Addison’s disease associated with advanced HIV may explain the high mortality

**TRP Mofokeng1, RS Millar5, TS Pillay6, J Dave2, NS Levitt2, R Erasmus2, PJ Raubenheimer2, C Dandara2, A Grossman3, G Johansson4, IL Ross2**

1Division of Endocrinology, Department of Medicine University of the Free State, South Africa,

2Division of Endocrinology, Department of Medicine University of Cape Town, South Africa

3Department of Endocrinology, St Bartholomew’s Hospital, London, UK

4Department of Endocrinology, Sahlgrenska Academy, Sahlgrenska University Hospital and Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

5Department of Immunology, Faculty of Health Sciences, University of Pretoria, Private Bag X323, Pretoria 0031, South Africa

6Department of Chemical Pathology and National health Laboratory Services, Tshwane Academic Division, Faculty of Health Sciences, University of Pretoria, South Africa

Correspondence should be addressed to:

Dr Thabiso RP Mofokeng,

Division of Endocrinology,

Department of Medicine (University of the Free State),

South Africa,

e-mail: [mofokengtrp@ufs.ac.za](mailto:mofokengtrp@ufs.ac.za)

22-12-22 Version

**Abstract:**

**Background:**

Sub-Saharan Africa is burdened by a vast HIV population, with many of those with CD4 < 100 subject to AIDS defining illnesses. Aids defining illnesses Including disseminated opportunistic infections have been associated with Primary Adrenal insufficiency (PAI). We hypothesized that hypoadrenalism may partially account for the high mortality in the subgroup with advanced HIV.

**Materials & Methods:**

We undertook a prospective case-finding study of newly diagnosed HIV patients presenting with advanced disease of patients aged 18 years or older with a CD4 count of 100 mm3, with an opportunistic infection. Exclusion criteria were use of oral or inhaled steroids in the previous 3 months.

**Results:**

The majority (90%) of patients in this cohort were black Africans, with a slight predominance of the males at 52%. The median and interquartile age range (IQR) of patients at enrolment was 36.0 (31.0-41.0) years. The median CD4 counts were 31 cells/L (14-60) and 31 cells/L (15-58) and opportunistic infections were mainly tuberculosis, with surprisingly low incidence of bacterial, CMV and fungal infections. The prevalence of hypoadrenalism was 21/439 (5%) in this cohort. There were significant differences between the groups who were diagnosed with hypoadrenalism versus those without, in respect of the random morning cortisol 332 nmol/L versus 513 nmol/L (*p*<0.001), basal cortisol 300 nmol/L versus 462 nmol/L (*p*<0.001), median ACTH 37 pmol/L versus 31 pmol/L (*p*=0.029), diastolic blood pressure 71 mmHg vs 70 mmHg (*p*=0.031), and potassium 3.70 versus 4.20 mmol/L (*p*=0.045). There was an overall 49/439 (11%) mortality in this cohort , 5/49 (10 %) of the total fatalities had adrenal insufficiency, and they contributed to higher mortality in the hypo adrenal subgroup at 5/21 (23%).

.

**Conclusion:**

Word count =

**Introduction:**

Adrenal insufficiency is a deadly medical condition caused by the deficiency of cortisol. Before the advent of glucocorticoid therapy, the overwhelming majority of the primary adrenal insufficiency patients died within 2 years of diagnosis. Primary autoimmune adrenal insufficiency predominates in European populations, 1and it is also the case in Moroccan population studies and a large South African study.2 However, our recent survey suggests that infection is a significant cause of primary adrenal insufficiency in sub-Saharan Africa.3

Acquired immune deficiency syndrome(AIDS) resulting from infection with HIV is known to affect all the organs either directly or indirectly, including endocrine glands.4 HIV has been linked with Secondary male hypogonadism via cytokine effects in the hypothalamus, adrenalitis, thyroid hypofunction, and HIV drug lipodystrophy5. Well described causes of adrenal destruction and clinical hypoadrenalism in HIV include *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, hemorrhage and cytomegalovirus infection,, and malignant infiltrations5

There are conflicting data describing the incidence and prevalence of hypoadrenalism in patients with HIV, particularly when comparing pathological adrenal involvement of 30-60% in autopsy reports with clinical adrenal insufficiency.4 Eldrisi et al6 reported that Adrenal insufficiency as very common in HIV patients, without giving precentages. Unachuku et al reported CMV adrenalitis range between 40-88% which is associated with hypoadrenalism in patients with HIV.7 In a study of 60 HIV infected patients, Afreen et al reported adrenal insufficinecy incidence of 9/60 (14 %) using the intravenous tetracosactide test of 250 micrograms and a 60min cortisol level of 18micrograms (500 nmol/L) as a cutoff.8 In their study of adrenal insufficiency in HIV positive patients, Odeniyi et al reported the incidence of 34.8% using 1mcg tetracosactide test.9

Similar to HIV infection, adrenal insufficiency is associated with decreased life expectancy which is worse if the diagnosis is delayed or missed. The quality of life in those with inadequate replacement therapy in LMIC has also been found to be decreased or dismal. There is a high prevalence of Human immune virus (HIV) infection4 in sub-Saharan Africa, which is associated with significant mortality in patients presenting with advanced disease. In 2018, South Africa had the highest mortality rate in HIV infected females at 391/100 000 and males at 467.7/100 00010, this is expected to improve with improving therapeutic armamentarium.

We hypothesize that the high mortality in patients seen with advanced HIV may be partially explained by undiagnosed adrenal insufficiency. Our objectives were to determine prevalence of hypoadrenalism among ill, hospitalized HIV-infected patients, and their clinical and biochemical features.

**Materials and methods:**

Permission to conduct the study (HREC 163/2015) was obtained from the University of Cape Town Faculty of Health Sciences Human Research and Ethics Committee, which endorses the latest Helsinki declaration (HREC 163/2015). All the participants were provided with verbal information and asked to sign consent for all aspects of the study. In case the patient was incapacitated by reason of delirium, consent was sought from the patient’s family for the benefit of the patient in case they should require the life-saving treatment.

We undertook a prospective case-finding, case-controlled study of newly diagnosed HIV patients presenting with advanced disease. Inclusion criteria included aged 18 years or older, who were HIV positive and had a CD4 count of 100 cells per mm3 or less, with an established opportunistic infection. Exclusion criteria included the use of oral or inhaled steroids in the previous 3 months. Patients were enrolled if they could provide informed consent or in the case of an opportunistic infection which impaired level of consciousness and capacity to grant consent, this was obtained retrospectively, while still in hospital as per the Faculty of Health Sciences Research and Ethics Committee. The rationale for including patients who were unable to grant immediate consent was to avoid bias in respect of exclusively enrolling patients of normal level of consciousness and cognition. Demographic and clinical data were recorded and included in a database. Patients who met the inclusion criteria, had blood samples taken for serum cortisol and plasma ACTH between 08:00 and 09:00.

Random cortisol and ACTH

Patients who had a serum cortisol less than 500 nmol/L underwent a 250 µg synthetic ACTH stimulation test.

Interpretation of synthetic ACTH stimulation test

Follow-up and determination of survival

**Statistical analysis:**

Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as medians 11 and were compared using the Wilcoxon-Mann-Whitney test. Proportions and categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test as appropriate. Univariate logistic regression was used to estimate the association between PAI and various risk factors. Multivariable logistic regression analysis was used to identify independent predictors of PAI. The statistical analysis was done using STATA Statistical Software version 15.The significance level was set at *p*<0.005

**Results**

**Clinical characteristics**

This is a study of HIV positive patients admitted at Groote Schuur hospital with advanced disease characterized by low CD4 count of less than 100 and presence of an opportunistic infection.

There were 439 patients referred for enrollment in the South African study on adrenal insufficiency in patients with advanced HIV infection. The median age at enrollment was 36yrs overall, 35 and 37yrs for the females and males, respectively Most of the participants were black Africans 356/429(83%), followed by those of mixed ancestry 68/429 (15.9%), and white 2/429(0.5%). The median duration of the current presenting illness was 14.days

Suggest you discuss the opportunistic infections

The predominant opportunistic infection was tuberculosis at 313 overall with 161/439 (73%) and 152/429 (72%) for males and females, respectively. Other undefined opportunistic infections were 113 overall with 54/429 (25%) and 59/429 (28.0%) in males and females, respectively. Surprisingly, opportunistic infection which are common in advanced HIV such as cryptococcus, cytomegalovirus and toxoplasmosis were not detected in this cohort.

Baseline biochemistry

The median CD4 counts were 32 cells/ml versus 30 cells/ml, and viral loads 4.07 Log10 copies /ml versus 4.61 Log10 copies/ml for females and males, respectively. Statistically significant differences were observed for sodium of 135 mmol/L versus 133 mmol/L (*p*<0.001), potassium 3.90 mmol/L versus 4.20 mmol/L (*p*<0.001) and hemoglobin 8.30 g/dL versus 9.30 g/dL (*p*<0.001), lymphocytes 0.8% versus 0.9% (p>0.9) and neutrophils 3x109/L versus 4.07 x 109/L in female versus male participants. There were no additional differences between males versus females. (Table 1)

Clinical features of hypoadrenalism

Apart from the statistically different diastolic blood pressure which were 71 mmHg versus 70 mmHg (p=0.031) in the hypoadrenal versus non-hypodarenal patients, the rest of the clinical features were not statistically significant, including the systolic blood pressure 120 mmHg versus 110mmHg *(p*=0.10), hypotension in 1(4.8%) versus 22(7.7%) (*P*>0.9), heart rate 90 bpm versus 95 bpm (*p*=0.5), weakness 16/21( 76.2%) versus 252/297 (88.4%) (*p*=0.2), tiredness 18/21(85.7%) versus 261/297 (91.3%) (*p*=0.4), poor appetite 18/21 (85.7%) versus 226/297 (79.9%) (*p*=0.8), weight loss 18/21 (85.7%) versus 264/297 (92%), nausea 12/21 (57%.1) versus 151/297 (52.8%) *(p*=0.7), vomiting 6/21 (28.6%) versus 82/297 (28.8%) (*p*>0.9), salt craving 14/21 (66.7%) versus 193/297 (68.0%) *(p*>0.9).

Biochemical features of hypoadrenalism :

Statistically significant difference was observed between the hypoadrenal versus non-hypoadrenal group in respect of the random morning cortisol 332 nmol/L versus 513 nmol/L (*p*<0.0001), basal cortisol 300 nmol/L versus 462 nmol/L (*p<*0.001), median ACTH 37 pmol/L versus 31 pmol/L (*p*=0.029), diastolic blood pressure 71 mmHg vs 70 mmHg (*p*=0.031), and potassium 3.70 versus 4.20 mmol/L (*p*=0.045). While the difference in potassium was statistically significant between the two groups at 3.7 mmol/L versus 4.20 mmol/L (*p*=0.045), sodium at 135 mmol/L versus 133 mmol/L (*p*=0.12), haemoglobin 8.4 g/dL versus 8.8 g/dL (*p*=0.9), white cell count 5.2 x 109 versus 5.7 x 109(*p*=0.3), lymphocytes 0.1 x 109 versus 0.7 x 109 (*p*=0.3), and neutrophils at 1.0 x 109 versus 3.0 x 109 (*p*=0.055) were not.

**Morbidity and mortality outcomes:**

Overall mortality was 49 /429 (11%) of which 5/49 (10.2%) were patients with confirmed hypoadrenalism, and mortality was highest in the hypoadrenal group at 5/21 (23%). Univariate analysis showed association of the following with AI in advanced HIV, while multivariate analysis showed following independent predictors of AI in advanced HIV.

Early mortality : at 3months follow-up was

Intermediate mortality : at 6months follow-up was

Late mortality : at 12months follow-up was

Mortality among patients with hypoadrenalism : 5/21 (23%)

**Discussion**

This biggest study on hypoadrenalism in advanced HIV in Africa revealed a prevalence of 21/432 (5%) using the tetracosactide test with the cortisol response target of less than 500 nmol/L. At 5% his prevalence is slightly higher than the one found in our previous study at 3%, but less than the estimated 14% according to the responses in our most recent survey. Most reports on Addison’s disease in HIV in Africa are case reports (Kibirige, )

Patient profile:

Clinical features:

Biochemical features:

Morbidity & Mortality:

**Conclusion:**

To the best of our knowledge, this is the largest prospective study exploring the prevalence of PAI in HIV patients in Africa. The prevalence of PAI in this cohort was 5% which is larger than the 2011 South African estimate of 3.0%. Although adrenal insufficiency was not found to be the overwhelming cause of death in patients with advanced HIV, its presence warrants screening for it in high risk, symptomatic patients with diarrhoea, paradoxical hyperkalaemia and low random cortisol in the presence of elevated ACTH. The predominant cause of death in the 47 fatalities was TB, which is AIDS-defining when dissemintated, especially in patients with CD4 below 100.

References:

1. Betterle C, Morlin L. Autoimmune Addison’s disease. *Pediatric Adrenal Diseases.* 2011;20:161-172.

2. Mofokeng TR, Beshyah SA, Mahomed F, Ndlovu KC, Ross IL. Significant barriers to diagnosis and management of adrenal insufficiency in Africa. *Endocrine connections.* 2020;9(5):445-456.

3. Mofokeng TRP, Ndlovu KCZ, Beshyah SA, Ross IL. Tiered healthcare in South Africa exposes deficiencies in management and more patients with infectious etiology of primary adrenal insufficiency. *Plos one.* 2020;15(11):e0241845.

4. Hofbauer LC, Heufelder AE. Endocrine implications of human immunodeficiency virus infection. *Medicine.* 1996;75(5):262-278.

5. Sinha U, Sengupta N, Mukhopadhyay P, Roy KS. Human immunodeficiency virus endocrinopathy. *Indian journal of endocrinology and metabolism.* 2011;15(4):251.

6. Eledrisi MS, Verghese AC. Adrenal insufficiency in HIV infection: a review and recommendations. *The American journal of the medical sciences.* 2001;321(2):137-144.

7. Unachukwu C, Uchenna D, Young E. Endocrine and metabolic disorders associated with human immune deficiency virus infection. *West African Journal of Medicine.* 2009;28(1).

8. Afreen B, Khan KA, Riaz A. Adrenal insufficiency in Pakistani HIV infected patients. *Journal of Ayub Medical College Abbottabad.* 2017;29(3):428-431.

9. Odeniyi I, Fasanmade O, Ajala M, Ohwovoriole A. Adrenocortical function in Nigerians with human immunodeficiency virus infection. *Ghana Medical Journal.* 2013;47(4):171.

10. Jani C, Patel K, Walker A, et al. Trends of HIV mortality between 2001 and 2018: An observational analysis. *Tropical Medicine and Infectious Disease.* 2021;6(4):173.

11. Karmpaliotis D, Kirtane AJ, Ruisi CP, et al. Diagnostic and prognostic utility of brain natriuretic Peptide in subjects admitted to the ICU with hypoxic respiratory failure due to noncardiogenic and cardiogenic pulmonary edema. *Chest.* 2007;131(4):964-971.

Table 1: Baseline sociodemographic and clinical characteristics of the patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | N | Overall, *N* = 429 | Females, *N* = 218 | Males, N = 211 | *p*-value |
| Median (IQR) age at enrolment in years | 429 | 36 (31, 42) | 35 (31, 41) | 37 (32, 43) | 0.058a |
| Ethnicity, n(%) | 427 |  |  |  | 0.069b |
| Asian |  | 1 (0.2%) | 0 (0.0%) | 1 (0.5%) |  |
| Black African |  | 356 (83.4%) | 176 (81.1%) | 180 (85.7%) |  |
| Mixed ancestry |  | 68 (15.9%) | 41 (18.9%) | 27 (12.9%) |  |
| White |  | 2 (0.5%) | 0 (0.0%) | 2 (1.0%) |  |
| Median (IQR) duration of current illness in days | 399 | 14 (14, 21) | 14 (14, 30) | 14 (14, 21) | 0.3a |
| Presence of an Opportunistic infection present, *yes* n(%) | 426 | 423 (99.3%) | 214 (98.6%) | 209 (100.0%) | 0.2b |
| Median (IQR) Viral Load Log10 copies/ml | 96 | 4.47 (3.13, 5.34) | 4.07 (3.22, 5.24) | 4.61 (3.04, 5.37) | >0.9a |
| Median (IQR) total CD4 count in cells/mm3 | 427 | 31 (14, 60) | 32 (15, 58) | 30 (12, 64) | >0.9a |
| Median (IQR) Sodium in mmol/l | 407 | 134.0 (130.0, 137.0) | 135.0 (131.0, 138.0) | 133.0 (129.0, 136.5) | **0.001a** |
| Median (IQR) Potassium in mmol/l | 408 | 4.05 (3.60, 4.60) | 3.90 (3.50, 4.40) | 4.20 (3.80, 4.70) | **<0.001a** |
| Median (IQR) Haemoglobin in g/dL | 425 | 8.70 (7.40, 10.30) | 8.30 (7.10, 9.50) | 9.30 (7.90, 10.90) | **<0.001a** |
| Median (IQR) White cell count in 109/L | 422 | 5.4 (3.6, 8.0) | 5.6 (3.7, 8.1) | 5.3 (3.5, 7.8) | 0.6a |
| Median (IQR) Lymphocyte count in % | 92 | 0.8 (0.4, 1.8) | 0.9 (0.3, 3.5) | 0.8 (0.4, 1.3) | >0.9a |
| Median (IQR) Neutrophils in 109/L | 92 | 3 (1, 8) | 3 (1, 10) | 3 (1, 7) | 0.6a |
| Tuberculosis, *yes* n(%) | 429 | 313 (73%) | 161 (74%) | 152 (72%) | 0.7c |
| Cryptococcus neoformans, *yes* n(%) | 429 | 1 (0.2%) | 1 (0.5%) | 0 (0%) | >0.9b |
| Kaposi’s sarcoma, *yes* n(%) | 429 | 1 (0.2%) | 0 (0%) | 1 (0.5%) | 0.5b |
| Cytomegalovirus, *yes* n(%) | 429 | 1 (0.2%) | 0 (0%) | 1 (0.5%) | 0.5b |
| Other, *yes* n(%) | 429 | 113 (26.0%) | 54 (25.0%) | 59 (28.0%) | 0.5c |
| Addison’s disease, *yes* n(%) | 318 | 21 (6.6%) | 10 (6.0%) | 11 (7.3%) | 0.6b |

aWilcoxon rank sum test

bFisher's exact test

cPearson's Chi-squared test

**Table 2: Comparing patients with severely immunocompromised HIV-positive patients with hypoadrenalism and those without it**

| Variable | N | Hypoadrenalism,  N = 21 | Without  hypoadrenalism,  N = 297 | *p*-value |
| --- | --- | --- | --- | --- |
| **Age at enrolment*, median (IQR) years*** | 318 | 36 (31, 43) | 36 (31, 42) | 0.6 |
| **Female-gender*, n (%)*** | 318 | 10 (47.6%) | 157 (52.9%) | 0.6 |
| **Ethnicity*, n (%)*** | 317 |  |  | 0.6 |
| Black African |  | 19 (90.5%) | 242 (81.8%) |  |
| Other |  | 2 (9.5%) | 54 (18.2%) |  |
| **Duration of current illness*, median (IQR) days*** | 300 | 14 (11, 21) | 14 (14, 30) | 0.2 |
| **Random morning cortisol*, median (IQR) nmol/L*** | 318 | 332 (253, 375) | 513 (388, 606) | <0.001 |
| **Basal cortisol*, median (IQR) nnol/L*** | 144 | 300 (185, 328) | 462 (352, 568) | <0.001 |
| **Stimulated cortisol*, median (IQR) nmo/L*** | 145 | 403 (316, 438) | 720 (616, 848) | <0.001 |
| **ACTH*, median (IQR) pmol/L*** | 318 | 37 (25, 72) | 31 (18, 48) | 0.029 |
| **BP (systolic)*, median (IQR) mmHg*** | 318 | 120 (111, 129) | 110 (100, 125) | 0.10 |
| **BP (diastolic)*, median (IQR) mmHg*** | 318 | 71 (70, 80) | 70 (60, 78) | 0.031 |
| **Postural drop in blood pressure** | 306 | 1 (4.8%) | 11 (3.9%) | 0.6 |
| **Heart rate*, median (IQR) bpm*** | 318 | 90 (77, 109) | 95 (81, 111) | 0.5 |
| **Hypotension*, n (%)*** | 305 | 1 (4.8%) | 22 (7.7%) | >0.9 |
| **Weakness*, n (%)*** | 306 | 16 (76.2%) | 252 (88.4%) | 0.2 |
| **Tiredness*, n (%)*** | 307 | 18 (85.7%) | 261 (91.3%) | 0.4 |
| **Poor appetite*, n (%)*** | 304 | 18 (85.7%) | 226 (79.9%) | 0.8 |
| **Weight loss*, n (%)*** | 308 | 18 (85.7%) | 264 (92.0%) | 0.4 |
| **Increased pigmentation of the skin*, n (%)*** | 292 | 8 (44.4%) | 131 (47.8%) | 0.8 |
| **Nausea*, n (%)*** | 307 | 12 (57.1%) | 151 (52.8%) | 0.7 |
| **Vomiting*, n (%)*** | 306 | 6 (28.6%) | 82 (28.8%) | >0.9 |
| **Liking for salt*, n (%)*** | 305 | 14 (66.7%) | 193 (68.0%) | >0.9 |
| **Hypoglycaemia*, n (%)*** | 306 | 0 (0.0%) | 7 (2.5%) | >0.9 |
| **Loss of consciousness*, n (%)*** | 304 | 0 (0.0%) | 2 (0.7%) | >0.9 |
| **Diarrhea*, n (%)*** | 304 | 6 (28.6%) | 121 (42.8%) | 0.2 |
| **Dizziness*, n (%)*** | 305 | 11 (55.0%) | 133 (46.7%) | 0.5 |
| **Shock*, n (%)*** | 308 | 0 (0.0%) | 3 (1.0%) | >0.9 |
| **Anorexia*, n (%)*** | 306 | 7 (33.3%) | 126 (44.2%) | 0.3 |
| **Loss of axillary and pubic hair in females*, n (%)*** | 164 | 2 (20.0%) | 51 (33.1%) | 0.5 |
| **Presence of anaemia*, n (%)*** | 303 | 12 (57.1%) | 155 (55.0%) | 0.8 |
| **Presence of an opportunistic infection*, n (%)*** | 317 | 21 (100.0%) | 296 (100.0%) |  |
| **Viral load*, median (IQR) (log10 Copies/mL)*** | 65 | 4.79 (4.67, 4.92) | 4.77 (3.28, 5.36) | >0.9 |
| **Total CD4 count*, median (IQR)*** | 317 | 23 (14, 48) | 31 (14, 57) | 0.6 |
| **Sodium, *median (IQR) mmol/L*** | 303 | 135.0 (132.0, 137.0) | 133.0 (130.0, 137.0) | 0.12 |
| **Potassium, *median (IQR) mmol/L*** | 304 | 3.70 (3.30, 4.00) | 4.20 (3.70, 4.60) | 0.045 |
| **Haemoglobin*, median (IQR) g/dL*** | 317 | 8.40 (7.60, 10.30) | 8.80 (7.40, 10.40) | 0.9 |
| **White cell count, *median (IQR) X109*** | 316 | 5.2 (2.5, 6.5) | 5.7 (3.9, 8.3) | 0.3 |
| **Lymphocyte count*, median (IQR) X109*** | 62 | 1.0 (0.6, 9.4) | 0.7 (0.4, 1.5) | 0.3 |
| **Neutrophils*, median (IQR)*** | 61 | 1 (1, 1) | 3 (1, 7) | 0.055 |

**Table 3: Adrenal insufficiency among those who died**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | N | Addison’s and died, N = 5 | Without Addison’s but died, N = 42 | p-value |
| **Age at enrolment median (IQR) (years)** | 47 | 40 (31, 41) | 38 (33, 44 | >0.9 |
| **Gender, n(%)** | 47 |  |  | >0.9 |
| Females |  | 3 (60.0%) | 25 (59.5%) |  |
| Males |  | 2 (40.0%) | 17 (40.5%) |  |
| **Ethnicity, n(%)** | 47 |  |  | >0.9 |
| 1 |  | 4 (80.0%) | 35 (83.3%) |  |
| 2 |  | 1 (20.0%) | 7 (16.7%) |  |
| **Duration of current illness, median (IQR) (days)** | 44 | 9 (7, 266) | 1,257 (340, 2,792) | 0.067 |
| **Random cortisol, *median (IQR) nmol/L*** | 47 | 332 (281, 337) | 508 (367, 623) | **0.019** |
| **Basal cortisol, *median (IQR) nmol/L*** | 26 | 315 (301, 381) | 485 (419, 631) | **0.002** |
| **Stimulated cortisol, *median (IQR) nmol/L*** | 26 | 403 (347, 431) | 763 (630, 880) | **<0.001** |
| **ACTH, *median (IQR) pmol/L*** | 47 | 48 (37, 88) | 39 (22, 53) | 0.3 |
| **BP (systolic)*, median (IQR) mmHg*** | 47 | 127 (120, 128) | 110 (102, 120) | 0.2 |
| **BP (diastolic)*, median (IQR) mmHg*** | 47 | 71 (63, 76) | 72 (67, 80) | 0.5 |
| **Heart rate, *median (IQR) bpm*** | 47 | 92 (68, 100) | 91 (80, 108) | 0.4 |
| **Hypotension, n(%)** | 46 | 0 (0.0%) | 5 (12.2%) | >0.9 |
| **Weakness, n(%)** | 46 | 3 (60.0%) | 38 (92.7%) | 0.084 |
| **Tiredness, n(%)** | 45 | 5 (100.0%) | 37 (92.5%) | >0.9 |
| **Poor appetite, n(%)** | 46 | 5 (100.0%) | 38 (92.7%) | >0.9 |
| **Weight loss, n(%)** | 46 | 4 (80.0%) | 36 (87.8%) | 0.5 |
| **Increased pigmentation of the skin, n(%)** | 44 | 2 (50.0%) | 24 (60.0%) | >0.9 |
| **Nausea, n(%)** | 46 | 4 (80.0%) | 27 (65.9%) | >0.9 |
| **Vomiting, n(%)** | 46 | 2 (40.0%) | 11 (26.8%) | 0.6 |
| **Liking for salt, n(%)** | 46 | 3 (60.0%) | 28 (68.3%) | >0.9 |
| **Hypoglycaemia, n(%)** | 46 |  |  |  |
| No |  | 5 (100.0%) | 41 (100.0%) |  |
| **Loss of consciousness, n(%)** | 46 | 0 (0.0%) | 1 (2.4%) | >0.9 |
| **Diarrhoea, n(%)** | 46 | 0 (0.0%) | 23 (56.1%) | **0.049** |
| **Dizziness, n(%)** | 45 | 3 (60.0%) | 25 (62.5%) | >0.9 |
| **Shock, n(%)** | 46 | 0 (0.0%) | 1 (2.4%) | >0.9 |
| **Anorexia, n(%)** | 46 | 2 (40.0%) | 24 (58.5%) | 0.6 |
| **Loss of axillary and pubic hair, if female, n(%)** | 45 |  |  | 0.8 |
| No |  | 2 (40.0%) | 11 (27.5%) |  |
| Not applicable |  | 2 (40.0%) | 15 (37.5%) |  |
| Yes |  | 1 (20.0%) | 14 (35.0%) |  |
| **Any postural drop in blood pressure, n(%)** | 45 | 0 (0.0%) | 2 (5.0%) | >0.9 |
| **Presence of anaemia, n(%)** | 46 | 3 (60.0%) | 24 (58.5%) | >0.9 |
| **Presence of an opportunistic infection, n(%)** | 47 | 5 (100.0%) | 42 (100.0%) |  |
| **Tuberculosis, n(%)** | 47 |  |  | 0.6 |
| Yes |  | 3 (60.0%) | 29 (69.0%) |  |
| No |  | 2 (40.0%) | 13 (31.0%) |  |
| **Cryptococcus neoformans, n(%)** | 47 |  |  | >0.9 |
| Yes |  | 0 (0.0%) | 0 (0.0%) |  |
| No |  | 5 (100.0%) | 42 (100.0%) |  |
| **Toxoplasmosis, n(%)** | 47 |  |  |  |
| No |  | 5 (100.0%) | 42 (100.0%) |  |
| **Mycobacterium avium-intracellulare, n(%)** | 47 |  |  |  |
| No |  | 5 (100.0%) | 42 (100.0%) |  |
| **Kaposis sarcoma, n(%)** | 47 |  |  | >0.9 |
| Yes |  | 0 (0.0%) | 0 (0.0%) |  |
| No |  | 5 (100.0%) | 42 (100.0%) |  |
| **Cytomegalovirus, n(%)** | 47 |  |  | >0.9 |
| Yes |  | 0 (0.0%) | 0 (0.0%) |  |
| No |  | 5 (100.0%) | 42 (100.0%) |  |
| **Other, n(%)** | 47 |  |  | >0.9 |
| Yes |  | 2 (40.0%) | 14 (33.3%) |  |
| No |  | 3 (60.0%) | 28 (66.7%) |  |
| **Viral load (log10 Copies/mL)** | 11 | \_ | 5.10 (4.55, 5.68) |  |
| **Total CD4 count, median (IQR) µ/mL** | 47 | 17 (15, 46) | 28 (14, 49) | 0.9 |
| **Sodium, *median (IQR)* mmol/L** | 45 | 134.0 (133.0, 139.0) | 133.0 (128.0, 137.0) | 0.3 |
| **Potassium, *median (IQR) mmol/L*** | 45 | 3.60 (3.30, 3.90) | 3.90 (3.60, 4.52) | 0.14 |
| **Haemoglobin, *median (IQR)* g/dL** | 47 | 8.70 (8.10, 10.50) | 8.85 (7.50, 10.70) | >0.9 |
| **White cell count, *median (IQR)* x109** | 47 | 5.8 (3.9, 10.8) | 5.4 (3.9, 7.7) | 0.7 |

**Table 4: describing mortality among the patients with hypoadrenalism**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | N | Addison’s and Died, N = 5 | Addison’s but Alive, N = 16 | p-value |
| **Age at enrolment median (IQR) (years)** | 21 | 40 (31, 41) | 36 (32, 44) | >0.9 |
| **Gender, n(%)** | 21 |  |  | 0.6 |
| Females |  | 3 (60.0%) | 7 (43.8%) |  |
| Males |  | 2 (40.0%) | 9 (56.2%) |  |
| **Ethnicity, n(%)** | 21 |  |  | 0.4 |
| 1 |  | 4 (80.0%) | 15 (93.8%) |  |
| 2 |  | 1 (20.0%) | 1 (6.2%) |  |
| **Duration of current illness, median (IQR) (days)** | 20 | 9 (7, 266) | 1,812 (346, 3,326) | 0.12 |
| **Random cortisol, *median (IQR) nmol/L*** | 21 | 332 (281, 337) | 298 (230, 376) | 0.8 |
| **Basal cortisol, *median (IQR) nmol/L*** | 21 | 315 (301, 381) | 275 (180, 326) | 0.2 |
| **Stimulated cortisol, *median (IQR) nmol/L*** | 21 | 403 (347, 431) | 398 (312, 447) | >0.9 |
| **ACTH, *median (IQR) pmol/L*** | 21 | 48 (37, 88) | 32 (25, 72) | 0.5 |
| **BP (systolic)*, median (IQR) mmHg*** | 21 | 127 (120, 128) | 120 (110, 130) | 0.9 |
| **BP (diastolic)*, median (IQR) mmHg*** | 21 | 71 (63, 76) | 74 (70, 85) | 0.3 |
| **Heart rate, *median (IQR) bpm*** | 21 | 92 (68, 100) | 87 (79, 115) | 0.5 |
| **Hypotension, n(%)** | 21 | 0 (0.0%) | 1 (6.2%) | >0.9 |
| **Weakness, n(%)** | 21 | 3 (60.0%) | 13 (81.2%) | 0.6 |
| **Tiredness, n(%)** | 21 | 5 (100.0%) | 13 (81.2%) | 0.5 |
| **Poor appetite, n(%)** | 21 | 5 (100.0%) | 13 (81.2%) | 0.5 |
| **Weight loss, n(%)** | 21 | 4 (80.0%) | 14 (87.5%) | >0.9 |
| **Increased pigmentation of the skin, n(%)** | 18 | 2 (50.0%) | 6 (42.9%) | >0.9 |
| **Nausea, n(%)** | 21 | 4 (80.0%) | 8 (50.0%) | 0.3 |
| **Vomiting, n(%)** | 21 | 2 (40.0%) | 4 (25.0%) | 0.6 |
| **Liking for salt, n(%)** | 21 | 3 (60.0%) | 11 (68.8%) | >0.9 |
| **Hypoglycaemia, n(%)** | 21 |  |  |  |
| No |  | 5 (100.0%) | 16 (100.0%) |  |
| **Loss of consciousness** | 20 |  |  |  |
| No |  | 5 (100.0%) | 15 (100.0%) |  |
| **Diarrhoea, n(%)** | 21 | 0 (0.0%) | 6 (37.5%) | 0.3 |
| **Dizziness, n(%)** | 20 | 3 (60.0%) | 8 (53.3%) | >0.9 |
| **Shock, n(%)** | 21 |  |  |  |
| No |  | 5 (100.0%) | 16 (100.0%) |  |
| **Anorexia, n(%)** | 21 | 2 (40.0%) | 5 (31.2%) | >0.9 |
| **Loss of axillary and pubic hair, if female, n(%)** | 21 |  |  | 0.8 |
| No |  | 2 (40.0%) | 6 (37.5%) |  |
| Not applicable |  | 2 (40.0%) | 9 (56.2%) |  |
| Yes |  | 1 (20.0%) | 1 (6.2%) |  |
| **Any postural drop in blood pressure, n(%)** | 21 | 0 (0.0%) | 1 (6.2%) | >0.9 |
| **Presence of anaemia, n(%)** | 21 | 3 (60.0%) | 9 (56.2%) | >0.9 |
| **Presence of an opportunistic infection, n(%)** | 21 | 5 (100.0%) | 16 (100.0%) |  |
| **Tuberculosis, n(%)** | 21 |  |  | >0.9 |
| Yes |  | 3 (60.0%) | 8 (50.0%) |  |
| No |  | 2 (40.0%) | 8 (50.0%) |  |
| **Cryptococcus neoformans, n(%)** | 21 |  |  | >0.9 |
| Yes |  | 0 (0.0%) | 0 (0.0%) |  |
| No |  | 5 (100.0%) | 16 (100.0%) |  |
| **Toxoplasmosis, n(%)** | 21 |  |  |  |
| No |  | 5 (100.0%) | 16 (100.0%) |  |
| **Mycobacterium avium-intracellulare, n(%)** | 21 |  |  |  |
| No |  | 5 (100.0%) | 16 (100.0%) |  |
| **Kaposis sarcoma, n(%)** | 21 |  |  | >0.9 |
| Yes |  | 0 (0.0%) | 0 (0.0%) |  |
| No |  | 5 (100.0%) | 16 (100.0%) |  |
| **Cytomegalovirus, n(%)** | 21 |  |  | >0.9 |
| Yes |  | 0 (0.0%) | 1 (6.2%) |  |
| No |  | 5 (100.0%) | 15 (93.8%) |  |
| **Other, n(%)** | 21 |  |  | >0.9 |
| Yes |  | 2 (40.0%) | 8 (50.0%) |  |
| No |  | 3 (60.0%) | 8 (50.0%) |  |
| **Total CD4 count, median (IQR) µ/mL** | 21 | 17 (15, 46) | 26 (13, 50) | >0.9 |
| **Sodium, *median (IQR)* mmol/L** | 21 | 134.0 (133.0, 139.0) | 135.0 (131.8, 137.0) | 0.9 |
| **Potassium, *median (IQR) mmol/L*** | 21 | 3.60 (3.30, 3.90) | 3.80 (3.27, 4.60) | 0.6 |
| **Haemoglobin, *median (IQR)* g/dL** | 21 | 8.70 (8.10, 10.50) | 8.20 (7.57, 10.22) | 0.6 |
| **White cell count, median (IQR) x109** | 21 | 6 (4, 11) | 4 (2, 6) | 0.3 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 5: Multivariate analysis** |  | **2.5 %** | **97.5 %** | **p\_value** |
| Addisons\_disease in\_advanced\_HIV | 0.845754826746634 | 0.33738131381043 | **2.12015662304032** | **0.7209** |
| ACTH result | 1.00668199441671 | 1.00255014869532 | **1.01083086886138** | **0.0015** |
| Synacthen 30.minute.cortisol.result | 0.997387593788454 | 0.995922665372902 | **0.998854677005113** | **5,00E-04** |
| Synacthen 0.minute.cortisol.result | 1.00233465100837 | 1.00108061300997 | **1.00359025992053** | **3,00E-04** |
| BP diastolic. | 1.03684432872055 | 1.00869092420465 | **1.06578351822451** | **0.01** |
| BP systolic. | 0.980198459267326 | 0.959492859626429 | **1.00135088021824** | **0.0664** |
| Gender | 0.64469586976378 | 0.365029363004972 | **1.13862830395048** | **0.1304** |
|  |  |  |  |  |

A picture containing chart

Description automatically generated

Fig 1: Kaplan-Meier survival curve over time

|  |  |
| --- | --- |
| **Table 3. Causes of AI in HIV-infected Patients** | |
| **Primary AI** | **Secondary/Tertiary AI** |
| Infection   * Cytomegalovirus * Tuberculosis * HIV * Histoplasmosis * Cryptococcus * Toxoplasmosis   Tumor   * Kaposi’s sarcoma * Lymphoma   Autoimmune  Hemorrhage  Medications   * Ketoconazole * Fluconazole * Rifampin * Etomidate | Infection/Infiltration   * Tuberculosis * Sarcoid * Hemochromatosis   Isolated ACTH Deficiency  Tumor  Trauma  Medications   * Exogenous steroids * Megesterol |