The B cell response in primary HIV infection

the effect of early intermittent treatment

Godelieve de Bree

29th September 2016

Protection by broadly neutralizing antibodies

Broadly neutralizing antibodies are key components in a protective HIV-specific immune response

Play a role in clearing of virus by blocking viral entry or by enabling killing by natural killer cells or monocytes

Offer protection in SHIV models

Reduce viremia in NHP and in studies in humans

Barouch 2013; Shingai Nature 2013; Caskey Nature 2015

Properties of the antibody response in HIV

BnAb responses occur in around 20 percent of individuals and development takes years

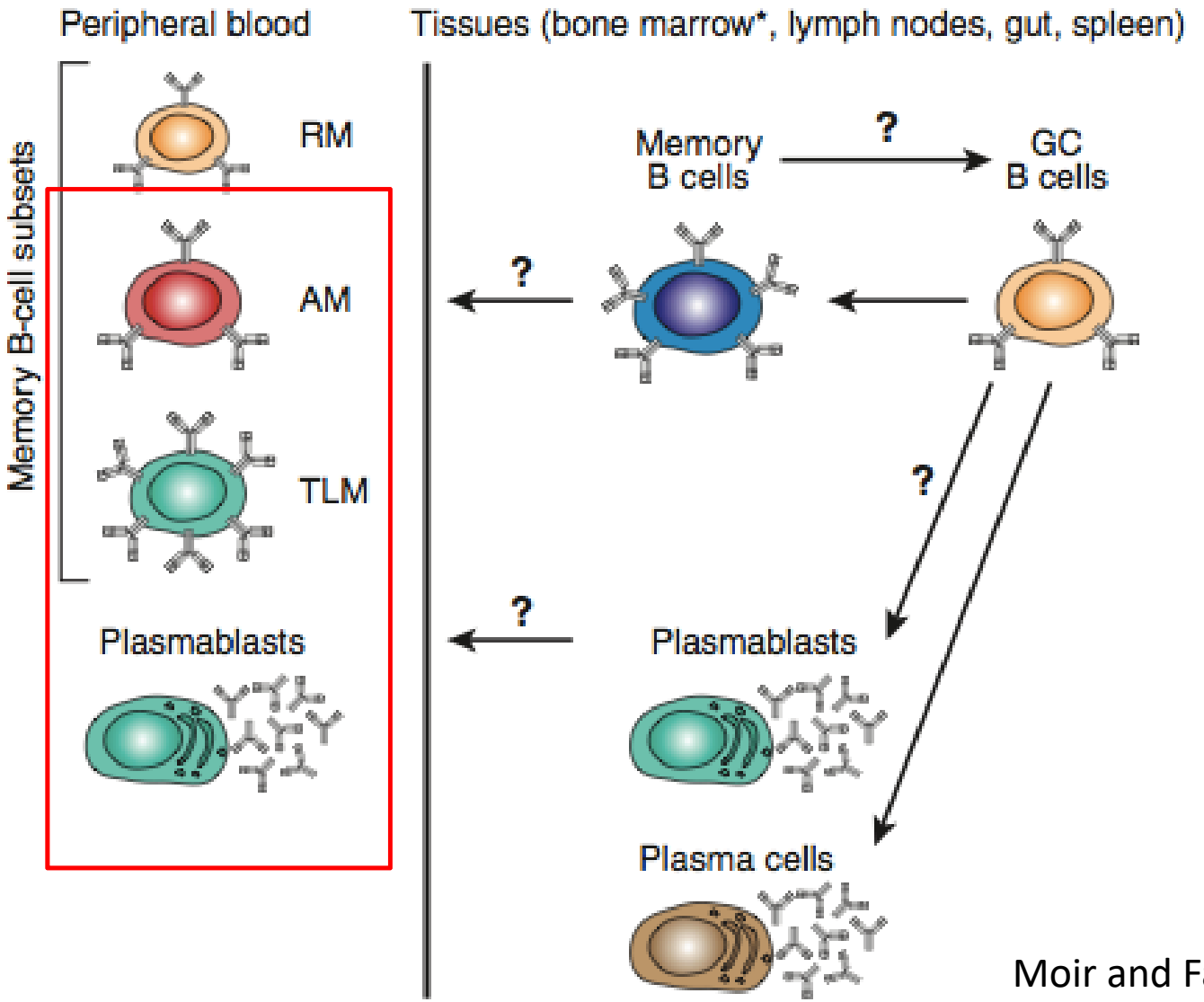
Hraber AIDS 2014; Doria-Rose J Virol 2014; Gray J Virol 2014

Short half life (6 months) in RV144 trial

Reks-Ngarm NEJM 2009

Duration of viral exposure, virus load and antigenic diversity are beneficial

Disturbances in the B cell compartment in HIV



Moir and Fauci Imm Rev 2013

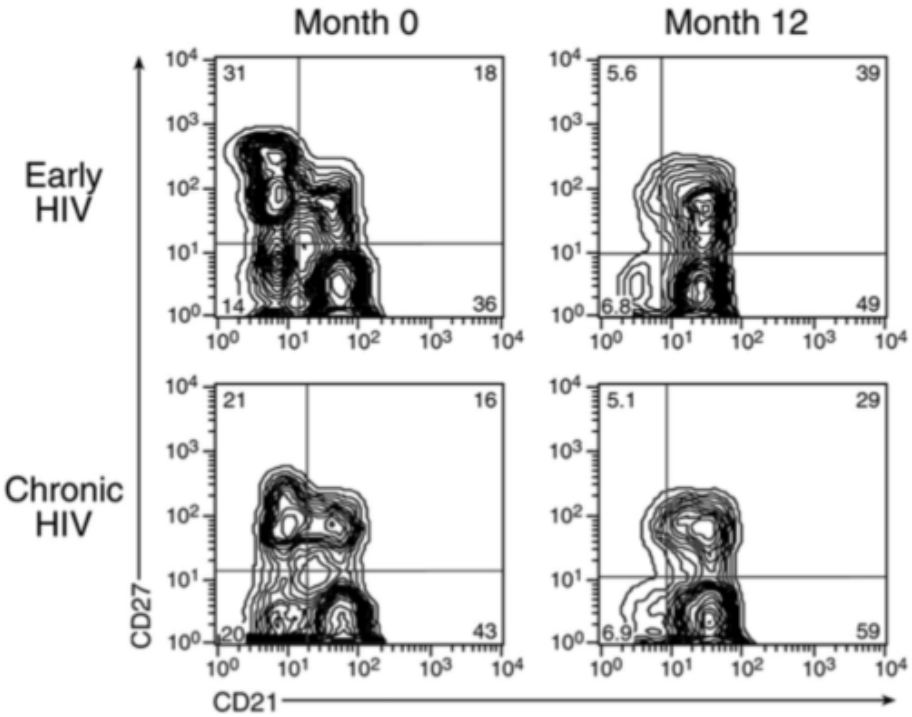
Disturbances in the B cell compartment in HIV

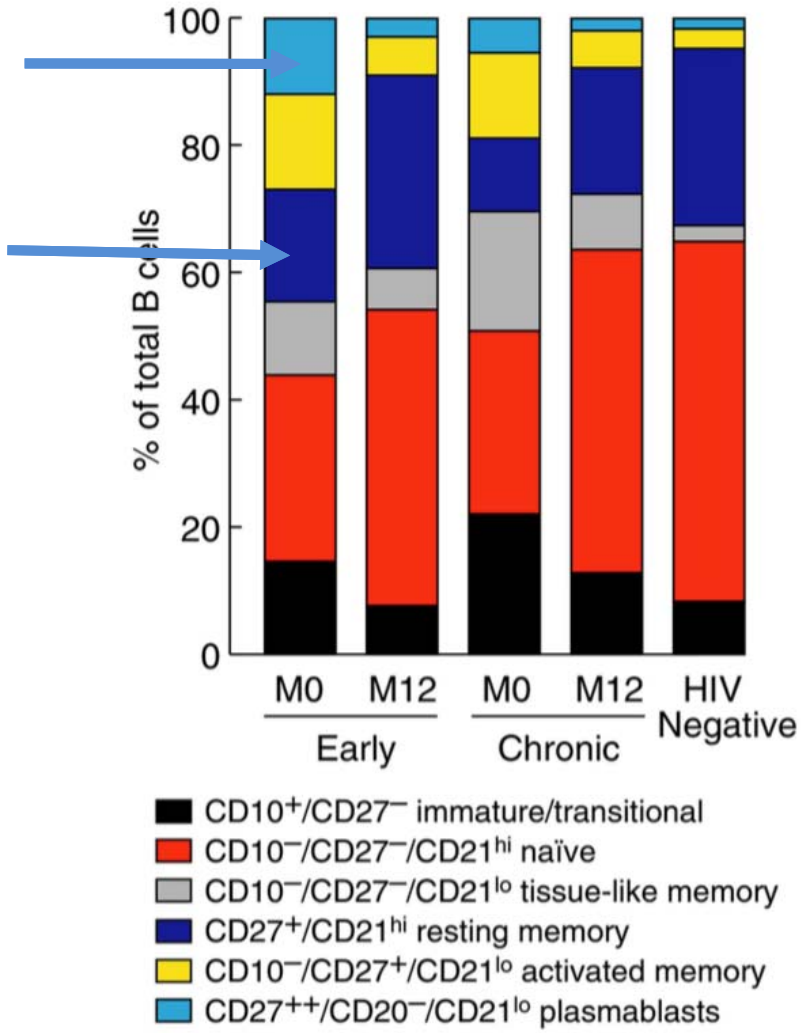
In HIV infection: additional B cell subpopulations

plasmablasts
activated memory B cells
exhausted B cells

Insight in factors that induce these alterations may help to explain defects in antibody responses (HIV-specific and against other infections)

Effect of antiviral treatment on the B cell compartment





Moir Blood 2010

Disturbances in the B cell compartment in HIV

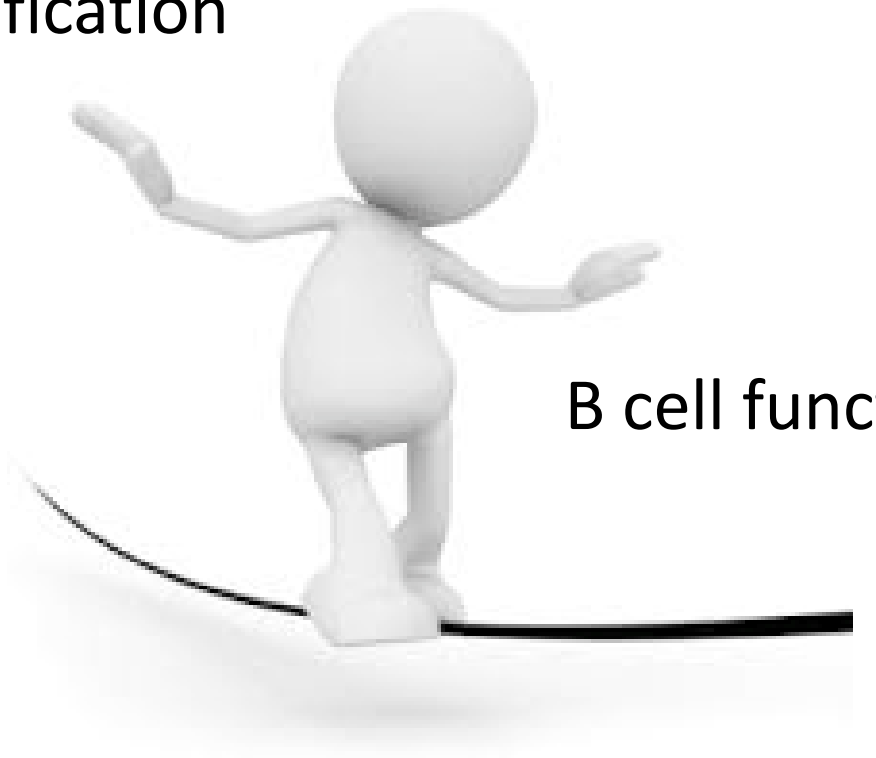
- Aberrant B cell subsets appear early in the course of infection
- cART to large extent preserves B cell phenotype
- Ongoing viral replication associated with B cell exhaustion

How are disturbances in the B cell compartment related to the induction of bnAb?

duration of infection

viral diversification

virus load



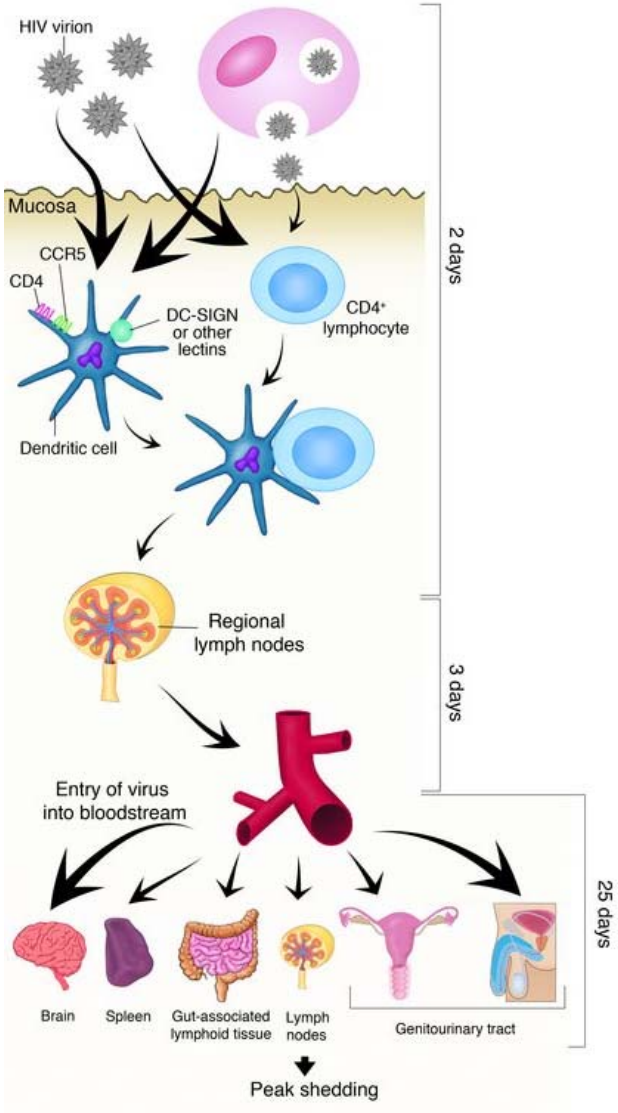
B cell function and phenotype

Acute HIV infection

In the acute infection phase instruction of the B cell response takes place

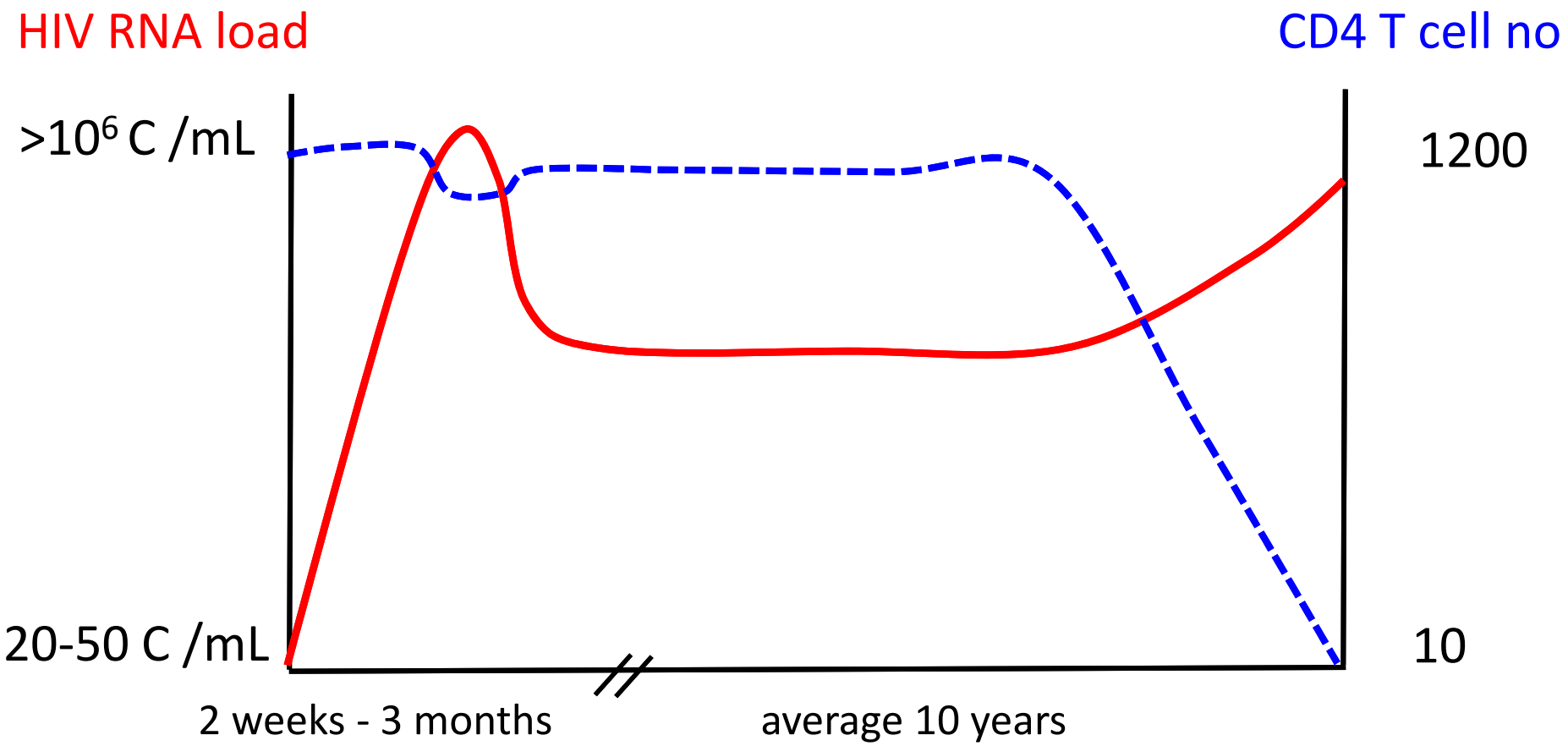
Early in the course of infection a viral reservoir is formed and the HIV-specific immune response becomes compromised

Acute HIV infection

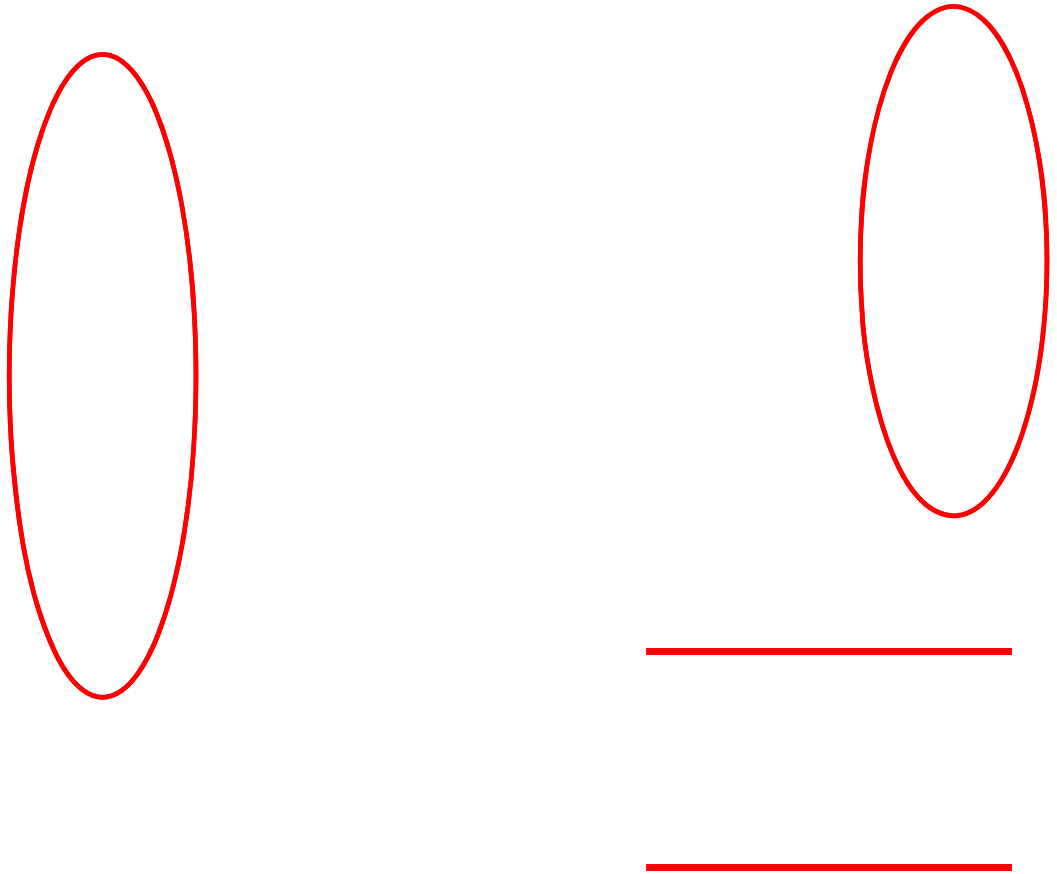


Pilcher CID 2004

Acute HIV infection



The Primo-SHM trial



weeks

Grijssen PlosMed 2012

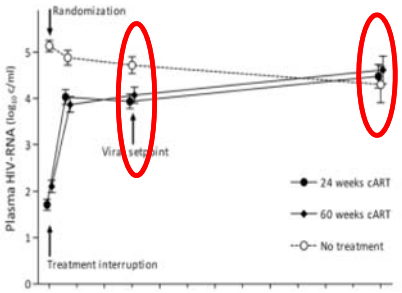
B cell responses in the Primo-SHM trial

B cell phenotype, transcriptional profile and HIV-specific antibody response

in treated versus untreated patients with an acute HIV infection

Over time: at viral set point and the latest available time point before start antiretroviral therapy

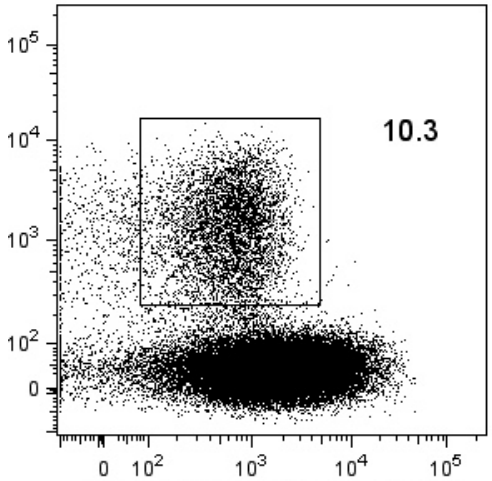
Patient characteristics

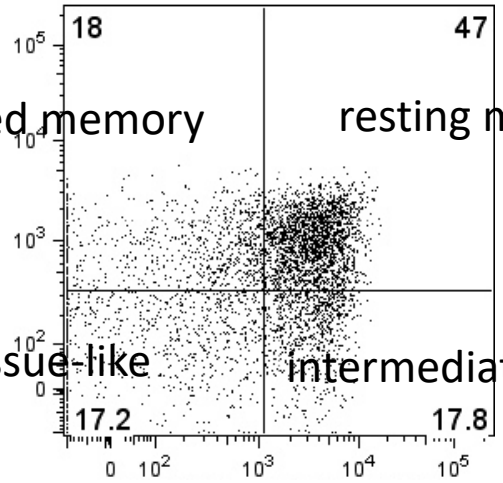


	untreated	treated	p-value
Number of patients	23	24	
Age	42 (26-56)	41 (25-60)	0.89
Viral setpoint			
CD4+ T cell count (cells/uL)	345 (210-610)	600 (230-1510)	0.0001
HIV RNA (copies/mL)	49061 (3347-1,2*10^6)	12429 (53-2,8*10^5)	0.004
Late time point			
CD4+ T cell count (cells/uL)	340 (170-730)	360 (190-670)	0.56
HIV RNA (copies/mL)	23319 (319-5,3*10^5)	13150 (268-2,5*10^5)	0.84

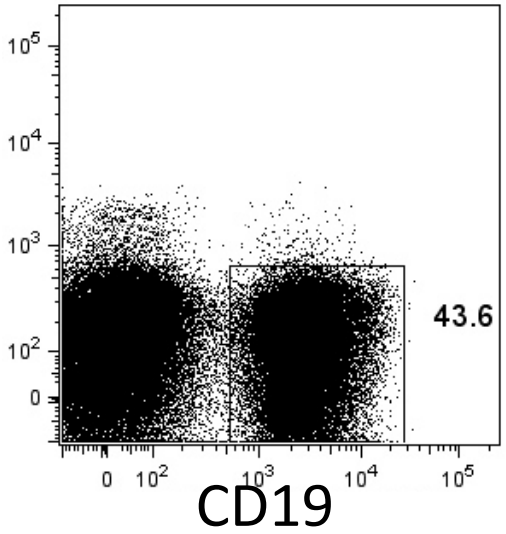
B cell phenotype

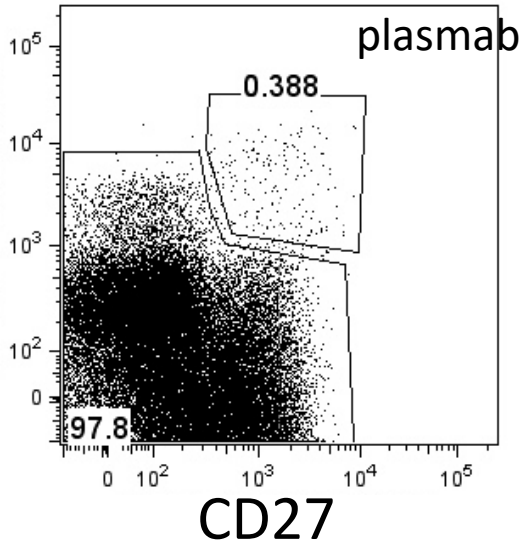
IgG



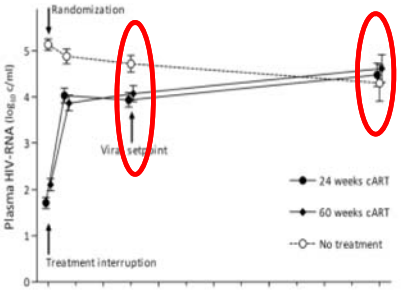


aqua





Increased CD21^{neg} fraction



CD21^{neg} cells
(% of CD19^{pos}IgG^{pos})

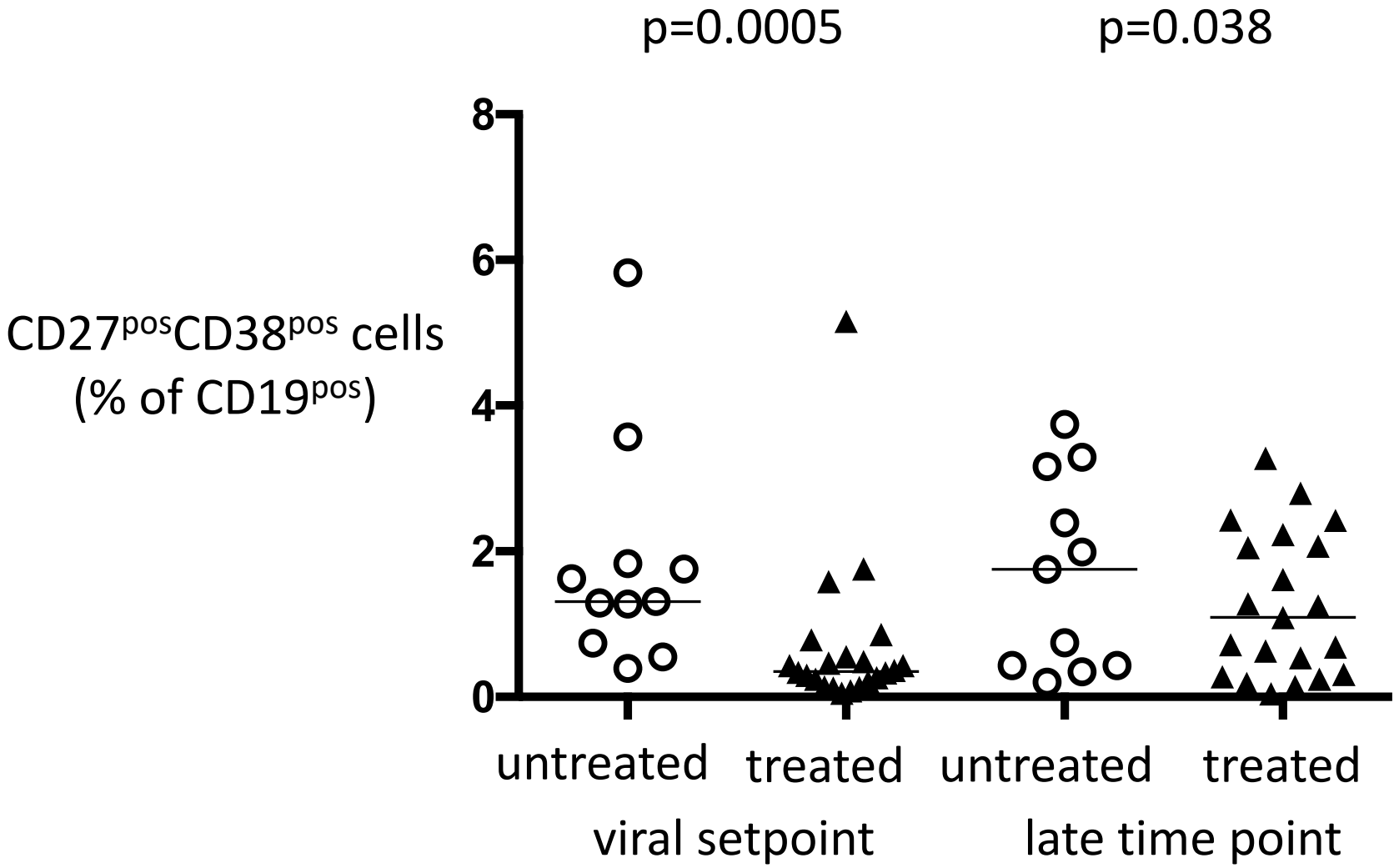
p=0.0065 p=0.06

60
40
20
0

untreated treated untreated treated

viral setpoint late time point

Increased fraction of plasmablasts

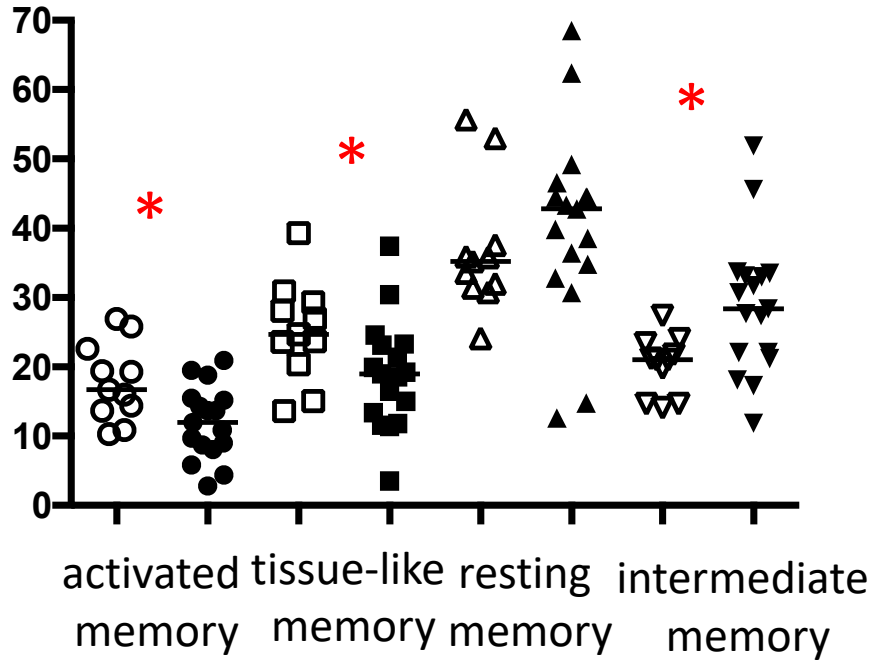


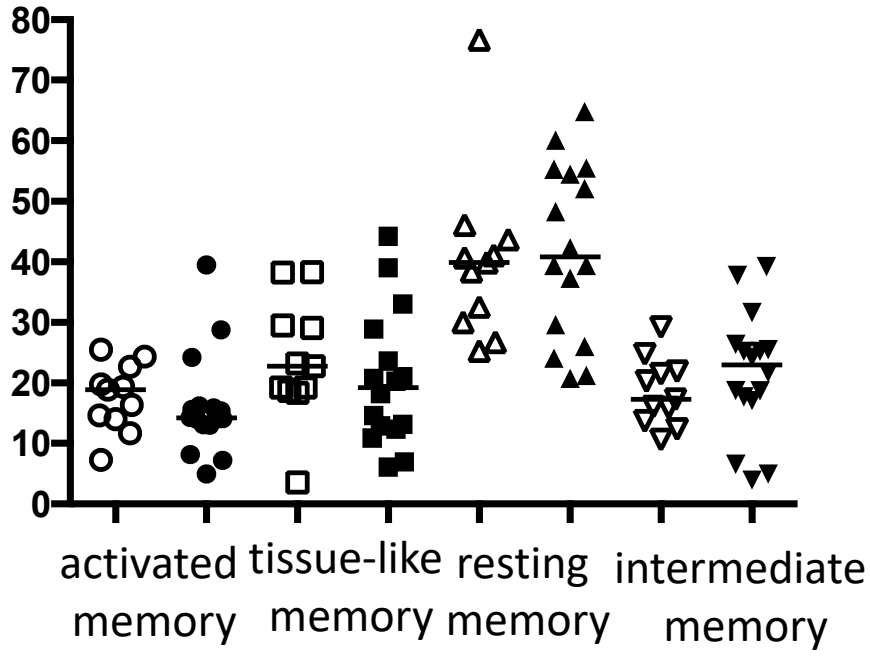
Higher fraction of activated B cells at viral set point in untreated patients

viral setpoint

late time point

open: untreated
closed: treated





Conclusion

- In treated patients at viral setpoint, B cell phenotype is shifted towards an activated, exhausted phenotype

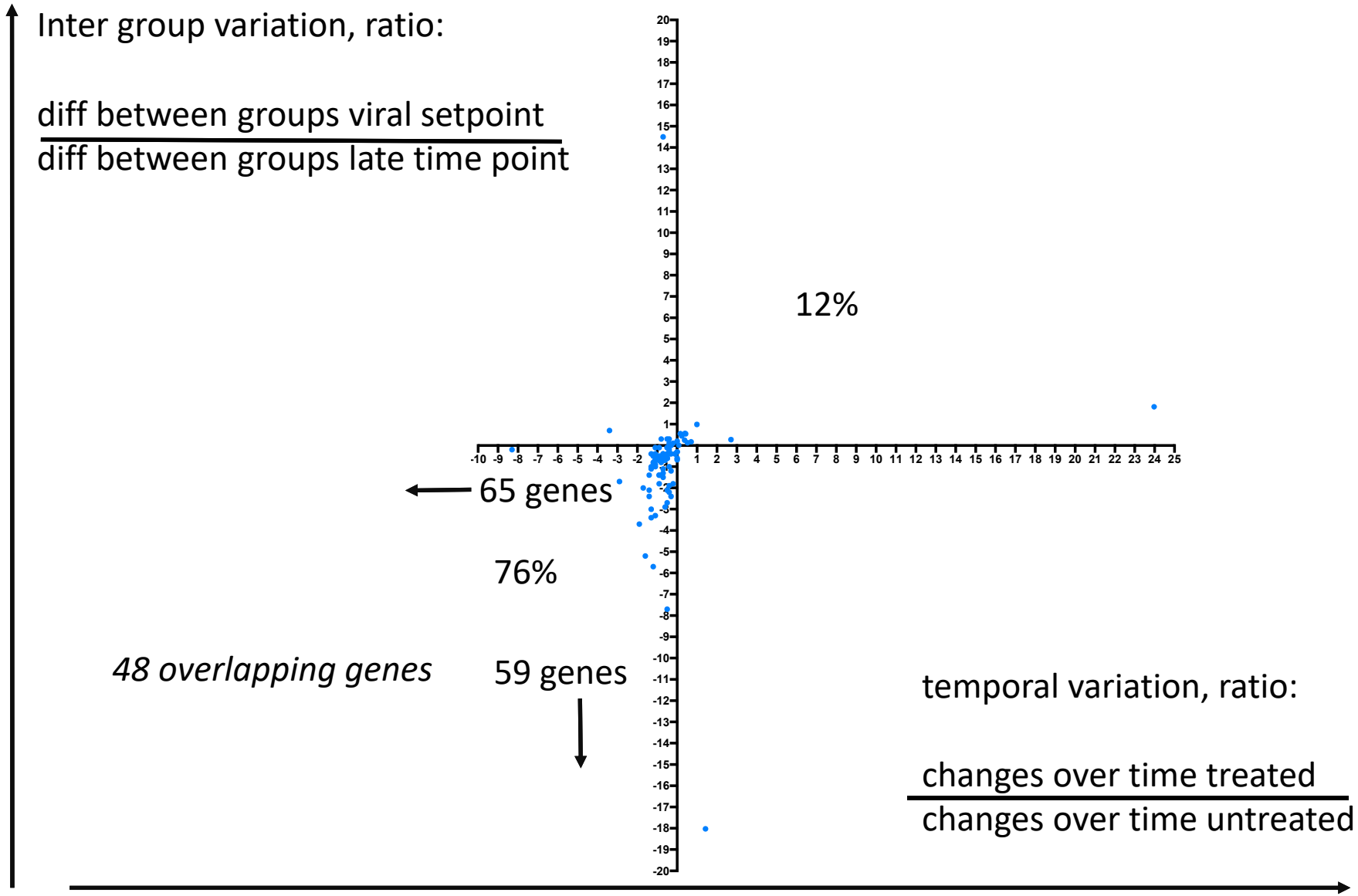
Transcriptional profile

Multiplex qPCR analysis on sorted ($IgG^{pos}CD21^{pos}CD27^{pos}$) memory B cells

96 gene panel: cell signaling, adhesion, differentiation, activation, maturation, proliferation and trafficking

Data Madhu Prabahakaran

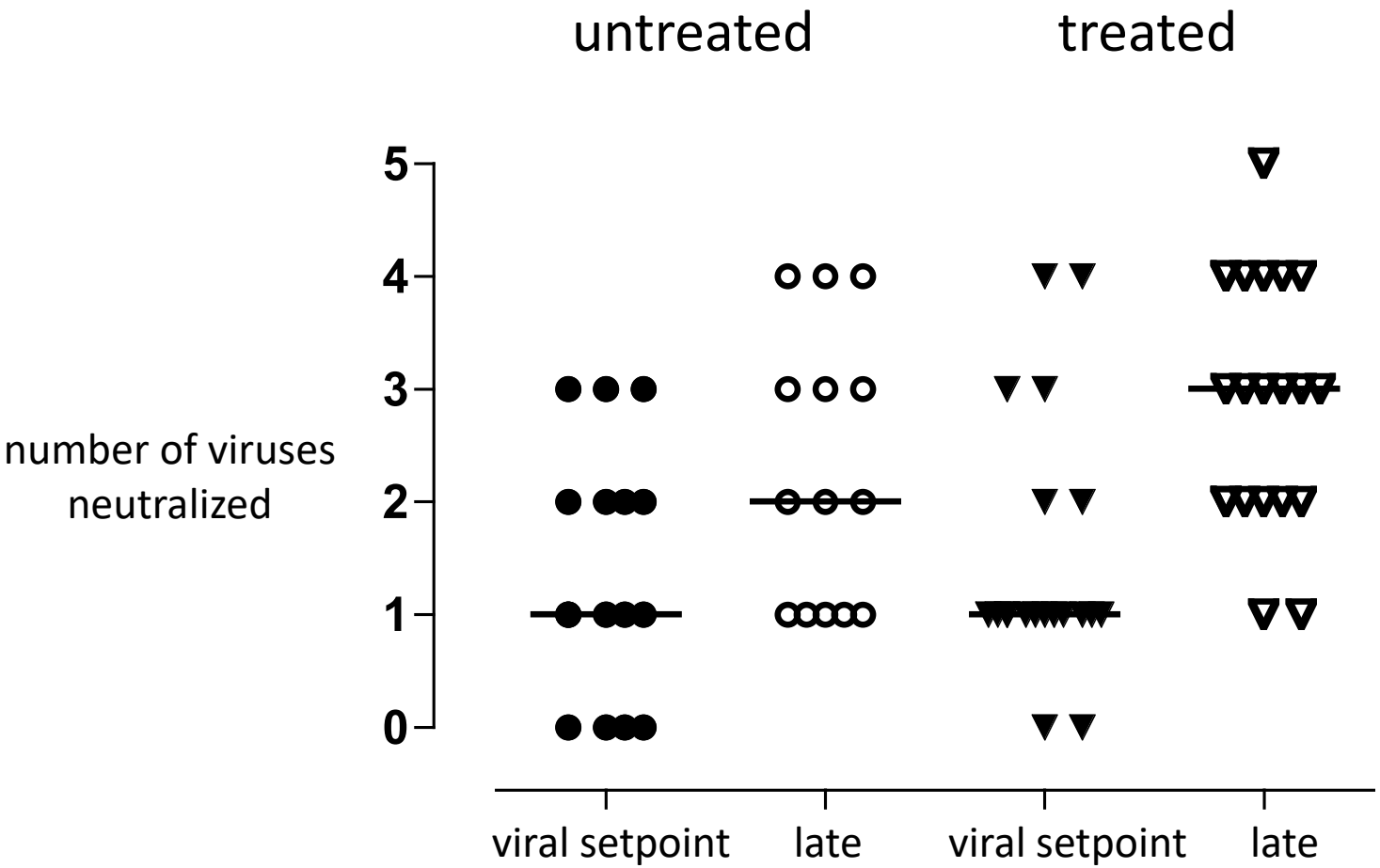
Transcriptional profile



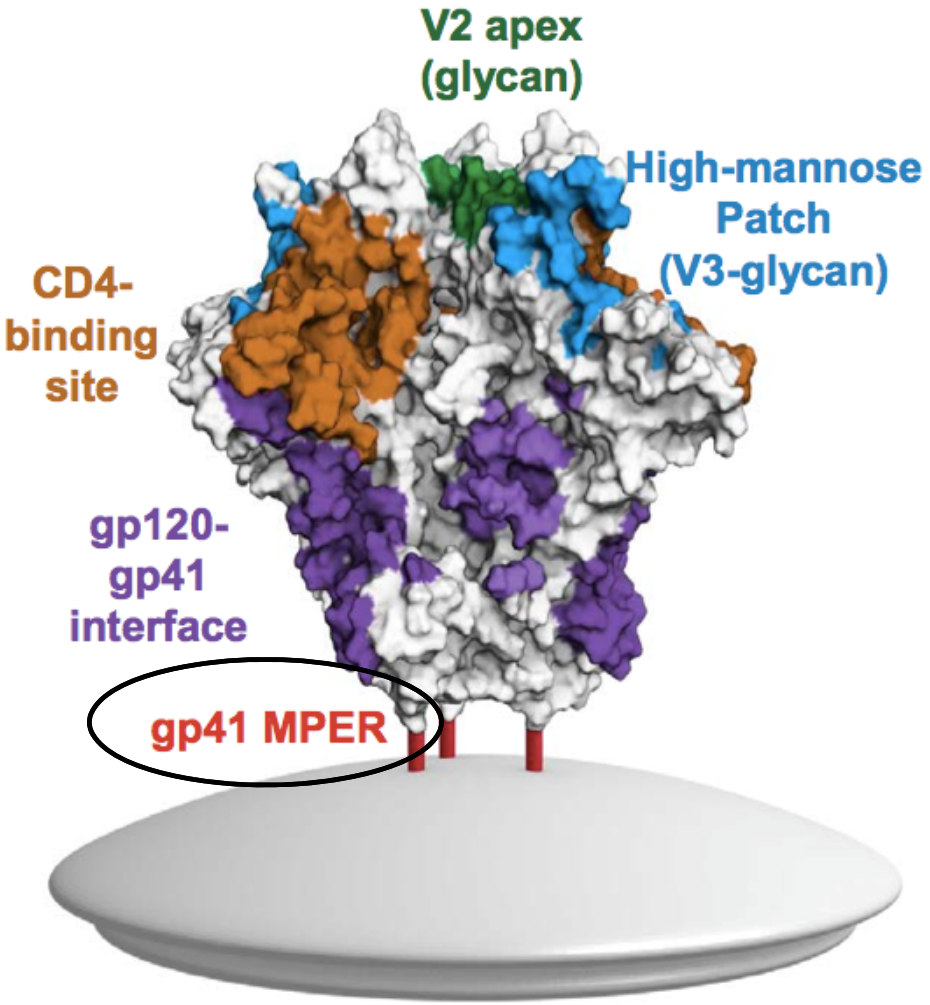
Transcriptional profile

the speculation that the greater differential observed between the two groups at the late time point might largely be a consequence of the sustained gene expression changes occurring over time in the untreated group due to greater viral exposure

Comparable neutralization breadth

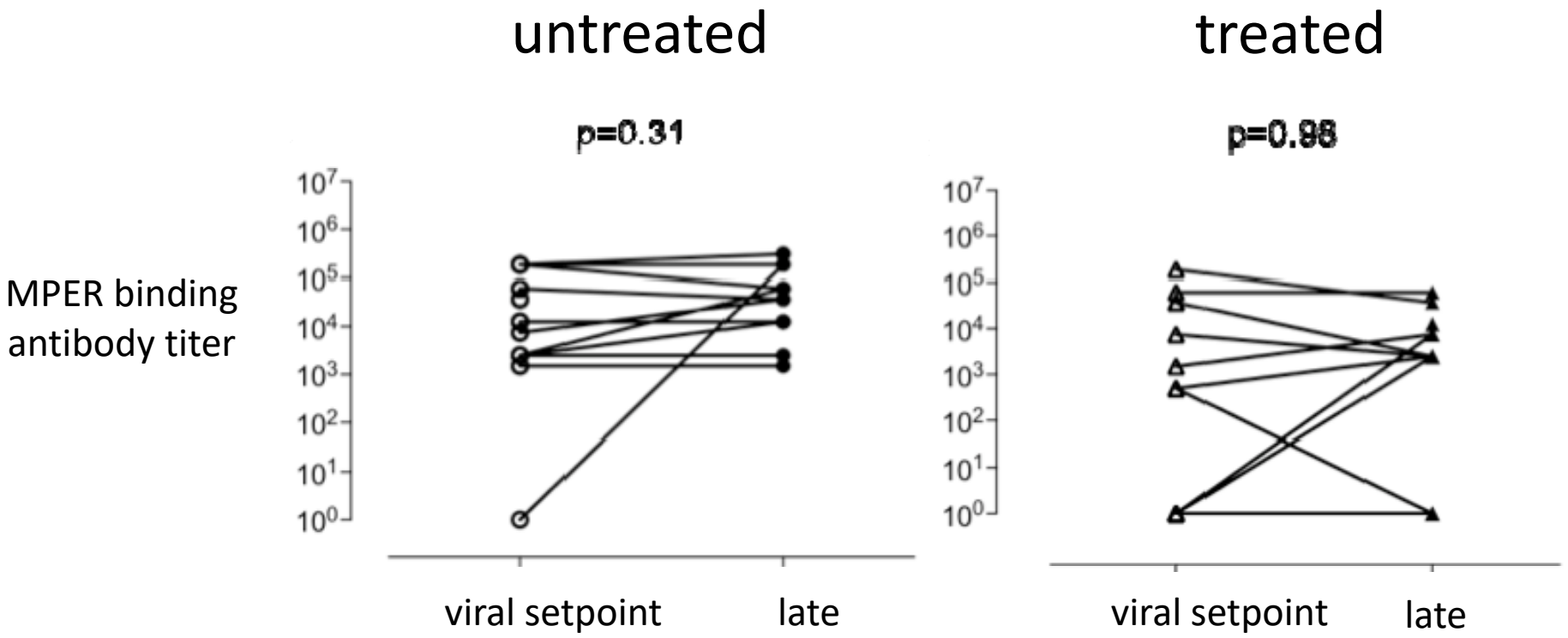


Envelope-specific antibodies

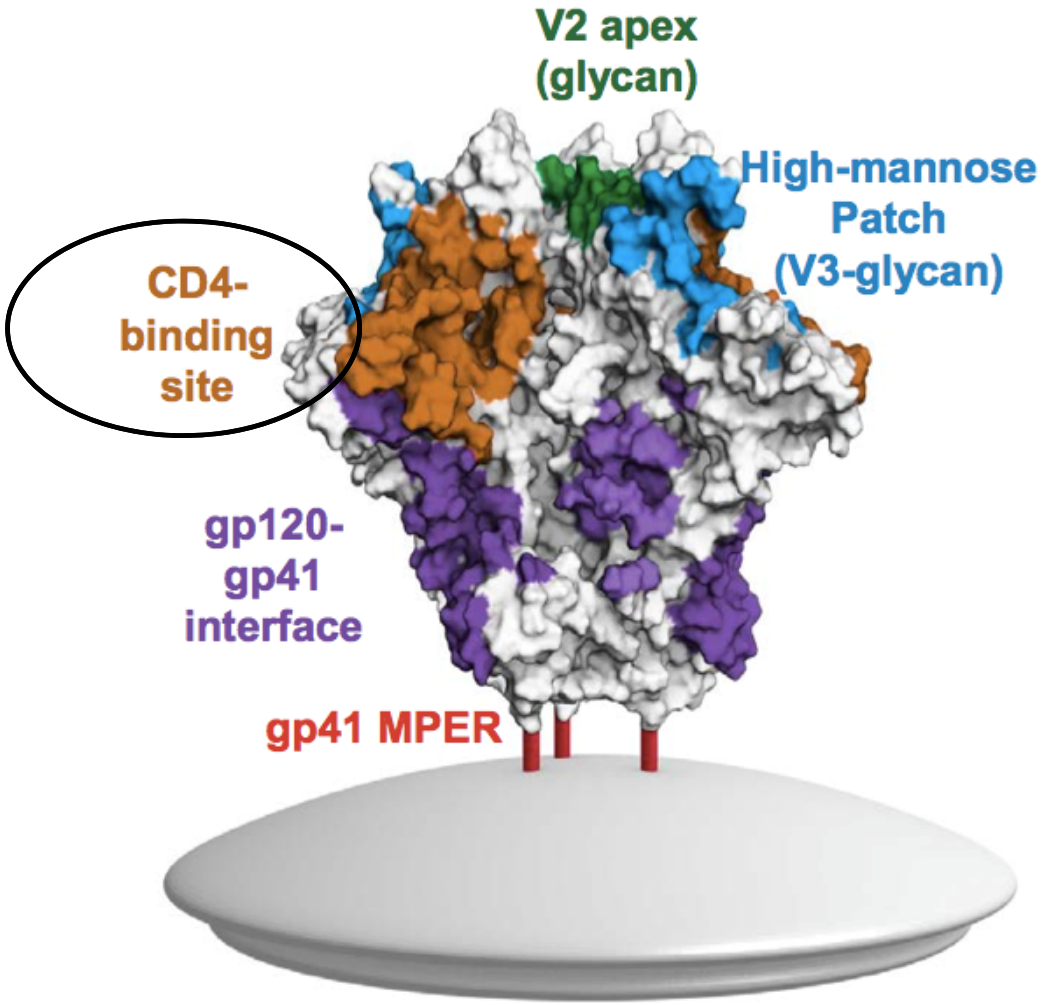


Slide JR Mascola

Dynamics of MPER-specific antibodies are comparable between groups



Envelope-specific antibodies



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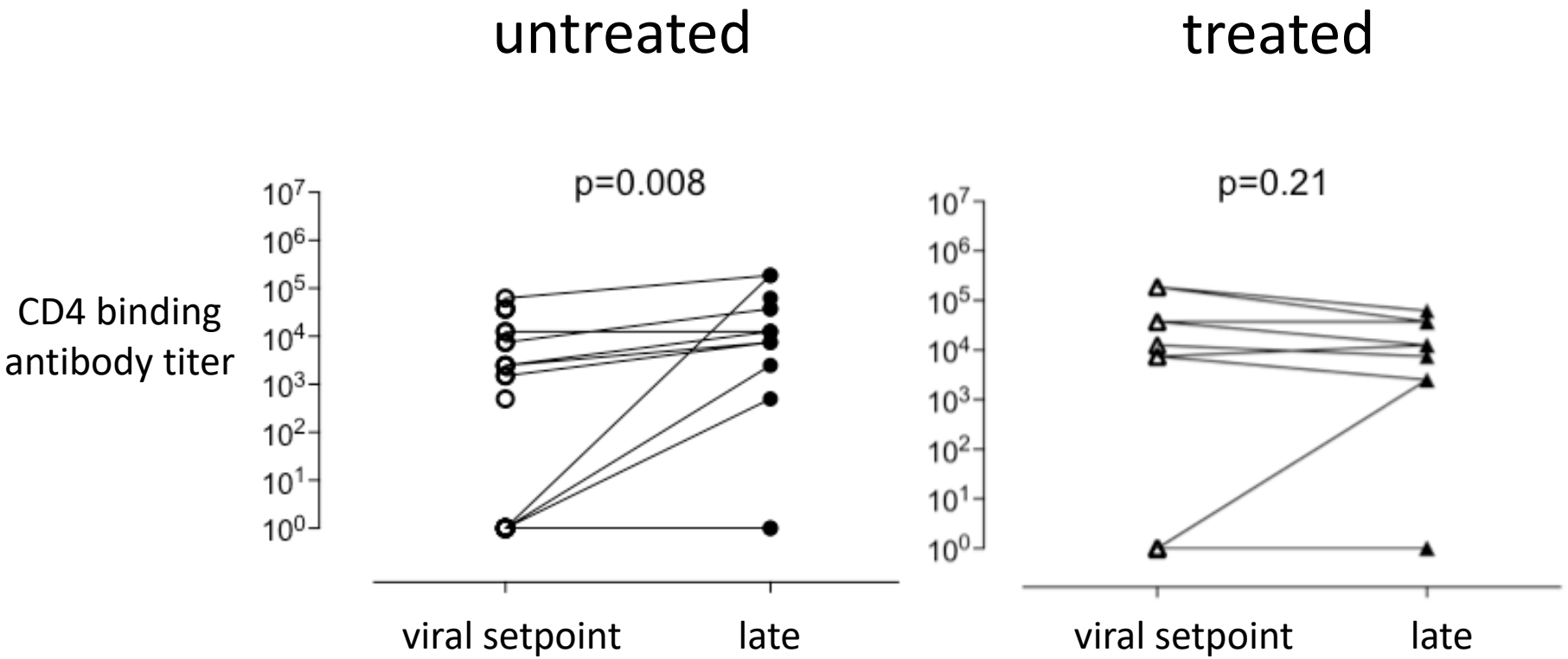
CD4 binding site-specific antibodies increase in untreated patients



Conclusion

- A shift towards B cells with an activated, exhausted phenotype in untreated patients at viral set point compared to treated individuals
- Possibly related to viral exposure (height of viral load at set point, diversification)
- The presence of this aberrant B cell subsets in untreated patients did not preclude the generation of the HIV-specific antibody response

Conclusion

- B cell priming may lead to genetic imprinting that is maintained over the course of infection
- resulting in decelerated gene expression changes over time in the treatment interrupted group

Implications

- Key paradox in HIV: at least a certain extent of viral replication is required for the selection of memory B cells that would give rise to a bNab response

- New era in HIV research: “cure” interventions focuses on therapeutic interventions in acute HIV infection

Therapeutic (T / B cell) vaccination

Early start of treatment may require extra efforts to design strategies to boost humoral immune response

Acknowledgements

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