The Incidence and Risk Factors of Renal Insufficiency among Korean HIV infected Patients: The Korea HIV/AIDS Cohort Study

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ABSTRACT

Renal insufficiency is one of the common issues in people living with human immunodeficiency virus (PLHIV). We studied the incidence and risk factors for renal insufficiency in male PLHIV using the Korea HIV Acquired Immunodeficiency Syndrome (AIDS) Cohort Study. Among the 830 enrolled patients, 32 (3.9%) cases of renal insufficiency occurred over 9576 patient-years of follow-up. The incidence of renal insufficiency in HIV-infected men in this study was 3.3 per 1000 patient-years. Diabetes mellitus, dyslipidemia, tenofovir or non-nucleoside reverse transcriptase inhibitor exposure for >1 year, and AIDS-defining illness were risk factors for renal insufficiency.

Keywords: HIV/AIDS; Renal insufficiency; Cohort study

Renal insufficiency is one of the common issues among people living with human immunodeficiency virus (PLHIV) infections [1, 2]. HIV patients have a higher risk for renal insufficiency than healthy people [3] due to their exposure to several factors that can result in decreased renal function. Renal dysfunction in HIV patients is attributable to the direct viral renal cell injury caused by HIV infection, chronic inflammation, and drugs, in addition to traditional risk factors such as diabetes, hypertension, and aging [1].

Advancements in combination active antiretroviral therapy (cART) have resulted in longer life expectancies in HIV patients [4, 5]. However, the incidence of non-communicable diseases (NCDs) in PLHIV has continued to increase concurrently [6]. Among the causes of death in PLHIV, the proportion of acquired immunodeficiency syndrome (AIDS)-related causes are...
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Ethics Statement
This study was approved by the Institutional Review Board (IRB) of the Severance hospital (IRB approval number: 4-2019-0419), and written informed consent was obtained from all participants.

Conflict of Interest
JYS is editorial board of Infect Chemother. However, he did not involve in the peer reviewer selection, evaluation, and decision process of this article. The other authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: JHK, JYC. Formal analysis: JHK, HJ, JYC. Investigation: JHK, HJ, JYC, JYS, SWK, SIK, BYC, JYC. Methodology: JHK, HJ, JYC. Writing - original draft: JHK. Writing - review & editing: HJ, JHK, JYS, SWK, SIK, BYC, JYC.

Decreasing while non-AIDS causes are increasing [7]. The incidence of renal dysfunction caused by NCDs like diabetes and hypertension is also increasing in PLHIV [3, 7].

Although several studies have evaluated the incidence of renal dysfunction in PLHIV, only a few have examined the incidence in Korean patients. In addition, the factors influencing the occurrence of renal dysfunction have been studied inadequately. Therefore, the purpose of our study is to describe the incidence of renal insufficiency and investigate the risk factors of renal insufficiency in this population by using data from the Korea HIV/AIDS cohort study.

The Korea HIV/AIDS cohort study is an ongoing prospective cohort study that has been conducted in Korea since 2006 with 21 participating hospitals [8]. Among Korean HIV-infected patients over 18 years old, those who were diagnosed with HIV infection by Western blotting and who agreed to participate in the cohort study were included in the study [8]. At the time of registration, a trained clinical researcher interviewed all enrolled participants and documented baseline clinical and epidemiological data [8]. The prospective cohort study recorded questionnaire assessments that included medical history, body measurements, laboratory tests with immunological status, and HIV viral load. The investigation was performed every six months [8]. This study was conducted on male patients aged more than 18 years who were enrolled in this cohort study between December 2006 and December 2018. Patients with an initial estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m² at baseline were excluded from the study. We investigated the incidence of renal insufficiency by following up with patients who were included in the cohort until December 2018.

We defined renal insufficiency as two eGFR ≤60 mL/min per 1.73 m² consecutively (≥3 months apart). The simplified modification of diet in renal disease (MDRD) equation was used to assess eGFR measurements based on serum creatinine levels. We analyzed data on the date of diagnosis of HIV infection, age, sex, height, weight, mode of transmission, diabetes mellitus (DM), hypertension (HTN), dyslipidemia, CD4 T-cell count, HIV viral load, AIDS-defining illness, Years on ART, and laboratory test at study enrollment. Patients without sufficient data and non-Korean patients were excluded from the analysis.

The incidence of renal insufficiency was evaluated by dividing the number of cases in which renal insufficiency was defined by the total observation period. We conducted Chi-square’s tests for categorical variables and paired t-tests for continuous variables to investigate the differences in characteristics between patients with renal insufficiency and those without. Cox proportional hazard regression was used to identify predictive variables for the incidence of renal insufficiency. A two-tailed test with a \( P < 0.05 \) was set as statistical significance. All of the statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

A total of 1,515 HIV-infected men were enrolled from December 2006 to December 2018, of which 685 patients were excluded from the analyses owing to missing data and the exclusion criteria. Among the 830 enrolled patients, 32 (3.9%) cases of renal insufficiency occurred over 9,576 patient-years of follow-up. A comparison of the baseline characteristics during the window period (Table 1) showed that more patients in the renal insufficiency group had DM, dyslipidemia, and a high HIV viral load at enrollment. 13 (40.6%), 25 (78.1%), and 18 (56.3%) of the patients took tenofovir, nucleoside reverse transcriptase inhibitor (NRTI), and protease inhibitor (PI), respectively, for >1 year in the renal insufficiency group. Renal insufficiency occurred in 32 patients at a rate of 3.3 events per 1,000 patient-years, while the incidence rate of renal insufficiency in men aged >60 years was 9.91 events per 1,000 patient-years. HIV-infected
patients with DM showed renal insufficiency at an incidence rate of 11.96 events per 1,000 patient-years, while those with dyslipidemia showed renal insufficiency at an incidence rate of 10.13 events per 1,000 patient-years (Table 2). In multivariate analyses, the risk factors for renal insufficiency were DM (hazard ratio [HR]: 13.72, 95% confidence interval [CI]: 4.39 - 42.91; \( P < 0.001 \)), dyslipidemia (HR: 3.10, 95% CI: 1.25 - 7.69; \( P = 0.01 \)), and AIDS-defining illness (HR: 2.48, 95% CI: 1.05 - 5.84; \( P = 0.04 \)). Among the cART-related risk factors for the development of renal insufficiency, tenofovir exposure for more than 1 year (HR: 2.41, 95% CI: 1.01 - 5.77; \( P = 0.047 \)) and non-nucleoside reverse transcriptase inhibitor (NNRTI) exposure for more than 1 year (HR: 3.88, 95% CI: 1.30 - 11.59; \( P = 0.01 \)) were statistically significant risk factors (Table 3).

The incidence of renal insufficiency in PLHIV varies according to definition of renal insufficiency, type of calculation equation, income level, regions, race composition, ART status and average age ranging from 1.9 to 29.2 per 1,000 patient-year [9-11]. The incidence of renal insufficiency in our cohort study was 3.3 per 1,000 person-years. This result is similar to the incidence rate of 3.4 per 1,000 persons in a study among populations in Asia [12]. The age and sex standardized incidence of end stage kidney disease (ESKD) was 24.0 per 100,000 people using the Korean National Health Insurance Service-National Sample cohort database in 2015 [13].

Although the incidence of CKD tends to decrease in HIV patients, the incidence is still higher than the general population [14]. In this study, we observed that the tenofovir-based regimen was related to a risk factor of renal insufficiency. Tenofovir is a widely known factor that increases the risk of CKD, which may lead to renal tubular damage [15]. Several reports have documented a higher incidence of CKD with tenofovir-based regimens [12, 16]. We performed the analysis about tenofovir without distinguishing between tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). TAF is a prodrug of tenofovir and is known to have low nephrotoxicity due to the low concentration of tenofovir in plasma [17]. Therefore, there is a possibility that the incidence of renal insufficiency in patients taking TAF would be lowered. In our study, taking NNRTIs for >1 year was considered a risk factor for renal insufficiency. The reason for this finding remains unclear. However, the possibility that renal insufficiency occurred in patients diagnosed HIV long time ago who maintain NNRTIs or cannot change NNRTIs to other drug due to poor compliance should be considered, rather than the possibility of drug toxicity. Further research is required to evaluate this finding. The CD4 T-cell count and HIV viral load at the time of enrollment were not statistically significant risk factors. However, the presence of AIDS-defining illness was a statistically significant risk factor. Thus, well-controlled HIV infection can reduce the incidence of renal insufficiency. In our study, the risk factors for renal insufficiency among patients with NCDs were DM and dyslipidemia. DM and dyslipidemia are an underlying disease that often accompanies HIV infections [18]. Especially, dyslipidemia may be induced by a kind of cART and natural course of HIV infection involves characteristic changes in lipid levels [19, 20]. In advanced HIV stages, triglyceride and very low density lipoprotein cholesterol are elevated [20]. DM and dyslipidemia are important risk factors for CKD and should be carefully managed. Our study had several limitations. First, the study was conducted with a small sample size and included only men due to the small number of women. Among female PWHIV, only 59 people were available for analysis, and none of them developed renal insufficiency. A further large study would be performed involving women. Second, we performed the analysis about tenofovir without distinguishing between TDF and TAF. However, considering the time when TAF was started in Korea since 2017, it is unlikely that many patients taking TAF were included. The incidence of renal insufficiency in HIV-infected men in this study was 3.3 per 1,000 patient-years. DM, dyslipidemia, Tenofovir or NNRTI exposure for >1 year, and AIDS-defining illness were risk factors for renal insufficiency.
# Incidence and risk factors of renal insufficiency

Table 1: Demographic and clinical characteristic of patients with and without renal insufficiency at baseline

| Characteristics                              | Overall (n = 830) | Incident renal insufficiency | P-value* |
|----------------------------------------------|-------------------|-----------------------------|----------|
|                                              | Yes (n = 32)      | No (n = 798)                |          |
| Age (years) [n (%)]                          |                   |                             | 0.0001   |
| <40                                          | 410 (49.4)        | 2 (6.2)                     |          |
| 40 - 49                                      | 227 (27.4)        | 14 (43.8)                   |          |
| 50 - 59                                      | 138 (16.6)        | 10 (31.3)                   |          |
| >60                                          | 55 (6.63)         | 6 (18.8)                    |          |
| BMI (kg/m²) [n (%)]                          |                   |                             | 0.469    |
| <18.5                                        | 62 (7.5)          | 1 (3.1)                     |          |
| 18.5 - 22                                    | 442 (53.3)        | 17 (53.1)                   |          |
| 23 - 25                                      | 152 (18.3)        | 9 (28.1)                    |          |
| >25                                          | 174 (21.0)        | 5 (15.6)                    |          |
| Mode of transmission [n (%)]                 |                   |                             | 0.440    |
| Homosexual                                   | 310 (37.4)        | 11 (34.3)                   |          |
| Heterosexual                                 | 271 (32.7)        | 13 (40.6)                   |          |
| Bisexual                                     | 219 (26.4)        | 6 (18.8)                    |          |
| Unknown                                      | 30 (3.6)          | 2 (6.2)                     |          |
| Diabetes mellitus [n (%)]                    |                   |                             | 0.002    |
| Yes                                          | 49 (5.9)          | 7 (21.9)                    |          |
| No                                           | 781 (94.1)        | 25 (78.1)                   |          |
| Hypertension [n (%)]                         |                   |                             | 0.060    |
| Yes                                          | 75 (9.0)          | 6 (18.8)                    |          |
| No                                           | 755 (91.0)        | 26 (81.3)                   |          |
| Dyslipidemia [n (%)]                         |                   |                             | 0.001    |
| Yes                                          | 96 (11.6)         | 11 (34.3)                   |          |
| No                                           | 734 (88.4)        | 21 (65.6)                   |          |
| eGFR, mL/min/1.73 m² [mean (SD)]             |                   |                             | 0.0001   |
| CD4 [n (%)]                                  |                   |                             | 0.146    |
| ≤100                                         | 65 (7.8)          | 5 (15.6)                    |          |
| 101 - 200                                    | 98 (11.8)         | 6 (18.8)                    |          |
| 201 - 350                                    | 195 (23.5)        | 5 (15.6)                    |          |
| >351                                         | 472 (56.9)        | 16 (50.0)                   |          |
| HIV viral load [n (%)]                       |                   |                             | 0.047    |
| <400 copies/mL                               | 486 (58.6)        | 20 (62.5)                   |          |
| 400 - 50,000 copies/mL                       | 231 (27.8)        | 4 (12.5)                    |          |
| >50,000 copies/mL                            | 113 (13.6)        | 8 (25.0)                    |          |
| AIDS-defining illness [n (%)]                |                   |                             | 0.108    |
| Yes                                          | 162 (19.5)        | 10 (31.3)                   |          |
| No                                           | 668 (80.5)        | 22 (68.8)                   |          |
| Years on antiretroviral treatment [n (%)]    |                   |                             | 0.663    |
| ≤2                                           | 530 (63.9)        | 19 (59.4)                   |          |
| 2 - 5                                        | 226 (27.2)        | 9 (28.1)                    |          |
| >5                                           | 74 (8.9)          | 4 (12.5)                    |          |
| Tenofovir exposure [n (%)]                   |                   |                             | 0.774    |
| Never                                        | 438 (52.8)        | 12 (37.5)                   |          |
| Less than 1 year                             | 138 (16.6)        | 7 (21.9)                    |          |
| 1 year or more                              | 254 (30.6)        | 13 (40.6)                   |          |
| NRTI exposure [n (%)]                        |                   |                             | 0.041    |
| Never                                        | 153 (18.4)        | 1 (3.1)                     |          |
| Less than 1 year                             | 148 (17.8)        | 6 (18.8)                    |          |
| 1 year or more                              | 529 (63.7)        | 25 (78.1)                   |          |
| NNRTI exposure [n (%)]                       |                   |                             | 0.268    |
| Never                                        | 572 (68.9)        | 19 (59.4)                   |          |
| Less than 1 year                             | 72 (8.7)          | 2 (6.2)                     |          |
| 1 year or more                              | 186 (22.4)        | 11 (34.4)                   |          |
| Protease inhibitor exposure [n (%)]          |                   |                             | 0.003    |
| Never                                        | 362 (43.6)        | 6 (18.8)                    |          |
| Less than 1 year                             | 132 (15.9)        | 8 (25.0)                    |          |
| 1 year or more                              | 336 (40.5)        | 18 (56.3)                   |          |

*aSignificance of difference between patient with and without renal insufficiency; Chi-square test for categorical variables and paired t-test for continuous variables were used.

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NRTI, nucleoside reverse transcriptase inhibitor except tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor.
### Table 2. Crude incidence rates of renal insufficiency per 1,000 person-years during the 12-year follow-up period

| Characteristics               | No. of total case | No. of events (%) | Person-year | Incidence rate |
|-------------------------------|-------------------|-------------------|-------------|----------------|
| Overall                       | 830               | 32 (3.9)          | 9,684       | 3.30           |
| Age (years)                   |                   |                   |             |                |
| <40                           | 410               | 2 (0.5)           | 4,903       | 0.41           |
| 40 - 49                       | 227               | 14 (6.2)          | 2,611       | 5.36           |
| 50 - 59                       | 138               | 10 (7.3)          | 1,564       | 6.39           |
| >60                           | 55                | 6 (10.9)          | 605         | 9.91           |
| BMI (kg/m²)                   |                   |                   |             |                |
| <18.5                         | 62                | 1 (1.6)           | 734         | 1.36           |
| 18.5 - 22                     | 442               | 17 (3.9)          | 5,163       | 3.29           |
| 23 - 25                       | 152               | 9 (5.9)           | 1,751       | 5.14           |
| >25                           | 174               | 5 (2.9)           | 2,035       | 2.46           |
| Mode of transmission          |                   |                   |             |                |
| Homosexual                    | 310               | 11 (3.6)          | 3,613       | 3.04           |
| Heterosexual                  | 271               | 13 (4.8)          | 3,138       | 4.14           |
| Bisexual                      | 219               | 6 (2.7)           | 2,588       | 2.32           |
| Unknown                       | 30                | 2 (6.7)           | 345         | 5.80           |
| Diabetes mellitus             |                   |                   |             |                |
| Yes                           | 49                | 7 (14.3)          | 585         | 11.96          |
| No                            | 781               | 25 (3.2)          | 9,099       | 2.75           |
| Hypertension                  |                   |                   |             |                |
| Yes                           | 75                | 6 (8.0)           | 911         | 6.59           |
| No                            | 755               | 26 (3.4)          | 8,773       | 2.96           |
| Dyslipidemia                  |                   |                   |             |                |
| Yes                           | 96                | 11 (11.5)         | 1,086       | 10.13          |
| No                            | 734               | 23 (3.2)          | 8,598       | 2.44           |
| CD4 (cells/mm³)               |                   |                   |             |                |
| ≤100                          | 65                | 5 (7.7)           | 731         | 6.84           |
| 101 - 200                     | 98                | 6 (6.1)           | 1,127       | 5.32           |
| 201 - 350                     | 195               | 5 (2.6)           | 2,300       | 2.17           |
| >351                          | 472               | 16 (3.4)          | 5,525       | 2.90           |
| HIV viral load                |                   |                   |             |                |
| <400 copies/mL                | 486               | 20 (4.1)          | 5,665       | 3.53           |
| 400 - 50,000 copies/mL        | 231               | 4 (1.7)           | 2,741       | 1.46           |
| >50,000 copies/mL             | 113               | 8 (7.1)           | 1,277       | 6.26           |
| Years on antiretroviral treatment |             |                   |             |                |
| ≤2                            | 530               | 19 (3.6)          | 6,196       | 3.07           |
| 2 - 5                         | 226               | 9 (4.0)           | 2,622       | 3.43           |
| >5                            | 74                | 4 (5.4)           | 866         | 4.62           |
| AIDS-defining illness         |                   |                   |             |                |
| Yes                           | 162               | 10 (6.2)          | 1,925       | 5.20           |
| No                            | 668               | 22 (3.3)          | 7,759       | 2.84           |
| Tenofovir exposure            |                   |                   |             |                |
| Never                         | 438               | 12 (2.7)          | 5,153       | 2.33           |
| Less than 1 year              | 138               | 7 (5.1)           | 1,590       | 4.40           |
| 1 year or more                | 254               | 13 (5.1)          | 2,941       | 4.42           |
| NRTI exposure                 |                   |                   |             |                |
| Never                         | 153               | 1 (0.6)           | 1,825       | 0.55           |
| Less than 1 year              | 148               | 6 (4.1)           | 1,728       | 3.47           |
| 1 year or more                | 529               | 25 (4.7)          | 6,131       | 4.08           |
| NNRTI exposure                |                   |                   |             |                |
| Never                         | 572               | 19 (3.3)          | 6,693       | 2.84           |
| Less than 1 year              | 72                | 2 (2.8)           | 848         | 2.36           |
| 1 year or more                | 186               | 11 (5.9)          | 2,143       | 5.13           |
| Protease inhibitor exposure   |                   |                   |             |                |
| Never                         | 362               | 6 (1.7)           | 4,299       | 1.40           |
| Less than 1 year              | 132               | 8 (6.1)           | 1,522       | 5.26           |
| 1 year or more                | 336               | 18 (5.4)          | 3,863       | 4.66           |

BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NRTI, nucleoside reverse transcriptase inhibitor except tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor.
Table 3. Multivariate analysis of risk factors for incident renal insufficiency

| Variables                              | HR (95% CI)                | P-value* |
|----------------------------------------|----------------------------|----------|
| Age (years)                            | 1.05 (1.01 – 1.09)         | 0.03     |
| BMI (kg/m²)                            |                            |          |
| <18.5                                  | 0.43 (0.04 – 4.19)         | 0.47     |
| 18.5 – 22                              | 1.00 (Ref)                 |          |
| 23 – 25                                | 0.66 (0.24 – 1.81)         | 0.42     |
| >25                                    | 0.42 (0.13 – 1.37)         | 0.15     |
| Mode of transmission                   |                            |          |
| Homosexual                             | 1.24 (0.50 – 3.08)         | 0.64     |
| Heterosexual                           | 1.00 (Ref)                 |          |
| Bisexual                               | 0.31 (0.10 – 0.94)         | 0.04     |
| Unknown                                | 2.91 (0.58 – 14.50)        | 0.19     |
| Diabetes mellitus                      |                            |          |
| Yes                                    | 13.72 (4.39 – 42.91)       | <0.0001  |
| No                                     | 1.00 (Ref)                 |          |
| Hypertension                           |                            |          |
| Yes                                    | 0.59 (0.18 – 1.97)         | 0.39     |
| No                                     | 1.00 (Ref)                 |          |
| Dyslipidemia                           |                            |          |
| Yes                                    | 3.10 (1.25 – 7.69)         | 0.01     |
| No                                     | 1.00 (Ref)                 |          |
| Baseline eGFR, mL/min/1.73 m²          | 0.91 (0.88 – 0.94)         | <0.0001  |
| CD4 at enrollment                      |                            |          |
| >350                                   | 1.00 (Ref)                 |          |
| 201 – 350                              | 0.47 (0.15 – 1.52)         | 0.21     |
| 101 – 200                              | 1.38 (0.42 – 4.530)        | 0.60     |
| ≤100                                   | 2.78 (0.73 – 10.65)        | 0.14     |
| HIV viral load at enrollment           |                            |          |
| ≤400 copies/mL                         | 1.00 (Ref)                 |          |
| >400 copies/mL                         | 1.23 (0.49 – 3.10)         | 0.65     |
| AIDS-defining illness                  |                            |          |
| Yes                                    | 2.48 (1.05 – 5.84)         | 0.04     |
| No                                     | 1.00 (Ref)                 |          |
| Years on antiretroviral treatment      |                            |          |
| <2                                     | 1.00 (Ref)                 |          |
| 2 – 5                                  | 0.49 (0.18 – 1.31)         | 0.15     |
| >5                                     | 1.38 (0.40 – 4.84)         | 0.61     |
| Tenofovir exposure                     |                            |          |
| Never                                  | 1.00 (Ref)                 |          |
| Less than 1 year                       | 1.45 (0.47 – 4.46)         | 0.52     |
| 1 year or more                         | 2.41 (1.01 – 5.77)         | 0.047    |
| NRTI exposure                          |                            |          |
| Never                                  | 1.00 (Ref)                 |          |
| Less than 1 year                       | 0.96 (0.08 – 11.96)        | 0.98     |
| 1 year or more                         | 1.68 (0.15 – 18.31)        | 0.67     |
| NNRTI exposure                         |                            |          |
| Never                                  | 1.00 (Ref)                 |          |
| Less than 1 year                       | 1.73 (0.32 – 9.27)         | 0.52     |
| 1 year or more                         | 3.88 (1.30 – 11.59)        | 0.01     |
| Protease inhibitor exposure            |                            |          |
| Never                                  | 1.00 (Ref)                 |          |
| Less than 1 year                       | 3.40 (0.79 – 14.61)        | 0.10     |
| 1 year or more                         | 2.81 (0.73 – 10.85)        | 0.13     |

*Cox proportional hazards regression model was adjusted for age, body mass index, mode of transmission, history of diseases (diabetes mellitus, hypertension, and dyslipidemia), level of eGFR, CD4, HIV viral load, AIDS-defining illness, Years on antiretroviral treatment, tenofovir exposure, NRTI exposure, NNRTI exposure, and protease inhibitor exposure.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NRTI, nucleoside reverse transcriptase inhibitor except tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor.
REFERENCES

1. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. N Engl J Med 2017;377:2363-74.

2. Cheung J, Puhr R, Petoumenos K, Cooper DA, Woolley I, Gunathilake M, Raymond N, Varma R, O’Connor CC, Gracey DM. Chronic kidney disease in Australian human immunodeficiency virus-infected patients: analysis of the Australian HIV observational database. Nephrology (Carlton) 2018;23:778-86.

3. Kim EJ, Ahn JY, Kim YJ, Wie SH, Park DW, Song JY, Choi HJ, Chang HH, Choi BY, Choi Y, Choi JY, Han MG, Kang C, Kim JM, Choi JY, Korea H; Korea HIV/AIDS Cohort Study. The prevalence and risk factors of renal insufficiency among Korean HIV-infected patients: The Korea HIV/AIDS cohort Study. Infect Chemother 2017;49:194-204.

4. GBD 2015 HIV Collaborators. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. Lancet HIV 2016;3:e361-87.

5. Boender TS, Smit C, Sighem AV, Bezemer D, Ester CJ, Zaheri S, Wit FWNM, Reiss P; ATHENA national observational HIV cohort. AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. BMJ Open 2018;8:e022516.

6. Cho YM, Chin B. Assessment of human immunodeficiency virus care continuum in Korea using the national health insurance system data. Infect Chemother 2021;53:477-88.

7. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, Kowalska JD, de Wit S, Law M, el Sadr W, Kirk O, Friis-Moller N, Monforte AD, Phillips AN, Sabin CA, Lundgren JD; D:A:D Study Group. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet 2014;384:241-8.

8. Choi BY, Choi JY, Han SH, Kim SI, Kee MK, Kim MJ, Kim SW, Kim SS, Kim YM, Ku NS, Lee JS, Lee JS, Choi Y, Park KS, Song JY, Woo JH, Kang MW, Kim J. Korea HIV/AIDS cohort study: study design and baseline characteristics. Epidemiol Health 2018;40:e2018023.

9. Shi R, Chen X, Lin H, Ding Y, He N. Incidence of impaired kidney function among people with HIV: a systematic review and meta-analysis. BMC Nephrol 2022;23:107.

10. Kaboré NF, Poda A, Zounggrana J, Da O, Ciaffi L, Sembdé A, Yamégou IB, Sawadogo AB, Delaporte E, Meda N, Limou S, Courjil N. Chronic kidney disease and HIV in the era of antiretroviral treatment: findings from a 10-year cohort study in a west African setting. BMC Nephrol 2019;20:155.

11. Quesada PR, Esteban LL, García JR, Sánchez RV, García TM, Alonso-Vega GG, Ferrández JS. Incidence and risk factors for tenofovir-associated renal toxicity in HIV-infected patients. Int J Clin Pharm 2015;37:865-72.

12. Joshi K, Boettiger D, Kerr S, Nishijima T, Van Nguyen K, Ly PS, Lee MP, Kumarasamy N, Wong W, Kantipong P, Cuong DD, Kamarulzaman A, Choi JY, Zhang F, Chaiwarith R, Ng OT, Kiertiburanakul S, Sim BLH, Merati TP, Yunihastuti E, Ditangeo R, Ross J, Pujari S. Changes in renal function with long-term exposure to antiretroviral therapy in HIV-infected adults in Asia. Pharmacoepidemiol Drug Saf 2018;27:1209-16.

13. Lee MJ, Ha KH, Kim DJ, Park I. Trends in the incidence, prevalence, and mortality of end-stage kidney disease in South Korea. Diabetes Metab J 2020;44:933-7.

14. Abraham AG, Althoff KN, Jing Y, Estrella MM, Kitahata MM, Wester CW, Bosch RJ, Crane H, Eron JI, Gill MJ, Horberg MA, Justice AC, Klein M, Mayor AM, Moore RD, Palella FJ, Parikh CR, Silverberg MJ, Golub ET, Jacobson LP, Napravnik S, Lucas OM; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the International Epidemiologic Databases to Evaluate AIDS (IeDEA). End-stage renal disease among HIV-infected adults in North America. Clin Infect Dis 2015;60:941-9.
15. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol 2013;24:1519-27.
   PUBMED | CROSSREF

16. Suzuki S, Nishijima T, Kawasaki Y, Kurosawa T, Mutoh Y, Kikuchi Y, Gatanaga H, Oka S. Effect of tenofovir disoproxil fumarate on incidence of chronic kidney disease and rate of estimated glomerular filtration rate decrement in HIV-1-infected treatment-naïve Asian patients: results from 12-year observational cohort. AIDS Patient Care STDS 2017;31:105-12.
   PUBMED | CROSSREF

17. Gupta SK, Post FA, Arribas JR, Wohl DA, Clarke AE, Sax PE, Stellbrink HJ, Esser S, Pozniak A, Podzamczer D, Waters L, Orkin C, Rockstroh JK, Mudrikova T, Negredo E, Elion RA, Guo S, Zhong L, Carter C, Martin H, Brainard D, SenGupta D, Das M. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. AIDS 2019;33:1455-65.
   PUBMED | CROSSREF

18. Pelchen-Matthews A, Ryom L, Borges ÂH, Edwards S, Duvivier C, Stephan C, Sambatakou H, Maciejewska K, Portu JJ, Weber J, Degen O, Calmy A, Reikvam DH, Jevtic D, Wiese L, Smidt J, Smiatacz T, Hassoun G, Kuznetsova A, Clotet B, Lundgren J, Mocroft A; EuroSIDA study. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. AIDS 2018;32:2405-16.
   PUBMED | CROSSREF

19. Chang HH. Weight gain and metabolic syndrome in human immunodeficiency virus patients. Infect Chemother 2022;54:220-35.
   PUBMED | CROSSREF

20. Malvestutto CD, Aberg JA. Management of dyslipidemia in HIV-infected patients. Clin Lipidol 2011;6:447-62.
   PUBMED | CROSSREF