

Prevalence of Adrenal Insufficiency in Clinically Stable Adults Living with HIV Attending Outpatient Clinics in Malaysia

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Abstract

Background. Adrenal insufficiency (AI) is a potentially life-threatening condition in people living with HIV/AIDS. Data on this topic are scarce and estimates of its prevalence vary.

Objective. To determine the prevalence of AI among people living with HIV and to guide the management strategies.

Methodology. This is a cross-sectional study conducted at the Infectious Diseases Clinics of two tertiary centres. Clinical and laboratory data were collected, and Synacthen (cosyntropin) stimulation tests were performed. Adrenal antibodies and Adrenocorticotrophic Hormone (ACTH) levels were analysed in those who had an inadequate Synacthen response. The data were analysed using SPSS (version 28.0).

Results. A total of 110 stable outpatient adults living with HIV, aged 18 to 80 years, were recruited. The mean age of the studied population was 37.5 ± 10.6 years, 81.8% were male, 23.6% had a normal BMI and 64.5% were either overweight or obese. The median disease duration was 4.5 years and all subjects had been on HAART for a median duration of 3.8 years. Treatment failure occurred in 20% of participants, 41.8% had a history of opportunistic infections and 4.5% had autoimmune diseases. The mean nadir CD4 count was $202 \text{ cells/mm}^3 \pm 200$ with 60.6% below 200 cells/mm^3 . At the time of the Synacthen tests, 88.2% had a viral load of $<40 \text{ copies/ml}$ while 89.1% had a CD4 count $>200 \text{ cells/mm}^3$. AI was identified in 2 participants (1.8%; 95% CI 0.2-6.4%). Their adrenal antibodies were negative, and ACTH levels were $4.5 \pm 5.9 \text{ pmol/L}$. Both had significantly lower nadir CD4 counts ($p < 0.001$), a history of treatment failure ($p = 0.039$) and symptoms suggestive of AI ($p = 0.004$).

Conclusion. This study revealed a low prevalence of AI (1.8%) among stable HIV patients on HAART. Significant associations with AI were found in participants with lower nadir CD4 counts, a history of treatment failure, and symptoms suggestive of AI.

Key words: adrenal insufficiency, adrenal cortex antibodies, HIV infections, adrenocorticotrophic hormone, highly active antiretroviral therapy

INTRODUCTION

Over the past few decades, human immunodeficiency virus (HIV) infection has shifted from being an inevitably fatal condition to a manageable chronic disorder, significantly improving life expectancy. This transformation is largely due to the introduction of Highly Active Antiretroviral Therapy (HAART), which has significantly improved the management of HIV and opportunistic infections. However, as life expectancy has increased, new challenges have emerged. Data from a long-term population-based cohort in Taiwan suggested an association between HIV infection and the development of autoimmune diseases.¹

Similarly, a prospective study in Brazil observed a higher frequency of autoantibodies in HIV-infected patients.² The presence of adrenal autoantibodies is linked to an increased future risk of developing overt primary adrenal insufficiency (AI).³ However, there is currently no data on the prevalence of adrenal auto-antibodies among HIV patients.

Adrenal gland involvement in HIV-infected individuals is a significant concern, with postmortem examinations showing adrenal abnormalities in up to two-thirds of these patients.⁴ Adrenal dysfunction can lead to either hypercortisolism or hypocortisolism.⁵ Previous studies

have reported inadequate adrenal response to synthetic ACTH stimulation in 7% to 24% of stable HIV patients.⁶⁻⁸ A small study of critically ill AIDS patients with advanced disease from southern India found that AI was diagnosed in 74% of patients.⁹ This suggested that adrenal gland dysfunction progresses with disease advancement. The causes of AI in this population are diverse, which include direct involvement and destruction of the adrenal glands by HIV, opportunistic infections or malignancies, as well as the dysfunction of the hypothalamic-pituitary axis.¹⁰ In developing countries, infections are the most common cause of AI, with a variety of viruses, fungi and bacteria affecting the adrenals. Malignancies such as lymphoma and Kaposi's sarcoma may also cause local infiltration and destruction of the adrenal glands. Additionally, certain antiretroviral therapy drugs, particularly protease inhibitors like ritonavir, can decrease the metabolism of glucocorticoids, leading to iatrogenic Cushing's syndrome and secondary AI upon withdrawal of glucocorticoids.^{11,12} Furthermore, medications used to treat AIDS-related comorbidities can directly inhibit adrenal steroidogenesis. For example, ketoconazole blocks multiple steps in the adrenal steroid biosynthesis pathway, while rifampicin induces hepatic steroid metabolism.

AI can be effectively treated with cortisol replacement therapy. However, failure to recognise the condition, especially during an adrenal crisis, can lead to significant morbidity and mortality. Diagnosing AI can be challenging, as its clinical presentation may closely mimic that of HIV itself.⁷ Subclinical alterations in cortisol levels, progressing to frank primary AI, as determined by the Synacthen test, have been found in HIV-infected patients without overt symptoms of AI. Moreover, symptoms typically do not appear until more than 80% of the adrenal gland has been destroyed.⁴

Given the potentially life-threatening consequences of untreated AI and the diagnostic challenges it presents in HIV-infected individuals, there is a critical need for early identification of clinical and laboratory markers, including adrenal autoantibodies. This study aims to address this gap by determining the prevalence and characteristics of AI among people living with HIV attending outpatient clinics in tertiary hospitals. To our knowledge, this is the first study of its kind in Malaysia, providing valuable data to guide future management strategies for this vulnerable population.

METHODOLOGY

This is a cross-sectional study conducted at the Infectious Diseases (ID) clinics in Hospital Melaka and Hospital Kuala Lumpur, spanning from December 1, 2022, to December 31, 2023. The study protocol received approval from the Medical Research Ethics Committee (MREC), with National Medical Research Register ID NMRR-22-02096-QID (IIR) and was funded by the Malaysian Endocrine and Metabolic Society (MEMS). The study was conducted in accordance

with the Declaration of Helsinki (1975, revised in 2013) and Good Clinical Practice guidelines. Patients' informed consent was obtained prior to any study-related activities.

A total of 110 subjects, aged 18 to 80 years, were recruited using convenience sampling. During the study period, consecutive adults living with HIV attending the infectious diseases outpatient clinics at Hospital Melaka and Hospital Kuala Lumpur were screened for eligibility. Eight subjects declined to participate, and 38 were excluded based on the pre-defined criteria. Exclusion criteria included pregnancy, active or recent infection, critical illness or hospitalisation within the past three months, and use of medications known to affect adrenocortical function (e.g., traditional medications, corticosteroids, or ketoconazole). The sample size was calculated using the formula for proportions, based on a 7% prevalence from Raffi et al.,⁷ with a 95% confidence level ($Z = 1.96$) and 5% precision ($d = 0.05$). This yielded a sample size of 100, adjusted to 110 to account for a 10% dropout rate. The patients underwent clinical assessments and review of their medical records. Relevant clinical and biochemical data were recorded. An infectious disease physician made the diagnosis of treatment failure. These individuals have either virologic failure, immunologic failure, clinical failure or some combination of the three. Immunologic failure refers to suboptimal recovery or a decline in CD4 counts despite being on therapy. Clinical failure is defined as the occurrence of new opportunistic infections despite therapy.¹³ Nadir CD4 is defined as a person's lowest recorded CD4 cell count. AI was diagnosed using the Synacthen test. All patients received an intravenous injection of 250 mcg Synacthen. Serum cortisol levels were measured at baseline, 30 minutes and 60 minutes post-administration. A peak stimulated cortisol level of less than 500 nmol/L indicated AI.^{14,15} Only those diagnosed with AI were further assessed for adrenal autoantibodies and ACTH levels.

The collected data were analysed using SPSS (version 28.0). Descriptive analysis summarised the subjects' socio-demographic characteristics. Numerical data were presented as mean (standard deviation) or median (interquartile range), depending on data normality, while categorical data were presented as frequency and percentage. Independent t-tests were performed to compare continuous variables, such as nadir and latest CD4 counts, between individuals with and without adrenal insufficiency. Fisher's exact test was used to assess associations between categorical variables. A p -value <0.05 was considered statistically significant for all tests. Missing and implausible values were minimal. Only one missing value was observed for the nadir CD4 count, for which no imputation or replacement was performed.

RESULTS

A total of 156 subjects were screened, and 46 were excluded. Hence, 110 subjects were included in the final analysis (Figure 1).

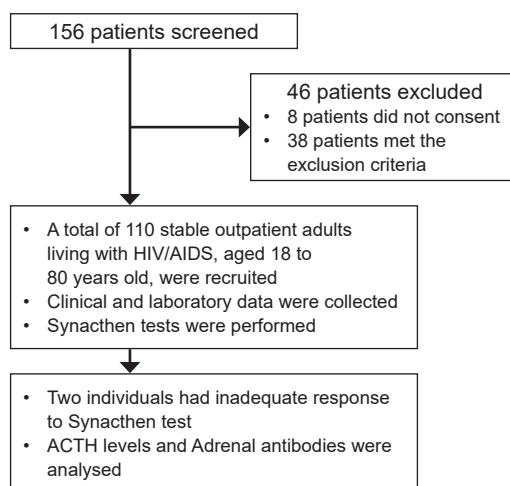


Figure 1. Flow diagram for the study cohort.

The baseline demographic, anthropometric and clinical characteristics of the study population are summarised in Table 1. The mean age of participants was 37.5 ± 10.6 years, with the majority being male (81.8%). Malays comprised the largest ethnic group (75.5%). Only 23.6% of subjects had a normal BMI, while 64.5% were classified as overweight or obese. All subjects were receiving HAART, with a median treatment duration of 3.8 years. Most had a latest CD4 count >200 cells/mm³ (89.1%) and a suppressed viral load <40 copies/ml (88.2%). A history of treatment failure and opportunistic infections was observed in 20% and 41.8% of participants, respectively, while 5 individuals (4.5%) had autoimmune disease.

In the assessment for adrenal insufficiency, 7 individuals (6.4%) reported suggestive symptoms, though only 2 were confirmed to have adrenal insufficiency by the Synacthen test (1.8%; 95% CI 0.2-6.4%). Although hyponatraemia was observed in 4 individuals (3.6%) and hyperkalaemia in 3 individuals (2.7%), none of these individuals had adrenal insufficiency. Comparison of the two subjects with adrenal insufficiency is shown in Table 2. Both had nadir CD4 counts <200 cells/mm³, previous opportunistic infections and a history of treatment failure, but their latest CD4 counts were >200 cells/mm³, viral loads were suppressed, electrolytes were normal, and adrenal antibodies were negative. Compared with those without adrenal insufficiency, the affected patients had significantly lower nadir CD4 counts (11 ± 8.5 vs 205 ± 200 cells/mm³, $p < 0.001$), a history of treatment failure ($p = 0.039$), and symptoms suggestive of adrenal insufficiency ($p = 0.004$). (Table 3)

DISCUSSION

In this study, the prevalence of AI among people living with HIV was 1.8%. While this is higher than in the general population,¹⁶⁻¹⁸ it is considerably lower than rates observed in other studies. Estimates of AI in HIV patients vary widely depending on diagnostic criteria, study methods, and the stage of illness in the population studied. A systematic review and meta-analysis by Kibirige, et al., found a

pooled prevalence of 28% in adults with HIV, with higher rates observed in Africa and Asia, regions with the highest burden of HIV globally.^{19,20} This may be attributed to late diagnoses, advanced disease and multiple co-infections.^{5,19} In contrast, in developed countries, the prevalence of AI is expected to be low, as many HIV patients are aware of their status, receiving treatment and virally suppressed.⁵

Table 1. Demographic, anthropometric and clinical characteristics of the study population (N = 110)

	n (%)
Age (years), Mean $\pm$ SD	37.5 $\pm$ 10.6
Gender	
Male	90 (81.8)
Race	
Malay	83 (75.5)
Chinese	17 (15.5)
Indian	6 (5.5)
Others	4 (3.6)
BMI (kg/m²) based on Asian classification	
<18.5	12 (10.9)
18.5-22.9	26 (23.6)
23-27.4	38 (34.5)
≥ 27.5	34 (30.9)
Hospital	
Hospital Melaka	96 (87.3)
Hospital Kuala Lumpur	14 (12.7)
Comorbidities	
Hypertension	14 (12.7)
Dyslipidaemia	13 (11.8)
Diabetes mellitus	7 (6.4)
Autoimmune disease ^a	5 (4.5)
HIV status	
Disease duration (years), median (IQR)	4.5 (5.6)
Receiving HAART	110 (100)
Subject on regimen with protease inhibitor ^b	15 (13.6)
Treatment duration (years), median (IQR)	3.8 (4.4)
Treatment Failure	22 (20)
History of Opportunistic Infection	46 (41.8)
Tuberculosis ^c	16 (14.5)
CD4 count and viral load	
Nadir CD4 (cells/mm ³), mean $\pm$ SD	202 $\pm$ 200
Nadir CD4 <200 cells/mm ³	66 (60.6) ^d
Latest CD4 (cells/mm ³), mean $\pm$ SD	494 $\pm$ 305
Latest CD4 >200 cells/mm ³	98 (89.1)
Latest VL <40 copies/ml	97 (88.2)
Assessment for adrenal insufficiency	
With symptoms of adrenal insufficiency	7 (6.4)
Symptoms of adrenal insufficiency	
Postural hypotension	4 (3.6)
Postural giddiness	1 (0.9)
Body weakness	1 (0.9)
Abdominal pain/ discomfort	1 (0.9)
Blood investigation	
Hyponatraemia	4 (3.6)
Hyperkalaemia	3 (2.7)
Albumin, Mean $\pm$ SD	44 $\pm$ 3.6
Baseline cortisol level, Mean $\pm$ SD	419 $\pm$ 169
Inadequate Synacthen Response	2 (1.8)

Abbreviations: BMI, body mass index; HAART, highly active antiretroviral therapy; VL, viral load

Data are expressed as numbers and percentages unless otherwise specified.

^a The autoimmune diseases identified include autoimmune hepatitis, Graves' thyrotoxicosis, Hashimoto's hypothyroidism, vitiligo, and psoriasis

^b Protease inhibitors include Kaletra, Atazanavir, Darunavir, and Ritonavir

^c Tuberculosis includes a history of pulmonary or extrapulmonary tuberculosis, or is currently undergoing the maintenance phase of treatment for tuberculosis

^d Total number of subjects with a nadir CD4 count was 109

Table 2. Comparison of clinical characteristics in two patients with adrenal insufficiency

Subject	1	2
Demographic, anthropometric and clinical characteristic		
Age, (years)	56	42
Gender	Female	Male
BMI, (kg/m ²)	34.5	16.5
HIV status		
Disease Duration, (years)	22.8	4.8
Receiving HAART	Yes	Yes
Regimen with protease inhibitor ^a	Yes	Yes
Treatment duration, (years)	14.5	4.5
Treatment failure	Yes	Yes
History of OI ^b	Yes	Yes
Tuberculosis ^c	No	No
Nadir CD4 (cells/mm ³)	5	17
Latest VL (copies/ml)	<40	<40
Latest CD4 (cells/mm ³)	271	392
Comorbidities		
Autoimmune disease	No	No
Other medical illness	Hepatitis C, treated in 2022 Dyslipidaemia	No
Assessment for adrenal insufficiency		
Symptoms	Abdominal discomfort	Body weakness
Blood investigation		
Hyponatraemia	No	No
Hyperkalaemia	No	No
Hypercalcaemia	No	No
Baseline cortisol (nmol/L)	361.8	<13.8
Peak cortisol (nmol/L)	472.8	89.4
ACTH level (NR 1.6-13.9pmol/L)	8.6	0.3
Adrenal antibodies	Negative	Negative

Abbreviations: ACTH, adrenocorticotrophic hormone; BMI, body mass index; HAART, highly active antiretroviral therapy; NR, normal range; VL, viral load

^a Both patients were on a regimen consisting of Kaletra

^b Subject 1 had a history of pneumocystis pneumonia and oral candidiasis in 2022, while Subject 2 had a history of Mycobacterium avium complex (MAC) in 2019

^c Tuberculosis includes a history of pulmonary or extrapulmonary tuberculosis, or is currently undergoing the maintenance phase of treatment for tuberculosis

Table 3. Comparison of clinical characteristics between HIV patients with and without adrenal insufficiency

	Adrenal insufficiency		p-value
	Yes (n = 2)	No (n = 108)	
Mean nadir CD4, cells/mm ³	11 ± 8.5	205 ± 200	<0.001 ^a
Mean latest CD4, cells/mm ³	331	497	0.450 ^a
Nadir CD4, cells/mm ³ †	<200	2 (100)	0.518 ^b
	>200	0 (0)	
Treatment failure	Yes	2 (100)	0.039 ^b
	No	0 (0)	
History of OI	Yes	2 (100)	0.173 ^b
	No	0 (0)	
Symptoms of AI	Yes	2 (100)	0.004 ^b
	No	0 (0)	

Abbreviations: AI, adrenal insufficiency; OI, opportunistic infection
Data expressed as n (%) unless otherwise specified. Percentages calculated within column.

† Nadir CD4 available in 109 subjects

^a Independent t-test p-value <0.05 indicates that there is a statistically significant difference between the group means.

^b Fisher's exact test p-value of <0.05 suggests that the association between the variables is statistically significant.

In a developing country like Malaysia, despite the implementation of the WHO recommendation in 2017 to initiate HAART regardless of CD4 counts, gaps in diagnosis and treatment remain, with more than half of the newly diagnosed HIV cases present with advanced disease.²¹ In our cohort, 61% of subjects had a nadir CD4 count of less than 200 cells/mm³, and 42% had a history of opportunistic infections, suggesting a population potentially at risk for AI. However, all participants were on HAART, were clinically stable and almost 90% achieved immune recovery and viral suppression at the time of assessment. The role of HAART in inhibiting HIV viral replication and improving immune function likely contributes to the reduced risk of opportunistic infections and, consequently, a lower prevalence of AI among individuals living with HIV in Malaysia. This finding aligns with another Malaysian study on endocrinopathies in HIV-infected patients, which observed hypocortisolism at a prevalence of 1.3%.²²

The two individuals in our study who were diagnosed with AI had significantly lower mean nadir CD4 counts, a history of treatment failure and symptoms suggestive of AI. No significant association was noted in the latest CD4 counts or history of opportunistic infections. None of them had positive adrenal autoantibodies, and their ACTH levels were not elevated, suggesting no adrenal gland destruction. However, given the very small number of patients with AI, statistical inferences from these comparisons may be limited, and the observed differences should be interpreted with caution.

While CD4 count is an important predictor of disease progression, opportunistic infections and mortality, it does not reliably predict the presence or absence of AI.²³ Our research suggests that the occurrence of AI may be more closely linked to a low nadir CD4 count and treatment failure rather than the latest CD4 count. A low nadir CD4 count and treatment failure may better reflect long-term immunosuppression, which increases the likelihood of opportunistic infections that can infect and damage the adrenal glands, leading to AI. Prolonged periods of viral replication during treatment failure also result in chronic inflammation, which may directly damage the adrenal glands or indirectly impair their function by stressing the hypothalamic-pituitary-adrenal axis.^{5,17} Furthermore, although Odeniyi et al., reported that typical clinical features of AI had poor predictive value for diagnosing hypoadrenalism²⁴, our study indicates that these symptoms can indeed serve as significant indicators, particularly in patients with a history of advanced disease or treatment failure. This aligns with the findings of Afreen et al.⁶ and underscores the importance of vigilant monitoring.

The key strength of this study is the use of the Synacthen test, the gold standard for assessing adrenal insufficiency. Besides, the study was conducted in an outpatient setting, which is representative of the typical care environment for most HIV patients, contributing valuable local knowledge and opening avenues for future research. However, several

limitations should be considered. The cross-sectional design and convenience sampling of only stable outpatients limit causal inferences and may introduce selection bias, thus restricting generalizability. As adrenal insufficiency may be more prevalent in advanced disease or during acute illness, the prevalence reported in this study may underestimate the true burden among all people living with HIV. Therefore, the findings are most applicable to clinically stable patients receiving outpatient care in tertiary centres. Financial constraints also limited our ability to assess the prevalence of adrenal autoantibodies in the study population, particularly among those with low CD4 counts. This additional data could have provided deeper insights into the development of adrenal insufficiency. As HIV is a dynamic disease that may involve epigenetic modulation—yet to be discovered and proven—further investigation into these areas could help uncover additional factors contributing to adrenal dysfunction. Future research should examine the long-term effects of HAART on the adrenal-pituitary axis in larger, more diverse populations. Longitudinal studies could offer valuable insights into the relationship between HAART, AI and clinical outcomes in HIV patients.

CONCLUSION

While AI remains a significant concern among people living with HIV. Our study revealed a low prevalence of AI among stable HIV patients on HAART. Screening for AI should be individualised and based on a clinician's high index of suspicion, particularly in patients with advanced disease, a history of treatment failure or those presenting with suggestive clinical features. Additionally, in patients diagnosed with AI, a careful assessment to identify the cause is crucial before attributing the condition solely to HIV/AIDS.

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Statement of Authorship

All authors certified fulfilment of ICMJE authorship criteria.

CRedit Author Statement

QCG,SR,NM,CVT: Writing – original draft and Writing – review and editing.

Data Availability Statement

The datasets generated and analysed are included in the published article.

Author Disclosure

The authors declared no conflict of interest.

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