Annals of International Medical and Dental Research
E-ISSN: 2395-2822 | P-ISSN: 2395-2814
Vol-7, Issue-3 | May-June, 2021
Page no- 103-111 | Section- Research Article (Medicine)

Assessment of Thyroid Dysfunction in Patients with HIV on HAART

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Received: November 2020
Accepted: December 2020

Abstract

Background: AIDS, the aquired immunodeficiency syndrome is a serious illness caused by retrovirus named human immunodeficiency virus (HIV) which attacks the immune system and causing various life threatening opportunistic infections, neurological disorders, or unusual malignancies to thrive in the host body. The functioning of thyroid gland may be affected in HIV,drug interaction and the immune reconstitution inflammatory syndrome(IRIS).This study aims to investigate the prevalence of thyroid dysfunction in patients with HIV on HAART. **Methods:** 100 HIV positive patients on HAART were selected in the out patients attending the general medicine OPD and ART centre, Guru Nanak Dev Hospital Amritsar between November 2018 to November 2020 after applying inclusion and exclusion criteria. Detailed history, physical examination and investigations like CBC,LFT,RFT,CD4 count,FT4, TSH and FBS were done. **Results:** In this study, the maximum patients were in the age group 41-50 years, followed by 31-40 years. The mean age of the patients was 43.57± 9.4 years with total 52% females and 48% males. The study showed that 85% of patients were euthyroid and 15% of patients were with thyroid dysfunction. The predominant drugs were TLD followed by TLE and ZLN in 33%,32% and 25% of patients. There was an inverse relation seen between CD4 and TSH counts which implies that as the value of CD4 count decreases, the levels of TSH increased but non-significant relation between FT4 and CD4 count was observed. Statistical significance was not seen in association between drug regimen, duration of drug regimen with thyroid dysfunction. **Conclusion:** In the present study, we observed the prevalence of thyroid dysfunction in the study population to be 15%.Subclinical hypothyroidism was the most common abnormality observed. There was significant variation observed in the CD4 count and thyroid status, signifying that low CD4 count was a risk factor for hypothyroidism.

Keywords: HIV, HAART, CD4, TSH, FT4.

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INTRODUCTION

AIDS, the acquired immunodeficiency syndrome is a serious illness that is caused by a retrovirus known as the Human immunodeficiency virus (HIV). This virus attacks the immune system that allows the various life threatening opportunistic infections, neurological disorders, or unusual malignancies to thrive in the host body.[1] The clinical manifestations of HIV infection can involve multiple organs. The severity of each manifestation varies by organ system and can be related in many cases to multifactorial causes, namely HIV replication in affected tissue, concomitant opportunistic infection of the organ, effect of concurrent immunodeficiency or autoimmune mechanisms on the organ, or adverse end organ drug effect (primary HIV therapy or prophylaxis regimens).[2]

Due to involvement of various organ system, the endocrine function may also bechangedinHIV infection because of the possible association between the immune and endocrine systems, direct involvement of the glands by the HIV itself, opportunistic infections or malignancies.[3,4] In recent years, the survival rate of patients with HIV infection has increased and they are able to survive for long periods because of the extensive application of highly active antiretroviral therapy (HAART) for the suppression of viral replication. Several non-acquired immune deficiency syndrome-(AIDS-) related diseases now primarily account for the disease burden in patients with HIV infection.[5]

Abnormalities of the endocrine function of the pituitary, thyroid, adrenals, gonads and pancreas and in metabolism are common in patients infected with HIV and are becoming the main conditions influencing the long-term quality of life in HIV-infected patients.[5] Thyroid disorders result from alteration in the levels of thyroid hormones. T3 and T4 are the two main hormones produced by thyroid gland and the main function of T3 and T4 is to regulate metabolism. Altered production of these hormones can lead to malfunctioning of thyroid gland, pituitary gland and hypothalamus. The overproduction of these hormones results in hyperthyroidism and underproduction of T3 and T4 leads to hypothyroidism. The functioning of thyroid gland may be affected in HIV, drug interaction and the immune reconstitution inflammatory syndrome (IRIS).[6]

Numerous studies have been conducted to assess the incidence of thyroid dysfunction in HIV patients. But there is huge disparity in the results of these studies ranging from high occurrence to no change in comparison to that in the general population. Therefore, further research into the prevalence of thyroid dysfunction in patients infected with HIV is required.

MATERIALS AND METHODS

This Non randomised prospective cross sectional study was conducted from November 2018 to November 2020 on the outpatient department attending the General Medicine OPD and Antiretroviral therapy (ART) centre, Government Medical College attached to Guru Nanak Dev hospital, Amritsar after approval from Institutional ethical committee's. Written informed consent was taken from all the patients before recruitment.

Inclusion and exclusion criteria

100 HIV Positive who were more than 18 years of age and on HAART for a period of

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more than a year were included in this study. Patients with subclinical/clinical

hypothyroid/hyperthyroid patients, active opportunistic infections, AIDS related neoplasia, Severely ill patients and with Neuro/ pituitary/ hypothalamic diseases were excluded from the study. Also patientstabking drugs that interfere with thyroid hormones and pregnant patients were not included in the study. They were categorised on the basis of CD4 counts and type of HAART regimen.

Detailed history, symptoms and signs of thyroid dysfunction was noted. History of medication and anthropometric measurements like height and weight was noted in a semi-structured proforma. All patients were completely examined and routine urine and blood investigations were taken to rule out comorbid conditions. After 8 hours of fasting, thyroid assay was done for the clinical evaluation of thyroid dysfunction in a single setting.

RESULTS

Above table shows maximum patients were in age group 41-50 years, followed by 31-40 years. The mean age of the patients was 43.57±9.4 years [Figure 1]. The study consisted of total 52% females and 48% males [Figure 2]. [Figure 3] shows that maximum patients had CD4 count more than 500 cell/mm3 followed by mild cases where 32% of cases were present while 15 patients were reported in severe category.

In the study, 85 patients were euthyroid (85%) and 15% patients of the population were with thyroid dysfunction; out of which 2% had low T4 syndrome, 1% had overt hypothyroidism and 12% patients reported withsubclinical hypothyroidism [Table 1].

The study population was under the above-mentioned triple drug regimens. The drugs are T=Tenofovir; L=Lamivudine; E=Efavirenz; Z=Zidovudine; N=Nevirapine; D=DolutegravirL(A)=Lamivudine Adult Dose; EFV(A)= Efavirenz Adult Dose; A=Abacavir; ATV=Atazanavir; r=Ritonavir. The predominant drugs were TLD and TLE that was given in 33% and 32% followed by ZLN in 25% patients. [Figure 4]

Table 2 shows the comparison of TSH, FT4 and CD4 levels in normal and abnormal.On comparing the mean between both the groups, it was seen that significant difference was observed between TSH within normal and abnormal group whereas in the values of FT4, non-significant difference was observed. The mean value for CD4 in normal and abnormal range of CD4 was 446±214.64 and 309.33 ± 155.03. On comparing the mean of both the groups, the significant difference was observed between both.

There was an inverse relation seen between CD4 and TSH counts which attained the level of significance which implies that as the value of CD4 count decreases, the levels of TSH increased [Table 3]. The correlation between CD4 and FT4 was not significant. There was no statistical correlation between these different drug regimens and the thyroid status [Table 4].

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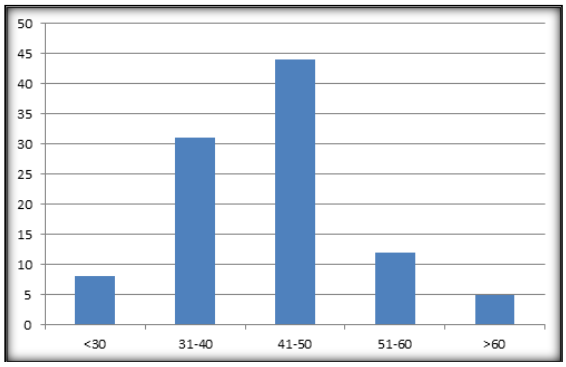

Figure 1: Age Distribution in HIV Patients on HAART Therapy.

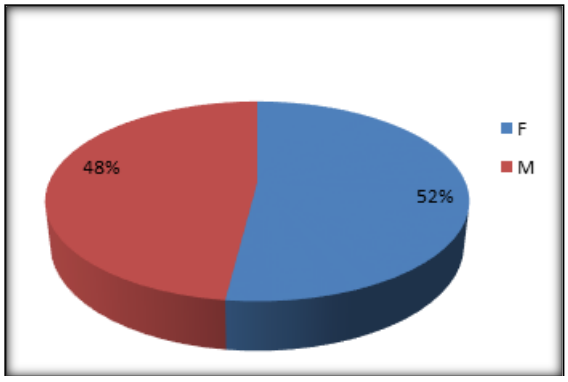

Figure 2: Gender Distribution in HIV Patients on HAART Therapy

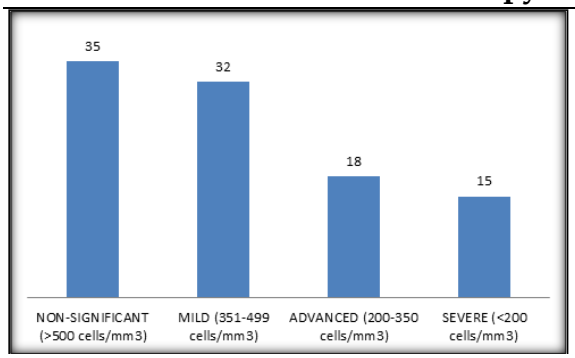

Figure 3: CD4 Count in HIV Patients on HAART Therapy

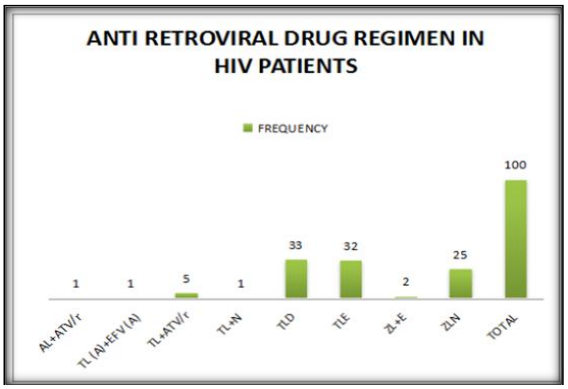

Figure 4: Anti-Retroviral Drug Regimen in HIV Patients

Table 1: Thyroid Status in Patients with HIV on HAART Therapy

Thyroid Status	Frequency%
Normal	85
Abnormal	15
LowT4 syndrome	2
Overt hypothyroidism	1
Sub-clinicalhypothyroidism	12
Total	15

Table 2: Thyroid Profile and Cd4 Counts of Patients Under Normal and Abnormal Thyroid Status

	Thyroid status	N	Mean	Standard deviation	p value
TSH	Normal	85	2.97	.73	.0001**
	Abnormal	15	7.44	2.01	
FT4	Normal	85	1.24	.230	.068
	Abnormal	15	1.10	.39	
CD4	Normal	85	446.07	214.64	.02*
	Abnormal	15	309.33	155.03	
p<.05 = Significant **p<.001=Higly-Significant p>.05=Non Significant					

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Page no- 103-111 | Section- Research Article (Medicine)

Table 3: Correlation between TSH and CD4 Count

Correlating Parameters		Pearson Correlation	P Value
CD4	TSH	-.251	.012*
CD4	FT4	-.072	.476
p<.05 = Significant **p<.001=Higly Significant p>.05=Non Significant			

Table 4: Association Between Drug Regimen and Thyroid Dysfunction

Regimen	Thyroid Status						p-value fisher exact test
	Normal		Abnormal		Total		
	Case	%Age	Case	%Age	Case	%Age	.355
AL+ATV/r	1	100%	0	100%	1	100%	
TL (A)+EFV (A)	1	100%	0	100%	1	100%	
TL+ATV/r	4	80.0%	1	20.0%	5	100.0%	
TL+N	0	100%	1	100%	1	100%	
TLD	28	84.8%	5	15.2%	33	100.0%	
TLE	29	90.6%	3	9.4%	32	100%	
ZL+E	2	100%	0	.0%	2	100%	
ZLN	20	80%	5	20%	25	100%	
Total	85	85%	15	15%	100	100%	
p<.05 = significant **p<.001=Higly significant p>.05=Non significant							

DISCUSSION

Endocrinal involvement is one such disorder that is commonly associated with HIV patients on HAART especially involvement of thyroid in the form of subclinical hypothyroidism. There is little data on abnormalities of thyroid function tests in HIV patients and only few studies undertaken in Indian subcontinent, hence the present study was conducted with the aim to assess the prevalence of thyroid dysfunction in patients infected with HIV on HAART. The study group consisted of 100 patients with HIV infection on HAART therapy.[5]

In the present the mean age of the patients was 43.57±9.[4]The results in our study were similar to Beltran et al who observed mean age in the patients on HAART to be 41.3± 10.4.[7] In another by study conducted by Madeddu et al, the mean age of the patient was 39·2 ± 6·6.[8] Present study consisted of total 52% females and 48% males. The results of our study were in discordance to the study conducted by PalaniswamyPashupathi and Madge et al where male predominance was observed. In another study by Kaneria MV et al, there were 65.3% males and 34.7% females enrolled in the study.[9-11] In a study by Verma et al, 68% of the subjects were males and 32% were females with male to female ratio of 2.125:1.[12]

In the present study, 35% had CD4 count more than 500 cell/mm3 followed by32% in stage II,18% cases in stage IIIwhile 15% patients were reported in stage IV. In a study by Kaneria et al,[11] there were 22.67% patients in stage I, 6 (8%) in stage II, 13 (17.33%) in stage III and 39 (52%) in stage IV which was in

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Page no- 103-111 | Section- Research Article (Medicine)

discordance to our results. In a study by Meena LP,[13] 52% patients were in stage IV, 44% in stage II and 26% patients were in stage II. Verma et al,[12] showed 10 patients to be in stage IV, 70% patients to be stage III and 20% patients to be in stage II.

85% of patients were euthyroid and 15% patients of the population were with thyroid dysfunction out of which 2% had low T4 syndrome, 1% had hypothyroidism and 12% patients reported with subclinical hypothyroidism. The results of our study were comparable to Verma et al,[12] who in their study showed majority of them to be euthyroid(80%), 12% had subclinical hypothyroidism while 6% subjects had overt hypothyroidism. Only 2% had subclinical hyperthyroid (TSH values of 0.21 and 0.11 with normal T3 and T4). Overall incidence of thyroid dysfunction was 20% in their study which is comparable to 15% in our study. Madge S10 et al, studied 1565 patients, out of which, 2.5% had overt hypothyroidism, 4% had subclinical hypothyroidism, and normal function was found in 75% of the patients.In another study by Ketsamathi et al,[14] Abnormal thyroid function test was detected in 16% patients, 13.5% had decreased thyroid function whereas 3% patients had increased thyroid function.

Thongam S et al, in their study also reported that thyroid dysfunction may be a marker of severity or progression of HIV.They observed highly significant correlation (P = 0.01) between TSH and CD4 count.[15]

Thyroid dysfunction in HIV positive individuals can result from glanddestructionbyopportunistic pathogens (Pneumocystis jirovecii or cytomegalovirus) or tumorigenicdiseases (Kaposi's sarcoma). These opportunistic infections could be associated with the sick euthyroid syndrome or could cause low reverse T3.[16] Pneumocystis thyroiditis has been reported to cause a painful low uptakethyroiditis like picturewithhyperthyroidism followed by hypothyroidism. [17]

Screening studies have demonstrated an increased prevalence of hypothyroidism in HIV infected patients. Quinn Tetal showed that an infectious trigger for immune activation (bymolecularmimicry) is one of the postulated mechanisms for autoimmune disease. However, hypothyroid is minHIV infected patients is not associated with autoimmunity. One case of Hashimoto's hypothyroid is has been are ported so far after highly active antiretroviral therapy (HAART) initiation.[18]

In present study oncomparing the mean between both the groups, it was seen that significant difference was observed between TSH and CD4within normal and abnormal group whereas in the values of FT4, non-significant difference was observed.

In the present study, significant variation in the CD4 count and thyroid status was observed, thereby signifying low CD4 cell count was a risk factor for hypothyroidism. Similar results were obtained by Beltran et al in their study. However Madge et al in their study showed no correlation.

Results showed that there was increased incidence of thyroid dysfunction with lower CD4 counts i.e. thyroid dysfunction increases with severity of the disease, these observations were found to be statistically significant.Results were comparable with the study of Jain G et al,[18] in which a direct

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Vol-7, Issue-3 | May-June, 2021
Page no- 103-111 | Section- Research Article (Medicine)

correlation between CD4 count and free T3 and free T4 values and an inverse correlation of CD4 counts with serum thyroid stimulating hormone (TSH) levels was seen. They concluded that thyroid dysfunction is frequent in HIV infection and with progression of disease, there is a primary hypothyroid like stage. Dev Det al.[19] in their study observed significant correlation was observed between CD4 count, free triiodothyronine and free thyroxine levels. The CD4 count inversely correlated with TSH and directly with FT4 and FT3. The results of their study were similar to that obtained in the present study where inverse relation was observed between CD4 and TSH; however the correlation between FT4 and CD4 was not significant.

Meena LPet al,[13] in a study of 150 HIV positive men observed negative correlation of TSH with CD4 count similar to our studyand in another small study of 25 AIDS and 25 non-AIDS patients, conducted by Lambart et al.The authors observed inverse correlation between CD4 count and TSH and positive correlation between CD4 count and FT3 and FT4 levels. 20 Thus, present study demonstrated high prevalence of thyroid dysfunction in HIV-positive patients. The dysfunction is subclinical in most cases and correlates well with declining CD4 counts.

Drugs used in HAART

The predominant drug regimen used in our study was TLD and TLE that was given in 33% and 32% followed by ZLN in 25% patients.The highest percentage of TLE drug regimen (90.6%) was given in Euthyroid (normal) patients.
TLD regimen was received by 84.8% patients in normal or euthyroid state. ZLE regimen was received by 100% patients of euthyroid group. Similarly, ZLN regimen was received by 80%of patients with normal range of thyroid profile group and 20%in abnormal range. Gangannavar et al,[21] in their studyobserved the highest percentages of TLE drug regimen (67.34%) in Euthyroid (normal) group followed by hypothyroid (15.30%), Hyperthyroid (10.20%) and sick euthyroid (7.14%) respectively. ZLE regimen was received by 84.61%, 7.69%, 7.69% patients of euthyroid, hypothyroid, sick euthyroid respectively. Similarly, ZLN regimen was received by 78.37%, 8.10%, 10.81% and 2.70% patients of euthyroid, hypothyroid, sick euthyroidand hyperthyroid respectively. The results were not significant which was similar to our study.

Similar non-significant results between drug regimen and thyroid abnormality were also observed by Afhami et al,[22] who found no association of these drug regimens. Similar results were obtained by Ketsamathiet al,[14] in his study. However, Beltran et al,[7] in their study reported a statistically significant relationship between subclinical hypothyroidism with ARV containing stavudine and the degree of immunodeficiency. The cumulative daily dose of stavudine and lamivudine were found to be significantly higher in patients with hypothyroidism than in those without it.

CONCLUSION

In the present study we observed the prevalence of thyroid dysfunction in the study population to be 15%. Subclinical hypothyroidism was the most common abnormality observed. This suggests that people with HIV on HAART should be screened for thyroid dysfunction. There was significant variation observed in the CD4 count and thyroid status, signifying that low

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Annals of International Medical and Dental Research
E-ISSN: 2395-2822 | P-ISSN: 2395-2814
Vol-7, Issue-3 | May-June, 2021
Page no- 103-111 | Section- Research Article (Medicine)

CD4 cell count was a risk factor for hypothyroidism. An inverse relation seen between CD4 and TSH counts which attained the level of significance which implies that as the value of CD4 count decreases, the levels of TSH increased. This indicates trend for hypothyroidism as HIV disease progresses. Since patients on HAART have high prevalence of thyroid dysfunction, larger studies are needed to confirm the findings to examine the epidemiology and health consequences of mild thyroid dysfunction in HIV infected patients.

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Source of Support: Nil, Conflict of Interest: None declared

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