Innate Immunity Predictors of HIV Risk Linked To Genital Herpes

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BACKGROUND

Incident HSV-2 infection is associated with over threefold increase in risk of HIV acquisition. Understanding the underlying mechanisms is a research priority given the high global HSV-2 prevalence (ranging from 39 to 83%) among women in Sub-Saharan Africa. We hypothesized that: 1) aberrant innate immunity predisposes to both HIV-1 and HSV-2, and 2) innate immunity differs between incident and established HSV-2 infection, which may explain the greater HIV acquisition risk associated with incident HSV-2.

METHODS

We analyzed longitudinal samples from HIV-1 negative visits of 1019 women before and after HSV-2 acquisition. We measured cervical and serum biomarkers of inflammation and immune activation previously linked to HIV-1 risk. Protein levels were Box–Cox transformed and odds ratios for HSV-2 acquisition were calculated based on top quartile levels (sCD14) or below/above median (all other immune mediators) for all HSV-2 negative visits. Bivariate analysis determined the likelihood of HSV-2 acquisition by biomarker levels preceding infection. Linear mixed-effects models evaluated if biomarkers differed by HSV-2 status defined as negative, incident, or established infections with an established infection cut-off starting at 6 months.

Distinct patterns of altered systemic and cervical immunity precede and predict risks of HSV-2 and HIV-1 acquisition.
Shared mechanisms of vulnerability to both viral infections include factors upregulating mucosal defensins (BD-2) and suppressing systemic immunity (CRP).

RESULTS

- In the cervical compartment (**Fig.1**) ↑BD-2 prior to seroconversion predicted both HSV-2 and HIV-1 acquisition, while ↑RANTES or ↓IL-1RA were sole predictors only of HIV-1 acquisition and ↓SLPI, ↓ICAM-1, ↑MIP-3α or ↑IL-6 were significant predictors of HSV-2 acquisition only.
- At the systemic level (**Fig. 2**), ↓CRP predicted HIV-1 while ↑sCD14 predicted HSV-2 acquisition. A pattern of low serum CRP combined with high cervical BD-2 was shared as a predictor of both HIV-1 and HSV-2 acquisition (**Fig 2)**
- Different patterns of grouped proinflammatory (IL-1β & IL-6 or IL-8 & MIP-3α) or suppressed antiviral (ICAM-1 & VEGF) cervical immunity preceded and predicted HIV-1 and HSV-2 seroconversion (**Fig. 3**).
- Most cervical biomarkers were lower after HSV-2 acquisition compared to HSV-2 negative visits, with incident infections associated with a larger number of suppressed cervical biomarkers and lower serum IL-6 compared to established infections (**Table 1**).

Fig. 1. Cervical immunity antecedents of HIV-1 and/or HSV-2 aquisition

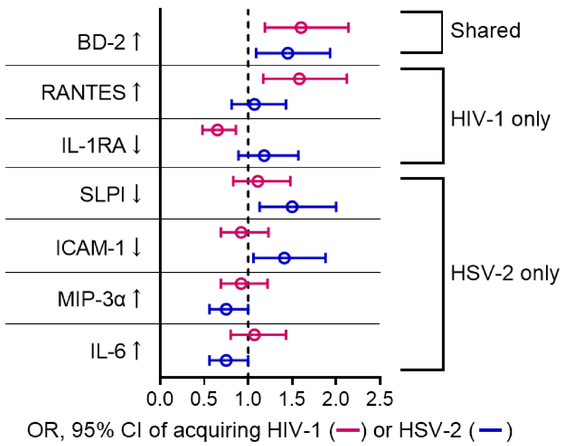


Fig. 2. Systemic and systemic-cervical immunity antecedents of HIV-1 and/or HSV-2 aquisition

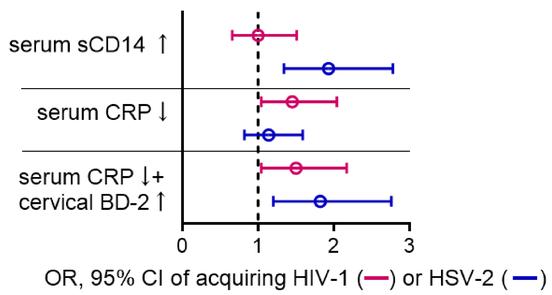
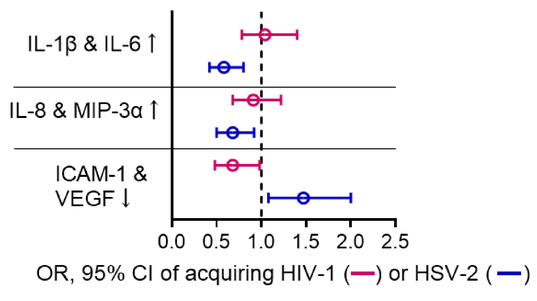


Fig. 3. Grouped cervical immunity antecedents predictive of HIV-1 and/or HSV-2 aquisition



CONCLUSIONS

- Predisposing factors impacting mucosal and systemic immune balance may be contributing to higher risk of both HIV-1 and HSV-2 acquisition.
- A combination of systemic immunoinflammatory and cervical immunosuppressed states is associated with higher odds of acquiring HSV-2.
- Decreased innate immunity persisting during incident herpes infection may add to the increased HIV-1 susceptibility in women infected with HSV-2.
- This study contributes to a better understanding of HSV-2 acquisition in women and the complex link between HSV-2 and HIV-1 by providing clinical evidence for shared biological mechanisms of vulnerability to viral infection based on antecedent profiles of systemic and mucosal innate immunity.
- By identifying molecular predictors of HSV-2 risk, this study provides targets and clinical safety endpoints for the development of preventive products.

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Table 1. Differences in levels of cervical and systemic biomarkers by HSV-2 infection status adjusted for covariates

	HSV-2 status at the visit		
Cervical Biomarker	**incident (n=491) vs. negative (n=1203)**	**established (n=838) vs. negative (n=1203)**	**incident (n=491) vs. established (n=838)**
BD2		↓**	
SLPI	↓*	↓**	
IL-1RA	↓**		
IL-1β	↓***		↓**
IL-6	↓***	↓***	
IL-8	↓**	↓*	
MIP-3α	↓***		↓**
VEGF	↓**	↓*	
Serum Biomarker	**incident (n=390) vs. negative (n=646)**	**established (n=361) vs. negative (n=646)**	**incident (n=390) vs. established (n=361)**
IL-6			↓**