Published in final edited form as:

AIDS. 2016 May 15; 30(8): 1221–1228. doi:10.1097/QAD.0000000000001041.

Incidence of Stage 3 Chronic Kidney Disease and Progression on Tenofovir-Based Antiretroviral Therapy Regimens: A Cohort Study in HIV-Infected Adults in Cape Town, South Africa

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Abstract

Objective—To describe the incidence of rapid kidney function decline (RKFD), and stage 3 chronic kidney disease (CKD) in HIV-1-infected adults initiated on tenofovir (TDF)-containing antiretroviral therapy (ART).

Methods—A retrospective cohort study at the infectious diseases clinic of Tygerberg Academic Hospital in Cape Town, South Africa. Patients with >3 ml/min/year decline in estimated glomerular filtration (eGFR) were classified as having RKFD, and stage 3 CKD was defined as a value <60 ml/min/1.73 m². We used logistic and Cox proportional hazards regression models to determine factors associated with RKFD and stage 3 CKD.

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DISCLOSURE:

All the authors declared no competing interest.

Results—Of 650 patients, 361 (55%) experienced RKFD and 15 (2%) developed stage 3 CKD during a median (interquartile range [IQR]) follow-up time of 54 (46.6–98) weeks. For every 10-year increase in age and 10mL/min lower baseline eGFR, the odds of RKFD increased by 70% (adjusted odds ratio [aOR] = 1.70, 95% CI 1.36 to 2.13) and 57% (aOR = 1.57, 95% CI 1.38 to 1.80), respectively. Each 10-year older age was associated with a 1.90-fold increased risk of developing stage 3 CKD (adjusted HR [aHR] = 1.90, 95% CI: 1.10 to 3.29). Women had about 4-fold greater risk of stage 3 CKD compared to men (aHR = 3.96, 95% CI: 1.06 to 14.74).

Conclusions—About half of our study population developed RKFD but only 2% progressed to stage 3 CKD. Approaches that provide balanced allocation of limited resources towards screening and monitoring for kidney dysfunction and HIV disease management are critically needed in this setting.

Keywords

HIV; Chronic kidney disease; Tenofovir; ART; Progression

INTRODUCTION

Tenofovir disoproxil fumarate (TDF), a nucleotide analogue reverse transcriptase inhibitor, is widely used in high-, middle-, and low-income countries around the world as part of combination antiretroviral therapy (ART) in the treatment of HIV[1] and is arguably the most valuable drug currently available in our armamentarium against this dreaded virus. The most recent ART guidelines published by the World Health Organization recommend starting all eligible patients on a first-line regimen that includes TDF[2]. In addition to being used in treatment regimens, TDF has been recently approved in the United States as part of a pre-exposure prophylaxis regimen to prevent infection in people who are at risk for contracting HIV[3].

In manufacturer-sponsored randomized clinical trials, TDF was found to have a good safety profile and low toxicity [4–8]. However, concerns have since been raised with regard to its potential nephrotoxicity. TDF is chemically similar to adefovir and cidofovir, which both have clinically significant nephrotoxicity[9]. In addition, renal tubular toxicity was demonstrated *in vitro* and in animal models when high doses of TDF were administered. Furthermore, several cases of kidney dysfunction and/or acute kidney injury have been reported in TDF recipients[10].

In contrast to industry-sponsored clinical trials, U.S. and European observational cohort studies, retrospective reviews, and a meta-analysis by Hall and colleagues have reported kidney dysfunction associated with TDF use, have concluded that the reduction in estimated glomerular filtration rate (eGFR using Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) equations, is mild and of questionable clinical significance [11–15]. These reports are contradicted by a Veterans Health Administration observational study of over 10,000 patients which reported that TDF use was associated with higher risk for chronic kidney disease (CKD) and rapid decline in kidney function when compared to other drug regimens [16].

Recent guidelines from the American HIV Medical Association and U.S. Department of Health and Human Services recommend biannual monitoring of kidney function in HIV-positive patients receiving a TDF-containing regimen[17]. In resource-limited settings, the need for frequent laboratory tests may limit the use of TDF[18]. Most studies described above included patients who were primarily male and were conducted in resource-rich settings. Therefore, these studies have limited usefulness in policy decisions regarding monitoring in resource-limited settings, where the use of TDF is the greatest. Less than a handful of such studies have been conducted in sub-Saharan Africa, where the HIV disease burden is highest, more women are HIV-positive, treatment is initiated when the disease is more advanced, and resources are limited [18–20]. Furthermore, there are sketchy data on the incidence and predictors of kidney failure in patients receiving TDF-containing regimens in a “real world” clinical setting in sub-Saharan Africa [21–23]. Given the prevalence of genetic susceptibility traits that place individuals of African descent at risk of kidney disease [24], especially HIV-associated nephropathy (HIVAN) [25], more research is needed regarding the impact of TDF on kidney function; this information is crucial to guide clinicians, especially in view of the limited access to dialysis should patients develop kidney failure.

To that end, we conducted a retrospective cohort study of HIV-positive patients initiating TDF in South Africa. The aim of the study was to describe the incidence of kidney failure in patients receiving TDF-containing regimens in a “real world” clinical setting in a public hospital in South Africa, a country with one of the highest burdens of HIV and the greatest numbers of patients on antiretroviral therapy in the world.

METHODS

Study Design, Settings and Population

A retrospective cohort study of HIV-positive individuals initiating ART-containing TDF was conducted at the outpatient Infectious Diseases Clinic (IDC) at Tygerberg Academic Hospital in Cape Town, South Africa. All patients in the cohort were ART-naïve HIV-positive adults who attended the IDC, between September 2010 and May 2013. Ethics committee approval for the study was obtained from Stellenbosch University and the University of Pittsburgh. All patients who received TDF and had a baseline serum creatinine measurement along with at least one follow-up creatinine measurement were included in the analysis (Figure 1).

Data Collection and Laboratory Analyses

Data were extracted from the IDC Microsoft Access Database which was created using a standardized data collection form following each patient visit. Missing data, incomplete data, and additional demographic and/or baseline information were abstracted from patient charts and laboratory results. Laboratory results for patients that were transferred to outside clinics following initiation of therapy were verified, and additional data on current ART regimen and patient weight at time of serum creatinine result were obtained from patient charts at these clinics, when available. The laboratory at Tygerberg Hospital performed the

serum creatinine tests using an isotope dilution mass spectrometry traceable calibration method to standardize measurements.

Variables

Baseline variables collected included age, gender, height, weight, CD4+ T-cell count, hepatitis B virus surface antigen status, diagnosis of diabetes or hypertension (determined by whether patient was on medication(s) for the condition), and pre-existing kidney disease (determined by recorded diagnosis of kidney failure and/or at least one abnormal serum creatinine result based on local normal laboratory values).

Quantitative Variables

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[26] and the four-variable Modification of Diet in Renal Disease formula (MDRD)[27] for standardized creatinine. Our primary analyses used eGFR based on the CKD-EPI formula, and the results were confirmed with the MDRD eGFR. For each patient, we estimated the rate of change (slope) of eGFR over time using two approaches: the least squares approach and the Bayesian approach. Long-term kidney function was evaluated in two ways: 1) rapid kidney function decline (RKFD); and 2) incident stage 3 CKD. Patients were classified as having RKFD if the estimated rate of kidney function decline exceeded -3 mL/min/year. We defined incident stage 3 CKD as the development of an eGFR <60 mL/min/ 1.73 m² during follow-up among patients who had an eGFR greater than or equal to 60 mL/min/ 1.73 m² at baseline.

Statistical Analysis

We used the Bayesian model simulations to estimate the posterior probability of RKFD for each patient and summarized the distribution of these probabilities with a histogram. We compared mean differences in baseline characteristics between patients who had RKFD and those who did not using the t-test, or the rank-sum tests when the data were skewed. We compared differences in proportions between two groups using chi-square tests. We performed logistic regression and Cox proportional hazard models to examine the associations between baseline demographic, clinical characteristics with the risk of RKFD and incidence of stage 3 CKD, respectively. Time to incident stage 3 CKD was calculated and described using the Kaplan-Meier survival curve. For both models, bivariate analyses were used to investigate the unadjusted (crude) associations between each baseline or clinical characteristics and the risk of RKFD and incidence of stage 3 CKD.

Multivariable analyses were used to determine variables independently associated with the risk of RKFD and incidence of Stage 3 CKD. Variables with p-values less than 0.2 in the bivariate analyses were included in the multivariate model. We adjusted for patient's age and gender irrespective of bivariate association. The results of the logistic regression and Cox proportional hazard models were presented as odds ratio (ORs) and hazard ratios (HRs), respectively, with 95% confidence intervals (CIs). The proportionality assumption was confirmed by log-log plots and Schoenfeld residuals [28]. We checked for informative drop-out by plotting the distribution of eGFR values over drop-out time and time on TDF. The plot suggests that there is no evidence of informative censoring (eFigure 1).

All statistical analyses were performed using Stata 13.1 statistical software (StataCorp, College Station, TX USA) except estimation of the Bayesian slopes which was performed using Rjags, a program for the statistical analysis of Bayesian hierarchical models by Markov Chain Monte Carlo simulation in R statistical software [29]. The paper is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [30].

RESULTS

Participants and Descriptive Data

Of 650 HIV-positive patients (426 women and 224 men) who initiated TDF, 361 (55%) experienced RKFD. The overall median (interquartile range [IQR]) follow-up time on a TDF-containing regimen was 47 (19–69.3) weeks. Patients who developed RKFD were on a TDF-containing regimen for a median of 30 (IQR: 13.2–53.4) weeks and patients who did not develop RKFD were on a TDF-containing regimen for a median of 51.8 (IQR: 26–96.3) weeks. There were 1736 creatinine measurements among patients with RKFD compared to 1538 creatinine measurements among patients without RKFD. Overall, patients who developed RKFD were similar in mean baseline age, body mass index, and CD4+ T-cell count, and had similar incidence of diabetes, hypertension, and hepatitis B surface antigen seropositivity when compared to those who did not develop RKFD (Table 1). Conversely, individuals who had RKFD had lower mean baseline weight (62.8 vs. 65.3 kg, $P=0.035$) and higher mean baseline eGFR (116 vs. 111 ml/min/1.73 m², $P<0.001$) than patients without RKFD.

Outcome Data

eFigure 2 shows the smoothed eGFR profile over time on TDF-containing regimen separately for a random sample of patients. Overall, eGFR declined over time. The median change in eGFR was -3.53 ml/min/1.73 m² (IQR: -9.94 , 2.93) during follow-up. Based on the Bayesian estimates, 120 (18%) patients had positive estimated kidney function slopes while 530 (81%) had negative estimated kidney function slopes. The distribution of the Bayesian posterior probabilities of RKFD showed that thirty-eight patients had a probability of experiencing RKFD of at least 90% while 62 patients had a probability of RKFD of at least 80% (eFigure 3).

In the adjusted model, age, baseline eGFR, and history of pre-existing kidney disease were significantly, independently associated with RKFD (Table 2). For every 10-year increase in age or 10ml/min lower in baseline eGFR (CKD-EPI), a patient's odds of RKFD increased by 70% (adjusted odds ratio [aOR] = 1.70, 95% CI 1.36 to 2.13) and 57% (aOR = 1.57, 95% CI 1.38 to 1.80), respectively. Patients with history of pre-existing kidney disease were more than twice as likely to experience RKFD (aOR = 2.33, 95% CI 1.04 to 5.19) than patients without pre-existing kidney disease.

Fifteen of 650 (2%) patients progressed to stage 3 CKD during a median (IQR) follow-up time of 54 (46.6–98) weeks (Figure 2). Older age, female gender, lower baseline eGFR, and lower CD4 count were independently associated with development of stage 3 CKD in the

adjusted model (Table 3). Each 10-year older age was associated with a 1.90-fold increased risk of developing stage 3 CKD (adjusted HR [aHR] = 1.90, 95% CI: 1.10 to 3.29). Women had an almost 4-fold greater risk of stage 3 CKD compared to men (aHR = 3.96, 95% CI: 1.06 to 14.74). A baseline CD4+ T-cell count $<200/\text{mm}^3$ was associated with more than a 4-fold increased risk of stage 3 CKD compared to a CD4 count of $200/\text{mm}^3$ or greater (aHR = 4.54, 95% CI: 0.98 to 21.04) (Table 3).

DISCUSSION

In this study of HIV-infected South Africans who initiated TDF-containing antiretroviral regimens, the great majority of individuals had negative eGFR slopes, and over half developed RKFD and only 2% developed stage 3 CKD during a median follow-up of approximately 30 and 54 weeks, respectively. The factors associated with greater likelihood of RKFD included older age, female gender and lower baseline eGFR. Our study quantifies the magnitude of risk for developing RKFD and stage 3 CKD among HIV-positive South African adults initiated on TDF-containing ART regimens.

Prior studies from sub-Saharan Africa have shown that kidney dysfunction is highly prevalent in HIV-infected individuals initiating ART. Studies set in Mwanza, Tanzania and Johannesburg, South Africa have shown that the prevalence of stage 2 CKD (eGFR 60 to 89 ml/min per 1.73 m) is 30–40% while the prevalence of stage 3 CKD (eGFR 30 to 59 ml/min per 1.73 m) is estimated to be 5.2% to up to 25% [21, 22]. Much of the incident kidney dysfunction in TDF patients was related to preexisting renal disorder [21].

Our findings of general decline in kidney function with TDF-treatment build upon these findings by evaluating a population in which the great majority of patients had preserved kidney function. Also, our results are consistent with those published by Mulenga and colleagues [31]. Among more than 60,000 patients who initiated ART in Zambia, those with abnormal baseline kidney function on TDF-containing regimens had a lower eGFR at 6- and 12-month of follow-up and were 2- to 3-times more likely to progress to advanced kidney dysfunction when compared to patients not on TDF regimens.

In contrast, Kamkuemah and colleagues demonstrated that the overall eGFR improved by $1.10 \text{ ml/min}/1.73 \text{ m}^2$ over 12 months following TDF initiation among 1092 HIV-infected individuals residing in Cape Town, South Africa [32]. However, their study population was younger compared to our study population (mean 33 vs. 38 years, respectively), and the disparate observations across studies are likely due to differences in study population characteristics. Also, Bygrave and colleagues in Lesotho reported that among 933 HIV-infected initiating ART, 176 (18.9%) had a baseline creatinine clearance $<50 \text{ ml/min}$ and that renal function improve in all but only 3 of these patients [33]. However, their operational data were highly limited by missing data and lack of key covariates for the analysis. Similarly, secondary analyses from the Development of Antiretroviral Therapy Trial (DART) conducted in Zambia, Uganda, and Zimbabwe, by Reid and colleagues documented that mild-to-moderate baseline renal impairment was relatively common, but these participants had the greatest increases in eGFR after starting ART-containing TDF.

However, severe eGFR impairment was infrequent regardless of ART regimen and was generally related to inter-current disease [19, 20].

Of note, the overall rate of eGFR decline on TDF was more rapid than previously reported in studies from the United States [34] or Europe [35]. The discrepancy with data from developed countries may be due to other prevalent co-morbidities (e.g. HIVAN, co-infection with Hepatitis B or parasites such as *Schistosoma haematobium* and *mansoni*) which have been shown to associated kidney dysfunction in sub-Saharan Africa [25, 36–40]. Schistosomiasis has been associated with cystitis, obstructive uropathy, and immune-mediated glomerulonephritis, and may have contributed to the prevalent renal dysfunction [37, 40]. Therefore, one would not necessarily expect similar rate of eGFR decline in our study population as compare to high-income settings [34, 35, 41].

Our observation that a lower baseline kidney function was associated with higher risk of both RKFD and stage 3 CKD are consistent with several prior studies. Young and colleagues found that among 19 patients with pre-existing kidney disease (baseline median eGFR 49 ml/min/1.73 m²) in the HIV Outpatient Study, eGFR declined in 5 of 19 patients over a median follow-up period of 1 year[15]. Similarly, Brennan and colleagues demonstrated a stepwise increase in risk of any decline in kidney function secondary to TDF among HIV-infected South Africans. Compared to those with eGFR ≥ 90 ml/min/1.73 m², those with eGFR of 60–89 ml/min/1.73 m² and 30–59 ml/min/1.73 m² had a 4.8-fold and 15-fold higher risk, respectively, of acute or chronic kidney function decline [21]. The reasons for these differing observations are unclear, although they may be attributable to differences across study populations in the underlying cause of kidney dysfunction and ART-status prior to initiating TDF. For example, the study population examined by Brennan *et al.* was comprised predominantly of ART-exposed individuals who had switched to TDF.

Finally, our results demonstrate that older age was associated with higher odds of RKFD and higher risk of stage 3 CKD, whereas female gender was associated with higher risk of stage 3 CKD, as also reported by Msango and colleagues in Tanzania [22]. These observations may reflect the impact of age and gender on TDF circulating levels. Among HIV-infected women in the Women's Interagency HIV Study, each decade older of age was associated with a 1.23 fold increase in TDF area under the curve (AUC) [42]. Although gender differences in TDF levels could not be assessed in the previous study, 10% incremental decreases in body mass index were also associated with a 1.04-fold higher TDF AUC [42]. In a report by Gervasoni and colleagues as well as Msango et al., low body mass index, particularly in HIV-positive women, was associated with higher risk of both TDF-related nephrotoxicity and bone toxicity [22, 43].

Our study has important clinical and research implications. While TDF-associated with CKD has been well-described among HIV-positive patients in developed countries, there has been a relative dearth of studies in low- and middle-income countries where limited resources present an impediment to both kidney function screening and monitoring. Our study, which utilized rigorous methodological approaches to assess longitudinal renal outcomes, represents one of the largest studies to date to assess TDF-related CKD risk in a resource-limited setting. Although the incidence of stage 3 CKD was small among TDF

users, in a country like South Africa with the largest numbers of HIV-positive individuals on ART worldwide, the absolute numbers of patients with TDF nephrotoxicity is expected to be high. Therefore, with increasing use of TDF-containing regimens as first-line treatment for HIV infection in LMIC, studies such as ours highlight an urgent need to assess future approaches to CKD monitoring and management in these settings. We identified gender as an important predictor for CKD among HIV-positive South Africans receiving TDF. While gender differences in TDF exposure due to differences in body mass index may explain our observations, additional studies are needed to evaluate for gender-based differences in other factors that may alter TDF-exposure, such as treatment adherence. Future research should focus on whether or not simple diagnostic tools, such as the combination of serum creatinine-based GFR estimates and a urine dipstick, can cost-effectively identify patients at greatest risk of TDF-related toxicity [44].

While informative, however, our study has also several limitations. First, the follow-up time was relatively short. While most studies suggest that the greatest TDF-related decline in kidney function occurs within the first year of initiation, longitudinal studies in sub-Saharan Africa are needed to better assess the impact of long-term TDF exposure on renal and bone health outcomes[44]. Secondly, we were unable to assess for proximal tubular injury that may occur despite preserved eGFR. To inform future guidelines for kidney disease screening and monitoring among HIV-infected individuals exposed to TDF, studies with more sensitive biomarkers for kidney injury are needed [44]. In addition, we defined stage 3 CKD based on a single eGFR estimate below 60 ml/min per 1.73 m²; this may lead to greater misclassification of CKD status. Finally, this was a single-center study; therefore, our findings may not be generalizable to the remainder of sub-Saharan Africa that is highly variable with regard to access to care and kidney health assessments for HIV-infected individuals.

In conclusion, we showed that TDF was associated with both a higher likelihood of RKFD and Stage 3 CKD among HIV-infected South Africans. While the majority of individuals experienced RKFD in our study, only a small minority developed Stage 3 CKD. Therefore, approaches that provide balanced allocation of limited resources towards screening and monitoring for kidney dysfunction and HIV disease management are critically needed in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research Grant Support: Hadas Zachor (NIH/NIDDK T35-DK-065521-09); Rhoderick Machekano (NIH/FIC 1D71-TW009758-01); Michelle M. Estrella (NIH/NIDDK-1K23-DK-081317; Johns Hopkins University Center for AIDS Research (CFAR, P30A1094189)); Olalekan A. Uthman (FAS Marie Curie International Post-Doc Award #2012-0064); Jean B Nachega (PEPFAR-HRSA:T84HA21652; Wellcome Trust: WT087537MA; NIH/NIAID: 2UM1AI069521-08).

Conference Presentation: This paper was presented at the World Congress of Nephrology, March 13–17, 2015, Cape Town, South Africa. (<http://www.wcn2015.org/>)

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Figure 1.
Study Flow Diagram

Figure 2.
Actuarial risk of progression to stage 3 Chronic Kidney Disease

Table 1

Comparison of baseline characteristics between Rapid Kidney Function Decliners (eGFR slope <-3 ml/min/yr) compared to Non-rapid Kidney Function Decliners (eGFR slope $\geq$ -3ml/min/yr).

Characteristic	All patients (N=650) n (%) or Mean $\pm$ SD or Median (IQR)	Rapid Kidney Function Decliners (N=361) n (%) or Mean $\pm$ SD or Median (IQR)	Non-rapid Function Kidney Decliners (N=289) n (%) or Mean $\pm$ SD or Median (IQR)	p-value
Age (yr)	37.9 $\pm$ 9.4	38.2 $\pm$ 9.3	37.5 $\pm$ 9.5	0.346
Female	426 (65.5)	247 (68.4)	179 (61.9)	0.084
BMI	24.9 $\pm$ 6.2	24.6 $\pm$ 6.2	25.3 $\pm$ 6.1)	0.169
Height (cm)	160.7 $\pm$ 10.5	160.2 $\pm$ 10.2	161.4 $\pm$ 11.0	0.198
Weight (kg)	63.9 $\pm$ 15.1	62.8 $\pm$ 15.1	65.3 $\pm$ 15.1	0.035
Diabetic	14 (2.2)	10 (2.8)	4 (1.4)	0.283
Hypertensive	51 (7.8)	27 (7.5)	24 (8.3)	0.697
History of renal failure	39 (6)	21 (5.8)	18 (6.2)	0.826
Hepatitis B surface Ag (+)	89 (13.7)	41 (11.4)	48 (16.6)	0.053
Creatinine clearance (mL/minute)	61.8 $\pm$ 16.0	58.1 $\pm$ 14.8	66.4 $\pm$ 16.2	< 0.001
eGFR – CK-EPI (mL/minute)	114 (102 – 123)	116 (107 – 125)	111 (96 – 120)	<0.001 ^{WR}
eGFR – MDRD (mL/minute)	108 (91 – 126)	113 (96 – 134)	100 (84 – 117)	<0.001 ^{WR}
CD4 count	186 (112 – 260)	183 (102 – 267)	189 (129 – 243)	0.990 ^{WR}

Table 2

Factors associated with Rapid Kidney Function Decline (yearly changes ≤ -3 ml/min/yr) based on eGFR (CKDEPI) using Bayesian estimation.

	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (per 10 years)	1.08 (0.92 to 1.28)	0.346	1.70 (1.36 to 2.13)	<0.001
Male (vs. female)	0.75 (0.54 to 1.04)	0.084	0.73 (0.51 to 1.04)	0.080
Baseline eGFR (per 10ml/min lower)	1.30 (1.18 to 1.43)	<0.001	1.57 (1.38 to 1.80)	<0.001
History of renal failure	1.82 (0.84 to 3.96)	0.129	2.33 (1.04 to 5.19)	0.038
History of diabetes	2.03 (0.63 to 6.54)	0.236		
History of hypertension	0.89 (0.50 to 1.58)	0.698		
History of renal failure	0.93 (0.48 to 1.78)	0.826		
Hepatitis B surface Ag positive	0.64 (0.41 to 1.01)	0.054	0.68 (0.43 to 1.11)	0.122
Height (per 10cm increase)	0.90 (0.81 to 1.05)	0.198		
Baseline weight (per 10kg increase)	0.89 (0.81 to 0.99)	0.036	0.95 (0.85 to 1.06)	0.324
Baseline CD4+ T-cell count (per 50 cells/cm ³)	1.01 (0.94 to 1.08)	0.833		
Body mass index	0.98 (0.96 to 1.01)	0.170		

CD4- cluster of differentiation 4; CI confidence interval; eGFR- estimated glomerular filtration rate; OR- odds ratio

Table 3

Factors significantly associated with risk of stage 3 CKD (Cox regression analysis)

Characteristics	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, per 10 year older	2.46 (1.56 to 3.89)	<0.001	1.90 (1.10 to 3.29)	0.021
Female vs. male	2.19 (0.62 to 7.75)	0.226	3.96 (1.06 to 14.74)	0.040
Baseline eGFR, per 10 ml/min higher	0.57 (0.42 to 0.76)	<0.001	0.71 (0.51 to 1.00)	0.110
CD4 <200 vs. 200 cells/ μ L	4.59 (1.04 to 20.37)	0.044	4.54 (0.98 to 21.04)	0.053
History of diabetes	2.60 (0.34 to 19.88)	0.363		
Hypertensive	2.53 (0.71 to 9.01)	0.153	0.80 (0.21 to 3.05)	0.757
History of abnormal creatinine	3.73 (1.05 to 13.22)	0.044	2.41 (0.59 to 9.89)	0.223
Hepatitis B surface Ag positive	2.27 (0.72 to 7.13)	0.162	2.30 (0.69 to 7.65)	0.176
Baseline weight (per 10kg increase)	0.82 (0.56 to 1.21)	0.317		
Baseline height (per 10cm increase)	0.80 (0.50 to 1.26)	0.350		

CD4- cluster of differentiation 4; CI confidence interval; eGFR- estimated glomerular filtration rate; HR- Hazard ratio