Overview of HIV and Viral Hepatitis Co-Infection

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1. Context

Infections with HIV and viral hepatitis B and C are a global public health burden. Worldwide, there are approximately 33 million people living with HIV (PLHIV)\(^1\), 350 million people with chronic hepatitis B virus (HBV) infection\(^2,3\), and 180 million people with chronic hepatitis C (HCV) infection\(^4\). The number of people living with HIV-HCV co-infection is estimated to be 4-5 million\(^5\), but there are limited data on the number of people living with HIV-HBV or HIV-HCV-HBV co-infection. Both HBV and HCV infection are more common in PLHIV than in the general population, because of shared risk factors for viral acquisition\(^4\). HIV is transmitted through sexual contact, mother to child vertical transmission and blood and body fluids exposure. Both viral hepatitis B and C share the same routes of transmission as HIV although sexual transmission of HCV is less common than with HIV and HBV. Efforts to reduce the global burden of these three viral infections will need to continue to focus on these specific routes of transmission. The prevalence of these infections varies from country to country and Figures 1-3 identify the global variability of the epidemics.
Figure 1 Global Diversity of HBV Prevalence 2010 (CDC)

Figure 2 HCV Prevalence by WHO Region, 2004 Estimates
In the era of expanded programs for highly active anti-retroviral therapy (HAART), morbidity and mortality of PLHIV due to opportunistic infections (OIs) is remarkably reduced. But, death due to liver-related diseases such as cirrhosis and hepatocellular carcinoma (HCC) in PLHIV has now become a major concern. Liver disease due to HBV and HCV infection in the HIV infected population has faster progression to complications including cirrhosis and hepatic cancer\textsuperscript{2,5}, resulting in an increased liver disease related mortality among PLHIV\textsuperscript{1}. The Global response to the HIV epidemic, although not yet sufficient, is generally much better than the response to the epidemics of HBV, HCV, and co-infection of HIV and viral hepatitis. HIV/AIDS is included in one of the millennium development goals (MDG) along with Tuberculosis and Malaria, but if viral hepatitis and co-infection with viral hepatitis are not included then an optimal outcome from the MDG funding will not be achieved. While many resource-limited countries succeed in decreasing HIV infection and its consequences and increasing access to HAART\textsuperscript{6}, HBV and HCV infection in these countries is still neglected or only addressed in a limited way.
2. Impact of Co-Infection

HIV infection adversely affects the natural history of both HBV and HCV infections. Adults with HIV infection who acquire HBV have a reduced likelihood of resolution. Increasing immunosuppression caused by HIV infection may also be associated with reactivation of HBV in people who have previously lost detectable HBsAg. People with untreated HIV–HBV co-infection have increased rates of HBsAg/HBeAg positivity and higher HBV DNA levels, but have lower transaminase values and reduced necro-inflammatory activity on histology compared with those people with HBV infection alone.

The likelihood of chronic HCV infection after acute infection is increased in HIV-positive people. People with HIV–HCV co-infection have higher levels of viraemia than those with HCV alone. A high level of viraemia is likely to result in a greater risk of transmission and a reduction in success of therapy. It is unlikely, however, that the increased HCV viraemia in people with HIV–HCV co-infection is responsible for greater rates of disease progression.

HIV infection is believed to cause chronic HBV and HCV infection to progress faster to liver fibrosis and liver-related morbidity and mortality from conditions such as cirrhosis and hepatocellular carcinoma. Therefore, patients with HIV and viral hepatitis co-infection require careful management and close follow up by well-trained health care workers.

3. Testing for HIV, HCV and HBV

Each of these viral infections is complex and testing algorithms have been developed to assist the:

- Initial diagnosis;
- Pre treatment assessment; and
- Monitoring of treatment to evaluate response to treatment and also to monitor for viral resistance.

Examples of testing strategies are shown in figures below.
3.1 HCV Testing

HCV screening is based on HCV antibody testing. A confirmed positive HCV antibody result indicates exposure to the virus. If active infection is suspected or cannot be excluded, then perform HCV RNA rests to define viral presence and then viral genotype and viral load.
3.2 HBV Testing

Testing for HBV exposure and infection is based on serological and viral studies. The standard serology markers are HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. By measuring each of these it is possible to determine for most patients their state of infectivity. Now that HBV DNA testing is possible much use is made of it to define viral load (which predicts disease activity but more closely risk of HCC) and more as a research tool at present HBV genotype. Appropriate testing pathways and the interpretation of HBV serology is discussed in more detail at the attached document [http://www.ashm.org.au/images/publications/PatientFactSheets/HBV/decision_making_hbv.pdf](http://www.ashm.org.au/images/publications/PatientFactSheets/HBV/decision_making_hbv.pdf).

Co-infection with one or two of these viruses in HIV infected patients can complicate the interpretation of the viral studies. The results of HBV serologic profiles can be interpreted as in mono HBV infection. However, isolated positive core antibody can be found more frequently (20-30%) in HBV co-infection than in mono HBV infection especially in advanced immunocompromise or HCV co-infected cases or IDUs. The clinical significance of positive anti-HBc antibody is not well understood but more evidence of occult infection with frequent hepatic flare and potential in transmission are increasingly reported. There are also controversial findings of undetectable
HBV DNA in cases with isolated core antibody.\textsuperscript{17,18} Since HBV/HIV co-infection is common so screening serologic tests for hepatitis B including HBs Ag, anti-HBs and anti-HBc antibody are recommended for every HIV-infected individual. If all 3 serologic tests show negative, hepatitis B vaccination is strongly encouraged for effective prevention. If isolated core antibody is detected, confirmatory HBV-DNA or complete liver function work-up may help guiding in long-term management. Hepatitis B vaccination is now not conclusive for HIV infected individuals with isolated core antibody. The vaccination may have a primary or anamnestic response.\textsuperscript{7} If HBs antigen is positive, HBe Ag, anti-HBe antibody, HBV-DNA and liver enzymes should be done to assure the viral replication, liver complications and treatment need.

Regarding HCV co-infection, the national guidelines recommend screening anti-HCV antibody before ART initiation for HIV-infected adults with symptoms or risk factors, especially intravenous drug users (IDUs). Anti-HCV antibody is available for screening the groups at risk. However, anti-HCV seroconversion may be significantly delayed in HIV infected patients and anti-HCV negative is still found in some cases despite ongoing viral replication for a year.\textsuperscript{19} A positive result would indicate exposure to HCV and this should be followed by HCV RNA testing. Where HIV may have suppressed immunity significantly it may be prudent to measure HCV RNA rather than HCV Ab to assess for the presence of an HCV coinfection.

Where co-infection with both hepatitis B and C is possible it should be recognized that HCV infection may suppress HBV replication giving rise to “occult” HBV infection. In these patients the only serological marker may be HBcAb and thus full evaluation of the patient will require HBV DNA testing.

In conclusion, routine screening for hepatitis B and C using serologic tests is beneficial to a patient in treatment and care for early suitable antiretroviral treatment initiation and close monitoring for hepatitis viral disease progression and complications. For public health concerns, it also helps reducing the risk of transmission if treatment is provided or by behavioral change and vaccination if in need. Given the relatively high reported prevalence of HBV and HCV infections, screening for HBV and HCV prior to ART initiation should be encouraged in resource-limited settings.

4. Treating HBV and HCV Infection in HIV Positive Patients
Treatment of patients with HIV-viral hepatitis coinfections is complex and choice of drug regimens demands a thorough work up of the patient to define the:

- State of the HIV infection;
- State of the hepatitis infection – active, inactive, coinfection with more than one HCV genotype, coinfection of HCV with HBV; and the
- State of the liver as some drugs will be contraindicated in the presence of advanced liver disease.

This section does not aim to define algorithms for treatment and readers interested in determining appropriate treatment algorithms are referred to the attached document available at [http://www.ashm.org.au/images/Publications/Monographs/Coinfection_HIV_ViralHep_2010/Coinfection_2010_Full.pdf](http://www.ashm.org.au/images/Publications/Monographs/Coinfection_HIV_ViralHep_2010/Coinfection_2010_Full.pdf)

Many drugs are available to treat the complex clinical situation involving HIV/HCV/HBV co-infection combinations. A number of HIV drugs also have a direct anti-HBV effect and these include lamivudine and tenofovir. Appropriate combinations of drugs are discussed in the above document.

5. References


