

HEPATITIS C TREATMENT UPDATE: A SELF-STUDY MODULE

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TARGET AUDIENCE

Physicians, physician assistants, pharmacists, nurse practitioners, nurses, and other interested medical providers

LEARNING OBJECTIVES

After reading this self-study module, you should be able to:

1. Identify the current and newly FDA-approved hepatitis C therapies.
2. Describe the most recent hepatitis C treatment guidelines.
3. List potential side effects of currently available hepatitis C medications.

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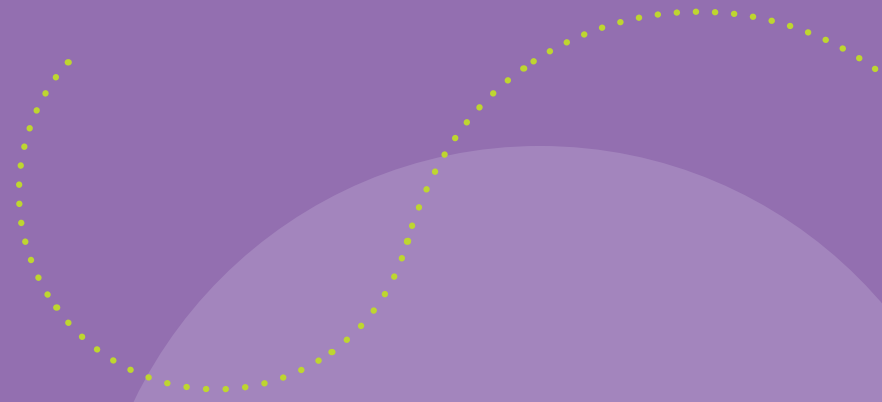
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HEPATITIS C TREATMENT UPDATE: A SELF-STUDY MODULE

Message to readers from the New York State Department of Corrections and Community Supervision (NYSDOCCS)

This module targets health care workers serving incarcerated populations and is done in partnership with the New York State Department of Corrections and Community Supervision (NYSDOCCS). As such, the Deputy Commissioner of Health Services reminds NYSDOCCS employees of the following:

“The two new hepatitis C virus (HCV) protease inhibitors have not been FDA-approved for use in HIV/HCV co-infected patients. The availability of these new HCV agents is anticipated for use in NYSDOCCS in the near future, but they will be restricted to HCV genotype 1 mono-infected patients only. At such a time that one or both agents obtain FDA approval for use in HIV/HCV co-infected patients, NYSDOCCS will reconsider this limitation.”

Carl J. Koenigsmann, MD
Deputy Commissioner and Chief Medical Officer
New York State Department of Corrections and Community Supervision

Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease that affects approximately 170 million people worldwide and almost 5 million people in the U.S.^{1,2} HCV is a small, single-stranded RNA virus belonging to the *Flaviviridae* family. There are six major genotypes of HCV, and genotype 1 is the most prevalent in the U.S. and Western Europe. The majority (up to 80%) of people exposed to HCV develop chronic hepatitis C that can ultimately lead to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Chronic hepatitis C is also the most common indication for liver transplantation worldwide³. As currently available drugs cannot eradicate HCV in all patients, the incidence of complications from chronic hepatitis C, such as cirrhosis and hepatocellular carcinoma, is predicted to

increase markedly during the next decade, making the infection one of the major global health problems⁴.

Viral transmission

Since HCV is a blood-borne pathogen, direct blood-to-blood contact is the most efficient mode of transmission. Prior to the isolation of HCV in 1989, principal transmission routes included blood transfusion, unsafe injections including procedures in health care settings, and injection drug use. After HCV serologic screening of the blood supply was introduced in 1992, injection drug use became the primary mode of transmission in developed countries. While sexual contact is generally considered to be very inefficient in HCV spread, recent data have indicated that HCV sexual transmission does occur in some populations, such as HIV-positive men who have sex with men⁵.

Acute infection

The acute phase of HCV infection is asymptomatic in the majority of patients and therefore, is rarely diagnosed until chronicity is well established. Consequently, most of our knowledge about acute hepatitis C has been gained through observational studies of infection among high-risk groups, such as injection drug users or health care workers with occupational HCV exposure. High viral loads could be detected in patients' blood within the first few weeks of infection. However, development of HCV-specific antibodies and cellular immunity is delayed and is usually detected in blood two to three months following viral exposure. The appearance of immune responses coincides with the elevation of alanine aminotransferase in peripheral blood, an indicator of liver cell injury. These findings suggest that HCV is relatively noncytopathic and that liver damage associated with hepatitis C is primarily caused by the host's immune responses.

Treatment of hepatitis C while it is still in the acute phase is significantly more successful compared to treatment initiated during the chronic phase of the infection. For example, treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) leads to HCV resolution in over 80% of acutely infected patients⁶ compared to only ~50% of patients with chronic infection. However, as the vast majority of acutely infected patients are asymptomatic, early treatment of the disease is usually not possible. In addition, as PEG-IFN and RBV therapy is long, costly and has significant side effects, all treatment decisions should consider the potential of spontaneous viral clearance, which occurs in at least 20% of patients. Certain host

factors, such as female sex⁷, the strength of early immune responses⁸ or host genetics⁹ have been associated with spontaneous resolution of acute HCV infection. Perhaps the strongest predictor of disease outcome is a genetic variation in IL28B, the gene that encodes IFN λ 3. A single nucleotide polymorphism (rs12979860), located 3 kilobases upstream of IL28B, has recently been shown to be strongly associated with HCV resolution. Patients with C/C genotype are significantly more likely to eradicate HCV than those with other genotypes^{9,10}.

Chronic infection

Traditionally, hepatitis C is considered to be in the acute phase during the initial 6 months after virus exposure and infection, as the majority of patients who spontaneously clear HCV do so within this time interval. After that interval, patients are considered to be chronically infected. In patients who develop chronic infection, HCV-specific cellular immune responses are incapable of viral eradication, as they are functionally impaired, with reduced breadth⁸. However, the continuous recruitment of immune cells to the liver contributes to the development and perpetuation of intrahepatic inflammation that promotes liver cell injury and is considered to be the primary driving force of liver fibrosis¹¹. Fibrosis progression varies significantly among chronic HCV-infected patients, with some developing severe liver disease and cirrhosis within 20-30 years and others progressing very slowly or not at all. While it is still not possible to predict the speed of hepatic fibrogenesis, certain factors other than inflammation, such as excessive alcohol consumption, smoking, older age at infection, male gender, higher body mass index, and co-infection with HIV, have all been associated with accelerated disease progression. Patients more likely to have progressive liver disease have conventionally been considered the highest treatment priority.

Hepatitis C Treatment

Pegylated interferon and ribavirin

Until recently, standard therapy for hepatitis C consisted of PEG-IFN subcutaneously injected once per week, and two daily oral doses of RBV, usually given for 24 to 48 weeks depending upon viral genotype. RBV is a nonspecific antiviral agent whose precise molecular mechanisms are not yet fully delineated. Therapeutic IFN- α , similar to endogenous IFN, has direct antiviral properties, but it also activates the hosts' innate antiviral immune responses. Attachment of polyethylene glycol to IFN- α , or pegylation, significantly extends the half-life of IFN thereby reducing the frequency of injections. Successful treatment leads to complete viral eradication, defined as a sustained virological response (SVR). Clinically, SVR has conventionally been defined as undetectable serum HCV RNA for at least 6 months following therapy cessation. Long-term follow-up of patients who have achieved an SVR has shown durable viral suppression in almost all patients, and improved liver histology in the majority of patients, including decreased fibrosis and cirrhosis regression¹². Unfortunately, approximately half of the patients treated with PEG-IFN/RBV do not achieve an SVR. Treatment efficacy depends on several host and viral factors. Specifically, HCV genotype is one of the most important predictors of treatment outcome: while up to 80% of people infected with genotypes 2 and 3 achieve an SVR, only ~50% of those mono-infected with genotypes 1 and 4 eradicate the virus after treatment with PEG-IFN/RBV. In addition, African American ethnicity, obesity, male gender, older age, higher HCV RNA levels, higher fibrosis stage, and HIV co-infection have all been associated with inferior responses to antiviral therapy. Recently, the same genetic variation in the IL28B gene that affects spontaneous HCV resolution has

been shown to also influence treatment outcome. Patients with C/C genotype are twice as likely to achieve an SVR compared to patients with other genotypes¹³.

In addition to low efficacy, PEG-IFN/RBV is associated with significant side effects. The majority of treated patients will experience at least some adverse events, the most common of which are flu-like symptoms, fatigue, hematologic and neuropsychiatric side effects¹⁴. Hematologic abnormalities, specifically anemia and neutropenia, are the most common reasons for PEG-IFN and RBV dose reduction and early treatment discontinuation. Anemia caused by RBV occurs in many patients, and it is usually managed by RBV dose reduction, transfusion, or supplementation with the growth factor erythropoietin. In cases of severe anemia, premature RBV discontinuation may be necessary. In some patients, treatment with PEG-IFN induces bone marrow suppression as well. These side effects are managed primarily through PEG-IFN dose reduction, and less frequently by treatment with specific growth factors, such as erythropoietin or granulocyte-colony stimulating factor. The most common neuropsychiatric side effect of PEG-IFN/RBV treatment is depression, with an incidence of 20- 60%. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or bupropion, are typically useful in the treatment of IFN-induced depression. Other side effects, such as mania or cognitive dysfunction, can also develop during the course of therapy. Importantly, psychiatric side effects are a frequent reason for exclusion from antiviral therapy.

Taking into consideration the significant side effect profile and the high cost of PEG-IFN/RBV therapy, identification of patients most likely to achieve a successful treatment outcome, as well as the minimal effective treatment duration, is of great importance. Treatment duration is usually tailored to the individual patient

depending upon viral genotype and early, on-treatment viral kinetics. For example, patients infected with genotypes 1 or 4 typically receive 48 weeks of PEG-IFN/RBV therapy, while 24 weeks of treatment is recommended for patients infected with genotypes 2 or 3. Additionally, patients infected with genotypes 1 and 4 who do not achieve a partial early virologic response (EVR), defined as at least a 2-log decline in HCV RNA by treatment week 12, as well as those who do not obtain undetectable HCV RNA levels by treatment week 24, should be discontinued from PEG-IFN/RBV, as an SVR is highly unlikely. In genotype 1 patients who do achieve a partial EVR but in whom HCV RNA remains detectable at treatment week 12, PEG-IFN/RBV is usually extended such that patients receive a total of 72 weeks of treatment. Genotype 1 patients with undetectable HCV RNA levels at week 12 (complete EVR) are treated for 48 weeks¹⁵.

HCV Protease Inhibitors

In May of 2011, two additional drugs were approved for the hepatitis C treatment: telaprevir (TVR) (Vertex) and boceprevir (BOC) (Merck). Both of these drugs are small molecules that directly inhibit the viral enzyme NS3-NS4A protease. Within the host cell, HCV RNA is translated into a single polyprotein, and the NS3-NS4A protease cleaves it into different functional enzymes and structural proteins. Therefore, without the protease, HCV cannot complete its life cycle. TVR and BCP, as well as other compounds that act by directly inhibiting specific steps in the virus life cycle, belong to a new category of therapeutic compounds termed directly-acting antivirals (DAAs).

Both TVR and BCP were designed specifically to target HCV genotype 1, which is the most prevalent genotype in the U.S. TVR is also a potent inhibitor of HCV genotype 2, and to lesser extent genotype 4. When given as a monotherapy,

these protease inhibitors induce rapid selection of HCV-resistant variants in almost all patients, which necessitates their use in combination with PEG-IFN/RBV. Both TVR and BCP are taken orally 3 times per day; TVR should be taken with high-fat food, while BCP should be taken with a snack. Triple therapy with protease inhibitors achieves outstanding therapeutic results, with SVR rates reaching 79% in genotype 1, treatment-naïve patients^{16,17}.

Telaprevir

Several phase 3 clinical trials have assessed the efficacy of TVR in combination with PEG-IFN and RBV for the treatment of chronic HCV infection. In the ADVANCE trial, naïve HCV genotype 1-infected patients were given triple therapy for either 8 (T8PR) or 12 weeks (T12PR), followed by PEG-IFN/RBV for a total treatment duration of either 24 or 48 weeks. Treatment duration was determined based upon early on-treatment viral response. Patients with an extended rapid virologic response or eRVR, defined as undetectable HCV RNA at weeks 4 **and** 12, received a total of 24 weeks of therapy, while all other patients received 48 weeks. SVR rates achieved in the T8PR and T12PR groups were 69% and 75%, respectively, a significant increase compared to the 44% SVR rate achieved in the control group treated with PEG-IFN/RBV without the addition of the DAA¹⁸.

In the REALIZE trial, triple therapy was evaluated in HCV genotype 1-infected patients who were previous PEG-IFN/RBV nonresponders¹⁹. Response rates were compared to those obtained in the control group, which consisted of patients retreated with PEG-IFN and RBV. Previous treatment relapsers achieved the best responses: the SVR rate was 86% among those who received triple therapy compared to 22% among those retreated with PEG-IFN/RBV. Among prior partial responders (patients who achieved ≥ 2 -log reduction in HCV RNA but who still had

detectable virus by treatment week 12), SVR rates were 59% in patients on triple therapy and 15% in the control group. The worst treatment responses were obtained in prior null responders (patients who did not achieve a 2-log HCV RNA reduction by treatment week 12). In this group, patients treated with triple therapy achieved a 32% SVR rate compared to only 5% achieved in controls.

Considering the remarkable increase in response rates, addition of TVR to the therapeutic regimen for hepatitis C is definitely an improvement. Triple therapy also permits shorter treatment duration in some patients. Current recommendations for treatment with TVR is 12 weeks with all three drugs followed by an additional 12 to 36 weeks with PEG-IFN/RBV, depending upon virologic response. Treatment-naïve patients and prior relapsers who achieve an eRVR can be treated for a total of 24 weeks. Patients who have HCV RNA levels <1000 IU/ml but who remain detectable at treatment weeks 4 and 12 as well as all prior partial and null responders should receive a total of 48 weeks of treatment. Treatment should be immediately stopped in patients with HCV RNA >1000 IU/ml at weeks 4 and 12, as well as in patients with detectable virus at week 24.

The addition of the third agent also increases treatment-related side effects. The most frequent serious adverse events associated with triple therapy include skin disorders, specifically rash and pruritus, as well as anemia. Rash and pruritus develop in the majority of treated patients. Rash can be particularly severe, requiring TVR discontinuation in approximately 6% of patients. Anemia, which is a common side effect of RBV, is further increased by the addition of TVR and occurs in more than one third of patients on triple therapy. Serious anemia that required TVR discontinuation was documented in 4% of patients.

Despite serious adverse events, strict adherence to the therapeutic regimen while patients are being treated with an HCV protease inhibitor is of utmost importance in order to minimize the likelihood of the development of resistant viral variants. On-treatment viral breakthrough due to the selection of resistant variants has been observed in 1-6% of previously treatment-naïve patients^{20,21}. That percentage was much higher among patients previously treated with PEG-IFN/RBV²². Many of the TVR-resistant viral variants confer resistance to other protease inhibitors, including boceprevir, which would limit future treatment options for the patients in whom these variants developed.

Boceprevir

The recommended regimen for triple therapy with BCP consists of a 4-week lead-in phase during which patients receive only PEG-IFN and RBV, followed by treatment with all three drugs. The rationale for the lead-in period, introduced in the phase 2 clinical trials, was to allow PEG-IFN/RBV to reach optimal, steady-state concentrations and to decrease the viral load before the addition of BCP, which should prevent it from functioning as monotherapy and therefore reduce the possibility of emergence of drug-resistant mutations. As patients who were treated with a lead-in phase with PEG-IFN/RBV achieved significantly higher SVR rates compared to those treated without induction therapy²³, the lead-in period was incorporated into phase 3 clinical trials and is currently part of the FDA-approved treatment regimen for BCP. Interestingly, the lead-in phase did not increase SVR rates in prior non-responders treated with TVR triple therapy¹⁹.

In phase 3 clinical trials, BCP triple therapy was evaluated in HCV genotype 1-infected patients who were either treatment-naïve (SPRINT-2)²⁴ or prior PEG-IFN/RBV non-responders (RESPOND-2)²⁵. After the 4 week PEG-IFN/RBV lead-in, patients received either 44 weeks of triple therapy or a response-guided regimen. In the response-guided group, patients with undetectable HCV RNA between treatment weeks 8 and 24 received 24 weeks of triple therapy, while those with detectable virus between treatment weeks 8 and 24 received either 24 weeks (SPRINT-2) or 32 weeks (RESPOND-2) of triple therapy followed by placebo plus PEG-IFN/RBV for a total of 48 weeks of treatment. Response rates were compared to those obtained in the control group in which the lead-in phase was followed by 44 weeks with placebo plus PEG-IFN/RBV. In both SPRINT-2 and RESPOND-2, patients on triple therapy achieved significantly higher SVR rates compared to those treated with PEG-IFN/RBV only. Overall, 63-66% of treatment-naïve patients on triple therapy achieved an SVR compared to 38% of control patients. Among prior treatment non-responders who received triple therapy, 59-66% achieved an SVR compared to only 21% among controls. Previous relapsers had the best outcomes with SVR rates as high as 75%. In patients with undetectable viremia at treatment week 8, SVR rates did not increase with longer triple therapy, suggesting that patients with an early viral response can benefit from shorter treatment duration. Of note, these studies did not enroll null responders, the most IFN treatment-resistant group. However, recent unpublished data showed that 38% of PEG-IFN/RBV null responders achieved

a sustained response when treated with a triple combination therapy that included BCP.

Based upon clinical trial results, the current recommendations for triple therapy with BCP suggest 4 weeks of PEG-IFN/RBV lead-in followed by 4 weeks with triple therapy, at which point HCV RNA should be measured in order to determine the total treatment duration. Patients with undetectable virus at week 8 should continue with triple therapy for a total treatment duration of 28 weeks if treatment-naïve, or 36 weeks if prior relapsers or partial responders without cirrhosis. Those with detectable HCV at treatment week 8 should receive additional 28 weeks of triple therapy followed by 12 additional weeks with PEG-IFN/RBV for a total treatment duration of 48 weeks. Treatment should immediately cease in patients with HCV RNA ≥ 100 IU/ml at treatment week 12, as well as in those with detectable virus at treatment week 24.

Similar to TVR, BCP can cause serious side effects. In the SPRINT-2 trial, 11-12% of patients on triple therapy had serious side effects, compared to 9% observed in controls. Discontinuation due to side effects did not differ significantly between patients on double compared to triple therapy. However, the addition of BCP to the PEG-IFN/RBV regimen significantly increased the number of anemic patients and those with dysgeusia (altered taste). Anemia occurred in 49% of patients on triple therapy compared to 29% in controls, while dysgeusia occurred in 37-43% of patients on triple therapy compared to only 18% in the control group²⁴.

In the SPRINT-2 trial, BCP-resistant viral variants were detected in 15-17% of patients at treatment week 4, but the percentage was much higher among those who did not have at least 1-log HCV RNA decline (40-52%). Because of cross-resistance with TVR and other protease inhibitors, strict adherence to the dosing of the triple therapy regimen, as well as immediate discontinuation of treatment in case of viral breakthrough, is very important.

Other protease inhibitors

Besides TVR and BCP, many other NS3-NS4A protease inhibitors are currently under development. For example, danoprevir (Genentech), TMC435 (Tibotec/Medivir), BI 201335 (Boehringer-Ingelheim), just to mention some, are currently being tested in phase 2 clinical trials. All of these protease inhibitors, similar to TVR and BCP, are very potent inhibitors of HCV genotype 1, but most of them cannot efficiently inhibit other HCV genotypes. An exception is TMC435, which is also active against genotypes 4, 5, and 6. None of the protease inhibitors currently in development has activity against HCV genotype 3.

Development of drug-resistance is a potentially important problem in treatment with protease inhibitors. Due to the high replication rate of HCV, its short half-life, and the low fidelity of its polymerase, the viral population in each HCV-infected patient is composed of many quasispecies. Drug-resistant variants have been shown to be preexistent in patients, but only as a minor HCV population²⁶. During treatment, the dominant, or “wild-type”, virus is eradicated by the activity of all

three drugs. However, if PEG-IFN/RBV is incapable of suppressing protease inhibitor-resistant variants, those variants will continue to replicate and will finally become the dominant HCV form after treatment failure. Unfortunately, many variants resistant to one protease inhibitor will be cross-resistant to other protease inhibitors, which may limit future treatment options in these patients.

Inhibitors of HCV Replication

Besides protease inhibitors, several other categories of drugs specifically target HCV replication, including inhibitors of NS5B polymerase, inhibitors of NS5A, as well as cyclophilin inhibitors. Inhibitors of NS5B polymerase can be further divided into nucleoside/nucleotide analogues and non-nucleoside inhibitors. All of these drugs remain under evaluation in clinical trials and to date, they have been combined with PEG-IFN/RBV.

Nucleoside/nucleotide analogue inhibitors resemble the natural NS5B substrate and are therefore incorporated into a newly synthesized viral RNA chain, causing its premature termination. These drugs are active against all genotypes and have a high resistance barrier, *i.e.* they rarely select for drug-resistant variants. Although several nucleoside/nucleotide analogues are currently being tested in clinical trials, RG7128 (Genentech/Pharmasset) is the most advanced and has, thus far, shown very promising results.

Non-nucleoside inhibitors act through binding to one of the four different allosteric sites on the NS5B polymerase, leading to a conformational change in the enzyme, which decreases its catalytic

capacity. This heterogeneous group of drugs includes filibuvir (Pfizer), BI 207127 (Boehringer-Ingelheim), ANA598 (Anadys), tegobuvir (Gilead), and others. Treatment with these drugs selects for resistant variants, and cross-resistance has been documented even with drugs that target different allosteric sites on NS5B.

NS5A inhibitors bind to and interfere with the NS5A protein, which has a role in HCV replication, assembly, and release. These drugs are potentially active against all HCV genotypes and can lead to selection of resistant viral variants. The most advanced drug in this category is BMS-790052 (Bristol-Myers Squibb), currently under investigation in several phase 2 clinical trials.

Cyclophilin inhibitors are analogues of cyclosporine A that lack its immunosuppressive properties. They interfere with the function of cyclophilins, ubiquitously expressed host proteins with a role in protein folding, and therefore cannot be classified as DAAs. However, cyclophilins have been shown to play an important role in HCV replication and possibly its assembly. Therefore, cyclophilin inhibitors have a capacity to potently inhibit HCV replication. Alisporivir (Novartis) is the most developed drug in this category, and it is currently being evaluated in phase 3 clinical trials. It has efficacy against HCV genotypes 1-4 and, although it has been shown to select for drug-resistant variants with mutations in NS5A in tissue culture, so far no viral breakthrough has been observed in clinical trials. This drug, when combined with PEG-IFN/RBV, has shown extremely promising results thus far.

IFN-free Therapies

As treatment with PEG-IFN and RBV is costly, lasts long, and causes adverse events that can significantly affect patients' quality of life, IFN-free regimens have become the primary goal for DAA therapy. To achieve this goal, these drugs will need to be used in combination to prevent development of drug-resistant viral variants. Several DAA combinations have been evaluated in clinical trials, some of which have shown

very promising results. An example is INFORM-1, a short-term, phase 1 study in which a polymerase inhibitor, RG7128, was combined with the protease inhibitor, danoprevir, for up to 13 days of treatment in naïve patients, as well as in prior non-responders to PEG-IFN/RBV²⁷. Treatment with these two DAAs was safe, well-tolerated, resulted in potent suppression of viral replication, and did not lead to selection of resistant variants. Although

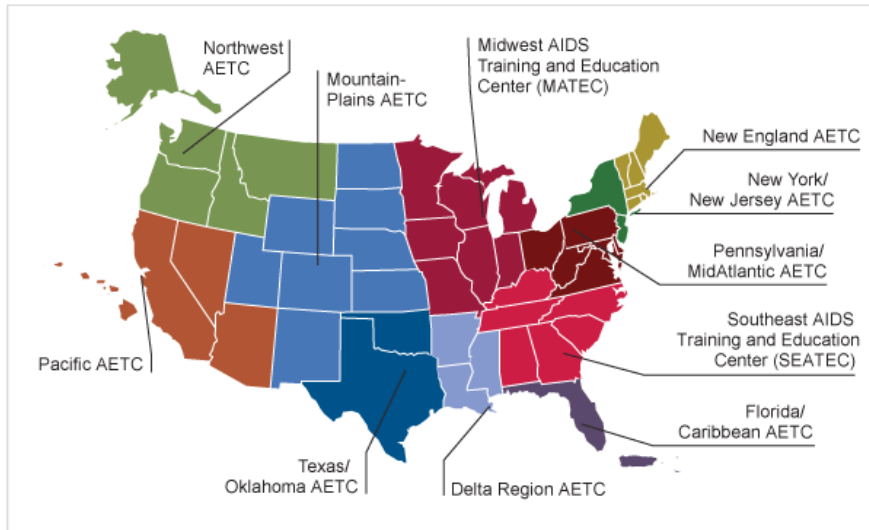
this trial did not address the safety or tolerability of long-term double DAA treatment and did not show if SVR would be possible in a regimen without PEG-IFN/RBV, the results achieved are extremely promising and form a solid base for future trials. Several other DAA combinations, including GS-9256 with GS-9190, BI 201335 with BI 207127, and BMS-790052 with BMS-650032, are also under clinical investigation.

Summary

Today, we are entering a new era in hepatitis C treatment, one that will be heavily dominated by DAAs. Besides TVR and BCP, many other DAAs are expected to be approved in the next several years. Most of the new drugs, including TVR and BCP, when combined with PEG-IFN/RBV lead to outstanding SVR rates, with as many as three quarters of patients or more eradicating the virus. These rates will most likely decrease when used in real-life treatment situations that include difficult-to-treat populations typically excluded from clinical trials, such as cirrhotics, previous null-responders, non-compliant patients, etc. Despite that, the new drug combinations promise viral eradication in the majority of infected individuals. Major efforts are currently proceeding towards the development of regimens that would allow IFN elimination, as well as those that would have a higher viral resistance barrier, fewer side effects, and more convenient dosing. In the next decade, we can expect to see dynamic changes in the hepatitis C battlefield that might even lead to eventual eradication of the disease that was once deemed incurable.

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Hepatitis C Treatment Update

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Yes No

PLEASE PROCEED TO THE NEXT PAGE AND COMPLETE THE SELF-ASSESSMENT TEST

SELF-ASSESSMENT TEST

DIRECTIONS: Referring to the module text, please select the BEST answer by circling your response directly on this test. To obtain education credit, a minimum of 70% of the questions must be answered correctly. **This learning activity is awarded 1.0 contact hour until June 30, 2012.**

Hepatitis C Treatment Update

- 1. Patients chronically infected with HCV genotype 3 should be treated with:**
 - A. PEG-IFN and RBV in combination with either TVR or BCP for 24 weeks
 - B. PEG-IFN and RBV in combination with either TVR or BCP for 48 weeks
 - C. PEG-IFN and RBV for 24 weeks
 - D. PEG-IFN and RBV for 48 weeks
- 2. Chronic hepatitis C is the most common indication for liver transplantation.**
 - A. True
 - B. False
- 3. Currently, the primary mode of HCV transmission in the United States is through:**
 - A. unsafe tattoos and body piercing
 - B. injection drug use
 - C. blood transfusions
 - D. sex
- 4. The effectiveness of HCV treatment with PEG-IFN/RBV is the same whether it is delivered during the acute phase or during the chronic phase of the infection.**
 - A. True
 - B. False
- 5. Duration of HCV treatment is usually determined based upon:**
 - A. early on-treatment viral kinetics
 - B. HCV genotype
 - C. IL28B single nucleotide polymorphism rs12979860 genotype
 - D. all of the above
 - E. a and b
- 6. Triple therapy with PEG-IFN, RBV, and either TVR or BCP should start with a 4-week PEG-IFN/RBV lead-in, as this regimen has increased SVR rates compared with a regimen in which PEG-IFN, RBV and TVR or BCP are all used together from the initiation of therapy.**
 - A. True
 - B. False
- 7. The acute phase of HCV infection is asymptomatic in the majority of patients.**
 - A. True
 - B. False
- 8. Partial early virologic response is defined as:**
 - A. undetectable HCV RNA at treatment week 4
 - B. at least a 2-log decline in HCV RNA at treatment week 4
 - C. undetectable HCV RNA at treatment week 12
 - D. at least a 2-log decline in HCV RNA at treatment week 12
- 9. What category of DAA drugs has a relatively high resistance barrier, i.e. it rarely selects for drug-resistant HCV variants?**
 - A. Protease inhibitors, such as TVR and BCP
 - B. Nucleoside/nucleotide analogue inhibitors of NS5B polymerase
 - C. Non-nucleoside inhibitors of NS5B polymerase
 - D. None of the above
- 10. What side effect(s) is the most common reason for PEG-IFN and/or RBV dose reduction and early treatment discontinuation?.**
 - A. Hematologic abnormalities, such as anemia and neutropenia
 - B. Fatigue
 - C. Dermatologic abnormalities, such as severe rash and pruritus
 - D. Depression

PLEASE PROCEED TO THE NEXT PAGE AND COMPLETE THE HRSA PARTICIPANT INFORMATION FORM

PIF

HRSA AIDS Education and Training Centers
PARTICIPANT INFORMATION FORM

To create your unique ID number, use the month of your birth, the day of your birth, and the last four digits of your social security number. For example, May 29, 123-45-6789 has the ID number 05296789.

1.

M	M	D	D	#	#	#	#

Unique ID Number

2.

M	M	/	D	D	/	Y	Y

Today's Date

Please completely fill in the circles (●) when answering the questions.

3. Your Primary Profession/Discipline (Select one)

- 1. Dentist
- 2. Other Dental Professional
- 3. Advanced Practice Nurse
- 4. Nurse
- 5. Pharmacist
- 6. Physician
- 7. Physician Assistant
- 8. Clergy/Faith-Based Professional
- 9. Dietitian/Nutritionist
- 10. Health Educator
- 11. Mental/Behavioral Health Professional
- 12. Other Public Health Professional
- 13. Social Worker
- 14. Substance Abuse Professional
- 15. Community Health Worker
- 16. Other Non-Clinical Professional (specify): _____

4. Your Primary Functional Role (Select one)

- 1. Administrator
- 2. Agency Board Member
- 3. Care Provider/Clinician
- 4. Case Manager
- 5. Client/Patient Educator
- 6. Clinical/Medical Assistant
- 7. Intern/Resident
- 8. Researcher/Evaluator
- 9. Student/Graduate Student
- 10. Teacher/Faculty
- 11. Other (specify) : _____

5. Your Principal Employment Setting (Select one)

- 1. Academic Health Center
- 2. Community Health Center
- 3. Family Planning Clinic
- 4. HIV Clinic
- 5. HMO/Managed Care Organization
- 6. Hospital-Based Clinic
- 7. Hospital/ER
- 8. Indian Health Services/Tribal Clinic
- 9. Infectious Disease Clinic
- 10. Long-Term Nursing Facility
- 11. Maternal/Child Health Clinic
- 12. Mental/Behavioral Health Clinic
- 13. Rural Health Clinic
- 14. Sexually Transmitted Disease Clinic
- 15. Substance Abuse Treatment Center
- 16. College/University
- 17. Community-Based Organization
- 18. Community/Retail Pharmacy
- 19. Correctional Facility
- 20. Military/VA
- 21. Private Practice
- 22. State/Local Health Department
- 23. Non-Health
- 24. Other Primary Care
- 25. Not Working (skip to Q. #9)

6a. Primary Employment Setting

- Rural
- Suburban/Urban

6b. Zip Code

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7. Is the employment setting a faith-based organization?

- Yes
- No
- Don't Know

8a. Does the employment setting receive Ryan White Program Funding?

- Yes (skip to Q9)
- No (skip to Q9)
- Don't Know (go to Q8b)

8b. If 8a=Don't Know, please write the full name of your agency:

NOTE: Please answer BOTH Question 9 about Hispanic origin and Question 10 about race.

9. Are you of Hispanic, Latino/a, or Spanish origin?

- Yes
- No

10. What is your racial background? (Select all that apply)

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White

11. What is your gender?

- Female
- Male
- Transgender

12a. Do you provide services directly to clients/patients?

- Yes
- No [Stop here. You are done with this form.]

12b. Please estimate the PERCENTAGE of your OVERALL CLIENT/PATIENT population in the past YEAR who were racial-ethnic minorities:

- None/yr.
- 1-24%/yr.
- 25-49%/yr.
- 50-74%/yr.
- ≥ 75%/yr.

13. Do you provide services directly to HIV-infected clients/patients?

- Yes
- No/Don't know (Stop here. You are done with this form.)

14. How many YEARS have you been providing services directly to HIV-infected clients/patients?

--	--

 (Round up to the nearest whole year.)

15. Estimate the NUMBER of HIV-Infected clients/patients to whom you provide direct services in an average MONTH.

- None/mo.
- 1-9/mo.
- 10-19/mo.
- 20-49/mo.
- 50+/mo.

For questions 16 through 19, estimate the PERCENTAGE of your HIV-infected clients/patients in the past YEAR who were:

16. HIV+ who are racial-ethnic minorities

- None/yr.
- 1-24%/yr.
- 25-49%/yr.
- 50-74%/yr.
- ≥75%/yr.

17. HIV+ who are co-infected with Hepatitis C

- None/yr.
- 1-24%/yr.
- 25-49%/yr.
- 50-74%/yr.
- ≥ 75%/yr.

18. HIV+ who are receiving antiretroviral therapy

- None/yr.
- 1-24%/yr.
- 25-49%/yr.
- 50-74%/yr.
- ≥ 75%/yr.

19. HIV+ who are women

- None/yr.
- 1-24%/yr.
- 25-49%/yr.
- 50-74%/yr.
- ≥ 75%/yr.

For Office Use Only	July 2010	1 0	0 1	1 1 1 2 0 1 0 1	2 3 0	Ryan White Program <input checked="" type="radio"/> Yes <input type="radio"/> No
		AETC	LPS	Program ID	Agency	

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