

Effect of HAART and STI on the Affinity Maturation of the Humoral Immune Response to HIV-1

Kim Wilson¹, Larissa Doughty¹, Hayley Croom¹, Kate Merlin⁴, Pat Grey⁴, Anthony Kelleher⁴, Don Smith⁴, Philip Cunningham⁶, Elizabeth Dax^{1,5}, Dale McPhee^{1,2,3,5}, and the Pulse Study Team.

¹National Serology Reference Laboratory, Australia; Fitzroy, Australia

²Department of Microbiology, Monash University, Clayton, Victoria, Australia

³Burnet Institute for Medical Research and Public Health, Melbourne, Australia

⁴National Centre for HIV Epidemiology and Clinical Research, Sydney, Australia

⁵Dept of Microbiology and Immunology, University of Melbourne, Parkville, Victoria, Australia

⁶Center for Immunology, St. Vincent's Hospital, Sydney, Australia.

Introduction: The administration of highly active antiretroviral therapy (HAART) immediately upon the appearance of symptoms of HIV-1 infection is widely accepted in clinical practice and results in suppression of viral load. However, the effects of early introduction of HAART on the development of effective immune responses to HIV-1 infection are ill-defined. While reduction of viraemia may preserve cellular immune responses (Bloch et al. 2006), low antigenic load may restrict or delay maturation of humoral immune responses. Using sequential plasma samples collected over a period of several years (commencing early following infection) we have investigated the effect of HAART and structured treatment interruption (STI) on the immune response and compared this with the profile generated in treatment naïve individuals. Viral load, CD4 counts and antibody profiles (specificity, affinity, titre and isotype distribution) were used in an attempt to predict immunological markers of those in whom STI could be confidently implemented without the risk of a rapid viral load rebound.

Methods: Viral lysate based Western blots were probed with antibody isotype specific secondary antibodies to provide a detailed profile of the humoral immune response to HIV-1 during seroconversion. Antibody isotype reactivity to specific HIV-1 proteins were then quantified using recombinant proteins in an ELISA format. Affinity maturation of these responses was followed using surface plasmon resonance on biosensor chips coated with recombinant p24, gp41, p32 and the immunodominant peptide gp41⁵⁷⁹⁻⁶¹³. The profiles observed in sequential samples obtained from individuals receiving HAART (with or without STI) were compared with the profiles observed in treatment naïve individuals. Changes in affinity, specificity and titre of antibodies were analysed against the corresponding changes in viral load and CD4 counts.

Results: As the humoral immune response to HIV-1 develops, different antibody isotypes, directed to discrete HIV-1 antigens, occur at different time points following infection and often these interactions are transient. The administration of HAART decreases the viral load to undetectable levels. This loss of antigenic stimulation halts maturation of the humoral immune response in an antigen dependent manner. Re-exposure to controlled levels of viral antigens during STI stimulates continuing maturation of the immune response.

Discussion: Thoroughly characterising the humoral immune response generated during HIV-1 infection may allow the identification of immunological markers that indicate if an individual can be confidently taken off therapy without the risk of a rapid viral load rebound. This may also provide insight into strategies that may be employed for the development of effective vaccines because the antibody profiles generated differ significantly between different antigens.

References: Bloch, M. et al. JAIDS, 2006, 42:(2) 192-202.