Volume **20** Issue **4** October/November **2012**

Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives

Cases From the Field

Topics in Antiviral Medicine™

IAS–USA
International Antiviral Society–USA

Topics in Antiviral Medicine™

Topics in Antiviral Medicine (formerly *Topics in HIV Medicine*) is published by the IAS–USA. This journal is intended to be a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV, hepatitis C virus, or other viral infections.

Editorial Policy

The views and opinions expressed in this journal are those of the contributors and do not necessarily reflect the views or recommendations of the IAS–USA. *Topics in Antiviral Medicine* is supported through grants from several commercial companies that are committed to supporting CME about HIV and other viral infections. In the interest of an objective, balanced, and scientifically rigorous publication, the IAS–USA seeks funding that is pooled from companies with competing products; these companies have no input or control over the journal content or the selection of contributors.

All authors and contributors provide disclosures of financial interests, and this information is available at the end of each article.

This journal may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in *Topics in Antiviral Medicine.*

Financial Disclosures

Financial disclosures for members of the IAS–USA Board of Directors and the Editorial Board of *Topics in Antiviral Medicine* are available online at www.iasusa.org.

Copyrights and Reprints

Subscription Information

Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in address, please create or update your user profile at www.iasusa.org or use the Subscription Request/Address Change form in this issue.

Correspondence

Topics in Antiviral Medicine welcomes editorial correspondence. Address letters to:

Editor, *Topics in Antiviral Medicine*
IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120

Phone: (415) 544-9400
Fax: (415) 544-9401

Website: http://www.iasusa.org
E-mail: journal"at"iasusa.org

On the Web

Current and previous issues of *Topics in Antiviral Medicine (*as well as *Topics in HIV Medicine)* are available online at www.iasusa.org.

ISSN 2161-5861 (Print)
ISSN 2161-5853 (Online)

Printed in USA on acid-free paper

Grant Support

Support for the 2012 *Improving the Management of HIV Disease* continuing medical education program:

PLATINUM SUPPORTER
Gilead Sciences, Inc

Gold Supporter
Janssen Therapeutics

Silver Supporters
Bristol-Myers Squibb
Merck & Co, Inc
Abbott Laboratories
ViiV Healthcare

Support for the 2012 *Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes* continuing medical education program:

PLATINUM SUPPORTER
Vertex Pharmaceuticals

Gold Supporters
Abbott Laboratories
Gilead Sciences
Merck & Co, Inc

Silver Supporter
Janssen Therapeutics

Topics in Antiviral Medicine™

A publication of the IAS–USA

Perspectives

Cases From the Field

Announcements

2012 marks the 20th year of the IAS–USA

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, hepatitis C virus, or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners who are actively involved in medical care. The educational activities are particularly intended to bridge clinical research and patient care.

2012 Webinars for Ryan White Clinical Providers

With the cancellation of this year's Ryan White Clinical Conference, the IAS–USA is offering key updates in HIV treatment in 2 continuing medical education (CME) 90-minute webinars for Ryan White clinical providers on **December 6** and **December 13, 2012**. The webinar series will cover updates in antiretroviral therapy, HIV and hepatitis C virus coinfection, complications in HIV management, and new data from scientific conferences. Speakers include Carlos del Rio, MD, Emory University School of Medicine, and Michael S. Saag, MD, University of Alabama at Birmingham. Register before the December 4 deadline at www.iasusa.org/webinars.

2013 Live 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™*.

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

Part of the IAS–USA focus on the management of HCV infection, these half-day, small-group, intensive CME workshops are presented by leading experts in the field. Attendance is limited to 35 practitioners, so ***early registration is encouraged.***

Half-Day, Small Group, Intensive Hepatitis C Virus Workshops

Atlanta, Georgia
Tuesday, April 9, 2013
Cobb Galleria Centre

New York, New York
Thursday, May 2, 2013
New York Marriott Marquis

San Francisco, California
Monday, June 3, 2013
South San Francisco Conference Center

Los Angeles, California
Tuesday, April 23, 2013
Center for Healthy Communities
(California Endowment Center)

Chicago, Illinois
Tuesday, May 21, 2013
Chicago Marriott Downtown Magnificent Mile

Washington, DC
Monday, June 17, 2013
Hyatt Regency Crystal City

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.

Atlanta, Georgia
Wednesday, April 10, 2013
Cobb Galleria Centre
Cochairs: Michael S. Saag, MD, Jeffrey L. Lennox, MD

Chicago, Illinois
Monday, May 20, 2013
Chicago Marriott Downtown Magnificent Mile
Cochairs: John P. Phair, MD, Paul A. Volberding, MD

Los Angeles, California
Monday, April 22, 2013
Center for Healthy Communities (California Endowment Center)
Cochairs: Ronald T. Mitsuyasu, MD,
Constance A. Benson, MD, FACP

San Francisco, California (tentative)
Tuesday, June 4, 2013
South San Francisco Conference Center
Cochairs: Robert T. Schooley, MD, Stephen E. Follansbee, MD

New York, New York (tentative)
Friday, May 3, 2013
New York Marriott Marquis
Cochairs: Gerald H. Friedland, MD, Paul A. Volberding, MD

Washington, DC
Tuesday, June 18, 2013
Hyatt Regency Crystal City
Cochairs: Henry Masur, MD, Michael S. Saag, MD

Educational Resources from past live courses are available on the IAS–USA website 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 • Website: www.iasusa.org

Topics in
Antiviral Medicine™

Continuing Medical Education

The following article in this issue is associated with continuing medical education (CME) credit: Stein JH. Cardiovascular risk and dyslipidemia management in HIV-infected patients. *Top Antiviral Med*. 2012;20(4):129-133

Instructions

This journal-based continuing medical education (CME) activity provides a review of cardiovascular disease and HIV infection. To complete the activity, the learner is instructed to:

- Read the article (see pages 129-133)
- Review a selection of the references
- Reflect on how the information might be applied to clinical practice
- Complete the posttest and CME claim form on page 124 and send both to the IAS–USA.

Learning Objectives

On completion of this activity, the learner will be able to: evaluate the traditional risks for coronary heart disease (CHD) in HIV-infected patients; identify any additional risks from HIV infection and some antiretroviral agents in each patient; and choose the best strategy to manage dyslipidemia and reduce CHD risk.

Accreditation

The International Antiviral Society–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 or other viruses. It is also relevant to nurse practitioners, physician assistants, nurses, pharmacists, and other health professionals who provide care for people with viral diseases.

Conflict of Interest and Financial Disclosures

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

Dr Stein has served on data and safety monitoring boards for Abbott Laboratories, Lilly, and Takeda. He has intellectual property rights licensed by the Wisconsin Alumni Research Foundation for carotid ultrasound and cardiovascular risk.

Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, Chimerix, Gen-Probe Inc, Gilead Sciences, Inc, Merck & Co, Inc, Monogram Biosciences, Inc, and Tobira Therapeutics. He has been the recipient of research grants or contracts from Merck & Co, Inc. He has held stock options for Chimerix.

Drs Hirsch and Benson have no relevant financial affiliations to report. Dr Benson's spouse, Dr Robert T. Schooley, has served as a consultant to 3-V Biologicals, Gilead Sciences, Inc, Inhibitex, Inc, Johnson & Johnson Services, Inc, Laboratory Corporation of America, Merck & Co, Inc, Santaris Pharma, and Tobira Therapeutics. He has stock in GlobeImmune, Inc, and stock options for Achillion Pharmaceuticals, Inc.

CME Posttest

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 higher.

1. Which statement below completes the following sentence accurately? A study in more than 36,000 HIV-infected patients at Veterans Affairs hospitals showed that as mortality rates declined in association with use of potent antiretroviral therapy:

- ❑ **A.** Rates of hospitalization for cardiovascular disease increased.
- ❑ **B.** Rates of hospitalization for cerebrovascular disease increased.
- ❑ **C.** Rates of hospitalization for cardiovascular disease remained stable.
- ❑ **D.** Rates of hospitalization for cardiovascular disease declined.

2. Which statement best describes findings of AIDS Clinical Trials Group 5152s, in which HIV-infected patients were given a protease inhibitor (PI)-sparing regimen, a nucleoside analogue reverse transcriptase inhibitor (nRTI)-sparing regimen, or a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-sparing regimen?

- ❑ **A.** All 3 regimens produced changes in endothelial function corresponding to changes in lipids.
- ❑ **B.** All 3 regimens produced similar improvement in endothelial function despite substantial differences in lipid changes.
- ❑ **C.** PI- and nRTI-sparing regimens resulted in decreased endothelial function.
- ❑ **D.** The NNRTI-sparing regimen but not the other regimens resulted in decreased endothelial function.

3. Which statement accurately describes smoking or its impact in HIV-infected people?

- ❑ **A.** HIV-infected individuals have cigarette smoking rates about the same as the general population.
- ❑ **B.** Smoking rates are lower in HIV-infected people than in the general population.
- ❑ **C.** Cigarette smoking appears to have a negligible impact on risk for coronary heart disease (CHD) events in HIV-infected people.
- ❑ **D.** Smoking is the strongest predictor of CHD events in HIV-infected people, after history of CHD and age.

4. Which statement describes the findings of the recent Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis? The results showed that, over the course of 5 years, every 39 mg/dL reduction in LDL cholesterol level on statin therapy was associated with:

- ❑ **A.** No reduction in all-cause mortality.
- ❑ **B.** No change in CHD mortality.
- ❑ **C.** A 21% reduction in major cardiovascular events.
- ❑ **D.** Little change in all-cause mortality, CHD mortality, or major cardiovascular events.

5. Which statement is an accurate assessment of evidence to guide management of dyslipidemia in HIV-infected patients?

- ❑ **A.** LDL cholesterol level is the best measure of atherogenic lipoproteins even when the triglyceride level is elevated.
- ❑ **B.** Triglyceride level is a primary target of lipid-lowering therapy even when the triglyceride level is only slightly elevated.
- ❑ **C.** Statin therapy can lower the level of non-HDL cholesterol, including LDL cholesterol, and an associated increase in risk for diabetes is outweighed by the reduction in risk for cardiovascular events.
- ❑ **D.** High-dose statin therapy was not associated with an increased risk of diabetes more than low-dose statin therapy in recent meta-analyses.

This continuing medical education activity is offered from November 15, 2012, to November 15, 2013. Physicians (MDs, DOs, and international equivalents) who receive a passing score on the test and submit the registration and evaluation forms are eligible to receive CME credit. Other health care practitioners will receive a certificate of participation.

Mail or fax this page along with the completed test to:
IAS–USA, 425 California Street, Suite 1450, San Francisco, CA 94104-2120 Fax: (415) 544-9401

Participant Information

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

First Name MI Last Name

Address (Please check one: ❒ Home ❒ Work)

Address 2nd Line

City State/Province

Postal Code Country

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

Institution or Organization

Telephone (❒ Home ❒ Work) Facsimile

E-mail address to receive your CME certificate (❒ Home ❒ Work)

The approximate amount of time (in hours) I spent on reading the article, reviewing the references, and reflecting on how the information might be applied to the practice was:
❒ >.5 ❒ 1.0 ❒ 1.5 ❒ 2.0 ❒ other _____

Evaluation

Please complete the following evaluation form for this journal-based CME activity:

	Excellent	Very Good	Good	Fair	Poor
Please rate the activity in terms of meeting the stated learning objectives (see page 123 for objectives)	❍	❍	❍	❍	❍
Please rate the extent to which the information presented was supported by the evidence	❍	❍	❍	❍	❍
Please rate the overall quality of the activity	❍	❍	❍	❍	❍
Please rate the activity's freedom from commercial bias	❍	❍	❍	❍	❍
Please rate the overall value of this activity to your practice	❍	❍	❍	❍	❍

Do you expect to make changes in your clinical practice based on the information presented in this activity? ❒ Yes ❒ No

If so, please list up to 3 measurable changes you expect to make:

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 comes from 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

Managing Adverse Effects and Complications in Completing Treatment for Hepatitis C Virus Infection

The addition of direct-acting antivirals (DAAs) to hepatitis C virus (HCV) treatment regimens has made treatment more effective and patient management more complex. Shepherding patients through a full course of HCV therapy requires motivation and involvement on the part of the patient and the physician. Indeed, physician inexperience and lack of confidence in guiding patients through the challenges of treatment appears to be a primary reason for early discontinuation of therapy. Among the many complications of HCV treatment that must be managed efficiently and effectively are depression and other psychiatric disorders; hematologic abnormalities including DAA- and ribavirin-associated anemia and peginterferon alfa-associated neutropenia and thrombocytopenia; rash and drug eruptions, including telaprevir-associated rash; and weight loss. Practical considerations in management of these common complications are offered. This article summarizes a presentation by Kenneth E. Sherman, MD, PhD, at the IAS–USA live continuing medical education course held in New York in June 2012.

In clinical trials, treatment with a direct-acting antiviral (DAA) in combination with peginterferon alfa and ribavirin for 48 weeks produced a sustained virologic response (SVR) in approximately 65% to 75% of patients with genotype 1 or 4 hepatitis C virus (HCV) infection. Peginterferon alfa and ribavirin treatment for 24 weeks produced an SVR in approximately 70% to 85% of patients with HCV genotype 2 or 3 infection. SVR rates in clinical practice are not as high, in large part because early discontinuation of HCV therapy is frequent for reasons unrelated to treatment futility (ie, stopping treatment for failure to achieve specific reductions in plasma HCV RNA level by specific time points). Major reasons for early discontinuation of anti-HCV therapy are discussed herein.

Physician Inexperience

Treating HCV infection with available regimens can be daunting to both patient and physician, and physician inexperience can result in a lack of confidence in initiating and following through with treatment. A recent analysis in a study population receiving peginterferon alfa and ribavirin therapy showed that treatment was discontinued in 44% of patients, with physician reasons accounting for 75% of discontinuations and patient reasons accounting for 25%.[1]

Whereas treatment futility accounted for 33% of physician discontinuations, no reason for discontinuation was given for 39% of cases. Comorbidities and lack of adherence were cited as reasons in 5% of cases each. Patients often cited adverse effects as a reason for stopping treatment, but some also reported that they got the sense from their physician that they should stop or were encouraged to stop. In the WIN-R (Weight-Based Dosing of Peginterferon alfa-2b and Ribavirin) trial, which was performed at 236 community and academic sites, 41.3% of subjects discontinued therapy.[2] Clinicians who are inexperienced and not confident in their ability to guide a patient through the treatment course may discontinue treatment early, depriving the patient of a chance for cure. As health care providers, we need to move past any such hesitancy in order to provide effective treatment and management.

Psychiatric Complications

Depression is the most common psychiatric complication encountered in HCV patients, with mild to moderate depression found in as much as 80% of patients. Bipolar disorder and schizophrenia are also not infrequently encountered.

There is little evidence to support a benefit of preemptive antidepressant therapy in all patients undergoing HCV treatment, though a recent randomized trial of HCV patients without psychiatric history suggested that major depression risk was decreased in a group of patients randomized to receive escitalopram prior to interferon-based therapy.[3] For patients who are actively depressed, antidepressant treatment is likely to be required. Mild and moderate depression can be assessed by and readily treated by the HCV physician and in most cases, referral to psychiatry is not necessary. The primary issue for the HCV physician is to determine whether the depression is manageable in the context of HCV treatment. The physician should become comfortable with the use and effects of several antidepressants, including sertraline, paroxetine, and mirtazapine.

A thumbnail guideline for use of these agents is to use sertraline if the depression is characterized by sadness and crying episodes and paroxetine if it is characterized by anger. Mirtazapine is especially useful in patients who are suffering weight loss, because it is associated with significant appetite stimulation and weight gain. All of these drugs have potential interactions with telaprevir and boceprevir and should be started at the lowest possible therapeutic dose. Psychiatric assistance is needed for patients with more severe depression—eg, those with suicidal ideation—and HCV treatment should be delayed until such patients are stable. The most effective way to

Dr Sherman is the Gould Professor of Medicine and Director of the Division of Digestive Diseases at the University of Cincinnati College of Medicine in Ohio, and a member of the IAS–USA Viral Hepatitis Advisory Board.

manage such patients is not to refer to psychiatry and wait for clearance, but to form a partnership with the psychiatrist throughout the duration of the patient's treatment.

Psychiatric expertise also usually is needed for patients with bipolar disorder or schizophrenia prior to starting HCV treatment. It is important that these patients have a commitment to psychiatric care. A contract with such patients sometimes ensures that they will stay with their psychiatric care. With patients who have bipolar disorder, it is best to try to initiate HCV treatment during a hypomanic phase. It is difficult to start and maintain therapy in a manic or actively delusional patient even with the help of a psychiatrist. There is evidence from several small studies that partnering with psychiatry can help in getting patients with bipolar disorder or schizophrenia through an HCV treatment course. In one study, 22 patients with psychiatric disorders and 17 control patients were treated with peginterferon alfa and ribavirin in an interdisciplinary setting that included psychiatry. The outcomes in the 2 groups were similar, with SVR being achieved in 50% and 58.6%, respectively.[4]

Hematologic Toxicities

Anemia

Anemia beyond that associated with ribavirin alone is a major adverse effect with both telaprevir and boceprevir. For example, anemia occurred in 37% and 41% of patients receiving telaprevir in the ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir)[5] and ILLUMINATE (Illustrating the Effects of Combination Therapy with Telaprevir)[6] trials, respectively, compared with 19% of patients receiving peginterferon alfa and ribavirin alone. No erythrocyte-stimulating agents were used in the telaprevir trials, with anemia being managed by ribavirin dose reduction. Similarly, 49% of patients in each of the 2 boceprevir arms in the SPRINT-2 (Serine Protease Inhibitor Therapy 2) trial developed anemia, compared with 29% of patients receiving peginterferon alfa with ribavirin and placebo.[7] Treatment was discontinued because of anemia in 2% of each boceprevir group and in 1% of placebo patients. Dose reductions were implemented in 20% to 21% of boceprevir patients and in 13% of placebo patients, and epoetin alfa was used to treat anemia in 43% of boceprevir patients and 24% of placebo patients.

Ribavirin dose reduction should be considered the first strategy for treating anemia in patients receiving DAA-containing regimens, because it does not appear to compromise response, and is less expensive and safer than initiating epoetin alfa treatment or other erythrocyte-stimulating growth factors. In a recent trial in 500 patients receiving boceprevir-containing regimens, patients with hemoglobin levels dropping below or about to drop below 10 g/dL were randomized to receive a 200 mg/d to 400 mg/d reduction in ribavirin dose or to get an addition of 40,000 U/wk of subcutaneous epoetin alfa.[8] SVR rates were approximately 70% in both groups, suggesting no difference between the 2 approaches with regard to compromising response. In addition, a retrospective analysis of outcomes in the ADVANCE and ILLUMINATE telaprevir trials showed slightly, but not statistically significantly lower SVR rates in patients with ribavirin dose reduced to a range of 800 mg/d to 1000 mg/d, or 600 mg/d, than in patients with no ribavirin dose reductions (all SVR rates were between 74% and 79%).[9] Similar outcomes were observed in an analysis of previously treated patients in the REVEAL (Risk Evaluation of Viral Load Elevation and Associated Liver Disease) study of telaprevir.

Neutropenia

Neutropenia is common during peginterferon alfa and ribavirin therapy and is attributed primarily to peginterferon alfa. Considerable anecdotal evidence, analyses of clinical trials, and one large single center experience indicate that there is no increased risk of infection associated with neutropenia, even when the absolute neutrophil count (ANC) drops below 500/µL.[10,11] Neutropenia should be managed with filgrastim (5-10 µg/kg) only when the ANC drops below 500/µL and before any reduction in peginterferon alfa dose.

Thrombocytopenia

Thrombocytopenia is a frequent cause of treatment discontinuation in clinical practice. Platelet counts plummet during the first 6 weeks to 8 weeks in some patients, and physicians justifiably become alarmed. However, it does not appear that a declining platelet count should prompt substantial concern until it reaches about 30,000/µL. When platelet counts are in the range of 20,000/µL to 30,000/µL, the thrombocytopenia should be managed by peginterferon alfa dose reduction. In the absence of substantial anemia, the ribavirin dose should not be changed, because ribavirin increases platelet count when compared with use of peginterferon alfa alone.[12]

Eltrombopag is a platelet growth factor that is very expensive, sometimes difficult to get insurance approval for, and not widely used. However, its use can be considered in a patient who has a platelet count of 20,000/µL to 30,000/µL in whom no further peginterferon alfa dose reductions can be made and who is otherwise doing well. A study reported several years ago showed that starting eltrombopag treatment in patients with low platelet counts prior to beginning HCV therapy was successful in increasing platelet counts such that they remained at high levels throughout the course of therapy.[13] This approach would be very expensive and is not a US Food and Drug Administration–approved use of eltrombopag, but the drug can be effective in adjunctive therapy for thrombocytopenia.

HCV treatment should be discontinued in most cases if the platelet count drops below 20,000/µL. In patients who have hemophilia, the threshold for stopping therapy is much higher (eg, about 50,000 cells/µL).

Dermatologic Issues

Peginterferon alfa, ribavirin, and telaprevir, but not boceprevir, are associated with rash. Peginterferon alfa can cause dermatitis, local reactions, and exacerbation of psoriasis. The local reactions are rare but can be quite severe. Treatment should be stopped in patients who develop a depression or ulcer at the injection site; if treatment continues, the lesion will continue to widen and deepen. Psoriasis may progress from tiny patches to that covering large portions of the body. In such cases, aggressive treatment with topical steroids should be started in consultation with a dermatologist. Light therapy sometimes helps. Treatment with injectable methylprednisolone or other injectable steroids has been successful at more advanced stages of psoriasis, but should not be used for initial treatment. Ribavirin is associated with drug eruption that often occurs between 6 weeks and 16 weeks and up to 20 weeks of therapy. It frequently overlaps with telaprevir-associated rash, which is the rash of greatest concern.

Telaprevir is associated with eczematous rash and drug rash with eosinophilia and systemic eruptions (DRESS). A summary of data from telaprevir placebo-controlled phase II and III trials indicates that rash occurred in approximately 56% of telaprevir patients compared with approximately 35% of control patients, with rash being mild in severity in 37% of telaprevir patients, moderate in 14%, and severe in 5%.[14] Rash was typically pruritic and eczematous, covering less than 30% of the total body surface area. Rash started within the first 4 weeks of treatment in approximately 50% of patients, but was observed at any time during treatment. Progression of rash to greater severity occurred in less than 8% of patients.

Grading of skin eruptions is important. It was learned in the telaprevir trials that even experienced clinicians overestimate the percentage of body surface area affected by rash compared with dermatologist findings. A mild eruption is a localized eruption with limited distribution in separate, isolated sites on the body.[15] A moderate eruption is a diffuse rash that involves less than 50% of body surface area. Severe rash affects more than 50% of body surface area or is accompanied by substantial systemic symptoms, mucous membrane ulceration, target lesions, or epidermal detachment. Severe cutaneous adverse reaction (SCAR) comprises DRESS (usually involving fever and increased liver enzymes); Stevens-Johnson syndrome with toxic epidermal necrolysis; acute generalized exanthematous pustulosis; and erythema multiforme. Figure 1 illustrates DRESS. The patient's skin was peeling off in layers, and he had lesions in the mouth, dramatic swelling of the lips, and a very high eosinophil count. DRESS requires immediate hospitalization.

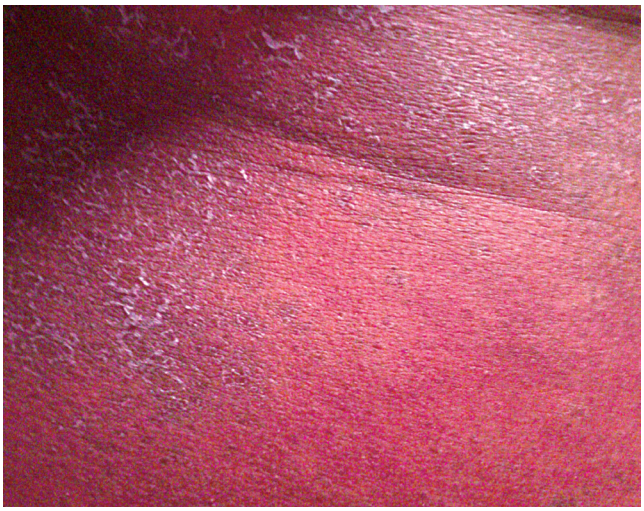


Figure **1**. Drug rash with eosinophilia and systemic eruptions (DRESS). This patient's skin is peeling off in layers, he had oral lesions in his mouth with blisters, and his lips were swollen. He had a high eosinophilic count.

Mild rash developing in patients receiving telaprevir should be managed conservatively with topical steroids. For moderate rash without mucosal involvement, management includes stopping telaprevir, especially if the patient has had more than 8 weeks of treatment, but continuing peginterferon alfa and ribavirin. If the physician suspects that the rash is caused by ribavirin, the drug can be held for 1 week to 2 weeks and then restarted at a lower dose. For patients with severe rash or SCAR, all HCV treatment should be stopped.

Weight Loss

Weight loss associated with peginterferon alfa treatment is fairly common. Body weight loss of more than 10% is considered serious. Serious weight loss is more common among patients who have HCV and HIV coinfection. Primary management consists of calorie supplementation using milk shakes or nutrition drinks. As noted above, the antidepressant mirtazapine is often effective in promoting weight gain.

Conclusion

With the availability of DAAs, the management of HCV treatment has become more, not less, complex. Specific management techniques are evolving as we learn more about both safety and efficacy of the currently available regimens.

The decision to initiate therapy now, versus waiting for next-generation therapies that may not contain peginterferon alfa, is also complex. In general, patients with stage 1 or 2 hepatic fibrosis are unlikely to progress to cirrhosis (stage 4) within 3 to 5 years and may choose to wait for newer therapies. However, these patients do represent a potential public health risk to others, and there is no guarantee that newer therapies will truly be more efficacious with fewer adverse effects than current therapy.

In contrast, patients with stage 3 fibrosis and compensated cirrhosis should probably be offered treatment now. Effective treatment may prevent

hepatic decompensation. A patient with decompensated disease (ascites, bleeding varices, encephalopathy) is not a candidate for the current generation of HCV antiviral therapies.

Management of treatment with the next generation of DAAs may be easier, but it is likely that challenges will continue for decades to come.

Financial Affiliations: Dr Sherman has served as a consultant to Abbott Molecular, Fibrogen Inc, Kadmon Corporation, and Merck Pharmaceuticals. He has served on data and safety monitoring boards and endpoint adjudication committees for MedPace Inc and Janssen Therapeutics. His institution has received research support from Abbott Laboratories, Anadys Pharmaceuticals, BMS, Boehringer-Ingelheim Corp, Genentech Inc, Gilead Sciences, Inc, Norvartis, and Vertex Pharmaceuticals, Inc. (Updated 10/22/12)

References

1. Clark BT, Garcia-Tsao G, Fraenkel L. Patterns and predictors of treatment initiation and completion in patients with chronic hepatitis C virus infection. *Patient Prefer Adherence*. 2012;6:285-295.
2. Jacobson IM, Everson G, Gordon SC, et al. Interim analysis results from a phase 2 study of telaprevir with peginterferon alfa-2a and ribavirin in treatment-naive subjects with hepatitis C. *Hepatology.* 2007;46(4):315A.
3. Schaefer M, Sarkar R, Knop V, et al. Escitalopram for the prevention of peginterferon-alpha2a-associated depression in hepatitis C virus-infected patients without previous psychiatric disease: a randomized trial. *Ann Intern Med.* 2012;157(2):94-103.
4. Schaefer M, Hinzpeter A, Mohmand A, et al. Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects. *Hepatology.* 2007;46(4):991-998.
5. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med.* 2011;364(25):2405-2416.
6. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med.* 2011;365(11):1014-1024.
7. Poordad F, McCone JJr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med.* 2011;364:1195-1206.
8. Poordad F, Lawitz EJ, Reddy KR, et al. A randomized trial comparing ribavirin dose reduction versus erythropoietin for anemia management in previously untreated patients with chronic hepatitis C receiving boceprevir plus peginterferon/ribavirin. [Abstract 1419.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.
9. Sulkowski M, Roberts S, Afdhal N, et al. Ribavirin dose modification in treatment-naive and previously treated patients who received telaprevir combination treatment: no impact on sustained virologic response in phase 3 studies. [Abstract 1162.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.
10. Roomer R, Hansen BE, Janssen HL, de Knegt RJ. Risk factors for infection during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. *Hepatology.* 2010;52(4):1225-1231.
11. Antonini MG, Babudieri S, Maida I, et al. Incidence of neutropenia and infections during combination treatment of chronic hepatitis C with pegylated interferon alfa-2a or alfa-2b plus ribavirin. *Infection.* 2008;36(3):250-255.
12. Thevenot T, Mathurin P, Moussalli J, et al. Effects of cirrhosis, interferon and azathioprine on adverse events in patients with chronic hepatitis C treated with ribavirin. *J Viral Hepat.* 1997;4(4):243-253.
13. McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med.* 2007;357(22):2227-2236.
14. Birnkrant D. FDA briefing documents on telaprevir NDA 201-917, prepared for the Antiviral Products Advisory Committee, April 1, 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252561.pdf. Accessed October 9, 2012.
15. Cacoub P, Bourlière M, Lübbe J, et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. *J Hepatol.* 2012;56(2):455-63.

Additional Suggested Reading

Sherman KE. Therapeutic approach to the treatment-naive patient with hepatitis C virus genotype 1 infection: a step-by-step approach. *Clin Infect Dis.* 2012;55(9):1236-1241.

Top Antivir Med. 2012;20(4):125-128

Perspective

Cardiovascular Risk and Dyslipidemia Management in HIV-Infected Patients

HIV infection and antiretroviral therapy each appear to increase cardiovascular disease risk. Increased risk may be attributable to the inflammatory effects of HIV infection and dyslipidemia associated with some antiretroviral agents. The prevalence of cardiovascular disease is increasing as patients live longer, age, and acquire traditional coronary heart disease (CHD) risk factors. In general, any additional cardiovascular risk posed by HIV infection or antiretroviral therapy is of potential concern for patients who are already at moderate or high risk for CHD. Long-term and well-designed studies are needed to more accurately ascertain to what degree HIV infection and antiretroviral therapy affect long-term cardiovascular disease risk. Management of dyslipidemia to reduce CHD risk in HIV-infected patients is much the same as in the general population, with the cornerstone consisting of statin therapy and lifestyle interventions. Smoking cessation is a major step in reducing CHD risk in those who smoke. This article summarizes a presentation by James H. Stein, MD, at the IAS–USA live continuing medical education activity held in New York City in March 2012.

Cardiovascular Disease Is Caused by the Usual Suspects

The leading cause of death of people in the United States is cardiovascular disease, mostly heart attack and stroke, followed closely by cancer. Data from 7 years ago show that the leading cause of non-HIV-related death in HIV-infected men taking antiretroviral therapy in New York City was cardiovascular disease.[1] As HIV-infected patients live longer and grow older as a result of effective antiretroviral therapy, the prevalence of cardiovascular disease will increase. There should be increased emphasis on preventing such disease now.

The major risk factors for heart disease—high blood pressure (BP), high total cholesterol level, diabetes mellitus, cigarette smoking, and aging—are well known. A key study from the past 10 years is the analysis of risk by Greenland and colleagues using 2 to 3 decades of follow-up of people with heart disease from 3 large longitudinal cohorts: CHA (Chicago Heart Association) Detection Project in Industry, the FHS (Framingham Heart Study), and MRFIT (Multiple Risk Factor Intervention Trial).[2] The analysis showed that, depending on sex and age group, between 86% and 100% of persons dying from coronary heart disease (CHD) had at least 1 major CHD risk factor: systolic BP at least 140 mmHg or diastolic BP at least 90 mmHg, total cholesterol 240 mg/dL or higher, cigarette smoking, or diabetes. More than 96% of persons dying from CHD had at least 1 risk factor at higher than favorable levels, eg, systolic BP of 120 mmHg or higher or diastolic BP of 80 mmHg or higher or use of antihypertensive medication; total cholesterol level of 200 mg/dL or above or use of cholesterol medication; current cigarette smoking; or diabetes.

The attributable contribution of major risk factors to death from CHD is well over 90%, and more than 80% of that risk is attributable to lifestyle-related risk factors—elevated BP, high cholesterol level, diabetes, and smoking. Little can be done to reduce age-related or sex-related risk, but interventions are available for lifestyle-related CHD risk.

Dr Stein is Professor of Medicine in the Division of Cardiovascular Medicine at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin.

Is Coronary Heart Disease Risk Different for HIV-Infected Persons?

Recently, Dr Stein has been approached by people expressing such opinions as "People with HIV are at greatly increased risk of heart disease" and "Since we know that HIV is a coronary risk equivalent to diabetes, should all patients with HIV have their low density lipoprotein (LDL) cholesterol levels below 50 mg/dL?" However, the data do not support the idea that HIV is as powerful a risk factor as the conventional major risk factors for CHD.

The D:A:D (Data Collection in Adverse Effects of Anti-HIV Drugs) study is one of the most useful observational studies examining risk factors for CHD in HIV-infected individuals. It showed that risk for myocardial infarction (MI) was statistically significantly increased by such traditional risk factors as older age, male sex, greater body mass index (BMI), family history of CHD, current or former smoking status, and history of a cardiovascular event.[3] It also showed that HIV protease inhibitor (PI) use was associated with increased cardiovascular risk; however, on adjusted analysis, much of this risk was attributable to the dysmetabolic effects of PI treatment—ie, increased risk of diabetes mellitus, hypertension, and dyslipidemia. This finding emphasizes the fact that traditional risk factors pose risk for CHD in HIV-infected persons and HIV-seronegative persons alike.

Reports of the association of antiretroviral therapy with risk of heart disease were accompanied by concerns of an epidemic of CHD in the HIV-infected population. However, what appears to be occurring is an increased prevalence of CHD among HIV-infected patients in association with aging of patients and increased exposure to traditional risk factors, much as is seen in patients with other chronic inflammatory conditions such as rheumatoid

arthritis, systemic lupus erythematosus, and inflammatory bowel disease.

Figure 1 shows all-cause mortality and measures of cardiovascular disease among more than 36,000 HIV-infected patients, most of them men, from Veterans Affairs hospitals.[4] The use of potent antiretroviral therapy resulted in a dramatic decline in mortality. At the same time, rates of hospitalization for cardiovascular or cerebrovascular disease remained relatively stable. These rates would not likely have remained stable if an epidemic of cardiovascular disease were occurring in patients receiving antiretroviral therapy. Although there may have been a slight increase in risk of cardiovascular disease among HIV-infected patients over the past decade, it is very small compared with the benefits of antiretroviral therapy on all-cause mortality.

If there is any increase in risk of cardiovascular disease associated with antiretroviral therapy, it appears to be counterbalanced by the beneficial antiinflammatory effects of antiretroviral therapy on blood vessels. In ACTG (AIDS Clinical Trials Group) study 5152s, researchers randomized 82 antiretroviral therapy-naive patients to receive a PI-sparing regimen, a nucleoside analogue reverse transcriptase inhibitor (nRTI)-sparing regimen, or a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-sparing regimen.[5] Short-term antiretroviral treatment significantly improved endothelial function (measured as brachial artery flow-mediated dilation) to a similar degree in all 3 groups despite substantial differences among the groups in lipid level changes. The only factor examined in the study that predicted improvement in arterial function was viral suppression. The greater the reduction in HIV RNA level, the greater the improvement in endothelial function, irrespective of the antiretroviral therapy regimen used.

This finding is consistent with one of the findings of the SMART (Strategies for Management of Antiretroviral Therapy) study, which compared a CD4+ cell count–guided "drug conservation strategy" (treatment interruption) with a viral suppression strategy (continuous antiretroviral therapy). The data showed that the treatment interruption strategy was associated with a 2.6-fold increase in risk of progression or death. Analysis of cardiovascular outcomes showed that treatment interruption was associated with a 57% increase in risk for the composite endpoint of MI, percutaneous coronary intervention/coronary artery bypass grafting (PCI/CABG), or cardiovascular death ($P = .05$). When peripheral vascular disease, congestive heart failure, and coronary artery disease requiring medication were added to the composite endpoint, the strength of the statistical association increased (49% increase in risk, $P = .03$).[6,7] These findings emphasize that viral activation and associated inflammation are deleterious for blood vessels. Effective antiretroviral treatment thereby reduces cardiovascular risk. Over time, exposure to some antiretroviral medications may slightly increase CHD risk more than others.

The D:A:D study indicates that cumulative exposure to the PIs indinavir and ritonavir-boosted (/r) lopinavir was associated with an increased risk of MI at a relative rate of approximately 1.1 per year.[8] This slight increase in risk probably does not matter for patients who are at otherwise low risk for CHD and must be assessed in light of the risk of poorly suppressed HIV infection. For patients at moderate or high risk, such an elevation in risk should be taken into account when considering antiretroviral therapy options. Similarly, the study found that recent or current use of abacavir was associated with increased risk of MI at a relative rate of approximately 1.6. Again, this finding should be considered when selecting an antiretroviral regimen for patients with preexisting moderate or high CHD risk.

Whether HIV infection or antiretroviral therapy increases cardiovascular risk beyond traditional risk factors remains difficult to determine as of 2012. The main predictor of heart disease is age. Most patients living with HIV infection today are relatively young (ie, 30 years old to 50 years old) and thus are at relatively low short-term cardiovascular risk from this perspective. The attempt to determine whether there is something unique about HIV infection that increases risk beyond traditional factors is confounded by the fact that antiretroviral therapy can affect lipid levels, BP, and diabetes risk, and may consequently affect cardiovascular disease risk.

An important and sometimes overlooked consideration in parsing cardiovascular disease risk factors in HIV-infected individuals is the high frequency of cigarette smoking in this population. The rate of smoking among HIV-infected individuals is approximately 2 to 3 times higher than that in the general population. After a personal history of heart disease and increased age, cigarette smoking is the strongest predictor of CHD events in HIV-infected individuals. It is very difficult to isolate the potential contributions of HIV infection or antiretroviral therapy to CHD risk in relatively small studies of a relatively young population with a substantial proportion of cigarette smokers.

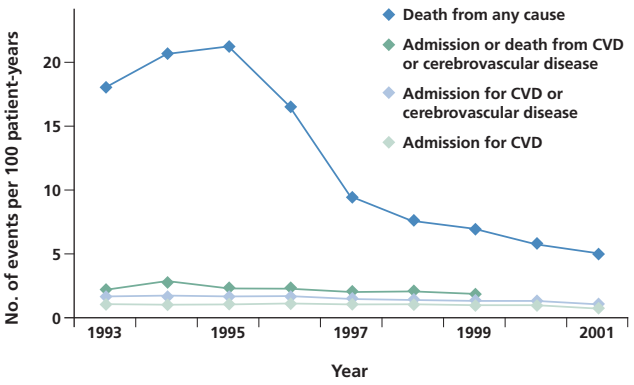


Figure 1. All-cause mortality and cardiovascular outcomes in HIV-infected patients in a Veterans Affairs population. Decrease in deaths is attributed to the introduction of potent antiretroviral therapy around 1996; no increase in cardiovascular disease (CVD) risk was observed from 1993 to 2001. Adapted from Bozzette et al.[4]

Our current state of knowledge with regard to cardiovascular risk and direct effects of HIV infection can best be summarized as "Most of what we think we know today, we don't really know for certain." The majority of research into the association of CHD risk and HIV infection has been small observational studies, which are subject to biases and potential confounding factors. As a result, the studies that have provided the data linking HIV infection to cardiovascular risk are somewhat inconclusive. Many of the studies have been conducted with a younger population that has experienced few cardiovascular events and have included limited follow-up periods, making it difficult to ascertain the potential contribution of risk factors to disease endpoints. Studies must often use surrogate markers and may not have well-matched control groups. It is likely to take at least 10 more years of research and concomitant accrual of cardiovascular events to robustly determine whether HIV infection or antiretroviral therapy themselves increase CHD risk. Until the research is more conclusive, humility regarding "what we know" is rational.

The Partners Health System Cohort study, one of the best studies of MI risk in HIV infection to date, provides an example of the problems in current studies of CHD risk in HIV-infected patients.[9] The cohort is derived from a large data registry of 3851 HIV-infected persons and 1,044,589 HIV-uninfected persons who were followed up for approximately 4.5 years. This cohort is extremely young (mean age, 38 years) for purposes of studying cardiovascular risk and the follow-up period is extremely short for examining cardiovascular risk. The acute MI rate was 1.1% per year in HIV-infected persons versus 0.7% per year in uninfected persons, yielding a statistically significant 53% increase in risk ($P < .0001$) associated with HIV infection. However, more HIV-infected persons had hypertension, dyslipidemia, and diabetes mellitus ($P < .001$ for each).

These findings raised a number of questions. Was the increased risk in HIV-infected persons attributable to HIV infection itself or to the other risk factors identified? How many of the HIV-infected patients who had an MI might have had such risk factors and had an MI if they were not HIV-infected? A multivariate analysis adjusting for age, sex, race, hypertension, dyslipidemia, and diabetes found that HIV-infection status was associated with a 75% increase in risk for MI (relative risk 1.75; $P < .0001$), with this increase being much smaller than the increase in risk associated with older age or dyslipidemia. The data thus suggest that HIV infection alone is associated with increased CHD risk. However, problems with the study include the fact that it was not specifically designed to examine MI risk in HIV infection, and as such it does not have complete covariate data. For example, cigarette smoking was not included in the risk models, raising the question of how much it may have contributed to the risk attributed to HIV-infected status. Further, because complete lipid and BP data were not available, lipid levels and BP were analyzed as dichotomous variables (considering only the presence or absence of hypertension or dyslipidemia, not specific levels of either) rather than as continuous variables, which would have provided a more accurate assessment of the contribution of these factors to overall risk. The net effect of these limitations is to introduce misclassification bias, whereby the effects of risk factors may be underestimated and the effects of HIV infection may be overestimated. For such a study to produce more conclusive results, researchers would need to know subjects' specific lipid levels and BPs, as well as smoking status; and the cohort would need 10 or more years of follow-up. This would provide better data on whether HIV infection is a substantial independent predictor of MI.

Based on the information that is available today, it appears that any long-term CHD risk increase in HIV-infected patients is relatively small. This increase is likely contributed to by the effects of certain antiretroviral drugs. Some HIV PIs may increase risk through dyslipidemia or other metabolic effects and abacavir may increase the short-term cardiovascular risk. Effects of persistent viral infection likely also contribute to the risk increase via persistent inflammation, viremia, and immune activation. These mechanisms reduce the ability of blood vessels to dilate and generate an anticoagulant surface, which may facilitate the plaque erosion and rupture that can cause acute coronary syndromes. For now, any absolute risk associated with antiretroviral therapy is most important in selecting treatment regimens for patients who are already at moderate to high CHD risk.

Management of Dyslipidemia to Reduce Coronary Heart Disease Risk

The guiding principle of CHD risk assessment and management is that a patient's absolute CHD risk determines the intensity of interventions. Table 1 shows the current National Cholesterol Education Program (NCEP) Adult Treatment Panel guidelines for LDL cholesterol goals and treatment thresholds according to 10-year risk of a CHD event. Risk is determined by counting risk factors and calculating the Framingham Risk Score. The categorical risk factors that modify LDL cholesterol goals are age (men ≥ 45 years, women ≥ 55 years), family history of premature CHD (CHD in male first-degree relative < 55 years of age or in female first-degree relative < 65 years of age), cigarette smoking, hypertension (BP ≥ 140/90 mmHg or use of antihypertensive medication), and low high-density lipoprotein (HDL) cholesterol level (< 40 mg/dL).

Non-HDL cholesterol level (total cholesterol minus HDL cholesterol) is a secondary target of therapy when triglyceride levels are above 200 mg/dL, with the non-HDL cholesterol level goal being 30 mg/dL above the LDL cholesterol goal for each risk category (eg, the non-HDL cholesterol goal is < 130 mg/dL when the LDL cholesterol goal is < 100 mg/dL). Non-HDL cholesterol is a measure of all cholesterol values in atherogenic lipoproteins and is actually

a more accurate predictor of cardiovascular events than LDL cholesterol.

The triglyceride level is a primary target of lipid-lowering therapy only when the triglyceride level exceeds 500 mg/dL, due to associated risk of pancreatitis. High triglyceride levels are associated with other cardiovascular risk factors (eg, low HDL cholesterol level, hypertension, and insulin resistance), although meta-analyses have indicated that an elevated triglyceride level is also an independent risk factor, albeit with a somewhat low odds ratio. Because LDL cholesterol level becomes a less accurate measure of atherogenic lipoproteins when the triglyceride level is elevated, non-HDL cholesterol is used as a target in the setting of elevated triglyceride levels.

The ACTG/Infectious Diseases Society of America-HIV Medicines Association (IDSA-HIVMA) guidelines for lowering lipid level to reduce CHD risk were published in 2003 and are similar to the NCEP guidelines. According to the ACTG/IDSA-HIVMA guidelines, lipid levels should be measured in HIV-infected patients prior to starting antiretroviral therapy and 3 to 6 months after starting therapy. Risk assessment is the same as in NCEP guidelines, as is the recommendation for intervention for modifiable nonlipid risk factors, including diet and smoking. If target lipid levels are not achieved with lifestyle modification, lipid-lowering therapy and modification of the antiretroviral regimen should be considered. New guidelines from the NCEP and IDSA-HIVMA are expected in the next year or two.

The LDL cholesterol level goal is below 70 mg/dL and below 100 mg/dL in persons at very high risk (eg, someone with CHD who smokes or has metabolic syndrome) and high risk, respectively, and below 130 mg/dL in those at moderately high or moderate risk. There is an option to treat persons with moderately high risk until the LDL cholesterol level falls below 100 mg/dL. It should be noted that an LDL cholesterol level of 130 mg/dL is not typical for non-Westernized humans and other primates and therefore is atherogenic. It is likely that many persons at moderately high risk with such an LDL cholesterol level will develop CHD. Thus, it is advisable to treat such persons until the LDL cholesterol level is below 100 mg/dL.

If there is a single take-home message about treating dyslipidemia to reduce CHD risk, it is to put patients on statin therapy. Statin therapy is very effective in lowering LDL cholesterol and non-HDL cholesterol levels and reducing cardiovascular risk. The recent Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis involved more than 160,000 subjects from randomized trials comparing statin therapy with no statin therapy and comparing high-dose statin therapy with low-dose statin therapy. The analysis showed that over the course of 5 years every 39 mg/dL reduction in LDL cholesterol level on statin therapy was associated with a 10% reduction in all-cause mortality; a 20% reduction in CHD mortality; and a 21% reduction in major cardiovascular events, including a 26% reduction in MI or CHD death, a 24% reduction in PCI/CABG, and a 15% reduction in stroke.[10] These reductions were consistent across subgroups (eg, diabetes or no diabetes, old age or young age, hypertension or no hypertension), and no increase in risk of death from other causes (eg, cancer) was observed, including among subjects with very low LDL cholesterol level.

However, recent meta-analyses indicate that statin treatment is associated with increased risk of diabetes mellitus.[11,12] A 9% risk increase with statin therapy versus placebo was observed, with the excess risk being predicted by older age, not baseline BMI or LDL cholesterol level. The number needed to harm (NNH) for 1 case of diabetes mellitus was estimated at 225 patients over 4 years. However, it also was estimated that 9 cardiovascular disease events are prevented for every case of diabetes attributable to statin therapy. Similarly, a 12% increase in risk of diabetes was found for high-dose versus low- or moderate-dose statin therapy, but the risk of diabetes was again outweighed by the reduction in risk for cardiovascular events. The mechanism of the association between statin therapy and diabetes is unclear.

The relative dose equivalences among available statins for lowering LDL cholesterol are shown in Table 2. Most patients at risk for CHD require large reductions to achieve safer levels of LDL cholesterol and thus most will receive higher doses of the more potent statins—simvastatin, atorvastatin, and rosuvastatin. The highest dose of simvastatin studied (80 mg) is associated with increased risk of rhabdomyolysis and should be avoided. Because simvastatin and lovastatin interact with cytochrome P450 3A4 (CYP3A4) inhibitors, as is the case with most PIs, these statins should avoided with PIs that inhibit CYP3A4. Simvastatin use is widely promoted in managed care

Table **1**. Current National Cholesterol Education Program (NCEP) Low-Density Lipoprotein (LDL) Cholesterol Goals According to Coronary Heart Disease (CHD) Risk

CHD Risk Category	CHD Status or Risk Factors (10-Year Risk of CHD Event)	Goal LDL Level (mg/dL)	LDL Threshold for Treatment Evaluation (mg/dL)
High (Very high)	CHD or risk equivalent (> 20%/10 years)	< 100 (< 70)	≥ 100*
Moderately high	2+ risk factors (10%-20%/10 years)	< 130	≥ 130*
Moderate	2+ risk factors (< 10%/10 years)	< 130	≥ 160*
Low	0-1 risk factor	< 160	≥ 190*

Adapted from NCEP Adult Treatment Panel III.[13]
*Also consider treatment if LDL level is below goal but above the goal for the next higher risk level.

Table 2. Approximate Dose Equivalences of Selected Statins for Lowering Low-Density Lipoprotein Cholesterol

Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
	20 mg	10 mg	10 mg		5 mg
5 mg	40 mg	20 mg	20 mg		10 mg
10 mg	80 mg	40 mg	40 mg	5 mg	20 mg
20 mg		80 mg	80 mg	10 mg	40 mg
40 mg				20 mg	80 mg
80 mg				40 mg	

Adapted from Stein JH and McBride PE.[14]

settings. If it is used, the maximum dose should be 10 mg per day in patients on cardiac medications such as amiodarone, diltiazem, and verapamil, or 20 mg per day in patients receiving medications such as amlodipine, ranolazine, niacin, or fibrates.

For triglyceride levels below 500 mg/dL, LDL cholesterol and non-HDL cholesterol should be targeted to reduce CHD risk. As noted, for higher triglyceride levels, the primary goal is to treat the hypertriglyceridemia to prevent pancreatitis. Fibrates are the preferred initial therapy in this setting. Dietary intervention can have a dramatic effect on triglyceride levels. Patients should restrict saturated fats and trans-fats, emphasize intake of omega-3 fatty acids and monounsaturated fats, limit simple carbohydrates and calories, and reduce alcohol intake.

Patients with combined dyslipidemia should be put on statin therapy and if therapy does not achieve lipid goals, lifestyle intervention should be added. There is no evidence that any medication add-on to statin therapy further reduces cardiovascular risk, despite evidence that such measures as fibrates, niacin, and fish oils are associated with varying degrees of risk reduction on their own.

Although lowering lipid levels to reduce cardiovascular risk is focused on statin therapy and lifestyle intervention, controlling virus levels is crucial as well. Controlling viral load and stopping smoking would reduce cardiovascular risk for many HIV-infected patients.

Presented by Dr Stein in March 2012. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Stein in October, 2012.

Financial Affiliations: Dr Stein has served on data and safety monitoring boards for Abbott Laboratories, Lilly, and Takeda. He has intellectual property rights licensed by the Wisconsin Alumni Research Foundation for carotid ultrasound and cardiovascular risk.

References

1. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med*. 2006;145(6):397-406.
2. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290(7):891-897.
3. D:A:D Study Group, Friis-Møller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735.
4. Bozzette SA, Ake CF, Tam K, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med*. 2003;348(8):702-710.
5. Torriani FJ, Komarow L, Parker RA, et al. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol*. 2008;52(7):569-576.
6. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.
7. Phillips AN, Carr A, Neuhaus J, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther*. 2008;13(2):177-187.
8. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330.
9. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92(7):2506-2512.
10. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
11. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375(9716):735-742.
12. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305(24):2556-2564.
13. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-239.
14. Stein JH and McBride PE. 2008 Guidelines for the Diagnosis and Management of Dyslipidemia for Adults >18 Years of Age. UW Health. http://www.unityhealth.com/intranet/groups/pubweb/documents/unity_nativefile/005442.pdf. Accessed September 26, 2012.

Top Antivir Med. 2012;20(4):129-133

Case Report From the Field

Syphilis Negatively Influences the Response to Hepatitis C Virus Treatment in an HIV-Infected Patient

Ellen H. Nagami, BA, Arthur Y. Kim, MD, Rachel P. Baden, MD, and Barbara H. McGovern, MD

Syphilis is a chronic inflammatory disease caused by the sexually transmitted pathogen, *Treponema pallidum*.[1] Concomitant HIV and syphilis infections are prevalent among men who have sex with men (MSM).[2] Syphilis negatively impacts disease management in the HIV-infected host by causing substantial immune activation, as evidenced by precipitous declines of CD4+ cells and by increased levels of HIV RNA.[3,4] Syphilis has also been reported as a risk factor for hepatitis C virus (HCV) acquisition among MSM.[5] Whether intercurrent syphilis has any negative impact on HCV treatment response is unknown.

We report a case of an HIV/HCV-coinfected man who was treated with peginterferon alfa and ribavirin. He had a very slow attainment of HCV RNA suppression and a dramatic fall of CD4+ cell count in excess of what would be expected in response to HCV therapy. During HCV treatment, the patient was diagnosed with intercurrent syphilis and admitted to the use of methamphetamines; HCV treatment was subsequently discontinued at week 28. After drug rehabilitation and administration of benzathine penicillin for syphilis, the patient underwent retreatment for HCV with remarkably improved viral kinetics and a modest decline in CD4+ cell count. We propose that active syphilis infection may have been a key contributor to the patient's slow virologic response to his initial course of HCV treatment. Within this report we discuss the public health implications of this case.

Case Presentation

In 2007, Patient J, a 46-year-old HIV-infected white man with HCV genotype 1b infection, underwent a liver biopsy that demonstrated moderately active chronic hepatitis with evolving cirrhosis and moderate steatosis. Prior to HCV treatment, Patient J's baseline HCV viral load was 1.5 million IU/mL and his plasma HIV RNA level was undetectable on antiretroviral therapy. A baseline rapid plasma reagin (RPR) test was nonreactive for treponemal infection 6 weeks before starting HCV treatment.

Patient J was started on peginterferon alfa-2a (180 mcg subcutaneously weekly) and weight-based ribavirin (1000 mg daily for a weight of more than 75 kg). During treatment, the patient reported excellent adherence to both his antiretroviral and HCV medications. His major adverse effect related to HCV treatment was anemia requiring darbepoetin alfa supplementation; ribavirin dose was not reduced. At weeks 4 and 12 of treatment, Patient J's HCV viral load was 147,000 IU/mL and 3,208 IU/mL, respectively. HCV RNA suppression was not achieved until 21 weeks into treatment, consistent with a slow virologic response. Although HIV RNA remained suppressed, his pre-treatment CD4+ cell count dropped from 834/μL to 311/μL at the time of discontinuation of HCV therapy and his CD4+ cell percentages remained fairly constant at 26% and 29%, respectively (normal range, 29%-62%).

During his course of HCV therapy, Patient J presented with a maculopapular rash at week 17 and acknowledged that he had had unprotected anal intercourse. An RPR test was reactive with a titer of 1 to 64 and a confirmatory test was reactive for *Treponema pallidum* antibody (TPA). Cerebrospinal fluid analysis after a lumbar puncture was unremarkable. Patient J was treated with three doses of intramuscular injections of benzathine penicillin over a 3-week period with an appropriate titer decline to 1 to 16 after 6 weeks of follow-up.

At week 28 of HCV therapy, Patient J was hospitalized because of acute onset of a transient febrile episode with hypotension and was started on broad-spectrum antibiotics. At this time, his HCV treatment was discontinued. All blood cultures were negative and his antibiotics were stopped when no obvious source of infection was found. Patient J subsequently admitted to use of intravenous crystal methamphetamine a few days prior to his hospitalization. His clinicians surmised that his acute and transient febrile event with hypotension may have been related to endotoxemia since no infectious etiology was identified.

At the end of 2008, 2 months after completion of benzathine penicillin therapy for syphilis, Patient J requested retreatment for his HCV infection because he felt that he was in stable substance abuse recovery. At the time of his presentation to our clinic (1 month after discontinuation of HCV therapy), Patient J's HCV RNA level had rebounded

Ms Nagami is an HIV and hepatitis C clinical coordinator at Harvard University Center for AIDS Research in Boston, Massachusetts. Dr Kim is Assistant Professor of Medicine at Harvard Medical School in Boston and Dr Baden is Assistant Professor of Medicine at Harvard Medical School. Dr McGovern is Associate Professor of Medicine at Tufts University School of Medicine in Boston. Send correspondence to Barbara McGovern, MD, Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain, Massachusetts 02130, or e-mail bmcgovern@tuftsmedicalcenter.org. Received April 3, 2012; accepted September 27, 2012.

to 1,590,000 IU/mL, consistent with his pretreatment baseline viral load level. His CD4+ cell count had risen while off of peginterferon alfa-2a and ribavirin treatment to 861/µL (CD4+ percentage: 41%) and his HIV RNA level remained suppressed on antiretroviral therapy. Etiologies for his initial slow HCV viral suppression were explored, including insulin resistance, which was negative.

The patient continued to abstain from any illicit drug use and was restarted on peginterferon alfa-2a and ribavirin. The dosing of ribavirin was decreased to 400 mg twice daily based on his current weight. By week 4, his HCV RNA level was 121 IU/mL. At repeat HCV RNA testing at week 7, his HCV RNA level was below 5 IU/mL by HCV RNA quantitative polymerase chain reaction. Patient J attained a sustained virologic response (SVR) after completing 48 weeks of HCV treatment. Of note, the patient did not require darbepoetin alfa during this second course of therapy. Despite receiving the same dose of peginterferon alfa during his second course of HCV therapy, the decline in his CD4+ cell count was less dramatic (861/µL to 529/µL) and his CD4+ cell percentage remained relatively stable, 41% and 36%, respectively.

Discussion

End-stage liver disease is a leading cause of death among HIV-infected patients taking antiretroviral therapy.[6,7] HIV/HCV-coinfected patients have higher rates of liver-related and overall mortality than patients with HCV alone.[8] However, successful treatment of HCV infection is associated with decreased liver-related disease and improved survival.[9] Therefore, treatment of HCV infection in the setting of HIV is of paramount importance.

Unfortunately, response rates to HCV treatment are generally lower among HIV/HCV-coinfected patients, although this finding has not been directly linked to immunosuppression.[9] Pretreatment predictors of virologic failure in HIV/HCV-coinfected patients include high baseline HCV viremia, HCV genotype 1 infection, male sex, African American race, older age, unfavorable IL-28 genotype, insulin resistance, and advanced fibrosis stage.[9-14]

Regardless of HIV serostatus, the most powerful predictor of attaining SVR to HCV treatment is rapid viral clearance.[9,15] In studies of dual HCV therapy in HIV seronegative patients with HCV genotype 1 infection, a rapid virologic response (RVR) is associated with SVR rates ranging from 75% to 89%.[16,17] In studies of HIV/HCV coinfection, the same principles apply. In a posthoc analysis of 323 HIV/HCV-coinfected patients in the RIBAVIC treatment trial, RVR at week 4 had a positive predictive value of 97% for sustained virologic clearance.[18,19] However, the proportion of coinfected patients who achieve rapid virologic clearance on dual therapy is low.

Even with the recent introduction of HCV protease inhibitors, the best on-treatment predictor of virologic clearance remains rapid viral suppression.[20] Patients who attained an undetectable viral load at week 4 on telapravir, peginterferon alfa-2a, and ribavirin had an SVR rate of 88%.[20] In contrast, those who had a greater than 1 $\log_{10}$ IU/mL decline in HCV RNA level after the 4 weeks of treatment had an SVR rate of 64%.[20,21] Similar trends were seen in the clinical trial evaluating boceprevir, peginterferon alfa, and ribavirin in treatment-naive patients.[22]

In this case report, we demonstrate that viral kinetics dramatically improved during the second course of HCV therapy after treatment of intercurrent syphilis infection. Such changes in viral kinetics have not been reported among patients undergoing retreatment for HCV with dual therapy.[23,24] In fact, retreatment with a different formulation of peginterferon alfa (switching from peginterferon alfa-2a to peginterferon alfa-2b or vice versa) has been largely unsuccessful. In a large study of patients with chronic HCV infection, only 9% achieved SVR after retreatment with peginterferon alfa and ribavirin for 48 weeks.[23] During the first course of treatment, the patient described herein did not achieve an undetectable viral load until week 21 of HCV therapy. In contrast, during retreatment our patient attained a 4 $\log_{10}$ decline in viremia by week 4 (to 121 IU/mL) and achieved complete viral suppression at 7 weeks, when he was next tested.

Several factors were explored to explain the dramatic differences in viral clearance. Patient J had no evidence of insulin resistance or hyperglycemia.[14] There were no changes in the interferon alfa formulation that he received between the first and second courses of therapy and his ribavirin dose was lower during retreatment (800 mg versus 1000 mg). Furthermore, during his first course of treatment, the patient had excellent adherence to both HCV and HIV therapies, evidenced by the development of anemia on ribavirin and maintenance of HIV RNA suppression.[9,11,25] Finally, there were no changes in his background antiretroviral regimen during this time frame, which could have potentially played a role in these differential treatment outcomes.[26]

Unfortunately, we do not have the original viral isolate and thus cannot rule out the possibility of HCV reinfection. However, it is unlikely that an HIV-infected patient with HCV genotype 1 infection and a high HCV RNA level would have achieved virologic eradication after only 28 weeks of treatment, especially since he attained late virologic suppression. In addition, after discontinuing the first course of treatment the patient's HCV RNA level returned to his pretreatment level. This is consistent with rebound viremia back to the viral setpoint.

Patient J's remarkable change in viral kinetics led us to question whether intercurrent syphilis may have modified the cytokine environment and negatively impacted his first course of treatment. Modulators of response to interferon alfa-based therapies include cytokines such as inducible protein-10 (IP-10) and interleukin 10 (IL-10).[27-31] In a study of 19 HIV/HCV-coinfected patients, pretreatment IP-10 levels were

statistically significantly lower among virologic responders (217 pg/mL; interquartile range [IQR], 181 pg/mL–301 pg/mL) than among nonresponders (900 pg/mL; IQR, 628 pg/mL–2048 pg/mL).[32] A similar inverse relationship has been described for IL-10. In a study of 79 patients with HCV genotype 1 infection, low baseline levels of IL-10 were strongly associated with high rates of virologic eradication.[31] Other factors predictive of HCV clearance include hepatic interferon-stimulated gene (ISG) expression levels. Patients who achieve rapid HCV clearance have strong up-regulation of ISGs in response to peginterferon alfa treatment. In contrast, HCV patients who do not respond have high levels of ISGs before therapy and are refractory to further stimulation.[33,34]

The role of cytokines in HCV treatment outcomes is pertinent when considering the possible negative impact of syphilis during our patient's first course of HCV therapy. *T pallidum* infection alters the balance of T helper cell 1 (T_H1) and T helper cell 2 (T_H2) CD4+ cell profiles of the host. Initially, *T pallidum* elicits vigorous inflammation characterized by a predominant T_H1 (cellular) response. This is followed by activation of T_H2 (humoral) responses that are thought to contribute to spirochete evasion of the host immune system and to the development of chronic infection, if left untreated. This switch to a T_H2 response is characterized by profound increases in IL-10 level, which may facilitate the persistence of various pathogens through interference with innate and adaptive immunity.[35-37] In a novel study of cytokine responses during syphilis infection in 36 HIV-infected patients, IL-10 levels increased substantially during primary and secondary stage syphilis, only to decline with penicillin therapy.[35] An attractive hypothesis is that early syphilis led to marked increases in IL-10 levels, which interfered with our patient's initial response to interferon alfa. Subsequent treatment of syphilis may have led to declines in IL-10 level, which facilitated clearance of HCV RNA in response to treatment.[31]

Interestingly, treatment response rates for acute HCV infection are generally lower among HIV/HCV-coinfected patients than among those who have HCV infection alone.[38,39] Although this lower response rate has been attributed to HIV-associated immunosuppression, an additional hypothesis is that undiagnosed intercurrent syphilis reduces treatment efficacy in a subset of patients.

We also suspect that our patient's dramatic decline in CD4+ cells during the first course of HCV therapy was related to several factors, including peginterferon alfa exposure and active syphilis. Treatment of HCV in HIV-infected patients is associated with substantial declines in the absolute CD4+ cell count, which resolve with discontinuation of peginterferon alfa therapy. In APRICOT (AIDS Pegasys Ribavirin International Coinfection Trial), which examined HCV treatment in the setting of HIV, the mean CD4+ cell decline was 157/μL.[9] However, Patient J had a dramatic drop of 523 cells/μL, which is much greater than would be expected with peginterferon alfa alone. This profound drop in CD4+ cell count is consistent with reports of immunologic changes seen in HIV-infected patients with primary or secondary syphilis, which may be attributed to increased cell turnover, apoptosis, and changes in T-cell homeostasis.[3,4,40] Generalized immune activation is associated with increased expression of CC chemokine receptor 5 (CCR5) and dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) receptors on human monocytes and dendritic cells, which enhances the cells' susceptibility to HIV infection.[1,3,41] Of note, syphilis has also been associated with increased HIV RNA levels in patients not on antiretroviral therapy.[3,4,40]

Overall incidence rates of primary and secondary syphilis have been on the rise since 2001, after decreasing throughout the 1990s.[42,43] Recent reports have shown an increasing incidence of syphilis specifically among MSM in the United States and Europe.[44,45] Between 2000 and 2004, the percent of cases of primary and secondary syphilis attributed to MSM in the United States rose dramatically from 7% to 64%.[43] Furthermore, the current syphilis epidemic among MSM has disproportionately affected those with HIV infection.[46] Many factors may have contributed to the resurgence of syphilis among HIV-infected MSM, including serosorting of sexual partners, initiation of higher-risk sexual activity due to a sense of security created by effective HIV therapeutics, and a longer lifespan of HIV-infected individuals.[46] Other risk factors associated with syphilis infection include underlying HIV infection and use of methamphetamines.[46]

A major obstacle to the diagnosis of syphilis is that many infected individuals are asymptomatic. In a cohort of 218 HIV-infected patients with newly detected and untreated syphilis, 60% were asymptomatic and, most likely, would have gone undiagnosed if not for annual screening.[2] A recent study in an Australian HIV clinic compared syphilis diagnoses in HIV-infected MSM before and after the implementation of syphilis serologic testing with every routine blood sample.[47] The proportion of asymptomatic HIV-infected MSM who tested positive for syphilis rose from 21% to 85% percent with the implementation of this routine screening intervention.[47] The Centers for Disease Control and Prevention and the United Kingdom National Screening and Testing Guidelines now recommend annual serologic testing for HIV and syphilis for sexually active MSM.[48,49]

The alteration of viral kinetics and the immunologic changes observed in Patient J support the possibility that intercurrent syphilis is a modulator of HCV treatment outcome. This would indicate that it is important to screen patients who are at risk for syphilis infection prior to initiating HCV antiviral therapy as well as counsel patients about the importance of safe sex. Syphilis screening may also be warranted among HCV-infected patients who demonstrate slow virologic clearance during HCV treatment, despite excellent adherence. Syphilis screening should also be considered among patients with dramatic CD4+ cell declines that exceed what is normally expected with peginterferon alfa therapy.

Acknowledgements and Disclosures

The authors extend their appreciation to the patient who is the subject of this report. Work on this paper was supported by the National Institutes of Health/National Institute of Allergy and Infectious Diseases (Hepatitis C Cooperative Center U19 AI066345, K23 AI054379 to AYK, Harvard University Center for AIDS Research P30 AI060354).

Financial Affiliations: Ms Nagami and Drs Baden and McGovern have no relevant financial affiliations to disclose. Dr Kim has served as a consultant to Vertex Pharmaceuticals, Inc.

References

1. Salazar JC, Cruz AR, Pope CD, et al. Treponema pallidum elicits innate and adaptive cellular immune responses in skin and blood during secondary syphilis: a flow-cytometric analysis. *J Infect Dis*. 2007;195(6):879-887.
2. Thurnheer MC, Weber R, Toutous-Trellu L, et al. Occurrence, risk factors, diagnosis and treatment of syphilis in the prospective observational Swiss HIV Cohort Study. *AIDS*. 2010;24(12):1907-1916.
3. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. 2004;18(15):2075-2079.
4. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. *Sex Transm Dis*. 2006;33(3):143-148.
5. Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. *Clin Infect Dis*. 2005;41(3):395-402.
6. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001;32(3):492-497.
7. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641.
8. Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin Infect Dis*. 2009;49(10):1605-1615.
9. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004;351(5):438-450.
10. Saludes V, Bracho MA, Valero O, et al. Baseline prediction of combination therapy outcome in hepatitis C virus 1b infected patients by discriminant analysis using viral and host factors. *PLoS One*. 2010;5(11):e14132.
11. Rodriguez-Torres M, Sulkowski MS, Chung RT, Hamzeh FM, Jensen DM. Factors associated with rapid and early virologic response to peginterferon alfa-2a/ribavirin treatment in HCV genotype 1 patients representative of the general chronic hepatitis C population. *J Viral Hepat*. 2010;17(2):139-147.
12. European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. *AIDS*. 2011;25:399-409.
13. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009;461(7265):798-801.
14. Nasta P, Gatti F, Puoti M, et al. Insulin resistance impairs rapid virologic response in HIV/hepatitis C virus coinfected patients on peginterferon-alfa-2a. *AIDS*. 2008;22(7):857-861.
15. Ferenci P, Fried MW, Shiffman ML, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol*. 2005;43(3):425-433.
16. Jensen DM, Morgan TR, Marcellin P, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology*. 2006;43(5):954-960.
17. Ferenci P, Laferl H, Scherzer TM, et al. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterology*. 2008;135(2):451-458.
18. Martin-Carbonero L, Nunez M, Marino A, et al. Undetectable hepatitis C virus RNA at week 4 as predictor of sustained virological response in HIV patients with chronic hepatitis C. *AIDS*. 2008;22(1):15-21.
19. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA*. 2004;292(23):2839-2848.
20. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med*. 2011;365(11):1014-1024.
21. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364(25):2405-2416.
22. Poordad F, McCone JJr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1195-1206.
23. Jensen DM, Marcellin P, Freilich B, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. *Ann Intern Med*. 2009;150(8):528-540.
24. Florian JA, Jadhav PR, Amur S, et al. Boceprevir dosing regimen for late responders and null responders: the role of bridging data between previously treated and untreated subjects. [Abstract 975.] 62nd American Association for the Study for Liver Diseases Annual Meeting. November 3-8, 2011; San Francisco, CA.
25. Lo Re V, III, Teal V, Localio AR, Amorosa VK, Kaplan DE, Gross R. Relationship between adherence to hepatitis C virus therapy and virologic outcomes: a cohort study. *Ann Intern Med*. 2011;155(6):353-360.
26. Vispo E, Barreiro P, Pineda JA, et al. Low response to pegylated interferon plus ribavirin in HIV-infected patients with chronic hepatitis C treated with abacavir. *Antivir Ther*. 2008;13(3):429-437.
27. Honda M, Sakai A, Yamashita T, et al. Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. *Gastroenterology*. 2010;139(2):499-509.
28. Dumoulin FL, Wennrich U, Nischalke HD, et al. Intrahepatic mRNA levels of interferon gamma and tumor necrosis factor alpha and response to antiviral treatment of chronic hepatitis C. *J Hum Virol*. 2001;4(4):195-199.
29. Darling JM, Aerssens J, Fanning G, et al. Quantitation of pretreatment serum interferon-gamma-inducible protein-10 improves the predictive value of an IL28B gene polymorphism for hepatitis C treatment response. *Hepatology*. 2011;53(1):14-22.
30. Lagging M, Askarieh G, Negro F, et al. Response prediction in chronic hepatitis C by assessment of IP-10 and IL28B-related single nucleotide polymorphisms. *PLoS One*. 2011;6(2):e17232.
31. Yoneda S, Umemura T, Katsuyama Y, et al. Association of serum cytokine levels with treatment response to pegylated interferon and ribavirin therapy in genotype 1 chronic hepatitis C patients. *J Infect Dis*. 2011;203(8):1087-1095.
32. Zeremski M, Markatou M, Brown QB, Dorante G, Cunningham-Rundles S, Talal AH. Interferon gamma-inducible protein 10: a predictive marker of successful treatment response in hepatitis C virus/HIV-coinfected patients. *JAIDS*. 2007;45(3):262-268.
33. Dill MT, Duong FH, Vogt JE, et al. Interferon-induced gene expression is a stronger predictor of treatment response than IL28B genotype in patients with hepatitis C. *Gastroenterology*. 2011;140(3):1021-1031.
34. Sarasin-Filipowicz M, Oakeley EJ, Duong FH, et al. Interferon signaling and treatment outcome in chronic hepatitis C. *Proc Natl Acad Sci U S A*. 2008;105(19):7034-7039.
35. Knudsen A, Benfield T, Kofoed K. Cytokine expression during syphilis infection in HIV-1-infected individuals. *Sex Transm Dis*. 2009;36(5):300-304.
36. Mege JL, Meghari S, Honstettre A, Capo C, Raoult D. The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis*. 2006;6(9):557-569.
37. Brooks DG, Trifilo MJ, Edelmann KH, Teyton L, McGavern DB, Oldstone MB. Interleukin-10 determines viral clearance or persistence in vivo. *Nat Med*. 2006;12(11):1301-1309.
38. Boesecke C, Rockstroh JK. Treatment of acute hepatitis C infection in HIV-infected patients. *Curr Opin HIV AIDS*. 2011;6(4):278-284.

39. 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.

40. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. *JAIDS*. 2007;44(3):356-359.

41. Sellati TJ, Wilkinson DA, Sheffield JS, Koup RA, Radolf JD, Norgard MV. Virulent Treponema pallidum, lipoprotein, and synthetic lipopeptides induce CCR5 on human monocytes and enhance their susceptibility to infection by human immunodeficiency virus type 1. *J Infect Dis*. 2000;181(1):283-293.

42. Twisselmann B. Rates of syphilis in England are rising. *Euro Surveill*. 2002;6(30):pii = 1909.

43. Centers for Disease Control and Prevention and US Department of Health and Human Services. Division of STD Prevention. Sexually transmitted disease surveillance, 2009. November 2010. http://www.cdc.gov/std/stats09/surv2009-Complete.pdf. Accessed September 19, 2012.

44. Syphilis on the rise in the USA. *Lancet*. 2011;378(9791):542.

45. Peterman TA, Furness BW. The resurgence of syphilis among men who have sex with men. *Curr Opin Infect Dis*. 2007;20(1):54-59.

46. Peterman TA, Heffelfinger JD, Swint EB, Groseclose SL. The changing epidemiology of syphilis. *Sex Transm Dis*. 2005;32(10 Suppl):S4-10.

47. Bissessor M, Fairley CK, Leslie D, Howley K, Chen MY. Frequent screening for syphilis as part of HIV monitoring increases the detection of early asymptomatic syphilis among HIV-positive homosexual men. *JAIDS*. 2010;55(2):211-216.

48. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep*. 2006;55:1-94.

49. Screening Guidelines Steering Committee. Sexually transmitted infections: UK national screening and testing guidelines. http://www.bashh.org/documents/59/59.pdf. Accessed September 19, 2012.

Top Antivir Med. 2012;20(4):134-138

Perspective

Beyond Telaprevir and Boceprevir: Resistance and New Agents for Hepatitis C Virus Infection

The addition of the hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir to peginterferon alfa with ribavirin therapy has increased cure rates in HCV infection. Numerous other direct-acting antivirals (DAAs) are in advanced stages of development, including next-generation protease inhibitors, nonstructural protein (NS)5A inhibitors, and nonnucleoside and nucleos(t)ide NS5B polymerase inhibitors. The classes have different potencies, different resistance mutation profiles, and different barriers to the emergence of resistance. A comprehensive table of resistance mutations for classes of DAAs is presented. Numerous combinations of DAAs with or without ribavirin have been evaluated in early studies of interferon alfa-free regimens, with results indicating that cure is indeed possible with such therapy and suggesting that identification of regimens that could produce cure in the majority of patients may occur within the foreseeable future. This article summarizes a presentation by David L. Wyles, MD, at the IAS-USA live continuing medical education activity held in New York in June 2012.

Hepatitis C virus (HCV) infection is characterized by a high rate of viral replication, the presence of an error-prone viral polymerase that acts twice in the replication cycle (converting positive to negative strand and negative to positive strand RNA), and absence of overlapping reading frames; these factors result in the generation of a large number of closely related viral variants (viral quasispecies) including drug-resistant variants. Infected cells have a turnover rate on the order of several weeks. However, the HCV replication unit is dynamic and is not integrated into host cell DNA. The absence of viral genome integration suggests that latent infection is highly unlikely. HCV replication occurs in the cytoplasm, and replication complexes turn over with a half-life on the order of 10 hours to 20 hours. These characteristics present a vulnerability that can be exploited to achieve eradication of the virus from infected persons through drug treatment. Antiviral resistance, however, may present challenges to development of effective direct-acting antiviral (DAA) regimens.

Dr Wyles is Associate Professor of Medicine at the University of California San Diego and a member of the IAS–USA Viral Hepatology Advisory Board and the IAS–USA *Cases on the Web* Editorial Board.

HCV Resistance to Telaprevir and Boceprevir

Initial studies of the nonstructural protein (NS)3 HCV protease inhibitors (PIs) telaprevir and boceprevir, each used alone over 2 weeks, showed rapid emergence of resistant mutants. In patients with breakthrough viremia during the 2 weeks of treatment with telaprevir, for example, there was a nearly complete replacement of wild-type virus with drug-resistant variants. In patients who exhibited a continuous decline in viral load throughout the treatment period, resistant variants could nevertheless be found as a more prominent component of the viral quasispecies weeks to months after treatment had ended. In patients with HCV genotype 1a, prominent resistance mutations were the R155K/T and V36A/M substitutions. In patients with HCV genotype 1b, the A156V/T mutation was prominent. It was found that individual resistance mutations conferred a somewhat decreased replicative fitness compared with wild-type virus and were not associated with complete loss of antiviral activity of telaprevir or boceprevir. However, double mutants (eg, the R155K + V36M found in HCV genotype 1a) often exhibited increased fitness compared with single mutations and were associated with larger changes in antiviral 50% effective concentration (EC_{50}).

In the PROVE (Protease Inhibitor for Viral Evaluation) 1 and 2[1,2] clinical trials with telaprevir in combination with peginterferon alfa and ribavirin, viral breakthrough occurred in approximately 7% of patients with HCV genotype 1a infection, compared with about 2% of those with genotype 1b infection; approximately 10% of patients with either genotype had relapse after cessation of HCV PI treatment. And, as shown in the boceprevir SPRINT-2 (Serine Protease Inhibitor Therapy 2)[3] trial, the rate of emergence of resistance variants depended to a considerable degree on activity of peginterferon alfa in the individual patients. Patients having a decrease in HCV viral load greater than 1 $\log_{10}$ IU/mL during the 4-week lead-in period of peginterferon alfa with ribavirin therapy had very low rates of emergence of boceprevir-resistant mutants (< 5%) during subsequent triple therapy, whereas those with less than a 1 $\log_{10}$ IU/mL decrease in HCV RNA had higher rates (> 30%-45%).

Overall, phase III telaprevir and boceprevir triple therapy trials in treatment-naive patients have shown that resistant variants are detected in 50% to 75% of patients not achieving sustained virologic response (SVR). Of the 10% to 15% with virologic failure (ie, excluding patients in whom therapy failed because of such factors as intolerance), greater than 90% have resistant variants as the predominant HCV species when viral breakthrough occurs. Viral breakthrough during treatment is associated with emergence of resistant variants conferring high-fold changes in sensitivity—eg, V36M plus R155K in HCV genotype 1a infection and A156T/V, T54S, and V55A in genotype 1b infection. Relapse after the end of treatment is associated with low-fold change variants, such as R155K or V36M alone in genotype 1a

and T54A, A156S, or V170A in genotype 1b. Data on telaprevir resistant variants in patients not achieving SVR suggest that reversion to wild-type virus occurs in 96% of patients over 16 months off treatment,[4] with less fit variants decaying more rapidly.

Population sequencing in patients from phase III trials of telaprevir and boceprevir showed that preexisting resistant variants were present in 5% to 7% of patients. Studies using ultradeep sequencing indicate that protease resistant variants are detectable at the 1% level in approximately 7% to 8% and include variants with substitutions at positions 155 and 156 that are associated with substantial loss of sensitivity. It is generally assumed that even when resistant variants cannot be detected, almost all single resistant variants are present prior to treatment at very low levels. An analysis of how preexisting resistant variants might affect clinical outcome from the boceprevir phase III trials suggested, again, that treatment response was dependent on whether patients had a good response to the 4-week lead-in treatment with peginterferon alfa and ribavirin. Overall, 66 (7%) of 980 patients had detectable resistant variants at baseline, including variants associated with treatment failure (V36M, R155K, T54A/S, and V55A; 65% of variants identified) and those that conferred reduced susceptibility to boceprevir but were not implicated in virologic failure (V36I/L, Q41H, V55I, V170M, and M175L; 35% of variants). Among patients who responded to peginterferon alfa, SVR rates were 80% overall, 78% in patients with the first group of variants, and 73% in patients with the second group of variants. Among patients with poor response to initial peginterferon alfa, SVR rates were approximately 30% overall, 0% in those with the first group of variants, and 50% in those with the second group. A total of 7 patients (<1% of the total population) did not respond to peginterferon alfa and had variants in the first group.

HCV resistance testing is clinically available, but given that the 2 available DAAs are completely cross-resistant (see Figure 1), results of testing have little clinical utility in making treatment decisions at this point. Baseline testing to determine the presence of resistant variants prior to therapy is also currently of little clinical value. It remains unclear what effect the identification of preexisting resistant variants has on treatment outcomes with the currently available PIs; telaprevir or boceprevir responses are still largely based on patient interferon-sensitivity. Available data suggest a very small proportion of treatment naive patients (<1%) will possess both baseline-resistant variants and be poor responders to interferon. Thus, there is no straightforward way to determine if patients with preexisting resistant variants should be spared telaprevir or boceprevir treatment.

With regard to preexisting resistant variants for other classes of DAAs in development, ultradeep pyrosequencing capable of identifying variants that account for as little as 0.5% of the viral population indicates that 10% of patients have a majority of preexisting variants resistant to nonnucleoside inhibitors of HCV nonstructural protein (NS)5B polymerase and 22.5% have a minority of resistant variants (in association with polymorphisms at the allosteric binding sites of the polymerase).[5] Thus far, no preexisting resistant variants (S282T) to nucleos(t)ide NS5B polymerase inhibitors have been identified. Preexisting variants resistant to HCV NS5A inhibitors have been identified in approximately 16% of patients.

With regard to next-generation investigational PIs such as TMC-435 (simeprevir), it is known that 1 resistant variant (Q80K) is present in approximately 20% of patients at baseline (particularly common in patients with genotype 1a infection). In a phase II study, SVR rates in patients receiving a lower dose of simeprevir (75 mg po qd) were approximately 82% in those without the Q80K polymorphism versus 57% in those with it. At the higher dose (150 mg po qd), rates were somewhat closer, approximately 85% versus 67%.[6] The higher dose is being tested in a phase III trial, which will include analysis to determine whether screening for the Q80K variant at baseline might have clinical utility in targeting patients for treatment.

Development of Interferon Alfa-Free Regimens

DAA Class Activity and Resistance

The currently identified mutations associated with resistance to telaprevir and boceprevir and investigational PIs, NS5A inhibitors, and nucleos(t)ide NS5B polymerase inhibitors are shown in Figure 1.

Among the current classes of HCV agents, the NS3 PIs have good potency (3-4 $\log_{10}$ IU/mL reductions in HCV RNA level) and established efficacy when used in combination with peginterferon alfa and ribavirin. However, they require several doses every day,

Figure 1 (next page). Mutations in hepatitis C virus (HCV) that impact susceptibility to HCV drugs approved by the US Food and Drug Administration (FDA) and to investigational drugs. The number on the bar refers to the amino acid position; the letter above the number refers to the wild-type amino acid and the letter(s) below the bar are relevant substitutions. Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. Bolded type under the amino acid position number represents the key mutations that are clearly associated with virologic failure and result in a resistant phenotype.

* The majority of mutations seen in HCV genotype 1a are I170F/T substitutions in which I is the consensus amino acid. The majority of mutations seen in HCV genotype 1b are V170A/T, in which V is the consensus amino acid.

** Variants rarely seen in vivo and of unclear clinical significance. These variants are most frequently seen in combination with other resistance-associated mutations. In vitro, they do not confer substantial resistance to telaprevir (< 2-fold increase in median effective concentration [EC_{50}]).

[a] Comprehensive resistance data have not been published. All mutations should be considered provisional.

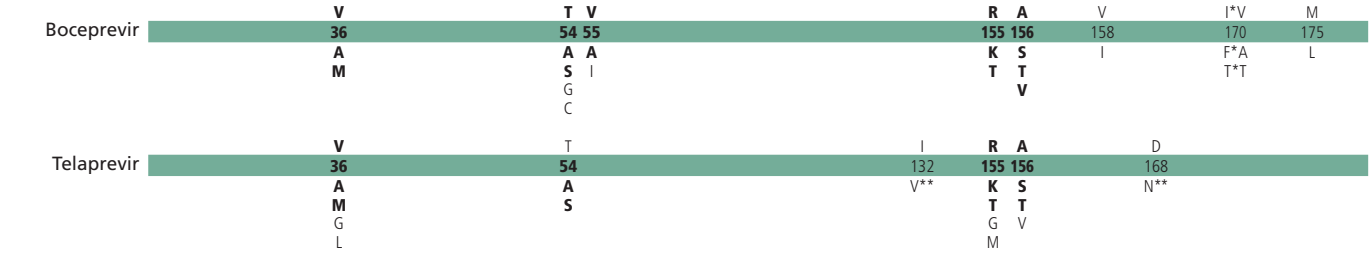
[b] Indicates wildtype in HCV genotype 1a only.

[c] Indicates HCV genotype 1b only.

[d] Nonnucleoside polymerase inhibitor position designations according to Pauwels et al.[7]

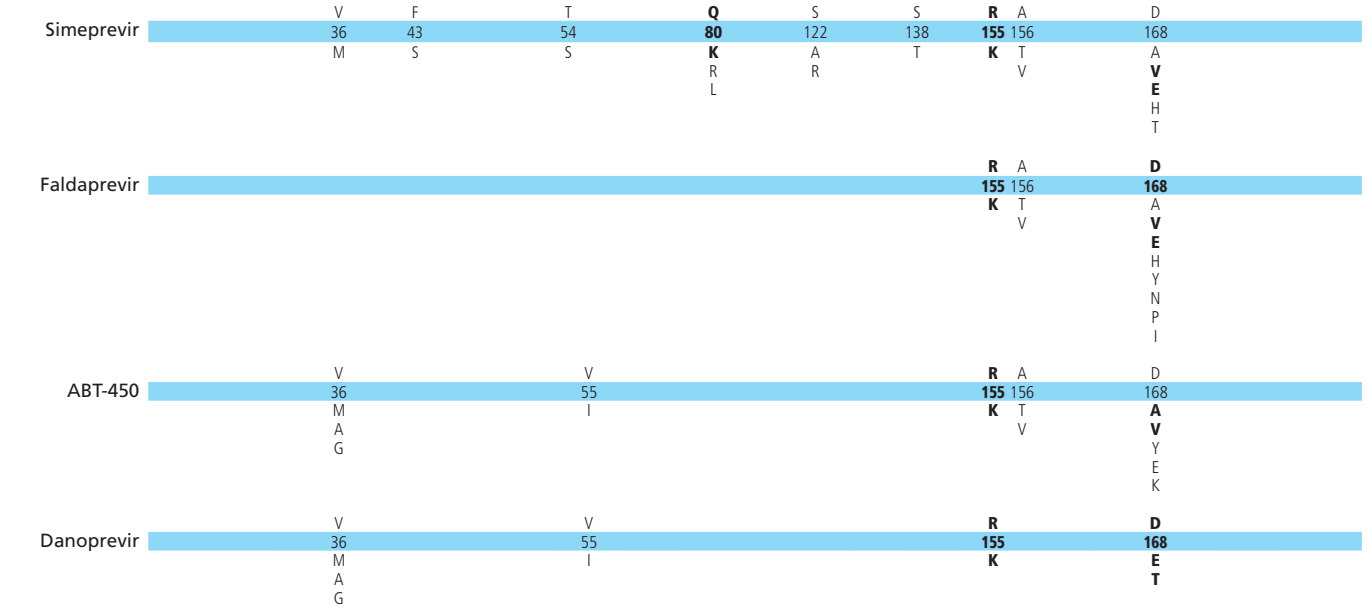
FDA-APPROVED HEPATITIS C VIRUS (HCV) DRUGS

MUTATIONS IN THE HCV PROTEASE GENE ASSOCIATED WITH RESISTANCE TO NONSTRUCTURAL PROTEIN 3 (NS3) PROTEASE INHIBITORS

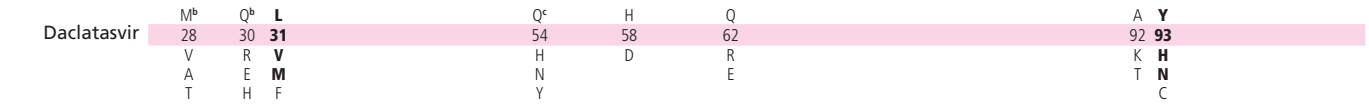


INVESTIGATIONAL HCV DRUGS[a]

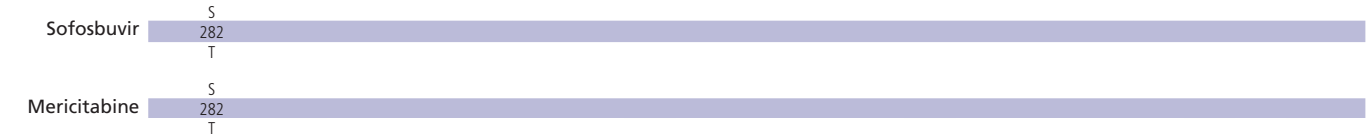
MUTATIONS IN THE HCV PROTEASE GENE ASSOCIATED WITH RESISTANCE TO NONSTRUCTURAL 3 PROTEIN (NS3) PROTEASE INHIBITORS



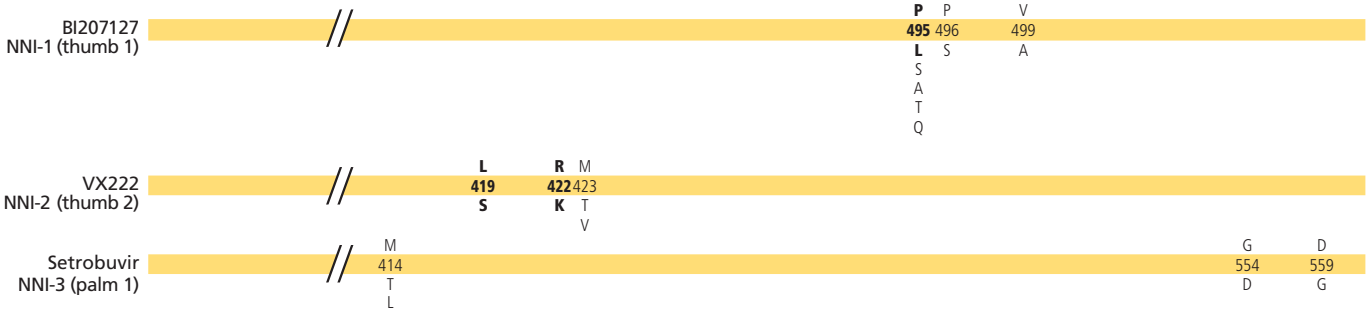
MUTATIONS IN THE HCV NONSTRUCTURAL PROTEIN 5A (NS5A) GENE ASSOCIATED WITH RESISTANCE TO NS5A INHIBITORS



MUTATIONS IN THE HCV POLYMERASE GENE ASSOCIATED WITH RESISTANCE TO NONSTRUCTURAL PROTEIN 5B (NS5B) NUCLEOS(T)IDE INHIBITORS



MUTATIONS IN THE HCV POLYMERASE GENE ASSOCIATED WITH RESISTANCE TO NONNUCLEOSIDE POLYMERASE INHIBITORS[d]



have adverse effect profiles that can be improved on, have low to moderate barriers to resistance with cross-resistance, and have considerable drug interaction potential, since many are metabolized by or affect cytochrome P450 (CYP450) isoenzymes. NS5A inhibitors are very potent (4-5 $\log_{10}$ IU/mL reductions in HCV RNA level), can be dosed once daily, appear to have good adverse effect profiles, and provide broader HCV genotype coverage. However, they have a low barrier to resistance and also exhibit cross-resistance. Available data to date suggest that the nucleos(t)ide NS5B polymerase inhibitors are potent, and later-generation agents can be given once daily and have improved adverse effect profiles. These drugs have the highest barrier to resistance among the current classes, and thus appear to be strong candidates for inclusion in potential interferon alfa-sparing regimens. The nonnucleoside polymerase inhibitors have numerous target sites but modest potency. They also have the lowest barrier to resistance, because allosteric binding sites are not highly conserved.

To determine how best to use and combine these agents, modeling studies have been performed to provide a basis for rational design of interferon alfa-free regimens. Some of these models assume that all single and double mutants are present prior to exposure to DAAs, accounting for the rapid emergence of resistance with exposure to single drugs, and that triple mutants are selected by drug pressure within a day of starting treatment. It has thus been posited that a successful interferon alfa-free regimen would need to require the virus to develop 4 resistance mutations (ie, possess a 4-mutation barrier to resistance).

The NS5B polymerase has at least 4 allosteric binding sites and an active site. For each of these sites, inhibitors have been developed and a unique resistance profile identified. There is potential for cross-resistance at the palm site of the polymerase, against which 2 different classes of inhibitor have been developed. As noted, the nonnucleoside polymerase inhibitors are characterized by relatively low potency and a low barrier to resistance, with a wide variability of response being observed among patients receiving single-agent treatment. In a study of an investigational inhibitor (ANA598), the highest dose produced an approximately 1.5 $\log_{10}$ IU/mL reduction in HCV RNA level, with viral breakthrough occurring rapidly thereafter and the C316Y resistant variant being found in more than 50% of patients.

An example of the higher barrier to resistance among the nucleos(t)ide polymerase inhibitors is the effect of the resistant variant S282T on viral sensitivity and replicative fitness. This variant produces a low-fold change in EC_{50} (approximately 3-fold shift) and has replicative fitness that is 5% to 15% that of wild-type virus. The activity of NS5A inhibitors is indicated by a phase II study of one such investigational inhibitor (BMS-790052 or daclatasvir) that showed an SVR rate of 83% when used in combination with peginterferon alfa and ribavirin. When studied as a single agent, 4-$\log_{10}$ IU/mL decreases in HCV RNA level over the first several days are seen followed by viral breakthrough with a variety of resistance mutations. Some resistance mutations observed in patients with HCV genotype 1a infection were not observed in genotype 1b, apparently reflecting a difference in polymorphisms present at baseline in the 2 HCV genotypes. Those resistant variants that are common to the 2 genotypes have different effects on drug sensitivity. Thus, in the study of BMS-790052 alone, the resistant variants M28T, Q30H, L31V, and Y93H were identified in patients with genotype 1a infection and the variants L31V and Y93H were found in those with genotype 1b infection. There were dramatic differences in the effect on drug susceptibility with the common mutations by genotype: the L31V variant caused a 3000-fold change in genotype 1a but only a 28-fold change in genotype 1b, and the Y93H variant caused a 5000-fold change and a 24-fold change, respectively.

These data highlight that there are differences between the HCV genotype 1 subtypes with regard to mutational and functional barriers to resistance. In another example, transition to the R155K variant requires only a single nucleotide change in genotype 1a, but requires 2 substitutions in genotype 1b. As shown in the study of the NS5A inhibitor, identical variants can have dramatically different effects on fold-change in susceptibility in genotype 1a versus genotype 1b.[8]

Promising investigational DAAs in phase II and III studies that are likely candidates for testing in interferon alfa-free regimens include the nucleoside polymerase inhibitor mericitabine and the nucleotide inhibitor GS-7977; the nonnucleoside inhibitor tegobuvir; the next-generation PIs simeprevir, BI-201335 (faldaprevir), and ritonavir-boosted danoprevir; and the NS5A inhibitor daclatasvir. Alisporivir, not a DAA, is a cyclophilin A inhibitor that interacts with HCV polymerase and NS5A. Although promising, this compound is on clinical hold because of an association with pancreatitis.

Initial Interferon Alfa-Free Studies

Early interferon alfa-free studies established that viral breakthrough is universal when combinations with low barriers to resistance, such as a nonnucleoside polymerase inhibitor plus a PI, are used, with addition of ribavirin often preventing early breakthrough and prolonging response. On the other hand, the higher resistance barrier combination of a PI with a nucleoside polymerase inhibitor resulted in a continuous antiviral response during short-term treatment, with no on-treatment viral breakthroughs observed.

The first trial to show that patients could achieve cure with an interferon alfa-free regimen was recently reported by Lok and colleagues.[9] This small trial compared the DAA combination of the NS5A inhibitor daclatasvir and the PI asunaprevir (2-drug regimen) with the 2 agents in combination with peginterferon alfa and ribavirin (4-drug regimen) in subjects who had not responded to peginterferon alfa and ribavirin. Breakthrough occurred in 6 of the 11 dual-therapy patients during treatment and in 1 after treatment had

stopped, with 4 being cured (Figure 2). All 10 patients receiving the 4-drug regimen achieved cure. It is of interest that both patients with HCV genotype 1b in the dual therapy arm achieved cure, suggesting a higher barrier to resistance in this genotype. The patient relapsing at the end of treatment had a preexisting R155K PI-resistant variant, with breakthrough being marked by emergence of the NS5A-resistant variant Q30E. Breakthrough was associated with a higher baseline viral load and was characterized by emergence of resistance to both drug classes.

The ability of a 2-drug regimen to achieve cure in genotype 1b patients was supported by a study in Japanese patients, who almost exclusively have genotype 1b infection. In this trial, the combination of daclatasvir and asunaprevir produced cure in 77% of more than 40 genotype 1b patients who had not responded to peginterferon alfa with ribavirin or who could not receive peginterferon alfa.[10]

The findings in the study reported by Lok and colleagues tend to support the notion that a 4-mutation barrier is needed for cure in genotype 1a patients, given the fact that most of these patients had breakthrough and that the dual-drug regimen did not provide such a barrier. It is less clear whether the regimen satisfies this theoretical requirement in patients with genotype 1b infection, in whom it nevertheless appeared to be successful in achieving cure. Another issue highlighted by this trial is whether continued administration of dual therapy in patients with viral breakthrough leads to emergence of additional resistance mutations. Patients with breakthrough on dual therapy continued treatment with the addition of peginterferon alfa and ribavirin. In one of these patients, a reduction in viral load occurred with the addition of peginterferon alfa and ribavirin, followed by another breakthrough, with the patient having 6 months of cumulative exposure to a failing regimen including a PI and NS5A inhibitor. PI resistance due to variants at the 168 position evolved from wild-type at baseline to D168Y and D168A during dual therapy. Both of these variants are associated with high fold changes in drug susceptibility (525-fold and 30-fold respectively) but very low relative fitness (23% and 1% respectively). Continued evolution during 4-drug therapy led to emergence of the D168T variant, which is associated with a high fold change in drug susceptibility (170-fold) and increased replicative fitness (160% that of wild-type). Such findings suggest that failing DAAs should be stopped if viral breakthrough occurs, to prevent continued evolution of resistance.

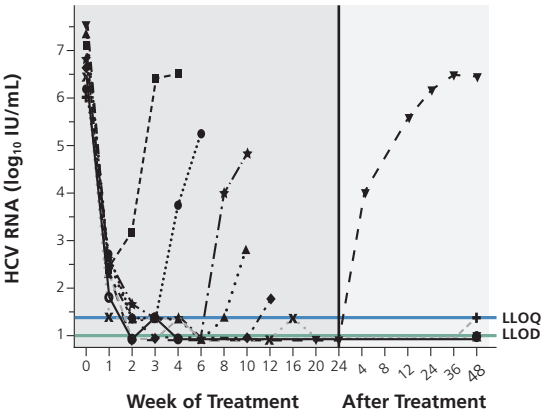


Figure 2. Virologic response to the investigational drugs daclatasvir and asunaprevir (interferon alfa-free regimen). Viral breakthrough occurred in 6 of 11 patients during dual therapy and 1 patient relapsed after therapy. The patient with relapse had a preexisting R155 hepatitis C virus (HCV) gene variant, with relapse marked by emergence of a Q30E variant. LLOQ indicates lower limit of quantification; LLOD, lower limit of detection. Adapted from Lok et al.[9]

More Recent Interferon Alfa-Free Studies

With regard to more recent studies of interferon alfa-free regimens, the results of the Gilead Sciences 0120 study with the 3 DAAs plus ribavirin was reported at the 2012 EASL (European Association for the Study of the Liver) conference. Sulkowski and colleagues evaluated quadruple therapy including a PI, NS5A antagonist (2 dosage levels), nonnucleoside polymerase inhibitor, and ribavirin.[11] Patients in the high-dose NS5A antagonist group (arm 2) were randomized to 12 weeks or 24 weeks of therapy if HCV RNA level was undetectable at 2 weeks (very rapid virologic response [vRVR]). All other patients received 24 weeks of treatment. Patients without vRVR had peginterferon alfa added to their treatment. Patients were also analyzed according to variants in IL28B, a gene in which the CC variant is predictive of response to peginterferon alfa with ribavirin. As shown in Figure 3, there was less difference between vRVR rates according to whether patients had IL28B CC or non-CC genotypes with the stronger regimen containing the higher NS5A antagonist dose. Viral breakthrough was more common in patients with genotype 1a HCV and was characterized by triple-class resistance variants in the majority of cases. Preliminary SVR data for patients with vRVR showed 4-week SVR in nearly all arm-2 patients after the 12-week treatment course (Figure 4). The data showed 12-week SVR in 80%. In the vRVR group getting 24 weeks of treatment, 4-week SVR was observed in all patients with available data and 12-week SVR was observed in most. Overall, 87% of patients without vRVR had viral suppression with the addition of peginterferon alfa.

Another study reported by Poordad and colleagues at the 2012 EASL conference[12] examined the triple combination of a ritonavir-boosted PI (ABT-450, at 2 dosage levels), a nonnucleoside polymerase inhibitor (ABT-333), and ribavirin for 12 weeks. This combination was given to treatment-naive patients and to prior null responders to peginterferon alfa who had genotype 1 infections. In treatment-naive patients, SVR rates 12 weeks after treatment were 95% in the higher-dose boosted PI group and 93% in the lower-dose group, and 47% in the prior nonresponders. Among the treatment-naive patients, 1 in each group stopped treatment within 2 weeks due to intolerance or nonadherence; thus, all patients completing treatment had a 12-week SVR. Reasons for the poor treatment outcomes in the prior nonresponders remain unclear; none had the IL28B CC genotype. These patients exhibited an initial decline in viral

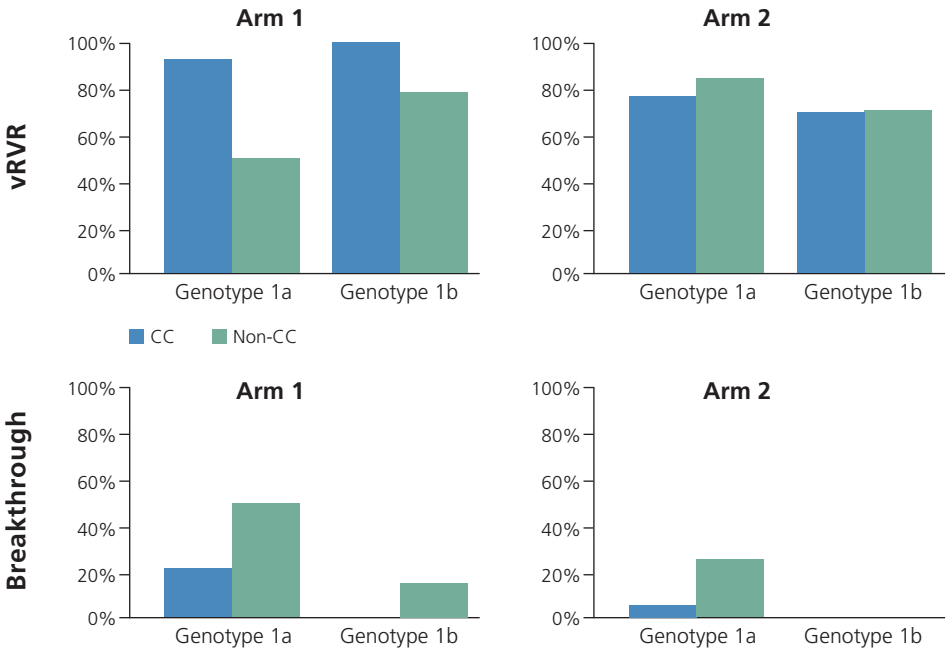


Figure **3**. Peginterferon alfa-free therapy with 4-drug combination of a protease inhibitor, nonstructural protein 5A antagonist (2 dosage levels), nonnucleoside polymerase inhibitor, and ribavirin. Very rapid virologic response (vRVR) rates shown in genotype 1a and 1b patients receiving therapy. Arm 2 patients received the highest dose of nonstructural protein 5A antagonist. Patients were also analyzed according to IL28B variant (CC or non-CC) [top]. Triple-class resistance was seen in most of 1a breakthroughs [bottom]. Adapted with permission from Sulkowski et al.[11]

load, but many had viral breakthrough during treatment or had relapse after treatment, with failure being associated with dual class resistance.

The ELECTRON study examined 12 weeks of treatment with the nucleotide polymerase inhibitor GS-7977 (sofosbuvir) plus ribavirin in patients with genotype 1 HCV who were treatment naive or were prior nonresponders to peginterferon alfa with ribavirin, and in patients with genotype 2 or 3 virus who were either treatment naive or had prior treatment failures.[13,14] The trial also examined the polymerase inhibitor alone in treatment-naive patients with genotype 2 or 3 HCV, and an additional arm assessed the combination of GS-7977, ribavirin, and peginterferon alfa in treatment-naive patients with genotype 2 or 3 virus. Suppression was observed in all groups during the 12 weeks of treatment, consistent with other observations indicating that virtually no patients receiving the nucleotide polymerase inhibitor exhibited viral breakthrough during treatment. However, shortly after stopping treatment, different relapse patterns emerged. Four-week SVR rates following GS-7977 plus ribavirin were 100% in the treatment-naive genotype 2 or 3 group, 88% in the treatment-naive genotype 1 group, 80% in the treatment-experienced genotype 2 or 3 group, and only 11% (1 of 9 patients) in the genotype 1 prior null responders. SVR rates at 4 weeks were 60% in the treatment-naive genotype 2 or 3 group receiving the polymerase inhibitor without ribavirin. Population sequencing and deep sequencing studies in 5 of the 8 patients with relapse in the genotype 1 null responder group showed no evidence of the S282T polymerase resistance variant. That observation leaves open the question of how relapse occurred in these patients in the absence of identified resistance mutations.

Finally, another study included 24 weeks of treatment with the nucleotide polymerase inhibitor GS-7977 and the NS5A inhibitor daclatasvir with or without ribavirin, in 3 groups of treatment-naive patients with genotype 1 infection.[15] One group started NS5A inhibitor therapy a week after starting polymerase inhibitor treatment and one started both concurrently, with neither group receiving ribavirin; the third group started all 3 drugs together. Four-week SVR rates were 100% in all 3 groups. Further follow-up will help determine whether the apparent lack of need for ribavirin with this DAA combination is borne out in this setting.

Conclusion

HCV variants that are resistant to DAAs emerge in patients who experience virologic failure. Multiclass resistance emerges in patients on interferon alfa-free regimens that contain DAAs, with the possible exception of resistance to nucleoside polymerase inhibitors. The long-term impact of emergence of resistant variants is not known at this point. It is known that such variants decay over time, but it remains unclear whether reexposure to the same drug classes will result in rapid reemergence of resistance. Progress in devising interferon alfa-free regimens is rapid and can be expected to continue

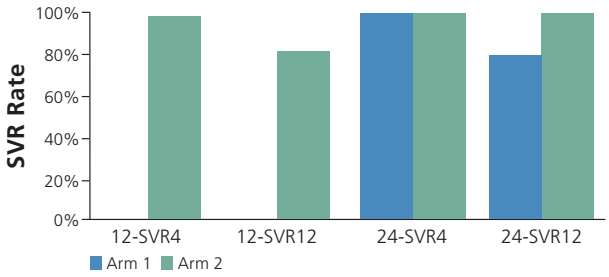


Figure **4**. Sustained virologic response (SVR) in patients with very rapid virologic response (vRVR) on 4-drug regimen that did not include peginterferon alfa. Patients in the high-dose nonstructural protein 5A antagonist group (arm 2) who achieved vRVR were randomized to 12 weeks (12-SVR) or 24 weeks (24-SVR) of therapy. Overall, 87% (26/30) of patients without vRVR had viral suppression with the addition of peginterferon alfa. Adapted with permission from Sulkowski et al.[11]

in this manner for the next several years. Hope remains that interferon-free regimens can be crafted for the vast majority of HCV patients within the near future.

Presented by Dr Wyles in June 2012. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Wyles in October 2012.

Financial Affiliations: In the past year, Dr Wyles has received grants awarded to the University of California San Diego from Gilead Sciences, Inc, Pharmasset, Inc, Merck & Co, Inc, and Vertex Pharmaceuticals. He also served as a consultant to Bristol-Myers Squibb, Janssen Pharmaceuticals, Inc, and Merck & Co, Inc. He has developed educational presentations for QuantiaMD. (Updated 10/31/12)

References

1. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med.* 2009;360(18):1827-1838.
2. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med.* 2009;360(18):1839-1850.
3. Poordad F, McCone JJr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med.* 2011;364:1195-1206.
4. Sullivan JC, De Meyer S, Bartels DJ, et al. Evolution of treatment-emergent resistant variants in telaprevir phase 3 clinical trials. *J Hepatol.* 2011;54(Suppl 1):S4.
5. Margeridon S, Pogam SL, Liu TF, et al. No detection of variants bearing NS5B S282T mericitabine (MCB) resistance mutation in DAA treatment-naïve HCV genotype 1 (G1)-infected patients using ultra-deep pyrosequencing (UDPS). *Hepatology.* 2011;54(S1):532A.
6. Lenz O, Fevery B, Vijgen L, et al. TMC435 in combination with peginterferon alpha-2a/ribavirin in treatment-naive patients infected with HCV genotype 1: virology analysis of the PILLAR study. [Abstract 1329.] 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD). November 4-8, 2011; San Francisco, CA.
7. Pauwels F, Mostmans W, Quirynen LM, et al. Binding-site identification and genotype profiling of hepatitis C virus polymerase inhibitors. *J Virol.* 2007;81(13):6909-6919.
8. Fridell RA, Wang C, Sun JH, et al. Genotypic and phenotypic analysis of variants resistant to hepatitis C virus nonstructural protein 5A replication complex inhibitor BMS-790052 in humans: in vitro and in vivo correlations. *Hepatology.* 2011;54(6):1924-1935.
9. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N Engl J Med.* 2012;366(3):216-224.
10. Suzuki F, Ikeda K, Toyota J, et al. Dual oral therapy with the NS5A inhibitor daclatasvir (BMS-790052) and NS3 protease inhibitor asunaprevir (BMS-650032) in HCV genotype 1b-infected null responders or ineligible/intolerant to peginterferon. [Abstract 14.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.
11. Sulkowski M, Rodriguez-Torres M, Lawitz E, et al. Interim sustained virologic response rates in treatment-naïve HCV genotype 1a and 1b patients treated for 12 or 24 weeks with an interferon-free all-oral Quad regimen. [Abstract 1421.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.
12. Poordad F, Lawitz E, Kowdley KV, et al. A 12-week interferon-free regimen of ABT-450/r + ABT-333 + ribavirin achieved SVR12 in more than 90% of treatment-naïve HCV genotype-1-infected subjects and 47% of previous non-responders. [Abstract 1399.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.
13. Gane EJ, Stedman CA, Hyland RH, et al. ELECTRON: once daily PSI-7977 plus RBV in HCV GT1/2/3. [Abstract 1113.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.
14. Gane E, Stedman C, Anderson J, et al. 100% Rapid virologic response for PSI-7977 + ribavirin in genotype 1 null responders (ELECTRON): early viral decline similar to that observed in genotype 1 and genotype 2/3 treatment-naïve patients. [Abstract 54LB.] 19th Conference on Retroviruses and Opportunistic Infections (CROI). March 5-8, 2012; Seattle, WA.
15. Sulkowski MS, Gardiner D, Lawitz E, et al. Potent viral suppression with the all-oral combination of daclatasvir (NS5A inhibitor) and GS-7977 (nucleotide NS5B inhibitor), +/- ribavirin, in treatment-naive patients with chronic HCV GT1, 2, or 3 (100% SVR gt1, 91% gt2). [Abstract 1422.] 47th Annual Meeting of the European Association for the Study of the Liver (EASL). April 18-22, 2012; Barcelona, Spain.

Top Antivir Med. 2012;20(4):139-145

Cases on the Web

Cases on the Web (COW) is a series of case-driven continuing medical education activities sponsored by the IAS–USA. The *COW* program was created to offer convenient online access to top-quality education in the management of HIV, hepatitis C virus, and other viral infections.

NEW Progressive Multifocal Leukoencephalopathy in HIV Infection

David B. Clifford, MD
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

Progressive multifocal leukoencephalopathy (PML) is one of the most serious complications of immunodeficiency associated with HIV. Although some opportunistic complications have almost vanished, PML continues to complicate HIV infection, particularly in the early months of therapy, and immune reconstitution inflammatory syndrome (IRIS) is regularly encountered. Dr Clifford describes how, with optimal management, survival with PML has greatly improved.

NEW The Use of Hepatitis C Virus (HCV) Protease Inhibitors in HIV/HCV-Coinfected Patients

Jennifer C. Lin, MD, and David L. Wyles, MD
CME Credit Available: 2.0 *AMA PRA Category 1 Credits*™
Level: Advanced

Hepatitis C virus (HCV) infection is now thought to be the leading chronic viral disease-related cause of death in the United States, having recently surpassed HIV infection. HIV infection in persons with HCV infection is associated with an increased risk of cirrhosis and decompensated liver failure. Dr Lin and Dr Wyles discuss the use of HCV protease inhibitors, which has markedly increased the success of HCV treatment, and address the complicating issues of adverse effects and drug-drug interactions of HCV PIs with antiretroviral drugs.

Sequencing Antiretroviral Drugs in the Patient With Numerous Treatment Failures and Multidrug-Resistant Virus

Snigdha Vallabhaneni, MD, MPH, and Harry W. Lampiris, MD
CME Credit Available: 1.5 *AMA PRA Category 1 Credits*™
Level: Advanced

Antiretroviral therapy options for treatment-naive and treatment-experienced patients have dramatically expanded in the past few years. Patient-specific factors inform the decision about which new antiretroviral agents to select. Dr Vallabhaneni and Dr Lampiris describe strategic approaches to using antiretroviral drugs in new and preexisting drug classes to design antiretroviral regimens for patients with numerous treatment failures and multidrug-resistant HIV.

Management of Chronic Hepatitis C Virus Infection in Advanced Liver Disease

Kenneth E. Sherman, MD, PhD, and Syed Hussain, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

Hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. Because the disease is largely asymptomatic until advanced liver disease develops, patients are often diagnosed after years of infection. Newer treatments offer a greater chance of cure, but may be challenging and are often contraindicated in patients with advanced disease. This activity presents important information on identifying and appropriately treating patients with advanced liver disease due to chronic HCV. Dr Sherman and Dr Hussain discuss disease management, including referral for liver transplantation.

www.iasusa.org/cow

Novel HIV-1 Resistance and Tropism Testing

Jonathan Li, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

When available, HIV drug-resistance testing should be used to guide the selection of an optimal antiretroviral regimen. Technologic advances in HIV sequencing and sequence detection have revolutionized the study of antiretroviral drug resistance and HIV diversity, and are increasingly moving from the laboratory to clinical practice. Dr Li provides clinicians with background information to choose HIV drug-resistance testing and to guide the selection of an optimal antiretroviral regimen.

Prevention of Mother-to-Child Transmission in Highly Treatment-Experienced HIV-Infected Women

Theresa Barton, MD, and Laura N. Armas-Kolostroubis, MD
CME Credit Available: 1.25 *AMA PRA Category 1 Credits*™
Level: Advanced

The use of antiretroviral therapy and prophylaxis has dramatically reduced HIV transmission to infants. However, ongoing use of antiretroviral agents can lead to emergence of viral resistance, especially as women experience antiretroviral treatment failures. Dr Barton and Dr Armas-Kolostroubis address maintaining low perinatal transmission rates in the presence of resistant HIV, which requires knowledge of recommendations for treatment and prophylaxis in pregnant women and neonates.

These Internet enduring material activities have been approved for *AMA PRA Category 1 Credit*™.

COMING SOON

Look for these new *Cases on the Web* activities.

November: Primary Care Issues in HIV Management

Howard Libman, MD

The care of HIV-infected patients has undergone dramatic changes over the past 15 years, owing to the advent of combination antiretroviral therapy and the introduction of plasma HIV RNA testing and resistance testing in clinical practice. Staying abreast of a rapidly changing but incomplete knowledge base of treatment options and addressing potentially complicated outpatient issues within time constraints are important challenges for the health care practitioner.

December: Managing and Counseling for Adolescents with HIV Infection

Donna C. Futterman, MD

The profile of HIV infection among youth has changed substantially since the 1990s, in large part because of the dramatic decrease in new perinatal transmission and the steady increase in behaviorally acquired HIV among adolescents. Thousands of HIV-infected children born before interventions to prevent perinatal transmission were in place are now adolescents and young adults, and a growing number of youth are also acquiring HIV primarily through sexual activity. The transition to adulthood involves an adjustment to new providers and surroundings as well as engagement in self-care.

For information about *Cases on the Web*, please contact the IAS–USA.
Phone: (415) 544-9400 • Fax: (415) 544-9401 • E-mail: info"at"iasusa.org • Web site: www.iasusa.org/cow

Topics in Antiviral Medicine™

Subscription Request
Address Change

Start or update your subscription online at www.iasusa.org. The redesigned website also enables readers to find information about IAS–USA activities and to create or update your profile. *Topics in Antiviral Medicine* is published 4 to 6 times a year.

Readers can also use the form below to subscribe and unsubscribe to *Topics in Antiviral Medicine* in paper copy, or to receive IAS–USA e-mailed newsletters with information about upcoming IAS–USA continuing medical education courses.

Please check the appropriate box:

- ❒ I am a new subscriber to the IAS–USA mail list
- ❒ I am a current subscriber requesting a change of address

IAS–USA ID Number _____
(if applicable) Please see upper left corner of mailing address as shown in sample.

SAMPLE

ID No.	IAS–USA #12345 SUE SMITH, MD 425 CALIFORNIA ST., STE. 1450 SAN FRANCISCO, CA 94104

Please check the *Top Antivir Med* subscription type:

- ❒ Paper form only
- ❒ Electronic form only
- ❒ Paper and electronic forms

Please print or type

First Name _____ MI _____ Last Name _____

Degree or License (MD, RN, PA, none, etc) _____ Title _____

Institution or Organization _____

Specialty / Primary Field of Interest _____

Address (please check one) (_____ Home Address _____ Work Address)

City _____ State / Province _____

Postal Code _____ Country _____

Mobile Phone _____ Facsimile _____

Home Phone _____ Work Phone _____

E-mail Address (_____ Home E-mail _____ Work E-mail)

Do you work for a commercial company in any capacity? Yes___ No___
(eg, pharmaceutical, diagnostic, medical product, advertising, insurance, investment, communications)

If yes, please indicate company:_____

Fax or mail this form to:

IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
Fax: (415) 544-9401

FOR INTERNAL USE ONLY

DATE _____ INITIALS _____ CHANGES_____

Guidelines for Authors and Contributors

The IAS–USA publishes *Topics in Antiviral Medicine*™ as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. The journal is indexed in Index Medicus/MEDLINE and is distributed to approximately 13,000 national and international subscribers.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact *Topics in Antiviral Medicine*™ at journal"at"iasusa.org.

Categories of Articles

Perspectives. *Perspective* articles are summaries of selected talks given at IAS–USA continuing medical education courses. An IAS–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the presenter and the journal's appointed peer reviewer(s).

Reviews. *Topics in Antiviral Medicine*™ welcomes original review articles on current issues related to infection with HIV or other viruses. *Topics in Antiviral Medicine*™ does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

Editorials. *Topics in Antiviral Medicine*™ invites submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

Special Contributions. A special contribution article often represents the unique contribution (such as a consensus statement) of an author or group of authors.

Cases From the Field. *Topics in Antiviral Medicine*™ invites submission of case reports accompanied by a scholarly literature review of the topic. Each case report should be 1500 to 3000 words (excluding references, tables, and figures), include numbered references, and seek to teach an important lesson for HIV or hepatitis virus care practitioners.

Stories. Stories for the *Telling Stories* column share the experiences of those involved in the care of people infected with HIV or other viruses. Stories may be approximately 800 to 3500 words; submissions are welcome for consideration.

Commentaries. Discussion on a current issue in the management of viral diseases is welcome as a *Commentary*. Commentaries should be 500 to 1500 words and include numbered references as appropriate. Commentaries may be invited by the editors; unsolicited submissions are also welcome for consideration.

Letters to the Editor. Letters to the editor are welcome and should be sent to the address listed below. Please limit letters to 300 words.

Special Issues. *Topics in Antiviral Medicine*™ publishes 1 or 2 issues each year with a special focus, such as reports from recent scientific meetings and summaries of special IAS–USA continuing medical education courses.

Online Articles: Occasional articles appear online only. They are distinguished from printed articles by pagination beginning with "e."

Reprints. Reprints of articles by expert panels convened by the IAS–USA are included periodically in *Topics in Antiviral Medicine*™.

Submission of Manuscripts

Manuscripts should be submitted via mail or e-mail to the address below. Each manuscript author should complete an Authorship Form, which is available online at www.iasusa.org/pub or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or e-mail.

Editor, *Topics in Antiviral Medicine*™
IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120
E-mail: journal"at"iasusa.org

Receipt of submitted manuscripts will be acknowledged by editorial staff, and submissions will be reviewed by peer reviewers. Acceptance for publication is based on the quality and relevance of the work.

Copyright

Copyright to all manuscripts and graphics published in *Topics in Antiviral Medicine*™ is owned by the IAS–USA unless worked otherwise. All authors and contributors of manuscripts accepted for publication, with the exception of US federal government employees, must sign a copyright transfer form as a condition of publication.

Authorship Requirements

Topics in Antiviral Medicine™ uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its *Uniform Requirements for Manuscripts Submitted to Biomedical Journals.*[1] This definition states: "Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3....Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship." *Topics in Antiviral Medicine*™ will not consider ghostwritten articles for publication.

Financial Disclosure

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. To that end, all authors and contributors of articles published in *Topics in Antiviral Medicine*™ are required to disclose to readers any significant financial interest or other relationship with any organization having financial interest in the content of the manuscript. Financial interests include employment, consultancy, honorarium, grant/research support, major stock ownership, or membership in a speakers bureau and paid lectures or other contribution. The complete financial disclosure statements for all authors and contributors are published with the articles.

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2008. Available at http://www.icmje.org. Accessed January 26, 2010.

IAS–USA
425 California Street, Suite 1450
San Francisco, CA 94104-2120

International Antiviral Society–USA

IAS–USA has a redesigned website!

www.iasusa.org

- **Improved search engine to locate information by activity, topic, speaker, and more**
- **Ability to manage personal profiles for easier registration, to start journal subscriptions, and to customize information from IAS–USA**
- **User-friendly interface to deliver educational materials and offer a range of CME activities to practitioners**
- **Registration for upcoming courses in HIV and HCV**