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The Effect of Stress on the Progression and Development of HIV/AIDS

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ABSTRACT

There is substantial evidence to indicate that the biological human stress response, when activated frequently or during long periods of time, can cause physiological health problems, including immunosuppression, which is particularly dangerous among patients with AIDS and HIV. The secretion of stress hormones, such as glucocorticoids, leads to a decrease in CD4 white blood cells, and this can facilitate the progression of HIV to AIDS and also exacerbate the course of the disease. HIV/AIDS is often associated with elevated stress levels, as well as mental illnesses such as anxiety and depression. Mental illness can also affect disease progression through similar biological mechanisms, although there is a lack of definitive research in this area. Stress alleviation therapy should be considered an important part of the treatment of people living with HIV and AIDS. Research indicates that as well as preventing the negative effects of stress, stress reduction treatments may also alleviate the symptoms of antiretroviral therapy, both of which could vastly contribute to the quality of life and health of patients. In this paper, we examine the biological mechanisms through which stress can impact the immune system and review relevant research on stress, its impact on HIV, potential future research, the role of mental health in disease progression, and implications of these findings.

Introduction

Human immunodeficiency virus (HIV) is a virus that attacks the afflicted person's immune system, generally measured by CD4 cell count, weakening the body's defences. HIV increases the chances that even a common virus or cancer, that a healthy person would easily survive, could have serious health consequences and even lead to death (HIV/AIDS, 2021), given the evidence that activation of the biological stress response leads to immunosuppression.

Immunosuppression, which clearly aids the progression of HIV and AIDS, is provoked via numerous mechanisms initiated by the triggering of the stress response. The virus destroys CD4 cells, which are white blood cells that have the CD4 protein on their surface, which acts as a co-receptor for the T-cell receptor. It destroys CD4 cells by using replication to create new copies of itself, ultimately causing the cell to burst (Nall, 2020). HIV is regarded as having progressed to AIDS, the last and most dangerous stage of the virus, once the cell count of CD4 drops to beneath 200, in comparison to the healthy range of 500 to 1500 cell/mm^3 (Garcia, & Guzman, 2020). In this stage, the immune system is so severely impaired that any fungi, bacteria, or virus that would not likely cause sickness in a healthy person can lead to life-threatening infections. (Mayo Clinic, 2020).

In 2020 alone, approximately 680,000 people have died from AIDS out of a total of approximately 37.6 million people living with HIV, 1.7 million of which were children (WHO, 2021). Since the start of the HIV epidemic, 36.6 million people have died of AIDS-related illnesses, (UNAIDS, 2021). The vast majority of people afflicted with HIV live in low and middle-income countries, of which 20.6 million people with HIV live in southern and eastern Africa (corresponding to roughly 55% of the total number of people with HIV), 4.7 million (corresponding to 13%) in central and western Africa, 5.7 million (15%) in the Pacific and Asia, and

2.2 million (6%) in Central and Western Europe as well as North America just in 2020. In the US, bisexual, gay, and men who have sex with men (MSM) are the population most afflicted with HIV (HIV.gov, 2021).

AIDS may also leave an afflicted person vulnerable to an opportunistic cancer, increasing their chances of developing a Kaposi sarcoma (500 times more likely), non-Hodgkin lymphoma (12 times more probable), and 3 times as likely to be diagnosed with cervical cancer. Furthermore, people living with HIV are more likely to be diagnosed with anal cancer (19 times more likely), liver cancer (three times more likely), two times the probability of being diagnosed with lung cancer, approximately two times more likely to be diagnosed with pharynx/oral cavity cancer, and around eight times as likely to be diagnosed with Hodgkin lymphoma compared with the general population. (National Cancer Institute, 2017). Cancer is among the most prevalent causes of death in the UK, making these statistics particularly concerning; hence the need to investigate possible causes of HIV/AIDS exacerbation. There is much evidence to support the hypothesis that stress is one of these causes and that it could be severely impacting the health and longevity of people living with HIV/AIDS.

Given the detrimental effects of HIV and AIDS, it is crucial to determine risk factors for AIDS development. One potential risk factor could be stress, given that stress has been shown to exacerbate many other health issues and weaken the immune system (Sapolsky, 2004). When the stress response is activated for an elongated period of time, hormones, such as glucocorticoids, are released and begin to harm the body with the intent to save energy to continue fuelling the fight or flight response. This overactive stress response is particularly harmful in modern society as many stressors are long-term and ongoing, relative to short-term life-threatening stressors that the stress response is evolved to aid. Glucocorticoids' primary purpose is to prioritize survival over any function in the body, so every necessary process takes a back seat. This is useful when in danger and has helped humans survive throughout the centuries, but often now works against our health and can be incredibly detrimental to the health of patients with HIV. This leads to a myriad of different problems including but not limited to memory loss, difficulty sleeping, strokes as well as hypertension, and an increased risk of cardiovascular disease outcomes. (Tyra, Soto, Young, & Ginty, 2020).

Out of the many long-term negative health outcomes of chronic stress, the most concerning, however, for the progression of HIV to AIDS, is that continuous stress has been shown to lead to immunosuppression through several mechanisms (Bagath, et al., (2019). First, exposure to stress hormones, such as catecholamines and glucocorticoids, released during chronic stress periods has been shown to decrease the number of lymphocytes (white blood cells that produce antibodies). Stress hormones do so by increasing regulatory T cell numbers (the functions of which include the prevention of autoimmune diseases by maintaining self-tolerance, the suppression of allergy, asthma, and pathogen-induced immunopathology, the feto-maternal tolerance, and oral tolerance; (Corthay, 2009) in circulation. This response then triggers apoptosis, a genetically regulated form of cell death, (Renehan, Booth, & Potten, 2001) even in healthy, functioning lymphocytes. (Antoni, & Dhabhar, 2019).

Corticosteroids keep sensitized lymphocytes (a white blood cell that has been activates by exposure to an antigen) out of peripheral circulation by storing them in immune tissues and preventing them from traveling around the body (Smith, 2002). It is also worth noting that glucocorticoids inhibit the production of the chemical messengers between leukocytes (white blood cells), as shown in an experiment examining the effects of dexamethasone on inflammatory markers such as Interleukin-1 alpha (IL-1), Interleukin-1 beta, and Interleukin-6 (IL-6). The corticosteroid, dexamethasone was found to have immunosuppressive effects on these inflammatory markers by destabilizing Interleukin-1 beta mRNA (the single strand of DNA that codes for the IL-1 beta gene) and decreasing both its levels and the levels of IL-1 alpha. Levels of both of these proteins within the cells were decreased and this glucocorticoid was also found to strongly inhibit IL-1 induced expression of the IL-6 gene in connective tissue-type cells (Amano, Lee, & Allison, 1993). IL-1 stimulates T helper cells (white blood cells that act by releasing of substances to help control parts of the immune system) once a pathogen is identified by a macrophage (a white blood cell that surrounds and kills microorganisms and stimulates the action of other immune system cells (National Cancer Institute, n.d.), which in turn releases IL-

2 to trigger cytotoxic killer cells, (Topham, & Hewitt, 2009). These are white blood cells that kill damaged or foreign cells. Furthermore, this then also triggers differentiation and proliferation of B cells to produce antibodies. Both of these essential chemical messengers are suppressed by glucocorticoids, as IL-2 gene expression is also inhibited when exposed to them (Northrop, Crabtree, & Mattila, 1992). There are several other mechanisms of suppression caused by glucocorticoids, but these suffice to show the strong impact of chronic stress on the immune system.

The negative impact of stress on the immune system is particularly relevant when considering HIV/AIDS, given that the virus attacks the immune system and causes death by rendering the afflicted person highly vulnerable to any and all infections. Stress can therefore exacerbate the effects of HIV and increase the rate of disease progression to AIDS as lymphocytes exposed to glucocorticoids are more likely to be infected with the virus. Norepinephrine, which is another product of the stress response, can facilitate and enhance the replication of the virus via invasion of lymphocytes, leading to further debilitation of the immune system. This follows the "psychoneuroimmune route" that Sapolsky discusses which shows the steps from the change in level of stress to altered survival (psychosocial manipulation leads to a change of level of stress which changes level of glucocorticoids, which in turn affects immune function and this impacts disease resistance), as shown in an experiment done on nonhuman primates (Sapolsky, 2004). The monkeys who were more socially isolated (a stressor) had higher glucocorticoid levels and therefore fewer antibodies against the virus and a higher mortality rate. Hence, via the mechanisms previously discussed, the immunosuppression caused by HIV can be magnified by hormones secreted during chronic stress (glucocorticoids), leading to a faster drop in CD4 as the immune system helps the virus by weakening itself allowing for faster progression to AIDS.

Given this background on how stress may impact the biological processes of AIDS and HIV, I conduct a literature review to answer the following questions:

1. Does chronic stress increase the likelihood that someone with HIV develops AIDS?
2. Once AIDS is developed, does chronic stress worsen its course, as measured by general mortality, development of other diseases, or lower quality of life?

We hypothesize that stress will increase the likelihood of HIV developing into AIDS and that stress worsens HIV progression by causing further immune suppression, and negatively impacting patients' mental and physical health.

Methods

In order to answer these research questions, we conducted a literature review in the following way. We searched for relevant articles using the databases Google, Google Scholar, and Pubmed. We began by using the search terms ""HIV" OR "human immunodeficiency virus" OR "AIDS" OR "Acquired immunodeficiency syndrome" AND "Stress"". We originally restricted the time-period to be between 2016 and 2021, because research on stress and HIV is constantly evolving and we wanted to include the most recent discoveries. The initial search was a "title search" only. We screened the first 30 articles out of approximately 250 that came up. In addition to this, we used the advanced settings to exclude any article containing the word "oxidative" in the title as oxidative stress is not what we were researching. We were mostly interested in studies that examined the relationship between a population that was afflicted with HIV or AIDS, the progression of their disease, and their levels of stress/stressful life experiences. Hence, we also excluded any articles that were focused on the stress caused by HIV, although it was noted that anyone with HIV has generally higher levels of glucocorticoids than the unafflicted. We then screened the first 30 from PubMed using the same search terms and restrictions, and from here we gathered more relevant articles. However, there were fewer accessible relevant articles of those in which we were interested so we widened the time frame to include the last 30 years (1991 onwards), and this was much more successful. We also expanded our search so that the terms may be included in the full text, rather than just the title. We then included articles that explored the relationship between stress

management methods and disease regression to see if the relationship between stress and HIV/AIDS progression worked both ways.

Given the early dating of a few of the articles included we conducted additional searches in various search engines (including google scholar and PubMed as well as any articles found online and educational websites such as WHO) to quickly check if anything negated these articles' findings and verify that the material we included was correct to the best of our knowledge. We included approximately nine sources yielded from this search. We also include information from "Why Zebras Get Ulcers" by Robert M. Sapolsky.

Results

In this manuscript, we include 9 articles selected as relevant from the above search.

Does chronic stress increase the likelihood that someone with HIV develops AIDS, as measured by CD4 count?

We conclude that stress can exacerbate the course of HIV and could potentially lead to the development of AIDS. Any stress-related disorders, such as PTSD and anxiety, were harmful and led to decreased CD4 cell count, via mechanisms previously discussed in the introduction. When looking at the effects of a big stressor on different categories of people, the results were quite clear. In a study looking at the CD4 cell count of people living with HIV before and after hurricane Katrina (Robinsona, Wendella, & Gruber, 2011), the total mean number of CD4 cells dropped from 419.52 to 412.97, in the 18-month period immediately before and after the event. While this may not be a huge or particularly significant drop, the overall trend in all categories, which included gender, race, sexuality, and time of diagnosis, showed decreased CD4 count, indicating disease progression. Evacuees were shown to have the largest drop in CD4 count, from a mean of 365.27 to a mean of 336.79. The study also notes that non-returning evacuees showed a stronger decline in average CD4 counts pre to post Katrina, than returning evacuees or the non-impacted population. This drop in CD4 cell count post-Katrina is concerning as it shows how a continued stressor might lead to a diminishing CD4 count, and once this reaches 200, it has progressed to AIDS.

Another study looked at perceived stress, rather than the impact of one stressor, and used the PSS scale to find a relationship between CD4 cell count in people living with HIV and their levels of stress (Effendy, Amin, de Vega, & Utami, 2019). The PSS scale is the most widely used psychological instrument for measuring a person's perception of stress. It is a measure of the degree to which situations in someone's life are appraised as stressful, (Cohen, Kamarck, & Mermelstein, 1994) The study looked at 46 afflicted people living in Indonesia, and found a significant correlation between perceived stress levels and CD4 count ($p<.05$). When comparing the impact of a globally acknowledged stressor, such as Katrina, and the everyday perception of stress, both studies found a negative impact on the health of people living with HIV, supporting the hypothesis that stress worsens the impact of HIV and could lead to it developing into AIDS.

Many individual research papers showed evidence for this hypothesis, however, when looking at a global literature review of stress related to clinical outcomes of HIV and AIDS, the overall results were mixed (Weinstein & Li, 2016), and the overall impact of different mental health problems, as well as alleviation strategies, were not considered. Out of 23 studies examined, nine signalled significant or mixed results regarding whether stress affected CD4 count in people living with HIV/AIDS, which corresponds to roughly 40% of studies.

These very mixed results give an unclear idea of the relevance of stress directly on CD4 cell count, especially given the different methods used to measure stress and disease progression. However, the review

discusses how the studies that did find a correlation between stress and decreased CD4 cell count measured acute biological stress, which might indicate how the severity of stress experienced is a very significant factor.

Does chronic stress worsen the course of HIV/AIDS, as measured by general mortality, development of other diseases, or lower quality of life/negative mental health?

Unsurprisingly, studies find that HIV and AIDS can lead to a decrease in mental health as well as the development of mental illnesses such as depression and anxiety, both of which can exacerbate the course of the disease. It is possible that individuals develop other diseases as well, but our search terms did not yield enough information to draw conclusions in this area. A study that we looked at used a sample of 402 HIV-positive people living in Australia aged 18 years or older. Of these, 357 identified as gay men. It was found that a large risk factor for mental health problems was internalized stigma and discrimination, and that anxiety was associated with a decreased CD4 cell count. Anxiety levels in this sample of people were higher than the population mean, and so were generalized stress score levels. CD4 cell count under 250 was associated with anxiety, which might be caused by fear of the health implications of a compromised immune system. Protective factors included access to social support and, most importantly, emotional support. People living with HIV/AIDS are also more vulnerable to depression, which, aside from being a very serious mental health problem, can also exacerbate disease progression as found by a review that states that depression can cause elevated cortisol secretion (Chaudhury, Bakhla, & Saini, 2016). Cortisol is a glucocorticoid, and it is also the main stress hormone which indicates that different mental health issues may have similar effects via mechanisms linked to similar, specific hormone secretion. It was also found that both depression and anxiety were associated with persistent symptoms of HIV, along with alcohol and tobacco use, which both negatively affect health outcomes. Associated findings about anxiety reaffirmed that anxiety was associated with low CD4 count and lack of social support. We did not find any articles that examined a connection between the effect of stress on HIV/AIDS by measuring mortality or development of other diseases, so perhaps more research should be conducted in this area.

Additional Findings: Protective factors, Stress reduction Treatments and Social support

In addition to exploring our research questions, the search also yielded information on protective factors against HIV/AIDS development. Whilst much of our research was focused on the negative impacts of stress on the progression of HIV/AIDS, there is also evidence that stress alleviation treatments can have a positive effect on the disease (Riley & Kalichman, 2015). When looking at a review that examined the effects of mindfulness-based stress reduction (MBSR) on people living with HIV, the results indicated higher CD4 count, fewer symptoms of ART (antiretroviral therapy - which refers to any HIV treatment that uses a combination of two or more drugs) and an improved psychological state. Of the 11 studies included in the review, every study that tested MBSR demonstrated some evidence for efficacy, spanning the domains of health, emotional, coping, and behavioural outcome. Most importantly, perhaps, when considering the progression of HIV, CD4 cell count was shown to increase with respect to control groups or stay the same while the control groups' decreased. It should be noted, however, that in one study, CD4 did increase compared to controls up to the 9-month follow-up, but then declined back to baseline at 12-month follow-up (Alinaghi et al., 2012). There was also found to be a positive impact on the psychological well-being of the patients, with 5 out of the 6 studies that measured general psychological distress showing significant increases in psychological well-being, or a decrease in negative psychological symptoms

Discussion

For this study, we conducted a literature review of manuscripts examining the association between stress and HIV/AIDS progression. First, we examined how the eligible articles relate to our original research questions:1) Does chronic stress increase the likelihood that someone with HIV develops AIDS?, and 2) once AIDS is developed, does chronic stress worsen its course, as measured by general mortality, development of other diseases, or lower quality of life? Then, we highlight additional themes revealed through our literature search including protective factors against worsening HIV/AIDS.

Overall, for our first research question, we conclude that stress does exacerbate the danger of HIV developing into AIDS, as there is considerable evidence that stress leads to a lower CD4 cell count and increased viral load. It also interferes with the functioning of the immune system by suppressing production of antibodies such as IL-2, (Amano, et al., 1993). Whilst overall, a review found that stress leads to lower CD4 counts, it should be noted that out of the 14 studies that found a non-significant relationship between stress and CD4 cell count, 8 found significant or mixed results concerning viral load, disease progression, and treatment adherence. This demonstrates that the stress response could affect the course of HIV and AIDS via alternative mechanisms, other than CD4 count. It should also be taken into account that stress could affect clinical outcomes indirectly by affecting how a patient sticks to their treatment plan and that stress caused by the disease itself could be as impactful as stressful life events. On the other hand, a study examined in this review found that for every one severe stress or per 6-month study interval, the risk of early disease progression was doubled (Evans et al., 1997). In addition, multiple major stressors may increase the effect that stress has on AIDS development, as seen by the study of Hurricane Katrina which shows that evacuees showed greater reductions in CD4 counts than returnees, which could be related to the stress of moving to a new environment as well as potential PTSD from the hurricane.

For our second research question, we found that the mental health of HIV and AIDS patients is worse on average than other patients due mainly to self-stigma, and social isolation, which both in turn can worsen the course of AIDS. The most common risk factors associated with the development of HIV include these (social isolation, internal stigma), as well as discrimination, which can all be considered stressors, and provide further evidence for how the activation of the stress response can lead to immunosuppression. Furthermore, these factors may also cause stress disorders or depression, which exacerbate the course of HIV through the release of stress hormones such as glucocorticoids which we discussed previously, among other things. Thus, via the mechanisms explained in the introduction, exposure to stressors can be very detrimental to people living with HIV or AIDS. Our research then indicated that protective methods for people living with HIV/AIDS include mindfulness-based stress reduction (MBSR) as well as social and emotional support, which are all shown to decrease levels of stress and have been found to either cause CD4 cell count to increase or to not decrease whilst count of control groups does. The returns to baseline CD4 count after improvements in numbers could further indicate that continued MBSR might prevent or slow the progression of HIV. Although this was the case in many of the articles we screened, it is important to note that findings in some papers were mixed and that stress does not always cause CD4 count to decrease or viral load to increase.

Limitations

This study is not without limitations. First, this review is not a systematic review, as we did not screen all articles that came up in our search and we did not double-code for eligibility. Given the broad scope of the research questions, the author selected the 30 most relevant articles and endeavoured to maintain objectivity in selecting the articles. Regarding limitations of the studies included, stress may be negatively affecting patients by non-biological mechanisms, such as decreasing the likelihood that they stick to their course of treatment or

increasing chance of unhealthy habits such as drinking or smoking. Lastly, many of the studies aren't randomized control trials for stress reductions treatments, so we cannot infer causality.

Future Directions

More research is needed to investigate why results are variable, and what the differences are between large stressors, continued stressors, and stress disorders such as anxiety or PTSD. This would be helpful to identify the scale of a risk factor and incorporate that knowledge into patient care. More research is needed to look at the variations of the biological stress response in individuals with HIV/AIDS so that treatment plans can include management of stressful life events, or just the general everyday stress of living with the disease.

Broad or Clinical Implications of Findings

Given the findings that a major risk factor is social rejection and isolation, we suggest that social support groups for those living with HIV and AIDS should be set up. This follows from the conclusion of many articles that emotional support from other people, including friends and family can alleviate the negative health outcomes of stress and can be beneficial to patients' health. The inclusion of MBSR in treatment plans should also be considered as there is considerable evidence that this therapy contributes to positive effects on patient health. These groups may be particularly helpful for individuals with co-morbid mental health conditions such as depression, anxiety, and posttraumatic stress disorder.

Conclusions

To conclude, we have found that activation of the stress response can exacerbate the course of HIV and AIDS and that this mainly impacts patient health outcomes through increasing immunosuppression, especially via the decrease of CD4 white blood cells, but also through the interference of chemical messengers between different parts of the immune system, preventing it from working as it should. This also contributes to the decline of mental and physical health in some cases, although more research is needed into the variation of results. We found associations between alleviation of stress and positive health outcomes, regarding methods such as MBSR and social support, and believe that these should be examined and included in treatment plans of afflicted patients.

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