DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC)

Wednesday, August 7, 2002

8:00 a.m.

Holiday Inn Bethesda
Versailles Ballroom
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Roy M. Gulick, M.D., M.P.H. Chair
Tara P. Turner, Pharm.D., Executive Secretary

MEMBERS
Victor G. DeGruttola, Sc.D.
Janet A. Englund, M.D.
Courtney V. Fletcher, Pharm.D.
Princy N. Kumar, M.D.
Wm. Christopher Mathews, M.D.
Jonathan M. Schapiro, M.D.
Sharilyn K. Stanley, M.D.
Brian Wong, M.D.
Lauren V. Wood, M.D.

CONSULTANT (VOTING), PENDING NEW AVAC MEMBER
Kenneth E. Sherman, M.D., Ph.D.

CONSULTANT (VOTING)
Maria H. Sjogren, M.D.

INDUSTRY REPRESENTATIVE (NON-VOTING)
Eugene Sun, M.D.

PATIENT REPRESENTATIVE (NON-VOTING)
Timothy Block, Ph.D.

GUESTS (NON-VOTING)
Anna S. F. Lok, M.D.
Jay H. Hoofnagle, M.D.
Zachary D. Goodman, M.D., Ph.D.

GUEST SPEAKER (NON-VOTING)
Nathaniel A. Brown, M.D.

FDA
Mark Goldberger, M.D., M.P.H.
Debra Birnkrant, M.D.
Katherine A. Laessig, M.D.
Jeffrey Murray, M.D., M.P.H
Greg Soon, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GULICK: Good morning. I am Trip Gulick from Cornell. I would like to call to order this meeting of the Antiviral Advisory Committee.

We will start with the introduction of the committee members. Dr. Sun, can you lead us off? Please state your name and your affiliation.

DR. SUN: Eugene Sun, Abbott Laboratories.

DR. LOK: Anna Lok, University of Michigan.

DR. HOOFNAGLE: Jay Hoofnagle, NIDDK, NIH.

DR. GOODMAN: Zachary Goodman, Armed Forces Institute of Pathology.

DR. BLOCK: Tim Block, Jefferson Medical College and the Hepatitis B Foundation of America.

DR. KUMAR: Princy Kumar, Georgetown University.

DR. SCHAPIRO: Jonathan Schapiro, Stanford.

DR. WOOD: Lauren Wood, NCI, NIH.

DR. ENGLUND: Janet Englund, University of Washington, Seattle.

DR. STANLEY: Sharilyn Stanley, Texas Department of Health.

DR. TURNER: Tara Turner, Executive Secretary for the committee.

DR. FLETCHER: Courtney Fletcher, University of Colorado Health Sciences Center.

DR. DeGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

DR. SHERMAN: Ken Sherman, University of Cincinnati.

DR. MATHEWS: Chris Mathews, U.C., San Diego.

DR. WONG: Brian Wong, V.A. Hospital in Westhaven, Connecticut and Yale University.

DR. SOON: Greg Soon, FDA.

DR. LAESSIG: Katie Laessig, FDA.

DR. MURRAY: Jeff Murray, FDA.

DR. BIRNKRANT: Debra Birnkrant, FDA.

DR. GOLDBERGER: Mark Goldberger, FDA.

DR. GULICK: Thank you.

Tara Turner will now read the conflict of interest statement.

Conflict of Interest Statement

DR. TURNER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at

this meeting.

The Food and Drug Administration has approved general-matters waivers for the following special government employees which permits them to participate in today's discussions; Drs. Victor DeGruttola, Janet Englund, Courtney Fletcher, Roy Gulick, Princy Kumar, Wm. Christopher Mathews, Jonathan Schapiro, Kenneth Sherman, Maria Sjogren, Brian Wong, Lauren Wood.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building. In addition, Sharilyn Stanley, M.D., does not have any current financial interests in pharmaceutical companies. Therefore, she does not require a waiver to participate in today's discussions.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. The committee members and invited guests have been screened for their financial interests as they may apply to the general topics at hand.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each participant. FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We would also like to note that Dr. Eugene Sun is participating in today's meeting as a non-voting industry representative. In addition, Dr. Nathaniel Brown is participating in today's meeting on behalf of an informal industry collaborative group. As such, they have not been screened for conflicts of interest.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. GULICK: Thanks.

We will turn now to Dr. Jeff Murray from the division for opening remarks.

Opening Remarks

DR. MURRAY: Good morning.

[Slide.]

I would like to welcome everybody, the committee, guests and everyone to this very important meeting on clinical-trial-design issues for drugs to treat chronic hepatitis B.

[Slide.]

So why are we having this meeting now? As Dr. Birnkrant mentioned yesterday, the number of drug products undergoing development for chronic hepatitis B has really increased. It has become a large proportion of our work now in the division.

Additional drug availability such as now adefovir and lamivudine may change the types of clinical trials that are now feasible. I think we are entering into a new period maybe of active controls, combination therapies and, perhaps, new trial designs.

It is always good to have a discussion like this after consideration of a new drug product. It is a good exercise for the committee

and guests to go through to see the positive aspects and pitfalls of a drug-development program. I think it is really time that we reflect on the lessons learned from the first two drug-development programs in moving ahead. I think that we will have better drug development in the future for having some reflection now.

[Slide.]

So the meeting focus is primarily on antiviral drugs. We will mention interferon and, perhaps, other immunomodulators but, basically, we are focusing trial-design issues for drugs.

The focus is also primarily on phase III studies and, perhaps, postmarketing studies. Although some phase II drug development, phase I drug development, can be addressed, I think the primary focus is phase III.

We want to address both compensated and decompensated liver disease and we hope that all this will aid in the planning of future clinical trials. We have to realize that there are ongoing clinical trials now and so any recommendations made today, however strong, we have to realize that these may not be able to be incorporated into ongoing trials.

[Slide.]

So the key issues, and these are how the questions will be divided in groups for the committee to address, are what are the essential patient populations for a marketing application, selection of control arms, choice of primary endpoint, also secondary endpoints and, really, a very crucial topic is long-term follow-up data, the type of data that might allow us better prescribing information, when to stop and start treatment.

[Slide.]

Moving on to the next slide is the agenda for today. Before the break, we will have two talks that will provide background that will help the committee focus on the questions at hand. Dr. Jay Hoofnagle from NIH will start at 8:30 with Natural History and Clinical Virology of Hepatitis B followed by an Overview of the Treatment Outcomes in Trials for Chronic Hepatitis B by Dr. Anna Lok from the University of Michigan.

We will have a short break. Following the break, a couple more presentations. An industry perspective by Dr. Brown from Idenix Pharmaceuticals. I might say that it is impossible for one industry to represent or speak for all, but

portion of his talk does involve a collaboration where several pharmaceutical sponsors had filled out a survey indicating what were important issues that the committee should address today and what are the important issues facing current drug development.

Then two talks following that. I have a couple of brief comments and then Dr. Soon, a statistician from our division, has done quite a few analyses correlating measurements such as ALT and HBV DNA and histologic outcome. Following lunch, there will be an open public hearing. Then we will address the questions. This will be done in a slightly different format. We wanted to have more widespread participation so, after each block of questions, and those are dealing with the key issues, I think we are going to allow five to ten minutes of open-mike time at Dr. Gulick, our chair's, discretion.

During that time, anybody can pose a comment, a question or a clarification to the committee if they felt that an issue has not been addressed that they were interested in.

So, with that, I will turn it over, actually, to Dr. Hoofnagle for our first

presentation.

Natural History and Clinical Virology of Hepatitis B

DR. HOOFNAGLE: Thank you, Dr. Murray and all, for inviting me to come to talk.

[Slide.]

When I first entered the field of treatment of hepatitis B it was very much different. I had to go around the country to drug companies to convince them to try to let us use drugs to treat hepatitis B. I am glad now they are coming to the NIH in Bethesda with interest.

I was asked to give an overview of the virology and natural history of the disease.

[Slide.]

So, for many of you, this is very simple but, to begin with the hepatitis-B virus, which is a quite unique virus; it is small double-stranded DNA virus that belongs to the family called Hepadenoviridae. It is the only human form of this in this family. There are some rodent and bird viruses that are very similar.

Infection with hepatitis B is restricted to humans and higher apes, a very endangered species, so we don't have nice, easy animal models

of the disease. But, the human provides a lot of source for study.

The virus is found in the blood in very high levels, extremely high levels, and quite variable from as low as barely detectable to as high as 10 10 to 1011 virions per ml. Now, to compare this to, like, hepatitis C, there, most people circulate viruses in a very tight, narrow area between 10 5 and 107. Here, there is a broad range and the different ranges of the viral levels are important clinically.

The virus can cause both an acute and a chronic hepatitis but, unlike in hepatitis C, chronic hepatitis is somewhat the uncommon outcome of this disease, at least in adulthood. Probably only 5 to 10 percent of patients with acute hepatitis B virus infection after the age of 20 will develop chronic infection.

It is spread by parenteral, sexual and maternal-infant routes. In this country, the major route of spread is sexual spread. We do see a lot of imported hepatitis B, immigrants from areas of the world where this disease is common.

It has a marked geographical variation and incidence. This disease, for instance, was almost

a university disease in China and Southeast Asia so that, by the age of 20, 80 percent of people had been infected with hepatitis-B virus unlike in the United States where this is really an uncommon disease.

Population-based surveys suggested about 5 to 10 percent of Americans, at most, will get infected sometime during their life.

[Slide.]

Here is a cartoon of the virus-like particles that you see in serum. The virus, itself, is this particle called the Dane particle, named for Dr. Dane. It is a double-shelled particle with a surface-antigen environment and a core-antigen nucleocapsid core.

Inside of the core is a double-stranded circular molecule of DNA. Interestingly, the virus in the liver produces a lot of other particles. Spherical particles and tubular particles actually outnumber the Dane particle by 10 to 10,000 to 1. These are incomplete virus particles made up only of surface antigen and, of course, this is the basis for the hepatitis-B vaccine to immunize with incomplete noninfectious particles.

Also in serum is another antigen, the hepatitis-B e-antigen. It is a soluble antigen. It doesn't have structure. You can't see it on the electron microscope. It is about 19 kilodaltons in size. Interestingly, it is a byproduct of the production of core antigen.

[Slide.]

This is the typical type of display of the hepatitis-B virus DNA. These here show you the double-stranded circular molecule of DNA. Actually, it is neither circular nor double-stranded.

One of the strands is incomplete here, so it is partially double-stranded. Furthermore, both strands are actually linear molecules held together by overlapping bases. This slide is incorrect. There is actually a nick right here, a nick right there, so that the ends of the DNA are not covalently closed as it circulates in serum.

Once it gets in the liver, this is repaired and it becomes a double-stranded molecule that sits in the nucleus, the so-called circular DNA, and that makes RNA of the hepatitis-B virus which is reverse-transcribed in the replication of the virus back into DNA. So it has a very peculiar

replicative cycle.

It is very important for the natural history and the treatment of this disease that the molecule that we are trying to get rid of is the most difficult to get rid of and that is this double-stranded circular DNA that sits in the nucleus of hepatocytes and spits out RNA.

So, inhibiting the replication of virus, it is very hard to get to that stable molecule of DNA.

The DNA has four open reading frames as shown in these color arrows. First of all, the surface antigen, the enveloped gene. It is a complex antigen and it has three start sites so it has three different sizes, large, middle and small hepatitis-B surface antigen.

Here is the core-antigen gene. It also has a strange structure. It has a precore region and two start sites. You can synthesize--if you start from here, you synthesize core antigen that is incorporated and is the nucleocapsid of the virus. If you begin at the precore region, you synthesize a protein that is post-translationally cleaved into a soluble molecule, e-antigen.

So there is no separate open-reading frame

for e-antigen. It is synthesized off the core gene and it shares sequence with the core gene. It is probably one of the secrets to the immunology of this virus but I haven't figured out what that secret is.

Then the large brown arrow is the polymerase gene. It is a multifaceted polymerase that can synthesize both the negative and positive strands off of its own DNA or off of its own RNA. You see how it overlaps. These genes are overlapping. It is amazing that there is no nucleotide base in the hepatitis-B virus that isn't used, so it is not based like the human genome on entrons and exons.

Furthermore, most bases are used twice in that they are used either to produce surface or polymerase, or polymerase and core and so forth. There are also a lot of enhancing and promoter regions so that this is one of the most compact DNAs of any virus.

This is meaningful in several ways. For one thing, the virus can't mutate very much because, if it mutates, it has got a lot of compensation to do. For instance, if you mutate a base here, you can affect both the surface and the

polymerase gene. This is important also in talking about mutants and antiviral resistance.

This region here is called Region X. Its function is somewhat unknown. It is a transactivating factor that is somehow important in the replication of the virus.

[Slide.]

Here are the RNAs of the virus. There are multiple RNAs that are of different sizes, some that just synthesize surface antigen and the pregenome from which DNA is made by reverse transcriptase. This is so-called pregenome, the purple one. This shows you the nick here on the incomplete strand.

[Slide.]

Circular, partially double-stranded, poor open-reading frames. Replicates largely in the liver. It may replicate in stem cells in the pancreas and in the spleen and bone marrow, but not in very high levels. Furthermore, I don't think it is a privileged site. If you inhibit hepatitis-B virus one place, you are probably inhibiting it elsewhere. It replicates through an RNA intermediate and reverse transcription.

[Slide.]

So the infectious cycle of hepatitis-B infecting the liver with a very rapid production of virus, 10 11 to 1013 virions per day in someone with a very productive infection, virus half-life of one to two days.

[Slide.]

So let's talk about mutants of the hepatitis-B virus. Variations in nucleotide sequence in one of the hepatitis-B virus genes can result in a change, either in the virological nature or, in some cases, the clinical features of the disease. Various genes that have been found mutations in each. The famous mutations of the surface-antigen gene are vaccine-escaped variants where the virus is not neutralized by antibody to--the typical antibody to hepatitis-B surface antigen.

The core gene has important mutations which can affect disease severity or the serological and clinical manifestations. An important mutation in the precore region makes a virus that cannot produce e-antigen, for instance. Finally, the polymerase gene which is important to this audience because it can affect replicative efficiency of the virus and resistance to antiviral

agents.

[Slide.]

So the core region mutants. An important one is in the precore region. A mutation can occur that results in the inability to produce e-antigen. What happens is there is a G to A change at nucleotide 1896.

[Slide.]

Which creates a stop codon in the precore region. So it blocks the synthesis of e-antigen. This nucleotide, again because of the compact nature of the hepatitis-B virus, doesn't affect just e-antigen. It also affects replication of the virus because this is in the highly structured stem loop called epsilon encapsidation signal region of the RNA. So it is a part of the RNA structure that is responsible for replication.

If this mutation disrupts the stem loop, the virus won't replicate. For this reason, this nucleotide which is opposite this one in the stem loop, you have to have a T for the stem loop to be stable. The importance of that is that this mutation, this e-negative mutation of hepatitis-B virus occurs largely in three of the four major genotypes of hepatitis B.

Genotypes B, C and D have a T at this region whereas genotype A does not. Therefore, patients with genotype A rarely develop e-negative-variant disease.

[Slide.]

Enough of the molecular biology. We will come back to that a little bit in talking about the natural history of hepatitis B. This virus infection has multiple outcomes and these percentages are based on studies long in the past of acute hepatitis B which showed that the majority of people infected with the virus--this is adults--do not have clinical disease. They have an asymptomatic subclinical infection, clear virus and make antibody, and they are protected for life.

This is 65 percent of people infected with the virus, so that when you test people for antibody, you find people in the population that have antibody to hepatitis B but they deny a previous history of hepatitis B.

They have been infected. They have been lucky and have had an asymptomatic subclinical infection. About a third of patients develop clinically apparent disease with jaundice and symptoms. They may not be diagnosed correctly but

they had a period of disease. This can be severe and lead to fulminant hepatitis, somewhat rarely, and it usually resolves.

But, in a proportion of cases, and, as I said, in adults it is about 5 percent chronic infection ensues. This 5 percent applies to adults. It doesn't apply for children. Children are more likely to develop chronic hepatitis B. In fact, infection during the newborn period results in chronic hepatitis B in 80 to 90 percent of infected children.

So part of the natural history is that if it is spread by maternal-infant spread, if it is spread in childhood, it is more likely to become chronic and the disease perpetuates in it population.

So what happens with chronic hepatitis B? Does it invariably lead to cirrhosis? The answer is no. Like most chronic liver diseases, only a proportion of patients with these diseases develop cirrhosis. This is a guesstimate, that about 30 percent of people with chronic hepatitis B virus infection develop cirrhosis.

Of course, if you take a population of patients that come to see me in the liver clinic,

it will be higher than 60 percent because these people are self-referred, or they are selected. There is this selection bias. But if you take the whole population of people with hepatitis-B infection, if you went around and screened everybody, there are a lot of people who have a somewhat benign outcome that develop what is called the inactive carrier state and are left with hepatitis-B surface antigen but very low levels of viral replication and no accompanying liver disease.

Liver cancer can result from chronic hepatitis B. It occurs largely in people with cirrhosis but sometimes not. Sometimes, it appears to occur in people who are so-called healthy carriers, inactive carriers.

[Slide.]

Let me go through some of the serology of what I have just shown you. This is typical resolving acute hepatitis B if you happen to have blood samples and everything from the very point of exposure on. Within a few weeks of exposure, HBV DNA is detectable in the serum and it rises to fairly high levels. These are in millions of copies per ml, high-level virus infection.

Once it reaches about that level, you have onset of symptoms and ALT elevation. During this period, also the patient is positive for surface antigen and the e-antigen, the e-antigen reflecting high levels of viral replication.

With the clinical disease, the virus is cleared and e-antigen goes away. It is one of the first things to go away, then HBV DNA, then surface antigen. The symptoms resolve and the ALT falls to normal and patients with acute resolving hepatitis B appear to have recovered from this disease.

That is not entirely true. This is a DNA virus and, as a virologist will tell you, DNA viruses often stay forever in the body and it is probably true of hepatitis B. A person with resolved hepatitis B is likely to harbor small levels of the hepatitis-B virus in the liver. It is not harmful to them at all.

How do we know that? We know that because if you take a liver from a person who has recovered from hepatitis B who has the markers of recovery, antibody to surface antigen and antibody to core, and you transplant that liver into a naive person at the time of liver transplantation, that person will develop hepatitis B.

It is kind of the experiment in nature that shows you that the hepatitis-B virus is harbored in the liver and people who recover, recover probably for life; maybe not 100 percent but for many.

If you do a liver biopsy in these patients, you can often find small levels of HBV DNA in the liver. But you don't find it in the blood, usually.

[Slide.]

Here is what happens to a person who doesn't resolve the disease but develops chronic hepatitis B. Again, HBV DNA appears in the serum and goes up. The patient develops e- and surface antigen and, usually, if you are testing, at the time, will have ALT elevations but rarely jaundice or symptoms so they have a somewhat mild subclinical hepatitis B.

The problem is they don't clear virus. They remain surface-positive, e-positive and DNA-positive. Why do people develop chronic hepatitis B and not recover? The answer to that is we don't know for sure. It is probably immunological, usually a poor T-cell response to core antigen and surface antigen in people who

develop chronic infection.

So high levels of HBV DNA and usually ALT elevations persist in these people. They may be very low. In fact, in children who develop this, the ALT usually is normal or near normal when they develop chronic hepatitis B despite high levels of virus and e-antigen. This has been called the immune-tolerance state. I don't like that term but that is what it has been called. So children with chronic hepatitis B usually have minimal ALT elevations but high levels of virus.

What happens to them in the end is the question. What you generally see is that once they reach adulthood, the disease starts to turn on. Their enzymes go up and they start developing the complications of hepatitis B.

[Slide.]

Here is what we call the transition to the inactive-carrier state. A patient with chronic hepatitis B, high levels of DNA, ALT elevations, here out, let's say, three or four years after onset of infection, has a flare of disease spontaneously and clears DNA, clears e-antigen but doesn't clear surface antigen.

That remains. Develops anti-e. Generally

the enzymes return to normal. This is the generation of the so-called inactive-carrier states. It can occur spontaneously. In fact, in following patients with chronic hepatitis B in clinical studies, this occurs in about 5 to 10 percent of patients a year.

The importance of this is that this is what we accomplish with antiviral therapy. We get chronic hepatitis B to resolve but it doesn't go away completely. You usually don't clear surface antigen. You are usually left with surface antigen and you are left with what, for lack of a better term, we call the inactive-carrier state. In this state, the liver disease is generally not progressive--generally.

So that is what we accomplish sometimes with antiviral therapy but it is important to remember this occurs spontaneously. As I said, in 5 to 10 percent of patients that we follow each year, they do it on their own. This is what plagues studies of hepatitis B, spontaneous improvement. Hepatitis C, we never see spontaneous improvements. It is an easier disease to study and, as you know, the FDA doesn't require placebo controls for hepatitis C. But, for hepatitis B,

with this type of thing, maybe it is still needed. I don't know.

The other problem is you can't predict it, I don't think. You can predict it once this type of thing occurs, once a flare occurs and the level of virus drops. You can predict it a little bit, not completely.

This is the slide I would have ended with about ten years ago but the disease is not that simple.

[Slide.]

That is what I refer to as the e-mutant disease, patients who develop a mutation in the hepatitis-B virus DNA that prevents the virus from making e-antigen. So what happens there?

Here is what happens. This is a patient, basically, that we were following, Asian-born patient, who had e-antigen and active disease. We are getting ready to treat the patient and he cleared DNA, or went down fairly low, and he lost e-antigen. We thought he was going into the inactive-carrier state.

But, no. His enzymes went up again. His HBV DNA has been low-level positive, intermittently positive. Now, again, I ought to stress here that

what we are measuring in DNA here is fairly high levels. This is using hybridization-based assays so that this goes down to negative for DNA, but that level is about 100,000 copies per ml. That is about as low as you can go using typical hybridization assays.

So, when it is negative by that assay, it may still be positive if you test it by polymerase chain reaction, and, indeed it is. So this is evolution to the e-negative mutant disease and this is no better than the e-positive disease. In fact, it may be worse.

These people tend to have flares of disease, intermittent worsenings and exacerbations. It makes it very difficult to treat because, just about the time you decide, well, this patient really needs to be treated, they start to get better on their own. So, an up-and-down course. It makes it difficult to study particularly if you want a stable level before you enroll the patient, like most of these trials try to do.

These patients will be knocked out if you use stringent enrollment criteria of a stable lever of HBV DNA.

[Slide.]

These are the three clinical forms that are important, general forms, e-positive disease, e-negative chronic hepatitis B and inactive-carrier state. The disease is associated with raised ALT and high levels of HBV DNA in serum.

[Slide.]

These are the average levels of virus that you see in patients with e-positive and e-negative disease, a little bit lower in e-negative disease but it is a moving target in these patients whereas the e-positive patient generally maintains a fairly stable level of HBV DNA.

Inactive-carrier; we say, they are DNA-negative, but they are not, really. They have low levels. One of the things that we have trying to work out recently is what level of HBV DNA--what is the level above which you see clinical disease, you see liver disease. This is a guesstimate, about 10 4, 105. Below that, the disease is usually inactive.

[Slide.]

Why don't we know that? We don't know that because there haven't been good assays for detection of HBV DNA. It has been corrected in the last couple of years with the development of

quantitative PCR assays that are commercially available and appear, to my mind, to be quite accurate and reliable. Using these assays that measure HBV DNA down to around 100 to 500 copies per ml, you find that what we call the healthy carrier usually maintains somewhat low levels of virus, but the virus is there.

Why does it stay at that low level and not go up? That hasn't been resolved. So patients with active disease usually have virus high enough that can be detected by other assays. This slide is a little bit dated so some of these assays may be a little more sensitive now. But the conventional hybridization assays just measure down to 10 5 to 106 virions per ml which is plenty sensitive enough for the average e-positive patient with chronic hepatitis B.

It is a bit troublesome in the e-negative group because they go up and down below that level and it, of course, will not detect patients who are so-called healthy carriers who are usually negative.

[Slide.]

I mentioned genotypes of hepatitis B virus. These are somewhat important. We used to

subtype virus. Now the virus can be genotyped. These are seven genotypes that have been described. The first four are the most common in this country. In fact, in the United States and Northern Europe, the major genotype is Genotype A.

This is the genotype that has difficulty evolving into the precore mutant. The important thing here is that, in the studies in the 1980s in the United States, when we were dealing with largely Western patients, non-Asian patients, in this country who were being treated for hepatitis B or being studied, most of them, 90 percent of them, had Genotype A. That is what we found.

In our studies of interferon from the 1980s, 90 percent of our patients had Genotype A and the rest had Genotype D which is seen in Southern Europe. It is also seen in drug abusers in the country, Genotype D-ay.

Genotypes B and C are the genotypes of Asia, China and Southeast Asia and Viet Nam. One is an adw so it wasn't separable from Genotype A by serotyping. The other is adr which was.

So, now, when we see patients, I would say 50 percent of the new patients I see are Asian in background, Asian or African in background. We are

seeing a lot more genotypes B and C.

[Slide.]

Changing to what we think about the disease. I was going to mention something about the epidemiology of the disease to show you that acute hepatitis B, unfortunately, is still with us despite the fact that we have a vaccine. It accounts for about 34 percent of acute hepatitis B that is seen. It has declined in incidence but it is still here with us, seen in injection-drug users, men who have sex with men. The major source is heterosexual activity.

So the United States has a way to go before we control acute hepatitis B.

[Slide.]

Next slide after that.

[Slide.]

Here is chronic liver disease in the United States. What proportion is due to hepatitis B? Hepatitis B is not a very big piece of the pie. It represents about 4 to 5 percent of the chronic liver disease that is newly diagnosed in the United States. This is a multicenter study conducted by the CDC. Hepatitis C is the big one here.

[Slide.]

What are the complications of hepatitis B? The main ones are cirrhosis and end-stage liver disease and, in that context, hepatocellular carcinoma. There are a few extrahepatic manifestations, glomerular nephritis and polyarteritis nodosa which are somewhat uncommon.

[Slide.]

So how do we look at hepatitis B? What are the features that are looked at in grading this disease and staging it, assessing it? The major one is liver histology. I think that, in hepatitis B, we are still very dependent upon liver biopsy to assess the need for therapy and prognosis of the disease.

When looking at the liver biopsy, we look at two things. We look at the activity, the necroinflammatory changes, necrosis and inflammation. Second, we look at fibrosis. Now, necroinflammation can come and go. The enzymes go up, it's higher. The enzymes go down, it's lower. The liver biopsy changes lag behind the enzymes and they integrate the enzymes over the previous year or so.

So it is a more integrated look at the activity of the liver disease over time. I know

the ALT may not correlate very well with these, but if you have a large enough series, it does.

You usually look at the inflammation and necrosis in three different things and you come up with a score. The fibrosis goes from none to portal fibrosis to septal formation to bridging between portal and central veins, and then cirrhosis.

The bottom line in chronic liver disease in general is fibrosis, progression to cirrhosis. Why do we even look at this? We look at this because we think that the degree of necroinflammatory change is prognostic for the progression of fibrosis. That is what we believe. I think most pathologists will agree with that, that if you have a high level of disease activity, fibrosis development will be more rapid.

[Slide.]

So here are the scoring systems for hepatitis. These are the U.S. systems. They are basically based on systems developed at the AFIP by Dr. Ishak and Dr. Knodell who developed the first system here, Histology Activity Index. You will hear about HAI. It includes the three elements of inflammation and necrosis as well as fibrosis, goes

from 0, 1, 3 and 4.

This is the original system. We don't like it because it doesn't use enough numbers and, also, it jumps from 1 to 3. 1 is mild, and 3 you are already in trouble a little bit. You have got bridging.

[Slide.]

So we moved away from this system to the next slide which is the system devised by Dr. Ishak again. Actually, the first one is his system as well where fibrosis is categorized from 0 to 6 so we have more numbers to deal with and a better gradation, where portal fibrosis is 1 or 2, bridging 3 or 4 and cirrhosis early are incomplete cirrhosis and complete cirrhosis. So this is a better scoring system and I think we are all more pleased with this.

The estimation of inflammation in necrosis is about the same. It goes from 0 to 18.

[Slide.]

Let me go a little bit into therapy as it relates to the natural history

[Slide.]

And the issue of why do we treat patients, what are the goals of therapy, which we will be

dealing with today. Well, three major things; to improve systems and quality of life. The trouble is that the majority of patients with chronic hepatitis C have minimal or no symptoms. Many of the drugs we treat them with make them more symptomatic. So this is a pretty hard thing to measure and we have been remiss in our measurements of symptoms and quality of life in studies of hepatitis B.

To decrease infectivity; this is important for some patients, particularly if you are a surgeon and you want to operate and you have hepatitis B. But, for many patients, it is not an enormous problem. It can be a problem for the heterosexual single person who wants to have more sexual partners but for a person in a family, you can vaccinate family members. So this is a less important goal.

The most important goal, the one that we usually use, is to prevent progression of disease to cirrhosis, to hepatic compensation and death. This is a slow thing to occur, though. If you did a trial that showed prevention of end-stage liver disease, you would have to do a study for ten or fifteen years.

Furthermore, you would like to treat patients earlier before they even come close to decompensation. So we are not going to see trials that prevent progression to end-stage liver disease unless they are trials in patients with preexisting cirrhosis.

[Slide.]

So what surrogate endpoints can we use to correlate with these outcomes and what are the appropriate endpoints; loss of e, loss of surface. That would be a good endpoint, wouldn't it? I think we would all agree with that. We wouldn't need much data to support that as an endpoint. I think we would all agree with that. We wouldn't need much data to support that as an endpoint.

Loss of HBV DNA or its fall below a certain level. Normalization of ALT or improvement in histology. The answer to that is you need all of these put together.

[Slide.]

In hepatitis C, the endpoints of therapy have been kind of carefully defined and people have joined together and used them in all studies of natural history and therapy. In hepatitis B, we haven't gotten together as well, but let's remind

you about the types of responses and timings that are important in hepatitis C. I think they apply to hepatitis B as well.

There are virological responses, loss of e and HBV DNA. Of course, if you don't have e, this you can't use as an endpoint but you could use HBV DNA as an endpoint. Biochemical, normal ALT, histological, improvement in histology. Or a complete response for hepatitis B would be all of those and loss of surface antigen as well, resolution of disease.

It is also important and I think this is what I would like to stress to the group here is to define the timing of the response. Initial we be something that occurs early during treatment, either at three or six months. End of therapy is what is the status when therapy is stopped.

In trials of antiviral therapy in hepatitis B, end-of-therapy response is what has been used in lamivudine and, I guess, adefovir as well. The problem is that, when you stop therapy, patients may relapse. So a more important endpoint would be a sustained response. The question is at what point after stopping can you call the response sustained, six months or twelve months.

In hepatitis C, it looks like six months is quite adequate. I don't know that that is adequate for hepatitis B, whether relapses that occur when you stop therapy all occur within the first six months. That has not been defined. So this is a problem.

Let me add another type of response which is called a maintained response. That means the response is present while continuing therapy. This is the important issue in hepatitis B is that we are going to start talking about maintenance, continuous therapy, not therapy for a defined period like four months or six months or a year but long-term maintained therapy. So we need to have a definition of a maintained response.

[Slide.]

So here is a virological response. This is the typical one that has been used in trials; loss of e and fall of HBV DNA levels below 10 5, negative by hybridization assays. This occurs in 25 to 48 percent of patients given interferon, alpha interferon, at least in the old studies, in Western patients. It is my opinion that it is less common in Asian patients although this is still argued.

It occurs in 20 to 32 percent of patients given a twelve-month course of lamivudine. It occurs, unfortunately for the clinical trialists in 8 to 12 percents on no therapy. So you have to show a difference here. Sometimes, that is hard to do.

The question is is this response durable and does it result in long-term improvements in disease.

[Slide.]

Loss of e cannot be used as an endpoint in patients with e-negative disease and we generally rely, in them, on a decrease in HBV DNA below 10 5.

The trouble is HBV DNA levels fluctuate widely, particularly in this disease. So how do we know that we really have gotten anywhere, that the response is sustained? How durable is the decrease without other changes in viral status?

I don't have an answer for that.

[Slide.]

Here is the response that we wish we could achieve which is loss of surface antigen and development of antibody to surface antigen. It occurs in about 8 percent of patients given a four-to-five-month course of alpha interferon, at

least in the studies from the 1980s. It occurs in 1 to 2 percent of patients given a 12-month course of lamivudine. It is rare on patients on no therapy, actually. One of the most convincing pieces of evidence that these drugs work is the loss of surface antigen on a portion of patients.

It is extremely rare in the treatment of e-negative form of disease, though, unfortunately. This response is durable.

[Slide.]

The second type of response is a biochemical response, fall of ALT into the normal range. This often accompanies loss of e-antigen and a decrease in HBV DNA below 105. It is not durable unless the decrease in DNA is durable, so it is a surrogate indirect marker. But it is a surrogate indirect marker for the necroinflammatory disease.

[Slide.]

For most clinical trials, we do rely upon histological improvements using virtually all studies of antiviral therapy. Actually, in hepatitis C, it may stop being used as the virological response is so convincing that it may not be as necessary anymore. But, in hepatitis B,

it still is necessary.

Typically, in clinical trials, improvement is called a two-point or greater improvement in the HAI score which ranges from 0 to 22 compared to baseline. But we don't know whether that is really a significant change, two points.

As I pointed out to you in HAI score designed by Knodell, there is this skip between 0, 1 and 3. So a two-point change could be from a 1 to a 3 which could easily be due to sampling error or to a different pathologist looking at the slide.

Furthermore, necroinflammatory scores can change rapidly and get better and worse. If the person relapses when therapy is stopped, that improvement that you saw on therapy is likely to disappear with time.

Fibrosis scores represent the best evidence for progression of disease but they are unlikely to improve much with treatment and they improve, if they improve, very slowly.

[Slide.]

Alpha interferon is the first drug that was licensed for hepatitis B. It is a cytokine, acts through receptors. Repegylated forms are now available and I suspect the trial of pegylated

interferon will be starting up in hepatitis B.

[Slide.]

This is the type of response, the character of response that occurs with interferon treatment--I mean, a good response in a patient who is called a responder. This person had elevated ALT and HBV DNA here by dot blot--this is an old patient treated in the 80's with alpha interferon treatment.

The levels go down and it becomes negative by the end of treatment. He clears e-antigen. A couple of things to point out. First of all, his enzymes actually get worse on treatment rather than better. This is typical of the response to alpha interferon. There is a flare of disease that usually begins at about two months.

It is usually asymptomatic but occasionally it will be symptomatic. Occasionally, a patient will develop jaundice. With this flare, the DNA falls and e is clear.

The second point I would like to make is that the loss of e didn't occur during treatment. It occurred after treatment. This is typical as well. So, at the end of treatment, there is no improvement in this patient whatsoever. The

end-of-treatment response doesn't look very good, does it? The enzymes are higher, still DNA-positive, still e-positive.

What is important is that, at twelve months, he has a sustained response. He is e-negative. His enzymes are not normal. He has anti-e. This patient was followed indefinitely at the NIH and, actually, at two years, when he came back, he had also cleared surface antigen. This is what we had found at the NIH. Other people haven't found it as commonly as we have, but in five- to ten-year follow up, the patients who have lost e on alpha-interferon therapy, 70 to 80 percent of them will clear s, sometimes many years later. That is very supportive.

So this is the best response with alpha interferon. The trouble is not everybody has such a response. Some people don't clear e. Some people have a flare and don't clear e.

[Slide.]

Some people do this. This person was treated. He had a nice flare. In fact, he was flaring when he started therapy. He clears e-antigen rapidly, develops anti-e. His enzymes are normal. He does have an end-of-treatment

response. But, at nine months, he is e-positive again and his enzymes have gone up again. He has relapsed before the twelve-month period.

This is Patient B. I will show you Patient B again. Patient B has genotype B.

[Slide.]

Here is e-negative chronic hepatitis B with alpha interferon, what we used in the past. We gave it up. We found that this is what happened to virtually every patient we treated with e-negative disease. You have a nice response on-treatment. Almost before treatment, they become DNA-negative by hybridization. The enzymes are normal.

But, when you stop therapy, these patients relapse. We have never had a long-term response to interferon on an e-negative patient. There has been reported from Italy, where this is more common, that they can get a long-term response in about a quarter of people with a year of interferon treatment.

One of the difficulties is you don't know when the patient really has responded. There is not something nice like clearance of e-antigen. You rely upon the DNA test.

[Slide.]

So interferon for hepatitis B had many problems and was effective only on a third of patients. It is expensive. The side effects are very difficult, can be very severe. We use high doses of interferon in hepatitis B. It is not appropriate for many categories of patients.

[Slide.]

Lamivudine came along and was the answer to many of those problems with alpha interferon. You have heard about this. It is approved for use in chronic hepatitis B as a one-year course of therapy but continuous long-term use is common in this disease because it is so easy to administer and has so few side effects.

[Slide.]

This is what I call a maintained response in talking about responses in a patient on lamivudine long-term. This is my Patient B that I showed you before who relapsed after interferon. He has bad disease again, responds immediately, becomes DNA-negative, becomes e-negative, after a year and a half of therapy.

Here are the histology scores. He begins with very active disease, a score of 14. At one

year, it has decreased markedly, you see more than two points, to 4. A four-year biopsy is 1. So it looks like terrific response. He is still surface antigen. He is still on lamivudine. It is a maintained response.

[Slide.]

For e-negative chronic hepatitis B, also a maintained response on lamivudine, a patient with fluctuating disease develops normal enzymes that stay normal. There is no loss of e but HBV DNA falls here from 53 million down to 200 copies per ml by PCR. We don't detect it now. It is less than 100 and his histology has also has improved markedly. He is still on lamivudine, a maintained response.

[Slide.]

The problem with lamivudine is viral resistance where HBV DNA goes down but then creeps up again towards baseline. This is associated with a mutation in the polymerase gene, in the so-called highly conserved YMDD motif either to YVDD or YIDD. These patients generally lose their biochemical response and their histology may not improve.

This patient was improved at one year, 12 months. He had resistance at this point. You can

see his histology had improved by more than two points. His ALT was improved, quite a bit, actually. His DNA was little bit less, so it looked like a good response.

The problem is, with time, this is lost and this patient developed cirrhosis on lamivudine.

[Slide.]

These are the histology scores of patients. This is the activity, remember, the necroinflammatory activity, before treatment, at one year and at four years. These are patients with a maintained response, beautiful resolution of disease. With resistance, there is a decrease you see. On average, at four years, they are still a little bit better in necroinflammation.

[Slide.]

The problem is fibrosis. I told you fibrosis didn't go away, but it looks like it may improve in patients who have maintained responses largely resolved. Fibrosis scores go from 4 to 3 to 1. But in patients with resistance, there is no improvement in fibrosis over time. So we are not sure these patients are really better off.

[Slide.]

The other problem is this, the plague,

which is late relapse. This is my famous Patient B who relapsed after interferon, had a nice maintained response to lamivudine at one year. His histology was basically resolved. At five years, he has relapsed. His disease is back. HBV DNA close to where it started and ALT elevated. So maintained response may not be durable either in a person who remains surface-antigen positive.

[Slide.]

This is the rate of resistance in our studies in e-positive patients, very high. E-negative, less with long-term lamivudine therapy.

[Slide.]

The major shortcoming of long-term lamivudine therapy for hepatitis B is the emergence of resistance. In larger studies, it occurs in about 20 percent of patients per year so it can approach a very high rate of five years. The loss of surface antigen appears to reliably predict long-term benefit and you can stop lamivudine if the surface antigen is lost.

But loss of e does not insure that you will not have relapse. Future studies should focus on combinations that might prevent resistance.

[Slide.]

So what is the optimal therapy of hepatitis B? The first paper on treatment of hepatitis B using interferon came out twenty-five years ago and we still don't have a good answer for this question. Should it be monotherapy or combination therapy, for a defined period or continuous, for all patients or only those with moderately severe disease?

If you use monotherapy, which agent? If you use combination therapy, which combination?

[Slide.]

This was a meeting that we held about two years ago on the management of hepatitis B. We had to put a question mark after therapy. It is very hard to make statements recommending therapy in this disease, what exactly to use. Should you use interferon first? If you use interferon, should you use pegylated interferon? What dose should you use? How long should you treat people for? I don't know.

I find it kind of counterproductive to use standard interferon today with the presence of pegylated interferon on the market. Yet, we don't know what dosage to use or how long to use it for or whether it works very well.

What about lamivudine? What patients should use it? It is very hard to decide. In patients with decompensated liver disease, it is pretty clear. But, in those with compensated liver disease, the problem of resistance is one that can plague one. And what will be the role, now, of adefovir as it comes to market?

[Slide.]

So we have a lot of work to do in hepatitis B. I think the future direction should be on combination therapy with long-term outcomes assessed, not just one year on-therapy outcomes with histology verification of long-term benefit, not just a decrease in inflammatory scores by a couple of points.

Loss of surface antigen; it would nice to have that as the gold standard if it could be reached in a large proportion of patients.

These are some appropriate directions, I think, combinations of interferon with one of the nucleosides, nucleoside combinations, long-term, and so forth.

Thank you.

DR. GULICK: Thanks, Dr. Hoofnagle. We probably have time for a few questions from the

panel, if you wouldn't mind staying.

Dr. Mathews?

DR. MATHEWS: Thank you. That was a great talk. Could you clarify something about the e-negative state? The example you showed was a patient who apparently had wild-type virus and developed a mutant and had e-antibody. But, presumably, the precore mutant is transmissible. Are patients who are initially infected with the precore mutant different clinically from those who acquire it in the course of chronic infection?

DR. HOOFNAGLE: I wish I knew the answer to that, and we should know the answer to that, but we don't. The precore mutant is not very transmissible. This is the truth. If it is transmitted, it usually results in acute self-limited disease.

In fact, I don't know that it has been very well shown that you can get chronic hepatitis B from a precore mutant infection. Chronic hepatitis B generally results from an e-positive infection, de novo chronic hepatitis B. So it is probable that most patients begin with a period of e-positivity and then evolve into a precore mutant. That is probably the natural history.

But we don't know for sure. The precore mutant can cause hepatitis B, acute hepatitis B. In fact, there is a little evidence that it is more severe than exposure to e-positive disease. So newborns, for instance, who are infected with the precore mutant develop clinically apparent acute hepatitis, which is virtually unheard of in newborns infected with e-positive disease.

So this isn't very clear, is it? But the patient I showed you evolved from a wild-type to a mutant-type virus. The interesting thing is that was a child and his father is being treated by us for e-positive hepatitis B. So that is the source of the disease, e-positive. But the child has evolved to a precore mutant and he has Genotype--I believe he had Genotype C. This was an Asian child.

DR. MATHEWS: So presumably someone who was infected with the precore mutant would not have e-antibody so you could serologically distinguish them that way?

DR. HOOFNAGLE: No. The precore-mutant patients do have e-antibody. They are also called e-antibody-positive chronic hepatitis B.

DR. MATHEWS: But if they were infected

with the precore mutant, why would they make e-antibody if they never were exposed to antigen?

DR. HOOFNAGLE: Because, as I showed you, the e-antigen has the same amino-acid sequence as core antigen. In fact, the t-cell responses to e are the same as to core. It is just the b-cell responses are different. It is wild. It was really a shock when this was first shown by the cloning of the hepatitis B virus. We all kind of just dropped our mouths open that there was no separate gene for e-antigen, that it was part of core.

So if you take purified core particles, which is what I did, and immunize animals, you get anti-core but you also get anti-e. So, just because you can't synthesize it and secrete it from the liver cell doesn't mean e-antigen epitopes are not being made.

Confusing; right?

DR. GULICK: We have time for one or two more questions. Dr. Block?

DR. BLOCK: Jay, thanks for a very nice overview. In speaking about the e-negative hepatitis-B carriers, you spoke mostly about those who are e-antigen-negative because of the mis-sense

mutation. That was nicely covered, and you discussed their eligibility for treatment.

I am wondering, could you talk again just briefly about the population of individuals who are e-antigen-negative spontaneously, not because of a mis-sense mutation, not because of the precore mutation. You alluded to them briefly. There was a paper in Hepatology a couple of months ago that talked about the risks of disease in individuals who are simply low DNA, e-antigen-negative, but surface-antigen-positive.

I am thinking about the eligibility of those for treatment, that population.

DR. HOOFNAGLE: Do you mean patients with normal liver enzymes?

DR. BLOCK: Well, they may or may not have normal enzymes. Usually, they do, of course, but they are characterized by e-antigen-negative relatively low DNA. Their risk of liver disease is still, of course, greater than those of the general population. They also present a challenge for treatment because of the markers. They are surface-antigen positive.

What is your thinking about that group?

DR. HOOFNAGLE: I am not sure we are

talking the same language, Tim. Not everybody with e-negative chronic hepatitis B has the classical precore mutant. There are other mutations in the so-called basic core promoter that can result--

DR. BLOCK: No; I'm sorry. I didn't mean the molecular biology in that detail. I just mean this would be people who would be--this is what you would call the inactive-carrier state.

DR. HOOFNAGLE: Inactive carrier. Should these people be treated?

DR. BLOCK: That's right. What is their risk and are they eligible for treatment?

DR. HOOFNAGLE: The risk of chronic liver disease and cancer is somewhat low in them if they do not have cirrhosis. As I showed you, most people begin with a period of chronic hepatitis and then they resolve it. During that period of chronic hepatitis, they can develop cirrhosis. So some people that we call inactive carriers actually have 3-plus fibrosis or cirrhosis as a result of the disease they had in the past.

This is what makes these cross-sectional studies very confusing. So, in those patients, in a patient who has cirrhosis who then seroconverts as normal enzymes, the disease burns out, that

patient has increased risk of cancer. There is no question about it.

But if a person is truly an inactive carrier and if you do a liver biopsy, it is usually not done, and it shows minimal or no fibrosis, it is the general feeling that risk of cirrhosis in those patients is uncommon.

Now, the disease can reactivate. You can reactivate hepatitis B by manipulations; for instance, high-dose steroids or cancer chemotherapy, and so forth. We see a case at the NIH once a year in our cancer group who have treated someone for cancer who is a carrier to begin with and they reactivate the disease and they get an acute flare of hepatitis after their third or fourth cycle of chemotherapy.

So you can reactivate an inactive carrier to active disease but, in general, it is fairly benign. Now, can you treat them? Is it worthwhile treating them? Nothing happens when you do is the problem.

We haven't treated many inactive carriers with lamivudine. I have treated a couple and it doesn't--well, what can you do. There is nothing to do. The enzymes are normal. The DNA is low.

The liver histology is mild. So there is no kind of endpoint. But they don't clear surface antigen.

In fact, the levels of surface antigen don't decrease. This comes up in delta hepatitis because delta hepatitis usually is superinfection of hepatitis B with a delta agent and it typically occurs--when it occurs, the B is inactive. It is like an inactive-carrier state of B and they have delta on top of that.

If you treat those patients with lamivudine, for instance, nothing happens to the underlying B and the delta goes on. Interestingly, if you treat the delta, sometimes the B will reactivate. So there is this interactive--making delta the most confusing disease to treat, and difficult.

So I don't know that the therapies that are currently available are of use, but I think, actually, something should be tried to look at it carefully, looking at surface antigen titers, maybe even looking at histology in a small group of patients who are so-called inactive carriers.

DR. BLOCK: Thank you.

DR. GULICK: We will take one last question from Dr. Stanley.

DR. STANLEY: This may be a little too lengthy question but, at some point, I would like to have someone address for us the capability or the technology available to do genotypic or phenotypic resistance testing of hep B.

DR. HOOFNAGLE: I'm sorry; the technology available to what?

DR. STANLEY: To do genotypic and phenotypic resistance testing for hepatitis B.

DR. HOOFNAGLE: Well, those tests are--there is a commercial company that has a test for some of the classic mutations as well as--their sequencing is usually done to characterize the mutations. For instance, with lamivudine resistance, it is almost invariably in this YMDD--in fact, I think it has been invariably in the YMDD motif. So you don't need to do a lot of sequencing to detect that.

Furthermore, Glaxo and the companies that make adefovir have been doing this for investigators

DR. STANLEY: But I am more interested in the phenotypic capability.

DR. HOOFNAGLE: Phenotypic

DR. STANLEY: In vitro testing of--like we

do with HIV where we can culture and show that it is resistant or not. I know that it is not the same technology for hepatitis B.

DR. HOOFNAGLE: Cell-culture systems have been developed that used cloned hepatitis-B virus and put these mutations in that show that with the YMDD mutation, the virus in vitro as well is resistant to lamivudine and is sensitive to other agents like adefovir and entecavir. So you can show the lack of cross-resistance with the various agents and assess them.

DR. GULICK: We will take one more last question from Dr. Kumar.

DR. KUMAR: Dr. Hoofnagle, can you comment on this two-point decline in histology activity index. Is that a validated point? Has that proven to be, in the long term, if somebody has a two-point decline, that, over the long run, that they are going to do well?

DR. HOOFNAGLE: Zack Goodman is smiling at me, the pathologist from the AFIP who can comment on this. I think a two-point change in histology is not very significant. Of course, when you are doing a large study and you are looking at statistics, yes, it means that there is

improvement. But, in an individual patient, a two-point improvement in histology is not very significant.

I think a new algorithm has to be developed for what is a histological response, yes or no. It has to be more than two points and it should probably take other things in mind. For instance, it should be improvement in necroinflammatory and no worsening of the fibrosis, for instance. That would be bad, wouldn't it, if the fibrosis got worse but the inflammation was down a little bit.

Furthermore, I think if you start with an inflammatory score of 18 and you go to 16, that is different than if you start with an inflammatory score of 4 and you go to 2. So the pathologist at the NIH has suggested it, that we use a percent drop, that a greater than 50 percent drop in necroinflammatory should be worthwhile.

But I think this is the type of thing that needs to be tested on cohorts or samples to show what really correlates with a long-term improvement.

DR. GULICK: Can I suggest that we delay further discussion until the questions on that

particular point.

We will move on to Dr. Anna Lok from the University of Michigan who is going to discuss the treatment of chronic hepatitis B.

Treatment of Chronic Hepatitis B

DR. LOK: Good morning.

[Slide.]

First of all, I would like to thank the organizers for inviting me here and I would like to thank Jay Hoofnagle for setting the tone. He has provided a lot of the introductions which is going to make my job a little easier.

[Slide.]

I was asked to review sentinel trials on treatment of hepatitis B specifically focussing on interferon and lamivudine and to talk a little bit about what we currently do in practice and discuss some of the issues for future clinical trials.

[Slide.]

Jay had touched upon the goals of treatment. Actually, what we would like to do is have sustained suppression of hepatitis-B virus replication because we believe that, if we are able to suppress hepatitis-B virus replication, that this would lead to remission of liver disease and

ultimately to improvement in clinical outcome.

What the FDA is interested in knowing is really whether, if we achieve No. 1 and No. 2, that we would get No. 3. This, unfortunately, is going to be a very difficult question to answer and prove because of the very long natural history. But we will try to see if there is some data out there.

[Slide.]

Some of the things that we need to consider when we review a clinical trial or we plan a clinical trial is to ask ourselves what are the patients that we want to include in the study. I think that we now understand the natural history enough that we can't just lump hepatitis B as one group. It is a very heterogeneous disease with multiple phases and patients in different phases behave differently.

I think we can broadly consider patients with e-antigen-positive chronic hepatitis B. As defined by Dr. Hoofnagle's talk, these are patients who are e-antigen-positive with high levels of virus DNA, elevated liver enzymes, evidence of chronic hepatitis on liver biopsy.

The e-antigen-negative chronic hepatitis B patients are the ones who are

surface-antigen-positive, e-antigen-negative. The majority of them are e-antibody-positive. They have high levels of virus DNA. They are a little lower than the e-antigen-positive ones, but, generally speaking, the DNA levels are in the region of 10 5 to 106 to 107.

They should have elevated liver enzymes and evidence of chronic hepatitis on biopsy. We are not talking about the inactive carriers that Dr. Block asked about. Those are the patients that, right now, we are not sure that they should be included for treatment. Certainly, patients with decompensated cirrhosis, whether they are waiting for transplant or not, they need to have something to help stabilize them.

We need to think within each of these groups of patients what are the specific inclusion-exclusion criteria. I will come back to some of these issues. Obviously, we need to think about treatment regimens. Should this be monotherapy? Should this be combination therapy?

We need to think about sample size. Is this a properly done study? What are the endpoints for treatment and how do we assess response. Obviously, the most important question for today's

meeting is whether any of these things allow us to predict clinical outcome.

[Slide.]

Let's do a little bit of comparison about interferon and lamivudine clinical trials for patients with hepatitis B e-antigen-positive chronic hepatitis B.

Before we start comparing, it is very important for us to understand that we are comparing studies done about ten years apart. Our understanding of the disease and our capability of measuring various things differ in the era of the interferon trials versus the era of the lamivudine trials and, as we move forward to other new trials, what applies in the past may not apply in the future as we understand the disease better.

A lot of the interferon trials were actually controlled trials but the control patients did not receive treatment because it is very hard to justify giving patients placebo injections. Therefore, the controls usually received no treatment whereas with lamivudine, adefovir and many of the other orally administered nucleoside-nucleotide analogues, because they are orally administered with very little signature side

effects that the patients are aware of, placebos can be administered.

Interferon trials tend to be a lot smaller in size. In fact, there are very few industry-sponsored hepatitis-B clinical trials. The majority of them were investigator-driven and, therefore, they were single-center, small trials.

Lamivudine trials tend to be a little bit bigger. In the era of interferon trials, we didn't think about sample size. It wasn't something that we knew too much about. The lamivudine trials, and subsequently in all the licensing trials, the studies are powered for the primary endpoint.

Here we are talking about e-antigen-positive chronic hepatitis B but the primary endpoint for the interferon trials and the lamivudine trials are different. For the interferon trials, we used virological endpoints. Most studies used e-antigen loss and hepatitis-B virus DNA dropping to undetectable levels using whatever assay was available at that time point as the primary endpoint.

The assays were, in general, home-brew, dot-blot hybridization assays or some of them used the commercially available liquid hybridization

assays. The majority of these assays had a lower limit of detection of 1 million or 10 7 copies per ml.

The lamivudine trials used histology as an endpoint. As you have all heard, this is done with a decrease in the HAI by two points or more. Whether the fibrosis changed or not was not considered and the virological assays used in most of the lamivudine trials was the liquid hybridization assay which had a detection limit of about 10 7 even though the manufacturer claimed it to be 10 6.

[Slide.]

What about e-antigen-negative chronic hepatitis B patients? Again, the entry criteria for both interferon and lamivudine trials was whether the patients had detectable hepatitis-B virus DNA, but, again, detectable using whatever assays are available. Most of the patients had detectable DNA based on dot-blot or liquid hybridization assays for the interferon trials meaning that they had viral levels that were at least above a million copies per ml.

The majority of the lamivudine trials also used a liquid hybridization assay although some of

the studies used the branch-DNA assay or the hybrid-capture assays and many of the recent studies also report PCR data. Nonetheless, almost every study would only include patients with high viral load, probably 10
5, 106 or even higher. All these patients had elevated liver enzymes.

Some of the interferon trials include controls. There is only one trial of lamivudine that included controls, placebo controls, and, even then, the placebo controls ran through only half of the duration of the study. Unfortunately, with e-antigen-negative chronic hepatitis B, the studies tend to be smaller. Until very recently most people were saying that this is a rare disease, let's not put too much attention to it. So many of these studies tend to be smaller and less well organized.

Duration of treatment is highly variable. With interferon, it ranges from about three to 24 months. Most of the studies had been about six to twelve months. With lamivudine, initial studies treated patients for about twelve months and it was realized that the relapse post-treatment is very high. Many of these studies now go on to indefinite life-long treatment which is a major

concern, particular with issues of drug resistance.

What about primary endpoints? Histology, surprisingly, is not included as primary endpoint in many of these studies of e-antigen-negative chronic hepatitis B although this probably is very important. Since we are not really able to look at e-antigen loss or e-antigen seroconversion as an endpoint and, therefore, the endpoint tends to be fairly soft, ALT dropping to normal levels and hepatitis-B virus DNA undetectable, again using the assay of the day.

[Slide.]

Let's go on now to some of the interferon trials. Since there are really not that many good sentinel interferon trials, I took the liberty of sharing with you some data that will be presented at the ISAL Consensus Conference in a month from now. This is an update of a meta-analysis of randomized controlled trials of interferon presented by Craxi, et al.

They looked at 24 randomized controlled trials with about 900 interferon-treated patient and 400 control patients because, in some of the trials, there were several different dose regimens of interferon so the number of treated patients

outnumber the controls.

If you look at the difference in response rate between the treated patients and the controls, the interferon treatment does affect a positive response whichever parameter you use, ALT normalization, difference of 26 percent, clearance of e-antigen, difference of 24 percent, sustained loss of HBV DNA, again mostly hybridization assays, difference of 23 percent and clearance of surface antigen, a difference of 6 percent. All these are highly statistically significantly different.

You can also see a fairly tight 95 percent confidence interval.

[Slide.]

What about longer-range outcome. Here is where you get into trouble. First, you don't have 24 studies; you have twelve studies. Secondly, you start asking, the number of treated patients is fairly similar but how come you now have more controls. That is because a lot of these studies throw in a lot of historical controls, nonconcurrent controls. That makes this data very, very muddy.

The mean follow up is about six years. All the parameters indicate that the

interferon-treated patients did better in terms of loss of surface antigen, in terms of less hepatic decompensation, less development of hepatocellular carcinoma as well as less liver-related death. But, because of the use of nonconcurrent controls and because all these studies show significant heterogeneity of results, we are not sure how meaningful these results are.

[Slide.]

I am going to show you just one measure of the clinical trial of interferon therapy and that is Perillo's study. It actually led to approval of interferon therapy for chronic hepatitis B.

This is a study that involved about 160 patients, patients who received prednisone priming that was fashionable in the 1980s. We thought that if we give patients a short course of prednisone, suppress the immune system, bring down the liver enzymes and then abruptly withdraw it, that the immune system might rebound and the patients might now respond better to interferon therapy.

We have since then recognized that this may not be the smartest thing to do and it doesn't always do what you want. Then there were two groups that received interferon alone, 5 milliunits

daily or 1 milliunit daily--we now recognize that this is a suboptimal dose--and then an untreated control group.

Again, what you see is that, in terms of the primary endpoint which, in this study, was loss of hepatitis-B virus DNA by the Abbott liquid hybridization assay and loss of hepatitis B e-antigen. The two groups that received optimal dose of interferon had about 36, 37 percent response. The suboptimal dose obviously had a lower rate of response.

Again, we sort of saw that some patients dropped their virus DNA down to undetectable level but they still remained hepatitis-B e-antigen-positive. I should clarify, however, that, in this study, the patients received only sixteen weeks of interferon and treatment response was actually assessed six months after interferon was stopped. So it wasn't really while the patients were still on treatment but, rather, after the patients had come off treatment.

When you look at normal ALT normalization at the last follow up which is six months after stopping treatment, that is seen in about 44 percent of patients and a couple of patients that

reactivate after stopping treatment.

[Slide.]

So much for interferon treatment of e-antigen-positive chronic hepatitis B. What about interferon treatment of e-antigen-negative chronic hepatitis B. As I have mentioned, this is much more muddy. There were very few controlled trials so there were only a handful of untreated controls that one can compare against.

Since it is recognized that, in patients with e-antigen-negative chronic hepatitis B, sustained spontaneous improvement is rare. Dr. Hoofnagle mentioned that these patients tend to run and up-and-downhill course but, after they go down, they tend to go up again. So sustained remission is extremely uncommon and, therefore, inclusion of controls is rarely considered in clinical trials.

Often, clinical trials compare different regimens of interferon therapy or comparing some of these patients against active treatment. Many of these were just single clinical trials.

[Slide.]

I borrowed this data from Dr. Alfredo Alberti who presented data at the NIH-organized workshop two years ago. This is really summarizing

700, 800 patients treated with interferon therapy. As you can see, at the end of treatment, while the patient, be it three months or six months or twelve months duration of therapy, the biochemical response, meaning normalization of liver enzymes, was seen in about 55 percent of patients with a range of about 40 to 70 percent.

The virological response, meaning hepatitis-B DNA, undetectable in most instances by non-PCR-based assays, in about 50 percent of patients with a range of about 40 to 60 percent.

There are some studies that report on sustained response, and sustained response was, in general, assessed six to twelve months after stopping treatment. Overall, about 20 percent of the patients had sustained response with a range of about 7 to 38 percent. Much of this variability was related to the duration of treatment.

[Slide.]

What about histology? There are a couple of studies that did report on histology of interferon treatment in patients with e-antigen-negative chronic hepatitis B. As you can see, in the patients who received treatment, there was a decrease in the HAI score, fairly significant

in some of these studies, which you don't see in the controls.

The repeat biopsies were, in general, taken a year after the patients got into the treatment, most of the time at the end of the treatment duration, a few months after stopping treatment. But, with this very short follow up, you don't see an improvement in fibrosis even in the treated patients despite the dramatic drop in inflammatory score. This is what Dr. Hoofnagle had pointed out; changes in fibrosis score is important but it tends to lag behind. So, if you do biopsies very soon after you start the patients on treatment, even if there is an improvement, you are unlikely to see it unless you repeat a biopsy several years later.

[Slide.]

Because of the difficulties in finding good interferon trials for e-antigen-negative chronic hepatitis B, I have also shown you some slides which review the experience of a single center. Now, this is very muddy. This is, perhaps, the largest experience but they really report the entire clinical experience of the investigators over a ten-year period of time,

patients being treated with varying durations.

So this is 216 patients followed up for a median of seven years. Initially, they though a short duration of treatment would be sufficient, like for e-antigen-positive chronic hepatitis B. So the first 78 patients had a median of five months of treatment. Subsequently, they realized that the patients needed a longer duration of treatment and gave the patients a median of twelve months of treatment.

Some of these patients initially did not respond or responded and relapsed and were retreated. The data is really lumped together. But one thing which was consistent was that they used a low dose, 3 milliunits three times a week for the entire experience.

If you look at response at the end of treatment which was defined as normal ALT and hepatitis-B virus DNA dropping to below detection in hybridization assay, they saw, in 54 percent of patients. A year after stopping treatment, this is post-treatment, they had 24 percent of all patients who were able to maintain the response and, at the end of follow up, which is a median of seven years from the beginning, 18 percent of patients

continued to maintain the response.

But, again, I have to quality that some of the patients relapses and were retreated again in order to have this maintained response.

Predictors of response have been identified for interferon treatment of e-antigen-positive chronic hepatitis B and that is really mainly pretreatment ALT as well as pretreatment hepatitis-B virus DNA level. Predictors of response are far less clear for e-antigen-negative chronic hepatitis B, in general, duration of treatment appears to play a role. If you treat the patients for less than six months, the chance of having a sustained response is lower. If you treat the patients for twelve months, the chance is better.

It has also been shown by these investigators that patients respond very early, normalize their liver enzymes, drop their DNA. Within the first two to three months of treatment, they have a better chance of having and end-of-treatment response and a sustained response.

[Slide.]

So much for interferon treatment. Let me now move to lamivudine treatment. I am going to

focus mostly for e-antigen-positive chronic hepatitis B on three trials that are very familiar to most of the audience; the multicenter Asian trial reported in 1998, the U.S. trial reported in 1999 and an international trial reported in 2000.

These two trials compare lamivudine with placebo. They are all e-antigen-positive patients with hepatitis B virus DNA detectable by the liquid hybridization assay. In the Asian trials, patients with normal or elevated ALT can be enrolled. In the U.S. trial, patients all had elevated ALT. In the international trial, it is a three-armed trial. There was lamivudine alone for a year. There was interferon alone for sixteen weeks. And there was combination therapy of lamivudine for 24 weeks and interferon therapy for sixteen weeks with lamivudine starting eight weeks prior to the start of interferon.

Response was assessed at Week 52. If you look at e-antigen seroconversion, and, again, I have to clarify that, in most interferon trials, when we talk about e-antigen response, we talk about e-antigen loss and HBV DNA dropping to undetectable level using the DNA assay of the day. But, with the lamivudine trials, e-antigen

seroconversion was defined except for the pediatric study as e-antigen loss, detection of e-antibody, detection of e-antibody was not specified in most interferon trials and hepatitis B virus DNA dropping to undetectable level in general using the Abbott liquid hybridization assay.

Here you see that, for the lamivudine group, it is fairly consistent across the different studies, 16 to 18 percent of patients with e-antigen seroconversion compared to 46 percent in the placebo controls. You can also see very nicely in this particular study that 52 weeks of lamivudine and sixteen weeks of interferon had almost identical response rate in terms of e-seroconversion with higher e-seroconversion rates in the group that received combination therapy.

[Slide.]

What about histologic response? Histologic response here is defined as a decrease in HAI by two points or more with a liver biopsy performed at Week 52 which would mean that the patients were still on treatment in these two studies and, in this particular study, the lamivudine patients were still taking lamivudine at the time of the repeat biopsy whereas the group

that received interferon alone and the group that received combination therapy, they had been off treatment for 28 weeks at the time of repeat liver biopsy.

So, here again, in terms of histologic response, it is fairly consistent, about 50 to 55 percent of patients have improvement in HAI score by at least two points but note that, as Dr. Hoofnagle mentioned repeatedly, hepatitis B is a disease in which sometimes you can see improvement even in untreated patients. Whether this is a genuine improvement or whether this just reflects the up-and-downhill course of the disease is not clear, but about 25 percent of placebo patients also meet the criteria for histologic response.

Surprisingly, the combination-therapy group, even though there was a higher e-seroconversion rate, histologic response was actually less. But that may, in part, be related to the timing of the repeat liver biopsy because this was performed 28 weeks after stopping treatment whereas these folks were still on treatment.

[Slide.]

What about normalization of liver enzymes?

Again, fairly consistent. The treated patients, about 50 to 70 percent have normalization of liver enzymes compared to placebo which is much lower. In the multicenter studies, there were more patients with normalization of liver enzymes on treatment, but this was also true for the placebo group.

Again, when you look at the international studies, normalization of liver enzymes was fairly comparable across the three treatment arms.

[Slide.]

A big problem with lamivudine obviously is drug resistance. So, although at one year, the e-seroconversion rate is higher than the rate of drug-resistance mutation, this is genotypic resistance. This is really looking for the resistant mutation and the patients may or may not necessarily have breakthrough infection although the majority of them would have.

However, as you prolong the duration of treatment, and this is in the multicenter Asian study, to four years, you find that, even though continuation of treatment does increase, the e-seroconversion rate, but the two lines have crossed and now you actually have more patients

with genotypic resistance than patients with e-seroconversion. It does make you wonder if extending the duration of treatment is beneficial to these patients.

[Slide.]

What about lamivudine treatment of e-antigen-negative chronic hepatitis B? This, again, gets into muddy territories. We don't have good controlled trials because almost everyone believes that the patients won't get better on their own. This is really the only real controlled trial, or partially controlled trial, because the study is designed in such a way that the patients on lamivudine were to receive lamivudine for a year.

The patients randomized to placebo would only be on placebo for up to 24 weeks and then, unless they go into spontaneous remission, they are allowed to go into open-label treatment. So the comparison-group analysis can only occur at Week 23. Here, obviously, you see that the treated patients did better with about 60 percent of patients achieving response defined as hepatitis B virus DNA dropping to undetectable level using the branch-DNA assay which has a detection limit of

about 700,000 copies per ml as well as normal liver enzymes compared to about 4 or 5 percent in the placebo group, again showing that in the e-antigen-negative chronic hepatitis B patients, spontaneous improvement is not common.

As this group of treated patients continues out to Week 52, the majority of these patients, about 65 percent, still had maintenance of the response and roughly 35 percent actually dropped their DNA level to undetectable even using the PRC assay, and about 55 or 60 percent of these folks have improvement in histology as defined as decrease in HAI by at least two points.

[Slide.]

That is the good news. The bad news is if you try to take them off treatment after one year, you are going to get 90, 95 percent of the patients relapsed. The relapse in many of these cases is really not due to selection of drug-resistant mutation but, rather, you haven't actually controlled the disease well enough so that, if you stop treatment, everything is just going to come back.

[Slide.]

So this, again, is a slide that I borrowed

from Hadziyannis who put together a very nice review. This summarizes interferon treatment, lamivudine treatment and adefovir treatment for e-antigen-negative chronic hepatitis B while the patients are still on treatment and sustained response as assessed six to twelve months after stopping treatment.

If you look at interferon, short-duration, on-treatment response is in the region of 60 to 90 percent, sustained response, 10 to 15 percent. If you treat the patients for at least twelve months, on-treatment response is about the same. You don't have issues of drug resistance so whether you treat the patients for six months or twelve months, the difference is very small.

But you do get a higher rate of sustained response if you put the patients on treatment for a little longer, 20 to 25 percent sustained response.

Lamivudine is somewhat different. If you treat the patients for one year, at the end of treatment, you get about 70, 80 percent response but the response rate actually drops with longer duration of treatment because of the issue of drug resistance and the patients initially have virologic breakthrough and, ultimately, most of

them will develop biochemical breakthrough.

If you stop treatment at the end of one year, you get, at most, 10 percent sustained response and some people even say less than 10 percent. We don't really know what happens if you treat the patients for two years and then stop, or three years and then stop, because everyone is just terrified. Everyone thinks that you need to put the patients in treatment for the rest of his or her life.

I am not sure that that is a wise thing to do. We need to reexamine whether, after two or three years, there would be a subset of patients in whom, if they fulfill certain criteria, we can consider stopping the treatment.

You all have heard the adefovir data with one-year treatment. You get about 70 percent rate of on-therapy response and, again, we don't know anything about sustained response because these patients are, in general, left on-treatment.

[Slide.]

Let's now move on to decompensated cirrhosis. How do we actually assess response? This is getting more tricky because just bringing down the level of virus may not save a patient's

life because you are now talking about patients who have got end-stage cirrhosis. They may have ascites. They may have hepatoencephalopathy. They may already have had a couple of episodes of life-threatening variceal bleeding.

Even if you bring the level of virus down from 10 7 to 105, that is still a very small, shrunken liver. So we need to look at more than virus suppression. We do want to see biochemical improvement due to transaminases coming down. Thus the bilirubin comes down. Thus the albumin goes. Thus the prothrombin time or the INL improves.

Unfortunately, you find that, in some patients, these problems just go in different directions. Also you may some patients with a very high bilirubin level but the albumin is pretty decent, or some with a very low albumin level but the bilirubin is only 3. So it is very hard to actually take one biochemical parameter and say, okay, we are going to use this for monitoring the patients because different patients really have worsening of different parameters.

Therefore, it is important perhaps to look at more global parameters, a combination of markers. What has been used in many of the

clinical trials has been the Child-Turcotte-Pugh score. This is the CTP score which combines three laboratory parameters and two clinical parameters; albumin, bilirubin, prothrombin time, ascites and hepatoencephalopathy.

This has a lot of advantages because it allows us to look at biochemical improvement and clinical improvement. We are looking at not just one facet but trying to be generalized. There are, however, disadvantages with the CTP score because your score of ascites and encephalopathy is very subjective.

I can say that the patient has mild ascites. But a different investigator would say that the patient has got moderate ascites. Some patients appear to be a little bit mentally sluggish when I see them in clinic because they drove three hours to my clinic and they had to get up at 4:00 in the morning, so I thought that they were encephalopathic. But maybe they are not truly encephalopathic. So these can be subjective.

There are also problems with the laboratory parameters which are supposed to be objective because the CTP score assigns a numerical score based on the range of log values. So, for

example, a bilirubin of 3 and a bilirubin of 30 has the same score in the CTP scale. Clearly, someone with a bilirubin of 30 is a lot sicker than someone with a bilirubin of 3.

That is the reason why recently, in the transplant community, we have switched from the CTP scoring system to the MELD scoring system which allows a continuous range of log values. Whether that is better or not remains to be determined.

One can also assess these patients by looking at clinical complications, whether we can prevent development of ascites or whether we can make the ascites go away so that the patient can stop taking diuretics and ascites won't come back. We can look at decreased need for transplantation, decrease in hepatocellular carcinoma. And we can look at improvement in survival.

What have we learned so far? Of the studies that have been reported, we can see that lamivudine can bring about viral suppression, can bring about biochemical improvement, can bring about improvement in the CTP score. There are some studies that suggest that you can actually reduce clinical complications and there are some studies that suggest that you may obviate the need for

transplant although I would argue against that.

I think that, in most of these patients, you are delaying the need for transplant. I am not so sure that we actually decrease the need for transplant.

It seems that we are not doing much good here so far because there are still patients on treatment that have been reported to have developed hepatocellular carcinoma and it is hard to actually know whether you improve survival or not because this is not the type of clinical situation where we can do a randomized controlled trial.

I am going to just talk about lamivudine and not about interferon because none of us are really going to use interferon in patients who decompensate to cirrhosis because of the side effects.

[Slide.]

I am only going to show one study because there are many studies, none of them are perfect, and it is impossible to do perfect studies in patients who are that sick. But this is a study from Canada. It involves some several centers. They looked at 35 patients who decompensate to cirrhosis.

You notice that--and this is a common observation --some of these patients are so sick that, unless God is around and can turn on the switch, there is no magical treatment. Therefore, within the first few months, they had five deaths in seven patients who went on to transplant. But, for those patients who were able to take treatment for at least six months, and there were 23 of them, 22 out of these 22 patients had improvement in liver disease as defined by decrease in the CTP score by at least some two points. Only one patient had no improvement and went on to transplant.

So, the moral of the lesson is, some patients come to you and they are way too sick, they have already crossed the line and there is no magic treatment that would work fast enough to save those patients. However, if you are able to catch the patients before they have reached the point of no return and are put on treatment, you can stabilize the disease. You drop the virus level. You can stabilize the disease and they can do better.

That is better for some time but is it really a cure? Is it really these patients getting

out of the woods? That is where you start seeing problems because, even though these 22 patients had decrease in CTP score by at least two points, two patients subsequently died, one from spontaneous bacterial peritonitis which often is a complication of end-stage liver disease and one patient developed hepatocellular carcinoma.

So the fact that the patient is maintained on treatment and appears to be doing better does not necessarily mean that these complications will never occur. So, while some investigators are very gung-ho and think that they can take their patients off the transplant waiting list, I think is really--a more appropriate thing to do is probably to put the patients on hold.

What about these 20 patients who have not developed any problems? At the time of the reporting, 20 patients were still alive. They are about a year and a half from the start of treatment. It is hard to know whether the treatment improved the survival because there was no control group, but three patients had developed resistant mutations.

There is a lot of debate as to what happens if these patients were to go to transplant.

There have been case reports that these patients can be transplanted without evidence of recurrence if you give them adequate prophylaxis with hepatitis-B immunoglobulin and lamivudine. But there are also several reports from Europe showing 100 percent recurrence rate in the absence of other drugs that can suppress the lamivudine-resistant mutations.

[Slide.]

Let me now move on to what we do in practice. The issues are who to treat, what treatment and when to stop treatment.

[Slide.]

I am going to sort of borrow some of these things from the AASLD Practice Guidelines and this, in turn, was borrowed from some of the conclusions that we made at the NIH workshop two years ago.

Essentially, we said that it is very clear that current therapy for hepatitis B works short-term but has very limited long-term efficacy. It is still very worrisome if we have to put patients on treatment forever and ever when you have a twenty-two-year old patient or, worse still, when you have a child.

It is very important that we think very

carefully before we start the patients on treatment, particularly if we don't know when to stop. We must balance the benefits and the risks before we start the treatment. The factors that we need to consider are, really, how old is the patient, how bad is the liver disease, what is the likelihood of the patient's responding to treatment and what are the potential side effects.

[Slide.]

This is what we recommended. This is really based on just interferon and lamivudine data. Clearly, as new therapeutic agents become available, these guidelines need to be reassessed. But what we said was if we have someone who is e-antigen-positive with high levels of DNA but the liver enzymes are normal or minimally elevated, at the moment, we are going to just observe these patients.

It is not that we are not worried about these patients. It is we don't have effective treatment for them. None of the treatments, be it interferon, be it lamivudine, is effective in these patients with high levels of virus but normal liver enzymes. Therefore, we choose to observe them.

For people who are e-antigen-positive,

high levels of DNA, with elevated liver enzymes, we can consider using interferon, we can consider using lamivudine, because it appears that sixteen weeks of interferon has similar efficacy to lamivudine and it is really the patient's choice or the physician's choice.

Clearly, patients who are interferon nonresponders, they do respond to lamivudine and they can be considered for lamivudine therapy. Patients with contraindications can use interferon, which does happen quite often if the patient has underlying autoimmune disease. If the patient has some significant depressive illness, they are good candidates for interferon therapy and they should be considered for lamivudine.

For e-antigen-negative patients who have high levels of DNA, elevated liver enzymes, again, they can receive interferon therapy or lamivudine treatment. With both treatments, longer-term therapy is required but we don't really know what longer-term means. Is it two years? Is it three years? Is it truly for life?

For the patients who are e-antigen-negative with very low levels of DNA, this is not actually negative DNA but negative

using assays with a detection limit of 100,000 copies and normal liver enzymes. At the moment, we don't recommend treatment because we don't believe that there is any treatment out there that is going to make the situation any better. So why take a treatment that is not going to make you any better.

For patients who have already developed cirrhosis, if the levels of virus are high and they are very well compensated--when I say compensated, I mean you don't know that a patient has cirrhosis until you do the biopsy--these patients can sometimes still be considered for interferon therapy.

Some of the early interferon trials did include a bunch of patients with histological cirrhosis but you didn't know that they had cirrhosis until the biopsy reports comes back. Certainly, you can consider lamivudine. But, by the time the patients have decompensated, interferon is not an option. Lamivudine would be the treatment. Of course, as we know, alternative treatment, we would have to reconsider these options.

The biggest problem in the decompensated patients is when do we start treatment? Ideally,

you want to start treatment early so that you have a chance to improve the patient's clinical condition, give them a chance to get on a transplant waiting list. If they don't need a transplant, maybe the transplant can be deferred for five years. If they need a transplant, you give them time to wait for the transplant.

However, there is also the argument that if you put patients on treatment too early and now they develop resistance, and now they decompensate and an organ is not available, or now you bring the virus level up ten-fold higher and they develop recurrence transplant, that is not a very good option.

But, again, with availability of other drugs, we have to rethink all these and maybe starting patients on treatment early might be an option that we should consider. Certainly, these decompensated patients ought to be put on a transplant list.

[Slide.]

I keep giving people options because I do think that, in terms of efficacy, pure efficacy, the two drugs are fairly comparable, both for e-antigen-positive chronic hepatitis and for

e-antigen-negative chronic hepatitis. But there are other considerations.

One of the advantages of interferon is that one can consider a more finite, more limited, duration of therapy. It seems that, for the e-antigen-positive patients and, perhaps also, for e-antigen-negative patients, you have a better likelihood of getting a durable response.

In most of the e-antigen-positive studies, as we follow the responders out to eight to ten years, we find that there is an 85 percent durability. With lamivudine treatment, it appears that durability is lower. There is no issue, no concern, about resistant mutants.

Most patients don't like parenteral medications and most patients walk away as long as soon as they hear the long list of side effects of interferon therapy. So the course as well as the side effects sway patients as well as some physicians away from using interferon therapy.

Lamivudine is convenient. It is orally administered, negligible side effects. Certainly one year of lamivudine is far cheaper than sixteen weeks of interferon but, if you put patients on treatment for five years, it all adds up

eventually. So I am not so sure that it is less expensive.

The biggest concern is no one knows when to take the patients off treatment. This is really not a good thing. When you put patients on and you just keep saying to them, "Well, I don't know. I don't know. Let's wait and see and think about it again six months from now."

Perhaps a more important issue is the resistant mutants, a regimen, we have been told, "Well, don't worry. The resistant mutant has diminished replication fitness and maybe it is not going to be a big deal." But, as we follow more and more of these patients out, we do see some patients in whom the virus level keeps creeping up. The disease comes back and, from time to time, we hear of patients acutely decompensating and we do hear of patients dying.

Again, as we get other alternative treatment that we can offer these patients, hopefully, we don't hear about those sad stories anymore. But this continues to be a concern.

[Slide.]

These are the doses that we recommended for interferon therapy. The interesting thing with

interferon therapy is that there wasn't really good dose-response studies. Doses were picked from a hat. I remember twenty years ago when I was a fellow, I used some 50 million units I.V. infusion and I, as a fellow, was asked to stand by the patient's bed to make sure that the shaking and rigor wouldn't throw the patient off the bed and that the patient wouldn't become very hypotensive.

We have come a long way. We have scaled down. But whether these are really the appropriate doses, we don't know for sure. For e-positive patients we recommend sixteen weeks. There is some data to suggest that, in a subset of patients, a longer duration of therapy might be of benefit. Patients how haven't quite responded at sixteen weeks might benefit if you continue to 24, 32 weeks. But we don't really have a lot of data.

For e-negative patients, we think that perhaps at least twelve months, maybe longer, but, again, it is a lot of maybes, a lot of question marks.

[Slide.]

With interferon, there are, again, a lot of question marks. We know the dose--and, actually, I am not sure. I don't even know the

dose--because the dose-response curve were really based on using the Abbott liquid hybridization assay, a fairly bad HBV DNA assay and, had a better HBV DNA assay been used, whether we would have picked 100 milligram or whether we might have ended up picking a higher dose because we would be able to see that a higher dose actually brings a further drop in viral load, I don't know for sure.

With patients with HIV coinfection, we do recommend a higher dose and, in conjunction with other HIV treatment.

The biggest problem with lamivudine treatment is we don't know what is the duration of treatment. For the e-positive chronic hepatitis B patient, we say, well, at least one year and, at the end of one year, we are going to think. If the patient has developed e-seroconversion, you should certainly consider stopping treatment.

But do you stop treatment the moment has e-seroconversion? Probably not because increasing data suggests that, if you do so, the patient is going to relapse very quickly. So we believe that we need to maintain the patients on treatment for a little longer before we stop treatment. But what is a little longer? Is a little longer three

months? Is a little longer six months? Is a little longer twelve months?

Those are questions that we don't know. But what is more of a problem would be these patients whose DNA continues to be at low level but they are still e-antigen-positive. Remember only about 16, 17 percent of patients will have e-seroconversion at the end of one year. So the majority of the patients are going to be here, or here.

What do we do? The data from the multicenter Asian studies would suggest that if you leave the patient on treatment for a second year and a third year and a fourth year, some of these patients are going to e-seroconvert subsequently but you also run the risk of these patients developing resistance with longer duration of treatment. So, is it a wise thing for us to leave the patients on continued treatment or should be stop if they haven't e-seroconverted at the end of one year?

What about patients with break-through infection? At the time when we wrote these guidelines, adefovir was still investigational. So we said, well, continue treatment if the patients

remain clinically stable, if their current ALT and DNA levels are lower than pretreatment because we were worried that, if we stopped the treatment and the wild-type virus comes back, the disease will be worse.

We recommend stopping treatment only if the patients clinically deteriorate. If the patients are worse off than before treatment, there is no point in leaving the patients on that treatment. But, again, the recommendations will change as we have other alternatives available to us.

With the e-negative chronic hepatitis B patients, we know that the patients need longer than one year of duration of treatment. But how much longer? That is the question that we don't know.

[Slide.]

Let me now move on and wrap up by talking about some issues for future clinical trials. We need to talk about study population, entry criteria, treatment regimens, indications for assessing treatment response, endpoints, durability of response and short- and long-term safety and efficacy.

[Slide.]

We have mentioned that, with the study population, we should consider these different groups separately. The e-positive chronic hepatitis B, the e-negative chronic hepatitis B, the decompensated cirrhosis. So far, most of the studies have forgotten about these other groups. The patients with coinfection, the patients with extrahepatic diseases, the patients on immunosuppressive or chemotherapy. Some of the trials have involved children.

[Slide.]

What about entry criteria? For the e-positive patients--well, actually, for both groups--we have to consider viral load, liver enzymes and liver histology. For the e-positive patients, the majority of them have viral loads from 10 5 to 1010. So an entry criteria of 105 or 106 sounds reasonable.

For the e-negative patients it is less clear because these patients tend to run fluctuating viral levels and a lot of these patients do run lower viral levels. So we lower the entry criteria such that we take patients in with 10 4 to 105 or do we need to insist on higher

levels. What about liver-enzyme levels? Because pretreatment ALT is a very predictor of response, patients with normal ALT or minimally elevated ALT tend not to respond.

So we tend to recommend a pretreatment ALT of two times the upper limit of normal. The Asian Pacific Guidelines actually recommend going up to five times the upper limit of normal as the entry criteria for starting patients on treatment. Again, for e-negative patients, we only treat patients with disease, not the inactive carriers. But what is the cutoff that we use?

Do we need to insist on having histology as an entry point for starting patients on treatment? This seems to be still important for clinical trials but what about in clinical practice and if we want to have a liver biopsy, how much liver disease, in terms of inflammation and fibrosis, should we use as an entry criteria?

[Slide.]

What about the treatment regimens? Should we still be looking at monotherapy or should we really be moving from the stage of monotherapy to look at monotherapy versus combination therapy? Should we be using placebo controls or, in view of

the availability of so many different drugs, be thinking of active controls? Placebo-controlled trials have their advantages, but we also need to look at feasibility. What is the likelihood of enrolling a patient into a study in which there is placebo when there are so many other treatments available.

What about the duration of treatment? Should we be looking at finite duration, treatment of one year or two years, or should we actually mandate that there is built-in follow up and follow on so that we can address the issues of durability of response, long-term safety, drug resistance and what are the additional responses if we extend treatment.

These need to be planned ahead of time so that there are not gaps between the licensing studies and the subsequent studies because, once you have gaps in between, all the data become messy and muddled.

[Slide.]

What about endpoints? So far, many of the antiviral trials in hepatitis B have focused on histology as an endpoint, in particular using a decrease in HAI by two or more points. There are

advantages of using histology because this is a direct assessment of liver disease. This is to look at inflammation which is more dynamic and fibrosis which is, perhaps, a more long-lasting effect.

But there are disadvantages with looking at histology. I requires two biopsies. Liver biopsy is not a fun thing for the patient. It is not a fun thing for the physician either because there is risk of complication, it is an expensive test, there are problems of sampling error, inter- and intra-observer variability.

The scores are not linear. Even when the score is 1, 2, 3, 4, 5 and 6, the increment from 1 to 2 versus the increment from 2 to 3 is not, necessarily, the same in terms of increment in inflammation, increment in fibrosis. These are all very subjective.

Certainly, histology does not apply outside of clinical trials and, as Dr. Hoofnagle mentioned, we don't know what it means if someone drops their HAI by two points, particularly if this occurs only when a patient is still on treatment.

[Slide.]

What, then, are the alternatives that we

can think of? For the e-antigen-positive patients, I propose that we should seriously consider--I am not saying that this is definitive, but I would throw this out for discussion--that we should look at e-antigen loss. I am still not sure whether we need to insist on detection of e-antibody and whether this means a more durable response or not.

We want a substantial decrease in HBV DNA level, probably to less than 100,000 copies because studies in the 1980s show that if we drop the DNA level to undetectable by hybridization assays, many of these patients do have improvement in the liver disease and we do want to see normalization of liver enzymes.

For the e-negative chronic hepatitis B patients, we want to have a drop, a substantial drop, in DNA level. Here I am not so sure where we want it to be dropped down to. These patients start at a lower level. I believe that these patients need to be dropped at lower levels than the e-positive patients. Many of us think that it should be dropped down to less than 1,000. Some people think that we should drop it to below detection by PCR and I throw it out for discussion.

We also want to see normalization of liver

enzymes. For the patients with decompensated cirrhosis, we also want a drop in viral load. We want to see improvement in biochemistry and clinical outcome so we want to see improvement in CTP score and, perhaps now that the transplant community has moved to using the MELD score, which is a combination of INR, bilirubin and creatinine, we may want to use this as an endpoint as well.

[Slide.]

So the question is if we use as endpoints, do they correlate with histology? Do they correlate with improvement in clinical outcome?

[Slide.]

There is very limited data because of the prolonged natural course. Most prospective studies have limited follow up. I am going to lose my job if I tell my boss that I publish a paper every twenty years. There are very few randomized controlled trials and many of them have small sample size.

So a lot of times, people use retrospective studies, use historical controls, nonconcurrent controls. But then you run into the risk of disease heterogeneity. You are comparing apples and oranges.

[Slide.]

Let's now review a few studies to see if there is some data out there. This is Perillo's study of interferon therapy of e-antigen-positive chronic hepatitis B that I showed you earlier. He looked at treated patients that had paired biopsies. The repeat liver biopsy was done six months after stopping treatment.

In the treated patients who had a response, you see a dramatic reduction in HAI score, about two points, with rank assessment improvement outweighing deterioration. In patients with no response, you don't see much in the way of improvement and, on balance, it is about the same.

On treated controls, not much in the way of improvement. So the virological endpoints do correlate with histological improvement if you look at it in that way.

[Slide.]

What about clinical outcome? Here is a study from the German group where they included interferon-treated patients and untreated controls. Here, unfortunately, some of the untreated controls were nonconcurrent controls. They included controls from previous clinical trials as well as

nonconcurrent controls. But what you do see is that, in the treated patients, if they clear e-antigen, they did much better than the patients who remained e-antigen-positive in terms of proportion with complication-free survival.

These are patients with survival without liver decompensation. This is also true for untreated patients indicating that clearance of e-antigen is a good thing if this is associated with viral suppression as well.

[Slide.]

What about e-negative chronic hepatitis B patients? There is some data from Hadziyannis' group again that overall you don't see as dramatic improvement but, in the interferon-treated patients with sustained response, there was also improvement in transplant-free survival compared to the patients who were treated and did not respond or the patients who were not treated.

Again, this is not randomized controlled trials. These are really lumping patients who got treated versus those who didn't get treated.

[Slide.]

What about lamivudine, then? This is a complicated slide and this is some data that Lynn

Combray and Steve Gardner provided. This really combines the U.S. e-positive study and the multicenter Asian study. The orange represents the placebo, the yellow represents the lamivudine-treated patients.

The shaded part represents the patients with e-seroconversion. This is looking at Week 52 DNA levels and e-seroconversion. As you would imagine, the treated patients, the DNA levels shifted to lower levels. In the initial published report, they used the liquid hybridization assay and this is really reanalysis of some of the patients using the PCR assay.

So the DNA level shifted with the treated patients and you find that there is a reasonable correlation between the viral load at Week 52 and e-seroconversion in the sense that most of the patients with e-seroconversion had HBV DNA level dropped down to below 103.

Then you get some e-seroconversion with viral load of 10
3 to 105, but very few when the viral load is above 10
5.

[Slide.]

What about correlation between viral load and ALT normalization. Again, orange is placebo,

yellow is lamivudine and the shaded bars are the patients with normal liver enzymes. Here, you find that you can normalize liver enzymes even with higher viral levels. With e-seroconversion, you need to drop the viral load to about 10 3 but if you drop the viral load to about 10 6, the majority of these patients will have normalized liver enzymes.

You also get normalized liver enzymes in some of these patients amazingly with viral levels of 10 8 and 109. But, obviously, many of these patients have elevated liver enzymes.

[Slide.]

What about histology. Once you get into histology, it gets a little bit more complicated. I think, in part, it is because of the way we define histologic response. At low viral levels, the majority of these patients have improvement in histology. Certainly, when the viral level is below 10 4, almost everyone had improvement in histology. Between 10 4 to 106, you still get the majority, more than 50 percent, with improvement in histology, less improvement in histology with higher viral levels but, surprisingly, a fair number have improvement in histology again even at viral levels of 10 8 and 109 which makes us wonder

what this all means.

[Slide.]

Finishing up with two slides that John Fry and Carol Brosgart shared some of the data in the adefovir studies. This slide shows the e-positive chronic hepatitis B patients, adefovir Trial 437. These are all the patients on adefovir 10 milligram.

If we look at a composite endpoint with e-seroconversion and with decreasing viral level and with normalized liver enzyme, do we actually get improvement in histology? The first thing you see is the patients with e-seroconversion compared to the patients who didn't have e-seroconversion, the viral load shifted to the left side. So they tend to have much lower viral levels and almost every one of them had HBV DNA levels of less than 10 4.

ALT normalization represents the orange bar so the majority of the patients with e-seroconversion also had normalized liver enzyme and almost every one of them had the shaded bar which means that they also have improvement in histology.

But, if you look at the patients without

e-seroconversion, some of them also had low viral levels but didn't seroconvert. Some of them even have normal liver enzymes but still didn't serconvert. Some of them even have normal improvement in histology.

So, again, regardless of e-seroconversion, if the viral level is low and the person has normalized liver enzymes, a lot of them also had improvement in histology. But, again, the amazing thing is if the viral level is high and, even in patients whose ALT remains elevated, you also see a fair number of them with improvement in histology. So, again, what does this mean?

Is it a problem, all these virological and biochemical endpoints or is it a problem with the way we interpret liver histology?

[Slide.]

This is the e-negative chronic hepatitis B study, adefovir patients, placebo patients, patients on treatment, viral load shifted to the left side, lower levels, compared to the untreated patients. Again, if you have low viral load, most of these patients have normalized liver enzyme, the orange bar, and most of them have the shaded bars with improvement in histology.

But, even in the placebo patients, even in those of elevated ALT, you also have improvement in histology and, again, you tend to see improvement in histology spread all the way and it doesn't correlate as well. So it raised, really, a lot of questions as to what the histology response means.

[Slide.]

This is my last slide. One of the things that we really need to address is not just the primary endpoint which then allows FDA to decide whether a drug is approved, but in clinical practice, it is also when do we stop treatment? The primary endpoint for a clinical trial is one thing, but we have learned that it may not necessarily mean that this is an indication for stopping treatment.

This is something that we all need to understand because, in practice, we have to be able to advise physicians how long to treat the patients, what do you need to see in order to stop treatment. Obviously, we want to see that they achieve on treatment response or the primary efficacy endpoint.

We need to see that, but it seems that these patients also need to have the ability to

maintain these responses for a certain duration of time while they are still on treatment before you can take them off treatment. The indications for stopping treatment may vary depending on the severity of the underlying liver disease and the immune status of the host. By that, I mean that, in a patient who started off with decompensated cirrhosis, even if they achieve some of these endpoints, you might still not have the courage of stopping the treatment and running the risk of relapsing.

For patients who require long-term immunosuppression, for example, a renal transplantation who requires lifelong immunosuppressive therapy, even if everything looks good, is it safe to stop the patient's treatment? These are all questions that we need to deal with.

Thank you.

DR. GULICK: Thanks, Dr. Lok.

Are there one or two quick questions from the panel? Dr. Wood?

DR. WOOD: I had a question regarding the decompensated patients with cirrhosis. What would you consider a significant magnitude drop in terms of the HBV DNA levels as far as an endpoint

response in that specific patient population?

DR. LOK: I think, what that specific population, the degree of viral drop is, perhaps, not as important as looking at biochemical and clinical endpoints because many patients with decompensated cirrhosis have fairly burned-out disease. Even if they have what we call high viral load, seldom do we see it 10 9, 106. We might see it at 10 6, 107. So, to actually expect a hundred-fold or a thousand-fold drop might now realistic and it may not be necessary because, perhaps, a tenfold drop is sufficient to bring about some clinical improvement.

I really think that biochemical and clinical parameters might be more important in those settings.

DR. GULICK: Dr. Wong?

DR. WONG: I guess my question also concerns the decompensated liver patients. Both yesterday and today, we have seen presentations where there seem to be clinical improvement but there was no comparator group. How should these sorts of data be interpreted? How much improvement does one have to see and what should be the proper control group even if it is historical controls?

What are the criteria that should be used for deciding that something really worked in the clinical sense or the biochemical sense rather than the virological sense?

DR. LOK: Controlled trials are never going to be possible if you have a patient who is sitting in front of you with the risk of dying within three months and you say, "I am going to randomize you to placebo." So that is impossible to do.

We can use historical controls. Unfortunately, this is not a disease for which we have really very good data. Or you can actually use the patients themselves as some controls if you have data on the patient. By the time patients come to you with decompensated liver disease, in general, we don't see a spontaneous improvement unless they have recently had a flare and, for some reason, you are able to turn off the flare.

So, for example, if a patient comes to you with a bilirubin of 15 and now drops to 3, you have to say that whatever I put the patient on, it is doing its job and this is not just the act of God. Likewise, if a patient develops ascites and had required huge amounts of diuretics, multiple

paracentesis and, six months later, you find that the patient can be off diuretics with no ascites, this has to be a clinical improvement.

Therefore, I think that we are probably going to sort end up trying to define how much improvement in bilirubin is an improvement, how much improvement in pro-time, how much improvement in albumin and how much improvement in some of these aggregate scores, whether we use the CPT score or the MELD score, is considered to be clinically relevant.

Again, this is an issue that is going to be complicated because you can't say, well, a drop in the bilirubin by 2 milligrams per deciliter is important because, if you drop from 4 to 2, it is, perhaps, important but if you drop from 15 to 13, it is not.

So these are really tricky issues. But I think, ultimately, it is sitting down and figuring out do we use a percentage drop or do we use a percentage drop and dropping below a certain level because, for example, you can say, a 50 percent drop in bilirubin, and it should be less than 3. That is perhaps an improvement.

Other than that, I am not sure. Mortality

is very hard because, when you have the way out of transplanting the patients. So you are not allowing your patients to die. You are going to get your patients transplanted. Using transplant as an endpoint also is tricky because, across the country, and certainly across different countries, the availability of transplant varies.

In some states, the patients need to wait for a little longer than in another state. So it isn't necessarily true that, if your patient waited six months versus waited nine months, that this is always a reflection of the clinical severity of liver disease. Sometimes, it is a reflection of organs being available versus not being available.

DR. GULICK: Thanks again, Dr. Lok.

We will take a break now and we will reconvene at ten minutes of 11:00.

[Break.]

DR. GULICK: Our next speaker is Dr. Nathaniel Brown from Idenix Pharmaceuticals to give a pharmaceutical perspective on development issues for hepatitis B.

Pharmaceutical Development Issues for Hepatitis B

DR. BROWN: I thank the FDA organizers for inviting me here today.

[Slide.]

As Dr. Murray indicated in his overview comment, part of my talk will be on an effort to present a perspective of what many of the companies in industry working in hepatitis B consider to be the most important issues for discussion and potential resolution today so that we can go forward with progress in this therapeutic field.

But, as was implicit also in Jeff's comment, the first part of my talk will really be a personal perspective based on eleven years of developing hepatitis-B drugs. I think, when the organizers called, I woke up and realized I had actually worked on four nucleosides and one interferon project over the last eleven years.

I think my wife tells me to stop worrying about hepatitis B, at least on the weekend.

The other thing that I have noticed at scientific meetings is it has become popular to replace the opening humor with disclaimers. So I think I will try that. I think both my current and past company would want you to know that my perspectives today are largely personal and do not represent the views of either Glaxo or Idenix.

With that, let's start out. I think you

will find there are some common themes in my talk that play off of things you have heard from Jay and Anna and, hopefully, share a lot of experience using these kinds of endpoints in clinical trials.

[Slide.]

What I am going to talk about today in the first part are some personal reflections and perspectives based upon working in this area for about eleven years trying to develop new drugs for hepatitis B.

Toward the end, I will present an industry perspective--I guess this is the one place I forgot to change the word "consensus"--but a perspective among a number of people working at companies. That will be clearly identified at the end so, up to that point, these are personal perspectives.

[Slide.]

I thought it might be worthwhile--the point was made yesterday, it is very important to learn from the HIV experience. Personally, I think it is also important to keep in mind some of the important disease differences which are not always highlighted in the race toward combination therapy.

So let me try that. First, I think, as probably Jay alluded to early on, while, in HIV

infection, there is really one end-stage pathway which is essentially protein-immune failure due to loss of depletion of the CD4 compartment. In hepatitis B, there are two ways patients can die and I think we are aware of both of those; liver failure related to cirrhosis and, of course, hepatocellular carcinoma.

These may have a common pathway early on with regard to the necroinflammatory liver disease acting as kind of a promoting environment for tumor formation. I think that was highlighted in the New England Journal editorial a couple of weeks ago by Jake Liang and Mark Gainey. But I think the implication for this group is we need to understand that a lot of clinical trials so far have been founded more on the predicate of knocking down the liver inflammation and hopefully preventing end-stage cirrhosis.

We don't yet really know whether we are going to have an impact on HCC. It is a fair guess that if the necroinflammatory response and the neoregenerative response in the liver is important in HCC genesis, that, if we treat patients early, we might be able to have an effect on HCC. But if we treat patients in their 40s and 50s when there

may have already been malignant transformation, then I think experience suggests that we will have successes with regard to necroinflammatory responses and failures with regard to patients dying of HCC. So I think we need to keep that in mind.

Probably the two strongest arguments for early treatment, I believe, are that argument that maybe, early on, just knocking down necroinflammatory response, if we have any chance on HCC, it may be at that stage of tumor development. Then the second one may be to prevent advanced fibrosis and cirrhosis.

Another important disease difference which has been highlighted by both clinical speakers so far is that this infection can spontaneously revert to low replicative states, typically galdeans and anesians, in seroconversion. This can happen, as previous speakers mentioned, spontaneously or with therapy.

So, as you already know, the therapeutic goal becomes, in e-positive patients, to try to induce this state before the patient is already cirrhotic. I think there are smidgens of data that say that e-seroconversion, when the patient has

advanced disease, may actually be dangerous and can knock out the last few hepatocytes.

But this leads to a very important observation that has been discussed today. A very important goal in trials is to look at the issue of can we stop patients on therapy. The answer in e-positive patients, as Anna and Jay well highlighted, e-seroconversion or e-clearance, e-loss with DNA suppression, that does appear. We are getting toward an appreciation of when patients can be stopped in e-positive disease and simply followed.

It is important to emphasize that patients who are stopped still need close observation because they are still s-positive and they can potentially reactivate.

Another important point that was covered was HBV infection is quite a bit slower than HIV to cause irreversible damage to the target organ, perhaps ten to fifty years for hepatitis B compared to about five to twenty for HIV.

[Slide.]

There are some important biologic reasons for why the disease is slower to irreversibly damage the target organ. These are partly related

to the virology. Hepatocytes are not known to be a life-long cell type. There appears to be neoregenerative activity in the liver almost continuously.

The life span of uninfected hepatocytes is poorly established but it may be as short as months. The life span of infected hepatocytes is even shorter than that. It may go down to days. So the primary target cells for hepatitis B are turning over at variable rates. That is one important concept.

Whereas, with HIV or herpes viruses, which this group has a lot of previous experience with, the primary cell types, the primary targets, may be long-lived cell types, n the case of herpes viruses, for example, neurons or memory CD4 cells and other long-term cell types.

Another key virologic difference is that the replication templates for hepatitis B are maintained by a continuing level of polymerase activity in the so-called intracellular conversion pathway and not by cellular alpha polymerases whereas, with herpes viruses and HIV, once that double-stranded DNA integren or episome has been formed, those have maintained by cellular

polymerases and, in those cases, in the long-term cell types.

So it is hard to get rid of viral templates in herpes virus and HIV infections, but in HBV, they are continually turning over and you can get a net reduction when you the infected hepatocytes die.

So what that means, I think, biologically and clinically, and it does influence my thinking about hepatitis-B trials, is that treatment of chronic hepatitis B infection can be more realistically associated with long-term template reduction compared to HIV and herpes viruses. But it may take a very long time and the current treatments are probably not adequate to eradicate infection.

But there is a theoretic chance for virologic cure. These considerations also add up to the concept that HBV is less likely to be associated with early resistance and I think the lesson with lamivudine is a perfect example there, polymerases are ten-fold better fidelity for the HBV polymerase compared to the HIV reverse transcriptase.

Sure enough; with hepatitis B with

lamivudine the medial time to detectable YMDD mutants is on the order of three years whereas, in HIV, it is on the order of three months, almost parallel to that ten-fold difference in polymerase fidelity. So I think, to my mind, these are important considerations that do bear upon the issue of how valuable would monotherapy be versus sequential switches versus combination therapy.

[Slide.]

Should we investigate combination therapies in hepatitis B? I believe the answer is yes but we need to say that the combination therapy needs to prove its worth in this disease just as it has in HIV. The underlying biologic and virologic considerations are somewhat different particularly with regard to target cells and templates. So I personally believe that combination-therapy investigations should focus around the issue of combination therapy with any of two categories of goals. If combination therapy does actually improve durable responses in the overall compensated patient population, we, of course, would all like that.

Short of that, there are patient subpopulations where combination therapy may have

value. These are patient subgroups where virologic breakthrough may happen more frequently or the medical consequences of virologic breakthrough are often more severe with quicker progression of hepatic disease. The includes decompensated cirrhotics whom you have heard about today. Transplant recipients can progress quite rapidly after reinfection or reactivation.

HIV or other coinfected patients have proved to be a rather difficult group to manage with monotherapies and possibly precore mutant disease, which has been talked about a lot today, may be a little more refractory to monotherapy for the reasons I think highlighted in Dr. Lok's talk and Dr. Hoofnagle's.

So combination therapy may have value. But I would like to approach it with specific goals in mind. The improved efficacy, of course, in any one of these categories must offset the potential increase in cost and potential toxicities.

[Slide.]

You have heard about the array of endpoints that are used in hepatitis-B clinical trials over the last ten to twelve years; e-loss, e-seroconversion, s-loss, s-seroconversion. These

are becoming fairly standard. I think highlighted in the publication at both the NIH workshop and the AASLD Practice Guideline is the possibility of composite endpoints which, I think, Anna touched upon quite extensively, the possibility of e-loss coupled with some measure of DNA suppression.

Those endpoints are attractive. Let me mention that I think what was also apparent on both Jay's and Anna's slides that actually is the very endpoint that was used in the early interferon trials. So composite endpoints are not new but I think there was a sense that that might be a good way to go with regard to linking viral suppression with some of these surrogate endpoints.

You have heard a lot about histology, really, since yesterday morning onward. I will talk about that a little bit.

[Slide.]

I have tried to pick data slides that have been very important to my perspective thinking about hepatitis B and hepatitis-B trial design. So, when you see a data slide, most of them are going to be lamivudine slides. I am using them to illustrate some scientific points around endpoints. I tried to pick the ones that have taught me the

most of the last eight years or so of experience.

This is a now rather famous cohort of 58 Asian patients out of the original Asian multicenter study, the Lai study, so to speak, who were treated with lamivudine continuously for up to four years in this display.

There are some important lessons in this with regard to the endpoint of e-seroconversion or any endpoint that incorporated e-loss. We think the pattern would be similar if we had just done this according to e-loss. This happens to be the e-seroconversion endpoint of e-loss and antibody gain but, probably, the lessons are the same for any measure of e-clearance.

Some of the important lessons are quite apparent here. I think to get to one of Tim's points, should we be treating patients with inactive disease? What you see here is the result--oh; I think Anna highlighted it. I should mention in this cohort, almost a third of the patients were actually ALT normal at the start. The Asian study was the only one that allowed normal ALT patients in and that gives us some interesting scientific observations.

If we talk about patients with relatively

inactive disease who are actually ALT normal at the start, the e-seroconversion rate in those patients was quite low over four years. I think it was just under 20 percent.

The overall seroconversion rate for all patients with elevated ALT at entry, anything above the upper limit of normal, is illustrated here in the difficult-to-see tan line. I tried black background for better contrast. I hope people can see these endpoints.

What this says is that, for any elevation of ALT, the e-seroconversion rate is substantially higher than patients with normal ALT. So is the 1.5 X or the 2 X number a magic number? I don't know, but there does appear to be a treatment effect for any patient with elevated ALTs at any level.

But that is, perhaps, not the only interesting lesson. Another interesting lesson is the rate of seroconversion appears to be maximal in the first year at all ALT levels. That may be an important lesson for the future. I think the real question here is, in the first year, are we disproportionally selecting out patients who need an antiviral nudge into a seroconverted state and

is seroconversion more difficult for the remaining patients.

I think this is an extremely important biologic question that was, perhaps, underlying some of Anna's and Jay's concerns about long-term therapy. I don't think this slide answers it. This happens to be a lamivudine slide and, of course, as you know, resistance starts to kick in toward the end of the first year and becomes cumulative during time frame of this data display.

So the real question is, as we develop treatment regimens, whether they are combination or monotherapies, are we going to be able to keep the slope of seroconversion that we see in the first year here which would imply that this tapering off of slope among these various ALT cohorts is due to the cumulative development of resistance.

We do know that the seroconversion rate goes down when patients develop lamivudine-resistant virus. It doesn't become zero, however. I should point out, and it wasn't mentioned, I don't think in Anna's talk, but about a third of these patients who seroconverted over the four years actually had YMDD mutant virus so they did contribute to this overall area under the

curve of seroconversion at any ALT level. But their rate was substantially lower than the patients who still had PCR-detectable wild-type or were non detectable.

So the important lesson, I think, is is there a different biology in treatment response in the first year compared to subsequent years. I don't think we know the answer to that but I think we will find out as viral suppression gets better for longer-term therapy. We may see that the slope for seroconversion goes up in this direction which I think we would all be pleased by.

[Slide.]

That was an Asian cohort of 58 patients followed continuously. We took a look in the lamivudine data and, by the way, I want to recognize the large group from Glaxo here that helped generate these data and slide that have been previously presented at various meetings and their permission to present these slides.

The Week 52 data from all of the four lamivudine trials in e-positive hepatitis B were integrated electronically and we examined, through univariate and multivariate analyses, what pretreatment factors influence the e-seroconversion

rate.

There were not big surprises here. This shows that, in a multivariate-adjusted analysis, lamivudine was superior to placebo treatment but, after that, the most important influence was baseline ALT, as is implicit in the slide I just showed you moments ago, absolutely important for both interferon and lamivudine that we treat patients with active liver disease indicated both by the ALT level as well as by the HAI score. This is a somewhat novel observation where HAI actually had the second greatest predictive value at baseline after multivariate adjustment.

In the lamivudine database, viral load at baseline was not a statistically significant predictor of e-seroconversion response although there was some trend in that direction. The data for interferon have been controversial there. Some people feel that viral load does influence e-response. Others feel that it may not be as strong as in the original report.

But these are absolutely key features when we think about this durable response which I want to emphasize, I think I agreed with the preparatory document by the agency staff that said this is the

only endpoint that has been associated in the literature with long-term clinical benefit. The world is a factious place, so even that is not a uniform opinion. There have been studies to the contrary, but I think there is a consensus and I think both Dr. Hoofnagle and Dr. Lok tried to highlight that e-antigen clearance does appear to be--the best consensus is that it probably is associated with long-term clinical benefit.

Of all the endpoints you have seen today, this is the only one that appears to have that statement behind it.

[Slide.]

Certainly, during the lamivudine program and subsequently, I always worried abou is antibody important to the durability response. I don't think Anna is going to be completely happy with me on this slide, but we did try to address that--yeah; I knew it--we did try to address that very question in the lamivudine database, and we can talk about whether this is a final answer to the question or not.

But the best impression that we had out of analyzing lamivudine data by looking, again, at integrated phase III data looking at patients with

various known parameters of e-antigen-related response at Week 52 and following them, in this case, just for twelve to sixteen weeks post treatment. This is very short-term data.

If you look at patients where the only statistical requirement for inclusion was e-antigen loss, you see that on the left column. The next one is e-antigen loss plus DNA nondetectable by the solution hybridization assay. That is the second from the left.

Third from the left is e-antigen loss with antibody present and DNA nondetectable. Then the last column, over to the right, is that same response documented on two successive clinic visits. This displays what proportion of patients were still e-antigen-negative at end of study. These were all off-treatment patients, three of the four lamivudine trials, and e-positives required an off-treatment period after Week 52.

My interpretation of these data was that the durability is all between about 74 and 77 percent regardless of whether antibody is present, et cetera, et cetera. Now, this is not long-term data. I will offer one comment to Jay's comment about when do patients relapse when they are going

to relapse. My view of primarily the lamivudine data but some other data would be that, as Jay said, the story in hepatitis B is not as clear as it is in hepatitis C. I think in hepatitis C the data is very strong the 90 percent of relapses, or 90-plus percent of relapses, occurs in the first six months post-treatment, as I think Dr. Hoofnagle said.

In hepatitis B, with very limited data, my guess would be most of the relapses occur in the first twelve to eighteen months after these kinds of responses. But I think it is well established in the literature that these patients are at risk for reactivation at almost any time, particularly if they get debilitated or immunosuppressed. So I think the current and long-standing goal to follow all surface-positive patients essentially for life with at least observation certainly is supported by an understanding of the relapse phenomenon.

So I think, personally, relapse is relative to eighteen months after e-antigen clearance but it can be sporadic thereafter, particularly if patients get debilitated.

[Slide.]

So that bottom line is e-loss alone,

perhaps coupled with the DNA suppression criterion, just as the AASLD Practice Guideline recommended, I think that was data to support that kind of recommendation.

Now, everybody has their favorite slide about what important things have we learned from liver histology. I think one of the themes yesterday is highlighted here, but there are some other ones. If we have learned anything for liver histology, I think at least half of it is thanks to Dr. Goodman who, I think, is still here this morning. So he has been a big part of this evolving story for the last ten years in hepatitis B and C.

It probably needs to be emphasized that there are a relatively small number of hepatopathologists who are truly expert in doing these kinds of scoring techniques.

This is my personal list of what we have learned from liver histology. I think that we have learned that, a the FDA guidance document kind of highlights, probably the mechanism of action of these antiviral drugs is viral suppression leading to the range of improvement on clinical parameters that you are seeing.

So I, personally, believe that the data do suggest that viral suppression is associated with decrease of necroinflammatory activity in the liver. The correlation is not nearly as good as we would like. I think that is a theme today that the FDA speaker will continue to address and it has been apparent, I think, so far.

But one of my first realizations of this fairly important feature is that I looked at I think it is Table 4 in Bob Perillo's original multicenter study. They had a category in the interferon studies called indeterminate responders. They were patients who were still e-positive but had actually gone undetectable for DNA in the Abbott assay.

If you look at the HAI reductions in those patients where they were still e-positive but had a reduction below roughly six logs or so, the HAI improvement in those patients was about three to four points, very similar to what you see in the seroconverted patients. Seroconverted patients usually have about one point more improvement. So that was an early lesson to us on the lamivudine program because we are going into phase III with no data on our primary endpoint of histologic

response.

That gave us some faith that DNA suppression might be associated with histology improvement. I believe that association exists, but it is an imperfect association, as you saw in some detail in Anna's talk.

Both the lamivudine and adefovir trials have produced some interesting data on fibrosis and worsening of placebo patients. It does appear that placebo patients, even over the course of a year, get detectably worse although not markedly so with regard to liver histology including some worsening in fibrosis. That was the bad news of placebo controls in those studies.

The good news was analysis of quite a lot of lamivudine and now adefovir data indicate that fibrosis and in even early degrees of cirrhosis can probably improve in antiviral therapy, at least in some patients. So, perhaps, this progression of stages is not as irrevocable as we have thought for a long time. I see Dr. Hoofnagle is probably going to want to comment on that, but I think he did show patients who went from 14 or 13 down to a score of about 1.

So, again, it is probably not something

that we can achieve in patients with very advanced cirrhosis but I personally think, in both hepatitis C and B, there is increasing data that the constant plasticity of the liver can lead to improvements, at least for earlier degrees of fibrosis.

One of the issues with interferon in the mid-'90's was largely from hepatitis-C trials, did cirrhotics respond as well as noncirrhotics. So we did look at that question in the lamivudine program and adefovir probably has some more data. The answer was that histologic stage of disease did not appear to influence most of the array of endpoints that you saw displayed for hepatitis B.

So that left the compensated cirrhotics in the same treatment category as the compensated noncirrhotics to my mind.

Now, a couple of exploratory studies have been interesting. I don't consider these to be established facts but there was a study from the North Carolina group, Mike Fried and colleagues, using some biopsies from the lamivudine program and looking at them in a blinded fashion, both placebo and drug-treated.

They published this in the Journal of Hepatology, the effect the antiviral therapy does

appear to be associated with decreased stellate-cell activation, so that may be a mechanism for antiviral therapy resulting in preventing worsening of fibrosis.

The adefovir group produced a very interesting presentation at ISAL just this spring in a subgroup of about twenty patients or so. It did look like there was a chance for long-term reduction of cccDNA in the liver in collaboration with a European collaborator. I think they reported about a nine-fold reduction over the course of a year.

Again, I consider these two last points to be rather exploratory but, interesting observations that have come from liver-biopsy material from clinical trials.

[Slide.]

There are some problems with liver biopsies, both scientific and practical. The practical problems, I should say, are looming worse and worse as the FDA guidance document I think accurately forecasts that we are going into an era of large active-control studies, and the larger the studies get, the more they need to be multinational and these kinds of problems become magnified with

that assumption.

So I have come to call, thanks to a couple of colleagues, the liver biopsy is certainly a direct picture of the disease but it is only a snapshot in time and space. We used to call it a snapshot in time, but the biopsy sampling error is the result of the space addition to this concept.

So the problem is, until patients get either very consistent very early disease or very consistent very late disease, in between, the disease can be somewhat patchy and there is a significant sampling error even in a well-done biopsy.

Then the waxing and waning nature of this disease coupled with the sampling error, I think it has probably been highlighted by others using different words that a lip in hepatitis B probably is less predictive of long-term outcome than, let's say, in the hepatitis C patient where the disease is a little more constant.

The flare activity of this disease can result in sudden worsenings of the necroinflammatory activity which, within a few months, will lead to worsenings in fibrosis so a patient may look fine one year and be dead the next

year from a nasty flare. I think that is an important concept with we think about how important are liver biopsies in hepatitis-B trials.

Another issue is the histologic scoring does have very wide inter- and intraobserver variation. That variation, in much of the trial data you have seen, has been minimized by the fact that number of people doing these scorings has been very, very small. I think Dr. Goodman has been involved in probably at least half of the data you have seen, and Zach is a recognized expert.

But, as you go to other scores, you do find increasingly wide variation. I think an example in the lamivudine program was when we had a European-Canadian study with a different pathologist. With a similar patient population, the histologic response estimated rate was 15 percent less than in the other trials. So there can be significant variation.

Another good example of that variation was in the data that you saw yesterday. I don't mean to, in any way, discount the marvelous efforts of the adefovir team in getting all those biopsies, and I think the same would be true for lamivudine, but if you noticed in the data yesterday, the

treatment effect was exceeded by the standard deviation. When you have treatment effects that are smaller than the standard deviation--this was for the 437 study I believe where the mean reduction was 2.8 points and the standard deviation was 3.2 points.

I don't think we primarily analyzed lamivudine by medians so I don't know if that would have been true with lamivudine but it is an example of how difficult it is to precisely assess histologic changes, very large standard deviations and standard errors when you approach that with mean reductions.

Nonetheless, there are consistent treatment effects with antivirals that have a consistent DNA suppression effect.

Now, the missing data thing becomes important as we move to larger trials especially. It is potentially feasible, when you are working at tertiary university centers with well-trained and enthusiastic hepatologists--it is potentially feasible to get the missing-data rate down to about 10 percent as you saw yesterday. The original interferon trials, I think, had 30, 35 percent missing data. The lamivudine trials typically had

15 to 20 percent missing data.

But, as we go to larger studies, studies of 800, 1,000, 1,300 patients, there is just a limited number of centers that take care of large numbers of hepatitis-B patients who also have confidence and expertise in serial level biopsies. So that becomes a real problem and it predicts that the missing data rate we may never, even with good efforts, exceed the relatively low missing-data rate you saw yesterday.

But if you consider the adefovir missing-date rate of around 10 percent, and you consider that the delta is probably 15 percent, you can see how important the missing data is to estimating noninferiority or superiority.

The other key this is that, as we go toward active-control-trial designs, the attempt to treat assumption that missing data is treatment failure, as the FDA officers, I think, would want to remind us, if you use that intent-to-treat assumption in active designs, that tends to make two treatments artificially look more similar than they really are. So in active designs, you actually need to go to an efficacy subset analysis. I think the FDA feels this way and, in my

experience, the European agencies as well.

So missing data with liver biopsies becomes a key issue and can we really limit that to 10 percent or less in these huge multinational trials. I am not optimistic, personally.

But these considerations do cause a real problem when you are trying to design a trial and with histology as the primary endpoint, it becomes very iffy with regard to sample-size calculation. You really don't know ahead of time how much missing data there will be and you don't know ahead of time what your chosen histopathologist's scoring record is compared to some other histopathologist who might be chosen whose result on the same patient population might be 15 percent different.

So it causes real problems in trial design when histology is the primary endpoint. But, fundamentally, in my view, one of the greatest problems as we go to these very large trials is it is extremely difficult to find centers, in Asia, particular, particularly in Mainland China, who are very comfortable with serial liver biopsies. So we do end up excluding a lot of sites if serial liver biopsies are required for the primary endpoint.

There is an issue around liver biopsies

which came up yesterday. There are two liver biopsies involved. One, the pretreatment, is presumably a good idea on the basis of disease stage and, as somebody mentioned, that is really an issue for a practice guideline. I think the AASLD Practice Guideline does continue to recommend staging biopsies in B as, perhaps, Anna or Jay alluded to.

But the real issue is the follow-up liver biopsy. I want to get into that shortly.

[Slide.]

Let me back up for a second. We have heard a lot about the correlations among efficacy endpoints. I am not going to speak to that a lot because you have heard a lot from two speakers and you are going to hear more from the FDA speaker. But we did look at the lamivudine data for one key issue having to do with how valuable is that second liver biopsy.

My personal view is that monitoring of serological markers is at lest adequate to predict lack of worsening in the follow-up biopsy. So let me walk you through that thinking.

This was presented, I think, at the NIH workshop in a poster form about two years ago. In

the integrated database, we ended up with a very simple kind of analysis. If patients were normalized in their ALT or at least improved by 50 percent during the course of the first year of lamivudine therapy, the chances of the HAI score being worse at Week 52 were only 5 percent.

Looking at the other principle serologic parameter of DNA, if viral load was nondetectable by the Abbott assay or reduced by 50 percent, the HAI was worse in only 9 percent of patients at Week 52. I think most of us would agree that these 5 and 9 percent numbers are within the scoring error of the histologic scoring techniques.

So my bottom line out of this experience was that monitoring of viral load and ALT, just as you imagine in the clinic when you are looking at the numbers from your patient's clinic visit, does, in fact, have an adequate prediction of whether the patient is getting worse. It doesn't say that the histology is getting better but it at least says they are probably not getting worse. So that is a somewhat happy message for routine clinic monitoring which is what we do nowadays with viral load and ALT.

For seroconversion, the story is a little

different. It is quite apparent that you need an ALT response and the correlations there are affected by that. But I think what I took away from Anna's talk was there is probably a better correlation among serologic efficacy parameters than there is between serology and histology. Maybe that is a theme or an issue we could address in today's discussions.

[Slide.]

I am going to talk a little bit about experience with some of the endpoints you heard about from Dr. Lok in decompensated-disease trials; survival, improvement in Child-Pugh. I am not calling it here Child-Pugh-Turcotte, although it was an improvement in the biochemical parameters reflecting liver function.

[Slide.]

This is an overall--we put together three lamivudine cohorts in an integrated database because they had somewhat similar entry criteria. Their laboratory parameters were all sent to a central lab with consistent performance of the HBV markers as well as the biochemical markers.

What you see here is an overall survival curve for this assembled cohort of 133 patients.

This is the initial slide from AASLD from a couple of years ago that was expanded to a 154 patient database and these results will be coming out in Gastroenterology within the next two to three months in a paper by Bob Fontana and myself and possibly others in this room.

When you look at overall survival, I think this really reflects some of the observations in the Villeneuve paper that Anna talked about. There is kind of a break at about six months in overall where you see 20 to 25 of patients dying in the first six months essentially all of liver-related complications. Then there is almost a kind of leveling off or a quasi-stabilization of these patients with regard to survival.

This suggested, just seeing that initial survival curve when we were putting these data together suggested that there are really two groups of patients here, as Anna talked about, those who are going to die anyway and those who can be stabilized with antiviral therapy.

But the important point was, out of this--I should mention these protocols were relatively open-ended so there were a lot of Child C cirrhotics in these ALT requirements. The only

ALT requirement was you had to be under 1500. For example, we didn't want people who were in huge flares right at the start.

Other than that, it was pretty open-ended. The only albumin requirement was 1.5, for example. But this suggested--this is an important observation and suggested there were two populations of patients, those who can be stabilized with antiviral therapy and those who can't. The important observation looks like it was the majority of patients can at least be stabilized with antiviral therapy.

If this infection kills 1 million to 2 million people a year worldwide, most of them in places where you can't get a liver transplant, there is some hope that antiviral therapy can stabilize or help a lot of patients toward long-term survival.

[Slide.]

I need to caution you, these are uncontrolled data. The survival did look better in historical, as I think Anna mentioned.

In fact, when we divided the two groups up according to those who died early, and, again, they were all of liver complications, and those who died

late, the actuarial survival for the patients who survived six months was actually 80 percent for three years, and kind of the historical range was anywhere from about 14 percent to about 50 percent for these kinds patients.

So, in an historical comparison, there were a lot of patients experiencing fairly prolonged survival. In a univariate analysis, these parameters showed up. But, in a multivariate analysis, the most important parameters predicting early mortality were elevated bilirubin, elevated creatinine and detectable DNA in the Abbott assay. There were some surprises there that I see Dr. Hoofnagle perking up on.

The DNA was particularly interesting because we looked at were there any kind of markers of patient response that could predict six-months survival; in other words, early-on therapy responses. It turned out ALT normalization and viral-load response or viral DNA reduction really didn't predict six-month survival. It was really the extent of preexisting liver disease because both groups had viral suppression in the Abbott assay. We didn't have an assay sensitive enough to discriminate by PCR.

But, at least when using the Abbott assay and looking at ALT normalization, early ALT and DNA responses did not differentiate these groups. It appeared to be, really, the degree of liver damage early on and, in the multivariate, bilirubin essentially wiped out albumin as an independent predictor so it was only bilirubin in the multivariate contrary to some other series.

But elevated creatinine was the other surprise here so marginally or bad renal together with bad liver function logically does predict worse survival early on. Needless to say, these are interesting data but long-term control data are going to be more feasible now that we have multiple agents available.

I should mention we did try to do a placebo-controlled study with lamivudine in decompensated disease and five out of the eight IRBs turned it down. I think some people in this room will remember that effort. That was around 1996, 1997. So that is why you don't see placebo-controlled data with lamivudine.

[Slide.]

Here is the performance of Child-Pugh score in one of these three patient groups, a

70-patient cohort Group A out of the so-called compassionate-use study for lamivudine. What you see is, again I think Anna probably alluded to this parameter as an interesting endpoint that does have some validity, at least performance validity, in decompensated disease.

Here you see, over the course of six to twelve months, patients get an average of about a two-point reduction in Child-Pugh score. This is not quite as dramatic as the result that Anna showed in the Villeneuve series which is a little smaller but, nonetheless, relatively dramatic in the sense that most patients either improved or stabilized in their Child-Pugh score with only three patients out of the cohort worsening. The average follow up on these data was just over a year.

[Slide.]

Biochemical parameters; thankfully, there is sometimes a correlation between text books and what we see in clinical trials. Sure enough, with prolonged therapy, let's say of six to twelve months or more, one can appreciate, in patients with elevated bilirubin at the start or patients with low albumin, one can appreciate improvements

over time, albumin improving with bilirubin declining in this case over a period of one and then two years.

[Slide.]

My personal view of the array of endpoints that you have seen displayed today is that there is at least a correlation between viral suppression and histologic responses in ALT normalization. There is some correlation of viral suppression with e-antigen responses, e-clearance, as you saw, I think, in the data that Anna showed from both the lamivudine and adefovir programs.

It is not an absolute correlation, but e-antigen loss does appear to be more common under about four or five logs. But, in that case, it is clear that preexisting immune response is heralded by, or I should say marked by, pretreatment. Elevated ALT levels are required for any real treatment effect, any appreciable seroconversion rate.

Serologic monitoring, again, I mentioned, out of the integrated data, was at least good enough to predict lack of histologic worsening. That speaks to does the follow-up biopsy really give you any independent information. It might

give you information on fibrosis improvements which, I think, has been highlighted by the FDA speakers. That is an important issue for discussion.

But at least we can generally tell by monitoring ALT levels and DNA levels that the histology has not generally worsened overall. That actually was somewhat apparent in the discussion of the adefovir data as well yesterday in one of Carol Brosgart's responses.

Clinical and biochemical signs of disease progression are rare. I didn't highlight this in my talk so far but, in the one-year lamivudine studies, there were actually no deaths and no hepatic decompensates in the four controlled trials involving something like 958 patients during one year.

Now, we have gone to two-year trials and I am not sure the same will be true and I haven't seen all the adefovir data but, at least during relatively short periods in compensated patients, the incidence of hepatic decompensate is rare in placebo recipients as well as in drug recipients. There were 200 placebo recipients in the phase III lamivudine trials.

However, there was some histologic deterioration that I mentioned in placebo recipients.

The markers that are appropriate in decompensated disease clearly need to be different, as we have all highlighted. The good news is we do have some parameters available that do appear to respond to clinical trials to antiviral therapy.

[Slide.]

One slide that I thought the group might be interested in and, certainly from yesterday's discussion I think there may be some interest in some of the stuff that is happening now in clinical trials in hepatitis B. I think there was a plea yesterday, can we get combination-therapy trials started.

As Carol indicated, there are some collaborative studies between Glaxo and Gilead in treatment-naive patients, I should say, for lamivudine plus adefovir. We also heard from her that there is a plan or ongoing plan to have a trial of adefovir plus m-tricytovene, FTC.

There is also an ongoing phase II-B trial with about 104 patients in five countries. This trial investigates two doses of LDT but it does

include two combination arms of LDT plus lamivudine and a lamivudine reference arm, as well. So that trial is ongoing.

I think that my understanding is that abstracts from both of these trials at least regarding early virologic observations that may show up at AASLD this fall. So, hopefully, you will start to see data from some of these nucleoside, nucleotide, combination trials.

Again, in my book, the jury is still out on what will be the benefit of combination therapy in hepatitis B. I have been involved in trying to help set up both of these so, while I might be seen as a skeptic on combination, I have tried to be supportive in my involvements, at least.

There is a large clinical-endpoints trial that has just been stopped. I think the group needs to be aware of this and I do have the Glaxo folks permission to mention this. It was, apparently, mentioned at a meeting recently so it is not a total secret. But there was a large study set up prospectively by Glaxo four or five years ago, was when it started.

It became fully enrolled I think over three years ago. There are people from Glaxo here

to answer any specific questions but probably not on the data yet. But, in any case, this was set up as a placebo-controlled--we couldn't do the trial in decompensated disease but we flipped over the endpoint and tried to do a trial suggested essentially by one of Jay's comments this morning.

As you heard, you can't do a clinical-endpoints trial if you start with people who only have lobular hepatitis. But if you start with people who are cirrhotic, there is a chance that they still have enough hepatocytes left that you can stabilize them or even improve them and that you can get clinical decompensation endpoints over a relatively shorter period.

So that was the concept behind this very large placebo-controlled lamivudine trial. I don't know the exact numbers because, again, this has just happened, but there were over 600 patients involved in the initial--enrolled in the study. I think the study was roughly two to three years after full enrollment so many patients were far along.

In fact, the study was stopped. This study, I should mention, had an external steering committee verifying each of the clinical endpoints

which were protocol-specified. And then it also had an external independent DSMB. The DSMB stopped the trial for overwhelming efficacy on clinical disease progression in favor of lamivudine.

You will be seeing those data, I imagine, soon. I think those data will speak to a lot of issues that are on people's minds right now with regard to the benefit of antiviral therapy as well as the benefit of continuing treatment after Year 1 particularly in patients with resistance virus.

The other issue that I realize hadn't been talked about so far and might not be talked about by others is the issue is there a role for perinatal prevention in hepatitis B. There is a current ongoing trial with a little over 400 patients as the accrual goal where lamivudine is being looked not as a substitute for vaccine but as an adjunct to both vaccine and HBIg.

That is the primary role because there is a certain leak-through of infection in high viremic mothers. The vaccine failures in the perinatal setting are often in moms who have nine logs of virus or above or even in the high 8s. So it has been traditionally known that e-positive moms had a fair failure rate, and the Glaxo folks got together

some data about how could one specify that by DNA entry criterion.

So that trial will be ongoing but I think we are probably several years from that result.

[Slide.]

We have a couple of slides on an effort that involved a questionnaire and then a follow-up telecon trying to get a sense of what do people working in hepatitis-B development right now with drugs sort of in phase IV and beyond, what are our primary concerns for the committee to discuss today.

Those are really illustrated on the next couple of slides. The people who contributed to this process are indicated here. The Gilead folks were also canvassed but they were really tied up trying to prepare for yesterday. So we did have pretty good contributions from all the companies indicated here.

I think we decided to call this a perspective rather than a consensus because I don't mean to imply that everybody was uniform on every issue.

[Slide.]

Interestingly, the questionnaire responses

where 1 was a critically important rating, all of the respondents rated discussion of histology as absolutely critical for the committee to discuss today. The second issue that was uniformly rated as critically important was the issue of active versus placebo controls in trials going forward.

There was also very high interest in the group discussion of the correlations between endpoints which I think is a big topic discussed by others and will come out further in the discussion, and also some of the criteria for noninferiority versus superiority. Particularly discussed were the endpoints in e-negative hepatitis B where we still don't know when to stop treatment there, but the therapeutic-response endpoints might at least be more clearly identified.

So there was very clear consensus on these issues and we hope the committee will take note of them and discuss today.

[Slide.]

We thought maybe an interesting framework to try to get at those issues would be to first discuss what are the therapy goals in chronic hepatitis B, discussing therapeutic-response endpoints versus treatment-discontinuation

endpoints as one way to frame it. What are the choices of endpoint in e-positive, e-negative, and then what endpoint really best discriminates in active-control-trial designs. That is a key issue.

[Slide.]

Scientific issues? I don't think I want to highlight a lot here today but we are probably as frustrated as anybody that we still don't know what other targets, other than the polymerase, might produce tractable therapeutics. One of the reasons we don't have a good handle on that are some of the scientific unknowns including one of the key ones which is what immune factors result in clearance versus persistence of the virus.

I think we will stop there on elaborating this slide.

[Slide.]

In closing, I would really like to offer this as a set of personal perspectives based upon a number of years in trials in this area. We very much value the FDA and committee guidance today on endpoint and trial-design issues. The future registration trials, in my view, particularly as we move toward large active designs, are going to need to be large multicenter international trials

incorporating many sites in Asia, North America, Europe and elsewhere.

The active-trial designs my have monotherapy arms or combination arms, but the principles of design are similar and, in my view, we do need primary serologic endpoints for precision and the ability--to really come up with accurate assumptions and accurately design trials, I think we need serologic endpoints, possibly the composite type that Dr. Lok mentioned toward the close of her talk, clinical endpoints linked to viral suppression.

I think there is a need to get assay standardization before we can really move to viral load as a primary endpoint in this disease. I think you have heard enough vagaries in that regard that I don't have to elaborate further. But, after we achieve assay standardization, might it be possible to use viral load as a primary or at least as a conditional endpoint in some patient populations where the death rate is particularly high such as decomp patients and then follow on with more clinically related endpoints. I think that paradigm might be visited in the discussion.

I think I need to close by saying that,

under today's condition of HBV drug development, it takes about four to six years from the time an IND is filed until approval. During that time, if the global death rate of this disease is 1 million to 2 million a year, then, during the time of clinical development of a single drug, somewhere between 4 million and 8 million people have died from this disease.

We need to find a way to make a quicker impact on that.

Thank you very much.

DR. GULICK: Thank you.

Are there one or two quick questions? Dr. Block?

DR. BLOCK: Very quick question. Nat, very nicely done. On your slide where you were showing the decompensated chronic hepatitis B treatments with lamivudine, you had one of the early predictors of early mortality, if I understood this correctly, detectable HBV DNA.

DR. BROWN: That was in the integrated database for decompensated patients, viral load positive at baseline in the Abbott assay which is roughly a six-log threshold.

DR. BLOCK: Was a positive predictor--

DR. BROWN: Was a predictor of early mortality.

DR. BLOCK: If I flip that, then you are saying if there was low DNA or no DNA, that had a positive predictive value.

DR. BROWN: Even short-term survival was better; that's correct.

DR. BLOCK: But then what would the rationale of lamivudine be, an antiviral that would then serve to--

DR. BROWN: Clearly, none of these observations are absolute. So my take on why viral load and six logs and above was a predictor of early mortality probably had to do with the intensity of infection in the liver. But it did appear that quite a number, roughly three-quarters, of the patients can be stabilized with antiviral therapy.

By implication of that multivariate analysis, those tend to be patients whose liver disease is not as far along and whose viral load may be a little lower.

DR. GULICK: Why don't we move along. The final presentation of the morning will be from the agency, Dr. Greg Soon.

DR. MURRAY: I was going to make some initial comments but I think we will just have Greg do the statistical talk and then my comments would be better left for the charge to the committee right before the questions.

DR. GULICK: Okay, if you like.

Surrogate Endpoints for Hepatitis B Trials

DR. SOON: Good morning. I'm Greg Soon, the statistical team leader for the Antiviral Division.

[Slide.]

This talk will examine the feasibility of replacing biopsy by several potential outcome variables and using them as the primary efficacy measures; that is, to find surrogate endpoints to replace biopsy for hepatitis B trials. This is work done with Dr. Bhore.

[Slide.]

What are the potential replacement measures for biopsy? The measure could be the ALT, viral load and various serologic markers. Different metrics of the same measurement could be used like the changes of baseline, end of treatment, duration, suppression, et cetera. There are many possibilities here.

In this talk, liver biopsy will be measured by the necroinflammatory component of the Knodell score. I will simply refer to this as the Knodell score.

[Slide.]

The next one will be based on the NDA submissions, one from the adefovir submission that you have seen yesterday and the other NDA is from the Epivir HBV submission that was reviewed in 1998. The Epivir submission had four studies with a total of five treatment groups. The four studies I will refer to as the U.S. study, IFN nonresponder study, Asian study and active-control study.

The five groups are placebo, lamivudine 100 milligrams, lamivudine 25 milligrams, lamivudine plus interferon, and interferon alone. These three groups are treated for 52 weeks plus. These two groups are treated for 24 weeks with additional follow up. The total number of patients is about 900 and there are substantial missing biopsies at the end of week 52. The average missing rate is 16 percent.

[Slide.]

The two adefovir trials are 437 and 438. I will refer to them as the e-antigen-positive

study and the e-antigen-negative study. The duration of these trials are slightly shorter, 48 weeks, compared to the 52 weeks for the Epivir trials. The number of patients is 672 and the missing rates are much lower. It is about 80 percent on average, particularly lower for the e-antigen-negative study at 5 percent.

These two submissions, in combination, have 1573 patients. Of these patients, 1372 had both baseline and year-end biopsy. There were an additional 17 patients that are either missing ALT or the HBV DNA at either baseline or Year 1. So there are 1355 patients who had both biopsy, ALT and HBV DNA at both baseline and Year 1. So once a year it means we treated for the Epivir trials and Week 48 for the adefovir trials.

[Slide.]

One difference between the Epivir and the adefovir trials is the assay. The Epivir trials used the Abbott hybridization assay which has a lower limit of about 500,000. Some people say it is higher, but the same magnitude. In the Epivir trials, we see many patients achieve a suppression. But the estimate is so high that even if there are differences between these patients, the assay will

not be able to differentiate these patients on the HBV DNA.

For this presentation, I have converted the units for this assay into copies per ml to be comparable to the adefovir trials. The adefovir trials have the PCR assay that had a lower limit of 400 copies per ml.

[Slide.]

So this is an overview of the talk. There are five sections. First, I will go over the efficacy again and also describe the variabilities of both efficacy and also the measurement over time.

Next, I will look at the patient-level correlation of the HBV DNA, ALT and measure these with the Knodell scores. Next, I will look at trial-level correlation as well as the proportion of treatment effect explained. Lastly, I will do a summary.

[Slide.]

First, I will go over efficacy.

[Slide.]

The first efficacy I will go through is the Knodell score.

[Slide.]

This is a convention, the color convention, I will be using for the talk. The white will be for the placebo arm. The yellow will be for the lamivudine 100 milligram adefovir 10 milligrams. These are the markings of those. The orange will be for the lamivudine 25 milligrams or adefovir 30 milligrams. Red will be for the interferon-plus-lamivudine treatment. Green will be for the interferon-alone arm.

[Slide.]

This plots the baseline Knodell score against the change from baseline of the Knodell score. The X axis is the baseline Knodell score and the Y axis is the change of Knodell score.

The Knodell score has a range of from 0 to 18 which roughly you can see from the X axis. It is not the whole range but it is close. Patients who have a baseline Knodell score close to 0, by definition, will not have a chance to see much improvement while patients on this end of the baseline will not see a worsening because they have already reached the upper limit of the Knodell score.

These two lines indicate the upper bound and the lower bound for the change that could have

been achieved. The solid white line is for the placebo arm that indicates a trend for the placebo arm. The yellow curve is for the lamivudine--sorry; for Study 438. That is the e-antigen-negative study. So this will be the adefovir 10-milligram arm.

We can see several things from this graph. First, we can see that the yellow line, this line, is separate from this white line. The separation is roughly consistent over the whole range of the baseline Knodell score which means that the treatment-effect size is roughly the same regardless of what is the baseline status.

Secondly, we can see the negative correlation in both treatment groups so that means the higher the baseline score, the more change you are going to see. Thirdly, we can see the variability at each point between the patients. So there is a range of about 10 points in total.

[Slide.]

This is the same plot, but this is for the adefovir e-antigen-positive study. The orange line is for the adefovir 30 milligrams. You can see roughly the 30 milligram and the 10 milligram are overlapping, but both of them are separate from the

placebo group. The conclusions are roughly the same as in the previous slide.

[Slide.]

So these are for the lamivudine studies, the four lamivudine studies. We can see here, in the U.S. study, there is a similar pattern here. For the interferon-nonresponder study, these two groups in the middle, they have a similar separation, but at the two ends, there is some crossing here.

The red line is the interferon-plus-lamivudine arm which is not very clear in the picture. For this graph, the Asian study, we can see roughly the same pattern here. The 100 milligram is separated from the placebo, and the orange is somewhere in between here.

This is the active study without a placebo arm. The yellow one, again, is the lamivudine 100 milligram and the red is the combination, the interferon plus lamivudine. The white in the middle is interferon alone.

[Slide.]

The next measure I will go over is ALT. In this presentation, the ALT will be transformed by the log10 and also divided by the upper limit of

normal.

[Slide.]

The same order. I will show the adefovir e-antigen-negative study first. This is the median of the ALT over time for the two groups and the bars are the 95 percent confidence interval for the medians. So you can see a clear separation here between the two curves which is indicates the treatment-effect effects. That starts very early probably from Week 4 or maybe even earlier.

[Slide.]

This is for e-antigen-positive study. Again, we can see the same pattern. Also, additional, we have the adefovir 30 milligrams which is traces the 10 milligram also time except at the end, it has a separation.

[Slide.]

So, for the lamivudine studies, I combined all four studies. This is the 100-milligram group and this is the placebo group. You can see roughly the same pattern as we have seen for the adefovir trials. The orange one is lamivudine 25 milligrams.

This may be artificially lower because this appears on one study. The red one is

interferon plus lamivudine which, initially, it is somewhere between the placebo and the lamivudine 100 milligrams, but, it is off the treatment here, it stands to rebound back to more like the placebo here.

The interferon-alone arm bounces around and eventually ends up somewhere around the placebo.

[Slide.]

This is, again, the same plot except here the bounds are for the individual patient variability. So this patient variability shows a range of the numbers. So we can see a shift of the effects again.

[Slide.]

This is a case study for about fifteen patients for the adefovir 437 study. That is the e-antigen-positive study. I randomly picked fifteen patients from the placebo arm so we can see the history of each patient. Later, I will show also fifteen patients randomly selected from the adefovir 10 milligrams.

This graph is somewhat busy so I will break this down into several graphs.

[Slide.]

Here we can see, there are four patients on this graph. This patient drops down, seems to be going the other way gradually. This patient is gradually dropping down, then coming down somewhat more rapidly, then went back. This patient has an initial drop and rebounded, then seems to be stable. This patient is stable, then has a small drop, then has a rebound and then comes back again, then somewhat moves down, is stabilized here.

[Slide.]

These are an additional four patients here. This patient goes up, then comes down fairly dramatically. This patient gradually decreases, then has a rise, then has a drop again. This patient is fairly stable, starts to decrease over time. This patient is only on the trial maybe for four weeks and then drops out. There is no more data.

[Slide.]

This is an additional four patients. This patient has a slight drop here and then it is maintained. This patient has a slight rise, then he had a slight drop, then slight rise again. This patient is going down most of the time except here there is a small flare.

This patient has a drop here and then goes up gradually, then has a drop again in the end.

[Slide.]

There are three patients here. One patient is still a dropout. We don't have long enough data. This patient has some ups and downs and then not very big drop or rise. This patient is fairly stable.

So, in summary of these fifteen patients we sampled from the placebo arm, some are stable, some vary to a certain degree and some have relatively large variations.

[Slide.]

This is fifteen patients chosen from the 10-milligram arm. I will not go into details of this but here you can see the same thing here. There are ups and downs. Some patients have fairly subtle drop, then it goes back and then goes down again. But it seems to be that more patients have smaller ups and downs here in this graph.

[Slide.]

This, I will show you three patients out of those fifteen patients to see in detail here. This is a patient who had a drop, then goes up, goes down again. These two patients seem to be

relatively stable.

[Slide.]

The next endpoint I will talking about is HBV DNA, again on a log10 scale.

[Slide.]

Again, we are seeing treatment effects over time.

[Slide.]

This is an e-antigen-positive study. This graph is different from the graph with the ALT in that the 30 milligrams showed a significant different from the 10 milligrams here over time.

[Slide.]

This is the lamivudine study. Here you see the graph appears to be very different. That is because of the assay problem. Patients' viral load cannot go down below this level. That is the lower assay limit. Still, you can see the separation between the lamivudine 100 milligrams and the lamivudine 25 milligrams against the placebo arm.

The combination arm, interferon plus lamivudine, had a drop initially. Once off the treatment, it rebounded back to the same level as placebo. The interferon-alone arm seems to be

bouncing up and down but, in the end, it is close to the placebo arm.

[Slide.]

This shows the Study 437. That is e-antigen-positive study for adefovir as an example to show the range of the variability for the individual patients.

[Slide.]

Again, these are some fifteen case studies for the placebo patients. Here, again, you can see--I will go over this in detail and splitting it up into several graphs.

[Slide.]

This are four patients here. You can see this patient had a drop here, then a rise again. Then it sort of stabilizes. This patient goes up, then has a sharp drop and then has a sharp rise, then also stays there. This patient has a sharp drop, then a gradual rise here. This patient has a sharp drop and a sharp rise, then another not-so-gradual drop.

[Slide.]

These are the additional four patients. Here you have a smaller drop but a quick rise, smaller drop, quick rise again. This patient is

relatively stable but decreases over time. This patient has an initial rise, then relatively rapid drop, then a rise so it goes up and down. This patient is gradually dropping over time.

[Slide.]

These are the additional four patients. I will skip this one because it is not that clear on the screen.

[Slide.]

These are three additional patients. This patient drops, rises, rather sharp drop. This patient is stable here, sharp drop, sharp rise. This patient, gradual drop, gradual rise, gradual drop again.

[Slide.]

For the placebo patients, for the HBV DNA, we also see ups and downs for the investment patients. So these are fifteen patients from the adefovir 10 milligram arm. Again, I will not go through the details but you can see ups and downs here for the patients.

[Slide.]

I will just show you three patients here as an example.

[Slide.]

The last endpoint is e-antigen loss over time.

[Slide.]

This is Study 437, the e-antigen-positive study. I looked at the proportion of patients who become e-antigen-negative at any given visit. You can see the placebo arm is also gradually rising over time together with the other two arms also rising gradually over time. Actually, the 30 milligram has a separation from the placebo arm and then, in the end, the 10 milligram also is nearly separated from the placebo arm.

[Slide.]

This is the lamivudine studies. The placebo arm also gradually rises here. The yellow one is lamivudine 100 milligrams. There are some variations here but, in the end, it is separated from the placebo arm. However, the 25-milligram arm is here. It bounces around, but it is closer to the placebo here.

The combination arm also bounces around, ends somewhere here, I think. The green one is the interferon alone. It comes in the middle here, in the end.

[Slide.]

This table shows the transition probabilities for e-antigen status. I combined all the lamivudine plus the adefovir data here. I think divided them into the placebo, adefovir 10 milligrams, 30 milligrams combined here, the lamivudine 100 milligrams and 25 milligrams combined here, and then the interferon-containing arms.

This column will be the patients who were e-antigen-positive at baseline, then became e-antigen-negative before the end of the year. That is either Week 48 or Week 52.

Let's look at the placebo arm first. You can see 14 percent of the 364 patients become e-antigen-positive somewhere during the one-year period of time. But, of these 14 percent of patients, that is roughly about 50 or 60 patients. 37 percent of them become positive again, also within the one-year period of time.

Of these 37 percent of patients, 26 percent of them become negative again. Of these patients, 40 percent become positive again, and so on.

So, for the three other groups which are being actively treated, there are a higher

proportion of patients who become e-antigen-negative for the first time. But, afterward, roughly about 20 to 28 percent reverted back to the e-antigen-positive status. Of these patients, 28 to 58 percent become negative again. Of these patients, somewhere between 0 to 37 percent become positive again.

So some patients even changed their status four times in one year.

[Slide.]

Next I will go over the patient level correlation which examines how the reverse measurements on a single patient correlate to each other.

[Slide.]

I will go over this study-by-study and arm-by-arm. Each row is a single study. The first row is the U.S. study and this is the placebo and this is lamivudine 100-milligram arm. This is the interferon-nonresponder study and the three treatment groups.

Here you see--the curve in the middle is, again, sort of the average of the things, at least at each level of the HBV DNA to indicate a trend. For example, for this curve, we can see a slightly

upward trend but also, on the patient level, there is lots of variability around this line. That is indicating some correlation but also probably a fairly weak correlation.

In the other graphs, we can see some similar patterns here. In this graph, the trend is probably somewhat stronger. This one had a sharper rise, then is flat. But if you just look at the average, probably it is going to have a stronger trend.

[Slide.]

These are the other two studies for lamivudine. This is the Asian study and this is for the active-control study. Again, here, there is a slight uptrend. This is fairly hard to tell, almost flat. This maybe has some very minimal trend here. This has a trend. This is hard to tell. This has a trend here.

But, still, again, you see lots of variability. Also, you can see this line. That is the assay limit. So the patient cannot pass that line.

[Slide.]

This is a summary of those graphs in numbers, in a correlation coefficient. The overall

correlation coefficient is 0.3. Also, one star means the p-value is less than 0.05, two stars means the p-value is less than 0.001. So if you combine all the data, you get a correlation of about 0.30 which is significant at the 0.001 level.

However, there are variations between the arms or between the studies. For the U.S. study, the lamivudine 100-milligram had a correlation of 0.41 and the placebo arm, 0.19. It seems to be different. For the interferon-nonresponder study, the correlation here is fairly strong at 0.62 compared to the other two arms which is relatively small at around 0.3.

Between studies, the Asian study seems to have a weaker correlation at 0.22.

[Slide.]

So this is plotted for the adefovir trials. This is for the e-antigen-positive study. That is Study 437. This is for 438, the e-antigen-negative study. Here, it appears to see more clear of a trend. That is partially because of the range of the assay is broadened here. The lower limit is around here compared to the lamivudine, the lower limit is here. So everything was cut off here for the lamivudine.

For the e-antigen-positive, we can see in all three graphs an uptrend but also lots of variation between the patients. For the e-antigen-negative study, the trend here--you may see a slight trend here but the trend here is not apparent at all.

[Slide.]

This is, again, a summary of the graph in numbers. The overall correlation is 0.29. That is fairly consistent with what we see for the lamivudine trial at 0.30. For the e-antigen-negative study, the correlation is 0.09, overall it is 0.09. It is fairly small for the adefovir 10-milligram arm at 0.05. None of them are significant, whereas, for the e-antigen-positive study, the correlation is fairly similar and the overall is 0.34.

[Slide.]

I will now move to the correlation of the ALT versus Knodell score. This is, again, for the lamivudine study, the U.S. study and the interferon-nonresponder study. The correlation seems to be stronger here, at least the uptrend seems to be sharper here.

[Slide.]

These are the other studies. Again, you can see the uptrend in most of the graphs, except for this study here, it seems to be fairly flat. This has a trend but not that dramatic.

[Slide.]

This is a summary of ALT correlations in numbers. The overall correlation is 0.43 which, again, is significant from 0 at a p-value of less than 0.001. Some of the patterns are similar and some of them are not. For example, the U.S. study, these correlations are similar whereas, for the HBV DNA, these correlations seem to be different.

However, the correlation here is, again, stronger for this study, for this arm, than the two other treatment groups. That is consistent with what we have seen for the HBV DNA. However, this correlation is not--in the active-control study, it also has this combination arm but the combination is smaller there.

[Slide.]

This is the adefovir trials. Again, we can see an upward trend, up trend, up trend here. But, for the e-antigen-negative study, the trend is not clear here. There may be a slight trend here.

[Slide.]

The overall correlation is 0.46. Again, it is fairly similar to what we have seen for the lamivudine trial. The correlation is 0.43 for the lamivudine trials. Again, we see a weaker correlation for the e-antigen-negative study. Overall, it is 0.29. But it is significant here at the p-value of 0.001.

For the e-antigen-positive study, the correlation is 0.52.

[Slide.]

I will digress from what we have just talked about and to examine the threshold issue for the viral load. In this analysis, I grouped the patients according to their Year 1 viral load into less than 400, 400 to 1000, 1000 to 10,000, 10,000 to 100,000 and greater than 100,000. So there are five groups of patients here.

Then I will combine the data for the 30 milligram, placebo and also 10 milligram, all treatment arms. This red line is from Study 437. That is the e-antigen-positive study and the combined all the three treatment groups. It appears to be flat here up to about 10,000. These three groups have a similar response on the Knodell score.

Here are the Knodell responses, the percent of patients who have a two-point improvement. For the other group--sorry; these are patients who are e-antigen-positive at the end of one year. So these are patients who are e-antigen-negative at the end of one year. You see a drop here. There is a sharper drop here and then a rise.

This is for the e-antigen-negative patients at baseline. That is Study 438. So, you have up, down, then sharp drop, then flat, started up.

Here the numbers of the sample size at each point. Note that the sample sizes are relatively small between 400 and 100,000. So that is one problem that is probably making this graph difficult to interpret.

There is another issue that is not apparent from the graph. When you further break down this graph according to the treatment arms, some of these patterns will disappear. For example, in Study 438, if you break it down, then, you can roughly get two almost parallel curves here whereas the placebo arm will be here and has a lower response rate and the adefovir 10 milligram

will be here, also flat.

So we don't see the threshold effect anymore. Overall, they say, because of the limitations of the data, we don't have a conclusion on this issue.

[Slide.]

Now we turn to the prediction of the correlations here. We have seen that the ALT and the viral load are correlated with a Knodell score, particularly in the e-antigen-positive group. But the correlation, in general, is fairly weak.

A natural question is can we do better if we put several variables together to do the prediction.

[Slide.]

In this exercise, I incorporated the baseline viral load and the baseline ALT into a linear model for the change in the Knodell score. They are stratified by the study and also treatment.

These are the predictors I considered. One is baseline Knodell score. One is the change of log10 ALT. One is the DAVG of the log10 ALT. Another one is time to ALT rebound to the 1-times upper limit of normal.

For the DNA, I have end-of-one-year DNA and the DAVG for the DNA and, also, time to the nadir. That is the lowest value for the DNA. Also, e-antigen-negative nadir. That means the status of patients--if the patient ever achieved e-antigen-negative activity. Also, the status of the e-antigen at the end of one year.

As a reference, the model that only has the baseline log10 ALT and the baseline DNA has an r-square of 14 percent. So if you add to the model one of them each time--if you add this one to these two variables, you get an r-square of 47 percent, which is quite some improvement in terms of precision for the prediction.

But if, instead, I add this change of the log10 ALT into these variables in the model, I get an r-square of 29 percent. So there is about a 15 percent improvement here for this variable. If, instead, I added the DAVG for the log10 ALT, I get 27 percent here. It is fairly similar to the change for the ALT.

For the time to ALT rebound to the one-times upper limit of normal, it is 15 percent so there is not much change here from the 14 percent reference point. For the Year-1 log10 DNA,

the r-square is 20 percent. It is an increase of about 6 percent from 14 percent. It is a much smaller increase.

For the DAVG of the log10 HBV DNA, the increase is 21 percent. The time to the nadir of the DNA is 15 percent. Not much. For the Year-1 e-antigen-negativity, if the patient ever achieved e-antigen-negative in the 48 weeks or the 52 weeks, the r-square is 18 percent, so about a 4 percent improvement just using these variables alone.

The Year-1 e-antigen status is 17 percent. It is fairly similar to the nadir.

[Slide.]

The previous table is for each time I added only one variable. This table shows what if I put in more than one variable into the model. The first variable I put in is the change in log10 ALT and also Year-1 HBV DNA into the same model. I get an r-square of 30 percent. Remember, that even the change of log10 ALT alone, you get an r-square of 29 percent. So there is really no improvement, not much improvement adding the log10 DNA into this model.

If, instead, I use the DAVG DNA replacing the Year-1 DNA, it is slightly better at 33

percent. I looked at some other combinations here, 34 percent and 34 percent. In my extreme case, I have eight predictors and I get an r-squared of 38 percent. It is not much of an increase.

[Slide.]

So, in summary, for the e-antigen-positive patients, the Year-1 HBV DNA and the change of ALT are associated with the change in the Knodell score. But the associations are typically weak to moderate. For the e-antigen-negative patients, the evidence is weaker, particularly for the HBV DNA. Multiple predictors do not improve much upon the change of the ALT alone.

[Slide.]

The next topic will be about the validation. The first method will be the trial-level correlation.

Earlier, when I talked about the correlation between the surrogates and the Knodell score for the individual patients, the unit of study is the patient. Here, for this validation, the unit of study is the trial. So each trial, you get a treatment-effect size for, say, the Knodell score, for the HBV DNA or for the ALT.

Then you try to go through many trials to

correlation the effect size of each trial.

[Slide.]

Because the study unit is clinical trials instead of individual patients, it is important to have many trials for this analysis. However, we only have six studies and five of them have placebo controls. So we have too few trials for this analysis.

One approach to address this issue is to break each study into smaller trials to have more trials. The way I broke this down is, first, according to where the study is conducted; is it Asia, is it Europe or is it North America. If, afterwards, if the trial is still large, I will break that further down according to the ethnic background.

So, in the end, I have about 40 such smaller trials. The sample size ranges from 20 to 70.

[Slide.]

Before the validation, I have two graphs to show the response in each arm. First we look at the HBV DNA versus the Knodell score at one year. The plot graphically summarizes the treatment response in all studies and all treatment arms for

the viral load and for the Knodell score. The X axis is the treatment response of the Year-1 HBV DNA on the log10 scale. The Y axis is the response for each trial for the change of the Knodell score. These blue points are from the adefovir trials. The yellow points here are from the lamivudine trials. The size of the symbols are referent to the size of the trial after breaking it down from those six studies.

The capital letter A stands for adefovir 10 milligrams. The lower-case a stands for adefovir 30 milligrams. The capital letter L stands for the lamivudine 100 milligrams. The lower-case l stands for the lamivudine 25 milligrams. The zeros are the placebo arms. The M is a mixture of the lamivudine plus interferon and the F stands for the interferon alone.

You can see here that, in this graph, the points are separated by the treatment arms. The adefovir 10 milligrams and 30 milligrams are clustered here in this region. The lamivudine, these are 100 or 25 milligrams here. The placebo arms are here. The interferon arms are here.

Also, you notice there is a separation

between the lamivudine trial and the adefovir trial. This separation may be artificial because of the assay limit. The lamivudine trial can only show a response lower than this level.

One thing to notice here, if you know the treatment groups, you can see some kind of trend, upward trend. But the trend is probably driven by between-treatment differences. In other words, in these trials, the adefovir trials, you see better response in both arms, HBV DNA and also on the Knodell score. But, in the placebo arms, you see a worsening response on both scores. That has pretty much driven the correlation here.

[Slide.]

This is the same plot but it is for the ALT change. One notable difference from the previous graph is the overlapping of lamivudine and adefovir arms. Both of them are now here. Both graphs show that, overall, the lamivudine or adefovir arms showed a better response in Knodell score, viral load and ALT compared to the placebo. That has pretty much driven the correlation here.

The interferon-containing arms are somewhere in between but closer to the placebo arms.

In the next few slides, I will go through the validation units measured; that is, to plot the treatment-effect size of each trial for the surrogate versus this Knodell score.

[Slide.]

The first two slides are for the viral load at the end of one year versus a Knodell score change. In this slide, we only show the adefovir trials and the next slide is for the lamivudine trials. The two drugs were not shown on the same graph because of the assay-limited issue.

Each number in the plot stands for one trial. That is the trial we broke down from the six studies. So 7s are from Study 437 and 8s is from Study 438. Again, the size of the symbol represents the size of the trial.

For example, this would be one of the trials which has a treatment effect on the Year-1 HBV DNA about 3.7, roughly there. For the Knodell score, it has an improvement of about 4.3 points. That is relative to the placebo arm.

We see the range for the response for the HBV DNA is somewhere between a negative 1.something to 4.something indicating improvements in all these smaller trials. For the Knodell score, it ranges

from somewhere between a negative 1 to a negative 5. Again, all of them are showing improvements. So all these trials show improvements both in the HBV DNA and also on the Knodell score.

The red line is indicating the average. That is the same as we have seen before. So it indicates an uptrend, so that means that the trials that have a better response on the HBV DNA tended to have a better response on the Knodell score. But, also, you see lots of variation around this line which means the correlation may not be great.

One measure for this kind of correlation is r-square. That is 25 percent which is not significantly different from 0.

[Slide.]

So this is the same plot but for the lamivudine trials. The r-square is 6 percent here. It is not significant again.

[Slide.]

This is for the ALT. Here I combined the adefovir and the lamivudine trials because we no longer have the assay-limited problem. The r-square here is 24 percent. Again, it is not significantly different from 0.

In this graph, it is only the lamivudine

100 milligram, lamivudine 25 milligram, adefovir 10 milligram, adefovir 20 milligram. There are no interferon arms.

[Slide.]

If I add the interferon arms, the interferon comparisons are here, the 2s and the 4s from the interferon arm, the comparison with interferon. That is generally located in this corner, indicating probably not much response on the Knodell score in these trials.

But the treatment-effect size on the ALT varies from trial to trial so two of these trials probably are showing worsening, actually. This trial is showing some kind of improvement, about 0.25 log10 ALT improvement. Despite this variability, because this points seem to be conforming to the trend that is a lower response on the ALT, has a lower response on Knodell score. So it is actually an increase in the correlation here to 33 percent, the r-square to 33 percent and the lower bound is 80 percent here. It is significant.

So, from these four plots, we see r-square is typically is less than 33 percent and this is the best r-square we see among the four graphs. The question is why are we seeing what we are

seeing here? What are the factors that are influencing this association?

I will discuss a few factors next.

[Slide.]

One potential factors is the variability of the biopsy. This variability could arise in several ways. If you repeated the same biopsy on the same patient, you could get a different piece of liver that have been affected by the disease differently. Plus the same sample may be rated by different readers or maybe even the same reader reading the same sample could have different numbers at different times.

Collectively, with-patient variation measures variability of doing the biopsy two or more times on the same patient at a given time by following the same procedure. The total variability in the Knodell score we observe arises from both within-patient variability and also the true difference between the patients.

For these trials, the total variability, if you use the standard deviation as a measure for this variability, it is about a 3. The adefovir trials have slightly smaller variability.

If the ideal situation, the biopsy

variability is not influenced by the magnitude of the actual biopsy measurement, then the relationship can be formulated here, the observer correlation is the true correlation multiplied by the factor here. By true correlation, I mean the true biopsy. Suppose you can do the biopsy an infinite number of times, if you take the average and that is going to be the true liver biopsy.

The correlation of the true liver biopsy, which is the surrogate endpoint, that is the true meaning of true correlation here. This factor is determined by the within-patient variability with a total Knodell score variability between the patients you have observed.

So the question is, how different will be the two biopsies on the same patient at the same time.

[Slide.]

So I will give you some numbers to see how--because we don't have data to say how much variability in the biopsy, so I will go over several different scenarios.

The first case is where there is no variability. That means if you do the biopsy on the same patient twice, you are going to get

identical results. In this case, the true correlation will be the same as the observed correlation. For the HBV DNA, it is 0.3 and for the ALT is it about 0.43.

If you assume the correlation, the standard deviation for the within-patient variability is about 1.5, 1.5 roughly means that, if the patient's true Knodell score is 7, let's say, one would have about two thirds of a chance to observe a score that is between 6 and 8. In the other one-third of a chance, you are going to see a score not between 6 and 8, something either smaller or larger.

If that is the case, then the true correlation for the HBV DNA would be about 0.35 and for the ALT it would be 0.50. In the other case, if you believe the standard deviation is larger, let's say 2.25, this would roughly correspond to the case where, if the subject's biopsy is truly seven points, you would have about two-thirds of a chance to observe something between 2 and 12.

In this case, the correlation for the HBV DNA versus--for the Knodell score is 0.45. For the ALT, it is 0.65.

[Slide.]

You have seen the rather weak correlations on the individual levels, but how does that translate into the trial-level correlation. To fix the idea, let's imagine that you have followed the same protocol, doing the same trial, let's say, one-thousand times. Among these one-thousand times, you are going to get a treatment effect on a surrogate, you are going to get treatment effects on the Knodell score. How will those treatment-sizes will correlate?

We really cannot the same trial one-thousand times so, instead, I did some simulation here.

[Slide.]

This is the further study, nonresponder study. I picked lamivudine 100 milligram plus interferon versus placebo. I put this on because, for this group, lamivudine 100 plus interferon, the individual correlation is 0.74 and the placebo correlation is 0.31. They seem to be different.

If I repeat the trial one thousand times, you get this plot. Each point is one trial and the X axis is the effect size on the log10 ALT and the Y axis is the effect size on the Knodell score.

So you can see a trend here, but also the

variability is around this line. The correlation for this graph is 0.56. So it is somewhere in between these two individual correlations.

[Slide.]

This is another scenario. This is Study 437, e-antigen-positive study, adefovir 10 milligrams versus placebo. In this case, the two correlations are roughly the same in the two arms. So if we do the trial one-thousand times, this will be the pattern we are going be seeing. The trial-level correlation in this case would be 0.44. It is, again, somewhere fairly close to the individual-level correlation.

So these two simulations show that, when you have the trials, when the effect sizes are similar, almost like a replicate of a single trial, then the trial-level correlation will be similar to the individual-level correlation.

[Slide.]

That comes back to what we have seen for the adefovir and lamivudine studies. In these trials, the effect sizes are somewhat similar, actually. For example, the effect size on the ALT, given only the lamivudine 100 or lamivudine 25 milligrams versus placebo, it ranges from about

0.25 reduction to 0.35 reduction. So it is a fairly narrow range.

For the HBV DNA, in the Epivir trials, it ranges from a 0.67 reduction to 1.16. For the adefovir trials, it ranges from -2.5 to -3.39.

So, given the similarity of the effect size between these trials, it would be very difficult to have a trial-level correlation which is much better than the individual-level correlation.

[Slide.]

Given that difficulty and the limitation of the data, I will go through another concept for the validation. It is called the proportion of the treatment-effect size explained. Briefly, I will call this PTE.

This method has a longer history and has been used widely for HIV trials.

[Slide.]

Contrary to the trial-level-correlation method, which utilizes many trials for analysis, the PTE method can be computed for each individual trial. In the PTE analysis, the overall treatment effect on the Knodell score is decomposed into two components, the component that was not predicted by

the surrogate endpoint and the component that was predicted by the surrogate endpoint.

This decomposition relies on the modeling, typically linear models. The PET is the ratio of the effect that is considered to be due to the surrogate endpoint over the total effect size on the Knodell score. So it measures the percent of the overall effect that is probably due to the presence of the effect on the surrogate endpoint.

Ideally, this number should be 1.0. That would mean that the treatment effect on the Knodell score is mediated through the surrogate endpoint. This method has been used for a long time but also has been widely debated.

[Slide.]

This table shows PTE for the year-one HBV DNA as a surrogate and the change in the Knodell score. The first three columns are the study drug name and also which study and also which treatment comparisons. The left column is the PTE and this is the 95 percent confidence interval for this PTE.

Let's go through the e-antigen-negative study first. For this study, the comparison of adefovir 10 milligram versus placebo, the PTE is 15 percent. The confidence interval is from a -8

percent to 39 percent. So we are not sure if there is anything that is going through the HBV DNA for this population.

For the e-antigen-positive studies, that is adefovir Study 437 also all the lamivudine studies, for the 10 milligram versus the placebo comparison, the PTE is 65 percent. For the 30 milligram versus placebo, it is 78 percent. The confidence interval is 41 to 100 percent, 49 to 110 percent. So it appears, at least the proportion of effect is mediated through the HBV DNA.

If you go to the Epivir studies--first, we look at the rows in white. Those are the comparisons that do not involve the interferon arms. The numbers are 33 percent, 37 percent, 40 percent, 48 percent. The lower bounds range from 6 percent to the highest is 22 percent. But we also see that the upper bounds in three of the comparisons are less than 100 percent.

So all this is saying that probably there is something, at least a fraction of the treatment-effect size on the Knodell score, is going through the HBV DNA at one year. But, also, definitely not all the effects.

The green rows are the comparisons

involved in the interferon arms. If you look at the confidence interval, it is very wide, extremely wide. So it is fairly noninformative for this purpose.

[Slide.]

Next we turn to the change of ALT versus the Knodell score, the same order. We look at the e-antigen-negative population first. The PTE is 17 percent but, in this case, it has a positive lower bound from 7 percent to 31 percent. So there may be a small fraction of the effects that are going through the ALT.

For the e-antigen-positive study, the numbers are 43 and 40 percent, again with a positive lower bound but, also, the upper bound is less than 1.0. For the Epivir trials, the numbers are 6, 5, 27, 42 and 49. Again, the lower bounds range from 13 to 30 percent. Three of the upper bounds are less than 1.0. So, again, it is showing that maybe a fraction of the effects on the Knodell score is going through the ALT, but certainly not all the effects.

[Slide.]

Finally, a summary of the presentation.

[Slide.]

First, we summarized the efficacy and described both variability between the patients and the variability over time for each patient. Specifically, we saw effects on the Knodell score and its correlation with the baseline Knodell score. We saw effects on the HBV DNA, ALT and the e-antigen loss and all three measures vary over time.

For e-antigen loss, one-quarter to one third of patients cannot maintain the status.

[Slide.]

We studied the correlation of the e-antigen HBV DNA and the change in ALT versus the Knodell score. We saw that the overall correlation for the HBV DNA is about 0.3 and for the ALT it is about 0.45. But, for the e-antigen-negative population, these correlations are weaker, especially for the HBV DNA. It is not even certain if that has any correlation.

Combining these various predictors did not improve the prediction much.

[Slide.]

The two validation measures. The first validation is the trial-level correlation where we didn't see much correlation at all. That is

probably due to several factors. One could be partially influenced by the biopsy variability. Another factor is the similarity of the trials between the lamivudine and the adefovir trials.

[Slide.]

Finally, the PTE method which showed that maybe a proportion of the effects is going through the HBV DNA and also the ALT but certainly not all the effects.

That's it. Thank you.

DR. GULICK: Thanks.

Are there one or two quick questions? We are certainly going to have time to discuss these so, if there are no questions at this point, as someone famous once said, "It's lunchtime." It is ten of 1:00. We will reconvene at twenty of 2:00. Thanks.

[Whereupon, at 12:50 p.m., the proceedings were recessed to be resumed at 1:40 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:45 p.m.]

DR. GULICK: There were a couple of members of the committee who wanted to ask a couple questions of Dr. Soon.

Dr. DeGruttola, you had a couple of questions?

DR. DeGRUTTOLA: First of all, just to make sure I understand the goals, the goal here is to see if we can predict at the individual level and at the trial level what the Knodell score or the histological results will show and also to see if there is variability in that ability to predict across different treatments and different groups.

Dr. Soon, is that a fair statement?

DR. SOON: Yes.

DR. DeGRUTTOLA: So one question I have is do you see evidence of variability in the associations between Year 1 bDNA and Knodell-score change across different treatments and groups, or do you see them as being, although, of course, the numbers are different because of random variation, essentially fairly similar?

DR. SOON: Unfortunately, I don't have the numbers for the HBV DNA but I do have the numbers

for the ALT versus the Knodell score testing the significance of the homogeneity of the correlations.

For the Epivir trials, the overall homogeneity of the correlations between the treatment groups and also between studies has a p-value of 0.013. That is significant.

DR. DeGRUTTOLA: So that is showing that there is heterogeneity.

DR. SOON: Correct. Yes.

DR. DeGRUTTOLA: Which is very relevant. And for the bDNA, you don't have it, but I think that is--

DR. SOON: I don't have the p-values; correct.

DR. DeGRUTTOLA: But I think that would be at least of interest to me and, perhaps, others on the committee as well to find out if there is variability in that association because the question is, obviously, is it relevant in some settings and not others to use DNA as the endpoint.

In your discussions about the within-patient variability, I just want to understand the goals of those analyses a little bit further. Was the point there to show the way in

which our ability to detect association between the predictor bDNA and the Knodell score degrades as the within-patient variability increases or were there other points as well, because that struck me as being very relevant to what the committee needs to address.

DR. SOON: Your question is about if the assay variability on the biopsies, how that is affecting the individual-level correlation; correct?

DR. DeGRUTTOLA: Yes.

DR. SOON: We have looked at the range of values, as you have seen in the presentation, from with no correlation to there is some correlation to maybe some large correlation--sorry; variations in the biopsies. That is affecting the correlations of either the HBV DNA or the ALT versus the Knodell score you are observing.

When you have more noise in any of the measurements, that is going to drive the correlations lower.

DR. DeGRUTTOLA: So, for example, in your table, what you were saying is if the within-patient standard deviation was 2.25, then you would need to have a true correlation of 0.45

to observe a correlation of 0.3? Is that the correct way to read that table?

DR. SOON: That's correct.

DR. GULICK: Victor, which table are we talking about?

DR. DeGRUTTOLA: I'm sorry. It is variability in correlation on Page 33.

DR. SOON: Maybe you can show the slide if you know the slide number.

DR. GULICK: 66.

DR. DeGRUTTOLA: It is probably 66, doubling 33.

DR. SOON: Slide 66, maybe. In any case, that is correct. With some exceptions here, the variability is homogenous across the different values of biopsy. Then you can say in order to observe a correlation of 0.3, we need a true correlation coefficient of about 0.45 for the HBV DNA.

DR. DeGRUTTOLA: I see. Then, one final question. We saw the two different assays were being used, the PCR and the bDNA, I believe. When you plotted the trial-level data from trials that were using the two different assays, we saw the datapoints from the different studies sort of

clustered. But, do you have any sense that--and it is confounded because there were different both different assays and different drugs used in those two different studies.

Do you have any sense of whether the difference between the two different treatments--I believe it was interferon and adefovir--whether there was truly a difference there or whether it was an artifact of the fact that different assays were used?

DR. SOON: Dr. DeGruttola is referring to the difference between the lamivudine and the adefovir treatments. There is a cluster difference for the HBV DNA versus Knodell plot where you see a separation of the two clusters. It is hard to tell if that is really all due to the difference in assay. Sometimes, the assay difference is a contributing factor because, for the lamivudine trials, there is no chance for them to exceed the lower limit of the assay for the response whereas, for the adefovir arm, all the responses are below that limit of the Epivir trials.

So, certainly, it is responsible for the separation of the two clusters, but it is hard to tell if it is solid due to that reason.

On the other hand, if you look at the ALT plot, the lamivudine and adefovir arms overlap so it is sort of suggesting that maybe it is due to just the assay limit.

DR. DeGRUTTOLA: Okay; so there isn't really any evidence there that there is a difference between the lamivudine and adefovir in these associations.

DR. SOON: Right.

DR. GULICK: I am going to suggest that we hold the rest of the questions because I will guess that many of them will come out in the discussion of the charge questions to the committee.

So I would like to move this time to the open public hearing. We have two people that have signed up. the first is Lee Crooks from the Hepatitis B Foundation.

Open Public Hearing

MR. CROOKS: My name is Lee Crooks. I am here as the patient representative of Hepatitis B Foundation. I would like to take a few minutes to tell you about my experiences with hepatitis B and the drug adefovir.

I was first diagnosed with hepatitis B in 1994. Prior to that time, I had no symptoms of any

kind that I could recall. As my disease progressed and as I look back now on what people have experienced, I probably did have fatigue but I wrote most of it off as low blood sugar because I had had that problem for some years.

But, after my doctor diagnosed me, he did a biopsy and said that the bad news was that I did have hepatitis B, and the good news was that I didn't have cirrhosis. So he put me on interferon and I was on that for only about six weeks. I came off of interferon because of my white blood cells dropping below the protocol.

It seems, though, that just the six weeks of being on interferon had some effect because my viral load did drop and my ALT went down. So my physician suggested that we just track it for a while. So, for about three months, I had monthly lab work done and things seemed to be somewhat stable. He moved me to a three-month review period.

At the end of that first three-months review period, he was astonished at the change, and not for good. My viral load had jumped dramatically and so did my ALT. At that time, he felt that there was nothing more that he could for

me and suggested that I go to the University of Miami and see either Dr. Reddy or Dr. Schiff.

So I did that. I saw Dr. Reddy. Seeing Dr. Schiff, you need an appointment like two years in advance. But the studies, of course, that are ongoing are under Dr. Schiff. Anyway, I did see Dr. Reddy. He did lab work. He did not do another biopsy. What he said was, with an ALT score as high as I had and the high viral load, that he was certain that I had to have cirrhosis.

This is kind of surprising because, between the time I was first diagnosed as having no cirrhosis and seeing Dr. Reddy, no more than eighteen months has passed. Dr. Reddy told me that there was something they could do for me and that was a new drug called lamivudine.

However, he didn't think that lamivudine would be the total answer, that the total answer would be to receive a transplant, which was sort of a shock to me because I was still bouncing back and forth with, "I'm not that sick." But I did go on the transplant list in June of 1995 and I started treatment with lamivudine.

My condition did worsen. I live five hours away from Miami so I had to drive back and

forth every couple of weeks for an evaluation. As my condition deteriorated, I was unable to do that drive so I ultimately relocated temporarily to the Miami area and I always say just in time because my condition got worse. I ended up in the hospital. I had edema and ascites and the fluid buildup was pushing through my abdomen up through the diaphragm and filling up my chest cavity so I couldn't breathe.

I was in the hospital for seven days like that and every day I was tapped, and, every day, they removed two liters of fluid. So, to this day, I can't stand to see liter bottles of drinks because I think of all that fluid being in me.

That went on for seven days straight. Dr. Reddy was very concerned with the possibility of infection because of sticking me every day. I said, "Maybe we should put a drain in." He said, "That is a possibility but there is even a bigger chance of infection with that." He said, "The only real solution to this problem is for you to get a transplant and get it very soon." Two days later, I was transplanted.

I came out of the transplant feeling better. I knew right away, as soon as I was alert

enough, to know that I was feeling good. I continued on lamivudine and, for about two years after the transplant, everything seemed fine. Then I started having some symptoms and some of my numbers were going up and they determined that I had the mutation.

At that time--this was, like, '97--at that time, they thought that the mutation was so mild that it wouldn't do much damage to the new liver. But, as time went on, there was more and more concern that my new liver was being attacked.

Trials for adefovir had been announced but they had not put the protocol together yet. Dr. Schiff, talking with Gilead Sciences, they approved me to get adefovir on a compassionate-use basis. I was one of two or three transplant patients who got that.

So, in the long run, I have been on adefovir for almost four years. Initially, when I started with it, I had one relatively minor symptom and that was simply loose stools, not diarrhea but just loose stools, something that you are just aware of. That lasted about two months and then it went away.

So I went on adefovir in September of '98

and I was on 10 milligrams. Because I take Prograf, which is my anti-rejection medication and that happens to be somewhat toxic to the kidneys, there was some current concern about the combination of 10 milligrams of adefovir and the Prograf, and my dose was reduced to 5 milligrams.

I have been on 5 milligrams since July of '99 until just three months ago when I was moved back to 10 milligrams. My understanding of that was it was in order to develop a standard dosing. I don't feel any changes. I feel fine. However, my creatinine level has increased from 1.5 to 1.9 in the last couple of months and it is my understanding that that dosing change will be changed based on my creatinine clearance.

But, overall, what I would like to say is that, when I got a transplant, I felt like I got the gift of life again. I came out of that feeling like a whole new person. I sometimes did things that I didn't used to do and I think that was probably from my donor, but there are no studies being done on that. I am a chocoholic now and I never ate chocolate before. So, go figure.

So my second gift, to me, was adefovir because it was obvious that the way the liver was

being attacked that I was going to be back in the same situation that I was originally. So adefovir is my second gift and I am very appreciative to have had it.

Recently, I attended a patient conference held by Hepatitis B Foundation in Pennsylvania. At that meeting, I met a lot of other people who have hepatitis B and they were all interested in hearing me talk about my experience with adefovir because they are all looking for something like that. I am hoping that adefovir will prove to be the help that a lot of people in this country as well as other countries need.

Those are my prepared comments. If you have any questions, I would be happy to try and answer them.

DR. GULICK: Thanks very much.

The next person to sign up for the open public hearing is Dr. Michael Wulfsohn from Gilead Sciences.

DR. WULFSOHN: I am Michael Wulfsohn. I am Vice President of Biometrics at Gilead Sciences. We have done a lot of work in parallel with the agency and I would like to confirm much of what Greg has presented and summarize our own findings

which are pretty much in sync with Greg Soon's analyses.

I would like to talk about three areas, firstly baseline predictors, secondly, surrogate markers and, thirdly, the issue of delta with active-control studies.

In terms of our multivariate models looking at baseline predictors, in both of our pivotal studies, the e-antigen-positive--that is the 437 study--as well as the e-antigen-negative study, 438, we found that the two variables that were predictive of histologic outcome were baseline HBV DNA and baseline total Knodell score.

The baseline ALT, although it was a univariate predictor for outcome, was not a predictor in the multivariate model. As you could see from one of Greg's slides, he started out with the baseline ALT and DNA and when he put in the baseline Knodell score, the percent of the variability explained when up to 47 percent. I am sure that if you look at the pairwise DNA in Knodell score, we will probably have identical results in terms of that pair explaining the most of the histology improvement.

One thing we were also curious about in

terms of baseline predictors is the question of who to treat. For each of these three variables, we found that the patients that responded least to treatment were patients with, as you would expect, low baseline ALT, high baseline DNA and low baseline Knodell score.

In each of these three subsets, the low ATL, et cetera, we found that treatment had a significant effect on histology outcome which our preliminary assessment of this is we were unable to find a subset of patients that is not responding to treatment. These are unadjusted analyses and further work needs to be done adjusting these subset analyses for the other known predictors.

In other words, when we looked at the low ALTs, we didn't adjust for Knodell and DNA but that is the next set of analyses that we will do.

Moving on to surrogate markers, I certainly have, and my group have, found results very much in sync with what Greg found. Specifically, in 437, the e-antigen-positive study, DNA is a slightly better predictor, or, rather, surrogate, of treatment outcome than ALT. The results you saw earlier looked at absolute levels of DNA and that was a moderately good surrogate.

It was, I think, explaining two-thirds of the treatment response.

We looked at change in HBV DNA from baseline and we looked at various time points. The change at Week 16 appeared to be the strongest surrogate for histologic outcome. Specifically, the change at Week 16 explained 100 percent of the histologic outcome where histologic outcome is defined as we defined it in our primary endpoint, the two-point improvement with no worsening in fibrosis.

The confidence interval on the surrogacy of 100 percent was pretty narrow. I can't remember exactly what it was, but it is somewhere like 85 to 115. In the e-antigen-negative study, we got very different results, similar to what Greg presented. In other words, the HBV DNA change at Week 16 explains less than half of the treatment effect.

We also observed a wide confidence interval including both 0 and 100 indicating that there is no confidence at all in that particular population that HBV DNA is a surrogate for treatment effect. We don't have a rationale for these discordant findings and it is something that we are certainly intrigued by and we would like to

see it confirmed in additional studies before we get too excited about it.

On the face of it, it would seem that it is certainly possible that HBV DNA change from baseline could be a surrogate in a specific population, specifically the e-antigen-positives, and this would at least allow studies to be done in that population without histology as a primary endpoint.

The third area I would like to talk about is the delta for active-control studies. The delta refers to the percent of, or rather the magnitude of, your treatment of effect that you are prepared to give up and still claim that your new drug is noninferior to some active control.

Generally, the delta is what you would call a clinically insignificant amount of treatment effect. The so-called Bob Temple rule for how deltas are calculated is that firstly you need to know what your active control is contributing to the active-control group and, in your new treatment arm, you shouldn't be give any more than half of your active-control effect.

Clearly, even giving up half of your effect may be more than you would want to give up

and half of your effect may be highly clinically significant. We have looked at designing new studies based on deltas and, in fact, since we observed a net treatment effect of three logs relative to placebo, even giving up one log which is a pretty large amount and only a third of your treatment effect would result in extremely small sample sizes of the order of ten patients per arm.

Clearly, we should even think of giving up way less than half of the treatment effect or even a third. Probably we could get by with 10 percent of the treatment effect. Our results would only suggest that you would want to use this in e-antigen-positive studies, of course.

Where histology is the primary endpoint, the effect of the delta becomes much more obvious in that, even giving up half of your treatment effect or--well, even giving up half or a third of your treatment effect would result in enormous sample sizes. In other words, you would be dealing with more than 1,000 or 2,000 patients per clinical trial. So careful thought needs to be given to how we propose endpoints for clinical trials.

Thank you.

DR. GULICK: Thanks very much.

That concludes the people that signed up for the open public hearing. Is there anyone else who would like to make a statement who did not sign up? If not, we will close the open public hearing. That puts us almost right back on schedule.

Dr. Murray wants to lead the charge to the committee.

Charge to the Committee

DR. MURRAY: I think we had an ambitious schedule and there are questions that we do want to get through. I probably will reorder them and kind of prioritize what are the most important issues.

[Slide.]

As I said before, these are the key issues. I think, as was suggested by Dr. Brown, from what the industry was interested in, clearly selection of controls, active versus placebo and then the choice of primary endpoint. I think we will try to address these questions which I will read off to you in just a moment.

Probably, when talking about choice of primary endpoint beyond that primary-endpoint assessment, what kind of other long-term follow-up data collection would you think that is essential.

Just a couple of things that I did want to

get through. First of all, I wanted to thank all of the pharmaceutical sponsors for their submissions. They did help us greatly in planning for this meeting and in preparing the backgrounder.

We also got one additional analysis from collaborators at Triangle looking at a meta-analysis of HBV DNA as a surrogate for histology outcome. I did want to show that. This is an article that has been submitted for publication and there was one important figure there that we have gotten permission from Triangle to show.

So if you could skip a couple of slides.

[Slide.]

There was a meta-analysis that was done from research from looking at all of the studies in the literature, a pretty thorough list of prospective studies. For the particular analysis looking at HBV DNA and histology, several studies were selected.

Actually, go back one slide.

[Slide.]

This is an article by Drs. Mommeja-Marin, Mondou, Blue and Rousseau looking at serum HBV DNA as a marker of efficacy during antiviral therapy

for chronic hepatitis B infection.

[Slide.]

Five studies with several treatment arms including lamivudine at several doses, famcyclovir at a couple of doses, placebo, and lamivudine and interferon in both e-antigen-negative and e-antigen-positive subgroups in this last study

[Slide.]

On your X axis here, each of these treatment arms from these five studies, so there are eleven or twelve datapoints here, were plotted. X axis is change in median viral load from baseline. The Y axis is the change in histology activity index and the necroinflammatory score. This data was reported in these studies.

For this correlation, I guess the datapoints at the right upper side of the graph are the lamivudine and interferon. In the middle, some lamivudine arms. In between, the famclyclovir arms and, kind of down near the ordinates, are the placebo arms.

In this particular analysis, this meta-analysis, there was a relatively good correlation, a good fit of the data, between changes in viral load and histology grading with a

pretty good r-value here that was highly statistically significant. So, in addition to the analysis of the datasets from adefovir and lamivudine, we did look at a lot of other data and, in fact, I want to thank the authors of this particular publication, I guess, for submission in reviewing the literature in this regard. That was also very helpful.

Let me see if I can prioritize the questions

[Slide.]

I think that, if we have time, we will deal with the patient population issues. These are what would be the essential patient populations for study.

[Slide.]

So these are Questions 1 and 2. Let's go on to the next section here.

[Slide.]

Control arms. We wanted you to discuss the role of the following controls in the compensated liver-disease group, placebo controls, delay of initiative treatment and for what duration would be appropriate, if an active control, lamivudine or another antiviral drug, I guess and,

if monotherapy is appropriate for drugs like lamivudine or other antivirals, or another choice of control arm could be interferon.

[Slide.]

We also want you to discuss controls for patients with decompensated liver disease or those who have failed previous regimens. So I think we will have you address Questions 3A and B first.

[Slide.]

Then, as far as study endpoints and timing of the evaluation, we want you considering the patient populations in Question 1 and the information presented today and the necessity that endpoints for registration be clinically meaningful. Please answer the following. Here is where they are divided up into a, b and c.

Which endpoint, or combination of endpoints, should be the primary in clinical trials. Please discuss histology, serologic, meaning seroconversion, biochemical, meaning ALT, and virologic, meaning HBV DNA. In addition to the choice, of course, the timing is appropriate. We saw yesterday where, with longer-term data, that there was more of a viral-load decrease and a higher seroconversion rate going out from 48 to 72

weeks.

So, when should the assessment of the primary endpoint be made, b. And list the most appropriate secondary endpoints and try to rank order them in order of importance.

For histologic endpoints, what is the preferred method of histologic scoring? I might say that the endpoint, I think, for lamivudine was a two-point change in Knodell score. That was modified for the adefovir development program to include no worsening in fibrosis. Then, yesterday, we saw that actually, by looking at a fibrosis score that could discriminate different levels of fibrosis a little bit better than the Knodell score that changes in fibrosis could be visualized within a year. So we might want you to address that based on data you have heard yesterday and today.

For virologic endpoints, which assay is best suited for clinical trial and what do you think the most appropriate cutoff for HBV DNA suppression should be, 10
5 which is kind of based on the assay limit of some of the other assays.

I think we will leave off, should viral genotyping be done and why at this point, unless somebody specifically wants to address that.

For patients with decompensated liver disease, please discuss the feasibility, validity of the following endpoints. These are some of the endpoints that Dr. Lok and others had listed on their slides; mortality, Child-Pugh, MELD score, time to transplant or occurrence of liver-disease complications.

So I think those are the questions. The endpoint and the controls that you are going to address in your discussion, if you can, of the endpoints, also address, beyond the assessment of the primary endpoint, what else would you like to see in longer-term studies.

The primary endpoint could occur at 48 weeks but it should not be limited to that. Maybe 72 weeks is better. Maybe a shorter time period is better. For studies of HIV and hepatitis B, 48 weeks has been arbitrary so don't feel like you have to be limited to that time point.

Why don't you go back, then, to Question 3a and 3b, which deals with control arms.

DR. GULICK: Thank you.

Discussion

DR. GULICK: The first topic we are going to take up as a group, once again, is the control

arms. Let's start with, discuss the role of the following controls in the compensated liver-disease group; placebo controls, monotherapy with lamivudine, interferon. I suppose we could add adefovir to that list at this point.

Who would like to start? Compensated liver disease, controls for future studies. Thank you, Dr. Sherman.

DR. SHERMAN: There are several competing issues in trying to make a decision about the use of controls and whether placebo controls are indicated in the compensated patients. Clearly, the use of placebo-controlled study is the most satisfying for a clinical trialist in terms of trying to make a determination about efficacy of an agent.

You also have the problems related to the natural history, as you heard this morning, of hepatitis B, that there is some degree of variability in certain endpoints, particularly in HBE conversion associated with spontaneous occurrence of that in the untreated control arms and that that occurs at different rates and we are not completely sure what controls those rates.

One of the things may be the duration of

chronic infection in an individual patient. Patients that have been chronically infected for many years are going to be less likely to spontaneously convert than one that was infected four years ago and became a chronic carrier.

So, for endpoints that include the serologic parameters, it seems that we really are still forced to use control arms that are placebo-controlled.

The other endpoints including DNA and use of histology characterization may not require that as much at this point. So I think, that to answer this question, we are really going to have to first answer what do we define as the key endpoint for response in these patients.

Ethically, it is now getting more difficult to take compensated patients and give them placebo when you have determined that they have an activity of disease that is reasonable to merit treatment. Part of that is related to the ease of administration and the relative tolerability of the drugs that we currently have available. So it both gets hard to find the patients and, when you sit and face that patient, it is very difficult to say, "I think you should be

on a placebo control."

So I think that, really, the discussion of this is related first to the discussion of the endpoints that we will use and to choosing endpoints that may not be as determinate or as variable when we decide to use an active control rather than a placebo control.

DR. GULICK: Let me suggest that the endpoint question we are certainly going to get to next. Let's try to stay with the control question although I appreciate your point, that it may differ for different endpoints.

Dr. Schapiro?

DR. SCHAPIRO: Actually, to continue that thought, looking also at the other options of delaying therapy, since we are having trouble deciding how long we have to treat, I think we are going to get, again, into the same problem and I think, once again, until we really define how long we are going to have to treat delaying, let's say, a year but then, again, that patient starts therapy, we are not going to be able to do a comparison.

So I think that is going to make that option very difficult and I think, again, if there

is a finite number of biopsies we can do on a patient, and I think, as the consensus is that you do have to do biopsies, it is going to get very, very difficult to take those options.

I think, although those sound like possibilities, I don't think that we will be able to do any of those in trials.

DR. GULICK: Would others like to weigh in on either placebo controls or the option of delaying treatment, delaying active treatment, being randomized to that?

Dr. Hoofnagle?

DR. HOOFNAGLE: Well, I think this has been an ongoing problem for a long time, the use of placebo controls in studies of hepatitis B when there are licensed treatments for hepatitis B. The issue is what is the standard of care? Are you not following the standard of care when you enroll a patient in a trial and they are going to get a placebo for a year and have two liver biopsies.

The trouble is the standard of care hasn't been clear as we kind of made out to you today. There are many people who don't think interferon should be used in anyone. There are people like us at the NIH who don't enroll patients into

nucleoside or nucleotide studies unless they have failed interferon or refused to take it.

So, it is kind of based upon what you think the standard of care is. But I think we heard today early results from a study in China using lamivudine in compensated cirrhosis that the advisory board told them to stop because there was evidence of benefit.

So how could you enroll a patient with cirrhosis on liver biopsy into a trial where there is a placebo arm. I agree. It is become more and more difficult and I think if patients are to be treated with a placebo for a year, there has to be some cutoff of clinical severity to allow for that. That is my personal feeling.

I agree about long-term therapy, but maybe for mild disease on biopsy. I kind of agree that it might be worthwhile kind of wading through the results of the study before you really commit them to a long-term therapy. But in a patient with bridging fibrosis or with cirrhosis, I think we should be concerned that they not be treated with one of the three agents that will be available after the next couple of months, we think, at least.

DR. GULICK: Dr. Stanley and then Dr. Mathews

DR. STANLEY: I just want to concur with that. I think we have now--and I am going to separate them. You have got interferon which is one mechanism of action. Now you have got two antivirals that we, by voting for them, have said are effective. If you have made the decision that this patient likely needs to be treated, then how do you randomize them to a non-treatment arm.

And I have some concerns about what you said, Dr. Hoofnagle, about, then, maybe they are the mildest ones. Now you are skewing your arms and they are not going to be equal arms for the treatment arm and the placebo arm, and how do you do that blinded, anyway? So I just think we are in an age where we can't deny treatment to the patient if the decision has been made that they ought to be treated.

DR. GULICK: Dr. Mathews?

DR. MATHEWS: It might be useful to draw a distinction between the phase III trials for long-term efficacy and earlier trials to look for drug activity because, in my mind, it might be justifiable, at least in e-antigen-positive

patients if you were going to use a placebo control with short-term follow up to look for virologic response since, in both the lamivudine trial and the adefovir trials, the initial virologic responses seemed to be very rapid.

But in the longer-term efficacy trials, which, obviously, would be studying the development of resistance also, I agree that placebo controls are problematic for the same reasons others have mentioned.

DR. GULICK: Dr. Sun and then Dr. Lok.

DR. SUN: I agree that the fact that there are available drugs and even available drugs that have been shown to have benefit weighs into the consideration, but I don't think those automatically negate the possibility of doing placebo-controlled trials as long as you can articulate a downside to therapy.

I think that we know that there are known downsides and potential downsides related to all of the drugs that are available, toxicity, long-term outcome and resistance. So if you can reasonably define a population in which there is a risk-benefit to be had with or without therapy, I think that you can proceed.

I would just refer us all back to HIV where, given where the treatment guidelines are today, you could do a placebo-controlled trial in patients that are HIV-positive that have high CD4 low viral load. That might not have been possible a few years ago.

DR. GULICK: Dr. Lok?

DR. LOK: To some degree, I agree with what has just been mentioned. I think, in general, you want to have placebo-controlled trials because that is cleanest and because hepatitis B, unlike hepatitis C, does have these spontaneous variations.

It is becoming more and more difficult to do placebo-controlled trials because of all the reasons that were mentioned and with approval of a second orally administered drug, that will make it even more difficult to enroll patients.

But all this is predicated on the study design, what patients you are going to enroll, how long the patients are going to stay in the study and what involvement is required of the patients. So, for example, I agree that, phase II clinical trials where you just are doing a dose-response study or where you are testing only a very limited

duration, it is still possible to still include some placebo controls because there you are looking at a much shorter duration and you are deferring treatment for a very short duration of time.

The phase III clinical trials are more problematic because you are talking about at least one year. If we still want to use histology as an endpoint where you are going to do paired biopsies, it is very hard to actually tell a patient, "You can be enrolled into the trial, get randomized to placebo. We are going to do two biopsies and it is going to be a year," when, in fact, you can go to any doctor and get treated right now.

It also is dependent on whether we are going to stick to selecting patients with moderate to severe disease to be enrolled into clinical trials or whether we will continue to have, for example, in the e-antigen-positive patients, allow people with normal ALT who basically won't benefit from the treatment anyway.

For those patients with very mild disease and who are not going to progress in a short period of time, deferring for a year is, perhaps, not as critical. But if we decide that the treatment trials should cater to patients with more severe

disease, then deferring becomes more problematic.

DR. GULICK: Dr. DeGruttola?

DR. DeGRUTTOLA: I think the issues about whether to choose placebo control or delayed treatment would depend, obviously, on the standard of care as has been mentioned. But I think it also depends on the scientific question that is being answered.

It might depend on whether the goal was to do an equivalence trial to show that a new treatment was equivalent to some other treatment but, perhaps, had some other benefit or whether you were planning to do a superiority trial where you are showing that a new treatment is superior to what is currently available.

I think it partly depends on what the standards of this committee and the FDA will be about new treatments, do they only need to be equivalent to what is available or do they need to be superior in terms of toxicity or resistance profile to what is currently available.

So I think that this design question is going to be influenced by the overall scientific question.

DR. GULICK: Could we have some comments

on the possible act of control arms, assuming that that is--certainly, that is a possibility. So, to consider lamivudine as the active control, interferon, or adefovir as the active control in a new study.

Dr. Lok?

DR. LOK: This is a relatively simple question because, if the new treatment that you are looking at is an orally administered, one pill a day, your control should be very comparable, since, when we look down the pipeline, that is what we are going to get mostly. So you would not be using interferon as a control where it is going to be parenterally administered with a completely different side-effect profile.

There are certainly ongoing trials where lamivudine is used as active control. The question that is going to come up in the future would be, now that there would be adefovir, should lamivudine be the active control or should adefovir be the active control.

This is going to be a key thing in terms of talking about superiority, what is the question that is being addressed. In some ways, using lamivudine as an active control, if you do the

study for long enough, it is easy to show a difference because of the issue of drug resistance. So, whereas, at one year, it is going to be hard to actually show a significant advantage, but if the new drug has very little issue of drug resistance, by two years, you would be able to show an advantage.

However, if eventually we choose adefovir, for example, as an active control and it continues not to have problems with resistance, then it would be very hard to actually show a difference or superiority.

DR. GULICK: Dr. Block?

DR. BLOCK: I was just going to say that it will depend on what the mechanism of action of the drug to be tested is and the endpoints to be used, really echoing what Dr. Lok was saying, that if this committee would anticipate a time when new immune modulators will be used, that would require--at least until clear endpoints are decided, that would require one kind of active control arm whereas antivirals that work against the viral polymerase would require another one, and you can anticipate using resistance as a factor. So it will depend on the study. I imagine the

committee would have to anticipate that.

DR. GULICK: Other thoughts on choices of active control arm? Dr. Hoofnagle?

DR. HOOFNAGLE: We have a lot of statisticians here but I don't see much wrong with using historical controls. You have a large amount of data from Glaxo and Gilead on non-treatment for a year and two liver biopsies. So you know what happens in a year.

You will say, the patients we enroll next year are not going to be the same, but you can also do these multivariate analyses where you look at the determinants of outcome or the predictors of what will happen and can adjust for these. This is exactly what the MELD score is all about and how that can be used as a control in treating patients with decompensated liver disease.

The MELD score predicts the rate of death, decompensate and death, given a patient with decompensated liver disease's rate of death. So one can use the MELD score to predict, align the estimate rate of liver transplantation or mortality and use that as the control.

So I think the data that you have is very valuable. I guess it now belongs to the FDA and

you can use it in the future, but I am sure that Glaxo and Gilead would also be willing to allow you to mine this very valuable information.

DR. GULICK: Dr. DeGruttola.

DR. DeGRUTTOLA: Let me comment on that point because I think that it is certainly true that you can try and do statistical adjustment for differences in populations when you do historical controls. But I think the issue that you have to be able--I, personally, think you need to be able to explain most of the variability in the response in order to be able to do that with a fairly high degree of assurance that you are going to get the correct answer because historical controls are notoriously problematic.

I think we saw, from some of the analyses that Dr. Soon presented, that it is difficult to capture most of the variability in the responses. So I think that we have to be cautious about believing that we understand mechanisms of disease well enough so that we can properly adjust in a statistical model for differences among populations and get valid responses.

I think it is a very valuable thing to do to try and understand the data processes and

mechanisms of action of drugs and I think it is great secondary analyses. As primary analyses have concern, the great advantage of randomization, of course, is that it adjusts for confounders you know about and it adjusts for confounders you don't know about.

It is always the things that you don't know about that I think we need to be concerned about.

DR. GULICK: Dr. Wong?

DR. WONG: I guess, just on that last point, we have seen a few studies here within the last couple of years that used historical controls some of which were done really with exhaustive care. But I think the consensus around the table every time is that those studies have been unsatisfactory for a number of reasons.

They just weren't as believable as they should have been. So I, personally, would counsel that we accept or advise acceptance of historical controls only in situations where there is a profound ethical reason not to do it any other way, such as, for example--I mean, you could probably make a very good case that, in the decompensated patients with advanced cirrhosis who are expected

to die at a certain defined rate, that a placebo-controlled study in that group almost surely would be unethical.

But, on the other hand, in the patients with compensated chronic hepatitis B, we have seen evidence, I guess, for three different drugs now, that, at an assessment of one year, we can demonstrate a benefit of therapy. But I haven't seen any evidence except just what we heard from Jeff about the cirrhosis study that there is any evidence that any group of patients needs to be treated now as opposed to in several months or maybe one year.

Until we have evidence that treatment really must be immediate, I, personally, would be pretty reluctant to rule out having a placebo group. Now, that is not to say that the best design for a particular question might be a comparative study with an active control group.

But I, also, wouldn't be willing to say that we can't do placebo-controlled trials in hepatitis B. I haven't seen any evidence that would suggest that.

DR. GULICK: Let me try to sum up what we have said about the role of controls in compensated

liver disease; consensus that controls continue to be important particularly because of the natural history and variability of the disease. However, people thought the controls may actually be different with different endpoints or different severity of the disease. You might think of mild patients differently than moderate or severe.

Late in the conversation, what about the issue of historical controls. We heard some of the traditional debates about the acceptability of that.

Considering placebo controls; a consensus forming that it is less desirable, given that we have current approved effective options for treatment. However, it was noted that the standard of care is quite unclear, that, perhaps, there is a risk-benefit ratio that needs to be concerned with traditional elements of effectiveness versus toxicity resistance and long-term results of these.

The analogy was made to HIV disease regarding the long-term pros and cons. Pragmatic issues about the fact that these drugs are available so it might be difficult to enter someone into a placebo-controlled trial when they could certainly get an effective treatment from their

physician.

Then some thoughts that, in some cases, placebo controls might be okay, particularly short-term use, particularly in patients with early disease. The thought was that may be a phase-II-like study would be more appropriate for a placebo control because it is of shorter duration.

In terms of the strategy of delaying treatment, the big question is how long. We don't have good data, or there is as lot of uncertainty about how long it is appropriate to delay. The cutoff, or the actual time period, is critical, no consensus on what that might be. Again, this might be an appropriate strategy in mild disease.

So then considering active control, the basic issue is what is the standard of care. There is not a good answer for that. Dr. DeGruttola brought up the point that you have to think about equivalence versus superiority. Others brought up very pragmatic issues about which choice of active control you make. It might be based on the mode of administration or the mechanism of action or the endpoint that you are trying to look at.

With the three specific agents that we talked about, interferon, probably not the best

choice given its parenteral administration and unique immunologic mechanism of action. Lamivudine is the current standard of care, at least it is being used as an active control in some studies although the point was made that resistance, of course, is an issue with this drug, particularly long-term.

Adefovir, thought to be as suitable a control as lamivudine, might have the potential benefit of less resistance although Dr. Lok made the point that, perhaps, you couldn't detect a difference as easily with that agent.

Let's move to the second part of the question which is what is the best control for patients with decompensated liver disease. That is one group. Or those who have failed prior regimens.

So let's take those two separately. What is the optimal control for a patient group with decompensate liver disease for a new agent.

Dr. Lok?

DR. LOK: I think that decompensate cirrhotic patients, it is very hard to really have controls. Certainly, not placebo controls. I just don't think that, ethically, it is possible--you

are not going to get through any IRB so you can forget about doing the study.

The question is whether you can have active control. For example, lamivudine has been used for these patients for several years now. Whether we can use lamivudine as an active control or whether we will just say study a new drug on its own and compare the patients based on, as Dr. Hoofnagle pointed out, predictions based on model--based on other historical studies. But I don't think the placebo control is going to be a viable option.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I feel that it is quite clear that in the decompensated liver disease that they need active control and that any other step would be unethical and unable to be done, and that it a perfect situation to actually be investigating the questions and get answers in a shorter period of time than we might even be able to get in our uncompensated liver disease.

DR. GULICK: Dr. Mathews?

DR. MATHEWS: Again, I think it is going to depend on what other options the patient has and the toxicity profile of the drugs, particularly

with nucleoside analogues which might have the potential for mitochondrial toxicity. There may be a subset of patients where actually no treatment would be preferable to known treatment with certain potentials to worsen the patients.

So, while, in general, I agree with that, there are circumstances where I think no treatment compared to a new active drug might be an ethical option.

DR. GULICK: Other thoughts on the decompensated liver-disease group? Dr. Wong?

DR. WONG: Can we just ask our hepatology colleagues, is it generally accepted that 3TC is effective in this situation and is that the current standard of care?

DR. HOOFNAGLE: Yes; that is the generally accepted view and, in view of the data of the so-called Fontana study where survival is excellent in decompensated patients, after they get through the first six months of treatment. The treatment for decompensated liver disease is liver transplantation, referral for liver transplantation. So that really should be the first act.

Now, there is a downside to the use of

lamivudine in decompensated liver disease and that is, okay, you treat a patient. Let's say they get a little bit better and they hang on, they don't need a transplant right away. But, a year later, or two years later, they develop viral resistance and they end up with high levels of virus and then they need liver transplant.

The risk of reinfection after liver transplant is directly related to the level of virus that you have when you go into transplant. Reinfection can be prevented by high doses of hepatitis-B immunoglobulin. But, of course, there is a limitation. The limitation is high levels of virus. So, if you have a patient with lamivudine resistance going into liver transplantation, he has a strike against him, right there.

This would have been the advantage, if you know when the patient is going to get a transplant, to start the lamivudine maybe four months or six months ahead of time and not two years ahead of time. But you never know when you are going to get a liver transplant unless you are doing living-donor liver transplant. So this is a real problem and this is actually where a major use for adefovir will be, in this situation of lamivudine

resistance before transplant.

Anna knows a lot about this. What proportion of patients coming to transplant, at the time of transplant, have lamivudine resistance? It is probably a very high rate.

DR. LOK: It is a high rate and it is increasing. Like it or not, lamivudine is widely use in practice for patients with decompensated cirrhosis although we try to educate gastroenterologists who refer the patients to us for liver transplant. We have no control over when transplant is going to occur. Everyone has to wait for a certain period of time.

As you see the patients deteriorating while they are on the waiting list and you have a treatment that could temporize things and stabilize the patient, it is impossible to say, "Well, I'm worried about something bad is going to happen to you a year from now when you develop resistance." If the patient is going to die in three months, why do we worry about something that is going to happen in twelve months?

So, in some ways, you are compelled to put the patients on treatment. It has been a very effective treatment for patients who come to you

who are not beyond the point of no return and they get stabilized and improved for a while.

But then, after a period of time, we now have to deal with the issue of worsening of liver disease as a result of resistance. So I think it is hard to do a placebo-controlled trial. This is the situation where we will have to say what actually is the right active control. Maybe lamivudine is not an appropriate active control in this situation because resistance is almost invariable.

Unfortunately, although there is an enormous amount of data of adefovir as a salvage therapy for those patients, we really don't have any data on adefovir as a first-line treatment in those patients. Is adefovir the right first-line treatment for that subset of patients? We really don't have any data.

What I am anticipating is going to happen is that, once it is approved, there would be many different people doing their own little trial on their own one patient.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: I think, before you know it, what you will really be dealing with here is

the controls for patients with decompensated liver disease and lamivudine resistance. That is what is going to happen. There is not much control that we have over it.

DR. GULICK: So let's consider that, then, which is the second part of the question, what to do with lamivudine-experienced patients, what is the optimal control for them. Is it worth considering interferon-experienced patients as a separate group? It sounds like it is probably not, given where we are today.

DR. HOOFNAGLE: They are a little bit different. But, if you have a controlled trial, you can stratify for previous therapy. I think you have to include people who have previously received interferon in registration trials. But that is one of those things that probably should be stratified for in the randomization.

DR. GULICK: Sure. I didn't mean to be unclear.

Let's focus, then, on what is the appropriate control in the lamivudine-experience group. So you are testing a new agent in the lamivudine-experienced group.

DR. LOK: This is a difficult question.

Until now, a lot of the recommendations have been to leave the patients on lamivudine. So that is how we are managing most of these patients because, unless you can get the patient into a clinical trial, your option is either to take the patients off lamivudine and hope for the best or leave them on lamivudine and also hope for the best.

Either way, you sort of have to able to pray and pray effectively. But now, as the scene changes, it gets a little complicated because you now have another new drug comes along. Like it or not, there is another drug that we haven't been mentioning but is widely use in the community already and that is tenofovir because it has become available as an HIV treatment for several months.

For physicians in the community who do not have access to a clinical protocol and access to adefovir, people have heard about it, read about it and have put patients on it. Hey; if you have a patient who is dying and they cannot get into a clinical trial, that is going to happen.

So it gets complicated now that you have more options. So you can leave the patients on lamivudine. You can use adefovir as a control. I guess tenofovir is somewhere as an option, although

we have far less data on it.

Of course, one of the issues has been when you add on a new drug, do you need to leave the patients on lamivudine or can you take the patients off lamivudine and get your hands on some of those data. I wasn't here yesterday. I wasn't sure if they showed all that data. But the data would suggest that perhaps you can just stop lamivudine and add the patients on adefovir.

So, as a third drug comes along--for example, with entecavir--if they want to do a study like that, should they be comparing against adefovir? Should they be comparing against lamivudine? Again, it comes back to the question that was asked; do you want to show superiority? Do you want to show comparability because, if you want to show superiority, comparing it against a drug like adefovir that has already been shown to be effective against lamivudine-resistant virus, I think it will be very hard to show superiority.

You are lucky if you can actually show that there is some comparability. So I don't know. I don't know what the right answer is.

DR. GULICK: Let me push you a little bit on this. Is it ethical today, given yesterday's

meeting, that a trial is designed of lamivudine-experienced patients with a new drug and they are randomized to continue lamivudine as one of the arms of the study? Is that an appropriate study at this point given what we saw with adefovir yesterday?

DR. LOK: I think it would be inappropriate, particularly in patients with decompensated disease. In patients with decompensated disease who are very fragile, in patients with recurrent hepatitis B post-transplant at home, if they deteriorate, the outcome is very serious.

I think to leave them on lamivudine or to randomize them to continue to stay on lamivudine would be inappropriate.

DR. GULICK: Again, I will push you--and it doesn't have to be you, Dr. Lok, but thanks. Suppose it is a person with compensated liver disease who is lamivudine-experienced. Again, you have a new drug and what is the appropriate control arm there? Is it okay the randomize that group to lamivudine versus the new drug? Anyone else can chime in also.

DR. HOOFNAGLE: There is this evidence

that patients with lamivudine resistance have a somewhat milder course than patients with the wild type that, despite resistance, there is an improvement of the course. So, in that situation, patients with lamivudine resistance, I think a control trial of placebo versus adding the second drug is reasonable with suitable ways out if there is evidence of deterioration.

Some people's lamivudine resistance--I think they fall into two categories, those who have a continuing effect of lamivudine--their levels of virus are lowish and they usually have minimal enzyme elevations or normal enzymes--and those who really kind of--the lamivudine-resistant gets nasty and these people have very high levels of virus, close to where they started and very active disease.

That is the group that probably need to be taken off of lamivudine, needs to be taken off of them. There have been reports of virus that grows--that replicates better in the presence of lamivudine than without lamivudine, lamivudine-dependent strains. I think that is the situation where you see very bad disease, I suspect.

So I think it is appropriate, with sufficient ways of getting out if the patient deteriorates, breaking the code, transferring them, calling it a failure, and so forth, to use a placebo in lamivudine-resistant disease.

DR. GULICK: Dr. Goldberger?

DR. GOLDBERGER: I just wanted you to clarify. When you spoke of lamivudine-experienced, were you implying that those were patients no longer being adequately treated by it or were they simply patients who had been on it for some period of time?

DR. GULICK: I didn't make that distinction. I guess that is what came up in the fact that some people actually may still be benefitting or have benefitted from lamivudine versus those with frank resistance. Clinically, sometimes maybe you don't know the difference between those two groups. So I was intentionally vague about that.

Dr. Sherman?

DR. SHERMAN: Going back to the decompensated lamivudine-resistant patient, I think that, based on the data that was seen yesterday and the discussions, it is going to be very, very

difficult to have any patient that you don't choose to use adefovir in that setting at this point versus, perhaps, another agent.

In that group of patients, we also recognize, based on the data yesterday, that that is the group that probably presents the highest risk for complications from renal toxicity and, therefore, the bar today is adefovir as the standard comparator for that group. Someone else will have to show, perhaps, equivalence.

If someone comes in for a specific identify saying, "I want to test this drug in decompensated lamivudine-resistant patients," then the bar today is adefovir and a comparison of equivalence and, perhaps, a better toxicity profile. That is where we stand right now and, yes, people may put people on tenofovir but, if you are doing a formal study, you have to make a choice and the choice is the drug that is approved for the hepatitis-B indication.

DR. GULICK: Let me see if I can summarize where we are. The situation controls for decompensated liver disease is quite different for with compensated liver disease. There was a consensus that controls are desirable in this

group. Dr. Wong made the comment yesterday about the 435 study, actually.

It was generally felt that placebos are unethical in this particular in this particular group given the risk of progression of disease. Historical controls was once again raised as a possibility.

Active control, it was pointed out that, practically speaking, probably most people in this group had have had 3TC experience and that that drug is actually the standard of care for someone with decompensate liver disease right now and that would limit the options for the active control in this group. As Dr. Sherman just said, that really leaves adefovir as the standard drug to be used as the control in this group.

Also pointed out was the risk of delaying liver transplant and the complications that may ensue because of treatment of this particular group.

When we considered those who had failed prior treatments, Dr. Mathews mentioned maybe no-treatment might be appropriate in that group, in particular. No; I'm sorry. That is not what you said. Take that one back. It was important to

include interferon-experienced people, that that could be dealt with by stratification, that when you got to 3TC experience, you needed to distinguish between people with experience versus those with resistance.

As Dr. Hoofnagle made the important point that there may be continued effects from 3TC lamivudine in some patients, versus those who have frank resistance and highly active liver disease. In that particular group, we heard a couple of thoughts. Leaving on lamivudine was thought to be inappropriate for those with decompensated liver disease. It might be appropriate with appropriate safety measures for a compensated group.

Adefovir, obviously, is the drug that has shown activity in 3TC experience and that kind of rose to the top of the list as, perhaps, the active control of choice. It was mentioned that tenofovir is being used in the community and then Dr. Lok reminded us that prayer is also important in that case.

Dr. Block?

DR. BLOCK: I would just like, before we leave this question, to add one more thing to Question 3a, or one response, very briefly. For

myself, it is important to make this point. I think we should anticipate, or this committee should anticipate or have the imagination to anticipate therapies other than those that have been approved or are immediately in the pipeline.

It is easy for the committee to focus on those because obviously the nucleoside analogues and interferon are the two drugs that we have dealt with. Placebo controls are still, to my mind and, I'm sure, to everyone's mind here, the best way to conduct a clinical trial or design a clinical trial. Whether or not that is ethical or appropriate will depend on the patient population.

The patient populations for which the current designs have been made now may demand--I don't think they will, but may frequently demand the standard of care that calls for therapy. However, often, or you can anticipate drugs choosing other patient populations for which placebo controls are entirely appropriate.

Moreover, the active control that would be used or dictated the relevance of it is also going to be influenced by the mechanism of action of the test drug. If the test drug is another DNA polymerase inhibitor that is going to reduce DNA

levels, well, then, of course, it makes sense to have the active control if there is going to be one, a like drug.

If it is going to work by another mechanism of action, particularly when you talk about endpoints, you may talk about sixteen-week analyses for predictions, then DNA polymerase inhibitors might not be the relevant ones.

I know that saying a lot, but I just wanted to at least reserve that bit of real estate to imagine mechanisms of action other than polymerase inhibitors.

DR. GULICK: Shall we move on to endpoints?

DR. MURRAY: At your discretion, you can open it up five minutes.

DR. GULICK: Oh, right; thanks.

DR. MURRAY: If you think there is still time.

DR. GULICK: Okay. I do.

At the suggestion of the agency, we would like to open it up for public comments on the subject of appropriate control arms. This is going to relatively limited, but is there anybody sitting behind me that would like to make a comment about

control arms?

DR. BROWN: Dr. Nat Brown, Idenix, guest of the panel today, I guess, in some form. I can speak to an experience that I think some here are aware of. We recently put two proposals for a phase III trial program to about 120 clinicians worldwide. One of them was an intricate 9-to-9-to-2 randomization with the 2 on placebo resulting in about 10 percent of patients getting placebo for one year and putative active drug in Year 2, so had one year of deferred treatment.

Putting that proposal with a straight head-to-head active--this was in compensated liver disease. The other proposal was straight active control. There were only four hepatitis specialists, clinicians, out of 120 that we put that proposal to that liked the placebo control. The rest said they either couldn't do it or their patients wouldn't enroll.

So we came to the conclusion that placebo controls in compensated liver disease are really not practical at this point.

DR. DUNKLE: Lisa Dunkle from Achillion. I would certainly concur with what Nat has said, but the one point that has not come up which I

think--this may not be as pressing in the U.S. as it is outside the U.S. is the understanding of how a new drug compares clinical to existing drugs on the market and what drugs should be reimbursed and what drugs should be supported.

Many regulatory authorities outside the U.S. not only wish for but demand active comparators to understand how a new drug compares to existing drugs.

DR. DIENSTAG: Jules Dienstag, Mass General Hospital, Boston . The one point that hasn't been mentioned here is that when lamivudine was studied and when adefovir was studies, the placebo-control groups studied for a year had 20 to 30 percent progression of fibrosis which is the most important histologic landmark.

I, personally, can't recommend to a patient that he go, or she go, on a year's worth of therapy with a 30 percent chance of progressive fibrosis. My IRB won't allow it and I think that Nat basically expressed what happens in real life.

DR. GULICK: Anybody else?

On to endpoints. You are shaking your head because you like the format; is that right?

DR. BIRNKRANT: We thought the comments

were very helpful, actually.

DR. GULICK: Yes; I did, too.

Dr. Stanley?

DR. STANLEY: Some of us talked about this at lunch. As we move on to endpoints, I need some clarification from maybe our hepatologists. Dr. Lok and Dr. Hoofnagle both said, in their talks, that seroconversion of e-antigen is really kind of a gold standard, agreed-upon, helpful thing to look at.

Yet, when Dr. Soon presented his data, he apparently showed patients that went back and forth and back and forth and back and forth during the course of the study. So, do you all really see that or was this an anomaly, or did I misunderstand something? Can somebody clarify that for me, please?

DR. GULICK: Dr. Soon, can you review--a number of us were surprised at that one slide.

DR. SOON: I think the difference is in the definition. What I looked at was the e-antigen status, that is when you have e-antigen alone as a component. The seroconversion refers to three components. Maybe other people can comment on that.

DR. LOK: Actually, I was very surprised with that, also. Having managed a lot of hepatitis-B patients, you do see that some patients go from e-antigen-positive to e-antigen-negative and then revert back. But, if I understood that slide correctly, you showed that the majority of the patients flip-flopped. It is only a minority of the patients after they became e-antigen-negative that they stay persistently negative from that time onwards, which is really an anomaly, from my personal experience in fifteen, twenty years, that the people who flip-flop are really a minority.

You see it anywhere between 10 to 30 percent of patients, but, certainly, not 70 to 80 percent.

DR. GULICK: It is Slide No. 40, I think.

DR. SOON: The majority of patients maintain their status. Two-thirds maintain their status. About a quarter to one-third rebound.

DR. LOK: So one-third of the patients flip-flopped but two-thirds of the patients, once they become e-antigen-negative, they stay e-antigen-negative.

DR. SOON: Correct.

DR. LOK: Okay.

DR. SOON: If you look at this slide, if you look at the placebo arm, we have 364 patients. 14 percent become negative sometime in the 48 weeks, or the 52 weeks, for the period of the trial. So that is about 50 or 60 patients. Among these patients, 37 percent will go back to positive again. That means, the other 63 percent will maintain their status until the end of one year.

So two-thirds maintain their status one-third will go back. Among those who go back, about a quarter will go down again to the negative.

DR. HAMERSTROM: Those numbers become progressively smaller.

DR. SOON: Right.

DR. HAMERSTROM: That 52 people. That 37 percent is about fourteen people.

DR. GULICK: Can you come to the mike, please.

DR. HAMERSTROM: The rest of those numbers are so small--

DR. GULICK: Can you come up so that everyone can hear your comments?

DR. HAMERSTROM: Tom Hamerstrom, statistician, FDA. You should remember, in

interpreting this table, that those numbers have to be multiplied progressively. So you start with 364. 14 percent--that's 52 people--go from plus to minus. To go from plus to minus to plus, that is 37 percent of 52, which is about--

DR. SOON: Seventeen patients.

DR. HAMERSTROM: Seventeen. The next group, the 26 percent, that is 26 percent of 17.

DR. SOON: Four patients; yes.

DR. GULICK: So, perhaps, that is not the best way to--

DR. SOON: The same pattern for the other patients, actually. Two-thirds will maintain their status, one third will rebound. Among those who rebound, one-third will go back again. So it is always the traditional probability is about one-third from one status to the other state for any given patient.

DR. GULICK: So that is somewhat confusing way of portraying that data, I would say.

DR. HOOFNAGLE: Was the 14 percent at Year 1 the Year-1 specimen or any time during Year 1?

DR. SOON: 14 percent of those 364 patients will become negative in the one-year period of time.

DR. HOOFNAGLE: Oh; during the period of one year.

DR. SOON: Correct.

DR. HOOFNAGLE: I guess this shows that, with the spontaneous seroconversion, there is about maybe a 25 percent relapse rate that is persistent.

DR. SOON: Yes; so the same pattern here. Once they become negative, in all the groups of patients, one-third will go back in the one-year period of time. Among those that go back, one-third of that group will go down again to negative. So it will still be in that window.

DR. LOK: On second look at this slide, if I understand it correctly, if you look at the three groups of patients who received treatment, once they have become e-antigen-negative, the chance that they will revert back to e-antigen-positive is between 72 percent and 80 percent. Of those, they might sometimes still become negative again.

It is the minority that flip. It is between 20 to 28 percent that flip, but 72 to 80 percent will stay e-antigen-negative. So it is the majority.

DR. SOON: Yes.

DR. GULICK: Does that replicate your

clinical experience?

DR. LOK: That replicates clinical experience. What happens is when you see patients develop e-antigen loss or e-antigen seroconversion, you tend to get about 10, maybe 20, percent of the patients who would lose their response. Sometimes, they lose their response transiently and then they sort of get back to the response state. Sometimes, they just lose their response forever. So 10 or 20 percent is not too surprising.

And, yes, we do agree that, at least for the e-antigen-positive patients, if you see a sustained e-antigen loss with or without the detection of e-antibody, that has been shown to correlate with histological improvement. That has been shown to correlate with improvement in clinical outcome.

But, as Dr. Hoofnagle pointed out, we now know that some patients, when they go from e-antigen-positive to e-antigen-negative, they may be selecting for the precore mutant. So now we should qualify a e-antigen response as e-antigen loss with suppression of viral DNA with normalization of liver enzyme so that if you lose the antigen but your DNA still at 10

7, your ALT is

still high, then we shouldn't call that a response.

DR. GULICK: May I take a step back now that we have clarified this particular slide, to go back to what the actual question is to us? Can we go back to Question 4?

DR. WOOD: Before we do, may I ask one more question about e-antigen loss?

DR. GULICK: Yes.

DR. WOOD: This is, again, a question for Dr. Lok and Dr. Hoofnagle. For those patients who have e-antigen loss, what percentage of them have seroconversion in terms of a gain of antibody? Does everyone who loses their e-antigen gain antibody?

DR. HOOFNAGLE: No, they don't. A large proportion do, that do it spontaneously or with interferon treatment. It was my impression with lamivudine that a lower proportion actually made antibody. But maybe Nat Brown can comment on the proportion of patients who lost e who made antibody, who lost e and it was sustained over not just these flip-flops.

DR. BROWN: There are probably some Glaxo people here who might speak to that. Do you want to try that, or do you want me to try it out of my

memory? I could be rusty and if I say something wrong, hopefully, they will correct me.

My impression was, in the Western studies, e-loss rate was in the 30 percent range essentially and the antibody gain rate was only around 18 percent, as you saw. That is a rather broad generalization. Whereas, if you noticed, in the multicenter Asian study, the e-loss rate was, what, only, still, 17 or 18 percent and the e-conversion rate was 16 percent.

So, for whatever reason, in the Asian study, almost all the e-losers gained antibody whereas, in the Western studies, only about two-thirds gained antibody and the 18 percent gain of antibody actually checked out very nicely with the table in the meta-analysis, the first Wong meta-analysis, where the gain of antibody in interferon was about 18 percent listed in one of the tables in that paper.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: I have to also say something about--the tests for e and anti-e are not great tests. Furthermore, the FDA, in their brilliance, actually did away with the company that was doing the test for many years and we had to

switch to a new company. I, frankly, don't have a good feel for the reliability now.

But the test for anti-e was not a very good test. Basically, to test for anti-e, you have a control sample that has e and you mix your sample in it at 50 and you see if you drop the counts per minute. So, it isn't a very good test for anti-e.

Furthermore, you can't have both--using this test, you really can't have both e and anti-e because of the way the test is done. It is not a very good test.

DR. BROWN: Do I need to identify myself again? I agree with Dr. Hoofnagle. It may be somewhat assay-dependent. What is it called, the IMAX, the automated version of some of the Abbott assays may give a little different readout on this proportion than the older assays. So I agree. It could be somewhat assay-dependent.

DR. GULICK: Dr. Kumar?

DR. KUMAR: I have a follow-up question. Once, in patients who lose their e-antigen and develop an e-antibody, can we conclude that our prayers have been very effective and they will not go back to the e-antigen status?

DR. LOK: The challenge of hepatitis B is

that this is a highly unpredictable disease and nothing is permanent. In general, actually, Dr. Lao from Taiwan was the first to describe the so-called e-window period way back about fifteen years ago. You could have patients who lose e-antigen and some of the patients you would detect e-antibody pretty much at the same time.

The first time, they become e-antigen-negative, you really show up e-antibody. Some of these patients, the e-window period is very long. He showed that a majority of these patients, the e-antibody shows up within twelve months but some patients can be as long as five years or six years later, you still don't develop e-antibody.

While the patients are in the so-called e-window phase, the likelihood that they flip back and become e-antigen-positive is higher than in people who have developed detectable e-antibody. But the detection of e-antibody is not a proof that the patient will not flip back. It is just a matter of probability being lower.

DR. HOOFNAGLE: Actually, in patients who develop AIDS, too, you see spontaneous reactivation. Indeed, with interferon treatment, we had very nice response rates and many gay men

who then developed HIV, they all will reactivate eventually under the immune suppression of HIV disease.

DR. GULICK: With those clarifications, I am going to suggest we take a ten-minute break and then we will come back and answer the last two questions. So we will reconvene at 3:30.

[Break.]

DR. GULICK: Welcome back. Dr. Murray wanted to clarify something before we get started on the next question.

DR. MURRAY: Yes. Regarding noninferiority or superiority. A new drug product does not have to show superiority to gain marketing approval. That is not a regulatory standard, or have that sort of relative efficacy standard. So they could be comparable or actually, in some cases, products inferior but known to have activity and they could still actually get on the market. They just have to show that they do have efficacy, so it doesn't have to be superior. It is usually comparable in a noninferiority study.

Then the second point was using a non-approved drug as a control. We think it would be very difficult to design a study at this point

with tenofovir as a control for hepatitis B because its longer-term us for hepatitis B has not been adequately established in control trials. So we would think that the use of tenofovir would require a whole lot of background work before using it as a control in a trial for registration.

DR. GULICK: Great. Thank you.

So we are on to Question No. 4; considering the patient population, and the necessity that endpoints for registration be clinically meaningful, please answer the following; which endpoint or combination of endpoints should be primary in clinical trials? We are going to want to touch on histologic, serologic, biochemical and virologic endpoints; so the primary endpoint in future hepatitis B studies.

Dr. Goodman?

DR. GOODMAN: It is my turn to comment on some of the things that have been said about histology today. I want to clarify things that have been said over the last two days. One of the most important ones is about the criterion of a two-point change in histology as an endpoint, is that clinically meaningful.

I have never been entirely sure where that

came from but, as I understand it, it was in negotiations between the agency and the sponsors of previously approved drugs. I think using the histology activity index, it was originally conceived of as being a continuous variable even though there are missing numbers.

I think that was the way it was intended to be used, but the agency statisticians were unhappy with that, as I understand it, and they asked the sponsors to pick out something that they considered a clinically meaningful degree of change.

Two points was decided on. I am sure whose idea that was. How can you get a two-point change? You can get a two-point change in several ways. The natural history of the disease; this is a disease that flares and subsides. So some patients are going to improve by two points spontaneously. Some will worsen by two points spontaneously.

You can get it by sampling error. I have seen liver biopsies where one end has a score than is more than two points higher than the other end. If you only have half of that biopsy, you can get a change that way. That was referred to in Dr.

Soon's presentation. Then the interpretation by the pathologist. This is a continuous variable, but the pathologist has to put it into discrete categories. If it is on the borderline, you can get a two-point change just that way, even if nothing absolutely happened to that patient.

There are lots of ways you can get a two-point change irrespective of the virologic response.

Now, a two-point mean change, I think that is extraordinarily meaningful. The agency statistician yesterday showed the box plots from the adefovir study showing a whole shift of the entire population who was being treated with the active drug.

That is a big change. The entire population shifted by more than two points. I think that is the way all of this histologic data ought to be used is in terms of a cohort rather than an individual. I tell that to pathologists when they ask me how to go about scoring it because Dr. So-and-So wants the Knodell score on this patient. So I say, "Just refuse to do it. Tell them that is not the way to do it."

The way you should do it is, if you want

to know if an individual patient improves, you look at the two biopsies together. If you want to know whether a cohort improves, then you need something to do with statistics that you can do a test on that can show a meaningful improvement.

What would be a better way? You could use the mean change. But, in fact, that two-point proportion still worked. As I said yesterday, that is the absolutely most conservative way you could interpret the data, but it still works. It showed a highly statistically significant change between the placebo and the active drug. So that is possible, but it is not necessary and that is really not the right question to ask, though.

The real question is whether the entire cohort improved. I think, with the drugs that have been approved, they have. Anyway that you look at the data, it shows improvement.

That's the main thing. I am not going to say whether I think the liver biopsies are the best way. I was confused by some of the data that was presented. I think Dr. Lok's data that she presented showing a total lack of correlation between histologic improvement and the other parameters was because histologic improvement was

defined as a two-point change.

Dr. Soon showed that actually, and I think Dr. Wulfsohn mentioned, that the best predictor of improvement was the baseline score, that people who have a lot of inflammation are going to be spontaneously improving but more of them will improve if you treat them with an active drug and they will improve to a greater degree. So it is another thing to take into consideration.

Dr. Soon showed what looked like a lot of lack of improvement but it was based on the change in the score rather than the absolute score, so I am not sure whether it wouldn't have been better if you looked at the absolute amount of inflammation, as to whether that correlated. And I was totally befuddled when Dr. Murray showed that graph showing an absolutely perfect correlation of histology with DNA. How can that be? I don't understand that at all.

Since I enjoy looking at liver biopsies, I am not going to tell you that you have to liver biopsies. I do have a conflict of interest there, but I think that there is more to be gained from looking at liver biopsies than just doing these scores. There is all sorts of other information

that you get about the patient including where he is in the natural history of his disease and what his prognosis is going to be.

DR. GULICK: Dr. Birnkrant?

DR. BIRNKRANT: Do you have a preference, though, for Knodell over the Ishak score?

DR. GOODMAN: In the adefovir study, we analyzed it both ways using the two-point improvement, looking at the mean improvement, and it comes out the same, basically. I think it is a matter of personal preference. Probably since the Ishak score did away with that group, the missing number 2, why not do it that way in the future. But I don't think it will make any difference in the outcome of the studies, as long as we are talking about cohorts as opposed to individual patients.

DR. BIRNKRANT: You would never anticipate, then, a discrepancy between the Knodell and the Ishak?

DR. GOODMAN: Oh, anything could happen when you are dealing with numbers. That is the other that I meant to mention. How do you do away with these other reasons for variability? Besides having a placebo control, you have to have adequate

sample size for statistical analysis, not just looking at individual patients.

DR. GULICK: Dr. Wong and then Dr. Hoofnagle?

DR. WONG: I guess I want to ask Dr. Goodman, yesterday we saw, from the FDA reviewer, that the adefovir treatment arm caused a measurable improvement in fibrosis score, not just an improvement in inflammation and necrosis score.

Then Dr. Hoofnagle's presentation this morning, I think you showed that if you follow people out longer than one year, that is not so surprising, that that was seen in other cohorts as well. Which would be your preference? I guess, from my point of view, prevention of fibrosis is what we are really trying to achieve as opposed to prevention of inflammation. If one could expect that that would be demonstrable in a reasonable period of time such as one year with a highly effective agent, would that be a preferable endpoint of the two choices for histology?

DR. GOODMAN: The absolute change in fibrosis is actually pretty small. It is statistically significant. It is definitely going in the right direction. But, in one year, it is

really not very large. Most of the patients don't have that much fibrosis to start with and it becomes less.

If you started with people with more fibrosis, you would have a harder time getting them into it. I suppose, then, there might be more room for improvement but I think you would probably need larger samples. There, again, we are not dealing with probably a clinically meaningful improvement in fibrosis in terms of individual patients, even though it is definitely happening and I presume that, over the course of many years, there would be statistical, even clinically meaningful improvement.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: I think you have answered one question and that is when you give all these HAI scores, are you using the old system where you skip the number 2?

DR. GOODMAN: We collected the data both ways for the study. The primary endpoint was defined as the original Knodell score and that is what we used. When you analyze it using the modern one, it comes out about the same.

DR. HOOFNAGLE: The second issue is a

mathematical statistical one that I have never been able to understand how to analyze changes in scores. As you showed very clearly, if you begin with a low score, 5, you can't improve very much. So these multivariate analyses that show that improvement in histological score correlates with the initial histological score is stating obvious, isn't it? It is not really very helpful.

So the reason why the two-point change was used was basically you wanted to change this from a parametric to a nonparametric number. Basically, are they improved? Are they the same? Or are they worse? Improved would be one point better. But they said, "Oh; one point isn't enough. Let's make it two." So that is how it was to categorize the patients as improved, the same or better.

But when we talk about the amount of improvement, that is so dependent upon where you start that I am not sure how that can be interpreted.

DR. SOON: That is why I have been showing the two lines, basically to say it has to be forced even if there is no correlation. If it varies wide enough, because you cannot see various above, below, the two lines, so you are going to see an

artificial trend there. So it is really hard. You cannot tell if it is really because this is the upper and lower limit in the scoring system or is that because there was really a correlation. It cannot be separated.

DR. BLOCK: I just had a quick question and also a point. One, first, I wasn't surprised--I was, actually, encouraged--by what Dr. Murray presented showing the tight correlation that was change in DNA from baseline rather than absolute levels as was shown previously at Year 1. I think that is very telling. It was the change in DNA and, actually, you or someone else may have mentioned that that might be best taken at a particular time under therapy.

Again, I will emphasize that the endpoints used will have to be influenced, I believe, by the mechanism of action of the drugs. But, having said that, since the drugs that are being considered are, again, the nucleoside analogues, the change in DNA correlation was, I think, satisfying and actually consistent with what we saw before.

I just have a question for the group because I really don't know the answer to this and it may be known. Given the fact that hepatitis B,

obviously, causes liver cancer as much as cirrhosis or fibrosis, is it clear that the HAI scores and Knodell scores are the best predictor of length of life or quality of life or in other clinical terms? Is that clear, because that is what is we are all aiming for.

DR. GULICK: So the question is does histology predict clinical outcome.

DR. LOK: There is not a whole lot of data. Most people quote a paper that was published from the Stanford group many, many years ago where they biopsied a bunch of patients using the old terminology, chronic persistent hepatitis, chronic active hepatitis and cirrhosis. These were patients who were not on treatment. These were patients who just happened to be biopsied.

You follow them ten years out and you found that the patients who had cirrhosis in initial biopsy obviously had higher mortality. The patients who had CPH initially had better survival compared to dose with chronic active hepatitis.

So that is really the most widely quoted study and that was a study from fifteen years ago. I find that one of the problems with using histologic response as endpoint and trying to

understand whether that predicts clinical outcome is it is so much dependent on whether you do the biopsy when the patients are still on treatment because, with all these nucleoside analogues, if you do the second biopsy while the patients are still on treatment, and if the viral load is still suppressed, the liver enzymes are down. You are not surprised that the second biopsy looks better.

Does that actually predict better clinical outcome? It depends on whether you are able to maintain the patient in that state. If you stop the treatment and everything comes back, then I don't believe that the initial histological response would be of benefit to the patient or, if it is, it is probably only very minimal benefit to the patient.

Likewise, if the patient subsequently developed resistance and there is beginning to be some data emerging that show that the patient's Year-1 biopsy improved, but the Year-4 biopsy, after the patients have now developed resistance, the HAI score has gone back up again. So you have the pretreatment one and then the Year 1 comes down. Then, if they have developed resistance later on, it will go back up again.

So you really need to understand the timing at which the biopsy is done and whether the patient was still on treatment. I, personally, would like to see that we can get away from histologic response as an endpoint not because I think that Zach is too busy. We can certainly give him more work and he certainly enjoys looking at biopsies anyway, but I think that, from a practical standpoint, if there is a way by which you can use a noninvasive endpoint, you would prefer to use a noninvasive endpoint because it is certainly more acceptable to the patients.

We also have a hard time, as we just discussed--liver biopsy is not bad but if you want to use histology, how do you define what is clinically meaningful. We are not sure that a two-point decrease is clinically meaningful. It depends on what your starting point is. It depends on whether you repeat the liver biopsy when the patients are on treatment.

So if we want to stay with histology, we should review whether we should stay with a two-point improvement or whether we should have a more creative way of looking at it. Dr. Hoofnagle had, in the past, proposed a 50 percent reduction.

So, if you start off with sixteen points, you need to drop down to eight points.

Or maybe we need to have a percentage drop and drop below a certain level, because if you start off with 18 and you drop down to 9, it is still fairly high. It is still not very good. So, do we want it to drop below 6 or 7 before we say that this is clinically meaningful because if we talk about clinically meaningful and not just to play around with statistics, then we really should decide what is clinically meaningful.

I also want to suggest that we should carefully examine the possibility of using virologic endpoint or, better still, I think we should use composite endpoint. I don't believe that we should just look at ALT normalization. I don't believe that we should just look at HBV DNA level at one time point or even at multiple time points.

I believe that, for the e-antigen-positive patients, we should certainly look at the composite of e-antigen loss plus or minus development of e-antibody, a DNA that drops below a certain level--I propose maybe 10
5--and ALT being normalized as a composite endpoint.

For the e-antigen-negative patients, obviously, we can't talk about e-antigen loss. If we use a composite endpoint, it would have to be a drop in the viral load and normalization in liver enzyme. How much should the viral load be dropped down to? I believe that it should be dropped down to a lower level because these patients start off with lower levels so they should drop to lower levels.

These patients fluctuate. So are we satisfied with just looking at these endpoints at one time point or do we need to see that this is consistent, that you can actually reproduce it and that you can see that this is occurring over two months and three months.

So I think we should look at using other endpoints. We should look at composite endpoints and, if we do decide on histology, we should definitely reexamine whether a drop in HAI by two points is the right criteria.

DR. GULICK: Dr. DeGruttola?

DR. DeGRUTTOLA: I just wanted to comment on a previous issue but I also believe it relates to Dr. Lok's comments about the histology. As Dr. Hoofnagle pointed out, it someone starts at a lower

value, they can't decline as much as someone who starts at a higher value.

But there are statistical methods for censored data that can handle that situation, so I don't think that need, necessarily, be a concern although you have to bear in mind that some of the data are actually censored because you can't drop below a certain level.

The issue of where you start in terms of the Knodell score may affect how much of a drop you had can also be handled using methods like analysis of covariates. So I don't think that these issues prevent being able to do valid analyses although, as I think Dr. Lok pointed out, the crucial question here is what is most clinically relevant.

In terms of the bDNA analyses, obviously the ones that are the most straightforward are the ones just discussed going below a particular threshold. I think that, as part of a composite score, obviously that would be an interesting endpoint that would reflect a lot of things that were going on. But one of the concerns that I would have about the DNA being used as an exclusive endpoint is that the association with the Knodell score appeared to vary, as Dr. Soon pointed out,

earlier.

Therefore, you couldn't assume that a certain level of DNA meant the same thing in terms of its predicting a Knodell score whether or not you were on therapy or it could also depend on what therapy a patient was taking. So I think that would be a concern about using DNA on its own.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: I agree with Dr. Lok with the need for probably developing some composite markers and that those are going to have to be individualized based on each individual treatment. In other words, what is defined as the primary endpoint for a patient on interferon in e-antigen-positive group of compensated disease may be different than what you are seeking on nucleoside analogue in a patient with HIV infection.

In other words, the population that you are treating will partially define what you select as your primary endpoint. I think that the agency is going to have to be somewhat flexible and cognizant of that fact.

The issue about two points isn't enough and maybe we should use a greater drop or percent

drop or a certain decrease is not validated by anything either. There is no prospective data that tells us that, gee, a 50 percent drop in HAI is going to be clinically more relevant then a two-point change. It sounds good. It feels right. But it is not based on anything.

The other point that I wanted to make relative to what Dr. Lok said was that issue of looking at histology and making a decision about when you would like to biopsy is partially dependent upon your philosophy of treatment.

If we had a treatment that cured disease, similar to that which we see in hepatitis C now, then a reasonable time point would be after the end of treatment and a time has passed. But that is not our goal of therapy here. Our goal is, itself, kind of vague. We would like to see e-antigen conversion and e-antigen-positives.

But a large percentage of patients are not e-antigen-positive that have this disease. Particularly, with the newer agents that are out there, we, in fact, are dealing and must come to grips with the fact that we are dealing with suppressive therapy and here invoking the model of what we do with HIV, that it is going to require

long periods of treatment, that some patients will have a conversion of a type that may take them to a less replicative state and maybe some of those patients won't need therapy, but that the majority of patients, in fact, will need, with the therapies that we have now and the data that we have seen on all the therapies, to need suppressive therapy.

Therefore, a histologic model that shows you the effect of treatment of therapy is reasonable. Now, that is separate from the practical issues related to getting those biopsies that have been brought up, but it is still reasonable to consider that as a marker for therapy unless we feel confident that one of the other endpoints is highly correlated; for example, a drop of some level in HBV DNA.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: I wanted to ask a question of Dr. Goodman and then make a comment. When you read the biopsies in clinical trials, you are blinded to the treatment assignment. But are you reading the paired biopsies? You know you are reading the same patient?

DR. GOODMAN: It is different in different trials. Sometimes, I am totally blinded. I don't

even know which ones go together. Sometimes, I do look at them both together. I don't think it has made any difference in the outcome of the studies.

DR. MATHEWS: But, in terms of the correlation between the baseline biopsy and the reading, the score, the numerical score on the Knodell and the follow-up biopsy, I would think that that could explain part of the high correlation between the baseline and the subsequent biopsies if you knew that you were reading the same patient, because you are doing them at the same time, presumably.

DR. GOODMAN: It is not that they come out the same. It is that those with a higher baseline HAI are more likely to have improvement. That is the only correlation there. It is not that the biopsies correlate with one another. Sometimes they do look the same and sometimes they look dramatically different. Do you see what I mean?

The predictor was how high the HAI was predicts whether or not the patient is going to have a two-point improvement.

DR. MATHEWS: The other point I wanted to make is that the histology is really--I mean, it is being treated as the equivalent of a clinical

endpoint but, in fact, it isn't and it is quite fallible because of all of these measurement variabilities that you talked about; sampling error, the reading error, and so on.

As I think about it, I wonder if it isn't possible to actually do a true clinical endpoint study where hepatic decompensate or death is the endpoint to validate some of the virologic markers if you started with people with cirrhosis at baseline, where the event rates are not small, as I understand it. Maybe the hepatologists could comment on that?

DR. HOOFNAGLE: You are talking about a very large study that goes on for a long time. In hepatitis C, we are engaged in such a study looking at long-term interferon therapy for patients with stage 3 and 4 disease. But it is an enormous study, very long.

This goes to the question that Dr. Wong brought up that I didn't answer which is why not use fibrosis rather than the histology necroinflammation part of the HAI score. That actually is right on target as far as we think of the natural history of the disease is progressive fibrosis that leads to cirrhosis and end-stage

liver disease.

So the name of the game, really what we are trying to do, is prevent the progression of fibrosis on liver biopsy. So, as an endpoint, that would be certainly harder although it, also, has not been proven to be the clinical endpoint. The FDA has had a lot of input into our trial in hepatitis C in patients with advanced disease for this very reason.

It hasn't been shown that preventing progression from, let's say, an ISHAK 4 to an ISHAK 5 is clinically meaningful. So these are difficult issues but the fibrosis progression is the endpoint that would be much harder if you are going to use liver biopsy. The trouble is it takes a long time so that a liver biopsy, after one year, is unlikely to show much improvement or worsening in fibrosis.

When you go two years, you start to see something, though, I think and, in these trials, you will begin to see big differences in progression of fibrosis in patients who have maintained low levels of virus and so forth. So I think that can be achieved. It just requires a very large number of cases.

I agree with Dr. Lok that we are using

liver biopsy as the be-all and end-all, the gold standard, without it really being proven to be the gold standard, particularly the activity on the liver disease, the necroinflammation, really hasn't been proven to be the factor that needs to be calmed down. It hasn't been proven to be any more accurate than ALT levels, for instance.

DR. GULICK: Dr. Stanley

DR. STANLEY: On my way out. I tend to agree with Dr. Lok that composite endpoints are probably a way to go, a good way to go, but what Dr. Sherman said, I want to expand on. It is not just that you may have to change those based on the population you are studying but also the drug you are studying.

When I looked at Dr. Soon's data on all of the interferon arms, DNA was just off the chart, up and down, up and down, as well as ALT. So you couldn't really necessarily use those as part of your composite for interferon treatment or any other potential immunomodulator possibly.

So then that begs the question of how are you going to compare trials with different drugs, do you need a standard, and I don't know whether that is biopsy or not, where you can compare what

the results were in a lamivudine trial with what the results were in an interferon trial or an adefovir trial. So that is just a concern that I express.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: If I had to answer Question 4, I would say that, based on what we saw today, we did not see the correlations with histology for the other endpoints. So I would say that the primary endpoint should remain histological although I think we have heard some suggestions that it would not have to be more than two points.

I think, using it as a continuum and doing censoring, as Victor mentioned, might be a better way. I think the fact that the data from the other trials can probably be also compared in that way would be helpful. That would be the primary endpoint.

I think using 48 weeks despite the fact the patient may be treated longer remains a reasonable time point to look at. There are many therapies which are continued beyond that but, if we see a good response at 48 weeks, it is not to say that it won't be continued. So I think that is reasonable.

I think secondary endpoints might be appropriate. What was suggested earlier, a composite of the others would be a possible secondary endpoint although, again, I think I was, I won't say disappointed, but the data we saw from Dr. Soon didn't heavily support that those correlated with histology. I do think, still, histology has better correlation with clinical outcome than the others.

DR. GULICK: Thanks for being provocative there. Dr. Schapiro is proposing that we recommend at this point that the primary endpoint for future studies continues to be histology, even given all the limitations that people have mentioned. Can we just focus on that one point for a minute?

Dr. Wong?

DR. WONG: That is attractive, but I am a little bit reluctant because the lack of correlation that we saw in Dr. Soon's presentation might have been because virologic and biochemical measures don't correlate well with clinical outcome. But I guess it is just as possible that the inflammatory score doesn't correlate with clinical outcomes and the virologic and biochemical correlate measures do.

So I am not sure that we can decide. That is why I asked the question about fibrosis just because, on the basis of biological plausibility, it would seem to me that if we could demonstrate clearly in a clinical-setting that we prevented progression of fibrosis in one treatment group as opposed to another, just on the basis of general biological plausibility, I would say that is something that we really want to achieve.

But, beyond that, I don't know that we choose a priori that any other is better than any--Group A is better than Group B.

DR. GULICK: Dr. Lok?

DR. LOK: I agree with Brian. We sort of assume that a liver biopsy is really the gold standard and we take it at faith without really showing the data. In fact, when you try to review the literature and see whether there is, indeed, data to show correlation between histology and clinical outcome, like I said, other than that old standard paper from fifteen years ago, there is really no data.

On the other hand, there are numerous studies that show that in e-antigen-positive patients who have sustained e-antigen clearance

that is associated with improvement in clinical outcome, there is less liver-related death. There is less hepatic decompensation whether it is spontaneous e-antigen loss or whether it is interferon-related e-antigen loss.

Lamivudine trials haven't gone on long enough for us to really show that. Even in the e-antigen-negative patients, I showed you data, although the graphs were not very convincing, but, nonetheless, Stephanos Hadziyannis and his group have shown that, in the e-antigen-negative patients who had sustained response to interferon therapy define as normalization of liver enzyme and hepatitis-B DNA dropping to undetectable using hybridization assay.

They also had better transplant three survival compared to the patients who were treated and didn't respond and compared to the patients that were not treated. Granted, that is not parallel controls. Some of those were nonconcurrent controls.

So we do have some data, not perfect data, to show that these serological and virologic and biochemical endpoints, if it is sustained, can correlate with good clinical outcome.

Instead, we actually don't have data to show good histology and improvement in clinical outcome in part not because there is no correlation but, because we don't repeatedly do biopsies on patients on the time, it is much harder to generate those data.

DR. GULICK: Let me push you again on this. I don't know why it is always me pushing you, Dr. Lok. So let's answer the question, then, again. The new drug is coming along. What should the primary endpoint of the study be? Should it be histological or should it be a composite based on the other measures we have been talking about?

DR. LOK: I would like to see that we move to a composite endpoint. I would like the panel and FDA to seriously consider using a composite endpoint and I do think that, perhaps, with Dr. Soon's help and with the industry's help, that we can define specific questions, go back to the database and try to understand some of these questions a little bit better and define how low we want the viral level to drop down to.

What I really is serious consideration of moving to a composite endpoint.

DR. GULICK: Could others ring in on this

issue, too? Dr. Wong?

DR. WONG: I think that the agency should remain flexible on that point. I think it really depends on the population and the drug that they are studying. I personally would be convinced that a drug was effective if a sponsor could show that there was a reduction of progression of fibrosis or if the sponsor could show that there was a sustained virologic response including, for example, conversion to e-negative, e-antibody-positive and all the enzymes disappear and all the DNA appears.

Either of those, to me, would constitute convincing evidence of antiviral effect and I don't think one has to choose one as the primary endpoint for all future trials. I think that the sponsor should be able to choose any convincing data showing antiviral--or actually any convincing data showing clinically relevant effect. It may well be different for different sorts of drugs or different sorts of populations.

DR. GULICK: Dr. Hoofnagle. Dr. Sherman, do you want to ring in on this?

DR. HOOFNAGLE: I think one of the major issues is are we looking at suppressive therapy or

somewhat curative. Are you going to give therapy long-term continuously as we often do now with lamivudine and probably adefovir will be the same, or do you give a short defined course like we do with interferon for only six months?

If you are going to talk about continuous long-term therapy, I think using a composite viral definition is good, a sustained suppression of HBV DNA below 10 5 with normal ALT. I'll bet if you maintain that for four years, you are going to show marked improvement on biopsies.

So this goes to the issue of how long should studies go on that are looking at maintained continuous therapy? Should it be a year? Should it be two years?

DR. GULICK: That is our next question, actually. We will get to that shortly.

Dr. Sherman?

DR. SHERMAN: I agree with Dr. Wong that it is very reasonable to have each drug brought in by a sponsor, be evaluated by one or more parameters that they suggest in discussion with the agency. We know what the relevant markers are. We know that some drugs will probably do better in some areas than others. The way that you structure

your application, the way that you decide to position yourself, whether it is for suppressive therapy in the short-term, recovery of decompensated patients or seroconversion of patients that are e-antigen-positive are all good goals and all will create market niches that can be utilized appropriately by clinicians.

This committee will be the one that will, then, ultimately, review those data and try and decide if it is viable and that there is going to have to be some flexibility because we have so much uncertainty in picking a single outcome that we can say is the outcome that should be used in all studies.

DR. GULICK: Dr. Englund, and then we will try to come to some conclusions.

DR. ENGLUND: I would agree with that. I think that it is very reasonable that one has to be flexible depending on the drug, the mechanism of action, the patient population studied. I do like the idea of composite scores especially as we are moving to larger, more multinational, studies. It makes sense to have something that is going to be less open to different types of interpretation across different medical centers or investigators.

What I would like to say, though, is if we move to the composite scoring system, we have to be very careful not to give weights to different parts of the composite score and add it together and make it a total scoring system, which we have seen and seen misadventures in the past with, for example, other antiviral studies.

You can't add together and make a relative judgment that an ALT is worth so much weight and a bDNA is worth so much weight in a clinical score. You cannot do that. I would still like to have the composite score, the individual measures, and not attach different values. So you don't want to end up with a single scoring system to assess whether the antiviral therapy was actually good or not because I think that will attach value judgment to what is potentially unknown.

DR. GULICK: Last comment. Dr. Wong.

DR. WONG: Just a brief comment. If we are going to accept composite scores, I would just like to make a point I have made before. Make sure that the toxicity measures are kept out of the efficacy measures. We have just had terrible problems with that with other classes of drugs and just confusing the issue.

So efficacy and toxicity have to be clearly demarcated.

DR. GULICK: So, regarding endpoints, clearly we want the most clinically meaningful. Yet it is just not clear to this committee which that is. Mechanistically, from a biological plausibility point of view, perhaps it is preventing the progression of fibrosis but that, too, is unproven. In general, the endpoints may need to be individualized according to the patient population.

Also, the endpoints depend on the goal of therapy. As Dr. Hoofnagle pointed out, is it suppression or is it curative disease and then, as many said, flexibility of endpoints may be the key in choosing the right one for the right drug and the right population.

With regard to the question of which should be the primary endpoint, we are uncertain as a group. Some advocate histology, others leaning more towards a composite endpoint and the realization that neither is perfect and, actually, that neither is prove to correlate with clinical outcome.

Histology, certainly a direct measure of

inflammation and fibrosis and the current gold standard. But, lots of variability realized. It has been treated as a continuous variable in the past which may be not appropriate. It is really a parametric variable. It depends on where you start.

It can vary according to the natural history or sampling errors and the choice of two points is somewhat arbitrary. Different ways of looking, of course, at scoring the histology. Mean change for a population cohort was advocated. Change versus absolute number, percentage change were other things that people mentioned.

Does it predict clinical outcome? Lots of weight to a fifteen-year-old Stanford study. The timing of the biopsy and the presence of resistance were also pointed out as things that need to be considered.

Regarding the other measures, people really did not pick one out although we were intrigued with Dr. Murray's data correlating--Triangle's data, I should say, that Dr. Murray got to present--showing a nice correlation, at least in e-antigen-positive of the change in DNA. Most others gravitated towards a

composite endpoint including a sustained e-antigen loss, decrease in HBV DNA and ALT.

Several people made the point that, perhaps, multiple time points is better than one time point for assessing that. Also, once again, the question, does that correlate with clinical outcome and then very practical suggestions toward the end of the conversation. This should not be a weighted score, that the individual measures are important and that it should not include toxicity.

Let's open it up to comments from--oops.

DR. MURRAY: Can I just ask one question? On the composite for e-antigen-positive patients, must the composite include e-antigen seroconversion. It is a lower-frequency event and, if you add that to the composite, then, in an active controlled study, you are going to need a very small delta or perhaps go out to two years. Or would you look at ALT and DNA as a composite and they must have the trend in e-antigen seroconversion?

Do people understand what I am asking? When you add e-antigen to a composite endpoint, the seroconversion, it really drives up your sample size because it is a lower-frequency event at one

year.

DR. HOOFNAGLE: Of course, there are people who have been maintained on lamivudine or adefovir for several years who remain e-positive who have no detectable HBV DNA, normal ALT and an improved biopsy. So, I think you need to move--if you are talking about suppressive therapy, long-term suppressive therapy, to just suppression of HBV DNA below a certain level and ALT.

Your friends in the hepatitis-C area of the FDA have come up with somewhat of a nice approach. They have virologic, biochemical and histological responses. When people come in with a drug, they basically say you have got to do two out of the three; we are not going to accept a drug that just affects virus or just affects ALT or just affects histology. It has got to affect two of the three.

That actually turned out to be a very smart approach, I think.

DR. GULICK: Dr. Lok?

DR. LOK: Just a comment on Dr. Murray's point. I think it all depends on whether you are thinking of suppressive therapy and, as long as you can maintain this, you can just continue to stay

on the treatment or whether this is an endpoint which would provide guidance for stopping therapy.

If this is an endpoint which would provide guidance to stopping therapy, then I think some sort of change in e-antigen is important. This comes back to the point, is the e-antigen loss good enough because, in every single study, we see that the e-antigen-loss rate occurs higher and the difference between the treated patients and the patients on placebo is more dramatic whereas, if you look straight at the e-antigen conversion, then, yes, the difference is tighter and it drives the sample size.

So I think it is really worthwhile going back and looking at is the e-antigen loss good enough and, if the e-antigen loss is good enough and you don't need the antibody, that might be important.

But the ultimate thing is what is the purpose of the endpoint? Is the endpoint going to provide guidance to practicing physicians that, when you see this, this is an indication that you might consider stopping treatment. On the other hand, if we all sort of throw up our hands and say that, from now onwards, we are going to treat all

our patients forever and ever, then we don't need to look e-antigen as long as the DNA stays down and ALT stays down, we are happy.

DR. GULICK: Dr. Block.

DR. BLOCK: Very quickly. A reason against favoring both or either of those three endpoints, as Dr. Hoofnagle was talking about, because I think it is going to depend on the claims that are made by the applicant, what it is they are representing their drug to do.

If you had, hypothetically, a drug that was wonderful at improving histology but very poor in antiviral or lab values, that might have a great value. And you have the luxury, now, with drugs that are antiviral, of saying, "All right; I can imagine a combination." It just depends on what the claims are that are made by the applicant.

DR. GULICK: Let's go ahead and open this up to the observers. A couple of people already tossed me some notes or caught my eye. So we are open for public comments for about five minutes.

DR. BROSGART: I just wanted to share with you some data. We call this the "Hoofnagle analysis." Our primary analysis in our study was to look at the greater-or-equal-to-two-point

decline in the Knodell necroinflammatory score with no accompanying worsening in fibrosis.

We met that endpoint. If you looked at an endpoint by mean change in total or median change in total, we met that. If you looked at the rank assessment, it was a statistically different result.

If you looked at whether or not you had at least a five-point decline or a four-point decline or a two-point or a three or a one, no matter how you cut it, it is always statistically different from the treated group to the placebo group. But we did the Hoofnagle analysis because Jay threw down the gauntlet at the NIH meeting a couple of years ago because he thought the two-point wasn't good enough and you should look at at least a 50 percent decline.

So, in our e-antigen-positive study, looking at at least a 50 percent decline in Knodell score, for 30 milligrams, it was 35 percent. For 10 milligrams, it was 32 percent. For placebo, it is 6 percent.

Then, in the e-antigen-negative study, again, a greater or equal to 50 percent decline in Knodell. For 10 milligrams, it is 43 percent. For

placebo, it is 5 percent. In each of those studies, the active arms, as compared to placebo using at least the 50 percent decline, are highly significant statistically.

So I think this goes back to I think Zack's adage that no matter whether you are looking at the individual components or the total component and whether you use a greater or equal to two-point or you take the 50 percent, if you have an adequately powered study that has been appropriately randomized so that there are enough people and you have a full range of demographic characteristics and they are balanced for baseline disease characteristics, if the agent is active, no matter what the threshold is, you are going to see a statistical difference because you are looking at moving the entire cohort away from the natural history of disease.

That has been shown. Nat spoke to it, and others have, similar kinds of results were seen when you looked at histology from a number of different ways. So I am not sure whether using the two-point plus no fibrosis or looking at the greater or equal to 50 percent, I think each of them are highly discriminatory.

DR. GULICK: Thank you.

DR. BROWN: I was going to make a scientific comment. I was hoping Anna would still be here, but I think we can still discuss it briefly. I had the impression from this morning's analyses that I think were the most thorough done to date that there may be a little more correlation between the serologic parameters than there is between any serologic parameter in histology improvement.

I don't know if that is worth digging up at this point or whether we have moved on, Mr. Chair, but that might speak to the kind of precision that we need in large active-control designs. If there is more correlation between the serologic endpoints, it does speak to the composite serologic approach that Anna talked about and it may be related to the issue that Brian Wong mentioned that I also mentioned which is the variance in histology measures is part of the scientific issue here.

DR. GULICK: Thanks.

DR. BROWN: So the question is, is there more correlation between serologic parameters. I don't know if Greg Soon can comment on that or

whether he looked at that. I had the impression from Anna's data that she got from both Glaxo and Gilead that that might be true. But I don't know if Dr. Soon can comment.

DR. GULICK: Dr. Soon?

DR. SOON: The only thing I looked at is the e-antigen loss versus the Knodell score. That has a correlation of approximately about 0.3, the same strength as in HBV DNA.

DR. GULICK: Anybody else?

We have a number of sort of rapid-fire endpoint questions. So let's try to rapidly fire them. What is the timing of the primary endpoint. Dr. Schapiro, before he left, suggested that 48 weeks is a reasonable time point. Dr. Wood?

DR. WOOD: I think one of the issues is that the appropriate timing of endpoints is also going to depend on the patient population because we have clearly seen with e-antigen-negative individuals, given the fluctuation in their clinical course, that they may actually require a longer duration for evaluation in terms of efficacy. So it might not only be 48 weeks but then, again, at 72 and 96 for that particular cohort since they are e-antigen-negative.

DR. GULICK: So, long-term follow up critical.

Dr. DeGruttola?

DR. DeGRUTTOLA: I just had a question for the clinicians whether you might have an endpoint like time to reaching certain kinds of improvement; for example, in the composite endpoint, if you need to go below a certain level in the Knodell score and ALT or something else, could that be an endpoint where you wouldn't require that it would be a specific length of time but follow until certain benefit occurred.

DR. GULICK: Dr. Kumar was getting at that yesterday.

DR. KUMAR: And I really got to that which, again, in my mind is not resolved, is at what point do you say that a patient is not responding to the treatment?

DR. GULICK: Dr. Wong?

DR. WONG: I think, Victor, that is a nice idea. If someone could come in and show that a new drug is superior to a standard drug in that respect, that would be very convincing, that that was an effective drug. But the other point I wanted to make about the timing, I think that there

are also situations in which substantially shorter periods of time than 48 weeks might be relevant such as the patients with decompensated liver disease.

If someone could come in and show that, in twelve weeks, for example, there was a substantial increase in albumin, prothrombin time, et cetera, as compared to either historical controls or, let's say 3TC, that would also be, to me, a convincing demonstration of efficacy and it wouldn't be necessary to show long-term results in a different sort of population.

So, any of these. If a sponsor can show that a drug has clinically relevant beneficial effects as compared to an appropriate control group, that should do it. I don't think that there is any specific length of time specific endpoint, that should be put up as a necessary condition.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I just want to say that Dr. DeGruttola's approach is going to be particularly useful when we talk about moving these drugs into the pediatric patient population because we really don't want to put five-year-old children on 40 years of drugs. We are going to want to try and

limit the amount of drug exposure.

So you can see for certain patient populations, that approach is really going to help give an answer.

DR. GULICK: Other comments about timing? Dr. Birnkrant?

DR. BIRNKRANT: What about moving to the hepatitis C model--that is, looking at sustained viral response off therapy. Are there any comments related to that? You end your treatment at 48 weeks and then, six months to twelve months later, off therapy is when you assess.

DR. SHERMAN: Can I try that one?

DR. GULICK: Sure.

DR. SHERMAN: We are not getting anything comparable to sustained response. The comparable outcome would be clearance of HbSAg. Since that has not been discussed at all and is a very, very rare event, I don't think that that is what we can use as an outcome at this point.

DR. BIRNKRANT: So then are we seeing that we are comfortable with 48-week data predicting chronic use? In other words, 48-week data supports five years of the drug?

DR. SHERMAN: No.

DR. BIRNKRANT: Which is a way of asking when do we stop treatment.

DR. SHERMAN: No. I mean, this is obviously the issue that came up yesterday. On the part of a pharmaceutical company, they have to have a line and say, here is what I am going to come forward with my information for you all to make a decision. But they also have a responsibility for these drugs that don't lead you to, in essence, a cure of the condition, to continue to provide data and come back to the agency with that data supports continued use as time goes on. In clinical practice, that it what will happen in most of these patients.

DR. GULICK: Other comments about duration? Dr. Kumar?

DR. KUMAR: But shouldn't there be something that says, in patients who finally we made the decision to stop because they converted from e-antigen to e-antibody, that, in these patients, the durability of response I think may be important as one of our endpoints.

DR. GULICK: So, in general, we reaffirm that 48 weeks for compensated disease, although all of us were interested in longer-term follow up as

come out yesterday, Dr. Sherman's point that shorter endpoints might be appropriate--or, sorry; Dr. Wong's--for decompensated disease to show a difference. Patient population is important. And then Dr. DeGruttola's suggestion, maybe time to response would be a novel way of looking at this, particularly in the pediatric population. We dismissed the Hepatitis C model because this is not a curative therapy, at least at this point.

Secondary endpoints, rank order. Do you want us to consider that or have we spent some time talking about--

DR. MURRAY: I don't think you need to order them. I think we have got the idea on their relative value.

DR. GULICK: The next question was about histology. I think we have spent some time talking about this already, too.

DR. MURRAY: Yes; I think we have devoted sufficient time to that.

DR. GULICK: How about the virologic assay?

DR. MURRAY: If anybody has any comments. I know we didn't spend much preparation time in talking about what the different assays were, but

if anybody has an opinion on if an assay should be used. Sometimes, we get a question whether PCR versus just an assay which has a higher sensitivity limit, so if there is a strong feeling that a PCR assay should be included in all development plans, then we would like to hear that voiced, I guess.

DR. GULICK: Dr. Wong?

DR. WONG: I think the viral load should be treated as continuous variables. Having specific cutoffs is probably misleading. I, personally, believe it has been misleading in HIV Since it is a continuously variable function, it should be treated that way.

DR. GULICK: Dr. Stanley, before she left, really had a question about the viral cutoffs and what the clinical significance of those cutoffs is. I guess both Drs. Lok and Hoofnagle suggested some cutoffs for different populations. Where do those numbers come from? What do they mean clinically?

DR. HOOFNAGLE: I think the Glaxo and Gilead trials will help to answer these, is there a level below which you see histology improvement and above which you don't. But in a couple of studies that have been done in so-called inactive carriers of hepatitis B, virtually 95 percent have levels of

HBV DNA below 10^5. So that has been kind of used as the upper limit of defining someone as an inactive carrier.

The trouble with that is that there are people with e-negative chronic hepatitis B who fluctuate down and may actually fall even to undetectable by PCR spontaneously and yet come back up, and so forth. So it is a bit of a moving target.

But if we are looking at suppressive therapy, I think it would be good to know at what level of suppression do you see biochemical and histological improvement.

DR. GULICK: Has that correlation really been done up until now?

DR. HOOFNAGLE: It hasn't been done until we had these more sensitive assays that are reliable. We had assays in our lab, but they weren't as reliable as the ones that are commercially available now. The hybridization tests of old are just above what you need. We say 10^5, but that is very optimistic. It is really like two times 10^5 or 10^6 that they become negative.

Furthermore, at the low levels, those assays have problems with false positivity.

DR. WONG: Right. But one of the problems with--even if 10 turns out to correlate, if we say that 10 5 is what we are going to shoot for, that might result in our deciding that a drug that, let's say, moves people from 10 10 to 106 will not be considered an active drug. I think that would not be right.

So if we look at change in viral titer, at least in addition--I am not necessarily suggesting instead--but at least that that is an additional criterion for antiviral effect, I think we will be better off.

DR. HOOFNAGLE: We would be better off if everybody were PCR-negative on therapy. So all these things can be looked at as secondary endpoints but, if you wanted a composite endpoint and you need a viral definition, I am not sure we can give it to you yet.

DR. BLOCK: But if I can just add, of course we would all rather see PCR negativity. Actually, it would be very nice to have some kind of standardization--that is another plea--some kind of standardization for these tests which can vary wildly from laboratory to laboratory.

But what I saw from the briefing documents

and from what Dr. Murray gave was surprising to me and that was that the best correlations with other endpoints was a change in DNA, a relative change in DNA, of at least 10

2. Actually, it didn't have to be 10

2. I mean, if you followed that chart that you put up, it actually kind of plateaued. Once you dropped about a thousand-fold, 10

2, 103, it didn't buy you much more correlation or improvement.

That, obviously, has to be looked at more, but it looked to me, and that was consistent with what I inferred from the briefing document, that it was actually the relative change. That may reflect the poor standardization from one test to the other, so one person's 10

5 might be another person's so many genome equivalents.

So that's why I would suggest that you don't get hung up on absolute values yet. Some day, that probably would make sense. But it seemed to me like it was relative change. If you had to aim towards something, you probably could get there with the data you have now deciding what the relative change should be.

DR. HOOFNAGLE: As far as the FDA is concerned, as far as new drugs coming in, I think

you have to ask them to use these more sensitive assays. I think you miss a lot with the just hybridization assays.

DR. BLOCK: I agree with Dr. Hoofnagle. But then, of course, bear in mind that will create a whole new world, a new family, of data in terms of values. It shouldn't, but it will. You are talking about the real-time PCR.

DR. HOOFNAGLE: This is just a standard PCR. It is not real-time is it? It is the Roche assay.

DR. BLOCK: Even that would be different than the branch change, than the dot blot.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I just want to say that I think that we, the committee, should endorse standardization. If we are going to use a company's assay, then that has to be standardized, which other people are doing. But we also need to be saying that, in terms of resistance assays and looking toward the future, that those should be standardized so that the values from one study can somehow be comparable to values from another study. I am talking more of the phenotype as opposed to genotype.

DR. GULICK: Dr. Wood? Same point, huh?

DR. WOOD: Exact same point. I think that, by using an assay that we know is now commercially available that is standardized, that is sensitive, that is better than earlier generations, then, when applicants come, that will add to the database and allow cross-comparison studies so that we can better able get at, maybe, surrogate markers that might correlate with clinical outcomes because we have the identical surrogate marker across multiple larger studies in larger patient populations.

DR. GULICK: So, in brief, we suggest using the more sensitive test. We would like to require standardization of the assays for comparison and that goes for resistance testing, too. Regarding cutoffs, some uncertainty whether the change in DNA versus the absolute value is important and we are looking forward to the correlation of this with other markers and histology.

Shall we open it up for other comments about virologic assays?

DR. BROWN: There are a number of companies engaged that I think have already pretty

well gone with the quantitative PCR precedent although all the points that have been made today, I think we all realize are perfectly valid. But I think we are doing so, and maybe Carol and others could comment, precisely with the idea, hopefully, you have in mind which is we can learn more scientifically about what is important in terms of viral suppression.

I agree with Dr. Wong's comment as well.

DR. BROSGART: I would agree with Nat. I think that it was a limitation within the lamivudine database with using the Abbott Genostics assay is that you couldn't probe deep enough to look, then, at correlations. One opportunity now that we have, along with the agency where we have used a very sensitive assay, is to begin doing these more exploratory analyses that take a number of different endpoints and ask questions, what proportion of patients normalize ALT and get below a certain level of HBV DNA or have a certain delta in their HBV DNA and who, if it is an e-antigen-positive patient, lose e-antigen.

We are beginning to do a lot of that work now. I think it is very interesting. I think, again, certainly in the e-antigen-positive patient,

a lot of correlation with the delta in HBV DNA. It is a little different in the e-antigen-negative patient. There is a difference in the natural history of disease, and I think it is reflective, than in some of the outcomes.

But I imagine, over the next number of months, that we will be able to work with the agency and they will get a clearer idea of what might be reasonable composites by looking at an existing database.

DR. GULICK: Thanks.

Let's go on to the last part of this endpoints question which I think is looking at appropriate endpoints for decompensated liver disease. That is the next one, I think. What is the feasibility and validity, and the particular suggested endpoints to consider are mortality, change in Child-Pugh or MELD score, need for transplant or liver-disease-associated complications.

DR. SHERMAN: Can I try that one?

DR. GULICK: Absolutely.

DR. SHERMAN: Mortality is an endpoint that can be considered. Change in Child-Pugh or MELD is reasonable although, again, we don't know

the validity of what degree of change is meaningful. There is tremendous variability in what MELD scores mean in different places, even today.

In our region, a patient with a MELD less than 20 virtually never gets a liver so you could arbitrarily say that, if you took a patient less than 20, then maybe that is a good thing because it suggests that either they don't need a liver right away or, more likely, they are not going to get one right away.

But those are arbitrary. Although the model has somewhat validated the decision about how much of a change would you need and from where you would need to go or some cutoff to get below to be meaningful is really not established. We would have to say something to the effect of predicted survival of one year is acceptable or unacceptable. Then you need to get above or below that point.

Dr. Lok addressed, before, the issue of getting a transplant is highly variable. There are places in this country where you can get a liver within 30 days of listing, still, and other places where you wait two to three years. That is reflected, then, in the differences in mortality on

the waiting list.

So, if you do a multicenter trial and you use that as an endpoint, you will have considerable variability. The occurrence of liver-disease-associated illnesses, again, highly variable. Not every patient develops variceal bleeding. Not every patient develops SBP. Those are all added complications of late-stage decompensated disease but, if you can prevent those things as a cumulative group relative to two treatment arms, it would be important but what difference, again, would be important would be ultimately a clinical judgment and it would be very difficult to put a number on that.

DR. HOOFNAGLE: Actually, Glaxo went through a long exercise of looking at endpoints here. The Child-Turcotte-Pugh score has been repeatedly shown to correlate with outcomes in patients with cirrhosis. We have to have cirrhosis to correlate with outcomes; for instance, survival after a portacable shunt, or survival to transplantation.

So, I think a two-point improvement in the CPT score is a very good endpoint to use. The MELD score is supposedly an improvement on the CPT

score and actually uses some of the same values. It has been refined nicely so that you can give a estimate of survival and you can use the MELD score, or the average MELD score, to give you your natural-history study.

The trouble with the MELD score, then, though is, once you put a person on therapy and their MELD score begins to change, you don't know whether that correlates with improvement in survival. That is the problem, particularly because the MELD score includes the serum creatinine which may be a problem for adefovir, in particular. So it gets involved in the effects of the drugs independent of their effects on the disease.

So I think it needs to be included in all the studies to test it out. But, for the time being, you are going to have to stick with the CPT score.

DR. GULICK: Could you comment on mortality and liver-disease complications, just as suitable endpoints?

DR. HOOFNAGLE: Oh, yes; those are solid endpoints. The trouble with mortality in liver disease is liver transplantation. Some people get

it. Some people don't. So it becomes a variable.

If you have decompensation, if you qualify for this, you already qualify to be on transplant lists. So time to entry into a transplant list, you also can't use. Time to transplantation is affected by so many other things that you don't have control over.

DR. GULICK: It is getting kind of lonely at this end of the table. Was it something I said? Can we do something else today, or are we kind of--

DR. MURRAY: I think we can finish. The only thing is if anybody has any strong feelings on the questions under 1 and 2 about essential patient populations. So if anybody would like to just voice any comments on the populations that are essential that you would not like to see a marketing application not have.

DR. GULICK: So which populations are essential for the marketing of a new drug.

DR. MURRAY: For the initial marketing. If a sponsor came in without population X, you would tell them to resubmit at a later date.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: I guess you are referring to something like HIV-positive patients. There,

the problem is they are on lamivudine already, on Epivir, and you shouldn't give them interferon, I don't think. So it is a very different group. They get tenofovir instead of adefovir. So they are not really a group that is real important here in this analysis.

Children are very important group. It is a different disease in childhood. You have different outcomes there. Long-term suppression doesn't sound too good to us. We would like to see it cured. So, there, the focus should really be on a defined period of treatment and trying to induce the seroconversion or loss of e or s.

Other populations, both men and women, are included in trials. I am not sure what else would be excluded.

DR. MURRAY: If it was restricted to just e-antigen-positive disease. Let's say, if there was no e-antigen-negative disease, could a drug get on the market without investigating that, they just looked at positive or compensated liver disease, no data in decompensated liver disease?

DR. HOOFNAGLE: I would think any company really should try the e-negative group. They are really the group that responds best to these

nucleosides so they are the nicest group to treat, in a way. I think they should be included. Decompensated liver disease is not that common a problem and I think there are a lot of things being thrown at them, so I am not sure that it is important that it be included in an initial evaluation.

Racial and ethnic should be taken in mind. This is a disease that is very common in the Asian population. It is more common in blacks than whites, but the Asian population is the one with the largest--

DR. MURRAY: And your drug has activity to previous drugs such as lamivudine resistance and any drug coming along should know if it is active or not against that? It seems obvious, but--

DR. HOOFNAGLE: They would have to define whether it is effective at all against lamivudine-resistant virus, both in vitro and in humans, because, otherwise, you are looking at a lamivudine "me too" drug to compare. So the design there would be a little bit different than if you feel that it was a drug that was effective against lamivudine-resistant.

DR. GULICK: Okay. How did we do?

DR. BIRNKRANT: Very good.

DR. GULICK: Good. I would like to thank the agency and those stalwart members of the committee who stayed right until the end, and the observers. Thanks very much. We will close the session.

[Whereupon, at 4:45 p.m., the meeting was adjourned.]

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