THYROID FUNCTION TESTS IN HIV/AIDS PATIENTS AND THERE CORRELATION WITH CD4 COUNT AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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LIST OF ABBREVIATIONS

ABBREVIATION	PARAMETER
HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
CD3	Clusters of differentiation 3
CD4	Clusters of differentiation 4
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
T4	Thyroxine
HAART	Highly active antiretroviral therapy
FT3	Free triiodothyronine
FT4	Free thyroxine
NNRTI	Non-nucleoside reverse transcriptase inhibitors
ART	Antiretroviral therapy
ANTI -TPO	Anti-thyroid peroxidase
ACTH	Adrenocorticotropic homone
WHO	World health organisation

ABSTRACT

THYROID FUNCTION TESTS IN HIV/AIDS PATIENTS AND THERE CORRELATION WITH CD4 COUNT AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

INTRODUCTION:

Human immunodeficiency virus (HIV) infection is one of the most severe diseases globally

And is known to cause progressive decrease in CD4 T cells, which leads to immune system failure. many disease conditions generated by HIV have been reported,in particular there have been controversies on the influence of HIV on thyroid functioning reports on the increased incidence of thyroid disease amongst HIV patients compared to general population have been published. Endocrine dysfunction is well recognized in HIV infected patients, pituitary, adrenal, gonadal, thyroid, bone,and metabolic disorders have all been reported. Abnormal thyroid function tests are common among HIV infected patients .several complications have been reported with the use of HAART, among them are hypertriglyceridemia ,lipdystrophy, type 2 diabetes mellitus, gonadal dysfunction and osteoporosis the mechanism by which HAART causes these changes has not been fully elucidated. Abnormal thyroid function test results are common among HIV infected individuals. This is especially true during HAART.

AIM:

To evaluate the Thyroid function tests in Human immunodeficiency virus (HIV) infected patients

To correlate the results with CD4 count and Highly active antiretroviral therapy.

MATERIALS AND METHODS

A hospital based prospective study was conducted with 120 patients to evaluate the thyroid function tests in HIV infected patients and to correlate with the CD4 count and HAART therapy the patients were divided in the following groups of 40 patients each.

GOUPA-40 PATIENTS NOT COMMENCED ON HAART

GROUP B-40 PATIENTS ON HAART FOR LESS THAN A YEAR

GROUP C-40 PATIENTS ON HAART FOR A YEAR OR MORE .

RESULTS:

Thyroid disorders were more prevalent in group B and group C as compared to group A

There was significant increase in T4 levels with increase in CD4 count,while there was significant decrease in TSH levels with increase in CD4 counts.

Majority of patients with hypothyroidism (50%) and subclinical hypothyroidism (66.7%) had CD4 counts less than 100,there was significant correlation of thyroid dysfunction and CD4 count .

It was also noted that patients who were naive HAART therapy had less occurrence of thyroid dysfunction compared to those already on HAART therapy.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The human immunodeficiency virus (HIV) infection is among the most critical diseases worldwide, resulting in around 940,000 fatalities in 2017[1,] and is known to cause a progressive decrease in CD4 T cells, which leads to immune system failure, increase in vulnerability to opportunistic infections and cancer development. Because of antiretroviral drugs, the prognosis for HIV has improved over time.

Numerous medical disorders resulting from HIV have been progressively recorded, including abnormalities in pancreatic, endocrine, and gonadal metabolism.[2,3]Moreover, research has demonstrated that antiretroviral drugs might cause problems like hypercholesterolaemia, lipoatrophy, and glucose intolerance.[4]

Controversies have developed over the impact of HIV on thyroid function. Studies indicate a high prevalence of thyroid disorders in HIV patients relative to the general population.[5]Both pathological changes and functional disturbances are examples of thyroid issues that have been reported. Although the exact process causing thyroid dysfunction (TD) in HIV-positive people has not been determined, various theories have been put out, such as the concept that opportunistic microorganisms cause the loss of thyroid organs in a reversible manner.[6]Since thyroid hormones are vital for many bodily metabolic processes, their malfunction can lower HIV patients' "quality of life (QoL)" and alter the course of the disease.

HIV-infected people are known to have endocrine abnormalities. Thyroid, gonadal, pituitary, adrenal, bone, and metabolic issues have all been observed. HIV, cytokines, related opportunistic infections, immunological activation, and ART (Antiretroviral Therapy) can all have a detrimental effect on endocrine function.

When the AIDS epidemic first started, opportunistic infections, neoplasms (that include HIV-related cancers), and associated systemic disease were the leading causes of endocrine disruption.

HIV-positive patients frequently have abnormalities in the pituitary, thyroid, adrenal glands, gonads, pancreas, and metabolism. These abnormalities are increasingly the primary factors that affect long-term QoL of HIV-positive patients.[7]

The use of HAART has been related to a number of side effects, that involve osteoporosis, gonadal dysfunction, lipodystrophy, hypertriglyceridemia, and type 2 diabetes mellitus.[8]The precise process by which HAART carries about these alterations remains unknown.[9-12]"Immune reconstitution inflammatory syndrome (IRIS)" is an additional problem. Despite having low plasma viral loads and high CD4+ counts, some HAART-treated patients experience this disease when their immunity returns and causes clinical deterioration. An elevated CD4+ count exceeding 200cells/mm^3 in individuals whose prior CD4+ counts had been below 100-200 cells/mm3 is known as immune reconstitution (IR).

HIV patients are increasingly developing autoimmune disorders (AD) (8,9). Increased patient survival and IR are two benefits of HAART that may be related to autoimmune. An opportunistic pathogenic infection that causes an autoimmune trigger in patients with IRIS or immunodeficiency is one proposed mechanism of molecular mimesis (10-12). CD8+ T lymphocytes can mediate autoimmune disorders in immunocompromised people as soon as CD4+ cells are compromised.[13]

The onset of autoimmune disorders, which can occur during an acute viral infection (phase I), can be related to the stages of HIV infection. Clinical latency is another stage at which autoimmune disorders might arise, and CD4+ cells (phase II) gradually decrease even in the absence of overt AIDS symptoms. The development of

CD4+ cell-related autoimmune disorders is more challenging when the CD4+ count falls significantly (phase III). Following start of HAART, IR may result in autoimmune illness (stage IV) due to impaired immune control and an increase in CD4+ cells.

The increased overall frequency of autoantibodies, that may be directly created by the virus in hematopoietic cells, synovial fluid, and endothelium, enhances the cytotoxic activity of immune cells and autoantigen expression in HIV-infected patients. Despite having no relation to clinical symptoms of autoimmune disorders, elevated autoantibody expression is usually related to decreased CD4+ cell counts and higher mortality.[14]"Rheumatoid arthritis", "Graves' disease (GD)", and, in rare cases, "Hashimoto's thyroiditis (HT)"have all been observed as side effects of IR.[15-17]

The possible pathogenic processes that connect thyroid autoimmunity and immunological restoration are considered to involve HAART. Autoimmune thyroid disease has been related to the immunological reconstitution inflammatory syndrome (IRIS), which can develop as a side effect soon after initiating HAART.[18]

People with HIV frequently have abnormal thyroid function test findings. This is especially true during HAART, when IR and subclinical hypothyroidism (sHypo) may exacerbate Graves' sickness and isolated low FT4 levels seem to be very frequent.

Euthyroid illness syndrome is marked by low or normal TSH levels, low or normal FT4 levels, low or low T3 levels, and elevated reverse T3 (rT3) levels.[19]The body uses this physiologically adapted phenomena to save energy during infections and times of high stress. Patients with HIV usually exhibit higher resting energy expenditure, decreased appetite, and resultant weight loss. The procedure involves decreasing peripheral T4-to-T3 conversion and accumulating rT3. The severity of the

sickness or stress determines rT3 increase and T3 and T4 suppression. Normal FT4 and T3 levels and a brief rise in TSH are indicative of the recovery phase of euthyroid sick syndrome (ESS). This disruption was typical of terminal phase AIDS patients prior to the HAART era.[16]

Following HAART, thyroid dysfunction was very common in HIV-infected people and is usually related toasymptomatic patients, especially those with sHypo. Though the precise mechanism is unknown, stavudine has been suggested as a direct intervening agent in the synthesis and/or metabolism of thyroid hormones. This suggests that thyroid function must be monitored in HIV patients on the drug.[7,20-21]There have also been reports of drug interactions between levothyroxine and protease inhibitors through a common glucuronidation metabolic pathway. It is unknown how common these interactions occur or how they affect clinical outcomes.[22]

In India, there is currently not enough data to support screening HIV-positive people for thyroid problems. Moreresearchisrequired to determine the health impacts of TD in HIV-infected people in order to better inform screening and therapy recommendations.

In order to determine thyroid function tests in HIV-positive patients and correlate the results with CD4 count and highly active antiretroviral drugs, the current researchhas beencarried out at our tertiary care center.

AIMS AND OBJECTIVES

- To evaluate the thyroid function tests in patients infected with human immunodeficiency virus (HIV) infection
- To correlate the results with the CD4 count and highly active antiretroviral therapy.

REVIEW OF LITERATURE

Historical Aspects

A brief report of rare pneumonia caused by Pneumocystis carinii (currentlycalled P jiroveci) and other uncommon diseases in five young homosexual males in Los Angeles in 1981, which was published in the "Morbidity and Mortality Weekly Report", marked the beginning of widespread awareness of HIV disease.[23]Case reports increased and similar immune deficiency disorders were recorded in New York, California,[24–25], and other places among intravenous drug users, homosexual men, hemophiliacs, transfusion recipients, Haitians, infants, 29 female sexual partners of infected men, [30–31] inmates, [32] and Africans, awareness that a serious epidemic was emerging increased.[33] Numerous theories on the origin of the mysterious disease emerged as researchers started to systematically characterize the epidemiology and risk factors. A new human retrovirus had been identified in 1983 as the possible causative agent after an infectious agent was hypothesized.[34-36]Eventually, that virus was known as HIV or human immunodeficiency virus.[37]HIV infection has grown into a global epidemic, affecting tens of millions of people and affecting many more, despite significant advancements in fundamental virology and clinical care. HIV is a clinically complex infection with comparatively few treatment resources in most areas, posing a challenge to clinicians.

Serologic tests were created in 1985 to screen blood donors, detect new infections through seroconversion, and test for HIV infection in asymptomatic individuals.[38]Early trials of immune modulators and antiviral therapies for HIV were disappointing.[39-44]The U.S. "Food and Drug Administration (FDA)" authorized zidovudine (also called azidothymidine, or AZT) as the first drug to treat AIDS in 1987.[45]As patients receiving this single-drug therapy started to experience disease

progression, in the majority of cases, led to death, the initial intrigue in the drug's life-extending properties quickly decreased. Nevertheless, knowledge of the prevalence, management, and prevention of “opportunistic infections (OIs)” related to HIV-induced immunodeficiency has resulted in important life-saving developments, specifically in the fields of “Mycobacterium avium complex (MAC)” and P.jiroveci infection.[46-47]

The treatment of HIV was completely changed when PIs (protease inhibitors) were introduced in the middle of the 1990s. The primary form of care in United States and Western Europe is now an effective combination of “antiretroviral therapy (ART)”. Shortly after, countries with access to effective ART started to observe an enormous reduction in HIV-related morbidity and mortality.

Research on individuals undergoing the novel treatments provides insight into the pathophysiology of HIV. HIV RNA levels in serum dropped sharply in patients receiving strong antiretroviral therapy (ART), suggesting that the virus was interfering with its ability to replicate, which can generate around 10 billion viral particles daily if left unchecked. Furthermore, CD4 T-cell counts in treated people started to rise following effective inhibition of viral replication, indicating the immune system's ability to regenerate.[48]This knowledge of the dynamic interaction between viral replication and host immune system was supported by studies that started to demonstrate the value of quantifying HIV RNA (viral load) as a predictor of disease progression and as an indicator of treatment efficacy.

However, strong treatment was not without its disadvantages, and the late 1990s maximum, "hit early, hit hard,"[49] was counterbalanced by the understanding that people with HIV infection were now likely to live longer, healthier lives due to long-term pharmaceutical toxicity.Once more, the HIV treatment paradigm was

changed, and people with more advanced disease were now the main candidates for treatment.[50]

HIV in India[51]

Dr. Suniti Solomon identified the first documented case of HIV in India in 1986 in female sex workers in Chennai. About 135 further cases were discovered by 1987. Fourteen of them had already developed AIDS. By 1990, the prevalence among high-risk categories had surpassed 5%.

The National AIDS Control Programmehad beenestablished by the Indian government in 1987 to coordinate national actions, including health education and blood screening, in an effort to stop the virus's spread.

In 1992, government created the "National AIDS Control Program (NACP)" for HIV prevention and the "National AIDS Control Organization (NACO)" to regulate HIV and AIDS policies along with prevention and control initiatives. To improve blood safety, 25 societies and 7 union territories developed "State AIDS Control Societies (SACS)".

The NACP second phase (NACP II) was launched in 1999 with the objective of reducing HIV's spread through changes in behavior. ART and the PMTCT (prevention of mother-to-child transmission) initiative become a reality.

Among other advantages, the NACP third phase (NACP III) in 2007 focused on high-risk populations and carried out outreach initiatives. Additionally, it decentralized the effort to "non-governmental organizations (NGOs)" and local levels to offer the impacted individuals social services.[51]

Overview of Antiretroviral Medications

Nowadays, one of the three phases of the HIV life cycle is blocked by all FDA-approved antiretroviral drugs:

Blocking the reverse transcriptase (RT) enzyme. The virus employs the RT enzyme to convert its RNA into DNA after entering the cell but before it reaches the nucleus. NNRTIs and every nucleoside and nucleotide analogs function by blocking this enzyme's function.

Blocking the protease enzyme. The classification of protease inhibitors indicates that they prevent the HIV protease from functioning, specifically cleaving the protein products of structural genes of the virus into the functional components required for the creation of new infectious agents.

Inhibiting fusion of the viral and host membranes. Fusion inhibitors impede the formation of the ‘hairpin’ structure important for the fusion of HIV and host cell membranes by binding to the HIV envelope glycoprotein gp41, hence obstructing viral entry into the host cell.

New antiretroviral drugs under development involve enhanced formulations of existing approved drugs (to improve bioavailability, extend half-life, or mitigate adverse effects); novel drugs within the same classes as currently approved drugs (that include PIs or NNRTIs with diminished adverse impacts or distinct resistance profiles); and substances with novel modes of action, including as HIV coreceptor antagonists, entrance inhibitors, and integrase inhibitors.

Initiating Treatment

Not all patients infected with HIV necessitate antiretroviral therapy at any certain time. For individuals with a CD4 count and clinical evaluation suggesting a lowerchance of imminent illness development, the possible negative consequences of

rapid treatment will likely exceed any advantages.Individuals may encounter psychosocial obstacles to adherence that prevent effective ART, at least temporarily, until circumstances pertaining to these concerns might be ameliorated (e.g., through secure housing, substance addiction counseling, or treatment of medical or mental disorders). Due to the potential for inadequate adherence to swiftly result in permanent resistance to current antiretrovirals, it is often recommended to resolve factors that may inhibit adherence prior to initiating ART. Some individuals may choose CAM ("Complementary and Alternative Medicine") for disease management.In a comprehensive population-based survey, 3% of patients with HIV opted for complementary and alternative medicine as a replacement for conventional medication.[52]The effectiveness of CAM in enhancing clinical status or survival in HIV infection, however, is not well supported by data.

Individuals for whom the beginning of ART is not necessary should be regularly evaluated for variations in immunological status (e.g., CD4 counts) that may suggest an elevated risk of opportunistic diseases, hence necessitating the initiation of ART, opportunistic infection prevention, or other interventions. CD4 levels and viral loads must generally be assessed every 3 to 6 months in persons with stable infections. CD4 count measurements may be temporarily reduced and HIV viral load measurements can be briefly elevated during acute infections with other pathogens[53] or soon following immunization; therefore, physicians should refrain from assessing these parameters in these situations.

Clear objectives that take into consideration both the patient's and the provider's concerns should inform the decision to initiate (or reinitiate) ART. It is expected that active viral replication along with antiretroviral drugs will result in the selection of drug-resistant viruses, which will ultimately result in treatment failure. As

a result, the goal of any antiretroviral treatment mustoptimally be total viral suppression. If total suppression is not possible, secondary treatment objectivesmightinvolve immunologic reconstitution, symptom relief (that includes fever, night sweats, or weight loss), or partial virologic suppression (that might be the best course of action if the virus is extremely resistant to antiretrovirals). The effectiveness of any treatment plan also depends on providing patients with sufficient details about the antiretroviral regimen they have chosen, including the dosage schedule, food limitations, potential side effects, and how to manage them. One of the most difficult and crucial components of effective therapy is individual adherence.[54]

Patients as well as clinicians must be aware of the possibility of short- as well as long-term drug toxicities or adverse effects when starting or changing an antiretroviral therapy.

As per Revised guidelines of NACO

(National AIDS Control Organization) May 2017:

Antiretroviral drugs will be used to treat all HIV patients, regardless of their clinical stage, CD4 count, age, or population.

NACO guidelines of ART Treatment:

First-line ART regimen for HIV1-infected patients

A. Zidovudine+Lamvudine+Nevirapine (2NRTI+1NNRTI)

First-line regimen for **HIV 1** infected patients with Hb>9gm/dl

B. Tenofovir+Lamvudine+Efavirenz (2NRTI+1NNRTI)

First-line regimen for **HIV 1** infected patients with Hb>9gm/dl

First-line ART regimen given for HIV2 infected patients:

A. Zidovudine+Lamvudine+Lopinavir+Ritonavir (2NRTI+2PI)

First-line regimen for **HIV 2** infected patients with Hb>9gm/dl.

B. Tenofovir+Lamvudine+Lopinavir+Ritonavir (2NRTI+2PI)

First line regimen for **HIV 2** infected patient with Hb<9gm/dl.

Monitoring ART

Regular measurements of the HIV viral load and CD4 count must be used to track the effectiveness of an antiretroviral treatment. A decline in the viral load is the first sign that treatment is working. There are two phases to the viral load reduction. Most patients experience a beginning (rapid) decay phase within the first two weeks of treatment, followed by a second (slow) phase of decay. The antiviral actions of drugs may be the main cause of the first phase, whereas immunological factors such as CTL antiviral activity may help eradicate virally infected cells in the second phase. Individual differences exist in response kinetics, which appear to be primarily affected by drug doses or adherence. Furthermore, even though viral decay rates don't always indicate virologic failure in the future,[55]there is a correlation between the virologic response at 4 weeks of treatment and the response at 48 weeks.[56]Slower rates will allow for a more complete evaluation of patient adherence, viral resistance, and any drug-drug interactions. The viral load should, on average, have dropped by at least one log by the time therapy begins. However, it could take four to six months or more to achieve undetectable virus levels, even with a successful regimen.

The number of circulating CD4 cells starts to rise as the viral load decreases. It has been suggested that a redistribution of cells that have been recorded from lymphoid tissue is the main cause of the initial elevations in CD4 count that occur during the first one to three months of treatment. The rate at which CD4 counts improve after treatment varies from person to person, and with treatment that effectively inhibits HIV reproduction, CD4 count rises may be modest for years.

While those who begin treatment with higher CD4 counts and continue to suppress their virus with antiretroviral drugs may achieve CD4 levels comparable to those of those who are HIV-negative, those with low nadir CD4 counts might experience a slower and less full CD4 recovery.[57]

In the early stages of ART, the immune system may develop strong inflammatory reactions against certain pathogens as it begins regenerating itself. Therefore, the recovery of immune function may paradoxically increase some coexisting OIs, a condition called "immune reconstitution syndrome." Pneumocystosis,[58] cryptococcosis, “cytomegalovirus (CMV)” retinitis, MAC infection, and tuberculosis (TB) are among the infections for which IR syndrome has been noted. Immune reconstitution syndrome usually appears as inflammation of the infection-related tissues (such as significant lymphadenopathy in tuberculosis or possibly blinding vitreous inflammation in CMV retinitis), which is likely due to a localized antigen load. The syndrome appears to be more prevalent in those with low CD4 counts and begins within the first few weeks of ART.It could be difficult for medical professionals to diagnose, so it should be carefully examined to rule out other causes including treatment failure or infections. Guidelines for the treatment of immunological reconstitution syndrome and precise diagnostic standards are currently being developed. Although there are no established protocols for treating immune reconstitution syndrome, various strategies include systemic corticosteroid therapy or, in the most extreme situations, preventing antiretroviral therapy.

Changing ART

Numerous factors, such as inadequate adherence, poor absorption, toxicity that results in lacking or reduced doses, pharmacokinetic interactions, inadequate antiviral effectiveness, and preexisting drug resistance, can cause antiretroviral regimens to fail

to inhibit viral reproduction. According to population-based research, up to 63% of patients have experienced virologic failure. However, 72% of patients on treatment achieved HIV RNA <500copies/mL at six months in a recent large cohort study, indicating that virologic outcomes may be improving over time.[59]

Human Immunodeficiency Virus Infection and the Endocrine System

The incidence of endocrinopathies related to neoplasms and opportunistic infections decreased with the advent of ART and its extensive use. Given the longer life expectancy associated with ART, the management of chronic metabolic complications of HIV therapy—such as hypogonadism, diabetes mellitus (DM), dyslipidemia, insulin resistance (IR), changes in body fat distribution, and bone disease—became more crucial.

Pituitary Function

In the age of ART, opportunistic infections and pituitary gland neoplasms—primarily lymphomas—are rare. Most of the time, anterior pituitary function is maintained. In patients with HIV, dynamic assessment of the hypothalamo-pituitary-target organ is generally normal.[20]Although the mechanism underlying this altered response continues to be unknown, post-stimulus peak levels of thyroid-stimulating hormone, growth hormone (GH), prolactin, and "adrenocorticotropic hormone (ACTH)" may even be slightly elevated.[60]

Hypogonadotrophichypogonadism, which indicates hypothalamic dysfunction, is frequent in HIV-infected patients[61], despite the normal gonadotropin response to GnRH ("Gonadotropin Releasing Hormone") stimulation. Chronic systemic disease is one of the multifactorial conditions that can cause the HPG ("Hypothalamic-Pituitary-Gonadal Axis") to be suppressed.

Hyperprolactinemia has been observed.[62]When elevated prolactin levels are reported, the source is essentially unknown. The presence of macroprolactin and immunologic dysregulation have been proposed as potential mechanisms.[63]

HIV infection has little effect on GH secretion, although it is impacted by a person's state of nutrition and changes in body composition. Like other undernutrition conditions, AIDS wasting is related to a GH-resistant state, which is defined by elevated GH levels but decreased "IGF-1 (Insulin-Like Growth Factor 1)" levels.[64]

Patients with HIV-associated lipodystrophy, which is marked by decreased subcutaneous fat and increased visceral adiposity, have normal GH pulse frequency and IGF-1 levels. However, compared to HIV patients without lipodystrophy, the amplitude of the GH pulse and the mean and basal at-night GH concentrations are lower. These alterations could be carried on by either decreased GHRH secretion or elevated somatostatin tone. Insulin resistance, elevated free fatty acids, and decreased ghrelin might possibly be involved. Visceral obesity and decreased growth hormone levels are negatively correlated with HIV lipodystrophy, as demonstrated in the non-HIV population.[65]Up to one-third of HIV-positive patients exhibit biochemical 'growth hormone deficiency (GHD)', but to a lesser extent than patients with structural pituitary illness, according to the arginine stimulation test and GHRH. Because of differences in the distribution pattern of adipose tissue, males with HIV are more likely than women to suffer biochemical GHD. Clinical GHD is not always indicated by a stimulatory test diagnosis of GHD. Currently, it is unclear which situations call for GH replacement therapy or how to treat GHD in HIV patients. In the part that follows, the application of recombinant GH to the management of lipodystrophy will be covered.

Changes in the thyroid and HPA axis will be covered in the sections on thyroid and adrenal function that follow. It is uncommon for primary diseases to impact posterior pituitary function. Inappropriate antidiuretic hormone secretion syndrome is widespread and typically results from infections, tumors, or drugs.

Effect of medications on pituitary function

Four HIV-infected individuals receiving protease inhibitors (PIs) experienced significant increases in prolactin levels along with galactorrhea; however, three of these patients had previously taken other drugs that are known to cause hyperprolactinemia. The exact mechanism by which PIs affect prolactin is unknown, but it may have to do with how they directly stimulate prolactin production or how they affect P450 system to intensify the dopamine antagonistic effects of different drugs.[66]Both the suppression of the HPA and HPG axis and hyperprolactinemia may be related to opiate usage.

Adrenal Function

Adrenal insufficiency

One of the earliest endocrinopathies identified in HIV-positive individuals was adrenal insufficiency. Acute adrenal dysfunction is rare, but AIDS patients may have modest adrenal reserve deficits.

Hospitalized AIDS patients frequently have biochemical signs of adrenal insufficiency. In a preliminary investigation, a cosyntropin stimulation test revealed that 17% of 74 patients had insufficient adrenal response. On the other hand, only four percent of AIDS patients exhibit hypoadrenalism symptoms.[67]

Patients with advanced HIV illness mostly experience reduced adrenal function due to opportunistic infections, among which CMV is the most prevalent

pathogen. At autopsy, 40 to 90% of AIDS patients who suffer from CMV infection have CMV adrenalitis. Adrenal insufficiency is unlikely to result from CMV's typically less than 50% adrenocortical tissue damage. CMV illness is uncommon in people receiving powerful ARTs these days.

In the environment of HIV, Mycobacterium TB, Mycobacterium aviumintracellulare, and Cryptococcus are additional pathogenic pathogens that might cause adrenal insufficiency. Adrenal insufficiency can also result from tissue damage, idiopathic inflammation, or bleeding. Rarely, opportunistic infections (that include toxoplasmosis, Cryptococcus, and CMV) that affect the pituitary gland can result in secondary adrenal insufficiency.

Despite the rarity of adrenal insufficiency, the significant mortality rate associated with this disorder means that relevant testing must be done with a low threshold of clinical suspicion. Due to the prevalence of nonspecific complaints including fatigue and weight loss, the clinical diagnosis of adrenal insufficiency is challenging. In situations of primary adrenal insufficiency, glucocorticoid replacement therapy combined with mineralocorticoid supplements must be administered according to the same guidelines as other forms of adrenal failure.

Conversely, HIV-positive patients may have elevated serum cortisol levels, usually in the presence of a stress reaction, low body weight, or a more severe stage of the disease. On cosyntropin testing, several studies showed a decreased dehydroepiandrosterone/cortisol ratio, which may indicate an intra-adrenal shunting toward cortisol synthesis because of 17,20-lyase dysfunction.[68]

Cytokines and other non-pituitary stimuli may stimulate adrenal steroidogenesis, which raises cortisol levels. Despite elevated cortisol and ACTH levels, signs of adrenal insufficiency may be evident in patients who have advanced

HIV infection, indicating a glucocorticoid resistance state. Initially, during the initial stages of the AIDS epidemic, hyporeninemic hypoaldosteronism was identified in a limited case series.[69]

Effect of medications on adrenal function

Patients with AIDS or HIV are frequently treated with antifungal, appetite-stimulating, and antituberculous medications. A number of these medications have the potential to directly impact adrenal function or interact with ART.

When used in excess, the antifungal drug ketoconazole may cause adrenal insufficiency because it inhibits the steroidogenesis cascade's side-chain cleavage enzyme and 11-β-hydroxylase. In general, itraconazole, fluconazole, and more recently created imidazole derivatives—that are now more commonly utilized as antifungal drugs—do not have such effects.

Strong cytochrome P450 enzyme 3A4 (CYP3A4) inducers, phenytoin, and rifampin may have an impact on cortisol metabolism. Rifampin used to treat tuberculosis may cause adrenal insufficiency in persons with decreased adrenal reserve.

Megestrol acetate is a strong synthetic progestational derivative with glucocorticoid effects that is used as an appetite stimulant. Adrenal insufficiency may result from abruptly stopping megestrol acetate because it inhibits pituitary ACTH secretion through feedback. To enable physiologic glucocorticoid replacement when necessary, it is crucial to assess the HPA axis's integrity before stopping drugs.[70]

The interaction between ART and glucocorticoids is probably the most prevalent cause of adrenal dysfunction at the moment. Ritonavir or cobicistat are strong CYP3A4 inhibitors that are frequently used in combination with integrase inhibitors (elvitegravir) and various HIV medications (particularly, PIs: atazanavir,

darunavir, and lopinavir) to increase the concentrations of these medications and allow once-daily dosing. Because the CYP3A4 pathway metabolizes a large number of glucocorticoids, co-administration with strong CYP3A4 inhibitors can raise glucocorticoid levels. One frequent instance is the occurrence of iatrogenic Cushing syndrome in individuals receiving ritonavir who also get inhaled fluticasone for asthma. Fluticasone is processed by this cytochrome enzyme at higher levels when ritonavir inhibits CYP3A4. Therefore, it is advised that asthmatic patients receiving ritonavir or cobicistat take steroids such as beclomethasone that are not metabolized by CYP3A4.[71]Patients with low cortisol and ACTH levels and symptoms of adrenal excess should be suspected of having interactions between exogenous steroids and ART.

Doctors must be informed that secondary adrenal insufficiency can also result from alternative glucocorticoid delivery routes. About 5% of patients on PIs, particularly ritonavir, who received intra-articular steroids have been shown to experience persistent suppression of the HPA axis. Intra-articular triamcinolone might suppress the HPA axis in these patients even after a single injection; the risk rises if multiple doses have been administered over a period of months.[72] After a single injection of triamcinolone, the adrenal axis may take many months to heal, and the metabolic profile may gradually improve.

Adequate replacement drugs are required if endogenous cortisol secretion is persistently suppressed following the cessation of exogenous glucocorticoid therapy. When ritonavir is administered concurrently with CYP3A4 inhibition, prednisolone metabolism is similarly impacted, resulting in a roughly 30% increase in levels. Therefore, in order to prevent over-replacement, smaller prednisolone dosages (e.g., 2

to 4 mg/day) should be recommended. Consideration should be given to stopping CYP3A4 inhibitor treatment if at all possible from the perspective of HIV care.

Gonadal Function

Male hypogonadism

Early on during the HIV epidemic, hypogonadism was identified in men with HIV. Despite the fact that HIV therapy has been increasingly effective, new research has revealed that between 9% and 16% more men with HIV had hypogonadism, primarily secondary hypogonadism, than non-infected controls.[73]

The impact of severe sickness, undernutrition, and weight loss on gonadotropin secretion are the main causes of gonadal dysfunction in males with HIV. Age, obesity, and IR—especially in men with visceral adiposity—are risk factors.

Secondary hypogonadism in HIV-positive patients with advanced illness may result from opportunistic infections that impact the hypothalamus or pituitary. Pituitary/hypothalamic magnetic resonance imaging is advised for these patients.[74]

Hypogonadism is related to chronic HCV infection that causes chronic liver damage in HIV-infected males, much like in general population. In this context, patients with chronic liver diseases often have increased levels of "sex hormone binding globulin (SHBG)", that can complicate the diagnosis of hypogonadism.

Less frequently, primary hypogonadism is described. Rochira et al. [19] discovered that 16% of young patients in a large Italian cohort, with a median age of 45, had low morning testosterone related to elevated gonadotropin levels. The testes may be directly affected by cytokines as one of the potential causes of primary hypogonadism. There have been instances of tumor necrosis factor (TNF) blocking

the side-chain cleavage enzyme and IL-1 (interleukin 1) blocking Leydig cell steroidogenesis and luteinizing hormone binding to the Leydig cell.

Even though opportunistic infections like CMV and toxoplasmosis affect up to 25% of AIDS patients, testicular involvement in these illnesses has hardly ever been documented. The concept that testicular lymphoma, Kaposi sarcoma, and systemic neoplasms may be the etiology of primary hypogonadism is not well supported by data.[70]A scrotal ultrasonography must be done on HIV-positive males who exhibit primary hypogonadism if an infectious disease is suspected.

It might be challenging to accurately diagnose hypogonadism in HIV-positive patients, especially if total testosterone levels are the sole method used. Between 30% and 55% of patients with HIV have elevated SHBG levels, particularly when they also have hepatitis B or C virus coinfection. As a result, a total testosterone reading when SHBG levels are high could understate the incidence of hypogonadism in this group. A measurement of total testosterone only will miss up to 30% of patients with biochemical hypogonadism. Consequently, it is advised to employ free or bioavailable testosterone for diagnosis. If an HIV-positive male exhibits signs of hypogonadism and has total testosterone levels in the lower half of the normal range (below 500 ng/dL in most assays), a free or bioavailable testosterone assay is required.

In addition to low testosterone levels, it's critical to evaluate androgen insufficiency symptoms that involvedecreased libido, erectile dysfunction, fatigue, and muscular wasting. The same guidelines that are applied to the general population are utilized to treat male hypogonadism in male HIV patients.HIV-positive males who exhibit muscle weakness and weight loss related to low testosterone levels should receive extra attention. It has been demonstrated that short-term testosterone therapy

increases lean body mass and body weight in these patients while also improving muscle strength.

Female hypogonadism

Hypogonadism showing as amenorrhea is frequent in women with HIV, affecting about 25% of patients. Up to 50% of women with HIV who have a lower cluster of differentiation 4 (CD4) numbers exhibit anovulation. A decline in gonadotropin secretion and production during the stressful phase of illness is the most likely explanation. Up to eight percent of women living with HIV are considered to have early menopause.[75]

Women with HIV frequently have lower amounts of androgen. Intra-adrenal shunting toward cortisol synthesis and away from androgen production, specifically during weight reduction, may contribute to HIV-related androgen insufficiency.

Effect of medications on gonadal function

Hypogonadism may result from the use of ketoconazole to treat fungal infections that are common in the immunocompromised state associated with HIV. Male sexual dysfunction and decreased testosterone production result from inhibition of the side-chain cleavage enzyme and other steroidogenesis-related enzymes.Female patients experience irregular menstruation as a result of ovarian steroidogenesis.

Gonadal activity may be impacted by megestrol acetate, a synthetic progestational drug primarily utilized as an appetite stimulant. Megestrol acetate suppresses the release of gonadotropin, which results in hypogonadism. Similarly, by inhibiting GnRH secretion, opiates can cause hypogonadotrophichypogonadism.

Regarding ART's impact on the hypothalamus pituitary-gonadal axis, opinions differ. According to some research, starting ART causes testosterone levels to return to normal, while other studies found no change.[76-77]Although male sexual dysfunction

has been related to ART, particularly PIs, the majority of ART patients have “normal testosterone levels.

Thyroid Function

Thyroid function tests (TFT)”often show alterations in patients with HIV. ‘Thyroxin binding globulin (TBG)’ levels are greater in HIV-positive patients and are inversely connected with CD4 counts. In other cases of "euthyroid sick syndrome," abnormal thyroid function tests could be a sign of more advanced disease. However, unlike nonthyroidal illness, reverse T3 (rT3) levels do notincrease in response to a drop in T3 levels. The thyroid function changes that occur in increasing HIV disease involvereduced T3 levels, elevated TBG, and decreasing rT3 levels with worsening disease. AIDS patients frequently have lower rT3 and higher T3 levels than would be predicted for nonthyroidal conditions. Normal thyroid function is typically maintained by asymptomatic HIV-positive people who maintain a constant body weight.

Several screening studies have demonstrated that overt thyroid disease is not more common than in general population.“Overt hypothyroidism (OH)” was 2.5%, subclinical hypothyroidism was 4%, OT was 1%, and nonthyroidal disease was 17% in research of 1,565 HIV-positive patients.[78]The IRIS has been related to thyroid dysfunction. Here, improved immune function caused by ART treatment, typically 12-36months after ART is initiated, results in the formation of new immune cells that target thyroid antigens.[79]This is where Graves' disease is most frequently observed. According to reports, the predicted prevalence of thyroid illness related to immunological reconstitution was 0.2% in males and 3% in women.

In HIV-positive individuals, opportunistic infections may result in thyroid dysfunction. There have been reports of a painful thyroiditis-like appearance caused by pneumocystis thyroiditis. Although discovered in thyroid tissue from autopsies,

CMV, M. aviumintracellulare, Cryptococcus, and Kaposi sarcoma have not been related to any clinical signs.There have also been reports of thyroid impairment caused by Aspergillus and Rhodococcusequi thyroidal abscesses. Pituitary and hypothalamic opportunistic infections with CMV and Toxoplasma gondii can cause secondary hypothyroidism.

Effect of medications on thyroidal function

sHypois more common in ART-using individuals than in ART-naïve patients.[7]In patients with minimal thyroid reserve, rifampin and ritonavir can cause hypothyroidism by increasing the hepatic clearance of thyroxine. In this situation, patients undergoing thyroid replacement therapy might need larger dosages. While IL-2 therapy has been related to Graves' disease in HIV-infected patients, interferon treatment has been related to an increased prevalence of hypothyroidism.

Thyroid Function Abnormalities in HIV-Infected Patients

35% of people with HIV might have mild abnormalities in thyroid function test results, and 1% to 2% of them have overt thyroid illness.[80]As a result, the HIV doctor frequently has to interpret abnormal thyroid function test findings.

Thyroid Function Tests

Thyrotropin (TSH)

TSH-releasing hormone, which is released by the hypothalamus, positively regulates the anterior pituitary's release of TSH, while the thyroid hormones T4 and T3 provide negative feedback. The majority of clinical labs employ TSH tests that can detect the majority of instances of both hyperthyroidism and hypothyroidism since they have a limit of detection of less than 0.02mU/L.[81]

Information based solely on the TSH level, however, can be deceptive in a few rare cases. These consistof central hypothyroidism, that can occur when the TSH level is within the reference range; hypothyroidism following thyrotoxicosis treatment, where TSH suppression may continue; genetic thyroid hormone resistance, which is characterized by abnormally normal or increased TSH levels with increased thyroxine levels; and nonthyroidal illness. Presentregulations state that the TSH level must be abnormal, or there must be a sign of central hypothyroidism or thyroid hormone resistance before the T4 level should be examined.[82]

T4

When the thyroid hormone storage glycoprotein, thyroglobulin, is hydrolyzed, thyroid follicular cells release T4. Only the free hormone is biologically active and available for cell absorption, despite the fact that 99.9% of T4 in serum is associated with “thyroxine-binding globulin (TBG)” and different proteins. Total T4 levels may not correlate well with disease states due to the extensive protein binding; for instance, TBG concentrations are elevated in pregnancy, acute hepatitis, estrogen use, and some genetic abnormalities, which can lead to a falsely elevated T4 level. However, in clinical conditions related to low TBGconcentrations (e.g., nephrotic syndrome, hepatic failure, hereditary TBG deficiency, high-dose androgen use, and glucocorticoid use), the T4 level measurement may underestimate the amount of active thyroid hormone. These factors necessitate estimating the free T4 (FT4) level.This was previously achieved by T3 resin absorption, which is inversely correlated with the number of thyroid hormone-binding sites that are available. The overall uptake of T4 and T3 resins results in the ‘free thyroxine index'. This has largely been replaced by the EIA's more direct measurement of FT4, commonly called "unbound T4".

T3

Only 20% of T3 is generated from the thyroid; the majority is created by systemic 5′-deiodination of T4 [6]. 3,3′,5′-triiodothyronine, often known as reverse T3, is an inert hormone that is produced by a second T4 deiodination pathway. Even though T3 has been considered the most active form of thyroid hormone, there are just a few conditions in which testing T3 is clinically useful. T3 should be tested in individuals with low TSH levels (1) to assess for isolated rise of the T3 level (i.e., T3 toxicosis), (2) to assess the severity of thyroid disease, or (3) to track the effectiveness of antithyroid drug. However, in individuals with elevated TSH levels, enhanced peripheral conversion of T4 to T3 maintains T3concentrations within the normal range; hence, this assay has a decreased sensitivity for identifying hypothyroidism.[83]

Mostof the T3 is also protein-boundwhile having a lower binding affinity for serum proteins than T4. The free fraction level can now be measured more directly thanks to newer assays, although their application is restricted by their cost, lack of accuracy, and inconsistent tests.

Thyroid autoantibodies

Autoantibodies can target several thyroid antigens. Patients with positive antibodies may acquire autoimmune thyroid disease, but this is not always the case. There are very few medical situations where measurement is useful, despite the fact that the antibodies' presence might be easily detected in serum specimens.Anti-"thyroid peroxidase (TPO)" or anti-thyroglobulin antibodies are found in up to 90% of individuals with autoimmune thyroiditis; nevertheless, even when there are no detectable autoantibodies present, the majority of hypothyroidism cases are autoimmune caused (i.e., HT). Similar to this, thyroid-stimulating immunoglobulins are present in 80% to 100% of patients with Graves' disease, but their presence is not

necessary for the diagnosis. They may assist in identifying the etiology of hyperthyroidism when radioiodine uptake is unattainable, predicting the progression of Graves' disease, assessing euthyroid ophthalmopathy, and estimating the probability of an afflicted mother having a neonate with Graves' disease.

Thyroglobulin

Thyrocytes generate a glycoprotein called thyroglobulin. Monitoring for thyroid cancer recurrence following thyroidectomy or radioiodine ablation is the primary clinical setting where thyroglobulin testing is useful. When hyperthyroidism and poor radioiodine uptake exist together, a low thyroglobulin level may suggest an exogenous thyroid hormone source. Moreover, thyroglobulin level assessment may at times be helpful in the differential diagnosis of hyperthyroidism. It is not advised to perform routine measurements when other thyroid disorders are present.

Abnormal Thyroid Function Test Patterns

Decreased Thyroid Hormone

Overt hypothyroidism

Insidious onset of weakness, fatigue, paresthesia, cold intolerance, dry skin, bradycardia, hoarse voice, constipation, and delayed tendon reflex relaxation are all common indications and symptoms of overt hypothyroidism. In addition to hypothyroidism, patients might also have hyperprolactinemia, hyponatremia, anemia, or elevated low-density lipoprotein cholesterol. A higher TSH level along witha lower FT4 level usually represents the outcome of OT, which is caused by the thyroid's inability to synthesize and secrete enough T4 levels in spite of TSH stimulation. Hashimoto thyroiditis, an autoimmune thyroid gland degeneration, is the most prevalent cause of hypothyroidism in general population. Rarely, central (secondary or tertiary) hypothyroidism can result from anterior pituitary or hypothalamic

insufficiency. The FT4 level declines in central hypothyroidism, while the TSH level is either reduced or within the normal range.

In the general population, approximately 0.3% of people develop overt hypothyroidism, but in HIV-infected people, an incidence of 0% to 2.6% has been recorded in limited studies. Although the majority of hypothyroidism patients have an autoimmune cause, HT does not seem to frequently develop after HAART-associated IR. There is only one case report of HT that we are aware of, and it occurred after starting HAART.

The goal of levothyroxine treatment for overt hypothyroidism is to keep the TSH level between 0.5 and 2.5mU/L. Clinical evidence suggests that adding the synthetic T3 equivalent, liothyronine, to levothyroxine drugs does not enhance symptoms, including mood and cognitive performance.[84]

Iron preparations, calcium carbonate, sucralfate, and cholestyramine all reduce thyroid hormone absorption, as does the reduction in stomach acidity brought on by proton pump inhibitor use.Protease inhibitors and levothyroxine have also been shown to interact with one another, probably due to their comparable glucuronidation metabolic pathways. It is unknown how common these interactions occur or how they affect clinical outcomes.

Subclinical hypothyroidism (sHypo)

It is marked by a slightly elevated TSH level, a normal FT4 level, and either no symptoms or mild, unspecific ones. Anti-thyroid peroxidase antibodies are found in 50-80% of people with subclinical hypothyroidism, which affects 4.3% of the general population. HIV-positive individuals also frequently have subclinical hypothyroidism, particularly those on HAART (prevalence: 3.5%–12.2%). Anti-thyroid peroxidase antibodies are infrequently seen in patients with HIV infection and

sHypo, indicating that the pathogenesis may not be autoimmune.[85]However, some—but not all—researchhas related the utilization of stavudine to subclinical hypothyroidism. Uncertainty surrounds the mechanisms associated with this connection, which requires more research.

Management of subclinical hypothyroidism

For up to 30% of individuals, TSH levels in HIV-uninfected patients return to normal within a year; nevertheless, the proportion of HIV-infected patients whose levels return to normal may be lower. Therefore, the TSH level must be rechecked one to three months after laboratory testing revealssubclinical hypothyroidism. Levothyroxine medication may be considered if the elevated TSH level continues, nonetheless, there is an absence of data regarding HIV-infected patients and scant proof of its benefits for the broader population. HIV-uninfected patient having a serum TSH level <10mU/L.[86]According to current general population guidelines, patients with TSH levels between 4.5 and 10mU/L must be managed individually, and those with levels above 10mU/L must get drugs. Individuals who have no symptoms that could be related to TD or who test positive for anti-TPO antibodies may benefit from treatment. To monitor any progress, the TSH level should be measured again every 6 to 12months if the patient is not receiving treatment.

Isolated low FT4levels

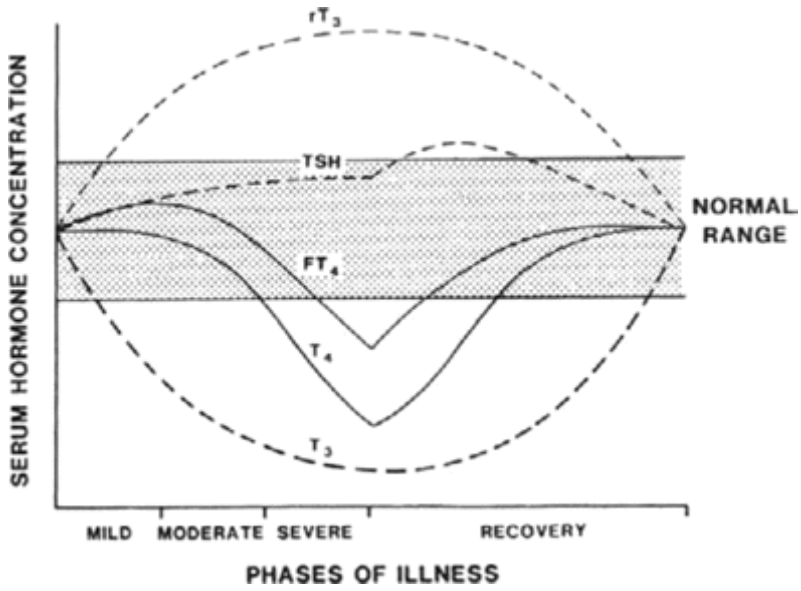
With a reported incidence of 1.3% to 6.8%, lower FT4 levels with associated normal TSH levels are common in HIV-infected people. In a pediatric trial, 16 (31%) out of 52 children who were all on HAART exhibited this anomaly, indicating an even higher frequency among youngsters.[87]Receiving didanosine, stavudine, and ritonavir has been correlated with isolated low FT4 levels in adults.

A centrally mediated process involving anterior pituitary or hypothalamic dysfunction may be consistent with the low FT4 status. Exogenous TSH-releasing hormone treatment, however, did not show a delayed or absent TSH response in one study's patients with low FT4 levels, reducing the likelihood of either pituitary or hypothalamic insufficiency. Patients on carbamazepine or phenytoin have also been reported to have an isolated low FT4 level, which was found to be an artifact associated with interference in the free T4 assays.[88]It has not been determined if one or more HAART drugs produce comparable interference.

Since patients havinglow FT4 levels do not have a higher frequency of hypothyroid symptoms than control subjects, the clinical relevance of a low FT4 level is not well understood. Additionally, there hasn't been enough follow-up data in recent papers to evaluate the natural history of low FT4 levels. Levothyroxine medication is not advised; however, it is normal to perform repeated annual thyroid function tests (of the TSH and FT4 levels).

Abnormal results from a thyroid function test because of nonthyroidal disease.The consequences of nonthyroidal sickness, commonly known as "euthyroid sick syndrome," must also be taken into account in individuals with low thyroid hormone levels. Thyroid dysfunction is suggested by a pattern of thyroid tests where 5-deiodination of T4 to inactive reverse T3 is elevated and 5′-deiodination of T4 decreases during severe illness, such as advanced AIDS, which results in reduced T3 production and reverse T3 metabolism. However, rather than being the product of aberrant thyroid function, this pattern is the physiological reaction to sickness. Since prolonged HIV infection itself can produce nonthyroidal disease, patients with uncontrolled HIV infection and abnormal TFT findings should always be investigated for this diagnosis.

In patients with advanced AIDS, a modest rise in reverse T3 levels has been observed; however, the predominant thyroid function pattern during nonthyroidal illness consists of decreased T3 levels, elevated reverse T3 levels, varying FT4 levels, and relatively normal or reduced TSH levels, dependent upon the severity of the disease (figure 1).[19]Since both FT4 and T3 levels return to baseline levels after illness recovery, the TSH level may briefly rise and at times exceed the normal range, which could resemble subclinical hypothyroidism.



Testing for thyroid function when suffering from non-thyroidal illness, often known as ‘euthyroid sick syndrome’.Reprinted, with permission, from The Thyroid Gland: A Practical Clinical Treatise [31].

Prior to the HAART period, people with terminal AIDS had the greatest rate of nonthyroidal disease among HIV-infected populations, accounting for up to 16% of cases.[89] Instead of administering levothyroxine drugs, management involves addressing the underlying problem. Repeated thyroid hormone testing must be done four to six weeks after the acute sickness is over or after antiretroviral medication has been used to control HIV infection if the diagnosis of nonthyroidal illness is not

evident. It is not advised to measure the reverse T3 level in people who may not have a thyroid condition.

AIDS-related conditions that cause thyroid dysfunction

Various systemic opportunistic infections that affect the thyroid might either augment or diminish T4 production in individuals with advanced HIV disease. Thyroiditis cases have been related to suppurative bacterial thyroid infections, visceral leishmaniasis, Cryptococcus neoformans infections, and Pneumocystis jiroveci infections.Destructive thyroiditis is caused by these infiltrating diseases and is typically accompanied by increased thyroxine release, thyroid hypertrophy, and neck pain. Thyroid function can return to normal once the infection has been treated, but until it does, it should be continuously monitored. Furthermore, Kaposi sarcoma and lymphoma can both invade the thyroid and affect its function. Thyroid illness was rarely observed before death; however, postmortem studies have often found cytomegalovirus inclusions.[90]Thyroid infection or infiltration with symptoms has rarely been observed, and in nations where HAART is accessible, it has become relatively infrequent.

Condition	TSH level	FT_4 level	T_3 level	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 FT_4	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 T_4 to T_3

NOTE. Anti-TPO, anti-thyroid peroxidase; FT_4, free thyroxine; N, normal; TSH, thyrotropin; T_3, tri-iodothyronine; ↑, increase; ↑↑, marked increase; ↓, decrease.

Clinical conditions characterized by low thyroid hormone levels.

Increased Thyroid function

Overt hyperthyroidism

In addition to a low TSH level (typically less than 0.02mU/L) and elevated FT4 and T3 levels, OH is marked by irritability, sweating, warm, heat intolerance, fatigue, tachycardia, palpitations, moist skin, weight loss with increased appetite, hyperreflexia, muscle weakness, tremor, diarrhea, and lid retraction.[91]

The predominant etiology of hyperthyroidism in both general population and individuals infected with HIV is GD, an AD characterized by the production of anti-TSH receptor antibodies. Graves' disease may develop in HIV-positive individuals following IR from HAART. Graves' illness is often identified 12 to 36 months after the start of HAART, in contrast to the traditional IRIS, that is caused by mycobacteria and different pathogens and appears during the initial three months of HAART. The CD4 cell count that increases throughout these two periods may vary, thereby explaining the time imbalance. According to certain research, the growth of CD4 cells following HAART beginning appears to occur in two stages, with the first being the redistribution of memory CD4 cells from lymphoid tissue and the second being the proliferation of naive CD4 cells months later. The observation of temporary GD in HIV-infected patients with naive CD4 cell expansion induced by IL-2 therapy is consistent with this theory. Investigations are ongoing to determine the time and pattern of cell types in CD4 cell reconstitution. IFN-α is associated with GD and is commonly utilized in hepatitis C treatment [92]

A radioiodine uptake and thyroid scan might be useful in distinguishing the causes of hyperthyroidism in patients with an increased FT4 level and a low TSH level. Thyroid scans reveal widespread distribution and increased 24-hour radioiodine uptake in patients with Graves' disease. Thyroid scans show diverse areas of uptake in

the two other prevalent diseases related to enhanced radioiodine uptake (multinodular goiter and hyperfunctioning adenomas).

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; FT_4, free thyroxine; N, normal; TSH, thyrotropin; T_3, tri-iodothyronine; ↑, increase; ↑↑, marked increase; ↓, decrease; ↓↓, marked decrease.

Clinical syndromes characterized by hyperthyroidism.

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

Hyperthyroid situations with elevated and decreased radioiodine uptake.

Subacute thyroiditis and painless thyroiditis are the predominant causes of hyperthyroidism related to reduced uptake across all populations. An enlarged, fever, sore thyroid, and an elevated erythrocyte sedimentation rate are generally—though not invariably—related to subacute thyroiditis, commonly known as 'subacute granulomatous thyroiditis,' which normally follows a viral upper respiratory tract infection. It usually lasts up to 6 weeks, and before thyroid function returns to normal,

there may be a 4 to 6-week period of hypothyroidism. Thyroiditis that is painless or "silent" (often confusingly referred to as "subacute lymphocytic thyroiditis") is a temporary autoimmune inflammation of thyroid that is frequently related to antibodies against thyroid peroxidase. The clinical history is comparable to that of subacute thyroiditis, witha period of hyperthyroidism, followed by a brief period of hypothyroidism and recovery. Transient hyperthyroidism caused by autoimmune thyroiditis generally occurs after giving birth (postpartum thyroiditis).

Management of hyperthyroidism

The underlying diagnosis determines how hyperthyroidism is managed. Antithyroid drugs such as methimazole or propylthiouracil can be used to suppress the production of thyroid hormones in Graves' illness. Some persons with Graves' disease may benefit from definitive therapy through radioiodine thyroid ablation or surgery, especially those with toxic multinodular goiter or toxic adenoma, which is the preferred therapeutic strategy. Analgesia for subacute thyroiditis can be attained with a regimen of “nonsteroidal anti-inflammatory drugs (NSAIDs)” or, in more severe instances, prednisone. The sole required treatment for painless thyroiditis is usually β-blockers, which effectively manage hyperadrenergic symptoms regardless of the reason.[93]It is advised that patients suffering from hyperthyroidism consult with an endocrinologist to create a plan that works for them.

Subclinical hyperthyroidism

Lower TSH levels, normal FT4 and T3 levels, and the lack of thyrotoxicosis are characteristics of subclinical hyperthyroidism, which can occur before overt hyperthyroidism in certain cases, however, patients may also exhibit mild hyperthyroidism symptoms. If symptoms exist, consider antithyroid drugs or radioiodine thyroid ablation. sHypocauses decreased bone mineral density and

elevated atrial fibrillation, which is associated with thyroid hyperfunction. As a result, current regulations recommend treating patients with osteopenia or osteoporosis, a TSH level <0.1mU/L, or an age greater than 60. For those with lesser condition (TSH level, 0.1 to 0.45mU/L), no treatment is advised; nonetheless, it is normal to have thyroid tests done again in 6–12 months. Patients on dopamine or glucocorticoid therapy or those with nonthyroidal diseases may have low TSH levels despite normal thyroid hormone levels, so these diagnoses must also be taken into consideration.

Screening for Thyroid Disease

Thyroid function tests can identify thyroid disorders in patients with thyroid-related symptoms or generalized systemic symptoms. Thyroid function screening for asymptomatic people is controversial, nevertheless, for both the general public and HIV-positive patients. The higher rate of sHypo and the possible advantages of levothyroxine medication in this demographic may support screening older people regardless of their HIV status.[94]Cross-sectional studies reveal a higher prevalence of sHypo than in the general population, but there is insufficient data to require systematic screening of all HIV-positive people. Patients with HIV may also have different subclinical hypothyroidism pathophysiologies. Similarly, an isolated lower FT4 level has uncertain consequences and must not be the subject of routine screening, although being identified often.

TSH levels should be measured in patients who exhibit symptoms of atrial fibrillation, depression, dyslipidemia, decreased bone mineral density, or thyroid dysfunction. A patient with a lower TSH level should have both the FT4 and T3 levels examined (to rule out T3 toxicosis), while a patient with a high TSH level ought to promote the healthcare professional to measure the FT4 level. Nonthyroidal sickness must be taken into consideration during testing to make a differential diagnosis of

abnormal TFToutcomes, specifically for patients suffering from advanced AIDS or uncontrolled HIV infection.

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

Indications for thyroid testing for HIV-infected patients.

Rosa da Silva GA et al[95] in 2015 in a cross-sectional study estimated the incidence of thyroid diseases and anti-TPO status and an association among presence of IR and utilization of didanosine, stavudine, and protease inhibitors with thyroid diseases. The authors discovered that 34.18% of people had thyroid illness, and 4.34% of those people tested positive for anti-TPO. Subclinical hypothyroidism had beenrelated to a higher likelihood of stavudine use (OR=4.19, 95% CI: 1.29 to 13.59, X2 = 6.37, p = 0.01). Thyroid disease protection from immune reconstitution was almost statistically significant. The authors came to the conclusion that the sample under study showed a low positive anti-TPO frequency and a larger prevalence of thyroid illness than had been reported in the literature. Stavudine usage in the past has been related to an elevated risk of subclinical hypothyroidism, while immunological reconstitution has been related to a reduced risk of thyroid disorders.

In cross-sectional research conducted in 2015, ThongamSet al[96] evaluated thyroid function in children with HIV who were receiving or had not been receiving HAART.The writers discovered Five out of thirty patients, both those receiving HAART and those not, had abnormal thyroid function. Two individuals on HAART

had the biochemical characteristic of sick euthyroid syndrome, while three patients had hypothyroidism. Four members of the HAART-naive group showed subclinical hypothyroidism, and one of them had the biochemical sign of sick euthyroid syndrome. Clinical signs of thyroid dysfunction had been absent in all of the patients. The relationship between TSH and CD4 count is quite significant. The scientists came to the conclusion that thyroid issues are rather prevalent in HIV cases in children. TSH and CD4 count show an inverse relationship, suggesting an increased risk of hypothyroidism as HIV illness worsens.

In cross-sectional prevalence research conducted in 2016, KaneriaMVet al.[97] assessed the frequency of thyroid abnormalities in a subgroup of patients who tested positive for HIV. The authors discovered that 19 patients (25%) had sick euthyroidism, 2 patients (3%), isolated low FT4 in 2 patients (3%), and 10 patients (13%), had overt hypothyroidism. The FT3 as well as FT4 levels continued to decline as the HIV stage progressed. TSH levels and the stage of infection, however, did not correlate. TSH levels and CD4 counts were shown to be inversely correlated, while FT3 and CD4 counts were found to be directly correlated. Patients on HAART had considerably higher mean TSH levels than those not on HAART. sHypo, CNS toxoplasmosis with isolated low FT4 levels, and TB with ill euthyroidism have all been related to cryptococcal meningitis. The authors concluded that most HIV-infected patients had asymptomatic thyroid impairment. Serum FT3 and FT4 levels had been directly correlated with the WHO clinical stage of illness. As CD4 numbers dropped, TSH levels elevated.sHypowas very common in HAART patients. There is little indication that opportunistic infections (OIs) and thyroid dysfunction are related.

Thyroid dysfunction risk factors were identified by Sebastian SA et al.[28] in 2018, who also assessed the prevalence of TD and autoimmunity (antithyroid peroxidase auto-antibodies [TPO-Ab]) in patients on first-line HAART and investigated any possible connections between the two. The authors discovered that the length of HAART was 44.4 (33.54) months, and the mean (SD) age was 43.3 (10) years. CD4 count was 502.8 (274.45) on average. Thyroid problems affected 47 patients or 29.6% of the total. Six patients had TPO-Ab positive. There was no correlation found between thyroid malfunction and any kind of medication or regimen. Thyroid-stimulating hormone (TSH) and CD4 counts showed a significant negative connection, indicating that thyroid dysfunction may be more common in cases with low immunity.The authors came to the conclusion that patients on HAART have a significant prevalence of thyroid impairment, primarily sHypo. In this subgroup of patients, thyroid autoimmunity is low. Higher TSH levels have been associated with lower immunity. To determine the progression of hypothyroidism in patients on HAART, larger longitudinal studies are necessary.

In a retrospective cohort study conducted in 2019, ProperziM et al.[99] evaluated the risk factors and incidence of symptomatic thyroid disorders, including thyroid malignancies, in individuals with HIV. The authors discovered that the mean age of the patients was 47.15yrs. (SD: 11.56) and that nearly half of them were female (n = 59, 48%). The majority of patients had undetectable HIV-RNA (n=117, 95.12%) and the mean T CD4+ cell count upon TD diagnosis was 491 cells/uL. Of these, 81 individuals had hypothyroidism (63 had HT), 21 had hyperthyroidism (17 had GD), and 11 had a primitive thyroid cancer diagnosis. Papillary thyroid carcinoma (n=7, 63.63%) was the most common histotype. Subsequently appeared medullary thyroid cancer (n=2, 18.18%) and follicular thyroid cancer (n=1, 9.1%). Although CD4+ cell

nadir <200 cell/mm^3 was linked to symptomatic hyperthyroidism (p=0.005), age was related to both hypothyroidism (p=0.03) and thyroid cancer (p=0.03). The development of TDs was protected by male gender, especially for hypothyroidism (p<0.001). The authors concluded that the rate of symptomatic thyroid dysfunction in HIV-infected patients receiving treatment is minimal. Along with T CD4+ cell nadir, age, and gender are important factors in the development of thyroid disorders. It's interesting to note that medullary thyroid cancer appears to be far more prevalent in HIV-positive individuals than in overall population.

In a cross-sectional study conducted in 2019, AkinseteAet al.[100] evaluated the range and incidence of thyroid problems in children with HIV receiving HAART. The authors found thyroid abnormalities in 9.6% of the children living with HIV, including sHypoin 6%, ESS in 2.4%, and OH in 1.2%, than those 2% subclinical thyroid disease among the controls (p=0.15). Hypothyroidism had been associated with both the viral load and the CD4 count. Clinical signs of thyroiddisorder were absent in all of the patients. The scientists came to the conclusion that children with HIV were more likely to have thyroid abnormalities, and they recommended yearly screening with follow-up.

In a cross-sectional, hospital-based comparison researchcarriedout in 2020, Abubakar et al.[101] observed that patients with HIV/AIDS had higher rates of thyroid problems and autoimmunity than did HIV-negative controls (HNC). In both groups, the authors discovered N (20%) males and N (80%) females. The cases and controls had respective mean ± SD ages of 38.2±9.54 and 35.9±13.57yrs. (p=0.138). Thyroid dysfunction was present in 32.7% of the cases and 34.5% of the controls, respectively (p=0.775). The most common thyroid conditions in the patients were primary hypothyroidism (PH) and isolated low FT3, while the most prevalent abnormalities in

the controls were primary hypothyroidism and subclinical hypothyroidism. 13.6% of controls and 14.5% of individuals had thyroid autoimmunity. The authorsconcluded that whereas sHypowas more prevalent in non-HIV/AIDS patients, primary hypothyroidism was the most prevalent thyroid disease among HIV/AIDS patients. Anti-TPO antibody prevalence seems to be quite comparable in HIV-positive subjects and HNC. Our findings suggest that routine thyroid monitoring for HIV/AIDS patients may not be advised.

MATERIAL AND METHODS

In order to assess thyroid function tests in patients with HIV infection and to correlate the outcomes with the CD4 count and HAART drugs, prospective researchhad beenperformed in a hospital with 120 patients. Three groups of 40 patients each were formed from the patients:

Group A: **"**40 patients not commenced on HAART"

Group B: **"**40 patients on HAART for less than a year"

Group C: **"**40 patients on HAART for a year or more"

Study design: Ahospital-based prospective study

Study Duration: Eighteen months

Study area: The study had been conducted on OPD/IPD visits at our tertiary care center in the general medicine departmentat BLDE University in Bijapur, Karnataka, at the "Civil Hospital Vijaypur Art Center" and the "Shri B.M. Patil Medical College Hospital Research Center".

Study population: All patients, male and female, who fulfill the inclusion criteria and had been diagnosed with HIV and were enrolled in the Tertiary Care Hospital's OPD or IPD.

Sample size: 120 patients

The following formula was employed to compute the sample size:

$$n= [z^2p(1-p)]/d^2$$

Here: Z representstable value of alpha error from Standard Normal Distribution table (0.95)

Power (p) = 80%

Precision error of estimation (d) = 0.06

$$n= [0.95 \times 0.95 \times 0.8 (0.2)] / 0.06 \times 0.06 = 40.11$$

Sample sizes of 120 individuals were chosen for the study since it will take 40 patients in each group to identify an important difference.

Inclusion criteria

- All patients with HIV/AIDS who are older than 18, HAART-naive, and currently on HAART
- Any probable HIV/AIDS cases with opportunistic infections and a low CD4 count (<200), whether or not they exhibit symptoms.

Exclusion criteria:

- History of TD before HIV diagnosis; history of other conditions that affect thyroid hormone levels, that include DKA, CRF, or physiological stress; and individuals taking drugs such as arniodarone, lithiurn, or stavudine.
- Pregnant woman.
- Patients on steroids.

METHODOLOGY

After receiving the importantapproval from the "Institutional Ethics Committee and Review Board", as well as after obtaining the patient's written informed consent, the researchhad beenperformed at our tertiary care center in the general medicine department of BLDE University, Bijapur, Karnataka"Shri B.M. Patil Medical College Hospital Research Center" and "Civil Hospital Vijaypur Art Center" on attending OPD/IPD.

Valid informed consent was obtained following Institutional Ethics Committee approval. According to the proforma, each trial participant had a thorough history and physical exam. Written informed permission had beenacquired from the patient or their attendant.

Three groups of 40 patients each were formed from the patients:

Group A: **“**40 patients not commenced on HAART”

Group B: **“**40 patients on HAART for less than a year”

Group C: **“**40 patients on HAART for a year or more”

The patient'santicubital vein yielded a total of 2 milliliters of venous blood, which was then sent for thyroid hormone measurement.

Elisa estimated TSH, while competitive binding ELISA was used to quantify T3 and T4.

Both the current condition and thyroid-related issues were examined, and a thorough clinical history was taken. According to the WHO clinical stage for HIV, patients were categorized. To diagnose the disease for which they were admitted, patients underwent specific microbiological, pathological, and radiological examinations in addition to routine ones. These included sputum studies, blood cultures, chest radiographs, abdominal or thoracic ultrasounds, and CT scans of the head or chest. CD4 counts were done in all the patients. At our hospital's Endocrine Laboratory, FT3, FT4, and TSH levels were determined using a chemiluminometric immunoassay (Advia Centaur CP, Siemens, Germany). TSH, FT3, and FT4 all had coefficients of variance below 5%. TSH typically ranged between 0.3 and 5.5mIU/L. The typical range had been 1.7-4.2 pmol/L for FT3 and 0.8 to 1.8ng/dl for FT4.

Using chemiluminometric immunoassay, anti-thyroid peroxidase (anti-TPO) antibodies had been produced in every instance. Anti-TPO has a coefficient of variance below 10%.

STATISTICAL ANALYSIS

The mean and SD are employed to present quantitative data. According to the outcomes of the normality test, the unpaired t-testhas beenemployed to compare the research groups. Frequency and percentage tables are employed to convey qualitative data. The student "t" test, Mann “Whitney test”, and “Chi-Square test” are employed to evaluate the associations between the research groups. A "p" value below 0.05 is considered significant.

Pearson's chi-squared test

$$\mathrm{X}^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

Here X2 represents Pearson's cumulative test statistic.

Oi represents an observed frequency;

Ei represents an expected frequency, asserted by null hypothesis;

n represents the number of cells in table.

Where appropriate, the results were displayed graphically.

For statistical analysis, the proper statistical software—including but not limited to Microsoft Excel and SPSS version 20—can be utilized. Microsoft Excel 2010 will be used for the graphic representation.

OBSERVATIONS AND RESULTS

In order to assess TFTs in patients with HIV infection and to correlate the outcomes with the CD4 count and HAART drugs, a prospective study had beenperformed in a hospital with 120 patients. Three groups of 40 patients each were formed from the patients:

Group A: **"**40 patients not commenced on HAART"

Group B: **"**40 patients on HAART for less than a year"

Group C: **"**40 patients on HAART for a year or more"

Distribution of patients according to Age

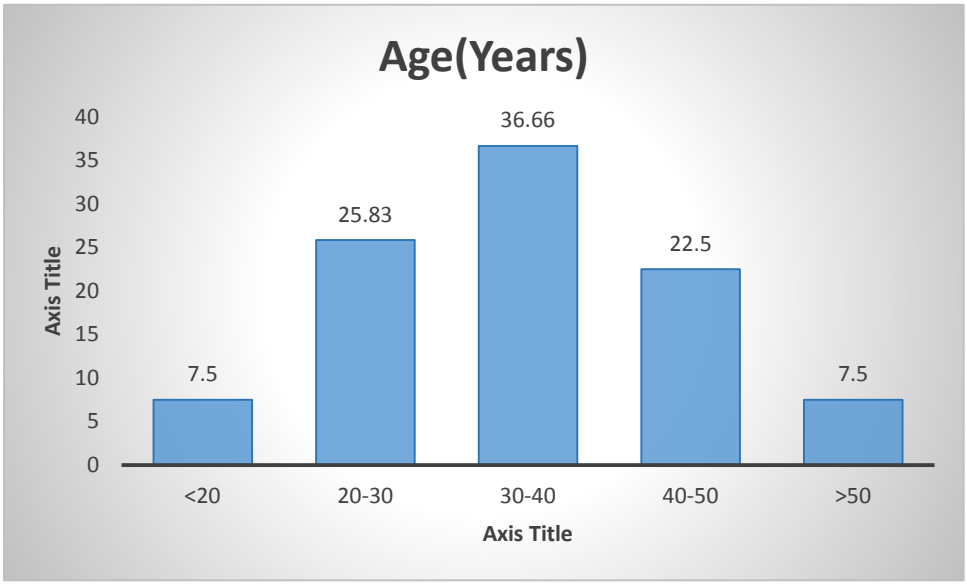
Group A had 7 (17.5%) patients in 21 to 30 years age range, and 13 (32.5%) patients in the 31 to 40yrs. age range, 11 (27.5%) patients in the 41 to 50yrs. age range and 9 (22.5%) patients in 51 to 60yrs. age range. The patients' mean age was 40.40 ± 10.12yrs.

Group B had 11 (27.5%) patients in 21 to 30yrs. age range, 7 (17.5%) patients in the age group of 31 to 40 years, 9 (22.5%) patients in 41-50yrs. age range and 13 (32.5%) patients 51-60yrs. age range. The mean age of the patients was39.88 ± 11.47yrs.

Group C had 6 (15%) patients in 21-30yrs. age range, 11 (27.5%) patients in 31-40yrs. age range 16 (40%) patients in 41-50yrs. age range and 7 (17.5%) patients in 51-60yrs. age range. The patients' mean age was 40.73±9.81 years. There was no significant difference among the groups as per Student t-test ($p>0.05$).

Table 1: Distribution of patients according to Age

Age(yrs)	Frequency	Percent
<20	9	7.5
20-30	31	25.83
30-40	44	36.66
40-50	27	22.5
>50	9	7.5
Total	120	100.0



Distribution of patients according to Sex

Male patients constitutemost of the patients in Groups A, B, and C (67.5%, 55%, and 60%), whereas female patients made up 32.5%, 45%, and 40% of the groups, respectively. Based on the Chi-Square test, there was no significant difference between the groups ($p>0.05$).

Sex	Frequency	Percent
Male	44	36.7
Female	76	63.3
Total	120	100.0

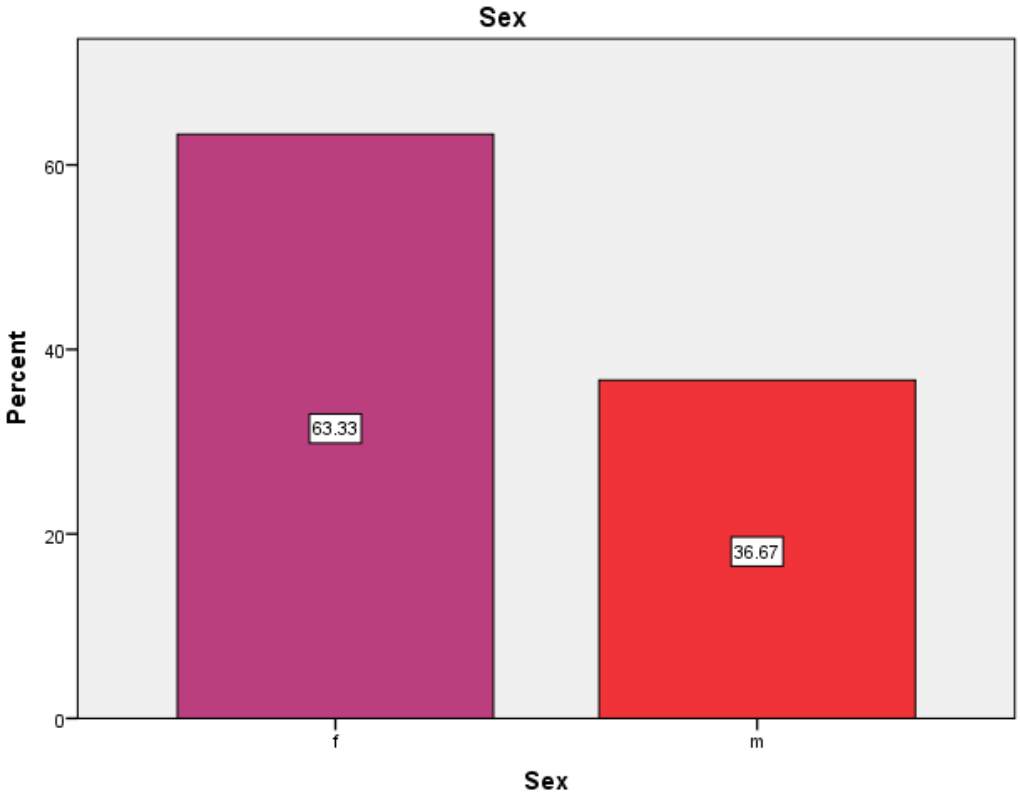
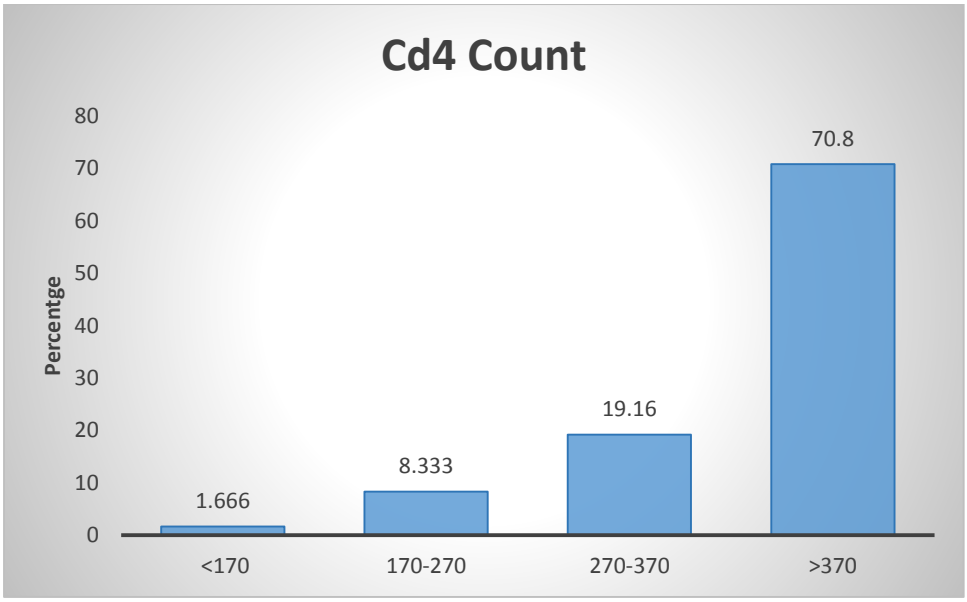


Table 3 Distribution of patients according to CD4 Count

Group A's mean CD4 count was 245.05 ± 226.33, whereas Groups B and C had mean CD4 counts of 239.90 ± 242.21 and 235.13 ± 197.39, respectively. Based on Student t-test, the differences among the groups were comparable and not statistically significant (p>0.05).

Cd4	Frequency	Percent
<170	2	1.666
170-270	10	8.333
270-370	23	19.16
>370	85	70.8
Total	120	100.0

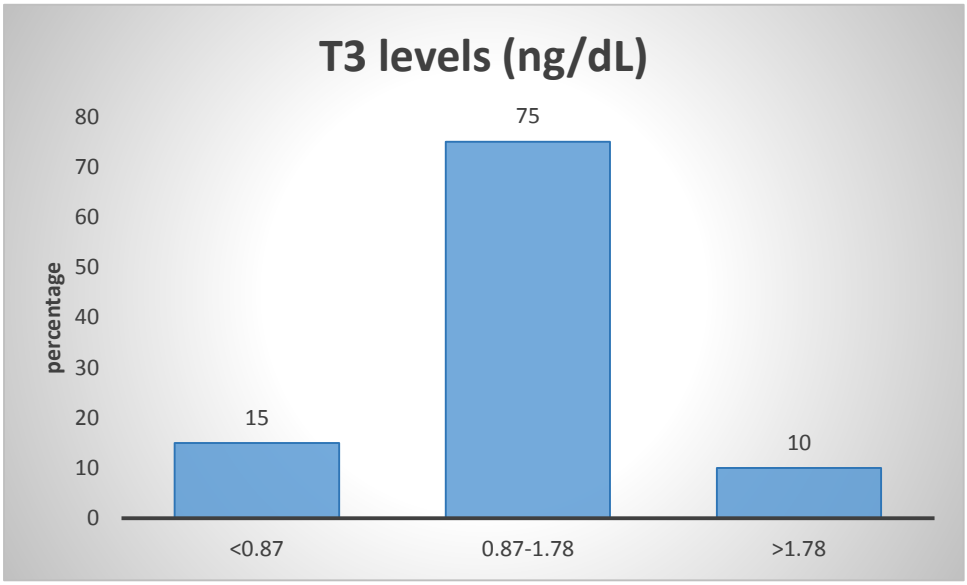


Distribution of patients according to Thyroid parameters

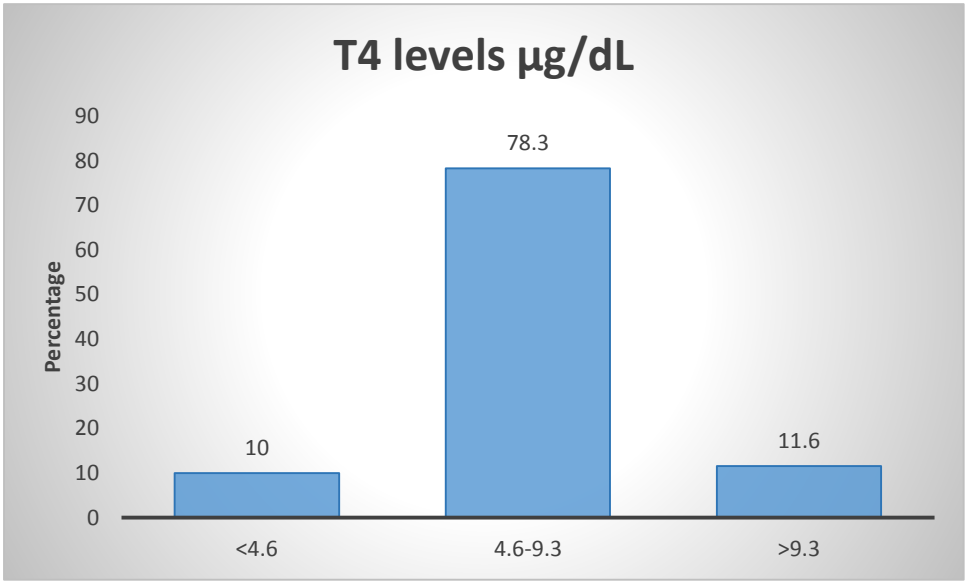
114 (95%) patients had T3 levels between 70-190 ng/dL while 85 (70.8%) patients had T4 levels between 5-12µg/dL. 74 (61.7%) patients had TSH levels between 0.5-5mIU/L.

Table 4: Distribution of patients according to Thyroid parameters

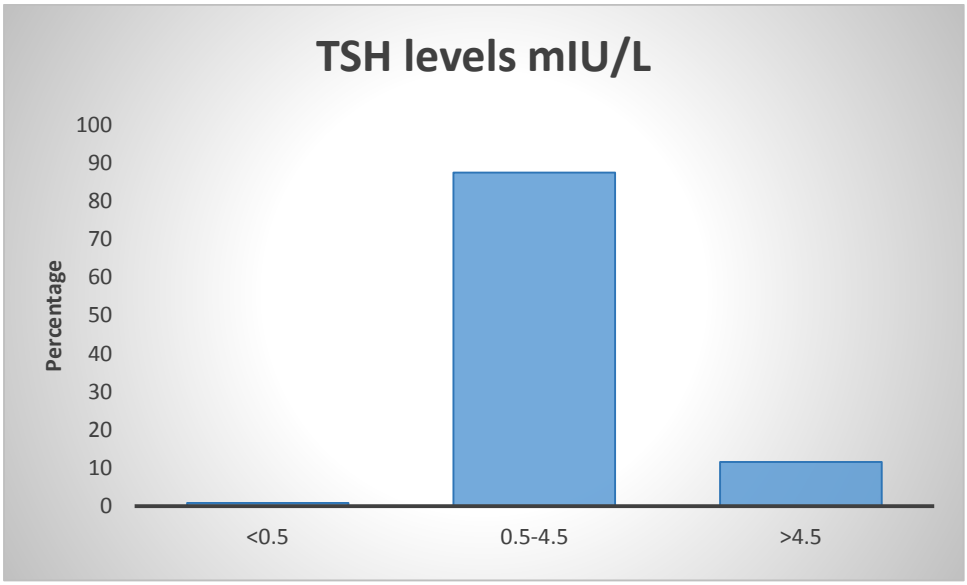
T3	Frequency	Percent
<0.87	18	15
0.87-1.78	90	75
>1.78	12	10
Total	120	100.0



T4	Frequency	Percent
<4.6	12	10
4.6-9.3	94	78.3
>9.3	14	11.6
Total	120	100.0



TSH	Frequency	Percent
<0.5	1	0.83
0.5-4.5	105	87.5
>4.5	14	11.6
Total	120	100.0

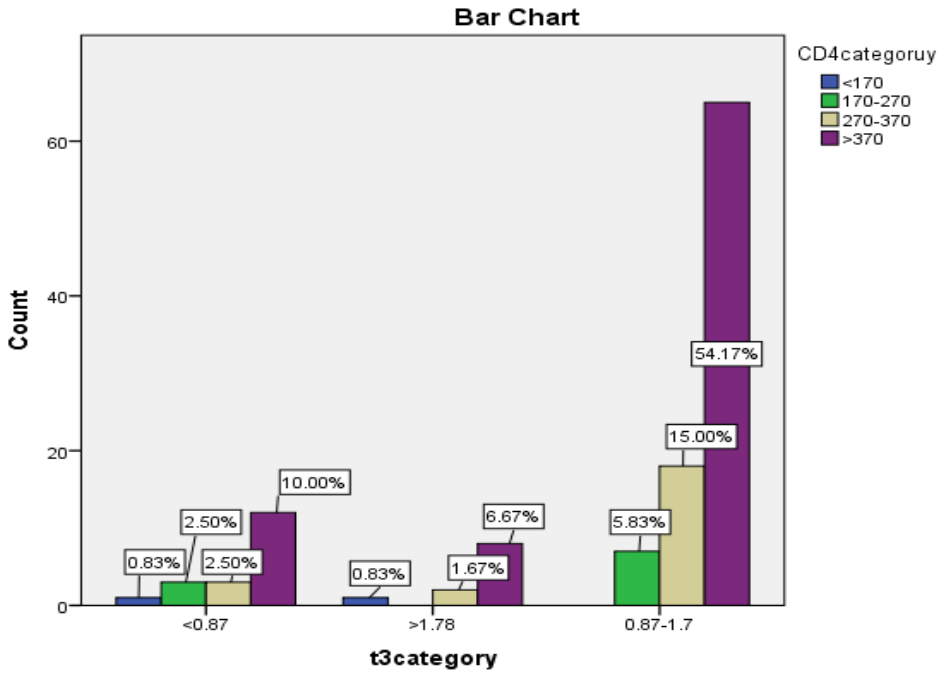


Correlation of T3 with CD4 count

It was shown that whereas TSH levels significantly decreased as the CD4 count increased, T4 levels significantly increased as the CD4 count increased. When the CD4 count increased, the difference in T3 levels was similar. According to the ANOVA test, there was a significant relationship (**$p<0.05$**) between T4, TSH, and CD4 count.

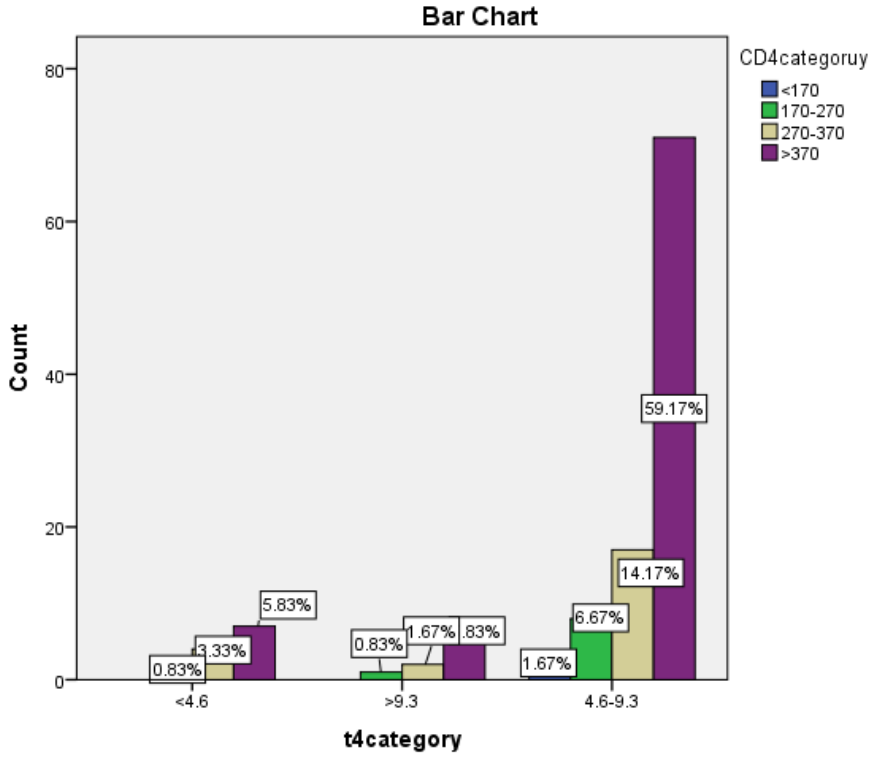
Table 5: Correlation of T3 with CD4 count

			CD4categoruy				Chi-square Value	P-value
			<170	170-270	270-370	>370		
t3category	<0.87	Count	1	3	3	12	9.169	**0.164**
		% within CD4categoruy	50.0%	30.0%	13.0%	14.1%		
	>1.78	Count	1	0	2	8		
		% within CD4categoruy	50.0%	0.0%	8.7%	9.4%		
	0.87-1.7	Count	0	7	18	65		
		% within CD4categoruy	0.0%	70.0%	78.3%	76.5%		
Total		Count	2	10	23	85		



Correlation of T4 with CD4

			CD4categoruy				Chi-square Value	P-value
			<170	170-270	270-370	>370		
t3category	<0.87	Count	1	3	3	12	9.169	**0.164**
		% within CD4categoruy	50.0%	30.0%	13.0%	14.1%		
	>1.78	Count	1	0	2	8		
		% within CD4categoruy	50.0%	0.0%	8.7%	9.4%		
	0.87-1.7	Count	0	7	18	65		
		% within CD4categoruy	0.0%	70.0%	78.3%	76.5%		
Total		Count	2	10	23	85		



			CD4 category				Chi-square Value	P-value
			<170	170-270	270-370	>370		
Tsh category	< 0.5	Count	0	1	0	0	14.566	**0.024**
		% within CD4categoruy	0.0%	10.0%	0.0%	0.0%		
	>4.5	Count	1	1	3	8		
		% within CD4categoruy	50.0%	10.0%	13.0%	9.4%		
	0.5-4.5	Count	1	8	20	77		
		% within CD4categoruy	50.0%	80.0%	87.0%	90.6%		
Total		Count	2	10	23	85		

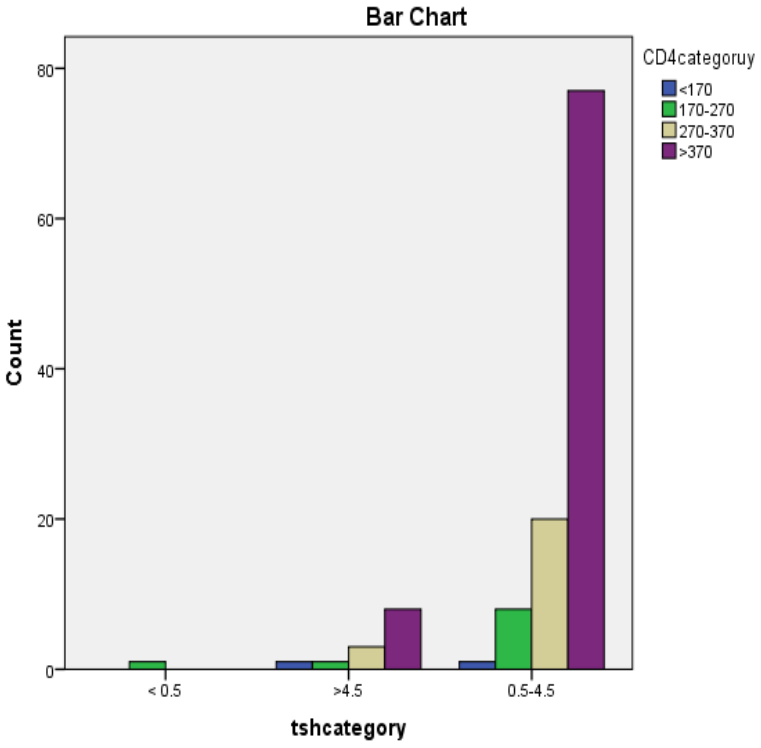
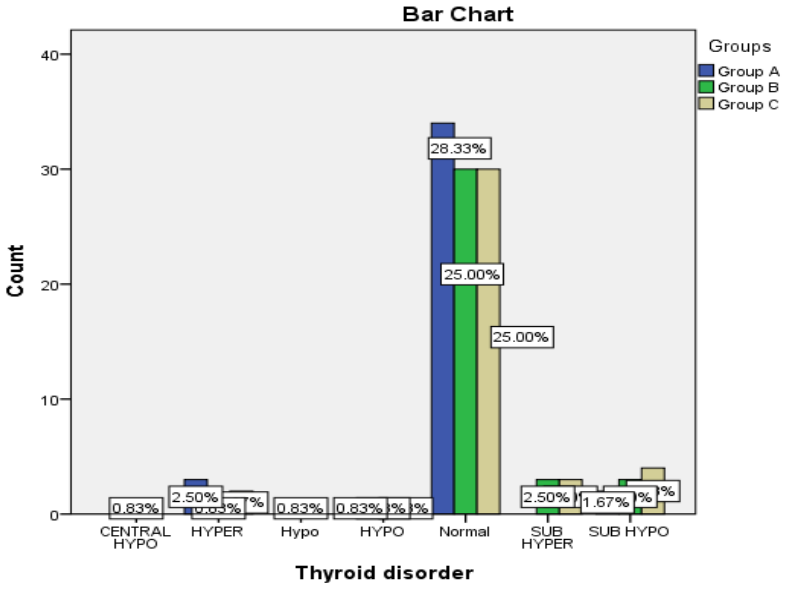


Table 6: Prevalence of Thyroid Dysfunction in our Study

			Groups			Chi-square Value	P-value
			Group A	Group B	Group C		
Thyroid disorder	CENTRAL HYPO	Count	0	1	0	9.007	**0.702**
		% within Groups	0.0%	2.5%	0.0%		
	HYPER	Count	3	1	2		
		% within Groups	7.5%	2.5%	5.0%		
	Hypo	Count	0	1	0		
		% within Groups	0.0%	2.5%	0.0%		
	HYPO	Count	1	1	1		
		% within Groups	2.5%	2.5%	2.5%		
	Normal	Count	34	30	30		
		% within Groups	85.0%	75.0%	75.0%		
	SUB HYPER	Count	0	3	3		
		% within Groups	0.0%	7.5%	7.5%		
	SUB HYPO	Count	2	3	4		
		% within Groups	5.0%	7.5%	10.0%		
Total		Count	40	40	40		

Prevalence of Thyroid Dysfunction in our Study



Graph 6: Prevalence of Thyroid Dysfunction in our Study

There was 1 (2.5%) case of hypothyroidism in Group A and 5 cases of hypothyroidism in Group C. There were 3 (7.5%) cases of subclinical hypothyroidism in Group C. In contrast to Group A, thyroid diseases were more common in Groups B and C; however, the Chi-Square test demonstrated that difference was not statistically significant ($p>0.05$).

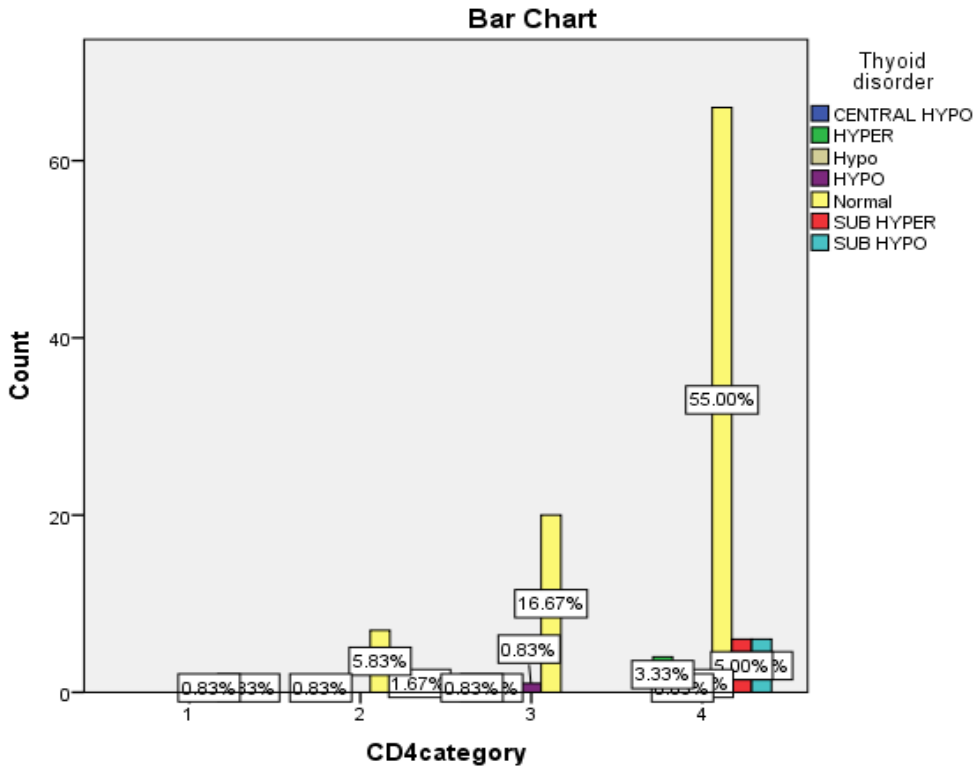
Correlation of Thyroid Dysfunction and CD4 count

Most patients with hypothyroidism (50%) and subclinical hypothyroidism (66.7%) had CD4 count <100. There was a significant correlation between thyroid dysfunction and CD4 count as per Chi-Square test (**p<0.05n)**.

Table 7: Correlation of Thyroid Dysfunction and CD4 count

			Thyroid disorder							Chi-square	P-value
			CENTRAL HYPO	HYPER	Hypo	HYPO	Normal	SUB HYPER	SUB HYPO		
CD4category	<170	Count	0	0	0	0	1	0	1	17.520	**0.488**
		% within Thyroid disorder	0.0%	0.0%	0.0%	0.0%	1.1%	0.0%	11.1%		
	170-270	Count	0	1	0	0	7	0	2		
		% within Thyroid disorder	0.0%	16.7%	0.0%	0.0%	7.4%	0.0%	22.2%		
	270-370	Count	1	1	0	1	20	0	0		
		% within Thyroid disorder	100.0%	16.7%	0.0%	33.3%	21.3%	0.0%	0.0%		
	>370	Count	0	4	1	2	66	6	6		
		% within Thyroid disorder	0.0%	66.7%	100.0%	66.7%	70.2%	100.0%	66.7%		
Total		Count	1	6	1	3	94	6	9		

Graph 7: Correlation of Thyroid dysfunction with cd4



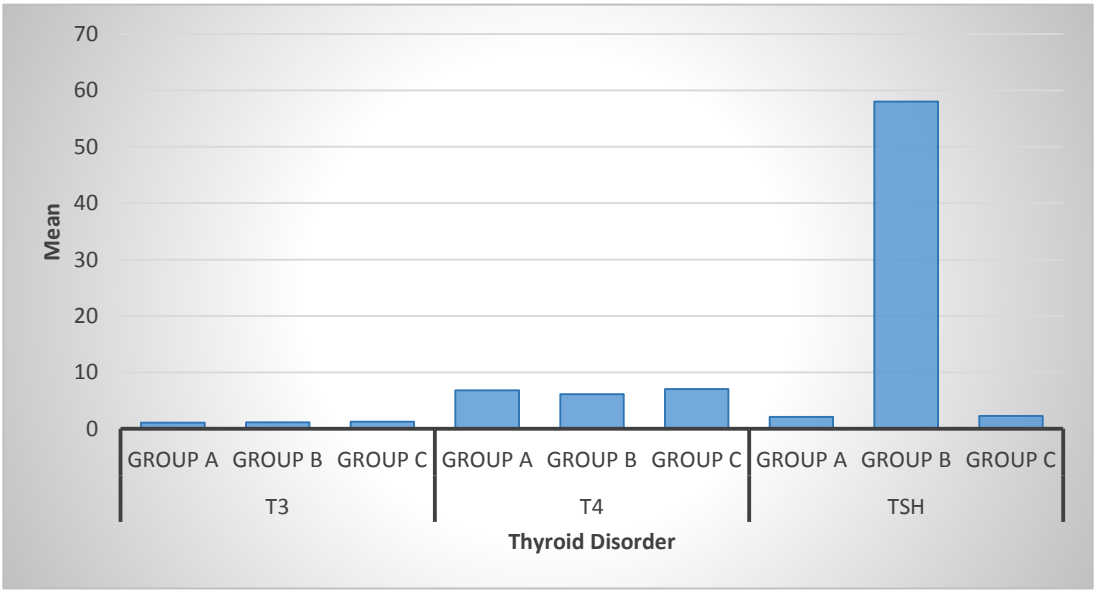
Correlation of Thyroid Dysfunction between groups

The mean T3 levels (135.85±34.59 ng/dl vs. 113.58±39.93 ng/dl vs. 101.45±32.73 ng/dl) and T4 levels (4.83±2.45µg/dL vs. 3.65±2.24 µg/dL vs. 2.73±1.28 µg/dL) had been significantly low in Group B and Group C than Group A as per ANOVA test (**p<0.05**). The mean TSH levels (1.73±0.47mIU/L vs. 2.83±2.15mIU/L vs. 4.43±3.44mIU/L) had been significantly greater in Group B and Group C in contrast to Group A based on ANOVA test (**p<0.05**).

Table 8: Correlation of Thyroid Dysfunction between groups

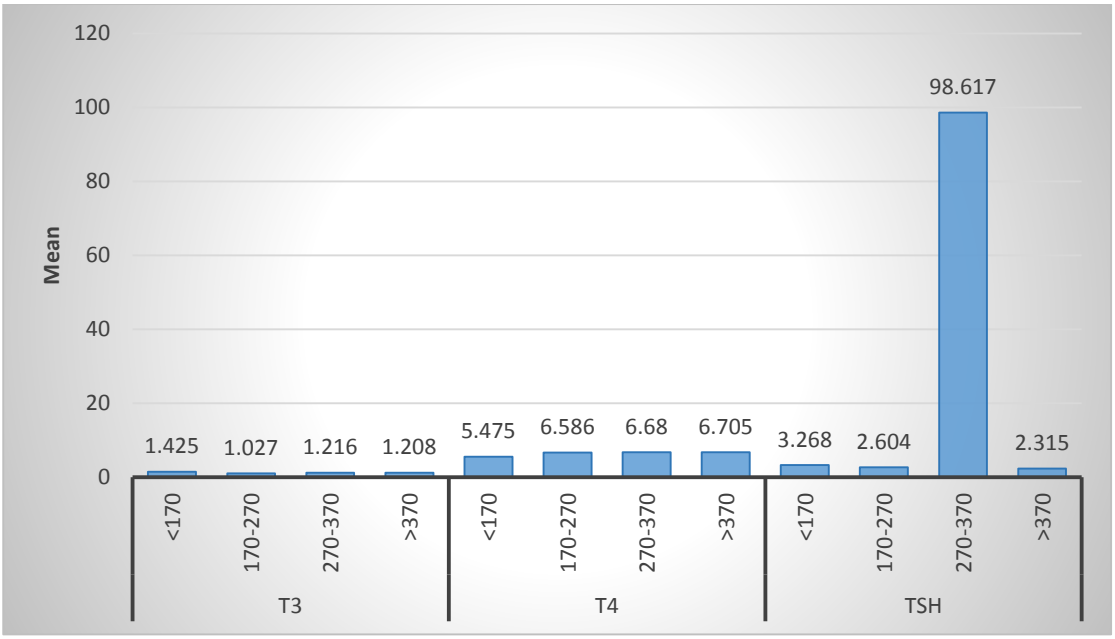
ANOVA T3,T4,TSH with respect to groups

Thyroid Function Tests	Groups	Mean	Std. Deviation	F-value	P-value
t3	Group A	1.121	0.2867	1.955	**0.146**
	Group B	1.176	0.4333		
	Group C	1.298	0.4862		
	Total	1.198	0.4141		
t4	Group A	6.816	1.8337	2.241	**0.111**
	Group B	6.14	1.7823		
	Group C	7.054	2.3468		
	Total	6.67	2.0247		
TSH	Group A	2.143	1.7632	1.017	**0.365**
	Group B	58.014	349.9623		
	Group C	2.28	1.3758		
	Total	20.812	202.0838		

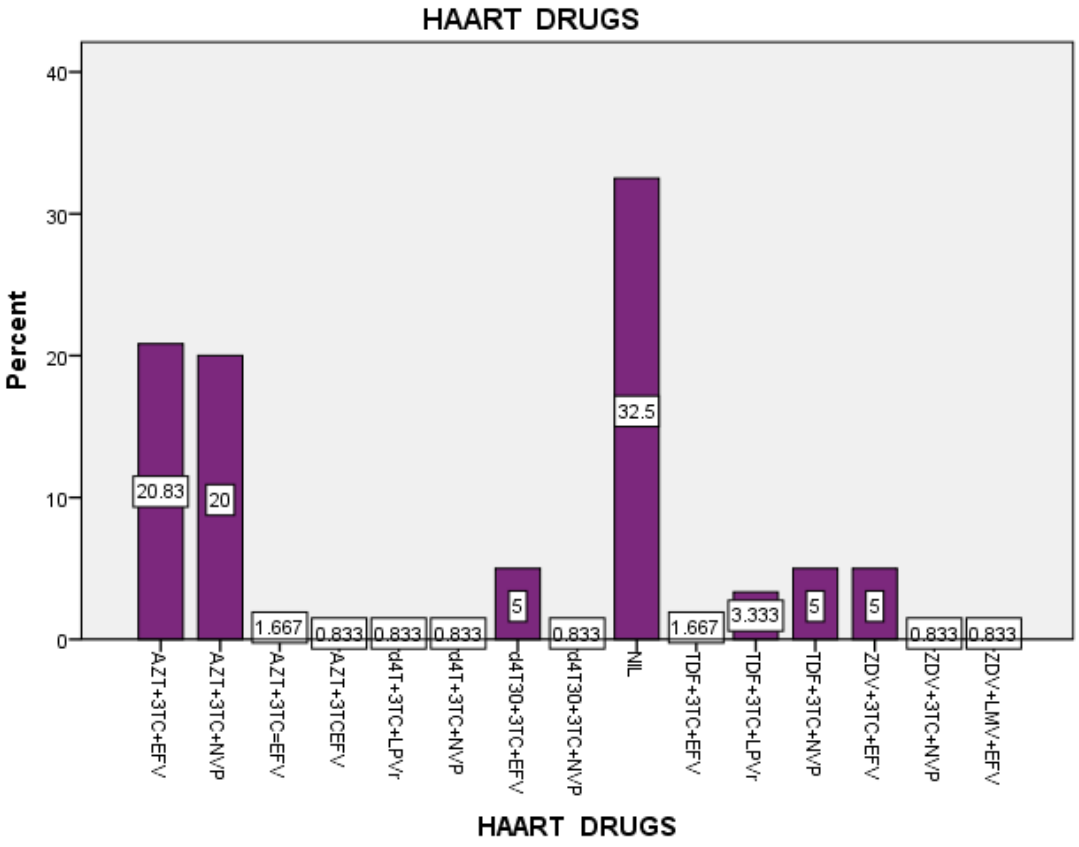


Thyroid Function Tests	CD4 Count	N	Mean	Std. Deviation	F-value	P-value
t3	<170	2	1.425	0.9546	0.796	**0.499**
	170-270	10	1.027	0.3046		
	270-370	23	1.216	0.3845		
	>370	85	1.208	0.4225		
	Total	120	1.198	0.4141		
t4	<170	2	5.475	1.1243	0.242	**0.867**
	170-270	10	6.586	2.2555		
	270-370	23	6.68	1.9885		
	>370	85	6.705	2.0434		
	Total	120	6.67	2.0247		
TSH	<170	2	3.268	2.9614	1.421	**0.240**
	170-270	10	2.604	1.78		
	270-370	23	98.617	461.579		
	>370	85	2.315	1.5708		
	Total	120	20.812	202.0838		

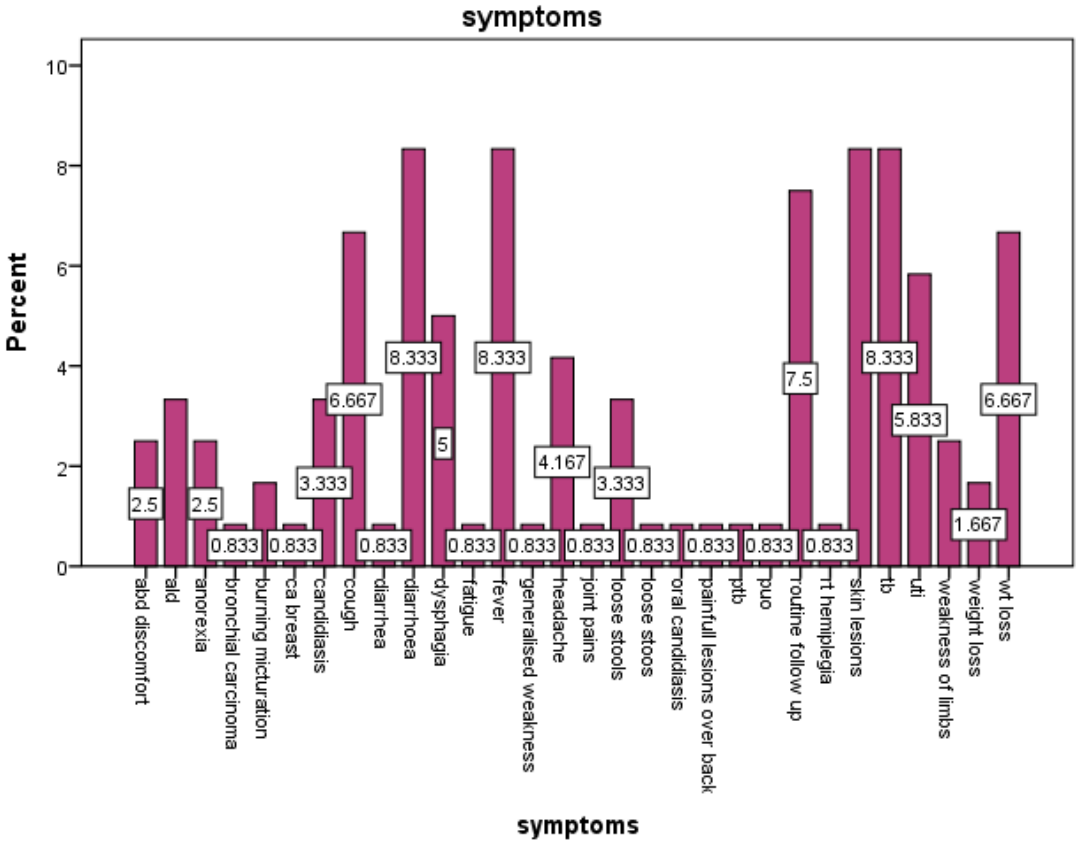
ANOVA T3,T4,TSH with respect to CD4 counts



Haart Drugs	Frequency	Percent
AZT+3TC+EFV	25	20.8
AZT+3TC+NVP	24	20.0
AZT+3TC=EFV	2	1.7
AZT+3TCEFV	1	.8
d4T+3TC+LPVr	1	.8
d4T+3TC+NVP	1	.8
d4T30+3TC+EFV	6	5.0
d4T30+3TC+NVP	1	.8
NIL	39	32.5
TDF+3TC+EFV	2	1.7
TDF+3TC+LPVr	4	3.3
TDF+3TC+NVP	6	5.0
ZDV+3TC+EFV	6	5.0
ZDV+3TC+NVP	1	.8
ZDV+LMV+EFV	1	.8
Total	120	100.0



Symptoms	Frequency	Percent
abd discomfort	3	2.5
ald	4	3.3
anorexia	3	2.5
bronchial carcinoma	1	.8
burning micturation	2	1.7
ca breast	1	.8
candidiasis	4	3.3
cough	8	6.7
diarrhea	1	.8
diarrhoea	10	8.3
dysphagia	6	5.0
fatigue	1	.8
fever	10	8.3
generalized weakness	1	.8
headache	5	4.2
joint pains	1	.8
loose stools	4	3.3
loose stoos	1	.8
oral candidiasis	1	.8
painfull lesions over back	1	.8
ptb	1	.8
puo	1	.8
routine follow up	9	7.5
rt hemiplegia	1	.8
skin lesions	10	8.3
tb	10	8.3
uti	7	5.8
weakness of limbs	3	2.5
weight loss	2	1.7
wt loss	8	6.7
Total	120	100.0



DISCUSSION

A prospective study was carried out in a hospital with 120 patients to evaluate thyroid function tests in HIV-infected patients and correlate the results with the CD4 count and HAART drugs. Three groups of 40 patients each were formed from the patients:

Group A: **"**40 patients not commenced on HAART"

Group B: **"**40 patients on HAART for less than a year"

Group C: **"**40 patients on HAART for a year or more"

The literature has extensively shown the correlation between endocrine disorders and HIV infection. Thyroid dysfunction was primarily caused by opportunistic infections before the introduction of HAART. The effect of HIV on the thyroid gland after HAART is still being studied, though. Thyroid dysfunction in post-HAART time has been related to autoimmunity, non-thyroidal diseases, HAART medications, and IRIS as a result of treatment.[79].

7 (17.5%) of the patients in Group A were between the ages of 21 and 30; 13 (32.5%) were between the ages of 31 and 40; 11 (27.5%) were between the ages of 41 and 50; and 9 (22.5%) were between the ages of 51 and 60. The patients were 40.40 ± 10.12 years old on average. Eleven (27.5%) patients in Group B were between the ages of 21 and 30; seven (17.5%) were between the ages of 31 and 40; 9 (22.5%) were between the ages of 41 and 50; and 13 (32.5%) were between the ages of 51 and 60.The patients were 39.88 ± 11.47 years old on average. Six (15%) of the patients in Group C were between the 21 and 30 age range; eleven (27.5%) were between the ages of 31 and 40; sixteen (40%) were between the 41 and 50 yrs. age range; and 7 (17.5%) were between the ages of 51 and 60. The patients were 40.73 ± 9.81 years old

on average. According to Student t-test, there was no significant difference between the groups (p>0.05).

Male patients made up the majority of our study's patients in Groups A, B, and C (67.5%, 55%, and 60%), while female patients made up 32.5%, 45%, and 40% of the groups, respectively. Based on the Chi-Square test, there was no significant difference between the groups (p>0.05). Abubakar UI et al. (101), ProperziM et al. (99), Sebastian SA et al. (98), and Kaneria MV et al[97].

The mean ± SD age of subjects and controls was 38.2±9.54 and 35.9±13.57, correspondingly, in the cross-sectional, hospital-based study by Abubakar UI et al[101] that compared the incidence of thyroid disorders and autoimmunity among patients with HIV/AIDS with that of HNC. The mean age of the two groups did not differ statistically significantly (p=0.138). Most subjects and controls were between 30 and 39yrs. age range, with a male-to-female ratio of 1:4.

Based on retrospective cohort research by ProperziM et al., all patients had HIV at the time of thyroid dysfunction, and their mean age at TD diagnosis was 46.6±11.5 years.[99] that evaluated symptomatic thyroid abnormalities, including thyroid malignancies, in HIV-infected individuals.Almost 50% of patients in the TDs group were female (n = 59, 48%), 67 individuals (54.5%) had CD4+ cells with a nadir <200/mm3, and 71.54% (n = 88) had previously had an AIDS-defining event. The average interval between HIV and TD diagnosis was 11.04±9.6 years.

In research by Sebastian SA et al. [98], the incidence of TD and autoimmunity in patients receiving first-line HAART was evaluated, and risk factors for TD were identified in 159 patients, 94 of whom were male. The mean (SD) duration of HIV infection was 55.0 (38.12)months, and the mean (SD) age at diagnosis was 38.8 (10.8)years.

According to Kaneria MV et al.[97] cross-sectional prevalence research, which assessed the frequency of thyroid anomalies in individuals with HIV, there were 26 females (mean age 36.77±8.74) and 49 males (mean age 39.82±12.04). Most of the patients were between 30 and 50yrs. age range.

In this particularresearch, it was shown that Group A had a mean CD4 count of 245.05 ± 226.33, whereas Groups B and C had mean CD4 counts of 239.90 ± 242.21 and 235.13 ± 197.39, respectively. Based on Student t-test, differences between the groups had been comparable and not statistically significant ($p>0.05$). This has beencomparable to the research performed by Sebastian SA et al. [98], Akinsete A et al. [100], and ProperziM et al. [99].

As per the ProperziM et al.[99] retrospective cohort analysis, the majority of patients had undetectable HIV-RNA (n = 117, 95.12%), and the mean T CD4+ cell count was 491cells/uL (range 1 to 1556cells/uL).

According to cross-sectional research by Akinsete A et al.[100], which assessed the prevalence of thyroidanomalies in children with HIV receiving HAART therapy, CD4 count was less than 200 in 20 (24.1), followed by 200-500 9 (10.8), >500-1000 21 (25.3), and >1000 33 (39.8), in that order.

According to the Sebastian SA et al. [98] study, the median TSH had been 2.58 (IQR 1.8, 4.0) and the median CD4 count was 460 (IQR 341, 596).

In our study, we found that 85 (70.8%) patients had T4 levels between 5 and 12 µg/dL, while 114 (95%) patients had T3 levels between 70 and 190 ng/dL. TSH values in 74 (61.7%) of the patients ranged from 0.5 to 5mIU/L. TSH levels significantly decreased as the CD4 count increased, but T4 levels significantly increased as CD4 count increased. When the CD4 count increased, the difference in T3 levels was similar. According to the ANOVA test, there was a significant

association (**p<0.05**) between T4, TSH, and CD4 count. Comparableoutcomes were reported by Jain G et al. [102] and Beltran S et al. [80].

A hypothyroid-like control of the pituitary-thyroid axis has been proposed as the pathophysiological underpinning for this. The concept is supported by the higher 24hr.Mean TSH levels and the larger TSH peak response to thyrotropin-releasing hormone stimulation were observed in these patients.[103] HAART-induced assay interference could be a contributing factor[79]. The non-thyroidal disease syndrome may be the cause of isolated fT4 elevation, however, there is no way to characterize or explain isolated fT3 elevation.

Such a relationship with CD4 was observed by Jain G et al. [102]. They proposed that as the disease progresses, thyroid problems become apparent when CD4 counts decline.

According to Beltran S. et al. [80], individuals with CD4 counts below 200 had an OR of 2.5, which indicates that low CD4 counts are linked to the prevalence of subclinical hypothyroidism.

Five cases of hypothyroidism were found in Group C and one (2.5%) in Group A of the current investigation. In Group C, there were 3 (7.5%) instances of subclinical hypothyroidism. Compared to Group A, thyroid diseases were more common in Groups B and C; however, the Chi-Square test specified that the difference was not statistically significant ($p>0.05$). This is in concordance with the research of Akinsete A et al[100], Abubakar UI et al[101,] and ProperziM et al[99].

According to a cross-sectional study by AkinseteA et al.,[100] the incidence of thyroid abnormalities was 2% in the control group and 9.6% in HIV-positive children. ($P = 0.15$). The most frequent thyroid problem found was hypothyroidism, and there

was no correlation between the thyroid abnormalities and the type of HAART being administered.

The general incidence of TDamong the subjects was 32.7% (male 9.1%, female 23.6%), and among the controls was 34.5% (male=10.9%, female=23.6%), according to a cross-sectional, hospital-based comparative research by Abubakar UI et al[101]. The prevalence among males (10.9%) and females (23.6%) was statistically significant among the controls, but not among the subjects. Subclinical hypothyroidism (16.4%) was the most common TD among the participants, followed by primary hypothyroidism (11.8%).

The 96 TDs incident cases in the ProperziM et al.[99] retrospective cohort analysis had an overall "crude incidence rate (CIR)" of 2.2/1000 people; the CIR for males was 1.6/1000 people, while the CIR for females was 3.8 per 1000 people.

The CD4 count was less than 100 in the majority of individuals with hypothyroidism (50%) and subclinical hypothyroidism (66.7%) in our study. According to the Chi-Square test, there had been a significant connection (**$p<0.05$**) between thyroid dysfunction and CD4 count. Comparable observations had beenobserved in the research of Sebastian SA et al[98], Kaneria MV et al[97], Akinsete A et al[100], Loomba-Albrecht LA et al[104], ProperziM et al[99], Sebastian SA et al[98] and Kaneria MV et al[97].

In research by Sebastian SA et al. [98], 47 patients had thyroid dysfunction. sHypowas the most often seen thyroid function anomaly, occurring in 29 patients. Only four of the thirty hypothyroid patients exhibited high TPO-Ab titres.

Numerous theories have been put up to explain the sickness states of individuals living with HIV/AIDS, and thyroid gland is an essential organ for growth. Thyroid problems in multiple cohorts have been related to the virus and even some

treatments[105]. Although the condition's clinical relevance is still unknown, a steady rise in thyroid-binding globulin has been associated with it.

Kaneria MV et al[97]cross-sectional prevalence study showed out of the 75 patients, overt hypothyroidism had beenobserved in 2 (3%) patients, subclinical hypo-thyroidism was observed in 10 (13%) patients, isolated low FT4 had beenobserved in 2 (3%) patients and sick euthyroidism was seen in 19 (25%) patients. 42 (56%) patients were euthyroid. Anti-thyroid peroxide antibodies were not detected in any of the individuals. Hyperthyroidism was absent in every case.

AkinseteA et al[100] cross-sectional study observed FT3 levels had been correlated with CD4 count levels and viral load. Age, dietary status, and the duration of HAART therapy did not correlate with thyroid function.

Loomba-Albrecht LA et al[104] observed those with sHypo generally have higher TSH levels, that has been related to more progressive disease. It is thought that an elevation in the amount of TBG in the blood impairs thyroid response and function in cases of severe immunosuppression.

Retrospective cohort research by ProperziM et al.[99]observed that a T CD4+ cell nadir <200cells/mm^3 was independently linked to hyperthyroidism symptoms. The mean CD4+ T cell rise in this cohort was 437.54 ± 306.13, which was the most significant increase between the nadir and the TD diagnosis.

Sebastian SA et al[98]studies showed TSH levels had a negative association with duration of ART and CD4 counts. CD4 counts had been negatively correlated with age. There had been a negative connection between TSH levels and CD4, even after controlling for age and ART duration. Between patients who got zidovudine and those who did not, there had been only one statistically significant variation. It has little

clinical importance, though, because the median TSH concentrations were within the normal range.

Kaneria MV et al[97]cross-sectional prevalence study reported out of 36 patients in group A (CD4 count ≤200 cells/mm3), 22 had thyroid function abnormalities. 1 (2.8%) had overt hypothyroidism, 6 (16.7%) had subclinical hypothyroidism, 2 (5.6%) patients had isolated FT4 levels and 13 (36.1%) patients showed sick euthyroidism. Out of 25 patients in group B (CD4 count between 201 and 350 cells/mm3), 10 had thyroid function abnormalities. 1 (4%) had OH, 4 (16%) had sHypoand 5 (20%) had sick euthyroidism. Out of 14 patients in group C (CD4 count >350 cells/mm3), only 1 patient had thyroid function abnormality, i.e. sick euthyroidism. None had isolated low FT4 levels, sHypo, or overt hypothyroidism. While there was a direct correlation between FT3 and CD4 count, there was an inverse relationship between TSH levels and CD4 count. It was discovered that the FT3 and TSH levels of the two groups—those receiving HAART and those not receiving it—were significantly different. Patients on HAART had considerably higher mean TSH levels than those not on HAART. This indicates that people on HAART are more likely to have hypothyroidism than those who are new to HAART.

Group B and C had significantly lower mean T3 levels (135.85±34.59 ng/dl vs. 113.58±39.93 ng/dl vs. 101.45±32.73 ng/dl) and T4 levels (4.83±2.45 µg/dL vs. 3.65±2.24µg/dL vs. 2.73±1.28µg/dL) than Group A, according to the ANOVA test (**p<0.05**). The ANOVA test revealed that Group B and Group C had considerably higher mean TSH levels (1.73±0.47 mIU/L vs. 2.83±2.15mIU/L vs. 4.43±3.44 mIU/L) than Group A (**p<0.05**). This has beencomparable to the researchof Abubakar UI et al[101] and ProperziM et al[99].

Abubakar UI et al[101] cross-sectional, hospital-based comparative study observed isolated low FT3, while among controls. Subjects and controls had corresponding prevalences of thyroid autoimmunity (Anti-TPO Ab positive) of 14.6% (male=5.5% and female=9.1%) and 13.6% (male=4.5% and female=9.1%). The distribution of Anti-TPO Ab between the participants and controls did not differ statistically significantly. Intrinsic hypothyroidism and combined low FT3 and FT4 were the most common causes of anti-TPO Ab in the subjects (4.5% each); in the controls, intrinsic hypothyroidism (9%) and combined low FT3 and FT4 (3.6% each) were the most common causes. The subjects' mean levels of TSH, FT3, and anti-TPO had beenobserved to be lesser than those of the controls; the difference was more significant for TSH.

ProperziM et al[99] retrospective cohort study observed that TDs were negatively related to male gender and positively related to age at HIV test per 10yr. increase. All TD patients exhibited serum levels of TSH, T3, and T4 within the reference limits at the conclusion of the follow-up period.

SUMMARY

In order to assess TFTs in patients with HIV infection and to correlate the outcomes with the CD4 count and HAART drugs, a prospective study had beenperformed in a hospital with 120 patients. Three groups of 40 patients each were formed from the patients:

Group A: **"**40 patients not commenced on HAART"

Group B: **"**40 patients on HAART for less than a year"

Group C: **"**40 patients on HAART for a year or more"

The following findings were observed:

1. Group A had 7 (17.5%) patients in 21-30 years age range, and 13 (32.5%) patients in the31-40yrs. age range, 11 (27.5%) patients in the 41-50yrs. age range and 9 (22.5%) patients in the age group of 51 to 60 years. The mean age of the patients was 40.40 ± 10.12yrs. Group B had 11 (27.5%) patients in the 21-30yrs. age range, 7 (17.5%) patients in 31-40yrs. age range, 9 (22.5%) patients in the 41 to 50yrs. age range and 13 (32.5%) patients in 51-60yrs. age range. The patients' mean age was 39.88 ± 11.47 years. Group C had 6 (15%) patients in the 21-30yrs. age range, 11 (27.5%) patients in 31-40yrs. age range, 16 (40%) patients in 41-50yrs. age rangeand 7 (17.5%) patients in 51-60yrs. age range The mean age of the patients was 40.73 ± 9.81 years. As per the Student t-test, there was no significant difference between the groups ($p>0.05$).
2. The majority of the patients in Group A, Group B, and Group C were male (67.5%, 55% and 60%) while female patients constituted 32.5%, 45% and 40% of the groups respectively. There had been no significant difference among the groups as per Chi-Square test ($p>0.05$).

3. The mean CD4 count in Group A was 245.05 ± 226.33 while the mean CD4 count in Group B and Group C was 239.90 ± 242.21 and 235.13 ± 197.39 respectively. The difference between groups had beensimilar and statistically not significant as per Student t-test (p>0.05).
4. 114 (95%) patients had T3 levels between 70-190 ng/dL while 85 (70.8%) patients had T4 levels between 5-12µg/dL. 74 (61.7%) patients had TSH levels between 0.5-5mIU/L.
5. It had beennoted that there was a significant increase in T4 levels with an elevation in CD4 count while there was a significant decline in TSH levels with an increase in CD4 count. The difference in T3 levels was comparable when there was an increase in CD4 count. There had beena significant correlation among T4, and TSH with CD4 count as per ANOVA test (**p<0.05**).
6. There was 1 (2.5%) case of hypothyroidism in Group A and 5 cases of hypothyroidism in Group C. There were 3 (7.5%) cases of subclinical hypothyroidism in Group C. Thyroid disorders were more prevalent in Group B and Group C thanin Group A but the difference was statistically not significant as per Chi-Square test (p>0.05).
7. Most of the patients with hypothyroidism (50%) and subclinical hypothyroidism (66.7%) had CD4 count <100. There was a significant correlation of thyroid dysfunction and CD4 count as per Chi-Square test (**p<0.05**).
8. The mean T3 levels (135.85±34.59 ng/dl vs. 113.58±39.93 ng/dl vs. 101.45±32.73 ng/dl) and T4 levels (4.83±2.45 µg/dL vs. 3.65±2.24µg/dL vs. 2.73±1.28µg/dL) had beensignificantly lower in Group B and Group C than Group A as per ANOVA test (**p<0.05**). The mean TSH levels

(1.73±0.47mIU/L vs. 2.83±2.15mIU/L vs. 4.43±3.44 mIU/L) were significantly higher in Group B and Group C than Group A as per ANOVA test (**$p<0.05$**).

CONCLUSION

Abnormal thyroid function test results are common among HIV-infected individuals. Currently, there is insufficient evidence in favor of screening for thyroid abnormalities among asymptomatic HIV-infected individuals. Patients on HAART have high prevalence of subclinical hypothyroidism as compared to patients‟ naïve to HAART. Hence, patients on HAART may need regular monitoring of thyroid function tests.

The study highlights that thyroid abnormalities occur in patients living with HIV and it may be important to perform yearly screening especially with moderate to severe immunosuppression.

LIMITATIONS OF THE STUDY

This study has considered a population of 120 and thus the appropriate representation of the population and better outcomes could be attained by increasing the sample size .The restriction of study to small geographical area is also constraint.

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 *at* 3-30pm. *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "Thyroid Fuction Test in HIV/AIDS. Patients and Its Correlation with CD4 Count and Highly Active Antiretroviral Therapy (Haart)"

Name of P.G. student Dr. Puneet. Gunapal. Pakkal.
Dept of General medicine.

Name of Guide/Co-investigator Dr Sanjeev. N. Bentoor. Professor.
Dept of General Medicine

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

BLDE (DU)SHRI B.M .PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTREVIJAYPURA-586103

TITLE OF THE PROJECT "**THYROID FUNCTION TESTS IN HIV/AIDS PATIENTS AND THERE CORRELATION WITH CD4 COUNTS AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY"**

PRINCIPAL INVESTIGATOR - **Dr.PUNEETH G PAKKAL**

P.G GUIDE NAME - **Dr.SANJEEV. N. BENTOOR**
HOD &PROFESSOR OF MEDICINE

CHAIRMAN ETHICAL COMMITTEE

All aspects of this consent form are explainable to the patient in the language understood by them.

1) **PURPOSE OF RESEARCH**

I was informed about this study. I also have a free choice of participation in this study.

2) **PROCEDURE**

I am aware that the investigator can question me in addition to routine care received. I must undergo the necessary investigations and treatment to help the investigator in this study.

3) **RISK AND DISCOMFORTS**

I understand that I may experience pain and discomfort during the examination or my treatment. It is mainly the result of my condition,and the procedure of this study is not to exaggerate these feelings associated with the usual course of treatment.

4) **BENEFITS:**

I understand that my participation in this study will help patients survival and better outcome.

5) **CONFIDENTIALITY:**

I understand that the medical information produced by this study will become a part of hospital records and will be subject to confidentiality and privacy regulation. Information of sensitive personal nature will not be part of the medical records .Still,it will be stored in the investigators research file and identified only by a code number.The code key connecting name to numbers will be kept in a separate location .Suppose the data is in the medical literature or teaching.I will not use words;others, such as photographs and audio or videotapes,will be used only with my special

written permission.I understand that I may see the pictures and videos and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION

I understand that I may ask more questions about the study at any time **Dr.PUNEET G PAKKAL** is available to answer my questions or concerns.I know that I will inform any significant new findings discovered during this study ,which might influence my continued participation.if, during the investigation or later,I wish to discuss my involvement concerning this study with a person not directly involved,I know that the hospital social worker is available to talk with me.I will be giving a copy of this consent form for carefull reading.

7) REFUSAL OR WITHDRAWL OF PARTICIPATION

I understand that my participation is voluntary and that I may refuse to participate or withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital .I also understand that **Dr. PUNEETH G PAKKAL** may terminate my participation in the study after he has explained the reasons for doing so and has helped arrange for my continued care by my physician or physical therapist if this is appropriate.

8) INJURY STATEMENT

I understand that in the unlikely event of injury to me resulting directly from my participation in the study,the appropriate treatment would be available but will not provide compensation.I understand my agreement to participate in this study.I have explained the purpose of the research,the procedures required,and the possible risks and benefits in the patients language to the best of my ability.

Dr. PUNEETH G PAKKAL

(Investigator)

Date:

STUDY SUBJECT CONSENT STATEMENT

I confirm that DR.PUNEETH G PAKKAL has explained the purpose of the research,the study procedures that I will undergo,and the possible risks and discomforts as well as benefits that I may experience in my language.I have read,and I understand,this consent form. Therefore, I agree to consent to participate as a subject in this research project.

Participant/Guardian **Date:**

B.L.D.E (DEEMED TO BE UNIVERSITY)

SHRI B.M .PATIL MEDICAL COLLEGE VIJAYPURA, KARNATAKA

SCHEME OF CASE TAKING

Informant:

Name: CASE

NO: I.P NO:

Age: D.O.A:

Sex: D.O.D:

Religion:

Past occupation:

Present occupation:

Residence:

Past History:

Family History:

General Physical Examination

Height:

Weight:

Body mass index:

Vitals

PR:

B.P:

R.R:

Temp:

Head to Toe examination:

SYSTEMIC EXAMINATION

GASTROINTESTINAL SYSTEM:

CENTRAL NERVOUS SYSTEM:

RESPIRATORY SYSTEM:

CARDIOVASCULAR SYSTEM:

HAEMOTOLOGY

Hemoglobin	Gm%
Total WBC counts	Cells/mm3
Differential counts	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
Platelet count	10*
MEAN PLATELET VOLUME	fl

BIOCHEMISTRY

CD4 COUNT

T3

T4

TSH

DAIGNOSIS:

MASTER CHART

S. no	IP no.	Groups	Age yrs	Sex	Cd4	t3	t4	tsh	symptoms
1	475060	Group A	30	f	861	1.11	8.14	0.964	fever
2	475061	Group A	18	f	566	1.11	6.13	2.947	joint pains
3	475063	Group A	60	f	726	1.15	7.14	2.666	wt loss
4	475062	Group A	42	m	656	1.25	8.44	2.962	fever
5	466097	Group A	28	f	459	1.54	6.23	1.012	tb
6	475046	Group A	36	m	569	0.92	5.68	1.7	skin lesions
7	475044	Group A	46	m	600	1.56	8.51	0.986	fever
8	469562	Group A	29	f	210	1.45	8.89	2.075	diarrhea
9	475043	Group A	40	m	663	1.08	7.55	1.407	skin lesions
10	469548	Group A	47	f	511	0.93	8.11	2.988	dysphagia
11	475056	Group A	40	m	326	1.19	5.89	0.692	loose stools
12	475050	Group A	38	f	600	0.88	4.92	2.223	fever
13	469576	Group A	58	f	350	0.96	8.14	2.268	dysphagia
14	466068	Group A	21	f	516	1.15	7.66	1.811	oral candidiasis
15	475059	Group A	36	f	310	0.88	7.11	1.276	fever
16	469579	Group A	18	f	612	1.51	8.44	1.27	headache
17	467813	Group A	32	m	355	1.54	7.22	1.522	painfull lesions over back
18	469579	Group A	40	f	959	1.19	7.24	2.56	cough
19	467813	Group A	36	f	405	1.26	8.44	1.016	tb
20	469579	Group A	27	f	569	1.01	9.56	1.369	abd discomfort
21	475053	Group A	45	f	613	1.56	12.5	0.655	fever
22	475055	Group A	35	m	721	1.08	8.22	2.617	tb
23	475052	Group A	35	f	496	1.05	7.81	1.783	tb
24	475049	Group A	25	f	527	1.06	7.27	1.492	loose stoos
25	464194	Group A	30	m	631	0.92	7.58	1.048	dysphagia
26	469570	Group A	35	f	329	0.52	5.48	4.406	dysphagia
27	467832	Group A	37	m	304	1.44	5.63	1.589	headache
28	475038	Group A	18	f	729	1.54	5.51	2.829	cough
29	475036	Group A	40	m	422	1.23	9.04	2.137	uti
30	475042	Group A	19	f	477	0.99	5.14	3.504	skin lesions
31	466091	Group A	35	m	362	1.36	4.02	11.67	diarrhoea
32	466057	Group A	40	m	171	0.72	4.69	3.088	cough
33	467809	Group A	26	m	612	0.52	4.8	0.756	candidiasis
34	466062	Group A	35	m	279	1.12	7.01	1.287	abd discomfort
35	466055	Group A	37	f	362	1.2	5.32	1.581	weakness of limbs
36	466064	Group A	28	f	346	0.76	3.89	1.877	skin lesions
37	466066	Group A	35	f	413	0.84	4.5	1.465	cough
38	466067	Group A	18	m	853	1.14	4.98	1.412	tb
39	466068	Group A	19	m	380	1.5	6.12	2.101	ald

40	466077	Group A	20	m	633	0.6	3.68	2.717	headache
41	466074	Group B	20	f	567	1.92	5.82	1.673	skin lesions
42	466078	Group B	45	f	634	1.87	4.67	1.87	diarrhoea
43	466080	Group B	38	m	633	1.03	5.26	1.877	uti
44	466082	Group B	38	f	569	1.05	5.71	1.738	loose stools
45	467832	Group B	49	m	271	0.81	3.52	1.381	tb
46	466085	Group B	50	m	253	1.22	4.62	1.852	candidiasis
47	466088	Group B	40	m	499	0.92	5.63	1.106	headache
48	469579	Group B	37	f	455	1.13	7.18	2.237	loose stools
49	466093	Group B	40	f	364	1.25	3.92	2.533	loose stools
50	466097	Group B	26	f	456	1.07	6.52	1.18	routine follow up
51	466099	Group B	52	f	232	0.65	4.21	0.65	dysphagia
52	466101	Group B	30	f	775	1.67	5.25	1.162	cough
53	466103	Group B	24	f	532	0.86	3.89	0.545	fever
54	467808	Group B	55	f	279	1.12	7.01	1.287	fever
55	466060	Group B	38	f	512	1.23	8.9	1.856	burning micturation
56	467810	Group B	36	m	226	1.1	6.27	1.193	skin lesions
57	467812	Group B	38	f	441	0.91	8.3	3.149	diarrhoea
58	467813	Group B	43	m	296	0.87	7.1	2,216	diarrhoea
59	464176	Group B	40	m	396	1.17	6.11	1.755	weight loss
60	467817	Group B	46	m	443	0.65	8.5	1.593	weight loss
61	467818	Group B	40	f	566	0.77	6.7	1.909	cough
62	467819	Group B	25	f	415	1.07	8.12	8.809	uti
63	467820	Group B	28	m	466	0.67	4.26	1.304	anorexia
64	467821	Group B	40	m	166	2.1	6.27	5.362	bronchial carcinoma
65	467823	Group B	45	m	390	0.98	5.12	2.267	skin lesions
66	467825	Group B	48	f	211	0.92	5.4	4.553	fever
67	467826	Group B	30	f	744	0.89	3.6	4.65	puo
68	467828	Group B	19	f	555	0.87	4.6	3.45	skin lesions
69	469586	Group B	29	m	488	0.84	5.1	1.468	routine follow up
70	467830	Group B	38	m	569	1.69	7.22	8.27	routine follow up
71	466087	Group B	48	m	322	1.97	11.3	1.28	routine follow up
72	467833	Group B	29	m	777	1.5	6.27	3.304	ald
73	467835	Group B	35	m	277	1	7.18	1.162	ald
74	467837	Group B	30	f	566	1.09	6.37	5.942	tb
75	467812	Group B	28	f	455	1.08	5.34	6.34	ald
76	469544	Group B	27	f	426	2.56	5.42	1.831	uti
77	464198	Group B	30	f	536	1.19	7.79	1.135	tb
78	469546	Group B	48	m	379	0.72	5.1	1.127	diarrhoea
79	475068	Group B	30	f	379	1.12	5.21	5.282	routine follow up
80	464195	Group B	23	f	421	1.5	10.82	4.483	generalised weakness
81	464194	Group C	70	m	631	0.76	7.83	0.944	wt loss

82	464193	Group C	21	f	677	1.3	13.38	2.431	weakness of limbs
83	464182	Group C	24	m	599	1.12	10.76	0.866	ca breast
84	464181	Group C	31	f	611	1.24	6.87	2.858	uti
85	464179	Group C	41	m	342	1.13	8.68	1.558	diarrhoea
86	464170	Group C	28	f	359	1.37	8.98	2.389	wt loss
87	464171	Group C	45	f	569	0.94	8.72	0.74	wt loss
88	464176	Group C	33	f	231	1.18	9	6.165	uti
89	464174	Group C	29	m	213	1.45	10.94	0.421	tb
90	464203	Group C	20	f	345	1.55	9.46	1.953	candidiasis
91	464187	Group C	23	f	977	1.59	8.97	2.455	rt hemiplegia
92	464191	Group C	31	m	455	1.25	10.79	2.305	fatigue
93	464189	Group C	40	f	478	1.37	11.16	1.251	wt loss
94	464185	Group C	42	m	488	1.06	6.43	1.766	anorexia
95	469580	Group C	38	f	410	1.12	5.48	1.829	diarrhoea
96	469566	Group C	42	f	556	1.08	5.23	2.561	wt loss
97	469568	Group C	28	f	311	1.02	5.22	0.81	tb
98	469585	Group C	31	f	394	1.12	6.9	3.405	wt loss
99	469573	Group C	22	f	566	1.07	5.29	1.657	diarrhoea
100	466090	Group C	22	f	263	0.95	5.61	3.156	routine follow up
101	466103	Group C	20	f	566	2.49	6.71	0.999	diarrhoea
102	469554	Group C	25	f	456	2.1	6.41	1.071	dysphagia
103	469545	Group C	30	f	496	2.31	0.79	1.818	cough
104	469556	Group C	30	f	360	1.26	6.23	3.355	weakness of limbs
105	469562	Group C	32	f	210	0.63	6.23	2.884	abd discomfort
106	469552	Group C	30	m	410	1.44	5.62	5.438	burning micturation
107	469551	Group C	50	f	810	1.4	7.71	3.513	skin lesions
108	469549	Group C	19	m	311	1.4	9.01	5.003	ptb
109	469564	Group C	18	f	546	1.09	6.28	1.536	headache
110	469550	Group C	32	f	942	0.62	5.58	1.645	cough
111	469548	Group C	30	f	379	0.87	5.21	5.282	wt loss
112	469576	Group C	58	f	131	0.75	4.68	1.174	anorexia
113	469577	Group C	25	f	410	1.39	6.44	1.604	uti
114	469578	Group C	51	f	560	0.53	4.36	3.136	candidiasis
115	469575	Group C	30	f	894	1.23	6.23	3.554	skin lesions
116	469544	Group C	37	f	426	2.56	5.42	1.831	routine follow up
117	469582	Group C	32	f	456	1.08	5.96	0.675	routine follow up
118	469557	Group C	35	f	848	1.86	6.44	2.224	routine follow up
119	467825	Group C	35	f	344	2.25	6.32	1.305	fever
120	469570	Group C	28	f	469	0.99	4.82	1.631	diarrhoea

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