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Presence, patterns & predictors of hypocortisolism in patients with HIV infection in India

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***Background & objectives*: Adrenal insufficiency (AI) is rarely diagnosed in patients with HIV infection, in spite of autopsy studies showing very high rates of adrenal involvement. This study was aimed to determine the presence, patterns and predictors of AI in patients with HIV infection.**

***Methods*: Consecutive HIV patients, 18-70 yr age, without any severe co-morbid state, having at least one-year follow up at the antiretroviral therapy clinic, underwent clinical assessment and hormone assays.**

***Results*: From initially screened 527 patients, 359 patients having good immune function were analyzed. Basal morning cortisol <6 µg/dl (<165 nmol/l; Group 1), 6-11 µg/dl (165-300 nmol/l; Group 2), 11-18 µg/dl (300-500 nmol/l; Group 3) and ≥18 µg/dl (500 nmol/l; Group 4) were observed in 13, 71, 199 and 76 patients, respectively. Adrenocorticotropic hormone (ACTH) stimulation test revealed 87 patients (24.23%) to have AI. AI in groups 1-4 was 100, 56.34, 17.09 and 0 per cent, respectively. AI patients were more likely to be females (P<0.05), having longer disease duration (P<0.05), immune reconstitution inflammatory syndrome, hyperkalaemia (P<0.01), lower fasting glucose (P<0.01), dehydroepiandrosterone sulphate (DHEAS) and vitamin D. Regression analysis revealed morning cortisol and DHEAS to be best predictors of AI (P=0.004 and 0.028, respectively).**

***Interpretation & conclusions*: AI is a significant problem in HIV-infected individuals, observed in nearly a quarter of patients. Diagnosis warrants high index of suspicion and low threshold for screening, especially in those having low DHEAS and hyperkalaemia. Morning cortisol is a reasonable screening test, with ACTH stimulation warranted to confirm diagnosis, especially in patients with morning cortisol <11 µg/dl (300 nmol/l).**

Key words Acton prolongatum - adrenal insufficiency - adrenocorticotropic hormone - dehydroepiandrosterone-sulphate - HIV - hypoadrenalism - synacthen - vitamin D

The pattern of HIV infection in India is that of concentrated epidemic[1,2]. The prevalence rates of HIV infection in India in people with injection drug abuse, female sex workers, men who have sex with men were 18.1, 16.5 and 7 per cent, respectively[1,2]. Unfortunately, these individuals often constitute the

fringe sections of the society and often do not have timely access to appropriate healthcare. Endocrine abnormalities are increasingly been reported in patients with HIV infection, a likely result of improved clinical outcomes and increased survival due to highly active antiretroviral therapy (HAART)[3,4]. We have reported thyroid dysfunction to be very common in patients with HIV infection with subclinical hypothyroidism being the predominant form observed in 14.76 per cent patients[3]. We have also reported hypogonadism to be a significant problem in HIV-infected men and women in India, effecting 39 and 29 per cent patients, respectively[4].

Adrenocortical dysfunction is believed to be one of the common endocrinopathies in HIV[5,6]. Autopsy studies have demonstrated adrenal involvement in 40-90 per cent of HIV-infected patients[7]. Studies from Africa have consistently demonstrated a high prevalence of adrenal insufficiency (AI) in HIV-infected patients ranging from 27.5 to 34.5 per cent[8,9]. However, AI/hypocortisolism is rarely diagnosed in routine clinical practice in patients with HIV infection in India. Non-specific clinical features (anorexia, nausea, weight loss, fatigue and hypotension), which are very common in patients with HIV infection, along with subclinical nature of the disease may explain this. Accurate and appropriate diagnosis of hypocortisolism is imperative, as both lack of diagnosis and treatment of hypocortisolism, as well as unnecessary use of glucocorticoids is associated with increased morbidity and mortality. The recent endocrine society clinical practice guideline recommends low threshold for screening for AI[10]. Screening for AI has been recommended in all patients with suggestive symptoms and signs as well as in acutely ill patients[10]. Further, no data are available on the burden of hypocortisolism in patients with HIV infection from India. Hence, this study was aimed to determine the presence, patterns and predictors of hypocortisolism/AI in patients with HIV infection in India.

Material & Methods

Antiretroviral therapy (ART) clinic at Post-graduate Institute of Medical Education and Research and Dr Ram Manohar Lohia Hospital, New Delhi, India, an apex referral centre established by the National AIDS Control Organization, India and the World Health Organization, provides for all the necessary investigations, medications (including HAART), counselling and education to all patients with HIV infection. Consecutive ambulatory patients, 18-70 yr age, with serologically documented HIV infection, in stable clinical condition without any acute, severe illness, attending the ART clinic of the hospital during August 2014 to December 2015 were considered. Severely ill patients with multiple co-morbid states, who would warrant hospital admission, were excluded. Patients with previous history of steroid supplementation and those with vitamin D and/or calcium supplementation in the last six months were also excluded. Patient records were reviewed and patients having clinical data of at least one year of follow up were further evaluated. Patients with available CD4 cell counts at diagnosis and at first follow up (6-12 months after diagnosis) were included in the study. The study protocol was explained to the considered patients and only those who gave informed written consent were included in this study. The institutional ethics committee approved the study protocol.

Sample collection: All patients underwent detailed clinical assessment. The patients were called the subsequent day in fasting state for blood sampling. Blood samples (5 ml) were collected in plain and ethylenediaminetetraacetic acid (EDTA) vacutainers (Becton Dickinson, USA) between 8 and 9 am in the morning. Serum was separated from blood collected in plain vacutainer and processed immediately for routine biochemical analysis, and one aliquot of serum was stored at −20°C. EDTA sample processed for haematological analysis.

Hormone and biochemical analysis: Chemiluminescent microparticle immunoassay (VITROS® ECiQ Immunodiagnostic System, Johnson & Johnson, USA) was used for the estimation of morning cortisol, thyroid hormones and 25-hydroxy-vitamin-D [25(OH)D]. Cortisol assay had analytical sensitivity of 0.10 µg/dl (2.83 nmol/l), analytical range of 4.46-22.7 µg/dl (123-626 nmol/l) with intra- and inter-assay coefficient of variation (CV) of 2.2 and 4.7 per cent, respectively. Serum 25(OH)D assay had analytical sensitivity of 8.0 ng/ml, analytical range of 8-150 ng/ml, intra- and inter-assay CV of 3.4 and 5.5 per cent, respectively. Free tri-iodo-thyronine (FT3) assay had analytical sensitivity of 0.50 pg/ml, analytical range of 0.50-22.8 pg/ml, intra- and inter-assay CV of 2.2 and 6.3 per cent, respectively. Free tetra-iodo-thyronine (FT4) assay had analytical sensitivity of 0.07 ng/dl, analytical range of 0.07-6.99 ng/dl with intra- and inter-assay CV of 2.4 and 5.8 per cent, respectively.

Thyroid-stimulating hormone (TSH) assay had analytical sensitivity of 0.015 mIU/l, analytical range of 0.015-100 mIU/l with intra- and inter-assay CV of 3.3 and 7.2 per cent, respectively. CD4 cell count was performed using flow cytometry (Becton Dickinson Immunocytochemistry Systems, San Jose, CA, USA). Serum calcium, phosphate, alkaline phosphate and renal function tests were done using clinical chemistry autoanalyzer based on dry chemistry micro-slide technology (VITROS® 350 chemistry system, Johnson & Johnson, USA).

Patients with morning cortisol ≥18 µg/dl (500 nmol/l) were defined to have normal adrenal function[11]. All patients were called the following day for adrenocorticotropic hormone (ACTH) stimulation test for the assessment of the adrenal reserve. Twenty five units of ACTH (Acton Prolongatum®, Ferring, Saint-Prex, Switzerland; which is equivalent to 250 mcg of Synacthen®) were injected intramuscularly by 40 IU insulin syringe (up to 16 mark), and blood sample was collected after 60 min for the estimation of post-ACTH stimulation cortisol[11]. Patients with post-ACTH cortisol ≥18 µg/dl (500 nmol/l) were defined to have normal adrenal reserve. Patients with post-ACTH cortisol <18 µg/dl (500 nmol/l) were defined to have AI (hypocortisolism).

Immune reconstitution inflammatory syndrome (IRIS) has been defined as an increased CD4 count above 200 cells/µl in patients who previously had <100-200 cells/µl of CD4 counts[12,13]. Hence, patients in our study with baseline CD4 counts <200 cells/µl, which increased to >200 cells/µl at the first follow up following initiation of HAART were defined to have IRIS.

Sample size calculation: The prevalence of AI among HIV patients in India is not known. However, studies done in South Africa and Nigeria have shown 27.5 and 34.5 per cent of HIV positive patients had AI, respectively[8,9]. Keeping a power of 80 per cent and Type-I error at 5 per cent, a sample size of 246 patients was required in our study for accurate assessment of hypoadrenalism.

Statistical analysis: Normality of the distribution of variables was checked using the Kolmogorov-Smirnov test. All normally distributed variables have been elaborated as mean±standard deviation. All non-normally distributed variables have been mentioned as median (range). Range is a measure of the deviation of the variable and was calculated as the difference between the highest and the lowest value of the variable. Independent *t* test and Wilcoxon rank-sum test were done for normally distributed and skewed variables, respectively. Chi-square test was used for categorical variables. Multiple logistic regression analyses were done to determine variables that independently influenced the occurrence of hypoadrenalism after adjusting for factors in different models. Statistical Package for the Social Sciences (SPSS) version 20 (Chicago, IL, USA) was used for data analysis.

Results

Five hundred and twenty seven consecutive patients were screened, of whom 359 patients (225 males and 134 females) who fulfilled the inclusion and exclusion criteria and gave informed written consent were included in this study (Figure). The mean duration of HIV infection was 61.44±39.42 months with 88.58 per cent (318/359 patients) receiving HAART and 40.67 per cent (145/359 patients) (40.38%) having a history of tuberculosis (Table I). Three hundred and twenty two (89.69%) patients had serum 25(OH)D <30 ng/ml with mean levels of 20.23±9.13 ng/ml. At the time of hormonal analysis, 9.75 (35/359), 58.50 (210/359) and 31.75 per cent (114/359) patients had CD4 count <200 µl, 200-500 µl and >500 µl, respectively.

A total of 283 patients had morning cortisol <18 µg/dl (500 nmol/l). Of these, 13 patients (3.62%) had morning cortisol <6 µg/dl (<165 nmol/l) (Group 1), 71 (19.24%) had morning cortisol between 6 and 11 µg/dl (165-300 nmol/l) (Group 2) and 199 (55.43%) had morning cortisol between 11 and 18 µg/dl (300-500 nmol/l) (Group 3). Seventy six patients (21.17%) had morning cortisol ≥18 µg/dl (500 nmol/l) (Group 4). ACTH stimulation test revealed 87 patients (24.23%) to have one hour post-ACTH cortisol to be <18 µg/dl (<500 nmol/l) who were diagnosed to have AI (hypocortisolism). The increments in serum cortisol levels post-ACTH stimulation as compared to morning basal cortisol (Δ cortisol) [median (range)] in Groups 1, 2, 3 and 4 were 118 (288.5), 209 (474.9), 194 (1106) and 224 (549) nmol/l, respectively, which was significantly different (P<0.05). The presence of AI (hypocortisolism) in patients with baseline morning cortisol <6 µg/dl (165 nmol/l), 6-11 (165-300 nmol/l), 11-18 (300-500 nmol/l) and ≥18 µg/dl (500 nmol/l) was 100 per cent (13/13 patients), 56.34 per cent (40/71 patients), 17.09 per cent (34/199 patients) and 0 per cent (0/76 patients), respectively (Table II).

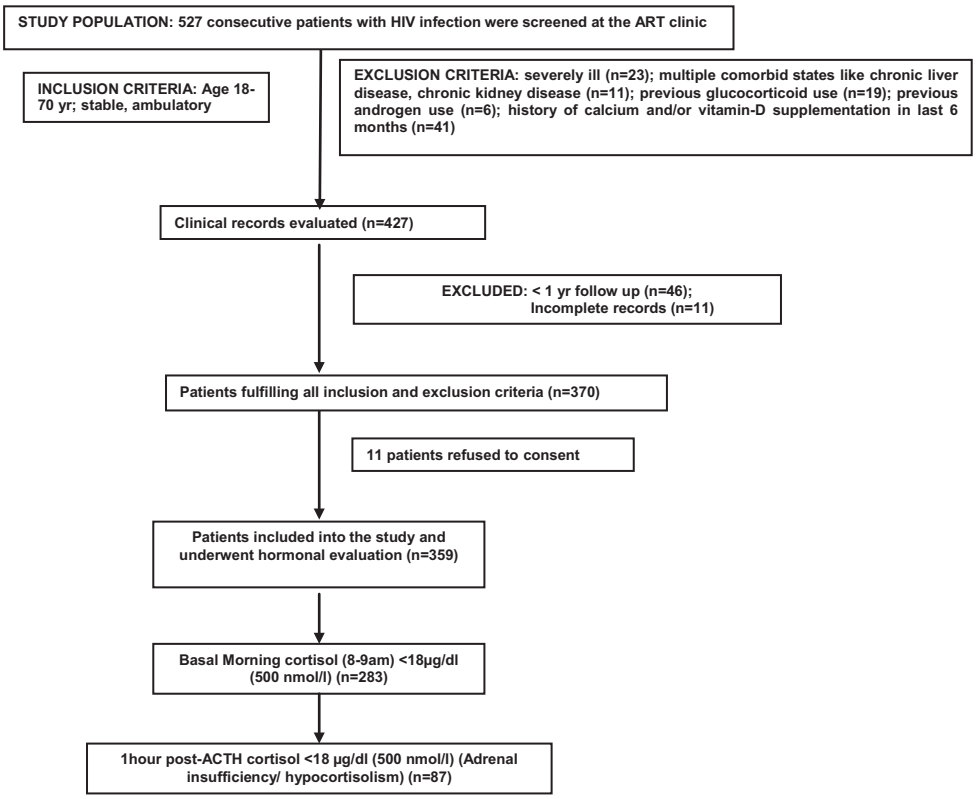

Figure. Flowchart elaborating the study protocol and flow of patients.

Both basal morning cortisol and dehydroepiandrosterone sulphate (DHEAS) were significantly lower in females as compared to males (P<0.01) (Table III). In our study, patients with AI had significantly longer disease duration (P<0.05). Diabetes and prediabetes were observed in seven (1.95%) and 26 (7.24%) patients (Table I). The occurrence of diabetes was significantly lower in patients with AI (Table I). Patients with AI had significantly higher serum potassium (P<0.05) and lower fasting blood glucose (P=0.01), (Table IV). Two and six patients with AI had evidence of hypoglycaemia and hyperkalaemia, respectively (Table IV). Majority of the patients with AI had morning cortisol between 6 and 11 µg/dl (165-300 nmol/l) (Table II).

Basal and post-ACTH stimulation cortisol levels had no correlation with CD4 counts. One-hour post-ACTH stimulation but not basal cortisol had significant positive correlation with DHEAS (σ=0.213; P=0.025). Binary logistic regression analysis revealed that basal morning cortisol and serum DHEAS to be the two best independent predictors of AI among patients with HIV infection (P=0.004 and 0.028, respectively) (Table V).

Discussion

The entire spectrum of hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been reported in HIV ranging from normal to high basal cortisol levels with blunt response to ACTH, a state of glucocorticoid resistance characterized by features of AI with high circulating levels of glucocorticoids to frank hypocortisolism/ AI[14]. Hypocortisolism usually occurs only after >80 per cent of the adrenal gland been destroyed[15].

High baseline cortisol >18 µg/dl (500 nmol/l) was observed in 21.17 per cent patients in our study who had an intact adrenal response to ACTH stimulation. One group has reported hypercortisolaemia in HIV with blunted ACTH and cortisol response to stress and corticotropin-releasing hormone, especially in patients with advanced disease[16]. Increased systemic inflammation (increased circulating levels of cytokines) is believed to stimulate adrenal glucocorticoid synthesis[16,17]. Increased circulating cortisol binding globulin levels may also contribute to the hypercortisolaemia in HIV infection[18]. Hypercortisolism was observed in patients with advanced disease and increased viraemia[19]. HIV envelope protein gp-120 has been linked to induction of HPA axis hyperactivity[19]. Stable clinical condition

Table I. Clinical, demographic, and immunologic characteristic of HIV-infected patients with and without adrenal insufficiency (hypocortisolism)

Parameter	Patients with adrenal insufficiency (n=87)	Patients without adrenal insufficiency (n=272)
Age (yr)[a]	35 (39)	38 (48)
Sex (male:female)	47:40*	178:94
Duration of HIV infection (months)[a]	64 (136)*	54 (168)
Nature of HAART (%)		
NRTI	75 (86.21)	243 (89.34)
NNRTI	71 (81.61)	234 (86.03)
PI	4 (4.60)	15 (5.51)
History of tuberculosis (%)	36 (41.38)	109 (40.07)
History of opportunistic fungal infection (%)	2 (2.30)	2 (0.74)
History of viral infection† (%)	3 (3.45)	5 (1.84)
IRIS (%)	41 (47.13)	98 (36.03)
BMI (kg/m^2)[a]	21.22 (28.52)	21.92 (28.47)
Glycaemic status		
Normoglycemia	83	243
Pre-diabetes	4	22
Diabetes	0*	7
CD4 cell count (at diagnosis)[a] (cell/µl)	163 (1920)	179.5 (1242)
CD4 cell count (6-12 months after diagnosis)[a] (cell/µl)	291 (1598)	280 (947)
CD4 cell count (at present)[a] (cell/µl)	414 (1355)	398.5 (1068)

All continuous variables expressed as mean (SD). [a]All non-normally distributed variable expressed as median (range); all discrete variables have been expressed as absolute n (%); *P<0.05 compared to patients without adrenal insufficiency. †Viral infections include hepatitis-B, hepatitis-C and others. AZT, 3TC, d4T and/or TDF were the NRTIs received by the patients; NVP or EFV was NNRTIs received by the patients; ATV or RTV was the PI received the patients. HAART, highly active antiretroviral therapy; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-NRTIs; PI, protease inhibitor; IRIS, immune reconstitution inflammatory syndrome; BMI, body mass index; SD, standard deviation; AZT, zidovudine; 3TC, lamivudine; d4T, stavudine; TDF, tenofovir; NVP, nevirapine; EFV, efavirenz; ATV, atazanavir; RTV, ritonavir; HIV, human immunodeficiency virus

Table II. Adrenal and thyroid function characteristics of HIV-infected patients with and without adrenal insufficiency (hypocortisolism)

Parameter	Patients with adrenal insufficiency (n=87)	Patients without adrenal insufficiency (n=272)
Basal morning cortisol (%)		
<6 µg/dl (165 nmol/l) (Group 1)	13 (14.94)	0
6-11 µg/dl (165-303 nmol/l) (Group 2)	40 (45.98)***	31 (11.40)
11-18 µg/dl (303-500 nmol/l) (Group 3)	34 (39.08)***	165 (60.66)
≥18 µg/dl (500 nmol/l) (Group 4)	0	76 (27.94)
Baseline morning 8-9 am cortisol (nmol/l)	277.48±101.03***	434.06±127.05
One hour post-ACTH cortisol (nmol/l)[a]	407 (404)***	648.5 (920)
DHEAS (µmol/l)[a]	0.783 (2.04)	0.920 (2.98)
Free tri-iodo-thyronine (T_3) (pg/ml)[a]	3.31 (4.67)	3.47 (14.08)
Free tetro-iodo-thyronine (T_4) (ng/dl)[a]	0.83 (0.91)	0.84 (2.52)
Thyroid stimulating hormone (mIU/l)[a]	2.87 (26.15)	2.93 (19)

All continuous variables expressed as mean±SD. [a]All non-normally distributed variable expressed as median (range); all discreet variables have been expressed as absolute n (%); ***P<0.001 compared to patients without adrenal insufficiency. ACTH, adrenocorticotropic hormone; SD, standard deviation; DHEAS, dehydroepiandrosterone-sulphate

with good immune function (90.25% patients had CD4 cell count >200 cells/µl) may explain the intact adrenal response to ACTH stimulation in patients with basal hypercortisolaemia observed in our study. HIV viral load was not assessed and is a limitation of this study. Lack of estimation of ACTH and levels of inflammatory cytokines are also a limitation.

AI was seen in 24.23 per cent patients, which was comparable to previous reports from other parts of the globe. Studies from Brazil, Uganda, South Africa and

Table III. Adrenal function characteristics in males as compared to females with HIV infection

Parameter	Males (n=225)	Females (n=134)
Basal morning cortisol (%)		
<6 µg/dl (165 nmol/l) (Group 1)	7 (3.11)	6 (4.48)
6-11 µg/dl (165-303 nmol/l) (Group 2)	35 (15.56)**	36 (26.87)
11-18 µg/dl (303-500 nmol/l) (Group 3)	134 (59.56)	65 (48.51)
≥18 µg/dl (500 nmol/l) (Group 4)	49 (21.78)	27 (20.15)
Baseline morning 8-9 am cortisol (nmol/l)	411.78±137.53**	369.8±136.63
One hour post-ACTH cortisol (nmol/l)[a]	602 (325)	545 (1188)
DHEAS (µmol/l)[a]	0.983 (2.98)*	0.621 (1.80)
One hour post-ACTH cortisol <18 µg/dl (<500 nmol/l) (adrenal insufficiency) (%)	47±20.89*	40±29.85

All continuous variables expressed as mean±SD. [a]All non-normally distributed variable expressed as median (range); all discreet variables have been expressed as absolute n (%); P^{*}<0.05, **<0.01 compared to females. ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone-sulphate; SD, standard deviation

Table IV. Haematologic, renal, hepatic, lipids and calcium profile of HIV-infected patients with and without adrenal insufficiency (hypocortisolism)

Parameter	Patients with adrenal insufficiency (n=87)	Patients without adrenal insufficiency (n=272)
Haemoglobin (g/l)	12.40±1.57	12.5±1.74
Total leucocyte count (cells/µl)[a]	6000 (11,500)	6530 (10,700)
Erythrocytic sedimentation rate (mm/h)[a]	17 (77)	16 (90)
Creatinine (mg/dl)	0.72±0.17	0.70±0.16
Sodium (mEq/l)	141.63±4.54	142.41±4.98
Potassium (mEq/l)	4.66±0.48*	4.42±0.48
Hyperkalaemia[b]	6***	0
Fasting blood glucose (mg/dl)[a]	85 (44)**	91 (164)
Hypoglycaemia[c]	2**	0
Serum glutamic-pyruvic transaminasea (IU/l)	30 (144)	32 (240)
Total cholesterol (mg/dl)	186.24±41.13	191.61±43.93
Triglycerides (mg/dl)[a]	138 (417)	154.5 (610)
Calcium (mg/dl)	9.06±0.48	9.22±0.59
Phosphate (mg/dl)	3.67±0.44	3.64±0.65
Alkaline phosphate (U/l)	125.6±74.25	128.83±45.53
25-(OH) D (ng/nl)[a]	18.10 (32.20)	19.30 (75.40)

All continuous variables expressed as mean±SD. [a]All non-normally distributed variable expressed as median (range); all discrete variables have been expressed as absolute n (%); P^{*}<0.05, **<0.01 compared to patients without adrenal insufficiency. [b]Hyperkalaemia was defined as serum potassium >5.5 mEq/l; [c]Hypoglycaemia was defined as blood glucose values <70 mg/dl. 25-(OH) D, 25-hydroxyvitamin D; SD, standard deviation

Nigeria have reported the prevalence of AI ranging from 19 to 34.5 per cent[8,9,20,21]. In a small study of critically ill AIDS patients with advanced disease from southern India (n=50), AI was diagnosed in 74 per cent patients using ACTH stimulation test[22], which was much higher than that in this report. However, it must be highlighted that patients in our study were clinically stable, asymptomatic with good immune function. It is important to highlight that none of the patients diagnosed with AI in this study had hyperpigmentation or postural hypotension. However, patients with AI had significantly higher serum potassium and lower fasting blood glucose. Plasma ACTH was not measured in this study. Hence, it was not possible to differentiate primary from secondary AI in this study, which is a limitation of this study.

The presence of vitamin-D insufficiency [25(OH)D <30 ng/ml] among HIV-infected patients in our study was 89.69 per cent, which was higher than that observed in the general Indian population (70-75%)[23,24]. Several pleotropic functions have been attributed to vitamin-D including its impact on immune function, autoimmunity, insulin resistance and cardiovascular function[25,26]. Vitamin D deficiency has been linked with more rapid decline in CD4 cell count, higher occurrence of osteoporosis, cardiovascular disease, diabetes, autoimmune disease and cancer in HIV-infected patients[27,28]. Vitamin-D receptor gene polymorphism has been linked to increased occurrence of AI[29]. Hence, further studies are needed to evaluate the link between vitamin D and hypocortisolism.

Table V. Binary logistic regression analysis showing factors that independently predict the occurrence of adrenal insufficiency (hypocortisolism) in patients with HIV infection

Variable	*B*	Exp (*B*)	*P*
Age	−0.014	−0.014	0.608
Sex	−0.816	0.442	0.153
Duration of HIV infection	0.002	1.002	0.715
Basal morning cortisol	−0.007	0.993	0.004
DHEAS	−0.885	0.413	0.028
History of tuberculosis	0.374	1.453	0.450
NRTI use	1.426	4.161	0.097

Binary logistic regression was initially performed with all parameters which are likely to influence the occurrence of adrenal insufficiency [age, sex, BMI, duration of HIV infection, baseline CD4 count, delta CD4 count (change in CD4 count at 6-12 months follow up with regards to CD4 cell count at diagnosis (baseline)], basal morning cortisol, DHEAS, haemoglobin, erythrocytic sedimentation rate, history of tuberculosis, opportunistic fungal infections, viral infections (hepatitis-B and hepatitis-C), serum 25-(OH) D and individual anti-retro-viral agents received by the patient]. Parameters with $P<0.2$ were included into the final model as elaborated in the Table. Exp (*B*), exponentiation of the B coefficient, change in odds ratio with 1 unit change in predictor variable; for categorical variables sex, history of tuberculosis and NRTI use, females, absence of tuberculosis and absence of NRTI use were taken as reference group. DHEAS, dehydroepiandrosterone sulphate; NRTI, nucleoside reverse transcriptase inhibitor; BMI, body mass index; 25-(OH) D, 25-hydroxyvitamin D

Certain studies have suggested serum DHEAS to have an important role in predicting clinical outcomes in HIV[30,31]. A reduced DHEAS/cortisol ratio has been reported to be associated with a deterioration of immune status characterized by a shift from Th1- to a Th2-driven immune response[30]. Reduced DHEAS levels, accompanied by increased cortisol levels, were observed in patients with AIDS wasting syndrome[31]. This is believed to be a result of shift of steroid metabolism from adrenal androgens to glucocorticoids in patients with advanced HIV infection[31]. A decreased adrenal 17,20-lyase activity may explain this phenomenon[30,31]. In our study, patients with AI had lower DHEAS levels and low serum DHEAS was an independent predictor of increased risk for AI in patients with HIV infection. The occurrence of dysglycaemia among patients with HIV infection in our study [diabetes (1.95%) and prediabetes (7.24%)] was not increased as compared to the occurrence rates in the general population in India[32,33]. In large cross-sectional studies, the prevalence rates of diabetes among HIV-infected patients from Cameroon, Guinea-Bissau and Italy were reported to be 3.8 per cent (n=500), 5.8 per cent (n=953) and 4.5 per cent (n=755), respectively[34-36]. There are conflicting reports with a few, but not all studies reporting increased prevalence of diabetes in HIV infected patients[34-37]. A study from Spain documented lower insulin resistance and lower incidence of diabetes in HIV-infected patients on ART[37]. In our study, the decreased occurrence of diabetes among HIV-infected patients with AI can be explained by the physiologic role of cortisol in increasing blood glucose through increased glycogenolysis and gluconeogenesis[38]. Low cortisol levels in AI is known to have a favourable impact on blood glucose values, which also explains the increased occurrence of hypoglycaemia in these patients[38].

In conclusion, AI is a significant problem in HIV-infected patients in India with stable clinical and immune function, observed in nearly a quarter of the patients. Diagnosis of AI in HIV requires a high index of suspicion, as the typical symptoms associated with AI are usually absent. A low threshold of screening is advisable, especially in patients with low serum DHEAS and hyperkalaemia. Morning basal cortisol is a good screening test, with ACTH stimulation warranted to confirm diagnosis, especially in patients with morning cortisol <11 µg/dl (300 nmol/l). Low basal morning cortisol and DHEAS were the two predictors of AI. All patients with morning cortisol <6 µg/dl (165 mmol/l) and more than half of the patients (61%) with morning cortisol <11 µg/dl (300 nmol/l) had AI.

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***Conflicts of Interest*:** None.

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