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Hypothesis

Hypothalamus-Pituitary-Adrenal cell-mediated immunity regulation in the Immune Restoration Inflammatory Syndrome

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Abstract:
Over one third of the patients sero-positive for the human immunodeficiency virus (HIV) with signs of the acquired immune deficiency syndrome (AIDS), and under treatment with anti-retroviral therapy (ART), develop the immune reconstitution inflammatory syndrome (IRIS). It is not clear what variables are that determine whether a patient with HIV/AIDS will develop ART-related IRIS, but the best evidence base thus far indicates that HIV/AIDS patients with low CD4 cell count, and HIV/AIDS patients whose CD4 count recovery shows a sharp slope, suggesting a particularly fast "immune reconstitution", are at greater risk of developing IRIS. Here, we propose the hypothesis that one important variable that can contribute to low CD4 cell count number and function in ART-treated HIV/AIDS patients is altered hypothalamic-pituitary-adrenal (HPA) cell-mediated immune (CMI) regulation. We discuss HPA-CMI deregulation in IRIS as the new frontier in comparative effectiveness research (CRE) for obtaining and utilizing the best evidence base for treatment of patients with HIV/AIDS in specific clinical settings. We propose that our hypothesis about altered HPA-CMI may extend to the pathologies observed in related viral infection, including Zika.

Keywords: human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), anti-retro viral therapy (ART), immune reconstitution inflammatory syndrome (IRIS), hypothalamic pituitary adrenal axis (HPA), cell mediated immunity (CMI), corticotropin releasing hormone (CRH), adenocorticotropin hormone (ACTH), glucocorticoids (GC), comparative effectiveness research (CER),

Background:
Incontrovertible clinical evidence has established the effectiveness of antiretroviral therapy (ART) in patients with HIV or AIDS. For example, ART-treatment can lead to a marked decrease in the incidence of AIDS-defining opportunistic infections, in AIDS-associated cancers, in neuro-AIDS, and in AIDS-related mortality, which together are attributed to an ART-driven immune reconstitution. However, certain HIV-AIDS patients under ART-mediated immune reconstitution exhibit a syndrome of deregulated inflammatory responses, the Immune Reconstitution Inflammatory Syndrome (IRIS). The variables that determine whether a patient with HIV/AIDS develops ART-related IRIS are unclear. What is known is that HIV/AIDS patients with low CD4 cell count, or whose CD4 count shows a sharp recovery slope, are at greater risk of manifesting IRIS **[1, 2].**

Taken together, the clinical and laboratory evidence to date suggests that an exorbitantly fast immune reconstitution may be indicative of important alterations in CMI, which may contribute to deregulated cellular immune inflammatory responses. It is possible and even probable that the physiological regulation of immune reconstitution is brought about in part by non-immune processes. Case in point, it has long been recognized that the nervous and the endocrine systems play timely and critical roles in modulating cellular immune responses, including inflammation **[3,4].** We have described the role of psychoneuro-endocrine modulation, and specifically of the hypothalamus-pituitary-adrenal (HPA) axis, in CMI regulation in normal healthy adults **[5,6],** as well as patient populations **[6,7]**. Others have described significantly altered HPA regulation in certain patients with HIV/AIDS **[8,**

9]. Data also suggest that the progression of IRIS is often curbed when HPA-stimulating symptoms of stress and anxiety are controlled and diminished (e.g., by better educating the patients about anticipated IRIS-side effects) **[10,11].** Therefore, we propose that one important variable that can contribute to the onset of IRIS in ART-treated HIV/AIDS patients is altered HPA-CMI regulation.

The inflammatory response, a sign of IRIS, a complex immuno-physiological process that requires and involves a plethora of cytokines, and factors that are not non-cytokines. Together these elements are involved in a delicately balanced orchestra of effects and counter-effects, activation and feedback loops that together signify the fine regulation of cellular immune surveillance. This myriad of events that inform the immune-inflammation microenvironment as it pertains to viral immune surveillance, was recently described by our group for Dengue **[12]** and Ebola **[13],** and undoubtedly applies to HIV immune surveillance. In brief, the inflammatory response is composed of two phases: the first, triggered and sustained by myeloid CD45+CD14+ cells (some of which are CD4+dim) that produce interleukin (IL)6, IL1b and tumor necrosis factor (TNF)a in addition to prostaglandins and other non-cytokines that favor inflammatory processes - this is a rather sharp and short-lived response; and the second, triggered by lymphoid CD45+CD14- cells (many of which are CD4+high) that engender a TH17 response (i.e., predominant cytokines: IL17 & IL23), which is finely regulated by IL9 and other TH9 cytokines representatives - this, by contrast, is a sustained inflammation, such as that we observe in inflammatory diseases (e.g., inflammatory bowel disease). Both arms are subject to fine regulation brought up in part by regulatory T cells (CD4+CD25+FoxP3+) **[12,13].** One important gap in knowledge in the immuno-pathology of IRIS is the characterization, within the fast rising CD4 cell population, of which subpopulation of CD4+ cell is fast proliferating, and of whether or not the rise in cell number corresponds to increased specific functional responses. Testing the responsiveness of HPA-CMI following dynamic and static challenges, as discussed previously **[6]** and outlined below, may provide this timely and critical evidence about the state of chaotic inflammation observed in IRIS.

Methodology:
In brief, we propose the hypothesis that the sub-population of patients with HIV/AIDS who develop IRIS during ART-mediated treatment intervention are those with deregulated HPA-CMI homeostasis and glucocorticoid resistance. Our corollary hypothesis states that the patients with HIV/AIDS and HPA/CMI deregulation will manifest a disorderly sharp CD4 recovery slope and signs of exorbitant inflammation upon removal of the chronic viral stressor, as observed when these patients are treated with ART- mediated interventions.

In an experimental design with patients with HIV/AIDS randomly sampled from the population, we will test the HPA response to external stressor (e.g., cold press or test, mental arithmetic), as well as internal static and dynamic challenges. The static approach tests the functionality of the HPA axis by temporarily arresting the glucocorticoid feedback mechanism **[5]** Participants will be administered 1-5mg of metyrapone after a meal during midafternoon to early evening. Metyrapone acts as a glucocorticoid synthesis inhibitor, thus preventing the metabolism of plasma cortisol. Alternatively, subjects will be administered a 5 mg bonus of the synthetic glucocorticoid, dexamethasone at 11:00 PM. Participants will have their plasma cortisol and ACTH levels measured at 8:00 AM and 5:00 PM the following day. Peripheral glucocorticoid receptor resistance will be assessed in peripheral blood lymphocytes at the 8:00AM time point **[6-7].** CMI responses to the HPA stimulation will be monitored by examining sub-populations of peripheral blood lymphocytes for cell number and proportion, by dual fluorescence flow cytometry, and function, following non-specific (i.e., mitogens such as concavalin-A) and specific activators (e.g., via the CD3 pathway with CD28 co-stimulation). Functional responses will be recorded as TH1 vs. TH2 vs. TH17 cytokines production in response to specific stimuli. Circulating cytokines in plasma and in saliva will be used as reference levels. To take into account circadian variation intervening variables, measurements should be obtained at both time points **[6-8].** The dynamic tests of HPA response will be obtained by challenging the subjects in vivo with ACTH or CRH at 11:00 PM. Measurements of plasma ACTH (following the CRH push), cortisol, of peripheral blood lymphocytes glucocorticoid receptor resistance, and peripheral blood lymphocytes distribution and function will be tested at 8:00AM as above.

Discussion:
The HPA axis is a sophisticated psychoneuroendocrine system that is activated by and responds to a variety of stressors, including challenges to cellular immunity. CMI in turn regulates HPA responses. Stressors can be physical, mental or immunological in nature, and induce a finely coordinated HPA-CMI response **[3-9,14].** Upon activation of higher brain processes to a potentially threatening stressor, the hypothalamus releases corticotropin-releasing hormone (CRH) which in turn stimulates the production of the adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. The release of ACTH into the systemic circulation stimulates the adrenal cortex to synthesize and produce glucocorticoids, namely cortisol and cortisone. These glucocorticoids find their way to cells throughout the body and bind as ligands to glucocorticoid receptors, in which this signal translocates to the nucleus of the cell where it can regulate transcription of glucocorticoid-related genes **[15].**

As the end-products of the HPA axis, the two primary effects of interest to us of stress-response glucocorticoid production are the increasing levels of serum blood glucose for available energy sources and suppression of certain immune functions to protect long term damages of immune pathology. However, the effects of serum glucocorticoids are not limited to the aforementioned; its overarching function can be best described by understanding that this form of stress response is a main function of our sympathetic nervous system and the effects of glucocorticoids coincide appropriately. Another important feature of the HPA axis is a negative feedback loop – a regulation mechanism. This mechanism allows the body to refrain from producing excessive products of different parts of the HPA axis and ultimately attaining the goal of the HPA axis: homeostasis. Most commonly, as the production of glucocorticoids reaches the sufficient level needed for the body to properly adjust to a specific stressor, the further concentration of serum glucocorticoids will signal the hypothalamus to halt the production of CRH; directly reducing ACTH production by the pituitary and glucocorticoids by the adrenal cortex **[15,16].**

During the invasion of a viral pathogen such as HIV-1, the body's natural innate immune response, from immune cells of infected tissues, elicits the production of TH1 cytokines and other inflammatory mediators (i.e., TNFa, IL-1b, IL-6) **[17].** HIV infection is an immune stressor, which activates the HPA axis and subsequent glucocorticoid production [16]. The secreted glucocorticoids prevent the potential damaging of excessive immune response by reducing inflammation of affected tissues, a process mediated by TH2 cytokines and other anti-inflammatory mediators and cytokines that counter TH1 responses, such as IL-10 **[15].** The intertwined nature of HPA-activating CMI responses, and immunosuppressive HPA activation is a critical and timely key aspect of homeostasis, which is seriously hampered and deregulated in certain patients with HIV/AIDS.

The immunosuppressive character of glucocorticoids has been shown to prevent the reduction of CD4 lymphocytes caused by HIV-mediated immune activation thereby increasing CD4 lymphocytes and their therapeutic effects **[18],** and to inhibit HIV viral replication **[19,20].** Reciprocally, diminished secretion of ACTH to CRH, and consequential low serum cortisol suggested an imbalance of cytokine production needed to suppress the consequential immune response from HIV-infected tissues **[21],** an observation confirmed by an experimental study that reported lowered HPA response (i.e., blunted ACTH and GC response to the cold press or test) in in patients with HIV/AIDS **[22].** Related studies established that altered HPA and HPA/CMI responsiveness in patients with HIV/AIDS may be due to a form of glucocorticoid resistance, detectable both centrally and peripherally in peripheral blood mononuclear cells **[23],** as we previously reported for patients with Anorexia Nervosa **[6,7],** who also exhibit HPA/CMI deregulation and glucocorticoid resistance. Data suggest that glucocorticoid resistance in patients with HIV/AIDS may result from inactivation of mutated glucocorticoid receptor gene **[24].**

Taken together, these lines of evidence form the fundamental rationale for the hypothesis we propose here that the subpopulation of patients with HIV/AIDS with deregulated HPA-CMI homeostasis and glucocorticoid resistance will be shown to overlap with those patients who develop IRIS during ART-mediated treatment intervention, because the underlying homeostatic deregulation blunts the physiological modalities responsible for ordered immune reconstitution. Consequently, in these patients, a disorderly sharp CD4 recovery slope and signs of exorbitant inflammation are observed.

Conclusion:
In conclusion, certain patients with HIV/AIDS suffer severe deregulations in the HPA axis. The physiologically important intertwined cross-regulation between the HPA axis and the modulation of cell-mediated immunity (CMI) [**3,11]** suggest that deregulated HPA-CMI may contribute to IRIS in a significant subset of ART-treated HIV/AIDS patients **[25],** including aggressive recurrence in HIV/AIDS-related oral pathologies **[26].** We outlined a methodology for testing the functioning and the resilience of the HPA axis and of HPA-CMI interactions *in vivo*, in a cluster randomized stepped wedge blinded controlled trial (CRSWBCT) of the type we have discussed **[27].** The hypothesis we propose could serve as an important resource in determining the best evidence-base interventions for the affected patients **[28].**

It is possible and even probable that this hypothetical model will also contribute to the elucidation of the pathological mechanisms that underlie Zika virus infection. Proof of principle is given in our recent discussion of neuroendocrine-immune interactions in Dengue **[29].** Zika and Dengue are members of the genus *Flavivirus*, which also includes the West Nile virus, the tick-borne encephalitis virus, the Chikungunya virus, the Yellow Fever virus, and contribute to the incidence of and morbidity of encephalitis, among other pathologies. Flaviviruses are 40–65 nm in size, enveloped with an icosahedral nucleocapsid, positive-sense single-stranded RNA viruses, which are transmitted to humans by means of a bite of the infected mosquito of the genus *Aedes* (i.e., *A. albopictus*, *A. aegypti*).

HIV, of the genus *Lentivirus* (family *Retroviridae*), transmitted by body fluid contact, is also an enveloped positive-sense single-stranded RNA virus. In a vein similar to the arguments discussed here on HPA-CMI deregulation as a putative etiologic factor for the incidence of IRIS, we proposed that the dengue virus might significantly modulate HPA-CMI regulation, and result immune-physiologically in remarkable shifts in TH1, TH2, TH17 and TH9 cytokine levels. It is interesting, and even suggestive of further concerted investigative effort, that both virus geni may lead to altered HPA-CMI regulation, including important elevations in members of the IL-17 family systemically and centrally. Central elevation of IL-17, which could contribute to the profound pathologies of the central nervous system **[30],** such as those observed in lentivirus (e.g., neuro-AIDS) and flavivirus infection (e.g., altered brain development and microencephaly in Zika virus infection *in utero*).

In brief, our hypothesis that altered HPA-CMI may contribute to the onset of IRIS in ART-treated HIV/AIDS patients may extend to the pathologies observed in related viral infection, including most alarmingly the current explosive rise of micro-cephalic infants born of women infected with Zika virus during pregnancy **[31].**

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