

D:A:D

Nature of Immunosuppression and Risk of Chronic Kidney Disease in HIV-positive Persons

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BACKGROUND

- It is well documented that HIV-positive persons are at increased risk of chronic kidney disease (CKD) compared to the general HIV-negative population [1-2]
- Likewise, immunosuppression has, in several studies, been independently associated with CKD [3-7] with a relatively low CKD prevalence in HIV-positive persons with preserved immune function [8]
- As the exact nature of the association between immunosuppression and CKD is unknown, the objectives of this analysis was to investigate the association between various measures of impaired immune function and CKD in the settings of a large heterogeneous cohort

METHODS

- D:A:D study participants without CKD and with ≥ 2 Cockcroft Gault (estimated glomerular filtration rate) eGFR measurements after 01-Jan-2004 (baseline) were followed until the earliest of a CKD diagnosis (eGFR ≤ 60 , confirmed ≥ 3 months apart), last eGFR plus 6 months or 01-Feb-2014
- Measures of immunosuppression included baseline, current and nadir CD4 count, 6-months' time-lagged CD4 count, % of follow-up time (%FU) with CD4 count ≤ 200 , time-averaged AUC for CD4 count and CD4 count recovery (baseline CD4 count ≤ 200 followed by a current CD4 count > 200)
- Poisson regression models were used to determine the relationship between CKD and each measure of immunosuppression (in separate models) accounting for relevant confounders including demographics, viral hepatitis status, hypertension, diabetes, antiretroviral treatment (ART) and other HIV-related factors
- Akaike Information Criteria (AIC) was used to indicate which measures of immunosuppression were better CKD predictors
- The strongest immunosuppression CKD predictor was tested for interactions with the D:A:D CKD risk score, demographics, ART and HIV-related factors

RESULTS

- Of the 33,144 persons included in analyses 1,588 developed CKD (incidence rate, IR, 7.2 [95%CI 6.8-7.5]/1000 PYFU) during a median 7.2 years FU (IQR 5.0-8.9), **Figure 1**

References

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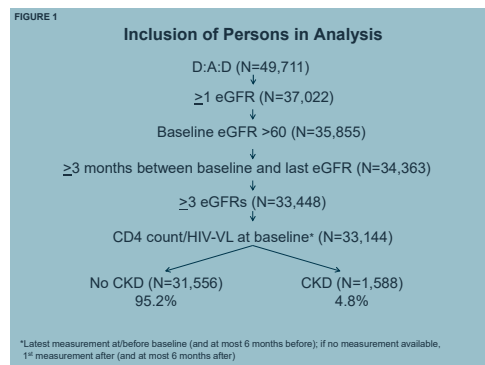
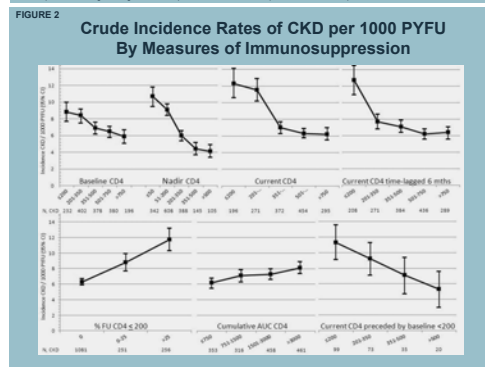


TABLE 1 Baseline Characteristics

	All	CKD
All	N=33144	N=1588
Gender	Male 24510 (74.0)	Male 1201 (75.6)
Race	White 15770 (47.6)	White 855 (53.8)
HIV acquisition risk	MSM 15318 (46.2)	MSM 732 (46.1)
IDU 4186 (12.6)	IDU 231 (14.6)	
Heterosexual 11656 (35.2)	Heterosexual 5058 (31.8)	
Other 1982 (6.0)	Other 120 (7.6)	
HBV	Positive 150 (0.4)	Positive 75 (4.7)
HCV	Positive 5947 (17.9)	Positive 350 (22.0)
ART	Not on 7919 (23.9)	Not on 180 (11.3)
Smoking status	Current 13706 (41.4)	Current 597 (37.6)
CVD family history	2538 (7.7)	163 (10.3)
Hypertension	2845 (8.6)	278 (17.5)
Prior CVD	201 (0.6)	31 (2.0)
AIDS	8015 (24.2)	567 (35.7)
Diabetes	1206 (3.6)	170 (10.7)
HIV-VL < 400 copies/mL	19448 (58.7)	1105 (69.8)
Age	Median 41, IQR 35-47	Median 54, IQR 46-61
CD4 count	mm ³ 440 (292-626)	413 (269-592)
Nadir CD4 count	mm ³ 229 (108-354)	160 (65-270)
eGFR	mL/min/1.73m ² 102 (88-118)	75 (67-85)

Baseline: first eGFR measured during prospective follow-up after 1/1/2004. CVD: cardiovascular disease, MSM: men that have sex with men, HBV: positive, HCV: positive, IDU: injection drug use, HIV-VL: HIV viral load, ART: antiretroviral treatment, AIDS: acquired immunodeficiency syndrome, HIV-VL < 400: undetectable viral load.



- Those included in analysis were predominately white (47.6%), male (74.0%) with a baseline median age of 41 years (IQR 35-47) and median CD4 count of 440 (292-626), **Table 1**
- Although the crude IR of CKD varied for different measures of immunosuppression, the rate was consistently higher with more advanced immunosuppression, **Figure 2**
- Univariately, all measures of immunosuppression were significantly associated with CKD most strongly for nadir CD4 (count > 500 vs. ≤ 50 , IR 0.39 [0.31-0.48]) and %FU CD4 count ≤ 200 ($> 25\%$ vs. 0%, 1.86 [1.62-2.13])
- Multivariately, the strongest CKD predictor was %FU CD4 count ≤ 200 ($> 25\%$ vs. 0%, 1.28 [1.10-1.48]), **Table 2**
- There was a significant ($p < 0.0001$) interaction between %FU CD4 count ≤ 200 and the D:A:D CKD risk score. Those at the lowest estimated CKD risk had a significantly higher CKD IR ($> 25\%$ vs. 0%, 3.57 [2.23-5.70]) compared to those at the highest estimated CKD risk ($> 25\%$ vs. 0%, 1.24 [1.05-1.46]), **Figure 3**
- There was no significant interaction between ethnicity, age, HIV-RNA, ART status or use of nephrotoxic antiretrovirals including tenofovir, atazanavir/r, indinavir and lopinavir/r and measures of immunosuppression for development of CKD

LIMITATIONS

- The analysis was limited by the lack of data on proteinuria, and a relatively low proportion of individuals with confirmed Black African ethnicity

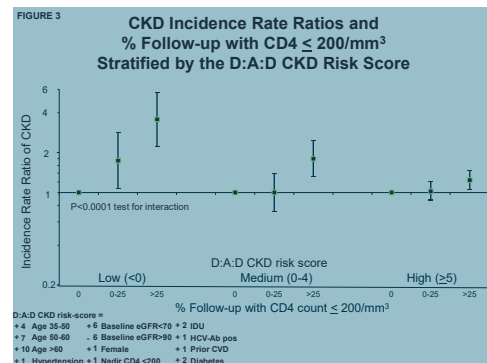
CONCLUSIONS

- The strongest association between CKD and immunosuppression was observed for the relative duration of severe immunosuppression
- Immunosuppression was of greatest relative importance as a CKD predictor in persons at low estimated CKD risk, whereas more traditional renal risk factors dominated at higher levels of CKD risk
- On-going analyses are investigating the association between various measure of HIV-viremia and CKD
- These observations support aggressive ART to maintain or restore immune function and thereby reduce the immunosuppression associated increased risk of CKD

TABLE 2 Multivariate Relationship Between Immunosuppression Measures and CKD

		aIRR	95% CI	P	AIC
Baseline	≤ 200	0.94	0.77 - 1.15	0.55	25156
	201-350	1.00	0.84 - 1.19	0.99	
	351-500	0.94	0.78 - 1.12	0.46	
	501-750	0.95	0.79 - 1.13	0.53	
	> 750	1.00	-	-	
Nadir	≤ 50	0.85	0.67 - 1.07	0.17	25149
	51-200	0.80	0.64 - 0.99	0.044	
	201-350	0.75	0.60 - 0.93	0.010	
	351-500	0.77	0.60 - 1.00	0.047	
	> 500	1.00	-	-	
Latest	≤ 200	1.04	0.86 - 1.26	0.66	25153
	201-350	0.90	0.75 - 1.06	0.21	
	351-500	0.91	0.78 - 1.07	0.24	
	501-750	0.91	0.78 - 1.06	0.21	
	> 750	1.00	-	-	
Latest lagged 6 months	≤ 200	1.00	0.91 - 1.13	0.33	25147
	201-350	0.84	0.71 - 1.00	0.056	
	351-500	0.92	0.78 - 1.08	0.29	
	501-750	0.87	0.75 - 1.01	0.073	
	> 750	1.00	-	-	
%FU ≤ 200	≤ 25	1.28	1.10 - 1.48	0.0011	25143
	26-25	1.07	0.93 - 1.24	0.34	
	0	1.00	-	-	
	> 750	0.92	0.81 - 1.05	0.23	
	761-1500	0.84	0.68 - 1.03	0.43	
AUC	1501-3000	0.82	0.70 - 0.97	0.019	25148
	> 3000	1.00	-	-	
	1001-1500	0.82	0.70 - 0.97	0.019	
	501-1000	0.82	0.70 - 0.97	0.019	
	> 3000	1.00	-	-	

¹Lower AIC indicates a better model/multivariable predictor



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