**Perspectives CME**

The Fragile Relationship Between Hepatitis C Virus and Its Human Host

*Robert T. Schooley, MD*

- Lessons From HIV Biology
- Responsiveness of HCV
- Effect of Treatment on the Equilibrium Between HCV and Innate or Adaptive Immunity
- Conclusion

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Cure of Hepatitis C Virus Infection Without Interferon Alfa: Scientific Basis and Current Clinical Evidence

*David L. Thomas, MD, MPH*

- The Context
- The Tools
- Interferon Alfa-Sparing Treatment
- Conclusion

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An Update on Hepatitis B, D, and E Viruses

*Jennifer Price, MD*

- Hepatitis B Virus Infection
- Hepatitis D Virus Infection
- Hepatitis E Virus Infection
- Summary

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**Cases From the Field CME**

Ergotism in Thailand Caused by Increased Access to Antiretroviral Drugs: A Global Warning

*Anchalee Avihingsanon, MD, PhD, and Others*

- Case Presentations
- Conclusion
Perspectives

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Perspective

The Fragile Relationship Between Hepatitis C Virus and Its Human Host

Based on viral dynamics and replicative fidelity alone, suppression of hepatitis C virus (HCV) should be a substantially greater challenge than suppression of HIV. Factors underlying the greater than expected responsiveness of HCV to direct-acting antiviral (DAA) drugs include the vulnerability of HCV during acute infection, acceleration of second-phase viral decay kinetics with increased anti-HCV regimen potency, and the effect of DAA treatment in upsetting the equilibrium between the virus and the host immune system. Several potential mechanisms might explain the considerable vulnerability of HCV to potent antiviral therapy. It is possible that anti-HCV treatment destabilizes HCV replication complexes, thereby permitting cure of infected cells, and that with the rapid reduction of HCV within the hepatocyte, mechanisms by which HCV evades the innate and adaptive immune responses are undermined, thus enhancing the antiviral effect of potent anti-HCV regimens. This article summarizes a presentation by Robert T. Schooley, MD, at the IAS–USA continuing education program held in New York, New York, in June 2013.

Keywords: HCV, hepatitis C, innate, adaptive, immunity, immune evasion, direct-acting antivirals, treatment, replication complex, host interaction

The response of hepatitis C virus (HCV) to direct-acting antivirals (DAAs) has been better than might be expected based on experience with antiretroviral chemotherapy, reflecting aspects of HCV biology and the relationship between HCV and the host that are now being more fully appreciated. To understand some of the initial pessimism regarding the length of time necessary to develop interferon alfa–free regimens following the availability of new, small-molecule anti-HCV drugs, it is useful to review what has been learned from the study of HIV biology.

Lessons From HIV Biology

In the early days of studying the viral dynamics of HIV, made possible by the introduction of potent antiretroviral drugs, it was observed that the level of virus in plasma could be reduced by more than 100-fold within several days of exposure to a potent drug. This was a surprising finding as HIV replication was initially believed to be slow paced. With these findings it became clear that HIV is a virus with rapid turnover that destroys a large number of lymphocytes each day and that the beneficial impact of antiretroviral therapy could be directly traced to the reduction of T cell turnover associated with suppression of viral replication. From these observations, virion production was estimated at 4 x 10^8 to 3 x 10^10 per day.

A virus that replicated this rapidly, particularly an RNA virus with an error-prone polymerase, would be expected to readily generate resistant mutants. HIV mutants differing from wild type by 5 point mutations were expected to occur as the replication level approached the estimated daily range of virion production. Data such as these contributed to the prediction that control of viral replication would require 3 potent antiretroviral drugs to overcome 5 to 8 collective resistance mutations—a prediction that was borne out in the development of potent antiretroviral regimens.

It was first observed in the Merck 035 study^1 that a 3-drug combination of zidovudine, lamivudine, and indinavir provided sufficient potency and mutational barriers to suppress HIV below detection limits for a prolonged period. Treatment with the 2-drug combination of zidovudine and lamivudine had less potency and a lower barrier to resistance than the 3-drug combination and was associated with virologic breakthrough within several weeks. Initiating therapy with indinavir and then adding zidovudine and lamivudine resulted in a failure to suppress virus to undetectable levels, because the initial exposure to the single drug indinavir resulted in selection of resistant mutants.

Studies of HCV kinetics have shown that 100- to 3000-fold (4 x 10^16 to 1 x 10^15) more HCV virions are produced per day than is seen with HIV infection.\(^2\) The HCV polymerase is also error-prone, but its function differs from that of the HIV polymerase in that it must copy a positive strand to a negative strand and then a negative strand to a positive strand each time a new viral particle is produced, thereby giving the enzyme twice the opportunity to introduce mutations with each replicative cycle than in the case of the reverse transcriptase of HIV-1. The high replication rate of HCV results in a tremendous genetic heterogeneity. On a global scale, HCV is more than 10 times more genetically diverse than HIV; HCV genotype 1 alone is as diverse as all clades of HIV. Further contributing to genetic diversity is the fact that HCV has no overlapping reading frames. HIV, on the other hand, has overlapping reading frames, placing substantially greater evolutionary constraints on genetic diversification. The implication of these considerations is that based solely on calculations of viral dynamics and replicative fidelity, HCV suppression should pose a substantially greater challenge than was experienced with HIV.

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Responsiveness of HCV

Why might HCV be more responsive to DAA therapy than expected based on viral dynamics and fidelity modeling? Factors contributing to this greater responsiveness include the vulnerability of HCV during acute infection, the acceleration of second-phase viral decay kinetics with increased anti-HCV regimens potency, and the effect of DAA treatment in upsetting the equilibrium between HCV and innate and adaptive immunity.

Vulnerability During Acute Infection

One factor contributing to the responsiveness of HCV to potent therapy is that HCV appears to be precariously balanced in the host. HCV infection is cleared during acute infection in approximately 15% to 40% of individuals. Much of the host’s ability to clear HCV infection is determined by polymorphisms in the IL28B gene, which is active in regulating the endogenous morphisms in the IL28B gene, which is important primer of the adaptive immune system and cellular immune response. During acute infection, HCV is highly responsive and sensitive to interferons and other elements of innate immune response.

A study of cytokine expression in 18 patients who cleared acute infection and in 35 patients who developed chronic infection revealed that viral clearance is characterized by high levels of tumor necrosis factor alpha, a proinflammatory cytokine that is an important primer of the adaptive immune system and cellular immune response. Persistent HCV infection was characterized by increased levels of interleukin (IL)-2, which is active in stimulating T regulatory cells that downregulate the cellular immune response. Thus, at the time of first viremia, the host is already initiating either a scenario to clear the infection or a program of immune modulation that will allow the virus to persist. Persistence was also characterized by increased levels of IL-10 and IL-13, which skew immune response toward T helper 2 (T_{H2}) cells, resulting in decreased T cell activation. Treatment with interferon alfa during the acute phase of HCV infection markedly augments viral clearance, which further emphasizes the interferon responsiveness of HCV.

Such observations indicate that the natural history of HCV infection, unlike that of HIV infection, includes a fragile early phase during which the virus is attempting to establish itself in the liver. Once established, the virus stays within the infected liver cells for the remainder of the host’s life. Unlike HIV, HCV cannot retreat to latently infected cells with integrated, unexpressed viral DNA. As noted above, HCV must replicate continuously within infected liver cells, displaying its proteins and RNA within these cells in the presence of potent innate and adaptive immune responses.

Acceleration of Second-Phase Kinetics With Increased Regimen Potency

Initial studies of HCV kinetics during treatment with interferon alfa revealed a biphasic decay of the virus from the plasma. The first, steeper phase was thought to correspond to cessation of virus production and release from infected cells, and the second, more gradual phase was thought to correspond to the turnover of infected liver cells. Sustained virologic response (SVR) would be expected with the death of the last infected hepatocyte. In this model, increased effectiveness at turning off virus production would produce steeper first-phase decay but would not be expected to affect the dynamics of second-phase decay. However, studies assessing HCV decay using interferon alfa–based regimens combined with the DAA telaprevir indicated that the increased reduction in viral replication with the addition of telaprevir produced not only steeper first-phase viral RNA decay but also steeper second-phase decay (Figure 1).

This suggests a linkage between second-phase decay and how rapidly virus production is turned off.

The understanding of HCV kinetics has been improved by examining the response of gamma-interferon–induced protein (IP) 10 (IP-10) to HCV infection. IP-10 is a chemokine that attracts monocytes, T cells, and natural killer cells. Produced by a number of cells, including hepatocytes, IP-10 is upregulated by HCV infection and by the administration of interferon alfa. When HCV infects hepatocytes in tissue culture or in a human host, there is a rapid increase in levels of IP-10 RNA and IP-10 protein, which remain elevated during chronic infection and return to baseline with viral clearance following effective therapy. Higher pretreatment levels of IP-10 predict a lower likelihood of efficacy with an interferon alfa–based regimen. A greater fold change in plasma IP-10 levels from baseline immediately after the initiation of interferon alfa–based therapy predicts a better treatment response.

Recent studies of IP-10 report a correlation between low levels of IP-10 at 149
baseline and IL28B CC genotype, both of which are favorable for HCV clearance. The IP-10 response to anti-HCV treatment may reflect the clearance of HCV replication complexes from infected cells, thus explaining the increase in slope of second-phase decay with the use of more potent HCV treatment. These studies show that initiation of treatment with DAAs is associated with a rapid decline in IP-10 levels. The decline was biphasic both in patients whose previous interferon alfa–based therapy had failed and in treatment-naive patients. Between weeks 1 and 2 of treatment, the change in IP-10 level was more pronounced in treatment-naive patients than in treatment-experienced patients. IP-10 level decreased by approximately 50% in both groups during the first week; in the second week, the decline among treatment-naive patients was substantially greater than that among treatment-experienced patients.

Although patients had a wide distribution of IP-10 levels prior to treatment, the average was approximately 250 pg/mL. Because normal IP-10 levels are approximately 100 pg/mL, the initial 50% reduction achieved with DAA treatment rapidly brought many patients’ levels to within normal range. If IP-10 is a measure of how much virus is present in the liver—that is, if it serves as a sensor to monitor live HCV RNA replication complexes—then these findings indicate an extremely rapid decline of these complexes, suggesting that potent treatment with DAAs may actually be eradicating HCV replication complexes from the liver cells. The more rapid second-phase decay of HCV infection observed following potent treatment with DAAs may therefore represent this clearance of HCV replication complexes rather than the slower kinetics expected if this phase of the decay merely reflected the turnover of HCV-infected cells.

**Effect of Treatment on the Equilibrium Between HCV and Innate or Adaptive Immunity**

HCV infection induces a robust interferon-stimulated gene (ISG) profile, and IL28B and HCV stimulate interferon signaling pathways in hepatocytes in vitro. In patients, exogenous alpha-interferon binds to interferon cell receptors that, through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, induce ISGs and promote production of a cascade of effectors that can shut down viral replication within the cell. HCV induces lambda-interferon, which engages lambda-interferon receptors and, also through the JAK-STAT pathway, stimulates alpha-interferon production.

In basic terms, within an infected cell, HCV is rapidly uncoated and situated in the endoplasmic reticulum. HCV RNA is exposed, and sequences in the 3’ end of the RNA are recognized by pattern recognition receptors that stimulate the retinoic acid–inducible gene (RIG) I (RIG-I) pathway. This activates the host’s innate immune response, including production of alpha- and beta-interferons, and clears the virus from the cell. These responses also protect adjacent cells from infection.

However, it is now known that the HCV nonstructural protein (NS) 3/4A (NS3/4A) protease cleaves mitochondrial antiviral-signaling protein (MAVS; also called virus-induced signaling adapter [VISA]) and Toll/IL-1 receptor domain–containing adaptor inducer (TRIF), 2 adaptor molecules essential for interferon signaling activation, inhibiting RIG-I, and shutting down the downstream cascade that results in activation of the innate immune response, including production of type 1 interferons. In addition to this crucial component of the host-virus interaction, there are other mechanisms by which HCV interferes with the host’s innate immune response, including inhibition of pattern recognition receptor signaling by NS4B via interaction with stimulator of interferon genes (STING; also called mediator of interferon regulatory factor 3 activation [MITA]) adaptor protein, another molecule that mediates HCV-induced interferon signaling and inhibits the activation of interferon regulatory factor 3 genes; interference with interferon signaling via inhibition of ISG expression by the viral core; and antagonism of ISGs by the HCV NS5A and envelope (E) 2 (E2) proteins. In essence, once it enters the cell, the virus acts to undermine innate immune response using viral enzymes and core and envelope proteins.

In this context, the use of potent DAAs that very rapidly inhibit viral replication also results in rapid elimination of those viral products active in evading the innate immune response. In addition to inhibiting viral replication and destabilizing HCV replication complexes, DAAs may allow for restoration of innate immune activity against HCV, which further primes adaptive immune responses, including production of cytotoxic T cells and virus-specific, neutralizing antibodies. The rapid and profound reduction in HCV replication induced by DAAs may also undermine viral mechanisms that permit evasion of innate and adaptive immune responses and thereby result in a net effect on viral replication that is more than the sum of the parts of the regimen itself.

**Conclusion**

Remarkable improvements in the treatment of HCV infection have been observed since the availability of HCV DAAs. Evidence is emerging that with increasingly potent and sustained antiviral pressure, the sum of the anti-HCV effect is greater than its parts. The inhibition of viral replication with these drugs results in destabilization of HCV replication complexes, permits cure of infected cells, and promotes the activity of the innate immune response axis in shutting down viral replication by abrogating HCV immune evasion mechanisms.

DAA-containing therapy provides an outstanding platform from which to study virus-host interaction. This will have important implications not just for HCV but for other flaviviruses, such as West Nile virus, dengue virus, and yellow fever virus, that exhibit many of the same mechanisms of immune evasion.
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References


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**Perspective**

Cure of Hepatitis C Virus Infection Without Interferon Alfa: Scientific Basis and Current Clinical Evidence

Cure of hepatitis C virus (HCV) infection is achievable without interferon alfa through the use of new direct-acting antiviral (DAA) drugs. In this era of interferon alfa–sparing therapy, however, interferon alfa sensitivity still matters, even as it turns out, if interferon alfa is not used. Inclusion of ribavirin in the treatment regimen remains a factor in treatment response, as does duration of treatment. HCV genotype and subtype remain relevant considerations in choosing a treatment regimen, and viral resistance may emerge when treatment fails. The potency and barrier to resistance of new DAAs and the use of appropriately designed interferon alfa–sparing combinations can overcome obstacles to cure posed by HCV resistance, interferon alfa resistance, and differences in response based on HCV genotype and subtype. Studies demonstrating the use of new DAAs to overcome these obstacles are discussed. This article summarizes a presentation by David L. Thomas, MD, MPH, at the IAS–USA continuing education program held in New York, New York, in June 2013.

**Keywords:** HCV, hepatitis C, treatment, interferon, sparing, interferon alfa–sparing, direct-acting antivirals, DAAs, genotype, protease inhibitor, NS5A, NS5B, resistance, sofosbuvir, simeprevir

The first hepatitis C virus (HCV)-infected patients were cured in 1984 and 1985, before it was known that a virus was causing their disease. In studies at the National Institutes of Health (NIH), Hoofnagle and colleagues used interferon alfa to treat individuals with non-A or non-B hepatitis and observed a normalization of liver enzymes in these individuals.

After the virus was identified, it became clear that eradication of HCV had also been achieved. Since then, interferon alfa has been the mainstay in the treatment and cure of HCV infection. Regimens that include interferon alfa have been associated with marked improvement in important therapeutic outcomes, including reductions in mortality, liver cancer, and other serious liver-related events. However, interferon alfa–based treatments are not always successful and have been associated with considerable toxicity and morbidity. Now, a new era of interferon alfa–sparing HCV treatment has begun, and soon it will be possible to achieve cure for most patients with as little as one pill once a day.

**The Context**

There are viral replication foci in approximately 10% to 20% of hepatocytes distributed throughout an HCV-infected liver. Approximately 1 to 50 viruses can be detected at any one time in a single hepatocyte, but there are places in the liver with no detectable HCV RNA. Thus, to be effective, HCV treatment must reach all sites in the liver that harbor infected hepatocytes. Further, in an HCV-infected liver, there are approximately 1 trillion viruses produced every day. If an environment becomes inhibitory for one variant, another will quickly take its place. To be successful, HCV treatment must also overcome the genetic and phenotypic heterogeneity of HCV.

The ongoing host immune response to the virus sometimes clears infection. When it does not, those patients with chronic infection seem to have 1 of 2 different states. One state is characterized by inflammation and the upregulation of interferon-stimulated genes (ISGs). The HCV infections of persons with this high-ISG state are less responsive to exogenous interferon alfa, and these individuals often have a haplotype around the genes for the lambda interferons. In particular, the commercially available IL28B test to determine specific genotype indicates that individuals with a high-ISG state HCV infection have what is called the unfavorable IL28B T allele genotype. Persons with the other state have low expression of ISGs, and their HCV infections remain responsive to exogenous alpha-interferon. They are much more likely to have different genotypes near IL28B, and in particular, the favorable IL28B C allele genotype. Interestingly, persons in these 2 states of differing interferon sensitivity and the associated IL28B genotypes continue to have different susceptibilities to interferon-sparing treatments, reflecting their intrinsic tendency to eradicate infection.

The context of infection can also be important when liver tissue is markedly distorted by cirrhosis. Patients with cirrhosis are harder to treat effectively, even with new interferon alfa–sparing regimens, possibly because the distorted tissue inhibits drug penetration or because of factors such as changes in portal pressure.

**The Tools**

Almost all of the major steps in the HCV life cycle are potential targets for inhibiting viral replication, including entry, endosomal release and internal ribosome entry site (IRES)-dependent translation, protease cleavages, membranous web formation and lipoprotein assembly linked to nonstructural protein (NS) 5A (NS5A), and NS5B RNA-dependent RNA polymerase (RdRp) activity. Investigational drugs have been developed to target nearly all of these steps but several drugs are further along in development.

Currently, the 3 main groups of HCV drugs are protease inhibitors (PIs; ie, telaprevir and boceprevir), NS5A-acting agents, and nucleos(t)ide RdRp inhibitors.
HCV can be cured with investigational drugs faldaprevir and deleobuvir, with or without ribavirin, for various treatment durations in treatment-naive patients with HCV genotype 1 infection. Thirty-three patients enrolled in the trial had compensated cirrhosis. BID indicates twice daily; QD, once daily; TID, thrice daily. Adapted with permission from Zeuzem et al.²

Interferon Alfa–Sparing Treatment

Although there are data to show that HCV can be cured with investigational treatments that do not include interferon alfa, sensitivity to interferon alfa may still be a factor in treatment response and resistance may emerge when a treatment is unsuccessful. HCV genotype and subtype, ribavirin use, and duration of treatment may also be factors in the efficacy of HCV therapy. However, a drug’s potency or its barrier to resistance can trump these other factors.

A study assessing the use of the investigational HCV PI faldaprevir (once daily) combined with the investigational nonnucleoside (nn) NS5B inhibitor deleobuvir (formerly BI 207127; twice or thrice daily), with or without ribavirin, for various treatment durations in treatment-naive patients with HCV genotype 1 infection illustrates many of these points (Figure 1).²³

Figure 1. Design of a trial evaluating the use of the investigational drugs faldaprevir and deleobuvir, with or without ribavirin, in 362 treatment-naive patients with genotype IL28B (CC or non-CC) and hepatitis C virus (HCV) genotype 1 (subtype 1a or 1b) infection. Thirty-three patients enrolled in the trial had compensated cirrhosis. BID indicates twice daily; QD, once daily; TID, thrice daily. Adapted with permission from Zeuzem et al.²

Substantial rates of sustained virologic response (SVR) 12 weeks after cessation of treatment (SVR12), considered to constitute cure, were observed with all regimens, indicating that cure of HCV infection is indeed possible without the use of interferon alfa (Figure 2).²

Several PIs show marked differences in their ability to eradicate genotype 1a virus compared with genotype 1b virus. In this study, the SVR12 rate in patients with HCV genotype 1a infection whose regimens did not include ribavirin was only 11%.² Faldaprevir may be indicated for use only in patients with HCV genotype 1b infection.

In another study, 19 treatment-naive patients with HCV genotype 1 infection received a 12-week regimen of the ritonavir-boosted investigational PI ABT-450, the investigational nnNS5B inhibitor ABT-333, and ribavirin.⁴ Of these 19 patients, 47% had IL28B T genotype and 89% had HCV genotype 1a infection. All 19 patients achieved virologic suppression; SVR12 was achieved in 18 patients (95%), with 1 patient withdrawing from the study due to elevated levels of alanine transaminase. However, when the same regimen was given to 17 of the study patients whose previous regimen of interferon alfa and ribavirin had failed (all patients had IL28B T genotype and 94% of patients had HCV genotype 1a infection), SVR12 was achieved in only 8 patients (47%), 6 experienced breakthrough viremia, and 3 relapsed. Of
Similar principles of treatment may be observed when a nucleotide inhibitor (ie, sofosbuvir) with broad genotypic activity is used with or without ribavirin in individuals with HCV genotype 2 or 3 infection. Sofosbuvir has been approved by the US Food and Drug Administration (FDA) since the June presentation summarized here.

In an initial study of sofosbuvir given with or without ribavirin to treatment-naive patients with HCV genotype 2 or 3 infection, the SVR24 rate was 100% (10 of 10) in patients who received sofosbuvir and ribavirin and 60% (6 of 10) in patients who received sofosbuvir monotherapy. Likewise, in 25 treatment-naive patients with HCV genotype 1 infection who received a combination of sofosbuvir and ribavirin, the SVR24 rate was 84%. However, SVR24 was achieved in only 1 of 10 HCV genotype 1–infected patients with prior nonresponse to interferon alfa. Therefore, the use of sofosbuvir and ribavirin can achieve high SVR rates in treatment-naive patients who are relatively sensitive to interferon alfa, whether they have HCV genotype 1, 2, or 3 infection. However, as represented in patients with prior nonresponse, resistance to interferon alfa still plays a role and, as discussed below, it can be overcome.

A study of sofosbuvir and ribavirin in 201 patients with prior nonresponse and HCV genotype 2 or 3 infection demonstrated that genotype and duration of treatment were factors in achieving SVR. Among patients with HCV genotype 2 infection, SVR was achieved in 94% of those who received 16 weeks of treatment and in 86% of those who received 12 weeks of treatment. Among patients with HCV genotype 3 infection, SVR rates were lower but still reflected a benefit with longer treatment duration: SVR was achieved in 62% of the 16-week treatment group and 30% of the 12-week treatment group. Longer duration of treatment was also beneficial to patients with cirrhosis: SVR was achieved in 66% of the 16-week treatment group and 51% of the 12-week treatment group.

In another study, the addition of the investigational NS5A-acting agent ledipasvir to a 12-week regimen of sofosbuvir and ribavirin produced SVR in 100% (9 of 9) of HCV genotype 1–infected patients with prior nonresponse and in 100% (25 of 25) of treatment-naive, HCV genotype 1–infected patients. Sofosbuvir and ledipasvir, coformulated as a single, once-daily pill, taken with or without ribavirin for a 12- or 16-week treatment period is currently being assessed in phase III trials.

Early phase studies have evaluated investigational HCV drugs from 2 different pharmaceutical companies. Although combination forms of these drugs do not seem destined for FDA approval anytime soon, there is some preliminary evidence that the treatments are effective. FDA approval of some of these individual drugs may offer clinicians the possibility of devising interferon alfa–sparing regimens in the very near future and prior to FDA approval of combination regimens. For instance, simeprevir was recently approved by the FDA for use in combination with ribavirin and interferon alfa in HCV genotype 1–infected patients with compensated liver disease, including cirrhosis. And an early phase study has shown that the investigational combination of the PI simeprevir and the nucleotide inhibitor sofosbuvir, with or without ribavirin, produced SVR in more than 90% of HCV genotype 1–infected patients with prior nonresponse. Similarly, the combination of the investigational NS5A-acting agent daclatasvir and the nucleotide inhibitor sofosbuvir, with or without the addition of ribavirin,
produced an SVR rate of nearly 100% in a study of 41 patients whose prior treatment with telaprevir, boceprevir, and interferon alfa–sparing treatment had failed.12

### Conclusion

Interferon alfa–sparing treatment for HCV infection is coming. Presently, many practitioners are faced with the decision of whether to treat their patients with currently available drugs or to wait until new drugs are available. As availability of the newer options approaches, many practitioners are choosing to wait or are enrolling their patients in clinical trials that evaluate new treatments.

With the recent approval by the FDA of sofosbuvir in combination with ribavirin for patients with HCV genotype 2 or 3 infection and in triple therapy with interferon alfa and ribavirin for treatment-naive patients with HCV genotype 1 or 4 infection, waiting to begin treatment may no longer be necessary for some patients. The recent FDA approval of simeprevir to treat HCV infection for the foreseeable future in settings where new treatments may initially be too expensive.

The widespread use of interferon alfa–sparing treatment options for all HCV-infected patients, whether in resource-rich or resource-poor locales, can be envisioned.

Presented by Dr Thomas in June 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Thomas in December 2013.

**Financial Affiliations:** Dr Thomas has received grants awarded to his institution from Gilead Sciences, Inc, and Merck & Co, Inc.

### Additional Suggested Reading


### References


HCV GT1 infection: results from the AVIA-TOR study. 48th Annual Meeting of the European Association for the Study of the Liver. April 24-28, 2013; Amsterdam, The Netherlands.


8. Gane E, Stedman C, Anderson J, et al. 100% Rapid virologic response for PSI-7977 + ribavirin in genotype 1 null responders (ELECTRON): early viral decline similar to that observed in genotype 1 and genotype 2/3 treatment-naive patients. 19th Conference on Retroviruses and Opportunistic Infections (CROI). March 5-8, 2012; Seattle, WA.


NEW WEBSITE LAUNCH!
www.HCVguidelines.org

- Developed by a panel of experts in the field.
- Provides practitioners with regularly updated, evidence-based, consensus recommendations for screening, treating, and managing patients with HCV.
- Assists practitioners in treating the estimated 3 to 4 million Americans infected with HCV by highlighting the latest information in improved diagnostics and new drug options as they meet FDA approval.
- Offers guidance to practitioners about how to best use the next generation of direct-acting antivirals and other treatment options in the care of their patients.

Recommendations for Testing, Managing, and Treating Hepatitis C

Recommendations for Testing, Managing, and Treating Hepatitis C is a new web-based resource sponsored by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) to provide the most current guidance for the treatment of hepatitis C virus (HCV).

Sections to be released in late January:
- HCV Testing and Linkage To Care
- Recommendations for Initial Treatment of HCV Infection in Patients Starting Treatment
- Retreatment in Persons In Whom Prior Therapy Has Failed
- Unique Patient Populations

Coming soon:
- Who Should Be Treated
- Monitoring Patients on HCV Therapy
**Perspective**

**An Update on Hepatitis B, D, and E Viruses**

Although newer and more effective treatments are now available for hepatitis C virus (HCV) infection, non-HCV viral hepatitis remains an important cause of liver disease, especially among HIV-infected individuals. Hepatitis B virus (HBV) is the leading cause of cirrhosis worldwide, and approximately one-quarter of patients with cirrhosis develop decompensated liver disease within 5 years. Initial treatment for chronic HBV infection includes peginterferon alfa, entecavir, and tenofovir. Approximately 15 million of the estimated 350 million individuals with chronic HBV infection have evidence of exposure to hepatitis D (delta) virus (HDV), which requires hepatitis B surface antigen for transmission and packaging. HBV/HDV coinfection is associated with more severe acute hepatitis and higher mortality than acute HBV monoinfection. Chronic coinfection is associated with a higher risk of cirrhosis and decompensated liver disease. The mainstay of treatment for HDV infection is peginterferon alfa for at least 48 weeks. Cases of hepatitis E virus (HEV) infection in HIV-infected persons have been reported. HEV infection can become chronic in immunosuppressed patients, and chronic infection is associated with rapid development of cirrhosis. There are no established guidelines for treating HEV infection in HIV-infected persons. This article summarizes a presentation by Jennifer Price, MD, at the IAS–USA continuing education program held in San Francisco, California, in June 2013.

**Keywords:** hepatitis, HCV, HBV, HDV, HEV, peginterferon alfa, nucleoside analogue, nucleotide analogue

**Hepatitis B Virus Infection**

Worldwide, approximately 350 million individuals are chronically infected with hepatitis B virus (HBV). HBV is the leading cause of cirrhosis globally (Figure 1). The United States is considered a low-prevalence region for HBV with less than 2% of the population infected. This still represents approximately 1.25 million people. The prevalence of chronic HBV is higher among individuals who have emigrated from endemic regions, as well as in populations at increased risk for transmission such as HIV-infected individuals, in whom the prevalence of chronic HBV infection is approximately 10%.

The presence of hepatitis B surface antigen (HBsAg) in the serum on 2 occasions at least 6 months apart defines chronic HBV infection. Hepatitis B surface antibody (anti-HBs) is the marker of immunity to HBV. Anti-HBs is found in individuals who have cleared their infection or responded to HBV vaccination.

The presence of HBV DNA indicates ongoing viral replication, with levels correlating with replication and infectivity. Hepatitis B core antibody (anti-HBc) is the antibody to hepatitis B core antigen and serves as a marker for prior exposure. Individuals who have been exposed to HBV are positive for anti-HBc regardless of whether or not they have cleared the virus or developed chronic infection. Thus, individuals who have immunity after exposure (ie, are anti-HBc positive) can be distinguished from those who have immunity due to vaccination (ie, are anti-HBs positive).

The hepatitis B e antigen (HBeAg) was traditionally used as an index of viral replication and infectivity but has been largely replaced in this regard by measuring HBV DNA. An individual can have HBeAg-negative disease with ongoing viral replication in the setting of hepatitis B core promoter or precore mutants that either do not produce the antigen or produce it at low levels. HBeAg status remains important when deciding on treatment initiation and (in the case of HBeAg-positive disease) monitoring treatment response.

Greater than 90% of infants with acute infection progress to chronic HBV infection, compared with less than 5% of adults. In adults, progression to chronic infection is more common in immunocompromised individuals, such as those who acquire HBV during infancy.
HIV infection. Once chronic infection is established, approximately 30% of patients will develop cirrhosis, and approximately one-quarter of patients with cirrhosis develop decompensated liver disease within 5 years. Cirrhosis also substantially increases the risk for hepatocellular carcinoma (HCC). Chronic HBV infection itself increases the risk for HCC even in the absence of cirrhosis and is the sixth leading cause of liver transplantation in the United States.

Table 1 summarizes treatment guidelines for chronic HBV infection from several liver organizations. There are subtle differences among the guidelines, but the general principles are the same. The decision whether to treat requires knowing HBeAg antigen status, HBV DNA levels, and alanine transaminase (ALT) levels. Liver biopsy provides decisive information but is not uniformly available.

Patients can be categorized into HBeAg-positive or -negative disease. Among patients with HBeAg-positive disease, those with elevated HBV DNA levels, with a consensus threshold of 20,000 IU/mL, who have ongoing inflammation as manifested by elevated ALT meet the criteria for treatment. The ALT threshold used to determine whether a patient should be treated is somewhat controversial, with some experts believing that anyone with persistently elevated ALT warrants treatment and others requiring ALT to be greater than 2 times the upper limit of normal (ULN). It should be noted that ULN levels for ALT have been updated to 30 IU/L for men and 19 IU/L for women. Among patients with HBeAg-negative disease, the same principle applies whereby those with ongoing viral replication and persistently elevated ALT meet the criteria for treatment. However, in these patients the HBV DNA threshold is lower, at greater than 2000 IU/mL.

There are 7 US Food and Drug Administration (FDA)-approved treatment regimens for HBV infection, consisting of conventional interferon alfa, peginterferon alfa, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Characteristics of these regimens, excluding conventional interferon alfa, are shown in Table 2. An advantage of peginterferon alfa is that it has a fixed-duration course, whereas the oral nucleos(t)ide analogues have somewhat indefinite treatment courses. Peginterferon alfa, entecavir, and tenofovir are used as initial antiviral agents. Treatment with peginterferon alfa is considered in patients with concomitant hepatitis C virus (HCV) infection and in patients with favorable predictors of response, including low HBV DNA level and high ALT, both of which are also predictors of response to nucleos(t)ide analogues, infection with genotype A or B rather than C or D, and absence of advanced disease. Peginterferon alfa may also be preferred in younger individuals, including women looking to become pregnant in the near future, and patients without comorbidities.

Entecavir and tenofovir have high potencies and high barriers to resistance. Reported 5-year resistance rates in treatment-naïve patients are 70% for lamivudine, 29% for adefovir, and 17% (2-year rate) for tenofovir. Compared with 1.2% for entecavir and 17% (2-year rate) for tenofovir and 17% (2-year rate) for tenofovir. Therefore, tenofovir and entecavir are the preferred initial oral agents. Notably, although

**Table 1. Treatment Criteria for Chronic Hepatitis B Virus Infection, Based on Antigen Status**

<table>
<thead>
<tr>
<th>Guidelines/Algorithm</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA (IU/mL)</td>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>AASLD 2009</td>
<td>&gt;20,000</td>
<td>&gt;2x ULN or (+) biopsy</td>
</tr>
<tr>
<td>US Treatment Algorithm 2008</td>
<td>≥20,000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>EASL 2009</td>
<td>&gt;2000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>APASL 2008</td>
<td>≥20,000</td>
<td>&gt;2x ULN or (+) biopsy</td>
</tr>
</tbody>
</table>

AASLD indicates American Association for the Study of Liver Diseases; ALT, alanine transferase; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; ULN, upper limit of normal. Information derived from Lok and McMahon, Keeffe et al., EASL, and Liaw et al. *ULN for US Algorithm 2008 and AASLD 2009: 30 IU/mL (men), 19 IU/mL (women). ULN for EASL 2009 and APASL 2008 is based on laboratory reference range.

**Table 2. Suggested Treatment Regimens for Hepatitis B Virus Infection**

<table>
<thead>
<tr>
<th>Peginterferon alfa 2a</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose</td>
<td>180 μg/wk</td>
<td>100 mg/day b</td>
<td>10 mg/day b</td>
<td>0.5 mg/day b</td>
<td>600 mg/day b</td>
</tr>
<tr>
<td>Duration</td>
<td>48 wks</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Resistance</td>
<td>None</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Anti-HIV?</td>
<td>Weak</td>
<td>Yes</td>
<td>Weak</td>
<td>Weak</td>
<td>No</td>
</tr>
<tr>
<td>Initial Agent?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Anti-HIV indicates HIV antibody. Information derived from Lok and McMahon and Keeffe et al. Conventional (nonpegylated) interferon alfa is also approved for chronic HBV infection. Renal dosing is necessary, a higher dose of entecavir may be required in cases of lamivudine resistance.
entecavir resistance is uncommon in previously untreated patients, in those with prior lamivudine treatment, the resistance rate for entecavir is approximately 50%.

Figure 2 demonstrates the patterns of HBV virologic breakthrough and rebound as well as biochemical breakthrough. Virologic breakthrough is defined by increased HBV DNA after suppression and usually precedes biochemical breakthrough, which is indicated by increased ALT. When resistant mutants are initially selected, HBV DNA increases relatively slowly because mutant strains typically have diminished replication capacity. However, over time these strains develop compensatory mechanisms that increase replication fitness, resulting in a more severe virologic rebound that can precede severe hepatitis flare and even decompensation. Thus, it is important to recognize virologic breakthrough early in order to intervene appropriately and prevent hepatitis flare.

Figure 3 shows the HBV polymerase gene mutations that confer resistance to the various oral agents. Resistance to lamivudine, or emtricitabine, and telbivudine is conferred by mutations in the YMDD motif in the C domain of the polymerase. These mutations are often associated with compensatory mutations in the B domain that restore higher replication capacity. Entecavir resistance requires a 2-hit mechanism consisting of the YMDD M204V mutation and another mutation in the polymerase gene. Therefore, the barrier to entecavir resistance is lower in patients who have previously received lamivudine, because these patients are likely to harbor YMDD mutants from lamivudine exposure. This is an important factor when considering treatment regimen in patients with HIV/HBV coinfection, many of whom have a history of lamivudine exposure.

Lamivudine resistance does not confer cross-resistance to tenofovir and may even increase susceptibility to it. Thus, tenofovir may be preferred in patients with lamivudine resistance. Moreover, tenofovir is much more effective against HIV than is entecavir. It is recommended that initial antiretroviral agents include tenofovir and either emtricitabine or lamivudine. Some patients have contraindications to tenofovir, and in those cases, entecavir can be used, but not concomitantly with lamivudine or emtricitabine due to the overlapping resistance patterns.

Hepatitis D Virus Infection

Hepatitis D (delta) virus (HDV) is a small, defective RNA virus that requires HBsAg for transmission and packaging. Of the 350 million individuals with chronic HBV infection, approximately 15 million have also been exposed to HDV. In general, the highest rates of HDV infection are in areas where HBV is endemic, although that is not uniformly the case (Figure 4). Acquiring HBV and HDV during the same exposure (HBV/HDV coinfection) is associated with more severe acute hepatitis and higher mortality than that which occurs with acute HBV monoinfection. The fate of HDV is determined by the host response to HBV, and HDV is cleared if HBV is cleared. HDV superinfection in an HBV carrier can manifest as an acute hepatitis and usually results in chronic HDV infection. Compared with chronic HBV infection, chronic HBV/HDV coinfection is associated with a higher risk of cirrhosis and liver decompensation.

Figure 5 shows diagnostic markers of HDV infection and serologic profiles of HBV/HDV coinfection and superinfection. HBV DNA is usually low or negative in chronic HDV infection because HDV suppresses HBV replication. HDV immunoglobulin M antibody (anti-HDV IgM) is positive in acute infection and can persist in chronic infection; if it does persist, it can be used as a surrogate marker for HDV replication. Anti-HDV IgG is indicative of HDV exposure; it may persist or decline with viral clearance and persists in cases of chronic infection. Qualitative HDV RNA is a marker of viral replication that is positive in chronic infection. Quantitative

![Figure 2. Indicators of antiviral resistance: virologic and biochemical breakthrough and rebound of hepatitis B virus (HBV) over time. ALT indicates alanine transaminase. Adapted from Lok and McMahon.](image-url)

![Figure 3. Primary resistance mutations of hepatitis B virus (HBV). ADV/TDF indicates adefovir/tenofovir disoproxil fumarate; ETV, entecavir; LAM, lamivudine; LdT, telbivudine; Pol/RT, Pol/ reverse transcriptase; RNaseH, ribonuclease H. Adapted from Allen et al. Based on in vitro data and therapy switch following emergence of genotypic adefovir resistance. Adapted from Allen et al.](image-url)
HDV RNA is useful to monitor treatment response but is not readily available and the assays are not standardized. HBsAg is useful to monitor treatment response if quantitative HDV RNA is not available. Decreasing HBsAg titers often herald surface antigen loss and HDV clearance, although surface antigen loss is rare in treatment.

The mainstay of treatment for HDV infection is peginterferon alfa for at least 48 weeks. Conventional interferon alfa can also be used. In the most recent and largest treatment trial, 90 patients with HDV infection were randomized to receive peginterferon alfa with or without adefovir or adefovir alone for 48 weeks. Sustained virologic response (SVR) rates at 6 months after treatment were 31% in the peginterferon alfa group, 26% in the combination group, and 0% in the adefovir group. The oral nucleos(t)ides appear to have limited activity against HDV, because the virus uses host enzymes for replication and thus lacks enzyme targets. An ongoing 2-year trial is examining peginterferon alfa with or without tenofovir in 120 patients; evaluation of this longer treatment duration was prompted by the observation that in some patients response is observed only after prolonged treatment. Week 48 data presented at the 2012 American Association for the Study of Liver Diseases meeting showed undetectable HDV RNA in 42% of the combination patients and 34% of the peginterferon alfa monotherapy group. Final results are awaited. A National Institutes of Health phase II trial of lonafarnib, a prenylation inhibitor, is currently enrolling patients.

An algorithm for managing HDV infection is shown in Figure 6. Anti-HDV IgG should be measured in patients with chronic HBV infection, and if test results are positive, qualitative HDV RNA should be measured. Patients with chronic HBV/HDV coinfection should undergo biopsy to determine the stage of disease as ALT level does not correlate well with histology, and coinfection is associated with a much more severe disease progression. Based on biopsy results and individual patient characteristics, the risks and benefits of peginterferon alfa treatment should be weighed. Ribavirin should be added to treatment for individuals who also have HCV infection. If HBV DNA is greater than 2000 IU/mL, addition of a potent oral nucleos(t)ide analogue to peginterferon alfa should be considered. In patients who clear HDV, reactivation of HBV can occur, and an oral nucleos(t)ide analogue should then be considered for these patients.

Hepatitis E Virus Infection

Hepatitis E virus (HEV) is a single-stranded, nonenveloped RNA virus of the Hepeviridae family that enters the hepatocyte via an unknown mechanism. Five genotypes have been identified, the first 4 of which infect humans. HEV is endemic in many countries of Asia, Central America, and Africa (Figure 7). The genotype distribution of HEV varies geographically. Genotype 1 is most common in Asia, genotype 2 in Central America and Africa, and genotype 3 in the United States. Genotype 4 is seen in Eastern Europe and Asia.

Classic epidemic HEV infection is due to genotype 1 or 2 and is the most common cause of acute hepatitis in endemic areas. There is no known animal reservoir for these genotypes. Epidemic HEV infection is transmitted via the fecal-oral route and is associated with large waterborne outbreaks. Epidemic HEV infection typically occurs in adolescents and young adults and is clinically associated with a high rate of jaundice and cholestasis. Acute epidemic HEV infection is associated with an especially high fatality rate among pregnant women. Genotype 1

Figure 4. Prevalence of hepatitis D (delta) virus (HDV). Adapted from Hughes et al.¹⁹

Figure 5. Diagnostic markers of hepatitis D (delta) virus (HDV) infection and profiles of hepatitis B virus (HBV)/HDV coinfection and superinfection. ALT indicates alanine transaminase; anti-HDV IgG, HDV immunoglobulin G antibody; HBsAg, hepatitis B surface antigen. Adapted from Hughes et al.¹⁹
or 2 HEV infection should be considered in individuals with acute hepatitis who have recently traveled to an endemic area.

Autochthonous cases of HEV infection acquired in the United States and Europe are due to genotype 3 or 4 infections. The clinical course is generally transient and asymptomatic. Autochthonous HEV infection was believed to occur very infrequently in the United States until recently, when seroprevalence studies showed that a substantial proportion of the population has anti-HEV IgG but has never presented with clinical symptoms. In autochthonous HEV infection, as opposed to epidemic HEV infection, the fatality rate is not increased in pregnant women. Also unlike epidemic HEV infection, autochthonous HEV infection can become chronic in immunocompromised patients.

Genotype 3 HEV should be considered in persons with unexplained hepatitis, especially if they are older (older men in particular), solid organ transplant recipients, or HIV-infected or present with acute or chronic liver failure. Acute HEV infection accounts for a small proportion of unexplained hepatitis A virus (HAV), HBV, and HCV. His ALT remained elevated for 2 years. After a report of chronic infection in a solid organ transplant recipient, the patient’s physicians performed HEV RNA testing and detected HEV RNA in serum and feces. Testing of 18-month-old samples also showed HEV RNA in

However, most individuals in the United States with evidence of HEV exposure have no recognized risk factors.

Diagnostic markers for HEV infection and the biochemical profile of acute infection are shown in Figure 8. The clinical course of acute HEV infection is characterized by a 3-week to 8-week incubation period, during which HEV RNA can be detected in the stool or serum. After 8 weeks, symptoms develop in some patients and are usually accompanied by a rise in ALT and the appearance of anti-HEV IgM. IgM persists for months and declines with the resolution of infection. Anti-HEV IgG can persist for years. A diagnostic test that measures HEV IgM is commercially available, although it has not been approved by the FDA and sensitivities and specificities of the assays vary widely. The confirmatory test is HEV RNA, which is not commercially available but can be requested through the National Institutes of Health. In immunocompromised patients, IgM and IgG may be falsely negative. Suspected HEV infection in such patients should also be confirmed by an HEV RNA test.

Initial reports of autochthonous acute HEV infection were in the setting of solid organ transplantation. Subsequently, reports of acute HEV infection in HIV-infected patients in the United States began to appear, including the first case report of HEV genotype 3 as the cause of acute hepatitis in a patient in 2008, another report of HEV genotype 3 and jaundice in a pregnant woman in the same year, and a third report in 2009. Later in 2009, Dalton and colleagues reported the first case of chronic HEV infection in a patient with HIV infection.
HIV-infected individuals are not likely to spontaneously clear HEV infection even with immune reconstitution with antiretroviral therapy. A small number of case reports indicate successful treatment with peginterferon alfa with or without ribavirin or with ribavirin monotherapy, but as of yet, there are no established guidelines or approved regimens for treating these patients.29-32

Summary

Non-HCV viral hepatitis is an important cause of morbidity and mortality, particularly among HIV-infected individuals. HBV is the leading cause of cirrhosis worldwide, and coinfection with HDV causes accelerated progression of liver disease. Autochthonous cases of HEV have been reported among HIV-infected and -uninfected persons and can lead to chronic infection in the setting of immunosuppression. Chronic HEV infection is associated with rapid development of cirrhosis. Reliable antibody assays and molecular tests for HDV and HEV are needed. Peginterferon alfa continues to have a role in treating viral hepatitis, even as we move toward newer, peginterferon alfa-free regimens in the treatment of HCV infection.21

Presented by Dr Price in June 2013. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Price in December 2013.

Financial Affiliations: Dr Price has no relevant financial affiliations to disclose. Her spouse has held stock options for Bristol-Myers Squibb and Johnson & Johnson.

Additional Suggested Reading


References


HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. Am J Gastroenterol. 2006;101(2):297-303.


NEW! Initiating Antiretroviral Therapy in Resource-Limited Settings
Habib Ramadhani Omari, MD, MPH, MHS, and John A. Bartlett, MD
CME Credit Available: 1.50 AMA PRA Category 1 Credits™
Level: Advanced
Antiretroviral therapy has been tremendously successful in reducing morbidity and mortality among HIV-infected persons, and an estimated 10,000,000 people globally are now receiving it. Stigma and the need for strict medication adherence are commonly encountered throughout the world. In resource-limited contexts, there is an additional challenge of maintaining a continuous drug supply and having the ability to properly monitor treatment. A unifying concept is the recognition that early treatment initiation is essential to preserve immunity, prevent the emergence of AIDS-defining illnesses, and decrease HIV transmission.

NEW! Antiretroviral Drugs as Prevention in Men Who Have Sex With Men: Breakthroughs and Challenges
Demetre C. Daskalakis, MD
CME Credit Available: 1.50 AMA PRA Category 1 Credits™
Level: Advanced
Several biologic strategies have been added to the HIV prevention toolbox in the past few years to supplement behavioral and barrier methods of prevention. Data from clinical trials support the use of antiretroviral therapy at all phases of transmission and acquisition risk. These treatments, taken daily, may be used before an HIV exposure to prevent transmission. This intervention, called preexposure prophylaxis (PrEP), is used in individuals at high risk for HIV acquisition. Postexposure prophylaxis (PEP), although supported only by limited data in observational studies, may be used immediately after a high-risk exposure to prevent HIV infection. Treatment of people with HIV infection is itself a preventive intervention, with strong evidence of reduction of transmission in serodiscordant partners in some populations.

NEW! HIV Patient Engagement in the United States: Linkage to and Retention in Care
Sarah E. Rowan, MD, Edvard M. Gardner, MD
CME Credit Available: 1.00 AMA PRA Category 1 Credit™
Level: Basic
Maintenance of a suppressed plasma HIV RNA level is associated with decreased morbidity, mortality, and viral transmission. However, estimates suggest only 25% of HIV-infected individuals in the United States have a suppressed HIV RNA level. The HIV care continuum identifies the stages of HIV care from initial infection through diagnosis, linkage to care, retention in care, and attainment of suppressed HIV RNA levels. By measuring proportions of individuals engaged in each stage of the care continuum, important gaps in HIV care access and delivery, disparities that exist along the care cascade, and ideas for improvement can be identified.

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Hepatitis C Viral Targets
Stuart C. Ray, MD, and Justin R. Bailey, MD, PhD
Approximately 170 million people worldwide are infected with hepatitis C virus (HCV). In the United States and other developed countries, transmission of HCV occurs primarily through injection drug use. Because this is also a common mode of HIV acquisition, approximately 16% of HIV-infected people in the United States and Europe also have HCV infection, and HCV-related liver disease is a major cause of death in persons with HIV infection. All persons born between 1945 and 1964 should be screened for HCV, as should all persons with HIV infection; in those with continued risk behaviors, screenings should be regularly scheduled.

HIV Infection in Older Adults
Harjot K. Singh, MD, ScM, and Eugenia Siegler, MD
Acute HIV Infection in Men Who Have Sex With Men
Leah A. Burke, MD, and Kristen Marks, MD, MS
HIV Cardiovascular Risk
Michelle N. Zikusoka, MD, and Wendy S. Post, MD, PhD

SELECTED CURRENT CASES ON THE WEB
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Clinical Significance of Very Low-Level Viremia
Timothy J. Henrich, MD
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Timothy J. Wilkin, MD, MPH
Dermatologic Complications of HIV Infection
Jennifer A. Cafardi, MD, and John M. Cafardi, MD

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Ergotism is a toxic condition resulting from overexposure to the ergot compounds produced by various fungi of the genus *Claviceps*. Traditionally, such exposure was due to ingestion of infected grains, but long-term or excessive use of medications containing ergot derivatives or drug-drug interactions between these medications can result in ergotism. Ergotamine, typically used to treat migraine, has less than 5% bioavailability due to extensive first-pass metabolism by cytochrome P450 3A4 (CYP3A4). Concurrent intake of ergotamine and strong CYP3A4 inhibitors, such as the HIV protease inhibitors (PIs), can lead to clinical ergotism. A total of 15 cases of clinical ergotism in HIV-infected patients has been published since 1997 (most recently reviewed by Frohlich et al). A total of 15 cases of clinical ergotism in HIV-infected patients has been published since 1997 (most recently reviewed by Frohlich et al).

At a 2011 international HIV symposium in Bangkok, Thailand, a new case of ergotism in an HIV-infected patient was presented that led to subsequent notifications from symposium attendees about additional cases. A questionnaire was then sent to 5 large hospitals in Thailand requesting that they report any cases of ergotism in HIV-infected patients. The first submitted case and a summary of 22 additional cases are presented below.

### Case Presentations

A 47-year-old HIV-infected woman was on an antiretroviral regimen consisting of lamivudine (300 mg once daily), tenofovir (300 mg once daily), and ritonavir-boosted (Ir) saquinavir (1500 mg/100 mg once daily). She presented with necrosis of the left foot and generalized peripheral cyanosis (Figure 1) and reported having had severe headache the day before admission. The pharmacist at her local drugstore advised her to take ergotamine for the relief of her migraine. After taking ergotamine for 1 day, she developed severe pain in both legs and numbness in both feet. She was admitted to the intensive care unit and diagnosed with ergotism. Ergotamine was discontinued immediately and she was given sodium nitroprusside and heparin intravenously. The boosted PI was also discontinued and replaced with the HIV integrase inhibitor raltegravir (400 mg twice daily); the nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs) were continued. Although repeated surgical debridement of the wound was required, amputation was avoided. The patient was discharged after 2 weeks and had a full recovery.

Other responses to the questionnaire yielded an additional 22 new cases of clinical ergotism in Thailand between 2004 and 2011 (Table 1). Patients had used ergotamine for a median of only 1 day (range, 1-14 days). Fortunately, 18 (78.3%) patients had full recovery, but in the remaining 5
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Days on Ergotamine</th>
<th>HIV Protease Inhibitor / Dose (mg) in the Regimen</th>
<th>Signs of Ergotism</th>
<th>Treatment for Ergotism</th>
<th>Treatment Outcome</th>
<th>Hospital Stay: Yes or No (days, if reported)</th>
<th>Prior to Ergotamine Use</th>
<th>CD4+ Count (cells/μL)</th>
<th>HIV RNA Level (copies/mL)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>2</td>
<td>ATV/r 300/100 qd</td>
<td>Severe headache, brain swelling, arterial spasm in all extremities with occlusion of bilateral radial and ulnar arteries on CTA</td>
<td>Heparin IV, nifedipine</td>
<td>Full recovery</td>
<td>Yes (11)</td>
<td>360</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>31</td>
<td>14</td>
<td>SQV/r 1600/100 qd</td>
<td>Severe arterial spasm in all extremities with cyanosis and pain</td>
<td>Heparin IV, nifedipine</td>
<td>Full recovery</td>
<td>Yes (4)</td>
<td>273</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>44</td>
<td>1</td>
<td>LPV/r 400/100 bid</td>
<td>Severe arterial spasm in all extremities with cyanosis and pain; nausea and vomiting</td>
<td>Nitroprusside, nifedipine</td>
<td>Full recovery</td>
<td>Yes (5)</td>
<td>420</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>44</td>
<td>1</td>
<td>PEP: LPV/r 400/100 bid</td>
<td>Severe arterial spasm with cyanosis and pain</td>
<td>Nitroprusside, nifedipine, heparin</td>
<td>Full recovery</td>
<td>Yes (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>30</td>
<td>1</td>
<td>IDV/r 400/100 bid</td>
<td>Severe arterial spasm with cyanosis of both legs</td>
<td>Nitroprusside, heparin, iloprost</td>
<td>Autoamputation of all toes on right foot</td>
<td>Yes (6)</td>
<td>267</td>
<td>&lt;40</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>47</td>
<td>1</td>
<td>SQV/r 1500/100 qd</td>
<td>Severe arterial spasm with cyanosis and pain in all extremities</td>
<td>Nitroprusside, nifedipine, heparin</td>
<td>Dry gangrene in left big toe</td>
<td>Yes (16)</td>
<td>300</td>
<td>&lt;40</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>38</td>
<td>1</td>
<td>LPV/r 400/100 bid</td>
<td>Severe arterial spasm with cyanosis and pain in all extremities</td>
<td>Nitroprusside, heparin, iloprost</td>
<td>Full recovery</td>
<td>Yes (5)</td>
<td>556</td>
<td>&lt;40</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>46</td>
<td>1</td>
<td>SQV/r 1000/100 bid</td>
<td>Severe arterial spasm with cyanosis and pain in all extremities</td>
<td>Nitroprusside, nifedipine, heparin</td>
<td>Full recovery</td>
<td>Yes (4)</td>
<td>800</td>
<td>&lt;40</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>39</td>
<td>1</td>
<td>DRV/r 600/100 bid</td>
<td>Severe nausea and vomiting; palpitation, fatigue, and numbness in right leg</td>
<td>None</td>
<td>Full recovery</td>
<td>No</td>
<td>360</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>36</td>
<td>1</td>
<td>IDV/r 800/100 bid</td>
<td>Severe nausea and vomiting; palpitation, fatigue, and numbness in right leg; cyanosis of right leg; hypotension</td>
<td>Nitroprusside, nifedipine, heparin</td>
<td>Full recovery</td>
<td>Yes (5)</td>
<td>460</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>38</td>
<td>1</td>
<td>IDV/r 600/100 bid</td>
<td>Severe nausea and vomiting; palpitation, fatigue, numbness, and cyanosis in right leg</td>
<td>Nitroprusside, nifedipine, heparin</td>
<td>Full recovery</td>
<td>Yes (4)</td>
<td>780</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>43</td>
<td>3</td>
<td>SQV/r 1500/100 qd</td>
<td>Nausea and vomiting; palpitation, fatigue, numbness, and cyanosis in right leg</td>
<td>Nitroprusside, nifedipine, heparin</td>
<td>Ulcer on right foot, persistent numbness in right leg (&gt;3 mo)</td>
<td>Yes (8)</td>
<td>630</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Age (y)</td>
<td>Weeks of Exposure</td>
<td>Regimen</td>
<td>Symptoms</td>
<td>Treatment</td>
<td>Outcome</td>
<td>CD4 Count (cells/mm³)</td>
<td>Viral Load at Baseline (copies/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>38</td>
<td>1</td>
<td>SQV/r 1500/100 qd</td>
<td>Severe nausea and vomiting; palpitation and numbness in left leg</td>
<td>Observation only</td>
<td>Full recovery</td>
<td>No</td>
<td>780</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>38</td>
<td>1</td>
<td>IDV/r 800/100 bid + EFV 600 qd</td>
<td>Fainting; nausea and vomiting; pulseless lower extremities; numbness and paresthesia in both legs</td>
<td>Nitroprusside, nifedipine</td>
<td>Full recovery</td>
<td>Yes</td>
<td>757 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>NA</td>
<td>7</td>
<td>EFV 600 qd</td>
<td>Hypotension, limb ischemia</td>
<td>Nitroprusside, heparin, nifedipine</td>
<td>Full recovery</td>
<td>Yes</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>NA</td>
<td>7</td>
<td>IDV/r 800/100 bid</td>
<td>Hypoxemia, shock</td>
<td>Nitroprusside</td>
<td>Death</td>
<td>Yes</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Female</td>
<td>44</td>
<td>7</td>
<td>LPV/r 400/100 bid</td>
<td>Peripheral cyanosis of both legs</td>
<td>Nitroprusside, amlodipine, heparin</td>
<td>Full recovery</td>
<td>Yes (11)</td>
<td>799</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Female</td>
<td>44</td>
<td>3</td>
<td>LPV/r 400/100 bid</td>
<td>Numbness and pain in both legs, arterial occlusion</td>
<td>Warfarin, nitric oxide donor drug</td>
<td>Full recovery</td>
<td>Yes (10)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Female</td>
<td>31</td>
<td>2</td>
<td>LPV/r 400/100 bid</td>
<td>Diffuse ischemia and bluish discoloration of both lower extremities with nonpalpable pulse and undetectable BP</td>
<td>Off LPV/r; vasodilator</td>
<td>Full recovery</td>
<td>Yes</td>
<td>320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Female</td>
<td>36</td>
<td>NA</td>
<td>LPV/r 400/100 bid</td>
<td>Gangrene in feet and hands with an undetectable pulse and low BP</td>
<td>Off LPV/r</td>
<td>Amputation of both legs below the knee</td>
<td>Yes</td>
<td>363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Female</td>
<td>33</td>
<td>NA</td>
<td>LPV/r 400/100 bid</td>
<td>Dizziness, dropping BP, bluish extremities</td>
<td>Off LPV/r; vasodilator</td>
<td>Full recovery</td>
<td>Yes</td>
<td>655</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Male</td>
<td>38</td>
<td>NA</td>
<td>IDV/r 400/100 bid</td>
<td>Bluish extremities</td>
<td>Off IDV/r</td>
<td>Full recovery</td>
<td>Yes</td>
<td>266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Female</td>
<td>32</td>
<td>1</td>
<td>LPV/r 400/100 bid</td>
<td>Severe nausea and vomiting; palpitation, fatigue, and numbness in left leg</td>
<td>Observation only</td>
<td>Full recovery</td>
<td>No</td>
<td>459</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATV indicates atazanavir; bid, twice daily; BP, blood pressure; CTA, computed tomography angiography; DRV, darunavir; EFV, efavirenz; IDV, indinavir; LPV, lopinavir; NA, not available; PEP, postexposure prophylaxis; qd, once daily; /r, ritonavir boosted; SQV, saquinavir.

*Cases occurred between 2004 and 2011.*
(21.7%) patients, amputation, gangrene, ulcer with persistent numbness, and 1 death occurred. There were no apparent risk factors, for example, length of ergotamine use, type of HIV PI, or administration of vasodilators, that could predict the outcome of the drug-drug interaction. The questionnaire asked only for the third agent in the antiretroviral drug regimen, assuming that the nRTIs were not responsible for the interaction.

This series of 23 cases of clinical ergotism in patients taking antiretroviral drugs is unique in many ways. It is the largest number of reported patients with clinical ergotism. It also includes the first cases of ergotism in patients on relatively new HIV PIs such as atazanavir and darunavir and in a health care worker who received post-exposure prophylaxis after a needle stick injury. One patient in the series (patient 15 in Table 1) was taking the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) efavirenz, which can act as a CYP3A inducer. Possibly, the drug-drug interaction in this patient occurred at the first dose of efavirenz, when CYP3A inhibition may be the dominant effect. In the combination of efavirenz and a boosted PI, the PI effect is stronger, thus the drug-drug interaction in patient 14 was likely caused by indinavir/r. It comes as no surprise that the majority of patients in this case series were women as migraine occurs more often in women than in men.

Conclusion

This report is a warning that increased global access to antiretroviral drugs, boosted PIs in particular, together with poor monitoring of potential drug-drug interactions can have severe clinical consequences. Also, the use of cobicistat, a CYP3A inhibitor prescribed as an alternative boosting agent to ritonavir, is contraindicated in patients taking ergot alkaloids. Patients and health care workers must be instructed to discuss the use of any coadministered medications, including over-the-counter products, with their HIV practitioner or supervising physician. The potential for drug-drug interactions can be further increased when individuals do not inform pharmacists of their positive HIV serostatus because of concerns about potential stigma. The importance of Internet access in resource-limited settings cannot be underestimated, and many excellent HIV-related online resources geared to the practicing clinician are available (reviewed in Krakower et al4). Short of dispensing ergotamine by prescription only, and in the absence of automated medication surveillance systems, education and effective communication about the potential for drug-drug interactions is necessary and important. Concurrent intake of ergotamine and strong CYP3A4 inhibitors, such as HIV PIs, can produce a potentially life-threatening drug-drug interaction that can be prevented.

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References

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