Case Report

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The biobehavioral impacts of sexual violence: Findings from an acute repeat survivor of vaginal rape

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Abstract

Background: Individuals who have experienced repeat sexual violence victimization face adverse mental and physical health outcomes, including immune and stress response functioning. We aim to further understand repeat sexual violence victimization to develop responsive and appropriate treatment for survivors of sexual violence.

Methods: We present the immunological and contextual findings of a participant ($N = 1$) who experienced repeat sexual violence victimization during her enrollment in The THRIVE Study, a prospective case–control study of women aged 14–45 years, who have experienced recent consensual vaginal penetration ("controls") or forced vaginal penetration ("cases"). Participants complete a survey, HIV/sexually transmitted infection, and pregnancy testing, blood sampling for C-reactive protein and adrenocorticotrophic hormone, collection of cervicovaginal fluid for immunological biomarkers, and self-collection of saliva samples for cortisol measurements, across study visits (Baseline, 1, and 3 months).

Results: The case study participant, aged 18 years upon enrollment, experienced sexual trauma before four of five study visits. Trends in the mental health indicators demonstrate reciprocal fluctuations in adverse mental health and resilience in accordance with revictimization and circumstantial changes. Suppressed immune biomarkers appear to correlate with increased adverse mental health, while mental health recovery trends with immunological recovery. The participant presents with dysregulated hypothalamic–pituitary–adrenal axis diurnal profile.

Conclusions: This profile illustrates the intra-individual biobehavioral impact of experience with revictimization over the course of 6 months, capturing experiences that are rarely studied either longitudinally or with the depth of the current research. The findings underscore the value of monitoring cervicovaginal immune functioning and hypothalamic–pituitary–adrenal axis dysregulation in coordination with changes in mental health over the course of repeated sexual trauma.

Keywords

female genital tract, immunology, mental health, sexual violence

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Introduction

Women in the United States (U.S.) continue to experience a high burden of sexual violence, with profound consequences for health and wellbeing. Approximately 20% of U.S. women experience rape, defined as "any completed or attempted unwanted vaginal (for women), oral, or anal penetration through the use of physical force (such as being pinned or held down, or by the use of violence) or threats to physically harm,"[1] while 44% experience any sexual violence (SV), including sexual coercion or unwanted sexual contact.[2] Community-based samples report an even higher prevalence, particularly for women of color.[3] Young women face the highest burden of SV with 79% of rape experiences occurring before the age of 25.[2] Furthermore, two-thirds of survivors of SV experience revictimization.[4] SV impacts survivors throughout their lifespan, with physical impacts lasting for years,[5] and stress from trauma causing morbidity long-term.[6]

Numerous studies have documented the behavioral links between SV and HIV acquisition among women.[7] However, the biological mechanisms are less understood. Hypotheses include disruption of the cervicovaginal epithelium leading to immune activation and inflammation, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, impacting innate and adaptive immune responses in the female genital tract.[8] Among adolescents, cervical ectopy, inflammation, comorbid sexually transmitted infections (STIs), and maturational changes in reproductive hormone regulation may increase HIV susceptibility.[9] In addition, downstream effects of chronic stress[7] may moderate immune responses and wound healing.[7,10] Advancing our understanding of these complex biobehavioral pathways is essential for efforts to develop robust HIV prevention for women exposed to SV.

Engaging survivors of acute SV in research is challenging.[11] Identification and recruitment of recent survivors is difficult due to limited reporting and service seeking. Survivors may perceive high participant burden, particularly with research that is longitudinal, focuses on recent SV, or involves physical examinations. Although engagement of survivors in research is acceptable even acutely post-violence, researchers must be aware of the possibility of re-traumatization and/or stigmatization of experiences,[12] and the discomfort some survivors experience during participation.[11]

It is at this apex that biobehavioral research on SV and HIV sits, wherein participants must agree to (1) discuss their experience of SV that allows capture of contextual factors on risk behavior mechanisms, (2) consent to a physical examination and biospecimen collection that contributes to understanding of the physiological alterations to the systemic and local immune responses, and (3) be enrolled acutely in these biobehavioral processes.

This report presents a case study of a single participant enrolled in The THRIVE Study. This case provides a contextual profile of acute SV, repeat SV, mental health, systemic and genital inflammation, and stress response outcomes 2 months post-SV. The nature of the circumstances and the multilevel assessments represent novel observations and contribute to the literature related to immune and stress responses to SV.

Case report

Parent study

The THRIVE Study is a prospective case–control study of women residing in San Diego County, California. Eligible participants have a cervix and vagina, are 14–45 years of age, and self-report nonconsensual vaginal penetration by a phallus perpetrated by a male (cases) or consensual vaginal sex with a male (controls), within the past 2 weeks. Detailed methods are published elsewhere.[13] Participants attend three study visits (Month 0, Month 1, Month 3). At each study visit, participants complete (1) an interviewer-administered survey; (2) pregnancy testing; (3) a blood draw for progesterone, C-reactive protein (CRP), HIV testing, and adrenocorticotrophic hormone (ACTH); and (4), a minimally invasive cervicovaginal exam with swabs for STIs and collection of cervicovaginal lavage (CVL) fluid by rinsing the cervical–vaginal area with 10 mL of normal saline. Survey measures include validated scales for alcohol use (Alcohol Use Disorder Identification Test (AUDIT)),[14] illicit drug use (NIDA Modified ASSIST),[15] suicide risk (Suicide Behaviors Questionnaire-Revised (SBQ-R)),[16] posttraumatic stress disorder (PC-PTSD),[17] depression (CESD-10),[18] perceived stress (PSS),[19] resilience (CD-RISC),[20] and battering (WEB).[21] Immediately following each study visit, participants self-collect saliva samples three times a day for 3 consecutive days. Participants receive US$50 in compensation per study visit, and US$35 per round of saliva samples, up to US$255 for participation.

Measurement of biomarkers

As described in detail elsewhere,[13] saliva samples are assayed for cortisol and DHEA-S. CVL is assayed for pro-inflammatory cytokines/chemokines (IL-6, IL-8, IL-1α, IL-1β); tumor necrosis factor alpha (TNF-α), macrophage inflammatory protein-3 alpha (MIP-3α); interferon gamma-induced protein 10 (*IP*-10), anti-inflammatory/anti-HIV biomarkers secretory leukocyte protease inhibitor (SLPI), Elafin, Serpin A1, and human beta defensin 2 (HBD-2), and wound-healing biomarker platelet-derived growth factor (PDGF).

Ethical approval and informed consent

All research procedures are approved by University of California San Diego Human Research Protections Program Institutional Review Board (Project #181898). All participants provide written informed consent prior to

enrollment into the study. The Case Study Participant provided written consent to be enrolled, written consent to be re-enrolled, and written informed consent for these data to be published as a case study.

Case analysis

This case report details a THRIVE Study participant enrolled as an adolescent case in July 2019. Following notification of revictimization acutely prior to her Follow-Up 2 visit, the participant was offered the opportunity, and chose, to re-enroll in the study. Her original Follow-Up 2 visit was treated as the Baseline visit for her re-enrollment. In total, this resulted in five study visits: Month 0, Month 1, Month 3, Month 4, and Month 6. By the end of her study enrollment, the participant identified re-victimization in the form of nonconsensual (using physical force or threats) vaginal penetration perpetrated by a male prior to four out of five visits: Baseline (M0), Follow-Up 1 (M1), Follow-Up 2 (M3), and Follow-Up 3 (M4). Saliva sample results are only available for months 0–3 (Baseline, Follow-Up 1, and Follow-Up 2) due to COVID-19 study disruptions. For this case study, scale indicators of mental health have been summed. All other data are reported as collected. Re-enrollment of this participant was guided by a Data and Safety Monitoring Board.

Participant support

In The THRIVE Study, a standard safety protocol is in place to ensure that women are appropriately connected to local support agencies with low-cost or free services. We integrated the principles of Trauma-Informed Care,[22] including the building of rapport and trust between patient and provider. Standard safety protocols were executed, including assessments of suicidality and risk of danger/lethality by an intimate partner, discussions about desired services, and provision of a document with local and national free or low-cost services with the offer of connection. However, for the participant in question, several additional measures were taken. These included (1) provision of direct contact information for a staff member at an SV support service agency in the county of the participant's primary residence; (2) provision of contact information for SV support services at the participant's school; (3) provision of contact information for SV support services external from the school, but within the county of school attendance; (4) provision of counseling on pre-exposure prophylaxis (PrEP) for HIV prevention; (5) regular check-ins between staff and the participant between visits; and (6) after revictimization, discussions at each study visit about safety planning. The goal of staff was to create space for discussions about the participant's needs and safety and facilitate access to support services. At the time of submission, the participant is known to be in a safe relationship.

Participant profile

The case study participant is a White woman, born female, aged 18 years upon enrollment. As part of the baseline data collection, the participant provided information on past experiences of SV. The participant experienced a physically forced vaginal and oral sexual debut at 13 perpetrated by a male stranger. At the time of enrollment, she had engaged in consensual sexual activity with three male partners and no female partners, but experienced forced sex multiple times—one or more male partner(s) used threats to force sex 2–3 times, and used physical force 4–5 times, while one or more male non-partner(s) used threats to force sex 2–3 times, and used physical force more than 10 times. To our knowledge, this participant was not involved in sex work.

Alcohol and drug use

As assessed by the AUDIT, the participant reported no hazardous drinking during her enrollment. Per the NIDA Modified ASSIST, the participant endorsed moderate risk drug use at baseline, and low risk drug use at subsequent visits.

Mental health indicators

The participant identified previous diagnosis of depression, current medication for treatment of depression, and previous suicide ideation and attempts. At every study visit, she was classified as being at significant risk for suicidal behaviors (score $\geqslant 7$ based on the SBQ-R). At each visit, the participant received counseling consistent with the study's suicide risk protocol, including questions about means and intention to harm oneself, and support resources. The participant had a known suicide attempt while enrolled in the study, prior to M6 (Follow-Up 4), resulting in hospitalization.

The participant endorsed experiences consistent with PTSD at all study visits, and displayed variation in depression, perceived stress, resilience, and battering, with the most adverse mental health at M3, and the least at M6. Figure 1 displays the changes in each continuous measure across study time-points.

Stress response dysregulation and systemic inflammation

ACTH circulation is part of a cascade initiated by hypothalamic activation, resulting in production of ACTH in the anterior pituitary gland,[23] characteristic of the HPA axis response. ACTH, reported in Figure 2, remains consistent across all visits except at M0.

Cortisol is synthesized and secreted in response to ACTH, both as part of a circadian rhythm for awakening, and in response to stress stimuli.[23] This response can be

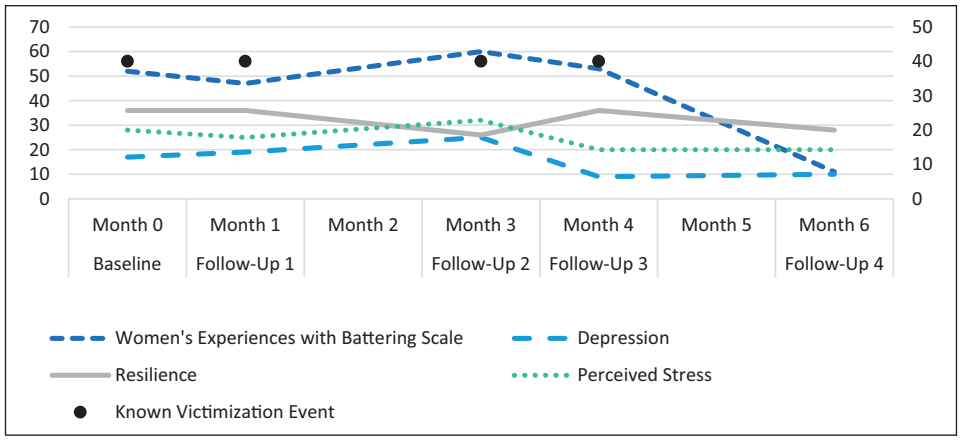

Figure 1. Mental health indicators.

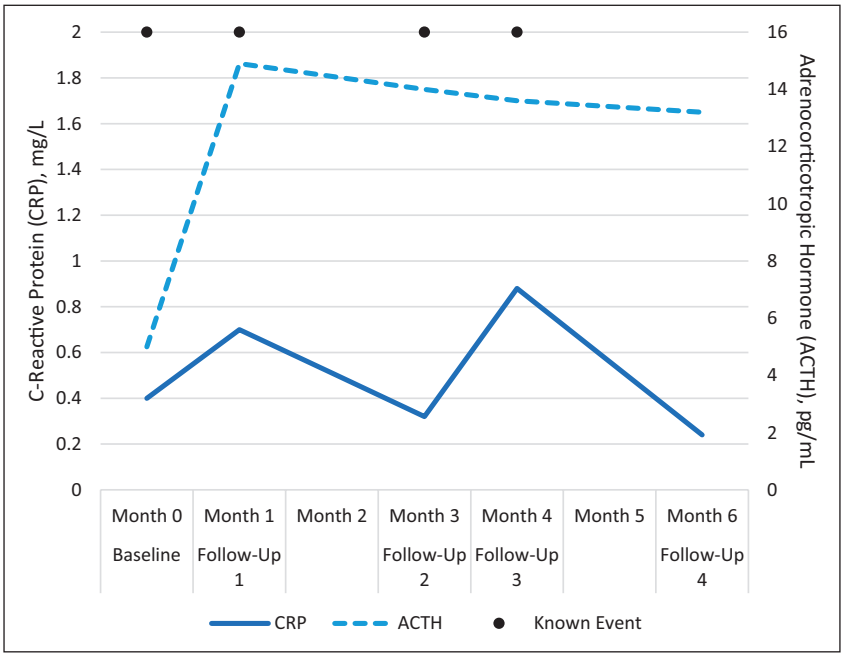

Figure 2. Adrenocorticotropic hormone (ACTH) and C-reactive protein.

dysregulated trauma and under circumstances of adverse mental health.[24] Cortisol release follows a diurnal pattern, reaching a peak after approximately 30-min post-awakening or post-stimulus, and then decreasing,[25] known as the cortisol awakening response (CAR). Impairment of the process that regulates cortisol production is considered to be dysregulation of the HPA axis.[26] Figure 3 displays the average CAR after each visit, demonstrating a distinctive response only at M0.

CRP, a marker of systemic inflammation, is a sign of immune activation. Alteration of immune functioning from HPA axis dysregulation may be evidenced in inflammation biomarkers.[27] Figure 2 displays CRP across visits, demonstrating low levels and variability.

Female genital tract immune dysregulation

Healing of the female genital tract following injury or trauma is a tightly regulated process, beginning with inflammation and ending with resolution of inflammation and tissue remodeling.[28] Incorrectly timed or executed expression of mediators of this process, may result in chronic non-healing wounds that lead to increased susceptibility to infections by HIV and other STIs.[28]

Most of the biomarkers (both pro and anti-inflammatory) we measured showed a decline in M1 which continued through M2 and M3, followed by a trend in recovery at M4 and M5 (Figure 4). M6 typically showed values less than M0 and may indicate return to baseline. As hormone fluctuations associated with the menstrual cycle can affect

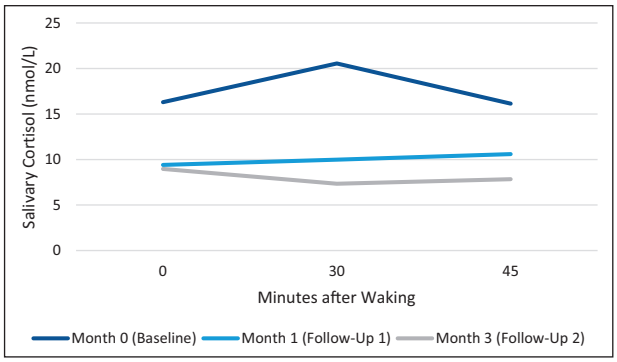

Figure 3. Salivary cortisol, cortisol awakening response (CAR).

concentrations of genital immune biomarkers, we analyzed progesterone levels to eliminate this possibility.[29]

Discussion

The current presentation of one participant enrolled in The THRIVE Study is intended to offer immunological and contextual findings for a woman within a difficult-to-access population, under extreme circumstances, to increase understanding of SV and HIV susceptibility, including four known SV events over the course of 6 months. Findings underscore the value of monitoring cervicovaginal immune functioning and HPA axis dysregulation in coordination with changes in mental health over the course of repeated sexual trauma. These findings are not intended to be generalizable, nor would we presume to offer them as evidence without adequate comparison. However, the current case does have value in its unique ability to demonstrate the immunological and contextual profile of repeat SV victimization with data collection acutely following victimization events. With that in mind, we discuss the patterns and implications of this case.

Mental health and contextual factors

The changes in mental health indicators throughout the participant's enrollment reflect experiences and state of mind resulting from both victimization events and contextual factors. Measures for experiences with battering, depression, perceived stress, and resilience throughout the 6 months of enrollment encompass four victimization events, with notable variations. At M1, there is a slight decrease in depression, perceived stress, and experiences of battering, while resilience is steady. While the participant disclosed an experience of forced or threatened sex during this time-period, the proximity of that event to her study visit is unknown. The slight improvement in mental health may be indicative of a greater period of time between victimization and data collection than at M0 (18 days between SV and enrollment), allowing for a "recovery" period. It is also possible that participation in the study enhanced positive coping mechanisms. Conversely, at M3, mental health indicators show increased adverse mental health compared to M1, exceeding the documented adverse mental health and experiences with battering of M0. This is likely secondary to the victimization event that occurred prior to M3 (occurred 10 days prior). While M4 demonstrates a decrease (improvement) in adverse mental health, the M4 visit coincided with the participant's return from college for the holiday break and removal from the environment in which she was experiencing violence, which may also account for these improvements. M6 shows an extension of the decline in battering, and a continuation of the mental health state seen at M4. At this time, the participant had not experienced revictimization since her previous visit, and disclosed that she was in a safe relationship despite being back in the victimization-associated environment. This accounts for the sharp decrease in her experiences with the battering score and may provide documentation of mental health "recovery" following extended time post-SV.

Across visits, depression, perceived stress, and experiences with battering trend together. Associations between depression and perceived stress are well documented,[30] as is the relationship between violence victimization, including battering, and adverse mental health.[31] Meanwhile, resilience trends in an inverse manner—as adverse mental health and battering increase, resilience decreases. Resilience has been found to buffer the impact of perceived stress on depression,[32] suggesting that the opposite may also be true—lower resilience may contribute to the increasingly adverse mental health indicators. The exception to this is at M6, at which time there is a slight decrease in resilience, despite a steady level of depression and perceived stress indicators, and steeply declining experiences with battering. At this time point, there may be additional contextual factors at play, such as a return to the victimization-associated environment or influences on resilience other than SV victimization.

Attenuation of hypothalamic–pituitary–adrenal axis activity

The case study participant demonstrates what may be considered dampened or attenuated HPA axis activity. ACTH values are below the expected range of 7.2–63 pg/mL[33] at baseline, while remaining at the low end of the expected range at all other study visits, with little variability. Consistent with the findings for ACTH, there was a dampening of the CAR over time and associated with sexual trauma.[24] Attenuated HPA axis activity seen in the case study participant mirrors the findings of numerous studies documenting the neuroendocrine consequences of the effects of intense, chronic stress and trauma.[24,34] These neuroendocrine effects are particularly noteworthy, as the

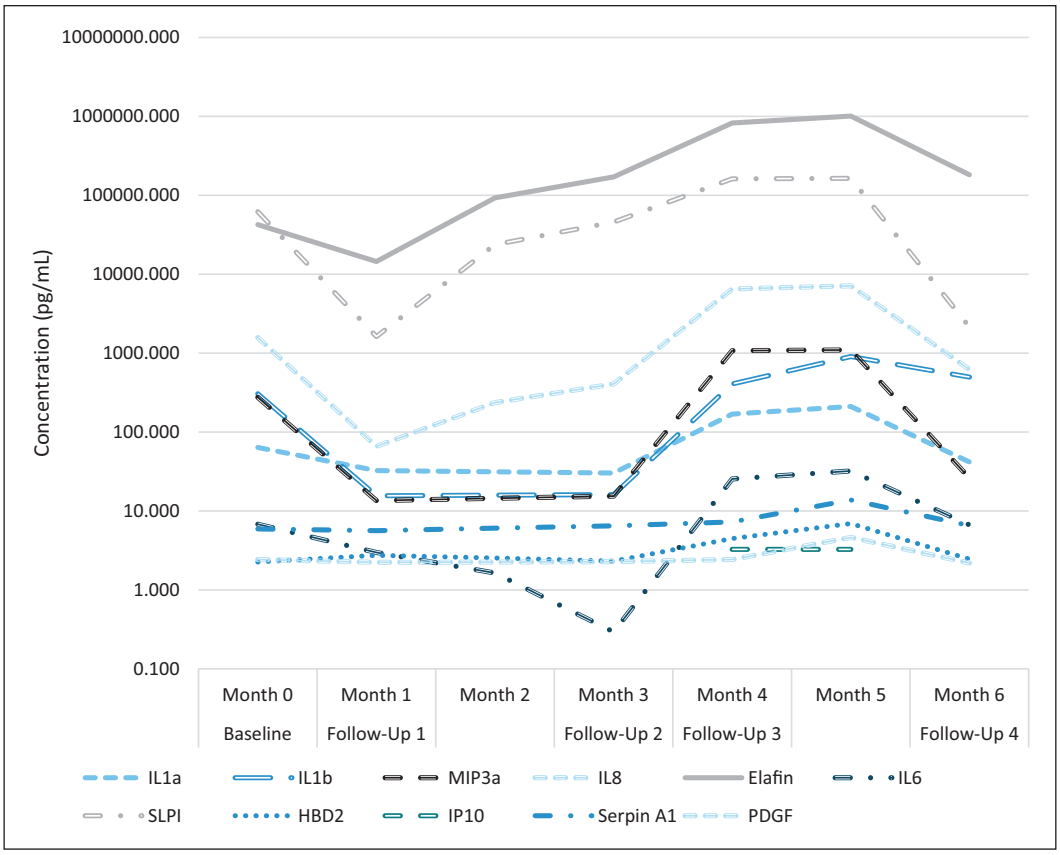

Figure 4. Female genital tract inflammatory biomarkers.

literature suggests these changes have the potential to have considerable consequences for downstream physiological systems and contribute to allostatic load.[35]

CRP demonstrated variability across visits, though consistently stayed at levels below 1.0 mg/L. CRP is considered to have an expected range of below 8.0 mg/L[36]—therefore, while within the normal range, systemic inflammation as reflected by CRP is lower than we would anticipate for an individual experiencing cumulative trauma.[37,38] In settings of acute trauma CRP may peak within a few hours of an event, followed by decline over a few days.[39] However, it is possible that by the time of data collection, this acute rise has already dissipated separate from any alterations due to cumulative trauma. Alternatively, it is possible that her cumulative experiences of violence may contribute to chronic immunosuppression (low CRP) as previously described.[40]

Female genital tract immunity

In the genital tract, we observed a trend toward suppression of both inflammatory (IL-6, IL-8, IL-1α, IL-1β); MIP-3α), and anti-inflammatory/anti-HIV biomarkers (SLPI, Elafin, HBD-2) at M1 and M3. In M5, we observed a recovery pattern for all biomarkers. At M5, all biomarkers shown a downward trend, in some cases dipping lower than at M0. Interestingly, at M3, the suppressed biomarker pattern coincides with increased perceived stress, high perceived battering, and increased depression. This immune suppressed pattern may result in higher susceptibility to infection and poor general immune responsiveness. However, at M5, the upward trend (or immune recovery) in biomarkers coincide with lower perceived stress, lower depression and increased resiliency. This is in spite of revictimization 10 days prior to each M3 and M5 visit. The responses and concurrent immune measurements were clearly distinct. As previously discussed, the change in physical environment, from school to home for an extended period of time could have influenced the mental health outcomes, which in turn may have impacted immune responsivity. Finally, M6, the only study visits without acute victimization prior, demonstrated immune biomarkers values lower than those seen at M0, possibly indicating a return to baseline values for the participant.

Strengths and limitations

Given that the current case represents only one participant, who was a White adolescent, the findings are not generalizable, nor should they be applied to individuals with

differing contexts. Inclusion criteria for The THRIVE Study encompass nonconsensual vaginal penetration that is either physically forced or facilitated by threats. We recognize that these two profiles may result in different manifestations of physical and psychological trauma, and therefore may have different immunological consequences. To reduce the likelihood of re-traumatization to participants, these are not distinguished between for the purposes of this study, limiting our ability to discuss divergent profiles.

Despite limitations, this case study demonstrates the possible utility of understanding biobehavioral factors as they relate to provision of care, particularly with implications for HIV prevention after SV. These contextual factors bear significant weight for clinical practice and emphasize the importance of holistic and trauma-informed care for survivors of SV, for whom their context matters more than that of the "average" individual.

Conclusion

The results from this study illustrate a single participant's experience with revictimization over the course of 6 months. The current presentation represents circumstances on which data are sparse, and a unique picture of the evolution of mental health, cervicovaginal immunity, and HPA axis dysregulation across SV revictimization and recovery. Findings demonstrate the responsive and related nature of mental health and cervicovaginal immune functioning, with consideration for HPA axis dysregulation, and implications for systemic immune and HIV susceptibility.

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Author contributions

K.M.A. conceptualized the current manuscript, collected data, and authored the first draft of the manuscript; M.G. obtained funding for the project, interpreted data, and contributed significantly to reviewing and revising the paper; M.Y.K. contributed to obtaining funding for the project, collecting data, and reviewing and revising the paper; E.C. conducted analyses and contributed to data curation; D.A.G. contributed to interpretation of findings, and reviewing and revising the paper; J.K.S. obtained funding for the project, provided supervision for data collection and writing of the first draft, and contributed significantly to reviewing and revising the paper.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: D.A.G. discloses that he is founder and chief scientific and strategy advisor at Salimetrics LLC (Carlsbad, CA) and Salivabio LLC (Carlsbad, CA) and these relationships are managed by the policies of the committees on conflict of interest at the University of California, Irvine and Johns Hopkins University School of Medicine. M.Y.K. received funding from the institution of Gilead Sciences and ViiV Healthcare. All other authors have no conflicts of interest to disclose.

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