Associations between female birth sex and risk of chronic kidney disease development among people with HIV in the USA: A longitudinal, multicentre, cohort study

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Summary

Background Women represent a meaningful proportion of new HIV diagnoses, with Black women comprising 58% of new diagnoses among women. As HIV infection also increases risk of chronic kidney disease (CKD), understanding CKD risk among women with HIV (WWH), particularly Black women, is critical.

Methods In this longitudinal cohort study of people with HIV (PWH) enrolled in CFAR Network of Integrated Clinical Systems (CNICS), a multicentre study comprised of eight academic medical centres across the United States from Jan 01, 1996 and Nov 01, 2019, adult PWH were excluded if they had ≤2 serum creatinine measurements, developed CKD prior to enrollment, or identified as intersex or transgendered, leaving a final cohort of 33,998 PWH. The outcome was CKD development, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/ 1·73 m² calculated using the CKD-EPI equation, for ≥90 days with no intervening higher values.

Findings Adjusting for demographic and clinical characteristics, WWH were 61% more likely to develop CKD than men (adjusted hazard ratio [aHR]: 1·61, 95% CI: 1·46-1·78, p<0·001). This difference persisted after further adjustment for *APOL1* risk variants (aHR female sex: 1·92, 95% CI: 1·63-2·26, p<0·001) and substance abuse (aHR female sex: 1·70, 95% CI: 1·54-1·87, p<0·001).

Interpretation WWH experienced increased risk of CKD. Given disparities in care among patients with end-stage kidney disease, efforts to engage WWH in nephrology care to improve chronic disease management are critical.

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Keywords: HIV; Kidney disease; Health disparities

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Introduction

Kidney disease has emerged as a leading comorbidity among people with HIV (PWH) with estimated chronic kidney disease (CKD) prevalence between 2·4% and 17·0%.[1−3] Beyond established CKD risk factors such as aging, obesity, diabetes, and hypertension, PWH also

Research in context

Evidence before this study

We searched PubMed for research articles published up to September 1, 2021 using combinations, abbreviations, and variations of the terms "HIV", "women", "kidney disease", "kidney failure", "chronic kidney disease", and "end-stage kidney disease." We identified multiple cohort studies from the United States, Europe, and Brazil through this search. Consistently these studies demonstrated female sex was a risk factor for either chronic kidney disease or end-stage kidney disease among people with HIV. These studies, however, were limited in their approach or by the data available to them.

Added value of this study

To our knowledge, this is the first study to examine the association of female sex with chronic kidney disease after accounting for sex-specific differences in serum creatinine levels and known genetic risk factors for kidney disease. We used the CFAR Network of Integrated Clinical Systems (CNICS) to examine the association of female sex with incident chronic kidney disease development. Even after accounting for known genetic risk factors and African ancestry, female sex was associated with increased risk of chronic kidney disease as compared to men. Moreover, accounting for patient-reported outcomes such as substance use and for sex-based differences in serum creatinine level failed to mitigate this heightened risk of chronic kidney disease development.

Implications of all the available evidence

Women with HIV in the United States appear to have increased risk of chronic kidney disease. While the majority of women with HIV are African American or Black, accounting for African ancestry or APOL1 renal risk variants does not completely mitigate this risk. Thus, early detection of kidney dysfunction and linkage to nephrology care are crucial for women with HIV.

accrue risk attributable to HIV-specific factors such as HIV viraemia, low CD_4 counts, and the nephrotoxic effects of antiretroviral therapy (ART), which can approximate the level of risk associated with traditional risk factors.[4–10] While effective ART may slow the decline of estimated glomerular filtration rate (eGFR), it does not guarantee this deterioration will be completely halted.[11] Thus, without efforts targeted to halt this process, some PWH will progress to CKD and, ultimately, to end-stage kidney disease (ESKD) with some studies demonstrating 2·1-fold higher odds of kidney impairment among PWH as compared to those without HIV.[6,12,13] Moreover, once PWH develop CKD, they are two-fold more likely to die than individuals without HIV, necessitating efforts to further

understand development and progression of CKD in this population.[14]

Consistent with the studies conducted among those without HIV, disparities in CKD/ESKD among PWH are well-established, including sex-specific disparities.[15] In a cross-sectional study from Brazil, women with HIV (WWH) experienced 1·2-fold higher odds of mild kidney impairment compared to male counterparts.[16] A multicentre study of PWH in the United States corroborated this finding, demonstrating both Black women and non-Black women experienced 1·5-fold higher incidence rates of CKD as compared to men.[7] Critically, however, neither study accounted for sex-based differences in baseline serum creatinine levels. Existing eGFR equations include a correction for female sex, as women typically have lower serum creatinine levels than men attributable to lesser muscle mass or hormonal differences between the sexes,[17–19] that results in the assignment of a lower eGFR to women as compared to men with the same serum creatinine.[17,20] Thus, accounting for sex-based differences in serum creatinine when examining risk of CKD is crucial.

The burden of CKD risk is also not equitably distributed across racial groups, as Black individuals comprise the majority of CKD/ESKD cases among PWH.[5] Evidence suggests that perhaps genetic risk factors, specifically apolipoprotein-L1 (APOL1), may contribute to this enhanced level of risk among Black PWH.[21–23] Additionally, APOL1 is highly correlated with genetic African ancestry, which has been shown to significantly increase serum creatinine, resulting in lower eGFRs.[24] Self-reported Black race, however, is not a good surrogate for APOL1 or for genetic African ancestry and, instead, serves as a surrogate for societal factors such as culture, diet, and discrimination.[25] Beyond self-reported race and genetic markers, other factors such as socioeconomic status, HIV-related stigma, and systemic racism may also contribute to the observed racial disparity in CKD/ESKD, as these factors influence retention in care and ART adherence through increased depression, lower self-efficacy, and avoidant coping.[26–30] While Black individuals are disproportionately represented among new HIV diagnoses, this inequity is starker among WWH of whom 58% of new diagnoses occur among Black women.[31] Thus, as the majority of WWH are Black,[32] inability to control for genetic risk factors such as APOL1 or for sex-based differences in serum creatinine levels may have confounded previous estimates of CKD risk. As such, this study was designed to determine whether WWH are at increased risk of CKD after adjusting for both sex-based differences in baseline serum creatinine levels and known genetic CKD risk variants. We hypothesized female sex was associated with increased risk of CKD development.

Methods

Study design and population

The CNICS cohort is a prospective, longitudinal, multi-centre cohort of adult PWH. Participants enrolled at eight academic medical centres across the US (Case Western Reserve University, University of Alabama at Birmingham, University of California San Francisco, University of Washington, University of California San Diego, Fenway Health/Harvard University, University of North Carolina Chapel Hill, and Johns Hopkins University). CNICS collects detailed clinical, demographic and laboratory data including participant age, sex, self-reported race/ethnicity, comorbidities, medications, lab results, and vital status.[33] Patients must provide written informed consent to participate in CNICS. Of the >37,000 current adult participants, more than 8,000 have genetic data available for analysis to date with ongoing expansion. PWH were excluded if they had ≤2 creatinine measurements during the study period (01/01/1996-11/01/2019), developed CKD prior to study entry (defined as an eGFR <60 mL/min/1·73m² for ≥90 days without an intervening higher value), or identified as intersex or transgendered, leaving a final cohort of 33,998 PWH (Figure 1). The Institutional Review Board at the University of Alabama Birmingham approved this study (protocol: 30001300). This study adhered to the items outlined in the STROBE reporting tool.

Genotyping

DNA was extracted from peripheral blood mononuclear cells or buffy coats using the FlexiGene DNA kit (Qiagen Inc, Chatsworth, CA). Genotyping was performed using the expanded Illumina Multi-Ethnic Genotyping Array as described elsewhere.[34] Single nucleotide polymorphisms (SNPs) with call rates < 95%, minor allele frequency < 5%, deviation from Hardy-Weinberg equilibrium (p-value $< 1 \times 10^{-29}$), and regions of high linkage disequilibrium (LD),[35] as well as samples with call rates < 95%, sex discrepancies between genotype data and self-report, and pairwise identity- by- descent ('pi-hat') > 0·9 were excluded as implemented in Plink v1·9.[36] For linkage disequilibrium pruning, linked SNPs were removed using $r^2 \geq 0·1$. The ADMIXTURE
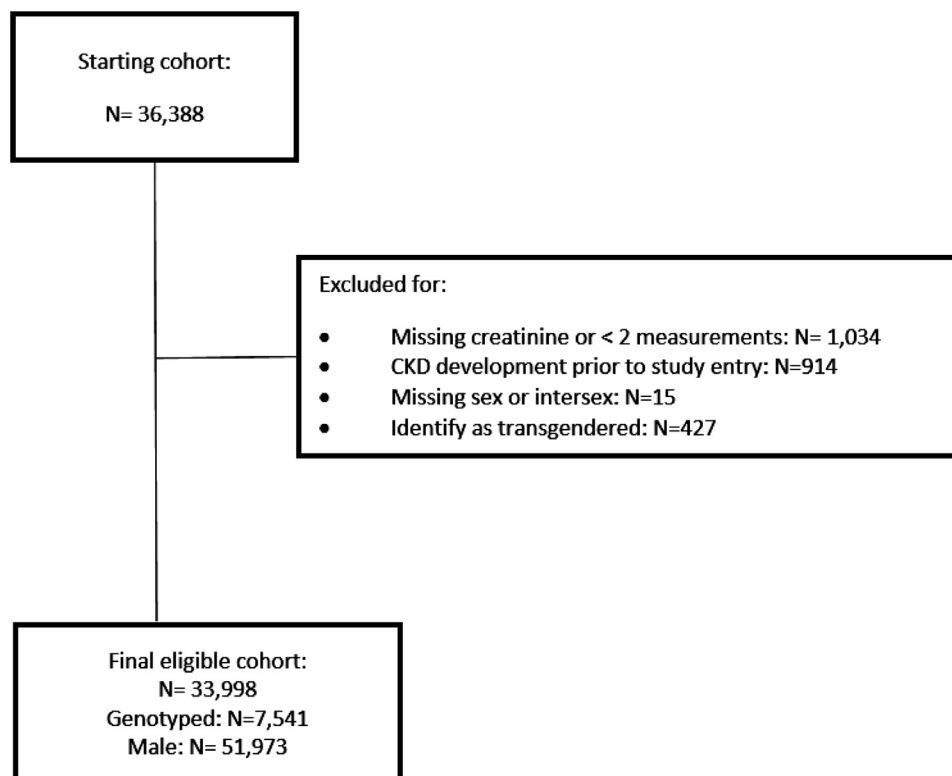

Figure 1. Cohort construction diagram.

There were 36,388 PWH enrolled in CNICS. 1,034 PWH were excluded for either no serum creatinine measurements or fewer than 2 measurements during the study period. 914 PWH developed CKD prior to study enrollment, 15 were either intersex or had no birth sex recorded, and 427 PWH were transgendered. Consequently, a final cohort of 33,998 PWH was derived of whom 6,105 were female and 27,893 were male.

algorithm was used to determine the global proportions of genetic African ancestry,[37,38] and *APOL1* was assessed using the recessive model (0/1 vs. 2).[39]

Patient-reported outcomes

PWH were surveyed approximately every 6 months as part of routine clinical care using validated instruments for substance abuse (drug, alcohol, and tobacco use). These surveys were administered via a web-based survey software application that may reduce social desirability bias. Data from the Alcohol Use Disorders Identification Test and the National Institute of Drug Abuse-modified Alcohol, Smoking, and Substance Involvement Test were utilized to examine the association of past or current substance abuse with CKD development.[40−43] Each substance (marijuana, methamphetamine, illicit opioid, intravenous drug use, cocaine/crack, and high risk alcohol use) was examined independently given the distinctly different mechanisms by which they may impact kidney function.

Statistical analyses

Outcome of interest was CKD development, defined as an eGFR of <60 mL/min/1·73m² for ≥90 days with no intervening higher values.[44] eGFR was calculated using the 2009 CKD-EPI equation.[17] Time-at-risk was defined as time from study enrollment to CKD development, death, or loss to follow-up (defined as one year after the last creatinine measurement). In Cox proportional hazards models, PWH were censored if time-at-risk ended in death or loss to follow-up. Women are known to have a longer life expectancy than men in developed countries and as such, there was the potential for this differential death rate to bias our results. Accordingly, Fine and Gray competing risks models were performed in which death was treated as a competing risk for CKD development.

Covariates

The primary exposure was self-reported sex at birth. In models among genotyped PWH, the primary exposure was biological sex. Variables considered for both Cox and Fine and Gray model inclusion included the following: age at study entry, self-reported race, baseline serum creatinine, body mass index, hypertension, diabetes, hepatitis C infection, hepatitis B infection, CD4 count, log-transformed HIV viral load, baseline tenofovir use, baseline protease inhibitor use, baseline indinavir use, baseline atazanavir use, baseline lopinavir use, baseline integrase inhibitor use, total antiretroviral therapy use, and study enrollment year. Functional form for continuous variables was assessed using Martingale residuals to ensure the linear form of continuous variables was most appropriate. Variables were retained for model inclusion if significant at p<0·10. Missingness of

variables was compared across sexes to assess for potential bias. All analyses were presented are complete cases analyses. The proportional hazards assumption was tested by interacting all predictor variables with the log-function of survival time.

Sub-group and sensitivity analyses

Genetic data and patient-reported outcomes were only available on select PWH based on availability of samples genotyped to date and introduction of the surveys within each site respectively. Given the potential for unintended bias due to estimation of risk in select sub-groups, models were built within each sub-group to permit inclusion of their unique data elements and confirm our inferences with respect to female sex. Models were stratified by era of study enrollment, defined as five calendar year periods, to assess for potential confounding by secular trends, specifically improvement in HIV-specific therapeutics. Inferences were confirmed in each of our sub-cohorts. The inclusion of race in existing eGFR estimating equations has recently been debated,[45,46] with many centres dropping the race coefficient from these calculations. To increase generalizability, eGFR was recalculated excluding the race coefficient from the CKD-EPI equation, and additional analyses were performed. As both body mass index (BMI) and eGFR at study entry could confound the relationship between female sex and CKD development, sensitivity analyses in which both factors were controlled for were conducted. Inferences, presented in the Supplemental Materials, were consistent with those presented in the body of this manuscript demonstrating female sex's association with increased risk of CKD.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the dataset used in this study. JEL had final responsibility for the decision to submit this manuscript for publication.

Results

The CNICS cohort was examined using three distinct cohorts (overall, genotyped, and PRO) as there were notable differences in patient demographics and era of study entry. There was a lower proportion of Hispanic PWH in the genotyped cohort as compared to the overall and PRO cohorts (9·0% vs. 12·0% vs. 13·7%), and a higher proportion of Black PWH (43·4% vs. 38·5% vs. 38·6%). Diabetes was more common (19·0% vs. 11·7% vs. 15·5%) and CD4 count lower in the genotyped cohort as compared to the overall and PRO cohorts (Table 1).

	Overall		Genotyped		PRO cohort	
	Female N=6,105	Male N=27,893	Female N=1,445	Male N=6,017	Female N=2,844	Male N=12,827
Demographics						
Age at study entry, median (IQR)	39 (31-46)	39 (31-46)	39 (32-46)	40 (33-46)	39 (32-47)	39 (31-47)
Hispanic, n (%)	479 (7·9)	3,629 (13·0)	67 (4 6)	603 (10 0)	252 (8 9)	1,895 (14 8)
Black race, n (%)	3,909 (64 0)	9,301 (33·4)	1,006 (69 6)	2,248 (37 4)		
HIV Characteristics						
ARV at baseline, n (%)	3,152 (50·8)	14,966 (52·4)	794 (55·0)	3,016 (50 1)	1,391 (48 9)	5,907 (46 1)
CD4 count, median (IQR)	363 (168-588)	351 (158-557)	352 (154-572)	319 (129-521)	381 (179-608)	362 (172-566)
Log viral copy-years, median (IQR)	9·8 (7·8-11 3)	9 4 (7 5-11 0)	10 6 (9 0-11 8)	10 2 (8 4-11 5)	9 8 (7 8-11 4)	9 3 (7 4-11 1)
Comorbid Conditions						
HCV infection, n (%)	1,574 (25·8)	5,313 (19.1)	397 (27 5)	1,365 (22 7)	655 (23 0)	2,344 (18 3)
HBV infection, n (%)	222 (3·6)	1,781 (6·4)	66 (4 6)	471 (7 8)	100 (3 5)	809 (6 3)
Diabetes, n (%)	1,007 (16·6)	2,930 (10·6)	343 (23 8)	1,076 (17 9)	619 (21 9)	1,803 (14 1)
Hypertension, n (%)	1,023 (16·9)	2,781 (10.1)			601 (21 2)	1,529 (12 0)
2 APOL1 risk variants[a], n (%)	—		148 (10·2)	350 (5·8)		
≥50% African ancestry	—		1,003 (69 4)	2,224 (37 0)		
Baseline creatinine, median (IQR)	0·8 (0·7-1·0)	1·0 (0·9-1·2)	0 9 (0·7-1·1)	1 1 (0 9-1 2)	0 9 (0 7-1 0)	1 0 (0 9-1 2)
Baseline eGFR, median (IQR)	93 (71-112)	94 (77-109)	85 (63-103)	87 (70-103)	88 (69-106)	89 (74-104)
BMI, kg/m^2						
<19	333 (6 0)	1,025 (4 0)	62 (4 5)	221 (3 8)	136 (4 8)	470 (3 7)
19-24	1,894 (34 2)	12,141 (47 8)	456 (33 1)	2,724 (46 4)	891 (31 7)	5,928 (46 8)
25-29	1,506 (27 2)	8,778 (34 6)	405 (29 4)	2,108 (35 9)	789 (28 0)	4,429 (35 0)
≥30	1,801 (32 5)	3,456 (13 6)	453 (32 9)	820 (14 0)	999 (35 5)	1,841 (14 5)
Patient Reported Outcomes						
High risk alcohol abuse	—		—		397 (14 0)	2,183 (17 0)
IDU	—		—		189 (14.2)	1,213 (18 8)
Methamphetamine use	—		—		395 (14 6)	4,660 (37 3)
Marijuana use	—		—		1,327 (48 9)	8,602 (69 0)
Illicit opioid use	—		—		473 (18 3)	2,418 (19 9)
Cocaine/crack use					985 (36 2)	5,928 (4761)
Study Entry Era						
1995-1999	1,088 (17 8)	4,062 (14 6)	352 (24 4)	1,188 (19 7)	335 (11 8)	1,134 (8 8)
2000-2004	1,696 (27.8)	6,791 (24 4)	484 (33 5)	1,584 (26 3)	594 (20 9)	2,159 (16 8)
2005-2009	1,346 (22 1)	6,834 (24 5)	423 (29 3)	2,063 (34 3)	742 (26 1)	3,414 (26 6)
2010-2014	1,371 (22 5)	6,993 (25 1)	184 (12 7)	1,153 (19 2)	883 (31 1)	4,381 (34 2)
2015-2020	604 (9.9)	3,213 (11 5)	2 (0 1)	29 (0 5)	290 (10 2)	1,739 (13 6)

Table 1: Baseline characteristics by cohort among people living with HIV engaged in HIV care.
[a] Among genotyped only.
ARV: antiretroviral use, HCV: hepatitis C virus, HBV: hepatitis B virus, *APOL1*: apolipoprotein 1, eGFR: estimated glomerular filtration rate, CKD: chronic kidney disease, IDU: intravenous drug use.

Overall cohort

There were 33,998 PWH in the overall CNICS cohort. WWH were more commonly Black (64.0% vs. 33.4%), had higher prevalence of HCV co-infection (25.8% vs. 19.1%), higher prevalence of diabetes (16.6% vs. 10.6%), and higher prevalence of BMI ≥30 (32.5% vs. 13.6%). Median baseline serum creatinine was lower among WWH as compared to men (0.8, IQR: 0.7-1.0, vs. 1.0, IQR: 0.9-1.2) (Table 1).The cumulative incidence of CKD during the study period was 24% among women and 19% among men. Percent of WWH free of CKD at one, three, and five years were 94.2%, 90.4%,

and 87.9% as compared to 95.3%, 92.7%, and 90.6% of men with HIV (p<0.0001) (Figure 2). In unadjusted analyses, female sex was associated with a 67% increased risk of CKD (HR: 1·67, 95% 1·39-2·01, p<0·001) (Supplemental Tables 1 and 3). While the absolute risk difference in CKD development was 5%, after adjustment for sex-based differences in baseline serum creatinine and known risk factors, female sex was associated with a 61% increased risk of CKD as compared to men (adjusted hazard ratio [aHR]: 1·61, 95% CI: 1·46-1·78, p<0·001) (Table 3) and a 63% increased risk of CKD after treating death as a competing risk (adjusted

	Female N=6,105	Male N=27,893	P-value
Demographics			
Age at study entry, median (IQR)	39 (31-46)	39 (31-46)	0·17
Hispanic, n (%)	484 (7·8)	3,708 (13·0)	<0·0001
Black race (ref: White), n (%)	3,964 (63·9)	9,474 (33·2)	<0·0001
HIV Characteristics			
ARV at baseline, n (%)	3,152 (50·8)	14,966 (52·4)	0·02
CD4 count, median (IQR)	362 (167-587)	352 (159-557)	<0·0001
Log viral copy-years, median (IQR)	4·8 (3·0-6·0)	4·2 (2·5-4·9)	0·01
ART duration, yrs	0 (0-245)	0 (0-540)	<0·0001
PI duration, days	379 (91-1,283)	697 (195-1,623)	0.05
INSTI duration, days	256 (58-796)	363 (66-1,190)	0.24
Atazanavir duration, days	351 (73-1,076)	548 (126, 1,676)	0.61
Indinavir duration, days	365 (103-763)	580 (204-1,190)	<0.0001
Comorbid Conditions			
HCV infection, n (%)	1,587 (25·6)	5,371 (18·8)	<0·0001
HBV infection, n (%)	224 (3·6)	1,797 (6·3)	<0·0001
Diabetes, n (%)	1,010 (16·3)	2,942 (10·3)	<0·0001
Hypertension, n (%)	1,027 (16·6)	2,803 (9·8)	<0·0001
2 APOL1 risk variants[a], n (%)	152 (10·4)	353 (5·8)	<0·0001
Baseline creatinine, median (IQR)	0.8 (0·7-1·0)	1·0 (0·9-1·2)	<0·0001
Baseline eGFR, median (IQR)	93 (71-112)	94 (77-109)	0·04
Patient Reported Outcomes			
High-risk alcohol abuse, n (%)	1,750 (28·7)	8,218 (29·5)	<0·0001
IDU, n (%)[b]	161 (16·8)	1,110 (21·6)	0·001
Amphetamine use, n (%)[b]	334 (16·9)	4,166 (42·1)	<0·0001
Marijuana use, n (%)[b]	982 (49·8)	6,905 (70·4)	<0·0001
Opiate use, n (%)[b]	394 (21·3)	2,122 (22·1)	0·49
Crack/cocaine use, n (%)[b]	764 (38·6)	5,009 (50·4)	<0·0001
Study Entry Era			
1995−1999	1,112 (18.1)	4,157 (14.8)	<0.0001
2000−2004	1,700 (27.7)	6,825 (24.3)	
2005−2009	1,350 (22.0)	6,871 (24.4)	
2010−2014	1,376 (22.4)	7,032 (25.0)	
2015−2020	607 (9.9)	3,240 (11.5)	

Table 2: **Baseline characteristics by birth sex.**
   [a] Among genotyped only.
   [b] Among PRO cohort only.
ARV: antiretroviral use, HCV: hepatitis C virus, HBV: hepatitis B virus, *APOL1*: apolipoprotein 1, eGFR: estimated glomerular filtration rate, CKD: chronic kidney disease, IDU: intravenous drug use.

subdistribution hazard ratio [asdHR]: 1·63, 95% CI: 1·50-1·78, $p<0·001$) (Table 4) The calculated E-value, defined as the strength of association with CKD an unknown confounder would need to impact the observed association between female sex and CKD, was 2.60 (lower limit: 2.28) and 2.64 (lower limit: 2.37) for the Cox proportional hazards and Fine and Gray competing risk regressions respectively. After controlling for both BMI and baseline eGFR, female sex was associated with 36% and 29% increased risk of CKD development in both Cox proportional hazards models and Fine and Gray competing risk regressions respectively (aHR: 1.36, 95% CI: 1.22-1.52, $p<0.0001$; asdHR: 1.29, 1.18-1.42, $p<0.0001$) (Supplemental Tables 3 and 4).

Genotyped cohort

There were 7,435 PWH in the CNICS cohort with serum creatinine values who were also genotyped at the *APOL1* locus with accompanying genetic African ancestry data available for analysis. WWH were more commonly Black (69.6% vs. 37.4%), more commonly had 2 *APOL1* renal risk variants (10.2% vs. 5.8%), had higher prevalence of diabetes (23.8% vs. 17.9%), and higher prevalence of BMI ≥30 (32.9% vs. 14.0%) as compared to men (Table 1). There was substantial variation in the proportion of genetic African ancestry with many PWH having admixed ancestry (Supplemental Figure 1). In unadjusted analyses, female sex was associated with 55%
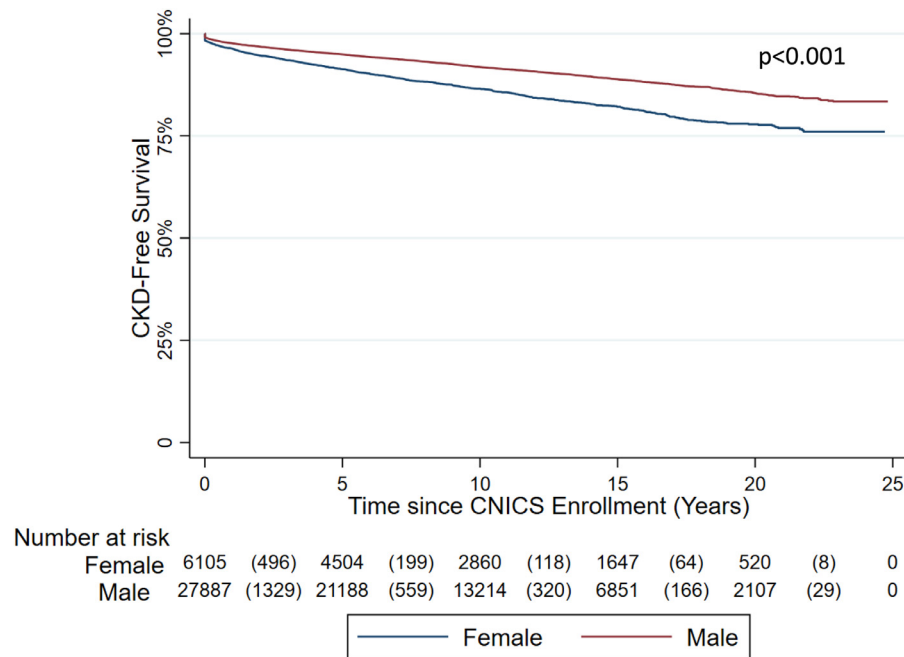
Figure 2. Survival curve for CKD development among PWH by birth sex.
    PWH were followed from date of study enrollment to the earliest of CKD development, loss to follow-up, or death. Women with HIV, shown in red, had lower CKD-free survival as compared to men with HIV, shown in blue (*p*<0.001).

increased risk of CKD as compared to men (HR: 1·55, 95% CI: 1·26-1·90, *p*<0·001) (Supplemental Tables 1 and 3). After adjustment for demographic characteristics, comorbid conditions, HIV characteristics, *APOL1* CKD risk variants, and genetic African ancestry, female sex was associated with 92% increased risk of CKD as compared to men (aHR: 1·92, 95% CI: 1·63-2·26, *p*<0·001) (Table 3). Genetic African ancestry was not significantly associated with CKD, but presence of two *APOL1* risk variants was associated with 35% increased risk (aHR: 1·35, 95% 1·03-1·81, *p*<0·001) (Table 3). After accounting for death as a competing risk, female sex was associated with a 79% increased risk of CKD and 2 *APOL1* risk variants with 56% increased risk (asdHR: 1·79, 95% CI: 1·47-2·18, *p*<0·001; asdHR: 1·56, 95% CI: 1·15-2·14, p<0·001) (Table 4). The calculated E-value was 3.25 (lower limit: 2.64) and 2.98 (lower limit: 2.28) for the Cox proportional hazards and Fine and Gray competing risk regressions respectively. Lastly, after controlling for both BMI and baseline eGFR in addition to *APOL1* renal risk factors and African ancestry, female sex was associated with 36% and 29% increased risk of CKD development in both Cox proportional hazards models and Fine and Gray competing risk regressions respectively (aHR: 1·36, 95% CI: 1·16-1·60, p<0·0001; asdHR: 1·29, 95% CI: 1·06-1·57, p=0·01) (Supplemental Tables 3 and 4).

Patient reported outcomes cohort

There were 15,671 PWH with history of substance use data and with creatinine data. WWH were less commonly Hispanic (8.9% vs. 14.8%), more commonly coinfected with HCV (23.0% vs. 18.3%), and more commonly had diabetes (21.9% vs. 14.1%). BMI of 30 or greater was more common among WWH than men (35.5% vs. 14.5%). Women less commonly reported methamphetamine use (14.6% vs. 37.3%), marijuana use (48.9% vs. 69.0%), and cocaine/crack use (36.2% vs. 47.6%). (Table 1). In unadjusted analyses, female sex was associated with 47% increased risk of CKD as compared to men (aHR: 1·47, 95% CI: 1·24-1·74, *p*<0·001) (Supplemental Tables 1 and 2). After adjusting for demographics, comorbid conditions, HIV-specific risk factors, and high-risk alcohol use and methamphetamine use, female sex was associated with 70% increased risk of CKD development as compared to men (aHR: 1·70, 95% CI: 1·54-1·87, *p*<0·001) (Table 3). Female sex was associated with a 60% increased risk of CKD, after accounting for death as a competing risk (asdHR: 1·60, 95% CI: 1·26-2·04, *p*<0·001) (Table 4). Female sex was associated with 41% and 32% increased risk of CKD development in both Cox proportional hazards models and Fine and Gray competing risk regressions respectively, even after accounting for the potential confounding effects of BMI, baseline eGFR, and high-risk alcohol use (aHR: 1·41, 95% CI: 1·17-1·70, p<0·0001; asdHR:

	Overall	Genotyped	Patient Reported Outcomes Cohort	Genotyped and Patient Reported Outcomes
	N=33,998	*N*=7,462	*N*=15,671	*N*=5,344
	aHR (95% CI)[a]	aHR (95% CI)[a]	aHR (95% CI)[a]	aHR (95% CI)[a]
Demographics				
Female sex	**1·61 (1·46-1·78)**	**1·92 (1·64-2·26)**	**1·70 (1·54-1·87)**	**1·76 (1·46-2·12)**
Age at study entry	**1·08 (1·08-1·09)**	**1·08 (1·07-1·09)**	**1·09 (1·086-1·10)**	**1·08 (1·07-1·09)**
Black race	**0·71 (0·65-0·78)**	**0·52 (0·34-0·79)**	**0·65 (0·59-0·71)**	0·63 (0·39-1·02)
Baseline creatinine	**1·07 (1·05-1·09)**	**1·46 (1·39-1·55)**	**1·45 (1·43-1·48)**	**1·41 (1·31-1·52)**
APOL1 risk	–	**1·35 (1·03-1·81)**	–	**1·65 (1·22-2·24)**
African ancestry	–	1·10 (0·67-1·80)	–	0·85 (0·49-1·49)
Comorbid Conditions				
HCV infection	**1·25 (1·14-1·37)**	**1·21 (1·02-1·45)**	**1·25 (1·14-1·36)**	–
HBV infection	**1·43 (1·24-1·66)**	–	**1·26 (1·09-1·46)**	–
Diabetes	**1·65 (1·50-1·82)**	**1·42 (1·21-1·67)**	**1·39 (1·28-1·52)**	**1·34 (1·14-1·58)**
Hypertension	**1·77 (1·59-1·97)**	**1·51 (1·25-1·82)**	**1·42 (1·29-1·57)**	**1·48 (1·22-1·80)**
ART Naïve	**0·81 (0·74-0·89)**	–	**0·80 (0·73-0·88)**	0·42 (0·17-1·05)
Log Viral Copy-years	**1·02 (1·00-1·04)**	1·01 (1·00-1·05)	**1·03 (1·00-1·06)**	–
ART duration, yrs.	**0·97 (0·95-0·99)**	–	**0·93 (0·92-0·95)**	**0·96 (0·93-0·99)**
PI duration, yrs.	**1·03 (1·00-1·05)**	–	**1·03 (1·01-1·06)**	–
INSTI duration, yrs.	**1·10 (1·06-1·14)**	**1·14 (1·06-1·23)**	**1·11 (1·08-1·14)**	**1·15 (1·06-1·24)**
Atazanavir duration, yrs.	–	–	**1·07 (1·04-1·11)**	–
Indinavir duration, yrs.	–	–	**0·88 (0·83-0·94)**	–
CD4 < 200 cells/mL	**1·38 (1·27-1·51)**	**1·20 (1·02-1·40)**	**1·20 (1·11-1·31)**	**1·24 (1·06-1·46)**
High-risk alcohol use	–	–	**0·68 (0·59-0·78)**	**0·64 (0·50-0·83)**
Methamphetamine use	–	–	0·85 (0·70-1·02)	0·85 (0·70-1·02)
Illicit opioid use	–	–	–	**1·24 (1·02-1·52)**

Table 3: **Adjusted risk of chronic kidney disease development among people living with HIV using Cox proportional hazards regression.**
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, Hepatitis C virus; HBV, Hepatitis B virus; ART: antiretroviral therapy; VCY: viral copy-years.
[a] Bold indicates significance at *p*<0.05.

1.32, 95% CI: 1.14-1.52, p<0.0001) Supplemental Tables 3 and 4). Inclusion of *APOL1* and African ancestry with substance use data yielded similar inferences (aHR: 1·82, 95% CI: 1·40-2·38, p<0·001; asdHR: 1·60, 95% CI: 1·33-1·92, p<0·001) (Tables 3 and 4). Addition of genetic factors to models containing BMI and baseline eGFR suggested female sex was associated with 35% and 22% increased risk of CKD development in both Cox proportional hazards models and Fine and Gray competing risk regressions respectively (aHR: 1.35, 95% CI: 1.02-1.78, p=0.04; asdHR: 1.22, 95% CI: 1.02-1.45, p=0.03) (Supplemental Tables 3 and 4). The calculated E-value was 2.79 (lower limit: 2.45) and 3.04 (lower limit: 2.58) for the Cox proportional hazards and Fine and Gray competing risk regressions respectively.

Discussion

This comprehensive study of kidney function in PWH is the first to account for sex-based differences in serum creatinine and genetic risk factors for CKD. We found female sex was consistently associated with increased risk of CKD independent of baseline serum creatinine.

Moreover, the disparity in CKD was not mitigated after adjustment for *APOL1* and degree of African ancestry. Inclusion of history of substance abuse similarly failed to mitigate the increased risk of CKD found among WWH compared to men.

Several studies have demonstrated an increased risk of CKD in women regardless of HIV status with multiple proposed biological mechanisms. Specifically, the increased risk of CKD among WWH observed in this study may in part be due to biologic factors such as sex-specific differences in antiretroviral pharmacokinetic parameters, pregnancy, or genetic variants located on sex chromosomes. Multiple studies have suggested women have higher plasma drug concentrations than men at the same dosing level.[47,48] While tenofovir alafenamide has similar tolerability to tenofovir disoproxil fumarate (TDF) and lower risk of adverse events, including those specific to kidney injury,[49] TDF was the most common formulation of tenofovir prescribed in this retrospective cohort, reflecting contemporary practice patterns. Women have been reported to have approximately 19% higher concentrations of TDF than men,[50] which may explain some of the increased risk of

	Overall	Genotyped	Patient Reported Outcomes Cohort	Genotyped and Patient Reported Outcomes
	N=33,998	N=7,462	N=15,671	N=5,344
	aHR (95% CI)[a]	aHR (95% CI)[a]	aHR (95% CI)[a]	aHR (95% CI)[a]
Demographics				
Female sex	**1·63 (1·50-1·78)**	**1·79 (1·47-2·18)**	**1·60 (1·26-2·04)**	**1·60 (1·33-1·92)**
Age at study entry	**1·07 (1·06-1·07)**	**1·07 (1·06-1·08)**	**1·07 (1·06-1·08)**	**1·07 (1·06-1·08)**
Black race	**0·79 (0·73-0·86)**	**0·73 (0·54-0·99)**	**0·58 (0·49-0·69)**	**0·64 (0·41-1·00)**
Baseline creatinine	**1·07 (1·05-1·08)**	**1·39 (1·34-1·44)**	**1·44 (1·37-1·52)**	**1·41 (1·31-1·51)**
APOL1 risk	–	**1·56 (1·15-2·14)**	–	**1·64 (1·18-2·28)**
African ancestry	–	0·76 (0·48-1·22)	–	0·83 (0·48-1·41)
Comorbid Conditions				
HCV infection	**1·11 (1·02-1·21)**	–	–	–
HBV infection	**1·43 (1·25-1·63)**	–	–	–
Diabetes	**1·98 (1·81-2·16)**	**1·50 (1·25-1·79)**	**1·37 (1·16-1·63)**	**1·36 (1·16-1·59)**
Hypertension	**1·93 (1·75-2·12)**	**1·65 (1·49-1·79)**	**1·60 (1·44-1·78)**	**1·58 (1·32-1·90)**
ART Naïve	0·86 (0·79-1·07)	–	–	–
Log Viral Copy-years	**1·06 (1·04-1·07)**	**1·05 (1·02-1·07)**	**1·06 (1·03-1·08)**	**1·07 (1·03-1·10)**
ART duration, yrs.	**0·98 (0·96-0·99)**	–	–	–
PI duration, yrs.	1·02 (0·999-1·05)	–	–	–
Tenofovir duration, yrs.	–	1·05 (0·998-1·11)	–	–
INSTI duration, yrs.	**1·10 (1·06-1·13)**	**1·11 (1·05-1·17)**	**1·12 (1·08-1·15)**	**1·11 (1·03-1·20)**
Indinavir duration, yrs.	–	0·93 (0·86-1·00)	**0·86 (0·80-0·93)**	–
CD4 < 200 cells/mL	**1·33 (1·23-1·44)**	**1·14 (1·04-1·25)**	**1·14 (1·03-1·27)**	**1·18 (1·02-1·37)**
High-risk alcohol use	–	–	**0·60 (0·46-0·79)**	**0·64 (0·50-0·81)**
Methamphetamine use	–	–	–	0·87 (0·73-1·04)

Table 4: **Adjusted risk of chronic kidney disease development among people living with HIV using Fine and Gray competing risks regression.**
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, Hepatitis C virus; HBV, Hepatitis B virus; ART: antiretroviral therapy; VCY: viral copy-years.
[a] Bold indicates significance at *p*<0.05.

CKD development among women observed in this study as TDF plasma concentrations are associated with increased risk of kidney tubular dysfunction.[51] Additionally, numerous studies suggest, when engaged in HIV care, WWH have lower HIV viral loads than men and higher levels of inflammatory markers.[52−58] Even with effective ART therapy, this increased inflammation may persist and mimic the natural inflammation process associated with aging in the general population thereby increasing the baseline risk of CKD development among PWH.[59,60] As an experience unique to women, the effect of pregnancy on renal function must also be considered. It is known women with low baseline eGFR experience heightened risk of CKD progression in pregnancy and, as we were unable to account for pregnancy history, may contribute to some of the unexplained, increased risk observed in this study.[61] Relatedly, sex hormones have been implicated in CKD risk and progression, with estrogen protective against kidney disease and testosterone increasing risk of kidney disease.[62,63] Last, genetic analyses of sex chromosomes are infrequent, with many of those published performed incorrectly.[64] Thus, it is relatively unknown whether there are risk variants for CKD on the X chromosome or perhaps a protective variant present on the Y chromosome. Further work exploring the potential for sex-specific genetic variants is needed. Cumulatively, these biologic factors may explain some proportion of the observed disparity in CKD development.

Beyond biologic factors, social factors including access to and compliance with care are known to differ between men and WWH and may contribute to the increased CKD risk observed among WWH in this study.[65,66] WWH have been found to disengage from care more frequently than men due to a number of potential reasons including increased depression, greater stigma associated with HIV infection, and lower socioeconomic status.[67,68] Recent work found HIV stigma was highest among Black, Hispanic/Latinx, and white women as compared to white men with potentially important implications for clinical care. Stigma was associated with lower ART use and adherence, greater numbers of missed HIV care visits, and increased prevalence of symptoms associated with depression or anxiety.[66,67] Moreover, WWH face multiple hurdles to clinic attendance including insurance issues and presence of childcare. Recent work among WWH highlighted private insurance was associated

with three-fold higher odds of retention in care as compared to lack of insurance with no AIDS Drug Assistance Program coverage.[69] In a mixed methods study of WWH in the Southeast, women reported childcare as disruptive to their schedules, leading them to subsequently forget to take their ART,[70−72] though other research has reported children act as a meaningful facilitator of retention in care as WWH recognize the need to care for themselves in order to subsequently care for their children.[73] Additionally, substance use among WWH has been consistently associated with failure to achieve viral suppression.[74−76] As active viraemia is a known risk factor for kidney disease progression,[77] these may represent meaningful points of intervention as actions taken to reduce HIV stigma and eliminate barriers to clinical attendance may improve retention in care, ART adherence, and chronic disease management. Consequently, interpersonal and societal factors may compound upon and interact with each other to increase risk factors for CKD and perhaps for subsequent CKD risk.

The finding of increased CKD risk among WWH has been described in previous cohort studies but is incongruent with data highlighting the significantly lower rates of CKD progression and ESKD development among women in the general population. Correspondingly, existing risk calculators for ESKD confer protective status to women.[78] Among PWH, this discrepancy between risk of CKD and ESKD also persists. In adjusted analyses of a national cohort of PWH, WWH experienced no significant increased risk of ESKD as compared to men.[5] The reasons for this apparent contradiction are unclear. Age has been shown to act as a significant effect modifier of risk such that ESKD risk is lower among older women as compared to younger men, but higher among younger women as compared to younger men, potentially motivating further study of the role of sex hormones in CKD progression and ESKD development.[79] Additionally, the CKD-EPI equation itself may contribute to some of this perceived increased risk of CKD as, at any given serum creatinine level, it assigns women a lower eGFR than it does men and thereby also assigns them a more advanced CKD stage.[17] Nevertheless, understanding CKD risk among WWH and measures that may mitigate such risk is of paramount importance given the known disparities in ESKD care.

As with all observational studies, there are limitations to these analyses. While this is a diverse cohort of PWH, our analysis is restricted to those who enroll in CNICS at eight academic medical centres across the United States and may not reflect all PWH in the United States including those who are not yet diagnosed or not in care. As patients must consent to participate in CNICS, selection bias is possible in which patients who are more engaged in care are also more likely to participate in CNICS. However, CNICS consent rates are high

(>90%) so the impact of this limitation is likely minimal. While CNICS has standardized protocols at enrollment to capture prior ART regimens and other HIV history, there may be missing data for HIV care occurring prior to CNICS enrollment. As the majority of WWH are Black and Black individuals are known to present later to care, and while we control for CD4 count and HIV viral load,[80,81] we cannot fully account for this disparity in access to care that may confound our findings. A new race-less eGFR equation was recently published.[82] Given time lags in adoption, these data reflect practice during the study period. Moreover, creatinine-based estimates of kidney function are more imprecise than cystatin C-based estimates but, as cystatin C values are not routinely captured in clinical practice, we were reliant upon creatinine-based estimating equations. Similarly, we were unable to assess other measures of kidney disease among PWH, such as proteinuria, as these data were not captured within this dataset. As such, our inferences are limited to kidney function reflected in creatinine-based estimating equations. Among PWH, there are numerous factors that may influence serum creatinine levels and subsequently affect ascertainment of CKD, of which the most pertinent may be ART. Ultimately, this interrelationship between ART, serum creatinine levels, and ascertainment of CKD may illustrate the importance of a holistic approach to assessing kidney function that considers serum creatinine levels in the context of patient drug regimens or that even prioritizes collection of additional labs such as cystatin C or iothalamate GFRs among patients whose kidney function appears particularly impaired. Importantly, models were built to best estimate the measure of association for sex rather than other characteristics such as race, ART regimens, and history of substance use. As such, those covariates are subject to unmeasured confounding, bias, and effect modification and must subsequently be interpreted with caution.[83] Last, there are other sex-specific differences including hormones, physiology, and pregnancy history for which we could not adjust that may confound our results. Despite these limitations, this study has a large sample size with racial and geographic diversity that enhance the generalizability of our findings.

This study is the first to clearly associate female sex with increased risk of CKD development by accounting for sex-based differences in serum creatinine, genetic factors, and other risk factors including substance use. Importantly, these data highlight this increased risk persisted even after adjustment for covariates known to contribute to diminished kidney function. As life expectancy for this population increases, managing CKD risk among WWH is critical, particularly given the epidemiology of HIV infections, known disparities in access to kidney transplantation, and risk of subsequent mortality. Further work examining the mechanisms by which WWH are at increased CKD risk is warranted.

Contributors

Data sharing statement

Declaration of interests

Acknowledgements

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101653.

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