Management Of Viral Hepatitis In HIV Seropositive Individuals

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Chronic hepatitis C affects more than 180 million people worldwide and in the USA about 2.7-3.9 million individuals are chronically infected with HCV, including 0.2 million people co-infected with HCV and HIV. Up to 86% HCV and HIV co-infection in injection drug users has been documented in India. Though some HCV infected patients clear their infection spontaneously, most become chronic carriers with risk of serious complications including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Hepatitis C is the leading indication for liver transplant in the USA and the major etiologic factor responsible for the recent doubling of HCC. Current therapy consists of pegylated interferon and ribavirin, which results in 70-80% sustained virologic response (SVR) in patients infected with genotypes 2 and 3 and SVR is significantly lower for genotype 1, at 29-56% which is the predominant genotype in the USA. Genotype 1 and 3 are the most prevalent HCV genotypes in India.

Hepatitis B and C have the same risk factors for transmission as HIV. Concurrent infection with HIV and hepatitis B and/or C is of great concern in the developed world where coinfection rates are as high as 89 per cent in some cohorts. In India, rates of co-infection with HIV and hepatitis B are reported between six and 33 per cent. In a study in the eastern state of Manipur, where intravenous drug use is high, 92 per cent of HIV-positive intravenous drug users (IVDUs) were coinfected with hepatitis C. In addition, in a study of slum residents in Chennai, IVDUs were almost 28 times more likely to be HCV infected than those denying injection drug use (IDU). In a predominantly non-IVDU population, HIV-HCV coinfection rates have been reported between 4.8 and 21.4 percent. End-stage liver disease caused by HCV is an important cause of death among HIV patients in the United States. In India, co-infection with hepatitis C has been found to be associated with almost an 8 fold increased risk of disease progression. Compounded by the prevalence of chronic alcoholism in HIV infected persons, and hepatotoxic drugs used in the treatment of HIV disease, co-infection with hepatitis B and C are important considerations in the management of patients with HIV. A study in south India of high risk individuals attending a HIV voluntary counselling and testing centers found the prevalence of hepatitis B and C to be 5 and 3 per cent, respectively. Because the prevalence of hepatitis B and C in HIV infected patients is generally low, routine baseline, testing for these viruses is not recommended unless the patient has a history of injection drug use, or has elevated transaminase levels.

HCV and HIV comorbidity is a global health concern. Both HIV and HCV shares common risk factors for viral transmission. Due to the introduction of highly active antiretroviral therapies, HIV-infected persons have a longer life expectancy than untreated infected persons. Consequently increased rates of cirrhosis and HCC have been observed in patients concurrently infected with HIV and HCV. HIV infection may directly or indirectly promote the development and progression of HCV diseases through its regulatory proteins and/or impairment of host immune surveillance. HCV-induced hepatitis complicates the HIV therapy by increasing the risk of liver toxicity and altering the rate of drug metabolism.

In India, HIV/HCV coinfection is mostly prevalent in
injection-drug users and sex workers \textsuperscript{29,8,28}. A study carried out in children born to HIV positive parents in North India revealed that 26.7\% of HIV infected children were co-infected with HCV \textsuperscript{6}. A 10 year follow-up investigation showed that children coinfected with HIV and HCV had two fold higher risk of progression to AIDS development and death \textsuperscript{27}. In India, the available HCV treatment option is too expensive to afford for many infected individuals. The prevalence of HIV/HCV coinfection, disease progression and viral co-evolution in Indian patients are currently unknown. Indian women acquire HIV infection mainly through sexual contact. Married women mostly contract through husbands who engage in high-risk behavior including injection-drug use, bi-sexuality and interaction with infected sex workers. Since both HCV and HIV are vertically transmitted, children of coinfected pregnant women have high risk of acquiring both the viruses. Detailed study on clinical management of HIV/HCV coinfection would provide insights to improve the quality of life by developing or modifying treatment and prevention strategies.

**Acute Viral Hepatitis**

**Hepatitis A** is an acute infectious disease of the liver caused by the hepatitis A virus (HAV) which is transmitted person-to-person by ingestion of contaminated food or water or through direct contact with an infectious person. Tens of millions of individuals worldwide are estimated to become infected with HAV each year. The time between infection and the appearance of the symptoms, (the incubation period), is between two and six weeks and the average incubation period is 28 days.

In developing countries, and in regions with poor hygiene standards, the incidence of infection with this virus is high and the illness is usually contracted in early childhood. As incomes rise and access to clean water increases, the incidence of HAV decreases. Hepatitis A infection causes no clinical signs and symptoms in over 90\% of infected children and since the infection confers lifelong immunity, the disease is of no special significance to those infected early in life. In Europe, the United States and other industrialized countries, on the other hand, the infection is contracted primarily by susceptible young adults, most of whom are infected with the virus during trips to countries with a high incidence of the disease or through contact with infectious persons.

HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease. However, 10\%-15\% of patients might experience a relapse of symptoms during the 6 months after acute illness. Acute liver failure from Hepatitis A is rare (overall case-fatality rate: 0.5\%). The risk for symptomatic infection is directly related to age, with >80\% of adults having symptoms compatible with acute viral hepatitis and the majority of children having either asymptomatic or unrecognized infection.\textsuperscript{6} Antibody produced in response to HAV infection persists for life and confers protection against reinfection. The disease can be prevented by vaccination, and hepatitis A vaccine has been proven effective in controlling outbreaks worldwide.

**Hepatitis A Treatment**

There are no specific medicines to cure infection with hepatitis A. Most people require no treatment except to relieve symptoms. If you have been exposed to someone who is infected with HAV, there is a treatment that may prevent you from becoming infected. It is called immune globulin and is more likely to be effective when given within 2 weeks of exposure.

**Clinical History:** Symptoms including; weight loss, loss of appetite, fever, chest pain, dyspnoea, cough, haemoptysis, night sweats, numbness or tingling in hands or feet, diarrhea, blood in stool, oral ulcers, visual disturbances, headaches, painful swallowing, difficulty in swallowing, skin rash, type of rash (a=Macular-papular b=Petechial), swollen lymph nodes, fatigue, abdominal pain, jaundice, itching, flu-like symptoms, bruising and bleeding tendency, cognitive impairment, history suggestive of a. vasculitis, b. bullous skin lesions, c. skin thickening, d. increase or decrease in urine output, jaundice, haematemesis, and malena.

**Hepatitis E** is a viral hepatitis (liver inflammation) caused by infection with a virus called hepatitis E virus (HEV). HEV is a positive-sense single-stranded RNA icosahedral virus with a 7.5 kilobase genome. HEV has a fecal-oral transmission route. It is one of five known hepatitis viruses: A, B, C, D, and E. Infection with this virus was first documented in 1955 during an outbreak in New Delhi, India. Although it was originally classified in the Caliciviridae family, the virus has since been classified into the genus Hepevirus, but was not assigned to a viral family. The virus itself is a small non-enveloped particle. The genome is approximately 7200 bases in length, is a polyadenylated single-strand RNA molecule that contains three discontinuous and partially overlapping open reading frames (ORFs) along with 5’ and 3’ cis-acting elements, which have important roles in HEV replication and transcription. ORF1 encode a methyltransferase,
protease, helicase and replicase; ORF2 encode the capsid protein and ORF3 encodes a protein of undefined function. A three-dimensional, atomic-resolution structure of the capsid protein in the context of a virus-like particle has been described. An in vitro culture system is not yet available. As of 2009 there are approximately 1,600 sequences of both human and animal isolates of HEV available in open-access sequence databases.

**Treatment List for Hepatitis E**
The list of treatments mentioned in various sources for Hepatitis E includes the following list.
- Watchful waiting - HepE often resolves itself within weeks.
- Supportive care - fluids, rest
- Prevention - clean drinking water, personal hygiene

**Treatment Chronic Viral Hepatitis**

**Treatment for HCV and HIV mono infection or coinfection.**
HIV infected patient group will undergo standard anti-retroviral therapy regimen. HCV infected patients with or without HIV will receive peginterferon alfa-2a at a fixed dose of 180 µg/week for 48 weeks, together with ribavirin 1,000 to 1,200 mg daily based on body weight. After completion of the study, the patients will be followed up for 24 weeks. The combined use of peginterferon alfa-2a and ribavirin is approved by the FDA for treatment of hepatitis C in HIV-infected persons. The HIV clades and HCV genotype information will be taken into account. For HCV isolation baseline serum will be obtained before the commencement of treatment. During treatment 1, 3, 6, 9 and 12 month serum will be used for HCV isolation. The cohort will receive standard medical care (26). Hematological, immunological (CD4+ count), serum chemistry, abdomen scan for liver cirrhosis or HCC and liver function tests will be performed regularly to monitor adverse side effects. In the event of drug-mediated adverse effects either dose modification or treatment discontinuation will be considered. Since ribavirin potentiates the toxicity of anti-retroviral drugs azidothymidine (AZT) and didanosine (DDI), the AZT and DDI will not be combined with ribavirin. The HIV and HCV viral load will be monitored by RT-PCR and ELISA. Liver biopsy or alpha-fetoprotein level in the serum will be monitored in every 6-12 months to assess cirrhosis and HCC. The serum of the study patients will be stored at -80°C until used for isolation of infectious HCV or HCV genomic RNA for functional characterization. During the study period rapid viral response (RVR), early viral response (EVR), and sustained viral response will be evaluated. Data will be subjected to Statistical analysis.

**Treatment for HBV infection**
Universal vaccination against HBV is effective in preventing the transmission of disease. In Canada, where chronic HBV infection is largely a disease of immigrants, some provinces offer neonatal vaccination, while others offer preadolescent vaccination. Because chronic HBV is the largest reservoir for the transmission of disease, neonatal vaccination may be preferable in provinces with a high proportion of immigrants from areas of the world highly endemic for HBV. In these populations, horizontal transmission in childhood is more likely.

In neonates, the use of the HBV vaccine and HBV immune globulin is highly effective in preventing HBV transmission. Furthermore, once infected, the risk of a neonate developing chronic infection is greater than 90%. Therefore, screening of pregnant women in the third trimester of pregnancy for hepatitis B surface antigen (HBsAg) is mandatory. There are also Canadian economic data indicating that this is a highly cost-effective strategy.

**Assessment**
Baseline assessment should include HBV serology (HBsAg/anti-HBs, hepatitis B e antigen [HBeAg]/anti-HBe), and tests of disease activity (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and disease severity (clinical evaluation, albumin, prothrombin, bilirubin and complete blood count). Viral replication (quantitative HBV-DNA measurement) should be measured in patients with evidence of active disease (elevated ALT) (Level A; II). Liver histology, although not mandatory, is highly recommended in patients with active disease (Level A; II). Patients with mild disease may not require treatment despite active viral replication.

All HBV carriers should be offered testing for anti-HIV antibodies (Level A; I). Although the prevalence of HIV is low in some populations (eg, South East Asians), the impact of monotherapy with lamivudine, adefovir or tenofovir in a patient with undiagnosed HIV infection is great due to the potential for the HIV to develop drug resistance. Anti-HCV antibodies should also be measured because HBV-HCV coinfection may impact on the selection of treatment (Level A; I).

Hepatitis A (HAV) vaccination is recommended in patients with chronic HBV (Level B; II).
HBV and hepatocellular carcinoma
Because of the increased risk of developing hepatocellular carcinoma (HCC), it is recommended that patients with chronic HBV undergo regular surveillance to detect early HCC (Level C; III). However, the risk is not equal in all infected individuals. Patients with established cirrhosis are at highest risk, but patients with noncirrhotic liver disease may also be at risk. Patients who have been documented as having inactive disease for many years and who are not cirrhotic (usually anti-HBe-positive and usually white) are at much lower risk (Level A; II). Such patients may not require surveillance.

Although there is no evidence that surveillance for HCC reduces disease-specific or all-cause mortality, surveillance with abdominal ultrasound and serum alphafetoprotein every six months is common practice. However, what little evidence exists suggests that annual surveillance is just as effective.

Who should be treated?
Acute HBV infection does not require antiviral therapy (Level B; III).

HBV-infected individuals, whether HBeAg-positive or HBe-negative with elevated AST and/or ALT, and HBV-DNA levels greater than 100,000 copies/mL are candidates for therapy (Level A; I). When the HBV-DNA is less than 100,000 copies/mL, the likelihood of HBV-induced injury is thought to be low. The distinction between HBeAg-positive and HBeAg-negative patients may impact on the choice and duration of therapy. The decision to treat or not may also be influenced by the severity of disease on liver biopsy.

Observation without treatment is appropriate in patients with mild disease. However, such patients should be followed at close intervals.

How should response to treatment be assessed?
Response to treatment can be defined virologically or biochemically. A complete virological response is defined as the sustained loss of HBsAg after treatment, but this occurs only rarely (Level I). In HBeAg-positive carriers, a partial virological response is defined as the sustained loss of HBeAg with gain of anti-HBe after treatment (HBeAg seroconversion). An alternate endpoint for a partial virological response is a decrease in serum HBV-DNA to less than 100,000 copies/mL. A biochemical response is defined as a normalization of serum AST and ALT. Liver biopsy is not mandatory to assess treatment efficacy (Level B; II). Response is initially assessed while on therapy (on-treatment response). For patients treated with time-limited regimens (eg, interferon), response is also assessed after completion of therapy. The optimal time post therapy for assessing this response has not been defined. The utility of determining HBV genotype needs to be explored, as it may impact on treatment efficacy.

What treatment should be used?
Lamivudine and interferon are both acceptable as initial treatment (Level A; I).

Interferon in HBeAg-positive patients:
Treatment should consist of 10 million international units (MIU) interferonalpha subcutaneously three times per week (TIW) or 5 MIU subcutaneously daily for 16 weeks (Level I). Some believe that longer duration therapy (up to 24 weeks) may be justified in selected cases, such as those with high viral loads (greater than $10^8$ copies/mL). A partial virological response (HBeAg seroconversion) may be expected in 25% to 40% of patients six months after the completion of therapy. Response rates are decreased in the presence of high viral loads (greater than $10^8$ copies/mL), mild hepatic inflammation (AST or ALT less than 1.5 x the upper limit of normal [ULN]), age over 40 years, presence of cirrhosis and male sex.

The durability of HBeAg seroconversion after interferon treatment in white populations is high (68% three years after stopping therapy) (Level II). However, in other populations (eg, South East Asian), the durability of seroconversion may be lower (Level III).

In white populations, interferon therapy has been shown to enhance overall survival and complication-free survival in HBeAg-positive patients who maintain post-treatment seroconversion (Level II). The effect of interferon therapy on survival in Asian populations may not be as pronounced.

Interferon may be more appropriate than lamivudine as initial treatment in young patients, particularly in the absence of cirrhosis, but there is no consensus on this issue. One rationale is that it may be preferable to use a time-limited form of therapy in a young patient who may otherwise have to be on therapy for many years, and who can tolerate the side effects of interferon.

Interferon in HBeAg-negative patients:
The recommended dosage of interferon is 5 MIU TIW.
subcutaneously to 10 MIU TIW subcutaneously for one to two years. The response rate is lower than for HBeAg-positive patients, and the durability of response is also less well established (Level II).

**Lamivudine in HBeAg-positive patients:**
The recommended dosage is 100 mg subcutaneously daily for up to five years or more, until a partial virological response (HBeAg seroconversion) occurs, or until lamivudine resistance develops (Level I). A partial virological response (HBeAg seroconversion) can be expected in 18% to 25% of patients within the first year of therapy, rising to approximately 60% after three years of therapy.

The durability of HBeAg seroconversion after lamivudine is not as good as after interferon therapy. Continuing treatment for six months after seroconversion may improve the durability of seroconversion (Level II).

There are several areas of uncertainty concerning lamivudine resistance. Phenotypic resistance is defined as the reappearance of HBV-DNA following initial disappearance using a nonpolymerase chain reaction (non-PCR)-based assay, or by a rise in HBV-DNA concentration to greater than 100,000 copies/mL in a PCR assay. Genotypic resistance refers to the demonstration of mutations in the YMDD motif of the HBV polymerase gene. Patients with phenotypic resistance have a 97% probability of having genotypic resistance and, therefore, the utility of confirming phenotypic resistance by genotyping is unclear. Once resistance occurs (approximately 60% after four years of therapy), it is unclear whether lamivudine should be withdrawn. Disease severity does appear to progress once resistance develops, but it is uncertain whether the rate of progression is slower than in the absence of lamivudine. HBeAg seroconversion has also been reported after the development of lamivudine resistance. There is also a concern that lamivudine withdrawal may precipitate a flare of hepatitis, which could be fatal in patients who have underlying cirrhosis. However, the evidence supporting this is only anecdotal. No recommendation can be made regarding whether lamivudine should be withdrawn once resistance develops. Once lamivudine resistance has developed, patients can be offered treatment with interferon (if they have not previously failed interferon) or adefovir dipivoxil (see below).

**Lamivudine in HBeAg-negative patients:**
In HBeAg-negative patients, lamivudine is used at the same dosage (100 mg by mouth daily) (Level I). The optimal duration of treatment is uncertain. For patients with a biochemical and virological response (eg, normal AST, ALT, and HBV-DNA less than 100,000 copies/mL) on therapy, there are no guidelines as to when treatment should be stopped. In patients in whom treatment is stopped after one year, the relapse rate is high, and possibly no more than approximately 13% of patients remain in remission. Possible end points for stopping treatment might be negative HBV-DNA by PCR or negative hepatitis B core antigen on liver biopsy. Similarly, it is unclear whether treatment should be stopped or continued once lamivudine resistance develops. However, as in patients with HBeAg-positive chronic HBV, the options to use interferon or adefovir remain.

**Adefovir dipivoxil**
Adefovir dipivoxil is a new nucleotide analogue that is effective in both treatment-naïve and lamivudine-resistant HBV infection (Level I) that will soon be available in Canada. Although initially studied as first-line therapy for chronic HBV, its role as first-line treatment in patients remains unclear. It seems to be less effective than lamivudine in inducing HBeAg seroconversion, and may also be less potent in inducing viral suppression. Its use as a first-line drug may also be limited because of cost considerations. It is indicated for therapy of lamivudine-resistant infection and in patients who have failed to respond to lamivudine initially and who do not tolerate or have failed interferon. Because adefovir is a new therapy, there are still several areas of uncertainty. Renal toxicity can occur in some cases and dose adjustments are required for patients with established renal disease. The rate of development of resistance to adefovir appears to be much lower than with lamivudine, but experience is limited. The durability of seroconversion in HBeAg-positive patients remains unknown. As with all forms of HBV therapy, flares of hepatitis can occur after cessation of therapy. Combination therapy with adefovir and lamivudine to limit the development of resistance (by analogy with HIV-positive patients) needs to be explored.

**Pegylated interferon**
The efficacy of pegylated interferon (peginterferon) in the treatment of HBV infection is being investigated, but the available data are too limited to allow specific recommendations to be made. Preliminary data suggest that the efficacy of peginterferon is at least comparable with that of standard interferon.
ART for Hepatitis B co-infected patients

The Technical resource Group on ART has recommended in August 2010 that in situations where there is evidence of confirmed Chronic active hepatitis & Hep B treatment is indicated, ART will be initiated irrespective of CD4 count. In situations where person is HBsAg positive but there is no evidence of Chr active hepatitis (or patient cannot be evaluated for the same), ART will be initiated when CD4 count is < 350 cells/mm3 (Harmonization principle). In both situations, it was decided that in order to prevent emergence of drug resistance to hep B, at least two ARV drugs active against Hep B will be used i.e. Tenofovir plus Lamivudine. It was also decided it will be better to use Efavirenz in these patients instead of Nevirapine due to increased chances of toxicity with the later.

REFERENCES


