

Topics in Antiviral Medicine™

A publication of the IAS–USA

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Cases on the Web



www.iasusa.org/cow

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 and other viral infections.

NEW Quality Measures in HIV Care

Kathleen Clanon, MD, and Steven Bromer, MD

CME Credit Available: 1.75 *AMA PRA Category 1 Credits*[™]

Level: Advanced

Choosing a set of quality of care measures and a strategy for using them is an investment in time and resources—the resulting information can be either a powerful tool for improving care or a useless paper exercise. Dr Kathleen Clanon and Dr Steven Bromer provide guidelines and advice on selecting performance measures, determining data collection methods, and using and leveraging the eventual results to improve care.

NEW Initiation of Antiretroviral Therapy in Treatment-Naive HIV-Infected Patients

Greer A. Burkholder, MD

CME Credit Available: 1.75 *AMA PRA Category 1 Credits*[™]

Level: Advanced

What impact does the timing of antiretroviral therapy (ART) initiation have on the prognosis of HIV-infected patients? Dr Greer Burkholder discusses the influence of CD4+ cell count, plasma HIV RNA level, AIDS-related and non–AIDS-related comorbidities, pregnancy, and patient willingness to take lifelong medications. Because of the evolving nature of guidelines and evidence regarding timing of ART, HIV practitioners need to update their knowledge on this topic regularly.

NEW New Treatments for Hepatitis C Virus Infection

Melissa K. Osborn, MD

CME Credit Available: 1.5 *AMA PRA Category 1 Credits*[™]

Level: Advanced

Dr Melissa Osborn explains how the 2 new HCV protease inhibitors, telaprevir and boceprevir—direct-acting antiviral agents that inhibit viral replication—will affect therapy for treatment-naive and treatment-experienced patients with HCV infection. Her presentation describes the effects of telaprevir and boceprevir on sustained virologic response (SVR) rates, and includes response-guided treatment algorithms.

CREDITS

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

NEW Smoking Cessation

Steven A. Schroeder, MD and Margaret Meriwether, PhD

CME Credit Available: 1.0 *AMA PRA Category 1 Credits*[™]

What are the obstacles to smoking cessation, and how can they be overcome? Dr Steven Schroeder and Dr Margaret Meriwether discuss the medical practitioner's role in assisting HIV-infected patients with smoking-cessation-related issues such as weight gain and fatalism. They introduce treatment modalities that increase the likelihood of a successful quit attempt.

NEW Approaching the HIV-Infected Patient With Addiction

R. Douglas Bruce, MD, MA, MSc

CME Credit Available: 1.75 *AMA PRA Category 1 Credits*[™]

Level: Advanced

Substance-use disorders are prevalent in HIV clinical settings. Impaired judgment due to ongoing substance use can mean increased sexual risk taking, which further contributes to HIV infection rates and incidence of other sexually transmitted diseases. Dr R. Douglas Bruce describes how screening, evaluation, and a compassionate approach to patient care can be combined to provide effective treatment.

Diagnosis and Treatment Options for Acute HIV Infection

Elizabeth Reddy, MD, and Charles B. Hicks, MD

CME Credit Available: 1.75 *AMA PRA Category 1 Credits*[™]

Level: Advanced

“Acute” HIV infection generally refers to the phase of rapidly evolving HIV antibody test results when viral replication is at its peak. “Primary” HIV infection often refers to the entire period from transmission through the first year of infection. Despite its perceived importance, diagnosing primary or acute HIV infection remains challenging for many reasons. Health care practitioners who are likely to come in contact with newly infected persons should be versed in recommendations and options for diagnosis and treatment. Dr Elizabeth Reddy and Dr Charles B. Hicks discuss important concepts in the diagnosis of and treatment options for acute HIV infection.

Dermatologic Complications of HIV Infection

Jennifer Cafardi, MD, and John Cafardi, MD

CME Credit Available: 2.5 *AMA PRA Category 1 Credits*[™]

Level: Advanced

A variety of common skin conditions often develop in HIV-infected patients that may be difficult to treat and may provide clues to the patients' underlying immune status. Three major categories of skin conditions are observed: dermatoses specific to HIV infection, common dermatoses that occur with greater frequency in HIV infection and AIDS, and less common conditions that have been reported in association with HIV. Dr Jennifer Cafardi and Dr John Cafardi discuss a selection of some common and some serious cutaneous diseases and the options for treating them.

For information about any of these *Cases on the Web*, please contact the IAS–USA.

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Topics in Antiviral Medicine™

Continuing Medical Education

The following article in this issue is associated with CME credit:
Sherman KE. Advanced liver disease: what every hepatitis C virus treater should know.
Top Antivir Med. 2011;19(3):121-125

Instructions

This journal-based continuing medical education (CME) activity provides a review of hepatitis C virus–related liver disease. To complete the activity, the learner is instructed to:

- Read the article (see pages 121-125)
- Review a selection of the references
- Reflect on how the information might be applied to the clinical practice
- Take the posttest
- Complete the CME claim form and send it to the IAS–USA office.

Learning Objectives

Upon completion of this activity, learners will be able to describe the principles of managing HCV-related liver disease, including staging and monitoring for complications.

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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, and other health professionals who provide care for people with viral diseases.

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Dr Sherman has served as a consultant or scientific advisor to Boehringer Ingelheim Pharmaceuticals, Inc, Genentech, Inc, GlaxoSmithKline, Merck & Co, Inc, Regulus Therapeutics Inc, SciClone Pharmaceuticals, Three Rivers Pharmaceuticals, and Vertex Pharmaceuticals, Inc. He has served on data and safety monitoring boards and end-point adjudication committees for MedPace, Inc, Pfizer Inc, and Tibotec Therapeutics.

Posttest Questions

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

1. Hepatocellular carcinoma (HCC) develops in what percentage of patients with HCV-related cirrhosis each year?
 - A. 0.5%
 - B. 1% - 2%
 - C. 7% - 10%
 - D. About 15%
2. A reliable diagnosis of HCV-related advanced fibrosis is made using:
 - A. Ultrasound
 - B. Abdominal computed tomography
 - C. Liver biopsy
3. Which statement about liver fibrosis progression rates in HCV-infected patients is **correct**?
 - A. Progression rates are predictable and linear
 - B. HIV coinfection does not influence progression rate
 - C. Approximately 10% of HCV-infected patients will have fibrosis that progresses to severe cirrhosis over 20 or more years
 - D. Progression from compensated cirrhosis to decompensated liver disease occurs in about 5% patients per year
4. Which statement about diagnostic tapping of ascites is **correct**?
 - A. The patient should sit upright at a 90-degree angle during the procedure
 - B. Bacterial cultures on the ascitic fluid should be performed using bedside culture bottles
 - C. Bacterial cultures on the ascitic fluid should be performed by using collection tubes that are sent to the laboratory
 - D. Albumin replacement is required for all patients after tapping is complete
5. Which of the following is the most appropriate treatment for ascites and its complications?
 - A. 160 mg furosemide with 4 mg bumetanide, taken daily
 - B. Sodium restriction to maximum of 2 g/day
 - C. Insertion of a chest tube in cases of hepatic hydrothorax
 - D. Repeated large-volume paracentesis with a 4.0-inch, medium-gauge needle

This CME activity is offered from **September 15, 2011, to September 15, 2012**. Participants who receive a passing score on the posttest and submit the registration and evaluation forms are eligible to receive credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Nonphysician health care practitioners will receive a certificate of attendance.

To receive CME credit, please complete the posttest, participant information, and evaluation forms and return all to the IAS–USA.

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

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Which parts of this journal-based CME activity could have been improved?

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Perspective

New Insights Into HCV Replication: Potential Antiviral Targets

The ultimate goal of hepatitis C virus (HCV) treatment is the eradication of the virus. Ongoing research continues to add to knowledge of the HCV life cycle, revealing new potential viral and host targets for the development of therapy. Understanding of HCV was initially hampered by the inability to achieve viral replication in cell culture. Advances such as the HCV replicon and complete cell culture systems, however, have permitted rapid growth in knowledge and accelerated testing of candidate antiviral agents. Among potential targets are viral entry factors, including scavenger receptor type B1 (SR-B1) and CD81, as well as neutralizing antibodies against the viral glycoproteins. Popular targets related to translation and replication are the NS3/4A protease (inhibited by telaprevir and boceprevir) and the NS5B polymerase, as well as the NS2/3 autoprotease, the NS3 helicase, and nonenzymatic targets such as NS4B and NS5A proteins. Host targets are also available, including microRNAs and cyclophilins. This article summarizes a presentation by Charles M. Rice, PhD, at the IAS–USA live continuing medical education course, Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes, held in New York City in April 2011.

History: Roadblocks to Hepatitis C Virus Research

The development of antiviral agents effective against hepatitis C virus (HCV) was hindered for many years by the inability to achieve viral replication in laboratory cell cultures and by the absence of a small-animal model for infection. These roadblocks slowed both the understanding of the HCV life cycle and the investigation of potential antiviral drugs.

HCV was discovered in 1989 as the major causative agent of non-A, non-B hepatitis.¹ This positive-strand RNA virus has a genome approximately 9.6 kilobases (kb) in length. It encodes a single long polyprotein that is processed into 10 individual proteins by viral enzymes (NS2/3 and NS3/4A) and cellular enzymes (signal peptidase and signal peptide peptidase) (Figure 1).²⁻⁴ The NS3/4A serine protease, which cleaves the viral polyprotein at 4 sites, is the target of the only direct-acting HCV antivirals that have been approved by the US Food and

Drug Administration (FDA) to date—telaprevir and boceprevir.

It was almost a decade after the discovery of HCV that the first infectious complementary DNA (cDNA) clone was constructed. Full-length viral RNA transcribed from the cDNA in vitro was capable of establishing infection in chimpanzees but, somewhat paradoxically, could not replicate in cell culture. A major breakthrough in the development of cell-based systems was the construction of the HCV replicon in 1999.⁵ In the initial version, the genome of a genotype-1b HCV

isolate was modified to contain only the key viral RNA replication genes and a neomycin resistance marker for drug selection. Transfection of this “subgenome” into a human hepatoma cell line, Huh-7, resulted in a low frequency of neomycin-resistant cell colonies containing persistently replicating HCV RNA. The replicon provided the first tractable system for the study of HCV RNA replication in the laboratory and the first opportunity to investigate candidate inhibitors in cells.

Improvements to the replicon system followed its initial description. It was recognized that adaptive mutations, which emerged spontaneously in the subgenomic replicons during their growth in cells, could dramatically increase RNA replication levels and transduction efficiency. Furthermore, using interferon alfa to cure cells that had previously harbored the viral RNA resulted in new hepatoma lines that were much more permissive to HCV replication. Despite these improvements, however, the system suffered a major drawback: replicons encoding the full-length HCV genome failed to produce infectious virus in cell culture.

It was not until 2005 that this hurdle was overcome and the first complete

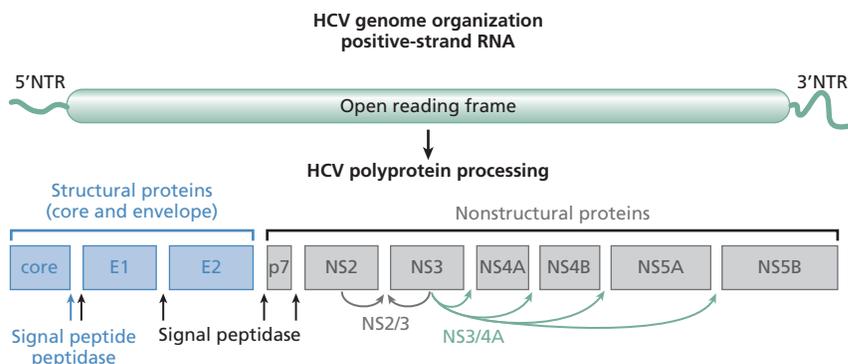


Figure 1. Delineation of hepatitis C virus (HCV) genome organization and polyprotein processing. Schematic shows structural proteins, nonstructural proteins, and enzymatic activities required for cleaving the polyprotein. Adapted from Bartenschlager et al,² Grakoui et al,³ and Hijikata et al.⁴

HCV cell culture system was developed.⁶⁻⁸ The breakthrough came when an HCV genotype 2a clone, derived by Takaji Wakita from a rare case of acute fulminant HCV infection (Japanese fulminant hepatitis 1 [JFH-1] strain), was shown to initiate efficient replication in hepatoma cells without the need for adaptive mutations. Remarkably, electroporation of JFH-1 RNA into cells also led to the release of filterable infectious particles, meeting the classic criterion for a virus. These virus particles were capable of infecting naive hepatoma cells, chimpanzees, and a mouse model harboring human hepatocytes. Both animal models produced virus particles that were still infectious in cell culture. Thus, almost 20 years after the discovery of the virus, all steps in the HCV life cycle could finally be recapitulated in the laboratory.

What We Have Learned: Viral Entry and Spread

HCV is an enveloped virus that displays 2 glycoproteins on its surface: E1 (up to 6 glycosylation sites), the exact role of which is unknown, and E2 (11 glycosylation sites), which appears to be responsible for receptor binding. The proteins are embedded in a lipid bilayer surrounding a nucleocapsid composed of core protein and the genomic RNA. Surprisingly, the virus is often associated with serum lipoproteins (ie, very-low-density and low-density lipoproteins), which are thought to play crucial roles in entry, virus assembly, and possibly in immune evasion. The association of lipoproteins and virus results in material that is heterogeneous in terms of buoyant density; particles with the lowest density often exhibit the highest infectivity. This heterogeneity has made it difficult to gain precise structural information on the HCV particle.

The list of molecules that are active in HCV lipoviral particle entry into liver cells continues to grow. At present, glucosaminoglycans (GAGs) and low-density lipoprotein receptors (LDLRs) on the hepatocyte surface are implicated as putative initial attachment factors. Entry factors scavenger receptor type

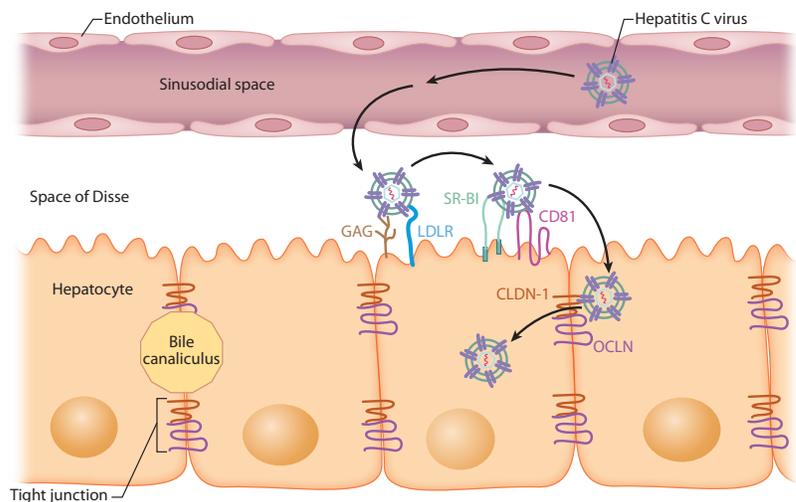


Figure 2. Current model of hepatitis C virus entry into the hepatocyte. GAG indicates glucosaminoglycan; LDLR, low-density lipoprotein receptor; SR-B1, scavenger receptor type B1; CLDN-1, claudin-1; OCLN, occludin. Adapted from an animated slide from Shihyun You, PhD, and Charles Rice, PhD.

B1 (SR-B1), CD81, and tight-junction proteins CLDN-1 (claudin-1) and OCLN (occludin) are essential for uptake. The restriction of HCV to human and chimpanzee hepatocytes appears to be related to the characteristics of the CD81 and OCLN orthologs.

The current model for initial infection posits that the virus enters the liver through the bloodstream, passing through the endothelium and the space of Disse. The particle then interacts with GAG, LDLR, SR-B1, and CD81 on the basolateral surface of the hepatocyte, followed by movement to tight junctions formed by CLDN-1 and OCLN (Figure 2). The mechanisms by which HCV utilizes all 4 entry factors are not entirely clear, as so far only SR-B1 and CD81 have been shown to interact directly with the E2 glycoprotein. It is also not completely understood to what degree spread through the liver occurs via virus released into circulation versus by cell-to-cell transmission between closely connected hepatocytes.

The processes of viral entry and spread are potential drug targets, although uptake inhibitors might best be used in combination with other antiviral agents inhibiting replication. Such combinations might protect cured or uninfected cells and could delay spread of resistant variants. Furthermore, in-

hibition of entry might prevent reinfection of liver allografts in HCV-infected patients receiving transplants. Potential treatments targeting entry include antibodies or small molecules against the entry factors and virus-neutralizing antibodies.

What We Have Learned: HCV Translation and Replication

Following translation and processing of the 10 viral proteins, all of the gene products remain associated with intracellular membranes (Figure 3).⁹ This is a feature common to all positive-strand RNA viruses and is not yet well understood. The HCV nonstructural proteins, which include NS3, NS4A, NS4B, NS5A, and NS5B, comprise the RNA replication machinery. The membrane-associated replicase works by copying incoming genome RNA into a negative-strand intermediate, which is then used to generate additional positive-strand RNAs for subsequent rounds of translation and packaging into virus particles. The replication factories use microtubules to move around the cell as they function, coalescing into vesicular structures termed the membranous web.

The most popular targets for the development of HCV antiviral drugs have been 2 enzymatic components of

the replicase: the NS3/4A serine protease and the NS5B RNA-dependent RNA polymerase. These are attractive in part because both are enzymes required for HCV replication. In addition, their functions are amenable to the development of biochemical assays for inhibitor screening, an important consideration especially in the era before cell-based systems. Other enzymatic targets have been less well explored, including the NS2/3 autoprotease, which mediates a single cleavage in the polyprotein, and an RNA helicase encoded in the C-terminal two-thirds of NS3, which appears to unwind RNA structures during replication.

A number of nonenzymatic targets have also received considerable attention. The NS4B protein may scaffold the RNA replication machinery and is sufficient to form the membranous web. It is the target of several compounds recently identified in novel biochemical assays. The NS5A protein is involved in both RNA replication and infectious virus assembly. Despite these important roles, the protein was initially an unpopular target because it has no known enzymatic activity. Recently, however, a compound acting on NS5A, BMS-790052, has emerged as one of the most potent and broadly active inhibitors of HCV replication observed to date. In a study by Gao and colleagues, the drug exhibited 50% effective concentration (EC₅₀) values of 9 pM to 146 pM against replicons and infectious HCV in culture. Early-phase clinical trials revealed promising pharmacokinetics and a rapid decrease in HCV RNA levels.¹⁰

Host factors involved in translation and replication present an intriguing alternative strategy for drug design. MicroRNAs are small noncoding RNAs that fine-tune cellular gene expression, usually by sequestering an mRNA or inducing template turnover in a highly selective manner. In the liver, microRNA-122 (miR-122) is responsible for regulating the expression of approximately 200 cellular genes, including those involved in cholesterol biosynthesis and lipid metabolism. Interestingly, miR-122 was found to bind to 2 short recognition sequences

near the 5' end of the HCV genome. Rather than downregulating HCV gene expression, however, miR-122 binding augments viral RNA replication. Recently, Lanford and colleagues have shown that a stabilized “locked nucleic acid” antagonist of miR-122 can be efficiently delivered to the livers of HCV-infected chimpanzees. Delivery of the antagonist reduced HCV viremia by several orders of magnitude, with the effect persisting for several weeks after treatment was stopped.¹¹

HCV Assembly and Release

Thus far, there are relatively few data on how virus assembly and release might be inhibited. In addition to the viral structural proteins (core, E1, and E2), the nonstructural proteins p7, NS2, NS3, and NS5A are required for production of infectious virus. This hints at coordination between the machinery involved in making new copies of the genome RNA and the machinery packaging it into particles.

As mentioned above, HCV particles are typically associated with serum lipoproteins in circulation. In fact, HCV uses the lipoprotein production pathway to assemble viral particles and to move them out of the infected cell. Thus, interfering with lipoprotein components or disrupting the pathways involved in lipoprotein secretion are

potential areas for intervention in assembly and release, as well as entry.

Host Targets for Antiviral Drug Development

HCV is dependent on host cells to provide numerous factors for its replication, and there is ongoing discussion about whether viral targets or host targets are optimal for antiviral drug development. Strategies for identifying potential host targets include screening small interfering RNA (siRNA) or short hairpin RNA (shRNA) libraries to identify human genes required for HCV replication. Another strategy is to pursue already-known targets, such as SR-B1 (eg, with anti-SR-B1 antibody), CD81 (eg, with anti-CD81 antibody), lipoproteins (eg, with anti-apolipoprotein E antibody), or microRNAs (eg, with locked nucleic acid compounds). Furthermore, existing pharmacologically active compounds, for example, those potent against other pathogens, can be screened using cell-based systems for inhibiting HCV.

One of the most interesting outcomes of a screen of preexisting drugs was the finding that cyclophilins, which are targeted by cyclosporin A, are required for HCV replication. Cyclophilin A is a cellular peptidyl-prolyl isomerase, which appears to act on the HCV NS5A protein, as well as possibly on

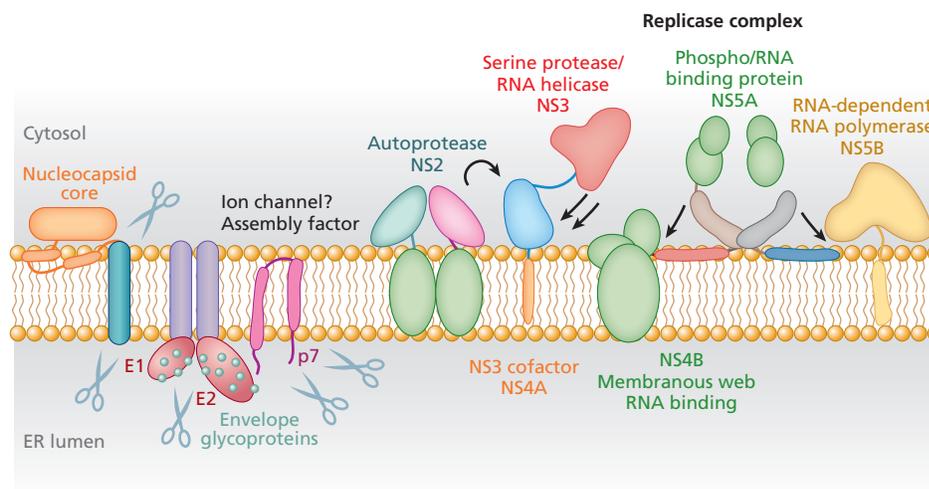


Figure 3. Hepatitis C virus proteins and functions. ER indicates endoplasmic reticulum. Scissors indicate cleavage by host enzymes, arrows represent processing by viral proteases. Adapted from Moradpour et al.⁹

NS2 and NS5B. It has been shown that nonimmunosuppressive analogues of cyclosporin A, such as the compound Debio 025, can bind cyclophilin A and inhibit HCV replication. Debio 025 was found to markedly reduce HCV viremia in clinical trials when used alone or in combination with pegylated interferon alfa.

Although host factors may be feasible antiviral targets, the debate continues on the benefits of this approach. On the plus side, host proteins present a wide array of strategies; viral targets are limited to 10 proteins and 1 RNA molecule. Drug development time may be reduced by evaluating compounds already known to target host processes relevant to HCV. In addition, host proteins are well conserved. This is in contrast to the huge genetic variability of the virus, which can lead to rapid emergence of resistance. The genetic heterogeneity of HCV can be appreciated when it is considered that approximately 10^{12} viral particles are produced each day in a chronically infected individual. As with HIV and other RNA viruses, replication of HCV is error prone, easily resulting in patients who harbor all single- and double-substitution resistance-associated mutations prior to starting any drug treatment. Agents that act on host targets may also be more potent across the different viral genotypes.

Importantly, inhibiting a host factor is inherently less virus-specific than targeting an HCV protein. Disrupting important roles of a cellular protein could lead to increased side effects. Host factor polymorphisms may also affect drug

activity. Ideally, therefore, a combination of host and viral inhibitors will provide a variety of drug regimens appropriate for different patients.

Summary

HCV is a cytoplasmic RNA virus that does not integrate into the host cell DNA, making eradication a seemingly achievable goal. Understanding of the HCV life cycle and potential drug targets has increased considerably over the last decades, and there is now a large number of candidate antivirals in the development pipeline. Very recently, the first direct-acting antiviral drugs were approved in combination with peginterferon alfa and ribavirin. For the near future, a major goal is to develop interferon-free therapies that can consistently clear the virus. As more agents effective in inhibiting the HCV life cycle are identified, the chances of achieving cure in most, if not all, HCV-infected patients are likely to increase dramatically.

Presented by Dr Rice in April 2011. First draft prepared from transcripts by Matthew Stenger. Edited by Catherine Murray, PhD, in August 2011, and reviewed by Dr. Rice.

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References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*. 1989;244:359-362.
2. Bartenschlager R, Ahlborn-Laake L, Mous J, Jacobsen H. Nonstructural protein 3 of the hepatitis C virus encodes a serine-type proteinase required for cleavage at the NS3/4 and NS4/5 junctions. *J Virol*. 1993;67:3835-3844.
3. Grakoui A, Wychowski C, Lin C, Feinstone SM, Rice CM. Expression and identification of hepatitis C virus polyprotein cleavage products. *J Virol*. 1993;67:1385-1395.
4. Hijikata M, Mizushima H, Tanji Y, et al. Proteolytic processing and membrane association of putative nonstructural proteins of hepatitis C virus. *Proc Natl Acad Sci USA*. 1993;90:10773-10777.
5. Lohmann V, Körner F, Koch J, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science*. 1999;285:110-113.
6. Wakita T, Pietschmann T, Kato T, et al. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nat Med*. 2005;11:791-796.
7. Zhong J, Gastaminza P, Cheng G, et al. Robust hepatitis C virus infection in vitro. *Proc Natl Acad Sci USA*. 2005;102:9294-9299.
8. Lindenbach BD, Evans MJ, Syder AJ, et al. Complete replication of hepatitis C virus in cell culture. *Science*. 2005;309:623-626.
9. Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol*. 2007;5:453-463.
10. Gao M, Nettles RE, Belema M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. *Nature*. 2010;465:96-100.
11. Lanford RE, Hildebrandt-Eriksen ES, Petri A, et al. Therapeutic silencing of micro-RNA-122 in primates with chronic hepatitis C virus infection. *Science*. 2010;327:198-201.

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Perspective

Advanced Liver Disease: What Every Hepatitis C Virus Treater Should Know

Identification and treatment of advanced hepatitis C virus (HCV) infection is often challenging. Accurate fibrosis staging can be performed only by liver biopsy. For patients with advanced fibrosis (Metavir score, F3 or F4), progression to decompensated liver disease occurs at a rate of approximately 5% per year and progression to hepatocellular carcinoma occurs at a rate of 1% to 2% per year. Liver decompensation primarily results from altered hepatic blood flow caused by liver scarring and is characterized by ascites and its complications (hepatorenal syndrome, hepatic hydrothorax, and spontaneous bacterial peritonitis), hepatic encephalopathy, bleeding varices, and coagulopathy. Patients with advanced fibrosis need to be regularly monitored for evidence of decompensated disease, and complications need to be aggressively managed. This article summarizes a presentation by Kenneth E. Sherman, MD, at the IAS–USA live continuing medical education course, Management of Hepatitis C Virus in the New Era, held in New York City in April 2011.

Hepatitis C virus (HCV) infection is a curable infectious disease. It is also a liver disease. A critical component of managing HCV-related liver disease is to determine the patient's severity of liver fibrosis. Patients with advanced fibrosis should be regularly monitored for bleeding varices using esophago-gastroduodenoscopy (EGD), and for ascites and hepatocellular carcinoma (HCC) using ultrasound. Complications of liver disease require prompt management and aggressive follow-up. Knowing when to refer patients to a transplant center and doing so in a timely manner is crucial.

Dr Sherman noted that the basic principles in understanding and managing HCV-related liver disease are as follows:

- Hepatic fibrosis is not reliably diagnosed by ultrasound examination.
- Liver fibrosis rates are not predictable or linear.
- Progression from compensated cirrhosis to decompensated liver disease occurs in 5% of patients per year.

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- Hepatocellular carcinoma develops in 1% to 2% of patients with HCV-related cirrhosis each year.

Hepatitis C Virus–Related Hepatic Fibrosis

Reliable diagnosis of HCV-related advanced fibrosis or cirrhosis depends on liver biopsy (Figure 1). Ultrasound techniques may reveal a shrunken liver or evidence of portal hypertension but do not permit visualization of fibrosis or cirrhosis. Cirrhosis is a histologic diagnosis and is often confused with portal hypertension, which results from cirrhosis. However, not all portal hypertension is caused by cirrhosis. The extent of fibrosis is classified into 4 stages using the Metavir schema. In stage 1, fibrous expansion can be observed in some portal areas. In stage 2, fibrous expansion is observed in most portal areas, with occasional portal-to-portal bridging. Stage 3 fibrosis is characterized by fibrous expansion of portal areas with marked bridging, including portal-to-portal and portal-to-central bridging. Stage 4 fibrosis indicates cirrhosis, which is strictly defined as a liver lobule completely surrounded by scarring.

Liver fibrosis progression rates are not predictable or linear. They vary widely among patients with HCV infection, with rates being more rapid

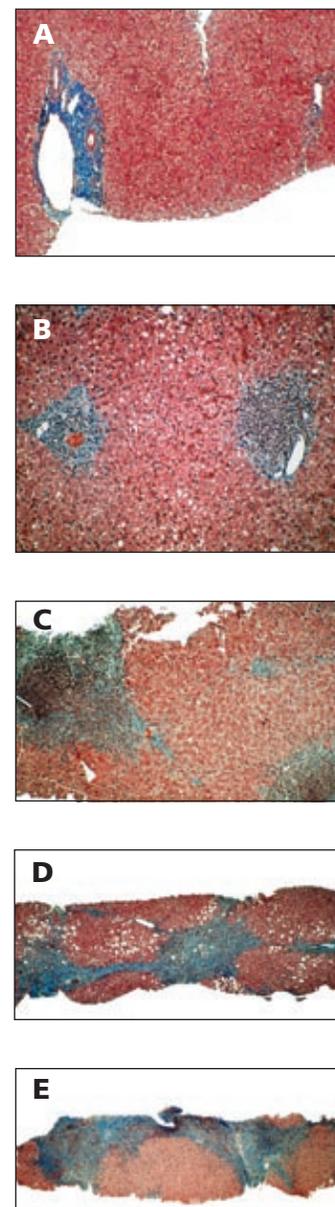


Figure 1. Progression of liver fibrosis as shown on a series of biopsy specimens and as classified by the Metavir schema. **A:** Liver with no fibrosis. **B:** Stage 1, fibrous expansion into some portal areas. **C:** Stage 2, fibrous expansion in most portal areas, with occasional portal-to-portal bridging. **D:** Stage 3, fibrous expansion of portal areas with marked bridging, including portal-to-portal and portal-to-central bridging. **E:** Stage 4, cirrhosis. Adapted with permission from Gregory T. Everson, MD, University of Colorado Denver.

Case: A 48-Year-Old Man with HCV Infection

The patient is a 48-year-old man with HCV infection, a history of 2 years of injection drug use from age 19 years to 21 years, and moderate social alcohol use. The patient presents with fatigue and insomnia, with laboratory evaluation showing alanine aminotransferase (ALT) level of 89 U/L, aspartate aminotransferase (AST) level of 67 U/L, bilirubin level of 1.5 mg/dL, alkaline phosphatase level of 197 IU/L, hemoglobin level of 13.4 gm/dL, platelet count of 111,000/ μ L, HCV RNA level of 2.7 million IU/mL, and HCV genotype 1b. Right upper quadrant ultrasound shows an echogenic liver consistent with fat or liver disease. Instead of undergoing biopsy for staging of fibrosis, the patient is started on a 3-drug regimen containing pegylated interferon alfa, ribavirin, and a direct-acting antiviral.

After 12 weeks of treatment, virus is undetectable. The patient notes a 10-lb weight gain, and his wife complains that he sometimes appears drunk, though he denies alcohol use. What is the best next step in the treatment of this patient: 1. Prescribe an antidepressant? 2. Reassure the patient that he is experiencing common side effects of interferon alfa therapy? 3. Order a stat ultrasound? 4. Suggest diet and exercise?

Dr Sherman explained that an ultrasound will determine if the weight gain is associated with the development of ascites, and is thus the best next step. Although the severity of fibrosis in this patient is unknown, his workup prior to treatment initiation produced some findings that raise concern over the potential for decompensated liver disease, including a somewhat low platelet level and the presence of fatigue and insomnia. Reversal of sleep patterns is a common very early symptom of hepatic encephalopathy.

Weight gain is not expected in patients receiving interferon alfa; in fact, interferon alfa treatment is more commonly associated with anorexia and weight loss. Ultrasound reveals that the patient has ascites, indicating the presence of advanced liver disease that became decompensated as a result of anti-HCV therapy.

in those with cofactors for progression that include concurrent HIV infection and excessive consumption of alcohol. Overall, some 15% to 33% of HCV-infected patients may exhibit mild or moderate liver fibrosis over the course of 40 or more years, whereas 20% to 33% have disease that progresses to severe cirrhosis or HCC over 20 or more years. Some patients, however, have liver fibrosis that progresses to severe disease in as little as 3 or 4 years.¹

In a sense, there are 2 timelines to keep in mind when considering progression of HCV-related liver disease. One timeline begins when a patient becomes infected with HCV, marking the onset of liver injury and a course of progression (in the absence of successful treatment) that varies from several years to as long as 50 years. The second timeline begins at the onset of cirrhosis. Progression from compensated asymptomatic cirrhosis to decompensated

liver disease occurs in approximately 5% of HCV-infected patients per year. In addition, HCC develops in 1% to 2% of patients with HCV-related cirrhosis per year and eventually results in symptomatic decompensated disease.

Cirrhosis and Hepatic Decompensation

Approximately 5% of HCV-infected patients with cirrhosis will have progression to hepatic decompensation per year. Hepatic decompensation is characterized by: (1) ascites, which itself may be complicated by hepatorenal syndrome (HRS), hepatic hydrothorax, and spontaneous bacterial peritonitis (SBP); (2) encephalopathy; (3) bleeding varices; and (4) coagulopathy (indicated by a prothrombin time [PT] 3 seconds above the control time or by an international normalized ratio [INR]

greater than 1.5). Clinical staging of cirrhosis was traditionally performed using Child-Turcotte-Pugh scoring, a scoring system initially developed to predict a patient's survival associated with portal shunt surgery. It was later adapted to determine priority for liver transplantation. Scores are based on presence and degree of abnormalities in bilirubin level, albumin level, INR, and on presence and severity of hepatic encephalopathy and ascites. Cirrhosis staging under this system is divided into class A, B, or C, with each class having an assigned 1- and 2-year survival rate.

The Child-Turcotte-Pugh scoring system is not highly reliable for predicting mortality, however, and in recent years has been replaced by the more complex model for end-stage liver disease (MELD) scoring system. MELD scoring uses bilirubin, creatinine levels, and the INR to predict mortality risk and determine timing of orthotopic liver transplantation. For example, for a patient with end-stage liver disease, a creatinine level of 1.6 mg/dL, bilirubin level of 1.4 mg/dL, and an INR of 1.6, the MELD system will predict a 3-month mortality risk of 18%.

Most of the damage in decompensated liver disease is related to alteration in blood flow through the liver. The portal vein, which supplies the blood to the liver, is formed by the confluence of the superior and inferior mesenteric veins and the splenic vein (Figure 2). A buildup of fibrotic scar tissue in the liver can cause obstruction of blood flow into the liver, causing blood to back up in the many vessels in the splanchnic circulation and resulting in numerous adverse consequences. The spleen becomes enlarged and begins to filter non-senescent blood cells from the circulation, resulting in decreased levels of platelets, red blood cells, and white blood cells. Decreased absorption of fluids along the peritoneal surface also occurs because lymphatic drainage is supplemented by blood flow from the peritoneal space into the splanchnic circulation, resulting in ascites.

A response to reduced blood flow into the liver is the development of collateral vessels. These vessels grow

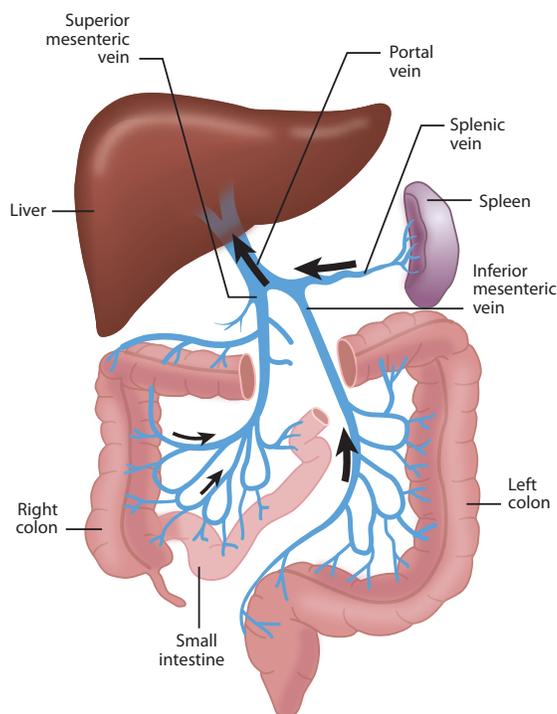


Figure 2. Splanchnic circulation. Arrows indicate direction of blood flow.

mostly in mucosal junction areas and can result in the development of varices in the esophagus, stomach, and rectum. Recanalization of vessels at the umbilical vein occurs in some patients, driving the development of new vessels across the anterior abdomen (called caput medusae).

Management of Ascites and its Complications

Ascites can cause substantial pain and discomfort. Patients may ask for narcotics for pain relief, but narcotic use should be avoided if possible by patients who already have hepatic impairment. As noted, complications of ascites include HRS, hepatic hydrothorax, and SBP. Large ascites should also be relieved at first observation by tapping (also known as large volume paracentesis [LVP]). Every time the patient is admitted to the hospital and with every change in health status (eg, worsening ascites, development of bleeding varices, or worsening hepatic encephalopathy), a diagnostic tap should be performed. Tapping at the time of hospital admission is important because a high proportion of patients with ascites

have SBP at the time of admission, whether or not fever or abdominal pain is present, and SBP is associated with marked morbidity and mortality.

Tapping does not require that the patient be sent to interventional radiology for a computed tomography (CT)-guided tap. The procedure is safely performed in the midline subumbilical area with the patient sitting at a 30-degree angle. For a diagnostic tap, the procedure can be accomplished in any patient with a 1.5-inch needle (and with a 1.0-inch needle in most). Tapping is very safe regardless of the patient's degree of coagulopathy, as the area beginning approximately 2 cm below

the umbilicus is relatively avascular. There is no need to have fresh frozen plasma or platelets on hand for the procedure. Cell counts on the fluid should be performed and fluid should be injected directly into bedside culture bottles, because false-negative results occur in 40% to 50% of cases in which the fluid is processed in the laboratory rather than inoculated at bedside. For therapeutic taps, a large-gauge multi-perforated Caldwell or similar needle is used. Albumin replacement is required if the patient's creatinine level is elevated or if more than 5 L of fluid is removed.

Management of ascites is diagrammed in Figure 3. At the initial visit for patients with tense ascites, a large-volume tap is performed to relieve discomfort as quickly as possible. Patients are placed on a sodium-restricted diet (maximum of 2 g/day) and diuretic therapy is initiated. The most effective approach in diuretic treatment of ascites is not to start with higher doses of the rapid-acting agent furosemide, but rather to start with slower-acting treatment such as the aldosterone antagonist spironolactone (50 mg/day) in combination with lower doses of furo-

semide (20 mg/day or 40 mg/day) or bumetanide (1 mg/day); doses are then titrated upward at 2-week intervals to maximum doses of 400 mg/day for spironolactone with 160 mg/day for furosemide, or 4 mg/day for bumetanide.

When ascites is managed appropriately, the risk of progressing to refractory ascites is relatively low. When refractory ascites does occur, it is treated with repeated large-volume paracentesis. Consideration should be given to placement of a transjugular intrahepatic portosystemic shunt (TIPSS), which is successful in reducing ascites in 60% to 70% of cases and eliminating it in 20% to 30% of cases. Placement of TIPSS should only be performed by highly experienced interventional radiologists after evaluation of the patient by a hepatologist. Finally, the patient's candidacy for liver transplantation should be considered.

Spontaneous Bacterial Peritonitis

SBP is diagnosed by examining the ascitic fluid: greater than 500 white blood

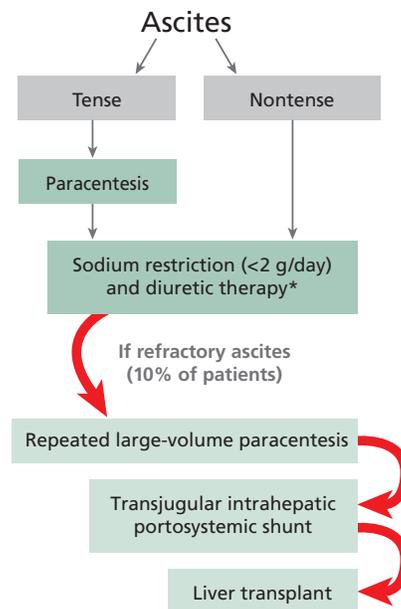


Figure 3. Schematic representation of the management of ascites. *For diuretic therapy, initiate treatment with spironolactone (50 mg/day) in combination with furosemide (20 mg/day or 40 mg/day) or bumetanide (1 mg/day). Titrate stepwise at 2-week intervals to spironolactone 400 mg/day, furosemide 160 mg/day, or bumetanide 4 mg/day, as long as regimen is tolerated.

cells/mL, greater than 250 polymorphonuclear cells/mL, or a positive culture result are indicative of SBP. Each definition listed is trumped by the next one on the list. Treatment is with a 5-day course of intravenous cefotaxime or other cephalosporin. For beta-lactam allergy, ciprofloxacin may be used. Repeat paracentesis should be considered at 48 hours to 72 hours after treatment initiation to check for white blood cell response; absence of response may suggest the presence of an organism with drug resistance or a complex polymicrobial process that is not SBP. Albumin infusions should be given to patients with SBP, as they have been shown to reduce mortality.

One study showed a reduction in 60-day mortality from 29% with cefotaxime alone to 10% with cefotaxime plus 1.5 g/kg albumin administered within 6 hours of SBP diagnosis, followed by 1.0 g/kg on day 3.² Antibiotic prophylaxis with ciprofloxacin (750 mg/week) has been shown to prevent SBP in patients with ascites, with one classic study showing a 6-month incidence of SBP of 4% with ciprofloxacin versus 22% with placebo.³ Alternative antibiotics for prophylaxis are norfloxacin and trimethoprim-sulfamethoxazole.

Hepatic Hydrothorax

The ascites complication of hepatic hydrothorax results from a break in the diaphragm that creates a ball-valve effect such that each breath causes inflow of fluid from the abdomen into the pleural space. The right pleural space is much more frequently involved than the left. Hepatic hydrothorax is not to be confused with primary pleural effusion, and it is not to be treated with insertion of a chest tube. Placement of a chest tube in a patient with hepatic hydrothorax results in a continuous loss of protein that rapidly renders the patient nutritionally depleted, making liver transplantation impossible. Patients with hepatic hydrothorax may or may not have visible ascites.

Hepatic hydrothorax should be suspected for any patient with advanced liver disease and right-sided effusion. Hepatic hydrothorax should be man-

aged by aggressive diuresis, pleural taps when needed, and immediate consideration for liver transplantation. Patients requiring frequent pleural taps may gain additional MELD points on the transplant list.

Varices

Patients with cirrhosis must be monitored for the development of varices (Figure 4) and variceal bleeding using EGD.



Figure 4. Gastroscopy image of esophageal varices.

Those with no varices should have repeat EGD performed at 3 years for well-compensated liver disease and at 1 year for decompensated disease. Patients with small varices (Grade 1) may begin nonselective beta-blocker prophylaxis. Patients with medium (Grade 2, 5-10 mm) or large (Grade 3, > 10 mm) varices who have no red wales (evidence of impending bleeding) should receive beta-blocker treatment; those with red wales should be given beta-blocker treatment and considered for esophageal band ligation. Esophageal varices develop in 35% to 80% of patients with cirrhosis, and bleeding occurs in 25% to 40% of those with varices. Of those with bleeding, 30% to 50% die within 90 days. Of the 50% to 70% who survive an initial bleeding episode, 70% will experience subsequent bleeding.

Hepatic Encephalopathy

Hepatic encephalopathy is classically detected by the observation of hand asterixis (also known as liver flapping or flapping tremor). It is caused by the shunting of gut-derived neuroactive substances that cross the blood-brain barrier; these substances are mostly nitrogen based and act as inhibitory neurotransmitters. Survival probabilities for patients with hepatic encephalopathy are 42% at 1 year and 23% at 3

years. Precipitating factors for hepatic encephalopathy include a high-protein diet, gastrointestinal bleeding, infection (including SBP), vascular thrombosis, HCC, and poor adherence to hepatic encephalopathy treatment. Traditional treatments for hepatic encephalopathy include the use of lactulose or other nonabsorbable sugars, which cause osmotic diarrhea and movement of nitrogen compounds out of the gut, and the use of antibiotics such as neomycin and metronidazole that change the gut flora.

A recent phase III trial showed that, compared with placebo, the nonabsorbable antibiotic rifaximin administered at 550 mg twice daily was associated with a statistically significant reduction in episodes of breakthrough hepatic encephalopathy in patients in remission from recurrent hepatic encephalopathy (breakthrough episodes occurred in 22.1% of patients taking rifaximin vs 45.9% with placebo; $P < .001$).⁴ More than 90% of patients in the trial received concomitant lactulose therapy. Rifaximin treatment was also associated with a statistically significant reduction in frequency of hospitalization for hepatic encephalopathy (13.6% hospitalization rate with rifaximin vs 22.6% with placebo, $P = .01$). The incidence of overall and serious adverse events was similar in the rifaximin and placebo recipients.

Liver Transplantation

Criteria for referring patients for liver transplantation include any signs of hepatic decompensation (eg, ascites, hepatic encephalopathy, or variceal bleeding), a MELD score greater than 10, or HCC at any level of MELD. Unfortunately, the need for liver transplantation outstrips the availability of liver donors. In the United States, only about 5500 livers become available each year. Referring patients for transplantation expeditiously can be lifesaving. Encouraging people to become donors is lifesaving at the community level.

Presented by Dr Sherman in April 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Sherman in August 2011.

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References

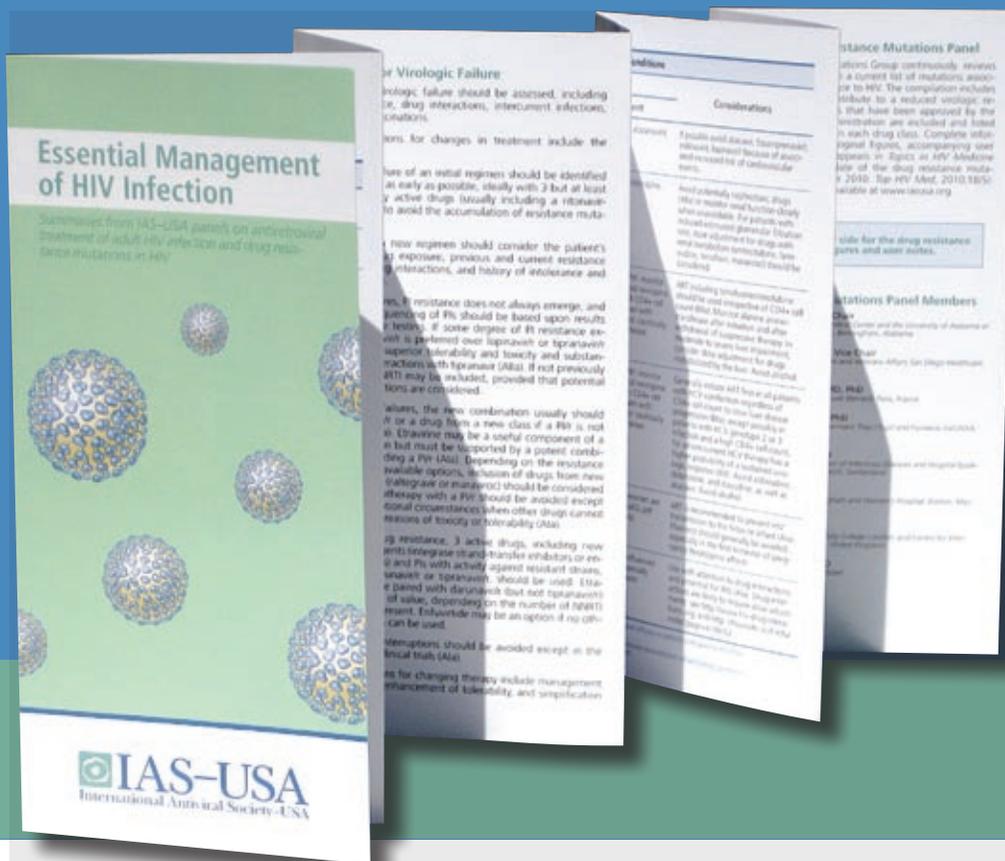
1. Afdhal NH. The natural history of hepatitis C. *Semin Liver Dis.* 2004;24(Suppl 2): 3-8.
2. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med.* 1999;341:403-409.
3. Rolachon A, Cordier L, Bacq Y, et al. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial.

Hepatology. 1995;22:1171-1174.

4. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362:1071-1081.

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Review

When Patients Cannot Take Pills: Antiretroviral Drug Formulations for Managing Adult HIV Infection

Chessa R. Nyberg, PharmD, Brooke Y. Patterson, PharmD, and Meghan M. Williams, PharmD

Providing antiretroviral therapy for the HIV-infected population is a complex and challenging task. Treatment is often complicated by the shifting demographic of HIV-infected patients that now includes a large aging population in which patients often have multiple comorbidities. HIV clinicians are challenged with choosing the optimal combination of antiretrovirals based on potency, tolerability, bioavailability, and ease of administration. The issue of bioavailability is of paramount importance for those patients who can't swallow tablets, are unable to take anything by mouth before a procedure, or who need medication through a nasogastric tube or percutaneous endoscopic gastrostomy tube. A thorough search of several drug databases, a literature search of MEDLINE through Ovid, and a review of full prescribing information for each currently available antiretroviral drug, was performed to obtain insight into the bioavailability of antiretrovirals. Implications for the findings are discussed as they relate to adherence, resistance, alternative methods of administration, and the sometimes conflicting information on bioavailability that exists for various antiretroviral agents.

Introduction

Thirty years have passed since the global recognition of HIV as the cause of AIDS. Since that time, scientists have developed a number of medications with activity against the virus—the antiretroviral drugs—that exert their effects by inhibiting viral replication, thereby allowing for immune system recovery. Since 1996, scientists and practitioners have recognized the benefits of multidrug therapy in the treatment of HIV infection. Strategies for implementing triple-drug therapy were created in response to the treatment challenge presented by the rapidly evolving nature of HIV; the virus acquires mutations that cause decreased efficacy of antiretroviral drugs (ie, resistance), thereby leading to viral rebound and immune system destruction.

Because of the increased understanding of the appropriate use and combinations of antiretroviral drugs,

HIV infection has evolved from a disease associated with high mortality to a chronic disease for patients who have full access to well-managed care and who adhere to treatment. The demographic of HIV-infected patients also has shifted throughout the years; what was once a viral infection primarily associated with young men has become an epidemic that includes a large aging population. HIV care practitioners must now consider that the patient groups infected with the virus are living longer and receiving their diagnosis at later stages of the disease than patients affected in earlier years of the epidemic. For example, in the United States, the population of HIV-infected patients over age 50 years increased by almost 20% from 2001 to 2005.¹

This enhanced longevity of HIV-infected patients is largely the result of the development of potent antiretroviral regimens, before which coinfections and complications of HIV disease often resulted in negative or

fatal outcomes for patients. In the current treatment era, mortality has substantially decreased, and HIV-seropositive patients have an improved quality of life.²

With advanced age from declining mortality, however, comes a new subset of health care issues for patients. Current treatment involves not only the use of complex antiretroviral regimens for life but may also require periodic hospital stays or outpatient visits to manage comorbidities or complications of treatment, particularly diabetes and cardiovascular or cerebrovascular effects. HIV infection as an inflammatory disease is recognized to contribute to increased risks of myocardial infarction or stroke, as has been demonstrated in the SMART (Strategies for Management of Antiretroviral Therapy) trial³ and the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study.⁴

With this increased understanding, so too has understanding of the importance of sustained viral suppression in reducing these long-term risks associated with HIV infection and its treatment. In 2008, treatment guidelines from the IAS–USA⁵ began to reflect the field's paradigm shift toward treating HIV infection earlier in the course of the disease to prevent long-term sequelae, a trend that continued in the 2009 US Department of Health and Human Services (DHHS) guidelines,⁶ the 2010 IAS–USA guidelines,⁷ and the 2011 DHHS update.⁸ Although the benefits of early treatment are many, so is the importance of increased understanding of the bioavailability and alternative dosage forms of these

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drugs for patients across the treatment spectrum.

Current Challenges in Bioavailability of Antiretrovirals

Currently, more than 20 antiretroviral drugs have been approved by the US Food and Drug Administration (FDA) for treatment of HIV infection. The majority of these drugs are available solely in tablet form for ease of administration; however, this limited formulation availability creates problems for patients unable to take medications orally. Examples of such situations include patients undergoing inpatient or outpatient procedures that do not allow them to take drugs by mouth, patients with swallowing disorders, and those with gastrointestinal diseases for which they receive nutrition through an alternative route.

A study of HIV-infected patients between 2000 and 2002 revealed that 20% utilized hospital inpatient services.⁹ The impact of hospital stays on antiretroviral drug adherence and long-term viral suppression can be damaging if treatment is not managed properly during the inpatient period. In a study by Heelon and colleagues, most prescribing errors involving antiretroviral drugs included those in the following categories: incomplete regimens, incorrect dosages, incorrect schedules, medication-disease interactions, incorrect formulations, incorrect antiretroviral drugs, duplication of therapy, and prescription of drugs with drug-drug interactions.¹⁰ With appropriate monitoring of patients by HIV specialists, these prescribing errors can be reduced.

Because complications and subsequent mortality can be lessened with viral suppression and immune restoration, it is vital for HIV-infected patients to continue receiving their antiretroviral regimens without interruption whenever possible. For patients unable to take oral medications, many issues need to be addressed when analyzing the bioavailability of the various antiretroviral drugs. For several medications, conflicting information exists. Alternative administration of many

antiretroviral drugs may profoundly change the drugs' bioavailabilities, pharmacokinetics, and subsequent efficacies. To ensure that health care practitioners are best able to make antiretroviral treatment decisions when facing alternative drug administration issues, a literature search was conducted and information guide created.

Search Methods and Results

Full prescribing information from respective manufacturers of each currently available oral antiretroviral drug formulation was reviewed for any data indicating that the medication could be crushed, opened, or added to water or food. In addition, a search was performed on each drug using information in databases from Lexi-Comp,¹¹ Clinical Pharmacology,¹² and Facts & Comparisons.¹³ For any drug without a specific formulation recommendation, a MEDLINE search through Ovid was completed using the drug trade name, the generic name, and the search terms "crush," "sprinkle," "extemporaneous preparation," and "bioavailability." The manufacturers were contacted for information on alternative administration of each product. For any drug that still lacked information, it was assumed that the medication could not be crushed or opened because of a lack of evidence. The search results are compiled in Table 1.

Discussion

The medical management of persons living with HIV infection or AIDS can be challenging for health care practitioners who are not experienced with antiretroviral drugs.¹⁴ Given the growing complexity and longevity of this patient population, HIV care has become highly specialized. HIV-infected patients are about 25% more likely to experience a medication error while in the hospital than are patients admitted without HIV infection.¹⁵ These drug errors are most likely the result of incorrect dosing, incorrect regimens, incorrect formulations, or incorrect scheduling.

Although current treatment of HIV infection consists of combinations of drugs and lower pill burdens than in the past, the regimens are increasingly complex, and their design requires careful and frequent monitoring to prevent drug interactions and avoid unwanted adverse events and antiretroviral drug resistance. Although outcomes have improved, successful outcomes may be precluded by the emergence of drug resistance.¹⁶ Adherence rates of less than 95% can lead to antiretroviral drug resistance and ultimately, treatment failure.¹⁷ Prevention of HIV resistance requires strict adherence to treatment, without which long-term suppression of HIV cannot be maintained because of rapid replication and mutation of the virus.¹⁸

The challenge of maintaining dosage schedules of antiretroviral drugs under different patient conditions (eg, patients using nasogastric or percutaneous endoscopic gastrostomy tubes or those for whom oral foods and liquids are being withheld) is one of substantial clinical importance. Although this challenge often presents itself in an inpatient care setting, the aging HIV-infected population, whether inpatient or outpatient, should not be overlooked with respect to this issue. Aging HIV-infected patients may have many of the same issues associated with dysphagia and aphagia as do inpatient HIV-infected persons. Bioavailability data should be considered for any HIV-infected patients with comorbid conditions that affect normal function.

The bioavailability of antiretroviral drugs is complicated by interactions with certain foods, different chemical forms of the drugs, and the physiologic state of the patient. The literature and database search revealed that 79.3% (23/29 listed in Table 1) of antiretroviral medications cannot be crushed, sprinkled, or administered through a percutaneous endoscopic gastrostomy or nasogastric tube. Some regimens may thus need to be taken in a different formulation or ultimately changed to ensure that the patient receives the full benefit of treatment.

Currently, there is not sufficient evi-

Table 1. Current Antiretroviral Drug Formulations for the Management of Adult HIV Infection

Drug	Can Be Crushed or Sprinkled	Solution or Suspension Available	Food Considerations	Special Administration
Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)				
Delavirdine ^{19,a}	100-mg tablets: Yes 200-mg tablets: No (Do not readily disperse in water)	No	May be taken without regard to meals	100-mg tablets may be dispersed in water. To prepare dispersion, add 4 100-mg tablets to ≥ 3 ounces of water, let stand for a few minutes, then stir until a uniform dispersion occurs. Administer immediately, rinse glass, and have patient swallow each rinse completely to ensure entire dose is consumed.
Efavirenz ^{12,20}	Yes	No	Take on an empty stomach	Has a peppery taste; grape jelly has been used to disguise this.
Etravirine ²¹	Yes	No	Take after meals	Tablets may be dispersed in water; stir well and have patient drink mixture immediately. Rinse glass with water several times, and have patient swallow each rinse completely to ensure entire dose is consumed.
Nevirapine ²²	No information	50 mg/5 mL suspension	May be taken without regard to meals	
Rilpivirine ²³	No (25-mg tablets do not readily disperse in water)	No	Should be taken with food	Needs to be taken with a meal (> 533 calories). Protein drinks should not replace a meal when taking this medication.
Nucleoside Analogue Reverse Transcriptase Inhibitors (nRTIs)				
Abacavir ²⁴	No information	20 mg/mL solution (strawberry-banana flavored)	May be taken without regard to meals	
Didanosine ^{11-13,25}	No	Pediatric powder for solution, in 2g/bottle and 4g/bottle	Take on an empty stomach (30 minutes before or 2 hours after food)	
Emtricitabine ²⁶	No information	10 mg/mL solution (cotton candy flavored)	May be taken without regard to meals	
Lamivudine ²⁷	No information	10 mg/mL solution (strawberry-banana flavored)	May be taken without regard to meals	
Stavudine ^{13,28}	Yes	1 mg/mL powder for solution (fruit flavored)	May be taken without regard to meals	Capsules can be opened carefully and mixed into 30 mL of yogurt or applesauce.
Tenofovir ⁴⁷	No information	No	May be taken without regard to meals	No pharmacokinetics studies performed on crushed versus whole tablet. Tablet lacks enteric coating or sustained-release mechanism and will disintegrate in water, grape juice, or orange juice. Drug is moisture sensitive and must be consumed immediately after mixing. Rinse container and consume rinse.
Zidovudine ^{13,29}	No (Even unopened, the capsule can cause esophageal irritation and ulceration)	50 mg/5 mL syrup (strawberry flavored) and 10 mg/mL injection solution	May be taken without regard to meals	

^aDelavirdine is rarely prescribed and is not recommended for initial therapy for HIV infection

(continued on next page)

Table 1. Current Antiretroviral Drug Formulations for the Management of Adult HIV Infection (continued)

Drug	Can Be Crushed or Sprinkled	Solution or Suspension Available	Food Considerations	Special Administration
Protease Inhibitors				
Atazanavir ^{12,30}	No	No	Absorption increases with food	
Darunavir ^{13,31}	No	No	Absorption increases with food	
Fosamprenavir ³²	No information	50 mg/mL solution (grape, bubblegum, or peppermint flavored)	Adult solution must be taken without food Pediatric solution must be taken with food	
Indinavir ³³	No information	No	Should be taken on an empty stomach, but with 48 ounces of water daily	
Lopinavir/ritonavir ^{11-13,34}	No	80 mg/mL or 20 mg/mL solutions	Solution should be taken with food	
Nelfinavir ³⁵	Yes	50 mg/g oral powder for suspension	Should be taken with food	May place whole or crushed tablets in small amount of water to disperse before ingestion, or mix crushed tablets in small amount of food. Once mixed, entire contents must be consumed within 6 hours to obtain the full dose. Entire contents should be consumed immediately after mixing. The drinking glass should be rinsed and each rinse swallowed completely to ensure entire dose is consumed. Acidic foods or juices (eg, orange juice, apple juice, or applesauce) are not recommended for mixing because the combination may have a bitter taste.
Ritonavir ^{12,36,37}	No	80 mg/mL solution (peppermint or caramel flavored)	Should be taken with food	
Saquinavir ³⁸	Yes	No	Take within 2 hours of a meal	Opening capsules is permissible for patients unable to swallow them. No clinical studies evaluate the safety or efficacy when administered as extemporaneous preparation. Capsules were the most palatable when contents were mixed with simple syrup or strawberry-flavored jelly or jam. Bioavailability as an extemporaneous preparation in simple syrup was similar to that of unopened capsules. When administered as extemporaneous preparation in jelly, jam, or baby formula, there was a 44%-60% increase in area under the curve and a 42%-48% increase in maximum plasma concentration over the unopened capsules.
Tipranavir ^{13,39}	No	100 mg/mL solution (butternut or butter-toffee flavored)	May be taken without regard to meals	

(continued on next page)

Table 1. Current Antiretroviral Drug Formulations for the Management of Adult HIV Infection (continued)

Drug	Can Be Crushed or Sprinkled	Solution or Suspension Available	Food Considerations	Special Administration
Integrase Strand-Transfer Inhibitor				
Raltegravir ^{12,40}	No	No	May be taken without regard to meals	
NNRTI-nRTI Combinations				
Efavirenz/emtricitabine/tenofovir ⁴¹	No (Efavirenz is water insoluble; manufacturer recommends not crushing for this reason)	No	Should be taken on an empty stomach	
Rilpivirine/emtricitabine/tenofovir ⁴²	No information	No	Should be taken with food	Need to be taken with a meal (>533 calories). Protein drinks should not replace a meal when taking this medication.
nRTI Combinations				
Abacavir/lamivudine ⁴³	No information (Individual drugs available in solution)	No	May be taken without regard to meals	
Abacavir/lamivudine/zidovudine ⁴⁴	No information (Individual drugs available in solution)	No	May be taken without regard to meals	
Emtricitabine/tenofovir ⁴⁵	No information	No	May be taken without regard to meals	No pharmacokinetics studies performed on crushed versus whole tablet. Tablet lacks enteric coating or sustained-release mechanism and will disintegrate in water, grape juice, or orange juice. Drug is moisture sensitive and must be consumed immediately after mixing. Rinse container and consume rinse.
Lamivudine/zidovudine ⁴⁶	No information (Individual drugs available in solution)	No	May be taken without regard to meals	No pharmacokinetics studies performed on crushed versus whole tablet. Tablet lacks enteric coating or sustained-release mechanism and will disintegrate in water, grape juice, or orange juice. Drug is moisture sensitive and must be consumed immediately after mixing. Rinse container and consume rinse.
Fusion Inhibitor^b				
Maraviroc ⁴⁸	No information	No	May be taken without regard to meals	

^bEnfuvirtide was not included in this table because it is administered subcutaneously and thus has virtually no bioavailability issues.⁴⁹

dence to support crushing or sprinkling of many of the available antiretroviral drugs. Further research needs to be conducted to determine more specific bioavailability data. These studies also need to identify cohorts of older persons to provide information on antiretroviral drug bioavailability in the aging population.

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References

- Centers for Disease Control and Prevention. HIV/AIDS surveillance report, 2005. Vol 17. Revised June 2007. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/pdf/2005SurveillanceReport.pdf>. Accessed August 12, 2011.
- Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med.* 1998;338:853-860.
- El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355:2283-2296.
- Law M, Friis-Møller N, Weber R, et al. Modelling the 3-year risk of myocardial infarction among participants in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study. *HIV Med.* 2003;4:1-10.

5. Hammer SM, Eron JJ, Jr., Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society–USA panel. *JAMA*. 2008;300:555-570.
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. Accessed June 22, 2011.
7. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society–USA panel. *JAMA*. 2010;304:321-333.
8. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1-166. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed June 16, 2011.
9. Fleishman JA, Gebo KA, Reilly ED, et al. Hospital and outpatient health services utilization among HIV-infected adults in care 2000-2002. *Med Care*. 2005;43 (Suppl 9):II140-II152.
10. Heelon M, Skiest D, Tereso G, et al. Effect of a clinical pharmacist's interventions on duration of antiretroviral-related errors in hospitalized patients. *Am J Health Syst Pharm*. 2007;64:2064-2068.
11. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. *Drug Information Handbook*. 18th ed. Hudson, OH: Lexi-Comp, Inc.; 2009.
12. *Clinical Pharmacology*. Tampa, FL: Elsevier/Gold Standard; 2006. <http://www.clinicalpharmacology.com>. Accessed August 12, 2011.
13. Facts & Comparisons. St. Louis, MO: Wolters Kluwer Health; 2010. <http://www.factsandcomparisons.com>. Accessed June 22, 2011.
14. Stone VE, Mansourati FF, Poses RM, Mayer KH. Relation of physician specialty and HIV/AIDS experience to choice of guideline-recommended antiretroviral therapy. *J Gen Intern Med*. 2001;16:360-368.
15. Rastegar DA, Knight AM, Monolakis JS. Antiretroviral medication errors among hospitalized patients with HIV infection. *Clin Infect Dis*. 2006;43:933-938.
16. Kiertiburanakul S, Sungkanuparph S. Emerging of HIV drug resistance: epidemiology, diagnosis, treatment and prevention. *Curr HIV Res*. 2009;7:273-278.
17. Lima VD, Harrigan R, Murray M, et al. Differential impact of adherence on long-term treatment response among naive HIV-infected individuals. *AIDS*. 2008;22:2371-2380.
18. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA*. 1999;282:1135-1141.
19. Delavirdine [package insert]. New York, NY: Pfizer Inc; 2008.
20. Efavirenz [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2010.
21. Etravirine [package insert]. Titusville, NJ: Tibotec Therapeutics; 2010.
22. Nevirapine [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2010.
23. Rilpivirine [package insert]. Titusville, NJ: Tibotec Pharmaceuticals; 2011.
24. Abacavir [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
25. Didanosine [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2010.
26. Emtricitabine [package insert]. Foster City, CA: Gilead Sciences, Inc; 2008.
27. Lamivudine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
28. Stavudine [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2009.
29. Zidovudine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2010.
30. Atazanavir [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2010.
31. Darunavir [package insert]. Titusville, NJ: Tibotec Therapeutics; 2010.
32. Fosamprenavir [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2010.
33. Indinavir [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2010.
34. Lopinavir/ritonavir [package insert]. Abbott Park, IL: Abbott Laboratories; 2010.
35. Nelfinavir [package insert]. La Jolla, CA: Agouron Pharmaceuticals, Inc; 2010.
36. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. February 23, 2009; 1-139. <http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>. Accessed June 22, 2011.
37. Ritonavir [package insert]. Abbott Park, IL: Abbott Laboratories; 2010.
38. Saquinavir [package insert]. South San Francisco, CA: Genentech, Inc; 2010.
39. Tipranavir [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2010.
40. Raltegravir [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2010.
41. Fixed-dose combination efavirenz/emtricitabine/tenofovir [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2010.
42. Fixed-dose combination rilpivirine/emtricitabine/tenofovir [package insert]. Foster City, CA: Gilead Sciences, Inc; 2011.
43. Fixed-dose combination abacavir/lamivudine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
44. Fixed dose combination abacavir/lamivudine/zidovudine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
45. Fixed-dose combination emtricitabine/tenofovir [package insert]. Foster City, CA: Gilead Sciences; 2009.
46. Fixed-dose combination lamivudine/zidovudine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
47. Tenofovir [package insert]. Foster City, CA: Gilead Sciences, Inc; 2010.
48. Maraviroc [package insert]. New York, NY: Pfizer Inc; 2009.
49. Enfuvirtide [package insert]. South San Francisco, CA: Roche Laboratories; 2011.

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