CHRONIC KIDNEY DISEASE IN PEOPLE WITH HIV OF AFRICAN ANCESTRY IN THE UK

690

Lisa Hamzah[1], **Rachel Hung**[1], John Booth[2], Rachel Hilton[3], Mark Harber[4], Catherine Cosgrove[5], Sarah Pett[6 7], Fiona M. Burns[4], Amanda Clarke[8], Andrew Ustianowski[9], Beatriz Santana-Suarez[1], Julie Fox[3], Jane Minton[10], Elizabeth Binns-Roemer[11], Cheryl Winkler[11], Caroline Sabin[7], Frank Post[1], for the GEN-AFRICA study team

[1]King's College Hospital, London, UK, [2]Barts Health NHS Trust, London, UK, [3]Guy's and St Thomas' NHS Foundation Trust, London, UK, [4]Royal Free Hospital, London, UK, [5]St. George's University of London, London, UK, [6]Mortimer Market Centre, Central and Northwest NHS foundation Trust, [7] University College London, London, UK, [8]Brighton & Sussex University Hospitals NHS Trust, Brighton, UK, [9]Manchester Royal Infirmary, Manchester, UK, [10] Leeds Hospital NHS Trust, Leeds, UK [11]Frederick National Laboratory for Cancer Research, Frederick, MD, USA

Background

In people of African ancestry

- Chronic kidney disease (CKD) is a leading cause of morbidity and mortality, and CKD is more likely to progress to end stage kidney disease (ESKD) as compared to Caucasians (1).
- Infection with Human Immunodeficiency Virus (HIV) further increases the risk of ESKD (2).
- Two apolipoprotein L1 (APOL1) risk alleles are associated with HIV-associated nephropathy (HIVAN), focal/segmental glomerulosclerosis (FSGS) and hypertensive kidney disease (3).
- APOL1 risk alleles are not uniformly distributed across African populations; up to 61% of people in Nigeria vs. 9% in Kenya carry at least 1 risk variant (4).

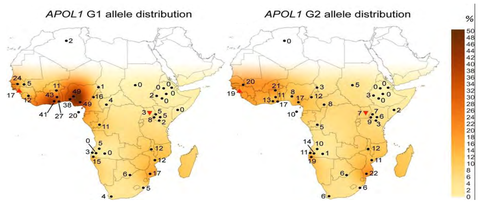


Figure 1 : Prevalence of APOL1 risk alleles (5)

Aims

To explore the odds of ESKD and CKD in people living with HIV in the UK by region of African ancestry (as a proxy of APOL1 distribution), adjusting for potential confounders.

Methods

Study design and data source

- Cross sectional study of adults receiving routine care at HIV or dialysis/transplantation clinics across 16 UK hospitals.
- Individuals of African ancestry with HIV were approached with targeted recruitment of those with ESKD.
- Analyses were restricted to participants with both parents born in the same region (East/Southern/West Africa/Caribbean).

Exposures, outcomes and covariates

Exposure	Region of ancestry, i.e. East, Southern, West Africa or Caribbean
Primary Outcome	ESKD, defined as an eGFR <15 (CKD-EPI) or receiving permanent renal replacement therapy (RRT)
Secondary Outcomes	CKD (eGFR<60), proteinuria (uPCR >15mg/mmol in those without ESKD)

Variables:

Renal Risk Factors	Hypertension (clinical diagnosis and treatment, or blood pressure >140/>90), diabetes mellitus, and cardiovascular disease (CVD; composite of myocardial infarction, heart failure, coronary artery disease, other heart disease, stroke, peripheral vascular disease)
Participant demographics	Age, gender, sexual orientation
HIV measures	Prior AIDS, CD4 count, viral load
Co-infections	Hepatitis B (surface antigen +), hepatitis C (antibody +), tuberculosis (TB; clinical diagnosis)
Lifestyle factors	Obesity (Body Mass Index (BMI)>30), smoking

Analysis

We performed logistic regression analysis to identify factors associated with ESKD, CKD, and proteinuria.

All variables significant in univariate analysis (p<0.1) were considered for inclusion in multivariable analysis.

Results

A total of 1904 participants were included: 408 from East Africa, 565 from Southern Africa, 658 from West Africa and 273 from the Caribbean. While demographic and HIV characteristics differed by region, the prevalence of hypertension, diabetes mellitus and cardiovascular disease was similar.

Table 1 : Baseline demographics and variables according to region

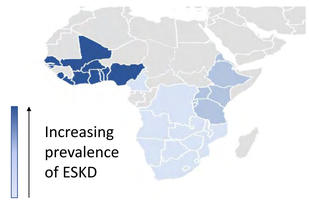
		All regions N=1904	East (EE) N=408	South (SS) N=565	West (WW) N=658	Caribbean (CC) N=273	P value
Age	Mean (SD)	48.4 (9.8)	48.8 (9.6)	48.5 (9.8)	47.3 (9.6)	50.4 (10.4)	<0.001
Gender							
Female	N (%)	1088 (57.1)	257 (63.9)	364 (66.6)	342 (52.9)	97 (35.9)	<0.001
Male	N (%)	816 (42.9)	146 (35.8)	188 (33.3)	307 (46.7)	175 (64.1)	
Time since HIV diagnosis (months)	Mean (SD)	13.2 (6.4)	15.9 (7.2)	14.2 (5.6)	10.8 (5.5)	12.9 (6.7)	<0.001
Time since ART start (months)	Mean (SD)	10.9 (5.8)	12.8 (6.4)	11.7 (5.5)	9.3 (5.1)	10.1 (5.7)	<0.001
Prior AIDS	N (%)	220 (12.0)	57 (14.5)	58 (10.8)	78 (12.3)	27 (10.3)	0.3
Prior TB	N (%)	242 (13.5)	71 (18.5)	102 (18.9)	55 (9.1)	13 (5.1)	<0.001
CD4 nadir, cells/mm^3	Median (IQR)	196 (76, 328)	180 (78, 317)	190 (73, 314)	190 (73, 332)	241 (91, 362)	0.06
CD4 current, cells/mm^3	Median (IQR)	552 (399, 721)	533.5 (381, 720)	580 (413, 750)	529.5 (391, 703)	580 (423, 756)	0.002
HIV RNA <50	N (%)	1487 (78.5)	319 (77.4)	455 (80.8)	512 (78.4)	201 (73.9)	0.2
Hepatitis B	N (%)	139 (7.6)	29 (7.4)	40 (7.3)	62 (9.9)	8 (3.1)	0.007
Hepatitis C	N (%)	29 (1.6)	4 (1.0)	8 (1.5)	9 (1.5)	8 (3.1)	0.3
Hypertension	N (%)	839 (44.4)	174 (43.1)	243 (43.1)	310 (47.3)	112 (41.8)	0.3
Diabetes	N (%)	191 (10.2)	45 (11.1)	51 (9.1)	67 (10.3)	28 (10.5)	0.8
CVD	N (%)	81 (4.3)	18 (4.4)	20 (3.6)	25 (3.9)	18 (6.7)	0.2
BMI >30, kg/m^2	N (%)	749 (40.6)	144 (36.9)	265 (48.7)	258 (40.3)	82 (30.2)	<0.001

Prevalence of Kidney Disease

People of West African ancestry had the highest prevalence of ESKD and CKD. There were no differences in prevalence of proteinuria between the different regions.

Table 2 : Prevalence (N [%]) of kidney disease according to region of ancestry

	All regions	East Africa	Southern Africa	West Africa	Caribbean	P value
ESKD	**78 (4.2)**	**13 (3.2)**	**13 [2.3]**	**42 [6.4]**	**12 [4.4]**	**0.001**
CKD	**169 (8.9)**	**26 [6.4]**	**38 [6.7]**	**75 [11.4]**	**30 [11.0]**	**0.004**
Proteinuria	392 (21.4)	88 [22.3]	111 [20.6]	133 [20.9]	60 [22.6]	0.9



End Stage Kidney Disease

Factors associated with ESKD included West African ancestry, CD4 (current and nadir), hypertension, cardiovascular disease and BMI>30. The association of ESKD with West African ancestry remained after adjustment for potential confounders.

Table 3: Crude and adjusted odd ratios for ESKD

		OR [95%CI]	P value	aOR [95%CI]	P value
Age (per 5 year increment)		1.09 [0.97, 1.22]	0.16		
Gender		1.43 [0.90, 2.24]	0.12	0.77 [0.43, 1.38]	0.38
Region of Ancestry	**East Africa**	1			
	Southern Africa	0.67 [0.31, 1.48]	0.4	1.02 [0.42, 2.48]	0.96
	West Africa	2.07 [1.09, 3.92]	0.02	2.45 [1.19, 5.08]	0.02
	Caribbean	1.38 [0.62, 3.08]	0.4	2.18 [0.90, 5.30]	0.09
HIV parameters	**AIDS**	1.20 [0.61, 2.32]	0.6		
	CD4 nadir, cells/mm^3 *	0.89 [0.84, 0.94]	<0.001	0.94 [0.86, 1.04]	0.22
	CD4 current, cells/mm^3 *	0.89 [0.85, 0.92]	<0.001	0.87 [0.81, 0.93]	<0.001
	HIV RNA <50, copies/ml	0.82 [0.48, 1.39]	0.4		
Co-infections	**Hepatitis B**	1.77 [0.89, 3.50]	0.1		
	Hepatitis C	2.54 [0.76, 4.57]	0.08	2.42 [0.69, 8.55]	0.17
Renal risk factors	**Hypertension**	16.37 [6.96, 38.52]	<0.001	15.37 [7.23, 32.66]	<0.001
	Diabetes	3.05 [1.77, 5.35]	<0.001	1.60 [0.81, 3.15]	0.18
	Cardiovascular disease	5.63 [3.12, 10.15]	<0.001	3.42 [1.57, 7.46]	0.002
	BMI >30, kg/m^2	0.57 [0.34, 0.95]	0.03	0.37 [0.20, 0.70]	0.002

* per 50 cell increment

Chronic Kidney Disease

West African ancestry, CD4 (nadir and current), hepatitis C co-infection, hypertension, diabetes and CVD, but not age or gender, were associated with CKD.

Table 4 : Crude and adjusted odds ratios for CKD

	OR (95%CI)	P value	aOR (95%CI)	P value
Age (5 year increase)	1.34 [1.25, 1.44]	<0.0001	1.06 [0.49, 1.20]	0.8
Gender	1.77 [1.25, 2.39]	0.0004	1.14 [0.77, 1.69]	0.7
Region of Ancestry				
East Africa	1		1	
Southern Africa	1.00 [0.60, 1.67]	0.8	1.32 [0.71, 2.43]	0.38
West Africa	1.89 [1.18, 3.01]	0.006	1.87 [1.09, 3.32]	0.02
Caribbean	1.86 [1.08, 3.22]	0.03	1.91 [0.90, 3.82]	0.08
HIV parameters				
AIDS	2.20 [1.51, 3.34]	<0.001	1.31 [0.81, 2.24]	0.3
CD4 nadir*	0.88 [0.84, 0.92]	<0.001	0.91 [0.84, 0.98]	0.01
CD4 current*	0.93 [0.89, 0.95]	<0.001	0.94 [0.90, 1.03]	<0.001
Co-infections				
Hepatitis B	1.21 [0.72, 2.14]	0.5		
Hepatitis C	2.30 [0.90, 6.04]	0.09	3.44 [1.49, 7.95]	0.004
Renal risk factors				
Hypertension	12.31 [7.32, 20.69]	<0.001	13.81 [7.61, 25.13]	<0.001
Diabetes	3.84 [2.60, 5.68]	<0.001	1.98 [1.17, 3.35]	0.01
Cardiovascular disease	4.99 [2.98, 8.34]	<0.001	2.67 [1.40, 5.12]	0.003

*cells/mm^3 (per 50 cell increment)

Proteinuria

HIV parameters, co-infection status and region of ancestry were not associated with proteinuria (p>0.1); age (aOR 1.12 [1.00, 1.24], p=0.01) hypertension (aOR 1.81 [1.42, 2.44], p<0.001) and diabetes (aOR 2.04 [1.41, 3.00], p <0.001) were the only factors associated with proteinuria.

Discussion

- People with HIV of West African ancestry were at greater risk of ESKD and CKD.
- The prevalence of ESKD and CKD is broadly in line with the known distribution of the APOL1 risk variants which are highly prevalent in West Africa.
- Limitations of our study include the cross sectional study design with ascertainment of kidney function at one timepoint and potential for unmeasured confounding.
- APOL1 genotyping of this cohort is planned and will provide important insights into the relationship between APOL1 risk variants and CKD/ESKD in people of African ancestry with HIV.

Conclusion

- The prevalence of ESKD and CKD, but not proteinuria, varied significantly among black people with HIV from across Africa and was not explained by traditional CKD risk factors.
- The highest rate of ESKD was observed among West Africans, highlighting the need for increased renal vigilance in people from this region.

References

(1) van den Beukel TO, de Goeij MC, Dekker FW, Siegert CE, Halbesma N; PREPARE Study Group. Differences in progression to ESRD between black and white patients receiving predialysis care in a universal health care system. Clin J Am Soc Nephrol. 2013 Sep;8(9):1540-7.
(2) Abraham AG, Althoff KN, Jing Y, et al. End-stage renal disease among HIV-infected adults in North America. *Clin Infect Dis*. 2015;60(6):941–949.
(3) Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*. 2011;22(11):2129–2137.
(4) Siemens TA, Riella MC, Moraes TP, Riella CV. APOL1 risk variants and kidney disease: what we know so far. *J Bras Nefrol*. 2018;40(4):388–402.
(5) Cooper, A., Ilboudo, H., Alibu, V.P., Ravel, S., Enyaru, J.C., Weir, W., Noyes, H., Capewell, P., Camara, M., Milet, J., Jamonneau, V., Camara, O., Matovu, E., Bucheton, B., & MacLeod, A. APOL1 renal risk variants have contrasting resistance and susceptibility associations with African trypanosomiasis. *eLife* 2017; 6: e25461.

The GEN-AFRICA study received support from the Medical Research Council (UK) [through the KHP R&D Challenge Fund] and the NIHR clinical research network