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Exposing the Initial Encounter of the Immune System with HIV – A Tool for Very Early Diagnosis of Infection, and A Potential Clue for New Drugs and Vaccines.

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***Background*:** Unlike most infections, HIV antibodies are not detectable in the blood within 7-10 days from infection. The delay in seroconversion, estimated to be either 22 days or several months, is termed the seronegative window period (WP). It is caused by specific, active, immune suppression by the virus, resulting in delayed HIV diagnosis. Early detection of HIV infection is a key to curtailing the epidemic, as early infections are the most infectious, and should be treated. The WP phenomenon also means that the very first encounter of the immune system with the virus is hidden from us. The antibodies which are eventually produced may not be the ones which would have been produced in the first days of infection.

***Methods*:** Stimmunology™ (ST) is a technology which was developed to solve the problem of the WP, by enabling the production of antibodies, *in-vitro*, in a whole blood sample, within days of infection. ST overcomes the initial immune suppression caused by the virus, and activates the lymphocytes which were primed by the virus *in-vivo*, to differentiate and proliferate *in-vitro*, leading to antibody production during the culture step. In the reported studies, the activation step was done using one ml of fresh (<24h) whole blood, cultured in the SMARTube™ HIV&HCV, a ST device, used as per manufacturer's instructions. The resulting supernatant, the SMARTplasma, and the concordant plasma, were tested for HIV antibodies using approved kits and algorithms for HIV diagnosis. For studying the antibody repertoire, HIV-peptide ELISAs were set up.

***Results*:** Using SMARTubes in a study of 602 blood samples from individuals at high risk for HIV (HRG), in USA, all seropositives were also SMARTplasma positive. An additional HIV infection, still seronegative, was identified with SMARTplasma on the commercial kit, and confirmed positive by western blot. In a cross-sectional study of 1137 HRG in South Africa, 3 new infections were identified, by SMARTplasma. Two of the three WP cases were followed monthly and seroconverted 1 and 4 months later. The plasma of the third WP case was positive by PCR ($9.5x10^4$copies/ml). HIV antibody positive plasma and SMARTplasma samples, from HRG in Mexico, were analyzed using a small panel of HIV-peptide ELISAs. Antibodies to several peptides were found mostly, or exclusively, in SMARTplasma samples only.

***Conclusion*:** Stimmunology, and its commercial application, the SMARTube, enabled detection of infection weeks and months prior to seroconversion, providing a critical yet simple and cost effective tool for very early diagnosis of HIV infections. Preliminary results, regarding the HIV antibody repertoire indicate that antibodies to some epitops are not found in the plasma of those who seroconverted, while found in the SMARTplasma. Thus Stimmunology exposed early immune epitops hidden to us due to silencing by the virus.