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Endocrine Manifestations of HIV Infection

Bakari Adamu Girei and Sani-Bello Fatima

Additional information is available at the end of the chapter

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1. Introduction

Human Immune deficiency Virus (HIV) infection has assumed pandemic proportion since after its identification as the causative agent of Acquired Immunodeficiency Syndrome (AIDS). The spectrum of HIV infection and AIDS is quite wide and variable. HIV infected patients have an increased risk of developing endocrine abnormalities [1]. The endocrine glands are affected in a variety of ways such as functional derangement, direct effects of HIV infection and the resultant immune suppression, effects of opportunistic infections both acute and chronic, invasion by neoplasms and the effects of the various medications used to treat HIV or any of the opportunistic infections associated with it (Table 1). While endocrine dysfunction has not been a prominent clinical feature of AIDS, all endocrine glands may be affected by the opportunistic infections and malignancies; as a result of antiretroviral treatment or indeed as a result of the direct invasion of the glands by the virus (Table 2). The introduction of anti-retroviral (ARV) drugs has significantly reduced both morbidity and mortality attributable to HIV infection [2]. The prolonged administration of these drugs however, has led to new challenges for both physicians and patients [3- 8].

Apart from the effects of acute and chronic illnesses, the relentless progression of immune dysfunction in AIDS affects endocrine function through the activation of several cytokines, chemokines and antibody formation. The use of protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) is associated with multiple abnormalities in glucose and lipid metabolism such as insulin resistance, increased triglycerides and increased levels of low-density lipoprotein cholesterol. These metabolic disturbances might be due to a combination of factors, including the direct effect of medications, restoration to health; HIV disease as well as individual genetic predisposition. Of the available antiretroviral medications, indinavir had been associated with causing the most insulin resistance and ritonavir with causing the most hypertriglyceridemia.

a. Destruction of endocrine tissue
<ul style="list-style-type: none">• Cancer• Infection• Haemorrhage• Non-specific inflammation
b. Interference with Endocrine function
<ul style="list-style-type: none">• Acute illness• Chronic illness• Cytokines (tumour necrosis factor, interleukin-1, interferon)• Antibodies
c. Effects of medications
<ul style="list-style-type: none">• ARV's• Anti Tuberculosis drugs.• Antifungal drugs.• Antiviral drugs.• Antibiotics.

Table 1. Mechanisms of Endocrine dysfunction in patients with HIV [1]

a. Endocrinopathies as a result of direct effects of the virus.
<ul style="list-style-type: none">• HIV adrenalities and impaired adrenal reserve• Hypercortisolism• Idiopathic adrenohypophyseal necrosis• Hyperprolactinaemia• Primary hypogonadism• Growth factor• AIDS wasting syndrome
b. Endocrinopathies as a result of structural destruction of glands
<ul style="list-style-type: none">• Cytomegalovirus (CMV) adrenalitis• Pneumocystis thyroiditis• Mycobacterial infection, cryptococcosis, toxoplasmosis (pituitary, thyroid, adrenals)• Haemorrhages and abscesses causing insufficiency of glands (pituitary, thyroid and adrenals)

Table 2. Common Endocrine abnormalities in HIV infected patients [1].

2. The pituitary

Involvement of the pituitary gland is common in advanced HIV infection, at autopsy; varying degrees of infarction and necrosis are the most common findings occurring in nearly 10% of cases [1]. Also common are opportunistic Infections by CMV, Pneumocystis carinii, Toxoplas-

mosis and mycobacteria among others [9]. Furthermore, the pituitary may also be affected by neoplasms such as cerebral lymphoma with peripheral involvement of the gland.

Despite the foregoing, evaluation of anterior pituitary reserve in HIV infected patients by TSH or gonadotropin stimulation has demonstrated a normal response in nearly all patients. Suggesting that panhypopituitarism is rare in these patients.

GH deficiency does not appear to be common [1]. Posterior pituitary function may be altered in HIV patients with Hyponatremia occurring in up to 50% of inpatients and about 20% of outpatients with AIDS; two-thirds of these patients are clinically euvoletic with serum arginine vasopressin levels that are inappropriately high for the serum osmolality, consistent with the syndrome of inappropriate antidiuretic hormone secretion [10 - 12]. The presence of *Pneumocystis carinii* pneumonia and/ or treatment with trimethoprim appears to be the most significant risk factors for this complication. Furthermore, central diabetes insipidus has been reported in AIDS patients with herpetic meningoencephalitis.

3. Thyroid dysfunction

Although thyroid function tests are often abnormal in HIV patients, the prevalence of overt thyroid disorder is not significantly different from that of the general population [13]. Most asymptomatic patients with HIV infection have normal thyroid function. Some, however, exhibit increased serum total thyroxine (T_4) and triiodothyronine (T_3) concentrations. These increases are as a result of increases in serum thyroxine-binding globulin, the cause of which is unknown [14]. However, with progression of HIV infection and as the patients become more ill, serum T_4 and T_3 concentrations decline, as is obtained in most if not all chronically ill patients; serum thyrotropin concentrations however remain normal or slightly depressed. These changes are as a result of reduction in serum binding proteins, decreased extrathyroidal conversion of T_4 to T_3 , and decreased secretion of thyrotropin [13], [14]. Cytokines may be involved in some of these; especially the reduction in the peripheral conversion of T_4 to T_3 [15].

An increasing number of patients taking anti-HIV drugs are presenting with thyroid disorders as a result of improved immune function (immune reconstitution syndrome). Graves' disease is the commonest among immune reconstitution syndromes; others include Hashimoto's thyroiditis and hypothyroidism. Autoimmune Thyroid Disease (AITD) occurs in 3% of women and 0.2% of men [13- 17]. Goddard proposed a staging of autoimmune manifestations related to HIV/AIDS (table 3) [18].

The prevalence of immune reconstitution Autoimmune Thyroid Disease (AITD) (Graves' disease, Hashimoto thyroiditis, and hypothyroidism) is about 3% for women and 0.2% for men. Patients with lower CD4 counts at baseline with greater increments in the CD4 counts following HAART are more likely to develop AITD.

Stage	Features
Stage I	Acute HIV infection, the immune system is intact and autoimmune diseases may develop.
Stage II	The quiescent period without overt manifestations of AIDS associated with a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found.
Stage III	Immunosuppression with low CD4 count and the development of AIDS. CD8 T cells predominate and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren's syndrome) may present or even be the initial manifestation of AIDS. No autoimmune diseases are found.
Stage IV	Restoration of immune competence following HAART. In this setting, there is a resurgence of autoimmune disorders.

Table 3. Stages of autoimmune manifestations in HIV/AIDS.

Thyroid dysfunction in HIV-positive individuals can result from gland destruction by opportunistic pathogens such as *Pneumocystis jirovecii* which has been reported to cause a painful low uptake thyroiditis like picture with hyperthyroidism followed by hypothyroidism. Other opportunistic pathogens that could affect the thyroid gland in HIV infected individuals include *Cryptococcus neoformans*, *Aspergillosis* and cytomegaloviurs [19 - 23]. The gland may also be invaded by Kaposi Sracoma with resultant hypothyroidism [24].

Overt Hypothyroidism should be treated with levothyroxine keeping in mind that drug interactions between levothyroxine and protease inhibitors have been reported, perhaps through the shared metabolic pathway of glucuronidation. In subclinical hypothyroidism however, the TSH level should be determined again within three months as the levels normalize within a year in up to 30% of affected patients. In cases of overt hyperthyroidism, it is paramount to establish whether it is as a result of Graves' disease, or thyroiditis and the appropriate therapy instituted.

4. Adrenal dysfunction

Biochemical evidence of adrenal insufficiency is relatively common in hospitalized AIDS patients occurring in almost a fifth of such patients however, only about 4% are clinically symptomatic patients [25]. Adrenal dysfunction may be suspected in HIV-infected patients with advanced stage of AIDS. High index of suspicion is required; subtle impairment of adrenal function is manifested as fatigue, hyponatremia or rarely with clinical symptoms of adrenal insufficiency. At autopsy, the adrenal gland shows evidence of both inflammation and necrosis¹, [26 - 28]. Adrenal secretion of aldosterone and adrenal androgens may also be impaired. In fact, there appears to be a shift from adrenal androgen and aldosterone production toward glucocorticoid production. However, the secretion of aldosterone in response to assumption of the upright posture and the administration of angiotensin II is normal. The mechanisms by which HIV might affect adrenal secretion appear to be dependent on effects of cytokines and other immunomodulatory substances on the hypothalamo-pituitary-adrenal axis [29 - 32]. The potential sites of immune modulation of this is shown in this figure 1.

Interleukin-1 is a likely candidate as either a direct or an indirect adrenal stimulator. Its production by macrophages is stimulated by tumor necrosis factor, and the production by macrophages of both interleukin-1 and tumor necrosis factor is stimulated by HIV infection [33].

Interleukin-1 may affect the hypothalamus, pituitary, or adrenal glands in a variety of ways [29]. Interleukin-1 stimulates the release of corticotropin-releasing hormone from the hypothalamus into the portal circulation leading to the increases in corticotropin and consequently cortisol secretion. Furthermore, Interleukin-1 has been shown to directly stimulate cultured pituitary cells to release corticotropin. Cultured adrenocortical cells secrete more cortisol when cocultured with mononuclear cells most likely as a result of a response to the production of interleukin-1 by mononuclear cells [30 - 32]. Interferon, another product of HIV-infected monocytes and macrophages, is also an immunomodulator of the hypothalamo-pituitary-adrenal axis [34].

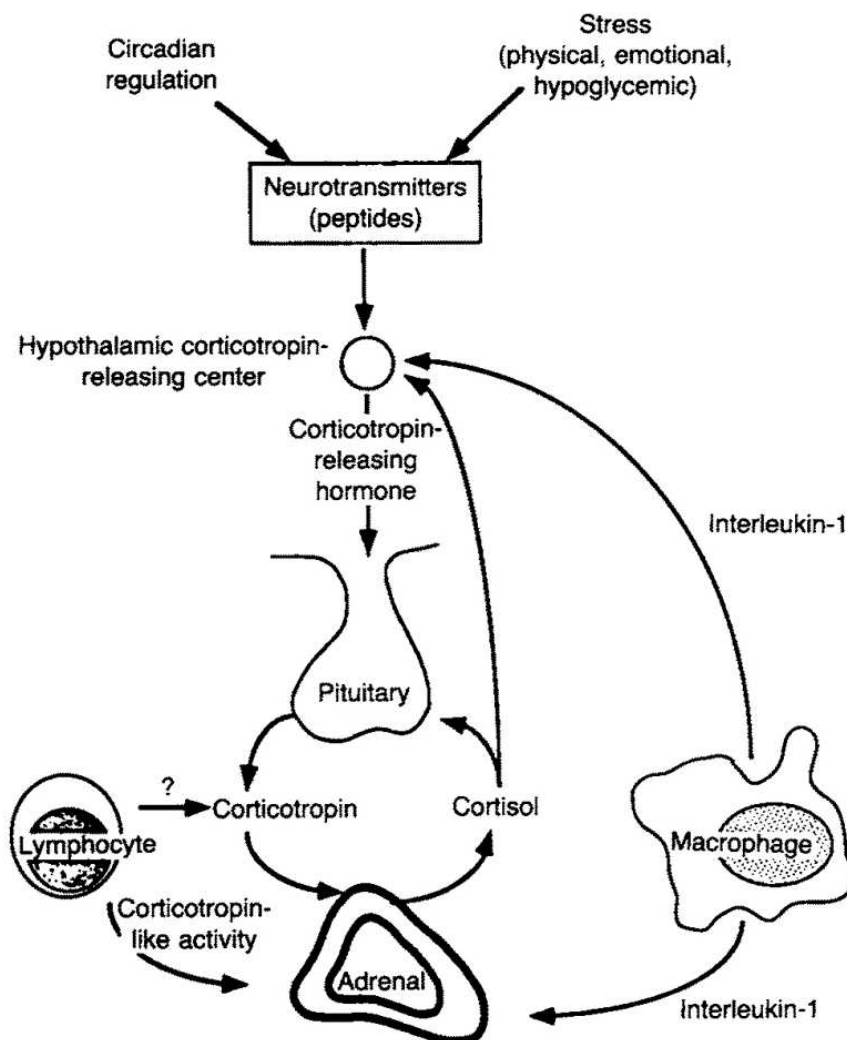


Figure 1. Effects of cytokines on the Hypothalamo-pituitary-adrenal axis.

Both interleukin-1 and interferon thus have effects that could stimulate adrenal function. Conversely, adrenal function could be inhibited in patients with HIV infection as a result of polyclonal B-cell activation and the production of anti—adrenal-cell antibodies. The specific cellular or hormonal antigenic determinants and the pathogenetic importance of these antibodies are unclear. In addition to these mechanisms of adrenal dysfunction in patients with HIV infection, drugs which impair adrenal function directly such as Ketoconazole which inhibits adrenal steroidogenesis, Rifampicin, phenytoin, and opiates which accelerate the degradation of cortisol and therefore lower serum cortisol concentrations are frequently prescribed in HIV infected patients. Although the resulting need for increased cortisol secretion is easily met in normal subjects, it may not be so in patients with HIV infection.

5. Glucocorticoids

The adrenal corticosteroids (Cortisol and Aldosterone), exert profound influences on many physiologic functions by virtue of their diverse roles in growth, development and maintenance of homeostasis [35]. The actions of these corticosteroids are mediated by intracellular receptor proteins, the glucocorticoid (GR) and mineralocorticoid (MR) receptors respectively. These receptors act as hormone-activated transcription factors which regulate the expression of the glucocorticoid and mineralocorticoid target genes respectively. The GR is ubiquitous and is found in virtually all human tissues and organs [1, 35].

Glucocorticoids are essential to maintain the integrity of central nervous system and cardiovascular function, as well as the maintenance of metabolic and immune function.

Tissue hypersensitivity to glucocorticoids was recently hypothesized in patients with Human Immunodeficiency Virus type-1 infection via the accessory proteins Vpr and Tat which enhance GR transactivation [36]. Since HIV-1 long terminal repeat (LTR) and glucocorticoid-responsive promoters use the same set of co-activators, these proteins may stimulate HIV-1-LTR and glucocorticoid-inducible genes concurrently. The former may directly stimulate viral proliferation, while the latter may indirectly enhance viral propagation by suppressing the host immune system through glucocorticoid mediated mechanisms.

6. Glucocorticoid hypersensitivity in AIDS

AIDS patients have several manifestations compatible with tissue hypersensitivity to glucocorticoids [37]. Some of the manifestations include reduction of innate and cellular immunity mediated through T helper 1 cells with resultant reduction in the secretion of interleukin (IL)-2, IL-12 and interferon and increased secretion of IL-4. These changes are similar to what obtains when exogenous glucocorticoids are administered as well as in hypercortisolemic patients with endogenous Cushing's syndrome. Furthermore, hippocampal atrophy similar to what is observed in individuals who exhibit hypercortisolism is seen in HIV infected patients especially in pediatric AIDS patients. Other features seen in HIV/AIDS pa-

tients that are similar to features of hypercortisolism include muscle wasting and myopathy, dyslipidemia and visceral obesity and insulin resistance. From the foregoing, it seems possible that some unknown factor(s) modulate tissue sensitivity to glucocorticoids in HIV infected patients.

The observed glucocorticoid hypersensitivity in HIV infected patients seem to preferentially affect the brain, fat cells, the liver, the musculoskeletal system and the immune system. It is noteworthy that the hypothalamo-pituitary-adrenal axis is not affected suggesting that appropriate negative feedback sensitivity to glucocorticoids is preserved.

There is evidence to suggest that glucocorticoid hypersensitivity in HIV/AIDS is mediated through one of the HIV-1 accessory proteins the virion-associated protein (Vpr). This is a 96 amino acid protein with multiple functions. This protein is known to act as a transcriptional activator of several viral promoters and as an enhancer of HIV-1 long terminal repeat promoter activated by Tat as well as enhances the replication of HIV-1 virus in lymphocyte- and monocyte-derived cell lines. Furthermore, the protein also increases the translocation of the HIV-1 pre-integration complex into the nucleus promoting efficient infection of non-dividing macrophages.

The protein circulates in HIV-1-infected individuals and has the capacity to penetrate cell membranes. This suggests that its effects have the potential to involve all cells including those not infected by HIV-1. It is indeed this protein that has been shown by Kino *et al* [36] to increase the tissue sensitivity to glucocorticoids by functioning as a coactivator of the GR on its responsive promoters. By inducing hypersensitivity to glucocorticoids, these proteins contribute to the proliferation of the virus indirectly by suppressing the host immune system. Extensive further clinical and basic investigations are crucial to examine the clinical importance of glucocorticoid hypersensitivity and to develop novel effective therapeutic approaches in AIDS.

Although the involvement of the adrenal gland is common in HIV patients, routine screening is not however recommended as adrenal insufficiency is a relatively rare complication of HIV infection. Its presence should however be considered, however, in those with disseminated cytomegalovirus infection or tuberculosis. It should also be suspected, in patients with otherwise unexplained symptoms and signs compatible with adrenal insufficiency, such as anorexia, nausea, weight loss, and fatigue, and especially in patients with more specific manifestations of adrenal insufficiency, such as postural hypotension, hyponatremia, or hyperkalemia. It is also reasonable to be concerned about adrenal reserve in patients who are about to undergo major stress, such as surgery. The simplest test is to measure the serum cortisol concentration in the morning, when it is highest in normal subjects. A concentration of 10 µg per deciliter (280 nmol per liter) or less suggests the presence of adrenal insufficiency. However, higher cortisol concentrations do not rule out the possibility of diminished adrenal reserve. If the basal serum cortisol concentration is low or the suspicion of adrenal insufficiency persists, provocative testing with corticotropin is indicated. Such testing involves measuring the serum cortisol concentration before and 30 and 60 minutes after the intravenous or intramuscular administration of 0.25 mg of cosyntropin. The cortisol concentration should increase by at least 7 µg per deciliter (196 nmol per liter) at 30 minutes and 11

µg per deciliter (308 nmol per liter) at 60 minutes. Alternatively, a normal response is a concentration twice the basal value at 60 minutes. Whether one considers the extent of a change in the cortisol concentration or the multiple of the basal value, the peak stimulated value should be 18 µg per deciliter (504 nmol per liter) or more for the response to be considered normal [48, 49]. Glucocorticoid therapy should be given only in cases of documented adrenal insufficiency or when there is a medical emergency in which the possibility of adrenal crisis cannot be excluded.

7. Gonadal dysfunction in male

Male gonadal dysfunction is common among AIDS patients. With more than two-thirds of male patients with advanced HIV disease exhibit of loss of libido and up to one-third of them having erectile dysfunction [38, 39]. The prevalence and severity of male gonadal dysfunction is directly proportional to disease severity. In advanced disease stages, biochemical hypogonadism is found in up to half of male AIDS patients. With the advent of HAART, the prevalence of male gonadal dysfunction has reduced to about 20% among those receiving HAART [40]. Gonadal dysfunction in HIV/AIDS is usually attributable to secondary causes such as the effect of under nutrition, infection-inflammation and several drugs on gonadotropin production. Other secondary causes include the role of cytokines produced in response to systemic illness may impair the secretion of gonadotropin-releasing hormone or gonadotropin [41]. Low levels of interleukin-1 enhance testicular steroidogenesis in vitro, whereas higher doses inhibit the binding of gonadotropin to Leydig cells and steroidogenesis by these cells. Ketoconazole used in the treatment of fungal infections in HIV/AIDS patients inhibits gonadal as well as adrenal steroid production and could therefore also contribute to the observed gonadal dysfunction.

Furthermore, hyperprolactinaemia and gynecomastia have been reported among HIV-infected patients [42]. Prolactin has for long been known to be an immunostimulatory hormone and is also known to be elevated in other immunostimulatory states such as systemic lupus erythematosus (SLE). Similarly, prolactin receptors are found in T and B lymphocytes as well as monocytes [43], while lymphocytes are known to produce a prolactin like protein. The men with low serum testosterone concentrations may have inappropriately normal serum gonadotropin concentrations, suggesting involvement of the pituitary gland or hypothalamus however, there is neither CT scans nor autopsy data provide evidence of pituitary or hypothalamic disease.

As sex hormone binding capacity increases in up to a third of HIV patients, the use of free testosterone assay is recommended for diagnosis. [38] Physiologic testosterone replacement that does not suppress endogenous gonadal function results in increased lean body mass, improved quality of life and reduction in depression. Standard therapy for hypogonadism has been intramuscular testosterone (enanthate or cipionate esters) every 1–3 weeks to provide 100 mg per week. Alternate transdermal or oral routes for androgen administration are also available. Prostate-specific antigen level should be monitored in elderly patients receiving testosterone.

8. Gonadal dysfunction in female

Ovarian dysfunction among female AIDS patients is less common. Amenorrhoea is seen in about a quarter of women during stress of illness; while failure of ovulation is seen among half of the female patients with low CD4 counts [44]. Early menopause has been seen in up to 8% of HIV-infected female patients. Androgen deficiency has been reported especially in women with significant weight loss. The reasons for the above observations are not clear, but could be as a result of intra-adrenal shunting toward cortisol production from androgen synthesis. Human chorionic gonadotropin levels suggest intact ovarian androgen production. Delivery of low doses of testosterone using transdermal patches improves functional capacity without hirsutism or virilisation but does not increase lean body mass [38].

9. Glucose homeostasis in HIV/AIDS

Normal glucose metabolism is largely dependent on normal insulin secretion, insulin sensitivity and to a lesser extent on the influences of other hormones and cytokines. Before the advent of highly active anti-retroviral therapy (HAART), HIV infection on its own was thought to be protective against the development of diabetes mellitus¹, this may be due to the following observations in clinically stable, symptomatic HIV-infected patients. These individuals have been shown to have higher rates of insulin clearance and increased sensitivity of peripheral tissues to insulin as well as an increase in noninsulin-mediated glucose uptake. The increase in glucose uptake is predominantly accounted for by an increase in non-oxidative glucose disposal.

Pancreatic abnormalities are common in AIDS patients as a result of opportunistic infections and malignancies¹. However, the majority of these lesions are not extensive enough to cause clinically significant pancreatic dysfunction. Clinically significant pancreatic dysfunction is usually as a result of therapeutic interventions; noteworthy in this regard is Pentamidine [45], which is used in the management of *Pneumocystis carinii* and may cause pancreatic β -cell toxicity with resultant hypoglycaemia in the acute phase and some of these patients may later develop diabetes mellitus.

With the advent of HAART however, a new dysmetabolic syndrome with substantially increased risk for cardiovascular events emerged [46]. This syndrome has variable expressibility; and includes insulin resistance, visceral adiposity, peripheral lipodystrophy, dyslipidaemia and glucose intolerance. Several studies have demonstrated an increased risk of diabetes among HIV infected individual on HAART especially when protease inhibitors (PIs) are included in the regimen. Among HIV infected minority patients in the USA for example, the prevalence of diabetes after three years of PI therapy was 12%, compared to none among those not receiving PI's⁴. However, although PI's are the most frequent agents associated with metabolic complication, there are evidences to suggest that virtually all classes of agents used in ART has the potential to cause metabolic derangements. Although the mechanism by which ART drugs induce these metabolic changes are not fully clear; it has been

shown that indinavir, a PI dramatically inhibits glucose uptake in a dose dependent manner in adipocytes by selectively inhibiting the Glut-4 transporter function [47]. Furthermore, there is evidence at least in laboratory studies to show that indinavir down regulates the peroxisome proliferator-activated receptor γ (PPA γ) receptor in adipocytes [48]. Obviously some genetic predisposition could explain why not all patients on PI's develop diabetes, or any of the other metabolic complications.

10. Bone mineral dysfunction

Both osteoporosis and osteopenia are common among AIDS patients. Reduced bone mineral density is seen in almost three quarter of HIV-infected patients compared to about 30% in HIV-negative individuals of similar age [49]. Reduced vertebral bone density is associated with visceral adiposity among HIV-infected patients. Similarly, reduced bone density also occurs in HIV-infected children receiving HAART with maximum reduction seen among those with lipodystrophy. Several factors are thought to be responsible for the observed effects on the skeleton. The effects of low GH and IGF1, hypogonadism and excess visceral adiposity are possible factors as they have been found to correlate significantly with vertebral bone density [50 - 52]. Protease Inhibitors are also known to induce relative vitamin D deficiency and may also act as an additive factor.

11. Calcium and vitamin D balance

Hypocalcemia is common in HIV infected patients occurring in more than 5% of them [53]. It appears the level of calcium has an inverse relationship with the stage of the disease and its severity. Factors responsible for hypocalcaemia in these patients include vitamin D deficiency and reduced parathyroid hormone (PTH) level. The cause of the relatively reduced PTH is not known but may be as a result of the effects of cytokines; and presence of hypomagnesemia which is relatively common among HIV infected patients especially those with chronic diarrhoea. On the other hand, the cause of Vitamin D deficiency is multifactorial in the setting of HIV/AIDS and may include malabsorption, decreased hydroxylation as a result of the effects of protease inhibitors. Furthermore, several therapeutic agents such as foscarnet, pentamidine, and ketoconazole, may affect calcium homeostasis [53].

Hypercalcemia is uncommon in AIDS. When present it is likely to be due to infectious, malignant, or granulomatous processes [54 - 55]. Patients with lymphoma who have hypercalcemia typically have increased serum 1,25-dihydroxyvitamin D concentrations, because the tumors contain vitamin D 1-hydroxylase and therefore convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Cultured lymphoma cells infected with HIV have the same synthetic activity. Human T-cell lymphotropic virus Type I (HTLV-I), a retrovirus linked to T-cell leukemia and lymphoma may be associated with hypercalcemia. Increased bone resorption in this syndrome may be due to lymphokines such as interleukin-2 or to parathy-

roid hormone-related protein. A HTLV-I gene product, *tax*, has been implicated in the activation of the parathyroid hormone-related protein gene. Serum concentrations of parathyroid hormone and 1,25-dihydroxyvitamin D are not elevated in HTLV-I—related hypercalcemia.

12. AID wasting syndrome

Wasting is an age-old terminal event of AIDS, even with the advent of HAART, wasting remains common affecting more than one-third of patients [57]. Unfortunately, weight loss is a significant predictor of mortality in HIV infection. Those with a body mass index (BMI) of less than 18.4 kg/M² are at 2.2-fold increased risk of mortality, while those with a BMI less than 16 kg/M² are at 4.4-fold increased risk of mortality [58].

Currently, AIDS wasting syndrome is defined as body weight less than 90% of ideal weight or weight loss of more than 10% of body weight over 3 months. The condition is characterised by a disproportionate loss of lean body mass with a relative sparing of body fat as the disease progresses this is associated with muscle wasting, weakness, increased resting energy expenditure and hypertriglyceridemia. The exact mechanisms involved in the aetiology of this condition are not clear. However, the roles of Cytokine related increased energy expenditure and decreased appetite, diarrhoea, malabsorption and hypogonadism are likely mechanisms behind such wasting [59, 60].

Management of this condition include optimal antiretroviral therapy and adequate nutrition. Testosterone (intramuscular/transdermal) has been successfully used to increase lean body mass in men with this syndrome, whereas it has also been shown to be safe and well tolerated in women. A number of agents like anabolic steroids (oxandrolone, nandrolone), megestrol acetate, thalidomide, human chorionic gonadotropin, pentoxifyline, amino acid mixtures and omega 3 fatty acids have been tried in this setting with variable efficacy but potential side effects. Only testosterone administration has proved useful to increase lean body mass, especially in conjunction with progressive resistance training. Administration of supraphysiologic doses of growth hormone is currently reserved for severe wasting refractory to other treatments.

13. HIV lipodystrophy syndrome

HIV lipodystrophy syndrome is associated with metabolic derangements, changes in body composition and abnormal fat distribution. It has been most widely recognized since the era of HAART but can also be seen in antiretroviral-naïve patients [61]. It is characterized by phenotypic changes similar to those observed in Cushing's syndrome, such as like truncal obesity, buffalo hump, peripheral fat loss, atrophy of facial fat and breast enlargement in women. Considering some physical similarities to Cushing's syndrome, it has been termed as "a pseudo-Cushing's syndrome" though no other specific stigmata of Cushing's syndrome (proximal muscle weakness, bruising and facial plethora) nor biochemical paramete-

ters are associated with this syndrome. Normal cortisol level with its normal diurnal variation and adequate suppressibility to dexamethasone are also seen in HIV lipodystrophy syndrome. However, it is very often associated with insulin resistance, hyperglycemia, and hypertriglyceridemia. In particular, dyslipidemia and diabetes mellitus are increasingly common among patients receiving HAART. management consist of exercise and lifestyle modification, switching to less-toxic NRTIs or PIs, fenofibrates to decrease serum triglyceride level, and use of insulin sensitizers like metformin to reduce visceral fat and thiazolidinediones to improve subcutaneous fat loss. Testosterone and anabolic steroids have no effect in reducing visceral fat in this syndrome.

14. Conclusion

Although HIV endocrinopathy is common, overt glandular failure is a rare clinical entity. HIV infection, acting by a number of mechanisms, may be responsible for subtle clinical and not-so-subtle biochemical abnormalities. Drug-induced endocrine toxicity is important cause of endocrinopathy in HIV infected patients.

Author details

Bakari Adamu Girei and Sani-Bello Fatima

Endocrinology Unit, Department of Medicine, Ahmadu Bello University, Zaria, Nigeria

References

- [1] Sellmeyer, D. E., & Grunfeld, C. Endocrine and metabolic disturbances in Human Immunodeficiency virus infection and the acquired immune deficiency syndrome. *End. Rev.* (1996). , 17, 518-532.
- [2] Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* (1998). , 338, 853-60.
- [3] Deeks, S. G., Smith, M., Holodny, M., Kahn, J. O. H. I. V., proteaseinhibitors, a., review, for., & clinicians, J. A. M. *JAMA* (1997). , 145 EOF-53 EOF.
- [4] Salehian, B., Bilas, J., Bazargam, M., & Abbasian, M. Prevalence and incidence of diabetes in HIV infected minority patients on protease inhibitors *J Nat Med Ass* (2005). , 97, 1088-92.
- [5] Hutchinson, J., Murphy, M., Harries, R., & Skinner, C. J. Galactorrhoea and hyperprolactinoma associated with protease inhibitors. *Lancet.* (2000). , 356, 1003-4.

- [6] Cozzolino, M., Vidal, M., Arcidiacono, M. V., Tebas, P., Yarasheski, K. E., & Dusso, H. I. HIV-protease inhibitors impair vitamin D bioactivation to 1, 25-dihydroxyvitamin D. *AIDS*. (2003). , 17, 513-20.
- [7] Hadigan, C., Borgonha, S., Rabe, J., Young, V., & Grinspoon, S. Increased rates of lipolysis among HIV-infected men receiving highly active antiretroviral therapy. *Metabolism*. (2002). , 51, 1143-7.
- [8] Madeddo G, Spanu A, Chessa F et al: Thyroid function in Human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): a longitudinal study. *Clinical Endocrinol* 2006;64:375-83.
- [9] Ferrerio, J., & Vinters, H. V. Pathology of pituitary gland in patients with acquired immune deficiency syndrome (AIDS) *Pathology*. (1988). , 20, 211-5.
- [10] Vitting KE, Gardenswartz MH, Zabetakis PM, Frequency of hyponatraemia and non osmolar vasopressin release in the acquired immunodeficiency syndrome. *JAMA* (1990). , 263, 973-978.
- [11] Cusano AJ, Thies HL, Siegal FP, Hyponatraemia in patients with acquired immunodeficiency syndrome. *J AcquirImuneDeficSyndr HumRetrvir* (1990). , 3, 949-953.
- [12] Agarwal, A., Soni, A., Ciechanowsky, M., Chander, P., & Treser, G. Hyponatraemia in patients with the acquired immunodeficiency syndrome. *Nephron* (1989). , 53, 317-321.
- [13] Hoffman CJ, Brown TT. Thyroid function abnormalities in HIV infected patients. *Clin Infect Dis*. (2007). , 45, 488-94.
- [14] , 5., Bourdoux, P. P., De Wit, S. A., Servais, G. M., Clumeck, N., & Bonnyns, . Biochemical thyroid profile in patients infected with human immunodeficiency virus. *Thy. roid*. (1991). , 1, 147-9.
- [15] Jimenez C, Moran SA, Sereti I: Graves' disease after interleukin-2 therapy in patients with HIV infection : *Thyroid* 2004;14:1097-1102
- [16] Nelson, M., et al. Thyroid dysfunction and relationship to antiretroviral therapy in HIV-positive individuals in the HAART era. *J Acqu. ir Immune DeficSyndr*. (1990). , 50, 113-14.
- [17] Madeddo G, Spanu A, Chessa F et al: Thyroid function in Human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): a longitudinal study. *Clinical Endocrinol* 2006;64:375-83.
- [18] Goddard, G. Z., Shoenfeld, Y. H. I. V., autoimmunity, ., & autoimmunity, reviews. *autoimmunity reviews* : (2002).
- [19] Ragni, M. V., Dekker, A., De Rubertis, F. R., Watson, C. G., Skolnick, M. L., Goold, S. D., Finikiotis, M. W., Doshi, S., & Myers, D. J. (1991). *Pneumocystis carinii* infection presenting as necrotizing thyroiditis and hypothyroidism. *Am J Clin Path*, 01, 95-489.

- [20] Guttler, R., Singer, P. A., Pneumocystis, carinii, & thyroiditis, . Report of three cases and review of the literature. Arch Intern Med. (1993). , 153, 393-396.
- [21] Frank TS, LiVolsi VA, Connor AM. Cytomegalovirus infection of the thyroid in immunocompromised adults. Yale J Biol Med (1987). S, 60, 1.
- [22] Machac, J., Mejatheim, M., & Goldsmith, S. J. (1985). Gallium-67 citrate uptake in cryptococcal thyroiditis in a homosexual male. J Nucl Med Allied Sci , 29, 283-285.
- [23] Martinez-Ocana, J. C., Romen, J., Llatjos, M., Sirera, G., & Clotet, B. Goiter as a manifestation of disseminated aspergillosis in a patient with AIDS. Clin Infect Dis.(1993). , 17, 953-954.
- [24] Mollison, L. C., Mijch, A., Mc Bride, G., & Dwyer, B. 1991Hypothyroidism due to destruction of the thyroid by Kaposi's sarcoma. Rev Infect Dis. 1991; , 13, 826-827.
- [25] Membreno, L., Irony, I., Dere, W., Klein, R., Biglieri, E. G., & Cobb, E. Adrenocortical function in acquired immune deficiency syndrome. J ClinEndocrinolMetab. (1987). , 65, 482-7.
- [26] Tapper, M. L., Rotterdam, H. Z., Lemer, C. W., Al'Khafaji, K., & Seitzman, P. A. Adrenal necrosis in the acquired immunodeficiency syndrome. Ann Intern Med. (1984). , 100, 239-241.
- [27] Findling, J. W., Buggy, B. P., Gilson, I. H., Brummitt, C. F., & Bernstein, Raff. H. Longitudinal evaluation of adrenocortical function in patients infected with the human immunodeficiency virus. J ClinEndocrinolMetab. (1994). , 79, 1091-1096.
- [28] Verges, B., Chavanet, P., Desgres, J., Vaillant, G., Waldner, A., Brim, J. M., & Putelat, R. Adrenal function in HIV infected patients. ActaEndocrinol (Copenh). (1989). , 121, 633-637.
- [29] Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor . Science 1987;238:522-4.
- [30] Woloski BM, Smith EM, Meyer WJ, Fuller GM, Blalock JE. Corticotropin-releasing activity of monokines. Science (1985). , 230, 1035-1037.
- [31] Whitcomb RW, Linehan WM, Wahl LM, Knazek RA. Monocytes stimulate cortisol production by cultured human adrenocortical cells. J ClinEndocrinolMetab (1988). , 66, 33-8.
- [32] Meyer, W. J. I. I., Smith, E. M., Richards, G. E., Cavallo, A., Morrill, achéal., & Blalock, J. E. In vivo immunoreactiveadrenocorticotropin (ACTH) production by human mononuclear leukocytes from normal and ACTH-deficient individuals. J ClinEndocrinolMetab (1987). , 64, 98-105.
- [33] Merrill JE, Koyanagi Y, Chen ISY. Interleukin-1 and tumor necrosis factor α can be induced from mononuclear phagocytes by human immunodeficiency virus type 1 binding to the CD4 receptor . J Virol 1989; 63:4404-8.

- [34] Szebeni, J., Dieffenbach, C., Wahl, S. M., et al. Induction of alpha interferon by human immunodeficiency virus type 1 in human monocyte-macrophage cultures. *J Virol* (1991). , 65, 6362-4.
- [35] Guire, M. A. P., & Holbrook, N. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrinol. Rev* (1984). , 5, 25-44.
- [36] Kino T, Gragerov A, Kopp JB, Stauber RH, Pavlakis GN & Chrousos GP. The HIV-1 virion-associated protein vpr is a coactivator of the human glucocorticoid receptor. *Journal of Experimental Medicine* 1999;189: 51-62.
- [37] Kino, T., & Chrousos, G. P. Glucocorticoid and mineralocorticoid resistance/hypersensitivity syndromes. *Journal of Endocrinology* (2001). , 437-445.
- [38] Mylonakis, E., Koutkia, P., & Grinspoon, S. Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. *Clin Infect Dis*. (2001). , 33, 857-64.
- [39] Dobs AS, Dempsey MA, Ladenson PW, Polk BF. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med*. (1988). , 84, 611-6.
- [40] Rietschel, P., Corcoran, C., Stanley, T., Basgoz, N., Klibanski, A., & Grinspoon, S. Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. *Clin Infect Dis*. (2000). , 31, 1240-4.
- [41] Calkins JH, Sigel MM, Nankin HR, Lin T. Interleukin-1 inhibits Leydig cell steroidogenesis in primary culture. *Endocrinology* 1988; 123:1605-10.
- [42] Graff AS, Gonzalez SS, Baca VR, Ramirez ML, Daza LB et al. High serum prolactin levels in asymptomatic HIV-infected patients and in patients with Acquired Immune deficiency syndrome. *Clin Immunol. Immunopath* (1994). , 72, 390-3.
- [43] Russell, D. H., Matrisian, L., Kibler, R., et al, , Prolactin, receptors., on, Human. T., lymphocytes, B., their, modulation., & by, Cyclosporine. *J. Immunol* (1985). , 134, 3027-31.
- [44] Grinspoon, S., Corcoran, C., Miller, K., Biller, Askari. H., Wang, E., et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *J Clin Endocrinol Metab*. (1997). , 82, 1332-7.
- [45] Perronne, C., Bricaire, F., Leport, C., Assan, D., Vilde, J. L., & Assan, R. Hypoglycaemia and diabetes mellitus following parenteral pentamidine mesylate treatment in AIDS patients. *Diabetic Med* (1990). , 7, 585-9.
- [46] Hruz PW. Molecular mechanisms for altered glucose homeostasis in HIV infection. *Am J Infectious Dis*. (2006). , 2, 187-192.
- [47] Murata, H., Hruz, P. W., & Mueckler, M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy *J Biol Chem* (2000). , 275, 20251-4.

- [48] Caron M, Auclair M, Vigouroux C et al. the HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation and induces insulin resistance. *Diabetes* 2001; 50:1378-88.
- [49] Tebas, P., Powderly, W. G., Claxton, S., Marin, D., Tantisiriwat, W., Teitelbaum, S. L., et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS*. (2000). F, 63-7.
- [50] Stagi, S., Bindi, G., Galluzzi, F., Galli, L., Salti, R., & de Martino, M. Changed bone status in human immunodeficiency virus type 1 (HIV-1) perinatally infected children is related to low serum free IGF-1. *ClinEndocrinol (Oxf)* (2004). , 61, 692-9.
- [51] Glass, A. R., & Eil, C. Ketoconazole-induced reduction in serum 1,25-dihydroxyvitamin D. and total serum calcium in hypercalcemic patients. *J ClinEndocrinolMetab* (1988). , 66, 934-8.
- [52] Effects of growth hormone-releasing hormone on bone turnover in human immunodeficiency virus-infected men with fat accumulation. *J ClinEndocrinolMetab.*; , 90, 2154-60.
- [53] Kuehn EW, Anders HJ, Bogner JR, Obermaier J, Goebel FD, Schlöndorff D. Hypocalcemia in HIV infection and AIDS. *J Intern Med*. 1999;245:69-73.
- [54] Adams JS, Fernandez M, Gacad MA, et al. Vitamin D metabolite-mediated hypercalcemia and hypercalciuria in patients with AIDS- and non-AIDS-associated lymphoma . *Blood* 1989;73:235-9.
- [55] Dodd RC, Newman SL, Bunn PA, Winkler CF, Cohen MS, Gray TK. Lymphokine-induced monocytic differentiation as a possible mechanism for the hypercalcemia associated with adult T-cell lymph. oma. *Cancer Res* (1985). , 45, 2501-6.
- [56] Motokura, T., Fukumoto, S., Matsumoto, T., et al. Parathyroid hormone-related protein in adult T-cell leukemia-lymphoma. *Ann Intern Med* (1989). , 111, 484-8.
- [57] Wanke, Silva. M., Knox, T. A., Forrester, J., Speigelman, D., & Gorbach, S. L. Weight loss and wasting remain common complications in individuals infected with HIV in the era of highly active antiretroviral therapy. *Clin Infect Dis*. (2000). , 31, 803-5.
- [58] Anthropometric indices as predictors of survival in AIDS adults. Aquitaine Cohort, France, 1985-1997. Group d'Epidemiologie Clinique du Sida en Aquitaine (GECSA) *Eur J Epidemiol.*; , 16, 633-9.
- [59] Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome . *J ClinEndocrinolMetab* 1992; 74:1045-52.
- [60] Macallan, D. E., Noble, C., Baldwin, C., Jebb, S. A., Prentice, A. M., Coward, W. A., et al. Energy expenditure and wasting in human immunodeficiency virus infection. *N Engl J Med*. (1995). , 333, 83-8.

- [61] Miller, K. K., Daly, P. A., Sentochnik, D., Doweiko, J., Samore, M., Basgoz, N. O., et al., & Pseudo, . Pseudo-Cushing's syndrome in human immunodeficiency virus-infected patients. *Clin Infect Dis.* (1998). , 27, 68-72.

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