Scientific Research Publishing

Open Journal of Gastroenterology, 2019, 9, 135-140
http://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Antiretroviral Therpay Induced Liver Toxicity among Immunecompromised HIV Patients at Chu Brazzaville

Florient Jile Mimiesse[1,2], Clausina Ahoui-Apendi[1,2], Ngala Akoa Itoua-Ngaporo[1,2], Ursula Ingride Koukha[1], Lucie Charlotte Atipo Ibara Ollandzobo[1,3], Arnaud Mongo-Onkouo[1,2], Marlyse Ngalessami-Mouakosso[2], Céline Adoua[2], Jean Bruno Mokoko[1], Rody Stéphane Ngami[2], Deby-Gassaye[1,2], Eric Rutaganda[4,5], Blaise Irénée Atipo Ibara[1,2], Ibara Jean-Rosaire[1,2]

[1]Faculty of Health Sciences, Marien Ngouabi University, Brazzaville, Congo
[2]Gastroenterolgy service University Hospital of Brazzaville, Brazzaville, Congo
[3]Infant pediatric service University Hospital of Brazzaville, Brazzaville, Congo
[4]Medical Depertment, University Teaching Hospital, Kigali, Rwanda
[5]College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda
Email: jilemimiesse@yahoo.fr

How to cite this paper: Mimiesse, F.J., Ahoui-Apendi, C., Itoua-Ngaporo, N.A., Koukha, U.I., Ollandzobo, L.C.A.I., Mongo-Onkouo, A., Ngalessami-Mouakosso, M., Adoua, C., Mokoko, J.B., Ngami, R.S., Deby-Gassaye, Rutaganda, E., Ibara, B.I.A. and Jean-Rosaire, I. (2019) Antiretroviral Therpay Induced Liver Toxicity among Immunecompromised HIV Patients at Chu Brazzaville. *Open Journal of Gastroenterology*, **9**, 135-140.
https://doi.org/10.4236/ojgas.2019.98016

Received: November 28, 2018
Accepted: August 3, 2019
Published: August 6, 2019

Abstract

Introduction: Human immunodeficiency virus (HIV) infection is a public health problem of concern. Anti-retroviral therapy (ART) is associated with multiple side effects. This study aimed at identifying the different hepatic manifestations of antiretroviral therapy and the responsible molecules. **Patients and Methods:** This was an eight months period prospective descriptive study, from January 1st to August 31st, 2015, conducted in the Department of Gastroenterology and Internal Medicine at the Brazzaville University Teaching Hospital. Study participants were treatment-naïve HIV patients who were initiated on ART treatment during the study period. Patients with liver disease, liver cytolysis prior to initiation of therapy, and those with alternative therapy that may cause hepatotoxicity were excluded. The sample size was 110 patients. **Results:** The age was ranging from 25 to 70 years with a mean age of 47.5 ± 7.5 years. During the six months of follow-up, the alarming hepatic signs were observed in 26.36% of cases (n = 29) in the 3rd month of treatment. There was no observed alarming sign in the 6th month of follow-up. The cytolytic pattern was observed in 54.55% of cases (n = 60) in the 3rd month. The cholestatic pattern was observed in 6.36% of cases (n = 7) in the 3rd month. Triple therapy combination of Zidovudine, Lamivudine and Nevirapine (AZT + 3TC + NVP) was the most used in 57.27% (n = 63) with a statistically significant p value to the occurrence of cytolytic pattern ($p < 0.03$) in the 3rd month of treatment. **Conclusion:** Drug induced liver toxicity oc-

curs in a significant number of patients starting ART. The prevalence of hepatic events was high at the third month of treatment and the triple therapy of Zidovudine, Lamivudine and Nevirapine (AZT + 3TC + NVP) was the most incriminated.

Keywords

Drug Induced Liver Toxicity, HIV, Anti-Retroviral Therapy, Brazzaville

1. Introduction

Human immunodeficiency virus (HIV) infection is a public health problem of concern due to its elevated prevalence, its morbidity and its mortality [1] [2].

The introduction of antiretroviral therapy (ART) in 1996 has revolutionized the treatment of HIV infection, but the long-term survival of patients is based on the lifetime compliance on treatment which is a combination of multiple different molecules. As a result, the side effects of ART become growing causes of morbidity during HIV infection. The drug induced liver toxicity is an important part of these side effects [3]. This is a cause of early interruption of treatment. Indeed, a Danish study reports that nearly 10% of patients have an increase in transaminases at the introduction of ART, and nearly 30% have a moderate elevation of transaminases on long-term therapy [4].

To our knowledge, there is no single study in Congo done to evaluate the liver drug toxicity secondary to ART. The purpose of this study was to contribute to improving the care of people living with HIV (PLWH) in Congo.

2. Patients and Methods

This was an eight months period prospective descriptive study, from January 1st to August 31st, 2015. Epidemiological, clinical and biological data were collected in the Department of Gastroenterology and Internal Medicine of the Brazzaville University Teaching Hospital. The study population was selected among HIV inpatients admitted or outpatients consulted during the study period. Study participants were treatment naïve HIV patients who were initiated on ART treatment during the study period. Patients with liver disease, liver cytolysis prior to initiation of therapy, and those with alternative therapy that may cause hepatotoxicity were excluded. By the simple consecutive random method, we selected 110 study participants meeting the inclusion criteria.

All patients were informed about their HIV status and had the initial inclusion checkup before to start on ART treatment. The initial laboratory assessment included liver transaminases, alkaline phosphatase (ALP), total and direct bilirubinemia, gamma glutamyl transpeptidase (GGT), triglycerides, cholesterol, blood glucose, serum creatinine, viral markers of hepatitis B and C viruses, T lymphocytes CD4 count and HIV viral load. After the start of the treatment, the liver panel was assessed at third and then at sixth months. The liver cytolytic

pattern was defined by an elevation of liver transaminases of more than twice normal values. The liver cholestatic pattern was defined as the elevation of total bilirubin above 12 µmol/L, the elevation of GGT above 55 IU/L, and the elevations of ALP above 100 IU/L. For any hepatic cytolysis and/or hepatic cholestasis occurring between the fifth and 90th day after therapy initiation, it was attributable to ART therapy.

The variables studied were age, gender, clinical signs (fever, jaundice, pruritus, hepatomegaly), biological signs (transaminases, PAL, GGT, bilirubinemia) and different taken ART molecules.

Data entry and cleaning were done using the Epi info 7.1.1 software. Data analysis was done using the SPSS Public Health Software Version 17.0. Chicago-USA. The proportions were compared using the Mann-Whitney test. For any p-value less than 0.05, the statistical test was considered significant.

The present study was a scientific research. The data confidentiality was guaranteed during the whole process of this research. No single participant was included without free informed consent.

3. Results

In total, 110 patients fulfilling the inclusion criteria were selected and participated in this study. The female gender was more prevalent representing 86.9% with a sex ratio, male to female, of 0.39. The mean age was 47.5 ± 7.5 years, ranging from a minimum age of 25 to a maximum age of 70 years. During the six months of follow-up, hepatic signs of clinical importance were observed in 26.36% of cases (n = 29) in the 3rd month of treatment. Those were jaundice in 6.36% of cases (n = 7), pruritus in 3.64% of cases (n = 4), hepatomegaly in 4.55% of cases (n = 5) and hepatitis in 9.09% of cases (n = 10). There was no observed alarming sign in the 6th month of follow-up. Liver cytolysis was observed in 54.55% of cases (n = 60) in the 3rd month and in 33.63% of cases (n = 37) in the 6th month. Liver cholestasis was observed in 6.36% of cases (n = 7) in the 3rd month. No cases of liver cholestasis were observed in the 6th month.

In this study, 57.27% (n = 63) of the patients were on triple therapy with Zidovudine, Lamivudine, and Nevirapine (AZT + 3TC + NVP) followed by Emtricitabine, Tenofovir, and Efavirenz (FTC + TDF + EFV) in 21.82% (n = 24) of cases (Table 1).

However, we noted a statistically significant difference between AZT + 3TC + NVP and liver cytolysis ($p < 0.03$) in the 3rd month of treatment. On the other hand, in the 6th month of treatment, the same difference was not found.

Table 2 and Table 3 show the distribution of the liver cytolytic pattern of triple therapy in the 3rd and 6th months of treatment respectively.

4. Discussion

Our prospective study was conducted to evaluate clinical and laboratory liver manifestations in people living with HIV/AIDS on antiretroviral therapy. The

Table 1. Number of patients by drug regimens.

	n	%
AZT + 3TC + NVP	**63**	**57.27**
FTC + TDF + EFV	24	21.82
AZT + 3TC + EFV	8	7.27
D4T + 3TC + NVP	8	7.27
AZT + 3TC + LPV/r	3	2.73
FTC + TDF + NVP	2	1.82
D4T + 3TC + EFV	2	1.82
Total	**110**	**100**

Table 2. Distribution of liver cytolysis at the 3rd month according to the ART.

Initial Molecules	ALAT		ASAT	
	Cytolysis	No cytolysis	Cytolysis	No cytolysis
Combination/NVP	**45 (63.38%)**	26 (36.62%)	2 (2.82%)	**70 (97.18%)**
Combination/EFV	9 (24.32%)	**28 (75.68%)**	3 (8.11%)	**34 (91.89%)**
Combination/Lpr	1 (50%)	1 (50%)	0 (0.0%)	1 (100%)
Total	**55 (50%)**	**55 (50%)**	**5 (4.5%)**	**105 (95.45%)**

P-value: 0.03.

Table 3. Distribution of liver cytolysis at the 6th month according to the ART.

Initial Molecules	ALAT		ASAT	
	Cytolysis	No cytolysis	Cytolysis	No cytolysis
Combination/NVP	26 (59.09%)	**55 (70.51%)**	2 (40%)	**78 (74.29%)**
Combination/EFV	5 (33.33%)	**23 (29.48%)**	3 (60%)	**25 (23.81%)**
Combination/Lpr	**1 (100%)**	0 (0,0%)	0 (0.0%)	**2 (1.9%)**
	32	**78**	**5 (100)**	**105 (100)**

P-value: 0.5.

difficulties encountered were related on the one hand to the irregularity of the patients in consultation and on the other hand to the unavailability of certain complementary examinations such as the rate of prothrombin, the abdominal ultrasound which are not supported by the national HIV program. The abdominal ultrasound would have eliminated any cause of extrahepatic cholestasis. Despite these difficulties, the forward-looking nature of our study and the results we have arrived at have given us some comments.

In this study, the mean age was 47.5 ± 7.5 years, ranging from 25 to 70 years. The female gender was more prevalent. The same observations were made by Sawadogo *et al.* [5] in Burkina Faso as well as Zannou *et al.* in Benin [6], who also found a female predominance in an HIV-infected population. It should be noted that Congolese demography has been represented by a high prevalence of

female gender for some decades [7]. In England, Frater *et al.* [8] reported a male predominance. This difference may be explained by the high frequency of men who have sex with men in Europe as compared to Congo where this practice is rare.

In our study, the clinical signs were dominated by pain at the liver aspect (9.09%) followed by jaundice (6.35%) and pruritus (3.64%). These signs are related to drug-induced hepatitis occurring during ART treatment [9]. Sungkaupath *et al.* and Moreno *et al.* observed respectively 10% and 69% of patients with pruritus under a protocol including nevirapine [10] [11].

A half of the study participants had liver cytolysis at 3 months, followed by a 29% decrease at 6 months. These findings are almost similar to those of Orenstein *et al.* who noted the susceptibility of ART to lead to an elevation of liver transaminases and to induce clinical and biological hepatitis [12].

Nevirapine based regimens were the most used in this study (57.27%), this is the result of clinicians to be bound on standard guidelines of the national program against HIV-AIDS. Our findings are similar to other findings from different literature [13] [14] [15]. However, these protocols are also the most likely causes of liver toxicity [15] [16].

5. Conclusion

Drug induced liver toxicity occurs in a significant number of patients starting antiretroviral combination therapies. The prevalence of liver toxic events was high in the third month and was subsiding at the sixth month of treatment. Liver toxicity with nevirapine based combination was most prevalent during the study period.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Rosenbach, K., Allison, R. and Nadler, J. (2002) Daily Dosing of Highly Active Antiretroviral Therapy. *Clinical Infectious Diseases*, **34**, 686-692. https://doi.org/10.1086/338255

[2] Taburet, A.-M., Paci-Bonaventure, S., Peytavin, G. and Molina, J.-M. (2003) Once-Daily Administration of Antiretroviral. Pharmacokinetic of Emerging Therapies. *Clinical Pharmacokinetics*, **42**, 1179-1191. https://doi.org/10.2165/00003088-200342140-00001

[3] Sterling, R.K., Chiu, S., Suider, K. and Nixon, D. (2008) The Prevalence and Risk Factors for Abnormal Liver Enzymes in HIV-Positive Patient without Hepatitis B or C Coinfections. *Digestive Diseases and Sciences*, **53**, 1375-1382. https://doi.org/10.1007/s10620-007-9999-6

[4] Lohse, N., Hansen, A.B., Pedersen, G., Kronborg, G., Gerstoft, J., Sorensen, H.T., *et al.* (2007) Survival of Persons with and without HIV Infection in Denmark, 1995-2005. *Annals of Internal Medicine*, **146**, 87-95.

https://doi.org/10.7326/0003-4819-146-2-200701160-00003

[5] Sawadogo, A.B., Drabo, J., Meda, N., Compaore, G., *et al.* (2007) Etude prospective d'une cohorte de patients infectés par le VIH traits par les antirétroviraux: comparaison de dispositifs de prise en charge centralisé et décentralisé au Burkina Faso. *Médecine Sciences*, **23**, 88.

[6] Zannou, D., Houngbé, F., Acapko, J., Adé, G., Gougounou, A. and Akondé, A. (2007) Undesirable Effect of Antiretroviral Drugs in Patients Infected with HIV at Cotonou Benin. *Le Mali Medical*, **22**, 37-43.

[7] Centre National de la Statistique et des Études Économiques (2009) CNSEE Enquête de Séroprévalence et sur les Indicateurs du Sida au Congo (ESISC-I) 2009. http://www.cnsee.org/pdf/RapSyntESISC.pdf

[8] Frater, A.J., Dunn, D.T., Beardall, A.J., Ariyoshi, K., Clarke, J.R., McClure, M.O. and Weber, J.N. (2002) Comparative Response of African HIV-1-Infected Individuals to Highly Active Antiretroviral Therapy. *AIDS*, **16**, 1139-1146. https://doi.org/10.1097/00002030-200205240-00007

[9] Neuman, M.G., Schneider, M., Nanau, R.M. and Parry, C. (2012) HIV-Antiretroviral Therapy Induced Liver, Gastrointestinal, and Pancreatic Injury. *International Journal of Hepatology*, **2012**, Article ID: 760706.

[10] Sungkanuparph, S. and Mootsikapun, P. (2001) Efavirenz-Based Regimen in Advanced AIDS with Cryptococcal Meningitis: A Prospective Multicenter Study. 14*th International AIDS Conference*, Barcelone, December 2001, 64.

[11] Moreno, A., Perez-Elias, M. and Casado, J. (2001) Toxicity Profile of Antiretroviral Drugs in First Line ART in Routine Clinical Practice. 14*th International AIDS Conference*, Barcelone, December 2001, 1-4.

[12] Orenstein, R. (1999) Treatment-Associated Hepatitis. *AIDS Read*, **91**, 339-346.

[13] Sulkowski, M.S., Thomas, D.L., Chaisson, R.E. and Moore, R.D. (2000) Hepatotoxicity Associated with Antiretroviral Therapy in Adults Infected with HIV and the Role of Hepatitis B or C Virus Infection. *The Journal of the American Medical Association*, **283**, 74-80. https://doi.org/10.1001/jama.283.1.74

[14] Emejulu, A.A., Ujowundu, C.O., Igwe, C.U., *et al.* (2010) Hepatotoxicity of Antiretroviral Drugs in HIV Sero Positive Nigerian Patients. *Australian Journal of Basic and Applied Sciences*, **4**, 4275-4278.

[15] Kalyesubula, R., Kagimu, M., Opio, K., Kiguba, R., Semitala, C., Schlech, W., *et al.* (2011) Hepatotoxicity from First Line Antiretroviral Therapy: An Experience from a Resource Limited Setting. *African Health Sciences*, **11**, 16-23.

[16] Mulu, W., Gidey, B., Chernet, A., Alem, G. and Abera, B. (2013) Hepatotoxicity and Associated Risk Factors in HIV-Infected Patients Receiving Antiretroviral Therapy at Felege Hiwot Referral Hospital, Bahirdar, Ethiopia. *Ethiopian Journal of Health Sciences*, **23**, 217-226. https://doi.org/10.4314/ejhs.v23i3.4