Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Feb 19; 11(B):376-379.
https://doi.org/10.3889/oamjms.2023.11511
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Infective Disease*

Effect of Antiretroviral Therapy to Thyroid Function Status on New Stage 1 and 2 Human Immunodeficiency Virus Patient

Melati Silvanni Nasution[1]*, Dharma Lindarto[1], Tambar Kembaren[2]

[1]*Endocrine, Metabolic and Diabetes Division, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia;* [2]*Tropical Medicine and Infectious Disease Division, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia*

Edited by: Ksenija Bogoeva-Kostovska
Citation: Nasution MS, Lindarto D, Kembaren T. Effect of Antiretroviral Therapy to Thyroid Function Status on New Stage 1 and 2 Human Immunodeficiency Virus Patient. Open Access Maced J Med Sci. 2023 Feb 19; 11(B):376-379. https://doi.org/10.3889/oamjms.2023.11511
Keywords: Human immunodeficiency virus; Antiretroviral therapy; Thyroid function test
***Correspondence:** Melati Silvanni Nasution, Endocrine, Metabolic and Diabetes Division, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
E-mail: melati.silvanni@usu.ac.id
Received: 29-Jan-2023
Revised: 06-Feb-2023
Accepted: 09-Feb-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Thyroid hormone is very important in regulating energy metabolism in all tissues of the human body. Thyroid dysfunction plays an important role in osteoporosis, hyperlipidemia, and cardiovascular disease, all of which are associated with human immunodeficiency virus (HIV) infection or therapy for HIV. Medications used to treat HIV infection are also said to be important factors that can cause thyroid abnormalities.

AIM: This study aim is to see the effect of giving antiretroviral therapy (ART) to the thyroid function of new HIV patients in stage 1 and 2.

METHODS: This prospective cohort study was conducted at Medan city health center and Medan Haji Adam Malik Hospital in March–June 2019. HIV patients who met the inclusion criteria were tested for thyroid function (Ft4 and thyroid-stimulating hormone [TSH]) before and after 3 months on ART, body mass index (BMI), routine blood, CD4, and quality of life using the SF-36 questionnaire. Data analysis used paired t-test and Pearson correlation.

RESULTS: Thirty-four patients with stage 1 and 2 HIV showed normal thyroid function; the average FT4 level was 1.03 ± 0.14 ng/dL; and the average TSH level was 1.44 ± 0.68 μIU/mL. After 3 months of ART, the mean thyroid function changes were obtained from the study subjects, where the mean FT4 results were 0.87 ± 0.13 ng/dL and the average TSH results were 1.76 ± 0.91 μIU/mL and the results were statistically significant with p 0.006 ($p < 0.05$). There was a statistically significant relationship between TSH and CD4 levels with BMI after ART administration ($p < 0.05$), but no statistically significant relationship was found between FT4 and BMI ($p = 0.957$). No statistically significant relationship was found between CD4 levels in study subjects and changes in fT4 levels ($p = 0.557$, $r = 0.104$) and TSH ($p = 0.267$, $r = 0.196$). There was also no significant difference in the quality of life of study subjects as seen from the SF-36 questionnaire both from changes in thyroid function and from CD4 levels.

CONCLUSION: Stage 1 and 2 HIV patients who are on ART for 3 months experienced thyroid dysfunction.

Introduction

Thyroid hormones are very important in regulating energy in all tissues of the human body [1]. The direct relationship between the immune system and the thyroid axis can take place both ways [2]. Thyroid hormones also play a role in producing cytokines such as γ-interferon, in terms of antibody production and *vice versa*, some leukocytes such as monocytes, have the ability to secrete thyroid-stimulating hormone (TSH) as used instead [2], [3]. Thyroid dysfunction can help in treating osteoporosis, hyperlipidemia, and cardiovascular disease, all of which are associated with human immunodeficiency virus (HIV) infection or therapy for HIV [4].

Pathogenesis that allows thyroid dysfunction in patients with HIV infection, among others, is caused by the destruction of the thyroid and/or pituitary tissue due to infection and neoplasms, interference with thyroid hormone secretion or secondary metabolism due to the debilitating effect of HIV virus disorders and involvement of thyroid function by substances therapeutic or cytokines. However, several recent studies have found that antiretroviral therapy (ART) is involved in the occurrence of thyroid dysfunction in HIV-infected patients [5].

Several studies have shown an association between ART therapy in HIV-infected patients with changes in thyroid function that shows a significant improvement in the prognosis of HIV and AIDS [6], [7]. If thyroid test abnormalities occur, they are usually asymptomatic in both adult and pediatric patients and are most associated with subclinical hypothyroidism. In particular, anti-retroviral containing stavudine has a direct effect on the production/metabolism of thyroid hormones, although the mechanism is still unclear. Nelson *et al*. reported that patients who received non-nucleoside reverse transcriptase inhibitors, especially efavirenz, tended to experience hyperthyroidism [8].

Until now, there has been no research that looks at how the function of thyroid in HIV patients receiving ART therapy in Indonesia, where the regimen of ART in Indonesia differs from in other countries. For

this reason, the researcher is interested in conducting research on how the effect of ART treatment on thyroid function in new HIV patients in stage 1 and 2.

Methods

This prospective cohort study was carried out in *Puskesmas kota Medan* and *RS Haji Adam Malik* Medan in March–June 2019. The target population was HIV-positive patients who went to *Pusyansus*. Populations reached are HIV-positive patients with stage 1 or stage 2 who have not received prior ART therapy during the study period. The sample or research subject is part of a population that meets the study's inclusion and exclusion criteria. The inclusion criteria were (1) patients newly infected with HIV, (2) patients who had never received ART therapy, (3) patients with stage 1 or stage 2 HIV, and (4) willing to participate in the study. The exclusion criteria are (1) patients with severe active opportunistic infections, (2) patients with neoplasia/malignancy associated with HIV, (3) patients with severe renal and hepatic dysfunction, and (4) patients with the use of medications which interfere with the work of thyroid hormones such as beta-blockers, steroids, dopamine, rifampicin, and others.

HIV patients who met the inclusion criteria were tested for thyroid function (FT4 and TSH) before and after 3 months of taking ART, body mass index (BMI), routine blood, CD4, and quality of life using the SF-36 questionnaire. Data analysis uses the mean ± SD for normally distributed data and paired t-tests for data that are not normally distributed. Correlation analysis uses Pearson correlation for normally distributed data and Spearman for data that is not normally distributed.

Results

The study was participated in by 34 subjects, namely, patients infected with HIV in stages 1 and 2 who had not received prior ART therapy. From the basic characteristics found, the majority of research subjects were 32 males (94.12%) and two females (5.88%), with an average age of 28.7 ± 7 years. Based on BMI, the HIV patients studied were mostly normal weight (47.1%), followed by underweight (23.5%), overweight (17.6%), and first-degree obesity (11.8%). The largest source of transmission came from heterosexuals of 21 people (61.8%) followed by homosexuals of 13 people (38.2%).

From laboratory tests, the average Hb was 14.2 ± 1.8 g/dL, leukocytes 6237 ± 2291 cells/mm^3, platelets 270147 ± 64979 cells/mm^3, and CD4 358 ± 168 cells/μL. While from thyroid function examination, the average initial TSH level was 1.44 ± 0.68 μIU/mL and the initial FT4 level was 1.03 ± 0.14 ng/dL. All HIV patients use the same drug regimen, namely, the TDF+ 3TC + EFV regimen. Patients have also examined the quality of life with the SF-36 questionnaire and obtained in the physical health domain of 23 patients (67.6%) with good quality, ten patients (29.4%) with fair quality, and one patient (2.9%) with poor quality. Whereas in the mental health domain, it was found that 13 people (38.2%) had good and fair quality and five patients (14.7%) had poor quality (Table 1).

Table 1: Characteristics of research subjects

Category	n = 34
Gender (%)	
Male	32 (94.1%)
Female	2 (5.9%)
Age (year)[a]	28.7 ± 7.0
Body mass index (kg/mm^2)	
Underweight (<18.5)	8 (23.5%)
Normal weight (18.5–22.9)	16 (47.1%)
Overweight (23–24.9)	6 (17.6%)
Obesity I (25–29.9)	4 (11.8%)
Obesity II (≥30)	0
Transmission (%)	
Heterosexual	21 (61.8%)
Homosexual	13 (38.2%)
Hb (g/dL)[a]	14.2 ± 1.8
WBC (sel/mm^3)[a]	6237 ± 2291
Trombosit (sel/mm^3)[a]	270147 ± 64979
CD4 (sel/μL)[a]	358 ± 168
fT4 (ng/dL)[a]	1.03 ± 0.14
TSH (μIU/mL)[a]	1.44 ± 0.68
Type of ARV	
TDF+3TC+EFV	34 (100%)
AZT+3TC+EFV	0 (0%)
TDF+3TC+NVP	0 (0%)
Quality of life	
Physical domain	
Good	23 (67.6%)
Fair	10 (29.4%)
Poor	1 (2.9%)
Mental domain	
Good	13 (38.2%)
Fair	13 (38.2%)
Poor	5 (14.7%)

[a]normal distribution, mean ± SD.

Initial thyroid function in the study subjects was within normal limits, where the average fT4 level was 1.03 ± 0.14 ng/dL and the average TSH level was 1.44 ± 0.68 μIU/mL. After 3 months of ART, mean thyroid function changes were obtained from the study subjects, where the average fT4 yield fell from 1.03 ± 0.14 to 0.87 ± 0.13 ng/dL and the average TSH result the average increased from 1.44 ± 0.68 to 1.76 ± 0.91 μIU/mL and the results were statistically significant with $p = 0.006$ ($p < 0.05$) (Table 2).

There was a statistically significant relationship between TSH and CD4 levels with BMI after ART administration ($p < 0.05$), but no statistically significant relationship was found between fT4 and BMI ($p = 0.957$) (Table 3).

Table 4 shown that no significant differences occurred in the quality of life of the study subjects as seen from the SF-36 questionnaire both from changes in thyroid function and from CD4 levels. This occurs in both dimensions of quality of life, namely, the dimensions of physical health and mental health dimensions.

Table 2: Comparison of thyroid function tests before and after administration of ARVs

Parameter	P1	P2	p
fT4 (ng/dL) [a]	1.03 ± 0.14	0.87 ± 0.13	0.006*
TSH (μIU/mL) [a]	1.44 ± 0.68	1.76 ± 0.91	0.006*

Paired t-test, [a]normal distribution, mean ± SD, *p<0.05.

Table 3: Correlation of BMI with thyroid function test and CD4 levels after giving ART

Parameter	IMT r	p
fT4 (ng/dL)	0.01	0.957
TSH (μIU/mL)	0.39	0.020*
CD4 (sel/μL)	0.45	0.007*

Pearson correlation, *p<0.05

Table 4: Correlation of thyroid function test and CD4 levels with quality of life (SF-36)

Parameter	Dimensions of physical health r	P	Dimensions of mental health r	p
fT4 (ng/dL)	−0.104	0.558	−0.281	0.107
TSH (μIU/mL)	0.088	0.621	0.226	0.198
CD4 (sel/μL)	0.165	0.350	0.164	0.355

Spearman correlation

Discussion

HIV infection has long been known to be associated with disorders of the endocrine system. Before the era of ART use, these disorders were usually associated with opportunistic infections such as cytomegalovirus and tuberculosis infections. In the era of ART, more complex situations occur, where many patients experience insulin resistance, diabetes, sex hormone abnormalities, and osteoporosis, but it is not known how these conditions occur. And in recent years, thyroid dysfunction has been reported to increase the prevalence of abnormal thyroid function tests, especially subclinical hypothyroidism in both adults and children on ART.

In this study, from 34 newly HIV patients in stages 1 and 2, no thyroid dysfunction was found in all patients from the start of the study before being given ART and all patients were in a stable condition. This can be seen from all new HIV patients in stage 1 and 2 who have not yet received ART showing thyroid function within normal limits. These results are not in accordance with a study conducted by Noureldeen *et al*., 2012 [9], where they found 70% of HIV patients who had not received ART showed normal thyroid function. This was also the case with research conducted by Madge *et al*. 2007 [10]. They found that 75.5% of HIV patients who had not received ART had normal thyroid function as well. The differences that occur may be due to the long duration of suffering from HIV infection in this study. The differences that occur may be due to the long duration of suffering from HIV infection in this study, where in the previous studies conducted on patients with a duration of suffering from HIV for more than 1 year, while in this study conducted on HIV patients who were newly diagnosed with HIV.

After 3 months of ART, HIV patients are re-examined for thyroid function. This study found a decrease in FT4 levels and an increase in TSH levels in only 4 patients. This indicates the occurrence of a state of hypothyroidism in HIV patients after taking ART for 3 months. This study is in accordance with a study conducted by Madeddu *et al*., 2016 [11], in which the highest incidence of subclinical hypothyroidism was found in HIV patients who had been treated with ART.

Thyroid function is known to be related to nutritional status. Starvation triggers euthyroid sick syndrome (ESS) where the mechanism is still unclear. However, it is said that protein and/or carbohydrate intake is important to balance normal levels of thyroid hormone [12]. In this study, there was a statistically significant relationship between TSH and CD4 levels with BMI after ART administration ($p < 0.05$), but no statistically significant relationship was found between fT4 and BMI ($p = 0.957$). A study by Raffi *et al*., 1991 reported that FT3 levels were associated with BMI, and were interpreted as ESS. Ricart-Engel *et al.*, in 1996, also reported low T3 and rT3 levels in malnourished HIV patients.

In this study, all HIV patients received the same ART therapy, tenofovir (TDF) plus lamivudine (3TC), and efavirenz (EFV). No patient took a protease inhibitor (PI). Verma *et al*., in 2017, found a significant association between thyroid dysfunction and the administration of TLE regimens (Tenofovir, lamivudine, and efavirenz) in HIV patients given for more than 1 year. They also found that thyroid dysfunction was associated with the administration of the ZLN regimen (Zidovudine, lamivudine, and evafirenz) if given <1 year. Similar results were also found by Shujing *et al*., 2016, where thyroid dysfunction was more common in older ART users (41/140, 39.4%) than patients who were recently on ART (naïve ART) (18/74, 24.3 %) with $p < 0.05$.

Protopopescu *et al*., in 2007, reported the results of his research on the quality of life for 5 years in 1000 participants using SF-36. Quality of life, both in terms of physical, and mental aspects of HIV patients increase during the 1st year of therapy and are relatively stable in subsequent years. In contrast to the results of a cohort study conducted by Liu *et al*., reported, the quality of life in the physical health dimension after taking ART did not improve but was lower than before undergoing such therapy, while a significant increase occurred in the mental health dimension after 4 years on ART. Age, low socioeconomic status, chaperones, drinking habits, and the stage of a disease that developed became a significant predictor of the low SF-36 score in physical health dimensions.

The strength of this study is that it is the first study in Indonesia to examine thyroid function in HIV patients who are just getting the ART. The weaknesses of this study are first, the sample studied is very small, which does not present the overall HIV patients in stages 1 and 2. Second, the duration of the study is only briefly for 3 months. Third, there were no ART variations from this study, where all samples used only one type of ART regimen.

Conclusion

Found the influence of giving anti-retroviral therapy (ART) to thyroid function tests in patients with HIV stage 1 and 2, where there is a decrease in FT4 levels and an increase in TSH levels after 3 months ART therapy.

References

1. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev. 2001;81(3):1097-142. https://doi.org/10.1152/physrev.2001.81.3.1097
   PMid:11427693
2. Klecha AJ, Genaro AM, Lysionek AE, Caro RA, Coluccia AG, Cremaschi GA, *et al*. Experimental evidence pointing to the bidirectional interaction between the immune system and the thyroid axis. Int J Immunopharmacol. 2000;22(7):491-500. https://doi.org/10.1016/s0192-0561(00)00012-6
   PMid:10785546
3. Klecha AJ, Genaro AM, Gorelik G, Arcos ML, Silberman DM, Schuman M, *et al*. Integrative study of hypothalamus-pituitary-thyroid-immune system interaction: Thyroid hormone-mediated modulation of lymphocyte activity through the protein kinase C signaling pathway. J Endocrinol. 2006;189(1):45-55. https://doi.org/10.1677/joe.1.06137
   PMid:16614380
4. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Lo Y, Klein RS, *et al*. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. AIDS. 2007;21(5):617-23. https://doi.org/10.1097/QAD.0b013e3280148c05
   PMid:17314524
5. Madeddu G, Spanu A, Chessa F, Calia GM, Lovigu C, Solinas P, *et al*. Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): A longitudinal study. Clin Endocrinol (Oxf). 2006;64(4):375-83. https://doi.org/10.1111/j.1365-2265.2006.02472.x
   PMid:16584508
6. Harslof M, Knudsen AD, Benfield T. No evidence of increased risk of thyroid dysfunction in well treated people living with HIV. AIDS. 2018;32(15):2195-9. https://doi.org/10.1097/QAD.0000000000001954
   PMid:30005023
7. Santisteban P. Development of the hypothalamic-pituitary-thyroid axis. In: Braverman LE, Cooper DS, editors. Thyroid a Fundamental and Clinical Text. 10th ed. United States: Lippincott Williams and Wilkins; 2013.
8. Nelson M, Powles T, Zeitlin A, Sen P, Scourfield A, Bower M, *et al*. Thyroid dysfunction and relationship to antiretroviral therapy in HIV-positive individuals in the HAART era. J Acquir Immune Defic Syndr. 2009;50(1):113-4. https://doi.org/10.1097/QAI.0b013e31818ce835
   PMid:19092451
9. Noureldeen AF, Qusti SY, Khoja GM. Thyroid function in newly diagnosed HIV-infected patients. Toxycol Ind Health. 2012;30(10):919-25. https://doi.org/10.1177/0748233712466133
   PMid:23188649
10. Madge S, Smith CJ, Lampe FC, Thomas M, Johnson MA, Youle M, *et al*. No association between HIV disease and its treatment and thyroid function. HIV Med. 2007;8(1):22-7. https://doi:10.1111/j.1468-1293.2007.00422.x
    PMid:17305928
11. Madeddu G, Spanu A, Chessa F, Calia GM, Lovigu C, Solinas P, *et al*. Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): A longitudinal study. Clin Endocrinol (Oxf). 2006;64(4):375-83. https://doi.org/10.1111/j.1365-2265.2006.02472.x
    PMid:16584508
12. Ricart-Engel W, Fernandez-Real JM, Gonzalez-Huix F, Del Pozo M, Mascaro J, Garcia-Bragado F. The relation between thyroid function and nutritional status in HIV-infected patients. Clin Endocrinol (Oxf). 1996;42(1):1270-6. https://doi.org/10.1046/j.1365-2265.1996.623445.x
    PMid:8706293