Histomorphological Effects of Quinine and Triple Antiretroviral Regimen (Efavirenz/Lamivudine/Tenofovir) on Fetal Kidney of Albino Wistar Rats

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Abstract

The Histomorphological Effects of Quinine and Triple Antiretroviral Regimen on Fetal Kidney of Albino Wistar Rats was studied. Forty female Wistar rats in estrous cycles weighing between 180 - 220g were divided into eight groups with 5 rats in each group. Sexually active male of the same strain was added into each group to ensure fertilization. Vaginal smear from each of the females was collected following overnight mating and checked for spermatozoa under microscope. The present of sperm in the vaginal smear indicated day zero of pregnancy and administration started on day 7. Group 1 served as the control while Groups 2 - 4 were given 10 mg/kg, 20 mg/kg and 30 mg/kg body weight of quinine hypochloride injections intraperitoneally respectively every 8 hours for seven days. Group 5 animals were administered 17.1 mg/kg body weight of triple antiretroviral regimen orally, respectively for 7 days. Groups 6 - 8 were administered concomitantly 17.1 mg/kg triple antiretroviral regimen daily + Quinine 10 mg/kg 8 hourly, 17.1 mg/kg of triple antiretroviral regimen daily + quinine 20 mg/kg body weight 8 hourly and 17.1 mg/kg of triple antiretroviral regimen + quinine 30 mg/kg body weight 8 hourly for 7 days respectively. At the end of the experiment, the rats were euthanized to remove the fetuses and each fetus was sacrificed to harvest the kidney for histological analysis. The result revealed a significant ($p > 0.05$) reduction in the fetal body weight and placental weight following administration of quinine, antiretroviral combination drugs and more significant ($p > 0.05$) reduction was observed in quinine and antiretroviral combination drugs co-administration treated groups dose dependently compared with the control group. Administration of quinine and antiretroviral combination drug produce notable distortions to the his to architecture of the fetal kidney within the experimental groups with the quinine and antiretroviral drugs co-treated groups showing a severe degeneration dose dependently. This is suggestive of intrauterine growth retardation and fetal renal toxicity caused by these drugs.

Keywords — *Quinine, Triple Antiretroviral Regimen, Fetus, Renal Toxicity, Intrauterine Growth.*

I. INTRODUCTION

HIV/AIDS and malaria are diseases that affect both the young and old, male and female as well as pregnant women. HIV/AIDS is considered a pandemic - a disease outbreak which is present over a large area and is actively spreading [1]. The HIV prevalence rate among adults ages 15-49 was 3.17%, in 2014 about 36.9 million people were living with HIV and it resulted in 1.2 million deaths [2]. Malaria is a serious illness that is spread by mosquito bites and can result in death. Malaria infection during pregnancy is a significant public health problem with substantial risks for the pregnant woman, her fetus, and the newborn child. Malaria in pregnancy causes several adverse outcomes that include maternal anaemia, intrauterine growth retardation, low birth weight, preterm deliveries and abortion [3]. Nigeria accounts for roughly 25 % of the malaria burden in sub-Saharan Africa. Often undetected and untreated, malaria adversely affects pregnant women and their fetuses or neonates.

Currently the WHO recommends the use of quinine plus clindamycin for treating malaria in the first trimester of pregnancy [4]. Evidence for the safety of quinine in pregnancy is mostly historical and there are few clinical trials published [5]. Quinine is schizonticidal against intra-erythrocyte malaria parasites. Quinine belongs to the aryl amino alcohol group of drugs, extremely basic compound and always presented as salt [6]. Although quinine occurs naturally in the bark of the cinchona tree, it has also been synthesized in the laboratory [7]. Quinine is rapidly absorbed both orally and parenterally, reaching peak concentrations within 1-3 hours [8].

In addition to functional adverse effects, in-utero exposure to drugs may affect renal structure itself and produce renal congenital abnormalities [9]. Also Triple antiretroviral on the other hand has a good safety record compared with zidovudine and single-dose nevirapine prophylaxis in pregnant women infected with HIV. Though some studies have suggested triple ART may be associated with low birth weight or prematurity, whereas others have not found an association between adverse pregnancy outcomes and treatment, but with advanced maternal

disease but no recent research has been conducted to know the effects on fetal kidney [10].

The kidneys provide the final common pathway for the excretion of many drugs and their metabolites, and therefore are frequently subjected to high concentrations of potentially toxic substances. Drugs and their metabolites are taken up selectively and concentrated by the renal tubular cells before excretion into the urine, so high intracellular concentrations are attained, particularly in the renal medulla, which has relatively little vasculature compared with the cortex. As a result, direct toxic damage occurs, generally affecting the renal tubular cells and renal papillae. Nephrotoxicity of this type tends to be dose-dependent. Many groups of drugs can cause renal damage, and these effects are accentuated in patients with pre-existing renal impairment [11].

HIV/AIDS pregnant women who are infected with malaria and are often treated with quinine during the first trimester of their pregnancy, they would likely also be taking this prescription together with the antiretroviral drug as such it is necessary to know each drug reacts as well as a combined effect of both drugs on the histology of the fetal kidney. Studies on the effect of quinine and antiretroviral drugs on the fetal kidney are limited, resulting to scanty information on the safety of these drugs. This study was therefore designed to evaluate the effects of quinine and triple antiretroviral regimen on fetal kidney of albino Wistar rats.

II. MATERIALS AND METHODS

A. Animal Care and Protocols

Forty female Wistar rats weighing 180 – 220 g were used in this study. They were obtained from the Animal House of the Faculty of Basic Medical Science University of Uyo, Uyo, Nigeria. The animals were acclimatized in the animal house of the Faculty of Basic Medical Sciences for two weeks during which they were fed with rat chow and clean water *ad libitum*. The animals were randomly grouped into 8 (eight) groups with 5 rats in each group. Group 1 served as the control group while Groups 2 – 8 were the experimental groups. All the animals were handled and cared for throughout the experiment in accordance and in compliance with applicable guidelines, standard for the care and use of laboratory animals as approved by the Faculty Animal Care and Use Committee (FACAUC) of the Faculty of Basic Medical Sciences, University of Uyo.

B. Drug Preparation and Administration

Injectable quinine hypochloride was obtained from Buchler GmbH Pharmaceuticals while the triple antiretroviral regimen (a combination therapy consisting of Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate) was gotten from a University of Uyo Teaching hospital, Uyo. Appropriate conversion practice was used to calculate the therapeutic and experimental dosages determined per kilogram (kg) body weight of the animals. The injections were given intraperitoneally.

C. Treatment and Experimental Design

At the commencement of the experiment, the animals were sorted into eight groups with 5 rats each whose estrous cycles were monitored. Sexually active males of the same strain were added in the ratio of (3 females to 1male and 2 females to 1 male) in each group to ensure fertilization. Virginal smear from each of the females was collected following overnight mating by putting few drops of saline in vagina, then recollected and checked for spermatozoa under microscope. The present of sperm in the virginal smear indicated day zero of pregnancy and administration started on day 7. After completion administration, the animals were sacrificed and fetuses were harvested. The fetal kidneys were harvested and rinsed in normal saline to remove excess blood before fixing in 10% buffered formalin and labelled. The kidneys were processed for histological analysis. The treatment protocol for each group is detailed in Table 1.

Table 1: Administration Protocol for Quinine and Triple Antiretroviral regimen to Rats in Control and Experimental Groups.

Groups	Treatment	Duration
Group 1 (Control)	Normal rat feed (No Treatment)	-
Group 2	10 mg/kg of quinine	8 hourly for 7 days
Group 3	20 mg/kg of quinine	8 hourly for 7 days
Group 4	30 mg/kg of quinine	8 hourly for 7 days
Group 5	17.1 mg/kg of triple antiretroviral regimen	Daily for 7 days
Group 6	17.1 mg/kg of triple antiretroviral regimen + 10 mg/kg of quinine.	quinine 8 hourly for 7 days and antiretroviral daily
Group 7	17.1 mg/kg of triple antiretroviral regimen + 20 mg/kg of quinine.	quinine 8 hourly for 7 days and antiretroviral daily
Group 8	17.1 mg/kg of triple antiretroviral regimen + 30 mg/kg of quinine.	quinine 8 hourly for 7 days and antiretroviral daily

D. Histological Tissue Processing

Organ sections were passed through the processes of fixation, dehydration, clearing, infiltration, embedding, sectioning and staining with

haematoxylin and eosin (H and E) and microscopy as stated by Umoh *et al*., [12].

III. RESULTS

The results of the effects of quinine and triple antiretroviral regimen on fetal body weight and placental weight presented in Table 2 reveals a reduction in fetal body weight and placental weights following administration of quinine dose dependently and antiretroviral combination drugs compared with control group.

Table 2:
The effects of Quinine and Triple Antiretroviral Regimen on Fetal Parameters

Groups	Fetal Body Weight (g)	Placental Weight (g)
Group 1	4.84 ± 0.33	0.73 ± 0.55
Group 2	3.63 ± 0.24[a]	0.60 ± 0.33[a]
Group 3	2.98 ± 0.58[a]	0.49 ± 0.25[a]
Group 4	2.86 ± 0.22[a]	0.42 ± 0.22[a]
Group 5	2.71 ± 0.33[a]	0.44 ± 0.58[a]
Group 6	2.37 ± 0.38[a]	0.36 ± 0.33[a]
Group 7	2.20 ± 0.33[a]	0.30 ± 0.25[a]
Group 8	2.01 ± 0.58[a]	0.27 ± 0.27[a]

Data are reported as Mean ± SEM, c = significant difference ($p < 0.05$) compared to control group.

Histopathological Analysis of Effects of Quinine and Antiretroviral Combination Drugs on the Fetal Kidney

The fetal kidney from the control group (Group 1) animal is histologically illustrated in Plates I. The sections of the normal fetal kidney of rats stained with haematoxylin and eosin revealed normal architecture of glomeruli renal corpuscles, renal tubules and no morbidity was recorded (Plate I). The section indicated a detailed cortical parenchyma and the renal corpuscles appeared as dense rounded structures. The renal corpuscle consisted of a tuft of blood capillaries surrounded by the Bowman's capsule. The latter had a parietal layer lined by squamous cells and a visceral layer lined by podocytes. The renal tubules included proximal convoluted tubules, distal convoluted tubules, loop of Henle and collecting tubules. No histological alterations of the kidney were observed in the untreated control groups.

Quinine treated groups (groups 2, 3 and 4) revealed mild to severe distortions. The histology of fetal kidney of the rats revealed the tubules showing acute necrosis in a manner that were dose dependent (Plates II, III and IV). Decrease in the Bowman's capsule space and areas of fibrosis (Pate II) of the animals in group 2 treated with 10mg/kg body weight of quinine was observed. Most of the tubules showed degeneration of their lining epithelial cells associated with marked reduction of the tubular lumina.

Histopathology examination of renal slices from rats in Group 5 treated with 17.1kg/mg body weight of antiretroviral combination drugs alone showed different alterations, including acute tubular necrosis, disorganized renal structural details, atrophic, shrunken glomeruli plus droplets in the tubules, vascular congestion, haemorrhage and degenerated glomeruli with acute tubular necrosis (Plate V). The renal tubules became vacuolated and lost their brush borders. Reduction in size of the glomerulus (hypoplasia) and apparent widen of Bowman's capsular spaces, some of which lacked glomeruli (Plate V) compare with the control. Bowman's capsule appears loose and partially degenerated and the glomeruli became swollen and degenerated.

The result of co-administration of quinine and triple antiretroviral regimen on fetal body weights and placental weight in group 6, 7 and 8 revealed that the glomeruli showed marked increase of cellularity and swollen glomeruli leading to reduced Bowman's capsule space (Plate VI, VII and VIII). The sections of the fetal kidney from rats exhibited marked dilation of proximal convoluted tubules with slogging of almost entire epithelium due to desquamation of tubular epithelium. Severe degenerated glomeruli with periarterioler haemorrhages, urinary space enlargement and acute tubular necrosis were observed in fetal kidney of group 8 treated with 30mg/kg+ 17.1kg/mg body weight of antiretroviral combination drugs (Plate VIII).

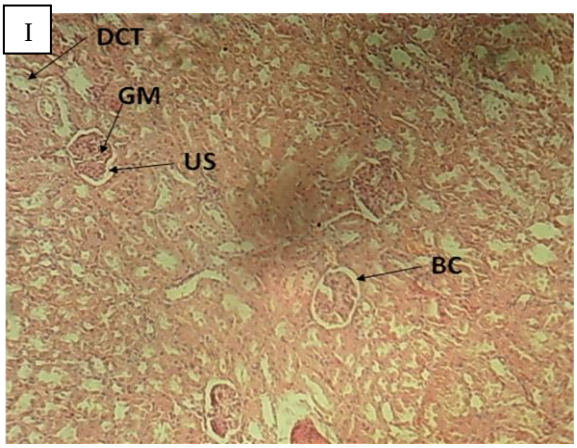

Plate I: Photomicrograph of Kidney of Control Group Rats Without Treatment Showing Normal Glomerulus (GM), Bowman Capsule (BC), Distal Convoluted Tubule (DCT) And Urinary Space (US). H&E. Mag. X 100.

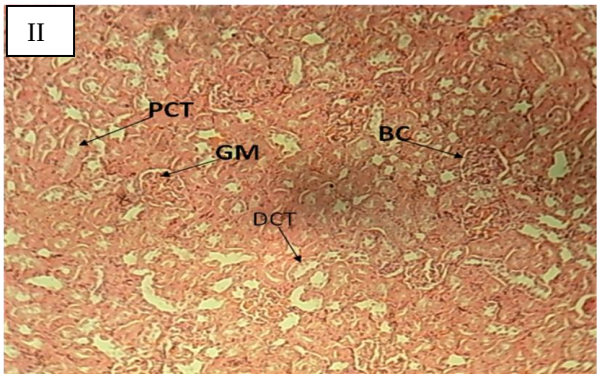

Plate II: Photomicrograph of Kidney of Group 2 Rats Treated with 10 Mg/Kg of Quinine Showing Proximal Convoluted Tubule (PCT) with Mild Vacuolation, Glomerulus (GM), Distal Convulated Tubule (DCT) and Decrease in the Bowman's Capsule Space and Areas of Fibrosis (BC). H&E. Mag. X 100.

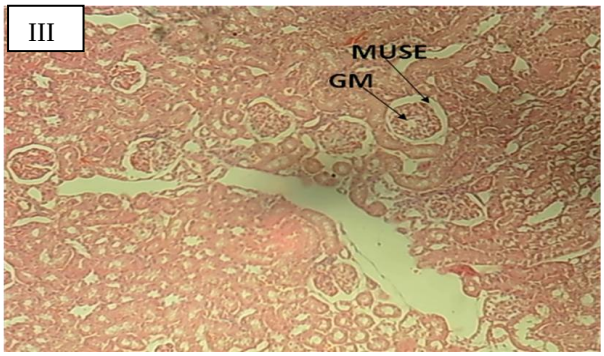

Plate III: Photomicrograph of Kidney of Group 3 Rats Treated with 20 Mg/Kg of Quinine Showing Mild Urinary Space Enlargement (MUSE) and Apparent Widen of Bowman's Capsular Spaces with Vacuolation. H&E. Mag. X 100.

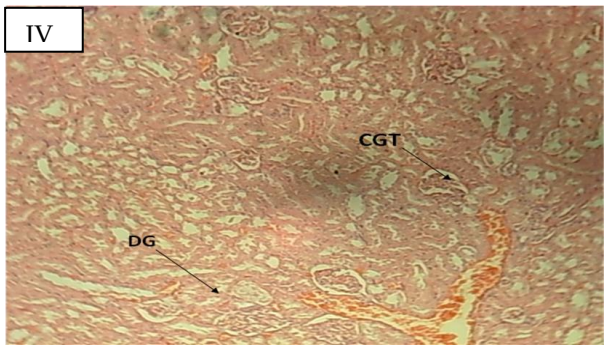

Plate IV: Photomicrograph of Kidney of Group 4 Rats Treated with 30 Mg/Kg of Quinine Showing Distorted Glomerulus (DG) and Collapsed Glomerulus Tuft (CGT) with Vascular Congestion. H&E. Mag. X 100.

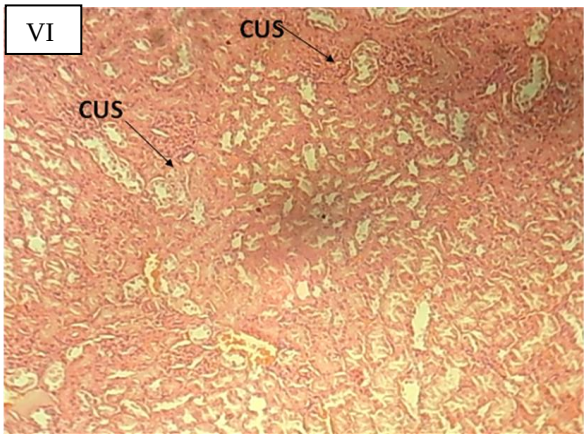

Plate VI: Photomicrograph of Kidney of Group 6 Rats Treated with 10 Mg/Kg of Quinine + 17.1kg/Mg of Antiretroviral Drug Showing Partial to Complete Closure of Urinary Space (CUS). The Glomeruli Showed Marked Increase of Cellularity and Swollen Glomeruli Leading to Reduced Bowman's Capsule Space. H&E. Mag. X 100.

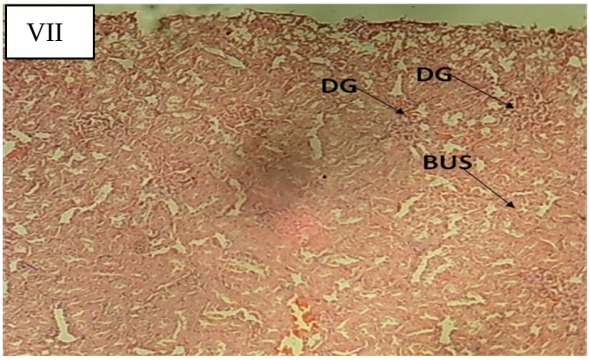

Plate VII: Photomicrograph of Kidney of Group 7 Rats Treated with 20 Mg/Kg of Quinine + 17.1kg/Mg of Antiretroviral Drug Showing Distorted Glomeruli (DG) and Breakage of Urinary Space (BUS). The Glomeruli Showed Marked Increase of Cellularity and Swollen Glomeruli Leading to Closure of the Bowman's Capsule Space H&E. Mag. X 100.

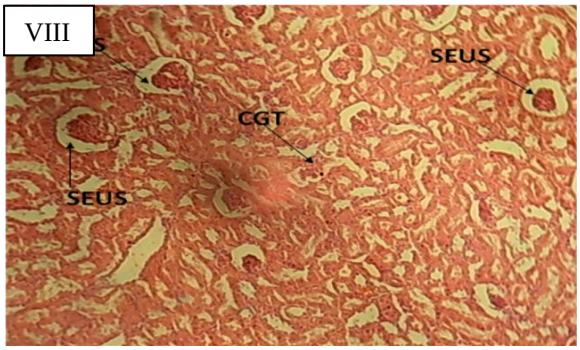

Plate VIII: Photomicrograph of Kidney of Group 8 Rats Treated with 30 Mg/Kg of Quinine + 17.1kg/Mg of Antiretroviral Drug Showing Severe Enlargement of Urinary Space (SEUS) And Collapsed of Glomerulus Tuft (CGT) Marked Dilation of Proximal Convoluted Tubules. H&E. Mag. X 100.

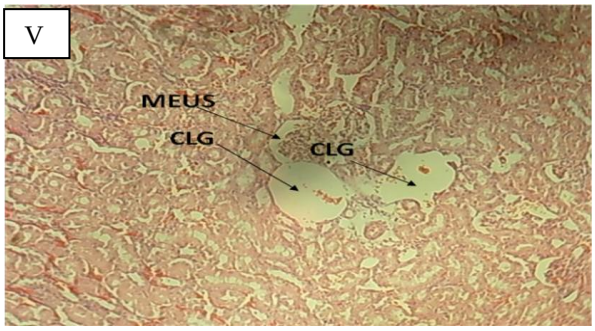

Plate V: Photomicrograph of Kidney of Group 5 Rats Treated with 17.1kg/Mg of Antiretroviral Drug Showing Complete Loss of Glomerulus with Vacuoles (CLG) And Mild Enlargement of Urinary Space (MEUS) Reduction In Size of The Glomerulus (Hypoplasia) And Apparent Widen of Bowman's Capsular Spaces, Some of Which Lacked Glomeruli and Vascular Congestion. H&E. Mag. X 100.

IV. DISCUSSION

The kidney is an essential organ of metabolism and elimination of toxic components, it serves as very important site of attack by various chemical agents including quinine and antiretroviral drug, in the form of its activated metabolite. Observations on the fetal and placental weights of albino Wistar rats have been reported following the administration of artesunate, artemether and arteether [13]. Similar observation was also made when artesunate was administered to pregnant Wistar rats in order to study its effect on the morphometry of fetal parameters [14]. Mesembe *et al.* [14] also reported that antiretroviral drugs had a deleterious effect on the fetal epiphysis thereby leading to growth retardation and developmental anomalies. In addition, Wei *et al.* [15] also reported decreasing values of fetal parameters compared to the control group when antiretroviral drug combination of Zidovudine, Lamivudine and Nelfinavir was administered during pregnancy.

The results also revealed that quinine and triple antiretroviral regimen simultaneous administration had a severe fetal weight losses and placental weight reduction in a dose dependent manner. In a cohort study in pregnant women an increased risk of low birth weight (<1500 g) in 2% of exposed infants and premature delivery in exposed fetuses was observed [10, 16]. Increased embryotoxicity and fetal malformation and embryo lethality in various studies in which near to lethal dose of Zidovudine and Lamivudine was used have been reported [17].

From our present investigation, we speculate that reduction in fetal and placental weights might have been due to a compromised nutritional status of the maternal rat consequent on gastrointestinal tract derangement. Hausman *et al*, [18] administered quinine and antiretroviral drugs to pregnant rabbits and observed that the placental prostaglandin and nitrous oxide levels increased compared to controls, while thromboxane levels were suppressed. Following administration of quinine to pregnant rats [19] revealed some adverse effects in maternal livers and kidneys including cytoplasmic derangement, mitochondrial cristolysis and abnormally shaped rough endoplasmic reticulum. Similarly, fetal parameters, livers and kidneys exhibited degenerative cytoplasmic vacuoles and ballooned mitochondria.

The kidney filters and removes toxic substances from the body. Certain drugs have been found to be nephrotoxic. Mild to severe alteration in the histology of the fetal kidney was observed in this study following the administration of quinine. The changes in the present study are in agreement with the prior observations, wherein it was reported that quinine treatment in rabbits caused nephrotoxicity, which was evidenced by significant loss of brush-border microvilli which is supposed to be responsible for reducing the area for active glucose reabsorption [20, 21]. Histopathological examination showed widespread tubular necrosis and dilatation in quinine treated rats which states quinine induced nephrotoxicity [21]. The obtained results showed that the applied drug treatments induced dense accumulation of inflammatory cells forming peri-glomerular cellular granulomatous lesions. Many of the renal tubules showed massive degeneration of their epithelial lining cells, as well as reduction of their tubular lumina. Similar findings have been achieved by [22] on lambs where artemether treatment during pregnancy induced a significant decrease in urine volume, free water clearance, arterial pH, and an increase in blood lactate.

Antiretroviral drugs treatment for pregnant women not only addresses their health and well-being but also dramatically reduces the risk of maternal to child transmission, particularly for women who are at an advanced stage of disease. Treatment decisions for pregnant women should be based on their need and eligibility for antiretroviral drugs. The benefits of antiretroviral drugs are compromised by numerous side-effects, adverse clinical events and toxicities [13].

In the present study, histological changes of rat kidney after antiretroviral drug treatment revealed acute tubular necrosis which confirms irreversible injury to kidney. Antiretroviral drug intoxication also showed a severe atrophy of glomerulus, which was apparent due to the reduction in its size. Marked dilation of proximal convoluted tubules with slogging of almost entire epithelium due to desquamation of tubular epithelium was evident. The changes obtained in the present study run parallel with the report documented by Shirwaikar *et al*., [23] where the investigators had demonstrated antiretroviral combination drugs induced acute renal necrosis with marked congestion of the glomeruli and glomerular atrophy. In the present study, we observed interstitial fibrosis of the kidney, a decrease in the Bowman's capsule space, which are side effects similar to those reported in humans undergoing antiretroviral

combination drugs treatment. However, none of the evident functional changes reported in patients under antiretroviral combination drugs treatment [24] were present.

Antiretroviral drug use can cause renal failure through a variety of mechanisms: direct renal tubular toxicity (ATN, Fanconi-like syndrome, distal tubular acidosis, etc.), obstructions (crystal deposition in the kidney), and glomerular lesions [25, 24]. It has been shown that hypokalemia constitutes a risk factor for the development of acute kidney injury [27]. It is also known that hypokalemia enhances the tubular damage resulting from ischemic injury [27]. Lamivudine, stavudine, abacavir and didanosine have been implicated in case reports of fanconi syndrome and nephrogenic diabetes insipidus [26, 28, 17].

The exact mechanism of nephrotoxicity associated with antiretroviral agents is not well understood but may involve alterations in renal tubular transporters, apoptosis, or mitochondrial toxicity [25]. The proximal renal tubule is most commonly affected presumably due to the high concentration of drug seen during glomerular filtration of these agents. Less common patterns of kidney injury include nephrogenic diabetes insipidus [25]. Several lines of evidence reported so far states that reactive oxygen species play a deleterious role in causing nephrotoxicity [20]. It has been recognized that the nephrotoxic effect of antiretroviral combination drugs has been witnessed by the spectrum of injury ranging from mild sub-lethal changes to a catastrophic necrotic death which lead to an inflammatory response [29].

The continuous use of antiretroviral therapy (ART) has been associated with a number of undesirable side effects that are associated with a range of metabolic complications and include dyslipidaemia, insulin resistance, overt diabetes mellitus and sudden death [25]. These side effects may be a result of the drug itself or of combination with the effects of HIV infection. In the quinine and antiretroviral combination drugs treated groups 6, 7 and 8 glomeruli showed marked increase of cellularity and swollen glomeruli leading to reduction of the Bowman's capsule space. Quinine and antiretroviral drug treatment induced the marked renal damage when compared with control, quinine and antiretroviral drug treated groups. The observed nephrotoxicity confirmed the similar adverse effects that have been reported by [30] who observed increased risk of nephrotoxicity in patient undergoing anti-malarial and antiretroviral drugs treatment and the work of [31] clarified that the same drugs induced nephrotoxicity by detectable sodium retention and a decrease of glomerular filtration rate.

The present adverse effects of quinine and antiretroviral combination drugs may be attributed to one or more of the drug metabolites. The fetotoxicity of the drugs may be attributed to the transplacental passage of the drugs or their metabolites retarding the proliferation of renal tissues as well as induced different pattern of cell death and immune responses as mentioned by perivascular round cell infiltration. Histopathological changes observed in kidney of fetus could be the result of the mechanism of action of the drugs which is structurally related to endogenous nucleoside thymidine, differing in the replacement of hydroxyl group at the 3'- position of the ribose ring with an unreactive azido (N3) group [31].

REFERENCES

[1] D. Kirby, B. Laris, A. Rolleri. "Sex and HIV Education Programs: Their Impact on Sexual Behaviours of Young People throughout the World". Journal of Adolescents Health. 2007; 40(3): 206 – 217.

[2] M. Gilbert, P. Thomas, A. Rambaut, G. Walsiuk, J. Thomas, E. Arthur. "The Emergence of HIV/AIDs in the Americas and Beyond. Proceedings of the National Academy of Sciences. 2007; 104(47): 18566 – 18570.

[3] W. Steketee, L. Nahlen, E. Parise, C. Menendez. The Burden of Malaria in Pregnancy in Malaria-Endemic Areas. American Journal of Tropical Medical Hygiene. 2001; 164: 28 – 35.

[4] World Health Organization. National Medicines List/Formulary/Standard Treatment Guidelines. Available at http://www.who.int /selection_medicines/country_lists/en/index.html. 2015.

[5] R. McGready, T. Cho, V. Samuel, A. Brockman, V. Van, S. Looareesuwan, N. White, F. Nosten. Randomized Comparison of Quinine-Cindamycin versus Artesunate in the Treatment of Falciparum Malaria in Pregnancy. 2001, p 465.

[6] J. Achan, J. Tibenderana, D. Kyabyinze, H. Mawejje, R. Mugizi, B. Mpeka, B., A. Talisuna, U. D'Alessandro. Case Management of Severe Malaria- a Forgotten Practice: Experiences from Health Facilities in Uganda. Plos One, 2011; 6(3): 170 – 253.

[7] N. White, P. Chanthavanich, S. Krishna, C. Bunch, K. Silamut, Antimalarial Pharmacokinetics and Pharmacology. British Journal of Clinical Pharmacology, 1996; 44(2): 55 – 60.

[8] S. Pukrittayakamee, S. Wanwimolruk, K. Stepniewska, A. Jantra, S. Huyakorn, S. Looareesuwn, N. White. Quinine Pharmacokinetic-Pharmacodynamic Relationship in Uncomplicated Malaria. Antimicrobial Agents and Chemotherapy. 2003; 47(11): 3458 – 3463.

[9] F. Boubred, M. Vendemmia, P. Garcia-Meric, C. Buffat, V. Millet, U. Simeoni. Effects of Maternally Administered Drugs on the Fetal and Neonatal Kidney. Drug safety, 2006; 29(5): 397 -419.

[10] E. Tuomala, E. Shapiro, M. Mofenson, Y. Bryson, M. Culnane, D. Hughes. Antiretroviral Therapy during Pregnancy and the Risk of an Adverse Outcome. National English Journal of Medicine. 2002; 346: 1863 – 1870.

[11] C. Ashley. Renal Failure - How Drugs can damage the Kidney. Pharmaceutical Journal. 2009; 7(1): 34 – 38.

[12] I. U. Umoh T. B. Ekanem, M. A. Eluwa, U. E. Bassey. Fetal Hepatorenal Toxicity of Artemether/Lumefantrine (Coartem®) in Second Trimester of Pregnancy in Albino Rats. European Journal of Pharmaceutical and Medical Research, 2017; 4(2): 240 – 246.

[13] K. Anastos, M. Schechter, E. Balestre, L. Myer, A. Boulle, D. Bangsberg, H. Toure, P. Braitstein, E. Sprinz. Antiretroviral Therapy in Resource-Limited Settings 1996 to 2006: Patient Characteristics, Treatment Regimens and Monitoring in Sub-Saharan Africa, Asia and Latin America. Trop. Medical International Health, 2008; 13: 870 – 879.

[14] O. Mesembe, A. Igiri, I. Naikot, V. Ekam, J. Odukana, V. Fischer. Liver and Kidney Morphologies Following Vitamin E Supplementation During Caffeinated and Non-Caffeinated Paracetamol Administration in Rats. Journal of Experimental & Clinical Anatomy, 2004; 3(1): 35 – 38.

[15] X. Wei, K. Ghosh, E. Taylo, A. Johnson, A. Emini. Viral Dynamic in Human Immunodeficiency Virus Type 1 Infection. Nature, 1999; 373: 117 – 122.

[16] M. Cotter. Is Antiretroviral Therapy during Pregnancy associated with an Increased Risk of Preterm Delivery, Low

Birth Weight, or Stillbirth? Journal of Infectious Diseases, 2006; 193(9): 1195 – 1201.
[17] M. Nelson, A. Azwa, A. Sokwala, R. Harania, J. Stebbing. Fanconi Syndrome and Lactic Acidosis Associated with Stavudine and Lamivudine Therapy. AIDS, 2008; 22: 1374 – 1376.
[18] N. Hausman, K. Beharry, K. Nishihara, Y. Akmal, T. Asrat. Effect of the Antenatal Administration of Celecoxib during the Second and Third Trimesters of Pregnancy on Prostaglandin, Cytokine, and Nitric Oxide Levels in Rabbits. American Journal of Obstetric Gynecology, 2003; 189(6): 1737 – 1743.
[19] S. Espiridiao, R. Oliveira-Filho, M. Simoes, J. Mamede, L. Kulay. Liver and Kidney Ultrastructural Changes caused by Acetylsalicylic Acid Treatment during Pregnancy in Rats. Clinical and Experimental Obstetric Gynecology, 2002; 29(1): 37 – 39.
[20] S. Devipriya, D. Shamala. Protective Effects of Quercetin in Cisplatin-Induced Cell Injury in the Rat Kidney, Indian Journal of Pharmacology, 1999; 3: 422 – 426.
[21] E. Meral, E. Levent, N. Yusuf, K. walker. The Effects of Nifedipine on Renal Perfusion Pressure and Kidney during Cisplatin-Induced Nephrotoxicity in Rats. Dicle. Tıp. Dergisi. Cilt, 2007; 34(4): 248 – 253.
[22] H. Kajino, C. Roman, R. Clyman. Renal Effects of Cyclooxygenase-2 Inhibition in Fetal Lambs. Biological Neonate, 2002; 82(4): 257 – 262.
[23] A. Shirwaikar, S. Malini, C. Kumari. Protective Effect of Pongamia pinnata Flowers against Cisplatin and Gentamicin Induced Nephrotoxicity in Rats. International Journal of Experimental Biology, 2003; 4: 58 – 62.
[24] E. Daugas, P. Rougier, G. Hill. HAART-Related Nephropathies in HIV-Infected Patients. Kidney International, 2005; 67: 393 – 403.
[25] H. Izzedine, V. Launay-Vacher, G. Deray. Antiretroviral Drug-Induced Nephrotoxicity. American Journal of Kidney Disease, 2005; 45: 804 – 817.
[26] M. Ahmad. Abacavir-Induced Reversible Fanconi Syndrome with Nephrogenic Diabetes Insipidus in a Patient with Acquired Immunodeficiency Syndrome. Journal of Postgraduate Medicine, 2006; 52: 296 – 297.
[27] A. Menahem, J. Perry, J. Dowling, M. Thomson. Hypokalaemia-Induced Acute Renal Failure. Nephrology Daily Transplant, 1999; 14: 2216 – 2218.
[28] G. D'Ythurbide, C. Goujard, F. Mechai, A. Blanc, B. Charpentier, R. Snanoudj. Fanconi Syndrome and Nephrogenic Diabetes Insipidus Associated with Didanosine Therapy in HIV Infection: A Case Report and Literature Review. Nephrology Daily Transplant, 2007; 22: 3656 – 3659.
[29] C. Dobyn, J. Levi, C. Jacobs, J. Kosek, W. Weiner. Mechanism of Cis-Platinum Nephrotoxicity: Morphologic Observations, Journal of Pharmacological Experimental Therapy, 1980; 213: 551 – 556.
[30] S. Alkhuja, R. Menkel, M. Alwarshetty, A. Ibrahimbacha. Celecoxib-Induced Nonoliguric Acute Renal Failure. Pharmaceutical therapy, 2002; 36(1): 52 – 54.
[31] D. Brater. Renal Effects of Cyclooxygyenase-2- Selective Inhibitors. Journal of Pain Symptom Manage, 2002; 23: 15 – 20.