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ABOUT IDCR

IDCR, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, IDCR provides up-to-the moment information on HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by The Medical Education Collaborative (MEC). This activity is jointly sponsored by IDCR and The Medical Education Collaborative (MEC). IDCR is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).

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

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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 serological 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



Hepatitis B Virus Source: Barth K, Frese M. Freiburg University

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.

DW: What if in this case the HBsAg is found to persist during the first year? What would you do then?

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

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LETTER FROM THE EDITOR *(continued from page 2)*

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,

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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 $450/\text{mm}^3$ who has a HBV DNA of 10^5 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 not to 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 damage 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 HBV-HIV 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, Epir-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 try to treat this patient with lamivudine mono-therapy but, 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-Intron) because it does not have any effects on developing HIV drug resistance (4). Here an HBV genotype 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 (Baraclude). 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)

DW: Our goal is undetectable? Not just a substantial reduction in viremia?

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.

DW: Let's talk for a moment about the HIV-infected patient who has a history of lamivudine exposure. How is the management of this patient different?

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).

DW: If you were going to start HIV therapy what would you choose?

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.

DW: What about HBV treatment for the HIV-uninfected patient?

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.

DW: I am going to shift gears and ask you to clarify an issue that is getting increasingly confusing. How should we screen people with HIV-infection for HBV infection? A recent study by Raj Gandhi and colleagues from Harvard Medical School suggests that isolated Hepatitis B core antibody (anti-Hbc) may be falsely positive in a large proportion of HIV-infected people (7). In this particular study patients with anti-Hbc detected on HBV serologic testing but no other serologic evidence of HBV infection had a very muted response to HBV vaccination suggesting the absence of an anamnestic response that would be expected if there was prior HBV exposure.

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 anti-Hbc. That way you are never stuck with the situation of the isolated anti-Hbc. If both the surface antigen and antibody were negative, I would vaccinate. This is one approach. In cases where there is isolated core antibody detected, I would obtain an HBV DNA. If that reveals no virus detected I would check it again in six months along with their serologies. If the result were the same I would vaccinate them for HBV.

DW: Do you ever check for HbeAg or anti-Hbe?

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.

DW: While we are on the topic of HBV vaccine, what dose do you use? The data on response to HBV vaccination among HIV-infected patients indicates a generally low response rate. Dialysis patients often receive a higher dose (40 ug) of the vaccine compared to the standard dose (20 ug) to overcome a similar suboptimal response rate.

CT: I initially start out with the standard dose vaccine and then if they do not respond, I administer the renal dose of the vaccine.

DW: Then you must be checking for hepatitis B surface antibody (anti-HBs)

response in everyone you vaccinate?

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.

DW: Thanks for taking time out to do this.

CT: Thank you.

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Hepatitis B Surface Antigen Prevalance

- >8% High
- 2%-7% Middle
- <2% Low

Geographic distribution of Hepatitis B prevalence, 2005
Source: CDC

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

Bethany Weaver, DO MPH
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Disclosures: Consultant: Merck & Co. Speaker's Bureau: Merck & Co., Gilead Sciences, Inc. Advisory Board: Merck & Co. Stockholder: Pfizer Inc.

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 laboratories 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

The 12-week rule	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.
The 24-week rule	Treatment should be discontinued in genotype 1-4 patients who have detectable viremia at week 24 despite a 2-log reduction in viral load in the 12th week.

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

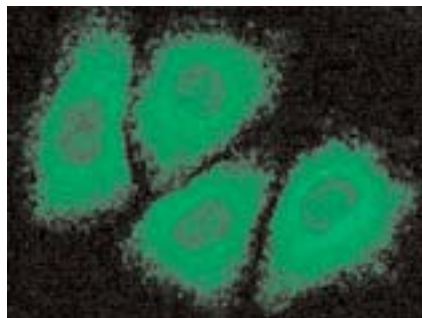
Peginterferon alfa-2a	For all genotypes 180 mcg SQ once weekly
Peginterferon alfa-2b	For all genotypes 1.5 mcg/kg SQ once weekly
Ribavirin-2 (divided oral doses daily)	All genotypes: weight <75 kg 1,000 mg All genotypes: weight >75 kg 1,200 mg
Duration of therapy	
Genotype 1 or 4:	48 wks
Genotype 2 or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

Modified from: Cotler S. Hepatitis C: transmission to treatment. Infectious Disease Special Edition. 2004;7:15-22 and Strader DB et al. Diagnosis, management, and treatment of hepatitis C (AASLD Practice Guideline). Hepatology. 2004;39(4):1147-71.

SPOTLIGHT...**(continued from page 5)**

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,



Hepatitis C Virus - Source: CDC

or to determine the degree of fibrosis. Experts currently recommend treating those with advanced HIV/AIDS (absolute CD4 cell count less than 200/mm³) 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 should 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 those with HCV genotype 1. A baseline 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 affect 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.

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HBV 101 MEDICATIONS FOR TREATMENT OF CHRONIC HEPATITIS B

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

Modified from: Thio CL, Sulkowski MS, Thomas D. Treatment of Chronic Hepatitis B in HIV-Infected Persons: Thinking Outside of the Black Box. *Clin Infect Dis*. 2005;41:1035-40.

* Anti-HIV activity was noted in an HIV-hepatitis C virus coinfection trial - Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004;351:438-50.

** Marcellin P, Lau GKK, Bonino F, et al. Peg-interferon alfa-2a (40KDa) (Pegasys) monotherapy is more effective than lamivudine monotherapy in the treatment of HBeAg negative chronic hepatitis B: 72 week results from a phase III, partially double-blind study of Pegasys alone vs. Pegasys plus lamivudine vs. lamivudine [abstract 95]. In: Program and abstracts of the 39th Meeting of the European Assoc. of the Study of Liver Disease (Berlin). Geneva, Switzerland: Keyes International, 2004.

SAVE THE DATES

7th Annual Inside/Out Summit

"Rehabilitation Re-emerges: Working Together to Help Those Affected by Incarceration"

September 11-12, 2006

San Francisco, CA

Program and Hotel Info:

Visit: www.centerforce.org/summit

Tiffany Barber, Summit Coordinator

415 456 9980 X 135

E-mail: ybarraj@mail.amc.edu

Correctional Medicine Institute's 2006

Intensive Review in Correctional Medicine

September 15-17, 2006

Baltimore, MD

Visit: <http://www.cmi2006.org/>

2006 United States Conference on AIDS (USCA)

September 21-25, 2006

Hollywood, FL

Westin Diplomat Hotel

Visit: http://www.nmac.org/conferences___trainings/USCA/

46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

September 27-30, 2006

San Francisco, CA

Visit: <http://www.icaac.org/>

44th Annual Infectious Diseases Society of America (IDSA) Conference

October 12-15th, 2006

Toronto, Ontario, Canada

Visit: www.idsociety.org

"Managing Addiction in the HIV-infected Patient"

Live Satellite Video Conference

Part of Management of HIV/AIDS in the

Correctional & Community Setting

October 18, 2006

Albany Medical College 12:30-2:30

CME & CNE credits available

Visit: www.amc.edu/HIVconference

E-mail: ybarraj@mail.amc.edu

Infectious Disease in Corrections Report (IDCR) Symposium

"Intensive review of ID in Correctional Health"

Pre-conference before the NCCHC Conference

Saturday Afternoon, October 28, 2006

CME credits available

Hyatt Regency Hotel Atlanta, GA

Visit: <http://www.ncchc.org/education/national2006/atlanta.html>

National Commission on Correctional Health Care (NCCHC) Conference

October 28- November 1, 2006

Hyatt Regency Hotel

Atlanta, GA

Visit: <http://www.ncchc.org/education/national2006/atlanta.html>

134th Annual American Public Health Association (APHA) Meeting and Exposition

November 4-8, 2006

Boston, MA

Visit: <http://www.apha.org/meetings/>

6th National Harm Reduction Conference

November 8-12, 2006

Oakland, CA

Visit: <http://www.harmreduction.org/6national/>

University of Texas Medical Branch (UTMB) HIV Mini-Fellowship

November 13-15, 2006

Moody Gardens Hotel and Convention Center Galveston, TX

\$50.00 Registration Fee

CME and CNE credits available

Contact: Victoria Korschgen

E-mail: vikorsch@utmb.edu

Phone: (409)772-8799

NEWS AND LITERATURE REVIEWS

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 these clinics baseline and post-vaccination HAV antibodies are measured routinely. Those who are found to be HAV susceptible are administered two doses of the HAV vaccine (1440 ELISA units given IM 6-12 months part). Of the 503 patients who had HAV serologic testing performed, 138 were HAV seronegative at baseline and completed both injections of the series. Less than half (48.5%) of these patients had evidence of a serologic response to the HAV vaccine series. In a multivariate analysis examining response to the HAV vaccine, being female and having a CD4 count >200 cell/mm³ at the time of initial vaccination were independent predictors of adequate response. Hepatitis C virus (HCV) exposure, antiretroviral therapy use, age and race were not different between responders and non-responders. These data suggest that delay of HAV vaccination until CD4 cell counts increase following HAART initiation may improve immune responses to HAV vaccine, especially among men.

Weissman S, Feucht C, Moore BA. *Journal of Viral Hepatitis*. 2006;13(2):81-86.

A comparison of entecavir and lamivudine for chronic hepatitis B virus infection.

Two large clinical trials pitted entecavir and lamivudine for the treatment of chronic HBV infection in HIV-uninfected patients. Chang and colleagues in Taiwan randomized 715 HBeAg-positive patients naïve to nucleoside analogues to lamivudine or entecavir for at least 52 weeks. The primary efficacy end point was histologic improvement (a decrease by at least two points in the Knodell necroinflammatory score, without worsening of fibrosis) at week 48. Secondary end points included a reduction in the serum HBV DNA level, HBeAg loss and seroconversion, and normalization of the alanine aminotransferase level. At 48 weeks, histologic improvement was seen in 72% of the entecavir assigned patients compared to 62% of those receiving lamivudine ($p = 0.009$). Further, entecavir treated patients had deeper declines in HBV viral load (6.9 vs. 5.4 log₁₀ copies/mL, $P < 0.001$). There was no difference in HBeAg seroconversion between the study arms (~20% in each group). Entecavir resistance was not detected during the first year of treatment and tolerability to the two agents was similar.

Lai and colleagues across the South China Sea in Hong Kong conducted a similar head-to-head of entecavir and lamivudine but enrolled HBeAg-negative patients. A total of 648 patients were randomized and as was seen in the trial of HBeAg-positive patients, entecavir yielded significantly greater

rates of histologic improvement. Again, 70% of those assigned entecavir versus 60% of those receiving lamivudine had histologic improvement on liver biopsy ($p = 0.01$). 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 doses 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.

Chang TT, Gish R, de Man, R et al. *A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis B*. *N Engl J Med*. 2006;354(10):1001-10.

Lai CL, Shouval D, Lok AS. *Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B*. *N Engl J Med*. 2006;354(10):1011-20

Hoofnagle J. *Hepatitis B--preventable and now treatable*. *N Engl J Med*. 2006 Mar 9;354(10):1074-76.

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

Continued on page 9

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

http://www.fda.gov/medwatch/safety/2006/Aptivus_P1.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.

The U.S. Food and Drug Administration. FDA News. Available <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01395.html>

RESOURCES

Bureau of Justice Prison Statistics Hepatitis Testing and Treatment

<http://www.ojp.usdoj.gov/bjs/abstract/httspp.htm>

CDC Patient Information on Viral Hepatitis

<http://www.cdc.gov/ncidod/diseases/hepatitis/>

CDC Hepatitis C Coordinator Web site Portal

http://www.cdc.gov/ncidod/diseases/hepatitis/resource/coordinators_portal.htm

Federal Bureau of Prisons Hepatitis C Clinical Practice Guidelines 2005

<http://www.bop.gov/news/PDFs/hepatitis.pdf>

Diet Recommendations for Hepatitis C Infected Individuals

http://www.dietitians.ca/resources/HepatitisC_Guidelines.htm

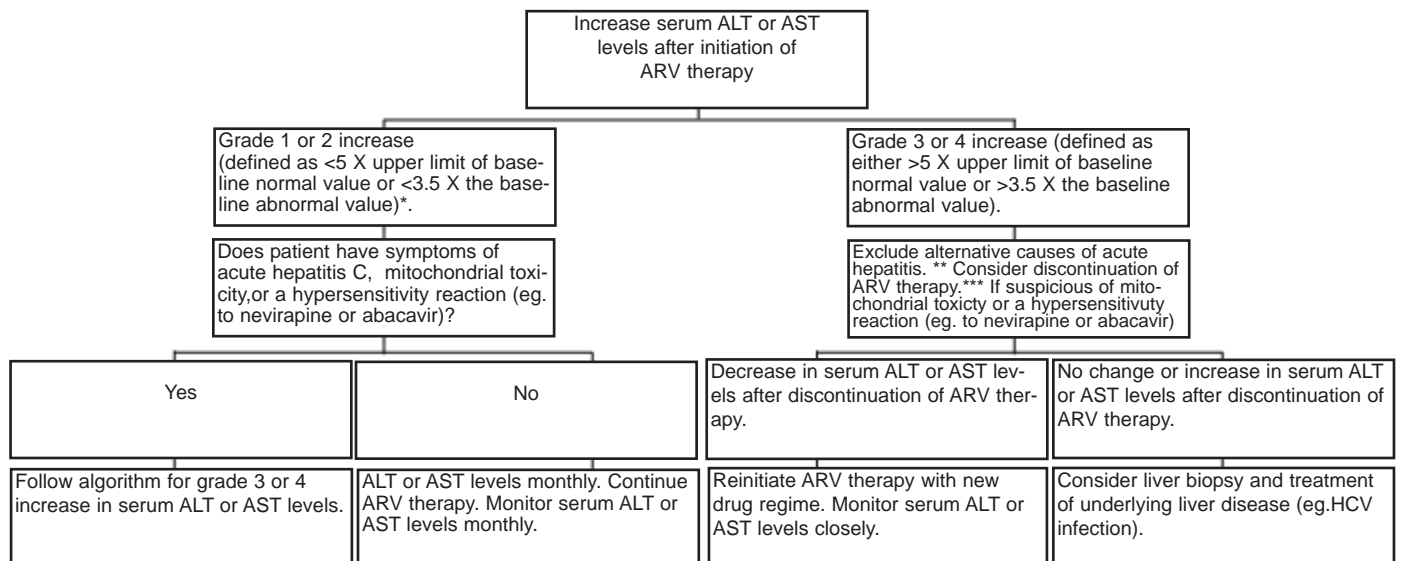
Hepatitis B Vaccination Coverage Among Adults --- United States, 2004

MMWR May 12, 2006 / 55(18);509-511

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5518a3.htm>

IDCR-o-GRAM

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



Modified from: Berggren R. Management of patients coinfecting with HIV and hepatitis C virus. Infectious Disease Special Edition. 2004;7:26-29.

* Based on Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001;15:1261-1268.

** Consider acute hepatitis A and B virus infection, other infectious causes of hepatitis, and nucleoside 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.

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)TM. 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.

- | | |
|---|--|
| <p>1. Treatment of hepatitis B virus (HBV) infection is indicated in patients with the following EXCEPT:</p> <ul style="list-style-type: none"> 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 <p>2. In patients who meet criteria for HBV therapy and have never been exposed to lamivudine which of the following are considered suitable therapies:</p> <ul style="list-style-type: none"> A. Lamivudine B. Entecavir C. TDF D. A or B E. Neither A or B <p>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?</p> | <ul style="list-style-type: none"> A. Tenofovir B. Lamivudine (3TC) C. Emtricitabine (FTC) D. Entecavir E. A, B and C <p>4. Factors associated with response to HCV therapy include which of the following:</p> <ul style="list-style-type: none"> 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 <p>5. Didanosine should never be co-administered with HCV therapy True or False?</p> <ul style="list-style-type: none"> 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: _____

Please Submit Completed Application to:

Medical Education Collaborative
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 Phone: 303-420-3252 FAX: 303-420-3259
 For questions regarding the accreditation of this activity, please call (303)420-3252

COURSE EVALUATION

I. Please evaluate this educational activity by checking the appropriate box:

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

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
