

# Treatment Options for Children with Hepatitis B

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When given the news that their child has chronic hepatitis B, the first question many parents ask is: What treatment is available to eradicate the virus and prevent or slow liver disease?

Normally, chronic hepatitis B is a mild disease in children and teens. Often, young people experience an immune tolerant stage during the first two to three decades of infection, during which there is little damage to their livers. As a result, the incidence of liver inflammation, scarring, cirrhosis and liver cancer is low in children and adolescents.

However, in some children, the virus rapidly replicates and causes extensive liver damage when the child's immune system attacks infected liver cells. It is these children who may need immediate medical intervention from the small arsenal of drugs currently available to halt this liver disease.

The primary treatment goals for children (and adults) are to:

- strengthen the immune system so that it can effectively attack the infection
- prevent the virus from replicating, showing an undetectable HBV viral load
- halt any liver damage
- spur the immune system to create the hepatitis B e antibody (HBeAb)
- produce the surface antibody (HBsAb), which signifies recovery from the infection

In addition to slowing liver disease in children, medical researchers have another goal in mind: to eradicate the disease in the pediatric population today in order to prevent cirrhosis and liver cancer in the adults of tomorrow.

Unfortunately, the treatments available for hepatitis B infection in children have had limited success.

There are only a handful of pediatric clinical trials taking place to test drugs on children that so far have been used only in adults. Few studies have followed large numbers of children with chronic hepatitis B infections and fewer yet have tracked children a decade or more after treatment.

When to treat hepatitis B in children is an area of debate within the medical research and treatment communities. In 2009, the American Association for the Study of Liver Diseases (AASLD) published an update to their Chronic Hepatitis B Practice Guidelines to provide flexible, data-supported treatment recommendations to physicians and other healthcare providers. Also in 2009, a panel of nationally recognized North American pediatric liver

specialists met to develop recommendations for screening, monitoring and referral for primary physicians to use with pediatric patients who are diagnosed with hepatitis B.

### **WHAT TREATMENTS ARE AVAILABLE FOR CHILDREN TODAY**

When reading this section, please keep in mind that most of the following information deals with loss of e antigen, not surface antigen. Loss of surface antigen and development of surface antibody along with an undetectable viral load signals recovery from infection.

Loss of e antigen is important but is not a cure.

The development of hepatitis B surface antibody is the ultimate goal of treatment, but that does not occur very often with today's treatment options.

As of June 2007, there were only two drugs approved by the U.S. Food and Drug Administration (FDA) to treat hepatitis B in children: standard interferon and lamivudine. More recently, three other drugs have been added to the treatment options for older children. These drugs include adefovir (labeled for use in children over the age of twelve), entecavir (labeled for use in children over the age of 16), and telbivudine (labeled for use in children over the age of 16).

### **Standard Interferon**

Interferons are naturally occurring proteins that spur the immune system to fight viral infections and tumors. Synthetic or "conventional" interferon has been the most studied drug for treatment of chronic hepatitis B infection in children and adults. It has been used to treat adults since 1991, and it was the first FDA-approved treatment for children infected with the hepatitis B virus (HBV).

It is typically administered for six months in three weekly injections, which parents generally learn to administer at home. Historically, interferon has been used in children who were experiencing liver damage, as evidenced by laboratory results, including elevated liver enzymes, or ALTs. These enzymes are released when liver cells are damaged or die.

According to the 2009 Pediatric Report, pediatric liver specialists prefer to get baseline testing and wait six months to ensure the patient is chronic and to see if seroconversion occurs before considering treatment. If ALT levels are initially elevated, they may modify the frequency of blood work to ensure the status of the child. Treatment is not typically considered until a child's ALT levels are greater than twice the normal limit for longer than 6 months before trying treatment. A liver biopsy may also be considered to confirm evidence of liver damage.

Although still considered the first line of treatment, interferon has proven to be a lackluster performer. Interferon generally has been found to produce the loss of hepatitis B e antigen (HBeAg) in approximately 33 percent of treated children. It is even less effective among children who have normal ALT levels; interferon produces HBeAg clearance in only 10 percent of those cases.

Various studies published between 1997 and 2004 have shown that 80 to 90 percent of patients who achieved HBeAg clearance with treatment sustained that response for four to eight years, resulting in a decreased risk of hepatic decompensation later in life.

*Hepatic decompensation* means the liver becomes less able to compensate for injury or damage; so, with e antigen clearance, hepatic decompensation is less likely to occur. Early evidence of hepatic decompensation could include jaundice, out-of-range liver enzymes (excluding elevated ALT/AST values), platelets and prothrombin time. It is important to note that most children do not have decompensated livers despite hepatitis B infection, and that these lab values are being tracked regularly by the child's liver specialist.

Elevated ALT levels indicate that the immune system has noticed the virus and gone on the attack. The interferon is effective only if the immune system is already engaged in war against the virus.

But interferon doesn't work in everyone, and it can cause uncomfortable side effects, including fever, flu-like symptoms, growth impairment during the treatment phase, and anxiety and depression. However, in general, children are typically much more resilient than adults on interferon and less symptomatic, and experience adverse effects for shorter periods of time. Depression is much more common with adults. More serious side effects are rare, but may include hyper- or hypo-thyroidism or retinal changes. One advantage to interferon is that the child cannot develop a "resistance," and it can be used more than once.

According to the Chronic Hepatitis B: Update 2009 (AASLD Practice Guidelines), "Judicious use of NA (nucleoside/nucleotide analogs) in patients with chronic hepatitis B is the most effective prophylaxis against the development of antiviral-resistant HBV."

Thus, patients with minimal disease and those who are unlikely to achieve sustained response should not be treated with NA, particularly if they are young (<30).

However, newer research indicates that lamivudine should be avoided if possible because it has a high resistance profile. This means that most users of lamivudine will develop a resistance to the antiviral, and more importantly, a cross resistance to more effective antivirals. It is an important factor for a young child, who could be on antiviral treatment for many years, or even indefinitely, who might well run out of antiviral options at a young age.

### **Lamivudine (Epivir)**

In 2000, the FDA approved lamivudine, sold under the brand name Epivir, for children infected with hepatitis B. This drug is a nucleoside analog (artificial genetic material that prevents viral replication) that was originally developed to treat patients infected with HIV.

Administered as a pill or oral solution, lamivudine works by inhibiting the HBV polymerase, the viral enzyme that helps the virus replicate. When the number of viruses in the liver is reduced, liver damage and inflammation also decline.

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While lamivudine rarely offers a permanent or complete cure, it appears to safeguard the liver while a patient is taking it, and there is no resistance. The 2009 AASLD guidelines state that an optimal daily dose for children is 3 mg per kilogram of body weight for one year.

During the first year of treatment, laboratory testing should be done every 3-6 months for liver chemistries and to test for HBeAg seroconversion. Seroconversion occurs when people develop e antibodies to the e antigen, seroconverting from antibody-negative to antibody-positive. The same holds true for surface antigen/antibody.

If lab work shows that HBeAg seroconversion has occurred, lamivudine treatment should continue for six more months. Viral relapse (flip-flopping) may occur within the first year of seroconversion. Lab work should be performed every 1-3 months for the first 6 months and every 3-6 months afterwards.

If HBeAg seroconversion hasn't occurred after one year of lamivudine treatment, the AASLD 2009 guidelines suggest therapy can continue for a second year. However, should another option exist, it is important to consider the alternative rather than risk mutant strains associated with lamivudine.

Of those who do experience HBeAg seroconversion with lamivudine treatment, relapses are expected to occur within one year of treatment completion in up to 30 percent of patients.

Three factors have been identified as predictors for successful HBeAg clearance with lamivudine treatment:

- higher ALT levels
- low serum HBV DNA load prior to initiation of therapy
- older age at the initiation of therapy

Besides the convenience of a once-a-day tablet or a liquid oral solution, lamivudine has fewer and less severe side effects than interferon. The most common side effects are fatigue, headache, nausea and abdominal pain.

But, lamivudine has some notable drawbacks:

- ALT levels and the volume of viruses (HBV DNA) in the bloodstream appear to decline only while lamivudine is taken. When patients stop taking lamivudine, their ALT levels and HBV DNA will climb again. In fact, patients may experience a rebound effect where the virus begins to reproduce rapidly. Basically, lamivudine works, but often the gains are lost once treatment ends. Even improved histologic changes may be lost by patients with breakthrough infection.
- Some patients who lost HBeAg and produced HBeAb while treated with lamivudine relapsed when treatment ended and the HBeAg returned. The relapse rates vary, depending on length of treatment and a patient's genotype of the virus.
- While lamivudine is effective against most hepatitis B viruses, its most significant limitation is the risk for developing lamivudine-resistant YMDD virus mutations in the

hepatitis B virus with prolonged treatment. The AASLD Chronic Hepatitis B: Update 2009 indicates the risk of mutation development increases the longer one uses lamivudine, ranging from 14 – 32% percent after one year of treatment (variability due to genotype) to 60 to 70 percent after five years of treatment. Resistant YMDD mutations are difficult to treat and they can result in replication of the mutated virus and acute exacerbations of liver disease.

Although not yet FDA-approved for pediatric treatment under 12 years of age, adefovir dipivoxil, a nucleotide drug, is sometimes used to treat the resistant YMDD variant commonly caused by longer periods of lamivudine treatment. Kidney damage has been associated with high doses of adefovir, so low doses are given and kidney functions are frequently tested throughout the treatment period.

Most physicians discontinue lamivudine once the YMDD mutation emerges as the dominant virus. Although current guidelines discourage use of combination therapies for children because of problems with side effects, risk for developing mutations, and lack of well-designed research supporting the practice, some studies combining lamivudine with interferon have examined whether or not this therapy can keep the viruses from replicating while simultaneously bolstering the immune response to the infection. For example, a pilot study published in 2006 examined results from a combined therapy. This study examined use of lamivudine and standard interferon in immune-tolerant children with vertically-acquired HBV infection. The children were given an 8-week course of lamivudine treatment followed by a 44-week course of standard interferon. At the end of the 52-week study, 78% of the children were negative for HBV DNA and 22% had seroconverted HBeAg. Thirty-six months later, 17% of the subjects continued to have viral suppression and no YMDD mutants occurred.

### **Adefovir (Hepsera)**

In 2002, the FDA approved the first nucleotide analog drug, adefovir dipivoxil, marketed as Hepsera, for treatment of hepatitis B in adults. Clinical trials for use of this drug in children were in process in 2007. As of May 2010, adefovir has been approved for use in children over the age of twelve.

For patients 12-17 years of age, treatment with adefovir is recommended for HBeAg positive patients who have compensated liver function.

Adefovir is a daily pill that works similarly to lamivudine. Both are antiviral medications that work by preventing viruses from reproducing.

But adefovir has an important advantage: it appears to be quite effective against all hepatitis B viruses, even the lamivudine-resistant YMDD mutation. Compared with lamivudine, resistance rates for adefovir are significantly lower. While lamivudine resistance rates are 64 percent after 5 years of treatment, adefovir's resistance rate is 11 percent after 3 years of treatment, and 29 percent after 5 years of treatment, according to data from adult studies published in 2005 in *Hepatology*.

An important pediatric study using adefovir was published in 2008 in *Hepatology*. In this randomized and controlled study, 173 children and adolescents were treated with either adefovir or placebo for 48 weeks. Results found adefovir effectively reduced HBV DNA in 23% of subjects in the 12-18 year age-range compared to 0% with placebo. Adefovir did not have the same level of effectiveness among children in the study who were less than 12 years of age. In fact, there were no statistically significant differences between adefovir and placebo in the younger age groups.

None of the subjects developed mutations from the adefovir. The study results determined that adefovir was effective in children between the ages of 12-17 who also had HBeAg positive chronic hepatitis B, though knowledge related to duration of effect in children is currently lacking. Adefovir offers another benefit—it appears effective against the hepatitis B viruses that are able to replicate without secreting HBeAg. This other type of viral mutation is found most frequently in Asians and often emerges in adults when the immune tolerant stage ends and their immune systems try to clear the virus.

The immune system has a hard time identifying and zeroing in on this type of hepatitis B infection, which is called HBeAg-negative hepatitis.

The only potential problem researchers are aware of at this time is that adefovir can cause kidney problems when administered at high doses. This potential renal toxicity makes the process of establishing safe dose levels in children critically important.

However, like lamivudine, when adefovir is no longer administered in adults, ALT levels and HBV DNA levels tend to rebound. And like lamivudine, adefovir has a high resistance profile and cross resistance to tenofovir.

Adefovir also appeared to work best in patients who had elevated liver enzymes.

### **Entecavir**

In April 2005, the FDA approved entecavir, a carbocyclic analog, for adult treatment. As of April 2007, several centers in the United States were in the early stages of recruitment for initial pediatric trials for entecavir; currently, the drug has been FDA-approved for use for children age 16 and older based on the success of studies in adults.

Entecavir (along with another drug called tenofovir that is only approved for adults) is currently considered one of the most powerful antivirals for treating chronic hepatitis B. In fact, it is one of the first-line treatments for adults because of its low level of risk for developing resistance.

Compared to lamivudine, entecavir has demonstrated superior effectiveness in reducing HBV DNA levels in patients with and without HBeAg; it is uniquely able to stop the replication action of the HBV virus at three different points in the virus' replicating process, greatly increasing the resistance profile.

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Entecavir can be used in patients who are negative or positive for HBeAg who have compensated liver disease.

Entecavir is available in tablet form or as an oral liquid solution. For patients who have never been treated with a nucleoside drug (such as lamivudine), the recommended dosage for patients aged 16 and older is 0.5 milligrams daily. For patients who have used lamivudine or other nucleoside drugs, the dosage is 1 milligram every day. The drug should be taken on an empty stomach.

In a phase III trial, reported in *Gastroenterology* in 2006, entecavir reduced HBV DNA more effectively than lamivudine in both HBeAg positive and HBeAg negative patients.

In adult patients treated with entecavir at 0.5 mg/day, 67 percent had an HBV DNA level below the lower limit of detection, compared with 36 percent treated with 100 mg/day of lamivudine after 48 weeks.

However, rates of HBeAg seroconversion were similar between the two groups. Among those patients taking entecavir, 21% experienced HBeAg seroconversion. Among those taking lamivudine, 18% experienced HBeAg seroconversion.

For those patients who experienced suppressed HBV DNA but were still HBeAg positive after one year, continuing treatment for a second year resulted in an HBeAg seroconversion rate of 11% in the entecavir patients, and a rate of 12% in the lamivudine group.

Entecavir is associated with a low rate of drug resistance and studies show that entecavir is able to suppress both the lamivudine-resistant and the adefovir-resistant viruses.

Entecavir was well tolerated by adults and most adverse events were mild to moderate and temporary.

It is important to note that this drug can cause extreme damage to the liver and cause lactic acidosis, a build-up of acid in the blood.

In 2010, Dr. Philip Rosenthal reported that a “phase IIb clinical trial for entecavir use in patients as young as 2 years old is currently underway and a phase III study is about to begin.” This suggests that expanding use of entecavir to younger children might become possible in the future.

### **Telbivudine (LdT)**

In October 2006, telbivudine (Tyzekda), a nucleoside analog, was approved for treatment of hepatitis B in adults. Based on studies that have been done in adults, telbivudine has also been approved by the FDA for children 16 years of age and older. Telbivudine is another antiviral compound that inhibits HBV replication by interfering with its DNA polymerase.

In clinical trials, telbivudine exhibited antiviral qualities that suppressed the hepatitis B virus and decreased liver inflammation at rates comparable to lamivudine.

Telbivudine is effective against lamivudine-resistant mutations and is associated with somewhat lower rates of drug resistance compared with lamivudine. However, compared to adefovir and entecavir, the resistance rates for telbivudine are higher, and like lamivudine, the resistance rates increase with duration of treatment.

Most of the drug's reported side effects were mild to moderate, with the most common side effects being fatigue, abdominal pain, cough and an elevated creatinine phosphokinase (CPK), which is an enzyme in muscle tissue that enters the blood stream when muscle tissue is broken down.

### **OTHER DRUGS THAT HAVE BEEN APPROVED TO TREAT ADULTS**

Since 2005, two other drugs have been FDA-approved to treat chronic hepatitis B in adults. In the U.S., any new drug must first gain approval for use in adults before drug makers can plan pediatric clinical trials. Any combination usage of the drug, such as combining an interferon drug with a nucleoside analog drug must also win approval from the FDA. These newly-approved adult drugs will be or are being studied for use in children.

### **Pegylated Interferon**

Pegylated interferon was approved for treatment for adults in 2005. Many doctors and parents are anxiously waiting to see how effective this formulation of interferon will be in boosting a child's immune system that is trying to clear the virus. And some pediatric liver specialists are currently prescribing pegylated interferon off-label.

While conventional interferon is administered in three weekly injections—traumatic for parents and children alike—pegylated interferon requires only one weekly injection.

Pegylated interferon is formulated so it remains in the body longer, and ideally the immune-boosting interferons remain at a more consistent level in the bloodstream over the course of a week.

What is interesting from a pediatric perspective is that this interferon formula has proven effective in adults who have the HBeAg, high HBV DNA levels and normal ALT levels. These



three characteristics are common in children who are in the immune tolerant stage of the infection.

Another factor that raises hopes for successful treatment for children is that pegylated interferon appears to have greater effectiveness in patients younger than 25 year of age when compared to patients who are older. As of 2010, there have been few studies of pegylated interferon and its use in children. However, in one small study published in *Gastroenterology* in 2008, 7 of 13 children had stable undetectable HBV DNA after 48 weeks of treatment.

More studies of pegylated interferon use in children are needed; consequently it has not yet been approved for use in children.

### **Tenofovir**

In 2008, tenofovir (Viread), a nucleotide analog, was approved for treatment of hepatitis B in adults. Tenofovir is similar in structure to adefovir. However, because it is less toxic to the kidneys, the approved dosage is much higher. This factor has likely contributed to its successful antiviral activity in clinical studies. This drug, along with entecavir and pegylated interferon, is considered to be among the first-line treatments for hepatitis B in adults.

Tenofovir works by blocking HBV replication in liver cells. Once the drug attaches to the HBV DNA, the virus is unable to reproduce.

Clinical trials indicated increased antiviral qualities when compared to adefovir, which had previously been held in high regard for its effectiveness.

Tenofovir has also demonstrated effectiveness against lamivudine-resistant mutations. Limited data suggests that it is not as effective against adefovir-resistant mutations.

Tenofovir also appears to have a low resistance profile. Currently, no cases of tenofovir resistance have been established. One study established no cases of resistance after 72 weeks of therapy.

Tenofovir is well-tolerated and the drug is considered to have a favorable safety profile. The most troublesome side effects included nausea in 9% of cases and abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash in more than 5% of patients. The most serious side effects included an ALT flare in 1% of the cases (where ALT levels become suddenly higher), and thrombocytopenia (in less than 1%),

As of summer 2010, Dr. Philip Rosenthal reports that “tenofovir is currently being tested in an adolescent HBV cohort.” This suggests that tenofovir might at least be approved for use in treating older children, similar to the way entecavir has already been approved for children aged 16 and older. Studies for younger children are currently in planning stages.

### **OTHER TREATMENTS THAT HAVE NOT YET BEEN APPROVED BY THE FDA**

A number of other treatments have emerged in recent years but are not yet FDA-approved.

#### **Combination Treatments**

Because combination treatments have great success when used for treating other viral infections such as HIV and HCV, studies have focused on use of combination treatments for hepatitis B infection as well.

In theory, combination treatments are advantageous because their combined effect will often be more powerful than either drug used separately. Additionally, use of two drugs together can have the effect of delaying or decreasing the risk for drug resistance.

Drawbacks associated with using multiple drugs include increased medication costs, risk for increased toxicity when more than one drug is used, and increased potential for undesired drug interactions.

Although many drug combinations have been studied in the adult population, to date, none of these have been identified as notably more effective than treatment with a single drug. In spite of these results, one very important benefit from using combination therapy to treat hepatitis B is the fact that combination therapies can reduce the likelihood of lamivudine resistance compared to using lamivudine alone. Additionally, combinations of different nucleotide and nucleoside therapies are often useful for treating resistance in adults.

#### **Standard or Pegylated Interferon with Lamivudine**

Given the mild to moderate success of lamivudine and interferon when taken alone, researchers have tried a combination of the two against hepatitis B. They hoped the double whammy of boosting the immune system with interferon combined with the antiviral action of lamivudine would deliver a fatal one-two punch to the virus.

The AASLD guidelines do not recommend use of interferon and lamivudine in combination. Data from five large adult studies occurring between 2000-2005 confirmed interferon and lamivudine combined were more effective than using lamivudine alone, but not more effective than using interferon alone.

In 2007, Dr. Kathy Schwarz, Director of the Pediatric Liver Center at Johns Hopkins University, stated that “combination treatments should not be given to children outside of clinical trials (because) there are no FDA-approved combination treatments.” However, she adds “My opinion is that these treatments are certainly worthy of clinical trials.”

[Note: It’s our understanding at this time, May 2010, that such trials will soon commence.]

Many researchers continue to experiment with the lamivudine and interferon combination treatment. One of the first groups of researchers to try the combination in HBV infected children

was a group of Turkish doctors who reported their findings in the *Pediatric Infectious Disease Journal* in 2001.

They tried two durations of combination treatment: six months of treatment in 30 children and 12 months of treatment in 27 children. They administered fairly high doses of both interferon (10 MU/m<sup>2</sup> of body surface) and lamivudine (4 mg/kg of body surface, with a maximum 100 mg dose).

In the group treated for six months, 33 percent cleared HBeAg at the end of the treatment period. Six months after treatment ended, an additional 4 percent of patients had cleared the HBeAg.

In the group treated for 12 months, 59 percent cleared HBeAg at the end of treatment. Six months after treatment ended, the HBeAg had returned in only 3 percent of the patients.

About 96 percent of both groups had undetectable levels of HBV DNA six months after therapy ended, and everyone maintained normal ALT levels six months after treatment.

Twenty percent of the entire group treated for six months, and 37 percent of the group treated for 12 months achieved complete clearance of the virus—they cleared not only the HBeAg, but also the HBsAg and produced the HBsAb.

While the combination of interferon and lamivudine appears more effective in producing a sustained HBeAg seroconversion, its success rate is not outstanding and researchers are looking for more effective types of interferon and antiviral agents with which to vanquish the virus, including those that vanquish all viruses, including the YMDD mutants.

A second study in Turkey that compared children treated with only interferon against a group treated with the combination of interferon and lamivudine found that, while the combination therapy had a more beneficial effect than interferon alone in normalizing ALT and clearing HBV DNA, the response rate at six months after the therapy ended was not statistically significant between the two groups.

A *Management of Hepatitis B 2006* report by Dr. Jean Molleston cited several small pediatric combination interferon/lamivudine studies that were originally published between 2002 and 2006.

These studies demonstrated a 55 percent HBeAg seroconversion rate and loss of detectable HBV DNA compared to a 33 percent HBeAg seroconversion rate with interferon alone, and a 34 percent HBeAg seroconversion rate with lamivudine alone.

The report states that combination treatment resulted in a 22 percent HBeAg seroconversion rate among a group of Asian children who had normal ALT levels compared to a 10 percent HBeAg seroconversion rate with interferon used in children with normal ALTs, and a 19 percent HBeAg seroconversion rate with three years of lamivudine treatment used in subjects with normal ALTs.

### **Lamivudine and Adefovir**

One study published in the *Journal of Hepatology* in 2008 compared use of lamivudine with adefovir to lamivudine alone in a group of patients who had never used one of the nucleoside drugs.

At weeks 52 and 104, both randomized groups had no difference in HBV DNA suppression, ALT normalization, or HBeAg loss. Although the rates of lamivudine resistance were lower in the group that used both medications, lamivudine resistance still occurred in 15% of the group compared to 43% in the group that used lamivudine alone.

Another smaller study published in 2004 compared the use of lamivudine in combination with adefovir with using adefovir alone to treat patients who already had lamivudine resistance. The study found no significant difference between using adefovir alone or with lamivudine in reducing HBV DNA levels. However, two other benefits to using the drugs together have been identified. First, adding the second drug to the lamivudine therapy reduced the occurrences of hepatitis flares when transitioning between the drugs. Second, studies have found that continuing the lamivudine while adding the adefovir decreases the rate of developing resistance to adefovir. Consequently, in cases where lamivudine resistance already exists, studies indicate it is better to add adefovir to the therapy rather than switching to adefovir and using it alone.

### **Lamivudine and Telbivudine**

A study published in *Gastroenterology* in 2005 compared use of lamivudine and telbivudine to using telbivudine alone in patients who had never been previously treated. The result found that using telbivudine alone was superior in all measurements including HBV DNA reduction, ALT normalization, and HBeAg loss.

## **OTHER DRUGS SOMETIMES USED TO TREAT ADULTS**

### **Emtricitabine ( Emtriva or FTC)**

Emtricitabine, marketed as Emtriva or FTC, is a cytosine nucleoside analog drug that has been approved for HIV treatment. Ongoing studies suggest the drug has effectiveness against the hepatitis B virus as well, although the FDA has not yet given approval for the drug to be used for treating hepatitis B.

Emtricitabine is similar in structure to lamivudine. Consequently, emtricitabine also carries with it a similar risk for development of drug resistance. As a result, its usefulness as a monotherapy is unlikely, but it may fill a niche for use in combination treatments.

According to a study of 98 patients treated with emtricitabine presented to the AASLD in 2002 by Dr. Robert Gish, after 48 weeks of treatment:

- 55 percent of patients treated had undetectable HBV DNA levels
- 50 percent lost HBeAg
- 23 percent seroconverted and produced HBeAb

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- 6 percent developed signs of viral resistance

After two years of treatment, of the 98 patients originally enrolled in the study:

- 76 percent had normal ALT levels
- 41 percent had undetectable levels of virus
- 51 percent had lost HBeAg
- 29 percent had seroconverted to HBeAb

After two years, the incidence of resistance was 19 percent for patients receiving 200 mg for the full two years. Preliminary data from the post-treatment period show that eight patients experienced a return of hepatitis B with resurgence of HBV DNA.

Interestingly, among patients who had undetectable serum viral DNA at least at one point during the two-year treatment period, 68 percent lost HBeAg and 43 percent seroconverted to HBeAb.

Among patients with detectable HBV DNA levels, only 12 percent had lost HBeAg and 3 percent seroconverted to HBeAb at two years.

Results from this two-year study show:

- a sustained virologic response with 41 percent of the patients
- a favorable response with 51 percent of the patients with HBeAg loss and 29 percent seroconversion to HBeAb
- the drug was well tolerated
- viral resistance appeared in 19 percent of patients who received the 200 mg dose

The biggest drawback to use of emtricitabine is the problem of developing drug resistance, so studies have moved toward learning about the drug's effectiveness in combination with other proven hepatitis B treatments such as adefovir and tenofovir.

In 2008, the *Journal of Hepatology* published a study that compared use of emtricitabine plus adefovir to use of adefovir alone. For this study, 30 HBeAg-positive adult patients who had not been previously treated received either the combination treatment or adefovir alone for 96 weeks. After 96 weeks of therapy, the combination group experienced a greater reduction in HBV DNA and increased ALT normalization. Rates of HBeAg seroconversion were similar between the two groups. Neither group experienced adefovir or emtricitabine resistance after 96 weeks of treatments. The results of this study suggest the combination treatment did the better job of suppressing HBV DNA while on treatment.

Another study published in 2006 compared 164 adults who received either emtricitabine plus clevudine or emtricitabine alone for 24 weeks with an additional 24 weeks of follow-up. After the patients received their 24 weeks of treatment, follow-up testing was completed 24 weeks later. At that time, 74% of patients in the combination group (compared to 65% of patients in the single-therapy group) experienced a reduction in HBV DNA; 40% in the combination group had undetectable HBV DNA (compared to 23% in the single-therapy group), 63% of the combination

group experienced ALT normalization (compared to 42% in the single-therapy group). The results of this study found no significant differences after receiving 24 weeks of treatment, but the results taken 24 weeks after stopping the therapy were better for the group who used the combination therapy.

A U.S. phase II trial is currently in process examining the effectiveness of adding emtricitabine to tenofovir to treat adult patients for hepatitis B. This study has been recruiting participants since 2007.

### **Clevudine**

In 2006, clevudine was in phase III trials for adult use. The study was examining use of clevudine in combination with adefovir. In 2009, the trial was stopped due to problems with unwanted adverse effects causing muscle damage. While the drug has been used successfully in other countries for treating hepatitis B, study results are indicating these problems are associated with longer-term clevudine use of approximately one year or more.

It is unlikely at this time that use of clevudine will progress in the United States, but its study will likely continue in other countries.

### **Thymosin (Zadaxin)**

Thymosin was discovered to be an important molecule that is a natural part of the human immune system. Since the late 1900s, scientists have been developing ways to recreate thymosin and other molecules that play a role in a functional human immune system.

Thymosin is approved for use to treat hepatitis B in over 35 countries. It was first approved for use in Singapore in 1993. Currently, thymosin is not FDA-approved for hepatitis B treatment in the U.S., although it has been studied in the U.S.

Thymosin is a drug that functions by enhancing the way the immune system functions. Immune enhancers are similar to interferon in the way they stimulate or enhance the immune system, but this drug specifically assists T-cells to find and fight tumors and viruses. It is a hormone that stimulates T-cells to mature.

In combination with standard interferon, this drug resulted in a long-term sustained response rate indicated by normal ALT levels and negative HBV DNA in difficult-to-treat patients.

In one analysis of five studies including a total of 353 patients, patients using thymosin alone compared to placebo experienced a significant increase in virologic response at the end of treatment that continued up to twelve months. In fact, results from four randomized controlled studies suggest treatment with thymosin achieved almost double the sustained response compared to controls.

Tests examining thymosin in combination with standard interferon have also shown promise, and it has also been studied in combination with lamivudine.

An analysis of results published in 2009 examined and compared the results of eight trials that examined lamivudine monotherapy to the combination of lamivudine plus thymosin in HBeAg-positive patients. Analysis of these studies found that combination therapy was superior to lamivudine alone for achieving ALT normalization, HBV DNA reduction, and loss of HBeAg. No serious adverse events were experienced in either group.

Results from this and other studies suggest a future role for thymosin would likely be for use in combination with other therapies.

### **WHEN SHOULD A CHILD BE TREATED?**

In November 2008, a panel of North American pediatric liver specialists developed a series of recommendations to assist practitioners in determining the best strategies for diagnosing, monitoring, and referring children for treatment who have chronic hepatitis B. The resulting recommendations were published in the November 2009 issue of Pediatrics.

Because of the dearth of medical treatments available, doctors have usually treated only children who had clear signs of liver disease—those whose liver enzyme levels were at least double what is considered normal in children.

Also, it was primarily children with elevated ALT levels who responded to interferon or lamivudine treatment, thus reinforcing the belief that only those with elevated ALT levels should receive treatment.

The pediatric recommendations published in 2009 suggest that treatment is not indicated in HBeAg positive patients who have normal ALT levels.

Rather than proceeding with treatment when ALT levels are normal, guidelines recommend ongoing lab testing for HBeAg, HBV DNA, ALT and AFP levels. AFP levels are useful as a tool to assess risk for developing hepatocellular carcinoma, which is also known as liver cancer or HCC. As long as ALT levels remain normal, the lab testing should recur at 6-12 month intervals.

The recommendations suggest that a liver specialist should be consulted if or when two or more of the following occur: elevation of ALT, AFP greater than 10ng/ml, HBV DNA greater than 2000 IU/mL, or family history of liver disease. The liver specialist will be able to give guidance for further monitoring and treatment if needed, and can also offer evaluation for liver cancer.

In the 2009 recommendations, the panel of pediatric liver specialists is quick to identify the many unanswered questions that surround treatment strategies. Of particular concern is the development of resistance that so often results from use of lamivudine and adefovir, the two nucleoside/nucleotide drugs that are approved for use in children younger than twelve.

The development of drug resistance in a child is an important problem. First, a drug resistant strain becomes more difficult to treat. Because of the limited arsenal of drugs available for



pediatric use, treatment options at that point are extremely limited and the problem becomes a lifelong challenge. And from a public health perspective, breeding resistant strains of hepatitis B increases the risk of transmitting resistant strains to others.

As more nucleos(t)ide drugs have become available for adults, entecavir and tenofovir have risen to the top as first line treatments for adults with chronic hepatitis B because of their very low rates for drug resistance development. As pediatric trials for entecavir and tenofovir progress, pediatric specialists are hopeful that these treatments will prove to be superior for use with children as well.

In spite of the drawbacks associated with using lamivudine and adefovir in children, children with high levels of ALT and HBV DNA are most likely to respond to treatment with any of the currently approved treatments. However, several key questions remain, including whether treatment can positively affect lasting outcomes or prevents cirrhosis.

Evidence suggests that many untreated children with chronic hepatitis B will have mild or inactive disease for many years. Often, these children who develop active disease will lose their HBeAg spontaneously and for a sustained period of time without ever using treatment.

However, chronic hepatitis B can be a lifelong disease and concerns for developing cirrhosis and HCC are more likely to occur as children become adults.

For example, according to authors Chu and Liaw in the *Journal of Viral Hepatitis*, 90 percent of infected children will spontaneously clear the HBeAg and produce HBeAb between the ages of 15 and 35. But meanwhile, the virus can damage their livers—and cause scarring and set the stage for liver problems later in life—even when liver enzyme levels are normal.

A researcher in England had some surprising successes treating children with chronic hepatitis B who were asymptomatic and had no obvious sign of active liver damage.

Dr. Giorgina Mieli-Vergani, Alex Mowat Professor of Paediatric Hepatology at the Institute of Liver Studies, Kings College Hospital in London, treated 23 children who had normal ALT levels with lamivudine and interferon and found that after one year:

- five patients (22 percent) cleared the HBeAg and developed HBeAb
- of these five, four cleared the virus and the infection completely and developed surface antibodies

Dr. Mieli-Vergani began researching in the mid-1990s whether asymptomatic children could be treated. In a study published in *Hepatology* in 1996, she and other researchers described an innovative approach that set the groundwork for her later work with asymptomatic children.

The researchers “primed” or administered prednisolone (a steroid similar to prednisone) followed by interferon-alpha treatment in 34 children. They administered only interferon in another 30 children, and had a control or untreated group of 31 infected children.



## Hepatitis B Treatment

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Nearly all of the children, even those with normal ALT or AST levels, had received liver biopsies that showed some liver inflammation before treatment began.

After treatment, researchers found that of the 20 children with normal liver enzymes, 5 of the 11 children (with normal ALT/AST levels) who had been pretreated with steroids seroconverted and produced HBeAb.

Only one of the nine who received interferon but was not pre-treated with steroids seroconverted.

Of 50 children with slightly elevated or normal liver enzymes, 16 of them seroconverted compared to two out of 31 children in the untreated group.

For the first time, researchers noticed that even children with normal or only slightly elevated liver enzymes could benefit from treatment.

Next, Dr. Mieli-Vergani tried a new approach with 23 children (8 boys and 15 girls, 16 of Asian descent, avg. age 10) who had been infected with HBV during the first year of life. Liver biopsies were performed on all the children and showed only mild inflammation in most patients and minimal fibrosis (scarring) in a few patients.

Except for two children, these children all had normal or only slightly elevated liver enzymes and all tested positive for:

- surface antigen (HBsAg)
- e antigen (HBeAg)
- and HBV DNA

First, the group was pretreated for eight weeks with just lamivudine, and then Dr. Mieli-Vergani added conventional interferon for 44 weeks of combination treatment.

At the end of the 52 weeks of treatment, of the 23 children:

- 22 percent (5 patients) seroconverted and developed HBeAb.
- 17 percent (four of the five who developed the e antibodies) also completely cleared the virus, developed the surface antibody and have remained negative for HBV DNA long-term.
- 82 percent (19) of those treated had no HBV DNA at the end of treatment. (HBV DNA eventually rebounded in all but five children after treatment with lamivudine stopped.)

Among the five who responded to the combination treatment, four were of Asian descent. All five had started treatment with normal liver enzymes and four had HBV DNA of less than 1,000 pg/ml when treatment began.

There was no control arm, or untreated group of children in this trial.

Does this study suggest asymptomatic children with normal liver enzymes and the HBeAg should be treated? Dr. Mieli-Vergani is careful in her response, “We need more studies in these children before saying how they should be treated,” she said. But she points out that children do tolerate interferon better than adults, and it is important to hasten the HBeAg seroconversion and produce antibodies in children as soon as possible to lessen the chance of liver damage.

In 2006, Mieli-Vergani’s research focused on using lamivudine in combination with interferon to treat immunotolerant children who have been perinatally infected with HBV. In a pilot study reported in *The Journal of Pediatrics*, 23 eligible subjects recruited from a chronic HBV infection database of 202 were accepted into the study. Eligible subjects were accepted according to the following criteria:

- infection had to have been acquired perinatally
- ages had to be between 2-16 years old
- HBsAg and HBeAg had to be positive for at least one year
- HBV DNA had to be positive twice during the previous year
- normal or nearly normal ALT levels

These patients were initially given lamivudine 3mg/kg daily (not to exceed 100mg/day) for eight weeks in an effort to lower HBV DNA. After eight weeks, interferon was added to the lamivudine treatment for an additional 44 weeks. Interferon was given daily for the first 5 doses and then 3 times weekly for 44 weeks.

At the end of the 52-week study, HBV DNA was positive in 22 percent of subjects, 22 percent seroconverted to HBeAb, and 17 percent cleared HBsAg and seroconverted to HBsAb.

These results challenge current trends to exclude children with normal ALT levels from treatment by suggesting treatment rates in this population are similar to those with elevated ALT levels that are more likely to be accepted for treatment.

Mieli-Vergani’s future research will examine treatment results in similar populations using pegylated interferon (which is not currently approved for use in children in the U.S.) in combination with lamivudine.

In 2007, Mieli-Vergani clarified her belief that “the subjects for whom it is important to get rid of the virus are those unlikely to clear it spontaneously and who have the highest risk of developing later complications.”

### THE CHALLENGE OF TREATMENT IN THE IMMUNE TOLERANT STAGE

When the hepatitis B virus is transmitted perinatally or during the first 12 months of life, the child's immune system is not sophisticated enough to recognize the virus as a danger. The immune system thinks the virus is just a normal part of the body and doesn't try to create antibodies against it.

During this "immune tolerant" stage, the virus rapidly replicates in the liver and moves into the blood, producing high HBV DNA serum levels, but little actual damage occurs.

The challenge of treating a child in the immune tolerant stage is to convince the child's immune system to activate against this virus, which it thinks is just a normal part of the body.

In Dr. Anna Lok's "Clinical Manifestations and Natural History of Hepatitis B Virus Infection," in *UpToDate*, she writes about children infected perinatally and why they may not respond well to interferon treatment.

In the initial phase of the disease, there are high levels of viral replication (hepatitis B e antigen is present and there are high levels of HBV DNA in serum) but not much active liver disease—the child is asymptomatic, has normal ALTs and little change on the liver biopsy.

According to Dr. Lok, during the second and third decades of life, there is a transition from immune tolerant to immune clearance. During this time, many patients begin to lose the e antigen and show abrupt increases (exacerbations) in ALT levels.

Elevated ALT levels are believed to be caused by a sudden increase in immune-mediated lysis (breaking down or disintegration) of infected liver cells (hepatocytes) preceded by an increase in HBV DNA in serum and a shift of hepatitis B core antigen from nuclear to cytoplasmic (the cytoplasm is the contents of a cell other than the nucleus) sites within the structure of the liver cell.

This may suggest that immune clearance is triggered by an increase in the number of viruses replicating in the body, or a change in cellular make-up of the virus's antigens. It's unknown how these changes occur.

However, not all exacerbations lead successfully to e antigen seroconversion and clearance of HBV DNA from serum—this is called abortive immune clearance.

These patients may have recurring exacerbations with intermittent disappearance of serum HBV DNA with or without a temporary loss of the e antigen. These repeated episodes of hepatitis might increase the risk of developing cirrhosis and liver cancer (hepatocellular carcinoma).

Abrupt elevations in serum ALTs appear to happen more frequently in men than women, although no one knows why. This may account in part for the higher incidence of HBV-related cirrhosis and liver cancer in men.

In a few patients, abrupt ALT elevations can lead to hepatic decompensation or, rarely, to death from hepatic failure.

Dr. Lok suggests those with severe exacerbations should be referred to specialized centers for liver transplantation or treatment with an antiviral. She feels interferon treatment isn't indicated for these cases because it can cause additional exacerbations or flares of the disease.

In those who are infected as children (but not perinatally), the disease tends to start out differently. It begins with a phase of viral replication and active liver disease and later, a phase of nonreplication and remission of liver disease. As adults, this group tends to have a lower percentage of people who test positive for e antigens.

A person with chronic hepatitis B may be e antigen negative, e antibody positive, have undetectable HBV DNA in serum and even lose the hepatitis B surface antigen and still develop cirrhosis or even liver cancer, although this doesn't happen very often.

According to Dr. Lok, the ability of the virus to cause complications despite clearance of the surface antigen probably results from its integration into the genome, or genetic material, of liver cells.

Factors that indicate a poorer prognosis include:

- a prolonged replication phase
- older age
- hypoalbuminemia (the liver produces albumin—a protein in blood—and when the liver isn't working well, less albumin is produced)
- thrombocytopenia (low platelet counts)
- splenomegaly (enlarged spleen)
- hyperbilirubinemia (high bilirubin or jaundice)
- general decompensated liver disease

### **cccDNA – FUTURE TARGET FOR TREATMENT**

In *Viral Hepatitis*, Dr. Elizabeth Fagan identifies the cccDNA as a critical part of the hepatitis B virus. HBV cccDNA (covalently closed circular DNA) is a form of the viral genome that gets into the nucleus of liver cells and sets up shop. (The life cycle of the hepatitis B virus goes through various stages or forms, much like insects do in their maturation process.)

Essentially, this cccDNA form of the virus acts like a factory, churning out copies of the hepatitis B virus that are then released into the blood of the infected person in a slightly altered version. It's this second form of the virus that is measured in the serum when a blood test is evaluated to detect HBV DNA.

The available arsenal of drugs can sometimes make the blood level of HBV DNA in a patient undetectable, creating the impression that the body has successfully defeated the virus, or reduced it to small, inconsequential levels. But, the cccDNA residing in the liver is still holding

firm, ensconced (integrated) in the nucleus of the liver cells. It's very resistant to treatment. The only way to find out what is happening to the cccDNA is to sample the liver through a liver biopsy.

To find a true cure for hepatitis B, it's imperative to develop a treatment that will kill the cccDNA in a patient's liver cells and clear the HBV DNA from the blood. Because the harm done to the liver of a hepatitis B patient is done not by the virus itself, but by the body's immune system trying to kill the virus by killing the cells in which it's hiding, a way must be found to eliminate the cccDNA without killing the host (the liver cells) in which it lives. When that is accomplished, the viral factory will close and the patient will truly be cured of hepatitis B.

As of 2007, work with cccDNA focused on measuring cccDNA and understanding how cccDNA measurements relate to measurements of HBV DNA, HBeAg, and HBsAg.

In the future, treatment goals will focus on elimination of cccDNA from liver cells. Real-time PCR (a testing technique that is more sensitive to polymerase chain reaction assays compared to gel-based assays which were previously used) has become the gold standard for distinguishing cccDNA from the other forms of HBV DNA present in a liver biopsy specimen.

In 2007, Bourne et al. reported in the *Journal of Viral Hepatitis* that they found and measured cccDNA in liver cells and compared that value to measured amounts of HBV DNA found in liver cells. The study made comparisons between levels of cccDNA in liver cells and levels of HBV DNA in the blood.

For the study, liver cell and blood HBV DNA, liver cell cccDNA, and blood HBeAg and ALT levels were monitored during a 52-week study of eight adult patients who were treated with lamivudine, or lamivudine and standard interferon, or a placebo.

Most patients experienced a decrease in HBV DNA in their liver cells, including those who were using the placebo.

HBeAg seroconversion was associated with reduced levels of cccDNA in the liver cells. HBeAg seroconversion was also associated with a change in the ratio of cccDNA in the liver cells compared to the total HBV DNA in the liver cells. This is a desired result in that it indicates the nonreplicating viruses had become the predominant form of HBV DNA after HBeAg seroconversion.

The study also found that decreases in blood HBV DNA levels were always associated with decreases in HBV DNA in the liver cells, but decreases in HBV DNA in the liver cells were not always associated with immediate reduction in blood HBV DNA levels.

In two-thirds of the placebo recipients, increased ALT levels in the blood were associated with decreasing HBV DNA levels in the liver cells. HBV DNA levels in the blood did not decrease, presumably because the natural cellular response necessary to decrease the circulating virus had not yet occurred.

Future research will try to clarify the relationship between cccDNA and total HBV DNA levels in liver cells and the way the levels affect the overall liver health of the patient.

An article published in the *Journal of Hepatology* in 2009 describes more current understandings of cccDNA. This article identifies advances that have been made in understanding the complex network of genetic, biologic and virologic events that cause cccDNA to make hepatitis B viruses. While understanding has progressed, there are still many questions to answer.

In the future, drugs will be able to eliminate or reduce HBV cccDNA, which will eliminate the virus's ability to replicate.

Measurement of HBV DNA and cccDNA in liver cells has become an important piece of the puzzle in current drug studies. Among currently approved drug therapies, entecavir has demonstrated an ability to reduce cccDNA levels.

### **IDENTIFYING AND TREATING HEPATITIS B-RELATED LIVER CANCER**

Eighty percent of all primary liver cancers are caused by chronic hepatitis B in people who have been infected since birth or early childhood.

Sustaining positive HBeAg past the age of 40 is associated with a higher risk for developing cirrhosis and liver cancer. Other factors that increase risk for liver cancer include male gender, lifestyle choices, a family history of liver cancer, and cirrhosis, although 30 to 50 percent of liver cancer cases do not show evidence of cirrhosis.

Scientists at the Asian Liver Center at Stanford University state that 25 percent of chronic HBV carriers will die from either liver cancer or cirrhosis.

Although not well understood, liver cancer likely occurs as a result of chronic hepatitis B infection because of the long-term effects of liver cell disruption caused by the presence of the virus. Over time, as the virus causes liver cells to die, the body responds by rapidly forming new liver cells. This process of rapid liver cell regeneration increases the risk that cell mutations will develop and reproduce which can eventually result in cancer. According to an article published in the *Journal of Viral Hepatology*, it usually takes about 25-30 years of chronic infection for this to occur. However, there are exceptions and vigilant monitoring is necessary to prevent HCC.

Research has also found some viral factors that can help predict risk for developing liver cancer. For example, a high presence, over time, of HBV DNA in the blood is a strong predictor.

Analysis of several studies has shown that risk for liver cancer increases as HBV DNA levels increase. For parents, it is important to keep in mind that children often have extremely high HBV DNA viral levels. It is not at all uncommon for children in the immune tolerant stage to have viral loads in the millions and even billions.

Although rare, liver cancer can occur in children.

There is no evidence that antiviral therapy decreases the risk of liver cancer, but it can decrease or even prevent cirrhosis, which in turn decreases the risk of liver cancer. The challenge is to determine when, or if, antivirals should be given to prevent cirrhosis.

Some individuals have developed liver cancer and tumors even after clearing HBV surface antigen.

Researchers have discovered that patients can develop liver cancer without active liver disease. It's imperative to detect liver cancer early enough so that it can be removed or treated to improve long-term survival, even if the risk of recurrence remains.

In "Screening for Hepatocellular Carcinoma in Alaska Natives Infected with Chronic Hepatitis B: A 16-year Population-Based Study," published in the journal *Hepatology*, Dr. Brian McMahon followed 1,400 people with chronic hepatitis B in Alaska for 16 years, between 1982 to 1998.

In the study, 30,000 alpha fetoprotein tests (a test that can detect cancer and tumors) were performed and those at risk for liver cancer were notified.

The risk group had blood drawn and sent to labs, using 15 pg/ml as a ceiling. If levels were above the cut-off and the participants were not pregnant, they underwent liver function tests and sometimes a computed tomography imaging (CT or CAT) scan.

Dr. McMahon discovered 32 carcinomas (malignant cancers); one-third of the cancers were in children under the age of 19. All of these pediatric patients were asymptomatic.

Most of the 32 patients did not have cirrhosis and 23 of the 32 cancerous tumors were small enough to be removed. Fifty percent had recurrence of cancer within five years of the surgery.

There was no control group because it would have been unethical, but there was significant long-term survival compared to historical controls.

The benefit of screening was greatest in children and younger patients—significant numbers of tumors were removable in children, and it is more cost-effective to do this versus fighting full-blown liver cancer many years later.

Dr. McMahon noted he felt it was more effective but much more expensive to use both an alpha fetoprotein and an ultrasound to detect liver cancer early in the disease stage. He suggested limiting that combination to those with cirrhosis, men over 45, and those with a family history of liver cancer.

In 2007, Dr. McMahon's research, published in *The Journal of Infectious Diseases*, focused on identifying cases of liver cancer by hepatitis B genotype among Alaska Native people.



Currently, there are eight strains or genotypes of hepatitis B virus that have been identified throughout the world. These genotypes are referred to as types A-H. Dr. McMahon's research attempted to determine which genotypes, if any, were more likely to cause liver cancer.

The 2007 study compared HBV genotypes among Alaska Native people who had liver cancer to HBV genotypes among Alaska Native people who did not have liver cancer.

A registry identified 47 patients who were diagnosed with liver cancer and chronic HBV infection between 1969 and 2003. For the study, these patients consented to testing for HBV genotype.

Previous studies conducted between 2000 and 2005 recognized an association between HBV genotype C and liver cancer in Asian populations. The 2007 study among Alaska Native people confirmed an association between HBV genotype C and liver cancer, but found that HBV genotype F was most significantly associated with the development of a liver cancer called hepatocellular carcinoma, or HCC, in this population. In fact, 32 of the 47 patients studied had genotype F.

The study also found a significant difference between ages at the time of liver cancer diagnosis. Persons with genotype F and liver cancer were diagnosed with liver cancer at a median age of 22.5 years compared to a median age of 60 years at the time of liver cancer diagnosis for all the other genotypes. In this study, genotype B was not found in any of the patients with liver cancer.

An analysis of several cohort studies published in 2009 in the *Journal of Viral Hepatitis* also described the effect genotype has on predicting HCC risk. For example, the risk for developing HCC is higher for genotypes B, C and D than it is for genotype A. Genotype C has a higher risk for HCC than genotype B. The article also restates that genotype F is known to be associated with developing HCC in Alaskan natives.

Future studies will examine the qualities of genotype F in hopes of gaining an understanding of the role it plays in causing liver cancer.

### **TREATMENTS ON THE HORIZON**

Better treatment is needed to combat hepatitis B at any age and during any stage of infection.

Treatment trials become an important part of discovering better treatments. In 2010, the U.S. National Institutes of Health committed to funding a HBV Consortium that will fund additional treatment trials for both adults and pediatric patients. Dr. Rosenthal explains that these will be well-done studies with the potential to contribute to the knowledge base that is already developed.

There is no treatment available that is consistently effective in curing this infection, and currently no medication produces durable results in lowering HBV DNA and ALT levels in the majority of those treated.



For children, therapy with only interferon or lamivudine is effective in only a minority of patients.

Bottom line: current therapies are inadequate for 60 to 90 percent of patients with chronic hepatitis B.

### **Non-Nucleoside Antivirals (sometimes called HAPs)**

A new class of compounds, non-nucleoside antivirals, which are sometimes called HAPs (for heteroaryldihydropyrimidines), has been found to inhibit HBV replication in a way that is distinctly different from existing antiviral medications.

Unlike lamivudine or adefovir, non-nucleoside antivirals do not inhibit the HBV polymerase. Investigators aren't clear exactly how non-nucleoside antivirals work to stop viral replication, but because they don't impact the viral polymerase, non-nucleoside antivirals may stop the virus without allowing "mutated" viruses to survive.

In a study reported in the Feb. 7, 2003, issue of *Science*, researchers found that non-nucleoside antivirals work by inhibiting formation of the nucleocapsids, the nucleic acid core of the virus that is needed for viral replication.

In 2006, five drugs of this class were in early stages of study. One of these, BAM-205, has been approved for use in Russia since 2001. This drug has demonstrated a reduction in viral load and ALT levels. This drug is in phase II/III clinical trials in the US.

Another nucleoside antiviral, (Bay 41-4109), has shown particular promise as a potent therapeutic agent in mice.

### **Therapeutic Vaccination**

For several years, researchers have been investigating whether it is possible to use a vaccine with surface antibodies to spur a patient's immune system into action against the hepatitis B virus.

In 2005, Akbar and Onji, two researchers in Japan, summarized research findings in the use of therapeutic vaccination for people with chronic hepatitis B.

Akbar and Onji report in the *Hepatitis B Annual* that several vaccine therapy clinical trials have occurred over the last decade. They also point out that while Western therapies have focused on use of antiviral therapies, it is becoming apparent that antivirals will not be able to completely cure hepatitis B in chronic cases.

Because of the limitations of antivirals, they believe it is worthwhile to approach treatment from a different angle. To do this, they examined the differences between acute infection and chronic infection and found the main difference is that chronic patients have an impaired immune response to HBV-related antigens.

## Hepatitis B Treatment

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The problem is not an impaired immune system in general, but in mounting an immune response to the hepatitis B virus in specific. Therefore, an ability to induce a normal immune response without causing harm to hepatocytes could be a valuable therapy.

Three types of vaccines have been studied: peptide vaccine, DNA vaccine, and antigen-based (current vaccines are surface antigen-based) vaccine:

- The peptide vaccine injects modified HBV-related proteins to enhance the immune system's cytotoxic T cells' (CTL) ability to identify and destroy liver cells that are infected with HBV.
- The DNA vaccine injects encoded HBsAg to cause the body's natural immune system to produce HBsAb.
- The antigen-based vaccine injects HBsAg to restore the immune system's ability to recognize the HBV as a foreign object so that a natural immune response can occur.

In 2003, researchers investigated whether vaccinating children who were in the immune tolerant phase of HBV infection—with normal liver enzymes and high levels of HBV DNA—with an antigen-based vaccine would cause an immune response.

Twenty-three children were vaccinated with three standard injections of the GenHevac B vaccine. Twenty-eight children in a control group received no medication or vaccine.

They were evaluated at six months after the first injection and at the end of the 12th month.

Unfortunately, the vaccine had little or no effect on HBV DNA levels or ALT levels. It was also ineffective in causing any HBeAg to HBeAb seroconversion.

Research in adults has produced similar results, though this continues to be an area of research interest.

Akbar and Onji explain that peptide-based vaccines and DNA vaccines have shown effectiveness in a few studies, but their use is still in early stages. There are also concerns about ethical use and long-term side effects of DNA vaccine. These types of therapies show little promise.

However, in 2005, drug researchers presented data from a U.S. Phase II study of a DNA-based immune-boosting vaccine. At week 26 of treatment, results demonstrated loss of HBeAg in 29 percent of vaccine recipients and seroconversion in 14 percent of vaccine recipients.

When compared to a control group of lamivudine recipients, there were no cases of seroconversion at 26 weeks, and only 9 percent demonstrated HBeAg loss.

Akbar and Onji suggest future therapeutic vaccine research should continue to focus on animal study to induce an immune response either with the HBsAg, hepatitis B core antigen, other HBV antigens, or any of these in combination.

One promising next-generation vaccine that has been trialed in humans is HBsAg-pulsed DCs. Here, HBsAg is injected, and dendritic cells (DCs) present at the injection site recognize and internalize the HBsAg. Then, the DCs communicate with T and B lymphocytes present in the immune system. As a result, B lymphocytes learn to recognize HBsAg and secrete HBsAb.

When the HBsAg is pulsed, the HBsAg is paired with DCs in the laboratory and then injected back into the body to concentrate the effect of the vaccine.

In 2004, human studies demonstrated an increase of HBsAb in all participants with no adverse side effects. Future research will consider differences among races and individuals.

Akbar and Onji also recommend development of HBsAg-based vaccination protocols and better systematic study of the vaccines.

They blame the current disorganization of vaccination study on a lack of funding and technical support for trials, but advocate that vaccine therapy is a less costly option when compared to interferon treatment or treatment for drug resistant mutations.

Because of cost, many individuals in the world have been told that no treatment options exist for them.

### BIBLIOGRAPHY

Akbar S Onji M. *Preventive and therapeutic approaches against hepatitis B virus by vaccine*. Hepatitis B Annual [serial online]. Volume 2 (2005) pp31-55. Retrieved from <http://www.hepatitisbannual.org/article.asp?issn=0972-9747;year=2005;volume=2;issue=1;spage=31;epage=55;aulast=Akbar>

Ando T, Sugiyama K, Goto K, Pediatrics, Nagoya City University Medical School, Nagoya, Aichi, Japan. *Emergence of Core Promoter or Precore Gene Mutations is Associated with Genotype but Rather with Age at Seroconversion from HbeAg to Anti-Hbe in Anti-Hbe-Positive Japanese Children*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #197 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Bae SH, Chung JY, Ko JS, Seo JK, Pediatrics, College of Medicine, Seoul National University, Seoul, Korea. *Long-Term Efficacy of Hepatitis B Vaccine in Korean Children: Ten Years After the Primary Vaccination in Early Infancy*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #513 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Ballauf A, Baumann U, Koehler H, Ross S, Wirth S, Pediatric Gastroenterology, University Children's Hospital, Essen; University Children's Hospital, Duesseldorf; Dpt. of Virology, University Hospital, Essen; Children's Hospital, Wuppertal, Germany. *Lamivudine Pretreatment to Standard Interferon in Children with Chronic Hepatitis B-A Pilot Study*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #200 from the World

Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Barbaro G, Zechini F, Pellicelli A, Francavilla R, Scotto G, Bacca D, Bruno M, Babudieri S, Annese M, Matarazzo M. *Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B. An Italian multicenter, randomized trial. Journal of Hepatology.* Vol. 35 (3) (2001) pp. 406-411.

Bourne F, Dienstag JL, Lopez VA, Sander TJ, Longlet JM, Hall JG, Kwiatkowski RW, Wright T, Lai CL, Condreay LD. *Quantitative analysis of HBV cccDNA from clinical specimens: correlation with clinical and virological response during antiviral therapy.* Journal of Viral Hepatitis. Volume 14 (2007) pp. 55-63.

Bortolotti F, et al. *Long Term Effect of Alpha Interferon in Children with Chronic Hepatitis B.* Gut. 2000; 46:715-718(May).

Brunetto MR, Calvo PL, Pace M, Baldi M, Maina A, Barbera C, Pediatric Gastroenterology, University, Torino; Gastroenterology and Hepatology, S. Chiara Hospital, Cinasello, Pisa, Italy. *Pre-core Heterogeneity: A Favourable Course of Chronic Hepatitis B Despite a Prevalent HBeAg Defective HBV Infection.* Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #202 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Castaneda C, Delgado G, Galindo MA, Department of Epidemiology, National Institute of Gastroenterology, Ministry of Public Health, Havana, Cuba. *National Hepatitis B Vaccination Program for Children and Adolescents in Cuba.* Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #777 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Cervantes-Bustamante R, Ramírez-Mayans J, Mata-Rivera N, Zárte-Mondragón F, Palacio-del Carmen L, Piña-Romero N, Navarrete-Delgadillo N. *Hepatitis B Prevalence in Mexican Children.* Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #207 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Chang MH. *Towards Control of Hepatitis B in the Asia-Pacific Region: Natural History of Hepatitis B Virus Infection in Children.* Journal of Gastroenterology and Hepatology. 15 (s5), E16-E19.

Chang MH, Shau WY, Chen CJ, Wu TC, Kong MS, Liang DC, Hsu HM, Hsu HY, Chen HL, Chen DS, Taiwan Childhood Hepatoma Study Group; Pediatrics, National Taiwan University Hospital, Taipei, Taiwan. *The Gender Effect of Universal Hepatitis B Vaccination on Hepatocellular Carcinoma in Children: Gender Difference.* Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #516 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Chang TT, Gish RG, Hadziyannis SJ, Cianciara J, Rizzetto M, Schiff ER, et al. *A dose-ranging*

*study of the efficacy and tolerability of entecavir in Lamivudine-refractory chronic hepatitis B patients. Gastroenterology.* 2005;129:1198-1209.

Chu CM, Liaw YF. *Chronic Hepatitis B Virus Infection Acquired in Childhood: Special Emphasis on Prognostic and Therapeutic Implication of Delayed HBeAg Seroconversion.* Journal of Viral Hepatitis, 2007, 14(3), 147-152.

Coffin CS, Lee SS. *Chronic Hepatitis B—Who Should be Treated?* Medscape General Medicine. 8(1):75. Retrieved May 11, 2007 from [http://www.medscape.com/viewarticle/521352\\_print](http://www.medscape.com/viewarticle/521352_print)

Comanor L, Minor J, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, Rosenthal P, Lachaux A, Shelton M, Sarles J, Sokal EM. *Statistical Models for Predicting Response to Interferon- $\alpha$  and Spontaneous Seroconversion in Children with Chronic Hepatitis B.* Journal of Viral Hepatitis 7, 2000, 144-152.

D'Antiga L, Aw M, Atkins M, Moorat A, Vergani D, Mieli-Vergani G. *Combined Lamivudine/Interferon- $\alpha$  treatment in 'immunotolerant' children perinatally infected with hepatitis B: a pilot study.* The Journal of Pediatrics. 2006;February:228-233.

DeMan R, Nevens F, Chua D. *A Study of Oral Entecavir Given for 28 Days in both Treatment-naïve and Pre-treated Subjects with Chronic Hepatitis.* 51<sup>st</sup> Annual Meeting of the AASLD, 2000, Abstract # 865.

Deres K, et al. *Inhibition of Hepatitis B Virus Replication by Drug-Induced Depletion of Nucleocapsids.* Science. 299:893-896, Feb. 7, 2003.

Dikici B, Bosnak M, Ucmak H, Dagli A, Ece A, Haspolat K. *Therapeutic Vaccine Against Hepatitis B Infection: Failure of therapeutic vaccination using hepatitis B surface antigen vaccine in the immunotolerant phase of children with chronic hepatitis B infection.* Journal of Gastroenterology and Hepatology. Vol.18 Issue 2 Page 218-Feb. 2003.

Dikici B, Bosnak M, Bosnak V, Dagli A, Davutoglu M, Yagci RV, Haspolat K. *Comparison of treatments of chronic hepatitis B in children with lamivudine and alpha-interferon combination and alpha-interferon alone.* Pediatr Int. 2002 Oct; 44(5):517-21.

Dikici B, Bosnak M, Kara IH, Dogru O, Dagli A, Gurkan F, Haspolat K. *Lamivudine and interferon-alpha combination treatment of childhood patients with chronic hepatitis B infection.* Pediatric Infectious Disease Journal. 2001 Oct; 20(10):988-92.

Ertem D, Acar Y, Ozguven E, Kotiloglu E, Pehlivanoglu E, Div. Pediatric Gastroenterology, Marmara University Faculty of Medicine; Pediatrics, Social Security Okmeydani Hospital, Istanbul, Turkey. *High Dose Interferon Alpha-2B Treatment in Children with Chronic Hepatitis B.* Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #1052 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Gerner P, Karimi A, Leoffler-Mary H, Prange R, Costa Lores AI, Wirth S, Children's Hospital, Affiliated Clinic of the University of Witten/Herdecke, Wuppertal; University of Mainz, Institute for Medical Microbiology and Virology, Germany; Hospital de St. Maria, Lisbon, Portugal. *Hot Spots of Hepatitis B Virus Mutations in Chronically Infected Children in Relation to Liver Inflammation*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #533 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Giacchino R, Cappelli B. *Treatment of Viral Hepatitis B in Children*. Expert Opinion Pharmacotherapy. 2010;11(6):889-903.

Gish R, Wright T, Wang C, et al. *Emtricitabine (Coviracil; FTC): Results From a 24-week Dose-selection Trial in Patients with Chronic HBV Infection*. 51<sup>st</sup> Annual Meeting of the AASLD, 2000, Abstract #873.

Gish R, et al. *Antiviral Activity, Safety and Incidence of Resistance in Chronically Infected Hepatitis B Patients Given Once Daily Emtricitabine for Two Years*. Abstract 838. 53rd AASLD. November 1-5, 2002. Boston, MA.

GlaxoSmithKline. (1997-2007). EPIVIR-HPV—First-Line Therapy for Chronic Hepatitis B Treatment in Adults and Children. *Hepatitis B Treatment*. Retrieved April 26, 2007 from [http://www.hepatitisbhelp.com/hepatitis\\_b\\_treatment.html](http://www.hepatitisbhelp.com/hepatitis_b_treatment.html)

Goldstein AL, Goldstein, AL. *From Lab to Bedside: Emerging Clinical Applications of Thymosin a-1*. Expert Opinion Biological Therapy. 2009;9(5):593-608

Gurakan F, Kocak N, Ozen H, Yuce A, Division of Pediatric Gastroenterology, Hacettepe University School of Medicine, Ankara, Turkey. *Comparison of Standard and High Dosage Recombinant Interferon Alpha 2b for Treatment of Children with Chronic Hepatitis B Infection*. *Pediatr Infect Dis J*. 2000 Jan; 19(1):52-6.

Haber BA, Block JM, Jonas MM, Karpen SJ, London WT, McMahon BJ, Murray KF, Narkewicz MR, Rosenthal P, Schwarz, KB. *Recommendations for Screening, Monitoring, and Referral of Pediatric Chronic Hepatitis B*. *Pediatrics*. 2009;124(5):1007-1013.

Hadziyannis S, Tassopoulos N, Chang TT, Heathcote J, Kitis G, Rizzetto M, et al. *Long-term adefovir dipivoxil treatment induces regression of liver fibrosis in patients with HBeAg-negative chronic hepatitis B: Results after 5 years of therapy [Abstract]*. *Hepatology*. 2005;42(Suppl):754A.

Hadziyannis S, Tassopoulos N, Heathcote EJ, Chang T, Kitis G, Rizzetto M, Marcellin P, Lim S, Goodman Z, Wulfsohn M, Xiong S, Fry J, Brosgart C. *Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen-Negative Chronic Hepatitis B*. *New England Journal of Medicine*. Vol. 348:800-807 Feb. 27, 2003 No. 9.

Hagmann S, Chung M, Rochford G, Jani M, Trinh-Shevrin C, Sitnitskaya Y, Neumann A,



Pollack H. *Response to Lamivudine Treatment in Children with Chronic Hepatitis B Virus Infection*. *Chronic Infectious Diseases*. 2003;37:1434-1440.

Han K, Ahn S, Song K, et al. *Efficacy of Clinic-based Screening for HCC in HBV-endemic Areas*. 51<sup>st</sup> Annual Meeting of the AASLD, 2000, Abstract #178.

Hepatitis B Foundation. (2003-2007). *Approved Drugs for Children*. Retrieved April 26, 2007, from [http://hepb.org/patients/treatment\\_for\\_children.htm](http://hepb.org/patients/treatment_for_children.htm)

Hepatitis B Foundation. (2003-2007). *Approved Hepatitis B Drugs in the United States. Approved Drugs for Adults*. Retrieved May 5, 2007, from [http://www.hepb.org/patients/hepatitis\\_b\\_treatment.htm](http://www.hepb.org/patients/hepatitis_b_treatment.htm)

Hepatitis B Foundation. (2006, February). *Compounds in Development for Chronic Hepatitis B. HBF Drug Watch*. Retrieved May 5, 2007 from [http://www.hepb.org/professionals/hbf\\_drug\\_watch.htm](http://www.hepb.org/professionals/hbf_drug_watch.htm)

Hepatitis B Foundation. (2003-2006). *Hepatitis B and Primary Liver Cancer*. Retrieved May 11, 2007 from [http://www.hepb.org/professionals/hepb\\_and\\_liver\\_cancer.htm](http://www.hepb.org/professionals/hepb_and_liver_cancer.htm)

Hepatitis B Foundation. *Hepatitis B and the Asian Community*. Retrieved May 11, 2007 from <http://www.hepb.org/06-0265.hepb>

Hepatitis B Foundation. (2003-2007). *Highlights from HBV Treatment for Children Today. Sixth Annual B Informed Patient Conference 2006, Stanford California*. Retrieved April 26, 2007 from [http://www.hepb.org/patients/patient\\_conference2006\\_Rosenthal\\_HBV\\_Treatment\\_for\\_Children.htm](http://www.hepb.org/patients/patient_conference2006_Rosenthal_HBV_Treatment_for_Children.htm)

Hepatitis B Foundation. (2003-2007). *Living with Hepatitis B: FAQ*. Retrieved May 5, 2007 from [http://www.hepb.org/patients/living\\_with\\_hepatitis\\_b.htm](http://www.hepb.org/patients/living_with_hepatitis_b.htm)

Hui, CK, Zhang HY, Bowden S, Locarnini S, Luk JM, Leung KW, et al. *96-Weeks Combination of Adefovir Dipivoxil Plus Emtricitabine vs. Adefovir Dipivoxil Monotherapy in the Treatment of Chronic Hepatitis B*. *Journal of Hepatology*. 2008; 8:60-6.

*Impact of the 1999 AAP/USPHS Joint Statement on Thimerosal in Vaccines on Infant Hepatitis B Vaccination Practices*. *MMWR*. February 16, 2001/50(06);94-7.

Inui A, Fujisawa T, Komatsu H, Sogo T, Sekine I, Kosugi T, Pediatrics, National Defense Medical College, Tokorozawa, Saitama; Pediatrics, Kanto Teishin Hospital, Shinagawa, Tokyo, Japan. *Long-Term Outcome of Chronic Hepatitis B in Children*. *Journal of Pediatric Gastroenterology and Nutrition*. Volume 31, Supplement 2, 2000, Abstract #1058 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Jenh, AM., Thio, CL, Pham, A. *Tenofovir for the Treatment of Hepatitis B Virus*.

Pharmacotherapy. 2009;20(10):1212-1227.

Jonas M, Kelley D, Mizerski J, Badia I, Areias J, SchwarzK, Little N, Greensmith M, Gardner S, Bell MS, Sokal E. *Clinical Trial of Lamivudine in Children with Chronic Hepatitis B*. New England Journal of Medicine. Vol. 346:1706-1713, May 30, 2002, No. 22.

Jonas, M, Kelly D, Pollack H, et al. *Safety, Efficacy, and Pharmacokinetics of Adefovir Dipivoxil in Children and Adolescents (age 2 to < 18 years) with Chronic Hepatitis B*. Hepatology. 2008;47:1863-71.

Kansu A, Kalayci AG, Berberoglu M, Girgin N, Öcal G, Ped. Gastroenterology, Ped. Endocrinology, Ankara University, Ankara, Turkey. *Evaluation of Growth in Children with Chronic Hepatitis B*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #1060 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Kansu A, Kalayci AG, Berberoglu M, Kuloglu Z, Girgin N, Öcal G, Dept. of Ped. Gastroenterology, Dept. of Ped. Endocrinology, Ankara University, Ankara, Turkey. *Thyroid Dysfunction in Children with Chronic HBV Infection Treated with Interferon Alpha*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #1061 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Karayiannis P. *Hepatitis B virus: old, new and future approaches to antiviral treatment*. Journal of Antimicrobial Chemotherapy. 2003; 51:761-785.

Kasirga E, Isenlik S, Aksoylar S, Kansoy S, Department of Pediatrics, University of Celal Bayar, Manisa; Department of Pediatrics, Tepecik Social Security Hospital, Izmir, Turkey. *Efficacy of Interferon Alpha-2B for Chronic Hepatitis B Virus Infection in Children with Cancer*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #208 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Koçak N, Özen H, Saltik IN, Gurakan F, Yüce A, Pediatric Gastroenterology, Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey. *Comparison of Lamivudine (LMV) with LMV+Interferon (IFN)-A Treatments in Children with Chronic Hepatitis B (CHB) Who Were Nonresponders to Previous IFN-A Treatment*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #1063 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Kutlu T, Cullu F, Erkan T, Tumay G, Pediatric Gastroenterology Unit, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey. *Lamivudine and Interferon Combination Therapy for Chronic Hepatitis B Infection in Children: A Preliminary Trial*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #443 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Lacaille F. Letter to the Editor. Hepatology. November 2000; 32:No. 5.



- Lai CL, et al. *Entecavir is superior to lamivudine in reducing hepatitis B virus DNA in patients with chronic hepatitis B infection*. Gastroenterology. 2002 Dec; 123(6): 1831-1838.
- Lai CL, Leung N, Teo EK, et al. *A 1-Year Trial of Telbivudine, Lamivudine, and the Combination in Patients with Hepatitis B e Antigen-Positive Chronic Hepatitis B*. Gastroenterology. 2005;129(2):528-536.
- Lampertico P, Viganò M, Manenti E, Iavarone M, Sablon E, Colombo M. *Low Resistance to Adefovir Combined with Lamivudine: A 3-Year Study of 145 Lamivudine-Resistant Hepatitis B Patients*. Gastroenterology. 2007;133(5):1445-1451.
- Liberek A, Luczak G, Bako W, Korzon M, Rytlewska M, Sikorska-Wisniewska G, Szlagatys-Sidorkiewicz A. *Prognostic factors in the treatment of chronic hepatitis B with interferon alpha in children*. Med Sci Monit. 2001 May;7 Suppl 1:127-37.
- Lim SG, Krastev Z, Ng TM, Mechkov G, Kotzev IA, Chan S, et al. *Randomized, Double Blind Study of Emtricitabine (FTC) Plus Clevudine Versus FTC Alone in Treatment of Chronic Hepatitis B*. Antimicrobial Agents and Chemotherapy. 2006;50:1624-1648.
- Lim SG, Ng TM, Kung N, Krastev Z, Volfova M, Husa P, et al. *A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B*. Archives of Internal Medicine. 2006;166:49-56.
- Livingston S, Simonetti J, McMahon B, Bulkow L, Hurlburt K, Homan C, Snowball M, Cagle H, Williams J, Chulanov V. *Hepatitis B Virus Genotypes in Alaska Native People with Hepatocellular Carcinoma: Preponderance of Genotype F*. Journal of Infectious Diseases. 2007;195:5-11.
- Lok ASF, University of Michigan Medical School. *Clinical Manifestations and Natural History of Hepatitis B Virus Infection*. UpToDate 2000, Medscape.
- Lok ASF, McMahon BJ. *Chronic Hepatitis B*. Hepatology. 2007 Feb; 34(2): 507-539.
- Lok ASF, McMahon BJ. *AASLD Practice Guidelines Chronic Hepatitis B: Update 2009*. Hepatology. 2009;50(3):1-36,
- Lyra P, Mota E, Cavalcante SS, Paes F, Dantas F, Barros F, Goes M, Filho A, Silva LR, Pediatrics, UFBA, Salvador, Bahia, Brazil. *Study About Obstetrician Diagnostic Practices for B Hepatitis*. Journal of Pediatric Gastroenterology and Nutrition. Volume 31, Supplement 2, 2000, Abstract #783 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.
- Manegold C, Hannoun C, Wywiol A, Dietrich M, Polywka S, Chiwakata CB, Gunther S, Klinische Abteilung, Bernhard-Nocht-Institut für Tropenmedizin, Hamburg, Germany. *Reactivation of Hepatitis B Virus Replication Accompanied by Acute Hepatitis in Patients Receiving Highly Active Antiretroviral Therapy*. Clin Infect Dis. 2001 Jan;32(1):144-148.

Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. *Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B*. New England Journal of Medicine. 2004;351:1206-1217.

McMahon BJ, Bulkow L, Harpster A, Snowball M, Lanier A, Sacco F, Dunaway E, Williams J. *Screening for Hepatocellular Carcinoma in Alaska Natives Infected with Chronic Hepatitis B: A 16-year Population-based Study*. Hepatology. 2000;32:842-846.

Mieli-Vergani G, Vergani D. *Practical Issues in the Management of Chronic Hepatitis B in Children*. Viral Infections in Liver and Hepatobiliary Disease, Pathophysiology and Therapy. Satellite Symposium at the 50<sup>th</sup> Annual Meeting of the AASLD, 1999.

Mitchell M, University of North Carolina School of Medicine. *Reports on New Therapies for Chronic Hepatitis B*. 51<sup>st</sup> Annual Meeting of the AASLD, 2000.

Molleston JP. (2006), *Management of Hepatitis B 2006*. Retrieved April 26, 2007 from [http://www.niddk.nih.gov/fund/other/hbv2006/25\\_percent20Molleston%20Abstract.pdf](http://www.niddk.nih.gov/fund/other/hbv2006/25_percent20Molleston%20Abstract.pdf)

Neudorf-Grauss R, Bujanover Y, Dinari G, Broide E, Neveh Y, Zahavi I, Reif S, Department of Pediatrics, Dana Children's Hospital, Tel Aviv Sourasky Medical Center, Israel. *Chronic Hepatitis B Virus in Children in Israel: Clinical and Epidemiological Characteristics and Response to Interferon Therapy*. Isr Med Assoc J. 2000 Feb;2(2):164-8.

Nevens F, DeMan R, Chua D, et al. *Effectiveness of a Low Dose of Entecavir in Treating Recurrent Viremia in Chronic Hepatitis B*. 51<sup>st</sup> Annual Meeting of the AASLD, 2000, Abstract # 869.

Nunen A, Hansen B, Mutimer D, et al. *Rare Study of Combination Therapy for Chronic Hepatitis B*. 51<sup>st</sup> Annual Meeting of the AASLD, 2000, Abstract #878.

Oon CJ, Chen WN, Goo KS, Goh KT, Ransome Research Laboratory, Singapore General Hospital, Republic of Singapore. *Intra-familial Evidence of Horizontal Transmission of Hepatitis B Virus Surface Antigen Mutant G145R*. J Infect. 2000 Nov;41(3):260-264.

*Oxxon Therapeutics Reports Positive Preliminary Phase IIa Data with Chronic Hepatitis B Therapeutic Vaccine*. Business Wire. November 11, 2005. Retrieved May 11, 2007 from [http://findarticles.com/p/articles/mi\\_m0EIN/is\\_2005\\_Nov\\_11/ai\\_n15791587](http://findarticles.com/p/articles/mi_m0EIN/is_2005_Nov_11/ai_n15791587)

Ozen H, Kocak N, Yuce A, Gurakan F, Department of Pediatrics, Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey. *Retreatment with Higher Dose Interferon Alpha in Children with Chronic Hepatitis B Infection*. Pediatr Infect Dis J. 1999 Aug;18(8):694-697.

Özkan T, Budak F, Meral A, Göçet N, Göral G, Özeke T, Dept. of Ped. Gastroenterology, Uludag Univ., Faculty of Medicine, Bursa, Turkey. *IL-12 and IFN $\gamma$  Levels in Children with Chronic Hepatitis B Receiving IFN Therapy*. Journal of Pediatric Gastroenterology and

Nutrition. Volume 31, Supplement 2, 2000, Abstract #196 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Özkan T, Tarim O, Sevinir B, Gider C, Özeke T, Pediatric Gastroenterology, Pediatric Endocrinology, Pediatric Oncology, Uludag Univ., Faculty of Medicine, Gorukle, Bursa, Turkey. *Hormonal Side Effects of Interferon-Alpha Therapy*. Journal of Pediatric Gastroenterology and Nutrition. Vol. 31, Supplement 2, 2000, Abstract #442 from the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition.

Palumbo, E. *Emtricitabine in Chronic Hepatitis B: A Mini Review*. Hepatitis Monthly. 208;8(2):125-127.

Personal interview with Dr. Anna Lok, Professor of Internal Medicine and Director of Clinical Hepatology, Division of Gastroenterology, University of Michigan, 2001.

Personal interview with Dr. Ardath Yamaga, Assistant Professor of Pediatrics, Division of Gastroenterology & Nutrition, Children's Hospital, Los Angeles, 2001.

Personal interview with Dr. Boris Kaganov, Professor and Deputy Director, Academy of Medical Science of Russia, 2001.

Personal interview with Dr. Brian McMahon, Clinical Hepatologist and Alaska Area Native Health Service, Director, Viral Hepatitis Program Anchorage, Alaska, Senior Medical Epidemiologist, Centers for Disease Control, Anchorage, Alaska, Alaska Native Medical Center, staff physician, Internal Medicine, Alaska Native Medical Center, 2001, 2007

Personal interview with Dr. Elizabeth Fagan, Professor of Medicine and Pediatrics, Rush Medical Center and Rush Children's Hospital, Chicago and Consultant to the Centers for Disease Control (CDC) in Acute Liver Failure, 2001.

Personal interview with Dr. Etienne Sokal, Service de Pédiatrie Générale, Université Catholique de Louvain, Cliniques St. Luc, 2001.

Personal interview with Dr. Flavia Bortolotti, Internist, Internal Medicine ward for adult patients, University of Padua, Italy, 2001.

Personal interview with Dr. Giorgina Mieli-Vergani, Professor, Paediatric Hepatology, Paediatric Liver Service, Institute of Liver Studies, King's College Hospital, London, 2001, 2007.

Personal interview with Dr. Kathleen Schwarz, Director, Pediatric Liver Center, Division of Pediatric Gastroenterology and Nutrition, and Professor of Pediatrics, Johns Hopkins University School of Medicine, 2001, 2003, 2007.

Personal interview with Dr. Leonard Seeff, Senior Scientist for Hepatitis C Research, National Institutes of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, 2001.

Personal interview with Dr. Lynda Brady, pediatric hepatologist, University of Chicago Children's Hospital, 2001.

Personal interview with Dr. Mei-Whei Chang, Professor and Chairman, Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan, 2001.

Personal interview with Dr. Michael Favorov, Centers for Disease Control and Prevention Central Asia Program Director, 2001.

Personal interview with Dr. Philip Rosenthal, Professor of Pediatrics and Surgery, Medical Director, Pediatric Liver Transplant Program, and Director, Pediatric Hepatology, University of California, San Francisco, 2001, 2003, 2007, 2010

Personal interview with Dr. Regino Gonzalez-Peralta, pediatric hepatologist, University of Florida, Gainesville, 2001, 2003.

Peters MG. *Special Populations with Hepatitis B Virus Infection*. Hepatology. 2009;49(5):S146-S153.

Peters, MG, Hann H, Martin P, et al. *Adefovir Dipivoxil Alone or in Combination with Lamivudine in Patients with Lamivudine-Resistant Chronic Hepatitis B*. Gastroenterology. 2004;126(1):91-101.

Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio S, Vianello L, Zanuso F, Mozzi F, Milani S, Conte D, Colombo M, Sirchia G. *Updated Definitions of Healthy Ranges for Serum Alanine Aminotransferase Levels*. Annals of Internal Medicine. July 2002, Vol. 137, p 1-9.

Rasi G, et al. *Journal of Viral Hepatitis*. 1996;3:191-196.

Roberts EA, Division of Gastroenterology and Nutrition, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada. *Why Treat Chronic Hepatitis B in Childhood with Interferon?* Gut. 2000;46:591-593 (May).

Rosenthal, P. *Hepatitis B Treatment in Children Today*. (2006). Retrieved May 5, 2007, from [http://www.hepb.org/pdf/Rosenthal\\_HBV\\_Treatment\\_Children\\_06.pdf](http://www.hepb.org/pdf/Rosenthal_HBV_Treatment_Children_06.pdf)

Schalm, SW. Editorial: *Lamivudine-interferon combination therapy for chronic hepatitis B: further support but no conclusive evidence*. Journal of Hepatology. Vol. 35 (3) (2001) pp. 419-420.

Schlager F, Schaefer S, Metzler M, Gratzki N, Lampert F, Gerlich WH, Repp R, Kinderheilkunde, Justus-Liebig-Universitat, Giessen, Germany. *Quantitative DNA Fragment Analysis for Detecting Low Amounts of Hepatitis B Virus Deletion Mutants in Highly Viremic Carriers*. Hepatology. 2000 Nov;32(5):1096-1105.

SciClone Pharmaceuticals International. (2003-2004), *Zadaxin: The Power to Fight Hepatitis B*. Retrieved July 14, 2007, from [http://www.scicloneinternational.com/hepatitis\\_b.shtml](http://www.scicloneinternational.com/hepatitis_b.shtml).

Shah U, Kelly D, Chang M, Fujisawa T, Heller S, Gonzalez-Peralta RP, Jara P, Mieli-Vergani G, Mohan N, Murray KF. *Management of Chronic Hepatitis B in Children*. Journal of Pediatric Gastroenterology and Nutrition. 2009; 48:399-404.

Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, et al. *Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B*. Gastroenterology. 2006;130:2039-2049.

Sokal E. *Hepatitis B in Children: Natural History and Therapy*. Bull Mem Academy R Med Belgium 2001; 156(7-9):367-75.

Sokal EM, Kelly DA, Mizerski J, Badia IB, Areias JA, Schwarz KB, et al. *Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B*. Hepatology. 2006;43:225-232

Sokal EM, Kelly D, Wirth S, Mizerski J, Dhawan A, Fredrick D. *The Pharmacokinetics and Safety of Adefovir Dipivoxil in Children and Adolescents With Chronic Hepatitis B Virus Infection*. Journal of Clinical Pharmacology. 2008;48(5):512-517.

Sung, JJ, Lai, JY, Zeuzem, S, et al. *Lamivudine Compared with Lamivudine and Adefovir Dipivoxil for the Treatment of HBeAg-Positive Chronic Hepatitis B*. Journal of Hepatology. 2008;48:728-735.

U.S. Food and Drug Administration. (2007, January-February). Updates. *FDA Consumer magazine*. Retrieved April 26, 2007, from [http://fda.gov/fda/dearts/2007/107\\_upd.html](http://fda.gov/fda/dearts/2007/107_upd.html)

Vryheid RE, Kane MA, Muller N, Schatz GC, Bezabeh S. *Infant and adolescent hepatitis B immunization up to 1999: a global overview*. Vaccine. Vol. 19 (9-10) (2000) pp. 1026 – 1037.

Westland C, Yang H, Fry J, et al. *Genotypic and Phenotypic Analysis of HBV Isolated From Patients Exposed to Adefovir Dipivoxil for up to 36 Weeks*. 51<sup>st</sup> Annual Meeting of the AASLD, 2000, Abstract # 1184.

Wong et al. *DNA Vaccine Stimulates Unique Immunogenicity for HBV*. 38<sup>th</sup> Annual Meeting of the Infectious Disease Society of America, 2000.

Yuce A, Kocak N, Ozen H, Gurakan F. *Prolonged interferon alpha treatment in children with chronic hepatitis B*. Ann Trop Paediatr. 2001 Mar; 21(1):77-80.

Zhang Y, Chen E, Yang J, Duan Y, Tang H. *Treatment with Lamivudine Versus Lamivudine and Thymosin alpha-I for e Antigen-Positive Chronic Hepatitis B Patients: A Meta-Analysis*. Virology Journal. 2009;6(63).