JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000003002

"Validation of the D:A:D Chronic Kidney Disease Risk Score Incorporating Proteinuria in People Living with HIV in Harare, Zimbabwe"

Matthew A. Anderson[1], Cleophas Chimbetete[2], Tinei Shamu[2,3,4], Rumbizai Dahwa[2,5], David M Gracey[1,6]

[1]Department of Renal Medicine and Renal Transplant, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, New South Wales, Australia

[2]Newlands Clinic, Harare, Zimbabwe

[3]Institute of Social and Preventive Medicine, University of Bern, Switzerland

[4]Graduate School of Health Sciences, University of Bern, Switzerland

[5]Department of Medicine, University of Zimbabwe College of Health Sciences, Harare, Zimbabwe

[6]Central Clinical School, Faculty of Medicine, University of Sydney, Camperdown, New South Wales Australia

Conflict of Interest and Source of Funding: None of the authors declare a conflict of interest. None of the authors received grants or funding related to publication of this work.

Corresponding Author: Matthew Allan Anderson, BMed MMed Royal Prince Alfred Hospital Camperdown, NSW AUSTRALIA

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Word Count: 1997 words (abstract 249 words)

Abstract

Objective: We sought to validate the D:A:D risk score for chronic kidney disease (CKD) in people living with HIV (PLWH) in a cohort from Harare, Zimbabwe. Additionally, we aimed to evaluate proteinuria as a predictive variable in the risk score model, being the first study to do so.

Design: Data from PLWH attending a clinic in Harare was evaluated. Those with a baseline estimated glomerular filtration rate >60ml/min/1.73m^2 and at least two subsequent eGFR measurements were included. A modified version of the D:A:D risk score model was applied to categorise participants as 'low', 'medium' and 'high-risk' of progression to CKD. Potential predictors of renal impairment were assessed by logistic regression in univariate and multivariate models. Proteinuria was evaluated in a nested model using D:A:D risk categories.

Results: 2793 participants were included. 40 participants (1.4% of the cohort) progressed to CKD during the median follow-up time of 4.2 years. Progression rates were 1%, 3% and 12% in the low, medium, and high-risk groups respectively. Proteinuria data was available for 2251 participants. Presence of proteinuria was strongly associated with progression to CKD [OR 7.8, 95% CI 3.9-15.7], and its inclusion in the risk score improved the discrimination of the model with the c-statistic increasing from 0.658 to 0.853).

Conclusion: A modified version of the D:A:D CKD risk score performed well in predicting CKD events among this Sub-Saharan African cohort of people living with HIV. Inclusion of proteinuria into the risk score model significantly improved predictability.

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Key Words: HIV/AIDS, Chronic Kidney Disease, Proteinuria, Risk Prediction Tools, Sub-Saharan Africa

Background

The global burden of HIV is disproportionately concentrated in Sub-Saharan Africa, which is home to more than two-thirds of the world's population of people living with HIV (PLWH) [(1)]. The widespread implementation of anti-retroviral therapy has seen the major challenge of HIV shift from AIDS-related mortality [(2)] to the management of chronic non-communicable diseases [(2)], including chronic kidney disease [(3) (4) (5)]. CKD can arise as a direct consequence of the HIV virus (as in HIV-associated nephropathy), as a complication of anti-retroviral therapy, or secondary to other associated comorbidities including hypertension and diabetes [(6) (7)].

The prevalence of CKD in Sub-Saharan Africa is estimated at 10-15% and is rising[(8) (9)]. The consequences of this trajectory include increasing cardiovascular morbidity and mortality and greater demand for expensive renal-replacement therapy. Sub-Saharan Africa is ill-equipped to deal with this demand, being one of the most resource-poor regions of the world, with the lowest health-care spending per-capita globally [(10)]. It is thus imperative to identify the subgroup of PLWH at highest risk of developing CKD, so that resource allocation and prevention strategies can be efficiently targeted.

Mocroft *et al* [(11)] used data from the D:A:D study group to develop a score to predict the risk of developing CKD in PLWH. The score has primarily been validated in cohorts from high-income countries[(12-15)] with only one study to date evaluating it in an African population[(15)].

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Despite being a known risk factor for CKD, none of the validation studies have been able to assess the predictivity of proteinuria in their models.

In this paper, we sought to contribute to the body of evidence validating the D:A:D risk score in the Sub-Saharan African population. We also aimed to be the first to evaluate the predictivity of proteinuria when incorporated into the risk score.

Methods

Source of Data

A retrospective analysis was conducted using patient data from the Newlands Clinic in Harare, Zimbabwe. The clinic is an NGO run by the Ruedi Lüthy Foundation which provides primary care to financially disadvantaged individuals in the suburbs of Harare. Data was extracted from the electronic medical records (eMR) for eligible adults who attended the clinic between 1 January 2010 and 31 January 2019.

Eligibility

The study population included adult participants (>18 years) with a known diagnosis of HIV who were anti-retroviral (ARV) naïve and had a baseline eGFR >60ml/min/1.73m^2.
Participants with fewer than three eGFR measurements (including baseline) or with follow up shorter than 3 months were excluded.

Outcome

Progression to CKD was defined as a decrease in the eGFR to <60ml/min/1.73m^2 on at least two consecutive eGFR measurements, sustained over more than 3 months.

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Predictors

The short version of the original D:A:D risk score[11] included age, sex, nadir CD4 count, baseline eGFR, hepatitis C co-infection and intravenous drug use. The long version also included hypertension, diabetes, and cardiovascular events. We developed a 'modified' D:A:D risk score more applicable to Sub-Saharan African populations, similar to Poda *et al* [15]. This removed hepatitis C and IVDU as risk variables and included hypertension and diabetes (identified as documented diagnoses in the eMR) given their independent association with CKD in PLWH[16,17].

Proteinuria was not included in Mocroft's D:A:D risk score due to lack of data in the original study cohort; however, given its established association with progression of CKD in HIV-infected patients[18,19] we included it as an additional variable in a nested model to evaluate if it improved ability to predict CKD. Presence of proteinuria was defined as an albumin-creatinine ratio of >30mg/g, or >1+ on reagent strip urinalysis[20].

Individual risk scores were calculated by assigning points to the presence of each risk factor identified at or prior to the baseline eGFR measurement. The value assigned to each risk factor was based on the original D:A:D model (figure 1). Missing data were allocated a coefficient of zero. Risk score was categorised as low, medium or high based on the D:A:D cut-offs (<0, 0-4, >5).

Statistical Analysis

Values were reported as median (IQR) or mean (95%CI). Data which were not normally distributed were transformed (square root for CD4 counts and $\log_{10}$ for creatinine and eGFR) to allow for parametric statistical comparison, and back-transformed for the calculation of means and confidence intervals. Comparisons were by unpaired t-test or Chi-squared test as appropriate. Potential predictors of renal impairment were assessed by logistic regression.

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Predictors with a $p < 0.1$ in univariate analysis were included in a multivariate model. In nested models, log-likelihoods were used with the Chi-squared distribution to determine the significance of including other variables with the D:A:D score categories used as dummy variables. For all analyses, $p < 0.05$ was considered statistically significant. Discrimination, calibration and reclassification were used to assess the performance of the models[21]

Results

Participant Characteristics

Based on the eligibility criteria, a total of 2793 participants were included in the study. They were followed for a median of 4.2 years [range 0.3, 12.5]. Baseline characteristics of the participants are summarised in Table 1. Participants were predominantly female (63%) with a median age of 36 years [30, 43] and median eGFR of 131ml/min [115,142]. 15% had known hypertension, 2% had known diabetes. Most had a CD4 count >200cells/uL (89%). Proteinuria data was available for 81% of participants, with 8% found to have proteinuria. The incidence of eGFR< 60 was 3.2 per thousand patient years.

All patients were ARV naïve at enrolment, with most (92%) commenced on therapy with tenfovir disoproxil fumurate, lamivudine and Epivir (TDF/3TC) over the follow up period. Using the modified D:A:D CKD risk score, 2439 (87%) participants were categorised as 'low risk' of progression at baseline, while 280 (10%) were 'medium risk', and 74 (3%) were 'high risk'.

Development of Chronic Kidney Disease

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Forty participants developed CKD over the median four years of follow-up, including 12% of the 'high-risk' group, 3% of the 'medium-risk' group, 1% of the 'low-risk' group. Factors confirmed to be associated with development of CKD in univariate analysis included older age, CD4 <200cell/μL, hypertension, baseline eGFR <90ml/min and proteinuria. Female sex was not associated with increased risk of CKD (p=0.17).

In multivariate analysis without proteinuria, baseline eGFR <90ml/min was strongly associated with development of CKD, increasing the odds almost five-fold [OR 4.9, CI 2.3,10.5, p=0.001]. Hypertension doubled the risk of CKD development [OR 2.4, CI 0.8,1.2], and risk increased by approximately 4% for each year of increase in age. Higher modified D:A:D risk category was strongly associated with development of CKD. Those in the medium risk group were more than twice as likely to develop CKD compared to those in the low-risk group [OR 2.6, CI 1.2,5.9], while those in the in the high-risk category had twelve-fold higher odds [OR 12.4, CI 5.6,27.5]. (Figure 2)

When proteinuria was evaluated in a nested model, presence of proteinuria was found to increase the odds of developing CKD almost 8-fold [OR 7.8, CI 3.9,15.7]. In this model, the odds of developing CKD for those in the medium risk group was like the model without proteinuria [OR 2.53, CI 1.04,6.16], while the odds of developing CKD for those in the high-risk group increased to fifteen-fold [OR 15.1, CI 6.5,34.9]. Including proteinuria in the risk score model improved discrimination of the model; the c-statistic was 0.658 for the model without proteinuria and 0.853 when proteinuria was included.

The Net Reclassification Improvement (NRI) was 0.22; the proportion correctly classified increased from 0.43 to 0.70 with the addition of proteinuria to the model. Calibration showed

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a rate of 0.6% with the simpler model; that increased to 1.0% when proteinuria was added, comparable to the observed rate of 1.4%.

Discussion

In this analysis we used data from a small cohort of PLWH in Harare to evaluate the performance of a modified version of the D:A:D risk score. We included the variables that are most relevant to HIV populations in Sub-Saharan Africa, and which are routinely available in most resource-limited settings. The model performed well in our cohort despite our small sample size and low rate of progression to CKD. Only 1% and 3% of those classified as 'low' and 'medium-risk' at baseline went on to develop CKD, compared to 12% of those classified as 'high-risk.'

Strengths

Due to a paucity of data, proteinuria was not included as a risk-score variable in the original D:A:D cohort or subsequent validation studies from the US, Asia-Pacific or West Africa[11-13,15] despite it being a well-established predictor of CKD in PLWH[18,19]. The Australian validation study[14] attempted to evaluate proteinuria as a risk variable but did not find a significant association with progression to CKD, likely due to the low proportion of patients with proteinuria data available (7%). In our study, proteinuria data was available for 2251 participants (81% of the total cohort). We identified that it was a strong risk factor for development of CKD- more so than any of the other included variables. Including proteinuria significantly improved the predictivity of the model, demonstrated by the increased c-statistic. Our study thus represents the first validation study to confirm the role of proteinuria as part of the D:A:D risk score model. Our findings also emphasise the importance of

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screening for proteinuria in PLWH so that risk of progression to CKD can be accurately stratified.

The HIV epidemic in Sub-Saharan Africa has unique epidemiologic characteristics compared to that in Western populations[23,23]; it therefore cannot be assumed that risk scores created for Western cohorts will be valid. A key example is that the original D:A:D cohort and subsequent validation studies from Asia, Australia and the US predominantly included males (73% of the cohort), and all identified female sex as a risk factor for progression to CKD. In contrast, most participants in our study were female (63%), a similar proportion to Poda's West African validation study (73%), paralleling the population prevalence of HIV across Southern and Western Africa[24]. In our cohort sex was not identified to be a significant predictor of CKD in multivariate analysis (p=0.17). This suggests that socio-cultural factors may confound risk estimation for CKD progression in females with HIV rather than an inherent biologic risk difference risk existing.

Limitations

Several limitations of our study should be acknowledged. Though the Newland's clinic is freely accessible for all PLWH in Harare, being a single-centre study introduces potential for selection bias. Due to the retrospective nature of the data collection from the medical record, we relied on documentation of an established diagnosis of hypertension and diabetes rather than a uniform screening process, potentially leading to under-recognition of these conditions. The national prevalence of hypertension in Zimbabwe is estimated at 30%, while the prevalence in our study was only 15%. The proportion in our cohort with diabetes was 2.3%, while reported prevalence in Zimbabwe ranges from 1.5% to 5.7%, with 66.1% of cases estimated to be undiagnosed [25,26]. The only other validation study from Sub-Saharan

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Africa[15] did not evaluate diabetes or hypertension as risk variables. Despite the well-established association of APOL1 risk alleles and CKD in Black Africans[27], our resource-limited setting meant we did not have access to genotyping for our cohort and were thus unable to determine the influence of these risk alleles. Owing to drug availability at the Newland's Clinic, most patients who commenced anti-retroviral therapy in our cohort were started on a regimen with TDF, and this homogeneity limited our ability to assess the specific influence of the potentially nephrotoxic anti-retroviral. Lastly, the short median follow-up of 4.2 years is likely to be insufficient to determine the true rate of progression to CKD in this cohort.

Conclusion

Our modified version of the D:A:D risk score performed well in predicting CKD in the unique population of people living with HIV in Sub-Saharan Africa. Incorporating proteinuria improved the predictivity of the score, highlighting the importance of its utilisation in risk stratification for PLWH. Use of the D:A:D risk score in resource-limited settings such as Sub-Saharan Africa can ensure accurate identification of individuals at highest risk of developing renal dysfunction, and allow for targeted interventions including more frequent screening, intensive risk factor modification and timely switch to less nephrotoxic anti-retrovirals.

Acknowledgements

The authors would like to acknowledge Dr Valerie Gracey for her statistical expertise in the creation of this manuscript

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Table 1. Baseline Characteristics				
	Developed CKD, N or median (% or IQR))	**Did Not Develop CKD N or median (% or IQR)**	**All N or median (% or IQR)**	***p* value**
Total	40 (100)	2753 (100)	2793 (100)	
Sex				
Male	19 (48)	1014 (37)	1033 (37)	0.166
Female	21 (52)	1739 (63)	1760 (63)	
Age (years)	44 (38, 49)	36 (30, 43)	36 (30, 43)	<0.001
Nadir CD4 Count (cells/uL)				
<200	9 (23)	289 (10)	298 (11)	<0.001
>200	31 (77)	2464 (90)	2495 (89)	
Hypertension				
No	22 (55)	2330 (84)	2352 (85)	
Yes	18 (45)	433 (16)	451 (15)	<0.001
Diabetes Mellitus				
No	39 (97)	2690 (98)	2729 (98)	
Yes	1 (3)	63 (2)	64 (2)	0.929
eGFR (ml/min)	110 (89, 127)	130 (116, 142)	131 (115, 142)	<0.001
Proteinuria				
No	16 (40)	2016 (73)	2032 (73)	
Yes	16 (40)	203 (8)	219 (8)	
Unknown	8 (20)	534 (19)	542 (19)	
Risk Category				<0.001
Low	23	2416	2439 (87)	
Medium	8	272	280 (10)	
High	9	65	74 (3)	

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Figure 1: Modified D:A:D Risk Score		
Risk Factor		**Value**
Age	≤35	0
	>35 to ≤50	4
	>50 to ≤60	7
	>60	10
Baseline eGFR (ml/min.1.73m^2)	>60 to ≤70	6
	>70 to ≤90	0
	>90	-6
Sex	Male	0
	Female	1
Nadir CD4 count (cells/mm^3)	≤200	0
	>200	-1
Hypertension	No	0
	Yes	1
Diabetes	No	0
	Yes	2
Risk Score Categories Low Risk: <0 Medium Risk: 0-4 High Risk: >5		

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Figure 2: Modified D:A:D Risk Score Models						
2.1: Without Proteinuria: c-statistic 0.658						
variable	**odds ratio**	**std. error**	**95% CI**		**z-score**	**p-value**
Medium vs Low	2.64	1.08	1.18	5.89	2.37	0.018
High vs Low	12.44	5.03	5.63	27.50	6.23	0.000
constant	0.01	0.002	-0.015	0.007	-22.51	0.000
2.2: With Proteinuria: c-statistic 0.853						
variable	**odds ratio**	**std. error**	**95% CI**		**z-score**	**p-value**
Medium vs Low	2.53	1.48	1.04	6.16	2.05	0.040
High vs Low	15.08	6.48	6.50	34.99	6.32	0.000
Proteinuria						
No	1	0				
Yes	7.79	2.79	3.86	15.73	5.72	0.000
constant	0.006	0.002	0.003	0.01	-18.40	0.000

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