## Title

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# The incidence of and risk factors for hospitalized acute kidney injury among people living with HIV on antiretroviral treatment

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## Abstract

**Objectives:** The epidemiology of hospitalized acute kidney injury (AKI) among people living with HIV (PLWH) in the era of modern antiretroviral therapy (ART) for all PLWH is not well characterized. We evaluated the incidence of and risk factors for hospitalized AKI from 2005 to 2015 among PLWH on ART.

**Methods:** We conducted a retrospective analysis of PLWH from the Johns Hopkins HIV Clinical Cohort. We defined hospitalized AKI as a rise of ≥ 0.3 mg/dL in serum creatinine (SCr) within any 48-h period or a 50% increase in SCr from baseline and assessed associations of risk factors with incident AKI using multivariate Cox regression models.

**Results:** Most participants (75%) were black, 34% were female, and the mean age was 43 years. The incidence of AKI fluctuated annually, peaking at 40 per 1000 person-years (PY) [95% confidence interval (CI) 22–69 per 1000 PY] in 2007, and reached a nadir of 20 per 1000

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AUTHOR CONTRIBUTIONS

Research idea and study design: ANM, EM, MGS, and MME; data acquisition: MGS, RM, CCV, JMMT, and MME; data analysis/interpretation: ANM, EM, ADR, RS, CYH, MGS, MME; statistical analysis: EM; supervision or mentorship: RS, MGS, CYH and MME. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ANM takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors have read and approved of the final version of this manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

SUPPORTING INFORMATION

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PY (95% CI 11–34 per 1000 PY) in 2010. There was no significant temporal trend (−3.3% change per year; 95% CI −8.6 to 2.3%; $P = 0.24$). After multivariable adjustment, characteristics independently associated with AKI included black race [hazard ratio (HR) 2.44; 95% CI 1.42–4.20], hypertension (HR 1.62; 95% CI 1.09–2.38), dipstick proteinuria > 1 (HR 1.86; 95% CI 1.07–3.23), a history of AIDS (HR 1.82; 95% CI 1.29–2.56), CD4 count < 200 cells/μL (HR 1.46; 95% CI 1.02–2.07), and lower serum albumin (HR 1.73 per 1 g/dL decrease; 95% CI 1.02–2.07).

**Conclusions:** In this contemporary cohort of PLWH, the annual incidence of first AKI fluctuated during the study period. Attention to modifiable AKI risk factors and social determinants of health may further reduce AKI incidence among PLWH.

### Keywords

acute kidney injury; antiretroviral therapy; chronic kidney disease; HIV; proteinuria

## INTRODUCTION

Antiretroviral therapy (ART) has improved the life expectancy of people living with HIV (PLWH) [1,2]. Unfortunately, noninfectious comorbidities including kidney diseases have tempered the improved longevity among PLWH [3–5]. Acute kidney injury (AKI) affects ~20% of hospitalized patients in the general population [6,7]. While the incidence of hospitalized AKI in the general population is rising [6,7], few studies have described the epidemiology of AKI among PLWH in the era of universal ART.

Since the approval of zidovudine in 1987 [8], there have been more than two dozen drugs approved for HIV treatment [9]. Furthermore, newer ART regimens are associated with less nephrotoxicity compared with older ART [10]. However, prior AKI studies included PLWH on older more nephrotoxic agents or untreated PLWH [11–15]. Furthermore, some of these studies relied on administrative data to define AKI [13], which have low sensitivity in detecting AKI [16]. Given the rapid evolution in ART and changing treatment guidelines over time, we quantified the longitudinal trends in AKI over a decade spanning 2005–2015 and evaluated risk factors for AKI among PLWH.

## METHODS

### Study design and setting

We conducted a cohort study nested within the Johns Hopkins HIV Clinical Cohort (JHHCC) [17]. Briefly, the JHHCC is an longstanding open cohort that enrolls PLWH receiving care at the Johns Hopkins Bartlett Practice—the largest provider of HIV care in Maryland, USA [17]. Patients are approached for participation in the cohort when they initiate longitudinal HIV care in the clinic. As per JHHCC protocol, data are collected through patient interviews and electronic health records. The data capture information from all hospitalizations, outpatient clinics and emergency department visits within the Johns Hopkins Hospital. More than 95% of the laboratory data are collected electronically through direct linkage to the Johns Hopkins electronic databases and outside laboratories. Our study analysed data from participants enrolled in the JHHCC from 1 January 2005 to 31 December 2015. The Institutional Review Boards at the Johns Hopkins School of Medicine,

the University of California at San Francisco, and the San Francisco Veterans Affairs health care system approved this study.

## Patient population

We identified 1637 patients enrolled in the JHHCC from 1 January 2005 to 31 December 2015 who had been initiated on ART [9]. The ART index date was the enrolment date for prevalent users and the earliest ART start date post-enrolment for new users. We excluded patients who met any of the following criteria: (1) end-stage kidney disease (ESKD), defined as an outpatient estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 $m^2$ on two occasions at least 90 days apart, outpatient dialysis, or chart/encounter-based ESKD diagnosis on or prior to the ART index date ($n$ = 46); (2) AKI event or diagnosis within 6 months prior to the index date (in order to exclude serum creatinine fluctuations during AKI recovery) ($n$ = 121); and (3) hospitalization lacking serum creatinine within 6 months prior to the index date (because we could not ascertain whether AKI occurred during those hospitalizations) ($n$ = 37). A total of 1433 patients met the inclusion criteria.

## Outcome

The primary outcome was time from ART index date to first hospitalized AKI event. We defined AKI as: (1) a rise of ≥ 0.3 mg/dL in serum creatinine within any 48-h period during the hospitalization (outpatient serum creatinine was considered if it preceded the inpatient serum creatinine within 48 h); or (2) maximum inpatient serum creatinine ≥ 50% higher than baseline serum creatinine. For these purposes, we defined baseline serum creatinine as the mean outpatient serum creatinine between 7 and 90 days prior to admission; most participants had serum creatinine frequently measured as part of usual care at the Bartlett Clinic. The median number of serum creatinine values used to define mean creatinine was 2 [interquartile range (IQR) 1–3], and the median time from the closest serum creatinine measurement to hospital admission date was 62 days (IQR 27–139 days). When no serum creatinine was available 7–90 days prior to admission, the mean serum creatinine from 91–365 days prior to admission was used ($n$ = 65). Finally, if there was no serum creatinine measured between 7 and 365 days prior to admission, we used the lowest serum creatinine value from 1–6 days prior to admission ($n$ = 5). With this approach, no participant had a missing baseline creatinine value.

Participants were censored at the earliest of the following: death ($n$ = 21), loss to follow-up (last encounter date for persons who did not have an encounter in the subsequent 24 months) ($n$ = 323), start of a hospitalization lacking a serum creatinine measurement, which prevented determination of AKI status ($n$ = 88), development of ESKD ($n$ = 8), or administrative end of the study (31 May 2016) ($n$ = 811).

We defined AKI severity according to serum creatinine thresholds in the Kidney Disease Improvement Global Outcomes (KDIGO) AKI guidelines [18].

## Risk factors and covariates

Baseline demographic and behavioural characteristics included the ART index date (to account for temporal trends), whether the individual was a prevalent or a new user of ART,

age, sex, self-reported race, injecting drug use, smoking status, and type of insurance. Comorbidities included diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), ischaemic heart disease, hepatitis C virus (HCV) infection (defined by diagnosis codes or HCV antibody sero-positivity), history of AKI > 6 months prior to the index date (defined by diagnosis codes or the serum creatinine-based schema as described above), chronic kidney disease (CKD) (outpatient eGFRs < 60 mL/min/1.73 $m^2$ on two occasions at least 90 days apart), and dipstick proteinuria.

We combined encounter- (international classification of diseases-coded) and chart-based diagnoses to define comorbid conditions [19,20]. We used outpatient serum creatinine to calculate the CKD epidemiology collaboration eGFR [21]. GFR estimates exceeding 150 mL/min/1.73 $m^2$ ($n$ = 23 observations) were capped at 150 mL/min/1.73 $m^2$. We defined proteinuria as outpatient urine dipstick ≥ 1 on at least two occasions at least 90 days apart.

We ascertained body mass index (BMI) and systolic and diastolic blood pressures at the date closest to the index date (up to 1 year prior and 7 days post). We used serum albumin, haemoglobin, HIV-1 RNA and CD4 cell count measurements that were closest to the index date up to 1 year prior and 7 days post. HIV viral load was irregularly captured during follow-up and thus we did not include time-updated HIV viral load in the Cox models [22]. For total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, we used measurements that were also closest to the index date but up to 18 months prior and 30 days post.

We defined history of AIDS as any history of an opportunistic infection. Medication of interest at the index date included diuretics, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), tenofovir disoproxil fumarate (TDF) and atazanavir. We defined medication use as having ever started the medication prior to the study index date to avoid misclassifying users as nonusers because patterns of use appeared implausible for some patients. To avoid immortal time bias, we strictly defined baseline measures as those ascertained prior to or on the index date (except where noted above), which meant that some measures were commonly missing for patients whose ART index date coincided with their date of enrolment in the JHHCC.

## Statistical analysis

We summarized baseline characteristics with frequency distributions for categorical variables and means and standard deviations (SDs) for continuous variables. The percentage of missing baseline data was calculated for each variable (Table S1). Missing baseline data were addressed with multiple imputation ($m$ = 30 imputations, as recommended for moderate-high proportion of missingness, using the fully conditional specification method) [23]. The model used to impute missing values included the event indicator, the Nelson–Aalen estimate of the cumulative hazard to the survival time, and all of the risk factors and covariates listed above [24].

Incidence rates of first hospitalized AKI event were calculated using person-years at risk, and the corresponding 95% confidence intervals (CIs) were based on Poisson distribution [25]. Each person was allowed to contribute a maximum of one episode of AKI, and thus

participants were removed from the risk set after the first AKI, or after experiencing a censoring event. We presented incidence rates of first hospitalized AKI event by calendar year to show longitudinal trends. The incidence of first hospitalized AKI stratified by level of severity was calculated in a similar manner to overall AKI.

We then assessed associations between potential risk factors and incident AKI using univariable and multivariable Cox regression models (combining inferences from the multiply imputed data sets). We checked the functional form of continuous covariates with tests of quadratic terms and plots of the cumulative martingale residuals. We also assessed the proportional hazards assumption with Kolmogorov-type supremum tests, plots of Schoenfeld residual vs. covariates, and tests of interaction between covariate and log of time to event. For highly correlated risk factors, we retained the most clinically meaningful variable in the multivariable Cox model. To address potential bias resulting from informative censoring, we estimated the probability of remaining uncensored and weighted each patient by the inverse (inverse probability of censoring weighting [IPCW]). We considered the following reasons for censoring to be informative: lack of serum creatinine measurements during hospitalization, loss to follow-up and death. We modelled the censoring process for each type of censoring separately, and then calculated the joint stabilized inverse probability of censoring [26]. The models of the censoring process included all risk factors (multiply imputed data) and, importantly, indicators of missingness for all risk factors.

As recommended, we assessed sensitivity of Cox regression models to large IPCW weights by running the multivariable regression model with the weights truncated at the $99^{th}$ percentile and comparing the regression coefficients with those from the model using untruncated weights (results not shown) [27].

In order to avoid channelling bias [28], and confounding by indication associated with certain HIV medications [29], we used a slightly different analytical approach to estimate the associations of TDF and atazanavir use with AKI. We first compared TDF users and nonusers on baseline characteristics and found TDF users to have significantly higher mean eGFR compared to nonusers (108 vs. 99 mL/min/1.73 $m^2$, respectively; $P < 0.001$). We then performed logistic regression of ever prior TDF use with all the other covariates as predictors and then calculated stabilized inverse probability of treatment weights (IPTWs). We assessed covariate balance in the inverse probability-weighted TDF users compared with nonusers by calculating standardized differences and found no evidence of imbalance (all standardized differences < 0.1). We then analysed the association of TDF with AKI by including an indicator for TDF use and other covariates in a Cox regression model weighted by IPTW and IPCW.

Next, we analysed the association of atazanavir with AKI using a similar approach as described above for TDF. First, we compared atazanavir users and nonusers on baseline characteristics and found that atazanavir users had similar baseline eGFR to nonusers; however, they were slightly more likely to have proteinuria (7.8% vs. 3.6%, respectively; $P = 0.01$) and to have been hospitalized in the past year (22.5% vs. 16.3%, respectively; $P = 0.01$) compared to nonusers. Then we estimated IPTWs for atazanavir. We assessed covariate balance in the inverse probability-weighted atazanavir users compared with

nonusers by calculating standardized differences and found no evidence of imbalance for all covariates, except that atazanavir users were slightly less likely to be TDF users compared to atazanavir nonusers (standardized difference = −0.2). Finally, we analysed the association of atazanavir with AKI by including an indicator for atazanavir use and other covariates in a Cox regression model weighted by IPTW and IPCW.

All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

## RESULTS

### Baseline characteristics

We included a total of 1433 PLWH on ART in this analysis. The median follow-up time was 4 years (IQR 1.8–6.4 years). Baseline sociodemographic and clinical characteristics are shown in Table 1. Most participants self-identified as black (75%), and 34% were female. The mean age at enrolment was 43 years (SD 11 years). Sociodemographic characteristics that were more common among participants with hospitalized AKI when compared with those without AKI included self-identified black race, older age, earlier date of ART initiation, history of injecting drug use, and reliance on government insurance. In addition, individuals who experienced hospitalized AKI had a higher prevalence of comorbidities such as hypertension and HCV infection. The prevalence of CKD and dipstick proteinuria ≥ 1 was higher among individuals with hospitalized AKI when compared with those without AKI. PLWH with hospitalized AKI had less controlled HIV infection, with higher viraemia, lower CD4 counts and a higher likelihood of a history of AIDS, and a higher proportion of TDF use.

### AKI incidence

The incidence of AKI fluctuated from year to year with a peak of 40 (95% CI 22–69) per 1000 person-years (PY) in 2007 and a nadir of 20 (95% CI 11–34) per 1000 PY in 2010 (Figure 1). Overall, there was no significant temporal trend: −3.3% per year (95% CI −8.6 to 2.3%; $P = 0.24$). Stage 1 AKI accounted for most AKI cases in this study (74%), and nearly all cases occurred among individuals with CKD (eGFR < 60 mL/min/1.73 $m^2$). Stage 2 AKI accounted for 12%, and stage 3 AKI accounted for 14% of incident AKI hospitalizations.

### AKI risk factors

Table 2 shows our univariable and multivariable Cox regression models assessing the associations between potential risk factors and hospitalized AKI. In the multivariable models, we observed that self-identified black race was the only sociodemographic factor that was strongly associated with hospitalized AKI [adjusted hazard ratio (aHR) 2.44; 95% CI 1.42–4.20]. Comorbid conditions that were associated with hospitalized AKI included hypertension (aHR 1.62; 95% CI 1.09–2.38), dipstick proteinuria (aHR 1.86; 95% CI 1.07–3.23), and lower serum albumin (aHR 1.73 per 1 g/dL decrease; 95% CI 1.24–2.40 per 1 g/dL decrease). Of the HIV-related risk factors, a history of AIDS (aHR 1.82; 95% CI 1.29–2.56) and CD4 count ≤ 200 cells/μL (aHR 1.46; 95% CI 1.02–2.07, when compared with CD4 count > 200 cells/μL) remained strongly associated with risk of AKI in the multivariable analysis.

In a separate analysis, using IPTW to account for indication and channelling bias for TDF and atazanavir use, neither was associated with the risk of AKI (TDF aHR 0.80; 95% CI 0.54–1.19; atazanavir aHR 0.81; 95% CI 0.52–1.27).

Our results were almost identical in our analysis testing the sensitivity of the Cox regression models to large IPCW.

## DISCUSSION

We evaluated the incidence of and risk factors for hospitalized AKI among PLWH on ART in a large urban medical centre in Northern America. We observed that the incidence of AKI fluctuated from year to year, and history of AIDS, lower CD4 cell count, black race, hypertension, proteinuria, and lower serum albumin concentrations were independently associated with AKI.

Our study builds on one prior study of PLWH that defined AKI according to international guidelines [18]. Li *et al.* reported a gradual decrease in hospitalized AKI from 1995 to 2006 among US military veterans [12]. The nadir in incidence of AKI in that study was 29 per 1000 PY in 2006, which is similar to our findings; however, we did not find any strong temporal trend from 2005 onwards. The decline in AKI incidence in Li *et al.* was largely attributed to ART [12]. In the absence of ART, progressive immunodeficiency ensues and leads to AIDS-defining opportunistic infections that drastically increase the risk of hospitalized AKI [30]. In addition, untreated HIV infection can lead to various forms of HIV-associated kidney disease such as immune complex kidney disease [31,32], or HIV-associated nephropathy (HIVAN) [33], which can present with AKI. We only included participants on ART in our study, so that may be why we did not observe any strong trends in AKI incidence over time. However, of the HIV-related risk factors examined in our study, markers of immune suppression, including CD4 count < 200 cells/μL and a history of AIDS, were associated with increased risk of AKI.

In the setting of ART, traditional AKI risk factors such as proteinuria remained strongly associated with AKI in our study. Proteinuria is highly prevalent among PLWH [34–36], and current Infectious Diseases Society of America (IDSA) guidelines recommend screening for proteinuria and treatment with ACE-Is/ARBs [37]. These medications may be particularly useful among hypertensive PLWH [38]. Hypertension is another highly prevalent condition among PLWH [38,39], and was associated with AKI in our population and among veterans with HIV infection [12].

Our study also adds to the literature showing an increased risk of kidney disease among black PLWH [4,12]. Despite adjustment for sociodemographic factors, comorbidities, degree of HIV control and other kidney-preserving treatments, we could not explain the increased risk of AKI associated with black race in our analysis. We do not believe that our findings can be attributed to a genetic predisposition to HIVAN and other forms of kidney diseases as a consequence of apolipoprotein L1 (*APOL1)* genetic variants [40,41]. *APOL1* variants are not associated with AKI [42], and the wide roll-out of ART has substantially decreased the incidence of biopsy-proven HIVAN [43]. Racial disparities in AKI risk were partially

attributed to differences in income and health insurance in one community-based cohort study of individuals without HIV infection [42]. While we accounted for health insurance in our multivariable models, we did not have data regarding family income, and differences in income may explain some of the increased risk of AKI observed among black individuals. Efforts to better identify and address other modifiable determinants of health outcomes among black individuals such as systemic inequities (including racism and bias) are urgently needed [44–46].

The major strengths of our study are its large sample size, which leveraged a long-standing clinical cohort, and exclusion of untreated PLWH. ART is recommended for all PLWH [47], and thus our study is more representative of PLWH in the current era of universal ART. In addition, we used acute changes in serum creatinine to define AKI according to the KDIGO guidelines [18]. However, we also acknowledge several limitations. First, this was a single-centre study. Secondly, although there are numerous causes of AKI, we lacked information regarding the aetiology of AKI, which limits our ability to further explain the observed incidence of AKI and racial differences. Thirdly, we only captured AKI events that occurred in the setting of hospitalization and could not capture cases that may have been managed in the outpatient setting. Fourthly, it is possible that participants obtained care outside of Johns Hopkins, leading to incomplete AKI ascertainment and underestimation of incidence. Fifthly, medication exposure was ascertained using electronic medical records which may lead to misclassification of medication exposure and does not capture treatment adherence. In addition, using electronic medical records has inherent biases which we attempted to address using IPCW.

In conclusion, we report that the AKI incidence has been fluctuating in the decade spanning 2005–2015 without strong temporal trends among those uniformly on ART. With universal roll-out of ART among all PLWH, it is important to treat proteinuria and hypertension and eliminate barriers to equitable care that black PLWH face.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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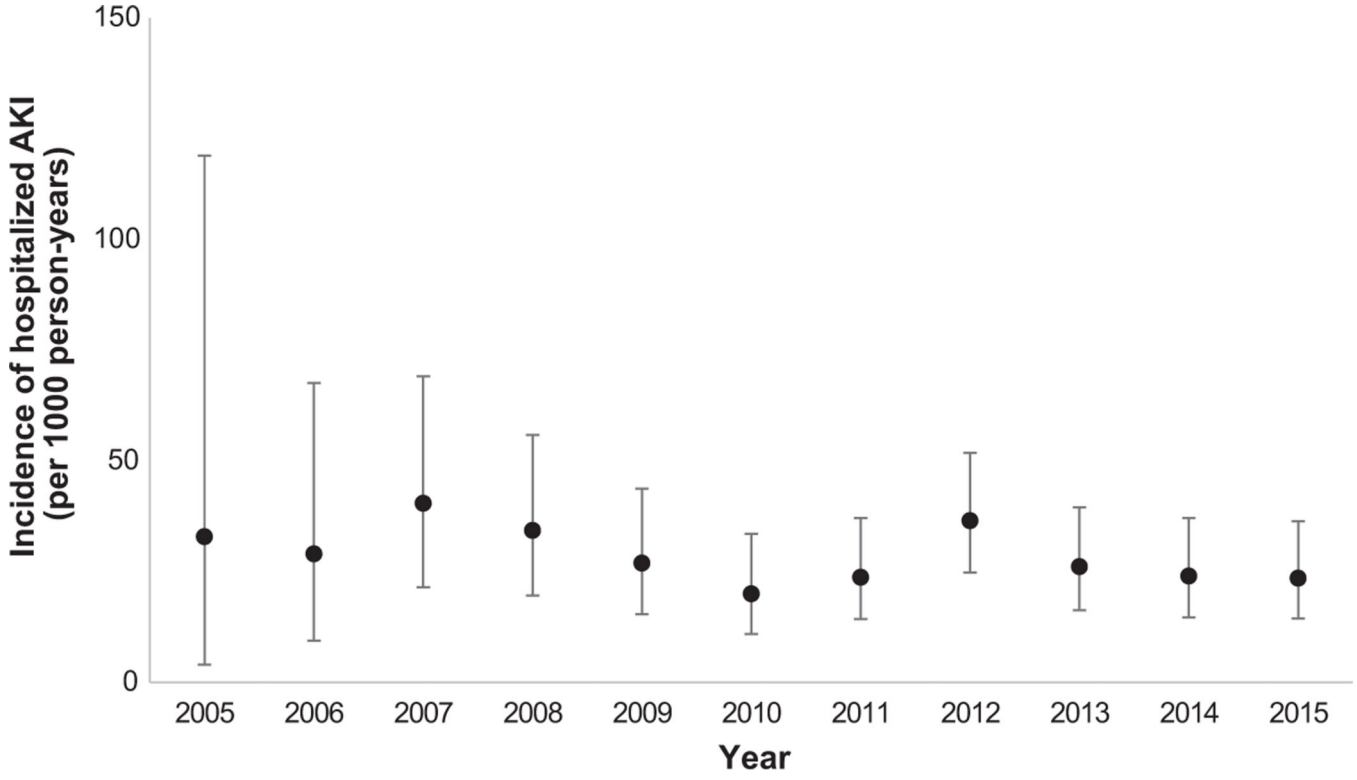


**FIGURE 1.**

Crude incidence of first acute kidney injury (AKI) by calendar year among people living with HIV from 2005 to 2015 enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC)

**TABLE 1**

Baseline characteristics stratified by acute kidney injury (AKI) status in the Johns Hopkins HIV Clinical Cohort from 2005 to 2015 (*n* = 1433)

| Characteristic | No AKI (*n* = 1251) | AKI (*n* = 182) | *P*-value[a] |
|---|---|---|---|
| Sociodemographic | | | |
| Age at index (years) [mean (SD)] | 42.7 (11.2) | 46.7 (11.0) | <0.001 |
| Female (%) | 34 | 37 | 0.45 |
| Self-identified black race (%) | 73 | 91 | <0.001 |
| Injecting drug use (%) | 23 | 42 | <0.001 |
| Smoking status at index (%)[b] | | | |
| Current | 67 | 77 | 0.24 |
| Former | 8 | 5 | |
| Nonsmoker | 25 | 19 | |
| Insurance type at index (%)[b] | | | |
| Government[c] | 69 | 86 | <0.001 |
| Private | 29 | 12 | |
| Uninsured | 2 | 2 | |
| Comorbid conditions (%) | | | |
| Diabetes mellitus | 8 | 12 | 0.08 |
| Hypertension | 30 | 49 | <0.001 |
| Chronic obstructive pulmonary disease | 5 | 15 | <0.001 |
| Ischaemic heart disease | 3 | 8 | 0.001 |
| Chronic kidney disease[d] | 2 | 9 | <0.001 |
| Hepatis C virus infection | 28 | 51 | <0.001 |
| History of AKI (> 6 months from index date) | 5 | 16 | <0.001 |
| Clinical measurements[b] | | | |
| Body mass index (kg/m$^2$) [mean (SD)] | 26.2 (11) | 25.4 (6.3) | 0.40 |
| Systolic blood pressure (mm Hg) [mean (SD)] | 127 (167) | 125 (32) | 0.92 |
| Diastolic blood pressure (mm Hg) [mean (SD)] | 78 (144) | 73 (25) | 0.63 |
| eGFR (mL/min/1.73 m$^2$) [mean (SD)] | 106 (24) | 101 (30) | 0.01 |
| Serum albumin (g/dL) [mean (SD)] | 4.1 (0.5) | 3.8 (0.5) | <0.001 |

| Characteristic | No AKI (*n* = 1251) | AKI (*n* = 182) | *P*-value[a] |
|---|---|---|---|
| Dipstick proteinuria (≥ 1) (%) | 9 | 24 | <0.001 |
| HIV-related factors | | | |
| HIV RNA ($log_{10}$ copies/mL)[b] [mean (SD)] | 4.9 (5.4) | 5.1 (5.4) | 0.05 |
| CD4 count (cells/μL)[b] [mean (SD)] | 345 (267) | 242 (282) | <0.001 |
| History of AIDS (%) | 29 | 56 | <0.001 |
| New users of ART (%) | 58 | 61 | 0.37 |
| Any tenofovir disoproxil fumarate use (%) | 73 | 62 | 0.002 |
| Any atazanavir use (%) | 19 | 24 | 0.10 |
| Medication use (%) | | | |
| Diuretic use | 7 | 14 | 0.001 |
| ACE-I or ARB | 8 | 14 | 0.01 |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a] *P*-values are based on pooled variances *t*-test for continuous variables and on $\chi^2$ test for categorical variables.

[b] Multiply imputed.

[c] Medicare/Medicaid/other public/Ryan White.

[d] Outpatient eGFRs < 60 mL/min/1.73 $m^2$ on two occasions at least 90 days apart.

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**TABLE 2**

Association of baseline demographic and clinical characteristics with risk of acute kidney injury (AKI)

| Risk factor | Unadjusted HR (95% CI) | *P*-value | Adjusted HR (95% CI) | *P*-value |
|---|---|---|---|---|
| ART index date (per year) | 1.00 (0.94, 1.07) | 0.97 | 1.01 (0.94, 1.08) | 0.86 |
| Sociodemographic characteristics | | | | |
| Age at index (per decade) | 1.43 (1.24, 1.65) | <0.001 | 1.11 (0.93, 1.33) | 0.24 |
| Female | 1.16 (0.84, 1.6) | 0.36 | 1.18 (0.84, 1.66) | 0.33 |
| Self-identified black race | 4.03 (2.36, 6.89) | <0.001 | 2.44 (1.42, 4.20) | 0.001 |
| Injecting drug use | 2.13 (1.56, 2.91) | <0.001 | 1.02 (0.65, 1.59) | 0.93 |
| Smoking status at index | | | | |
| Current smoker vs. nonsmoker | 1.67 (0.83, 3.36) | 0.16 | 1.52 (0.74, 3.12) | 0.25 |
| Former smoker vs. nonsmoker | 0.66 (0.18, 2.41) | 0.53 | 0.55 (0.14, 2.26) | 0.40 |
| Insurance type at index | | | | |
| Private vs. government[a] | 0.40 (0.24, 0.69) | <0.001 | 0.71 (0.41, 1.22) | 0.21 |
| Uninsured vs. government | 0.52 (0.13, 2.07) | 0.35 | 1.29 (0.28, 6.0) | 0.74 |
| Comorbid conditions | | | | |
| Chronic kidney disease | 5.06 (3.01, 8.49) | <0.001 | 1.77 (0.96, 3.26) | 0.07 |
| Diabetes mellitus | 1.75 (1.11, 2.76) | 0.02 | 1.13 (0.66, 1.92) | 0.66 |
| Hypertension | 2.36 (1.73, 3.23) | <0.001 | 1.62 (1.09, 2.38) | 0.02 |
| COPD | 3.85 (2.53, 5.85) | <0.001 | 1.48 (0.90, 2.43) | 0.12 |
| Ischaemic heart disease | 3.18 (1.84, 5.49) | <0.001 | 1.67 (0.90, 3.09) | 0.10 |
| HCV infection | 2.29 (1.69, 3.12) | <0.001 | 1.27 (0.82, 1.95) | 0.28 |
| History of AKI (> 6 months prior to index) | 3.4 (2.25, 5.12) | <0.001 | 1.13 (0.68, 1.89) | 0.63 |
| Dipstick proteinuria (≥ 1) | 3.28 (2.04, 5.27) | <0.001 | 1.86 (1.07, 3.23) | 0.03 |
| Clinical measurements Body mass index (kg/m$^2$) | | | | |
| 18.5–24.9 (ref) | 1.0 | | | |
| 25.0–29.9 | 0.87 (0.58, 1.31) | 0.50 | 0.98 (0.65, 1.48) | 0.93 |
| ≥ 30.0 | 0.84 (0.53, 1.34) | 0.47 | 0.92 (0.57, 1.50) | 0.75 |
| < 18.5 | 1.16 (0.47, 2.82) | 0.74 | 1.11 (0.54, 2.26) | 0.77 |
| Serum albumin (per 1 g/dL decrease) | 2.51 (1.94, 3.25) | <0.001 | 1.73 (1.24–2.40) | 0.001 |
| HIV-related factors | | | | |

| Risk factor | Unadjusted HR (95% CI) | *P*-value | Adjusted HR (95% CI) | *P*-value |
|---|---|---|---|---|
| HIV VL ≥ 400 vs. < 400 copies/mL | 1.99 (1.37, 2.88) | <0.001 | 1.33 (0.85, 2.08) | 0.22 |
| History of AIDS | 2.72 (1.98, 3.74) | <0.001 | 1.82 (1.29, 2.56) | <0.001 |
| CD4 count < 200 vs ≥ 200 cells/μL | 2.28 (1.65, 3.15) | <0.001 | 1.46 (1.02, 2.07) | 0.04 |
| Medication use | | | | |
| Diuretics | 2.38 (1.55, 3.65) | <0.001 | 1.53 (0.93, 2.51) | 0.09 |
| ACE-I or ARB | 1.76 (1.14, 2.71) | 0.01 | 0.76 (0.45, 1.29) | 0.32 |
| Prevalent use of ART | 0.74 (0.54, 1.01) | 0.06 | 1.04 (0.68, 1.59) | 0.85 |
| Separate analysis of TDF and atazanavir, using IPTW | | | | |
| TDF | 0.73 (0.51, 1.05) | 0.09 | 0.80 (0.54, 1.19) | 0.28 |
| Atazanavir | 0.89 (0.58, 1.36) | 0.58 | 0.81 (0.52, 1.27) | 0.36 |

Multivariable Cox regression models were adjusted for: sociodemographic factors, kidney-related risk factors (estimated glomerular filtration rate, dipstick proteinuria, history of prior AKI, diabetes mellitus and hypertension), HIV-related factors (serum albumin, HIV viral load, history of AIDS and CD4 count), other comorbid conditions (HCV infection, chronic obstructive pulmonary disease and ischaemic heart disease), medications (diuretics, ACE-I or ARB) and body mass index. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ART, antiretroviral therapy; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus; HR, hazard ratio; IPTW, inverse probability of treatment weight; TDF, tenofovir disoproxil fumarate; VL, viral load.

[a]Medicare/Medicaid/other public/Ryan White.