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Physiological Changes from Violence-Induced Stress and Trauma Enhance HIV Susceptibility among Women

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Abstract

Purpose of review: This theoretical review identifies physiological mechanisms by which violence against women (VAW) may increase women's susceptibility to HIV through trauma, stress, and immune dysfunction.

Recent findings: Research documents systemic and local immune responses are related to stress and trauma from abuse across the life course (i.e., childhood, IPV, adulthood re-victimization). Findings are interpreted within a theoretical framework grounded in the Social Stress Theory and the concept of toxic stress, and highlight the current state of the science connecting: (1) VAW to the physiological stress response and immune dysfunction, and (2) the physiological stress response and inflammation to HIV susceptibility and infection in the female reproductive tract.

Summary: Despite a dearth of research in human subjects, evidence suggests that VAW plays a significant role in creating a physiological environment conducive to HIV infection. We conclude with a discussion of promising future steps for this line of research.

Keywords

HIV; violence against women; trauma; physiological stress response; immune dysfunction

INTRODUCTION

The United Nations defines violence against women (VAW) as "any act of gender-based violence that results in, or is likely to result in, physical, sexual or psychological harm or suffering to women" [1]. In the landmark World Health Organization (WHO) multi-country study, 30-60% of women reported lifetime physical and/or sexual violence [2]. The most

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recent US population-based estimates show that 33% of women experienced lifetime physical intimate partner violence (IPV), 19% experienced rape, and 45% experienced other sexual violence [3]. Consistently, IPV survivors experience more mental health problems than non-abused women [4–6]. As much as 30% of IPV survivors experience psychological sequelae as a result of violence, including post-traumatic stress disorder (PTSD), anxiety, depression, and suicidality [3].

VAW is a primary driver of the heterosexual HIV epidemic. Research has demonstrated significant overlap among the epidemics of VAW and HIV [7, 8]. Kouyoumdjian et al. (2013) revealed that HIV prevalence is between 1.7 and 8 times greater among women who experience IPV compared to those who have not. VAW and HIV are bi-directional: between 19.8% and 62.2% of HIV+ women have also experienced IPV, which is twice the prevalence of IPV among HIV-negative women [8, 9].

The behavioral pathways linking VAW and HIV may be bi-directional (described elsewhere [10]) and include: (1) (unhealthy) behaviors – such as drug use, alcohol use, and multiple concurrent sexual partners – that can either result from coping with violence-related trauma or enhance women's exposure to violence, (2) women's inability to negotiate sexual risk in violent relationships (e.g., condom use, type and frequency of sexual acts, partner risk behaviors), and (3) serostatus-driven violence perpetrated against women living with HIV. In addition, experiencing child sexual abuse (CSA) is linked to HIV/STI risk behaviors, including early sexual debut (≥14 years old), concurrent sexual partners, and condomless sex [11].

The physiological pathways driving VAW and HIV risk are less understood, yet potential mechanisms indicate that stress and trauma from VAW lead to: (1) dysregulated stress response, and (2) changes in the vaginal microenvironment that facilitate HIV infection in the female reproductive tract [12]. Violence-induced stress and trauma has also been linked to the unhealthy coping behaviors listed above [13]. It is likely a combination of behavioral and physiological factors that enhance risk for HIV among women who experience stress and trauma from VAW and we aim to review the literature in these areas.

THEORETICAL FRAMEWORK

The Social Stress Theory posits that individuals are embedded within socio-structural contexts that determine the stress they encounter and their coping resources. It provides a useful framework to explain how health disparities based on social disadvantage and gender inequity, as well as experiences of violence, confer stress-immune dysregulation [14]. Toxic stress posits that: (1) early stress experiences are built into our bodies creating a vulnerability to future stressors; (2) chronic stress produces physiologic disruptions or biological memories that undermine the body's stress response systems and affect the developing brain, cardiovascular system, immune system, and metabolic regulatory controls; and (3) these physiologic disruptions can persist into adulthood and may lead to physical and mental health problems, as well as increased risk behaviors [15].

Although toxic stress helps explain the long-term effects of early stress and trauma, it does not account for subsequent experiences of violence, which is reflected in our framework depicted in Figure 1. This framework, along with physiological models of stress and immune system dysfunction, will guide our review of the evidence linking VAW and HIV susceptibility. Our review focuses on the direction of relationships laid out in Figure 1, but we acknowledge that many of the proposed pathways may involve bi-directional relationships.

EXPOSURE TO STRESS AND THE PHYSIOLOGICAL STRESS RESPONSE: A REVIEW

The Central Nervous System (CNS), which consists of the brain and the spinal cord, plays a critical role in coordinating the body's response to stress. *Stress* is a natural and non-specific force that disrupts homeostasis and demands the body to adapt [16]. *Stressors* are any environmental, physical, psychological, social, or physiological stimuli that activate the CNS. Upon exposure to a stressor, the CNS incites a cascade of physiological reactions (known as the *stress response*) that occur throughout the body coordinating a series of complex, bi-directional interactions between the nervous, endocrine, and immune systems.

The two major neuroendocrine systems involved in the stress response are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. The HPA axis is comprised of the hypothalamus, the pituitary gland, and the adrenal gland [17]. When the body is exposed to stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which travels to the pituitary gland to signal the release of adrenocorticotropin (ACTH). ACTH then travels to the adrenal cortex to signal the release of glucocorticoids. The primary glucocorticoid released during the stress response is cortisol, which helps the brain and body adapt to the stressor by increasing energy, arousal, and attention [18].

In order to shift energetic resources to these functions during periods of stress, the body shifts resources away from the immune response. In addition to conserving energy, immune system suppression also prevents high levels of inflammation that might otherwise damage the body. Cortisol suppresses the body's immune response by inhibiting the transcription of immune response genes; it does so via three mechanisms: 1) suppressively binding gene promoter sequences, 2) inducing the transcription of anti-inflammatory genes, and 3) using protein interactions to antagonize pro-inflammatory transcription factors [19].

The SAM axis, located in the sympathetic nervous system (SNS), controls the "fight-or-flight" response. The nerves of the SNS release catecholamine and norepinephrine (i.e., noradrenaline), which travel to the adrenal gland to signal the release of epinephrine (i.e., adrenaline). Norepinephrine and epinephrine then travel to lymphoid organs where they signal the transcription of inflammatory biomarkers, which subsequently recruit immune cells to the site of injury (e.g., neutrophils, macrophages, then leukocytes – B cells and T cells).

The HPA axis and the SAM axis work together in response to stress. Whereas the HPA axis suppresses expression of *both* antiviral genes (including type I interferon – IFN-α/ß –

antiviral responses) and pro-inflammatory genes (including interleukins – IL-1ß, IL-6, and tumor necrosis factor), the SAM axis suppresses expression of antiviral genes and increases expression of pro-inflammatory genes [19]. Therefore, the SAM axis regulates the level of inflammation in the body by steering between these two immune responses. Both the HPA and SAM axes are regulated through negative feedback mechanisms controlled by pattern recognition receptors that respond to the body's inflammation levels [19].

Inflammation is an essential immunological response to protect against harm or injury [19]. During inflammation, immune cells communicate with each other via signaling proteins known as cytokines (including interleukins) to recruit more cells to the site of injury as part of a positive feedback loop – whereby cytokines activate the HPA-axis and stimulate the release of more cortisol. Inflammation can be acute (localized to one location) or systemic. This response can be beneficial or detrimental [19]. For example, an acute inflammatory reaction promotes healing in a wound or infection. When healing is unresolved or when the acute inflammatory response persists, chronic inflammation can result [16]. Chronic inflammatory responses accompany diseases such as diabetes, cancer, obesity, heart disease, and increased mortality, which may explain some of the associations between repeated violence, increased morbidity, and early mortality [20].

STRESS-IMMUNE DYSREGULATION

Chronic stress results in dysregulated patterns of cortisol production [24]. In well-regulated systems, cortisol production exhibits a strong circadian rhythm with a diurnal pattern where cortisol production peaks 20-30 minutes post-waking (i.e., cortisol awakening response–CAR), then rapidly declines over the next few hours and through the rest of the day until reaching a low late in the evening. In chronically stressed systems, cortisol production exhibits a flatter diurnal pattern, with higher midday levels and more attenuated decreases across the day [21]. Dysregulated cortisol production affects the ability of the HPA-axis to suppress the inflammatory response.

HPA-axis dysregulation from chronic stress, and altered cortisol levels, results in chronic inflammation and immune dysfunction [22]. HPA-axis dysregulation may lead to the unabated production of inflammatory mediators such as immune cells, cytokines, C-reactive protein (CRP), interferon gamma (IFN-γ), IL-6, and tumor necrosis factor-alpha (TNF-a). HPA-axis dysregulation can also contribute to glucocorticoid insensitivity, preventing cortisol from binding to its receptors, and suppressing anti-inflammatory gene transcription and immune response gene transcription. The chronic exposure to stress from violence and trauma in childhood, adolescence, and adulthood causes lasting alterations to the HPA-axis and stress-immune dysregulation; these alterations are referred to as *toxic stress* [15].

EXPOSURE TO VIOLENCE, STRESS, AND STRESS-IMMUNE DYSREGULATION

HPA-axis dysregulation is common among women exposed to violence [23–25] and CSA [26], although research is scant. Women exposed to stress from violence are found to have lower levels of morning cortisol [4, 25] and higher levels of evening salivary cortisol

compared to non-abused women (net of women's age, presence of childhood abuse, and other adulthood victimization) [23]. Furthermore, the extent of violence exposure appears to have a gradient effect on the magnitude of cortisol dysregulation. Women with greater violence exposure exhibit flatter patterns of diurnal cortisol characterized by both higher midday levels and more attenuated decreases across the day than women with less violence exposure [24]. Chronic and severe exposure to physical violence is associated with lower cortisol awakening response (CAR) [27].

Childhood and adolescence violence may permanently alter the stress response causing damage to the HPA-axis. Female CSA survivors are six times more likely to experience forced sex in adulthood and five times more likely to experience IPV in adulthood than women who did not experience CSA or other childhood maltreatment [28]; this may have implications for long-term and chronic dysregulation of the HPA-axis from cumulative trauma [29]. Childhood maltreatment affects genes that mediate physiological and behavioral adaptions to stress, including modulation of the HPA-axis. Emotional neglect and physical abuse have a demonstrated gene effect on HPA-axis function resulting in aggressive and other negative behaviors [30]. Furthermore, the physiological effects of stress on HPA dysregulation can be detected years after the violence occurred [31–33]. The inflammatory response to IPV has been found to persist among victims no longer in abusive relationships, who demonstrated increased CRP, IL-6 [31, 32], and interferon-c production [31, 33]. This kind of dysregulation is likely greater in women who were exposed to CSA or other abusive or adverse childhood experiences.

Literature on the physiological effect of VAW on cortisol are inconsistent: some studies find a positive relationship, whereas others find a negative or null relationship (for a meta-analysis see [34]). The cause of this inconsistent cortisol response to violence-induced stress is unknown. One theory—the *attenuation hypothesis*—states that initial exposure to violence/trauma results in pituitary-adrenal hyperactivity, followed by hypoactivity if the trauma and stress persist over a long period of time [35]. Another explanation is a neurobiological adaptation (i.e., resilience), wherein the body adapts to stress via anti-inflammatory mediators [36]. A third explanation is methodological variations in cortisol measurements (e.g., saliva vs. hair, CAR vs. basal), the type and frequency of VAW [27], underpowered studies, and other factors such as genetic variation or cumulative trauma [6, 37].

PHYSIOLOGICAL STRESS RESPONSE

The Role of Mental Health Problems

Overall, chronic or prolonged activation of the HPA-axis from violence may harm women's psychosocial and cognitive functioning and result in disproportionate mental health problems such as PTSD, depression, and anxiety [4, 18, 21]. Mental illness among IPV victims exacerbates HPA-axis dysregulation [23, 24, 38]. Violence-induced dysregulated stress response is linked to recent and lifetime histories of PTSD [35, 39] and depression [40], and increases the likelihood of social dysfunction, personality disorders, sleep and eating disorders, low self-esteem, and suicidal behavior [6]. Dysregulated diurnal cortisol rhythms are correlated with psychiatric disorders, including depression [41], and evidence

suggests these may be cumulative. Trauma-exposed individuals with co-morbid major depressive disorder and PTSD had lower daily cortisol outputs than trauma-exposed individuals with only depressive symptoms [6, 38]. The mental health mediating effect appears to function with inflammatory mediators. Elevated IL-6 and TNF-α are linked to mood disorders, depression, and anxiety [42] and childhood trauma [43]. These findings provide critical insight into mechanisms connecting VAW, HPA dysregulation, and inflammation, as well as increased vulnerability to stress brought on by adverse childhood experiences.

As we have already established, chronic and sustained activation of the HPA-axis in response to stress can lead to abnormal levels of cortisol among other hormones, which alter the immune system [22]. These changes may elevate susceptibility to infections including HIV. As we describe below, immune dysfunction can enhance HIV susceptibility directly, by cortisol binding to receptors on immune cells, or indirectly, by disrupting regulation of cytokines [22, 44].

VAGINAL MICROENVIRONMENT AND ENHANCED HIV SUSCEPTIBILITY IN THE FEMALE REPRODUCTIVE TRACT FROM VIOLENCE EXPOSURE

Stress and immune dysfunction resulting from VAW can enhance HIV susceptibility by altering the mucosal lining and vaginal micro-environment in the female reproductive tract (FRT). The mucosal lining consists of epithelial cells bathed in mucous, which provides both a physical barrier and an immunological barrier against HIV and other STIs. CD4+ T cells, the primary targets for HIV infection, are found in the mucosal lining. The probability of HIV transmission during a single episode of vaginal sex is low (1/200 to 1/2000), but approximately 40% of HIV transmission occurs in the FRT [45]. Although the epithelial cells of the lower FRT (i.e., vagina, ectocervix) provide better mechanical protection against HIV than the epithelial cells of the upper FRT (i.e., fallopian tubes, endometrium, endocervix), the lower FRT has 15 times more exposed surface area for HIV infection, especially in the event of breaches in the epithelial-cell layer [45]. The transformation zone – the region where the multilayered squamous epithelium of the lower FRT transitions to the single-layer columnar epithelium of the upper FRT— has a weak barrier capacity and a high CD4+ T-cell density [45]. Early HIV infection in the FRT is thought to occur through the mucosal epithelium, in which HIV infects sub-epithelial lymphocytes (e.g., T cells, B cells, NK cells), enters the lymph nodes, and initiates systemic HIV infection [46]. Research is lacking to delineate the exact mechanics of HIV infection *in vivo*, but several hypothesized mechanisms include the following (see review [45]): (1) rough vaginal intercourse [47], (2) tears in the epithelium from anal sex [48], or (3) STIs that cause cell death, mucosal inflammation, or ulcerations (a mechanism whereby gaps or microlesions allow the virus to penetrate into the FRT stroma) [49, 50].

Stress-immune dysregulation from violence exposure may also affect key immune system responses and mucosal lymphoid tissue thought to play a major role in enhancing women's susceptibility to HIV infection [44]. Individual HIV susceptibility may result from variation in mucosal CD4+ T cell numbers or subset distributions [51], which could likely be driven

by violence-induced HPA dysregulation. Furthermore, women in sexually abusive relationships are more likely to have micro-lesions in the vaginal and anal epithelium, which may explain connections between VAW and HIV [7, 35, 44, 52]. Genital injury causes systemic and local immune system activation [44]. Although the specific inflammatory response after sexual trauma has not been studied, the stress and immune system promptly reacts to epithelial injury [53]. Resultant stress from abuse increases activation of CD4+ T cells and the likelihood of HIV replication and transmission [54]. Tissue damage signals the release of inflammatory mediators which may result in an increased risk of infection [53]. Furthermore, stress as a result of sexual abuse can disrupt the production of pro-inflammatory cytokines and may substantially delay wound repair, extending the period in which a woman's vaginal/anal epithelia integrity is compromised [22].

PHYSIOLOGICAL STRESS RESPONSE

The role of mucosal inflammation in HIV susceptibility

Violence-induced stress may change the mucosal immunity in the FRT and increase susceptibility to HIV infection [55]. Innate and adaptive immune responses are highly influenced by HPA dysregulation [56]. As a result, there is a hypothesized window of HIV vulnerability that lasts from seven to ten days post-ovulation, during the secretory phase that coincides with the dampening of protective immune responses in the FRT [57]. These processes lead to FRT mucosal inflammation that heightens HIV susceptibility [58] as plasma and immune cells are sent to the site of injury producing pro-inflammatory cytokines and chemokines in epithelial cells, tissue-resident dendritic cells and macrophages, innate lymphoid cells, and other cells [59]. HIV infection at the mucosal surface is enhanced by pro-inflammatory cytokines, including IL-1a, TNF-α, and to a lesser degree IL-8, IL-6, and IFN-γ [60].

Several studies support the hypothesis that systemic and genital inflammation increases women's susceptibility to HIV. First, high levels of pro-inflammatory genital cytokines are correlated with damage to the vaginal epithelial barrier [51], facilitating HIV access to FRT stroma. For example, TNF-α degrades the integrity of the epithelial barrier by disrupting tight junction proteins and enhancing HIV access to submucosal target cells. Second, pro-inflammatory genital cytokines are correlated with CD4+ T cells in the FRT [61]. One study found that women who had elevated levels of (5 of 9) genital inflammatory cytokines had 3.2 times greater odds (OR, 3.2; 95% CI, 1.3–7.9) of acquiring HIV than women with normal levels [62]. Pro-inflammatory cytokines and chemokines cause the recruitment of activated CD4+ T cells to the mucosa, increasing the overall number of CD4+ targets and promoting a greater density of activated T cells, which enhances susceptibility to HIV infection [51]. This provides even more targets for HIV virons that pass through the epithelial barrier, already weakened by inflammation [51]. Third, seronegative individuals exposed to HIV have reduced systemic and mucosal immune activation [63], which supports the hypothesis that a lack of inflammation may protect against HIV acquisition. Lastly, for individuals at high risk for HIV, baseline immune activation and/or inflammation in the FRT [64] and in the blood [65] is directly associated with an increased risk of HIV infection via sexual intercourse. Chronic stress from violence and prolonged HPA dysregulation could

greatly increase women's risk of HIV inflammatory cytokines in the FRT, which persists for an average of one year before HIV infection [62].

Other confounders correlated with VAW and HIV susceptibility

Genital co-infections (e.g., STIs, bacterial vaginosis) are more common among women exposed to violence, are more likely to infect in an inflammatory environment, and are also likely to enhance systemic and genital inflammation via increased local inflammatory cytokines [66], enhancing susceptibility to HIV infection [67]. Herpes Simplex Virus-2 (HSV-2) infection, for example, confers a threefold increase in HIV acquisition [68]. HSV-2 facilitates HIV infection with genital ulcerations, and alters mucosal immunity by increasing the number of genital CD4+ T cells, increasing expression of the CCR5 co-receptor for HIV to bind to CD4+ T cells, and increasing levels of immune activation [69]. Additionally, bacterial vaginosis (BV), unexplainably and disproportionately experienced by Black women [48], is associated with vaginal inflammation, increased HIV acquisition, and increased onward transmission. BV may be responsible for up to one-fifth of HIV transmissions [70].

Many of the stress hormones and immune factors operative in stress-related HIV susceptibility are dependent on sex hormones and are, thus, variable over the life course. For instance, activation of HPA-axis impacts the hypothalamic-pituitary gonadal axis to ultimately release estrogen and progesterone through the gonadotropin-releasing hormone, which may render women particularly susceptible to the immune-suppressive effects of the sex hormones [71]. Mucosal inflammation can result in enhanced production of estradiol and progesterone.

Hormonal contraceptives—particularly depot medroxyprogesterone acetate (DMPA)—amplify risk of HIV infection in the FRT [72]. DMPA is associated with a 50% increase in HIV acquisition, although some studies found inconsistent results [72]. Although IPV is associated with reduced utilization of contraceptives [73], women who experience IPV may rely on female-controlled birth control methods, which are predominantly hormone-based.

Age-related factors increase HIV susceptibility. Adolescent girls (an age group hard-hit by a disproportionate rate of HIV), whose FRT is still maturing physiologically and anatomically, are at increased risk due to exposure of the endocervix's single-layered epithelium and variability in bacteria and immunological mechanisms within the vaginal microbiome [74]. One study found that young women had higher genital concentrations of some inflammatory cytokines (e.g., IL-6, IP-10, MCP-1, and MIP-1β) than older women, which adds to the evidence that young women are more susceptible to HIV infection [62]. Relatedly, genital injuries after sexual assault, a known risk for microlesions, are more likely in very young and post-menopausal women [75], possibly due to friability of tissue in both age groups and atrophy of the vaginal epithelium in older women.

FUTURE DIRECTIONS

The complex pathways linking VAW, stress, trauma, and HIV susceptibility demand interdisciplinary translational research to advance our understanding of these mechanisms.

Although these pathways have been substantiated *in vitro*, many have yet to be understood *in vivo.* Longitudinal, prospective studies should be conducted to examine the causal relationships (conveyed in Figure 1) across age groups to account for variation in developmental stage and hormonal influence (e.g., adolescent girls, pre- and post-menopause). Given that most women experience multiple violent and traumatic experiences across their life course (e.g., CSA, witnessing familial abuse, discrimination, and physical and sexual assault in adolescence and adulthood), we must account for the cumulative nature of these experiences in elucidating the mechanistic pathways linking VAW to HIV susceptibility.

The overall sexual health profile of women should also be taken into account. Comprehensive assessment of current and past STIs are critical as they may contribute to genital inflammation, altering the local stress response. Some important considerations include the genital inflammatory roles of BV, human papilloma virus, and genital schistosomiasis; vaginal hygiene practices; exposure to seminal proteins; lubricants; and hormone cycling [62].

Future research must establish the correlation between plasma and genital levels of inflammatory cytokines, as concentrations may differ [63]. This can be achieved by comparing cytokine concentrations of matching genital tissue from women before they became HIV infected to assess the level of HIV target-cell infiltration. Establishing the cause of genital cytokine concentrations would provide a more in-depth understanding of their role in HIV susceptibility.

It is critical to understand the immunological makeup of the violent male partner, as the strongest predictor of HIV transmission is the level of virus in genital secretions. The semen microbiome is a correlate of genital viral load in ART-naïve men [76]. STIs can cause a compartmentalized increase in viral load limited to the genital tract [77]. For example, the treatment of gonorrhea in ART-naïve men reduces the semen HIV VL without affecting blood plasma VL [77]. Additionally, the male partner experiences stress and trauma during violent events, which may further increase HIV VL. Future research on violence and HIV should examine how the immunological makeup of men varies by violence victimization experience, violence perpetration, and STI infection. Furthermore, it is critical to understand patterns of viral shedding in male genital secretions based on violence profiles.

A more comprehensive program of intervention research for abused women is needed to account for physiological, psychosocial, and behavioral outcomes. Intervention research utilizing the toxic stress theory across the life course would more holistically address young and adult women’s prevention needs. Given the physiological stress response that occurs following sexual violence, interventions that integrate mindfulness-based stress reduction skills [78], and meditation combined with physical exercise [79] may prove to facilitate reductions in HIV susceptibility. These interventions can be implemented at the point of service for women who have experienced sexual violence (e.g., local community hospital, long-term domestic violence shelter). Additionally, traditional intervention approaches that utilize cognitive behavioral therapy can be modified to include trauma-informed care and models to support recovery [80, 81]. Ultimately, elucidating these causal relationships and

developing targeted interventions will facilitate reductions in HIV infections among women worldwide, with the most significant impact observed in women of color.

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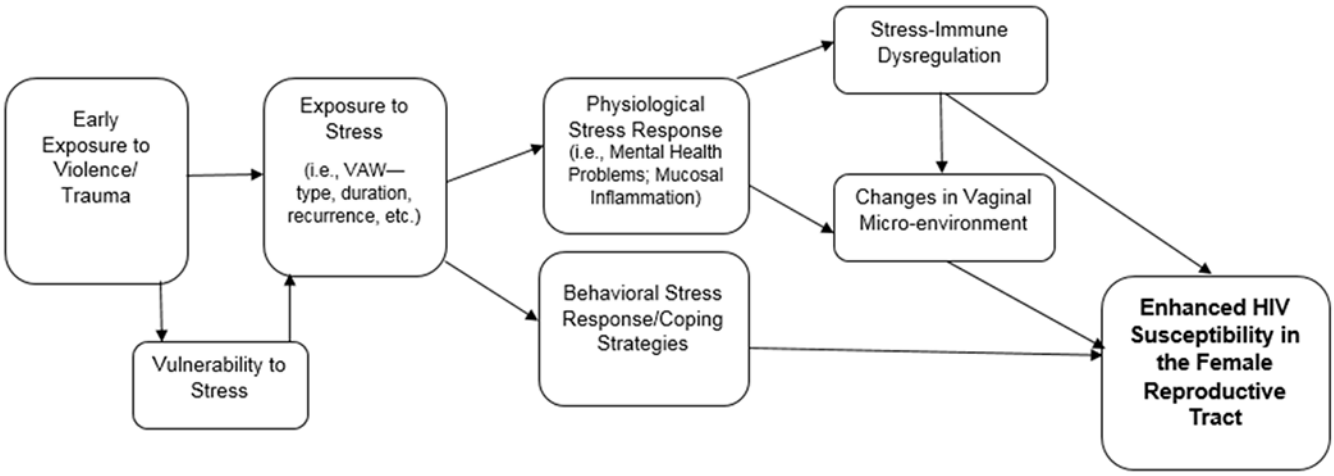

Figure 1.
Stress/Trauma–HIV frame work