

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Relative Risks associated with increased cortisol in patients with HIV.

Deepak Nilsoge Guruswamy^{1*}, Rajeshwari Kenchappanavar¹, and SN Mothi².

¹Research scholar, Karnataka University, Dharwad, Karnataka, India.

¹Head of department, department of psychology Karnataka Arts College, Karnataka University, Dharwad, Karnataka, India.

²Chairman, Asha Kiran Hospital, Mysore, Karnataka, India.

ABSTRACT

Stress is the result of a state of real or perceived threat to homeostasis. The principal effector of the stress response lies in the hypothalamic– pituitary–adrenal (HPA) axis. Glucocorticoids represent the downstream effectors of the HPA axis and regulate biological changes. Activation of the HPA axis, commonly assessed in terms of cortisol levels, may contribute to the development of pathologies and has been recognized as one of the major pathways linking psychological stress to negative systemic outcomes in human beings. Many individuals living with HIV infection are confronted with chronic psychosocial stressors (eg, stigma, illness) that may lead to chronic cortisol dysregulation and HPA axis activation. So our study aims at elucidating the relative risks associated with the increased cortisol in patients with HIV. This single-arm cross-sectional study enrolled 160 patients. After obtaining patient consent, the patients were administered the Becks depression scale; for assessment of depression mood. Furthermore, 5 mL of blood was drawn from all patients for measuring their cortisol by using spectrophotometric analysis. Complete demographic data collected from all the patients including smoking, Alcoholic, marital, spouse living and socioeconomic status. Relative risk ratio is been high in Depressed mood (2.88) and recent death of spouse or relatives (2.75) however Alcohol (1.57), Smoking (1.64), Above poverty line family's (1.53) have been contributed in increasing the cortisol level of patients with HIV irrespective of the Anti retroviral therapy or not. Our study mainly determined the relative risks associated with increased cortisol level in patients with HIV. Statistical analysis revealed that HIV patients with depressed mood, recent death of spouse, smoking and alcoholic is seems to be a major contributing factor for increased cortisol level among patients with HIV.

Keywords: Cortisol, HIV, relative risks

**Corresponding author*

INTRODUCTION

An imbalance in the maintenance of homeostasis is perceived as stress, for homeostasis maintenance with stressors is a complex phenomenon involving endocrine, nervous and immune system, which are collectively referred to as the stress response. (Dickerson PA,2005; Chrousos GP ,1992; Carrasco GA ;2003)The principal effector of the stress response lies in the hypothalamic– pituitary–adrenal (HPA) axis, and from hypothalamus the corticotrophin releasing hormone is secreted for the activation of HPA axis by stimulating secretion of adrenocorticotropin hormone from anterior pituitary gland and this adrenocorticotropin hormone which stimulates zona fasciculata of the adrenal cortex to produce glucocorticoids (cortisol in humans). The effectors of HPA axis is glucocorticoids which regulate biological changes. (Munck A,1984; Bamberger CM,1996) HPA axis activation is commonly assessed from its end term of cortisol levels, which may contribute to the pathologies(Munck A,1984; McEwen BS;1993) this cortisol levels has been recognized as one of the major linking between psychological stress to the negative systemic outcomes in human beings. (McEwen BS;1998)

People living with the HIV AIDS will be confronted with the many psychological stressors which are chronic (McIntosh RC;2012)(eg, stigma, illness)and this chronic stressors activate the HPA axis leading to dysregulation of cortisol .Some of the Psychosocial factors like anxiety, have been associated with disease progression among people living with HIV-1 infection,(Chida Y;2009) and its also associated with the patients antiretroviral therapy and this factors also influencing on rates of adherence (Remor E;2007) Cortisol a stress hormone is a major link to a health related issues among the people living with HIV.(Kopnisky KL;2004; Schneiderman N;2005) Cortisol is capable of enhancing the ability of a Human Immune Virus, by infecting lymphocytes of an infected human which will downregulate the immune system and thereby accelerating the progression of HIV.(Chida Y, 2009; Antoni MH;1990; Leserman J ;2002)Several studies have demonstrated abnormalities of the HPA axis in HIV-1 infection(Azar ST,1993; Laudat A;1995; Mayo J, 2002; Kumar M;2002) and basal cortisol levels have been related inversely with the CD4 counts with the infected man of HIV.(Lortholary O;1996)

In the case of chronic stress, the components of the immune system will decline in normal functioning which may lead to increased susceptibility to infections (colds, herpes, HIV) and worsen existing disease processes, such as cancer (Rosen et al., 1984; Kiecolt-Glaser and Glaser, 1995)

Methodology:

In this randomised, single-arm, cross-sectional study, approval was obtained from the Human Ethics Committee of the Asha Kiran Hospital, Mysore, Karnataka. Before enrolment, consent was obtained from seropositive patients; they were subsequently administered the Becks depression scale. For the assessment of depressed mood of patients. Furthermore, from all patients, 5 mL of blood was drawn into an ethylenediamine tetraacetic acid (EDTA) tube, which was further subjected to centrifugation and plasma separation. By using the spectrophotometric enzyme-linked immunosorbent assay (ELISA) method, cortisol levels were quantified. The study procedure was explained to the patients before obtaining their consent.

Becks depression scale:

This is a self-administered scale with 21 items. After test completion, each question can be scored according to the number on the right of the question. A highest score of 63 can be obtained in this test, indicating that number three was marked for all questions. The lowest score in this test can be zero, indicating that zero was marked for all questions.

Spectrophotometric ELISA

Five millilitres of blood was drawn in an EDTA tube between 4 to 4:30 pm and immediately centrifuged at 3,800 rpm for 10 min. Plasma was stored at –20°C until thawing for assay. The plasma levels of cortisol were measured using the ELISA commercial kit, Calbiotech for cortisol (10461 Austin Dr, spring valley, CA, 91978) .The sensitivity of the plasma cortisol is 1.5 pg/mL, according to the manufacturers' instructions. The optical density of each well was measured using a microplate reader (Varioskan Flash Multimode Reader Version 4.00.53) set at 450 nm. Duplicate readings were averaged for each standard and sample and

normalised by subtracting the average zero standard optical density. For the standard curve, the data points were linearised by plotting the log of the cortisol level versus that of the optical density; the most desirable fit line was determined using regression analysis. The Cortisol levels of each sample were determined by reading the level from the standard curve.

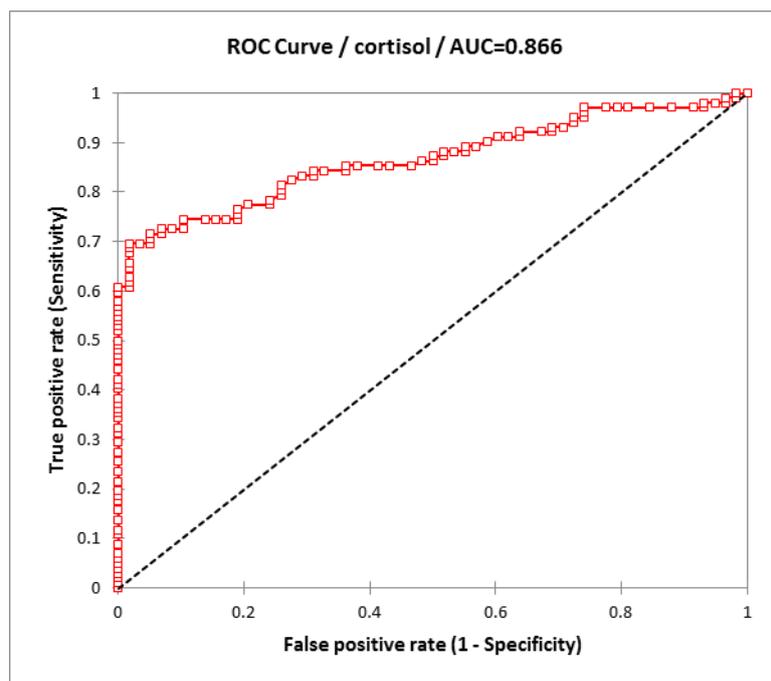
RESULTS

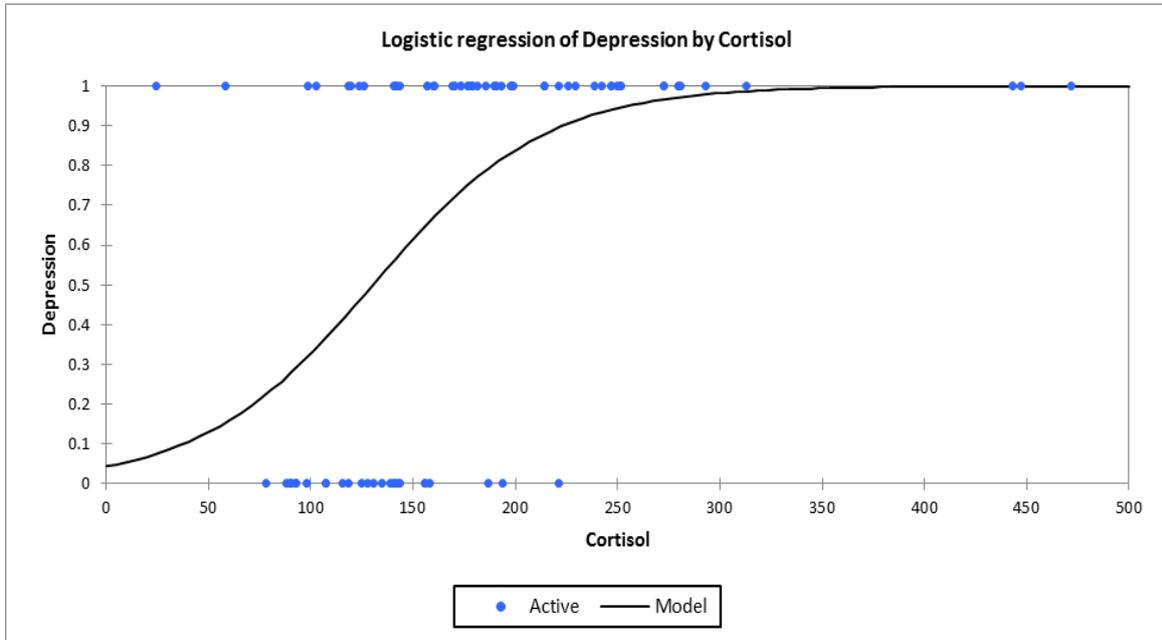
The patients in the pre-antiretroviral therapy (ART) had a mean age of 36.25 years, and 47.5% and 52.5% of the patients were women and men, respectively. After spectrophotometric ELISA analysis of this patients with HIV it's been recorded 56.25% are above 150 pg/ml which come's under distress state, According to Becks classification, 66.25% of the patients are in depressed mood. Among them 10 % of population are in borderline clinical depression, 12.5 % are under moderate depression, 30% of population severe depression,13.75% of population are in extreme depression.

Patients who were are on Antiretroviraltherapy had a mean age of 37.91 years; 55% and 45% of these patients were men and women, respectively. Its been recorded 53.75% are in distressed state in ART patients. According to becks classification 30 % are normal, 8.75% are with mild mood disturbance, 18.75% of population are moderate depressed mood, 15% of population are in borderline clinical depression, 27.5% of population are severe depressed mood.

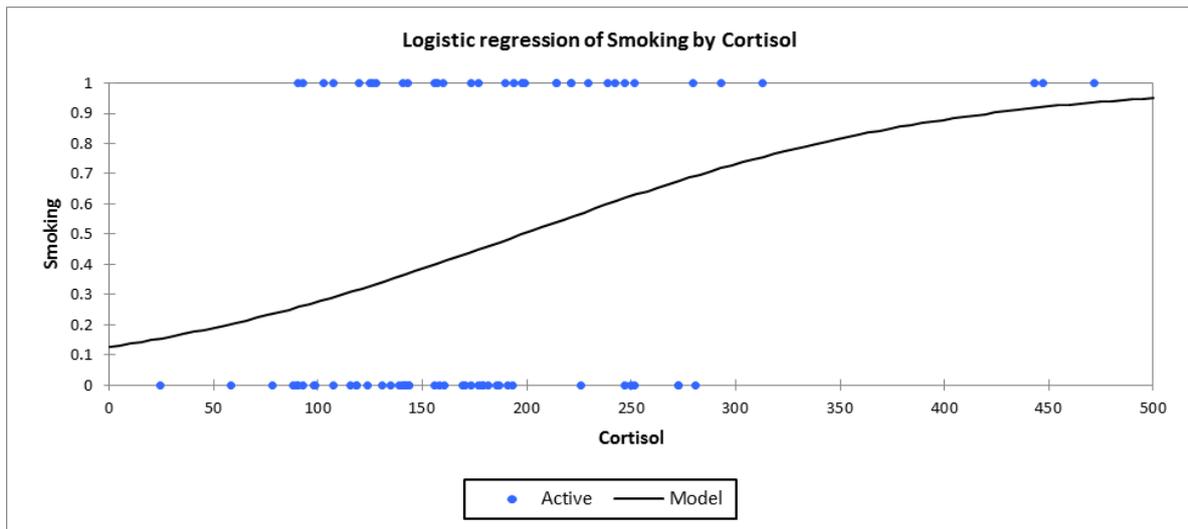
Relative risk ratio is been high in Depressed mood(2.88) and recent death of relatives(2.75) however Alcohol (1.57), Smoking (1.64), Above poverty line family's (1.53) have been contributed in increasing the cortisol level of patients with HIV irrespective of the Anti retroviral therapy or not. By this it can be analyzed emotional factor is playing a major role in increasing the cortisol level in patients with HIV. To understand the association of Cortisol and the CD4 count a statistical analysis of relative risk ratio is performed by recording the past 6 months CD4 count from medical records of patients enrolled in study Few factors were analyzed to understand the relative risks associated with increased cortisol, Pre art group as shown RR- 1.71, and OD- 5.77, where as ART group as shown RR-2.13, OD- 6.014.

Logistic regression out put indicates that the smoking is significantly associated with probability of increased cortisol (p=0.002,wald test).the out put also provides the coefficients for intercept = -1.408 and cortisol= 7.372. The equation is been mentioned in tables. Also alcohol (p=0.03 wald test) and depression (p=0.0167 Wald test)is also been significantly associated with Increased cortisol.





Equation: $\text{Pred}(\text{Depression}) = 1 / (1 + \exp(-(-3.08989232513763 + 2.37122276669449E-02 * \text{Cortisol})))$



Equation: $\text{Pred}(\text{Smoking}) = 1 / (1 + \exp(-(-1.94144085537479 + 9.81967333443288E-03 * \text{Cortisol})))$

Relative risks of increased cortisol associated with following variables	Risk Ratio	Odds ratio	P-value (Fisher exact)
Alcohol	1.57	3.07	0.0006
Smoking	1.64	3.40	0.0002
Partner living status	2.75	4.55	0.00006
APL	1.53	3.08	0.002
Depression	2.88	8.37	0.00000
Less than two years HIV status	1.2	1.72	0.110

DISCUSSION

Our study aims at studying the relative risks associated in Increasing cortisol level in the HIV patients. Since this patients are hampered with stressors for the long term few studies have proved hypothesis of significantly higher cortisol in patients with HIV(Brown holy:2013), no other studies have contributed in reveling relative risks associated with increased cortisol which is a major set back, for further studies on planned management of HIV care and prognosis related mental health care. Increased cortisol level is been

noted in female and male patients with HIV, who are under ART regimen supporting our study this study has been conducted with a control group (seronegative), whereas our study included PRE ART patients also for the better result which as shown increased cortisol level of 53.75% increased cortisol level of total pre ART sample collected (Ebuehi, O.A.T.;2015). Our previous study as elucidated a negative correlation with cortisol and Human IL12 cytokine with HIV patients with Depression, the association between cortisol and decrease in CD4 count in HIV subjects suggests that cortisol probably plays an important role in the normal function of the immune system through its effects on cytokines and also lymphocytes (Oduenyi, I.A.;2013). Supporting to this studies our studies as shown the some of the risk factors contributing in increasing cortisol.

Long term exposure to severe life stresses may outweigh the persons coping resources leading to feeling of depressed mood (Miranda off,1999) and patients with HIV are one of them with significant impact on their quality of life, persons living with HIV and AIDS are also associated with HIV diseases progression and mortality (Starace F,1999), Since the principal effector of the stress response lies in the hypothalamic–pituitary–adrenal (HPA) axis, (Munck A.;1984; Bamberger CM 1996) the activation of this response is assessed by cortisol levels. our study conducted statistical analysis for associated relative risks in increasing the cortisol level and it has been interesting to understand that depressed mood, and spouse or close relative death recently have contributed majorly in increasing the cortisol, however smoking, alcoholic and above poverty line peoples also contributed in increasing the cortisol irrespective of the on anti retroviral therapy and without anti retroviral therapy.

ACKNOWLEDGEMENT

This research work was carried out for attaining Phd by self funding no organization as supported financing for this study. The authors would acknowledge the help of the Mr Sunil, Mr Swamy from the GASYM organization, Dr Swamy, Dr srirama, Dr Sudheer, from the Asha Kiran Hospital Mysore for the data collection. DR Hilda R, Lobo from the St Mary's Hospital HD Kote, Mysore for the moral support.

REFERENCES

- [1] Antoni MH, August S, LaPerriere A, et al. Psychological and neuroendocrine measures related to functional immune changes in anticipation of HIV-1 serostatus notification. *Psychosom Med.* 1990; 52(5):496–510. [PubMed: 2247555]
- [2] Azar ST, Melby JC. Hypothalamic-pituitary-adrenal function in non-AIDS patients with advanced HIV infection. *Am J Med Sci.* 1993; 305(5):321–325. [PubMed: 8484393]
- [3] Brown Holy1, Elechi-Amadi, Kemzi Nosike2, Assessment of Antioxidant Enzymes and Cortisol Levels among HIV Patients on HAART. *International Journal of Science and Research (IJSR)* ISSN (Online): 2319-7064 Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391 Volume 5 Issue 4, April 2016 www.ijsr.net Licensed Under Creative Commons Attribution CC.
- [4] Bamberger CM, Schulte HM, Chrousos GP. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. *Endocr Rev.* 1996; 17(3):245–261. [PubMed: 8771358]
- [5] Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. *Eur J Pharmacol.* 2003; 463(1-3):235–272. [PubMed: 12600714]
- [6] Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992; 267(9):1244–1252. [PubMed: 1538563]
- [7] Chida Y, Vedhara K. Adverse psychosocial factors predict poorer prognosis in HIV disease: a meta-analytic review of prospective investigations. *Brain Behav Immun.* 2009; 23(4):434–445. [PubMed: 19486650]
- [8] Dickerson PA, Lally BE, Gunnell E, Birkle DL, Salm AK. Early emergence of increased fearful behavior in prenatally stressed rats. *Physiol Behav.* 2005; 86(5):586–593. [PubMed: 16197971]
- [9] Ebuehi, O.A.T., Awolola, A. & Akanmu, A. (2015). Changes in serum cortisol, thyroid hormones and lipid profiles in Nigerian men and women on first and second line antiretroviral therapy for 52 weeks. *International Journal of Virology and Molecular Biology*, 4(1), 12- 18.
- [10] Kopnisky KL, Stoff DM, Rausch DM. Workshop report: the effects of psychological variables on the progression of HIV-1 disease. *Brain Behav Immun.* 2004; 18(3):246–261. [PubMed: 15050652]
- [11] Kumar M, Kumar AM, Waldrop D, Antoni MH, Schneiderman N, Eisdorfer C. The HPA axis in HIV-1 infection. *J Acquir Immune Defic Syndr.* 2002; 31(suppl 2):S89–S93. [PubMed: 12394788]

- [12] Kiecolt-Glaser, J.K., Glaser, R., 1995. Psychoneuroimmunology and health consequences: data and shared mechanisms. *Psychosomatic Medicine* 57, 269-274.
- [13] Laudat A, Blum L, Guechot J, et al. Changes in systemic gonadal and adrenal steroids in asymptomatic human immunodeficiency virus-infected men: relationship with the CD4 cell counts. *Eur J Endocrinol.* 1995; 133(4):418–424. [PubMed: 7581964]
- [14] Leserman J, Petitto JM, Gu H, et al. Progression to AIDS, a clinical AIDS condition and mortality: psychosocial and physiological predictors. *Psychol Med.* 2002; 32(6):1059–1073. [PubMed: 12214787]
- [15] Lortholary O, Christeff N, Casassus P, et al. Hypothalamo-pituitary-adrenal function in human immunodeficiency virusinfected men. *J Clin Endocrinol Metab.* 1996; 81(2):791–796. [PubMed: 8636305]
- [16] Mayo J, Collazos J, Martinez E, Ibarra S. Adrenal function in the human immunodeficiency virus-infected patient. *Arch Intern Med.* 2002; 162(10):1095–1098. [PubMed: 12020177]
- [17] McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med.* 1993; 153(18):2093–2101. [PubMed: 8379800]
- [18] McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med.* 1998; 338(3):171–179. [PubMed: 9428819]
- [19] McIntosh RC, Rosselli M. Stress and coping in women living with HIV: a meta-analytic review. *AIDS Behav.* 2012; 16(8):2144–2159. [PubMed: 22434282]
- [20] Miranda Olf “Stress, depression and immunity: the role of defense and coping styles” *Psychiatry Research Volume 85, Issue 1, 18 January 1999, Pages 7–15*
- [21] Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev.* 1984; 5(1):25–44. [PubMed: 6368214]
- [22] Oduenyi, I.A., Fasanmade, O.A., Ajala, M.O. & Ohwovoriole, A.E. (2013). CD4 counts as a predictor of adrenocortical insufficiency in persons with human immunodeficiency virus: how useful? *Indian Journal of Endocrinology and Metabolism*, 17(6), 1012-1017
- [23] Remor E, Penedo FJ, Shen BJ, Shneiderman N. Perceived stress is associated with CD4+ cell decline in men and women living with HIV/AIDS in Spain. *AIDS Care.* 2007; 19(2):215–219. [PubMed: 17364401]
- [24] Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioral, and biological determinants. *Annu Rev Clin Psychol.* 2005; 1:607–628. [PubMed: 17716101]
- [25] Starace F¹, Ammassari A, Trotta MP, Murri R, De Longis P, Izzo C, Scalzini A, d'Arminio Monforte A, Wu AW, Antinori A; AdICoNA Study Group. NeuroICoNA Study Group Depression is a risk factor for suboptimal adherence to highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2002 Dec 15; 31 Suppl 3:S136-9.