

A Neurodevelopmental Model for the Origin of Depression Amongst People living with HIV: Convergence of Social and Neuroimmunological Mechanisms

Modelo neurodesenvolvimentista da origem da depressão entre as pessoas que vivem com o HIV: convergência de mecanismos sociais e neuroimunológicos

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Abstract

Depression is a major challenge facing people living with HIV (PLHIV), with prevalence rates ranging from 25-36%. Depression impacts negatively upon adherence and response to combined antiretroviral therapy (CART) and the transmission of HIV infection through increased sexually risky behavior. This article proposes a neurodevelopmental model of depression, which tries to integrate the interplay between psychosocial adversity and HIV related- stigma, on one hand, and HIV associated neuroinflammation, on the other hand, in the etiology of depression amongst PLHIV. We conclude that PLHIV should be provided an individualized treatment program that develops strategies including personal empowerment for coping with, and overcoming, psychosocial adversity. Further, neurobiological studies should be vigorously pursued to understand the neuroplastic changes leading to depression in PLHIV and to identify biomarkers of depression to be employed for clinical diagnosis, treatment follow-up and investigational purposes.

Keywords: HIV; depression; AIDS; stigma; neuroinflammation; neurodevelopment

Resumo

A depressão é um grande desafio para as pessoas que vivem com o HIV (PVHIV) com taxas de prevalência entre 25-36%. A depressão tem um impacto negativo sobre a aderência e a resposta à terapia antirretroviral (CART) e a transmissão da infecção pelo HIV, devido ao aumento do comportamento sexual de risco. Este artigo propõe um modelo neurodesenvolvimentista da depressão, que tenta integrar a interação entre adversidade psicossocial e estigma relacionado ao HIV, por um lado, e a neuroinflamação associada ao HIV, por outro, na etiologia da depressão entre as PVHIV. Nós concluímos que as PVHIV deveriam receber um programa de tratamento individualizado que desenvolvesse estratégias de empoderamento para o enfrentamento e a superação da adversidade psicossocial. Ademais, estudos neurobiológicos deveriam ser vigorosamente incentivados, visando compreender as mudanças neuroplásticas que levam à depressão nas PVHIV e identificar biomarcadores de depressão, aplicáveis para fins de diagnóstico e de acompanhamento clínicos, assim como para fins de pesquisa.

Palavras-chave: HIV; depressão; AIDS; estigma; neuroinflamação; neurodesenvolvimento.

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Introdução

Psychiatric co-morbidities are a major challenge facing people living with HIV (PLHIV). Epidemiological data indicate that during the course of the disease, over 60% of PLHIV are affected by at least one psychiatric disorder, with depression being the most frequent diagnosis, followed by anxiety disorders and substance abuse, which are also highly prevalent among these patients (Kessler, Gruber, Hettema, Hwang, Sampson, & Yonkers, 2008; Kopnisky, Bao, & Lin, 2007; Rabkin, McElhiney, & Ferrando, 2004). Several studies have demonstrated the high prevalence of depression among PLHIV, with rates ranging from 25-36% (Bing et al., 2001; Gibbie et al., 2006; Judd et al., 2005; Mello & Malbergier, 2006; Olatunji, Mimiaga, O’Cleirigh, & Safren, 2006; Wright et al., 2008).

Depression has a negative impact on the course of HIV infection, reducing adherence to treatment (Ammassari et al., 2004; Kacanek et al., 2010; Lima et al., 2007; Tegger et al., 2008; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003), increasing the frequency of sexually risky behavior (Kalichman & Weinhardt, 2001), accelerating disease progression and increasing mortality (Burack et al., 1993; Cook et al., 2004; Ickovics et al., 2001). Moreover, there is evidence that depressive symptoms adversely affect the clinical response to antiretroviral therapy (Gibbie et al., 2006; Vlassova, Angelino & Treisman, 2009).

Although relevant research is extensive, the explanation of the high rates of depression among PLHIV is still a challenge. First, the pathophysiology of depression in the general population is still poorly understood, and to complicate the matter, depression may result from the additive or synergistic effects of many different factors of both environmental and neurobiological nature. The diagnosis of depression is based only on patient reports and clinical observations, as there is no biomarker for its detection, or quantification or for control of the response to treatment of depression (for review, see Del Guerra, Fonseca, Figueiredo, Ziff

& Konkiewitz, 2013). It is possible that different conditions lead to a final common pathway, or even that there are different diseases that we do not recognize as distinct and group together under the rubric “depression”. For instance, depressive symptoms vary widely, and based on this heterogeneity, depression may be classified as melancholic, atypical or psychotic, though this classification has little theoretical and empirical support (Van Loo, de Jonge, Romeijn, Kessler, Schoevers &, 2012). Second, PLHIV must cope with a range of HIV-related symptoms for extended periods of time. These symptoms may be related to the infection itself, to comorbid illnesses, or to CART side effects (Fonseca & Bastos, 2007). Third, PLHIV face social and cultural problems, for instance, stigma, fear of disclosure and lack of social support (De Santis, Gonzalez-Guarda & Vasquez,, 2012). Fourth, statistically, minority groups, such as homosexuals, transgender individuals, drug users and sex professionals, are overrepresented among PLHIV relative to the general population and these groups are already, apart from HIV infection, at greater risk for depression (Gonzalez, Seley, Martorano, Garcia-Moreno & Troncoso, 2012). Fifth, persons with a history of childhood abuse and childhood adversity are also overrepresented among PLHIV, as the HIV epidemic occurs largely within a context of considerable social inequality (Bing et al., 2001; UNAIDS, 2004; Fonseca & Bastos, 2007; Vlassova et al., 2009; CDC, 2010/2013). These prenatal and early life experiences may cause neuroplastic and epigenetic changes with life-long effects that predispose to neuropsychiatric conditions (Andersen et al., 2008; Heijmans et al., 2008; Brown & Susser, 2008; Clark et al., 2012). Sixth, HIV infection is associated with chronic virally-induced neuroinflammatory and neurotoxic processes which may predispose to depression (Del Guerra et al., 2013).

This article proposes an integration of the social and the neurobiological factors into a neurodevelopmental model of the origin of depression amongst PLHIV.

2. Socioeconomic status mediating the risk for depression amongst PLHIV

According to the “fundamental social causes” theory, social conditions must be seen as fundamental causes for disease, as they shape access to health-relevant determinants (Link & Phelan, 2001). Health status will depend on the individual’s ability to benefit from socioeconomic resources, such as access to knowledge about healthy behaviors, to adequate healthcare, and access to an appropriate neighborhood in which to live (without pollution, noise, violence), to good and secure jobs, as well as to access to sufficient food, etc. (Colgrove, 2002). Thus, poverty and low education are, as such, contributing factors to disease in a broader sense and to poor quality of life (Pickett & Wilkinson, 2010), as they correlate with lower access to information and appropriate health care, and to greater exposure to violence (Wilkinson, 2005). Moreover, the “relative income hypothesis” (psychosocial hypothesis) proposes that income inequality has a greater impact on health than absolute low income as such, because social comparisons lead to stress and shame, which, in turn, enhance the propensity for several diseases (Wilkinson, 2005). Indeed, several studies show socioeconomic inequalities in health parameters and health outcomes, which cannot be satisfactorily explained solely by differences in

individual access to social resources. It has been suggested that the degree of social stratification across the whole society is a determinant of population health (Pickett & Wilkinson, 2010). For instance, these authors compared data from the WHO International Consortium in Psychiatric Epidemiology (2000) concerning developed countries and demonstrated a strong positive association between income inequalities and the proportion of adults who had been mentally ill in the 12 months prior to being interviewed. Inequality was associated with a threefold difference in prevalence of mental disorders across those countries (Pickett & Wilkinson, 2010).

As Brazil is historically a country with high levels of poverty and great income disparity (Ribeiro & Lago, 2000; Torres, Marques, Ferreira & Bitar, 2003), it fits well with both the “fundamental social causes” theory and the “relative income hypothesis”. Moreover, Brazil is characterized by deeply rooted social segregation and social prejudice (the inheritance of centuries of slavery) (Trujillo, Vernon, Wong & Angeles, 2009), providing a basis for different forms of stigmatization.

3. Role of Stigmatization

Stigma is defined as the co-occurrence of labeling, stereotyping, separation, status loss, and discrimination in a context in which power is exercised (Link & Phelan, 2001). According to Hatzenbuehler, Phelan & Link, (2013), stigma must, like socioeconomic status, also be considered as a fundamental cause of disease, as it remains persistently associated with health inequalities over time, despite dramatic changes in diseases, risk factors, and health interventions. Stigma operates through diverse mechanisms impacting access to resources and influencing multiple disease outcomes among a considerable part of the society. Stigma can be related to a large and diverse group of outcomes, ranging from opportunity for housing and for employment or income, quality of social relationships, psychological or behavioral responses to health care treatment (Hatzenbuehler et al., 2013).

HIV is highly stigmatized because it is historically related to morally discriminated behaviors, such as drug use, homosexuality and sex work. As a consequence, PLHIV who belong to marginalized groups may experience multiple layers of stigma due to their sexual orientation, gender identity, race and ethnicity in addition to their HIV status (Herek & Capitano, 1999). Moreover, a considerable portion of society still attributes HIV infection to personal responsibility, a view rooted in stereotyped ideas that HIV is caused by immoral, or promiscuous behavior (Des Jarlais, Galea, Tracy, Tross & Vlahov, 2006).

HIV and AIDS-related stigma may act at either societal or individual levels and can be manifested in prejudice, discounting, discrediting and discrimination directed at people perceived to have HIV, along with the groups and communities

with which they are associated (Charles et al., 2012). Seropositive men and women may be shunned by family, friends, and intimate partners and often experience overt acts of discrimination in employment, health-care and housing (Gostin & Webber, 1998). Further, it has been estimated that in the U.S., 21% of women, and 12% of men who have sex with men, and who are PLHIV have experienced physical violence since learning of their diagnosis (Zierler et al., 2000). In addition to actual stigma experienced by those infected with HIV, other forms of negative experience also occur in this context, such as fear of being stigmatized, concern with public attitude towards PLHIV, disclosure concerns, and self-stigmatization (internalization of the negative societal perceptions).

HIV and AIDS-related stigma may have devastating health consequences at several levels, leading to depression (Venable et al., 2006; Murphy, Austin, & Greenwell, 2006; Steward et al., 2011), to poor QoL (Thomas et al., 2005; Mahalakshmy., Hamide & Premarajan, 2011), to poor CART adherence (Chandra, Deepthivarma & Manjula, 2003; (Schuster, Collins, Cunningham et al. 2005; Venable et al., 2006; Kinsler, Wong, Sayles, Davis & Cunningham, 2007; Steward et al., 2008) and to lack of disclosure and avoidance of HIV testing, which, in turn, enhance the risk of reinfection and transmission (Venable et al., 2006; Deblonde et al., 2010).

Investigations based on different theoretical approaches converge by demonstrating that the environment greatly influences individual thought processes (for example, low self esteem, low self appraisal, guilt, self reproach), which in turn greatly determine emotional reactions and behavior (depressive humor, hopelessness, self isolation, apathy). Aaron Beck (1999) proposed that depression arises from and is sustained by thoughts that are shaped by unquestioned beliefs acquired and consolidated during life, especially

3. Infection, Inflammation and Depression

There is strong support for a role for virally mediated chronic neuroinflammation and neurotoxicity in the origin of depression amongst PLHIV. Several studies provide support for the

during early life. They are transmitted by parents, school and other significant relations. Stigma fits well into this category of unquestioned and socially maintained assumptions, which pave the way for negative interpretations and emotions. According to the Stress and Coping Theory, appraisal of an event determines the emotional response to the event and the coping strategy (Lazarus & Folkman, 1984). The term, "Illness appraisal", encompasses the significance that an illness and its sequelae have for the individual's future health and well-being, and may include beliefs about the course and consequences of an illness, and the experience and interpretation of symptoms (Fife, 1994; Leventhal, Nerenz, & Steele, 1984). Indeed, individuals who are subject to stigma show greater vulnerability to internalized negative stereotypes of themselves in the form of guilt, shame and low self-esteem (Kalichman & Weinhardt, 2001). These convictions induce negative emotional reactions, such as depression, anxiety and hopelessness (Lee, Kochman & Sikkema, 2002), and maladaptive behaviors, such as self-imposed isolation and not taking advantage of opportunities that promote employment and independent living (Murphy et al., 2006; Dowshen, Binns & Garofalo, 2009). Coping by denial (avoidance) has been shown to correlate with low self-esteem and depression in HIV patients (Fleishman et al., 2000).

Studies show that in the general population, individuals with lower personal resources (income, education, social support), worse mental health status, and poorer CART knowledge possess greater stigmatizing beliefs concerning HIV and AIDS (Des Jarlais et al. 2006, Agnarson, Levira, Masanja, Ekström & Thorson, 2013). This supports the proposal that poverty and low education are intermingled with stigma in society and may have complex synergistic effects by mechanisms that perpetuate each other with far-reaching health consequences.

"cytokinergic theory of depression", which was further developed into the "inflammatory and neurodegenerative theory of depression" (Maes, Galecki, Chang & Berk, 2011). This framework

proposes that during evolution, mammals developed adaptive mechanisms involving inflammation and behavioral changes to respond to injury. While inflammation helps the organism to isolate and fight the source of injury, behavioral changes, called “sickness behavior”, which consist of social withdrawal, anhedonia, hypomotility and fatigue, restrict the individual from involvement in competitive activities, such as fighting for food or for sexual interactions, which could make the individual susceptible to injury and impair the course of recovery (Readler, 2011).

“Sickness behavior” displays many similarities to the depressive state and results from neuroplastic changes induced by cytokines (Readler, 2011). In the case of an acute disease, the inflammatory process culminates in overcoming the source of injury and restores health and normal behavior. However, in the case of a chronic inflammatory disease, for example autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease and multiple sclerosis, the inflammatory state is perpetuated and may lead to depression. Indeed, clinical data show a higher prevalence of depression among such patients (Yirmiya et al., 1999).

Because HIV infection causes a chronic inflammatory state, it fits well into this framework. Moreover, HIV is a neurotropic virus and it is well established that HIV-infected monocytes can cross the blood brain barrier and infect the microglia and astrocytes in the central nervous system (CNS) (Ances & Ellis, 2007). Although neurons are themselves not infected by the virus, the infection gradually disrupts synapses and kills neurons, impairing CNS function (Kraft-Terry, Stothert, Buch, & Gendelman, 2010). Infected microglia

release proinflammatory cytokines, including TNF-alpha, IL-1-beta and IL-6, which lead to synaptic changes that contribute to neurodegeneration, affecting the cortex, the limbic system and the basal ganglia (Del Palacio, Alvarez, & Munoz-Fernandez, 2012). The basal ganglia, including the caudate, putamen (CP) and nucleus accumbens (NA), are direct regulators of motivated behavior and reward. Disruption of their functions results in lethargy, anhedonia and depression, all of which may be experienced by HIV/AIDS patients. Autopsy and functional imaging studies show that HIV attacks basal ganglia, causing decreases in volume and function that result from neuron death (Aylward et al., 1993; Berger & Arendt, 2000; Nath et al., 2000; Theodore, Cass, Nath, & Maragos, 2007). Viral proteins, including gp120 and Tat, also contribute to the neurotoxic and neuroinflammatory processes (Barreto, Viegas, Ziff, & Konkiewitz, 2013).

It has been reported that the viral infection can be under control systemically and nevertheless still active in the CNS (Gartner, 2000; Lindl, Marks, Kolson & Jordan-Sciutto, 2010). Because CD4 is a parameter of systemic infection, it therefore may not directly reflect the virally mediated neuroinflammatory and neurotoxic processes, which are thought to be related to depression (Barreto et al., 2013). This could account for the lack of positive association in the current study between depressive symptoms and CD4 cell count. Thus, there is a great need to find appropriate biomarkers of CNS infection, which could be used for diagnostic and therapy follow-up purposes. Moreover, such biomarkers could also contribute to the understanding of the pathophysiological pathways underlying depression associated with HIV infection.

4. Convergence of Social and Neuroimmunological Mechanisms: a Neurodevelopmental Model for the Origin of Depression Amongst PLHIV

Considering the “inflammatory and neurodegenerative theory of depression” in the context of the psychosocial burden, especially with regard to socioeconomic and educational disadvantage and stigma, it is remarkable that similar to physical injury, psychological stress also leads to elevation of cytokine levels in the CNS (Kiecolt-Glaser et al., 2005; Miller et al., 2008). This suggests that the brain interprets both physical

injury and psychological stress as threats to the individual’s survival or integrity and recruits similar adaptive mechanisms in both situations. This may represent a pathway that explains the finding that stress enhances the risk for numerous diseases, such as ischemic infarct and autoimmune diseases, not just the risk for neuropsychiatric disorders (Valente, 2003; Bookman et al., 2011). The higher depression rates among PLHIV could therefore result from the

complex and as yet poorly understood synergistic neuroimmune and endocrinological responses to virally and psychosocially induced injuries.

Recent fMRI studies have identified brain regions that may mediate the induction of depression by negative psychosocial factors, such as stigmatization. When the brain perceives social threats, the amygdala, the dorsal anterior cingulate cortex (dACC) and the anterior insula (AI) (reviewed by Muscatell & Eisenberger, 2012) stimulate the sympathetic nervous system (SNS), elevating heart rate, blood pressure and, significantly, an inflammatory response. They also stimulate the HPA axis and elevate cortisol. Significantly, chronic activation of the HPA axis leads to glucocorticoid resistance, in which immune cells become refractory to elevated cortisol (Miller et al., 2008). These studies begin to provide a basis for the ability of specific CNS areas to detect threatening signals arising from complex social interactions, value attributions and hierarchies. They also suggest that the individual may mediate a coordinated response to viral infection and negative psychosocial factors through convergent immunological and neurobiological mechanisms.

Although the physiopathology of depression in the general population and in the context of different systemic diseases is not yet clarified, the current report identifies socioeconomic mediators of risk for depression in PLHIV. By incorporating these findings together with evidence from translational and clinical research, we propose in Figure 1 a neurodevelopmental model for depression in PLHIV.

First, in the development of psychiatric disorders, genetic polymorphisms including ones involving monoaminergic systems, shape the sensitivity of the individual to environmental factors, a form of “gene-environment interaction” (Bookman et al., 2011).

Second, early life events including prenatal

circumstances act through epigenetic mechanisms to influence patterns of gene expression in adolescence and adulthood and to modulate neurodevelopment. Epigenetic influences of prenatal origin have been demonstrated in the offspring of mothers who endured hunger during pregnancy, who had high cortisol levels and who experienced severe trauma, such as the during holocaust (Brown & Susser, 2008; Heijmans et al., 2008; Kellermann, 2013) .

Third, adversity, such as enduring social hardship, neglect, violence and sexual abuse, are risk factors for various neuropsychiatric disorders. The most studied mechanism explaining this is the stress response and the resulting HPA axis changes (Wilkinson & Goodyer, 2011). The stress response, although providing an acute benefit for survival, may, when long lasting, create enduring neuroplastic changes that predispose the brain to act in an individual and maladaptive way to future negative events, such as socioeconomic challenges, poverty, low education and stigma,

Fourth, PLHIV are statistically more prone to have had adverse early life experiences, and for this reason are more likely to have already undergone the above mentioned neurodevelopmental and neuroplastic changes (Clark et al., 2012; Pence et al., 2012). These changes can render PLHIV more vulnerable to additional adversity, and indeed HIV infection may constitute the final insult that leads to depression. On one hand, the virus will induce chronic neuroinflammatory and neurotoxic changes that are damaging, especially for the monoaminergic system. The virus will also decrease neurotrophic factors, diminish neuroplasticity and stimulate the HPA axis and cortisol resistance (for review, see Del Guerra et al., 2013). On the other hand, in addition to the medical complications of the disease and the side effects of CART, HIV infection may induce severe psychosocial burdens related to stigma, to concerns about having a chronic disease, which may impair their occupational function compromising their earning ability, as discussed above in this text.

5. Conclusions and Future Perspectives

In view of the strong implications of neuropsychiatric comorbidities for disease

outcome, we suggest two types of effort for countering HIV depression. First, PLHIV should

be provided an individualized treatment program that takes into account their particular psychological dimensions and develops strategies including personal empowerment for coping with, and overcoming, psychosocial adversity. Second, neurobiological studies should be vigorously pursued to understand the neuroplastic changes leading to depression in PLHIV and to identify biomarkers of depression to be employed for clinical diagnosis, treatment follow-up and investigational purposes. Furthering the newly emerging neurobiological understanding of how the brain mediates the body's response to negative psychosocial factors will play an increasingly significant role in maintaining health and Quality of Life for PLHIV.

A deep understanding and investigation of societal mechanisms should be incorporated in the training of health professionals. Health professionals themselves cannot afford to be alienated or to keep living under the illusion of doing their part when patient needs are not fully met. Without considering these powerful disease-perpetuating mechanisms and without incorporating strategies to fight them, the resources applied in the HIV public health politic run a risk of being ineffective and partially wasted. Thus, health professionals must use their knowledge to promote awareness, orientation and empowerment, which could lead to reductions in HIV incidence and reductions in health inequities in order to achieve the goals of the National HIV/AIDS Strategy.

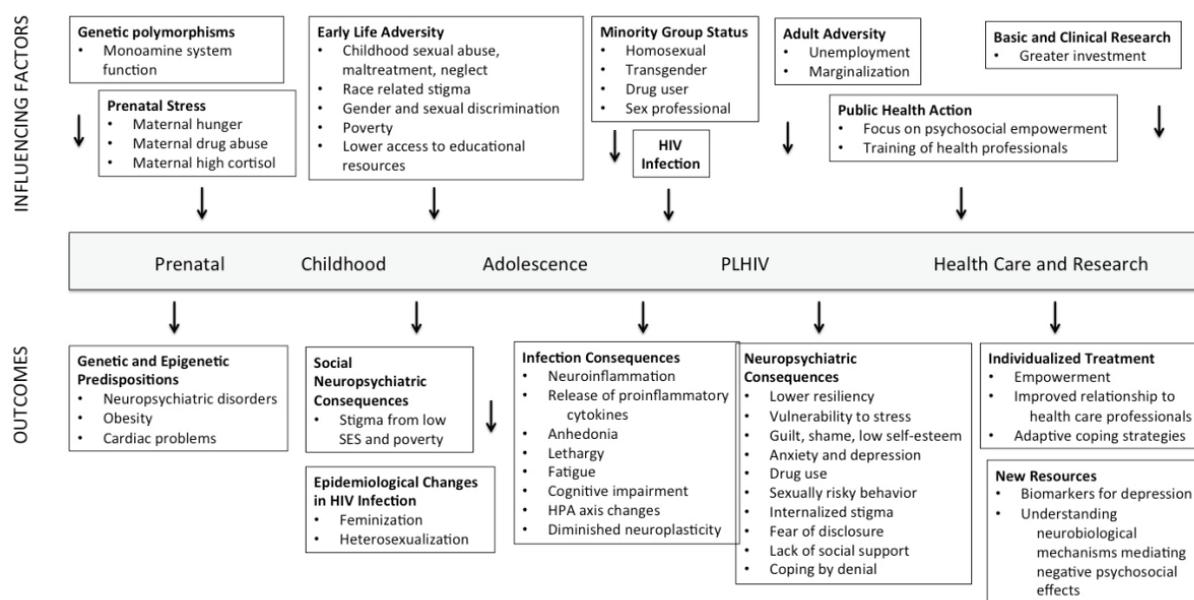


Figure 1. Neurodevelopmental model of the origin of depression in PLHIV. The model shows environmentally induced epigenetic and neuroplastic changes, from the prenatal period to adulthood, brain mediated responses to psychosocial experiences, virally induced neuroinflammatory and neurotoxic processes, HIV related psychosocial burden and finally suggestions for future research and AIDS care strategies.

Conflict of interest

The authors declare that they have no conflict of interest.

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