



# Hepatitis B Infection in Special Populations

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## Introduction

Hepatitis B virus (HBV) infection is a challenging global health problem. More than 350 million people in the world are chronically infected by the hepatitis B virus. Treatment of this infection has entered a new era with the advent of effective antiviral agents since 1998.

The treatment of hepatitis B virus infection is special in certain patient groups, who have management issues different from usual patients. The purpose of this article is to summarise, firstly, the treatment of HBV infection in haemodialysis patients and patients after kidney transplantation. Additionally, reactivation of hepatitis B and its treatment in transplant recipients and patients undergoing chemotherapy will be addressed. Other special groups like HBV-HIV and HBV-HCV co-infected patients, pregnant women and patients with extrahepatic disease will be discussed. Finally, early treatment with antiviral agents in severe acute and fulminant hepatitis B and the available evidence for preventing liver failure will be reviewed.

## Haemodialysis Patients

As a result of the high infectivity of HBV and its route of transmission, many patients on dialysis have been infected with HBV in the past associated with either blood transfusion or the dialysis procedure itself<sup>1</sup>. Active HBV vaccination is recommended for all patients with end stage renal disease (ESRD). However, non-response or incomplete response to standard HBV vaccines is more frequent in these patients. No controlled trials for the treatment of HBV with either nucleoside analogues (NUCs) like lamivudine or interferon in haemodialysis patients are currently available. Indications for treatment intervention should be similar to immunocompetent patients. Liver biopsy is recommended if transaminases are elevated. Because of side effects, NUCs appear to be superior to interferon in this patient population. Lamivudine is often chosen as it has the most data in this group<sup>2</sup> and entecavir has also been successfully used<sup>3</sup>. Adefovir, though found to be efficacious<sup>4</sup>, has been reported to worsen renal function. Its analogue, tenofovir, should be cautiously used in renal failure as well due to its potential nephrotoxicity.

## Kidney Transplant Recipients

All patients awaiting kidney transplantation should be

vaccinated against HBV, although the likelihood of an effective antibody response is low. Chronic HBV infection can be found in a significant number of kidney recipients because of their previous dialysis. Survival of HBsAg positive kidney recipients is impaired<sup>5,6</sup> and liver failure becomes the leading cause of death in HBsAg positive patients 10 years post kidney transplantation<sup>5</sup>. Interferon can lead to rejection precluding its use<sup>7</sup>. On the other hand, lamivudine leads to biochemical remission and reduction of viral load in up to 100% of treated patients<sup>8</sup> but resistance can emerge. In case of resistance adefovir should be considered<sup>9</sup>. There is a special severe form of hepatitis B occurring in immunosuppressed patients, including kidney recipients, so called fibrosing cholestatic hepatitis (FCH)<sup>10</sup>. FCH is universally fatal within a few months after diagnosis. However, some cases of successful intervention with lamivudine have recently been reported<sup>11,12</sup>.

## Chemotherapy and Immunosuppressed Patients

HBsAg testing should be done in all patients before initiation of chemotherapy or immunosuppressive treatment<sup>13</sup>. Seronegative patients are highly recommended to receive vaccination against HBV. When the immunosuppressive is stopped, reactivation of hepatitis B infection can frequently be observed. It occurs in 21-53% of chronic HBsAg carriers<sup>14,15</sup>, commonly after the first 2-3 cycles of chemotherapy. Hepatitis B flares, during or shortly after chemotherapy, are due to the return of immune competence, followed by liver damage of varying severity, including fulminant hepatitis. The use of corticosteroids among the protocol drugs has to be considered a predisposing factor for treatment-induced HBV reactivation<sup>16</sup>. Nevertheless, high baseline viral load is the most important risk factor for HBV reactivation<sup>17</sup>. It has also been reported that the frequency as well as the severity of HBV flares were higher in HBeAg-negative patients<sup>18</sup>. It is important to note that reactivation can also emerge in anti-HBc positive but HBsAg negative patients (<5%) as HBV persists even after clearance of HBsAg<sup>19</sup>. PCR based detection of HBV-DNA prior to chemotherapy is advised<sup>20</sup>. Close monitoring of anti-HBc positive / HBsAg negative patients is recommended, and antiviral treatment should be started only if HBsAg turns positive or HBV-DNA levels increase.

As chemotherapy usually only lasts for a few months, suppression of HBV is only required for about half a



year. Within this short time period the development of viral resistance to currently applied nucleosides is unlikely to occur. Recombinant-interferon is not recommended because of its haemopoietic toxicity and anticipated low efficacy in immunocompromised patients. Lamivudine has been used extensively and proven effective both in the treatment and as a prevention of chemotherapy-related HBV reactivation<sup>21,22</sup>. Treatment of HBV reactivation does not completely avoid the significant risk of fulminant hepatitis, particularly in HBeAg-negative patients. Primary prevention of HBV reactivation appears to be a more appropriate strategy. The only agent that has been studied during immunosuppression is lamivudine. Thus a pre-emptive antiviral treatment with lamivudine appears to be indicated for HBsAg-positive patients undergoing immunosuppressive therapy. Lamivudine (or more potent agents, if required) should be started pre-emptively in HBsAg-positive patients at least a few days before immunosuppressive therapy or chemotherapy is begun<sup>23</sup>. There is no information to guide how long to treat such patients. For patients with HBV DNA levels of <2000 IU/mL, it would be reasonable to treat them for an additional six months after discontinuing immunosuppressive therapy or chemotherapy. Discontinuation of anti-HBV treatment after 6 months might not be sufficient for patients with high HBV DNA. It is recommended that patients with HBV DNA levels of >2000 IU/mL should continue antiviral therapy until HBV DNA is undetectable, and ALT levels become normal. Less data have been accrued with newer, more potent agents with a high barrier to resistance like entecavir and tenofovir. They may take up a more prominent position with more experience as pre-emptive treatment choices, especially if the patients have a high HBV DNA level or long-term immunosuppressive therapy is required.

## HBV-HIV Co-infected Patients

Cirrhosis is more common in HBV-HIV co-infected patients<sup>24,25</sup>. The indications for treatment are similar to HIV-negative patients<sup>26</sup>. Flares of hepatitis B may occur during HIV treatment because of immune restitution. Most co-infected patients should receive de novo treatment for HIV and HBV simultaneously<sup>27</sup> with tenofovir and emtricitabine plus a third agent active against HIV<sup>28</sup>. If HBV has to be treated before HIV in a minority of patients, adefovir and telbivudine are the preferred agents.

## HBV-HCV Co-infected Patients

In HBV-HCV co-infection, HCV often suppresses HBV DNA to a low or undetectable level. Therefore, the treatment should be pegylated interferon alpha and ribavirin as for HCV<sup>29</sup>. The sustained virological response is quite similar to that of patients with HCV mono-infection<sup>30</sup>. HBV reactivation may occur during or after HCV clearance and NUC treatment will then be required.

## Pregnant Women

The management of HBV-infected women in the child-

bearing age will start with careful planning in the pre-pregnancy stage. It includes recognition of maternal virological status, assessment of liver disease and minimisation of risks for perinatal transmission of infection. This may include simple monitoring, changes in obstetrical care or administration of antiviral therapy in late pregnancy or throughout pregnancy. For women who desire pregnancy and if their liver disease is mild with low viraemia, they are recommended to have pregnancy before treatment. For those with moderate liver disease and no cirrhosis, they can be treated before pregnancy. If they respond, treatment can be stopped before pregnancy and they are monitored closely for hepatic flare. The subset of women having advanced disease must be treated before conception, during pregnancy and after delivery<sup>31</sup>. Those patients with mild disease and very high viraemia should be treated in the last trimester with a category "B" agent (see below) since high maternal HBV DNA levels are likely associated with increased risk of intrauterine and perinatal transmission. The risk may increase from 0% in mothers with HBV DNA <1.1 x 10<sup>7</sup> IU/mL to 32% in mothers with HBV DNA >1.1 x 10<sup>7</sup> IU/mL<sup>32</sup>. Uncontrolled studies have shown the risk can be reduced by lamivudine<sup>33,34</sup> but so far, no convincing prospective controlled trials have demonstrated the benefit of antiviral therapy.

All NUCs are category "C" drugs whereas telbivudine and tenofovir are category "B". Nevertheless, there is a long history of use of lamivudine during pregnancy, both for women with HIV infection and for those with chronic HBV. Safety data of tenofovir, lamivudine and emtricitabine in pregnant HIV-positive women are quite abundant<sup>35</sup>. There are no standards regarding managing HBV in women who become pregnant while receiving antiviral therapy. HBV may be detected in breast milk but infants who are correctly immunised can be breastfed<sup>31</sup>. One caveat is NUCs can also be detected in breast milk but the significance is unknown<sup>36</sup>.

The majority of HBV-infected women have no worsening of liver disease during pregnancy and the liver enzymes frequently normalise postpartum<sup>37</sup>. However, cases of hepatic exacerbations/ fulminant hepatic failure have been reported<sup>38</sup>. It appears prudent to monitor HBV-infected women closely for several months after delivery for hepatitis flares and seroconversion.

## Patients with Extrahepatic Disease

The extrahepatic manifestations in HBsAg positive patients with active HBV replication, e.g. polyarteritis nodosa, glomerulonephropathy, essential mixed cryoglobulinemia, serum sickness-like syndrome etc., may respond to antiviral therapy. Lamivudine has been extensively used and other NUCs like entecavir and tenofovir are expected to have similar indications and higher efficacy. A useful adjunct therapy to NUCs is plasmapheresis.

## Severe Acute and Fulminant Hepatitis B

No therapy is currently established for fulminant hepatitis B. Interferon is immune-stimulating and thus may be dangerous in fulminant hepatitis B, where an



overwhelming immune reaction is believed to be involved in the pathogenesis<sup>39</sup>. Interferon is thus contraindicated because of the risks of worsening hepatitis and the frequent side effects. In contrast, lamivudine inhibits hepatitis B viral replication with an immediate decline of serum HBV DNA. It is a matter of debate whether lamivudine therapy should be initiated in patients with fulminant hepatitis B, as lamivudine treatment might be useless in this situation, since HBV-DNA is usually low in these patients. Anyway, studies have proved lamivudine to be safe in patients with fulminant hepatitis B, and might have the potential to prevent fatal liver failure or liver transplantation when administered early. Prospective controlled trials are necessary in order to define an established treatment for fulminant hepatitis B.

## Conclusion

Major advances have been made in the management of the special populations with hepatitis B infection owing to recent increasing availability of NUCs, which have little adverse effects and are highly effective despite the presence of co-morbidities and other viral infections. The recommendations are summarised in Table 1. However, these recommendations are mainly based on small, usually uncontrolled, short-term studies. Carefully performed larger cohort studies and comparisons of various approaches to therapy should be the way forward.

**Table 1. Treatment recommendations for special patient groups of hepatitis B**

	Interferon- $\alpha$	Nucleos(t)ide analogues
Haemodialysis patients	(+)	+#
Renal transplant recipients	—	+#
Prevention of HBV reactivation	(+)*	+++
Fulminant hepatitis B	(+)	+++

( ) option with reservation

\* in selected cases, when interferon might be used as anti-cancer therapy

# dependent on liver biopsy and biochemical disease activity

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