

Review Article**Effect of Hepatitis B and C Virus in HIV Co- Infected Patients: A Fifteen Year Review****Chika F Ubajaka*, Bonaventure C Ibeh, Ifeoma A Modebe, Alphonsus C. Okaro**

Department of Community Medicine and Primary Health Care, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria

***Corresponding author**

Chika F Ubajaka

Email: chika@grunzlink.com

Abstract: Co-infection of Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) or hepatitis C virus (HCV) is the simultaneous presence of these viruses in a host. One third of HIV-infected individuals suffer from chronic HCV infection. Chronic HBV infection on the other hand occurs in 10% of HIV-infected persons. The consequences of associated hepatitis B and C virus infection on HIV patients are quite enormous. This paper aims at studying the effects of hepatitis B and C virus co-infection in HIV-patients. This article reviews peer-reviewed literature and expert opinion published from 2000 to 2014 in medical journals, health databases, books, health survey reports, electronic libraries and health-related websites. The evidences from the studies conducted show that despite the fact that highly active antiretroviral therapy has dramatically improved the prognosis of those with HIV disease, the consequences of associated illness such as hepatitis B and C have grave consequences on these individuals and are currently among the leading causes of hospital admission and death in the HIV infected population. It is obvious that the prevalence of HBV/HCV co-infection in HIV infected patients is very common owing to shared route of transmission of these viruses. Therefore, adequate management of viral hepatitis should now be considered a priority in HIV co-infected patients.

Keywords: Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus, Co-infection

INTRODUCTION

Hepatitis B and Hepatitis C co-infection with Human Immunodeficiency Virus (HIV), is associated with accelerated progression to cirrhosis and thus a higher mortality [1]. These viruses are the three most common chronic viral infections all over the world and they share similar routes of transmission, with sexual, parenteral and perinatal transmission being the most frequent modes of acquiring these infections, hence HIV-HCV co-infection and HIV-HBV co-infection and/or both are common [2, 3]. While, HIV and HCV are both ribonucleic acid (RNA) viruses, HBV is a deoxyribonucleic acid (DNA) virus; but they are all similar in terms of how high they replicate in the body. In contrast, exposure to these viruses is followed by an immune respond which differs markedly in its ability to clear the infection. Clearance is maximal for HBV, much lower for HCV and negligible (or non-existent) for HIV. Thus there is a high prevalence of co-infection with these agents.

Moreover, among the HIV infected patients, 2-4 million are estimated to have chronic HBV co-infection while 10-12 million are co-infected with HCV [4]. An estimated one-third of the deaths in HIV patients are directly or indirectly related to liver

diseases associated with HBV or HCV, which makes HBV and HCV a major problem in the HIV population. This aligns with the submission of the Centre for Disease Control (CDC) in the XIX International AIDS Conference 2012, in Washington USA which holds that about one-third of HIV infected persons are co-infected with either hepatitis B or hepatitis C which can cause long term (chronic) illness and death. The prevalence rate of co-infection with HBV and HCV in HIV patients have been variable worldwide depending on the geographic regions, risk groups and the type of exposure involved which may be different not only from country to country, but also in different regions of the same country [5, 6]. However, co-infections of HBV and HCV with HIV have been associated with reduced survival, with an increased risk of progression to severe liver diseases and an increased risk of hepatotoxicity associated with antiretroviral therapy. Co-infection with hepatitis may also complicate the management of HIV infection. Hence, understanding the effect HBV and HCV has on HIV co-infected patient is essential in informing any potential treatment plan. As a result, it is advisable that all persons living with HIV be tested for hepatitis B and C. Furthermore, to prevent co-infection with hepatitis B, the advisory committee on immunization practices recommends

universal hepatitis B vaccination of susceptible patients with HIV infection or AIDS [7].

The diagram below shows the estimated burden of the population currently living with each of these viruses and the number of co-infected persons.

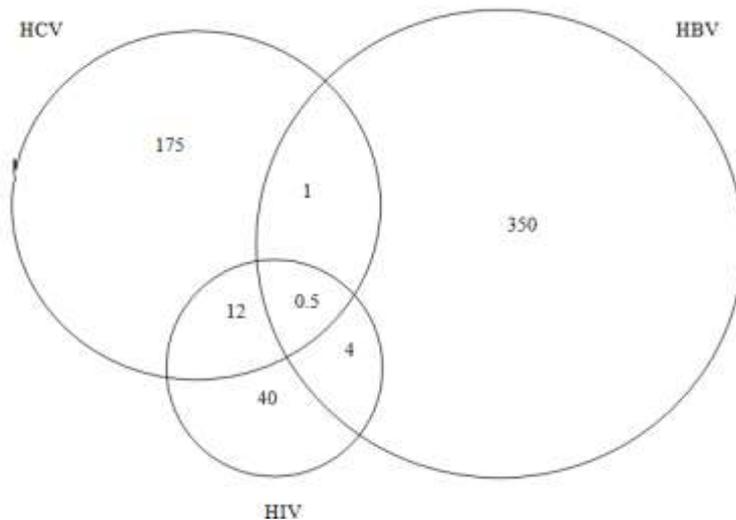


Fig. 1: Estimated number (in million) of subjects infected with HIV, HBV and HCV worldwide

HIGH RISK GROUPS FOR HBV/HIV AND HCV/ HIV CO-INFECTION

The reported prevalence of HBV/HIV and HCV/HIV co-infection varies significantly among studies. Although the three viruses are transmitted through parenteral, sexual, and vertical exposure, they differ in the transmission efficiencies of these routes. Thus, the risk factors of the population under study directly influence the prevalence in that particular population. Parenteral exposure modes such as intravenous drug use (IVDU) or multiple transfusions (especially in hemophiliacs) have been consistently found to be the most important risk factors for HCV/HIV co-infection [8]. For instance, in the United States, the prevalence of co-infection with HIV and HCV is highest among those infected via percutaneous route. In HIV-positive patient with a history of IVDU, the rate of HCV infection is reported to be 82 to 93% [9, 10]. This tend to agree with the report of the San Francisco AIDS Foundation which states that among some populations of injection drug users, the HCV/HIV co-infection rate may be as high as 90% .Also reported by this foundation was a high rate of HCV/HIV co-infection among prisoners [11]. On the other hand, sexual transmission of HCV is relatively inefficient and the rate of co-infection among HIV-infected patients with a sexual risk factor is less than 10% [12]. Men who have sex with men (MSM) do not seem to have an overall increased risk for HCV/HIV co-infection [8, 13], although epidemics of acute HCV have been described for HIV-infected men who have sex with men with high risk behaviors [14]. The overall burden of HCV/HIV co-infection is estimated at 10 to 12 million people worldwide. In the case of HIV/HBV co-infection, sexual transmission is responsible for the majority of the cases .This supports a US study in which 16,248 HIV infected patients were examined and

the prevalence of chronic HBV was seen to be higher in men who have sex with men and in intravenous drug users (IVDU) [15]. According to this study, in developed countries, laboratory markers of prior HBV are more common in MSM and IVDU [16-18]. However these findings can be marched with the views of the researchers from Mayo Clinic in America in which an outline of those who fall into the known high risk groups for HIV and / or hepatitis B includes promiscuous homosexual or heterosexual men, intravenous drug users, hemophiliacs, people who have lived in sub-Saharan Africa since 1975, mentally handicapped people who have lived in hospitals or group homes, sexual partners or babies of any of the above and prison inmates.

EFFECT OF HCV/HIV CO-INFECTION

During acute HCV infection, viral clearance is correlated to strong CD4+ T helper cell response. On the other hand, the accelerated decline in HCV/HIV – co-infected patients occurs in part because they have diminished cellular immune responses to HCV infection, characterized by weak HCV specific CD8+ T cell and CD4+ T cell immune activity [19]. Thus, they are less able to clear HCV viraemia after initial infection [20].

However, the impact of HCV infection on HIV – related disease progression is not entirely clear. Analysis in this population with different HCV risk factors indicate an increased rate of mortality in HIV/HCV co-infected individuals compared to HIV-monoinfected [21] patients and this increased death rate cannot be attributed entirely to increased incidence of liver diseases. The presence of both HIV and HCV co-infection may complicate the natural history of both viruses and their treatment. For example, co-infected

patients have higher HCV viral loads than patients infected with HCV alone. This correlates with the report of the 8th Retrovirus Conference held in the United States of America in February 2001, where reporters from Madrid reported that 902 study participants with HIV – 72% of whom were co-infected with HCV – responses to HAART differed dramatically. Participants with HIV alone experience an average HIV viral load decrease of over 5,700 copies/ml and an average CD4 cell count increase of 111 cells/mm³. In contrast, the HIV/HCV – co-infected participants experienced an HIV viral load decrease of only 606 copies/ml and a CD4 cell count increase of just 53 cells/mm³.

In addition, HIV infection and related immune suppression may be associated with more rapid progression of liver disease to cirrhosis which is observed in 15% to 20% of co-infected patients within 10-15 years after HCV infection compared to only 2% to 6% of people with HCV infection alone [21]. This fact agrees with the report of the 52nd annual meeting of the American Association for the Study of Liver Diseases (AASLD) held in November 2001 where researchers with the French MULTIVIRC study team reported that co-infected people die earlier than those with only HCV because they progress to cirrhosis sooner. Similarly, at the XIV International AIDS Conference held in Barcelona in 2002, researchers from St. Thomas School of Medicine in London estimated that the average time between HCV infection and the development of cirrhosis is 22 years in co-infected people compared with 33 years in those with HCV alone – a 1.5 fold increase in the rate of liver disease progression [21].

Meanwhile, the mechanism by which HCV influences HIV progression remains speculative. HCV may down regulate proliferation of T-cells or increase apoptosis of T cells by apoptotic pathways. Co-infected patients have higher HCV RNA levels and more rapid progression of hepatic fibrosis than those infected with HCV alone [14]. Compared with HCV infection alone, HCV/HIV co-infection is associated with an increased risk of end stage liver disease and hepatocellular carcinoma [20]. This support the views of the report of the National Institute of Health (NIH) consensus meeting in which a scientist cited a meta – analysis showing that HIV/HCV co-infected people had a two-fold greater risk of progression to cirrhosis and a six-fold greater chance of developing end stage liver diseases. The views of the reporters from Madrid and Spain in the January 2001 issue of the American Journal of Gastroenterology that HIV/HCV co-infected individual have a higher rate of hepatocellular carcinoma than people with HCV alone were not left out. Also, similar study by researcher from the University of Pennsylvania holds that HIV co-infected people have a significantly high rate of liver decompensation.

HIV mediated immune suppression appears to facilitate HCV replication impairs immune – mediated HCV clearance or both [19]. HIV co-infection worsens the histological course of HCV infection by increasing and accelerating the risk of cirrhosis or leading to rare but lethal fibrosing cholestatic hepatitis which is clearly related to direct cytotoxicity of HCV with high viraemia, leading to accumulation of viral proteins in the endoplasmic reticulum and hepatocyte death [22].

EFFECT OF HBV/HIV CO-INFECTION

The primary goal of treating chronic hepatitis B is to halt progression of liver disease by suppressing viral replication. On the other hand, since the introduction of suppressive combination Anti Retroviral Therapy (ART), survival in HIV-infected people has been extended. Data are scarce on the clinical course of prolonged HIV/HBV co-infection and the effects of highly active anti retroviral therapy (HAART). Nonetheless, a study of people co-infected with HIV and HBV revealed that responses to HAART were inferior relative to those infected with HIV only [23]. Although both patient groups achieved similarly significant immunologic responses to treatment, co-infection was associated with excess risk of virologic failure and of death. Virologic response was impaired in co-infected subjects, however, frequently as a result of interruptions in treatment driven by hepatic complications.

Furthermore, co-infected patients are more likely to develop hepatitis after HARRT initiation [11, 17], and they face a higher risk of hepatic decompensation and hyperbilirubinemia [24]. Hence, it could rightly be said that the natural history of hepatitis B is deleteriously influenced by HIV. In an overview, increased HBV carriage rates, greater levels of HBV viraemia, more rapid decline in hepatitis B surface antibody (anti-HBs), increased reactivation episodes, faster progression to liver cirrhosis are all characteristics of HBV/HIV co-infected patients. Moreover, hepatocellular carcinoma may develop at a younger age and is more aggressive in this population. However, the confluence of these events significantly contributes to the greater risk of liver related mortality that occurs in co-infected people [15, 25]. All these were captured in several other recent reports by many researchers including those of the HIV-HBV International Panel which holds that among HBV patients HIV infection is associated with decrease rate of spontaneous hepatitis B surface antigen (HBsAg) clearance after acute infection, decreased hepatitis B e antigen (HBeAg) sero-conversion, increase incident of end stage liver disease and increase rate of HAART – related hepatotoxicity.

MANAGEMENT OF HBV/HIV AND HCV/ HIV CO-INFECTION

The application of good clinical management of underlying HBV or HCV co-infection in HIV infected individuals cannot be emphasized enough. It can evaluate options and determine the most appropriate treatment approach and is one that fully informs the co-infected person of options and likely outcomes, pros and cons of any proposed treatment plan. However, several guidelines with regard to management of co-infection have been introduced. These guidelines, endorsed by the European AIDS clinical society, result from the short statement of the first European consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients as well as from the updated recommendations of the HCV/HIV International Panel follows thus:

- All HIV infected patients should be screened for hepatitis B and C at diagnosis and then on annual basis [26].
- Psychological, social and medical support should be made available to assist patients who consume alcohol to abstain or stop alcohol consumption as this has been identified as an important co-factor in liver disease progression [26].
- Opioid replacement therapy in patients experiencing problematic illicit opiate use or dependence. This is a step towards cessation of the use of these parenteral drugs and thus a reduction in the risk of HCV re-infection
- As Hepatitis B, C and HIV are transmitted sexually, adequate counseling, including the use of condoms, is advisable [26]. Mucosally traumatic sexual practices associated with high risk of blood contact should be discouraged [27]. These recommendations also received a nod by the guidelines on the management of HIV/HCV co-infection published by the British HIV Association (BHIVA) in 2005 [28].

Vaccination

Patients lacking anti-HAV IgG antibodies or HBsAg and anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection, regardless of their CD4 count. The response to the vaccine is dependent on CD4 count at the time of vaccination, and may be reduced in patients with a CD4 cell count <500 cells/mm. In all patients, the anti-HBs antibody titre should be monitored 4 weeks after the end of the HBV vaccination schedule. When there is insufficient response (anti-HBs <10 IU/l) re-vaccination should be considered. In patients eligible for highly active antiretroviral therapy (HAART), vaccination should be deferred until a clinically significant immune reconstitution has been achieved. People who fail to seroconvert after vaccination and remain at risk of HBV infection should be annually

monitored for serological markers of HBV (HBsAg and antibodies to the hepatitis B core antigen (anti-HBc) [26].

Screening for late complications of Hepatitis B or C: Patients with liver cirrhosis should be monitored for the presence of esophageal varices using upper-gastrointestinal endoscopy every 1–2 years. Patients with advanced HBV or HCV-associated fibrosis/cirrhosis have a high risk of developing Hepatocellular carcinoma, and therefore surveillance with ultrasound and serum alpha-fetoprotein (AFP) is advised. As the development of HCC in co-infected patients may be faster, monitoring intervals shorter than 6 months should be considered [26].

Treatment

Acute HCV infection in HIV positive persons should be treated for 24 weeks with a combination of peginterferon plus weight – based Ribavirin. However, responses are lower than in HIV uninfected individuals [29].

The current treatment of chronic Hepatitis C infection in HIV positive persons should be peginterferon at standard doses plus weight based Ribavirin (1000mg/ day if less than 75kg and 1200mg/ day if greater than 75kg [29]. However, if a co-infected patient has severe immune deficiency (CD4 count less than 200 cells /mm³), the CD4 count should be improved using HAART before commencing anti- HCV treatment [26]. It is recommended that HIV positive patients with chronic Hepatitis B or C infection should be initiated on HAART [30].

Drugs that are currently licensed in Europe for the treatment of HBV include standard IFN- α 2a and 2b and pegylated-IFN- α (PEG-IFN) 2a, lamivudine, and adefovir. All these drugs have antiviral activity, and IFN has additional immune modulatory effects. Tenofovir and emtricitabine are approved for HIV and are also active against HBV. Drugs under development with anti-HBV but not anti-HIV activity include entecavir, clevudine, telbivudine and a number of other compounds [26].

Data on the efficacy of some of these drugs in HIV/HBV co-infected individuals are still very limited and no large-scale randomised controlled trials have been conducted to define their efficacy and safety when used alone or in combination. Therefore, recommendations for the treatment of HBV in HIV co-infected patients need to be derived from what is known about the treatment of HBV mono-infected patients, and from the limited data available in HBV/HIV co-infected patients [26]. Most cases of acute Hepatitis B resolve spontaneously and do not need antiviral therapy. In patients with chronic hepatitis B and HIV infection, the

decision to treat or not to treat should be based as much as possible on an integrated evaluation of the following: HBV-DNA level, Liver disease activity and stage (derived from ALT profile, liver necroinflammatory activity and fibrosis assessment, when indicated) and careful evaluation of the presence of cirrhosis [26].

In HBV-HIV co-infected patients, the HBV-DNA threshold for starting therapy has not been defined. In HBeAg-positive HBV mono-infected patients, HBV DNA >approximately 20,000 IU/ml is the cut off to indicate antiviral therapy, while a cut-off >approximately 2000 IU/ml is more often used for HBeAg-negative (anti-HBe-positive) patients. These thresholds can also be applied to co-infected patients. If HBV-DNA is high (>2,000 IU/ml), HAART including two drugs with dual anti-HBV and anti-HIV activity is recommended. In patients with low HBV-DNA levels (<2000 IU/ml), the recommendation is to initiate the HAART regimen of choice (it is optional to use a HAART regimen containing two dual-activity drugs) [26].

EVALUATION, ASSESSMENT AND PROGNOSIS

Measurement of liver enzymes, such as aminotransferases (i.e. Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)), bilirubin, etc serves as useful tools in the evaluation and assessment of hepatic damage. Also determination of HCV and HBV genotypes serves as a useful risk assessment technique.

Measurement of viral load is a major determinant of the risk of liver cirrhosis, hepatocellular carcinoma and death [31]. Assessment of liver fibrosis has prognostic value and is important for making therapeutic decisions in HCV and HBV diseases. Liver biopsy was the only method until recently. However, new noninvasive tools to measure liver fibrosis have begun to replace or complement histology [32]. They can be divided into two major categories; imaging techniques such as Elastometry (Fibro scan) and serum biochemical indexes (i.e. Fibro test e.g. AST to platelet ratio index APRI, ALT to AST ratio etc) measurement of serum and hepatic iron concentration is a useful prognostic tool of liver fibrosis.

CONCLUSION

In summary, liver diseases associated with HCV and HBV is a growing problem in HIV positive individuals. In addition to more rapid liver disease complications seen in this population, the relatively low efficacy of current medication and its low tolerability should prompt early and efficient clinical management.

RECOMMENDATIONS

Upon routine screening for HCV and HBV infections in HIV positive patients, patients who are negative to HBV and are susceptible to infection should

be vaccinated to prevent co-infection. An assessment of HBV/HCV disease stage in HIV co-infected patients should be seen as a sine-qua-non before the commencement of clinical management to avoid complications. On the other hand, the provision of treatment should be promoted without unnecessary delay in the absence of clear contradiction in the co-infected population.

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