

## ORIGINAL ARTICLE

## ADRENAL INSUFFICIENCY IN PAKISTANI HIV INFECTED PATIENTS

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**Background:** Adrenal insufficiency (AI) is the most common endocrine complication among patients with AIDS/HIV infection and there are number of causes of AI in HIV patients. Human immunodeficiency virus directly as well as indirectly destroys adrenal glands. The estimates of its prevalence and severity vary. AI is the most life threatening but readily correctable endocrine complication that occurs in persons with HIV infection. This study was carried out to determine the frequency of Adrenal Insufficiency in HIV patients and their clinical features as proper diagnosis and timely treatment have been shown to improve quality of life and long-term mortality in AIDS patients.

**Methods:** It was a cross sectional survey conducted at HIV clinic and Jinnah Allama Iqbal Institute of Diabetes and Endocrinology, Jinnah Hospital Lahore. Sixty-four HIV positive patients, both male and female, aged above 15 years were included in the study. HIV patients who had recently taken steroids, ketoconazole or rifampicin, determined on history, were excluded from the study. The data was collected on a structured proforma and analysis was performed in SPSS-21.0. Frequency and percentages for adrenal insufficiency and its characteristics were calculated. Chi-square test was used with  $p < 0.05$  as statistically significant. **Results:** In this study, 9 (14.06%) HIV patients were diagnosed with adrenal insufficiency, male to female ratio was 3.5:1 and AI was found statistically significantly associated with fatigue ( $p < 0.008$ ) and weight loss ( $p < 0.001$ ). **Conclusion:** Adrenal insufficiency was high among the patients with HIV, it was not gender specific but it was found to be associated with fatigue and weight loss.

**Keywords:** Adrenal insufficiency; HIV, Clinical features; Endocrinopathies

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## INTRODUCTION

Human immune deficiency is associated with many complications and complaints like reduced growth in young patients,<sup>1</sup> nutritional alterations like lipodystrophy,<sup>2</sup> cardiovascular diseases, impaired renal functioning<sup>3</sup> and abnormal endocrine functioning<sup>4</sup>. Among the endocrine complications, Adrenal Insufficiency (AI) is most common among patients with AIDS/HIV infection. There are a number of causes of AI in Human Immuno-deficiency Virus (HIV) patients. Human immunodeficiency virus directly destroys adrenal glands. Opportunistic infections may also cause adrenalitis.<sup>5</sup> Cytomegalo virus (CMV) adrenalitis is the most common cause. Autopsy studies reveal that adrenal glands undergo both inflammation and necrosis. Furthermore, patients with HIV infection are given therapy that could inhibit or reduce production of glucocorticoids which leads to adrenal insufficiency.<sup>6</sup>

Adrenal dysfunction may be suspected in HIV-infected patients with advanced stage of Acquired Immunodeficiency Syndrome (AIDS). The sign and symptoms in advanced HIV infection are also consistent with AI. This makes it difficult to differentiate between the two only on clinical grounds without biochemical diagnosis of AI. In AIDS patients, subtle adrenal dysfunction is manifested as fatigue, hyponatremia or rarely with clinical symptoms of adrenal insufficiency such as anorexia, abdominal complaints; weight loss,

hypotension, and hyperpigmentation. It has been reported in several studies that biochemical presentation of adrenal insufficiency is relatively more common in hospitalized AIDS patients from 17–19% in comparison to clinically symptomatic patients (4%).<sup>7,8</sup> HIV-infected patients have impaired adrenal reserve. It is evident by reduced aldosterone and dehydroepiandrosterone (DHEA) levels with normal cortisol in response to ACTH stimulation. With progressive immunosuppression with HIV infection, ACTH level increases over time, suggesting further decline in adrenal reserve. Subnormal adrenal response is also demonstrated in the studies involving hospitalized AIDS patients after cosyntropin stimulation test. On the other hand, increased cortisol levels may be seen in HIV-infected patients. It seems to be a stress response to the disease burden. Few studies have suggested an intra-adrenal shunting toward cortisol synthesis due to 17,20 lyase dysfunction.<sup>9</sup>

Drug interactions of anti-retroviral therapy are a common cause of AI. Concomitant use of ritonavir and inhaled fluticasone in children with HIV has led to Cushing's syndrome with secondary adrenal insufficiency.<sup>10</sup> Glucocorticoid resistance at receptor level has been shown in advance HIV infection. Such patients demonstrated increased cortisol and ACTH level with Addisonian symptoms.<sup>7,9,10</sup>

In literature, the frequency of the adrenal insufficiency is documented as a highly frequent

manifestation among patients with HIV infection. In review researches it is found frequently and is life threatening.<sup>11,12</sup> Since the burden of comorbidities in HIV infection is quite high, it is imperative to identify and treat the modifiable comorbidities like adrenal insufficiency in HIV patients to reduce overall mortality and morbidity.

The extent to which HIV patients are affected with adrenal insufficiency in our country is not known. Currently no study regarding adrenal insufficiency in local HIV population is available. The results of this study would be used as baseline for management of our HIV patients with adrenal insufficiency and this will improve the diagnosis and treatment of these patients. Through this research, it has been attempted to determine the frequency of adrenal insufficiency in HIV patients and their clinical features in our population.

**MATERIAL AND METHODS**

It was a cross sectional survey conducted in HIV clinic and Jinnah Allama Iqbal Institute of Diabetes and Endocrinology, Jinnah Hospital Lahore. Sixty-four HIV positive patients of either gender, aged above 15 years were included in the study using non-probability, purposive sampling. HIV patients who had recently taken steroids, ketoconazole or rifampicin determined on history were excluded from the study. Presenting complaints like fatigue, weight loss, nausea, vomiting and diarrhoea; hypotension and CD4+ count, all were recorded on pre-designed questionnaire. Adrenal Insufficiency was diagnosed by performing an ACTH stimulation test. All patients received intravenous injection of 250 µg of synthetic ACTH; and serum cortisol was measured at 60 minutes. A peak stimulated cortisol of less than 18 µg per dL was diagnosed as AI. Data was stratified for age, sex and BMI to avoid any bias in study. Data was entered and analyzed using SPSS 21. The numeric data is presented in the form of mean±S.D and qualitative data is presented in the form of frequency and percentage. The qualitative data is analyzed using Chi Square Test with level of significance ≤0.05.

**RESULTS**

In this study, among 64 HIV infected patients, Mean duration of AIDS / HIV was 4.23 ±2.46 years. 15.6% (10) were females and 84.4% (54) were males. 14.06% (09) patients were diagnosed with adrenal insufficiency, while 84.94% (55) patients did not have adrenal insufficiency. Mean age of patients with adrenal insufficiency was 33.67±6.86 years, 20.0% (02) of females and 13.0% (07) males had adrenal insufficiency. (p=.557). 32.8% (21) were diagnosed as having HIV infection and 67.2 % (43) were

diagnosed as having AIDS (based on CDC 1993 Classification System for HIV Infection). Among the patients with adrenal insufficiency (AI) the cortisol level was 13.34±2.28 which was statistically significantly lower than patients without AI (p-value <0.001). Whereas CD4 cell count was less than patients without AI, but the difference was not statistically significant (p-value 0.074).

Among the patients with HIV/AIDS 67.4% had fatigue and 51.2% had weight loss, nausea, vomiting and diarrhoea; and in patients with adrenal insufficiency, fatigue was present in 8 (88.9%) of the patients (p-value 0.008); similarly, weight loss was also present in 8 (88.9%) patients (p-value 0.001). Nausea, vomiting or diarrhoea was present in 4 (44.4%) and Hyperpigmentation and Hypotension were present in 1 (11.1%) patient each.

**Table-1: Mean Cortisol level and CD4 count among patients. (n=64)**

Statistics	Cortisol level	CD4 cell count
n	64	64
Mean	21.9984	507.16
Std. Deviation	4.88836	282.776
Minimum	10.50	86
Maximum	31.00	1268

**Table-2: Comparison of ACTH stimulated Cortisol level and CD4 cell count among HIV patients with and without adrenal insufficiency (n=64)**

	Adrenal Insufficiency	n	Mean	SD	p-value
Cortisol level	Yes	9	13.34	2.28	<0.001*
	No	55	23.41	3.55	
CD4 cell count (cells/ µL)	Yes	9	351.00	173.93	0.074
	No	55	532.71	289.96	

Independent sample t-test, \*p-value significant at 0.05

**Table-3: Distribution of symptoms among HIV patients Multiple response frequencies**

Symptoms	Responses		Percent of Cases
	n	Percent	
Fatigue	29	37.7	67.4
Weight Loss	22	28.6	51.2
Nausea, vomiting, diarrhoea	22	28.6	51.2
Hyperpigmentation	1	1.3	2.3
Hypotension	3	3.9	7.0
	77	100.0	179.1

**Table-4: Distribution of symptoms among HIV patients and adrenal insufficiency Multiple response frequencies**

Symptoms	Adrenal Insufficiency		Total
	No	Yes	
Fatigue	21	8	29
	61.8%	88.9%	
Weight Loss	14	8	22
	41.2%	88.9%	
Nausea, vomiting, diarrhoea	18	4	22
	52.9%	44.4%	
Hyperpigmentation	0	1	1
	0.0%	11.1%	
Hypotension	2	1	3
	5.9%	11.1%	
Total	34	9	43

## DISCUSSION

Primary Adrenal insufficiency is known as Addison's disease. It is caused by reduced production of adrenal cortical hormones known as glucocorticoid and mineralocorticoid.<sup>13</sup> Adrenal insufficiency is a known complication of HIV infection. It is the most serious endocrine complication that can occur in persons with HIV infection. The estimates of its prevalence and severity vary depending upon the criteria and method used for diagnosis. In this study, the adrenal insufficiency was 14.06%. It is comparable with the current research which documents adrenal insufficiency up to 20% in HIV patients.<sup>8,14-16</sup> A study done by Gonzalez et al showed frequency of adrenal insufficiency of 21.2% and by clinical categories, the frequency in AIDS and HIV infected patients was 26.4% and 9.4%, respectively.<sup>17</sup> In another study, reported frequency of adrenal insufficiency was 34.8%.<sup>18</sup>

Adrenal insufficiency is a life-threatening complication of AIDS. In a study in Taiwan, incidence of adrenal insufficiency among patients with human immunodeficiency virus infection, was 0.19 per 100 patient-years (95% confidence interval, 0.17–0.21 per 100 patient-years)<sup>19</sup> and Meya *et al.* found 19% prevalence of AI among patients infected with HIV.<sup>8</sup>

In another study by Madi *et al.*, 50 patients with confirmed diagnosis of HIV were included, 37/50 (74%) of study subjects had adrenal insufficiency. Basal cortisol was 10.09 µg/dl and Cortisol post ACTH stimulation test was 9.49 µg/dl. Mean CD4 cell count was 138.7±56.17 cells/µl ( $p<0.05$ ).<sup>20</sup>

In my study, among the patients with adrenal insufficiency the cortisol level was 13.34±2.28 which was statistically significantly lower than patients without AI ( $p$ -value <0.001) and mean CD4 count was 351 cells/uL.

CD4 cell count is done in routine to evaluate the extent and progression of HIV infection. CD4 cell count has been studied to predict the presence or absence of AI. In a study done by Odeniyi *et al.* 15/43 HIV patients had AI and there was no significant correlation between stimulated cortisol level and CD4 count ( $r = -0.09$ ,  $p=0.516$ ).<sup>21</sup> Similarly, in another study done by Ekpebeg *et al.* no significant association between cortisol levels and CD4 counts was found, and the mean CD4 counts were comparable for patients with and without hypoadrenalism.<sup>22</sup> In this study 14.06% (9/64) patients were diagnosed with adrenal insufficiency and CD4 cell count in AI patients was less than in patients without AI; but the difference was not statistically significant ( $p$ -value 0.074).

Sinha *et al* reported that biochemical presentation of adrenal insufficiency is relatively more common in hospitalized AIDS patients (17%) in comparison to clinically symptomatic patients (4%).<sup>7</sup> The typical clinical features of AI like fatigue and weight loss have shown to have poor predictive value for diagnosis of hypoadrenalism in HIV infection.<sup>21</sup> However, our study found that adrenal insufficiency was associated with fatigue and weight loss, which were more marked in those HIV patients with AI than in those without AI.

Drug interactions of Highly Active Anti-Retroviral Therapy (HAART) with other medications used in the treatment of HIV have been associated with the precipitation of endocrine complications. There have been increasing reports of AI among HIV infected patients in the setting of glucocorticoid exposure. AI has been frequently reported in patients receiving inhaled fluticasone with concomitant HAART. AI with inhaled budesonide has also been reported. In addition, adrenal suppression with topical steroids has been described. The cause of the increase in adrenal suppression appears to be a pharmacologic interaction between glucocorticoids and anti-retrovirals. Glucocorticoids are metabolized by the cytochrome P450 enzyme CYP3A4, which is inhibited by some HIV protease inhibitors e.g., low-dose ritonavir.<sup>23</sup> Ritonavir, therefore, can boost the concentrations of steroids leading to systemic effects of using steroid doses and routes of administration previously thought to have minimal adverse effects.<sup>24</sup>

Recent studies have documented that the human immunodeficiency virus associated mortality has been significantly decreased globally due to improvement in the therapeutics. With increased life expectancy, the manifestations of endocrine and metabolic complications of HIV infection have been increased. Adrenal insufficiency is the commonest HIV endocrinopathy.<sup>25</sup> Therefore, it is important to screen HIV patients for these complications.

It is crucial to evaluate all the risk factors for adrenal insufficiency in a HIV patient; such as opportunistic infection, neoplasms e.g., Kaposi's sarcoma or lymphoma, and drug interactions of HAART. The treatment of AI is simple and cheap. It is done in the same way as in HIV-negative patient using the lowest possible dose of glucocorticoid.

Untreated adrenal insufficiency has such potentially dire consequences that evaluation for glucocorticoid deficiency should be done in HIV patients. It should be suspected in HIV patients with persistent or unexplained symptoms and signs consistent with adrenal dysfunction. Urgent diagnosis and initiation of glucocorticoid replacement along with antiretroviral therapy may improve the survival chances of an HIV infected patient.

## CONCLUSION

The frequency of adrenal insufficiency was high among the local HIV infected population; and is comparable with the reported literature. It was found to be associated with fatigue and weight loss in HIV patients. Further research is required to substantiate the results of this study.

## AUTHORS' CONTRIBUTION

BA and KK worked on the concept and design of the study. BA and AR collected the data. BA analyzed the data. BA and AR worked on the manuscript. BA prepared the final draft of the manuscript. KK supervised the study. All authors have read and approved the final draft of the manuscript.

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