*Sys Rev Pharm 2020; 11(3): 635 – 639*
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

# TSH, FT4, and CD4 Profile in HIV/AIDS Patients Before and After Antiretroviral Fixed-Dose Combination Tenofovir, Lamivudine, Evafirenz Therapy

Djati Susilo[1], Sony Wibisono[2*], Usman Hadi[3]

[1]Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

[2]Endocrine and Metabolic Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

[3]Tropical Disease and Infection Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia

*Article History:* *Submitted: 02.01.2020* *Revised: 12.02.2020* *Accepted: 15.03.2020*

## ABSTRACT

HIV infection can cause thyroid abnormality, and the use of Antiretroviral (ARV) can make it worse. The objective of this study was to identify the difference of thyroid profile level in HIV/AIDS before and after fixed-dose combination (FDC) therapy. This was a descriptive longitudinal observational study using one group pretest and posttest comparative design involving 20 samples. The subjects were all HIV/AIDS patients receiving ARV FDC but never received such therapy before. The mean age of the subjects was 32.9±9.19 years, with a range of 20-50 years. The majority of the subjects were males 15 (75%) and the most risk factor was vaginal sex as much as 11 subjects (55%). TSH and FT4 mean levels before therapy were 1.1±0.22 µIU/ml FT4 and 1.15±0.17 ng/dl, respectively and after receiving FDC ARV were of 2.34±1.23 µIU/ml and 1.01 ± 0.14 ng/dl, respectively. There were significant differences in TSH (p = 0.000), FT4 (p = 0.012), and CD4 (p = 0.000) in HIV/AIDS patients before and after receiving FDC ARV for 3 months. There was a significant difference in thyroid profile before and 3 months after received ARV FDC.

**Keywords:** HIV/AIDS, thyroid profile abnormality, antiretroviral

**Correspondence**:
Sony Wibisono
Endocrine and Metabolic Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
E-mail: sonywibisono@yahoo.com

**DOI:** 10.31838/srp.2020.3.85



## INTRODUCTION

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) has a high mortality rate and is the fourth leading cause of death in the world. Besides, HIV is rapidly growing, chronic, progressive and serious illness compared with other diseases.(1,2) However, the discovery of Highly Active Anti-Retroviral Therapy (HAART), or commonly called antiretroviral (ARV), is given to decrease the viral load in the blood. This helps to reduce the damage caused by HIV.(3,4) Almost 37.9 million people are living with HIV worldwide and it is estimated that 36.2 million of them are adults aged 15–49 years. Also, data in 2018 showed that there were 1.7 million new infections of HIV and around 770, 000 people have died because of AIDS-related illnesses.(2) However, there are still some obstacles in the treatment of HIV patients who take ARVs. Also, HIV/AIDS prevention is very important and necessary.(5)

The incidence of thyroid abnormalities in HIV patients is about two to three times the general population. This condition is exacerbated by the use of ARVs. Various spectrums of thyroid abnormalities that often arise include overt hypothyroidism, subclinical hypothyroidism, isolated low Free Thyroxine (FT4)

and euthyroid sick syndrome (ESS). The detection of thyroid abnormalities is often difficult so that it increases the morbidity and mortality of HIV/AIDS patients.(6–8) Some studies recommended examining thyroid status in HIV patients to reduce morbidity and mortality, but until now there have been no official recommendations, both national and international, which suggest that data is still lacking and many aspects still need further investigation.(7,9)

The cause of the emergence of this thyroid disorder itself, the HIV/AIDS, can lead to a chronic inflammatory process that affects the secretion of thyroid hormones, as similar with other infections,(10,11) and is exacerbated by the use of antiretroviral drugs through a disruption mechanism in the process of production and metabolism of thyroid hormone itself. Thyroid dysfunction in HIV patients can reduce the quality of life, increase morbidity and mortality.(12)

Thyroid hormones affect the body's immune system, where the process of maturation, differentiation, and activation is influenced by the levels of the thyroid hormones present. Besides, the incidence of cardiovascular disease due to hypothyroid and subclinical hypothyroidism is increasing, so thyroid profiles are important to evaluate.(13–15) This study aims to examine differences in thyroid profile level, represented by thyroid-stimulating hormone (TSH) and FT4, in HIV patients before and after 3 months of ARV therapy, especially those receiving the fixed-dose combination FDC (tenofovir, lamivudine, efavirenz) regimen as first-line treatment based on the 2015 Minister of Health Regulation.

## METHODOLOGY

This study was a longitudinal observational study using one group pretest and posttest the design. The purpose of this study was to determine differences in TSH and FT4 levels before and 3 months after the administration FDC ARV. The study was conducted in the Outpatient Clinic of Infectious Disease Intensive Care, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia. Data were collected from May to September 2018.

The study population was patients diagnosed with HIV/AIDS who visited the Outpatient Clinic, Infectious Disease Intensive Care, Dr. Soetomo Hospital, Surabaya, Indonesia. Samples were patients diagnosed with

HIV/AIDS who visited the clinic from May to September 2018, who met the inclusion and exclusion criteria. Sampling in this study was conducted by consecutive sampling. If there were patients who met the inclusion and exclusion criteria in the population, the patients would be immediately included in the study. The number of the samples taken were total samples in the predetermined period.

The inclusion criteria in this study were HIV/AIDS patients who had not received ARV therapy in the Outpatient Clinic, Infectious Disease Intensive Care, Dr. Soetomo Hospital, Surabaya, Indonesia, between May - September 2018 according to Karnofsky performance status scale 80-100, patients aged 18-50 years, history taking can be performed on the patients, and the patients are willing to take part in the study by signing informed consent.

Exclusion criteria were patients undergoing ARV therapy, receiving anti-thyroid drugs and thyroid hormone agonists, consuming phenytoin, carbamazepine, amiodarone, ethionamide, PAS interferon, being critically ill or experiencing severe acute infection, having a history of routine alcohol use and smoked, had undergone thyroidectomy, had tuberculosis treatment with rifampicin regimen, had chronic diarrhea, was in a state of pregnancy, had liver disease/impaired liver function and chronic kidney disease, disobeying ARV treatment rules, having poor compliance and or loss to follow up, having adverse events that cause harm and/or hazard to life health and safety-related to ARV drugs used, and refusing to continue research for any reason.

Before the analysis, the normality of the data was tested. If the available data were normally distributed, a paired T-test was carried out and if the available data were abnormally distributed then the data were subjected to the Wilcoxon test. Paired T or Wilcoxon tests were used to compare TSH and FT4 levels before and 3 months after receiving FDC ARV therapy. The statistical test was regarded as significant if $p<0.05$.

## RESULTS

The general characteristics of the subjects were shown in Table 1. The mean age of the subjects was 32.9 ± 9.19 years, with the youngest being 20 years and the oldest 50 years. The majority of the subjects were males, 15 (75%), and the most risk factor was vaginal sex as much as 11 subjects (55%). Regarding the WHO clinical stage, subjects with clinical stage 1 were 5 subjects (25%), clinical stadium 2 were 13 subjects (65%), clinical-stage 3 were 2 (10%), and none of the subjects had clinical stage 4. Subjects with a CD4 cell count of less than 200 were 12 (60%), 4 subjects (20%) were in CD4 range of 200-349, 4 subjects (20%) were in CD4 range of 350-499 and none of the subjects had CD4 above 500.

TSH and FT4 levels were examined before and 3 months after receiving FDC ARV. Subjects' TSH and FT4 levels before receiving FDC ARV showed TSH mean levels of 1.1 ± 0.22 µIU/ml with normal data distribution. The FT4 level had mean value of 1.15 ± 0.17 ng/dl with normal data distribution. There was 1 subject (5%) with isolated low FT4 in the sample before receiving FDC ARV. TSH and FT4 levels of the subjects after receiving FDC ARV showed mean TSH of 2.34 ± 1.23 µIU/ml with normal data distribution. FT4 levels showed mean value of 1.01 ± 0.14 ng/dl with normal data distribution. There were 2 subjects (10%) with isolated low FT4, 2 subjects (10%) with subclinical hypothyroidism, and 1 subject (5%) with overt hypothyroidism (Table 2).

The difference of TSH before and three months after receiving FDC ARV treatment had normal data distribution, we used paired comparative T-test to analyze the difference. Comparative analysis between TSH and FT4 level in month 0 and month 3 in this study can be seen in Table 3. The table showed that there were significant differences in TSH, FT4, and CD4 with $p = 0.000$; $p = 0.012$; $p = 0.000$, respectively, in HIV/AIDS patients after receiving FDC ARV for 3 months.

## DISCUSSION AND CONCLUSION

Findings from this study showed significant differences in TSH and FT4 levels before and after 3 months of treatment with FDC ARV. Thyroid profile abnormalities, such as overt hypothyroidism, subclinical hypothyroidism, and isolated low FT4, were found more in patients after ARV treatment. This indicates that thyroid profile abnormalities can occur in the first 3 months of consuming FDC ARV. There were significant differences in CD4 before and 3 months after receiving FDC ARV, where the mean post-FDC ARV treatment had a higher CD4 value. CD4 count was the most important biomarker of disease stage and progression in patients with an HIV infection.(16) Thyroid abnormalities were found more in CD4 >200, i.e. in patients after 3 months of ARV treatment.

In this study, the mean age of the subjects was in the range of 20-50 years. This is in accordance with statistical data from the Ministry of Health in 2017 that most individuals with HIV ranged in age from 25-49 years.(8) We limited the age in this study, because of the older the age, the higher the incidence of thyroid abnormalities. Besides, the number of individuals with HIV/AIDS in older age is also low. The majority of the subjects were males. Based on the data from the Ministry of Health in 2017, most individuals with HIV/AIDS were males with ratio male: female 2:1, probably because of the high risk of risky vaginal sex and anal sex, where the key group was the homosexual males with risky anal sex.(8,17)

The risk factor characteristics of this study were found with risky anal sex, and risky vaginal sex. None of our research subjects had risk factors for injecting drugs, because even in the world HIV/AIDS risk factors in the form of injecting drug use is declining, perhaps due to increased alertness among injecting drug users to HIV/AIDS infection.

Among 20 subjects in this study, most subjects were in clinical stage 2 and no subject with clinical stage 4. There were none of our study subjects with clinical stage 4 because our inclusion criteria were outpatients with good performance status. We also excluded the condition of patients with severe active infections, because it could become a confounding result of thyroid function examination. The clinical progression in HIV patients

receiving treatment is estimated by the different levels of viral load and CD4 count.(3)

Isolated low FT4 is one of the thyroid disorders quite often found in patients with HIV/AIDS. TSH levels before the starting of the treatment could be different between studies. This could result from several factors, including the method of TSH examination. Previous studies revealed that immunoassay examination for TSH measurements used different calibrations. Also, human TSH has different glycoforms, so that a different immunoassay examination may detect the TSH differently. This condition causes difficulty in the standardization of examinations and the presence of different results between each individual.(18) The results of the examination of thyroid profiles in the 3rd month could be regarded as quite significant, and, according to the theory we have discussed, there were significant thyroid abnormalities compared with the results before receiving FDC ARVs.(19,20)

In the post-treatment sample, subjects with CD4 levels <200 were decreased and those with CD4 >200 were increased. This increase in CD4 levels may indicate that the subjects were disciplined enough to take medication. The previous study obtained a correlation between CD4 and thyroid profile.(13) A study in India also found a correlation between CD4 and FT4. These findings differed from the findings of our study, where the number of subjects with CD4 <200 decreased after administration of ARV for three months and the population with CD4 levels >200 increased, where thyroid profile abnormalities were mainly obtained in patients with CD4 levels >200. There are remain a challenge to control the HIV epidemic in developing countries due to the financial burdens for people living with HIV in accessing and receiving HIV care.(3)

There were significant differences in thyroid profile and CD4 before and 3 months after receiving ARV FDC, but the etiology of thyroid disturbances cannot be explained, if its caused by ARV or HIV infection itself. Future studies need to include periodic physical examinations with the ultrasound of the thyroid gland to help establish the occurrence of side effects in the thyroid gland; exclude confounding factors such as direct infection of the thyroid gland, radiological mass in the thyroid gland, and thyroid peroxidase antibody examination to rule out other causes of increased TSH; and the use of better research methods, such as prospective cohort analysis, with longer periods and involving control groups.

## ACKNOWLEDGMENT

The authors thank Poernomo Budi Setiawan, MD, the Head of the Department of Internal Medicine, Universitas Airlangga, to Prof. Agung Pranoto, MD, Ph.D., the Head of Endocrine and Metabolic Division of the Department of Internal Medicine for valuable advice for this research, and Musofa Rusli, MD, Head of the Intermediary and Infectious Disease Treatment Unit, Dr. Soetomo Hospital, Surabaya, and all the nursing staff.

## REFERENCES

1. Ardianto A, Khairunisa SQ, Kotaki T, Witaningrum AM, Qushay M, Juniastuti J, et al. The Prevalence Of Human Immunodefiency Virus-1 (Hiv-1) Subtypes And Transmission Method Among Hiv/Aids Infection Patient In Tulungagung, East Java Indonesia. Indones J Trop Infect Dis. 2015;5(5):124–8.
2. Latif AI, Irwan AM. Models and benefits of palliative care for the quality of life of people with hiv: A systematic review. HIV Nurs [Internet]. 2019;19(4):80–5. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85078775535&partnerID=40&md5=d5951b0c3a15fb78c3e7d9418ca285a8
3. Lubis R, Bulgiba AM. Anti-retroviral therapy of HIV infected patients. J Heal Transl Med [Internet]. 2014;17(1):18–22. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84920691942&partnerID=40&md5=2e7e9f9a7509ce0a24e84959a14756c5
4. Kembaren T. The role of drugs in HIV prevention. In: IOP Conference Series Earth and Environmental Science. 2018.
5. Toetik Koesbardiati, Kinasih SE, Mas'udah S. Integrating The Roles Of Stakeholders In Preventing The Hiv/Aids Transmission In East Java, Indonesia. Indones J Trop Infect Dis. 2017;6(5):124–30.
6. Ketsamathi C, Jongjaroenprasert W, Chailurkit L, Udomsubpayakul U, Kiertiburanakul S. Prevalence of thyroid dysfunction in Thai HIV-infected patients. Curr HIV Res [Internet]. 2006 Oct;4(4):463–7. Available from: https://pubmed.ncbi.nlm.nih.gov/17073621
7. Bongiovanni M, Adorni F, Casana M, Tordato F, Tincati C, Cicconi P, et al. Subclinical hypothyroidism in HIV-infected subjects. J Antimicrob Chemother [Internet]. 2006/09/01. 2006 Nov;58(5):1086–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16950823
8. Rastogi, P., Singhal, R., Sethi, A., Agarwal, A., Singh, V.K., Sethi, R. Assessment of the effect of periodontal treatment in patients with coronary artery disease : A pilot survey (2012) Journal of Cardiovascular Disease Research, 3 (2), pp. 124-127. DOI: 10.4103/0975-3583.95366
9. Indonesia Ministry of Health. Infodatin AIDS. Jakarta: Ministry of Health; 2017.
10. Collaboration H-C, Ray M, Logan R, Sterne JAC, Hernández-Díaz S, Robins JM, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. AIDS [Internet]. 2010 Jan 2;24(1):123–37. Available from: https://pubmed.ncbi.nlm.nih.gov/19770621
11. Uotani T, Miftahussurur M, Yamaoka Y. Effect of bacterial and host factors on Helicobacter pylori eradication therapy. Expert Opin Ther Targets. 2015;19(12):1637–50.
12. Miftahussurur M, Yamaoka Y. Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev

Gastroenterol Hepatol. 2015;9(12):1535.
13. Sprinz E, Lazzaretti RK, Kuhmmer R, Ribeiro JP. Dyslipidemia in HIV-infected individuals. Brazilian J Infect Dis. 2010;14(6):575–88.
14. Beltran S, Lescure F-X, Desailloud R, Douadi Y, Smail A, El Esper I, et al. Increased prevalence of hypothyroidism among human immunodeficiency virus-infected patients: a need for screening. Clin Infect Dis [Internet]. 2003/07/28. 2003 Aug 15;37(4):579–83. Available from: https://pubmed.ncbi.nlm.nih.gov/12905143
15. Mezosi E, Szabo J, Nagy E V, Borbely A, Varga E, Paragh G, et al. Nongenomic effect of thyroid hormone on free-radical production in human polymorphonuclear leukocytes. J Endocrinol [Internet]. 2005 Apr;185(1):121–9. Available from: https://pubmed.ncbi.nlm.nih.gov/15817833
16. Miyake S, Yamamura T. NKT cells and autoimmune diseases: unraveling the complexity. Curr Top Microbiol Immunol [Internet]. 2007;314:251–67. Available from: https://pubmed.ncbi.nlm.nih.gov/17593664
17. Lumbanraja SN, Siregar DIS. Association between red blood cell indices and CD4 count in HIV-positive reproductive women. In: IOP Conf Series: Earth and Environmental Science [Internet]. Institute of Physics Publishing; 2018. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85045672326&doi=10.1088%2F1755-1315%2F125%2F1%2F012027&partnerID=40&md5=f3d9f7b9374edf2337a3c2986a60e23d
18. Davies SC, Madjid B, Pardohudoyo S, Wiraguna AAGP, Patten JH, Upadisari LP. Prevalence of sexually transmissible infections (STI) among male patients with STI in Denpasar and Makassar, Indonesia: Are symptoms of urethritis sufficient to guide syndromic treatment? Sex Health [Internet]. 2007;4(3):213–5. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-34548361877&doi=10.1071%2FSH07017&partnerID=40&md5=9fdf34f1f1a1ffb85e29940634108e8d
19. Saravanan P, Dayan CM. Thyroid autoantibodies. Endocrinol Metab Clin North Am. 2001;30(2):315–37.
20. Erhirhie, Earnest Oghenesuvwe, Chinwuba Paul, and . 2019. Edible Insects' bio-actives as anti-oxidants: Current status and perspectives.. Journal of Complementary Medicine Research, 10 (2), 89-102. doi:10.5455/jcmr.20190130100319
21. Collazos J, Ibarra S, Mayo J. Thyroid hormones in HIV-infected patients in the highly active antiretroviral therapy era: evidence of an interrelation between the thyroid axis and the immune system. AIDS [Internet]. 2003 Mar 28;17(5):763–5. Available from: https://pubmed.ncbi.nlm.nih.gov/12646804
22. 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) [Internet]. 2006 Apr;64(4):375–83. Available from: https://pubmed.ncbi.nlm.nih.gov/16584508

Table 1. General characteristics of subjects

| Characteristics | N (%) |
|---|---|
| Sex | |
| Male | 15 (75%) |
| Female | 5 (25%) |
| Age (years) | |
| Mean±SD | 32.9±9.19 |
| Median | 20-50 |
| Risk Factor | |
| Anal sex | 9 (45%) |
| Vaginal sex | 11 (55%) |
| Clinical Stage | |
| Stage 1 | 5 (25%) |
| Stage 2 | 13 (65%) |
| Stage 3 | 2 (10%) |
| Stage 4 | 0 |
| CD4 levels | |
| <200 | 12 (60%) |
| 200-349 | 4 (20%) |
| 350-499 | 4 (20%) |
| >500 | 0 |

Table 2. Distribution of TSH, CD4, FT4, and abnormalities in samples, pre and post

| | TSH (mean) | FT4 (mean) | Abnormalities |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Sample "pre" | 1.1 ± 0.22 µIU/ml | 1.15 ± 0.17 ng/dl | |
| CD4 <200 | | | 1 (5%) *isolated low FT4* |
| CD4 >200 | | | (-) |
| Sampel "post" | 2.34 ± 1.23 µIU/ml | 1.01 ± 0.14 ng/dl | |
| CD4<200 | | | (-) |
| CD4>200 | | | 2 (10%) isolated low FT4, 1 (5%) subclinical hypothyroid, 2 (10%) overt hypothyroid |

Table 3. Results of comparative test of thyroid profile and CD4, pre and post-test (paired sample test)

| | Mean | Sig (2-tailed) |
|---|---|---|
| TSH pre | 1.1 ± 0.22 µIU/ml | p = 0.000 |
| TSH post | 2.34 ± 1.23 µIU/ml | |
| FT4 pre | 1.15 ± 0.17 ng/dl | p = 0.012 |
| FT4 post | 1.01 ± 0.14 ng/dl | |
| CD4 pre | 196 ± 157.67 | p = 0.000 |
| CD4 post | 331.6 ± 179.2 | |