Management of Chronic Hepatitis B: Consensus Guidelines

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Introduction

Chronic viral hepatitis continues to be a major public health and medical problem in Canada. There are an estimated 500,000-600,000 people in Canada infected with either the hepatitis B virus (HBV) or the hepatitis C virus (HCV). Both viruses cause liver disease that is usually indolent and takes many years to cause symptoms and to cause the life-threatening conditions of cirrhosis, liver failure and liver cancer. There are data suggesting that the incidence of these conditions is increasing in Canada (1). Furthermore, the demographics (age, country of origin, etc) of the infected population in Canada suggest that the incidence of these dire consequences will continue to increase in frequency over the next 20 years or more unless effective treatment is widely deployed (1). Effective treatment is now available for both hepatitis B and hepatitis C that should reduce the frequency of adverse outcomes. New drugs have recently become available, and new information on the use of older drugs should result in more patients being successfully treated. However, the treatment regimens are complex and are still evolving. This complexity is a barrier to uptake of treatment, since inexperienced physicians are reluctant to undertake such complex regimens. In addition there are structural barriers to treatment in Canada that result from the restrictive regulation of funding of laboratory tests and drug therapy that currently prevent optimal treatment being provided to many of those who need it.

The Canadian Association for Study of the Liver (CASL) has for more than 10 years spearheaded the development of guidelines to assist practitioners in the management of viral hepatitis. More recently the guidelines have been developed in conjunction with partner organizations, both medical and governmental. Given the substantial changes that have occurred in the management of these diseases over the last 3-4 years, CASL, in conjunction with the Association of Medical Microbiologists and Infectious Disease (AMMI) Canada organized another consensus conference on the management of viral hepatitis. This report is the proceeds of that conference, held in Toronto on Jan 4-5 2007.

Funding

Funding for this meeting was provided through unrestricted grants from the following pharmaceutical companies, all of which have products that were discussed at the meeting. These were (in no particular order) Schering Canada, Bristol Myers Squibb, Roche Canada, Gilead, Novartis, and Valeant Canada. Additional funding was provided by the Hepatitis C Secretariat of the Ministry of Health and Long Term Care of the Province of Ontario and the Hepatitis C Division of the Public Health Agency of Canada. Funding from the pharmaceutical industry is not the preferred method of funding consensus conferences, but in the absence of adequate governmental sources the pharmaceutical industry is the only avenue to fund these important conferences. In other Western countries these consensus management conferences are fully supported by the national governments (e.g., NIH in the USA).

1. **Recommendation: The Federal and/or Provincial Ministries of Health should agree to support periodic consensus development and treatment guidelines development conferences that involve diseases of public health importance (III).**

Disclosures

This will serve as a general disclosure for all speakers and the members of the writing committee. Many, but not all of the speakers and writers have or have had relationships with the industry sponsors. These relationships include having received research grants, honoraria for speaking engagements, or for work on advisory boards related to all of the products discussed in this document. Some participants have received consulting fees from the Ontario Ministry of Health and Long Term Care and Health Canada.

Process

The process used to come to consensus was as follows: An Organizing Committee was appointed by the two sponsoring organizations. This committee invited speakers considered expert to review the current literature on different topics. After the presentation questions were entertained from the audience. A Writing Committee, also selected by the Organizing Committee, synthesized the information from the presentations, and from other sources, and prepared a document that was circulated to the speakers for comment. The strength of the recommendations and the strength of the evidence supporting the recommendations are given (see Table 1 for explanation.) In preparing this document we have been guided by the principle that the advice provided should represent best medical practice and is meant to indicate optimal therapy for patients. Considerations of cost were taken into account. We clearly indicated where cost considerations dictated treatment that was less than optimal, as well as providing recommendations for optimal treatment. For example, lamivudine remains a recommended therapy for hepatitis B. However, if cost were not a factor lamivudine would no longer be recommended as first line therapy for hepatitis B.

Structural Barriers to Effective Management of Viral Hepatitis

Over the years, as the cost of treatment of viral hepatitis has increased, provincial drug formularies have put restrictions on the use of antiviral therapy into place. These vary from province to province so that there is no uniformity of access across the country. However, as knowledge has advanced many of these restrictions are out of date and severely restrict the ability of physicians to provide optimal care to patients, particularly those with less advanced disease. Provincial reimbursement formularies have not keep up to date with the changes in practice. Liver disease should be considered as a chronic disease with severe long-term outcomes that can be prevented by timely application of treatment. In this respect it is no different than treating hypertension or hyperlipidemia. Funding for treatment of other chronic diseases is available long before the advent of severe complications. So too should funding should be available for the management of viral hepatitis before advanced disease is diagnosed. Other structural barriers include the slow approval process for medications (a problem not restricted to viral hepatitis) and

the multiple layers of bureaucracy that approvals have to pass though, including licensing through Health Canada, the Patented Medicines Price Review Board, the Common Drug Review, and finally provincial Drugs and Therapeutics Committees. There are many examples of access to effective therapies for viral hepatitis being delayed (sometimes for years) or denied through these processes.

2. **Recommendation: Liver disease should be considered as a chronic disease with severe long-term outcomes that can be prevented by timely application of treatment (III).**

Another structural barrier is that most virological blood tests are done in public health laboratories that restrict the type and frequency of tests that they are prepared to do and the frequency of testing. As a result useful, even vital, tests such as hepatitis B resistance genotyping are not widely available. Finally, effective management of viral hepatitis requires the services of many disciplines, physicians, nurses, addiction medicine specialists, social workers, etc. These services can only be effectively delivered in a clinic setting. There are very few government-funded clinics for the management of viral hepatitis.

Government funding agencies generally rely only on the highest levels of evidence from randomized controlled trials to fund specific drugs. Short term pharmaceutical company sponsored trials are not designed to evaluate long term outcomes such as survival. Yet these endpoints are often required by reimbursement agencies (e.g., Common Drug Review). In many cases evidence of improved survival from randomized controlled trials is unlikely to ever be available. Lesser levels of evidence are often not acceptable, no matter how convinced expert physicians may be. Sir Austin Bradford Hill, one of the fathers of the randomized controlled trial had this to say "All scientific work is incomplete - whether it be behavioural or experimental. All scientific work is liable to be upset by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action it appears to demand at a given time". This suggests that the absence of high levels of evidence is not a reason not to act on what appears to be appropriate given current knowledge.

There was consensus that was strongly expressed at the meeting that the current limitations on drug use and laboratory testing were too restrictive, and severely interfered with the delivery of optimal care, particularly to patients with hepatitis B, and to a lesser extent hepatitis C. In the interests of the best patient outcomes and in fairness to hepatitis patients compared to patients with other chronic diseases limitations on drug use and viral testing must be made less restrictive and more responsive to patient needs.

3. **Recommendation: Limitations on drug reimbursement and viral load testing must reflect current best practices as recommended by experts in the management of hepatitis B and hepatitis C (III).**

Nursing support in the management of chronic viral hepatitis

Specialist hepatitis nursing support is essential in the management of viral hepatitis. It is not an exaggeration to say that without nursing support treatment of viral hepatitis, particularly hepatitis C, is not

possible. Very few physicians have the time needed to educate patients and monitor them during treatment. This task has been assumed by specialist hepatitis/hepatology nurses who are now the main providers of care for and education of patients about their disease and about the treatment. The nurses teach self-injection and they monitor patients on therapy. However, they also do much more. They provide support to the patient that busy physicians cannot. They are more accessible than physicians. It is fair to say that by assuming many of the patient care responsibilities they support both the patient and the physician. Currently, most hepatitis nurses in Canada are funded by the pharmaceutical industry. This results in a conflict of interest on the part of the nurse, when his/her income comes from the company that makes the drug used. That only a minority of nursing positions across the country are publicly funded is unacceptable to doctors and nurses, and should be unacceptable to government.

4. **Recommendation: Publicly funded comprehensive hepatitis nursing programs should be instituted in all provinces as a matter of urgency (III).**

Normal Alanine Amino Transferase (ALT) Concentration and the Management of Viral Hepatitis

Traditionally the blood test that has been used as a marker of liver injury and as the gate-keeper test for treatment of viral hepatitis was the ALT. Previous guidelines from professional societies (including CASL) stressed that the ALT should be elevated (to varying levels in different diseases) before treatment was undertaken (2,3,4,5). Recent data however, have shed doubt on the use of ALT as a measure of severity of liver disease, as a predictor of outcome of liver disease, and as a threshold to consider treatment.

There is variation in the methods used in different laboratories to measure ALT, resulting in different normal ranges being reported. The majority of laboratories do not report differences for males and females, and give an upper limit of normal of 35-40 IU/mL. However, the normal range, established as 2 standard deviations from the mean, was derived many years ago from populations of subjects in which occult liver disease must have been present (hepatitis C, non-alcoholic fatty liver disease, and even alcoholic liver disease) since none of these conditions could be diagnosed serologically. More recent data, in large populations that excluded patients at risk for these conditions have suggested that the true upper limit of normal for ALT for men is 30 IU/mL, and for women is 19 IU/mL (assuming an assay with an upper limit of normal of 35-40 IU/mL)(6).

Studies in very large populations have shown that liver-related and overall mortality in patients and in so-called normal populations starts to rise when the ALT exceeded 0.5x the upper limit of the usual laboratory normal and increased with increasing ALT. This has been shown in large unselected populations (7), and in patients with chronic hepatitis B (8). In addition, there are many studies in hepatitis B and hepatitis C that show that a normal ALT may be associated with significant liver injury, including cirrhosis (9,10). Furthermore, patients with hepatitis C and "normal" baseline ALT who undergo

anti-HCV therapy and who achieve a sustained virological response experience a significant decline in ALT, suggesting that their baseline ALT was not truly normal (11). Since there is a wide variation in the laboratory normal ranges for ALT it is preferable, when calculating the true normal range that results be expressed as a percentage of the upper limit of that laboratory normal. Finally, ALT does not reflect fibrosis, but rather reflects inflammation. Yet fibrosis, not inflammation is the histological finding upon which severity of disease and prediction of outcome is based.

5. **Recommendation: Active viral hepatitis should be considered in men in whom the ALT is more than 0.75 x the standard laboratory upper limit of normal and in women in whom the ALT is more than 0.5 x the standard laboratory upper limit of normal. All laboratories should report these new normal ranges (II-2).**

6. **Recommendation: Normal ALT does not exclude significant liver disease. Normal ALT does not correlate with ultimate outcome. Patients should not be denied treatment on the basis of a normal ALT (II-1).**

Hepatitis B

Epidemiology of hepatitis B infection in Canada

Chronic hepatitis B prevalence data are not collected by provincial and federal public health authorities. Although all positive HBsAg tests are reported to local Public Health Units, only test results associated with an acute infection are tracked. Positive tests that are a result of chronic hepatitis are not collated nor reported. As a result the prevalence of chronic hepatitis B in Canada is unknown. There have been no large scale studies representative of the communities at risk to assess overall prevalence. Hepatitis B in Canada is largely a disease of immigrants, who bring with them the high prevalence of hepatitis B in their home countries. Since immigrants tend to choose to live large urban areas of Canada, any seroprevalence survey would have to take into account that hepatitis B is not uniformly distributed across the country.

There have been some attempts to estimate the number of infected individuals in Canada. Statistics Canada attempted to estimate the number of hepatitis B infected individuals by calculating a 6% rate in immigrants, assuming a 1% rate in Canadian-born individuals and a 4% rate in aboriginals. This calculation suggested that there were about 600,000 people in Canada infected with hepatitis B (12). However, this may be an over-estimate because the rate of 1% in the Canadian-born population seems high.

It is important to know the prevalence of chronic hepatitis B, because the disease has a high mortality rate (20-25% untreated), and requires complex algorithms for management. There are major resource implications. Without knowing the prevalence of hepatitis B no planning for resource allocation can be undertaken. Second, there is a reservoir of infected individuals in Canada, and as with any infectious

disease, the risk to the general population, or more specifically, to the populations in which hepatitis B is endemic, should be known.

Immigration to Canada continues to introduce additional hepatitis B-infected individuals to this country. The prevalence in recent immigrants is unknown. Recent data from New York suggest that 15% of recent immigrants from China and Korea are infected with hepatitis B (13). This is likely to be true in Canada as well. Thus, rather than the pool of infected patients decreasing as a result of vaccination, it is increasing as a result of immigration.

7. **Recommendation: Chronic hepatitis B should be a notifiable disease, with appropriate records kept and appropriate risk factor information collected (III).**

8. **Recommendation: The Federal Ministry of Health and/or the provinces should develop seroprevalence surveys to determine the numbers of hepatitis B infected individuals in the country and in each province (III).**

Hepatitis B Vaccination Policy in Canada

The ideal vaccination policy against hepatitis B is universal neonatal vaccination, with catch-up vaccination of adolescents who have not been vaccinated to date. Successive Canadian consensus conferences on the management of chronic viral hepatitis have recommended this policy. The National Advisory Committee on Immunization (NACI) has not adopted these recommendations. Many provinces in Canada still rely on maternal screening to identify at-risk babies who should be vaccinated, rather than universal neonatal vaccination. This ignores the reality in Canada that hepatitis B is a disease of immigrants, not all of whom are visible minorities, and ignores the possibility of fathers or other family members being infected, rather than mothers. The current vaccination strategy has been accompanied by a decrease in acute hepatitis B in all ages (including adults too old to have been included in adolescent vaccination strategies). The decline in incidence is therefore not entirely due to vaccination. Data from Quebec shows that there is still a significant incidence of acute hepatitis B in children under age 10 (14). Approximately 25% of cases of acute hepatitis B in Quebec could be prevented by universal neonatal vaccination.

The thirteen health care jurisdictions that administer hepatitis B vaccination in Canada have each developed their own infant and adolescent vaccination program. No two programs are identical! There is no scientific rationale to support these differences. This has the consequence that children who move from province to province run the risk of being excluded from the local vaccination program in both their home and destination province.

Current vaccination practices for children of carrier mothers, or where a family member is known to be a carrier are appropriate, and should remain in place.

9. **Recommendation: The ideal hepatitis B vaccination policy for Canada is universal infant vaccination, and catch-up vaccination for those who have not yet received adolescent vaccination (I).**

10. **Recommendation: The provinces should harmonize their hepatitis B vaccination programs and must institute universal neonatal or infant vaccination (III).**

Hepatitis B vaccination is also recommended for patients who have chronic liver disease other than hepatitis B (15,16) because patients with liver disease may not be able to sustain a second injury to the liver. The efficacy of vaccinating this population is not good. Only about 14% of patients with cirrhosis develop protective antibody levels (17). Nonetheless this recommendation by NACI should remain. However, NACI also recommends hepatitis B vaccination for all patients who are to be treated with hepatotoxic drugs. There is no scientific rationale for this recommendation. Most drugs are potentially hepatotoxic. Therefore this recommendation will eventually apply to virtually everyone at some stage. The vast majority of hepatotoxic drug reactions are acute and self-limited in nature. It is hard to understand how hepatitis B vaccination might change the outcome of these reactions. The presence of liver disease is not a contraindication to most potentially hepatotoxic drugs, because the vast majority of these reactions are idiosyncratic, and are not more likely in patients who have pre-existing liver disease of any cause. NACI is strongly urged to reconsider this recommendation. The consensus of this meeting was that this recommendation should actively be opposed.

The meeting did support the NACI recommendations on vaccination of potential organ transplant recipients.

11. **Recommendation: Hepatitis B vaccination is not required for patients who are exposed to potentially hepatotoxic drugs (III).**

Hepatitis B Laboratory testing

HBV DNA Viral Load Testing

HBV DNA assays have undergone significant evolution in the past few years. In the past, assays lacked sensitivity, were poorly standardized, poorly reproducible, and reported in different units. This made interpretation and comparison between studies difficult. Recently, the HBV DNA International Unit (IU/mL) was adopted (18), leading to improved comparability between commercial assays. Newer assays are now usually PCR based (19-21), with a wider dynamic range (concentration range over which the dose response curve is linear) that allow accurate determination of the viral load in most patients (Fig.1). HBV DNA measurement is now a crucial tool in the evaluation of a patient with HBV. Indeed, it is not possible to properly manage hepatitis B patients without this assay. Furthermore, since it has become important to identify patients with undetectable HBV DNA in serum the most sensitive assays available

should be used. Currently this is the Taqman PCR, which has a lower limit of sensitivity of 6 IU/mL and a dynamic range that encompasses all clinically significant variations in viral load. Viral load measurements will usually need to be repeated at 3-6 monthly intervals, and sometimes more frequently to confirm viral resistance. Therefore there should be no restriction on the frequency of testing.

12. **Recommendation: Clinicians caring for hepatitis B patients should have ready access to HBV DNA testing for all patients. Reporting of results should be timely (within two weeks), and should include the dynamic range. Results should be reported in IU/mL to allow for correlation between laboratories, and with published studies. The most sensitive assay available should be used (II-3).**

Throughout this document reference is made to "high" and "low" hepatitis B viral loads. The HBV DNA concentrations associated with these states are not clearly defined and vary in different circumstances. Therefore, when these terms are used a range of HBV DNA concentrations are provided that most would accept are appropriate. However, these are not discrete separate conditions, and "high" merges imperceptibly into "low" HBV DNA concentrations.

HBV Genotyping

There are currently 8 recognized genotypes (A through H) based on sequence variations of the HBV genome. Genotype A is common in Europe, North America, and Africa. Genotypes B and C predominate in the Far East. Genotype D is found worldwide, genotype E occurs in Africa, genotype F in South America and Alaska, genotype G in North America and genotype H in Central America. (22,23).

Genotype B has been associated with less severe liver disease, lower rates of HBeAg reactivity, and higher spontaneous HBeAg seroconversion than genotype C (24). Genotype D may be associated with higher rate of hepatoma and higher rates of post-transplant recurrence and mortality compared with genotype A (24). Genotypes C and D are associated with a lower response to interferon when compared to genotypes A and B (25). Various test methods are available for genotype determination with sensitivity and specificity approaching 95-99%. Although, the clinical utility of genotype determination in individual patients remain to be defined, knowing genotype may help determine choice of antiviral therapy.

13. **Recommendation: Clinicians should have access to HBV genotype testing, which may help in the selection of antiviral therapy, and prediction of response with interferon based therapy (II-3).**

Natural History of Chronic Hepatitis B Infection

Hepatitis B is an indolent disease that seldom causes symptoms until complications of cirrhosis and liver cancer occur. However, hepatitis B infection is associated with an excess mortality, mainly from hepatocellular carcinoma (HCC) and cirrhosis and its complications, which may reach 458/100,000/year (26).

The natural history of HBV infection is thought to evolve through 4 phases (Table 2)(27). Not all patients go through every phase. In perinatal or childhood infection, the immune tolerant phase may last for less than 10 years to more than 20 years. Strictly speaking the definition of the immune tolerant phase also includes a liver biopsy with no or minimal inflammation. In practice biopsies are seldom used to diagnose this phase, so most rely on the ALT. As patients get older the likelihood of liver injury increases, despite an apparently normal ALT. This is because inflammation may be mild, and because intermittent ALT testing may miss short-lived periods of elevated ALT. Complicating the diagnosis of the immune tolerant phase is that the ALT can be intermittently normal during the immune clearance phase. Thus when a patient apparently meeting the criteria (Table 2) for the immune tolerant phase is initially seen, close follow-up is necessary to determine whether the ALT might become elevated, signifying that either the immune clearance phase is starting, or that the patient was in the immune clearance phase all the time.

The immune clearance phase may last a variable period of time, ranging from less than 5 years to more than 25 years and is terminated by seroconversion from HBeAg-positive to anti-HBe-positive. Predictors of seroconversion are high ALT, low HBV DNA, age less than 40 years and absence of cirrhosis (28,29). These factors also identify patients who are more likely to seroconvert on therapy. Seroconversion, whether spontaneous or treatment-induced, is almost invariably associated with initial remission of disease activity and normalization of ALT (30). In some patients this inactivation is permanent and these patients become inactive carriers. Thus, in the short term seroconversion is associated with improved outcomes compared to those who do not seroconvert. However, over the longer term there is a risk for reactivation to the HBeAg-negative chronic hepatitis B state (see below).

The inactive carrier state is characterized by a lack of HBeAg, presence of anti-HBe, persistently normal ALT and low (<2000 IU/mL) or undetectable levels of HBV DNA (Table 2)(3). The inactive carrier state does not preclude the presence of significant disease, including cirrhosis. Whether cirrhosis is present or not depends on the amount of preceding inflammation prior to seroconversion. However, in the inactive state there is little or no inflammation, and fibrosis does not progress. Patients who seroconvert before the development of major fibrosis are probably at low risk for HCC. However, patients who develop cirrhosis prior to seroconversion continue to have a high risk of HCC. It is important to recognize that cirrhosis can regress over time, so that a biopsy done years after either spontaneous or treatment-induced inactivation of disease may show minimal fibrosis. Careful histological evaluation might show evidence of regressed cirrhosis. In these patients the risk of HCC remains. Sero-reversion to HBeAg-positive can occur, and is usually associated with reactivation of hepatitis (29).

Some anti-HBe-positive patients may continue to have HBV DNA concentrations that are in the range that might be associated with disease. Other patients may have inactive disease for variable periods of time (up to many years), but eventually develop active disease once more, despite being anti-HBe-positive. This is HBeAg-negative (or anti-HBe-positive) chronic hepatitis B. Thus, a single finding of normal ALT and HBV DNA below 2000 IU/mL does not prove the diagnosis of the inactive carrier state. Only

prolonged close follow-up and persistence of these markers of inactivity provide a confident diagnosis of inactive carrier state, rather than a transient remission of HBeAg-negative chronic hepatitis B.

HBeAg-negative chronic hepatitis B is most often seen in patients after a variable duration of inactive carrier state, but some may progress directly from HBeAg positive chronic hepatitis to HBeAg-negative chronic hepatitis (31). This means that even patients who have apparently had inactive disease for years must continue to be followed for the possibility of reactivation.

The risks for cirrhosis and HCC development are multi-factorial, but are correlated with the degree and severity of chronic inflammation, older age, male gender, concomitant causes of liver injury (i.e., co-infection with HCV or alcohol abuse) and HBV DNA levels (see later)(32-36). Chronic hepatitis progresses to cirrhosis at an estimated rate of 2-10%/year (37-39). Subsequent evolution to decompensated cirrhosis or HCC occurs at a rate of 5-10%/year, with an annual death rate of 20-50% in these patients. Spontaneous natural clearance of HBsAg occurs in only 0.5-0.8% of chronic carriers/year (40,41).

Evaluation of the Hepatitis B Infected Patient

The initial assessment of all HBsAg-positive patients should include a detailed history, including family history of hepatitis and hepatocellular carcinoma, risk factors for hepatitis B acquisition, and alcohol use. A physical examination should be performed to detect signs of chronic liver disease, and liver decompensation. Laboratory testing should include serum ALT and/or aspartate aminotransferases (AST), alkaline phosphatase (ALP), bilirubin, albumin, creatinine, INR, and complete blood count. Specific HBV testing should include HBsAg, HBeAg, anti-HBe, and serum HBV DNA quantitation. This should be done in all patients at first assessment. If available the genotype should be obtained. Resistance genotyping should also be done for patients who have had prior treatment with nucleoside analogues, and who are currently off treatment (see later). Screens for co-morbid conditions should include anti-HCV, and anti-HIV. Anti-HDV testing should be performed in those with a history of past or current intravenous drug use or who have a history of sex with a past or present injection drug user or who come from geographic regions endemic for HDV. Anti-HDV testing should also be done in patients with chronic hepatitis B who have elevated ALT and low to undetectable HBV DNA concentration. An exact cut-off that defines low HBV DNA has not been defined, but in this instance is probably below 2000 IU/mL. A baseline abdominal ultrasound should be done to detect obvious signs of cirrhosis and/or portal hypertension, and presence of hepatoma. (Note that ultrasound does not detect mild degrees of cirrhosis).

Liver biopsy

A liver biopsy is currently the only method to assess the extent of fibrosis to diagnose early cirrhosis and to identify coexisting liver diseases. In the past, a liver biopsy was usually recommended in patients with active viral replication and elevated ALT. It is now appreciated that the normal ranges of serum ALT and

AST provided by most laboratories are too high (see earlier), and significant histologic damage may be present in 13-43% of patients with "normal" liver enzymes (6-10). Hence, a liver biopsy may aid in the assessment of the patient for antiviral therapy. The patient selection algorithm provided in Figure 2 indicates that it is acceptable and often necessary to perform a biopsy in patients with a normal ALT. Indeed, in some patients this may be the only method determining the presence of liver disease. A liver biopsy may not be needed if there are clinical, laboratory, or radiological findings to suggest cirrhosis. Recent developments in non-invasive testing for fibrosis such as Fibrotest or Fibroscan may eventually decrease the need for biopsy, but these tests lack the ability to assess inflammation or coexisting diagnoses and require additional validation.

HIV testing

Hepatitis B and HIV are acquired by the same transmission routes. Many HBV endemic areas also have high rates of HIV with heterosexual contact as the major risk factor. There is general move to more widespread testing for HIV because patients may not disclose risk factors. Many of the nucleoside analogues used to treat hepatitis B are also active against HIV. The impact of monotherapy on HIV resistance means that all patients with HBV should be screened for HIV.

14. **Recommendation: All patients infected with the hepatitis B virus should be tested for HIV infection with appropriate pre and post test counseling (II-2).**

Selection of patients for treatment

The objective of treatment in chronic hepatitis B is to prevent the development of cirrhosis, and its consequences, liver failure and hepatocellular carcinoma. However, not all hepatitis B infected patients are destined to develop these complications. The challenge is to identify those who are at risk for the development of these adverse consequences, and to offer them treatment. Conversely identifying those who will not progress may spare some patients unnecessary treatment. Our tools to do this are at present rudimentary. The factors that have been identified as indicating risk of adverse outcomes include the HBV DNA concentration, age, fibrosis on histology, and ALT (8,33-36,41,42). Of these, HBV DNA has been best studied. There are now several large-scale long-term prospective studies that have correlated HBV DNA at recruitment with outcome (33-36). These have all come to the same conclusion, i.e., that the risk of developing cirrhosis and HCC, and the risk of dying from these conditions increases with higher HBV DNA concentration at recruitment and with persistence of high HBV DNA levels. However, in considering the role of HBV DNA as a marker of prognosis, it is important to be aware of the nature of the populations in these studies. The studies did not include patients under age 25, and the number of patients under age 30 was small. The proportion of anti-HBe-positive patients ranged from about 50% to about 80%. Thus, in patients over age 30, and in particular in those who are anti-HBe-positive, HBV DNA is a good predictor of risk of adverse outcomes. This is likely also true in patients over

age 30-40 who are HBeAg-positive. However, this is not the case in younger patients. The studies also showed a correlation between ALT and outcome, but the association was not as strong as for HBV DNA. In particular, patients with ALT within the laboratory normal range were also at risk for the development of cirrhosis and HCC as long as the HBV DNA concentration was higher than 10^4 copies/mL (about 2000 IU/mL). This reinforces the concept that it is no longer defensible to exclude patients with normal ALT from therapy. However, in order to reduce the likelihood of treating patients who may never develop significant liver disease, if the HBV DNA is high and the ALT is normal there should be other indicators of significant liver disease before starting therapy. These may come from ultrasound evidence of cirrhosis, or biopsy evidence of at least moderate fibrosis and/or inflammation. Transient ALT elevations, particularly if mild may not be associated with significant disease. However, prolonged ALT elevation is more likely to be associated with significant injury. Thus, contrary to previous practice, biopsy of patients with "normal" ALT may be required to determine the presence of liver disease and to make a treatment decision.

In summary, the decision to treat requires several factors to be considered: patient age, the level of viral replication, HBeAg status, and evidence of significant liver disease in the form of prolonged elevation of ALT, fibrosis or inflammation on biopsy, or ultrasound evidence of cirrhosis.

For HBeAg-positive patients treatment should be considered if the HBV DNA is higher than 20,000 IU/mL. HBeAg-positive patients with lower concentrations of HBV DNA might be in the process of sero-converting. For HBeAg-negative patients treatment should be considered if the HBV DNA is greater than 2000 IU/mL because studies have suggested that severe outcomes are uncommon if the HBV DNA is below than that level (34,35). Although liver injury is uncommon if the HBV DNA is below 2000 IU/mL some patients may have HBV-induced liver disease at lower viral loads. A biopsy is helpful to exclude alternative diagnoses and to confirm the picture of viral-induced injury. Furthermore, the HBV DNA concentration may fluctuate, so that repeat measurements are required. An HBV DNA measurement greater than 2000 IU/mL is diagnostic of HBeAg-negative chronic hepatitis B and suggests that the patient may need treatment since HBeAg-negative hepatitis B is associated with more advanced and progressive liver disease, and never completely remits spontaneously. However, in individual patients the severity of underlying liver disease is unpredictable, so a biopsy may be necessary.

Young adults who are HBeAg-positive usually have very high viral loads (>10^7 IU/mL), with variable ALT concentrations (43,44). Most often these individuals have no or minimal liver disease on biopsy. Immediate treatment may not be necessary, even with elevated ALT. It is impossible to predict whether these individuals will undergo seroconversion with remission of disease prior to the development of significant liver injury. In these patients high viral loads do not carry the same implications for outcome as in older patients. Treatment can be withheld in the hope of seroconversion. However, these patients must be closely monitored, because they may develop more severe disease. Thus, not every HBeAg-

positive patient with elevated ALT needs treatment. Figure 2 provides an algorithm for identifying individual patients who might need treatment.

> **15. Recommendation: HBeAg-positive patients in whom the HBV DNA is >20,000 IU/mL with an elevated ALT should be considered for treatment. Patients with significant inflammation or fibrosis on biopsy should also be treated, even if the HBV DNA is lower than 20,000 IU/mL, or if the ALT is normal (II-1).**

> **16. Recommendation: HBeAg-negative patients in whom the HBV DNA is >2,000 IU/mL with an elevated ALT should be considered for treatment. Patients with significant inflammation or fibrosis on biopsy should also be treated, even if the HBV DNA is lower than 2,000 IU/mL, or if the ALT is normal (II-1).**

Drugs to treat hepatitis B and their use

The next section provides information on the individual drugs available to treat hepatitis B. A comparison of the efficacy of the different agents is provided in Figures 3a and 3b and Table 3a.

Interferons

Interferons have both antiviral and immunomodulatory properties which make them effective in inducing HBeAg seroconversion. Potential advantages of interferons over nucleoside analogues include the absence of resistance mutations and a shorter fixed duration of therapy. The major disadvantages, however, are the numerous adverse effects and the route of administration (subcutaneous injection).

HBeAg-positive chronic hepatitis B:- HBeAg seroconversion occurs in 25-40% of treated patients (45-49). Interferon is generally less effective in inducing HBeAg seroconversion in patients with high viral loads. The studies which defined this were performed using assays of limited sensitivity, and that are difficult to translate into IU/ml. However, interferon is les effective in patients in whom the HBV DNA is >2×10^7 IU/mL. Seroconversion rates are also reduced in those with low ALT (<2 times the upper limit of laboratory normal) and therefore interferons are not recommended for treatment of patients with high viral load or low ALT. Other predictors of poor response include age over 40, male gender and cirrhosis. Interferons are contraindicated in decompensated cirrhosis, but can be used in patients with fully compensated cirrhosis (normal albumin, INR and bilirubin and no significant portal hypertension). Response rates in cirrhosis are low. Treatment of decompensated cirrhotics with interferon should be only be considered in special circumstances (e.g. multi-drug resistance) and in specialized treatment centers. Standard interferon is given at a dose of 10 million international units (MIU) three times per week (TIW) or 5 MIU daily subcutaneously for 16 to 24 weeks (45-49) Interferon induced HBeAg seroconversion is durable in 70-80% with up to 8 years of follow up (50-54). Delayed HBsAg clearance occurs more frequently in interferon treated patients than in untreated controls, however this is seen in only a minority (approximately 6-8%)(53).

Pegylated interferon (PEG IFN) alpha 2a (180 μg subcutaneously once weekly) is approved for the treatment of hepatitis B. PEG IFN alpha 2b has been submitted for approval for the hepatitis B indication. There were two studies that evaluated PEG IFN alpha 2a in chronic hepatitis B (55,56). The first compared 24 weeks of PEG IFN alpha 2a against standard interferon. The dose of standard interferon used in this study would be considered inadequate in North America (55). This showed that PEG IFN induced HBeAg seroconversion in 28% (180ug dose) vs 12% for standard interferon. The second study looked at the use of PEG IFN with or without lamivudine for 48 weeks (56). In this study the HBeAg seroconversion rate was similar to that seen in the 24-week study, at 32%. An additional study using a similar design evaluated PEG IFN alpha 2b with or without lamivudine for 48 weeks and found an HBeAg seroconversion rate of 29% (25). Thus, it is not certain that 48 weeks of PEG IFN therapy is superior to 24 weeks,. Nor has it been clearly established that 24 or 48 weeks of PEG IFN is superior to 16-24 weeks of standard interferon at adequate doses.

The addition of lamivudine to interferon-based therapies offers no advantage. The role of other nucleoside analogues in combination with interferons requires further study.

Interferon-induced HBeAg seroconversion is associated with improved overall survival and complication free survival (57,58,59). There are conflicting data on the impact of interferon therapy on the incidence of hepatocellular carcinoma, although most reports conclude that the incidence of HCC is reduced. Similar evidence for nucleoside analogue treated patients has not yet been obtained.

HBeAg-negative chronic hepatitis B:-   The response rates to standard interferon in HBeAg-negative patients are inferior to and less durable than those achieved in HBeAg positive patients. The assays used to define response in studies of standard interferon were insensitive compared to today's tests. Therefore it is not clear whether patients defined as having negative HBV DNA by these assays were truly negative, or would still be considered as having relapsed if today's assays were used. It is therefore impossible to compare those results with current results using PEG IFN.

PEG IFN alpha 2a given for 48 weeks is effective therapy in HBeAg-negative patients. Responses are less durable than those achieved in HBeAg-positive patients. Pegylated interferon alpha 2a given at 180 μg subcutaneously once weekly for 48 weeks results in suppression of HBV-DNA to below 20,000 copies/mL (~4,000 IU/mL) in 43% of patients on therapy (60). However only 19% continue to have undetectable HBV DNA 24 weeks after stopping therapy. Pegylated and standard interferon have not been compared directly in HBeAg-negative patients. However, at equivalent cost a weekly injection seems preferable to daily or thrice weekly injections.

Lamivudine (Heptovir®)

Lamivudine is a pyrimidine nucleoside analogue that inhibits binding of nucleosides to the HBV polymerase. The standard dose is 100 mg/day (61). It was the first oral agent approved in the treatment of HBV in Canada and until 2006 was the only such agent available. Thus, a large proportion of treated

HBV patients are currently on this agent or have received it in past. Generally, lamivudine is effective at lowering HBV viral load and experience acquired over many years in HBV and HIV diseases has established its safety (62). The relative potency of lamivudine compared to other antivirals is given in Figure 3. However, HBV becomes resistant to lamivudine with the prevalence of lamivudine resistance approaching 70% at 4 years (63). Furthermore, the development of lamivudine resistance also increases the likelihood of resistance to other antiviral agents, and may compromise the response to e.g., adefovir, entecavir and telbivudine (64). Therefore, lamivudine is no longer a suitable first line choice for the treatment of hepatitis B, although there are still some patients and some situations for whom lamivudine can be used. These are described below. The consensus was that lamivudine should continue to be recommended as a first line agent for the treatment of hepatitis B only because of its cost advantage. However, lamivudine should only be used under circumstances that limit the development of resistance (see below).

Lamivudine has been shown to improve the outcome of hepatitis B infection in cirrhotics (65). There is as yet no high level evidence that lamivudine (or other nucleoside analogues) improves survival. However, such data will likely never be available from high quality studies, because it is no longer considered ethical or practical to randomize patients to no treatment. Therefore, the evidence of efficacy of lamivudine comes from studies that are less rigorous. Cirrhotic patients treated with lamivudine have slower progression of disease than untreated patients (65). This benefit is lost if lamivudine resistance develops, implying that it is the suppression of viral replication that mediates the response. Cirrhotics who develop lamivudine resistance have worse survival than those whose infection remains sensitive to lamivudine (66), again suggesting that the improvement in outcome is mediated through viral suppression. There are also data suggesting that improvement in histology following antiviral therapy is correlated with the degree of viral suppression, rather than with any specific agent (67). Although these improved outcomes have mainly been demonstrated with lamivudine, any agent that induces viral suppression is expected to have the same effect.

Because the consequences of developing lamivudine resistance can be dire, lamivudine has to be used under circumstances that will prevent or at least minimize the development of resistance. Factors that predict the development of antiviral resistance in general and lamivudine resistance specifically include high baseline viral load (68,69), and incomplete suppression of viral replication after 6 months of treatment. Thus lamivudine should not be used in patients with high viral loads ($>2x10^6$ IU/mL). Furthermore, studies have shown that failure to suppress virus adequately, (below 60 IU/mL at 24 weeks) is associated with high levels of resistance at over time (69).

HBeAg-positive chronic hepatitis B:- HBeAg seroconversion can be expected in about 20% at one year, rising about 40% after 3 years (Table 3) (70-73). The durability of lamivudine-induced seroconversion is not as good as for interferon (about 50-70%)(74,75). These results may be improved with a period of

consolidation therapy of 6-12 months beyond seroconversion (75). This is probably required for all nucleoside analogues.

HBeAg-negative chronic hepatitis B:- These patients require long term therapy. Lamivudine is not a good choice for long-term therapy because of the high risk of resistance (63,76). However, in patients in whom the baseline viral load is low (in the range of $2x10^4$ to $2x10^5$ IU/mL) lamivudine can be considered as long as response is assessed at six months and if the HBV DNA is still detectable, treatment should be changed to a more potent nucleoside analogue (69). Resistance testing should be done to determine future choice of antiviral therapy. Patients currently on lamivudine who have undetectable levels of virus and who have been stable for some time do not need to have their therapy changed.

Other indications for lamivudine will be described below.

Adefovir (Hepsera®)

Adefovir dipivoxil is a purine nucleotide analogue. The standard dose is 10 mg/day. Adefovir is not a highly potent agent and does not achieve complete viral suppression in the majority of patients within the first year (see Figure 3), but it has a relatively high genetic barrier to resistance. As with lamivudine, the risk factors for adefovir resistance are high baseline viral load and inadequate suppression of virus on therapy (77). Therefore adefovir should not be used in patients with high viral loads. In addition, an inadequate response defined as HBV DNA greater than 200 IU/mL after 48 weeks requires a change in treatment regimen (77). Failure to achieve this level of control is associated with significant rates of viral resistance. Resistance testing should be done to determine future choices of therapy. Assuming no resistance almost any other agent can be substituted for adefovir.

Adefovir is the drug of choice for patients with lamivudine resistance, provided adefovir is added early after the initial development of resistance (see later).

There is potential drug toxicity from adefovir use. Hypophosphatemia is common, but does not appear to have any clinical consequences, such as metabolic bone disease. Nephrotoxicity in the form of an elevated creatinine has been reported (78). Therefore renal function (eGFR) should be monitored at baseline and at three monthly intervals during therapy. Potentially nephrotoxic drugs (e.g., NSAIDS) should be avoided where possible, as there is a possibility of potentiation of nephrotoxicity. Fanconi syndrome has also been reported. All these effects are reversible if detected early, but may not reverse if drug withdrawal is delayed.

HBeAg-positive chronic hepatitis B:- The HBeAg seroconversion rate in the first year is about 12% (78), but over time the on-treatment HBeAg seroconversion rate increases to about 40% (Table 3)(79). Seroconversion is durable in more than 90% of patients (79). Resistance rates in this population, who generally have a higher viral load than the HBeAg-negative patients, has not been described, but is likely to be higher than in the HBeAg-negative population.

<u>HBeAg-negative chronic hepatitis B:-</u> Despite the lack of potency five year follow-up data for HBeAg-negative patients on this drug that show that complete viral suppression and normalization of ALT is achievable in 50-60% of patients (80). The data indicate that the viral load falls progressively over time with an improvement in histology. Genotypic adefovir resistance occurs in about 29% after 5 years (80). Because of its resistance profile adefovir is suitable for long term use, provided that the initial response, within the first year is adequate (see above).

Entecavir (Baraclude®)

Entecavir is a selective guanosine analogue and is the most potent inhibitor of HBV DNA replication currently available. It has been shown to more effectively suppress viral replication than lamivudine in treatment naïve patients in both HBeAg positive (73) and HBeAg-negative subjects (81) and may be effective therapy for some HBeAg-positive patients with resistance to lamivudine (82). Entecavir was well tolerated and had a similar side-effect profile to lamivudine. However, the long term safety has not yet been established. In treatment naïve subjects only about 1% of subjects developed resistance to entecavir after three years (83,84). However, this is not the case for patients with prior lamivudine resistance. Resistance to entecavir requires the presence of the YMDD mutations that confer resistance to lamivudine, and also requires the presence of one of two or three additional mutations (85). These additional mutations, if present without the YMDD mutation do not confer resistance to entecavir. Therefore lamivudine resistance pre-disposes to entecavir resistance, and after three years of therapy about 32% of lamivudine-resistant entecavir-treated patients have developed resistance to entecavir (86). entecavir should be used to treat lamivudine-resistant infection only when no other alternative is available to treat lamivudine resistance,

The standard dose is 0.5 mg/day. The dose in lamivudine-resistant patients is 1 mg/day. However, the 1 mg tablet has not been approved in Canada. Failure to achieve undetectable virus in the first year does not require a change in therapy, except in he case of primary non-response, because by the end of year 3 more than 80% of patients will be HBV DNA negative and selection of resistant mutants is so uncommon. There are published cost-efficacy data for entecavir, that suggests that it use is cost-effective, particularly in cirrhotic subjects (86).

<u>HBeAg-positive chronic hepatitis B:-</u> The expected rates of HBeAg seroconversion at one year are similar to other nucleoside analogues at 21% after year 1 and 39% after year 3 (Table 3) (73,87). The HBeAg seroconversion persists in about 80% of patients 24 weeks after withdrawing treatment. However, persistent off-therapy suppression of virus to undetectable levels occurs in only about 75% of cases.

<u>HBeAg-negative chronic hepatitis B:-</u> Entecavir is a good choice for these patients because of the favourable resistance profile (84). On withdrawal of therapy most patients relapse, again indicating the need for long term treatment.

Telbivudine (Sebivo®)

Telbivudine is a pyrimidine nucleoside analogue with potent antiviral efficacy against HBV. Telbivudine will suppress HBV replication more effectively than lamivudine in the HBeAg positive and HBeAg negative. chronic hepatitis B. The standard dose is 600 mg daily (88,89). Genotypic resistance rates of 5% and 11% were reported after 1 and 2 years of telbivudine treatment, respectively (89). Telbivudine was generally well tolerated. An asymptomatic increase in creatine kinase occurred in approximately 12% of patients. Symptomatic myositis has also been described.

Telbivudine is more potent than lamivudine and can be used in patients with high viral loads. However, as with lamivudine, inadequate suppression of virus is associated with significant rates of development of resistance. Therefore, if after 6 months of therapy the HBV DNA is still above 60 IU/mL a change in therapy is needed to reduce the risk of developing resistance (90). Resistance testing should be done to determine future choices of therapy.

HBeAg-positive chronic hepatitis B:- Seroconversion will occur in about 22% in the first year, rising to about 33% in the second year of treatment (90,91). However, efficacy needs to be checked at 6 months, and if the viral load is >60 IU/mL treatment should be changed.

HBeAg-negative chronic hepatitis B:- Telbivudine is suitable for use in these patients because it has a good resistance profile. However, efficacy needs to be checked at 6 months, and if the viral load is >60 IU/mL treatment should be changed.

Tenofovir (Viread®)

This is a purine analogue that has been licensed for treatment of HIV, but not hepatitis B. However, it has potent activity against hepatitis B. Its efficacy has been demonstrated in small studies in patients who were either resistant to adefovir (91,92), or who had an initial inadequate response to lamivudine and in studies in HIV-co-infected patients (93). These studies showed that viral suppression was rapid and potent. To date, resistance has only rarely been described, but adequate studies are lacking (94). Since tenofovir is not licensed for hepatitis B no recommendations can be made about its use as first line therapy. However, in the setting of patients with an inadequate response to adefovir or resistance to both adefovir and lamivudine it seems to be an effective antiviral. Tenofovir is also a drug of choice in HBV/HIV co-infection as part of highly active antiretroviral therapy.

Emtricitabine Emtriva®

Emtricitabine (FTC) has recently been licensed in Canada for HIV in combination with tenofovir (Truvada®). It has been used in studies to treat hepatitis B (95,96), but it is not licensed for that purpose. This is a pyrimidine nucleoside analogue, with a spectrum of activity and resistance spectrum that is very similar to lamivudine (3TC). It is not available as monotherapy.

De Novo Combination Therapy,

Although combination therapy for hepatitis B may be appropriate there is little data to support its use. In a single study a combination of lamivudine and adefovir was compared to lamivudine alone. There was no difference in HBV DNA suppression, HBeAg-seroconversion, or ALT normalization (97). Resistance to lamivudine was not completely prevented. The combination of lamivudine and telbivudine was less effective that telbivudine alone for all endpoints (98). In cirrhotic patients, particularly those with some degree of hepatic decompensation the development of resistance to antiviral agents may be associated with a flare of disease activity that may be fatal. Therefore, in this setting combination therapy can be considered. Suggested combinations are lamivudine and adefovir, tenofovir and lamivudine or emtricitabine, or entecavir plus adefovir or tenofovir. Entecavir monotherapy may also be suitable in these patients).

Figure 4 provides an algorithm to help select suitable agents to treat hepatitis B.

17. **Recommendation: Standard interferon alpha at a dose of 30-35 MU/week (5 MU daily or 10 MU TIW) for 16-24 weeks can be used to treat HBeAg-positive chronic hepatitis B (I).**

18. **Recommendation: Pegylated interferon alpha 2a 180 μg sc weekly given for 24-48 weeks can be used to treat HBeAg-positive chronic hepatitis B. Pegylated interferon alpha 2a for one year is suitable treatment for HBeAg-negative chronic hepatitis B (I).**

19. **Recommendation: Lamivudine should be reserved for patients with low viral load (not clearly defined, but probably less than $2X10^6$ IU/mL)(mostly HBeAg-negative). If serum HBV DNA is > 60 IU/mL at 6 months of therapy the therapeutic regimen should be changed. Alternatives include switching to entecavir, or adding adefovir. The role of telbivudine in these circumstances is not clear (I).**

20. **Recommendation: Adefovir as primary therapy should be reserved for patients with a viral load less than about $2x10^6$ IU/mL (mostly HBeAg-negative). If the viral load has not fallen to below 200 IU/mL at the end of the first year of therapy the treatment strategy should be changed. All pyrimidine analogues and tenofovir are suitable alternatives (I).**

21. **Recommendation: Entecavir is effective first line therapy for all patients regardless of viral load because it appears to be the most potent agent available and it is associated with very low rates of resistance (I).**

22. **Recommendation: Telbivudine is suitable for first line use in all patients, including those with high viral load (>200,000 IU/mL). However, because of the risk of resistance, treatment efficacy should be assessed at 6 months (I). If HBV DNA is > 60 IU/mL at 6 months the treatment strategy should be changed (II-2).**

23. **Recommendation: Following HBeAg seroconversion with nucleoside analogue treatment a further 6-12 months of therapy is required (consolidation therapy) to maximize the durability of the response (II-2).**

On treatment monitoring

Interferon therapy

Patients treated with interferons need to be monitored closely. Liver tests, and CBC should be performed at monthly intervals. TSH should be measured every three months. When using PEG IFN for HBeAg-positive disease HBV DNA and HBeAg/anti-HBe can be measured after 6 months and at the end of treatment to determine response. These tests should also be performed 6 monthly for 12-18 month after treatment withdrawal. A successful outcome is defined as anti-HBe-positive with normal ALT for more than 6 months, with the HBV DNA being less than 20,000 IU/mL. Ideally the HBV DNA should be undetectable since the presence of detectable virus suggests a risk of disease relapse. In HBeAg-negative chronic hepatitis B patients treated with interferon should be monitored as for HBeAg-positive hepatitis, except that HBeAg and anti-HBe testing does not need to be repeated. Post therapy the HBV DNA and ALT should be monitored at 3 monthly intervals.

Nucleoside analogues

Patients treated with nucleoside analogues should be monitored with HBV DNA and ALT initially at 3 and 6 months after starting treatment. This is to confirm an initial fall in viral load, and in the case of lamivudine and telbivudine, to determine whether treatment with the same drug can be maintained, or whether another drug should be added or substituted (see above). Patients on all nucleoside analogues should thereafter be monitored at 3 monthly intervals to determine the lowest HBV DNA concentration that is achieved (nadir), and subsequently to allow for early detection of the development of viral breakthrough leading to resistance. Patients on adefovir also require 3 monthly monitoring of serum phosphate levels and renal function. Patients on telbivudine require monitoring of creatine kinase.

24. **Recommendation: The target HBV DNA on antiviral therapy is undetectable virus. This should be measured using the most sensitive test available, i.e., currently the Taqman assay. Assays of lower sensitivity are not recommended (III).**

Resistance to antiviral therapy

HBV Antiviral Resistance Testing

Mutations that confer resistance to antiviral agents occur spontaneously and are not caused by the antiviral agents. Most resistant mutants have diminished replication competence and do not survive. However, in the presence of a selective pressure that inhibits the growth of wild-type virus proliferation of some mutant virus species occurs, until they come to be the dominant species. Depending on replication

competence the mutants can replicate at high levels over time. When a patient is on antiviral therapy, antiviral resistance may be suspected when serial HBV DNA testing shows increases in viral load of more than 10 fold (1 $\log_{10}$ IU/mL) over nadir. Thus, monitoring for antiviral resistance requires regular assessment of HBV DNA concentrations. When resistance develops, particularly resistance to lamivudine, mutations in addition to the primary resistance mutation may occur that may lead to reduced susceptibility to other antivirals (99). Genotypic resistant virus can be detected by various methods, such as direct genetic sequencing, reverse hybridization, restriction fragment analysis, and other sequence-based detection. Sequencing requires that the mutant virus to comprise at least 20-25% of the viral mixture. Reverse hybridization (INNO-LIPA) may be able to detect lower frequency mixed infection (100). Since lamivudine resistance is associated with additional mutations besides the YMDD mutations knowing the genetic mutations involved in resistance in any individual patient is essential to determine the most appropriate treatment for patients with lamivudine resistant virus.

25. Recommendation: Clinicians must have access to genetic testing for mutant virus. This is used to differentiate between non-adherence and emergence of resistant virus. Viral breakthrough (defined later) should be assessed by resistance testing before any new agents are introduced (III).

The development of resistance to antiviral therapy is not benign. There is considerable evidence that the benefits of viral suppression are lost (101,102). Acute flares of hepatitis can occur, which in cirrhotic patients can be life-threatening. The development of resistance to antivirals is therefore a strong indication to change therapy. It is not acceptable for patients with e.g., lamivudine resistance to continue to be treated with lamivudine monotherapy when effective alternatives exist.

Definitions of Non-Response (see Table 4)

All nucleoside analogues are associated with the development of viral resistance. The rate at which antiviral resistance to individual nucleoside analogues develops has not been accurately defined because the long term studies that have been used to determine these rates were not designed to quantify resistance. Furthermore, resistance was evaluated in subgroups of patients that were considerably smaller than the group initially recruited into trials. Nonetheless, the studies have allowed some sense of the comparative rates at which each agent is subject to the development of resistance (103). These are given in Figure 5.

Table 5 shows the substitutions in the viral polymerase gene that are associated with resistance to various agents (104). Table 6 shows the relative potency of the different antiviral agents in the face of some of the mutations known to confer resistance (104).

Resistance to antiviral therapy increases in frequency with baseline viral load, with failure of adequate suppression of virus, and with viral genetic factors. Thus the higher the viral load prior to treatment, the

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more likely that resistance will develop. The more slowly that viral load falls on therapy and the higher the nadir of viral load the more likely that resistance will occur.

It is important to detect resistance early, before viral load rebounds fully and before the ALT rises. Treatment is more likely to be effective if a new agent is introduced when the viral load is low than when it is high.   To ensure that viral breakthrough is detected early HBV DNA concentration load should be measured at three monthly intervals. Virologic testing should be done to confirm that viral breakthrough is due to resistance rather than poor adherence. Treatment should be modified as soon as resistance is identified, once more, because it is easier to treat while the viral load is low, than when it is high.

26. **Recommendation: HBV DNA should be monitored at three-month intervals to allow early detection of viral resistance, at a stage when the viral load is still low (II-2).**

27. **Recommendation: Resistance genotyping should be performed in all patients in whom a viral rebound is detected to determine whether this is due to resistance or to poor adherence (II-2).**

Management of primary non-response

Primary non-response (Table 4) should be investigated by resistance genotyping. If resistance mutations are not present the most likely explanation for the lack of response is poor adherence. Occasionally there may be problems with absorption, or other pharmacologic reasons for non-response, but these are poorly defined, and cannot be tested for.

Management of resistance to specific antivirals

Lamivudine resistance

Recent studies have shown that addition of adefovir after viral breakthrough, but before clinical breakthrough, i.e., when the viral load is still low is the preferred treatment (105).   Under these circumstances control of viral replication is almost invariably effective, and the rates of resistance to adefovir are very low. Switching to adefovir is associated with higher rates of adefovir resistance and is not recommended (106,107). Entecavir is not a good choice for lamivudine resistance because the response to entecavir is blunted. Furthermore, resistance to entecavir occurs only in the setting of the mutations associated with lamivudine resistance and is 32% after 3 years (84). Virus that is resistant to lamivudine will have a high likelihood of also being resistant to telbivudine. Tenofovir is effective in suppressing lamivudine-resistant hepatitis B, but whether tenofovir should be added or simply substituted for lamivudine has not been addressed.

28. **Recommendation: The treatment of choice for lamivudine resistant infection is the addition of adefovir (I).**

Resistance to adefovir monotherapy

Genotypic resistance to adefovir monotherapy occurs in about 29% of patients after 5 years (80). Clinical breakthrough occurs in about 11% (80). Lamivudine, tenofovir, telbivudine or entecavir can all be used. There are no large scale trials confirming the efficacy of these agents, but in vitro data supports these substitutions.

Resistance (or inadequate response) to combination lamivudine/adefovir in lamivudine-resistant patients

Evidence suggests that adequate suppression can be obtained with tenofovir (91,108,109). Whether tenofovir should be added to lamivudine or simply substituted for adefovir has not been addressed.

Entecavir

Entecavir resistance requires the pre-existence of the YMDD mutation. The presence of YMDD mutations decreases entecavir potency somewhat, but not enough to produce resistance. Nonetheless, in the presence of specific YMDD mutations (M204V and L180M) one or more additional mutations (I169T, T184G, S202I, M250V) do confer resistance (110). However, in the absence of the M204V and L180M mutations these additional mutations are not associated with any decrease in potency. In the registration studies of entecavir in lamivudine resistant patients entecavir resistant mutations were detected in a proportion of patients prior to the introduction of entecavir (82). As a result genotypic resistance was identified in 7% and viral breakthrough in 1.6% at the end of the first year of therapy (82). This rose to more than 30% and the end of the third year of therapy (84). In nucleoside naïve subjects, in contrast the rate of resistance to entecavir after 3 years was less than 1 % (84).

Entecavir resistance can be treated with either adefovir or tenofovir (based on in vitro data only)

Telbivudine

Little is known about treatment of resistance to telbivudine, which occurs in 18% at the end of two years of therapy (94). Resistance is mainly mediated by the M204I mutation and uncommonly by other mutations at the YMDD locus. Therefore cross resistance with lamivudine and emtricitabine can be expected. However, theoretically adefovir and tenofovir could be used for telbivudine resistance. It is not clear whether entecavir can be used.

Other agents

Tenofovir is has been shown to be an effective hepatitis B antiviral. Although it is not recommended for first line use (because it is not yet licensed for this purpose) it is recommended for inadequate response to adefovir or adefovir resistance in patients with prior lamivudine resistance. Resistance to tenofovir has been rarely described in hepatitis B, but studies are small, follow-up is short, and so the true resistance rate is not known.

Post treatment and long term off treatment monitoring

Patients in whom treatment has not been offered still need continued follow up, regardless of the status of their disease. Patients who have active viral replication are at risk for exacerbation of their hepatitis at any time. These flares may be short-lived, although cumulatively over time they may be very damaging. Since the period of ALT elevation may be brief frequent testing is necessary. Patients who are at risk for the development of flares should be monitored at least every three months, if not more often. Monitoring should include HBV DNA, ALT, tests of liver function and CBC. In HBeAg-negative patients who have low levels of viral replication ($<2x10^3$ IU/mL) that are stable over 1-2 years the frequency of monitoring can be reduced to initially 6 monthly, and eventually yearly. Monitoring should however still include HBV DNA, ALT and tests of liver function.

Hepatoma Screening

The annual incidence of hepatoma in HBV infected individuals without cirrhosis is 0.4-0.6% in Asians (26), 0.2% in Alaskan natives (111), and ~0.3% in Caucasians (112). There are insufficient data on the incidence of HCC in Africans or North American Blacks. In cirrhosis, the incidence is >2% per year, with a cumulative 5 year incidence between 15-20% (113,114).

Surveillance should be performed every 6 months using abdominal ultrasound in those deemed to be high risk for hepatoma (115). Alphafetoprotein testing is not an effective screening method (116). Not all patients with hepatitis B are at equal risk of developing HCC. The categories of patient who should be screened are given in Table 7.

Management of Hepatitis B Cirrhosis

All patients with well-compensated cirrhosis should be considered for therapy if the HBV DNA level is above 2000 IU/mL whether they are HBeAg or anti-HBe positive. A suggested algorithm is shown in Figure 6. If the HBV DNA is lower than this threshold, patients may be observed closely with measurements of HBV DNA and ALT every three to six months or they may be considered for therapy. Standard or pegylated interferon may be used with caution in these patients, but nucleos(t)ide analogues are preferred. Nucleoside analogue treatment should continue indefinitely in patients with cirrhosis, even if such patients undergo HBeAg seroconversion.

Hepatic decompensation

All patients with hepatic decompensation due to hepatitis B should be treated with nucleoside analogues 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 HBV therapy should be made in consultation with the local liver transplant program. Lamivudine and adefovir have been shown to improve hepatic function in such patients and may stave off the need for liver transplantation (117-119). However, as the development of resistant mutants can be

associated with flares of hepatitis and hepatic decompensation (102), it is preferable to use drugs (entecavir or tenofovir) with the lowest rates of resistance. Combination of adefovir and lamivudine remains an option. Another alternative is the combination of tenofovir and emtricitabine, which is available as a single tablet for daily use. The renal function must be monitored carefully if tenofovir or adefovir are used in cirrhotics as these patients are prone to renal dysfunction. Entecavir has not been fully evaluated for use in this situation, but, barring unexpected toxicity, should also be an effective agent.

Management of Hepatitis B/HIV co-infection

The prevalence of HBV co-infection in HIV-infected patients is approximately 10% (120). HIV co-infection tends to accelerate the natural history of HBV and co-infected patients tend to have more histologically advanced disease and higher rates of liver related mortality (121-123). All HIV positive individuals should be screened for HBsAg and anti-HBs and if negative should be vaccinated (three double doses is recommend for such immunosuppressed individuals)(126). The treatment of the co-infected individual is complex and ideally these patients should be managed by a multidisciplinary approach by specialists with an understanding of both infectious disease and liver disease. An understanding of the activity of various nucleoside analogues against both viruses, the potential for hepatotoxicity with certain HIV medications and issues regarding timing of HIV therapy are required.

Interferon, has only weak activity against HIV. Adefovir at the 10 mg dose has limited activity against HIV. Adefovir results in effective HBV suppression in lamivudine resistance HBV in co-infected individuals (124,125). There is in vitro cross resistance between adefovir and tenofovir for the HIV DNA polymerase. Entecavir is said not to be active against HIV. However, recent data hint that use of entecavir leads to selection of HIV polymerase mutants resistant to lamivudine and emtricitabine (126). Twenty-four weeks of entecavir has been shown in a placebo controlled trial to result in a -3.66 log drop in HBV DNA in co-infected patients (127). Until the role of cross resistance between HIV and hepatitis B is better defined for these agents their neither adefovir nor entecavir are recommended for use as monotherapy against hepatitis B in HIV-positive individuals.

Lamivudine (3TC), tenofovir and emtricitabine all have activity against both HIV and HBV. Lamivudine is associated with higher rates of HBV resistance in co-infected individuals (90% after 4 years) (128), and should never be used as monotherapy for HBV infection in untreated HIV patients as it may lead to HIV resistance to future therapies including emtricitabine. Tenofovir is a potent suppressor of HBV DNA replication in both HBeAg positive and HBeAg negative co-infected patients (129). A small study in HIV infected subjects with lamivudine resistant HBV, tenofovir was superior to adefovir in achieving HBV DNA negativity (100% vs. 44% after 48 weeks of therapy)(92). Furthermore, the vast majority of patients with lamivudine resistant HBV who have incomplete viral suppression on adefovir can achieve HBV DNA negativity by switching to tenofovir (91).

Highly active antiretroviral therapy (HAART) regimens containing tenofovir with lamivudine or emtricitabine in combination with the non-nucleoside reverse transcriptase inhibitors or protease inhibitors

are ideal as these regimens have virologic activity against both HIV and HBV and infrequently cause hepatotoxicity. Therapy may not be needed for HIV in early stages of the disease. If therapy is required against both viruses then a combination of tenofovir with lamivudine or emtricitabine is recommended up front to avoid the development of resistance. Tenofovir is the preferred drug in patients with HBV resistance to lamivudine. Immune reconstitution syndrome in advanced HIV therapy may occur after initiating HAART, and could result in a flare of hepatitis.

29. **Recommendation: The need for hepatitis B therapy in HIV-positive patients remains an indication for the use HAART (III).**
30. **Recommendation: Lamivudine should not be used as monotherapy for hepatitis B in HIV-positive patients (II-2).**
31. **Recommendation: Hepatitis B antivirals cannot yet be recommended as monotherapy for hepatitis B in HIV-infected patients (III).**

Management of HBV-HCV Co-infection

In patients infected with both hepatitis B and hepatitis C viruses usually have only one of the two diseases active (130). Such patients should have both HBV DNA and HCV RNA measurements. Subjects with high levels of HBV DNA but negative HCV RNA should be treated as any other HBV-infected patient. If the HBV DNA level is low (<20,000 IU/mL) and the HCV RNA is positive, these patients should be treated as other patients with chronic HCV infection. Recent studies have suggested that their response to interferon and ribavirin is similar to patients who are not co-infected (131). In patients treated for hepatitis C HBV DNA levels should be monitored on therapy. If levels are >2000 IU/mL and do not fall with PEG IFN and ribavirin therapy consideration should be given to adding a nucleoside analogue such as entecavir, adefovir or lamivudine.

Management of Hepatitis B before pregnancy

Decisions on antiviral therapy in young women must take into account the woman's desire for a family. Women planning a family should be treated with drugs that are safe in pregnancy. Lamivudine, adefovir and entecavir are Category C drugs (i.e., mutagenic in *in vitro* assays) and tenofovir and telbivudine are Category B drugs (no mutagenicity). Although lamivudine is a category C drug it has a record of safety in pregnancy. Tenofovir is also considered safe in pregnancy, although the experience with this drug is not as extensive as with lamivudine. As with other young patients not all patients with high viral loads and elevated ALT need treatment and it may be reasonable to temporarily withhold treatment in these patients. If withholding treatment is being contemplated a biopsy is advised to confirm that the liver disease is mild. Close monitoring during pregnancy is necessary if the patient is not treated.

Although telbivudine is a category B drug, there is no experience with its use in pregnancy.

Management of Hepatitis B during pregnancy

All pregnant mothers should be screened for HBsAg and those who test positive should have an HBV DNA measurement, as women with high levels of HBV DNA are at greater risk for transmission of virus to their offspring. Babies born to HBsAg positive mothers must receive passive and active immunization after birth. In general this strategy is approximately >95% effective (132). In a US study of approximately 800 children born to HBsAg positive pregnant women between 1992 and 1997, 97% had anti-HBs $\geq$10 mIU/mL and only 2.2% became HBsAg positive (132).

An uncontrolled study from the Netherlands found that pregnant women with high HBV DNA levels ($>10^9$ IU/mL) had rates of vertical transmission of 28% despite neonatal vaccination. This was reduced to 13% in eight pregnant women treated with lamivudine 150 mg daily in the third trimester of pregnancy (133). In a randomized controlled trial from China of lamivudine 100mg daily or placebo introduced at week 32 ± 2 of gestation and continued post-partum for one month, there was a reduction of failure of neonatal active and passive vaccination in the lamivudine treated group (18% vs 39% HBsAg positive children at one year (134). To date there appears to be no increased risk of fetal injuries due to lamivudine (135). The low risk of mother-to-infant transmission of hepatitis B in the presence of neonatal vaccination does not support the routine use of nucleoside analogues during the third trimester of pregnancy to reduce the risk of vertical transmission. However, pregnant women with high levels of HBV DNA should be referred to specialists for consideration of this treatment.

Hepatitis B and renal failure

HBV infection is associated with an increased risk of renal disease including membranous nephropathy and glomerulonephritis, as well as other immune-complex associated diseases such as polyarteritis nodosa (136). Suppression of HBV DNA can result in improved renal function in these patients. There is evidence that patients with HBV related renal disease may have increased rates of responsiveness to interferon therapy (137). There are case reports of improvement of renal function with lamivudine in patients with hepatitis B-induced renal disease (138). Adefovir should be used with caution in this population, as the drug itself may be associated with renal dysfunction. There is no experience reported with entecavir in patients with HBV associated renal failure. All antiviral agents are excreted by the kidney, and dose adjustments are required in renal failure.

Chemotherapy and Immunosuppression in HBV-infected Patients

All patients undergoing chemotherapy, 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. Thirty to 50% of HBV-negative individuals can experience reactivation of viral replication associated with increased ALT upon immunosuppression (139). These changes may occur in 30-50% of patients (139). The only agent that has been studied during immunosuppression is lamivudine (140). However, any antiviral is likely to be effective if the viral load is initially low. Patients who start off with

high viral loads might need more potent antivirals if resistance is to be avoided. Lamivudine (or more potent agents if required) should be started preemptively in HBsAg positive patients at least a few days before immunosuppressive or chemotherapy is begun (141). There is no information to guide how long to treat such patients, but it would be reasonable to treat for an additional 3-6 months after discontinuing immunosuppressive therapy or chemotherapy. Resistance is less of a concern as treatment is usually short-term in these patients, therefore lamivudine may be considered the first line therapy (unless the initial viral load is very high). However, if long-term immunosuppressive therapy is required consideration should be given to using entecavir or adefovir.

Whether subjects with markers of past HBV infection (HBsAg negative but anti-HBc positive) should also be treated prophylactically is unclear. Although the risk of reactivation may be low (<5%) in such patients, re-emergence of HBV may be severe and even fatal in some of these patients. If patients are anti-HBs negative, attempts should be made to improve immunity with a booster dose of the HBV vaccine. 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 anti-viral therapy should be initiated as soon as there is evidence of HBV reactivation, without waiting for a rise in ALT.

All patients awaiting solid organ transplantation should be vaccinated against HBV, although the likelihood of an effective antibody response is low (142). The risk of transmission of HBV is highest for recipients of livers, and low for other solid organ transplants. Recipients of organs other than liver from anti-HBc-positive anti-HBs-negative donors should receive lamivudine prophylaxis for at least the first post-transplant year during which time immunosuppression levels are at their highest. Recipients with documented seroconversion following HBV vaccination and persistent protective levels of anti-HBs (>10 IU/mL) do not require antiviral prophylaxis (143). Prophylaxis against hepatitis B reactivation in patients undergoing liver transplantation will not be discussed, as this is a highly specialized field, and is limited to a small number of practitioners in the country.

32. **Recommendation: All patients undergoing chemotherapy (including chemoembolization), bone marrow or solid organ transplantation, treatment with immunosuppressive monoclonal antibodies or other immunosuppression should be screened for hepatitis B markers. Those testing positive for HBsAg should receive antiviral prophylaxis prior to treatment, and should be monitored during and after therapy (I).**

Management of Hepatitis B in children

In highly endemic areas, childhood infection, either vertical or horizontal in early childhood remains the predominant mode of transmission. In Canada, immigration and adoption of children from endemic regions account for most cases of HBV infection in children.

The age at acquisition of the virus influences the natural history of the HBV infection. Neonates and young children develop chronic disease in about 90% of cases. In children ages 1-5 the chronicity rate is

about 50%, in older children about 6-10%, and in young adults less than 5%. Cirrhosis and HCC are rare in children, and when they do occur, usually occur in older children. However, cases in young children are also well described. The spontaneous HBeAg seroconversion rates in children is high, and therefore treatment may not be necessary (145-149).

HBeAg-positive adolescents with elevated ALT should be observed for at least 6-12 months to determine if they will spontaneously undergo HBeAg seroconversion. Those who continue to have high HBV DNA and fail to spontaneously undergo seroconversion can be considered for therapy, especially if the liver biopsy shows significant inflammation or fibrosis.

Children who have elevated ALT or evidence of active disease on liver biopsy may be candidates for therapy (150). There is data however, that suggests that treatment induced seroconversion in children merely advances spontaneous seroconversion by a few years. This may not be a worthwhile treatment goal. The long term impact interferon therapy in children remains unknown (151,152). Only standard interferon and lamivudine have been assessed in children. Interferon-alpha 6MIU/m2 sc (maximum 10MIU) TIW for 24 weeks has been approved for children with HBeAg-positive disease based on a study that found greater HBeAg loss and HBV DNA negativity in interferon treated children compared to controls (26% vs. 11%, p<0.05)(153). In addition to the usual side effects interferon may interfere with growth of young children, although transiently. Interferon should not be used in children under age 3 because of a risk of neurotoxicity. Lamivudine, 3 mg/kg/day (maximum 100 mg) for one year is also approved. However, as with adult disease, lamivudine resistance in developed in 19% after one year (154). A follow-up to this study, showed the durability of virologic response to be 89% two years after stopping therapy (155). Although an additional two years of lamivudine increased the virologic response rates, the YMDD mutation rate increased to 64% after 3 years of therapy. Thus lamivudine may not be suitable for use in young children because this is a group of patients with high viral loads, and in which many will require many years of therapy, or who may require treatment later after a period of inactive disease, after which the presence of lamivudine-resistance will severely limit treatment choices.

Regardless of type of therapy, all children should continue to be followed at one to two-year intervals to monitor for durability of response.

Hepatitis B infected medical professionals

Many jurisdictions have developed guidelines that restrict the practice of physicians, dentists and other healthcare professional because of hepatitis B infection. We do not intend to revisit those restrictions, nor the issue of disclosure to patients. However, hepatitis B infected health professionals may choose to take treatment to reduce viral load and thereby preserve their careers. There is no clear cut level of HBV DNA below which infection cannot occur, although the lowest viral concentration associated with documented transmission was 4000 copies/mL (about 800 IU/mL)(156). In Europe the consensus was that if the HBV DNA was below 2000 IU/mL transmission risk was sufficiently low to permit continued exposure prone procedures (156). In the U.K. if the HBV DNA is below 200 IU/ surgeons can continue to operate. It is

recommended that if such a course of action is undertaken the lower the viral load in serum the better, and undetectable by Taqman PCR should be the goal.

Chronic hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus that requires HBsAg for entry into and exit from the hepatocyte. HDV therefore may be acquired as a co-infection simultaneously with hepatitis B or as a super-infection in a patient who already is a carrier of HBV. Infection with hepatitis D usually causes an aggressive hepatitis and is associated with a higher risk of cirrhosis than HBV mono-infection. Although there is no seroprevalence data, the prevalence of HDV infection in Canada is thought to be low. Those at highest risk for HDV infection are HBsAg carriers who acquired their infection through injection drug use and immigrants from countries where HDV is endemic (such as Italy, Russia, Romania, Spain Turkey and Egypt). Patients with these risk factors, particularly in the setting of a high ALT with undetectable HBV-DNA, should be tested for HDV antibody. If the HDV antibody is positive, active infection should ideally be confirmed with an HDV RNA and treatment considered in those with active infection. Unfortunately, the HDV RNA assay is not commercially available, and home grown assays are not standardized. Patients with active hepatitis D should be treated in expert centers.

Unfortunately there are limited data to guide the treatment of HDV. Lamivudine and ribavirin appear to have no role in the management of HDV. Several small studies suggest that standard interferon and pegylated interferon result in sustained virological response (SVR) rates between 17% and 43% with the highest response rates seen in those treated with prolonged pegylated interferon (157-159). If possible treatment response should be monitored with an HDV RNA at month 6 and in those who fail to achieve at least a 3 log drop therapy should be discontinued. Alternatively, in the absence of HDV RNA monitoring, normalization of the ALT suggests suppression of virus.

33. **Recommendation: Hepatitis D should be treated with PEG IFN monotherapy at standard doses for a minimum of 12 months (II-2).**

Table 1. Levels of evidence according to study design (160)

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case controlled studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinion of respected authorities. Descriptive epidemiology

Table 2. Phase of hepatitis B infection

Phases	HBsAg	HBeAg	Anti-HBe	ALT pattern	HBV DNA range
Immune tolerant	Positive	Positive	Negative	Normal ALT	~ >2×10^4 to >2×10^8 IU/mL
Immune clearance	Positive	Positive	Negative	Normal or elevated	~ >2×10^4 to>2×10^8 IU/mL
Inactive disease	Positive	Negative	Positive	Normal	< 200 IU/mL
HBeAg-negative chronic hepatitis B	Positive	Negative	Positive	Normal or elevated	undetectable to >2×10^8 IU/mL
Resolved hepatitis B infection	Negative	Negative	Positive	Normal	undetectable

Table 3. Seroconversion rates with hepatitis B antiviral therapy. A: HBeAg seroconversion rates. B: HBsAg seroconversion rates by the end of follow-up. (The duration of follow-up was not the same in all studies).

A

	Duration of treatment	HBe seroconversion rate
Standard interferon	16-24 weeks	33% (HBeAg loss)[49]
Pegylated interferon	24-48 weeks	29-32%29,[55,56]
Lamivudine	1 year	17-20%[70-73]
	3 years	40%[76]
Adefovir	1 year	12%[78]
	3 years	43%[80]
Entecavir	1 year	21%[73]
	3 years	39%[87]
Telbivudine	1 year	22%[90]
	2 year	33%[91]

Table 4. Definitions of response to hepatitis B nucleoside antiviral agents

Primary treatment failure	Less than 2-$\log_{10}$ IU/mL decrease in viral load measured at 6 months of treatment. This is not antiviral resistance, and is most commonly related to lack of adherence with medication.
Genotypic resistance:	Mutation of HBV-DNA polymerase known to decrease the efficacy of the antiviral agent
Phenotypic resistance	Defined by an in vitro assay demonstrating decreased inhibition of viral replication in the presence of the specific mutation in the polymerase gene.
Viral breakthrough	Increase in viral load of 1 $\log_{10}$ IU/mL or greater above the nadir, measured on two consecutive samples one month apart, occurring after the first three months of therapy. This is commonly due to genotypic resistance, but may also be due to lack of adherence.
Clinical/biochemical breakthrough	A rise in ALT from its nadir during treatment associated with a rise in viral load of 1 $\log_{10}$ IU/mL or greater. This is may also be due to either genotypic resistance or to lack of adherence.

Table 5. Mutations conferring resistance to hepatitis B nucleoside antivirals. The number refers to the amino acid position. The letters before the numbers represents the wild type amino acid. The letters after the number represents the substituted amino acid.

Agent	Domain A	Domain B	Domain C	Domain D
Lamivudine	L80V/I	V173L, L180M	M204V/I/S	
Adefovir		A181V/T		N236T
Entecavir*		I169T, T184G	S202I	M250V
Telbivudine			M204I	

* The entecavir mutations only confer resistance in the presence of the M204V, M204I and the L180M mutations. In the absence of these additional mutations the entecavir mutations do not cause resistance.

Table 6.   Relative activity of hepatitis B antivirals in the presence of pre-existing mutations in the polymerase gene.

	Resistance mutation		
	LAM-resistant	ADV-resistant	ADV-resistant
	L180M + M204V, M204I	N236T	A181V
Mutation confers reduced sensitivity to listed drugs	Entecavir, Telbivudine	Tenofovir	Lamivudine
Drugs remaining active	Adefovir, Tenofovir	Lamivudine, Entecavir, Telbivudine	Tenofovir, Entecavir

Table 7. Hepatitis B carriers who should undergo regular screening for hepatocellular carcinoma

All patients with cirrhosis

Other hepatitis B infected individuals

- Africans > 20 years old
- Asians > 30-35 years old (if infected early in life)
- Asian men > 40 years old
- Asian women > 50 years old
- Patients with family history of hepatoma
- Patients with active inflammation on liver biopsy
- Patients awaiting liver transplantation

Figure 1. Dynamic range of assays for hepatitis B virus DNA.

HBeAg +ve range

Abbott RealTime PCR
Artus-Biotech

Digene Hybrid Capture I
Digene Hybrid Capture II
Ultra-sensitive Digene Hybrid Capture II

Amplicor HBV Monitor
Cobas Amplicor HBV Monitor
Cobas TaqMan 48 HBV

Versant HBV bDNA 1.0
Versant HBV bDNA 3.0

$1 \quad 10 \quad 10^2 \quad 10^3 \quad 10^4 \quad 10^5 \quad 10^6 \quad 10^7 \quad 10^8 \quad 10^9 \quad 10^{10}$

HBV DNA IU/mL
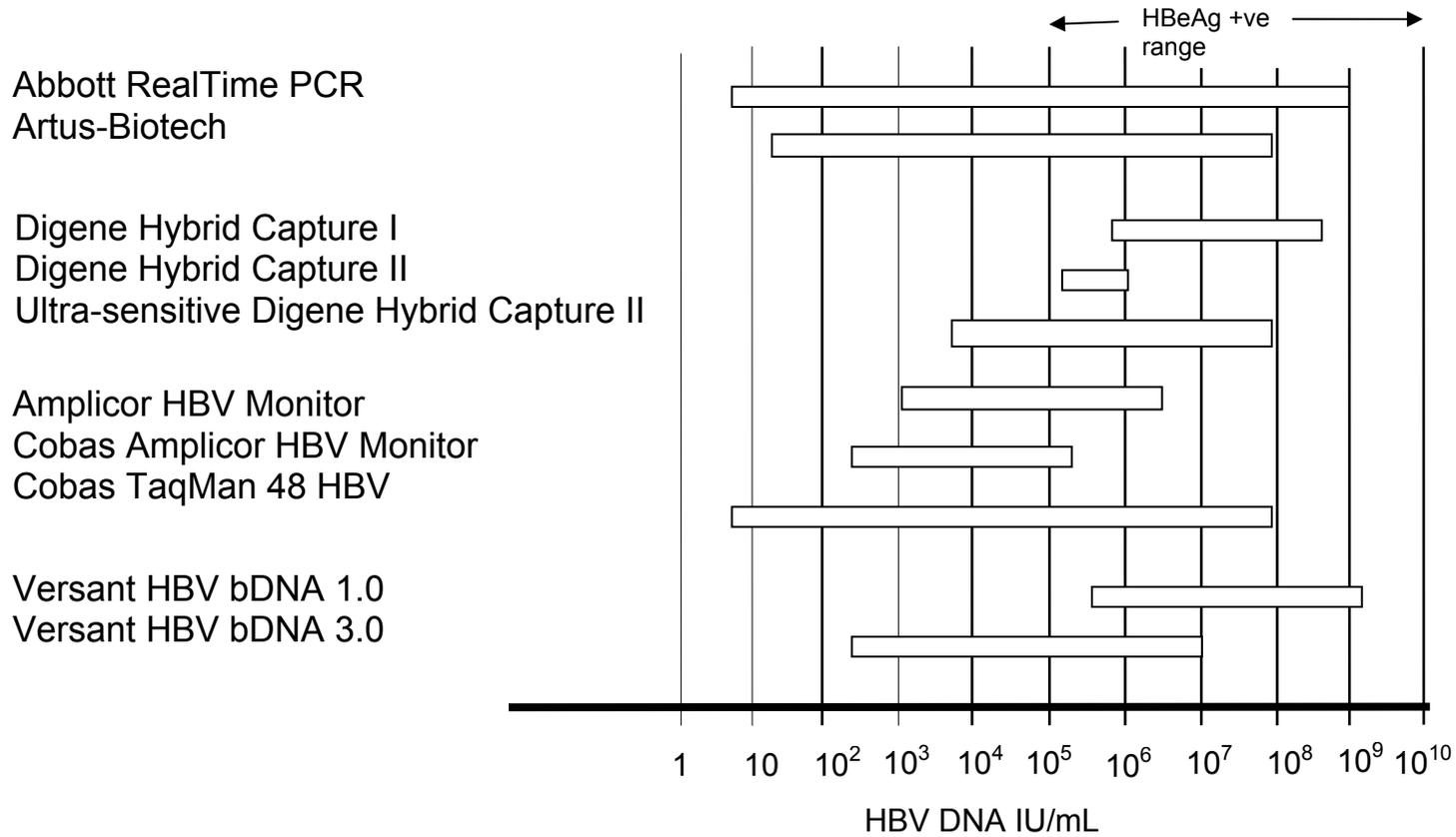
High concentration samples require dilution and retesting

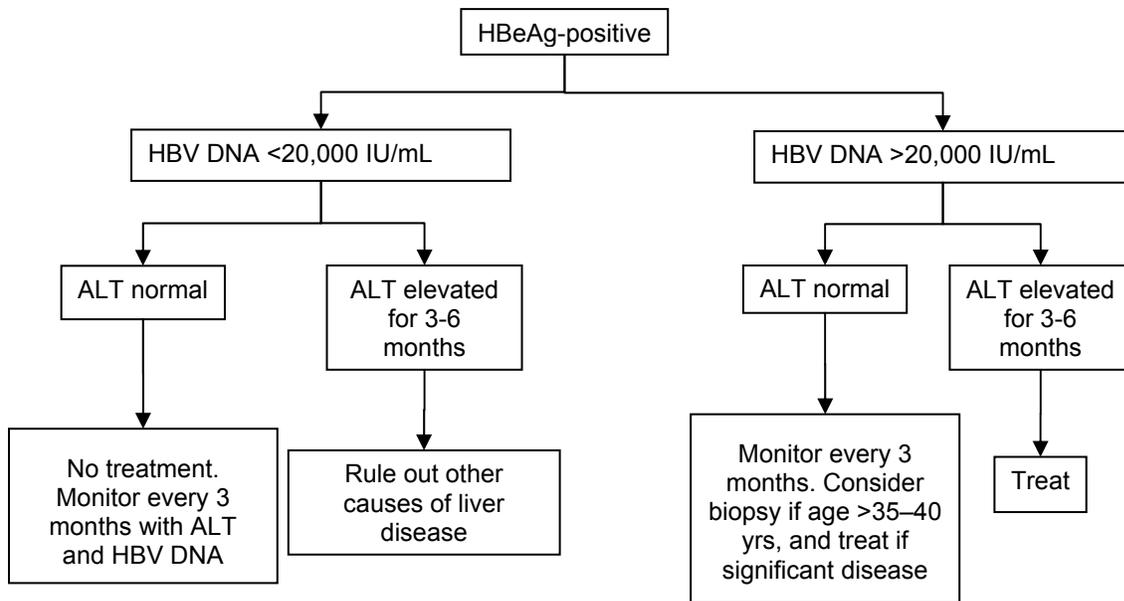Figure 2a. Algorithm for selecting HBeAg-positive patients for treatment.

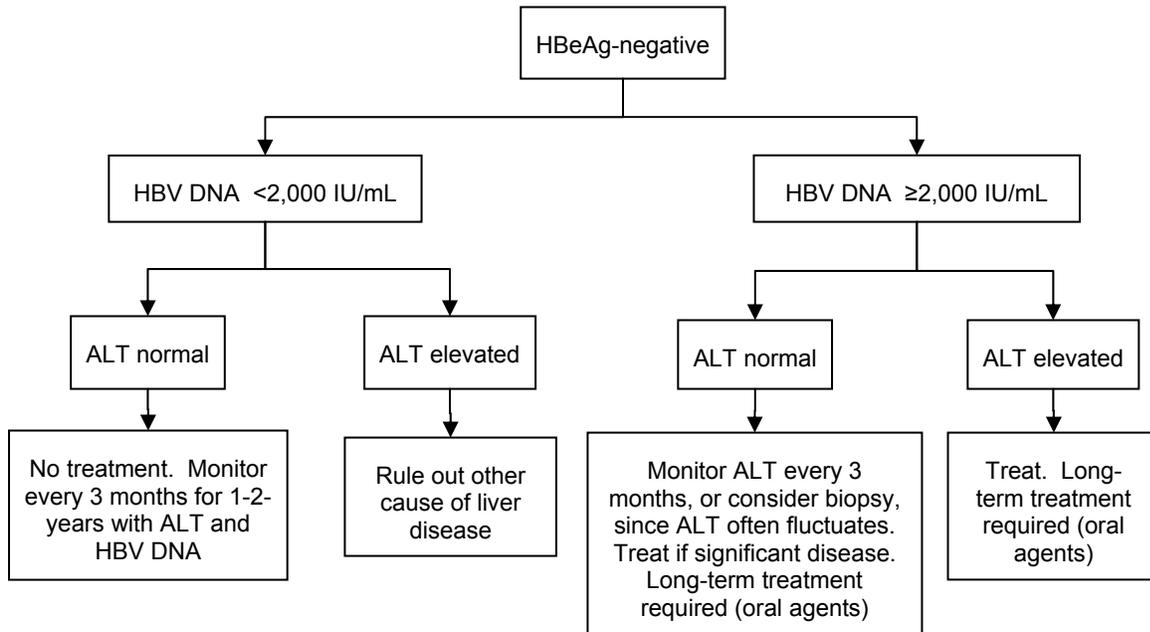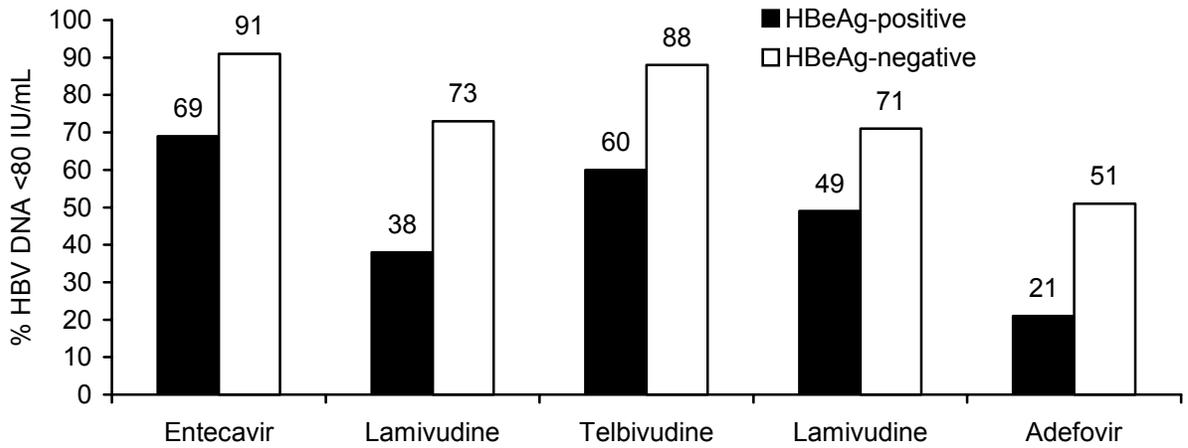Figure 2b. Algorithm for selecting HBeAg-negative patients for treatment

Figure 3. Relative potencies of different hepatitis B antivirals at 48-52 weeks of therapy. Lamivudine has been compared to entecavir and to telbivudine in two separate randomized controlled trials. Adefovir has not been compared directly to the other agents (73,81,98,161,162).
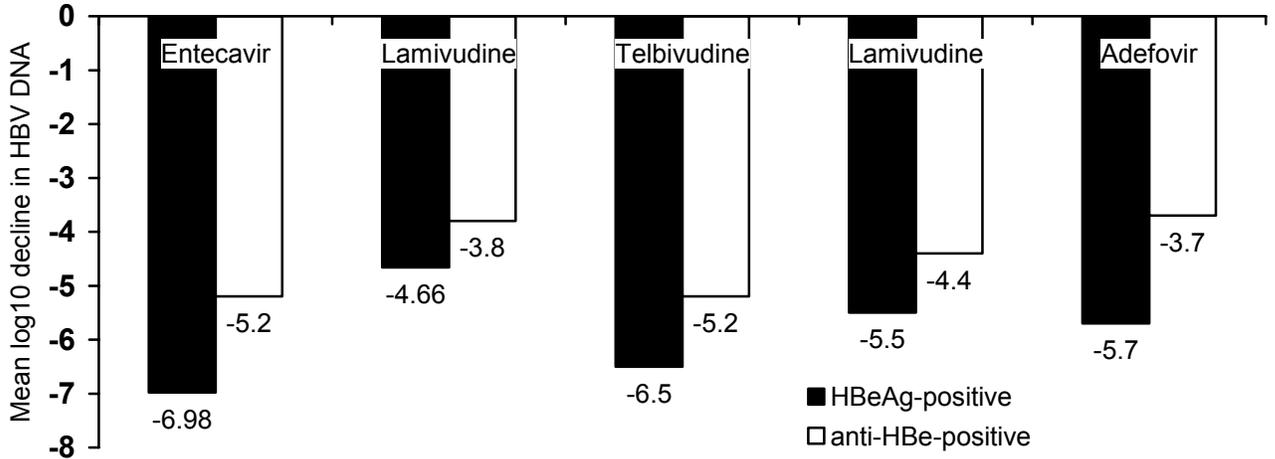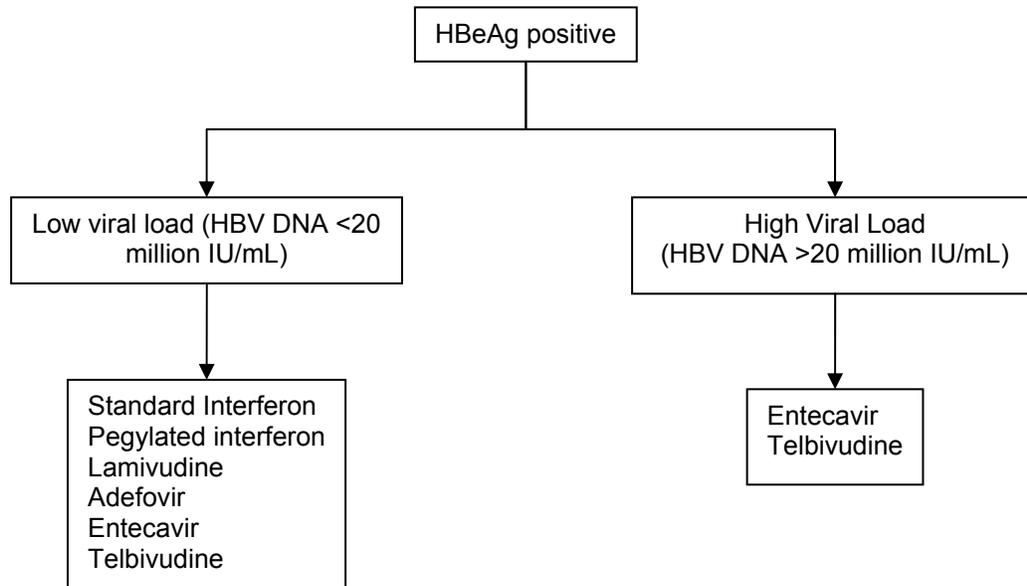
A

B

Figure 4. Algorithms for selection of specific agents for hepatitis B. Response to adefovir, lamivudine and telbivudine should be assessed according to discussion above.

A

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                          ┌─────────────────────┐
                          │   HBeAg positive    │
                          └──────────┬──────────┘
                   ┌─────────────────┴──────────────────┐
                   ▼                                     ▼
   ┌─────────────────────────────┐      ┌─────────────────────────────┐
   │ Low viral load (HBV DNA <20 │      │        High Viral Load      │
   │       million IU/mL)        │      │  (HBV DNA >20 million IU/mL)│
   └──────────────┬──────────────┘      └──────────────┬──────────────┘
                  ▼                                     ▼
   ┌─────────────────────────────┐         ┌────────────────────────┐
   │ Standard Interferon         │         │ Entecavir              │
   │ Pegylated interferon        │         │ Telbivudine            │
   │ Lamivudine                  │         └────────────────────────┘
   │ Adefovir                    │
   │ Entecavir                   │
   │ Telbivudine                 │
   └─────────────────────────────┘
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B

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                          ┌─────────────────────┐
                          │   HBeAg negative    │
                          └──────────┬──────────┘
                   ┌─────────────────┴──────────────────┐
                   ▼                                     ▼
   ┌─────────────────────────────┐      ┌─────────────────────────────┐
   │ Low viral load (HBV DNA     │      │        High Viral Load      │
   │      <20 million IU/mL)     │      │  (HBV DNA >20 million IU/mL)│
   └──────────────┬──────────────┘      └──────────────┬──────────────┘
                  ▼                                     ▼
   ┌─────────────────────────────┐         ┌────────────────────────┐
   │ Pegylated interferon        │         │ Entecavir              │
   │ Lamivudine                  │         │ Telbivudine            │
   │ Adefovir                    │         └────────────────────────┘
   │ Entecavir                   │
   │ Telbivudine                 │
   └─────────────────────────────┘
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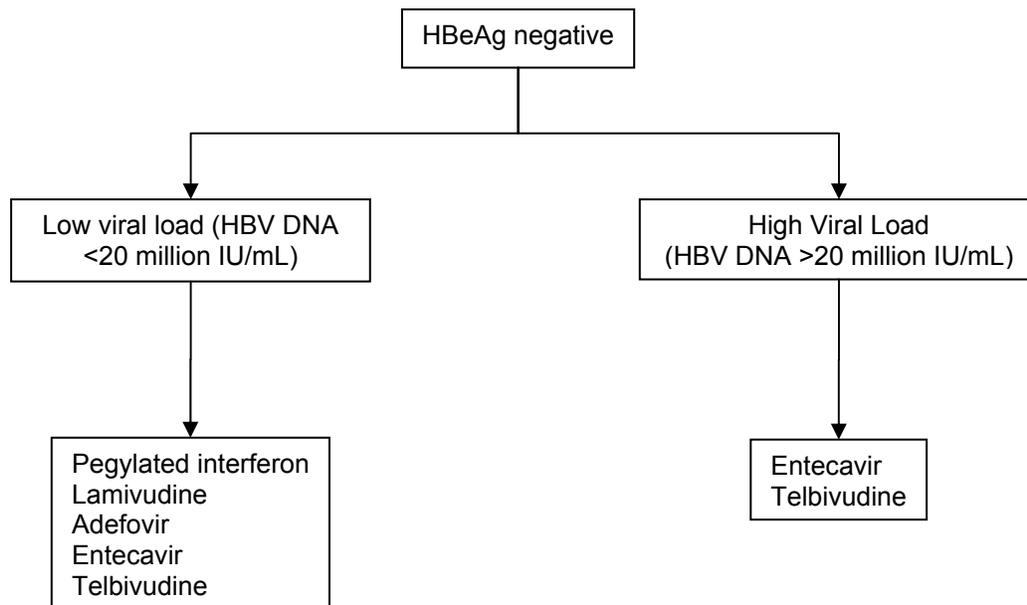
Figure 5. Rates of resistance to antiviral agents by duration of therapy (76,80,84,88,89).
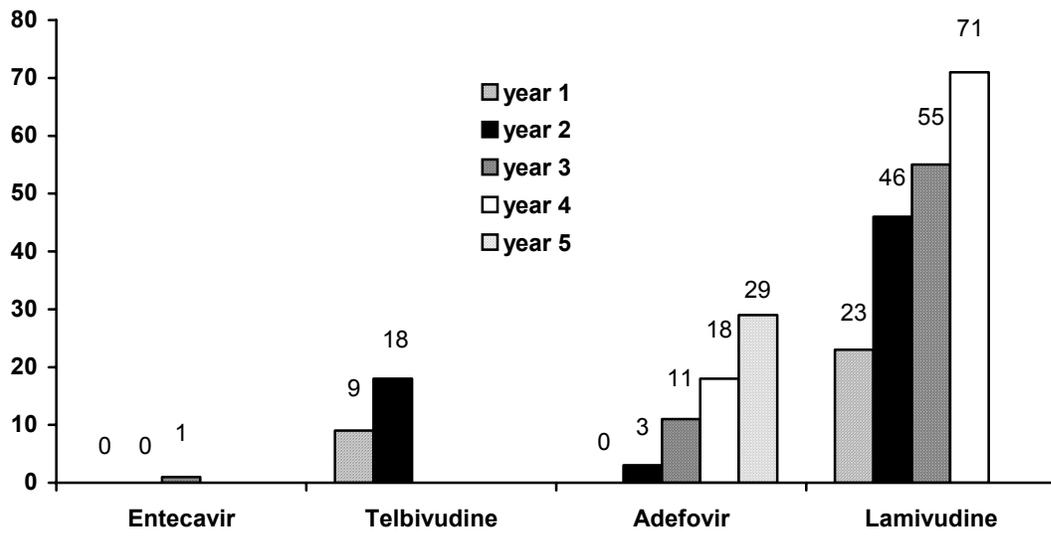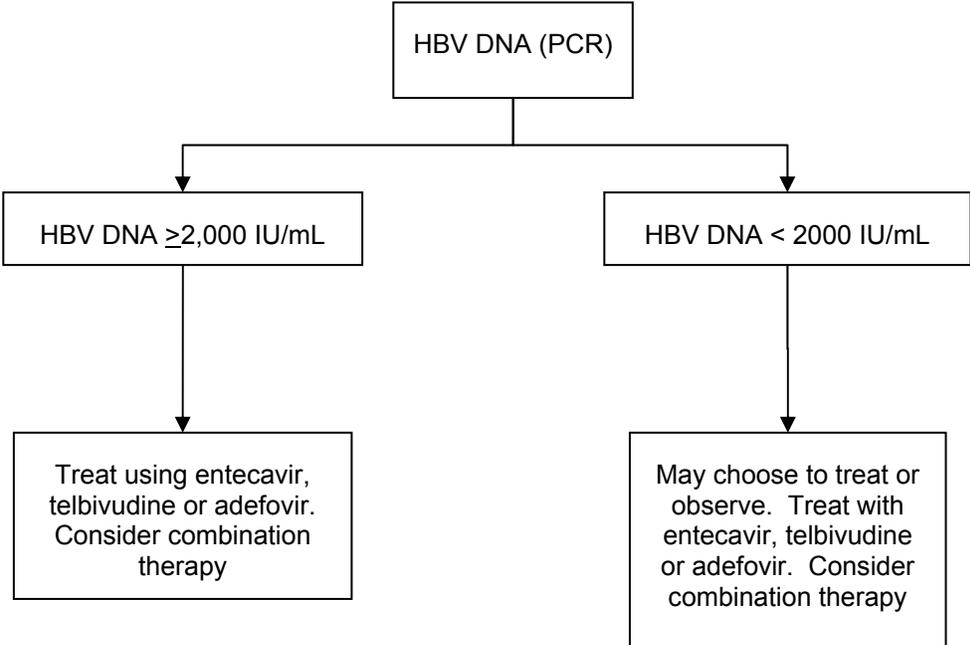
Figure 6. Suggested algorithms for management of patients with hepatitis B viral cirrhosis.

References

1.   Remis R. Estimating the Number of Persons infected with Hepatitis C in Canada: Submitted to the Health Canada 2005.

2.   Sherman M, Bain V, Villeneuve JP, Myers RP, Cooper C, Martin S, Lowe C. The management of chronic viral hepatitis: a Canadian consensus conference 2004. Can J Gastroenterol. 2004 Dec;18(12):715-28.

3.   Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007 Feb;45(2):507-39.

4.   de Franchis R, Hadengue A, Lau G, Lavanchy D, Lok A, McIntyre N, Mele A, Paumgartner G, Pietrangelo A, Rodes J, Rosenberg W, Valla D; EASL Jury. EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002 Geneva, Switzerland. Consensus statement (long version). J Hepatol. 2003;39 Suppl 1:S3-25.

5.   Liaw YF, Leung N, Guan R, Lau GK, Merican I, McCaughan G, Gane E, Kao JH, Omata M; Asian-Pacific consensus update working party on chronic hepatitis B. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. Liver Int. 2005 Jun;25(3):472-89

6.   Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, Vianello L, Zanuso F, Mozzi F, Milani S, Conte D, Colombo M, Sirchia G. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002 Jul 2;137(1):1-10

7.   Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I   Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ. 2004 Apr 24;328(7446):983.

8.   Yuen MF, Yuan HJ, Wong DK, Yuen JC, Wong WM, Chan AO, Wong BC, Lai KC, Lai CL. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. Gut. 2005 Nov;54(11):1610-4.

9.   Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ; Taiwan Community-Based Cancer Screening Project Group. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med. 2002 Jul 18;347(3):168-74.

10.   Lai M, Hyatt B, Afdhal N. Role of liver biopsy in patients with normal ALT and high HBV DNA. Hepatology 2005; 42:720A

11.   Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, Shiffman M, Farci P, Gitlin N, O'Brien CB, Lamour F, Lardelli P; PEGASYS Study NR16071 Investigator Group. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology. 2004 Dec;127(6):1724-32

12.   [No authors]. Decision Analysis on Screening for HBV in Immigrants. Statistics and Risk Assessment Section of the Blood Safety Surveillance and Health CareAcquired Infection Division, Population and Public Health Branch Health Canada.

13.   Centers for Disease Control and Prevention (CDC). Screening for chronic hepatitis B among Asian/Pacific Islander populations--New York City, 2005. MMWR Morb Mortal Wkly Rep. 2006 May 12;55(18):505-9

14.   Gilca V, Duval B, Boulianne N, Dion R, De Serres G. Impact of the quebec school-based hepatitis B immunization program and potential benefit of the addition of an infant immunization program. Pediatr Infect Dis J. 2006 Apr;25(4):372-4.

15.   Canada Immunization Guide, 7th Edition. 189:204 2006

16.   Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM Jr, Janssen RS, Ward JW; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention   A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006 Dec 8;55(RR-16):1-33

17.   Villeneuve E, Vincelette J, Villeneuve JP. Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation. Can J Gastroenterol. 2000 Jul-Aug;14 Suppl B:59B-62B

18.   Saldanha J, Gerlich W, Lelie N, Dawson P, Heermann K, Heath A. An international collaborative study to establish a World Health Organization international standard for hepatitis B virus DNA nucleic acid amplification techniques. Vox sanguinis. 2001 Jan;80(1):63-71.

19. Laperche S, Thibault V, Bouchardeau F, Alain S, Castelain S, Gassin M, et al. Expertise of laboratories in viral load quantification, genotyping, and precore mutant determination for hepatitis B virus in a multicenter study. Journal of clinical microbiology. 2006 Oct;44(10):3600-7.

20. Ronsin C, Pillet A, Bali C, Denoyel GA. Evaluation of the COBAS AmpliPrep-total nucleic acid isolation-COBAS TaqMan hepatitis B virus (HBV) quantitative test and comparison to the VERSANT HBV DNA 3.0 assay. Journal of clinical microbiology. 2006 Apr;44(4):1390-9.

21. Pawlotsky J-M, Bastie A, Hezode C, Lonjon I, Darthuy F, Remire J, et al. Routine detection and quantification of hepatitis B virus DNA in clinical laboratories: performance of three commercial assays. Journal of Virological Methods. 2000;85(1-2):11.

22. Norder H, Courouce AM, Coursaget P, Echevarria JM, Lee SD, Mushahwar IK, et al. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. Intervirology. 2004 Nov-Dec;47(6):289-309.

23. Miyakawa Y, Mizokami M. Classifying hepatitis B virus genotypes. Intervirology. 2003;46(6):329-38.

24. Liu CJ, Kao JH, Chen DS. Therapeutic implications of hepatitis B virus genotypes. Liver Int. 2005 Dec;25(6):1097-107.

25. Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet. 2005 Jan 8-14;365(9454):123-9.

26. Beasley RO, Hwang, LU. Epidemiology of hepatocellular carcinoma. In Viral Hepatitis and Liver Disease (Eds Vyas GN, Dienstag J and Hoofnagle J): 209-223; 1984. Grune and Stratton :New York

27. Lee W. Hepatitis B virus infection. N Engl J Med. 1997;337:1733-1745

28. Liaw YF, Chu CM, Huang MJ, Sheen IS, Yang CY, Lin DY. Determinants for hepatitis B e antigen clearance in chronic type B hepatitis. Liver. 1984 Oct;4(5):301-6.

29. Lok AS, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology. 1987 Jun;92(6):1839-43

30. Chu CM, Hung SJ, Lin J, Tai DI, Liaw YF. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal serum aminotransferase levels. Am J Med. 2004 Jun 15;116(12):829-34

31. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2001 Oct;34(4 Pt 1):617-24

32. Yim HJ, Lok AS. Natural History of Chronic Hepatitis B Virus Infection: What we knew in 1981 and What we know in 2005. Hepatology 2006: S173-S181.

33. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. Am J Gastroenterol. 2006 Aug;101(8):1797-803.

34. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006 Mar;130(3):678-86.

35. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006 Jan 4;295(1):65-73

36. Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst. 2005 Feb 16;97(4):265-72

37. Liaw YF, Sollano JD. Factors influencing liver disease progression in chronic hepatitis B. Liver Int. 2006 Dec;26 Suppl 2:23-9.

38. Fattovich G, Rugge M, Brollo L, Pontisso P, Noventa F, Guido M, Alberti A, Realdi G. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. Hepatology. 1986 Mar-Apr;6(2):167-72.

39. Lin X, Robinson NJ, Thursz M, Rosenberg DM, Weild A, Pimenta JM, Hall AJ. Chronic hepatitis B virus infection in the Asia-Pacific region and Africa: review of disease progression. J Gastroenterol Hepatol. 2005 Jun;20(6):833-43

40.   Liaw YF, Sheen IS, Chen TJ, Chu CM, Pao CC. Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. Hepatology. 1991 Apr;13(4):627-31

41.   Yu MW, Hsu FC, Sheen IS, Chu CM, Lin DY, Chen CJ, Liaw YF. Prospective study of hepatocellular carcinoma and liver cirrhosis in asymptomatic chronic hepatitis B virus carriers. Am J Epidemiol. 1997 Jun 1;145(11):1039-47

42.   Park BK, Park YN, Ahn SH, Lee KS, Chon CY, Moon YM, Park C, Han KH. Long-term outcome of chronic hepatitis B based on histological grade and stage. J Gastroenterol Hepatol. 2007 Mar;22(3):383-8.

43.   Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. Hepatology. 1988 Sep-Oct;8(5):1130-3

44.   Chang MH, Hsu HY, Hsu HC, Ni YH, Chen JS, Chen DS. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. Hepatology. 1995 Nov;22(5):1387-92

45.   Brook MG, McDonald JA, Karayiannis P, et al. Randomised controlled trial of interferon alfa 2A (rbe) (Roferon-A) for the treatment of chronic hepatitis B virus (HBV) infection: factors that influence response. Gut 1989;30:1116-22

46.   Brunetto MR, Oliveri F, Colombatto P, Coco B, Ciccorossi P and Bonino F. Treatment of HBeAg-negative chronic hepatitis B with interferon or pegylated interferon. J Hepatol 2003;39 Suppl 1:S164-7

47.   Craxi A, Di Bona D and Camma C. Interferon-alpha for HBeAg-positive chronic hepatitis B. J Hepatol 2003;39 Suppl 1:S99-105

48.   Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. N Engl J Med 1990;323:295-301

49.   Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS and Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. Ann Intern Med 1993;119:312-23.

50.   Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. Gastroenterology 1997;113:1660-7

51.   Lin SM, Sheen IS, Chien RN, Chu CM and Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. Hepatology 1999;29:971-5

52.   Lok AS, Chung HT, Liu VW and Ma OC. Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. Gastroenterology 1993;105:1833-8

53.   Korenman J, Baker B, Waggoner J, Everhart JE, Di Bisceglie AM and Hoofnagle JH. Long-term remission of chronic hepatitis B after alpha-interferon therapy. Ann Intern Med 1991;114:629-34

54.   Krogsgaard K. The long-term effect of treatment with interferon-alpha 2a in chronic hepatitis B. The Long-Term Follow-up Investigator Group. The European Study Group on Viral Hepatitis (EUROHEP). Executive Team on Anti-Viral Treatment. J Viral Hepat 1998;5:389-97

55.   Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat 2003;10:298-305

56.   Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682-95

57.   Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Haussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med. 1996 May 30;334(22):1422-7

58.   Fattovich G, Giustina G, Realdi G, Corrocher R, Schalm SW. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European Concerted Action on Viral Hepatitis (EUROHEP). Hepatology. 1997 Nov;26(5):1338-42.

59.   Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, Liaw YF. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol. 2007 Jan;46(1):45-52.

60.   Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germanidis G, Yurdaydin C, Diago M, Gurel S, Lai MY, Button P, Pluck N; Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group.

Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2004 Sep 16;351(12):1206-

61.   Lai CL, Ching CK, Tung AK, Li E, Young J, Hill A, Wong BC, Dent J, Wu PC. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: a placebo-controlled trial. Hepatology. 1997 Jan;25(1):241-4.

62.   Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology. 2003 Dec;125(6):1714-22.

63.   Lai CL, Dienstag J, Schiff E, Leung NW, Atkins M, Hunt C, Brown N, Woessner M, Boehme R, Condreay L. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. Clin Infect Dis. 2003 Mar 15;36(6):687-96

64.   Lee YS, Suh DJ, Lim YS, Jung SW, Kim KM, Lee HC, Chung YH, Lee YS, Yoo W, Kim SO. Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. Hepatology. 2006 Jun;43(6):1385-91

65.   Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004 Oct 7;351(15):1521-31

66.   Di Marco V, Di Stefano R, Ferraro D, Almasio PL, Bonura C, Giglio M, Parisi P, Cappello M, Alaimo G, Craxi A. HBV-DNA suppression and disease course in HBV cirrhosis patients on long-term lamivudine therapy. Antivir Ther. 2005;10(3):431-9.

67.   Mommeja-Marin H, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. Hepatology. 2003 Jun;37(6):1309-19

68.   Suzuki F, Tsubota A, Arase Y, Suzuki Y, Akuta N, Hosaka T, Someya T, Kobayashi M, Saitoh S, Ikeda K, Kobayashi M, Matsuda M, Satoh J, Takagi K, Kumada H. Efficacy of lamivudine therapy and factors associated with emergence of resistance in chronic hepatitis B virus infection in Japan. Intervirology. 2003;46(3):182-9

69.   Yuen MF, Sablon E, Hui CK, Yuan HJ, Decraemer H, Lai CL. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. Hepatology. 2001 Oct;34(4 Pt 1):785-91

70.   Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med. 1998 Jul 9;339(2):61-8.

71.   Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, Crowther L, Condreay LD, Woessner M, Rubin M, Brown NA. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med. 1999 Oct 21;341(17):1256-63.

72.   Schalm SW, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, Dhillon A, Moorat A, Barber J, Gray DF. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut. 2000 Apr;46(4):562-8

73.   Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, Lok AS, Han KH, Goodman Z, Zhu J, Cross A, DeHertogh D, Wilber R, Colonno R, Apelian D; BEHoLD AI463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006 Mar 9;354(10):1001-10.

74.   Dienstag JL, Cianciara J, Karayalcin S, Kowdley KV, Willems B, Plisek S, Woessner M, Gardner S, Schiff E. Durability of serologic response after lamivudine treatment of chronic hepatitis B. Hepatology. 2003 Apr;37(4):748-55

75.   Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology. 2000 Oct;32(4 Pt 1):803-6.

76.   Chang TT, Lai CL, Chien RN, Guan R, Lim SG, Lee CM, Ng KY, Nicholls GJ, Dent JC, Leung NW. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. J Gastroenterol Hepatol. 2004 Nov;19(11):1276-82.

77. Locarnini S, Qi X, Arterburn S, Snow A, Brosgart CL, Curfie G, Wulfsohn M, Miller MD, Xiong S Incidence and predictors of emergence of adefovir resistant hbv during four years of adefovir dipivoxil (adv) therapy for patients with chronic hepatitis b (chb). J Hepatol 42, Suppl 2, April, 2005; 17.

78. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 437 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):808-16

79. Chang TT, Shiffman ML, Tong M, Liaw YF, Komolmit E, Sorbel J, Arterburn S, Mondou E, Chuck S, Marcellin P. Durability Of HBeAg seroconversion following adefovir dipivoxil treatment for chronic hepatitis B (CHB). J of Hepatol 44, Suppl 2, April, 2006; S187

80. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Ma J, Brosgart CL, Borroto-Esoda K, Arterburn S, Chuck SL; Adefovir Dipivoxil 438 Study Group. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology. 2006 Dec;131(6):1743-51

81. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, Wilber R, Zink RC, Cross A, Colonno R, Fernandes L; BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2006 Mar 9;354(10):1011-20.

82. Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, Boron-Kaczmarska A, Martin P, Goodman Z, Colonno R, Cross A, Denisky G, Kreter B, Hindes R; AI463026 BEHoLD Study Group. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. Gastroenterology. 2006 Jun;130(7):2039-49.

83. Colonno RJ, Rose R, Baldick CJ, Levine S, Pokornowski K, Yu CF, Walsh A, Fang J, Hsu M, Mazzucco C, Eggers B, Zhang S, Plym M, Klesczewski K, Tenney DJ. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. Hepatology. 2006 Dec;44(6):1656-65

84. Colonno R, Rose RE, Pokornowski, baldick CJ, Klesczewski, Tenney, D. Assessment at three years show high barrier to resistance is maintained in entecavir-treated nucleoside naïve patients while resistance emergence increases over time in lamivudine refractory patients. Hepatology 2006;44:229A.

85. Tenney DJ, Rose RE, Baldick CJ, Levine SM, Pokornowski KA, Walsh AW, Fang J, Yu CF, Zhang S, Mazzucco CE, Eggers B, Hsu M, Plym MJ, Poundstone P, Yang J, Colonno RJ. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. Antimicrob Agents Chemother. 2007 Mar;51(3):902-11.

86. Kanwal F, Farid M, Martin P, Chen G, Gralnek IM, Dulai GS, Spiegel BM. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. Am J Gastroenterol. 2006 Sep;101(9):2076-89

87. Chang TT, Chao YC, Kaymakoglu S3, Cheinquer H, Pessoa M, Gish R, Poordad F. Entecavir maintained virologic suppression through 3 years of treatment in antiviral-naïve HBeAg(+) patients (ETV 022/901). Hepatology,. 44, No. 4, Suppl. 1, 2006;66A

88. Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, Han S, Poynard T, Myers M, Chao G, Lloyd D, Brown NA; Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology. 2005 Aug;129(2):528-36;

89. Lai CL, Gane E, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov N, Zeuzem S Di Bisceglie A, Chao GC, ConstanceAF, Brown NA, Globe Study Group. Two-year results from the globe trial in patients with hepatitis B: greater clinical and antiviral efficacy for telbivudine (Ldt) vs. lamivudine Hepatology. 2005;42(suppl 1):748A)

90. DiBisceglie A, LaiCL, GaneE, Chen YC, Thongsawat S, Wang Y6, Chen Y, Heathcote EJ, Zeuzem S, Rasenack S, Bzowej N, Han SH, Naoumov N, HwangSG, Lim SG,Chao GC, Fielman BA, Brown NA, Study Group The GLOBE. Telbivudine GLOBE trial: maximal early HBV suppression is predictive of optimal two-year efficacy in nucleoside-treated hepatitis B patients. Hepatology 44, No. 4, Suppl. 1, 2006;230A

91. van Bommel F, Zollner B, Sarrazin C, Spengler U, Huppe D, Moller B, Feucht HH, Wiedenmann B, Berg T. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. Hepatology. 2006 Aug;44(2):318-25.

92. van Bommel F, Wunsche T, Mauss S, Reinke P, Bergk A, Schurmann D, Wiedenmann B, Berg T. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology. 2004 Dec;40(6):1421-5

93. Peters MG, Andersen J, Lynch P, Liu T, Alston-Smith B, Brosgart CL, Jacobson JM, Johnson VA, Pollard RB, Rooney JF, Sherman KE, Swindells S, Polsky B; ACTG Protocol A5127 Team. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. Hepatology. 2006 Nov;44(5):1110-6.

94. Sheldon J, Camino N, Rodes B, Bartholomeusz A, Kuiper M, Tacke F, Nunez M, Mauss S, Lutz T, Klausen G, Locarnini S, Soriano V. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. Antivir Ther. 2005;10(6):727-34.

95. Lim SG, Ng TM, Kung N, Krastev Z, Volfova M, Husa P, Lee SS, Chan S, Shiffman ML, Washington MK, Rigney A, Anderson J, Mondou E, Snow A, Sorbel J, Guan R, Rousseau F; Emtricitabine FTCB-301 Study Group. A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. Arch Intern Med. 2006 Jan 9;166(1):49-56

96. Gish RG, Trinh H, Leung N, Chan FK, Fried MW, Wright TL, Wang C, Anderson J, Mondou E, Snow A, Sorbel J, Rousseau F, Corey L. Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: a two-year study. J Hepatol. 2005 Jul;43(1):60-6.

97. Peters MG, Hann Hw H, Martin P, Heathcote EJ, Buggisch P, Rubin R, Bourliere M, Kowdley K, Trepo C, Gray Df D, Sullivan M, Kleber K, Ebrahimi R, Xiong S, Brosgart CL. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology. 2004 Jan;126(1):91-101

98. Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, Han S, Poynard T, Myers M, Chao G, Lloyd D, Brown NA; Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology. 2005 Aug;129(2):528-36.

99. Lee YS, Suh DJ, Lim YS, Jung SW, Kim KM, Lee HC, Chung YH, Lee YS, Yoo W, Kim SO. Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. Hepatology. 2006 Jun;43(6):1385-91.

100. Lok AS, Zoulim F, Locarnini S, Mangia A, Niro G, Decraemer H, et al. Monitoring drug resistance in chronic hepatitis B virus (HBV)-infected patients during lamivudine therapy: evaluation of performance of INNO-LiPA HBV DR assay. Journal of clinical microbiology. 2002 Oct;40(10):3729-34.

101. Wang JH, Lu SN, Lee CM, Lee JF, Chou YP. Fatal hepatic failure after emergence of the hepatitis B virus mutant during lamivudine therapy in a patient with liver cirrhosis. Scand J Gastroenterol 2002; 37:366-9.

102. Fung SK, Andreone P, Han SH, Rajender Reddy K, Regev A, Keeffe EB, Hussain M, Cursaro C, Richtmyer P, Marrero JA, Lok AS. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. J Hepatol. 2005 Dec;43(6):937-43.

103. Dienstag JL, Wei LJ, Xu D, Kreter B. Cross-study analysis of the relative efficacies of oral antiviral therapies for chronic hepatitis B infection in nucleoside-naive patients. Clin Drug Investig. 2007;27(1):35-49.

104. Zoulim F Mechanism of viral persistence and resistance to nucleoside and nucleotide analogs in chronic hepatitis B virus infection. Antiviral Res. 2004 Oct;64(1):1-15.

105. Lampertico P, Vigano M, Manenti E, Iavarone M, Lunghi G, Colombo M. Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine. Hepatology. 2005 Dec;42(6):1414-9

106. Rapti I, Dimou E, Mitsoula P, Hadziyannis S. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. Hepatology. 2007 Feb;45(2):307-13.

107. Liaw YF, Lee CM, Chien RN, Yeh CT. Switching to adefovir monotherapy after emergence of lamivudine-resistant mutations in patients with liver cirrhosis. J Viral Hepat. 2006 Apr;13(4):250-5

108. Brunelle MN, Jacquard AC, Pichoud C, Durantel D, Carrouee-Durantel S, Villeneuve JP, Trepo C, Zoulim F. Susceptibility to antivirals of a human HBV strain with mutations conferring resistance to both lamivudine and adefovir. Hepatology. 2005 Jun;41(6):1391-8

109.   Villeneuve JP, Durantel D, Durantel S, Westland C, Xiong S, Brosgart CL, Gibbs CS, Parvaz P, Werle B, Trepo C, Zoulim F. Selection of a hepatitis B virus strain resistant to adefovir in a liver transplantation patient. J Hepatol. 2003 Dec;39(6):1085-9

110.   Tenney DJ, Levine SM, Rose RE, Walsh AW, Weinheimer SP, Discotto L, Plym M, Pokornowski K, Yu CF, Angus P, Ayres A, Bartholomeusz A, Sievert W, Thompson G, Warner N, Locarnini S, Colonno RJ. Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to Lamivudine. Antimicrob Agents Chemother. 2004 Sep;48(9):3498-507

111.   McMahon BJ, Alberts SR, Wainwright RB, Bulkow L, Lanier AP. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. Arch Intern Med. 1990 May;150(5):1051-4

112.   Realdi G, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, Christensen E, Giustina G, Noventa F. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). J Hepatol. 1994 Oct;21(4):656-66

113.   Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevret S. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut. 2000 Jul;47(1):131-6.

114.   Chiaramonte M, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, Lobello S, Farinati F, Naccarato R. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. Cancer. 1999 May 15;85(10):2132-7

115.   Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology. 2005 Nov;42(5):1208-36.

116.   Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, Domenicali M, De Notariis S, Roda E, Bernardi M. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol. 2001 Apr;34(4):570-5

117.   Villeneuve JP, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, Leduc R, Peltekian K, Wong F, Margulies M, Heathcote EJ. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. Hepatology. 2000 Jan;31(1):207-10.

118.   Sponseller CA, Bacon BR, Di Bisceglie AM. Clinical improvement in patients with decompensated liver disease caused by hepatitis B after treatment with lamivudine. Liver Transpl 2000; 6:715-20.

119.   Kuwahara R, Kumashiro R, Inoue H, Tanabe R, Tanaka E, Hino T, Ide T, Koga Y, Sata M. Adefovir dipivoxil as a treatment for hepatic failure caused by lamivudine-resistant HBV strains. Dig Dis Sci. 2004 Feb;49(2):300-3.

120.   Homann C, Krogsgaard K, Pedersen C, Andersson P, Nielsen JO. High incidence of hepatitis B infection and evolution of chronic hepatitis B infection in patients with advanced HIV infection. J Acquir Immune Defic Syndr. 1991;4:416–420.

121.   Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, Thomas DL; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002 Dec 14;360(9349):1921-6

122.   Gilson RJ, Hawkins AE, Beecham MR, Ross E, Waite J, Briggs M, McNally T, Kelly GE, Tedder RS, Weller IV. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. AIDS. 1997 Apr;11(5):597-606

123.   Wong EK, Bodsworth NJ, Slade MA, Mulhall BP, Donovan B. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. Int J STD AIDS. 1996 Nov-Dec;7(7):490-4.

124.   Benhamou Y, Bochet M, Thibault V, Calvez V, Fievet MH, Vig P, Gibbs CS, Brosgart C, Fry J, Namini H, Katlama C, Poynard T. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. Lancet. 2001 Sep 1;358(9283):718-23

125.   Benhamou Y, Thibault V, Vig P, Calvez V, Marcelin AG, Fievet MH, Currie G, Chang CG, Biao L, Xiong S, Brosgart C, Poynard T. Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1. J Hepatol 2006; 44: 62-7.

126. McMahon M, Jilek B, Brennan T, Shen L, Zhou Y, Bhat S, Hale B, Hegarty R, Silicano R, Thio C. The Anti-Hepatitis B Drug Entecavir Inhibits HIV-1 Replication and Selects HIV-1 Variants Resistant to Antiretroviral Drugs. Unpublished data presented at CROI 2007.

127. Pessoa W, Gazzard B, HuangA, et al.. Entecavir in HIV/HBV co-infected patients (safety and efficacy in a phase II study (ETV-038)). XIIth Conference on Retroviruses and Opportunistic Infections 2005;(A123).

128. Benhamou Y, Bochet M, Thibault V, Di Martino V, Caumes E, Bricaire F, Opolon P, Katlama C, Poynard T. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology. 1999 Nov;30(5):1302-6.

129. Benhamou Y, Fleury H, Trimoulet P, Pellegrin I, Urbinelli R, Katlama C, Rozenbaum W, Le Teuff G, Trylesinski A, Piketty C; TECOVIR Study Group.   Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. Hepatology 2006; 43: 548-55.

130. Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, Saitta C, Squadrito G, Tono N; Associazione Italiana Studio Fegato Cooperative Group. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. Hepatology. 2006 Jan;43(1):100-7

131. Liu CJ, Chen PJ, Lai MY, Kao JH, Jeng YM, Chen DS. Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients. Hepatology. 2003 Mar;37(3):568-76.

132. Euler GL, Copeland JR, Rangel MC, Williams WW. Antibody response to postexposure prophylaxis in infants born to hepatitis B surface antigen-positive women. Pediatr Infect Dis J 2003; 22: 123-9.

133. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat 2003; 10: 294-7.

134. Xu WM, Cui YT, Wang L, et al. Efficacy and safety of lamivudine in late pregnancy for the prevention of mother-child transmission of hepatitis B (a multicenter, randomised, double-blind, placebo-controlled study). Hepatology 2004; 40: 273A.

135. Watts DH, Covington DL, Beckerman K, Garcia P, Scheuerle A, Dominguez K, Ross B, Sacks S, Chavers S, Tilson H. Assessing the risk of birth defects associated with antiretroviral exposure during pregnancy. Am J Obstet Gynecol 2004; 191: 985-92.

136. Han SH. Extrahepatic manifestations of chronic hepatitis B. Clin Liver Dis 2004; 8: 403-18.

137. Lin CY. Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon. Kidney Int. 1995 Jan;47(1):225-30

138. Gan SI, Devlin SM, Scott-Douglas NW, Burak KW. Lamivudine for the treatment of membranous glomerulopathy secondary to chronic Hepatitis B infection. Can J Gastroenterol 2005; 19:625-9.

139. Simpson ND, Simpson PW, Ahmed AM, Nguyen MH, Garcia G, Keeffe EB, Ahmed A. Prophylaxis against chemotherapy-induced reactivation of hepatitis B virus infection with Lamivudine. J Clin Gastroenterol. 2003 Jul;37(1):68-71

140. Lau GK, He ML, Fong DY, Bartholomeusz A, Au WY, Lie AK, Locarnini S, Liang R. Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. Hepatology. 2002 Sep;36(3):702-9

141. Kohrt HE, Ouyang DL, Keeffe EB. Systematic review: lamivudine prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. Aliment Pharmacol Ther 2006; 24:1003-16.

142. Gish RG, McCashland T. Hepatitis B in liver transplant recipients. Liver Transpl 2006; 12 (11 Suppl 2):S54-64.

143. [No authors listed] Viral hepatitis guidelines in hemodialysis and transplantation. Am J Transplant. 2004 Nov;4 Suppl 10:72-82.

144. Chung RT et al . Approach to the Management of Allograft Recipients Following the Detection of Hepatitis B Virus in the Prospective Organ Donor. Am J Transplant 2001;1:185-91

145. McMahon, B. J., P. Holck, L. Bulkow, M. Snowball. Serologic and clinical outcomes of 1,563 Alaska natives chronically infected with hepatitis B virus. Ann Int Med 2001; 135: 759-68.

146. Bortolotti, F., P. Cadrobbi, C. Crivellaro, et al. Longterm outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. Gastroenterology 1990; 99: 805-810.

147.   Lok, A. S. F., C. L. Lai. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. Hepatology 1988; 8:1130-1133.

148.   Evans, A. A., M. Fine, W. T. London. Spontaneous seroconversion in hepatitis B e antigen-positive chronic hepatitis B: Implications for therapy. J Clinical Infect Dis 1997 ; 176: 845-850.

149.   Marx, G., S. R. Martin, J. F. Chicoine, F. Alvarez. Longterm follow-up of chronic hepatitis B virus infection in children of different ethnic origin. J Infect Dis 2002 ; 186:295-301.

150.   Bortolotti F. Treatment of chronic hepatitis B in children. J Hepatol. 2003;39 (Suppl 1):S200-5.

151.   Vo Thi Diem H, Bourgois A, Bontems P, Goyens P, Buts JP, Nackers F, Tonglet R, Sokal EM. Chronic hepatitis B infection: long term comparison of children receiving interferon alpha and untreated controls. J Pediatr Gastroenterol Nutr 2005; 40: 141-5.

152.   Bortolotti F, Jara P, Barbera C, Gregorio GV, Vegnente A, Zancan L, Hierro L, Crivellaro C, Vergani GM, Iorio R, Pace M, Con P, Gatta A. Long term effect of alpha interferon in children with chronic hepatitis B. Gut 2000; 46: 715-8.

153.   Sokal, E. M., H. S. Conjeevaram, E. A. Roberts, F. Alvarez, E. M. Bern, P. Goyens, P. Rosenthal, et al. Interferon alfa therapy for chronic hepatitis B in children: A multinational randomized controlled trial. Gastroenterology1998; 114: 988-995.

154.   Jonas, M. M., D. A. Kelley, J. Mizerski, et al. Clinical trial of lamivudine in children with chronic hepatitis B. N Engl J Med 2002; 346: 1706-13.

155.   Sokal EM, Kelly DA, Mizerski J, Badia IB, Areias JA, Schwarz KB, Vegnente A, Little NR, Gardener SD, Jonas MM. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. Hepatology 2006; 43: 225-32.

156.   Gunson RN, Shouval D, Roggendorf M, Zaaijer H, Nicholas H, Holzmann H, de Schryver A, Reynders D, Connell J, Gerlich WH, Marinho RT, Tsantoulas D, Rigopoulou E, Rosenheim M, Valla D, Puro V, Struwe J, Tedder R, Aitken C, Alter M, Schalm SW, Carman WF; European Consensus Group. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in health care workers (HCWs): guidelines for prevention of transmission of HBV and HCV from HCW to patients. J Clin Virol. 2003 Aug;27(3):213-30.

157.   Farci P, Roskams T, Chessa L, Peddis G, Mazzoleni AP, Scioscia R, Serra G, Lai ME, Loy M, Caruso L, Desmet V, Purcell RH, Balestrieri A. Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. Gastroenterology. 2004 Jun;126(7):1740-9

158.   Castelnau C, Le Gal F, Ripault MP, Gordien E, Martinot-Peignoux M, Boyer N, Pham BN, Maylin S, Bedossa P, Deny P, Marcellin P, Gault E. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. Hepatology. 2006 Sep;44(3):728-35

159.   Niro GA, Ciancio A, Gaeta GB, Smedile A, Marrone A, Olivero A, Stanzione M, David E, Brancaccio G, Fontana R, Perri F, Andriulli A, Rizzetto M. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. Hepatology. 2006 Sep;44(3):713-20.

160.   American Gastroenterological Association Medical Position Statement: Guidelines for the use of enteral nutrition" Gastroenterology 1995 pp. 1280-1281

161.   Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 438 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):800-7.

162.   Bzowej n, Chan H, Lai, CL, Cho M, Moon YM, Chao YC, Heathcote EJ, Myers R, Minuk G, Marcellin P, Jeffers L, Sievert W, Kaiser R, Harb G, Chao GC, Brown NA. A randomized trial of telbivudine (LDT) vs.adefovir for HBeAg-positive chronic hepatitis B: final week 52 results. Hepatology, Vol. 44, No. 4, Suppl. 1, 2006; 563A