Perspective  CME

Neurologic Complications in Persons With HIV Infection in the Era of Antiretroviral Therapy 97
Dennis Kolson, MD, PhD

Dynamics of HIV Infection in the Central Nervous System  Early Neurologic Manifestations of Acute HIV Infection  Chronic Neurologic Manifestations of HIV Infection

Special Contribution  CME

Understanding Hepatitis C Virus Drug Resistance: Clinical Implications for Current and Future Regimens 103
David L. Wyles, MD; Anne F. Luetkemeyer, MD

Nomenclature and Identification of Resistance  Considerations for Resistance Testing for NSSA Inhibitor Treatment–Naive Individuals With HCV Genotype 1 Infection  Considerations for Resistance Testing for NSSA Inhibitor Treatment–Naive Individuals With HCV Genotype 3 Infection  RAS Testing at Time of Failure of NSSA Inhibitor–Based Treatment  Retreatment After Failure of an NSSA Inhibitor–Based Regimen  Retreatment After Failure of an NSSA Inhibitor–Based Regimen: Tailoring to the NSSA RAS Profile  Future Therapies for Retreatment After Failure of an NSSA Inhibitor–Based Regimen  When Resistance Testing Is Not Available

Cases From the Field  CME

Barriers to Treatment Access for Chronic Hepatitis C Virus Infection: A Case Series 110
Alexander J. Millman, MD; Boatema Ntiri-Reid, JD, MPH; Risha Irvin, MD, MPH; Maggie H. Kaufmann, MA, MPH; Andrew Aronsohn, MD; Jeffrey S. Duchin, MD; John D. Scott, MD, MSc; Claudia Vellozzi, MD, MPH

Sustained Off-Treatment Response After Discontinuation of Long-Term Nucleos(t)ide Analogue Treatment in HBeAg-Seronegative Hepatitis B: A Case Series 114
Marion Muche, MD; Ulrike Meyer, MD; Britta Siegmond, MD; Rajan Somasundaram, MD; Hans-Joerg Epple, MD
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Upcoming Activities
Guidelines for Authors and Contributors
Important Dates

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On completion of this activity, the learner will be able to:

- Describe neurologic complications in persons with HIV disease
- Describe how viral resistance to direct-acting antiviral drugs may impact their effectiveness during treatment of hepatitis C virus (HCV) disease
- Identify barriers to treatment for chronic HCV disease
- Describe the sustained off-treatment response after discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg-sero-negative persons with hepatitis B disease

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 infections.

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

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Neurologic Complications of HIV Infection in the Era of Antiretroviral Therapy

Neurologic complications in persons with HIV infection are less severe in the era of potent antiretroviral therapy but remain highly prevalent. Prior to the use of antiretroviral therapy, opportunistic infections of the central nervous system (CNS) and CNS malignancy were common. Progressive multifocal leukoencephalopathy (PML), however, remains a diagnostic challenge in HIV-infected individuals, and no effective antiviral treatment for PML is currently available. Primary neurologic complications of acute HIV infection include aseptic meningitis and acute inflammatory demyelinating polyneuropathy. Among the neurologic complications of chronic HIV infection, HIV-associated neurocognitive disorders (HAND) remain most prevalent. The use of antiretroviral therapy has greatly reduced the severity of HAND, under which progressive HIV-associated dementia once predominated, to a milder chronic form of potentially disabling neurocognitive impairment. The persistence of HAND in individuals with virologic suppression suggests a need for adjunctive therapies for limiting its morbidity. This article summarizes a presentation by Dennis Kolson, MD, PhD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, held in Chicago, Illinois, in May 2017.

Keywords: HIV, HIV-associated neurocognitive disorders, HAND, inflammatory demyelinating polyneuropathy, polyneuropathy, immune reconstitution inflammatory syndrome, IRIS, progressive multifocal leukoencephalopathy, PML

In the era of potent antiretroviral therapy, neurologic complications of HIV infection are less severe but are still surprisingly common. Before the availability of antiretroviral therapy, approximately 20% of HIV-infected persons died with HIV-associated dementia (HAD), the most severe form of HIV-associated neurocognitive disorder (or disorders; HAND), and most individuals who died with HAD and underwent autopsy were found to have HIV encephalitis. HAD is now observed in a much smaller proportion of persons (1%-4%), and HIV encephalitis is, essentially, never seen at autopsy.

Before the availability of antiretroviral therapy, HIV-infected persons were also at increased risk for severe complications of opportunistic infections (OIs) such as cytomegalovirus infection, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML). Nonetheless, in the era of suppressive antiretroviral therapy, there remains a high prevalence of primary manifestations (those not due to OIs) of HIV infection, including persistent HAND and peripheral neuropathy. Although severe HAND, in the form of HAD, is much less common, a less severe but potentially disabling form termed mild neurocognitive disorder (MND) is seen in approximately 15% of individuals with virologic suppression. The prevalence of peripheral neuropathy (approximately 30%-40% with the earliest antiretroviral regimens), particularly the classic distal symmetric polyneuropathy (DSP), has been reduced with the use of less toxic antiretroviral regimens.

Dynamics of HIV Infection in the Central Nervous System

HIV enters the central nervous system (CNS) early in the course of infection, within days to 1 or 2 weeks of systemic inoculation. A major entry mechanism is likely transendothelial migration of infected CD4+ T lymphocytes, and another potential entry mechanism is migration of infected monocytes. Within approximately the first 4 months of systemic infection, HIV-infected T cells may establish a compartmentalized reservoir in which the virus can evolve independently from virus in plasma, and there is evidence of the emergence of macrophage-tropic virus within the first 2 years of HIV infection. Compartmentalization of virus within T cells in the CNS is estimated to occur in 20% to 50% of HIV-infected persons during this time. Whether this potential CNS compartmentalized HIV reservoir (perivascular macrophages) is established through transendothelial migration of infected blood monocytes, infection through entry of free virions, or cell-mediated virus transfer is controversial. Evidence suggests that MDMs can phagocytose HIV-infected T cells, which has been suggested to lead to a nonproductive “infection” without the release of infectious virions.

Viral replication within the CNS is associated with production of proinflammatory cytokines and neurotoxins, including glutamate and reactive oxygen species, which indicates a state of oxidative stress that likely drives HAND. Uncontrolled HIV replication is associated with more severe HAND, and well-controlled HIV replication (suppression) is associated with less severe HAND. In the pre-antiretroviral therapy era, uncontrolled CNS HIV replication was associated with profound neuronal apoptosis and dropout in association with HIV encephalitis. In the era of suppressive antiretroviral therapy, these characteristic pathologic findings in the CNS are no longer observed, suggesting that microscopic structural alterations or functional physiologic alterations in neuronal populations might contribute substantively to the clinical symptomatology of HAND. As with systemic HIV infection in the context of suppressive antiretroviral therapy, there is evidence for immune activation, inflammation, and oxidative...
Early Neurologic Manifestations of Acute HIV Infection

Acute CNS HIV infection can be associated with aseptic meningitis and the rarer acute inflammatory demyelinating polyneuropathy (AIDP) syndrome (Figure). Aseptic meningitis typically occurs within the first 10 to 20 days after systemic HIV infection in up to 25% of individuals. Classic symptoms of aseptic meningitis are headache, fever, and stiff neck, which are self-limited over a 2- to 4-week period. Individuals are generally HIV antibody negative during this time, and the diagnosis of HIV infection is often missed in those presenting with such symptoms.

Acute Inflammatory Demyelinating Polyneuropathy

AIDP, also called Guillain-Barré syndrome, occurs in less than 1% of HIV-infected individuals and is likely to go undiagnosed in the primary care setting. Onset of AIDP is most often observed during HIV seroconversion 3 to 4 weeks after initial infection, and following the symptoms of aseptic meningitis (Figure). Typically, AIDP progresses rapidly as a uniphasic illness over a period of days to fewer than 4 weeks. AIDP is characterized by a white blood cell count in the cerebrospinal fluid of 50/μL or lower and an elevated protein level. It presents as ascending symmetric motor weakness of the distal extremities, with potentially life-threatening respiratory and autonomic dysfunction occurring in up to one-third of individuals.

Treatment of AIDP in HIV-infected individuals includes plasmapheresis and the administration of intravenous γ-globulin. Emerging evidence suggests that short-term treatment with corticosteroids may be effective when AIDP occurs in the setting of immune reconstitution inflammatory syndrome (IRIS) after initiation of antiretroviral therapy.

Chronic Neurologic Manifestations of HIV Infection

Chronic neurologic complications of HIV infection include chronic inflammatory demyelinating neuropathy (CIDP), DSP, IRIS, PML, and HAND (Figure). Each of these complications is discussed below.

Chronic Inflammatory Demyelinating Neuropathy

CIDP is typically observed after 1 or more years of HIV infection (Figure). The condition is marked by motor paralysis that may progress slowly over 8 or more weeks or express a relapsing or remitting course of exacerbations and remissions. CIDP is a demyelinating-remyelinating disease that, in biopsy of peripheral nerves, shows evidence of myelin loss followed by partial remyelination in what is described pathologically as “onion bulb formation,” reflecting new layers of myelin at the nerve terminal.

Treatment of CIDP includes plasmapheresis and administration of intravenous γ-globulin or corticosteroids, and responses to these treatments among HIV-infected individuals are generally similar to those among uninfected individuals. However, data from a recent study suggest that corticosteroids might be somewhat more effective among HIV-infected individuals than among uninfected individuals.

Distal Symmetric Polyneuropathy

The most common neuropathic problem in people with HIV infection, whether or not they are taking antiretroviral...
therapy, is classically recognizable DSP.\textsuperscript{18,19} DSP is thought to have at least 2 etiologies: 1) peripheral nerve injury associated with replication of virus in macrophages within the dorsal root ganglia or within macrophages in the peripheral nerves;\textsuperscript{20} and 2) neurotoxic effects of antiretroviral drugs. A primary culprit in the latter regard was the nucleoside analogue reverse transcriptase inhibitor stavudine, although other nucleoside reverse transcriptase inhibitors (didanosine and zalcitabine) and, occasionally, protease inhibitors (indinavir, saquinavir, and ritonavir) are also associated with DSP.\textsuperscript{21} Although the prevalence of DSP resulting from the toxic effects of antiretroviral therapy has decreased with the use of newer treatments, DSP persists in some individuals, perhaps because of damage resulting from residual effects of HIV replication or past use of neurotoxic antiretroviral therapy.\textsuperscript{14,21}

In contrast to demyelinating polyneuropathies, this axonal neuropathy is characterized by burning pain in the distal extremities following a stocking-glove distribution and is often without motor manifestations. DSP is easily distinguished from demyelinating neuropathies in nerve conduction studies. However, DSP is often mistaken for diabetic neuropathy in people with type 2 diabetes.

DSP is not readily treatable. Antiepileptic drugs (eg, gabapentin, lamotrigine, and pregabalin) have been used to treat DSP, but evidence of the benefits of such treatments is weak. However, single-dose applications of high-dose, topical capsaicin to the soles and sides of affected feet reportedly provided relief in up to 30% to 40% of individuals over a 12-week period.\textsuperscript{22} Thus, several annual treatments of high-dose, topical capsaicin may be appropriate for some people.

**Immune Reconstitution Inflammatory Syndrome**

IRIS in the CNS is most common approximately 1 to 6 months after the initiation of suppressive antiretroviral therapy (Figure), particularly in individuals who begin therapy with a lower CD4+ cell count and higher viral load.\textsuperscript{23} Findings can be vague and symptoms may range from mild (eg, headaches and some dizziness) to very severe (eg, encephalopathy, disorientation, delirium, coma, and stupor). CNS IRIS results from heightened immunologic and inflammatory responses, generally in the setting of a history of infection with opportunistic pathogens. However, IRIS can also occur in HIV-infected individuals with exposed CNS antigens from other causes, as in the case of multiple sclerosis\textsuperscript{24} or stroke.\textsuperscript{25} Thus, the diagnosis of CNS IRIS may be missed in individuals with no history of OIs. The prevalence of CNS IRIS is approximately 1% among all HIV-infected individuals initiating antiretroviral therapy, but up to 30% or higher in those initiating therapy with a history of concurrent or antecedent cryptococcal meningitis, tuberculosis, or PML.\textsuperscript{23,26}

CNS IRIS is diagnosed using magnetic resonance imaging (MRI) of the brain, with administration of intravenous gadolinium to detect regional defects in the blood-brain barrier consistent with inflammation. Treatment for IRIS-related complications includes supportive care, treatment of an underlying OI if one is present, and abscess drainage in cases of cryptococcal meningitis with increased intracranial pressure. Treatment with steroids has reportedly been helpful, and available evidence suggests that intravenous methylprednisolone for several days up to a week followed by oral prednisone tapered over the course of 2 to 3 weeks may be beneficial.\textsuperscript{23} Results from the COAT (Cryptococcal Optimal ART Timing) trial demonstrated that delaying antiretroviral therapy after the initial diagnosis and treatment of cryptococcal meningitis substantially reduced mortality from all causes, including CNS IRIS.\textsuperscript{27} Recent HIV treatment guidelines recommend delaying initiation of antiretroviral therapy at least until after completion of antifungal induction therapy (2 weeks)\textsuperscript{28} and even through completion of consolidation therapy (10 weeks) for individuals with increased intracranial pressure or low white blood cell counts in cerebrospinal fluid.\textsuperscript{29}

**Progressive Multifocal Leukoencephalopathy**

Asymptomatic infection with JC virus, which causes PML, is widespread in the general population (70%-80%), and among HIV-infected populations not receiving antiretroviral therapy, the prevalence of PML is approximately 4%. With suppressive antiretroviral therapy, the incidence of PML has decreased from approximately 10 cases per 1000 person-years to 1 case per 1000 person-years,\textsuperscript{30} with a 1-year fatality rate of approximately 30% in antiretroviral therapy–experienced individuals.

The diagnosis of PML requires a high level of clinical suspicion, as its clinical symptoms and radiographic features are sometimes mistaken for an acute stroke. PML is characterized by changes in white matter that can often be observed early in the occipital areas of the brain, although other regions are also affected. PML lesions tend to be large and expand over time, unlike those observed with stroke. PML is sometimes confused with stroke because of the slow evolution of hemiparesis in association with memory loss, slurred speech, and dysarthria, which mimic a slowly evolving stroke. However, in clinical presentation, PML is accompanied by seizures in 15% to 30% of cases, in comparison with classic cortical stroke, in which seizure frequency is estimated at approximately 3% to 6%.\textsuperscript{31} Further, PML is often accompanied by visual symptoms including blind spots in visual fields, reflecting occipital predominance.

There are no known effective direct antiviral treatments for PML; studies of treatment with intrathecal cytosine arabinoside and cidofovir have failed to show benefit. However, reconstitution of immune function with suppressive antiretroviral therapy is associated with increased long-term survival.\textsuperscript{30}

**HIV-Associated Neurocognitive Disorders**

HAND and DSP remain the most common HIV-associated neurologic complications in the era of suppressive antiretroviral therapy. HAND is believed to largely reflect the persistence of immune activation, inflammation, and oxidative stress.
in the CNS despite viral suppression. The risk of developing HAND might increase with age in the HIV-infected population. Studies of cerebrospinal fluid and plasma in individuals with HAND have shown elevated low-molecular-weight neurofilament in the CNS, indicating neuronal damage, and elevated soluble CD163 and neopterin (markers of monocyte-macrophage activation) in plasma and the CNS. Historically, the best plasma biomarker for risk of HAND has been nadir CD4+ cell count, but soluble CD163 may take its place.

Diagnosis of HAND is based on formal neuropsychologic testing using the Frascati criteria and assessment of activities of daily living. HAND often goes undiagnosed in individuals who present without overt symptoms of dementia. Although the prevalence of HIV-associated dementia has declined in the era of suppressive antiretroviral therapy, MND (the less severe form of HAND) still functionally impairs approximately 20% of individuals with virologic suppression. Individuals with MND, by definition, suffer cognitive dysfunction and functional impairment in certain activities of daily living. There are no typical MRI findings for HAND, although approximately one-third of individuals exhibit abnormalities in white matter, distinct from those seen in PML, with or without brain atrophy.

There are conflicting reports on the effectiveness of using antiretroviral regimens with increased CNS antiviral efficacy to treat or prevent HAND, using a scaling system that estimated antiviral activity of antiretroviral drugs within the CNS compartment (CNS penetration effectiveness [CPE]). There are currently no clear recommendations for altering antiretroviral regimens based on CPE. That antiretroviral drugs may directly induce oxidative stress and neuronal damage in the CNS, as they have been shown to do in studies in vitro, remains a concern.

Intensification of antiretroviral therapy may currently be the best hope for managing and perhaps decreasing the prevalence of HAND. Intensification of antiretroviral therapy with maraviroc led to improvements in neurocognitive dysfunction in individuals with MND, by definition, suffer cognitive dysfunction and functional impairment in certain activities of daily living. There are no typical MRI findings for HAND, although approximately one-third of individuals exhibit abnormalities in white matter, distinct from those seen in PML, with or without brain atrophy.

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Intensification of antiretroviral therapy may currently be the best hope for managing and perhaps decreasing the prevalence of HAND. Intensification of antiretroviral therapy with maraviroc led to improvements in neurocognitive dysfunction over a 12-month period. The large AIDS Clinical Trials Group 5324 study, which is currently enrolling participants, will examine the effects of intensification of antiretroviral therapy with dolutegravir and maraviroc on neurocognitive performance in individuals with HAND.

**Adjunctive Neuroprotective Strategies**

The future of treatment for HAND is likely to involve adjunctive therapies to control neuroinflammation and oxidative stress, in addition to antiretroviral therapy. Studies of the brains of individuals who have died with HIV infection have identified what might be a unique brain “signature” in those with HAND: a deficiency of the cytoprotective enzyme heme oxygenase-1. Heme oxygenase-1 is a rapidly inducible endogenous cytoprotective enzyme that serves to reduce cytotoxic injury in cells undergoing oxidative stress from a variety of insults. Therapeutic strategies for increasing heme oxygenase-1 expression in several inflammatory diseases are being pursued in preclinical and in vitro studies. Other adjunctive neuroprotective strategies for HAND that target pathways of inflammation and immune activation have been suggested.

**Summary**

The acute neurologic complications of HIV infection (eg, meningitis and AIDP) have not changed since the availability of suppressive antiretroviral therapy, although several of the chronic neurologic complications have changed. Opportunistic CNS infections, including PML, are now rare, although PML risk might increase with advancing age. DSP from the toxic effects of antiretroviral drugs has decreased, but DSP attributed to the damaging effects of HIV replication (pre- or post-antiretroviral therapy) in the dorsal root ganglia or peripheral nerves might represent a separate and persistent contributor to this condition. HAND is less severe with suppressive antiretroviral therapy but is still common enough to represent a significant morbidity among HIV-infected individuals, and its prevalence might increase with the advancing age of this population.


Affiliations in the past 12 months: Dr. Kolson has no relevant financial affiliations to disclose.

**References**


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Presenter: Jennifer J. Kiser, PharmD, University of Colorado

Finding and Eliminating the HIV Reservoir—September 7, 2017
Presenter: Daniel C. Douek, MD, PhD, National Institutes of Health

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

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Presenter: Dana W. Dunne, MD, Yale University

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Milwaukee, Wisconsin, Half-Day HCV Workshop—November 28, 2017
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Immunizations for HIV-Infected Persons
Authors: Brian T. Montague, DO, MS, MPH, University of Colorado; Steven C. Johnson, MD, University of Colorado. Released July 13, 2017.

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.

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These activities have been approved for AMA PRA Category 1 Credit™.

102
Special Contribution
Understanding Hepatitis C Virus Drug Resistance: Clinical Implications for Current and Future Regimens

David L. Wyles, MD; Anne F. Luetkemeyer, MD

Viral resistance to direct-acting antiviral drugs may impact their effectiveness during treatment of hepatitis C virus (HCV) infection. Most data on HCV drug resistance concern genotypes 1 and 3. The clinical impact of resistance to HCV nonstructural protein 5A (NS5A) inhibitors and a practical approach to indications and methods for resistance testing are discussed.

**Keywords:** hepatitis C virus, HCV, resistance, resistance-associated substitution, RAS, mutations, HCV treatment, HCV retreatment, direct-acting antiviral, NS5A

Viral resistance to hepatitis C virus (HCV) direct-acting antiviral (DAA) drugs has emerged as an important consideration to optimal DAA use during treatment of HCV infection. The replication dynamics of HCV in chronically infected humans combines a high rate of viral production with an error-prone RNA polymerase, providing a favorable setting for the emergence and enrichment of viral nucleotide substitutions that confer resistance to specific drugs or drug classes, particularly under drug selection pressure. Although, in theory, all resistance-associated substitutions (RASs) in all HCV proteins are generated daily in an infected individual, RASs that have clinical impact are much more limited. These limitations are determined by drug class, viral genotype, replication fitness conferred by the RAS, and patient characteristics such as prior HCV treatment and the presence of cirrhosis.

Most data on the impact and selection of RASs concern HCV genotype 1 infection, and to a lesser extent, genotype 3 infection. Certain polymorphisms that confer resistance to some DAA drug classes are present with other HCV genotypes (eg, genotype 2). However, these polymorphisms have limited clinical impact and there is a lack of commercially available diagnostic testing options. In HCV genotype 1 infection, viral subtype plays an important role in the prevalence of preexisting (baseline) nonstructural protein 5A (NS5A) RASs and their clinical impact.

Of the major HCV antiviral drug classes, there is only compelling evidence for the impact of NS5A inhibitor RASs on treatment outcome. The RASs impacting the NS5B nucleotide inhibitor sofosbuvir are not present in individuals who are not exposed to this drug, and these RASs emerge infrequently (in approximately 1%) in those whose therapy with this drug has failed. The signature NS5B mutation, S282T, confers a modest level of resistance based on in vitro data (3×-10× fold-change in median effective concentration [EC₅₀]) and is unfit for viral replication (replication fitness approximately 8% of wild-type). However, clinically, S282T has not been shown to impact the efficacy of sofosbuvir. Thus, there is no current role for NS5B resistance testing in treatment-naive or -experienced individuals.

Clinically significant RASs to NS3 protease inhibitors (PIs) are also rare in the absence of prior drug exposure. Although much attention has been paid to the Q80K polymorphism in HCV genotype 1a, current evidence does not support a substantial effect of this variant on responses to treatment with simeprevir plus sofosbuvir at recommended durations, with the exception of treatment-experienced individuals with cirrhosis, for whom Q80K testing is recommended.

Further, no impact is expected of the Q80K polymorphism on other NS3 inhibitors such as ritonavir-boosted paritaprevir and

**Table 1. Resistance-Associated Substitutions in the Hepatitis C Virus (HCV) Nonstructural Protein 5A (NS5A) Gene Associated With Resistance to NS5A Inhibitors, by Genotype**

<table>
<thead>
<tr>
<th>Resistance-associated substitutions</th>
<th>HCV Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
</tr>
<tr>
<td>K24 E/R/N</td>
<td>M/L 28 M/G/T</td>
</tr>
<tr>
<td>M28 A/T/G/V</td>
<td>R30 H</td>
</tr>
<tr>
<td>Q30 R/K/E/H/L/Y/G/T/D/I</td>
<td>L31 V/M/F/I</td>
</tr>
<tr>
<td>L31 M/V/F</td>
<td>P58 S</td>
</tr>
<tr>
<td>H54 R</td>
<td>Y 93 H/N/C/S/R</td>
</tr>
<tr>
<td>H58 D/P/R</td>
<td></td>
</tr>
<tr>
<td>E62 D</td>
<td></td>
</tr>
<tr>
<td>Y93 H/N/C/S/F/L</td>
<td></td>
</tr>
</tbody>
</table>

*The letter preceding the number is the wild-type amino acid; the number is the position on the gene; and the letter or letters after the position are the amino acid substitution(s) at that position that are associated with NS5A inhibitor resistance.

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gazoprevir. NS3 RASs emerge in approximately 50% (range, 25%-78%) of cases of virologic failure of a PI-containing regimen, with the most prominent variants at positions 155, 156, and 168. The R155K variant is only observed in genotype 1a HCV and does not impact the activity of grazoprevir. By contrast, variants of D168 and A156 are the most clinically relevant, as they emerge with relative frequency, impact the activity of all currently available HCV PIs, and are observed in both genotype 1a and 1b infections. Fortunately, most variants at these positions display poor replicative fitness in vitro and are lost rapidly following removal of drug selective pressure. It is not known if previously selected variants can still impact subsequent therapy once they are no longer detectable by sequencing.

RASs in NS5A are the most important clinically. The major RASs are depicted in Table 1. General characteristics of NS5A RASs are outlined in the Box. Substantial cross-resistance among currently available NS5A inhibitors is also notable. RASs at key positions (28, 30, 31, and 93) in HCV genotype 1a result in broad cross-resistance to early-generation NS5A inhibitors. Exceptions include the lack of impact of the L31M RAS on ombitasvir and of the M28V RAS on elbasvir or ledipasvir. Although velpatasvir is less impacted by these NS5A RASs, Y93H/N RASs in genotype 1a still confer high levels of resistance to this drug. The investigational next-generation NS5A inhibitors pibrentasvir (ABT-530) and razuvir (MK-8408), which are anticipated to become available in the next year, retain activity against all of the key single-position NS5A RASs in HCV genotypes 1a and 1b and, therefore, may retain activity despite resistance to current NS5A inhibitors.

### Nomenclature and Identification of Resistance

The prevalence and clinical impact of RASs correlate with how RASs are defined and the sequencing methods used to detect them within RNA quasispecies. In order of decreasing prevalence, the RASs studied for NS5A are: 1) NS5A inhibitor resistance–associated polymorphisms, defined as any variation from the consensus sequence at all positions associated with resistance to any NS5A inhibitor (a specific amino acid change does not necessarily impact the in vitro activity of any NS5A inhibitor); 2) NS5A inhibitor class RASs, defined as amino acid variants at all positions associated with resistance to any NS5A inhibitor that confer in vitro resistance to at least 1 NS5A inhibitor; and 3) NS5A drug-specific RASs, defined as amino acid variants that impact the activity in vitro of a specific drug. The threshold for considering the impact of RASs on a specific drug varies based on the in vitro fold-change in EC50 and ranges from 2x to 20x or even 100x fold-change in EC50 (see Table 2).

Assays vary in their threshold for detecting NS5A RASs. Ultradeep sequencing (UDS, or next-generation sequencing) allows the detection of RNA substitutions present in 1% of the viral population (subject to the input RNA and number of reads obtained). This technique is often used in research supporting clinical drug–development programs. This approach provides a detailed assessment of RASs but, at the 1% threshold, is too sensitive for optimal clinical decision making.

### Box. Characteristics of Nonstructural Protein 5A (NS5A) Resistance-Associated Substitutions (RASs)

- **Baseline (ie, prior to drug exposure)** NS5A RASs are relatively prevalent (13% prevalence in genotype 1a infection, 18% prevalence in genotype 1b infection and 12%-17% prevalence in genotype 3 infection).
- The clinical impact of baseline NS5A RASs varies by hepatitis C virus (HCV) genotype and subtype, with the largest impact in genotype 1a and 3 infections.
- Key NS5A RASs by genotype are:
  - **Genotype 1a.** M28A/T/V, Q30E/H/K/R, L31M/V, and Y93H/N
  - **Genotype 1b.** L31I/M/V and Y93H
  - **Genotype 3.** A30K and Y93H
- Patient characteristics, including the presence of cirrhosis and prior HCV treatment (non-NS5A inhibitor based), increase clinical impact of NS5A RASs.
- Following failed NS5A-based treatment, the majority of individuals have HCV with NS5A RASs (75%-90%).
- NS5A RASs persist in most individuals for more than 2 years.
- The impact of NS5A RAS is relative and can often be overcome by increasing the length of therapy and/or by adding ribavirin.

### Considerations for Resistance Testing for NS5A Inhibitor Treatment–Naive Individuals With HCV Genotype 1 Infection

For individuals with HCV genotype 1 infection who have not been exposed to an NS5A inhibitor, NS5A RAS testing.
Adding ribavirin or extending treatment with ledipasvir/sofosbuvir to 24 weeks mitigated the effect of baseline NS5A RASs. Similarly, individuals with cirrhosis, genotype 1a infection, and ledipasvir RASs with greater than 100-fold reduced susceptibility had a decreased SVR12 of 92% if treatment naive and SVR12 of 67% if treatment experienced. Adding ribavirin or extending treatment with ledipasvir/sofosbuvir to 24 weeks mitigated the impact of NS5A RASs. In contrast, data from registrational trials of sofosbuvir/velpatasvir have not demonstrated an impact of baseline NS5A RASs on HCV cure rate in individuals with HCV genotype 1 infection, including in those who experienced a prior treatment failure (non–NS5A inhibitor based) or those with cirrhosis. Thus, NS5A RAS testing is not recommended before use of sofosbuvir/velpatasvir in these populations.

### Considerations for Resistance Testing for NS5A Inhibitor Treatment–Naive Individuals With HCV Genotype 3 Infection

Genotype 3 HCV infection is the second most prevalent HCV infection globally, and highly efficacious DAA therapy (>95% SVR) remains elusive in some populations such as those with cirrhosis or prior treatment experience. Recommended regimens for individuals with genotype 3 infection include sofosbuvir plus daclatasvir and sofosbuvir/velpatasvir. Data on the impact of baseline NS5A RASs on the outcome of NS5A inhibitor–containing therapy are limited. Further, clear data on appropriate therapeutic modifications to mitigate the impact of baseline RASs do not exist. The NS5A RAS of most clinical importance in HCV genotype 3 is Y93H, which confers a high level of resistance to daclatasvir and to velpatasvir. The prevalence of the Y93H RAS is 5% to 10% for individuals with HCV genotype 3 infection and no prior exposure to NS5A inhibitor–containing therapy. The Y93H RAS emerges in the vast majority of individuals with HCV genotype 3 infection.

### Table 2. Fold-Changes in EC₅₀ for Select Resistance-Associated Substitutions for HCV Drugs, by Genotype

<table>
<thead>
<tr>
<th>HCV Drug</th>
<th>RASs in HCV Genotype 1a</th>
<th>Fold-Change</th>
<th>RASs in HCV Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M28T</td>
<td>Q30R</td>
<td>L31M</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>&gt;100×</td>
<td>&gt;1000×</td>
<td>&gt;100×</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>20×</td>
<td>&gt;100×</td>
<td>&gt;10×</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>20×</td>
<td>&gt;100×</td>
<td>&gt;100×</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>&gt;1000×</td>
<td>&gt;100×</td>
<td>&gt;100×</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>&lt;3×</td>
<td>&lt;3×</td>
<td>&lt;3×</td>
</tr>
<tr>
<td>Ruzasvir</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
<td>&lt;10×</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>&lt;10×</td>
<td>&lt;3×</td>
<td>20×</td>
</tr>
</tbody>
</table>

Abbreviations: EC₅₀, median effective concentration; HCV, hepatitis C virus; NA, data not available; RAS, resistance-associated substitution.

NS5A RAS testing may be considered for individuals with genotype 1a infection who plan to take ledipasvir/sofosbuvir and have cirrhosis or whose prior treatment (non–NS5A inhibitor based) failed (see Table 3).

Baseline NS5A resistance to elbasvir (RASs conferring >5-fold reduced susceptibility) is infrequent, occurring in 5% of individuals tested with population-level sequencing. However, when elbasvir RASs were present, sustained virologic response 12 weeks after cessation of treatment (SVR12) decreased to 58%, compared with 98% in those without elbasvir RASs. Thus, NS5A testing is recommended for individuals infected with HCV genotype 1a considering treatment with elbasvir/grazoprevir. If elbasvir RASs are identified, therapy with elbasvir/grazoprevir should be extended to 16 weeks and weight-based ribavirin should be added, or an alternative regimen should be selected if available. This guidance is extrapolated from data on individuals with HCV genotype 1a infection and prior nonresponse to treatment who were treated with 16 or 18 weeks of elbasvir/grazoprevir, 100% of whom attained an SVR12 regardless of the presence of elbasvir RASs. Elbasvir RASs for genotype 1a are M28T/Q30R, L31M/V/F, H58D, and Y93C/H/N/S.

NS5A RAS testing may be considered for individuals with genotype 1a infection who plan to take ledipasvir/sofosbuvir and have cirrhosis or are treatment experienced (see Table 3), as RASs may impact the duration of therapy and the need for addition of ribavirin. For treatment-experienced individuals, the presence of baseline RASs with greater than 100-fold reduced susceptibility to ledipasvir was associated with an SVR12 of 64.7% with 12 weeks of treatment with ledipasvir/sofosbuvir, compared with an SVR12 of 97.4% for those with no NS5A RASs and 100% for those with RASs conferring less than 100-fold reduced susceptibility to ledipasvir.

Extending treatment with ledipasvir/sofosbuvir to 24 weeks or adding ribavirin to a 12-week course of ledipasvir/sofosbuvir mitigated the effect of baseline NS5A RASs. Similarly, individuals with cirrhosis, genotype 1a infection, and ledipasvir RASs with greater than 100-fold reduced susceptibility had a decreased SVR12 of 92% if treatment naive and SVR12 of 67% if treatment experienced. Adding ribavirin or extending treatment with ledipasvir/sofosbuvir to 24 weeks mitigated the impact of NS5A RASs. In contrast, data from registrational trials of sofosbuvir/velpatasvir have not demonstrated an impact of baseline NS5A RASs on HCV cure rate in individuals with HCV genotype 1 infection, including in those who experienced a prior treatment failure (non–NS5A inhibitor based) or those with cirrhosis. Thus, NS5A RAS testing is not recommended before use of sofosbuvir/velpatasvir in these populations.
baseline velpatasvir-specific RASs (A30H/K, L31F/M, and Y93H), compared with 97% in those without NS5a RASs. Of the 4 participants whose treatment failed, 3 had the Y93H RAS and 1 had the A30K RAS before treatment. The overall SVR12 rate was 84% (21/25) for participants with a baseline Y93H RAS (1% cutoff used with identification of 1 additional Y93H RAS). Given the lower SVR12 (89%) in treatment-experienced individuals with cirrhosis than in treatment-naive individuals without cirrhosis (97%), the addition of ribavirin is recommended a priori for those with both treatment experience and cirrhosis.\textsuperscript{16} Therefore, resistance testing is not advised for this population, as it would not change the recommended treatment.

However, resistance testing should be considered for treatment-experienced individuals without cirrhosis and treatment-naive individuals with cirrhosis. Ribavirin should be added if the Y93H RAS is detected, or therapy can be extended to 24 weeks if ribavirin cannot be added.

### RAS Testing at Time of Failure of NS5A Inhibitor–Based Treatment

Cure rates with NS5A inhibitor–based regimens are remarkably high. However, when NS5A inhibitor–based treatment fails, NS5A RASs frequently emerge. More than 90% of individuals have NS5A resistance mutations at the time of failure of treatment with ledipasvir-, elbasvir-, or ombitasvir-containing therapies. Such mutations may persist for years (86% were still detectable 96 weeks after the failure of ledipasvir-containing treatment)\textsuperscript{24}. Therefore, NS5A resistance testing is recommended at the time of failure of NS5A inhibitor–based treatment and still may be useful months to years afterward, given the persistence of NS5A RASs. Current guidance also recommends HCV NS3 PI resistance testing to inform treatment options for individuals pursuing retreatment,\textsuperscript{16} with particular attention to the Q80K mutation, which impacts response to simeprevir in those with cirrhosis.\textsuperscript{25} Given that HCV NS3 PI RASs wane more quickly than NS5A RASs, it may be advisable to obtain NS3 PI RAS testing at the time of treatment failure even if retreatment is not planned, to document the presence of PI mutations that could impact future treatment options for individuals pursuing retreatment.

### Daclatasvir Plus Sofosbuvir

The impact of baseline NS5A RASs on treatment with daclatasvir plus sofosbuvir for individuals with HCV genotype 3 infection was suggested by results from the ALLY-3 study.\textsuperscript{22} The SVR12 among participants treated with daclatasvir plus sofosbuvir (without ribavirin) was 92% in those without baseline NS5A RASs and 54% in those with baseline NS5A RASs. The presence of cirrhosis also impacted the response to this regimen. However, given the small number of participants with both cirrhosis and baseline NS5A RASs (n = 4; SVR12 of 25%), the relative contribution of each is difficult to discern. An SVR12 of 67% was observed in participants without cirrhosis but with the Y93H RAS. The addition of ribavirin improved SVR12 in participants with cirrhosis to 86% (12-16 weeks of therapy).\textsuperscript{23}

Given these data, the presence of NS5A RASs may impact therapeutic approaches for treatment-naive persons with cirrhosis or treatment-experienced persons without cirrhosis, and baseline NS5A RAS testing is recommended for these populations. Identification of the Y93H variant should prompt the addition of ribavirin in the absence of absolute contraindications. Twelve weeks of therapy with daclatasvir plus sofosbuvir is recommended for individuals without cirrhosis, and 24 weeks of therapy is recommended for those with cirrhosis, given the suboptimal response of 86% with 12 to 16 weeks of daclatasvir plus sofosbuvir with ribavirin. The role of RAS testing for treatment-naive individuals with HCV genotype 3 infection without cirrhosis is unclear.

### Sofosbuvir/Velpatasvir

Velpatasvir has an improved resistance profile compared with early generation NS5A inhibitors, although the Y93H variant in HCV genotype 3 infection still confers a high level of resistance (\(> 100 \times EC_{50}\)) to velpatasvir.\textsuperscript{11} In the ASTRAL-3 study, which evaluated 12 weeks of treatment with sofosbuvir/velpatasvir, SVR12 was 88% (28/32) in participants with baseline velpatasvir-specific RASs (A30H/K, L31F/M, and Y93H), compared with 97% in those without NS5a RASs. Of

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**Table 3. Recommendations for NS5A RAS Testing by Regimen and Clinical Characteristics (Treatment Experience and Cirrhosis)**

<table>
<thead>
<tr>
<th>HCV Regimen</th>
<th>HCV Genotype 1a</th>
<th>HCV Genotype 1b</th>
<th>HCV Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TN</td>
<td>TE\textsuperscript{a}</td>
<td>TN</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir\textsuperscript{b}</td>
<td>NC</td>
<td>C</td>
<td>NC</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir\textsuperscript{b}</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir\textsuperscript{b} plus dasabuvir</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sofosbuvir plus daclatasvir</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir\textsuperscript{b}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: +, resistance testing recommended; +/-, resistance testing may be considered; -, resistance testing not recommended; C, cirrhosis; HCV, hepatitis C virus; NA, not applicable; NC, no cirrhosis; NS5A, nonstructural protein 5A; RAS, resistance-associated substitution.

\textsuperscript{a}With peginterferon alfa–based regimen; excludes prior NS5A-containing regimens.

\textsuperscript{b}Slash indicates a coformulation.
PI-containing treatment. NS3 PI RAS testing for sofosbuvir is not recommended, as sofosbuvir-associated RASs are rare and, generally, have not impacted the efficacy of subsequent sofosbuvir use.

Retreatment After Failure of an NS5A Inhibitor–Based Regimen

Timing and options for retreatment after failure of an NS5A inhibitor–based regimen are challenging, given the limited options and data supporting retreatment. Guidance currently suggests deferring HCV treatment for individuals without cirrhosis and when there is not another indication for urgent retreatment, in anticipation of the availability of better retreatment options currently in development. For individuals who are retreated with currently available regimens, tailoring retreatment based on results of NS5A and NS3 resistance testing is recommended as follows: if no NS5A RASs are present, treat with sofosbuvir plus an NS5A inhibitor (ledipasvir or velpatasvir) plus ribavirin for 24 weeks; if NS5A RASs are present but no NS3 PI RASs (specifically Q80K) are present, treat with simeprevir plus sofosbuvir plus ribavirin for 24 weeks; and if NS5A and NS3 RASs are present, defer therapy or consider a clinical trial or a regimen as outlined below.

Retreatment After Failure of an NS5A Inhibitor–Based Regimen: Tailoring to the NS5A RAS Profile

Ledipasvir/Sofosbuvir

Several studies have examined retreatment with ledipasvir/sofosbuvir after failure of an NS5A inhibitor–based regimen. Among individuals whose treatment with 8 to 12 weeks of ledipasvir/sofosbuvir failed, efficacy of retreatment with ledipasvir/sofosbuvir for 24 weeks (without ribavirin) was impacted by the presence of NS5A RASs.26 SVR12 was 100% if no NS5A RASs were present and 60% if they were present. The presence of 2 or more RASs was associated with a 50% SVR12, and the presence of Y93H/N RASs was associated with a 33% SVR12.

The addition of ribavirin may mitigate the impact of NS5A RASs. Among 9 HIV/HCV-coinfected individuals whose treatment with 12 weeks of ledipasvir/sofosbuvir failed, 7 of 9 had ledipasvir RASs at the time of treatment failure, including 4 with Y93H/N RASs, and 8 of 9 attained an SVR12 with 24 weeks of treatment with ledipasvir/sofosbuvir plus ribavirin.27 The single treatment failure occurred in an individual who had an L31M RAS before retreatment. Based on the limited data available, ledipasvir/sofosbuvir plus ribavirin for 24 weeks may be considered for retreatment after failure of an NS5A inhibitor–containing regimen, but is not recommended if ledipasvir RASs are present.

Sofosbuvir/Velpatasvir

In a single-arm study of individuals treated with 4 to 12 weeks of sofosbuvir/velpatasvir or sofosbuvir/velpatasvir plus the investigational HCV PI GS-9857 during phase II studies, retreatment with 24 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin led to a 91% SVR (59/65).28 Individuals with HCV genotype 1, 2, or 3 infection were included. Pretreatment NS5A RASs (detected using a 1% UDS cutoff) were present in 18% of individuals with genotype 1 infection, 62% of those with genotype 2 infection, and 81% of those with genotype 3 infection. The presence of NS5A RASs did not impact SVR in participants with genotype 1 (33/54; SVR12, 97%) or 2 (13/14; SVR12, 91%). Among 13 participants with genotype 3 infection, 11 (85%) had the Y93H NS5A RAS, and 9 (82%) attained an SVR12. These results indicate that the presence of the Y93H RAS may reduce HCV cure rates among individuals with genotype 3 infection retreated with sofosbuvir/velpatasvir. However, the majority of participants in this study with genotype 3 infection and the Y93H RAS were cured. Individuals with HCV genotype 3 infection in whom NS5A inhibitor–based treatment has failed remain a population for whom improved retreatment options are needed.

Simeprevir Plus Sofosbuvir

Simeprevir plus sofosbuvir has been studied in treatment-experienced (with peginterferon alfa–based regimens) individuals with cirrhosis and led to a 79% SVR12.29 Data on simeprevir plus sofosbuvir for individuals experienced with NS5A inhibitor–based treatments are limited.

In a small observational study, 14 of 16 participants with HCV genotype 1 infection attained SVR12 with 12 weeks of retreatment with simeprevir plus sofosbuvir after failure of a prior daclatasvir-based regimen (most included peginterferon alfa); 13 of 16 participants had NS5A RASs, and 8 of 16 participants had NS3 RASs (2 with Q80K).19 Of the 2 participants whose retreatment with simeprevir plus sofosbuvir failed, 1 had the Q80K RAS and 1 had the R155K RAS (which confers a high level of resistance to simeprevir). Of note, simeprevir plus sofosbuvir was only given for 12 weeks and without ribavirin. Current guidelines recommend 24 weeks of therapy with simeprevir plus sofosbuvir plus ribavirin for individuals whose prior treatment with an NS5A inhibitor failed, to optimize treatment success in this hard-to-treat population for whom options are limited.16 Testing for the NS5 PI mutation Q80K is recommended before simeprevir use in individuals with HCV genotype 1a infection only in the presence of cirrhosis, due to reduced response when Q80K is present (74%) versus when it is absent (92%).

3- and 4-Class Combination Therapies for Retreatment

Retreatment with elbasvir/grazoprevir plus sofosbuvir and ribavirin led to a 100% SVR in 25 individuals whose prior treatment with elbasvir/grazoprevir plus sofosbuvir for 4 to 8 weeks failed; 52% had elbasvir RASs before retreatment (15% cutoff), which did not impact SVR12, nor did the presence of NS3 PI RASs.29 Therapy with paritaprevir/ritonavir/ombitasvir plus dasabuvir plus sofosbuvir (and ribavirin for those with genotype 1a infection) led to a similarly strong SVR rate of 95% in 22 individuals with HCV genotype 1a infection retreated after failure of a variety of regimens. Of 20 individuals...
with genotype 1a infection, 16 (80%) had NS5A RASs before treatment and 19 (95%) attained an SVR12; 2 of 2 (100%) individuals with genotype 1b infection attained an SVR. Of note, 13 of 14 individuals with the HCV PI Q80K mutation also attained an SVR.30

The high SVR rates achieved with these combination therapies despite the presence of baseline NS5A resistance are encouraging. However, combining drugs from different classes made by different pharmaceutical manufacturers creates additional barriers to treatment access and increases cost. Triple-class combination regimens currently in development may be more accessible if provided as coformulations from the same manufacturer.

**Future Therapies for Treatment After Failure of an NS5A Inhibitor–Based Regimen**

Investigational, ribavirin-free combination therapies have shown tremendous promise for retreatment after failure of an NS5A inhibitor–based regimen,31-33 regardless of whether NS5A resistance preexists. In a study of 44 DAA treatment–experienced individuals without cirrhosis (50% NS5A experienced, 84% PI experienced), the combination of the investigational NS3 inhibitor glecaprevir and the investigational NS5A inhibitor pibrentasvir yielded a 100% SVR in those without NS5A RASs and 83% to 96% SVR12 in those with NS5A resistance with 12 and 16 weeks of treatment, respectively. There was a high cure rate even in the presence of NS5A resistance, including 100% SVR in those with the NS5A RAS Y93H/N.30

The multiclass combination of sofosbuvir, velpatasvir, and the investigational NS3 inhibitor voxilaprevir given for 12 weeks without ribavirin led to cure in 96% of HCV-infected individuals (all genotypes) who had a prior NS5A treatment failure.32 Seventy-nine percent of individuals had NS5A resistance before retreatment, and 96% attained an SVR. The presence of NS3 and NS5B RASs did not impact SVR. Six virologic failures occurred, all of which were among individuals with cirrhosis.

Similarly, treatment with the multiclass combination of grazoprevir, the investigational NS5A inhibitor ruzasvir, and the investigational NS5B polymerase inhibitor uprifosbuvir given for 16 weeks with ribavirin or for 24 weeks without ribavirin led to a 100% SVR4 in individuals with HCV genotype 1 infection whose prior NS5A inhibitor–containing regimens failed; 84% had NS5A RASs and 65% had NS3 RASs at baseline.33 Collectively, these data suggest that ribavirin-free combination therapies in development should be highly effective for most individuals whose prior NS5A inhibitor–based regimen failed, regardless of the presence of preexisting NS5A, NS5B, or NS3 RASs.

**When Resistance Testing Is Not Available**

In the scenarios outlined above, RAS testing may help guide treatment choices. However, RAS testing is not recommended for the majority of individuals initiating HCV treatment. Further, a lack of RAS testing should not be a barrier to HCV treatment. Practitioners may not have access to RAS testing because of a lack of insurance coverage or limited access in their practice setting. In the absence of RAS testing, an effective DAA regimen can almost always be constructed using the patient’s clinical history and the expected efficacy of the available regimens.

**Summary**

When available, NS5A resistance can have important clinical implications for treatment-naive and -experienced individuals with HCV infection. NS5A resistance testing is recommended for individuals who have not received prior NS5A inhibitor–based treatment if treatment with elbasvir/grazoprevir is planned (for those with genotype 1a infection), if treatment with ledipasvir/sofosbuvir is planned (only for those with genotype 1a infection and cirrhosis or a prior treatment failure), and in the case of genotype 3 infection in the presence of cirrhosis or a prior treatment failure. NS5A resistance testing is also recommended for all individuals whose prior NS5A inhibitor–based treatment failed.

Future HCV treatments combining next-generation antiviral drugs that have improved resistance profiles, in some cases from as many as 3 different drug classes, are effective even in the setting of previous DAA-based treatment failure with drug resistance. Although additional data are needed, such regimens may obviate the need for resistance testing in most situations.

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**Cases From the Field**

**Barriers to Treatment Access for Chronic Hepatitis C Virus Infection: A Case Series**

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Restrictive policies on access to new, curative hepatitis C treatments represent a substantial barrier to treating patients infected with hepatitis C. This case series demonstrates challenges experienced by patients and practitioners in accessing these treatments and highlights several strategies for navigating the treatment preauthorization process.

**Keywords:** hepatitis C virus, HCV, treatment, insurance

**Background**

In the United States, hepatitis C virus (HCV) infection is a leading cause of liver-related deaths, cirrhosis, and hepatocellular carcinoma.\(^1\) Infection is primarily acquired through percutaneous blood exposure, including injection drug use and historically contaminated blood products, which has led to the greatest prevalence among individuals born from 1945 through 1965.\(^1\) Individuals chronically infected with HCV require ongoing monitoring to assess for progression of liver fibrosis, classified according to the Metavir histological scores of F0 to F4. A Metavir score of F0 indicates no fibrosis and a score of F4 indicates cirrhosis. HCV treatments were historically used sparingly because of toxic effects and modest efficacy.\(^1\) However, since 2013, highly effective, safe, and curative peginterferon alfa–sparing direct-acting antiviral (DAA) drugs for HCV have been available, increasing the number of individuals willing and able to be treated.\(^1\)

Although new DAAs are becoming available and costs are continuing to decline, the initial retail costs of $83,000 to $153,000 per treatment course prompted health plans and payers to institute restrictive policies and preauthorization procedures for treatment.\(^2,4\) Health plan and payer policies vary but have often included restrictions based on liver fibrosis stage, documented alcohol and drug abstinence, and the practitioner’s clinical specialty.\(^2,4\) High drug costs, in addition to restrictive policies, limit treatment access and create a substantial barrier to curing the 3.5 million people estimated to be chronically infected with HCV in the United States.\(^3-5\) Currently, patient access to HCV treatment requires health care practitioners and staff to expertly navigate a complex authorization process.

The Centers for Disease Control and Prevention (CDC) Hepatitis C Community-based Test and Cure Project supports clinical and public health partners with improving HCV testing, linkage to care, and treatment activities in Baltimore, Maryland; Chicago, Illinois; and Seattle–King County, Washington. This case series presents examples from each partner site to illustrate challenges in obtaining HCV treatment for patients with private or public insurance undergoing routine clinical care. All patients mentioned in this case series gave their consent to be included.

**Baltimore, Maryland**

Patient A is a 55-year-old man with a history of chronic HCV genotype 1a infection, a Metavir score of F4 (cirrhosis), depressive disorder, traumatic brain injury, and alcohol use disorder. He is insured through a Medicaid managed care organization. His primary care practitioner prescribed sofosbuvir/ledipasvir (slash indicates a coformulation) in January 2016; however, the managed care organization immediately denied the preauthorization because of an isolated episode of excessive drinking in 2014. His practitioner determined the drinking episode documented in the medical record was erroneous and in a written appeal provided evidence of patient A’s abstinence from alcohol. The appeal was denied, and the physician filed a second one directly to the managed care organization’s chief medical officer. Estimated staff time spent on the approval process totaled 4 hours. The preauthorization was approved on March 2, 2016, and patient A initiated treatment on May 4, 2016, which was approximately 3 to 4 months after the treatment was prescribed. He had an undetectable viral load 4 weeks after treatment initiation, but did not return for follow-up care. Efforts to reengage him in care have been unsuccessful.

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Chicago, Illinois

Patient B is a 60-year-old man with chronic HCV genotype 3a infection and a Metavir score of F4 (cirrhosis). He had a history of alcohol and illicit drug use and has been abstinent for 11 years. He has employer-based private insurance, which restricts HCV medication to patients having a Metavir score of F2 or greater.

Patient B enrolled in the Hepatitis C Community Alliance for Testing and Treatment case management program in Chicago in July 2015 for assistance in obtaining HCV treatment. At that time, no effective peginterferon alfa–sparing therapy for individuals with HCV genotype 3a infections with cirrhosis was available. Patient B was advised to defer treatment until daclatasvir received US Food and Drug Administration (FDA) approval so he could receive a more efficacious peginterferon alfa–sparing regimen. Daclatasvir was licensed approximately 1 month after he enrolled in the program, and the preauthorization was submitted for 16 weeks of daclatasvir, sofosbuvir, and ribavirin. Preauthorization was denied because daclatasvir would not be available on the insurance company’s formulary for 6 months. Attempts to obtain the medication more quickly through the pharmaceutical company’s patient assistance program were unsuccessful.

In January 2016, after daclatasvir was added to the formulary, the patient’s gastroenterologist submitted a new preauthorization request for the medication that was approved, and he initiated treatment in March 2016, 7 months after the initial preauthorization request was submitted. In April 2016, his prescription benefits carrier changed, necessitating a new preauthorization for the remaining 12 weeks of the then adjusted 24-week treatment schedule. In total, the estimated staff time for all preauthorization processes was 40 hours. The new preauthorization was approved and patient B completed treatment. In November 2016, 12 weeks after the end of therapy, he had a sustained virologic response (SVR).

Seattle–King County, Washington

Patient C is a 58-year-old man with chronic HCV genotype 1b infection. His liver fibrosis was assessed as F0–F1 in 2012 and F1 in 2014 using serum biomarker testing. He had previously used injection drugs but had been abstinent since 2006. The patient also reported abstinence from alcohol since 2010. He was insured through a Medicaid managed care organization.

In December 2014, he was seen by a specialist and found to have a transient elastography score of 1.56 m/s, corresponding to Metavir scores F2–F3. At that time, he was prescribed sofosbuvir/ledipasvir, but the preauthorization request was denied because the payer stated he did not satisfy the fibrosis criteria of F3 and greater (A fibrosis criteria of ≥F3 was previously required by Washington State Medicaid for HCV treatment authorization. The requirement was removed in June 2016 after a legal challenge). His insurance status made him ineligible for the pharmaceutical company’s patient assistance program. After 14 months, an estimated 20 hours of staff time, and numerous appeals by pharmacists at the specialty clinic, Medicaid authorized the prescription. In February 2016, he initiated sofosbuvir/ledipasvir and successfully completed the 12-week course of therapy in June 2016. In October 2016, 12 weeks after the end of therapy, he had an undetectable viral load.

Discussion

At present, increasing access to HCV treatment requires overcoming numerous barriers at the levels of the health care system, clinic and practitioner, and patient, as shown in the Box. Health care system barriers are generally related to the high initial list prices of HCV medications and efforts by health plans and payers to control costs through preauthorization requirements. These requirements, which have been amply described, can create impediments to treatment access. A study of 2321 patients in 4 states showed that 46% were denied Medicaid payments even after appeal, compared with 10% of patients with private insurance. Changes in drug prices and health plan and payer restrictions have resulted in fewer denials in subsequent studies. However, the burden of these denials falls disproportionately on publicly insured and marginalized populations, resulting in systematic obstacles to HCV treatment access for vulnerable people. In addition, as the cases above illustrate, even if individuals eventually gain access to treatment, burdensome preauthorization requirements divert staff time from patient care and limit the ability of practitioners to scale up treatment initiation for HCV-infected individuals. At the clinic and practitioner level, barriers to treatment access include not testing for anti-HCV antibody (despite recommendations from guidelines), clinic referral practices, and extent of a practitioner’s knowledge of HCV treatments. Not testing for anti-HCV antibody appropriately based on recommended guidelines, for instance, or not obtaining confirmatory RNA testing represents a substantial hurdle to HCV treatment access because a lack of diagnosis precludes access to treatment. The impact of this barrier can be reduced by various interventions such as the use of...
electronic medical records and clinical decision tools, reflex RNA testing, and patient navigators.\textsuperscript{10,11,13} Also, individual practitioners may lack familiarity with new HCV treatments. Although current HCV treatment regimens are considered simple to manage compared with peginterferon alfa-based regimens, a survey of practitioners found that 70% did not feel sufficiently knowledgeable about HCV treatment, and 71% refer persons with HCV to subspecialty care.\textsuperscript{11} This knowledge gap can be addressed through training, and primary care physicians have been shown to have treatment outcomes similar to those of subspecialists.\textsuperscript{14} Although referrals to subspecialists for HCV treatment may be required by certain health plans and payers,\textsuperscript{4,11} this may cause individuals to be lost to follow-up and unable to access treatment. This barrier can be addressed through interventions such as patient navigators and colocation of services, or it can be removed completely by enabling primary care clinicians to prescribe HCV treatments independently or through comanagement with a specialist.\textsuperscript{10,11,13} Finally, at the patient level, individuals without health care access, either due to no linkage to care, lack of insurance, or being underinsured, will likely be unable to receive HCV treatment.

As illustrated by this case series, persons who live with HCV infection, whether privately or publicly insured, face numerous challenges in accessing treatments. The time from treatment decision to treatment initiation in these cases took as long as 16 months and generally involved denials of initial preauthorization. Do and colleagues examined drug authorizations for sofosbuvir/ledipasvir among publicly and privately insured individuals and found 18.6% of initial preauthorizations were not approved.\textsuperscript{8} Overall, the average time-to-decision on the initial preauthorization was 26.1 days (standard deviation [SD], 25.2 days), and the decision on appeal required an additional 18.6 days on average (SD, 22.1 days). Although the majority of patients eventually received therapy based on appeal, unnecessary treatment delays occurred because the initial preauthorization was denied. In total, 4.7% of patients were ultimately denied therapy.\textsuperscript{8} Similarly, Younossi and colleagues found that among 3841 patients prescribed a sofosbuvir-containing regimen, 315 (8%) did not start therapy; 81% of the nonstarts were due to insurance-related processes and financial reasons even among those with Metavir fibrosis scores of F3 and greater.\textsuperscript{5} In addition, Younossi and colleagues reported that although 10% of the total study population had Medicaid coverage, 43% of the 315 nonstart patients were in the Medicaid-covered population.\textsuperscript{5} Overall, those with private insurance were approximately 6.5 times more likely to receive treatment than a propensity score–matched group of those with Medicaid.\textsuperscript{5} The current approval process for HCV treatments can be unpredictable and burdensome for clinic staff, and the reasons for denial may not be clinically based.\textsuperscript{13,4}

Although treatment of HCV-infected individuals is cost-effective from a societal perspective,\textsuperscript{15} the high cost of HCV therapy is a budgetary issue for state Medicaid programs on 1- to 2-year cycles. In 2014, as much as 6.7% of state Medicaid prescription drug spending was attributable to HCV treatment.\textsuperscript{16} Fortunately, the entry of new DAAs into the market, mandated 23% rebates for HCV-infected patients on Medicaid, and negotiated price reduction by payers have lowered the cost of HCV medications.\textsuperscript{3,17} In addition, in November 2015, the Centers for Medicare and Medicaid Services (CMS) notified states that limitations on coverage “should not result in the denial of access to effective, clinically appropriate, and medically necessary treatments using DAA drugs” for HCV-infected persons.\textsuperscript{18} This should prompt health plans and payers to reevaluate current restrictive reimbursement policies. In fact, some health plans and payers have revised coverage policies to remove previous authorization requirements, some of which were prompted by successful legal challenges such as the one in Washington state.\textsuperscript{19,20} At this time, it is too early to evaluate the long-term impact of these changes on the preauthorization process; however, they will likely improve treatment access for individuals covered by these health plans and payers.

Regardless of health plan and payer decisions to reevaluate coverage policies, health care practitioners will still be responsible for prescribing HCV treatment and obtaining necessary preauthorization. Several strategies can be used to assist with preauthorization. Case managers can serve as a useful resource for patient support and for navigating an appeals process. Specialty pharmacies and in-clinic pharmacy support or pharmacy benefits managers, if available, may also be a resource for assisting health care practitioners in successfully completing the approval and appeal processes. Additional training for primary care practitioners to become specialized HCV care clinicians can expand the number of practitioners able to prescribe HCV treatment in areas where health plans and payers restrict by specialty. All of these strategies incur costs but not necessarily to the third-party payer. Finally, advocacy groups such as the National Viral Hepatitis Roundtable have developed and compiled resources for health care practitioners, including checklists and guides for initiating HCV treatment and template letters for appealing insurance denials, to reduce the administrative burden on practitioners.\textsuperscript{21}

This case series has several limitations. It reflects individual patient experiences and should not be considered representative of HCV treatment access for all health plans or payers, including Medicare. Uninsured individuals, who may be eligible for treatment access through patient assistance programs at pharmaceutical companies, were also not included. Finally, policies regarding preauthorization requirements and treatment access are not static. Although policy changes may be expected to increase treatment access, such as the Washington state ruling in 2016, the long-term impact of this specific change and others on the preauthorization process cannot be formally evaluated at this time.

Despite a decrease in the price of HCV medications, access to HCV treatment remains a barrier to reducing HCV-associated morbidity and mortality. In addition to decreases in the costs of HCV medications, health plans and payers should reevaluate restrictive criteria that limit access to HCV treatment.
References


Cases From the Field

Sustained Off-Treatment Response After Discontinuation of Long-Term Nucleos(t)ide Analogue Treatment in HBeAg-Seronegative Hepatitis B: A Case Series

Marion Muche, MD; Ulrike Meyer, MD; Britta Siegmund, MD; Rajan Somasundaram, MD; Hans-Joerg Epple, MD

International guidelines recommend lifelong nucleos(t)ide analogue (NA) treatment in individuals with chronic hepatitis B (CHB) infection who are hepatitis B e antigen (HBeAg) seronegative, because hepatitis B surface antigen (HBsAg) seroconversion is rarely achieved. However, after terminating therapy, sustained responses and HBsAg loss have been observed. Clinical characteristics identifying persons with favorable outcomes after discontinuing NA therapy have not yet been defined. This case series describes outcomes of 6 individuals with HBeAg-seronegative CHB infection without cirrhosis and low plasma levels of HBsAg who discontinued long-term NA treatment. All individuals had a virologic relapse and 4 of 6 had a biochemical relapse; but 5 of 6 later developed a sustained virologic and biochemical response and a marked reduction of quantitative HBsAg (qHBsAg). Two of the 6 individuals experienced HBsAg loss. Only 1 patient was retreated, and none showed signs of hepatic decompensation. NA treatment can be safely stopped in selected HBeAg-seronegative patients. Sustained off-treatment responses seem to be frequently preceded by a virologic and biochemical flare. Loss of HBsAg possibly reflects restoration of antiviral immunity during prolonged NA treatment. Predictive factors, such as qHBsAg, may be valuable in selecting patients who could benefit from NA discontinuation.

Keywords: Hepatitis, chronic, hepatitis B, HBeAg, CHB, nucleos(t)ide analogue, treatment

Introduction

The duration of nucleos(t)ide analogue (NA) therapy is an unresolved issue in the treatment of persons with chronic hepatitis B (CHB) infection who are hepatitis B e antigen (HBeAg) seronegative. In these individuals, HBeAg clearance or seroconversion to hepatitis B e antigen antibodies (anti-HBe) cannot be used as an endpoint, and the treatment goal of hepatitis B surface antigen (HBsAg) clearance or HBsAg antibody (anti-HBs) seroconversion is rarely achieved.1 American and European CHB infection guidelines recommend lifelong NA therapy for patients with CHB infection who are HBeAg seronegative.2,3 These recommendations are unsatisfactory for several reasons. First, although NA therapy is well tolerated in general, the issue of potential long-term adverse effects is still unresolved. Second, the cost of lifelong therapy represents a considerable financial burden and may not be affordable in countries with limited financial resources. Finally, the prospect of strict adherence to lifelong therapy can inflict a substantial psychologic strain on the individual.

Defining rules for stopping NA therapy in individuals with CHB infection who are HBeAg seronegative is important. However, factors that can predict a favorable off-treatment response are presently unknown as is the typical clinical course after NA discontinuation. This case series presents the biochemical, serologic, and virologic responses of 6 carefully selected HBeAg-seronegative patients with CHB infection who discontinued long-term NA therapy.

Case Descriptions

Individuals with CHB infection who were HBeAg seronegative and presented at our outpatient clinic between September 2011 and January 2014 had to meet specific criteria for discontinuing NA treatment. These criteria included hepatitis B virus (HBV) monoinfection; treatment duration of more than 5 years with a complete virologic and biochemical response; quantitative HBsAg (qHBsAg) level below 2000 IU/mL; no signs of advanced liver disease on liver function test results; and an absence of more than mild fibrosis as shown in abdominal ultrasound and elastography.

This is not a prospective study with documented informed consent but a retrospective review of persons who stopped therapy. The patients did receive detailed information about potential risks associated with treatment discontinuation, including hepatitis flare and liver failure. After careful

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consideration, 6 persons were approved to discontinue NA therapy. After treatment cessation, the individuals were monitored clinically, biochemically (liver enzyme levels), and virologically (HBV DNA level) every 4 weeks for the first 3 months and every 3 months thereafter. Virologic relapse was defined as HBV DNA levels of 2000 IU/mL or more and biochemical relapse as an alanine aminotransferase (ALT) level above the upper limit of normal (ULN). Conversely, virologic and biochemical responses were defined by an HBV DNA level of 2000 IU/mL or less and an ALT level below ULN, respectively.

Patient characteristics before the end of treatment (EOT) are presented in Table 1. The median age at EOT was 55.5 years. One person was Asian, 1 person was African, and the others were white. The median duration of NA therapy was 11.5 years; the median duration of suppressed viral load was 7 years. Outcomes after treatment cessation are summarized in Table 2. All patients showed a virologic relapse, and 4 of 6 showed a biochemical relapse with peak values 2 months after EOT. In one individual (patient 4), the ALT level continued to be elevated and the HBV DNA level remained high (>2000 IU/mL). This person was asymptomatic and did not show signs of impaired liver function (ie, normal bilirubin level and international normalized ratio) at all times. Upon resuming therapy at week 24, this patient reached viral suppression after another 12 weeks. All other persons remained off treatment and showed a sustained virologic and biochemical response. In individuals with a sustained virologic response, HBV DNA level dropped below 2000 IU/mL until month 3 and ALT levels normalized until month 4 after EOT. Except for 1 individual who was retreated (patient 4) and 1 individual who was qHBs seronegative at EOT (patient 3), qHBs decreased or became negative in all patients. In 2 persons, complete loss of HBsAg and hepatitis B surface antibodies (anti-HBs) occurred.

### Discussion

In this case series, favorable outcomes after discontinuing long-term NA treatment were observed in HBeAg-

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**Table 1. Characteristics of Patients With HBe Antigen–Seronegative Chronic Hepatitis B Infection at End of Treatment**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (years), Sex</th>
<th>Previous NA Therapy</th>
<th>Duration of Therapy (years)</th>
<th>Viral Load &lt;LOD (years)</th>
<th>Genotype</th>
<th>qHBsAg (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62, female</td>
<td>Lamivudine</td>
<td>12</td>
<td>11</td>
<td>Unknown</td>
<td>730</td>
</tr>
<tr>
<td>2</td>
<td>55, female</td>
<td>Lamivudine, adefovir, tenofovir disoproxil fumarate, entecavir</td>
<td>12</td>
<td>8</td>
<td>B</td>
<td>790</td>
</tr>
<tr>
<td>3</td>
<td>61, male</td>
<td>Lamivudine, adefovir, tenofovir disoproxil fumarate</td>
<td>13</td>
<td>4</td>
<td>Unknown</td>
<td>0a</td>
</tr>
<tr>
<td>4</td>
<td>45, male</td>
<td>Lamivudine, adefovir, tenofovir disoproxil fumarate</td>
<td>9</td>
<td>4</td>
<td>D</td>
<td>1900</td>
</tr>
<tr>
<td>5</td>
<td>36, male</td>
<td>Entecavir, tenofovir disoproxil fumarate</td>
<td>6</td>
<td>6</td>
<td>E</td>
<td>123</td>
</tr>
<tr>
<td>6</td>
<td>56, male</td>
<td>Lamivudine, adefovir, tenofovir disoproxil fumarate</td>
<td>11</td>
<td>6</td>
<td>D</td>
<td>620</td>
</tr>
</tbody>
</table>

*Abbreviations: LOD, limit of detection; NA, nucleos(t)ide analogue; qHBsAg, quantitative hepatitis B surface antigen.

*aQuantitative HBsAg became negative in this person during NA treatment.*

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**Table 2. Off-Treatment Responses of Patients With Hepatitis B e Antigen–Seronegative Chronic Hepatitis B Infection After Treatment Discontinuation**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Relapse</th>
<th>Off-Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak VL (IU/mL) / month</td>
<td>Peak ALT (ULN) / month</td>
</tr>
<tr>
<td>1</td>
<td>6030/2</td>
<td>2x/2</td>
</tr>
<tr>
<td>2</td>
<td>34,200</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>9890/2</td>
<td>1.5x/2</td>
</tr>
<tr>
<td>4</td>
<td>495,000,000/2</td>
<td>10x/2</td>
</tr>
<tr>
<td>5</td>
<td>8110/2</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>2,060,000/2</td>
<td>49x/2</td>
</tr>
</tbody>
</table>

*Abbreviations: ALT, alanine aminotransferase; anti-HBs, hepatitis B surface antibodies; EOT, end of treatment; qHBsAg, quantitative hepatitis B surface antigen; ULN, upper limit of normal; VL, viral load.*
seronegative persons with CHB infection who did not have cirrhosis. Five of 6 persons had sustained off-treatment biochemical and virologic response, 2 of 6 persons lost HBsAg, and 2 of 6 persons developed anti-HBs seroconversion. A hepatic flare after treatment discontinuation occurred in 4 individuals but did not lead to hepatic decompensation. These results add to the growing evidence that NA treatment cessation not only is safe in individuals without cirrhosis and poses a promising therapeutic option for selected individuals with CHB infection who are HBeAg seronegative. Presently, the question of treatment duration in individuals with CHB infection who are HBeAg seronegative is a matter of debate. Although European and US guidelines recommend NA treatment cessation 12 months after anti-HBe seroconversion for HBeAg-seropositive patients, there is no generally accepted stopping rule for those who are HBeAg seronegative. Most studies reporting about treatment discontinuation in HBeAg-seronegative individuals focused on cumulative relapse rates rather than on analysis of sustained off-treatment responses. Further, the methods and analyses of these studies vary with respect to NA treatment duration, viral suppression duration, application of discontinuation rules, definition of outcomes, and length of follow-up. For these reasons, the therapeutic value of NA treatment cessation in individuals with CHB infection who are HBeAg seronegative is unclear as are the factors in identifying those most likely to have a favorable outcome.

Toward that end, a pilot study by Hadzyannis and colleagues showed promise. In the study, 33 HBeAg-seronegative patients with CHB infection in whom complete viral suppression was achieved with adefovir had their treatment discontinued after 4 to 5 years of continuous therapy. These persons all experienced a virologic relapse, and 76% experienced a biochemical relapse soon after treatment ceased. However, 55% of these persons subsequently had a virologic and biochemical response, and 39% experienced HBsAg loss. Based on data suggesting that prolonged viral suppression allows for a substantial restoration of antiviral T-cell immunity, the biochemical relapse after NA discontinuation was interpreted as a hepatitis flare caused by restored antiviral immunity.

The observations presented in our case series are in agreement with the concept proposed by Hadzyannis. Although all 6 individuals in our series had a virologic relapse and 4 of 6 persons (67%) had a biochemical relapse during the first 2 months after treatment discontinuation, 5 of 6 individuals (83%) later developed a sustained virologic and biochemical response. In addition, in these individuals with a sustained response, qHBsAg levels decreased markedly, and in 2 individuals anti-HBs seroconversion occurred. In total, 5 of 6 persons (83%) experienced persistent loss of or a strong reduction in HBsAg after discontinuing NA treatment. In comparison, during the first 4 to 5 years of NA treatment, HBsAg loss is virtually never observed, and the rate of annual HBsAg loss under continual NA treatment has been reported to be as low as 0.33%. Because loss of HBsAg in HBeAg-seronegative individuals with CHB infection is regarded as the closest equivalent to a clinical cure, the excellent overall outcomes demonstrated by persons in this case series emphasize the strong potential of NA treatment discontinuation in selected individuals.

In order to formalize this concept into a clinical rule for treatment discontinuation, valid predictive factors for identifying patients who could safely and successfully stop treatment need to be defined. Because these factors have not yet been identified, criteria for when patients could safely stop treatment in this retrospective review were based on evidence about safety and sustained off-treatment responses described in earlier studies. As summarized recently, in 22 studies with a total of 1732 patients, only 1 episode of hepatic decompensation in a patient with liver cirrhosis was reported. Therefore, treatment discontinuation was offered only to CHB patients who did not show signs of cirrhosis or advanced liver fibrosis as indicated by biochemical test results and abdominal ultrasound and elastography. Furthermore, all 6 individuals in the series had received long-lasting suppressive NA therapy (>6 years) before treatment was discontinued. In the absence of adequate study data, the duration of NA treatment necessary to restore antiviral immune function is presently unknown. However, treatment duration does seem to play a role, as earlier studies showed relapse rates as high as 90% after 1 year of NA treatment, whereas subsequent studies with longer treatment periods reported far better sustained response rates.

In summary, the results of this case series suggest that treatment cessation in individuals with CHB infection who are HBeAg seronegative and do not have cirrhosis is safe and, as reflected by a high rate of HBsAg loss and anti-HBs seroconversion, may prove to be a therapeutic option for some patients. However, stringent patient selection is likely crucial, and the criteria for selecting patients who could benefit from NA discontinuation will have to be defined in properly designed prospective studies.

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References


Correction note: An earlier version of this article listed the wrong nucleos(t)ide analogue therapy in Table 1. It should be entecavir, not etravarine as originally stated.
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The 17th Ryan White HIV/AIDS Program (RWHAP) Clinical Care Conference will be held in San Antonio, Texas, from **August 21 to 23, 2017**. The conference will be co-chaired by Laura W. Cheever, MD; Michael S. Saag, MD; and Marshall J. Glesby, MD, PhD.

Webcasts of the Clinical Care Conference will be available within 24 hours of the end of the relevant session. Visit [www.iasusa.org/RWCC2017](http://www.iasusa.org/RWCC2017) for more information.

The 25th Conference on Retroviruses and Opportunistic Infections (CROI) will be held from **March 4 to 7, 2018**, in Boston, Massachusetts, at the Hynes Convention Center. Webcasts, abstracts, electronic posters, and other electronic resources from CROI 2018 will be available online after the conference.

General abstract submission will open on **August 30, 2017**, and will close on **September 27, 2017**. Visit [www.CROIconference.org](http://www.CROIconference.org) for more information.