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Infectious Diseases in Corrections

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INFECTIOUS DISEASES IN CORRECTIONS REPORT

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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 Brown University Office of Continuing Medical Education. IDCR is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).

SUPPORTERS

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IDCR MISSION STATEMENT

We changed our name from HEPP Report to IDCR (Infectious Diseases in Corrections Report) to encompass all infectious diseases that impact the correctional setting. IDCR's goal is to educate correctional health care providers about the appropriate medical management of prisoners infected with HIV, hepatitis, TB, and other infectious diseases; to encourage these providers to improve their networks with correctional, academic or community-based infectious disease experts; and to promote a level of infectious disease care in correctional facilities that is equivalent to the "community standard."

HEPATITIS B IN CORRECTIONS

By Beth Schwartzapfel, BA and Josiah D. Rich**, MD, MPH, Brown University, The Miriam Hospital, Providence, RI*

Hepatitis B in the United States

Hepatitis B virus (HBV) is a bloodborne virus that causes both acute and chronic liver disease. Viremia can last for several months in acute infections, and for many years in chronic infections. Because of crowding and high-risk behaviors that take place within many jails and prisons, the transmission of HBV becomes a serious issue. The following article will outline HBV in corrections, HBV transmission, the clinical course of HBV, and vaccine possibilities.

An estimated 1.25 million, or 5% of the United States population has serologic evidence of past or present HBV, and 0.4% - 0.5% have chronic infection.[1] Chronic HBV infection accounts for 5%-10% of cases of chronic liver disease and cirrhosis in the United States, and acute HBV continues to affect approximately 8,000 people each year,[2] despite the fact that a safe and effective HBV vaccine has been available for more than two decades.

The incidence of acute HBV infection has been decreasing steadily since the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) began recommending universal childhood vaccination and vaccination of high-risk groups more than a decade ago.[3] Partially as a result of this aggressive vaccination policy, the incidence of acute HBV infection in 2002 was reported to be 2.8 per 100,000 population, down from a rate of 8.5 per 100,000 in 1990. However, after more than 10 years of decline, the incidence of HBV among men over age 19 and women aged 40 or older has increased. The most common risk factors reported among adults with acute HBV continue to be multiple sexual partners, men having sex with men, and injection drug use.[2]

Hepatitis B in Corrections

The high prevalence of markers for HBV infection among incoming inmates to prisons and jails was described as early as 1978.[4] Since then, there has been an explosion of the incarcerated population in the United States, particularly in the last two decades, fueled largely by tougher penalties for drug offenses. The number of people incarcerated in state or federal prisons whose most serious crime was a drug offense has increased 13-fold, from 23,749 in 1980 to 324,601 in 2001.[5] Due to this increase in drug user incarceration, the prevalence of blood-borne infections in those who are incarcerated also increased. Despite the emergence of a HBV vaccine, seroprevalence studies among inmates have continued to document high rates of HBV markers - 30% in Tennessee,[6] 35% in Virginia,[7] 43% in Suffolk County, Massachusetts,[8] and most recently, 20% in Rhode Island.[9] It should be noted that approximately 95% of these cases have

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resolved infection, and only 5% would be expected to have chronic HBV. Additionally, 30% of persons with acute HBV infection in the United States report having been in prison or jail at some point.[10]

Several recent publications have highlighted the transmission of HBV within prison walls. In 2001, the CDC reported on an HBV outbreak in a state correctional facility; 11 inmates living in four separate dormitories were identified with acute HBV, for an overall infection rate of 1.2% among inmates in the facility. Most of the infected inmates were asymptomatic.[11] A serosurvey conducted from 1999-2002 among inmates of Georgia's correctional system identified 92 cases of acute HBV infection. While it is not know how many of these 92 cases were acquired in prison, what is known is that of 57 acute HBV cases reported between January 2001 and June 2002, 72%, or 41 cases, were acquired in prison.[12] A study in the RI Department of Corrections identified a HBV incidence of 2.7 per 100 person-years among 446 continuously incarcerated inmates.[9]

Transmission
HBV is bloodborne and sexually transmitted. The virus is found in moderate to high concentrations in blood, serum, wound exudates, semen, vaginal secretions, and saliva, and is transmitted by percutaneous or mucosal exposure to these fluids.[13]

In correctional settings, a disproportionately high prevalence of chronic HBV infection among inmates provides a reservoir for infection of susceptible inmates. Given the lack of access to condoms (only two state and five municipal correctional systems make condoms available to adult inmates for use in their facilities), sexual contact between inmates is a major risk factor for intra-prison transmission; the CDC reports that 2%-30% of inmates have sex while incarcerated.[14]

Similarly, lack of access to needle exchange (or, indeed, needles) makes drug use behind bars especially risky, even if it occurs less frequently than in the community. A recent survey of injection drug users in Los Angeles County found that 15% of 197 participants released from detention in the previous year reported having injected drugs while incarcerated, and that 79% of those who had ever injected while incarcerated reported sharing needles.[15]

Other HBV transmission risks in the correctional setting include: fights, bites, cuts, injuries, sharing razors, tattooing and piercing.[16]

Clinical Course and Natural History
The incubation period of HBV ranges from 45-160 days. Acute HBV infection is asymptomatic in 50% of adults. When clinical manifestations do occur, they usually correspond with the following phases: preicteric (lasting three to 10 days, characterized by malaise, anorexia, nausea, vomiting, right upper quadrant abdominal pain, fever, headache, myalgias, skin rashes, arthralgias and arthritis, and dark urine), icteric (lasting one to three weeks, characterized by jaundice, light or grey stools, hepatic tenderness and hepatomegaly), and convalescence (other symptoms disappear but fatigue or malaise may persist for up to several months).[17]

> After more than 10 years of decline, incidence of HBV among men over age 19 and women aged 40 or older has increased.

Fulminant hepatitis is rare, occurring in 1%-2% of newly infected persons, but its mortality rates are high, ranging from 63% to 93%. Between 200 to 300 people in the United States die each year of HBV-induced fulminant hepatitis.[17]

Most adults with acute HBV recover completely, with elimination of HBV surface antigen (HBsAg) from the blood and production of antibody to the surface antigen (anti-HBs), creating immunity from future infection. However, up to 10% of adults with acute infection develop chronic HBV infection. Most of the serious complications associated with HBV are the result of chronic infection.

The majority of adults with chronic HBV are asymptomatic, though they are capable of infecting others. One third of chronically infected persons have no evidence of liver disease. In the other two thirds of those with chronic HBV infection, long term effects on infection include chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC). An estimated 3,000 to 4,000 persons in the United States die each year from HBV-related cirrhosis, and approximately 1,000 to 1,500 die from HBV-related HCC. Persons with chronic HBV infection are up to 300 times more likely to develop HCC than persons without HBV infection.[17]

There is some interest lately in occult HBV, defined as the demonstration of antibodies to the HBV core antigen (anti-HBc), without either HBsAg or anti-Hbs, with or without the presence of low-level circulating virus.[16] Cohorts of persons with HIV, hepatitis C virus (HCV), and HIV/HCV coinfection have all been found to have a higher prevalence of occult HBV infection than previously expected when tested for HBV with ultra-sensitive assays.[18] However, the clinical significance and transmissibility of HBV DNA in patients with occult HBV infection is a matter of some debate.[19]

Hepatitis B vaccine
The first vaccine against HBV, a plasma-derived vaccine, was introduced in 1981. This vaccine was thought to be safe and was effective, but not well accepted due to the use of thimerosal, an ethyl mercury-containing preservative used in the drug, and was removed from the market in 1992. The vaccine that is currently licensed and used widely is a recombinant HBV vaccine, first licensed in 1986 and produced by Merck and Company (Recombivax HB) and SmithKline Beecham (Energix-B). Vaccines made by the two manufacturers both induce the same immunity against HBV. Twinrix, a combined hepatitis A and B virus vaccine manufactured by GlaxoSmithKline Biologicals, was licensed in 2001.[20]

After 3 intramuscular doses of HBV vaccine, over 90% of healthy adults develop adequate antibody responses. Larger vaccine doses or an increased number of doses are often required to induce an antibody response in hemodialysis patients and may be necessary in immunocompromised patients. Vaccine-induced immunity levels decline with time, but immune memory remains intact for at least 13 years following immunization, and adults with declining antibody levels are still protected from clinically significant HBV infection. Therefore, for adults with normal immune status, neither booster doses nor routine serologic testing to assess immune status are indicated.[20] The standard HBV vaccination schedule consists of the second and third doses being administered 1 and 6 months after the first.[21]

The first official recommendations for the use of the HBV vaccine, published in 1982, included a recommendation to vaccinate "inmates of long-term correctional facilities".[21] However, difficulty providing the vaccine to some populations, such as men who have sex with men and injection

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drug users, led to the assumption in the late 1980s and early 1990s that high-risk adults could not be vaccinated before exposure to the virus, even by "aggressive vaccination programs."[22] Therefore, priority was given to universal childhood vaccination as a national policy over targeted vaccination of high-risk adults.[3]

Throughout the evolution of the national vaccination policy, the CDC has continued to recommend vaccination of adults in correctional facilities.[14] In a survey published in 2001, the only states to routinely offer HBV vaccine to inmates included Michigan and Texas.[23] Texas has since discontinued its program due to a lack of funds.[12] However, Texas continues to routinely administer HBV vaccine to HIV+ inmates who are seronegative for HBV. Between 2002-2003, Indiana initiated a program in which HBV vaccination was offered to all incoming inmates. Nearly 100% of inmates participated, many receiving three shots before release. Unfortunately, this program has also ended, due to lack of funds. Other states have since initiated vaccination programs for adult inmates.[24] However, the practice remains rare and the exact number of states currently offering routine HBV vaccination to inmates is difficult to ascertain.

While HBV vaccination for those who are incarcerated presents a cost to correctional systems, the intervention overall is a cost savings since net savings accrue to the entire health care system. Nonetheless, the vaccinations have been a difficult "sell" to correctional health care officials with ever-restrictive budgetary concerns. Because prisons and jails acquire a substantial portion of the population at risk for HBV infection and often offer a first-time opportunity for medical care, the opportunity that prisons and jails have for an effective health intervention to prevent HBV infection is substantial.[25]

Several pilot programs have demonstrated the feasibility of implementing such a program in the correctional setting. In a pilot program in the Women's Division of Rhode Island State Prison, 65% of those offered HBV vaccine accepted at least one dose.[26] The program has since been expanded to include the Men's Division; acceptance rates there have been upwards of 90% (unpublished data). From 2000 to 2002, the Texas Department of Criminal Justice offered HBV vaccine to all of its estimated 40,000 entering inmates, with acceptance rates of 85% in jail and 72% in prison.

Though the length of stay for many incarcerated persons is not long enough to complete the three-dose HBV vaccine series (this is especially true for jail facilities where up to one half are released within 24-48 hours[27]), a single dose offers immunity in up to 55% of those vaccinated, and two doses offers immunity in up to 85%.[28] Alternative vaccination schedules can speed the process and allow inmates who are only incarcerated for a short time to complete the series. An alternative schedule that can be used for vaccination is zero, two, and four months. In this shortened series, the third dose needs to be given two months after the second dose and four months after the first dose. Given the high rate of recidivism in prisons and jails and the fact that one need not restart an HBV vaccine series if the interval between doses is longer than recommended, inmates who are re-entering prison or jail after being released may restart a series where they left off at their last incarceration.[17]

Conclusion

Though the United States has made substantial progress towards eliminating HBV with universal childhood vaccination, an opportunity to prevent 30% of new HBV cases is missed each year in the correctional setting. Though most adults infected with HBV recover, acute HBV can cause substantial morbidity, and chronic infection can cause chronic hepatitis, cirrhosis, HCC, and death. Education of correctional personnel, as well as providing vaccines to personnel, may encourage vaccination programs of inmates. Routine HBV vaccination of inmates is in the best interest of the health of prisoners and the public.

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**Nothing to disclose.*
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Letter from the Editor

Dear Correctional Colleagues:

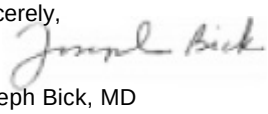
All of us working in correctional public health are familiar with the horrendous costs associated with the treatment of preventable diseases. Our patients come to us from the free community with a lifetime of neglected or undiagnosed medical problems: HIV, HCV, HBV, gonorrhea, chlamydia, syphilis, mental illness, diabetes, hypertension, hyperlipidemia…. Once they step through our gates, they finally achieve something that all Americans deserve but many do not have - a constitutional right to a minimum standard of health care.

Not surprisingly, many correctional systems are running chronic budgetary deficits as they struggle to cover the rising costs associated with diagnosis and treatment of chronic medical problems. The irony is that more affordable approaches exist that could be implemented to address many of these societal problems. For over 20 years, a safe, effective vaccine has been available that can in a cost-effective manner decrease the burden of HBV and associated chronic liver disease. However, not all children are vaccinated for HBV, and an alarming number of at-risk individuals eventually end up as wards of our correctional system. Most of the life-time costs associated with chronic liver disease will not fall upon jails and prisons, but rather upon society after inmates are released. As a result, many systems that struggle to provide treatment for other medical conditions have not intensively invested in vaccination programs for at-risk inmates. The opportunity is therefore lost; the potential savings to society are squandered.

As my colleagues in correctional medicine have before me, I again call for the establishment of a *Vaccines for At-risk Adults* program. By making free or deeply discounted vaccines available for all at-risk adults, including those who are incarcerated, we can turn a correctional challenge into a public health opportunity. Only by working together with our free-world colleagues can we formulate an effective societal response to the medical needs of those who have been temporarily entrusted to our care.

This month, Drs. Rich and Schwartzapfel provide an excellent review of hepatitis B in corrections. Drs. Dieterich, Aftab, and Martin discuss HBV treatment options and we also reprint algorithms for the diagnosis and treatment of those with chronic hepatitis B. At the conclusion of this issue, readers will have a better understanding of the prevention, epidemiology, natural history, and treatment of hepatitis B. We hope that you find this issue useful, and we look forward to seeing you at our annual preconference infectious diseases seminar, to be held on Saturday, November 13, 2004 in conjunction with the fall meeting of the National Commission on Correctional Health Care in New Orleans.

Sincerely,



Joseph Bick, MD

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Faculty Disclosure

In accordance with the Accreditation Council for Continuing Medical Education Standards for Commercial Support, the faculty for this activity have been asked to complete Conflict of Interest Disclosure forms. Disclosures are listed at the end of articles. All of the individual medications discussed in this newsletter are approved for treatment of HIV and hepatitis unless otherwise indicated. For the treatment of HIV and hepatitis infection, many physicians opt to use combination antiretroviral therapy which is not addressed by the FDA.

Hepatitis B Management Algorithms

Screening Labs

Initial screening: HBsAg, anti-HBc (lgG and lgM), anti-HBs

All HBsAg+ subjects: HBeAg, anti-HBe, quantitative HBV DNA level by PCR

	Acute HBV Infection	Past Exposure (Immunity)	Vaccine Responder	Chronic HBV Infection	Chronic Precore Mutant	Inactive Carrier
HBsAg	+	-	-	+	+	+
Anti-HBs	-	+	+	-	-	-
HBeAg	+	-	-	+	-	-
Anti-HBe	-	+/-	-	-	+	+
Anti-HBc lgG	+	+	-	+	+	+
Anti-HBc lgM	+	-	-	-	-	-
HBV DNA (PCR)	+	-	-	+	+	-

Treatment of e Antigen Negative Patients

HBeAg Negative
(precore and core promoter mutations)

Quantitative HBV DNA by PCR

HBV DNA 10

No treatment
Monitor ALT
every 6 to 12 months

Normal ALT
Biopsy, treat if disease

Elevated ALT
Treatment with IFN, LAM or ADV*
Consider ADV/LAM combination therapy and longer duration
*Preferred
(low rate of resistance)

OTHER CONSIDERATIONS

Hepatocellular Carcinoma (HCC): Screen high risk populations, i.e. men >45 years, patients with cirrhosis or family history of HCC, every 6 months with AFP and liver imaging (ultrasound, CT or MRI).

Inactive Carriers: ALT and quantitative HBV DNA by PCR every 3 to 6 months and exclude other causes of disease. Screen for HCC in relevant populations.

Treatment of Patients with Cirrhosis

In conjunction with a Liver Specialist

Compensated Cirrhosis

Quantitative HBV DNA by PCR

Treat with ADV* or LAM
Consider ADV/LAM combination therapy
*Preferred
(low rate of resistance)

Observe or treat with ADV or LAM
Consider ADV/LAM combination therapy

Decompensated Cirrhosis

HBV DNA Detectable by Quantitative PCR?

Treat with ADV or LAM
Waitlist for transplant

Observe
Waitlist for transplant

Reprinted from Hepatitis B Resource Network www.h-r-n.org

SPOTLIGHT: HEPATITIS B VIRUS (HBV)/HIV CO-INFECTION AND TREATMENT OPTIONS

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HIV AND HBV CO-INFECTION

Up to 96% of HIV-infected people have been co-infected with HBV.[1,2] In the 15 years after its emergence, HIV-associated mortality was so high that treating HBV infection did not appear to be a priority. Fortunately, with the development of successful highly active antiretroviral therapy (HAART), individuals with HIV infection now have a better prognosis with a steady decline in the number of new cases of HBV infection over the last 10 years.[3] Aggressive treatment of HBV in co-infected patients will hopefully lead to improved tolerability of antiretroviral therapy and decreased morbidity and mortality.

The goal of therapy for hepatitis B includes prevention of cirrhosis and other consequences of chronic liver disease. Therapy for HIV-HBV co-infected patients needs to be individualized. The liver-related mortality in HIV-HBV co-infected patients is 14-fold higher than that for either virus alone[4] and HIV-positive patients are 3 to 6 times more likely to develop chronic hepatitis B following occult infections rather than HIV-negative patients. HIV-HBV co-infection is associated with a higher rate of cirrhosis than HBV infection alone. In co-infected individuals HBV DNA and HBeAg levels tend to be higher; ALT and AST levels are lower; and there is a lower rate of spontaneous HBeAg seroconversion.[5] Co-infected patients have accelerated histologic progression of liver disease, although there are conflicting data on the impact of HBV on HIV infection.[6] While some studies have shown an increased rate of HIV progression to AIDS among individuals with markers of exposure to HBV (anti-HBc), others have not shown any change in the progression of HIV disease or survival.[7,8,9,10]

CHRONIC HEPATITIS B THERAPY

The overall aim of management of chronic HBV is to prevent progression of liver disease to cirrhosis and HCC. Since HBV replication is important, effective therapy should suppress HBV DNA to the lowest levels possible. Molecular assays such as PCR enables the accurate monitoring of HBV DNA at levels as low as 100-1000 copies/mL and should ideally establish a patient's baseline HBV DNA prior to treatment, and thus monitor response to antiviral therapy or viral rebound associated with resistance. That is, as therapy is extended to more HBeAg-negative chronic HBV individuals, the use of HBV DNA testing will be increasingly incorporated into clinical decision-making.

The threshold level of HBV DNA for determination of candidates for therapy is $\geq 10^5$ copies/mL for patients with HBeAg-positive chronic hepatitis B.[11] Patients should also have elevated ALT levels and/or evidence of liver injury on liver biopsy. A lower serum HBV DNA threshold is needed for patients with HBeAg-negative chronic hepatitis B and those with decompensated cirrhosis. Current guidelines recommend thresholds of $\geq 10^4$ copies/mL and $\geq 10^3$ copies/mL for these patient groups, respectively. Individuals with serum HBV DNA of less than 10^5 are deemed inactive carriers, whereas those with levels greater than 10^5 copies/ml have chronic infection with ongoing viral activity and more potential for progressive liver disease. HBV levels are used to guide therapy but other factors such as liver histology are also required.

Interferon alpha (IFN), lamivudine and adefovir are approved as initial therapy for chronic hepatitis B, although the advantages and disadvantages of the three therapies should influence their selection.

(i)Combination therapy

Combination therapy, at least theoretically, is likely to be more effective than monotherapy in suppressing viral replication and may decrease or delay the emergence of drug resistance. It may be of particular value in decompensated cirrhosis. Several large studies are underway exploring the use of two nucleoside/nucleotide antiviral agents or an antiviral plus IFN in compensated patients.

(ii)Pegylated Interferon

Peginterferon alfa-2a has a long mean half-life of 80 h, sustained plasma drug concentrations and little peak-to-trough fluctuation.[12] The potential for development of viral resistance with lamivudine and possibly adefovir is the critical step in allowing for treatment discontinuation. In a recent study HBeAg-negative chronic HBV individuals had significantly higher rates of response, sustained for 24 weeks after the cessation of therapy, with peg interferon alfa-2a (180 µg once weekly) plus lamivudine than with lamivudine alone (100 mg daily).[12] The rates of sustained suppression of HBV DNA to below 400 copies per milliliter were 19 percent with peg interferon alfa-2a monotherapy, 20 percent with combination therapy, and 7 percent with lamivudine alone. Loss of hepatitis B surface antigen occurred in 12 patients in the peginterferon groups, compared with 0 patients in the group given lamivudine alone.

(iii)Lamivudine and concept of resistance

Selection of resistant HBV during lamivudine treatment is a multifactorial process in which the replicative capacity of the virus, host immune response (reflected by pretreatment ALT values), and the HBV genotype itself play important roles.[13] Thus, different mutational patterns of resistant HBV genotypes A and D may have an impact on the treatment strategies for lamivudine-resistant HBV.[14]

In patients with HBV infection alone, resistance ranges from 24% in the first year of treatment to 66% by year 4; in HIV-HBV-coinfected patients, resistance is more frequent, with 47% resistant to lamivudine at year 2 and 90% at year 4.[15,16,17]

(iv)Emtricitabine (FTC)

FTC was approved in July 2003 by the FDA for the treatment of HIV and appears to be a potential useful drug in the management of HIV-HBV co-infection. FTC is a fluorianted nucleoside reverse transcriptase inhibitor, similar to lamivudine, but with a longer half life, that produces similar suppression of HBV DNA in HIV co-infection as that observed in patients with HBV alone. What is encouraging is that the safety profile of FTC in HIV-HBV-coinfected patients was similar to that observed in patients infected with HBV alone. FTC is well tolerated and has potent anti-HIV activity, although due to cross-resistance, it is not indicated after lamivudine failure.[18] Previous FTC studies have shown significant in vitro activity against HBV. This was confirmed from two controlled randomized clinical trials with different dose ranges of FTC (25 to 300 mg) which demonstrate a 3.4 log10 reduction of viral HBV load in a total of 147 patients, performed for the treatment of HIV (n = 52).[18,19]

(v)Adefovir

Adefovir (a phosphorylated nucleotide analog of adenosine monophosphate) acts by inhibiting HBV DNA polymerase, thereby causing HBV DNA chain termination. Adefovir is indicated in the treatment of chronic HBV in adults with evidence of active viral replication and either evidence of elevation of ALT or AST, or histologi-

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IN MEMORIAM: DR. STEPHEN TABET 1961-2004

The 1st Annual Stephen Tabet Prison Medicine Advocacy Award

This award will be given in memoriam of Dr. Stephen Tabet, correctional physician and advocate, who passed away this past July. The presentation of this award will take place at the NCCHC on Saturday, November 12, 2004 following the IDCR pre-conference seminar.

The individual presented with this award will have demonstrated selfless commitment to HIV-positive incarcerated persons, and show a continued interest and passion for caring for those with HIV in corrections in the future.

This individual must be dedicated not only to improving prison health care, but must also serve as a mentor to other health care providers.

This individual must present with a compassion for treating the most challenging, most underprivileged patients. Nominations for this award should be sent to idcr@brown.edu by November 6, 2004.

SPOTLIGHT…*(continued from page 6)*

cally active disease, and is given orally, once daily, at a dose of 10mg. Treatment with adefovir has lead to histologic improvement, as defined by as a decrease in the knodell necroinflamatory score and HBeAg seroconversion. Significant in the findings during clinical trials of adefovir is the low adefovir-associated HBV resistance; the incidence of adefovir resistance-associated mutations was 0% at 48 weeks, 2% at 96 weeks, and 1.8% at 144 weeks. Adefovir has demonstrated anti-HBV activity in patients with HBV containing lamivudine resistance-associated mutations.[20]

(vi)Tenofovir (TDF)

There is an increasing interest in TDF in the treatment of HBV-HIV co-infection. The anti-HIV properties of TDF found lacking in adefovir, coupled with its excellent tolerability in advanced HIV infection, makes TDF more attractive for the patient with limited therapeutic options in which the goal of antiretroviral therapy is to lower the HIV RNA load. Preliminary results demonstrate the anti-HBV efficacy of TDF (300mg) in HIV-infected patients with lamivudine resistance after 9 months of antiretroviral therapy.[20] Although not approved by the FDA for the treatment of HBV, TDF has excellent activity against HBV and many co-infected patients have been treated with TDF plus lamivudine. It is likely that we will see studies looking at the combination of FTC and TDF in the management of HIV-HBV-coinfected individuals. Newly emerging data demonstrate the need for appropriate dosing to avoid renal toxicity of TDF.[21] This is a rare occurrence; however, when this toxicity does occur, it resembles adefovir renal toxicity, which is a Fanconi-like syndrome that is reversible.

(vii)Entecavir (ETC)

ETC is a novel guanine analogue which is active against the HBV DNA polymerase and thus prevents priming, negative strand formation, and positive strand synthesis.[22] ETV has been proven to be effective in patients previously treated with interferon and against lamivudine-resistant HBV strains.[23] These findings must be confirmed in the larger, ongoing, worldwide phase 3 studies of ETC in nucleoside analogue-naïve patients and in lamivudine-refractory patients.

In conclusion, there have been many changes in the therapies associated with treatment of hepatitis B and HIV-HBV co-infection. Ultimately, the goals are to achieve a significant decline in the morbidity and mortality attributed to HBV infection among those infected with HIV.

Disclosures

**Nothing to disclose.*
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Save the Dates

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In The News

Study Shows Hepatitis B Transmission High in R.I. Prisons
In the first study to gauge the risks of contracting HIV and hepatitis B virus (HBV) infections in Rhode Island prisons, Brown University researchers found that a significant number of men acquire HBV while incarcerated-a finding that led the team to call for prison-wide vaccinations. To conduct the study, blood was analyzed from mandatory, consensual tests taken when inmates entered the Adult Correctional Institute in Cranston, R.I. Researchers gathered test results on 4,269 men sentenced between 1998 and 2000. Nearly two percent of incoming inmates tested positive for HIV. Twenty percent had SEROLOGIC EVIDENCE OF HBV and 23 percent had serologic evidence of HCV infection. To determine if transmission of these infections was occurring within the prison, researchers retested 446 men who were still incarcerated at least one year later. While none of the inmates contracted HIV infection, and less than one percent of inmates contracted HCV, almost three percent of inmates contracted HBV infection-a rate higher than indicated in previous prison research and markedly higher than the national average. Since the time of the study, routine vaccination has been expanded to the men's division of the R.I. Department of Corrections (a vaccination program was already in place for women), making the state one of only a few in the nation that routinely offers hepatitis B vaccinations to all its inmates.
NATAP - www.natap.org

Roche Seeks Approval for Pegasys Use for Chronic Hepatitis B
Roche recently announced the submission of a new supplemental license application with the U.S. Food and Drug Administration to market Pegasys® (peginterferon alfa-2a) for the treatment of chronic hepatitis B (CHB). Pegasys received FDA approval for the treatment of chronic hepatitis C in October 2002. Roche submitted this filing based on Pegasys data from its comprehensive clinical development program in hepatitis B. This program involved more than 1,500 patients with chronic hepatitis B infection from three separate studies. One phase II study compared Pegasys to standard interferon in patients with HBeAg-positive disease. Two phase III studies compared Pegasys to Epivir-HBV® (lamivudine) in patients with HBeAg-positive disease and in patients with HBeAg-negative disease (a more difficult to treat mutation of the hepatitis B virus), respectively. Researchers found that peginterferon alfa-2a alone or in combination with lamivudine resulted in higher rates of sustained response (19% and 20%, respectively) among patients with HBeAg-negative chronic hepatitis B than did lamivudine monotherapy (7%). The two studies are the largest trials conducted to date in the patient populations infected with either variation of hepatitis B.
NATAP - www.natap.org
New England Journal of Medicine

New Nucleoside Analogue Against HBV: New Answers, New Questions
In a phase II dose finding study of clevudine (L-FMAU), a new pyrimidine nucleoside analogue, 32 patients were treated with 10, 50, 100, or 200 mg clevudine once daily for 28 days. A profound -2.5 to -3.0 log10 reduction of hepatitis B virus (HBV) DNA was observed at all doses. Viral suppression was associated with a transient alanine aminotransferase increase in some patients, particularly at the 100 mg dose. Suppression was unusually prolonged in most patients (-1.2 to -2.7 log10 at six months post-dosing) and resulted in HBe antigen loss and anti-HBe seroconversion in an unexpectedly high number of six and three out of 27 patients, respectively. The mechanisms of activity for this medicine remain unclear. Study authors question whether it is possible that this particular nucleoside analogue may have immunomodulatory or other additional effects, as well as the etiology of the transient alanine aminotransferase increases observed in some patients.
Marcellin et al. HEPATOLOGY. 2004;40:140-148.
NATAP - www.natap.org

Study: Tenofovir Disoproxil Fumarate Effective in Patients Coinfected with HIV/ HBV
Coinfection with HIV-1 increases the risk of HBV-associated progressive liver disease. Among individuals coinfected with HIV and HBV in two phase III randomized controlled trials, therapy with tenofovir DF has clearly demonstrated anti-HBV virologic efficacy. During 48 weeks of therapy with tenofovir DF, a mean reduction of 4 - 5 log10 copies/mL in the HBV DNA level was seen in antiretroviral therapy-experienced HIV-HBV-coinfected individuals with or without resistance to lamivudine. A similar reduction in the HBV DNA level was seen in antiretroviral therapy-naive HIV-HBV-coinfected individuals who received combination therapy with lamivudine and tenofovir DF as a component of their initial three-drug HAART regimen.
Gregory J. Dore et al. Jour Inf Dis. 2004;189:1185-1192
NATAP - www.natap.org

Resources

The CDC's website on Viral Hepatitis B
www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm

Hepatitis B Foundation
www.hepb.org

MedlinePlus: Hepatitis B
www.nlm.nih.gov/medlineplus/hepatitisb.html

Self-Assessment Test for Continuing Medical Education Credit

Brown Medical School designates this educational activity for 1 hour in category 1 credit toward the AMA Physician's Recognition Award. To be eligible for CME credit, answer the questions below by circling the letter next to the correct answer to each of the questions. A minimum of 70% of the questions must be answered correctly. This activity is eligible for CME credit through April 30, 2005. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. Correctional systems that have offered HBV vaccine to inmates have:
   a) Experienced an increase in HBV infection among inmates
   b) Experienced high percentages of participation by inmates
   c) Lost funding and have had to discontinue vaccination programs
   d) b and c
   e) All of the above

2. Seroprevalence studies among inmates have continued to document low rates of HBV markers. True or False.
   a) True
   b) False

3. The HBV vaccine was/is:
   a) First introduced in 1981
   b) Recommended by the CDC to all adults in correctional facilities
   c) Given at zero, one, six months, or alternatively, at zero, two, four months
   d) All of the above

4. According to a recent study of injection drug users, the percentage of previously incarcerated persons who injected drugs while incarcerated, is closest to:
   a) 0
   b) 20
   c) 40
   d) 80

5. All of the following statements are true except:
   a) HBV is found in blood, semen, and saliva.
   b) Fulminant hepatitis occurs in approximately 63%-93% of newly infected persons.
   c) HBV vaccine consists of three intramuscular doses.
   d) Two doses of HBV vaccine offers immunity in up to 85% of those vaccinated.

6. The majority of adults with chronic HBV are asymptomatic and are not capable of infecting others. True or False.
   a) True
   b) False

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