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Kidney disease in antiretroviralnaïve HIV-positive adults with high CD4: prevalence and predictors of kidney disease at enrolment in the INSIGHT Strategic Timing of AntiRetroviral Treatment trial

AC Achhra[1], **A Mocroft**[2], **MJ Ross**[3], **L Ryom**[4], **GM Lucas**[5], **H Furrer**[6], **J Neuhaus**[7], **C Somboonwit**[8], **M Kelly**[9], **JM Gatell**[10], and **CM Wyatt**[3] **for the INSIGHT START Study Group**

[1]Kirby Institute, UNSW Australia,, Sydney, Australia [2]Research Department of Infection and Population Health, University College London, London, UK [3]Department of Medicine, Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY USA [4]Copenhagen HIV Programme, Rigshospitalet, University of Copenhagen, Department of Infectious Diseases, Section 2100, Finsencentret, Copenhagen, Denmark [5]Department of Medicine, Division of Infectious Disease, Johns Hopkins Medicine, Baltimore, MD [6]Department of Infectious Disease, Bern University Hospital and University of Bern, Bern, Switzerland [7]Division of Biostatistics, University of Minnesota School of Public Health, Minneapolis, Minnesota [8]Department of Medicine, Division of Infectious Disease and International Medicine, University of South Florida, Tampa, FL [9]Department of General Medicine, John Hunter Hospital, Newcastle, Australia [10]Clinical Institute of Medicine and Dermatology, Infectious Diseases & AIDS Units, Hospital Clinic/ IDIBAPS, University of Barcelona, Barcelona, Spain

Abstract

Introduction—HIV infection has been associated with increased risk of chronic kidney disease (CKD). Little is known about the prevalence of CKD in individuals with high CD4 cell counts prior to initiation of antiretroviral therapy (ART).

Methods—We describe the prevalence of CKD among 4637 ART-naïve adults (mean age 36.8 years) with CD4 cell counts >500 cells/μL at enrolment in the Strategic Timing of AntiRetroviral Treatment (START) study. CKD was defined by estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2 and/ or dipstick urine protein ≥1+. Logistic regression was used to identify baseline characteristics associated with CKD.

Results—Among 286 (6.2%, 95% CI 5.5%, 6.9%) participants with CKD, the majority had isolated proteinuria. 268 participants had urine protein ≥1+, including 41 with urine protein ≥2+. Only 22 participants (0.5%) had an estimated glomerular filtration rate <60mL/min/1.73m^2,

Corresponding Author: Christina Wyatt, MD, Icahn School of Medicine at Mount Sinai, Box 1243, One Gustave L. Levy Place, New York, NY 10029, T: (212) 241-6689, F: (212) 987-0389, christina.wyatt@mssm.edu.

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including 4 who also had proteinuria. Baseline characteristics independently associated with CKD included diabetes (adjusted odds ratio, aOR 1.73, 95% CI 1.05, 2.85), hypertension (aOR 1.82, 95% CI 1.38, 2.38), and race/ ethnicity (aOR 0.59, 95% CI 0.37, 0.93 for Hispanic versus white).

Discussion—We observed a low prevalence of CKD associated with traditional CKD risk factors among ART-naïve clinical trial participants with CD4 cell counts >500 cells/μL.

Keywords

START trial; antiretroviral therapy; kidney disease

Introduction

HIV infection has been associated with an increased risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (1–3). Both traditional CKD risk factors and markers of HIV disease severity have been associated with the risk of clinically significant CKD or ESRD (2, 4), and the prevalence of CKD is expected to increase with aging of the HIV-positive population. Little is known about the prevalence of CKD and the contribution of HIV and comorbid conditions to CKD risk in individuals with asymptomatic HIV infection and high CD4 cell count prior to the initiation of combination antiretroviral therapy (ART).

The Strategic Timing of AntiRetroviral Treatment (START) study enrolled 4685 ART-naïve adults with asymptomatic HIV infection and CD4 cell counts >500 cells/μL from 35 countries (5). With broad entry criteria and multinational recruitment, START offers a unique opportunity to estimate the prevalence of CKD in ART-naïve adults with asymptomatic HIV infection. We describe the baseline prevalence of CKD and traditional CKD risk factors among ART-naïve adults with CD4 cell counts >500 cells/μL prior to randomisation in START and to identify factors associated with the presence of CKD in this population.

Methods

The design of START has been described in detail (5). Briefly, START randomised ART-naïve adults ≥18 years of age with asymptomatic HIV infection and CD4 cell count >500 cells/μL to immediate versus deferred initiation of ART. Broad enrolment criteria were designed to increase the generalisability of the results. Relevant exclusion criteria included dialysis, cardiovascular event, or non-AIDS cancer within six months of randomisation, or any history of decompensated liver disease. There were no exclusion criteria based on serum creatinine, estimated glomerular filtration rate (eGFR), or traditional CKD risk factors such as diabetes and hypertension. The START protocol was approved by the local institutional review board or institutional research ethics committee at each enrolling site, and all participants provided written informed consent. The current analysis includes baseline data collected from randomised participants within 60 days prior to randomisation in START.

Study Measurements and Definitions

After informed consent was obtained, demographic and clinical data were collected by standardised case report forms and structured questionnaires. Data collected included the

date of diagnosis and likely mode(s) of HIV infection, comorbid medical conditions and concomitant medication use, and history of tobacco and recreational drug use, including injecting drug use (IDU). A brief physical examination was performed, including the measurement of height, weight, pulse, and seated blood pressure.

Within 60 days prior to randomisation, two screening CD4 cell counts >500 cells/μL were required at least 2 weeks apart. Laboratory testing, including CD4, HIV RNA, serum creatinine, fasting lipids and glucose, and urine dipstick for protein, was performed within 60 days of randomisation. Serologic testing for hepatitis B virus (HBV) coinfection (HBV surface antigen) and hepatitis C virus (HCV) coinfection (anti-HCV antibody) was required within 60 days of randomisation except in participants with a documented positive result.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the CKD Epidemiology Collaboration (CKD-EPI) equation (6), which has been shown to have the best performance in adults with asymptomatic HIV infection when compared to a direct measure of GFR (7–9). To allow for comparison with other populations, eGFR <60 mL/min/ $1.73m^2$ was also estimated using the original 4-variable Modification of Diet in Renal Disease (MDRD) eGFR equation (10). CKD was defined as a CKD-EPI eGFR <60mL/min/ $1.73m^2$ and/ or dipstick urine protein ≥1+, based on the single baseline measure. Sensitivity analyses were performed considering a less stringent alternative diagnosis including CKD-EPI eGFR <60mL/min/$1.73m^2$ and/ or any dipstick urine protein (≥ trace).

Diabetes mellitus was defined by prior diagnosis, use of insulin or oral hypoglycemic medications, or fasting blood glucose ≥ 126 mg/dL. Hypertension was defined by use of antihypertensive medications, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg. Dyslipidemia was defined by use of lipid-lowering medications or LDL ≥ 160 mg/dL. Cardiovascular disease was defined as having a history of myocardial infarction, coronary revascularisation, or stroke. Body mass index (BMI) was defined as weight (kg)/height (m^2).

Statistical analysis

Descriptive statistics were used to describe the prevalence of CKD and traditional CKD risk factors. Univariate and multivariate logistic regression were used to identify baseline characteristics associated with CKD. Continuous variables were assessed for any nonlinear relationship with the outcome. Multivariate models were built using backwards elimination procedure starting with the full model with the following variables: age, sex, race (black, Hispanic, Asian, white and other), IDU, time since HIV diagnosis, CD4 count at randomisation cells/mm^3 (continuous variable), log(base 10) of HIV RNA copies/mL, BMI (categorised as <18.5, 18.5–25, 25.1–29.9, ≥30), hypertension, diabetes, CVD, dyslipidemia and current smoking (yes/no). In cases where there was a strong correlation between two covariates (race and region of enrolment, history of IDU and HCV coinfection, and hypertension and systolic or diastolic blood pressure), a single covariate was selected for inclusion in the multivariate models (race, IDU and hypertension, respectively). Backwards elimination continued till all the variables in the model were statistically significant ($p<0.05$). We performed the following sensitivity analyses: 1) Using conditional logistic

regression models (stratified by the region of enrolment) to analyse the primary outcome; 2) analysing several alternative definitions of CKD using logistic regression models.

All analyses were performed using Stata, version 12 (StataCorp, Texas, United States).

Results

Among 4685 HIV-positive participants enrolled in START, 4637 (99%) had baseline data available for serum creatinine and dipstick urine protein and were eligible for inclusion in this analysis (Table 1). Participants excluded because of missing serum creatinine (n=20) or urine protein (n=28) were more likely to be white and to be coinfected with HCV, and had higher median CD4 cell counts compared to included participants. There was also some variability in the region of enrolment, with excluded participants more likely to be enrolled in Europe and Israel. Other baseline demographic and clinical characteristics were similar in included and excluded participants (data not shown).

Among the 4637 included participants, the mean age was 36.8 years, and only 10% were over age 50 years. The median baseline CD4 cell count was 651 cells/μL, and HBV and HCV coinfection were uncommon (2.9% and 3.7%, respectively). With respect to traditional CKD risk factors, 30% of included participants self-reported their race as black, 19% had hypertension, and 3.5% had diabetes.

Prevalence of CKD

Baseline eGFR was ≥90 mL/min/1.73m^2 in 86% of included participants (Table 1). Only 22 participants (0.5%) had an eGFR <60 mL/min/1.73m^2, including 21 with eGFR 30–59 mL/min/1.73m^2 (Stage 3 CKD) and 1 with eGFR <15 mL/min/1.73m^2 (Stage 5 CKD). Dipstick urine protein was ≥1+ in 268 participants (5.8%), including 41 participants with urine protein ≥2+. Only 4 participants had both urine protein ≥1+ and eGFR <60 mL/min/1.73m^2. Overall, 286 participants (6.2%) met our *a priori* definition of CKD based on eGFR <60mL/min/1.73m^2 and/ or urine protein ≥1+. The prevalence of CKD varied by region of enrolment, ranging from as low as 4.8% in Africa to as high as 9.5% in North America.

Baseline characteristics associated with CKD

Baseline characteristics significantly associated with increased odds of CKD in univariate analysis included older age, BMI >30 kg/m^2, history of IDU, diabetes, hypertension, dyslipidemia, and cardiovascular disease (Table 2). Hispanics had significantly lower odds of CKD, while black and Asian race were both associated with a nonsignificant increase in the odds of CKD compared to whites. Markers of HIV disease and serologic evidence of viral hepatitis coinfection were not significantly associated with CKD, although there was a nonsignificant increase in baseline CD4 and time since HIV diagnosis in participants with CKD compared to those without CKD.

In multivariate analysis, only diabetes (adjusted odds ratio, aOR 1.73, 95% CI 1.05, 2.85), hypertension (aOR 1.82, 95% CI 1.38, 2.38), and race/ ethnicity remained significantly associated with the odds of CKD (Table 2). Compared to whites, Hispanics had a nearly 40% reduction in the odds of CKD (aOR 0.59, 95% CI 0.37, 0.93). Black and Asian race,

markers of more severe HIV disease, and serologic evidence of viral hepatitis coinfection were not significantly associated with increased odds of CKD in the multivariate analysis. Stratifying models on region of enrolment resulted in an increase in the aOR for black race, although it did not reach statistical significance (aOR 1.39, 95% CI 0.94, 2.05; Supplementary Table 1).

Alternative definitions of CKD

In sensitivity analyses, we evaluated baseline factors associated with several alternative definitions of CKD, both more and less stringent than that used in the primary analysis (Table 3). The most consistent finding was that CKD was associated with diabetes and hypertension – traditional CKD risk factors – regardless of the CKD definition used. When we considered two more stringent CKD definitions based on eGFR <60mL/min/1.73m^2 alone (n=22, 0.5%) and the combination of eGFR <60mL/min/1.73m^2 and/ or urine protein ≥2+ (n=60, 1.3%), older age was also independently associated with increased odds of CKD. In addition, time since HIV diagnosis and HIV RNA was associated with a small increase, and black race and diabetes with a nonsignificant (P<0.1 but >0.05) increase, in the odds of CKD as defined by decreased eGFR and/ or urine protein ≥2+. When we considered a less stringent CKD definition based on eGFR <60mL/min/1.73m^2 and/ or urine protein ≥ trace (n=785, 16.9%), additional baseline factors independently associated with increased odds of CKD included non-Hispanic ethnicity, history of IDU, and current cigarette smoking.

Discussion

In this large and well-characterised population of ART-naïve clinical trial participants with CD4 cell count >500 cells/μL, we observed a low prevalence of CKD as defined by eGFR <60mL/min/1.73m^2 and/ or dipstick urine protein of 1+ or greater. While participants with ESRD on dialysis were excluded from START by protocol, there were no exclusion criteria based on serum creatinine or eGFR. Despite these broad entry criteria, only 0.5% of START participants had an eGFR 60mL/min/1.73m^2 at enrolment. Prevalent CKD was associated with traditional CKD risk factors, including diabetes and hypertension, but not with markers of HIV disease severity.

Race/ethnicity was also independently associated with the odds of prevalent CKD in START. The observed relationship was driven by a significant decrease in the odds of CKD in Hispanics, with no significant association observed between black race and CKD. Although black race is a strong predictor of advanced CKD and ESRD in HIV-positive adults, our results are consistent with prior studies demonstrating little or no association with earlier stages of CKD in HIV-positive blacks (11, 12). Our findings are also consistent with observations in the general US population, where the low prevalence of early stage CKD in African-Americans and Hispanics contrasts sharply with the disproportionate burden of ESRD in those populations (13). In sensitivity analysis considering more severe CKD as defined by low eGFR and/ or heavy proteinuria, the protective effect of Hispanic ethnicity was no longer evident, and black race was associated with a nonsignificant increase in the odds of CKD (Table 3). Of note, two thirds of black participants were enrolled in Africa, and that the prevalence of CKD was actually lower in Africa than in any other region. With

limited access to ART for individuals with high CD4 cell count outside the context of a clinical trial, it is possible that the reasons for participation, and thus the participants themselves, may be different in Africa compared to resource-rich settings. In addition, the current analysis does not account for differences in genetic susceptibility to CKD across African populations. Variants in the *APOL1* gene encoding apolipoprotein L1 have been strongly linked to increased risk of HIV-associated nephropathy and nondiabetic kidney disease in individuals of West African ancestry. The highest enrolling African sites in START were in East Africa, where prevalence of the *APOL1* risk variants is lower than that observed in West African and African-American populations (14).

In this population with uniformly high CD4 cell count, markers of HIV disease severity were not significantly associated with the odds of CKD as defined by a single measure of decreased eGFR and/or proteinuria. The observed prevalence of eGFR <60 mL/min/1.73m^2 (0.5% by both CKD-EPI and MDRD equations) was lower than that observed in prior studies of HIV-positive individuals with more advanced HIV disease. In an analysis of 1547 HIV-positive US women enrolled in the Women's Interagency HIV Study (WIHS) cohort prior to 1996, 99% were ART-naïve, mean CD4 cell count was approximately 400 cells/μL, and nearly 8% of participants had an MDRD eGFR <60 mL/min/1.73m^2 (15). Among 23,155 HIV-positive US military veterans followed in the Veterans Aging Cohort Study (VACS) virtual cohort, only 17% were on ART at baseline, median CD4 cell count was 336 cells/μL, and 12% had a baseline MDRD eGFR <60mL/min/1.73m^2 (16). Despite broad entry criteria in START, participants tended to be younger and healthier than those enrolled in these observational studies, and by design CD4 was uniformly higher. Nonetheless, even among carefully selected participants in prior international HIV treatment trials, the baseline prevalence of decreased eGFR was higher than that observed in START. For example, in a combined analysis of 3441 participants enrolled in the standard treatment arms of SMART and ESPRIT (CD4 cell count entry criteria was >350 cells/μL and >300 cells/μL, respectively), 1.7% of participants had a baseline MDRD eGFR <60 mL/min/1.73m^2 (17).

The observed prevalence of decreased eGFR in START participants is similar to that observed in the general population. As an example, the prevalence of CKD-EPI eGFR <60mL/min/1.73m^2 is estimated to be 0.2% in US adults age 20–39 years and 2.2% in US adults age 40–59 years in the National Health and Nutrition Examination Survey (NHANES) (18). In contrast, there appears to be a higher than expected prevalence of dipstick proteinuria in START participants compared to the general population. Overall, 5.8% of START participants had dipstick urine protein ≥1+ and 16.7% had dipstick urine protein ≥ trace. The prevalence of dipstick urine protein ≥1+ and ≥ trace was similar in a nationally representative sample of Australian adults (8.0% and 16.1%, respectively) and at the fifteenth biennial visit in the Framingham Heart Study (4.5% and 14.7%, respectively); however, the age distribution was much younger in START compared to the other study populations (10% versus 50% and 100% of participants ≥ 50 years, respectively) (19, 20). Unfortunately, the limited accuracy of dipstick proteinuria for the detection of microalbuminuria does not allow for direct comparison with nationally representative estimates in similarly aged adults (19).

Although this is the first study to provide generalisable estimates of CKD prevalence in a well-characterised international sample of HIV-positive adults with high CD4 cell count, several limitations must be acknowledged. Most importantly, the CKD definition was based on a single measure of serum creatinine and dipstick urine protein prior to randomisation in START, while clinical practice guidelines recommend confirmation of decreased eGFR and/or proteinuria on at least two measures at least three months apart (21). It is possible that participants with acute kidney injury or transient proteinuria were misclassified as having CKD based on our definition; however, all participants were asymptomatic at the time of randomisation in START, making it unlikely that they had transient changes in eGFR or proteinuria in the setting of acute illness. In addition, both acute kidney injury and transient proteinuria have also been associated with adverse long-term outcomes in the general population and in HIV-positive individuals (15, 20, 22). In a cohort of 17,325 HIV-positive US military veterans who survived at least 90 days after hospital discharge, a single episode of stage 1 acute kidney injury (increase in serum creatinine of only 0.3 mg/dL or by 150–200%) was associated with a 20% increase in mortality (adjusted hazard ratio, aHR 1.20, 95% CI 1.13, 1.28) and a nearly 40% increase in the risk of ESRD (aHR 1.37, 95% CI 1.02, 1.84) (22). In the WIHS analysis described above, HIV-positive women with only one of two urine specimens positive for dipstick protein ≥1+ or microalbuminuria had a threefold increase in the risk of all-cause mortality compared to those with two negative results (aHR 3.4; 95% CI 2.2, 5.2) (15). While these and other studies have demonstrated the clinical significance of isolated abnormalities in kidney function and proteinuria, it is possible that a more rigorous definition of CKD based on repeated measurements would be more closely associated with markers of HIV disease in addition to traditional CKD risk factors. It is also likely that the estimated prevalence of CKD would be lower using a more rigorous definition; for all comparisons with other patient populations, we used a similar definition of CKD based on a single measure of eGFR and/ or dipstick urine protein.

Second, while the CKD-EPI eGFR is the most accurate creatinine-based GFR estimate for use in HIV-positive adults (7–9), the CKD-EPI equation is intended for use with serum creatinine assays traceable to isotope dilution mass spectrometry (“IDMS-traceable”), which were not available at all enrolling sites. Nonetheless, the prevalence of eGFR <60 mL/min/1.73m^2 was similar when calculated using the original MDRD equation (24 versus 22 participants), which does not require an IDMS-traceable creatinine. Third, data on more sensitive measures of urine protein and tubular function are not available in START, although the standardised collection and banking of urine may allow for future testing. Fourth, despite broad entry criteria, clinical trial participants are generally healthier than an unselected HIV-positive population with high CD4 cell count. Fifth, it is possible that providers may have chosen to initiate ART in individuals with pre-existing CKD, rather than referring them to a clinical trial that includes a deferred initiation arm. Together, these last three limitations would tend to result in more conservative estimates of CKD prevalence.

In this cross-sectional analysis of ART-naïve clinical trial participants with CD4 cell count >500 cells/μL, the baseline prevalence of eGFR <60mL/min/1.73m^2 was lower than that observed in previous studies in HIV-positive populations and similar to that observed in the general population. In contrast, the high prevalence of dipstick proteinuria suggests that the prevalence of microalbuminuria and low-grade proteinuria is higher than expected in this

relatively young healthy cohort. Traditional CKD risk factors, but not markers of HIV disease, were associated with prevalent CKD as defined by a single measure of decreased eGFR and/ or proteinuria. The ongoing START study is investigating the impact of immediate versus deferred ART on the risk of incident ESRD, and longitudinal assessments of eGFR and proteinuria will provide valuable insight into the course of early CKD and whether early versus deferred ART strategies affect clinical outcomes in patients with CKD. Future studies should confirm the increased prevalence of proteinuria in ART-naïve adults with high CD4 cell counts using repeated assessments and a quantitative measure of urine protein and should consider the contribution of HIV infection, traditional CKD risk factors, and factors such as HCV, IDU, and cigarette smoking that are over-represented in this population.

Supplementary Table 1. Conditional logistic models stratified by region of enrolment for associations with prevalent chronic kidney disease in START participants.

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Table 1

Baseline characteristics of START study participants stratified by the presence of prevalent chronic kidney disease.

	All Eligible (n=4637)	CKD (n=286)	No CKD (n=4351)	P-value*
Age, years				
Mean (SD)	36.8 (10.2)	38.3 (11.3)	36.7 (10.1)	0.008
Male, n (%)	3388 (73.1)	201 (70.3)	3187 (73.2)	0.273
Race, n (%)				
Black	1402 (30.2)	96 (33.6)	1306 (30.0)	0.011
Hispanic	631 (13.6)	23 (8.0)	608 (14.0)	
White	2054 (44.3)	131 (45.8)	1923 (44.2)	
Asian	388 (8.4)	31 (10.8)	357 (8.2)	
Other	162 (3.5)	5 (1.7)	157 (3.6)	
Exposure category, n (%)				
Injecting drug use	63 (1.4)	8 (2.8)	55 (1.3)	0.120
Same sex contact	2544 (54.9)	146 (51.1)	2398 (55.1)	
Heterosexual contact	1778 (38.3)	116 (40.6)	1662 (38.2)	
Other	252 (5.4)	16 (5.6)	236 (5.4)	
Years since HIV diagnosis				
Mean (SD)	2.3 (3.4)	2.7 (4.0)	2.3 (3.3)	0.064
Baseline CD4, cells/μL				
Median (IQR)	651 (584–764)	662 (589–783)	651 (583–763)	0.069
Log10 HIV RNA, copies/mL				
Mean (SD)	4 (0.9)	4.1 (0.9)	4 (0.9)	0.273
Body mass index, kg/m^2				
<18.5	135 (2.9)	11 (3.8)	124 (2.9)	0.047
18.5–25	2399 (51.7)	142 (49.7)	2257 (51.9)	
25.1–29.9	1340 (28.9)	71 (24.8)	1269 (29.2)	
≥30	763 (16.5)	62 (21.7)	701 (16.1)	
Systolic blood pressure, mmHg Mean (SD)	121.5 (14.7)	125.1 (16.5)	121.2 (14.6)	<0.001
Diastolic blood pressure, mmHg Mean (SD)	76.4 (10.6)	78.7 (11.1)	76.2 (10.5)	<0.001
Hepatitis C coinfection, n (%)	167 (3.7)	14 (5.0)	153 (3.6)	0.228
Hepatitis B coinfection (%)	130 (2.9)	4 (1.5)	126 (3.0)	0.145
Diabetes mellitus, n (%)	164 (3.5)	20 (7.0)	144 (3.3)	0.001

	All Eligible (n=4637)	CKD (n=286)	No CKD (n=4351)	P-value*
Hypertension, n (%)	891 (19.2)	88 (30.7)	803 (18.5)	<0.001
Dyslipidemia, n (%)	382 (8.2)	35 (12.2)	347 (8.0)	0.011
Cardiovascular disease, n (%)	22 (0.5)	5 (1.7)	17 (0.4)	0.001
Current smoker, n (%)	1474 (31.8)	101 (35.3)	1373 (31.6)	0.186
Region of enrolment				
North America	504(10.9)	48 (16.8)	456(10.5)	
South America/Mexico	1165 (25.1)	59 (20.6)	1106 (25.4)	0.002
Europe/Israel	1509(32.5)	93 (32.5)	1416 (32.5)	
Africa	996(21.5)	48 (16.8)	948 (21.8)	
Asia	356(7.7)	29 (10.1)	327 (7.5)	
Australia	107 (2.3)	9 (3.2)	98 (2.3)	
Serum creatinine, mg/dL				
Mean (SD)	0.86 (0.2)	0.95 (0.5)	0.85 (0.2)	
eGFR, mL/min/1.73m^2				
Mean (SD)	110.2 (18.4)	103.7 (25.2)	110.5 (17.7)	
≥90	3973 (85.7)	214 (74.8)	3759 (86.4)	
60–89	642 (13.8)	50 (17.5)	592 (13.6)	
<60	22 (0.5)	22 (7.7)	---	
Dipstick proteinuria, n (%)				
Negative protein	3864 (83.3)	12 (4.2)	3852 (88.5)	
Trace protein	505 (10.9)	6(2.1)	499 (11.5)	
≥1+ protein**	268 (5.8)	268 (93.7)	---	

CKD, chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 and/ or dipstick urine protein ≥1+; eGFR calculated by the CKD-Epidemiology Collaboration (CKD-EPI) 2009 equation. Hepatitis C coinfection based on positive antibody at enrolment. Hepatitis B coinfection based on positive surface antigen at enrolment. See text for definitions of hypertension, diabetes, dyslipidemia, and cardiovascular disease. Data were missing in <4% of participants for the following variables: HIV RNA (n=8), blood pressure (n=3), hepatitis C antibody (n=104), and hepatitis B surface antigen (n=119).

* p-values were calculated using t-tests for continuous variables and chi-square test for categorical variables; median CD4 was compared by rank-sum test.

** 25 participants had 2 urine protein and 16 participants had 3+ urine protein.

Table 2

Univariate and multivariate associations with prevalent chronic kidney disease in START participants.

Characteristics	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age, per 5 years increment	**1.08 (1.02 to 1.14), 0.008**	-
Male	0.86 (0.66 to 1.12), 0.273	-
Race		
Black	1.08 (0.82 to 1.42), 0.583	1.01 (0.77 to 1.33) 0.939
Hispanic	**0.56 (0.35 to 0.87), 0.011**	0.59 (0.37 to 0.93) 0.023
White	Reference	Reference
Asian	1.27 (0.85 to 1.92), 0.243	1.36 (0.90 to 2.05) 0.143
Other	0.47 (0.19 to 1.16), 0.101	0.48 (0.19 to 1.19) 0.113
Overall p-value	0.013	0.023
Injecting drug use	**2.25 (1.06 to 4.77), 0.035**	-
Time since HIV diagnosis, years	1.03 (1.00 to 1.06), 0.051	-
Baseline CD4, per 50 cells/mm^3	1.02 (0.99 to 1.06), 0.153	-
HIV-RNA, per log[10] copies/mL	1.08 (0.94 to 1.24), 0.274	-
Body mass index, kg/m^2		-
<18.5	1.41 (0.74 to 2.67), 0.294	
18.5–25	Reference	
25.1–29.9	0.89 (0.66 to 1.19), 0.418	
≥30	**1.41 (1.03 to 1.92), 0.032**	
Overall p-value	0.048	
Hepatitis C coinfection	1.41 (0.80 to 2.47), 0.230	-
Hepatitis B coinfection	0.48 (0.18 to 1.31), 0.154	-
Diabetes mellitus	**2.20 (1.35 to 3.56), 0.001**	**1.73 (1.05 to 2.85), 0.034**
Hypertension	**1.96 (1.51 to 2.55), <0.001**	**1.82 (1.38 to 2.38), <0.001**
Dyslipidemia	**1.61 (1.11 to 2.33), 0.012**	-
Cardiovascular disease	**4.06 (1.50 to 10.94), 0.006**	-
Current smoking	1.18 (0.92 to 1.52), 0.187	

Prevalent chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73m^2 and/ or urine protein ≥1+. Hepatitis C coinfection based on positive antibody from any time before enrolment. Hepatitis B coinfection based on positive surface antigen within a year before enrolment. See text for definitions of hypertension, diabetes, dyslipidemia, and cardiovascular disease.

Table 3

Sensitivity analyses: multivariate associations with alternative definitions of chronic kidney disease in START participants.

Characteristics	eGFR <60 (n=22) OR (95% CI)	eGFR <60 and/ or urine protein ≥2+ (n=60) OR (95% CI)	eGFR <60 and/ or urine protein ≥trace (n=785) OR (95% CI)
Age, per 5 years increment	1.54 (1.25 to 1.90)	1.32 (1.16 to 1.51)	---
Male	---	---	---
Race	--	*	
Black			1.11 (0.92 to 1.33)
Hispanic			0.64 (0.49 to 0.84)
White			1.17 (0.88 to 1.55)
Asian			Reference
Other			0.42 (0.24 to 0.76)
Injecting drug use	---		2.26 (1.32 to 3.85)**
Time since HIV diagnosis, years	---	1.08 (1.03 to 1.13)	
Baseline CD4, per 50 cells/mm^3	---		---
HIV-RNA, per log[10] copies/mL	---	1.41 (1.03 to 1.92)	---
Body mass index, kg/m^2	---		---
<18.5		2.66 (0.77 to 9.19)	
18.5–25		Reference	
25.1–29.9		0.48 (0.23 to 1.03)	
≥30		1.43 (0.75 to 2.71)	
Hepatitis B coinfection	---	---	---
Diabetes mellitus	2.95 (1.07 to 8.14)	*	1.51 (1.04 to 2.18)
Hypertension	4.43 (1.58 to 12.40)	2.64 (1.46 to 4.76)	1.37 (1.14 to 1.66)
Dyslipidemia	---	---	---
Cardiovascular disease	---	---	---
Current smoking	---	---	1.21 (1.03 to 1.44)

eGFR <60, estimated glomerular filtration rate <60 mL/min/1.73m^2 calculated by the CKD-EPI equation. Hepatitis B coinfection based on positive surface antigen within a year before enrolment. See text for definitions of hypertension, diabetes, dyslipidemia, and cardiovascular disease.

* Addition of race and diabetes resulted in a non-significant (P<0.1 but >0.05) association of each of them as follows: blacks (vs. whites/other as reference): 2.17 (95% CI 1.16, 2.09) and diabetes: 2.04 (95% CI 0.94, 4.39) when CKD was defined by decreased eGFR and/ or urine protein ≥ 2.

** In a model excluding IDU, HCV coinfection was also independently associated with CKD as defined by decreased eGFR and/ or urine protein ≥ trace (aOR 1.82, 95% CI 1.28, 2.59).