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HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy

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Abstract

Objective—To identify risk factors associated with kidney function decline in a contemporary cohort of treated and untreated HIV-infected patients.

Methods—We followed individuals enrolled in the Study of the Consequences Of the Protease inhibitor Era cohort for longitudinal changes in kidney function, defined as glomerular filtration rate estimated from serum creatinine (eGFR). eGFR slope was calculated using linear mixed effects models adjusted for age, sex, race, and time-updated CD4 cell count, viral load, antiretroviral therapy (ART), and comorbid conditions.

Results—We followed 615 patients for a mean of 3.4 (± 2.5) years. In multivariable adjusted analyses, predictors of eGFR decline included female sex, diabetes, and hyperlipidemia; CD4 cell count and viral load were not associated with eGFR loss. Among patients who initiated treatment, antiretroviral exposure was associated with a +2.8 (95% confidence interval 0.8–4.7) ml/min per 1.73 m^2 per year effect on eGFR slope. Although these patients appeared to benefit from ART based on the slowing of their eGFR decline, they continued to lose kidney function at a rate of −1.9 (95% confidence interval −3.7 to −0.1) ml/min per 1.73 m^2 per year. In the subgroup of individuals receiving suppressive ART with viral loads maintained below 500 copies/ml, intermittent viremic episodes (blips) were strongly associated with more rapid rates of eGFR loss [−6.7 (95% confidence interval −11.1 to −2.4) ml/min per 1.73 m^2 per - year].

Conclusion—Although ART appears to help curb kidney function decline, patients who achieved durable viral suppression continue to manifest substantial loss of eGFR. Loss of kidney function may be attributable to treatment-related factors, intermittent viremia, and traditional risk factors for kidney disease.

Keywords

antiretroviral therapy; glomerular filtration rate; HIV; kidney diseases; viral load

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Background

In the era of antiretroviral therapy (ART), non-AIDS-related complications of HIV such as chronic kidney disease (CKD) have become increasingly important. Kidney disease, defined by proteinuria, can be found in up to 30% of HIV-infected individuals, and the prevalence of CKD is expected to increase as the HIV-infected population ages [1-3]. HIV-infected persons with CKD have an increased risk of hospitalization, are less likely to receive ART, and have higher mortality [4-6]. Recognizing that, CKD is a common and clinically important complication of HIV infection, current guidelines recommend that kidney function should be assessed in all patients at the time of HIV diagnosis and annually in high-risk populations [2].

Despite the impact of CKD on the health of HIV-infected persons, little is known about its underlying pathogenic mechanisms. In particular, the respective roles of ART, immune function, and viremia in the development of HIV-related kidney disease have not been clearly characterized. In the Strategies for Management of Antiretroviral Therapy (SMART) Study, patients randomized to intermittent ART experienced higher rates of end-stage renal disease (ESRD) than those on continuous therapy, suggesting that ART helps to preserve kidney function among HIV-infected individuals. However, it remains unknown whether the benefit of ART is related to improved immune function, a reduction of viremia, or both. The interpretation of these data are further complicated by reports of nephrotoxicity due to ART, and the development of risk factors for CKD, such as diabetes, among those on chronic therapy [2,7,8].

We conducted this study to identify risk factors associated with loss of kidney function in a contemporary cohort of HIV-infected persons, and to assess whether effective ART reduces the risk of kidney dysfunction over time. Because of the complex interaction that occurs between ART, CD4 cell count, and viral load, we included in our analysis a unique group of HIV-seropositive individuals who had undetectable or low-level viremia in the absence of treatment (‘untreated controllers’) [9]. In contrast to other groups, untreated controllers lack many of the possible HIV disease factors associated with renal dysfunction, including high levels of viral replication, advanced immunodeficiency, and exposure to antiretroviral drugs.

Methods

Patients

Patient data were obtained from the ongoing University of California, San Francisco-based Study of the Consequences Of the Protease inhibitor Era (SCOPE) cohort. We studied all SCOPE participants, at least 18 years old, with known HIV infection for more than 6 months, receiving care in the Community Health Network of the City and County of San Francisco. Among this group of patients, we identified two subgroups of patients for further study: ‘untreated controllers’ who were defined as those with all HIV viral load levels of 500 RNA copies/ml or less in the absence of therapy and ‘treated controllers’ who were defined as individuals successfully treated with ART with all HIV viral load measurements of 500 RNA copies/ml or less. We also required that these patients had HIV RNA levels consistently below 75 RNA copies/ml with only occasional transient, detectable viremia of 500 RNA copies/ml or less. The conduct of the study using the SCOPE cohort was approved by the Committee on Human Research at the University of California, San Francisco.

Variables

Kidney function, or estimated glomerular filtration rate (eGFR), was calculated using the Modification of Diet in Renal Disease formula based on age, sex, race, and standardized serum

creatinine [10]. We utilized serial outpatient serum creatinine measurements recorded since the time of entry into SCOPE for our estimates of kidney function. Demographic data (age, sex, and self-reported race), CD4 cell counts, and viral load were collected as part of the SCOPE protocol. Diagnoses of comorbid conditions [diabetes, hypertension, heart failure, atherosclerotic vascular disease (defined as coronary artery disease, peripheral arterial disease, stroke, or transient ischemic attack), hyperlipidemia, hepatitis C virus coinfection, smoking, and opportunistic infections] were collected from the electronic medical record and defined using validated algorithms [4,11].

Statistical analysis

We estimated rates of kidney function decline (eGFR slope) using linear mixed effects models with repeated measures of kidney function. This model included random intercepts and slopes to compare linear trends in the mean eGFR and accounted for variations in the number and spacing of creatinine measurements, length of follow-up for each patient, and the within-person correlation of observations by participant. In multivariate models, we included baseline age, sex, and race as fixed effects, and adjusted for current CD4 cell count and viral load, ART exposure, and comorbid conditions as time-updated covariates. We identified risk factors for eGFR decline in the total cohort using this multivariate model. The effects of specific drugs and drug classes were not considered in these analyses because of the lack of statistical power to assess drug exposures. In addition, we also checked for effect modification by race or baseline CKD (defined as an eGFR <60 ml/min per 1.73 m^2).

To determine the effect of ARTon rates of eGFR decline, we performed a subgroup analysis limited to those who began treatment during the study period (‘new users’ of ART) [12]. We further adjusted our estimates using time-dependent propensity scores to address confounding by indication, which could bias results [13,14]. Propensity scores were calculated using a logistic regression model including the receipt of ARTas the outcome and adjusted for sex, race, age, CD4 cell count, viral load, and comorbid conditions at baseline, 1 year prior, and at the most recent visit.

Finally, we also prespecified subgroup analyses among untreated and treated controllers. Risk factors for kidney function loss were also identified in the treated controller group using mixed effects linear regression models including covariates listed above. The analysis was performed using Stata 10.1 (College Station, Texas, USA).

Results

Baseline characteristics

There were 615 SCOPE participants receiving care in the San Francisco Community Health Network included in our analysis. The mean age was 45.3 [standard deviation (SD) 8.4] years and 13% were women (Table 1). Half of the participants self-identified as white (51%), 29% were black, and 10% were Hispanic. Risk factors for kidney disease such as hepatitis C virus coinfection and hypertension were present in approximately 15% of the study population at the time of study entry. There were 45 (7%) untreated and 173 (20%) treated controllers. Compared with treated controllers, a larger proportion of untreated controllers were black and hepatitis C coinfected, whereas atherosclerotic vascular disease, hyperlipidemia, and smoking were more common in treated controllers. The mean CD4 cell count was higher among untreated controllers (749, SD 316 cells/μl versus 486, SD 331 cells/μl).

Rates of kidney function decline in 615 SCOPE participants

We analyzed a total of 9145 serum creatinine measurements over a mean period of 3.4 (SD 2.5) years. The overall unadjusted rate of eGFR decline in the cohort was −2.6 [95% confidence

interval (CI) −3.0 to −2.1] ml/min per 1.73 m^2 per year. In multivariate models, female sex, diabetes, and hyperlipidemia were associated with kidney function decline (Table 2). In contrast, CD4 cell count and HIV viral load were not associated with eGFR decline. There was no evidence of effect modification by race or baseline CKD status.

Impact of antiretroviral therapy on kidney function over time

To evaluate the effect of ART, we calculated eGFR decline in the subgroup of 82 new users of ART. The median pretreatment CD4 cell count and viral load were 205 [interquartile range (IQR) 131–293) cells/μl and 4.7 (IQR 4.1–5.3) RNA log copies/ml, respectively. These patients were followed for a mean of 4.5 (SD 2.1) years, the mean observation time prior to receiving ART was 1.2 (SD 1.3) years, and the mean duration of time on therapy was 2.9 (SD 2.1) years. The average rate of GFR decline before receiving ART was −4.7 (95% CI −6.7 to −2.6) ml/min per 1.73 m^2 per year and improved to −1.9 (95% CI −3.7 to −0.1) ml/min per 1.73 m^2 per year after starting treatment. In fully adjusted models, ART was associated with a +2.8 (95% CI 0.8–4.7) ml/min per 1.73 m^2 per year improvement in eGFR slope.

Comparisons between untreated versus treated controllers

We next compared eGFR slopes in the two groups of patients with undetectable or low viral loads (<500 copies/ml): those who were on an effective ARTregimen ($n = 173$) and those who were untreated controllers ($n = 45$). Patients successfully treated with ART experienced eGFR loss, at levels much higher than controllers, despite similar levels of viremia (Table 3). In fully adjusted models, the average difference in the rate of kidney function loss was −4.4 (−6.7 to −2.1) ml/min per 1.73 m^2 per year in treated versus untreated controllers. Among ART controllers with undetectable viral load, intermittent episodes of detectable viremia (or 'blips' defined as isolated episodes of detectable virus ≤500 copies/ml) were strongly associated with eGFR loss [−6.9 (95% CI −10.9 to −2.9) ml/min per 1.73 m^2 per year]. Although traditional risk factors such as hypertension [−4.0 (95% CI −7.6 to −0.5) ml/min per 1.73 m^2 per year] and diabetes [−5.6 (95% CI −10.3 to −0.8) ml/min per 1.73 m^2 per year] were also strongly associated with kidney function decline in treated controllers, CD4 cell count was not predictive of eGFR decline (Table 4).

Discussion

In this diverse, contemporary cohort of HIV-infected patients, we found that patients receiving ART continued to lose kidney function despite achieving durable viral suppression. Consistent with prior studies, we found that untreated poorly controlled HIV infection was associated with ongoing loss of kidney function and provision of ART had a beneficial effect on kidney function over time [15-17]. However, effective ART did not fully reverse the risk of eGFR loss. Although traditional risk factors for kidney disease such as diabetes and hypertension were found to be important risk factors for continued kidney function decline in this group, episodes of low-level viremia of below 500 copies/ml ('blips') were stronger predictors of eGFR loss. Overall, these findings suggest that ART is beneficial to kidney function, but fully suppressive treatment may be needed to curb eGFR decline.

Our results build on the observations of previous studies [15-17] by demonstrating the benefit of ART in a relatively unselected population of patients (i.e., heterogeneous in terms of race and underlying kidney disease). However, it is important to note that patients receiving ART continued to lose kidney function and even small increases in the viral load were strongly associated with eGFR loss. The observed effect of active viral replication on kidney function is consistent with laboratory studies [18-21] that have demonstrated that HIV directly infects all cell types in the kidney and actively replicates there in a wide variety of patients, including those with and without HIV-associated nephropathy (HIVAN) or clinically overt kidney

disease, and in patients of nonblack race. It is possible that breakthrough viremia (or 'blips') provide reasons for the continued decline in kidney function among HIV patients receiving ART, and suggest that complete and durable viral suppression may be needed to minimize risk.

The impact of HIV disease, its treatment, and immune function on kidney function is complex. Although most prior studies have indicated that ART is beneficial for the treatment of HIV-related kidney diseases, more recent long-term data from the SMART continuation study demonstrate that the relationship between ART and kidney function may be more complicated than originally thought [2,22,23]. In the SMART trial, ART-associated renal benefit was suggested by the observation that participants who interrupted therapy had higher rates of ESRD than those receiving continuous therapy. However in contrast, a more recent analysis [23] from this study reported that after re-initiation of ART, more ESRD events were observed in the group that received continuous versus interrupted therapy. Similarly, a study [24] of patients with biopsy-proven kidney disease found that only individuals with HIVAN benefited from ART, whereas the ART effect in those without HIVAN suggested possibility of harm. In our study, among patients effectively controlling viral replication with ART compared with those who maintained low levels of viremia via host mechanisms (treated versus untreated controllers), we found that those exposed to ART manifested higher rates of kidney function decline.

Taken together, these findings suggest that factors related to race, underlying kidney disease, immune status, or viral replication may interact with ART to produce contrasting effects. Additional studies are needed to identify HIV-infected persons who may be susceptible to declines in kidney function as a result of ART and to determine whether declines in kidney function are related to complications of treatment, such as diabetes or hypertension, or nephrotoxicity associated with the drugs themselves. This information will be relevant to clinical practice, as today most HIV-infected patients receive or will receive ART and lifetime exposure to ART may increase with earlier initiation of therapy [25,26]. Clinicians will need to counsel patients on the risk of kidney disease with long-term therapy.

Prior studies [3,17,24,27-33] of HIV-related kidney disease have conflicted in their assessment of risk factors such as CD4 cell count. These discrepancies may be in part due to study design, as most have analyzed CD4 cell count and viral load measured at a single time point as fixed baseline covariates [27,28], use dichotomous versions of these variables (e.g. CD4 cell count <200 cells/μl) [3,24,29,30], or analyze CD4 cell count or viral load in isolation [17,31-33]. We found that CD4 cell count was not prognostic of kidney function decline in any of the groups studied. Our results are consistent with Post *et al.* [30] who reported no difference in CD4 cell counts above 200 cells/μl between those who developed ESRD and those who maintained stable renal function in a cohort of HIVAN patients. Similarly, Gardner *et al.* [31] found that viral load, but not CD4 cell count, was associated with changes in creatinine clearance in a cohort of women. On the basis of these studies and the results reported here in treated controllers, it appears that virus-specific mechanisms may be more important than host immunity in the development of HIV-related kidney disease, and the benefit of ART is more closely tied to a reduction in viremia versus improvements in immune status. Alternatively, mechanisms of the host response (such as inflammation), not captured by the CD4 cell count, may influence the development of kidney disease [34,35]. Novel measures, such as T-cell activation, may be needed to further investigate the role of host immunity in HIV-related kidney diseases [36].

Limitations

Our study has several limitations that deserve comment. First, the determination of treatment effects from observational data is difficult because hidden confounding may bias results. Similarly, our comparison of treated and untreated controllers may be affected by factors not

available in the SCOPE data set. However, it is reassuring that these analyses were consistent in their conclusions and with previous studies [2,22-24] of ART and kidney function. Second, although eGFR has not been validated against the gold standard of measured GFR in HIV-infected persons or in the upper range of kidney function in the general population, change in eGFR over time is a valid and clinically relevant outcome measure [37]. In addition, although the magnitude of eGFR loss in this study was substantial, it was consistent with prior studies in HIV-infected persons [16,38]. Third, we did not have histopathologic data or specific kidney disease diagnoses available for this analysis. Therefore, it is possible that certain disease entities found among HIV-infected persons may behave differently than what we found in our study. Fourth, we were unable to analyze the contribution of several important factors including signs of kidney damage (e.g. proteinuria or hematuria), vital signs (e.g. blood pressure measurements), or antihypertensive medication exposure (e.g. angiotensin-converting enzyme inhibitors) because these data were not systematically collected in SCOPE. Finally, we were under-powered to analyze the impact of individual antiretroviral drugs, which may have been responsible for eGFR loss in treated patients. Specifically, tenofovir and indinavir have been identified as predictors of kidney disease in other studies, but could not be reliably analyzed in this study because these drugs were poorly represented in our cohort. Further study is needed to replicate our results and prospectively examine the effects of these key predictors in a larger cohort of treated persons with HIV.

Conclusion

We found that ART is associated with improvements in kidney function over time; however, overall rates of eGFR decline were still significant among those successfully treated with ART. Among the risk factors studied, viremia appears to be most strongly associated with loss of kidney function and may contribute to continued rates of kidney function decline among those who are successfully treated with ART.

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Table 1

Characteristics of the Study of the Consequences Of the Protease inhibitor Era cohort

	Total cohort, *n* = 615	Untreated controllers, *n* = 45 (7%)	Treated controllers, *n* = 173 (28%)
Number of eGFR measurements per individual (median, 25–75%)	11 (4–23)	7 (2–13)	9 (3–20)
Observation time [years (mean, SD)]	3.4 (2.5)	3.1 (1.7)	3.7 (2.6)
Age [years (mean, SD)]	45.2 (8.0)	45.6 (7.3)	46.3 (8.0)
Women (%)	81 (13.2)	10 (22.2)	21 (12.1)
Race (%)			
White	312 (50.7)	15 (33.3)	107 (61.9)
Black	175 (28.5)	18 (40.0)	37 (21.4)
Hispanic	59 (9.6)	7 (15.6)	13 (7.5)
Other	69 (11.2)	5 (11.1)	16 (9.3)
$CD4^+$ cell count [cells/μl (mean, SD)]	434 (307)	749 (316)	486 (331)
HIV viral load [RNA log copies/ml (mean, SD)]	3.1 (1.3)	1.9 (0.4)	1.9 (0.2)
Comorbid conditions (%)			
Opportunistic infection	200 (32.5)	10 (22.2)	55 (31.8)
Diabetes	29 (4.7)	3 (6.7)	7 (4.1)
Hypertension	87 (14.2)	8 (17.8)	34 (19.7)
Hepatitis C	89 (14.5)	15 (33.3)	28 (16.2)
Atherosclerotic vascular disease	35 (6.1)	1 (2.2)	14 (8.1)
Hyperlipidemia	66 (10.7)	1 (2.2)	33 (19.1)
Heart failure	11 (1.8)	1 (2.2)	5 (2.9)
Smoking	18 (2.9)	1 (2.2)	7 (4.1)
CKD (% with eGFR <60 ml/min per 1.73 m^2)	45 (7.8)	2 (4.4)	13 (7.5)
eGFR [ml/min per 1.73 m^2 (mean, SD)]	93.9 (27.7)	95.3 (28.9)	89.5 (26.7)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2

Risk factors for kidney function decline in 615 Study of the Consequences Of the Protease inhibitor Era cohort participants

	Effect on eGFR slope (ml/min per 1.73 m^2 per year)	95% CI	*P*
Women	−1.8	−3.1 to −0.6	0.004
Diabetes	−4.7	−8.7 to −0.7	0.020
Hyperlipidemia	−2.7	−4.7 to −0.7	0.008
CD4 cell count (per 100 cells/μl)	0.2	−0.1 to 0.5	0.183
HIV viral load (per log copy)	0.1	−0.4 to 0.6	0.776

Only CD4 cell count, HIV viral load, and risk factors reaching statistical significance are shown. Variables tested in the mixed effects linear regression model, but not found to be statistically significant include: age, race, hypertension, atherosclerotic vascular disease, heart failure, smoking, opportunistic infection, and antiretroviral therapy. CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table 3

Rates of kidney function change in subgroups

	Rate[a]	Adjusted difference[a,b]
New users of ART[c]		
Before treatment	−4.7 (95% CI −6.7 to −2.6)	Referent
After treatment	−1.9 (95% CI −3.7 to −0.1)	+2.8 (95% CI 0.8–4.7)
Patients with suppressed viremia[d]		
Untreated controllers	−0.4 (95% CI −2.0 to 1.2)	Referent
Treated controllers	−2.6 (95% CI −3.3 to −1.9)	−4.4 (95% CI −6.7 to −2.1)

ART, antiretroviral therapy; CI, confidence interval; GFR, glomerular filtration rate; SCOPE, Study of the Consequences Of the Protease inhibitor Era.

[a] Results reported as change in GFR (ml/min per 1.73 m^2 per year).

[b] Adjusted for age, sex, race, diabetes, hypertension, vascular disease, heart failure, smoking, hyperlipidemia, opportunistic infection, CD4 cell count, and HIV RNA level.

[c] Subgroup analysis performed in 82 patients who initiated ART during observation in the SCOPE cohort.

[d] Suppressed viremia defined as having all viral load measurements below 500 copies/ml.

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Table 4
Risk factors for kidney function decline in treated controllers

	Effect on eGFR slope (ml/min per 1.73 m^2 per year)	95% CI	*P*
Hypertension	−4.0	−7.6 to −0.5	0.031
Diabetes	−5.6	−10.3 to −0.8	0.016
CD4 cell count (per 100 cells/μl)	0.0	−0.4 to 0.4	0.904
HIV viral load (per log copy)	−6.7	−11.1 to −2.4	0.003

Results are expressed as the change in eGFR slope (ml/min per 1.73 m^2 per year) associated with the indicated change in CD4 or viral load variable. 95% CIs included in parentheses. CI, confidence interval; eGFR, estimated glomerular filtration rate.