**Adrenal insufficiency associated with advanced HIV may explain the high mortality.**

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**Abstract:**

**Background:**

Sub-Saharan Africa is burdened by a vast HIV-positive population, at risk of life-threatening AIDS defining illnesses. AIDS defining illnesses and disseminated opportunistic infections have been associated with both primary adrenal insufficiency (PAI) and secondary adrenal insufficiency (SAI). We hypothesized that hypoadrenalism may partially account for the high mortality seen with advanced HIV.

**Materials & Methods:**

We undertook a prospective case-finding study of HIV-positive patients presenting with advanced disease who were 18 years or older, with a CD4 count of less than 100 cells/ mm3, and a coexistent opportunistic infection. Exclusion criteria were use of oral, intravenous or inhaled steroids in the previous 3 months. A tetracosactide test was performed in patients with random cortisol concentrations in the morning of less than 500 nmol/L.

**Results:**

**Conclusion:**

**Introduction:**

Adrenal insufficiency caused by deficiency of glucocorticoids and mineralocorticoids is an invariably fatal medical condition without treatment. Prior to the availability of glucocorticoids, the majority of the primary adrenal insufficiency patients died within 2 years of diagnosis (1). Autoimmune adrenal insufficiency predominates in European populations, (2) and in South Africa, despite the high background prevalence of tuberculosis (TB) (3). Our recent survey suggests that coexistent infections are a significant cause of primary adrenal insufficiency in sub-Saharan Africa with34% and 29.8% of the cohort being accounted for by TB and Acquired Immune Deficiency Syndrome (AIDS), respectively (4).

Patients with Human Immune Deficiency Virus (HIV) may suffer from primary adrenal insufficiency due to *inter alia* tuberculosis, *Mycobacterium avium Intracellulare* (MAI), cytomegalovirus (CMV), toxoplasmosis, *Pneumocystis carinii*, histoplasmosis, malignancies such as non-Hodgkin’s lymphoma and Kaposi sarcoma (KS), fungal infections such as cryptococcus, blastomycosis, and histoplasmosis. (Reference) Secondary adrenal insufficiency may be caused by tuberculosis, toxoplasmosis and cytomegalovirus infection. (Eldrisi & Verghese).

There are varied results describing the prevalence of hypoadrenalism in patients with HIV. In a Pakistan study by Afreen *et al*, of 64 HIV infected, predominantly male patients (84.9%), adrenal insufficiency (AI) was reported in 9 (14.0%), using the of 250 microgram intravenous tetracosactide test and a 60 minutes cortisol concentration of less than 18 microgram/dl (500 nmol/L),(8) whereas in a Nigerian study of 43 newly diagnosed HIV positive patients who had not been initiated on antiretroviral treatment, reported the AI incidence to be 34.8%, using a 1 microgram tetracosactide test (9) and a 30minute cortisol of less than 500 nmol/L.

There is a high background prevalence of 9% (10) of HIV infection (7) in sub-Saharan Africa, which is associated with significant mortality estimated in 2001 to be 2.2 million of 3 million deaths worldwide (12). Compared to Europe and North America, early mortality in HIV positive patients is higher in resource limited settings, including South Africa, (12) due to late presentation and inadequate health resources.

Although undiagnosed adrenal insufficiency is associated with invariably high mortality (13), patients receiving replacement therapy have poorer survival due in part to cardiovascular, malignant and infectious diseases, compared to background populations (14) (15). It has also been established that both overtreatment and insufficient replacement with glucocorticoids during infections and stress-related events confer a higher mortality. (Gudmundur (2015), 82, 2-11)

Since adrenal insufficiency is one of the endocrine complications of HIV, we hypothesized that it may also be one of the additional causes of mortality. Moreover, we considered that initiation of appropriate replacement therapy for adrenal insufficiency may confer a positive impact on mortality. Our objectives were to determine the incidence of hypoadrenalism among ill, hospitalized HIV-infected patients. In addition, we wished to explore the positive predictive clinical and biochemical characteristics for adrenal insufficiency, and the predictors for survival.

**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 of 2013. We undertook a prospective case-finding of HIV positive patients, presenting with advanced disease and an opportunistic infection to an acute tertiary care medical ward. All the participants provided written informed consent. If participants were affected by delirium the research and ethics committee permitted us to take retrospective informed consent, with the view of limiting bias and providing an opportunity for all patients to receive potentially life-saving treatment.

*Inclusion and exclusion criteria*

Inclusion criteria included age 18 years and older, and a CD4 count of 100 cells per mm3 or fewer and an opportunistic infection. The use of oral, topical or inhaled steroids in the previous 3 months represented an exclusion criterion.

*Data extraction*

Demographic and clinical data were obtained from history and physical examination. Records of routine biochemistry, haematology and microbiology were extracted from the National Health Laboratory Service (NHLS) repository. Patients who met the inclusion criteria had blood samples taken for serum cortisol and plasma ACTH between 08:00 and 09:00 on the day of enrolment. Where the random serum cortisol was less than 500 nmol/L, a short 250 µg intravenous tetracosactide stimulation test was performed, usually on the following day.

*Biochemical measures of plasma ACTH and serum cortisol*

For the random plasma ACTH and cortisol concentration, clotted blood and plasma were submitted to Lancet laboratory which analyzed the samples on the Cobas immunoassay platform.

*The tetracosactide test*

The samples for plasma ACTH and cortisol were submitted to the National Health Laboratory Services (NHLS). The method employed by this laboratory is the Roche (Modular Analytics E170). Blood was taken at 0 minutes for serum cortisol, followed by 250 µg of intravenously administered tetracosactide and a 30-minute serum cortisol was taken at conclusion of the test. Adrenal insufficiency was excluded if a 30-minute serum cortisol exceeded 500 nmol/L. In patients with confirmed cortisol deficiency, a plasma ACTH above the upper limit of the reference range (67.7 pg/mL) was consistent with primary adrenal insufficiency, (Bornstein et al 2016) while low or normal ACTH is consistent with secondary adrenal insufficiency. (Pazderka et al 2017)

*Determination of survival*

Telephonic follow-up was performed to determine post discharge survival via direct patient or family contact. A hospital database (Clinicom®) also corroborated survival, by virtue of their attendance at various clinics in the drainage area of our tertiary hospital facility.

**Statistical analysis:**

Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as medians 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 AI and various risk factors. Multivariable logistic regression analysis was used to identify independent predictors of AI. We ranked CD4 counts into tertiles of 0-33; 34-66 and 67-100, respectively to determine if AI was associated. Statistical analyses were performed using STATA Statistical Software version 15 (StataCorp, College Station, Tx, USA, 2017).The significance level was set at *p*<0.005. For analysis of survival data, we described those who were discharged from the hospital within 3 months (early survivors), followed by 6 months (intermediate survivors), and 12 months follow-up (late survivors).

**Results:**

A total of 559 patients were recruited, of whom 10 withdrew from participation and 549 participants were included in the final analysis. The median age at enrollment was 36 years interquartile range (IQR) (31.5-43.0) years and when subdivided by CD4 count, the median age for the lowest tertile was 35 years (30.5-42.0) years compared to 37 years (32.-43.3) and 37 (33.0-46.0) years for the remaining tertiles, respectively. See Table 1.

When comparing patient characteristics of CD4 counts by tertiles, patients with the lowest CD4 count, were significantly younger at enrolment 35.0 IQR (30.5-42) compared with 37.0 (32.0-43.3) years and 37.0 (33.0-36.0) years; *p*=0.016. The distribution of gender and ethnicity did not differ significantly by CD4 count. Duration of illness in days median (IQR) was 14 days *p*=0.036. As expected, the participants with lowest CD4 CD4 counts had the highest viral load; *p*=0.001.

The occurrence of opportunistic infections for example, tuberculosis, pneumonia, candida and cryptococcus did not differ across the CD4 tertiles. The log viral load was higher in the lowest tertile 11.6 (9.3-12.8); *p*<0.001. The white cell count, lymphocyte and neutrophil counts were lower in the lowest CD4 tertile; 5.0 (2.9-7.4), 0.6 (0.3-1.3), and 2.4 (0.3-1.3) respectively compared to the remaining tertiles. You do not discuss duration of current illness

**Clinical characteristics**

Table 1: Patient presentation by CD4 count in tertiles

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable |  | **0 - 33**, N = 2711 | **34 - 66**, N = 1521 | **67 - 100**, N = 1191 | **p-value**2 |
| Age at enrolment, median (IQR) (years) |  | 35.0 (30.5, 42.0) | 37.0 (32.0, 43.3) | 37.0 (33.0, 46.0) | **0.016** |
| Gender, *N*(%) |  |  |  |  | 0.3 |
| Female |  | 137 (50.6%) | 85 (55.9%) | 55 (46.6%) |  |
| Male |  | 134 (49.4%) | 67 (44.1%) | 63 (53.4%) |  |
| Ethnicity, *N*(%) |  |  |  |  | 0.3 |
| Black African |  | 220 (81.2%) | 117 (77.0%) | 89 (74.8%) |  |
| Other |  | 51 (18.8%) | 35 (23.0%) | 30 (25.2%) |  |
| Duration of current illness, median (IQR) (days) |  | 14.0 (14.0, 21.0) | 14.0 (12.5, 22.5) | 14.0 (7.0, 21.0) | **0.036** |
| Weight loss |  | 231 (87.5%) | 129 (87.2%) | 92 (82.9%) | 0.5 |
| log10 viral load |  | 11.6 (9.3, 12.8) | 8.9 (6.5, 12.2) | 7.3 (3.9, 10.6) | **<0.001** |
| Opportunistic infections |  |  |  |  |  |
| Tuberculosis |  | 230 (84.9%) | 131 (86.2%) | 98 (82.4%) | 0.7 |
| Cryptococcus neoformans |  | 16 (5.9%) | 5 (3.3%) | 9 (7.6%) | 0.3 |
| Pneumonia |  | 30 (11.1%) | 19 (12.5%) | 13 (10.9%) | 0.9 |
| Staph aureus |  | 1 (0.4%) | 0 (0.0%) | 0 (0.0%) | >0.9 |
| Kaposis sarcoma |  | 6 (2.2%) | 0 (0.0%) | 0 (0.0%) | 0.055 |
| Cytomegalovirus |  | 0 (0.0%) | 1 (0.7%) | 0 (0.0%) | 0.5 |
| Herpes simplex virus |  | 3 (1.1%) | 4 (2.6%) | 1 (0.8%) | 0.4 |
| Hepatitis B |  | 9 (3.3%) | 8 (5.3%) | 1 (0.8%) | 0.13 |
| Candida |  | 21 (7.7%) | 11 (7.2%) | 2 (1.7%) | 0.064 |
| Gastroenteritis |  | 12 (4.4%) | 7 (4.6%) | 4 (3.4%) | 0.9 |
| Parvo B19 |  | 0 (0.0%) | 1 (0.7%) | 0 (0.0%) | 0.5 |
| Syphilis |  | 8 (3.0%) | 7 (4.6%) | 1 (0.8%) | 0.2 |
| Bacterial meningitis |  | 3 (1.1%) | 1 (0.7%) | 2 (1.7%) | 0.8 |
| Urinary tract infection |  | 4 (1.5%) | 0 (0.0%) | 3 (2.5%) | 0.13 |
| Pneumocystis Jiroveci Pneumonia |  | 4 (1.5%) | 1 (0.7%) | 0 (0.0%) | 0.5 |
| COVID-19 |  | 1 (0.4%) | 1 (0.7%) | 0 (0.0%) | >0.9 |
| Neurocysticercosis |  | 1 (0.4%) | 1 (0.7%) | 0 (0.0%) | >0.9 |
| Haematological parameters |  |  |  |  |  |
| White cell count X109 |  | 5.0 (2.9, 7.4) | 5.8 (4.2, 8.4) | 6.8 (4.5, 9.7) | **<0.001** |
| Lymphocyte count X109 |  | 0.6 (0.3, 1.3) | 0.9 (0.5, 5.8) | 1.3 (0.8, 3.0) | **0.011** |
| Neutrophils X109 |  | 2.4 (1.0, 5.9) | 6.6 (2.8, 15.7) | 5.1 (2.9, 11.5) | **0.002** |
| ART exposure |  | 101 (37.3%) | 62 (40.8%) | 44 (37.0%) | 0.7 |
| Kidney medication |  | 27 (10.0%) | 16 (10.5%) | 9 (7.6%) | 0.7 |
| TB medication |  | 5 (1.8%) | 3 (2.0%) | 6 (5.0%) | 0.2 |
| Fungal medication |  | 2 (0.7%) | 1 (0.7%) | 3 (2.5%) | 0.3 |

*1* Median (IQR); 2Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

The cohort comprised mainly black Africans 430/549 (78.3%), mixed ancestry 105/549 (20%), and white 2/549 (0.4%) participants. Most of the patients were female 280/549 (51.1%). The median (IQR) duration of the presenting illness was 14 (14-21) days with the major complaint being weight loss 461/549 (86.1%). By far the most common opportunistic infection was tuberculosis in 461/549 (84%), followed by pneumonia at 62/549 (11.3%), candida in 34/549 (6.2%), and Cryptococcus infection in 30/549 (5.5%).

Table 2: Clinical associations with antiretroviral therapy in this cohort

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Treatment naïve N = 341 | HAART\* N = 207 | p-value |
| Age at enrolment | 36.0 (31.0, 43.0) | 36.0 (32.0, 43.0) | 0.7 |
| Gender, *N* (%) |  |  | 0.4 |
| Female | 169 (49.6%) | 111 (53.6%) |  |
| Male | 172 (50.4%) | 96 (46.4%) |  |
| Black African Ethnicity, *N* (%) |  |  | **0.040** |
| Black African | 258 (75.7%) | 172 (83.1%) |  |
| Other | 83 (24.3%) | 35 (16.9%) |  |
| Duration of current illness, median (IQR) (days) | 14.0 (12.0, 21.0) | 14.0 (10.0, 21.0) | 0.6 |
| Weight loss | 279 (86.6%) | 172 (85.1%) | 0.6 |
| Viral load (log10 copies/ml) | 10.6 (6.2, 12.3) | 10.8 (7.8, 12.3) | 0.5 |
| Opportunistic infections |  |  |  |
| Tuberculosis | 282 (82.7%) | 179 (86.5%) | 0.2 |
| *Cryptococcus neoformans* | 24 (7.0%) | 6 (2.9%) | **0.039** |
| Pneumonia | 38 (11.1%) | 24 (11.6%) | 0.9 |
| Staph aureus | 1 (0.3%) | 0 (0.0%) | >0.9 |
| Kaposis sarcoma | 3 (0.9%) | 3 (1.4%) | 0.7 |
| Cytomegalovirus | 1 (0.3%) | 0 (0.0%) | >0.9 |
| Herpes simplex virus (HSV) | 3 (0.9%) | 5 (2.4%) | 0.2 |
| Hepatitis B | 10 (2.9%) | 8 (3.9%) | 0.6 |
| Candida | 23 (6.7%) | 11 (5.3%) | 0.5 |
| Gastroenteritis | 11 (3.2%) | 12 (5.8%) | 0.15 |
| Parvo B19 | 0 (0.0%) | 1 (0.5%) | 0.4 |
| Syphilis | 14 (4.1%) | 3 (1.4%) | 0.082 |
| B menigitis | 4 (1.2%) | 2 (1.0%) | >0.9 |
| Urinary tract infection | 4 (1.2%) | 3 (1.4%) | >0.9 |
| Pneumocystis Jiroveci pneumonia | 5 (1.5%) | 0 (0.0%) | 0.2 |
| COVID-19 | 2 (0.6%) | 0 (0.0%) | 0.5 |
| Neurocysticercosis | 0 (0.0%) | 2 (1.0%) | 0.14 |
| Total CD4 count | 32.5 (13.3, 61.8) | 34.0 (16.0, 61.5) | 0.8 |
| White cell count x109 | 5.2 (3.4, 7.6) | 5.8 (4.0, 8.9) | 0.076 |
| Lymphocyte count x109 | 0.9 (0.4, 3.9) | 0.7 (0.4, 1.3) | 0.2 |
| Neutrophils | 3.7 (1.5, 8.3) | 3.3 (1.7, 7.4) | 0.8 |
| **Kidney medication** | 30 (8.8%) | 22 (10.6%) | 0.5 |

1Median (IQR); n (%); 2Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

**Comparison of patients with adrenal insufficiency and those without**

When comparing patients with those without adrenal insufficiency, there were no differences. See table 3 As expected, there were differences in the random basal and stimulated cortisol between the AI and non-AI groups, with the former group demonstrating lower concentrations of all serum cortisol parameters; p<0.001. Cryptococcal infection occurred more prevalently among patients with adrenal insufficiency compared with those without 37% vs 3.8%; p<0.001, The median serum sodium concentration was elevated 135 mmol/L (IQR: 133.0-137.5) vs 133 mmol/L (IQR: 130.0-137.0) in the non-adrenal insufficiency group; p=0.033, while the absolute neutrophil count was lower adrenal insufficiency group 1.3 mmol/L (IQR: 0.9-1.6) vs 3.8 mmol/L (IQR: 1.6-8.9); p=0.037. Table 3

Table 3: Comparison of clinical characteristics in patients with adrenal insufficiency with those without

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | AI, N = 271 | No-AI, N = 5221 | p-value2 |
| Age at enrolment, median (IQR) (years) | 36.0 (32.0,47.5) | 36.0 (31.8,43.0) | 0.4 |
| Gender, N(%) |  |  | >0.9 |
| Female | 14 (51.9%) | 266 (51.1%) |  |
| Males | 13 (48.1%) | 255 (48.9%) |  |
| Ethnicity, N(%) |  |  | 0.4 |
| Black African | 23 (85.2%) | 407 (78.0%) |  |
| Other | 4 (14.8%) | 115 (22.0%) |  |
| Duration of current illness, median (IQR) (days) | 14.0 (14.0, 27.8) | 14.0 (11.8, 21.0) | 0.4 |
| Weight loss | 22 (81.5%) | 430 (86.3%) | 0.4 |
| Viral load (log10 Copies/mL) | 11.0 (10.7, 11.3) | 10.8 (7.1, 12.3) | 0.9 |
| PTB | 11 (40.7%) | 337 (64.6%) | **0.012** |
| EPTB | 10 (37.0%) | 99 (19.0%) | **0.022** |
| Cryptococcus neoformans | 10 (37.0%) | 20 (3.8%) | **<0.001** |
| Pneumonia | 3 (11.1%) | 59 (11.3%) | >0.9 |
| Kaposis sarcoma | 1 (3.7%) | 5 (1.0%) | 0.3 |
| Herpes simplex virus | 1 (3.7%) | 7 (1.3%) | 0.3 |
| Hepatitis B | 2 (7.4%) | 16 (3.1%) | 0.2 |
| Candida | 1 (3.7%) | 33 (6.3%) | >0.9 |
| Gastroenteritis | 0 (0.0%) | 23 (4.4%) | 0.6 |
| Total CD4 count | 28.0 (13.5, 49.5) | 34.0 (15.0, 63.0) | 0.4 |
| White cell count X109 | 5.2 (2.8, 8.9) | 5.6 (3.8, 8.1) | 0.5 |
| Lymphocyte count X109 | 0.9 (0.5, 1.2) | 0.8 (0.4, 2.0) | 0.7 |
| Neutrophils mmol/L | 1.3 (0.9, 1.6) | 3.8 (1.6, 8.9) | **0.037** |
| Sodium mmol/L | 135.0 (133.0, 137.5) | 133.0 (130.0, 137.0) | **0.033** |
| Potassium mmol/L | 3.9 (3.3, 4.3) | 4.1 (3.6, 4.6) | 0.069 |
| Haemoglobin g/dL | 8.7 (7.6, 10.4) | 8.7 (7.4, 10.3) | 0.6 |
| BP (systolic) | 120.0 (102.5, 128.5) | 111.0 (102.0, 125.0) | 0.4 |
| BP (diastolic) | 71.0 (66.5, 80.0) | 70.0 (60.0, 79.0) | 0.08 |
| Heart rate | 87.0 (78.5, 107.0) | 91.0 (79.0, 108.8) | 0.7 |
| Hypotension | 1 (3.7%) | 46 (9.3%) | 0.5 |
| Weakness | 21 (77.8%) | 422 (85.1%) | 0.3 |
| Tiredness | 23 (85.2%) | 423 (85.1%) | >0.9 |
| Poor appetite | 22 (81.5%) | 374 (75.9%) | 0.5 |
| Increased pigmentation of the skin | 9 (37.5%) | 247 (50.8%) | 0.2 |
| Nausea | 16 (59.3%) | 263 (53.0%) | 0.5 |
| Vomiting | 8 (29.6%) | 137 (27.7%) | 0.8 |
| Liking for salt | 19 (70.4%) | 262 (53.0%) | 0.078 |
| Hypoglycaemia | 0 (0.0%) | 11 (2.2%) | >0.9 |
| Loss of consciousness | 0 (0.0%) | 7 (1.4%) | >0.9 |
| Diarrhoea | 8 (29.6%) | 219 (44.5%) | 0.13 |
| Dizziness | 13 (50.0%) | 236 (47.8%) | 0.8 |
| Shock | 0 (0.0%) | 5 (1.0%) | >0.9 |
| Anorexia | 8 (29.6%) | 234 (47.3%) | 0.073 |
| Loss of axillary and pubic hair, if female |  |  | 0.5 |
| Any postural drop in blood pressure | 2 (7.4%) | 21 (4.3%) | 0.3 |
| Presence of anaemia | 13 (50.0%) | 290 (58.8%) | 0.4 |
| mortality | 6 (50.0%) | 60 (43.5%) | 0.7 |
| ART exposure | 6 (22.2%) | 201 (38.5%) | 0.089 |
| Kidney medication | 5 (18.5%) | 47 (9.0%) | 0.2 |
| Rifampicin | 1 (3.7%) | 44 (8.4%) | 0.7 |
| Fluconazole | 11 (40.7%) | 63 (12.1%) | <0.001 |
| Opiates | 12 (44.4%) | 114 (21.8%) | 0.006 |

1Median (IQR); n (%); 2Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variable | **Non-AI vs AI** | | | | | |
| **No-AI, *N* = 5221** | | **AI, *N* = 27** | | **p-value2** | |
| Age at enrolment, median (IQR) (years) | 36.0 (31.8,43.0) | | 36.0 (32.0,47.5) | | | 0.4 |
| Gender, *N*(%) | | |  | | | >0.9 |
| Female | 266 (51.1%) | | 14 (51.9%) | | | |
|  |  | |  | | | |
| Ethnicity, *N*(%) | | |  | | | 0.4 |
| Black African | 407 (78.0%) | | 23 (85.2%) | | | |
| Other | 115 (22.0%) | | 4 (14.8%) | | |  |
| Duration of current illness, median (IQR) (days) | 14.0 (11.8, 21.0) | | 14.0 (14.0, 27.8) | | | 0.4 |
| Weight loss | 430 (86.3%) | | 22 (81.5%) | | | 0.4 |
| Viral load (log10 Copies/mL) | 10.8 (7.1, 12.3) | | 11.0 (10.7, 11.3) | | | 0.9 |
| Tuberculosis | 440 (84.3%) | | 21 (77.8%) | | | 0.4 |
| *Cryptococcus neoformans* | 20 (3.8%) | | 10 (37.0%) | | | **<0.001** |
| Pneumonia | 59 (11.3%) | | 3 (11.1%) | | | >0.9 |
|  |  | |  | | |  |
| Kaposis sarcoma | 5 (1.0%) | | 1 (3.7%) | | | 0.3 |
|  |  | |  | | |  |
| Herpes simplex virus | 7 (1.3%) | | 1 (3.7%) | | | 0.3 |
| Hepatitis B | 16 (3.1%) | | 2 (7.4%) | | | 0.2 |
| Candida | 33 (6.3%) | | 1 (3.7%) | | | >0.9 |
| Gastroenteritis | 23 (4.4%) | | 0 (0.0%) | | | 0.6 |
|  |  | |  | | |  |
| Total CD4 count | 34.0 (15.0, 63.0) | | 28.0 (13.5, 49.5) | | | 0.4 |
| White cell count X109 | 5.6 (3.8, 8.1) | | 5.2 (2.8, 8.9) | | | 0.5 |
| Lymphocyte count X109 | 0.8 (0.4, 2.0) | | 0.9 (0.5, 1.2) | | | 0.7 |
| Neutrophils mmol/L | 3.8 (1.6, 8.9) | | 1.3 (0.9, 1.6) | | | **0.037** |
| Sodium mmol/L | 133.0 (130.0, 137.0) | | 135.0 (133.0, 137.5) | | | **0.033** |
| Potassium mmol/L | 4.1 (3.6, 4.6) | | 3.9 (3.3, 4.3) | | | 0.069 |
| Haemoglobin g/dL | 8.7 (7.4, 10.3) | | 8.7 (7.6, 10.4) | | | 0.6 |
| BP (systolic) | 111.0 (102.0, 125.0) | | 120.0 (102.5, 128.5) | | | 0.4 |
| BP (diastolic) | 70.0 (60.0, 79.0) | | 71.0 (66.5, 80.0) | | | 0.080 |
| Heart rate | 91.0 (79.0, 108.8) | | 87.0 (78.5, 107.0) | | | 0.7 |
| Hypotension | 46 (9.3%) | | 1 (3.7%) | | | 0.5 |
| Weakness | 422 (85.1%) | | 21 (77.8%) | | | 0.3 |
| Tiredness | 423 (85.1%) | | 23 (85.2%) | | | >0.9 |
| Poor appetite | 374 (75.9%) | | 22 (81.5%) | | | 0.5 |
| Increased pigmentation of the skin | 247 (50.8%) | | 9 (37.5%) | | | 0.2 |
| Nausea | 263 (53.0%) | | 16 (59.3%) | | | 0.5 |
| Vomiting | 137 (27.7%) | | 8 (29.6%) | | | 0.8 |
| Liking for salt | 262 (53.0%) | | 19 (70.4%) | | | 0.078 |
| Hypoglycaemia | 11 (2.2%) | | 0 (0.0%) | | | >0.9 |
| Loss of consciousness | 7 (1.4%) | | 0 (0.0%) | | | >0.9 |
| Diarrhoea | 219 (44.5%) | | 8 (29.6%) | | | 0.13 |
| Dizziness | 236 (47.8%) | | 13 (50.0%) | | | 0.8 |
| Shock | 5 (1.0%) | | 0 (0.0%) | | | >0.9 |
| Anorexia | 234 (47.3%) | | 8 (29.6%) | | | 0.073 |
| Loss of axillary and pubic hair, if female | | 95 (18.9%) | | 3 (11.1%) | | 0.5 |
| Any postural drop in blood pressure | 21 (4.3%) | | 2 (7.4%) | | | 0.3 |
| Presence of anaemia | 290 (58.8%) | | 13 (50.0%) | | | 0.4 |
| mortality | 60 (43.5%) | | 6 (50.0%) | | | 0.7 |
| ART exposure | 201 (38.5%) | | 6 (22.2%) | | | 0.089 |
| Kidney medication | 47 (9.0%) | | 5 (18.5%) | | | 0.2 |

1Median (IQR); n (%); 2Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

**Please describe the P-value and what it compares here.**

.

A graph of a number of different colored squares

Description automatically generated with medium confidence

**Fig 1:** Comparison of cortisol concentrations in adrenal insufficiency versus those without adrenal insufficiency in respect of the random serum, basal, stimulated cortisol concentrations and plasma ACTH. Cortisol in nmol/L and ACTH in pg/ml. \*\*\*\* representing p<0.001 and ns representing a non-significant p-value.

Please label the table adequately and put in the units and remove the group please. For the p value, you can put an asterisk with a P-value <0.001 or whatever the case is

**Mortality analysis among the AI and Non-AI patients**

The mortality rate was 60/522 (11.49%) and 6/27 (22.22%) in the patients without versus those with adrenal insufficiency, respectively. There was no significant difference immortality at three months, six months and 12 months for the Patients with adrenal insufficiency when compared with those without adrenal insufficiency .

A graph showing the results of a test

Description automatically generated with medium confidence

Fig 1: The Kaplan-Meier survival curve over time comparing patients with and without adrenal insufficiency

please insert an asterisk in the figure where it is significant

**Please describe the differences in cortisol concentrations in detail (Table 4)**

expected, the cortisol concentrations were elevated in non-AI patients with the random cortisol concentration of 477 (368-615) nmol/L vs 307 IQR (262-336) nmol/L p=0.004, basal cortisol of 500 IQR (433-636) vs 308 IQR (246-365) p<0.001, stimulated cortisol concentration of 795 IQR (662-890) vs 375 IQR (338-424) p<0.001). Mortality in the adrenal insufficiency group was significantly higher than in the non AI group with respect to extra pulmonary tuberculosis at 3/6(50%) versus 7/60 (11.7%), *p=0.04*. Mortality due to cryptococcal neoformans was significantly higher in the adrenal insufficient group this is the non-adrenal insufficient group at 3/6 (50%) versus 3/60 (5%), p=0.008. There were no significant differences in mortality between these groups in respect to other demographics, clinical history, clinical findings, and other investigations. Table 4

**Table 4: Comparison of Mortality among Non-AI vs AI patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **1, N = 601** | **2, N = 61** | **p-value2** |
| **Age at enrolment, median (IQR) (years)** | 38 (33, 44) | 41 (33, 46) | 0.6 |
| **Gender, n(%)** |  |  | >0.9 |
| **Female** | 32 (53.3%) | 3 (50.0%) |  |
| **Male** | 28 (46.7%) | 3 (50.0%) |  |
| **Black African ethnicity, n (%)** |  |  | 0.2 |
| **Black African** | 52 (86.7%) | 4 (66.7%) |  |
| **Other** | 8 (13.3%) | 2 (33.3%) |  |
| **Duration of current illness, median (IQR) (days)** | 14 (14, 21) | 14 (11, 14) | 0.079 |
| **Random cortisol** | 477 (368, 615) | 307 (262, 336) | **0.004** |
| **Basal cortisol** | 500 (433, 636) | 308 (246, 365) | **<0.001** |
| **Stimulated cortisol** | 795 (662, 890) | 375 (338, 424) | **<0.001** |
| **Weight loss** | 51 (87.9%) | 4 (66.7%) | 0.2 |
| **Viral load (log10 Copies/mL)** | 11.74 (9.55, 13.08) | - |  |
| **PTB** | 42 (70.0%) | 2 (33.3%) | 0.090 |
| **EPTB** | 7 (11.7%) | 3 (50.0%) | **0.040** |
| **Cryptococcus neoformans** | 3 (5.0%) | 3 (50.0%) | **0.008** |
| **Pneumonia** | 7 (11.7%) | 0 (0.0%) | >0.9 |
| **Herpes simplex virus HSV** | 1 (1.7%) | 0 (0.0%) | >0.9 |
| **Hepatitis B** | 0 (0.0%) | 1 (16.7%) | 0.091 |
| **Candida** | 4 (6.7%) | 0 (0.0%) | >0.9 |
| **Syphilis** | 3 (5.0%) | 0 (0.0%) | >0.9 |
| **Bacterial meningitis** | 1 (1.7%) | 0 (0.0%) | >0.9 |
| **Urinary tract infection** | 1 (1.7%) | 0 (0.0%) | >0.9 |
| **Pneumocystis Jiroveci Pneumonia** | 2 (3.3%) | 0 (0.0%) | >0.9 |
| **COVID-19** | 0 (0.0%) | 0 (0.0%) |  |
| **Neurocysticercosis** | 0 (0.0%) | 0 (0.0%) |  |
| **Total CD4 count** | 28 (14, 55) | 30 (16, 45) | 0.7 |
| **White cell count x109** | 5.2 (3.4, 7.4) | 8.3 (4.3, 27.5) | 0.2 |
| **Sodium mmol/L** | 133.0 (128.0, 136.0) | 136.5 (133.3, 139.0) | 0.15 |
| **Potassium mmol/L** | 3.95 (3.60, 4.57) | 3.70 (3.37, 3.88) | 0.077 |
| **Haemoglobin g/dL** | 8.20 (7.00, 9.63) | 9.60 (8.25, 10.95) | 0.3 |
| **BP (systolic)** | 110 (102, 120) | 128 (122, 130) | 0.059 |
| **BP (diastolic)** | 71 (67, 80) | 74 (65, 78) | 0.8 |
| **Heart rate** | 91 (82, 108) | 87 (72, 98) | 0.3 |
| **Hypotension** | 7 (12.1%) | 0 (0.0%) | >0.9 |
| **Weakness** | 54 (93.1%) | 4 (66.7%) | 0.093 |
| **Tiredness** | 53 (93.0%) | 6 (100.0%) | >0.9 |
| **Poor appetite** | 51 (87.9%) | 6 (100.0%) | >0.9 |
| **Increased pigmentation of the skin** | 36 (63.2%) | 2 (40.0%) | 0.4 |
| **Nausea** | 37 (63.8%) | 5 (83.3%) | 0.7 |
| **Vomiting** | 15 (25.9%) | 2 (33.3%) | 0.7 |
| **Liking for salt** | 38 (65.5%) | 4 (66.7%) | >0.9 |
| **Hypoglycaemia** | 2 (3.4%) | 0 (0.0%) | >0.9 |
| **Loss of consciousness** | 2 (3.4%) | 0 (0.0%) | >0.9 |
| **Diarrhoea** | 33 (56.9%) | 1 (16.7%) | 0.090 |
| **Dizziness** | 34 (59.6%) | 3 (50.0%) | 0.7 |
| **Shock** | 2 (3.4%) | 0 (0.0%) | >0.9 |
| **Anorexia** | 35 (60.3%) | 2 (33.3%) | 0.2 |
| **Loss of axillary and pubic hair, if female** | 19 (33.3%) | 1 (16.7%) | 0.8 |
| **Any postural drop in blood pressure** | 4 (7.0%) | 0 (0.0%) | >0.9 |
| **Presence of anaemia** | 38 (65.5%) | 3 (50.0%) | 0.7 |

1Median (IQR); n (%); 2Wilcoxon rank sum test; Fisher's exact test.

**Factors associated with time to mortality**

When we performed bivariate Cox proportions regression analyses, a pg/L increase in the ACT was significantly associated with a 1% increase in the hazard of mortality (HR = 1.01, (95%CI:1.00, 1.01), *P <0.001*). a nmol/L increase in the incremental cortisol was significantly associated with X% hazard of mortality (HR = X.XX, (95%CI: X.XX, X.XX), P = 0.032). Patients with a poor appetite were significantly associated with 2.66 increased hazard of mortality (HR = 2.66, (95%CI: 1.21, 5.83), *p = 0.015*). Having Nausea was significantly associated with 73% increase in the hazard of mortality (HR = 1.73,) ((%%CI:1.03, 2.89), *P = 0,038*). Salt craving was significantly associated with 69% increase in the hazard of mortality (HR = 1.69, ((%%CI: 1.01, 2.83), *P = 0.046*). Loss of auxiliary and pubic hair was significantly associated with a 2.62 increased hazard of mortality (HR = 2.62, ((%%CI: 1.32, 5.18), *P =0.006*). Pneumocystis Jiroveci Pneumonia was a associated with a 4.24 increase in the hazard of mortality (HR = 4.24, ((%%CI: 1.04, 17.30), *p = 0.044*). A one log10 copies/ml increase in the HIV viral load was significantly associated with a19% increase in the hazard of mortality (HR = 1.19, (95%CI:1.01, 1.41), *p = 0.036*).

In the multivariate analysis, after adjusting for viral load, cryptococcus neoformans, and CD4 count, a 50 nmol/L increase in the basal cortisol was associated with 9% increase in the hazard of mortality (aHR = 1.09, (95%CI:1.01, 1.17), P = 0.027)

**Table 5: Bivariate and Multivariate analysis of the entire cohort.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Characteristic | Bivariate | | | multivariate - Cox PH | | |
| HR1 | 95% CI1 | p-value | aHR1 | 95% CI1 | p-value |
| Age at enrolment | 1.02 | 0.99, 1.04 | 0.2 |  |  |  |
| Gender | 0.92 | 0.56, 1.49 | 0.7 |  |  |  |
| Black African Ethnicity | 1.59 | 0.8116, 3.117 | 0.176 |  |  |  |
| Random cortisol | 1.00 | 1.00, 1.00 | 0.6 |  |  |  |
| Basal cortisol | 1.00 | 1.00, 1.00 | 0.15 | 1.09 | 1.01, 1.17 | **0.027** |
| Stimulated cortisol | 1.00 | 1.00, 1.00 | >0.9 |  |  |  |
| ACTH | 1.01 | 1.00, 1.01 | **<0.001** |  |  |  |
| BP systolic | 0.99 | 0.98, 1.01 | 0.3 |  |  |  |
| BP diastolic | 1.02 | 1.00, 1.03 | 0.066 |  |  |  |
| incremental cortisol | 1.00 | 0.99, 1.02 | **0.032** |  |  |  |
| Heart rate | 1.00 | 0.99, 1.02 | 0.5 |  |  |  |
| Hypotension | 1.25 | 0.57, 2.75 | 0.6 |  |  |  |
| Weakness | 1.78 | 0.77, 4.12 | 0.2 |  |  |  |
| Tiredness | 2.67 | 0.97, 7.35 | 0.057 |  |  |  |
| Poor appetite | 2.66 | 1.21, 5.83 | **0.015** |  |  |  |
| Weight loss | 0.98 | 0.48, 1.98 | >0.9 |  |  |  |
| Increased pigmentation of the skin | 1.60 | 0.96, 2.66 | 0.072 |  |  |  |
| Nausea | 1.73 | 1.03, 2.89 | **0.038** |  |  |  |
| Vomiting | 0.95 | 0.55, 1.65 | 0.9 |  |  |  |
| Liking for salt | 1.69 | 1.01, 2.83 | **0.046** |  |  |  |
| Hypoglycaemia | 1.49 | 0.36, 6.07 | 0.6 |  |  |  |
| Loss of consciousness | 2.57 | 0.63, 10.5 | 0.2 |  |  |  |
| Diarrhoea | 1.48 | 0.91, 2.42 | 0.12 |  |  |  |
| Dizziness | 1.59 | 0.96, 2.63 | 0.069 |  |  |  |
| Shock | 3.85 | 0.94, 15.7 | 0.061 |  |  |  |
| Anorexia | 1.62 | 0.99, 2.66 | 0.057 |  |  |  |
| Loss of axillary and pubic hair | 2.62 | 1.32, 5.18 | **0.006** |  |  |  |
| Any postural drop in blood pressure | 1.50 | 0.54, 4.13 | 0.4 |  |  |  |
| Presence of anaemia | 1.28 | 0.77, 2.14 | 0.3 |  |  |  |
| Tuberculosis | 0.84 | 0.45, 1.58 | 0.6 |  |  |  |
| Cryptococcus neoformans | 1.82 | 0.78, 4.21 | 0.2 | 1.98 | 0.85, 4.63 | 0.11 |
| Pneumonia | 0.94 | 0.43, 2.06 | 0.9 |  |  |  |
| Herpes simplex virus HSV | 1.00 | 0.14, 7.18 | >0.9 |  |  |  |
| Hepatitis B | 0.44 | 0.06, 3.15 | 0.4 |  |  |  |
| Candida | 0.99 | 0.36, 2.73 | >0.9 |  |  |  |
| Syphilis | 1.44 | 0.45, 4.58 | 0.5 |  |  |  |
| Bacterial meningitis | 1.41 | 0.20, 10.2 | 0.7 |  |  |  |
| Urinary tract infection | 1.19 | 0.17, 8.61 | 0.9 |  |  |  |
| Pneumocystis Jiroveci Pneumonia | 4.24 | 1.04, 17.3 | **0.044** |  |  |  |
| Viral load | 1.19 | 1.01, 1.41 | **0.036** | 1.05 | 0.94, 1.17 | 0.4 |
| CD4 count | 0.99 | 0.98, 1.00 | 0.2 | 1.00 | 0.99, 1.01 | 0.7 |
| Sodium | 1.00 | 0.98, 1.02 | >0.9 |  |  |  |
| Potassium | 0.98 | 0.94, 1.03 | 0.5 |  |  |  |
| Haemoglobin | 0.97 | 0.87, 1.08 | 0.6 |  |  |  |
| White cell count | 1.00 | 1.00, 1.00 | >0.9 |  |  |  |
| Lymphocyte count | 0.92 | 0.81, 1.05 | 0.2 |  |  |  |
| ART exposure | 1.16 | 0.71, 1.89 | 0.6 |  |  |  |
| Kidney medication | 2.04 | 1.07, 3.91 | **0.030** |  |  |  |
| Addisons disease | 2.11 | 0.91, 4.89 | 0.081 |  |  |  |

**Discussion**

In the biggest case-finding study on adrenal insufficiency in patients with advanced HIV in Africa, we recruited 549 participants. The majority of the patients were black African females (51.1%) who were significantly younger at the median age of 35 years *p*=0.016. The overall median age at presentation was 36 years with the older age group associated with higher CD4 counts. The females were significantly younger at enrollment *p*=0.017. The median duration of illness was 14 days. Most of the patient presented with weight loss (86.1%) and CD4 counts of around 33 cells /mm3. The opportunistic infections of note in this cohort were tuberculosis (84%), pneumonia (11.3%), Candida (6.2%), and cryptococcus (5.5%). Table 1.2

The largest proportion of the patients 271/549 (49.4%) were found in the lowest tertile of (0 to 33) cells/mm3 and they had significantly higher viral loads 11.6 IQR (9.3-12.8) *p*<0.001 together with low CD4 counts, white cell counts 5.0 IQR (2.9-7.4) *p*<0.001, lymphocytes 0.6 IQR (0.5-5.8) *p*=0.011 and neutrophils 2.4 IQR (1.0-5.9) *p*=0.002 . Though not significant, Kaposi sarcoma was exclusively found in the lowest CD4 tertile which was also significantly populated by the youngest age group at *p*=0.016. (Table 1.1)

At enrollment, 341/549 (62.1%) of the participants were not on antiretroviral therapy, this could be due to late presentation, limited access to the health system or poor compliance. When compared with the group of patients on anti-retroviral (ARV) treatment, the group that was not on ARV's was predominantly male 172/341 (50.4%) with slightly more weight loss (86.6%), candida (6.7%) and low white blood cells 5.2 IQR (3.4-7.6) which were not statistically significant. However, with respect to opportunistic infections, there was a statistically significant predominance of Cryptococcal infection in patients who were not on ARV treatment at the time of enrollment at 7% versus 2.9% *p*=0.039. Table 2

Of the 27 patients with adrenal insufficiency 20/27 (74.1%) had secondary adrenal insufficiency (SAI) whereas 7/27 (25.9%) had primary adrenal insufficiency (PAI). When comparing the SAI and the PAI groups, there were no significant differences in the demographics, the clinical history, the clinical signs, the biochemistry, and the investigations. When comparing the group with no adrenal insufficiency and the one with adrenal insufficiency, the patients with hypoadrenalism 27/549, looked the same as the rest of the cohort in all respect except random, baseline, stimulated cortisol, Cryptococcal infection 37% versus 3.8% *p*<0.001, Staph aureus 3.7% versus 0.0% *p*=0.049, cytomegalovirus 3.7% versus 0.0% *p*=0.049, Parvo B19 3.7% versus 0.0 *p*=0.049, and neutrophil counts 1.3 versus 3.8 mmol/L *p*=0.037 which were significantly lower in the hypoadrenal group. There was a paradoxically significant elevation in sodium in the hypoadrenal group at 135 mmol/L IQR (133.0 – 137.5) versus 133 mmol/L IQR (130.0-137.0) p=0.033. Neutrophil levels can be elevated by steroid-induced de-margination during inflammatory states, including HIV infection(17). We consider the lower neutrophil count in the AI group to be inappropriate and perhaps a marker of low cortisol state in advanced HIV which we consider to be a state of medical stress. Steroids can exert both pro and anti-inflammatory effect on the neutrophils depending on the inflammatory microenvironment (18). On the other hand, natural killer cell cytotoxicity (NKCC) lymphocyte dysfunction leading to increased infections has been associated with adrenal insufficiency(19), and increased mortality. Table 3

There were, otherwise, no other significant differences between the two groups in respect of the demographics, clinical history, clinical signs and investigations, which makes it difficult to identifying the adrenal insufficiency group which is at a higher risk of increased morbidity and mortality when missed in this cohort. Our attempt to innovate a predictive tool for adrenal insufficiency using artificial intelligence to bridge this gap yielded mixed results due an uneven distribution of the AI and non-AI populations. The Random Forest classifier was the most promising of several classifiers that we experimented with; its recall was good as evidenced by its ability to identify 92.4%. However, it was only able to accurately predict AI in 52.6% of the patients with advanced HIV. Refinement of this predictive tool is work in progress.

On linear regression analyses, only random cortisol, basal cortisol and stimulated cortisol and other opportunistic infections, were associated with AI. A 10 nmol/L increase in random cortisol was associated with an 18% increase in the odds of being diagnosed with AI, 1.18 (95%CI:1.13, 1.25). A 10 nmol/L increase in basal cortisol was associated with a 10% increase in the odds of being diagnosed with AI, 1.10 (95%CI:1.06, 1.15), while a 10 nmol/L increase in stimulated cortisol was associated with a 34% increase in the odds of being diagnosed with AI, 1.34 (95%CI:1.20, 1.59).

At multivariate analysis, after adjusting for lymphocyte count, both random morning cortisol and ACTH were independently associated with AI. A 10 nmol/L increase in random morning cortisol was associated with a 19.6% increase in the odds of being diagnosed with AI, 1.196 (95%CI:1.131, 1.265), while a 10 pmol/L increase in ACTH was associated with a 12.6% reduction in the odds of being diagnosed with AI, 0.874 (95%CI:0.786, 0.971) after adjusting for lymphocyte count. At multivariate analysis ACTH was significant together with incremental cortisol, poor appetite, nausea, liking of salt, loss of axillary hair, PJP infection in predicting mortality. This finding is consistent with a study by Grossman et al in which elevated cortisol levels were associated with poor outcomes in ICU patients with community acquired pneumonia (CAP).

**Morbidity & Mortality:**

HIV is highly prevalent, and it has a high mortality, especially if patients are severely immunocompromised. Mortality rate was 60/522 (11.49%) and 6/27 (22.22%) in the patients without versus those with adrenal insufficiency, respectively. Kaplan-Meier curve confirms the higher mortality rate in AI group over time. At six months of follow-up patients with AI demonstrated a statistically significant higher mortality with a *p*=0.022. Mortality occurred throughout the tertiles in non-AI groups. The main causes of mortality in this cohort were tuberculosis 81.7% vs 83.3% and Cryptococcus 5.0% vs 50% *p*=0.008 in non-AI vs AI groups, respectively.

**Strengths and Weaknesses:**

This is the largest prospective study of patients with advanced HIV in a draining area with a high background of tuberculosis. One weakness is the population selection bias with the black Africans making most of the participants due to the state hospital draining area being predominantly Black African.

**AI predictive tool:** Our current ten variable machine learning (ML) model which is based on unbalanced data is biased towards the non-AI group due to its over-representation. One can artificially oversample AI or under sample non-AI thus making it harder to generalize the hypothesis of Adrenal insufficiency using the current model. It is our belief that in future, with increased AI population or improved classifier sensitivity, it may be possible to improve the precision in predicting AI in patients with advanced HIV.

**Conclusion:**

The largest study on hypoadrenalism in advanced HIV in Africa revealed overall mortality of 12.0%. The overall mortality in the AI group was 22.22% versus 11.49% for the non-AI groups, respectively. Mortality was bigger in the PAI group at 25% compared to the 16.7% in the SAI group. Higher mortality rate in the PAI group which is double the non-AI group suggests that hypoadrenalism carries a higher risk of mortality in patients with advanced HIV and thus justifies screening for it in these patients.

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Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |

**Table 3: Should compare Total AI with Non-AI patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variable | Non-AI vs AI | | | PAI vs SAI patients | | |
| no-AI, N = 5221 | AI, N = 271 | p-value2 | SAI, N = 201 | PAI, N = 71 | p-value3 |
| Age at enrolment, median (IQR) (years) | 36.0 (31.8,43.0) | 36.0 (32.0,47.5) | 0.4 | 36.0 (32.0, 48.5) | 40.0 (35.0, 45.0) | 0.6 |
| Gender, n(%) | |  | >0.9 |  |  | 0.7 |
| Female | 266 (51.1%) | 14 (51.9%) | | 11 (55.0%) | 3 (42.9%) |  |
| Male | 255 (48.9%) | 13 (48.1%) | | 9 (45.0%) | 4 (57.1%) |  |
| Ethnicity, n(%) | |  | 0.4 |  |  | >0.9 |
| Black African | 407 (78.0%) | 23 (85.2%) | | 17 (85.0%) | 6 (85.7%) |  |
| Other | 115 (22.0%) | 4 (14.8%) |  | 3 (15.0%) | 1 (14.3%) |  |
| Duration of current illness, median (IQR) (days) | 14.0 (11.8, 21.0) | 14.0 (14.0, 27.8) | 0.4 | 21.0 (14.0, 30.0) | 10.0 (7.0, 12.5) | 0.019 |
| Weight loss | 430 (86.3%) | 22 (81.5%) | 0.4 | 15 (75.0%) | 7 (100.0%) | 0.3 |
| Viral load (log10 Copies/mL) | 10.8 (7.1, 12.3) | 11.0 (10.7, 11.3) | 0.9 | 10.5 (10.5, 10.5) | 11.6 (11.6, 11.6) | >0.9 |
| Tuberculosis | 440 (84.3%) | 21 (77.8%) | 0.4 | 16 (80.0%) | 5 (71.4%) | 0.6 |
| Cryptococcus neoformans | 20 (3.8%) | 10 (37.0%) | <0.001 | 7 (35.0%) | 3 (42.9%) | >0.9 |
| Pneumonia | 59 (11.3%) | 3 (11.1%) | >0.9 | 3 (15.0%) | 0 (0.0%) | 0.5 |
| Staph aureus | 0 (0.0%) | 1 (3.7%) | 0.049 | 1 (5.0%) | 0 (0.0%) | >0.9 |
| Kaposis sarcoma | 5 (1.0%) | 1 (3.7%) | 0.3 | 1 (5.0%) | 0 (0.0%) | >0.9 |
| Cytomegalovirus | 0 (0.0%) | 1 (3.7%) | 0.049 | 1 (5.0%) | 0 (0.0%) | >0.9 |
| HSV | 7 (1.3%) | 1 (3.7%) | 0.3 | 1 (5.0%) | 0 (0.0%) | >0.9 |
| HepB | 16 (3.1%) | 2 (7.4%) | 0.2 | 2 (10.0%) | 0 (0.0%) | >0.9 |
| Candida | 33 (6.3%) | 1 (3.7%) | >0.9 | 1 (5.0%) | 0 (0.0%) | >0.9 |
| GE/c diff | 23 (4.4%) | 0 (0.0%) | 0.6 | 0 (0.0%) | 0 (0.0%) |  |
| Parvo B19 | 0 (0.0%) | 1 (3.7%) | 0.049 | 0 (0.0%) | 1 (14.3%) | 0.3 |
| Syphilis | 17 (3.3%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| B menigitis | 6 (1.1%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| UTI / Leptospirosis | 7 (1.3%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| PCP | 5 (1.0%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| COVID-19 | 2 (0.4%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| Neurocysticercosis | 2 (0.4%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| Total CD4 count | 34.0 (15.0, 63.0) | 28.0 (13.5, 49.5) | 0.4 | 19.0 (10.0, 48.8) | 46.0 (25.5, 61.0) | 0.2 |
| White cell count X109 | 5.6 (3.8, 8.1) | 5.2 (2.8, 8.9) | 0.5 | 5.3 (2.8, 11.9) | 3.5 (3.0, 5.5) | 0.4 |
| Lymphocyte count X109 | 0.8 (0.4, 2.0) | 0.9 (0.5, 1.2) | 0.7 | 0.7 (0.5, 1.0) | 1.3 (1.3, 1.3) | 0.6 |
| Neutrophils | 3.8 (1.6, 8.9) | 1.3 (0.9, 1.6) | 0.037 | 1.5 (1.0, 1.7) | 0.9 (0.9, 0.9) | 0.7 |
| Sodium mmol/L | 133.0 (130.0, 137.0) | 135.0 (133.0, 137.5) | 0.033 | 135.5 (134.0, 137.3) | 133.0 (131.5, 136.5) | 0.2 |
| Potassium mmol/L | 4.1 (3.6, 4.6) | 3.9 (3.3, 4.3) | 0.069 | 4.0 (3.3, 4.5) | 3.6 (3.3, 3.9) | 0.4 |
| Haemoglobin g/dL | 8.7 (7.4, 10.3) | 8.7 (7.6, 10.4) | 0.6 | 8.7 (7.6, 10.7) | 10.2 (7.9, 10.3) | 0.7 |
| BP (systolic) | 111.0 (102.0, 125.0) | 120.0 (102.5, 128.5) | 0.4 | 118.0 (99.5, 129.3) | 120.0 (120.0, 123.5) | 0.7 |
| BP (diastolic) | 70.0 (60.0, 79.0) | 71.0 (66.5, 80.0) | 0.080 | 72.0 (60.0, 80.0) | 70.0 (70.0, 82.0) | 0.8 |
| Heart rate | 91.0 (79.0, 108.8) | 87.0 (78.5, 107.0) | 0.7 | 85.0 (76.8, 102.3) | 97.0 (88.0, 111.0) | 0.10 |
| Hypotension | 46 (9.3%) | 1 (3.7%) | 0.5 | 1 (5.0%) | 0 (0.0%) | >0.9 |
| Weakness | 422 (85.1%) | 21 (77.8%) | 0.3 | 17 (85.0%) | 4 (57.1%) | 0.3 |
| Tiredness | 423 (85.1%) | 23 (85.2%) | >0.9 | 18 (90.0%) | 5 (71.4%) | 0.3 |
| Poor appetite | 374 (75.9%) | 22 (81.5%) | 0.5 | 16 (80.0%) | 6 (85.7%) | >0.9 |
| Increased pigmentation of the skin | 247 (50.8%) | 9 (37.5%) | 0.2 | 6 (31.6%) | 3 (60.0%) | 0.3 |
| Nausea | 263 (53.0%) | 16 (59.3%) | 0.5 | 11 (55.0%) | 5 (71.4%) | 0.7 |
| Vomiting | 137 (27.7%) | 8 (29.6%) | 0.8 | 4 (20.0%) | 4 (57.1%) | 0.14 |
| Liking for salt | 262 (53.0%) | 19 (70.4%) | 0.078 | 14 (70.0%) | 5 (71.4%) | >0.9 |
| Hypoglycaemia | 11 (2.2%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| Loss of consciousness | 7 (1.4%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| Diarrhoea | 219 (44.5%) | 8 (29.6%) | 0.13 | 7 (35.0%) | 1 (14.3%) | 0.6 |
| Dizziness | 236 (47.8%) | 13 (50.0%) | 0.8 | 9 (45.0%) | 4 (66.7%) | 0.6 |
| Shock | 5 (1.0%) | 0 (0.0%) | >0.9 | 0 (0.0%) | 0 (0.0%) |  |
| Anorexia | 234 (47.3%) | 8 (29.6%) | 0.073 | 4 (20.0%) | 4 (57.1%) | 0.14 |
| Loss of axillary and pubic hair, if female | | | 0.5 |  |  | 0.8 |
| No | 159 (31.7%) | 11 (40.7%) | | 9 (45.0%) | 2 (28.6%) |  |
| Not applicable | 248 (49.4%) | 13 (48.1%) | | 9 (45.0%) | 4 (57.1%) |  |
| Yes | 95 (18.9%) | 3 (11.1%) |  | 2 (10.0%) | 1 (14.3%) |  |
| Any postural drop in blood pressure | 21 (4.3%) | 2 (7.4%) | 0.3 | 2 (10.0%) | 0 (0.0%) | >0.9 |
| Presence of anaemia | 290 (58.8%) | 13 (50.0%) | 0.4 | 9 (47.4%) | 4 (57.1%) | >0.9 |