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Review Article

A Review of Hepatitis C Virus (HCV) Co-Infection with HIV

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Abstract

Aim: Hepatitis C Virus (HCV) Co-infection with HIV is a fairly common occurrence. Most studies have determined that usually 1/3 of a population of HIV positive individuals are co-infected with HCV. It is a serious condition in terms of the dual infection itself and treatment options. The aim of this article is to highlight the important aspects of this co-infection and possible treatment options.

Method: Personal observation and research. Desk top search.

Results: HIV/HCV co-infection is a condition which has been found to have general effects and systemic effects e.g. on the kidney, nervous system, skeletal system, immunological and cardiovascular systems.

Conclusion: If this condition is not recognized and treated promptly but with necessary caution it may negatively affect the treatment outcomes of HIV patients in terms of morbidity and mortality. Thereby rolling back the effect of HAART which essentially converted the diagnosis of HIV/AIDS from a death sentence to a chronic ailment.

Keywords: Co infection; HCV; HIV; HIV/HCV; Transmission

Introduction

Co-infection and opportunistic infections are a major source of concern in HIV positive patients on Highly Active Antiretroviral Therapy (HAART). The hepatitis viruses are of particular importance and also the re-emergence of Tuberculosis in parallel with incidence of HIV. Hepatitis C Virus Co-Infection (HCV) with HIV though less common than hepatitis B virus co-infection with HIV is considered a major source of public health concern. This is due to the effect of HIV on the life cycle of HCV and subsequently on the hepatic system.

The mechanisms underlying accelerated liver disease in hepatotropic viruses/HIV co-infected individuals are poorly understood but may include the following: direct viral effects on hepatocytes and hepatic stellate cells, and immunologic alterations such as immune activation, apoptosis and diminished HCV specific T-cell responses. Also to be considered is the liver toxicity of antiretroviral drugs and the burden of metabolic diseases contributing to a faster progression of liver fibrosis in HIV/ HCV co-infection. HIV immune activation induces cytokine changes (e.g., IL -4, IL -5, and IL -13, TGF -β) that increase liver inflammation and fibrosis.

Co-infection also increases apoptosis of hepatocytes through a Fas/Fas L pathway that could account for accelerated liver disease. Accumulation of Cytotoxic CD8 T cells in the liver that increases inflammatory mediators in co-infected compared to HCV mono infected patients may also lead to increased tissue damage in co-infected patients. Recent evidence shows HIV-specific CD8 T-cells accumulate in the liver in co-infection and produce TNF -∞, which is associated with liver fibrosis.

The reported prevalence of HIV/HCV co infection notoriously varies significantly among studies even within the same geographical location, suggesting that an environmental factor probably hygiene is operating but this is yet to be confirmed. HIV and HCV are both transmitted through parental, sexual and vertical exposure but differ in the transmission efficiencies of these routes. The parenteral routes being more efficient for transmission of HCV hence nosocomial infections caused by this virus and intravenous drug users being more susceptible to HCV infection than HIV.

However, it appears though that the effects of co infection with these viruses on the liver are somewhat limited to developed countries or the western world. This could be considered to be a wide assumption however numerous reports of severe hepatic damage have been cited in Europe and America but very little from Africa. The majority of studies carried out in Africa are mainly descriptive and do not reveal actual incidence rates or occurrence of liver disease as opposed to HCV prevalence in these patients, some studies even report hepatoxicity as being uncommon. In a study carried out in southwest Nigeria in 2013, the prevalence rate of HCV among HIV patients in our facility was found to be 23.3%. It is generally accepted that one third of HIV patients are co-infected with HCV. Three years later of all the co-infected patients screened at the time none had developed any significant clinically overt liver damage. The main findings among them was a persistently low CD4 count despite being on highly active antiretroviral therapy (HAART including Zidovudine, Lamivudine and Nevirapine) which is not unexpected and mildly raised liver enzymes (serum aspartate transaminase and serum alanine transaminase). None were on treatment for the HCV component of the co-infection. Though liver biopsy and histology is the gold standard for detecting liver fibrosis it is invasive and has associated complications such as pain and bleeding. It may be necessary however to further subject these patients to more studies such as AST to platelet ratio index (APRI) and transient hepatic elastography a simple non invasive method which measures liver stiffness. The results of all these tests combined may give a clearer picture of the situation in the developing world. The limitation here is a pernicious lack of funds despite being a country with vast oil fields and now unfortunately the price of oil is at an all-time low to further compound the problem of health care among this subset of patients.

Human immune deficiency infection has a negative impact on the natural history of HCV infection as already stated, including a higher rate of viral persistence, increased viral load, and more rapid progression to fibrosis, end-stage liver disease, and death. Over time it has become one of the most important co-morbidities regarding HIV infection, such that a comprehensive discussion of HCV which omits its relationship with HIV could be regarded as being incomplete.

The hepatitis C virus is a member of the hepatic viruses and is transmitted most efficiently among intravenous drug users and also as nosocomial infections from hospital procedures. However, it could also be transmitted sexually similar to HIV. Hence the increasing emphasis that HIV positive patients should be screened for HCV at baseline investigation. The point to be made here is to emphasize that though HCV and HIV have similar routes of transmission (sexual and parenteral), it should be noted that HCV is transmitted more efficiently through certain routes (parenteral) while HIV is also transmitted more efficiently through certain routes(sexual). There is then the overlap of infection routes. Hence the need for every facility to perform a baseline screening for the hepatitis viruses (A, B, C, E) once a patient has tested positive for HIV. This cannot be over emphasized.

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense virus. The genus consists of a single open reading frame that is 9600 nucleotide bases long [1] It is a member of the *Hepacivirus* genus in the family Flaviviridae.

There are six major genotypes of HCV (1-6), with several subtypes within each genotype represented by lower case letters [2,3]. Genotypes differ by 30-35% of the nucleotide sites over the complete genome [4]. The difference in genomic composition of subtypes of a genotype is usually 20-25%.

Subtypes 1a and 1b are found worldwide and cause 60% of all cases. Evolutional studies have suggested that the virus spread from the developed world to the developing world mainly by traders. The genotype 2 strains from Africa can be divided into four clades that correlate with their country of origin: (1) Cameroon and Central African Republic (2) Benin, Ghana and Burkina Faso (3) Gambia, Guinea, Guinea-Bissau and Senegal (4) Madagascar [5,6]. There is also strong evidence now for the dissemination of (HCV) genotype 2 from West Africa to the Caribbean by the Trans-Atlantic slave trade. Once introduced to a country its spread has been influenced by many local factors including blood transfusions, vaccination programmes, and intravenous drug use and treatment regimes. Again, here we can identify the close association of transmission of HCV with parenteral routes. A low risk of sexual and vertical transmission has been established unlike for HIV [7].

Given the reduction in the rate of spread once screening for Hepatitis C in blood products was implemented in the 1990s it would seem that at least in recent time's blood transfusion had been an important method of spreading this virus. The half-life of the virus particles in the serum is around 3 hours and may be as short as 45 minutes. In an infected person, about $10^{[12]}$ virus particles are produced each day. In addition to replicating in the liver the virus can multiply in lymphocytes. HCV is a well known cause of hepatocellular carcinoma (HCC) and is also associated with the aetiology of the lymphomas. The lymphomas are a very important group of lymphoproliferative malignancies with a significant frequency of occurrence in this part of the world (Sub-saharan Africa). Sixty percent (60%) of childhood malignancies in this region are caused by Burkitts lymphoma. A particularly aggressive form of lymphoma, it is the fastest growing tumor known to man with a doubling time of about 24 hours and a growth potential of approximately 100%.

The human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) that causes HIV infection and over time acquired immunodeficiency syndrome (AIDS) [8,9]. AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic

infections and cancers to thrive. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype [10]. Infection with HIV occurs by the transfer of blood, pre-ejaculate, semen, vaginal fluids, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

Having firmly established the preferred routes and overlap of these routes of transmission of the two viruses which explains why they would tend to occur together, it is necessary to analyze the pathology of the viruses and why they can be toxic and fatal when occurring together in the same individual. Starting out it should be mentioned that HIV patients who are co-infected with HCV have delayed sero-conversion in that there is a delay in the production of anti-HCV antibodies and this may lead to delay in diagnosis of HCV co-infection and ultimately delay in treatment which could mean poor treatment outcomes and poorer prognosis. Having said this it may be necessary to deliberately delay treatment of HCV to allow the highly active antiretroviral therapy(HAART) enhance regeneration of the liver in order to withstand any further assault.

This is why it is recommended that when there is a clinical suspicion of recent HCV infection together with raised alanine transaminase infections the patient be screened for HCV RNA by reverse transcriptase PCR (RT-PCR). An outline of this write up would include the effect of HCV on HIV disease progression. This would be followed by a systemic approach including the hepatic system (liver disease in the setting of HIV/HCV co-infection), the immune system, and renal system, cardiovascular and neurological systems. Such a discussion would be incomplete without a review of current anti-HIV and HCV therapies concluding with an examination of proposed new treatment strategies.

Despite a reduction in morbidity and mortality in HIV-positive patients on highly active antiretroviral therapy (HAART), there has been an increase in liver related deaths and this has been attributed to co-infection with HCV. HCV associated liver disease including fibrosis, cirrhosis and end stage liver disease (ESLD) is accelerated in HIV positive individuals. Progression to cirrhosis is three times higher in co-infected than mono infected patients. [11]. It is important to note that severe liver fibrosis and cirrhosis despite normal levels of serum alanine aminotransferase (ALT) was determined in a study of co-infected HCV viraemic patients [12,13]. This demonstrates the diversity with which these co-infected patients may present clinically and in the laboratory such that it is often necessary to combine findings from the two sources to reach a firm diagnosis. Hepatic steatosis (HS), a common complication of HCV mono-infection and HCV/HIV co-infection is associated with rapid progression of fibrosis, but not necessarily more common in co-infected than HCV monoinfected individuals [14].

HS is associated with increased body mass index, diabetes, elevated ALT levels, HCV genotype 3, necro inflammation and fibrosis [14,15]. The processes by which liver disease is accelerated in these co-infected individuals is not well understood. However various mechanisms have been proposed which include direct viral effects and immunological changes, such as immune activation, apoptosis, and diminished HCV specific T-cell responses. Immune activation by HIV induces cytokine changes (eg IL-4, IL-5, IL-13 and TGF-β) that increase liver inflammation and fibrosis [16,17]. HIV/HCV coinfection increases apoptosis of hepatocytes through a Fas/FasL pathway that can account for accelerated hepatic disease. In co-infection (HIV/HCV) compared to mono-infection with HCV, there is increase cytotoxic CD8+ cells that leads to an increase in inflammatory mediators which could also lead to increased tissue damage within the hepatic cytoarchitecture. It is confirmed that these CD8+ cells produce TNF-α, which is associated with liver fibrosis. Recently, HIV-related microbial translocation that causes systemic activation has been linked with severity of HCV-related liver disease [17-19]. In addition to infection, HIV proteins induce hepatocytes to apoptosis and release of inflammatory chemokines and cytokines that promote fibrosis. Further, HIV and HCV co-infection may increase tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)-mediated apoptosis of hepatocytes [16,17,20].

This group of patients are prone to diabetes mellitus as it is known that those with liver fibrosis and hepatic steatosis (HS) develop insulin resistance (IR). The mechanism for IR in liver disease among HCV-infected patients is unknown, but hyperinsulinemia and hyperglycemia stimulate hepatic stellate cells (HSC), leading to increased connective tissue growth factor and accumulation of extracellular matrix [21]. Although the gold standard for determination of liver fibrosis is the liver biopsy, however alternatives to this method are being sought because it is invasive, associated with serious complications, sampling error and inherent heterogeneity. Promising alternatives include transient elastography/elastometry(TE) and serological biomarkers. TE is well tolerated and can accurately stage fibrosis and cirrhosis by using ultrasound readings to measure liver elasticity or stiffness. TE may also be useful in those with normal aminotransferase levels.

Serological biomarkers associated with staging of liver fibrosis can be classified into three groups 1) indices from routine blood tests of liver function [eg, APRI (aspartate aminotransferase [AST]-to-platelet ratio index) and Fib-4 (age, AST, platelets, and ALT level)]; 2) markers of extracellular matrix metabolism (eg, hyaluronic acid); and 3) indices combining markers of both types [22]. These are valid markers of liver fibrosis and predictive of HCV-related liver mortality in monoinfected and co-infected individuals [23,24].

DNA microarray analysis to identify novel biomarkers to assess fibrosis [25] and MRI to measure steatosis and predict adipose tissue and metabolic factors associated with steatosis in co-infected patients [26] are other promising noninvasive technologies.

Other complications of HCV/HIV coinfection include immune dysregulation and other haematologic disorders. Though B cells are activated by HCV and HIV and induced to synthesize cryoglobin [27] recent studies have found only a marginal effect of this with HIV infection.

A large retrospective study found HCV co-infected patients had lower C-reactive protein (CRP) levels than HIV monoinfected patients, suggesting that HCV decreases the liver's ability to secrete CRP [28]. HIV-associated thrombocytopenia remains an important problem in the HAART era and is associated with cirrhosis but also HCV infection without serious liver disease [29]. This may be an important consideration in staging liver disease using APRI, which is calculated using platelet count.

Kidney Disease

There is evidence of kidney involvement by the observation of proteinuria and acute renal failure in HCV coinfected patients compared to monoinfected patients. Also, there is evidence of increase in chronic disease rates together with worsening of glomerular filtration rate. HCV/HIV associated nephropathies and reduced survival compared to monoinfected patients [30-32].

Cardiovascular Disease

There is a higher incidence of cardiovascular disease (CVD) in co-infected compared to monoinfected patients. HCV co-infection is associated with increased risk of cerebrovascular disease and a trend toward increased risk of acute myocardial infarction among HIV-infected patients. These group of patients have an increased CVD risk because HAART and HIV-associated chronic inflammation can cause endothelial dysfunction. Circulating soluble cellular adhesion molecules (CAMS) released by the vascular endothelium, including soluble intercellular adhesion molecule-1 (sICAM-1) and vascular adhesion molecule-1 (sVCAM-1), are higher in co-infected patients stably treated with HAART than healthy controls. HAART can lower sICAM-1 and sVCAM-1, suggesting that HAART can improve endothelial cell function and decrease CVD risk by decreasing plasma HIV-RNA levels, increasing T-cell number and function, and decreasing immune activation. Patients with advanced HCV infection have higher levels of sICAM-1 and sVCAM-1, suggesting that HCV infection also causes endothelial dysfunction, and response to HCV treatment might reduce CVD risk [33,34].

Neurological Status

HIV and HCV can replicate both in the brain and the cerebrospinal fluid (CSF), leading to neurocognitive and peripheral neuropathy syndromes. In co-infected patients there is significant cognitive-motor impairment compared to HIV monoinfected patients and higher rates of global cognitive impairment, especially in learning and memory. HCV, RNA and antigens have been found in brains of co-infected patients. HCV core proteins activate human glia and contributes to HIV-associated neurotoxicity.

Plasma lipopolysaccharides (LPS), indicators of microbial translocation from the gut, induce monocyte activation in HIV infection and may contribute to HIV-associated dementia (HAD) by increased trafficking of activated monocytes into the brain. That LPS levels are higher in HCV co-infected patients suggests that HCV may influence HAD pathogenesis [35-39].

Because sensory neuropathy (SN) is a common complication of HIV infection and certain HIV treatments and is associated with HCV infection, there are concerns about possible synergistic effects of these viruses on the peripheral nervous system [40]. However, a survey among HIV-infected patients in six international sites found HCV sero-positivity was not associated with increased SN risk [40].

Diabetes Mellitus

It has been found that HIV in itself does not pose an increase risk for diabetes mellitus (DM) , however co-infection with HCV and associated higher HCV RNA levels are associated with increased risk for DM and as such it is suggested such patients are screened for DM [41,42].

Skeletal Complications

Studies have shown that co-infection (HCV/HIV) has contributed more to reduced bone mineral density (BMD) and osteoporosis than in patients uninfected with either virus or those monoinfected with just HIV. More recent studies have revealed that HCV mono-infection with hepatic decompensation are more likely to develop low BMD than in those with HCV mono-infection but with normal hepatic function. This further emphasizes the link between calcium level determination and investigation of hepatic activity using bilirubin levels in addition to liver enzymes. It may be interesting at this point to mention the concept of hepatic osteodystrophy (HO) which is thought to be implicated in the reduced BMD associated with HIV/HCV co-infected patients. HO refers to the destabilization in bone mineral density found in patients with chronic liver disease (CLD). The alterations in BMD usually include osteopenia and or osteoporosis. It has already been mentioned that the hepatitis C component of HIV/HCV co-infection is an important cause of varying degrees of hepatopathy including fibrosis, cirrhosis and hepatic carcinoma [43] Active monitoring of co-infected patients skeletal surveys is necessary to prevent pathological fractures.

The timing of initiation of HAART in relation to anti-HCV therapy in co-infected patients poses challenges for clinicians. HAART may slow liver disease progression and might therefore be initiated earlier in co-infected than HIV monoinfected patients . On the other hand, HAART might increase fibrosis in co-infected patients through cumulative hepatotoxicity . Recent guidelines recommend that HAART generally be initiated first to slow liver

disease progression and increase CD4 count, but certain drugs should be avoided (eg, ZDV, didanosine, stavudine, and abacavir) and others should be monitored for hepatoxicity. Although HAART interruption is deleterious to the HIV-infected population, the first randomized study of HAART interruptions in HCV co-infected persons found that interruption was particularly unsafe in co-infected persons because of elevated non-opportunistic disease and death, though not liver disease death [44,45].

Treatment of chronic HCV in co-infected individuals is a priority because of their more rapid progression to ESLD, poor tolerance of HAART, and greater risk of hepatoxicity. Clearance is associated with regression of liver fibrosis and reduced risk of HAART hepatoxicity. However, anti-HCV treatment is less effective in co-infected patients.

HCV treatment guidelines for co-infected patients are published, but there is a lack of consensus regarding key factors that might inform initiation and duration of therapy, including stage of HIV and HCV disease and viral load, HCV genotype, degree of hepatic fibrosis, and patient's readiness to tolerate and adhere to treatment. These have clinical importance because they influence safety, tolerability, and success of therapy. Investigations continue to identify better predictors of treatment response that could guide the pretreatment evaluation process and permit earlier termination of ineffective treatment, reducing additional cost and adverse effects of ineffective therapy. There are no guidelines for the clinical management and treatment of co-infected children, and the limited experience in their management and lack of evidence base to guide policy is a barrier to achieving optimal care [46-49].

The current standard treatment is pegylated interferon and ribavirin (pegINF+RBV) in both monoinfected and co-infected patients. There are guidelines that recommend a fixed course of 48 weeks to optimize HCV treatment in co-infected patients. A recent study explored response – guided therapy with duration based on virologic response at treatment weeks 4,12,24. The results were encouraging with up to 55% achieving a sustained virologic response (SVR). For those who failed a prior suboptimal treatment regimen retreatment with pegIFN+RBV for 12 months achieved a SVR in almost 1/3 of cases, an encouraging outcome in the light of earlier studies with lower retreatment response rates.

The best predictors of treatment outcome are virologic response kinetics, including rapid viral response (RVR), defined as HCV viral load below the level of detectability 4 weeks after treatment initiation, early viral response (EVR), defined as undetectable HCV load or a 2 log drop from baseline 12 weeks after therapy initiation, and SVR, defined as undetectable HCV load 24 weeks after therapy completion. While undetectable HCV RNA at week 4 is the best predictor of SVR in co-infected patients, baseline serum HCV RNA is an independent predictor of SVR in HCV genotype 1 patients. Although these predictors use absence of serum HCV RNA as the marker of treatment success, negative-strand HCV RNA in PBMCs in the absence of plasma HCV RNA has been reported [50-52].

Results of investigations of impact of baseline CD4 count on viral response kinetics are mixed. In a large randomized study of pegIFN + RBV in co-infected patients that included a small number of patients with CD4 counts <200 cells/μL, SVR rates tended to increase with higher CD4 counts in genotype 1, but were independent of baseline CD4 counts for genotypes 2/3. Another large randomized study of co-infected patients found the efficacy of pegIFN + RBV was not different in patients with and without severe immunodeficiency, suggesting that advanced immunosuppressant is not a major factor in predicting SVR [53,54]. In the AIDS Clinical Trials Group (ACTG), HCV quasispecies complexity was an important predictor of treatment outcomes, with lower baseline complexity associated with EVR and a decrease in complexity by 4 weeks associated with RVR. Extrahepatic replication in B, CD4, CD8, and NK cells at the end of 48 weeks of treatment has predicted viral relapse and, although the assays are cumbersome, they might identify patients whose treatment should be extended to 72 weeks [55] IFN-related adverse events (AEs), specifically CD4 cell declines and psychiatric effects, are reported to be more common in co-infected virologic responders than non-responders [56]. Also, with successful IFN therapy, alterations in cytokine pools necessary to improve immune function may have negative effects in the brain by traversing the blood–brain barrier [56].

The first meta-analysis of sex difference in AEs in co-infected individuals showed that women were more likely to develop AEs requiring treatment discontinuation or dose modification and to develop them earlier, but the types of AEs were similar [57] .Women on NNRTIs were more likely to discontinue therapy, and women on AZT were more likely to experience AEs, suggesting that in women antiviral regimen is an important predictor of treatment discontinuation and modification.

Early HAART may protect co-infected patients from liver fibrosis progression. HAART can significantly decrease liver HCV necroinflammatory activity in co-infected patients with relatively preserved immune status, possibly by inhibiting HIV replication in the liver or decreasing level of proinflammatory cytokines. In vitro, the HIV protease inhibitor nelfinavir inhibits HCV replication at concentrations showing no cytotoxicity and acts synergistically with IFN against HCV, suggesting that nelfinavir could improve the antiviral effects of IFN in co-infected patients [58,59].

Some ART medications, especially abacavir, may compromise the response to anti-HCV therapies, perhaps by competing intracellularly with RBV [59] However, a large cohort study did not find an association of abacavir or other ARTs with reduced EVR or SVR [60].

The combination of HAART and pegIFN + RBN may also increase the frequency of AEs. HCV therapy with zidovudine

(ZDV) has been associated with higher anemia rates. RBV with NRTIs such a didanosine has been associated with increased risk of mitochondrial toxicity (MT) and worsening steatosis/fibrosis [61]. MT-associated laboratory abnormalities are frequent during pegIFN + RBV therapy in combination with HAART, especially when high RBV doses are used [61]. However, patients with signs of MT show faster decreases in HCV RNA levels and achieve higher SVR rates, probably because MT reflects increased intracellular RBV levels. Clinicians should be aware of potential interactions between NRTIs and RBV in co-infected patients, and increased lactate levels might be useful to adjust RBV dosage to optimal efficacy [61].

Co-infected patients may experience liver enzyme elevation (LEE) following HAART initiation [62]. CD4 T-cell increases early after HAART initiation were higher among co-infected patients who developed LEE than co-infected or monoinfected patients who did not develop LEE, suggesting that LEE early in HAART is a form of Immune Restoration Disease (IRD) or Immune Reconstitution Inflammatory Syndrome (IRIS) involving an immune reconstitution-induced inflammatory response to HCV-specific antigens [63]. The risk of LEE after HAART initiation is lower in co-infected patients with SVR to anti-HCV therapy, arguing for HCV treatment before commencing HAART. In contrast, an Italian multicenter study found that HAART is not a risk factor for LEE in co-infected patients and does not modify the association between co-infection and the risk of LEE [64]. As in HIV, triple-combination therapies may be more effective in achieving virologic cure and less prone to resistance development in monoinfected and co-infected patients. NS3 protease and NS5B polymerase enzymes, essential for HCV replication, are primary targets. Results for inhibitors targeting these enzymes (combined with pegIFN + RBV) are positive in clinical trials [65,66] and preclinical studies [67-69]. The most promising of these are the protease inhibitors telaprevir and boceprevir, which are expected to be approved this year [70,71]. Taribavirin, an oral RBV prodrug with significantly lower anemia rates, is in phase III trials [72].

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