The Australian and New Zealand Management and Treatment

Chronic Hepatitis B (CHB) Recommendations

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Levels of Evidence
I       Randomised controlled trials
II-1     Controlled trials without randomisation
II-2     Cohort or case controlled studies
II-3     Multiple time series, dramatic uncontrolled experiments
III      Opinion of respected authorities. Descriptive epidemiology
Glossary of Acronyms

ADV   adefovir dipivoxil
AFP   alpha-fetoprotein
AIDS  acquired immunodeficiency syndrome
ALT   alanine aminotransferase
anti-HAV IgM  IgM antibody to hepatitis A antigen
anti-HBc  antibodies to the hepatitis B core antigen
anti-HBe antibodies to the HBe antigen
anti-HBs antibodies to the HBsAg (surface) antigen
ART   antiretroviral treatment
CHB   chronic hepatitis B
CHC   chronic hepatitis C
CI    confidence interval
DNA   deoxyribonucleic acid
ETV   entecavir
FTC   emtricitabine
HAART  highly active antiretroviral therapy
HAV   hepatitis A virus
HAV IgM  IgM antibody to hepatitis A antigen
HBCAg  hepatitis B core antigen
HBeAg  hepatitis B e antigen
HBIG  hepatitis B immunoglobulin
HBsAg  hepatitis B surface antigen
HBV   hepatitis B virus
HBcMgM  IgM antibodies to HBV core antigen
HCC   hepatocellular carcinoma
HCV   hepatitis C virus
HDV   hepatitis D virus
HIV   human immunodeficiency virus
HRQoL health-related quality of life
IDU inject drug user
IFN   standard interferon alfa (2a or 2b)
INR   international normalised ratio
ITT   intention-to-treat
IU    International units
LAM   lamivudine
LAM-R lamivudine resistance
LdT   telbivudine
MIU   million international units
MU    million units
PCR   polymerase chain reaction
pegIFN pegylated interferon alfa-2a
QALY quality-adjusted life-year
QoL   quality of life
RCT   randomised controlled trial
RNA   ribonucleic acid
TDF   tenofovir
ULN   upper limit of normal range
US    ultrasound
1. CHB Disease Burden in Australia and NZ

While prophylactic vaccination has significantly reduced the incidence of de novo hepatitis B virus (HBV) infections among populations where it has been introduced, chronic hepatitis B (CHB) is a serious global public health challenge. CHB affects over 350 million people worldwide and around 1.2 million die annually of HBV-related chronic liver disease.

Although many individuals eventually achieve a state of nonreplicative infection, the prolonged immunologic response to infection leads to the development of cirrhosis, liver failure, or hepatocellular carcinoma (HCC) in up to 40% of people. CHB is the major cause of HCC, causing 60-80% of the world’s liver cancer.

Acute and chronic HBV infections are a major public health problem in Australia and New Zealand, which are considered by World Health Organisation (WHO) criteria to have a low prevalence (< 2%) of HBV infection. However population groups with a high prevalence of HBV markers exist within both countries.

Australia

Recent estimates of the prevalence of CHB infection obtained from the first national sero-survey in Australia in 1996–99 range from 91,500 to 163,500 persons (0.49%–0.87%). This is considerably more than the number infected with HIV and comparable to the estimated 260,000 people infected with hepatitis C virus (HCV). There are 6000 – 8000 new notifications to the National Notifiable Diseases Surveillance System (NNDSS) annually. A large proportion of these infections are known to occur in selected populations, including indigenous people. Studies in the 1980s and early 1990s estimated that nearly half of all indigenous schoolchildren had serological markers of HBV infection and up to 26% of rural Aboriginal and Torres Strait Islanders populations were HBsAg-positive. In 1991–1995, the death rates (for all causes of chronic liver disease and cirrhosis) were 4 and 5.5 times higher for Aboriginal men and women respectively, compared with rates for the general Australian population. A more recent report showed that HBV notification and hospitalisation rates in Australia are at least four times higher in Aboriginal and Torres Strait Islander people. The seroprevalence of HBV infection is likely to differ significantly from the national rate in some areas, particularly the Northern Territory, where approximately 25% of the population is indigenous and universal infant HBV immunisation has been in place since 1990.

Table 1: Estimates of CHB in Selected Countries of Birth from Asia and the Pacific Islands

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence of CHB in Country (%)</th>
<th>Number of Australians born in that country (% of total Australian population)</th>
<th>Estimate of CHB among Australians born in that country</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>15</td>
<td>181,987 (0.8)</td>
<td>27,300</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>8.8</td>
<td>76,513 (0.4)</td>
<td>6,700</td>
</tr>
<tr>
<td>Taiwan</td>
<td>15-20</td>
<td>30,705 (0.2)</td>
<td>5,400</td>
</tr>
<tr>
<td>Vietnam</td>
<td>15-20</td>
<td>176,616 (0.7)</td>
<td>30,900</td>
</tr>
<tr>
<td>Philippines</td>
<td>12</td>
<td>125,144 (0.5)</td>
<td>15,000</td>
</tr>
<tr>
<td>Fiji</td>
<td>10-20</td>
<td>54,949 (0.3)</td>
<td>8,200</td>
</tr>
<tr>
<td>India</td>
<td>3.3</td>
<td>128,650 (0.6)</td>
<td>4,200</td>
</tr>
<tr>
<td>Malaysia</td>
<td>5.2</td>
<td>97,786 (0.5)</td>
<td>5,100</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.8</td>
<td>44,925 (0.2)</td>
<td>1,300</td>
</tr>
</tbody>
</table>

* CHB prevalence estimates based on seroprevalence studies in countries of origin
* Australian Bureau of statistics, Australia 341.2, 2003-2004
* Estimate of CHB based on prevalence estimate or mid-point of prevalence range, with rounding close to 100
Prevalence of CHB is extremely high in many countries within the Asia-Pacific region. People born in South-East Asia and the Pacific Islands constitute a significant proportion of people with CHB in Australia. Table 1 shows the prevalence of CHB in selected countries of the Asia-Pacific region, and a crude estimate of the size of the foreign-born populations with CHB in Australia. Despite constituting only approximately 5% of the Australian population, people born in these selected countries of the Asia-Pacific region make up more than 50% of the estimated population in Australia with CHB. Furthermore, the descendants of people with CHB born in these countries are likely to have been at increased risk of HBV through perinatal (prior to introduction of infant immunisation) and horizontal (household) transmission.

Evidence of the expanding burden of CHB related liver disease in Australia can be found in the NSW Cancer Registry and National Death Index. Between the 1990s and 2002, deaths from CHB doubled from 100 to near 200 per annum. People with CHB had a 40 - 90% increased risk of mortality compared to a matched population and the risks of total liver disease-related and liver cancer-related mortality were 12 and 28 times higher respectively, than those for the background population. The burden of CHB including HBV-related HCC among Asia-Pacific born Australians has increased over the past three decades and is projected to increase further during the next two decades.

New Zealand

In 2005, an estimated 67,000 New Zealanders had CHB. The prevalence of HBsAg, among 177,000 participants in the successful New Zealand (NZ) Hepatitis B Screening Programme, was 5.6% for Maori and 0.43% for New Zealanders of European extraction, similar to previously reported data. Significantly higher rates were found in Pacific Islanders (median 7.3%, Tongan 13%) and Asians (median 6.2%, 8.1% in South East Asian, 8.9% in Chinese) reflecting higher prevalence rates in those countries of birth.

In 2005, the vast majority (85%) of HBsAg-positive New Zealanders remained unaware of their status. Men were more likely to test HBsAg-positive (6.1%) than women (5.4%). Disturbingly, approximately 3.5% of screened individuals under the age of 15 years had CHB infection, a population thought to be protected by the universal neonatal HBV vaccination programme (introduced that year). HBV DNA was detected in 30–40% of HBeAg-negative patients with persistently elevated enzymes. Morbidity is similar to that in Australia.

2. High-Risk Groups

- Birth in areas where there is high and intermediate prevalence rates for HBV including immigrants and adopted children e.g. Asia, the Pacific Islands, North Africa, the Middle East, and the Mediterranean region
- Indigenous populations
- Injecting drug use
- Household contact with someone diagnosed with CHB
- HIV infection
- Inmates of correctional facilities
- Men who have sex with men
- Individuals with HCV or HIV
- Patients undergoing dialysis
- Patients undergoing chemo- or immunosuppressive therapy
3. Natural History

Acute HBV

Acute hepatitis B develops 6-12 weeks following exposure to the virus and is marked by serological and biochemical evidence of infection. HBV related symptoms are rare in the perinatal setting but relatively common in adult-acquired infection. Mortality from development of acute liver failure occurs in <1% of cases.

Acute HBV infection may have variable outcomes. Depending on the interactions among several virus and host-related variables, complete recovery with development of anti-HBV immunity may occur or it may evolve into chronic infection. Progression to chronic infection varies from >90% among perinatally exposed (and unvaccinated) infants, to 30% among children aged under 5 years, to <5% for adults.

Using sensitive assays, HBV DNA can be detected in liver up to 10 years after ‘recovery’ from an acute HBV infection. This may account for chemo- and immunosuppressive therapy-induced reactivation of HBV replication in persons with serological markers of recovered HBV infection.

Progression to Chronic HBV Infection

CHB is defined as persistent detection of HBsAg for >6 months after initial exposure to the virus. The natural history of CHB can be categorized into four potentially successive phases of variable duration classified by serum ALT, HBV DNA and HBeAg status.

Phase 1- Immune Tolerance

The early phase of CHB is characterized by the presence in serum of hepatitis B e antigen (HBeAg), HBV DNA and normal ALT levels indicating a lack of host immune response against HBV infected hepatocytes. Spontaneous and treatment-induced HBeAg seroconversion is infrequent (<5% per year). The prognosis is generally favourable because of the absence of significant liver injury.

Phase 2- Immune Clearance

The factors that lead to loss of immune tolerance and the development of an active host immune response against infected hepatocytes are unclear. The immune clearance phase is characterized by persistently or intermittently elevated ALT levels, fluctuating viral loads and moderate-to-high levels of liver inflammation and liver enzymes. Rapid progression of liver disease can occur.

In some patients the host immune response will result in seroconversion of HBeAg to anti-HBe accompanied by a state of nonreplicative infection, characterized by low or undetectable serum levels of HBV DNA and normal ALT levels. The annual rate of HBeAg seroconversion is estimated to be ~5 to 15%. Following HBeAg seroconversion there is a relatively low risk of disease progression. However, increasing viraemia and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg-negative strain of the virus.

The development of antiHBs and clearance of HBsAg occurs spontaneously in 0.5–2% of people with CHB each year in western countries. Clearance of HBsAg is most likely to occur in the year following HBeAg seroconversion and signifies resolution of the chronic infection.

Phase 3 - Immune Control

Individuals in this phase are characterized by persistent HBV infection without significant necroinflammatory disease. Immune control is associated with undetectable to low serum levels of HBV DNA, persistently normal liver enzymes and low risk of advanced disease. Individuals in this category need to be distinguished from those in the immune tolerant phase of infection who have high levels of serum HBV DNA (see Figure 1). The inactive replication phase may persist indefinitely; in which case the prognosis is generally favourable, especially if significant fibrogenesis has not
occurred prior to an effective host immune response. Reactivation of HBV may occur spontaneously or as a result of immunosuppression.

**Figure 1: Natural History of CHB**

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>&gt; 6 months</th>
<th>&gt; 6 months</th>
<th>&gt; 6 months</th>
<th>&gt; 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>–</td>
<td>Spontaneous seroconversion to anti-HBe may occur</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ALT</td>
<td>Persistently normal</td>
<td>Persistently or intermittently elevated</td>
<td>Persistently normal</td>
<td>Persistently or intermittently elevated</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>≥ 20,000 IU / mL</td>
<td>Persistently or intermittently ≥ 20,000 IU / mL</td>
<td>&lt; 2000 IU / mL</td>
<td>Persistently or intermittently ≥ 2,000 IU / mL</td>
</tr>
<tr>
<td>Liver Histology</td>
<td>Minimal or mild hepatitis</td>
<td>Inflammation score ≥ 4</td>
<td>Inflammation score &lt; 4</td>
<td>Inflammation score ≥ 4</td>
</tr>
<tr>
<td></td>
<td>Usually no fibrosis</td>
<td>Fibrosis: + / -</td>
<td>Fibrosis: + / -</td>
<td>Fibrosis: +</td>
</tr>
</tbody>
</table>

**Phase 4 - Immune Escape**

Active HBeAg-negative disease is due to a mutant virus that does not secrete HBeAg (the ‘precore or core-promoter mutant’ strain) and causes recurrence of active liver disease. People can be infected with the HBeAg-negative virus following initial exposure or, more commonly, the viral mutation emerges late in the course of infection in those initially infected with wild type (HBeAg-positive) virus. The prevalence of HBeAg-negative hepatitis varies geographically; and is more common in Asia and the Mediterranean region. Infection with HBeAg-negative CHB is associated with a fluctuating course, progressive fibrosis and a poor prognosis.

Active disease is associated with either persistent ALT elevation or an erratic pattern of ALT changes with “flare-ups” resembling acute hepatitis B that can be severe or even fatal. Serum HBV DNA levels are usually lower than in HBeAg-positive patients, but generally higher than those seen in patients in the immune control phase. Few patients with HBeAg-negative CHB achieve a lasting remission.
HBeAg-negative CHB may escape clinical recognition and liver disease may have progressed to advanced stages of fibrosis, including cirrhosis and even HCC when reactivations are finally identified.\textsuperscript{77, 78} Progression to cirrhosis of the liver has been estimated to occur in 8 -10\% of people with HBeAg-negative CHB each year.

**HBV DNA and Disease Progression**

Although the pathogenesis of CHB liver injury is complex, chronic intrahepatic replication of HBV results in an ongoing cascade of inflammation, injury, and repair. Without resolution, this inflammatory cycle leads to scarring and fibrosis - ending in cirrhosis and loss of hepatic function - and to uncontrolled hepatocyte regeneration with the potential for HCC.

Recent studies have provided strong evidence the serum level of HBV DNA is the major clinical feature related to liver disease progression. Even persistent low level viraemia causes liver damage independent from other disease factors such as HBeAg serostatus and baseline ALT levels, particularly in Asian patients and others infected early in life.

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus Study (REVEAL-HBV), a community based survey conducted in Taiwan, demonstrated an association between persistently elevated HBV DNA and the development of cirrhosis and HCC in patients infected with CHB early in life.\textsuperscript{79, 80} Over a period of 11.4 years, representing 41,779 person-years of follow-up,\textsuperscript{79} the risk of HCC increased significantly in patients with HBV DNA levels > 200,000 IU/mL at the time of study entry.

The risk of HCC was reduced in individuals who had lower viral loads at follow-up compared with baseline levels, whereas subjects with persistent HBV DNA elevation throughout the study had the highest HCC incidence. The development of HCC was 10 times greater in patients with persistent HBV DNA > 20,000 IU/mL than in those with HBV DNA levels < 2,000 IU/mL at enrolment. However, even when HBV DNA levels decreased from 20,000 to 2,000 IU/mL, there was still a substantial risk for HCC development. These results highlight the concept that cirrhosis and HCC may continue to develop after HBeAg seroconversion with ALT normalisation even with relatively low viral loads in patients infected early in life.

Cirrhosis incidence rates showed a similar correlation with HBV DNA levels. The relative risk of developing cirrhosis was significantly elevated for those with HBV DNA levels as low as 2,000 IU/mL and was six fold greater for those with HBV DNA of ≥ 200,000 IU/mL at enrolment.

Elevated ALT levels also affect liver disease progression.\textsuperscript{81} Patients with near-normal ALT levels of 0.5-1.0 x ULN were significantly more likely to develop complications of liver disease than patients with normal ALT levels.

These findings have implications for treatment goals suggesting that early detection and maximal HBV DNA suppression should be important aims of antiviral therapy.
4. Recommendations for Patient Evaluation

Diagnosis
HBV infection is confirmed by the detection of hepatitis B surface antigen (HBsAg) or HBV DNA in serum. In addition to patient exposure history, serology can assist in determining whether infections are newly acquired or chronic.

Diagnosis of newly acquired infections requires one of the following:
- HBsAg in a patient shown to be negative within the last 24 months
- HBsAg and high levels of specific IgM to hepatitis B core antigen (HBcIgM) in the absence of prior evidence of HBV infection
- HBV DNA and high levels of specific IgM to hepatitis B core antigen (HBcIgM) in the absence of prior evidence of HBV infection.

Diagnosis of chronic infection requires:
- Detection of HBsAg or HBV DNA (PCR) in the serum of a patient on two occasions at least six months apart.
- No clinical or laboratory evidence of acute hepatitis B

Baseline Evaluation
The initial evaluation of patients with CHB should include a thorough history and physical examination, with special emphasis on risk factors for co-infection, alcohol use, and family history of HBV infection and liver cancer.

Table 2 summarises the tests that should be performed at the initial evaluation of patients with CHB, and in Table 3 the suggested follow-up evaluation.

<table>
<thead>
<tr>
<th>Table 2: Initial Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
</tr>
<tr>
<td>Laboratory testing: Liver function tests, full blood examination, and INR</td>
</tr>
<tr>
<td>HBeAg/anti-HBe, HBV DNA (quantitative viral load)</td>
</tr>
<tr>
<td>HCV antibody, hepatitis D virus antibody and antigen, total antibody to hepatitis A virus; vaccinate if no immunity</td>
</tr>
<tr>
<td>HIV antibody</td>
</tr>
<tr>
<td>Alfa-foetoprotein (AFP) and abdominal ultrasound (US) to screen for HCC</td>
</tr>
<tr>
<td>Consider gastroscopy to look for oesophageal varices if clinical, laboratory or imaging evidence of cirrhosis</td>
</tr>
<tr>
<td>Liver biopsy is strongly recommended prior to initiating antiviral therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Suggested evaluation for patients who are not treatment candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotolerant Phase</td>
</tr>
<tr>
<td>HBV DNA, HBeAg, ALT every 6 - 12 months if ALT levels are normal or only minimally elevated.</td>
</tr>
<tr>
<td>Consider liver biopsy and treatment if ALT levels are persistently &gt; 2 x ULN, HBV DNA &gt; 20,000 IU/mL and HBeAg seroconversion does not occur within 6 months.</td>
</tr>
<tr>
<td>Consider HCC screening in high risk patients.</td>
</tr>
<tr>
<td>HBV DNA, HBeAg, ALT every 12 months</td>
</tr>
<tr>
<td>If ALT levels increase, check serum HBV DNA and exclude other possible causes of ALT elevation.</td>
</tr>
<tr>
<td>Consider liver biopsy and treatment if HBV DNA &gt; 20,000 IU/mL; ALT remains elevated and no other cause found and/or if liver biopsy shows significant fibrosis.</td>
</tr>
<tr>
<td>Consider HCC screening in high risk patients.</td>
</tr>
</tbody>
</table>
5. Treatment Goals & Objectives

Treatment Goal
Eradication of HBV infection is not achievable with currently available therapy, therefore the primary goal is to improve patient survival by preventing or delaying the development of cirrhosis and hepatocellular carcinoma.  

Treatment Objectives
The primary treatment objectives are:  

1. HBV DNA suppression (< 2000 IU/mL; preferably PCR undetectable < 50 IU/mL)  
2. ALT within normal limits  
3. Histological improvement

HBsAg Loss and Seroconversion
Loss of HBsAg and seroconversion to anti-HBs is considered a complete response and is durable in most cases. However, loss of HBsAg is not frequent after therapy, occurring in 3 - 8% of patients receiving IFN and < 5% of patients receiving nucleoside analogue (NA) therapy.

HBeAg Loss and Seroconversion
Loss of HBeAg and seroconversion to anti-HBe is associated with decreased viral replication and improved liver histology. Seroreversion to detectable HBeAg following treatment has been reported in 10 - 30% of patients following interferon therapy and up to 60% after NA therapy, particularly if treatment is stopped soon after HBeAg becomes undetectable. Furthermore, some patients may evolve into HBeAg-negative CHB.

Patients to Treat
Treatment is always an individual decision based on stage and activity of liver disease (serum HBV DNA and ALT levels) and the patients’ wishes, anticipated compliance and consideration of any contra-indications to treatment.

Table 4: Current and Future Treatment Options

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Type</th>
<th>Name</th>
<th>Current Indications</th>
<th>Future Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral Agents</td>
<td>Nucleoside Analogues</td>
<td>Lamivudine (LAM)</td>
<td>First line therapy(pending)</td>
<td>Emtricitabine (FTC)</td>
</tr>
<tr>
<td></td>
<td>L-nucleosides</td>
<td>Telbivudine (LdT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclopentane/pentene ring</td>
<td>Entecavir (ETV)</td>
<td>First line therapy and LAM resistance</td>
<td>Abacavir</td>
</tr>
<tr>
<td></td>
<td>Nucleotide Analogues</td>
<td>Adefovir (ADV)</td>
<td>LAM resistance</td>
<td>Tenofovir (TDF)</td>
</tr>
<tr>
<td></td>
<td>Acyclic Phosphonate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>Standard Interferon and Pegylated interferon (pegIFN)</td>
<td>First line therapy or antiviral failure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment Options

Although CHB is vaccine preventable, once established, the sole option for preventing long-term liver disease is antiviral treatment.

Currently approved first and second line CHB therapies in Australia and NZ, and drugs that may be approved in future are listed in the Table 4. These agents can be employed either for a finite duration to achieve a long-lasting outcome (nucleoside / nucleotide analogues or interferons in HBeAg positive or HBeAg negative patients) or as continuous therapy to achieve long term HBV DNA suppression (nucleoside / nucleotide analogues in HBeAg positive or HBeAg negative patients).

Interferons (standard and pegylated)

The interferons (standard IFN and pegIFN) act as immunomodulators and promote an antiviral state that inhibits viral replication. In Australia and NZ, pegIFN has replaced standard IFN in CHB treatment.

The benefits of pegIFN are the lack of antiviral resistance, a defined duration of therapy (48 weeks), HBeAg seroconversion in 30% and loss of HBsAg in 5-8% of patients. PegIFN is more effective in patients who have an active host immune response to HBV, characterised by serum ALT levels >2 x ULN and HBV DNA levels < 8 log IU/mL. Patients who wish to avoid long term treatment, such as young person's planning a family, should be considered for first line therapy with PegIFN.

The adverse effects of pegIFN include myalgias, muscle aches, arthralgias, and flu-like symptoms, such as fever and chills. These symptoms typically occur within the first month of therapy and subside during the course of therapy. pegIFN may exacerbate underlying autoimmune conditions and may worsen neuropsychiatric disorders, particularly depression. Neutropenia and thrombocytopenia due to interferon induced bone marrow suppression are common and requires regular FBC monitoring. Less common adverse events include hypothyroidism, cardiac and retinal toxicity.

The immunomodulatory effects can cause severe exacerbations of hepatic inflammation (“ALT flares”) in patients treated with either standard or pegIFN, including hepatic decompensation in patients with cirrhosis. Neutropenia was the most common reason for dose reduction or early discontinuation, events that were both more common in patients with cirrhosis. Interferons are contraindicated in patients with decompensated cirrhosis.

Nucleoside / Nucleotide Analogues (NAs)

Nucleoside / nucleotide analogues act as competitive inhibitors of HBV reverse transcriptase / DNA polymerase to prevent the incorporation of natural nucleosides leading to chain termination. These agents are effective as first line therapy for all patients and have particular use in subgroups that may not tolerate pegIFN, for example in patients with decompensated liver disease, viral co-infections, during pregnancy, and following organ and stem cell transplantation. As with IFN, individuals with high ALT levels are more likely to achieve HBeAg seroconversion and overall NA lead to loss of HBeAg at a rate similar to IFN.

Drug resistance is common with prolonged treatment and occurs in up to 70% of patients treated with LAM for 5 years. Resistance has been shown to occur with most of the other NAs when they are administered as monotherapy in a time-dependent fashion. Accordingly, around 30% of authorities maintain that combination nucleoside / nucleotide analogue therapy may be preferable to monotherapy as first-line therapy. NA therapy can be tailored for individual patients to take advantage of the lack of cross-resistance between some agents (see later).

NAs are remarkably well tolerated and discontinuation due to adverse effects is rare. The potential development of lactic acidosis associated with hepatomegaly and steatosis is rare but can occur with all of the currently available antiviral agents, including LAM, ADV, ETV and LdT.

Hepatic function should be monitored closely in patients who discontinue NA therapy since some patients may develop a severe acute exacerbation of hepatitis. All oral antiviral agents require dose
reductions in the setting of renal insufficiency and dose adjustments according to creatinine clearance are appropriate.

ADV has been associated with a small risk (2% of patients after 96 weeks of ADV treatment) of dose-dependent and reversible kidney toxicity. There is minimal concern for patients with normal renal function and 10mg ADV has shown to be safe for the treatment of CHB in patients with varying degrees of kidney dysfunction and LAM-R, resulting in biochemical and virological efficacy similar to that reported in the general population.110

Table 5: Advantages and Disadvantages of NAs and Interferon as First-Line Therapy for CHB

<table>
<thead>
<tr>
<th>Nucleoside / Nucleotide Analogues</th>
<th>PegIFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>Easy to administer and monitor</td>
<td>Generally requires prolonged therapy</td>
</tr>
<tr>
<td>Safe in patients with cirrhosis / decompensated liver disease</td>
<td>Antiviral resistance is common with prolonged therapy</td>
</tr>
<tr>
<td>Few, if any, side effects</td>
<td>Durability of HBeAg seroconversion is excellent</td>
</tr>
</tbody>
</table>

Treatment Responses

Unlike the situation with hepatitis C therapy, there are no generally agreed definitions for treatment response. A response to therapy can be either biochemical (normalisation of serum ALT) or virological (undetectable HBV DNA by PCR, HBeAg seroconversion to anti HBe, HBsAg seroconversion to anti HBs). Treatment response can be assessed during therapy, initially at weeks 12 and 24. Most clinicians will monitor treatment response every three months to ensure that an initial response is maintained. Following the end of therapy, a sustained response can be determined at either six or twelve months; however, CHB is not curable with current therapy, so most patients will require long term monitoring (for example yearly or second yearly).

Monitoring CHB Therapy

Patients should be monitored for the development of adverse effects and tolerance to therapy at least once every 3 months while receiving treatment with NAs and monthly when treated with pegIFN. The current duration of pegIFN therapy is 48 weeks. Therapy is stopped prematurely only if intolerable adverse effects develop, which occur in < 5% of patients.

When to Stop Treatment

The traditional treatment endpoint for HBeAg-positive CHB patients is HBeAg seroconversion to anti-HBe in association with very low or undetectable serum HBV DNA. For patients treated with NAs, treatment is typically continued for an additional 6-12 months to reduce the risk of relapse; whether this will be necessary for patients treated with newer, more potent NA is unknown. PegIFN is not continued beyond 48 weeks and HBeAg seroconversion is usually durable. Long-term treatment with NA is generally recommended for patients with cirrhosis, even after HBeAg seroconversion.

Treatment endpoints for patients with HBeAg-negative CHB treated with NAs have not been determined. Current practice favours long-term therapy since relapse rates are high if treatment is stopped when serum HBV DNA becomes undetectable. Preliminary data suggest that relapse rates are lower, although still substantial, if treatment is stopped after several years of undetectable levels
of serum HBV DNA in patients receiving LAM or ADV. The level of HBV DNA suppression following pegIFN therapy was generally higher than that following NA therapy, making direct comparisons and recommendations problematic.

**Treatment Failure**

Treatment failure can be defined as either primary failure or an inadequate response while receiving NA therapy. The definition of key virologic response categories are: 111

- **Primary treatment failure:**
  Decline in HBV DNA < 1 log IU/mL at treatment week 12

- **Complete virologic response:**
  Undetectable HBV DNA by PCR at treatment week 24

- **Partial virologic response:**
  Detectable HBV DNA by PCR < 2,000 IU/mL (3.3 log IU/mL) at treatment week 24 or 48

- **Inadequate virologic response:**
  HBV DNA ≥ 2,000 IU/mL (3.3 log IU/mL) at treatment week 24

For primary treatment failure, which is uncommon, the first strategy is to ensure that patients are compliant with their treatment regimen. If they are not, they should be counselled on the importance of adherence. If they are compliant, the optimal strategy is to switch to a more potent drug or possibly a combination of drugs.

If patients have achieved a complete virologic response at Week 24 - 48, the optimal strategy is to continue treatment with the same drug and monitor at 3 monthly intervals.

For individuals only partially responding by Week 24 or 48, it is recommended that a second drug that is not cross-resistant be added if the current therapy has a low genetic barrier to resistance. If the drug has a high genetic barrier to resistance, it is recommended that patients stay on the current therapy, monitoring at 3 month intervals. If response remains partial or becomes inadequate during further monitoring, a more potent drug should be added or substituted.

For patients with an inadequate virologic response, the optimal approach is to add or switch to another drug (preferably one that is more potent, or if such a drug is not available, then one that is not cross-resistant) and repeat monitoring at 3-month intervals. Monitoring should be maintained at 3 months intervals if the virologic response becomes complete.
6. Treatment of HBeAg-positive CHB

Improving Outcomes

A recent observational study designed to determine the long-term survival of untreated HBeAg-positive CHB at diagnosis,112 identified the risk of liver-related death was strongly associated with sustained disease activity and a high level of HBV replication (HBV DNA level and HBeAg status). In this study, a total of 70 patients in northern Italy were followed for a median of 25 years (range 1.3 – 33 years). While most patients underwent sustained HBeAg seroconversion that conferred a survival benefit regarding liver disease-related mortality (particularly for those with suppressed HBV replication before cirrhosis onset), older age, male sex, and cirrhosis at study entry was strongly associated with an increased risk of mortality.

The REVEAL study also correlated clinical outcomes, such as cirrhosis and HCC, with the level of viral replication.113 Patients who remain HBeAg-positive with high levels of HBV DNA are more likely to die from liver disease. By contrast, those who are able to clear HBeAg have better outcomes suggesting improvement in survival with control of HBV replication.

Persistent or intermittent serum ALT elevation is frequently associated with attempted immune clearance of infected hepatocytes in patients with HBeAg positive CHB. When this occurs, patients should be observed for 3 – 6 months for spontaneous HBeAg seroconversion. If this does not occur, and HBeAg remains detected with HBV DNA levels ≥ 20,000 IU/mL and serum ALT levels > 2 x ULN, then antiviral therapy should be considered.

Liver biopsy is highly recommended before initiating treatment to determine the degree of liver inflammation and fibrosis. ETV and pegIFN are preferred as first-line therapy for treatment naïve patients with HBeAg-positive disease. ADV is also appropriate, but LAM is not recommended due to high resistance rates.89, 94, 98

Virological suppression is indicated by HBeAg loss, with or without seroconversion to anti-HBe, as well as low-level or non-detectable HBV DNA by quantitative PCR assay. Viral suppression without HBeAg seroconversion is invariably associated with relapse, whereas HBeAg seroconversion is associated with sustained responses in 50 - 90% of patients. Virologic response is usually accompanied by biochemical and histologic improvement.

For those responding suboptimally with detectable HBV DNA after 24 weeks of therapy, switching to an alternative therapy or adding a second agent is recommended to avoid resistance.114,98, 115-118 Antiviral treatment must be continued for at least 6-12 months after HBeAg seroconversion and long term antiviral treatment may be required. HBV DNA and ALT levels should be monitored at least 3 monthly after cessation of antiviral treatment to identify rebound. All HBsAg positive patients should continue to be monitored long-term regardless of HBeAg status.
Figure 2: Treatment Algorithm for HBeAg-positive CHB

ALT normal\(^5\) (men < 30 IU/mL; women < 19 IU/mL)

ALT elevated (men > 30 IU/mL; women > 19 IU/mL)

HBV DNA ≥ 20,000 IU/mL

**Immune Tolerance**
HBeAg (+) CHB with normal ALT & high HBV DNA

Treatment Considerations:
- Consider liver biopsy if age > 35-40 yrs (II-3)
- Treat if moderate / greater inflammation or fibrosis on biopsy (I)
- ETV preferred
- PEG-IFN and ADV also appropriate (I)\(^6\)
- Low rate of HBeAg seroconversion for all treatments
- Review HBV DNA & ALT every 3 months (III)\(^6\)

**Immune Clearance**
HBeAg (+) CHB with elevated ALT & high HBV DNA

Treatment Considerations:
- Liver biopsy prior to treatment (II-3)
- Treat (I)
- ETV preferred (I)\(^6\)
- PEG-IFN and ADV also appropriate (I)\(^6\)
- Review HBV DNA & ALT every 3 - 6 months (III)\(^6\)
- Long term antiviral treatment may be required (I)
- Continue antiviral treatment after HBeAg seroconversion for at least 6 - 12 months (I)

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\(^5\) Please refer to PBS / Pharmac Schedule for reimbursed indication

\(^6\) The upper limit of normal for serum ALT concentrations
pegIFN

HBsAg Loss or Seroconversion
HBsAg loss is the hallmark of a complete response to CHB treatment. Two clinical trials of pegIFN 2a reported small percentages (≤ 5%) of HBsAg loss or seroconversion among patients receiving pegIFN either as monotherapy or in dual therapy with LAM, while no HBsAg loss or seroconversion was reported in those receiving LAM alone. One year of pegIFN 2b in 266 HBeAg-positive patients led to HBsAg loss in 7% and HBsAg seroconversion in 6%. A further study found an association between HBsAg loss and HBV genotype (14% genotype A; 9% genotype B; 3% genotype C, and 2% genotype D).

HBeAg Seroconversion
HBeAg-positive seroconversion rates across trials over 24 - 48 weeks were between 29 - 32%. In the partially blind study, patients were randomised to pegIFN plus placebo, pegIFN plus LAM, or LAM alone. While the differences at the end of treatment (48 weeks) were not statistically significant, the rate of HBeAg seroconversion at week 72, after 24 weeks of follow up) was significantly higher in the pegIFN plus placebo group (32%) than in those treated dual therapy (pegIFN/LAM) (27%) or with LAM alone (19%) (p < 0.001).

Virological Response (HBV DNA)
PegIFN monotherapy and dual (pegIFN / LAM) treatment had a similar in effect on HBV DNA and both were significantly superior to LAM monotherapy at the end of off-treatment follow up. In general, patients with lower ALT had lower rate of virological response with pegIFN and response rates were lower for HBeAg-positive patients compared to HBeAg-negative CHB. In a separate study, the rate of sustained virologic response (defined as loss of HBeAg and HBV DNA level < 100,000 IU/mL) was 36% for the dual treatment group and 14% for the LAM monotherapy group (absolute difference, 22 percentage points [95% CI, 6 to 38 percentage points]). End-of-treatment outcomes showed patients receiving dual therapy more often had virologic response (60% vs. 28% [absolute difference, 32 percentage points (CI, 14 to 50 percentage points)]) compared with monotherapy.

Biochemical Response (ALT levels)
Although not statistically significant, ALT levels were more likely to return to the normal range in pegIFN treated patients (36% for all three doses combined compared with 25% for IFN).

In the pegIFN studies (multicentre, randomised, partially double-blind study), people treated with LAM monotherapy had the highest rates of ALT normalisation at end of treatment (48 weeks), but the lowest at end of follow-up (24 weeks). Response rates were lower in HBeAg-positive patients compared to HBeAg-negative patients. By the end of follow-up, ALT normalisation occurred in 41% in the pegIFN group, 39% in the dual treatment group, and 28% in the LAM monotherapy group. Differences between pegIFN and LAM monotherapy were statistically significant at end of follow-up (P = 0.002). Adding LAM to pegIFN did not improve the response rate for this endpoint (ALT normalisation 39%). Despite achieving virological improvement, the percentages of patients with normalisation of ALT levels and histologic improvement did not differ, in a separate randomised, controlled, open-label trial, comparing LAM (100 mg daily for 52 weeks) and dual (pegIFN / LAM) treatment.

Histological Improvement
Changes in liver histology were reported by two studies. There was no statistically significant difference in histological improvement between the pegIFN groups, the LAM groups and the dual therapy groups.

Normal Pre-treatment ALT
Only one study was identified that enrolled subjects with ALT levels ranging from normal levels. In general, patients with lower ALT had lower rate of virological response.
Predictors of Response 89, 91, 119-122

- Higher pre-treatment ALT levels 123
- Low viral load / low baseline HBV DNA
- Absence of previous IFN treatment

Influence of Genotype

Among patients with typical HBeAg-positive CHB, response rates to pegIFN appear higher among those infected with genotype A and B than genotypes C and D, although the differences have not been statistically significant in all studies. 89, 120, 121, 119, 124, 125 Two other studies identified that patients with genotype C appeared to respond equally well to pegIFN as genotype B patients. 89, 122

Lamivudine (LAM)

HBsAg Loss or Seroconversion

The rate of HBsAg seroconversion in most studies does not differ from what would be anticipated to occur spontaneously. 126 Although rare, LAM has been shown to result in HBsAg seroclearance at an early age (late teens / early twenties) after 27 and 24 month use. 128

HBeAg Seroconversion

HBeAg seroconversion increases with duration of LAM treatment from 16-18% at year 1 to 27%, 40%, 47%, and 50% at years 2, 3, 4, and 5, respectively. 87, 93, 127-130 Unfortunately, the incidence of LAM resistance increases with duration of therapy from 14% at 1 year to 70% at 5 years. 107 HBeAg seroconversion rates appear to increase with elevated pretreatment ALT levels. 131, 132 Data from 406 patients who received LAM 100 mg daily for one year showed HBeAg seroconversion occurred in 2%, 7%, 20%, and 42% of patients with pretreatment ALT levels within normal, 1-2 times normal, 2-5 times normal, and more than 5 times normal. 132 The corresponding figures for 196 patients in the placebo group were 0%, 5%, 9%, and 15%, respectively. If therapy is stopped before HBeAg seroconversion, viral replication returns; hence, long-term therapy is required in most patients.

Virological Response (HBV DNA)

One year of LAM therapy results in suppression of serum HBV DNA. 92, 93, 133 One randomised placebo controlled trial showed that almost all patients treated with LAM (98%) had a reduction of serum HBV DNA levels. 134 Serum HBV DNA levels became undetectable under LAM (< 0.7meq/mL) in 44% versus 16% in the placebo group.

Biochemical Response (ALT levels)

One year of LAM therapy results in ALT normalisation in a significant number of patients. 92, 93, 133 One randomised placebo-controlled trial showed normalisation of ALT levels in 41% versus 7% in the placebo group over a one year period. 134

Histological Improvement

Over a one year period, LAM therapy results in histologic improvement in three clinical trials involving a total of 713 naïve patients. 92, 93, 133 Histologic improvement, defined as a reduction in necroinflammatory score by ≥ 2 points, was observed in 49-56% treated patients and in 23-25% of controls. 134

Normal Pre-treatment ALT levels

Lower HBeAg seroconversion rates appear to be achieved in patients with normal ALT levels, and higher rates with elevated ALT levels. 131, 132 Pooled data from LAM treated patients with normal pretreatment ALT levels show HBeAg seroconversion occurred in only 2%.
Predictors of Response
Pre-treatment factors predictive of response are higher serum ALT level and high degree of histologic necroinflammatory activity. Success of antiviral therapy and degree of viral suppression by nucleoside analogues appears independent of HBV genotype.

Adefovir divipoxil (ADV)

HBsAg Loss or Seroconversion
HBsAg loss or seroconversion is observed in ≤ 5% of patients taking ADV.

HBeAg Loss or Seroconversion
HBeAg loss increases with extended treatment duration. In the ADV trials, rates of HBeAg loss and seroconversion were higher in treatment-naïve patients than LAM-R patients.

In short (48 week) studies in naïve patients, Marcellin et al. reported statistically significant differences in HBeAg seroconversion rates between ADV (12-14%) and placebo (6%). HBeAg loss was 21%. In another short comparative study, 22% ADV-treated patients achieved HBeAg seroconversion compared to 15% of ETV-treated patients (N.S.).

Patients treated beyond 48 weeks achieved a high rate of seroconversion and HBeAg loss with extension of therapy. By week 96 and 144, 29% and 53% of ADV patients had lost HBeAg, and by 144 weeks 46% had HBeAg seroconversion and 48% had HBV DNA undetectability.

The HBeAg seroconversion achieved during ADV treatment was found to be durable in >90% of patients with a median follow-up of 3 years. The four patients (9%) who seroreverted within 16 weeks were all genotype C.

In HBeAg-positive LAM-R patients, rates of HBeAg loss and seroconversion were higher among patients receiving ADV, either alone or in combination with LAM, compared with patients receiving LAM monotherapy or placebo.

Virological Response
ADV shows a biphasic viral kinetic profile. Among treatment-naïve HBeAg-positive patients, ADV 10 mg daily for 48 weeks can effectively suppress HBV DNA and 28% of patients achieved undetectable HBV DNA by PCR. No patient developed genotypic resistance to ADV in 48 weeks.

Compared to ETV in young anti-viral naïve patients, ADV demonstrated less early reduction in antiviral activity, a higher variability of viral load reduction and a lower reduction in HBV DNA at week 12 (p < 0.0001). While differences were also apparent at 24 weeks, the primary efficacy endpoint was not significant. The mean estimate of efficacy was 99.9% for ETV and 99.5% for ADV, with a difference estimate of 0.41 (95% CI [0.09, 0.73]).

Among LAM-R patients HBeAg-positive patients, the addition of ADV to on-going LAM was significantly more effective than maintenance with LAM alone. In one study, HBV DNA levels were undetectable (<200 IU/mL) in 26% of ADV/placebo patients and 35% of ADV/LAM patients, in comparison with 0% receiving LAM/placebo (P < 0.005). Previous preliminary analysis did not find any significant difference in the HBV DNA suppression and HBeAg seroconversion between LAM-R patients and treatment-naïve patients on ADV.

Biochemical Response
The proportion of HBeAg-positive patients with normalisation of ALT at 48 weeks was 48-55% (ADV 10mg - 30mg dose) compared with 16% for placebo-treated patients (P < 0.001 for both comparisons). After 48 weeks, there was no significant difference in ALT normalisation between ETV and ADV patients (76% vs. 63%).
Patients treated beyond 48 weeks derived additional benefit. By week 144, 80% had achieved ALT normalisation.\textsuperscript{138}

The proportion of LAM-R patients with normalised ALT levels at weeks 48 and 52 was 9% for the LAM/placebo group, compared with 37% for patients treated with LAM/ADV ($P < 0.003$).\textsuperscript{140} Another study\textsuperscript{141} found response rates for LAM-R patients who switched to ADV were similar to those who received a combination of LAM/ADV (47% and 53%, respectively). Rates for both groups were significantly higher than for patients who continued with LAM/placebo (5%).

**Histological Improvement**

At 48 weeks, histologic response was observed in 25% of those on placebo vs. 53% and 59% of patients who received ADV 10 mg and 30 mg, respectively ($p < 0.001$, ADV 10mg or 30mg vs. placebo).\textsuperscript{94} Results of the blinded ranked assessment of baseline and week-48 biopsies demonstrated that patients treated with ADV 10mg had better improvement of necroinflammatory activity ($P < 0.001$) and fibrosis ($P < 0.001$) than patients receiving placebo. Using the Ishak fibrosis score, fibrosis improved in 34% compared with 19% and fibrosis progressed in 11% compared with 21%.

**Entecavir (ETV)**

**HBsAg Loss or Seroconversion**

Over 48 weeks, HBsAg loss or seroconversion was observed in 2% of patients taking ETV versus 1% for LAM.\textsuperscript{98}

**HBeAg Seroconversion**

There was no difference in HBeAg loss or seroconversion between ETV and LAM after one and two years of therapy.\textsuperscript{98,145} Over 48 weeks, 15% of ETV-treated patients achieved HBeAg seroconversion, compared with 22% ADV-treated patients (N.S).\textsuperscript{137}

**Virological Response (HBV DNA)**

48 weeks of ETV treatment resulted in a significantly greater HBV DNA reduction (-6.9 vs -5.4 log10) and HBV DNA undetectability <15 IU/mL (67% vs 36%) compared with LAM.\textsuperscript{98} Patients who had a partial virologic response at 48 weeks were offered continued therapy for up to 96 weeks.\textsuperscript{145} Two years of ETV therapy, compared with LAM, resulted in a significantly higher rate of undetectable serum HBV DNA (80% vs 39%, $p < 0.0001$). In the ETV group this increased to 90% at 144 weeks (3 years).\textsuperscript{146} A total of 69 HBeAg-positive, antiviral treatment-naive, patients were randomised to receive either ETV or ADV once daily for a minimum of 52 weeks. ETV demonstrated superior early antiviral activity and viral kinetic profiles compared to ADV, with superior reduction in HBV DNA at Week 12. By Week 48, 58% ETV-treated patients vs 19% ADV-treated patients achieved undetectable HBV DNA by PCR (significance not stated).\textsuperscript{137}

In LAM-R patients, ETV suppressed HBV DNA levels to below the level of detection by PCR in 21% and 34% of patients by Weeks 48 and 96, respectively.\textsuperscript{147}

**Biochemical Response (ALT levels)**

Treatment with ETV over 48-weeks resulted in ALT normalisation in 68% vs 60% for LAM.\textsuperscript{98} In the two year follow up, for patients who had a partial virologic response after 48 weeks, normalisation of ALT increased to 79% and 68% of patients in the ETV and LAM treatment groups respectively.\textsuperscript{145} In the ETV group this increased to 80% at 144 weeks (3 years).\textsuperscript{146} In another study, there was no significant difference in ALT normalisation at 52 weeks of treatment between ETV and ADV (76% vs. 63%).\textsuperscript{137}
7. Treatment of HBeAg-negative CHB

Improving Outcomes

HBeAg-negative CHB may be referred to as anti-HBe-positive, or precore mutant, CHB. It is thought that HBeAg-negative CHB is caused by HBV strains with mutations in the core promoter or precore regions that prevent e antigen expression. HBeAg-negative CHB is distributed worldwide but the prevalence is higher among people born in Africa, the Middle East, and Eastern or Southern Europe, compared with those of French or Asian origin. Development of HBeAg-negative CHB occurs more frequently in patients with genotypes B and D compared to those with genotypes A and C.

Patients with HBeAg-negative CHB, have significantly lower HBV DNA and ALT levels than HBeAg-positive patients (P < 0.05), are significantly older (P < 0.001) and the severity and stage of liver disease is usually more advanced (P < 0.01). Development of cirrhosis is frequent, associated with increased morbidity and mortality; if left untreated, 15 – 20% of patients will develop liver decompensation within 5 years, 15% will die within 5 years of any cause and 15 - 30% will die of liver disease.

HBeAg-negative CHB patients are a difficult-to-treat group; only 15 to 27% have sustained virologic responses to standard interferon, and although antiviral agents can suppress the virus and lead to undetectable HBV DNA levels, long term treatment is required as viral rebound occurs following treatment cessation in almost all patients.

The present recommendation is to withhold therapy from HBeAg-negative individuals with normal ALT activity, low HBV DNA without evidence of significant histological disease and to treat those with increased ALT ( >30 IU/mL (men) >19 IU/mL (women)) and / or HBV DNA levels ≥ 2000 IU/mL. A liver biopsy is advisable in HBeAg-negative CHB patients when ALT and / or HBV DNA levels are elevated and in those with clinical suspicion of significant liver disease. Closely follow those cases with minimal or even mild histological liver disease and initiate therapy if the biochemical and liver disease profile deteriorates. Treatment is essential in all patients with advanced fibrosis/cirrhosis, decompensated chronic liver disease and in the pre- and post-transplantation setting.

As HBeAg seroconversion cannot be an end point, the efficacy of therapy is evaluated on the basis of suppression of HBV replication and ALT normalisation. ADV and ETV are the preferred treatment options, and pegIFN is also appropriate. In practice, pegIFN has replaced the use of standard IFN, and LAM has been omitted due to its high resistance profile. To maximise long term treatment, non-responders should be identified after 12 - 24 weeks, and for those responding suboptimally with detectable HBV DNA after 24 weeks of therapy, switching to an alternative therapy or adding a second agent is recommended to avoid resistance. Long term treatment is usually required.
**Figure 3: Treatment Algorithm for HBeAg-negative CHB**

<table>
<thead>
<tr>
<th>Category</th>
<th>ALT normal&lt;sup&gt;§&lt;/sup&gt; (men &lt; 30 IU/mL; women &lt; 19 IU/mL)</th>
<th>ALT elevated (men &gt; 30 IU/mL; women &gt; 19 IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA &lt; 2,000 IU/mL</td>
<td>HBV DNA &lt; 2,000 IU/mL</td>
</tr>
<tr>
<td></td>
<td>HBV DNA ≥ 2,000 IU/mL</td>
<td>HBV DNA ≥ 2,000 IU/mL</td>
</tr>
<tr>
<td><strong>Immune Control</strong></td>
<td><strong>HBeAg (-) CHB with normal ALT &amp; low HBV DNA</strong></td>
<td><strong>HBeAg (-) CHB with elevated ALT &amp; low HBV DNA</strong></td>
</tr>
<tr>
<td><strong>Treatment Considerations:</strong></td>
<td>No treatment</td>
<td>Consider liver biopsy (II-2)</td>
</tr>
<tr>
<td></td>
<td>Consider therapy only in patients with known significant histological disease even if low level replication (II-1)</td>
<td>Treat if moderate/greater inflammation or fibrosis on biopsy (I)</td>
</tr>
<tr>
<td></td>
<td>Monitor HBV DNA, HBeAg, ALT every 3 months (III)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>ADV or ETV preferred† PEG-IFN also appropriate (I)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Long-term treatment required (I)</td>
<td>PEG-IFN also appropriate (II)</td>
</tr>
<tr>
<td></td>
<td>Review HBV DNA &amp; ALT levels every 3 months (III)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Long-term treatment required (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue antiviral treatment until HBsAg clearance is achieved</td>
</tr>
</tbody>
</table>

<sup>†</sup>Please refer to PBS / Pharmac Schedule for reimbursed indication

<sup>§</sup>The upper limit of normal for serum ALT concentrations
**pegIFN**

**HBsAg Loss or Seroconversion**

Both pegIFN and dual therapy (pegIFN/LAM) achieved greater HBsAg seroconversion than patients on LAM alone.\textsuperscript{89, 90} In a roll-over long-term observational study, additional parameters were measured up to 3 years post-treatment. Not unexpectedly, HBsAg loss and seroconversion was 0% for LAM at 1, 2, and 3 years. pegIFN HBsAg loss increased from 3% at 1 year to 8% after 3 years. HBsAg seroconversion was 3% at year 1 to 4% after 3 years. For dual therapy (pegIFN/LAM) HBsAg loss was 4% at 1 year and 8% after 3 years; and HBsAg seroconversion was 3%, 2%, and 3% after year 1, 2 and 3 respectively.\textsuperscript{155}

**Virological Response (HBV DNA)**

Response rates were higher for HBeAg-negative patients than for HBeAg-positive patients.\textsuperscript{90}

pegIFN 2b (180 ug/week) monotherapy has been investigated in 177 HBeAg-negative patients and compared to LAM monotherapy and to pegIFN/LAM dual therapy for 48 weeks.\textsuperscript{90} Taking as endpoint the response at 6 months after therapy, pegIFN was significantly better than LAM for HBV-DNA suppression <2,000 IU/mL (43% vs. 29%). More profound HBV-DNA suppression (undetectable) was seen in 19% vs. 7%.

Forty-eight patients received pegIFN 2b either alone or with LAM for 48 weeks and were followed for an additional 24 weeks. At the end of follow-up, virological response rates (HBV DNA undetectability) were similar in the monotherapy (24%) and the dual therapy (26%) groups.\textsuperscript{156}

The durability of viral responses (< 2000 IU/mL) to pegIFN and dual treatment (pegIFN/LAM) were relatively stable over the course of follow up: at 1 year 35% and 35%, respectively; at 2 years 29% and 25%, respectively, at 3 yrs 30% and 27%, respectively. For LAM the viral responses were 24% at year 1, 14% after 2 years, and 15% after 3 years. Reviewing a selected segment of the patients taking pegIFN alone over three years showed there was 88% durability of the HBV DNA response.\textsuperscript{155}

**Biochemical Response (ALT levels)**

In the pegIFN studies, people treated with LAM monotherapy had the highest response rates at end of treatment, but the lowest at end of follow-up. In HBeAg-negative patients,\textsuperscript{90} the proportions of patients with an ALT response at week 72 (end of follow-up) were 59%, 60% and 44% in the pegIFN, pegIFN and LAM and LAM groups, respectively. The differences between the pegIFN group and the LAM group were statistically significant (\(P = 0.004\)), as were those between the pegIFN + LAM and LAM groups (\(P = 0.003\)). Summary of results 3 years post-treatment identified the long-term biochemical responders (with ALT < 30 IU/mL) to pegIFN, pegIFN + LAM and LAM alone were 28%, 28% and 16% respectively.\textsuperscript{155}

**Predictors of Response**

Pretreatment predictors of response:\textsuperscript{157, 158}

- High baseline ALT
- Low baseline HBV DNA
- Younger age and
- Female sex
- Genotype (A,B,C > D)

At 1 year post-treatment HBV genotype was significantly predictive of efficacy for patients treated with pegIFN with or without LAM.\textsuperscript{158}

Patients who become HBV DNA negative by PCR after 12 weeks of treatment with pegIFN have been shown to have a better chance for a sustained virological response.\textsuperscript{159} Longer treatment duration and an early biochemical response to therapy may also be associated with a greater likelihood of a sustained virological response.\textsuperscript{160}
Lamivudine (LAM)

HBsAg Loss or Seroconversion
Low HBsAg pretreatment levels are significantly associated with HBsAg seroconversion. LAM treatment suppresses HBsAg levels but at a significantly slower rate compared with IFN (P = 0.022). Serial HBsAg measurements may be useful for prediction of HBsAg loss and data suggest that to achieve this, 5.4 years of sustained response to IFN or 10.6 years of effective LAM therapy are potentially needed.

Virological Response (HBV DNA)
Several studies have reported that serum HBV DNA is suppressed to undetectable levels (PCR assays) in 60 to 70% patients after one year of treatment. However, the vast majority (90%) of patients relapsed when treatment was stopped. High rates of responses maintained up to year 2 of therapy have recently been observed with LAM treatment of HBeAg-negative (and HBeAg-positive) patients included in large Phase III multi-centre trials comparing ETV with LAM, and LdT with LAM. The rates of long-term sustained responses increased significantly if undetectable HBV DNA is achieved within 24 weeks of therapy. For example, virologic remission (undetectable HBV DNA by PCR assay) at week 24, had a positive predictive value of > 90% for maintenance of the response ≤ 4 - 5 years. Non-achievement of this early end point indicated a need for the addition of other compounds without cross-resistance (e.g. ADV).

An extended duration of treatment results in a progressively lower rate of response due to the selection of LAM-resistant mutants. Only about 30 – 40% of LAM-treated HBeAg-negative patients can maintain virologic remission under therapy with up to 5 years of continuous treatment with long-term benefit. In one study of 201 patients, virologic remission (undetectable HBV DNA by PCR assay) decreased from 73% at 12 months to 34% at 48 months. In contrast, one study suggested LAM could be stopped after 2 years in patients with persistently undetectable HBV DNA levels, with lower rates of relapse than reported in prior studies. The optimal duration of long-term LAM therapy in HBeAg-negative patients is unknown at this stage.

Biochemical Response (ALT levels) & Histological improvement
Overall, approximately two thirds of patients have a biochemical response after 6-12 months of LAM therapy, with necroinflammation improving in a similar proportion. In one study, biochemical remission decreased from 84% at 12 months to 36% at 48 months in proportion with the increase in LAM resistance.

Adefovir divipoxil (ADV)

HBsAg Loss or Seroconversion
Over a 240-week period, 5% of patients experienced HBsAg loss and seroconverted to anti-HBs on ADV monotherapy.

Virological Response (HBV DNA)
Virological response rates were significantly higher for ADV than placebo. ADV treatment of HBeAg-negative CHB for 48 weeks has been found to suppress HBV DNA levels to < 200 IU/mL in ~70% of treated individuals compared with 8% of patients who had switched from ADV to placebo and 76% who had switched from placebo to ADV at 48 weeks. Long term treatment with ADV maintains or increases the satisfactory initial response rates. At 144 weeks, 79% of patients had HBV DNA levels < 200 IU/mL and resistance mutations rtN236T and rtA181V were identified in only 5.9% of patients. After 240 weeks, 67% (ADV-ADV group) and 53% (placebo-ADV group) had HBV DNA less than < 200 IU/mL.
The decrease of HBV DNA levels to < 200 IU/mL at week 48 of therapy is highly predictive of maintenance of the response at year 3 with a probability of HBV resistance as low as < 4%. In addition, all 37 patients from a single centre with undetectable HBV DNA at the end of 4 or 5 years of ADV monotherapy had lost HBV DNA detectability much earlier than week 48. At the same time, ADV-treated HBeAg-negative CHB patients maintaining HBV DNA levels > 20,000 IU/mL at week 48 have a 67% probability of genotypic HBV resistance to ADV at year 3.

Biochemical Response (ALT levels)

Compared with placebo, normalisation of ALT levels after 48 weeks of ADV occurred in 75% of patients. At 96 weeks, 73% of those who continued with ADV for the second phase had normalised ALT. This proportion of patients was generally sustained through 240 weeks when the effect of patients dropping out for reasons other than resistance or hepatocellular carcinoma is considered. There were no statistically significant differences in the percentages with ALT normalisation after 48 or 240 weeks with ADV.

Histological Improvement

Significant improvements in liver histology were observed following long-term treatment with ADV. By ranked assessment, liver biopsies after 192 (placebo-ADV group) or 240 weeks (ADV-ADV group) of treatment showed that 86% and 83% of patients had improvement in necroinflammation and 73% and 75% had improvement in fibrosis compared with their pretreatment biopsy, respectively. The median change in Knodell necroinflammation score from the time patients started on ADV was −4.5 points at 192 weeks and −5.0 points at 240 weeks, and the median change in Ishak fibrosis score was −1.0 point for both groups. The proportion of patients with at least a 1-point improvement in Ishak fibrosis score increased from 39% after 48 weeks of ADV to 55% and 71% after 192 and 240 weeks of treatment, respectively. 58% patients with pretreatment bridging fibrosis or cirrhosis improved in their Ishak fibrosis scores by at least 2 points, and 3 of the 4 patients with cirrhosis improved by 4 points.

Predictors of Response

In a retrospective analysis of HBeAg-negative patients who had ADV withdrawn by study design, the longer duration of HBV DNA suppression while on ADV treatment, the lower the risk of post-treatment flare. The decrease of HBV DNA levels to < 200 IU/mL by week 48 of therapy has been found to be highly predictive of maintenance of the response at year 3 with a probability of HBV resistance as low as < 4%. This, combined with the fact that HBeAg-negative patients usually harbour low HBV DNA levels, makes ADV suitable for long-term treatment of this subset of patients.

Entecavir (ETV)

Virological Response (HBV DNA)

In treatment-naïve patients with HBeAg-negative CHB, 48-week treatment with ETV was found to be significantly more effective than LAM regarding suppression of HBV replication. More patients treated with ETV had undetectable HBV DNA levels according to a PCR assay (90% vs. 72%, P<0.001) Similarly to LAM and ADV, therapy cessation is followed by relapses and data on treatment continuation are restricted to a few patients with only a partial response to the 1-year ETV course. There was no evidence of resistance to ETV over the 48 week period. Safety and adverse-event profiles were similar in the two groups.

Biochemical Response (ALT levels) & Histological Improvement

More patients treated with ETV than LAM had normalisation of ALT levels (78% vs. 71%, P=0.045). Histologic improvement after 48 weeks of treatment occurred in 70% patients in the ETV group who had adequate baseline liver-biopsy specimens that could be evaluated, as compared with 61% such patients in the LAM group (P=0.01).
8. Compensated and Decompensated Disease

The incidence of cirrhosis was estimated to be 2 to 5 per 100 person-years\textsuperscript{178, 179} in HBeAg positive CHB and 8 to 9 per 100 person-years in HBeAg-negative CHB.\textsuperscript{180} Approximately 20\% of patients with compensated CHB-cirrhosis will decompensate over 5 years.\textsuperscript{181} There is a marked decrease in survival among patients with decompensated cirrhosis, and lower survival among HBeAg-positive patients. The 5-year survival rates of HBeAg-positive and HBeAg-negative patients with compensated CHB-cirrhosis have been estimated to be 72 and 97\%, respectively.\textsuperscript{182} The corresponding figures for patients with decompensated cirrhosis are substantially lower, 0 and 28\%, respectively. Risk factors associated with an increased risk of progression to cirrhosis or hepatic decompensation, include active viral replication, older age, advanced fibrosis on biopsy, concomitant alcohol use, co-infection with other hepatitis viruses (C or D) or HIV.\textsuperscript{182, 183}

Figure 4: Survival of Patients with CHB-Cirrhosis\textsuperscript{184}

Goal of Therapy

The principal goal of treatment are to prevent or delay the development of complications of cirrhosis, decompensation and hepatocellular carcinoma.\textsuperscript{185} To achieve this, treatment objectives are:

1. HBV DNA suppression (< 2000 IU/mL; preferably PCR undetectable < 50 IU/mL)
2. ALT within normal limits
3. Histological improvement

Patients to Treat

All patients with well-compensated cirrhosis should be considered for therapy if the HBV DNA level is ≥ 2000 IU/mL whether they are HBeAg-positive or anti-HBeAg-negative. If HBV DNA is lower than this threshold, observe patients closely and monitor HBV DNA and ALT every 3 months. If HBV DNA is low but ALT levels are elevated, consider treatment.

All patients with hepatic decompensation should be treated early with an antiviral agent regardless of HBV DNA concentration to either suppress viral replication, or prevent possible flares in disease activity. Such patients should be considered for liver transplantation and selection of the appropriate CHB therapy should be made in consultation with the local liver transplant program.

Patients with compensated and decompensated cirrhosis should be screened for HCC with ultrasound (US) and AFP examination every 6-12 months.
Treatment Considerations

**Compensated Cirrhosis**

pegIFN has been studied in patients with HBeAg-positive CHB with well-compensated cirrhosis.\(^88\) Doses of pegIFN up to 270mcg/week were not associated with hepatic decompensation, although some patients required permanent dose modification or premature discontinuation of treatment because of marked transaminase flares. If ALT increases are severe and progressive despite reduction of pegIFN dose or are accompanied by increase in bilirubin or evidence of hepatic decompensation, pegIFN should be immediately discontinued. The safety and optimal dose of pegIFN in patients with compensated HBV-cirrhosis need to be established in larger studies.

For patients with compensated cirrhosis, antiviral treatment can reduce the risk of hepatic decompensation and possibly the development of HCC, but the risk of HCC is not entirely eliminated. LAM and ADV treatment have been shown to reduce hepatic necroinflammation and to a smaller extent hepatic fibrosis, in patients with CHB.\(^92,\)\(^93,\)\(^166,\)\(^169\) Regression of fibrosis and even cirrhosis have been reported in patients with maintained viral suppression during long-term LAM treatment. These data indicate cirrhosis can be prevented or even reversed if viral suppression can be maintained.

There is limited data available for ETV in these patients. Patients with cirrhosis in the phase III ETV study were analysed retrospectively for their response to therapy. Results showed ETV was well tolerated and superior to LAM for the end points of histologic improvement, ALT normalisation, and undetectable serum HBV DNA.\(^186\)

**Hepatic Decompensation**

All patients with decompensated cirrhosis, with any level of detectable HBV DNA, should be started on antiviral therapy as soon as the diagnosis is established, with the dual goals of stabilising or improving liver function and achieving viral suppression prior to transplantation in those who are transplant candidates.

A combination of a nucleotide (ADV) and a nucleotide (LAM or ETV) or a drug with a high barrier to resistance is recommended. pegIFN is contraindicated in patients with decompensated liver disease, largely because of the high rate of serious, sometimes life-threatening adverse events.\(^187\)

LAM and ADV have been shown to stabilise or improve hepatic function, may stave off the need for liver transplantation and reduce CHB recurrence post-transplant.\(^188-191\) Clinical improvements tend to lag behind virological responses. Studies of LAM and ADV in patients with decompensated disease found a median clinical response time of ~6 months.\(^186,\)\(^191,\)\(^192\) Thus, patients with severely decompensated liver disease may die before the clinical benefits of antiviral treatment can be realised, emphasising the importance of concurrent consideration of liver transplantation. LAM and ADV has established safety and tolerability in patients with decompensated cirrhosis and those awaiting liver transplantation. ETV has not been fully evaluated for use in this situation, but, barring unexpected toxicity, should also be an effective agent.

The emergence of drug-resistance is associated with an increased frequency of hepatitis flares, clinical deterioration, worsening of liver decompensation, and even liver-related death.\(^193\) Thus, monitoring of HBV DNA levels at regular intervals should be used to detect virological breakthrough early and prior to worsening of clinical status.

Patients presenting with decompensated cirrhosis and LAM-R are challenging. ADV therapy is the best studied. In decompensated cirrhotics with LAM-R, treatment with ADV resulted in improvement in liver enzymes, indices of liver synthetic function, and clinical stabilisation.\(^140,\)\(^191\) The risk of ADV resistance in these patients appears higher if ADV replaced LAM rather than added on (combination therapy), and greater in those with a suboptimal virological response to ADV.\(^194\) For patients with ADV resistance or both LAM and ADV resistance, data suggest ETV and tenofovir (TDF) are options.\(^194,\)\(^195\) Genotypic ETV resistance has been reported in 7% of LAM-refractory patients after 1 year of treatment.\(^196\) TDF is an approved agent for HIV, which also has activity against wild-type and LAM-resistant HBV; case reports of TDF treatment in patients showing a suboptimal virological response to
ADV have been published, though the total number of treated patients is small. Taken together, the best options for patients with decompensated cirrhosis with LAM-R HBV infection appears to be combined ADV plus LAM. Other drug combinations that have not been studied but would be predicted to be effective are LAM plus TDF, or ETV plus ADV.

Dose adjustments are required with use of LAM, ADV, and ETV in patients with kidney dysfunction. Due to concerns regarding potential kidney toxicity related to higher dose ADV therapy, monitoring of renal function is recommended in those on long-term ADV therapy.

**Figure 5: Treatment Algorithm for Compensated and Decompensated Cirrhosis**

- **Compensated Cirrhosis (HBeAg+ or HBeAg-)**
  - **HBV DNA < 2,000 IU/mL**
    - Treatment Considerations:
      - Treat or observe (II-2)
      - ETV or ADV preferred (II-3)
      - To avoid flares PEG-IFN should only be used with caution in early, well-compensated cirrhosis (II-3)
      - Long term treatment required (I)
  - **HBV DNA ≥ 2,000 IU/mL**
    - Treatment Considerations:
      - Treat (II-2)
      - ETV or ADV preferred (II-3)
      - To avoid flares PEG-IFN should only be used with caution in early, well-compensated cirrhosis (II-3)
      - Long term treatment required (I)

- **Decompensated Cirrhosis (HBeAg+ or HBeAg-)**

- **Any detectable level of HBV DNA**
  - Treatment Considerations:
    - Treat early (II-1)
    - Combination with a nucleotide (ADV) and a nucleoside (LAM or ETV) or use a drug with a high barrier to resistance (II-2). PEG-IFN is contraindicated (II-3)
    - Life-long treatment required (II-3)
    - Consider / refer to transplant centre for evaluation for OLT (III)

†Please refer to PBS / Pharmac Schedule for reimbursed indication
The upper limit of normal for serum ALT concentrations
9. Special Populations

Co-infection HIV / HBV

Co-infection with HBV in human immunodeficiency virus (HIV)-infected patients is common. Both share transmission patterns and risk factors. Among the estimated 40 million persons infected with HIV worldwide, an estimated 2–4 million have CHB. CHB prevalence is higher among HIV-infected persons than among the general population.

CHB does not significantly affect the course of HIV disease, but HIV does alter the course of CHB. HIV-infected persons are less likely to clear acute HBV infection spontaneously, will more likely have a higher level of HBV replication, and face a higher risk of liver-related death than those monoinfected with either virus.

Conditions associated with CHB are currently among the leading causes of hospital admission and death in the HIV-infected population. Therefore, the adequate management of CHB is now being considered a priority in HIV/HBV co-infected patients.

Goal of Therapy

The principal goal of treatment in co-infection are the same as monoinfection, i.e. prevent or delay the development of complications of cirrhosis, decompensation and hepatocellular carcinoma. To achieve this, treatment objectives are:

1. HBV DNA suppression (< 2000 IU/mL; preferably PCR undetectable < 50 IU/mL)
2. ALT within normal limits
3. Histological improvement

When to Treat

All patients with detectable HBV DNA should be treated. The optimal time to initiate CHB treatment in HIV co-infected patients has not been established. Based on available evidence, consensus suggests using the HBV DNA criteria applied to CHB-monoinfected patients. These depend on HBeAg serostatus. In HBeAg-positive patients, a serum HBV DNA level >20,000 IU/mL justifies consideration of treatment. In HBeAg-negative patients, the cut off is a serum HBV DNA level >2,000 IU/mL. ALT levels also should be considered. If the results of liver function tests are out of proportion to HBV DNA levels, check for other causes of liver disease. Patients who do not meet criteria for anti-HIV treatment should undergo a biopsy to evaluate the hepatic inflammation and fibrosis stage. Those with a METAVIR ≥A2 and/or ≥F2 should receive CHB therapy.

Treatment Considerations

Co-infected patients who do not meet criteria for anti-HIV(HAART) treatment In HBeAg-positive patients, consider pegIFN or ADV. Typically, pegIFN is not preferred for the treatment of HBeAg-negative patients, because the chance to achieve HBsAg seroconversion and to maintain HBV DNA suppression off therapy is low. These patients should not receive agents with dual (anti-HIV) activity (e.g. LAM, ETV*, TDF, and FTC) as it raises the risk of early HIV resistance, and may limit future HIV therapeutic options. Patients generally need long-term maintenance therapy and combination therapy.

Co-infected patients who meet criteria for anti-HIV(HAART) and CHB treatment The immune restoration associated with highly active antiretroviral therapy (HAART) can improve control of HBV replication and loss of HBeAg in some patients, but can also lead to increased immune-mediated liver injury. On balance, use of HAART before severe immunosuppression develops may be beneficial. Still, the complexity of CHB, HIV, and HAART interactions must be evaluated for each individual.

HAART that includes two dual-acting drugs (e.g. LAM, TDF, FTC) constitutes the preferred option for these patients. The best choice is to combine a nucleoside and a nucleotide analogue to prevent long-term resistance (ie, TDF plus LAM or FTC). ADV can be substituted for TDF if the latter is contraindicated or otherwise not a desirable option. Similarly, ETV offers an alternative to FTC or LAM.
If HAART treatment is altered because of intolerance or lack of efficacy, the CHB component should be continued, or substituted with another agent. Stopping CHB therapy has been associated with HBV reactivation and ALT flares. If the patient has achieved HBeAg seroconversion an adequate course of consolidation treatment must be undertaken prior to discontinuation of CHB treatment.

**Co-infected patients who meet criteria for HAART only** Individuals with persistent controlled HBV replication may not need agents with dual activity. Monitor ALT and serum HBV DNA every 3 or 4 months. If CHB treatment does not begin at the same time as ART, delay its introduction until HIV replication is controlled or there is evidence of liver disease. Specifically, monitor HBV DNA for the anti-HBV treatment thresholds.

**Co-infected patients with LAM-Resistance** LAM resistance is reported to be higher in HBV/HIV co-infection. Detectable HBV viraemia > 200 IU/mL at 48 weeks is a risk factor for the development of CHB drug resistance. These patients require a HAART regimen with maximum activity against both viruses. LAM should be maintained and ADV or TDF should be added.

**Co-infected patients with cirrhosis** As preventing resistance and ensuring compliance are paramount considerations, cirrhotic patients should receive combination CHB therapy (e.g., TDF plus FTC or LAM included in the HAART regimen or ADV plus ETV or LdT if there is no indication for anti-HIV therapy). Patients with cirrhosis should be monitored closely during the first 12 to 24 weeks of therapy because of risk of ALT flare and immune reconstitution hepatitis. Serum HBV DNA should be assessed every 12 weeks. This is especially true for those with CD4 counts <200 cells/mm³.

**Co-infection HBV / HCV**

HBV and hepatitis C virus (HCV) co-infection is common. Patients who are co-infected represent a unique group with diverse serologic profiles. In patients with CHB, estimates of the rates of HCV coinfection vary from 9 to 30%, depending on the geographic region. These numbers may underestimate the true number of patients with both viral infections because no large-scale studies have been performed, and there is a well-described phenomenon of "serologically silent" occult HBV infection (i.e., patients with negative HBsAg but detectable serum HBV DNA) in patients with chronic hepatitis C (CHC). Combined CHB and C leads to more severe liver disease, higher rates of cirrhosis with decompensation and an increased risk of hepatocellular carcinoma. Co-infected HBV/HCV patients represent a treatment challenge. Several studies have shown that the two infections interact with each other, affect immune responses and can reciprocally (and simultaneously) inhibit each other. Either virus can play a dominant role and both viruses have the ability to induce seroconversion of the other. The chronology of infection has a role in determining the dominant virus; and HBV and HCV can alternate their dominance. However, the overall dominant effect appears to be HCV suppression of HBV. Furthermore, co-infected patients have been demonstrated to have lower levels of both HBV DNA and HCV RNA than corresponding monoinfected controls, indicating that concurrent suppression of both viruses by the other virus can also occur.

**Goal of Therapy**

The principal goal of treatment in co-infection are the same as monoinfection, i.e. prevent or delay the development of complications of cirrhosis, decompensation and hepatocellular carcinoma. To achieve this, treatment objectives are:

1. HBV DNA suppression (< 2000 IU/mL; preferably PCR undetectable < 50 IU/mL)
2. ALT within normal limits
3. Histological improvement

**When to Treat**

There is no currently established standard of care for patients who are co-infected with HBV and HCV, although assessment of the "dominant" virus is helpful in determining a treatment strategy. Thorough serologic and virologic testing is required in dually infected patients prior to consideration of therapy. Caution must be taken with treatment of co-infected individuals, as exacerbations of liver
Traditionally, the spread of HDV is linked with HBV, strategies to decrease the incidence of HBV will result in a corresponding decrease in CHD, e.g. universal HBV vaccination and post-exposure prophylaxis will help eliminate HDV co-infection in the future. Education to reduce high-risk behaviours among persons with CHB will also reduce the incidence of HDV superinfection.
Goal of Therapy
The principal goal of treatment in co-infection are the same as monoinfection, i.e. prevent or delay the development of complications of cirrhosis, decompensation and hepatocellular carcinoma. To achieve this, treatment objectives are:
1. HBV DNA suppression (< 2000 IU/mL; preferably PCR undetectable < 50 IU/mL)
2. ALT within normal limits
3. Histological improvement

Treatment Considerations
CHD is difficult to treat but, as the risks of end-stage liver disease are higher, active therapeutic intervention for CHB and D is required.247-254

IFN treatment has proven efficacy in CHD. 254-257 Although the response to IFN varies and occurs at different time points, sometimes after discontinuation,258 the rate of response is generally proportional to the dose of IFN, with 9 million units (MIU) three times a week being more effective than 3 MIU thrice weekly.254, 257 In CHD patients, there is no evidence that ribavirin,249, 250 acyclovir259 or LAM,251, 260-263 alone or in combination with IFN-based therapy, enhances treatment outcomes.

As side effects may prohibit IFN use, pegIFN treatment in standard doses for one year is a promising option. Persistent disappearance of HDV RNA after 6-12 months of treatment with pegIFN in previous IFN nonresponders has recently been reported.248, 264 In small studies, a sustained virological response (categorised as undetectable HDV RNA by PCR and normalisation of ALT six months after treatment) was achieved in 17- 43% of CHD patients.247, 265, 266 Sustained biochemical responses were higher in these studies. Nonresponders were identified by a < 3 log decrease of HDV RNA at 6 months of treatment.

Chemotherapy & Immunosuppressive Therapy
Reactivation of HBV is a serious cause of morbidity / mortality in patients undergoing cytotoxic or immunosuppressive therapy. While the majority of cases have been reported among patients who are HBsAg positive, any previous exposure to HBV infection (HBsAg-negative, anti-HBc) increases risk of reactivation.267 Patients in this group can suffer from reactivation in response to immune suppression either as a result of cancer chemotherapy,69, 268-271 short courses of corticosteroids, immuno-modulatory agents (anti-cytokines),272, 273 heart, kidney and liver transplantation274 and even as a result of advancing immune deficiency due to HIV infection.275 Rates of HBV reactivation in HBsAg positive patients receiving chemotherapy can be as high as 70%.267, 276 Mortality rates, primarily related to liver failure, range from 4 - 60%.277 Reactivation also leads to interruption of anticancer treatment and jeopardise the patient’s prognosis. Treatment delays for up to 100 days contribute to lower disease free and lower overall survival for these patients.278 In a study of breast cancer patients, over 70% with HBV reactivation required premature termination of chemotherapy or disruption of treatment.

Reactivation of HBV infection may occur during or after completing a full course of chemo- or immunosuppressive therapy.279 Enhanced viral replication may occur during intense cytotoxic or immunosuppressive therapy or may be related to the restoration of immune function following withdrawal of cytotoxic or immunosuppressive therapy, which causes rapid immune-mediated destruction of infected hepatocytes.270, 279

When to Treat
HBsAg screening (and HBcAb measurements) should be performed in all patients prior to initiation of chemo- or immunosuppressive therapy. All patients undergoing bone marrow or solid organ transplantation and some forms of monoclonal antibody therapy (rituximab, infliximab, etc.) should be screened for HBV markers prior to treatment. Recipients of organs (e.g. kidney, lung) should receive LAM prophylaxis for at least the first post-transplant year during which time immunosuppression levels are at their highest.280-282
Treatment Considerations

**HBV naïve patients** should be immunised against hepatitis B, as should haematopoietic stem cell donors.

**HBsAg or HBV DNA positive patients** Prophylactic antiviral therapy is recommended in all HBsAg positive patients at the onset of chemo- or immunosuppressive therapy to improve clinical outcomes. The greatest experience in preventing HBV reactivation with chemotherapy has been with LAM. Several studies have shown that preemptive prophylactic LAM can prevent or at least ameliorate the course of reactivation. Delaying therapy until HBV DNA levels rise is ineffective. Preemptive prophylactic LAM therapy has also increases the likelihood of patients completing their chemotherapy without interruption. In immunosuppressed patients, a cumulative resistance rate of 41% after 31 months in HBsAg positive patients receiving LAM has been observed. In these cases, the administration of additional or alternative antiviral drugs such as ADV may be necessary.

The optimal duration of LAM prophylaxis remains controversial. People with high baseline HBV DNA > 2,000 IU/mL should continue treatment until they reach treatment end points for CHB. Those with baseline HBV DNA < 2,000 IU/mL should continue treatment for at least 1 year following the completion of chemotherapy. However, some patients, based on their liver histology and viral status, may require treatment indefinitely.

While studies to date have focused on LAM, ETV with an improved resistance profile may be an alternate treatment, particularly in patients who require more than 12 months of therapy in whom there is a higher risk of resistance to LAM.

pegIFN / IFN should be avoided in view of the bone marrow suppressive effect and the risk of exacerbating immune-mediated diseases (autoimmune disorder, graft rejection, or graft vs host disease).

**HBsAg negative patients** Although the risk of reactivation may be low (<5%) in these patients, reemergence of HBV may be severe and even fatal. If nucleoside analogues are not used prophylactically in anti-HBc positive patients, these individuals should be monitored regularly with ALT and HBsAg testing every 1-3 months and antiviral therapy should be initiated as soon as there is evidence of HBV reactivation, without waiting for a rise in ALT.

While HBV reactivation can occur in persons who are HBsAg negative but anti-HBc and anti-HBs positive and in those with isolated anti-HBc, this is infrequent, and there is not enough information to recommend routine prophylaxis for these individuals.

All patients undergoing cytotoxic / immunosuppressive therapy should be checked for HBV serologic markers and serum HBV DNA levels.

Organ Transplant Patients

CHB frequently requires liver transplantation. Reactivation of HBV after organ transplantation in HBsAg carriers may be fatal. Other solid (non-liver) organ transplants can also get infected de novo or through reactivation from previous active or inactive infections. CHB infection in kidney, heart, and other organs has become a serious long-term problem and an important co-morbidity affecting graft and patient survival.

For much of the 1990s, CHB was considered a formal contraindication for liver transplantation, since recurrence of infection without prophylaxis occurs in 75 - 90% of the patients, with significant morbidity and mortality and few therapeutic alternatives. Significant improvements in surgical techniques and immunosuppressive regimens, means organ transplantation has become the most effective and lifesaving therapy for patients with chronic renal failure, acute and chronic liver failure, hepatocellular carcinoma, heart failure and respiratory failure.
Goal of Therapy
The principal goal of treatment is to prevent or delay the development of complications of cirrhosis, decompensation and hepatocellular carcinoma. To achieve this, treatment objectives are:

1. HBV DNA suppression (< 2000 IU/mL; preferably PCR undetectable < 50 IU/mL)
2. ALT within normal limits
3. Histological improvement

Treatment Considerations
All patients awaiting solid organ transplantation should be vaccinated against HBV, although the likelihood of an effective antibody response is low. Recipients with documented seroconversion following HBV vaccination and persistent protective levels of anti-HBs (>10 IU/mL) do not require antiviral prophylaxis.

HBeAg-negative/HBV DNA-negative No treatment is necessary prior to transplantation. HCC screening with alpha-fetoprotein levels and imaging of the liver every 6 months is recommended.

High-risk group (HBeAg-positive/HBV DNA-detectable) In order to prevent HBV recurrence post-transplant, and control viral replication to the lowest possible level at the time of surgery, patients should be commenced on antiviral therapy at the time of placement on the transplant waiting list (if not before) and started on combination LAM plus HBIG during the anhepatic phase or immediately post-operatively.

Resistance occurs more frequently, and at an earlier time point in the transplantation setting with immunosuppressed patients. Life-long combination prophylaxis with low-dose intramuscular HBIG and LAM is effective in preventing recurrent HBV, may protect against the emergence of resistant mutants, and is significantly more cost-effective than HBIG monotherapy, or high dose HBIG combination therapy.

In patients with YMDD mutations and evidence of viral reactivation, combination of LAM and ADV, or the latter alone, is recommended. ADV is effective and safe in wait-listed or posttransplantation CHB patients with LAM-R and prevents graft reinfection with or without HBIG.

Low-risk group (HBeAg-Negative/HBV DNA-Negative) HBIG should be initiated during the anhepatic phase. LAM and/or ADV (in presence of YMDD mutations) should be given starting the day of the transplant and both monthly intramuscular low dose HBIG and an antiviral drug should be given indefinitely.

HBsAg-negative/HBV DNA-negative/anti-HBc-positive/anti-HBs-positive No treatment is necessary prior to transplant since the risk of recurrence is very low.

Pregnancy / Lactation
Women with CHB generally do quite well during pregnancy, providing they have not progressed to decompensated cirrhosis. While there are case reports and studies indicating an increased incidence of maternal and neonatal morbidity (e.g. premature delivery, raised incidence of antepartum haemorrhage, foetal distress, and meconium peritonitis, gestational diabetes), as a general rule, a stable liver equals a safe pregnancy.

During pregnancy all markers of liver function (e.g. AST, ALT and total bilirubin) are generally reduced or low due to the expansion of extracellular fluid and pregnancy-associated immunosuppression. The only exception is serum alkaline phosphatase, elevated due to ALP of placental origin. In late pregnancy, or shortly after delivery, many HBeAg-negative and positive women experience significant increases in both ALT and viral load. Vertical transmission, in one study, was only seen in HBeAg-positive mothers with very high levels of viraemia.

HBsAg-positive women who become pregnant may continue treatment only if the potential benefit of treatment outweighs the risk to the foetus. Careful consideration should be given to discontinuing pegIFN / IFN (Category B3) and antiviral therapy (Category B3) unless absolutely indicated. Given the uncertainties regarding foetal risks, no clear recommendations on treatment can be made at this time.
Mother to child transmission occurs often, either in utero or through exposure to blood or blood contaminated fluids at, or around, birth. The risk of perinatal transmission is associated with the HBeAg status of the mother. If a mother is positive for both HBsAg and HBeAg, 70% to 90% of her children become chronically infected.\textsuperscript{317, 318} If a mother is HBsAg-positive but HBeAg-negative the risk of transmission is significantly lower.\textsuperscript{319-321}

**HBsAg screening** All pregnant women should be screened for HBsAg, even if previously tested or vaccinated.

**Modes of delivery** Although elective caesarean delivery has been proposed as a means of reducing mother to child transmission,\textsuperscript{322} the mode of delivery does not appear to have a significant effect.\textsuperscript{323}

**Management of infants** All infants born to HBsAg positive women should receive hepatitis B vaccine and Hepatitis B Immunoglobulin (HBIG) (0.5 mL) ≤12 hours of birth, administered at different injection sites.\textsuperscript{324-327} HBIG and concurrent hepatitis B vaccine have been shown to be 95% efficacious in the prevention of perinatal transmission of HBV.\textsuperscript{328} The evidence on immunisation for infants of HBsAg-positive mothers is strong, and weaker for HBeAg-negative patients.\textsuperscript{326} In general, the risk of perinatal transmission from HBeAg-negative mothers for hepatitis is considered much lower than that from mothers who are HBeAg-positive.\textsuperscript{319, 321, 329} Further, the infants of HBeAg-negative mothers often clear an asymptomatic infection.

**Management of pregnant women with high viral loads** The efficacy of HBIG and the hepatitis B vaccine may be lower in mothers with very high serum HBV DNA levels (>8 log\textsubscript{10} IU/mL) at the time of delivery.\textsuperscript{327, 330} In these patients there is some limited evidence to suggest LAM, taken in the last month of pregnancy, may reduce high viral load and reduce, but not eliminate, the risk of child vaccination breakthrough.\textsuperscript{331-334}

At this stage the evidence does not support routine use of antiviral agents during the third trimester of pregnancy to reduce the risk of vertical transmission and pregnant women with high levels of HBV DNA should be referred to specialists for consideration of this treatment.

**Breastfeeding** HBsAg-positive mothers are encouraged to breastfeed their babies.\textsuperscript{335} The benefits of breast-feeding for the health of an infant far outweigh any theoretical increased risk.\textsuperscript{335} While HBV has been isolated in breast milk,\textsuperscript{337} the risk of HBV transmission is very low and comparable for both breast-fed and formula-fed infants.\textsuperscript{336, 338-341} Transmission may be more common in women with the HBeAg.\textsuperscript{342, 343}

It is recommended the baby breastfeeds after the administration of the HBIG.\textsuperscript{325, 336} As the virus is most commonly passed by blood-to-blood routes and mothers should be counselled to take good care of their nipples, ensure proper latch-on and allow the nipples to dry before covering to avoid cracking or bleeding. Breastfeeding should be avoided if the mother has cracked or bleeding nipples.
10. Review of Antiviral Resistance

Antiviral therapy of CHB has changed in the last decade with the development of antiviral treatment. However, due to the slow kinetics of viral clearance and especially that of intrahepatic cccDNA, and to the spontaneous viral genome variability, the efficacy of long-term administration of these antiviral agents is moderated by the emergence of drug-resistant mutants. 344, 345

Clinical Consequences of Resistance

The emergence of resistance mutations has been associated with ALT flares, and occasionally with fatal liver failure. 163, 208, 213, 297, 346, 347 In patients with cirrhosis, LAM resistance may result in severe exacerbation of hepatitis and eventually hepatic failure. 348 Resistance mutations may reduce HBV replication fitness, resulting in lower plasma HBV DNA levels, and hepatitis flares after LAM removal. 212, 349 However, reversion of histological improvement and progression of liver disease occurs in most patients after selection of LAM resistant strains. 169, 380, 357

Definitions of Resistance

The clinical definition of drug resistance to antiviral agents requires standardisation to allow the comparison of resistance data across the different clinical trials and to improve the standard of care. 345 A sensitive and specific HBV DNA assay with a wide dynamic range of quantification, calibrated to express results in WHO international units per ml (IU/mL), should be used to quantify serum HBV DNA levels prior to treatment, to assess response, and to detect virologic breakthroughs. Table 6 outlines standard definitions.

Table 6: Nomenclature for Antiviral Resistance

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Treatment Failure</td>
<td>Inability of NA treatment to reduce serum HBV DNA by $\geq 1 \log_{10}$ IU/ml after the first 3 months of treatment. Primary non-response may be due to factors related to the host, virus, or drug. It is mostly commonly related to lack of adherence to medication. 174, 352, 353</td>
</tr>
<tr>
<td>Genotypic Resistance</td>
<td>The detection of mutation(s) in the HBV genome has been found to develop specifically during antiviral therapy and to confer resistance (and decreased efficacy) to the antiviral agent. With antiviral therapies it currently corresponds to the detection of specific mutations in the viral polymerase gene.</td>
</tr>
<tr>
<td>Virologic Breakthrough</td>
<td>The rise in serum HBV DNA levels during therapy, following the development of genotypic resistance. It is usually defined by a confirmed increase of $\geq 1 \log_{10}$ IU/mL rebound in serum HBV DNA level from nadir, in two consecutive samples one month apart, in patients who have responded and have been compliant with antiviral medication(s). 354, 355</td>
</tr>
<tr>
<td>Clinical / Biochemical Breakthrough</td>
<td>Elevation in serum ALT while on treatment, after achieving normalisation in a medication compliant patient. Serum aminotransferases may remain normal for a few weeks or a few years after virologic breakthrough. Biochemical breakthrough often coincides with a viral rebound, in some cases a marked increase in aminotransferases occurs resulting in a hepatitis flare and rarely hepatic decompensation. 347, 356</td>
</tr>
<tr>
<td>Cross Resistance</td>
<td>Decreased susceptibility to more than one antiviral drug conferred by the same amino acid substitution or combination of amino acid substitutions</td>
</tr>
</tbody>
</table>

Dynamics of Antiviral Resistance

After the emergence of genotypic resistance, clinical deterioration has been shown to occur in the majority of patients (Figure 6). 128, 357 Some patients may show a rapid deterioration with acute
exacerbation of the disease and sometimes liver failure. These severe exacerbations are more frequent with pre-existing liver cirrhosis and a pre-core mutant infection. In other cases, deteriorating liver disease starts progressively after the development of viral drug resistance. In studies of cirrhotic patients, antiviral resistance led to a loss of the clinical benefit as patients developed liver decompensation and hepatocellular carcinoma. These data strongly suggest that careful monitoring of antiviral efficacy is required to adapt antiviral therapy prior to the deterioration of the disease.

**Figure 6: Dynamics of Anti-viral Resistance**

**Rates of Antiviral Resistance**

The incidence of genotypic resistance is related to viral (pretreatment serum HBV DNA level, pre-existing antiviral-resistant mutations), host (immune status, pharmacodynamics), and treatment characteristics (potency, genetic barrier to resistance [number of mutations required to produce a marked decrease in susceptibility to the antiviral drug], and duration of treatment). The incidence of genotypic resistance also varies with the sensitivity of the methods used for detection of resistant mutations and the patient population being studied. The different approaches result in reports of LAM-associated resistance mutations after one year of therapy varying from 15 to 30%.

**Table 7: Rates of Antiviral-Resistant HBV Mutations Reported in Clinical Trials**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rates of genotypic resistance (%)</th>
<th>Yr1</th>
<th>Yr2</th>
<th>Yr3</th>
<th>Yr4</th>
<th>Yr5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleosides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAM</td>
<td>15 - 30</td>
<td>10 - 56</td>
<td></td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[92, 93, 133, 347, 359]</td>
<td>[162, 166, 360]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV (treatment naive patients)</td>
<td>0&lt;sup&gt;0.02&lt;/sup&gt;</td>
<td>&lt;1&lt;sup&gt;0.05&lt;/sup&gt;</td>
<td>&lt;1&lt;sup&gt;0.02&lt;/sup&gt;</td>
<td>&lt;1&lt;sup&gt;0.03&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV (LAM-R patients)</td>
<td>&lt;1&lt;sup&gt;0.04&lt;/sup&gt;</td>
<td>1&lt;sup&gt;0.03&lt;/sup&gt;, 30&lt;sup&gt;0.04&lt;/sup&gt;</td>
<td>27&lt;sup&gt;0.03&lt;/sup&gt;, 30&lt;sup&gt;0.04&lt;/sup&gt;</td>
<td>39&lt;sup&gt;0.03&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nucleotide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADV (treatment naive patients)</td>
<td>0&lt;sup&gt;0.03&lt;/sup&gt;</td>
<td>2&lt;sup&gt;0.02&lt;/sup&gt;</td>
<td>4&lt;sup&gt;0.02&lt;/sup&gt;</td>
<td>18&lt;sup&gt;0.03&lt;/sup&gt;</td>
<td>29&lt;sup&gt;0.03&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>ADV (LAM-R patients)</td>
<td>20&lt;sup&gt;0.02&lt;/sup&gt;, 12&lt;sup&gt;0.03&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Predictive Factors of Resistance

Several baseline and on-treatment predictive factors of resistance have been characterised for LAM in clinical trials and cohort studies:92, 93, 358, 366,115, 352

- High baseline serum HBV DNA levels
- High baseline ALT levels
- High body mass index
- High histologic activity index
- Time to complete viral suppression
- Duration of therapy

While female gender may also predict early resistance, genotype did not influence treatment response nor time to onset of resistance.355, 367

Factors associated with virologic response in ADV treated patients with LAM-R are female gender, HBeAg-negative status and low baseline serum HBV-DNA levels.368 Genotype D HBV infection and low baseline HBV-DNA levels independently predict HBeAg loss.

For the other antiviral agents, little information is available regarding the prediction of resistance.

Multidrug Resistance from Sequential Monotherapy

Sequential treatment with antiviral monotherapy has resulted in the sequential selection of mutations conferring resistance to the initial therapy and subsequently the rescue therapy leading to multi-drug resistance.369,370 For example, sequential resistance to LAM and later ADV or ETV has been reported in patients who were switched to ADV or ETV monotherapy after LAM-resistance developed.370, 371

While constructs with mutations resistant to either drug remain sensitive to the other drug,371 studies show HBV constructs with mutations resistant to both LAM and ADV have marked (> 50 fold) reduction in sensitivity to combination of LAM and ADV, indicating that combination therapy of the two drugs may not be effective in suppressing multidrug resistance once it emerges.372, 373

While clinical trials with high doses of ETV have shown its antiviral efficacy in patients with LAM-R,374 cases of multiple drug resistance were observed in 10% of patients after two years of therapy.375 Persistence of LAM-R mutations in patients who are switched to ETV is worrisome as resistance is greatly enhanced and susceptibility to ETV is decreased by >100-fold, particularly when two or more ETV-associated mutations are present. In one study,374 LAM-R mutations remained detectable in all 20 clones 2 - 4 years after withdrawal of LAM. This specific finding raises concerns about the long-term efficacy of ETV in patients with LAM-resistant HBV.

Clonal analysis shows mutations conferring resistance to multiple antiviral agents co-locate on the same viral genome, suggesting that combination therapy directed against mutants resistant to each treatment may not be adequate in suppressing multi-drug resistant CHB.370-372 This data argues for the benefits of combination therapy over sequential monotherapy to prevent the emergence of multi-drug resistant mutants and de novo combination therapy may prevent the emergence of multi-drug resistant mutants.

Resistance Prevention Strategies

A reasonable clinical goal is to develop an overall strategy that prevents the selection of resistance. Prevention of resistance requires the adoption of strategies that effectively control virus replication. Available evidence indicates the best way to prevent resistance is to:376

<table>
<thead>
<tr>
<th>Table 8: Resistance Prevention Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximise antiviral activity</td>
</tr>
<tr>
<td>Maximise genetic barriers to resistance</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Monitor resistant profiles

Increase pharmacologic barriers
- Ensure patient compliance
- Add-on regimen: Combine nucleotide (ADV) + nucleoside (LAM, ETV)
- Modify treatment strategy early i.e. before biochemical load rebounds

Monitoring Virologic Response and Breakthrough

Monitoring during antiviral therapy serves two purposes:

1. Estimation of the response based on early viral kinetics
2. Early recognition of the development of viral resistance with an increase in the viral load after initial reduction or by mutation monitoring.

During treatment all patients receiving antiviral therapy should be closely monitored for virologic response and breakthrough. After treatment has stopped patients need to be monitored for durability of response and viral relapse.

**Figure 7: Monitoring Virological Response and Breakthrough**

**Serum HBV DNA Level at Week 12**
Assess serum HBV DNA level at Week 12 of therapy to determine whether an initial response to treatment has occurred. If the patient is confirmed to have been compliant with their treatment regimen but has not had a > 1 log10 decrease in serum HBV DNA, then the medication is not effective. Consider switching to an alternative therapy or adding-on a second agent to avoid resistance. If the patient has been noncompliant, then compliance should be emphasised and the patient followed more closely.

**Serum HBV DNA Level at Week 24**
Serum HBV DNA levels for patients on nucleoside analogues (LAM and ETV) should next be assessed after 24 weeks of therapy and repeated at 36 and 48 weeks. This time point was chosen based on the majority of existing data suggesting that HBV DNA levels at Week 24 are predictive of later outcomes at weeks 48 and 96, including suppression of HBV DNA and the likelihood of antiviral drug resistance.

**Serum HBV DNA Level at Week 48**
Serum HBV DNA levels for patients on nucleotide analogues (ADV) should be assessed at 24, 36 and 48 weeks of therapy. For a nucleotide, 48 weeks was chosen based on the majority of existing data suggesting that HBV DNA levels at this time are highly predictive of later outcomes at year 3.
including suppression of HBV DNA and the likelihood of antiviral drug resistance.\textsuperscript{174} In addition, all patients with undetectable HBV DNA at the end of 4 or 5 years of ADV monotherapy had become HBV DNA undetectable before week 48. ADV-treated HBeAg-negative CHB patients maintaining HBV DNA levels $> 20,000$ IU/mL at week 48 have a 67\% probability of genotypic HBV resistance to ADV at year 3.\textsuperscript{175, 176}

**Modification of Therapy Based on Week 24-48 Response**

Based on these data, the expert panel classified responses ideal, adequate, or sub-optimal (Figure 7). Patients who achieve an ideal response (i.e. HBV DNA < 200 IU/mL) should remain on their current therapy and be reassessed every 3 months. Patients who achieve an adequate response (i.e. HBV DNA 200 – 2000 IU/mL) should continue treatment and be reassessed every 3 months. For patients who experience a sub-optimal response (i.e. HBV DNA $> 2,000$ IU/mL) rescue add-on therapy should be considered before the development of true resistance.

During long-term treatment, a 3 monthly assessment of viral load and serological markers is required to monitor antiviral treatment efficacy and determine whether the response is maintained or whether drug resistance is developing. Drug compliance is important, as any drug interruption may lead to a rebound of viral replication and ALT flares. The detection of polymerase mutations can be performed by sequencing, line probe assay, and DNA chip technologies.
11. Combination & Dual Therapy Strategies

Recommendations to prevent, or maximise treatment for those with antiviral-resistance depends on knowledge of the history of treatment, virologic response to treatments, the pattern of mutations detected at the time of virologic breakthrough, and *in vitro* data on antiviral activity against HBV isolates that harbor the mutations detected. Recent data suggest that initiating rescue therapy when virologic breakthrough is detected is more effective than delaying rescue therapy until viral rebound or biochemical breakthrough.\(^{168}\)

<table>
<thead>
<tr>
<th>Table 9: Strategies for Treating Antiviral-Resistant CHB</th>
</tr>
</thead>
</table>
| **LAM Resistance** | Add ADV  
| | Switch to ETV (risk of subsequent ETV resistance and multi-drug resistance) |
| **ADV Resistance\(^*\)** | Add LAM or  
| | Add ETV (if no prior LAM-R) |
| **ETV Resistance\(^*\)** | Add ADV |
| **Multidrug Resistance\(^#\)** | Add ETV to ADV  
| | Discontinue LAM  
| | Genotypic ETV resistance has been reported in 7% of LAM-refractory patients after 1 year of treatment, increasing to 10% at 2 years  
| | Adding TDF to LAM may be an option  
| | These combinations that have not been studied but would be predicted to be effective. |

\(^*\) Limited *in vivo* data, available data indicate that addition of rescue therapy is less likely to result in sequential drug resistance than switching to rescue therapy. \(^#\) *In vivo* data lacking

Avoid Cross Resistance

Cross-resistance can be characterised and defined in vitro and in vivo. In vitro resistance is defined as a significant shift in the IC\(_{50}\) (ie, the drug concentration producing 50% inhibition of replication) of one drug when a resistance mutation selected by a second drug is present. This cross-resistance can be characterised as low, intermediate, or high levels of cross-resistance.\(^{355}\) *In vivo* cross-resistance means having one mutation that confers viral breakthrough independently in more than one drug. Therefore, cross-resistance patterns are important determinants of therapy choices for patients.

In general, drugs within the same structural family (e.g. nucleoside analogues) are more likely to exhibit cross-resistance. For instance, ETV has a similar resistance profile as LAM. Therefore, as expected, patients who have LAM resistance mutations may respond poorly to ETV. For all of the L-nucleoside analogues, the mutational patterns show overlap with those of LAM. Combining two antiviral agents which are not cross-resistant (e.g. a nucleotide and a nucleoside) may delay or prevent the occurrence of viral resistance without compromising tolerance. The nucleotide analogues (ADV and TDF) show consistent activity against the wild-type and all patterns of LAM-R strains. HBV isolates with ETV-associated mutations are also sensitive to ADV and TDF *in vitro* and *in vivo* data.\(^{380}\)
However, there are exceptions to the rules of cross-resistance within the same structural family of drugs. One example is the case of ADV and TDF, which do not exhibit any apparent cross-resistance, despite structural similarities. Therefore, when evaluating treatments for HBV, consequences of drug resistance and cross-resistance need to be carefully considered.355

**Combination Therapy**

Combination therapy with antivirals, either at the beginning of therapy, or early in the course of therapy, may be the most appropriate option for patients with CHB. Combination therapy theoretically conveys two advantages:168, 355, 381

- The most potent agent may provide an ‘additive’ effect and produce a deeper suppression of viral replication than the weaker single agent in the pair; and
- The risk of treatment-emergent resistance may be reduced by targeting multiple sites, thus requiring multiple mutations to occur to produce antiviral resistance.

**De Novo Combination**

A first strategy would be to combine de novo two drugs at the beginning of therapy. The drugs should have a different cross resistance profile to minimise the risk in resistance in the long-term.

**Early-Add On**

A second strategy, based on a very early add-on regimen, is to start with a drug having a very low rate of resistance and add a second drug if viraemia levels do not decline below a threshold exposing to further resistance. Locarnini suggests,382 when possible, therapy should begin with drugs which having a high genetic barrier, adding another compound with minimal cross-resistance if HBV-DNA is still detectable at Week 24. It is advisable to avoid LAM monotherapy as initial therapy.382
Drug A has a high genetic barrier. Initiate with a drug A. If the viral load remains detectable at Week 24, another compound (B) with minimal cross-resistance should be added.

**Combinations for LAM-R**

Both ADV and ETV have antiviral activity against LAM-R and other L-nucleoside-resistant HBV mutants, but the activity of ETV against these mutants is substantially lower than for wild-type HBV.\(^{383}\)

Clinical trials with ETV have shown its antiviral efficacy at higher doses (1.0 mg daily) in patients with LAM-R,\(^{384}\) but cases of multiple drug resistance were observed in 10% of patients after 2 years of therapy,\(^{375}\) because LAM and ETV have some level of cross-resistance.\(^{362, 374}\) It is now recommended that if ETV is used, LAM should be discontinued.

In LAM-R, combination of ADV/LAM effectively protected against the emergence of ADV-resistance.\(^{141, 194, 385, 386}\) In HBeAg-positive patients ADV resistance was not observed in any subjects receiving up to 4 years of ADV/LAM therapy with improvements in liver function and HBeAg seroconversion.\(^{387}\)

The first randomised, controlled study on the efficacy of combination therapy with ADV/ LAM versus ADV monotherapy was completed in LAM-R HBeAg-negative CHB. Adding ADV to LAM effectively suppressed HBV replication and ALT normalised in 90% of patients, although this was not significantly different compared to patients switched from LAM to ADV monotherapy (71%). While the response was durable (median treatment duration 40 months) in all patients with combination ADV/LAM, virological and biochemical breakthroughs due ADV resistance mutations occurred in 21% switched to ADV monotherapy 15 - 18 months from start of treatment (P = 0.0174).\(^{388}\) Another study has reported no resistance over 3 years with add-on rather than switch therapy.\(^{168, 389, 390}\) Early add-on therapy in this study reduced the risk of cirrhosis, but did not reduce the risk of HCC.

In LAM-R patients with bridging fibrosis or cirrhosis, the continuation of LAM administration after initiation of ADV was advantageous due to a significant decrease of serum HBV DNA and ALT was obtained.\(^{141}\) Furthermore, ADV therapy may be more effective in suppressing HBV DNA levels if begun soon after emergence of LAM-R, before HBV DNA rises to high levels or disease activity worsens, as shown by uncontrolled but sizeable studies in patients with advanced fibrosis.\(^{168, 381}\)

Resistance surveillance for 3 years has been reported in pre- and post transplant LAM-R patients (a majority had decompensated liver disease). Those patients maintained on ADV/LAM did not develop ADV resistance. However, in patients where ADV resistance emerged, it was found that LAM had been stopped.\(^{306}\)

**Combinations for ADV-R**

LAM and ETV have antiviral activity against ADV-resistant HBV mutants and are effective in suppressing serum HBV DNA levels in patients with ADV-resistant HBV.\(^{373, 392}\) However, the durability of response, particularly in patients with prior LAM-R is unknown. Furthermore, in the latter patients, a rapid re-emergence of LAM-resistant mutations has been observed on reintroduction of LAM.\(^{370, 393}\) ETV has been reported to be efficacious in two patients with ADV-resistant HBV.\(^{193}\)

**Combinations for ETV-R**

In vitro studies demonstrated ADV has antiviral activity against ETV-resistant HBV mutants\(^{374, 394}\) however clinical data on the efficacy of these treatments in patients with ETV-resistant CHB are not yet available.

**Combinations for Multidrug Resistance**

For patients with both LAM and ADV resistance, data suggest ETV and tenofovir (TDF) are options.\(^{194, 195}\) Genotypic ETV resistance has been reported in 7% of LAM-refractory patients after 1
year of treatment, increasing to 10% at 2 years. TDF is an approved agent for HIV, which also has activity against wild-type and LAM-resistant HBV; case reports of TDF treatment in patients showing a suboptimal virological response to ADV have been published, though the total number of treated patients is small. Other drug combinations that have not been studied but would be predicted to be effective are LAM plus TDF, or ETV plus ADV.

The most effective treatment of multidrug-resistant CHB is prevention through judicious use of antiviral therapy and avoidance of sequential antiviral monotherapies.

**Dual Therapy (Antiviral + pegIFN)**

There are theoretical advantages for dual therapy with an immunomodulator (IFN / pegIFN) and an antiviral agent. Synergistic activity is potentially created by targeting dual pathways. pegIFN may enhance immune clearance of infected hepatocytes, while the antiviral stops viral replication.

To date, studies assessing dual therapy have implemented concomitant use of the two agents at commencement of therapy. Although there is some evidence in the benefits of dual therapy, these trials have only been conducted over a 48 week treatment period. Standard clinical practice would be to not stop antiviral agents after only 48 weeks, and therefore the relevance of the long term data from all of these studies are limited.

**LAM + pegIFN**

The combination of pegIFN and LAM has been assessed in three large, multicentre trials. All failed to show an increase in sustained response rate of the combination of pegIFN and LAM over pegIFN alone assessed 24 weeks after discontinuation of treatment. On the other hand, the on-treatment suppression of HBV DNA levels was superior in patients who received dual therapy: by the end-of-treatment, HBV DNA levels decreased by 5.2 logs₁₀ in LAM-, 5.1 logs₁₀ in pegIFN-, and 7.2 logs₁₀ in combination-treated HBeAg-positive patients. These results suggest that combinations of agents that have different targets against HBV may provide additive antiviral activity and higher potency.

**ADV + pegIFN**

Dual therapy with pegIFN2b and ADV led to marked decreases in serum HBV DNA and intrahepatic cccDNA, which was significantly correlated with reduced HBsAg. Median serum HBV DNA decreased by -20,000 IU/mL at the end of treatment and was undetectable 54% of patients. 53% of HBeAg-positive patients lost HBeAg, and 30% developed anti-HBe antibodies during treatment. ALT normalised in 73% of patients. After the 48 weeks of dual therapy, all subjects in this study continued with 96 additional weeks of ADV monotherapy.
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