RENAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS IN THE ERA OF ANTIRETROVIRAL TREATMENT IN SOUTH AFRICA

DR SHIRELLE ASSARAM

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A dissertation submitted to the College of Health Sciences, University of KwaZulu-Natal, in fulfilment of the requirements for the degree of Master of Medical Sciences (Internal Medicine)

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This is to certify that the contents of this thesis are the original research work of Dr Shirelle Assaram

As the candidate's supervisor, I have approved this thesis for submission

Supervisor:

Signed:----------Name: **Prof Nombulelo P Magula** Date:30.03.2017

Co-supervisor:

Signed: Name: **Dr Tivani P Mashamba-Thompson** Date:-28 March 2017--

ABSTRACT

Background:

Sub-Saharan Africa carries the global burden of human immunodeficiency virus (HIV) infection. Renal disease is a well-recognized and closely associated complication of HIV infection. The burden of kidney disease in Africa is aggravated by poor socio-economic factors and by the lack of access to healthcare and to resources. Most of what is known regarding HIV related kidney disease has come from research done in high income countries.

Aim: Demonstrating the current stance on renal manifestations of HIV in South Africa in the era of antiretroviral treatment (ART).

Study design: This is a cross-sectional study. Mixed data acquisition methods using qualitative and quantitative research approaches were applied in this study in order to achieve the objectives. These included a systematic scoping review and a retrospective chart review.

Data collection and analysis: The systematic scoping review began with a database search of published literature based on studies conducted in South Africa. The following databases: Google Scholar, PubMed, Medline, Cochrane Library, Worldcat.org and EBSCO host were searched to obtain relevant literature. We formulated a standardized data extraction table according to the PICO model. We presented a narrative account of the findings by performing a thematic content analysis of the included studies. For the chart review we extracted data from medical records of all new patients initiated on ART from April 2010 to December 2013. The sample size was 350 patient records. We collected data at baseline (pre-ART) and then at 6, 12, 18 and 24 months on ART. Descriptive statistics were used to describe the characteristics of HIV-related renal manifestations at the King Edward VIII Hospital ART clinic.

Results: The results of the systematic scoping review showed that normal renal function occurred in 28.4% to 79% of patients, mild renal impairment occurred in 19% to 57.1% and moderate renal impairment in 2% to 14.4%. Only 1.3% of patients had severe renal impairment. Both the Cockcroft-Gault equation (after correcting for bias) and the 4-variable Modification of Diet in Renal Disease equation (without the ethnicity factor for African Americans) have been validated for the estimation of glomerular filtration rate (eGFR) in Black South Africans. HIV-associated nephropathy was the most prevalent histology seen (57.2%). Older age, a lower CD4 count, a low haemoglobin and a detectable viral load were linked to renal impairment. Renal function improved in the first year of commencing ART.

With regards to the chart review, 64% of the cohort was female, 99% were African and the mean age was 36.9±9.7 years. At baseline, 10 patients had hypertension, 6 had diabetes, 61 were co-infected with tuberculosis (TB) and 157 patients had a high body mass index (BMI) with 25.4% being categorized as

overweight and 19.4% obese. Regarding baseline renal function, the majority of the patients had a normal renal function: 90.4% (95% confidence intervals (CI):86%-93%); 7.0% (CI:5%-10%) had moderate renal impairment; 1.3% (CI:0%-3%) had severe renal impairment; and 1.3% (CI:0%-3%) had kidney failure. The risk of renal impairment increased by 1.06 (CI: 1.03 – 1.10) times as BMI increased by one unit. The association of hypertension (HPT) with abnormal renal function was found to be insignificant, $p>0.05$. The majority of patients were initiated on tenofovir disoproxil fumarate (TDF) (90.6%), in combination with lamivudine (3TC) (100%) and either efavirenz (EFV) (56.6%) or nevirapine (NVP) (43.4%).

Conclusion: The scoping review highlights age, CD4 cell count, haemoglobin, detectable viral load as factors associated with renal impairment and the improvement in renal function with use of ART. As more patients are started on ART according to the 'test and treat' approach to HIV prevention and management in South Africa, it is possible that the benefit may extend to the burden of kidney disease, however, hypertension, diabetes and obesity may reduce these benefits. The chart review found a low prevalence of baseline renal impairment in HIV-infected ART-naïve outpatients. An improvement in renal function after the commencement of ART has been demonstrated among this population. However, the long-term outcomes of patients with HIV-related renal disease is not known.

Keywords: Renal manifestations; HIV; antiretroviral treatment; South Africa

DECLARATION 1 – PLAGIARISM

DECLARATION

I.....DR SHIRELLE ASSARAM…….declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

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(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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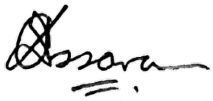
Signed:  Date: 28 March 2017

DECLARATION 2 – PUBLICATIONS & CONTRIBUTIONS

1. HIV Renal Manifestations during the Antiretroviral Era in South Africa: A Systematic Scoping Review

Contribution: Dr Shirelle Assaram contributed to the project by developing the proposal, carrying out data collection, data analysis, interpretation of the results as well as manuscript preparation and writing under the supervision of Prof NP Magula and Dr TP Mashamba-Thompson. Dr Suman Mewa Kinoo contributed in the abstract, full article screening and the quality assessment of the included studies.

2. Risk Factors and Co-Morbidities Associated with Changes in Renal Function among ART-naïve Adults in South Africa: A Chart Review

Contribution: Dr Shirelle Assaram contributed to the project by developing the proposal, carrying out data collection, data analysis, interpretation of the results as well as manuscript preparation and writing under the supervision of Prof NP Magula and Dr TP Mashamba-Thompson.

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DEFINITION OF TERMS

Chronic kidney disease - The presence of 3 months or more of kidney damage or a glomerular filtration rate (GFR) of <60mL/min/1.73m^2 irrespective of cause. Kidney damage can be detected by the presence of albuminuria, defined as albumin-to-creatinine ratio >30mg/g in two of three spot urine specimens.

Hypertension - Persistent elevation of blood pressure (BP) ≥ 140/90. Repeat measurements should be performed on 3 separate occasions within a period of 2 months, to determine whether a diagnosis of hypertension is valid.

Incidence – Incidence is the rate of new (or newly diagnosed) cases of the disease. It is generally reported as the number of new cases occurring within a period of time.

Prevalence - Prevalence is the actual number of cases alive with the disease either during a period of time (period prevalence) or at a particular date in time (point prevalence). It is most meaningfully reported as the number of cases as a fraction of the total population at risk.

ACRONYMS AND ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ARF	Acute renal failure
ART	Antiretroviral treatment
ATN	Acute tubular necrosis
BP	Blood pressure
CG	Cockcroft-Gault
CKD	Chronic kidney disease
d4T	Stavudine
EFV	Stocrin
eGFR	Estimated glomerular filtration rate
FDC	Fixed dose combination
GFR	Glomerular filtration rate
HAART	Highly active antiretroviral treatment
HIV	Human immunodeficiency irus
HIVAN	HIV-associated nephropathy
HPT	Hypertension
HSRC	Human Science Research Council
MDRD	Modification of diet in renal disease
MMAT	Mixed methods appraisal tool
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NSP	National Strategic Plan
NVP	Nevirapine
PI	Protease inhibitor
PMTCT	Prevention of Mother to Child Transmission
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
3TC	Lamivudine
WHO	World Health Organization
UNAIDS	Joint United Nations Programme on HIV/AIDS

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CHAPTER 1: INTRODUCTION

1.1. Background

Human immunodeficiency virus (HIV) infection affects multiple organs and its manifestations in the kidney are variable (1). The incidence of kidney disease is higher in low income countries than in high income countries (2). Most of the data regarding renal involvement in HIV infection has come from research done in high-income countries. However, the presentation of renal disease in Africa is different to that reported in high income countries (3).

In high income countries the burden of the cost of dialysis is carried by the government e.g. the Medicare Chronic Kidney Disease program in the United States which allows for close to universal access to treatment for chronic kidney disease (CKD) (4). The availability and accessibility of dialysis and transplantation in Africa varies and is limited due to the high costs involved and the scarcity of donors (2). Also in the United States, due to the production and early increased access to antiretroviral treatment (ART), the incidence of HIV-associated renal disease progressing to end stage renal disease has remained steady or has decreased (5). On the other hand, Mayosi et al. reports for instance a 67% increase in deaths related to nephritis or nephrosis in South Africa from 1999 to 2006 (6). The increase in the prevalence of kidney disease may be causally linked to the rising burden of HIV infection and HIV related kidney disease in South Africa (3). Those affected are mainly young black adults who present with severe opportunistic infections mainly tuberculosis (TB) and who have no past history of illness (3). The estimated number of nephrologists per million population in the United Kingdom is 5.3 (7) as opposed to Nigeria and South Africa where the number of nephrologists per million population is estimated to be 0.6 and 1.1, respectively. This suggests that Africa has the lowest number of nephrologists per million population globally (8, 9). The third leading cause of end stage renal disease among Black American men aged 20 to 64 years old was found to be HIV associated nephropathy (HIVAN) (10, 11). The peak prevalence of CKD in Nigeria is between 30 and 50 years of age (12, 13). HIVAN is the most common pattern of renal disease seen in South Africans based on renal biopsies performed on HIV infected individuals in Cape Town between January 2000 and December 2009 (8). The early detection of acute and chronic renal failure is delayed by the lack of routine screening of renal function due to overburdened clinics and laboratory facilities in the public health sector (3) and by the limited access to renal biopsies in parts of Africa (8).

Access to health care including to ART varies in Sub-Saharan Africa due to socio-economic and political factors (1, 3). Therefore, a study in a single country in Sub-Saharan Africa cannot be used to make deductions about the epidemic in the entire region (1). The data on the incidence, prevalence

and causes of HIV-related renal disease in Africa thus far have been unreliable because there have been no large epidemiological studies in this region (3, 8). Recently, several reports have emerged which emphasize the lack of knowledge about renal disease in Africa and the need for further research in this continent (1).

1.2. Problem statement

Most of what is known regarding the renal involvement in HIV infection has come from research done in high income countries. At some stage of their HIV infection, 10% of patients will develop HIV-related renal disease, according to data from the United States (14). Extrapolating this to the South African context, suggests that an estimated 650 000 patients may develop HIV-related renal disease (14). A large burden of CKD would place immense pressure on the resource strained health system (15). There has been an increase in mortality in South Africa related to CKD (6). Early detection of renal disease and quick referral to a nephrologist is crucial in the management of the disease but a lack of resources and finances hinders this process in low income countries such as South Africa (15). Although Sub-Saharan Africa carries the global burden of HIV infection, there is a lack of research in this region particularly with respect to HIV-related kidney disease (16). Mapping published peer reviewed evidence and demonstrating the current stance on renal manifestation of HIV in South Africa in the era of ART could help identify the research gaps and novel ideas for future research. This could also produce evidence to guide health policy makers and implementer of health interventions on the most appropriate intervention for reducing renal manifestations of HIV in high disease burdened settings.

1.3. Research questions

Main research question

What are the renal manifestations of HIV infection in South Africa in the era of ART?

Specific research questions

1. What is the research gap on the renal manifestations of HIV infection in South Africa in the era of ART?
2. What is the current pattern of HIV-related renal manifestations reported in South Africa in the era of ART?

1.4. Aims and objectives of this study

Main aim

Demonstrating the current stance on renal manifestations of HIV infection in South Africa in the era of ART.

Objectives

1. To conduct a scoping review in order to identify the literature available on the renal manifestations of HIV in South Africa in the ART era.
2. To conduct a retrospective chart review focussing on the following renal manifestations:
    - Change in estimated glomerular filtration rate (eGFR) from baseline to 24 months on ART
    - Change in blood pressure (BP) from baseline to 24 months on ART
    - Urine dipstick abnormalities documented in patients who had the test done
    - Risk factors and co-morbidities associated with abnormal renal function.

1.5. Overview of this thesis

This thesis consists of four chapters (including the current chapter):

Chapter 1: This chapter presents the background, aim, objectives and significance of the study as well as providing a general outline of the thesis and its structure and the literature review and methodology.

Chapter 2: This chapter presents the results of the systematic scoping review, aimed at investigating the renal manifestations of HIV in South Africa in the era of antiretroviral treatment (ART). The manuscript is presented in the form of a journal article entitled 'HIV Renal Manifestations during the Antiretroviral Era in South Africa: A Systematic Scoping Review'. This manuscript is currently under review at the BMC: Systematic Reviews Journal.

Chapter 3: This chapter presents a retrospective chart review aimed at determining the risk factors and co-morbidities associated with renal impairment in an HIV-cohort to influence changes in policy and to guide future research. The chapter is presented in the form of a manuscript entitled: 'Risk Factors and Co-Morbidities Associated with Changes in Renal Function among ART-naïve Adults in South Africa: A Chart Review'. The manuscript is currently under review at the South African Journal of Infectious Diseases.

Chapter 4: This chapter is a discussion of study findings, strengths and limitations as well as a conclusion which contains some observations on the findings of this study, suggests future plans and makes recommendations for future research, based on the findings of this study.

1.6. Literature Review: Renal manifestations of HIV in South Africa

1.6.1 Introduction

Tackling the HIV and acquired immunodeficiency syndrome (AIDS) pandemic is the world's most challenging public health issue (17). Thomas Quinn described HIV/AIDS as "our modern day plague" (18). In 2003, two thirds of the worlds' people living with HIV were from Africa (17). The early stages of the epidemic in South Africa was limited to a few hundred cases among men who had sex with men and recipients of unsafe blood transfusions (19). However, heterosexual transmission came to the forefront in the early 1990's and the epidemic grew exponentially, extending to new-borns and children through perinatal transmission (19). The government at the time was subjected to intense criticism both locally and internationally for the denial of the causal relationship between HIV and AIDS (20). In 2006, 34% of AIDS related deaths globally occurred in South Africa (21). South Africa had the highest number of people living with HIV worldwide, estimated at 5.3 million as of December 2007 (10, 22).

The National HIV/AIDS and Sexually Transmitted Infections (STI) National Strategic Plan (NSP) was implemented to tackle this epidemic. The primary objectives of this plan were to reduce HIV incidence by 50% and to expand the availability and access of ART to 80% of the population who required it (22). An amount of R8.4 billion was budgeted in 2010-2011 for the expansion of the ART and Prevention of Mother to Child Transmission (PMTCT) programmes, for the promotion of HIV and tuberculosis (TB) treatment integration and for greater investments in HIV prevention (23). For the ART rollout in South Africa to reach full circle, an understanding of patient knowledge, attitudes and behaviours was essential because cultural factors can influence attitudes toward medication and health care practices (24, 25). Between August and October 2002, Nachega et al. conducted such a study in Soweto, South Africa and revealed good knowledge (averaging 86%) of the study population about HIV/AIDS (24). The media plays a vital role in education and awareness of the disease and this needs to be continually reinforced. However, the low rate of disclosure of HIV status to sexual partners, family and friends suggests that HIV/AIDS related stigmatization is rife and could play a role in impeding access to ART and affect compliance to ART (25).

According to the Human Sciences Research Council's (HSRC's) National HIV Prevalence, Incidence and Behaviour Survey, the number of South Africans infected with HIV increased from 10.6% in 2008 to 12.2% in 2012 taking the total number of people infected with HIV in South Africa to 6.4 million in 2012 (26). The increased prevalence of HIV in 2012 can be contributed to a combination of the effects of new infections and a successful ART programme (resulting in decreased mortality amongst infected individuals) (26). Females continue to bear the brunt of the disease with the

incidence rate in females aged between 15 to 24 years of age being 3.1% as opposed to their male counterparts at 1.3% (in 2012) (27). The population knowledge on the basics of HIV/AIDS decreased from 2008 to 2012 suggesting a shift in the holistic management of HIV to biomedical interventions such as ART and less on the social and behavioural aspects (26). A domino effect is evident in the increase in risk seeking behaviour and the resultant high rate of new HIV infections in 2011. Sub-Saharan Africa accounted for 71% of new infections in adults and children worldwide (27). In 2015 the HIV prevalence rate in South Africa was estimated at 7 million people living with HIV according to the Joint United Nations Programme on HIV/AIDS (UNAIDS), with 19.2% of adults aged 15 to 49 years being HIV infected (28). In this review, the ART regimes, renal disease and renal manifestations of HIV infection with a specific focus on South Africa will be discussed.

1.6.2 ART in South Africa

It has been globally acknowledged that combination Antiretroviral Treatment (ART) improves the quality of life for infected individuals, reduces opportunistic infections and AIDS related mortality (29). There is growing scientific evidence that supports the use of early ART for both prevention of HIV transmission and clinical care.

In 1983 the first case of AIDS was diagnosed in South Africa (19). The National ART programme in South Africa was launched in April 2004 (30, 31). This delay in access to ART for the many infected South Africans resulted in the death of more than 300 000 people living with HIV (19). Initially South Africa had difficulty procuring ART for its population infected with HIV due the costs involved (24, 32). Wood et al. in their study in 2000 found that the cost of treating 25% of HIV infected South Africans with triple ART would be more than $19 billion (32). This was soon rectified as a result of a combination of reduction in drug prices, private donations, the availability of generic drugs and the establishment of the Global Fund to Fight AIDS, Tuberculosis (TB) and Malaria (24).

The South African ART guidelines are based on the World Health Organization (WHO) guidelines which has two treatment regimens: a first line regimen that includes two nucleoside reverse transcriptase enzyme inhibitors (NRTI) with a non-nucleoside reverse transcriptase enzyme inhibitor (NNRTI); and a second line regimen that contains two NRTI'S with a protease enzyme inhibitor (PI) (31). Stavudine (D4T) was the NRTI widely used in the first line as part of the 2004 ART guidelines (31). This drug was implicated in causing peripheral neuropathy, hyperlactataemia and lipodystrophy (33, 34). Boulle et al.'s study found that almost all drug substitutions due to drug toxicity in patients on a longer duration of ART, occurred in patients who were on D4T (33). In April 2010, tenofovir replaced D4T as the NRTI in first line treatment (35). On 1 April 2013, tenofovir in the form of a fixed dose combination (FDC) tablet was made universally available (36). All patients on D4T were changed to the FDC tablet and ART naïve patients were initiated on FDC as per the national guidelines (36). By mid-2011 adult ART coverage was close to 80% of all HIV-infected patients

eligible for ART (37). The number of patients who started ART in 2010/2011 was in excess of the number of people who became eligible to receive ART over the same period, thereby exceeding the targets set in the 2007-2011 NSP (37). In 2012, the number of HIV infected people on ART in South Africa increased to 31.2% from 16.6% in 2008 (26).

The other notable change in the guidelines over the years has been the CD4 count threshold for initiation of ART. This was initially set at a CD4 count < 200µl in 2004 (31) and was increased to a CD4 count of ≤ 350µl in 2013 (36). Granich et al. proposed that by expanding ART to CD4 < 500µl, there would be a significant decrease in death, disability and expenditure on HIV/AIDS over 40 years, an assumption based on a well-run ART programme (38). This supports South Africa's decision to adopt this policy and expand its ART programme to include patients with a CD4 count ≤ 500µl (39). As of September 2016, South Africa has adopted the WHO policy and has initiated all HIV infected individuals on ART irrespective of CD4 count (40). This will help ensure that the South African ART programme reaches targets set by the Joint United Nations Programme on HIV/AIDS to have 90% of all people tested for HIV, treated and virologically suppressed by 2020 (40). Currently, South Africa has the largest ART programme in the world.

1.6.3 Renal disease in the general population

Worldwide the incidence of CKD is increasing at an annual growth rate of 8% (2). CKD is defined as the presence of 3 months or more of kidney damage or an eGFR of <60mL/min/1.73m^2 irrespective of cause (41). eGFR can be calculated from calibrated serum creatinine and estimated equations such as the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault (CG) equations which have been suggested to most closely approximate GFR in many African populations (41).

South Africa is experiencing a double burden of disease with an increase in infectious diseases namely HIV/AIDS and TB along with an increase in non-communicable diseases such as hypertension (HPT), diabetes and cancer (6). The risk factors for renal disease include communicable diseases e.g. HIV, infectious glomerulonephritis, schistosomiasis, non-communicable diseases such as HPT, diabetes and the use of traditional/herbal medication (42). In their systematic analysis, Stanifer et al. found that CKD is a prevalent and potentially growing disease in Sub-Saharan Africa with 24% of hypertensives, 18.9% of diabetics and 10% of HIV infected patients having co-morbid chronic kidney disease (42). HPT was the most common cause of end-stage renal disease in Black South Africans (43). As per the South African Hypertension Guidelines, HPT is defined as a persistent elevation of blood pressure (BP) ≥ 140/90 (44). In South Africa in the year 2000, elevated BP was the second leading risk factor for deaths following sexually transmitted disease (45).

1.6.4 Renal manifestations of HIV in South Africa

Fabian et al. described the clinical spectrum of renal disease seen in the course of HIV infection, as acute renal failure (ARF), electrolyte disturbances, intrinsic renal diseases e.g. co-morbid hypertension or diabetes mellitus and the group of HIV-associated glomerulonephropathies that may present with acute or chronic renal failure (46). It is this group of glomerulonephropathies that contribute to the burden of CKD in HIV infection (46).

Due to the large number of people infected and living with HIV in South Africa, the prevalence of CKD has increased (3). At the Groote Schuur Hospital in Cape Town, South Africa, acute dialysis for HIV infected patients has become the most common indication for acute dialysis since January 2009 (3). The commonest cause of ARF in HIV infected patients is acute tubular necrosis secondary to sepsis, hypotension, dehydration or nephrotoxic drugs (3, 46). Although ARF is potentially reversible with treatment, it carries a high mortality in the HIV population (11). Morbidity from acute kidney injury is significant in black communities where HIV infected individuals seek the herbal treatment offered by traditional healers to assist them with AIDS related symptoms (3).

In April 2010, the National ART programme in South Africa added tenofovir disoproxil fumarate (TDF) to the first line ART regimen (35). TDF is excreted from the kidneys by glomerular filtration and active proximal tubular secretion and it can accumulate in the proximal tubular cells causing renal toxicity and renal failure (47). It is therefore now imperative for all patients to be screened for renal dysfunction prior to starting ART, as any patient with pre-existing renal impairment would need alternative ART (35, 48). The recent South African ART guidelines recommend doing a serum creatinine and creatinine clearance at baseline (prior to ART initiation) and then at 3 months, 6 months, 12 months and annually thereafter for patients on TDF (35).

Ultrasound to assess kidney size are available at most public hospitals in South Africa but renal biopsy facilities are limited to tertiary level institutions (3). In a retrospective review by Gerntholtz et al. of 104 renal biopsies performed at Chris Hani Baragwanath Hospital in South Africa, classic HIVAN was found in 30% of the reviewed biopsies while about 20% were classified as “HIV immune complex kidney disease” (16). This emphasizes the key role of renal biopsy in diagnosing HIV-associated renal disease, as only one third of the biopsies met the criteria for classic HIVAN (1). The lack of resources for renal biopsy precludes many patients from accurate diagnosis and proper treatment.

The data from another study in South Africa, Han et al. suggested that HIVAN is possible in patients without overt nephrotic syndrome and in patients who have only microalbuminuria. Therefore microalbuminuria can be considered an early marker of HIVAN (10). The data on urinary screening by Fabian et al. showed that urinary abnormalities are common in the HIV infected and ART naïve

outpatients, and routine urinary screening of all new patients at ART clinics should be standard practice (49). Stanifer et al. showed that the prevalence of proteinuria when measured in people with HIV, HPT or diabetes is substantial. However the best method of urine protein detection is unknown (42).

1.6.5 Discussion

The HIV prevalence in children under 14 years old has declined over the past decade suggesting the success of the PMTCT programme (26, 50). Mayosi et al. reported that mortality related to HIV/AIDS has declined by 20% in adults and 43% in children respectively and life expectancy has increased by 6 years as a result of the successful ART programme in South Africa (51). South Africa has made significant progress with the ART programme since its implementation in 2004. The longer life expectancy on ART has implications for other chronic diseases, the burden of which will surely increase. Until recently, the MDRD and CG equations to estimate GFR had not been validated in the South African population or in HIV infected patients (1, 42). This is important to note as GFR can be affected by diet and creatinine clearance can be altered by factors such as intake of meat and protein, muscle mass, medication and concurrent illness (important factors for patients in sub-Saharan Africa) (1). The extensive rollout of TDF, a potentially nephrotoxic drug, in first line ART in South Africa implies aggressive screening for baseline renal dysfunction and continued renal function monitoring whilst on TDF. However, access for patients to services such as renal ultrasound, renal biopsy and nephrology assessment is limited.

1.6.6 Conclusion

The increased burden of HIV infection and other non-communicable diseases, will require the integration of the care of both communicable and non-communicable diseases. Improved urine diagnostics that are cheap and accessible to even rural areas are needed to detect renal dysfunction early so that potentially nephrotoxic ART can be avoided and patients can be timeously referred to nephrologists/CKD clinics. Dedicated CKD clinics should be established and accessible to patients in rural and urban areas to access specialised services e.g. renal biopsy and dialysis. More research is necessary to determine the association between baseline renal insufficiency and ART outcomes in patients on TDF.

More patients on ART will probably result in a further increase in chronic disease in South Africa, mainly CKD, hypertension and diabetes. The impact of this burden of chronic disease on the already resource strained healthcare system is not known. However, with a lack of dedicated CKD clinics and specialist renal services particularly in the rural settings, as well as a deficiency in knowledge on the long term impact of ART on CKD, a further strain on the health systems is anticipated.

1.7. Methodology: Renal Manifestations of HIV in the era of ART in South Africa

Theoretical Framework

We considered the various systematic approaches available for reviewing published literature and chose to undertake a systematic scoping review of published literature as the best method to map the renal manifestations of HIV infection in South Africa in the era of ART. Scoping review methodology is particularly useful for examining a broadly covered topic to comprehensively and systematically map the literature and identify key concepts, theories, evidence, or research gaps. Unlike systematic reviews or meta-analyses, scoping reviews do not narrow the parameters of the review to research trials or require quality assessment. It is rigorous and methodical in its approach to examining the extent, range and nature of research activity in a particular field while encompassing both empirical and conceptual research with broadly framed questions (52). Arksey and O'Malley's scoping review framework outlines a five stage approach (53) with each stage listed below:

- Stage One - Identifying the research question: maintain a broad scope to research questions to summarize a breadth of evidence.
- Stage Two - Identifying relevant studies: breadth and comprehensiveness of scoping studies are important and must be balanced with the feasibility of resources.
- Stage Three - Study selection: entails post hoc inclusion and exclusion criteria based on the research question and new information on the subject through reading the studies.
- Stage Four - Charting the data: a data-charting form is developed for use to extract data from each study. A 'narrative review' or 'descriptive analytical' method is used for data extraction.
- Stage Five - Collating, summarising and reporting the results: this involves a descriptive numerical summary and a thematic analysis.

We have adapted the Arksey and O'Malley's conceptual framework to suit our study. The broad nature of the research question can create a deficiency in the clarity, direction and focus required to inform subsequent stages of the research process such as study inclusion (54). Levac et al. 2010 suggest combining the broad research question with clear articulation considering the concept, target population and health outcomes of interest to clarify the focus of the scoping study and establish an effective search strategy (54). This is the approach we chose to adopt to assist our search strategy. We assembled a scoping review team to enhance Stage 2 by providing the methodological and context expertise required when making decisions regarding breadth and comprehensiveness. In Stage 3 of Arksey and O'Malley's framework, they do not indicate a team approach for this step (53). However,

other researchers found a multidisciplinary team approach more practical and vigorous in study selection (54, 55) as did we. We developed a data extraction table according to the patient, population or the problem, intervention, comparison and outcome (PICO) model for clinical questions (56). Two reviewers performed a quality assessment of the included studies using the mixed methods appraisal tool (MMAT) for mixed methods studies to evaluate the risk of bias (57). In our scoping review study we performed thematic content analysis to identify patterns of renal manifestations in the included studies. We chose to replace Stage 6 of Arksey and O'Malley's framework which is the consultation with major key holders with a retrospective chart review. We believed that the chart review would provide a higher quality of evidence as opposed to the consultation process which provides mainly subjective data. The systematic scoping review will provide a broad overview and will highlight key concepts and deficiencies that will guide the chart review (58).

The retrospective chart review uses existing data (medical records) that have been documented for reasons other than research (59). Conducting a chart review is an inexpensive method of analysing readily accessible data. It allows for the study of rare occurrences and it facilitates the formation of hypotheses which can be tested prospectively(58).

Study Design

Mixed data acquisition methods using qualitative and quantitative research approaches were applied in this study in order to achieve the objectives. These were a systematic scoping review and a retrospective chart review.

Study setting

We assessed literature on the renal manifestations of HIV infected patients in South Africa. The chart review was that of patients attending the ART clinic in King Edward VIII Hospital in Durban.

1.7.1. Objective 1: To conduct a scoping review in order to identify the literature available on the renal manifestations of HIV infection in South Africa in the ART era.

Criteria for considering studies for this review:

- HIV infected patients in South Africa only with evidence of renal manifestations
- Studies published from 2004 to 2015
- Adult patients (≥18 years old) with evidence of renal manifestations
- English language publications

- Articles on South African data only

Exclusion Criteria:

- Patients <18 years of age
- Literature from outside South Africa
- Non-English literature
- Pregnant females with renal disease

Search methods for identification of studies

The study began with a database search of published literature based on patients in South Africa. We developed a list of primary and secondary search terms along with filtering methods. The primary search terms related to the kidney specifically (i.e. kidney, renal, nephrology). The secondary terms were manifestations, renal failure, complications, South Africa, antiretroviral treatment, proteinuria, glomerular filtration rate and hypertension. In order to direct the search to our research question, we used the filtering method which included the data range (2004 to 2015), human subjects, English language and adult patients (≥18 years old). MESH terms were also used.

Electronic search

We made use of the following databases: Google Scholar, PubMed, Medline, Cochrane Library, Worldcat.org and EBSCO host.

Data source and analysis

The research team formulated the search strategy to be implemented and two reviewers independently perused eligible studies for trial study selection. Various publications, including academic journals on the subject were used to collect the relevant data. Information was gathered from studies that included randomized controlled trials, non-randomized controlled trials, observational studies, review articles, case reports and systematic reviews. Only literature published from the year 2004 to 2015 was used for this review.

Selection of studies

This occurred in 2 stages. First one reviewer conducted a comprehensive screening of titles and decided on eligibility based on the inclusion and exclusion criteria. For example, titles stating research carried out in countries other than South Africa were excluded. If the reviewer was uncertain of the eligibility of a title, it was not excluded but rather carried on to the next stage of the selection process. All literature search results were uploaded to EndNote X7 software and duplicates were

removed. In the second stage of study selection, 2 independent reviews of the titles and abstracts using inclusion and exclusion criteria were undertaken. Where differences of opinion arose, a third reviewer was involved to reach consensus. The study selection procedure is illustrated using a PRISMA chart.

Charting the Data

We formulated a standardised data extraction table according to the PICO model. The table included bibliographic details, study design and setting, sample size, aim of the study, interventions, comparisons, outcomes and conclusions. Two reviewers performed a quality assessment of the included studies using the mixed methods appraisal tool for mixed methods studies to evaluate the risk of bias (57).

Collating, summarizing and reporting results

We presented a narrative account of the findings by performing a thematic content analysis on the extracted literature. Results were structured into the following themes: urine analysis, estimated glomerular filtration rate, renal biopsy, risk factors for renal dysfunction and clinical and histological responses to ART. The findings were scrutinised in relation to the overall aim of the study. Conclusions were drawn and recommendations for future research and clinical advancement were suggested.

1.7.2. Objective 2: To conduct a retrospective chart review focussing on the following renal manifestations:

- Change in GFR from baseline to 24 months on ART
- Change in BP from baseline to 24 months on ART
- Urine dipstick abnormalities in patients who had the test done
- Risk factors and co-morbidities associated with abnormal renal function.

Data sources

We collected data from the clinical charts of patients attending the ART clinic at King Edward VIII Hospital.

Sampling

We selected medical records of all new patients initiated on ART from April 2010 (as this was when TDF was commenced in first line ART regimens) to December 2013. We have selected a convenient sample size of 350 patient records. We collected data over a period of 24 months on ART.

Variables

The study variables were defined and determined by the nature of the investigation which was guided by the scoping review. They included the following:

- Demographic data: name, age, gender, ethnic group
- Medical history: history of diabetes, hypertension, tuberculosis, pregnancy.
- Medication history: ART regimen
- Clinical data: weight, height, body mass index (BMI), BP, urine dipstick (was evaluated in patients who had the test done), fingerprick glucose.
- Laboratory data: CD4, HIV viral load, full blood count, urea and electrolytes, glomerular filtration rate, plasma glucose, hepatitis B and C, cholesterol and triglycerides.

Variables were collected at baseline and thereafter at months 6, 12, 18 and 24 on ART.

Data Analysis

Data was analyzed during the research timeline. Analysis was rigorous, consistent and structured in a way which that matched the standards for quality assurance. Data was entered in the Excel database at the UKZN office in Durban, and was cleaned until there were no longer any discrepancies. Descriptive statistics which included frequency distribution, percentages and percentiles, means and standard deviations and cross-tabulations were used to describe the characteristics of HIV-related renal manifestation at King Edward VIII Hospital ART clinic.

1.7.3. Ethical Considerations

Risk to participants

This study consists of a scoping review and a retrospective chart review. Therefore, it did not pose any physical, biological or emotional risk to participants.

Benefits

To identify gaps in research and to generate a hypothesis for a prospective study.

To describe the magnitude of HIV or ART related renal complications in the local population.

Confidentiality/De-identifying data

We have not disclosed patient identification details.

Consent

None needed as there was no interaction with patients.

Permissions

- King Edward Hospital, Family Clinic, Department of Internal Medicine
- Biomedical Research and Ethics Committee (BREC), reference number BE486/15 and
- KwaZulu-Natal Department of Health

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CHAPTER 2: A SYSTEMATIC SCOPING REVIEW

Chapter 1 presented the background, aim, objectives and significance, as well as the literature review and methodology followed in this study. The literature review provided an overview of HIV, ART and HIV-related renal disease in South Africa. In order to get a closer look at the literature on the renal manifestations of HIV in South Africa during the ARV era, a systematic scoping review was conducted.

This chapter responds to objective 1 of this study viz. to conduct a systematic scoping review to identify the literature available on the renal manifestations of HIV infection in the era of ART in South Africa. This study was guided by Asksey and O' Malley's scoping review framework and revealed gaps in the research as well as helping to guide future research on HIV and renal disease in South Africa. The chapter is presented in the form of a manuscript entitled 'HIV Renal Manifestations during the Antiretroviral Era in South Africa: A Systematic Scoping Review'. This manuscript is currently under review at the BMC: Systematic Reviews Journal.

Renal Manifestations of HIV during the Antiretroviral Era in South Africa: A Systematic Scoping Review

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Abstract

Background: It is estimated that 650 000 patients may develop human immunodeficiency virus (HIV) related renal disease in South Africa. South Africa has recently adopted the World Health Organisation (WHO) policy, stipulating that all HIV-infected patients have access to antiretroviral treatment (ART) irrespective of CD4 cell count. The aim of this study is to explore the evidence of renal manifestations of HIV in South Africa in the era of ART.

Methods: We searched Google Scholar, PubMed, Medline, Cochrane Library, Worldcat.org and EBSCO host databases for articles pertaining to renal manifestations of HIV infection in South Africa. We independently reviewed the articles for quality. Thematic content analysis was performed to identify patterns of renal manifestations from the included studies. The risk of bias (e.g. internal validity) in the included studies was evaluated using the mixed methods appraisal tool.

Results: Eleven out of 21 studies were eligible for data extraction. The incidence of urine abnormalities on urine dipsticks was high but had poor sensitivity and specificity for detecting renal impairment. Normal renal function occurred in 28.4% to 79% of patients, mild renal impairment occurred in 19% to 57.1% and moderate renal impairment in 2% to 14.4%. Severe renal impairment occurred in 1.3% of patients. Both the Cockcroft-Gault equation (after correcting for bias) and the 4-variable Modification of Diet in Renal Disease equation (without the ethnicity factor for African Americans) have been validated for the estimation of glomerular filtration rate (eGFR) in Black South Africans. HIV-associated nephropathy was the most prevalent histology seen (57.2%). Older age, a lower CD4 count, a low haemoglobin and a detectable HIV viral load were associated with renal impairment. Renal function improved in the first year of commencing ART as evidenced by the regression of proteinuria and the increase in eGFR.

Conclusion: Evidence show that more patients on ART will probably result in a further increase in chronic disease in South Africa, mainly chronic kidney disease (CKD), hypertension and diabetes. The findings of the review have implications for the recently adopted ‘test and treat’ approach to HIV prevention and management.

PROSPERO registration number: CRD42016039270

Keywords: HIV; Antiretroviral treatment; Renal failure; South Africa

Background

South Africa recently (01 September 2016) adopted the World Health Organization(WHO) "test and treat" approach, which was introduced as a possible means of controlling the global HIV epidemic (3). This approach entitles every patient who tests positive for HIV to a lifelong antiretroviral therapy (ART) regardless of their CD4 count or clinical staging (3). With the successful rollout of ART in South Africa, the lifespan of people living with human immunodeficiency virus (HIV) has been prolonged thereby transforming HIV into a disease of chronicity (1), adding to the burden of infectious and non-communicable diseases (2). Renal disease is a recognised complication of HIV infection and its incidence can be perpetuated by drug induced toxicity, comorbid diseases such as diabetes and hypertension and infectious diseases (3). Data from the United States suggest that at some stage of their HIV infection, 10% of patients will develop HIV-related renal disease (4). If this is extrapolated to the South African context, it is estimated that 650 000 patients may develop HIV-related renal disease (4). This large burden of chronic kidney disease (CKD) would place immense pressure on our resource-strained health system where access to renal biopsy, renal replacement therapies and nephrologists is limited (5).

Mayosi et al. report a 67% increase in deaths related to nephritis/nephrosis in South Africa from 1999 to 2006 causally linked to the increasing HIV prevalence (2). In their systematic analysis, Stanifer et al. found that CKD is a prevalent and potentially growing disease in Sub-Saharan Africa with 24% of hypertensives, 18.9% of diabetics and 10% of HIV-infected patients having co-morbid CKD (6). The guidelines published by the Infectious Diseases Society of America (IDSA) in 2005, recommended that all individuals be assessed for kidney disease at the time of HIV diagnosis by way of a screening urinalysis for proteinuria and a calculated estimate of renal function (7) in order to detect renal disease early. The South African ART guidelines incorporate this policy and the recent implementation of ART initiation irrespective of CD4 count allows for earlier access to ART before the onset of advanced disease (3).

Despite the earlier initiation of ART and the screening for urinary abnormalities, renal disease in HIV infected patients is still prevalent (7, 9). In addition, HIV associated nephropathy (HIVAN)

has become the third leading cause of end stage renal disease amongst HIV infected African-American patients (9, 10). To the best of our knowledge, this is the first systematic scoping review that attempts to investigate the renal manifestations of HIV infected in South Africa in the ART era. In light of the current upsurge of research and publications on the topic (9, 11-14), the contribution of a systematic scoping review gains importance and relevance by demonstrating the current data in order to identify research gaps and suggest novel ideas for future research.

Methods

Study design

The protocol of this study is registered in PROSPERO with registration number: CRD42016039270 and available via this website: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016039270.

In this study, we chose to undertake a systematic scoping review of published reviews as the best method to map the renal manifestations of HIV in South Africa in the era of ART. Guided by Arksey and O'Malley's scoping review framework (15), we searched cross-sectional studies, randomised controlled trials, non-randomised controlled trials, observational studies, review articles, case reports and systematic reviews that examined renal manifestations on HIV-infected patients in South Africa.

Literature search

We conducted a systematic literature search in the following databases: Google Scholar, PubMed, Medline, Cochrane Library, Worldcat.org and EBSCO host, for articles pertaining to renal manifestations of HIV in South Africa. The primary search terms related to HIV and the kidney specifically (i.e. kidney, renal, nephrology). The secondary terms were manifestations, renal failure, complications, South Africa, antiretroviral treatment, proteinuria and glomerular filtration rate. In order to direct the search to our research question, we used the filtering method which included the data range (2004 to 2015), human subjects, English language and adult patients (≥18 years old). Medical subject headings (MeSH) terms were also used.

Eligibility criteria

Inclusion criteria

- Evidence of renal manifestations in HIV infected patients in South Africa
- Evidence from the period 2004 to 2015
- Evidence of renal manifestations in adult HIV infected patients (≥18 years old)
- English language publications

Exclusion criteria

- Evidence of renal manifestations in HIV infected patients outside South Africa
- Studies reporting on other HIV manifestations
- Studies before freely available ART in the public sector of South Africa
- Non-English language studies

Study selection occurred in two stages. First a single reviewer went through the titles from the database search and decided on eligibility based on the inclusion and exclusion criteria. For example, titles stating research carried out in an ineligible country would be excluded. If a reviewer was uncertain of the eligibility of a title, it was not excluded but rather carried onto the next stage of the selection process. In the second stage, two independent reviews of the titles and abstracts, using inclusion and exclusion criteria, was undertaken. Where differences of opinion arose, a third reviewer would be consulted to reach consensus. The remaining articles were then assessed for eligibility for data extraction. A PRISMA flow diagram (Figure 1) shows the process involved in obtaining eligible studies.

Quality of the evidence

The risk of bias (e.g. internal validity) in the included studies was evaluated using the mixed methods appraisal tool (MMAT) for mixed methods studies (16). The risk of bias scale scored studies was based on 14 criteria. Studies were assessed by the following domains: representativeness of population; selection of exposed and non-exposed cohorts drawn from the same population; confidence in the assessment of exposure; confidence that the outcome of interest was not present at the start of the study; matching exposed and unexposed variables for all those that are associated with the outcome of interest or the adjustment of statistical analysis for these prognostic factors; confidence in the assessment of the presence or absence of prognostic factors;

confidence in the assessment of outcome; adequacy of the follow up of cohorts; and the adequacy and similarity between groups of co-interventions. Studies were allocated scores per domain. Two reviewers (SA and SMK) independently performed each quality assessment. Differences in ratings were resolved through discussion.

Thematic analysis

Thematic content analysis was performed to identify patterns of renal manifestations from the included studies. The included manuscripts were manually coded into categories which were grouped into the following five themes:

- Urine analysis
- Estimated glomerular filtration rate
- Renal biopsy
- Risk factors for renal dysfunction
- Clinical and histological responses to ART

Results

A total of 6 808 articles were retained from our initial search. Applying our exclusion criteria reduced the number of studies to 11 (Figure 2.1). The level of agreement between reviewers was 80% versus 50% expected by chance. This constitutes moderate to substantial agreement, with estimated kappa statistic =0.22 95% (confidence interval [CI] 0.70; 0.26) (Appendix C).

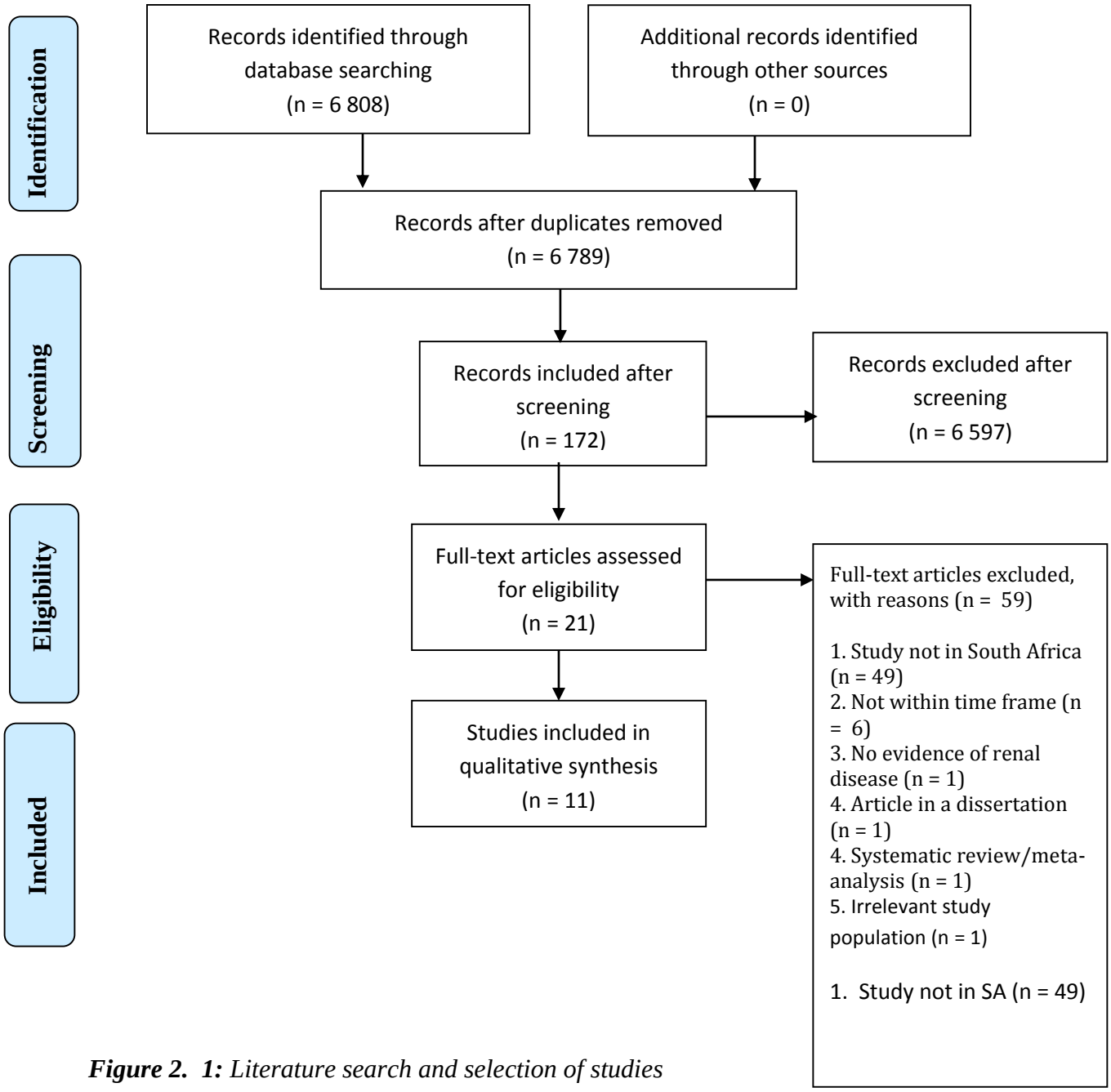

Figure 2. 1: *Literature search and selection of studies*

Characteristics of included studies

Eleven out of the 21 reviewed articles were eligible for data extraction (Table 2.1). All 11 studies were published in English and they were conducted in South Africa. Of these, eight were conducted in an urban setting (12, 13, 17-22) and three were carried out in a rural setting (23-25).

All included studies were published between 2008 and 2015. Study participants were predominantly female (total female percentage 57.9%) in all included studies except two (19, 20). The total sample size of all 11 studies was 6 595 participants. The sample size in each study was 100 participants or more. The average age in all the included studies was 35 years. The study designs of the included studies were as follows: four retrospective chart/cohort reviews (17, 19, 21, 22); one cohort study (26); one descriptive study (13); two prospective studies (12, 20); one combined retrospective chart review and prospective cohort study (23); one case control study (18); and one cross-sectional analysis of patient records (27).

All the included studies were aimed at assessing the renal status, risk factors and renal outcomes in HIV-infected patients either before ART, whilst on ART or both. Seven of the 11 studies (63.6%) assessed for the prevalence of renal impairment in HIV-infected patients (13, 17, 19, 22, 23, 26, 27); two studies (18.1%) analysed renal biopsies to evaluate the clinical and histological responses of HIV-associated kidney disease to ART (12, 21); one study (9%) assessed the performance of the 4-variable Modification of Diet in Renal Disease (4-v MDRD) and Cockcroft-Gault (CG) equations for estimating glomerular filtration rate (eGFR)/creatinine clearance in South African Black patients (20); and one study (9%) extracted genomic DNA from kidney samples to determine the prevalence of APOL1 risk variants and their effect on CKD in Black South Africans (18). General and specific characteristics of all included studies are summarised in Table 2.1. From Table 2.1 we extracted data specific to the evidence of renal dysfunction among HIV infected patients in South Africa during the ARV era and formulated Table 2.2.

A total of 6 758 studies were excluded as they did not meet the inclusion criteria for this study. Of those, 10 underwent a full manuscript review and were found to have no valuable data for analysis in this study for the following reasons: not within the specified time frame (9, 14, 28-31); outcomes of chronic haemodialysis (32); systematic review and meta-analyses of countries in Sub-Saharan Africa (6); irrelevant study population (33); and a dissertation published at a later stage (34).

***Table 2. 1**: Characteristics of included studies*

AHR = adjusted hazards ratio; AIDS = Aquired Immunodeficiency Syndrome; AKI = acute kidney injury; aOR = adjusted odds ratio; ART = antiretroviral treatment; CG = Cockcroft-Gault; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular

Author and date	Setting (rural/ urban/ semi-urban)	Sample number (n)	%Male	%Female	Average age	Intervention	Comparison (if applicable)	Outcome	Aim of the study	Study Design	Conclusion
Brennan et al., 2011	Urban	890	26.5%	73.5%	37.1	Either newly initiated patients on TDF or patients switched to a TDF containing regimen	ART outcome (nephrotoxicity and death) by 48-months of followup stratified by renal function at TDF initiation	Of 890 patients initiated on tenofovir, 573 (64.4%) had normal renal function (>90ml/min), 271 (30.4%) had mild renal dysfunction (60–89ml/min) and 46 (5.2%) had moderate renal dysfunction (30–59ml/min). 2.4% experienced nephrotoxicity, 7.8% died and 9.7% were lost during 48-months of follow-up. Patients with mild or moderate renal dysfunction were at greatest risk of nephrotoxicty, while those with mild	Analyse relationship between renal dysfunction at TDF initiation, nephrotoxicity and mortality	Retrospective cohort analysis	All patients need to be screened for baseline renal dysfunction to decrease nephrotoxicity and improve outcomes

								or moderate renal dysfunction vs. normal renal function were at highest risk of death by 48-months.			
Fabian et al., 2009	Urban	578	37.5%	62.5%	37	Urine dipsticks on all ART naïve, HIV infected outpatients was done	None	84% of the screened population had AIDS (CD4 count, 200 cells/mm3), and the incidence of abnormalities on urinary dipstick testing was high: 30% had leukocyturia, 33% had microscopic hematuria, and 44% had microalbuminuria/proteinuria. In patients with leukocyturia, an infective organism was cultured in only 29.1% of cases, predominantly Escherichia coli (70%) with sterile leukocyturia	To detect early kidney disease in ART naïve HIV infected patients by screening for proteinuria	Descriptive study	Urine abnormalities in ART naïve HIV outpatients are common. Routine urine screening of all new patients attending ART clinics in South Africa should be compulsory

filtration rate; HIV = human immunodeficiency virus; HIVAN = human immunodeficiency virus associated nephropathy; HIV-ICD = human immunodeficiency virus immune complex disease; HR = hazards ratio; IQR = inter-quartile range; MDRD – Modification of Diet in Renal Disease; OR = odds ratio; SD = standard deviation; STI = sexually transmitted infection; TB = tuberculosis; TDF = tenofovir disoproxal fumarate; WHO = World Health Organization

								comprising the remainder.			
Fabian et al., 2013	Urban	20 renal biopsies performed out of the 578 patients screened	55%	45%	37	Kidney biopsies were performed before and after initiation of ART to assess clinical and histological response to treatment	Renal histology pre-ART compared to renal histology following initiation of ART (at variable times on ART)	There was a rapid immunological and renal response to ART. The renal response was reflected by a significant rise in the estimated glomerular filtration rate (eGFR) and rapid regression of proteinuria. The histological patterns were highly variable, ranging from non-specific lesions such as mesangial hyperplasia and interstitial nephritis to HIV-immune complex disease (HIV-ICD) with or without features of HIV-associated nephropathy (HIVAN). In the follow-up biopsies, the histological	To prospectively document the clinical and histological responses of biopsy proven HIV-associated renal lesions to ART	Prospective cohort study	Demonstrated a rapid virological and renal response to ART in HIV infected South Africans with histologically documented HIV associated renal disease irrespective of the histology

								response to treatment was variable with a combination of no change, progression or regression of lesions			
Franey et al., 2009	Rural	2189 in the retrospective review and 149 in the prospective study	31.2%	68.8%	36	1.Retrospective review of medical records. 2. Single blood pressure reading, random glucose and urine analysis performed on the cohort of patients initiating ART	None	1. Moderate renal impairment was more frequent (287/2189), low prevalence of severe renal impairment (29/2189).Age >40yrs, male gender and CD4<100 associated with significant renal impairment. 2.Urine analysis had poor sensitivity and specificity for detecting renal impairment	1.A review of the prevalence and risk factors for renal impairment in patientss initiating ART 2.To assess the utility of urine analysis for the detection of impaired renal function in pts initiating ART	1.Retrospective chart review 2. Prospective cohort study	1. Significant renal impairment is uncommon in patients initiating ART in that rural setting. 2.Urine analysis alone may be inadequate for identification of those with impaired renal function where resources for biochemistry are limited

Kamkuemah et al., 2015	Urban	1092	38%	62%	34	Data was from HIV-infected patients initiating TDF. Renal function was assessed for the first 12 months on ART by estimating glomerular filtration rate (eGFR) calculated using the Cockroft–Gault equation	Change in eGFR over the 12-month period	Majority had normal renal function pre-ART (79%), 19% had mildly reduced eGFR, and 2% had moderate renal impairment. Older age, more advanced WHO stage and anaemia were independently associated with prevalent renal impairment. On average, estimated glomerular function improved over the first year on tenofovir. Male gender, anaemia and immunosuppression (WHO Stage III/IV and CD4 cell counts <100 cells/mm3) were associated with lower average eGFR levels over time. Overall, 3% developed eGFR <50 ml/min/1.73 m2 during this period.	To assess the prevalence and incidence of renal impairment in a primary care setting in sub-Saharan Africa.	Retrospective review of medical records	Renal function improved in HIV-infected adults initiating ART in this primary healthcare setting during the first year on ART. While monitoring of renal function is recommended in the first 4 months on ART, renal impairment appears uncommon during the first 12 months of tenofovir containing ART in

								Serum creatinine tests conducted before 4 months on ART had low predictive value for predicting change in eGFR after a year on ART.			primary care populations
Kasembeli et al., 2015	Urban	228	42.9% HIV with CKD, 28% HIV controls, 58.1% HIV negative CKD, 44.4% population controls	57.1% HIV with CKD, 72% HIV controls, 41.9% HIV negative controls, 55.6% populations controls	36.1 HIV with CKD, 38.8 HIV positive controls, 36.4 HIV negative CKD, 38.5 population controls	Genomic DNA was extracted from formalin-fixed paraffin-embedded kidney samples, and a modified in house salting-out procedure was used to extract genomic DNA from peripheral blood samples.	Comparisons were made between HIV-positive patients and HIV-positive controls and between HIV-negative patients and population controls, comparing the distribution of two risk alleles (explanatory exposure) to	79% of patients with HIV-associated nephropathy and 2% of population controls carried two risk alleles. In a recessive model, individuals carrying any combination of two APOL1 risk alleles had 89-fold higher odds of developing HIV-associated nephropathy compared with HIV-positive controls. Population allele frequencies were 7.3% for G1 and 11.1% for G2. APOL1 risk alleles were not significantly	To determine the prevalence of APOL1 risk variants and the effect of these variants on HIVAN and CKD in black South Africans in a setting of high HIV-1 prevalence.	Case control study	HIV-positive, antiretroviral therapy–naïve South-African blacks with two APOL1 risk alleles are at very high risk for developing HIV-associated nephropathy

							zero or two risk alleles (no exposure)	associated with other forms of CKD			
Madala et al., 2014	Rural	302	45.4	54.6	47.1	Reviewed records, kept at the CKD clinic, of all patients seen from 31st January 2008 to 31st January 2011	None	290 (96%) were black African. Mean age ± SD was 47.1 ± 17.0 years. Approximately 86.4% of females and 54.5% of males were overweight/ obese. Dyslipidaemia was observed in 47.9% females and 29.2% males (P < 0.001). Estimated glomerular filtration rate (eGFR) was <30 ml/min/1.73 m2 in 50.6% patients. CKD risk factors observed were: hypertension (77.8%), diabetes (29.8%), HIV (28.5%), glomerulonephritis (7.0%) and tubulointerstitial diseases (5.6%).	To describe the prevalence of CKD and CVD risk factors and determine factors associated with CKD severity in patients presenting at a CKD clinic	Cross-sectional analysis of patient records	Diabetes and HIV are prevalent in CKD patients at primary/regional level healthcare in South Africa. With registry data lacking, dedicated CKD clinics at lower healthcare levels may provide valuable data on CKD epidemiology including changes in aetiology. There is a need for

											nephrology outreach programs.
Vachiat et al., 2013	Urban	101	55%	45%	38 ± 9.9yrs	Review of 101 HIV-positive anti-retroviral therapy (ART)-naïve patients presenting with renal failure from 1 October 2005 to 30 September 2006 was undertaken	HIV negative patients with acute kidney injury	Ninety-nine (98%) of HIV-positive patients were black and 56 (55%) were male, with mean age 38 ± 9.9 years (range 21–61 years). HIV-positive patients demonstrated severe immunosuppression, with mean CD4 count of 135 cells/μL Fifty-seven (56%) HIV positive patients presented with AKI, 21 (21%) with acute-on-chronic kidney disease and 23 (23%) with CKD; seven patients with AKI were excluded due to lack of records. The causes of AKI in the HIV-positive group included sepsis (60%), volume	Reviewing data of HIV-positive patients with renal failure and primarily compared HIV-positive and HIV-negative patients with AKI presenting in the same period, matched as closely as possible with regard to age and gender, selected as monthly	Retrospective review of patients	HIV-positive patients, compared with the HIV-negative group, presented with AKI at a younger age and at an advanced stage of immunosuppression. HIV-negative patients were older and presented with more chronic comorbidities such as hypertension and diabetes.

								depletion and haemodynamic instability (19%), toxins (9%), urological obstruction (7%) and miscellaneous (14%). Forty-four per cent of HIV positive and 47% of HIV-negative patients with AKI demised; P=0.45. Hyponatraemia (P = 0.018), acidosis (P=0.018), anaemia (P=0.019) and hyperphosphataemia (P=0.003) were predictors of mortality in HIV-positive patients with AKI.	consecutive referrals after the HIV-positive patients.		
Van Deventer et al., 2008	Urban	100	51%	49%	47	Measurement of GFR and serum creatinine in HIV infected patients with varying	Ethnicity factor established for African Americans in the 4-v	The Spearman correlation coefficient between measured and estimated GFR for both equations was similar. Using the 4 vMDRDequation with the ethnicity	To evaluate the performanc e of the 4-v MDRD and CG equations for	Prospective study	Both the 4-v MDRD equation, without the ethnicity factor of 1.212, and the

						degrees of renal function	MDRD equation.	factor of 1.212 as established for African Americans resulted in a median positive bias of 13.1 (95% CI 5.5 to 18.3) mL/min/1.73m2.With out the ethnicity factor, median bias was 1.9 (95% CI_0.8 to 4.5) mL/min/1.73m2.	estimating GFR in black South Africans against measured GFR and to assess the appropriate ness for the local population of the ethnicity factor established for African Americans in the 4-v MDRD equation.		Cockcroft-Gault equation, after correcting for bias, can be used for estimating GFR in black South Africans.
Wearne et al., 2012	Urban	192	48.75%	51.25%	34	Analysis of renal biopsies to determine outcomes and prognostic indicators based on histology and	None	HIV-associated nephropathy (HIVAN) was the most common histology. ART reduced the mortality in those with any feature of HIVAN by	Analysis of kidney biopsies to describe the histological spectrum, develop clinical	Retrospective analysis of kidney biopsies and prospective thereafter	Early detection of HIV associated renal diseases and initiation of ART in the setting of

						clinical features.		57%. Of those patients with HIVAN who died, 79% died of renal failure as registered on their death certificate. Proteinuria and microcysts were shown to be poor prognostic indicators In patients with HIVAN alone followed for up to 2 years on ART, estimated glomerular filtration rate remained stable and there was a trend towards decreased proteinuria. ART improved survival in patients with isolated immune complex disease.	correlations and prognostic indicators and determine outcomes based on histological findings.		HIVAN is of paramount importance. ART dramatically improves outcome in any patient demonstratin g any of the histological features of HIVAN (with or without immune complex disease) on renal biopsy. Renal biopsy is thus essential to correctly document renal disease in the HIV-positive population.

Wensink et al., 2015	Rural	903	31%	69%	40	HIV-infected adult patients were randomly selected and data on HIV-infection and cardiovascular risk factors were collected. Glomerular filtration rate (eGFR) was estimated	Patients who had been on ART for at least six months	The median duration since HIV diagnosis was 26 months and 787 (87%) received antiretroviral therapy. Thirty-six (4%) of the subjects were shown to have diabetes and 205 (23%) hypertension. In the cohort, 21% had albuminuria and 2% an eGFR <60 mL/min/1.73m2. Albuminuria was associated with hypertension, total cholesterol, eGFR and detectable viral load.	To provide epidemiological data on the prevalence of decreased GFR and albuminuria. Additionally, to describe the association of cardiovascular and HIV-related factors with albuminuria among HIV-positive patients in a rural population in South Africa as an essential	Cohort study	Glomerular filtration rate was well conserved, while albuminuria was common amongst HIV infected patients in rural South Africa. Both cardiovascular and HIV-specific variables were associated with albuminuria. Improved cardiovascular risk prevention as well as adequate virus suppression might be the key to escape

									first step towards the identification of factors amenable to therapeutic intervention.		the vicious circle of renal failure and cardiovascular disease and improve the long-term prognosis of HIV-infected patients

Table 2.2. *Evidence of renal dysfunction among HIV infected patients in South Africa during the ARV era*

AUTHOR	MARKERS FOR RENAL IMPAIRMENT	DEFINITION OF RENAL DISEASE	RESULTS
Brennan et al, 2011[17]	Creatinine clearance using Cockcroft-Gault (CG) equation.	Nephrotoxicity defined as any decline in kidney function from baseline (acute or chronic) that is secondary to a toxin (including drugs) documented within 48 months of initiating tenofovir (TDF). Normal renal function (>90ml/min), mild renal dysfunction (60-89ml/min) and moderate renal dysfunction (30-59ml/min)	The risk of nephrotoxicity and death by 48 months increased with decreasing renal function at initiation of TDF. Patients switched onto TDF had a higher risk of nephrotoxicity and death compared to ART naïve patients. Median time to nephrotoxicity after TDF initiation is 3.6 months confirming the importance of the month 3 creatinine clearance.
Fabian et al, 2009[13]	Urine dipstick for proteinuria and microalbuminuria	Microalbuminuria: microalbumin-to-creatinine ratio 3.4-33.9mg/mmol independent of sex; Overt proteinuria: protein-to-creatinine ratio of 0.03-0.3g/mmol; Nephritic range proteinuria: protein-to-creatinine ratio >0.3g/mmol.	18.5% had microalbuminuria, 6.4% had overt proteinuria and 2.4% had nephrotic range proteinuria.
Fabian et al 2013[12]	Urine dipstick for proteinuria. Estimated glomerular filtration rate (eGFR) using both CG and 4 variable Modification of Diet in Renal Disease (MDRD) formulae. Renal biopsy	Persistent microalbuminuria: microalbumin-to-creatinine ratio of 3.4-33.9mg/mmol; Persistent overt proteinuria: protein-to-creatinine ratio of 34mg/mmol-0.3g/mmol; Nephrotic proteinuria: protein-to-creatinine ratio >0.3g/mmol.	68% had microalbuminuria, 23% had overt proteinuria and 9% had nephrotic proteinuria. There was an improvement in eGFR on antiretroviral treatment (ART). There was partial or complete remission of proteinuria in response to treatment. Despite the rapid clinical response to ART, there was relative lack of histological resolution.
Franey et al, 2009[23]	Urine dipstick for proteinuria. eGFR using the four variable MDRD equation. Urine dipstick for proteinuria	Severe renal impairment: eGFR <30mls/min/1.73m^2; Moderate renal impairment: eGFR 30-60mls/min/1.73^2; Mild renal impairment: eGFR 60-90mls/min/1.73^2. Proteinuria ≥ 1+ protein on dipstick. Renal dysfunction defined as either reduced eGFR and/or proteinuria/haematuria.	Severe renal impairment was uncommon while moderate and mild renal impairment were more common. Mild and moderate renal impairment improve on ART. Urine analysis may not be sufficiently sensitive to be used as a single screening test for renal disease at baseline.
Kamkuemah et al, 2015[35]	eGFR calculated using CG equation	Severe renal function reduction was defined as	79% had normal renal function at baseline, 19% had mildly reduced renal function and 2 % had

		eGFR <30 ml/min/1.73 m^2, moderate reduction as eGFR of 30–59 ml/min/1.73 m^2 and mild reduction as an eGFR of 60–89 ml/min/1.73 m^2.	moderate renal impairment at basleine. Overall renal function improved over the first year after starting TDF-containing ART regimens.
Madala et al, 2014[24]	Urine dipstick for proteinuria. eGFR calculated using the MDRD equation for ≥ 18 years and the Schwartz equation for < 18 years old.	Chronic kidney disease (CKD) defined by eGFR < 60ml/min/1.73m^2 and/or proteinuria and/or abnormal renal ultrasound, persistent for ≥ 3 months.	eGFR was < 30ml/min/1.73m^2 in 50.6% of patients as this was a CKD clinic. Main risk factors for CKD were diabetes, hypertension and HIV.
Vachiat et al, 2013[19]	Urine for proteinuria either dipstick or spot urine protein creatinine ratio. Serum creatinine levels.	Acute kidney injury (AKI) defined as an improvement in admission serum creatinine of > 50%. They were further subdivided using the rifle criteria: Risk – serum creatinine < 194µmol/L; Injury – serum creatinine 195 to 291µmol/L; and Failure – serum creatinine > 291µmol/L.	Majority had AKI 56%, followed by CKD 23% and 21% had acute on chronic kidney disease. Proteinuria did not predict recovery or death in HIV-infected patients with AKI. AKI was common in HIV-infected patients and occurred at a younger age than HIV negative patients.
Wearne et al, 2012[21]	Renal biopsy Serum creatinine Urine protein creatinine ratio	HIV-associated nephropathy (HIVAN) defined as a constellation of glomerular, interstitial and tubular abnormalities and there must be epithelial cell hyperplasia if only tubular or interstitial disease was present.	For patients with HIVAN there was an improvement in proteinuria and stabilization of renal function after commencing ART. Renal biopsy is essential to diagnose renal disease in HIV-infected patients.
Wensink et al, 2015[25]	Urine for albuminuria eGFR calculated using MDRD and CKD Epidemiology Collaboration formula	Moderately increased albuminuria: albumin creatinine ratio 30 to 299mg/g; Severely increased albuminuria: albumin creatinine ratio > 300mg/g.	Albuminuria occurred in 20% of patients while only 2% had eGFR < 60ml/min/1.73m^2. Higher eGFR was significantly linked to lower prevalence of albuminuria. Albuminuria was linked to higher frequency of diabetes, hypertension, high total cholesterol and decreased eGFR.

Risk of bias assessment

The studies' quality scores ranged from 16 to 20 out of a maximum score of 28 (Appendix D). Four of the ten included studies scored the highest quality score with an estimated average score of 10 in each study (13, 21, 23, 25). The two studies scoring the lowest had an average score of 8 each (12, 18). Overall the body of evidence was considered at serious risk of bias due to the

following: description of randomisation; allocation concealment; retention percentage in study; minimising selection bias; and selection and comparativeness of the control groups.

Findings of the study

Kidney disease is a complication of HIV infection and can present as acute kidney injury (AKI) or CKD. Only one study assessed AKI in HIV-infected ARV naïve patients (19). Their findings demonstrated that 56% had AKI, 21% had acute or chronic kidney disease and 23% had CKD (19). The causes of AKI included sepsis, volume depletion, haemodynamic instability, toxins, urological obstruction and miscellaneous causes (19).

We identified patterns of renal manifestations from the included studies and grouped them into the following five themes: urine analysis; estimated glomerular filtration rate; renal biopsy; risk factors for renal dysfunction; and clinical and histological responses to ART.

Urine analysis

The incidence of urine abnormalities on urine dipsticks was high: 30% to 57% had leukocyturia (13, 19), 16% to 40% had microscopic haematuria (13, 19, 23) and 20% to 44% had microalbuminuria/proteinuria (12, 13, 23, 26). Two studies investigated the cause of leukocyturia and detected an infective organism, mainly E.Coli, in 29.1% of culture positive cases in one study (ART naïve outpatients) (13) and in 8.9% of culture positive cases in the other study (ART naïve outpatients with renal failure) (19). Franey et al. performed urine dipstick analysis on 149 patients who were initiating ART in a rural clinic, to assess its utility to detect impaired renal function (23). They concluded that urine dipsticks analysis alone had poor sensitivity and specificity for detecting impaired renal function (PPV 0.22) (23).

In three studies on ART naïve patients, positive proteinuria on dipsticks was quantified by sending the specimen for a spot protein:creatinine ratio (PCR) (12, 13, 19). If the dipsticks were negative for protein they were screened for microalbuminuria which, if positive, were then sent for a spot microalbumin-to-creatinine ratio test (MCR) (12, 13). In their study, Fabian et al. found that, of the 253 dipsticks positive for proteinuria on ART naïve patients, only 193 were confirmed by the laboratory (13). Wensink et al. (26) submitted random urine samples directly to the lab for the

albumin:creatinine ratio (ACR), bypassing urine dipsticks analysis. Two studies quantified the degree of proteinuria using either the MCR (12) or the ACR (26). Microalbuminuria (MCR 3.4-33.9 mg/mmol) occurred in 68% of patients, overt proteinuria (MCR 34 mg/mmol-0.3 g/mmol) in 23% and nephrotic proteinuria (MCR >0.3 g/mmol) in 9% of ART naïve patients (12). Similar figures were noted in the study that quantified the ACR in a mixed study population predominantly on ART (87% on ART): 20% of patients had moderately increased albuminuria (ACR 30–299 mg/g) and 1% had severely increased albuminuria (ACR >300 mg/g) (26). In the same study, a detectable HIV viral load, hypertension, total cholesterol and eGFR were all independently associated with albuminuria (26).

Estimated Glomerular Filtration Rate (eGFR)

Six studies utilised eGFR as a marker of renal dysfunction (12, 17, 20, 22, 23, 26). eGFR was calculated using the CG equation (17, 22), the 4-v MDRD equation (23), comparing the CG and 4-v MDRD equations (12, 20) or comparing the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and the 4-v MDRD equation (26). Both the CG equation (after correcting for bias) and the 4-v MDRD equation (without the ethnicity factor for African Americans), have been validated for the estimation of eGFR in Black South Africans (20).

The eGFR was classified as follows: severe renal impairment eGFR <30mls/min/1.73 m^2, moderate renal impairment eGFR 30–59mls/min/1.73 m^2, mild renal impairment eGFR 60–89mls/min/1.73 m^2 and normal renal function eGFR >90mls/min/1.73 m^2. Using the afore-mentioned classification, baseline (before ART initiation) renal function was documented as follows: normal renal function occurred in 28.4% to 79% of patients, mild renal impairment occurred in 19% to 57.1% and moderate renal impairment in 2% to 14.4% (17, 22, 23). Baseline severe renal impairment occurred in 1.3% of ART naïve patients in the study by Franey et al. (23). Wensink et al. had a mixed study population of ART naïve patients and HIV-infected patients on ART and the majority of patients had normal renal function, 2% had moderate renal impairment and 10% had mild renal impairment (26).

Brennan et al. confirmed the importance of the 3 month creatinine clearance by demonstrating that the median time to nephrotoxicity after tenofovir disoproxil fumarate (TDF) initiation was 3.6

months (17). A study by Kamkuemah et al. showed that early serum creatinine testing at months 1 and 2 after initiation of TDF may not be useful in predicting those at risk for renal dysfunction (22).

Renal Biopsy

Renal histological findings have been inconsistently classified in patients on ART (21). HIV-associated nephropathy (HIVAN) was the most prevalent histology seen (57.2%) followed by HIVAN with immune complex glomerulonephritis (ICGN) at 21.8%; without HIVAN or ICGN (12.5%); and ICGN in isolation (8.3%) (21). However, in another study by Fabian et al., there was a paucity of HIVAN lesions on histology (12).

Risk factors for renal dysfunction

Two studies were unanimous that abnormal renal function at baseline was associated with older age, World Health Organisation (WHO) stage III/IV disease and a lower CD4 count (22, 23, 35). In addition to these variables, a low haemoglobin and a detectable HIV viral load were also associated with abnormal renal function in a mixed cohort of ART naïve patients and patients on ART (17, 22). In the same study, patients who were switched onto TDF from another regimen had a higher risk of nephrotoxicity and death, than ART naïve patients initiated on TDF (17). Younger age and advanced immunosuppression were found to be risk factors for AKI (19). There was no consensus regarding gender as a risk factor for renal dysfunction, as one study found women to be at greater risk (22) whilst another found men to be at greater risk (23). The APOL1 risk allele found on chromosome 22 occurred in more than 30% of African American individuals with HIVAN (36). Kasembeli et al. showed that 79% of Black patients with HIVAN carried two copies of APOL1 risk alleles as opposed to 2% in the general population, suggesting that ART naïve Black South Africans were at high risk of developing HIVAN(18). CKD (defined as eGFR < 60ml/min/1.73m^2 and/or proteinuria and/or abnormal renal ultrasound persistent for ≥ 3 months) risk factors which were noted in two studies of South African patients attending CKD clinics, were: hypertension (36% to 77.8%), diabetes (25% to 29.8%) and HIV (20% to 28.5%) (20, 27). It is interesting to note that 51.1% of these patients had more than one CKD risk factor (27).

Clinical and histological response to ART

In the majority of patients, renal function improved in the first year of commencing ART, as evidenced by the regression of proteinuria and the increase in eGFR (12, 21, 22). However, there was no significant change in morphology noted on histology before and after ART initiation to explain the improvement in proteinuria (12).

Discussion

A systematic scoping review of the available literature on the renal manifestations of HIV in the era of ART in South Africa was conducted. This review provided a general overview of renal impairment (diagnostics, histological features and risk factors) in South African HIV-infected patients mainly prior to ART initiation. Most of what we know about HIV-related kidney disease has come from research performed in high income countries where the patient profiles and demographics are discordant to that of South Africa. The salient points unravelled by our review indicate a paucity of data on ART-related renal complications, specifically TDF nephrotoxicity; a deficiency of research on the impact of ART on AKI and CKD and the long term outcomes of renal disease for patients on ART; and a relatively unknown prevalence of HIV-related kidney disease for patients on ART in South Africa. Bearing in mind that South Africa recently (1 September 2016) adopted the WHO "test and treat" approach to HIV prevention and management (3), these findings have major implications for the near future.

TDF is widely used as first line ART in South Africa. A biopsy series revealed that TDF nephrotoxicity is essentially a reversible form of toxic acute tubular necrosis with features of mitochondrial injury (37). Numerous studies have demonstrated a decrease in kidney function with TDF usage and suggest monitoring of renal function to prevent TDF nephrotoxicity (17, 38-40). Early detection of proteinuria using accurate screening tests is important to decrease nephrotoxicity and improve outcomes in HIV-infected individuals (17). The current South African ART guidelines recommend routinely performing urine dipstick analysis on patients before and while on ART, as well as assessing the serum creatinine and eGFR at baseline (prior to ART initiation) and then at 3 months, 6 months, 12 months and annually thereafter for patients on TDF. The rate of compliance to these guidelines however, is not known.

The use of urine dipsticks alone as a screening tool has become a contentious issue with research both locally (23) and overseas (41) suggesting the poor validity of urine dipsticks in detecting proteinuria. Data from another South African study, Han et al., suggested that HIVAN is possible in patients without overt nephrotic syndrome and in patients who have only microalbuminuria. Therefore microalbuminuria can be considered an early marker of HIVAN (9). Szczech et al. concluded that miroalbuminuria predicts the development of proteinuria in HIV-infected patients (42). Stanifer et al. showed that the prevalence of proteinuria when measured in people with HIV, hypertension or diabetes is substantial. However the best method of urine protein detection is unknown (6). Currently, our urine dipstick analyses detect proteinuria only (not microalbuminuria). In other countries, alternate methods of urine analysis are already being sought. In a recent study set in Mexico City, a comparison was made between the protein reagent strip (PRS) and the urinary protein/creatinine ratio (uPCR) to detect proteinuria. It was concluded that there was a high concordance between the detection of urine protein by PRS and uPCR and therefore the PRS could be useful in low income countries to detect proteinuria (43).

Two South African studies in our review demonstrated the importance of an early creatinine clearance, prior to 4 months after the initiation of TDF (17, 22). Both the CG equation (after correcting for bias) and the 4-v MDRD equation (without the ethnicity factor for African Americans) have been validated for the estimation of eGFR in Black South Africans (20). The production of creatinine is determined mainly by muscle mass and dietary intake (44). Therefore, using the ethnicity factor in the 4-v MDRD equation overestimates the eGFR in Black South Africans (20) due to differences in diet, muscle mass and body composition between Black South Africans and African Americans (20). In the current review, the majority of the patients had mild to moderate renal dysfunction with a low prevalence of severe renal impairment prior to ART initiation. Similar findings were seen in a study by Overton et al. set in Washington (45). The prevalence of significant renal impairment in a South African study (23) was slightly higher than that of a Kenyan study (46), possibly because of the differences in the two African populations and because the eGFR method used in the South African study has not been validated for use in other African countries. Though the prevalence of chronic renal failure is low in the HIV-infected population, it has been shown to be higher than that of the general population in an American study (45). One South African study showed that approximately 6% of ART naïve outpatients who

presented with proteinuria had HIV-related kidney disease (9) and another study of 99 in-patients who underwent renal biopsy showed that 27 patients (27.3%) had HIVAN, only 3 of which were on ART (14).

In the current review, HIVAN was the most common histology seen on renal biopsy (12, 21). Other histologies have been documented in various studies both locally (9, 14, 21, 30) and overseas (47). The third leading cause of end stage renal disease (ESRD) in African Americans aged between 20 to 64 years was found to be HIVAN (10). HIVAN is commonly found in HIV-infected Black patients, suggesting a role of genetics in the development of HIVAN (10). Kasembelli et al. proved that Black South Africans who carried two copies of the APOL1 risk alleles were at higher risk of developing HIVAN (18). Lucas et al. demonstrated that ART can prevent or reduce the risk of developing HIVAN and, should it occur, patients on ART may have a slower course and lower mortality than patients not on ART (48). Following the diagnosis of HIVAN, patients can progress to end stage renal failure within months (14). In a South African study over a 10 year period of renal biopsies, the incidence of HIVAN increased from 6.6% in 2000 to 25.7% in 2009 (30). Furthermore, of the 27 patients diagnosed with HIVAN on renal biopsy in a study in South Africa, only 3 were on ART (14). This reaffirms the importance of renal biopsy in accurately diagnosing renal disease, particularly HIVAN (9, 14, 47), and that ART can be initiated early to improve outcomes. Sadly, due to a lack of resources and specialists, access to renal biopsy is limited to urban tertiary hospitals in South Africa.

From September 2016, when ART was to have been made universally available to all HIV-infected South Africans in accordance with WHO ART guidelines (3), even patients with undiagnosed HIVAN would have been initiated on ART. We know from studies in other countries that renal function improves with ART. In a randomised ART trial in Uganda and Zimbabwe, there was stabilisation or a slight improvement in renal function after the initiation of ART (49). Another study demonstrated the resolution of renal disease with ART and the recurrence of renal disease after stopping ART (50). TDF-induced renal toxicity usually resolves after TDF cessation, but the TDF related renal damage is not always completely reversible (51). Our systematic scoping review demonstrated that renal function essentially improved on ART (12, 21, 22). However, data on the long term outcomes of renal function and CKD for patients on ART in South Africa is lacking. It

was noted that 2015 had the most publications applicable to the topic of our scoping review, indicating a recent increase in interest on this subject in South Africa.

Recommendations for future research

The majority of the included studies were conducted in an urban setting where access to healthcare and laboratories was readily available. However, research shows high HIV prevalence and fewer patients on ART, in rural South Africa (52). Females bear the brunt of the HIV epidemic in South Africa having a significantly higher prevalence of HIV than their male counterparts (52). In the current review, consensus was not reached regarding gender as a risk factor for renal dysfunction possibly because females predominated in most studies. Therefore, comparative studies to determine the differences in renal manifestations between HIV infected males and females, preferably in rural settings, during the ART era, are recommended. More males need to be recruited to participate in research.

Currently, our urine dipstick analyses, detect only proteinuria, and not microalbuminuria. This suggests a novel idea for research: looking at the significance of microalbuminuria versus proteinuria in our HIV-infected population, the outcome of which could guide future urine diagnostics in baseline screening for renal disease. Cost effective methods for urine screening and estimating GFR are needed, especially for rural areas where access to laboratories is limited.

Considering that the majority of South African HIV-infected patients are Black and with a genetic predisposition to HIVAN, we anticipate that the prevalence of undiagnosed HIVAN will be significant. As far as we know, there are no prospective randomised controlled trials in South Africa investigating treatment options for HIVAN and no data on the actual prevalence of HIVAN.

Data on TDF nephrotoxicity and its impact on long term renal function are lacking in South Africa. Prospective clinical trials focussing on TDF nephrotoxicity and its long term renal outcomes are needed.

The overall prevalence of renal disease in South Africa is unknown. We urgently need epidemiological studies assessing the prevalence of renal disease and HIV-related renal disease in

South Africa in order to efficiently plan and sustain an effective CKD programme. The establishment of renal registries will assist with much needed statistics on the morbidity and mortality of renal disease in general and specifically to HIV and ART.

Implications for practice

Risk factors associated with proteinuria and albuminuria in HIV-infected patients (low eGFR, older age, diabetes and HPT) (25, 53) overlap with those for CKD patients (27, 54). Stanifer et al. found that 24% of hypertensives, 18.9% of diabetics and 10% of HIV-infected patients have co-morbid CKD in Sub-Saharan Africa (6). With the high burden of HIV and non-communicable diseases such as CKD, hypertension and diabetes in South Africa, it would be wise for the Health Department to invest in CKD clinics in rural areas and nephrology outreach services as previously proposed by Madala et al. (27). All staff must be trained in screening for renal dysfunction and referral pathways and support systems must be in place for patients to access specialist care. In South Africa, the number of nephrologists per million population is estimated to be 1.1 (55). The lack of specialists must be addressed in order to have optimally functioning and widely accessible CKD facilities, as well as access to renal biopsy and renal replacement services. We must build on our current infrastructure.

Lastly, we need to empower our patients with knowledge regarding ART complications, and the monitoring and recognition of side effects. In over-burdened health facilities, it is not unusual for important management steps to be overlooked. Therefore, if we educate our patients, these can be avoided.

Strengths and Limitations

An important strength of this study is the exhaustive search for relevant studies. Scoping review methodology is rigorous and methodical in its approach to examining the extent, range and nature of research activity in a particular field (15). There are no limitations in this study.

Conclusion

The findings of the review are in keeping with that of international literature. South Africa has recently adopted the WHO policy and as of September 2016, all HIV-infected patients have access

to ART irrespective of CD4 cell count. Though this is a victory for the millions still awaiting ART in South Africa (in this context particularly patients with undiagnosed HIVAN), the impact on the current health infrastructure that this strategy will have, is unknown. More patients on ART may result in a further increase in chronic disease in South Africa, mainly CKD, hypertension and diabetes. Early initiation of ART can prevent HIVAN and improve outcomes for patients with HIVAN thereby potentially decreasing the incidence of CKD. With a lack of dedicated CKD clinics and specialist renal services particularly in the rural settings, as well as a deficiency in knowledge on the long term impact of ART on CKD, this may be a victory for which the healthcare system could be ill-prepared.

More research is urgently needed on the impact of ART on renal disease, ART-related renal complications and the prevalence of CKD, as well as cost effective methods for routine screening of renal disease in resource-poor settings

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

None declared.

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Authors' contributions

SA, NPM and TPM-T conceptualised and designed the study. SA prepared the first draft of the study and SMK contributed in the abstract, full article screening and the quality assessment of the included studies. TPMT contributed in the synthesis of data and the design of the sifting and data extraction processes. TPMT and NPM assisted with the manuscript preparation. All authors reviewed draft versions of the manuscript and approved the final version of the manuscript.

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Additional files

Additional file 1 (Appendix C): List of studies included for full article screening and reviewers' responses. All the studies that were reviewed independently by two reviewers to reach consensus on the articles eligibility for data extraction.

Additional file 2 (Appendix D): Quality assessment tool. Two reviewers used the MMAT format to assess the quality of the content of the included studies.

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CHAPTER 3: A CHART REVIEW

Chapter 2 demonstrated the current stance on HIV-related renal disease in South Africa. It revealed research gaps in this area. With the universal access to ART for all HIV-infected South Africans, the burden of renal disease and other chronic diseases is anticipated to increase. Therefore, more research on the long term effects of ART on renal disease and on the morbidity and mortality of renal disease, is required. There are guidelines in place regarding monitoring of patients on ART but it is not known whether these guidelines are being adhered to. Guided by the results obtained in Chapter 2, a chart review was conducted in an HIV-infected cohort from the clinic medical records.

Chapter 3 presents a retrospective chart review aimed at addressing objective 2 of the study viz. to determine the risk factors and co-morbidities associated with renal impairment in a cohort of HIV-infected patients. The results of this will help to influence policy and guide future research on HIV management. The chapter is presented in the form of a manuscript entitled: 'Risk Factors and Co-Morbidities Associated with Changes in Renal Function among ART-naïve Adults in South Africa: A Chart Review'. The manuscript is currently under review at the South African Journal of Infectious Diseases.

Risk Factors and Co-Morbidities Associated with Changes in Renal Function among ART-naïve Adults in South Africa: A Chart Review

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ABSTRACT

Introduction : Our systematic scoping review has demonstrated a research gap on antiretroviral treatment (ART) nephrotoxicity, as well as the long term outcomes of renal function for patients on ART in South Africa. Bearing in mind the high prevalence of human immunodeficiency virus (HIV) in South Africa, this is of great concern. The aim of this study is to determine the risk factors and co-morbidities associated with changes in renal function in HIV infected adults in South Africa.

Methods: We conducted a retrospective study of 350 ART-naïve adult patients attending the King Edward VIII HIV clinic, Durban, South Africa. Data was collected at baseline (pre-ART), and at 6, 12, 18 and 24 months on ART. Renal function was assessed in the 24 month period using the modification of diet in renal disease (MDRD) equation and was categorised into normal renal function (estimated glomerular filtration rate (eGFR) $\geq$ 60), moderate renal impairment (eGFR 30-59), severe renal impairment (eGFR 15-29) and kidney failure (eGFR < 15ml/min/1.73m^2). Generalised linear models for binary data were used to model the probability of renal impairment over the 5 time periods, controlling for repeated measures within participants over time. Risk ratios and 95% confidence intervals were reported for each time point versus baseline.

Results: The cohort was 64% female and 99% were Black The mean age was 36.9±9.7 years. At baseline, 10 patients had hypertension, 6 had diabetes, 61 were co-infected with tuberculosis (TB) and 157 patients had a high body mass index (BMI) with 25.4% being categorised as overweight and 19.4% obese. The majority of the patients (59.3%) were normotensive. At baseline the majority of the patients (90.4%) had a normal renal function (95% confidence intervals (CI):86%-93%), 7.0% (CI:5%-10%) had moderate renal impairment, 1.3% (CI:0%-3%) had severe renal impairment, and 1.3% (CI:0%-3%) had kidney failure. As BMI increased by one unit, the risk of renal impairment increased by 1.06 (CI: 1.03 – 1.10) times. The association of hypertension (HPT) with abnormal renal function was found to be insignificant, p>0.05. The vast majority of patients were initiated on tenofovir disoproxil fumarate (TDF) (90.6%), in combination with lamivudine (3TC) (100%) and either efavirenz (EFV) (56.6%) or nevirapine (NVP) (43.4%). Seven patients of the 29 patients (24%) with baseline renal impairment, had persistent renal impairment at 24 months on ART while the eGFR of 13 patients (44.8%) normalised at 24 months on ART.

Conclusion: This study reports a low prevalence of baseline renal impairment in HIV-infected ART-naïve outpatients. An improvement in renal function after the commencement of ART has been demonstrated among this population. However, the long-term outcomes of patients with HIV-related renal disease is not known.

Keywords: Renal failure; HIV; antiretroviral therapy; South Africa

BACKGROUND

South Africa accounts for approximately 18 % of global human immunodeficiency virus (HIV) infections, with an estimated prevalence of 6.7 million HIV-infected people (1). There are almost 1000 new HIV infections, the majority of which are heterosexually transmitted (2). In an attempt to end the surge of HIV plaguing the African continent, the Joint United Nations Programme on HIV/AIDS (UNAIDS), have established an ambitious but achievable target to have 90% of all people tested for HIV, and treated and virologically suppressed by 2020 (3). Providing antiretroviral treatment (ART) to all people living with HIV (PLHIV) irrespective of CD4 count can help prevent HIV-related illness, avert acquired immunodeficiency syndrome (AIDS)-related deaths and prevent new HIV infections (3). South Africa (SA) implemented the UNAIDS policy in September 2016 (4). This universal access to ART for PLHIV is likely to lead to an increase in the burden of chronic diseases in SA as people are living longer with HIV (5).

Stanifer et al.'s 2014 study has shown that chronic kidney disease (CKD) has been prevalent and at an increase in Sub-Saharan Africa with 24% of patients with hypertension, 18.9% of diabetes and 10% of HIV infected patients having co-morbid CKD (6). The use of long-term medication for chronic illnesses can pose a threat to the kidneys and the use of ART is no exception (7-9). Tenofovir disoproxil fumarate (TDF), a potentially nephrotoxic drug (10, 11), is widely utilised as first line ART in SA and screening for baseline renal dysfunction prior to TDF initiation is essential (12). The SA ART guidelines recommend a serum creatinine and creatinine clearance at baseline (prior to ART initiation) and then at 3 months, 6 months, 12 months and annually thereafter for patients on TDF (13).

Our systematic scoping review has demonstrated a research gap on ART nephrotoxicity, particularly with TDF, as well as the long-term outcomes of renal function for patients on ART in South Africa. This is of great concern because we do not know the burden of ART nephrotoxicity or morbidity that our population may experience. Further, with the current health infrastructure, access to nephrologists and dedicated renal services are limited to a few tertiary hospitals. In this study, we aim to determine the risk factors and co-morbidities associated with changes in renal function in HIV infected adults in South Africa. We anticipate that the results of this study will pave the way for prospective studies regarding the morbidity

and mortality of ART nephrotoxicity and influence the expansion of renal services offered in the public health sector.

METHODOLOGY

Design

We conducted a retrospective study of 350 ART-naïve adult patients (18 years and older) attending the King Edward VIII HIV clinic, Durban, South Africa.

Study population

Our study population was ART naïve HIV-infected adult patients who presented to us from across KwaZulu-Natal seeking initiation of ART. We included patients who were initiated on ART from April 2010 to December 2013 and followed up over a 24 month period. Patients already on ART who were transferred to the clinic were excluded.

Data extraction

Clinical data was extracted from medical records of patients attending the HIV clinic at King Edward VIII Hospital in the study period from April 2010 to December 2013. To minimise selection bias, we selected clinical charts sequentially for ART naïve patients. Data was collected at baseline (pre-ART), and at 6, 12, 18 and 24 months on ART. Data collected included socio-demographics, clinical parameters (weight, height, body mass index, blood pressure, pulse, finger prick glucose, urine dipstick analysis), history of co-morbidities (hypertension, diabetes, tuberculosis, pregnancy), laboratory data (serum creatinine and estimated glomerular filtration rate) and the type of ART regimen. We also documented patients who were lost to follow up.

Outcome measures

CKD was defined as either kidney damage or a glomerular filtration rate (GFR) of $<60 mL/min/1.73m^2$ for ≥ 3 months irrespective of cause (14). Estimated GFR (eGFR) used in data analyses was calculated using the simplified modification of diet in renal disease (MDRD) equation without the ethnicity factor: eGFR ($mL/min/1.73m^2$) = $175 \times [S_{cr}(\mu mol/L)/88.4]^{-1.154} \times Age(years)^{-0.203} \times$ (0.742 if female) (15) and was performed at the National Health Laboratory Services (NHLS) at King Edward VIII Hospital. The formula was adjusted to

correct for the use of µmol/L as the unit of measure for serum creatinine (15). For this study we modified the staging of chronic kidney disease from that of the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (Table 3.1) (14) because the NHLS reports creatinine levels above 60µmol/L as >60µmol/L and does not specify the actual eGFR level. For those patients who did not have a documented eGFR from the lab either because the age or gender was not documented on the laboratory request form, we calculated the value using the MDRD equation above, with the age and gender captured during data collection. Proteinuria detected on urine dipstick analysis refers to the presence of protein of 1+ or more in the urine.

TABLE 3. 1: STAGING OF CHRONIC KIDNEY DISEASE

DESCRIPTION	**eGFR ml/min/1.73m^2**
Normal renal function	≥60
Moderate renal impairment	30 – 59
Severe renal impairment	15 - 29
Kidney failure	< 15 (needs dialysis)

GFR – glomerular filtration rate

An adaptation of the CKD classification of the KDOQI of National Kidney Foundation

As per the South African Hypertension Guidelines, hypertension (HPT) is defined as a persistent elevation of blood pressure(BP) ≥140/90 (16). The classification of HPT into 4 categories was made in accordance with the JNC8 guidelines (Table 3.2) (17). Body mass index (BMI) is an index of weight-for-height that is used to classify persons as underweight, normal, overweight or obese. BMI is calculated as the weight (kilograms) / height (metres) ^{2}. Classification of BMI was based on that of the World Health Organisation (WHO) (Table 3.3) (18).

TABLE 3. 2: CLASSIFICATION OF HYPERTENSION

Classification	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Normal	<120	AND	<80
Prehypertension	120-139	OR	80-89
Stage 1	140-159	OR	90-99
Stage 2	≥ 160	OR	≥ 100

NB. BP should be categorised according to the highest level of BP whether systolic or diastolic.

Classification as per JNC8 guidelines.

TABLE 3. 3: CLASSIFICATION OF BMI

Classification	BMI
Underweight	<18.50
Normal Range	18.50 – 24.99
Overweight	≥ 25.00
Obese	≥ 30.00

BMI – body mass index = weight (kilograms) / height (meters). Classification as per WHO guidelines.

Statistical Analysis

IBM SPSS version 24 and Stata version 13 were used for data analysis. To assess the effect of time on ordinal outcomes, the outcomes were first categorised into binary variables indicating the presence or absence of a condition. eGFR categories were collapsed into normal (eGFR ≥ 60), versus renal impairment (moderate to kidney failure, eGFR < 60). Blood pressure categories were dichotomised to normal versus hypertension – the latter included pre-hypertension. Generalised linear models for binary data were used to model the probability of renal impairment over the five time periods, controlling for repeated measures within participants over time. Risk ratios and 95% confidence intervals were reported for each time point versus baseline. A *p* value of <0.05 represented statistical significance.

Ethical approval

Full ethical approval was obtained from the Biomedical Research and Ethics Council (BREC) and permission to conduct the research was granted by King Edward VIII hospital management.

RESULTS

Demographics

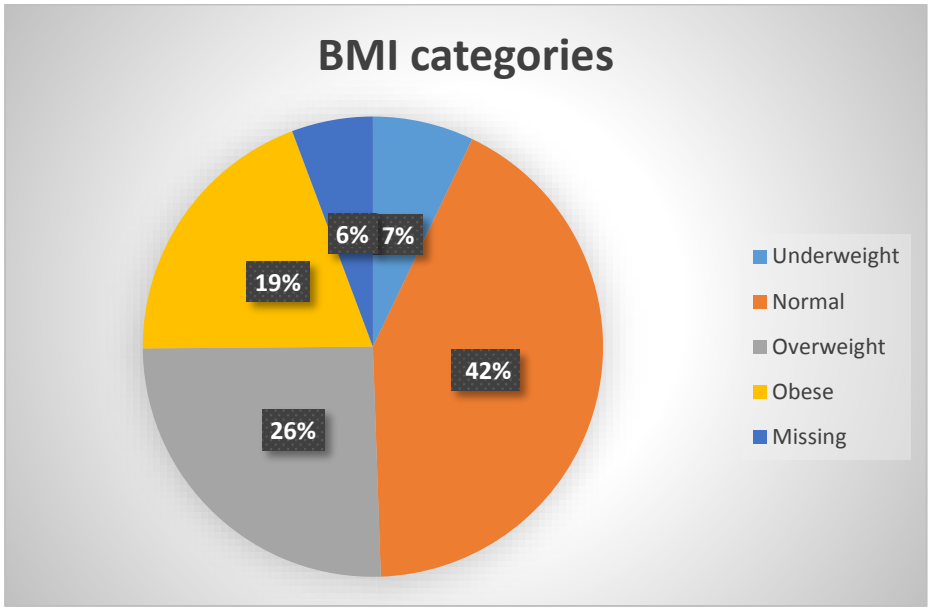
The baseline characteristics of the 350 patients included in the analysis are illustrated in Table 3.4. Their mean age was 36.9 years with a standard deviation of 9.7 years. The range was from 18 years to 72 years. The cohort was 64% female and 99% were African. Of the women, 16% were pregnant at baseline. Also at baseline, 10 patients had hypertension, 6 had diabetes and 61 were on tuberculosis (TB) treatment. At baseline, 157 patients had a high BMI with 25.4% being categorised as overweight and 19.4% obese (Figure 3.1). Due to a lack of documentation of either the weight or height or both, 20 patients did not have a BMI documented at baseline. The majority of the patients (59.3%) were normotensive while 24.1% were classified as pre-HPT, 9.9% as stage 1 HPT and 6.7% as stage 2 HPT (Figure 3.2).

TABLE 3. 4: BASELINE DEMOGRAPHICS

		Count	Variable (%)	95% Confidence intervals (CI)
Gender	Female	224	64.0	0.59 – 0.69
	Male	126	36.0	0.31 – 0.41
Race	African	348	99.4	0.98 – 1.00
	Indian	0	0.0	0.0
	White	0	0.0	0.0
	Coloured	2	0.6	0.00 – 0.02
HPT	No	340	97.1	0.95 – 0.98
	Yes	10	2.9	0.02 – 0.05
DM	No	344	98.3	0.96 – 0.99
	Yes	6	1.7	0.01 – 0.04
TB	No	288	82.5	0.78 – 0.86
	Yes	61	17.5	0.14 – 0.22
PREGNANT (women)	No	188	83.9	0.86 – 0.93
	Yes	36	16.1	0.07 – 0.14

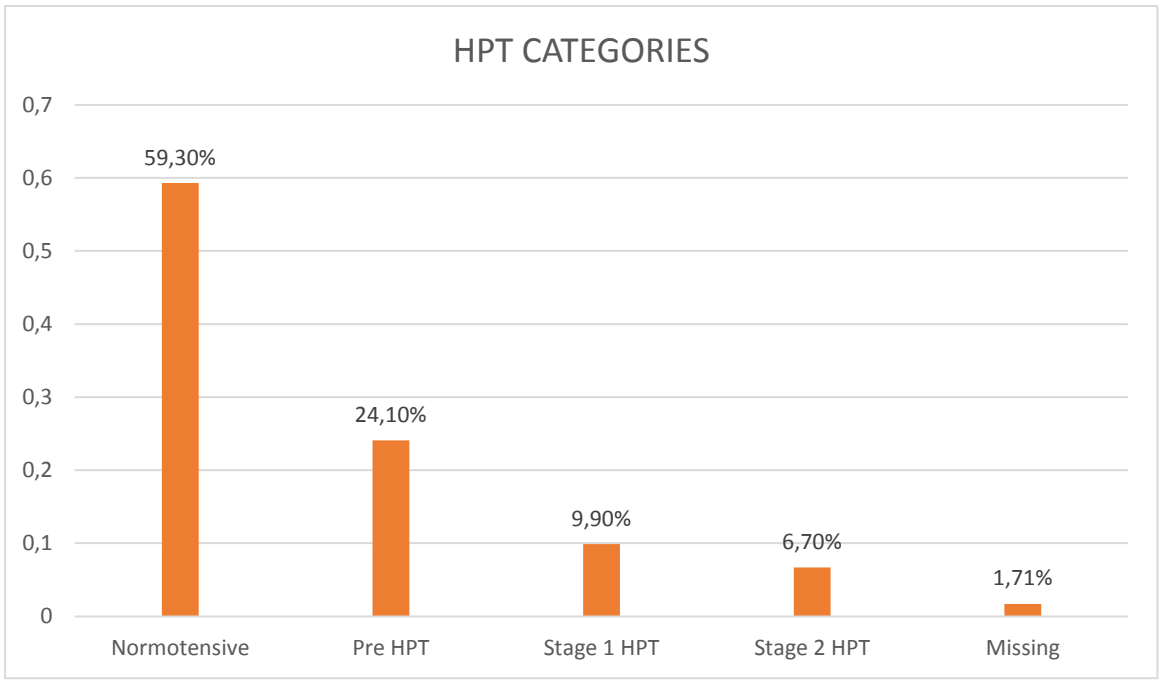
HPT – hypertension; DM – diabetes; TB – tuberculosis

FIGURE 3. 1: BASELINE BMI CATEGORIES



Underweight – BMI < 18.50; Normal – BMI 18.50 to 24.99; Overweight – BMI ≥ 25; Obese – BMI ≥ 30.

FIGURE 3. 2: BASELINE HPT CATEGORIES



Normotensive – BP <120 and <80; Pre HPT – BP 120 to 139 or 80 to 89; Stage 1 – BP 140 to 159 or 90 to 99; Stage 2 – BP ≥ 160 or ≥ 100. Measurement of BP in mmHg.

Baseline renal function

At baseline, the majority of the patients had a normal renal function 90.4%, [95% confidence intervals (CI):86%-93%], 7.0% (CI:5%-10%) had moderate renal impairment, 1.3% (CI:0%-

3%) had severe renal impairment, and 1.3% (CI:0%-3%) had kidney failure (Table 3.5). The eGFR for 49 patients was not documented at baseline. Relative to baseline the risk of developing renal impairment decreased at the subsequent time points (Appendix E). At 6 months the risk of having renal impairment was 82% (CI:5%-72%) lower than baseline, at 12 months it was 56% (CI:22%-87%) lower, at 18 months 72% (CI:10%-77%) lower and at 24 months the risk was 49% (CI:29%-91%) lower than baseline.

TABLE 3. 5: CATEGORIES OF RENAL IMPAIRMENT (RI) FROM BASELINE TO 24 MONTHS

eGFR categories (eGFR ml/min/1.73m^2)	**Baseline N (%)**	**6 Months N (%)**	**12 Months N (%)**	**18 Months N (%)**	**24 Months N (%)**
Normal (eGFR > 60), 95% Confidence intervals (CI)	272 (90.4%) 0.86-0.93	112 (98.2%) 0.93-1.00	181 (95.8%) 0.92-0.98	143 (97.3%) 0.93-0.99	212 (95.1%) 0.91-0.97
Moderate RI (eGFR 30 – 59), (CI)	21 (7.0%) 0.05-0.10	1 (0.9%) 0.00-0.06	6 (3.2%) 0.01-0.07	2 (1.4%) 0.00-0.05	9 (4.0%) 0.02-0.08
Severe RI (eGFR 15 – 29), (CI)	4 (1.3%) 0.00-0.03	0 (0.0%) 0	1 (0.5%) 0.00-0.04	0 (0.0%) 0	1 (0.4%) 0.00-0.03
Kidney Failure (eGFR < 15), (CI)	4 (1.3%) 0.00-0.03	1 (0.9%) 0.00-0.06	1 (0.5%) 0.00-0.04	2 (1.4%) 0.00-0.05	1 (0.4%) 0.00-0.03
TOTAL	**301**	**114**	**189**	**147**	**223**

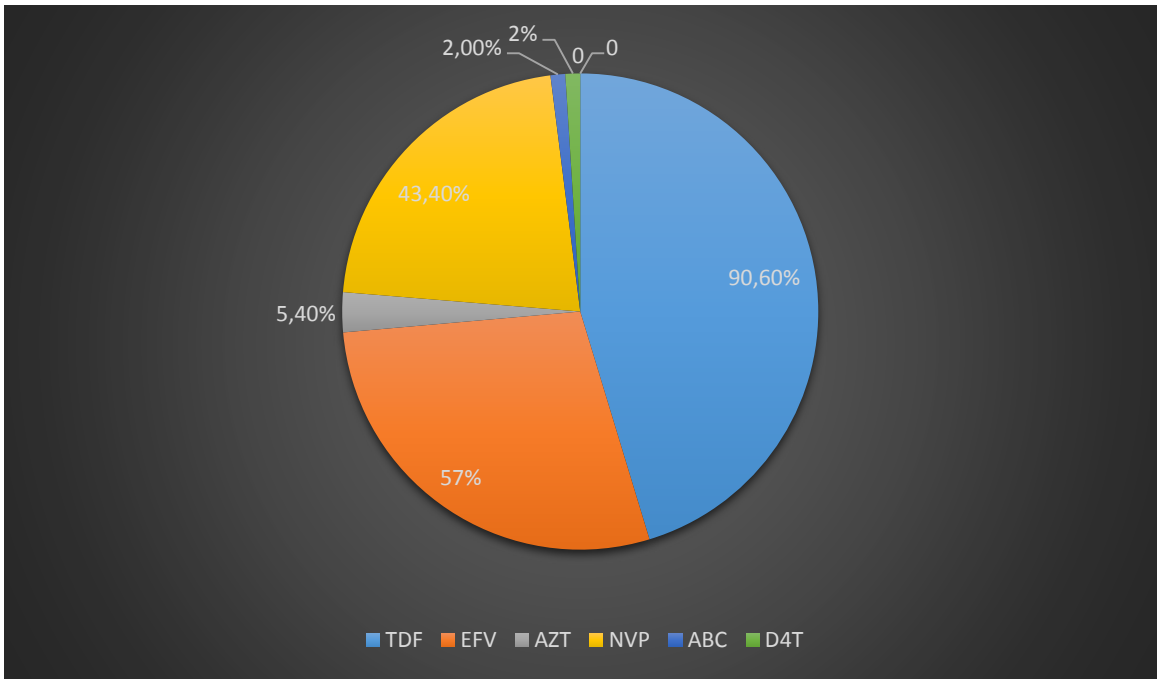
Missing data at various time points as data was not documented at these times possibly because clinicians were attending to large clinic numbers with a poorly kept paper filing system and these routine checks were missed.

Appendix F demonstrates the characteristics of the 29 patients with baseline renal impairment and depicts the trend of the eGFR over various time points. Of those patients with abnormal renal impairment at baseline, females predominated with renal impairment at 79%. 24% were

co-infected with TB while one patient had HPT. The average age of the 29 patients was 45 years. Seven patients of the 29 patients (24%) with baseline renal impairment, had persistent renal impairment at 24 months. Eight of the 29 patients did not have an eGFR done at 24 months. One patient was lost to follow up at 24 months. The eGFR of 13 patients (44.8%) normalised at 24 months.

In 2010, fixed dose combinations were unavailable in the public sector therefore patients were initiated on individual antiretroviral agents. The vast majority of patients were initiated on TDF (90.6%), in combination with lamivudine (3TC) (100%) and either efavirenz (EFV) (56.6%) or nevirapine (NVP) (43.4%). Twenty-three of the 29 patients with baseline renal impairment (eGFR's < 60ml/min/1.73m^2), were commenced on a TDF based regimen. Of the 10 patients with a baseline eGFR <50ml/min/1.73m^2 who were commenced on TDF, 7 had a normalisation of eGFR by 24 months while three experienced a deterioration in renal function. Two of the patients had TDF discontinued at 18 months and replaced with ABC. The remaining patients with renal impairment were either initiated on abacavir (ABC) (3 patients), zidovudine (AZT) (2 patients) or stavudine (D4T) (1 patient). Fourteen of the 36 pregnant women were initiated on AZT whilst the remaining 22 were initiated on TDF. The remaining patients were initiated on either D4T, AZT or ABC by the attending clinician as first line treatment with no reason specified. Figure 3.3 demonstrates this distribution of ART at baseline.

FIGURE 3. 3.DISTRIBUTION OF ART AT BASELINE



TDF – tenofovir, EFV – efavirenz, AZT – zidovudine, ABC – abacavir, D4T – stavudine.
All 350 patients were on lamivudine (3TC) at baseline in combination with 2 other ART.

Risk factors associated with abnormal renal function

The factors tested for association with abnormal renal function were age group, time, BMI, hypertension. The factors which remained significant in the model are shown in Appendix G and summarised in Table 3.6.

TABLE 3.6. RISK FACTORS ASSOCIATED WITH ABNORMAL RENAL FUNCTION

Variables	**Risk Ratio**	***P value***	**95% confidence interval**
Time – 6 months	0.19	0.018	0.48 – 0.75
12 months	0.40	0.007	0.21 – 0.78
18 months	0.24	0.005	0.85 – 0.65
24 months	0.42	0.002	0.24 – 0.73
BMI	1.06	0.000	1.03 – 1.09
HPT	1.89	0.194	0.72 – 4.95
Age – 30 to 49 years	2.51	0.128	0.77 – 8.22
≥ 50 years	6.82	0.003	1.90 – 24.54

Compared to those under 30 years old, there was no significant difference in renal impairment in those aged 30 to 49 years, $p>0.05$ (CI: 0.77 – 8.22) while those aged ≥50 years were 6.8 (CI: 1.90 – 24.54) times more likely to develop renal impairment, $p<0.05$. Time still remained a significant predictor. As time increased, so the risk of abnormal renal function decreased. As BMI increased by one unit, the risk of renal impairment increased by 1.06 (CI: 1.03 – 1.10) times. The association of HPT with abnormal renal function was found to be insignificant, $p>0.05$. A total of 21 patients (6%) were lost to follow up over the two years and 94% were retained in care (Table 3.7). Of those patients who were lost to follow-up, there was no documentation regarding tracing of these patients therefore we do not know if any of these patients demised.

TABLE 3.7. LOST TO FOLLOW-UP

TIME	LOST TO FOLLOW-UP N (%) 95% CI	RETENTION N (%) 95% CI
Baseline	0 (0%),	350 (100%)
6 months	2 (0.6%), CI: 0.00-0.02	348 (99.4%), CI: 0.98-1.00
12 months	2 (0.6%), CI: 0.00-0.02	348 (99.4%), CI: 0.98-1.00
18 months	9 (2.6%), CI: 0.01-0.05	341 (97.4%), CI: 0.95-0.99
24 months	8 (2.3%), CI: 0.01-0.05	342 (97.7%), CI: 0.95-0.99

Urine dipstick analysis

Only 5 patients in the entire cohort had urine dipsticks performed at various time points (3 at baseline, 1 at 6 months and 1 at 12 months). The test strip was positive for proteinuria in 4 out of the 5 patients (80%) and 3 out of the 4 patients (75%) with proteinuria were on a TDF based regimen with a normal eGFR. The remaining patient had renal impairment and was on an ABC regimen.

DISCUSSION

We aimed to determine the risk factors and co-morbidities associated with changes in renal function in an adult cohort with HIV in SA. The cohort was mainly female and a large proportion of patients were either pregnant or co-infected with TB. The prevalence of renal impairment at baseline was found to be relatively low. Females predominated with baseline renal impairment and the majority of the patients were co-infected with TB. Of those patients with baseline renal impairment, the majority had a normalisation of their eGFR by 24 months. The risk of developing renal impairment decreased over the two year period while patients were on ART. Risk factors found to be significant for renal impairment were older age, $p<0.05$ and an increase in BMI, $p<0.05$. In this cohort HPT did not impact renal impairment

significantly, $p>0.05$. TDF was the ART of choice for ART initiation along with 3TC and either NVP or EFV in keeping with South African National ART guidelines (13). Surprisingly, one third of patients with baseline renal impairment were initiated on a TDF based regimen in contravention of the standard ART guidelines. These guidelines state that TDF should not be initiated in patients with an eGFR of <50 ml/min/1.73m^2. This probably reflects the practice in clinics that may be under-staffed where errors may have a tendency to occur.

Similar studies conducted in South Africa showed a low prevalence of baseline renal impairment in an HIV-infected cohort (12, 19, 20) and some showed the improvement in eGFR after starting ART (19, 21, 22). Similar findings were noted in an African study by Reid et al. carried out in Mozambique and Zimbabwe (23). As HIV has been shown to have a direct renal pathogenic role (24, 25), we can deduce that treating the disease with ART diminishes the renal pathogenic effect. However, there is a lack of information on the long term outcomes of renal disease in HIV-infected patients. Not all our patients experienced a resolution in their renal function as described earlier. Our cohort comprised mainly Black patients and therefore we were unable to compare the renal function of different ethnicities. Consensus regarding gender as a risk factor for renal dysfunction could not be determined, as some studies found women to be at greater risk (19, 26) whilst others found men to be at greater risk (20). Older age has been documented in numerous studies including ours as a risk factor for renal impairment (19, 20, 27). A low CD4 count, high viral load and low haemoglobin are other variables found to be associated with a lower eGFR (12, 19, 20, 27). We did not assess these variables in our study.

A high BMI has been documented in international literature as a modest risk factor for renal impairment over time (27). To the best of our knowledge, this is the first South African study to demonstrate BMI as a risk factor associated with changes in renal function in an HIV-infected cohort. This is a significant finding as a high BMI is also a risk factor for other chronic diseases such as HPT, diabetes and cardiovascular disease (28, 29) which in turn are risk factors for CKD (6). Although we did not find a significant link between HPT and renal impairment, this has been observed in other studies (26, 27). A possible explanation for our findings could be the duration we collected data (2 years) and ethnicity (our cohort mainly Black), whilst in the other studies the duration was 96 weeks and 31 months respectively in predominantly white cohorts (26, 27).

Several studies have described TDF associated nephrotoxicity as a pattern of renal injury involving the proximal renal tubule sometimes with Fanconi syndrome occurring together with a decreased renal function (7, 30). They recommend monitoring of renal function to prevent these outcomes (10, 30, 31). The South African ART guidelines recommend monitoring of renal function with urine dipsticks, a serum creatinine and eGFR levels at baseline, 6 months, 12 months and annually thereafter for patients on TDF (13, 32). The rate of adherence to these guidelines is not known. In our study we found missing serum creatinine and eGFR levels at 6 months, 12 months and 24 months. A possible explanation for this is that clinicians were attending to large clinic numbers with a poorly kept paper filing system and these routine checks were missed. In addition, clinicians were missing the 12 month serum testing because they calculated this test as one year from the 6 month blood test hence the blood was taken at 18 months. Of those patients initiated on TDF with an eGFR < 50 ml/min/1.73m^2, only a few patients had a deterioration in renal function resulting in the discontinuation of TDF. Most likely this is because the majority had a reversible cause for the renal impairment, for example dehydration rather than actual renal disease.

Urine analysis is important to detect proximal renal tubular damage in patients on TDF as well as undiagnosed HIVAN, yet they were rarely performed in our clinic setting, again, possibly due to large volumes of clinic patients combined with staff shortages and limited ablution facilities. Fabian et al. showed that urinary abnormalities were common in HIV-infected, ART naïve outpatients and recommended that routine urinary screening of all new patients at ART clinics should be practiced (33). However, urine dipstick usage as a solitary screening tool is a topic with much debate, as research both locally and internationally suggests their poor validity in detecting proteinuria (20, 34).

A study conducted in South Africa by Han et al. showed that microalbuminuria alone could be an early marker for HIV associated nephropathy (HIVAN) (35). HIVAN is the most common histology seen on renal biopsy in South African patients (21, 22). HIVAN is commonly found in Black patients who seem to have a genetic predisposition for the disease (36) and Kasembelli et al. documented this finding in a South African cohort (37). Therefore, by deferring urine analysis, we may be missing an opportunity to detect early HIVAN in our predominantly Black high-risk cohort. The best method for urine screening is not known (6). Relying solely on serum creatinine levels and eGFR is inappropriate for this group of patients as HIVAN can occur with a normal renal function (35).

A strength of this study we feel is that we had a good sample size of 350 patients and a good representation of the profile of patients who are currently attending ART clinics across SA. The main limitation of the study would be that of missing data, for example the weight, height, blood pressures and baseline serum creatinine were not documented in some patients. Another limitation is that renal impairment that occurred between the data collection months was not captured therefore episodes of acute renal impairment were not ascertained. Lastly, we cannot comment on the diagnosis of those with persistent renal impairment at 24 months as renal biopsies were not done.

Conclusion

This study shows a low prevalence of baseline renal impairment among HIV-infected ART naïve outpatients and an improvement in renal function after the commencement of ART. This highlights the possibility of HIV being the likely cause of the renal impairment at baseline or that there is a beneficial effect of ART on early HIVAN. Caution should be exercised when excluding TDF as an option at initiation due to renal impairment as most patients have a reversible cause for the renal dysfunction which can be corrected before ART initiation. Ultimately, TDF as part of a fixed dose combination is a once daily dose which greatly improves adherence. Long-term outcomes of patients with HIV-related renal disease are not known. BMI has been associated with the development of renal impairment in an HIV-infected cohort. With the recently introduced universal access to ART in SA, we anticipate the affliction of chronic diseases and their complications including renal disease to increase. Therefore, prospective studies targeting patients with HIV-related renal disease are needed in South Africa. Research on the most cost-effective and accurate urine diagnostics are also needed to detect early renal disease. Urine microalbumin screening is not routinely practiced at ART clinics despite being found to be an early marker for HIVAN (35). We need to improve and reinforce optimal primary care in our clinics including regular BP monitoring, anthropometry and urine analysis. Lastly, we need to explore the influence of a high BMI in our HIV-infected patients and its link to CKD and other chronic diseases in order to promote a healthy lifestyle and dietician services as part of holistic management of our patients (an area often neglected in clinical practice).

Declarations

Ethics approval and consent to participate

Ethical approval from KZN Department of Health and Ethical approval from UKZN BREC Ethics Committee

Consent for publication

Not applicable

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

None declared.

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Authors' contributions

SA, NPM and TPM-T conceptualised and designed the study. SA prepared the first draft. TPMT contributed in the synthesis of data and the design of the sifting and data extraction processes. TPMT and NPM assisted with the manuscript preparation. All authors reviewed draft versions of the manuscript and approved the final version of the manuscript.

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Additional Files

APPENDIX E- Risk of Developing Renal Impairment over time

APPENDIX F- Followup of eGFR of patients with baseline renal impairment

APPENDIX G- Risk factors and co-morbidities associated with abnormal renal function

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CHAPTER 4: SYNTHESIS: SUMMARY, DISCUSSION, CONCLUSION AND RECOMMENDATIONS

This chapter presents a summary of our research findings, and assesses the strengths and limitations of this study. It also presents the conclusions, recommendations for improvement of existing services and offers suggestions for further research.

4.1 Background

The main aim of this study is to portray the current stance on the renal manifestations of HIV in SA in the era of ART. The significance of this study cannot be denied as South Africa carries the global burden of HIV infection and the rollout of ART has now been extended to all HIV infected individuals irrespective of CD4 count or clinical stage (1). As early as 2010, a South African study demonstrated an increase in the prevalence of CKD in HIV-infected individuals (2). We anticipate the domino effect of universal ART access to be further increases in the prevalence of CKD as well as HIV-related kidney diseases as HIV transforms into a disease of chronicity.

Recently, there has been an upsurge of research and publications on the topic (3-8), therefore the contribution of a systematic scoping review gains importance and relevance by demonstrating the current data in order to identify research gaps and suggest novel ideas for future research. The retrospective chart review gives an overview of what is being practised at an HIV clinic as well as a description of the presentation of renal impairment in an HIV cohort. Comparing these findings with that of the systematic scoping review, will unravel areas where research is lacking as well as indicate domains in clinical practice that need improvement or refinement. Ultimately, the conclusions drawn will benefit the millions living with HIV in SA and particularly those with renal disease.

4.2 Key Findings of the Study

The research questions needed answers on the gaps in research on HIV-related renal diseases in SA and the current volume of HIV-related renal manifestations reported in SA. Our study shared similarities with other studies demonstrating that the prevalence of baseline renal impairment in HIV-infected patients is low (8-10) and that renal function improves with ART (5, 11). However, the long-term effects of ART on renal disease is not known and the morbidity and mortality of those with CKD and HIV-related renal disease is not well documented. HIV cohorts in SA comprise mainly Black individuals who are at high risk for developing HIVAN due to a possible genetic predisposition to the disease (12). HIVAN was also the most common histological finding on renal biopsy (5, 11). HIVAN can occur with only microalbuminuria and a normal renal function (4). Therefore, urine dipstick analysis is essential for the early detection of renal impairment. The best method for urine protein detection is not known. However, as revealed by the chart review, urine analysis is rarely performed at

a clinic level; therefore we could be missing patients with undiagnosed renal disease. We do not know the actual prevalence or incidence of HIV-related kidney diseases and CKD in SA. We believe that our chart review was the first South African study to link a high BMI as a risk factor for renal impairment.

4.3 Strengths of the study

The systematic scoping review focussed on studies carried out in South Africa, a hyper-HIV burdened country. The strength of a systematic scoping review is undoubtedly its rigorous methodology. This included parallel screening of abstracts and full articles by two screeners and methodology quality assessment of included studies. Kappa statistics was employed to estimate the degree of agreement among screeners. The study team utilised Arksey and O'Malley's scoping review framework (13) and adapted it to suit the study based on recommendations made by Levac et al. in 2010 (14). This framework was best suited to answer the research questions as it involved 'mapping', a process that summarises a range of evidence to convey the breadth and depth of the research topic (14). It is systematic, transparent and replicable (15). This type of review is advantageous in that it provides a preliminary assessment of the potential size and scope of available research literature on a particular topic and identifies the nature and extent of research evidence (15). Ultimately, it is able to inform researchers if a full systematic review or primary research study should be undertaken (15). Even though renal function improves with ART, the long-term outcomes of renal disease for patients on ART is not well documented.

In order to ensure eligibility of the research question for this research method, the team formulated a data extraction table based on the PICO model (16). Bias was reduced throughout the scoping review process. Screening of literature was conducted by two independent researchers with a third for resolving discrepancies. In addition, all included studies were assessed for quality by use of the tried and tested mixed methods appraisal tool (17). Systematic reviews form part of evidence-based medicine (EBM) research methods, considered the gold standard of study design and which perch at the very top of the hierarchy of the evidence pyramid (18, 19).

The main strength of the retrospective chart review is that is utilises secondary data, that is data that has already been already collected for purposes other than research. This is advantageous as the data is readily accessible, economical, improves understanding of the problem and provides a basis for comparison of the data collected. A representative sample size of 350 medical records of patients attending the ART clinic in eThekwini, KwaZulu-Natal was used. The data was obtained from a high HIV pandemic region, eThekwini, KwaZulu-Natal is known as the epicentre of the HIV epidemic. The demographic profile of the study cohort is representative of other ART clinics across South Africa. Overall, the results of the chart review will impact and improve patient care as they unravel errors in clinical practice and adverse events (20).

4.4 Limitations of the study

Overall, the study has made significant findings. Nonetheless, there are some limitations that must be acknowledged. Most of the evidence obtained from the scoping review was derived from observational studies. Even though observational studies are an important source of data when randomised controlled trials are unavailable, they are prone to bias (21).

With regards to the retrospective chart review, there are a few limitations. Firstly one of the unavoidable limitation is that of missing data from the clinic charts. For example the weight, height, blood pressure, urine dipstick and baseline serum creatinine were not documented in some patients at the various data collection times. Episodes of acute renal failure that may have occurred between the data collection points were not documented. Though this missing data was not substantial it could possibly influence the results obtained. Lastly, we cannot distinguish between or account for the incidence of TDF nephrotoxicity versus HIV nephropathy at 24 months, as the study did not document renal biopsy or ultrasound findings in the cohort.

4.5 Conclusions

This study demonstrates the current stance on the renal manifestations of HIV in the era of ART in South Africa and illustrates the deficiencies in knowledge and their implications for the future. The findings of the study are in keeping with that of international literature. Universal access to ART for all HIV-infected South Africans will likely result in an increase in chronic diseases namely HIV, HPT, CKD and diabetes. The impact on the current health infrastructure that this strategy will have is unknown. There is a shortfall in knowledge and statistics on the incidence and prevalence of CKD, HIV-related renal diseases and ART related nephrotoxicity in SA currently. Furthermore, there is a deficiency in evidence on the long-term morbidity and mortality of HIV-infected patients with renal disease. This information is imperative to assist policymakers in management decisions as well as enhancing the health infrastructure to support patients with CKD. There is a lack of dedicated CKD clinics and specialist renal services particularly in the rural settings (22) as well as a shortage of nephrologists in SA (23). Though urine diagnostics are vital for the early detection of renal disease, it is not being routinely performed. The current South African ART guidelines also make no clear guidance on exactly when and how this test should be performed.

4.6 Recommendations

Based on the study conclusions, the following recommendations are suggested:

1. Renal registries should be established which will assist with much needed statistics on the morbidity and mortality of both HIV-related and non-related renal disease as well as ART nephrotoxicity.

2. The National Department of Health should establish CKD clinics in rural areas and nephrology outreach services.
3. Clear guidelines for the use of urine dipstick analysis as routine screening for all patients attending ART clinics should be included in the National ART guidelines. The recommendation is for urine dipstick analysis at baseline, 3 months and 6 monthly thereafter.
4. Patients and clinical staff should be educated (and therefore empowered) about the importance of urine dipstick analysis, BP and glucose monitoring and anthropometry, which will ensure these routine screening tests are regularly performed in overburdened facilities.
5. Training on adherence to guidelines.

4.7 Dissemination of Research

Based on the study findings and the flaws detected by the chart review regarding poor adherence to ART guidelines, we recommend training all clinic staff timeously about ART guidelines and routine checks that must be performed at clinic visits. The conclusions from our research will be shared with the hospital management as well as the Provincial Department of Health. Both manuscripts will be published in reputable journals to further disseminate information.

4.8 Future Studies

Based on the study findings, the following areas of research are recommended:

1. More research to be carried out in rural areas where access to healthcare and laboratories is not easily accessible.
2. Comparative studies to determine the differences in renal manifestations between HIV infected males and females, preferably in rural settings, are recommended. More males must be recruited to participate in research.
3. Research into cost effective methods for urine screening - microalbuminuria versus proteinuria as well as the development of an algorithm for screening and confirming proteinuria.
4. Comparative studies looking at microalbuminuria versus proteinuria on urine dipstick analysis as a more cost effective and accessible marker for early HIVAN.
5. A prospective randomised controlled trial investigating diagnosis options for HIVAN.
6. Cohort study focussing on TDF nephrotoxicity and its long term renal outcomes.
7. A survey to determine the prevalence of renal disease and HIV-related renal disease in South Africa in order to strengthen primary healthcare services to reduce the burden of CKD.
8. A cohort study to determine the link between high BMI and renal impairment (to confirm the findings of our study) – vicious circle as it contributes to other chronic disease which are also risk factors for CKD.
9. Prospective study regarding the use of TDF in a patient with proteinuria. Should TDF be avoided?

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APPENDICES

APPENDICES: SUPPLEMENTARY MATERIAL

A.1 **APPENDIX A- Ethical approval from KZN Department of Health**

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

Reference: 32/16
KZ_2015RP25_189

Date: 23 February 2016

Dear Dr S. Assaram
Email:

Approval of research

1. The research proposal titled **'Renal manifestations of HIV in the era of ART in South Africa'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson: Health Research Committee
Date: 23/02/16

Fighting Disease, Fighting Poverty, Giving Hope

A.2 APPENDIX B- Ethical approval from UKZN BREC Ethics Committee

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
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KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

13 March 2017

Dr A Assaram (993210127)
Discipline of Medicine
School of Clinical Medicine
shirelleassaram@gmail.com

Protocol: Renal manifestation of human immunodeficiency virus in the era of antiretroviral therapy in South Africa.
Degree: MMedSc
BREC reference number: BE486/15

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	28 February 2017
Expiration of Ethical Approval:	27 February 2018

I wish to advise you that your application for Recertification dated 28 February 2017 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The approval will be ratified by the full Committee at a meeting to be held on 11 April 2017.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

A.3 APPENDIX C- List of studies included for full article screening and reviewers' responses

Author and Date	Response: Reviewer 1	Response: Reviewer 2
Arendse et al., 2011	No	No
Brennan et al., 2011	No	Yes
Fabian et al., 2009	Yes	Yes
Fabian et al., 2013	Yes	Yes
Fabian et al., 2015	No	Yes
Franey et al., 2009	Yes	Yes
Kamkuemah, 2013	Yes	Yes
Kamkuemah et al., 2015	Yes	Yes
Kasembelli et al., 2015	Yes	Yes
Madala et al., 2014	No	Yes
Okpechi et al., 2010	No	No
Stanifer et al., 2014	No	No
Vachiat et al., 2013	Yes	Yes
Van Deventer et al., 2008	Yes	Yes
Wearne et al., 2012	Yes	Yes
Wensink et al., 2015	Yes	No
Gerntholz et al., 2006	No	No
Han et al., 2006	No	No
Okpechi et al., 2010	No	No
Van Rensburg et al., 2009	No	No
Madala et al., 2012	No	No

Agreement	Expected Agreement	Kappa	Std. Err.	Z	Prob>Z

```
-------------------------------------------------------------

 80.95%     49.66%    0.6216    0.2143      2.90      0.0019


            | Controls            |
Cases       |  Exposed   Unexposed  |     Total
----------------+-----------------------+------------
       Exposed |        9         1  |        10
     Unexposed |        3         8  |        11
----------------+-----------------------+------------
         Total |       12         9  |        21

McNemar's chi2(1) =      1.00    Prob > chi2 = 0.3173
Exact McNemar significance probability      = 0.6250

Proportion with factor
      Cases      .4761905
      Controls   .5714286    [95% Conf. Interval]
               ---------    --------------------
      difference -.0952381    -.3250218   .1345456
      ratio      .8333333     .5826548   1.191863
      rel. diff. -.2222222    -.7037382   .2592937

      odds ratio  .3333333     .0063495   4.151441   (exact
```

A.4 APPENDIX D- Quality assessment tool

Reviewers	Author and date	Question 1: Are there clear qualitative and quantitative research questions (or objectives*), or a clear mi	Add comment for question 1	Question 2: Do the collected data allow address the research question (objective)? E.g., consider whether	Add comm ent for question 2	Question 3: Is there a clear description of the randomization (or an appropriate sequence generation)?	Add comments for question 3	Question 4: Is there a clear description of the allocation concealment (or blinding when applicable)?	Add comment for question 4	Question 5: Are there complete outcome data (80% or above)?	Add comment to question 5	Question 6: Is there low withdrawal/drop-out (below 20%)?	Add comments to question 6	Question 7: Are participants (organizations) recruited in a way that minimizes selection bias?	Add comments to question 7	Question 8: Are measurements appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding	Add comment to question 8	Question 9: In the groups being compared (exposed vs. Non-exposed; with intervention vs. Without; cas	Add comments to question 9	Question 10: Are there complete outcome data (80% or above), and, when applicable, an acc	Add comment to question 10	Question 11: Is the sampling strategy relevant to address the quantitative research question (quantitative asp	Add comment to question 11	Question 12: Is the sample representative of the population understudy?	Add comment to question 12	Question 13: Are measurements appropriate (clear origin, or validity known, or standard instrument)?	Add comments on question 13	Question 14: Is there an acceptable response rate (60% or above)?	Add comment to question 14

		xed methods question (or objective *)?		the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components).												the exposure/intervention and outcomes?		es vs. Controls), are the participants comparable, or do researchers take into account (control for) the difference between en		epta ble e res pons e rat e (60 % or abov e), or an acc epta ble follow-up rate for coho rt stu die s (dep end ing on		ect of the mixed methods question)?								

																			these groups?		the duration of follow-up)?											
1	BRENNAN 2011	Yes		Yes		N/A	CASE SERIES	N/A	NOT DOUBLE BLINDED	Yes		Yes		No	EXCLUDING PTS CAN INTRODUCE BIAS	Yes		N/A	NO CONTROL GROUP	Yes		Yes		No	SMALL SAMPLE SIZE	Yes		Yes			
2	BRENNAN 2011	Yes		Yes		N/A		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		No		Yes		Yes	18		
1	FABIAN 2009	Yes		Yes		N/A	ALL NEW PTS	N/A	NOT DOU	Yes		Yes		No		Yes		N/A	NO CONTROL	Yes		Yes		Yes		Yes		Yes			

							SCREENED		BLEBLINDED										GROUP													
2	FABIAN2009	Yes		Yes		N/A		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		Yes		Yes		Yes		Yes	20		
1	FABIAN2013	Yes		Yes		N/A	Case series	N/A	Not double blinded	Yes		No	Rate 25.9%	No		Yes		N/A	No control group	Yes		Yes		No	Small sample size	Yes		Yes				
2	FABIAN2013	Yes		Yes		N/A		N/A		Yes		No		No		Yes		N/A		Yes		Yes		No		Yes		Yes		16		
1	FRANEY2009	Yes		Yes		N/A	CASE SERIES	N/A	NOT DOUBLE BLIND	Yes		Yes		No		Yes		N/A	NO CONTROL GROUP	Yes		Yes		Yes		Yes		Yes				

									ED																						
2	FRANEY 2009	Yes		Yes		N/A		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		Yes		Yes		Yes	20		
1	KAMKUEMAH 2015	Yes		Yes		N/A	CASESERIES	N/A	NOTDOUBLEBLINDED	Yes		No	RATE 22%	No	PRONETOSELECTIONBIAS	Yes		N/A	NOCONTROLGROUP	Yes		Yes		Yes		Yes		Yes				
2	KAMKUEMAH 2015	Yes		Yes		N/A		N/A		Yes		No		No		Yes		N/A		Yes		Yes		Yes		Yes		Yes	18		
1	KASEMBELI 2015	Yes		Yes		No		N/A		Yes		Yes		No		Yes		No		Yes		Yes		No		Yes		N/A			
2	Kasembeli	Yes	Quant	Yes		No		N/A	This is	Yes		Yes		No	Control	Yes		No	Control	Yes		Yes		No	Study	Yes		N/A	16		

	, 2015		itative						a case control study						group presumed 'Healthy" - renal function not assessed				group presumed healthy. Some pts on ART and others naive						lacked sufficient numbers						
1	MADALA 2014	Yes		Yes		N/A	CASE SERIES	N/A	NOT DOUBLE BLINDED	Yes		Yes		No		Yes		N/A	NO CONTROL GROUP	Yes		Yes		No	SMALL SAMPLE SIZE	Yes		Yes			

2	MADALA2014	Yes		Yes		No		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		No		Yes		Yes	18		
1	VACHIAT2013	Yes		Yes		N/A	CASESERIES	N/A	NOTDOUBLEBLINDED	Yes		Yes		No	NOTIDEALLYMATCHED	Yes		No	NOTIDEALLYMATCHED	Yes		Yes		No	SMALLSAMPLESIZE	Yes		Yes			
2	VACHIAT2013	Yes		Yes		N/A		N/A		Yes		Yes		No		Yes		No		Yes		Yes		No		Yes		Yes	18		
1	VANDEVENTER2008	Yes		Yes		N/A	CASESERIES	N/A	NOTDOUBLEBLINDED	Yes		Yes		No		Yes		N/A	NOCONTROLGROUP	Yes		Yes		No	SMALLSAMPLESIZE	Yes		Yes			

2	VAN DEVENTER 2008	Yes		Yes		N/A		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		No		Yes		Yes	18		
1	WEARNE 2012	Yes		Yes		N/A		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		Yes		Yes		Yes			
2	WEARNE 2012	Yes		Yes		N/A	CASE SERIES	N/A	NOT DOUBLE BLINDED	Yes		Yes		No		Yes		N/A	NO CONTROL GROUP	Yes		Yes		Yes		Yes		Yes	20		
1	WENSINK 2015	Yes		Yes		No		N/A	NOT DOUBLE BLIND	Yes		Yes		No	RANDOM SELECTION	Yes		N/A	NO CONTROL GROUP	Yes		Yes		Yes		Yes		Yes			

									ED																						
2	WENSINK 2015	Yes		Yes		No		N/A		Yes		Yes		No		Yes		N/A		Yes		Yes		Yes		Yes		Yes		20	
				22						22		18				22				22		22		10		22		20			

A.5 APPENDIX E- Risk of Developing Renal Impairment over time

Generalized linear models No. of obs = 973

Optimization : MQL Fisher scoring Residual df = 968

(IRLS EIM) Scale parameter = 1

Deviance = 401.4853798 (1/df) Deviance = .4147576

Pearson = 972.9991345 (1/df) Pearson = 1.005164

Variance function: V(u) = u*(1-u/1) [Binomial]

Link function : g(u) = ln(u) [Log]

BIC = -6258.726

(Std. Err. adjusted for 348 clusters in STUDYNO)

	Semirobust				
GFR_binary	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]
time					
6 months	.1820932	.1277103	-2.43	0.015	.0460582 .7199133
12 months	.4393359	.1536724	-2.35	0.019	.2213403 .8720329
18 months	.2824302	.1451236	-2.46	0.014	.1031646 .7731993
24 months	.5142902	.1508526	-2.27	0.023	.2894223 .9138699
_cons	.0963455	.0170317	-13.24	0.000	.0681331 .1362401

A.6 APPENDIX F- Followup of eGFR of patients with baseline renal impairment

FILE		BASELINE	6MONTHS	12MONTHS	18MONTHS	24MONTHS
49/11 72yrs Female Bmi 27.1	**eGFR**	54.79	Nd	>60 75.04	Nd	Nd
	ART	TDF,3TC,EFV				
205/11 53yrs Female Bmi 28.7	**eGFR**	56.81	>60 78.51	>60 69.05	>60 60.68	>60 60.68
	ART	TDF,3TC,EFV				
568/10 51yrs Female Bmi nd	**eGFR**	49.00	nd	nd	nd	>60 86.41
	ART	TDF,3TC,EFV				
275/11 32yrs Female Bmi 28.1	**eGFR**	50.46	Nd	Nd	>60 124.02	Nd
	ART	TDF,3TC,EFV				
371/11 36yrs Male, TB Bmi nd	**eGFR**	59.42	Nd	>60 105.45	>60 108.88	nd
	ART	TDF,3TC,EFV				
567/11 59yrs Male Bmi 21.3	**eGFR**	46.13	nd	nd	>60 63.40	40.61
	ART	TDF,3TC,EFV				
578/11	**eGFR**	58.00	Nd	47.40	Nd	44.95

51yrs Female, TB 34.60						
	ART	TDF,3TC,EFV				
587/11 56yrs Female Bmi 46.5	**eGFR**	38.45	nd	>60 78.97	nd	>60 72.68
	ART	TDF,3TC,EFV				
788/11 40yrs Male Bmi 27	**eGFR**	51.65	nd	nd	>60 154.48	Nd
	ART	TDF,3TC,EFV				
1033/11 60yrs Female Bmi 37.8	**eGFR**	47.95	nd	>60 90.18	nd	Nd
	ART	TDF,3TC,EFV				
1111/11 36yrs Female Bmi 26.4	**eGFR**	52.59	>60 86.38	>60 82.12	>60 70.40	>60 68.42
	ART	TDF,3TC,NVP	TDF,3TC,EFV			
1145/11 50yrs Male Bmi 20.7	**eGFR**	57.81	nd	>60 63.45	>60 62.11	>60 72.79
	ART	TDF,3TC,EFV				
819/10 33yrs Male, HPT	**eGFR**	3.68	4.01	nd	LTFU	LTFU
	ART	ABC,3TC,EFV				

Bmi 22.5						
51/12 46yrs Female Bmi 46.1	**eGFR**	20.63	59.23	11.88	34.26	34.83
	ART	TDF,3TC,EFV			ABC,3TC,EFV	
150/12 42yrs Female Bmi 27.0	**eGFR**	53.98	nd	>60 73.50	>60 79.59	Nd
	ART	TDF,3TC,NVP			AZT,3TC,Aluvia	
341/12 51yrs Male Bmi 32.3	**eGFR**	14.17	nd	nd	LTFU	15.78
	ART	AZT,3TC,EFV	ABC,3TC,EFV			
346/12 49yrs Male, TB Bmi 25.1	**eGFR**	25.33	nd	54.25	Nd	43,82
	ART	ABC,3TC,EFV				
416/12 46yrs Female Bmi 45.6	**eGFR**	51.18	nd	>60 71.06	Nd	>60 80.80
	ART	TDF,3TC,EFV				FDC
475/12 30yrs Female, TB	**eGFR**	37.98	nd	>60 83.84	Nd	>60 117.48
	ART	TDF,3TC,EFV			FDC	

Bmi 14.6						
843/12 42yrs Female Bmi 38.1	**eGFR**	58.80	nd	>60 61.12	Nd	58.07
	ART	TDF,3TC,EFV		FDC		
431/12 69yrs Female, TB Bmi 52.8	**eGFR**	19.82	>60 77.02	nd	>60 71.96	>60 73.17
	ART	ABC,3TC,EFV				
476/12 30yrs Female Bmi 14.6	**eGFR**	14.49	nd	>60 83.84	nd	>60 101.81
	ART	TDF,3TC,EFV				
600/12 44yrs Female Bmi 42.5	**eGFR**	49.38	nd	>60 106.38	nd	>60 85.89
	ART	TDF,3TC,EFV				FDC
1039/10 40yrs Female Bmi 24.8	**eGFR**	39.70	nd	nd	>60 69.91	>60 76.59
	ART	AZT,3TC,NVP				
1266/10 49yrs Female, TB	**eGFR**	24.22	nd	24.82	nd	nd
	ART	TDF,3TC,EFV			ABC,3TC,EFV	

Bmi 37.4						
1273/10 47yrs Female Bmi 47.5	**eGFR**	51.55	LTFU	LTFU	LTFU	nd
	ART	TDF,3TC,EFV				
494/10 26yrs Female Bmi 22.8	**eGFR**	50.48	nd	>60 100.92	nd	>60 77.43
	ART	D4T,3TC,EFV		D4T,3TC,NVP		
1336/10 49yrs Female Bmi 21.3	**eGFR**	56.99	nd	>60 99.80	nd	6.90
	ART	TDF,3TC,EFV				
1339/10 25yrs Male, TB Bmi 19.4	**eGFR**	6.24	>60 110.06	nd	nd	>60 125.36
	ART	TDF,3TC,EFV				

Nd – not done, ART – antiretroviral treatment, TB – tuberculosis, BMI – body mass index, LTFU – lost to follow up, FDC – fixed dose combination

A.7 APPENDIX G- Risk factors and co-morbidities associated with abnormal renal function

Generalized linear models No. of obs = 972

Optimization : MQL Fisher scoring Residual df = 963

(IRLS EIM) Scale parameter = 1

Deviance = 353.6712349 (1/df) Deviance = .3672598

Pearson = 991.4235583 (1/df) Pearson = 1.029516

Variance function: V(u) = u*(1-u/1) [Binomial]

Link function : g(u) = ln(u) [Log]

BIC = -6271.148

(Std. Err. adjusted for 348 clusters in STUDYNO)

	Semirobust				
GFR_binary	Risk Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]
time					
6 months	.1905768	.133623	-2.36	0.018	.0482225 .7531656
12 months	.4020471	.1349437	-2.71	0.007	.2082468 .7762033
18 months	.2356236	.1224814	-2.78	0.005	.0850646 .6526627
24 months	.4218433	.1191978	-3.05	0.002	.2424556 .7339563
BMI	1.060231	.0130867	4.74	0.000	1.03489 1.086194
HPT					
yes	1.891108	.9282237	1.30	0.194	.7226302 4.94899
agegroup					

```
       2 |   2.512881   1.519828     1.52   0.128     .767985     8.22226
       3 |   6.822283    4.45519     2.94   0.003     1.896991    24.53546
         |
   _cons |   .0066735   .0045581    -7.33   0.000     .0017497    .0254532
------------------------------------------------------------------------------
```