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eViralHepatitis Review
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We're glad you've decided to participate in this CME program and hope you find it valuable. In this volume, we will provide you with current, clinically relevant reviews of topics that we believe will help improve outcomes in your patients with Hepatitis B. The topics will be delivered in 3 newsletters and include: 2010 conference coverage of the American Association for the Study of Liver Disease (AASLD), HBV Screening and how best to interpret positive screening, and HBV Counseling and how to treat, monitor and refer patients with HBV. In our next volume we hope to expand our coverage to Hepatitis C and co-infections.

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In this Issue...

Despite recent advances, liver disease resulting from viral hepatitis is a growing epidemic in the US, continuing to draw the attention of public health officials as well as clinical and basic researchers. In this year's President's Choice lecture at the Liver Meeting, Dr. Howard K. Koh, the 14th Assistant Secretary for Health at the US Department of Health and Human Services, and leader of a newly created public health team on viral hepatitis, described "a rising tide of viral hepatitis that is fueling increases in liver cancer and increasing the need for liver transplants." Characterizing it as a "silent epidemic," Dr. Koh noted that "two-thirds to three-quarters [of individuals] are not even aware that they are infected." This startling figure emphasizes the need for better screening and diagnosis. "We need to make sure people know what their risk factors are and make sure people know they are infected," he continued. In particular, he said, "Asian Americans and Pacific Islanders make up 50% of HBV cases in our country."

Dr. Koh's call for increased awareness of and screening for viral hepatitis of all types, and hepatitis B in particular, was echoed by much research presented at the 2010 AASLD Conference that described the considerable gap between screening guidelines and actual rates of screening in the US. At the same time, researchers drew attention to substantial opportunities to vaccinate against hepatitis B and to the availability of highly effective therapies. It appears that, in the case of hepatitis B at least, many of the tools to defeat this epidemic are already at hand. This newsletter describes research results on screening, epidemiology, and treatment of chronic HBV infection that were presented at this year's meeting. Much of the information generated by these studies has clear practical implications, both for primary care physicians and for gastroenterology specialists.

LEARNING OBJECTIVES

After completing this activity, participants will demonstrate the ability to:

- Identify and screen patients at risk for HBV
- Analyze and explain positive HBV screening
- Counsel patients regarding their HBV status for both treatment and/or vaccination
- Implement proven treatment regimens and refer patients as needed
- Expand treatment options, based on the evidence supporting the use of new and emerging therapies in particular patient types

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THIS ISSUE

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Megan Stephan, PhD, has no relevant financial relationships to disclose.

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COMMENTARY

While the excitement about novel therapies for hepatitis C was palpable at the 2010 Liver Meeting, the global importance of hepatitis B virus infection and the clinical benefit of antiviral therapy for HBV disease were also readily apparent. Indeed, researchers in the United States highlighted the high prevalence of disease in specific populations such as persons from Asia, but other studies suggest persons with HBV infections are not being identified in the community and in some medical practices.

Screening of persons at risk for HBV infection is the critical first step in providing immunization to those not infected and referring those found to be infected for appropriate medical evaluation and care. Research presented at the meeting also underscored the importance of counseling chronically infected persons to avoid alcohol as well as the long-term potency and durability of first-line antiviral agents for the treatment of chronic HBV: entecavir, tenofovir, and peginterferon alfa.

However, the most important HBV clinical trial presented at the meeting was a study by Pan and coworkers, who demonstrated that mother-to-infant transmission of HBV was reduced by oral antiviral therapy during the third trimester of pregnancy in mothers who had high blood levels of HBV DNA. Thus, chronic HBV continues to be a major medical and public health concern. This report summarizes the important highlights of HBV research presented at the 2010 Liver Meeting.

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HBV SCREENING IN PRIMARY CARE

Weinbaum CM, Williams I, Mast EE, et al. **Recommendations for identification and public health management of persons with chronic hepatitis B virus infection**. *MMWR Recomm Rep*. 2008;57(RR-8):1-20.

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Poster 787. Loo NM, et al. Effectiveness of hepatitis B screening in primary care setting.

Poster 788. Ha NB, et al. Prevalence, risk factors, and disease knowledge of chronic hepatitis B infection in Vietnamese Americans in California: A cross-sectional study.

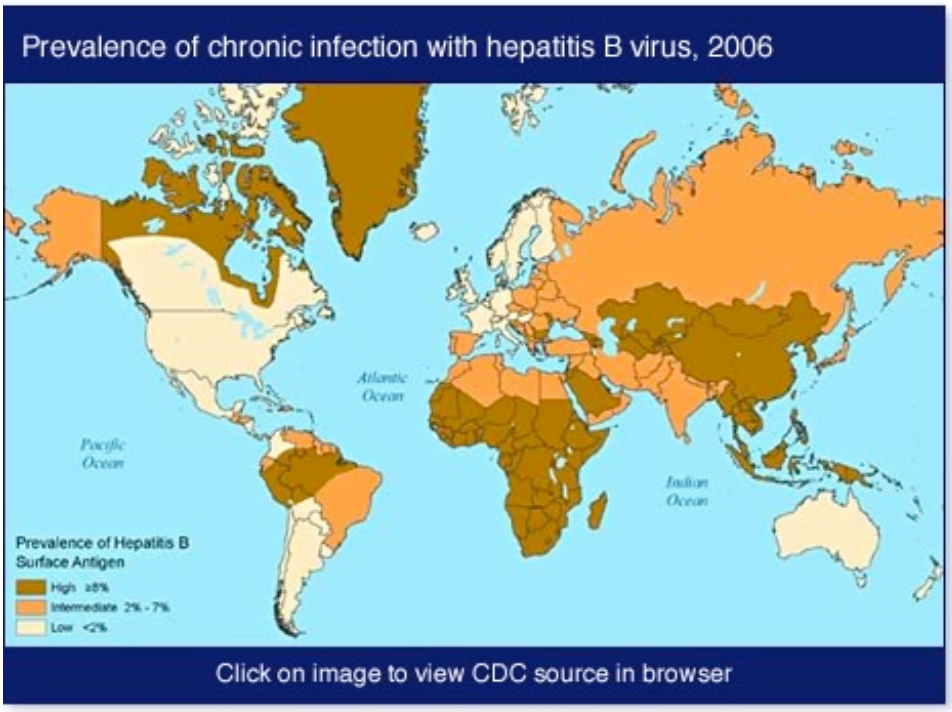
Poster 796. Perumalswami P, et al. Hepatitis Outreach Network (HONE): HBV and HCV screening of ethnic urban populations of New York City with linkage to care.

According to CDC guidelines, all persons with an anticipated HBV prevalence greater than 2% should be screened; this group includes virtually all persons from Asia. Until lately, there was very little data on the frequency with which such screening is carried out in primary care settings. Nicole Loo, MD and coworkers studied the rate of HBV screening among Asian patients receiving care in the primary care/internal medicine department of a large academic medical center. They examined medical records for the 15 years between 1994 and 2009. Of 5143 Asian patients seen during that period, only 1598, or 31%, were screened, a proportion the authors called "grossly inadequate."

Among those who were screened, HBV prevalence was high, with 8% testing positive for HBsAg. More than one-third of those who tested positive for HBsAg had normal liver enzyme levels (ALT/AST), a finding that supports CDC guidelines that HBV screening should not be guided by liver biochemistry tests. Of those who tested negative, 30% showed no evidence of immunity to HBV, representing a need for immunization in a significant proportion of these individuals.

Similar high rates of HBV prevalence were found by Nghiem Ha, MD and colleagues in California, which is home to about half of all Vietnamese persons in the US. These researchers investigated HBV prevalence among 698 Vietnamese individuals who participated in a series of screening events held in the San Francisco Bay area and Orange County, CA. They found a prevalence of 13.6% chronic HBV infection in this group. Prevalence was higher among males, among individuals between the ages of 30 and 39, and in those who resided in Orange County (southern California).

Dr. Ha commented, "The US is considered a low-endemic country for HBV, but all Asian persons should be screened, especially those who are Chinese or Vietnamese. Physicians should screen any foreign-born person from a highly endemic area, since the rates in immigrants reflect those of their native country." He noted that physicians can consult CDC guidelines as well as maps available at the CDC website identifying areas where HBV is highly endemic.



Ha's study also investigated treatment knowledge and cultural beliefs about HBV among Vietnamese individuals. Fully half of individuals surveyed believed that a positive attitude can prevent HBV infection, and about one-third believed that herbal medicine can prevent it. "More education is needed," Ha said. "Many immigrants have cultural misconceptions about viral infections." He emphasized the importance of addressing cultural barriers to screening, vaccination, and treatment of HBV.

In another screening study, Ponni Perumalswami, MD reported results from the Hepatitis Outreach Network (HONE) project, a community screening program for adult foreign-born individuals living in New York City. Reporting on the results of 602 patients screened, Perumalswami and her colleagues found that of those who tested HBsAg positive, 29.6% were from Korea, 48.1% were from China, and 9.3% were from Taiwan. Overall prevalence of chronic HBV infection among foreign-born Korean and Chinese immigrants was 9%. Although less well documented, HBV was detected in immigrant populations other than Asians, including Egyptians, Russians, and individuals from the Carribean, Perumalswami said. "The CDC guidelines do not specifically mention race and ethnicity as factors for determining risk," she noted, "but our results strongly suggest that this information should be taken into account." In addition, 18.4% of individuals screened lacked immunity to HBV, representing an important opportunity for increasing immunization rates.

Take-home lesson: Consider race, ethnicity, and country of origin when making decisions about screening for hepatitis B in routine practice, particularly for persons from Asia. Increased screening can identify important opportunities to immunize, in addition to identifying persons in need of monitoring and/or treatment.

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COMORBIDITIES: ASSOCIATION OF DIABETES AND ALCOHOL ABUSE WITH WORSE OUTCOMES AMONG CHRONIC HBV PATIENTS

Peters MG. **Special populations with hepatitis B virus infection**. *Hepatology*.2009;49(5 Suppl):S146-155.

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Parallel Session 175. Manos M, et al. Correlates of severe liver disease outcomes among chronic hepatitis B patients: a 9-year longitudinal study in a managed care setting.

In his President's Choice lecture, Dr. Koh noted that "people with hepatitis often have major comorbidities," which can make treatment more challenging. These comorbidities also represent risk factors for poorer outcomes among chronic HBV patients, and may suggest a need for closer surveillance and follow-up. Michelle Manos, MD presented the results of a large study intended to identify such comorbidities and quantify their effects on HBV outcomes. They used a retrospective, longitudinal cohort study of about 14,000 chronic HBV patients in managed care, extracted from the Kaiser Permanente database between 1999 and 2007. Incidence and correlates were determined for outcomes of hepatocellular carcinoma, decompensated cirrhosis, and liver-related death. Patients with HCV or HIV coinfection, or a history of severe liver disease were excluded from this cohort, which was about half men, with a mean age of 42 years at entry, and 75% Asian. Six percent of the cohort were ever diabetic, and 3% had ever had a diagnosis of alcohol abuse. Follow-up ranged from 1 to 9 years.

The researchers observed substantially higher rates of all 3 liver outcomes in patients who were older, male, and diabetic and/or had a record of alcohol abuse. The risk of hepatocellular carcinoma was higher among chronic HBV patients who had abused alcohol (adjusted RR = 2.84), and both alcohol abuse and diabetes contributed to higher risks of decompensation (adjusted RR 3.80 and 3.16, respectively). Risk of liver-related death was 3.67 times higher for men, 4.37 times higher for those with a diagnosis of alcohol abuse, and 1.85 times higher among diabetics.

These results suggest that diabetic and alcoholic patients with chronic HBV may benefit from more intensive monitoring of disease progression, as well as medical management of these comorbid conditions. Dr. Manos suggested that "we can do a low-tech version of personalized medicine by identifying patients whose comorbidities place them at highest risk for these serious outcomes."

Take-home lesson: Chronic HBV patients should be assessed for the presence of diabetes and alcohol use and/or abuse. Persons with these comorbid conditions may warrant closer monitoring for hepatic decompensation and HCC, and they may benefit from directed interventions to improve diabetes control and alcohol abstinence.

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USE OF QUANTITATIVE HBSAG TO DISTINGUISH INACTIVE CARRIERS FROM CHRONICALLY INFECTED HBV PATIENTS.

Marcellin P, Liang J. **A personalized approach to optimize hepatitis B treatment in treatment-naive patients**. *Antivir Ther*. 2010;15 Suppl 3:53-59.

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Poster 1397. Martinot-Peignoux M, et al. Quantitative HBsAg: A new specific marker for the diagnosis of HBsAg inactive carriage.

Current guidelines recommend that patients who are inactive HBV carriers should be monitored but generally should not receive HBV treatment. Inactive carrier status is identified by making serial determinations of serum ALT and HBV DNA levels; persons with persistently normal ALT levels and low HBV DNA levels are termed inactive. However, in 45 to 65% of cases, ALT activity fluctuates widely, with long periods of time spent at normal ALT levels. That can make it difficult to distinguish patients who are true, inactive carriers of HBV from those who have chronic HBV infections, potentially leading to inappropriate care.

Michele Martinot-Peignoux, MD and colleagues evaluated the use of quantitative HBsAg as a new marker to be used in combination with HBV DNA to distinguish true inactive

carriers from chronically infected HBV patients. The study included 165 untreated patients who were HBsAg and anti-HBe positive and HBeAg negative, and had had 3 serum ALT measurements within a one-year period. At the end of one year of follow-up, they classified as inactive carriers 76 patients whose liver enzymes were persistently normal and whose serum HBV levels were less than 2000 IU/mL and classified as chronic hepatitis B patients the other 89 patients, whose liver enzymes fluctuated and/or whose viral load was >2000 IU/mL. They followed these patients for 5 to 6 more years to confirm their status as inactive carriers or chronic HBV patients. Looking back at the test results for these patients at baseline, they determined that a single measurement of HBsAg <1000 IU/mL, combined with a viral load of <2000 IU/mL, allowed the identification of inactive carriers with a positive predictive value of 90%. These results suggest that quantitative HBsAg can be used to diagnose inactive carrier status in HBeAg negative individuals.

Take-home lesson: These results warrant further study and suggest that quantitative HBsAg measurement may be a useful tool to determine HBV disease activity and the need for more aggressive medical care.

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HBV IN PREGNANCY: PREVENTING TRANSMISSION TO NEWBORNS.

Beasley RP, Hwang LY, Lee GC, et al. **Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine**. *Lancet*. 1983;2(8359):1099-1102.

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Lee C, Gong Y, Brok J, Boxall EH, Gluud C. **Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis**. *BMJ*. 2006;332(7537):328-336.

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Bzowej NH. **Hepatitis B Therapy in Pregnancy**. *Curr Hepat Rep*. Nov 2010;9(4):197-204.

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Parallel Session 212. Han G, et al. A prospective and open-label study for the efficacy and safety of telbivudine (Ltd) in pregnancy for the prevention of perinatal transmission of hepatitis B virus (HBV) to the infants

Poster 372. Mi L, et al. Outcomes of eight Chinese-American pregnant patients with chronic hepatitis B (CHB) treated with tenofovir DF (TDF) during pregnancy.

Mother-to-infant transmission is an important factor in the spread of HBV infection. Although currently recommended immunoprophylaxis prevents perinatal transmission of HBV to infants in over 90% of cases, there is evidence of transmission despite these interventions, particularly among HBV-infected women with high levels of HBV DNA. Several studies have suggested that lamivudine is safe and effective in this context, but evidence about other antiviral agents remains scarce, and there has been no expert

consensus on whether or not highly viremic mothers should be treated with antivirals to reduce the risk of vertical transmission. Two presentations at the meeting addressed these questions.

Calvin Pan, MD and coworkers reported on the results of a prospective, nonrandomized case control study of 190 pregnant Asian women who had HBeAg positive chronic HBV and high levels of viremia, HBV DNA >6 log10 copies/mL. Of this group, 95 women were treated with 600 mg/day telbivudine from weeks 12 to 32 of gestation until 4 weeks postpartum, and 95 women were enrolled in a control group. It is important to note that, based on considerations raised by the local ethics committee, the decision to take telbivudine was the mother's decision and was not randomized. All infants born to both groups received immunoprophylaxis in the form of 200 IU HBIg given within 24 hours of birth and HBV vaccination at 0, 1, and 6 months.

Telbivudine treatment was associated with markedly reduced HBV DNA levels compared to no treatment. At baseline, the mean HBV DNA level was 8.07 log10 copies/mL in the telbivudine group and 7.94 log10 copies/mL in the control group, while at the time of delivery it was 2.35 and 7.83 log10 copies/mL respectively. Of the treated mothers, 30% had undetectable HBV DNA at delivery, compared to none of the control patients. There were no cases of telbivudine discontinuation because of adverse events. More important, at birth, 6% of infants in the telbivudine group were HBsAg positive, compared with 30% in the control group ($p>0.001$). At 28 weeks post-birth follow-up, the rate of HBV infection among infants who returned for testing was 0% in babies born to treated mothers and 9% in babies born to untreated mothers. In an intention-to-treat analysis in which missing follow-up was counted as "failure," the findings were similar. No birth defects were observed at postpartum week 4, and the infants of both groups were similar in gestational age, height/weight, and Apgar scores.

In another study, Li-Jun Mi, MD and colleagues presented outcomes of 8 pregnant Chinese American women with chronic HBV who were treated with tenofovir DF during pregnancy. All of the women received 300 mg/day tenofovir beginning in the third trimester, except for one woman who became pregnant while taking tenofovir. All of the infants received immunoprophylaxis. Seven of the 8 women began with high viral loads, and all of these women experienced a 2 to 4 log10 copies/mL reduction in the first 4 weeks of treatment. At 9 months postpartum, 4 infants were HBsAg negative, and results from the other 4 were pending. All of the infants had normal birthweights and no birth defects were observed. Dr. Mi said that although the Antiretroviral Pregnancy Registry already included women who were treated with tenofovir in pregnancy, hers is among the first reports of its use in women who were not also co-infected with HIV. "The results are promising," she noted, "but further study will be needed. We will continue to monitor these women and their babies."

Take-home lesson: The study by Dr. Pan and colleagues provides the best evidence to date that antiviral therapy given in the third trimester to mothers with high HBV DNA levels ($>10^6$ copies/mL) is safe and may prevent mother-to-infant transmission compared to no treatment.

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HBV TREATMENT: CONTINUING RESULTS FROM LONG TERM STUDIES OF TENOFOVIR AND ENTECAVIR.

Woo G, Tomlinson G, Nishikawa Y, et al. **Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses.** *Gastroenterology*. Oct 2010;139(4):1218-1229.

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Poster 476. Marcellin P, et al. Continued efficacy and safety through 4 years of tenofovir disoproxil fumarate (TDF) treatment in HBeAg-negative patients with chronic hepatitis B (study 102): preliminary analysis.

Poster 477. Heathcote E, et al. Long term (4 year) efficacy and safety of tenofovir disoproxil fumarate (TDF) treatment in HBeAg-positive patients (HBeAg+) with chronic hepatitis B (study 103): preliminary analysis.

Poster 478. Pan C, et al. Long-term entecavir treatment for up to 5 years in Asians with HBeAg-positive nucleos(t)ide naïve chronic hepatitis B: results from ETV-022 and -901.

A recent systematic review and Bayesian meta-analysis concluded that tenofovir and entecavir are the most effective antiviral agents currently available for treating chronic hepatitis B in the first year. High efficacy, good tolerability, and low rates of viral resistance for these agents were supported by ongoing results of long-term studies presented at the meeting. Posters by Patrick Marcellin, MD and colleagues and by Jenny Heathcote, MD and colleagues presented the 4-year results of tenofovir treatment in 250 patients with HBeAg negative chronic HBV and 176 patients with HBeAg positive chronic HBV, respectively. The Marcellin study, in which 84% of patients were retained, showed that tenofovir alone continued to suppress viral activity in 99% of patients who stayed on treatment, with levels of <400 copies of HBV DNA/mL at week 192. In the Heathcote study, fewer patients were retained (74%), and tenofovir alone resulted in continued viral suppression in 84% of patients on treatment. Neither study found evidence of antiviral resistance among patients who became viremic. Study drug-related severe adverse events were 1% in both studies, and discontinuation because of an adverse event was 2% or less. Serum creatinine levels remained stable over time in both populations.

In another study, Calvin Pan, MD and colleagues presented the results of long-term treatment with entecavir (up to 5 years) in Asians with HBeAg positive chronic hepatitis B. Some of these patients also received lamivudine in an earlier phase of the study. In the part of the study presented here, 95% of 94 patients who received 5 years of continuous treatment with entecavir maintained HBV DNA levels <300 copies/mL. None of the patients showed evidence of developing entecavir resistance through year 5. Rates of serious adverse events were higher than in the tenofovir study, at 13%, although none of the patients discontinued because of adverse events.

Take-home lesson: Ongoing, long term studies of tenofovir and entecavir continue to show high rates of viral suppression, good tolerability, and low rates of adverse events. Antiviral resistance remains low in persons treated with these first-line agents. To date, tenofovir resistance has not been observed in these cohorts, and entecavir resistance has been rare in persons naïve to HBV treatment.

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HBV TREATMENT IN THE FUTURE: WHAT ARE THE CURRENT PROSPECTS FOR PERSONALIZED MEDICINE?

Imazeki F, Yokosuka O, Omata M. **Impact of IL-28B SNPs on control of hepatitis C virus infection: a genome-wide association study.** *Expert Rev Anti Infect Ther*. 2010;8(5):497-499.

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Kotenko SV, Gallagher G, Baurin VV, et al. **IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex**. *Nat Immunol*. 2003;4(1):69-77.

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Ge D, Fellay J, Thompson AJ, et al. **Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance**. *Nature*. 17 2009;461(7262):399-401.

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Poster 1408. Kurbanov F, et al. An IL28B SNP that is associated with HCV outcome is not associated with HBV or HIV outcome.

Parallel Session 237. Lampertico P, et al. Genetic variation in IL28B polymorphism may predict HBsAg clearance in genotype D, HBeAg negative patients treated with interferon alfa.

Recent discovery of the relationship between HCV spontaneous clearance and response to interferon-based treatment and genetic variation in the IL28B gene of chromosome 19 have raised the exciting possibility of personalized medicine in hepatitis therapy. Between August 2009 and January 2010, four research groups independently identified single nucleotide polymorphisms (SNPs) in the IL28B region as associated with patients' responses to the standard therapy for hepatitis C infection (peginterferon plus ribavirin). IL28B encodes interferon-lambda, a type III interferon that is associated with antiviral activity, leading to speculation that these SNPs might be associated with interferon-based treatment responses in other types of viral infections such as HBV or HIV.

Fuat Kurbanov, MD and colleagues investigated whether there was an association between IL28B SNP rs12979860 and treatment outcome in over 2000 individuals from several prospective cohorts that follow individuals with or at risk for HIV or HBV infection. They found that this SNP, which is strongly associated with HCV outcome, had no association with spontaneous HBV recovery or HIV disease progression. Unfortunately, these results suggest that the unknown mechanistic role of this SNP is specific to HCV infection, rather than being generalizable to other types of viral infections. Other studies presented at the meeting examined the relationship between the IL28B polymorphism and response to interferon therapy for chronic HBV infection. In a retrospective study by Dr. Lampertico and colleagues in Italy, IL28B CC genotype patients with chronic HBeAg negative HBV (genotype D) infection were more likely than those who had the CT or TT genotypes to respond to peginterferon treatment given over 23 months.

Take-home lesson: Recently discovered IL28B polymorphisms have been linked to HCV clearance with and without treatment, but their role in HBV infection is unclear. While the IL28B genotype does not appear to play a role in spontaneous HBV clearance, the jury is still out on whether these polymorphisms influence the response of chronic HBV to interferon treatment.

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