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ANTI-RETROVIRAL THERAPY RELATED LIVER INJURY (ARLI): A SERIES OF 11 CASES
A. E. O. Otedo, MBChB, MMed (Int.Med), Cert. Gastroenterology, Consultant Physician/ Gastroenterologist/DDMS, Kisumu District Hospital, P.O. Box, 4685-40103, Kisumu, C. F. Otieno, MBChB, MMed (Int. Med), Associate Professor, Consultant Physiscian, G. O. Oyoo, MD, MMed (Int.Med), FACR, Senior Lecturer, Consultant Physician and Rheumatologist and E. O. Omonge, MBChB, MMed (Int.Med), Consultant Physician, Lecturer, Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, P.O. Box, 19676-00202, Nairobi

Request for reprints to: Dr. A. E. O. Otedo,Consultant Physician/ Gastroenterologist/DDMS, Kisumu District Hospital, P.O. Box, 4685-40103, Kisumu, Kenya, email: otedoamos@yahoo.com

ANTI-RETROVIRAL THERAPY RELATED LIVER INJURY (ARLI): A SERIES OF 11 CASES

A. E. O. OTEDO, C. F. OTIENO, G.O. OYOO and E. O. OMONGE

ABSTRACT

Background: **HIV Anti-retroviral therapy (ART) related liver injury (ARLI) is associated with elevated liver transaminases (AST/ALT), potential liver failure and death. It is commonly associated with nevirapine. Identification of pre- clinical risk factors is important in its management to prevent unnecessary morbidity, ART drug discontinuation and mortality. Hepatitis B and C viruses (HBV, HCV), nevirapine and protease inhibitors, low body mass index, low platelet count and deranged renal functions prior ART initiation are associated with development of hepatotoxicity.**
Objective**: To describe anti-retroviral-related liver injury (ARLI) in HIV positive patients, their CD4+ cell counts, biochemical and viral markers and liver ultrasound.**
Design**: Prospective, descriptive, consecutive entry study.**
Setting**: Kisumu District Hospital liver clinic/medical outpatient clinic, Nairobi Rheumatology Clinic and Mater Hospital.**
Main outcome measures**: Biochemical, ultrasound and virological characteristics**
Subjects**: Eleven patients with HIV infection and ARLI .**
Results**: Eleven patients with M:F ratio of 2 : 9 were included with a mean age and CD4+ cell count of 36.5 years (27-45) and 69.3 cells/μl (11-199) respectively. The low CD4+ cell count indicates severe immunosuppression. Mean ART duration use was 11.1 weeks (3-19 weeks). Mean AST, ALT, INR, ALP, and direct bilirubin was 273.1 IU/L (40-869), 337 IU/L (65-1030), 2.77 (2.27-3.9), 728.5 IU/L (352-2353) and 174.57 μmol/L (59.0 -530.8) manifesting severe liver injury. Mean albumin and creatinine were 25.2 g/dl (16.0-32.4) and 162.25 mmol/L (69.8 - 247). Mean platelet count was 128.0X106/L (20-292). Mean BMI was 18.40 Kg/M2 (16.0 - 31.14). Ultrasound was normal in two, hepatomegally and ascites in six, liver cirrhosis in two and gallstones and hepatomegaly in one. Mean random blood sugar was normal at 5.23 mmol/L (3.9 - 7.4). Three cases had HBV infection (all HBsAg positive, 2 anti-HBc IgG and IgM positive and 1 e antigen positive). Two patients died of fulminant hepatic failure.**
Conclusion**: ARLI is recognised. The patients had severe immunosuppression and severe liver injury secondary to the ARTs. Risk factors for liver injury should be evaluated before initiating anti-retroviral therapy (ART).**

INTRODUCTION

Anti-retroviral therapy (ART) has revolutionised the management of HIV since 1996 and has positively transformed the prognosis of HIV infection during the past decade. Anti-retroviral treatment related liver injury is a significant clinical problem resulting in elevation of liver transminases, aspartate transaminase and alanine transaminase (AST / ALT) and potentially liver failure and death. The risk of hepatotoxicity associated with HAART has not been fully assessed especially in the resource constrained setting (1, 2).

Non-nucleoside reverse transcriptase inhibitors (NNRTI's) like nevirapine, though noted to be superior alternatives to protease inhibitors as first

line therapies, have been associated with adverse effects. Indeed, NNRTI's are very popular in resource-constrained settings as first line ART therapies (3, 4, 5). We report a series of 11 cases of HAART related liver injury.

CASE REPORTS

This series comprises of eleven patients (two males and nine females) who were on ART for a period of three to 19 weeks. They suddenly developed deep jaundice. Table 1 shows biodata, biochemical, clinical and immunological parameters of the cases. Prior initiation of HAART, the patients had normal liver function tests as evidenced by the normal AST and ALT. There was no history of pre-existing liver diseases. These were seven referals from peripheral centres offering HIV care and HAART, two were from medical outpatient clinic and two from Nairobi Rheumatology Clinic.

HAART combinations used

Combination	No. of Patients
Triomune 30/40	7
Efavirenz/Combivir	4

Triomune-Fixed dose combination of nevirapine, lamivudine and stavudine
Combivir (Lamivudine + zidovudine)

MATERIALS AND METHODS

This was a prospective descriptive, consecutive entry of on going study of adult patients with HIV and on ARTs and have developed ART-related liver injury. They were eligible for the study when they had been known to be HIV positive; on HIV care programme and developed features of ART related liver injury.

Seven patients were referred from peripheral HIV care clinics, two were being followed up at the Kisumu District Hospital medical out-patient clinic and Nairobi Rheumatology Clinic (2). All the patients underwent physical examination by one of the authors.

The ethics and standards committee of the Kisumu District Hospital approved the study. Biodata was taken, and informed signed consent obtained. From each patient, under aseptic technique, 15mls whole blood was obtained from the cubital fossa. The blood was used for analysis of complete blood count , liver function tests :- Alanine transaminase, aspartate transaminase and alkaline phosphatase (ALT,AST,ALP) , INR, Hepatitis B virus markers (s antigen, core antibody-IgG and IgM, and e antigen), hepatitis C virus (anti-HCV) antibodies, CD4+ cell counts, random blood sugar, antinuclear antigen (ANA), albumin, and creatinine levels.

Weight (Kg) using a Salter weighing scale and height (Cms) using a tape measure was taken to assess the body mass index (BMI). History of alcohol intake and concomitant drug/herbs use was taken to ascertain other risk factors which affect ART related liver injury.

Hepatitis B surface antigen was analysed using micro-ELISA system hepanostika (HBsAg Uni-FormII). Anti-HCV was analysed using AxSYmHCV version 3.0 micro particle enzyme immunoassay (MEAIA), (Abbott diagnostic laboratories, Germany). CD4+ cell count was analysed using the FACS (fluorescent activated cell sorter) flow cytometry method with a sensitivity of 1-2000 cells/μl.

Creatinine was analysed using the calorimeter method.

ALT and AST analysis was done using the technicon R.A. 1000 machine (Technicon RA systems No. sm-0034 D91 and SM 4-0137, D 91,1996). ALP was analysed using the reverse passive haemagglutination test (RPHA) method.

Intervention: The patients were admitted to the medical wards at the Kisumu District Hospital and Nairobi West Hospital. The ARTs were stopped immediately and the patients were given palliative and supportive care as in-patients; intravenous fluids, 5% dextrose, iv. Vitamin K 10 mg daily for seven to 14 days and was stopped when the INR was normalising, iv ceftriaxone 1gm daily in patients who had neutrophilia or ascites (to prevent spontaneous bacterial peritonitis), hepermerz (a liver tonic containing ornithine 150mg, pacrytine 100 mg, ozanide 150 mg) 2 × 3 daily-till liver functions normalised, Lactulose 15 mls nocte, Ketosteril tablets, one thrice daily, (were used for the patients with high creatinine levels), low protein diet (0.6 gm/Kg body weight) and high carbohydrate diet.

The patients were followed up daily in the wards by one of the authors till discharge.

RESULTS

Two patients with hepatitis B virus infection died on day 11 and 15 of treatment respectively from fulminant hepatic failure with bleeding and hepatic encephalopathy.

All the patients were HIV positive, initially

HAART naïve and had normal AST and ALT prior HAART initiation. There were no data on platelets, HBV status, and creatinine prior ART initiation but BUN was reported to be normal.

The male: female ratio was 2:9. Two patients died from fulminant hepatic failure (ascites, bleeding, hepatic encephalopathy, deep jaundice, hepatorenal syndrome, INR of 3.9 and 3.0 respectively). Mean ART use was 9.5 weeks (3-19 weeks). Mean age and CD4+ cell count was 35.6years (27-45) and 86.57 cells/ μl (11-199) respectively. The means of demographic and biochemical parameters are as shown in Table 3.

Mean platelet count was 128.0 × 109/L (20-292) depicting a relative thrombocytopaenia.

Three (1 male and 2 females) patients had demonstrated HBV infection markers (3 HBsAg positive, 2 I gM and I gG anti-HBc positive , and 1 HBeAg positive). HCV infection was negative in all the patients.

Abdominal ultrasound scan features were: Normal 2, hepatomegaly and ascites 6, gallstones and haepatomegaly 1, liver cirrhosis 2.

Two patients consented to using alcohol, quantity was not clear. The patients were also on multivitamins as part of care from the HIV care clinics. No patient used herbs.

Table 1

Ultrasound features of the patients with ARLI

Event	Number
Haepatomegaly and ascites	6
Haepatomegaly and gall stones	1
Liver cirrhosis	2
Normal	2

Table 2

Biodata, biochemical, virological and immunological parameters of the 11 cases of ART induced liver injury (ARLI).

Clinical paremeter	1	2	3	4	5	6	7
Age	28	27	28	45	39	37	45
Sex	F	F	F	F	F	F	M
Duration of ART use (weeks)	3	8	12	16	16	12	14
INR(0.6-1.17)	2.27	2.21	1.90	2.14	2.12	1.5	3.9
AST(5-37 IU/L)	268	137	161	138	40	869	207
ALT(5-40 IU/L	438	132	207	65	55	269	78.4
ALP(64-306 IU/L)	957	431	2353	611	401	746	352
Random Blood sugar (mmol/L)(3.5-7.1)	5.10	4.70	5	7.4	4.72	6.1	3.9
CD4+ cells/μl (350-1600)	12	108	100	73	90	24	199
HBs Ag status	Positive	Negative	Negative	Negative	Negative	HBsAg, c Ab+ve (IgG,IgM), +ve eAg	HBsAg +ve, c Ab (IgM +ve)
BMI(Kg/M^2)	16.8	17.5	17.1	16.9	16.8	31.14	16.0
ANA	Negative	negative	Negative	–	–	–	–
Alcohol Use	Nil	Nil	Nil	Nil	Nil	Yes	Yes
Albumin (g/L) (38-50)	16	32.4	30.4	28.9	25	28.2	17.0

Platelets (150-450 × 10^3/ml)	29	170	110	203	149	170	20
Creatinine(60-120μmol/L)	180	112	114	157	138.3	150.7	247
Concomitant drugs used	Multi Vitamins	Multi Vitamins	Multi Vitamins	Multi Vitamins	Multi Vitamins	Multi Vitamins	Multi Vitamins
MCV	78	80	80	104	85	100	93
Bilirubin (Direct) (0-4μmol/l)	194	59.0	101	79	49.1	139	183.9
HCV antibodies	–	–	–	–	–	–	–
Herbs Used	–	–	–	–	–	–	–

Clinical parameter	8	9	10	11
Age (Years)	40	30	42	41
Sex	F	F	M	M
Duration of ART use (weeks)	19	11	4	7
INR (0.6-1.17)	3.1	3.79	3.80	3.7
AST (5-37 IU/L)	176	398	309	301
ALT (5-40 IU/L)	78	1030	648	507
ALP (64-306 IU/L)	456	417	618	671
RBS (3.5-7.1mmol/L)	4.9	4.8	5.8	5.1
CD4+ cell (350-1600 cells/μl)	38	80	11	27
HBsAg	NIL	NIL	POSITIVE	NIL
BMI (Kg/M2)	20	16.8	16.5	16.9
ANA	–	–	–	–
Alcohol	YES	–	–	–
Albumin (32-52g/L)	19	28	25	27
Platelets (150-450 × 10^9/L)	100	99	86	90
Creatinine (60-120μmol/L	207	192	69.8	217
Concomitant drugs used	Multivitamins	Multivitamins	Multivitamins	Multivitamins
MCV(76-93 fl)	78	80	80	77
Bilirubin (Direct 0-4μmol/L)	201	530.8	193.5	190
Anti-HCV anti-bodies	–	–	–	–
Herbs Used	–	–	–	–

BMI-<18.5-underweight, 18.5-24.9-Normal, > 25-overweight
ART-anti-retroviral therapy drugs
INR-international normalising ratio
BMI-body mass index
ANA-anti-nuclear antibodies; RBS-random blood sugar, HBsAg-Hepatitis B virus surface antigen. MCV-mean corpuscular volume
ANA - Antinuclear Antibodies

Table 3

Summary of baseline characteristics: means of biodata and biochemical features of the 11 patients with ARLI

Parameter	Results/Range
M:F ratio	2:9
Mean age (years)	36.5 (27-45)
Mean CD4+ cell counts(350-1600 cells/μl)	69.3 (11-199)
Mean ART use (weeks)	11.1 (3-19)
Mean AST (5-40 IU/L)	273.1 (40-869)
Mean ALT (5-37 IU/L)	337.0 (65-1030)
Mean INR (0.6-1.17)	2.77 (2.27-3.9)
Mean ALP (98-270 IU/L)	728.5 (352-2353)
Mean direct bilirubin (0-4 μmol/L)	174.57 (59.0-530.8)
Mean albumin (32-52 g/dl)	25.2 (16.0-32.4)
Mean creatinine (60-120 μmol/L)	162.25 (69.8-247)
Mean platelet counts(150-450 X 106/L)	128.0 (20-292)
ody mass index (BMI- (kg/M2))	18.40 (16.0-31.14)
MCV(76-93 fl)	85 (77-104)
Mean random blood sugar (2.5-7.1 mmol/L)	5.23 (3.9-7.4)
Hepatits B virus infection (HBV)	3 cases (3 HBsAg positive, 2 IgM and IgG anti HBc positive, 1 HBeAg positive)
Hepatits C virus infection (anti-HCV)	Nil
Alcohol Use	2
Herbs use	Nil
Multivitamins use	11

DISCUSSION

Anti-retroviral related liver injury (ARLI) is a common cause of morbidity, ART treatment discontinuation and mortality in HIV infected patients. Virtually every licensed ART medication is potentially associated with liver enzyme elevation, although certain drugs may cause liver injury more frequently than others. The clinical syndrome of ART-related liver injury in adults is being identified with the widespread access to ARTs. ARLI is elevated liver enzymes in serum with ALT characteristically greater than AST (6).

The patients recruited had low mean platelet count, thrombocytopaenia of 128.0 × 109/L, abnormal renal functions, very low CD4+ cell count mean of 69.3 cells/μl (11-199). The HIV-viral RNA levels were not done due to high cost. They also had low body mass indices, high creatinine level and evidence of HBV infection in three patients. No patient had evidence of HCV infection.

The ACTG (AIDS clinical trial group) has a grading system of ARLI: ALT 2× ULN is minimal injury, and in patients with a normal pre-therapy liver enzymes, ALT or AST 5× ULN and 10× ULN is graded as moderate or severe respectively. In patients with abnormal serum ALT and AST prior to ART therapy, a > 3.5× ULN and > 5× ULN increase in ALT and AST is moderate or severe hepatotoxity respectively (6-8).

The frequency of hepatotoxicity was associated with nevirapine and efavirenz at a frequency of 17 and 0.1% respectively (1, 10, 12).The onset of hepatotoxicity associated with nevirapine is between 19-426 days (mean of 29 days) (l). The incidence of severe liver injury after initiating HAART ranges from 2-18% (8-10). These cases were on nevirapine based, fixed dose combinations (7), and combivir(lamivudine plus zidovudine)/ efavirenz 4 and they developed jaundice and hepatotoxicity after mean ART use of 11.1 weeks (3-16) which is comparable with other

cases in other studies. Studies have shown that the onset of jaundice has been observed to be between 14-60 days (1).

The earlier onset of hepatotoxicity in these patients is associated with multiple factors with a propensity to increase ART-related liver injury. The risk factors associated with the development of ARLI include chronic HBV and chronic HCV infections especially HCV genotype 3, alcohol intake, cocaine, high ALT/AST prior initiating HAART, female gender, old age >45years, first exposure to ARV treatment and a significant CD4+ cell count gain following HAART initiation and advanced liver cirrhosis (8-13). Other factors include low body mass index (BMI) of < 18.5 kg/m^2, serum albumin of <35 g/L and HIV-RNA of < 20000 copies/ml (1, 14-16). Host genetics is also an important factor and persons with HLA-DRB1*0101 background have an increased propensity to develop nevirapine-associated hypersensitivity (14, 15). These factors were independently associated with development of hepatotoxicity (1, 14, 15).

Other notable factors include thrombocytopaenia (platelets of < 150 × 103/ml), renal insufficiency (creatinine > 140 μmol/L), low CD4+ cell count < 200 cells/μl prior HAART initiation and mean Corpuscular volume, MCV >85 fl (1,14,17). Low platelets, low albumin and low body mass index (BMI) and high creatinine as seen in this cohort are associated with an increased propensity to develop ART related liver injury.

The patients had normal ALT and AST prior initiating ARTs. Weekly monitoring of hepatic enzymes after initiation of nevirapine therapy is recommended to earlier detect potentially reversible drug induced toxicities to reduce chances of drug induced liver injury . The risk of nevirapine toxicity is high within the first 12 weeks of therapy and its higher in women with BMI < 18.5 kg/M2 (18).

Mechanisms of ARLI include:

(i) Hypersensitivity reactions-idiosyncratic to host, not dose related and occurs within few days to eight weeks of initiating the ART. It is more common in patients with HIV infection than the general population (19).

(ii) Mitochondrial toxicity- chronic use of NRTIs (nucleoside reverse trancsriptase inhibitors) selectively inhibits DNA polymerase γ (gamma), which is responsible for replication of mitochondrial DNA. This diminishes mitochondrial function with attendant decreased oxidative phosphorylation, aberrations in pyruvate metabolism and accumulation of lactic acid causing metabolic lactic acidosis syndrome and fulminant hepatic failure with AST> greater than ALT (20-22).

(iii) Immune reconstitution phenomenon: there is HAART induced CD4+ T cell recovery, particularly in the setting of chronic HBV and occasionally chronic HCV infections (23). The mechanism of nevirapine induced liver toxicity may be mediated by an immunoallergic reaction to the parent drug or a reactive metabolite favored by a relative over-exposure of selected subjects with low body mass indices (BMIs). This is supported by appearance of a rash, fever and increased eosinophil counts (20). This was noted only in one patient in this series. The lower BMI as seen in these patients could be responsible for a relative over exposure to nevirapine or one of its metabolites thereby triggering toxicity.

(iv) Hepatic steatosis: Studies have shown that hepatic steatosis is highly prevalent in HIV sero-positive patients receiving NRTIs or chronic HCV infection with mitochondrial toxicity (24).

Co-infection with HBV and HCV has been associated with increased incidence of exacerbating nevirapine toxicity (8). Three patients in this cohort had chronic HBV infection and none had HCV infection. The patients who had HBV infection had acute chronic infections with attendant active HBV multiplication in one patient who was "e antigen" positive. This can predispose to development of ascites, acute liver failure and hypoalbuminaemia and high INR as evident in these patients and could have increased the risk of ARLI. Anecdotal studies have identified chronic HBV infection as a risk to liver injury in patients on ARTs (25). Indeed hepatitis B virus and HIV (HBV/HIV) co-infection has been described in a cohort of hospital patients in Kenya (26). HBV causes liver injury, which may then be worsened by ART. This is also worsened by other risk factors like thrombocytopaenia, renal insufficiency as seen in this cohort of patients. Suffice it to note that, increased liver enzymes in a patient with chronic HBV infection does not necessarily imply drug injury but may reflect HBV related hepatic flares, which often occur during the natural course of the HBV disease (6, 8).

Alcohol has been shown to have a multiplier effect in worsening ARLI and two patients consented to taking alcohol. There were no other hepatotoxic drugs/herbs, which were being concomitantly taken with the ARTs.

The clinical relevance of ARLI is its negative

impact on clinical out comes, creates an economic burden on an already stretched medical and patients budgets since additional visits and hospital admissions are required for appropriate patient care and management (27). Further more, ART drug discontinuation hampers maintenance of HIV suppression. The identification of pre-treatment risk factors for severe hepatotoxicity is important to prevent unnecessary morbidity, treatment discontinuation and mortality from ART- induced liver injury.

Early identification of ALT / AST increase enables detection of early liver injury and early withdrawal of the offending drug which is the mainstay of management. The management of ARLI is based on its clinical severity as depicted by the levels of serum ALT and AST (6, 27). Stopping the medications at the very first sign of mild liver injury can prevent serious consequences.

Higher mortality rates are associated with increased levels of direct bilirubin, higher INR, higher ALT or AST greater than 10× ULN (grade 4) and associated advanced liver cirrhosis (29, 30). The mean direct bilirubin levels in this cohort were 28× ULN. This causes direct injury to the liver. Management is conservative once the offending drug is stopped. Address the modifiable risk factors like alcohol, dyslipidaemia, hyperglycaemia, steatosis, and HCV genotype 3, which is associated with staetosis and an increased risk of drug injury (23).

Most patient support centres only assays AST and ALT and omit other liver function test parameters like gamma glutamyl transferase (gGT), alkaline phosphatase (ALP) and bilirubin levels which are informative like in cases of extrabiliary duct obstruction in Kaposi's Sarcoma, tuberculous adenitis, lymphomas and cholecystitis / cholangitis. Early identification of liver injury and withdrawal of the drug is the key to management. Patient support centres should be empowered to assay complete liver and renal profiles to enable early detection of ART related liver injury. This has a public health implication of how frequently the AST, ALT and bilirubin should be monitored after initiating HAART.

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