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Clinical characteristics and outcomes of HIV-associated immune complex kidney disease

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ORIGINAL ARTICLE

ABSTRACT

Background. The pathogenesis and natural history of HIV-associated immune complex kidney disease (HIVICK) is not well understood. Key questions remain unanswered, including the role of HIV infection and replication in disease development and the efficacy of antiretroviral therapy (ART) in the prevention and treatment of disease.

Methods. In this multicentre study, we describe the renal pathology of HIVICK and compare the clinical characteristics of patients with HIVICK with those with IgA nephropathy and HIV-associated nephropathy (HIVAN). Poisson regression models were used to identify risk factors for each of these pathologies.

Results. Between 1998 and 2012, 65 patients were diagnosed with HIVICK, 27 with IgA nephropathy and 70 with HIVAN. Black ethnicity and HIV RNA were associated with HIVICK, receipt of ART with IgA nephropathy and black ethnicity and CD4 cell count with HIVAN. HIVICK was associated with lower rates of progression to end-stage kidney disease compared with HIVAN and IgA nephropathy ($P < 0.0001$). Patients with HIVICK who initiated ART and achieved suppression of HIV RNA experienced improvements in estimated glomerular filtration rate and proteinuria.

Conclusions. These findings suggest a pathogenic role for HIV replication in the development of HIVICK and that ART may improve kidney function in patients who have detectable HIV RNA at the time of HIVICK diagnosis. Our data also suggest that IgA nephropathy should be viewed as a separate entity and not included in the HIVICK spectrum.

Keywords: ART, HIV, HIVAN, HIVICK, immune complex kidney disease

INTRODUCTION

HIV-associated immune complex kidney disease (HIVICK), characterized by the presence of glomerular immune deposits on immunostaining and/or electron microscopy (EM) of renal biopsies, represents the dominant histological entity in several contemporary biopsy series of HIV-positive patients [1–3]. In contrast to HIV-associated nephropathy (HIVAN), the archetypal HIV-associated glomerular lesion, there is a paucity of data on the pathogenesis and natural history of HIVICK [4]. Key questions include whether HIV is directly or indirectly involved in the pathogenesis of HIVICK and whether HIVICK responds to or may be exacerbated by antiretroviral therapy (ART). Previous studies of HIVICK have yielded conflicting conclusions and have been limited by their small sample size and the heterogeneity of pathological conditions considered collectively for the purposes of analysis [1, 5, 6]. As a consequence, recently published international guidelines offer no recommendations on the optimal treatment of HIVICK in HIV [7, 8]. In this study, we describe the histopathology of patients with HIVICK and compare the clinical characteristics, risk factors and renal outcomes with IgA nephropathy and HIVAN.

MATERIALS AND METHODS

Study design

HIV-positive patients attending eight clinics in the UK who had undergone native renal biopsies between January 1998 and December 2012 were identified by searching local renal and histopathology databases. Renal biopsy reports were reviewed by a team of two histopathologists (C.H., P.O) and one nephrologist (J.W.B.), blinded to clinical outcomes. Where patients had undergone multiple biopsies, the first biopsy was included unless this had proved non-diagnostic. Where reports were deemed equivocal or insufficient, sections were re-examined or, if unavailable, excluded. Patients with evidence of dual HIVAN and immune complex (IC) disease were also excluded from analysis.

Renal biopsy review

Immune complex kidney disease (ICKD) was defined by the unequivocal presence of glomerular immunoglobulin deposits and corroborated, where available, by the presence of electron dense-deposits (EDDs) on electron microscopy (EM). Biopsies classified as ICKD were further categorized by the dominant histological pattern using the following diagnostic features: membranous nephropathy if they exhibited capillary loop thickening ± glomerular basement membrane 'spike' or 'chain' appearances on silver stain, IgG ± C3 deposition along capillary loops and subepithelial EDDs on EM; mesangiocapillary glomerulonephritis if they exhibited mesangial hypercellularity and proliferation, broadening of capillary loops with membrane reduplication, glomerular immunoglobulin ± C3 deposition and subendothelial EDDs on EM; IgA nephropathy if they exhibited dominant or co-dominant mesangial ± capillary loop IgA immunostaining and mesangial EDDs on EM; lupus nephritis if they exhibited International Society of Nephrology/Renal Pathology Society Class I–V disease in patients satisfying diagnostic criteria for systemic lupus erythematosus (SLE). Biopsies showing ICKD but not classifiable into any of these histological subpatterns were designated ICKD-NOS. Based on our hypothesis that ICKD in HIV is unlikely to represent a single clinical and pathologic entity, membranous nephropathy, mesangiocapillary glomerulonephritis and ICKD-NOS were *a priori* grouped together as a single entity for analysis (designated HIVICK), distinct from IgA nephropathy and lupus nephritis. Biopsies were classified as HIVAN if they exhibited at least two of the three characteristic features: glomerular tuft 'collapse', tubular microcysts or podocyte proliferation. Consistent with previous studies, both collapsing and non-collapsing forms of FSGS were considered part of the HIVAN spectrum [3].

Definitions

End-stage kidney disease (ESKD) was defined as the need for renal replacement therapy (either dialysis or kidney transplantation), excluding temporary dialysis for acute kidney injury. Hypertension and diabetes were defined by recorded clinical diagnoses or the prescription of antihypertensive or anti-diabetic drugs, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [9]. Proteinuria was expressed as urine 24-h total protein excretion; where a 24-h collection had not been performed, the urine protein:creatinine ratio (expressed as mg/mmol) was multiplied by a factor 10 to provide a 24-h proteinuria estimate.

Statistical analyses

Kaplan–Meier curves were used to compare progression to ESKD from the time of renal biopsy for each of the histological patterns. For these analyses, patients with biopsies showing dual pathology (IC disease and HIVAN, $n = 3$) were excluded and follow-up was censored at 20 April 2013, ESKD or date last seen, whichever came first.

Six of the eight study centres are part of the UK Collaborative HIV Cohort (CHIC study) [10], an ongoing observational cohort study collecting prospective data from many of the largest HIV treatment centres in the UK. Poisson regression models were used to identify factors associated with HIVICK, IgA nephropathy and HIVAN in the UK CHIC cohort, with ethnicity included as a fixed covariate and age, CD4 cell count, HIV RNA, exposure to ART, hepatitis B surface antigen and hepatitis C antibody status as time-updated covariates; gender and exposure group were not included in the multivariable models, as these factors are highly correlated with ethnicity in this cohort. Univariate Poisson regression was used to analyse factors associated with progression to ESKD in patients with HIVICK and HIVAN. Due to the small number of ESKD events, multivariate analyses were not performed for patients with HIVICK.

To determine whether viraemia had an impact on eGFR slopes, individuals were classified according to ART and HIV viral load status. Those who were off treatment and/or had detectable HIV RNA (>200 copies/mL) at the time of biopsy and thereafter were classified as 'remained viraemic'. Those who started treatment within 3 months of biopsy and were rendered undetectable (HIV RNA <200 copies/mL) within 6 months of biopsy were classified as 'became undetectable'. Those on ART before and after biopsy with persistently undetectable HIV RNA were classified as 'remained undetectable'. Linear mixed effects models were used to generate eGFR slopes for each viral load category. Data were censored at 4 years, ESKD, death or loss to follow-up, whichever occurred first.

RESULTS

During the 14-year study period, 278 HIV-positive patients underwent kidney biopsy. Thirteen biopsies were non-diagnostic and five required re-examination of original material to confirm the diagnosis; of the 265 patients with a renal diagnosis, 70 (26.4%) had HIVAN, 92 (34.7%) had ICKD and 103 had other pathologies. The ICKD pathologies comprised membranous nephropathy ($n = 17$), mesangiocapillary glomerulonephritis ($n = 5$) and ICKD-NOS ($n = 37$)—collectively designated HIVICK ($n = 59$), IgA nephropathy ($n = 27$) and lupus nephritis with features of SLE ($n = 6$). Three patients with HIVAN had evidence of concomitant ICKD—two ICKD-NOS and one IgA nephropathy.

Table 1. Clinical characteristics of patients with HIVICK, IgA nephropathy and HIVAN at the time of kidney biopsy

		HIVICK ($n = 55$)	HIVICK subtypes			IgA ($n = 26$)	HIVAN ($n = 65$)
			MGN ($n = 16$)	MCGN ($n = 5$)	ICKD-NOS ($n = 34$)		
Age (years)	Mean (SD)	43.1 (10.8)	47.9 (11.4)	39.6 (8.1)	41.7 (10.7)	43.9 (9.7)	39.9 (9.0)
Gender (male)	*n* (%)	37 (67.3)	9 (56.3)	5 (100)	23 (67.6)	18 (69.2)	40 (61.5)
Ethnicity (black)	*n* (%)	28 (50.9)	8 (50)	0 (0)	20 (58.8)	10 (38.5)	64 (98.5)
HIV risk (IVDU)	*n* (%)	10 (18.2)	3 (18.8)	1 (20)	6 (17.7)	3 (11.5)	7 (10.8)
HBsAg positive	*n* (%)	10 (18.5)	3 (20)	2 (40)	5 (14.7)	4 (16)	6 (9.5)
HCV Ab positive	*n* (%)	4 (7.6)	0 (0)	2 (40)	2 (6.25)	2 (7.7)	2 (3.2)
Years since HIV diagnosis	Median (IQR)	6.2 (0.6–11.4)	7.4 (3.6–13.2)	11.4 (7.5–14.3)	3.1 (0.2–9.2)	6.7 (3.5–11.5)	0.09 (0.003–1.4)
On ART at biopsy	*n* (%)	32 (58.2)	13 (81.3)	2 (40)	17 (50)	23 (88.5)	21 (33.9)
Years since start of ART	Median (IQR)	0.5 (−0.04–4.9)	1.0 (0.2–7.6)	1.9 (0.003–6.4)	0.03 (−0.1–1.7)	4.2 (2.6–9.6)	−0.01 (−0.1–0.5)
CD4 nadir (cells/mm^3)	Median (IQR)	212 (96–329)	212 (140–312)	197.5 (65–307)	215 (93–357)	130 (70–205)	64 (22–181)
AIDS	*n* (%)	15 (27.3)	4 (25)	2 (40)	7 (21.1)	11 (42.3)	21 (32.8)
CD4 latest (cells/mm^3)	Median (IQR)	389 (260–691)	436 (357–564)	346 (122–389)	369 (160–460)	390 (276–590)	288 (199–344)
VL <200 copies/mL	*n* (%)	20 (37.7)	9 (64.3)	1 (20)	10 (29.4)	19 (82.6)	11 (18.0)
eGFR (mL/min/1.73 m^2)	Median (IQR)	49.8 (26.6–91.5)	85.2 (48.5–115)	57.6 (29.8–98.1)	34 (21.2–79.4)	47.1 (24.8–70.3)	20.5 (11.3–33.8)
Diabetes	*n* (%)	3 (5.5)	1 (6.3)	1 (20)	1 (2.9)	5 (19.2)	0 (0)
Hypertension	*n* (%)	10 (18.5)	3 (18.8)	0 (0)	7 (21.2)	12 (46.2)	20 (32.3)
Proteinuria (g/24 h)	Median (IQR)	2.4 (1.4–5.9)	3.1 (2.2–11)	6.8 (2.3–7.6)	2.1 (1.0–3.6)	2.5 (1.3–3.6)	4.5 (3.1–7.5)

HIVICK, HIV immune complex kidney disease; MGN, membranous nephropathy; MCGN, mesangiocapillary (membranoproliferative) glomerulonephritis; ICKD, immune complex kidney disease; NOS, not otherwise specified; IVDU, intravenous drug use; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus IgG antibody; ART, antiretroviral therapy; VL, HIV viral load; eGFR, estimated glomerular filtration rate.

Clinical data were available for 146 (94%) of the 156 patients with HIVICK, IgA nephropathy and HIVAN and are displayed in Table 1. Patients with HIVICK were diagnosed a median of 6.2 years after their initial HIV presentation; 27.3% had experienced an AIDS-defining illness, and their median nadir CD4 cell count prior to their renal diagnosis was 212 [interquartile range (IQR) 96–329] cells/mm^3. At the time of kidney biopsy, the majority of patients with HIVICK had initiated ART and achieved immune reconstitution, although only 37.7% had achieved suppression of HIV replication. The median eGFR of subjects with HIVICK was 49.8 mL/min/1.73 m^2 and the median amount of proteinuria was 2.4 g/24 h. Comparing subcategories of HIVICK, ICKD-NOS had lower eGFRs and less ART exposure than those with membranous nephropathy. As expected, the majority of patients with HIVAN were of black ethnicity. These patients had more advanced immunodeficiency, low rates of ART exposure and HIV suppression, lower eGFRs and more severe proteinuria than those with HIVICK.

Factors associated with a diagnosis of HIVICK, IgA nephropathy and HIVAN

Factors associated with HIVICK, IgA nephropathy and HIVAN among patients whose renal diagnosis occurred subsequent to their enrolment in the UK CHIC cohort ($n = 31\,483$) were analysed. The characteristics of the UK CHIC population are shown in Supplementary data, Table S1. Black ethnicity and HIV RNA were associated with HIVICK, receipt of ART with IgA nephropathy and black ethnicity and CD4 cell count with HIVAN (Table 2). In addition, HIVAN was strongly associated with an HIV diagnosis in the past year. No association was observed between hepatitis B or C and either HIVICK, IgA nephropathy or HIVAN.

Kidney disease progression

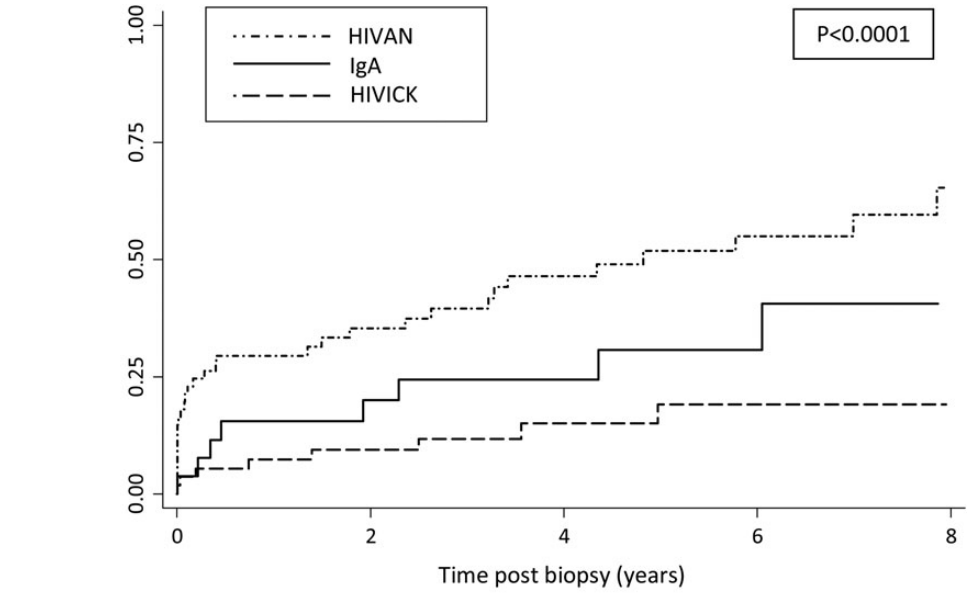
Patients with HIVICK, IgA nephropathy and HIVAN were followed up for a median (IQR) of 3.5 (2.0–6.8), 4.1 (1.7–6) and 2.4 (0.3–5.6) years, respectively. Of these, 7, 9 and 6% received immunosuppressive therapy and 62, 65 and 66% were initiated on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. During follow-up, 7.3, 7.7 and 21.5% died and 15, 32 and 52% were diagnosed with ESKD. We observed similar cumulative incidences of ESKD among HIVICK patients with membranous nephropathy, mesangiocapillary glomerulonephritis and ICKD-NOS ($P = 0.72$). The cumulative incidence of ESKD was lowest among patients with HIVICK, intermediate among those with IgA nephropathy and highest among patients with HIVAN ($P < 0.0001$, Figure 1). Among patients with HIVICK, age, CD4 cell count, HIV RNA, eGFR, proteinuria, hypertension and use of renin–angiotensin blockers or glucocorticosteroids were not associated with progression to ESKD ($P > 0.1$). The only factor associated with ESKD in patients with HIVICK was diabetes mellitus {rate ratio 42.4 [95% confidence interval (CI) 7.1, 254]}. In contrast, younger age [adjusted rate ratio 0.9 (95% CI 0.8, 1.0), $P = 0.01$], eGFR [2.9 (95% CI 1.8, 4.7) per 10 mL/min/1.73 m^2 decrease, $P < 0.0001$] and proteinuria [1.1 (95% CI 1.0, 1.2) per g/24 h increase, $P = 0.02$] at the time of biopsy were associated with progression to ESKD in patients with HIVAN (Supplementary data, Table S2).

The effect of HIV viraemia on the eGFR slope and the amount of proteinuria post–kidney biopsy in patients with HIVICK, IgA nephropathy and HIVAN were examined. For these analyses, patients were stratified into three groups: those who remained viraemic, those who initiated ART and whose HIV viral load became undetectable and those with undetectable HIV RNA at biopsy who remained undetectable. The results of these analyses are shown in Table 3. The eGFR post-biopsy improved in patients with HIVICK whose HIV RNA

Table 2. Factors associated with HIVICK, IgA nephropathy and HIVAN

	HIVICK ($n = 44$)				IgA nephropathy ($n = 20$)		HIVAN ($n = 32$)			
	Univariable		Multivariable		Univariable		Univariable		Multivariable	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Ethnicity										
Black	2.44 (1.35, 4.44)	0.003	2.23 (1.13, 4.40)	0.021	2.14 (0.88, 5.25)	0.095	17.37 (6.69, 45.11)	<0.0001	8.41 (3.04, 23.32)	<0.0001
Other	1.00		1.00		1.00		1.00		1.00	
Age at baseline										
per 10 year increase	1.01 (0.72, 1.41)	0.97			1.50 (0.97, 2.32)	0.067	1.34 (0.94, 1.92)	0.10		
Hepatitis B co-infection[a]										
No	1.00		1.00		1.00		1.00			
Yes	2.51 (0.88, 7.16)	0.085	2.50 (0.87, 7.17)	0.088	2.51 (0.57, 11.05)	0.22	1.46 (0.19, 11.26)	0.71		
No test/unknown	0.72 (0.37, 1.42)	0.35	0.27 (0.09, 0.78)	0.016	0.48 (0.16, 1.47)	0.20	2.67 (1.30, 5.51)	0.008		
Hepatitis C co-infection[a]										
No	1.00				1.00		1.00			
Yes	1.08 (0.33, 3.54)	0.90			1.49 (0.34, 6.52)	0.60	0.66 (0.09, 4.95)	0.68		
No test/unknown	0.56 (0.27, 1.14)	0.11			0.35 (0.10, 1.20)	0.095	1.43 (0.71, 2.90)	0.32		
CD4 count[a]										
per 50 cells/mm^3 increase	0.99 (0.92, 1.05)	0.69			0.98 (0.90, 1.08)	0.71	0.71 (0.63, 0.81)	<0.0001	0. 80 (0.71, 0.91)	0.001
HIV viral load[a]										
per $\log_{10}$ copies/mL	1.38 (1.10, 1.74)	0.004	1.48 (1.17, 1.86)	0.0009	0.82 (0.54, 1.25)	0.35	1.60 (1.23, 2.09)	0.0005	1.30 (0.99, 1.71)	0.062
ART[a]										
No	1.00				1.00		1.00			
Yes	0.75 (0.41, 1.38)	0.36			8.13 (1.09, 60.71)	0.041	0.48 (0.24, 0.97)	0.041		
Time since HIV diagnosis[a]										
≤1 year	1.00				1.00		1.00		1.00	–
1–5 years	0.39 (0.13, 1.11)	0.077			2.02 (0.25, 16.44)	0.51	0.16 (0.07, 0.37)	<0.0001	0.33 (0.13, 0.84)	0.02
5–10 years	0.82 (0.32, 2.10)	0.68			1.23 (0.14, 11.05)	0.85	0.04 (0.01, 0.17)	<0.0001	0.11 (0.02, 0.51)	0.005
>10 years	0.73 (0.28, 1.89)	0.51			2.49 (0.31, 19.91)	0.39	0.10 (0.04, 0.27)	<0.0001	0.33 (0.10, 1.09)	0.070

RR, relative rate; CI, confidence interval; HIVICK, HIV immune complex kidney disease; HIVAN, human immunodeficiency virus-associated nephropathy.
[a]These variables are time updated.



Number at risk

HIVAN	61	31	22	14	5
IgA	26	18	13	8	0
HIVICK	55	41	24	17	9

FIGURE 1: Probability of ESKD in HIVICK, IgA nephropathy and HIVAN.

became undetectable. In contrast, patients who developed HIVICK with fully suppressed HIV replication continued to lose kidney function post-biopsy, while eGFR slopes in patients whose HIV RNA remained detectable were highly variable. For patients with HIVAN, initiation of ART with subsequent viral suppression merely stabilized renal function, while patients with undetectable HIV RNA at biopsy continued to experience eGFR decline. Of note, substantial variability in eGFR slopes was observed in each stratum; as a result, between-group comparisons were not statistically significant. Post-biopsy, improvements in the amount of proteinuria were observed in all groups of patients, irrespective of HIV viral load status. The greatest reductions in proteinuria were observed in patients with HIVICK and HIVAN whose HIV RNA became undetectable (Table 4).

Renal histopathology

ICKD-NOS biopsies manifested varying degrees of mesangial expansion, capillary loop thickening or segmental sclerosis with or without endocapillary proliferation and crescent formation. Mesangial and/or capillary loop immunoglobulin deposition was observed in all ICKD-NOS biopsies; a 'full house' of immunoproteins (sometimes referred to as 'lupus-like' nephritis) was present in six (16%) biopsies. Where EM was performed (35 biopsies, 95%), mesangial EDDs were observed in 71%, subendothelial EDDs in 23% and subepithelial EDDs in 74%, with EDDs at all three locations in 14%. Tubulo-reticular inclusion bodies were positively identified in 40% of specimens. Subepithelial EDDs observed in ICKD-NOS were typically sparse and often hump-like in appearance. Two biopsies (6%) showed diffuse endocapillary proliferation in association with subepithelial hump-like deposits, suggestive of a post-infectious aetiology. In view of the morphological overlap of these cases with others in the ICKD-NOS category, together with difficulty in isolating a discrete infectious trigger, we chose not to consider these as a discrete histological entity.

Biopsies classified as membranous nephropathy (17 of 59, 29%) frequently displayed additional atypical features, including mesangial proliferation (47%), capillary loop duplication (12%), endocapillary proliferation (12%) or segmental sclerosis (24%). 'Full house' immunoprotein deposition was seen in four (24%) biopsies. Where EM was performed (14 biopsies, 82%), subepithelial EDDs were seen in all cases; in eight cases (57%), EDDs were also observed in an additional, atypical location (mesangial or subendothelial). The biopsies of five patients (5%) were classified as mesangiocapillary (membranoproliferative) glomerulonephritis; subepithelial EDDs were seen in addition to mesangial or subendothelial deposits in four of five cases where EM was performed. 'Full house' immunostaining was observed in one of five cases. In contrast, EM of the biopsies showing IgA nephropathy (available for 22 of 27, 81%) revealed an isolated atypical subepithelial deposit in only 1 of 22 (5%) cases. This case also exhibited 'full house' IgA-dominant mesangial immunoprotein deposition (unique among the series of IgA cases), but no staining for complement components or immunoglobulin along the capillary loops or endocapillary proliferation to suggest a post-infectious process.

DISCUSSION

We describe the histopathology, clinical and epidemiological characteristics of HIVICK in a large UK cohort. In keeping with several other recent biopsy series, IC disease has become the most frequent histological diagnosis in individuals living

Table 3. eGFR slopes in HIVICK, IgA nephropathy and HIVAN stratified by HIV viral load status in the first 4 years post-biopsy

Biopsy category by viral load status	*n* (%)	Median (IQR) CD4 at biopsy (cells/μL)	Median (IQR) HIV VL at biopsy (log_{10} copies/mL)	Median (IQR) eGFR at biopsy (mL/min/1.73 m^2)	Progressed to ESKD, *n* (%)	Rate of ESKD (95% CI) per 100 person-years	eGFR slope (95% CI)[a] from biopsy (mL/min/1.73 m^2/year)
HIVICK	41	389 (174–490)	3.3 (1.7–4.8)	74.3 (42.6–109.6)	3 (7.3)	1.5 (0.5, 4.5)	−0.6 (−3.9, 2.7)
Remained viraemic	8	364.5 (150.5–425)	4.5 (3.4–4.9)	67.7 (44.1–100.4)	0 (0)	–	−0.9 (−8.8, 7.6)
Became undetectable	14	382 (100–460)	4.9 (4.7–5.2)	73.5 (49.0–108.6)	0 (0)	–	4.5 (−0.5, 9.5)
Remained undetectable	19	440 (232–690)	1.7 (1.7–1.7)	80.8 (42.5–122.8)	3 (15.8)	4.2 (1.4, 13.2)	−4.2 (−7.7, −0.7)
IgA nephropathy	22	389.5 (310.5–620.5)	1.7 (1.7–1.7)	57.9 (36.8–83.6)	5 (22.7)	5.3 (2.2, 12.8)	−4.8 (−8.0, −1.6)
Remained viraemic	1	178 (178–178)	5.2 (5.2–5.2)	96.4 (96.4–96.4)	1 (100)	–	–
Became undetectable	3	202 (14–390)	5.6 (5.2–6.0)	57.9 (21.1–63.7)	1 (33.3)	4.8 (0.7, 33.7)	–
Remained undetectable	18	395 (321–631)	1.7 (1.7–1.7)	57.7 (43.5–86.1)	3 (16.7)	4.1 (1.3, 12.8)	−4.4 (−8.1, −0.8)
HIVAN	32	104 (40–217)	4.2 (2.7–5.4)	30.1 (18.2–52.3)	9 (28.1)	6.5 (3.4, 14.4)	0.5 (−1.8, 2.7)
Remained viraemic	6	137 (81–217)	4.2 (3.6–5.4)	36.2 (29.7–111.6)	2 (33.3)	10.0 (2.5, 39.9)	–
Became undetectable	18	57 (13–160)	4.6 (4.0–5.5)	31.6 (14.6–55.3)	4 (21.1)	5.1 (1.9, 13.6)	1.3 (−2.3, 4.9)
Remained undetectable	8	217.5 (104.5–353.5)	1.7 (1.7–2.3)	24.5 (16.8–34.9)	3 (37.5)	7.4 (2.4, 22.8)	−4.0 (−9.1, 1.0)

[a]Unable to model slope when $n \leq 6$.

with HIV [1–3]. In contrast to HIVAN, HIVICK was typically diagnosed several years after patients had tested HIV positive and engaged in care. Patients with HIVICK had higher eGFRs, less proteinuria, higher CD4 counts and lower HIV viral loads at the time of biopsy than patients with HIVAN, although none of these clinical markers are sufficiently specific to separate these conditions, meaning that biopsy remains essential for confirmation of the diagnosis. HIV viraemia was associated with the development of HIVICK, although many patients (especially those with a membranous pattern on biopsy) had suppressed plasma HIV RNA levels at the time of kidney biopsy. Patients with HIVICK had more favourable renal outcomes than those diagnosed with either IgA nephropathy or HIVAN, and we provide preliminary evidence that patients with HIVICK may benefit from fully suppressive ART.

Analogous to SLE, the archetypal IC disease, membranous nephropathy, mesangiocapillary glomerulonephritis and ICKD-NOS (including many cases exhibiting mesangial and/or endocapillary proliferation) were considered most likely to reflect the consequences of immune dysregulation and renal injury directly associated with HIV or its treatment. Hence, biopsies displaying these histological patterns were considered together for analysis and designated HIVICK. In contrast, IgA nephropathy was *a priori* considered unlikely to form part of this pathogenetic spectrum, as were cases where concomitant SLE had been diagnosed on clinical and serologic grounds. Review of histology reports substantiated this division: the majority of membranous and mesangiocapillary biopsies exhibited EDDs on EM in additional locations to those expected in primary disease, and atypical morphological features were common, with marked overlap between these pathologies and ICKD-NOS. In contrast, atypical subepithelial deposits were seen in only 5% of IgA cases, mirroring histological appearances in non-HIV-infected individuals with IgA disease [11].

Analysis of factors associated with biopsy-defined renal disease yielded expected associations of HIVAN with black ethnicity and CD4 cell count [12]. Consistent with previous reports, HIVICK was also associated with black ethnicity and HIV viral load [1]. In contrast, IgA nephropathy showed no signal to suggest that this condition was associated with either CD4 cell count or HIV viral load. However, the absence of an association with HIV viraemia may not preclude a pathogenic role of HIV, as HIV infection of kidney allografts [13] and new-onset HIVAN [14] have both been reported in patients with fully suppressed HIV replication. A clear and significant separation of survival curves was observed when comparing HIVICK with IgA nephropathy and HIVAN, with HIVICK having the best, HIVAN the poorest and IgA nephropathy intermediate survival, further supporting the hypothesis that the latter represents a discrete disease entity. While the eGFR and amount of proteinuria at renal diagnosis were similar for patients with HIVICK and IgA nephropathy, HIV control was superior in those with IgA nephropathy (82.6 versus 37.7%). The improved renal outcome with HIVICK may thus relate in part to more patients being able to benefit from fully suppressive ART.

Table 4. Baseline and first follow-up urinary protein after 48 weeks in HIVICK, IgA nephropathy and HIVAN stratified by viral load status

Biopsy category by viral load status	*n* (%)	Proteinuria (g/24 h) at biopsy, median (IQR)	*n* (%)	Proteinuria (g/24 h) after 48 weeks post-biopsy, median (IQR)	P-value for comparison	Proteinuria (% change) after 48 weeks post-biopsy, median (IQR)
HIVICK	41	2.4 (1.4–4.7)	35	0.7 (0.3–2.1)	0.0001	−66.9 (−82.1 to −23.4)
Remained viraemic	8	2.1 (1.0–5.6)	5	0.9 (0.5–2.1)	0.04	−41.2 (−72.5 to −34.1)
Became undetectable	13	2.2 (1.4–3.1)	13	0.7 (0.4–1.8)	0.009	−73.2 (−79.3 to −48.1)
Remained undetectable	19	2.9 (1.0–5.0)	17	0.6 (0.2–2.9)	0.02	−41.4 (−86.8 to −17.8)
IgA nephropathy	21	2.3 (0.9–3.1)	17	1.0 (0.6–2.3)	0.02	−41.5 (−81.1–0.4)
Remained viraemic	–	–	–	–	–	–
Became undetectable	3	6.6 (2.7–15.0)	3	1.5 (0.7–10.1)	0.6	−73.7 (−90.3–52.1)
Remained undetectable	18	2.0 (0.7–2.7)	14	1.0 (0.4–2.3)	0.01	−15.3 (−55.3–0.4)
HIVAN	31	4.1 (2.8–6.4)	25	1.1 (0.7–2.5)	0.0001	−71.5 (−79.5 to −28.5)
Remained viraemic	5	4.0 (2.8–5.3)	3	2.5 (0.9–2.7)	0.3	−11.4 (−55.9–3.1)
Became undetectable	18	4.7 (2.9–7.0)	16	1.1 (0.6–2.3)	0.003	−76.7 (−83.3 to −0.6)
Remained undetectable	8	3.6 (2.7–5.4)	6	0.9 (0.6–1.8)	0.03	−73.0 (−80.2 to −56.5)

The pathogenesis of HIVICK and its relationship to HIV replication is not well understood. Previous studies have demonstrated the presence of viral antigens, including p24 and gp120, in circulating ICs and ICs eluted from renal biopsy tissue in both HIV-associated proliferative nephropathy and IgA nephropathy, potentially implying that active viral replication or viral incorporation into renal tissue may be important in pathogenesis [15, 16]. Conversely, studies in HIV-negative individuals with IgA disease have detected antibodies against a wide range of other antigens within circulating ICs and kidney tissue, including common dietary proteins and ubiquitous bacterial and viral antigens, suggesting that the composition of ICs may simply reflect the nature of the prevailing antigenic milieu [17–19]. A potential benefit of viral suppression in some patients with IC nephropathy is suggested by the observation that histological IC deposition improved or completely resolved in three of five patients who commenced ART [20]. Consistent with this, we observed improvements in eGFR and significant reductions in proteinuria in patients with HIVICK who initiated ART.

The prevalence of co-infections associated with IC nephropathy (e.g. hepatitis B and syphilis with membranous nephropathy; hepatitis C with mesangiocapillary glomerulonephritis) is increased in people with HIV infection. Although no significant association between hepatitis B/C virus infection and HIVICK was observed in our cohort, a HIVICK diagnosis should prompt an exhaustive search for other potential injurious agents and treatment or elimination of these factors where practicable. A role for newer diagnostic tools such as the detection of antibodies to anti-PLA2R or renal tissue immunostaining for the PLA2R antigen to distinguish 'primary' from 'secondary' membranous nephropathy has not yet been established in the context of HIV.

Intercurrent and opportunistic infections are common among HIV-positive patients and may predispose to IC-mediated renal injury through post-infectious glomerulonephritis. While two patients in our cohort showed classical diffuse endocapillary proliferation with subepithelial deposits suggestive of a post-infectious aetiology, neither experienced an overt clinical infection prior to presentation. In HIVICK-NOS, subepithelial deposits were typically sparse and hump-like, similar to the original description of HIVICK in a South African cohort [3]. No such case displayed the C3-dominant pattern of immunostaining that is typical of a persistent or resolving post-infectious glomerulonephritis. While the present study has demonstrated an association between HIV viraemia and development of HIVICK, further mechanistic studies are required to refine this relationship, particularly with respect to the role of other infectious agents. The resemblance of some biopsies to a post-infectious pattern of injury may hypothetically reflect an immune response to HIV antigens *per se*, while occult or overt (opportunistic) infections may also prove contributory. It is also possible that HIV-induced immune dysregulation may account for the observed histological changes, similar to the observation that many HIV-negative patients who develop a persistent post-infectious GN have evidence of dysregulated activation of the alternative complement pathway [21]. These important questions will require a combination of prospective clinico-pathologic, epidemiological and basic science studies to answer.

Attempts to examine disease associations and outcomes in patients with IC disease in retrospective biopsy studies have yielded conflicting results. In a predominantly African American and Hispanic cohort, 27 of 30 of whom had ICKD, time to initiation of renal replacement therapy was not associated with non-detectable HIV RNA or non-exposure to ART [5]. Although the authors argue that immunomodulatory therapies other than ART should thus be considered in non-HIVAN renal disease, the small patient number, heterogeneity of conditions grouped together and the low rates of HIV suppression in this study limit these conclusions.

A small number of ICKD cases (16 of 221 biopsies) were included in a recent South African biopsy series [6]. A small improvement in proteinuria ($n = 6$) and stabilization of eGFR ($n = 8$) were reported among patients with ICKD receiving ART over a period of 3 years, although the confidence intervals were wide and the findings not statistically significant. A larger number of patients with dual HIVAN and ICKD pathology continued to progress rapidly towards ESKD despite ART and a reduction in measured proteinuria [6]. A recent US study of predominantly African American patients, many of whom were injecting drug users, HCV co-infected and in

which a high proportion of biopsies (49% of 83 ICKD cases) were categorized as post-infectious GN, found no difference in the incidence of ESKD between those with or without ART exposure within 30 days of biopsy [1]. The effects of ART on eGFR and proteinuria were not examined. The authors suggested that ART and immune reconstitution may augment humeral immune responses and increase IC formation, potentially making this a deleterious therapeutic strategy, although the small number of patients who progressed to ESKD in this study renders this an insensitive endpoint.

Our cohort has several differences to that of Foy *et al.* [1], notably a larger proportion of non-black ethnicity patients and a lower prevalence of hepatitis C co-infection. An association of HIVICK with HIV viral load and of ART with improved renal function was observed, the former corroborating the findings of Foy *et al.* and adding weight to the theory that active viral replication may be pathogenically linked to IC formation and deposition in the kidney [1]. The absence of an association with IgA nephropathy refines this link and suggests that HIVICK is more likely than IgA nephropathy to be HIV driven.

The present study comprises the largest ICKD cohort in HIV infection to date, analysed the clinical characteristics of the various pathologies that constitute ICKD and used data from >30 000 patients to examine associated risk factors. Despite this, our sample size remains a limitation in generalization of the results. Intra- and intercentre variations in biopsy practice may also have resulted in bias towards more severe kidney disease or to kidney disease unresponsive to ART. While the UK CHIC cohort is broadly representative of the HIV-positive population in the UK, this patient cohort differs considerably from cohorts in parts of the USA and Africa. The retrospective case ascertainment may have resulted in incomplete case acquisition, data collection or follow-up. The high rates of ART use and HIV viral suppression limited the ability to examine the contributing role of these factors to kidney disease progression. Finally, it was not feasible to review original histology slides for all patients; hence, patient classification was based on descriptions from the original reporting histopathologists, and quantitative analysis of biopsy characteristics was limited by potential heterogeneity in reporting. A detailed prospective analysis of morphology and immunostaining of biopsies from patients with ICKD. including a systematic search for atypical features of each subpattern, is clearly required to further our understanding of this disease.

In summary, we describe a group of overlapping morphologic IC patterns designated as HIVICK. HIVICK has lower rates of ESKD on follow-up when compared with IgA nephropathy and HIVAN, and bears an association with HIV viraemia. These findings support a mechanistic role for HIV viral replication in the development of HIVICK. Initiation of ART, in addition to general measures such as blood pressure control and provision of inhibitors of the renin–angiotensin system, was associated with improvement of renal function in patients with HIVICK. We propose that future studies of ICKD in HIV-positive patients subclassify these pathologies and consider HIVICK patterns and IgA nephropathy as separate entities to enhance our understanding of these syndromes.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

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APPENDIX

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