

## Association of Hepatitis B & C with HIV / AIDS: Management Issues

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HIV and HBV coinfection is a new challenge to hepatologists, internists and infectious disease specialists that has emerged over last two decades. With both sharing similar modes of transmission and with the advent of highly effective antiretroviral therapy leading to longer survival of HIV positive patients HBV positivity has become common in HIV positive patients. In fact, of 33.3 million HIV positive patients worldwide (in 2009), 4 million had coinfection with HBV<sup>1,2</sup>. This simple data speaks volumes of the magnitude of the problem. With HIV taking pandemic scales in some part of the world, HIV and HBV coinfection is also taking significant proportion. Hepatitis C virus (HCV) infection has emerged as a major cause of morbidity and mortality worldwide. Owing to shared modes of transmission, 20–30% of HIV-infected patients in the are coinfecting with HCV.<sup>3</sup> Sexual transmission of HCV is less efficient than sexual transmission of HIV. However, among HIV-infected MSM without percutaneous risk factors, multiple outbreaks of acute HCV infection indicate that sexual transmission occurs in the context of high-risk sexual practices such as unprotected receptive anal intercourse; non-injection recreational drug use is also frequently reported.<sup>4</sup> Interestingly, the increased detection of sexual transmission of HCV corresponds to the documented increase in high risk sexual behaviours in MSM who have suppressed HIV replication from ART.<sup>5</sup>

In HBV endemic regions of Africa and Asia, the majority of HBV infection is vertically transmitted at birth or before the age of five years<sup>6</sup>. On the other hand in western countries, majority of infection are acquired by sexual transmission or by intravenous route<sup>2,7</sup>. These difference in modes of transmission is clinically important regarding preventive methodology and with increased coverage of HBV vaccination, we can expect a decrease in new HBV infection, especially in young infants.

HIV and HBV virus both influence each other's natural history and it has significant clinical and therapeutic importance. HIV accelerates HBV associated liver disease, especially when CD4 count is low and HIV RNA load is high. HIV has a strong tropism for hepatic stellate cells through chemokine receptors (CXCR4 and CXCR5) and exerts a direct cytopathic effects on liver<sup>8</sup>. Further more, HIV also triggers a pro-inflammatory cascade in liver leading to myofibroblastic differentiation, which may enhance fibrosis and cirrhosis in already damaged liver<sup>9</sup>. HIV infection promotes higher rates of chronicity after an acute exposure, greater levels of HBV replication in chronic carriers and lower levels of HBeAg or HBsAg seroconversion. Over all, the two major complications of HBV infection, namely cirrhosis and hepatocellular carcinoma are more prevalent in HIV positive patients<sup>10,11</sup>. In fact, in western countries, liver related complications have become a leading cause of death in HIV positive persons and HBV is a major contributor.

On the other hand, recent studies suggest that HBV coinfection impacts the natural history of HIV in terms of all-cause mortality<sup>12</sup>

and AIDS events<sup>13</sup>. In patients treated with HIV-HBV dual active drugs, interruption in therapy was associated with a fast decrease in CD4 cell count and further deterioration. At the same time, the HBV vaccine response rate and durability are low in HIV positive individuals and it is influenced by CD4 cell count and HIV RNA levels.

During management of HIV and HBV coinfection a few important issues come up. First of all we need to start first and hit hard. Amongst the antivirals against HBV, tenofovir, lamivudine, emcitabine, adefovir and entecavir have significant activity against HIV as well. In patients receiving combined ART the patient should receive tenofovir along with another nucleot(s)ide analogue having dual action, which most commonly is lamivudine or emcitabine. In patients with high CD4 counts and favourable HBV genotype (A) with low viral load interferon is a good option. Discontinuation of antiretrovirals with anti HBV activity causes severe hepatic damage due to reactivation of HBV replication. So, if antiretroviral therapy is to be modified proper substitution of antiviral with anti-HBV activity is to be done. During cART another concern is ART induced hepatotoxicity. However, with ART reducing liver-related mortality in HIV/HBV coinfection, it should not defer or postpone their use. Another important issue is emergence of drug resistance. Lamivudine has over the years been used as the only active drug against HBV, and this has led to significant amount of lamivudine resistance. In fact, some of these strains show cross resistance to other antivirals e.g. entecavir and adefovir. Development of resistance is characterized by liver enzyme flares. Transmission of drug-resistant strains is another serious issue. However, with introduction of tenofovir and with initiation of cART with two drugs against HBV, we can expect lesser incidence of resistant strains in near future.

HIV coinfection is associated with a ~ 6-fold increased relative risk of ESLD and a ~ 2-fold increased relative risk of cirrhosis compared to HCV mono-infection. In the absence of effective antiretroviral therapy (ART), HCV disease is worsened by coinfection with HIV and the treatment of HIV disease has generally been associated with a decreased risk of liver disease progression, particularly with the use of antiretroviral agents with a minimal risk of hepatotoxicity. Among persons with effectively controlled HIV infection, (defined as an HIV RNA levels < 400 c/ml and/or CD4 cell count > 500/mm<sup>3</sup>), the progression of fibrosis is similar in persons with and without HIV infection. However, despite the positive impact of ART, HIV/HCV coinfecting patients remain at greater risk of the progression of liver disease than those with HCV mono-infection.

The standard treatment of HCV in HIV-infected patients is PEG-IFN/RBV. In summary, HCV coinfection and use of PegIFN/RBV with or without HCV NS3/4A PIs (telaprevir or boceprevir) to treat HCV may impact the treatment of HIV because of increased pill burden, toxicities, and drug-drug interactions. Because ART may

slow the progression of HCV-related liver disease, ART should be considered for most HIV/HCV-coinfected patients, regardless of CD4 count. If treatment with PegIFN/RBV alone or in combination with one of the HCV NS3/4A PIs (telaprevir or boceprevir) is initiated, the ART regimen may need to be modified to reduce the potential for drug-drug interactions and/or drug toxicities that may develop during the period of concurrent HIV and HCV treatment. The science of HCV drug development is evolving rapidly.

So in a nutshell, the clinical management of HIV-HBV and HIV-HCV coinfection is an evolving paradigm. With newer antivirals being introduced, we are now in a position to treat these patients more effectively. Successful management of these patients require proper assessment of the patient's immune status and consideration of the fact that whether the patient requires management of HBV or HCV alone or requires management of HIV-HBV or HIV-HCV both concomitantly. Finally regular monitoring for drug resistance and hepatotoxicity of the drugs are to be done. Further studies are to be done to find out the potential role of entecavir PEG-IFN and telbivudine in the background of HIV-HBV coinfection.

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## DRUG PROFILE

### Metadoxine

The detection rate of alcoholic liver disease in China is approximately 4.34%. The mechanism of action of metadoxine on prevention and treatment of alcoholic intoxication may be associated with its protection of reduced glutathione and its enzyme system therefore, reducing the damage of free radicals caused by alcohol. Metadoxine can increase adenosine triphosphate (ATP) concentration in liver, speed up intracellular transportation of amino acids and antagonize inhibitory effect of alcohol on tryptophan oxygenase. Metadoxine can prevent fatty liver and hepatocellular necrosis by preventing hepatocellular redox imbalance and reducing the secretion of tumor necrosis factor to maintain a normal intracellular oxidation-reduction equilibrium. Therefore, in addition to speeding up metabolism blood alcohol, cleaning up and reducing direct and indirect toxicity of alcohol, metadoxine also has antioxidant properties. Thus, metadoxine is clinically used as an activator for aldehyde dehydrogenase for the treatment of acute and chronic alcoholic intoxication and alcoholic liver diseases due to its capabilities of speeding up the elimination of alcohol and aldehyde in the plasma. **Indications** include alcoholic fatty liver; non alcoholic fatty liver disease; acute and chronic alcohol intoxication; Metadoxine prevents fatty liver and hepatocellular necrosis by preventing hepatocellular imbalance; reduces the secretion of TNF. The drug restores reduced glutathione and its enzyme system; thereby, reducing the damage by free radicals caused by alcohol. **Conclusion:** Metadoxine can increase adenosine triphosphate (ATP) concentration in liver, speed up intracellular transportation of amino acids and antagonize inhibitory effect of alcohol on tryptophan oxygenase. Metadoxine can significantly improve liver function whether drinking is stopped or not.