HIV-Immune Complex Kidney Disease: Risk Factors and Progression to End-Stage Kidney Disease

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BACKGROUND

- Effective antiretroviral therapy (cART) and ageing have changed the spectrum of kidney disease in the HIV infected population.
- Immune complex kidney disease (ICKD) has become the dominant pathology in multiple kidney biopsy series of HIV infected individuals.
- The natural history of ICKD and risk factors for ICKD remain poorly studied.

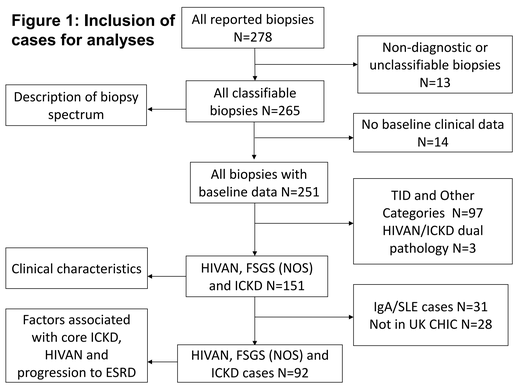
AIMS

- To compare patients with ICKD to those with HIV-associated nephropathy (HIVAN) in the UK CHIC cohort and to describe
  - Factors associated with the development of ICKD and HIVAN
  - Progression to end-stage kidney disease (ESKD) for ICKD and HIVAN

METHODS

- Consecutive kidney biopsies between 1998 and 2012 in HIV infected individuals attending eight clinics in the UK were reviewed by a team of two histopathologists and one nephrologist blinded to clinical outcomes. Where reports were deemed equivocal or insufficient, sections were re-examined or, if unavailable, excluded.
- ICKD was defined by the unequivocal presence of glomerular immunoglobulin deposits and corroborated, where available, by the presence of electron dense deposits on electron microscopy; membranous (MGN), membrano-proliferative (MPGN) and ICKD-not otherwise specified [NOS] displayed considerable overlap in both glomerular morphology and location of deposits and hence were considered together as 'core' ICKD.
- HIVAN was identified if at least two of the three characteristic features were seen: glomerular tuft 'collapse', tubular microcysts, and podocyte proliferation; conventional diagnostic criteria were applied for all other histological lesions.
- Poisson regression was used to identify factors associated with 'core' ICKD and HIVAN / (primary) FSGS (NOS)
- These analyses were restricted to patients in UK CHIC, an observational cohort study including many of the largest HIV centres in the UK www.ctu.mrc.ac.uk/UKCHIC
- Individuals with dual diagnoses of ICKD and HIVAN were excluded from the analyses.
- Kaplan-Meier curves were used to compare progression to ESKD from time of biopsy in different biopsy categories, censored at ESKD or date last seen, whichever came first.

Figure 1: Inclusion of cases for analyses



RESULTS

- Of the 265 diagnostic biopsies, 92 showed ICKD (of which 59 were 'core' ICKD) and 70 HIVAN. Of these, 55 and 65 had clinical data at the time of biopsy for 'core' ICKD and HIVAN respectively (excluding dual diagnoses) and 44 and 48 respectively were in the UK CHIC cohort.

Table 1: Comparison of characteristics of individuals diagnosed with core ICKD and HIVAN/FGSG		'Core' ICKD N=55	HIVAN/FSGS N=65	P value for comparison
Black ethnicity	N (%)	28 (50.9)	64 (98.5)	< 0.0001
Years since HIV diagnosis	Median (IQR)	6.2 (0.6, 11.3)	0.09 (0.02, 1.4)	< 0.0001
Years since start ART	Median (IQR)	0.5 (-0.04, 4.9)	-0.008 (-0.1, 0.5)	0.01
CD4 nadir (cells/µl)	Median (IQR)	212 (96, 329)	63.5 (21.5, 181)	< 0.0001
CD4 at biopsy (cells/µl)	Median (IQR)	389 (162, 489)	126 (40, 268)	< 0.0001
On cART at biopsy	N(%)	32 (58.2)	21 (33.9)	0.008
VL<200 (copies/ml)	N (%)	33 (62.3)	50 (82.0)	0.02
eGFR (ml/min)	Median (IQR)	49.8 (26.6, 91.5)	20.5 (11.3, 33.8)	< 0.0001
Proteinuria (g/24 hrs)	Median (IQR)	2.4 (1.4,5.9)	4.5 (3.1, 7.5)	0.003

CHARACTERISTICS AT BIOPSY OF PATIENTS WITH ICKD AND HIVAN/FSGS

Table 2: Characteristics of individuals with ICKD, HIVAN and FSGS		All ICKD N=86	'Core' ICKD N=55					HIVAN/FSGS N=65	
			MGN N=16	MPGN N=5	ICKD (NOS) N=34	IgA N=26	SLE N=5	HIVAN N=47	FSGS N=18
Age (Years)	Mean (SD)	43.4 (10.3)	47.9 (11.4)	39.6 (8.1)	41.7 (10.7)	43.9 (9.7)	43.8 (8.5)	38.9 (8.9)	42.4 (8.8)
Male gender	N (%)	57 (66.3)	9 (56.3)	5 (100)	23 (67.6)	18 (69.2)	2 (40)	31 (65.9)	9 (50)
Black ethnicity	N (%)	40 (46.5)	8 (50)	0 (0)	20 (58.8)	10 (38.5)	2 (40)	47 (100)	17 (94.4)
HIV risk (IVDU)	N (%)	13 (15.9)	3 (18.8)	1 (20)	6 (17.7)	3 (11.5)	0 (0)	5 (10.9)	2 (11.8)
Hepatitis B sAg positive	N (%)	14 (16.9)	3 (20)	2 (40)	5 (14.71)	4 (16)	0 (0)	6 (13)	0 (0)
Hepatitis C cAb positive	N (%)	7 (8.4)	0 (0)	2 (40)	2 (6.25)	2 (7.7)	1 (25)	1 (2.2)	1 (5.9)
Years since HIV diagnosis	Median (IQR)	6.3(0.9, 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)	8.6 (3.7, 11.5)	0.09 (0.02, 1.2)	0.4 (0.04, 4.8)
Years since start ART	Median (IQR)	1.7(-0.01, 6.6)	1.0 (0.2, 7.6)	1.9 (0.003, 6.4)	0.03 (-0.1, 1.7)	4.2 (2.6, 9.6)	7.2 (3.5, 8.6)	-0.008 (-0.09, 0.2)	-0.09 (-0.4, 1.3)
CD4 nadir (cells/µl)	Median (IQR)	160(84.5, 304)	212(140, 312)	197.5(65, 307)	215 (93, 357)	130 (70, 205)	70 (43, 320)	62 (22, 144)	84 (21, 254)
AIDS at biopsy	N (%)	25 (29.8)	4(25)	2(40)	7(21.1)	11(42.3)	1 (25)	14 (32.6)	6 (40)
CD4 at biopsy (cells/µl)	Median (IQR)	390(220, 510)	436 (357, 564)	346 (122, 389)	369(160, 460)	390 (276, 590)	474.5 (260, 698)	110 (40, 250)	254 (88, 337)
VL<200 (copies/ml)	N (%)	42 (52.5)	9 (64.3)	1 (20)	10 (29.4)	19 (82.6)	3 (75)	7 (15.6)	4 (25)
eGFR (ml/min)	Median (IQR)	50.8 (27.4, 91.5)	85.2 (48.5, 115)	57.6 (29.8, 98.1)	34 (21.2, 79.4)	47.1 (24.8, 70.3)	113.2 (88, 113.2)	16.9 (10.3, 33.3)	25.5 (18.9, 39)
Proteinuria g/24 hrs	Median (IQR)	2.4(1.3, 5)	3.1 (2.2, 11)	6.8 (2.3, 7.6)	2.1 (1.0, 3.6)	2.5 (1.3, 3.6)	1.3(0.9, 4.2)	4.8 (3.4, 8.9)	4.1 (2.3, 6.2)

ASSOCIATIONS BETWEEN DEMOGRAPHIC AND CLINICAL FACTORS IN 'CORE' ICKD' AND HIVAN/FSGS

- In multivariate Poisson regression analyses (**Table 3**) adjusted for baseline ethnicity, HIV exposure risk, sex and age, and time updated hepatitis B and hepatitis C co-infection, CD4 cell count, viral load, cART(yes/no), calendar year and duration of HIV diagnosis(<1 to >10 years); ethnicity and HIV viral load were associated with both 'core' ICKD and HIVAN/FSGS, whereas a low CD4 cell count was only associated with HIVAN/FSGS.

Table 3: Factors associated with core ICKD and HIVAN/FSGS		'Core' ICKD N=44				HIVAN/FSGS N=48			
		Relative risk (RR) (95% CI)	P-value	Adjusted$ RR (95% CI)	P-value	RR (95% CI)	P-value	Adjusted$ RR (95% CI)	P-value
Ethnicity	Black	2.44 (1.35, 4.44)	0.003	2.23 (1.13, 4.40)	0.02	17.37 (6.69, 45.11)	<0.0001	9.94 (3.69, 26.75)	<0.0001
	Other	1		1		1		1	
CD4 cell count (cells/µl)	per 50 cell increase	0.99 (0.92, 1.05)	0.69			0.71 (0.63, 0.81)	<0.0001	0.78 (0.68, 0.88)	0.0001
HIV viral load (copies/ml)	Per log10 increase	1.38 (1.10, 1.74)	0.004	1.48 (1.17, 1.86)	0.0009	1.60 (1.23, 2.09)	0.0005	1.35 (1.02, 1.79)	0.04

PROGRESSION TO ESKD

- Progression to ESKD was similar in HIVAN and FSGS (p=0.41) and MPGN, ICKD (NOS) and membranous (p=0.72) (***Figure 2 a, b***)
- At 1 year post biopsy, 2.3% and 33.3% of individuals with 'core' ICKD and HIVAN respectively had developed ESKD (p=0.02)
- At 5 years post biopsy, 16% and 49.7% of individuals with 'core' ICKD and HIVAN respectively had developed ESKD (p=0.0002)
- The only factor associated with developing ESKD in ICKD in univariate analysis was concurrent diabetes (RR 95% CI 42.4 (7.1, 254) p<0.0001)

Figure 2a: Kaplan-Meier curve showing survival from ESKD for 'core' ICKD: MPGN vs. ICKD (NOS) vs. MGN

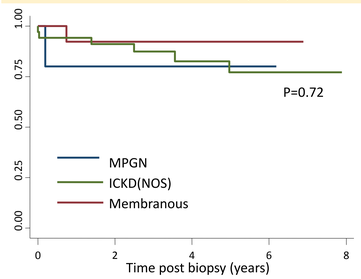


Figure 2b: Kaplan-Meier curve showing survival from ESKD for HIVAN vs. FSGS

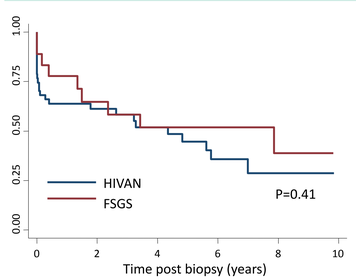
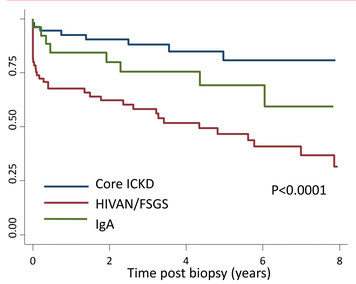


Figure 2c: Kaplan-Meier curve showing survival from ESKD for 'core' ICKD vs. HIVAN/FSGS vs. IgA



DISCUSSION

- MPGN, ICKD (NOS) and MGN ('core' ICKD) appeared to share similar clinical characteristics and outcomes; as did HIVAN and primary FSGS.
- Black ethnicity and viral replication were risk factors for both 'core' ICKD and HIVAN/FSGS.
- Immunodeficiency was associated with HIVAN/FSGS but not ICKD.
- Compared to HIVAN/FSGS, ICKD was associated with less severe kidney disease (using eGFR and proteinuria parameters) and a lower rate of progression to ESKD.
- The observed association with HIV viraemia for both 'core' ICKD and HIVAN may imply a pathogenetic role of HIV replication and associated immune activation; it also suggests that suppressive cART may reduce the risk of developing these types of kidney disease.

ACKNOWLEDGMENTS

UK CHIC Steering Committee Jonathan Ainsworth, Sris Allan, Jane Anderson, Abdel Babiker, David Chadwick, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard (Chair), Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Stephen Kegg, Clifford Leen, Nicola Mackie, Fabiola Martin, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Jillian Pritchard, Frank Post, Caroline Sabin, Memory Sachikonye, Achim Schwenk, Anjum Tariq, John Walsh

Central co-ordination **Research Department of Infection & Population Health, UCL, London** (T Hill, S Huntington, S Jose, A Phillips, C Sabin, A Thornton); **Medical Research Council Clinical Trials Unit (MRC CTU), London** (D Dunn, A Glabay).

Participating centres **Barts and The London NHS Trust, London** (C Orkin, J Lynch, J Hand, C de Souza); **Brighton and Sussex University Hospitals NHS Trust** (M Fisher, N Perry, S Tilbury, D Churchill); **Chelsea and Westminster NHS Trust, London** (B Gazzard, M Nelson, M Waxman, D Asboe, S Mandalia); **Health Protection Agency Centre for Infections London** (V Delpech); **Homerton University Hospital NHS Trust, London** (J Anderson, S Munshi, D Awosika); **King's College Hospital, London** (F Post, C Taylor, L Campbell); **UCL Medical School and The Mortimer Market Centre, London** (R Gilson, N Brima, I Williams); **North Bristol NHS Trust** (M Gompels, S Allen); **North Middlesex University Hospital NHS Trust, London** (A Schwenk, J Ainsworth, C Wood, S Miller); **Royal Free NHS Trust and Department of Infection & Population Health, UCL, London** (M Johnson, M Youle, F Lampe, C Smith, H Grabowska, C Chaloner, D Puradiredja); **Imperial College Healthcare NHS Trust, London** (J Walsh, N Mackie, A Winston, J Weber, F Ramzan); **The Lothian University Hospitals NHS Trust, Edinburgh** (C Leen, A Wilson); **University of Leicester NHS Trust** (A Palfreeman, A Moore, L Fox); **South Tees Hospitals NHS Foundation Trust** (D Chadwick, K Baillie); **Woolwich NHS Trust** (S Kegg, P Main); **Coventry NHS Trust** (S Allan); **St. George's NHS Trust** (P Hay, M Dhillon); **York Teaching Hospital** (F Martin, S Douglas) **Coventry & Warwick NHS Trust** ; **The Royal Wolverhampton NHS Trust** (A Tariq) **Ashford & St.Peter's Hospitals NHS Foundation Trust** (J Pritchard)

UK CHIC is funded by the UK Medical Research Council, references G0900274, G0600337 and qA137932. The views expressed in this poster are those of the researchers and not necessarily those of the Medical Research Council.