Afr. J. Med. Med. Sci. (2022) **52(3) 165 - 169**

Evaluation of nephrotoxicity of tenofovir, lamivudine, efavirenz and zidovudine, lamivudine, nevirapine drug combinations in HIV patients treated for three years

CC Nganwuchi[1], AJ Onuegbu[2], MI Olisekodiaka[2], JE Okwara[2], UK Amah[2], OC Okamgba[1], and SAU Offiah[1]

Department of Pathology, Abia State University, Aba Campus and Department of Chemical Pathology, Nnamdi Azikiwe University, Nnewi Campus

Abstract

Background: Human immunodeficiency virus (HIV) infection is a global health problem with increased burden on medical facilities worldwide. HIV/AIDS is associated with many complications especially when there is delayed diagnosis, late commencement of management and toxicity from antiretroviral therapy (ART). The onset of chronic kidney disease usually manifests with mild reduction in glomerular filtration rate. This study was designed to compare the nephrotoxic effect of Tenofovir, Lamivudine, Efavirez (DCA) and Zidovudine, Lamivudine, Nevirapine (DCB) combinations used in management of HIV Patients.

Methods: We measured serum creatinine and cystatin c levels in 55 HIV patients on three years ART and calculated glomerular filtration rates derived from serum creatinine and cystatin-c using Chronic Kidney Disease Epidemiology Collaboration equations.

Results: The mean serum creatinine (89.89 ±16.99µmol/L) and cystatin-c (1.02±0.10mg/L) values for HIV patients on DCA were significantly higher when compared with corresponding values in HIVpatients on DCB (79.00±10.39 µmol/L and 0.91±0.12 mg/L) respectively. Also the mean GFRcreat values (97.25±20.15) and GFRcyst values (80.71±9.96 ml/min/1.73m^2) of HIV patients on DCA were significantly lower when compared with corresponding values in HIV patients on DCB (115.85±12.82 ml/min/1.73m^2 and 93.78 ±15.30ml/ min/1.73m^2) respectively. *Conclusion***:** We concluded that the use of Zidovudine, Lamivudine, Nevirapine drug combination appears safer than Tenofovir, Lamivudine, Efavirenz combination.

Keywords: *ART, Creatinine, Cystatin-c, HIV, Nephrotoxicity*.

Correspondence: Dr. C.C.Nganwuchi, Departmentof Pathology, Abia State University, Aba Campus, Nigeria. E-mail: catetannganwuchi@gmail.com

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Introduction

Human Immunodeficiency Virus (HIV) infection and Acquired Immune Deficiency syndrome (AIDS) epidemic constitute a global health issue ravaging families and communities throughout the world. HIV/AIDS in 2016 was the 4th of the 10 top and still remain in the 10 top leading cause of death in low income countries in 2019 [1,2]. AIDS is a chronic viral disease caused by Human Immunodeficiency virus that is usually found in body fluids such as blood, semen, vaginal fluid and breast milk of infected person [3]. The virus can be transferred from one infected person to another mostly through sexual intercourse and sharing of unsterilized instruments like blades, knives and syringes which have recently been used by infected persons [4]. About 54% of new infections are transmitted by 25% of individuals that are unaware of their HIV status [5]. Undiagnosed HIV/AIDS infection and inadequate management result to high viral load, disease complication and poor prognosis. HIV/AIDS is characterized by profound immune suppression that leads to opportunistic infections and neurologic manifestations [6,7].

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS related morbidity and mortality [8,9]. Several strategies are in place to improve treatment, and efforts are being made to maximize the effectiveness of available treatment. Each antiretroviral medication is associated with its adverse effect and a group adverse effect may also occur during management [10,11]. The antiretroviral drugs approved by the food and drugs administration (FDA) before and after 2012 have been classified [12]. Treatment options involve a backbone of two nucleoside reverse transcriptase inhibitors (NNTRIs), protease inhibition (Pls), Integrase strand transfer inhibitors (INSTIs) and Fusion inhibitors (Fls). Besides reducing the viral load in HIV patients, these antiretroviral drugs cause a considerable level of toxicity including nephrotoxicity [13,14]. The gradual nephrotoxic effects of these drugs may lead to the onset of chronic kidney disease over a period of time.

Materials and method

Study area and design

Fifty five (27 males and 28 females) HIV sero-positive patients on antiretroviral therapy were enrolled in this study. All were patients attending HIV/AIDS clinic in Abia State University Teaching Hospital, Aba, Nigeria. Sample size was determined by 3.3% prevalence of HIV infection in Abia State [15] using Fisher's formula for sample size calculation, as described by Sin-Ho, 2014 [16]. The patients were grouped into two categories according to their antiretroviral combinations.

Group 1 comprises of 28 patients (15 males and 13 females) who are on Tenofovir(TDF)/ Lamivudine(ZTC)/Efavirenz(EFV) daily dose of 300mg/300mg/600mg which is coded with drug combination A (DCA).

Group 2 were 27age-matched patients (12males and 15 females) who are on Zidovudine(ZDV)/ Lamivudine(ZTC)/Nevirapine(NVP) twice daily dose of 300mg/150mg/200mg which is coded with drug combination B (DCB). Only patients who adhered strictly to therapy were selected. Patients with confirmed renal disease, other co-morbid diseases and/or any form of prophylactic drugs were excluded.

Ethical clearance (ABSUTH/MAC/49 VOL.II/215) for this study was obtained from the Ethical Committee of Abia State University Teaching Hospital, Aba, and was strictly complied with.

Sample collection

Six milliliters (6mls) of blood were collected from each patient into a vacutainer plain tube and allowed to clot. Serum was extracted and stored frozen.

Laboratory analysis

Measurement of serum creatinine and serum cystatin-c were performed on the samples by Jaffe's reaction method and enhanced immunoturbidimetric method respectively using Selectra, Pro S autoanalyzer by VITAL SCIENTIFIC BV, NETHERLAND. Serum creatinine and serum Cystatin-c values were expressed in µmol/L and mg/ L respectively.

Glomerular filtration rates (GFRs) were calculated for each patient using serum creatinine and serum Cystatin-c differently. Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation was used [17]. GFR results were expressed in ml/min/1.73m^2.

Statistical analysis

Statistical analysis was performed with statistical package for social sciences (SPSS) version 25.0 using student t-test and significant level was set at $P < 0.05$. The values were expressed in Mean ± SD. The mean values of age, serum creatinine, cystatin-c, GFRcreat and GFRcyst were calculated for DCA and DCB.

Results

There was no significant difference in the mean age of the HIV patients on DCA and DCB (p>0.05) (Table 1).

Table 1: Comparison of Mean ± Sd of age of HIV Patients on DCA and DCB

Parameters	Group 1 (Dca)	Group 2 (Dcb)	P – Value
Age (years)	39.00 ± 6.00	37.00 ± 4.00	0.121

The mean serum creatinine and serum cystatin c values of HIV patients on DCA were significantly higher when compared with values obtained from patients on DCB (P<0.05) (Table 2).

Table 2: Mean±SD Serum creatinine and cystatin C Levels of HIV patients on three-year art

Parameters	Group 1 (DCA)	Group 2 (DCB)	*P-Value.*
Creatinine (µmol/L)	89.89± 16.99	76.00± 10.39	0.001
Cystatin c (mg/L)	1.02±0.10	0.91±0.12	0.001

The mean GFRcreat and GFRcyst values of HIV patients on DCA were significantly lower when compared with values obtained from patients on DCB (p<0.005) (Table3).

Table 3: Mean estimated glomemlar filtration rate value of HIV patients (creatinine and cystatin C)

GFR (ML/min/1.73m2)	Group 1 (DCA)	Group 2 (DCB)	*P- value*
CKD-EPI (creatinine)	97.25±20.15	115.85±12.82	0.000
CKD-EPI (cystatin-c)	80.71±9.96	93.78±15.30	0.000

Discussion

The results obtained from this study suggest that HIV patients on DCB seemed to have lowered nephrotoxicity when compared with similar patients on DCA. Serum levels of creatinine and cystatine-c, a more sensitive marker for renal function were significantly lower while glomerular filtrate rate was significantly higher in HIV patients on DCB.

Single regimen earlier used in the treatment of HIV infection is associated with high rate of disease progression and viral resistance to drugs [18,19]. Pevelson *et al* and Kahlert *et al*, [20 and 21] had earlier reported that dual agent regimen and combination therapy could improve viral suppression and reduce the risk of emergence of resistance. However, efficacy of viral suppression must be balanced against the risk of unwanted effects from multi drug use.

Drug-drug interaction of these antiretroviral drugs when administered concomitantly may decrease efficacy, reduce excretion and increase toxicity. In three year use of antiretroviral therapy, the comparative renal toxicity of the drug combinations (DCA and DCB) was very clear. There was evidence that serum levels of creatinine and cystatin-c and also estimated glomerular filtration rates were significantly different. The toxicity of individual antiretroviral drug is associated with its metabolism and excretion. Tenofovir and Lamivudine are eliminated unchanged in the urine by a combination of glomerular filtration and tubular secretion [22,23]. Zidovudine, Efavirenz and Nevirapine are mainly excreted in urine in the glucoronide form [24,25]. Tenofovir could reach a very high concentration in proximal tubule cells as a result of active uptake in the cells and transported into the nucleus and mitochondria where it inhibits mitochondrial ribosome and protein synthesis. This process results in the shrinking of the cells and tubular necrosis as it was observed in patients who have a renal biopsy after development of Tenofovir related acute renal failure [26]

Furthermore, the possible nephron toxicity in patients receiving DCA combination is heightened by concomitant administration of Lamivudine and Efavirenz. A study by Ceckova *et al*, [27] reported that Lamivudine renal excretion was reduced by Efavirenz.

Conclusion and recommendation

Based on nephrotoxic effect from this study, the use of Zidovudine/Lamivudine/Nevirapine drugs combination is safer than Tenofovir/Lamivudine/ Efavirenz combination in the management of HIV patients with respect to delaying the onset of chronic kidney disease. HIV/AIDS facilities still using Tenofovir/Lamivudine/Efaviranz combination should key into safer options of drug regimen. It is also important to evaluate the renal status of every HIV naïve patient before commencement of antiretroviral therapy.

Acknowledgements

We wish to express our profound gratitude to the management of Abia State University Teaching Hospital, Aba for giving access to the Hospital facilities used in this study.

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Received = 27/10/2021
Accepted = 31/01/2022