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Original Article

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Prevalence of Adrenal Insufficiency in HIV Infected Patients and Its Correlation with CD4 Levels in a Tertiary Care Hospital in North East India: A Cross-Sectional Study

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ABSTRACT

Background & objectives: Human Immunodeficiency Virus (HIV) infection causes diseases with a wide spectrum of manifestations ranging from hematological manifestations to severe opportunistic infections, and rare malignancies and it also extends to endocrinological manifestations. This study has been undertaken with the aim to dwell deeper into the endocrinological complications, which have mostly been ignored and not keenly thought of. Clinical data pertaining to Adrenal Insufficiency (AI) in HIV infection have been lacking, with a few studies in India and none in North-eastern India, where the burden of HIV infection is high. This study will provide insight into this less explored array and help clinicians who have long been treating HIV infection-related complications but seldom arrived at the endocrine foray. CD4 count was also evaluated to correlate the degree of AI with the level of CD4.
Methods: In this cross-sectional study, 120 HIV-infected patients were evaluated for AI with the Short Synacthen Test. Simultaneously; CD4 levels were obtained and analyzed for the degree of AI.
Results: The Prevalence of AI in this study was found to be 20%, signs of AI like hypotension, skin hyper pigmentation, and menstrual abnormalities were significant, and there was no correlation between the CD4 levels and the degree of AI.
Interpretation & conclusions: This study found that AI is statistically significant between the group with AI and the unaffected group. There was no age or sex preponderance of AI and it is not associated with the duration of the disease. No correlation was found between the CD4 level and the degree of AIs.

Key Words: *Adrenal Insufficiency, Adrenalitis, CD4 level, HIV infection, Short Synacthen Test*

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INTRODUCTION

Endocrinological aspects of HIV infection remain one of the most important causes of morbidity and mortality in HIV patients and among them,AI is the most common and earliest endocrine disease documented with involvement of adrenal glands in as many as two-thirds of patients with HIV infection at post-mortem examination [1,2]. It may be due to nonspecific responses to infection, stress, and malnutrition or due to infiltration of the adrenal glands by tumor or infection. However, due to a lack of clinical diagnosis at an early stage, especially in developing countries, which may be due to the late presentation of the patient to the health care setup or due to lack of resources in terms of availability of diagnostic facilities, AI remains undiagnosed [3].

HIV directly destroys the adrenal glands and along with it, opportunistic infections (OIs) also destroy the gland by causing adrenalitis. Cytomegalovirus adrenalitis is the most common cause and autopsy findings show inflammation and necrosis of the gland. Additionally, co-infection with Mycobacterium tuberculosis predisposes the person to the risk of Tuberculous adrenalitis. Infiltration of the adrenal gland by malignant tumors either unrelated or related to immunosuppression like Kaposi's sarcoma or lymphoma can lead to primary AI [4].

In the Highly Active Anti-Retroviral Therapy (HAART) era, reports of AI among HIV patients have been attributed to glucocorticoid exposure. Patients receiving inhaled fluticasone and budesonide and topical steroids in the form of local injections for chronic inflammation have been reported to have AI due to the interaction between glucocorticoids and antiretrovirals [5].

Symptoms of AI include nausea, vomiting,muscle and joint pain, fatigue, and weight loss eventually leading to anemia and derangement in electrolytes like hyponatremia and hyperkalemia. Specific signs of primary AI include skin and mucosal hyperpigmentation, salt craving, andsevere manifestations like postural hypotension, and hypoglycemia [2].However, all these symptoms cannot be attributed to AI as the sole cause as the disease leaves the patient in an

immunocompromised state. Other causes like gastroenteritis, related gastrointestinal disorders, and infective etiology must be ruled out. Hence, it becomes imperative to suspect AI in patients presenting with the above symptoms.

AI can be diagnosed at an early stage with the help of the currently available diagnostic test i.e. Synacthen test. Low dose (1mcg) ACTH stimulation [2]. This will help identify patients with HIV infection who have impaired adrenocortical function and who pose a higher risk of AI at an early stage. So, AI detection is potentially relevant as cortisol deficiency could account for unexpected deaths due to HIV. Treatment for such patients with corticosteroids can be lifesaving [2]. Furthermore, it will enhance the overall management of HIV-infected patients. Changing HAART regimens may also be considered if needed.

This study was done with the primary objective to determine the prevalence of AI in HIV-infected patients. The secondary objective was to study the correlation of CD4 levels with the degree of AI.

RESEARCH MATERIALS AND METHODS

The study which is a cross-sectional study was conducted in a Tertiary Hospital in Manipur over a span of 2 years from November 2020 to November 2022. Informed written consent/assent was obtained from participating patients. The clearance of Institutional Ethics Committee (IEC) was obtained (No. Ac/03/IEC/JNIMS/2018).

Biodata and demographic information were collected. History and evidence of Tuberculosis were noted, drug intake especially anti-tubercular drugs, anti-convulsant drugs like Phenytoin, and anti-fungals like Ketoconazole were ruled out. Symptoms of AI including menstrual abnormalities in females were also taken into consideration. Clinical parameters included blood pressure measurements and examination of skin and mucous membranes for hyperpigmentation.

Inclusion Criteria:

(a) All HIV-seropositive patients, seropositivity being confirmed by National AIDS Control Organization (NACO) guidelines, either newly diagnosed or previously diagnosed, with and without HAART.
(b) Both males and females included
(c) Children <18 years of age were included provided parents/guardians consent to it.

Exclusion Criteria:

(a) All HIV seronegative patients
(b) Patients presenting in Addisonian crisis
(c) Patients who are on steroid drugs
(d) Patients on drugs that can interfere with Adrenal function like Ketoconazole, Phenytoin, and Rifampicin
(e) Those who refuse to undergo the test
(f) Pregnant females

Sample Size: From a previous studyby Odeniyi IA, *et a[2],*
Prevalence Rate, (P) of AI= 34%
Confidence level factor at 95% of Confidence Interval(Z) = 1.96
Absolute Allowable Error (E) = 8.5%
(Q) = (1-P)
Therefore, sample size(N) = Z^2 PQ/E^2
= $(1.96)^2$*0.34*0.66/$(0.085)^2$
= 118.9~119, round up =120.

Study tools: 1mcg of Synacthen (Acton Prolongatum)**,** 2ml syringe
Serum Cortisol level after ACTH stimulation was measured and a value of ≤ 18 µg/dl was considered as having AI.

Procedure:

1) Pretest: Baseline blood cortisol was obtained prior to administration of the drug.
2) 1 mcg (0.4ml)of Synacthen(Inj. Acton Prolongatum) was administered IV.
3) Post Synacthen: Blood sample was drawn after 1 hour of administration of Synacthen for Serum Cortisol.
4) The sample was analyzed by Enzyme-Linked Fluorescence Assay (ELFA).

No other instruments were required for the procedure.

Statistical analysis: Analysis of data was done using Microsoft Excel and SPSS 23.0. Chi-square test, Fisher's Exact test, and Independent Sample T-test were used to calculate the p-value for the comparison and all other compatible statistical techniques. A p-value of <0.05 is considered statistically significant.

RESULTS

A Cross-Sectional study was conducted in the Department of General Medicine, JNIMSamong 120 HIV-positive patients in order to determine the prevalence of AI and the correlation of CD4 level with the degree of AI. The following observations were made:

Table 1: Age Distribution of Respondents

AGE DISTRIBUTION	FREQUENCY (N)	PERCENTAGE (%)
<20 years	**6**	**5%**
20- 40 years	**30**	**25%**
40- 60 years	**75**	**62.5%**
>60 years	**9**	**7.5 %**

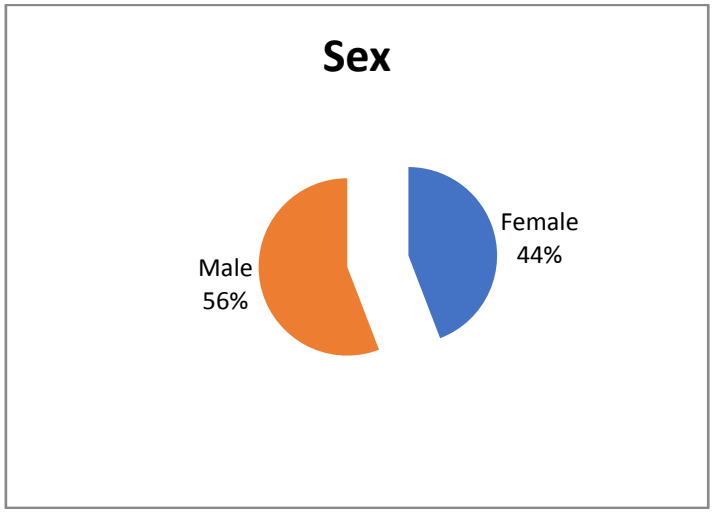

Figure 1: Pie Chart Showing Sex Distribution of the Respondents

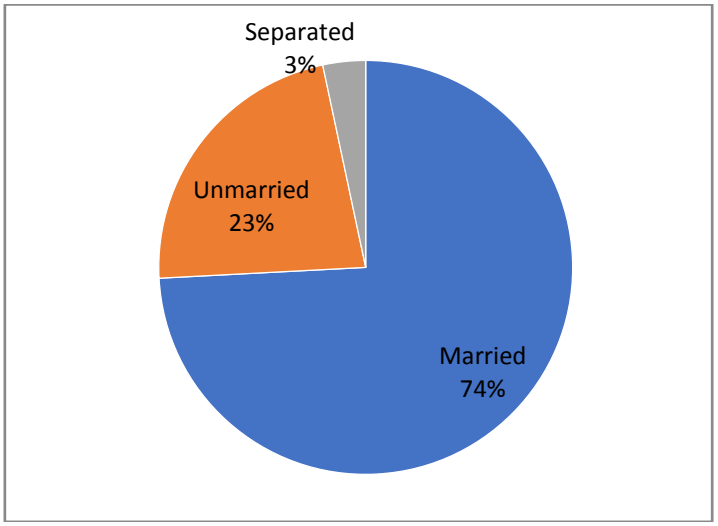

Figure 2: Pie Chart Showing the Marital Status Percentage

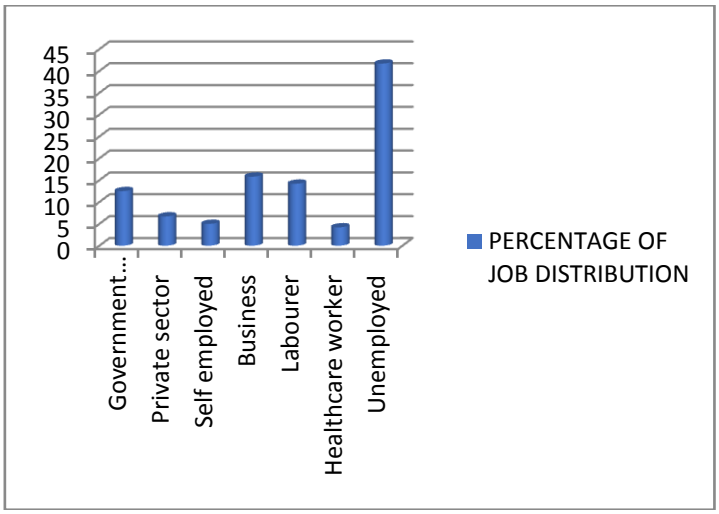

Figure 3:Bar Diagram Shows the Distribution of The Job Profile

Table 2: Risk Factors of the Respondents

RISK FACTORS	FREQUENCY	PERCENTAGE(%)
IVDU	**28**	**23.3**
BLOOD TRANSFUSION	**6**	**5**
VERTICAL TRANSMISSION	**9**	**7.5**
HOMOSEXUALITY	**1**	**0.8**
HIGH-RISK BEHAVIOUR	**37**	**30.8**
TRANSMISSION FROM SPOUSE	**38**	**31.7**
NEEDLE STICK INJURY	**1**	**0.8**

Table 3: Signs of AI

AI SIGNS	FREQUENCY	PERCENTAGE(%)
HYPERPIGMENTATION	**60**	**50**
MUCOSAL HYPERPIGMENTATION	**9**	**9.2**
BLOOD PRESSURE		
<90 mmHg	**12**	**10**
90-100 mmHg	**26**	**21.7**
100-120 mmHg	**62**	**51.7**
>120mmHg	**20**	**16.7**
MENSTRUAL IRREGULARITY		
Regular	**23**	**19.2**
Irregular	**14**	**11.7**
Menopause	**12**	**10**
Amenorrhoea	**3**	**2.5**

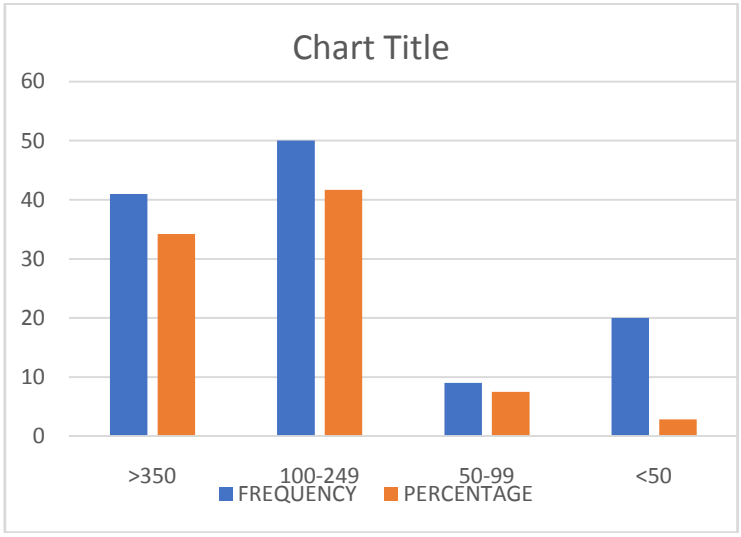

Figure 4: Bar Graph Depicting the CD4 Levels

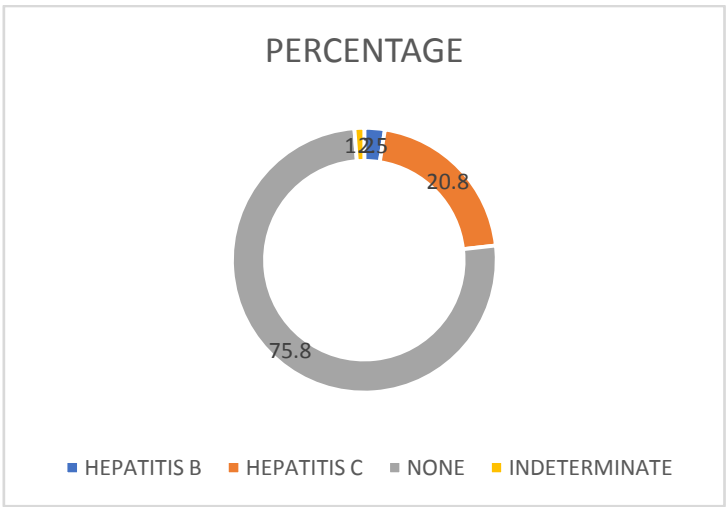

Figure 5:Diagram Depicting the HBV/HCV Co-Infection Rate

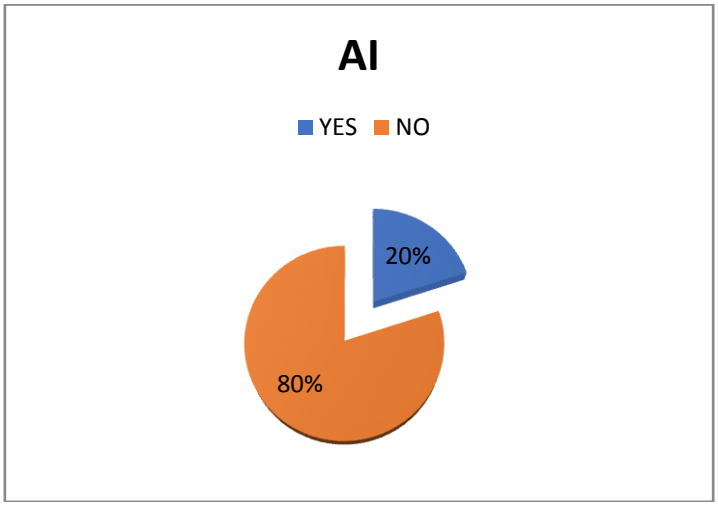

Figure 6: Pie Chart Showing the Prevalence of AI

Table 4: Significance of AI

AI	FREQUENCY	MEAN AND SD	P-VALUE
YES	**24**	**14+/-3.54**	**0.004**
NO	**96**	**30+/-14.74**	

Table 5: Association of AI with Sex

AI	FREQUENCY	PERCENTAGE(%)	P-VALUE
MALE	**12**	**50**	**0.520**
FEMALE	**12**	**50**	

Table 6: Association of AIwith Age

AI	AI GROUP	NON-AI GROUP	P-VALUE
0-20	**1**	**3**	**0.597**
20-40	**4**	**26**	
40-60	**16**	**61**	
>60	**3**	**6**	

Table 7: AI with Duration of HIV Positivity

DURATION OF HIV IN YEARS	AI GROUP	P VALUE
<5	**8**	**0.517**
5-10	**6**	
>10	**10**	

Table 8: AI Signs

SKIN HYPERPIGMENTATION	FREQUENCY	P-VALUE
FEMALES	**5**	**0.002**
MALES	**19**	
MUCOSAL HYPERPIGMENTATION	**6**	**0.08**
MENSTRUAL IRREGULARITY/AMENORRHOEA	**6**	**0.014**

Table 9: AI and Blood Pressure

BLOOD PRESSURE	AI GROUP	NON-AI GROUP	P-VALUE
<90	**6**	**6**	**0.014**
90-100	**5**	**21**	**0.140**
100-120	**11**	**51**	**0.7**
>120	**2**	**18**	**0.53**

Table 10: AI and CD4 Count

CD4 LEVELS	AI GROUP	NON-AI GROUP	P-VALUE
>350	**13**	**28**	**0.127**
100-350	**8**	**42**	
50-100	**1**	**8**	
<50	**2**	**18**	

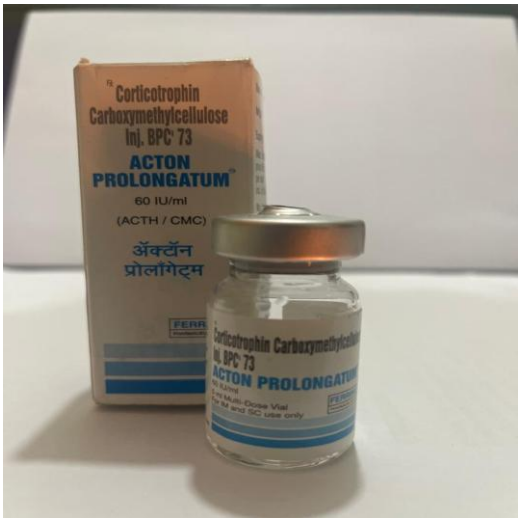

Figure7: ACTH Hormone

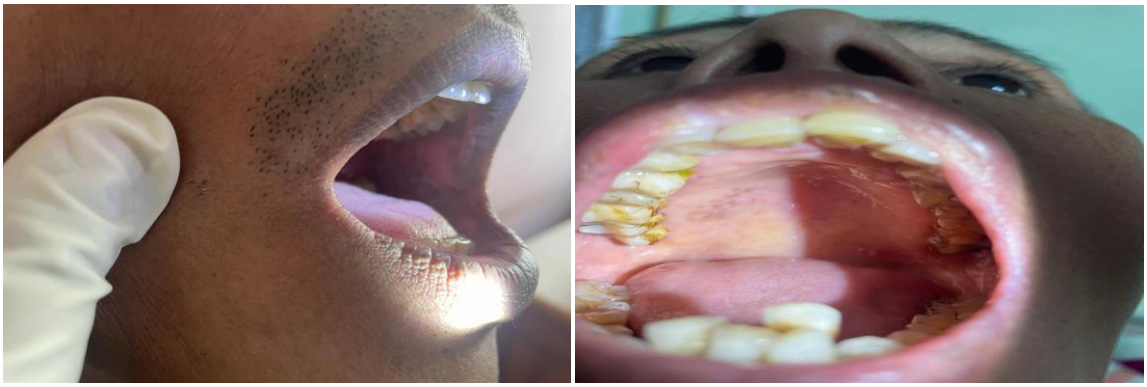

Figure 8: Mucosal Hyperpigmentation in AI

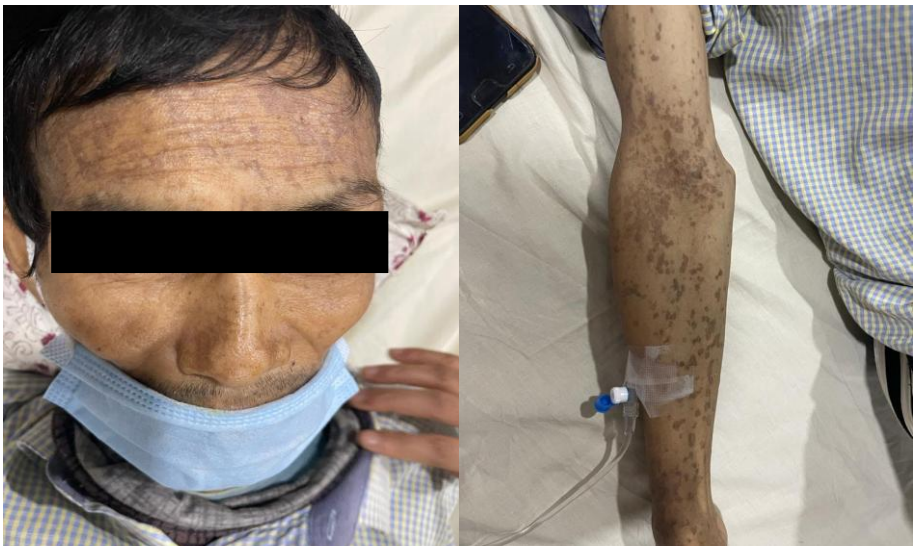

Figure 9: Skin Hyperpigmentation in AI

DISCUSSION

AI is one of the most serious and rarely diagnosed complications of HIV infection**.** It is not a well-thought-of entity when it comes to such long-term infectious disease even though it is not uncommon, but needs to be considered and looked into keenly keeping in mind the grave nature of the disease. In this study, 120 participants were enrolled, and the prevalence of AI amongst HIV patients was determined by the response to low-dose ACTH (1mcg)- Short Synacthen test and the correlation of CD4 levels with the degree of AI was done.

Majority of the patients were in the age group of 40-60 years(62.5%) followed by 20-40 years (25%). The mean age is 44.9 years ±11.639 years. It is worth noting that 40-60 years of age present to the healthcare set up with various OIs, thereby showing that it is these decades where most of the disease manifestations occur, maybe due to the progression of HIV into AIDS or due to a further decline in the immunity. However, statistically, our study finding indicates that there is no age preponderance for the development of AI and any age group can be affected depending on the severity of illness and the stress during critically ill periods.

Among the 120 participants enrolled, there were 67 males and 53 females which has a male sex preponderance. More number of male participants conform to the global scenario where males are more affected by HIV as stated by Sajadipour M*et al* [6], where IVDU, imprisonment were more common in men thereby increasing the odds of HIV. In our study, there wasno statistically significant difference between the male and female demographics with no sex preponderance for AI in HIV. This is consistent with previous studies done by Odeniyi IA *et a*[2], and Tripathy SK *et al*[7]. However, in another study by Afreen B *et al* [4],there was a significant difference in the male-to-female demographics. In terms of sex preponderance for AI in HIV,a study by Sharma N *et al* [8],found that AI patients were more likely to be females and also found an association with the duration of the disease which is not consistent with our study.

Traditional risk factors like IVDU, high-risk behavior, homosexuality, blood transfusion, and vertical transmission were noted. Most notable in our study is the female spousal transmission of HIV with 31.7%contributing to the study population. This may be explained by the high-risk behavior of the spouse and also the IVDU burden among males [6]in Manipur which shares a border with the infamous Golden Triangle.

Looking at the job profile, the unemployed make up most of the study population leading to a four-fold increase in the odds of HIV infection than those who had a mobile job as stated by Sajadipour M *et al* [6].

In our study, the HBV and HCV co-infection was found to be 2.5% and 20.8% respectively which is consistent with studies by Kermode M*et al* [9]. This is a much different scenario when compared to other parts of the country like the Southern states of India as seen in a study by Saravanan S*et al* [10].

Using the diagnostic criteria derived for the diagnosis of adrenocortical insufficiency in this study of ≤ 18mcg/dL, 24 persons (20%) with HIV infection had AI which is comparable with the current research which documents AI up to 19% [11]in HIV patients. It is also comparable to the study by Sharma N *et al* [8],where the prevalence is found to be 24.23% and in a study by Gonzalez *et al* [12],the prevalence was found to be 20%. In another study by Odeniyi IA *et al* [2], the prevalence was 34.8% which is much higher in comparison to our study. In another study by, Madi *et al* [13], where 50 HIV-confirmed patients were studied for the prevalence of HIV, the prevalence was as high as 74% i.e, 37/50 study subjects were having AI with a mean CD4 count of 138.7 cells/µL. From these comparisons, we can conclude that there are no geographical or racial demarcations of AI.

In our study, the Pre-Synacthen mean cortisol level was 16.08±14.08 µg/dl while the Post-Synacthen mean cortisol level is 14.22±3.54 µg/dl in the study group with AI and 30.58±14.74 µg/dl in the group without AI. Acquired cortisol resistance with functional glucocorticoid deficiency occurs with HIV infection which may be associated with a normal or supranormal cortisol level [14].Using Independent Sample T-test to compare the significance between the Post-Synacthen AI group and non-AI group, it was found that there was a statistically significant difference in Post-Synacthencortisol levels (p <0.004) among the AI and non-AI groups. This is consistent with the study by Afreen B*et al* [4],which found that the mean cortisol levels in patients with AI is 13.34±2.28µg/dl.

In our study, the mean CD4 count is 319.9 cells/µL and it is found that there is no correlation between the level of CD4 counts and the degree of AI (p-0.127). This is consistent with previous studies by Odeniyi *et al* [2]. In the study by Afreen B*et al* [4], CD4 cell count was found to be less in patients with AI than in patients without AI, however, the difference was not statistically significant (p-value-0.074). In another study by Tripathy SK *et al* [7], there was negligible or no correlation between CD4 count and cortisol levels.

Along with the biochemical parameters, the clinical signs were also compared between the group with AI and without AI. The majority of the participants with hypocortisolism (AI group) in this study did not have severe symptoms like postural hypotension and hypoglycemia, but had signs like skin hyperpigmentation, menstrual disturbance, and hypotension which were found to be statistically significant between the AI group and non-AI group except mucosal hyperpigmentation which is near significant. This is not consistent with the previous study by Ekpebegh CO*et al* [15],in which both the groups were comparable. And using Chi-square, hypotension with SBP <90mmHg was found to be statistically significantin correlation with AI whereas, SBP of > 90mmHg was found to be statistically insignificant. When it comes to menstrual irregularity and amenorrhea, they were statistically significant in the AI group.

The widespread availability of HAART in HIV patients has led to a prolongation and a better quality of life, but also endocrine abnormalities are coming to attention because of the success of HAART as patients are able to have a longer life span with the disease but also the progression of the disease adds newer comorbidities like AI [7]. However, in my study, it is also found that the duration of HIV positivity is not statistically significant with AI as consistent with the study by Akase IE *et al* [16].

The plasma from the patients with critical illness containsmediators that impair the synthesis of corticosteroids leading to hypocortisolism but without obvious structural defects in the HPA axis thus producing a 'functional or relative AI' [17]with high cortisol levels but insufficient to control the inflammatory response.

Limitations of the study:

1) It is a diagnostic study and not an intent-to-treat study
2) The test is a sophisticated test with respect to our setup, so procuring of ACTH hormone, availability of reagent for the test was a challenge.
3) Hesitancy of patients and families of patients to enrol in the study as it involves two-time blood sampling.

CONCLUSION

The findings in our study indicated that AI is not uncommon in immunocompromised patients, the prevalence of which is 20 % in our study and no correlation was found between the CD4 levels and the degree of AI. The high prevalence of AI (20%), along with its debilitating nature points that there is a need to extend this study to a larger population. This clinical data will pave way for multi-factorial thinking and help clinicians make informed decisions when immunocompromised and critically ill patients present to the health setup. Future hypotensive patients may no longer be thought of just in terms of sepsis and its subset septic shock but thinking in a different light of mineralocorticoid and glucocorticoid deficiency and timely supplementation. This will change the outlook on the management of the disease spectrum and thereby bring a change to the knowledge that we currently have about HIV infection.

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Conflicts Of Interest: None

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