MANAGING HEPATITIS B VIRUS INFECTION: AN INTERVIEW WITH CHLOE THIO, MD - ASSOCIATE PROFESSOR OF MEDICINE, JOHNS HOPKINS MEDICAL SCHOOL

David Alain Wohl, MD
Associate Professor of Medicine
AIDS Clinical Trials Unit
The University of North Carolina - Chapel Hill

Disclosures: DW - Speakers Bureau: Boehringer Ingelheim, Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Inc.
Research Grant: Roche Pharmaceuticals, Abbott Laboratories Consultant: Abbott Laboratories and Gilead Sciences, Inc.

There have been a number of significant developments in the management of HBV in recent years, particularly new therapeutic agents that can be used by both the HIV co-infected and the HBV mono-infected patient. IDCR Co-Editor, David Wohl, MD, interviewed Chloe Thio, MD to get her perspective on the state of the art of the management of HBV. Dr. Thio is an infectious diseases physician at Johns Hopkins in Baltimore specializing in the management of patients with HIV and viral hepatitis co-infection. She conducts clinical investigations of HBV therapy and recently published an article in Clinical Infectious Diseases titled, "Treatment of Chronic Hepatitis B Infection in HIV-Infected Persons: Thinking Outside the Black Box."

Dr. David Wohl (DW): The prevalence of hepatitis B virus (HBV) in prisons and jails in the US is several fold higher than the general population, and in many correctional facilities HBV screening is routinely conducted in inmates who are HIV-infected, therefore, I want to start by asking you about the management of HBV in the HIV-infected patient. What is your approach to managing HBV in HIV+ inmates who have active HBV but also have a high CD4 cell count and no indication for HIV therapy?

Dr. Chloe Thio (CT): Before I would even consider HBV therapy in a newly diagnosed patient with active HBV infection, I would monitor them for six months to a year just to be sure this is a chronic infection and not acute HBV. Specifically, I would look to see if hepatitis B surface antigen (HBsAg) was lost or if the serologic pattern shifted from hepatitis B e antigen (HBeAg) positive to negative. This would help me determine if this was a person in the midst of a recent infection and possibly clearing their virus. Importantly, even if this is chronic HBV infection, a small proportion of people will clear the virus on their own - approximately 0.5% per year (1). So, I would monitor closely for a time, as I’d want to be sure I know the patient before starting therapy, especially since HBV therapy is not as effective as we would like. However, if the patient has evidence of end-stage liver disease I would consider therapy sooner.

CT: First, I would check several serological tests including HBeAg, anti-HBe, and a HBV DNA level. I check the HBeAg status to know if the patient has HBeAg positive or negative chronic hepatitis B and to follow the HBeAg status with therapy. There are some people with positive HBSAg and normal liver transaminase levels who have undetectable or low HBV DNA...
Dear Corrections Colleagues,

Viral hepatitis is endemic in correctional populations. In some systems, over 40% of inmates are infected with hepatitis C virus (HCV) and outbreaks of hepatitis B virus (HBV) have been reported in correctional settings. Both viruses can co-infect HIV-positive individuals, complicating HIV management. Recent data describe increasing rates of mortality due to viral hepatitis among HIV-infected persons and liver disease is becoming a leading cause of death among patients with HIV. Given the heavy burden of hepatitis in prisons and jails, correctional clinicians must become familiar with the detection, prevention and management of both HCV and HBV.

In this issue of IDCR, Dr. Chloe Thio, a nationally recognized expert on HBV therapeutics, provides her perspective on the latest developments in HBV treatment and offers practical advice regarding commonly encountered dilemmas in HBV treatment. IDCR Board Member Dr. Bethany Weaver contributes a case study on HCV, highlighting the major issues related to counseling, staging and treatment of this all too prevalent infection. These instructive articles are supplemented by a list of resources readers can access to obtain further information.

While this issue was going to press, two major events occurred. The first was the International AIDS Society Conference (also called the World AIDS Conference). There were several major HIV therapeutic developments presented at the conference and special sessions focusing on prisoners, including a session chaired by IDCR Executive Editor Dr. Annie De Groot. Special coverage of the conference will be included in the September issue. In addition, the Institute of Medicine of the National Academies of Science issued their anticipated report on ethical considerations regarding research involving prisoners. This important report will also be covered in-depth in the next issue of IDCR.

Lastly, IDCR and the American Academy of HIV Medicine (AAHIVM) are teaming up to help make the resources of the AAHIVM accessible to correctional clinicians and are hoping to work together on future continuing education projects. Visit the AAHIVM website at www.aahivm.org to learn more about the academy.

We look forward to reading your responses to what you read in IDCR. Email me at wohl@med.unc.edu or Annie De Groot at Annied@brown.edu. Letters to the editor can be found on the IDCR website.

Sincerely,

David Alain Wohl, MD
Associate Professor of Medicine
Division of Infectious Diseases
AIDS Clinical Trials Unit
The University of North Carolina - Chapel Hill

Subscribe to IDCR

Fax to 401-272-7562 for any of the following: (please print clearly or type)

___ Yes, I would like to add/update/correct (circle one) my contact information for my complimentary subscription of IDCR fax/email newsletter.

___ Yes, I would like to sign up the following colleague to receive a complimentary subscription of IDCR fax/email newsletter.

___ Yes, I would like my IDCR to be delivered in the future as an attached PDF file in an email (rather than have a fax).

NAME: ___________________ FACILITY: ___________________

CHECK ONE:

O Physician       O Physician Assistant       O Nurse/Nurse Practitioner       O Nurse Administrator
O Pharmacist      O Medical Director/Administrator O HIV Case Worker/Counselor    O Other

ADDRESS: _____________ CITY: _____________ STATE: __ ZIP: _____________

FAX: _______________ PHONE: _______________

EMAIL: ________________________________
MANAGING HEPATITIS B VIRUS INFECTION...

(continued from page 1)

levels (i.e. less than $10^4$) and those people I would not treat (2). For those with higher HBV DNA levels I need to decide whether their HBV needs to be treated. In such cases I would consider getting a liver biopsy. The liver biopsy can be helpful in determining the need for HBV treatment - especially in a patient with low HBV DNA levels (3). So, for instance, in the case of a patient with a CD4 cell count of 450/mm$^3$ who has a HBV DNA of $10^9$ I would consider a liver biopsy to determine if treatment is needed now or can be deferred until HIV therapy is initiated later on. If the biopsy does not show significant liver disease, I might wait and do nothing except follow them every six months checking their ALT and their HBV DNA levels and look for development of liver problems such as cancer. Such patients will in the next few years probably need HIV therapy and at that time I can use drugs that have activity against both HIV and HBV.

DW: You are saying that liver biopsies can help the provider decide if HBV therapy is indicated but in many correctional facilities liver biopsy is difficult to obtain. How essential is the liver biopsy?

CT: The problem is that you cannot really rely on HBV DNA levels by themselves to tell you who needs HBV treatment. Therefore, the biopsy can be particularly helpful in determining whom to not treat. Certainly, if someone has an HBV DNA level of $10^9$ and an ALT of 100, that person needs treatment and you really do not need the liver biopsy. But, if someone has an HBV viral load that is $10^5$ and an ALT of 40 it is really hard to know how much liver disease is present, and a biopsy that shows minimal damage may dissuade you from treatment while the presence of more significant disease would support therapy. That said, outside corrections we often do get liver biopsies even in patients with clear cut indications for HBV therapy to have some idea as to what stage of the disease they have. But, without the luxury of the biopsy if there is a patient who by HBV DNA and transaminase levels plus clinical presentation you think needs HBV treatment, a biopsy is not essential. In cases where you are inclined not to treat, the biopsy becomes more imperative since you do not want to defer therapy of a patient with end-stage liver disease just because they have low levels of HBV DNA - which can happen.

DW: It sounds like persistent HBSAg positivity and a HBVDNA level at least $10^5$ copies/ml qualify a patient for therapy. What about ALT?

CT: ALT is something that we do look at. The main reason is that studies have shown that for people with active HBV and normal ALT the response to treatment is very low. So, we tend not to treat them unless they have evidence of liver disease. This relatively low treatment response is likely because you need an immune response to the virus in addition to antivirals and those with elevated ALT have more of an immune response to HBV.

DW: Any other criteria for treatment for HBV?

CT: For those from Asian countries but also for people from here, a family history of liver cancer is important and would tip me toward treating earlier as HBV is oncogenic and with that history I am more aggressive in trying to treat. Otherwise, that is it.

DW: For the patient we have been discussing who has HIV-HBV co-infection and high CD4+ cell counts and who does qualify for HBV therapy by persistent surface antigen positivity, HBV DNA levels and elevated ALT, what treatment would you recommend? Let's assume he does not want to or cannot have a liver biopsy.

CT: Foremost, no patient in this country should be treated with lamivudine (Epivir, Epi-HBV, 3TC) alone as the active HBV agent - HIV+ or HIV-. Resistance develops relatively quickly and can hamstring future therapy. In this case, it is unlikely anyone would want to treat this patient with lamivudine mono-therapy so, were he to need HIV treatment he could mistakenly be placed on an antiretroviral regimen in which lamivudine is the only active HBV drug. In the situation of a patient who does not require HIV treatment I might consider pegylated interferon-alpha (Pegasys, Peg-Interon) because it does not have any effects on developing HIV drug resistance (4). Here an HBV genotype B might be helpful as recent studies suggest that genotype A - the most common in the US - and genotype D, respond best to this agent. So, if he were genotype A that would push me to pegylated interferon. If pegylated interferon cannot be administered you would need to use drugs that will not be active against HIV so as to not risk HIV drug resistance. So, in a patient without prior HIV therapy and therefore unlikely to have lamivudine resistance my first choice would be entecavir (Baracut). It is more potent than the alternative, adefovir (Hepsera) (3, 4). In addition, to date, there is less resistance with entecavir than with adefovir - but this can be because entecavir has not been studied as much as adefovir. But, entecavir is more potent so I think we will see less resistance over the long term.

DW: We learned the hard way in HIV, and more recently hepatitis C virus (HCV), infection that mono-therapy is not as effective as combination therapy. Should we be treating HBV with more than one agent?

CT: In the long term we may find that there might be a combination that is more potent than mono-therapy. As I said before, I would not use lamivudine alone as resistance develops rapidly. Now, with entecavir I feel fairly comfortable using this agent alone since there is practically 0% risk of resistance in the first year of treatment. You can monitor the patient's HBV DNA levels during that year and if it falls to undetectable then the risk of resistance is even closer to zero and you may be able to get away with mono-therapy. However, if the HBV level during the first year does not become undetectable, you might become concerned that this patient is at increased risk for resistance and consider adding a second drug.

DW: So, you might add adefovir?

CT: Right, I might but there are no data to support this. As more data emerge my algorithm might change. I think dual therapy will have its role but unlike HCV and HIV it may not be a 'one size fits all' solution.

DW: And, how long are we talking about as far as HBV therapy?

CT: With pegylated interferon treatment is for a year if you are HBeAg positive. If the patient is HBeAg negative then we really do not know how long to give pegylated interferon. There is a study that showed 24 months of standard interferon alfa 2b is better than less than 24 months (5). We do not know if this is also the case for pegylated interferon alpha. In general, I am less excited about using pegylated interferon in someone who is HBeAg negative as it tends to be longer term therapy and the response rates are not that great compared to those who are Hepatitis B e antigen positive - especially if they are genotype A.

For the nucleoside and nucleotide analogues the duration of therapy differs based on the HBeAg status. In persons with HBeAg-negative chronic Hepatitis B, indefinite therapy is needed since rebound invariably occurs. In HBeAg-positive disease, therapy can be stopped a minimum of six months after anti-HBe seroconversion but patients need to be monitored for relapse since it does occur.

DW: How do you monitor for treatment success once starting HBV therapy?

CT: For the first year at least I like to monitor every three months by getting a HBV DNA level and liver enzymes. In a correctional setting if that is impractical, I think every six months is also fine but you get a better sense of how the patient is doing with more frequent monitoring. If the HBV DNA is not undetectable after a year of therapy, consultation with a hepatitis specialist is in order.
MANAGING HEPATITIS B VIRUS INFECTION...
(continued from page 3)

CT: Undetectable is my goal. We actually do not know what level of virus you need to obtain to reduce the risk of resistance mutations or stop the progression of liver disease but for now we should shoot for undetectable.

CT: With prior exposure to lamivudine, you have to suspect there is lamivudine resistance. There are resistance tests for HBV that can be performed by central laboratories but if there is a history of prolonged lamivudine treatment that may be all you need. If you are not ready to treat their HIV, then the options you have are adefovir or entecavir. I wouldn’t use pegylated interferon since there is a recent study showing that HIV-uninfected people with lamivudine resistance respond less well to this agent (6). Or, you can consider the combination of adefovir and entecavir. Adefovir has been shown to be effective in lamivudine-resistant HBV. Entecavir is also effective but the lamivudine resistance mutations are part of those that are required to lead to entecavir resistance. In the first year of treatment, about 7% of persons with lamivudine resistance develop entecavir resistance (4).

CT: This is an issue where we really do not know the answer. In terms of screening to vaccinate for HBV I would only order the HbsAg and anti-Hbs and not the core antibody being a false positive you could check it again in six months along with their serologies. If the result were the same I would vaccinate them for HBV.

CT: The paper by Raj Gandhi found that people who had anti-Hbe present were less likely to have their anti-Hbc be a false positive result (7). If you are worried about the core antibody being a false positive you could check the anti-Hbe but it would not change my management, as I would still vaccinate them to try to elicit surface antibody.

CT: I use tenofovir (Viread) along with lamivudine or emtricitabine (Emtriva, FTC) - Truvada (Tenofovir+FTC fixed dose combination) is easy to use. Obviously, in a patient with lamivudine-resistant HBV, emtricitabine would not be an active drug but we have learned from the HBV mono-infected that in lamivudine-resistant patients treated with adefovir, co-administration of lamivudine delayed adefovir resistance. So, I would use lamivudine or emtricitabine here even though there are no data looking at this phenomenon with tenofovir - but I am extrapolating from the adefovir experience.

CT: What therapy I use depends on whether someone is HBeAg positive or not. If someone is HBeAg positive there is much more resistance data for entecavir than for tenofovir so if I am only going to use one, I would choose entecavir over tenofovir. Their potency is probably equivalent and my guess is that there will be little tenofovir resistance in the first year but it has not yet been studied in mono-infected patients so I tend not to use tenofovir alone and instead use Truvada - even in the mono-infected patients. Being HBeAg negative changes things and these are almost two different diseases. People with negative HBeAg require long-term therapy. Those who are HBeAg positive you are able to monitor for conversion to anti-HBe positive and then, when that happens, stop therapy six months after seroconversion occurs. In HBeAg negative patients if you stop therapy they almost always rebound. So, in the HBeAg negative situation I virtually never use mono-therapy since I know they are going to be on the drug a long time.

CT: Correct. As you said, vaccine rates are low and you want to know if they respond appropriately. If they don’t, despite a higher dose vaccine, then you want to know just for the purpose of counseling the patient.

CT: Thank you.

References:

Visit IDCR online at www.IDCRonline.org

Hepatitis B Surface Antigen Prevalence

**Geographic distribution of Hepatitis B prevalence, 2005**

Source: CDC
SPOTLIGHT - HEPATITIS C VIRUS MANAGEMENT IN CORRECTIONAL SETTINGS: CASE FOR DISCUSSION

Bethany Weaver, DO MPH
Infectious Disease Consultant
Armor Correctional Health Services


Case 1: A 36 year-old man presents to your clinic five days after his arrest for driving with a suspended license. He reports that he has a 10-year history of hepatitis C virus (HCV) infection and was diagnosed with AIDS after developing Pneumocystis jiroveci pneumonia (formerly known as Pneumocystis carinii pneumonia). He has a prior history of injection drug and alcohol use but has not used alcohol or injected drugs for five years. He has a history of depression without psychosis but one previous suicide attempt seven years ago. Four years ago he was prescribed a selective serotonin reuptake inhibitor (SSRI) for depression and he continues on this antidepressant without symptoms of major depression.

At the time of his arrest he was in HIV care at a local community clinic. He is receiving didanosine (Videx-EC), lamivudine, and efavirenz (Sustiva) and his most recent laboratory obtained 2 months ago revealed a CD4 cell count of 250/mm3 and undetectable HIV-1 viral load. He has never received treatment for HCV. You ask him what the status of his liver disease is (i.e. liver biopsy results, HCV genotype, HCV quantitative viral load) and he tells you he has “no idea” and that he has never had a biopsy.

Question: Assuming he will only be at the jail for a short time (i.e. 3 months or less) thereby making HCV treatment at your jail facility an unrealistic option, what information could you offer this inmate so that his chances of survival are improved after release?

Discussion: Given the time constraint, counseling needs to focus on providing the patient with the information that will enable him to make informed choices regarding his HCV care once he returns to the community. That HCV and subsequent cirrhosis is now a leading cause of death among those with HIV infection is important for this inmate to appreciate. The inmate should be informed that there are many potential benefits of HCV treatment with pegylated interferon (peg-IFN) plus ribavirin. These include the possibility of achieving HCV eradication (i.e. sustained virologic response, SVR). The odds of such eradication depend on several factors including the genotype of the infecting virus and the degree of liver damage. If he has genotype 1 HCV - the most common in the US - he would have an approximately 15-40% chance of HCV eradication as someone co-infected with HIV. Large trials demonstrate that additional factors associated with SVR include lower baseline HCV RNA level (less than 800,000 IU/ml), absence of cirrhosis, lower body weight (< 75 kg), younger age, tolerance of a higher ribavirin dose (at least 10.6 mg/kg per day in those with genotype 1), and adherence to treatment. Beyond cure, there are other potential benefits of HCV therapy including reduced risk of liver failure and complications related to HCV, such as cryoglobulinemia and hepatocellular carcinoma, and possible reversal of early cirrhosis. HCV treatment may also retard or reverse disease progression for individuals with hepatic fibrosis who are at greatest immediate risk for end stage liver disease and death.

However, this inmate should also be cautioned regarding the demands and risks of HCV therapy. The patient should understand that treatment does require injected and orally administered medications and can lead to an array of predictable side effects such as worsening depression and fatigue. Most of these adverse effects are reversible with discontinuation of HCV pharmacotherapy, although a minority may be permanent.

Many patients and providers remain unaware that approximately 15% of individuals with HCV antibodies do not have detectable levels of HCV in the blood and have probably cleared the virus on their own. Thus all patients who are seropositive for HCV should have a plasma HCV RNA level checked.

Importantly, all persons with HCV infection and a history of substance and alcohol dependency must be informed that many providers will not offer HCV treatment unless the patient has been “clean” from alcohol and/or illicit drugs for six months or more, despite a paucity of supporting data. This incarceration is a good opportunity to discuss prevention of HCV transmission including shared needles, sexual behaviors involving blood such as fisting, and others (perinatal, occupational, hemodialysis, household exposure to contaminated blood).

Referral to a clinic or center where HCV therapy is available should be made prior to release.

Case 2: Now assume the same inmate is seen by you in prison after being sentenced to three years.

Questions: If HCV treatment is an option at your facility, what would be the most appropriate work-up for this patient before beginning a discussion of treatment with him and why? If you establish that he is a good candidate for HCV treatment, what other tests might you order before treatment? What toxicities associated with peg-IFN and ribavirin should you be aware of and counsel your patient about? Would you continue didanosine, lamivudine, and efavirenz during the HCV treatment?

Discussion: Conduct a thorough physical examination looking for signs of decompensated liver disease (e.g. ascites) and evidence of an untreated opportunistic infection. Decompensated liver disease and/or untreated opportunistic infection represent contraindications to HCV treatment. HCV treatment could be revisited as a potential option only if the opportunistic infection is treated and the patient stabilizes on treatment; once decompensation occurs, it is

---

Table 1: Rules for Discontinuation of Treatment with Peginterferon + Ribavirin in HIV/HCV Co-infected Patients

<table>
<thead>
<tr>
<th>Rule Type</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-week rule</td>
<td>Consider discontinuation of therapy in genotype 1-4 patients who do not achieve undetectable HCV RNA levels or a 2-log (100-fold) drop from baseline in the 12th week. Consider risks/benefits and base decision on case-by-case basis.</td>
</tr>
<tr>
<td>12-week rule</td>
<td>Treatment should be discontinued in genotype 1-4 patients with detectable viremia at week 24 despite a 2-log reduction in viral load in the 12th week.</td>
</tr>
</tbody>
</table>

Table 2: Peginterferon and Ribavirin Dosing in HIV/HCV Co-infected Patients

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Peginterferon alfa-2a</th>
<th>Peginterferon alfa-2b</th>
<th>Ribavirin-2 (divided oral doses daily)</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 or 4:</td>
<td>For all genotypes 180 mcg SQ once weekly</td>
<td>For all genotypes 1.5 mcg/kg SQ once weekly</td>
<td>All genotypes: weight &lt; 75 kg 1,000 mg All genotypes: weight ≥ 75 kg 1,200 mg</td>
<td>48 wks</td>
</tr>
<tr>
<td>Genotype 2 or 3:</td>
<td>For all genotypes: weight &lt; 75 kg 1,200 mg All genotypes: weight ≥ 75 kg 1,400 mg</td>
<td>48 wks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

too late for peg-IFN - refer for liver transplant. In individuals with decompensated liver disease/cirrhosis, an ultrasound and alpha-fetoprotein level every six months to screen for hepatocellular carcinoma should be performed. You might consider performing a liver biopsy to rule out other correctable causes contributing to the liver failure (e.g. hepatic steatosis secondary to antiretroviral therapy, iron overload) if non-invasive evaluations (e.g. serum alpha 1 antitrypsin, iron studies) are inconclusive, or to determine the degree of fibrosis. Experts currently recommend treating those with advanced HIV/AIDS (absolute CD4 cell count less than 200/mm²) with antiretroviral medications first, in an effort to achieve a CD4 cell count that is above 200/mm³ prior to HCV treatment, though some patients may not achieve this goal despite having a fully suppressed HIV viral load and would still be candidates for HCV treatment.

As far as laboratory studies, as described above, HCV genotype and RNA quantitative viral load should be ordered as soon as a complete metabolic panel (chemistries, transaminases, total bilirubin, albumin), a complete blood count with platelets, and a CD4 cell count. If the HCV RNA viral load is undetectable and remains undetectable at subsequent visits, no HCV treatment is necessary since there is no evidence of chronic HCV infection. In addition, knowing the HCV genotype allows you to give the patient a projected prognosis with treatment, as not all genotypes respond the same to treatment (see figure 1 - “Response to pegylated interferon alfa-2a/ribavirin in HCV patients by genotype”).

A subsequent evaluation for HIV/HCV co-infected patients who have evidence of viremia and no evidence of decompensated liver disease should include a prothrombin time-international ratio, ferritin, alpha 1 antitrypsin level, and ceruloplasmin to screen for other causes of hepatic fibrosis, hepatitis A and B serologies to screen for those eligible for immunization, a pregnancy test for women, a rapid plasmin reagent (RPR) to screen for syphilis, TSH, diabetes and depression screen, antinuclear antibody to screen for autoimmune hepatitis, a retinal exam, especially for those with pre-existing retinopathies of other causes (e.g. diabetes mellitus, cytomegalovirus, hypertension), and a liver biopsy, particularly the liver biopsy specimen is not standard. A baseline ophthalmic eye exam is recommended because the use of interferon has been associated with retinal vascular occlusion and hemorrhages, cotton-wool spots, and optic neuropathy.

A creatinine clearance less than 50 mL/min contraindicates the use of ribavirin, which is a component of the standard HCV treatment regimen. However, peg-IFN may still be used alone in patients with significant renal impairment. Other contraindications to HCV treatment with ribavirin and peg-IFN include autoimmune disease, coronary artery disease, pancreatitis, pregnancy, and current major depression - especially if untreated/unstable from a mental health perspective. Ongoing injecting drug or alcohol use is not necessarily a contraindication to HCV treatment and should be evaluated on a case-by-case basis. HCV treatment may be deferred in those with only mild histologic changes, in which case a liver biopsy could be repeated in 2-3 years to assess for disease progression. If abnormalities such as renal impairment, anemia, thyroid disease, depression, diabetes, retinopathy, iron deficiency or overload are detected, they should be addressed and controlled before considering HCV treatment.

When co-administered with peg-IFN and ribavirin, the use of several antiretroviral agents have been associated with higher risk of liver toxicity, such as hepatic steatosis and failure. For example, didanosine is absolutely contraindicated with HCV therapy given the increased risk of hepatic steatosis and lactic acidosis. In this case, didanosine must be discontinued if the patient is to receive HCV therapy. Alternatives include tenofovir and abacavir. Anemia secondary to the co-administration of zidovudine (Retrovir) and ribavirin can occur and be particularly severe requiring the use of other costly measures, such as erythropoietin and reduction of the dose of ribavirin - decreasing the likelihood of achieving SVR. Therefore, appropriate alternatives to zidovudine should be sought during HCV therapy. There is a potential inhibitory effect of ribavirin on zidovudine, and stavudine (Zerit) observed in vitro, but this has not been reported as a clinically significant effect in vivo. Neuropathy, a common side effect among those taking stavudine, didanosine, or zidovudine, may be exacerbated in patients also receiving peg-IFN.

Please refer to Tables 1 and 2 for rules for discontinuation and dosing of peg-IFN and ribavirin in HIV/HCV co-infected patients.

References:
## HBV 101  Medications for Treatment of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>FDA approved to treat CHB/HIV coinfection</th>
<th>Active Against HIV</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-alpha</td>
<td>5 MU daily or 10 MU 3x/wk</td>
<td>No</td>
<td>No</td>
<td>Few studies show success. Perhaps better with high ALT levels and CD4 lymphocyte count &gt;350 cell/mm³.</td>
</tr>
<tr>
<td>Pegylated IFN-alpha</td>
<td>180 ug/wk by injection for 6-12 mo.</td>
<td>No</td>
<td>Yes*</td>
<td>Better than lamivudine in one study of HBV HBeAg-negative patients w/ CHB. **</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>300 mg daily in HIV-infected patients minimum treatment duration of 12 mo.</td>
<td>No</td>
<td>Yes</td>
<td>Resistance rate of 20-25%/yr among HBV isolates from HIV-infected patients. Do not include in HAARTT as the only HBV active agent.</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>200 mg daily, optimal duration unknown.</td>
<td>No</td>
<td>Yes</td>
<td>Similar in structure to lamivudine, so expected have same rates of resistance.</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10 mg daily, optimal duration unknown</td>
<td>No</td>
<td>No</td>
<td>Concerns about HIV resistance emerging to tenofovir may limit use.</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>300 mg daily, optimal duration unknown</td>
<td>No</td>
<td>Yes</td>
<td>Recommended use as part of a HIV-replication-suppression regime.</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5 mg daily in lamivudine-naïve patients. 1.0 mg in lamivudine-experienced; optimal duration unknown</td>
<td>Yes</td>
<td>No</td>
<td>No resistance during first 48 wks in treatment naïve patients. Resistance at 48 wks in HBV isolates from 7% of patients with lamivudine-resistant HBV.</td>
</tr>
</tbody>
</table>


Predictors of response to hepatitis A vaccine in HIV-positive patients

US Public Health Service/Infectious Diseases Society of America guidelines for the prevention of opportunistic infections in HIV-infected individuals recommend that hepatitis A virus (HAV) vaccination be given to all HIV+ patients, particularly those with other chronic conditions such as hepatitis C virus infection. To determine the predictors of immune response to the HAV vaccine, researchers in New Haven, CT retrospectively examined the medical records of outpatients attending area HIV clinics. At decrease by at least two points in the Knodell fibrosis point was histologic improvement (a decline in necroinflammatory score, without worsening of fibrosis) at week 48. Secondary end points included decrease by at least two points in the Knodell fibrosis point was histologic improvement (a decline in necroinflammatory score, without worsening of fibrosis) at week 48. Secondary end points included normalization of ALT levels (p = 0.01). HBV DNA levels were undetectable in 90% of the entecavir group compared to 72% of the lamivudine group (p < 0.001). Normalization of ALT levels was seen in 78% and 71% of the entecavir and lamivudine patients, respectively (p = 0.045). As in the Taiwanese study, resistance to entecavir was not observed and there were no differences between arms in safety parameters.

In an editorial accompanying these papers, Jay Hoofnagle, MD of the National Institutes of Health, adds some temperance to any irrational exuberance concerning these results pointing out that current HBV therapies suppress but do not eradicate HBV infection - unlike successful HCV therapy. Therefore, there remains debate regarding which patients should be treated, with which agent(s) and for how long (see Main Article). These studies do demonstrate that entecavir is potent, relatively less prone to cultivate drug resistance and seemingly safe (high does of the drug in mice have been found to cause cancer). These qualities, Dr. Hoofnagle writes, make entecavir along with adefovir a reasonable first line therapy choice for HIV-negative chronic HBV-infected patients.


FDA updates black box warning on Aptivus (tipranavir)

On June 30th, 2006 the FDA updated the black box warning on tipranavir protease inhibitor that is used in combination therapy with ritonavir (Norvir) for HIV-infected patients resistant to other drugs. The new warning is a result of 14 documented cases of intracranial hemorrhage in 13 of 6,840 people who took tipranavir during clinical trials. Eight of the 13 people died as a result of the hemorrhaging. According to the company, during an in-vitro experiment, tipranavir was observed to inhibit human platelet aggregation. Further, studies in rodents found an increase in coagulation parameters - increased prothrombin time (PT) and activated partial thromboplastin time (PTT). Such changes were not observed in experiments of dogs. A ‘Dear Doctor’ letter sent to providers recommends that tipranavir/ritonavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents or...
**NEWS AND LITERATURE REVIEWS (continued from page 8)**

anticoagulants. The warning label has previously sited liver failure as a possible effect of the drug.

http://www.fda.gov/medwatch/safety/2006/Aptivus-tipranavir_DHCP.pdf

FDA Approves New HIV Medications:

**Fixed dose tenofovir, emtricitabine and efavirenz (Atripla)**

The US Food and Drug Administration on July 12th approved a fixed dose once daily tablet combining efavirenz, emtricitabine and tenofovir - efavirenz - for the initial treatment of adults with HIV-1 infection. In the Department of Health and Human Services Guidelines for the Use of Antiretroviral agents in HIV-1-Infected Adults and Adolescents, the components of Atripla are recommended as one of the first-line regimens for treatment naïve patients. The side effects of the medication should be no different than its individual components. In patients with chronic hepatitis B virus (HBV) infection, the disruption of this new treatment may cause greater severity of HBV infection as tenofovir and emtricitabine are potent anti-HBV agents. The efficacy and safety of this new treatment was demonstrated in a 48 week long clinical study and pharmacokinetic studies indicate comparable bioavailability of the components to that observed when administered individually.

The U.S. Food and Drug Administration. FDA News. Available at: http://www.fda.gov/bbs/topics/NEWS/2006/NEW01408.html

**Darunavir (Prezista)**

Tibotec’s darunavir, also known as TMC-114, a new protease inhibitor for HIV-infected patients who have developed resistance to other ARV therapy received accelerated FDA approval in June. The drug, co-administered with ritonavir, was approved based on the findings of two randomized controlled studies examining the safety and efficacy of the darunavir/ritonavir in heavily treatment experienced patients. As a condition of the accelerated approval of the drug, Tibotec will conduct studies to evaluate the clinical benefits of darunavir. It will also perform studies on the effects of the drug in children and patients with liver dysfunction.


**IDCR-o-GRAM**

Clinical management of ARV-associated hepatotoxicity in patients with HIV/HCV coinfection

<table>
<thead>
<tr>
<th>Increase serum ALT or AST levels after initiation of ARV therapy</th>
<th>Grade 1 or 2 increase (defined as &lt;5 X upper limit of baseline normal value or &lt;3.5 X the baseline abnormal value)*.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does patient have symptoms of acute hepatitis C, mitochondrial toxicity, or a hypersensitivity reaction (eg. to nevirapine or abacavir)?</td>
<td>Grade 3 or 4 increase (defined as either &gt;5 X upper limit of baseline normal value or &gt;3.5 X the baseline abnormal value).</td>
</tr>
<tr>
<td>Exclude alternative causes of acute hepatitis. ** Consider discontinuation of ARV therapy. *** If suspicious of mitochondrial toxicity or a hypersensitivity reaction (eg. to nevirapine or abacavir)</td>
<td>Decrease in serum ALT or AST levels after discontinuation of ARV therapy.</td>
</tr>
<tr>
<td>No change or increase in serum ALT or AST levels after discontinuation of ARV therapy.</td>
<td>Consider liver biopsy and treatment of underlying liver disease (eg. HCV infection).</td>
</tr>
</tbody>
</table>

Follow algorithm for grade 3 or 4 increase in serum ALT or AST levels.


** Consider acute hepatitis A and B virus infection, other infectious causes of hepatitis, and nucloside analog reverse transcriptase inhibitor-related lactic acidosis syndrome due to mitochondrial toxicity.

*** Patients that have grade 3 or 4 hepatotoxicity and no symptoms of acute hepatitis who remain on ARV therapy should be monitored closely.

**RESOURCES**


CDC Patient Information on Viral Hepatitis http://www.cdc.gov/ncidod/diseases/hepatitis/


Diet Recommendations for Hepatitis C Infected Individuals http://www.dietitians.ca/resources/HepatitisC_Guidelines.htm

Hepatitis B Vaccination Coverage Among Adults — United States, 2004 MMWR May 12, 2006 / 55(18);509-511 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5518a3.htm

SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medical Education Collaborative, Inc. (MEC) and IDCR. MEC is accredited by the ACCME to provide continuing medical education for physicians.

Medical Education Collaborative designates this educational activity for a maximum of 1.25 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Statements of credit will be mailed within 6 to 8 weeks following the program.

Objectives:
- The learner will be able to list major criteria for treatment of hepatitis B virus (HBV) infection.
- The learner will understand the need to choose HBV therapies that will not cultivate HIV drug resistance in the HBV-HIV co-infected patient.
- The learner will be able to cite predictors of response to treatment of hepatitis C virus (HCV) infection.

1. Treatment of hepatitis B virus (HBV) infection is indicated in patients with the following EXCEPT:
   A. Evidence of chronic HBV infection such as persistent positive HBsAg
   B. HBV DNA level that is greater than 104 copies/mL
   C. Normal ALT level
   D. A family history of hepatocellular carcinoma

2. In patients who meet criteria for HBV therapy and have never been exposed to lamivudine which of the following are considered suitable therapies:
   A. Lamivudine
   B. Entecavir
   C. TDF
   D. A or B
   E. Neither A or B

3. In the setting of HBV-HIV co-infection treatment of HBV must take into consideration overlapping drug resistance of antivirals for each infection. Which of the following agents have activity against both HIV and HBV?
   A. Tenofovir
   B. Lamivudine (3TC)
   C. Emtricitabine (FTC)
   D. Entecavir
   E. A, B and C

4. Factors associated with response to HCV therapy include which of the following:
   A. HCV genotype (genotype 1 is less responsive)
   B. Lower plasma HCV viral load
   C. Lower body weight
   D. Tolerance of higher doses of ribavirin
   E. All the above

5. Didanosine should never be co-administered with HCV therapy True or False?
   A. True
   B. False

In order to receive credit, participants must score at least a 70% on the post test and submit it along with the credit application and evaluation form to the address/fax number indicated. Statements of credit will be mailed within 6-8 weeks following the program.

Instructions:
- Applications for Credit will be accepted until August 31, 2007.
- Late applications will not be accepted.
- Please anticipate 6-8 weeks to receive your certificate.

Please print clearly as illegible applications will result in a delay.

Name: ________________________________________  Profession: ______________________________________
License #: ___________________  State of License: ___________________
Address: ________________________________________________________________
City: ___________________  State: ________  Zip: ___________________  Telephone: ___________________
Please Check which credit you are requesting  ___ ACCME   or   ___ Non Physicians

I certify that I participated in IDCR monograph - August 2006 Issue
Please fill in the number of actual hours that you attended this activity.
Date of participation: ___________________
Number of Hours (max. 1.25): ___________________
Signature: ___________________
I. Please evaluate this educational activity by checking the appropriate box:

<table>
<thead>
<tr>
<th>Activity Evaluation</th>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faculty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How well did this activity avoid commercial bias and present content that was fair and balanced?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is the likelihood you will change the way you practice based on what you learned in this activity?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, how would you rate this activity?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

II. Course Objectives

Were the following overall course objectives met? At the conclusion of this presentation, are you able to:

- The learner will be able to list major criteria for treatment of hepatitis B virus (HBV) infection. **YES** **NO** **SOMEWHAT**
- The learner will understand the need to choose HBV therapies that will not cultivate HIV drug resistance in the HBV-HIV co-infected patient. **YES** **NO** **SOMEWHAT**
- The learner will be able to cite predictors of response to treatment of hepatitis C virus (HCV) infection. **YES** **NO** **SOMEWHAT**

III. Additional Questions

a. Suggested topics and/or speakers you would like for future activities.

b. Additional Comments