Reporting the Evidence for Optimal Treatment Options and Formulary Management: Antiviral Drugs in HIV and Hepatitis B

Schumarry H. Chao, MD, MBA
Jason Smith, PharmD
Ian R. McNicholl, PharmD, BCPS
William J. Cardarelli, PharmD
Subject all supplements to expert peer review.

Seek and publish content that does not duplicate content among supplement contributors, including financial or specific off-label indication.

Any off-label (unapproved) use is identified by drug name and specific off-label indication among supplement contributors, including financial or specific off-label indication.

Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

Disclose the principal sources of funding in a manner that permits easy recognition by the reader.

Effectively disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.

Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.

Any off-label (unapproved) use is identified by drug name and specific off-label indication.

Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

Seek and publish content that does not duplicate content among supplement contributors, including financial or specific off-label indication.

Subject all supplements to expert peer review.

Schumarry H. Chao, MD, MBA, president of the consulting firm SHC & Associates and founder of the Peer to Peer Advisory Council, has leadership, strategic, and operational experience on “all sides of the health care industry”—insurer, delivery system management, employer, and pharmaceutical and health care information technology. Chao serves on the Board of Trustees of the Foundation, Academy of Managed Care Pharmacy, the Editorial Board of American Journal of Medical Quality, member, Medical and Scientific Advisory Board, Healthways, Inc., and co-chair of the steering committee for Benefit Design Institute. From 1996 to 2003, Chao was chief medical officer and senior vice president, strategic development for MedImpact Health care System, Inc., where she had responsibility for clinical product development and pharmacy benefits management and spearheaded the development of medical informatics initiatives. Chao also served as vice president and corporate medical director for Aetna Life and Casualty Company. Chao developed and implemented innovative health benefit strategies for the University of Southern California (USC). As corporate medical director for Security Pacific Bank, Chao managed a pre-paid medical group, had responsibility for Emergency Trauma System in Los Angeles County, and served as chief medical officer for the Los Angeles Summer Olympics in 1984. Chao, who emigrated to the United States from China at age 12, received her BS and MBA from the University of California, San Francisco. Board certified in emergency medicine, her academic appointments include clinical professor of emergency medicine and family medicine, as well as adjunct professor of pharmacoeconomics at USC. She also serves on the Board of Trustees, University of Health Sciences, Philadelphia.

Jason Smith, PharmD, is clinical pharmacy specialist and manager of the Hepatitis C Virus (HCV) Clinical Case Registry at the Veterans Affairs Greater Los Angeles Healthcare System (GLA). He is the treatment coordinator and clinical pharmacy specialist for the viral hepatitis clinical and advanced liver disease program at GLA, where he oversees veterans receiving treatment for viral hepatitis. He is also a subInvestigator for a Phase III study evaluating the efficacy of a novel interferon agent in combination with ribavirin for the treatment of HCV. Smith actively publishes in the field of hepatology with an emphasis on the pharmacist’s role in the treatment and evaluation of patients with hepatitis C. In addition to speaking nationally for the American College of Clinical Pharmacy, GI/Liver PRN group, he is involved in CME projects focused on the field of hepatology with the National Hepatitis C Resource Center Pharmacy Workgroup in the development of clinical tools. Smith received his PharmD from The Ohio State University in 2002 and completed residency training at the Department of Veterans Affairs in Loma Linda, California, in 2003. He completed a fellowship program focused on hepatology at the Department of Veterans Affairs in Los Angeles, where he created a pharmacist-managed hepatitis C care clinic.

Ian R. McNicholl, PharmD, BCPS, (AQ-Infectious Diseases) is a clinical pharmacy specialist with the Department of Medicine/University of California at San Francisco (UCSF) Positive Health Practice and an assistant clinical professor with the UCSF School of Pharmacy. His primary clinical practice is at the UCSF Positive Health Practice at San Francisco General Hospital where the clinic provides comprehensive health care for more than 3,000 HIV-positive patients. Other major responsibilities include managing a pharmacist-staffed Adherence Support Program and serving on the Editorial Board, UCSF Center for HIV Information. Board certified in Pharmacotherapy (BCPS) with Added Qualifications in Infectious Diseases, McNicholl has held faculty appointments and/or had clinical practices at the University of Illinois-Chicago, University of Colorado, Kaiser Permanente, St. Louis College of Pharmacy, Veterans Affairs Medical Center-St. Louis, and Barnes-Jewish HospitalClinics.

William J. Cardarelli, PharmD, is currently director of pharmacy for Harvard Vanguard Medical Associates and Attius Health (formerly HealthOne Care System) in Boston. He is responsible for all pharmacy services in the 25-site integrated delivery system serving more than 800,000 lives. Cardarelli holds degrees from the University of Massachusetts and the Massachusetts College of Pharmacy and has completed post-graduate residencies at Peter Bent Brigham Hospital and Newton Wellesley Hospital. He continues his academic responsibilities as the principal manager of an American Society of Hospital Pharmacists (ASHP)-certified residency program in managed care. An experienced pharmacy administrator for more than 20 years, Cardarelli has extensive experience in cost containment and resource allocation in the managed care arena. He has also held progressive management positions at Harvard Community Health Plan, Harvard Pilgrim Health Care, and Harvard Vanguard Medical Associates.
Reporting the Evidence for Optimal Treatment Options and Formulary Management: Antiviral Drugs in HIV and Hepatitis B

**Synopsis**
Managed care organizations and specialty pharmacy professionals should be updated on new guidelines for the management of patients with HIV and/or HBV, especially due to the emergence of treatment-resistant strains in recent years. Formulary decision makers should also consider the impact and pharmacoeconomics of emerging resistance, as well as cross-resistances among co-infections, mainly HIV and HBV. This supplement also addresses the differences between guidelines and offers suggestions on improving medication adherence.

**Accreditation Statements**

**Physician**
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Creative Educational Concepts, Inc. and AMCP Horizons, LLC. Creative Educational Concepts, Inc. is accredited by the ACCME to provide continuing medical education for physicians.

CEC designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**Pharmacy**
Creative Educational Concepts, Inc. (CEC) is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

A total of 0.10 CEUs (1.0 contact hours) will be awarded for successful completion of this continuing education activity (ACPE #245-999-08-015-H04-P). CEC complies with the Criteria for Quality for continuing education programming.

**Notice:** If you attended the live presentation of this activity, you are not eligible to receive duplicate CE credit.

The *faculty* reported the following financial relationships or relationships to products or devices they or their spouses/life partner have with commercial interests related to the content of this CME activity.

<table>
<thead>
<tr>
<th>Name of Faculty or Presenter</th>
<th>Reported Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schumarry H. Chao, MD, MBA</td>
<td>Provides consulting services related to the subject of this educational activity.</td>
</tr>
<tr>
<td>Jason Smith, PharmD</td>
<td>He is a member of the Speakers’ Bureaus for Roche and Gilead.</td>
</tr>
<tr>
<td>Ian R. McNicholl, PharmD, BCPS</td>
<td>He is a member of the Speakers’ Bureaus for Boehringer Ingelheim, Bristol-Meyers Squibb, Gilead, and GlaxoSmithKline.</td>
</tr>
<tr>
<td>William J. Cardarelli, PharmD</td>
<td>No potential bias or conflict of interest.</td>
</tr>
</tbody>
</table>

The *planners and managers* reported the following financial relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity.

<table>
<thead>
<tr>
<th>Name of Planner or Manager</th>
<th>Reported Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creative Educational Concepts, Inc.</td>
<td>No potential bias or conflict of interest.</td>
</tr>
<tr>
<td>Susan Hansen, AMCP Horizons, LLC</td>
<td>No potential bias or conflict of interest.</td>
</tr>
</tbody>
</table>
# Table of Contents

**Reporting the Evidence for Optimal Treatment Options and Formulary Management: Antiviral Drugs in HIV and Hepatitis B**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>S4</td>
<td>Epidemiology, Economic Burden, and Risk Factors of Chronic Viral Diseases</td>
<td>Schumarry H. Chao, MD, MBA</td>
</tr>
<tr>
<td>S7</td>
<td>Therapy Analysis and Evidenced-Based Treatment Guidelines (Including Review of Antiviral Medications)</td>
<td>Jason Smith, PharmD</td>
</tr>
<tr>
<td>S12</td>
<td>Strategies to Enhance Adherence, Reduce Costs, and Improve Patient Quality of Life</td>
<td>Ian R. McNicholl, PharmD, BCPS</td>
</tr>
<tr>
<td>S17</td>
<td>Complexities and Challenges in Managed Care</td>
<td>William J. Cardarelli, PharmD</td>
</tr>
<tr>
<td>S21</td>
<td>Continuing Education: CE Submission Instructions, Posttest, Posttest Worksheet and Answer Sheet, Credit Application, and Evaluation Form</td>
<td></td>
</tr>
</tbody>
</table>

## Target Audience

This activity is intended for managed health care professionals, including pharmacists and physicians, seeking contemporary information and innovative strategies for appropriate treatment and management of antiviral therapy.

This activity will educate managed care professionals and health care providers about HIV and HBV patient care. The activity will provide a review of the current guidelines for diagnosis and treatment of HIV and HBV, discuss the complexities of co-infection, and identify potential patient barriers of adherence.

## Learning Objectives

Upon completion of this activity, participants should be able to:

1. Recognize the epidemiology, burden, and costs associated with the chronic viral diseases HIV and hepatitis B infection,
2. Identify gaps in understanding of current evidence around antivirals, including implications in the co-infected patient,
3. Analyze the impact and treatment efficacies associated with chronic hepatitis B, HIV, and related co-infections; and
4. Discuss evidence-based approaches to optimal treatment and management of co-infected and immunosuppressed patients.

## Source of Funding

This supplement was funded by an educational grant from Gilead Sciences, Inc.

## Presentation Forum

Articles in this supplement are based on the proceedings of a symposium held at the Academy of Managed Care Pharmacy’s 20th Annual Meeting and Showcase on April 17, 2008, in San Francisco, California. The symposium was supported by an educational grant from Gilead Sciences, Inc.

We gratefully acknowledge Gilead Sciences, Inc. for providing an educational grant for this activity.

* A total of 0.10 CEUs (1.0 contact hours) will be awarded for successful completion of this continuing education activity (ACPE #245-999-08-015-H04-P). CEC complies with the Criteria for Quality for continuing education programming. For accreditation information, please see page S1.

The content and views presented in this article are those of the faculty/authors and do not necessarily represent the official policies or views of the Academy of Managed Care Pharmacy, the authors’ institutions, the continuing medical education grantor, or Gilead Sciences, Inc., respectively. The authors have disclosed if any unlabeled use of products is mentioned in their articles. Before prescribing any medication, clinicians should consult primary references of full prescribing information.

(continued on next page)
Disclosure of Off-Label Use
In this educational activity, Dr. Smith discusses the use of 2 products for the treatment of hepatitis B that are not approved by the FDA for that indication: tenofovir and emtricitabine. Dr. Smith also discusses an investigational product for the treatment of hepatitis B: clevudine. Drs. Cardarelli, Chao, and McNicholl do not describe the use of any drugs for off-label uses. AMCP Horizons, LLC, Creative Educational Concepts, and Gilead Sciences, Inc. do not recommend the use of any agent outside of the labeled indications.

Disclaimer
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s conditions and possible contraindications on dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.

Acronyms Used in This Supplement

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>A181V</td>
<td>Alanine for valine at position 181</td>
</tr>
<tr>
<td>ABC</td>
<td>Abacavir</td>
</tr>
<tr>
<td>ADV</td>
<td>Adefovir</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Antibody to core hepatitis B antigen</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>AZT</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>CCR5</td>
<td>Chemokine (C-C motif) receptor 5</td>
</tr>
<tr>
<td>d4T</td>
<td>Stavudine</td>
</tr>
<tr>
<td>ETV</td>
<td>Entecavir</td>
</tr>
<tr>
<td>FTC</td>
<td>Emtricitabine</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral treatment</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Hepatitis B “E” antigen</td>
</tr>
<tr>
<td>HbsAb</td>
<td>Hepatitis B surface antibody</td>
</tr>
<tr>
<td>HbsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular cancer</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>M204I/V</td>
<td>Methionine to valine or isoleucine substitutions</td>
</tr>
<tr>
<td>N236T</td>
<td>Asparagine for threonine at position 236</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>NR</td>
<td>Not reported</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>Peg-IFN</td>
<td>Pegylated interferon</td>
</tr>
<tr>
<td>PI</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>TBV</td>
<td>Telbivudine</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>YMDD</td>
<td>Tyrosine methionine aspartate aspartate motif in the catalytic domain of the viral polymerase/reverse transcriptase</td>
</tr>
</tbody>
</table>
Epidemiology, Economic Burden, and Risk Factors of Chronic Viral Diseases

Schumarry H. Chao, MD, MBA

ABSTRACT

OBJECTIVE: To outline the epidemiology of the human immunodeficiency virus (HIV) and hepatitis B virus (HBV) epidemics and their economic burden.

SUMMARY: The global epidemics of HIV infection (40 million) and HBV infection (400 million) overlap so that approximately 4 million individuals worldwide are co-infected with HIV and HBV. Generally about 5%-10% of HIV-infected individuals are co-infected with HBV, but the numbers depend on the specific patient population.

In the most recent published comparison of costs of treating chronic viral infections, HIV accounts for higher medical expenses than HBV. The overall costs of treating HIV in the United States in 1997 were about $4.5 billion (in 1997 U.S. dollars), while the overall cost for treating hepatitis B in 1997 was $51.4 million. However, HBV complications are expensive.

Treatment options for HIV and HBV have evolved differently. In HIV treatment, the high pill burden and dietary restriction of early highly active antiretroviral therapy (HAART) have been replaced with simpler and more potent combination regimens that combine several agents in a single oral dose taken once or twice daily. For HBV infection, the issues are somewhat different: sequential monotherapy rather than combination therapy is the usual management approach. A substantial number of individuals are co-infected with HIV and hepatitis viruses, including HBV, which compiles clinical management because some antiviral agents have activity against both HIV and HBV.

J Manag Care Pharm. 2008; 14(5):S4-S6

Copyright © 2008, Academy of Managed Care Pharmacy. All rights reserved.

Introduction

This supplement to the Journal of Managed Care Pharmacy addresses key issues in the management of 2 important chronic viral diseases that sometimes affect the same patient: human immunodeficiency virus (HIV) infection, hepatitis B virus (HBV) infection, and HIV-HBV co-infection. Relevant evidence-based guidelines and current therapeutic options are outlined in the following articles, which include an extensive discussion of patient adherence in long-term therapy for chronic viral infection, current treatment options, and management of drug formularies.

Epidemiology

The global epidemics of HIV infection (40 million) and HBV infection (400 million) overlap so that approximately 4 million individuals worldwide are co-infected with HIV and HBV. Generally, about 5%-10% of HIV-infected individuals are co-infected with HBV, but the numbers depend on the specific patient population.

In the latest published comparison of costs of treating chronic viral infections, HIV accounts for higher medical expenses than HBV. The overall costs of treating HIV in the United States in 1997 were about $4.5 billion (in 1997 U.S. dollars), while the overall cost for treating hepatitis B in 1997 was $51.4 million. However, HBV complications are expensive.

Treatment options for HIV and HBV have evolved differently. In HIV treatment, the high pill burden and dietary restrictions of early highly active antiretroviral therapy (HAART) have been replaced with simpler and more potent combination regimens that combine several agents in a single oral dose taken once or twice daily. For HBV infection, the issues are somewhat different: sequential monotherapy rather than combination therapy is the usual management approach. A substantial number of individuals are co-infected with HIV and hepatitis viruses, including HBV, which complicates clinical management because some antiviral agents have activity against both HIV and HBV.
350 cells/cubic millimeter to evaluate an antiretroviral management strategy about 5% were co-infected with HIV and HBV, while a somewhat larger percentage were co-infected with hepatitis C virus (HCV). Of the 5,472 HIV-infected individuals followed, 17% (922/5,472) were co-infected with a hepatitis virus (798 were co-infected with HCV only, 110 with HBV only, and 14 with both HCV and HBV). The mortality rate of the co-infected patients was 2.52 (95% confidence interval [CI] =1.71-3.33) per 100 patient-years of follow-up, compared with 0.68 (95% CI =0.48-0.90) for patients with HIV but without either HBV or HCV.

Economic Burden
In the United States, HIV is associated with higher medical expenses than HBV. In the most recent published comparison, the comparative costs of treating chronic viral infections (a December 1998 report from the Kaiser Family Foundation in the United States), HIV costs were about $4.5 billion (in 1997 U.S. dollars), while hepatitis B costs were $51.4 million (1997 dollars). However, this report did not include HBV complications, which are expensive. The average cost per hospitalization of a patient with liver inflammation was $8,464 (1999 U.S. dollars) and for cirrhosis $14,063 (1999 U.S. dollars). In young adults aged 25-44 years, HIV infection and chronic liver disease are the sixth- and seventh-ranked causes of death. In children and young adults aged 1-24 years, liver disease has not manifested itself, but HIV infection is the tenth leading cause of death. In older adults aged 45-64 years, liver disease remains the seventh leading cause of death, but HIV is not among the top 10 causes of death (Table).

<table>
<thead>
<tr>
<th>Rank</th>
<th>1-24 Years</th>
<th>25-44 Years</th>
<th>45-64 Years</th>
<th>65 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Accidents</td>
<td>Accidents</td>
<td>Cancer</td>
<td>Heart disease</td>
</tr>
<tr>
<td>2</td>
<td>Homicide</td>
<td>Cancer</td>
<td>Heart disease</td>
<td>Cancer</td>
</tr>
<tr>
<td>3</td>
<td>Suicide</td>
<td>Heart disease</td>
<td>Accidents</td>
<td>Stroke</td>
</tr>
<tr>
<td>4</td>
<td>Cancer</td>
<td>Suicide</td>
<td>Diabetes</td>
<td>COPD</td>
</tr>
<tr>
<td>5</td>
<td>Heart disease</td>
<td>Homicide</td>
<td>Stroke</td>
<td>Alzheimer's</td>
</tr>
<tr>
<td>6</td>
<td>Flu/pneumonia</td>
<td>HIV infection</td>
<td>COPD</td>
<td>Flu/pneumonia</td>
</tr>
<tr>
<td>7</td>
<td>COPD</td>
<td>Liver disease</td>
<td>Liver disease</td>
<td>Diabetes</td>
</tr>
<tr>
<td>8</td>
<td>Stroke</td>
<td>Stroke</td>
<td>Suicide</td>
<td>Kidney disease</td>
</tr>
<tr>
<td>9</td>
<td>Septicemia</td>
<td>Diabetes</td>
<td>Kidney disease</td>
<td>Accidents</td>
</tr>
<tr>
<td>10</td>
<td>HIV infection</td>
<td>Flu/pneumonia</td>
<td>Septicemia</td>
<td>Septicemia</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

Treatments for HIV, HBV, and Dual HIV-HBV Infections
Treatment options for HIV and HBV have evolved differently. Therapy for HIV infection has changed as nucleoside analog reverse transcriptase inhibitors were supplemented with nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and finally nucleotide and acyclic nucleoside reverse transcriptase inhibitors (NRTIs). In addition, second-generation NNRTIs and PIs are now available along with drugs in new classes, including a fusion inhibitor, an integrase inhibitor, and a CCR5 coreceptor antagonist. The high pill burden and dietary restriction of early highly active antiretroviral treatment (HAART) regimens have been replaced with simpler more potent regimens that combine several agents in a single oral dose taken once or twice daily.

With these simple, potent antiretroviral regimens, HIV disease has become increasingly treatable, and mortality has decreased dramatically. However, as patients live longer, metabolic abnormalities, such as elevated lipids, which may affect long-term heart health, and lipodystrophy, which may cause disfiguring changes in the face and body, have emerged. These and other side effects of therapy decrease adherence. Suboptimal drug levels subsequent to pharmacokinetic issues or poor adherence, can promote viral drug resistance that leads to treatment failure.

As therapies for HIV disease have improved, medicines’ focus has shifted from considering HIV/AIDS as an aggressive terminal disease to considering HIV infection a treatable condition in which good treatment adherence improves survival and reduces morbidities. Effective HIV suppression with potent antiretroviral therapy must be continued indefinitely, because treatment interruptions and drug holidays result in negative outcomes. Any long-term therapy cost becomes an important consideration.

The issues are somewhat different for HBV infection. Several effective therapies to suppress HBV are available, but they are less advanced than those for HIV; sequential monotherapy rather than combination therapy remains the norm for treating HBV infection. Also, treatment of HIV-HBV co-infection is complicated by the fact that some antiviral agents have activity against both HIV and HBV.

REFERENCES


Background on HIV and HBV

Human immunodeficiency virus (HIV) infection and hepatitis B virus (HBV) infection, which overlap since they are transmitted by similar routes, including sex and injection drug use, have caused large global epidemics. HIV, a retrovirus with an RNA genome that has 2 variants (HIV-1 is most common in the United States), targets CD4 cells and damages the host immune system. HBV, a hepadnavirus with a DNA genome that has 8 genotypes, targets liver cells (hepatocytes), and also damages the host immune system. HBV is 50 to 100 times more infectious than HIV.1,2

While the tests (HIV-1 RNA viral load and CD4 cell counts) and clinical course for HIV infection are somewhat straightforward, the tests and clinical course for HBV are more complex. Chronic HBV infection is characterized by changes in HBV viral load (usually represented by viral counts in log units). Several tests measure HBV viral load and activity. The following are typical tests used to measure HBV viral load:3

- Serum HBV DNA levels, measured in log units
  
  Serum HBV DNA is present at measurable levels during acute infection, but may or may not be detected during chronic infection or during reactivation in hepatitis B “E” antigen (HBeAg)-negative chronic hepatitis.

- Alterations in liver function reflected in alanine transaminase (ALT) levels

- Various HBV-specific antigens and antibodies to them, measured in log units

  - HBeAg, a peptide normally detectable in the bloodstream when the hepatitis B virus is actively reproducing, associated with increased infectiousness and greater risk of progression to liver disease, is used clinically as a measure of viral replication, infectivity, and severity

  - Antibody to HBeAg (anti-HBeAg) is used clinically as a marker for reduced replication

  - Surface antigen (HBsAg) and antibody to core antigen (anti-HBc) are markers of both acute and chronic infection.

The progression of HBV disease after acute infection is very high (>90%) in children, but very low (<5%) in immunocompetent adults.4,5 About 30% of individuals with chronic HBV infection develop cirrhosis, and 5% to 10% develop hepatocellular cancer (HCC).4 About one fourth of patients with cirrhosis decompensate and develop liver failure within 5 years.6 Chronic HBV infection is the sixth leading cause of liver transplantation in the United States.7 It should also be noted that the presence of HBV antigen is considered as antigen “positive,” and lack of antigen is considered antigen “negative.”

Author

JASON SMITH, PHARM.D, is a clinical pharmacist, Gastroenterology and Hepatology, at the Veterans Affairs Greater Los Angeles Healthcare System.

AUTHOR CORRESPONDENCE: Jason Smith, PharmD, Clinical Pharmacist, Gastroenterology and Hepatology, Veterans Affairs Greater Los Angeles Healthcare System, 11301 Wilshire Blvd. 111C, Los Angeles, CA 90073. Tel.: 310.478.3711, Ext. 44664; Fax: 310.268.4245; E-mail: jason.smith2@va.gov
Therapy Analysis and Evidenced-Based Treatment Guidelines (Including Review of Antiviral Medications)

**TABLE 1**

<table>
<thead>
<tr>
<th>Resistance Status</th>
<th>Therapy Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine resistant</td>
<td>Add adefovir or tenofovir</td>
</tr>
<tr>
<td>Stop lamivudine, switch to emtricitabine/tenofovir</td>
<td></td>
</tr>
<tr>
<td>Stop lamivudine, switch to emtricitabine (pre-existing lamivudine resistance mutation predisposes to entecavir resistance)</td>
<td></td>
</tr>
<tr>
<td>Adefovir resistance</td>
<td>Add lamivudine</td>
</tr>
<tr>
<td>Stop adefovir, switch to emtricitabine/tenofovir</td>
<td></td>
</tr>
<tr>
<td>Switch to or add entecavir</td>
<td></td>
</tr>
<tr>
<td>Entecavir resistance</td>
<td>Switch to or add adefovir</td>
</tr>
<tr>
<td>Stop telbivudine, switch to emtricitabine/tenofovir</td>
<td></td>
</tr>
<tr>
<td>Stop telbivudine, switch to emtricitabine (re-existing telbivudine resistance mutation predisposes to entecavir resistance)</td>
<td></td>
</tr>
</tbody>
</table>

Entecavir is not appropriate to treat HIV-HBV co-infected patients unless used with a fully suppressive antiretroviral regimen.  

---

**TABLE 2**

<table>
<thead>
<tr>
<th>HIV Treatment</th>
<th>HBV Treatment</th>
<th>Recommended Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required</td>
<td>Not required</td>
<td>Use either tenofovir/emtricitabine or emtricitabine as single agents to avoid development of HBV resistance</td>
</tr>
<tr>
<td>Required</td>
<td>Required</td>
<td>Use either tenofovir plus lamivudine or tenofovir/entecavir as single agents to avoid development of HBV resistance</td>
</tr>
<tr>
<td>Not required</td>
<td>Required</td>
<td>Pegylated interferon does not lead to HIV or HBV resistance and may be considered</td>
</tr>
</tbody>
</table>

---

**Impact of Co-Infection With HIV and HBV**

In co-infection, HIV affects HBV disease progression more than HBV affects the course of HIV infection. In molecular terms, HIV decreases the rate at which HBsAg is lost and increases levels of HBV DNA. In clinical terms, HIV increases the progression to cirrhosis, increases the number of liver-related complications, and increases mortality. On the other hand, HBV affects HIV disease by activating the immune system and by the HBV-X protein (HBV-X protein stimulates viral genome replication), which may induce HIV replication and transcription, but there is typically no change in CD4 cell count and no evidence for clinical impact of HBV on HIV disease.

The decision to treat HIV in a patient with HIV-HBV co-infection depends on whether highly active antiretroviral therapy (HAART) for HIV is indicated, liver disease severity, likelihood of response, and adverse event potential. The goal of HBV therapy is eradication of the virus (by suppression of HBV DNA to undetectable levels) and to prevent complications of liver disease, including cirrhosis, decompensation, and liver cancer, and finally to reverse chronic carrier state HbsAg/HbsAb seroconversion. Complete response to HBV therapy involves biochemical (serum ALT within normal range), virologic (undetectable serum HBV DNA and loss of HBeAg in HBeAg-positive patients), and histologic improvement. The level of detection of HBV DNA depends on the assay used due to the sensitivity of these assays over wide concentrations.
HBV Antiviral Therapies

While interferon and pegylated interferon have been used to treat HBV infection, 3 additional classes of oral anti-HBV therapy are now available: L-pyrimidine nucleoside analogs, acyclic phosphonates, and a guanosine nucleoside analog. L-nucleoside analogs approved by the FDA include lamivudine, adefovir, dipivoxil, and tenofovir disoproxil fumarate, which is approved for use in HIV infection but not yet for HBV infection. Entecavir is a guanine nucleoside analog. A National Institutes of Health (NIH) clinical research workshop estimated the comparative activity of anti-HBV agents on various parameters used to measure response of HBV infection to therapy at 1 year; they used data from various clinical trials.16 HBeAg-positive patients have a more pronounced decline in HBV DNA in response to therapy than HBeAg-negative patients.16

Lamivudine was the first oral nucleoside approved for treatment of HBV infection. The other L-nucleosides are similar to lamivudine. While about half of patients who are HBeAg-positive at baseline become HBeAg-negative by 5 years, resistance to lamivudine in HBV emerges relatively rapidly (24% at 1 year, 49% at 3 years, and 69% at 5 years).17,18 As a result, lamivudine is no longer a first-choice therapy for HBV infection.8,18

Adefovir is an acyclic phosphonate indicated for HBV but not for HIV infection. An observational cohort followed 35 HIV-HBV co-infected patients resistant to lamivudine for up to 192 weeks. Adding adefovir to ART that included lamivudine was well tolerated and resulted in sustained reductions in both HBV DNA (percentage with <1,000 copies per mL was 6% at 48 weeks, 27% at 96 weeks, 46% at 144 weeks, and 58% at 192 weeks) and ALT (normalization in 14% at 48 weeks, 48% at 96 weeks, 68% at 144 weeks, and 70% at 192 weeks).20 During therapy for chronic HBV, resistance develops to adefovir over time (3% at 2 years, 11% at 3 years, 18% at 4 years, and 29% at 5 years).19

Tenofovir is an acyclic phosphonate that is very similar to adefovir indicated for HIV but not HBV, although tenofovir has been shown to inhibit HBV DNA polymerase. Tenofovir has been shown to have activity against both viruses in patients with HBV21 or co-infected with both HIV and HBV.22 For example, in a study of 53 patients with high levels (>6 log copies per mL) of HBV DNA, at week 48 the tenofovir-treated patients (n = 35) had decreased 5.5 log units compared with 2.8 log units for adefovir-treated patients (n = 18).21 In another study of 52 co-infected patients on stable ART with HIV viral load <10,000 copies per mL (74% had <50 copies per mL at baseline and 94% lamivudine resistant) and serum HBV DNA 5 log copies per mL or higher (86% HBeAg-positive), tenofovir was not inferior to adefovir without safety issues, and the study was terminated early.22 Other studies have shown that tenofovir was able to reduce HBV viral load despite resistance to adefovir or lamivudine, and no patients developed viral breakthrough while receiving tenofovir therapy.23-24

Entecavir is a guanosine analog that inhibits multiple steps in HBV replication without inhibiting human mitochondrial DNA polymerase-γ. Recent data indicated entecavir also has activity against HIV and tends to target HIV virus resistant to antiretroviral drugs.25 Over 3 years, the cumulative rate of resistance to entecavir in treatment-naive HBV-infected patients was 1.1%. Virologic rebound occurred in 20.6% (14/68) lamivudine-refractory patients treated with entecavir.26 A recent analysis determined that entecavir would be cost-effective versus lamivudine in the treatment of HBeAg-positive HBV infection.27 The activity of entecavir in HIV-HBV co-infected patients differs depending on prior exposure to ART. Some studies (although based on small patient numbers) have shown good viral suppression in ART-naïve patients but much less so in ART-experienced patients.27 Entecavir was shown to target the M184V (methionine to valine at position 184) mutation in the HIV reverse transcriptase gene.28 Therefore, entecavir is not appropriate to treat HIV-HBV co-infected patients unless used with a fully suppressive antiretroviral regimen.9

Liver-Related Mortality in Co-Infected Patients

The risk of liver-related mortality was estimated in the Multicenter AIDS Cohort Study (MACS) in which about 6% (326/5,293) of the men who had sex with men were HBsAg-positive at baseline.13 The rate of liver mortality for HIV-HBV co-infected patients was 14.2 deaths/1,000 patient-years compared with 1.7 deaths/1,000 patient-years for HIV-positive, HBV-negative patients and 0.8 deaths/1,000 patient-years for HIV-negative, HBV-positive patients. In MACS, concomitant HIV infection increased the relative risk for liver death from HBV infections 18.7 fold. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study that evaluated mortality in 23,441 HIV-infected persons followed for a total of 76,893 patient-years, the relative risk of liver-related death for those with HBV was lower, 3.7 (95% CI = 2.4-5.9).14

Response to Anti-HBV Therapy in Co-Infected Patients

Anti-HBV therapy is effective in patients with HIV-HBV co-infection. Data from a summary article published in 2006 pre-

### TABLE 3: Responses to Anti-HBV Agents in Patients with HIV-HBV Co-Infection

<table>
<thead>
<tr>
<th></th>
<th>Interferon</th>
<th>Lamivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBe sero-</td>
<td>9%</td>
<td>11%</td>
<td>NR</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>conversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>NR</td>
<td>2.7</td>
<td>3.6</td>
<td>4.7-6.0</td>
<td>4.4</td>
</tr>
<tr>
<td>decline (log units)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>12%-20%</td>
<td>30%-50%</td>
<td>49%</td>
<td>35%-66%</td>
<td>NR</td>
</tr>
<tr>
<td>Normalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic</td>
<td>NR</td>
<td>NR</td>
<td>33%-50%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT = alanine transaminase; NR = not reported.

**Note:** These values are comparisons of the results of various clinical trials, and, therefore, should be taken as only a guide to probable relative activity.
senting a treatment algorithm for HBV in HIV-infected patients are presented in Table 3.29

The following paragraphs summarize key observations about the response rate of HBV infection in selected clinical studies of HIV-HBV co-infected patients.

Interferon-α can be used in co-infected patients but seems to have some complications. A retrospective cohort study followed 144 HBeAg-positive patients (69 HIV-positive) for 45 months. HIV infection was associated with poorer response to interferon-α, more frequent HBV reactivations, and increased incidence of cirrhosis and cirrhosis-related death in cases of low CD4 cell count; however, interferon-α therapy reduced the incidence of HBV-related cirrhosis regardless of HIV status.32

Lamivudine appeared effective initially as monotherapy in co-infected patients, but resistance has been shown to develop quickly. In a randomized, controlled study of lamivudine therapy in 1,790 patients, the median decrease in HBV DNA level was 2.0 log units at 12 weeks and 2.7 log units at 52 weeks compared with no decrease in the placebo arm.30 A retrospective cohort study of 40 co-infected patients treated with lamivudine documented lamivudine resistance of 25% at 1 year and 52% at 2 years.31

Emtricitabine has been used experimentally in co-infected patients with some evidence of effect. In a double-blind, parallel study of co-infected patients, patients were given emtricitabine 25 mg, 100 mg, or 200 mg once daily for 48 weeks and followed for an additional 48 weeks on open-label 200 mg emtricitabine. Emtricitabine was associated with a mean decrease in HBV level of 3.4 log units at 56 days, which was maintained after 48 weeks of treatment in more than half the patients.32,33

Entecavir has shown some effect in lamivudine resistant virus. In co-infected patients with the tyrosine-methionine-aspartate-aspartate (YMDD) lamivudine-resistance mutation treated with entecavir, the mean decrease in HBV DNA level was 3.66 log units at 6 months, and 84% (57/68) had either an HBV DNA level <400 copies per mL or a 2 log or greater reduction from baseline.34

Combination therapy with adefovir and ART has been studied in co-infected patients and shown to reduce HBV viral load. For example, when adefovir was added to ART that included lamivudine in 35 co-infected patients with a median baseline HBV DNA level of 9.76 log copies per mL, the HBV DNA level dropped 5.08 log units at 48 weeks, 4.52 at 96 weeks, and 3.86 at 144 weeks, all P<0.001. Of the 29 who completed 144 weeks of therapy, 7 (25%) had HBV DNA levels <2.3 log units.20

In substudies, patients co-infected with HIV and HBV in the phase III studies of tenofovir therapy for treatment of HIV, there was a difference in response between ART-naïve (substudy 903) and antiretroviral-experienced (substudy 907) patients.35 In the ART-naïve patients, the mean decrease in HBV DNA at 48 weeks was 4.7 log units for the 5 patients receiving tenofovir and lamivudine compared with 3.0 log units for the 6 patients receiving only lamivudine. In the ART-experienced patients, the mean change in HBV DNA at 24 weeks was a decrease in 4.9 log units for the 10 patients who received tenofovir compared with an increase of 2.1 log units for the 2 patients randomized to receive placebo.

Resistance of HBV to Anti-HBV Agents

Resistance of HBV to drug treatment arises because of the high rate of viral production (1 to 10 trillion virions per day) combined with the high rate of spontaneous mutations due to the lack of proof-reading capacity of the HBV reverse transcriptase, which is necessary to the replication of this DNA virus that contains a single-stranded region in its 3,200 base pair genome. The base substitution rate of 1 in 100,000 means that all possible single-base changes in the HBV DNA are produced many times each day so that antiviral resistance mutations are present prior to therapy.

HBV resistance may be characterized as genotypic, viral, or clinical.

- Genotypic resistance identifies specific mutations in vitro or in vivo using molecular testing. These mutations underlie viral and clinical resistance. Interestingly, the mutations associated with lamivudine, emtricitabine, entecavir, and telbivudine (most commonly M204I/V, that is, a change from methionine to either isoleucine or valine at position 204 in the HBV polymerase gene in the YMDD region), do not overlap with those associated with resistance to adefovir or tenofovir (A181V and N236T). Genotypic testing should be used to confirm viral or clinical resistance.
- Viral resistance is characterized by an increase in HBV DNA levels by more than 10-fold (>1 log unit) from the lowest level achieved (the nadir) while adherent to therapy. Serum HBV DNA should be monitored frequently—every 3 to 6 months—during therapy.
- Clinical resistance is defined by a rise in serum ALT by more than 2-fold (100%) with a simultaneous rise in HBV DNA levels.16

Resistance may be prevented or reduced by avoiding unnecessary treatment and initiating treatment with an appropriate antiviral agent (one to which the virus is not already resistant) or without combination therapy. Maximizing patient adherence and checking carefully for medication adherence in patients with virologic breakthrough is crucial. Switching to an alternative drug in non-responders will also minimize emergence of resistance.8

Summary

Treatment of HBV infection reduces risk of liver complications, including cirrhosis and hepatocellular carcinoma, and death. Suppression of serum HBV DNA to the lowest levels achievable is important because HBV disease progression can occur even when HBV DNA levels are less than 10,000 copies per mL, which corresponds to about 2,000 International Units/milliliter (IU per mL). Available antiviral agents may need to be used in combination to achieve this goal, and improving adherence is important. Emergence of resistance to anti-HBV agents is a key consideration. Treatment of HBV infection should be considered in HIV-infected persons using available agents. It is important to consider the activity of the antiviral agents used against both viruses when selecting treatment regimens.
REFERENCES


20. Colombo RJ. Assessment at 3 years shows high barrier to resistance is maintained in entecavir treated nucleoside naïve patients while resistance emergence increases over time in lamivudine refractory patients. 57th Annual Meeting of the American Association for the Study of Liver Diseases, October 27-31, 2005, Boston, Massachusetts. Abstract 110.


ABSTRACT

OBJECTIVES: To (a) analyze recent evidence and research on adherence for human immunodeficiency virus (HIV) and hepatitis B treatment, including discussion on the dynamics and barriers of adherence, and (b) recommend strategies from the patient and clinician perspective to enhance patient adherence.

SUMMARY: Since the widespread use of highly active antiretroviral therapy (HAART) for HIV infection, individuals with HIV live much longer with fewer opportunistic infections.1 A substantial percentage of individuals with HIV also have co-existing medical conditions, including co-infection with hepatitis viruses. While adherence to guidelines does not guarantee success or improved quality of life, 3 key factors affect treatment success: (1) drug resistance and cross-resistance, (2) adverse drug reactions and drug interactions, and (3) the level of adherence, which also affects resistance development.

Adherence to treatment regimens remains 1 of the most important factors related to treatment success. Complete adherence to any medication regimen is difficult. In HIV disease, poor adherence is associated with development of resistance. Health care providers cannot predict patient adherence to therapy, but they can help patients overcome barriers to adherence and take their medication as directed. Simple regimens with once- or twice-daily dosing are preferred. The potential development of side effects depends on the individual patient. Treatment regimens must work with the patient's lifestyle and schedule. Psychosocial issues are also very important. Patient belief that HAART is effective, and a positive relationship between patient and provider can promote adherence.

Strategies to improve patient adherence can be grouped into 3 categories related to the patient: the clinic, the health-care team, and the regimen. Regimens should be simplified as much as possible: reducing the number of pills, their frequency, and dosing restrictions, as well as seeking to minimize drug interactions and side effects. The UCSF Positive Health Program Adherence Support Program is outlined.

CONCLUSION: Adherence is an important aspect of HIV treatment. The key take-home message is that changing the antiretroviral therapy for a non-adherent patient is futile without addressing adherence barriers first.

J Manag Care Pharm. 2008; 14(5):S12-S16

Copyright© 2008, Academy of Managed Care Pharmacy. All rights reserved.

Strategies to Enhance Adherence, Reduce Costs, and Improve Patient Quality of Life

Ian R. McNicholl, PharmD, BCPS

Since the widespread use of highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection, individuals with HIV live much longer with fewer opportunistic infections.1 A substantial percentage of individuals with HIV also have co-existing medical conditions, including co-infection with hepatitis B virus (HBV) and/or hepatitis C (HCV).2-5 HCV co-infection is common, particularly among injection drug users (IDUs).6 Mental illness and substance abuse are also observed in people with HIV more frequently than in the U.S. population in general.7 Because of these medical comorbidities, HIV treatment must also consider the use of multiple medications, drug interactions, and the treatment of other illnesses that may impact response to HIV therapy.2 These considerations are also relevant to patients co-infected with a hepatitis virus.

People infected with HIV today are also likely to die of non-opportunistic illnesses, especially liver disease, pulmonary diseases, cardiovascular disease, and renal problems.8,9 For example, in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study that evaluated mortality in 23,441 HIV-infected persons followed for a total of 76,893 patient-years, there were 1,246 deaths, of which 14.5% were liver-related and occurred at higher CD4 cell counts despite antiretroviral therapy (ART).10

The U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (DHHS Guidelines)9 note that the primary goals of antiviral therapy for HIV infection are 4-fold: (1) to reduce HIV-related morbidity and mortality, (2) to improve quality of life, (3) to restore and preserve immunologic function (measured by CD4 cell count), and (4) to maximally and durably suppress viral replication (measured by viral load).

Adherence to guidelines or treatment with any specific therapy does not guarantee success or improved quality of life. However, 3 key factors affect treatment success: (1) drug resistance and cross-resistance, (2) adverse drug reactions and drug interactions, and (3) the level of adherence, which also affects resistance development.

Resistance

Several special issues impact the emergence of resistance to various antiretroviral agents in HIV. First, HIV evolves rapidly because of its high replication and turnover rate combined with a high mutation rate due to error-prone replication. Second, virus diversity is constrained by selective pressures that include the need to evade the host immune system response and by exposure to antiretroviral agents. The key fact is that the evolution rate is proportional to the replication rate. Profound virus suppression achievable with current highly active antiretroviral therapy (HAART) regimens slows or may prevent emergence of resistance, which allows durable virus suppression (low or undetectable viral load) and can lead to immunologic recovery (increased CD4 cell count).
Currently, 2 types of HIV drug resistance assays are commercially available: (1) phenotypic assays directly measure a sensitivity of a patient’s virus to specific antiretroviral agents and (2) genotypic assays identify specific genetic mutations that cause resistance to certain drugs or drug classes. With genotypic assays, resistance is inferred through an algorithm or database analysis. An advantage of phenotype resistance assays is that they allow quantification of the concentration of a particular drug needed to inhibit HIV replication. For example, the new CCR5 receptor antagonist, maraviroc, requires documentation that a tropotyped test is completed of the co-receptor used by the patient’s virus before initiation of maraviroc therapy.

Resistance testing has been shown to result in short-term improvements in virologic response because ineffective antiretroviral agents may be eliminated from the regimen. However, drug resistance is only detectable by current commercial genotypic or phenotypic assays if resistant virus is present in at least 20% to 30% of the quasi-species (a group of viruses related by a similar mutation or mutations, competing within a highly mutagenic environment). In general, phenotyping should be reserved for complex ART-experienced patients among whom genotyping results may be difficult to interpret.

There are multiple indications for resistance testing, including primary infection, treatment failure, and pregnancy. Recommendations about when to use resistance testing vary slightly between the DHHS Guidelines and the International AIDS Society-United States of America (IAS-USA). The IAS-USA recommends use periodically during chronic infection and during pregnancy if the woman is viremic. The DHHS guidelines recommend considering resistance testing during chronic infection. Both guidelines recommend resistance testing in all patients with treatment failure and in primary/acute HIV infection, when it is identified. As early as 1999-2000, more than one fifth (22.7%) of newly-infected HIV patients had evidence of transmitted resistance to at least 1 antiretroviral agent and more than 10% were classified as resistant to multiple antiretroviral agents while still treatment-naive. Rates differ by drug class and other factors, which include risk group and geography.

Adverse Drug Reactions and Drug Interactions

Adverse drug reactions (ADRs) are common, especially for elderly patients, ranging from 1% to 35% in various studies, and occur in about 3% of all hospitalizations, resulting in increased length of stay and other costs. The total costs are estimated at $30 to $130 billion a year, which is several thousand dollars per patient affected. A hospital-related ADR was associated with an almost 2-fold increased risk of death.

In HIV disease, the main clinical significance of drug interactions is a decrease in HAART efficacy, and, therefore, an increase in emergence of viral resistance. Drug interactions also increase the rate of ADRs, including QTc prolongation (risk factors include concomitant anti-arrhythmics, certain antibiotics, phenothiazines, tricyclic antidepressants), rhabdomyolysis (risk factors include use of statins and protease inhibitors), and prolonged sedation and other mental status changes with anxiolytic treatment (for example, diazepam).

In HIV patients, common drug interactions, which may result in additive or synergistic toxicity, include hepatic metabolism changes, drug absorption alterations, and drug displacement. Drug interactions due to cytochrome P450 3A4 induction are seen with all commonly used nonnucleoside reverse transcriptase inhibitors (NNRTIs), including etravirine, nevirapine, and efavirenz, with rifamycins (rifampin, rifapentine, and rifabutin), and anti-convulsants (phenobarbital, carbamazepine, phentoin, oxcarbazepine).

Drug interactions due to P450 3A4 inhibition include antifungal azoles (ketoconazole, itraconazole, voriconazole, and fluconazole) and macrolides (erythromycin, clarithromycin, and azithromycin). Protease inhibitors (PIs) affect the metabolism of the phosphodiesterase type 5 (PDE5) inhibitors sildenafil, vardenafl, tadalafl. High-dose ritonavir (widely used as a pharmacologic enhancer with other protease inhibitors) causes the largest effect, while saquinavir causes the smallest. Tipranavir, atazanavir, lopinavir, fosamprenavir/amprenavir have an intermediate effect.

Grapefruit and grapefruit juice consumed concurrently with antiretrovirals is known to affect levels of other pharmaceuticals and should be used with caution by HIV patients.

Atazanavir interacts with both proton pump inhibitors (PPIs) and H2-blockers. Several commonly used pharmaceuticals (simvastatin, rifampin, PDE5 inhibitors, warfarin, and fluticasone) are known to interact with at least some antiretrovirals. Tipranavir, as well as the newer drugs darunavir and etravirine, are characterized by interactions with other antiretroviral agents.

Adherence

Adherence to treatment regimens remains 1 of the most important factors related to treatment success. Complete adherence to any medication regimen is rarely achieved. In HIV disease, various levels of adherence correspond to treatment success and are associated with development of resistance. Key predictors of long-term virologic success of antiretroviral therapy are listed in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Predictors of Long-Term Virologic Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potency of antiretroviral regimen</td>
<td>• Adherence to treatment regimen</td>
</tr>
<tr>
<td>• Adherence to treatment regimen</td>
<td>• Low baseline viremia</td>
</tr>
<tr>
<td>• Low baseline viremia</td>
<td>• Higher baseline CD4 cell count</td>
</tr>
<tr>
<td>• Higher baseline CD4 cell count</td>
<td>• Rapid (≥1 log in 1 to 4 months) reduction of viremia in response to treatment</td>
</tr>
</tbody>
</table>
Relationship among non-adherence, virologic failure, and progression to AIDS is shown (Figure). In this study, patients were characterized into 3 levels of adherence: high (>90%), moderate (70%-90%), and low (<70%). Increasing level of adherence to HAART was significantly associated with longer time to virologic failure \((P<0.001)\). The median time to virologic failure was 89 weeks among patients with a high level of adherence compared with 42 weeks among patients with moderate adherence, and 30 weeks among patients with a low level of adherence to HAART \((P<0.001)\). Patients with low adherence were almost 6 times more likely to progress to clinical AIDS or die than the high-adherence reference group, and this was statistically significant. Also, half of the high-adherence group achieved undetectable viral HIV-1 RNA compared with about 10% in the low-adherence group.\(^{21}\) Viral rebound has been linked with clinically significant resistance.\(^{22,23}\)

High-adherence levels are required for success of PI-based regimens.\(^{24}\) In a 2000 study that has remained the benchmark for adherence aspirations, only one fifth (21.7%) of patients with adherence of 95% or greater had virologic failure. Virologic failure (54.6%) was significantly lower than in patients with 90% to 94.9% adherence. Lower levels of adherence were associated with higher failure rates (up to 82.1% for patient with <70% adherence).\(^{24}\)

### Provider Perspectives on Adherence

First, health care providers cannot accurately predict patient adherence to therapy.\(^{24}\) In an adherence study using Medication Events Monitoring System (MEMS), physicians misjudged adherence (taking greater than 80% of the prescribed doses of antiretroviral medications) in 41% of patients. Nurses misjudged adherence in 30% of patients. While overestimation of adherence occurred in 28% of cases, 51% of patients that clinicians predicted to be less than 80% adherent, in fact, had adherence levels >80%, and 21% had adherence level >95%.\(^{24}\)

The patient factors that physicians said affected adherence\(^{24}\) were gender, socioeconomic level, psychiatric morbidity, age, employment status, HIV risk factors, race, and substance abuse. However, in multivariate analysis, older age, and lack of psychiatric morbidity are associated with adherence >95%. Univariate analysis also identified substance abuse as affecting a patient’s ability to achieve 95% adherence.

Data from the AIDS Clinical Trials Group (ACTG) indicated that 25% of participants admitted not understanding how to follow their regimens.\(^{25}\) Several factors have been found to be barriers to patient adherence to medication. Reducing regimen complexity with once- or twice-daily dosing is preferred. While pill burden is important, dosing schedules and food restrictions appear to have a more pervasive influence on adherence. The effect of side effects—transient (diarrhea, nausea) or longer lasting (lipodystrophy, dyslipidemia, neuropathy)—depends on the individual patient. Regimens must work with the patient’s lifestyle and schedule. Difficulty understanding medication schedules is a barrier to adherence. Psychosocial issues are very important. Substance abuse, depression, stress, hopelessness, and negative feelings each reduce motivation for self-care. Patient belief that HAART is effective, and a positive relationship between patient and provider can promote adherence.\(^{25}\) Predictors of poor adherence are listed in Table 2.\(^{25}\)

Patient perspectives on adherence include factors related to the
patient and to the regimen. The 3 most important reasons patients give for missing doses are: too busy/forgot (52%), away from home (46%), and a change in daily routine (45%). The next most common reason was feeling depressed or overwhelmed (27%).26

Based on scores for the impact of regimen attributes on adherence, the ideal regimen would be 2 small pills dosed once daily at the same time with an acceptable adverse event profile, and no dietary restrictions. This regimen should also come with a single prescription, as single refill, a single medication bottle, and a single insurance copayment.27 Although once daily was the preferred dosing frequency, once-daily regimens did not score better than other regimens in this study. Limitations in the study include the fact that patient perception is not necessarily reflective of actual patient behavior in clinical practice.

Strategies to Improve Adherence

While health care professionals may not be able to predict adherence, they can take steps to improve it. Strategies to improve patient adherence can be grouped into 3 categories related to the patient (Table 3), the clinic and health care team (Table 4), and the regimen.

The UCSF Positive Health Program to Improve Adherence

The approach to improving adherence taken at the University of California-San Francisco Positive Health Program includes many structured interactions between patients and members of the health care team.

Before initiating ART, patient readiness is assessed using the ACTG Readiness Questions:

- How sure are you that:
  - you will be able to take all or most of your medications as directed?
  - the medication will have a positive effect on your health?
  - if you don’t take this medication exactly as instructed, the HIV in your body will become resistant to HIV medications?

At each visit, patients are asked about depression. Since your last visit:

- have you felt depressed, sad, or blue much of the time?
- have you often felt helpless about the future?
- have you had little interest or pleasure in doing things?
- have you had trouble sleeping many nights?

During front-line counseling, drug-drug interactions are evaluated and then determined for that patient. An important factor to consider is whether restrictions related to taking medications with food or while fasting is important to the patient.

### TABLE 2: Predictors of Poor Adherence25

- Lack of trust between patient and provider
- Active drug/alcohol use
- Active mental illness
- Lack of patient education
- Lack of patient being able to identify meds
- Lack of reliable health care access
- Medication ADRs
- Domestic violence

### TABLE 3: Patient-Related Strategies to Improve Adherence

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Utilize educational aids
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with pharmacists, nurses, etc.
- Provide accessible, trusting health care team
- Assess literacy level
- Involve patient in regimen selection

### TABLE 4: Clinic and Health Team Strategies to Improve Adherence

1. Establish trusting relationship
2. Commit to
   - Communication between clinic visits
   - Ongoing adherence monitoring
   - Timely response to adverse events or interim illness
3. Establish interventions
   - Pharmacist-based adherence clinics
   - Street-level drop-in centers with medication storage/flexible hours for homeless persons
   - Adolescent-specific training programs
   - Medication counseling
   - Behavioral intervention
   - Directly observed therapy
4. Monitor adherence
5. Be aware of the effect of new diagnoses or symptoms on adherence

and consistent with his or her lifestyle. Therapeutic duplication and prescribing errors, such as tenofovir disoproxil fumarate/entricitabine (Truvada) and tenofovir disoproxil fumurate (Viread), which both contain tenofovir; abacavir sulfate/lamivudine (Epzicom) and abacavir sulfate (Ziagen), which both contain abacavir; stavudine (d4T) and zidovudine (AZT), which are both thymidine analogs; zidovudine (Retrovir) and ritonavir (Norvir), which have similar names and have been confused, are corrected as are any duplicate prescriptions. Creation of rapport and asking open-ended questions is important and does not take any more time.

Other patient-related strategies to improve adherence are listed in the DHHS guidelines (see Table 17 in the current version available at www.aidsinfo.org).2

**Summary**

In summary, adherence is an important aspect of HIV treatment. Factors that affect adherence include regimen complexity, side effects, patient-related factors (such as psychosocial issues, the patient’s belief system regarding antiretroviral medication and the health care system), and the relationship between the patients and the provider. Of importance to managed care is consideration of the development and implementation strategies to improve adherence and outcomes. The key take-home message is that changing the antiretroviral therapy for a non-adherent patient is futile without addressing adherence barriers first.

**REFERENCES**

ABSTRACT

OBJECTIVES: To (a) summarize the implications of human immunodeficiency virus (HIV) and Hepatitis B virus (HBV) guidelines for managed care, and (b) relate the challenges of caring for HIV, HBV, and HIV-HBV co-infected patients to managed care.

SUMMARY: The primary complexity for managed care related to human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV) infection is that treatment guidelines, recommendations, and consensus statements are rapidly changing as new information emerges and that significant uncertainties remain.

By 2017, total health care spending will be more than $4 trillion dollars per year, more than double the current level. One response of managed care is increasing use of cost-management tools, such as treatment guidelines, formulary restrictions, lists of preferred drugs, and implementation of disease management programs. A key component of programs to manage medication use involves the pharmacy benefit design.

Altrius Health/Harvard Vanguard Medical Associates use an algorithm to make formulary decisions that explicitly incorporate the clinical value and cost-effectiveness of proposed additions.

CONCLUSIONS: For chronic diseases, such as HIV, HBV, and co-infections with HIV and HBV, an approach that encourages the implementation of strategies to improve the treatment of patients diagnosed with these conditions is needed. This approach should include empowering front-line clinicians in addressing issues around access to, persistence with, and adherence to therapy. The challenge to managed care in antiviral medications for HIV and HBV is similar to that in other chronic medication categories. Managed care organizations must evolve the drug benefit design to provide access to chronic medications that are recommended by evidence-based treatment guidelines and to provide the data to support and empower clinical improvement.

J Manag Care Pharm. 2008; 14(5):S17-S20

Copyright© 2008, Academy of Managed Care Pharmacy. All rights reserved.

Key Changes in the DHHS Guidelines

<table>
<thead>
<tr>
<th>Change Context</th>
<th>Antiretroviral Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not offer Ever</td>
<td>Dual NNRTIs</td>
</tr>
<tr>
<td>No longer recommended Initial therapy in treatment-naive patients</td>
<td>3TC and d4T, 3TC, ABC, and AZT, Nelfinavir</td>
</tr>
<tr>
<td>Downgraded to alternative Use as dual nucleoside</td>
<td>3TC and AZT</td>
</tr>
<tr>
<td>Upgraded to alternative Use as in initial HAART</td>
<td>Ritonavir-boosted saquinavir</td>
</tr>
<tr>
<td>Upgraded to preferred In HLA-B*5701-negative patients only</td>
<td>3TC and ABC</td>
</tr>
<tr>
<td>Insufficient data as initial therapy New NNRTI</td>
<td>Etravirine (TMC125)</td>
</tr>
<tr>
<td>New CCR5 antagonist Maraviroc</td>
<td></td>
</tr>
<tr>
<td>New integrase inhibitor Raltegravir</td>
<td></td>
</tr>
<tr>
<td>New PI Ritonavir-boosted darunavir (TMC114)</td>
<td></td>
</tr>
<tr>
<td>Quadruple NRTI 3TC, ABC, AZT, and TDF</td>
<td></td>
</tr>
</tbody>
</table>

3TC = lamivudine, ABC = abacavir, AZT = zidovudine, CCR5 = chemokine (C-C motif) receptor 5, d4T = stavudine, HAART = highly active antiretroviral treatment; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir.
HIV infection. The section of the guidelines on treatment of co-infection with HIV and hepatitis B or C viruses was unchanged in this revision.¹

HIV guidelines have also been developed by other organizations, such as the World Health Organization (WHO), the New York State Department of Health AIDS Institute, and the International AIDS Society–United States of America (IAS–USA). A partial list is available from the HIV Medicine Association (hivma@idsociety.org).²

There is also a plethora of HBV guidelines and consensus statements. The American Association for the Study of Liver Diseases (AASLD) has approved and published practice guidelines for HBV infection that have been endorsed by the Infectious Diseases Society of America (IDSA).³ Other recent guidelines include the summary of a U.S. National Institutes of Health (NIH) clinical research workshop of management of HBV,⁴ an updated treatment algorithm for the management of chronic HBV infection in the United States,⁵ a roadmap for oral therapy based on an international workshop,⁶ and treatment of HBV-HIV co-infection from Europe.⁷ There have also been other algorithms proposed in the literature for co-infected patients.⁸

**Medication Use and Managed Care Response**

Medication use is a major challenge to managed care organizations due to the very high demand for prescription medications.⁹ As the baby-boomer generation ages, the Centers for Medicare and Medicaid Services (CMS) predict that by 2017 total health care spending will be more than $4 trillion dollars per year, more than double the current level. The cost of health care in 2017 is estimated to be $13,101 per person compared with $7,026 per person in 2006. Health care is projected to account for nearly one fifth (19.5%) of the gross domestic product.

One response of managed care is increasing use of cost-management tools, such as integrating evidence from treatment

---

*Algorithm for Formulary Decision Making (Adapted from Atrius Health/Harvard Vanguard Medical Associates 2008)*

1. **Drug review – oral/written presentation by clinical pharmacist**
2. **Experience/opinion – oral comments by invited consultants and committee members**
3. **Does drug offer substantial improvement in therapy over existing formulary drugs for like indications, or is it a completely new therapy for a disease not previously covered by medications?**
   - Yes
   - No

4. **Add to formulary with guidelines for cost-effective and safe use if needed.**
5. **Does drug offer at least equal clinical benefit to existing formulary drugs for like indications?**
   - Yes
   - No

6. **Can any safety concerns be managed?**
   - Yes
   - No

7. **Does financial impact of drug support formulary addition?**
   - Yes
   - No

8. **Add to formulary with guidelines for cost-effective use if needed.**

---

*Consider contract price/length and average wholesale price. Consider effect of decision on contracts of competing drugs. Consider tiers of major insurance payers.*
guidelines into formulary decisions or algorithms. Formulary restrictions and lists of preferred drugs are a key cost containment component as are implementation of disease management programs. Evidence-based medicine (EBM) is emerging to provide an underpinning for clinical practice, replacing clinical practices based on expert opinion and past practice patterns.

Measuring the clinical performance of physicians and health care organizations is critical. The National Committee for Quality Assurance (NCQA, www.ncqa.org), a private not-for-profit organization since 1990, provides programs and services reflecting a straightforward formula for improvement (Measure, Analyze, Improve, Repeat). The Bridges to Excellence (BTE, www.bridgestoexcellence.org), another non-profit organization, designs and creates programs that encourage physicians and physician practices to deliver safer and more effective care by providing financial and other incentives. The Agency for Health care Research and Quality (AHRQ, www.ahrq.gov) and the Centers for Medicare and Medicaid Services (CMS, www.cms.hhs.gov), both part of the DHHS, each provide a wealth of information about performance metrics and many other topics related to quality improvement in health care settings.

A key component of medication management programs involves the pharmacy benefit. Pharmacy benefit programs can be quite complex and include a variable number of benefit tiers (3, 4, 5, or more), as well as variations in co-insurance and co-payments. At the same time there are physician reimbursement and incentive programs that encourage the use of specific agents. It is conceivable that the tiering of pharmaceuticals and co-payments structure can be used to encourage improved care by being based on clinical value and improved outcomes rather than on being heavily weighted on cost, as well as formulary status in the traditional model. Prior authorization and step therapy are also used to call attention to the choices being made for therapy. The same approach could be used in the design of physician incentives. The traditional model also always assigns generic drugs the lowest copayments and ranks preferred brands in the second tier and non-preferred brands in the third tier. This may be the time to consider tiering based more on clinical value than a brand-versus generic--ranking system.

Making Formulary Decisions
At Altrius Health/Harvard Vanguard Medical Associates, the P&T Committee uses an algorithm to make formulary decisions that explicitly incorporates the clinical value and cost-effectiveness of proposed additions (Figure). The first decision is whether the proposed medication offers substantial improvement over medications on the formulary for similar indications or is for a new indication not previously treated. If so, it is added to the formulary. If not, the proposed drug will be added to the formulary only (1) if it offers at least equal benefit to existing formulary drugs, (2) if safety concerns can be managed, and, finally, (3) if the financial impact supports formulary addition. This financial impact includes several factors, such as rebates, current formulary status, and restrictions (i.e., prior authorizations). The contract price and length of the contract, as well as impact on contracts with competing drugs and the tiers of major insurance payers, are also considered.

Antiviral drugs account for an increasing share of medication costs. The trend in ARV spending is projected to increase by 12.3% in 2008, the same rate as in 2006 and 2007. This reflects an increase in unit costs because utilization growth was slow (4.7%). Other data indicate that the use of combination products contributed to the strong spending growth. Several managed care companies and pharmacies have implemented programs in specialty pharmacy management in order to control this trend in utilization growth. It is also important to monitor costs of these conditions as disease progression can be costly, as well as difficult for the patient. Not keeping an eye on proper management of these conditions can prematurely worsen the conditions due to under-treatment.

Summary
For chronic diseases, such as HIV, HBV, and HIV/HBV co-infection, a chronic care treatment approach that promotes patient adherence issues is required. In patients with HIV, reduced adherence to HIV medications was driven by dosing (14% by the daily pill burden and 13% by dosing frequency), adverse events (12%), dietary restrictions (11%), and pills size (10%). The number of co-payments and other prescription-related issues were less important to medication adherence, though they still contributed to less than optimal adherence.

The challenge to managed care in antiviral medications for HIV and HBV is similar to that in other chronic medication categories. Managed care organizations must evolve the drug benefit design to provide access to medications that are recommended by evidence-based treatment guidelines. These guidelines must be published and distributed. Furnishing physicians and other stakeholders with utilization data and rewarding best practices is essential.

REFERENCES


Reporting the Evidence for Optimal Treatment Options and Formulary Management: Antiviral Drugs in HIV and Hepatitis B

Method of Participation
There are no fees for participating in and receiving credit for this activity. During the period from June 1, 2008, through June 1, 2009, participants must (1) read the entire supplement; (2) complete the posttest, credit application, and evaluation form; and (3) complete the activity online at www.amcp.org (CE/CME Center) where you will access the posttest, credit application, and evaluation form.

These materials and all other materials provided in conjunction with continuing medical education activities are intended solely for purposes of supplementing continuing medical education programs for qualified health care professionals. Anyone using the materials assumes full responsibility and all risk for their appropriate use.

Continuing Education for this activity is processed through the AMCP.org Online Learning Center site at www.amcp.org (CE/CME Center).

The posttest worksheet on page S24 is provided to assist you in marking your answers prior to entering the online CE center for submission.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, “Reporting the Evidence for Optimal Treatment Options and Formulary Management: Antiviral Drugs in HIV and Hepatitis B,” on the AMCP.org Online Learning Center site. To receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program evaluation form.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Your statement of credit will be mailed to you within 3 weeks.

To complete the activity online, go to www.amcp.org (CE/CME Center), where you will access the posttest and evaluation form.
1. Approximately what percentage of HIV-infected patients is also infected with HBV?
   a. 1%
   b. 7%
   c. 15%
   d. 30%

2. Compared with HIV infection, the mortality rate of individuals co-infected with HIV and HBV is:
   a. Lower
   b. About the same
   c. Three times higher
   d. Ten times higher

3. Which of the following is not an effect of co-infection with HIV or HBV infection?
   a. Decreased rate of losing HBeAg if it is present
   b. Increased level of serum HBV DNA
   c. Increased rate of liver-related complications including death
   d. Decreased level of serum HBV DNA
   e. None of the above

4. Which of the following agents is NOT active against both HIV and HBV?
   a. Adefovir
   b. Emtricitabine
   c. Lamivudine
   d. Tenofovir

5. To which of the following agents is HBV most prone to develop resistance?
   a. Adefovir
   b. Entecavir
   c. Pegylated interferon
   d. Lamivudine
   e. Tenofovir

6. Which is considered the BEST treatment option for a patient with HBV infection who develops resistance to lamivudine?
   a. Add adefovir or tenofovir
   b. Switch to emtricitabine
   c. Switch to entecavir
   d. Increase dose of lamivudine

7. Which is NOT a recommended treatment option for a patient with HBV infection who develops resistance to entecavir?
   a. Add lamivudine
   b. Switch to or add adefovir in an HIV-positive patient
   c. Switch to or add adefovir in an HIV-negative patient
   d. Switch to or add tenofovir in an HIV-positive patient

8. Which is considered the LEAST preferred treatment option for a patient with HBV infection who develops resistance to telbivudine?
   a. Add adefovir
   b. Add tenofovir
   c. Switch to emtricitavine/tenofovir
   d. Switch to entecavir

9. Which anti-HBV agent was recently shown to have activity against HIV, as well as HBV?
   a. Adefovir
   b. Entecavir
   c. Telbivudine
   d. All of the above
   e. None of the above

10. Which type of drug resistance assay is most appropriate for an HIV-infected patient who has never received antiretroviral therapy?
    a. Either genotype or phenotype
    b. Genotype
    c. Phenotype
    d. Tropotype/tropism assay
# POSTTEST ANSWERS, CREDIT APPLICATION, AND EVALUATION FORM

**Reporting the Evidence for Optimal Treatment Options and Formulary Management: Antiviral Drugs in HIV and Hepatitis B**

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:

<table>
<thead>
<tr>
<th>1 = Strongly Disagree</th>
<th>2 = Disagree</th>
<th>3 = Neutral</th>
<th>4 = Agree</th>
<th>5 = Strongly Agree</th>
</tr>
</thead>
</table>

**EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES**

Upon completion of this activity, participants should be better able to:

1. Recognize the epidemiology, burden, and costs associated with the chronic viral diseases HIV and hepatitis B infection
2. Identify gaps in understanding of current evidence around antivirals, including implications in the co-infected patient
3. Analyze the impact and treatment efficacies associated with chronic hepatitis B, HIV, and related co-infections
4. Discuss evidence-based approaches to optimal treatment and management of co-infected and immunosuppressed patients

**OVERALL EFFECTIVENESS OF THE ACTIVITY**

5. Was timely and will influence how I practice
6. Enhanced my current knowledge base
7. Addressed my most pressing questions
8. Provided new ideas or information I expect to use
9. Addressed competencies identified by my specialty
10. Avoided commercial bias or influence

**IMPACT OF THE ACTIVITY**

Name one thing you intend to change in your practice as a result of completing this activity:

Please list any topics you would like to see addressed in future educational activities:

Additional comments about this activity:
FOLLOW-UP

As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes. I would be interested in participating in a follow-up survey
☐ No. I’m not interested in participating in a follow-up survey

POSTTEST ANSWERS

<p>| | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

REQUEST FOR CREDIT

Name (please print)  ____________________________________________  Degree  ____________________________

Organization  ____________________________________________  Specialty  ____________________________

Address  ____________________________________________

City, State, Zip  ____________________________________________

Telephone  ____________________________  Fax  ____________________________  E-Mail  ____________________________

Signature  ____________________________________________  Date Completed  ____________________________________________

FOR PHYSICIANS ONLY

I certify my actual time spent to complete this educational activity to be: ____________________________

☐ I participated in the entire activity and claim 1.5 credits.

☐ I participated in only part of the activity and claim _____ credits.