



HEPATITIS B FOUNDATION

B Informed Patient Conference

July 9-10, 2005

Doylestown, PA

INFORMAL CONFERENCE SUMMARY

HBF Disclaimer:

Please know that these conference notes are NOT official transcripts of the meeting! They are an informal summary that has been compiled from the notes of several people who attended, but are not experts in the field.

This summary is being made available as a courtesy only; therefore, please be sure to speak with your health care provider (or attorney if filing a disability claim) if you have any questions about the information in these notes.

INRODUCTION

The Hepatitis B Foundation (www.hepb.org), in collaboration with the Internet Hepatitis B Information and Support List (www.hblist.org), was pleased to host the 5th Annual *B Informed Patient Conference*, this summer. More than 80 people traveled from across the country (and as far away as Guatemala and Scotland!) to participate in this two day gathering of friends.

Between hearing about Wendy Marx who underwent two liver transplants due to chronic hepatitis B and transformed her experience into helping others, learning from experts in the field about disability and the latest treatment updates, and sharing informally with one throughout the weekend, this year's conference continues the momentum of building a strong and visible hepatitis B community of patients, families, health care providers and researchers.

SATURDAY, JULY 9, 2005

9:30 am Welcome – Molli Conti, VP for Community Outreach, HBF

On behalf of the Hepatitis B Foundation (HBF) and the Hepatitis B Support List (HB-L), Ms. Conti welcomed and thanked everyone for attending this year's conference. The goal of the meeting is to not only learn new information to help patients and families manage this disease, but to also make new friends and share experiences on a personal level.

The HBF is involved in a number of important national initiatives that is putting hepatitis B in the spotlight:

- National HBV Awareness Week – This year the U.S. Congress passed a unanimous resolution calling for the first ever National HBV Awareness Week, May 9-16, 2005! This was complemented by the “AIM for the B” awareness campaign that included two

patient forums (Phila and San Jose) and two media events (New York City and San Francisco). The HBF was the nonprofit sponsor in partnership with BMS.

- National Viral Hepatitis Roundtable (NVHR), which is a coalition working on a national strategy to eliminate viral hepatitis in the U.S. The final strategic plan is currently being reviewed by the NIH and CDC, and will be published this fall.
- First Congressional HBV Briefing – On July 21, 2005, the HBF has been invited to moderate the first ever Congressional Briefing on the problem of HBV in the U.S. This briefing was initiated by U.S. Sen. Rick Santorum (PA) and continues the momentum of the “AIM for the B” campaign started in May of this year.
- HBV Congressional Bill – U.S. Rep. Mike Honda (CA) has also continued to work with the HBF, and other nonprofit groups, towards the introduction of landmark legislation in Congress to promote and fund programs to increase HBV awareness, prevention, treatment and research. Hopefully, the HBV Bill will be introduced as early as this fall.
- Social Security Administration Briefing – HBF was invited to provide expert testimony as Social Security reviewed the “medical listings” for hepatitis B this past year. We were pleased to have testimony from members of the Hepatitis B Support List. Thank you!
- ACIP/CDC HBV Vaccine Recommendations – ACIP is reviewing the hepatitis B immunization requirements for adults and children. In June, the meeting focused on children, specifically strengthening the infant hospital birth dose recommendations. They will meet in October to talk about possible universal adult recommendations for HBV immunization, not just those considered to be at high-risk due to occupation or other risk factors. The HBF has been asked by the CDC to provide testimony at these meetings.

Ms. Conti concluded with a sincere thank you to the Hep B List for their ongoing support of the HBF efforts to provide education and support to patients and families, improve public awareness and knowledge, and increase research and research funding to find a cure. The HBF’s goal is to ensure that hepatitis B is not forgotten!

9:50 am Additional Comments – Dr. Timothy Block, President, HBF

Dr. Block believes that the HBF is becoming *THE* most important voice for hepatitis B advocacy and research and it is proud to have this responsibility. He is also pleased to say that the HBF is doing a remarkable job in outreach and advocacy, and this unique annual patient conference is just one example of the good work it does.

In research, HBF continues to advance its drug discovery program by screening more than 80,000 compounds. In less than a year, the HBF’s new research institute, called the “Institute for Hepatitis and Virus Research” (www.ihvr.org) has already identified a promising family of 3 compounds that show activity against the hepatitis B virus (HBV). Another example is that the HBF/IHVR proteomics lab has identified a serum marker to help determine who with chronic HBV will develop primary liver cancer, or hepatocellular carcinoma (HCC), which is one of the most serious consequences of chronic hepatitis B. This serum marker is now being developed in partnership with the “EDRN” at the National Cancer Institute of the NIH for studies in humans. It may prove to be more successful than AFP, the current blood test used to detect potential HCC development.

10:00 am Wendy's Story – Jeffrey Marx, Pulitzer Prize Winning Journalist

Mr. Marx is the author of "It Gets Dark Sometimes," which is the story about his sister Wendy who had two liver transplants due to chronic hepatitis B. He speaks publicly to raise awareness about the urgent need for organ donation and the problem of hepatitis B.

Mr. Marx began by saying, "Let me start with the fact that it's a privilege to join the HBF *Cause for a Cure* and to meet all of you today. During my many book tours, I have met a lot of people and I've learned that there are 'Go-givers' and 'Go-getters.' What impresses me most about the HBF is that it is full of 'Go-givers', people who actively pursue giving back to others in the community, locally and globally.

He then launched into the story of his sister Wendy Marx, who was his best friend and only sister. According to Mr. Marx, Wendy's story is a story of passion and purpose, of a life lived well. Although each person has their own story that's just as powerful as Wendy's, he hopes that his talk serves as encouragement and motivation to everyone at the patient conference.

There are four very important dates in "Wendy's Story" and the following summary is written in the "first person" to make it easier to appreciate the personal dimension of Mr. Marx's talk.

June 7, 1967 - In 1967, the hepatitis B virus was discovered; the first successful liver transplant was performed. And in this same year, my sister was born. How do I describe Wendy? Her laughter...it was constant and would always announce her arrival. She was so full of life, vibrant and connected to her family and friends. Kindness, integrity, passion and courage were her trademark characteristics. Courage, as Wendy lived it, is not the absence of fear, but rather, the courage to move on with dignity despite the fear.

Nov. 27, 1989 – Wendy was in a coma in a San Francisco ICU. Our family had been told that she had 24 hours to live unless she received a liver transplant immediately. Her diagnosis was acute fulminant hepatitis B. We think she was infected after her wisdom teeth extractions a few months earlier since she had only been diagnosed for a few weeks. At the time, she was one of 18,000 people in the U.S. waiting for a transplant of some kind and in 1989, 5 or 6 people died due to a shortage of organs. On November 27, we heard the four greatest words – "We have a donor"! Unfortunately, a 9 year old boy was in a fatal traffic accident, and instead of opening gifts the next day on his 10th birthday, he gave the greatest gift of all – the gift of life. Wendy's survival and recovery after the transplant was a miracle. And her commitment to organ donation was indelible. In 1990, we formed the Wendy Marx Foundation for organ donation awareness in partnership with Carl Lewis, the most decorated Olympic athlete the U.S. has ever had. Wendy created a message of hope for others and demonstrated living, breathing smiling proof that organ donation really works. The Wendy Marx Foundation produced a video about organ donor awareness for teens, launched the "Transplant Games" with Carl Lewis, and worked with Dr. Ruth on a campaign to reach teens at risk.

The primary things that Wendy and I shared during this time was the 10/90 Rule – that is, life is 10% what happens to you ,and 90% how you react to it. In other words, Wendy was thrown a curve ball, but she showed that you can live a full and vibrant life with chronic hepatitis B and post-liver transplant!

Oct. 28, 2003 – Although great progress had been made since 1989 in HBV treatments, Wendy needed to “keep treading water until the right life jacket was thrown to her.” She enrolled in many clinical drug trials in the hope of getting rid of her chronic hepatitis B infection that was destroying her new liver. Wendy passed away on Oct. 28, at the young age of 36 years. But we don’t measure her life in years, but rather, by how much she lived in the years she was given. Her life can be measured by the relationships she built, and the causes she fought for.

July 9, 2005 - More than 89,000 people are waiting for a transplant in the U.S. and today, 19 people die each day because of the shortage of organs (in 1989, there were 18,000 people on the transplant list and 5-6 deaths per day). These numbers are unacceptable and unnecessary. We need to talk to others about organ donation to solve this problem.

Mr. Marx concluded with an impassioned plea for people To Learn, To Think, and most importantly, To Talk. People need to be encouraged to take a negative experience and turn it into something positive for others, not only for themselves. Wendy did this. No one volunteers or signs up to become involved with the hepatitis B journey.

He reminded the audience that no one chooses to be chronically infected with hepatitis B. But the power to choose is still yours. What are you going to do from here forward? Try to remember and live by the 10/90 Rule – 10% is what life gives you, 90% is how you respond. The challenges are great, but if everyone works together, the obstacles can be overcome. Everyone needs to work within the current hepatitis B community; expand the numbers of people involved; and help others in your own community to learn, think and talk.

Ultimately, it’s not “Can I make a difference” -- it’s “Will I make a difference”. That’s the choice everyone has. And this is what drove Wendy. She became a symbol for the fight for organ donors and the fight against hepatitis B. Her favorite quote was, “I thank you from the bottom of my heart – and my liver – for allowing me this time with you.”

Q&A Session with Mr. Marx

* *Stigma* - Although it wasn’t part of Wendy’s experience, it’s an issue that affects many of those with chronic HBV. Need to increase education and awareness so the public doesn’t react with anxiety or hostility towards “hepatitis”. Also, need to encourage people to avoid seeing themselves as a victim of the disease. Remember the 10/90 Rule.

* *Education* - There are four major levels of education needed: public, news media, medical profession, and one’s self. Always need to start with yourself, and then reach out to others.

For more information about Jeffrey Marx , his book “It Gets Dark Sometimes”, and the Wendy Marx Foundation, visit <http://www.transplantbook.com>.

11:00 am *Hepatitis B Disability Issues* – Mark Silver, Esq., Silver & Silver

An overview about the disability process and how people living with chronic hepatitis B can qualify for disability benefits. Mr. Silver is a nationally recognized disability attorney.

Two disability programs currently available through the Social Security Administration (SSA).

Social Security Disability (SSD)

* Program for disabled workers who worked 5 of the last 10 years.
* Entitled to receive Medicare, 29 months after onset of disability

vs.

Supplemental Security Income (SSI)

*Program for uninsured workers.
*Essentially for those who qualify for welfare in their state.
*Eligible, if approved, for Medicaid immediately

The official definition of “*Disability*” – medically determined impairment expected to last at least 12 months (or result in death) and individual is unable to return to any past or other available work. *Practical test*: Can you work 5 days a week, 8 hours a day, and miss no more than 1-2 days a month?

Most people who apply to Social Security for disability benefits get turned down and have to go to a hearing before a judge. Individuals applying for disability are supposed to be re-evaluated every few years to see if they are still “disabled”.

What do you need to do?

- First, find a lawyer who is knowledgeable about disability. The rules change, and so do the judges hearing the cases. Therefore, your lawyer needs to be on top of these changes.
- Second, you don’t have to pay the disability attorney yourself. They are paid on a “contingency” basis, which means they only get paid if you are approved for disability and receive the funds! They usually receive 25% of the “back due” of the disability benefits (not future, though) if you are approved. This “back due” fee is governed by federal law (there is a cap around \$5,300, and the average fee is about \$2,500).

What kind of questions are asked in the disability application process?

1. Are you gainfully employed? Have you work fulltime in the past? If only part-time, then a different test is used. If you continue to earn more than \$800 per month, then you’re not eligible because you are considered to be “gainfully employed”.
2. If you are not working, then do you have a severe impairment that will last 12 months or result in death? Does it interfere with life activities or your job (examples: depression, serious breathing problems, chronic fatigue)?
3. Does the impairment meet or equal severity as defined in the “Medical Listings” (Social Security creates a “List” of diseases and the associated conditions that qualify as disabling.
4. Are you physically and emotionally capable of returning to your job or previous work
5. What is your ability to hold another job? Can you do other generally available work (could depend on your age, education, work background)? This is usually the most confusing step.

For example, two 55 year old men file for disability. One is a laborer, the other a physician. The laborer may qualify for disability because he can’t find other work

due to lack of “transferable” work skills. The physician, however, may not qualify for disability because he can transfer his skills – that is, even if he can’t see his patients, he could become an administrator or educator.

How do you file a claim for disability benefits?

- Go to the Social Security office in-person, telephone, or visit online at www.socialsecurity.gov. If your disabling problems are not easily identifiable, it is probably best to use the phone or visit the website.
- If you go in person, the clerk will surreptitiously take notes about you during the entire interview (do you appear to be in distress or pain, have trouble walking or sitting, shortness of breath, how you look, etc.). These notes are reviewed by the judge, in addition to your application. It is important that you don’t mask your problems.
- The government contacts a state agency to make a decision. The state agency may schedule a physical or mental exam if your own treating doctors don’t provide sufficient medical documentation.
- People are frequently discouraged by even their own doctors from applying for disability because most initial claims are denied and not all doctors understand all the rules about qualifying.
- If you persevere, then you are likely to be successful and the benefits will be granted usually retroactively.

What is the disability application process?

1. **Initial Filing** – Social Security staff will conduct the phone interview. Initial claims are denied 65% of the time, but there is much greater success on appeal.
2. **Hearing** – this is a formal, private, face-to-face meeting with an Administrative Law Judge. There are over 1,000 in the U.S. (60 in Philadelphia area) and it is supposed to be “non-adversarial”. At the hearing level, most claims are approved (60% nationally, 75% with a lawyer, and even greater success with a disability attorney). PA has faster turnaround than most states.

The Judge can bring in a medical advisor to help them understand your illness – Hep C is seen a lot, Hep B is not. If your problem is not common, then you need to educate the judge about your condition or disease. A disability lawyer is helpful with this. The hearing can be 30 minutes to 3 hours, and is private.

3. **Appeals Council** – this is a second chance for your application. If the decision is unfavorable, you have 60 days to appeal to the Appeals Council. At this point, only 2% are reversed, but 26% are remanded or sent back to the judge. Often Remands go to the same judge, and most will be positive at the remand (usually another year has passed and there is more documentation of the illness).
4. **Federal Court** - If the appeal is denied, it goes to federal court. About 6% of appeals are reversed, 40% are remanded, and the good news is that if you are approved, the government pays your attorney fees!

Social Security Administration’s Regulations on the Digestive System/Liver

Social Security has created “medical listings” for every disease that qualify as disabling. Conditions must last 12 continuous months. The listings for viral hepatitis need to be changed, but this has not yet happened.

Currently, chronic liver disease includes “chronic active hepatitis”, with:

- Esophageal varices, bilirubin of 2.5 or higher, persistent for 5 months
- Ascites
- Hepatic encephalopathy
- Liver biopsy, which confirms chronic disease

Why Your Doctors are So Important

Your doctors are important because they are needed to provide “Medical Source Statements” with your disability application where your doctor provides a professional opinion about how the disease affects you and your ability to work on a daily basis. It documents your physical, mental, and stress exertions, and how much you can do.

When filing a disability claim, your medical records are reviewed carefully for a history of symptoms such as chronic fatigue, pain, depression, or anything that would interfere with your ability to hold a fulltime job. The diagnosis is secondary to your symptoms, so tell your doctor at every visit about ALL of your symptoms (you’re tired, you take regular naps, have trouble sleeping at night, etc.) and all of the side effects from any treatment so that your medical records include everything that could support your disability claim.

It often takes 1 to 2 years to go through the disability claims process. Remember – persevere, appeal, and get good legal representation. Your doctor is an important ally in this process, and it is important to have a good relationship so he or she will make a strong medical case for your claim.

Final Recommendations

- Use your benefits from work (long and short term disability plans) during the disability claim process.
- For those who can’t afford doctors, qualify for public assistance, or locate low cost medical clinics to initiate treatment and document your symptoms and disabilities.
- For those who look healthy, do not apply in person! Use the phone or visit the website. At the hearing, the judges are usually more knowledgeable and will not use your healthy appearance against you.
- Should you work part-time while going through this process? You will not obtain benefits if you earn more than \$800/month, or run your own business and make all of the decisions.
- If you work part-time, does it help with the amount of disability benefits you get? Possibly – any additional earnings credited on your record may increase your benefit amount.
- There is a “Trial Work Period” – after you have qualified for benefits if you work and earn over approximately \$550.00/month in each of 9 months during a 5 year period, you may only qualify for an additional 36 months of benefits, after which are no longer considered disabled. If you can’t complete the 9 months, coverage continues.
- The “Ticket to Work Act” Social Security Administration has a new program where they will help you find a job and pay for training. You will continue to qualify for the medical benefits for 8 years if you go through this process.

Where can you find a disability attorney?

(1) The National Organization of Social Security Claimants' Representatives (NOSSCR) – www.nosscr.org – maintains a directory of attorneys listed by state, and most of them practice exclusively disability law.

(2) Contact Mike Silver, Esq., Silver & Silver, former President of NOSSCR, at msilver@silver2law.com, 42 W. Lancaster Avenue, Ardmore, PA. Most of Mr. Silver's work is done in PA, NJ and DE.

[Note: Be sure to visit www.hbvadvocate.org - Chris Kukka, HBV educator and advocate, is creating a handbook to help with short and long-term disability applications for people living with chronic hepatitis B who work. She explains that the basic definition for hepatitis B will not get most people covered by disability, but that patients can use other symptoms to help qualify (medication side effects, fatigue, etc).]

12:00 pm– Lunch and Tour of HBF Research Facilities by Dr. Tim Block, HBF President

2:00 pm Surprise Award Presentation by the HB-List!

Lorena and Ian presented beautiful Crystal Awards, designed by Michelle K., on behalf of all the patients, families and friends of the HB-List to Steve Bingham and Sheree Martin, list co-owners, for providing so much love and support through their Hep B Info & Support List. They also presented Tim and Joan Block, HBF co-founders, with a crystal award for the Hepatitis B Foundation's dedication and persistence in the *Cause for a Cure*.

2:15 pm “Everything You Wanted to Know About Hepatitis B, But Were Afraid To Ask”

Dr. Tom London, Dr. Minh Nguyen, Dr. Ken Rothstein, and Dr. Eddie Cheung

This was designed to be a highly interactive session with a panel of hepatitis B experts available to answer any and all questions from the attendees. There was no fixed agenda and Steve Bingham moderated this very lively and informative 90 minute dialogue!

Please note, questions were answered by different panelists, therefore, each bullet point represents a different doctor's response.

1. As an HBV carrier, how would I know whether I need treatment?

- It sounds like you're wondering how you will “feel” before requiring treatment. Most people feel OK, but nevertheless may need treatment. Once you feel “bad”, the liver disease could be quite serious. This is why you need to be regularly screened by your doctor.
- A treatment decision is based on inflammation (i.e. how high is the ALT?), viral DNA levels, physical exam, and perhaps a liver biopsy to see if there is any liver damage.

2. How often should I be seen by my liver doctor?

- Ideally you should see your doctor every 6 months, but there is no magic number. Some doctors want to see their patients every 2 months, but this is not realistic for everyone.

Some doctors say once a year is fine. But in general, every 6 months is a reasonable recommendation.

3. *Many patients experience “liver pain” on the right side – what causes this pain?*

- There are many reasons a person might feel right sided pain, and think it’s the liver. Pain can be caused by stomach problems, ulcers, heartburn, constipation - all of these symptoms occur in the right upper quadrant, where the liver is. People with chronic liver disease might be more sensitive to this type of pain.
- 75% of patients periodically have pain or discomfort in the right or left side of abdomen. The use of mild analgesics - Tylenol or NSAID – might help with this pain.

4. *What do you treat with, if at all, during the “immune tolerant phase”, when there is high viral load and little clinical evidence of disease?*

- It is very controversial; take a “wait and see” approach since the data is unclear and there is always a concern about viral resistance.
- Agrees, but treatment is becoming more liberal – don’t always wait until the ALT is 100; can treat if ALT is lower and viral load is a bit lower because there are more drugs, and better drugs; can be more liberal about when to start therapy. The key is immune response potential, which is best measured by ALT. The danger of treating high viral load with an oral drug is that resistance is likely to develop. Therefore, treating with two drugs like lamivudine or entecavir and adefovir may make sense because the resistance to one drug will be offset by sensitivity to the other drug.
- This is a complicated decision. You can’t always rely on or look at the ALT; may need a liver biopsy for a better evaluation of the situation (for example, immune tolerant people with evidence of fibrosis may need to be treated even if they have low ALT). Interferon needs an immune response to work and there is the issue of viral resistance to oral anti-viral drugs, but with new medications, there are now and will be more alternatives.

5. *If a 7 year old child has ALT 109 and a liver biopsy shows Stage II fibrosis, is this a point where there is obvious damage to the liver and is it time to treat?*

- Stage II fibrosis means that you are halfway to cirrhosis and the elevated ALT reflects inflammation. This is significant in a child – there is a strong indication to treat and try to turn the disease into an inactive state. Interferons might be more effective in this case than the oral agents, but there is some toxicity and inconvenience. Interferon slows down progression of disease – this is a goal, to slow down the disease until better drugs come along to cure it. Would consider off-label PEG interferon since it’s been well tolerated in children with HCV. Whichever treatment is used, would try to be aggressive.
- Would probably start with interferon since it has a limited duration (usually 48 weeks) and there’s no risk of viral resistance. Not sure what the long-term effects the oral drugs would have on a developing child. Since some kids might have to take treatment for years, the drugs could affect renal function, and have other unknown developmental side effects. Agrees that the results for PEG interferon look good.
- In a young patient with a strong, motivated family and evidence of liver damage by biopsy, normal ALT and high viral load, interferon makes sense, especially because of the finite length of treatment. Knocking down the viral load will help physically and mentally.

6. ***What happens when a person has stage II fibrosis, has “e-Antigen seroconverted” (the eAg+ converted to eAg-), ALT is normal, and DNA is almost undetectable?***
- There is no evidence for treatment with the available drugs right now. There are other factors that can impact fibrosis, such as smoking, increased age, alcohol, diabetes, being overweight, etc. However, this person is still at risk for liver cancer and needs to be screened closely – with ultrasound and AFP blood test at least every 6 months.
7. ***At what stage of fibrosis do you NOT recommend treatment with interferon?***
- Age, medical conditions, inflammation, viral load, ALT are all taken into consideration.
 - If someone comes in with low platelets, you hesitate to treat. If their bilirubin is high (which can indicate decompensated liver disease), would also not start on interferon.
8. ***Would you use PEG interferon in kids, even though it is not approved yet?***
- Yes, it is used all the time in children with hepatitis C. Research seems to say that it is very well tolerated in kids.
9. ***If regular interferon is not successful, would you put an adult patient on PEG interferon?***
- I would probably just go to the oral drugs.
10. ***If you are treated with interferon and it does not work, have you lost ground by being on it?***
- There have been attempts to study this. Studies imply that a patient’s lifetime risk of HCC and cirrhosis is still lower with long-term interferon, even if it does not work.
11. ***Are side effects worse with PEG interferon vs. regular interferon?***
- Patients say the side effects are the same as regular interferon, but they tolerate the PEG more easily because there is only one weekly shot (instead of 3 shots a week). Because PEG interferon lasts longer in the body, any side effects can be more severe, such as depression. With PEG, there is also a 10-15% increased incidence of pulmonary problems, such as pneumonitis. You need to have a good relationship with your doctors and be sure to tell them all of your symptoms to avoid problems.
12. ***Should I consider PEG interferon with a history of chronic HBV for 10 years, normal liver enzymes, e-antigen positive, normal liver biopsy 10 years ago, and DNA that is slowly increasing after being on Adefovir for two years (viral load was in the billions before treatment – went down to 182,000 - and now it is rising and up to 2 million)?***
- Need to remember that people who respond best to interferon have signs of liver inflammation, which is confirmed by an elevated ALT – without signs of inflammation, there is a decreased chance of responding to interferon. In this case, it appears that resistance to oral drugs has occurred, and combined with a normal ALT, this patient is probably not a good candidate for interferon.
 - Might consider switching to another oral agent before thinking of going to interferon. It looks like the virus is becoming resistant to oral treatment, so it might be time to switch drugs. There has never been a study about switching from oral drugs to PEG, so it is hard to have a clear answer. Since the oral meds became available, very few patients have chosen interferon because of the injections and side effects. The only studies compare

PEG-interferon with lamivudine, but there are no studies of interferon treatment for people who fail oral antivirals.

- The key thing to remember is that your first treatment is probably your best shot at a cure.

13. *A recent study compared regular interferon and PEG interferon, and it suggested that if you increased the dose of PEG interferon for heavier people, it might be more effective?*

- Very controversial. Does seem to make sense, however, and some studies show that heavier patients do not respond as well to treatment as other patients. PEG interferon dosage is calculated on a person's weight; whereas, regular interferon dosage is not dependent on weight. Certainly need more studies to answer this question.

14. *With PEG interferon, if there are no side effects in the beginning, will they show up later?*

- Most patients experience symptoms in the beginning, but some people do experience symptoms later during treatment.

15. *I responded to PEG interferon and am now HBsAg- and HBsAb+. My doctor says that I'm "cured" and that he never wants to see me again. Does this make sense?*

- Your doctor should continue to see you at least once a year since viral DNA and HBsAg can return. You are also still at greater risk for liver cancer than someone who has never been infected with HBV, so you should be screened for liver cancer every year.
- Although we do not know what the natural history will be in patients who lose the virus and develop surface antibodies, it is important to keep checking. Again, liver cancer is still a risk and should be screened for regularly.

16. *I was on lamivudine for 3 years and lost my e-antigen; I tried stopping after a year, but converted back to e-antigen+ (I never developed positive e-antibodies and my DNA increased). So I went back on lamivudine and am now still e-antigen+ with a normal ALT and undetectable viral load. Should I stop before I develop resistance?*

- This is a tough call. Probably would not change right now – wait to see what happens.
- Make sure your DNA test is the most sensitive it can be. Stay on lamivudine, but if resistance develops, then try another oral antiviral drug.

17. *What is the future for combination treatment – first using an antiviral to decrease viral load and then starting interferon?*

- Combination is the future of treatment, but safety of the drugs right now is an issue, so we are left with sequential treatment. Right now combination of lamivudine and adefovir may be useful.

18. *What about CT scans vs. ultrasounds and MRI for liver cancer (HCC) screening?*

- CT scans and MRI are reserved for those who have cirrhosis. A European study showed that ultrasounds can miss 1/2 of all liver cancers and MRIs can miss 1/3 of cancers. In a non-cirrhotic liver, it is easier to see a lesion via ultrasounds (it is more difficult with a cirrhotic liver). There are cirrhotic livers, however, that look normal on ultrasound, but you can still miss a tumor. For example, you can have a "normal" ultrasound, CT scan,

and MRI, but a liver biopsy can reveal cirrhosis. There is still controversy as to which imaging technique is better.

- If you use CT, you need intravenous (IV) contrast in order to see a new hypervascular lesion, or you might miss the tumor.
- We use a triple-phase CT, which is the best way to pick up a tumor. Having a normal ultrasound, CT scan, or MRI, does not rule-out cirrhosis (only a liver biopsy can accurately rule out cirrhosis). Once a patient has cirrhosis, ultrasound is not adequate for screening.

19. *Should I be concerned about the higher radiation risk from a CT scan? Since it has 20 times more radiation than an X-ray, is a CT scan twice a year dangerous?*

- Yes, you should be concerned. Although MRIs are more expensive, they are preferable because there is less radiation. But some patients do not want MRI because it can cause feelings of claustrophobia. Some doctors feel that CT scans are better for liver cancer screening.

20. *What is the prognosis of liver cancer (or HCC) due to chronic HBV?*

- Liver cancer, if found early, can be cured. Transplantation is preferable to resection. The success of transplanting cancer patients is just as good as those without cancer. Radio Frequency Ablation (RFA) slows down the liver cancer, but does not cure it. However, RFA can be useful while waiting for a liver transplant.
- We need to find better treatments so that people don't end up with HCC. Outside the U.S., people cannot get a liver transplant due to lack of money, access and resources. The goal is to make HBV treatments accessible to the world so that patients don't get liver cancer.

21. *If you are treating a young patient who has never been on treatment, what antiviral would you use first?*

- Every doctor will give you a different answer depending on their experience and preference.
- Would probably shy away from lamivudine. Might use a combination such as adefovir and lamivudine.
- Lamivudine resistance predisposes you to entecavir resistance, so by starting with it, you might be excluding yourself from two drugs. That is, if you develop resistance to lamivudine, your only option is adefovir since entecavir is not effective against lamivudine resistant virus. Currently, there are only 3 approved oral antivirals – lamivudine, adefovir and entecavir.

22. *What is the goal of treatment, if you are already e-antigen negative?*

- The goal is to achieve a lower viral load, normal liver enzymes, and a better histology on liver biopsy. The tough decision is to know when to stop treatment.

23. *How do you talk to your doctor when you disagree and are well informed about management and treatment issues?*

- Be polite! Ask question such as, "Have you heard about this....", or "Would you consider using a CT scan instead of an ultrasound for liver cancer screening?" Start with open-ended questions to encourage conversation rather than confrontation.

- Tell your doctor about this patient conference and all the information you learned at the HBF. Offer to share this new information and literature. Tell them you belong to an online support group where you learn a lot. If you have an unreasonable person, then there is not much you can do but find another doctor. But most will be reasonable if approached with courtesy and sincerity.

- 4:30 – 5:30 pm** **Break-Out Sessions** (unfortunately, there are no notes available)
- **HBV 101** – Fonta Reilly & Peggy Farley, HBF
 - **Parent Issues** – Chris Kukka & Maureen Kamische, HBV Educators
 - **API Task Force** – Chari Cohen & Molli Conti, HBF

SUNDAY, JULY 10, 2005

9:30 am *Current and Evolving Therapy of Chronic Hepatitis B – Dr. Rajender Reddy*

An update on the treatment options for those living with chronic hepatitis B is essential now that there a total of 5 approved drugs for HBV (interferon alpha, PEG interferon, lamivudine, adefovir, and entecavir).

Please note, these session notes were not reviewed by Dr. Reddy; therefore, there may be unintentional inaccuracies or errors. Be sure to discuss any of this information with your personal health care provider

Dr. Reddy started his presentation with the following overview: hepatitis B is a global health problem. The burden of hepatitis B infection in the U.S. includes about 75,000 new infections, 5,000 deaths, 3,100 cases of liver cancer or HCC, and 230 liver transplants due to chronic hepatitis B per year. There are at least 1.25 million Americans who have been chronically infected with the hepatitis B virus (HBV).

Chronic hepatitis B is the 6th leading indication for liver transplantation in the U.S. (this represents about 5% of all liver transplants). Most liver transplants in the U.S., however, are due to hepatitis C.

The following sections represent the different topics covered by Dr. Reddy, but he has not had the opportunity to review these notes for accuracy. So please be aware that there could be errors or inaccuracies in the following summary. Remember, talk to your health care provider if you have any questions about the management and treatment of your condition!

HBV disease progression – exposure to HBV can result in a chronic infection, and this progression depends on your age at infection. The younger you are, the greater the risk of developing chronic HBV. This is why it is important to institute effective prophylactic measures, such as immunization at birth and young childhood, to prevent HBV transmission.

Chronic HBV infections - need to be prevented because 30% of those with chronic HBV may develop cirrhosis, and 5-10% may develop liver cancer. Of those who develop cirrhosis, 6% will develop liver cancer in 5 years.

Acute flares – these can happen in chronic HBV infections. Physicians may even think it is a new infection. The virus can switch back and forth from a zero to low replication state to a high replication state. An acute flare can cause various symptoms depending on the severity of the flare and the extent of liver disease. Regardless of whether you are being treated or not, you should be followed by a doctor to monitor for possible flares.

HBV Reactivation and Chemotherapy - HBV reactivation is a serious risk if a patient starts any chemotherapy or immunosuppressive therapy, such as steroids.

Patients should be started on an oral prophylactic treatment, such as lamivudine, before starting any kind of chemotherapy or immunosuppressive therapy!

Patients should stay on the oral antiviral for the duration of therapy and at least 6 months after therapy is stopped to ensure suppression of the virus. HBV reactivation must be prevented in these therapeutic situations because it could lead to acute liver failure, and possibly even death.

HBV reactivation is an issue even if a person has undetectable viral DNA or has “recovered”.

Therefore, patients undergoing chemotherapy or immunosuppressive therapy should be asked whether they have ever been infected with HBV and should also be tested for the hepatitis B surface antigen (HBsAg). It's not expensive to test for HBV, and it could save lives from liver failure!

Question: *What about steroid inhalers or cholesterol-lowering drugs like the statins?*

Answer: *There is no data on steroid inhalers and HBV reactivation. Statins are not contraindicated in someone with HBV or liver disease; however, doctors regularly monitor the liver enzymes while patients are on a statin.*

Clinical Profiles of HBV

- A chronic HBV diagnosis cannot be made without a “hepatitis B surface antigen” blood test (HBsAg).
- It is uncommon to see replicating states in HBV and HCV co-infections. One virus typically dominates over the other.
- ALT – the usual normal range is 5-40. ALTs are different for people depending on their age, lifestyle and overall health. The “normal ranges” have to be adjusted for different health/weight conditions.
- HBeAg-negative is present in the “*immune tolerant phase*” (the e-antigen test is used to determine if a person’s HBV is actively replicating or reproducing).
- “*Immune tolerant phase*” – occurs when a person is infected early in life and the body doesn’t recognize the virus as “foreign”, but instead, “tolerates” the virus without attacking it. In this phase, a person has a normal ALT and high viral load - liver biopsies are mostly normal or show moderate disease. The ALT may fluctuate. When it comes to treatment, the risks and potential success should be considered before deciding to treat.
- “*Inactive HBsAg carrier state*” – represents an infection where the virus is not actively replicating (or reproducing). It includes positive HBsAg, negative HBeAg, normal ALT, low DNA, and normal histology on a liver biopsy. Traditionally, these patients do not benefit from treatment.
- *HBeAg-positive chronic HBV* – represents the “wild type” HBV infection that includes positive HBsAg, positive HBeAg, negative HBeAb, high ALT and high viral load.

- *HBeAg-negative chronic HBV* - represents a “precore mutant” HBV infection that includes positive HBsAg, negative HBeAg, positive HBeAb, high ALT, high viral load (one log lower than eAg-positive patients), active histology on liver biopsy. This patient will require treatment for an indefinite period, and there is a relatively high relapse rate when treatment is discontinued.

Natural history / historical studies of HBV - HBV vaccination and its effects on liver cancer and mortality have been studied extensively in Taiwan. Results show that in Taiwan, children from ages 6-14 had a decrease in the incidence of liver cancer from 0.70 to 0.36. Mortality was decreased from 0.80 to 0.34. These studies support the importance of universal HBV vaccination in significantly decreasing the risk of liver cancer and death from chronic HBV infections.

Hepatitis B Virology – the key point to finding a cure for HBV is to eradicate cccDNA. This is a stable intermediate in the virus life cycle and serves as template for viral protein production (i.e. mRNA). There are currently no drugs that get rid of cccDNA. Future treatment research must focus on cccDNA elimination because it is key to getting rid of the virus itself.

Global distribution of HBV genotypes - There are 8 HBV genotypes. Although there are no commercially available tests and doctors do not test for genotypes, research studies have shown that “genotype A” has the best response to therapy. As time goes by, we will start seeing genotype tests being done to determine potential response to therapy and/or risk of liver cancer.

Every genotype can be found on every continent, but there are certain types that are found more frequently in certain geographic areas (see table below):

<i>North America</i> – A, B, C, D	<i>Europe</i> – A, D, G	<i>Asia</i> – B, D
<i>Central America</i> - H, F	<i>South America</i> – F	<i>Africa</i> - A, D, E
<i>Australia</i> - A, B, C, D		

Goals of Therapy

- There are several treatment endpoints. In “wild type”, e-Antigen seroconversion (the loss of e-antigen and appearance of e-antibody), undetectable DNA, normal ALT, and histological improvement are the usual markers of success. Loss of hepatitis B surface antigen would be ideal, but this is rare and isn’t expected.
- Loss of cccDNA is possible with interferon therapy, but not common. A liver biopsy is needed to determine if there has been cccDNA loss. If a patient loses the hepatitis B surface antigen and develops positive surface antibodies, then you don’t usually worry about cccDNA.
- *Is “HBsAg seroconversion” the same for someone who spontaneously clears the virus after an acute infection vs. someone who clears the virus after treatment?* The end result may be the same, but the extent of possible liver injury is different since the person who was on treatment probably had more liver injury than someone who had an acute infection. But this isn’t known for sure. HBV reactivation isn’t usually seen with HBsAg seroconversion.
- *Are the treatment goals the same for e-antigen negative HBV infections (i.e. the precore mutant)?* No, since e-antigen seroconversion cannot be a goal in these patients. There is a high relapse rate if treatment is stopped; therefore, long-term treatment is the rule.

- *Is the cirrhotic patient different for the e-antigen positive or “wild type” infection?*
Patients with cirrhosis should be treated indefinitely even after achieving the endpoints.

HBV DNA Assays – There are different types of viral assays (tests) used to measure HBV DNA levels. Some are more sensitive than others. Use of different assays depends on the insurance company’s contract with a lab! Patients should know which type of assay is being used since DNA levels can vary with different types of assays (or at least should use the same lab to obtain consistent results, which is helpful in monitoring or evaluating treatment).

- Qualitative PCR (polymerase chain reaction) – most sensitive
- Quantitative PCR (Amplicore) – 2nd most sensitive test, but Dr. Reddy prefers this one
- bDNA (Versant) – branched DNA assay
- Hybridization (Abbott and Digene) – not used anymore

[DNA Conversion rate: 1 pg = 283,000 copies]

Clinical significance of viral replication - Viral replication leads to continued inflammation of the liver (will see elevated ALTs) and worsening histology on liver biopsy, including cirrhosis and then liver cancer. BUT, viral replication can also lead directly to liver cancer without the development of fibrosis or cirrhosis!

How high should the DNA levels be to justify treatment? This is an ongoing debate since there are risks associated with treatment as long as mutants and resistance occurs with current therapies. In general, though, high DNA levels are not considered to be good.

There is also no clear answer as to what the viral DNA level needs to be that will determine the risk of developing liver cancer. One of the factors that play a role in the development of liver cancer is the age at which a person is first infected. The American Association for the Study of Liver Diseases (AASLD) is in the process of developing guidelines for liver cancer surveillance based on consideration of lifestyle, age, ethnicity, etc.

How often would you recommend liver cancer screening for perinatal infection, high DNA? Every 6 months. Although data shows there is no clear advantage for screening between 6 and 12 months, every six months is the general standard of practice. Screening currently includes ultrasound and the blood test, alpha-feta protein or AFP test. The AFP blood test is controversial since it misses so much cancer. Some doctors would rather not use AFP, but others swear by it.

What is the best, most sensitive way to detect liver cancer? MRI is a diagnostic test rather than a surveillance tool. CAT scan exposes a person to increased radiation. Depending on age, you could subject a patient to 46 MRIs over 23 years and they may or may not ever develop cancer. Universally this decision is based on what is cost effective.

Five HBV Treatment Guidelines

1. **U.S. Algorithm** – 2004 (Keeffe, et al.) – These guidelines are a position paper that are used most frequently since they are user friendly and take a more aggressive approach to treatment.
2. **AASLD (U.S.)** – 2001/updated 2004 (Lok & McMahon) – These guidelines are evidence based and considered to take a conservative approach to treatment.

3. **NIH Conference (U.S.) – 2000/updated 2001 (Lok & Hoofnagle)** – These guidelines are a position paper based on a NIH workshop that focused on HBV treatments in 2000.
4. **EASL (Europe) – 2003 (deFranchis, et al.)** – These guidelines are evidence-based and recommend interferon alpha as a first line treatment.
5. **APASL (Asia) – 2003 (Liaw, et al.)** – These guidelines are a consensus statement.

Treatment of HBV patient with cirrhosis

- For patients with cirrhosis, treatment should be more aggressive. If they have decompensated cirrhosis, then treat with an oral antiviral and refer for liver transplant evaluation.
- 20% of patients with cirrhosis who had spontaneous e-antigen seroconversion risk reversion, which is why they should be treated indefinitely. If there is no cirrhosis, then the reversion rate is much lower.
- In patients with “wild type” chronic HBV, there is a histologic improvement in cirrhosis after 3 years of lamivudine therapy. This theory is now being debated.

Currently, there are 5 approved drugs for chronic HBV

1. Interferon alpha (IFN) - approved 1991

In 1993, a meta analysis showed that with interferon alpha there was 8% loss of hepatitis B surface antigen, 33% loss of e-antigen (not seroconversion, though), and 37% undetectable HBV DNA (but in 1993 the cut-off for undetectable DNA was $<10^6$, which is higher than today because tests are now more sensitive).

2. Lamivudine (LAM) – approved 1998

3. Adefovir (ADV) – approved 2002

4. Entecavir (ETV) – approved April 2005

5. PEG interferon (PEG) – approved May 2005

PEG Interferon (PEG) – approved May 2005

- With PEG, 32% of *eAg positive* patients had suppression of viral DNA $<100,000$ copies and 41% had normalization of ALT. With combination PEG and LAM, eAg seroconversion occurred in 27% and there was 34% DNA suppression. From this data, it appears there is no real advantage for combination treatment with PEG and LAM for e-antigen positive patients. This will probably be the same case with other oral antivirals (*according to a study reported by G. Lau in Hepatology 2004*).
- Combination of PEG and LAM in *eAg negative* patients is no better than monotherapy with PEG. With PEG alone, there was 43% DNA suppression $<20,000$ copies and 59% normalization of ALT. With combination therapy, there was 44% DNA suppression and 60% normalization of ALT (*according to a study reported by Marcellin in the New England J. of Medicine 2004*).
- With PEG, e-antigen loss by Genotype: A = 47%, B=44%, C = 28%, D = 25%

- Appears there is a greater chance of hepatitis B surface antigen loss in eAg positive patients with PEG than with LAM (3-7% with PEG, and 0-<1% with LAM). But there was no difference between PEG alone or in combination with LAM (*according to three different studies by Janssen, Marcellin and Lau*).

Lamivudine (LAM) – approved 1998

5 year Asian Trial in e-Antigen positive patients (Lai CL., 1998, NEJM)

After 5 years on LAM: Total eAg seroconversion was 50%

Those with YMDD variant, 38% eAg seroconversion

Those with non-YMDD variant, 78% eAg seroconversion

**Patients with YMDD mutant had the lowest eAg seroconversion rate.

Who will develop YMDD variant?

- Need to look at viral DNA levels: If there is effective viral suppression with therapy at 24 weeks, then continue LAM.
- If DNA is $>10^4$ after 24 weeks, then consider adding or switching to Adefovir, because there is a 64% chance of developing the YMDD variant since therapy is less effective in suppressing the virus.
- People who respond by 24 weeks have a much decreased risk of developing YMDD variant while on LAM (i.e. the less virus in you, the less risk of mutations developing).

Durability of e-Antigen loss with LAM

- This ranges from 77 – 90%, depending on which study you look at.
- Relapse rate depends on the duration of treatment after eAg seroconversion – studies show that LAM needs to be continued at least 6 months after eAg seroconversion to decrease risk of relapse (2 months extra LAM after seroconversion = 43% relapse rate; <6 months extra LAM after seroconversion= 20% relapse rate).

Adefovir (ADV) – approved 2002

Adefovir is effective against lamivudine resistance (mutations); has a low incidence of resistance, and has a long to indefinite duration. Only concern is potential kidney toxicity, so patients need to be watched closely while on the drug.

- **e-Antigen seroconversion** occurs in about 14% of patients in the first year of adefovir treatment (vs. 30% with interferon alpha). This jumps to about 46% seroconversion in the 3rd year of adefovir treatment.
- **Durability of e-Antigen seroconversion** is very good with ADV – about 90% when treatment is stopped (studies have evaluated durability up to 114 weeks off treatment).
- **Surface antigen loss** in pre-core HBV (eAg-negative) is about 3.2% (this is not complete eAg seroconversion, though).

- **Cumulative incidence of resistance** (or development of viral mutations) with adefovir is low (0% first year, 3% 2nd year, 11% 3rd year, and 18% 4th year) compared to lamivudine (24% first year, 42% 2nd year, and 70% by the 4th year).
- **Clinical profile of resistance** depends on comparing pre-treatment (or baseline) ALT and DNA levels with post-treatment values to evaluate any increases (for example, is the DNA increase within a log or two?).
- Adefovir resistance is different than lamivudine resistance.
- Consider starting both ADV and LAM together to avoid developing either resistance.

Entecavir (ETV) – approved March 2005

Entecavir is the most potent oral HBV antiviral to date. It results in the greatest suppression of viral DNA than any other HBV drug at this point. There is also no development of mutations (or resistance) after 1 year of treatment in “wild type” HBV infections.

Entecavir vs. Lamivudine in e-Antigen positive patients after 1 year of therapy

- With Entecavir, DNA suppression <400 copies/ml is 69% vs. 38% for LAM.
- There are no mutations after one year of therapy (vs. 24% resistance with LAM).
- If entecavir therapy is extended beyond 1 year, will there be a higher eAg seroconversion than with lamivudine? Unfortunately, there is no data to answer this question.

Entecavir vs. Lamivudine in e-Antigen negative patients after 1 year of therapy

- With Entecavir, DNA suppression <400 copies/ml is 91% vs. 73% for LAM.
- With Entecavir, there is 70% histologic improvement vs. 61% for LAM.

Tenofovir (TDF) - Clinical Trials Only

Tenofovir is a nucleotide analogue similar to adefovir, but shows greater suppression of HBV DNA levels than adefovir. It is approved for HIV therapy, and is in phase III clinical trials for HBV.

- Two studies show that DNA suppression is 5.5 log greater with tenofovir than with adefovir.
- After 48 weeks of treatment, with tenofovir, DNA suppression <400 copies/ml is 92% compared to 34% for adefovir and 58% for lamivudine.

HepeX-B Clinical Trials

This drug is a mix of two fully human monoclonal antibodies that can be used against the virus (i.e. surface antigen). It is currently being used in the transplant setting.

Therapeutic Advances in the management of HBV infections in the transplant setting.

The advances in HBV treatment strategies has increased access to liver transplantation among HBV patients and also improved their outcomes:

- 1991 – Interferon approved for HBV to manage the disease.
- 1993 – High dose HBIG available for pre-transplant treatment.
- 1995 – Lamivudine and famciclovir available to manage the disease.
- 1998 – Lamivudine and HBIG used in combination for pre-transplant treatment.
- 2002 – Adefovir and lamivudine plus HBIG available for pre-transplant treatment; Adefovir and tenofovir available to manage the disease.
- 2005 – Entecavir, adefovir, and lamivudine plus HBIG available for pre-transplantation.

Dr. Reddy concluded his presentation with the fact that although there have been many advances in the treatment of chronic hepatitis B, there is no “one size fits all” answer because the virus is so tricky. More studies need to be done in order to better evaluate what approach will work best for which patient.

11:00 am Concluding Remarks – Molli Conti, HBF, and Steve Bingham, HB-List

Both Ms. Conti and Mr. Bingham thanked everyone again for making the effort to attend the 5th annual B Informed Patient Conference in Doylestown, PA! They also took time to thank all of the expert speakers who donated their time at the conference, for the workshop moderators, and the HBF staff who coordinated the details and logistics of this successful meeting. Evaluation forms were distributed and people were encouraged to be honest with their comments so that the HBF and HB-List can benefit from the feedback. Hope to see everyone (and more!) next year.