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PTSD co-morbid with HIV: Separate but equal, or two parts of a whole?

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Abstract

Approximately 30 million people currently live with HIV worldwide and the incidence of stress-related disorders, such as post-traumatic stress disorder (PTSD), is elevated among people living with HIV as compared to those living without the virus. PTSD is a severely debilitating, stress-related psychiatric illness associated with trauma exposure. Patients with PTSD experience intrusive and fearful memories as well as flashbacks and nightmares of the traumatic event(s) for much of their lives, may avoid other people, and may be constantly on guard for new negative experiences. This review will delineate the information available to date regarding the comorbidity of PTSD and HIV and discuss the biological mechanisms which may contribute to the co-existence, and potential interaction of, these two disorders. Both HIV and PTSD are linked to altered neurobiology within areas of the brain involved in the startle response and altered function of the hypothalamic-pituitary-adrenal axis. Collectively, the data highlighted suggest that PTSD and HIV are more likely to actively interact than to simply co-exist within the same individual. Multi-faceted interactions between PTSD and HIV have the potential to alter response to treatment for either independent disorder. Therefore, it is of great importance to advance the understanding of the neurobiological substrates that are altered in comorbid PTSD and HIV such that the most efficacious treatments can be administered to improve both mental and physical health and reduce the spread of HIV.

Keywords

HIV; PTSD; Stress; Hormones; Startle

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1. Introduction

Although rarely in the spotlight of the world media, new HIV infections remain rampant, with 50,000 people newly diagnosed in the United States and 2.3 million people diagnosed world-wide each year (Committee on Review Data Systems for Monitoring HIVC and Institute of Medicine, 2012). The advent of highly active antiretroviral therapy (ART) dramatically reduced AIDS-related mortality such that approximately 30 million people currently live with HIV around the globe (Hallett et al., 2014). However, despite the availability of ART, people living with HIV (PLWH) are not uniformly responsive to treatment (Moniz et al., 2014), and poor adherence is a primary factor in suboptimal treatment response (Li et al., 2014). Incidents of stressful life events predict nonadherence and increased odds of virologic failure (Safren et al., 2003; Mugavero et al., 2009), possibly through avoidant coping (Martinez et al., 2012). Furthermore, nonadherence in PLWH is particularly prevalent in individuals with a history of early life trauma and post-traumatic stress disorder (PTSD) (Keuroghlian et al., 2011; Samuels et al., 2011; Machtinger et al., 2012a; Whetten et al., 2013a). In fact, PTSD predicts worse HIV-related outcomes for both women (Katz and Nevid, 2005; Brownley et al., 2015) and men (Yiaslas et al., 2014). Furthermore, increased emotional reactivity and stress can raise the risks to the larger community because along with increased nonadherence, elevated stress and emotional reactivity have been linked to increased sexual transmission risk behaviors (Machtinger et al., 2012a; O’Cleirigh et al., 2013; Adedimeji et al., 2014). Therefore, it is critically important to provide effective treatment for PLWH that suffer from PTSD. However, a major limitation to the effective treatment of PTSD for PLWH is the lack of understanding regarding the underlying neurobiology of these disorders by themselves and when they are co-morbid with one another. HIV is known to disrupt brain function and alter neuronal communication (Ferrando and Freyberg, 2008; McIntosh et al., 2015), so it is possible that HIV modifies neuronal activity in a manner that is consistent with increased likelihood to manifest stress-induced disorders such as PTSD. However, it is also plausible that these disorders are biologically separate, but co-exist in parallel. This review will delineate the information available to date regarding the comorbidity of PTSD and HIV and discuss the biological mechanisms which may contribute to the co-existence and even interaction of these two disorders.

2. Epidemiology of PTSD

PTSD manifests after a person has witnessed, has experienced, and/or has been confronted with a traumatic event (APA, 2013). Symptoms associated with PTSD include intrusive memories, avoidance of trauma reminders, numbness, hyper-arousal, and experiencing distorted or negative thoughts about oneself (APA, 2013). Among all the PTSD focused-research, the relationship between war veterans and PTSD has received the most attention. Despite the expansion of knowledge in regards to PTSD, there is still much to learn about the extent to which various non-military populations are affected and the bidirectional relationship between PTSD and preexisting conditions.

The cost of treating anxiety disorders including PTSD in the United Stated alone exceeds $42 billion, which represents half of the costs of total treatment for nonpsychiatric illness.
and a third of the cost of treating mental illness (Greenberg et al., 1999). PTSD is the fourth most common psychiatric diagnosis, affecting 10% of all men and 18% of women who survive a traumatic event (Breslau et al., 1998a). Of particular relevance to minority groups, data indicate that women and African Americans are more likely to be diagnosed with PTSD (Tolin and Foa, 2006), yet these populations continue to be understudied with regard to the neurobiology of PTSD.

Risk factors for mental illness, such as PTSD, include poverty, low education, homelessness, and exposure to trauma. Low socioeconomic status (SES) is strongly associated with increased exposure to traumatic events and elevated rates of mental and physical disorders (Breslau et al., 1991; Fitzpatrick and Boldizar, 1993; Breslau et al., 1998b; Selner-O’Hagan et al., 1998). Among civilians, economically disadvantaged African Americans living within urban environments experience particularly high levels of trauma (Breslau et al., 1991; Shakoor and Chalmers, 1991; Fitzpatrick and Boldizar, 1993; Breslau et al., 1998b; Selner-O’Hagan et al., 1998; Alim et al., 2006; Gillespie et al., 2009). Furthermore, American women and African Americans are more likely to live in poverty compared to other ethnicities and genders (Kates et al., 2012), and individuals living in impoverished neighborhoods with high rates of trauma exposure and unstable circumstances, are more likely to develop mental illnesses and engage in risky behaviors, such as substance abuse and unprotected sexual activity (Seedat, 2012).

Recently, appreciation has grown for the need for PTSD research to consider the frequently comorbid condition of HIV. Families living in low SES are also exposed to more health risks, including HIV (Adler, 2006). Based on current research concerning the American population, African Americans are most likely to contract HIV, especially African American women. In addition to low SES as mentioned above, additional risk factors for HIV include drug use, risky sexual behaviors, traumatic experiences, and geographical region (Johnson et al., 2014). Additionally, the psychiatric symptoms of PTSD have an adverse influence on patient compliance with treatment of concurrent medical illness (Shemesh et al., 2001; Delahanty et al., 2004; Hilerio et al., 2005; Sledjeski et al., 2005; Kartha et al., 2008), and may independently influence progression and risk for medical disease, (Delahanty et al., 2004; Kubzansky et al., 2007) such as HIV (Yiaslas et al., 2014; Brownley et al., 2015).

Further increasing the importance of addressing the comorbidity of HIV and PTSD is the finding that approximately 30% of women living with HIV also suffer from PTSD, an astonishing five times the incidence reported among uninfected women (Martinez et al., 2002; Machttinger et al., 2012b). This elevated prevalence may be related to the high rates of trauma exposure (Kimerling et al., 1999) because there is a positive correlation between trauma exposure and the likelihood of PTSD (Weiss et al., 2013). Typically, it is not one traumatic event that leads to PTSD but an accumulation of traumatic events. However, certain events have stronger influences on one’s progression to PTSD (Brumsey et al., 2013) including the diagnosis of HIV. According to the American Psychiatric Association’s definition of PTSD, the diagnosis of HIV qualifies for criterion A trauma for a PTSD diagnosis. Criterion A trauma is a category that encompasses the direct or indirect exposure to a traumatic situation that is life threatening (APA, 2013). Although the diagnosis of cancer, also considered a life-threatening illness, is sufficient to qualify as a criterion A
trauma for PTSD diagnosis, the exceptionally high prevalence of PTSD in PLWH is not replicated among individuals with cancer. For example, studies have found that the prevalence of PTSD in breast cancer patients is between 2.5–3% (Kessler et al., 2005; Kwakkenbos et al., 2014), similar to the 12-month prevalence of PTSD in females in the US at 5% (Kessler et al., 2005).

Although reports vary, PTSD as a result of a cancer diagnosis is reported to be between 6% to 15% of patients (Abbey et al., 2015), which is markedly below the 30% of HIV-positive individuals that manifest PTSD (Martinez et al., 2002; Machtinger et al., 2012b). Whether this is a result of the biology of either disease state or a differential impact of the socio-cultural connotation of each disease state, is unknown. However, it is known that of those who are HIV positive and have been exposed to a traumatic event, PLWH who met criteria for PTSD classified their diagnosis of HIV as the most traumatic event because of the experience of being diagnosed with an illness that can be life threatening (Olley et al., 2005; Olley et al., 2006). Furthermore, in addition to increasing the risk of PTSD, the duration of HIV infection has been shown to intensify PTSD symptoms (Rzeszutek et al., 2015) suggesting that these conditions not only co-occur but interact.

### 3. Expression of PTSD symptoms in the context of HIV

The DSM-5 diagnostic criteria for PTSD include twenty symptoms divided across four symptom clusters of intrusive re-experiencing (5 symptoms), effortful avoidance (2 symptoms), negative alterations in cognitions and mood (7 symptoms) and increased arousal and reactivity (6 symptoms)(APA, 2013). Additionally, trauma exposure itself is associated with a range of symptoms often including, but not limited to, those identified in the current DSM PTSD criteria. Further, variations in trauma-related symptom presentations have implications for level of adaptive functioning and distress as well as likelihood of recovery and response to treatment (Shea et al., 2010). For example, re-experiencing symptoms are the “hallmark” manifestation of PTSD and characteristically contain an exaggerated fear component. While avoidance symptoms may not be as easily apparent as re-experiencing or hyperarousal symptoms, they frequently contribute to long-term maintenance of symptoms. Avoidance of trauma reminders often includes avoidance of treatment, which may be especially pronounced with exposure-based psychotherapies (Lunney and Schnurr, 2007; Schnurr and Lunney, 2008). In the case of HIV comorbid with PTSD, symptoms of avoidance may be particularly detrimental because PTSD-associated avoidance may underlie reduced ART adherence in people with diagnosed PTSD (Brief et al., 2004; Nel and Kagee, 2011; Samuels et al., 2011; Whetten et al., 2013b) and those reporting recent traumas (Machtinger et al., 2012a). Furthermore, emotional numbing and detachment can reduce the number of patient opportunities to benefit from social support, a significant aid to recovery from PTSD (Andrews et al., 2003) and control of HIV (Breet et al., 2014).

Patterns of symptoms may be expected to vary over the course of time following trauma exposure, with fear and avoidance of specific trauma cues likely presenting first, followed by a more generalized avoidance and symptoms of depressed mood, which is often comorbid with PTSD symptoms (Lanius et al., 2002). Hyperarousal symptoms can often lead to more generalized impairments in function either due to sleep disturbance, or more frequently,
anger issues and subsequent occupational problems. In addition, a recent study of physiological reactivity in a sample with recurrent trauma exposure found that individuals with multiple traumas showed less reactivity compared to those with a single trauma (McTeague et al., 2010). The evidence suggests that trauma responses may present as different “subtypes” or “profiles” of illness. The heterogeneity of psychological outcomes of trauma, by nature, implicates the involvement of several divergent neural systems in the underlying neurobiology of trauma-related symptomatology (Frewen and Lanius, 2006). In addition, individual differences in one’s neurobiological makeup may also contribute to the variability observed in patient presentations following trauma exposure (Yehuda, 1997). The high comorbidity of HIV and PTSD and the treatment implications have been recognized recently in publications aimed at informing first-line medical professionals in the care and management of this volatile comorbidity (Tavakkoli et al., 2014; Brezing et al., 2015). Given the heterogeneity of PTSD, psychobiological metrics that provide insight to the underlying biological systems that have been impacted, may be essential to adequate treatment of PTSD variants. Such a progression in the assessment and treatment of PTSD co-morbid with HIV is in line with the Research Domain Criteria (RDoC) which advocate using neurobiological phenotypes to appropriately attend to psychopathology (Cuthbert and Insel, 2013).

4. Neurobiology of PTSD: startle response

Although there is little understanding of the neurobiology of PTSD within the context of HIV (Blank et al., 2013), the neurobiology of PTSD has been a topic of intense study over the past two decades (Nemeroff et al., 2006; Jovanovic and Ressler, 2010), and a framework of underlying biological substrates can be constructed from these previous findings (Fig. 1). In this section and the following sections, we discuss the biological components presented in the figure which may provide insight into the link between HIV and PTSD.

Dysregulated fear responses are one of the hallmark symptoms of PTSD and can be objectively measured using biological methods, such as brain imaging or psychophysiological tests such as startle responsivity. Neuroimaging studies have shown that the brain structures that are activated in response to fearful stimuli, such as the amygdala, show hyperactivation in PTSD subjects compared to controls (Liberzon and Martis, 2006; Shin et al., 2006). The amygdala, part of the limbic system located in the temporal lobe of the brain, is an integral part of the fear circuitry (Davis et al., 1993; LeDoux, 2000). Because the amygdala is one of the neural structures that has been found to be hyperactive in PTSD (Shin et al., 2006), fear conditioning methods provide focused laboratory tools for testing exaggerated fear symptoms in trauma-exposed individuals. In humans, the acoustic startle response provides an ideal translational tool to investigate fear conditioning, because the amygdala is directly connected with the startle circuit (Davis, 1992). The startle response can be further parsed to determine if deficits are at the level of conditioning, discrimination, or extinction; each of which have distinct neural circuitry. PTSD patients often show overgeneralization of fear and in tandem an inability to inhibit fear responses in the presence of safety. To this end, early studies with Vietnam and Gulf War veterans found enhanced fear conditioning in PTSD (Morgan et al., 1996; Grillon et al., 1998). Furthermore, two meta-analyses using fear conditioning found that patients with anxiety disorders showed greater levels of fear responses compared to healthy controls (Lissek et al., 2005; Duits et al., 2015).
Knowledge about the neurobiology of fear and the startle response indicates that impaired fear inhibition may be a specific biomarker of PTSD that could be a valuable clinical metric (Jovanovic et al., 2010).

Fear conditioning is based on a simple Pavlovian conditioning model in which a neutral conditioned stimulus (CS, for example, a light) is paired with an aversive unconditioned stimulus (US, for example, electric shock). After a number of pairings, the association is formed so that the CS alone elicits the conditioned response (CR, for example, a fear response). This basic laboratory model can be evaluated with fear-potentiated startle and is used in animal as well as human research to investigate mechanisms of fear acquisition. Fear-potentiated startle is the relative increase in the startle magnitude elicited in the presence of CS+ that was previously paired with a US. This basic model is used in animal as well as human research to investigate mechanisms of fear expression (Jovanovic and Ressler, 2010). Recent data indicate that both PTSD symptoms and fear-potentiated startle are associated with inflammation in traumatized individuals (Michopoulos et al., 2015), suggesting a further neurobiological link between PTSD and HIV.

5. Neurobiology of HIV and co-morbid anxiety disorders

With respect to HIV and PTSD neurobiology, little work has considered the impact of HIV or comorbid HIV and PTSD on the startle response, and the available research is limited to rodent studies. If we expand beyond startle responses to sensorimotor gating and the broader category of anxiety-like behaviors, a wealth of preclinical literature exists linking HIV proteins to the manifestation of anxiety-like behaviors. Rodent work has demonstrated an effect of the HIV protein gp120 on fear conditioning (Pugh et al., 2000; Fitting et al., 2006a). HIV proteins, Tat and glycoprotein 120, both have direct effects on sensorimotor gating when injected into the hippocampus during the neonatal period (Fitting et al., 2006c, 2006b, Fitting et al., 2007), and similar effects are produced when adult rats are exposed to intrahippocampal Tat, such that sensorimotor gating is impaired (Fitting et al., 2006a). Further studies have revealed effects of HIV proteins on hippocampal morphology (Fitting et al., 2008a; Fitting et al., 2008b) and dopaminergic transmission (Moran et al., 2012; Moran et al., 2013). Examination of the behavioral patterns of female HIV-1 transgenic rats which express seven of the nine HIV-related proteins, reveal profound anxiety-like behavior as well as depressive-like behavior and altered social behavior (Nemeth et al., 2014). Although it is not known if all the HIV proteins can independently induce anxiety-like behavior, Tat has been demonstrated to have a direct role in precipitation of anxiety behaviors (Paris et al., 2014).

Aside from these studies that help to characterize HIV’s effect on behavior, it has been demonstrated that HIV can exert effects in the brain through inflammation. Although HIV does not infect neurons, HIV viral proteins can cross the blood brain barrier and lead to neuroinflammation (Dohgu et al., 2011). IL-6 levels are increased in the cerebrospinal fluid of patients with HIV-associated neurocognitive disorder (HAND), the primary neurocognitive disorder in PLWH, and remained increased compared to controls 12 weeks after starting ART (Airoldi et al., 2012). Activation of central nervous system monocytes has been suggested as HIV’s primary mechanism for causing neuroinflammation.
monocytes are active, they express a high level of CD14, but a pro-inflammatory subset of monocytes (~10%) express CD16 on their surface (Belge et al., 2002). This pro-inflammatory monocyte population is increased in up to 40% of patients with HIV infection (Pulliam et al., 2004). Additionally, the virus may infect and subsequently activate microglia within the central nervous system; their activation can lead to the release of cytokotins and neuronal and astrocyte injury (Kaul et al., 2001; Lipton and Gendelman, 1995). The neuronal injury due to these inflammatory cytokines, chemokines, and excitotoxic substances released by the microglia has been hypothesized to contribute to the pathology found in HAND (Glass et al., 1995). Furthermore, microglial activation and cytokine expression has been linked to the manifestation of anxiety-like and depressive-like behaviors in rodent models of other neurodegenerative conditions such as cardiac arrest and cardiopulmonary resuscitation (Neigh et al., 2009) and microembolic stroke (Nemeth et al., 2012). This evidence of neuroinflammation provides insight as to how HIV can affect the brain. A specific connection between the neuroinflammation brought on by HIV and psychiatric illness is the strong correlation between levels of IL-6 (as previously mentioned to be elevated in HIV patients) and psychological stress and anxiety/depression (Fumaz et al., 2012).

Collectively, these data suggest that while we cannot undervalue the influence of stress on the manifestation of PTSD associated with HIV, it is essential that we also consider the potential contribution of HIV-related neurobiological alterations which may render the system more vulnerable to stress. Neurological disorders are common among those infected with HIV and include cognitive, motor, and behavioral deficiencies (Atluri et al., 2015). HIV and its byproducts have been demonstrated to disrupt circuits of the basal ganglia and other neurological components and cause neuropsychiatric symptoms (Berger & Arendt, 2000; Pugliese et al., 2005). Several studies that included neuroimaging techniques have demonstrated the impact of HIV on cognition, motor skills, and behavior. For instance, a study assessing positron emission tomography (PET) scans in PLWH suggests that a decrease in dopaminergic function has the potential to contribute to cognitive dysfunction (Chang et al., 2008). In addition, PET scans have been used to link HIV-related depression to dysregulated serotonergic function (Hammoud et al., 2010). Evidence of HIV-induced structural changes has also been reported such as reduced cortical and subcortical volumes in PLWH (Cohen et al., 2010). These changes can possibly lead to neural loss, therefore, potentially explaining motor, cognitive, and affective behavior impairments in HIV patients.

6. Neurobiology of PTSD and HIV: HPA axis

The hypothalamic-pituitary-adrenal (HPA) axis mediates the body’s response to a stressor and is named to describe its major component parts. The HPA axis response culminates with release of glucocorticoids (GCs), primarily cortisol in humans, from the adrenal glands into the circulation where all organs can be impacted.

Although adaptive in the short term, if the stress response becomes chronic due to repeated exposure to stressors or does not properly extinguish due to a traumatic stressor, the result is a sustained increase in the level of stress hormones and the initiation of pathological changes such as affective disorders and PTSD (McEwen, 2008). The HPA axis mediates the stress
response, which culminates when ACTH is humorally transported to the adrenal cortex
where it stimulates the release of GCs. The primary peripheral role of GCs is to release
stored energy, primarily through mobilization of glycogen as well as gluconeogenesis. This
chain of events that characterizes the HPA axis response typically takes several minutes to
fully engage and activation of the HPA axis is eventually reduced through negative feedback
via stimulation of GC receptors within the hippocampus, hypothalamus, and anterior
pituitary (Jacobson and Sapolsky, 1991). With respect to PTSD, the glucocorticoid pathway
has been implicated in PTSD-induced changes in the brain (Logue et al., 2015), and
manipulation of glucocorticoids has been proposed for treatment of PTSD (Yehuda et al.,
2015). Previous studies have also demonstrated dysfunction of the HPA axis in people living
with HIV (Kumar et al., 2003; Zapanti et al., 2008; Patterson et al., 2013; Chrousos and
Zapanti, 2014). Some studies indicate that HIV patients have higher cortisol levels compared
to non-infected controls (Membreno et al., 1987, Chrousos and Zapanti, 2014). In addition,
glucocorticoids have been demonstrated to directly influence HIV replication (Wiegers et
al., 2008). Furthermore, psychosocial interventions in combination with ART improve
treatment response and decrease 24-h urinary cortisol leading to the hypothesis that the
noted reduction in cortisol following psychosocial intervention is causative in improved
treatment response to ART (Antoni, 2003). These studies suggest that the HPA axis plays a
role in the pathology in both PTSD and HIV infection.

There are multiple points of potential interaction of HIV with the HPA axis. Starting with
the initiation of the response, HIV proteins could influence the action of CRH. In fact, the
HIV envelope protein gp-120 has been implicated in stimulating CRH release from the
hypothalamus and subsequently leading to a rise in ACTH (Costa et al., 2000). This is the
same envelope protein that was discussed earlier in having an effect on fear conditioning
(Pugh et al., 2000; Fitting et al., 2006a). This suggests that the effects that HIV has on fear
conditioning and HPA-axis dysregulation work through a similar mechanism that is inherent
to the protein and persists despite ART. In addition to a potential overstimulation of ACTH,
the adrenal response to ACTH has also been demonstrated to be enhanced in PLWH. When
stimulated with a synthetic derivative of ACTH, cosyntropin, non-infected subjects have a
much higher increase in cortisol release compared to HIV-infected patients (Membreno et
al., 1987). Collectively, these data suggest that the initiating events of the HPA axis response
are more responsive in PLWH.

HIV proteins also exert influence over the HPA axis at the level of the target organ response
or through effects on negative feedback by actions on the glucocorticoid receptor’s (GR)
affinity and expression (Norbiato et al., 1998). The GR is a pervasive protein and is present
on nearly every cell in the body. The GR is extremely powerful because it is a transcription
factor affecting thousands of genes that play roles in mood, cognition, neuropsychiatric
disorders, immune function and inflammation, cell growth and survival, and energy
allocation (Bourke et al., 2012). Although elevated cortisol levels have been observed in
HIV patients, they systemically appear to be in a hypo-cortisol state. This observation in
HIV patients has been attributed to the reduced affinity of GR to cortisol, leading to a
glucocorticoid resistance state (Norbiato et al., 1998). Subsequently, GR expression is
increased as the body attempts to compensate for the glucocorticoid insensitivity (Kino and
Chrousos, 2004). Inflammation due to HIV infection as well as intrinsic viral proteins have
been implicated in the alterations in GR. With HIV infection comes systemic inflammation and the expression of inflammatory cytokines such as IL-2 and IL-4. The combined presence of these cytokines can lead to a change in GR-binding affinity and increase in GR number (Kam et al., 1993). In terms of potential mechanisms, structural protein r of HIV (Vpr) has been observed as a co-activator of GR and may lead to glucocorticoid hypersensitivity (Kino and Chrousos, 2004).

The systemic inflammation present with HIV infection may also provide a potential alternate mechanism for the alterations in the HPA axis. As mentioned previously, inflammatory cytokines are expressed following HIV infection. Adults on ART were found to have significantly higher concentrations of IL-6 as well as high sensitivity C-reactive protein (hsCRP), a clinical indicator of systemic inflammation, compared to age-matched controls (Neuhaus et al., 2010). Some of these pro-inflammatory cytokines can stimulate the HPA axis, such as IL-1, IL-6, and tumor necrosis factor-α (TNF-α) (Bernton et al., 1987; Sapolsky et al., 1987; Perlstein et al., 1993). IL-1 has the ability to stimulate the hypothalamus and cause secretion of CRH (Bernton et al., 1987; Sapolsky et al., 1987) while IL-6 and TNF-α lead to an increase in plasma levels of ACTH. By stimulating the HPA axis, more cortisol will be produced and observed as the subsequent hypercortisolism found in many HIV patients.

Recently, genetic markers have been discovered that interact with early childhood abuse to increase risk for PTSD symptoms. Specifically, polymorphisms of the FKB5 gene (which encodes a co-chaperone that regulates the GR) have been associated with PTSD symptoms (Binder et al., 2008; Mehta et al., 2011). In addition, FKB5 has been shown to change in PLWH (Tatro et al., 2009) and to respond differentially to stress in a rodent model of HIV (Panagiotakopoulos et al., 2015). This gene is involved in regulating cortisol feedback function (Binder et al., 2008), the stress hormone mechanism that is one of the most frequently reported trauma-related neurobiological alterations (Yehuda, 2009). Heightened cortisol reactivity in response to psychosocial stress has been observed in victims of physical and sexual childhood abuse (Heim et al., 2000), and exaggerated suppression of HPA axis activity following administration of dexamethasone, a cortisol analog, has been a consistent finding associated with a diagnosis of PTSD (Yehuda et al., 1993; Yehuda, 2009). Recent studies indicate that this effect is strongest in individuals with higher genetic risk, i.e., carriers of the FKB5 risk allele (Binder et al., 2008). Although other mediators of the GR response are candidates for modulation of HIV and PTSD effects on HPA axis reactivity, FKB5 is one of the best characterized to date and offers an illustration of the range of levels at which GR function, and thereby HPA axis reactivity, can be modulated.

Taken together, these studies suggest that HPA dysregulations are long-term consequences of trauma that are associated with genetic risk for PTSD. Furthermore, the glucocorticoid pathways may be further impacted by HIV independent of stress as evidenced by rodent research (Panagiotakopoulos et al., 2015). The potential importance of the HPA axis in HIV-related pathology extends beyond PTSD because the GR has anti-inflammatory capacity, and disruption of this pathway could contribute to HIV-associated chronic inflammation. This relationship is highlighted by a recent study that reported that women with comorbid HIV and PTSD were more likely to develop shingles suggesting heightened disruption of the
immune system (Sinayobye et al., 2015). In addition, the HPA axis, and more specifically the GR, has an established role in cognitive impairment which is an increasing concern for PLWH (Rubin et al., 2015).

7. Conclusions
Collectively, the data highlighted here suggest that PTSD and HIV are more likely to actively interact than to simply co-exist within the same individual. While HIV and PTSD have similar risk factors and the order of manifestation can vary, once present in combination, these two conditions are positioned to create a feed-forward cycle of interaction at both the behavioral and neurobiological levels (Fig. 1). These multifaceted interactions have the potential to alter response to treatment for either independent disorder. Therefore, it is of great importance to advance the understanding of the neurobiological substrates that are altered in comorbid PTSD and HIV such that the most efficacious treatments can be administered to improve both mental and physical health as well as reduce the spread of HIV.

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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<td>GC</td>
<td>glucocorticoid</td>
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<td>GR</td>
<td>glucocorticoid receptor</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HPA</td>
<td>hypothalamic-pituitary-adrenal</td>
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<td>PLWH</td>
<td>people living with HIV</td>
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<td>SES</td>
<td>socioeconomic status</td>
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References

Neurobiol Dis. Author manuscript; available in PMC 2017 November 06.


APA. Diagnostic and Statistical Manual of Mental Disorders. 5th. APA; Washington, DC: 2013.


Dohgu S, Fleegal-DeMotta MA, Banks WA. Lipopolysaccharide-enhanced transcellular transport of HIV-1 across the blood-brain barrier is mediated by luminal microvesSEL IL-6 and GM-CSF. J Neuroinflammation. 2011; 8:167. [PubMed: 22129063]


Jovanovic T, Norrholm SD, Blanding NQ, Davis M, Duncan E, Bradley B, Ressler KJ. Impaired fear inhibition is a biomarker of PTSD but not depression. Depression and Anxiety. 2010; 27:244–251. [PubMed: 20143428]


Neigh et al. Neurobiol Dis. Author manuscript; available in PMC 2017 November 06.


Li JZ, Gallien S, Ribaudo H, Heisey A, Bangsberg DR, Kuritzkes DR. Incomplete adherence to antiretroviral therapy is associated with higher levels of residual HIV-1 viremia. AIDS. 2014; 28:181–186. [PubMed: 24361679]


Neubiot Dis. Author manuscript; available in PMC 2017 November 06.


Panagiotakopoulos L, Kelly S, Neigh GN. HIV-1 proteins accelerate HPA axis habituation in female rats. Physiol Behav. 2015


Proposed overlap of PTSD and HIV. The multidirectional relationships between trauma, glucocorticoid receptor function, post-traumatic stress disorder (PTSD), and the startle response have been well described in the literature. HIV has also been demonstrated to impact the individual components of these interactions. 1) Trauma exposure is an established requirement for the diagnosis of PTSD and HIV diagnosis if sufficient to meet the criteria for a criterion A trauma. 2) The impact of trauma exposure on fear-potentiated startle has been demonstrated in both humans and animal models. The impact of HIV on startle responsivity has been assessed in rodent models. To date, there have not been preclinical or clinical assessments of the interaction of trauma and HIV on fear-potentiated startle. 3) The use of fear-potentiated startle as a biomarker for PTSD has been established in HIV uninfected individuals but this work has not yet been extended to PLWH. 4) The impact of trauma and chronic stress on glucocorticoid receptor function has been well characterized. The role of glucocorticoid receptor function in fear-conditioned startle is a developing area of research and given the influence of HIV and...
trauma on GR function, this may be a mechanism by which HIV and trauma interact to alter PTSD symptoms and exacerbate the individual impact of each condition.