

Original Research Article
Prevalence of Chronic Kidney Disease (CKD) in ART-Naïve Patients in Southern Nigeria: Need for Creatinine Assay

Abstract

AIMS: CHRONIC KIDNEY DISEASE (CKD), A COMMON COMPLICATION OF HUMAN IMMUNODEFICIENCY(HIV) DISEASE, REPRESENTS AN INTERPLAY BETWEEN COMMUNICABLE AND CHRONIC NON-COMMUNICABLE DISEASE. RENAL IMPAIRMENT IS A CONTRAINDICATION TO THE USE OF SOME ANTIRETROVIRAL DRUGS. THE CURRENT HIV TREATMENT STRATEGY OF 'TEST AND START' REQUIRES CLIENTS DIAGNOSED WITH HIV TO BE COMMENCED ON ANTIRETROVIRAL THERAPY (ART) THE SAME DAY OR WITHIN ONE WEEK OF HIV DIAGNOSIS. THE AIM OF THIS STUDY WAS TO DETERMINE THE PROPORTION OF ART-NAÏVE PATIENTS WHO HAD SERUM CREATININE ASSAY DONE BEFORE COMMENCEMENT OF ANTIRETROVIRAL DRUGS (ARDS); THE PROPORTION OF ART –NAÏVE PATIENTS WITH CKD BEFORE COMMENCEMENT OF ARDS AND HIGHLIGHT THE NEED FOR RENAL FUNCTION TESTS BEFORE THE COMMENCEMENT OF ARDS.

STUDY DESIGN: THIS WAS A CROSS SECTIONAL STUDY.

PLACE AND DURATION OF STUDY: THE STUDY WAS CONDUCTED IN A HIV COMPREHENSIVE TREATMENT CENTER OF A TERTARY HEALTH FACILITY IN SOUTHERN NIGERIA FROM JULY TO DECEMBER, 2019.

METHODOLOGY: THE MEDICAL RECORDS OF 159 ART- NAÏVE ADULT CLIENTS NEWLY ENROLLED INTO HIV CARE OVER A 6 MONTHS PERIOD WERE REVIEWED.SOCIODEMOGRAPHIC AND CLINICAL DATA WERE ABSTRACTED. CKD WAS DEFINED AS eGFR OF <60ML/MIN/1.732M².

RESULTS: ONE HUNDRED AND FIFTY NINE PATIENTS WERE COMMENCED ON FIRST LINE ARDS. MORE THAN HALF, 92 (57.9%) WERE FEMALES. MEAN AGE OF RESPONDENTS WAS 37.3+/- 10.1 YEARS . EIGHT (5.0%) WERE KNOWN HYPERTENSIVES AND ONE (0.6%) WAS A KNOWN DIABETIC AT ENROLLMENT. NINETY ONE (57.2%) HAD CREATININE ASSAY DOCUMENTED PRE- ARD COMMENCEMENT WTH SIMILAR PROPORTION IN MALES AND FEMALES (p=.24) .THE PREVALENCE OF CKD WAS 15.5%. (95% CI: 8.7 - 24.5%)

CONCLUSION: THE BASELINE PREVALENCE OF CKD WAS HIGH IN ART - NAÏVE PATIENTS BEFORE COMMENCEMENT OF ARDS. POINT OF CARE CREATININE MACHINES FOR SCREENING OF ART-NAÏVE PATIENTS FOR CKD ARE STRONGLY RECOMMENDED IN ALL HIV TREATMENT CENTERS

Comment [SG1]: Does it mean its an adverse event associated with ARDs? This sentence is confusing so please paraphrase
Also suggest rearranging this way - "THE CURRENT HIV TREATMENT STRATEGY OF 'TEST AND START' REQUIRES CLIENTS DIAGNOSED WITH HIV TO BE COMMENCED ON ANTIRETROVIRAL THERAPY (ART) THE SAME DAY OR WITHIN ONE WEEK OF HIV DIAGNOSIS. However, RENAL IMPAIRMENT IS an adverse event associated with SOME ANTIRETROVIRAL DRUGS (ARDs).

Comment [SG2]: The "why" of this study is missing. Is it that ARDs lead to CKD so it is important to determine the creatinine before the treatment starts to ensure the ARDs with higher risk of ARDs is not given to those with already high creatinine? Please add this link of why this is important to capture

Comment [SG3]: patients

Comment [SG4]: Full form?

Comment [SG5]: All patients

Comment [SG6]: The intro says "Many studies among ART-naïve patients in Nigeria reported a high prevalence of CKD in PLHIV, with values ranging from 47.6% to 53%.". The prevalence in this study is lower comparatively. It's high compared to what?

Keywords: [ART-naïve, Ujo, creatinine assay, CKD]

1. INTRODUCTION

In sub-Saharan Africa (SSA), HIV/AIDS is a major public health problem and is known to account for 70% of the global disease burden.¹ The Nigeria AIDS Indicator and Impact Survey (NAIIS) of 2018 reported an HIV prevalence of 1.4% amongst adults aged 15-64 years in Nigeria² and about 1.1 million people were receiving antiretroviral therapy (ART) as at 2019.³ All HIV infected persons irrespective of clinical stage and CD4+ cell count without contraindications should be initiated on ART the same day or within seven days of HIV diagnosis.⁴ The ART should be offered in a comprehensive manner that includes access to ongoing adherence counselling, baseline and periodic clinical and laboratory monitoring, prevention and management of opportunistic infections (OIs), treatment monitoring and follow-up, with the ultimate goal of ART being the achievement of sustained virologic, immunologic, clinical, and epidemiologic control of HIV.⁴ Before ART commencement, the recommended baseline assessment and preparation of patients for ART should include re-testing for HIV to verify HIV positive status, history and clinical examination, assessment of patient's readiness for initiation of ART, development of patient-centred adherence strategy and baseline laboratory assessment though these assessments should not delay the commencement of ART.⁴

Comment [SG7]: Full form at first appearance

The benefits of initiating ART early in persons living with HIV (PLHIV) include reduced mortality and ill health.⁵ However, untreated HIV infection may be associated with the development of serious co-morbidities such as; cardiovascular, kidney and liver diseases, cancers and mental illness, while early ART initiation prevent these illnesses.⁴ Kidney disease is a common complication of HIV infection,^{6,7} and HIV infection is a common cause of chronic kidney disease (CKD) in SSA.^{8,9} Many studies among ART-naïve patients in Nigeria reported a high prevalence of CKD in PLHIV, with values ranging from 47.6% to 53%.¹⁰⁻¹⁴ Results in other African countries reported a prevalence of CKD in PLHIV of 2% and 12% in South Africa and Kenya, respectively.^{15,16} Generally, it has been shown that blacks, anywhere in the world, have a higher risk of CKD when they are HIV-infected.¹⁷

Comment [SG8]: includes

In addition to this risk, initiation of ART, especially a tenofovir-based regimen, is associated with an increased risk of development of tubular renal dysfunction.⁴ Increasing age and low CD4+ cell count at ART initiation are also independent CKD risk factors in the HIV population.¹³ In situations of renal impairment, from an underlying kidney problem or from tenofovir disoproxil fumarate (TDF) nephrotoxicity, replacement of TDF with abacavir or tenofovir alafenamide (TAF) is recommended.⁴ This switch from TDF to TAF has been associated with improved kidney function though the long-term safety of TAF has not been established.¹⁸ Other nucleotide reverse transcriptase inhibitors (stavudine, zidovudine, emtricitabine, abacavir and lamivudine are considered 'renal friendly', but dose adjustment is required in the setting of renal failure, except for abacavir. Abacavir is associated with acute interstitial nephritis and Fanconi's syndrome. Didanosine and abacavir are associated with Fanconi's syndrome and nephrogenic diabetes insipidus.¹⁹⁻²¹ Also, some medications used for the treatment of opportunistic infections (OIs) and some OIs (for example, mycobacterium tuberculosis) may also cause acute kidney diseases (AKI) or CKD.²² Thus, a kidney function test becomes important pre-ART initiation.

Comment [SG9]: Remove double space throughout the article

Comment [SG10]: Black race

Comment [SG11]: Suggest adding a summary sentence in the beginning of this paragraph - for example, "HIV treatments are commonly associated with adverse events, especially renal dysfunction including CKD". This will help the reader to know what to expect in this paragraph

Comment [SG12]: Please put end bracket

Comment [SG13]: Already abbreviated before

Comment [SG14]: Add space. Please check for similar formatting

The national HIV treatment policy recommends a schedule to monitor all adults on ART with laboratory tests which include serum creatinine (with the calculation of eGFR) and urinalysis at baseline, among other tests, to ensure the renal safety and well-being of clients on ART.⁴ However, these investigations are not free, and thus, patients pay out of pocket for these tests which may not be affordable for all patients before the commencement of ARTs. This study was conducted to determine the proportion of ART-naïve patients who have

Comment [SG15]: Full form?

Comment [SG16]: Is it not free at any stage or only before commencement? If latter, then would suggest rephrasing to "these investigations are not free before the commencement of ARTs, and thus..."

serum creatinine values before the commencement of ARTs; the proportion of ART-naïve patients with CKD determined using estimated glomerular filtration rate, eGFR and highlight the need for renal function tests before commencement of ARTs.

Comment [SG17]: Full form needed

Comment [SG18]: eGFR full form not needed here

Comment [SG19]: Missing the objective and why this study is conducted?

2. MATERIAL AND METHODS

2.1 Study Site: The study was carried out at the University of Uyo Teaching Hospital (UUTH) in Akwa Ibom State in Southern Nigeria, with a 2018 projected population of 5,737,270.²³ For over two decades, the State's HIV prevalence rate has continually been higher than the national average.² The Akwa Ibom AIDS Indicator Survey 2017 and the National HIV/AIDS Indicator and Impact Survey 2018, both population-based surveys, put the state HIV prevalence at 4.8% and 5.5%, respectively, making the state to be one of those with the highest prevalence in Nigeria.^{2,19} Akwa Ibom state has a federally owned teaching Hospital, the University of Uyo Teaching Hospital, UUTH, located in Uyo, the state capital. It is one of the numerous comprehensive HIV treatment centres in the state. The UUTH HIV comprehensive treatment centre is supported by United States Agency for International Development/FHI 360 and carries out voluntary counselling and testing for HIV, provision of ART, management of opportunistic infections, and follow-up care for PLHIV. It is currently equipped with a PCR laboratory which serves as a reference laboratory for PCR investigations for HIV treatment centres in the state and other states in the country.

Comment [SG20]: Already abbreviated

Comment [SG21]: Full form needed

2.2 Study Design and study instrument: This was a descriptive cross-sectional study involving the review of records of newly enrolled HIV-positive adult clients at UUTH comprehensive HIV treatment centre in Akwa Ibom state over a six-month period between July to December, 2019. Information on sociodemographic characteristics of clients, such as age and sex of clients were extracted. Laboratory data, including creatinine values and CD4+ cell counts, were also obtained using an abstraction tool designed for the study. Clinical variables like estimated glomerular filtration rate, eGFR was determined. Chronic kidney disease, CKD was defined as eGFR of $<60\text{ml}/\text{min}/1.732\text{m}^2$ and calculated using the CKD-EPI equation without the race factor.²⁵

Comment [SG22]: Throughout the manuscript, kindly check abbreviations and their first appearance for full form post which abbreviations can be used

2.3 Study population, sample size determination and study procedure: The study population consisted of all adults diagnosed with HIV infection and newly enrolled into the comprehensive HIV care at the teaching hospital. Children (less than 15 years usually seen at the paediatric HIV clinic) and pregnant HIV-positive women (usually seen at the ante-natal clinic) were excluded. The clients are usually counselled after confirmatory HIV test results and enrolled into care at the comprehensive HIV treatment centre. Using the current test and start strategy according to the National HIV treatment guidelines⁴, clients are commenced on first line Antiretroviral drugs (ARTs), with the preferred regimen being TDF, Lamivudine and Dolutegravir (TLD) the same day or within 7 days after confirmatory HIV test and counselling is done. Serum creatinine is recommended by the National HIV treatment guideline to be done at baseline before the commencement of ARTs, at the 3rd month on ART, and after the first 12 months, it is repeated every 6 months for patients on TDF.⁴ This test is, however, not covered by the support from HIV partners, nor is it offered free to clients by the government of Nigeria. Hence, clients pay for the test as out-of-pocket expenditure after being counselled by the designated health personnel on the need for the test.

2.4 Data analysis: Data obtained were analysed using Stata 13.0 for Windows (StataCorp, TX, USA). Results were presented in simple tables. Categorical variables were summarised as frequencies and percentages, while appropriate measures of central tendencies and dispersions were calculated for quantitative variables. Chi square test or Fisher's exact test were used to compare the associations between categorical variables at a statistical significant level set at $P < 0.05$.

3. RESULTS AND DISCUSSION

A total of one hundred and fifty nine (159) HIV positive ART-naïve patients were enrolled during the period under review and commenced on first-line ARDs. More than half, 92 (57.9%) were females. Mean age of respondents was 37.3±10.1 years with males significantly older than females (39.7±9.3 versus 35.6±10.2, p=0.02). Eight (5.0%) were known hypertensives and one was a known diabetic at enrollment. Forty (25.2%) had baseline CD4+ cell count recorded with a median CD4+ cell count of 297 cells/μl (136-460.5). Ninety-one (57.2%) had creatinine results. (Table 1)

Table 1. Sociodemographic and clinical characteristics of respondents

Variables	Gender		Total (n=159) n(%)	Statistical test and p value
	Male (n=67) n(%)	Female n=(92) n(%)		
Age (Mean± SD) (years)	39.7± 9.3	35.6±10.3	37.3 ±10.1	p=0.02*
Hypertensive				Fishers Exact
Yes	1 (1.5)	7 (7.6)	8 (5.0)	p=0.14
No	66 (98.5)	85 (92.4)	151 (95.0)	
Diabetic				Fishers Exact
Yes	0 (0.0)	1 (5.0)	1 (3.13)	p=0.99
No	12 (100.0)	19 (95.0)	31 (96.9)	
Had baseline CD4+cell count				
Yes	16 (23.9)	24 (26.1)	40 (25.2)	χ ² =0.100
No	51 (76.1)	68 (73.9)	119 (74.8)	p=0.75
Baseline CD4+cell count (Median(IQR) (cells/μl) (n=40)	280.5 (133.5-419)	336.5(145.5-550)	297.0(136.0-460.5)	p=0.46**
Had Baseline Creatinine				
Yes	42 (62.7)	49 (53.3)	91 (57.2)	χ ² =1.41
No	25 (37.3)	43 (46.7)	68 (42.8)	p=0.24

Comment [SG23]: Are other parameters available such as economic status, BMI, economic status / income level (especially since test needs to be paid out of pocket, this info can be relevant, etc.?)

Comment [SG24]: Diabetic status does not add up to the total. Was the status not known; if so, need to put it

Also. What is the rationale between splitting the cohort into males and females? Is a certain association expected? Is CKD prevalence generally higher in one group than other?

*=significant p value; SD= standard deviation; IQR=Interquartile range; **=Wilcoxon rank-sum test

The proportion of patients with documented creatinine results was similar between those that were known hypertensives and those that were not.(5, 62.5% versus 86, 57.0%, p=0.99)

The prevalence of CKD was 15.5% (95%CI. 8.7 to 24.5%) (Table 2).

Table 2. Prevalence of Chronic Kidney Disease (CKD) among ART Naïve patients in UUTH (n=91)

Variable	Frequency (Percent)	95% Confidence Interval
CKD	14(15.5%)	8.7 – 24.5%

Comment [SG25]: This does not require a table

3.1 Discussion

This study sought to determine the proportion of ART-naïve patients who had serum creatinine values before commencement of ARDs and the proportion of ART-naïve patients with chronic kidney disease before commencement of ARDs. The study was conducted in a relatively young population with an average age of respondents of 37.3+/- 10.1 years and with a female preponderance.

Comment [SG26]: Use short forms

A little more than half of the respondents had serum creatinine results in their folders. This falls short of the recommendation that all clients should have serum creatinine test done before commencement of ARDs.⁴ A retrospective study of ART-naïve patients in the same centre some years previously reported a similar finding.¹³ Hence, the system of allowing patients pay for renal function test out-of pocket results in many of them not able to afford this key investigation that allows them to be assessed for risk of CKD. Availability and documentation of creatinine results at enrollment was similar between the known hypertensives and those who were known hypertensives. This was because the test was paid for by the patients themselves irrespective of the presence of other chronic illnesses.

Comment [SG27]: If light of this study already conducted in some centers, what is the relevance of the current study? How old was the previous study / did it lack something? Need to highlight the importance of current study

The proportion of ART-naïve patients with CKD was 15.5%. This is comparable to 13.4% earlier reported in the same centre many years before¹³ and a Kenyan study that reported a CKD prevalence of 12%.¹⁶ This confirms the fact that PLHIV are at risk of CKD

Comment [SG28]: How much is the out of pocket burden? What is the amount? How many times does the test need to be conducted? What is the resource utilization?

For a laboratory test that can predict the renal status of clients who are ART-naïve or ART experienced and can also give clinicians information on effective drug management of patients either at commencement of ARDs or during the course of being on ARDs, having just a little above half of the patients with this result is not encouraging. Considering the fact that CKD is expensive to manage and the cost of management of CKD in Nigeria currently is neither covered by HIV care support programs nor by the government of Nigeria for PLHIV, but paid for by patients via out- of- pocket expenditure, there is need to have this singular test done for as many ART-naïve patients as possible before commencement of ARDs. This calls for intense patient education at enrollment on the benefits of this test and physicians/clinicians insistence for it to be done by clients though not denying them ARDs should they refuse or cannot afford it.

Comment [SG29]: Unclear of this sentence. Please recheck

This findings report the situation in a teaching hospital that has a full compliments of laboratory investigations including creatinine assay available in the centre. The situation in many primary health centres offering ART services where facilities for creatinine assay is not available or community ART services where no laboratory assays are done for patients before ART commencement can only be imagined as the patients are not even offered the opportunity to have this test done. Hence, point of care creatinine machines are strongly recommended in all HIV treatment centers. Referral of community ART patients to such centres with capacity for creatinine assay is encouraged. In as much as commencement of ARTs has numerous benefits including breaking the chain of HV transmission in the community, preventing them from developing CKD in the future should also be a major concern for the program

Comment [SG30]: Compare this to another nation where these rates are low to provide context to the reader of what low prevalence can look like

Comment [SG31]: Which test? Its not clear in the entire paragraph

Comment [SG32]: patients

3.2 Limitation: The use of secondary data for the study was one of the limitations as creatinine values of some patients who were registered at the clinic may be unavailable for assessment and inclusion into this study. Few records of urinalysis which is also recommended by the national treatment guideline for monitoring patients on ART were

Comment [SG33]: Are these put in other places and has it seen improvement in ckd rates?

Comment [SG34]: Suggest paraphrasing. "In many primary health centres or community ART service centers offering ART services in Nigeria, facilities for creatinine assay are not available or not offered for patients before ART commencement. This is a key unmet need for patients. Hence, point of care creatinine machines are strongly recommended in all HIV treatment centers"

Comment [SG35]: HIV

available and were not used to assess clients' renal function. In addition, using a single eGFR may overestimate CKD prevalence. However, we strongly believe that patients included with creatinine values who were more than half of the total patients enrolled over the period was an adequate representation of the enrolled patients and the prevalence calculated from using a single eGFR which agrees with previous findings gives a picture of the CKD in the setting.

4. CONCLUSION

This study reports a high prevalence of CKD in ART naïve HIV positive patients in a comprehensive HIV treatment centre in Akwa Ibom state, Nigeria. A little above half of all patients could afford serum creatinine tests at baseline before ART initiation. Free or subsidised serum creatinine test for all clients before ART initiation could contribute to further reduction in the prevalence of CKD

Comment [SG36]: How was this determined?
Need to clarify in results section as well that not getting the test done was due to affordability

ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Health Research Ethical Committee of the University of Uyo Teaching Hospital.

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