Factors associated with chronic kidney disease in HIV+ patients in Albert Luthuli Municipality of South Africa

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Factors associated with chronic kidney disease in HIV⁺ patients in Albert Luthuli Municipality of South Africa

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Abstract

Background: Current research indicates that chronic kidney disease is a global problem which poses a major health threat to people of poor countries who have HIV/AIDS and are on antiretroviral treatment. In this study, the prevalence of chronic kidney disease and the factors associated with it were investigated among the HIV/AIDS patients in a rural community of South Africa.

Methods: A cohort of HIV⁺ terminal ill patients was retrospectively followed from 2010 to 2017 until chronic kidney disease was diagnosed or until the end of the observation period at two hospitals (Carolina and Embhuleni). Patient information was obtained from the routine hospitals' records, and the data were analysed using logistic regression and survival analysis (Kaplan-Meier hazard functions and ratios, and log-rank tests) methods.

Results: Out of a random sample of 357 HIV/AIDS patients, 53 patients (14.85%) had chronic kidney disease. The factors associated with chronic kidney disease were: Gender (*p-value* < 0.0024); Age (*p-value* < 0.0420); Baseline creatinine (*p-value* < 0.0116); Baseline alanine transaminase (*p-value* < 0.0111); Treatment regimen 1 (*p-value* < 0.0001); ART adherence (poor, fair, good) (*p-value* < 0.0005); Hospital (*p-value* < 0.0001); and Lost to follow-up (ye, no) (*p-value* < 0.0069).

Discussion: Whilst antiretroviral treatment is associated with some improvement in virology and immunology in HIV-infected patients, research is still needed for the assessment of the impact of ART and other risk factors on renal function in marginalised communities in Africa.

Conclusion: The research findings on HIV⁺ patients in Albert Luthuli Municipality concurred with several previous research findings on risk factors to CKD. The expected action to alleviate the health threat due to CKD in South Africa is to educate the nation on prevention, early detection and on the management of the disease. The study established diverse baseline statistics against which future research may be based.

Keywords: HIV/AIDS, Renal disease, ART, Prevalence, risk factors, Logistic regression, Kaplan-Meier estimator, hazard ratio.

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Background

HIV/AIDS has been a major health problem worldwide for more than three decades now. According to the WHO global statistics: since the beginning of the epidemic, 75 million people have been infected with the HIV virus, about 32 million people have died of HIV and globally, 37.9 million people were living with HIV at the end of 2018.

According to United Nations Agency for International Development (UNAIDS) AIDSinfo (2018), South Africa has the biggest and most high-profile HIV epidemic in the world, with estimated 7.7 million living with HIV in 2018. South Africa's Mpumalanga province has the second highest HIV prevalence rate after KwaZulu-Natal province. Gert Sibande district which is in Mpumalanga province is leading all districts in the country with 46.1% HIV prevalence rate (Motsoaledi, 2013). Gert Sibande district has Albert Luthuli as one of its municipalities whose HIV prevalence stood at 43.2% (Nkosi, 2017).

A kidney contains millions of nephrons which are made up of blood vessels called glomeruli. The function of kidneys is to filter blood of waste products such as creatinine and urea and extra water which is removed in form of urine. Chronic kidney disease (CKD) is a slow and prolonged failure of the kidneys to filter impurities from the blood. The progression of the kidney damage is marked by the rise in creatinine and urea whose evaluation in serum helps to assess Glomerular Filtration Rate (GFR). CKD poses a major health threat to people living in poor countries, especially when it is combined with HIV, antiretroviral treatment (ART) or communicable and non-communicable diseases (Glaser et al., 2016).

According to Labuschagne and Nel (2017), chronic kidney disease is a global problem with about 10% of the world's population suffering from the disease, but in sub-Saharan Africa, about 14% of the adult population suffers from CKD. Crum-Cianflone et al. (2010) in

agreement with Eneyew et al. (2016) and Ekrikpo et al. (2018), pointed out that as the prevalence of HIV infection increases as a result of improved survival time, the prevalence of renal dysfunction is projected to increase.

The objective of this study is to determine the prevalence of CKD and the risk factors associated with it among HIV/AIDS patients on ART. As far as we are aware of literature, no other such study has been conducted in South Africa.

Methods

About the data

A cohort of HIV⁺ terminal ill patients was retrospectively followed from 2010 to 2017 until CKD was diagnosed or until the end of the observation period at the two hospitals (Carolina and Embhuleni) in Albert Luthuli Local Municipality. This is a South African municipality situated in the Gert Sibande District of Mpumalanga Province. Carolina and Embhuleni district hospitals offer comprehensive health care services which include HIV/AIDS and tuberculosis (TB) treatments to the surrounding communities in Albert Luthuli municipality. These hospitals are accredited antiretroviral (ARV) treatment initiation and on-going treatment sites. Both Hospitals serve mostly the rural population in Albert Luthuli Municipality. The target population which was used as a sampling frame included all HIV/AIDS patients admitted and started ART treatment in the two hospitals within the three-month period from the 1st of January to the 31st of March 2010 regardless of age. However, HIV/AIDS patients with missing essential records such as baseline creatinine, gender and date of birth or age were excluded from the study. An optimum sample size (357 out of 4900) was determined using Raosoft online sample size calculator (Rao and Rao, 1991) with a margin of error of 5% or 95%

confidence level. A stratified random sampling method, with hospital and gender as the stratifying variables, was used to select the study sample. The data used in this study consisted of records of 357 patients extracted from the routine hospitals' records. The variables in the data set are listed in Table 1.

Table 1: List of variables in the data set

Variable name	Codes/ Values /Description
CKD status	1=yes, 0-No
Gender	female, male
Hospital	Carolina, Embhuleni
WHO stage	1, 2, 3, 4
Marital status	1=single, 2=married, 3=staying together,
Treatment (regimen 1)	(NVP+D4T+3TC), (EFV+D4T+3TC), (EFV+AZT+3TC), (EFV+3TC+TDF, (NVP+3TC+TDF)
ART adherence	poor, fair, good
TB history	yes, no
Lost to follow-up	yes, no
Age	Age of the patient on 01/01/2010
Baseline mass	Mass of the patient on ART initiation date
Follow-up mass	Average mass of the patient during follow-up period
Baseline CD4 cell count	CD4 count on ART initiation
Follow-up CD4 cell count	Average CD4 count of the patient during follow-up period
Baseline haemoglobin	Haemoglobin level at ART initiation
Follow-up haemoglobin	Average haemoglobin level during the follow-up period
Baseline lymphocyte	Lymphocyte level at ART initiation
Follow-up lymphocyte	Average lymphocyte level during the follow-up period
Baseline white blood cell	White blood cell count at ART initiation
Follow-up white blood cell	Average white blood cell count during the follow-up period
Baseline viral load	Viral load at ART initiation
Follow-up viral load	Average viral load during the follow-up period
Baseline creatinine	Creatinine level at ART initiation
Follow-up creatinine	Average creatinine level during the follow-up period
Baseline total protein	Total protein level at ART initiation
Follow-up total protein	Average protein level during the follow-up period
Baseline sodium	Sodium level at ART initiation
Follow-up sodium	Average sodium level during the follow-up period
Baseline Alanine	Alanine transaminase level at ART initiation
Follow-up Alanine	Average alanine transaminase during the follow-up period
Time to kidney damage	Time it takes a patient to develop kidney damage after ART.

Ethical considerations

The ethical approval for this study was granted by UNISA Ethics Review Committee with the approval number being 2017/SSR ERC/005. The permission to conduct the study at Carolina and Embhuleni hospitals was obtained from Mpumalanga Department of Health with the permission number being MP_201708_013. All data related to the patients were handled with utmost confidentiality in all the stages of the research. In addition, no reference to an individual respondent was made as all results were handled in aggregate format. The electronic documents carrying confidential information on patients are all protected by some encryption and will be destroyed as per research policy.

Determination of CKD status

The patient's CKD status was determined by referring to the South African National Health Laboratory Service report on Chemical pathology. CKD status was determined from the estimates of the Glomeruli Filtration Rate (GFR) using Modification of Diet in Renal Disease (MDRD) formula (Iseki, 2008; Omuse et al., 2017). Iseki (2008) categorized a patient as having CKD if their GFR is less than $60\text{ml/min}/1.73\text{m}^2$ for more than 3 months, and various stages of CKD are defined in Table 2.2. In this study, any patient in stages 3-5 of the Staging of Chronic Kidney Disease (KDOQI of National Kidney Foundation) was identified as having CKD. The estimates of patient Glomerular Filtration Rate (GFR) were determined using the equation (Omuse et al., 2017):

$$GFR = \begin{cases} 175 \times [SCr/88.4]^{-1.154} \times (Age)^{-0.203} \times 1.212 & \text{if black male} \\ 175 \times [SCr/88.4]^{-1.154} \times (Age)^{-0.203} \times 0.742 \times 1.212 & \text{if black female} \\ 175 \times [SCr/88.4]^{-1.154} \times (Age)^{-0.203} & \text{other male} \end{cases} \quad (1)$$

and $175 \times [SCr/88.4]^{-1.154} \times (Age)^{-0.203} \times 0.742$ for other females, where Age is in years and SCr is serum creatinine in $\mu\text{mol/l}$.

Table 2: Stages of Chronic kidney disease

Staging of Chronic Kidney Disease (KDOQI of National Kidney Foundation):		
Stage	Description	GFR ml/min/1.73m ²
1 & 2	Kidney damage with mildly decreased or normal/increased GFR	> 60
3	Moderate decrease in GFR	30 - 59
4	Severe decrease in GFR	15 - 29
5	Kidney failure	< 15 (for dialysis)

Statistical methods

Let the random variable $Y_i = 1$ if the i^{th} patient ($i = 1, 2, \dots, 357$) has CKD within the observation period, and $Y_i = 0$ if otherwise. Thus, Y_i has Bernoulli distribution with mean $\pi_i = P(Y_i = 1)$ which was assumed to depend on the p -dimensional vector of the values of the covariates, $\mathbf{X}_i^T = (X_{i1}, X_{i2}, \dots, X_{ip})$, associated with the i^{th} patient through the logit link function:

$$\text{logit}(\pi_i) = \ln\left(\frac{\pi_i}{1-\pi_i}\right) = \mathbf{X}_i^T \boldsymbol{\beta}, i = 1, 2, \dots, n \quad (2)$$

where $\boldsymbol{\beta}^T = (\beta_1, \beta_2, \dots, \beta_p)$ is a p -dimensional vector of regression coefficients. Model (2) was fitted to the data using Proc logistic in SAS Version 9.5 to determine the risk factors associated with CKD status. Covariates with p -values less than 0.05 were retained in the model, and used in the nonparametric survival analysis of the times to the development of CKD by patients during the observation period.

Let $0 < t_1 < t_2 < t_3 < \dots < t_k < \infty$ be k observed times to the development of CKD by patients during the observation period; d_{ij} ($i = 1, 2, \dots, r; j = 1, 2, \dots, k$) be the respective number of patients in the i^{th} group with CKD at each of these times; and n_{ij} be the corresponding number of remaining patients in the cohort at the respective times. Then Kaplan-

Meier (KM) estimate of the survivor function $S_i(t)$ ($i = 1, 2, \dots, r$) when times to the development of CKD by patients in the i^{th} group are tied is given by (Etikan et al., 2017):

$$\hat{S}_i(t) = \prod_{j|t_j \leq t} 1 - \left(\frac{d_{ij}}{n_{ij}} \right), i = 1, 2, \dots, r \quad (3)$$

In this study, the r groups were the levels of the significant categorical covariates or categorized continuous covariates retained in the logistic regression analysis of CKD status. The log-rank test was used to test the null hypothesis (Etikan et al., 2017):

$$H_0: S_1(t) = S_2(t) = \dots = S_r(t) \equiv h_1(t) = h_2(t) = \dots = h_r(t) \quad (4)$$

for $t \geq 0$, where $h_i(t)$ is the hazard function of the i^{th} group patients. The test was conducted using Stata Version 15.

Results

Prevalence of CKD

From the sample of 357 HIV/AIDS patients: 53 patients (14.85%); 27 males (50.9%); and 47 patients (88.7%) from Embhuleni hospital had CKD. A follow-up of the patients with CKD gave rise to the following vital outcomes: 4% died; 24% were lost to follow-up; 40% were transferred from the original hospital; and 32% remained attached at the hospitals. Out of 176 (49%) who were transferred, 9% had CKD while from 93 (26%) who were lost to follow-up, 14% had CKD.

The ART treatment regimens which contributed most to CKD cases were (EFV+3TC+TDF) and (NVP+3TC+TDF) with 50% (24/48) and 45% (9/20) contributions respectively as shown in Figure 1. A closer analysis of Figure 1 isolates TDF as a component which outstandingly contributed to CKD cases, and this is reinforced in Figure 2 where the predicted probability for

CKD=1 is highest for patients whose treatment regimens contained TDF (that is (EFV+3TC+TDF) at Embhuleni and (NVP+3TC+TDF) at Embhuleni).

Figure 1: The frequency distributions of ART treatment regimens and Chronic kidney disease (CKD) cases

Risk factors associated with CKD status

Figure 2 shows the graphs of the predicted probabilities of positive CKD that were obtained from the fitted logistic regression model. The predicted probabilities and the observed responses had a high degree of association with a high concordance of 95.1% and a C-value of 0.951. The C-value corresponds to a high degree of discrimination between patients with and patients without CKD. The high degree of association confirms a good model fit and this is reinforced by the global fit of the logistic regression model ($p\text{-value} < 0.0001$). The figure also shows that the predicted probability for positive CKD increases with increase in duration on ART and/or with increase in time having HIV/AIDS.

Figure 2: Predicted probabilities for positive Chronic kidney disease (CKD) obtained from the fitted logistic model.

Table 3 contains the results from the logistic regression analysis of the data. The table shows that the significant factors which are positively associated with CKD at 0.05 level are: Gender ($p\text{-value} < 0.0024$); Age ($p\text{-value} < 0.0420$); Baseline creatinine ($p\text{-value} < 0.0116$); good relative to fair ART adherence ($p\text{-value} < 0.0001$); and Treatment ((NVP+3TC+TDF) relative to (EFV+3TC+TDF)) ($p\text{-value} < 0.0005$). Furthermore, males have hazard to CKD which is about 3.5 times the hazard of females to CKD and this hazard may be as high as 9.422 times and as low as 1.267 times. An increase in age by one year results in an increase in hazard for CKD by about 8.2% and this increase may be as high as 13.6% and as low as 2.9%. An increase in Baseline creatinine of the patient by one unit results in an increase in hazard for CKD by about

170 2%. Unexpectedly, patients with good relative to fair ART adherence are about 4.388 times
 171 likely to have CKD. Lastly, patients taking Treatment (NVP+3TC+TDF) relative to
 172 (EFV+3TC+TDF) are about 0.866 times likely to have CKD.

Table 3: Results from fitting the logistic regression model with binary response Chronic Kidney Disease (CKD) status (0 = CKD negative and 1= CKD positive)

Parameter	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Point Estimate	95% Wald Confidence Limits	
Intercept	-4.7177	1.1010	18.3610	<.0001			
Hospital (Carolina)	-1.4859	0.3477	18.2661	<.0001	0.051	0.013	0.200
Gender (Male)	0.7384	0.2434	9.2050	0.0024	4.379	1.687	11.369
ART adherence (Poor)	-1.8792	0.5442	11.9257	0.0006	0.125	0.026	0.595
ART adherence (Good)	1.6790	0.4254	15.5792	<.0001	4.388	1.531	12.576
Treatment (Regimen 1) (NVP+D4T+3TC)	0.0196	0.5045	0.0015	0.9690	0.105	0.030	0.375
Treatment (Regimen 1) (EFV+D4T+3TC)	-1.7653	0.4954	12.6970	0.0004	0.018	0.005	0.066
Treatment (Regimen 1) (EFV+AZT+3TC)	-2.6479	1.2985	4.1580	0.0414	0.007	0.001	0.200
Treatment (Regimen 1) (NVP+3TC+TDF)	2.1248	0.6102	12.1263	0.0005	0.866	0.197	3.800
Lost to follow-up (No)	-0.6361	0.2461	6.6805	0.0097	0.280	0.107	0.735
Age	0.0402	0.0198	4.1363	0.0420	1.041	1.001	1.082
Baseline creatinine	0.0202	0.00800	6.3771	0.0116	1.020	1.005	1.037
Baseline Alanine Transaminase	-0.0263	0.0104	6.4538	0.0111	0.974	0.954	0.994

Reference levels: Gender = female, Lost to follow-up =yes, Hospital = Embhuleni, ART adherence = fair, and Treatment (Regimen 1)=(EFV+3TC+TDF).

173
 174 On the other hand, the significant factors which are negatively associated with CKD at 0.05
 175 level are: Hospital (Carolina relative to Embhuleni) (*p-value* < 0.0001), poor relative to fair
 176 ART adherence (*p-value* < 0.0006), Treatment (EFV+D4T+3TC relative to (EFV+3TC+TDF)
 177 (*p-value* < 0.0004), Treatment (EFV+AZT+3TC relative to (EFV+3TC+TDF) (*p-value* <
 178 0.0414), Lost to follow-up (No relative to Yes) (*p-value* < 0.0097) and Baseline Alanine
 179 Transaminase (*p-value* < 0.0111). Explanations of the results which are negatively associated

with CKD follow. Carolina hospital, relative to Embhuleni hospital has a hazard reduction effect to CKD which is about 0.050 times the hazard reduction effect of Embhuleni hospital and this hazard reduction effect may be as high as 0.187 times and as low as 0.013 times. An increase in Baseline Alanine Transaminase by one unit results in reduction of hazard of CKD by about 9.67% and this reduction may be as high as 9.83% and as low as 9.51%. Surprisingly, patients with poor relative to fair ART adherence are likely to experience CKD hazard reduction by about 0.125 times. Patients taking Treatment (EFV+D4T+3TC) relative to (EFV+3TC+TDF) are likely to experience CKD hazard reduction by about 0.018 times while patients taking Treatment (EFV+AZT+3TC) relative to (EFV+3TC+TDF) are likely to experience CKD hazard reduction by about 0.7 times. Lastly, patients who are not lost to follow-up relative to patients lost to follow-up are likely to experience CKD hazard reduction by about 0.28 times.

Nonparametric inferences about the survivor functions

The cohort of HIV+ terminal patients in this study is not homogeneous with respect to their characteristics that may affect their survival from CKD. Hence, it will be necessary to test the equality of survivor functions among groups (strata) of patients. Log-rank tests and the Kaplan-Meier functions presented in this section are for the factors which were found to be statistically significant in the logistic regression analysis of CKD status (see Table 3) and which are also components of the GFR formula. Thus, inferences about the survivor functions were made for only creatinine, age and gender. The tables for hazard ratios for pairwise comparisons of strata for creatinine, age and gender are placed next to the respective survivor functions.

Kaplan-Meier survival functions and hazard ratios for Baseline creatinine

Baseline creatinine was categorised as done in the standard Laboratory report on Creatinine in South African hospitals. Figure 3 shows that survivor functions of the Baseline creatinine strata are statistically different at 0.05 significance level ($p\text{-value} \geq 0.0012$, from the log-rank test).

Furthermore, this is confirmed by the pairwise comparisons of the strata using the hazard ratios in Table 4 which show that patients with Baseline creatinine which is above normal are about 4.8 times likely to experience CKD relative to patients with Baseline creatinine which is below normal. In addition, patients with Baseline creatinine which is above normal are about 2.4 times likely to experience CKD relative to patients with normal Baseline creatinine.

Table 4: Hazard ratios for Baseline creatinine strata

Hazard Ratios for Baseline creatinine strata			
Description	Point Estimate	95% Wald Confidence Limits	
Baseline creatinine Above normal vs Below normal	4.770	1.700	13.383
Baseline creatinine Above normal vs Normal	2.428	1.299	4.538
Baseline creatinine Below normal vs Normal	0.509	0.198	1.307

Figure 3: Kaplan-Meier survival function estimates for Baseline creatinine strata

Kaplan-Meier survival functions and hazard ratios for Gender

Figure 4 shows that survivor functions of the Gender strata are not statistically different at 0.05 significance level ($p\text{-value} \geq 0.2168$, from the log-rank test) and this is confirmed by the confidence limits for all strata in Table 5 which include '1' which is a value of no effect.

Table 5: Hazard ratios for Gender strata

Hazard Ratios for Gender strata			
Description	Point Estimate	95% Wald Confidence Limits	
Gender Male vs Female	1.382	0.805	2.373

Figure 4: Kaplan-Meier survival function estimates for Gender strata

Gender is significant in modelling (Table 3) but not significant in the testing of the hypothesis of no difference of homogeneity using the Log-rank test and Kaplan-Meier functions (Figure 4) because in the logistic modelling the effects of other factors were accounted for whereas here the effects of the other factors were ignored. This made the Log-rank test less powerful in detecting gender differences.

Kaplan-Meier survival functions and hazard ratios for Age groups

Table 6: Hazard ratios for Age group strata

Hazard Ratios for Age group strata			
Description	Point Estimate	95% Wald Confidence Limits	
Age group Child vs Adolescent	0.610	0.055	6.731
Age group Child vs Adult	0.230	0.032	1.663
Age group Adolescent vs Adult	0.376	0.091	1.549

Figure 5: Kaplan-Meier survival function estimates for Age group strata

Figure 5 shows that survivor functions of the age strata are not statistically different at 0.05 significance level ($p\text{-value} \geq 0.0865$, from the log-rank test) and this is confirmed by the

confidence limits for all strata in Table 6 which include '1' which is a value of no effect. However, visually it can be observed that adults and adolescents have lower CKD survival probability in comparison to children.

Discussion

This research has several strengths. Firstly, research follow-up time is relatively long, it spans over period of 7.5 years, which is long enough to yield consistent records and hence reliable findings. Secondly, the research has diverse covariates with most of them having paired baseline and follow-up covariates for exhaustive comparisons of associations. Finally, this was not a single-center study, it involved two district hospitals namely Embhuleni and Carolina for comparison and for completeness in coverage.

The researched prevalence of CKD among HIV patients in Albert Luthuli municipality of South Africa was 14.85%. This prevalence is within the range 6% to 45% which is the CKD prevalence in HIV patients in Africa as cited by Moosa et al. (2015). Similar studies which were carried out in South Africa for example by Zachor et al. (2016) in Cape Town and by Moosa et al. (2015) in South Africa showed the prevalence of 2%-6%. The difference between the prevalence findings could be explained by research design, populations studied, variables considered and the criteria used for the diagnosis of CKD. The prevalence of CKD among the lost and transferred patients in this research were 14% and 9% respectively. The patients lost to follow-up and the patients who transferred from the hospital were presumed to be part of the research and to be alive until the end of the research (Etikan et al 2017, 2018; Goel et al, 2010).

The researched risk factors found to be associated with CKD by using multivariate logistic regression were gender, age, baseline creatinine, hospital, ART adherence, Treatment

(EFV+D4T+3TC), Treatment (EFV+AZT+3TC), lost to follow-up and Baseline Alanine Transaminase. The finding in this research on risk factors to CKD concurs in many ways with the study findings by Kalayjian et al. (2012), Menezes et al. (2011), Nishijima et al. (2017), Hilton (2013), Boswell & Rossouw (2017) and Crum-Cianflone et al. (2010) who had HIV, race, sex, age, low CD4, high viral load, diabetes, ART, weight, high sodium and hypertension as the risk factors to kidney disease. However, there is no consensus among researchers on the effect of TDF-containing ART regimens on CKD. Although ART may improve kidney function, TDF-containing regimens have been found to have the potential to cause nephrotoxicity and hence to significantly contribute to CKD among HIV-infected patients. This finding agrees with Boswell and Rossouw (2017), Wyatt (2015) and Kalayjian et al. (2012). Wyatt (2015) pointed out that TDF is associated with kidney toxicity and decrease in creatinine clearance or decrease in GFR. The effect of ART adherence on CKD is controversial in that good ART adherence is associated with hazardous effect to CKD while poor ART adherence is negatively associated with CKD. Could this mean that the avoidance of ART drugs could be associated with reduced chance of having CKD?

The baseline findings from Figure 3 and Table 4 show that patients with Baseline creatinine which is above normal are about 4.8 times likely to experience CKD relative to patients with Baseline creatinine which is below normal. In addition, patients with Baseline creatinine which is above normal are about 2.4 times likely to experience CKD relative to patients with normal Baseline creatinine. These statistically significant findings reinforce the need for inclusion of creatinine in GFR equation.

Although gender is modest in statistical significance at multivariate levels as shown in Table 4, it is a significant risk factor just like race as cited in several studies. Research study in Albert Luthuli found out that being a male increases the odds of having CKD by about 3.5 times the odds of female having CKD. The fact that males are more likely to experience CKD is

confirmed by baseline findings in Figure 4 and in Table 5. The significance of gender and race as risk factors to CKD is reinforced by their inclusion in the MDRD formula.

Another significant researched risk factor to CKD and which happens to be included in the GFR formula is age. The clinical and statistical significance of age is evidenced not only by its inclusion in GFR formula but also by its selection into logistic regression. The effect of age on CKD is due to glomerular filtration rate which declines at 6.3 ml/min/1.73m² per decade as cited by Denic et al. (2016). Baseline findings on age in Figure 5 and in Table 6 indicate that adults and adolescents are more likely to experience CKD relative to children.

On the management of CKD; Pedro, Ortiz and Soto (2016) supported the use of TDF but hinted on its nephrotoxic potential and pointed out the need for the adjustment of the dose when baseline creatinine clearance is below 50ml/min. Boswell and Rossouw (2017) pointed out that current local guidelines recommend that TDF be substituted by an alternative Nucleoside reverse Transcriptase Inhibitors (NRTI) when a patient's GFR is less than 50ml/min and when using MDRD method. Moosa et al. (2015) gave some guidelines on dose adjustments for ART in CKD cases for Lamivudine (3TC), Stavudine (d4T) and Tenofovir (TDF).

Some other points to note on the management of CKD as cited by many studies are:

- All individuals should be assessed for kidney disease at the time of diagnosis of HIV and annually thereafter.
- Prevention of CKD at the population level through interventions that improve lifestyles and diet that lead to a reduction in BP, obesity, type 2 diabetes mellitus, smoking and salt ingestion.
- Careful screening and monitoring of high-risk patients.
- Increased awareness of CKD and knowledge on how to manage kidney disease should be emphasized for general medical practioners.

Labuschagne and Nel (2017) cited main challenges in handling of CKD; firstly, the extent of HIV epidemic and its associated burden on CKD, secondly there are no measures to prevent renal disease in people living with HIV or to detect CKD early enough to treat it and lastly the challenge of a rise in diet-related non-communicable diseases such as obesity and hypertension. Some other challenges include costly dialysis, in 2017 South Africa had only three public hospitals which offered kidney transplants.

The researcher acknowledges several limitations in this study. First, despite hypertension and diabetes being regarded by many studies as important risk factors to CKD, they could not be included because of missing data. Second, the tool for the diagnosis of CKD has some limitations as pointed out by Danic et al. (2016) that the formula leads to over-diagnosis in the elderly and under-diagnosis in younger adults. Third, this research had predominantly black participants and hence it failed to evaluate the effect of race on CKD as was done by Winston et al. (2008) and by Hilton (2013), who showed that black race is the most important determinant of kidney disease prevalence in HIV-infected persons. Lastly, as was concluded by Bukabau et al. (2019), African American ethnic correction factors for MDRD and CKD-EPI should not be used in Sub-Saharan populations. This agrees with Ekrikpo et al. (2018) who pointed out that there is still inadequate information about the best creatinine based GFR formula for Africa in general and for HIV population in particular.

Conclusion

This study, through the application of multivariable logistic regression, found the factors associated with CKD as: gender, age, baseline creatinine, hospital, ART adherence, treatment (regimen 1), lost to follow-up and Baseline Alanine Transaminase. Given HIV/AIDS

325 background and the diversity of the worsening risk factors to CKD in Africa and in South
326 Africa, there is need for some concerted effort to alleviate health and economic burden caused
327 by CKD. This research has presented risk factors associated with CKD in Albert Luthuli
328 Municipality and the expected action is to educate the nation on prevention, early detection and
329 on informed management of CKD. The study established diverse baseline statistics against
330 which future research may be based.

Abbreviations and Acronyms

Abbreviation/Acronym	Meaning
3TC	Lamivudine
CD4	Cluster of Differentiation 4, a glycoprotein that is found primarily on the surface of helper T cells
d4T	Stavudine
DoH	Department of Health
EFV	Efavirenz
Gender(0)	Males
Gender(1)	Females
HIV	Human immunodeficiency virus
HIV/CKD	HIV patients with CKD or without CKD
HAART	Highly Active Antiretroviral Therapy
Hospital(1)	Carolina hospital
Hospital(2)	Embhuleni hospital
HR	Hazard ratio
Lost(0)	HIV patients not lost to follow-up.
Lost(1)	HIV patients lost to follow-up.
MDoH	Mpumalanga Department of Health
NVP	Nevirapine
OR	Odds ratio
TDF	Tenofovir disoproxil fumarate
SAS	Statistical Analysis System
R	Statistical Package
Stata	Statistical software package created by StataCorp
TB	Tuberculosis
Treat1 (1)	ART regimen one (NVP+D4T+3TC)
Treat1 (5)	ART regimen one (EFV+D4T+3TC)
Treat1 (6)	ART regimen one (EFV+AZT+3TC)
Treat1 (18)	ART regimen one (EFV+3TC+TDF)
Treat1 (19)	ART regimen one (NVP+3TC+TDF)
USAID	United States Agency for International Development
WHO	World Health Organisation

Source for most abbreviations: Ministry of Health and Social Services (2003). Guidelines for Anti-Retroviral Therapy. Windhoek, Namibia.

333 Definitions

334 **Transferred patient** - a patient who leaves a current health facility to another health facility
 335 because of personal reasons or because of *HIV treatment failure which may include drug*
 336 *resistance, drug toxicity or poor adherence to antiretroviral therapy (ART).*

Lost to follow-up patient - a patient who gives a threat to the long-term success of antiretroviral therapy programme by failing to visit the clinic for 90 days or more since the patient's last clinic visit.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the South African local and national research guidelines. Ethics approval for this project was obtained from UNISA Ethics Review Committee (ERC) with the approval number being (2017/SSR ERC/005). The permission to conduct the study at Carolina and Embhuleni hospitals was obtained from Mpumalanga Department of Health with the permission number being (MP_201708_013). The consent to participate does not apply since no reference to an individual respondent was made, all results were handled in aggregate format.

Availability of data and materials

The data that support the findings of this study are available from the Department of health, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Department of health.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Pepukai Bengura, Prof Principal Ndlovu and Mulalo Annah Managa contributed equally to this work hence the corresponding author is transferable if the need arises. PB was involved in obtaining ethics approval, data collection/analysis and drafting of the manuscript. PD and MAM contributed to data interpretation, project design and editing the manuscript. All authors read and approved the final manuscript.

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373 assisted with data collection while the administrative staff swiftly performed data collection
374 permissions protocols.

375 **Consent for publication**

376 Not applicable.

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Figures

Figure 1: The frequency distributions of ART treatment regimens and Chronic kidney disease (CKD) cases

Key for graphs for adjusted covariates based on Treatment by Hospital from top to bottom:
 1. (EFV+3TC+TDF) at Embhuleni 2. (NVP+3TC+TDF) at Embhuleni 3. (NVP+D4T+3TC) at Embhuleni 4. (EFV+3TC+TDF) at Carolina 5. (EFV+D4T+3TC) at Embhuleni 6. (NVP+3TC+TDF) at Carolina 7. (NVP+D4T+3TC) at Carolina 8. (EFV+AZT+3TC) at Embhuleni 9. (EFV+D4T+3TC) at Carolina. 10. (EFV+AZT+3TC) at Carolina.

Figure 2: Predicted probabilities for positive Chronic kidney disease (CKD) obtained from the fitted logistic model.

Figure 3: Kaplan-Meier survival function estimates for Baseline creatinine strata

Figure 4: Kaplan-Meier survival function estimates for Gender strata

Figure 5: Kaplan-Meier survival function estimates for Age group strata