

# STUDY OF THYROID PROFILE IN HIV PATIENTS ON HAART

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## ABSTRACT

**Background:** HIV infected patients are often encountered with abnormal thyroid function test results including sick euthyroid syndrome and at a times detectable in the early phase of disease as well as in late phase. Among thyroid dysfunctions asymptomatic conditions are more prevalent, including subclinical hypothyroidism and isolated low free thyroxine levels. So this study will probe into the abnormality in thyroid function in HIV infected subjects receiving HAART.

**Aim:** To study the prevalence of abnormal thyroid function among HIV patients receiving HAART.

**Methods:** This cross-sectional study was conducted at tertiary care center in collaboration with ART center among HIV positive patients attending OPD and IPD, over a period of 27 months.

**Results:** Out of 50 patients included in the study 66% were males, 34% were females, 86% showed euthyroid status, 10% showed subclinical hypothyroidism, 2% showed hypothyroidism, 2% showed isolated low T4 levels. Prevalence of thyroid dysfunctions were more in female 17%(n=3) than in male 12%(n=4).

**Conclusions:** Thyroid dysfunction is common in HIV patients on HAART. Subclinical hypothyroidism was the most common abnormality observed in the study population. There was no significant correlation between CD4 cell count and thyroid abnormality. There was no statistical significance in association between drug regimen, duration of drug regimen and duration of illness with thyroid dysfunction.

**Keywords:** HAART, HIV, Thyroid, Overt hypothyroidism, Sub clinical hypothyroidism

## INTRODUCTION

HIV infection is a chronic, systemic disease possibly leading to multi-organ involvement and affecting the endocrine system as well. However, since its identification in 1983<sup>(1)</sup> and the isolation of the human immunodeficiency virus type I (HIV-1) as the primary cause of the acquired immunodeficiency syndrome<sup>(2)</sup> almost 25 years have now elapsed. Twenty-five years, in which HIV infection has changed from a fatal condition to a manageable chronic illness, and with development of antiretroviral therapy (ART) has been one of the dramatic advances in the history of medicine. The endocrine glands are affected in a variety of ways such as functional derangement, direct effects of HIV infection and the resultant immune suppression, effects of opportunistic infections, invasion by neoplasms, sick euthyroid syndrome and the effects of the various medications used to treat HIV. Highly active antiretroviral therapy (HAART) has changed the clinical evolution of HIV infection. However, its adverse effects are increasingly being recognized, particularly those concerning endocrine dysfunction, and some of the secondary effects are probably not known yet. The observation in several studies of clinical and subclinical thyroid dysfunction at various stages of this infection suggests an effect of HIV and/or HAART on the endocrine system. However, the abnormalities in thyroid tests, when present, are commonly asymptomatic and are most frequently associated with subclinical hypothyroidism<sup>(5,6,10,11)</sup>, although the mechanism is unclear.

Among individuals infected with HIV, 1%–2% experience overt thyroid disease, and 35% may have subtle abnormalities in thyroid function test findings.<sup>(5,6)</sup> Overt hypothyroidism is common both among the general population, in which 0.3%<sup>(13)</sup> of persons are affected, and among HIV-infected individuals, among whom small studies have reported a prevalence of 1%–2.6%<sup>(5,10,11)</sup> Among patients with HIV infection anti-thyroid peroxidase antibodies are rarely identified, suggesting that the etiology may not be autoimmune<sup>(6)</sup> In some cases hyperthyroidism has been considered as late manifestation of immune reconstitution caused by HAART. Autoimmune thyroiditis has also been implicated in the development of subclinical hypothyroidism caused by long term HAART.<sup>(5)</sup> One postulated hypothesis is that the retinoid X receptor-selective ligand suppresses thyrotropin secretion; this higher prevalence could be related to the retinoid like effects of Protease inhibitors. Another hypothesis could be related to the lipodystrophy present in most of these patients. Lipodystrophy could simulate a fasting situation leading to a fall in the leptin level responsible for the suppression of the thyroid axis.<sup>(15)</sup>

In view of the variability of thyroid function tests in patients with HIV and HAART in previous studies, it was decided to undertake a prospective study of thyroid function in HIV patients on HAART in stable clinical conditions, in BJ Medical College and Civil Hospital, Ahmedabad from August 2019 to October 2021.

## MATERIALS AND METHODS

This single centre, non randomized cross sectional study was conducted at tertiary care setup B.J.medical college and civil hospital, in collaboration with ART center, ahmedabad over a period of 27 months (August 2019 to October 2021) among HIV positive patients attending OPD and IPD. Institute Ethical Committee's approval and permission from GSACS(Gujarat state AIDS control society) were obtained to conduct the study. After applying inclusion and exclusion criteria, 50 HIV positive patients registered at ART centre during the study period were included in the study. After obtaining consent from patient or patient's relatives data was recorded through direct personnel interview/investigation method on pre-designed and pretested questionnaire/record sheet.

### Inclusion Criteria

1. HIV positive patients on HAART for not less than 12 months.
2. Age >18 years

### Exclusion Criteria

1. Patients with Known thyroid dysfunction
2. Patients with Active opportunistic infection
3. Patient with AIDS related neoplasia
4. Severely ill patient
5. Patient with Renal & hepatic dysfunction(severe)
6. Pituitary/hypothalamic diseases
7. Patients on drugs known to cause thyroid dysfunction
8. Pregnancy

The cases selected were subjected to detailed physical as well as systemic examination & then investigated for various lab parameters. Besides routine investigations, patients were subjected to specific microbiological, pathological and radiological investigations. CD4 Count (Flow cytometry), Thyroid function tests-TSH, free T4, free T3(After 8 to 10 hours of fasting) were done in every patient. The data was collected on predesigned and pretested questionnaire/record sheet was compiled and master table was made on Excel accordingly. Most appropriate statistical tools (percentages and chi square test for association) were applied to analyse the data and conclusions were drawn accordingly.

## RESULTS AND OBSERVATION

**TABLE-1.BASELINE CHARACTERISTICS OF THE STUDY POPULATION**

Mean Age	Mean-37 years
Sex	64% male / 34% female
Mean CD4 count	360

The mean age of study population was 37 years. Majority of the patients were in the age group between 30 and 39 years – 27(54%).

**TABLE-2.DISTRIBUTION OF THYROID PROFILE IN THE STUDY GROUP**

Thyroid Status	No. of Patients(n=50)	Percentage (%)
Euthyroid	43	86
Hypothyroidism	1	2
Subclinical Hypothyroidism	5	10
Isolated low T4	1	2

In the study population, the thyroid dysfunction is prevalent in 14%(n=7) patients. Subclinical hypothyroidism is the most common abnormality among the study population with 10% constituting five patients Thyroid dysfunction was present in 4 males (12.12%) and 3 females (17.64%). There was no statistical significance as p value was 0.67.

**TABLE-3. SERUM CONCENTRATION OF THYROID PROFILE**

Thyroid Profile	Normal Range	Study Range	Mean	Std. Deviation
Free T4 ng/dl	0.7-2.5	0.33-1.8	1.16	0.33
Free T3 pg/ml	2.2-4.3	1.2-4.1	3.2	0.97
Serum TSH $\mu$ IU/ml	0.4-4.5	0.90-22.34	3.16	3.29

As shown in the above graphs, the study shows a downward shift in reference to normal range for FT3 and FT4 but upward shift for TSH.

**TABLE- 4. ASSOCIATION BETWEEN CD4 COUNT AND THYROID DYSFUNCTION**

Thyroid function (no of patients)	CD4 Mean	CD4 Range	p-value*
Abnormal(7)	349	186 - 652	0.83
Normal(43)	365	78 - 756	

\*Student's t- test

However, there was significant variation in the CD4 count, the analysis by Student's t- test showed a insignificant p value and hence no correlation could be established.

**TABLE-5. ASSOCIATION BETWEEN DRUG REGIMEN AND THYROID DYSFUNCTION**

Type of drug regimen	Thyroid function				Total	p-value*
	Abnormal		Normal			
	n	%	N	%		
1.AZT+3TC+ EFV (ZLE)	1	12.50	7	87.50	08	0.95
3.TDF+3TC+EFV (TLE)	4	15.38	22	84.62	26	
4. TDF+3TC+DTG (TLD)	2	12.50	14	87.50	16	

\*Chi-square test

AZT – Zidovudine, 3TC – Lamivudine, EFV – Efavirenz, TDF/TD – Tenofovir disoproxil fumarate, DTG – dolutegravir. There was no statistical correlation between these different drug regimens and the thyroid status.

**TABLE-6. ASSOCIATION BETWEEN DURATION OF DRUG THERAPY, DURATION OF ILLNESS AND THYROID DYSFUNCTION**

Thyroid function (no of patients)	Duration of drug in months Mean $\pm$ SD	p-value*	Duration of illness in months Mean $\pm$ SD	p-value*
Abnormal(7)	29 $\pm$ 10	0.62	32 $\pm$ 12	0.80
Normal(43)	27 $\pm$ 10		29 $\pm$ 10	

\*Student's t- test

Though a marginal increase in the duration was noted in thyroid abnormal group but the statistical correlation was absent. The duration of illness in both the groups were nearly the same and statistical correlation was absent.

### DISCUSSION

AIDS resulting from HIV infection may involve any organ system either directly or indirectly. HIV related endocrinopathies occurs during all stages of the disease, both early and late. In this study Fifty HIV positive patients on HAART were screened for thyroid abnormalities.

Majority of the patients were in the age group between 30 and 39 years –27(54% of study population) followed by 10 (20%) patients in 40-49 years age group. The mean age of patients in this study was 36.9  $\pm$  8.29 which was comparable to study group of Madeddu et al.<sup>(11)</sup> Similar age group is noted in the study done by Beltran et al.<sup>(5)</sup>

In our study the overall male(66%) population was more than their female(34%) counterpart, with male to female ratio 2:1. However in a study done by Palaniswamy et al<sup>(17)</sup> had 50 individuals with 100% males and study done by RK Verma et al<sup>(18)</sup> had 68% male. The prevalence of thyroid dysfunction was found to be more in female(17.64%) than male(12.12%) and similar result was noted in study done by RK Verma et al. There was no statistical correlation between gender and thyroid dysfunction.

Majority of patients in our study were found to have normal thyroid parameters. The thyroid dysfunction prevalence in our study was 14%(n=7). Madeddu et al<sup>(11)</sup> reported a prevalence of 12.6% of thyroid dysfunction in their study group on HAART and Beltran et al<sup>(5)</sup> had 16% prevalence of thyroid dysfunction. Grapin et al<sup>(10)</sup> noted that 12.3% presented with at least one abnormal test of thyroid function

In the present study, commonest thyroid dysfunction was subclinical hypothyroidism (10%). Beltran et al<sup>(5)</sup> reported the prevalence of subclinical hypothyroidism was especially high among HIV-infected men (8.1%), higher than in the general male population, in which the prevalence is 6.2%.<sup>(19)</sup> Grapin et al<sup>(10)</sup> study of 212 HIV-infected patients found that, 8.5% had subclinical hypothyroidism.<sup>(11)</sup> Calza et al.<sup>(6)</sup> also reported a high prevalence (12.2%) of subclinical hypothyroidism among HIV-infected patients receiving HAART. RK Verma et al<sup>(18)</sup> found that, 12% had subclinical hypothyroidism. In contrast, Collazos et al.<sup>(9)</sup> reported a lower prevalence, of 3.5%, in a Spanish population of 202 patients. Isolated low FT4 incidence in our study was 2%. Isolated low FT4 incidence shows marked variation in each of the population studied. Collazos et al.<sup>(9)</sup> reported the prevalence of low FT4 1.3%. Beltran et al<sup>(5)</sup> observed an increased prevalence (6.3%) of low FT4 in their study, whereas Madeddu et al<sup>(11)</sup> observed an incidence of about 2.7% in their patients.

Measurement of CD 4 cell count and correlation with thyroid dysfunction threw a result with lower mean CD 4 (349) cell count in the thyroid abnormal group. Statistical significance could not be ascertained for the same due to smaller sample population. Low CD4 cell count was a risk factor for hypothyroidism as per the Beltran et al<sup>(5)</sup> study. However, Madge et al<sup>(14)</sup> proved that none of these independent variables was significantly associated with overt hypothyroidism. Madeddu et al<sup>(11)</sup> was able to prove that TSH, but not FT3 and FT4, negatively correlated with CD4 count nadir which was difficult to replicate in other studies and countered by Afhami et al<sup>(16)</sup> with proofs of mean CD4 cell count not being significant risk factors of hypothyroidism. Quirino et al<sup>(12)</sup> found no significant relationship between the condition and CD4 cell count.

The three drug regimens in our study comprised of the following five drugs – Zidovudine, Lamivudine, Efavirenz, Dolutegravir and Tenofovir disoproxil fumarate of which Lamivudine was consumed in larger population. There was no significance correlation found between drug regimen and thyroid abnormality in our study population and prevalence of thyroid dysfunction is almost equal with all three drug regimen. Similar correlation by Afhami et al<sup>(16)</sup> found no significance on the association of these drug regimens. Madge et al<sup>(14)</sup> in their cohort study showed neither HAART regimen nor specific drug use was significantly associated with either overt hypothyroidism or subclinical hypothyroidism which was in contrast to the findings of correlation between stavudine use and thyroid abnormality by Madeddu et al<sup>(11)</sup>

The duration of drug regimen and correlation with thyroid dysfunction was of no statistical significance and this is in coordination with the findings of Quirino et al<sup>(44)</sup> who found no significant relationship between the condition and drugs or CD4 cell count and reinforced by Afhami et al<sup>(62)</sup> with no association between drug duration and thyroid abnormality. In our study the

mean duration of illness in both thyroid normal and abnormal group were nearly the same. Longer duration of disease in HIV-infected patients treated with HAART might allow the development of autoimmune thyroiditis as observed by Beltran et al.<sup>(35)</sup> Afhami et al<sup>(62)</sup> observed that duration of HIV infection is not a significant risk factor of hypothyroidism in HIV-infected patients on HAART.

### CONCLUSION

Thyroid dysfunction is common in HIV patients on HAART. The prevalence of thyroid dysfunction in the study population was 14%. Subclinical hypothyroidism(10%) was the most common abnormality observed in the study population. There was no significant correlation between CD4 cell count and thyroid abnormality. There was no statistical significance in association between drug regimen, duration of drug regimen and duration of illness with thyroid dysfunction. It is strongly recommended to screen all HIV patients with thyroid profile to look for subclinical hypothyroidism.

### LIMITATIONS OF STUDY

- Small size study population.
- Further studies with large population is recommended.

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### CONFLICTS OF INTEREST

NONE

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