

Poster presentation

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## **P09-12. Autologous neutralizing antibodies in early subtype C HIV-1 infection target variable regions of envelope and drive multiple pathways of viral escape**

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from AIDS Vaccine 2009  
Paris, France. 19–22 October 2009

Published: 22 October 2009

*Retrovirology* 2009, **6**(Suppl 3):P125 doi:10.1186/1742-4690-6-S3-P125

This abstract is available from: <http://www.retrovirology.com/content/6/S3/P125>

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### **Background**

A major challenge for an HIV vaccine is to elicit potent and broad neutralizing antibody (Nab) responses that protect against diverse viruses. However, the nature and location of available targets on the envelope (Env) glycoproteins of each incoming virus remain largely undefined. Furthermore, should a vaccine elicit Nab, there has been little consideration of how to prevent viral escape.

### **Methods**

Here we characterized autologous Nab and viral escape over the first two years of infection in 2 subtype C HIV-1 infected subjects in a Zambian cohort. Viral env genes were cloned through SGA and Nab resistant variants were identified at each time point using a pseudovirus-based neutralization assay. These variants were then used to create a series of Env chimeras and mutants within the background of the corresponding newly transmitted Env. Monoclonal antibodies (Mabs) were derived from one patient by EBV transformation of B cells to generate hybridomas.

### **Results**

Escape from early Nab was driven by substitutions in the V5 region in one subject, but an accompanying change in

the  $\alpha 2$  helix did not contribute directly. Nab resistance at later time points fluctuated between different molecular pathways and at times required cooperative interactions between gp41 and gp120. In contrast, V1V2 was the major determinant of escape in the second subject at all time points, and two Mabs derived from this patient targeted this domain. Escape from the Mabs required changes in two sites of potential N-linked glycosylation in V1 and V2 and the data suggests that escape from one Mab occurred within 48 days of infection.

### **Conclusion**

The findings provide strong evidence that the immunogenicity and perhaps exposure of the hyper-variable domains on the transmitted Env launch the initial Nab response, arguing that immunization strategies will need to circumvent these defenses, or target them directly, to induce a protective Nab response.