Comparison of Risk Factors and Outcomes in HIV Immune Complex Kidney Disease and HIV-Associated Nephropathy

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Summary
Background and objectives HIV-associated nephropathy (HIVAN) is well described, but the clinical features of a group of renal pathologies characterized by Ig or immune complex depositions referred to as HIV-associated immune complex kidney disease (HIVICK) have not been well established. The objective of this study is to assess risk factors for HIVICK compared with contemporaneous control participants.

Design, setting, participants, & measurements A nested case-control study of 751 HIV-infected patients followed from January 1996 to June 2010 was conducted. Groups were compared using the chi-squared test or rank-sum analysis. Conditional logistic regression was used to estimate odds ratios (ORs) for HIVICK. Incidences of overall ESRD and with/without combined antiretroviral therapy (cART) exposure were calculated.

Results HIVICK patients were predominantly African American (92%). Compared with matched controls, patients with HIVICK were more likely to have HIV RNA >400 copies/ml (OR, 2.5; 95% confidence interval [95% CI], 1.2 to 5.2), diabetes (OR, 2.8; 95% CI, 1.1 to 6.8), and hypertension (OR, 2.3; 95% CI, 1.2 to 4.5). Compared with HIVAN, patients with HIVICK had more antiretroviral therapy exposure, lower HIV viral loads, and higher CD4 and estimated GFR. ESRD was less common in the HIVICK versus the HIVAN group (30% versus 82%; P<0.001), and the use of cART was not associated with ESRD in HIVICK patients (25% versus 26; P=0.39).

Conclusions HIVICK was predominantly observed in African American patients and associated with advanced HIV disease. ESRD incidence is lower in HIVICK patients compared with those with HIVAN. Unlike HIVAN, cART use was not associated with the incidence of ESRD in HIVICK.


Introduction
Renal disease is common in HIV-infected patients, with the prevalence of impaired kidney function ranging between 2.4% and 12% (1,2) and proteinuria ranging from 10% to 30% (3–5). Kidney disease in HIV-infected patients encompasses an array of renal pathologies (6). These processes may be directly mediated by HIV, such as in HIV-associated nephropathy (HIVAN); related to HIV coexisting conditions, such as diabetes, hypertension, and intravenous drug use; or associated with drugs toxic to the kidneys. Although the racial predilection of, clinical risk factors for, and pathologic characteristics of HIVAN have been well described (7–11), less is known about a spectrum of pathologies ranging from post-infectious GN (PIGN) to “lupus-like” GN, collectively referred to as HIVICK (12–14).

Prior studies suggest that individuals with HIVICK present with significant but lower degrees of proteinuria and similar immunocompromise as those with HIVAN and with variable degrees of kidney dysfunction (13–17); these studies, however, were primarily conducted either in the era preceding the availability of combination antiretroviral therapy (cART) or were composed of study populations in which few participants were receiving cART. Furthermore, the majority of these studies were conducted in regions outside the United States. Therefore, these findings may not be applicable to those within the United States due to differences in sociodemographic and clinical characteristics. Whether racial predilection exists for HIVICK as it does for HIVAN is also unclear. In an early study of black and white Europeans, only 1 of the 29 black participants presented with immune complex kidney disease, whereas 16 of the 31 white participants had immune complex kidney disease on renal biopsy (13). Similar findings were observed by Boissier et al. in which 80% of HIV-infected patients with immune complex kidney disease were white (14). In contrast, a more recent study of black Africans suggests that these disorders are not uncommon among blacks, with 62% having immune complex kidney disease (17). Moreover, although untreated HIVAN progresses relentlessly to
ESRD, data on the natural history of HIVICK and its response to cART are lacking due to the paucity of data on renal outcomes in prior studies (12,13,18–20).

To better characterize HIVICK among HIV-infected persons in the United States, we first conducted a case-control study using the Johns Hopkins HIV Clinical Cohort to assess the risk factors associated with HIVICK or HIVAN renal histopathology. Next, we compared progression to ESRD in participants with HIVICK and HIVAN, and assessed other risk factors for progression to ESRD, including use of cART.

Materials and Methods

Setting
The Johns Hopkins HIV Clinical Cohort is an open cohort that includes data from >6000 participants who have received HIV care in the clinic from 1990 onward (10,21–24). Trained technicians abstracted comprehensive demographic, clinical, laboratory, and pharmaceutical data from clinical records using structured data collection forms. Data were collected at enrollment and at 6-month intervals thereafter. Clinical diagnoses, other selected conditions (including initiation of renal replacement therapy), and deaths were routinely abstracted since cohort inception. National vital statistics provided supplemental information on mortality. Electronic data sources provided laboratory, pathology, and procedural visit data. Participants provided written informed consent, and this study was approved by the Johns Hopkins Medicine Institutional Review Board.

Study Design and Patient Selection
Participants who had a kidney biopsy between January 1, 1995 and June 30, 2011, were identified through linkage with the institutional pathology database. Cases were defined as patients with either HIVAN or HIVICK. We defined HIVAN as glomerular segmental or global collapse plus podocyte hypertrophy (25). We defined HIVICK as pathologic findings consistent with “lupus-like” GN, membranous nephropathy, membranoproliferative GN, IgA nephropathy, PIGN, cryoglobulinemia, and immune complex renal disease not otherwise specified (12,13,18,19,26). Lupus-like GN was determined by the presence of IgA, IgM, IgG, and C3 deposition on immunofluorescence, whereas PIGN was determined based on the presence of subepithelial deposits on electron microscopy and C3 deposition on immunofluorescence.

Risk factors were assessed in patients with HIVAN or HIVICK and in contemporaneous control participants. Because kidney biopsies may have been performed at variable time intervals from the appearance of clinical kidney disease and because clinical care may have been modified in light of clinically apparent kidney disease, we defined a clinical recognition date for each participant with HIVAN or HIVICK through clinical record review. The recognition date was defined as the date before kidney biopsy when a laboratory abnormality indicating kidney disease was identified as a concern by the HIV primary care provider in clinical documents. This date was used to match control participants and to define exposures (e.g., CD4 cell count or use of cART before this date). Using incidence density sampling with replacement, we randomly selected four control participants from the clinical cohort for each HIVICK and HIVAN patient, matching on kidney disease recognition date, age (in six strata), sex, and duration of follow-up in the clinic. We did not match on race because we wanted to assess race as a risk factor for HIVICK.

Data Collection and Definitions
Histopathologic diagnosis was based on the pathology report generated by a renal pathologist at the time of a patient’s renal biopsy. When participants had >1 kidney biopsy, we used results from the earliest biopsy unless that specimen was inadequate for diagnosis. Concurrent findings of both HIVICK and HIVAN (n=19) were categorized as HIVAN. We defined cART as the use of ≥3 antiretroviral drugs within the previous 3 months. We determined the estimated GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration method (27). Diabetes and hypertension were defined according to the presence of a clinical diagnosis or prescription of antidiabetic or antihypertensive medications, respectively. We defined ESRD as the initiation of renal replacement therapy including renal transplantation but excluding temporary dialysis with renal recovery.

Statistical Analyses
We compared continuous and categorical factors using the Wilcoxon rank-sum and chi-squared tests, respectively. In the risk factor analysis, we aimed to assess and compare risk factors for HIVICK and HIVAN with reference to control participants. To assess risk factors for HIVICK and HIVAN, we conducted separate risk factor analyses for each condition (comparing with contemporary control participants) using conditional logistic regression. Potential risk factors included race, injection drug use, cART use in the 3 months before recognition date, CD4 cell count, HIV RNA level, hepatitis C virus antibody (HCV), hepatitis B virus surface antigen, diabetes, and hypertension. For both HIVICK and HIVAN, we conducted parsimonious models, by sequentially removing factors from the full model with a backward stepwise selection procedure (critereon for removal: P>0.10). This analysis was also performed after excluding patients with PIGN.

To compare progression to ESRD from the time of kidney biopsy between HIVAN and HIVICK patients, we utilized the Kaplan–Meier method, log-rank test, and Cox proportional hazards models. Because individuals who reached ESRD <31 days after kidney biopsy were unlikely to fully benefit from cART initiation, they were excluded. Participant follow-up was censored at death, January 1, 2012, or 1 year after the last clinic encounter. We adjusted for age, calendar period, and log10-transformed eGFR before kidney biopsy. In addition, we assessed factors associated with progression to ESRD in participants with HIVICK and HIVAN in separate Cox models. Factors of interest included use of cART in the 30 days after kidney biopsy, calendar period, HIV RNA <400 copies/mL, and CD4 count <200 cells/mm3. Sensitivity analyses were also performed whereby patients with PIGN were excluded from the HIVICK group and those with concurrent HIVAN and HIVICK
were evaluated as a separate group from those with only HIVAN.

Results
Among 6422 participants followed in the Johns Hopkins HIV Clinical Cohort, there were 308 kidney biopsies performed. After excluding biopsies obtained before January 1, 1995, renal transplant biopsies, and repeat kidney biopsies, there were 267 kidney biopsies from unique participants. Among these individuals, 145 had HIVICK or HIVAN. Six of these participants (three each with HIVAN and HIVICK) were excluded from the analysis due to inadequate clinical information. Of the remaining 139 participants, 83 had HIVICK and 56 had HIVAN and were included in the analysis (Figure 1). The subtypes of HIVICK are shown in Table 1. Of note, four of the individuals with membranoproliferative GN pathology were had positive HCV antibody test results. The majority of the PIGN patients occurred in the post-cART era, with 95% occurring after December 1, 2001.

Clinical Characteristics of Participants with HIVAN and HIVICK
The demographic and clinical characteristics of patients at the time of clinical recognition compared with matched controls are listed in Table 2. Patients with HIVICK were predominantly men (67%) and African American (92%). A large proportion also had a history of injection drug use (64%) and positive hepatitis C antibody test results (63%).

Patients with HIVICK were older than those with HIVAN at the time of clinical recognition ($P=0.03$). HIVICK patients were also more likely to have hypertension (51% versus 32%; $P=0.03$), were more likely to use cART (43% versus 18%; $P=0.002$), were less likely to have HIV RNA ≥400 copies/ml (68% versus 90%; $P=0.01$), had higher median CD4 counts (263 versus 122 cells/mm$^3$; $P<0.001$), and had higher median eGFR (54 versus 32 ml/min per 1.73 m$^2$;

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**Figure 1.** Screening and inclusion/exclusion of HIV patients for analysis. HIVAN, HIV-associated nephropathy; HIVICK, HIV-associated immune complex kidney disease.
P<0.001) at the clinical recognition date compared with HIVAN patients. Compared with HIVAN patients, HIVICK patients were slightly less likely to have proteinuria of ≥1+ on dipstick testing (97% versus 83%, respectively). Moreover, compared with HIVAN patients, those with HIVICK had milder degrees of proteinuria, with 69% of HIVAN and 35% of HIVICK patients having 3+ proteinuria. Patients with HIVICK were also enrolled in the cohort for a longer period of time before their disease was clinically recognized compared with patients with HIVAN (median 4.4 years versus 1.5 years for the HIVICK and HIVAN groups, respectively; P=0.01).

**Determination of Risk Factors for HIVICK and HIVAN**

All 139 participants were successfully matched to 4 control participants. Patients and control participants were closely matched on sex, age, calendar date, and duration of follow-up in the cohort (Table 2). Table 3 lists the unadjusted and adjusted analyses of clinical features associated with HIVIN renal pathology compared with matched controls. In unadjusted analysis, African-American race was a risk factor for HIVICK (odds ratio [OR], 4.8; 95% confidence interval [95% CI], 2.0 to 11.5) and for HIVAN (OR, 10.0; 95% CI, 2.3 to 42.9), although African-American race was not statistically significant for HIVICK after adjustment (OR, 2.3; 95% CI, 0.9 to 6.8). Conversely, race remained a strong risk factor for HIVAN (OR, 10.3; 95% CI, 1.3 to 79.5). In adjusted models, HIV RNA >400 cells/ml was significantly associated with both HIVICK and HIVAN (OR, 2.5; 95% CI, 1.2 to 5.1; and OR, 11.7; 95% CI, 2.6 to 52.7, respectively).

After adjustment for race, HIV RNA >400 cells/ml, CD4 <200 cells/mm³, and HCV coinfection, HIVICK was significantly associated with diabetes (OR, 2.8; 95% CI, 1.1 to 6.8) and hypertension (OR, 2.3; 95% CI, 1.2 to 4.5). The association with diabetes dissipated when individuals with PIGN were excluded from the analysis.

**Incidence of ESRD**

After exclusion of individuals who developed ESRD within 31 days, 74 HIVICK and 43 HIVAN patients were...
available for analysis. Cumulative progression to ESRD was lower in patients with HIVICK than in those with HIVAN (32% and 70% at 24 months, respectively; \( P<0.001 \)) (Figure 2). Exclusion of individuals with PIGN revealed similar disparities in cumulative progression to ESRD between those with HIVICK versus HIVAN (37% versus 65% at 24 months, respectively; \( P=0.01 \)). Similarly, exclusion of participants who had not received highly active antiretroviral therapy before the renal biopsy also yielded similar results, with a cumulative incidence of ESRD of 25% in those with HIVICK and 68% in those with HIVAN at 24 months (\( P=0.02 \)).

Among participants included in the ESRD progression analysis, 36 HIVICK patients and 18 HIVAN patients had cART exposure in the 30 days after biopsy. Among individuals with HIVICK, there was no difference in the incidence of ESRD between those with cART use versus without (25% versus 26%, respectively; \( P=0.39 \)) (Figure 3A). Of note, 71% of those with HIVICK who initiated cART after their renal biopsy achieved HIV-1 RNA levels <400 copies/ml. The proportion of HIVICK individuals who attained an HIV-1 RNA level <400 copies/ml was similar between those who did and did not progress to ESRD (31% versus 49%, respectively; \( P=0.11 \)). Despite exclusion of individuals with PIGN, cART remained unassociated with progression to ESRD among those with HIVICK (hazard ratio \([HR]\), 1.07; 95% confidence interval, 0.28 to 4.03). In contrast, cART use was associated with lower incidence of ESRD compared with no cART use among those with HIVAN (44% versus 72%, respectively; \( P=0.02 \)) (Figure 3B).

Unadjusted HRs associated with the development of ESRD for patients with HIVICK and HIVAN are shown in Table 4. Significant variables included HIVICK on biopsy (HR, 0.30; 95% CI, 0.18 to 0.51), cohort follow-up in 2002 onward compared with before 2002 (HR, 0.50; 95% CI, 0.30 to 0.83), older age (HR, 0.62 per 10 years; 95% CI, 0.43 to 0.91), and loge-transformed eGFR (HR, 0.32 per 1 loge higher; 95% CI, 0.23 to 0.44). After adjustment for all statistically significant variables from univariate analyses, only loge-transformed eGFR remained significantly associated with the risk of ESRD (HR, 0.35 per 1 loge higher; 95% CI, 0.24 to 0.52).

In parallel sensitivity analyses excluding PIGN patients and those who received highly active antiretroviral therapy before their renal biopsy, individuals with HIVICK remained at lower risk of progressing to ESRD compared with those with HIVAN (HR, 0.45; 95% CI, 0.23 to 0.87; and HR, 0.35; 95% CI, 0.14 to 0.90). Finally, unadjusted survival analyses in which participants with concurrent HIVAN and HIVICK were regarded as a third group yielded similar findings as the primary analyses, with HIVICK individuals at lower risk for progressing to ESRD (HR, 0.27; 95% CI, 0.15 to 0.46). Individuals with both HIVAN and HIVICK had similar risk for progressing to ESRD as those with HIVAN (HR, 0.82; 95% CI, 0.56 to 1.21), but higher than those with HIVICK (HR, 2.43; 95% CI, 1.11 to 5.33).

### Discussion

In this analysis of predominantly African-American HIV-infected patients, HIVICK was not an uncommon biopsy finding. HIVICK patients generally have milder renal disease and less advanced HIV infection at the time of clinical recognition compared with those with HIVAN consistent with previous studies (6,20). To our knowledge, our study is the first to analyze risk factors for the specific development of HIVICK against matched controls.

Risk factors for the development of HIVICK included HIV RNA levels >400 cells/ml, diabetes, and hypertension. The importance of HIV RNA in the development of HIVICK has been suggested by the failure to generate this entity in experimental models. Contrary to HIVAN, in which many HIV-1 transgenic models exhibit the clinical and pathologic features of HIVAN, none of these animal models exhibit features of HIVICK (28,29). This observation suggests that viral replication or immune responses to viral proteins may be essential to trigger HIVICK (30). The role of hypertension and diabetes in the development of immune complex disease is less clear. The presence of these conditions may have predisposed the patients to
receiving a kidney biopsy, although previous studies of non-HIVAN renal disease did not find these to be significant factors in patients receiving a kidney biopsy (6). Up to 43% of patients in this series with HIVICK were receiving cART at the time of clinical recognition. cART use has been associated with an increase of both hypertension and diabetes (31-34), which may explain why HIVICK patients were more likely to have hypertension than HIVAN patients. Alternatively, one may argue that HIVICK is more likely than HIVAN to cause, rather than being triggered by, hypertension. Furthermore, the association with diabetes was entirely driven by PIGN, which is consistent with the previous observation that diabetes was the most predisposing factor for postinfectious GN (35).

Over half of the patients in the HIVICK group were coinfected with HCV, which can predispose to immune complex kidney disease (36,37). Although George et al. recently published findings that showed an increase in immune complex GN among patients coinfected with HIV and HCV compared with those with HIV alone (38), there was no increased HCV coinfection in HIVICK versus HIVAN patients, nor was HCV associated with increased odds of HIVICK compared with matched controls in our adjusted analyses. Combined ART use was not associated with decreased odds of HIVICK despite higher cART use among patients with HIVICK compared with patients with HIVAN. Subsequent immune reconstitution may be associated with increased immune activity (39), thereby theoretically increasing antigen-antibody formation and the development of HIVICK. Recent evidence suggests that genetic factors may play an important role in determining renal histopathology in HIV-infected individuals (40,41). In a cohort of African-American patients with biopsy-proven non-HIVAN renal pathology, Fine et al. found that 76% of patients carrying two APOL1 risk alleles had FSGS. In contrast, immune complex GN was found more often on renal biopsy in patients with only one or no APOL1 risk allele (47% and 40%, respectively) (40,41). Although the findings may represent interplay between the APOL1 genotype and the immune system, it may also be explained by an earlier clinical presentation for patients with FSGS before having the opportunity to develop an immune complex GN (40).

Patients with HIVICK were less likely to progress to ESRD than those with HIVAN; this observation remained robust in sensitivity analyses. These findings are consistent with previous studies that suggest that non-HIVAN renal diseases progress more slowly than HIVAN (6,20,42). The use of cART was not associated with the incidence of ESRD in patients with HIVICK, with the two groups having nearly identical proportions developing ESRD by 24 months. A number of factors may explain our findings including the relatively lower overall incidence of ESRD in this population, small study group size, or the possibility of inducing HIVICK with cART due to immune reconstitution. Furthermore, one may argue that ART is unlikely to affect the vigorous polyclonal antibody responses driven by the high levels of circulating antigens in these patients and is responsible for the immune complex deposition with subsequent complement activation in the kidney. Wearne et al. recently suggested that cART may stabilize immune complex kidney disease (42), although there was no significant effect on ESRD incidence in their analysis. This study, however, had a substantially smaller sample size, with only 16 patients with isolated immune complex GN on kidney biopsy, which may limit the interpretations of those findings (42). Consistent with previous studies, cART use was associated with lower incidence of ESRD in patients with HIVAN (20,42,43).

Compared with previous studies of HIVICK, our study had a larger proportion of individuals with PIGN and immune complex that was not otherwise specified. Uncontrolled
HIV infection or different exposures such as injection drug use or HCV coinfection may underlie these differences. Compared with the previous studies by Boissier et al. (14) and Gerntholtz et al. (17), our study population had higher HIV-1 viremia and a larger proportion of participants with injection drug use and HCV antibody seropositivity. Conversely, we had fewer participants with any cART exposure compared with prior studies.

We acknowledge several limitations to this analysis. Our findings should be interpreted cautiously in light of the fact that the spectrum of pathologies considered as HIVICK does not necessarily share the same pathogenic mechanisms, clinical presentations, or natural history. Second, this is a single-center study in a predominantly urban setting, so the findings may not be generalizable to other geographic or clinical settings. The relatively small sample size may have influenced the results, although this is the largest biopsy cohort of HIVICK patients compared with the published literature. This group of patients was also predominantly African American, so the results may not be applicable to other patient populations. Finally, unrecognized modifying factors may have biased the results. Although the control group for this analysis was not a biopsy group, the control participants were closely matched on important clinical characteristics and included a robust sample size of HIV-infected patients with immune complex kidney disease that has not been evaluated in previous studies.

**Figure 3.** Incidence of ESRD by cART exposure. HIVAN, HIV-associated nephropathy; HIVICK, HIV-associated immune complex kidney disease; HAART, highly active antiretroviral therapy.
In conclusion, our study offers further understanding of the clinical factors and outcomes associated with HIVICK. The association of higher HIV viremia with findings of HIVICK on biopsy may suggest a pathogenic mechanism for the development of immune complex GN in HIV, either by disruption of normal immune function and regulation, or via direct antigenic stimulation and subsequent antibody response. Combined cART failed to significantly affect the incidence of ESRD in this cohort, and the routine use of cART for HIVICK is not suggested by our findings at this time.

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Disclosures
None.

References

Table 4. Unadjusted hazard ratios for developing ESRD in HIVICK and HIVAN patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
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<tr>
<td>HIVICK versus HIVAN</td>
<td>0.30</td>
<td>0.18 to 0.51</td>
</tr>
<tr>
<td>Cohort follow-up before versus after 2002</td>
<td>0.50</td>
<td>0.30 to 0.83</td>
</tr>
<tr>
<td>Log transformed eGFR</td>
<td>0.32</td>
<td>0.23 to 0.44</td>
</tr>
<tr>
<td>Women versus men</td>
<td>0.98</td>
<td>0.58 to 1.64</td>
</tr>
<tr>
<td>Black race</td>
<td>1.73</td>
<td>0.42 to 7.1</td>
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<tr>
<td>Injection drug use</td>
<td>0.82</td>
<td>0.50 to 1.35</td>
</tr>
<tr>
<td>HCV</td>
<td>1.10</td>
<td>0.50 to 2.42</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>0.88</td>
<td>0.40 to 1.94</td>
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<tr>
<td>Hypertension, n (%)</td>
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<td>0.49 to 1.34</td>
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<tr>
<td>Increase in age 10 yr</td>
<td>0.62</td>
<td>0.43 to 0.91</td>
</tr>
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</table>

HIVIC, HIV-associated immune complex kidney disease; HIVAN, HIV-associated nephropathy; eGFR, estimated GFR; HCV, hepatitis C virus.


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