Perspectives

Hepatitis C Virus, Inflammation, and Cellular Aging: Turning Back Time
Susanna Naggie, MD

Management of Advanced Fibrosis in the Context of Hepatitis C Virus Infection
Elizabeth C. Verna, MD

Kidney Disease and HIV Infection
Christina M. Wyatt, MD

HIV Treatment and Prevention: An Overview of Recommendations From the 2016 IAS–USA Antiretroviral Guidelines Panel
Paul A. Volberding, MD
Topics in Antiviral Medicine™

Editorial Board

Douglas D. Richman, MD
Editor in Chief
Professor of Pathology and Medicine
University of California San Diego and
Veterans Affairs San Diego Healthcare System

Constance A. Benson, MD
Editor
Professor of Medicine
University of California San Diego

Martin S. Hirsch, MD
Editor
Professor of Medicine
Harvard Medical School

IAS–USA Board of Directors

Roy M. Gulick, MD, MPH
Professor of Medicine
Weill Cornell Medicine

Donna M. Jacobsen, MD
President/Executive Director
International Antiviral Society–USA

Jeanne M. Marrazzo, MD, MPH
Professor of Medicine
University of Alabama at Birmingham

Douglas D. Richman, MD
Professor of Pathology and Medicine
University of California San Diego and
Veterans Affairs San Diego Healthcare System

Michael S. Saag, MD
Professor of Medicine
University of Alabama at Birmingham

Robert T. Schooley, MD
Professor of Medicine
University of California San Diego

Paul A. Volberding, MD
Professor of Medicine
University of California San Francisco

Staff and Contributors

Donna M. Jacobsen - Executive Editor
Charlotte Knabel - Associate Editor
Rachel Lastra - Associate Editor
Carolina Patiño - Editorial Assistant
Whit Clifton - Layout/Graphics

Matthew Stenger - Medical Writer
Cristin M. Toth - Director, CME Programs
Michelle Valderama - Production and Web Manager
Jennezel Peneda - Production and Web Associate

Grant Support

IAS–USA funding comes from a variety of sources. The largest single source of revenue is conference and participant registration fees. This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers.

Locations:
IAS–USA
- San Francisco, CA 94104-2120
- USA
- Phone: (415) 544-9400
- Fax: (415) 544-9401
- E-mail: journal"at"iasusa.org
- Website: http://www.iasusa.org

Correspondence

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

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

Financial Disclosures

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

Copyrights and Reprints

The contents of Topics in Antiviral Medicine are protected by copyright. We welcome reference
to and use of portions of this journal, however, we do require that permission to reproduce or use any part of the journal be obtained from the IAS–USA. In the case of reprinted or adapted materials where the IAS–USA does not own the copyright, permission to reproduce these materials must be obtained directly from the original source. For more information about reprints, please send an e-mail to journal"at"iasusa.org.

Subscription Information

Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in your e-mail address, please create or update your user profile at www.iasusa.org.

On the Web

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

ISSN 2161-5853 (Online)

©2017 IAS–USA. All rights reserved
Perspectives

Hepatitis C Virus, Inflammation, and Cellular Aging: Turning Back Time  
Susanna Naggie, MD

Management of Advanced Fibrosis in the Context of Hepatitis C Virus Infection  
Elizabeth C. Verna, MD

Kidney Disease and HIV Infection  
Christina M. Wyatt, MD

HIV Treatment and Prevention: An Overview of Recommendations From the 2016 IAS–USA Antiretroviral Guidelines Panel  
Paul A. Volberding, MD

Announcements

Continuing Medical Education (CME) Information  
Upcoming Activities  
Guidelines for Authors and Contributors

Visit www.iasusa.org to complete the posttest and evaluation for this activity and claim CME credit. You can also change your e-mail address by updating your user profile online.
Topics in Antiviral Medicine

CME Information

The IAS–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians. The IAS–USA designates this enduring material for a maximum of 3.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is offered from March 30, 2017, to March 30, 2018. Participants who successfully complete the activity posttest and submit the evaluation and registration forms are eligible to receive CME credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Other health care practitioners will receive a certificate of participation.

- CME credits available: 3.25 AMA PRA Category 1 Credits™
- Release date: March 30, 2017
- Expiration date: March 30, 2018

To claim CME credit, please read each article and successfully complete the posttest and evaluation form, which will help us evaluate this activity and plan future activities. Your responses will not affect your CME credit. The posttest, evaluation, and CME claim form can be found online at www.iasusa.org.

Learning Objectives

On completion of this activity, participants will be able to:

- Identify patients with hepatitis C virus (HCV) and advanced fibrosis or cirrhosis
- Describe the impact of antiretroviral therapy on the risk of kidney disease.
- List the end-organ diseases that are associated with chronic HCV infection
- Use the updated antiretroviral guidelines from the IAS–USA, including options for initiating antiretroviral therapy in HIV-infected persons, as part of clinical decision-making

Intended Audience

This enduring material is designed for physicians and other health care practitioners who are actively involved in the medical care of people with HIV and HCV infection.

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

Disclosure of Financial Interests

In the interest of maintaining the independence of its CME activities, and in accordance with the policies of the Accreditation Council for Continuing Medical Education (ACCME), the IAS–USA requires all persons with control of content (ie, authors, IAS–USA Board members, and program staff) to disclose any financial relationships that they (or their spouses or partners) have had with commercial companies within the past 12 months. Any real or apparent conflicts of interest of those parties are resolved prior to the continuing medical education activity being delivered. Individuals who refuse to disclose financial interests may not participate in an IAS–USA CME activity.

Financial affiliations with commercial entities: Dr Naggie has received research support paid to her institution from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Tacere, and Merck. Dr Verna has received grants awarded to her institution from Salix Pharmaceuticals, Inc. Dr Volberding has served on data and safety monitoring boards for Merck. Dr Wyatt has no relevant financial affiliations to disclose.

Grant Support

IAS–USA funding comes from a variety of sources. The largest single source of revenue is conference and participant registration fees. This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants in part, by charitable contributions from commercial companies. Funds are pooled and distributed to activities at the sole discretion of IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers. Generous support for this activity has been received from the below contributors:

- PLATINUM SUPPORTER: ViiV Healthcare
- GOLD SUPPORTER: Gilead Sciences, Inc
- SILVER SUPPORTERS: Bristol-Myers Squibb, Janssen Therapeutics
- BRONZE SUPPORTERS: Merck

Drug and Product Disclaimer

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

The views and opinions expressed herein are those of faculty and do not necessarily represent the opinions or recommendations of IAS–USA.

Posttest

Visit www.iasusa.org to complete the posttest and evaluation for this activity and claim CME credit.
**Perspective**

**Hepatitis C Virus, Inflammation, and Cellular Aging: Turning Back Time**

There is evidence that hepatitis C virus (HCV) infection, like HIV infection, may be associated with chronic inflammation, immune activation, and immune senescence, which contribute to increased risks for cardiometabolic or other diseases outside the liver, as well as to ongoing damage in the liver. These effects may persist after a sustained virologic response (SVR) is achieved with HCV therapy. Such findings support initiation of treatment for HCV-infected individuals before damage to the liver is apparent and monitoring of individuals for complications even after an SVR is achieved. Fibrosis is not always reversible after SVR is achieved, and this should serve as an argument against waiting until fibrosis develops before initiating treatment for HCV-infected individuals. This article summarizes a presentation by Susanna Naggie, MD, MHS, at the IAS–USA continuing education program, Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes, in New York, New York, in September 2015.

**Keywords:** HCV, HIV, inflammation, immune activation, immune senescence, fibrosis, extrahepatic disease

Consider the case of a 37-year-old man who was diagnosed with HIV and hepatitis C virus (HCV) infections in the 1990s. He had a nadir CD4+ cell count of 9 cells/µL and presented with *Mycobacterium avium* complex and *Pneumocystis jiroveci* pneumonia. Since his HIV diagnosis, initiation of antiretroviral therapy, and treatment of his opportunistic infections, he has lived well with HIV disease. He was infected with HCV genotype 1b and had a plasma HCV RNA level of 1.2 million IU/mL on presentation. A liver biopsy in 2009, when he was 31 years of age, showed signs of cirrhosis, although he has no history of alcohol use or liver decompensation. He had portal hypertension with thrombocytopenia, splenomegaly, and portal gastropathy (at his last esophagogastroduodenoscopy in March 2014). He was immune to hepatitis A and B viruses by prior immunization.

The finding of cirrhosis at what should be a relatively early stage of HCV disease in a young man with no history of alcohol use is surprising and raises questions: What other end-organ diseases should be considered in an individual with chronic HCV? What does a sustained virologic response (SVR) mean in the context of the potential adverse effects of HCV infection? Are payers right to limit access to HCV therapy based on severity of liver disease alone?

In the natural history of HCV infection, age is an important factor in the progression of disease. A low percentage of individuals with chronic HCV infection diagnosed at 20 to 30 years of age will develop severe fibrosis and cirrhosis over the next 30 years. Individuals who acquire HCV infection at 50 to 60 years of age generally exhibit more rapid progression of disease. However, individuals who are coinfected with HIV often have accelerated liver disease, potentially part of a phenomenon that many have called “accelerated aging,” used to describe the high rates of death from non–AIDS-related conditions such as malignancies, cardiovascular disease, and liver disease than their age-, race-, and sex-matched HIV-uninfected counterparts. For example, data show that HIV/HCV-coinfected persons matched for other factors have a result of 9 kPa on transient elastography, consistent with severe fibrosis, approximately 9 years earlier than those with HCV monoinfection.

**Inflammation and Immune Activation in the Context of HCV Disease**

Among the factors associated with more rapid progression of fibrosis in the context of HCV disease, apart from alcohol use, are age, steatosis, obesity, and insulin resistance. Factors in HIV infection that may contribute to the progression of fibrosis include chronic inflammation, associated metabolic disorders, medication toxicity, viral coinfections, and microbial translocation. Individuals with uncontrolled HIV infection, for example, often have elevated levels of lipopolysaccharide, resulting in monocyte-macrophage activation peripherally, but also the potential of activating hepatic Kupffer and stellate cells. Also, HIV proteins may potentially bind to cell receptors on stellate and Kupffer cells, activating intracellular pathways of fibrogenesis. Whether HIV directly infects these cell types is controversial.

In addition, whether the presence of inflammation and immune activation results in accelerated aging in the liver of an HIV/HCV-coinfected individual is a subject of current investigation. The ability to cure HCV infection with interferon-free regimens should provide the opportunity to evaluate the effects on the host immune system after the virus has been cleared from the body.

The relationship between inflammation, immune activation, and immune senescence is illustrated in the Figure. Inflammation is a general process, measured by levels of markers such as cytokines, interleukin-6 (IL-6), tumor necrosis factor (TNF), and high-sensitivity C-reactive protein (hs-CRP) and can be present in many different diseases. Immune activation is more specific, representing activation of certain cellular pathways, such as in monocytes and T cells (present in HIV and HCV infections), and is measured by such markers as soluble CD14 (sCD14), CXCL10, and CD38. Immunosenesce-ence is the progressive deterioration of the immune system

Dr Naggie is Associate Professor of Medicine at Duke University in Durham, North Carolina.
with age; for T cells, this results from chronic activation and inflammation due to persistent antigen exposure. One of the main markers of immunosenescence is CD57, sometimes referred to as a marker of cellular aging. Increased levels of CD57 have been associated with many HIV-associated, non–AIDS-related conditions.

Tumor suppressor protein p16[INK4a] has been associated with normal aging outside the context of HIV or HCV infection. Individuals with uncontrolled HIV infection have very high levels of this marker, and as the virus is controlled with antiretroviral therapy, the marker returns to near normal levels in the blood. Of interest, this marker is a tumor suppressor and is predictive of risk for malignancy. It is not known if the return to baseline blood levels of tumor suppressor protein p16[INK4a] after full viral suppression with antiretroviral therapy correlates with levels in the liver or other tissues. This marker has not been studied in the setting of HCV infection or other liver diseases.

The Broad Effects of HCV Infection

Chronic HCV infection has been associated with many end-organ diseases including neurocognitive effects; atherosclerosis and cerebrovascular disease; insulin resistance, hyperglycemia, and diabetes; fibrosis and steatosis; and B-cell non–Hodgkin lymphoma (NHL) and hepatocellular carcinoma (HCC). These diseases have many similarities with those attributed to chronic inflammation and immune activation in the context of HIV infection. Whether the pathogenesis is the same for HIV and HCV infections or if there are parallel mechanisms at play in the case of HIV/HCV co-infection is not known at this time.

HCV as a Cardiometabolic Disease

There is considerable evidence that HCV infection is a metabolic disease. Numerous studies have reported an increased risk for metabolic disorders among individuals with HCV infection compared with uninfected counterparts, including insulin resistance (odds ratio [OR], 2.06), diabetes (OR, 2.31), and atherosclerotic disease (OR, 4.2). Prevalence of steatosis in HCV has been reported as high as 50%, and when controlled for known risk factors such as diabetes, alcohol use, and obesity, the prevalence remains 30% to 40%. However, some of these data have been recently challenged. In reanalyzed National Health and Nutrition Examination Survey data on diabetes from 1999 to 2010, the adjustment for elevations in levels of aspartate aminotransferase and alanine aminotransferase, which are considered attributable to steatosis, eliminated the increased risk for diabetes associated with HCV infection. However, higher markers of inflammation have been observed among HCV-infected individuals with elevated liver enzymes than among those without such elevations, suggesting a relationship between liver and systemic inflammation.

Markers of cardiometabolic diseases that are elevated in HIV- and HCV-infected individuals include markers of inflammation (IL-6, hs-CRP), hypercoagulable state (fibrinogen, dimerized plasmin fragment D), endovascular dysfunction and cell adhesion (soluble vascular cell adhesion molecule–1 [sVCAM-1]), N-terminal fragment of the prohormone brain natriuretic peptide [NT-proBNP]), and markers of T-cell activation and immune senescence (sCD14 and sCD163). These markers have been associated with increased risk of cardiovascular disease–associated mortality, acute myocardial infarction, all-cause mortality, and more generally with atherosclerotic disease, diabetes, and insulin resistance. More research is needed to conclusively identify and quantify risk for such outcomes among HCV-infected individuals before and after an SVR is achieved.

On a similar note, positive HCV serology is reportedly associated with higher all-cause mortality, although the reasons behind this remain unclear. There are data indicating that most deaths among HIV/HCV-coinfected individuals are attributable to non–liver-related events. For example, in the SMART (Strategies for Management of Antiretroviral Therapy) trial of HIV-infected individuals, liver-related events were not the main drivers of death among participants with viral hepatitis; yet, HIV/HCV-coinfected individuals contributed to the majority of the study’s primary events. This suggests that HIV/HCV-coinfected patients are at greater risk of non–liver-related disease than HIV-monoinfected patients. Therefore, the argument can be made that treatment of HCV infection has benefits outside the liver and that all individuals should have an opportunity to achieve HCV cure before cardiometabolic conditions emerge.

HCV Infection and Cancer

Cancer is now the leading cause of non–AIDS-related death in HIV-infected persons. In a study reported by Nyberg and colleagues, unadjusted analysis showed that HCV infection was associated with statistically significantly increased risks for esophageal, stomach, colorectal, liver, pancreas, lung, head and neck, renal, and prostate cancers, myeloma, and NHL compared with no HCV infection. After adjustment for alcohol use or dependence, smoking status, and diabetes,
these associations were no longer statistically significant except for HCC and NHL. Thus, whether the increased risk of cancer among HCV-infected individuals is driven by known traditional risk factors or whether there is a component of this risk attributable to immune activation and inflammation remains unclear.

**Immune Activation and Immune Senescence**

Sustained virologic response has been associated with impressive decreases in liver-related events, but its effects on risk for other diseases over the short and long term is not known. A knowledge gap remains about the overall risks associated with HCV infection beyond liver fibrosis; this will be important to understand if care and outcomes are to be optimized beyond virologic cure. Improved insight may come from investigations into chronic immune activation and immune senescence in the context of HCV infection.

In the liver, the stellate cell has a primary role in fibrogenesis. It is the resident pericyte in the liver; pericytes are pluripotent cells found throughout the body, including in the endovascular space, blood-brain barrier, kidney, and heart. Natural killer T cells are the primary immune cells in the liver. We are currently investigating markers of active inflammation, chronic immune activation, and cellular aging in liver tissue of HIV and HCV-infected individuals. The preliminary results suggest that T-cell markers are substantially increased stepwise from uninfected healthy controls to those with HCV monoinfection, HCV monoinfection, or HIV/HCV coinfection. Levels of natural killer T cell markers are also higher in HIV-monoinfected individuals than in uninfected controls and are higher in HCV-monoinfected individuals than in HIV-monoinfected individuals. Markers of immune senescence (CD57) also exhibited stepwise increases from uninfected controls to those with HIV monoinfection, HCV monoinfection, and HIV/HCV coinfection, with a similar pattern evident for the marker for aging (P16INK4a). Such findings raise numerous questions, including why these markers are elevated in the liver tissue of HIV-monoinfected individuals who are HIV virally suppressed and whether cellular senescence and cellular aging are reversible processes with HCV clearance.

In addition, we have explored the possibility that aberrant Hedgehog pathway signaling may be involved in the accelerated aging observed in HIV/HCV-coinfected individuals. This pathway, which is involved in fetal organ development, is activated during tissue injury and acts as a primary factor in the healing of skin, the epithelium, and organs. Numerous inhibitors of the Hedgehog pathway have been evaluated for treatment of cancers, and inhibitors of this pathway might be of value in treatment of HIV/HCV coinfection. In preliminary studies, we have found that markers of Hedgehog pathway signaling (the Shh ligand and transcription factor GLI2) are elevated in the liver tissue of individuals with HIV monoinfection and are more elevated in those with HCV monoinfection, and levels observed in those with HIV/HCV coinfection are similar to those observed in individuals with HCV monoinfection.

Whether aberrant Hedgehog pathway signaling drives HCV disease processes outside the liver has been studied in animal models. Pericytes are activated during injury to the kidney, endovascular space, brain, and liver, and exhibit increased levels of Hedgehog transcription markers. The pericytes then transform into myofibroblasts that contribute to fibrosis. Implications of the above research are that the Hedgehog pathway is active during HIV monoinfection, with additive effects in the context of HIV/HCV coinfection, and that HIV/HCV coinfection increases T-cell recruitment, terminal differentiation, and immunologic aging and senescence. Further study is needed to confirm these findings and assess whether this intrahepatic immunologic phenomenon is reversible.

**The Impact of SVR**

All-cause mortality is higher among HCV-infected individuals who do not achieve an SVR than those who do achieve an SVR. In addition, liver-related outcomes, including incident hepatocellular cancer, hepatic decompensation, and liver-related death, are lower in patients achieving SVR.

A study reported in 2008 that examined paired liver biopsies showed improvements in virtually all liver-related outcomes in 59 participants who had SVRs compared with 57 participants who did not have SVRs. However, liver cancer developed in 8% of participants who had an SVR. Although the follow-up period of the study was only 3 years, a minority of participants exhibited regression of cirrhosis (18 with regression vs 78 without regression), which was a better predictor of reduced liver-related outcomes than was SVR. For example, HCC was found in 22% of individuals who did not have regression of cirrhosis versus 0% of those who did (P = .036). Such findings reinforce the concept that cirrhosis is not as reversible in the context of HCV infection as may generally be thought. Reversal of cirrhosis in the context of HCV infection appears to be a slow process, different from that observed in hepatitis B virus infection, in which 50% of individuals have resolution or improvement of cirrhosis by 5 years after nucleoside analogue initiation. Waiting until patients are already at risk of cirrhosis before initiating HCV treatment sets them up for a process that cannot be completely reversed and likely puts them at considerable risk for major liver-related events.

With regard to the impact of SVR on extrahepatic diseases, there is evidence that SVR achieved via treatment with peginterferon alfa and ribavirin is associated with improvements in coronary artery disease, diabetes, and renal disease, and possible regression of B-cell NHL. Thus far, there are few data on the effects of an SVR achieved with direct-acting antiviral therapy on extrahepatic disease apart from potential regression of B-cell NHL and improvement of renal disease.

Based on considerations such as those discussed herein, 2 commonly held assumptions regarding HCV treatment are inaccurate: 1) that HCV is only a liver disease; and 2) that HCV-associated fibrosis is always reversible. That fibrosis is not always reversible after SVR is achieved should serve as a...
potent argument for not waiting until fibrosis develops before initiating treatment for HCV-infected individuals.

Presented by Dr Naggie in September 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Naggie in February 2017.

Financial affiliations in the past 12 months: Dr Naggie has received research support paid to her institution from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Tacere, and Merck.

References


Perspective

Management of Advanced Fibrosis in the Context of Hepatitis C Virus Infection

Advanced fibrosis may be present in a substantial proportion of individuals with asymptomatic, chronic hepatitis C virus (HCV) infection, including those who have been newly diagnosed. HCV treatment improves all-cause and liver-related mortality in individuals with advanced fibrosis, and there is some evidence that reversal of decompensated liver disease may occur in those with a sustained virologic response. HCV treatment is also crucial for individuals undergoing liver transplantation, as recurrent HCV infection posttransplantation is associated with accelerated fibrosis progression and increased risk of poor outcomes. This article summarizes a presentation by Elizabeth C. Verna, MD, at the IAS–USA continuing education program, Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes, held in New York, New York, in September 2015.

Keywords: HCV, hepatitis C virus, hepatitis C, fibrosis, sustained virologic response, SVR, cirrhosis, hepatocellular carcinoma, liver transplantation

Identifying Advanced Fibrosis

Currently, the most common methods for staging of fibrosis on liver biopsy specimens are the 4-point Metavir and 6-point Ishak scoring systems. A Metavir score of F4 and an Ishak score of 6 indicate cirrhosis; a Metavir score of F2 and an Ishak score of 3 or 4 indicate moderate fibrosis.

Data indicating that even moderate fibrosis may be associated with worse outcomes in the context of hepatitis C virus (HCV) infection come from the HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) trial, which examined the effect of maintenance therapy with peginterferon alfa among individuals with chronic HCV infection and fibrosis. The 6-year cumulative incidence of first clinical event was 5.6% for Ishak stage 2; 16.1% for Ishak stage 3; 19.3% for Ishak stage 4; 37.8% for Ishak stage 5; and 49.3% for Ishak stage 6.1,2

In a report evaluating a cohort of 4 large provider networks, biopsy results or Fibrosis-4 (FIB-4) scoring indicated fibrosis of Metavir stage F2 or higher in more than 50% of individuals without decompensated cirrhosis who were assessed for HCV treatment.3 Thus, it is common for some individuals presenting to care for the first time after HCV diagnosis to already have fibrosis even if they are asymptomatic and have laboratory values and physical examination findings within normal limits.

Numerous serologic tests have been developed to detect liver fibrosis, including the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4 scoring, and various serum biomarker tests. However, none of these tests is very sensitive or specific, when used alone, for differentiating degree of fibrosis; they can be useful in determining the absence of fibrosis or presence of cirrhosis but are less useful in diagnosing intermediate grades of fibrosis. These tests may be even less accurate for individuals who have very marked liver inflammation or certain types of liver disease that affect the markers used in different ways.

Staging of fibrosis using imaging technology is likely to become the standard of care in the coming years. At present, the most common imaging modality in the United States for staging of fibrosis is transient elastography, but other modalities include magnetic resonance elastography (MRE), shear wave elastography (SWE), and cross-sectional imaging. Transient elastography, a major advance in the staging of fibrosis, generally performs much better than serologic markers and makes it easier to follow the same individual’s response to different therapies over time; however, it is not perfect. The advantages of transient elastography are that it is increasingly available, inexpensive, fast, and predictive of clinical outcomes, and that it has been tested in the context of many disease stages. The disadvantages of transient elastography are that it is operator dependent and that imaging findings, as with all types of ultrasound imaging, may be skewed by factors such as an individual’s body habitus and the presence of extensive inflammation or extensive fatty infiltration of the liver. MRE may be more accurate but is much more expensive and less available at present than transient elastography. Conventional cross-sectional imaging and ultrasound are considered inadequate for accurate staging of fibrosis. Transient elastography values for each fibrosis stage are shown in Table 1.

A combination of serologic testing and imaging is likely the best option for staging of fibrosis at this time. Liver biopsy confirmed the findings of serum biomarker testing.

**Table 1. Transient Elastography Values for Each Metavir Fibrosis Stage in Individuals With Chronic Hepatitis C Virus–Related Liver Disease**

<table>
<thead>
<tr>
<th>Transient Elastography Value</th>
<th>Metavir Fibrosis Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-7.4 kPa</td>
<td>F0-F1 (no or mild fibrosis)</td>
</tr>
<tr>
<td>7.5-9.4 kPa</td>
<td>F2 (moderate fibrosis)</td>
</tr>
<tr>
<td>9.5-12.4 kPa</td>
<td>F3 (severe fibrosis)</td>
</tr>
<tr>
<td>&gt;12.4 kPa</td>
<td>F4 (cirrhosis)</td>
</tr>
</tbody>
</table>

Dr Verna is Assistant Professor of Medicine at Columbia University and Director of Clinical Research at the Center for Liver Disease and Transplantation in New York, New York.
Extended duration of treatment or the addition of ribavirin is recommended for many regimens and particularly for treatment-experienced individuals with HCV genotype 1 disease, and more changes are recommended based on HCV genotype subtype (1a vs 1b). Similarly, extended treatment and the addition of ribavirin are recommended for individuals with HCV genotype 2 or 3 disease and compensated cirrhosis.

An integrated analysis of phase II and III studies of treatment with ledipasvir/sofosbuvir (slash indicates a coformulation) with or without ribavirin for participants with HCV genotype 1 infection and compensated cirrhosis showed high rates of sustained virologic response (SVR). A somewhat lower SVR rate was observed among treatment-experienced participants who received only 12 weeks of ledipasvir/sofosbuvir without ribavirin. Findings in the integrated analysis indicated little difference in SVR rates according to method of determination of cirrhosis, transient elastography score, or albumin level. However, SVR rates were lower among treatment-naive and -experienced participants with platelet counts below $75 \times 10^3/\mu L$, suggesting that individuals with borderline decompensated cirrhosis may have been included in the studies and in the analysis.

Table 2. Recommended Changes to HCV Regimens for Treatment-Naive and -Experienced Persons With Compensated Cirrhosis, by Genotype

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Treatment-Naive Persons</th>
<th>Treatment-Experienced Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype 1</td>
<td>Daclatasvir plus sofosbuvir(^b)</td>
<td>Extend to 24 weeks with or without ribavirin</td>
</tr>
<tr>
<td></td>
<td>Elbasvir/grazoprevir(^c) for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Ledipasvir/sofosbuvir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/ritonavir/ombitasvir plus dasabuvir (with ribavirin for genotype 1a) for 12 weeks(^d)</td>
<td>Extend to 24 weeks for genotype 1a</td>
</tr>
<tr>
<td></td>
<td>Simeprevir plus sofosbuvir with or without ribavirin(^b)</td>
<td>Extend to 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir/velpatasvir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td>HCV genotype 2</td>
<td>Daclatasvir plus sofosbuvir(^b)</td>
<td>Extend to 16-24 weeks with or without ribavirin</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir/velpatasvir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td>HCV genotype 3</td>
<td>Daclatasvir plus sofosbuvir with or without ribavirin</td>
<td>Extend to 24 weeks with or without ribavirin</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir/velpatasvir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td>HCV genotype 4</td>
<td>Elbasvir/grazoprevir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Ledipasvir/sofosbuvir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir/velpatasvir for 12 weeks</td>
<td>No change</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus. Adapted from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.\(^5\)

\(^a\)Slash indicates a coformulation.
\(^b\)Regimen is recommended as an alternative.
\(^c\)For individuals with HCV genotype 1a infection, 12 weeks if there are no baseline resistance-associated variants and extend to 16 weeks if there are baseline resistance-associated variants.
\(^d\)This regimen is recommended for individuals with HCV genotype 1b infection and is an alternative regimen with ribavirin for individuals with HCV genotype 1a infection.

and transient elastography, used in combination, for 84% of individuals with fibrosis of Metavir stage F2 or higher, 95% of those with Metavir stage F3 or higher, and 94% of those with Metavir stage F4.\(^4\) Although there remains a role for liver biopsy, the era of routine liver biopsy to confirm that an individual does not yet require HCV treatment has yielded to an era in which liver biopsies are infrequent, reflecting the beliefs that all HCV-infected individuals should receive treatment and that the risks associated with biopsy should be avoided when possible. Liver biopsy still plays an important role when the findings of noninvasive tests are discrepant or when other forms of chronic liver disease are suspected.

Widely used prognostic models for individuals with cirrhosis include the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores. In general, both CTP and MELD scoring should be used to help determine the appropriateness and safety of HCV treatment and evaluation for liver transplantation.

HCV Treatment

Recommendations for changes in HCV treatment in individuals with compensated cirrhosis according to HCV genotype are shown in Table 2.\(^5\) Extended duration of treatment or the addition of ribavirin is recommended for many regimens and particularly for treatment-experienced individuals with HCV genotype 1 disease, and more changes are recommended based on HCV genotype subtype (1a vs 1b). Similarly, extended treatment and the addition of ribavirin are recommended for individuals with HCV genotype 2 or 3 disease and compensated cirrhosis.

An integrated analysis of phase II and III studies of treatment with ledipasvir/sofosbuvir (slash indicates a coformulation) with or without ribavirin for participants with HCV genotype 1 infection and compensated cirrhosis showed high rates of sustained virologic response (SVR)\(^6,7\) A somewhat lower SVR rate was observed among treatment-experienced participants who received only 12 weeks of ledipasvir/sofosbuvir without ribavirin. Findings in the integrated analysis indicated little difference in SVR rates according to method of determination of cirrhosis, transient elastography score, or albumin level. However, SVR rates were lower among treatment-naive and -experienced participants with platelet counts below $75 \times 10^3/\mu L$, suggesting that individuals with borderline decompensated cirrhosis may have been included in the studies and in the analysis.
For individuals with decompensated cirrhosis and CTP class B or C disease, hepatic impairment represents a contraindication to the use of some anti-HCV drugs, including simeprevir, paritaprevir (part of the regimen of paritaprevir/ritonavir/ombitasvir plus dasabuvir), and grazoprevir (part of the regimen of elbasvir/grazoprevir), owing to degree of hepatic metabolism and reports of liver injury. Current recommendations for HCV treatment for individuals with decompensated cirrhosis are shown in Table 3. Many of the recommended regimens include ribavirin, reflecting the goal of improving the chances for an SVR despite the potential worsening of anemia in some individuals. Some experts suggest initiating ribavirin at 600 mg (not weight based) and titrating the dose according to tolerability.

The best data on treatment with ledipasvir/sofosbuvir plus ribavirin for individuals with CTP class B or C disease come from the SOLAR-1 and SOLAR-2 studies (Figure 1). There was no marked difference in SVR rates with 12 or 24 weeks of treatment, and there was some suggestion of lower SVR rates among participants with CTP class C disease. The safety profile was quite favorable, particularly given the degree of illness in these participants. Adverse events of any grade included fatigue (41%), anemia (20%), and headache (27%), and grade 3 or 4 adverse events occurred in 24% of participants; 4% of participants discontinued due to adverse events. No deaths were considered to be related to the study drugs.

### Complications of Cirrhosis and Evaluation for Liver Transplantation

Complications of cirrhosis include HCC and complications of portal hypertension, such as variceal bleeding, encephalopathy, hepatorenal syndrome, and synthetic dysfunction. Such complications have a marked impact on disease prognosis and should prompt an evaluation for liver transplantation.

Screening is recommended for variceal bleeding and HCC for all individuals with cirrhosis, because early intervention can lead to better outcomes. An esophagogastroduodenoscopy (EGD) should be performed at the time of diagnosis of cirrhosis to screen for variceal bleeding, with surveillance interval depending on clinical status: EGD should be repeated every 2 to 3 years for individuals with compensated cirrhosis.

### Impact of SVR on Treatment Outcomes

Findings from several studies have made it clear that SVR in individuals with advanced fibrosis is associated with reduced risk of hepatic decompensation and death. In an analysis of 530 individuals with advanced fibrosis, SVR versus no SVR was associated with improvements in all-cause mortality (8.9% vs 26.0%), liver-related mortality or liver transplantation (1.9% vs 27.4%), hepatocellular carcinoma (HCC; 5.1% vs 21.8%), and liver failure (2.1% vs 29.9%). Whether hepatic decompensation can be transformed into “recompensation” after an SVR has been achieved has not been definitively determined. However, some data indicate that an SVR is associated with improvement in MELD or CTP score in many but not all individuals. Nevertheless, some individuals have progressive liver disease despite an SVR, and little is known about how to determine whose disease will or will not progress.

### Table 3. Recommended HCV Regimens for Persons With Decompensated Cirrhosis, by Genotype

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype 1 or 4</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir plus sofosbuvir plus ribavirin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>24 weeks (without ribavirin&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir plus ribavirin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>24 weeks (with ribavirin for prior failed treatment with sofosbuvir, or without ribavirin&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir plus ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>24 weeks (without ribavirin&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>HCV genotype 2 or 3</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir plus sofosbuvir plus ribavirin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir plus ribavirin</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus. Adapted from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.<sup>f</sup> Slash indicates a coformulation. Low-dose ribavirin starting at 600 mg daily and increased as tolerated. If riboflavin is ineligible.

---

**Figure 1.** Rates of sustained virologic response 12 weeks after cessation of treatment with coformulated (i) ledipasvir/sofosbuvir plus ribavirin among hepatitis C virus–infected participants with Child-Turcotte-Pugh (CTP) class B or C disease in the SOLAR-1 and SOLAR-2 studies. Efficacy was comparable between the 2 studies. Adapted from Charlton et al and Manns et al. 8,9
who have no varices, every 1 to 2 years if small varices are present, and annually for individuals with decompensated cirrhosis. Nonselective β-blockers or band ligation (for very large esophageal varices) may be used to substantially reduce the incidence of variceal hemorrhage. Individuals with HCV-related cirrhosis should be screened for HCC via ultrasound every 6 months, as there is evidence that screening for HCC in high-risk populations, including those with viral hepatitis infection, is associated with reduced mortality.\(^\text{11,12}\)

HCC can still occur in the context of an SVR. In some cases, HCC may be present but relatively undetectable before initiation of HCV treatment. Local-regional therapy for HCC is not considered to be curative, although some individuals who undergo chemoembolization do not appear to experience recurrence. Screening for HCC using α-fetoprotein (AFP) testing alone is no longer recommended, as it is not considered sensitive or specific enough and a substantial proportion of individuals with HCC have normal results on AFP testing. The current indications for liver transplantation in the context of HCV disease are the presence of cirrhosis or a MELD score of 15 or higher and any decompensating event (e.g., HCC, ascites, hepatic encephalopathy, variceal hemorrhage, or hepatopulmonary syndrome).

Treatment for HCV infection in liver transplant recipients is crucial because the natural history of recurrent HCV infection after transplantation is accelerated (cirrhosis occurs in up to 25% of individuals by 5 to 10 years after liver transplantation, and complications of cirrhosis are more common). SVR improves survival rates among liver transplant recipients. In an ideal world, all HCV-infected individuals would receive treatment and achieve an SVR before liver transplantation, eliminating the risk for recurrence. In reality, an SVR is not always achieved before liver transplantation, and response rates in individuals with CTP class C disease are lower than in other subgroups receiving HCV treatment, including those with compensated cirrhosis post-transplant.

Further, depending on the region of the United States, access to a new organ may be difficult for individuals in whom HCV treatment has cleared the virus (e.g., if MELD score drops from 27 to 18 after HCV treatment in an

### Table 4. HCV Regimens Post–Liver Transplantation* Including Patient With Recurrent Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended for HCV genotype 1 or 4</td>
<td>Daclatasvir plus sofosbuvir with or without ribavirin 12 weeks (with ribavirin) 24 weeks (without ribavirin)</td>
</tr>
<tr>
<td></td>
<td>Ledipasvir/sofosbuvir with or without ribavirin* 12 weeks (with ribavirin) 24 weeks (without ribavirin)</td>
</tr>
<tr>
<td>Alternatives for HCV genotype 1</td>
<td>Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin* 24 weeks</td>
</tr>
<tr>
<td></td>
<td>Simeprevir plus sofosbuvir with or without ribavirin 12 weeks</td>
</tr>
<tr>
<td>Recommended for HCV genotype 2 or 3</td>
<td>Daclatasvir plus sofosbuvir plus ribavirin 12 weeks (with ribavirin) 24 weeks (without ribavirin)</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir plus ribavirin* 24 weeks</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus. Adapted from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.\(^\text{5}\)

*Slash indicates a coformulation.

*Currently recommended for persons with HCV genotype 2 infection or decompensated recurrent liver disease.

*Only recommended for patients with early stage recurrent fibrosis (F0-2).
individual with decompensated cirrhosis, that individual may be ineligible for liver transplantation in some locations). Thus, communication with local transplant groups regarding individuals with a moderate MELD score but several disease complications in whom it is believed that HCV treatment will not achieve complete recompensation should be considered.

Data are now emerging on the use of perioperative treatment immediately before or after liver transplantation. A small phase II study examined treatment with sofosbuvir plus ribavirin given immediately before transplantation to individuals with any HCV genotype, HCC, and CTP class A or B disease. Among 43 evaluable participants, 65% achieved a postransplantation VR. However, perioperative treatment is not generally recommended at this time due to high relapse rates with sofosbuvir plus ribavirin in individuals with HCV genotype 1 infection. It is not known whether this approach would be more effective with currently recommended regimens. More recently, a small group of individuals was treated with ledipasvir/sofosbuvir in the immediate postoperative setting for only 4 weeks, and SVR was achieved in 14 of 16 individuals.

Important considerations regarding HCV treatment immediately after liver transplantation include potential drug-drug interactions with anti-HCV drugs, particularly between HCV protease inhibitors and calcineurin inhibitors (eg, cyclosporine, tacrolimus), and the potential need for treatment interruption due to complications in the setting of high-dose immunosuppression. Most experience with HCV treatment in the posttransplantation setting is with ledipasvir/sofosbuvir plus ribavirin (in part because of the lower likelihood of drug interactions than with other HCV regimens). Data from the SOLAR-1 and SOLAR-2 studies among participants with HCV genotype 1 or 4 infection show that HCV treatment during the early period after liver transplantation produced high SVR rates 12 weeks after cessation of treatment (SVR12) in those with CTP class A or B disease (Figure 2); although rates were lower in those with CTP class C disease, SVR was still achieved in the majority of participants. Current recommendations for HCV treatment after liver transplantation are shown in Table 4.

**Conclusion**

Individuals with advanced fibrosis and liver transplant recipients are among those with the highest priority for HCV treatment owing to their high risk for severe complications. SVR among individuals with advanced liver disease may reduce the risk of life-threatening decompensation. However, even individuals with cirrhosis and preserved liver function remain at risk for decompensation and must be monitored indefinitely. Safe and effective HCV treatment with direct-acting antiviral drugs has revolutionized the care of liver transplantation candidates and recipients with HCV infection, although treatment must currently be individualized based on stage of disease, comorbidities, and access to a liver allograft.

*Presented by Dr Verna in September 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Verna in February 2017.*

**Financial affiliations in the past 12 months:** Dr Verna has received grants awarded to her institution from Salix Pharmaceuticals, Inc.

**References**

UPCOMING ACTIVITIES

Spring and Summer 2017

**Interactive Webinars With IAS–USA Faculty**

*Live, interactive continuing medical education (CME) in the comfort of your home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for more on past and upcoming webinars. Upcoming webinars include:*

- **Hepatology for the Nonhepatologist—April 6, 2017**
  Presenter: Alexander Monto, MD, University of California San Francisco

- **Neurology and HIV Infection—April 18, 2017**
  Presenter: Serena S. Spudich, MD, Yale University

- **Update From EASL 2017—May 4, 2017**
  Presenter: David L. Wyles, MD, Denver Health

- **Contemporary Issues in Antiretroviral Therapy—June 20, 2017**
  Presenter: Joel E. Gallant, MD, MPH, Southwest CARE Center

- **Next Generation Hepatitis C Virus Infection: Regimens and Their Role in the Clinic—June 29, 2017**
  Presenter: Susanna Naggie, MD, MHS, Duke University

- **Finding and Eliminating the HIV Reservoir—September 7, 2017**
  Presenter: Daniel C. Douek, MD, PhD

- **Practical Management for Transgender Patients at Risk for HIV Infection—October 24, 2017**
  Presenter: Tonia C. Poteat, PhD, PA, The Johns Hopkins University

**IAS–USA Live Courses**

*Full-day and half-day CME courses and workshops continue to focus on cutting-edge, scientifically rigorous issues presented by leading experts in the fields of HIV and hepatitis C virus (HCV) medicine. Visit the IAS–USA website for updated information on live CME activities. This spring, the 25th annual IAS–USA live activities focusing on the management of HIV infection will be held in the following cities:*

- **Los Angeles, California, Full-Day HIV Course—Friday, April 28, 2017**
- **Chicago, Illinois, Full-Day HIV Course—Wednesday, May 10, 2017**
- **Washington, DC, Full-Day HIV Course—Monday, May 22, 2017**
- **Berkeley, California, Full-Day HIV Course—Thursday, May 25, 2017**

**Cases on the Web**

*A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for more information. Here’s the latest:*

**New**

- **Initial Antiretroviral Therapy in the HIV-Infected Patient**
  Authors: Jameela J. Yusuff, MD, MPH, FACP, State University of New York; Katharine Kuntz, MD, State University of New York. Released March 6, 2017.

**Coming Soon**

- **Immunizations for HIV-Infected Persons**
  Authors: Brian T. Montague, DO, MS, MPH, University of Colorado; Steven C. Johnson, MD, University of Colorado

Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for e-mail updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities. Early registration for live courses is strongly recommended.

These activities have been approved for AMA PRA Category 1 Credit™. The American Board of Internal Medicine (ABIM) Maintenance of Certification (MOC) program will offer points to participants at live IAS–USA activities in 2017.
Kidney Disease and HIV Infection

The risk of acute and chronic kidney disease remains higher in HIV-infected persons than in the general population, and kidney disease in HIV-infected persons is associated with poor outcomes, including increased mortality. HIV-associated nephropathy occurs less frequently in the era of antiretroviral therapy. HIV immune complex kidney disease is being diagnosed more frequently, but the term is currently used to refer to a heterogeneous group of kidney diseases. Comorbid chronic kidney disease poses a growing burden in HIV-infected persons due to an overrepresentation of risk factors such as black race, diabetes, hypertension, and coinfection with hepatitis C virus. Drug-induced kidney toxicity also remains a concern. This article summarizes a presentation by Christina M. Wyatt, MD, at the Ryan White HIV/AIDS Program Clinical Care Conference held in New Orleans, Louisiana, in December 2015.

Keywords: HIV, acute kidney injury, comorbid kidney disease, chronic kidney disease, diabetes, tenofovir, hepatitis C virus

Kidney disease in HIV-infected persons manifests in a variety of ways, including acute kidney injury (AKI), HIV-associated kidney disease, comorbid chronic kidney disease (CKD), and treatment-related kidney toxicity. The burden of CKD and end-stage renal disease (ESRD) remains high in the HIV-infected population.

There are several important caveats to consider when diagnosing and managing kidney disease in HIV-infected persons. Glomerular filtration rate (GFR) estimates are not well validated in this population. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which incorporates serum creatinine level and demographic factors, appears to provide the most accurate estimates among HIV-infected persons who are stable on antiretroviral therapy. However, there are strengths and limitations for all currently used equations, and creatinine clearance by Cockcroft-Gault calculation remains the recommended kidney function estimate for drug dosing. Several antiretroviral and other medications (eg, dolutegravir, rilpivirine, trimethoprim, and the pharmacoenhancers cobicistat and ritonavir) can interfere with creatinine secretion without affecting true GFR. In addition, creatine supplements and diets high in animal protein can increase levels of serum creatinine, resulting in an inaccurate estimate of GFR. Cystatin C testing may be helpful in such situations but should be used with caution in patients with HIV infection. Although normal cystatin C test results can be reassuring, abnormal cystatin C test results could reflect a decrease in GFR or an increase in systemic inflammation.1-3

Dr Wyatt is Associate Professor of Medicine and Nephrology at Icahn School of Medicine at Mount Sinai in New York, New York.
HIV-Associated Kidney Disease

HIV-associated nephropathy (HIVAN) was the first kidney disease described in HIV-infected persons but is now infrequently encountered in populations with access to antiretroviral therapy. It is most commonly seen in persons who are newly diagnosed with late-stage HIV infection or in those who have discontinued antiretroviral therapy, and it may present as AKI or CKD. In addition to HIVAN, the spectrum of HIV-associated kidney disease includes HIV immune complex kidney disease (HIVICK) and, less commonly, thrombotic microangiopathy.

HIVAN is classically associated with rapid progression to ESRD, occurs in advanced HIV disease, and is observed almost exclusively in persons of African descent, who account for approximately 90% of HIVAN-related cases of ESRD. HIVAN has a distinct histology, representing a collapsing form of focal segmental glomerulosclerosis (FSGS). The pathogenesis of HIVAN requires local HIV infection of the kidney, with the virus infecting tubular and glomerular epithelial cells. Along with local infection of the kidney, systemic HIV infection and systemic immune dysfunction may also contribute to disease pathogenesis. The strong racial disparity in HIVAN and associated ESRD is related to polymorphisms in the APOL1 gene, a gene on chromosome 22 that encodes apolipoprotein 1 and is associated with susceptibility to trypanosomiasis. Antiretroviral therapy is the recommended initial treatment for HIVAN, and there is some evidence of benefit with adjunctive therapies including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and corticosteroids. Most experts would limit the use of corticosteroids to patients with progressive disease despite antiretroviral therapy.

HIVICK has not been as well studied, in part because the term has been used to refer to a broad spectrum of heterogeneous glomerular diseases. The causal relationship between HIV infection and HIVICK is less clear than for HIVAN, and whether antiretroviral therapy can reverse or delay the progression of HIVICK is also unclear.

Comorbid Kidney Disease

Although there has been a decrease in the incidence of HIVAN, comorbid CKD is a growing burden in the HIV-infected population. Traditional risk factors for CKD, including black race, diabetes, hypertension, and coinfection with HCV, are overrepresented in this population, making it difficult to distinguish the contribution of HIV infection. In a study by Medapalli and colleagues, HIV infection and diabetes had an additive effect on risk for CKD progression (Figure 2). Data from animal studies suggest that this may be related to synergistic inflammatory pathways upregulated by diabetes and HIV infection.

HCV infection is also associated with increased risk of kidney disease in HIV/HCV-coinfected persons. Whether injection drug use or other risk factors for HIV and HCV infections contribute to the increased risk of kidney disease has not been determined. Some studies have found an association between increased risk for kidney disease and HCV viremia and others have not: 2 secondary analyses of HIV treatment trials identified a strong association between HCV viremia and increased risk for CKD, whereas HCV infection was associated with an increased risk of CKD regardless of HCV RNA level in data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Although improvements in kidney disease have been observed in some HIV/HCV-coinfected persons receiving HCV treatment, the impact of more widespread treatment of HCV infection on CKD risk in HIV/HCV-coinfected persons remains unclear. As discussed below, practitioners should be aware of potential drug-drug interactions between direct-acting antiviral drugs and antiretroviral therapy when treating these patients.

Figure 2. Additive effect of HIV infection and diabetes on progression of chronic kidney disease. Adapted from Medapalli et al.9

Treatment-Related Kidney Toxicity

The antiretroviral drugs most strongly implicated in kidney injury are protease inhibitors (in particular indinavir and atazanavir) and tenofovir disoproxil fumarate (TDF). Practitioners still report cases of CKD resulting from prior use of indinavir, although this drug is rarely used any longer. These individuals may present with scarring from chronic interstitial nephritis or obstructive nephropathy, posing increased risk for future comorbid CKD or treatment-related kidney toxicity. Although indinavir is the most strongly linked to interstitial nephritis and nephrolithiasis, all protease inhibitors are poorly soluble in urine, resulting in crystalluria that can promote renal inflammation or stone formation. The risk of nephrolithiasis may be higher with atazanavir than with other commonly used protease inhibitors, and this drug has also been associated with decreased GFR in observational studies.

TDF-related kidney toxicity is generally a clinical diagnosis. A biopsy is not necessary for a person who is taking tenofovir who presents with typical tubular injury with hypophosphatemia, glycosuria, proteinuria, and an elevated creatinine level. If alternative therapy is available, the recommendation is
to discontinue TDF. A biopsy to confirm TDF-related kidney toxicity is warranted in cases in which there are atypical presentations or comorbidities or in which antiretroviral therapy options are limited.

In addition to being associated with proximal tubular dysfunction, TDF may also be associated with a decrease in creatinine clearance or GFR. In randomized and cohort studies, declines in creatinine clearance were greater with TDF-containing regimens than with regimens that did not contain TDF. In a study in the US Veterans Affairs population, the hazard ratio for developing an estimated GFR below 60 mL/min/1.73 m² when taking a TDF-containing regimen was statistically significant for all subgroups except for persons with preexisting CKD or diabetes, conditions which are likely stronger determinants of developing a low GFR. In addition to TDF, the pro tease inhibitors indinavir, atazanavir, and ritonavir-boosted lopinavir have been associated with CKD risk that increases with cumulative exposure. This increased risk has not been observed with other boosted protease inhibitors or with abacavir.

Drug-drug interactions may also increase the risk of TDF-related kidney toxicity by increasing exposure to tenofovir. In particular, the pharmacoenhancers ritonavir and cobicistat are both known to increase plasma concentrations of tenofovir. Vigilance is also warranted when using TDF with newer treatments for HCV infection. Tenofovir levels have been shown to increase when TDF is used concurrently with coformulated (r) ledipasvir/sofosbuvir with or without a ritonavir-boosted protease inhibitor.

In addition to the risk in HIV-infected persons, much remains to be learned about the potential for cumulative kidney toxicity in HIV-seronegative persons taking a TDF-containing regimen long term as HIV preexposure prophylaxis; available evidence suggests a small but statistically significant decrease in creatinine clearance or GFR but an absence of overt kidney toxicity.

The newer prodrug tenofovir alafenamide (TAF) may reduce the risk of kidney toxicity compared with TDF. TAF results in lower plasma concentrations of tenofovir than TDF, which is anticipated to result in a lower risk of exposure-dependent kidney and bone toxicities. Premarking clinical trials have demonstrated a favorable effect of TAF versus TDF on biomarkers of subclinical kidney injury or proximal tubular dysfunction, although adverse clinical events were very rare regardless of treatment assignment. In a small open-label study among individuals with creatinine clearance of 30 to 69 mL/min who were switched to a TAF-containing regimen, similar improvements in urine biomarkers were observed among those whose initial regimen included TDF. Two participants in the study discontinued TAF during the follow-up period because of decreased creatinine clearance, although both had traditional risk factors for progressive kidney disease. Because tenofovir levels are increased following TAF administration in the setting of decreased GFR, individuals in this setting should be monitored for potential drug-related kidney toxicity until ongoing studies confirm the safety of long-term use in this population. The safety of TAF in individuals with a prior history of TDF-related kidney toxicity has not been studied.

Management of ESRD in HIV-Infected Persons

Persons with well-controlled HIV infection and ESRD are candidates for both hemodialysis and peritoneal dialysis and should be evaluated for kidney transplantation. Early discussion and planning is important so that use of hemodialysis catheters can be avoided, as HIV-infected persons are at similar, if not higher, risk for infection and other complications related to catheter use. HIV-infected kidney transplant recipients are at risk for substantial drug-drug interactions, and any change in antiretroviral therapy should be communicated to the transplant team immediately. Based on promising data from South Africa, an ongoing US study will evaluate the safety of kidney transplantation from HIV-infected donors to HIV-infected recipients. If successful, this approach could reduce the wait time for kidney transplantation for HIV-infected persons, which may exceed 5 years in some urban areas.

Presented by Dr Wyatt in December 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Wyatt in February 2017.

Financial affiliations in the past 12 months: Dr Wyatt has no relevant financial affiliations to disclose.

References


**Perspective**

**HIV Treatment and Prevention: An Overview of Recommendations From the 2016 IAS–USA Antiretroviral Guidelines Panel**

Updated recommendations from the IAS–USA Antiretroviral Guidelines Panel on antiretroviral therapy for the treatment and prevention of HIV infection in adults were published in the *Journal of the American Medical Association* in 2016. The updated, evidence-based recommendations address when to initiate antiretroviral therapy, recommended initial antiretroviral regimens, including integrase strand transfer inhibitor (InSTI)-based regimens, recommended regimens for persons in whom an InSTI is not an option, and special treatment considerations. The interface between antiretroviral therapy and opportunistic infections, and when and how to switch antiretroviral therapy, laboratory monitoring, engagement in care, adherence to antiretroviral therapy, and use of antiretroviral therapy as HIV prevention are also discussed, as well as future directions in HIV treatment. This article summarizes an IAS–USA continuing education webinar presented by Paul A. Volberding, MD, in August 2016.

**Keywords:** HIV, antiretroviral therapy, recommendations, initial antiretroviral regimens, opportunistic infections, switching antiretroviral therapy, prevention

[Updated recommendations from the IAS–USA Antiretroviral Guidelines Panel on antiretroviral therapy for the treatment and prevention of HIV infection in adults were published in the *Journal of the American Medical Association* in 2016. The updated, evidence-based recommendations address when to initiate antiretroviral therapy, recommended initial antiretroviral regimens, including integrase strand transfer inhibitor (InSTI)-based regimens, recommended regimens for persons in whom an InSTI is not an option, and special treatment considerations. The interface between antiretroviral therapy and opportunistic infections, and when and how to switch antiretroviral therapy, laboratory monitoring, engagement in care, adherence to antiretroviral therapy, and use of antiretroviral therapy as HIV prevention are also discussed, as well as future directions in HIV treatment. This article summarizes an IAS–USA continuing education webinar presented by Paul A. Volberding, MD, in August 2016.]

Updated recommendations from the IAS–USA Antiretroviral Guidelines Panel on antiretroviral therapy for the treatment and prevention of HIV infection in adults were published in the *Journal of the American Medical Association* in 2016. The recommendations were updated based on data supporting that all HIV-infected persons should receive antiretroviral therapy regardless of CD4+ cell count, new data on antiretroviral approaches for the treatment and prevention of HIV infection, and data on investigational uses of antiretroviral drugs. The 2016 recommendations include updated options for initial antiretroviral therapy, guidance for switching antiretroviral therapy in persons who achieve virologic suppression, recommendations for improving retention in care and adherence to treatment, and discussion of future directions in HIV treatment and prevention. Table 1 provides the rating system for the strength of the recommendations and the quality of evidence supporting these recommendations. The full text of the article is available at no charge at www.jamanetwork.com.

Dr Volberding is Professor of Medicine, Co-Director of the University of California San Francisco–Gladstone Center for AIDS Research, Director of the AIDS Research Institute, Director of Research in the Division of Global Health Sciences at University of California San Francisco, and Founding Volunteer Chairperson of the IAS–USA.

**When to Initiate Antiretroviral Therapy**

Recommendations regarding when to initiate antiretroviral therapy are shown in Box 1. Initiation of antiretroviral therapy is recommended for all HIV-infected persons with detectable viremia, regardless of CD4+ cell count; persons with acute HIV infection in whom antiretroviral therapy should be initiated as soon as possible; and persons who have persistently undetectable viral loads without antiretroviral therapy (“elite controllers”) but who have declining CD4+ cell counts.

Planned discontinuation of early antiretroviral therapy after a specific duration of treatment is not recommended outside of a research setting. There is renewed interest in cure research using analytic treatment interruptions. However, planned discontinuation of antiretroviral treatment should only occur in the setting of a research trial in which individuals are closely monitored for viral relapse and promptly retreated.

**Recommended Initial Antiretroviral Regimens**

The recommended initial antiretroviral treatment is an integrase strand transfer inhibitor (InSTI) plus 2 nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs). InSTIs may

**Table 1. Ratings for Strength of Recommendation and Quality of Evidence**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Strength of recommendation</strong></td>
</tr>
<tr>
<td>A</td>
<td>Strong support for the recommendation</td>
</tr>
<tr>
<td>B</td>
<td>Moderate support for the recommendation</td>
</tr>
<tr>
<td>C</td>
<td>Limited support for the recommendation</td>
</tr>
<tr>
<td></td>
<td><strong>Quality of evidence</strong></td>
</tr>
<tr>
<td>Ia</td>
<td>Evidence from 1 or more randomized clinical trials published in the peer-reviewed literature</td>
</tr>
<tr>
<td>Iib</td>
<td>Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature</td>
</tr>
<tr>
<td>III</td>
<td>Recommendation based on the panel’s analysis of the accumulated available evidence</td>
</tr>
</tbody>
</table>

Adapted in part from Canadian Task Force on Periodic Health Examination.9

---

9 Adapted in part from Canadian Task Force on Periodic Health Examination.
on the use of raltegravir and tenofovir alafenamide (TAF) are limited). InSTIs have a lower risk for drug-drug interactions than other classes of antiretroviral drugs. Of note, dolutegravir is associated with low risk for resistance with virologic failure compared with the other 2 drugs in this class with or without the need for boosting, which is required for elvitegravir. In sum, current data support the use of InSTIs as part of initial antiretroviral therapy.

Recommended non–InSTI-containing initial antiretroviral regimens are darunavir (boosted with cobicistat or ritonavir) plus TAF/emtricitabine (slash indicates a coformulation), tenofovir disoproxil fumarate (TDF)/emtricitabine, or abacavir/lamivudine; efavirenz/TDF/emtricitabine; or rilpivirine plus TAF/emtricitabine or TDF/emtricitabine. It is likely that many HIV-infected individuals are taking these regimens at present. Advantages and disadvantages of these regimens are shown in Table 3.

Table 4 shows recommended initial regimens in the setting of special considerations: pregnancy, HIV/hepatitis B virus (HBV) coinfection, HIV/hepatitis C virus (HCV) coinfection, osteopenia or osteoporosis, and kidney disease. Some treatment recommendations for HIV-infected pregnant women, such as that for use of the InSTI raltegravir, reflect more clinical experience. TDF, TAF, lamivudine, or emtricitabine, which have activity against HBV infection, should not be discontinued.

Table 2. Recommended Initial InSTI-Containing Regimens

<table>
<thead>
<tr>
<th>InSTI-Containing Regimens</th>
<th>Evidence Rating</th>
<th>Advantages of InSTI</th>
<th>Disadvantages of InSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir/abacavir/ lamivudine</td>
<td>Ala</td>
<td>Superior to efavirenz and ritonavir-boosted darunavir in comparative clinical trials</td>
<td>Only available coformulation is with abacavir/lamivudine</td>
</tr>
<tr>
<td>Dolutegravir plus TAF/ emtricitabine or TDF/ emtricitabine</td>
<td></td>
<td>Once-daily dosing</td>
<td>Raises serum creatinine level owing to inhibition of tubular secretion of creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dolutegravir (not coformulated) pill size is small</td>
<td>Higher rates of insomnia and headache than comparators in some studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lowest risk of resistance with virologic failure</td>
<td>Largest tablet among coformulated single-pill regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relatively few drug interactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be taken with or without food</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior to raltegravir in treatment-experienced persons</td>
<td></td>
</tr>
</tbody>
</table>

Elvitegravir:  
Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine | Ala | Superior to ritonavir-boosted atazanavir in comparative clinical trial of HIV-infected women | Requires pharmacokinetic boosting with cobicistat or ritonavir for once-daily dosing |
|             |                 | Once-daily dosing | Most drug interactions |
|             |                 |                  | Cobicistat raises serum creatinine level owing to inhibition of tubular secretion of creatinine |
|             |                 |                  | Should be taken with food |

Raltegravir:  
Raltegravir plus TAF/ emtricitabine | AllI | Superior to ritonavir-boosted atazanavir and ritonavir-boosted darunavir in a comparative clinical trial | Currently must be taken twice daily |
|             |                 | Longest safety record | Not coformulated as part of a complete regimen |
|             |                 | Fewest drug interactions |                        |
|             |                 | Can be taken with or without food |                        |

Abbreviations: InSTI, integrase strand transfer inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.1

Slashes indicate a coformulation.

Formulation consisting of 2 pills given once daily is in development.

be unavailable in some resource-limited settings; however, they are likely to become more available in the near future.

The 3 main currently available InSTIs are dolutegravir, elvitegravir, and raltegravir, and other InSTIs are in development (Table 2). Data on these InSTIs vary (eg, prospective data on the use of raltegravir and tenofovir alafenamide [TAF] are limited). InSTIs have a lower risk for drug-drug interactions than other classes of antiretroviral drugs. Of note, dolutegravir is associated with low risk for resistance with virologic failure compared with the other 2 drugs in this class without the need for boosting, which is required for elvitegravir. In sum, current data support the use of InSTIs as part of initial antiretroviral therapy.

Box 1. Recommendations for When to Initiate Antiretroviral Therapy

Initiation of antiretroviral therapy is recommended for:

- All HIV-infected persons with detectable viremia, regardless of CD4+ cell count (Ala)
- Persons with acute HIV infection. Antiretroviral therapy should be initiated as soon as possible (BIII)
- Persons with persistent undetectable viral load without antiretroviral therapy (“elite controllers”) but who have declining CD4+ cell counts (BIII)

Planned discontinuation of early antiretroviral therapy after a specific duration of treatment is not recommended outside of a research setting (Ala)

Adapted from Günthard et al.1

Baseline resistance testing is recommended for all persons, but initiating therapy prior to availability of the results may be appropriate in some cases.
Entecavir may be considered as a treatment option for HIV/HBV-coinfected persons, although it can select for lamivudine- and emtricitabine-resistant HIV and should not be used if virus is not suppressed. The recommendations list the antiretroviral drugs that have the fewest interactions with current HCV direct-acting antiviral drugs. However, the field of HCV treatment is changing rapidly, with regular introduction of new HCV drugs, and HCV treatment guidelines should be consulted frequently for updated information.

Other special considerations include treatment for HIV-infected persons with known osteopenia or osteoporosis. TDF should be avoided in the setting of osteopenia or osteoporosis; there is evolving evidence that other nRTIs, including abacavir and TAF, may be used instead. Kidney disease also poses a challenge due to renal adverse effects associated with some antiretroviral treatments. The recommendations discuss various options for antiretroviral treatment depending on the degree of underlying renal impairment.

### Interface Between Antiretroviral Therapy and Opportunistic Infections

Discussion of the interface between antiretroviral therapy and opportunistic infections (OIs) is important because OIs are far less common in many settings and warrant the revisiting of treatment principles, and because they remain common in some resource-limited settings. Recommendations

### Box 2. Recommendations for the Interface Between Antiretroviral Therapy and Opportunistic Infections

- Initiate antiretroviral therapy within the first 2 weeks after diagnosis for most acute opportunistic infections, with possible exception of acute cryptococcal meningitis (Aa)
- Initiate antiretroviral therapy within the first 2 weeks of initiation of tuberculosis treatment for persons with CD4+ cell counts of 50/μL and within the first 2 to 8 weeks for those with CD4+ cell counts above 50/μL (Aa)
- Avoid using TAF or cobicistat-boosted elvitegravir with rifamycins (AIIb)
- Boosted protease inhibitor (PI)-based regimens should only be used if an InSTI is not an option, and rifabutin 150 mg daily should be substituted for rifampin in the anti-TB regimen (Aa)
- Primary MAC prophylaxis is not recommended if effective antiretroviral therapy is initiated immediately (AIIa)
- Primary PCP prophylaxis is still recommended for those who meet CD4+ cell count criteria (AIIa)

Abbreviations: MAC, Mycobacterium avium complex; PCP, Pneumocystis jiroveci pneumonia; PI, protease inhibitor; TB, tuberculosis. Adapted from Günthard et al.1
regarding the interface between antiretroviral therapy and OIs are shown in Box 2.

Antiretroviral therapy should be initiated within 2 weeks of diagnosis for most acute OIs. A possible exception is acute cryptococcal meningitis, as initiating HIV treatment too soon in this setting may result in immune reconstitution inflammatory syndrome, which can cause considerable challenges given the compressed space of the central nervous system. Although there has been much debate, it is recommended that antiretroviral therapy be initiated within the first 2 weeks of initiating tuberculosis (TB) treatment for HIV-infected persons with CD4+ cell counts below 50/µL and

Table 4. Recommended Initial Antiretroviral Regimens: Special Considerations

<table>
<thead>
<tr>
<th>Special Consideration</th>
<th>Evidence Rating</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Ala</td>
<td>Abacavir/lamivudine (if HLA-B*5701 negative), TDF/emtricitabine, or zidovudine/lamivudine. Raltegravir is the recommended InSTI. Recommended boosted PIs include atazanavir/ritonavir (once daily) or darunavir/ritonavir (twice daily). Efavirenz is the recommended NNRTI when initiated after the first 8 weeks of pregnancy.</td>
<td>Initiate antiretroviral therapy for the woman’s own health and to reduce likelihood of mother-to-child transmission of HIV (Ala)</td>
</tr>
<tr>
<td>HBV coinfection</td>
<td>Ala</td>
<td>Initiate recommended antiretroviral therapy regimen that contain TDF or TAF, lamivudine or emtricitabine, and a third component</td>
<td>High risk of HBV resistance and viral breakthrough if lamivudine or emtricitabine are used without TDF or TAF, and neither is recommended alone for HBV coinfection.</td>
</tr>
<tr>
<td>HBV coinfection</td>
<td>Alll</td>
<td>Entecavir may be used but should be avoided if HIV RNA is not suppressed</td>
<td>Entecavir may be used but should be avoided if HIV RNA is not suppressed.</td>
</tr>
<tr>
<td>HCV coinfection</td>
<td>Alla</td>
<td>Regimens that have the fewest drug interactions with current HCV treatments are: • dolutegravir/abacavir/lamivudine • dolutegravir or raltegravir plus TAF/emtricitabine</td>
<td>Avoid antiretroviral drugs with substantial drug interactions with HCV therapies. Clinicians should consult current HCV treatment guidelines prior to using any other antiretroviral therapy regimens, particularly those that include NNRTIs, boosted HIV PIs, or elvitegravir/cobicistat.</td>
</tr>
<tr>
<td>Osteopenia or osteoporosis</td>
<td>Ala</td>
<td>Dolutegravir/abacavir/lamivudine</td>
<td>TAF is not recommended (BIII)</td>
</tr>
<tr>
<td>Osteopenia or osteoporosis</td>
<td>Alal</td>
<td>Dolutegravir plus TAF/emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Osteopenia or osteoporosis</td>
<td>Alal</td>
<td>Elvitegravir/cobicistat/TAF/emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Osteopenia or osteoporosis</td>
<td>Alll</td>
<td>Raltegravir plus TAF/emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Kidney diseaseb</td>
<td>Ala</td>
<td>Dolutegravir/abacavir/lamivudine</td>
<td>Estimated glomerular filtration rate, urinalysis, and testing for glycosuria and albuminuria or proteinuria when antiretroviral therapy is initiated or changed and every 6 months (BIII). TDF should be avoided in persons with creatinine clearance rate below 60 mL/min (Ala). TDF or TAF should be discontinued if renal function worsens, particularly if there is evidence of proximal tubular dysfunction (Ala). Persons with end-stage renal disease should be evaluated for kidney transplantation with expectation of high rates of patient and graft survival (Ala).</td>
</tr>
<tr>
<td>Kidney diseaseb</td>
<td>Alal</td>
<td>Dolutegravir plus TAF/emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Kidney diseaseb</td>
<td>Alal</td>
<td>Elvitegravir/cobicistat/TAF/emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Kidney diseaseb</td>
<td>Alll</td>
<td>Raltegravir plus TAF/emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Kidney diseaseb</td>
<td>Alal</td>
<td>TAF can be used if creatinine clearance is above 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>Kidney diseaseb</td>
<td>Alal</td>
<td>TAF should be initiated only after tubulopathy has resolved, with monitoring for recurrence.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.1

aSlashes indicate a coformulation.

bLong-term data on TAF in individuals with renal disease are limited and safety has not been determined.
Reasons for switching antiretroviral therapy include adverse effects, simplification of regimen (doses or pills), drug-drug interactions, pregnancy or plans for pregnancy, food restrictions, and regimen modernization. Recommendations regarding switching antiretroviral therapy are shown in Box 3. As rapid initiation of antiretroviral therapy becomes more common, including in the setting of acute HIV infection, the necessity of performing these tests before initiation of antiretroviral therapy should be further considered. Genotypic testing for nRTI-, NNRTI-, and PI-associated resistance mutations is recommended for all HIV-infected persons. At this time, routine baseline genotype testing for InSTI-associated resistance mutations is not considered necessary. The rate of InSTI-associated resistance in transmitted virus remains low but warrants monitoring.

Laboratory Monitoring

Recommendations for laboratory monitoring reflect evidence that supports specific monitoring practices, although some recommendations for monitoring are based on less than optimal amounts of prospective clinical evidence. Recommendations for laboratory monitoring and a panel of tests that are recommended before initiation of antiretroviral therapy are shown in Box 4. As rapid initiation of antiretroviral therapy becomes more common, including in the setting of acute HIV infection, the necessity of performing these tests before initiation of antiretroviral therapy should be further considered. Genotypic testing for nRTI-, NNRTI-, and PI-associated resistance mutations is recommended for all HIV-infected persons. At this time, routine baseline genotype testing for InSTI-associated resistance mutations is not considered necessary. The rate of InSTI-associated resistance in transmitted virus remains low but warrants monitoring.

All laboratory specimens should be drawn prior to initiation of antiretroviral therapy, and resistance testing results should be used to modify a regimen as necessary. It is recommended that plasma HIV RNA level be monitored every 4 to 6 weeks after initiating or changing antiretroviral therapy until virus is undetectable.

Plasma HIV RNA level should be monitored every 3 months after viral suppression is achieved and until virus is suppressed for 1 year and at least every 6 months thereafter in persons who remain clinically stable. Individuals should be reassessed every 3 to 4 months if their pretreatment CD4+ cell count is below 200/µL and their viral load is reliably suppressed and CD4+ cell count is above 350/µL for 1 year. Thereafter, CD4+ cell count can be assessed at 6-month intervals until virus has been suppressed for at least 2 years and CD4+ cell count is stably above 500/µL.

Measurement of plasma HIV RNA level should be repeated within 4 weeks if it remains above the limit of quantification by 24 weeks after starting new treatment or if there is viral rebound above 50 copies/mL. Tropism testing should be performed at the time of virologic failure of a CC chemokine receptor 5 inhibitor (eg, maraviroc).

Repeat monitoring of CD4+ cell count is not necessary when virus has been suppressed for at least 2 years and CD4+ cell count is persistently above 500/µL, unless virologic failure or intercurrent immunosuppressive conditions occur or immunosuppressive treatment is initiated. However, improved quality of evidence is desired in support of this recommendation.
**Engagement in Care and Adherence to Antiretroviral Therapy**

Recommendations regarding engagement in care and adherence to antiretroviral therapy are shown in Box 5. These recommendations are designed to improve early diagnosis of HIV infection, access and linkage to care, retention in care, and adherence to antiretroviral therapy.

Routine opt-out HIV screening is recommended in primary medical care settings and emergency departments and for all pregnant women. Programmatic monitoring of time to care linkage following initial HIV diagnosis, of retention in care, of adherence to antiretroviral therapy, and of rates of viral suppression in all care settings is recommended to collect more and better data on the cascade of HIV care. Emerging evidence supports the role of brief case management after HIV diagnosis in improving engagement in care. Similarly, there is evidence that rapid intervention following a missed clinic visit can improve retention in care. Additional recommendations have been made for the use of directly observed antiretroviral therapy in methadone maintenance programs and other settings, opioid substitution therapy for opioid-dependent persons, validated adherence instruments for self-reporting and pharmacy refill data to monitor adherence to antiretroviral therapy, and routine screening for depression.

**Box 4. Recommendations for Laboratory Monitoring**

**Recommended:**
- Preantiretroviral therapy tests: CD4+ cell count, plasma HIV-1 RNA, HAV, HBV, and HCV serologies, serum chemistries, estimated creatinine clearance rate, complete blood cell count, urine glucose and protein tests, STI screening, and fasting lipid profile (AII)
- Genotyping testing for reverse transcriptase and protease mutations for all persons (AIIa)
- Confirmation of HLA-B*5701 and CC chemokine receptor 5 tropism test results prior to initiating therapy with abacavir and maraviroc, respectively
- Draw all laboratory specimens prior to first dose of antiretroviral therapy if antiretroviral therapy is initiated on the first clinic visit (AIIa)
- Monitor HIV RNA level every 4 to 6 weeks after initiating or changing treatment until virus is undetectable (AIIa)
- Monitor HIV RNA level every 3 months after viral suppression is achieved and until virus is suppressed for 1 year and at least every 6 months thereafter in adherent persons who remain clinically stable (AIII)
- Reassess every 3 to 4 months if pretreatment CD4+ cell count is below 200/µL, and every 3 to 4 months until viral load is reliably suppressed and CD4+ cell count is above 350/µL for 1 year; thereafter, assess CD4+ cell count at 6-month intervals until virus has been suppressed for at least 2 years and CD4+ cell count is stable above 500/µL (AIil)
- Repeat assay within 4 weeks if HIV RNA level remains above the limit of quantification by 24 weeks after initiating new treatment or if rebound above 50 copies/mL occurs (AIa)
- Tropism testing at the time of virologic failure of a CC chemokine receptor 5 inhibitor (Ala)

**Not recommended:**
- Routine screening for integrase resistance prior to treatment initiation unless the source virus is suspected to have been from someone in whom treatment containing an InSTI failed (BIII)
- Therapeutic drug monitoring except in specific circumstances (BIII)
- When virus has been suppressed for at least 2 years and CD4+ cell count is persistently above 500/µL, repeat monitoring of CD4+ cell count is not recommended unless virologic failure (AIa) or intercurrent immunosuppressive conditions occur or immunosuppressive treatments are initiated (AIII)

**Box 5. Recommendations for Engagement in Care and Adherence to Antiretroviral Therapy**

**Recommended:**
- Routine opt-out HIV screening in primary medical care settings and emergency departments and for all pregnant women (AIII)
- Programmatic monitoring of time to care linkage following initial HIV diagnosis, retention in care, adherence to antiretroviral therapy, and rates of viral suppression in all care settings (AIIa)
- Brief case management after HIV diagnosis (Ala)
- Rapid intervention following a missed clinic visit (Ala)
- Integration of directly observed antiretroviral therapy in methadone maintenance programs (Bla) and as a treatment strategy among persons with substance use disorders (Bla) and those who are incarcerated or released to the community (CIII)
- Opioid substitution therapy for opioid-dependent persons (Ala)
- Monitoring of adherence using self-reports by validated adherence instruments and pharmacy refill data (Ala)
- Routine screening for depression (AIII)

Adapted from Günthard et al.1
HIV Prevention

The use of antiretroviral drugs has expanded beyond treatment of HIV infection at an individual level to include treatment as prevention (by reducing transmission risk), preexposure prophylaxis (PrEP), and postexposure prophylaxis (PEP). Recommendations for HIV prevention are shown in Box 6.

PrEP is recommended for populations in which incidences of HIV infection are high and for HIV-uninfected partners of HIV-infected persons who are not virally suppressed. Currently, US Food and Drug Administration–approved PrEP for HIV infection is limited to daily TDF/emtricitabine. Potential alternatives are being evaluated.

There is evidence that rates of sexually transmitted infections (STIs) are high among persons taking PrEP.7 Thus, it is recommended that follow-up of persons taking PrEP occurs every 3 months to allow for HIV testing and STI screening. Persons taking PrEP who are at risk for HIV infection on clinical grounds or while awaiting HIV RNA confirmation of equivocal screening test results should receive a boosted PI or dolutegravir in addition to TDF/emtricitabine pending viral load and resistance test results.

TDF-based PrEP is not recommended for individuals with osteopenia, osteoporosis, or a creatinine clearance rate below 60 mL/min. TAF/emtricitabine as PrEP must be evaluated in clinical trials.

PEP should be started as soon as possible after exposure to HIV without waiting for confirmation of HIV serostatus or the results of viral load or resistance testing. Recommended PEP regimens are TDF/emtricitabine plus twice-daily raltegravir or once-daily dolutegravir, TDF/emtricitabine plus cobicitab- or ritonavir-boosted darunavir, and elvitegravir/cobicistat/TDF/emtricitabine. PEP regimens should be continued for 28 days. HIV serostatus should be reassessed at 4 to 6 weeks, 3 months, and 6 months after exposure.

Future Directions

New therapies for HIV infection must be potent, simple, safe, and tolerable and must fulfill specific needs, such as the need for treatments with activity against multidrug-resistant variants or treatments that are available in long-acting formulations. Investigational long-acting antiretroviral therapy may allow persons who have difficulty with daily oral therapy to maintain viral suppression, may allow for directly observed therapy in clinical or nontraditional settings, and may serve as alternative treatment during periods when oral therapy is difficult. Long-acting antiretroviral treatment and prevention approaches containing rilpivirine, the investigational InSTI cabotegravir, and the investigational microbicide dapivirine (in a vaginal ring) are currently being studied. With long-acting therapies, individuals and retention in care should be closely monitored to avoid risk for the emergence of resistance to treatment.

Broadly neutralizing antibodies are also being studied, and an increasing number of monoclonal antibodies have been identified. These agents, which act to clear replicating virus and infected cells, may have a role in cure strategies and may provide passive immunization to protect individuals at risk for HIV infection. Challenges with these therapies include the need for parenteral dosing, potential development of anti-idiotypic antibodies, and potential resistance to broadly neutralizing antibodies in HIV-infected persons.

The IAS–USA recommendations also discuss cure strategies. In functional cure, HIV infection is controlled without therapy and without the consequences of HIV-related immune activation or inflammation. In eradication cure, all replication-competent virus is purged. Cure strategies must have limited risk, given the safety and effectiveness of current treatments.

Box 6. Recommendations for HIV Prevention*

Recommended:
- PrEP for anyone from a population in which HIV incidence is at least 2% per year (Ala) or for HIV-sero-negative partners of HIV-infected persons who are not virally suppressed (Ala)
- Daily TDF/emtricitabine for PrEP (Ala)
- Follow-up at intervals of no longer than every 3 months to allow for HIV testing (Alib) and STI screening (Bib)
- Persons taking PrEP who have suspected HIV infection on clinical grounds or are awaiting HIV RNA confirmation of equivocal screening test results should have a boosted PI or dolutegravir added to TDF/emtricitabine pending HIV RNA and resistance testing results (Alib)
- PEP as soon as possible after HIV exposure without waiting for confirmation of HIV serostatus or results of HIV RNA or resistance testing (Alib)
- TDF/emtricitabine plus twice-daily raltegravir or once-daily dolutegravir, TDF/emtricitabine with cobicitab- or ritonavir-boosted darunavir, or TDF/emtricitabine/cobicistat/elvitegravir for PEP (Alib)
- PEP regimens should be continued for 28 days, and HIV serostatus should be reassessed at 4 to 6 weeks, 3 months, and 6 months after HIV exposure (Alib)

Not recommended:
- TDF-based PrEP for individuals with osteopenia or osteoporosis (7III) or a creatinine clearance rate of less than 60 mL/min (Alia); it should be used with caution in individuals with chronic HBV infection (Bila)
- TAF/emtricitabine for PrEP until effectiveness has been demonstrated in clinical trials (Alib). Use of non-TDF-containing PrEP or augmentation of PrEP with TDF/emtricitabine with other agents (Alib)

Abbreviations: HBV, hepatitis B virus; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis; STI, sexually transmitted infection; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Günthard et al.1 *Slashes indicate a coformulation.
antiretroviral therapy. Cure strategies being evaluated include the “shock-and-kill” strategy in which latent virus is reacti-
vated and purged from reservoirs; gene therapy, consisting of knocking in protective genes or knocking out susceptible
genes; and immune enhancement using therapeutic vac-
cines and immune checkpoint modulators.

The world of HIV therapeutics has progressed rapidly
since the 2014 IAS–USA recommendations on antiretroviral
treatment.8 There are now more potent and convenient regi-
mens available, often as single daily pills, and the potent role
these drugs can play in prevention as well as in treatment
is recognized. The possibility that the combination of uni-
versal treatment and appropriate use of PrEP may bring the
HIV epidemic finally under control is exciting, even as the
search for a cure continues. These developments will be fol-
lowed closely and the IAS–USA recommendations will be
updated as needed.

Presented by Dr Volberding in August 2016. First draft prepared from
transcripts by Matthew Stenger. Reviewed and edited by Dr Volberding
in February 2017.

Financial affiliations in the past 12 months: Dr Volberding has served
on data and safety monitoring boards for Merck.

References

treatment and prevention of HIV infection in adults. 2016 recom-
mendations of the International Antiviral Society–USA panel. JAMA.
2. AASLD/IDSA. HCV guidance: recommendations for testing, man-
February 16, 2017.
agement promotes entry into HIV medical care: results of the anti-
brief case management intervention to link recently diagnosed
5. Gardner LI, Giordano TP, Marks G, et al. Enhanced personal contact
with HIV patients improves retention in primary care: a random-
sage service on antiretroviral treatment adherence in Kenya (WelTel
with increasing use of HIV preexposure prophylaxis in a clinical
adult HIV infection: 2014 recommendations of the International
9. Canadian Task Force on the Periodic Health Examination. The peri-

Guidelines for Authors and Contributors

The IAS–USA publishes Topics in Antiviral Medicine™ as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. This open-access journal is now available as an online resource only. It is indexed in Index Medicus/MEDLINE.

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

Categories of Articles

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

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

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

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

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

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

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

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

**Special Issues.** Topics in Antiviral Medicine™ often publishes issues with a special focus, such as summaries of IAS–USA continuing medical education courses and reports from scientific meetings. For example, 2 special issues on the Conference on Retroviruses and Opportunistic Infections (CROI) are published annually, one summarizing coverage of major topics relating to HIV, HCV, and other viral infections and another containing all of the abstracts presented at the conference.

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

Submission of Manuscripts

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

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

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

**Copyright**

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

**Authorship Requirements**

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

**Financial Disclosure**

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

Topics in Antiviral Medicine™ is going green in 2017!

This open-access journal is now available as an online resource only.

- Access the latest issue (www.iasusa.org/pub), archived issues (www.iasusa.org/tam/previous-issues), and continuing medical education (CME) posttests (http://www.iasusa.org/tam/cme-issues) any time.

- Ensure that the e-mail address in your IAS–USA account is up to date to receive notifications of new issues. If you do not already have an IAS–USA account, please visit the IAS–USA homepage (www.iasusa.org) and select “Create new account.”

- Sign up for our e-mail list to receive updates on live continuing education courses and webinars, new activities from the online Cases on the Web program, and information on important scientific meetings (eg, the Conference on Retroviruses and Opportunistic Infections and the Ryan White HIV/AIDS Program Clinical Conference).