Low magnitude and frequency of HSV-2-specific interferon gamma-producing CD4(+) and CD8(+) T cell responses detected in HIV-1 heterosexual discordant couples

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Background: Many HIV databases and applications focus on a limited domain of HIV knowledge. Since even a “simple” organism like HIV represents a very complex system with many interacting elements, the fractured structure of existing databases and applications likely limits our ability to investigate and understand HIV. To facilitate research, therefore, we have built HIVToolbox, which integrates much of the knowledge about HIV proteins and presents the data in an interactive web application. HIVToolbox allows quick and convenient hypotheses generation, experiment interpretation, and potential new drug structure creation.

Methods: HIVToolbox was built as a standard three-tier J2EE web application, consisting of 1) an underlying relational MySQL database, 2) a set of standard Java data access objects that pull data from the database, and 3) a set of dynamic web pages the user interacts with. HIV-1 data from external sources such as the Protein Data Bank, NCBI, Los Alamos, etc. was collected, curated, and stored in the HIVToolbox database. Additional data, such as homology and position statistics matrices, was generated from existing data. Since version 1, drug binding site and drug resistant mutation data has also been added.

Results: HIVToolbox was used to create several new hypotheses about HIV-1 integrase, including predicting the location of a CK2 phosphorylation site, which was later confirmed by experiment.

Figure 1. Protease with drug Amprenavir shown [Interactive HIV protein page].
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**Background:** For 26 years a group of HESN women from Nairobi, Kenya who can be epidemiologically described as relatively resistant to HIV infection have provided clues towards the identification of natural correlates of protection against HIV-1 infection. Studies of these HIV-1-resistant women suggest they possess a unique mucosal environment which includes the overexpression of specific antiproteases and a unique proinflammatory cytokine expression pattern. Here we describe how these factors contribute to protection against HIV infection during mucosal transmission.

**Methods:** Cervical lavage fluid (CLV) from 277 women were collected from 76 HIV-1-resistant, 120 HIV-1 uninfected, and 97 HIV-1 infected women. CLV protein was analyzed both independently by SELDI-TOF MS technology and pooled groups by 2D-LC-FTICR MS. Of the more than 350 unique proteins identified 29 proteins were differentially expressed (greater than 2-fold cutoff) between HIV-1-resistant women and controls. These findings were confirmed by traditional ELISA and quantitative Western Blot (WB) analysis.

**Results:** The majority of overexpressed proteins were serpins, their breakdown products (p = 2.2 x 10^-6), and other antiproteases, as well as innate factors with known anti-HIV-1 activity. The overexpression of specific serpins and an epithelial-derived antiprotease was confirmed by ELISA and WB (p = 0.004, p = 0.05, and p = 0.02), respectively. Underexpressed proteins in HIV-resistant women included inflammatory proteases and immune response factors. Cytokine/chemokine analysis revealed that antiprotease expression correlated with pro-inflammatory cytokines (p < 0.0001). However, this was independent of the elevated antiprotease expression observed in HIV-resistant women who in fact expressed reduced levels of certain inflammatory chemokines (p = 0.018).

**Conclusion:** HIV-1-resistant women have elevated acute phase response antiproteases that may regulate inflammation in the female genital tract. Coupled with elevated expression of anti-viral proteins, this may provide a mucosal environment less susceptible to HIV-1. These antiproteases might contribute to a natural protective environment against HIV-1 infection. Understanding this mechanism could aid in microbicide or therapeutic development.

**THPDA0103**

Low magnitude and frequency of HSV-2-specific interferon gamma-producing CDA+ and CD8+ T cell responses detected in HIV-1 heterosexual discordant couples

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**Background:** Herpes simplex virus type 2 (HSV-2), the most frequent cause of genital ulcer disease (GUD), has been shown to play a more important role than any other sexually transmitted infections (STIs) in driving HIV prevalence in Africa. In turn, HSV-2 infection leads to more frequent HSV-2 reactivations and shedding. The exact immune mechanisms involved in this virological negative immuno-synergy are unknown. In the present study we sought to assess whether HSV co-infection would affects HSV-specific T cell immunity.

**Methods:** Nineteen HSV peptides, derived from HSV-2 glycoproteins gB and gD, were used to analyze the frequency and the magnitude of HSV-2-specific IFN-γ-producing CD4+ and CD8+ T cell responses in 30 HSV-2 seropositive patients and 17 HSV-2 seronegative individuals in a cohort of heterosexual Senegalese HIV-discordant couples, using ELISPOT assay. HIV RNA viral load has been run for HIV infected subjects and CD4 count run for all subjects using a flow cytometry method.

**Results:** The magnitude and frequency HSV-2-specific T cell responses was compared between 21 HSV-2 co-infected with HIV-1 and 9 HSV-2 mono-infected individuals. A significantly higher magnitude of IFN-γ-producing T cell responses were observed in HSV-2-infected patients compared to seronegative individuals (median, 61 vs. 0 spots/10^6 PBMC, P = 0.001). Moreover, twenty-four (80%) out of 30 HSV-2 seropositive patients showed significant HSV-2-specific IFN-γ-producing T cell responses compared with only 6 (35%) out of 17 HSV-2 negative individuals (P < 0.001). The HSV-2 mono-infected patients showed significantly higher magnitude of HSV-2-specific T cell responses compared to HSV/HIV co-infected patients (median, 140 vs. 42 spots/10^6 PBMC, P = 0.024).

**Conclusion:** Our finding suggest that co-infection with HIV-1 in HSV-2-infected patients might be associated with reduced HSV-2 cellular immune responses. However, the interaction between HIV and HSV-2 appears complex, and precise longitudinal studies will be required to dissect their exact temporal relationship.

**A10 - Mucosal immunity/defenses: responses and dysfunction**

**TUAA0304**

Oral serum-derived bovine immunoglobulin (SBI) administration leads to duodenal gastrointestinal-associated lymphoid tissue (GALT) CD4+ T-lymphocyte increases and improved small intestinal absorption function in an 8-week pilot study in patients with HIV-enteropathy

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**Background:** HSV-infection leads to GALT CD4+ T-cell depletion that persists despite prolonged antiretroviral therapy (ART). SBI is a medical food that neutralizes bacterial antigens and reduces gut inflammation in animal models.