Tubulointerstitial Nephritis: Underdiagnosed Kidney Disease in Person Living with HIV

Afiatin Makmun, Aditya Rangga Fandiarta, Lilik Sukesi, Yovita Hartantri

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

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 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 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 was 12 persons (9.8%). 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.

**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 m², 6.9% have experienced severe albuminuria. Explanation for risk stratification of kidney disease can be seen in Table 3.
Type of kidney disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulopathy (n = 74)</td>
<td></td>
</tr>
<tr>
<td>290-89</td>
<td>57 (56.4)</td>
</tr>
<tr>
<td>80-15</td>
<td>32 (31.7)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis (n = 27)</td>
<td></td>
</tr>
<tr>
<td>290-89</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>80-15</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

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 m² according to CKD-EP I 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 ratestill ≥90 mL/min/1.73 m², 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%. 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. 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 m² 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 m² 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 m². 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

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

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Total (n = 101)</th>
</tr>
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</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Glomerulopathy (n = 27)</th>
<th>Tubulointerstitial nephritis (n = 74)</th>
<th>Total (n = 101)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>7 (21.8)</td>
<td>25 (78.2)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>20 (29)</td>
<td>49 (71)</td>
<td>69</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>1 (11.1)</td>
<td>8 (88.9)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24 (28.6)</td>
<td>57 (71.4)</td>
<td>81</td>
</tr>
<tr>
<td>Tenofovir use</td>
<td>Yes</td>
<td>24 (29.6)</td>
<td>57 (70.4)</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3 (15)</td>
<td>17 (85)</td>
<td>20</td>
</tr>
</tbody>
</table>
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 $\alpha_2$-microglobulin, $\beta_2$-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. Efavirenz 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 $\geq$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.
Acknowledgment

We appreciate the helpful suggestions on study design, review, and enlightening conversation provided by Siti Aminah Abdurachman, Bachti Alisjahbana, Rudi Supriyadi, and Indra Wijaya for this work.

Ethics Statement

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

References


**Supplementary Figure 1**: Recommendation of monitoring kidney function in person living with HIV

**FIRST VISIT**

- Risk Factor Evaluation
  - a. Hepatitis B
  - b. Hepatitis C
  - c. Hypertension
  - d. Diabetes Mellitus
  - e. Tenofovir Use
  - f. Age > 60 years old

**Kidney Function Baseline**

- a. Serum creatinine and estimated glomerular filtration rate
- b. Dipstick protein urine

**Comprehensive evaluation with nephrologist**
- Evaluate type of kidney disorder with urine albumin-protein ratio
- Evaluate etiology of kidney disorder
- Therapy and monitoring renal function according risk stratification

**Routine evaluation**

- a. Blood pressure
- b. Dipstick protein urine
- c. Serum creatinine

- If there are no risk factors: check once a year
- If DM and hypertension are present: check every 6 months
- If using tenofovir: check every 3 months for the first year and then every 6 months after the first year.