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Correlation between Duration of Antiretroviral Therapy and Glomerular Filtration Rate in People Living with HIV/AIDS: A Cross-sectional Study in Cirebon, West Java, Indonesia

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ABSTRACT

Background: West Java ranks the highest Province with Human Immunodeficiency Virus (HIV) case in 2023. An estimated 1.648 patients estimated receive antiretroviral therapy (ART). Kidney disease contributes mortality amongst people living with HIV/AIDS (PLWH). Tenofovir disoproxil fumarate (TDF)-based ART was associated as risk factor of kidney disorders, indicate by declining glomerular filtration rate (GFR). However, there is limited study whether kidney disease among people living with HIV/AIDS (PLWH) were related to ART use in Indonesia.

Aims: To determine correlation between duration of antiretroviral therapy and glomerular filtration rate (GFR) in people living with HIV/AIDS.

Methods: This is an observational study with cross-sectional design. Eighty-nine HIV patients on antiretroviral therapy for at least three months with normal baseline GFR were studied. Estimated GFR calculated using the Cockcroft-Gault equation. Data obtained were analyzed with spearman correlation test.

Results: Among 89 subjects, as many as 38 patients (42.7%) on therapy less than 12 months, 29 patients (32.6%) were on ART more than 24 months, and 22 patients (24.7%) 12-24 months. ART with normal kidney function were 62 patients (69.7%). Whereas 29.2% were mildly decrease GFR, and only 1.1% were mild to moderate decrease GFR. The analytical statistic showed a no significant between duration of antiretroviral therapy and GFR in PLWH with a p-value of 0.199 and Spearman's r of 0.137.

Conclusion: There was no significant correlation between duration of antiretroviral therapy and glomerular filtration rate in PLWH.

Keywords: *Antiretroviral therapy; Glomerular Filtration Rate; People Living with HIV/AIDS.*

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1. Introduction

Human Immunodeficiency Virus (HIV) attacks and impairs the immune system, potentially resulting in Acquired Immune Deficiency Syndrome (AIDS) over time. AIDS is diagnosed when the CD4 cell count falls below 200 or when serious complications associated with AIDS, such as severe infections or cancer, occur.(World Health organization, 2023). Individuals diagnosed with HIV are referred to as People Living with HIV/AIDS (PLWH). (Kementrian Kesehatan Republik Indonesia, 2022).The use of Highly Active Antiretroviral Therapy (HAART) or often referred to as Antiretroviral therapy (ARV) brings major changes in the treatment of HIV-infected individuals and AIDS globally.(Eggleton, Shivaraj, & Affiliations, n.d.)

According to the World Health Organization's 2022 data, approximately 3.9 million individuals in Southeast Asia are living with HIV, with 2.6 million of them receiving antiretroviral treatment.(WHO, 2023).Between January and March 2023, data estimated that around 515,455 people in Indonesia were living with HIV, and 184,890 of these individuals were undergoing antiretroviral therapy. West Java had the highest number of reported HIV cases, with 2,417 individuals diagnosed, of which 1,648 had commenced antiretroviral treatment.(KEMENKES, 2023) Cumulative data through August 2022 recorded 2,491 cases of HIV/AIDS in Cirebon City.(Komisi Penanggulangan AIDS Kota Cirebon, 2022).

Mortality among individuals with HIV and AIDS is frequently attributed to kidney complications caused by the adverse effects of antiretroviral therapy. Antiretroviral medications can induce nephrotoxicity, leading to conditions such as tubular dysfunction, interstitial nephritis, and kidney stone formation.(Adnani et al., 2022). A 2023 study by Anastasie found that the prevalence of chronic kidney disease was 10.44% among patients who had been on HAART for more than a year.(Anastasie et al., 2023)

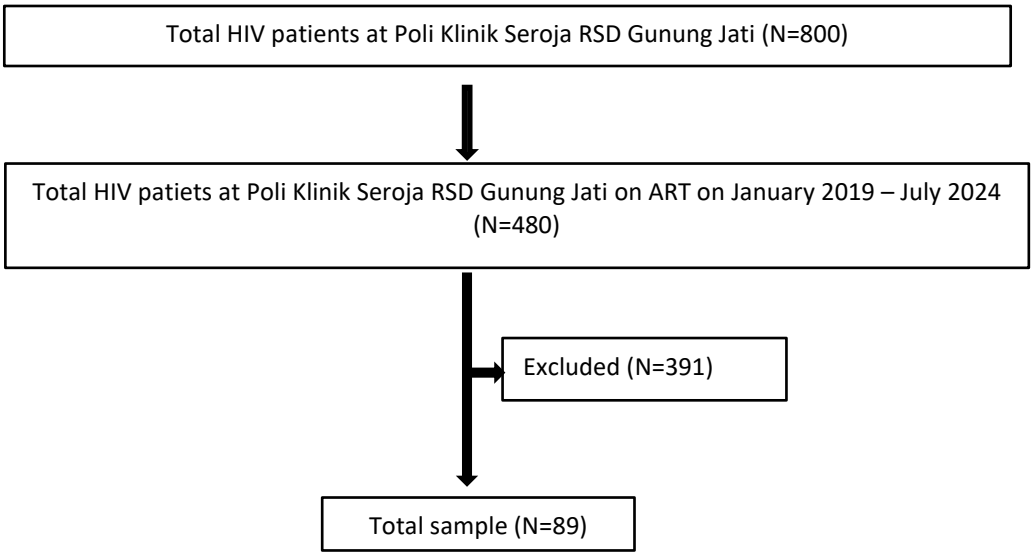
The glomerular filtration rate (GFR) is a measure of how quickly the kidneys filter blood through the glomeruli over a given period of time.(Daniel Kaufman, Basit, & Knohl Affiliations, n.d.) The guidelines from the HIV Medicine Association of the Infectious Diseases Society of America recommend that HIV-positive patients undergo screening for HIV-associated nephropathy, which should include serum creatinine levels and GFR assessments at the initiation of antiretroviral therapy, with follow-up screenings at least twice a year for stable patients.(Thompson et al., 2021) A 2019 study by the Department of Internal Medicine at the Faculty of Medicine, University of Indonesia, reported that 87 HIV patients on tenofovir disoproxil fumarate-based antiretroviral therapy for more than a year showed a decline in GFR. (Yuriandro, Yunihastuti, Marbun, & Nugroho, 2019)

However, the correlation between renal disease and the duration of antiretroviral use in Indonesia has not been well studied. This study aimed to determine correlation between duration of antiretroviral therapy and glomerular filtration rate (GFR) in people living with HIV/AIDS.

2. Methods

Study design/Research procedures

This is an observational study with cross-sectional design. The sample size for the present study was calculated using slovin formula by taking permissible error as 10% with 90% confidence interval. Meanwhile minimum sample size was calculated as n = 89. Quota sampling was used for sampling technique. Inclusion criteria, Patients confirmed with a reactive HIV test result, Aged 19 - 50 years, and On ART therapy for at least three months. Exclusion criteria, Laboratory test data on kidney function after at least three months of treatment is not available in the medical records.The initial assessment of glomerular filtration rate before using antiretrovirals showed a result of < 90 ml/min/1.72 m^2. Has comorbidities: hypertension, diabetes mellitus, lupus erythematosus as recorded in the medical records.



Measurements

The sociodemographic data (including gender, age, marital status, and risk factors), clinical data (such as weight, WHO clinical stage, and therapy regimen), and laboratory data (serum creatinine levels) were obtained from medical records. The duration of antiretroviral therapy (ART) use was used to put patients into three groups: stratum 1 comprised individuals on ART for less than 12 months, stratum 2 included those on ART for 12 to 24 months, and stratum 3 included those on ART for more than 24 months.

Based on the data available in the patient's medical record, Glomerular filtration rate (GFR) was calculated using Cockcroft- Gault equation:

$$\text{Female} = \frac{([140 - \text{Age}] \times [\text{weight in kilograms}])}{(72 \times \text{serum cretinie in mg/dl})} \times 0{,}85$$

$$\text{Male} = \frac{([140 - \text{Age}] \times [\text{weight in kilograms}])}{(72 \times \text{serum cretinie in mg/dl})}$$

The Kidney Disease Improving Global Outcomes (KDIGO) foundation's diagnostic and categorization guidelines for CKD served as the basis for defining the GFR stages. G1 stage: GFR > 90 mL/min/1.73 m^2; G2 stage: GFR 60 - 89 mL/min/1.73 m^2; G3 stage: GFR 30 - 59 mL/min/1.73 m^2; G4 stage: GFR 15 - 29 mL/min/1.73 m^2; G5 stage: GFR < 15 mL/min/1.73 m^2).

Statistical techniques

Univariate statistics, such as distribution and percentage, were used to examine and summarize the acquired data. The study employed the spearman correlation test to investigate the relationship between the duration of antiretroviral therapy and glomerular filtration rate (GFR) among people living with HIV/AIDS. Spearman correlation test is reliable in this study because the data is not normally distributed. A statistically significant result was defined as $p < 0.05$. SPSS 25 was used to process the data.

Ethical Clearance

This study has been ethically approved from the Health Research and Development Ethics Committee of RSD Gunung Jati, Cirebon City, with Ethical Approval No.022/LAIKETIK/KEPPKRSGJ/2024, and has been granted research permission by RSD Gunung Jati under No.000.9.2/992-Bidbang.

3. Results

Patient's characteristics

A total of 89 patients reactive to HIV test result participated to the study. There were 68 (76.4%) males and 21 (23.4%) females. The study participants had ages ranging from 19 to 50 years with a mean of 31.4 years-old. The majority (48.3%) was between 26 to 35 years-old. Regarding the participants marital status, 26 (29.2%) were married, 60 (67.4%) were Unmarried, 3 (3.4%) were divorced. Homosexual (46.6%) is the most common risk factors in this study. The majority of participants, 43 individuals (48.3%), were categorized as being in WHO clinical stage 3 prior to starting ART therapy. The most prescribed treatment (66.3%) is tenofovir (TDF) + lamivudine (3TC) + Dolutegravir (DTG). (Table 1)

Table 1. Characteristics of the subject

Characteristics	n	%
Gender		
Male	68	76.4
Female	21	23.6
Age	31.48 ± 6.941* 30**	
19-25 years	18	20.2
26-35 years	43	48.3
36-45 years	23	25.8
46-50 years	5	5.6
Marital Status		
Married	26	29.2
Unmarried	60	67.4
Divorced	3	3.4
Risk Factors		
Homosexual	41	46.1
Bisexual	8	9.0
Shared Needles	3	3.4
Transmission From a Partner	37	41.6
WHO Clinical Staging		
Stage 1	14	15.7
Stage 2	19	21.3
Stage 3	43	48.3
Stage 4	13	14.6
Therapy Regimen		
TDF+3TC+DTG	59	66.3
TDF+ 3TC+ EFV	30	33.7

***Mean ± Standard deviation; **Median**

Bivariate analysis

Bivariate analysis was conducted using the Spearman correlation test to determine the correlation between independent and dependent variables. According to Table 2, the highest number of individuals with a glomerular filtration rate (GFR) ≥90 mL/min/1,73m^2 was 62, with 28 having undergone therapy for less than 12 months, 17 for 12-24 months, and 17 for more than 24 months. Additionally, there were 26 individuals with a GFR of 60-89 mL/min/1,73m^2, with 10 having undergone therapy for less than 12 months, 5 for 12-24 months, and 11 for more than 24 months, and 1 individual with a GFR of 50 mL/min/1,73m^2. The analysis revealed no significant relationship between the duration of antiretroviral therapy and GFR at RSD Gunung Jati, as the Spearman test showed a p-value of 0.199 (>0.05). The correlation coefficient was 0.137, indicating a very weak correlation; however, the direction of the relationship suggesting a positive association between the two variables.

Table 2. Correlation between duration of ART therapy and Glomerular filtration rate

		Glomerular filtration rate (mL/min/1,73m^2)			P value	r
		≥90	60-89	45-59		
Duration of ART therapy (Months)	<12	28 (31.5%)	10 (11.2%)	0 (0%)	0.199	0.137
	12-24	17 (19.1%)	5 (5.6%)	0 (0%)		
	>24	17 (19.1%)	11 (12.4%)	1 (1.1%)		
Total		62 (69.7%)	26 (29.2%)	1 (1.1%)		

4. Discussion

Patient's characteristics

In this Study, the number of male patients was higher than that of female patients, with 68 males (76.4%). The results of this study are in line with research conducted in Samarinda in 2020, where the number of male patients was 236 (70.7%) and female patients was 97 (29.3%). (Juhaefah, Paramita, Kosala, & Gunawan, 2020)This is in line with the data from the Executive Report on the development of HIV AIDS and Sexually Transmitted Infections (STIs) for the first quarter of 2023, which shows that the prevalence of HIV-AIDS is higher among men (71%) compared to women (29%).(KEMENKES, 2023) Patients receiving ARV therapy were also more dominant in the age range of 26 - 35 years, with 43 individuals (48.3%), followed by the age range of 36 - 45 years, with 23 individuals (25.8%). This data is consistent with the results of the Basic Health Research of the Republic of Indonesia in 2022, which states that the highest prevalence is found in the age group of 25 - 49 years, with a percentage reaching 67.42%. (*PROFIL KESEHATAN INDONESIA 2022*, n.d.)

This condition is caused by high sexual activity in the productive age group as well as high rates of narcotic, psychotropic, and other addictive substance (NAPZA) use through syringes in that age group. This is consistent with the results of this study where the risk factor of homosexuality at 46.1% became the highest risk factor for HIV/AIDS transmission and in line with the Executive Report on the development of HIV/AIDS and Sexually Transmitted Infections (STIs) for the first quarter of 2023 where the risk factor of homosexuality was 29% and heterosexuality was 29%. (KEMENKES, 2023).

In this study, it was shown that patients with an unmarried status were more numerous than those with a married status and widowed/divorced status, totaling 60 people (67.4%). This result is in line with a study in Samarinda in 2020, where the highest number of patients with marital status were those who were unmarried, totaling 157 people(47.1%).(Juhaefah et al., 2020) From the results of this study, it was also found that the most common clinical stage of patients before receiving ARV therapy was stage III, with a total of 43 people (48.3%). Meanwhile, in the 2019 study, the most common stage was stage II. Many factors influence the number and stage of a patient's disease, one of which is the presence of social stigma and discrimination that causes patients to hide their illness and not seek treatment.(Noerliani Upt, Kesehatan, Murnajati, & Timur, 2022). The TDF+3TC+DTG regimen most commonly used by patients is 59 people (66.3%). This regimen is the first-line choice for adults and adolescents who are starting therapy. This is in accordance with the Regulation of the Minister of Health of the Republic of Indonesia Number 23 of 2022. ARV treatment is given to all people with HIV regardless of clinical stage and CD4 count. (Kementrian Kesehatan Republik Indonesia, 2022)

Correlation between duuration of antiretroviral therapy and glomerular filtration rate in people living with HIV/AIDS

In this study, the Spearman correlation test between between the duration of antiretroviral therapy and GFR showed statistically non-significant result with P = 0.199 (>0.05) and r = 0.137, which means there is a weak positive correlation. The result is different from the research by Prima Yuriandro in 2019 reported a rapid decline in GFR after one year of TDF use in HIV/AIDS patients, with an incidence rate of 53% (95% CI 45.4-60.4). However, this study are in line with study conducted by Gizachew et al (2022), which found there was no so significant association between duration of the treartment and GFR with p value 0.95.(Manaye, Abateneh, & Niguse, 2020)

Result of this study indicate a weak positive correlation (r =0.137) between the duration of antiretroviral therapy and GFR, meaning that the longer the duration of therapy, the more GFR decrease. Reaserch conducted in Tanzania found PLWH on ART for more than six months to 2 years had more prevalence of GFR less than 90 mL/min/1.73 m^2 than those on ART for six month or less.(Mwanjala, Urio, & Mtebe, 2022) The weak strength of the correlation between two variables in this study suggests that the majority of patients had ART for less than 12 months, totaling 38 individuals (42.7%). One study indicates that the risk and degree of nephrotoxicity depend on the duration of exposure to TDF, with significant increases in serum creatinine and rapid declines in GFR observed from the fourth week of TDF use. In a study conducted in Africa in 2022, where the most common regimen was TDF + 3TC + EFV, no significant association was found between the duration of treatment and the occurrence of chronic kidney disease, as indicated by a GFR below 60 mL/min/1.73 m^2.(Anastasie et al., 2023). Another study reported that the rapid decline occurred in the first three months of treatment and then stabilized.(Yuriandro et al., 2019).

The observed differences could be due to study design and the method used to estimate GFR. Previous studies have shown that patients on TDF with a baseline GFR ≥90 mL/min experienced a slight but significant decline in GFR over time, as calculated using the MDRD or CKD-EPI equations.(Anastasie et al., 2023) In contrast, this study measured GFR using the Cockcroft-Gault equation, which incorporates secondary factors such as age, sex, and serum creatinine levels. This formula accounts for muscle mass and sex differences, but does not adjust for tubular creatinine reabsorption. Additionally, other research has reported an incidence rate of renal dysfunction—defined as a GFR decrease of more than 25% from baseline using the CKD-EPI equation—at 9.66 per 100 person-years among HIV-infected patients who began TDF-based ART.(Agbaji et al., 2019).

Limitation

This study has several limitations, including this study used secondary data from PLWH patients' medical record. Hence, other risk factors that could affect the glomerular filtration rate cannot be identified due to limited data from medical record, such as patients also taking another medication alongside ARV and the patients' Body Mass Index. Other limitations are the relatively small sample size.

5. Conclusion

The glomerular filtration rate (GFR) in HIV/AIDS patients did not significantly correlate with the duration of antiretroviral therapy, according to this study. However, 18% of patients on ART therapy for more than one year showed mild GFR decline. The results highlight the importance of regular screening and monitoring of renal function to enable early detection of kidney impairment and ensure appropriate treatment. As a follow- up to this study, we recommend conducting a statistical analalysis to identify potential factors influencing glomerular filtration rate (GFR) that this study did not identify. Different method, such as cohort method with larger sample sizes are also needed to observe the decrease trend of GFR over a one-year period of antiretroviral use.

Conflict of Interest

There is no conflict of interest.

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