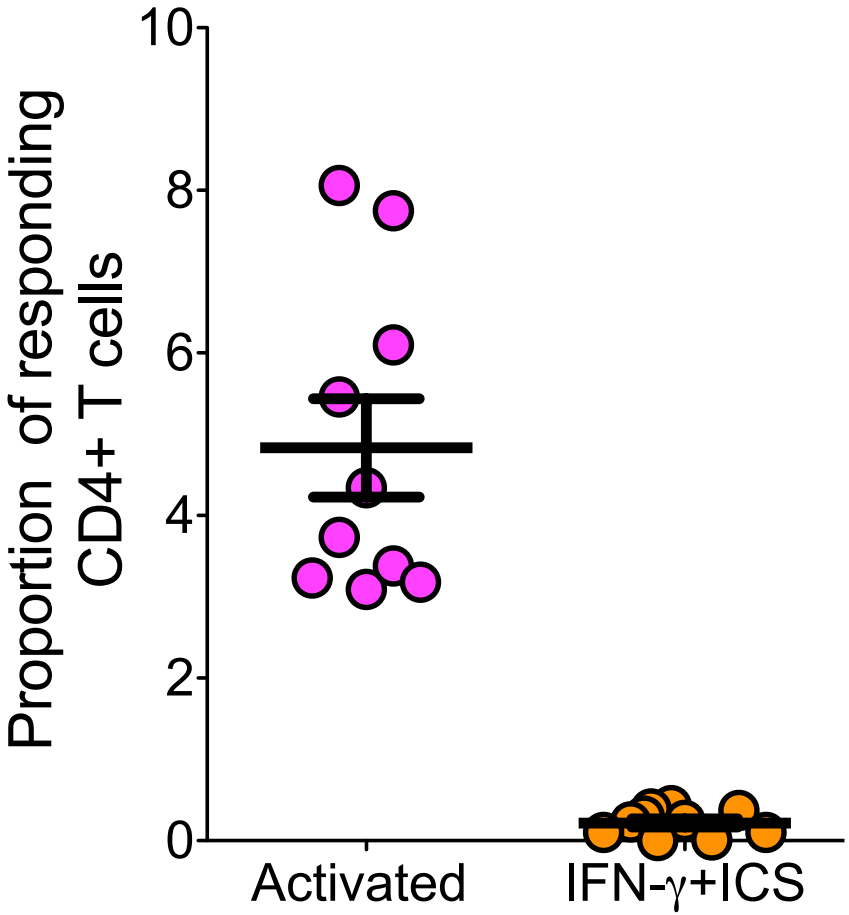




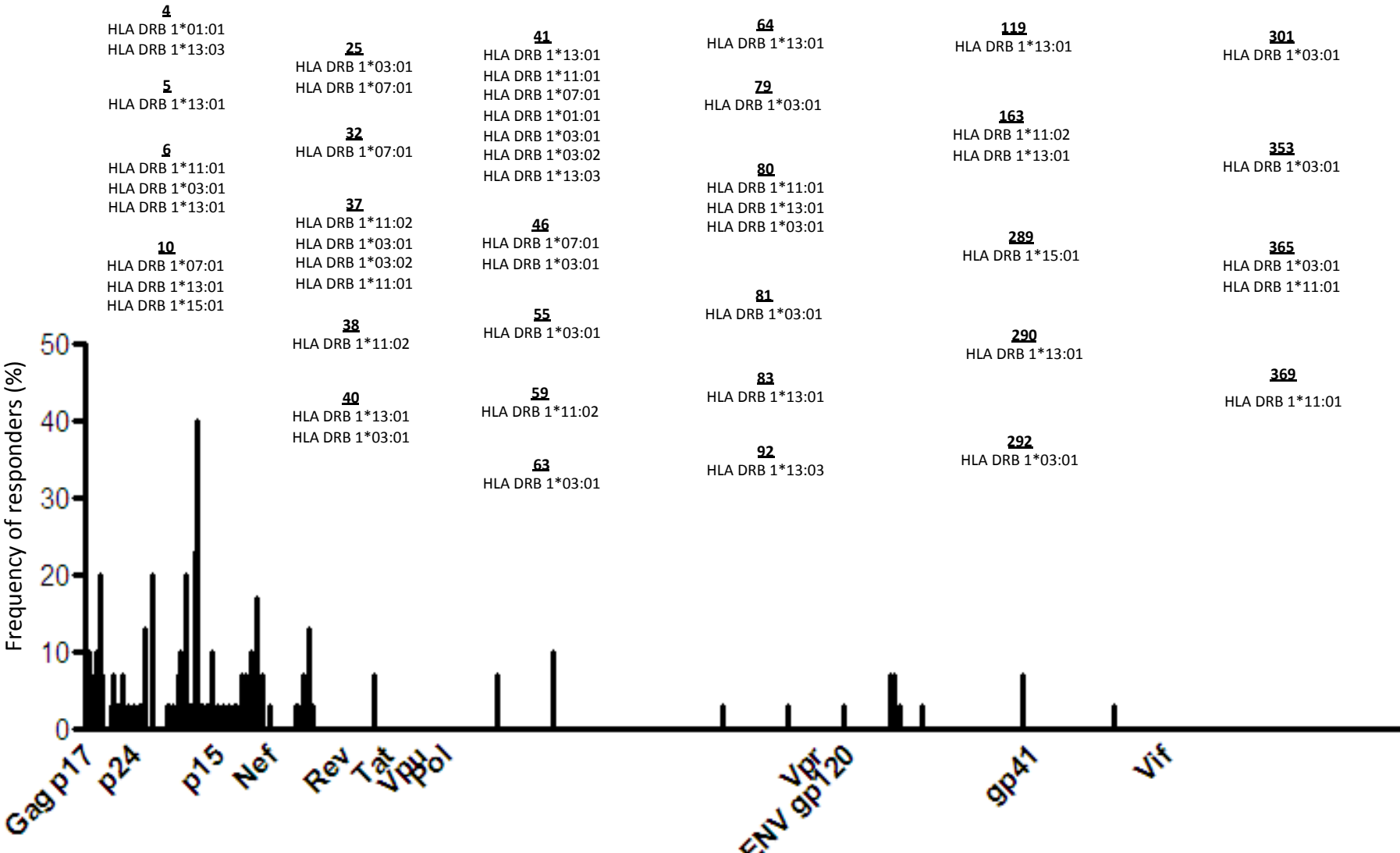
Dynamics of HIV-specific CD4+ T cell responses during acute HIV infection



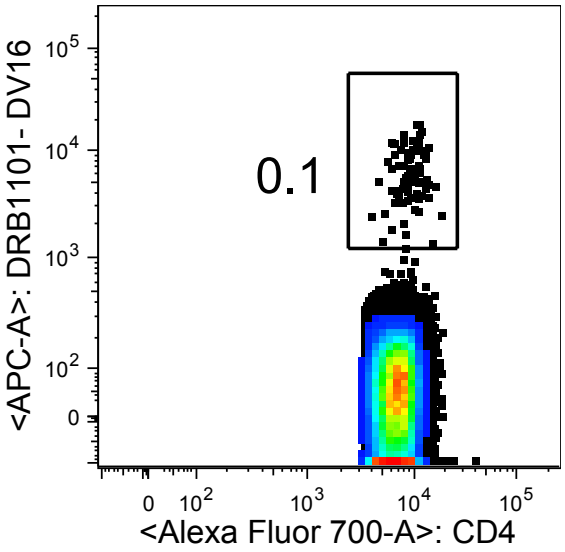
Comparison between activated CD4+ T cells and gamma secreting cells

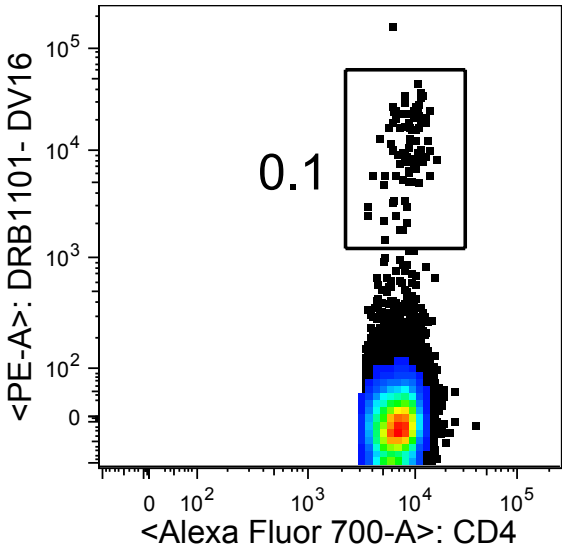


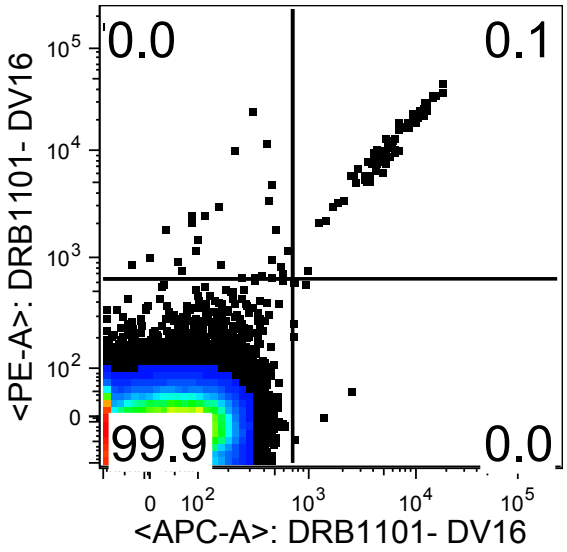
Number of HLA-DRB1 variants that can present each peptide



Class II tetramer staining

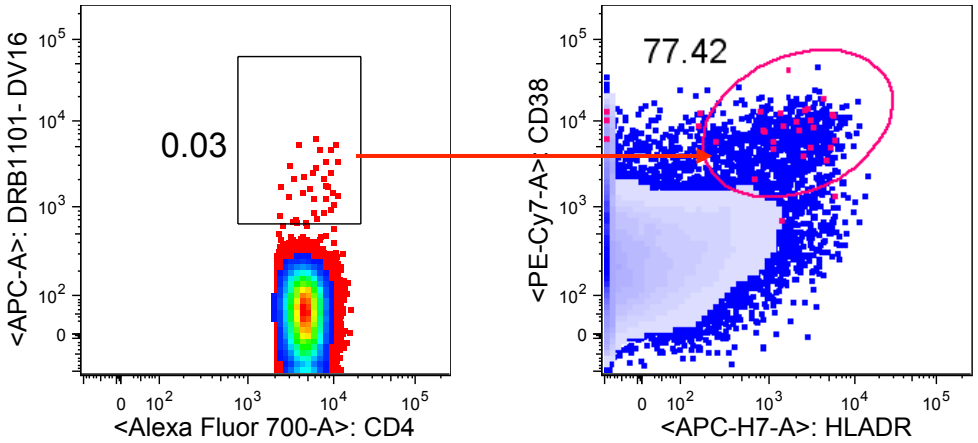




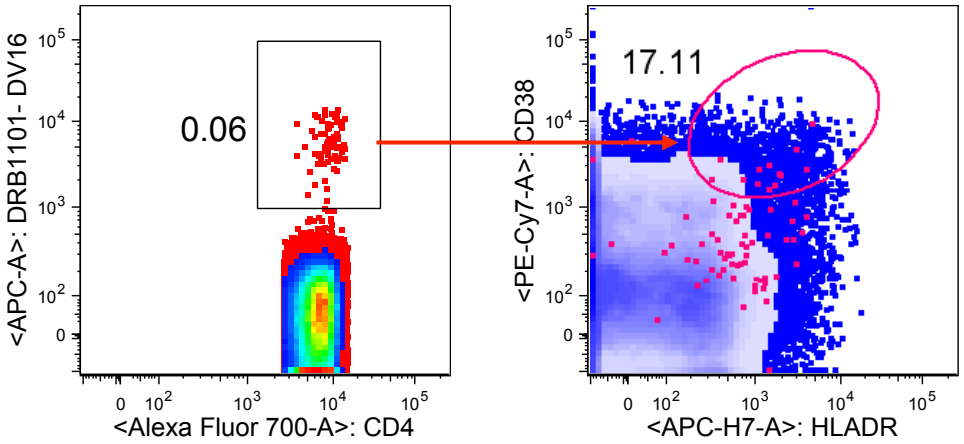


Activation profile of HIV-specific CD4 T cells

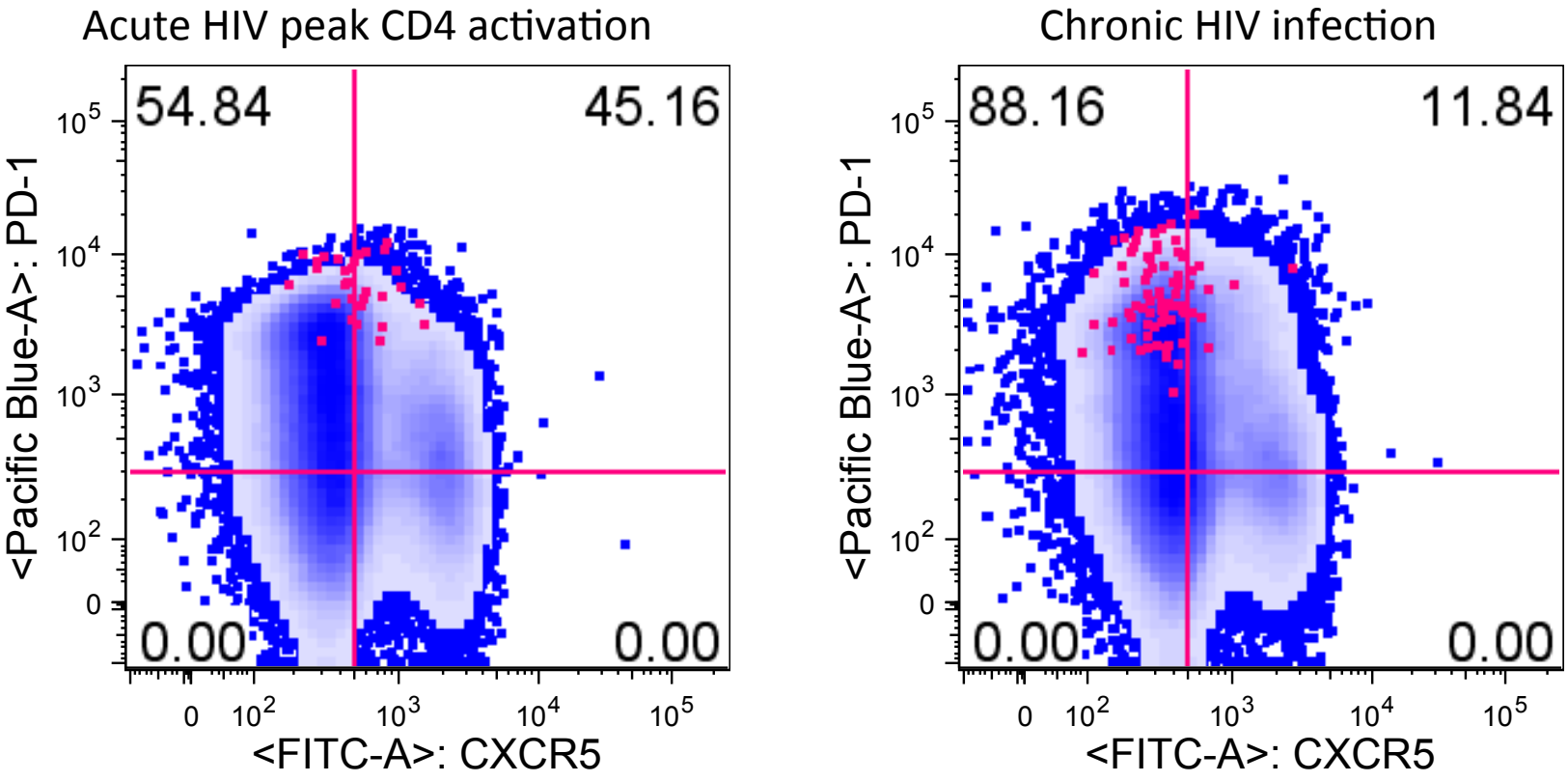
Acute HIV



Chronic HIV



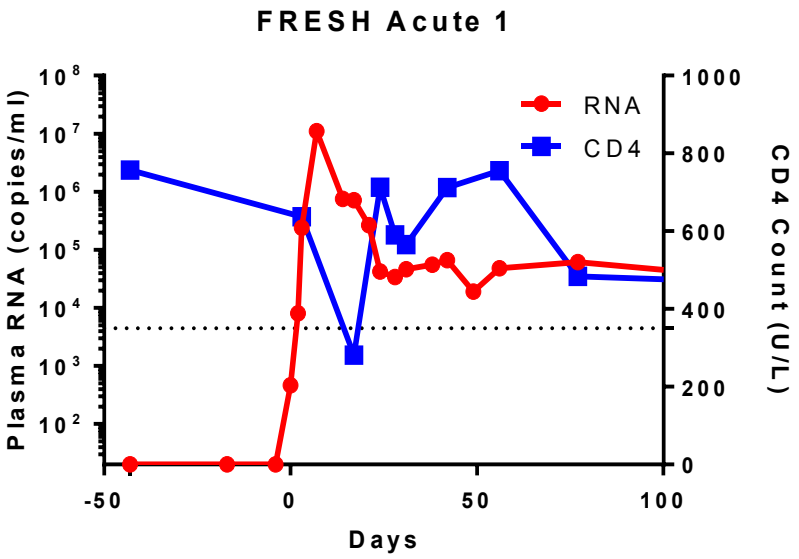
Phenotypic profile of HIV-specific $CD4^+$ T cells in acute and chronic HIV infection

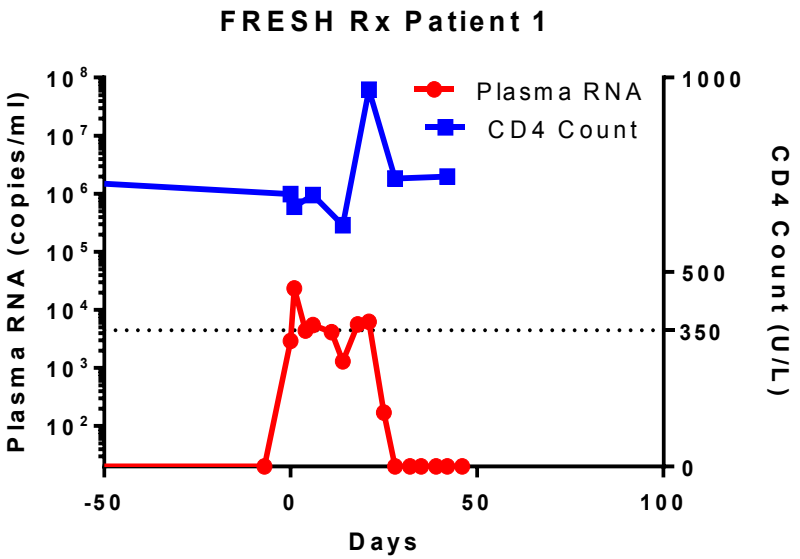


Conclusions

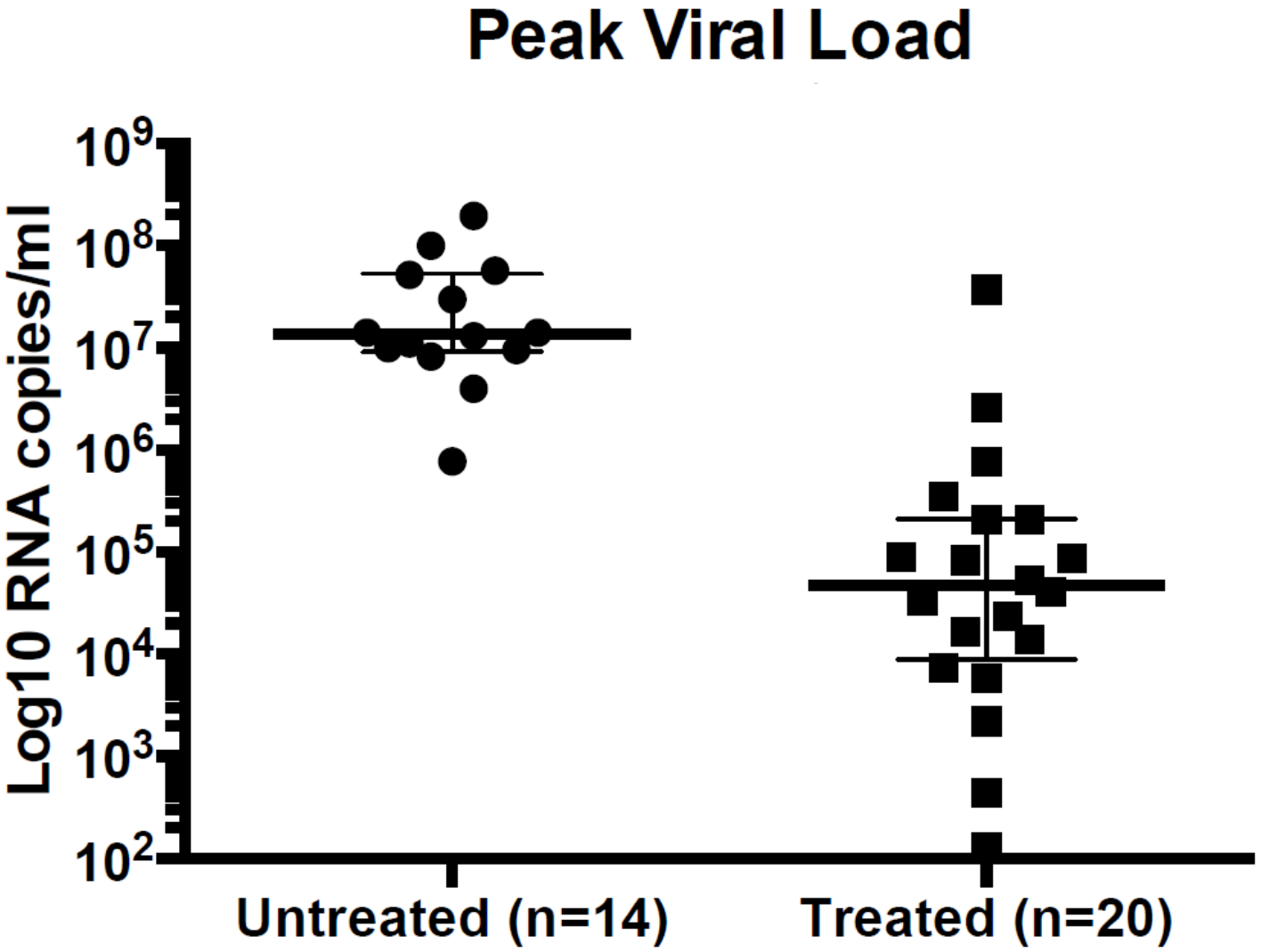
- CD8+ T cell immune responses during acute HIV-1 infection is broader than previously thought (Ndhlovu et al, 2015, *Immunity*)
  - Acute HIV infection rapidly induces massive activation and proliferation of CD8+ and CD4+T cells
  - The magnitude and timing of CD8+ T cell activation impact viral load set point
  - A high proportion of activated CD8+ cells are HIV-specific
- HIV-specific CD8+ and CD4+ T cells are defective for cytokine secretion, memory generation and prone to apoptosis during acute HIV infection following ex-vivo stimulation
- There is measurable expansion of HIV-specific peripheral TfH during hyperacute HIV infection

The impact of early treatment on generation and maintenance of HIV-specific T cell responses?

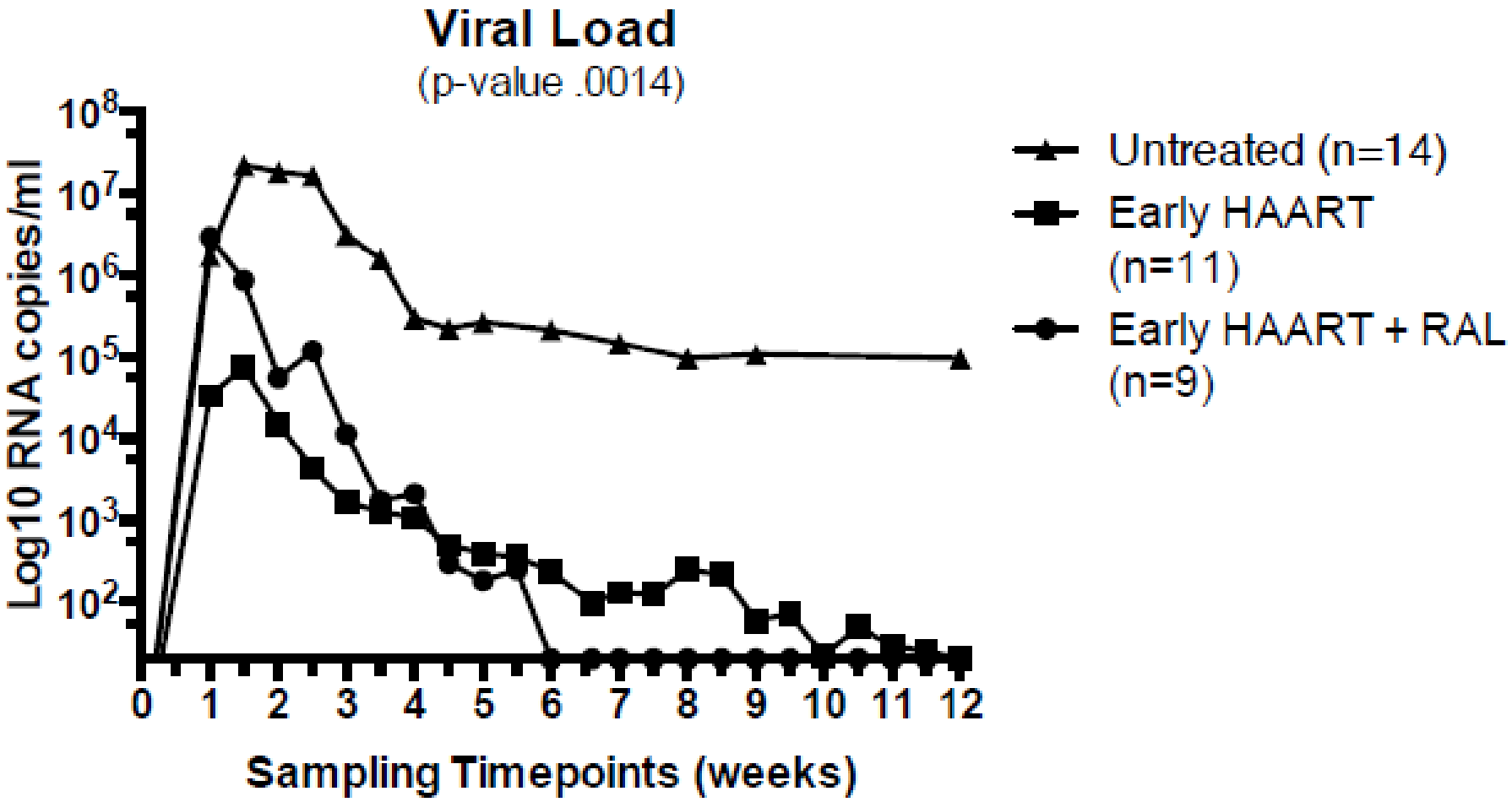




Treatment during hyperacute phase blunts peak viremia



Raltegravir intensification reduces time to full suppression

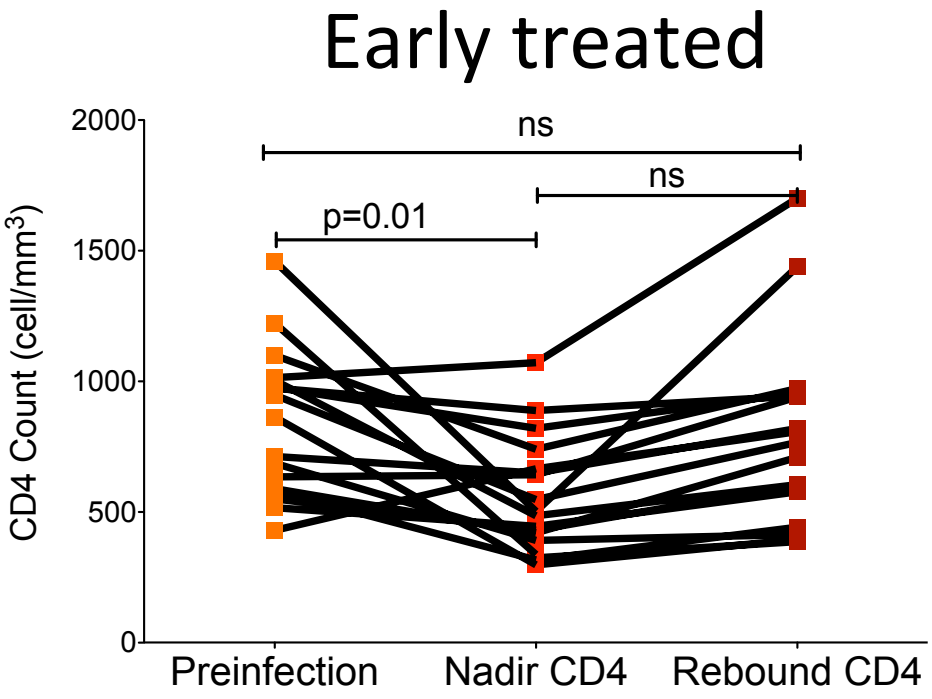


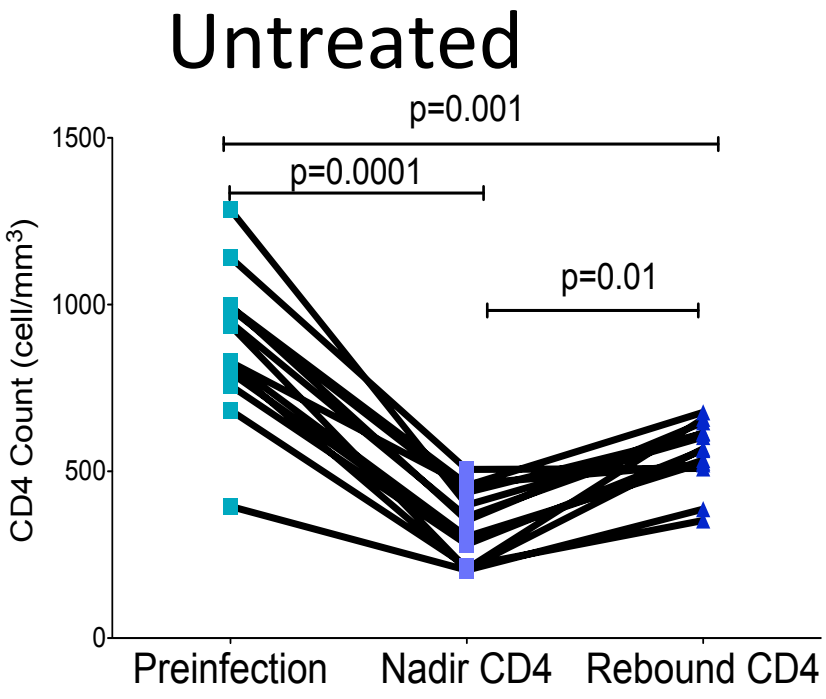
Impact of early ART on T cell responses

Investigate if very early ART treatment suppresses the subsequent development of HIV specific CD8 cell responses by removing the antigenic stimulus, OR.

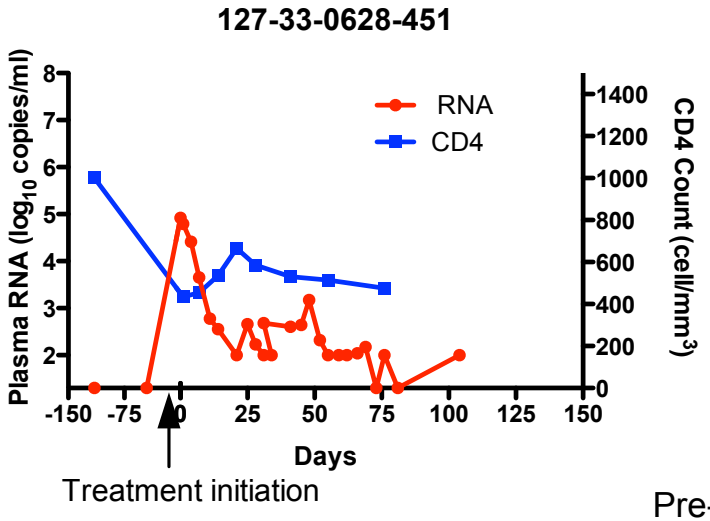
If early ART treatment might help preserve HIV specific CD4 to CD8 and B cell responses.

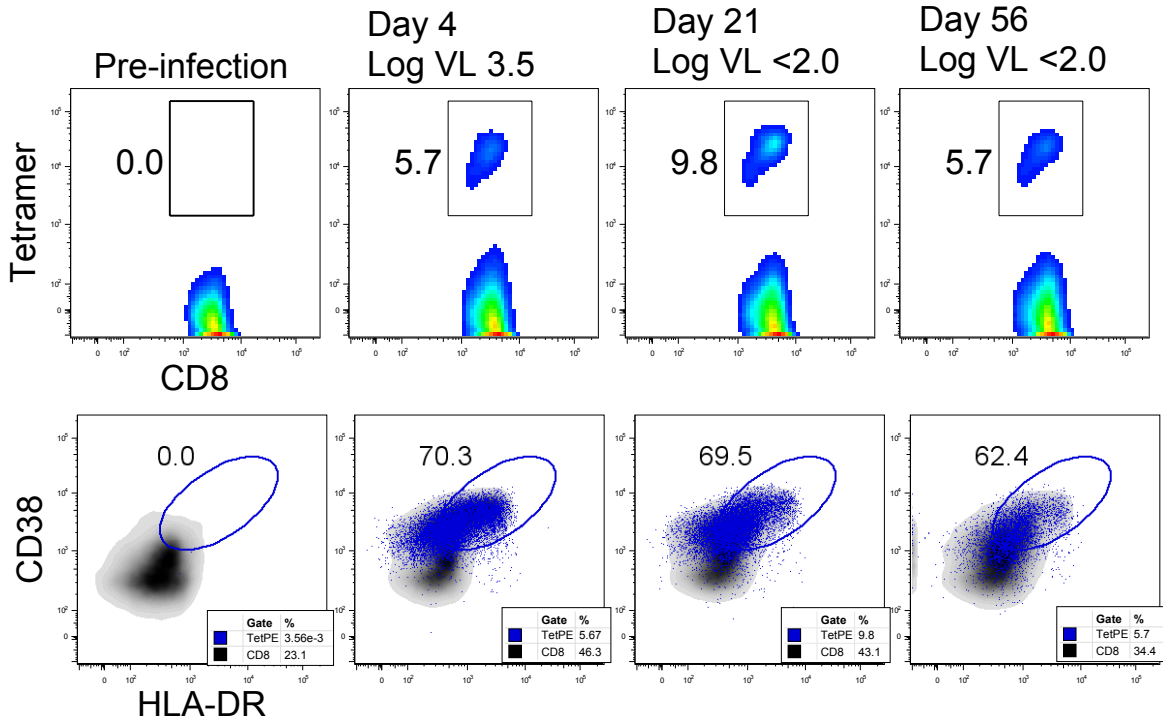
Very early ART limit CD4 T cell loss



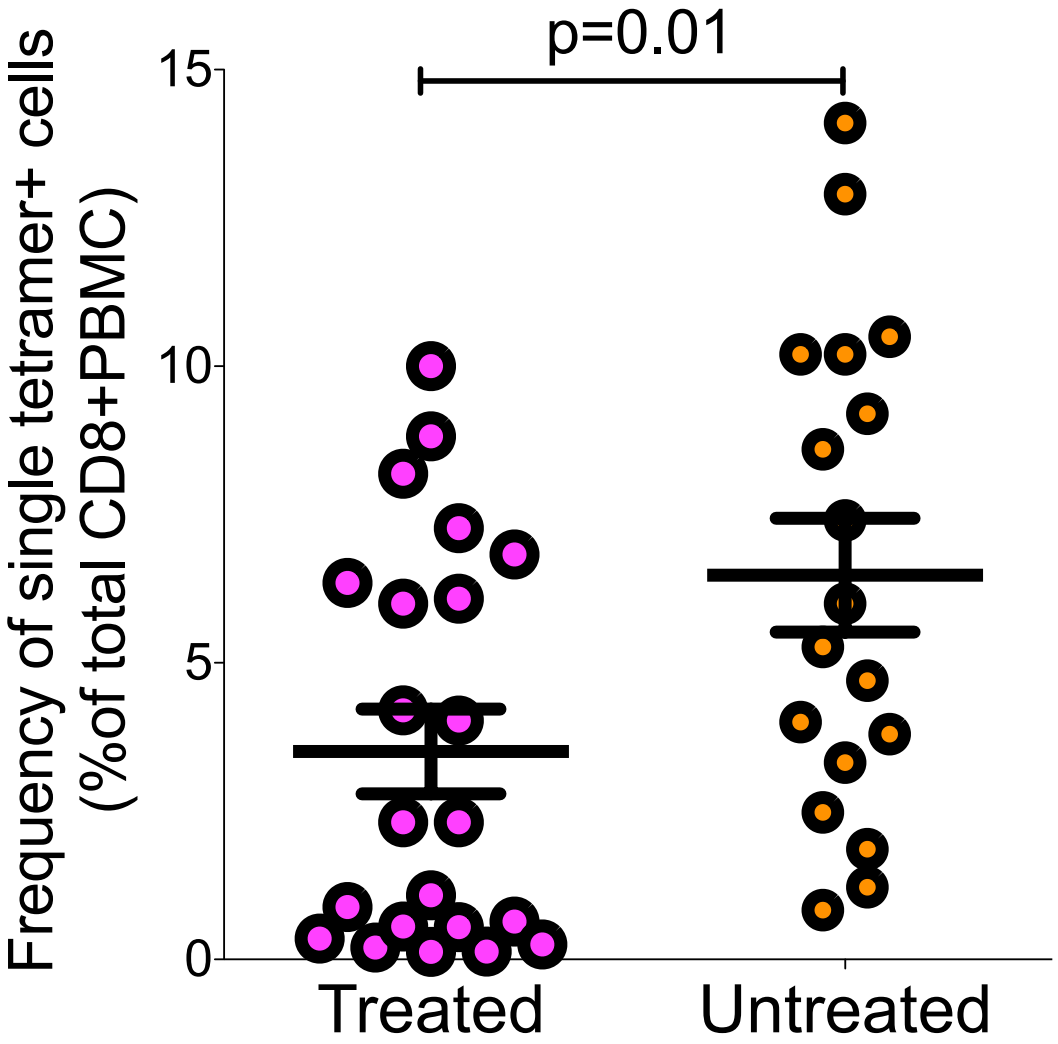


CD8+ T cell responses in early treated subject

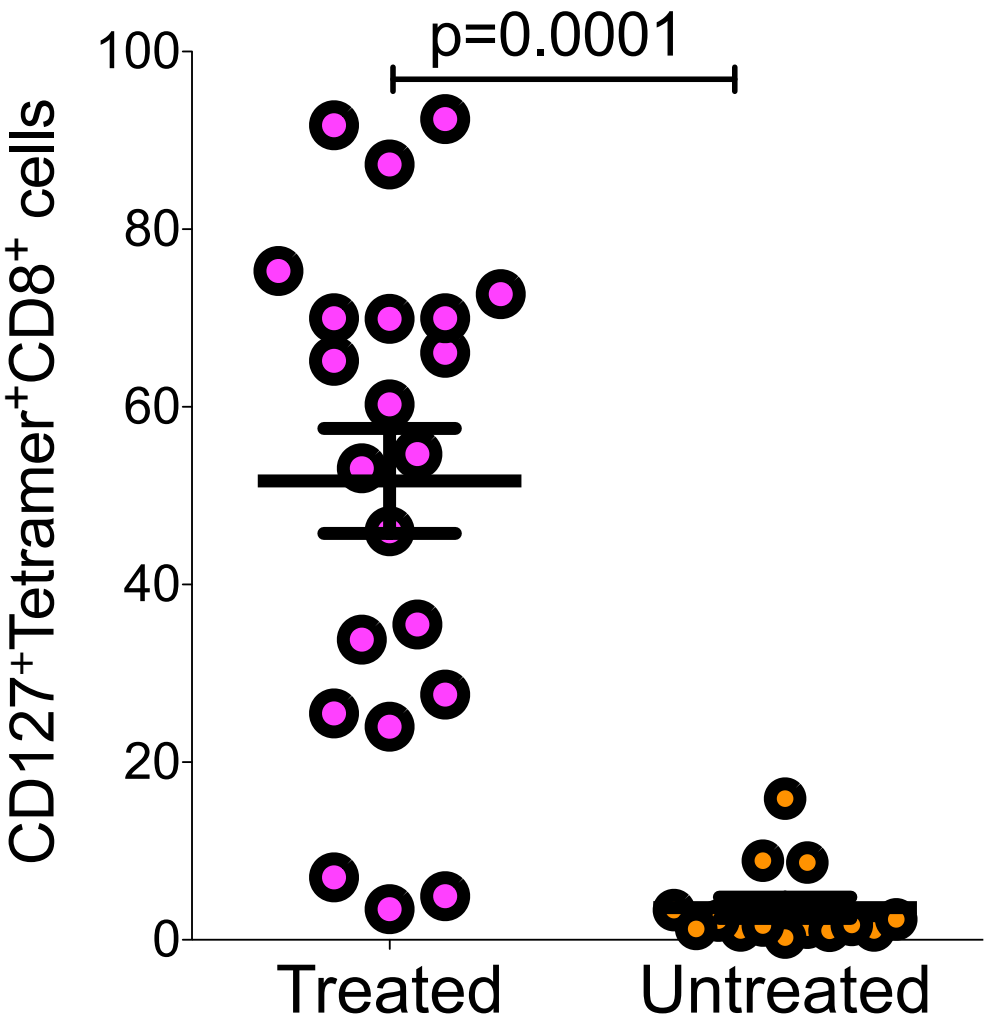




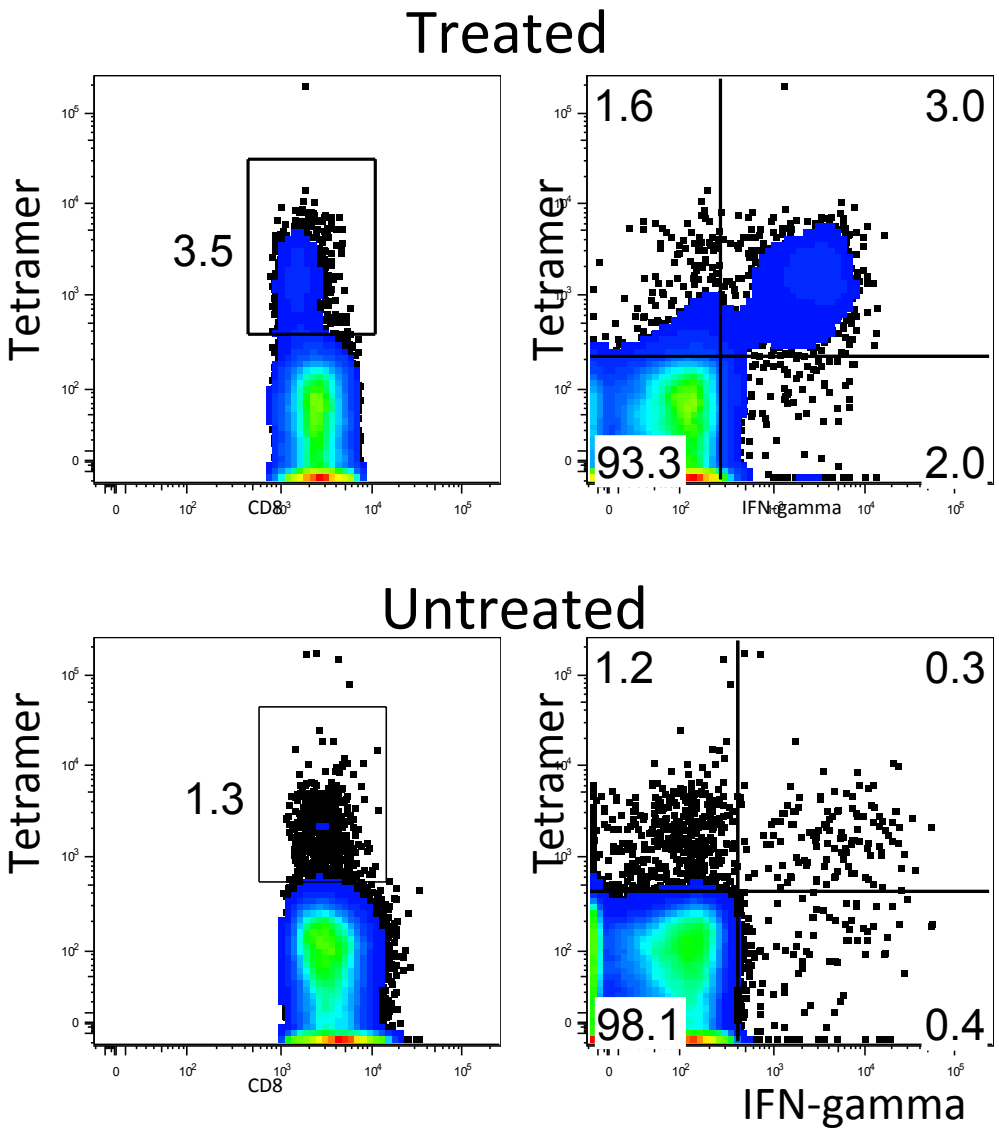
Frequency of individual tetramers^{+} CD8^{+} cells in early treated and untreated subjects



Increased CD127 expression on $CD8^+$ T cells during early treated hyperacute HIV infection



-specific CD8^{+} T cells in early treated subjects have a more more functionally competent



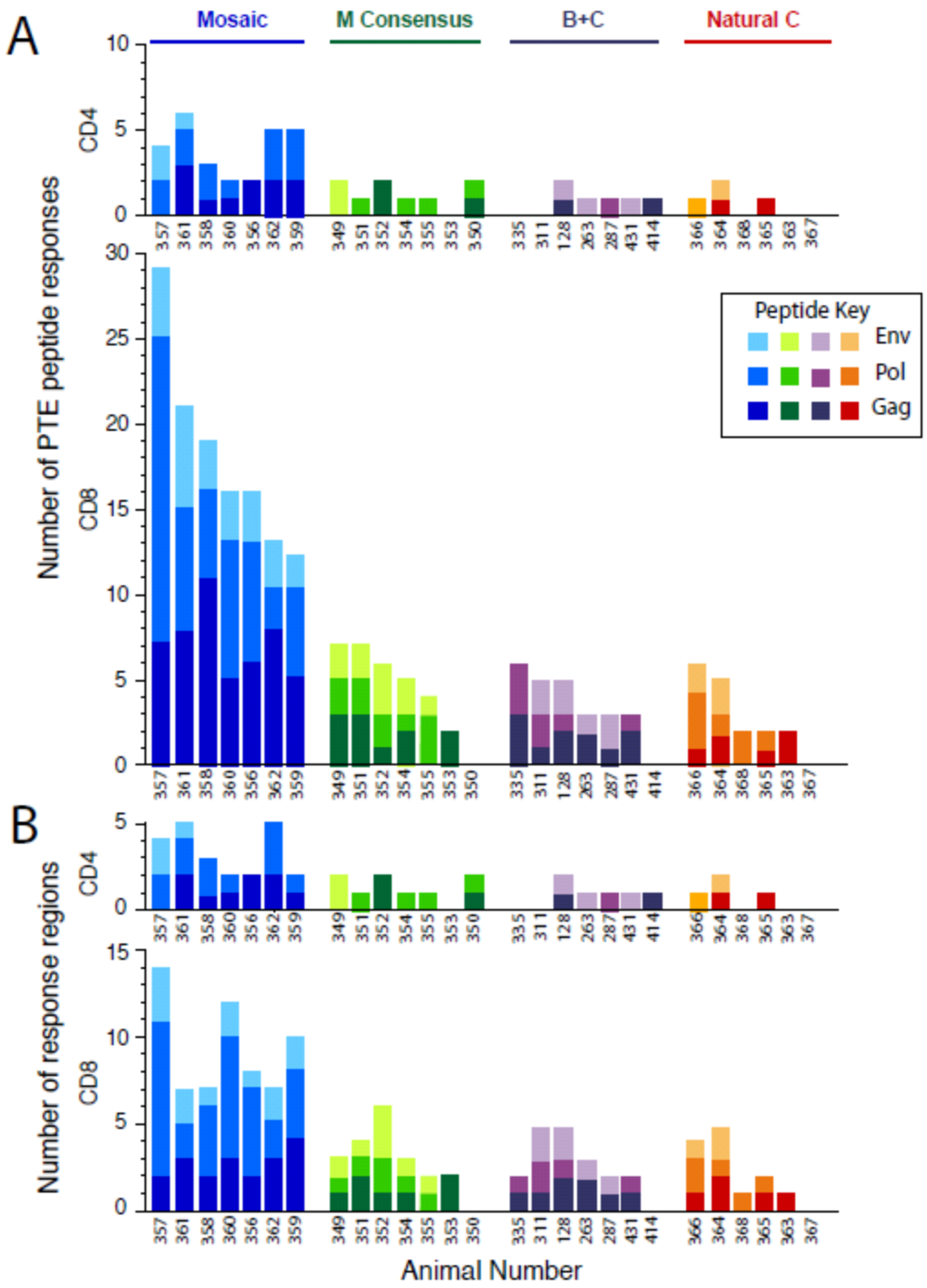
Conclusions

- Very early treated individuals have *measurable T cell responses that have a pro-survival phenotype*
- Prompt antigen withdrawal results in stable HIV-specific CD8 T cell clonal repertoire.

Future directions

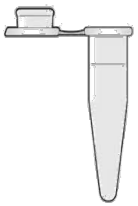
Vaccinate FRESH subjects with Ad26 mosaic vaccine

The Ad26 mosaic vaccine yielded many more epitope-specific responses than did the Ad26 M consensus, clade B + clade C, or optimal natural clade C vaccines



Barouch et al. Nat. Med. 2010; 16:319-323

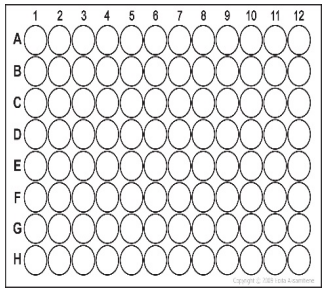
Assays to measure HIV Persistence



Cells

Proteinase K Lysis

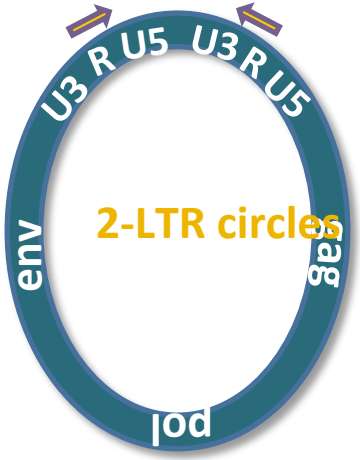
Pre-amplification from cell lysate

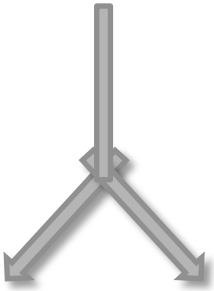


Single well pre-amplification of HIV and CD3

Total HIV DNA

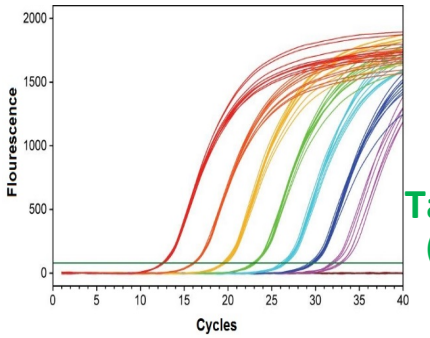
Integrated HIV D



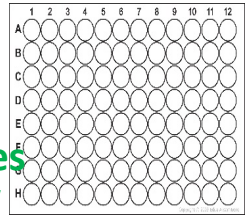


HIV copy number / 2 X CD3 copy number

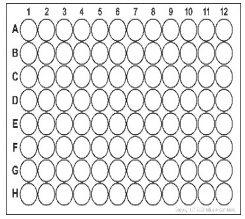
Frequency of cells harbouring HIV DNA



TaqMan Probes
(sensitivity: 1 HIV DNA copy)



HIV



CD3

Real-time nested PCR of pre-amplified products

adapted from Vandergeeten et. al., 2014, J

Conclusions I

- The FRESH study design allows us to address critical questions in HIV prevention research-
  - such as the impact of cervicovaginal microbiota on female genital inflammation (Anahtar et al, 2015, *Immunity*) and impact of IPC on HIV acquisition risk (Byrne, Anahtar et al, *Lancet ID*, in press)
- FRESH study participants initiated on cART during hyperacute HIV infection may offer new insights on long-term viral remission
- Understanding of immune responses following cART initiation may be useful for future intervention studies

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