

Thyroid Dysfunction in HIV-AIDS

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Human immunodeficiency virus (HIV) infection can lead to multiple organ involvement --- including the endocrine system. Endocrine function may be altered in these subjects because of the possible relationship between the immune and endocrine systems, direct involvement of the glands by the HIV itself, opportunistic infections or malignancies.^{1,2}

Any chronic illness associated with malnutrition or inflammation can cause abnormalities in thyroid function tests (TFTs). There are contradictory reports about thyroid function tests in subjects with HIV/AIDS.^{2,3} Among individuals infected with HIV, 1-2% manifest overt thyroid disease and subtle abnormalities in thyroid functions are frequently encountered.⁴

Abnormal thyroid functions in these patients may be caused by the stress of advanced disease or concomitant morbidities and may manifest as the classic sick euthyroid syndrome³ probably due to a hypothalamic pituitary deficit related to the progress of immunodeficiency and cachexia.¹ Cytokines such as IL-6 and TNF- α can acutely decrease TSH and T3 and increase rT3 levels.

LoPresti et al studied thyroid functions in HIV positive patients, to evaluate if they could be used to predict their progression and outcome. The nonsurvivors of *P. carinii* had lower T3 (0.56 nmol/L) than the survivors (1.3 nmol/L). The rT3 was higher in patients with AIDS-related complex (0.21 nmol/L) than in AIDS outpatients (0.17 nmol/L). As HIV infection progressed, rT3 decreased and thyroxine-binding globulin increased. They concluded that TFTs can provide information on the clinical course of HIV-infected patients and may be used to help make decisions regarding therapy.⁵

Bordoux found that thyroid binding globulin was increased in 16 out of 54 HIV infected patients and correlated inversely with CD4 counts.⁶ Grinspoon confirmed the fact that reverse T3 levels did not rise in association with decreasing T3 levels as expected in non-thyroidal illness.⁷

Jain et al in this issue of the journal, report abnormal thyroid levels which correlated with the CD4 counts and severity of the disease.⁸

These, however are not the only affectations of thyroid function in the HIV AIDS infection. Screening studies have demonstrated an increased prevalence of primary hypothyroidism in HIV infected patients. Beltran⁴ reported overt hypothyroidism in 2.6%, subclinical hypothyroidism in 6.6% and an isolated low T4 level in 6.8% of 350 subjects studied. Low free T4 levels (1.3%) and subclinical hypothyroidism (3.5%) which correlated with low CD4 counts were reported in a Spanish population.⁹

An infectious trigger for immune activation (by molecular mimicry) is one of the postulated mechanisms for autoimmune disease. However hypothyroidism in HIV infected patients is not associated with autoimmunity.¹⁰ One case of Hashimoto's hypothyroidism has been reported so far after highly active anti-retroviral therapy (HAART) initiation.¹¹

Thyroid disease in children is important to detect because it has an affect on growth and development. Chiarelli et al¹² demonstrated the presence of the sick euthyroid syndrome, associated with the severity of immunosuppression in perinatally

infected children. Fundaro¹³ demonstrated increased TSH levels (28%) and antithyroglobulin antibodies (34%) in symptomatic children. Growth rates increased in response to thyroid replacement in children with failure to thrive and exaggerated TSH responses to TRH testing.¹⁴

An increasing incidence of autoimmune disease and presence of auto antibodies is being recognized in HIV infected patients. Goddard proposed a staging of autoimmune manifestations related to HIV/AIDS, total CD4 counts and viral load that may be beneficial in identifying the type of autoimmune disease and establishing proper therapy.¹⁵

Stage I: Acute HIV infection, the immune system is intact and autoimmune diseases may develop.

Stage II : The quiescent period without overt manifestations of AIDS associated with a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found.

Stage III: Immunosuppression with a low CD4 count and the development of AIDS. CD8 T cells predominate and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren's syndrome) may present or even be the initial manifestation of AIDS. No autoimmune diseases are found.

Stage IV: Restoration of immune competence following HAART. In this setting, there is a resurgence of autoimmune disorders.

The immune reconstitution syndrome that is described above is associated with autoimmune thyroid disease. Chen estimated the prevalence of immune reconstitution Autoimmune Thyroid Disease (AITD) (Graves' Disease, hashithyrototoxicosis, and hypothyroidism) was 3% for women and 0.2% for men. The median duration of immune reconstitution was 17 months. Patients with lower CD4 counts at baseline who experienced greater increments in the CD4 counts following HAART were more likely to develop AITD.¹⁶

Subclinical hypothyroidism is more prevalent in the HIV infected population, compared to HIV-negative individuals.^{10,17} Quirino¹⁰ reported a similar prevalence of subclinical hypothyroidism in both naive and HAART treated subjects,

Beltran et al⁴ found that subclinical hypothyroidism was associated with the use of stavudine and lower CD4+ cell count, The cumulative daily dose of both stavudine and lamivudine was significantly related to the presence of hypothyroidism in Grappin's series.¹⁷ Didanosine and ritonavir were associated with a low free T4.⁴

Bongiovanni¹⁸ studied subjects on stable HAART (for at least 1 year) at baseline and at month 24 (G1); subjects naive at both baseline and month 24 (G2) and subjects starting HAART at baseline (G3). At baseline, the prevalence of subclinical hypothyroidism was similar in the three groups (14.4%, 10.6% and 8.7% respectively). At month 24, 4.8% (G1), 7.1% (G2) and 19.0% (G3) of the population developed de novo subclinical hypothyroidism, suggesting a possible acute effect of HAART on thyroid function.

The role of HAART was confirmed by a recent report that HAART interruption was associated with a normalization of TFTs.¹⁹

Besides HAART, IL-2 therapy is also reported to induce Graves' disease.²⁰

Thyroid dysfunction in HIV-positive individuals can result from gland destruction by opportunistic pathogens (*Pneumocystis jirovecii* or cytomegalovirus) or tumorigenic diseases (Kaposi's sarcoma). These opportunistic infections could be associated with the sick euthyroid syndrome or could cause low reverse T3.^{5,21}

Pneumocystis thyroiditis has been reported to cause a painful low uptake thyroiditis like picture with hyperthyroidism followed by hypothyroidism.²²

We come now to the questions this review raises:

Should thyroid functions serve as surrogates for progressive HIV infection?

In the opinion of the author, today, we have available direct measures to establish the severity of HIV infection e.g. CD4 counts, viral load estimation and the presence of opportunistic infections and hence, surrogate makers should really not be relied upon.

Should we screen all patients with HIV infections for thyroid dysfunction?

This remains an area of controversy. In a large cohort of HIV positive subjects followed for 3 years, Madge et al²³ found the prevalence of hypothyroidism to be 2.5% (overt) and 4% (subclinical). Hyperthyroidism (overt and subclinical) occurred in <1% of patients. Non-thyroidal illness was seen in 17% of patients whereas 75.5% had normal TFTs. Only eight new cases (1%) of overt thyroid disease occurred over 3 years. They made a strong case against universal screening in HIV positive subjects.

Nelson's study²⁴ revealed a higher than expected incidence of overt hypothyroidism in patients receiving HAART and they recommend universal screening of subjects on therapy.

What should be the management protocols for the various abnormalities reported?

Overt Hypothyroidism should be treated with levothyroxine keeping in mind that drug interactions between levothyroxine and protease inhibitors have been reported, perhaps through the shared metabolic pathway of glucuronidation.²⁵ Thyroid medications may also affect the course of the various comorbidities in HIV infected subjects.

Subclinical Hypothyroidism : The TSH level should be determined again in 1–3 months, because the levels in 30% of HIV-uninfected patients normalize within 1 year. However, the proportion of HIV-infected patients whose levels normalize is not known. Besides, during recovery from illness, the TSH level may temporarily overshoot the normal range, which may mimic subclinical hypothyroidism.¹⁹ No guidelines are available for the level of TSH that warrants the administration of therapy in this situation.

Hyperthyroidism: It would be important to differentiate between Graves' disease or thyroiditis and the appropriate therapy should be considered.

To conclude, abnormal TFTs are encountered often in HIV positive individuals. Management guidelines exist for overt dysfunction as described above. However, larger studies are needed to evaluate the prevalence and outcomes of mild thyroid dysfunction in HIV-infected patients and to formulate screening and treatment guidelines.

References

1. Raffi F, Brisseau JM, Planchon B et al : Endocrine function in 98 HIV-infected patients: a prospective study. *AIDS* 1991; 5: 729–33.

2. Dobs AS, Dempsey MA, Ladenson PW et al. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med* 1988; 84: 611–16.
3. Tang WW, Kaptein EM: Thyroid Hormone levels in the acquired immunodeficiency syndrome (AIDS) or the AIDS related complex. *West J Med* : 1989; 151:627-631.
4. Beltran S, Lescure FX, Desailoud R, et al: Increased prevalence of hypothyroidism among human immunodeficiency virus-infected patients : a need for screening : *Clin Infect Dis*: 2003; 37:579-83
5. Lo Presti JS, Fried JC, Spencer CA et al: Unique alterations of thyroid hormone indices in the acquired immunodeficiency syndrome (AIDS) *Ann Int Med*: 1989; 110: 970-975.
6. Bordoux PP, De Wit SA, Servais GM : Biochemical thyroid profile in patients infected with the HIV virus: *Thyroid* 1991;1:147-149
7. Grinspoon SK, Bilezikian JB : HIV disease and the endocrine system *NEJM* 1992;327:1360-1365
8. Jain G, Devpura G, Gupta BS. Abnormalities in the thyroid function tests as surrogate marker of advancing HIV infection in infected adults. *JAPI*:2009;57:508-510.
9. Collazos J, Ibarra S, Mayo J Thyroid hormones in HIV infected patients in the highly active antiretroviral therapy era: evidence of an interrelationship between the thyroid axis and the immune system *AIDS* 2003;17:763-765
10. Quirino T, Bongiovanni M, Ricci E: Hypothyroidism in HIV infected patients who have or have not received HAART. *Clin Infect Disease* 2004; 38: 596-597.
11. Rosenfeld CR, Calabrese LH. Progression of autoimmune thyroiditis in an HIV - infected woman on HAART. *AIDS Read* 1999; 9:393–4.
12. Chiarelli F, Galli L, Verotti A et al : Thyroid function in children with perinatal HIV Type 1 infection. *Thyroid* 2000;10: 499-505
13. Fundaro C, Oliveiri A, Rendeli C et al : Occurrence of antithyroid antibodies in children vertically infected with HIV 1. *J Pediatr EndocrinolMetab*1998;11:745-750.
14. Rana S, Nunlee Bland G, Valyasevi R, Iqbal M Thyroid dysfunction in HIV infected children: Is L thyroxine therapy beneficial? *Pediatric AIDS HIV Infect*:1996;7:424-428.
15. Goddard GZ, Shoenfeld Y, HIV and autoimmunity: *Autoimmunity Reviews*: 2002;1:329-337.
16. Chen F, Day SL, Metcalfe RA et al: Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus disease *Medicine (Baltimore)*:2005;84:98-104.
17. Grappin M, Piroth L, Verges B et al. Increased prevalence of subclinical hypothyroidism in HIV patients treated with highly active antiretroviral therapy. *AIDS* 2000; 14: 1070–2.
18. Bongiovanni M , Adorni F, Casana M , et al : Subclinical hypothyroidism in HIV-infected subjects. *Journal of Antimicrobial Chemotherapy* 2006;1086-1089
19. Madeddu G, Spanu A, Chessa F et al. Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): a longitudinal study. *Clin Endocrinol* 2006; 64: 375–83.
20. Jimenez C, Moran SA, Sereti I : Graves' Disease after Interleukin -2 therapy in a patient with HIV infection: *Thyroid* 2004;14:1097-1102
21. Merenich JA, McDermott MT, Asp AA et al. Evidence of endocrine involvement early in the course of human immunodeficiency virus infection. *J Clin Endocrinol Metab* 1990; 70: 566–71.
22. Drucker DT, Bailey D : Thyroiditis is the presenting manifestation of Disseminated extrapulmonary *Pneumocystis carinii* infection. *J Clin Endocrinol Metab* 1990;71:1663-1665.
23. Madge S, Smith C, Lampe F, Thomas M, Johnson M, et al :No association between HIV disease and its treatment and thyroid function. *HIV Med* 2006; 7(supp 1):23 abstract P49.
24. Nelson M, Powles T, Zeitlin A: Thyroid dysfunction and relationship to antiretroviral therapy in HIV positive individuals in the HAART era *J Acquired Immunodeficiency Syndromes* 2009;50:113-114.
25. Touzot M, Le Beller C, Touzot F, Louet AL, Piketty C. Dramatic interaction between levothyroxine and lopinavir/ritonavir in an HIV - infected patient. *AIDS* 2006; 20:1210–2.