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Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 79(5)

ISSN

1525-4135

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Publication Date

2018-12-15

DOI

10.1097/qai.0000000000001860

Peer reviewed

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J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2019 December 15.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2018 December 15; 79(5): 639–643. doi:10.1097/QAI.0000000000001860.

Association of HIV Suppression with Kidney Disease Progression among HIV-Positive African Americans with Biopsy-Proven Classic FSGS

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Abstract

Background: In the era of combined antiretroviral therapy (cART), classic focal segmental glomerulosclerosis (FSGS) is the most common histopathological finding in African American HIV-positive patients with kidney disease. We sought to determine whether HIV suppression is associated with lower risk of progression to end-stage-renal disease (ESRD) among HIV-positive African Americans with biopsy-confirmed classic FSGS.

Methods: HIV-positive African Americans who underwent kidney biopsies at a single tertiary hospital between January 1996 to June 2011 were confirmed as having classic FSGS by the presence of segmental glomerulosclerosis without features of HIV-associated nephropathy (HIVAN). Multivariable Cox proportional hazards models were used to examine the independent association of viral suppression (HIV RNA<400 copies/ml at biopsy) with time to progression to ESRD.

Results: Of the 55 HIV-positive African Americans with classic FSGS, 26 had suppressed viral loads at the time of biopsy. Compared to viremic patients, those who were virally suppressed had a significantly higher mean CD4+ cell count (452 vs 260 cell/mm^3, respectively; P=0.02) and median eGFR, (53.5 vs 35.5 mL/min/1.73 m^2, respectively; p=0.002). Adjusting for gender and baseline CD4+ cell count, eGFR and proteinuria, those with HIV RNA levels <400 copis/ml at baseline had a 75% lower risk of progressing to ESRD (HR=0.25; 95% CI: 0.07, 0.88) during a median follow-up time of 2.70 years (IQR: 0.80 – 5.15 years).

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Declaration of interest statement

The authors of this manuscript have no conflicts of interest to disclose

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Conclusions: HIV suppression is associated with significantly lower risk of progression to ESRD among HIV-infected African Americans with classic FSGS, supporting the potential role of cART for this histopathology in addition to HIVAN among HIV-positive individuals.

Keywords

Classic focal segmental glomerulosclerosis; HIV-infected patients; chronic kidney disease; viral suppression; renal biopsy

INTRODUCTION

Kidney dysfunction progressing to end-stage renal disease (ESRD) is a well-known complication of advanced human immunodeficiency virus (HIV) infection, particularly among African Americans[1–5] [6, 7]. In the era of combined antiretroviral therapy (cART), the distribution of glomerular diseases in HIV-positive patients has drastically changed, with a decreased proportion of HIV-associated nephropathy (HIVAN) characterized by collapsed glomeruli, tubular cystic dilatation and interstitial inflammation. In tandem with this decline in HIVAN is the emergence of classic focal segmental glomerulosclerosis (FSGS) [2, 4, 7–9] which may or may not be mediated by HIV. Despite declining rates of HIVAN due to cART [4, 9, 10], HIV-positive African Americans still remain at 6-fold higher risk for ESRD compared to their Caucasian counterparts [10]. Prior studies have shown that role of cART is unclear for some other forms of kidney disease among HIV-positive persons as it does for HIVAN [1–7, 10–12]. In a study of HIV-positive adults, cART initiation improved kidney function over a median follow-up time of 2.7 years [12]. Similarly, cART improved kidney function by 53% during 2 years of treatment among HIV-positive Ugandans[13]. In The Development of Antiretroviral Trial (DART) study[5], estimated glomerular filtration rate (eGFR) improved by 1.9 to 6 mL/min/ 1.73 m^2 after 4 to 5 years of cART; this improvement was also witnessed in the 2.8% of participants with baseline eGFRs below 30 mL/min/ 1.73 m^2 [5]. A positive impact of ART initiation on eGFR was also observed among ART-naive HIV+ patients with high CD4 in the START trial, and that benefit was only seen among those who reported African American race [21]. On the other hand, several antiretroviral drugs have potential nephrotoxicity including acute tubular toxicity, crystal nephropathy, or acute interstitial nephritis.

In the present study, we sought to determine whether HIV suppression with antiretroviral therapy is associated with lower risk of ESRD among HIV-positive African Americans with biopsy-confirmed classic FSGS.

Materials and Methods

Study design and population

We conducted a retrospective cohort study of HIV-positive African Americans (African or Caribbean immigrants are not included) who had biopsy-proven classic FSGS at a single tertiary hospital. Patients were followed from the time of kidney biopsy, which was considered the baseline, through January 1, 2013. Socio-demographic, clinical and laboratory data were abstracted from medical records on all HIV-positive patients aged 18 or

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older who underwent native kidney biopsy between January 1, 1996 and June 30, 2011 at The Johns Hopkins Hospital in Baltimore, Maryland. All cases were identified and traced. Patients who had eGFRs <15 ml/min/1.73 m^2 or were on renal replacement therapy (n=3) and those with missing data on HIV-1 RNA level within 3 months of kidney biopsy were excluded (n=5).

Kidney biopsy

Kidney biopsy specimens were reviewed by an attending renal pathologist using light microscopy, immunofluorescence, and, as needed, electron microscopy to formulate an overall final histopathologic diagnosis. Over the study period, two renal pathologists were involved in examining the kidney biopsy specimens. Non-HIVAN FSGS was defined by the presence of segmental glomerulosclerosis without HIVAN features of collapsing glomerulosclerosis, microcystic tubular dilatation and tubulointerstitial inflammation [14].

Data collection

Clinical and demographic data were extracted from the patients' electronic medical records. The Johns Hopkins Hospital Institutional Review Board approved the study.

Primary exposure: HIV-positive patients were categorized as to whether they did or did not receive cART at the time of the renal biopsy.

Clincal covariates: The following baseline demographic and clinical variables were assessed for all patients: age, sex, race, presence of diabetes mellitus or hypertension, history of active or past injection drug use, chronic infection with either hepatitis B or C virus, total blood CD4+ cell count and HIV-1 viral load, proteinuria either by 24-hour urine collection or as estimated from a random urine protein-to-creatinine ratio. HIV suppression was defined as a HIV-1 RNA level <400 copies/ mL at the time of kidney biopsy. Estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease equation (MDRD) equation[15].

Primary Outcome: The primary outcome was ESRD as defined by the initiation of chronic renal replacement therapy assessed by medical record review.

Statistical analysis

Baseline characteristics were compared by HIV suppression status using t-test or rank-sum test for continuous variables and X^2 test for categorical variables. Survival analyses censoring for loss-to-follow-up and death from the time of biopsy to January 1, 2013 were used to estimate the association between viral suppression and progression to ESRD. The relative hazard of ESRD associated with viral suppression was estimated using Cox proportional hazards regression analyses. The proportional hazards assumption was confirmed graphically and by Schoenfeld residuals. All analyses were performed using Stata version 14.0 (StataCorp LCC, College Station, TX).

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RESULTS

Study population

A total of 203 HIV-positive African Americans underwent a native kidney biopsy during January 1, 1996 and June 31, 2011. Of these patients, there were 63 (31%) who had segmental glomerulosclerosis without HIVAN features of glomerular collapse, microcystic tubular dilatation and tubulointerstitial inflammation on renal histopathology and were classified as having classic FSGS. We excluded 5 patients who had incomplete clinical data (missing HIV-RNA levels) and 3 patients who had ESRD at the time of the kidney biopsy, leaving 55 patients in the final cohort of patients with classic FSGS.

Table 1 displays the patient's sociodemographic and clinical characteristics at baseline, stratified by HIV viral suppression status at the time of kidney biopsy. Patients were considered virally suppressed if they had an HIV-1 RNA level <400 copies/mL at the time of kidney biopsy; 26 (47%) fulfilled this definition of HIV viral suppression. In general, patients who were not virally suppressed had similar sociodemographic characteristics and proportion of individuals with classic risk factors for chronic kidney disease (CKD) such as history of illicit drug use, diabetes, hypertension, and hepatitis C virus co-infection.

Compared with individuals who had unsuppressed HIV RNA levels at the time of kidney biopsy, those who were suppressed were more likely to be receiving cART at the time of biopsy (41% vs. 84%, respectively; p=0.002) and had higher mean CD4+ cell counts (260 vs. 452 cells/ mm^3, respectively; p=0.02). Among those who were not virally suppressed, the median HIV-1 RNA level was 38,600 copies/ mL (interquartile range [IQR]: 10,500 – 100,000 copies/mL). While the median eGFR was lower among those who were not virally suppressed (25.5 [IQR: 23 – 45.5] vs. 53.5 [38.2 – 66]) ml/min/1.73 m^2, respectively; p=0.002) compared to patients who were suppressed, the median proteinuria levels were similar by viral suppression status (1.6 [IQR: 0.2 – 3] vs. 0.7 [IQR: 0.2 – 2] g/g, respectively; p=0.16) (Table 1).

Association of HIV viral suppression status with progression to ESRD

To evaluate the association of HIV viral suppression status at baseline with progression to ESRD, we evaluated patients over a median follow up of 2.70 years (IQR: 0.80 – 5.15 years).

A total of 19 (65%) patients progressed to ESRD. Patients who had HIV-1 RNA levels ≥400 copies/ mL greater at the time of biopsy were more likely to progress to ESRD compared to those with HIV-1 RNA levels below 400 copies/ mL (65% vs. 38%, p <0.01) during a median follow-up time of 2.70 years (IQR: 0.80 – 5.15 years) (Figure 1).

We evaluated the independent association of baseline HIV viral suppression status with time to ESRD using multivariable Cox proportional hazards regression. Patients were censored at the time of death, last available clinical data, or end of the study's observation period. The model for ESRD was adjusted for known confounding factors for ESRD including sex, age, baseline eGFR and proteinuria, patients who were virally suppressed at baseline had 70%

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(adjusted hazard ratio [aHR] = 0.30; 95% CI: 0.10 – 0.90) lower risk of progression to ESRD compared to those who were not virally suppressed (Table 2).

Discussion

The present study shows that among African Americans with biopsy-proven classic FSGS, HIV viral suppression at the time of biopsy was independently associated with 70% lower risk of progression ESRD. In the era of cART, there has been a significant decline in the incidence of HIVAN, with an increasing prevalence of classic FSGS[2]. In recent years, classic FSGS is now one of the most common histopathological findings in HIV-positive patients, with the prevalence of this pathological finding having increased by almost 5-fold compared to the 1995–2000 period[2].

Several studies have demonstrated the overall improvement in kidney function when initiating cART among HIV-positive individuals with established CKD [2]. START trial showed a positive impact of ART initiation on eGFR among ART-naive African American HIV+ patients with high CD4 [21]. Two studies in South Africa showed improvement in kidney function with cART irrespective of renal histopathology [12, 13, 16]. One of these studies was a retrospective cohort of 171 HIV-positive adults receiving cART for a median of 2 years in northwest Tanzania. In that African study, there was a high prevalence of kidney dysfunction at the time of starting antiretroviral therapy. The prevalence of kidney dysfunction dropped from 77% pre-treatment to 29% at follow-up; the prevalence of microalbuminuria also declined significantly from 72% to 44%. In another study conducted in sub-Saharan Africa, kidney function continued to improve after 4–5 years on cART. This improvement was also observed among the few patients with very advanced CKD. These findings along with ours suggest that cART may lead to gradual improvement of CKD [5].

Unsuppressed viral load is an important risk factor for ESRD in our study, which is consistent with some prior studies[4, 10, 16, 17]. Our results suggest that HIV may also play a role in the pathogenesis of non-collapsing FSGS and that suppression of HIV among African Americans could ameliorate kidney disease progression similar to its effects on HIVAN. Fabian and colleagues documented the clinical and histological response of biopsy-proven HIV-associated kidney disease to cART in a small cohort of 20 South African patients. cART initiation produced a rapid and sustained clinical renal response in all participants, irrespective of the histology as demonstrated in successive biopsies[16]. Non-collapsing FSGS and HIVAN may represent a spectrum of HIV-mediated kidney injury. Indeed, some studies non-HIVAN FSGS may reflect an adaptive response to injury from HIVAN in HIV-positive African American patients, with alteration of the collapsing configuration by cART[1]. Viral proteins and/or immune response can have cytopathic effect on the kidney[18, 19]. Direct infection of glomerular and tubular epithelial cells by HIV-1 have been shown, and cART has been shown to partially reverse glomerular and tubular histopathological changes of HIVAN patients[3].

The lower risk of progression to ESRD associated with effective HIV viral suppression among HIV-positive African Americans with classic FSGS seen in our study counters the findings of other studies showing that viral suppression had no beneficial effect on kidney

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function in non-HIVAN lesions[8, 20]. The seemingly conflicting observations of cART-related effect on non-HIVAN kidney disease across studies are likely due to heterogeneity in underlying renal histopathology across study populations. For example, among 47 patients with biopsy-proven non-HIVAN kidney disease, Szczech and colleagues reported that antiretroviral use was not associated with the progression to renal replacement therapy (HR 3.29, P = 0.06)[8]. However, only 1 out of these 47 patients had classic FSGS, and the remainder of the patients had immune complex or membranoproliferative glomerulonephritis (n=18), membranous nephropathy (n=6), diabetic nephropathy (n=5), hypertensive nephrosclerosis (n=3) and other kidney pathology (n=10). Moreover, our group also showed a similar lack of renal benefit associated with cART use in a predominantly African American HIV-positive cohort with biopsy-proven immune complex glomerulonephritis[20].

While our study is the first to show HIV suppression is associated with significantly lower risk of progression to ESRD among HIV-positive African Americans with classic FSGS, it has several limitations for consideration. First, our study was restricted to African Americans who underwent clinically indicated kidney biopsies; therefore, the generalizability of our findings to the other racial groups is limited. Additionally, clinical benefit with the use of cART may not correlate with pathological attenuation as has been previously demonstrated among HIV-positive from the African continent [16]. The *APOL1* risk variants have been shown to be associated with increased odds of non-HIVAN FSGS in addition to HIVAN among HIV-positive individuals of African descent [5, 9]. Second, we do not have adequate data to assess how cART prevented progression of ESRD in patients with non-HIVAN FSGS. The mechanisms by which the cART alters kidney cell function is a matter of considerable interest. Our study lacked data on longitudinal viral suppression, nadir CD4 count and specific antiretroviral drugs. This may have led to residual confounding. Third, although there were few statistically significant differences, it is hard to ignore the clinically important differences in baseline eGFR/ proteinuria and traditional CKD risk factors such as diabetes, hypertension and HCV between those with and without suppressed HIV-RNA. Even with statistical adjustment, it seems likely that there is some residual effect of these differences, particularly since diabetes has not been included in the adjusted models. Fourth, the possibility that ART use and adherence reflect overall health behaviors. In addition, lack of data or consideration of other therapy (ie corticosteroids or RAAS blockade) and other risk factor such as baseline blood pressure. In addition, the small size of the study is a further limitation. Finally, this study is from a single institution, and our findings would need validation in other studies.

In conclusion, our findings support the potential role of HIV in classic FSGS. Moreover, HIV suppression appears to mitigate the risk of kidney disease progression among HIV-positive African Americans with classic FSGS

Acknowledgments

The authors declare no acknowledgements and no relevant financial interests.

Funding:

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This study was funded by the NIDDK grant K23DK081317

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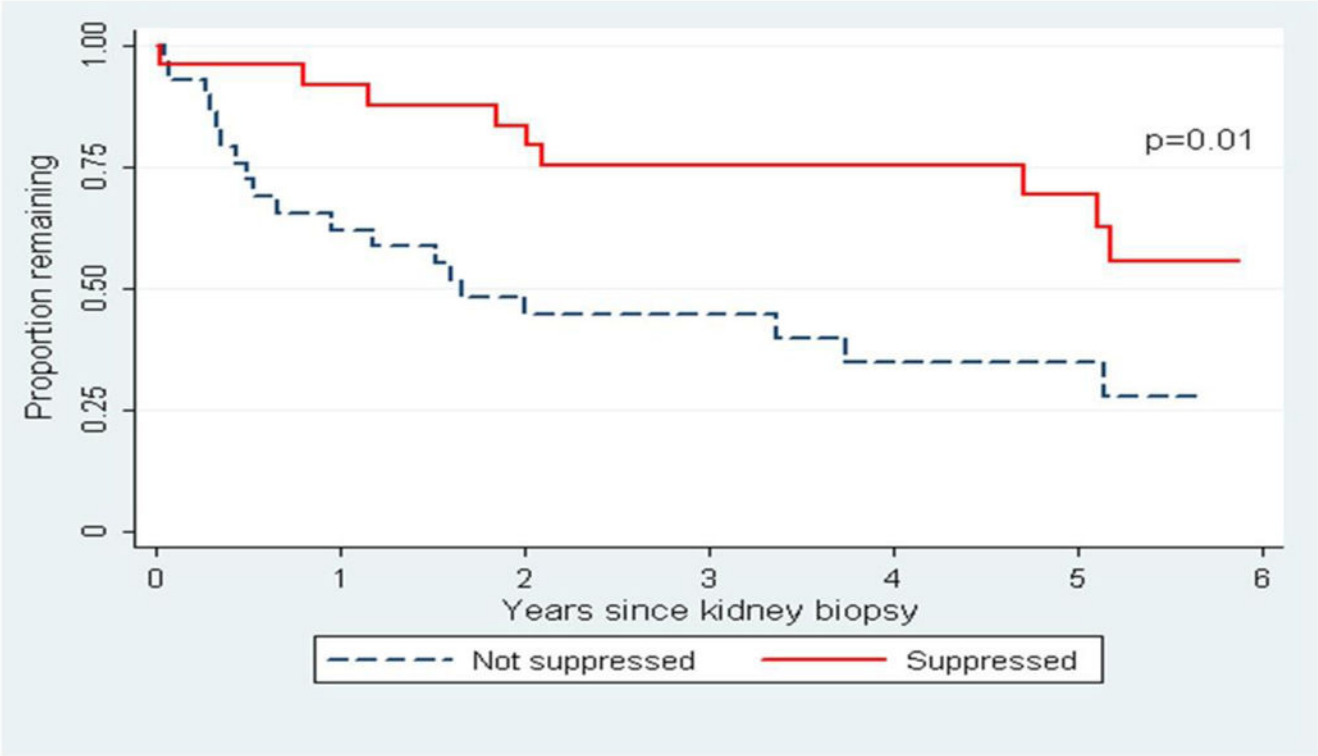

Year	0	1	2	3	4	5	6
Suppressed	29	18	14	10	7	5	1
Not Suppressed	26	22	20	16	13	10	7
Total	55	40	34	26	20	15	8

Figure 1.
Progression to ESRD by HIV Suppression Status at the Time of Biopsy

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Table 1

Study Participant Characteristics by HIV Suppression Status displays the participants' baseline sociodemographic and clinical characteristics by HIV suppression status at the time of kidney biopsy.

Characteristic	Virally not Suppressed (n=29)	Virally Suppressed (n=26)	P-value
Mean age, y (SD)	47.8 (1.4)	46.3 (1.4)	0.46
Male, n (%)	17 (59)	21 (81)	0.09
History of injection drug use, n (%)	15 (52)	15 (58)	0.79
Diabetes mellitus, n (%)	6 (21)	3 (11)	0.47
Hypertension, n (%)	20 (69)	19 (73)	0.77
Hepatitis C virus co-infection, n (%)	18 (62)	13 (50)	0.42
cART receipt, n (%)	11 (41)	21 (84)	0.002
Mean CD4+ cell count, cells/ mm^3 (SD)	260 (210)	452 (320)	0.02
Median HIV-1 RNA level, 1000 copies/ mL (IQR)	38.6 (10.5–100)	---	---
Median eGFR, mL/min/1.73 m^2 (IQR)	35.5 (23–45.4)	53.5 (38.2–66)	0.002
Median proteinuria, g/g (IQR)	1.6 (0.2–3)	0.7 (0.2–2)	0.16

cART; combined anti-retroviral therapy, HIV; human immunodeficiency virus, CD4+; cluster of differentiation 4 cells; eGFR; estimated glomerular filtration rate; SD; standard deviation, IQR; interquartile range

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Table 2.

Adjusted relative hazard of ESRD Associated with HIV Suppression (n=42).

Variable	aHR	(95% CI)	P-value
HIV suppressed vs. unsuppressed	0.30	(0.10, 0.89)	0.03
Age, per 10 years older	1.11	(0.63, 1.94)	0.71
Female vs. male	1.51	(0.55, 4.13)	0.42
Estimated GFR, per 10 ml/min higher	0.64	(0.44, 0.92)	0.02
Proteinuria, per 1 g/g higher	1.02	(0.80, 1.30)	0.87

Adjusted for sex, age, baseline eGFR and proteinuria. aHR; adjusted hazard ratio