Tenofovir Lamivudine Efavirenz Side Effect and Its Efficacy Among People Living with HIV in Jayapura

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Abstract. Tenofovir lamivudine efavirenz (TLE) as a single-tablet regimen is preferred to the long use of combination antiretroviral therapy. TLE is safer than another antiretroviral drug regimen for first-line of Human immunodeficiency virus (HIV) treatment. However, there is little information about the side effects of TLE during first-time therapy among people living with HIV in Jayapura. This study aimed to assess the TLE side effect and its efficacy among people living with HIV in Jayapura, Papua. This was a cross-sectional study involving 77 people living with HIV who took a single-tablet regimen of TLE for one to two years of antiretroviral therapy, comply the inclusion criteria, and provided consent to participate. Data collection was conducted through CD4 + tests, medical records, and interviews at Jayapura City Hospital. Descriptive statistics were used to determine the proportion of relevant variables. The results described that most groups of people living with HIV were adult group (93.5%), female (61.0%), Papuan (64.9%), had WHO clinical stage III-IV (67.5%), had CD4 + counts $<$ 350 cell/μL in the early therapy (79.2%) and CD4 + counts $\geq$ 350 cell/μL at the time of the study (57.1%), and experienced TLE side effect (71.4%). The most symptoms of TLE side effects among people living with HIV were headache (61.8%), nausea (34.5%), and nightmare (29.1%). As many as 70.9% of people living with HIV experienced these symptoms for less than 2 weeks. TLE was still effective, indicated by an increase of CD4 + cell count average from 242.6 cell/mm^3 at the early therapy to 436.6 cell/mm^3 during this study, with good adherence to drug therapy (>95% adherence) by 53.2% of people living with HIV. The side effects of TLE can still be tolerated by most people living with HIV so the therapy can be continued without altering the regimen.

Keywords: Single-tablet regimen · tenofovir lamivudine efavirenz · HIV

1 Introduction

Human immunodeficiency virus (HIV) is still a major disease problem in Indonesia, especially in the province of Papua, which is a generalized epidemic area. HIV cases

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in Indonesia tend to increase from year to year. According to data from the Indonesian Ministry of Health in 2019, there were around 50,282 HIV cases spread throughout Indonesia, while the reported HIV cases in Papua were around 3,753 cases, ranking 5th for HIV cases among 34 provinces in Indonesia [1]. Meanwhile, until March 2021, the cumulative reported national HIV cases reached 427,201 where the number of people living with HIV who were still undergoing antiretroviral therapy was only around 6,758 out of a total of 269,289 people living with HIV who had started antiretroviral therapy [2]. The small number of people living with HIV who are actively undergoing antiretroviral therapy is still a problem in realizing the second 90 of the triple 90-90-90 HIV, initiated by The Joint United Nations Program on HIV/AIDS (UNAID), which must be achieved in 2020, where 90% of people living with HIV must get antiretroviral therapy treatment [3, 4].

Antiretroviral treatment can prevent and control HIV transmission by suppressing the amount of virus in the blood plasma even without eliminating the virus from the body [5, 6]. To maintain viral suppression, people living with HIV must take antiretroviral drugs for a long life through Highly active antiretroviral therapy (HAART). People living with HIV who undergo antiretroviral therapy through HAART are proven to have a better quality of life [7]. However, despite the benefits of antiretroviral therapy, people living with HIV face problems that arise due to undergoing HAART such as drug effects [8]. Generally, the side effects of antiretroviral drugs are central nervous system disorders, gastrointestinal system disorders, as well as skin and subcutaneous tissue disorders [9]. According to a previous study in Tanzania, Uganda, and Zambia, the presence of drug side effects is the most common reason for people living with HIV to forget to take antiretroviral [10]. In addition, other problems arise from the use of HAART in the form of multi tablet regimen that people living with HIV must take every day [11]. The combination of antiretroviral drugs in the form of a multi-tablet regimen makes people living with HIV feel dissatisfied with their HIV medication [12]. Drugs' side effects and the combination of multi-tablet regimens may lead people living with HIV to not comply with their therapy, and even the worst to stop taking antiretroviral drugs [13, 14]. Finally, low adherence to therapy potentially causes therapy failure and drug resistance [15].

Previous studies have revealed the efforts to design antiretroviral regimens that are still effective and relatively safe from drug side effects. One of these approaches is the simplification of the multi-tablet regimen to a single tablet regimen that people living with HIV only take one dose of a single tablet per day [16, 17]. Another study stated there was a significant relationship between the use of a single tablet regimen and a high level of adherence to antiretroviral therapy [18, 19]. The combination of lamivudine, tenofovir, and efavirenz (LTE) was the first of a single-tablet regimen approved for antiretroviral therapy, which has been reported to cause neuropsychiatric side effects [20]. The LTE is relatively safer because of its mild side effects than another multi-tablet regimen [21].

Previous studies reported the effectiveness of using LTE, such as a study in India reported the efficacy of using LTE was 98.7% and without major side effects [22], also in Africa, the use of LTE for more than 126 days showed virus suppression at undetectable levels [23]. The efficacy of TLE can be evaluated from the change of CD4 T

lymphocyte count during therapy. The increase in CD4 counts is related to viral load suppression. Another study reported high levels of viral suppression during antiretroviral therapy associated with CD4 cell counts above 500 cells/μL [24]. In addition, the CD4 count of people living with HIV began to increase significantly at 18 months of LTE therapy [25]. CD4 T lymphocytes play an important role in the activation, modulation, coordination, and regulation of adaptive and innate immune responses [26]. HIV infection directly attacks CD4 T lymphocytes. Infected CD4 cells will be damaged and cause immunosuppression. The process of CD4 cell deficiency will continue along with the development of HIV infection [27]. Antiretroviral treatment prevents the virus from replicating to multiply. This gives an opportunity for CD4 T lymphocyte cells to recover and the number to increase again [28].

Studies on the side effects and efficacy of using LTE in Papua are not widely known. This study aims to assess the side effects and efficacy of a single tablet regimen of TLE among people living with HIV in Jayapura. Studying the side effects and efficacy of ARVs used in HIV treatment programs in Indonesia will provide benefits such as information for stakeholders to help people living with HIV manage the side effects of ARVs during therapy. This could reduce loss to follow-up among people living with HIV taking antiretrovirals, enable them to adhere the medication, and prevent their chances of receiving intensive care in hospital due to the side effects of antiretroviral drugs. In addition, this can be a consideration for policy makers to use effective antiretrovirals with fewer side effects in HIV treatment programs.

2 Materials and Methods

2.1 Study Design and Participants

This study data was obtained from Risbinkes, the research funding from the Indonesian Ministry of Health. This was a cross-sectional study design. Data collection was carried out at the Voluntary counseling and testing service at Jayapura City Hospital in Papua from June to September 2017. The study involved people living with HIV who were actively undergoing antiretroviral therapy using a single tablet regimen containing tenofovir disoproxil fumarate 300 mg, lamivudine 300 mg, and efavirenz 600 mg (TLE) and met inclusion. The inclusion criteria were people living with HIV who underwent therapy for a period of one to two years, aged over 15 years, HIV-positive men or women, had a complete medical record, and were willing to participate in the study after informed consent. There are 77 participants who met with inclusion criteria from total 85 participant. The minimum sample size was determined by the Lemeshow formula with a population proportion of 70%, 95% confidence level, and 10% deviation.

2.2 Data Collection

Demographic data (age, gender, ethnicity), data on the experience of TLE side effects, duration of TLE side effects, and symptoms of TLE side effects among people living with HIV were obtained through structured interviews. Clinical data (CD4 at the start of therapy, WHO clinical stage) and medication adherence were obtained from medical

records. CD4 data during the study were obtained from the CD4 test using venous whole blood stored in the EDTA vacutainer from every people living with HIV. The CD4 test was measured by a CD4 counter tool following the manufacturer's operating instructions (BD FACS Presto, Becton Dickinson).

2.3 CD4 Cell Counting

Approximately 100 μl of whole blood (about 3 drops of blood) was placed into the well of cartridge of CD4 counter according to the sample code. Every cartridge containing the sample was incubated for 18 min at room temperature then each cartridge was inserted into the FACSPresto BD CD4 counting machine for analysis. The CD4 count results for each sample will automatically appear on the screen of CD4 counter machine and can be printed.

2.4 Statistical Analysis

The data of demographic, clinical, and symptomatic characteristics of LTE side effects among people living with HIV were analyzed statistically to describe the proportion of each variable using IBM SPSS Statistics 26. The normal distribution test was carried out on CD4 data at the beginning of therapy and CD4 at the time of the study, then continued with the Wilcoxon Signed Rank Test to determine the efficacy of LTE.

2.5 Ethical Approval

This research received ethical approval from the Health Ethics Committee of the Health Research and Development Agency of the Indonesian Ministry of Health, with reference number LB.02.01/2/KE.118/2017, on April 3, 2017.

3 Results

3.1 Demographic and Clinical Characteristics of Study Participants

Characteristics of participants in this study were generally dominated by people living with HIV from the adult age group (20–60 years old) 72 (93.5%), women 47 (61.0%), Papuan 50 (64.9%), had CD4 count < 350 cells/μL at the start of antiretroviral therapy 61 (79.2%), had CD4 count ≥ 350 cells/μL at time of study 44 (57.1%), had WHO clinical stage III-IV at the start of antiretroviral therapy 52 (67.5%), experienced with TLE side effects at the beginning of antiretroviral therapy 55 (71.4%), and had good adherence to antiretroviral therapy $> 95\%$ as much as 41 (53.2%) (see Table 1). While the general description of 55 participants who experienced drug side effects at the beginning of TLE therapy in this study was mostly people living with HIV from the adult age group (20–60 years old) 51 (92.7%), women 33 (60.0%), Papuan 35 (63.5), have a CD4 count < 350 cells/μL at the start of antiretroviral therapy 43 (78.2%), had WHO clinical stage III-IV at the start of antiretroviral therapy 35 (63.6%) and experiencing TLE side effects for less than 2 weeks 39 (70.9%).

Table 1. Demographic and clinical characteristics of study participants

Variable	Frequency (n = 77)	Percent (%)
Age group		
15–19 years old	4	5.2
20–60 years old	72	93.5
>60 years old	1	1.3
Gender		
Men	30	39.0
Women	47	61.0
Ethnicity		
Papuan	50	64.9
Not Papuan	27	35.1
Experienced with LTE side effects		
Yes	55	71.4
No	22	28.6
CD4 counts at the start of antiretroviral therapy		
<350 cell/μL	61	79.2
≥350 cell/μL	16	20.8
CD4 counts at the time of study		
<350 cell/μL	33	42.9
≥ 350 cell/μL	44	57.1
WHO clinical stage at the start of antiretroviral therapy		
Stadium I–II	25	32.5
Stadium III–IV	52	67.5
Adherence to antiretroviral therapy		
>95%	41	53.2
80–95%	13	16.9
<80%	23	29.9

3.2 Symptoms of TLE Side Effects Among Study Participants

People living with HIV in this study experienced symptoms of TLE side effects at the start of antiretroviral therapy such as headache 34 (61.8%), nausea 19 (34.5%), and nightmares 16 (29.1%), followed by symptoms of sleepy or drowsiness 12 (21.8%), vomiting 9 (16.4%), insomnia 8 (14.5%), allergies 6 (10.9%), loss of appetite 5 (9.1%), and diarrhea 3 (5.5%). In this study, we found there were some study participants who experienced more than one type of LTE side effect symptom (Table 2).

Table 2. Symptom of TLE side effect at the start of antiretroviral therapy among study participants

Symptoms of TLE side effects	Frequency (n = 55)	Percent (%)
Headache	34	61.8
Nausea	19	34.5
Nightmare	16	29.1
Sleepy	12	21.8
Vomiting	9	16.4
Insomnia	8	14.5
Allergy	6	10.9
Loss of appetite	5	9.1
Diarrhea	3	5.5

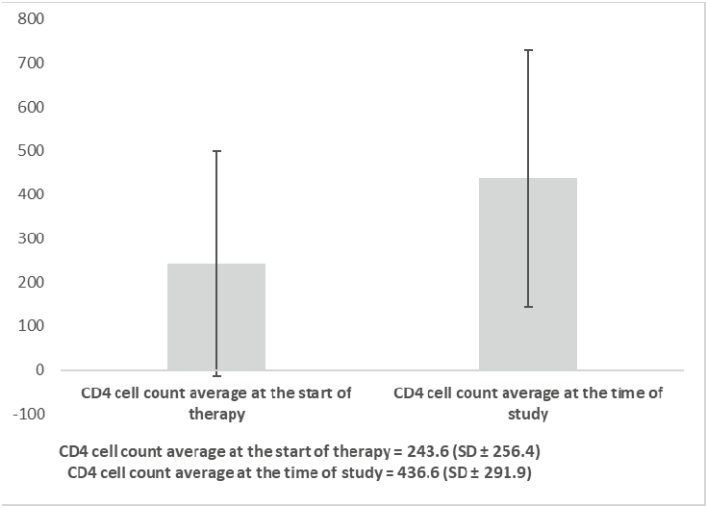

Fig. 1. Efficacy of TLE shown by the CD4 cell count among study participants increased after undergoing TLE therapy

3.3 The Efficacy of TLE Therapy Among Study Participants

Statistical results showed the CD4 cell count among people living with HIV increased after undergoing TLE therapy. The CD4 cell count average of people living with HIV at the start of therapy was 242.6 cells/μL (standar deviation (SD) ± 256.4) and changed to 436.6 cells/μL (SD ± 291.9) at the time of the study (Fig. 1). The results of the Wilcoxon Signed Rank Test showed a p-value of 0.000, with a significant p-value < 0.05, which indicates there was an effect of TLE therapy on the increase of CD4 count among people living with HIV, where 64 (83.1%) of people living with HIV experienced an increase in

CD4 count with a mean CD4 cell count 43 cells/μL and 13 (16.9%) of people living with HIV experienced a decrease in CD4 cell count with an average decrease of 19 cells/μL.

4 Discussion

The most common side effect symptom of LTE among study participants at the start of therapy is a headache. However, LTE was able to recover the CD4 cell counts of most of the participants in better immune conditions after they underwent antiretroviral therapy. Generally, the demographic and clinical characteristics of people living with HIV who experience LTE side effects were not much different from the overall character of people living with HIV in this study. Most people living with HIV who experience side effects were from the adult age group (20–60 years), women, Papuans, have CD4 counts below 350 cells/μL and were already in WHO clinical stage III–IV at the start of antiretroviral therapy. In addition, the majority of people living with HIV had good antiretroviral therapy compliance.

In this study, most people living with HIV started antiretroviral therapy when their HIV infection had progressed to acquired immunodeficiency syndrome, which was characterized by CD4 counts below 350 cells/μL and HIV clinical stage III–IV. This indicates a delay in the rapid detection of HIV infection or a delay in starting antiretroviral therapy. According to the findings of a study, several reasons cause a person to delay undergoing antiretroviral therapy, including feeling healthy, low social support and stigma, gender factors, high treatment costs, low quality of health services, concerns about confidentiality, and lack of knowledge about HIV treatment [29]. Also, another study in Zambia revealed reasons why people living with HIV delay antiretroviral therapy such as misinformation about HIV treatment, taking a long time to think and preparing for a lifelong commitment to antiretroviral therapy, worrying that their HIV-positive status will be known by others because of taking antiretroviral, still difficult to accept being diagnosed as HIV positive and feel healthy, and fear of experiencing side effects of antiretroviral including difficulty swallowing large pills [30].

Based on previous studies, the symptoms of antiretroviral side effects were significantly associated with the characteristics of people living with HIV, such as age, where those aged 45 years and over were riskier of experiencing side effects, also a low CD4 cell count below 200 cells/μL, advanced WHO stage disease (clinical stages III or IV), presence of comorbid disease, and concomitant use with other drugs [31]. Older age is associated with physiological changes such as a reduction in muscle mass and water content, as well as an increase in body fat that stored more drug compounds in the body. The change of mass body composition among elder people influences the drug absorption, distribution, metabolism, excretion, and drug effects on the body. If the drug doses are unadjusted there will be a risk of side effects [32].

Low CD4 cell count, as well as advanced HIV clinical stages III to IV among people living with HIV, were related to the condition of the weakened immune system. A weak immune system has implications for severe drug side effects. In addition, people living with HIV with the comorbid disease also experience severe drug side effects. This may be due to drug interactions between comorbid drugs and antiretrovirals they take for treatment [33].

More women in this study experienced LTE side effects. This was in line with a previous study that reported women experienced more side effects than men on tenofovir-based antiretroviral [28, 29]. Women were more prone to suffer from drug side effects than men because of differences in hormone, pharmacodynamics, and pharmacokinetics. In addition, women's lifestyle and psychosocial factors such as diet, and taking more medication that causes a higher chance of experiencing drug-drug interactions and side effect. The pharmacodynamics differences between men and women include differences in the drug target, membrane transport, receptor binding, receptor number, and interactions with macromolecules. While the differences in pharmacokinetics include differences in metabolism, body composition such as fat and organ blood flow, and bioavailability due to gastrointestinal mobility and absorption. Women's cells are more sensitive to drug exposure than men's [36].

Most of the people living with HIV in this study experienced LTE side effects at the start of therapy and were able to tolerate it for less than 2 weeks. These side effects include central nervous system disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders. This was in line with previous studies that reported various symptoms of LTE side effects from the central nervous system disorder group such as headache, insomnia, sleepy or drowsiness, and nightmares. Gastrointestinal disorders include symptoms of nausea, vomiting, and diarrhea. Also skin and subcutaneous tissue disorders, such as allergies or rashes [9].

We found the 3 most common LTE side effects among people living with HIV in this study, that were headache, nausea, and nightmares. This was slightly different from a study finding in Mataram that LTE side effects among people living with HIV were weakness, dizziness, and vomiting where these side effects were still in the mild category [37], while another study in India found the most common side effect of LTE among people living with HIV was drowsiness, followed by headaches and nightmares [21]. In general, the most common side effects experienced by people living with HIV in this study were symptoms due to central nervous system disorder.

A previous study reports that toxic effects of antiretrovirals cause mitochondrial cerebrovascular dysfunction, as well as disturbances in other metabolic pathways, such as endothelial dysfunction, calcium imbalance, and dysregulation of autophagy pathways. This dysfunction occurs not only in the central nervous system but also in other organs including the gut, kidneys, liver, major arteries, and other organs. These toxic mechanisms can lead to gastrointestinal, liver, renal, cardiovascular, and other disorders [38].

Previous studies also stated the side effects of drugs in the combination LTE regimen for treatment, that the common side effects of lamivudine include headache, nausea, vomiting, diarrhea, weight loss, abdominal pain, fever, and cough symptoms [39]. While the common side effects of using tenofovir include headache, rash, diarrhea, pain, depression, and nausea [40]. Another study reported the side effects of efavirenz including central nervous system disorders such as nightmares, confusion, insomnia, and sleepy symptoms. These symptoms occur in the first year of therapy and can be tolerated by people living with HIV in the range of 1 to 4 weeks [31].

In this study, most people living with HIV were able to tolerate the LTE side effects in less than 2 weeks. Although it causes short-term effects, LTE was relatively safe

for the therapy regimen and tolerable. In addition, LTE increases the CD4 count of most people living with HIV in this study. Increasing CD4 count during therapy is one indicator of recovering and improving the immune system. The TLE side effects can still be tolerated by most people living with HIV so they can continue the therapy without altering the regimen. Lamivudine and tenofovir are drug compound from the nucleoside reverse transcription inhibitor class. Drug compounds from this class work by directly inhibiting the transcription of viral RNA into proviral DNA. Meanwhile, efavirenz is a non-nucleoside reverse transcription inhibitor that works by inhibiting the late stages of HIV replication. LTE inhibits the viral replication process so that CD4 lymphocyte cells can be recovered [41].

The role of the counselor in VCT services is essential to inform people living with HIV about HIV treatment knowledge before starting therapy, including information about possible antiretroviral side effects, as well as information about what actions people living with HIV should do when experiencing antiretroviral side effects, including consulting doctor or nurse if they experience side effects of antiretroviral drugs. This is important to determine the next course of action whether to change the antiretroviral drug regimen to another combination or to continue therapy with the same antiretroviral drug regimen.

The limitation of this study was the unavailability of viral load tests from the medical records of people living with HIV. Viral load testing is the gold standard for monitoring viral suppression, but due to limited resources, the effectiveness of antiretroviral treatment can be monitored by CD4 cell count test periodically, such as at the start of therapy, 3 months of therapy, 6 months of therapy, 1 year of therapy, and so on, according to the antiretroviral treatment management guidelines given to patients by health care providers for HIV treatment. Further research is needed to determine the side effects and effectiveness of various antiretroviral regimens used by people living with HIV in Papua as a comparison to the use of TLE regimens.

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42. The adverse effects of the use of Tenofovir Lamivudine Efavirens (TLE) for people with HIV in Jayapura, Indonesia mostly take a form of central nervous system disorder. This is worsened as gastroinestinal and skin or subcutaneous disorders often present along. A tolerance response against antiretriviral therapy is shown by the majority of them for roighly 2 weeks time.