Perspectives

Advances in the Treatment of Hepatitis C Virus Infection  
David L. Thomas, MD, MPH

Treatment Outcomes With Telaprevir and Boceprevir • Comparison of Telaprevir- and Boceprevir-Containing Regimens • Ongoing Studies of HCV PIs • Potential for Cure Without Interferon Alfa

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Editorial

Hepatitis C Virus Therapeutics: At the End of the Beginning  
Robert T. Schooley, MD

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Educational Programs of the IAS–USA

Established in 1992, the IAS–USA is a not-for-profit, professional education organization. The mission of the IAS–USA is to improve the treatment, care, and quality of life for people with HIV or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners who are actively involved in medical care for people with viral infections. The educational activities are particularly intended to bridge clinical research and patient care.

Spring 2012 Continuing Medical Education Courses

IAS–USA CME course announcements are paperless. Please watch for e-mail updates, and visit www.iasusa.org for general course information, agendas, and online registration. Early registration is strongly recommended. These live activities have been approved for AMA PRA Category 1 Credit™.

Complete Fall 2012 Course Schedule Coming Soon!

Improving the Management of HIV Disease®

The full-day advanced CME course, now in its 20th year, continues to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the field, providing the latest insights and data on the full spectrum of HIV- and AIDS-related treatment issues.

Spring 2012 Full-Day HIV Courses

New York, New York
Tuesday, March 20, 2012
New York Marriott Marquis

Los Angeles, California
Friday, March 30, 2012
California Endowment Center

San Francisco, California
Monday, April 16, 2012
South San Francisco Conference Center

Atlanta, Georgia
Friday, April 27, 2012
Renaissance Waverly Hotel

Chicago, Illinois
Monday, May 14, 2012
Marriott Chicago Downtown

Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes

Part of the IAS–USA focus on the management of viral hepatitis infection, these half-day, small-group, intensive CME workshops and full-day CME courses are presented by leading experts in the field.

Spring 2012 Half-Day Intensive Viral Hepatitis Workshops

New York, New York
Monday, March 19, 2012
New York Marriott Marquis

Los Angeles, California
Thursday, March 29, 2012
Sheraton Los Angeles

San Francisco, California
Tuesday, April 17, 2012
South San Francisco Conference Center

Atlanta, Georgia
Thursday, April 26, 2012
Cobb Galleria Centre

Chicago, Illinois
Tuesday, May 15, 2012
Marriott Chicago Downtown

Washington, DC
Monday, June 18, 2012
Hyatt Regency Crystal City

Spring 2012 Full-Day Viral Hepatitis Course

New York, New York
Thursday, June 7, 2012
New York Marriott Marquis

Educational Resources from past live courses are available on the IAS–USA Web site at www.iasusa.org, including Webcasts (available for CME credit), Podcasts, downloadable key slides from lectures, and various presentation handouts.

For information about any of these programs, please contact the IAS–USA.
Phone: (415) 544-9400 • Fax: (415) 544-9402 • E-mail: Registration“At”iasusa.org • Web site: www.iasusa.org
The following article in this issue is associated with CME credit: Thomas DL. Advances in the treatment of hepatitis C virus infection. Top Antivir Med. 2012;20(1):5-10

Instructions

This journal-based continuing medical education (CME) activity provides a review of advances in the treatment of hepatitis C virus (HCV) infection. To complete the activity, the learner is instructed to:
- Read the article (see pages 5-10)
- Review a selection of the references
- Reflect on how the information might be applied to clinical practice
- Complete the posttest and CME claim form and send both to the IAS–USA office.

Learning Objectives

On completion of this activity, learners will be able to 1) describe results of clinical trials leading to the US Food and Drug Administration (FDA) approval of telaprevir (TPV) and boceprevir (BOC) for HCV treatment; 2) list the characteristics of TPV- and BOC-containing regimens; 3) describe current research on these drugs in HIV/HCV-coinfected patients.

Accreditation Statement

The IAS–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The IAS–USA designates this journal-based CME activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Intended Audience

This activity is intended for physicians involved in the care of patients infected with HIV, HCV, or other viruses. It is also relevant to nurse practitioners, physician assistants, nurses, and other health professionals who provide care for people with viral diseases.

Conflicts of Interest and Financial Disclosures

IAS–USA policy requires that the IAS–USA resolve any real or apparent conflict of interest that may influence the development, content, or delivery of its educational activity prior to the activity’s being delivered to learners.

Dr Thomas has received grants and research support from Gilead Sciences, Inc, and Merck & Co, Inc, and has served as a consultant to Merck & Co, Inc.

Dr Richman has been a consultant to Biotest, Bristol-Myers Squibb, CHIMERx, Gen-Probe Inc, Gilead Sciences, Inc, Idenix Pharmaceuticals, Inc, Johnson & Johnson, Merck & Co, Inc, and Monogram Biosciences, Inc; the recipient of research grants or contracts from Merck & Co, Inc; and a stock options holder of CHIMERx and Idenix Pharmaceuticals, Inc.

Dr Benson and Dr Hirsch have no relevant financial affiliations to disclose.

This activity was supported by grants as described on the inside front cover.

Continuing Medical Education

This CME activity is offered from April 15, 2012, to April 15, 2013. Physicians (MDs, DOs, and international equivalents) who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive CME credit. Nonphysician health care practitioners will receive a certificate of attendance.

Posttest Questions

Check the box next to the best answer to each of the questions below. To earn CME credit, you must receive a passing score of 80% or more correct.

1. Which statement is true regarding hepatitis C virus (HCV) protease inhibitors (PIs) for treatment of HIV/HCV-coinfected patients?

- A. There is no evidence that HCV PIs improve virologic response in HIV/HCV-coinfected patients
- B. Although not fully tested in coinfected patients, boceprevir (BOC) should be used for 4 weeks alone as a lead-in before being combined with 44 weeks of peginterferon alfa/ribavirin (PegIFN/RBV)
- C. More than half of coinfected patients receiving PegIFN/RBV and an HCV PI have a virologic response by the end of treatment
- D. Baseline resistance to HCV PIs reduces the chance of virologic response

2. Which statement most accurately describes the use of HCV PIs?

- A. Telaprevir (TPV) must be taken with a high-fat meal
- B. TPV treatment should be stopped if HCV RNA level is greater than 100 IU/mL at week 4
- C. TPV treatment should be continued for at least 24 weeks in HIV/HCV-coinfected persons until studies show safety of stopping earlier
- D. Both TPV and BOC are approved by the US Food and Drug Administration (FDA) for use in HIV/HCV-coinfected patients without cirrhosis

3. Which statement is true regarding the pivotal telaprevir trial reported by Jacobson et al (N Engl J Med. 2011;364:2405-2416)?

- A. Patients who stopped TPV and PegIFN/RBV therapy at 24 weeks after early virologic response had outcomes similar to those who received TPV and a full 48-week course of PegIFN/RBV
- B. SVR rates in black patients receiving TPV for 12 weeks were similar to SVR rates in nonblack patients receiving TPV for 12 weeks
- C. There was no difference in the SVR rates between the group receiving 8 weeks of TPV and those receiving PegIFN/RBV alone

4. Which statement most accurately describes the current knowledge of resistance to HCV PIs?

- A. There is substantial evidence that resistance to the HCV PIs will result in poorer response to subsequent treatment containing a PI
- B. HIV/HCV-coinfected patients should always be tested for HCV resistance before HCV treatment is initiated
- C. In patients with HCV PI resistance, a return to predominance of wild-type virus occurs in less than 20% of patients
- D. Resistance to TPV or BOC is detected in approximately 50% of patients in whom therapy fails

5. Which statement regarding the use of HCV PIs is true?

- A. For both TPV and BOC, there is about 1 log of activity against HIV. Therefore, TPV and BOC must be used with a full suppressive HIV regimen
- B. Response-guided therapy with either TPV or BOC is not recommended in patients with cirrhosis, but is acceptable in patients with HIV coinfection
- C. The addition of TPV or BOC to PegIFN/RBV therapy leads to increased risk for added adverse effects such as anemia
Participant Information

Number of CME credit hours I am claiming (maximum 1.5): 

Please indicate your academic degree or license:
- MD
- DO
- PA
- RN
- NP
- PharmD
- other (specify) 

First Name       MI       Last Name

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Evaluation

Please complete the following evaluation form for this journal activity:

Please rate the activity in terms of meeting the stated learning objectives (see p. 3 for objectives) 

Excellent   Very Good   Good   Fair   Poor

Please rate the extent to which the information presented was supported by the evidence

Please rate the overall quality of the article

Please rate the activity’s freedom from commercial bias

Please rate the overall value of this activity to your practice

Please list 3 specific measurable changes you will make in your practice based on the information presented in the article:

1. 

2. 

3. 

Other comments (please feel free to comment on any aspect of Topics in Antiviral Medicine):

What percentage of your patients has HIV infection?
- 0%  
- 1%–10%  
- 11%–25%  
- 26%–50%  
- 51%–75%  
- 76%–90%  
- 91%–100%

Please rate your expertise in treating HIV infection:  
- 1 (novice) 
- 2 
- 3 
- 4 
- 5 (expert)

What percentage of your patients are members of an underrepresented minority group?
- 0%  
- 1%–10%  
- 11%–25%  
- 26%–50%  
- 51%–75%  
- 76%–90%  
- 91%–100%

Are you a member of an underrepresented minority group?  
- Yes  
- No
Perspective
Advances in the Treatment of Hepatitis C Virus Infection

Since 2007, the annual age-adjusted mortality rate in hepatitis C virus (HCV) infection in the United States has been greater than that in HIV disease, reflecting the continuing decline in HIV-related mortality and the continuing increase in HCV-related mortality. The approval of 2 new direct-acting antivirals within the past year, as well as the promise offered by numerous other direct-acting agents in development, provides hope that we will be able to markedly improve our ability to cure HCV disease. The addition of a protease inhibitor (PI) to what has been the standard HCV therapy of peginterferon alfa and ribavirin dramatically improves sustained virologic response rates in treatment-naive patients with genotype 1 infection. Similar results have been observed in some treatment-experienced patients in whom prior peginterferon alfa/ribavirin therapy has failed. The use of these new agents has also permitted response-guided therapy, wherein early sustained virologic response to treatment allows for a shortened treatment duration. However, these new PIs add cost and adverse effects to HCV therapy. Boceprevir is associated with increased risk of anemia and dysgeusia, and telaprevir is associated with increased risk of anemia and skin and gastrointestinal adverse effects. Early studies indicate that the addition of PIs results in high response rates in patients with HCV/HIV coinfection. Other studies suggest that combinations of PIs and other direct-acting antivirals may ultimately permit cure when used in interferon-sparing regimens. This article summarizes a presentation by David L. Thomas, MD, MPH, at the IAS–USA live continuing medical education course held in New York City in October 2011.

Since 2007, the annual age-adjusted mortality rate in HIV disease in the United States has been surpassed by that of hepatitis C virus (HCV) disease, reflecting the continuing decline in HIV-related mortality and the continuing increase in HCV-related mortality. The prevalence of HCV-related cirrhosis is projected to continue to increase until it reaches a peak around 2020, reflecting what is commonly a 20- to 40-year period between HCV acquisition and the later-stage manifestations of cirrhosis, end-stage liver disease, and liver cancer. These projections assumed no changes in our ability to treat HCV infection.

The rate of sustained virologic response (SVR; ie, absence of HCV RNA in blood for 6 months after the end of treatment) with what has been the standard treatment of peginterferon alfa plus ribavirin is approximately 40% in patients with HCV genotype 1 infection, the predominant type of infection in the United States. The rate is less than 30% in HIV/HCV-coinfected patients with HCV genotype 1. However, the past year has brought the approval of 2 new drugs for treating HCV infection—the HCV protease inhibitors boceprevir and telaprevir—and numerous new drugs are in advanced stages of development. It is hoped that these new weapons will allow us to improve the projections for HCV disease outcomes.

Treatment Outcomes With Telaprevir and Boceprevir

Treatment-Naive Patients

In the trial supporting approval of telaprevir, more than 1000 treatment-naive patients with HCV genotype 1 infection were randomly assigned to receive telaprevir for 8 weeks or 12 weeks plus concurrent standard peginterferon alfa/ribavirin therapy for up to 48 weeks, or peginterferon alfa/ribavirin alone for 48 weeks. Patients receiving telaprevir who achieved a virologic response that was sustained between weeks 8 and 12 were further randomly assigned to stop peginterferon alfa/ribavirin after week 24 or continue for the full 48 weeks. Overall, cure (ie, SVR) was achieved in 69% of patients receiving 8 weeks of telaprevir and 75% of those receiving 12 weeks of telaprevir, compared with 44% of those receiving peginterferon alfa/ribavirin alone. In black patients, who are known to have lower rates of response to peginterferon alfa/ribavirin, SVR rates were 25% with standard therapy, versus 58% and 62% with 8 weeks and 12 weeks of telaprevir, respectively. Among nonblack patients, SVR rates were 48% with peginterferon alfa/ribavirin, compared with 73% and 79% with the addition of telaprevir for 8 weeks and 12 weeks, respectively.

Patients who stopped therapy at 24 weeks after an early response to telaprevir-containing therapy had outcomes similar to those who continued to receive peginterferon alfa/ribavirin for the full 48-week course. The 12-week course of telaprevir was approved in 2011 by the US Food and Drug Administration (FDA) for use in combination with peginterferon alfa/ribavirin, as was the shortened treatment duration in patients with early sustained response to treatment.

With regard to the ability to abbreviate therapy based on early response to treatment, Sherman and colleagues performed a study in treatment-naive, genotype 1–infected patients. Patients who achieved early rapid virologic response (eRVR; defined as undetectable HCV RNA at week 4 and week 12) with telaprevir plus peginterferon alfa/ribavirin were randomly assigned to continue receiving peginterferon alfa/ribavirin for the full 48 weeks or to stop treatment after a total of 24 weeks. The overall SVR rate was 72%, with 65% of the total of 540 patients achieving eRVR. SVR rates were 92% among those stopping treatment after 24 weeks and 88% among those receiving 48 weeks...
of treatment. Among those who did not achieve eRVR, the SVR rate was 64%.

In the pivotal boceprevir trial, approximately 1100 treatment-naive patients with genotype 1 infection received a lead-in of peginterferon alfa/ribavirin for 4 weeks. This was followed by either continuation of peginterferon alfa/ribavirin treatment for 44 weeks (total of 48 weeks); addition of boceprevir for 44 weeks (fixed-dur-ation group); or addition of boceprevir for 24 weeks followed by treatment discontinuation if virus was undetectable from 8 weeks to 24 weeks or treatment continuation with peginterferon alfa/ribavirin alone for 20 weeks if virus was detectable (response-guided therapy group). Overall, SVR rates were 63% in the response-guided therapy boceprevir group and 66% in the fixed-duration boceprevir group, compared with 38% in the peginterferon alfa/ribavirin treatment group. SVR rates were improved with the addition of boceprevir in black patients (42% in the response-guided therapy group) and 53% in the fixed-duration group vs 23% in the standard treatment group and nonblack patients (67% and 69% vs 41%, respectively). Boceprevir was approved by the FDA in 2011 for use in combination with peginterferon alfa/ribavirin, including a shortened response-guided course of therapy in treatment-naive patients.

**Treatment-Experienced Patients**

Telaprevir and boceprevir have each been shown to achieve cure in a substantial proportion of HCV-infected patients in whom prior peginterferon alfa/ribavirin therapy had failed. In a study of more than 600 treatment-experienced patients, Zeuzem and colleagues found SVR rates of 64% with the combination of 12 weeks of telaprevir plus 48 weeks of peginterferon alfa/ribavirin; 66% with a 4-week lead-in regimen of peginterferon alfa/ribavirin followed by 12 weeks of telaprevir and 44 weeks of peginterferon alfa/ribavirin; and 17% with retreatment with 48 weeks of peginterferon alfa/ribavirin. Among patients with relapse (ie, those who relapsed after having undetectable virus at the end of prior treatment) SVR rates were 83%, 88%, and 24%, respectively. Among those who had shown a partial virologic response to prior treatment, SVR rates were 59%, 54%, and 15%, respectively. For those with no virologic response to prior treatment (null responders), SVR rates were 29%, 33%, and 5%, respectively.

In a trial in approximately 400 treatment-experienced patients conducted by Bacon and colleagues, overall SVR rates were 66% in patients receiving boceprevir and 48 weeks of peginterferon alfa/ribavirin, 59% in those receiving boceprevir with response-guided therapy, and 21% in those receiving standard peginterferon alfa/ribavirin. SVR rates were 75%, 69%, and 29%, respectively, among patients who had relapsed after prior therapy and 52%, 40%, and 7%, respectively, among those who had partial response to prior treatment.

**Increased Toxic Effects With Addition of Telaprevir or Boceprevir**

Jacobson and colleagues reported that adverse events occurred more frequently in telaprevir-containing study arms than in the peginterferon alfa/ribavirin alone arm. Adverse effects included pruritus (45%-50% with telaprevir vs 36% with peginterferon alfa/ribavirin), nausea (40%-43% vs 31%), rash (35%-37% vs 24%), anemia (37%-39% vs 19%), and diarrhea (28%-32% vs 22%). In the boceprevir trial conducted by Poordad and colleagues, anemia (49% in the boceprevir group vs 29% in standard treatment group) and dysgeusia (37%-43% vs 18%, respectively) were more common in boceprevir-containing study arms.

**Resistance to HCV Protease Inhibitors**

Because neither interferon alfa nor ribavirin is a direct-acting antiviral agent, viral resistance is a new phenomenon in HCV treatment. Resistance to the protease inhibitors (PIs) telaprevir and boceprevir is detected in approximately 50% of patients in whom therapy containing these agents fails. To date, there is no evidence that resistant variants have greater replicative fitness or pathogenicity than wild-type virus. As has been observed with HIV, there is a return to predominance of wild-type virus generally within 18 months of stopping HCV PI treatment. However, unlike HIV,
there is no biologic basis for archiving of PI-resistant variants in the body.

The long-term consequences of selecting for HCV PI resistance are unclear at this time. Investigations are currently underway on whether emergence of resistance will result in poorer response to subsequent treatment containing a PI. There are no convincing data thus far that baseline resistance to HCV PIs affects response to treatment. Thus, although there is a commercially available assay for testing for HCV resistance, for now there is no indication for testing to guide immediate treatment decisions. However, it may be prudent to document resistant variants in case the information becomes useful in the future.

More Potent Therapy Reduces Predictive Value of Some Risk Factors for Poor Response

More potent anti-HCV therapy reduces the value of some of the traditional factors predictive of poor response to peginterferon alfa/ribavirin therapy. This is a good thing, however, because the loss of predictive value is the result of higher cure rates in subgroups of patients with traditionally greater risk of poor response. Most notable is the diminished effect of higher HCV viral load in predicting poorer treatment outcome with peginterferon alfa/ribavirin (see Table 1). For example, in the pivotal telaprevir trial, SVR rates were similar among telaprevir-receiving patients with baseline HCV RNA viral load 800,000 IU/mL or higher and those with viral load less than 800,000 IU/mL (74% and 78%, respectively).2 The SVR rate in those with elevated viral load receiving telaprevir represents a striking improvement over the response rate among patients with high viral load receiving peginterferon alfa/ribavirin alone (36%).2 In the pivotal boceprevir trial, the SVR rate among boceprevir recipients with elevated baseline viral load was 63%, compared with 53% among patients with elevated baseline viral load receiving peginterferon alfa/ribavirin alone.4

As noted previously, black race is also a risk factor for poorer response to peginterferon alfa/ribavirin. The difference in the frequency of the unfavorable interleukin-28B genotype explains about half of the difference in treatment response between black and nonblack patients. Although there was still a difference in SVR rates between black patients and white patients receiving telaprevir (62% and 75%, respectively), the SVR rate in black patients represents a striking improvement over that achieved with peginterferon alfa/ribavirin alone (25%).2 Similarly, black patients receiving boceprevir had a lower SVR rate than white patients, but the high cure rate in black patients receiving boceprevir compared with those receiving peginterferon alfa/ribavirin alone is another striking improvement—53% versus 23%, respectively.4 Some of the differences observed between the telaprevir and boceprevir studies, with regard to response rates in patient subgroups, likely reflect the fact that the post hoc analyses were performed in different patient populations.

Comparison of Telaprevir- and Boceprevir-Containing Regimens

Table 2 provides an overview of characteristics of HCV treatment with telaprevir- and boceprevir-containing regimens. A 4-week lead-in period with peginterferon alfa/ribavirin is recommended before adding boceprevir and no lead-in is recommended for patients receiving telaprevir.8,10 reflecting the way the drugs were developed in phase II and, especially, phase III studies. Boceprevir is administered for 24 weeks or 44 weeks in treatment-naive patients and for 32 weeks or 44 weeks in treatment-experienced patients, depending on early virologic response, whereas telaprevir is administered for 12 weeks in both treatment-naïve and treatment–experienced patients.

Response-guided therapy is not recommended in patients with cirrhosis or in HIV-coinfected patients. Response-guided therapy in HIV-seronegative, noncirrhotic, treatment-naïve patients is permitted based on an HCV RNA-negative response during weeks 8 to 24 with boceprevir treatment and at weeks 4 and 12 with telaprevir treatment. Based on clinical trial data, it is estimated that 44% of treatment-naive patients receiving boceprevir and 58% to 65% of treatment-naive patients receiving telaprevir are eligible for response-guided therapy. The total duration of anti-HCV treatment in treatment-naive patients, depending on presence or absence of early virologic response, is 28 weeks or 48 weeks for boceprevir, and 24 weeks or 48 weeks for telaprevir.

Response-guided therapy in treatment-experienced patients is not recommended for patients receiving boceprevir who were null responders to prior treatment or for patients receiving telaprevir who were partial or null responders. For treatment-experienced patients receiving boceprevir, total anti-HCV treatment duration is 36 weeks (for those with eRVR) or 48 weeks. Total treatment duration is 24 weeks or 48 weeks for patients receiving telaprevir. Anti-HCV therapy with boceprevir should be stopped due to futility if HCV RNA level is greater than 100 IU/mL at week 12 or if there is detectable HCV RNA at week 24. The recommended stopping rule for telaprevir-containing therapy is a viral load of greater than 1000 IU/mL at week 4 or 12, or detectable virus at week 24.

As noted previously, there are added adverse effects with the addition of either of the PIs to peginterferon alfa/ribavirin. There is an increased risk of anemia with boceprevir compared with peginterferon alfa/ribavirin therapy alone, and telaprevir is associated with increased risk of anemia and skin and gastrointestinal side effects. Pill burdens differ between the two treatments, with boceprevir requiring four 200 mg pills every 8 hours and telaprevir requiring two 375 mg pills every 8 hours. There is also a difference in food requirements: boceprevir needs to be taken with some food, whereas each dose of telaprevir needs to be taken with a meal containing at least 20 g of fat.

The addition of a new agent to HCV treatment regimens increases cost as well as cure rates. A 48-week course of
there is some evidence indicating that difficult to treat in many cases, and of a PI. Genotype 3 infection is more and there is some indication that cure interferon alfa/ribavirin in most patients, genotype 2 or 3 infection. Genotype been established in patients with HCV and efficacy of these drugs have not HCV coinfection. In addition, safety with HBV coinfection, and those with (eg, patients with decompensated cirrhosis and transplant patients), those are those with more advanced disease (eg, patients with decompensated cirrhosis and transplant patients), those with HBV coinfection, and those with HIV coinfection. In addition, safety and efficacy of these drugs have not been established in patients with HCV genotype 2 or 3 infection. Genotype 2 infection is responsive to peginterferon alfa/ribavirin in most patients, and there is some indication that cure rates are improved with the addition of a PI. Genotype 3 infection is more difficult to treat in many cases, and there is some evidence indicating that response rates are not improved with the addition of a PI.

**Studies in HIV Coinfection**

In a small study by Sulkowski and colleagues, patients with HCV/HIV coinfection received a full 48-week course of anti-HCV therapy with telaprevir plus peginterferon alfa/ribavirin or peginterferon alfa/ribavirin alone with or without antiretroviral therapy. The group receiving peginterferon alfa/ribavirin without antiretroviral therapy included patients with high CD4+ cell counts who did not meet current guidelines for initiation of antiretroviral therapy. Patients who received antiretroviral therapy took efavirenz/tenofovir/emtricitabine, or ritonavir-boosted atazanavir with tenofovir/emtricitabine or tenofovir/lamivudine. Patients who received the efavirenz-containing regimen received an additional telaprevir pill with each dose to compensate for lowered blood levels due to pharmacokinetic interaction with efavirenz. As shown in Figure 1, the telaprevir-containing regimen markedly improved week 4 and week 12 virologic responses in patients receiving and not receiving antiretroviral therapy. These promising findings need to be confirmed in larger studies.

A phase II trial of boceprevir with peginterferon alfa/ribavirin in HIV/HCV-coinfected patients is ongoing. A total of 99 coinfected patients with stable HIV disease are being treated with a lead-in of 4 weeks of peginterferon alfa plus weight-based ribavirin, then randomly assigned to add boceprevir (800 mg every 7-9 hours) or placebo for an additional 44 weeks. Subjects were allowed into the study if they were on raltegravir or ritonavir-boosted PIs. Baseline HCV RNA level was above 800,000 IU/mL for 88% of subjects; 82% were white, and 5% had cirrhosis.12

The proportion of patients with undetectable HCV RNA at week 8 was higher in the group receiving boceprevir (24 of 64 [37.5%] with undetectable HCV RNA) than in the group receiving placebo (5 of 34 [14.7%]). At week 24, HCV RNA was undetectable in 43 of 61 patients (70.5%) in the boceprevir arm and undetectable in 11 of 32 (34.4%) in the placebo arm. Treatment was discontinued in 3 (9%) and 9 (14%) of the patients in the placebo and boceprevir arms, respectively, because of adverse events.

Updates on the trials described above were presented at the 19th Conference on Retroviruses and Opportunistic Infections in March 2012. In the telaprevir trial in HIV/HCV-coinfected patients, 28 of 38 patients (74%) receiving telaprevir plus peginterferon alfa/ribavirin had undetectable levels of HCV RNA at week 24 (end of treatment), compared with 12 of 22 patients (55%) in the peginterferon alfa/ribavirin–only control group.13 Twelve weeks after stopping therapy, all 28 of the 38 (74%) who had undetectable levels of HCV RNA at the end of telaprevir treatment had sustained virologic response. In the control group, 10 of 22 patients (45%) had sustained virologic response.

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**Table 2. Selected Characteristics of Boceprevir and Telaprevir**

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-week peginterferon alfa/ribavirin lead-in</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PI duration</td>
<td></td>
<td></td>
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<tr>
<td>HCV treatment-naive</td>
<td>24 weeks or 44 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>HCV treatment-experienced</td>
<td>32 weeks or 44 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Criterion for RGT*</td>
<td>RNA-negative at weeks 8-24</td>
<td>RNA-negative at week 4 and week 12</td>
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<tr>
<td>RGT-eligible, treatment-naive patients</td>
<td>~44%</td>
<td>~58%-65%</td>
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<tr>
<td>RGT-eligible, treatment-experienced patients</td>
<td>Relapsers and partial responders (null responders not eligible)</td>
<td>Relapsers (partial and null responders not eligible)</td>
</tr>
<tr>
<td>Total duration of treatment in treatment-experienced patients</td>
<td>36 weeks (with eRVR) or 48 weeks</td>
<td>24 weeks or 48 weeks</td>
</tr>
<tr>
<td>Stopping rule for futility</td>
<td>HCV RNA &gt; 100 IU/mL at week 12</td>
<td>HCV RNA &gt; 1000 IU/mL at week 4 or week 12</td>
</tr>
<tr>
<td>Detectable virus at week 24</td>
<td>Detectable virus at week 24</td>
<td></td>
</tr>
<tr>
<td>Added adverse effects</td>
<td>Anemia, dysgeusia</td>
<td>Anemia, rash, pruritus, nausea, diarrhea</td>
</tr>
<tr>
<td>Dosage</td>
<td>Four 200 mg pills every 8 hours</td>
<td>Two 375 mg pills every 8 hours</td>
</tr>
<tr>
<td>Food requirement</td>
<td>Must be taken with some food</td>
<td>Must be taken with meal containing ≥ 20 g of fat</td>
</tr>
</tbody>
</table>

*RGT indicates response-guided therapy; PI, protease inhibitor; eRVR, early rapid virologic response. RGT is not recommended in patients with cirrhosis or HIV coinfection.

Ongoing Studies of HCV PIs

Patients with HCV infection in whom PI treatment has yet to be fully evaluated are those with more advanced disease (eg, patients with decompensated cirrhosis and transplant patients), those with HBV coinfection, and those with HIV coinfection. In addition, safety and efficacy of these drugs have not been established in patients with HCV genotype 2 or 3 infection. Genotype 2 infection is responsive to peginterferon alfa/ribavirin in most patients, and there is some indication that cure rates are improved with the addition of a PI. Genotype 3 infection is more difficult to treat in many cases, and there is some evidence indicating that peginterferon alfa/ribavirin costs approximately $38,000. Full courses of telaprevir (12 weeks) and boceprevir (up to 44 weeks) cost approximately $50,000.
In the boceprevir trial, 39 of 61 coinfected patients (63.9%) receiving boceprevir plus peginterferon alfa/ribavirin had undetectable HCV RNA at week 48 (end of treatment), compared with 10 of 34 (29.4%) receiving peginterferon alfa alone.14 Twelve weeks after stopping therapy, 37 of 61 patients (60.7%) who had received boceprevir had sustained virologic response, compared with 9 of 34 (26.5%) in the peginterferon alfa/ribavirin–only group.

These results in coinfected patients are notable because in both studies, virologic response was substantially better than with interferon alfa/ribavirin alone. Virologic response rates were also nearly as high as those in monoinfected patients.

**Potential for Cure Without Interferon Alfa**

Peginterferon alfa therapy is associated with considerable toxicity, and there is intense interest in developing treatments that would spare patients from the rigors of such therapy. An example of studies assessing this possibility was reported by Lok and colleagues.15 Patients who were prior null responders to peginterferon alfa/ribavirin therapy received a combination of an HCV PI and an HCV nonstructural protein 5A (NS5A) inhibitor (which is active at different steps of the viral replication process than PIs), with or without peginterferon alfa/ribavirin.

Four of 11 patients receiving the PI and NS5A inhibitors without peginterferon alfa/ribavirin had viral loads that fell below the limit of quantitation at week 12 and remained undetectable after stopping therapy, showing in principle that cure is achievable without interferon alfa therapy. Six of the 11 patients exhibited viral breakthrough. It is also noteworthy that all 10 patients receiving the 2 direct-acting antivirals in combination with peginterferon alfa/ribavirin had undetectable virus at week 12, a remarkable outcome of treatment in prior null responders. There is considerable excitement over what might be achieved with multidrug combinations of the numerous investigational direct-acting agents.

Although formal guidelines for treatment of HIV/HCV-coinfected persons are being planned, at this time treatment should be prioritized for those with advanced liver fibrosis (cirrhosis and bridging fibrosis). When possible, coinfected patients should be enrolled in clinical trials to expand the available information on optimal HCV treatments in that setting.

**Summary**

The current era in HCV treatment is reminiscent of the transformation of HIV treatment that occurred in the mid-1990s. With the new HCV treatments, cure and complications occur more frequently. We can make smart applications of the treatments available to us right now in some patients, and we await tomorrow’s treatments for other patients. As with the first wave of HIV medications in the potent antiretroviral era, the new HCV drugs offer huge advantages but also present substantial challenges.

**References**

portunistic Infections (CROI). February 27-March 2, 2011; Boston, MA.


NEW Preexposure Prophylaxis for HIV Infection
Jason R. Faulhaber, MD
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced
There may finally be a viable breakthrough in the prevention of new HIV infections, as data from recent studies have demonstrated. These studies evaluated the use of preexposure prophylaxis (PrEP) as oral medication or topical microbicide to reduce the risk of HIV acquisition. Dr Jason Faulhaber describes the role of health care practitioners in altering the future of HIV transmission.

NEW Osteomalacia and Osteoporosis in the HIV-infected Patient
Michael Yin, MD, MS, and Emily Stein, MD, MS
CME Credit Available: 1.5 AMA PRA Category 1 Credits™
Level: Advanced
The incidence of age-related comorbidities affecting bone mineral density has increased among HIV-infected individuals. HIV primary care practitioners will need to learn about the effects of antiretroviral drugs on vitamin D levels, bone metabolism, and the diagnosis and management of osteomalacia and osteoporosis. Dr Michael Yin and Dr Emily Stein describe the differences between these disease processes and the challenge of treating them.

HIV and Pain
Greer A. Burkholder, MD
CME Credit Available: 2.5 AMA PRA Category 1 Credits™
Level: Advanced
Patients with HIV infection now have near-normal life expectancies, but 40% to 55% still report pain. Various comorbid conditions, including cardiovascular disease, frailty, and non–AIDS-defining malignancies, are prevalent in the HIV-infected population, which also has high rates of substance abuse. Dr Jessica Merlin and Dr Rodney Tucker present an approach to the treatment of pain, an underdiagnosed and undertreated condition in HIV-infected patients.

Quality Measures in HIV Care
Kathleen Clanon, MD, and Steven Bromer, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
Level: Advanced
Choosing a set of quality of care measures and a strategy for using them is an investment in time and resources—the resulting information can be either a powerful tool for improving care or a useless paper exercise. Dr Kathleen Clanon and Dr Steven Bromer provide guidelines and advice on selecting performance measures, determining data collection methods, and using and leveraging the eventual results to improve care.

Initiation of Antiretroviral Therapy in Treatment-Naive HIV-Infected Patients
Greer A. Burkholder, MD
CME Credit Available: 1.75 AMA PRA Category 1 Credits™
What impact does the timing of antiretroviral therapy (ART) initiation have on the prognosis of HIV-infected patients? Dr Greer Burkholder discusses the influence of CD4+ cell count, plasma HIV RNA level, AIDS-related and non–AIDS-related comorbidities, pregnancy, and patient willingness to take lifelong medications. Because of the evolving nature of guidelines and evidence regarding timing of ART, HIV practitioners need to update their knowledge on this topic regularly.

COMING SOON
Look for these new Cases on the Web activities in coming months.

• Drug Interactions with Medications for Treating Hepatitis C Virus (HCV) Infection—Boceprevir and telaprevir have led to increased successful response rates in treating HCV infection. The use of these agents, however, is associated with drug interactions with primary care medications and many HIV antiretroviral drugs.

• Sexually Transmitted Infections in the HIV-Infected Patient—The presence of sexually transmitted infections may facilitate onward transmission and acquisition of HIV infections. Coinfection has an impact on individual health and on the health of partners and the community.

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Perspective
Sexually Transmitted Infections and HIV: Diagnosis and Treatment

Accurate assessment, diagnosis, and treatment of sexually transmitted infections (STIs) in HIV-infected persons can identify sexual risk behaviors and specific STIs that may increase transmission of STIs and HIV. HIV-infected men and women should be screened annually for syphilis and urogenital gonorrhea and chlamydia. Serologic testing for hepatitis A, B, and C viruses should also be performed. Women should be tested for trichomoniasis and undergo a cervical Papanicolaou test annually. Men who report receptive anal intercourse with men during the preceding year should be screened for rectal gonorrhea and chlamydia. Men who report receptive oral intercourse with men during the preceding year should be screened for oropharyngeal gonorrhea. More frequent screening at 3- to 6-month intervals may be indicated for men who have sex with men who have numerous or anonymous partners. STIs may have unusual presentations in HIV-infected patients. Aspects of diagnosis and management of common STIs will be discussed in this article. This article summarizes a presentation by Kimberly A. Workowski, MD, at the IAS–USA live continuing medical education course held in New York City in October 2011.

Current Guidelines for STI Screening

An accurate risk assessment for sexually transmitted infections (STIs) can identify sexual risk behaviors and specific STIs that may increase the risk of HIV and STI transmission. A crucial component of this evaluation is performing a detailed and accurate history at every visit. A detailed sexual history should include numbers of sexual partners, types of sexual behaviors, previous STIs, condom use, and a review of current symptoms and signs of STIs. Because many STIs are asymptomatic, especially at the pharyngeal and rectal sites, routine screening for curable STIs (syphilis, gonorrhea, chlamydia) should be performed at least annually for all sexually active, HIV-infected persons.

All HIV-infected men and women should be screened annually with syphilis serology and receive urogenital gonococcal and Chlamydia trachomatis (GC/CT) testing. Serologic testing for hepatitis A and B viruses, as well as hepatitis C virus (HCV), is also indicated. Women should be tested for trichomoniasis and undergo a cervical Papanicolaou test annually. Men who report receptive anal intercourse with men (regardless of condom use) during the preceding year should be screened for rectal gonorrhea and chlamydia, using a laboratory-validated nucleic acid amplification test (NAAT). Men who report receptive oral intercourse with men during the preceding year should be screened for oropharyngeal gonorrhea using NAAT. Women should be tested for trichomoniasis (using NAAT or culture) and undergo a cervical Papanicolaou test annually. More frequent STI screening (at 3- to 6-month intervals) is indicated for HIV-infected persons who have numerous or anonymous partners, and for those in a geographic area or population with a high prevalence of STIs.

The commercially available GC/CT NAAT tests are not approved by the US Food and Drug Administration (FDA) for use at pharyngeal and rectal sites, but they can be used by laboratories that have met all regulatory requirements for an off-label procedure. Laboratory personnel at the Laboratory Branch of the Division of Sexually Transmitted Diseases (STD) Prevention at the Centers for Disease Control and Prevention (CDC) are also available to help with test validation. Some private health laboratories have validated rectal and pharyngeal testing with NAATs and have specific laboratory ordering and billing codes that may be helpful for providers. Table 1 provides ordering and coding information for these tests.

Identification of an STI is an objective measure of unprotected sexual activity. Accurate diagnosis and effective treatment of STIs is important not only to reduce morbidity for the individual patient and reduce risk of STI transmission, but to also reduce risk of HIV transmission. The CDC STD Surveillance Network can monitor trends in the prevalence of sexually transmitted infections among men who have sex with men attending specific STD clinics within this network (Figure 1).1

Table 1. Commerical Laboratory Ordering and Billing Codes for Nucleic Acid Amplification Testing

<table>
<thead>
<tr>
<th>STI</th>
<th>Ordering Codes for Combined GC/CT NAAT</th>
<th>Ordering Codes for CT-only NAAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal Pharyngeal</td>
<td>LabCorp 188672, 188698</td>
<td>Quest 16506, 70051</td>
</tr>
<tr>
<td>CT detection by NAAT: 87491</td>
<td>GC detection by NAAT: 87591</td>
<td></td>
</tr>
</tbody>
</table>

Dr Workowski is Professor of Medicine in the Division of Infectious Diseases at the Emory University School of Medicine in Atlanta, Georgia.
Anogenital Ulcerative Lesions

Diagnosing anogenital lesions based only on medical history and physical examination can often be inaccurate. HIV can modify the presentation of a coexisting infection, bacterial superinfection may be present, and more than 1 etiologic agent can be present in a genital or perianal lesion. Herpes simplex virus (HSV) and syphilis infections are the most common infectious causes of anogenital lesions. However, point-of-care methods for accurate diagnosis of genital ulcers due to syphilis and genital herpes are not commercially available. Evaluation of persons with genital or perianal ulceration should include a serologic test for syphilis, HSV culture or PCR testing, and a test for 

Definitive diagnosis of early syphilis requires darkfield microscopy or PCR of lesion exudate or tissue. There are no commercially available tests for direct detection of Treponema pallidum (TP). The diagnosis of syphilis is often based on serologic testing for early syphilis, and is usually performed with

Although more rapid progression or severe disease might occur in HIV-infected persons with advanced immunosuppression, the clinical manifestations of syphilis are similar to those in HIV-uninfected persons. The most common clinical manifestations, macular, maculopapular, papulosquamous, or pustular skin lesions, can involve the palms and soles, and may be accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache. However, other characteristics may include numerous deep ulcers, simultaneous manifestation of primary and secondary syphilis, and lues maligna (papulopustular skin lesions that evolve into ulcerative lesions with sharp borders and a dark central crust). Uveitis and meningitis are more common in HIV disease, with neurologic involvement occurring at any stage. Syphilis is a disseminated disease, with invasion of the central nervous system occurring early in infection, irrespective of a patient’s HIV serostatus.

In general, the best management approach is to treat for the diagnosis considered most likely based on clinical presentation and epidemiologic circumstances. For example, if syphilis is suspected, empiric treatment with benzathine penicillin should be administered before serologic test results are available, because early treatment decreases the possibility of ongoing transmission. Biopsy of genital, anal, or perianal ulcers can help identify the cause of ulcers if there is considerable uncertainty regarding diagnosis or if the ulcers do not respond to initial therapy.

Syphilis

Recent surveillance data from CDC indicate that patients with syphilis, and especially MSM, are more likely to present for care in the secondary stage of disease. MSM have the highest rates of secondary syphilis compared with heterosexual women and men (see Figure 2).1

![Figure 1. Proportion of men who have sex with men attending sexually transmitted diseases clinics with primary and secondary syphilis, gonorrhea, or chlamydia, classified by HIV serostatus. Adapted from the 2010 Sexually Transmitted Diseases Surveillance Report.](image1)

![Figure 2. Cases of primary and secondary syphilis among men who have sex exclusively with women (MSW), women, and men who have sex with men (MSM). Adapted from the 2010 Sexually Transmitted Diseases Surveillance Report.](image2)
a nontreponemal test followed by a treponemal test. However, approximately 30% of nontreponemal tests performed during primary syphilis can report false-negative results, and up to 20% of cases of primary syphilis may present with oral manifestations that are often missed by the patient and the healthcare practitioner.

Newer technologies include reverse-sequence treponemal screening methods such as enzyme immunoassays (EIAs) and chemiluminescence immunoassays (CIAs). The traditional approach to syphilis diagnosis consists of quantitative rapid plasma reagin (RPR) followed by a Treponema pallidum passive particle agglutination (TP-PA) assay or other treponemal test. However, this approach may miss primary infection because of false-negative results in early infection.

In the reverse-sequence approach, EIA or CIA tests are performed, and if positive, are followed by quantitative RPR. This strategy identifies those persons with previous treatment for syphilis and those with untreated syphilis. If the nontreponemal test is negative, a different treponemal test should be performed to confirm the results of the initial test. If a second treponemal test is positive, persons with previous treatment will require no further management unless sexual history suggests reexposure. Those without a history of syphilis treatment should be offered treatment. If a second treponemal test is negative, further evaluation or treatment is not indicated.

This reverse-sequence serologic testing can lead to problems in interpretation and decision-making when nontreponemal and treponemal tests are discordant. In a study conducted in several laboratories in New York City, 56% of 6548 EIA-positive samples were RPR negative. In a more recent study in several cities, 57% of 4834 EIA- or CIA-positive samples were RPR negative. The proportion of false-positive EIAs or CIAs was affected by patient risk level, with false-positive results occurring in 46% of low-risk patients (including pregnant women) and 14% of high-risk patients (eg, MSM).

Unusual serologic responses have been observed among HIV-infected persons with syphilis. The patient shown in Figure 3A had advanced HIV disease with ulcerative nodular syphilis that was not diagnosed for months because of absence of a serologic response to syphilis. This phenomenon may be seen when the concentration of cardiolipin antibody is high, precluding visible agglutination using RPR testing. Dilution of sera 1:100 was required in this instance before agglutination was visible.

The patient shown in Figure 3B had advanced HIV disease with a CD4+ cell count of 3/µL and had hypopigmented rash for several months. During this time, extensive evaluation including many nontreponemal and treponemal tests was negative. It was initially thought that the patient had T-cell lymphoma or severe psoriasis. A skin biopsy revealed a lymphocytic infiltrate; treponemes were identified via silver stain of the tissue. Biopsy should be performed in instances in which the diagnosis is uncertain in persons with advanced HIV infection who fail to mount an adequate immune response because of advanced immunosuppression.

The treatment of choice for primary, secondary, and early latent syphilis is 2.4 million units of benzathine penicillin administered by intramuscular (IM) injection. There is no evidence of clinical benefit of additional doses of benzathine penicillin or other additional antibiotics in early syphilis, despite the somewhat common practice of administering 3 weekly doses of benzathine penicillin.

Use of any penicillin alternatives (eg, for patients with penicillin allergy) should be undertaken with close clinical and serologic monitoring. Several retrospective studies support the use of doxycycline for early syphilis; however, many of these studies were conducted in HIV-uninfected persons. Limited studies suggest that ceftriaxone also is effective for early syphilis, but the optimal dose and duration have not been clearly defined.

Azithromycin has not been well-studied in HIV-infected persons with early syphilis, and azithromycin resistance and treatment failures have been reported, especially in MSM. A recent study in 12 US cities showed that azithromycin resistance is fairly widely distributed and is more common in MSM than in men who have sex exclusively with women. Azithromycin should not be used in MSM, or in pregnant women because it does not reliably cross the placenta.

**HSV Infection**

HIV-infected persons can have prolonged, severe, or atypical presentations of genital herpes. External genital lesions may not be evident. Figure 4 shows an HIV-infected woman with vaginal discharge and numerous cervical ulcerations. The classic, ulcerative, external genital lesions may be absent in some instances and should prompt

![Figure 3. Presentations of syphilis in HIV-infected patients. A: Ulcerative nodular syphilis. B: Seronegative secondary syphilis.](image)

![Figure 4. Cervical lesions in an HIV-infected patient with herpes simplex virus-2 infection.](image)
the clinician to consider alternative clinical presentations such as herpetic cervical infection that can present as recurrent vaginal discharge.

Many persons may have also mild or unrecognized infection but can shed virus intermittently in the genital tract. A recent study observed 498 immunocompetent, HSV-2–infected men and women in whom self-administered genital swabbing was performed daily for 30 days. Persons with asymptomatic HSV-2 infection shed virus in the genital tract less frequently than those with symptomatic infection, but the quantity of virus shed during subclinical shedding was comparable to the quantity in those with symptoms. This suggests that the management of genital herpes should address the chronic nature of the disease, not just the treatment of genital ulceration.

Suppressive therapy with antiviral agents is effective in decreasing the clinical manifestations of genital herpes in HIV-infected persons. Higher doses or a more prolonged duration of acyclovir therapy may be required. Use of daily suppressive therapy can reduce the likelihood of the emergence of drug resistance, as demonstrated in patients with immunosuppression due to bone marrow transplantation. Resistance to antiviral therapy should be suspected for lesions that persist despite appropriate therapy. Clinical management of acyclovir-resistant HSV includes intravenous foscarnet or topical imiquimod or cidofovir gel.

**Nongonococcal Urethritis**

Several organisms can cause urethritis. Nongonococcal urethritis is diagnosed when examination indicates urethral inflammation without gram-negative intracellular diplococci. *Chlamydia trachomatis* can be present in 15% to 40% of cases. *Mycoplasma genitalium*, an emerging pathogen, accounts for 15% to 25% of nongonococcal urethritis. Currently, *M genitalium* is very difficult to culture and may be identified with PCR tests available only in the research setting. Consideration of *M genitalium* infection as an etiologic agent of nongonococcal urethritis may be important, as this organism responds more effectively to azithromycin than doxycycline. Other pathogens can include certain *Ureaplasma* strains, *Trichomonas vaginalis*, genital herpes, adenovirus, enteric bacteria, and *Candida* species.

**Gonorrhea**

Gonorrhea is important because of the high burden of disease, the reproductive and economic consequences of infection, and progressive antibiotic resistance. *Neisseria gonorrhoeae* has demonstrated a remarkable ability to develop resistance to numerous antimicrobials over the last 60 years, including sulphonamides, penicillins, tetracyclines, and fluoroquinolones. Because of concerns about emerging gonococcal antimicrobial resistance, the CDC developed a Gonococcal Isolate Surveillance Project to monitor antimicrobial susceptibility in the United States. The data from this project have provided a rational basis for recommended gonococcal treatment regimens.

The most effective treatment for uncomplicated gonococcal infection of the cervix, urethra, or rectum is combination therapy with ceftriaxone 250 mg IM and either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days. However, declining gonococcal susceptibility and treatment failure to cefalosporins (most notably with oral regimens) is occurring worldwide. The prevalence of isolates in the United States with elevated cefixime minimal inhibitory concentrations has increased substantially in the western United States and in MSM. These patterns are worrisome and may indicate the early development of clinically significant gonococcal resistance to cefalosporins. There have been oral and parenteral cefalosporin treatment failures reported around the world, but this has not yet been seen in the United States.

Providers who identify a gonococcal treatment failure should perform culture and antimicrobial susceptibility testing of relevant clinical specimens. The practitioner should consult an infectious diseases specialist for treatment advice and report the case to the CDC through the local or state health department within 24 hours. The initial treatment regimen should include ceftriaxone 250 mg IM plus azithromycin 2 g orally. A test of cure should be conducted 1 week after retreatment, and clinicians should ensure that the patient’s sexual partners from the preceding 60 days are promptly evaluated and treated.

**Gastrointestinal Syndromes**

Proctitis is a sexually transmitted gastrointestinal (GI) syndrome associated with anorectal pain, rectal discharge, or tenesmus. Gonorrhea, chlamydia, genital herpes, and syphilis are the most common pathogens involved. Proctocolitis is associated with symptoms of proctitis, diarrhea, or abdominal cramps and may be caused by *Campylobacter, Shigella, Salmonella, Entamoeba histolytica*, or lymphogranuloma venereum serovars of *C trachomatis*. Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis, and it may occur among those persons whose sexual practices include oral-anal contact. Giardia is the most frequently implicated pathogen causing enteritis.

Lymphogranuloma venereum (LGV) is an invasive, chlamydial infection that can lead to chronic fistulas and strictures if untreated, and its presentation can resemble inflammatory bowel disease (Crohn’s disease). Figure 5 shows the mucosa of an HIV-infected patient with LGV who had an initial diagnosis of inflammatory bowel disease based on clinical presentation and histology of a colonic biopsy. The finding of painful perianal ulcers or mucosal ulcers detected on anoscopy should raise suspicion for LGV in MSM or women who report receptive anal intercourse. Rectal *C trachomatis* infection can be diagnosed using NAAT on rectal specimens.

Commercially available NAATs are not FDA-approved for testing of rectal specimens, but can be used by labora-
Hepatitis A and B viruses can be screened at entry into care, with subsequent screening performed at least annually. TV infection in HIV-infected women might enhance HIV transmission by increasing genital shedding of the virus and treatment for TV has been shown to reduce HIV shedding.10,11 For sexually active women who are HIV-seropositive, screening for trichomoniasis is recommended at entry into care, with subsequent screening performed at least annually. TV testing is recommended based on the reported prevalence of infection, the effect of treatment at reducing vaginal HIV shedding, and the potential complications of upper genital tract infections among women who are left untreated.12,13 Rescreening 3 months after completion of therapy should be considered among HIV-seropositive women with trichomoniasis, a recommendation based on the high proportion of recurrent or persistent infection and the association between HIV and TV infections.7 The standard treatment recommendations for trichomoniasis have been based on studies that were conducted in HIV-seronegative persons. However, a recent randomized clinical trial in HIV-infected women demonstrated that a single 2 g dose of oral metronidazole was not as effective as metronidazole 500 mg twice daily for 7 days for treatment of trichomoniasis.14 Therefore, a multidose nitroimidazole treatment regimen for trichomoniasis can be considered in HIV-infected women. It is also likely that concomitant bacterial vaginosis influences treatment response.15

**Trichomoniasis**

*Trichomonas vaginalis* (TV) is the most prevalent curable STI in the United States and in the world. Trichomoniasis is frequently diagnosed among women infected with HIV, with prevalences reported between 6.1% and 52.6%, depending on the testing method used for diagnosis. TV infection in HIV-infected women might enhance HIV transmission by increasing genital shedding of the virus and treatment for TV has been shown to reduce HIV shedding.10,11 For sexually active women who are HIV-seropositive, screening for trichomoniasis is recommended at entry into care, with subsequent screening performed at least annually. TV testing is recommended based on the reported prevalence of infection, the effect of treatment at reducing vaginal HIV shedding, and the potential complications of upper genital tract infections among women who are left untreated.12,13 Rescreening 3 months after completion of therapy should be considered among HIV-seropositive women with trichomoniasis, a recommendation based on the high proportion of recurrent or persistent infection and the association between HIV and TV infections.7

**HPV Infection**

High-risk human papillomavirus (HPV) subtypes (eg, 16, 18) are associated with cervical, penile, vulvar, vaginal, and anal cancers. HPV is also associated with oropharyngeal cancers, recurrent respiratory papillomatosis, and anogenital warts. There is an increase in the incidence of oral cancers caused by HPV, such that the prevalence of oral cancers in the United States is expected to exceed the prevalence of HPV-associated cervical cancer by 2020.16 Patients with HPV infection need to be counseled regarding the risk of genital and oral transmission. Updated guidance on HPV, genital warts, and counseling messages is available.17

Because of the increased incidence of anal cancer in HIV-infected MSM, screening for anal intraepithelial neoplasia by cytology can be considered.18 However, evidence is limited concerning the natural history of anal intraepithelial neoplasias, the reliability of screening methods, the safety and response to treatments, and the programmatic considerations that would support this screening approach.

Sinecatechins ointment (15%), made from green tea leaves, is a new patient-applied treatment for genital warts. However, the safety and efficacy of this therapy in HIV-infected patients has not been established. It has adverse effects (eg, vitiligo) similar to imiquimod. The quadrivalent or the bivalent HPV vaccine can be used for women and girls, but the quadrivalent vaccine is the only approved vaccine for men and boys. Cervical cancer screening is recommended regardless of vaccine status. Publication of the updated HIV Opportunistic Infection Prevention and Treatment Guidelines is anticipated in 2012 and recommendations regarding HPV vaccination are likely to be addressed.

**Prevention of STIs**

Current efforts to prevent STIs should be based on risk assessment, screening, treatment, and partner services. As noted, routine evaluation of HIV-infected persons for STIs is important.
because an incident infection is an objective marker of unprotected sexual activity that may result in HIV transmission. Certain STIs can also increase plasma HIV shedding. Other important strategies include high-intensity behavioral counseling and preexposure vaccination (hepatitis A virus, hepatitis B virus, and HPV vaccines). Consistent and correct use of latex condoms by men can reduce the risk of acquiring other STIs (eg, HIV, gonorrhea, chlamydia, trichomoniasis) via mucosal fluids. Agents that disrupt the anal or vaginal epithelium (eg, spermicide with nonoxynol-9) can damage mucosal tissues and provide a portal of entry for sexually transmissible agents. Finally, male circumcision has been shown to reduce the risk for HIV and some STIs in heterosexual men in Africa (eg, high-risk HPV types and genital herpes).

Presented by Dr Workowski in October 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Workowski in April 2012.

Dr Workowski has no relevant financial affiliations to disclose.

References


Editorial
Hepatitis C Virus Therapeutics: At the End of the Beginning

Robert T. Schooley, MD

Those of us who have been engaged in HIV therapeutics for the past 2 decades remember all too well the excitement of the 24-month period from 1994 to 1996 that witnessed the treatment paradigm shift from sequential failing regimens of nucleoside analogue reverse transcriptase inhibitors (nRTIs) to stable, “fully” suppressive combination regimens. AIDS as we knew it during the first 15 years of our awareness of the illness has shifted in the most recent 15 years from an inexorably progressive disease to one that can be arrested for a prolonged period of time.1 The speed of this paradigm shift was the result of a well-integrated research effort that included basic, translational, and clinical components that were able to take advantage of a robust pipeline of antiretroviral drugs. Many have argued that the transformation in the prognosis of HIV infection was one of the most impressive demonstrations in recent history of the value of investments in biomedical research.

Although it has received less comment, the equally rapid application of research findings to clinical practice in the United States and Europe was also unprecedented. The translation of research findings to clinical practice was even more impressive in view of the complexity of initial combination-treatment regimens and the need for physicians to incorporate rapidly evolving laboratory management tools such as plasma HIV-1 RNA assays and genotypic and phenotypic resistance tests. The impact of the research findings would never have been realized in the absence of a talented and dedicated HIV treatment community that has continued to bring advances in therapy from clinical trials to the clinic in short order. By the efficient introduction of research findings into medical practice, it is estimated that more than 2.8 million quality-adjusted life-years were saved in the United States between 1989 and 2003.2

The HIV treatment community that emerged during the first phase of the epidemic included physicians from a number of different disciplines, including internal medicine, infectious diseases, oncology, dermatology, general medicine, and others. Despite the broad spectrum of professional training experiences, the HIV treatment community was relatively cohesive, interactive, and well defined. Because of the complexity of HIV management, it quickly became apparent that the best (and most contemporary) care came from those who devoted most of their professional time to HIV care and worked in multidisciplinary teams that included specialists with HIV-specific knowledge in their own subspecialties. The vast majority of those who stepped forward to do this were those who had been caring for patients with the illness during the “palliative era.” It was a natural step for those who had become comfortable with the disease and its patient population to follow therapeutic developments into the modern treatment era.

We have now entered an era in hepatitis C virus (HCV) therapeutics that promises to be analogous to the “wonder years” of 1994 to 1996 in HIV therapeutics. The first 2 direct-acting antivirals (DAAs) for HCV infection were approved less than a year ago, and more than 30 additional drugs are in clinical trials. When either of the 2 new HCV protease inhibitors is combined with peginterferon alfa and ribavirin, treatment success rates for previously untreated HCV genotype 1–infected patients have increased from approximately 45% to the 60% to 70% range.3,4 As with the case of HIV antiretroviral treatment, it is quite clear that combination treatment will be required for most (or all) patients with HCV infection. It is also clear that as more DAAs emerge from clinical trials and enter clinical practice, management decisions will be complex and will require substantial expertise in many of the same skill sets that characterize contemporary HIV management.

Since the introduction of interferon alfa monotherapy in the early 1990s, HCV therapeutics has been characterized by gradually improving treatment success rates but only incremental increases in the number of people seeking therapy. Most of those treated received therapy because progression of their liver disease forced the issue. Because accurate assessment of liver disease usually required a liver biopsy, most treatment candidates ended up in the hands of hepatologists before therapy was contemplated. Treatment for HCV was usually undertaken by hepatologists and their nurses, and patients were either cured and returned to the primary care system, or experienced treatment failure and returned to the primary care system for general medical care, with intermittent returns to the hepatologist for complications of liver disease. In the setting of a fairly steady number of new patients who entered the treatment population as treatment-initiation decisions were made on a one-by-one basis, the number of people actively treated for HCV has remained relatively stable over time (see Box).

In contrast, HIV-infected persons are generally referred to HIV specialists and even if treatment succeeds (as is the case for many), these patients then remain in care for life. Thus, the number of people in HIV care has continued to rise steadily, and HIV treatment capacity has expanded correspondingly. As in other areas of medicine, there are geographic disparities, but the overall capacity of the HIV care system has managed so far to keep up with demand.

Current indications are that over the next 18 months to 24

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months, we will witness the end of the “interferon alfa” era of HCV management. As this happens, the dialogue about whether to initiate HCV therapy will shift from “Are you telling me that my liver disease is so bad that I really can’t wait any longer?” to “I’m ready for my virectomy; what are we waiting for?” If treatment success can be achieved in 12 weeks to 24 weeks with well-tolerated, all-oral regimens, and if treatment success rates rise to the 90% to 95% range (which seems quite feasible), it is quite likely that there will be a very large influx of HCV-infected persons into the treatment queue. The roll-out of HCV awareness and screening campaigns will further stimulate treatment demand. Although treatment will be greatly simplified for the patient, it is assumed that for the near future, it will remain complicated for the practitioner. Treatment-initiation decisions will be easier, but treatment management may become more complex before it gets easier. In the peginterferon/ribavirin era, once treatment began, management mainly consisted of following HCV RNA levels for futility and managing well-defined toxicities with dose modification. Most management decisions were relatively simple, and most patients could be followed primarily by nurse practitioners and physician assistants.

The field of HCV therapeutics is moving rapidly and much remains to be learned; thus, firm predictions are inherently risky. It is likely, however, that for the foreseeable future, management decisions will require much more thought than they did in the “easy” days of interferon alfa–based regimens. Considerations in crafting combination regimens will likely include HCV genotype, treatment history, and drug-drug interactions as well as patient-centered considerations such as patient genetics, regimen complexity, toxic effect profile, and adherence challenges. Management of therapy will be guided by plasma HCV RNA kinetics, and decisions about drug discontinuation and substitution will require detailed knowledge of adverse-effect profiles; resistance-barriers, magnitude and pathways; and future treatment options. Therefore, at the same time that we can expect a large increase in the number of people seeking therapy, we should also expect that more complex treatment paradigms will require much more ongoing active management.

It is unlikely that the gastroenterology community alone can respond adequately to the challenges posed by dramatically increased numbers of HCV-infected patients seeking much more complex treatment regimens. Most HCV
care is currently provided by the minority within the hepatology community who are interested in viral hepatitis. It is also highly unlikely that gastroenterologists or hepatologists not currently primarily engaged in viral hepatitis therapeutics will be motivated by rapidly changing treatment paradigms to close their procedure rooms to manage a large influx of “E and M” (evaluation and management) patients. Second, as treatment decisions become less amenable to algorithm-guided management by nonphysicians, it seems likely that some of the current HCV treatment community will exit the field.

This leads us to ask from where the next generation of HCV treaters might be recruited. Given the complexity of treatment decisions (at least over the short- to mid-term), HCV care will likely not migrate from the subset of presently engaged hepatologists to the primary care community. It will instead require the development of a new community of treaters with an interest in complex treatment decisions guided by an appreciation of disease pathogenesis. These physicians will need to be comfortable dealing with psychosocial issues, close laboratory monitoring, response-guided therapy, drug-drug interactions, and a host of other issues. Having worked through all of these issues in the management of HIV disease, the community of HIV-treating physicians seems uniquely situated to step to the forefront and assume responsibility for managing a disease that is shifting from a liver disease to a viral disease in the coming all-oral treatment era. It will, of course, be essential to maintain strong relationships with the hepatology community because expert management of liver disease will continue to be a required element of multidisciplinary HCV care. The evolution of a care system in which hepatologists are called upon primarily to manage liver disease collaboratively could actually increase the number of hepatologists engaged in HCV care, because virtually the entire hepatology community would be comfortable managing liver disease, though only a subset will remain comfortable managing complex antiviral regimens.

Much research remains to be done as we work through the host of promising HCV therapeutics in the pipeline, but it seems likely that the current 24-month period following the approval of the first 2 DAAs will be viewed as the end of the beginning in HCV therapeutics. It is essential that we now thoughtfully plan for the coming treatment era if we are to bring research advances to the clinic as rapidly as we did in HIV therapeutics 15 years ago. Mortality from viral hepatitis has recently surpassed that of HIV. We are armed with a rapidly evolving understanding of disease pathogenesis and an exciting array of new therapeutic agents, so prospects for dramatic advances in HCV therapy have never been better. The HIV treatment community can and should play a pivotal role in bringing these advances to the clinic.

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