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Tubulointerstitial Nephritis: Underdiagnosed Kidney Disease in Person Living with HIV

Afiatin Makmun[1], Aditya Rangga Fandiarta[2]*, Lilik Sukesi[1], Yovita Hartantri[3]

[1]Nephrology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia; [2]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia; [3]Tropical Disease And Infection Division, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital,Bandung, Indonesia

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***Correspondence:** Aditya Rangga Fandiarta, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, 38th Eyckman Street, Sukajadi, Pasteur, Bandung, West Java, 40161, Indonesia. E-mail: arfandiarta@gmail.com
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Abstract

BACKGROUND: Kidney disease in human immunodeficiency virus (HIV) is often overlooked. The types of kidney disease in HIV consist of glomerulopathy and tubulointerstitial nephritis. Hypertension, diabetes mellitus, and the use of tenofovir increase the risk of kidney disease.

AIM: The purpose of this study is to analyze the type of kidney disease in person living with HIV using the urine albumin-protein ratio.

METHODS: This research is an analytic observational study. Data were collected using the consecutive sampling. The urine albumin-protein ratio was carried out to differentiate glomerulopathy from tubulointerstitial nephritis.

RESULTS: Screening with dipstick proteinuria in 1148 person living with HIV, total of 189 subjects (16.5%) with proteinuria were obtained, with a urinary protein-creatinine ratio over 150 mg/g in 101 persons (8.7%). The proportion of tubulointerstitial nephritis (73.3%) was higher than glomerulopathy (26.7%). Kidney disease mostly occurs at glomerular-filtration rate ≥90 ml/minute/1.73 m^2, specifically glomerulopathy (66.7%), and tubulointerstitial nephritis (52.7%). The risk stratification of cardiovascular complications and worsening of kidney function was mostly at moderate risk (60%), there were 6.9% of study subjects with a glomerular-filtration rate ≥90 ml/min/1.73 m^2 with high-risk stratification. There was no significant difference in the proportion of glomerulopathy and tubulointerstitial nephritis based on comorbidities.

CONCLUSION: Kidney disease in HIV is mostly tubulointerstitial nephritis. Evaluation of kidney function and risk stratification needs to be done to reduce the cardiovascular complications and progressive worsening of kidney function.

Introduction

Kidney disease in HIV is still underestimated. The prevalence of kidney disorders in HIV is most prevalent on the African continent [1]. Data from the Indonesian Renal Registry in 2018, routine screening in 20,000 patients with end-stage kidney failure on routine hemodialysis found 627 (3%) HIV-positive person [2]. The prevalence results may be small because the screening was conducted in the end-stage kidney disease population already on hemodialysis, the prevalence rate will increase if screening is carried out in the early stages of kidney disease.

Indonesian Renal Registry shows that hypertension and diabetes mellitus are the two most common causes of chronic kidney disease in Indonesia. The proportion of causes of chronic kidney disease due to hypertension is 36% while diabetes mellitus is 28% [2]. Person living with HIV with hypertension and diabetes mellitus have an increased risk of developing kidney disorders. The relative risk of hypertension causing kidney disorders is 1.4–3.5, whereas diabetes mellitus is 1.5–2.6 [3]. The incidence of albuminuria is more common in person living with HIV with comorbid hypertension or diabetes mellitus than in person living with HIV without comorbidities [4].

Tenofovir began to be used for HIV therapy in 2001 [5]. In 2010, the WHO recommended the use of tenofovir as a first-line antiretroviral drug [6]. Indonesia began officially using tenofovir as a first-line drug option in addition to zidovudine since 2011 [7]. Research by Ascher *et al*. showed that the administration of tenofovir-emtricitabine for 6 months can cause a decrease in glomerular-filtration rate and an increase in non-albumin urinary proteins such as α1 microglobulin and β2 microglobulin [8]. The study of Reynes *et al*. in France found that the risk of tubulointerstitial abnormalities associated with tenofovir exposure was obtained with an odds ratio of 3.52 [9]. The Indonesia Ministry of Health's National Guidelines for Medical Services for HIV Management recommends creatinine

clearance every 6 months when using tenofovir [10]. Tenofovir-based antiretroviral regimens are widely used for HIV treatment at HIV Clinic, Hasan Sadikin Hospital Bandung. According to the 2021 antiretro viral (ARV) annual report, proportion of tenofovir use in our hospital was 76%.

Kidney disorders in HIV can present as glomerulopathy or tubulointerstitial nephritis [11]. These must be differentiated as they determine further management. Urine protein albumin ratio assessment can differentiate them. Urine protein albumin ratio ≥0.4 indicates glomerulopathy while urine protein albumin ratio <0.4 indicates tubulointerstitial nephritis [9], [12]. Glomerulopathy is more common in person living with HIV with comorbid hypertension and diabetes mellitus while tubulointerstitial disorders are more common in person living with HIV using tenofovir [9], [13]. The detection of the type of kidney abnormalities needs to be differentiated as it relates to further management.

Methods

This analytic observational study was conducted at HIV Clinic Hasan Sadikin Hospital on July 20, 2022−September 28, 2022.

Study population

The inclusion criteria for this study were being over the age of 18, being an outpatient, receiving treatment for at least 6 months, and having a positive proteinuria dipstick examination. The exclusion criteria in this study were impaired consciousness, pregnancy, menstruation, urinary catheter inserted, acute fever for <7 days, hepatitis B, hepatitis C, autoimmune diseases, tuberculosis, and regular use of nonsteroid anti-inflammatory drugs for at least 2 weeks.

Data collection

Subjects in this study were taken by consecutive sampling. Subjects with inclusion and exclusion criteria were taken in order of arrival until the sample size was met. Subjects were explained the purpose of the study and asked for their consent. Information on age, duration of HIV diagnosis, WHO Clinical HIV stage, duration of ARV, ARV regimen, and comorbidities were obtained from interviews and data in medical records. Subjects were measured for weight and height for body mass index calculation. If protein urine dipstick was positive, creatinine serum and urine protein creatinine ratio were measured. If the urine protein creatinine ratio is ≥150 mg/g, the urine albumin creatinine ratio of the same urine sample is measured.

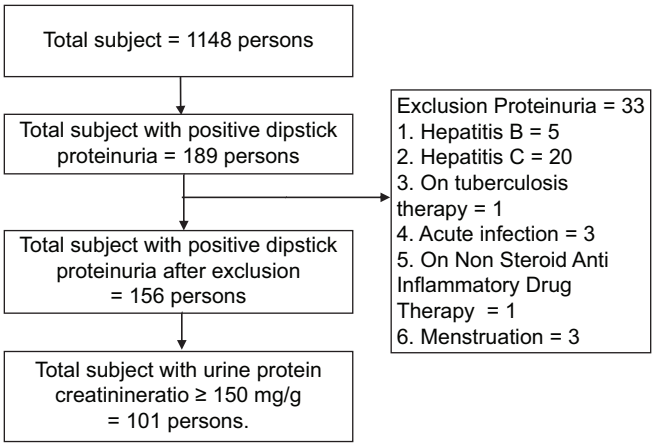

Figure 1: Enrollment flowchart. Proteinuria screening was performed by consecutive sampling on person living with HIV who visit the HIV clinic. Assessment of study subjects according to inclusion and exclusion criteria was carried out by history taking and medical record evaluation.

Definition

Baseline characteristics consisted of age, gender, duration of HIV diagnosis, WHO clinical stage at HIV diagnosis, comorbid hypertension, comorbid diabetes mellitus, duration of known hypertension, duration of known diabetes mellitus, duration of ARV therapy (ART), type of ARV regimen, nutritional status, smoking habit, blood pressure, and glomerular-filtration rate. The degree of proteinuria and albuminuria refer to the standard according to KDIGO [14]. Urine albumin protein ratio ≥0.4 indicates glomerulopathy, whereas urine albumin protein ratio <0.4 indicates tubulointerstitial nephritis.

Data analysis

An univariate analysis was used to determine the characteristics of the research subjects and the description of kidney disease. The Chi-square test was used to determine the significance of differences in the proportion of glomerulopathy and tubulointerstitial nephritis based on hypertension, diabetes mellitus, and tenofovir use.

Results

There were 1148 person with HIV screened. This number represents the average number of visitors to HIV Clinic in 1 month. The number of subject with proteinuria found by dipstick examination was 189 (16.5%), with 33 subjects excluded due to hepatitis B (5 subjects), hepatitis C (20 subjects), acute infection (3 subjects), exposure to nonsteroid anti-inflammatory drugs in the previous 2 weeks (1 subjects), anti-tuberculosis drug therapy (1 subjects), and menstruation (3 subjects). The number of subject with proteinuria

who participated in the study was 156. There were 101 (8.7%) person living with HIV with significant urine protein-creatinine ratio results of more than equal to 150 mg/g. Explanation for enrollment flowchart can be seen in Figure 1.

Baseline characteristic

The study subjects were mostly male, numbering as many as 79 person (78.2%), with a median age of 43 years. The most common HIV risk factor was heterosexuality, which accounted for 48 (47.5%) of all cases, followed by homosexuality, which accounted for 36 (35.6%). HIV has been known for a long time, with a median of 84 months. Most of the study subjects used tenofovir as many as 81 persons (80.2%) with a median duration of using ARV for 84 months. Subjects who had comorbid hypertension were 32 (31.7%). The duration of known hypertension was with a median of 12 months. Subjects who had comorbid diabetes mellitus were 9 persons (8.9%). The median duration of known diabetes mellitus was 132 months. Subjects who smoked were 44 persons (43.6%). The study subjects' nutritional status was mostly normal (34 persons, or 33.7%). The HIV stage at the time of diagnosis was mostly WHO Clinical Stage 4, with as many as 41 persons (40.6%). The baseline characteristics of the research subjects are shown in Table 1.

Table 1: Baseline characteristics

Baseline characteristics	Total (n = 101), n (%)
Age (years)	
Median	43
IQR (Q1–Q3)	34–49
Sex	
Male	79 (78.2)
Female	22 (21.8)
Risk factor	
Homosexual	36 (35.6)
Heterosexual	48 (47.5)
Perinatal	1 (1)
Intravenous drug user	16 (15.8)
Duration of HIV diagnosis (months)	
Median	84
IQR (Q1–Q3)	48–120
Medication	
Tenofovir	81 (80.2)
Nontenofoir	20 (19.8)
Duration of therapy (months)	
Median	84
IQR	36–120
Hypertension	
Proportion	32 (31.7)
Duration of hypertension (months)	
Median	12
IQR (Q1–Q3)	6–34
Diabetes mellitus	
Proportion	9 (8.9)
Duration of diabetes mellitus (months)	
Median	132
IQR	48–222
Smoking	44 (43.6)
Nutritional status	
Underweight	10 (9.9)
Normal	34 (33.7)
Overweight	18 (17.8)
Obesity grade 1	31 (30.7)
Obesity grade 2	8 (7.9)
Stage of HIV	
1	29 (28.7)
2	5 (5)
3	26 (25.7)
4	41 (40.6)

Data on risk factors, duration of HIV diagnosis, ART regimen, duration of ART, hypertension, and diabetes mellitus were obtained from history taking and medical record evaluation. Age is presented in years. The duration of HIV diagnosis, ART, hypertension, and diabetes are all given in months. Nutritional status is measured as BMI according to Asia-Pacific BMI criteria (underweight < 18.5; normal 18.5–22.9; overweight 23–24.9; obese 1 25–29.9; obese 2 ≥ 30), HIV stage is determined according to the WHO clinical stage. HIV: Human immunodeficiency virus, IQR: Interquartile range, BMI: Body mass index, ART: Antiretroviral therapy.

Table 2: Kidney disease characteristics

Kidney disease characteristics	Total (n = 101), n (%)
eGFR	
≥90	57 (56.4)
60–89	32 (31.7)
30–59	8 (7.9)
15–29	2 (2)
<15	2 (2)
Proteinuria dipstick	
+1	77 (76.2)
+2	14 (13.9)
+3	7 (6.9)
+4	3 (3)
Proteinuria severity	
Moderate proteinuria (urine protein creatinine ratio 150–500 mg/g)	60 (59.4)
Severe proteinuria (urine protein creatinine ratio >500 mg/g)	41 (40.6)
Albuminuria severity	
Mild albuminuria (urine albumin creatinine ratio <30 mg/g)	25 (24.8)
Moderate albuminuria (urine albumin creatinine ratio 30–300 mg/g)	68 (67.3)
Severe albuminuria (urine albumin creatinine ratio >300 mg/g)	8 (7.9)
Type of kidney disease	
Glomerulopathy	27 (26.7)
Tubulointerstitial nephritis	74 (73.3)

The eGFR is measured in units of ml/min/1.73 m^2 according to CKD-EPI 2019 equation from serum creatinine data. The degree of proteinuria and albuminuria severity is according to KDIGO standard. Type of renal disease was determined from the results of urine albumin protein ratio, Urine albumin protein ratio ≥0.4 indicates glomerulopathy while urine albumin protein ratio <0.4 indicates tubulointerstitial nephritis. KDIGO: Kidney Disease Improving Global Outcomes, eGFR: Estimated glomerular-filtration rate.

Kidney disease characteristic

Most of the research subjects have a normal estimated glomerular-filtration rate, as many as 57 persons (56.4%). The degree of proteinuria was dominated by moderate proteinuria in as many as 60 persons (59.4%) and moderate albuminuria in as many as 68 persons (67.3%). From the calculation of the urine protein albumin ratio, it was found that the type of kidney disorder in the study subjects was dominated by the type of tubulointerstitial nephritis disorder, specifically 74 persons (73.3%). Explanation for kidney disease characteristic can be seen in Table 2.

From the cross-tabulation between the degree of albuminuria and the estimated glomerular-filtration rate, it can be seen that the prognosis of the research subjects is related to the risk of worsening kidney function and the risk of cardiovascular complications. In as many as 61 persons (60%), the risk in the study subjects was dominated by moderate risk. Although mostly subjects have an estimated glomerular-filtration rate >90 ml/min/1.73 m^2, 6.9% have experienced severe albuminuria. Explanation for risk stratification of kidney disease can be seen in Table 3.

Table 3: Risk stratification of kidney disease

eGFR	Albuminuria severity			Total
	uACR <30, n (%)	uACR 30–300, n (%)	uACR >300, n (%)	
≥90	11 (10.9)	39 (38.6)	7 (6.9)	57 (56.4)
60–89	11 (10.9)	21 (20.8)	0	32 (31.7)
30–59	1 (1)	7 (6.9)	0	8 (7.9)
15–29	1 (1)	0	1 (1)	2 (2)
<15	1 (1)	1 (1)	0	2 (2)
Total	25 (24.8)	68 (67.3)	8 (7.9)	101 (100)

Risk stratification according to KDIGO 2012, The estimated glomerular filtration rate is measured in units of mL/min/1.73 m2 according to CKD-EPI 2019 equation from serum creatinine data. Urine albumin creatinine ratio is measured in mg/g. Risk of worsening kidney function and cardiovascular complications is classified in 4 colors (Green: Low risk, Yellow: Moderate risk, Brown: High risk, and Red: Very high risk). uACR: Urine albumin-creatinine ratio, eGFR: Estimated glomerular filtration rate, KDIGO: Kidney Disease Improving Global Outcomes .

Table 4: Cross tabulation of estimated glomerular-filtration rate and type of kidney disease

eGFR	Type of kidney disease		Total (n = 101)
	Glomerulopathy (n = 27), n (%)	Tubulointerstitial nephritis (n = 74), n (%)	
≥90	18 (66.7)	39 (52.7)	57 (56.4)
60–89	6 (22.2)	26 (35.1)	32 (31.7)
30–59	2 (7.4)	6 (8.1)	8 (7.9)
15–29	1 (3.7)	1 (1.4)	2 (2)
<15	0	2 (2.7)	2 (2)

Type of renal disease was determined from the results of urine albumin protein ratio, urine albumin-protein ratio ≥0.4 indicates glomerulopathy while urine albumin-protein ratio <0.4 indicates tubulointerstitial nephritis. The estimated glomerular-filtration rate is measured in units of mL/min/1.73 m^2 according to CKD-EPI 2019 equation from serum creatinine data. eGFR: Estimated glomerular-filtration rate.

The types of kidney disease, glomerulopathy, and tubulointerstitial nephritis were mostly found in the study subjects with a glomerular-filtration rate still ≥90 ml/min/1.73 m^2, namely the proportions of glomerulopathy (66.7%) and tubulointerstitial (52.7%). Explanation for cross tabulation analysis for estimated glomerular filtration rate and type of kidney disease can be seen in Table 4.

Difference proportion of glomerulopathy and tubulointerstitial nephritis

Table 5 states the results of the Chi-square test analysis for differences in the proportion of types of kidney disorders based on hypertension, diabetes mellitus, and use of tenofovir obtained results that are not significant ($p > 0.05$).

Discussion

Proteinuria is one of the important indicators of kidney disease. Proteinuria measurement detects kidney abnormalities earlier than creatinine measurement. The prevalence of proteinuria in HIV with dipstick proteinuria examination was 16.5%, while with urine protein-creatinine ratio ≥150 was 8.7%. According to Antonello *et al*., the prevalence of proteinuria (urine protein-creatinine ratio >150 mg/g) in person living with HIV was 20%. The degree of proteinuria was dominated by moderate proteinuria (59.4%) and moderate albuminuria (67.3%). According to Zeder *et al*., moderate proteinuria (urine creatinine-protein ratio of 100–500 mg/g) is a significant risk factor for decrease in glomerular-filtration rate to below 60 ml/min/1.73 m^2, an increase in microalbuminuria or phospaturia at 6-month follow-up [15].

Table 5: Proportion difference of glomerulopathy and tubulointerstitial nephritis based on comorbidities

Comorbidites	Glomerulopathy (n = 27), n (%)	Tubulointerstitial nephritis (n = 74), n (%)	Total n = 101), n (%)	p
Hypertension				
Yes	7 (21.8)	25 (78.2)	32	0.453
No	20 (29)	49 (71)	69	
Diabetes mellitus				
Yes	1 (11.1)	8 (88.9)	9	0.438
No	26 (28.3)	66 (71.7)	92	
Tenofovir use				
Yes	24 (29.6)	57 (70.4)	81	0.186
No	3 (15)	17 (85)	20	

Proportions difference was analyzed with Chi-square test or Fisher's exact test if it did not meet the requirements of the Chi-square test. p value is significant if the result is <0.05.

Most of the research subjects had a normal estimated glomerular-filtration rate (56.4%). This shows the importance of urinalysis examination for the evaluation of kidney disorders, we will miss a lot if we only look at creatinine examination alone. According to Reynes *et al*., the proportion of proteinuria in person living with HIV with a normal glomerular-filtration rate was 18.2% [9]. According to the consensus on chronic kidney disease from KDIGO, cross tabulation between the degree of albuminuria and glomerular-filtration rate can describe a prognosis related to the risk of worsening kidney function and the level of risk of cardiovascular complications [14]. From the cross tabulation analysis between the degree of albuminuria and the estimated glomerular filtration rate, the risk in the research subjects was dominated by a moderate degree of risk, as much as 60%, so that kidney function in Person living with HIV should be monitored more closely. A total of 6.9% of the research subjects had an estimated glomerular-filtration rate above 60 ml/min/1.73 m^2 which turned out to have a high risk of worsening kidney function and cardiovascular complications so normal creatinine does not mean low risk, it is necessary to check the urine albumin-creatinine ratio to prove it. According to Choi *et al*., estimated glomerular-filtration rate levels under 30 mL/min/1.73 m^2 were associated with hazard ratios for incident cardiovascular disease 1.99 (1.46–2.70), compared with estimated glomerular filtration rate ≥60 mL/min/1.73 m^2. Similarly, macroalbuminuria had hazard ratio for cardiovascular disease 1.71 (1.30–2.27) compared with absent albuminuria [16].

Proportion of tubulointerstitial nephritis (73.3%) was higher than glomerulopathy (26.7%). This is consistent with the Samarawickrama *et al*., in which tubulointerstitial disease is more prevalent than glomerulopathy. Graveman study on the evaluation of 945 person living with HIV also found tubular proteinuria (41%) more common than glomerulopathy proteinuria (20%). There is currently a paradigm shift in the causes of kidney disease in HIV. The incidence of HIV-associated nephropathy (HIVAN) and opportunistic infections in person living with HIV has decreased simultaneously with the start of effective ARV administration. Chronic kidney disease is becoming more common due to the longer life span of HIV-infected patients, role of comorbidities such as hypertension and diabetes, and progressive loss of kidney function due to ARV therapy [17].

In this study, 31.7% of person had hypertension and 8.9% had diabetes mellitus. Halle *et al*. showed that the most common comorbidities in person living with HIV with chronic kidney disease are hypertension (36.5%), diabetes mellitus (17.9%), and hepatitis C (7.9%). Poor blood pressure control leads to increased glomerular hydrostatic pressure which further causes

glomerular collapse, activation of mesangial cells resulting in glomerulosclerosis [18]. Poor blood sugar control leads to the formation of advanced glycation end products that can bind and modify laminin and collagen proteins in the glomerular basement membrane, leading to increased glomerular permeability and fibrosis [19]. Proportion of tenofovir use in this study was 80.2%. Tenofovir can cause a decrease in glomerular-filtration rate, an increase in tubular damage markers $\alpha_1$microglobulin, β_2 macroglobulin within 6 months of therapy. Tenofovir accumulation in proximal tubular cells causes impaired reabsorption of small molecular weight proteins, glucose, phosphate, and uric acid [8], [20]. In this study, the proportion of tubulointerstitial nephritis was higher than glomerulopathy so kidney damage was more dominant influence from ARV than comorbid hypertension or diabetes mellitus. The proportion of tubulointerstitial nephritis remained higher even without tenofovir exposure. This result may be due to the influence of drugs other than tenofovir. Lamivudine may cause Fanconi syndrome due to mitochondrial toxicity in proximal tubules. Efaviren may cause acute interstitial nephritis and focal interstitial fibrosis. Dolutegravir may increase serum creatinine by 10–14% due to inhibition of renal transporter OCT2, which is reversible. Lopinavir/ritonavir is also associated with decreased renal function. The decline in renal function increased significantly after 36 months of lopinavir/ritonavir use [21].

Kidney function should be evaluated at the time of diagnosis of HIV infection, prior to therapy and then periodically to evaluate the side effects of antiretroviral therapy or to monitor worsening kidney function due to comorbidities. Proteinuria dipstick testing is more commonly recommended in person living with HIV and should be used not only for screening prior to ARV treatment but also for monitoring side effects of ART [22].

This study recommends a basic kidney function examination consisting of serum creatinine and a complete proteinuria dipstick urinalysis plus urine sediment. If abnormal creatinine or dipstick proteinuria results are found, urine protein creatinine ratio and urine albumin creatinine ratio are examined using a sample of urine at the time. To evaluate the type of kidney disease, urine albumin protein ratio is calculated, if the urine albumin protein ratio is <0.4, the kidney disease is tubulointerstitial nephritis, if the urine albumin protein ratio is ≥0.4, the kidney disease is glomerulopathy. The types of kidney disease need to be differentiated because further management is different, evaluation of diagnosis and further management require consultation with a nephrologist.

HIV-associated nephropathy (HIVAN), HIV immune complex (HIVIC), or comorbidity-related glomerulopathy (hypertension, diabetes mellitus, hepatitis B, hepatitis C, autoimmune disease) are all possible causes of glomerulopathy. To exclude that differential diagnosis, a complete history taking, physical examination, and supporting investigations are required. A kidney biopsy may be required for a definitive diagnosis [11].

The etiology of tubulointerstitial nephritis in HIV can be due to side effects of ART with tenofovir or nontenofovir (lamivudine, efavirenz, lopinavir, and ritonavir), non-steroidal anti-inflammatory drugs, or opportunistic infections such as cytomegalovirus and tuberculosis. History taking, physical examination, and supporting examination are necessary to exclude the differential diagnosis. If the glomerular-filtration rate has started to decrease, the ARV dose also needs to be adjusted. Tenofovir regimen should not be started if the patient has a glomerular-filtration rate of less than 60 ml/min, if there is a decrease in estimated glomerular-filtration rate of more than 25% from baseline or has tubular dysfunction (tubular proteinuria, hypophosphatemia with increased phosphate excretion, glucosuria with normal blood sugar, and metabolic acidosis). If tubulointerstitial nephritis is due to tenofovir, the ARV needs to be replaced with abacavir or zidovudine. If there are no other options to replace tenofovir or patients with hepatitis B co-infection, tenofovir initiation can still be done with an adjusted dose, close monitoring of kidney function and avoid other nephrotoxic ARV drugs, especially protease inhibitors [3], [23].

The cross tabulation of estimated glomerular-filtration rate with the degree of albuminuria is used to stratify the risk of worsening kidney function and cardiovascular complications. This is necessary to determine the frequency of annual kidney function evaluation. A decrease in glomerular-filtration rate of 25% from baseline or a rapid decrease in glomerular-filtration rate of >5 ml/min/1.73 m^2/year indicates worsening kidney function [14]. This recommendation cannot be directly applied to all health facilities, in the initial phase it will be focused on the service where this study was conducted. The limitations of this study include the fact that it is still a preliminary study and a single-center study. Further research needs to be done to see the factors that influence glomerulopathy and tubulointerstitial nephritis in person living with HIV.

Conclusion

Kidney disease in HIV is mostly tubulointerstitial nephritis. To determine the factors that affect glomerulopathy and tubulointerstitial nephritis in person living with HIV, more research must be conducted. Evaluation of kidney function and risk stratification need to be done periodically to reduce the cardiovascular complication and worsening of kidney function at the time of diagnosis and after beginning treatment.

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Ethics Statement

This study protocol was approved by The Research Ethics Committee Hasan Sadikin Hospital. Informed consent was obtained from all patients.

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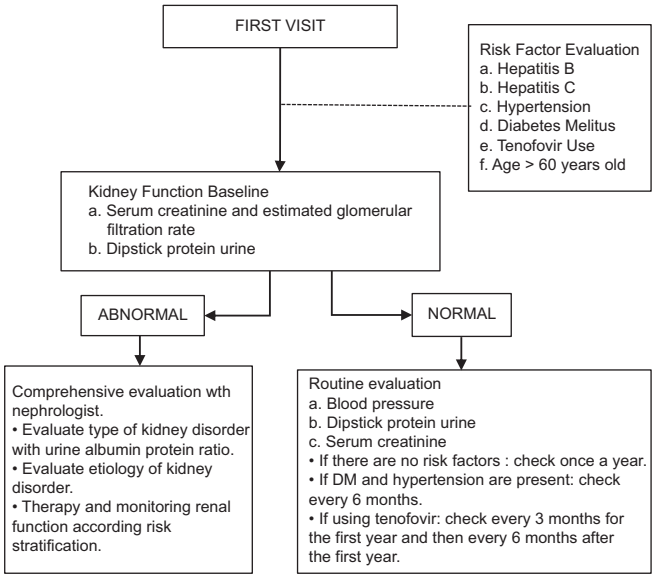
SUPPLEMENTARY FIGURE



Supplementary Figure1: Recommendation of monitoring kidney function in person living with HIV