Long-term Relationship of Tenofovir Use with Kidney Function in Pediatric Patients Infected with HIV at Haji Adam Malik Central General Hospital in Medan

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Abstract

Background: Tenofovir (TDF) is one of the recommended antiretrovirals that works by disrupting HIV DNA synthesis through competitive inhibition of Reverse Transcriptase and incorporation into the virus DNA. One of the side effects of TDF is kidney toxicity. **Methods**: This study is an analytical study with a cross-sectional design. Data were extracted from medical records to assess the long-term relationship of Tenofovir use with kidney function in pediatric HIV-infected patients at H. Adam Malik Central General Hospital (RSUP) in Medan. Data were statistically analyzed using independent t-test with SPSS software, with a significance level of $p < 0.05$. **Results**: No significant differences were found in glomerular filtration rate with Tenofovir use < 1 year or > 1 year ($p = 0.812$), between asymptomatic and symptomatic HIV stages ($p = 0.687$), and between groups without immunodeficiency and those with immunodeficiency ($p = 0.877$). **Conclusion**: There is no relationship between the duration of Tenofovir use and kidney function impairment in pediatric HIV-infected patients at H. Adam Malik Central General Hospital in Medan

Keywords: antiretroviral, kidney function, hiv, tenofovir.

Treatment of Human Immunodeficiency Virus (HIV) consists of several types of treatments, namely treatment to suppress HIV virus replication with antiretroviral drugs (ARV), treatment to address various opportunistic infections, and supportive treatment.[1] The basic principle in administering ARV is to maintain the quality of life for patients. HIV medications were first developed in 1987, primarily as monotherapy. In 1996, combination therapy was introduced. This new combination therapy is called Highly Active Anti-Retroviral Therapy (HAART), which is a combination of at least three types of HIV drugs. Like monotherapy, this combination of HIV drugs also does not have the ability to cure the disease The increased immune response in HIV-infected children against various potential opportunistic infections has led to an increase in life expectancy. Children with HIV infection undergoing ARV therapy have a very high likelihood of better survival.[3] After using HAART therapy, the survival rate of patients increases, while the mortality rate decreases. Currently, there are four classes of ARV available, namely Reverse Transcriptase Inhibitor (RTI), divided into two categories: Nucleoside Reverse Transcriptase Inhibitors (NRTI) consisting of Zidovudine (AZT), Stavudine (d4T), lamivudine (3TC), abacavir (ABC), Adefovir (ADV), and Tenofovir (TDF); and Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) consisting of Nevirapine (NVP), Efavirenz (EFV), and Rilpivirine (RPV).[4]

Tenofovir (TDF) is a first-line ARV for HIV treatment recommended as one of the HIV therapies due to fewer drug barriers, less fat redistribution, and fewer lipid disorders.[5] Tenofovir has the side effect of reducing the glomerular filtration rate. Tenofovir also has the potential for renal toxicity and tubular dysfunction. Several studies have examined the relationship between Tenofovir exposure and kidney function.[6]

Data on the duration of Tenofovir use with kidney function in children with HIV infection have not been studied at H. Adam Malik Central General Hospital in Medan. This research aims to determine the relationship between the duration of Tenofovir use in HIV- infected children and kidney function impairment at H. Adam Malik Central General Hospital in Medan.

1. Methods

This research is an analytical study with a cross-sectional design. Data were collected from April to June 2023 from medical records to assess the long-term relationship of Tenofovir use with kidney function in HIV-infected children at H. Adam Malik Central General Hospital in Medan. Inclusion criteria were children aged 2 to 18 years, with HIV infection confirmed by serology or virology, receiving combination ARV therapy based on Tenofovir (combination with Lamivudine + Nevirapine/Efavirenz), and having normal kidney function test results at the initiation of Tenofovir. Exclusion criteria included patients with a history of kidney disease, hypertension, and diabetes mellitus that could affect kidney function.

The collected data included name, age, gender, weight, height, HIV transmission method, duration of Tenofovir use, kidney filtration rate, HIV stage, and results of urea, creatinine, and CD4 tests. Data were recorded, collected, and statistically analyzed. The analysis was performed using SPSS software with a significance level of $P < 0.05$. An analytical design was used to analyze variables suspected of playing a role, employing independent t-tests.

2. Results

Data were obtained from 24 HIV-infected children in the outpatient or inpatient care at H. Adam Malik Central General Hospital in Medan. The characteristics of the research subjects are presented in Table 1. The average glomerular filtration rate based on Tenofovir use < 1 year was 134.1 (17.9), while the average glomerular filtration rate in patients using Tenofovir >1 year was 135.8 (13.0). The statistical test results with an independent t-test showed no significant difference in glomerular filtration rate between Tenofovir use < 1 year and > 1 year (p = 0.812) (Table 2).

The average glomerular filtration rate based on asymptomatic HIV stage was 133.8 (16.3), while the average glomerular filtration rate in symptomatic HIV stage was 136.3 (12.7). The statistical test results with an independent t-test showed no significant difference in glomerular filtration rate between asymptomatic and symptomatic HIV stages (p = 0.687) (Table 3). The average glomerular filtration rate based on immunodeficiency status, in the group without immunodeficiency, was 135.9 (13.7), while the average glomerular filtration rate in the group with immunodeficiency was 134.7 (15.3). The statistical test results with an independent t-test showed no significant difference in glomerular filtration rate between the group without immunodeficiency and the group with immunodeficiency (p = 0.877) (Table 4).

Table 1 . Subject characteristics

Characteristics	**n = 24**
Gender, n (%)	
Man	12 (50)
Woman	12 (50)
Age, years	
2 - 5 years, n (%)	4 (16.6)
5 - 12 years, n (%)	14 (58.3)
≥ 12 years, n (%)	6 (25)
Transmission, n (%)	
Mother	23 (95.8)
Etc	1 (4.2)
Nutritional Status, n (%)	
Good	10 (41.7)
Not enough	12 (50)
Bad	2 (8.3)
Duration of Tenovofir Use, years	
< 1 year, n (%)	5 (20.8)
> 1 year, n (%)	19 (79.2)
HIV stage, n (%)	
Asymptomatic	8 (33.3)
Symptomatic	16 (66.7)
Immunodeficiency Status, n (%)	
No	18 (75)
Yes	6 (25)
GFR, n (%)	
Normal	24 (100)
Abnormal	0

Table 2. Relationship between tenofovir use and GFR

Variable	Glomerular Filtration Rate		P Value
	n	X (SD)	
Duration of tenofovir use			
< 1 year	5	134.1 (17.9)	0.812
> 1 year	19	135.8 (13.0)	

Table 3. Relationship between HIV stadium and GFR

Variable	Glomerular Filtration Rate		P Value
	n	X (SD)	
HIV stages			
Asymptomatic	8	133.8 (16.3)	0.687
Symptomatic	16	136.3 (12.7)	

Table 4. Relationship between immunodeficiency status and GFR

Variable	Glomerular Filtration Rate		P Value n
	X (SD)		
Immunodeficiency status			
Non immunodeficiency	18	135.9 (13.7)	0.877
Immunodeficiency	6	134.7(15.3)	

3. Discussion

Tenofovir is widely recommended as an alternative first-line treatment for HIV infection. Tenofovir is generally considered safe and well-tolerated, replacing Zidovudine, which has bone marrow suppression side effects. Improvements in life expectancy associated with long- term ARV use require monitoring of the potential cumulative and long-term toxicity of ARVs.[7,8]

Several clinical descriptions of TDF-related nephrotoxicity have been consistently observed in available case series.[9] Most reported cases of TDF-related nephrotoxicity involve kidney injury with specific patterns, such as proximal renal tubulopathy, accompanied by the Fanconi syndrome, occurring concurrently with decreased GFR. Early detection or mild cases of TDF-related nephrotoxicity mayrequire specific testing for proximal tubular injury (such as urine analysis, bone density measurement, and serum phosphate levels).[10]

Most cases involving nephrotoxicity are associated with the use of didanosine and/or ritonavir. TDF-related nephrotoxicity occurs in elderly patients, patients with advanced HIV disease, or patients with mild kidney dysfunction before receiving TDF.[11] Observational research by Wood et al. suggests an interaction between TDF and other antiretroviral drugs (NNRTI) that may contribute to the development of TDF-related nephrotoxicity.[12] In this study, the subjects used a combination of three types of ARVs: Tenofovir, Lamivudine, and Efavirenz/Nevirapine, and none of these drugs, except Tenofovir itself, had nephrotoxic side effects.

Several observational cohort studies have linked low levels of kidney dysfunction to TDF use.[13] A study by Calmy et al. found a 1% incidence of severe nephrotoxicity requiring TDF therapy discontinuation.[14] Kohler JJ et al. and Van Rompay et al. found weak cytotoxic effects of TDF on kidney tubular cells in vitro, and animal studies indicated kidney tubular toxicity with very high doses of TDF.[15,16]

Considering the potential nephrotoxicity, recent guidelines recommend monitoring kidney function twice a year in HIV patients receiving TDF.[7] Repeat laboratory tests for rare toxicity are unnecessary in resource-limited areas.[14]

This study found no relationship between the duration of Tenofovir use and kidney function impairment in HIV-infected children at H. Adam Malik Central General Hospital in Medan. Cooper et al. identified a statistically significant decline in kidney function associated with TDF use, but the clinical effect was not substantial.[10] Wall et al. found that patients receiving TDF with an initial GFR ≥ 90 mL/min experienced mild GFR decline, but GFR increased in patients with GFR < 90 mL/min. It was also found that declines < 30 mL/min rarely occurred, and monitoring guidelines should focus on high-

risk patients.[17] A study by Janakiraman et al. found no association between the prevalence of albuminuria and kidney glomerular lesions in HIV-positive patients correlated with CD4 levels.[18] A cohort study by Sax PE et al. indicated that TDF- related nephrotoxicity may occur more frequently in the first few months after exposure.[8]

Future research should assess the impact of TDF on proximal tubulopathy consequences (such as proteinuria and bone mineral density) to ensure that clinically relevant cumulative toxicity is not overlooked. However, from several published cases and available cohort studies, TDF-related nephrotoxicity seems to occur more frequently in the first few months after exposure.[7] Whether the risk of TDF-related nephrotoxicity increases with long- term or cumulative use is crucial and will be an important area of future research, especially given recent clinical practice recommendations to initiate ARVs earlier in the course of HIV infection.[18]

This review identifies norelationship between the duration of Tenofovir use and kidney function impairment in HIV- infected children. However, further research is needed, especially long-term studies to monitor clinically relevant markers of proximal tubulopathy. Nevertheless, our findings do not support the need to restrict TDF use in areas where routine monitoring of kidney function and serum phosphate levels is difficult or impractical. The data in this study were obtained from medical records, so further research is still needed to examine the relationship between the duration of Tenofovir use and kidney function impairment in HIV- infected children.

4. Conclusion

There is no relationship between the duration of Tenofovir use, HIV stage, and Immunodeficiency Status with kidney function impairment in HIV-infected children at H. Adam Malik Central General Hospital in Medan.

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