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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**
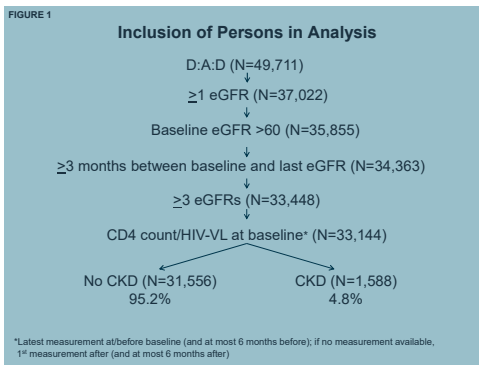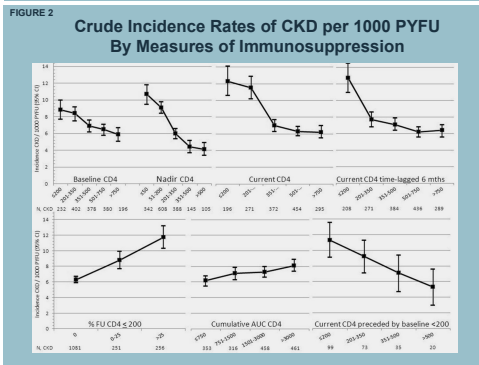

FIGURE 1
Inclusion of Persons in Analysis

D:A:D (N=49,711)
>1 eGFR (N=37,022)
Baseline eGFR >60 (N=35,855)
>3 months between baseline and last eGFR (N=34,363)
>3 eGFRs (N=33,448)
CD4 count/HIV-VL at baseline* (N=33,144)

No CKD (N=31,556) 95.2%   CKD (N=1,588) 4.8%

*Latest measurement at/before baseline (and at most 6 months before); if no measurement available, 1st measurement after (and at most 6 months after)

TABLE 1

Baseline Characteristics

		All N	All %	CKD N	CKD %
All		33144	100	1588	4.8
Gender	Male	24510	74.0	1201	75.6
Race	White	15770	47.6	855	53.8
HIV acquisition risk	MSM	15318	4.2	732	46.1
	IDU	4188	12.6	231	14.6
	Heterosexual	11656	35.2	5058	31.8
	Other	1982	6.0	120	7.6
HBV	Positive	150	4.6	75	4.7
HCV	Positive	5947	17.9	350	22.0
ART	Naïve	7919	23.9	180	11.3
	Current	13706	41.4	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	69.6

		Median	IQR	Median	IQR
Age	Years	41	35-47	54	46-61
CD4 count	/mm³	440	292-626	350	269-592
Nadir CD4 count	/mm³	229	108-364	160	65-270
eGFR	mL/min./1.73m²	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: HBS-Ag, HBe-Ag or HBV-DNA positive, HCV-Positive: seropositive and HCV-RNA positive or HCV-RNA unknown/not tested

FIGURE 2
Crude Incidence Rates of CKD per 1000 PYFU By Measures of Immunosuppression

- 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
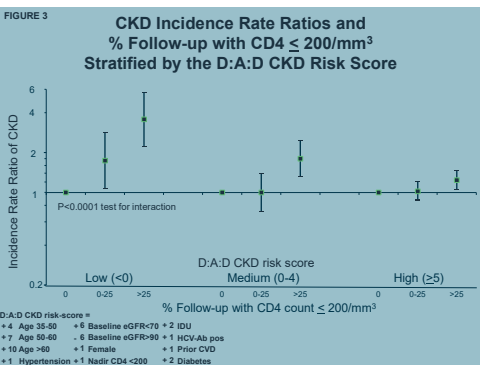
CONCLUSIONS

- 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

FIGURE 3
CKD Incidence Rate Ratios and % Follow-up with CD4 < 200/mm³ Stratified by the D:A:D CKD Risk Score

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