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Endocrine and Metabolic Disturbances in Human Immunodeficiency Virus Infection and the Acquired Immune Deficiency Syndrome*

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I. Introduction

A. Overview

MANY alterations in endocrine function have been reported in association with human immunodeficiency virus (HIV) infection and the acquired immune deficiency syndrome (AIDS). These changes may result from the direct effects of opportunistic infections and neoplasms or complications of medications used in the treatment of these disorders. However, alterations in endocrine function can be seen in any systemic illness, including HIV infection and its complications. This review will discuss abnormalities in endocrine gland pathology and function, considering whether alterations are functionally significant, HIV-specific, side effects of HIV therapy or a change consistent with a normal response to acute illness.

Because many articles represent case reports or series, it may not yet be possible to define the prevalence of endocrine abnormalities or the stage of disease at which the anomalies may occur. There are virtually no randomized trials of endocrine replacement therapy and few open-label studies. Therefore, recommendations for therapy are limited at this time. However, the potential for therapeutic trials will be discussed.

B. The clinical course of HIV infection and AIDS

The HIV virus affects many organ systems primarily through the immunocompromised state that results in the later phases; as viral load of HIV increases, the increasing host response to HIV itself may directly affect end-organs. The early phase of HIV infection is relatively asymptomatic; however, the virus is not latent, but rather actively contained by the immune system. As a consequence, metabolic changes occur in these early stages. Eventually immunosuppression occurs, in great part due to the progressive loss of CD4 T-helper cells.

The time between primary HIV infection and significant immunosuppression is long, averaging 10 yr, as well as very variable, ranging upward from 2 yr. As a result, most patients experience a prolonged, relatively asymptomatic period. Furthermore, recent studies indicate wide variations in HIV viral load early in the course of the disease. Viral burden is an independent predictor of immunosuppression and advancement to AIDS, suggesting actions by the virus beyond its detectable effects on CD4 cells. However, the onset of complications can be reasonably predicted by CD4 cell counts as presented in Table 1 (1).

II. The Thyroid

A. Infection and tumor invasion of the thyroid

In autopsy series, opportunistic pathogens such as Cytomegalovirus (CMV), *Mycobacterium avium*, *Cryptococcus neo-*

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TABLE 1. Onset of HIV-related infections in relation to CD4 cell counts

CD4 Cell count		
Less than 400	Less than 200	Less than 50
Bacterial infections	*Pneumocystis carinii*	Cytomegalovirus
Urinary tract infections	*Toxoplasmosis*	*Mycobacterium avium*
Shingles	Coccidiomycosis	*Cryptococcus*
Herpes simplex	Cryptosporidiosis	Aspergillius
Oral and vaginal candidiasis	Isospora	Histoplasmosis
Tuberculosis		

formans, and *Pneumocysitis carinii* as well as AIDS-related neoplasms such as Kaposi's sarcoma have been found in the thyroid (2). Most of these patients did not present with antemortem thyroid dysfunction.

Several patients with inflammatory thyroiditis due to *P. carinii* accompanied by thyroid function abnormalities have been described. Seven of these cases exhibited hypothyroidism (3–8) and three had hyperthyroidism (7, 9, 10). One additional patient with thyroiditis due to *P. carinii* had normal thyroid function (11). Another patient with thyroiditis was reported in whom thyroid function was not measured (12). In five cases with hypothyroidism (3–5, 7) and in one case with hyperthyroidism (9), antithyroid antibodies were measured and found to be negative. Radionuclide scanning was performed in seven cases. Poor visualization of the entire thyroid gland was seen in five patients (7, 9, 10). The remaining two patients had unilateral disease with nonvisualization of the affected lobe (5, 11). In two patients with hyperthyroidism, treatment of the *P. carinii* infection resulted in normalization of thyroid function (7, 10).

A series of five patients with CMV infection of the thyroid was reported by Frank *et al.* (13). Two of these patients had low FT_4I with normal TSH levels, and one had normal FT_4I and TSH; thyroid functions were not measured in the remaining two. Thyroid involvement in the setting of disseminated fungal infection with *C. neoformans* (14) and *Aspergillus fumigatus* (15) has been described. These two patients had low T_3 but otherwise normal thyroid function, consistent with the euthyroid sick syndrome. Kaposi's sarcoma has also been demonstrated to involve the thyroid in three cases (2, 16, 17), one of which involved significant destruction of the gland by the tumor, resulting in hypothyroidism (17).

In summary, several HIV-related opportunistic infections as well as Kaposi's sarcoma can involve the thyroid. These syndromes are rare and only occasionally result in altered thyroid function.

B. Abnormalities of thyroid function tests

Thyroid hormone homeostasis can be altered by any severe systemic illness or caloric deprivation. These changes, referred to as the "euthyroid sick syndrome," are characterized by impaired peripheral T_4 to T_3 conversion by 5'-deiodinase, resulting in decreased levels of T_3 and variable levels of T_4 (18, 19). The euthyroid sick syndrome is usually accompanied by increases in rT_3 due to decreased clearance of rT_3 (18, 20). TSH tends to remain in the normal range although mild elevations can be seen during recovery from nonthyroidal illness (18). Studies of the low T_3 state induced by fasting suggest that this decrease is a protective mechanism that limits muscle protein catabolism (21). Replacement with exogenous T_3 during fasting results in accelerated negative nitrogen balance (22).

An early study of thyroid function in HIV-infected patients showed minimal abnormalities. Dobs *et al.*(23) found four of 70 outpatient men with stages of HIV ranging from asymptomatic to AIDS to have a low serum total T_4. However, only one of these patients had a low FT_4I, and all other thyroid indices were normal. Hommes *et al.* (24, 25) also found normal T_3 and T_4 in stable HIV-infected men.

In contrast, Raffi *et al.* (26) studied 98 HIV-infected inpatients and found a significant decrease in free T_3 in AIDS patients compared with patients with AIDS-related complex, and a significantly lower free T_3 in AIDS-related complex patients than in asymptomatic patients. All patients with low T_3 had normal baseline and peak TSH after TRH stimulation. Lower T_3 values were observed in the sicker patients and correlated with weight loss and decreased CD4 cell counts. The lower T_3 values observed in this study may reflect a higher degree of illness among the study population, all of whom were hospitalized. However, Merenich *et al.* (27) found a similar result in his study of 46 asymptomatic HIV-positive patients. Compared with seronegative controls, these patients had a significant decrease in T_3 with no differences in basal or TRH-stimulated TSH levels.

LoPresti *et al.* (28) compared thyroid hormone status in 26 AIDS patients admitted with *P. carinii* pneumonia to equally ill intensive care unit patients, outpatients with various stages of HIV infection, and seronegative controls. HIV-infected patients were found to have a normal T_3 until hospitalized, whereupon T_3 levels fell. Serum T_3 was significantly lower in HIV patients who did not survive hospitalization and, in fact, a low T_3 on admission correlated with mortality. This association has been demonstrated in two other studies as well (29, 30).

Because T_3 levels in some of the AIDS patients in these studies have been normal, it has been questioned whether the failure to decrease T_3 may be inappropriate and in fact contribute to weight loss. However, Grunfeld *et al.* (31) demonstrated that when patients with HIV infection were categorized in terms of weight loss and caloric intake, T_3 levels remained normal during asymptomatic periods of stable weight and decreased by 19% in AIDS patients without active secondary infections whose weight remained stable. Furthermore patients with active secondary infection and weight loss demonstrated a 45% decrease in T_3. Thus, when AIDS is accompanied by acute infection, T_3 levels decrease, consistent with the euthyroid sick syndrome.

However, in contrast to the usual pattern found in nonthyroidal illness, where decreased T_4 to T_3 conversion resulting in lower levels of T_3 is usually accompanied by increased levels of rT_3, several series have demonstrated low rT_3 levels in patients at all stages of HIV infection (25, 27, 29–32). In the series of LoPresti *et al.*, rT_3 levels were reported to be low in outpatients, and increased to normal levels in hospitalized patients but did not become markedly elevated as is seen in non-AIDS intensive care unit patients (28). Thus, alterations in thyroid hormone metabolism leading to de-

creased rT_3, which are independent of the euthyroid sick syndrome, may occur early in HIV infection. However, the functional significance of rT_3 levels remains unknown.

Patients with HIV infection have elevated levels of thyroid-binding globulin (TBG) that rise with progressive stages of infection (25, 28, 31–34). This increase in TBG does not appear to be the result of generalized changes in protein synthesis as can be seen in liver disease or the inflammatory response, as most patients in these studies had normal liver function, and other binding proteins such as cortisol-binding globulin and sex hormone-binding globulin are not elevated in HIV-infected patients (32). Elevated TBG may occur during pregnancy when the sialylation state of TBG is increased, because the sialylated forms are cleared more slowly; however, the sialylation of TBG is not increased in AIDS (31). TBG can also be elevated by estrogen therapy; however, estrogen levels are normal in asymptomatic HIV patients (27). The clinical significance of HIV-related elevations in TBG is as yet unknown. However, elevated TBG affects interpretation of total T_3 and T_4 measurements.

TSH levels are also altered in HIV infection. Compared with HIV seronegative controls, stable HIV patients without infection have significantly elevated TSH values with lower free T_4 (and rT_3), although these values remain within the normal range (25, 34). In a study of 24-h TSH levels, Hommes *et al.* (25) found this increase in TSH levels to be due to higher TSH pulse amplitude while pulse frequency was unchanged. Additionally, the patients in this study had higher peak TSH values after TRH stimulation than seronegative controls. These alterations may represent a state of compensated hypothyroidism induced by HIV infection. The alterations in thyroid function found in HIV infection are summarized in Table 2 and compared with nonthyroidal illness.

Thyroid hormone homeostasis can be influenced by cytokines released by the host in response to infection. Interleukin-6 (IL-6) administration was studied in patients with metastatic renal cancer and normal thyroid function. IL-6 acutely decreased TSH and T_3 and increased in rT_3. However, after 10 weeks of daily IL-6 administration, T_4, T_3, and rT_3 were at normal levels while TSH was significantly elevated (35). Thus, while the effect of IL-6 on TSH resembles that seen in HIV infection, the effects of IL-6 on T_4, T_3, and rT_3 do not. The effect of tumor necrosis factor (TNF) on thyroid hormone levels has also been studied. In a 10.5-h study of normal men, infusion of TNF resulted in decreased TSH and T_3 with a significant increase in rT_3, the "euthyroid sick" pattern (36). There are several reports of increased IL-6 in HIV infection. Measurements of TNF levels are more variable; most laboratories do not find increased circulating levels of TNF in AIDS (24, 37–39). Further studies are needed to understand the mechanisms by which thyroid hormone levels are altered in HIV infection and to understand the roles of cytokines. However, it appears that, as in most nonthyroidal illnesses, T_3 levels decrease appropriately in AIDS patients with secondary infection, anorexia, and weight loss.

TABLE 2. Alterations in thyroid function tests in HIV infection

	Seronegative, severe nonthyroidal illness	HIV-infected, stable	HIV-infected, ill
T_3	↓↓	Normal	↓↓
rT_3	↑	↓	↓ or Normal
TBG	↑	↑	↑↑
T_4	Normal or ↓	Normal	Normal
TSH	Normal, may be ↑ in recovery	Normal	Normal

↓, ↓↓, Decreased; ↑, ↑↑ increased.

C. The effects of medication on thyroid function

Rifampin, used in *Mycobacterium avium* prophylaxis, induces hepatic microsomal enzymes and increases thyroid hormone clearance. In patients with normal thyroid function, rifampin results in decreases in T_4 and rT_3 with stable or increased T_3 without changes in TSH (40, 41). However, patients on L-T_4 replacement may require higher doses, and patients with decreased thyroid or pituitary reserve may develop overt hypothyroidism when treated with rifampin (42). The endocrinological effects of medications used in the treatment of HIV infection are summarized in Table 3.

D. Summary

Most changes in thyroid function in patients with AIDS resemble the euthyroid sick syndrome; replacement therapy under these circumstances is not indicated and may be harmful. There are no clear clinical implications of the few HIV-specific changes such as decreased rT_3 and elevated TBG.

III. The Adrenal

A. Invasion of the adrenal by infection and tumor

Opportunistic infection of the adrenal glands has been found frequently in pathology studies of patients dying of AIDS. In autopsy series, CMV infection, as evidenced by the presence of inclusion bodies, has been found in 40–88% of adrenals studied (2, 43–50). Adrenal histopathology varied from focal inflammation to extensive areas of hemorrhagic necrosis, which, in several series, was found to affect the medulla more than the cortex (44–48). In studies that quantified the degree of adrenal destruction, the maximum amount of adrenal cortical necrosis ranged from 60–70%, below the 90% thought to be necessary to cause clinical adrenal insufficiency (48, 51). However, CMV adrenalitis resulting in adrenal insufficiency has been reported in two patients (52, 53). Postmortem examination in these patients revealed extensive adrenal necrosis with CMV inclusions. Infection with *Cryptococcus, Toxoplasma, Mycobacterium tuberculosis,* and *Mycobacterium avium* complex as well as infiltration with Kaposi's sarcoma have also been found at postmortem, although they did not appear to be associated with adrenal destruction as was seen with CMV (2, 45, 46, 48, 50).

B. Glucocorticoid hormones

1. Early studies. The frequent pathological abnormalities of the adrenal gland in HIV as well as the similarity of clinical manifestations of AIDS, such as weakness and weight loss, to those of adrenal insufficiency led to early investigation of the adrenal axis in HIV infection. Greene *et al.* (54) found four

TABLE 3. The endocrinological effects of medications used in the treatment of HIV disease

Medication	Mechanism of action	Clinical effects
Rifampin	Induces hepatic microsomal enzymes→increased hormone clearance	No thyroid disease ↓ T_4, rT_3, ↑ T_3, nl TSH
		Hypothyroidism in patients with impaired thyroid reserve
		Adrenal insufficiency in patients with limited reserve
		Decrease 25-hydroxyvitamin D levels; no change in calcium levels
Ketoconazole	Inhibits adrenal and gonadal steroidogenesis	Adrenal insufficiency in patients with limited reserve
		Reduced 1,25 hydroxyvitamin D levels; decreased total, but not ionized calcium levels
		Decreased testosterone levels
Megestrol acetate	Intrinsic glucocorticoid-like activity	Lower serum cortisol levels, ↓ response to provocative testing
		Hyperglycemia
	Progesterone activity	Lower testosterone levels
Trimethoprim	Impairs potassium secretion by inhibiting sodium channels in distal nephron, impairs sodium conservation	Hyperkalemia
		Hyponatremia
Sulfonamides	Interstitial nephritis	Hyporeninemic hypoaldosteronism
Pentamidine	Nephrotoxicity	Hyperkalemia
	Pancreatic toxicity	Acute hypoglycemia
		Chronic hyperglycemia
Foscarnet	Complexes with ionized calcium, possible renal effects	Hypocalcemia
		Nephrogenic diabetes insipidus
Amphotericin B	Impairs proximal and distal tubular reabsorption of electrolytes	Renal magnesium and potassium wasting

of 20 HIV-infected patients with symptoms of adrenal insufficiency to have inadequate responses to a short ACTH stimulation test, with two of these patients demonstrating elevated ACTH levels. However, three patients had received rifampin and two ketoconazole, both of which can affect steroidogenesis and may have altered their cortisol responses. In another early case report, adrenal insufficiency preceded the patient's diagnosis of AIDS by 4 months and occurred at a time when the patient's helper to suppressor T cell ratio was normal (55).

2. *Basal hormone secretion.* In contrast, many larger series have demonstrated normal (23, 26, 56) or, more commonly, elevated basal cortisol levels (57–62) in almost all HIV patients studied. In the setting of elevated basal cortisol, morning ACTH levels were found to be elevated by Verges *et al.* (57), but normal by Membreno *et al.* (59). In a longitudinal study of ambulatory HIV-infected patients, eight of 25 patients had basal morning ACTH levels exceeding the normal range at the end of 2 yr, although cortisol levels remained normal (56). In contrast, a study of 24-h hormonal secretion found elevated basal cortisol with decreased ACTH, suggesting adrenal stimulation by a nonpituitary factor (58).

Elevations in cortisol levels are seen frequently during severe illnesses such as infection. These alterations are most likely mediated by circulating cytokines such as IL-1 or TNF, which have been shown to directly stimulate secretion of cortisol (63). Additionally, IL-1 and IL-6 appear to directly stimulate release of ACTH and CRH (64–67). In the setting of severe illness, when cortisol levels are elevated, tests of adrenal functional reserve may not be normal; however, adrenal function may return to normal upon recovery from illness (68). Hence, there is little evidence for adrenal insufficiency in AIDS. Rather, with progression of HIV disease, a stress response with mild hypercortisolism may ensue.

3. *Provocative testing.* ACTH stimulation testing in HIV-infected patients revealed adequate cortisol response in more than 90% of patients (23, 26, 27, 56, 57, 59, 60). One report examined basal ACTH and cortisol as well as response to CRH stimulation among 25 HIV patients with CD4 cell counts less than 500 but no acute illnesses and no symptoms of adrenal insufficiency. No differences were found in basal hormonal levels compared with HIV-negative controls. In response to CRH stimulation, 50% of these patients had normal cortisol and ACTH responses, 25% had normal ACTH response with reduced cortisol response, and 25% had both reduced cortisol and ACTH responses. These data suggest loss of reserve at either the pituitary or adrenal level in up to 50% of HIV-infected patients (69).

In contrast, among eight patients with symptomatic HIV infection but no opportunistic disease, Biglino *et al.* (62) found nearly absent ACTH and cortisol responses to CRH in six patients and delayed responses in the remaining two. Of note, these eight patients were all drug users; opiate use may blunt ACTH release (70).

Given the high normal or elevated basal levels of cortisol found in patients with HIV disease, a clear case for adrenal insufficiency often cannot be made. Longitudinal studies of glucocorticoid function would be helpful to determine whether the type of response found in HIV-infected patients predicts the development of adrenal impairment.

4. *Disturbances of hormone synthesis.* While clinically significant glucocorticoid deficiency is uncommon in HIV-infected patients, more subtle anomalies in adrenal biosynthesis have been described. Membreno *et al.* (59) demonstrated a significant reduction in the products of the 17-deoxysteroid pathway (corticosterone, deoxycorticosterone, and 18-OH-deoxycorticosterone) before and after ACTH stimulation compared with controls, while the products of the 17-hy-

droxy pathway (cortisol) secretion were normal or even elevated. At normal plasma concentrations, the 17-deoxysteroid products are probably not functionally significant; therefore, whether their decreased secretion is an early marker for evolving adrenal insufficiency or represents an adaptive response to preserve cortisol secretion by shifting away from secretion of steroids that appear to be less physiologically important has yet to be determined. Studies of adrenal androgens reported below suggest that other shifts in adrenal steroid synthesis occur. Serial examinations of adrenal function would help to determine the clinical significance of these changes.

5. Glucocorticoid resistance. A syndrome of glucocorticoid resistance has been described in HIV-infected patients (71). These patients manifest symptoms of weakness, fatigue, weight loss, and hyperpigmentation with elevated cortisol levels and mildly increased ACTH values. Studies of mononuclear lymphocytes from these patients demonstrate an increased number of receptors and decreased receptor affinity for glucocorticoids (71). Recently, a series of HIV-infected patients, 17% of whom were thought to have this syndrome, was reported. In this study, the abnormal glucocorticoid receptors resulted in continual stimulation of interferon-α secretion (72). The absolute prevalence of this syndrome is unknown; however, it is intriguing to consider a possible role of partial glucocorticoid resistance in explaining the elevations in basal cortisol observed in HIV infection as well as some of the variation in cortisol response to provocative testing.

6. The effect of medication on glucocorticoid metabolism. Several medications commonly used in the treatment of HIV-infected patients have been shown to alter glucocorticoid metabolism. Ketoconazole inhibits cortisol synthesis and could lead to adrenal insufficiency in patients with limited adrenal reserve (73). Megestrol acetate has been shown to lower serum cortisol concentrations, possibly by suppression of the hypothalamus-pituitary-adrenal axis through its intrinsic cortisol-like activity. Patients on megestrol with low cortisol levels have low ACTH levels even in response to metyrapone testing (74). Rifampin increases hepatic metabolism of steroid hormones, which could result in adrenal insufficiency in patients with limited adrenal reserve (75, 76). The endocrinological effects of medications used in the treatment of HIV infection are summarized in Table 3.

7. Summary and clinical approach. There is no evidence for adrenal insufficiency due to HIV infection itself; in fact, basal cortisol levels tend to be elevated. Adrenal insufficiency secondary to invasive infection is unusual but can arise as a complication of supervening infections such as occur in advanced HIV disease. Abnormalities of the hypothalamic-pituitary-regulating axis are present, but they are of unknown consequence and probably not HIV specific.

HIV-infected patients with symptoms of adrenal insufficiency should undergo provocative testing. Patients with low basal cortisol secretion and poor response to ACTH stimulation, insulin administration, or metyrapone blockade should be considered for maintenance therapy with glucocorticoids and certainly acute coverage for stress. The combination of low cortisol and elevated basal ACTH would also support a diagnosis of primary adrenal insufficiency. Patients with the common finding of high normal or elevated basal cortisol levels with minimal increase in response to provocative testing pose a more difficult problem, as the majority of these individuals will have a normal cortisol response to prolonged ACTH stimulation (59). The profile of high normal or elevated cortisol and decreased ACTH is common to other severe illnesses, and patients who are successfully treated do not have adrenal insufficiency. Based on these data, most HIV-infected patients with borderline stimulated cortisol values do not appear to require maintenance glucocorticoid therapy; however, short courses of steroids during stress could be considered.

Sequential testing of adrenal function may elucidate the timing or need for appropriate therapy for patients with minimal response to provocative testing. Chronic glucocorticoid therapy is not without risks in this population. Standard daily doses of glucocorticoids may be excessive in patients affected by HIV-associated weight loss and may result in further immunosuppression. Additionally, chronic exogenous steroids could impair the patient's adrenal glands' ability to respond to additional stressors.

C. Adrenal androgens

Basal adrenal androgen secretion in HIV-infected patients has been found to be lower than that in seronegative controls (77–79) and impaired in response to ACTH stimulation at all stages of HIV infection (56). In the study of hormonal circadian variations by Villette *et al.* (58), dehydroepiandrosterone (DHEA) and DHEA-sulfate levels were significantly lower in HIV-infected patients than controls. DHEA has been shown to decline in relation to decreasing CD4 cell counts (77). A fall in DHEA levels predicted progression to AIDS independent of CD4 cell counts in two studies (78, 79).

Urinary steroid excretion rates were compared among HIV-infected outpatients, hospitalized AIDS patients, seronegative intensive care unit patients, and normal controls by Honour *et al.* (80). Excretion of adrenal androgen metabolites was decreased in both HIV-infected groups as well as in the intensive care unit patients; thus, low adrenal androgens may also occur in other illness states. DHEA has been shown *in vitro* to reduce HIV replication (81), raising the question of whether the low DHEA levels observed in HIV-infected patients could influence the effects of the HIV virus. To date, there are no randomized controlled trials of adrenal androgen replacement therapy in AIDS. The efficacy of adrenal androgen replacement has not yet been demonstrated by placebo-controlled trials in other diseases accompanied by lower adrenal androgens.

D. Mineralocorticoid hormones

Deficiency of mineralocorticoid hormones results in sodium wasting, hyperkalemia, hypotension, and elevated levels of PRA. Hyponatremia and hyperkalemia are common findings in patients with AIDS, yet studies of the renin-angiotensin system in these patients are limited. Mineralocorticoid deficiency occurring in one AIDS patient with hy-

ponatremia, elevated plasma renin, relatively low plasma aldosterone, and a blunted cortisol response to ACTH stimulation has been reported (82). Of note, a random cortisol obtained a few days previously in this patient was elevated. Additionally, four AIDS patients with persistent hyperkalemia were found to have low renin activity and low aldosterone levels in response to diuretic and postural stimulation (83). However, all of these patients were being treated with trimethoprim-sulfamethoxazole. Trimethoprim impairs potassium secretion by inhibiting sodium channels in the distal nephron and can lead to hyperkalemia (84). In addition, sulfonamides can cause interstitial nephritis (85), which is associated with hyporeninemic hypoaldosteronism (86). Hyperkalemia has also been reported during treatment with pentamidine; it resolved upon discontinuation of the drug and was felt to be due to nephrotoxicity (87).

In larger series, mineralocorticoid deficiency is uncommon. Membreno *et al.* (59) found normal increases in plasma aldosterone in response to angiotensin III infusion and postural stimulation in 40 hospitalized HIV patients. Verges *et al.* (57) found no abnormalities in PRA or basal and ACTH-stimulated aldosterone levels in 63 HIV-infected patients compared with noninfected controls. In a study of 40 asymptomatic men with early HIV infection, two patients were found to have abnormal aldosterone responses to ACTH stimulation (27). However, Findling (56), in a longitudinal study of 53 ambulatory HIV patients, found that whereas basal aldosterone and PRA remained unchanged over a 2-yr period, up to 26% of CDC classes II-III patients and up to 53% of CDC class IV patients had an impaired aldosterone response to ACTH stimulation at each study interval. Given the relatively long follow-up in this study, these data suggest that a poor aldosterone response to ACTH stimulation does not predict the development of significant hypoaldosteronism. Similar types of studies are needed to evaluate glucocorticoid function.

Thus, electrolyte abnormalities in AIDS are not likely to be due to HIV infection. Rather, these patients should first be evaluated for drug toxicities, interstitial kidney disease, or the syndrome of inappropriate ADH secondary to pulmonary or central nervous system processes. The endocrinological effects of medications used in the treatment of HIV infection are summarized in Table 3.

IV. Mineral Homeostasis

Hypocalcemia and hypercalcemia have both been reported in association with HIV infection. Hypocalcemia has occurred during therapy with foscarnet, a pyrophosphate analog used in the treatment of CMV retinitis (88–90). *In vitro* studies suggest that hypocalcemia could be due to the formation of complexes of foscarnet with ionized calcium (90). However, some cases of hypocalcemia have been accompanied by hypomagnesemia and hypokalemia (88), suggesting renal tubular damage. Hypocalcemia and hypomagnesemia have also been reported following administration of pentamidine (91, 92). Furthermore, severe and, in one case, fatal hypocalcemia has been reported when foscarnet and intravenous pentamidine were used together (89). Ketoconazole

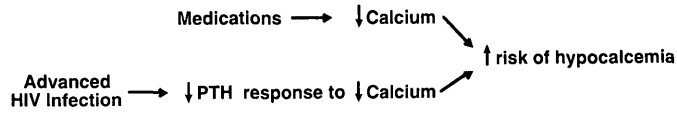

FIG. 1. Hypocalcemia in HIV infection. The interaction between drugs and HIV infection increases the risk of hypocalcemia.

has been shown to reduce serum levels of 1,25-dihydroxyvitamin D and to lower total, but not ionized, calcium levels in normal and hypercalcemic patients (93). Rifampicin has been found to lower 25-hydroxyvitamin D levels in normal patients without inducing changes in calcium or PTH levels (94).

AIDS patients have been demonstrated to have decreased PTH levels both at baseline and during EDTA-induced hypocalcemia, when compared with normals and severely ill patients with malignancies (95). The magnesium levels in these AIDS patients were similar to those of the control groups, suggesting poor PTH secretion in response to hypocalcemia, which would impair the homeostatic response to drug-induced hypocalcemia (Fig. 1).

Hypercalcemia associated with AIDS-related lymphoma has been reported in four patients, one of whom had a markedly elevated 1,25-dihydroxyvitamin D level (96). Elevated 1,25-dihydroxyvitamin D and hypercalcemia have also been reported in a patient with *M. avium* complex (97). Presumably, hypercalcemia in these settings is related to increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the tumor or granuloma of infection. Hypercalcemia and elevated 1,25-hydroxyvitamin D were reported in a patient with *P. carinii* pneumonia; however, this patient had hilar lymphadenopathy and his calcium improved during *P. carinii* therapy, which included high doses of prednisone (98). Thus, despite negative conjunctival and bone marrow biopsies, this patient could have had either sarcoid or lymphoma.

Amphotericin B impairs proximal and distal tubular reabsorption of electrolytes, leading to renal magnesium and potassium wasting (99).

In addition to its other effects, foscarnet therapy can also lead to nephrogenic diabetes insipidus (100). The endocrinological effects of medications used in the treatment of HIV infection are summarized in Table 3.

V. Gonadal Dysfunction

A. *Testicular pathology*

Histopathological changes in the testes of patients dying of AIDS are frequent. Common findings at autopsy include decreased spermatogenesis, thickened basement membrane, and an interstitial infiltrate (2, 101–106). HIV protein expression has been demonstrated in the lymphocytes of the seminiferous tubules and interstitium of the testes in nine of 23 patients studied by Pudney and Anderson (101). Additionally, Nuovo *et al.* (107), using PCR *in situ* hybridization, showed HIV DNA selectively infecting the spermatogonia in the testes of 11 of 12 HIV-infected men. However, the pathogenesis of the histological alterations seen in AIDS and the

possible consequences of direct infection of testicular cells with the HIV virus are unknown.

De Paepe *et al.* (108) described involvement of the testes with *Mycobacterium avium-intracellularis*, *Toxoplasma*, or CMV in 39% of patients with disseminated disease. Among 28 patients with disseminated tuberculosis, Chabon *et al.* (103) found testicular infection in 25%. Kaposi's sarcoma has also been found in the epididymis of an AIDS patient at autopsy (105).

The HIV patients examined in autopsy series have been almost exclusively men. To date, ovarian histology has not been adequately described in HIV-infected women.

B. Testicular function

Evaluation of gonadal function in HIV patients has been performed primarily in men. Although the functional significance of the histological changes in the testes is not clear, symptomatic hypogonadism is not uncommon among HIV-infected men. Dobs *et al.* (23) studied 42 men with AIDS, of whom 67% reported decreased libido and 33% were impotent. Twenty-four of these men had subnormal serum testosterone concentrations; 18 had low or inappropriately normal serum gonadotropin levels. Eight of these patients underwent GnRH stimulation testing; all but one had normal pituitary response, suggesting a functional abnormality of the hypothalamus. Subnormal testosterone levels in AIDS patients have been found in several other studies (26, 58, 61, 109, 110), one of which also demonstrated no elevations in FSH or LH among the hypogonadal men (26). Croxson *et al.* (111) also showed lower testosterone levels in men with AIDS but observed elevated FSH and LH values, suggesting primary hypogonadism. Some of this inconsistency may be explained by differences in study population. Croxson's study included only homosexual patients while Dobs' study also included drug users; opiate abuse is known to cause hypogonadotropic hypogonadism (112).

The pathophysiology of HIV-related hypogonadism is uncertain. Patients with other severe systemic illnesses have been shown to develop hypogonadotropic hypogonadism (113). This effect may be cytokine mediated. *In vitro*, interleukin-1 enhances testicular steroidogenesis at low doses while higher doses inhibit the binding of LH to Leydig cells and block steroidogenesis (114). TNF, when administered to healthy men in a study by van der Poll *et al.* (115), resulted in a rise in LH followed by a fall in testosterone; thus, cytokines and infection could lead to a form of primary hypogonadism. However, in the latter study, LH levels had returned to normal when testosterone levels reached their nadir after TNF, suggesting an effect both centrally and at the level of the gonads. As discussed elsewhere in this review, there is controversy over which cytokine levels are increased in AIDS.

Earlier in the course of HIV infection, testosterone levels have been found to be normal (26, 58, 111) or even elevated (27, 61). In the series of Merenich *et al.*, total and, particularly, free testosterone levels were elevated, basal LH tended to be higher, and the LH response to GnRH was significantly greater in the HIV-infected patients, suggesting an alteration at the pituitary-hypothalamic level (27). Sex hormone-binding globulin levels have been found to be normal at all stages of HIV infection in most studies (23, 27, 32, 111); however, in one study (116), sex hormone-binding globulin averaged 46% above controls and showed increased affinity for testosterone. The alterations in gonadal function found in HIV infection are depicted in Table 4 and compared with other states of hypogonadism.

C. The effect of medication on testicular function

While none of the patients in the above studies were receiving medications that could alter steroidogenesis, some drugs used in the treatment of AIDS can affect gonadal function. Ketoconazole inhibits gonadal steroid production, leading to lower testosterone levels, oligospermia, azoospermia, and gynecomastia (73). Use of megestrol acetate can lead to lower testosterone levels in HIV-infected men (109); megestrol acetate, a progestational agent, exerts feedback inhibition centrally. An interesting but unresolved question is whether the hypogonadism induced by megestrol contributes to the failure of this drug to increase lean body mass despite increasing weight. The use of testosterone in conjunction with megestrol is being studied. The endocrinological effects of medications used in the treatment of HIV infection are summarized in Table 3.

D. Ovarian function

Information on gonadal function in women with HIV infection is limited. Widy-Wirski *et al.* (117) reported amenorrhea in 26% of 308 HIV-infected women in Uganda. However, in a study of 55 HIV-infected women in the United Kingdom, Shah *et al.* (118) reported regular menstrual cycles in 92% of asymptomatic and 100% of symptomatic women; however, all of these women were in the early stages of HIV infection and had CD4 counts over 200. Another study by Shelton *et al.* (119) also suggests that HIV infection by itself does not induce menstrual irregularities or changes in hormone levels in women. It is likely that abnormalities in the female sex hormone axis are also related to the occurrence of complications of immunodeficiency. The effects of drugs used to treat AIDS and related opportunistic

TABLE 4. Alterations in gonadal function

	Primary hypogonadism	Secondary hypogonadism	HIV infection			Opiate use alone
			Early	Late	With opiate use	
LH	↑	↓ or normal	↑	↑	↓	↓
FSH	↑	↓ or normal	Normal	↑	↓	↓
Testosterone	↓	↓	↑	↓	↓	↓

↑, Increased; ↓, decreased.

infections on ovarian function have not been adequately described.

VI. The Pituitary

A. Pituitary gland pathology

In series that have examined the pituitary glands of AIDS patients at autopsy, varying degrees of infarction and necrosis were the most common findings, occurring in nearly 10% of glands (120–122). Infection with CMV, *P. carinii*, *Cryptococcus*, *Toxoplasma gondii*, and *Aspergillus* was also observed (121). No cases of malignant neoplasms directly affecting the anterior pituitary were found. However, three patients with cerebral lymphoma had peripheral involvement of the gland (121). Pituitary function was not evaluated antemortem in these studies.

B. Anterior pituitary function

Evaluation of anterior pituitary reserve by TSH or gonadotropin stimulation has demonstrated a normal response in nearly all patients tested (23, 26, 27). However, one patient with panhypopituitarism attributable to cerebral toxoplasmosis (123) and one patient with CMV-induced hypothalamic dysfunction (124) have been described. Thus, panhypopituitarism in AIDS is rare.

PRL levels in HIV-infected patients have been generally found to be normal (23, 27, 125) with a normal response to TRH stimulation (23). Modest elevations in PRL were reported in AIDS patients by Croxson *et al.* (111); however, the patients in this study were predominately hypogonadal with elevated gonadotropins, making the relationship between the altered PRL levels and gonadal dysfunction uncertain.

The situation with the GH-IGF-I axis is more complex. GH has been evaluated in HIV-infected children because of failure to thrive and poor growth velocity, especially during symptomatic infection. GH deficiency does not appear to be common. Among 22 hemophiliac boys with HIV infection who were asymptomatic except for lymphadenopathy, three developed growth failure. All three of these boys had normal peak GH levels, but two had low IGF-I levels (126). A similar pattern was found in 12 children with HIV infection and failure to thrive who were well at the time of testing but had been previously symptomatic. In response to glucagon stimulation, all had normal GH response, but eight had subnormal IGF-I levels (127). Matarazzo *et al.* (128) studied 24 perinatally infected children and found reduced IGF-I levels in 45% of asymptomatic children and 86% of children with more advanced disease. These percentages were much higher than those for growth failure or bone age delay in either group (128). A subnormal IGF-I level in the setting of an apparently normal GH level is a common finding in malnutrition (129); this may be a partial explanation for the low IGF-I values found in these studies. However, many of the children with low IGF-I demonstrated preservation of weight and were not felt to be malnourished at the time they were studied.

In contrast, Laue *et al.* (130) studied nine children with AIDS and failure to thrive and found normal basal IGF-I levels in all but one child. Additionally, eight of the nine patients had normal GH response to provocative testing. Of note, the children in this study were all below the fifth percentile for weight, and half were receiving parenteral or enteral supplementation. No differences in plasma IGF-I levels were observed between asymptomatic, symptomatic, or control patients by Geffner *et al.* (131). However, *in vitro* studies of these patients revealed a quantitative mean reduction in erythroid progenitor cells colony formation in response to IGF-I, GH, and insulin in the symptomatic patients compared with asymptomatic children and controls, suggesting resistance to the growth-promoting effects of these hormones (131).

In adults, one study found decreased IGF-I levels in malnourished HIV-infected patients (132). However, Mulligan *et al.* (133) found normal IGF-I levels in six patients who had lost an average of 19% of their body weight. The lowest IGF-I level was found in the one patient who was actively infected at the time of the study. These patients were given exogenous GH and were able to increase their IGF-I levels, although to a lesser extent than HIV-negative normal controls receiving GH.

Based on the above studies, it is likely that HIV-infected patients who are acutely ill with secondary infections will show decreased IGF-I despite relatively normal GH levels. Twenty-four hour GH profiles have not yet been reported in AIDS, leaving open the possibility of more subtle defects in GH secretion.

C. Abnormalities of antidiuretic hormone secretion

Posterior pituitary function may be altered in HIV patients. Hyponatremia occurs in 30–50% of inpatients (134–137) and approximately 20% of outpatients with AIDS (137). Agarwal *et al.* (134) reported 36 of 103 HIV patients admitted with opportunistic infections to have serum sodium less than 130 mEq/liter; two-thirds of these patients were clinically euvolemic and had serum arginine vasopressin levels that were inappropriately high for the serum osmolality, consistent with the syndrome of inappropriate antidiuretic hormone secretion. Many of these patients had *P. carinii* pneumonia, which, like any pulmonary infection, can induce the syndrome of inappropriate ADH. Furthermore, most were treated with trimethoprim, which could contribute to hyponatremia through impaired sodium conservation (138) and/or dilutional hyponatremia due to the large volumes of hypotonic intravenous fluid required for its administration (139).

Central diabetes insipidus has been reported in an AIDS patient with herpetic meningoencephalitis (140). Any pathology that destroys the pituitary or damages the hypothalamus can potentially cause diabetes insipidus.

VII. The Pancreas and Glucose Homeostasis

A. Pancreatic pathology

Pancreatic abnormalities are common in autopsy series of AIDS patients. In a study of 82 autopsied HIV-infected patients, opportunistic infections and malignancies were much

more frequent in the pancreases of AIDS patients than in other immunocompromised control patients (141); however, histopathological changes such as acinar dilatation and pancreatitis were not increased over the controls. The majority of these lesions in AIDS do not appear to be extensive enough to cause clinically significant pancreatic dysfunction.

B. Effects of HIV infection on glucose homeostasis

Clinically stable, symptomatic HIV-infected men have been shown to have higher rates of insulin clearance and increased sensitivity of peripheral tissues to insulin when compared with noninfected controls during euglycemic insulin clamp studies (142). There is also an increase in non-insulin-mediated glucose uptake (143). The increase in glucose uptake is predominantly accounted for by an increase in nonoxidative glucose disposal (133, 144). Glucose cycling is not increased (145). Hepatic glucose production rates tend to increase, perhaps to maintain plasma glucose levels in the face of increased disposal (133, 142). These findings in AIDS should be contrasted with those of sepsis or TNF infusion, where insulin resistance and hyperglycemia are common findings, except in the setting of septic shock with multiorgan failure when hypoglycemia can occur (146, 147). These disease states are contrasted in Table 5.

C. Effects of medication on glucose homeostasis and the pancreas

Clinically significant pancreatic dysfunction in HIV is often medication related. Pentamidine isothionate, used in the prevention and treatment of *P. carinii*, can cause pancreatic β-cell toxicity, leading to hypoglycemia acutely and later to diabetes mellitus. *In vitro*, when added to malignant insulinoma cells, pentamidine causes acute insulin release at 30 min followed by inhibition of insulin secretion (148). AIDS patients who become hypoglycemic during pentamidine therapy have inappropriately elevated insulin levels (149). Hypoglycemia in pentamidine-treated HIV patients is associated with longer duration of therapy, higher cumulative doses, and renal insufficiency (148, 150, 151).

A subset of patients who experience hypoglycemia with pentamidine will, over time, progress to hyperglycemia; these patients often have low c-peptide levels, suggestive of significant β-cell destruction (152). It is of interest that longer-term exposure of insulinoma cells to pentamidine results in cytolysis with no cell structure visible after 3 weeks (148). Both hypoglycemia and diabetes mellitus have also been reported after treatment with aerosolized pentamidine (153, 154). Pentamidine, trimethoprim-sulfamethoxazole, and the nucleoside analogs ddI and ddC have all been associated with acute pancreatitis (155).

Megestrol acetate, used as an appetite stimulant to treat anorexia and cachexia in AIDS, has been reported to cause diabetes mellitus (156); however, the prevalence of hyperglycemia in controlled trials is very low. The drug's hyperglycemic effect may be due to increased caloric intake and weight gain as well as to its intrinsic glucocorticoid-like activity. The endocrinological effects of medications used in the treatment of HIV infection are summarized in Table 2.

TABLE 5. Glucose homeostasis in HIV infection and sepsis

	HIV infection	Sepsis
Glucose	↓	↑
Insulin	↓	↑
Hepatic glucose production	↑	↑
Oxidative glucose disposal	↔	↑
Nonoxidative glucose disposal	↑	↑
Glucose cycling	↔	↑

↓, Decreased; ↑, increased; ↔, no change.

VIII. Lipid Metabolism

Triglyceride levels may be elevated in asymptomatic HIV infection. Triglyceride levels are above normal in patients with CD4 cell counts under 200 and approximately twice normal in symptomatic AIDS (37, 157–159). The elevation in triglycerides appears to be due to an increased level of very low density lipoproteins (VLDL) with normal composition (37). Lipoprotein lipase, the enzyme responsible for triglyceride clearance, has been found to be decreased by 27% in AIDS patients (37). The actual clearance of triglycerides, however, is even more markedly prolonged (37).

Increased *de novo* hepatic synthesis of fatty acids has been demonstrated in AIDS patients (39). Increased plasma FFA, presumably products of peripheral lipolysis, have also been reported in AIDS (37). Direct measurement of Ra glycerol in a small number of HIV-infected patients also suggests a tendency toward increased lipolysis (133). Both *de novo* synthesis and lipolysis can potentially contribute fatty acids to increased VLDL production, as has been reported in other infections (146). On the other hand, fatty acid oxidation tends to be increased in HIV infection (133, 144), which would direct some of the fatty acids away from VLDL secretion.

Elevated triglyceride levels in AIDS patients correlate strongly with circulating levels of interferon-α (37, 38). This cytokine, which appears in detectable levels as HIV infection progresses to AIDS, is also very strongly correlated with alterations in triglyceride metabolism, including decreased triglyceride clearance (38) and increased fasting hepatic synthesis of fatty acids (39). Although the exact role of interferon-α in triglyceride metabolism has yet to be determined, antiretroviral therapy reduces both interferon-α and triglyceride levels in patients with AIDS (160).

Plasma cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels are decreased in both asymptomatic HIV infection and AIDS (38, 157, 158, 161, 162). Decreases in HDL are seen before decreases in LDL (38, 157, 158, 162). These changes are accompanied by an increased prevalence of the small, dense LDL particle subclass known as LDL-B (157). LDL-B is found in other syndromes with hypertriglyceridemia and low HDL. The etiology of hypocholesterolemia in HIV infection has yet to be defined. While gastrointestinal dysfunction could theoretically play a role, these lipid changes are seen in clinically stable patients without evidence of malabsorption. Furthermore, the changes in HDL may begin before clinically significant immunosuppression occurs. The plasma lipid and lipoprotein changes found in HIV infection are listed in Table 6.

TABLE 6. Lipid and lipoprotein abnormalities in HIV infection

	Early	Middle	Late
Triglycerides	Normal	Normal or ↑	↑↑
Cholesterol	↓	↓	↓
VLDL	Normal	Normal or ↑	↑↑
HDL	↓	↓	↓
LDL	Normal	↓	↓

↑, ↑↑, Increased; ↓, ↓↓, decreased.

IX. The Wasting Syndrome

The wasting syndrome, defined as a greater than 10% involuntary loss from baseline weight, was an early AIDS-defining illness. Wasting is a particularly devastating aspect of HIV infection. In contrast to starvation, where adipose tissue is preferentially used to spare muscle protein, some AIDS patients lose relatively more lean body mass and less fat (163, 164), indicating the presence of metabolic abnormalities that prevent nitrogen sparing. Initially, these alterations were thought to be related to cytokine-induced changes in triglyceride metabolism. However, there is no relationship between triglyceride levels and wasting in AIDS patients (159). Patients with persistent hypertriglyceridemia demonstrate prolonged periods of stable weight (159).

Elevated resting energy expenditure (REE), an indicator of hypermetabolism seen in the setting of burns or trauma, may be found in patients at all stages of HIV infection (24, 133, 144, 165–169). REE is increased even in asymptomatic patients with normal CD4 cell counts (144), suggesting an immune system response to HIV infection; this finding was an early indication that the virus was not latent, but contained by the host. Additional elevations in REE may be seen with progression to AIDS, with further increases during opportunistic infections (166, 167). However, there is no correlation between the observed elevations in REE and weight loss (24, 166, 170).

In the absence of opportunistic infection, most HIV-infected patients do not have short-term weight loss (24, 159, 166). However, AIDS patients with active secondary infections lose an average of 5% of body weight in 28 days (166). In a prospective analysis of AIDS patients with rapid weight loss (defined as >4 kg in <4 months), 82% had secondary infection as a cause (171).

In metabolic studies, a cohort of AIDS patients with secondary infection and weight loss had a 36% reduction in their caloric intake while maintaining a 29% increase in REE (166). In contrast, normal patients exhibit a compensatory decrease in REE in the setting of reduced caloric intake. Another cohort of AIDS patients with rapid weight loss had decreased total energy expenditure despite increased REE and decreased caloric intake (169).

Most HIV-infected patients with slower weight loss (<4 kg in >4 months) have gastrointestinal disease (171); they do not show an increase in total energy expenditure (169) and tend to have decreased caloric intake.

These studies emphasize that hypermetabolism *per se* is not the driving force for weight loss. Rather, the failure to compensate for decreased caloric intake by adequately lowering REE leads to significant negative energy balance. It remains to be determined why increasing caloric intake in these patients produces predominately increased body fat, with little increase in lean body mass (172–175). Dronabinol, the synthetic form of the active ingredient in marijuana, has been used in the treatment of anorexia in AIDS patients; it appears to decrease the feeling of anorexia but does not induce significant weight gain (175). Megestrol acetate induces increased appetite and weight gain; however, the increased weight is due almost exclusively to increases in body fat (172–174). Megestrol acetate, a progestational agent, decreases testosterone levels, which may explain the failure to increase lean body mass during weight gain (176).

Therapies aimed at increasing lean body mass are currently under investigation. Anabolic steroids appear to increase weight in open-label trials (177). These drugs require further investigation in double-blinded studies, which include evaluation of changes in body composition with therapy. IGF-I induces transient increases in nitrogen balance but, after 1 week of therapy, nitrogen balance and protein turnover return to baseline (178). GH, given acutely in an inpatient metabolic ward study, induced nitrogen retention and weight gain in six HIV-infected patients who had previously lost 19% of body weight (133). Weight gain with increase in lean body mass as well as increased muscle power and endurance after 3 months of open-label GH therapy were demonstrated by Krentz *et al.* (179). The largest study to date examined the effects of GH on 178 HIV-infected patients who met criteria for the wasting syndrome (180). A sustained increase in body weight and lean body mass with a decrease in fat was found in the GH-treated subjects compared with placebo-treated controls, whose values were unchanged from baseline. Additionally, the GH-treated group demonstrated an increase in treadmill work output and reported increased quality of life (180).

As discussed above and elsewhere, there is controversy as to whether circulating IL-6 or TNF levels are elevated in HIV infection or AIDS. Soluble cytokine receptors and antagonists are elevated in AIDS (181–183). Many of the laboratories that do not find elevated cytokine levels measure free or active cytokines, while those that do find elevated cytokines measure total cytokine, which may be mostly receptor bound, hence inactive (183). No convincing correlations have been shown between cytokine or cytokine receptor levels and determinants of energy balance, such as REE, caloric intake, or even weight change (38, 166, 181, 184).

Other attempts have been made to demonstrate that cytokines induce wasting by treatment with cytokine inhibitors. Pentoxyfilline decreased TNF mRNA in white blood cells of patients with AIDS but failed to reverse wasting (185, 186). Thalidomide, which decreases TNF production, has been shown in a small study to lead to significant weight gain in patients with HIV infection, particularly those with tuberculosis (187). However, in this study, thalidomide did not decrease total (primarily soluble receptor-bound) TNF levels.

X. Summary and Conclusions

Numerous alterations in endocrine function are observed in HIV infection. Direct destruction of endocrine organs by HIV itself or by invasive infection with opportunistic organisms resulting in loss of function is rare.

When acutely ill, HIV patients can develop the metabolic derangements that accompany any severe systemic disorder. Studies of thyroid function tests emphasize that the presence of acute secondary infection must be analyzed when evaluating such patients. In addition to euthyroid sick syndrome, other hormonal axes are affected by severe illness. These alterations may be cytokine mediated. As with seronegative patients, these changes can be transient and resolve with successful treatment of the intervening illness.

Given the complexity of HIV disease, future reports should characterize patients by CD4 cell count, history of AIDS-indicating illnesses, and viral load. Viral burden is an independent predictor of immunosuppression and progression to AIDS.

A large number of medications used in the treatment of HIV infection and related illnesses can alter endocrine function, mineral and electrolyte balance, and substrate turnover. Drug therapy must be considered in the evaluation of endocrine abnormalities in HIV-infected patients and carefully characterized in studies of these patients. The endocrine effects of medications used in the treatment of HIV infection are summarized in Table 3.

Concomitant factors that affect endocrine function independent of the HIV virus can confound results in these patients. For example, opiate use affects PRL, gonadotropins, and cortisol response to ACTH stimulation. Investigations in HIV-infected patients must include careful descriptions of the study population and comparison to relevant controls.

HIV-infected patients may also demonstrate more subtle alterations in endocrinological function in early, relatively asymptomatic, stages. The etiology and clinical significance of these changes, particularly their relationship to cytokines, continues to be investigated. The sequential studies of stable aldosterone levels despite decreased aldosterone response to ACTH stimulation indicate that alterations in response to provocative testing do not predict the development of hormonal insufficiency in this patient population. Similar longitudinal studies need to be done for the other hormonal axes to further delineate the endocrinological alterations in HIV infection.

Finally, when the rationale for hormone replacement is debatable, double-blind, placebo-controlled studies are necessary. Transient improvement in clinical status during open-label treatment does not prove hormone insufficiency. The long-term efficacy and safety of hormonal therapy must be demonstrated.

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