

Thyroid Function Abnormalities in HIV-Infected Patients

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Abnormal thyroid function test results are common among human immunodeficiency virus (HIV)-infected patients. Although the prevalence of overt thyroid disease does not appear to be significantly increased in HIV-infected patients, compared with the general population, specific patterns of abnormal thyroid function test findings are more frequently identified among HIV-infected patients. Among patients with advanced acquired immunodeficiency syndrome, nonthyroidal illness (i.e., euthyroid sick syndrome) is common. During antiretroviral therapy, the prevalence of 2 generally asymptomatic conditions (subclinical hypothyroidism, which is characterized by isolated elevated thyroid-stimulating hormone levels, and isolated low free thyroxine levels) is increased. In addition, Graves disease, which is marked by low thyroid-stimulating hormone and elevated thyroxine levels, may occur during immune reconstitution. Testing for thyroid disease among symptomatic patients should begin with measurement of the thyroid-stimulating hormone level. However, there is insufficient evidence to recommend routine thyroid screening of asymptomatic HIV-infected individuals. This review summarizes the current evidence regarding the optimal laboratory evaluation of thyroid function; highlights the causes, presentation, and treatment of thyroid dysfunction in HIV-infected patients; and discusses the controversies regarding screening.

Among individuals infected with HIV, 1%–2% experience overt thyroid disease, and 35% may have subtle abnormalities in thyroid function test findings [1–3]. The HIV clinician, therefore, often must interpret abnormal thyroid function test results. Here, we review the interpretation of thyroid function tests, the diagnosis and treatment of thyroid dysfunction in HIV-infected patients, and the indications for screening. Throughout the review, we address current concepts in thyroid dysfunction in the general population, to provide a broader context for thyroid function abnormalities in HIV-infected patients.

THYROID FUNCTION TESTS

Thyrotropin (TSH). TSH is released from the anterior pituitary under positive regulation from TSH-releasing hormone (which is released from the hypothalamus) and negative feedback from the thyroid hormones tri-iodothyronine (T_3) and thyroxine (T_4). Most clinical laboratories use TSH assays that

have a limit of detection of <0.02 mU/L and that, therefore, are suitable for identifying the majority of cases of both hypothyroidism and hyperthyroidism [4].

However, there are rare circumstances in which information on the TSH level alone can be misleading; these include central hypothyroidism, which may occur with a TSH level within the reference range; hypothyroidism that occurs after the treatment of thyrotoxicosis in which TSH suppression may persist; genetic thyroid hormone resistance (i.e., inappropriately normal or elevated TSH levels with elevated thyroxine levels); and nonthyroidal illness [4]. Current guidelines recommend measuring the T_4 level only after the TSH level is found to be abnormal or if central hypothyroidism or thyroid hormone resistance is suspected [5].

T_4 . T_4 is secreted from thyroid follicular cells during hydrolysis of the thyroid hormone storage glycoprotein, thyroglobulin. In serum, 99.9% of T_4 is bound to thyroxine-binding globulin and other proteins, although only the free hormone is available for cell uptake and is thus biologically active [4]. Because of the extensive protein binding, total T_4 levels may correlate poorly with disease states; for example, estrogen use, pregnancy, acute hepatitis, and certain genetic abnormalities are associated with increased thyroxine-binding globulin concentrations and may result in a T_4 level that is misleadingly elevated. Conversely, in clinical situations that are associated with low thyroxine-binding globulin concentrations (e.g., ne-

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phrotic syndrome, hepatic failure, hereditary thyroxine-binding globulin deficiency, use of high-dose androgen, and glucocorticoid use), the T_4 level measurement can underestimate the concentration of active thyroid hormone. For these reasons, an estimation of the free T_4 (FT_4) level is necessary. In the past, this was done using T_3 resin uptake, which is inversely proportional to the number of thyroid hormone-binding sites available. The product of T_3 resin uptake and total T_4 has been termed the “free thyroxine index.” This has been largely replaced by the more direct measurement of FT_4 (also known as “unbound T_4 ”) by EIA.

T_3 . Most T_3 is produced by systemic 5'-deiodination of T_4 ; only 20% of T_3 is released from the thyroid [6]. A second T_4 deiodination pathway leads to the production of an inactive hormone, 3,3',5'-triiodothyronine or reverse T_3 . Although T_3 is the most active form of thyroid hormone, the clinical utility of measuring T_3 is limited to a few situations. In patients with a low TSH level, T_3 should be measured (1) to evaluate for isolated elevation of the T_3 level (i.e., T_3 toxicosis), (2) to determine the severity of thyroid disease, or (3) to monitor response to antithyroid therapy. However in patients with an elevated TSH level, T_3 concentrations are initially maintained in the normal range by increased peripheral conversion of T_4 to T_3 ; therefore, this measurement has reduced sensitivity for the diagnosis of hypothyroidism [7].

Although the binding affinity for serum proteins is lower for T_3 than T_4 , the majority of T_3 is also protein bound. Newer assays allow for more-direct measurement of the free fraction level, but use is limited by expense and lack of precision and standardization among various assays.

Thyroid autoantibodies. Multiple thyroid antigens can be targeted by autoantibodies. Some—but not all—patients with positive antibodies develop autoimmune thyroid disease. Although the presence of these antibodies can be readily measured in serum specimens, there are only a small number of clinical situations in which measurement is helpful. Up to 90% of patients with autoimmune thyroiditis will have anti-thyroid peroxidase or anti-thyroglobulin antibodies present; however, most cases of hypothyroidism are autoimmune mediated (i.e., Hashimoto thyroiditis), even in the absence of detectable autoantibodies. Similarly, although present in 80%–100% of patients with Graves' disease, the presence of thyroid-stimulating immunoglobulins are not required for the diagnosis of Graves' disease, but the presence is sometimes useful (1) to help establish the cause of hyperthyroidism when a radioiodine uptake cannot be done, (2) to predict the course of Graves' disease, (3) to evaluate euthyroid ophthalmopathy, and (4) to predict the probability of neonatal Graves' disease in an affected mother.

Thyroglobulin. Thyroglobulin is a glycoprotein produced by thyrocytes. The main clinical situation in which measure-

ment of thyroglobulin is helpful is to monitor for recurrence of thyroid cancer after thyroidectomy or radioiodine ablation. In addition, determination of the thyroglobulin level is sometimes useful in the differential diagnosis of hyperthyroidism (i.e., a low thyroglobulin level in the context of hyperthyroidism with low radioiodine uptake may signify an exogenous source of thyroid hormone). Routine measurement in the context of other thyroid conditions is not recommended.

ABNORMAL THYROID FUNCTION TEST PATTERNS

Decreased Thyroid Hormone

Overt hypothyroidism. Common symptoms and signs of overt hypothyroidism are insidious onset of fatigue, weakness, dry skin, cold intolerance, slowed mentation, constipation, hoarse voice, paresthesia, bradycardia, and delayed tendon reflex relaxation [8]. Patients with hypothyroidism may also have anemia, hyponatremia, hyperprolactinemia, or a high low-density lipoprotein cholesterol level [9]. Overt hypothyroidism usually results from failure of the thyroid to synthesize and secrete adequate T_4 levels, despite TSH stimulation, leading to a high TSH level and a low FT_4 level. In the general population, hypothyroidism is most commonly caused by Hashimoto thyroiditis, an autoimmune destruction of the thyroid gland [10]. In rare cases, anterior pituitary or hypothalamic failure can lead to central (secondary or tertiary) hypothyroidism. In central hypothyroidism, the FT_4 concentration is low, whereas the TSH concentration is either low or within the normal range.

Overt hypothyroidism is common both among the general population, in which ~0.3% of persons are affected [11], and among HIV-infected individuals, among whom small studies have reported a prevalence of 0%–2.6% [1, 2, 12, 13]. Despite the autoimmune etiology of most cases of hypothyroidism, onset of Hashimoto thyroiditis does not appear to be common during HAART-associated immune reconstitution. We are aware of a single case report of Hashimoto thyroiditis that developed after HAART initiation [14].

Overt hypothyroidism is treated with levothyroxine, with the goal of maintaining the TSH level at 0.5–2.5 mU/L [15]. The weight of clinical evidence reveals no improvement in symptoms, including mood and cognitive function, when the synthetic T_3 analogue (liothyronine) is added to levothyroxine therapy [16, 17].

The absorption of thyroid hormone is decreased by use of iron preparations, calcium carbonate, cholestyramine, and sucralfate, as well as by the decreased gastric acidity caused by use of proton pump inhibitors [8]. Drug-drug interactions between levothyroxine and protease inhibitors have also been reported [18–20], perhaps through the shared metabolic pathway of glucuronidation. The frequency and clinical impact of these interactions are not known.

Subclinical hypothyroidism. Subclinical hypothyroidism is characterized by a mildly elevated TSH concentration with a normal FT_4 concentration and either no or mild, nonspecific symptoms. In the general population, the prevalence of subclinical hypothyroidism is 4.3%; 50%–80% of these individuals have anti-thyroid peroxidase antibodies present [11, 21]. Subclinical hypothyroidism is also common among HIV-infected persons, especially among those who are receiving HAART (prevalence, 3.5%–12.2% [1–3, 12, 13]. Among patients with HIV infection and subclinical hypothyroidism, anti-thyroid peroxidase antibodies are rarely identified, suggesting that the etiology may not be autoimmune [3, 22]. Stavudine use, however, has been associated with subclinical hypothyroidism in some—but not all—studies [12, 22, 23]. The mechanisms underlying this association are unclear and deserve further investigation.

Management of subclinical hypothyroidism. If laboratory tests reveal subclinical hypothyroidism, the TSH level should be determined again in 1–3 months, because the levels in HIV-uninfected patients normalize within 1 year for up to 30% of persons; however, the proportion of HIV-infected patients whose levels normalize may be lower [24, 25]. If elevation of the TSH level persists, levothyroxine therapy can be considered; however, there is limited evidence in support of the benefits for the general, HIV-uninfected patient with a serum TSH level <10 mU/L, and no data are available for HIV-infected populations [26, 27]. Current guidelines for the general population recommend treatment if the TSH level is >10 mU/L and individualized management of patients with TSH levels of 4.5–10 mU/L. Patients who have nonspecific symptoms that may be attributable to thyroid dysfunction or who test positive for anti-thyroid peroxidase antibodies can be considered for treatment [26]. If the patient is not treated, determination of the TSH level should be repeated every 6–12 months to monitor for progression.

Isolated low FT_4 levels. Low FT_4 levels with concurrent normal TSH levels are found frequently among HIV-infected individuals, with a reported prevalence of 1.3%–6.8% [1, 2, 13]. An even higher prevalence was reported among children in a pediatric study in which 16 (31%) of 52 children, all of whom were receiving HAART, had this abnormality [28]. In adults, isolated low FT_4 levels have been associated with receipt of didanosine, stavudine, and ritonavir [22].

The low FT_4 state may be consistent with a centrally mediated process, with failure of the hypothalamus or anterior pituitary. However, in one study, administration of exogenous TSH-releasing hormone identified neither delayed nor absent TSH response among subjects with low FT_4 levels, making either hypothalamic or pituitary insufficiency less likely [22, 29]. An isolated low FT_4 level has also been reported in patients who are receiving phenytoin or carbamazepine and was shown to be an artifact related to interference in the free T_4 assays [30].

Whether one or more HAART agents cause similar interference has not been evaluated.

The clinical significance of a low FT_4 level is unclear, because patients with a low FT_4 level do not experience a higher frequency of hypothyroid symptoms, compared with control subjects. Furthermore, recent reports have lacked sufficient follow-up data to assess the natural history of low FT_4 levels [1]. Repeated annual thyroid function testing (of the TSH and FT_4 levels) is reasonable, but levothyroxine therapy is not recommended.

Abnormal thyroid function test findings due to nonthyroidal illness. In patients with low thyroid hormone concentrations, the effects of nonthyroidal illness, also referred to as “euthyroid sick syndrome,” also need to be considered. During severe illness, including advanced AIDS, 5'-deiodination of T_4 declines, leading to decreased T_3 production and reverse T_3 metabolism, and 5-deiodination of T_4 to inactive reverse T_3 is increased, creating a pattern of thyroid testing that suggests thyroid dysfunction. This pattern, however, is a result of the physiological response to illness and not a result of abnormal thyroid function. Because chronic HIV infection itself can lead to nonthyroidal illness, this diagnosis should always be considered for patients with uncontrolled HIV infection and abnormal thyroid function test results.

The most common thyroid function pattern during nonthyroidal illness is reduced T_3 level, elevated reverse T_3 level, variable FT_4 level, and relatively normal or decreased TSH level, depending on the severity of illness (figure 1), although a smaller increase in the reverse T_3 level has been observed among patients with advanced AIDS [32]. During recovery from illness, the TSH level may increase temporarily, sometimes overshooting the normal range, because both FT_4 and T_3 levels

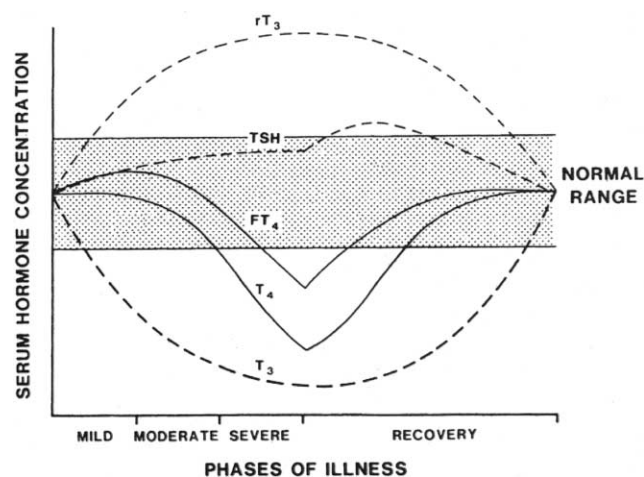


Figure 1. Thyroid function testing during nonthyroidal illness (“euthyroid sick syndrome”). Reprinted from *The Thyroid Gland: A Practical Clinical Treatise* [31], with permission.

return to baseline values, which may mimic subclinical hypothyroidism.

Among HIV-infected populations, the highest frequency of nonthyroidal illness was reported among patients with terminal AIDS before the HAART era, with as many as 16% of patients affected [3, 33, 34]. Management involves treatment of the underlying condition and not administration of levothyroxine therapy. If the diagnosis of nonthyroidal illness is unclear, repeated thyroid hormone testing is appropriate 4–6 weeks after the resolution of the acute illness or after the control of HIV infection with antiretroviral therapy. The measurement of the reverse T_3 level in persons with suspected nonthyroidal illness is not recommended.

AIDS-related conditions that cause thyroid dysfunction.

In patients with advanced HIV disease, a variety of systemic opportunistic conditions that infect or infiltrate the thyroid can decrease or increase T_4 secretion [35]. Cases of thyroiditis have been reported in association with *Pneumocystis jiroveci* infection, *Cryptococcus neoformans* infection, visceral leishmaniasis, and suppurative bacterial infection of the thyroid [36–39]. These infiltrating conditions lead to destructive thyroiditis, which is usually accompanied by neck pain, thyroid enlargement, and increased thyroxine release. After treatment of the infection, thyroid function can return to normal, but it should be closely monitored until it does so. In addition, both lymphoma and Kaposi sarcoma can infiltrate the thyroid and impair function. Cytomegalovirus inclusions have frequently been reported from autopsy studies, but thyroid disease was rarely noted before death [40]. Symptomatic thyroid infection or infiltration has always been uncommon, and in countries where HAART is available, it has become extremely rare. A summary of conditions associated with low thyroid hormone values is provided in table 1.

Increased Thyroid Function

Overt hyperthyroidism. Overt hyperthyroidism is characterized by irritability, heat intolerance, sweating, warm moist skin, palpitations, tachycardia, fatigue, weight loss with increased appetite, diarrhea, tremor, muscle weakness, hyperreflexia, and lid retraction, as well as a low TSH level (often <0.02 mU/L) and elevated FT_4 and T_3 levels [41].

Graves' disease, an autoimmune disease that leads to the production of anti-TSH receptor antibodies, is the leading cause of hyperthyroidism both in the general population and in HIV-infected individuals [39]. In persons with HIV infection, Graves' disease may occur after immune reconstitution from HAART. However, unlike classic immune reconstitution inflammatory syndrome caused by mycobacteria and other pathogens, which develops during the first 3 months of HAART [42, 43], Graves' disease is most commonly diagnosed 12–36 months after HAART initiation. The difference in timing may be explained by differences in the type of CD4 cell count that increases during these 2 periods. Some studies suggest the CD4 cells increase in a biphasic pattern after HAART initiation, with initial redistribution of memory CD4 cells from lymphoid tissue followed, months later, by expansion of naive CD4 cells [44]. Consistent with this explanation is the observation of transient Graves' disease among HIV-infected patients with naive CD4 cell expansion driven by IL-2 treatment [45]. However, delineating the timing and pattern of cell types in CD4 cell reconstitution remains an area of ongoing research [46]. IFN- α , which is commonly used to treat hepatitis C, has also been associated with Graves' disease [47].

In patients with a low TSH level and an elevated FT_4 level, a radioiodine uptake and thyroid scan can be helpful for differentiating causes of hyperthyroidism (tables 2 and 3) [39]. In patients with Graves' disease, the 24-h uptake of radioiodine

Table 1. Clinical syndromes involving decreased thyroid hormone levels.

Condition	TSH level	FT_4 level	T_3 level	Comment(s)
Overt hypothyroidism	$\uparrow\uparrow$	\downarrow	\downarrow	May be associated with anti-TPO
Subclinical hypothyroidism	\uparrow	N	N	More common during HAART; usually asymptomatic; rarely associated with anti-TPO in HIV-infected patients; health care providers should also consider recovery from nonthyroidal illness
Isolated low FT_4	N	\downarrow	N	More common during HAART; usually asymptomatic and of unclear significance; health care providers should also consider nonthyroidal illness
Central hypothyroidism	\downarrow	\downarrow	\downarrow	Very rare; when it occurs, symptoms of dysfunction in other endocrine systems are usually present (pan-hypopituitarism or hypothalamic dysfunction)
Nonthyroidal illness	N/ \uparrow	N/ \downarrow	\downarrow	Occurs during severe acute illness or cachexia as a result of down-regulation of conversion of T_4 to T_3

NOTE. Anti-TPO, anti-thyroid peroxidase; FT_4 , free thyroxine; N, normal; TSH, thyrotropin; T_3 , tri-iodothyronine; \uparrow , increase; $\uparrow\uparrow$, marked increase; \downarrow , decrease.

Table 2. Clinical syndromes involving increased thyroid function.

Condition	TSH level	FT ₄ level	T ₃ level	Comment(s)
Graves' disease	↓↓	↑↑	↑↑	Can occur 12–36 months after HAART initiation; thyroid scan is homogenous, and uptake is high
Toxic multinodular goiter	↓↓	↑↑	↑↑	Nodule on thyroid scan; high uptake; individual nodules are best visualized by ultrasound imaging
Painless thyroiditis	↓↓	↑↑	↑↑	Low radioiodine uptake
Subacute thyroiditis	↓↓	↑↑	↑↑	Low radioiodine uptake, usually associated with painful thyroid and elevated erythrocyte sedimentation rate; may follow upper respiratory infection
Subclinical hyperthyroidism	↓	N	N	Nonthyroidal illness and use of certain drugs (steroids or dopamine) should be considered
Infectious destructive thyroiditis	↓↓	↑↑	↑↑	Usually painful and enlarged thyroid; low radioiodine uptake

NOTE. Anti-TPO, anti-thyroid peroxidase; FT₄, free thyroxine; N, normal; TSH, thyrotropin; T₃, tri-iodothyronine; ↑, increase; ↑↑, marked increase; ↓, decrease; ↓↓, marked decrease.

is elevated, with diffuse distribution noted by thyroid scan. In the 2 other common conditions associated with increased radioiodine uptake (hyperfunctioning adenomas and multinodular goiter), thyroid scans reveal heterogeneous areas of uptake.

The most common causes of hyperthyroidism associated with low uptake, in all populations, are subacute thyroiditis and painless thyroiditis. Subacute thyroiditis (also known as “subacute granulomatous thyroiditis”) generally presents after a viral upper respiratory tract infection and is usually—but not always—associated with an enlarged, tender thyroid; fever; and an elevated erythrocyte sedimentation rate. It generally lasts up to 6 weeks and can be followed by a 4–6-week period of hypothyroidism prior to thyroid function normalization. Painless or “silent” thyroiditis (also sometimes confusingly called “subacute lymphocytic thyroiditis”) is a transient autoimmune inflammation of the thyroid; it is often associated with anti-thyroid peroxidase antibodies [10]. It follows a clinical course similar to that of subacute thyroiditis, with a hyperthyroid phase followed by transient hypothyroidism and recovery. Autoimmune thyroiditis that causes transient hyperthyroidism typically occurs in the postpartum scenario (postpartum thyroiditis).

Management of hyperthyroidism. The management of hyperthyroidism depends on the underlying diagnosis. In cases of Graves' disease, antithyroid drugs (propylthiouracil or methimazole) can be used to inhibit thyroid hormone production. Definitive treatment with radioiodine thyroid ablation or surgery may be appropriate for some patients with Graves' disease, and it is the treatment of choice for patients with toxic multinodular goiter or toxic adenoma. With subacute thyroiditis, a course of nonsteroidal anti-inflammatory drugs—or, in more-severe cases, prednisone—can help to relieve pain. Regardless of the cause, β -blockers are effective in controlling the hyperadrenergic symptoms and are generally the only necessary treatment for painless thyroiditis [35]. In patients with hyperthy-

roidism, consultation with an endocrinologist is recommended to develop a strategy that best suits the patient.

Subclinical hyperthyroidism. Subclinical hyperthyroidism may precede overt hyperthyroidism in some patients and is defined by low TSH levels, normal FT₄ and T₃ levels, and the absence of thyrotoxicosis, although patients may have subtle symptoms of hyperthyroidism [48]. Treatment with antithyroid drugs or radioiodine thyroid ablation should be considered if symptoms are present. The consequences of subclinical hyperthyroidism include reduced bone mineral density and an increased risk of atrial fibrillation, the risk of which is proportional to the degree of thyroid hyperfunction. For this reason, current guidelines suggest treating patients who have a TSH level <0.1 mU/L, are aged >60 years, or have osteopenia or osteoporosis. No treatment is recommended for persons with milder disease (TSH level, 0.1–0.45 mU/L), but follow-up thyroid testing in 6–12 months is reasonable [26]. Because a low TSH level with normal thyroid hormone concentrations can

Table 3. High and low radioiodine uptake hyperthyroid conditions.

High uptake (>25% uptake)
Graves' disease
Toxic adenoma
Toxic multinodular goiter
Thyrotropin-producing adenoma
Molar pregnancy
Low uptake
Subacute autoimmune thyroiditis
Postviral thyroiditis
Postpartum thyroiditis
Amiodarone toxicity
Radiation thyroiditis
Factitious hyperthyroidism
Functional metastatic follicular thyroid cancer
Infectious destructive thyroiditis

Table 4. Indications for thyroid testing for HIV-infected patients.

Symptoms of hypothyroidism (fatigue, weakness, cold intolerance, slowed mentation, constipation, bradycardia, and delayed tendon reflex relaxation)
Symptoms of hyperthyroidism (irritability, heat intolerance, sweating, warm moist skin, palpitations, tachycardia, fatigue, weight loss with increased appetite, diarrhea, tremor, muscle weakness, hyperreflexia, and lid retraction)
Osteopenia
Dyslipidemia
Depression
Atrial fibrillation

be observed in patients receiving dopamine or glucocorticoids or in patients with nonthyroidal illness, these diagnoses should also be considered.

SCREENING FOR THYROID DISEASE

Thyroid function testing is appropriate for the diagnoses of thyroid disorders in patients with thyroid-related symptoms or with nonspecific systemic symptoms. However, thyroid function screening of asymptomatic individuals is an area of controversy, both for HIV-infected patients and for the general population. Regardless of HIV status, screening of older patients may be justified by the high prevalence of subclinical hypothyroidism and by the potential benefit of levothyroxine therapy in this population [26]. Although cross-sectional studies have reported a higher prevalence of subclinical hypothyroidism than normally observed in the general population, the pathophysiology of subclinical hypothyroidism may differ in HIV-infected patients; at this point, there is insufficient evidence to support routine screening of all HIV-infected individuals. Similarly, although common, the finding of an isolated low FT₄ level has unclear consequences and should not be the target of routine screening.

Measurement of the TSH level is appropriate for patients with symptoms suggestive of thyroid dysfunction, reduced bone mineral density, dyslipidemia, depression, or atrial fibrillation (table 4). The finding of an elevated TSH level should prompt the health care provider to measure the FT₄ level, whereas both the FT₄ level and the T₃ level should be measured in patients with a low TSH level (to rule out T₃ toxicosis). When testing is performed, nonthyroidal illness should be considered in the differential diagnosis of abnormal thyroid function test results, particularly for patients with advanced AIDS or uncontrolled HIV infection.

CONCLUSIONS

Abnormal thyroid function test results are common among HIV-infected individuals. This is especially true during HAART, when Graves' disease may be triggered by immune reconsti-

tution and the presence of subclinical hypothyroidism, and when isolated low FT₄ levels appear to be more common. Currently, there is insufficient evidence in favor of screening for thyroid abnormalities among asymptomatic HIV-infected individuals [49]. Larger studies are needed to examine the epidemiology and health consequences of mild thyroid dysfunction in HIV-infected patients and to better inform screening and treatment guidelines.

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