Changes in Genital Inflammatory Biomarkers Associated with HIV pathogenesis in Survivors of Acute Sexual Assault

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Background

The mechanisms of how sexual violence affects women's risk for HIV remains unclear. Women are more likely to be affected by HIV/AIDS, as over 50% of all HIV infections were in women, particularly in young women[1]. Women are also disproportionately affected by sexual violence. In the United States alone, sexual assault is the sixth leading cause of injury in women[2]. Three longitudinal studies from Africa, for example, showed that intimate partner violence was associated with a 50% increase in HIV infection[1].

Increased HIV acquisition has been shown to be associated with inflammation in the genital tract[3]. Previous studies have also shown that there was a significant association between sexual assault and genital immune biomarkers linked to inflammation in women who experience life-long chronic sexual violence[2].

This study will evaluate the following biomarkers in survivors of acute sexual violence: cytokines interleukin 1 alpha (IL-1α), interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6), and chemokine macrophage inflammatory protein-3 (MIP-3α). IL-1α is a primary cytokine involved in the production of inflammation[4]. IL-1β is a mediator of that inflammatory response and is involved in immune cell proliferation, differentiation, and apoptosis[4]. TNF-α is also involved in the systemic inflammation and the acute phase reaction, and it is an important regulator of immune cells[4]. IL-6 is both a pro-inflammatory and anti-inflammatory cytokine; it mediates fever and the acute phase response, which is a part of the body's innate immune response[4]. MIP3α attracts lymphocytes and is a known anti-HIV factor[5].

Objectives

The principal aim of this study is to investigate the levels of genital inflammatory biomarkers in survivors of acute sexual assault violence. It is hypothesized that there will be an increase in biomarkers levels in Cases compared to Controls and inflammation will be highest immediately after assault.

Methods

Recruitment: Cases were collected from the Women and Infants Hospital of Rhode Island (WIHR) from women who experienced sexual assault within 5 days before their first visit to the clinic. Controls were taken from a previous study and were women recruited from the Washington D.C. metro community who have never experienced sexual assault.

Enzyme-Linked Immunosorbent Assay (ELISA): Cervicovaginal lavage (CVL) samples were collected. Each sample was tested in triplicate for IL-1α, IL-1β, TNF-α, IL-6, and MIP-3α according to manufacturer's protocol (R&D Systems).

Statistical Analysis: Median values of IL-1α, IL-1β, TNF-α, IL-6, and MIP-3α of the cases and controls were compared using Mann-Whitney U test. The hour of the first clinic visit after the assault for each biomarker were compared to each other using Kruskal-Wallis ANOVA test. Graphs were created using Graphpad PRISM.

Results

Fig. 1: Differential expression of biomarkers in Cases vs. Controls

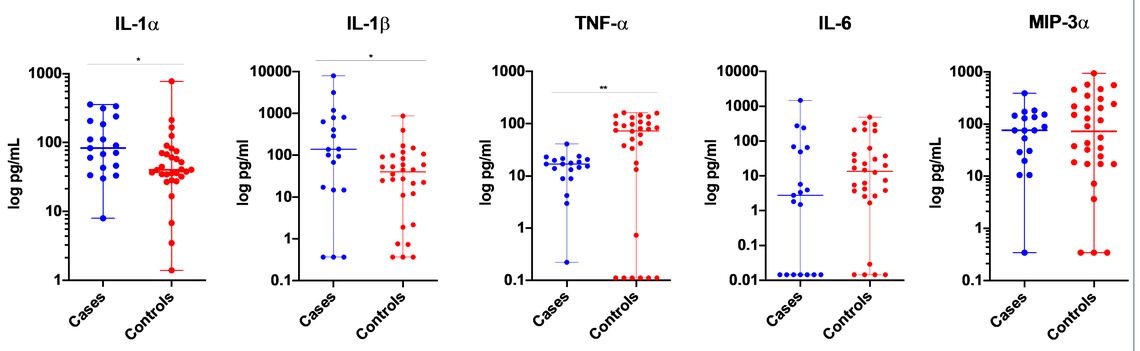

Fig. 2: Changes in biomarkers based on time after assault

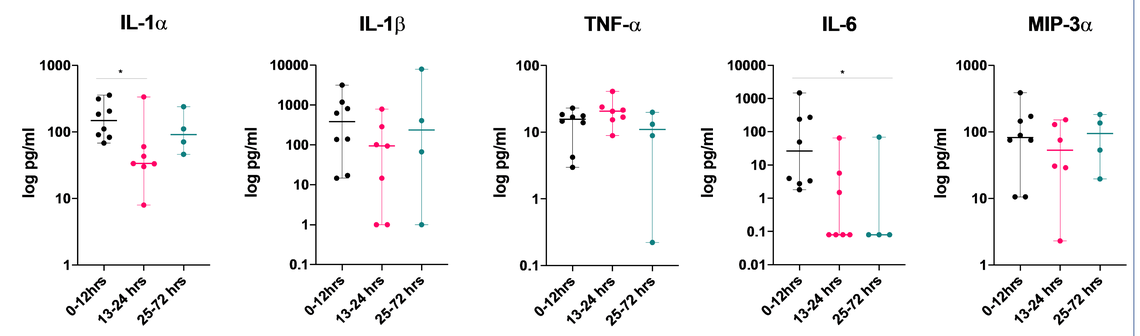

Table 1: Demographic Information

	Cases (%)	Controls (%)
N	19	30
Age Mean (Range)	28.4 (31)	33.3 (53)
Race		
White	8 (42. 1)	15 (50)
Black	2 (10.5)	6 (20)
Other	9 (47.4)	9 (30)
Hormonal Contraceptive Use		
Yes	11 (57.9)	15 (50)
No	10 (52.6)	15 (50)
Menstrual Cycle		
Proliferative	7 (36.8)	8 (26.7)
Secretory	1 (5.26)	10 (33.3)
Post-Menopausal	2 (10.5)	5 (16.7)
Unknown/Neither	9 (47.4)	7 (23.3)

Table 2: Differences in Biomarkers

	Median [IQR]	
	Cases	Controls
IL-1α	83.1 [163.0]	40.1 [40.22]
IL-1β	138 [777.9]	39.8 [84.61]
TNF-α	16.9 [11.79]	73.2 [92.48]
IL-6	2.75 [64.96]	13.7 [44.06]
MIP3α	75.4 [119.9]	72.8 [240.2]

Conclusions

- Significant changes in inflammatory biomarkers IL-1 α, IL-1β, and TNF-α between cases and controls. IL-1 α and IL-1β were increased, while TNF-α was decreased,
- Significant changes in IL-1α and IL-6 when comparing the hour of arrival to the clinic after the assault. IL-1α and IL-6 were increased in the 0-12 hours compared to the 13-24 hours and the 25-72 hours.
- This finding suggests an immediate inflammatory immune response following a sexual assault, which has the potential of increasing HIV risk in these women.

Future Directions

- Measure expression and perform statistical analysis of anti-inflammatory and wound-healing biomarkers.
- Understand mechanisms of wound-healing through in vitro cell culture-based model for TNF-α, IL-1 α, and IL-1β.
- Compare these results to other sexual assault studies with chronic and non-acute survivors .

References

1. Heise DL, McGory E. Green. Greentree II: Violence against Women and Girls, and HIV Report. *STRIVE*. 2016 August.
2. Ghosh M, Daniels J, Pyra M, et al. Impact of chronic sexual abuse and depression on inflammation and wound healing in the female reproductive tract of HIV-uninfected and HIV-infected women. *PLOS ONE*. 2018 June 12.
3. Passmore, J., Jaspan, H., & Masson, L. (2016, March). Genital inflammation, immune activation and risk of sexual HIV acquisition. Retrieved December 22, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6194860/
4. Punt, J., Owen, J. A., Stranford, S. A., Jones, P. P., & Kuby, J. (2019). *Kuby immunology*. New York: W.H. Freeman/Macmillan Learning.
5. Ghosh, M. (2014, April 23). Secreted Mucosal Antimicrobials in the Female Reproductive Tract that are Important to Consider for HIV Prevention. Retrieved December 21, 2020, from https://onlinelibrary.wiley.com/doi/full/10.1111/aji.12250

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