

Effects of HAART on the Integrity of the Liver and Kidney in HIV Patients at Coast Province General Hospital, Kenya

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Abstract: The emergence of highly active antiretroviral therapy (HAART) has led to dramatic improvements in prolonging survival of HIV-infected patients on treatment in resource-limited settings. However, the main drawback of HAART is its potential long-term hepatotoxicity and renal derangements which may be life-threatening and have emerged as important complications that warrant ART switch and/or discontinuation. Information on the prevalence of the above complications in Kenyan affected population is scanty. The current study assessed the prevalence of hepatic and renal toxicity events in one hundred and fifty HIV+ patients [50 HAART naïve and 100 HAART treated subjects] based on clinical laboratory assays. Data were matched for HAART status, age, sex and the duration patients had been on ARV treatment and were analyzed using SAS version 9.2. The prevalence of hepatotoxicity based on elevated alanine aminotransferase analyte above upper limit of normal was 18% in HAART treated and 8% in HAART naïve patients. The prevalence of renal derangements based on elevated creatinine analyte above upper limit normal was 4% in HAART treated and 8% HAART naïve group. However, the prevalence of hepatotoxicity and renal derangements cases did not vary significantly between HAART experienced and HAART naïve subjects (χ^2 ; P=0.59 and P=0.9 respectively). Renal insufficiency was more common in HAART naïve patients Results from this study can help healthcare actors and providers to pay greater attention to individualized treatment of HIV and AIDS using HAART so as to reduce toxicities and co-morbidities that reduce the quality of life and increases the risk of death. They can also help in fine-tuning HAART regimens and prescription dosage in order to reduce toxicity levels.

Key words: *Hepatotoxicity, Renal derangements, HAART*

Introduction

Background information

About 36.9 million people were living with HIV and AIDS worldwide in 2017 up from 33.4 million in 2008 and more than 35 million have died since the first cases were reported in 1981 (WHO, 2019). Sub-Saharan Africa is the worst-affected region with an estimated 22.5 million people (67%) of the global total population living with HIV yet it accounts for 11-12% of the world's population (UNAIDS, 2010) with the pandemic killing an estimated 1.8 million people in 2009 of which 1.3 million of the cases were from sub-Saharan Africa. The epidemic is more prevalent in low and middle income-countries where millions of people are infected each year (UNGASS, 2010). About 2.3 million Kenyans live with HIV/AIDS while an estimated 1.5 million have already died of the virus and each year, approximately 200,000 Kenyans develop the AIDS syndrome (Milkowski, 2004). HIV and AIDS pandemic affects all regions, communities and the health of individuals, it impacts negatively on households and economic growth of nations.

Benefits of HAART

Introduction of antiretroviral therapy (ART) for use in management of HIV and AIDS, compounded with the routine use of CD4+ T-cell counts as surrogate markers of drug efficacy and disease progression significantly increased the life expectancy among HIV-infected patients. Between 1996 and 1999 the advent of highly active antiretroviral therapy (HAART) dramatically improved the survival of patients with HIV infection with unprecedented changes in disease progression and mortality seen first

in the US and European population (Palella, 1998; Pezzotti, 1999). The goal of HAART is to suppress viral replication and have impaired immunity restored but its major drawback is adverse effects accompanying its use. HAART toxicity has emerged as an important complication and eventually a major reason for ART switch and/or discontinuation (Braitstein *et al.*, 2006). Despite substantial benefits of HAART, a variety of short and long-term adverse effects have been associated with their use which reduces adherence and efficacy levels of the medication (d'Arminio *et al.*, 2000). The frequency of drug toxicities is often described in clinical trials but not so thoroughly monitored and evaluated in clinics. Sulkowski *et al.*, (2000) observed that, 18 out of 31 drugs causing hepatotoxicity in humans showed toxicity in animal models and one-third of all drugs associated with hepatotoxicity in animals result in a rise in liver enzymes in humans. Drug-induced toxicity is often detected long after a drug enters the market because animal models may not accurately predict human toxicity (Vella and Palmisano, 2000). Drug toxicities is done by measuring the levels of organ-specific surrogate markers in blood and/or urine samples then compared with established reference range values of a normalised population in when making interpretations.

Adverse effects of HAART

Antiretroviral therapy has significantly improved prognosis of HIV and AIDS infections by restoring immune veracity and limiting the impact of opportunistic infections, however, its adverse effects has become a challenge for its successful outcome. Adverse effects have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy as well as for medication non-adherence (O'Brien *et al.*, 2003). According to Ickovics (1997) surveys, up to 30% of patients skip ART doses and 10%–15% discontinue treatment due to adverse effects. The HAART side effects have become an important public health problem contributing to more than 50% of acute liver failure cases, a fraction of which require immediate transplantation because of irreversible damage caused (d'Arminio *et al.*, 2000). Jevtovic (2008) attested to this when he observed that cumulative long-term toxicities, for instance drug-induced hepatotoxicity, have emerged as a significant complication. As the population of HIV-infected patient ages and remains on HAART for longer periods of time, age, HIV- and HAART-related metabolic disorders are increasingly being encountered by clinicians looking after these patients (Kalyesubula and Perazella, 2011). Despite scaling up of HAART treatment in Kenya, documented reports on the effects of these drugs on kidney and liver functions are still scanty. This study seeks to elucidate the effects of HAART on the functional integrity of the liver and kidney in HIV positive patients at Coast Province General Hospital (CPGH), Kenya.

HIV patients are more prone to developing adverse effects due to use of a cocktail of antiretroviral drugs. Adverse effects have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy as well as for medication non-adherence (O'Brien *et al.*, 2003). Such cohorts of patients are at high risk of developing short and long-term complications from use of HAART such as hepatotoxicity, cardiovascular disorders and renal insufficiency among other disorders. Hepatotoxicity is associated with many of the antiretroviral agents which make their use a double-edged sword (Sander *et al.*, 2007). Renal disease and other syndromes encountered in HIV patients are diverse, progressive, and frequently insidious and their presence is subtle until it is far advanced when very little renal function has remained (Ogundahunsi *et al.*, 2008). There are few data on the impact of ART on the liver and renal disease in Kenya, a resource-limited setting. Data on the HAART toxicities are plentiful, but findings are inconsistent therefore more robust studies are needed (Kramer, 2007) which augurs well with the intent of this study. It is against this backdrop that this study evaluated the prevalence of abnormal liver and renal analytes in HIV positive patients on HAART and compare variation of these analytes with respect to age, gender and duration the HIV patients have been on HAART.

Objective of the study

The study compared the prevalence of hepatotoxicity and renal insufficiency as reflected by organ-specific biomarkers respectively amongst HAART naïve and HAART treated patients at CPGH.

Literature Review

HAART-related liver toxicity and its diagnostic markers

The liver plays a central role in transforming and clearing chemicals such as drugs and is susceptible to damage from toxicity of these agents. Due to its unique metabolism and close relationship with the gastrointestinal tract, the liver receives blood coming directly from gastrointestinal organs and then spleen via portal veins which bring drugs and xenobiotics in near-undiluted form (Larry *et al.*, 2004). Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the liver causing them to be withdrawn from the market due to hepatotoxicity (Sulkowski, 2004). The National Institutes of Health presented findings on liver toxicity in International AIDS Society (IAS) conference and its retrospective analysis showed that hepatotoxicity is associated with all classes of antiretroviral medications in use (Clifford *et al.*, 2003). Liver problems, diarrhea, nausea, and other stomach problems are possible side effects of any HIV medication (Pataki, 2006).

Several mechanisms are responsible for either inducing hepatic injury or worsening the damage process due to HAART. Many chemicals damage mitochondria causing it to release excessive amount of oxidants which, in turn, injure hepatic cells releasing intracellular enzymes into blood circulation (Martinez, 2004). Many HIV patients do often take alternative and complementary medicines in association with HAART and several of those have been associated with clear-cut hepatotoxicity (Mocroft, 2005). In patients with HIV, the term hepatotoxicity may then be misleading because some of these elevated liver tests may not be directly caused by the medication in question but acute viral hepatitis, reactivation of chronic hepatitis B or C, alcohol ingestion may all play a role in such events (Sulkowski *et al.*, 2000).

Although most liver diseases cause only mild symptoms initially, it is vital that early diagnosis and detection is done by performing full liver function tests (LFTs). However, diagnosis of drug hepatotoxicity may be complicated by the fact that patients often take several medications so teasing out the actual culprit can present challenges. Patients with HAART-induced hepatotoxicity may be asymptomatic, with liver injury diagnosed during routine blood testing, while others develop symptoms including nausea, fatigue, itching and jaundice (O'Brien *et al.*, 2003) with the latter symptom being significant. There is a broad variability among studies in the criteria to categorize the severity of hepatotoxicity.

According to Kenya national clinical manual for ART providers (KNCMAP), patients with transaminases within normal limits at baseline are considered to develop hepatotoxicity when ALT and/or AST rise above the upper limits of normal (MoH, 2007). It defines severe hepatic injury (the primary study outcome) as defined as grade 3 or 4 change in AST and/or ALT levels during antiretroviral treatment and if AST and ALT grades are discordant, the highest should be used for classification purposes.

Liver function tests (LFTs) are carried out to detect the presence of liver disease, distinguish among different types of liver disorders, gauge the extent of known liver damage and response to treatment (Prognosis). LFTs are a group of clinical biochemistry laboratory blood assays designed to give information about the state of a patient's liver (Abrescia *et al.*, 2005). Some liver analytes/parameters in LFTs are associated with liver functionality e.g. Albumin (ALB) and total proteins (PROT), others are concerned with hepatocellular integrity e.g. aminotransferases (ALT & AST) and some associated with cholestasis - biliary tract blockage- e.g. gamma-glutamyl transferase (γ -GT) and alkaline phosphatase (ALP) (MoH, 2007). In most cases, hepatotoxicity due to drug toxicities is not mutually exclusive and mixed types of injuries are often encountered categorized in table 1.

Table 1: Grading hepatotoxicity

Type of injury	ALT	ALP	ALT/ALP RATIO
Hepatocellular	$\geq 2ULN$	$>2ULN$	High, ≥ 5
Cholestatic	Normal	$\geq 2ULN$	Low, ≤ 2
Mixed	$\geq 2ULN$	$\geq 2ULN$	2-5

Source: MoH, 2007.

ULN- Upper limit of normal

The two liver biomarkers (ALT and ALP) are useful in the monitoring, evaluation and management of patients with hepatic dysfunction due to drug toxicity. Categories of patients at higher risk for drug-induced hepatotoxicity include: Females, Obese individuals, Elderly patients, viral illnesses and pre-existing liver disease (Wit *et al.*, 2002).

Risk factors in HAART-related toxicities

The therapeutic goal of HAART is to suppress viral replication and restore the patients' immunologic function however; it has a drawback of associated organ-specific toxicities which can be aggravated by one or multiple risk factors. Physicians should maintain a high level of suspicion especially where there are known or established recent risk factors (NASCO, 2002). An overarching goal in antiretroviral therapy should be to select a regimen that is not only effective but is also safe and this requires physician to take into account individual patient's underlying medical conditions or history (Vella and Palmisano, 2000). Risk factors for pharmacological toxicity are numerous and depend mainly on underlying patient characteristics as well as the drug regimen under consideration. The patients' age, gender, body weight and size, nutrition and overall health status can play a role in how one experience drug's side effects (Pataki, 2006). Many other exotic factors such as occupation, altitude, race and distance from the ocean have been known to affect results (Waithaka *et al.*, 2009). High risk for development of chronic kidney disease with HIV infection are black race, CD4 count < 200 cells/mm³, family history of CKD and presence of diabetes mellitus, hypertension or hepatitis C co-infection (Naicker and Fabian, 2010). All these considerations underscore the significance of

taking blood or urine samples in a standardized and controlled fashion for performing and interpreting laboratory tests with advance knowledge in a wide array of confounding risk factors.

Materials and Methods

Study site and population

The study was carried out at the Coast Province General Hospital (CPGH) in the Comprehensive Care Centre (CCC) in liaison with the hospital clinical biochemistry laboratory. The hospital is located within Mombasa county of Coast Province of Kenya (Figure 1). The government of Kenya in partnership with RPM Plus and partners rolled out its extensive ART program and HIV care services to the populace within the region in the year 2003 with technical assistance and funding provided by United States Agency for International Development (USAID).

The hospital set up a comprehensive care center (CCC) to provide HIV care and treatment services through a comprehensive care-based counselling and testing service for HIV diagnosis; a clinical ability to diagnose, treat and manage opportunistic infections; counselling for treatment adherence and nutrition; and delivery of ART. PLHWA could also access a variety of additional services provided offsite via community health workers that ensured greater coordination in their HIV care and to save them time travelling to source to the hospital. These included treatment for tuberculosis, home-based care, inpatient care, services for prevention of mother-to-child HIV transmission (PMTCT) and management of sexually transmitted infections (STI) other than HIV. The site of study is marked out in the African map showing Kenya and where Mombasa is precisely located.

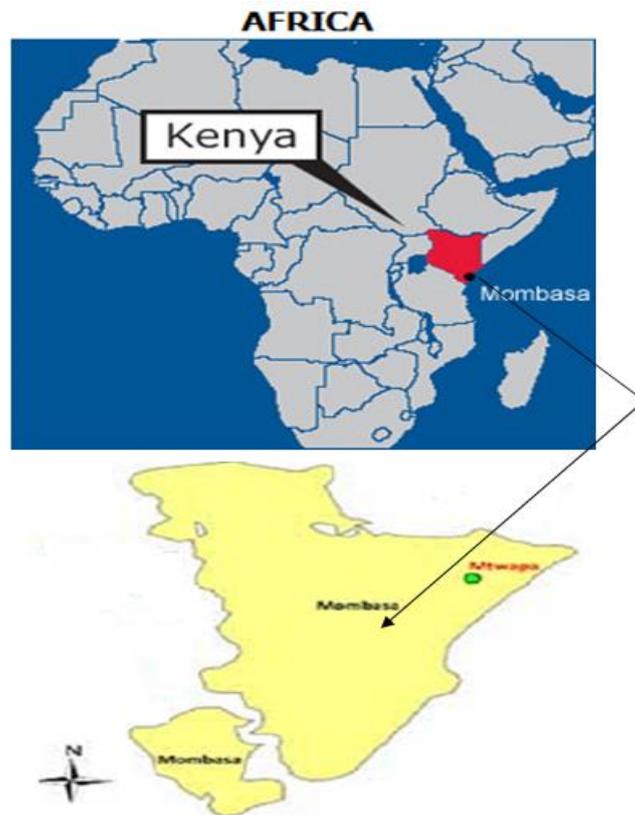


Figure 1: A Map of Africa showing location of Mombasa area in Kenya

The hospital draws people coming for various health care services from the entire province which covers an area of approximately 83,603 km² with a population of 3,325,307 inhabitants as per the 2009 census (KNBS, 2010). The province had one of the highest adult sero-prevalence of HIV in the country, estimated at 7.9% in 2007 (KAIS, 2008). Based on a baseline survey done before the start of the study in March 2011, a total of 12,735 HIV positive adults (>18 years) were registered for active HIV care at CCC, CPGH. Out of these, 8144 (64%) were females and 4591 (36%) were males. 7396 (58%) had not been started on antiretroviral therapy (HAART naïve cohort) while 5339 (42%) had already been started on HAART (HAART treated cohort).

Design of the study

HAART naïve and HAART treated patients attending HIV care clinics were recruited into the study and placed in two groups; ARM 1 and ARM 2 respectively.

Study sample

Surveys of people receiving HAART have shown that adverse effects account for 10% or more of those discontinuing treatment (Ickovics, 1997). The minimum sample size was determined using Fischers *et al.*, 1998 formula;

$$n = \frac{Z^2 P(1-P)}{\delta^2}$$

Where; n - minimum sample size, P – estimated prevalence, Z- Standard normal deviate that corresponds to 95% confidence interval (1.96) δ is the level of significance (5%). Assuming a prevalence rate of 10% as reported by Ickovics (1997), the minimum sample size was;

$$n = \frac{(1.96)^2 \times 0.1(1-0.1)}{(0.05)^2} = 138$$

Sample size; n = 138.

Assuming a 10% drop out rate (13.8) in the study, the sample size was adjusted and rounded to 150 participants. Since the major objective was to determine prevalence of HAART toxicities on the liver and kidney, one hundred HAART experienced patients who had been on ARVs for not less than one year against fifty HAART naïve were recruited into the study.

Ethical considerations

Ethical approval for the study was obtained from KEMRI/National Ethics Review Committee. In addition, a research permit plus letter of authority to carry out research in Kenya was granted for the study by National Council for Science and Technology (NCST).

Inclusion and exclusion criteria

The participants recruited into the study included were HIV positive males and females aged 18-60 years with CD4 cell counts not less than 200 cells/ μ L and willing to consent and attend periodic clinics for the study at Comprehensive Care Centre at CPGH. Excluded in the study were HIV patients with either confirmed diabetes, pregnant, hypertensive (blood pressure >145/90 mm/Hg), illicit drugs users or those with systemic opportunistic infections like TB or hepatitis medications.

HIV positive participants who met the set inclusion criteria signed an informed consent form witnessed by an either a nurse or clinician-in-charge or a community health worker or any other person or relative accompanying the patient. In the course of the study, HIV patients who got systemic infections or were started on antiretroviral medications were discontinued from the study and recorded appropriately.

Data collection

A structured questionnaire was administered to participants with questions for obtaining their age, sex, pregnancy status, drugs abuse and patient's duration on HAART among other medical conditions. The medical records kept at the clinic were used to verify the status and history of various medical conditions namely TB, diabetes, hypertension, hepatitis and pregnancy in addition to corroborating the information provided by the subjects. A laboratory request form accompanying urine and blood samples collected from participants was used to record results from urinalysis, liver and renal function tests done.

Collection of samples

Five milliliters of whole venous blood were collected monthly from the recruited subjects and placed into vacutainer tubes containing ethylene-diamine-tetraacetic (ETDA) from the months of March to August 2011. Blood samples were centrifuged at 3000rpm for two minutes to obtain serum used to assay liver and renal function. Urine samples collected from the study participants were used to determine the presence of glucose and protein by urine strip test.

Laboratory analytical methods

Eight liver function tests and five kidney function tests were determined on the sera specimens based on standard operating procedures (SOPs) written and maintained in the clinical chemistry laboratory at CPGH using Cobas c 111 and Roche 9180 electrode automatic analyzers (Germany).

Measurement of liver analytes

The blood sera collected from participants were used to determine the values of liver analytes; Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma Glutamyl-transferase (GGT), Total proteins (PROT), Albumin (ALB) Alkaline phosphatase (ALP), Bilirubin total (BIL-T) and Bilirubin direct (BIL-D) based on their respective test principles.

Measurement of kidney analytes

The blood sera collected from the participants were used to measure the values of kidney analytes; Creatinine (CREAT), Blood urea nitrogen (BUN), Sodium, Potassium and Chloride electrolytes based on their respective test principles.

Data management and statistical analysis

Data for liver and kidney parameters were recorded and analyzed to determine the prevalence of hepatotoxicity and renal insufficiency based on key liver and kidney surrogate markers respectively. Hepatotoxicity was classified as Hepatocellular (ALT>40U/L) and/or Cholestasis (ALP>160 U/L) whereas renal derangements were classified as renal insufficiency based on CREAT>120 U/L (MoH, 2007). The levels of liver and kidney analytes obtained were compared with published reference ranges obtained from a normalized population in Kenya (Waithaka *et al.*, 2009).

Data for liver and kidney function were profiled based on HAART status (naïve or treated) and imported into SAS 9.2 software. Variability in data was tested based on mean and standard deviation (SD) with the alpha level of significance set at 0.05. The prevalence of hepatotoxicity and renal insufficiency kidney toxicities was tested for significance difference between HAART treated and HAART naïve subjects using non-parametric chi-square (χ^2). RESULTS

Characteristics of the study participants

A total of 5339 (42%) HIV sero-positive patients aged 18 years and above had already been started on HAART at the Comprehensive Care Center (CCC) of CPGH at the onset of this study in March, 2011. Out of these, 1943 (36.4%) were males and 3396 (63.2%) females. A total of 150 (100 HAART treated and 50 HAART naïve) HIV positive persons were recruited into the study and had their blood and urine samples measured over a five-month period to determine the levels liver and kidney analytes that reflect on their functional integrity. Many of the patients were excluded from the study during the recruitment for either pregnancy, age>60years, CD4<200 cells/mm³, TB active, hypertensive, or diabetic. In overall, 134 (89.3%) subjects were followed in the study to the end while the rest dropped out. Table 2 shows the demographic characteristics of study participants.

Table 2: Demographic characteristics of the study participants

Characteristic	HAART naïve (N = 50)	HAART treated (N = 100)	P-value
Sex			
Male	11 (29.7) (22)	26 (70.3) (26)	0.06
Female	39 (34.5) (78)	74 (65.5) (74)	
Age (years)	38.06±8.7	40.2±8.65	0.16
CD4 count (cells/mm³)	347.0±102.8	397.9±127.5	0.02*
ARV duration (years)	0	4.77±1.6	
Status on termination			
Drop/Fall outs, n (%)	6 (12)	10 (10)	0.87
Followed, n (%)	44 (88)	90 (90)	

N, n = number of subjects (percentage in parenthesis). Results for age and CD4 are expressed as Mean ± standard deviation (SD) and were compared for variation between HAART treated and HAART naïve by t-Test.

In this study, 134 (89.3%) out of all recruited subjects were followed to the end of the study while the rest dropped out, 90 of them were on HAART while 44 were HAART naïve. Ten (10%) HAART treated and 6 (12%) HAART naïve participants dropped out from the study. Four patients from HAART naïve group were discontinued from the study after they were started on

ARVs. Age distribution differences between the HAART treated and HAART naïve groups did not vary significantly ($P = 0.16$). However, the mean CD4 count in the HAART treated group was significantly higher than in the HAART naïve group ($P = 0.02$).

Liver and kidney function test analytes for the study groups

Eight liver and five kidney analytes measured during the five-month study period were profiled and their mean values and standard deviations (SD) determined. These analyte values from participants were compared with reference ranges adopted from Waithaka *et al.* (2009) and those that fell outside the reference range were considered abnormal.

The percentage number of subjects with abnormal liver analytes in the HAART treated and HAART naïve groups based on mean values from liver function tests are presented in table 3 below.

Table 3: Percentage cases with abnormal liver analytes

Analyte (RR, Units)	HAART treated (N=100)	HAART naïve (N=50)
ALT (0-39U/L)	18 % elevated	8% elevated
AST (6-40U/L)	16% elevated	10% elevated
PROT (57-89g/L)	8% lowered	6% lowered
ALB (29-52g/L)	3% lowered	6% lowered
γ -GT (7-66U/L)	24% elevated	12% elevated
ALP (10 – 201U/L)	12% elevated	6% elevated

RR- Reference range adopted from Waithaka et al.(2009)

Based on percentage number of subjects with abnormal ALT analyte levels in table 3, 18 (18%) of the HAART treated patients and 4 (8%) HAART naïve patients had elevated ALT a key surrogate marker for diagnosing cellular hepatotoxicity whereas, 12 (12%) HAART treated patients and 3 (6%) HAART naïve patients had elevated ALP, a key surrogate marker for diagnosing cholestasis. The percentage number of subjects with abnormal AST, PROT and GGT were higher in the HAART treated subjects than the HAART naïve subjects with the exception of abnormal ALB which was more in the HAART naïve than in the HAART treated group. The percentage of subjects with abnormal kidney analytes in the HAART treated and HAART naïve groups based on mean values from kidney function tests are presented in table 4 below.

Table 4: Percentage cases with abnormal kidney analytes

Analyte (RR, Units)	% HAART treated (N=100)	% HAART naïve (N=50)
CREAT (59-127 μ mol/L)	4% elevated	8% elevated
BUN (1.5-5.9 mmol/L)	2% elevated	6% elevated
SOD (134-153 mmol/l)	2% lowered	6% lowered
POT (3-5.3 mmol/l)	8% elevated	4% elevated
CL (101-110 mmol/l)	3% lowered	6% lowered
Protein in urine	6% positive	8% positive
Glucose in urine	0% positive	0% positive

RR: Reference range. RR values were adopted from Waithaka et al., (2009)

From table 4 above there were 4 (4%) HAART treated patients and 4 (8%) HAART naïve patients with abnormal CREAT analyte values. Over all 5.3% had elevated CREAT, a key marker for diagnosing renal derangements. There were 3 (6%) of HAART treated subjects and 8 (8%) of the HAART naïve subjects with proteinuria (overall 9.3%). There were higher percentages of abnormalities in all kidney analytes except POT in HAART naïve than HAART treated subjects.

The prevalence of abnormal liver analytes (ALT and ALP) and renal analytes (CREAT and BUN) which are key surrogate markers for diagnosing drug-induced toxicities affecting the liver and kidney respectively were compared for any variation between HAART naïve and HAART treated groups using chi-square test and results are presented in table 5.

Table 5: Prevalence of abnormal liver and renal analytes in subjects

Type of organ injury (Key analytes)	HAART treated (%)	HAART naïve (%)	Sig*
Liver Toxicity	Hepatocellular (ALT>40 U/L)	18	0.59
	Cholestasis (ALP>160U/L)	12	
Renal insufficiency	CREAT>120 µmol/L	4	0.90
	BUN>5.9 mmol/L	4	

The prevalence of abnormal liver analytes; ALT and ALP did not differ significantly between HAART treated and HAART naïve subjects (χ^2 ; p=0.59). The prevalence of abnormal kidney analytes; CREAT and BUN did not differ significantly between HAART treated and HAART naïve subjects (χ^2 ; p=0.90).

Trend of abnormal liver and kidney analytes in participants

All the data from liver and kidney function test analytes were profiled monthly for the five-month period. The mean \pm SD values for all analytes were calculated and compared with the reference range established in a normalized Kenyan population (Waithaka *et al.*, 2009). The trend in a number of participants with abnormal liver and kidney function test analytes were presented graphically in figures 2 (a) and 2 (b). The trend in the number of HAART treated subjects with abnormal liver analyte values for the five-month study period is shown in figure 2 (a) below.

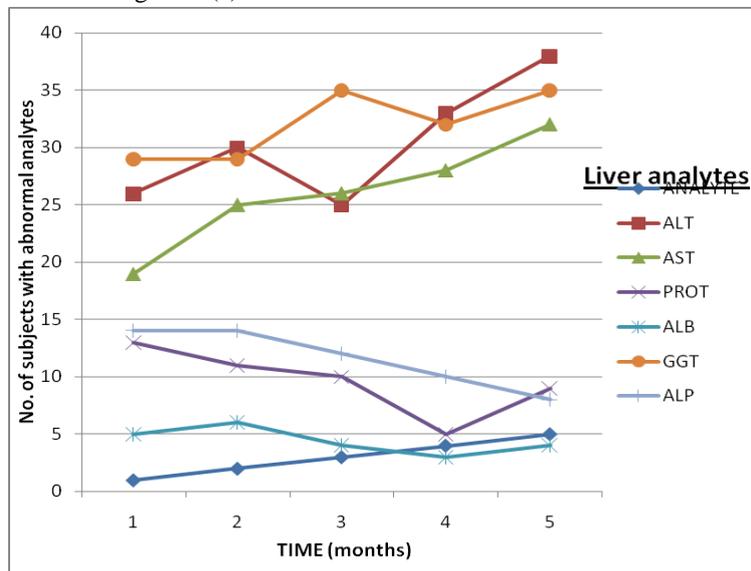


Figure 2a: Variation in liver analytes in HAART treated subjects with time

The number of subjects with abnormal liver function test analyte values showed an overall increasing trend in three liver analytes namely, AST, ALT, and GGT. However, there was an exception in the other three liver analytes, ALP, PROT and ALB where the abnormal cases showed a declining trend in the five-month period (Figure 2a).

The trend in number of HAART treated subjects with abnormal kidney function test analyte values is shown in figure 2 (b) below.

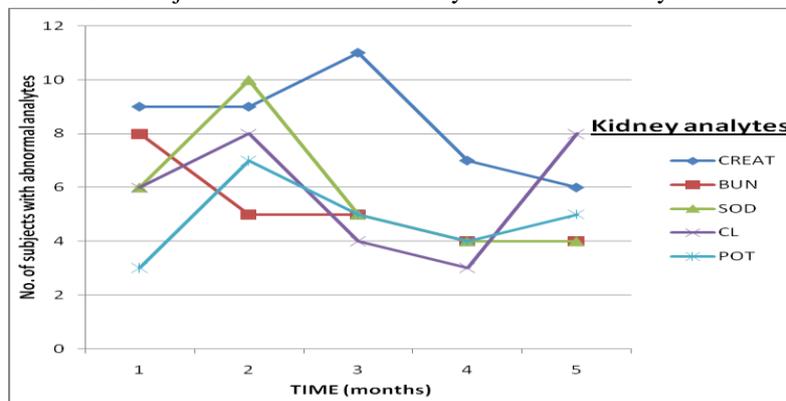


Figure 2b: Variation in kidney analytes of HAART treated subjects

There was a general decline in the number of subjects with abnormal creatinine (CREAT), urea (BUN), sodium (SOD) and potassium (POT), analyte values. There was an exceptional general increase to the above in the number of participants with abnormal chloride (CL) analyte values during the five-month period (Figure 2 b).

Conclusion and Recommendations

The mean ages of the HAART treated and HAART naïve groups were not significantly different ($P=0.164$). Similarly, sex distribution of the HAART naïve and HAART treated subjects in the study did not vary significantly (0.06). However, the HAART treated group had a significantly higher CD4 mean compared to HAART naïve group ($P=0.02$) and this was attributed to positive effects of ARV treatment which suppressed HIV replication in the body allowing CD4 cells to increase dramatically (Smith, *et al.*, 2004)

The data from the study pointed to hepatotoxicity and renal insufficiency in HAART treated subjects. However, prevalence of hepatotoxicity did not differ significantly between the HAART treated and HAART naïve subjects ($p=0.59$) implying that hepatotoxicity in HIV positive patients is not only caused by antiretroviral medications but may be attributed to other co-morbid factors like acute and chronic viral hepatitis, opportunistic infections, and non-steatotic antiretroviral toxicity (Larry *et al.*, 2004). HAART is associated with these adverse effects that may increase morbidity and mortality among HIV-infected patients (Núñez *et al.*, 2005). Drug induced hepatotoxicity characterized by elevation of AST/ALT levels to at least twice the upper limit of normal (ULN) is attributed to use of HAART (Sulkowski *et al.*, 2000). The 18% prevalence in hepatotoxicity among the HAART treated patients in this study could be attributed to exposure to HAART as reported by Evans *et al.*, 2000. This could explain why the 8% hepatotoxicity noted among the HAART naïve patients is low in this study.

HIV infection could be singled out in this study as the main cause of elevated liver analytes observed in HAART naïve subjects given that hepatitis B or C, systemic opportunistic infections e.g. TB, diabetes, hypertension, or pregnancy were controlled. Jevtovic (2008) observed that, HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure. The mechanisms of accelerated liver disease in HIV-infected patients have not been fully elucidated but Pozniak and others (2006) attributed HIV-related immunodeficiency and direct interaction of HIV with hepatic stellate and Kupffer cells as the main cause of hepatotoxicity in HAART naïve patients.

In this study, elevated CREAT/BUN analyte and positive presence of proteins in urine were translated to be indicative of renal insufficiency. This study found a prevalence of 8% in renal insufficiency in HAART naïve and 4% in HAART treated group based on CREAT analyte. Thompson (2011) reported a prevalence of 6% in kidney derangements as a cause of complications amongst HIV patients. This study noted a higher prevalence of kidney derangements in HAART naïve group than the HAART experienced group which can be attributed to HIV inflammation causing injury directly to the kidney tubules. Presence of protein in urine was found in the 6.7% patients in this study compared to a study by Quinn and others (2010) in which 16.6% patients had evidence of proteinuria with no other identifiable cause. HIV replication taking place in the kidneys tubules is the main cause of renal inflammation and loss of its function in HAART naïve patients (Rao, 2001). Kidney derangements prevalent in HAART naïve patients could be ameliorated upon initiation of ARV in the affected patients that suppresses viral load. The prevalence of renal derangements was not significantly different in the HAART naïve and HAART treated groups ($P < 0.90$).

The prevalence of renal derangements noted in the HAART naïve group in this study indicated that antiretroviral agents may not be the exclusive cause for kidney injuries in HIV positive persons. Elevated CREAT and proteinuria may have been due to HIV since the kidney is one of the replication sites for the virus. This reasoning concurs with Rao (2001) who documented that the kidney acts as one of the reservoirs for HIV replication and HIV causes injury to the kidney resulting in loss of function and elevated creatinine. Causes of renal disease in HIV-infected patients are multi-factorial and may include HIV infection itself, co-infections, co-morbidities, and HAART medications (Roling *et al.*, 2006). Antiretroviral agents are relatively free of renal toxicity although drug-related renal injury can occur (Daugas *et al.*, 2005). Nephrologists should be familiar with the potential toxicity of ARV agents that cause kidney damage to avoid delays in diagnosis.

It has been documented that HIV acute nephropathy (HIVAN) is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease (Wyatt *et al.*, 2009). The HAART administration seems to have had a positive impact in resolving kidney derangements among the HAART treated group in this study which supports findings advocating for ART to be started in HIV patients with HIVAN. Antiretroviral therapy in patients with HIVAN has been associated with both preserved renal function and prolonged survival (Ogundahunsi *et al.*, 2008). Steel-Duncan and others (2005) found in a prospective study that renal syndromes in Pre-ART patients resolve after eight months of HAART initiation.

Thompson (2011) further observed that with increasing availability and use of ARV, the risk of end-stage-renal-disease (ESRD) decreases by more than 50% in some populations which prolongs the survival of HIV-infected persons with ESRD. Renal toxicity is more likely to occur in HIV patients with pre-existing kidney disease or poorly controlled HIV infection with elevated baseline creatinine concentration, female gender, CD4 nadir <200cells/mm³, and concomitant administration of other nephrotoxic drugs (Crum-Cianflone *et al.*, 2010; Nelson *et al.*, 2008).

From this study it was observed that hepatotoxicity based on its key surrogate biomarkers was prevalent in HIV positive patients regardless of being on antiretroviral medications, an indication that the complication is derived not only from toxicity effects of antiretroviral agents but also from HIV-associated inflammation. Renal insufficiency based on its key surrogate biomarkers was more prevalent in HAART naïve than HAART treated patients which are attributed to the direct inflammation effects of HIV on the kidney tubules causing its malfunctioning.

Renal derangements are more prevalent in HAART naïve patients and resolved after the patients were put on HAART. This notwithstanding, HIV patients with such risk factors should not be denied appropriate HAART regimens but regular follow-ups, clinical reviews and monitoring be adopted to prevent emergence of liver and renal derangements. As efforts continue in the development of antiretroviral medications with less adverse effect profiles, treating physicians must remain aware of new and developing syndromes associated with their use. Since, liver and kidney derangements caused by HAART and/or HIV inflammation were prevalent with all available antiretroviral agents in an HIV aging population, mitigating them through clinically tested remedial actions like change of medication or discontinuation of the offending drug remained critical. It became apparent from the study that, uncontrolled risk factors such as nutrition, smoking, undisclosed chronic diseases and alcohol intake may precipitate or aggravate adverse effects in HIV positive patients in addition to giving a positive diagnosis which can be falsely attributed to antiretroviral agents. Finally, the use of adequate clinical laboratory tests to monitor early outcomes of HAART toxicities that can cause life threatening liver and kidney-specific disorders remains an essential prognostic tool useful in antiretroviral treatment.

Recommendations

Although occurrence of hepatic and renal derangements due to use of HAART and /or HIV inflammation are common, HIV patients whose conditions are clinically and virologically stable should continue using their antiretroviral medications unless severe or more complex complications emerge. When they occur, then the regimen after evaluation by the clinician should be changed, temporarily withdrawn or stopped completely.

Surveillance of liver and renal derangements in HIV/HAART patients with presence of co-morbid factors like advanced age, female-gender and prolonged HAART duration >4years should be stepped up through liver and kidney function tests. This should be done by adopting a periodic 3-month monitoring approach rather than the generalized six-month monitoring interval or the symptom-directed tests currently adopted by the Ministry of health, Kenya. This will end up reducing the excess resources used in the management of HAART side effects.

Finally, following the ubiquitous and essential use of a combination of different classes of antiretroviral medication in the management of HIV-infected patients, the study recommends a controlled research study to be carried out to evaluate the potential toxicity effects of class-specific antiretroviral drugs on liver and kidney whose outcome can probe redefining or fine tuning the HAART medication package.

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