Genital Immune Correlates of Prevalent and Incident Herpes Simplex Virus 2 (HSV-2) Infection

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Background

Herpes simplex virus type-2 (HSV-2) infection is usually asymptomatic[1], increases genital CD4+ T cell activation[2] and HIV acquisition risk[3]. We examine associations of seroprevalent and sero-incident HSV-2 infection with genital immune parameters, including soluble E-cadherin (sE-cad), a biomarker of epithelial barrier disruption[4], which can facilitate HIV acquisition[5].

Methods

- This longitudinal study was nested within the Maisha Fiti cohort of 1003 female sex workers in Nairobi, Kenya. Among 731 HIV-negative participants, HSV-2 serostatus was assessed by Kalon HSV-2 IgG assay at baseline and follow up.
- Genital immune factors were assayed in cervicovaginal secretions using multiplex electro-chemiluminescent immunoassay (MSD), and socio-behavioural characteristics assessed by questionnaire.
- Socio-behavioural characteristics and immune parameters were compared between HSV-2 seropositive and seronegative participants using chi-square and Mann-Whitney U tests and examined using linear regression models. Socio-behavioural characteristics and immune parameters predictive of HSV-2 acquisition were similarly compared between participants with incident infection and those who were seronegative throughout the study period.

Results

Table 1. Associations of prevalent and incident HSV-2 infection

Characteristic	Prevalent infection			Incident infection		
	Sero-negative (n = 317)	Sero-positive (n = 414)	p-value	Remained sero-negative (n = 286)	Sero-converter (n = 31)	p-value
Demographic (median, range)						
Age	29 (18-45)	35 (19-45)	**< 0.01**	28 (18-45)	31 (19-44)	**< 0.01**
Age at sexual debut	17 (2-26)	16 (6-25)	0.442	17 (2-26)	16 (9-25)	0.397
Number of clients in past week	4 (0-70)	3 (0-60)	0.120	4 (0-70)	6 (0-35)	**< 0.01**
Behavioural (n, %)						
Secondary education completion	123 (39%)	113 (27%)	**< 0.01**	107 (37%)	16 (52%)	0.140
Intravaginal practises (douching)	178 (56%)	267 (64%)	**0.027**	160 (56%)	14 (45%)	0.227
Clinical (n, %)						
Bacterial vaginosis	116 (37%)	155 (37%)	0.897	42 (15%)	10 (32%)	**< 0.01**

Figure 1. Genital immune markers and prevalent HSV-2 infection

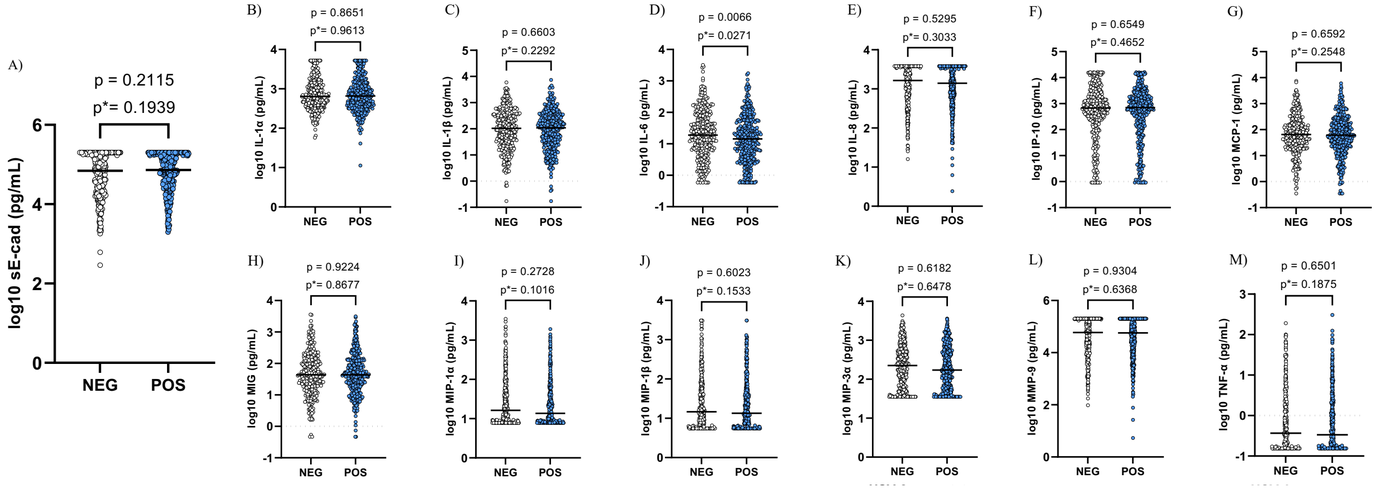

Figure caption: There was no association with HSV-2 serostatus and the evaluated immune markers (A-C, E-M), except for IL-6 (D). Results for Mann-Whitney U Test and p-values for each comparison are indicated above the graph. P-value with an asterisk indicates multivariate comparison results. Solid line indicates the median. Abbreviations: sE-cad, soluble e-cadherin; IL, interleukin; IP, interferon-inducible protein; MCP, monocyte chemoattractant protein, MIG, monokine induced by interferon-γ; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; NEG, negative; POS, positive; TNF, tumour necrosis factor.

Figure 2. Genital markers and incident HSV-2 infection

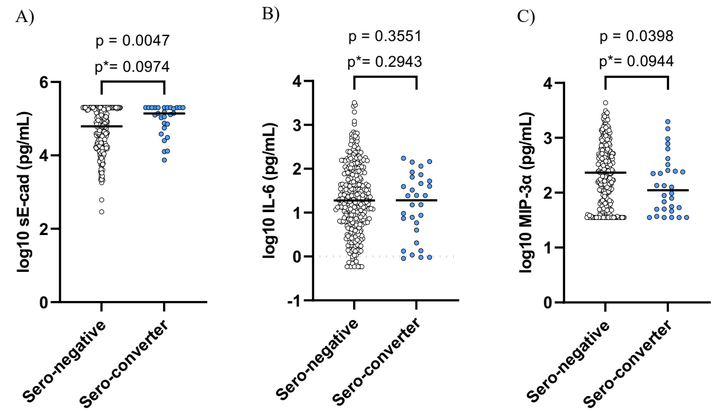

Figure caption: There was an association with incident HSV-2 infection sE-cad (A) and MIP-3a (C). Results for Mann-Whitney U Test and p-values for each comparison are indicated above the graph. P-value with an asterisk indicates multivariate comparison results. Solid line indicates the median. Abbreviations: sE-cad, soluble e-cadherin; IL, interleukin; MIP, macrophage inflammatory protein.

Conclusions

- Subclinical epithelial barrier disruption is unlikely to be a major mechanism underpinning increased HIV acquisition among individuals with HSV-2 infection.
- Though potential associations between HSV-2 incident infection and preceding genital levels of cytokines have been reported[6], we find that genital epithelial disruption and immune markers are not predictive of increased HSV-2 susceptibility when we control for BV Nugent score. This suggests that the genital microbiome may instead play an important role.
- Subsequent investigations should study the important associations between HSV-2 infection, BV and HIV.

References

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