Journal of Advances in Medicine and Medical Research

Volume 35, Issue 19, Page 45-52, 2023; Article no.JAMMR.102198
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Prevalence of Chronic Kidney Disease in ART-Naïve Patients in Southern Nigeria: Need for Creatinine Assay

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AME and MI designed the study. Authors AME, OOM and UEE performed the statistical analysis. Author AME wrote the protocol and the first draft of the manuscript while authors EB and AO managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i195139

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/102198

Original Research Article

Received: 02/05/2023
Accepted: 14/07/2023
Published: 24/07/2023

ABSTRACT

Aims: 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 if possible. However, chronic kidney disease (CKD) is a complication of Human Immunodeficiency Virus (HIV) disease and an adverse event associated with using some antiretroviral drugs (ARDs). The aim of this study was to determine the proportion of ART-naïve patients with serum creatinine

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assay to assess their kidney functions before the commencement of ART and the prevalence of CKD among them.
Study Design: This was a cross-sectional study.
Place and Duration of Study: The study was conducted in an HIV comprehensive treatment centre of a tertiary health facility in southern Nigeria from July to December 2019.
Methodology: The medical records of 159 ART-naïve adult patients newly enrolled into HIV care over a six months period were reviewed. Sociodemographic and clinical data were abstracted. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60ml/min/1.732m^2.
Results: All the newly enrolled patients were commenced on first-line ARDs. More than half (92,57.9%), were females. The mean age of respondents was 37.3± 10.1 years. Only ninety-one (57.2%) had creatinine assay documented pre-ART commencement, with a similar proportion in males and females (p=0.24). The prevalence of CKD was 15.5% (95% CI: 8.7 - 24.5%)
Conclusion: About two out of every five patients had no documented creatinine assay pre-ART commencement.The prevalence of CKD among ART-naïve patients with creatinine assay before the commencement of ARDs was moderate. A policy change that supports free or subsidized serum creatinine test using point-of-care creatinine machines in all HIV treatment centres to assess kidney function of HIV patients before ART initiation is recommended.

Keywords: ART-naïve; Uyo; creatinine assay; CKD.

1. INTRODUCTION

In sub-Saharan Africa (SSA), Human immunodeficiency virus disease (HIV) 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 Nigeria [2] 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 if possible [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.These assessments should not delay the commencement of ART [4].

Reduction in ill health and mortality are some of the benefits of initiating ART early in persons living with HIV (PLHIV) [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 prevents these illnesses [4]. Kidney disease is a common complication of HIV infection, [6,7] and HIV infection is a common cause of 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 people of the black race, anywhere in the world, have a higher risk of CKD when they are HIV-infected [17] Genetic contribution to CKD risk in the HIV-infected population, especially apolipoprotein L1 gene (APOL1)-related genetic risk among individuals in SSA. [18,19] have been suggested by recent studies as the reason for this finding. A study in the United Kingdom of HIV-infected patients of different African ethnicities documented a 6 fold increased risk for progression to kidney failure requiring kidney replacement therapy in HIV-infected individuals of West African origin compared with those of East African origin [20]. In addition, black individuals of Caribbean origin but with a shared ancestry with the West African subregion had a 5 times increased risk for progression to kidney replacement therapy compared with those of East African origin [20].

HIV treatments are associated with adverse events, especially renal dysfunction, including

CKD. 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, either from an underlying kidney problem or from tenofovir disproxil fumarate (TDF) nephrotoxicity, replacement of TDF with abacavir or tenofoviir 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 [21]. 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 [22-24] Apart from ARTs, some medications used for the treatment of OIs and some OIs (for example, mycobacterium tuberculosis) may also cause acute kidney injury (AKI), or CKD [25] Thus, a kidney function test becomes important pre-ART initiation.

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 estimated glomerular filtration rate, eGFR) and urinalysis at baseline, among other tests, to ensure kidney 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 serum creatinine values before the commencement of ARTs and those of them diagnosed with CKD determined using eGFR and highlight the need for a policy change that will make all HIV positive individuals tested for kidney dysfunction before the commencement of ARTs.

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 [26]. 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 of 2017 and the National HIV/AIDS Indicator and Impact Survey of 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 [2,27]. This federally owned teaching Hospital, the University of Uyo Teaching Hospital, is 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 Polymerase chain reaction (PCR) laboratory, which serves as a reference laboratory for PCR investigations for HIV treatment centres in the state and other states in the country.

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 from July to December, 2019. Information on socio-demographic 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. The Clinical variable, eGFR was determined. CKD was defined as eGFR of $<60ml/min/1.732m^2$ and calculated using the CKD-EPI equation without the race factor [28].

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 were counselled after confirmatory HIV test results and enrolled into care at the comprehensive HIV treatment centre. Using the current test and start strategy outlined in theNational HIV treatment guidelines [4], clients were commenced on first line Antiretroviral drugs with the preferred

regimen being Tenofovir disoproxil fumarate, Lamivudine and Dolutegravir (TLD) the same day or within 7 days following confirmatory HIV test and counseling. Serum creatinine as recommended by the National HIV treatment guidelines, is meant to be done at baseline before the commencement of ARTs, at the 3rd month on ART, and after the first 12 months, 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 as required, were used to compare the associations between categorical variables at a statistically 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. The 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).

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%).

3.1 Discussion

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

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 the commencement of ARTs, at the 3rd month on ART, and repeated every 6 months for patients on TDF after the first 12 months [4] The non-availability of creatinine results documented in patients medical records at baseline could mainly be due to inability to pay for the test as results of the free HIV screening test was documented in all folders. Thus, patients pay for creatinine test out-of pocket . As a result, many of them that are indigent with some even having challenges paying their transport fare to the treatment facility, could not afford this key investigation that allows them to be assessed for the risk of CKD. Availability and documentation of baseline creatinine results did not vary with the presence of other chronic illnesses like hypertension that are additional risk factors for CKD.

The proportion of ART-naïve patients with CKD was 15.5%. This is comparable to 13.4% earlier reported on ART-naïve patients in the same centre three years before [13] and a Kenyan study that reported a CKD prevalence of 12% [16] Hence, the effects of the virus itself on renal glomerular and tubular epithelial cells even when ARTs are not yet commenced, puts HIV infected patients at a high risk of CKD [29].

For a laboratory test such as serum creatinine assay that can predict the renal status of patients 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

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				
Yes	1 (1.5)	7 (7.6)	8 (5.0)	+p=0.14
No	66 (98.5)	85 (92.4)	151 (95.0)	
Diabetic (n=32)				
Yes	0 (0.0)	1 (5.0)	1 (3.13)	+p=099
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)	$x^2 = 0.100$
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)	x^2=1.41
No	25 (37.3)	43 (46.7)	68 (42.8)	p=0.24

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

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.

This findings report the situation in a teaching hospital that has a full compliments of laboratory investigations including creatinine assay available in the centre. 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 to 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 centres. 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 HIV transmission in the community, preventing them from developing CKD in the future should also be a major concern for the program

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 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 moderate prevalence of CKD in ART naïve HIV positive patients in a comprehensive HIV treatment centre in Akwa Ibom state, Nigeria. More than 40% of the patients had no documented serum creatinine tests in their medical records to assess renal function before ART initiation. A policy change that supports free or subsidized serum creatinine test using point-of-care creatinine machines to assess kidney function of all HIV patients before ART initiation is recommended. This could contribute to a reduction in the prevalence of CKD among them through early identification of kidney dysfunction and its timely management.

CONSENT

It is not applicable.

ETHICAL APPROVAL

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

ACKNOWLEDGEMENTS

The authors thank the staff of the ART unit for assisting in data abstraction and data entry.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/102198