ASSESSMENT OF THYROID DYSFUNCTION IN PATIENTS WITH HIV ON HAART

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CERTIFICATE

This is to certify that this dissertation entitled ***" ASSESSMENT OF THYROID DYSFUNCTION IN PATIENTS WITH HIV ON HAART"*** *is submitted by* ***DR.K.KARTHIKEYAN,*** *post graduate student of Internal Medicine, Institute of Internal Medicine, Madras Medical College, Chennai - 600003, appearing for M.D Branch I General Medicine Degree examination in March 2008 and is a bonafide record of work done by him under my direct supervision in partial fulfillment of regulations of The Tamil Nadu Dr.M.G.R. Medical University, during the academic year 2005-2008. I forward this to The Tamil Nadu Dr.M.G.R. Medical University, Chennai.*

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CONTENTS

INTRODUCTION

HIV infection is a chronic, systemic disease possibly leading to multi-organ involvement and affecting the endocrine system as well. However, since its identification in 1983[1,2],and the isolation of the human immunodeficiency virus type I (HIV-1) as the primary cause of the acquired immunodeficiency syndrome. (Barré-Sinoussi 1983, Broder 1984, Gallo 1984).[3,4,5,6,7] almost 25 years have now elapsed. Twenty-five years, in which HIV infection has changed from a fatal condition to a manageable chronic illness. Twenty-five years, in which the development of antiretroviral therapy (ART) has been one of the dramatic advances in the history of medicine.

Highly active antiretroviral therapy (HAART) has changed the clinical evolution of HIV infection. However, its adverse effects are increasingly being recognized, particularly those concerning endocrine dysfunction, and some of the secondary effects are probably not known yet. The observation in several studies of clinical and subclinical thyroid dysfunction at various stages of this infection suggests an effect of HIV and/or HAART on the endocrine system. However, the abnormalities in thyroid tests, when present, are commonly asymptomatic and are most

frequently associated with subclinical hypothyroidism [35,36,42,43], although the mechanism is unclear. These data, however, have not been confirmed by others [8,58]

Comparable data with respect to Indian population is not available till date, whereas the studies from our nearby nations, Iran and Thailand, reveal significant distribution of thyroid dysfunction [47,63]

In view of the variability of thyroid function tests in patients with HIV and HAART in previous studies, it was decided to undertake a prospective study of thyroid function on HIV patients on HAART in stable clinical conditions, in the Institute of Internal Medicine, Madras Medical College and Government General Hospital, Chennai.

AIMS AND OBJECTIVES

To investigate the prevalence of overt and subclinical thyroid disease in HIV-positive patients on HAART

To find the pattern of thyroid dysfunction prevalent within the study population

To find the correlation between the thyroid dysfunction and HAART

REVIEW OF THE LITERATURE

The thyroid is one of the largest endocrine glands in the body, weighing approximately 15 to 20 g. The presentation of thyroid conditions can range from clinically obvious to clinically silent. Their consequences can be widespread and serious, even life threatening. Persons of both sex and any age can be affected, although almost all forms of thyroid disease are more frequent in women than in men, and many thyroid ailments increase in frequency with age. The thyroid dysfunction is simply classified as hypothyroidism, hyperthyroidism, sub clinical hypothyroidism and sub clinical hyperthyroidism depending upon the TSH and thyroid hormone levels.

Clinical status	TSH level	Thyroid hormone
Normal	Normal	Normal
Hypothyroid	High	Low
Hyperthyroid	Low	High
Sub clinical Hypothyroid	High	Normal
Sub clinical Hyperthyroid	Low	Normal

HYPOTHYROIDISM

Hypothyroidism is the condition resulting from lack of the effects of the thyroid hormone on body tissues. Hypothyroidism is a common condition. [11, 12] The overall incidence in the population is approximately 1% to 2 %.[13, 14). In both sexes, the incidence increases during and after middle life. [10). The serum TSH levels are more than 10mU/L and associated with low values of thyroid hormones. Florid hypothyroidism can be diagnosed clinically.

The *symptoms* of hypothyroidism in descending order of frequency are:

- Tiredness, weakness
- Dry skin
- Feeling cold
- Hair loss
- Difficulty in concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (Later amenorrhea)

- Paraesthesia
- Impaired hearing

The *signs* of hypothyroidism in descending order of frequency are as follows:

- Dry coarse skin
- Cool peripheral extremities
- Puffy face, hands and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions.

SUBCLINICAL HYPOTHYROIDISM

The term subclinical hypothyroidism designates a situation in which an asymptomatic patient has a low-normal FT4 but a slightly elevated serum TSH level. Other terms for this condition are mild hypothyroidism, preclinical hypothyroidism, biochemical hypothyroidism, and decreased thyroid reserve. The TSH elevation in such patients is modest, even a high-

normal serum TSH level (e.g., 3.0 μU/L) may reflect very mild thyroid dysfunction, particularly in a patient who has other clinical or laboratory features of autoimmune thyroiditis. As a result, some authorities have recommended lowering the TSH assay's upper limit of normal to 2.5 μU/L.[15] The values typically between 4.5 and 10 μU/L. [9] associated with normal total or free T4 and T3 levels constitute subclinical hypothyroidism as stated in the latest consensus statement by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. .

HYPERTHYROIDISM

Hyperthyroidism is the condition resulting from the effect of excessive amounts of thyroid hormones in the body tissues. Thyrotoxicosis is a synonym. Graves's disease is the most common cause of hyperthyroidism. Approximately 0.5% to 1% of the population suffers from hyperthyroidism. The TSH levels are suppressed, usually <0.1 mU/L and associated with high levels of thyroid hormones.

The *symptoms* of hyperthyroidism in descending order of frequency are as follows:

- Hyperactivity, irritability, dysphoria.

- Heat intolerance and sweating
- Palpitations
- Fatigue and weakness
- Weight loss with increased appetite
- Diarrhoea
- Polyuria
- Oligomenorrhea, loss of libido

The *signs* of hyperthyroidism in descending order of frequency are follows: Tachycardia; Atrial fibrillation in the elderly

- Tremors
- Goitre
- Warm, moist skin
- Muscle weakness, proximal myopathy
- Lid retraction or lid lag
- Gynaecomastia

SUB CLINICAL HYPERTHYROIDISM

Sub clinical hyperthyroidism is defined as low serum TSH levels (0.1mU/l to 0.4mU/L) associated with normal free T4 and free T3 levels. [35] Sub clinical hyperthyroidism is much less common than sub clinical

hypothyroidism. The prevalence is about 2%; it is more common in women, blacks, and the elderly.

NON THYROIDAL ILLNESS

Alteration in serum thyroid hormones occurs in wide variety of illness which predominantly affect the T3 level and no intrinsic disease of thyroid gland is detected. It is variously termed as *Low T3 syndrome, Sick euthryoid syndrome, Non thyroidal illness syndrome and Thyroid hormone adaptation syndrome*.

This syndrome occurs in wide variety of illness as follows:

i. Acute critical illness and febrile illness such as infections, myocardial infarction etc.
ii. Injuries such as burns, trauma, etc.
iii. Surgery
iv. Fasting
v. Diabetes mellitus
vi. Liver disease
vii. Renal disease
viii. Ketogenic diet
ix. Drugs such as glucocorticoids, dopamine, phenytoin and beta blockers

x. Malignancy

xi. Psychiatric illness

In non thyroidal illness state, initially there is decrease in serum T3 level, both total and free T3 (FT3). This is associated with increase in reverse T3 (rT3).

As illness progresses, there is decrease in serum T4 also, a state called *"Low T3, T4 syndrome"*. Although total T4 level decreases, the free T4 (FT4) remains normal or slightly reduced. In spite of this reduced T3 and T4 level, serum TSH level remains normal or reduced, by which it is differentiated from primary hypothyroidism. However, many studies have showed slight elevation of TSH level in Non thyroidal illness in the absence of hypothyroidism.

THYROID FUNCTION TESTS

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 (T3) and thyroxine (T4). 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[48]

T4 is secreted from thyroid follicular cells during hydrolysis of the thyroid hormone storage glycoprotein, thyroglobulin. In serum, 99.9% of T4 is bound to thyroxine-binding globulin and other proteins, although only the free hormone is available for cell uptake and is thus biologically active.
Because of the extensive protein binding, total T4 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 T4 level that is misleadingly elevated. Conversely, in clinical situations those are associated with low thyroxine-binding globulin concentrations. Current guidelines recommend measuring the T4 level only after the TSH level is found to be abnormal or if central hypothyroidism or thyroid hormone resistance is suspected [49]

Most T3 is produced by systemic 5_-deiodination of T4;only 20% of T3 is released from the thyroid . A second T4 deiodination pathway leads to the production of an inactive hormone, 3,3_,5_-triiodothyronine or reverse T3. Although T3 is the most active form of thyroid hormone, the clinical utility of measuring T3 is limited to a few situations. In patients with

a low TSH level, T3 should be measured (1) to evaluate for isolated elevation of the T3 level (i.e., T3 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, T3 concentrations are initially maintained in the normal range by increased peripheral conversion of T4 to T3; therefore, this measurement has reduced sensitivity for the diagnosis of hypothyroidism[50]

HIV-AN OVERVIEW

HIV evolved from simian immunodeficiency virus (SIV) in chimpanzees and monkeys. Surprisingly, in its natural host, SIV does not cause disease, despite replicating to high levels in infected animals. This lack of pathogenicity may be from a lack of T cell activation in these hosts. Alternatively, these species may have developed tolerance to the infection through natural selection.[16,17] Data suggest that humans acquired HIV type 1 (HIV-1) from *Pan troglodytes troglodytes* chimpanzees infected with SIV, and that HIV-1 was introduced into the human population (as SIV)from these chimpanzees on at least three independent occasions[18] HIV-2 originated from the sooty mangabey monkey (*Cercocebus atys*).[19]

Since its identification in early eighties, HIV has attained epidemic proportions inspite of it being designated as biosafety level 2 pathogen.[20] The distribution of the spread is such that its incidence is racing alarmingly in Sub-Saharan Africa, South and South East Asia, eastern Europe whereas prevalence is on the rise in the developed nations.

TRANSMISSION

Person-to-person transmission can occur through

- Sexual contact
- Injection drug use
- Contaminated blood products
- Mother-child transmission
- Occupational exposure

PATHOGENESIS AND PROGRESSION OF DISEASE

HIV is a member of the lentivirus family of retroviruses. HIV appears as spherical particles that are approximately 110 nm in diameter, with knoblike projections on the surface of the virus and a cone-shaped viral core.[21] The genome is organized into three major regions (*gag, pol,* and

env) and has six regulatory genes that are vital for its life cycle and pathogenicity.[22]

Lifecycle

Two different HIV species have been identified: HIV-1 and HIV-2. Those isolates of HIV-1 that have been globally identified can be classified into the three major phylogenetic groups: M (main), N (neither M nor O), and O (outlier).[23] In the lifecycle of HIV the first point of interaction consists of the binding of the HIV envelope surface protein gp120 with the CD4 receptor on the host cell assisted by co receptors, significantly CCR5 and CXCR4 expressed predominantly by macrophages and lymphocyte respectively, and the subsequent exposure of the other HIV envelope protein, gp41.

After the fusion of the viral and cellular membranes, the viral capsid enters the cell and the HIV reverse transcriptase enzyme converts the single-stranded HIV RNA into a double-stranded DNA, which then is integrated with host chromosome by the viral enzyme integrase. Cellular enzymes transcribe the provirus into mRNA which is then translated into the structural proteins or which serve as genomic RNA for progeny virus. viral replication involve both the assembly of the viral particles, with each viral core incorporating two copies of the viral RNA genome, and the budding

and release of the virus from the cell surface mediated by HIV protease enzyme.

Disease Progression

Shortly after acute HIV infection, HIV begins to preferentially destroy HIV-directed CD4+ helper T cells; this process impairs the critical interaction between host CD4+ T cells and CD8+ T cells and thus weakens the host CTL response. HIV extensively seeds lymphoid organs and the central nervous system. As a result, the infection persists, and continued rounds of replication lead to the gradual depletion of all CD4+ T cells. At the same time, a subset of activated, HIV-infected CD4+ T cells returns to a quiescent state, remains latently infected.[25] The CD4+ T cell count provides an accurate way to assess the current immunologic status. The plasma HIV RNA level is a strong independent predictor of the progression to AIDS in untreated HIV-infected persons.[24] In essence, the higher the HIV RNA level, the more rapidly the disease will progress.

Clinical Features

Primary Infection

Primary infection is symptomatic in 70-80% of infected individuals and usually occurs 2-4 weeks after exposure. The major clinical manifestations

are fever (seen in 80% to 90% of patients), fatigue (70% to 90%), rash (40% to 80%), headache(32% to 70%), lymphadenopathy (40% to 70%), pharyngitis (50% to 70%), and myalgias or arthralgias (50% to 70%).[26] Acute HIV illness typically persists for less than 14 days, but some patients have had illnesses that have extended for longer than 10 weeks.

The appearance of specific anti-HIV antibodies in serum takes place later 3-12 weeks later, although very rarely seroconversion may take place after 3 months.

Asymptomatic stage-clinical latency

The median time of this stage is about 10 years during which HIV replication is ongoing and progressive. The rate of disease progression is directly correlated to with HIV RNA levels as stated above. Long-term nonprogressors show little, if any, decline in CD4+ T cell counts. During the asymptomatic phase, the average rate of CD4+ T cell decline is 50/μL per year. When the CD4+ T cell count falls below 200/μL, the resulting immunodeficiency leads to symptomatic disease.

Symptomatic disease-AIDS

Acquired immunodeficiency syndrome (category c disease) is defined by the development of specified opportunistic infections, tumors etc.

Common AIDS – Defining Conditions

- Oesophageal candidiasis
- Cryptococcal meningitis
- Chronic cryptosporidial diarrhea
- CMV retinitis
- Chronic mucocutaneous herpes simplex
- Disseminated mycobacterium avium intercellulare
- Military or extrapulmonary tuberculosis
- Pneumocystis pneumonia
- Cerebral toxoplasmosis
- Kaposi's sarcoma
- HIV encephalopathy/PML
- lymphoma

The listed AIDS defining conditions are as per revised CDC classification (1993) which categorizes persons on the basis of clinical conditions and CD4+ T-lymphocyte counts.[27] For children less than 13 years of age, there is a modified and revised classification system for HIV infection. The World Health Organization (WHO) has also published a staging system for HIV infection. The WHO classification is an approach for use in resource-limited settings and is widely used in Africa and Asia.

WHO staging of HIV infection

Clinical group-I

Acute HIV infection

PGL

Asymptomatic

Normal activity

Clinical group-2(Early stage disease)

Weight loss<10%

Muco-cutaneous problem

Herpes zoster

Recurrent URI

Normal activity

Clinical group-3 (Intermediate disease)

Weight loss<10%

Chronic diarrhea

Prolonged fever 1 month

Oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis

Severe bacterial infection

Bed ridden < 50% of day (previous month)

Clinical group-4 (Late stage disease)

Definitive or presumptive diagnosis of AIDS

Bed ridden > 50% of day (previous month)

DIAGNOSIS

The diagnosis of HIV infection depends upon the demonstration of antibodies to HIV and / or the direct detection of HIV or one of its components.

The standard screening test of HIV infection is the ELISA, also referred to as enzyme immunoassay (EIA). This solid – phase assay is an extremely good screening test with a sensitivity of >99.5%. Most diagnostic laboratories use a commercial EIA kit that contains antigens from both HIV -1 and HIV -2 and thus are able to detect either. These kits use both natural and recombinant antigens and are continuously updated to increase their sensitivity to newly discovered species, such as group O viruses. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity.

The most commonly used confirmatory test is the western blot. This assay takes advantage of the fact that multiple HIV antigens of different, well – characterized molecular weight elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the western blot.[28] A negative western blot is one in which no bands are present at molecular weights corresponding to HIV gene products.

While the western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a poor screening test. Among individuals with a negative EIA and PCR for HIV, 20 – 30 % may show one or more bands on western blot. While these bands are usually faint and represent cross-reactivity, their presence creates a situation in which other diagnostic modalities (such as DNA PCR, RNA PCR, RNA assay, or p24 antigen capture) must be employed to ensure that the bands do not indicate early HIV infection.

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which is the product of the percent of CD4+ T cells (determined by flow cytometry) and the total

lymphocyte count (determined by WBC and differential percent) has been shown to correlate very well with the level of immunologic competence.

Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3 to 6 months thereafter. More frequent measurements should be made if a declining trend is noted. According to most guidelines, a CD4+ T cell count <350 /μL is an indication of initiating antiretroviral therapy, and a decline in CD4+ T cell count of > 25% is an indication for considering a change in therapy.

ANTIRETROVIRAL THERAPY

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast and short-lived trends. Since the introduction of zidovudine as monotherapy in 1987, the treatment options have grown rapidly. Research has unleashed an array of drugs in each of the class of drugs and newer classes of drugs are fast coming upon the horizon.

Currently, four different classes of medications, target HIV:

(1) nucleoside reverse transcriptase inhibitors (NRTIs)—

abacavir, didanosine, emtricitabine, lamivudine, stavudine, *tenofovir disoproxil fumarate (tenofovir-DF), zalcitabine*,

and *zidovudine;*

(2) nonnucleoside reverse transcriptase inhibitors (NNRTIs)—

delavirdine, efavirenz, and *nevirapine;*

(3) protease inhibitors—

atazanavir, fosamprenavir, indinavir, lopinavir plus

ritonavir, nelfinavir, ritonavir and *saquinavir*

(4) fusion inhibitors—

Enfuvirtide

Newer drugs and classes of drugs that have or about to join these popular drugs are

New nucleoside analogs

Elvucitabine, Nicavir, Racivir, Stampidine

New NNRTIs

Etravirine, Rilpivirine

New protease inhibitors (PIs)

Darunavir, Brecanavir

Coreceptor antagonists - CCR5 antagonists.[30]

Maraviroc, Vicriviroc

Integrase inhibitors

Raltegravir.[29]

Other drugs in the pipeline are –

Maturation inhibitors

Fusion inhibitors

Attachment inhibitors

Entry inhibitors.

Mechanism of action

The NRTIs—also known as nucleoside analogues—structurally resemble the human nucleosides that HIV uses to make viral DNA. The HIV reverse transcriptase enzyme can mistakenly incorporate the synthetic nucleoside analogue into the elongating strand of viral DNA during the reverse transcriptase process; once incorporated into viral DNA, the nucleoside analogues act as chain terminators because they lack the 3′ hydroxyl group required for chain elongation.

The NNRTIs do not act as chain terminators; rather, they directly inhibit the proper functioning of the reverse transcriptase enzyme.

The HIV protease inhibitors selectively bind to HIV protease and prevent this enzyme from performing its normal function of cleaving viral polyprotein precursors into individual functional proteins.

The fusion inhibitor works by binding to the gp41 envelope protein of HIV to prevent it from mediating fusion of the viral and cell membranes.

HAART – IT'S IMPLICATIONS

The term 'highly active antiretroviral therapy' gained widespread acceptance since 1996 when the new class of protease inhibitors were approved for use. Since then HAART has maintained itself as the first line of defence against HIV infection. Traditionally HAART consists of combination of three or more drugs in any of the following class, not necessarily in the same order:

NRTI + NRTI + NRTI / NNRTI / PI

In the earlier phase HAART was shown to reduce, between 1994 and 1998, the incidence of AIDS in Europe from 30.7 to 2.5 per 100 patient years [(33)] which was replicated elsewhere.

In 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs [(31)]. Realization about lipodystrophy, a new term, followed by mitochondrial toxicity[(32)] reinforced the dictum: all effective drugs have side effects. The initial euphoria over eradication of viral load with HAART has turned bleak with HIV remaining

detectable in latently infected cells, even after long-term suppression and the most recent estimate for eradication of these cells standing at 73.3 years[34]

This has led us to coexist with the spectrum of dramatic improvement in the standard of living standard of HIV infected individuals on one hand and hitherto unheard of toxicities of associated with daily consumption of loads of drugs on a long term basis. Treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity

Common side effects associated with HAART therapy are

Gastrointestinal side effects

Abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting, Heartburn,abdominal pain, meteorism and constipation

Hepatotoxicity

Hepatic steatosis, hypersensitivity, toxic hepatitis, Elevated liver function tests, hepatic failure

Renal problems

Nephrolithiasis, Acute renal failure, Fanconi's syndrome, proximal tubular acidosis, normoglycemic glycosuria, hypophosphatemia, hypouricemia, hypokalemia, generalized aminoaciduria, and proteinuria

Pancreatitis

CNS disorders

Dizziness, insomnia, nightmares mood fluctuations, depression, depersonalization, paranoid delusions, confusion, suicidal ideation, psychosis.

Peripheral polyneuropathy

Haematological changes

Anemia, Leukopenia,

Allergic reactions

Lactic acidosis

Avascular necrosis

Osteopenia/osteoporosis

Lipodystrophy Syndrome

Endocrine dysfunction

Hypertriglyceridemia, hypercholesterolemia, lipodystrophy, glucose intolerance, gonadal dysfunction, type 2 diabetes mellitus, thyroid dysfunction.

HIV AND THYROID

While baseline thyroid profiles in HIV infection may remain normal, it becomes abnormal during the course of disease. Among individuals infected with HIV, 1%–2% experience overt thyroid disease, and 35% may

have subtle abnormalities in thyroid function test findings.[35,36] In patients with advanced HIV disease, a variety of systemic opportunistic conditions that infect or infiltrate the thyroid can decrease or increase T4 secretion.[37] Cases of thyroiditis have been reported in association with Pneumocystis jiroveci infection, Cryptococcus neoformans infection, visceral leishmaniasis, CMV infection and suppurative bacterial infection of the thyroid.[38,39,40,41]. 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. Less frequently, hypothalamic – pituitary failure due to central nervous system infections is involved. Symptomatic thyroid infection or infiltration has always been uncommon, and in countries where HAART is available, it has become extremely rare.

A retrospective and prospective study, from India, of thyroids obtained at autopsy found high incidence (35%) of abnormal thyroids and tuberculosis was the predominant finding in these specimens [67]

Overt hypothyroidism is common both among the general population, in which □0.3%[56] of persons are affected, and among HIV-infected

individuals, among whom small studies have reported a prevalence of 0%–2.6%.[35,42,43]

Low FT4 levels with concurrent normal TSH levels are found frequently among HIV-infected individuals, with a reported prevalence of 1.3%–6.8%[35,42,44] An even higher prevalence was reported among children in a paediatric study in which 16 (31%) of 52 children, all of whom were receiving HAART, had this abnormality[51]

Among patients with HIV infection and subclincal hypothyroidism, anti-thyroid peroxidase antibodies are rarely identified, suggesting that the etiology may not be autoimmune [36,52]

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.[36,53,54] During severe illness, including advanced AIDS, 5_-deiodination of T4 declines, leading to decreased T3 production and reverse T3 metabolism, and 5-deiodination of T4 to inactive reverse T3 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.

The most common thyroid function pattern during nonthyroidal illness is reduced T3 level, elevated reverse T3 level, variable FT4 level, and relatively normal or decreased TSH level, depending on the severity of illness, although a smaller increase in the reverse T3 level has been observed among patients with advanced AIDS.[55] 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.

Decreased CD4 cell count has been observed in patients who had low FT3 levels but who also exhibited weight loss, which points to NTI [59,]. Collazos et al. found a correlation between FT4 levels and CD4 cell counts in patients treated with HAART. They hypothesized that the correlation might be mediated by cytokines, especially IL-2. [42,] The infusion of IL-2 in asymptomatic HIV-infected patients resulted in transient increases in TSH, free thyroxine and CD4 cell counts [60,].

Experimental studies on the influence of thyroid hormones on the course of an alloimmune response revealed Murine T_3 and T_4 levels were increased a few days after the immunization of mice with allogeneic lymphoid cells. Besides in vivo treatment with T_4 was shown to increase alloantibody titers during the early stages of alloimmunization and to

enforce lymphoid proliferation in vitro in a mixed lymphocyte reaction. Conversely, lowering thyroid hormone serum levels by propylthiouracil treatment negatively modulates the humoral and cellular alloimmune responses. The evidence here points to the existence of a bidirectional communication between both systems [62].

Mean 24-hour TSH levels were increased in HIV patients, associated with increased mean TSH pulse amplitude and TSH responsiveness to TRH. No differences were observed between asymptomatic HIV-seropositive and AIDS patients. In conclusion, there is a hypothyroid-like regulation of the pituitary-thyroid axis in stable HIV infection, which differs distinctly from the euthyroid sick syndrome in non-HIV-nonthyroidal illnesses. These changes in thyroid hormones might be caused directly, as an HIV-associated impairment in thyroid function, or indirectly, as an adaptation to counteract hypermetabolism in HIV infection[64].

HAART AND THYROID

Several complications related to HAART have been described, including thyroid dysfunction, but the mechanism by which HAART causes these alterations remains unknown, even if is probably multifactorial with the HIV infection also being involved. Regarding thyroid function during HAART, an increased prevalence of thyroid function parameter

abnormalities have been reported by authors and these refer in most cases to asymptomatic patients, in particular those with subclinical hypothyroidism.[35,42,43,44,45] , although groups of patients with clinically evident hyperthyroidism, in particular Grave's disease, have also been observed.[46] In some cases hyperthyroidism has been considered as late manifestation of immune reconstitution caused by HAART. Autoimmune thyroiditis has also been implicated in the development of subclinical hypothyroidism caused by long term HAART[35]

Despite the autoimmune etiology of most cases of hypothyroidism, onset of Hashimoto thyroiditis does not appear to be common during HAART-associated immune reconstitution. Stavudine use, however, has been associated with subclincal hypothyroidism in some, but not all, studies [35,36,43] The mechanisms underlying this association are unclear and deserve further investigation

One postulated hypothesis is that the retinoid X receptor-selective ligand suppresses thyrotropin secretion; this higher prevalence could be related to the retinoid like effects of PIs. Another hypothesis could be related to the lipodystrophy present in most of these patients. Lipodystrophy could simulate a fasting situation leading to a fall in the leptin level responsible for the suppression of the thyroid axis.[61]

In adults, isolated low FT4 levels have been associated with receipt of didanosine, stavudine, and ritonavir.[52] Higher prevalence was reported among children in a paediatric study in which 16 (31%) of 52 children, all of whom were receiving HAART, had this abnormality.[51]

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.[57] In persons with HIV infection, Graves' disease may occur after immune reconstitution from HAART. Graves' disease is most commonly diagnosed 12–36 months after HAART initiation

The conclusions from Iranian study was different from others which stated that age, sex, HAART, mean CD4- cell count, duration of HIV infection, HCV co-infection, and opportunistic infections were not significant risk factors of hypothyroidism in HIV-infected patients. The occurrence of hypothyroidism may be related to other factors or HIV infection itself. Therefore, hypothyroidism should be considered in all HIV-infected patients.[63]

Beltran et al proved that none of the investigated mechanisms is able to explain the occurrence of hypothyroidism in HIV patients receiving highly active anti-retroviral therapy except the anti-retroviral treatment. In

light of the absence of autoimmunity, the normal adenohypophysis and thyroid responses to thyrotropin-releasing hormone, central hypothyroidism is suspected and could explain Low T4 and high TSH levels. Underlying mechanisms need further exploration. .[52]

Clinical syndromes involving decreased thyroid hormone levels

Condition	TSH	FT4	T3	Comment(s)
Overt hypothyroidism	↑↑	↓	↓	May be associated with anti TPO
Subclinical hypothyrodism	↑	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 FT4	N	↓	N	More common during HAART; usually asymptomatic and of unclear significance; health care providers should also consider nonthyroidal illness
Central hypothyrodism	↓	↓	↓	Very rare; when it occurs, symptoms of dysfunction in other endocrine systems are usually present (pan-hypopituitarism or hypothylamic dysfunction)
Nonthyroidal illness	N/↓	N/↓	↓	Occurs during severe acute illness or cachexia as a result of down-regulation of conversion of T4 to T3

MATERIALS AND METHODS

SETTING

The study was conducted on the out patients attending the Institute of Internal Medicine and Anti retroviral therapy (ART) centre, Madras Medical College and Government General Hospital, Chennai.

ETHICAL APPROVAL

Institute Ethical Committee's approval was. obtained to conduct the study.

STUDY DESIGN

Single Centre,

Non randomized prospective cross sectional study

STUDY PERIOD

Study was conducted between September 2006 and August 2007 for a period of 12 months.

SAMPLE SIZE

In the study period of 12 months among the patients attending the Institute of Internal Medicine and ART centre, after applying inclusion and exclusion criteria 54 patients were included in this study.

SELECTION OF STUDY SUBJECTS

The patients who were determined to be HIV positive and those on HAART for a period of more than a year

INCLUSION CRITERIA

HIV positive patients and those HIV patients on HAART for not less than 12 months.

EXCLUSION CRITERIA

1. Known Hypothyroid / Sub clinical Hypothyroid
2. Active opportunistic infection
3. AIDS related neoplasia
4. Severely ill patients
5. Renal & hepatic dysfunction(severe)

6. Neuro/pituitary/hypothalamic diseases
7. Drugs interfering with thyroid hormones
8. Age less than 18 years
9. Pregnancy

CONSENT

All participants gave written informed consent

METHODOLOGY

Detailed history, symptoms and signs of thyroid dysfunction were noted. History of medication, and anthropometric measurements like height, weight, waist circumference were noted in a semi-structured proforma. All patients were completely examined and routine urine and blood investigations were taken to rule out comorbid conditions.After eight hours of fasting, blood drawn for, thyroid assay in a single sitting.

Clinical evaluation of thyroid dysfunction

Patients were staged in accordance to WHO guidelines and grouped accordingly.

The following investigations were done to all patients selected in this study.

1) Thyroid profile (Free T4 and TSH)
2) Renal Function Test (Sugar, Urea, Creatinine, and Electrolytes)
3) Liver Function Test (S.Bilirubin, SGOT, SGPT, SAP, Total Protein and Albumin)
4) Complete Blood Count (Total Count, Differential Count, ESR, Hemoglobin, PCV and Platelets)
5) Electrocardiogram and Chest X-Ray – PA view
6) CD4 Count

Detection of HIV infection

The detection of HIV infection was done by ELISA (Enzyme Linked Immuno Sorbent Assay). The kit contains antigens for both HIV- 1 and HIV -2. These kits use both natural and recombinant antigens.

CD4 cell count

CD4 cell count was done by flow cytometry (Becton and Dickinson equipment). The FACS count method was used and laser principle technique was applied in it.

Estimation of Thyroid Hormones

The thyroid hormone assay (TSH and FT4) were done by Chemiluminescence Immuno Assay (CLIA) using ADVIA Centaur-equipment.

DEFINITIONS-as per recommendations of consensus statement by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. [15]

Euthyroidism

TSH – 0.4 mU/L to 4.5mU/L

FT4 – 0.70 ng/dl to 1.80 ng/dl

Sub clinical hypothyroidism

TSH – 4.51 mU/L to 10.0 mU/L

FT4 – 0.70 ng/dl to 1.80 ng/dl

Hypothyroidism

TSH – > 10.0 mU/L

FT4 – < 0.70 ng/dl

Sub clinical Hyperthyroidism

TSH – 0.1 mU/L to 0.4 mU/L

FT4 – 0.70 ng/dl to 1.80 ng/dl

Hyperthyroidism

TSH – < 0.1 mU/L

FT4 – > 1.80 ng/dl

Isolated low FT4

TSH – 0.4mU/L to 4.5mU/L

FT4– <0.70ng/dl

WHO CLINICAL STAGING (NATIONAL AIDS CONTROL ORGANISATION)

- Stage I
  - Asymptomatic
  - Persistent generalised lymphadenopathy
  - Performance scale 1:asymptomatic normal activity.
- Stage II
  - Wt. loss < 10% of body weight
  - Minor muco cutaneous manifestation (seborrheic dermatitis, fungal nail infection, recurrent oral ulcers, angular chelitis)

- Herpes zoster (within last 5 years)

  Recurrent upper resp. infection (bacterial sinusitis)

  Performance scale 2: Symptomatic, normal activity.

- State 3
  - Wt loss > 10% body weight

    unexplained chronic diarrhoea >1 month unexplained fever (intermittent/continuous) > 1 month
  - Oral Thrush
  - Oral hairy leukoplakia
  - Pulmonary TB within past 1 year.
  - Severe bacterial infection (preumonia, pyomyositis)
  - Performance Scale 3: bed ridden for <50% of day in last 1 month.
- Stage 4
  - HIV wasting synd (>10% BW loss + Unexplained fever (or) Unexplained diarrhoea >1 month chronic weakness)
  - Pneumocystitis carnii pneumonia
  - Toxoplasmosis of brain

- Cryptosporidiasis with diarrhoea >1 month
- Cyptococcosis (extra pulmonary)
- Cytomegalo viral disease of organ other tran liver, spleen and lymph node
- Herpes simplex infection, Mucocutaneous >1month (or) visceral
- Progressive multifocal leukoencephalopathy
- Disseminated endemic mycosis, histoplasmosis, Coccidiodomycosis
- Candidiasis of oesophagus, trachea, bronchi lung
- Atypical; Mycobacterial infection
- Non typhoid salmonella septicaemia
- Extra pulmonary tuberculosis
- Lymphoma
- Kaposi sarcoma
- HIV encephalopathy

- Performance scale 4: Bed ridden for >50% of day in last 1 month.

STATISTICAL ANALYSIS

SPSS 12 and Excel spreadsheet were used for data analysis

LIMITATIONS

Small no of study subjects.

FT3 levels not assessed.

CONFLICT OF INTEREST

None.

RESULTS AND OBSERVATION

POPULATION CHARACTERISTICS

The study group consisted of 54 patients with HIV infection on HAART therapy (35 males and 19 females). The following table lists the information about age and sex distribution of the study group

AGE AND SEX DISTRIBUTION

Age (years)	**Male**	**Female**
20 -29	1	5
30 – 39	21	12
40 -49	8	2
50 – 59	3	–
≥ 60	2	–

Observations were made for the presence of clinical and subclinical parameters of thyroid dysfunction in HIV infected patients on HAART

Among the 54 patients included in our study, 35 patients were men accounting for 64.8% of the total cases. The remaining 19 patients were (35.2%) women.

Majority of the patients were in the age group between 30 and 39 years - 33 patients (61% of study population) were in this group

Women were more in number in younger age group (20 – 29) whereas there were no women in the elderly age group (≥50).

THYROID DYSFUNCTION IN THE STUDY GROUP

TABLE - 2 : DISTRIBUTION OF THYROID PROFILE IN OUR STUDY

Thyroid Status	No. of Patients	Percent
Subclinical Hypothyroidism	5	9.25
Low T4 Syndrome	1	1.85
No Thyroid Dysfunction	48	88.9

In the study 48 patients were euthyroid (88.9%) and 6 patients of the population were with thyroid dysfunction (11.1%)

TABLE - 3 DISTRIBUTION OF THYROID DYSFUNCTION IN THE STUDY

Thyroid Dysfunction	No. of Patients	Percent
Low T4 Syndrome	1	1.85
Hypothyroidism	5	9.25

In the study population, the thyroid dysfunction is prevalent in 11.1% (6) of the patients on HAART therapy. Subclinical hypothyroidism is the most common abnormality among the study population with 9.25% constituting five patients. One case (1.85%) of isolated low FT4 is noted in the study.

TABLE - 4 SERUM CONCENTRATION OF THYROID PROFILE

Thyroid Profile	Normal Range	Study Range	Mean	Std. Deviation
Free T4ng/dl	0.7-1.8	0.58-1.6	1.05	0.22
Serum TSH µIU/ml	0.4-4.5	0.72-28.45	2.63	3.79

The TSH in this study is of range from 0.72 mU/L to 28.45 mU/L and free T4 levels ranging from 0.58ng/dl to 1.6 ng/dl.

The mean free T4 value was 1.05 $\pm$0.22ng/dl and the mean serum TSH values were 2.63$\pm$3.79 μIU/ml

The mean values for free T4 was shifted towards lower side of normal range.

TABLE – 5. AGE WISE THYROID DYSFUNCTION

Age	**Total**	**Euthyroid**	**Subclinical hypothroidism**	**Low FT4**
20-29	6	5	0	1
30-39	33	31	2	0
40-49	10	7	3	0

According to age wise distribution, thyroid dysfunction is most prevalent in 40 – 49 yrs group followed by 30 – 39 yrs group and no case from the elderly age group above 50 years of age was reported.

TABLE – 6. ASSOCIATION BETWEEN SEX AND THYROID DYSFUNCTION

Sex	Thyroid function				p-value*
	Abnormal		Normal		
	n	%	n	%	
Male	4	11.4	31	88.6	1.00
Female	2	10.5	17	89.5	

*Fisher's exact test

The distribution of thyroid dysfunction between the sex groups showed no statistical correlation. Thyroid abnormality was equally distributed in both the groups.

TABLE – 7. ASSOCIATION BETWEEN CD4 AND THYROID DYSFUNCTION

Thyroid function	CD4 Median	CD4 Range	p-value*
Abnormal	395	126 , 504	0.22
Normal	446	186 , 837	

*Mann-Whitney U test

The CD4 count in thyroid abnormal patients and in normal patients showed a difference with a mean of 395 and 446 respectively and the range of the CD4 count was 126 – 504 in the thyroid dysfunction group and in thyroid normal patients 186 – 837.

However, there was significant variation in the CD4 count, the analysis using Mann-Whitney U test showed a statistically insignificant p value and hence no correlation could be established.

TABLE – 8. ASSOCIATION BETWEEN DRUG REGIMEN AND THYROID DYSFUNCTION

Type of drug regimen	Thyroid function				p-value*
	Abnormal		Normal		
	n	%	n	%	
1. AZT+3TC+NVP	2	10.5	17	89.5	0.68
2. d4T+3TC+NVP	4	13.3	26	86.7	
3. d4T+3TC+EFV	-	-	5	100.0	

*Chi-square test

The study population was under the above-mentioned triple drug regimens. The drugs are

AZT – Zidovudine

3TC – Lamivudine

NVP – Nevirapine

d4T - Stavudine

EFV - Efavirenz

The predominant drug regimen was with stavudine, lamivudine and nevirapine, in both thyroid normal and abnormal group, but there was no statistical correlation between these different drug regimens and the thyroid status.

TABLE – 9. ASSOCIATION BETWEEN DURATION OF DRUG AND THYROID DYSFUNCTION

Thyroid function	**Duration of drug in months Mean ± SD**	**p-value***
Abnormal	27 ± 5	0.56
Normal	25 ± 9	

*Student's t- test

The duration of drug regimen in the thyroid abnormal population was of 27 ± 5 months and for the normal population was 25 ± 9 months. Though a marginal increase in the duration was noted the statistical correlation was absent in this population

TABLE – 10. ASSOCIATION BETWEEN DURATION OF ILLNESS AND THYROID DYSFUNCTION

Thyroid function	**Duration of illness in months Mean ± SD**	**p-value***
Abnormal	31 ± 12	0.80
Normal	33 ± 15	

*Student's t- test

The duration of illness in both the groups was nearly the same with abnormal group displaying a mean of 31 ± 12 months and no statistical correlation with the thyroid normal group.

DISCUSSION

Most asymptomatic HIV infected patients with stable body weight maintain normal thyroid function. Nevertheless, several thyroid dysfunctions appear to be more common among HIV-infected patients who have been treated with HAART.

AGE

The mean age of patients in this study was 37.1 $\pm$8.5 whichwas comparable to study group of Madeddu et al[44] Similar age group is noted in the study done by Beltran et al[35]

SEX

In our study the overall male population was more than their female counterpart, with a sex ratio of 1.84 in favour of males. The prevalence of thyroid dysfunction was found to be more in male than female. There was no statistical correlation between gender and thyroid dysfunction.

There are no studies available that has data available on thyroid dysfunction and gender influence in HIV patients on HAART.

THYROID DYSFUNCTION

Majority of patients in our study were found to have normal thyroid parameters. The thyroid dysfunction prevalence in our study was 11.1%

Madeddu et al[44] reported a prevalence of 12.6% of thyroid dysfunction in their study group on HAART and Beltran et al[35] had 16% prevalence of thyroid dysfunction. Grapin[43] et al noted that 12.3% presented with at least one abnormal test of thyroid function

The prevalence of thyroid dysfunction and hypothyroidism in HIV patients on HAART was higher than the prevalence in normal population, which is 5.9% for thyroid dysfunction and 4.6% for hypothyroidism (0.3% overt and 4.3% sub clinical hypothyroidism). [14]

In the population subgroup of males the prevalence of thyroid dysfunction was significantly higher at 13.8% which when compared to available data of Tran et al[65] is statistically significant. Abnormal thyroid function test was detected in 16% of patients in Thailand study [47].

However, our population group was restricted to 54, by applying the strict exclusion criteria and the financial constraint in conducting the laboratory investigations with external agency.

SUBCLINICAL HYPOTHYROIDISM

The highest prevalence of thyroid function parameter abnormalities during HAART observed in this study points to hypothyroidism, in particular subclinical hypothyroidism. The population of subclinical hypothyroidism in our study was 9.25%

Beltran et al[35] reported the prevalence of subclinical hypothyroidism was especially high among HIV-infected men (8.1%), much higher than in the general male population, in which the prevalence ranges from 0.9% to 1.9%..A French study of 212 HIV-infected patients found that, 8.5% who had subclinical hypothyroidism.[43] Calza et al. [36]also reported a high prevalence (12.2%) of subclinical hypothyroidism among HIV-infected patients receiving HAART.

An even higher prevalence of subclinical hypothyroidism (17.4%) was observed in a German study, but a small number of patients were included in that study [66] In contrast, Collazos et al.[42] reported a lower prevalence, of 3.5%, in a Spanish population of 202 patients.

ISOLATED LOW FT4

Isolated low FT4 incidence in our study was 1.9% Isolated low FT4 incidence shows marked variation in each of the population studied. While

generally the mean FT4 is on the lower side of normal, isolated low FT4 incidence is reported in a widely distributed spectrum of values. Collazos et al.[42] found 1.3% of the determinations of free thyroxine to be below the normal limits which is comparable with our population result.

Beltran et al[35] observed an increased prevalence (6.3%) of low FT4 in their study, whereas Madeddu et al[44] observed an incidence of about 2.7% in their patients. An even higher prevalence was reported among children in a paediatric study in which 16 (31%) of 52 children, all of whom were receiving HAART, had this abnormality [51]

CD4 AND THYROID DYSFUNCTION

Measurement of CD 4 cell count and correlation with thyroid dysfunction threw a result with lower mean CD 4 (395) cell count in the thyroid abnormal group, but the statistical significance could not be ascertained for the same probably due to smaller sample population. Low CD4 cell count was a risk factor for hypothyroidism as per the Beltran et al[35] study. However, FT4 and FT3 levels are not correlated with CD4 cell count, even when the CD4 cell count is $\leq$ 200 cells/mm^3 [68]. Madge et al proved that none of these independent variables was significantly associated with overt hypothyroidism [58]

Madeddu et al [44] was able to prove that TSH, but not FT3 and FT4, negatively correlated with CD4 count nadir which was difficult to replicate in other studies and countered by Afhami et al [63] with proofs of mean CD4 cell count not being significant risk factors of hypothyroidism. Quirino et al[45] . found no significant relationship between the condition and CD4 cell count.

DRUG REGIMEN AND THYROID DYSFUNCTION

Drug regimens in our study comprised three of the following five drugs – zidovudine, stavudine, nevirapine, lamivudine, and efavirenz, of which stavudine was consumed in larger population

There was no statistical significance on the correlation between drug regimen and thyroid abnormality in our study population. Similar correlation by Afhami et al [63] found no significance on the association of these drug regimens. Madge et al [58] in their cohort study showed neither HAART regimen nor specifically stavudine use was significantly associated with either overt hypothyroidism or subclinical hypothyroidism which was in contrast to the findings of correlation between stavudine use and thyroid abnormality by Madeddu et al[44]

The duration of drug regimen and correlation with thyroid dysfunction was of no statistical significance and this is in coordination with the findings of Quirino et al[45] who found no significant relationship between the condition and drugs or CD4 cell count and reinforced by Afhami et al [63] with no association between drug duration and thyroid abnormality.

DURATION OF ILLNESS AND THYROID DYSFUNCTION

Longer duration of disease in HIV-infected patients treated with HAART might allow the development of autoimmune thyroiditis.as observed by Beltran et al[35]. The observed values on the effect of duration of illness on the thyroid abnormality revealed no significant association in our study, statistically. Afhami et al [63] observed that duration of HIV infection is not a significant risk factor of hypothyroidism in HIV-infected patients on HAART.

CONCLUSION

- Thyroid dysfunction occurs significantly in HIV patients on HAART.
- The prevalence of thyroid dysfunction in the study population was 11.1%.
- Subclinical hypothyroidism was the most common abnormality observed in the study population.
- The patients whom we evaluated comprised predominantly of males (65%)
- There was no significant correlation between CD4 cell count and thyroid abnormality though CD4 cell count was on the lower side.
- Statistical significance was not seen in association between drug regimen, duration of drug regimen with thyroid dysfunction. Subsequent studies with larger sample may throw some light on this association.

Screening of thyroid parameters is warranted in this population in view of increasing prevalence of the study population.

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INSTITUTIONAL ETHICAL COMMITTEE
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Ref. No.: 12299 / P&D / Ethics / Dean / GGH / Chennai, dated July 19th, 2007

Title of the Work: Prevalence pattern of thyroid dysfunction in HIV pts on HAART

Principal Investigator: Dr. K.Karthikeyan

Department: Institute of Internal Medicine, MMC, Chennai

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on **July 19th 2007**, at the conference hall of the Dean, Tower Block I, GGH, Chennai.

The members of the committee, the secretary, and the chairman are pleased to
- approve the proposed work mentioned above, submitted by the principal investigator /
- ~~consider the proposed work but advised for revision and resubmission~~.

The principal investigator and their team are directed to adhere the guidelines given below:

01. You should get detailed informed consent from the patients / participants and maintain confidentiality.
02. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
03. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
04. You should not deviate form the area of the work for which I applied for ethical clearance.
05. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
06. You should abide to the rules and regulations of the institutions(s).
07. You should complete the work within the specific period, and if any extension of time is required, you should apply for permission again and do the work.
08. You should submit the summary of the work to the ethical committee on completion of the work.
09. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

Secretary,
IEC, GGH, Chennai.

Chairman,
IEC, GGH, Chennai.

~~Dean,~~
GGH & MMC, Chennai.

INSTITUTE OF INTERNAL MEDICINE, MMC
ASSESSMENT OF THYROID DYSFUNCTION IN HIV PTS ON HAART

NAME: AGE: SEX:

ADDRESS: OCCUPATION:

DURATION OF ILLNESS:
(SINCE DIAGNOSIS)

WT: HT: BMI:

HAART THERAPY-

NRTI: NNRTI:
PI:

(CURR)DURATION

SIGNS & SYMPTOMS OF OVERT HYPOTHYROID

/HYPERTHYROIDISM -+/-

Palpitation

Pedal Edema

Fatigue, weakness

Cold / heat intolerance

Hoarse voice

Dry / wet Skin

Weight Gain/ loss

Constipation/

Sleep Disturbance/depression

Others

INVESTIGATIONS:

HEMOGRAM:TC DC HB%
PCV

PLATELETS ESR

RFT- SUGAR UREA
CREATININE

LFT: BILIRUBIN SGOT SGPT
SAP
PROTEIN ALBUMIN

HBsAG HCV

12 Lead ECG

CHEST X RAY

Elisa for HIV I & II

CD4 COUNT

WHO STAGING
I
II
III
IV

THYROID PROFILE

TSH

FT3

ABBREVIATIONS

FT4/T4	-	Free Thyroxine / Thyroxine
TSH	-	Thyroid Stimulating Hormone
FT3/T3	-	Free Triodothyronine / Triodothyronine
HIV	-	Human Immuno deficiency Virus
AIDS	-	Acquired Immuno deficiency Syndrome
CD	-	Cluster differentiation
HAART	-	Highly Active Anti Retroviral Therapy
NTI	-	Non Thyroidal Illness
TPO	-	Thyroid peroxidase
NRTI	-	Nucleoside Reverse Transcriptase Inhibitors
NNRTI	-	NonNucleoside Reverse Transcriptase Inhibitors
PI	-	Protease Inhibitor

MASTER CHART

S.No.	Age	Sex	BMI	CD4	WHO Stage	TSH	FreeT4	AZT+3TC+NVP-MONTHS	d4T+3TC+NVP-MONTHS	d4T+3TC+EFV-MONTHS	DURATION OF ILLNESS-months
1	45	M	20.58	493	2	2.09	0.94	14			14
2	44	F	21.75	303	2	0.72	1.02		12		48
3	33	F	24.28	278	1	1.97	1.15		27		27
4	32	F	17.69	205	2	1.72	0.8		48		84
5	28	M	19.65	414	1	1.13	0.96	12			24
6	30	M	24.21	525	1	3.34	0.91	12			30
7	35	M	21.45	546	1	3.26	0.85			24	24
8	34	M	21.48	280	1	1.59	1.01	17			17
9	42	M	22.78	504	1	6.12	0.87		23		23
10	63	M	21.52	400	1	2.34	0.96	46	23		23
11	32	M	20.73	724	1	1.02	0.84		25		80
12	32	F	17.14	325	2	2.38	1.22		24		24
13	35	M	21.64	460	2	1.63	0.88			24	24
14	38	F	20.54	516	1	1.26	1.33		24		24
15	25	F	19.64	696	1	2.72	1.12	18			48
16	38	M	21.79	126	2	7.12	0.82		29		54
17	39	M	22.72	795	1	2.39	1.42	24			24
18	36	M	21.68	219	1	0.72	1.04			18	24
19	34	F	24.53	254	1	3.45	1.25		18		24
20	61	M	24.44	209	1	1.84	0.86		12		24
21	56	M	21.09	570	2	2.46	1.11	18			30
22	42	M	21.95	382	1	4.72	0.98		28		28
23	30	F	20.54	423	1	2.12	1.32		18		48

S.No.	Age	Sex	BMI	CD4	WHO Stage	TSH	FreeT4	AZT+3TC+NVP-MONTHS	d4T+3TC+NVP-MONTHS	d4T+3TC+EFV-MONTHS	DURATION OF ILLNESS-months
24	52	M	21.78	517	1	1.4	1.06	48			48
25	30	M	20.72	588	1	1.75	0.78		22		48
26	38	F	23.24	446	1	1.31	1.21		42		42
27	27	F	17.69	837	2	2.5	1.39		28		72
28	41	M	22.76	497	1	1.83	0.94		31		31
29	47	M	20.67	420	1	28.45	0.76	36			36
30	40	F	23.78	556	1	1.4	1.32			24	36
31	34	F	21.43	384	1	1.52	1.06	30			36
32	44	M	24.23	465	1	1.83	1.14		25		36
33	38	M	21.94	420	1	1.36	1.21		34		34
34	32	F	23.65	392	1	5.41	0.79		26		26
35	36	M	20.22	448	2	1.32	0.74	38			38
36	54	M	23.92	683	1	1.64	1.06		30		30
37	36	M	19.36	292	2	1.75	0.88		18		30
38	32	M	23.44	289	1	2.1	1.24			20	26
39	38	F	21.22	186	2	1.8	1.08		24		24
40	27	F	20.28	446	1	1.2	0.92	28			28
41	30	F	19.02	443	1	1.42	1.2	16			16
42	30	M	24.12	295	1	1.1	0.82		32		48
43	37	F	21.79	578	1	1.98	1.26	22			22
44	49	M	23.83	776	1	2.46	1.29	27			27
45	34	M	18.65	359	1	2.02	0.92		24		24
46	28	F	22.45	297	2	1.82	1.32		20		20
47	32	M	21.9	412	1	1.38	1.1	32			44
48	26	F	24.66	398	1	3.68	0.58	21			21

S.No.	Age	Sex	BMI	CD4	WHO Stage	TSH	FreeT4	AZT+3TC+NVP-MONTHS	d4T+3TC+NVP-MONTHS	d4T+3TC+EFV-MONTHS	DURATION OF ILLNESS-months
49	38	M	21.78	646	1	2.12	0.84		32		38
50	34	M	18.9	627	1	1.26	0.81		16		24
51	32	M	23.42	480	1	1.6	1.3		28		28
52	40	M	21.23	366	2	1.96	1.52		31		31
53	36	M	24.21	420	1	1.5	1.4		25		25
54	32	M	21.12	588	1	1.26	1.6	14			14