7-2005

IDCR: Infectious Diseases in Corrections Report, Vol. 8 No. 7

Infectious Diseases in Corrections

Brown Med
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INFECTIOUS DISEASES IN CORRECTIONS REPORT

FORMERLY HEPP Report

July 2005 Vol. 8, Issue 7

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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).

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HEPATITIS C IN CORRECTIONS: TESTING, TREATMENT AND CO-INFECTION

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DISCLOSURES: **Consultant: Schering, Roche, InterImmune. Grant/Research Support: Schering, Roche, Merck. Speaker's Bureau: Schering, Roche, GlaxoSmithKline, Merck*
***Nothing to disclose*
****Nothing to disclose*

Background
With an estimated worldwide prevalence of 2.2%, hepatitis C virus (HCV) is one of the most prevalent chronic viral infections in the world.[1] Incarcerated populations have dramatically higher rates of HCV infection than non-incarcerated populations. Approximately 2.0% of the United States (US) non-incarcerated population has been infected with HCV; 1.3% are chronically infected. In contrast, seroprevalence studies have found HCV infection rates ranging between 16-43%[2,3,4] among incarcerated populations; 12-35% of inmates have chronic infection.

HCV is a viral infection transmitted primarily through blood and blood products. Approximately 75% of acutely infected patients will develop chronic infection, and 20% of those with chronic infection develop cirrhosis within 20 years.[6] While there is no vaccine for HCV, effective strategies for preventing transmission exist.[5] Additionally, the current standard-of-care treatment regimen, pegylated interferon (PEG IFN) alfa plus ribavirin (RBV), has demonstrated higher sustained virologic response (SVR) rates, defined as the absence of HCV RNA in serum by a sensitive test at the end of treatment and six months later, compared to standard interferon. PEG IFN alfa plus RBV is safe and efficacious in both HCV mono-infected[7] and HIV/HCV co-infected patients.

Because nearly one-third of all HCV-infected persons pass through correctional facilities each year[8], and will eventually return to the communities from whence they came, providing HCV screening, testing, treatment and prevention education (including education regarding re-infection and basic primary prevention for those who do not test HCV-infected) within corrections could have important public health implications. Testing and, when appropriate, treating HCV-infected inmates could reduce disease transmission in the communities to which inmates return.

Testing
Currently, the United States Task Force for Preventive Services recommendations caution against routinely screening patients for HCV infection,[9] as screening tests have low positive predictive values (PPV) if the prevalence of the disease in the population being screened is less than 10%. Those recommendations do not apply to drug-using populations. The most efficient means of HCV transmission is through injection drug use; estimates of HCV prevalence for injection drug users (IDUs) are as high as 90% in some regions.[10] Since a large number of inmates have previously or currently inject drugs and because approximately one-third of HCV-infected persons pass through corrections every year, most experts recommend that prison inmates be screened for HCV infection.[11]

Accordingly, Centers for Disease Control and Prevention (CDC) recommendations regarding HCV screening in correctional settings includes the following statements: (1) All inmates should be questioned regarding risk factors for HCV infection during entry medical examinations, and those with risk factors should be tested for HCV; (2) The sensitivity of risk factor-based screening should periodically be determined by seroprevalence surveys, in combination with ascertainment of demographic and risk factor information. Serologic testing of expanded groups of inmates or all inmates is recommended when: (2a) self-reported history of risk factors alone identifies <75% of anti-HCV positive inmates or (2b) the prevalence of risk factors for HCV infection, including injection drug use, is known to be high (>75%), and a high prevalence (>20%) of HCV infection exists among inmates who deny risk factors.[5]

Persons who received a blood or organ transplant prior to 1992 should also be tested.[4] Although transmission from exposure to an infected sexual partner is less efficient, any individual who has had multiple sexual partners or who believes one of his or her partners is HCV-infected, should be tested. Lastly, persons with

Continued on page 2

WHAT'S INSIDE

HEPATITIS C IN CORRECTIONS... *(continued from page 1)*

unexplained elevations of aminotransferase levels, those who have ever been on hemodialysis, and those with HIV infection, should all be tested for HCV infection.[2]

Laboratory Diagnosis of HCV

Eighty percent of individuals with acute HCV infection are asymptomatic.[12] Identification of HCV infection is accomplished by initially testing for antibodies to HCV (anti-HCV.) To prevent false-positive results, testing should include an antibody screening assay, followed by confirmatory testing of positive results with a more specific assay (Table 1.) Because a positive test result for anti-HCV does not distinguish between acute and chronic infection, HCV RNA testing should be performed in individuals who test positive for anti-HCV. Chronic infection is defined as the presence of HCV RNA for a minimum of six months.[13]

HCV Genotypes

There are six different HCV genotypes. Because HCV genotype is the strongest predictor of response to treatment,[14] genotype should be determined in all HCV-infected persons prior to treatment. Studies indicate that individuals infected with HCV genotype 1 are the least likely to achieve a SVR, while those infected with genotypes 2 and 3 are much more likely to achieve a SVR.[1] It should be noted that 95% of HCV-infected African Americans are infected with genotype 1, while only 65% of non-African Americans are infected with genotype 1.[15] Two tests, which are not FDA-approved, are currently available for HCV genotyping. These include the Trugene HCV 5'NC Genotyping Kit (Visible Genetics) and the Inno LiPA HCV II (Innogenetics.) These tests fail to identify HCV genotype in less than 3% of HCV-infected persons, and may display a mixed genotype in 1%-4% of HCV-infected persons.[2]

Liver Biopsy

Various protocols exist in a number of correctional systems to determine who should receive a liver biopsy and tehse are not consistent among different state department of corrections. This point is important if liver biopsy is considered a prerequisite for treatment, because those who do not qualify for biopsy would not be considered candidates for treatment. The following criteria have all been used to determine who should receive a liver biopsy: (1) two elevated ALT levels greater than two times the upper limit of normal, at least three months apart; (2) one ALT level greater than two times the upper limit of normal; (3) one ALT level greater than 1.5 times the upper limit of normal; (4) any ALT elevation at any time (but not persistently normal ALT); (5) all HCV-infected persons. The California DOC offers liver biopsy to all HCV-infected persons 45 or older, regardless of ALT levels, while those younger than 45 must have elevated ALT levels. It should be noted that the available literature does not clearly lend support to any particular criteria as listed, and that decisions in individual cases should be guided by the totality of the clinical picture for each patient.

Liver biopsy results reveal information regarding the extent of fibrosis (staging) and degree of hepatic inflammation (grading), thus helping the patient and provider decide on the course, and urgency, of therapy.[16] Various scoring systems for defining staging and grading have been developed. The components of two of these scoring systems are shown in Table 2.

More-than-portal fibrosis on liver biopsy (Metavir score of ≥2 or an Ishak score of ≥3) is an important predictor of future progression of liver disease and the need for HCV treatment.[11] Scoring is usually provided in the pathology laboratory report.

Non-invasive tests, including the FibroSURE test and aspartate aminotransferase to platelet radio index (APRI), may be alternatives to liver biopsy. Both tests are limited in that they poorly differentiate between stages 1 and 2 fibrosis. Often this represents the cutoff wherein many protocols determine whether patients will or will not receive interferon/RBV therapy. Therefore, non-invasive tests are only helpful when severe liver damage or cirrhosis is the expected finding.

Because of decreased SVR rates in HCV genotype 1-infected patients, many clinicians obtain a liver biopsy for these patients to guide treatment recommendations. HCV genotype 2- and 3-infected patients have a higher likelihood of achieving a SVR and so some advocate treating all such patients, regardless of liver disease severity, and without liver biopsy. Current AASLD recommendations state that a liver biopsy should be performed, regardless of ALT levels, and for all genotypes, when the results will influence whether treatment is recommended. A biopsy is not required to initiate therapy. [7]

Table 1: FDA-Approved HCV Laboratory Tests

Antibody Screening Tests
◆ Abbott HCV EIA 2.0 (Abbott Laboratories)
◆ ORTHO HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics)
◆ VITROS Anti-HCV assay (Ortho-Clinical Diagnostics)
Confirmatory Tests
◆ Chiron RIBA HCV 3.0 SIA (Chiron Corp)
◆ AMPLICOR HCV Test, Version 2.0 (Roche Molecular Systems)
◆ COBRAS AMPLICOR HCV test (Roche Molecular Systems)

Table 2: HCV Scoring Systems

Stage	Metavir System	Ishak System
0	No fibrosis	No fibrosis
1	Periportal fibrosis expansion	Fibrous expansion of some portal areas, with or without short fibrous septae
2	Portal-portal (P-P) septae	Fibrous expansion of most portal areas, with or without short fibrous septae
3	Portal-central (P-C) septae	Fibrous expansion of most portal areas with occasional P-P bridging
4	Cirrhosis	Fibrous expansion of portal areas with marked bridging (P-P or P-C)
5	-	Marked bridging (P-P or P-C) with occasional nodules
6	-	Cirrhosis

Table adapted from: AASLD practice guideline: diagnosis, management, and treatment of hepatitis C.

Treatment

The current standard-of-care treatment regimen for HCV mono-infection and HIV/HCV co-infection is PEG IFN alfa plus RBV.[10] The two FDA-approved PEG IFN products; PEG IFN alfa-2a (Pegasys®, Hoffman-La Roche) and PEG IFN alfa-2b (Peg-Intron®, Schering-Plough Corporation) have demonstrated similar indicators of both treatment response and adverse events, but further studies are needed to compare the efficacy of the two products.[6,10]

If, at 12 weeks of treatment, the early virologic response (EVR) indicates that there has not been a 2 log decline in HCV RNA relative to baseline HCV RNA, the patient is unlikely to achieve a SVR and treatment should be discontinued.[17]

Treatment is not recommended for individuals under certain circumstances (Table 3.)

All HCV-infected patients should receive hepatitis A virus (HAV) and HBV vaccinations if they are non-immune (see this months IDCR-o-gram.)

Drug Side Effects

Side effects of PEG IFN alfa may include neutropenia, thrombocytopenia, depression, hypothyroidism, irritability, concentration and/or memory disturbances, fatigue, headaches, nausea, vomiting, weight loss, insomnia, and flu-like symptoms.[18]

Side effects of RBV may include hemolytic anemia, fatigue, and rash. Pregnant women should not be prescribed RBV, as it can result in birth defects. During treatment and for six months post-treatment, men and women should use contraception methods to avoid pregnancy.[11] RBV is contraindicated in patients on dialysis and in patients who have severely elevated creatinine clearance.

Continued on page 3

HEPATITIS C IN CORRECTIONS... *(continued from page 2)*

All adverse effects tend to decrease in severity after the initial few weeks of treatment, and may be managed with antidepressants, growth factors (i.e. epoetin, granulocyte colony-stimulating factor), and analgesics.[10]

Treatment Failure

Individuals who fail to achieve a SVR after initial treatment may be able to achieve a SVR with a re-treatment regimen of PEG IFN plus RBV. A SVR is typically achieved in 25%-40% and 10% of patients who failed to respond to interferon alfa monotherapy and interferon alfa plus RBV, respectively.[19] AASLD guidelines state that "retreatment with PEG IFN plus RBV should be considered for non-responders or relapsers who have significant fibrosis or cirrhosis and who have undergone previous regimens of treatment using non-pegylated IFN. Retreatment with PEG IFN plus RBV with the aim of eradicating HCV is not indicated in patients who have failed to respond to a prior course of PEG IFN plus RBV, even if a different type of PEG IFN is administered."[11]

Normal ALT Levels

The Federal Bureau of Prisons (FBOP) protocol currently states that the management of HCV-infected inmates should be restricted to those inmates with an ALT level greater than or equal to two times the upper limit of normal.[20] However, in a given patient, ALT levels may fluctuate. Additionally, when other laboratory abnormalities exist (i.e. low platelet count) further evaluation and/or treatment are indicated. Current controversy exists regarding whether patients, in whom all biochemical markers of liver injury are normal and in whom ALT levels are normal on multiple occasions, should be treated.

The 2002 National Institutes of Health (NIH) consensus conference statement on management of HCV-infected patients with persistently normal ALT levels stated, "Approximately 30% of patients with chronic HCV infection have normal ALT levels…Although most of these patients have mild disease, histologically, some may progress to advanced fibrosis and cirrhosis."[21]

A recent study evaluated the efficacy and safety of antiviral therapy for chronic HCV-infected patients with persistently normal ALT levels. Patients with at least three normal ALT values over an 18 month period were randomized to receive one of the following: PEG IFN alfa-2a 180 mg/wk plus RBV 800mg/day for 24 weeks, the same combination for 48 weeks, or no treatment. All patients were monitored for 72 weeks. An SVR was achieved by 30% and 52% of the patients treated for 24 and 48 weeks, respectively. No patient achieved a SVR in the untreated group. HCV genotype 1-infected patients achieved SVR rates of 13% and 40% with 24 and 48 weeks of treatment, respectively. HCV genotype 2- or 3-infected patients achieved SVR rates of 72% and 78% with 24 and 48 weeks of treatment, respectively. While there are no current recommendations regarding whether to treat patients with normal ALT levels, study authors concluded that the efficacy and safety of PEG IFN alfa-2a plus RBV for chronic HCV-infected patients with normal ALT levels is similar to that in patients with elevated ALT levels.[22]

HIV/HCV Co-Infection

Among HIV-infected individuals living in the US, nearly 30% are co-infected with HCV.[vi] HCV is common in HIV-infected individuals because of the shared routes of transmission of the two diseases. While HCV infection often takes 20 to 30 years to progress to cirrhosis, the course of HCV is accelerated in the presence of HIV.[vi] Aggressive treatment of HIV/HCV co-infected individuals is warranted, given the potential for increased immunosuppression and decreased response to antiretroviral therapy (ART.)

In the AIDS Pegasys Ribavirin Co-Infection Trial (APRICOT) involving HIV/HCV co-infected patients, 40% and 62% of HCV genotype 1- and HCV genotype 2- or 3-infected patients, respectively, achieved a SVR. These are the highest SVR rates among co-infected patients in any reported study thus far.[23] It should be noted that all participants in this study had well controlled HIV; viral load averaged 50 µg/ml and CD4 count averaged 500 cells/ml. In co-infected patients, the duration of HCV therapy is increased from 24 to 48 weeks for genotype 2- and 3-infected patients. Because of a high relapse rate for genotype 1-infected patients, extending HCV therapy from 48 to 72 weeks may improve therapy outcomes. For more information on co-infection, please refer to the case study in this month's issue.

Why Treat?

Treatment of chronic HCV infection has been shown to be cost-effective. In a recent study, a Markov model of disease progression was constructed to determine if the gain in SVR achieved with PEG IFN alfa-2a plus RBV would be worth the incremental cost. In the model, cohorts of patients received PEG IFN alfa-2a plus RBV for 48 weeks (genotype 1, genotype non-1 with fibrosis) or 24 weeks (genotype non-1 without fibrosis.) The model predicted that in HCV genotype 1-infected patients, PEG IFN alfa-2a plus RBV would increase life-years (LY) by .78 years and quality adjusted life years by (QALY)[i] by .67 years, compared with interferon alfa-2b plus RBV. The associated cost per LY and QALY gained would be $11,952 and $13,804, respectively. In HCV genotype non-1-infected patients, PEG IFN alfa-2a plus RBV would increase LY and QALY by 1.17 and 1.01 years, respectively, compared with interferon alfa-2b plus RBV; the associated cost per LY and QALY gained would be $4,132 and $4,772, respectively. The study authors concluded that PEG IFN alfa-2a plus RBV for the treatment of naïve adults with chronic HCV infection, regardless of HCV genotype, is cost-effective; halting the progression of disease and avoiding costly future morbidities largely offset costs associated with treatment.[24] Other studies have arrived at similar conclusions.[25]

Table 3: Treatment Recommendations

Treatment is not recommended for the following:

- Major, uncontrolled depression (interferons exacerbate depressive symptoms)
- Renal, heart, lung transplant recipient
- Any condition known to be exacerbated by interferon and RBV
- Pregnant women/women who are unable to comply with adequate contraception
- Severe concurrent disease (ie - severe hypertension)
- Known hypersensitivity to drugs used in HCV treatment

The correctional environment, with its high HCV prevalence rates among inmates, provides an opportunity to diagnose and treat populations at the highest risk of HCV infection. Because no formal national guidelines for the treatment of HCV within corrections exist, most guidelines are system-specific. Research on the implementation of cost-effective HCV screening, testing, and treatment among the incarcerated population is essential.

[i] ***Editor's Note:*** *QALY: A year of life adjusted for its quality or its value. A year in perfect health is considered equal to 1.0 QALY. The value of a year in ill health would be discounted.*

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Letter from the Editor

Dear Colleagues,

While providing medical care to increasing numbers of inmates, many of us often lose sight of the dramatic increase in incarceration that has occurred in the United States over the past two decades. This steady increase in the numbers of incarcerated individuals has given the United States the dubious distinction of being the world's lead incarcerator; we have a greater proportion of our population behind bars than any other country. Most of this increase in incarceration is related to the "war on drugs", which might be more aptly named the "war on drug users", as that is the population being locked up. As a consequence, there is an increased prevalence of many diseases associated with addiction in incarcerated populations. Chief among these is HCV infection. HCV is most efficiently and most commonly transmitted through shared injection equipment among injection drug users. With more than one out of every five inmates infected with HCV, this is clearly a critical problem to address.

This month, Cassidy, Guidry and Colton tackle the issue of routine screening for HCV. If people become aware of their diagnosis of HCV, they can, at a minimum, learn to avoid alcohol, the most preventable risk factor for progression to cirrhosis, be vaccinated against Hepatitis A and B and educated about how to prevent transmission to others. They can also be prepared for clinical evaluation and treatment. Current therapeutic options, although effective, are associated with predictable toxicities, are expensive, prolonged, and often fail to cure patients. Hopefully, in the not too distant future, more effective, less toxic and less expensive therapies will become available. If more people are aware of their infection, more people will be prepared to benefit from newer treatments. Identifying a significant number of the approximately four million individuals in the U.S. infected with HCV could also lead to an increased demand for resources to be devoted towards developing and implementing better therapies. Taylor and Mileno present a case highlighting the independent issues in HIV/HCV co-infection, which is critically important given the accelerated course of HCV disease in people dually infected with HIV and our IDCR-o-gram describes HCV management and vaccination schedules.

More people with chronic HCV pass through correctional systems each year than any other single institution. HCV, more than any other disease, underscores the need to view the provision of public health and health care as a primary mission of correctional facilities.

Respectfully,
Jody Rich*, MD, IDCR Editorial Board
*Disclosures: *Major Stockhlder: Repligen, Alkermes, Isis*

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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.

IDCR-O-GRAM: Hepatitis C Management Algorithm

Anti-HCV (2nd OR 3rd generation EIA)
Qualitative HCV RNA

NEGATIVE

Repeat Qualitative HCV RNA in 6 months to confirm

POSITIVE

Vaccinate for hepatitis A and/or hepatitis B as needed. See chart below.

Obtain HCV genotype, CBC, hepatic function panel, basic metabolic panel, PT, PTT, ferritin, iron, transferrin saturation, TSH, pregnancy test, HAV Ab total (lgG and lgM), HBsAb lgG and HBsAg, consider abdominal imaging. Consider liver biopsy.

pegylated interferon alfa-2b
1.5 ug/kg SC once/week
Plus
ribavirin 800mg PO daily
(For genotype 1 consider weight-based ribavirin dose)

OR

pegylated interferon alfa-2a
180 ug SC once/week
Plus
ribavirin 1.0-1.2g PO daily for genotype 1and 4
ribavirin 800mg PO daily for genotype 2 and 3

Refer to package inserts for dose.

During Treatment: CBC at week 2, then CBC, hepatic function panel and basic metabolic panel each month. TSH and HCV RNA every three months as clinically indicated.

Treatment Week 12
Quantitative HCV RNA

Negative or >2 log decrease in HCV RNA from baseline

Genotype 2 or 3*
Continue for an additional 12 weeks
(Total treatment of 24 weeks)
If patient has advanced hepatic fibrosis consider 48 weeks of therapy

<2 log decrease in HCV RNA from baseline

Viral response unlikely (≤1%)
Consider D/C or long-term PEG-IFN in patients with significant fibrosis

Treatment Week 24
Qualitative HCV RNA

Negative

Additional 24 weeks of therapy (total treatment of 48 weeks)
If week 12 HCV RNA positive consider longer duration of therapy

Positive

Stop therapy

*Editors' Note:*Among HCV genotype 2- or 3-infected patients in whom HCV RNA is undetectable after four weeks of therapy, 12 weeks of treatment is as effective as 24 weeks. Mangia, et al. NEJM. 2005; 352:2609-17.*

Adult Hepatitis Vaccination Schedules

Type	**Vaccine**	**Age**	**Dose**	**# Dose**	**Schedule**** (months)
Hepatitis A	Havirx	19+	1440 EI.U	2	0, 6-12
Hepatitis A	Vaqta	19+	50u	2	0, 6-12
Hepatitis B	Engerix-B	20+	20ug	3	0, 1, 6
Hepatitis B	Recombivax HB (R)	20+	10ug	3	0, 1, 6
Hepatitis A/B combination	Twinrix (R)	18+	720 EI.U Havrix /20ug Energix-B	3	0, 1, 6

***Editor's Note: In corrections, dosing schedules may be reduced to 0, 1, 4 months. CDC. MMWR. 2004; 53(3):681-3.*
Hepatitis B Doses and Schedules. http://digestive.niddk.nih.gov/ddiseases/pubs/vaccinationshepab/#B-doses Last accessed 11 July 2005.
Adapted from Hepatitis Resource Network, www.h-r-n.org

ASK THE EXPERT: An HIV/HCV co-infected ex-inmate in need of anti-HCV treatment

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***Disclosures:** *Grant research support, speakers bureau, Roche Laboratories*
***Nothing to disclose*

***CASE:** A HIV/HCV co-infected 49 year-old male presented to a dedicated HIV/HCV co-infection clinic for evaluation of the extent of liver disease and need for anti-HCV treatment. His CD4 count was 365 cells/mm^3, CD4 percentage 28.1% and HIV-1 viral load 195 copies/ml. Antiretroviral medications included efavirenz 600mg at bedtime, lamivudine 150mg twice daily and stavudine 40mg twice daily. The patient had been diagnosed with HIV and HCV six years prior while in federal prison and began antiretroviral therapy at that time. He reported a 20-year history of injection drug use involving heroin and cocaine along with alcohol abuse. He denied any drug or alcohol use in the prior seven years and was active in Narcotic's Anonymous (NA). He had been treated with fluoxetine 10 years earlier when he became depressed following the death of his partner. He had suffered multiple stab wounds to the chest 20 years earlier. He was a veteran of the Vietnam War. He was working full time. He had presented twice before during the prior two years for evaluation for anti-HCV treatment but had declined pharmacotherapy due to concerns about relapse of addiction and depression. He had recently attended a group education session on the natural history of HCV in HIV-seropositive persons and the benefits and potential risks of therapy.*

On physical exam, vital signs were within normal limits and the patient's affect was bright. There was no icterus, hepatomegaly, splenomegaly, abdominal mass, shifting dullness, lower extremity edema, jaundice or palmar erythema. There were no spider angiomas. The remainder of the physical exam was unremarkable. ALT and AST were elevated at 124 IU/mL and 82 IU/mL, respectively. HCV genotype was 3a. HCV RNA was 396,000 IU/mL. Laboratory tests including BUN, creatinine, electrolytes, CBC with differential, albumin, alkaline phosphatase, total bilirubin, prothrombin time, iron studies, TSH and urinalysis were within normal limits.

With a genotype of 3a, estimated duration of infection of 27 years (based on first year of injection drug use), elevated ALT, low HCV viral load, well-controlled HIV and no contraindications to anti-HCV pharmacotherapy, he was strongly encouraged to commence anti-HCV treatment with the goal of achieving a sustained virologic response (SVR). Given his reluctance, a liver biopsy was performed to determine the extent of fibrosis in the hopes of motivating him to be treated. When the biopsy demonstrated stage 3 of 4 fibrosis (by Batts-Ludwig criteria), he agreed to undergo anti-HCV treatment.

Q: How should HIV/HCV co-infected patients be treated for HCV?
Results from trials of pegylated interferon (PEG IFN) plus ribavirin (RBV) in co-infected patients demonstrate that this regimen is effective and relatively well-tolerated in HIV-infected individuals.[1-3] Although SVR rates are lower than in HIV/HCV co-infected patients as compared to HCV mono-infected patients, eradication of HCV is achieved at significantly higher rates with the combination PEG IFN/RBV than with standard interferon plus RBV or PEG IFN alone. The only FDA-approved drugs for treatment of HCV in HIV/HCV co-infected patients are PEG IFN alfa-2a (Pegasys®, Hoffmann-La Roche) plus RBV (Copegus®, Hoffmann-La Roche), both of which were approved in February 2005.

Several sets of evidence-based anti-HCV treatment guidelines have been developed for co-infected patients.[5-9] These guidelines indicate that all HIV-infected persons should be screened for HCV. HCV RNA testing should be performed to confirm chronic infection in all persons with positive HCV serology and in those with negative antibody tests and unexplained liver disease. All co-infected persons should be considered for antiviral treatment. This should consist of combination PEG IFN alpha plus RBV for 48 weeks, irrespective of genotype. The primary goal of therapy is to eradicate HCV by achieving a SVR. A secondary goal is to delay histologic and clinical disease progression. These goals are consistent with goals for HCV-mono-infected populations. A further goal specific to HIV-infected populations is to suppress HCV disease activity to prevent antiretroviral-related hepatotoxicity. Co-infected individuals undergoing HCV treatment should be closely monitored due to the potential for adverse events.

The patient initiated HCV treatment with 180mcg/mL PEG IFN alfa-2a sq weekly and RBV 400mg orally twice daily. He agreed to weekly clinic visits for PEG IFN administration to optimize adherence, permit close monitoring and aggressive management of any side effects that should arise, and provide him with the best chance of completing a full course of treatment with the recommended dosing. Baseline laboratory values were as follows: CD4 470 cells/mm^3, CD4% 26.1%, HIV plasma viral load (PVL) 248 copies/mL, HGB 15.1 G/dL, HCT 42.9%, ANC 2200 K/uL, ALT 159 IU/mL, AST 99 IU/mL and HCV RNA (quantitative) 311,632 IU/mL. He felt well until week four when he complained of myalgias. Laboratory values were significant for an ANC of 700 K/uL. At week five he complained of fatigue. Hemoglobin had declined to 11.6 G/dL.

Q: Are there side effects of anti-HCV treatment specific to co-infected persons?
Hematologic side effects of anti-HCV treatment including anemia, neutropenia and thrombocytopenia can be more common and severe among co-infected persons than among HCV-mono-infected persons receiving PEG IFN plus RBV.[5-9] The dose-dependent reversible hemolytic anemia caused by RBV is compounded by the bone marrow suppressant effect of PEG IFN. In HIV-infected persons, these predictable effects may be exacerbated by underlying anemia due to nutritional deficits, concomitant disease or medications such as zidovudine (AZT).[10] Anemia may be managed with dose reduction of RBV, which can lower treatment efficacy, or by administration of erythropoietin alfa, which can increase hemoglobin levels and enable maintenance of higher RBV doses.[6,8,10] Neutropenia, due to PEG IFN-induced myelosuppression, typically occurs within the first several weeks of treatment and resolves with PEG IFN cessation. Neutropenia may be managed by dose reduction of PEG IFN, which can lower treatment efficacy, or with granulocyte colony stimulating factor (GCS-F).[6,8]

Consideration must be given to the potential for drug interactions between anti-HCV medications and nucleoside reverse transcriptase inhibitors (NRTIs). AZT, which can be associated with anemia, may interact synergistically with RBV to worsen anemia during anti-HCV treatment. Options include avoiding AZT during anti-HCV treatment or closely monitoring hemoglobin, especially during the first weeks of therapy.[7]

Mitochondrial toxicity, including fatal lactic acidosis, pancreatitis and hepatic steatosis are rare effects that may occur with the concomitant use of RBV and didanosine (ddI), stavudine (d4T) and other NRTIs.[6] The proposed mechanism is the inhibition of DNA polymerase gamma,

Continued on page 7

ASK THE EXPERT... *(continued from page 6)*

the enzyme responsible for mitochondrial DNA synthesis. The affinity to DNA polymerase gamma is greatest for ddI, followed by d4T and then other NRTIs. This inhibition can result in decreased oxidative phosphorylation and the accumulation of lactate. RBV, a guanosine nucleoside analogue, can raise levels of intracellular ddATP, the active metabolite of ddI, increasing the risk for ddI-related mitochondrial toxicity. Consequently, co-administration of RBV and ddI is no longer recommended.[5-9] Additionally, cirrhotic co-infected patients receiving ddI may be at risk for hepatic decompensation.[11]

The role of d4T in the development of lactic acidosis is possible, but to a lesser extent than with ddI. The combination of RBV plus d4T may cause severe weight loss, mimicking the rapid progression of lipoatrophy, possibly due to the potentiation of mitochondrial damage in subcutaneous fat.[6] It may be beneficial to switch to an alternate antiretroviral agent.[6] *This potential risk was discussed with the patient and he was given the choice of continuing d4T or substituting an alternate NRTI. He elected to continue d4T and did not develop complications related to this medication with anti-HCV therapy.*

The patient's neutropenia and symptomatic anemia were supported with the use of erythropoietin alfa and GCS-F in an attempt to avoid dose reduction or treatment termination. He received a total of six erythropoietin alfa doses and eighteen GSC-F doses. He completed his recommended treatment course with no missed PEG IFN doses and no dose reductions of either PEG IFN or RBV; adherence to weekly visits for PEG IFN injections was 100%. He worked full-time throughout the course of therapy. His HCV RNA was undetectable at week 12 of treatment and remained undetectable through the end of treatment. At the end of treatment his laboratory values were as follows: CD4 385 cells/mm^3, CD4 % 27.5%, HIV PVL <75 copies/mL, HGB 15.2 G/dL, HCT 43.2%, ANC 2800 K/uL, ALT 41 IU/ mL, AST 33 IU/mL and HCV RNA PCR <50 IU/mL. Six months after treatment completion his HCV RNA PCR remained <50 U/mL, consistent with a SVR. Eighteen months after treatment, his HCV RNA remains non-detectable and he is thrilled with his accomplishment.

Q: How can the patient's PVL and CD4 changes be explained?

The patient's HIV RNA became non-detectable during the course of anti-HCV therapy, while the absolute CD4+ cell count declined by 85 cells/mm^3 and the CD4+ percentage increased slightly. These findings are consistent with those of HCV treatment studies in co-infected patients; individuals with detectable HIV RNA at baseline receiving PEG IFN experienced a reduction in HIV RNA, suggesting a positive impact on HIV replication,[3,5] and the interferon-induced reduction in absolute CD4+ count did not impact stability of the CD4+ percentage nor lead to development of opportunistic infections.[5] HIV PVL and CD4 counts/percentages return to baseline levels within several weeks of treatment cessation. PEG IFN plus RBV does not appear to have a negative impact on control of HIV.

Q: How was the patient's history of addiction addressed?

Injection drug use is the greatest risk factor for HIV/HCV co-infection.[12] Nevertheless, active or recent drug use are among the main reasons that co-infected persons are not being treated for HCV, given theoretical concerns about addiction relapse or exacerbation and the potential for re-infection.[18-21] Populations with HIV, HCV, and addiction have increased rates of depression and other psychiatric comorbidities.[18-21] Additional concerns thus include whether interferon may induce psychiatric symptoms including depression and/or suicidal tendencies.[17] Existing data about HCV treatment for drug-involved persons is promising.[22-25] HCV-mono-infected substance using and non-substance using patients demonstrate similar HCV treatment outcomes.[22,26] Persons with depression and other psychiatric diagnoses may be safely and effectively treated with interferon-based therapies with appropriate supports.[22, 27-30]

This patient's substance use was remote. He was active in NA. He agreed to engage in multidisciplinary care, which has been recognized as an effective approach to HCV treatment for this population, to monitor and support his mood and addiction status during treatment.[31] A baseline psychiatric evaluation showed adjustment disorder with mixed mood, which was considered stable. The recommendation was to observe only. The patient agreed to monthly visits with the team psychiatrist for the duration of therapy, weekly PEG IFN medical visits and occasional meetings with his case manager. He complained of mild depression and irritability for four weeks but otherwise his course was uneventful. It should be noted that NA, while often an adequate self-help program, is not a comprehensive substance abuse treatment program. Such programs, when available, are an important component of the treatment of HCV, and this is consistent with most anti-HCV treatment guidelines.

Supervised PEG IFN therapy is a promising intervention, allowing for close monitoring for complications while facilitating adherence.[24] Optimizing adherence may also reduce the impact of demographic variables on SVR. One study in a correctional facility setting suggests that SVR rates in African-American persons, which have been lower than those of Caucasians,[32] seem to match those of Caucasians when adherence is optimized.[33] The incarcerated setting is an extreme example of supervised therapy but has been shown to be a feasible and opportune setting for HCV pharmacotherapy.[26,34]

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Acknowledgements

We thank Stacey Chapman RN, and Dawn Hanley, RN, of The Miriam Hospital, Providence, RI; and Gene Jacobs, D.O. and John Buonavolonta, R.N., at Family Service of Rhode Island, Providence, RI. This discussion was made possible in part through the following NIH grant: a T32 Training Grant from the National Institute on Drug Abuse to The Miriam Hospital (5 T32 DA13911).

SAVE THE DATES

American Correctional Association Summer Congress
August 7-10, 2005
Baltimore, MD
Visit: www.aca.org/conferences

Centerforce Inside-Out Summit
September 10-13, 2005
San Francisco, CA
Visit: www.centerforce.org/summit

ICAAC Meeting
September 21-24, 2005
New Orleans, LA
Visit: www.icaac.org

United States Conference on AIDS
September 28-October 2, 2005
Houston, Texas
Visit: www.nmac.org

IDSA Conference
October 6-9, 2005
San Francisco, CA
Visit: www.idsociety.org

National Conference on Correctional Health Care
October 8-12, 2005
Denver, Colorado
Visit: www.ncchc.org

Society of Correctional Physicians Annual Meeting
October 9, 2005
Denver, Colorado
Visit: www.corrdocs.org

Management of HIV/AIDS in the Correctional Setting: A Live Satellite Videoconference Series "Drug-drug Interactions and Metabolic Complications of HIV"
October 26, 2005
Visit: www.amc.edu/patient/hiv/hivconf/index.htm

RESOURCES

Hepatitis Resource Network:
www.h-r-n.org
www.cdc.gov/hepatitis

NEWS AND REVIEWS

HCV Patients Can Overcome Depression
Currently, the standard of care treatment of hepatitis C virus (HCV) infection is combination pegylated interferon (PEG IFN) plus ribavirin (RBV). However, this regimen may aggravate already present depressive and psychiatric symptoms in patients. Kraus, et al. sought to determine the efficacy of treatment with selective serotonin re-uptake inhibitor (SSRI) therapy during secondary prophylaxis (re-treatment) in patients with chronic HCV. All study participants were previously unsuccessfully treated with interferon (IFN) therapy. Seventeen patients in two groups (prophylaxis and reference) were included. During initial IFN therapy (before SSRI prophylaxis), all eight patients, who were later assigned to the prophylaxis group during re-therapy, developed signs of a major depressive episode, according to DSM-IV criteria. During re-therapy, patients in the prophylaxis group received prophylactic SSRI treatment three weeks before beginning antiviral therapy; patients in the reference group received antiviral therapy, but did not receive SSRI therapy. With concomitant SSRI therapy, seven of eight patients in the prophylaxis group were able to complete PEG IFN re-therapy. None of the patients had to discontinue re-therapy due to psychiatric side effects. Kraus, et al. concluded that patients with a history of IFN-induced major depression may be safely re-treated with PEG IFN plus RBV with concomitant SSRI prophylaxis.
Kraus M, et al. Journal of Viral Hepatitis. 2005; 12(1):96-100.

Peginterferon alfa-2a Doesn't Alter Methadone Pharmacokinetics
Sulkowski, et al conducted a study to quantitatively evaluate the effects of peginterferon (PEG IFN) alfa-2a on the pharmacokinetics of methadone in patients with chronic HCV who were receiving a stable methadone maintenance regimen. The 24 subjects enrolled in the study continued their ongoing daily methadone maintenance therapy regimen and received 180 ug PEG IFN alfa-2a sq once weekly for four weeks. The measured pharmokinetic parameters of methadone were no different after four weeks of dosing than at baseline, despite that the four-hour methadone levels were increased by 10-15%. Sulkowski, et al. conclude that concurrent treatment with methadone is not a contraindication to therapy with PEG IFN alfa-2a for chronic HCV and that dose adjustments are not required.
Sulkowski M, et al. Clinical Pharmacology & Therapeutics. 2005; 77(3): 214-24.

Effective Treatment for HCV Non-Responders Examined
A recent retrospective study examined the safety and efficacy of re-treating HCV non-responders. Fifty patients previously treated with PEG IFN alfa-2 plus RBV, who did not achieve a >2 $\log_{10}$ decrease in HCV RNA at week 12, were retreated with 15 ug IFN alfacon-1 SQ daily plus 50 ug IFN gamma-1b SQ three times per week for 48 weeks. Thirty-four percent of patients achieved a sustained virologic response after re-treatment. A larger, dose-finding study of this combination treatment is ongoing.
Leevy V, et al. Poster S1537. Digestive Disease Week. May 13-19, 2005. Chicago, Il.

FDA Approves Once Daily Kaletra for Treatment-Naïve Patients
The U.S. Food and Drug Administration (FDA) approved the use of Kaletra (lopinavir [LPV]/ritonavir[RTV]) 800/200mg once-daily administration for the treatment of HIV infection in therapy-naïve adult patients. Approval for the new regimen is based on data from two clinical trials comparing the safety and efficacy of LPV/RTV 800/200mg once-daily and LPV/RTV 400/100mg twice daily, for a duration of 48 weeks in antiretroviral-naïve HIV-1 infected patients. The new dosing is available in both liquid and soft gel capsule formulations. At this time, once daily Kaletra is not approved for treatment-experienced patients and is not approved for children.
www.natap.org

New HCV Drug Under Development
Idenix Pharmaceuticals, Inc, a biopharmaceutical company based in Cambridge, MA, announced on May 31 that it has completed enrollment of its phase IIb clinical trial of valopicitabine (NM283) with more than 170 HCV genotype 1-infected patients who previously failed at least three months of PEG IFN plus RBV therapy. The efficacy and safety of NM283 plus PEG IFN alfa-2a will be compared to the current stand of care regimen, PEG IFN alfa-2a plus RBV. The drug is being developed for use in both treatment naïve and treatment-experienced patients.
Idenix Pharmaceuticals, Inc. Press Release March 31, 2005. Available at: http://ir.idenix.com/phoenix.zhtml?c=131556&p=irol-newsArticle&ID=715016&highlight= Last accessed 7 June 2005.

Clinicians Should Monitor for Nephrotoxicity in TDF-Treated Patients
Tenofovir disoproxil fumarate (TDF), a nucleoside reverse transcriptase inhibitor (NRTI) approved for the treatment of HIV disease, may cause nephrotoxicity in TDF-treated patients with prolonged use, particularly in patients with advanced HIV disease, diabetes, or a decreased renal function at baseline. While TDF has not been associated with nephrotoxicity in clinical trials, adefovir dipivoxil, a related NRTI, has caused proximal renal tubular dysfunction at a dosage of 60-120 mg/day. Clinicians should assess renal function prior to initiating TDF therapy and continue to monitor renal function in all TDF-treated patients.
Gallant J, et al. Clinical Infectious Diseases. 2005; 40: 1194-98.

Self-Assessment Test for Continuing Medical Education Credit

Brown Medical School designates this educational activity for one hour in category one 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 December 31, 2005. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. Approximately what percent of inmates are infected with HCV?
   a. 10%
   b. 35%
   c. 75%
   d. 90%

2. The following statement regarding pegylated interferon/RBV is not true:
   a. Pegylated interferon + RBV is the current standard of care
   b. Pegylated interferon + RBV should be administered to all HCV-infected patients
   c. Pegylated interferon alfa-2a/RBV was approved in December 2002
   d. Pegylated interferon is available as alfa-2a, alfa-2b, and alfa-2c
   e. A and B
   f. B and D

3. It is recommended that inmates be screened for HCV infection. True or False?
   a. True
   b. False

4. Which of the following statements is supported by the literature?
   a. The course of HCV is accelerated in the presence of HIV infection.
   b. The course of HIV is accelerated in the presence of HCV infection.
   c. The course of HCV is slowed in the presence of HIV infection.
   d. The course of HIV is slowed in the presence of HCV infection.

5. The ethnic group that has the highest prevalence rate of HCV genotype 1 infection is:
   a. Caucasians
   b. African-Americans
   c. Pacific Islanders
   d. Hispanic

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