PILOT COPY

HIV Management in Australasia

a guide for primary care

ashm
Australasian Society for HIV Medicine

2008 Edition

Editors: Jennifer Hoy,
Sharon Lewin,
Alan Street and
Jeffrey J Post

PILOT COPY

HIV Management in Australasia

a guide for primary care

Editors
Editors Jennifer Hoy, Sharon Lewin, Alan Street and Jeffrey J Post

ashm
Australasian Society for HIV Medicine Inc

Australian Government
Department of Health and Ageing

2008 Edition

20.5 Endocrine disorders in HIV-infection

Katherine Samaras Garvan Institute, Darlinghurst, NSW.
Jeffrey J Post Department of Infectious Diseases and Albion Street Centre, Prince of Wales Hospital and School of Medical Sciences and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW.

Endocrine abnormalities are relatively common in HIV-infection, due to specific effects of the virus, HIV-related disease, complications of drug therapy, drug-drug interactions and the effects of restoration of the immune system after the commencement of combination antiretroviral therapy (cART) (Table 20.8).

Diabetes mellitus

Disturbances in glucose metabolism (insulin resistance, impaired glucose tolerance and diabetes mellitus) are among the most common endocrine disorders found in treated HIV-infection and are mostly due to the effects of cART.[1] Before the availability of cART, most cases of diabetes occurred in patients treated with pentamidine for treatment of *Pneumocystis jirovecii* infection. These cases were characterised by insulin deficiency and ketoacidosis (type 1 diabetes mellitus), since pentamidine destroys pancreatic insulin-secreting beta-cells.[2-4] The most common form of diabetes mellitus in patients with HIV infection in the cART era is type 2 diabetes, occurring in up to 10% of patients.[5,6] It is due to a combination of cART effects on insulin resistance and insulin secretion.[1, 7, 8]

The symptoms of diabetes mellitus include excessive thirst, polyuria, fatigue, unintentional weight loss, skin infections (such as candidiasis or boils) or blurred vision. Complications of diabetes, such as peripheral neuropathy, may be present at diagnosis. The symptoms of peripheral neuropathy from diabetes include burning or painful dysaesthesia, the sensation of walking on cotton wool or numbness. Neuropathy in treated HIV-infection may also be contributed to by nucleoside reverse transcriptase inhibitors (NRTIs).

The diagnosis of diabetes mellitus is made by testing the random (> 11.0 mmol/L) or fasting glucose level (> 7.0 mmol/L) in accordance with the criteria of the American Diabetes Association.[9] Further, pre-diabetes could be considered if the fasting glucose is greater than 5.6 mmol/L. Impaired fasting glucose (6.0-6.9 mmol/L) represents a high risk for conversion to type 2 diabetes and represents a patient group where preventive strategies (including lifestyle change and weight loss predominantly, with the consideration of metformin treatment) can defer the onset of diabetes mellitus.

The treatment of diabetes mellitus in people with HIV infection requires lifestyle changes with an emphasis on healthy weight and, more importantly, healthy waist circumference, with appropriate nutritional and physical activity advice. Since the epidemic of overweight and obesity now affects more than 50% of Australians, this may affect more people with HIV infection in the future. Those with body fat changes due to cART or those in ethnic groups who are more susceptible to diabetes mellitus (e.g. people with South East Asian, South Asian and South American Indian heritage) need particular consideration.

Metformin is one of the main stays of antidiabetic therapy, since it is an insulin sensitiser, reduces abdominal obesity

Table 20.8 Endocrine disorders due to effects of HIV, HIV-related disease, immune reconstitution and drug therapy

	Direct HIV-1 virus effects	HIV-related disease	Immune reconstitution	Drug effects
Adrenal disease	Adrenalitis (rare)	Infections: Cytomegalovirus Toxoplasmosis Mycobacterial (*M. tuberculosis*, *M. avium*-intracellulare complex) Malignancy: Kaposi's sarcoma	Addison's disease (rare)	Reduced corticosteroid synthesis: Antifungals (ketoconazole) Pituitary suppression: Cytochrome P450 3A4 drug interactions with inhaled or oral steroids
Thyroid disease			Hashimoto's hypothyroidism Graves' disease	Interleukin-induced Graves disease Interferon-induced Graves' disease
Diabetes mellitus				Pentamidine-induced insulin deficiency (type diabetes) Protease inhibitor and NRTI-induced insulin resistance Type 2 diabetes mellitus
Calcium metabolism	Osteoporosis			NRTI-related osteroporosis
Sex hormones		Androgen deficiency		Androgen deficiency

NRTI = nucleoside reverse transcriptase inhibitor.

and improves glycaemic control.[10] In HIV-infection, its use is contraindicated by severe renal impairment or cardiac failure where it may induce lactic acidosis. Care should be taken in patients receiving NRTIs with impaired renal function and elevated lactic acid levels. Sulfonylurea drugs increase insulin secretion and improve glycaemic control and are generally considered second-line agents. Thiazolidinediones, insulin sensitising drugs, will also improve glycaemia. Insulin therapy is highly effective in achieving glycaemic control and becomes necessary in a proportion of people with type 2 diabetes. Newer drug classes include exenatide and the dipeptidyl peptidase IV inhibitors, sitagliptin and vildagliptin.[11] These drugs act through novel pathways involving gut-derived peptides influencing insulin secretion. At the time of writing, the latter were not listed on the Pharmaceutical Benefits Scheme.

Thyroid disease

Autoimmune thyroid disease can occur in patients with HIV infection, either as a consequence of highly active antiretroviral therapy or immunomodulatory therapy. Primary hypothyroidism due to Hashimoto's hypothyroidism (determined by the presence of anti-peroxisomal antibodies) occurs as a consequence of immune reconstitution, as can Graves' disease.[12-15] Immunomodulatory therapy with agents such as interferon-alpha used in the treatment of hepatitis C infection[16] and interleukin therapy for HIV can result in production of stimulatory antibodies that results in Graves' disease and thyrotoxicosis.[17] Clinicians should be alert to the possibility of hypothyroidism or thyrotoxicosis following immune reconstitution.[18]

Adrenal disease.

Adrenal deficiency is uncommon, but can occur as a consequence of infection (HIV-1, CMV, toxoplasmosis, Mycobacteria), neoplastic disease (Kaposi's sarcoma or other malignancies) or, very rarely, autoimmune disease (Addison's disease). Adrenal insufficiency is more common in the setting of HIV infection, with abnormal stimulated cortisol responses in 26% of tested subjects.[19]

The symptoms that should alert a clinician to the possibility of adrenal insufficiency include unexplained fatigue, weight loss, nausea, weakness, postural presyncope, myalgias, arthralgias, sweatiness and confusion. Drug therapy can be associated with reduced synthesis of adrenal hormones (e.g. ketoconazole) or induced metabolism of steroids (e.g. rifampicin, phenytoin).[20] A history of recent withdrawal of oral or inhaled corticosteroid drugs should be sought.[21] Clinical features of adrenal insufficiency include cachexia, pigmentation of the skin or oral mucosa, or a postural drop in blood pressure. Pigmentation will not be found in adrenal insufficiency of pituitary origin, due to deficiency of adrenocorticotrophin hormone (ACTH), which is rare. Biochemistry may show hyponatraemia, hyperkalaemia, or hypoglycaemia. The diagnostic test for primary adrenal insufficiency is the short synacthen test, where a normal stimulated cortisol response would exceed 550 nmol/L. Secondary adrenal insufficiency (due to pituitary disease) will produce a normal response to cosyntropin testing and is diagnosed by an insulin-induced hypoglycaemia test.

Adrenal insufficiency is treated with glucocorticoid and mineralocorticoid therapy. Examples of chronic glucocorticoid therapy are prednisone 2.5-5 mg on waking, with or without 1-2.5 mg early afternoon; or cortisone acetate 25 mg on waking, 12.5 mg early afternoon; or hydrocortisone 15-20 mg on waking, 5-10 mg early afternoon with some patients requiring a third later dose. Most patients will also require mineralocorticoid support with fludrocortisone (0.05-0.1 mg each day in divided doses, adjusted to clinical response in blood pressure).

Acute adrenal insufficiency may occur in the setting of acute infection, surgery or other physical stress and may manifest with vomiting, hypotension, haemodynamic shock and coma. It must be treated with intravenous glucocorticoids (e.g. hydrocortisone 100 mg every 6-8 hours) in addition to treatment of the underlying cause.

An excess of adrenal hormones (Cushing's syndrome) can occur in patients receiving protease inhibitors that inhibit the cytochrome p450 mediated metabolism of other drugs. Interference with the cytochrome p450 3A4 enzyme system results in the reduced elimination of oral and inhaled steroids. Cushing's syndrome can occur rapidly in patients receiving standard doses of oral steroids, in addition to inhaled steroids, with pituitary-adrenal suppression occurring with long-term therapy.[21] Cushing's syndrome should be suspected on historical and clinical evidence and diagnosed by detection of low or undetectable cortisol levels in a clinically Cushingoid patient. Treatment is by reduction of oral steroid doses or gradual reduction in inhaled steroids, where the underlying respiratory disease permits. For those patients receiving inhaled steroids, simple strategies will reduce steroid exposure and its side effects. These include using dosing devices with lower oral cavity deposition (e.g. aerosolised rather than inhalers) with spacers and always rinsing/gargling and spitting (not swallowing). Other strategies may include changing the inhaled steroid therapy to agents that are not predominantly metabolised by the specific cytochrome p450 isoenzymes.

Disorders of calcium metabolism and osteoporosis

Hypercalcaemia is uncommon in HIV infection. Primary hyperparathyroidism with hypercalcaemia could be expected at the same rate as the general population. If hypercalcaemia is found with low parathyroid hormone (PTH) levels, underlying infection, malignancy or lymphoma need exclusion.

Bone loss, low bone density and osteoporosis are found in HIV wasting syndrome and patients receiving long-term cART.[22] Multiple factors can contribute including viral effects, drug effects and low androgen levels. In male androgen deficiency/hypogonadism, treatment with androgen supplementation with testosterone has shown benefit.[23] In patients with established osteopenia or osteoporosis, clinicians should ensure an adequate intake of dietary calcium (at least 1000 mg each day) and that serum levels of 25-hydroxy vitamin D exceed 80 nmol/L. Weight bearing physical activity is essential (20 minutes of walking at least thrice weekly and, if possible, a weight training program) in addition to considering other lifestyle factors such as excessive alcohol or caffeine consumption and smoking. Other therapies such as the bisphosphonates or strontium ranelate may also have a role.[24]

Sex steroids

Male hypogonadism

Low androgen levels in men with HIV infection appear relatively common, often in the setting of low or inappropriately normal gonadotrophin levels. The cause of this is not completely understood, however contributors include the usual causes of hypogonadism in men. There appears to be an association with HIV wasting and lipodystrophy.[25]

Androgen deficiency in men leads to lean tissue and bone loss, fatigue and mood disturbance. Other symptoms may include a loss of body hair, testicular atrophy, reduced pubic hair and reduced libido. Clinical confirmation includes the findings of gynaecomastia and small soft testicles. Clinical signs that may suggest a secondary cause include the presence of a goitre and thyrotoxicosis, a testicular mass and signs of chronic liver or pituitary disease. Biochemical confirmation is undertaken by measuring an early morning testosterone level (at 8-9am), along with FSH and LH levels, prolactin and TSH levels.

Treatment options include injectable testosterone (testosterone cypionate or tenanthate, 200-250 mg every two to three weeks, or long-acting testosterone undecanoate 1000 mg by intramuscular injection every 10-12 weeks) or transdermal testosterone by patch or gel applied daily.[26] Men receiving androgen supplementation require annual digital rectal examination and prostate specific antigen measures.

Female hypogonadism

Secondary amenorrhoea is common in women with HIV, affecting about one in four women.[27] The prevalence of amenorrhea is higher among women who have lost significant amounts of weight in the setting of HIV wasting.[27] Evaluation should exclude pituitary disease (by measuring prolactin, LH and FSH), thyrotoxicosis, premature menopause, polycystic ovary syndrome, in addition to rare causes of hyperandrogenism.

Treatment in women with premature secondary amenorrhoea (i.e. aged less than 45 years) usually takes the form of the oral contraceptive pill or hormone replacement therapy, to alleviate symptoms of oestrogen deficiency and to help maintain bone mass. Therapy should be offered until the age of 50-53 years (i.e., about the usual age of menopause). The presence of a past history of stroke, deep vein thrombosis or pulmonary embolism or current cigarette smoking may alter recommendations for hormonal therapy.

References

1 Samaras K. Metabolic consequences and therapeutic options in highly active antiretroviral therapy in human immunodeficiency virus-1 (HIV) infection. J Antimicrob Chemother 2008;61:238-45.

2 Wood G, Wetzig N, Hogan P, Whitby M. Survival from pentamidine induced pancreatitis and diabetes mellitus. Aust NZ J Med 1991;21:341-2.

3 Perrone C, Bricaire F, Leport C, Assan D, Vilde JL, Assan R. Hypoglycaemia and diabetes mellitus following parenteral pentamdine mesylate treatment in AIDS patients. Diabet Med 1990;7:585-9.

4 Stahl-Bayliss CM, Kalman CM, Laskin OL. Pentamidine-induced hypoglycemia in patients with the aquired immunodeficiency syndrome. Clin Pharmacol Ther 1986;39:271-5.

5 Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.

6 Dube MP. Disorders of glucose metabolism in patients infected with human immunodeficiency virus. Clin Infect Dis 2000;31:1467-75.

7 Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 2005;352:48-62.

8 Bradbury R, Samaras K. Anti-retroviral therapy and the human immunodeficiency virus- improved survival but at what cost? Diab Obes Metabol 2008; 10(6):441-50

9 American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006;29 (Suppl 1):S43-S48.

10 Mulligan K, Yang Y, Wininger DA, Koletar SL, Parker RA, Alston-Smith BL, et al. Effects of metformin and rosiglitazone in HIV-infected patients with hyperinsulinemia and elevated waist/hip ratio. AIDS 2007;21:47-57.

11 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2008;368:1696-705.

12 Price P, Mathiot N, Krueger R, Stone S, Keane NM, French MA. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol 2001;22:279-87.

13 Sereti I, Sarlis NJ, Arioglu E, Turner ML, Mican JM. Alopecia univeralis and Graves' disease after immune restoration with HAART. AIDS 2001;15:138-40.

14 Jubalt V, Penfornis A, Schillo F, et al. Sequential occurrence of thyroid autoantibodies and Graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-infected patients. J Clin Endocrinol Metab 2000;85;4254-7.

15 Gilquin J, Viard JP, Jubalt V, Sert C, Kazatchkine MD. Delayed occurrence of Graves' disease after immune restoration with HAART. Lancet 1998;352:1907-8.

16 Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology 2006;4:661-72.

17 Jiminez C, Moran SA, Sereti I, Wynne S, Yen PM, Falloon J, et al. Graves' disease after interleukin-2 therapy in a patient with human immunodeficiency virus infection. Thyroid 2004;14:1097-102.

18 Hoffman CJ, Brown TT. Thyroid function abnormalities in HIV-infected persons. Clin Infect Dis 2007;45:488-94.

19 González-González JG, de la Garza-Hernández NE, Garza-Morán RA, Rivera-Morales IM, Montes-Villarreal J, Valenzuela-Rendón J, Villarreal-Pérez JZ. Prevalence of abnormal adrenocortical function in human immunodeficiency virus infection by low-dose cosyntropin test. Int J STD AIDS 2001;12:804-10.

20 Eledrisi MS, Verghese AC. Adrenal insufficiency in HIV infection: a review and recommendations. Am J Med Sci 2001;321:137-44.

21 Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in HIV-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. J Clin Endocrinol Metab 2005;90:9394-8.

22 Cazanave C, Dupon M, Lavignolle-Aurillac V, Barthe N, Lawson-Ayayi S, Mehsen N, Mercié P, Morlat P, Thiébaut R, Dabis F; Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors.AIDS 2008;22:395-402.

23 Lin D, Rieder MJ. Interventions for the treatment of decreased bone mineral density associated with HIV infection. Cochrane Database Syst Rev. 2007; CD005645.

24 McComsey GA, Kendall MA, Tebas P, Swindells S, Hogg E, Alston-Smith B, et al. Alendronate with calcium and vitamin D supplementation is safe and effective for the treatment of decreased bone mineral density in HIV. AIDS 2007;21:2473-82.

25 Grinspoon S, Corcoran C, Lee K, Burrows B, Hubbard B, Hubbard J, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab 1996;81:4051-8.

26 Allan CA, McLachlan RI. Testosterone deficiency in men. Diagnosis and management. Aust Fam Physician 2003;32:422-7.

27 Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab 1997;82:1332-37.

20.6 Ophthalmic diseases

Anthony J Hall Opthalmology Department, Alfred Hospital, Prahran and Eye Surgery Associates, East Melbourne, VIC.

AIDS-related ophthalmology

Retinal and choroidal disease

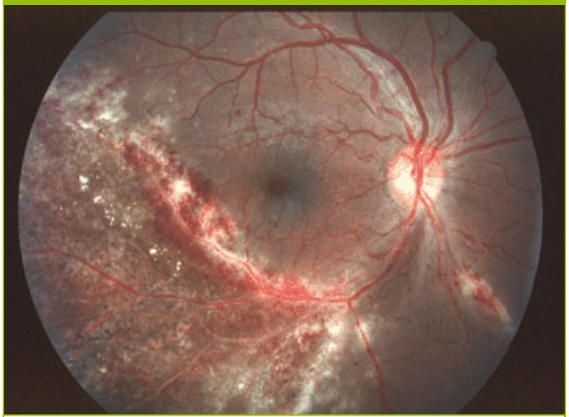
Cotton wool spots

Aside from its ability to cause retinal infection secondary to immunodeficiency, HIV is associated with a retinopathy in its own right. The retinopathy is characterised by transient nerve fibre layer infarcts (cotton wool spots) and scattered small retinal haemorrhages and rarely causes visual morbidity. It is caused by a combination of local capillary endothelial cell changes (possibly cytomegalovirus virally induced) and rheological changes and is a sign of established immunodeficiency. It does not require treatment.

Cytomegalovirus retinitis

Cytomegalovirus (CMV) retinitis is the most important cause of visual loss in patients with AIDS. The first clinical description of CMV retinitis was made in 1971 in a renal transplant recipient who had widespread systemic CMV disease and subsequently died. Before the AIDS pandemic, CMV retinitis was rare and the treatment of CMV retinitis was poor. None the less, it usually did not present a clinical problem because the immune deficit responsible for the retinitis was often reversible. The original report of CMV retinitis in patients with AIDS was made in 1983.[1]

Image 20.3 Cytomegalovirus retinitis.



Source: Anthony J Hall, Opthalmology Department, Alfred Hospital. Used with permission

Clinical features

CMV retinitis appears as confluent areas of full thickness necrotising retinitis with haemorrhage. There are usually associated areas of old retinitis with a granular pigmentary change behind the leading border of active retinitis. It is often associated with an accompanying retinal vasculitis (which may be severe) and only mild overlying vitritis and minimal anterior uveitis. There may be initial involvement at the posterior pole or in the periphery; when the disease occurs in the periphery, it has a more granular appearance than when it occurs at the posterior pole. Occasionally patients with small focal areas of involvement present a diagnostic problem. Visual loss in CMV retinitis may arise from optic nerve or macular involvement with retinitis, rhegmatogenous retinal detachment, serous macular detachment or cystoid macular oedema. Of these causes, only serous or rhegmatogenous detachment are reversible. The degree of visual loss at presentation depends on the site of the retinitis. Peripheral retinitis can be associated with normal vision and no symptoms.

Natural history of cytomegalovirus retinitis

The prognosis of untreated CMV retinitis is poor. In patients whose CD4 cell count remains low and who do not receive anti CMV treatment, there is relentless gradual progression and eventual blindness.

Diagnosis

CMV retinitis is usually diagnosed clinically without the need for confirmatory tests. CMV retinitis is a disease of the severely immunodeficient and, in patients with AIDS, it rarely occurs with a CD4 cell count of greater than 50 cells/μL.[2] At a given CD4 cell count, the risk of developing CMV retinitis is increased when other opportunistic infections occur,