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eViralHepatitis Review
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HUMAN IMMUNODEFICIENCY VIRUS AND HEPATITIS C VIRUS COINFECTION

In this Issue...

Hepatitis C virus (HCV) coinfection is common in people with human immunodeficiency virus (HIV). Recent reports highlight the importance of continuing transmission of HCV among HIV–infected men who have sex with men (MSM) and of the impact of HCV infection relative to that of HIV infection on mortality rates in the United States. Further, in an era of effective antiretroviral therapy, liver disease caused by HCV is a clinically significant issue among patients infected with HIV, emerging in some studies as the second leading cause of death in this population. In this context, treating HCV infection is recommended for patients with coinfection who have significant hepatic fibrosis. New data indicate that people who have HIV/HCV coinfections may benefit from HCV treatment with regimens that include the HCV NS3/4A protease inhibitors telaprevir (TPV) and boceprevir (BOC), in combination with peginterferon plus ribavirin (Peg–IFN/RBV). However, the use of such regimens is complicated by drug–drug interactions with antiretroviral therapy, a paucity of published data, and the lack of an approved indication for treating patients with coinfections.

In this issue, we review the current literature describing the sexual transmission of HCV in HIV–infected MSM, the impact of HIV and HCV on mortality rates in the United States, and treating HCV with TPV or BOC in combination with Peg–IFN/RBV in patients infected with HIV.

LEARNING OBJECTIVES

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

- Describe the role of sexual transmission of hepatitis C virus (HCV) among human immunodeficiency virus (HIV)-infected men who have sex with men
- Discuss the relative impact of HIV, HCV, or both on mortality rates in the United States
- Identify the potential benefits and risks associated with the use of HCV NS3/4A protease inhibitors for treating HCV in persons infected with HIV

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- **Raymond T. Chung, MD,** has disclosed that he has received grants/research support from Gilead, Pfizer, Roche/Genentech, Merck, and Romark.

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THIS ISSUE

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Unlabeled/Unapproved Uses

The author has indicated that he will reference the unlabeled/unapproved uses of telaprevir and boceprevir for the treatment of HCV in HIV-infected persons in this presentation.

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COMMENTARY

With the development of effective therapies against human immunodeficiency virus (HIV), hepatitis C virus (HCV) infection has become a major cause of morbidity and mortality among people infected with HIV. Indeed, in many regions of the world, liver disease is the second leading cause of death in this population.[1] Accordingly, clinicians who care for patients infected with HIV must focus their attention on preventing new HCV infections in

persons with HIV who are not coinfected and also preventing progressive liver disease, end–stage liver disease, hepatocellular carcinoma, and death in those coinfected with HIV/HCV.

In the absence of an effective vaccine, preventing acute HCV infection among those infected with HIV can be achieved by reducing behaviors that place uninfected persons at risk for HCV infection. Given the ease of HCV transmission through contaminated blood, reducing the frequency of injection–drug use and/or reusing syringes or other injection equipment is essential.[2] Although the efficiency of sexual transmission of HCV is lower than that of HIV or hepatitis B virus (HBV) infection, recent studies clearly demonstrate that HCV is a sexually transmitted infection, particularly among HIV–infected men who have sex with men. The July 2011 Morbidity and Mortality Weekly Report (MMWR), reviewed in this issue, underscores the role of the sexual spread of HCV infection among HIV–infected MSM in the United States, which has significant implications for disease prevention. First, persons infected with HIV should be screened for HCV and, if the results are negative, educated about the risk for infection and reminded to use condoms to prevent sexual transmission. Second, persons who are HCV–seronegative and continue to engage in risky behaviors should undergo serial testing of serum alanine aminotransferase (ALT) levels and annual HCV antibody assays. Those with acute elevations in serum ALT levels should be promptly evaluated for causes of hepatitis, which should include HCV with antibody and HCV RNA testing. Identifying acute HCV infection is critical because antiviral therapy is significantly more effective at this stage and should be considered for patients who are acutely coinfected with HIV and HCV.

Among patients with HIV who are chronically infected with HCV, the priority is preventing liver disease. Importantly, the study by Ly and colleagues (reviewed herein) revealed that in 2007, more Americans died of HCV infection (~15,000) than of HIV infection (~12,700). This study also demonstrated that HIV coinfection was independently associated with an increased risk for dying of HCV infection (adjusted odds ratio [AOR], 1.8), highlighting the negative impact of HIV infection on the natural history of HCV. The delivery of effective treatment to cure HCV infection is needed to prevent the consequences of the disease in the coinfected patient population. Over the last decade, treatment with peginterferon (Peg–IFN) plus ribavirin (RBV) has been recommended for coinfected patients who are at the greatest risk for liver disease; however, the effectiveness of HCV treatment in this population has been disappointing. The reasons for this limited effectiveness include low rates of treatment initiation, high prevalence of relative and absolute contraindications to these agents, and low rates of sustained virologic response (SVR) among treated patients —particularly those coinfected with genotype 1 HCV infection and African Americans. As such, considerable interest has focused recently on using the HCV NS3/4A protease inhibitors telaprevir (TVR) and boceprevir (BOC), in combination with Peg–IFN/RBV, for treating HCV in patients infected with HIV.

In March 2012, SVR results from two small phase 2 studies of TVR (n = 60) and BOC (n = 98), both reviewed in this issue, in combination with Peg–IFN/RBV were presented at the 19th Conference on Retroviruses and Opportunistic Infections (CROI).

- In the TPV study, SVR 12 weeks after stopping therapy (SVR–12) was observed in 28 of 38 patients infected with genotype 1 HCV who were treated with TPV plus Peg–IFN/RBV (74%), vs. 10 of 22 treated with Peg–IFN/RBV alone (45%). Data from drug interaction studies in healthy volunteers and data from coinfected patients in this trial support the administration of TVR with atazanavir and raltegravir at the standard recommended TVR dose (750 mg every 7 to 9 hours), and with efavirenz at an increased TVR dose (1125 mg every 7 to 9 hours).
- In the BOC study, SVR–12 was observed in 37 of 61 patients infected with HCV genotype 1 HCV who were treated with BOC plus Peg–IFN/RBV (60.7%), vs. 9 of 34 treated with Peg–IFN/RBV alone (26.5%). In this study, patients received antiretroviral therapy that included ritonavir–boosted HIV protease inhibitors plus dual nucleoside reverse–transcriptase inhibitors. After this study was completed, however, drug interaction studies in healthy volunteers revealed that BOC can be coadministered with raltegravir, but coadministration of BOC with ritonavir–boosted HIV protease inhibitors or efavirenz is not recommended because of bidirectional drug interactions.

Taken together, these limited data indicate that the HCV protease inhibitors TPV and BOC, administered in combination with Peg–IFN/RBV, increase cure rates (SVR–12)

among individuals with HIV/HCV coinfection, with manageable toxicity and drug–drug interactions observed. In the context of rapidly evolving HCV drug development, however, strong consideration should be given treating patients coinfected with HIV and HCV in clinical trials of direct–acting HCV therapies or deferring HCV treatment in those with minimal HCV–related liver disease.

Commentary References

1. Data Collection on Adverse Events of Anti-HIV drugs (D:A:D)Study Group, Smith C, Sabin CA, et al. Factors associated with specific causes of death amongst HIV-positive Individuals in the D:A:D Study. *AIDS.* 2010l24(10):1537-1548.
2. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV–infected men who have sex with men: an emerging sexually transmitted infection. *AIDS.* 2010;24(12):1799-1812.

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SEXUAL TRANSMISSION OF HCV INFECTION AMONG HIV–INFECTED MEN WHO HAVE SEX WITH MEN

Centers for Disease Control and prevention (CDC). **Sexual transmission of hepatitis C virus among HIV–infected men who have sex with men — New York City, 2005–2010.** *MMWR Morb Mortal Wkly Rep.* 2011;60(28):945-950

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Worldwide, the major mode of HCV transmission is by percutaneous exposure to blood; the contribution of sexual transmission of HCV to the epidemic has been difficult to quantify. Over the last decade, however, reports from large European cities have identified clusters of acute HCV infection attributed to sexual practices among MSM infected with HIV. In July 2011, collaborators at the Centers for Disease Control and Prevention (CDC) and the Mount Sinai School of Medicine (New York, NY) described the role of sexual transmission in a matched case–control study involving 74 men infected with HIV who were identified with acute HCV infection in the absence of reported injection–drug use between 2005 and 2010. In this analysis, Dr. Daniel Fierer and colleagues described the characteristics of these 74 men, who presented with acute HCV infection asymptomatic ALT elevations were discovered (median peak ALT, 665 U/L). Importantly, the majority of men were taking antiretroviral therapy (74%) and had undetectable HIV RNA levels at the time of HCV diagnosis (68%).

Interestingly, phylogenetic analysis of the NS5B region from HCV strains recovered from 50 of the 74 patients identified five clusters of closely related HCV genotype 1a variants from 26 of the men with acute infections. To further understand risk factors for HCV infection in this population, the researchers conducted a matched case–control study involving 22 MSM infected with HIV who had acute HCV (cases) and 53 age–matched, MSM with HIV who did not have acute HCV (controls). Both case and control patients completed self–administered questionnaires regarding their sexual practices and drug–use behaviors over the preceding 12 months.

Results from the multivariable, conditional, logistic regression analysis found that

unprotected, receptive anal intercourse with no condom and with ejaculation of the partner (AOR, 23.00) and sex while high on methamphetamine (AOR, 28.56) were both significantly associated with acquiring HCV infection (P = .009 and P = .02, respectively). Although the findings of this analysis are limited by the reliance of self-report to identify risk behaviors and exclude injection–drug use, the authors concluded that HCV should be considered a sexually transmitted disease among MSM infected with HIV. Therefore, patients infected with HIV should be counseled on the risk for HCV transmission by sexual encounters and reminded to use condoms. Additionally, routine screening for HCV infection with antibody testing and serum ALT levels should be performed in MSM infected with HIV.

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VIRAL HEPATITIS AND INCREASING BURDEN OF MORTALITY

Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. **The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007.** *Ann Intern Med.* 2012;156(4): 271-278.

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In the United States, the National Center for Health Statistics compiles information on multiple–cause mortality from all death records according to a standardized format. To understand the relative contribution of HBV, HCV, and HIV infection, researchers from the CDC described trends in the incidence of death associated with these infections between 1999 and 2007. Interestingly, over this time period, the annual average age–adjusted mortality rate for HIV–related deaths decreased significantly (–0.21 deaths per 100,000 person-years; *P* = .001), whereas the annual average adjusted mortality for HCV–related deaths increased (+0.18 deaths per 100,000 person–years; *P* = .002); HBV–related deaths were unchanged. Importantly, in 2007, the mortality rate for HCV–related deaths exceeded that for HIV–related deaths. In that year, HCV infection was the underlying or contributing factor in 15,106 deaths; in contrast, HIV and HBV infections were the underlying or contributing factor in 12,734 deaths and 1815 deaths, respectively.

In their analysis, the researchers also evaluated the contribution of coinfection with one or more of these pathogens, as well as alcohol–related conditions. Among persons with HBV–related deaths, the most frequently reported comorbid conditions were HCV coinfection (30% of deaths), alcohol–related conditions (13%), and HIV coinfection (6%). In multivariate models, HBV–related deaths were strongly associated with chronic liver disease and alcohol, as well as HCV coinfection (AOR, 31.5) and HIV coinfection (AOR, 4.0). Among persons whose deaths were related to HCV, the most frequently reported comorbid conditions were alcohol–related conditions (19% of deaths), HBV coinfection (4% of deaths), and HIV coinfection (3% of deaths). The majority of HCV–related deaths were reported in persons between 45 and 64 years of age. In multivariate models, HCV–related deaths were strongly associated with age (45 to 54 years old; 55 to 64 years old, nonwhite race or ethnicity, male sex, chronic liver disease, and alcohol–related conditions, as well as HBV coinfection (AOR, 29.9) and HIV coinfection (AOR 1.8).

The authors concluded that by 2007, HCV had surpassed HIV as a cause of death in the United States, with the majority of deaths occurring in middle–aged adults. Alcohol use and HIV coinfection were important, potentially modifiable comorbid conditions contributing to HCV–related deaths. The researchers cautioned that because of limitations in cause–of–death data derived from death certificates, this study likely underreports deaths related to HBV and HCV. Despite this possible underreporting of the impact of viral hepatitis, the study underscores the critical and unrecognized public health impact of these pathogens. Additionally, the analysis provides further evidence that HIV coinfection is strongly linked to both HBV– and HCV–related deaths, highlighting the medical significance of these infections in patients infected with HIV.

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TELAPREVIR PLUS PEGINTERFERON AND RIBAVIRIN IN HCV/HIV–COINFECTED INDIVIDUALS

Dieterich D, Soriano V, Sherman K, et al; on behalf of the Study 110 Team. **Telaprevir in combination with pegylated interferon-a-2a+RBV in HCV/HIV-co-infected patients: a 24-week treatment interim analysis**. Presented at: 19th Conference on Retroviruses and Opportunistic Infections; March 5-8, 2012; Seattle, Washington. Abstract 46.

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In May 2011, TVR, an HCV NS3/4A protease inhibitor, was approved by the US Food and Drug Administration (FDA) for treating genotype 1 chronic HCV infection, in combination

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with Peg-IFN/RBV. At the time of FDA approval, however, the safety and efficacy of TVR plus Peg-IFN/RBV in HIV/HCV–coinfected patients had not been established.

On March 5, 2012, the results of a phase 2a study of TVR vs. placebo in combination with Peg-IFN/RBV for the treatment of genotype 1 chronic HCV infection in adults infected with HIV adults were presented at the 19th CROI. In this study, 60 patients coinfected with HIV and HCV were randomized to treatment with 12 weeks of combination therapy with TPV (n = 38) or placebo (n = 22) plus Peg-IFN/RBV, followed by 36 weeks of Peg-IFN/RBV alone. Based on previously conducted drug-drug interaction studies, coinfected patients were required to be on one of three HIV treatment regimens: no antiretroviral therapy (n =13), atazanavir/ritonavir plus tenofovir/emtricitabine (n = 23), or efavirenz plus tenofovir/emtricitabine (n = 24). Notably, patients taking efavirenz-based antiretroviral therapy were treated with higher TVR doses (1125 mg every 8 hours) to offset the reduction in TVR levels associated with efavirenz use; other patients received the standard TVR dose (750 mg every 8 hours).

The majority of patients were male (67 – 100%), Caucasian (29 – 87%), and infected with genotype 1 subtype a HCV (43 – 80%). The median CD4 count was high (514 to 675 cells/mm^3) in all patient groups, ranging from 254 to 1189 cells/mm^3. The SVR-12 rate, defined as no detectable HCV RNA at 12 weeks after discontinuing treatment, was 74% (28 of 38) in patients treated with TVR plus Peg-IFN/RBV, compared with 45% (10 of 22) in patients treated with Peg-IFN/RBV alone. Although this study included a small number of patients, there was no difference in HCV virologic outcomes among patients who received no antiretroviral agents, those treated with ritonavir-boosted atazanavir (atazanavir/ritonavir) plus tenofovir and emtricitabine or lamivudine, or those receiving a fixed-dose combination of efavirenz with tenofovir and emtricitabine.

During treatment, virologic breakthrough was observed in three TVR-treated patients (8%); after treatment discontinuation, HCV virologic relapse was reported in one of 38 TVR-treated patients (3%). Adverse events (AEs) were common among TVR-treated patients, with a greater frequency of pruritus, dizziness, headache, nausea, rash, and anemia reported compared with those treated with placebo plus Peg-IFN/RBV; however, discontinuation of study drugs because of AEs was uncommon in both groups (TVR, 3 patients; placebo, 0 patients). Importantly, no adverse impact on HIV disease parameters (HIV RNA levels and CD4 cell counts) was observed, and the steady-state pharmacokinetic profiles of the antiretroviral agents (efavirenz and atazanavir/ritonavir) and TVR were acceptable.

The authors concluded that the overall safety, tolerability, and efficacy profile of TPV in combination with Peg-IFN/RBV in this small group of patients coinfected with HIV and HCV was similar to that previously reported in patients infected with genotype 1 HCV without HIV coinfection.

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BOCEPREVIR PLUS PEGINTERFERON AND RIBAVIRIN IN HCV/HIV–COINFECTED INDIVIDUALS

Sulkowski M, Pol S, Cooper C, et al. **Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV-co-infected patients: end of treatment (week-48) interim results.** Presented at: 19th Conference on Retroviruses and Opportunistic Infections; March 5-8, 2012; Seattle, Washington. Abstract 47.

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In May 2011, BOC, an HCV NS3/4A protease inhibitor, was approved by the US FDA for the treatment of genotype 1 chronic HCV infection, in combination with Peg-IFN/RBV. At the time of FDA approval, however, the safety and efficacy of BOC plus Peg-IFN/RBV in patients coinfected with HIV and HCV had not been established.

On March 5, 2012, the results of a phase 2a study of BOC vs. placebo in combination with Peg-IFN/RBV for treating genotype 1 chronic HCV infection in adults with HIV was presented at the 19th CROI. In this study, 98 coinfected patients coinfected with HIV and

HCV were randomized to treatment with four weeks of Peg-IFN/RBV (lead-in phase), followed by 44 weeks of combination therapy with BOC 800 mg every 8 hours (n = 64) or placebo (n = 34) plus Peg-IFN/RBV. Patients taking efavirenz or other nonnucleoside reverse-transcriptase inhibitors were excluded from the study because of findings in previously conducted drug-drug interaction studies. Patients taking ritonavir-boosted HIV-1 protease inhibitors, including darunavir, atazanavir, and lopinavir, were permitted to be enrolled in the study. However, subsequent drug-drug interaction studies were conducted and presented at the 19th CROI; these studies demonstrated significant bidirectional interactions leading to lower concentrations of the HIV-1 protease inhibitors and BOC. Pharmacokinetics of the HIV-1 protease inhibitors were not assessed in this phase 2a study.

The majority of patients were male (65 – 72%), Caucasian (81 – 82%), and infected with genotype 1 subtype a HCV (65 – 66%). The median CD4 count was high (577 to 586 cells/mm3) in all groups, ranging from 187 to 1539 cells/mm3). The SVR-12 rate was 60.7% (37 of 61 patients)) in patients treated with BOC plus Peg-IFN/RBV, compared with 26.5% (9 of 34) in patients treated with Peg-IFN/RBV alone. In addition, three patients treated with BOC plus Peg-IFN/RBV had an undetectable HCV RNA level at four weeks post treatment (SVR-4) but had not yet reached the 12-week posttreatment assessment. Although this study included a small number of patients, there was no difference in virologic outcomes among patients treated with ritonavir-boosted HIV protease inhibitors, despite the anticipated interaction with BOC resulting in lower BOC exposure.

During treatment, HCV virologic treatment failure was observed in six patients treated with BOC (9%); after treatment discontinuation, HCV virologic relapse was reported in two patients treated with BOC (5%). During treatment, HCV virologic treatment failure was observed in 6 BOC-treated patients (9%); after treatment discontinuation, HCV virologic relapse was reported in two patients treated with BOC (5%). AEs were common among patients treated with BOC, with a greater frequency of anemia, neutropenia, pyrexia, decreased appetite, diarrhea, vomiting, and dysgeusia reported compared with those treated with placebo plus Peg-IFN/RBV. Discontinuation of study drugs because of AEs was also more common among patients treated with BOC (n = 12; 20%) compared with placebo-treated patients (n = 3; 9%). All enrolled patients were required to have an undetectable HIV RNA level on antiretroviral therapy; HIV RNA breakthrough was reported in four of 34 patients taking placebo plus Peg-IFN/RBV and three of 64 patients taking BOC plus Peg-IFN/RBV.

The authors concluded that the overall safety, tolerability, and efficacy profile of BOC in combination with Peg-IFN/RBV in this small group of patients coinfected with HIV and HCV was similar to that previously reported in patients infected with genotype 1 HCV without HIV coinfection. Additional studies of antiretroviral agents and BOC are planned in collaboration with the AIDS Clinical Trials Group.

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