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THYROID FUNCTION AMONG HIV/AIDS PATIENTS ON HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY

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ABSTRACT

Objectives: To assess the thyroid function among Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) patients on anti-retroviral drugs: stavudine, lamivudine and nevirapine and to establish the prevalence of non-thyroid illness.

Design: Laboratory based comparative cross-sectional study.

Setting: Comprehensive care clinics at KNH and Mbagathi District Hospital.

Subjects: Eighty four HIV-infected patients on treatment with ARVs (ARV +ve) and an ARV naive (ARV naive) group of 26 HIV-infected patients.

Results: Thyroid stimulating hormone levels were not altered following treatment whereas the levels of FT4 decreased. The frequency of those with low FT4 were increasing with continued ARV use. The prevalence of non-thyroidal illness state defined by TSH within reference ranges and low FT4 was comparable among the ARV +ve and ARV naive groups (44 and 46% respectively).

Conclusion: Progressive use of HAART causes decline in FT4 hormone levels. It is debatable whether interventions for low FT4 is necessary in ARV treatment but a longitudinal study would explain the progressive trend of thyroid hormones and implications with HAART treatment. The prevalence of NTI is comparable to both HAART users and non-users. Low levels of thyroid hormone (FT 4) may be an adaptive response by thyroid gland to minimize calorie utilisation as in chronic diseases.

INTRODUCTION

Changes in pituitary-thyroid function occur in patients with virtually all illnesses and those undergoing major surgical procedures. Although such changes are referred to as the euthyroid sick syndrome, the key changes namely; decreases in serum triiodothyronine and thyroxine concentrations have multiple causes, vary considerably in different patients, and very likely have different effects on different tissues (1). Although it is generally assumed that the decreases have no pathophysiologic consequences, it is by no means clear that the patients are in fact euthyroid.

The most common change is a decrease in extrathyroidal conversion of thyroxine (T4) to triiodothyronine (T3), the active form of thyroid hormone. This reaction is responsible for the production of 75 to 80 percent of the circulating triiodothyronine in normal subjects and probably more of the intracellular triiodothyronine (2). In illness, the production and serum concentrations of triiodothyronine decrease as a result either of decreased

delivery of thyroxine to the widely distributed intracellular deiodinases that catalyze the conversion or of decreases in the activity of the enzymes (3).

A second change is a decrease in thyrotropin releasing hormone (TRH) secretion, which causes decreased TSH secretion and, in time, decreases serum thyroxine concentrations and further decrease in serum triiodothyronine concentrations; the latter due both to decreased thyroid secretion of triiodothyronine and decreased availability of thyroxine for peripheral conversion to triiodothyronine (4). Although relatively mild illness or caloric restriction alone may result in some decrease in thyrotropin secretion, especially at night, most patients with nonthyroidal illness who have low serum thyrotropin concentrations are very sick (5).

Several complications have been described in HIV patients during use of HAART, such as hypertriglyceridaemia and hypercholesterolaemia, lipodystrophy and lipoatrophy, glucose intolerance and type 2 diabetes mellitus, gonadal dysfunction, osteopaenia and osteoporosis (6); the latter two conditions have especially been reported in patients receiving protease inhibitors

(PI) (7) or when lipodystrophy (8) or an asymptomatic nucleoside reverse transcriptase inhibitors (NRTI)-related lactic acidemia were associated, suggesting a mitochondrial toxicity of the osteoblasts, which become less capable of bone formation (9). However, the mechanism by which HAART causes these alterations remains unknown; even if it is probably multifactorial with the HIV infection itself also being involved (9).

Asymptomatic subtle abnormalities of thyroid function tests, such as low serum levels of only T4, have been described in a small percentage of patients with stable HIV infection by some authors (10,11) but most asymptomatic patients with early HIV infection and stable body weight have had normal T3 and T4 levels, as well as low reverse triiodothyronine (rT3) and often high thyroid binding globulin (TBG) values (9).

Moreover, low T3 and FT3 levels associated with low rT3 and high TBG levels have been found in other groups of patients in relation to the worsening of HIV illness when anorexia and weight loss occur, as happens in a classic sick euthyroid syndrome which, unlike the HIV condition, is usually characterised by high rT3 levels as a result of its decreased clearance (12).

However, the clinical significance of rT3 and TBG abnormalities in HIV patients still remains unknown. The mechanism by which thyroid hormone levels are altered in HIV patients is not clear. It has been hypothesized that cytokines released in a great quantity by the host in response to infection may play a role in influencing thyroid hormone homeostasis (13).

Few and controversial results exist on thyroid function in HIV patients treated with highly active antiretroviral therapy (HAART) which, as is well known, has significantly improved HIV and AIDS prognosis. However, the abnormalities in thyroid tests, when present, are commonly asymptomatic both in adults and in children and are most frequently associated with hypothyroidism. Medications affecting thyroid hormone production, metabolism, or transport occasionally caused dysregulation. Although overt thyroid disease was uncommon, alterations in thyroid function consistent with nonthyroidal disease were observed. By contrast with nonthyroidal illness, however, relative preservation of T3 levels, non elevation of

reverse T3 levels, and elevation of thyroid-binding globulin levels were also described, and remain poorly understood. In particular, the anti-retroviral compound stavudine has been suggested to directly affect the production and/or metabolism of thyroid hormones, although the mechanism is unclear (14).

Along with the dramatic improvement in life expectancy that followed the introduction of HAART, a number of puzzling endocrine and metabolic disorders emerged. Much effort has focused on abnormalities of glucose and lipid metabolism, as well as body-fat redistribution. Less information is available regarding the thyroidal axis. Abnormalities consistent with non thyroidal illness have been observed. In the present study, we have investigated whether thyroid disorders occur in patients with HIV infection on HAART in stable clinical conditions and whether HAART may affect the serum levels of thyroid hormones. For this purpose, we enrolled patients treated with first regimen of HAART and compared them to HIV patients who had never received these drugs (naive).

MATERIALS AND METHODS

Study area: Kenyatta National and Mbagathi District hospitals HIV clinics.

Subjects: All consecutive patients presenting at the HIV clinic in September 2004 and January 2005 that satisfied the inclusion criteria below.

Data collection: Patients recruited were evaluated in the clinic and information on age, gender, HIV status and duration of treatment were obtained. Eligibility to the study was determined and consent form signed.

Laboratory analysis: Serum thyroid hormones levels; (TSH) and free thyroxine (FT4) were determined using enzyme linked immunosorbent assay (ELISA) kit from Human GmbH Germany. The assay procedure was followed according to the kit manufacturers.

Definitions: The levels of TSH and FT4 were used to make the various thyroidal states (Table 1).

Table 1
Levels of TSH and FT4 used to classify thyroid state clinically

Classification	TSH (mU/L)	FT4 (pmol/L)
Euthyroid	0.3-6.2	10.3-25.8
Non-thyroidal illness	0.3-6.2	<10.3
Sub-clinical hypothyroid	>6.2	10.3-25.8
Sub-clinical hyperthyroid	<0.3	10.3-25.8
Primary hypothyroid	>6.2	<10.3
Secondary hypothyroid	<0.3	<10.3

Abbreviations TSH; thyroid stimulating hormone; free thyroxine

Eligibility: Subjects must have been HIV positive and on HAART; stavudine, lamivudine and nevirapine and no symptoms of thyroid disease for ARV +ve population. The ARV naïve must have been HIV positive but not on HAART. All were between 18 and 70 years of age. Those on drugs affecting thyroid hormone levels, external irradiation around the neck, pituitary surgery or declined consent were excluded. Patients with AIDS-related malignancy, active opportunistic infections, pituitary, hypothalamic, or neurologic disease, and prior treatment with drugs known to affect thyroid hormone metabolism were excluded. Demographic and clinical characteristics were assessed. These included HIV test results, method of HIV test, HIV infection duration, CD4+ cell count, and hepatitis B and C status. Anti-retroviral regimen and duration of treatment were also noted. Patients with hepatitis B and C were not recruited for the study.

Ethical consideration: Approval was sought from the University of Nairobi and Kenyatta National Hospital Research and Ethics Committee.

Written informed consent was obtained from the participants.

Data analysis: SPSS 12.0.1 software was used for data entry and statistical analysis.

RESULTS

Patient characteristics: A total of 110 patients were recruited (84 on HAART and 26 not on anti-retroviral therapy). The age range was 20 and 64 years with a modal age set of 30 to 39 years followed closely by 40 to 49 years. The extremes of age formed the least group of patients (Table 2). The sample population had a mean of 36.5 years. There were 30 (35.7%) male and 54 (64.5%) female patients among ARV +ve and 13 (50%) both male and female for ARV naïve group. This formed a ratio of male to female of 1: 1.8 and 1: 1 respectively. The mean \pm SD duration of anti-retroviral administration among ARV +ve was 10.05 \pm 9.6 months.

Table 2
Social demographic characteristics of the study population

Demographic characteristics	ARV +ve (N)	ARV +ve (%)	ARV naïve (N)	ARV naïve (%)
Age distribution(years)				
20-29	8	9.5	5	19.3
30-39	39	46.4	13	50
40-49	29	34.5	7	26.9
50-59	7	8.3	0	0
60-69	1	1.2	1	3.8
Sex				
Male	30	35.7	13	50
Female	54	64.3	13	50

Abbreviation ARV +ve; HIV/AIDS Patients on anti-retroviral drugs (n=84): \surd ARV naïve, HIV / AIDS Patients not receiving anti-retroviral drugs (n=26).

Thyroid hormone levels: The TSH levels were within reference range in ARV +ve (85.6%) and ARV naïve (92.3%) (Table 3). However, there were no incidences of elevated FT4 levels among ARV naïve, but 12.0% ARV +ve had high TSH levels. There was no statistical significant in the levels of TSH ($p=0.233$) between ARV +ve and ARV naïve. The frequency of lower FT4 levels in ARV +ve (54.8%) compared to ARV naïve (30.0%) was not statistically significant ($p=0.45$).

Table 3

Thyroid hormone levels of the study participants ARV +ve (n = 84) and ARV naïve (n = 26)

Subjects	Thyroid hormones		TSH (%)	FT4 (%)
	TSH	FT4		
ARV +ve				
High	12.0	0.0		
Normal		85.6	45.2	
Low	2.4	54.8		
ARV naïve				
High		0.0	0.0	
Normal		92.3	70.0	
Low		7.7	30.0	

Abbreviation ARV +ve; HIV/AIDS Patients on anti-retroviral drugs (n=84): ARV naïve, HIV/AIDS Patients not receiving anti-retroviral drugs (n=26). The total number of study participants were 110.

Thyroid hormone levels and duration of treatment: The TSH levels did not change during treatment but remained within reference limits. The reference range was 0.3-6.2mU/L. The trend was that the levels remained within this range for both ARV +ve and ARV naïve groups (Figure 1). The FT4 levels was below reference range (10.3-25.8 pmol/L) ARV naïve. The levels of the hormone began to rise on beginning treatment and was within reference range in the first year of treatment. However, the levels declined after the first year of treatment (Figure 2).

Thyroidal state: The level of non thyroidal illness among ARV +(44%) were comparable with that ARV naïve (46.2%). There was a higher incidence of euthyroid among ARV +ve (42.9%) than ARV naïve(34.6%) (Figure 3). Abnormality with thyroidal state was more frequent in ARV naïve than in ARV +ve except for sub clinical hypothyroidism which was absent in the former (Figure 3).

Figure 1

The trend of TSH levels during treatment with HAART

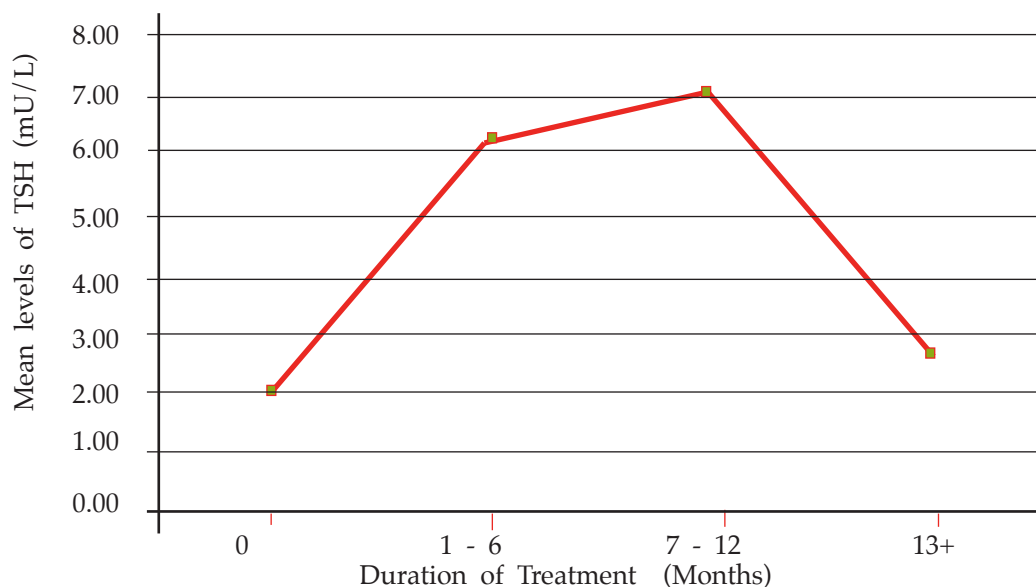


Figure 2
The trend of FT4 during treatment with HAART

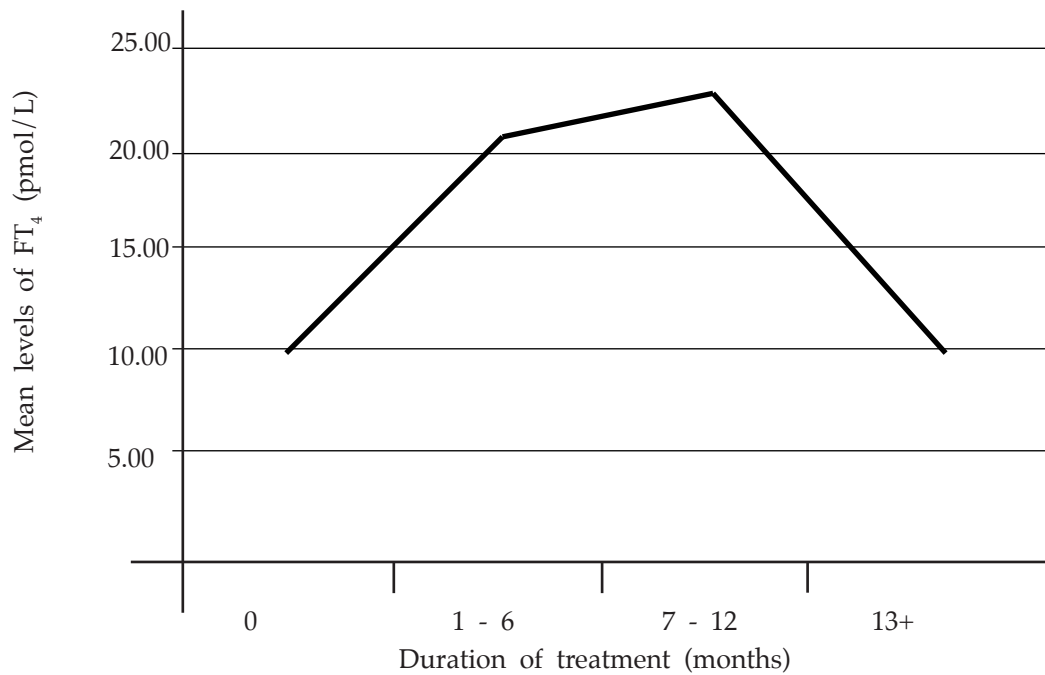
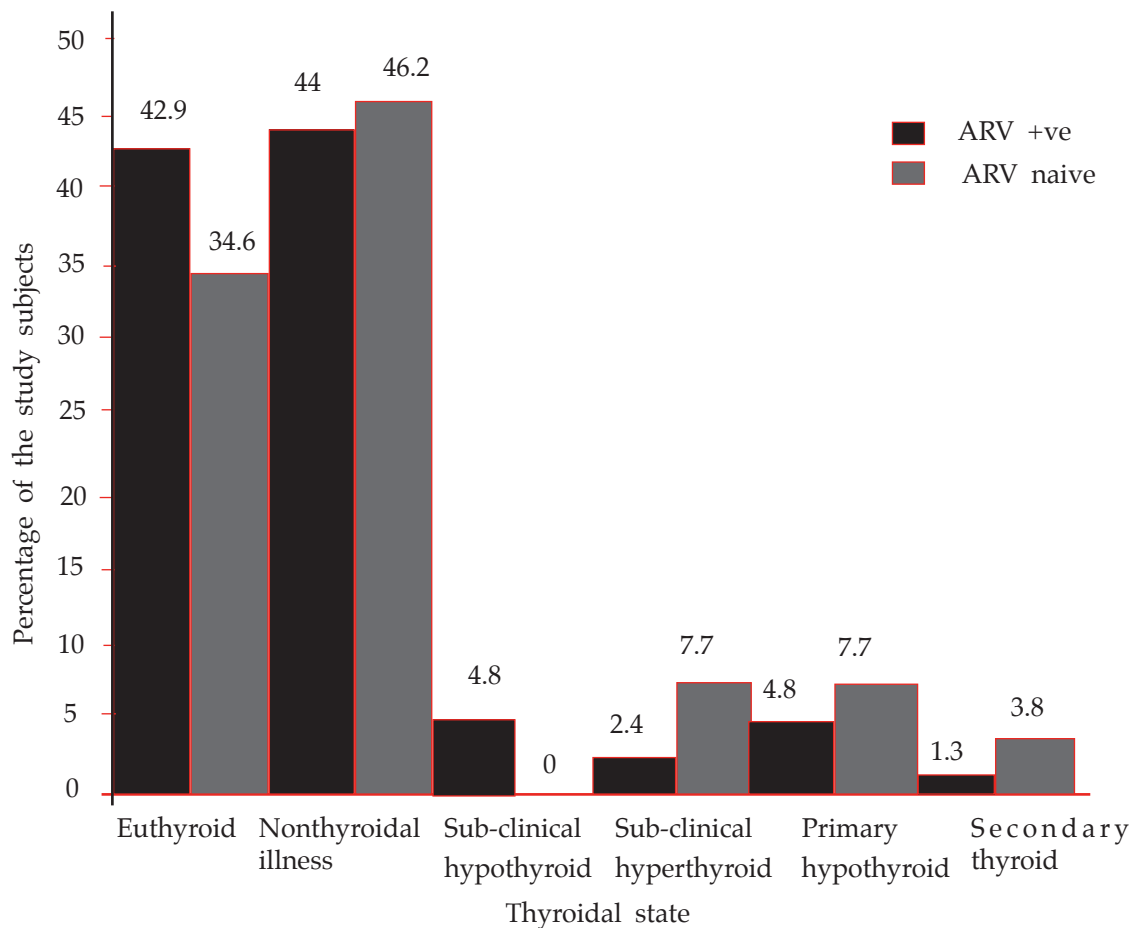


Figure 3
Percentage of thyroid status in the study participants in the time of study



DISCUSSION

Thyroid Hormone Levels: The TSH levels were not altered with HAART treatment. The FT4 levels were low before treatment. The trend changed and was within reference range in the first year of treatment. As the treatment progressed beyond one year, the levels of FT4 declined to below reference range (figure 2). This trend in low thyroid hormone levels may be adaptive response by the body to spare calories and protein by inducing hypothyroidism (17). Responsiveness of the pituitary to TRH during NTI varies; some patients respond normally, while many have a less-than-normal response (12). Normal responsiveness in the presence of low TSH may suggest that a hypothalamic abnormality is causing the low TSH and T4 levels. The down-regulation at the hypothalamus-pituitary provides an explanation for the decreased sensitivity to TSH leading to low serum T3 and T4 concentrations in patients with NTI. A diminution or loss of the diurnal rhythm of TSH also occurs. Some studies have produced evidence for a reduction of TSH glycosylation with lower TSH bioactivity (2). Cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha, and interferon beta affect the hypothalamus and pituitary by inhibiting production of TSH, thyroid releasing hormone (TRH), thyroglobulin and T3. They also decrease the activity of deiodinase Type I and binding capacity of T3 nuclear capacity (18). Patients on HAART develop symptoms of low levels of thyroid hormones, mainly T3 and T4 in the blood (11). In this study, the levels of FT4 were below reference range among the treatment and non treatment group.

Non-thyroidal Illness: The prevalence of non-thyroidal illness was 44% among the patients on HAART treatment and 46% among those not on treatment. The prevalence of non-thyroidal illness was comparable in both populations. Since the TSH levels is not elevated in the presence of low T4 indicates that the patients were not hypothyroid. Diminished release of TRH results in low TSH, and hence low output of thyroid hormones by the thyroid gland. Low TRH (messenger ribonucleic acid) mRNA in hypothalamic paraventricular nuclei has also been demonstrated (13).

Evaluating thyroid function in patients with NTI has considerable challenges. Supplementing low thyroid hormones levels may not be beneficial. Studies have shown that administration of replacement of doses of thyroxine did not improve or hasten recovery or improve survival neither does the administration of a large dose of triiodothyronine in seriously burned patients (16,18). Free T4 is believed to represent the hormone available to tissues. Measurement of total serum T4 has only

limited value since nearly all (99.97%) of the circulating T4 is bound to T4 binding globulin (TBG), T4-binding pre-albumin (TBPA), and albumin. The rest of the circulating T4 (0.2-0.03%) is free T4.

The circulating concentrations of these binding proteins is understood to affect the total T4 concentration without necessarily changing the amount of free T4. Usually, within the reference range in patients with NTI and somewhat lower in critically ill patients with low serum T4. Decreased concentrations of one or more of the binding proteins would explain low levels of total T4 but does not explain the significant increase in free T4 fraction, which some patients with NTI exhibit (4,6).

Normal TSH levels with low FT4 is characteristic of non-thyroidal illness. It can be deduced from results obtained from these studies that TSH levels did not change with treatment whereas those of FT4 exhibited a decreasing trend. TSH is a sensitive test that is useful in the diagnosis of primary and secondary hypothyroidism. Free T4 is an active hormone at cellular level. A combination of TSH and FT4 will provide specific diagnosis of thyroid status (15). The pattern of these hormones could be used as a pointer towards development of NTI.

In conclusion progressive use of HAART causes decline in FT4 hormone levels. It is debatable whether interventions for low FT4 is necessary in ARV treatment but a longitudinal study would explain the progressive trend of thyroid hormones and implications with HAART treatment. The prevalence of NTI is comparable to both HAART users and non-users. Low levels of thyroid hormone (FT4) may be an adaptive response by thyroid gland to minimize calorie utilisation as in chronic diseases.

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