Title

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Journal

American Journal of Transplantation, 17(7)

ISSN

1600-6135

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Publication Date

2017-07-01

DOI

10.1111/ajt.14235

Peer reviewed

HHS Public Access

Author manuscript

Am J Transplant. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Am J Transplant. 2017 July ; 17(7): 1823–1832. doi:10.1111/ajt.14235.

Risk of End Stage Renal Disease in HIV-positive Potential Live Kidney Donors

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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Abstract

New federal regulations allow HIV-positive individuals to be live kidney donors; however, potential candidacy for donation is poorly understood given the increased risk of end-stage renal disease (ESRD) associated with HIV. To better understand this risk, we compared the incidence of ESRD among 41,968 HIV-positive participants of NA-ACCORD followed for a median of 5 years with the incidence of ESRD among comparable HIV-negative participants of NHANES-III followed for a median of 14 years. We used risk associations from multivariable Cox proportional hazards regression to derive cumulative incidence estimates for selected HIV-positive scenarios (no history of diabetes, hypertension, AIDS, or HCV co-infection) and compared these estimates with those from similarly selected HIV-negative scenarios. For 40-year-old HIV-positive individuals with health characteristics that were similar to those of age-matched kidney donors, viral load <400 copies/mL, and CD4+ count ≥500 cells/μL, the 9-year cumulative incidence of ESRD was higher than their HIV-negative peers, yet still low: 2.5 versus 1.1 per 10,000 among white females, 3.0 versus 1.3 per 10,000 among white males, 13.2 versus 3.6 per 10,000 among black females, and 15.8 versus 4.4 per 10,000 among black males. HIV-positive individuals with no comorbidities and well-controlled disease may be considered low-risk kidney donor candidates.

INTRODUCTION

The Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act of 2013 ended the ban on HIV-positive-to-HIV-positive transplantation (1). For HIV-positive transplant candidates on the deceased donor waiting list, the pool of available organs may thus increase by 500–600 per year (2), the time from listing to transplantation may decrease significantly, and the benefits of transplantation may be realized sooner (3, 4). However, for HIV-positive transplant candidates who wish to consider HIV-positive live kidney donor transplantation, concerns about the long-term risks to the HIV-positive kidney donor may be a drawback (5).

An important risk associated with live kidney donation is end-stage renal disease (ESRD) (6–13). HIV-positive individuals may be considered too high risk for donor nephrectomy because they have an increased risk of ESRD when compared with their HIV-negative counterparts, especially in the presence of common risk factors such as diabetes and hypertension (14–19). However, the additional risk of ESRD among HIV-positive individuals who meet standard kidney donor eligibility criteria (20–22), and who meet the Department of Health and Human Services definition of well-controlled HIV infection (CD4+ T-cell count >500/μL for the 6 month period before donation, HIV-1 RNA <50 copies/mL, no evidence of invasive opportunistic complications of HIV infection) (5), is unknown.

To evaluate the additional risk of ESRD in HIV-positive potential live kidney donors, we estimated the cumulative incidence of ESRD for various low-risk clinical scenarios based on age, race, renal function, HIV viral load, and CD4+ count. We then compared these cumulative incidence estimates to similar clinical scenarios in an HIV-negative population.

METHODS

Data Source: HIV-positive Potential Donors

HIV-positive potential donors were drawn from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). NA-ACCORD is a consortium of clinical and interval HIV cohorts from Canada and the United States (23). It is one of 7 regional collaborations of the International Epidemiologic Databases to Evaluate AIDS supported by the National Institutes of Health and draws participants from over 100 clinical sites that represent HIV-positive individuals engaged in clinical care (23, 24). Each contributing cohort uses standardized cohort-specific methods of data collection. At scheduled intervals, cohorts securely transfer demographic, medication, laboratory, diagnosis, and vital status information to the NA-ACCORD central Data Management Core (University of Washington), where data undergo quality control for completeness and accuracy before they are combined into harmonized data files. The data are subsequently sent to the Epidemiology/Biostatistics Core (Johns Hopkins University), where they undergo additional quality control and assembly into analytic data files. The human subject activities of the NA-ACCORD and each participating cohort study have been reviewed and approved by their corresponding local institutional review boards. Eleven clinic-based cohorts (9 in the United States and 2 in Canada; n=41,968) within the NA-ACCORD used medical record evidence of AV fistula placement, dialysis, and kidney transplantation to validate cases of ESRD in clinical care between January 2000 and December 2009 (25). The study endpoint was defined as the earliest one of the following events (date of ESRD diagnosis, date of death, date of cohort administrative censorship, December 31, 2009).

Data Source: HIV-negative Potential Donors

Healthy HIV-negative individuals were drawn from Third National Health and Nutrition Examination Survey (NHANES III) (n=16,025) (26). In this survey medical information was obtained from patient self-report, physical examination, and radiologic and laboratory test results at NHANES III enrollment between 1988 and 1994. ESRD outcomes were ascertained by linkage to the Centers for Medicare & Medicaid Services' (CMS's) medical evidence Form 2728 (certification of ESRD) and to the CMS patient profile and death notification Form 2746 (including records through September 30, 2008), as we have previously reported (10). End-stage renal disease was defined as the initiation of maintenance dialysis or receipt of a kidney transplant, whichever was identified first.

Cumulative Incidence of ESRD

We evaluated the associations between the risk of ESRD and various demographic and clinical characteristics for the HIV-positive cohort (NA-ACCORD) and the HIV-negative cohort (NHANES-III). To ensure model stability (i.e., a sufficient number of events for multivariable regression), we included individuals with diabetes mellitus, hypertension, and

CKD-EPI eGFR 45–90ml/min/1.73 m^2 (27), as well as individuals with viral load >400 copies/mL and CD4+ count <500/μL in the HIV-positive cohort. In both the HIV-positive and HIV-negative cohorts, we considered age, race/ethnicity (white/other, black, Hispanic), sex, presence or absence of diabetes mellitus, hypertension, eGFR, smoking, body mass index (BMI), and HCV-positive serology. Additionally, in the HIV-positive cohort we considered HIV transmission risk group (men who have sex with men, current or history of injection drug use, heterosexual contact, other), years of antiretroviral therapy (ART) use, tenofovir use (TDF formulation), HIV viral load, CD4+ count, and history of AIDS. For the HIV-negative cohort, we additionally considered urinary albumin-to-creatinine ratio and SBP. The final variables were selected based on Akaike's Information Criteria (28).

We estimated risk associations using multivariable Cox proportional-hazards regression separately for each cohort since the HIV-negative cohort has no meaningful values for HIV transmission risk group, duration of ART use, duration of tenofovir use, HIV viral load, CD4+ count, and history of AIDS; the entire HIV-positive cohort has no data on urinary albumin-creatinine ratio and >50% of the cohort has missing values for systolic blood pressure. However, a priori, we explored a joint model including the HIV-positive cohort and HIV-negative cohort to test the hypothesis that the effects of black race may vary by cohort. Post hoc, we also tested the hypothesis that the effects of age and eGFR varied by cohort. In this model, viral load was set to "suppressed" (i.e., <400 counts/mL), CD4+ count to 1000 cells/μL, and history of AIDS to "no" for the HIV-negative cohort. The joint model included age, race, sex, diabetes, hypertension, eGFR, smoking history, HCV, viral load, CD4+ count, history of AIDS, and interaction terms for HIV status and age, race, sex, diabetes, and eGFR.

For both cohorts, a base-case scenario was defined to reflect the average kidney donor in the United States: a systolic blood pressure of 120 mmHg, a urinary albumin-to-creatinine ratio of 4 mg/g, no history of smoking, no diabetes, and no hypertension (10). For the HIV-positive cohort, a low-risk scenario was defined to reflect the average kidney donor characteristics as well as the Department of Health and Human Services criteria for well-controlled HIV infection: CD4+ T-cell count >500/μL for the 6 month period before donation, HIV-1 RNA <50 copies/mL, and no evidence of invasive opportunistic complications of HIV infection (5). The linear function for each participant was centered on that of the base-case scenario within each category of age, race, and sex. All reported cumulative incidence estimates were derived from the following expression:

$$1 - e^{-\int h_0(t)\exp(X\beta)}$$

Where $h_0(t)$ is the nonparametric hazard for the base-case; $\exp(X\beta)$ is the maximum-likelihood estimate of the difference (on a log scale) between the hazard for the base-case and the hazard for the specific clinical scenario with explanatory variables X; and, t is the number of years of follow-up (t=9 for all reported analyses). In other words, Cox regression on a vector of explanatory variables, X, yielded a vector of log hazard ratios, β. The baseline survival function was subsequently obtained by applying the value of zero to all explanatory variables in the mathematical expression depicted above. To obtain the survival function for

a given scenario, we specified the difference in value (e.g., 5 years) between the scenario (i.e., 45 years) and the base-case (40 years). To evaluate the Cox proportional hazards assumption, we used the global test developed by Therneau and Grambsch, which is equivalent to testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time. For our study the global test suggested proportional hazards (p=0.4).

Statistical Analysis

We compared the 9-year cumulative incidence of ESRD in HIV-positive potential donors with HIV-negative potential donors. The difference in cumulative incidence between HIV-positive potential donors and HIV-negative potential donors was reported as the risk increase associated with HIV infection. All analyses were performed using Stata 14.0/MP for Linux (Stata Corp, College Station, TX). All hypothesis tests were 2 sided ($\alpha = .05$).

RESULTS

Study population

The median age of the HIV-positive cohort was 41 years, 40% were black, 15% were Hispanic, 78% were male, 2% had diabetes, and 15% had hypertension. The median estimated glomerular filtration rate (eGFR) was 104 ml/min/1.73m^2, median systolic blood pressure (SBP) was 125mmHg, median body-mass index (BMI) was 25 kg/m^2, 74% reported having ever smoked cigarettes, and 19% were Hepatitis C Virus (HCV) co-infected. By HIV transmission risk group, 45% were men who have sex with men, 33% were heterosexual, 11% were current or had a history of injection drug use, and 12% belonged to other categories. At study entry, median viral load was 926 copies/mL, 47% had initiated antiretroviral therapy (ART), 43% had suppressed HIV viral load (<400 copies/mL), 32% had CD4+ count >500 cells/μL, and 20% had AIDS. The median age of the HIV-negative cohort was 42 years. Compared with the HIV-positive cohort, the HIV-negative cohort had a lower proportion of black (28%) and male (47%) participants, but a higher prevalence of diabetes (12%) and hypertension (26%). The median value of albumin-to-creatinine ratio was 6 mg/g, median eGFR was 103 ml/min/1.73m^2, median SBP was 122 mmHg, and median BMI was 26 kg/m2. There were 49% who reported ever smoking cigarettes and 2% were HCV-seropositive (Table 1).

Risk of ESRD

In the HIV-positive cohort, there were 126 ESRD events over a period of 212,804 person-years of follow-up; the median follow-up was 5 years (interquartile range, 3–8). In the HIV-negative cohort, there were 114 ESRD events over a period of 205,616 person-years of follow-up; the median follow-up was 14 years.

Table 2 shows the associations between the risk of ESRD and the demographic and clinical characteristics of both cohorts at baseline. In the HIV-positive cohort, the highest risks were observed among black individuals, those with diabetes, hypertension, low eGFR, history of smoking, HCV co-infection, high viral load, low CD4 count, history of AIDS, and with duration of exposure to ART (but only among those with less than 9 years of previous

exposure to ART). In the HIV-negative cohort, the highest risks were observed among black individuals, those with diabetes, low eGFR, high urinary albumin-to-creatinine ratio, high SBP, history of smoking, HCV-positive serology. Hypertension was not associated with risk of ESRD in this cohort; however, an association was observed in a sensitivity analysis that excluded urinary albumin-to-creatinine ratio and SBP.

An inverse association was observed between age and risk of ESRD in both the HIV-positive and HIV-negative cohorts; however, this effect was not observed among those <50 years in the HIV-negative cohort ($p<0.001$ for interaction term for age <50 years and HIV status; $p=0.4$ for interaction for age >50 years and HIV status). Similarly, an inverse association was observed between eGFR and risk of ESRD in both the HIV-positive and HIV-negative cohorts; however, this effect was not observed among those with eGFR>90 ml/min/1.73m^2 in the HIV-negative cohort ($p=0.004$ for interaction term for eGFR>90 ml/min/1.73m^2 and HIV status; $p=0.4$ for interaction for eGFR<90 and HIV status).

Black individuals had an increased risk of ESRD compared with white individuals; however, this increase in risk was >2-fold higher in the HIV-positive cohort compared with the HIV-negative cohort ($p=0.03$ for interaction of black race and HIV status in a joint HIV-positive and HIV-negative cohort model that excluded urinary albumin-to-creatinine ratio and SBP).

Cumulative Incidence of ESRD

The 9-year cumulative incidence of ESRD varied by orders of magnitude from low-risk scenarios (e.g. 3 ESRD events per 10,000 for a 40-year-old HIV-positive white male with no history of diabetes, no hypertension, eGFR 95 ml/min/1.73m^2, no HCV co-infection, using ART (including tenofovir) for 1 year, with suppressed viral load, CD4+ count >500 cells/uL, and no history of AIDS) to high-risk/base-case scenarios (e.g. 115 ESRD events per 10,000 for a 40-year-old HIV-positive black male with no history of diabetes, no hypertension, eGFR 105 ml/min/1.73m2, no HCV co-infection, using ART, but with a viral load of 100,000 copies/mL and CD4+ count 200 cells/μL)(Figure 1).

Risk Increase associated with HIV

The 9-year cumulative incidence of ESRD varied considerably by baseline eGFR. For the base-case of a 40-year-old, the 9-year cumulative incidence of ESRD in the HIV-positive and HIV-negative cohorts was 2.5 versus 1.1 per 10,000 among white females, 3.0 versus 1.3 per 10,000 among white males, 13.2 versus 3.6 per 10,000 among black females, and 15.8 versus 4.4 per 10,000 among black males (Figure 2). For the base case of a 50-year-old, the 9-year cumulative incidence of ESRD in the HIV-positive and HIV-negative cohorts was 1.5 versus 1.4 per 10,000 among white females, 1.8 versus 1.6 per 10,000 among white males, 8.0 versus 4.6 per 10,000 among black females, and 9.5 versus 5.5 per 10,000 among black males. By contrast, for the base case of a 30-year-old, the 9-year cumulative incidence of ESRD in the HIV-positive and HIV-negative cohorts was 3.6 versus 0.9 per 10,000 among white females, 4.3 versus 1.0 per 10,000 among white males, 19.3 versus 2.9 per 10,000 among black females, and 23.0 versus 3.5 per 10,000 among black males. The risk increase associated with HIV varied substantially by baseline clinical characteristics and was lowest

for older white individuals >40-years-old and highest for young black individuals <40-years-old (Table 3).

DISCUSSION

In this North American cohort study of HIV-positive individuals, the 9-year risk of ESRD varied by orders of magnitude across various clinical scenarios. However, in subgroups with no comorbidities and well-controlled HIV infection, the risk increase associated with HIV for the base case of a 40-year old was 1 per 10,000 among white females, 2 per 10,000 among white males, 10 per 10,000 among black females, and 11 per 10,000 among black males. For perspective, these estimates (particularly those for white individuals) are comparable to the risk increase in HIV-negative potential donors associated with cigarette smoking (12), which is not a contraindication to kidney donation (1 per 10,000 among white females, 1 per 10,000 among white males, 3 per 10,000 among black females, and 4 per 10,000 among black males)(20–22).

HIV infection may thus be viewed as a relative contraindication to kidney donation since carefully select HIV-positive donor candidates may have an acceptable risk of ESRD, comparable to the 1.8-fold increase in risk observed among smokers in this study and in the recent report by Grams et al (12). By contrast, risk factors that are traditionally viewed as absolute contraindications to kidney donation are associated with substantially higher risks compared with smoking: 5.2-fold increase in risk associated with diabetes; 3.4-fold increase in risk per 20mmHg increase in systolic blood pressure ≥120mmHg; and 4.0-fold increase in risk per 10mg/g increase in urinary albumin-to-creatinine ratio. For these outlined reasons, a white HIV-positive potential donor with no diabetes, no hypertension, no albuminuria, no history of smoking, and well-controlled infection may be viewed as a low-risk kidney donor candidate.

These findings and inferences reaffirm the observation that the risk of ESRD in HIV-positive individuals correlates directly with the quantity of replicating virus and, as such, that the use of ART may reduce this risk substantially (14, 19, 29). While our finding of a 3.2-fold higher risk of ESRD in black compared with white HIV-negative individuals is consistent with well-established literature (30, 31), our finding of a substantially stronger risk association (6.9-fold higher) of ESRD in black compared with white HIV-positive individuals is consistent with more recent and emerging literature (14, 15, 19, 32). In this literature, there is compelling evidence that the high-risk APOL1 haplotype – which is found in individuals with African ancestry – might interact biologically with HIV (33). According to studies of renal biopsy reports, HIV-positive individuals with high-risk APOL1 haplotypes have much higher risk of developing the collapsing variant of focal segmental glomerulosclerosis, and, as such, a much higher likelihood of rapid progression to ESRD (15).

Data on APOL1 haplotypes were not available to us for this study, limiting the inferences we may make. While approximately 13% of African Americans in the general population have the high-risk APOL1 haplotype (34), this prevalence estimate may not be generalizable to a population of kidney donor candidates and, as such, the diagnostic yield from genotyping

HIV-positive potential donors remains unknown. But our findings support the view that risk of ESRD is best understood in terms of a number of risk factors that a given individual harbors, since the risk of ESRD varies by orders of magnitude among black individuals (8 – 100+ events per 10,000 in our study). It is plausible, for instance, that an individual with the high-risk APOL1 haplotype may not develop progressive renal disease in the absence of other “hits” including diabetes, hypertension, cigarette smoking, uncontrolled HIV infection, HCV co-infection, and possibly other genetic risks (35).

A second limitation of our study was that we were not able to adjust for as many baseline risk factors in the HIV-positive cohort as in the HIV-negative cohort, including urinary albumin-to-creatinine ratio and systolic blood pressure. This may have limited our ability to stratify risk in the HIV-positive population and we may have overestimated the risk increase associated with HIV in the low-risk HIV-positive scenarios we describe. That said, in all low-risk HIV-positive scenarios we describe, participants had been using an ART regimen including older formulations of tenofovir (TDF) for 1 year; those using tenofovir are likely to have been clinically screened and closely monitored for renal disease (urinalysis for albuminuria). For these reasons, it is plausible that in the low-risk scenarios we describe the urine albumin-creatinine ratio was similar to that in comparable base-case scenarios in the HIV-negative cohort. In the future, individuals may switch to newer formulations of tenofovir (TAF) that are safer for the kidneys than TDF (36).

Continuous and long-term healthcare may, as such, be a crucial factor in the long-term health of HIV-positive kidney donors. By extension, longitudinal data on use of ART, HIV viral load, and CD4 count may indicate an association between good adherence to ART, adequate viral control, and the very best clinical outcomes. In this analysis we did not adjust for these longitudinal variables since they are drawn from a time after the hypothetical “decision to donate”; however, donors should be informed about the potential benefits of regular postdonation care with the caveat that the association between postdonation healthcare and risk of ESRD remains unknown for both HIV-positive and HIV-negative populations. Granted, our findings suggest that individuals with well-controlled infection at baseline subsequently had, on average, a low risk of ESRD.

While the association between baseline hypertension and risk of ESRD was observed only in the HIV-positive cohort, this is most likely because in the HIV-positive cohort model we did not adjust for both urine albumin-creatinine ratio and systolic blood pressure (markers of glomerular disease and secondary hypertension)(37–39). When both these variables were excluded from the HIV-negative cohort model, an association was observed between hypertension and risk of ESRD in a magnitude comparable to that observed in the HIV-positive cohort. Also, although we were able to adjust for BMI, a known risk factor for ESRD (40, 41), in our exploratory analyses BMI was not significantly associated with ESRD in the HIV-positive cohort and so we did not include it in the final model. However, this might merely reflect the limited follow-up duration of our study.

Since we report 9-year cumulative incidence estimates, a third limitation of our study was the short duration of follow-up. Ideally, the HIV-positive potential donor would wish to know the magnitude of the additional lifetime risk of ESRD associated with donation. To

obtain this estimate, we would need data on the projected lifetime risk of ESRD for HIV-positive potential donors in the absence of donation as well as data on the projected lifetime risk of ESRD for HIV-positive individuals in the event of donation; however, these data do not exist. Data from HIV-negative individuals suggest that donation is associated with a 4- to 11-fold increase in risk of ESRD (depending on race and sex); but the generalizability of these estimates to HIV-positive donors remains unknown (9, 10, 12). That said, in this study we provide the first description, to the best of our knowledge, of the risk of ESRD among highly select HIV-positive individuals who may be considered for live donor nephrectomy. In this selected population, the 9-year adjusted risk was lowest for older HIV-positive individuals and highest for the young. This inverse association, which we have previously reported (19), might reflect selective survival of healthier individuals; older age might represent a better risk profile and slower kidney disease progression in a manner that we were not able to characterize using the data available to us.

Our study also had several strengths worth considering. As a representative study of all HIV-positive individuals in care in North America (23, 24), the inferences we make are generalizable to the US population of HIV-positive potential donors. Since we compared the risk of ESRD in HIV-positive potential donors with the risk in a representative population of HIV-negative potential donors in the US (26), we were able to quantify the risk increase associated with HIV in potential donors. Also, our analytic approach allowed us to explore a wide range of scenarios that may guide decision-making in the unprecedented clinical setting ushered in by the recent passage of the HOPE Act. We have demonstrated biological gradients of risk based on renal function, viral load, CD4+ count, and various other clinical characteristics. Thus, the clinician and HIV-positive potential donor may make decisions based on a combination of health characteristics of the prospective donor. Finally, we used validated and comparable methods to ascertain ESRD in both the HIV-positive and HIV-negative populations; thus, our findings are unlikely to be explained by differential ascertainment of the study outcome between the cohorts.

In conclusion, the carefully selected HIV-positive donor may face a real but acceptable additional risk of ESRD. Whether careful selection of black HIV-positive donors should entail genotyping for the high-risk APOL1 haplotype is an important issue to explore in follow-up studies.

Acknowledgments

This study was supported by Health Resources and Services Administration contract 234-2005-370011C and by grants K24 DA035684 (GM Lucas), R01 DA026770 (GM Lucas), R01DK096008 (Segev) and K24DK101828 (Segev). NA-ACCORD was supported by National Institutes of Health grants U01AI069918, F31DA037788, G12MD007583, K01AI093197, K23EY013707, K24DA000432, K24AI065298, KL2TR000421, M01RR000052, N02CP055504, P30AI027757, P30AI027763, P30AI027767, P30AI036219, P30AI050410, P30AI054999, P30AI094189, P30MH62246, R01AA016893, R01CA165937, R01DA004334, R01DA011602, R01DA012568, R24AI067039, U01AA013566, U01AA020790, U01AI031834, U01AI034989, U01AI034993, U01AI034994, U01AI035004, U01AI035039, U01AI035040, U01AI035041, U01AI035042, U01AI037613, U01AI037984, U01AI038855, U01AI038858, U01AI042590, U01AI068634, U01AI068636, U01AI069432, U01AI069434, U01AI103390, U01AI103397, U01AI103401, U01AI103408, U01DA036935, U01HD032632, U10EY008057, U10EY008052, U10EY008067, U24AA020794,U54MD007587, UL1RR024131, UL1TR000004, UL1TR000083, UL1TR000454, UM1AI035043, Z01CP010214 and Z01CP010176; contracts CDC-200-2006-18797 and CDC-200-2015-63931 from the Centers for Disease Control and Prevention, USA; contract 90047713 from the Agency for Healthcare Research and Quality, USA; contract 90051652 from the Health Resources and Services Administration, USA; grants CBR-86906, CBR-94036, HCP-97105 and TGF-96118 from the Canadian Institutes

of Health Research, Canada; Ontario Ministry of Health and Long Term Care; and the Government of Alberta, Canada. Additional NA-ACCORD support was provided by the Intramural Research Program of the National Cancer Institute.

Research Data Center staff at the National Center for Health Statistics performed all NHANES social security number linkages to Centers for Medicare and Medicaid Services data.

Abbreviations

HIV-positive	human immunodeficiency virus seropositive
HIV-negative	human immunodeficiency virus seronegative
CKD	chronic kidney disease
ESRD	end stage renal disease
NA-ACCORD	North America AIDS Cohort Collaboration on Research and Design
NHANES	National Health and Nutrition Examination Survey
ART	antiretroviral therapy

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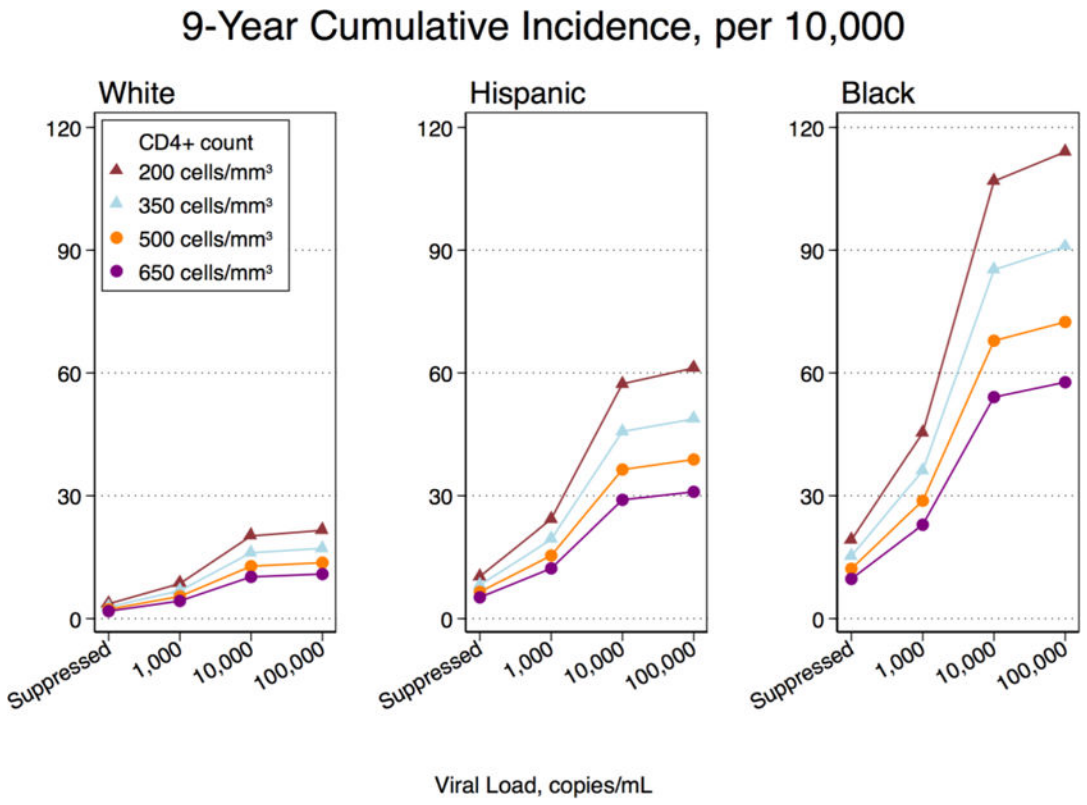

Figure 1.

Estimated 9-year cumulative incidence of ESRD among HIV-positive participants of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) according to HIV viral load and CD4+ cell count for the hypothetical profile of a 40-year-old male with no diabetes, no hypertension, no HCV co-infection, and expected eGFR by age and race/ethnicity (95, 95, and 105 ml/min/1.73m^2 for white, Hispanic, and black individuals).

Scenarios including suppressed viral load and CD4+ count >500 cells/μL meet the Department of Human and Health Services criteria for well-controlled HIV infection in a HIV-positive potential live kidney donor (5)

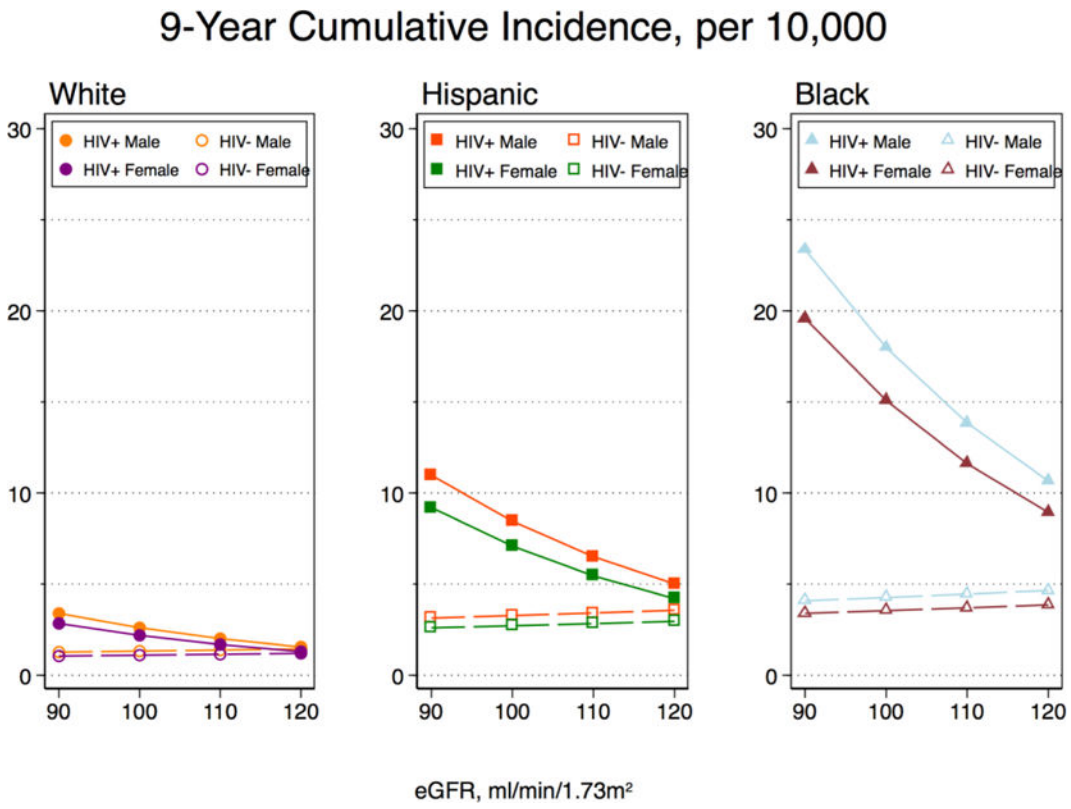

Figure 2.

Estimated 9-year cumulative incidence of ESRD in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) and the Third National Health and Nutrition Examination Survey (NHANES-III) for the hypothetical profile of a 40-year-old with no diabetes, no hypertension, and HCV seronegative*

*Characteristics specific to HIV-positive scenarios from NA-ACCORD: using ART for 1 year (including the TDF formulation of tenofovir), suppressed viral load (<400 copies/mL), CD4+ count 500 cells/μL, and no AIDS. Characteristics specific to HIV-negative scenarios from NHANES-III: urinary albumin-to-creatinine ratio 4 mg/g, systolic blood pressure 120

Table 1

Baseline characteristics of participants of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) and the Third National Health and Nutrition Examination Survey (NHANES-III)[a]

	NA-ACCORD	NHANES-III
	HIV-positive (n=41,968)	**HIV-negative (n=16,025)**
Age, median years (IQR)	41 (35–47)	42 (29–63)
Race/Ethnicity (%):		
White/Other	45	45
Black	40	27
Hispanic	15	28
Male (%):	78	47
Diabetes (%):	2	12
Hypertension (%):	15	26
Albumin/Creatinine ratio, mg/g (IQR)	NA	6 (3–12)
eGFR, median ml/min/1.73m^2 (IQR)	104 (92–116)	103 (86–120)
Systolic Blood Pressure, median mmHg (IQR)	125 (120–132)	122 (112–138)
Body-mass Index, median kg/m^2 (IQR)	25 (22–28)	26 (23–30)
Ever Smoked (%):[b]	74	49
HCV Seropositive (%):	19	2
HIV transmission risk group (%):		
Men who have sex with men	45	NA
Heterosexual	33	NA
Injection Drug Use	11	NA
Other	12	NA
Using Antiretroviral therapy (%):	47	NA
Viral load, median counts/mL (IQR)	926 (<400–20,000)	NA
Viral load, (%):		
<400 counts/mL	43	NA
400–9,999 counts/mL	25	NA
10,000–99,999 counts/mL	23	NA
100,000+ counts/mL	9	NA
CD4+ count, median cells/μL (IQR)	380 (226–554)	NA
CD4+ count (%):		
<200 cells/μL	21	NA
200–349 cells/μL	23	NA
350–499 cells/μL	24	NA
500+ cells/μL	32	NA
History of AIDS (%):	20	NA

[a]The HIV-negative cohort has no meaningful values for HIV transmission risk group, use of ART, HIV viral load, CD4+ count, and history of AIDS; the entire HIV-positive cohort has no data on urinary albumin-creatinine ratio; >50% of the cohort has missing values for systolic blood pressure (NA, not available for the HIV-positive cohort; not applicable to the HIV-negative cohort)

[b]Records on smoking were available for only 43% of the HIV-positive cohort, were imputed for an additional 16% of the cohort, and were left missing for 41% of the cohort

Table 2

Multivariable-adjusted hazard ratios that estimate the association of baseline characteristics with ESRD seperately for each cohort[a]

	NA-ACCORD (HIV-positive)		NHANES-III (HIV-negative)	
Subgroup	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, per increase of 10 years[b]				
<50 years	**0.5 (0.4–0.8)**	**<0.001**	**1.3 (0.9–1.9)**	**0.2**
50+ years	0.8 (0.4–1.6)	0.6	0.5 (0.4–0.7)	<0.001
Race/Ethnicity[c]				
White/Other	Reference		Reference	
Hispanic	3.2 (1.3–8.2)	0.01	2.5 (1.4–4.3)	0.002
Black	**6.9 (3.6–13.3)**	**<0.001**	**3.2 (1.9–5.5)**	**<0.001**
Male	1.2 (0.8–1.9)	0.5	1.2 (0.8–1.8)	0.4
Diabetes	3.0 (1.7–5.4)	<0.001	5.2 (3.4–8.1)	<0.001
Hypertension[d]	**2.7 (1.7–4.2)**	**<0.001**	**1.0 (0.6–1.6)**	**0.9**
Urinary albumin-to-creatinine ratio, per increase of 10 mg/g	NA		4.0 (3.2–5.1)	<0.001
eGFR, per decrease of 15 ml/min/1.73m^2 [e]				
<90 ml/min/1.73m2	3.0 (2.3–3.9)	<0.001	2.7 (2.0–3.5)	<0.001
90+ ml/min/1.73m2	**1.5 (1.1–1.9)**	**0.004**	**0.9 (0.7–1.3)**	**0.7**
Systolic Blood Pressure, per increase of 20 mmHg				
<120 mmHg	NA		2.3 (0.6–9.0)	0.2
120–139 mmHg	NA		3.4 (1.6–7.4)	0.002
>140 mmHg	NA		0.9 (0.7–1.1)	0.3
History of Smoking				
Never smoked	NA		Reference	
Ever smoked	1.7 (0.8–3.4)	0.2	1.8 (1.2–2.8)	0.006
HCV seropositive	2.0 (1.3–3.1)	0.003	3.0 (1.4–6.4)	0.003
Years of ART use, per increase of 1 year				
<9 years	1.1 (1.0–1.2)	0.07	NA	
>9 years	0.6 (0.4–0.8)	0.007	NA	
Years of tenofovir (TDF) use, per increase of 1 year	0.5 (0.4–0.7)	<0.001	NA	
Viral load, per increase of 1000 copies/mL				
<10,000 copies/mL	13.1 (3.7–47.0)	<0.001	NA	
>10,000 copies/mL	1.2 (0.2–6.1)	0.8	NA	
CD4+ count, per decrease of 50 cells/μL	1.1 (1.0–1.1)	0.01	NA	
History of AIDS	1.9 (1.2–2.9)	0.004	NA	

[a] We estimated the association of demographic and clinical characteristics with risk of ESRD seperately for each cohort partly because the effects of age, black race, hypertension, and eGFR varied significantly by cohort ($p<0.05$ for interaction terms with HIV status in a joint model in which viral load was coded as suppressed [i.e., 400 counts/mL], CD4+ count as 1000 cells/μL, and history of AIDS as “no” in the HIV-negative cohort). Also,

since the entire HIV-positive cohort has no data on urinary albumin-creatinine ratio and >50% of the cohort has missing values for systolic blood pressure, we excluded these variables from the joint model (NA, not available in the HIV-positive cohort; not applicable to the HIV-negative cohort).

[b] An inverse association was observed between age and risk of ESRD in both the HIV-positive and HIV-negative cohorts; however, this effect was not observed among those <50 years in the HIV-negative cohort ($p<0.001$ for interaction between HIV status and age <50 years; however, $p=0.4$ for interaction HIV status and age >50 years)

[c] Black individuals had an increased risk of ESRD compared with white individuals; however, this increase in risk was significantly higher (>2-fold higher) in the HIV-positive cohort compared with the HIV-negative cohort ($p=0.03$ for interaction)

[d] Hypertension was associated with the risk of ESRD only in the HIV-positive cohort; however, the HIV-positive cohort model did not account for urinary albumin-to-creatinine ratio and systolic blood pressure. When albumin-to-creatinine ratio and systolic blood pressure were excluded from the HIV-negative cohort model, hypertension was associated with the risk of ESRD (HR 2.0; 95% CI: 1.2–2.8; $p=0.004$)

[e] An inverse association was observed between eGFR and risk of ESRD in both the HIV-positive and HIV-negative cohorts; however, this effect was not observed among those with eGFR>90 years in the HIV-negative cohort ($p=0.004$ for interaction between those with eGFR>90 ml/min/1.73m^2 in the HIV-positive vs. the HIV-negative cohort; however, $p=0.4$ for interaction between those with eGFR<90 years in the HIV-positive vs. the HIV-negative cohort)

Table 3

Estimated 9-year cumulative incidence of ESRD among other hypothetical HIV-positive and HIV-negative populations[a]

					9-year risk[b]		
#	Age	Race	eGFR[c]	Hypertension	HIV-positive	HIV-negative	Risk Increase[d]
1	40	White	95	No	3.0	1.3	1.7
2	40	Black	105	No	15.8	4.4	11.4
3	**40**	**White**	**90**	**No**	**3.4**	**1.3**	**2.1**
4	**40**	**Black**	**90**	**No**	**23.4**	**4.1**	**19.3**
5	50	White	90	No	1.8	1.6	0.1
6	50	Black	100	No	9.5	5.5	4.0
7	50	White	90	Yes	4.8	1.7	3.1
8	50	Black	100	Yes	25.5	5.6	19.9
9	30	White	105	No	4.3	1.0	3.3
10	30	Black	115	No	23.0	3.5	19.5

[a] All HIV-positive scenarios specify the following characteristics: male sex, 1 year of ART use (including tenofovir), suppressed virus (<400 copies/mL), CD4+ count >500 cells/μL no diabetes, and no HCV co-infection; all HIV-negative scenarios specify the following characteristics: male sex, albumin-to-creatinine ratio 4 mg/g, SBP 120, no diabetes, and no HCV co-infection. Since these are hypothetical scenarios of potential HIV-postive donors, they do not include absolute contraindications to live kidney donation (presence of diabetes mellitus and HCV co-infection); however, two scenarios include a relative contraindication to live kidney donation (hypertension).

[b] Per 10,000 at risk

[c] Expected eGFR by age and race for all scenarios **except the values in bold (these are lower than expected for age/sex; but meet eligibility criteria for kidney donation)**. The expected eGFR for each age varied significantly by race after accounting for sex, diabetes, hypertension, urinary albumin-to-creatinine ratio, systolic blood pressure, BMI, and history of smoking. The the magnitude of the difference between white and black individuals (approximately 10 ml/min/1.73m^2) was observed consistenly across three populations: live kidney donors (SRTR), potential HIV-negative live kidney donors (NHANES-III) (42, 43), and HIV-positive potential live kidney donors (NA-ACCORD)(data not shown)

[d] Risk increase (Difference between HIV-positive and HIV-negative risk). We did not formally test the hypothesis Risk increase≠0. This was a limitation of our analytic approach.