APOL1 Genotype and Graft Function in South African HIV+ to HIV+ Kidney Transplant Recipients

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BACKGROUND

APOL1 renal risk variants (RRV) (G1: S342G and I384M; and G2: del N388 and Y389) significantly contribute to genetic risk of chronic kidney disease[1], particularly in people with HIV (PWH), where penetrance is highest. The effects of *APOL1* on kidney transplant outcomes in PWH has not been fully assessed.

OBJECTIVE

To determine whether *APOL1* RRV present in donors or recipients are associated with allograft outcomes in kidney transplant recipients living with HIV.

METHODS

- Genomic DNA was extracted from peripheral blood mononuclear cells from deceased HIV positive kidney donors and HIV positive transplant recipients enrolled in the HIV$^+$-to-HIV$^+$ transplant study in Cape Town, South Africa.[2]
- *APOL1* genotypes were determined by TaqMan probe assays (ThermoFisher, Waltham, MA) specific for *APOL1* G1 SNPs (rs73885319 and rs60910145) and the G2 deletion (rs717185313).
- Outcome was defined as a composite endpoint of death, graft failure, biopsy-proven rejection or development of HIV associated nephropathy (HIVAN) and were compared by donor *APOL1* RRV status (0 versus 1 risk allele).

RESULTS

- **Baseline characteristics are shown in table 1**. Genomic DNA was available for 21 donors and 43 recipients; 38 recipients had donor *APOL1* typing available of whom 12 (31.6%) received kidneys from donors with one risk allele. Median follow-up time from transplantation to first outcome was 3.58 (IQR 0.86-6.99) years.
- Recipients were evenly split between male (51%) and female (49%), and the majority were Black African (91%).
- Donors were significantly younger (median age 31 years) primarily male (76%), with greater ethnic diversity compared to recipients (57% Black African, 33% Mixed ethnicity, 10% White).
- **Seven (33%) donors had 1 *APOL1* RRV.**
- **Recipients had higher rates of *APOL1* RRV: 40% (n=17) had two RRV and 12% (n=5) had one RRV**.
- 88% (n=15/17) of recipients with two *APOL1* variants had HIVAN as the cause of their native kidney failure.

In a cohort of HIV+ to HIV+ kidney transplantation, outcomes were inferior in those who received kidneys from donors with one versus zero *APOL1* risk allele

- **Poorer outcomes and lower composite survival was significantly higher in recipients with *donors* who had one versus zero *APOL1* risk allele [aHR 2.9 (95% CI 1.1 – 7.4), Figure 1 and Figure 2].**
- **The composite outcome was not associated with *recipient APOL1* status [8/15, (53%) in those with 2 risk alleles versus 10/23, (43%) in those with 0/1 risk allele, p=0.55].**

Table 1: HIV-positive kidney transplant recipient and donor characteristics

	HIV+ to HIV+ Transplant Cohort		
	Kidney donors N=21	Recipients with HIV N=43	p-value
Demographic variables			
Age, yr, median (IQR)	31 (26-40)	37 (33-48)	0.006
HIV Positive	21 (100)	43 (100)	
Race, no. (%):			0.004
Black or African American	12 (57)	39 (91)	
Other	7 (33)	4 (9)	
White	2(10)	0 (0)	
Male sex, no. (%)	16 (76)	22 (51)	0.064
CD4, median (IQR)	257 (33-805)	447 (303-578)	0.140
***APOL1* Risk alleles (RA)**			
RA group, no. (%)			<0.001
0	14 (77)	21/43 (49)	
1	7 (33)	5/43 (12)	
2	0 (0)	17/43 (39)	
***APOL1* Haplotypes**			
WT/WT	14 (67)	21 (49%)	
WT/G1	4 (19)	4 (9%)	
WT/G2	3 (14)	1 (2%)	
G1/G1	0 (0)	7 (16)	
G1/G2	0 (0)	10 (23)	
G2/G2	0 (0)	0 (0)	

WT = wild-type *APOL1* allele; G1 and G2 = *APOL1* renal risk variants

Figure 1: Kaplan-Meier curves comparing time to first outcome of a composite endpoint (death, graft failure, HIVAN or biopsy-proven rejection) by donor *APOL1* risk variant status (0 versus 1 allele)

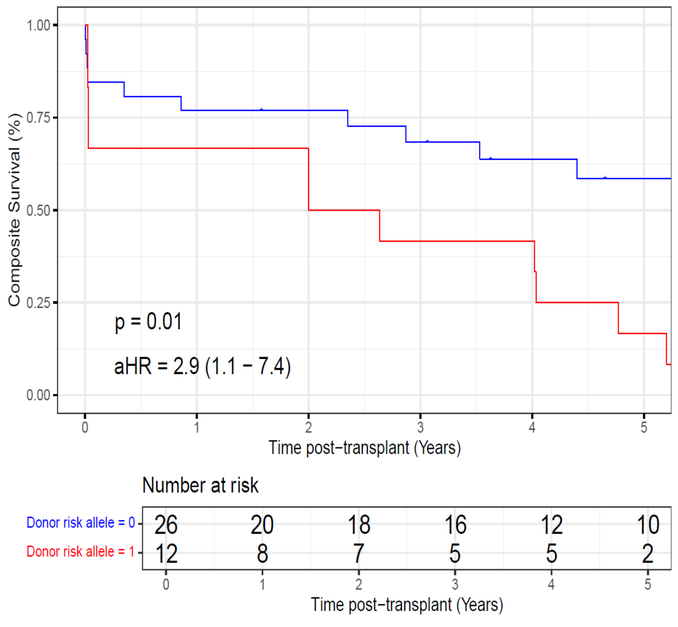
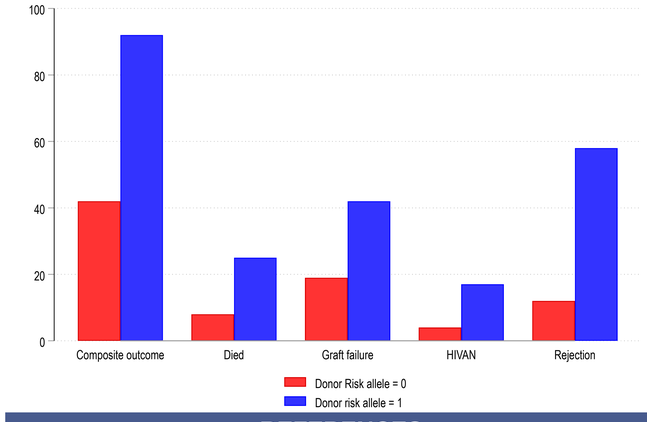


Figure 2: Death and poor kidney allograft outcomes compared by donor *APOL1* RRV status (0 versus 1 allele)



CONCLUSIONS

- **Dual *APOL1* RRV status with native kidney HIVAN was frequently observed in South African PWH undergoing kidney transplantation.**
- **Recipient *APOL1* genotype was not associated with allograft outcomes.**
- **The incidence of death and poorer kidney allograft outcomes were higher in those who received kidneys from donors with HIV and one *APOL1* RRV.**
- **The mechanisms for this remain unclear, although it is possible that toxic expression of APOL1 in the allograft is enhanced in kidney transplant recipients who also have HIV and by the transplant process itself, even were only one RRV is present.**

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