Health law inspires hope, worry among people living with HIV

By Anna Gorman and Ankita Rao
Kaiser Health News

Matt Sharp had high hopes for the nation's health law. The self-employed health consultant is HIV positive and has been denied insurance in the past because of his illness, so he was relieved to learn that the law wouldn't allow that to happen again.

But now, the 57-year-old San Francisco Bay Area resident is less sure that Obamacare will live up to his expectations.

He plans to enroll in coverage through the state’s insurance marketplace — but he still doesn’t know if his doctors will be included. And although he will get help with premiums and medications through an existing program for HIV patients, Sharp worries he won’t be able to afford co-payments and other out-of-pocket expenses.

"I am apprehensive," said Sharp, a former classical dancer. "There is a lot of unease with the whole rollout. But when you are talking about a person in my situation, there is even more unease."

The Affordable Care Act provides an unprecedented opportunity to reach the more than 1 million people nationwide living with HIV. The law requires private insurers to cover them and others with pre-existing conditions and bars companies from charging patients more because of their illness.

HIV-positive patients can also buy coverage through insurance marketplaces, often with the help of federal subsidies. And the law allows states to expand their Medicaid programs to cover low-income HIV patients who were not previously eligible.

Advocates and doctors agree that the changes will help a population that has struggled for decades to maintain regular access to care. New insurance options also could lead to more preventive care and earlier diagnosis and treatment, they said.

But they worry that the transition — along with confusion and unexpected costs — could lead to gaps in care for HIV patients, causing their illness to progress and be spread to others.

“Having an insurance card alone isn’t a guarantee that people will get high-quality HIV care,” said Jen Kates, who directs HIV policy for the Kaiser Family Foundation and helped put together an online guide about the health law for HIV patients. (Kaiser Health News is an editorially independent part of the foundation.) “There are ongoing questions: Will people be able to see the doctors they need to see? Will all the benefits they need be covered?”

Advocacy groups have criticized some health plans in the insurance exchanges for failing to cover key HIV medications, charging high amounts for necessary drugs or failing to tell consumers which

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FDA approves two new hepatitis C drugs

The U.S. Food and Drug Administration recently approved Olysio (simeprevir) and Sovaldi (sofosbuvir), both drugs designed to treat chronic hepatitis C virus (HCV) infection.

Sovaldi is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need for co-administration of interferon. Sovaldi is a nucleotide analog inhibitor that blocks a specific protein needed by the hepatitis C virus to replicate. Sovaldi is to be used as a component of a combination antiviral treatment regimen for chronic HCV infection.

There are several different types of HCV infection. Depending on the type of HCV infection a patient has, the treatment regimen could include Sovaldi and ribavirin or Sovaldi, ribavirin and peginterferon-alfa. Ribavirin and peginterferon-alfa are two drugs also used to treat HCV infection.

Olysio is a protease inhibitor that blocks a specific protein needed by the hepatitis C virus to replicate. It is to be used as a component of a combination antiviral treatment regimen. In clinical studies, Olysio was evaluated in combination with peginterferon-alfa and ribavirin, two drugs also used to treat hepatitis C virus infection. Olysio is intended for adults with compensated liver disease (a diseased liver that is still functioning), including cirrhosis, who have not received treatment for their infection (treatment naive) or for whom previous treatment has not been effective (treatment experienced).

Sovaldi trials
Sovaldi’s effectiveness was evaluated in six clinical trials consisting of 1,947 participants who had not previously received treatment for their disease (treatment-naive) or had not responded to previous treatment (treatment-experienced), including participants co-infected with HCV and HIV. The trials were designed to measure whether the hepatitis C virus was no longer detected in the blood at least 12 weeks after finishing treatment (sustained virologic response), suggesting a participant’s HCV infection has been cured.

Results from all clinical trials showed a treatment regimen containing Sovaldi was effective in treating multiple types of the hepatitis C virus. Additionally, Sovaldi demonstrated efficacy in participants who could not tolerate or take an interferon-based treatment regimen and in participants with liver cancer awaiting liver transplantation, addressing unmet medical needs in these populations.

The most common side effects reported in clinical study participants treated with Sovaldi and ribavirin were fatigue and headache. In participants treated with Sovaldi, ribavirin and peginterferon-alfa, the most common side effects reported were fatigue, headache, nausea, insomnia and anemia.

Sovaldi is the third drug with breakthrough therapy designation to receive FDA approval. The FDA can designate a drug as a breakthrough therapy at the request of the sponsor if preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over available therapies for patients with serious or life-threatening diseases. Sovaldi was reviewed under the FDA’s priority review program, which provides for an expedited review of drugs that treat serious conditions and, if approved, would provide significant improvement in safety or effectiveness.

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doctors and medications are included.

In December 2013, a coalition detailed the problems in a letter to Health and Human Services Secretary Kathleen Sebelius. It cited several examples of health insurers requiring consumers to pay a large percentage of the cost for preferred HIV medications and expressed concern that insurers were trying to discourage people with HIV from enrolling in their plans.

"In the long run, this is a move forward for people with HIV," said Anne Donnelly, director of health care policy for Project Inform, an HIV and Hepatitis C advocacy organization in the San Francisco Bay Area. "In the short run, this is going to be a rough road."

Only about a third of U.S. residents living with HIV now receive regular medical care. HIV patients receive coverage through work, private insurance plans or government programs such as Medicare and Medicaid. In the past, to qualify for Medicaid in most states, HIV-positive patients had to be sick enough to be deemed disabled.

Lower income HIV-positive patients now often rely on the Ryan White HIV/AIDS Program, which helps pay for primary care, support services and medications. The $2 billion program provides services to about a half million people each year. But as many of these patients become eligible for new insurance options under the health law, advocates fear Ryan White funding could be reduced or fall away.

John Hogan, a doctor who has worked with HIV-positive patients in the Washington D.C. area since 1993, said the Ryan White program is still needed, including for some who are gaining new coverage. The funding will be essential in 23 states that don’t plan to expand Medicaid and for undocumented immigrants, who don’t qualify for Obamacare, experts said.

Oscar Lopez, 34, who works in retail merchandising, is in the country illegally and was diagnosed with HIV two years ago. He has been receiving care funded by Ryan White in Pasadena, Calif. He knows he isn’t eligible for insurance under the Affordable Care Act but still is afraid the new law could cost him access to his doctors and medications.

"We need our meds, and we need to take them every day," he said. "I am trying to stay calm and figure out what is the next step."

Even HIV patients with insurance often turn to the Ryan White program for help. Bradley Land, who was infected three decades ago, is covered through both Medicaid and Medicare. He receives his medical care at Kaiser Permanente (not affiliated with Kaiser Health News) for both HIV and a heart condition and goes to the Pasadena Public Health Department for additional Ryan White services including therapy, dental care and case management.

"My medical is very well-managed," said Land, an insurance adjuster before he retired in 1993 because of his illness. "But I also need that wrap-around care that helps me live every day. In my 15 minutes with the doctor at Kaiser, I am not going to get that."

In cities across the nation, HIV-positive patients have been attending workshops to learn more about their options and how their coverage and medical care may change under the health law. Many are trying to navigate a world of private insurance that wasn’t open to them in the past. At the same time, advocates for HIV patients are scrambling to find enough people with expertise in both insurance and HIV to help.

Vanessa Velez, 25, infected when she was raped as a young girl, is uncertain about how the law will affect her and her family. She is covered by her husband’s insurance plan but turns to Ryan White when the coverage falls short. The two drugs she has taken in recent years each cost $800 a month and her Cigna plan has a cap of $10,000 a year.

She knows what it’s like to feel anxious when money runs short, and how weak she feels when she isn’t at her healthiest. But she said living with the illness and trying to deal with expensive medical care has taught her confidence, faith and patience. "Everyone has something they’re going through," she said.

Sharp, the former dancer in California, said he, too, is anxious but thankful. "I am lucky to be able to even get any kind of insurance," he said.

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Olysio studies
The safety and effectiveness of Olysio were evaluated in five clinical studies of 2,026 treatment-naive and treatment-experienced participants randomly assigned to receive Olysio plus peginterferon-alfa and ribavirin or placebo plus peginterferon-alfa and ribavirin. The studies were designed to measure whether a participant’s hepatitis C virus was no longer detected in the blood at least 12 weeks after finishing treatment (sustained virologic response), suggesting a participant’s infection had been cured.

Results showed 80 percent of treatment-naive participants given Olysio plus peginterferon-alfa and ribavirin achieved sustained virologic response, compared to 50 percent of participants receiving peginterferon-alfa and ribavirin alone. In one of the studies with treatment-experienced participants whose infection returned (prior relapsers), 79 percent receiving Olysio plus peginterferon-alfa and ribavirin achieved sustained virologic response compared to 37 percent of participants receiving peginterferon-alfa and ribavirin alone.

Another study examined Olysio’s safety and effectiveness in treatment-experienced participants, including prior relapsers, those who partially responded to prior therapy (partial responders) and those who did not respond to prior therapy (null responders). Adding Olysio improved response rates in each of these subgroups compared to peginterferon-alfa and ribavirin alone.

A reduction in Olysio’s effectiveness was observed in participants infected with the genotype 1a hepatitis C virus with an NS3 Q80K polymorphism, a strain of the hepatitis C virus commonly found in the United States. Olysio’s drug label includes a recommendation to screen for the presence of the strain prior to beginning therapy and to consider alternative therapy if the strain is detected.

The most common side effects reported in clinical study participants treated with Olysio in combination with peginterferon-alfa and ribavirin were rash (including photosensitivity), itching (pruritis) and nausea. Serious photosensitivity reactions resulting in hospitalization were reported. Patients will be advised to limit sun exposure and to use sun protective measures during treatment with Olysio in combination with peginterferon alfa and ribavirin. Olysio should not be used alone to treat chronic hepatitis C infection.

Olysio was reviewed under the FDA’s priority review program, which provides for an expedited review of drugs that, if approved, would provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared to available therapies.

Olysio is marketed by Janssen Pharmaceuticals, based in Raritan, N.J. Sovaldi is marketed by Gilead, based in Foster City, Calif.

Press release from US Food and Drug Administration
Research shows combo cures toughest cases of hepatitis C

Efforts to cure hepatitis C, the liver-damaging infectious disease that has for years killed more Americans than HIV/AIDS, are about to get simpler and more effective, according to new research at Johns Hopkins and elsewhere.

In a study recently reported in the Jan. 16 issue of the New England Journal of Medicine, researchers say combination treatments involving a pair of experimental, oral antiviral drugs, daclatasvir and sofosbuvir, were safe and highly effective in the treatment of hepatitis C. The combination therapy worked well even in the patients who are hardest to treat, in whom the conventional “triple therapy” with hepatitis C protease inhibitors, telaprevir or boceprevir, plus peginterferon and ribavirin had failed to cure the infection.

“This research paves the way for safe, tolerable and effective treatment options for the vast majority of those infected with hepatitis C,” says study leader Mark Sulkowski, M.D., medical director of the Johns Hopkins Center for Viral Hepatitis. “Standard treatments for the disease are going to improve dramatically within the next year, leading to unprecedented advances for the treatment of patients infected with the hepatitis C virus.”

The research was conducted on 211 men and women with any of the three major types of the disease who were treated at 18 medical centers across the United States and Puerto Rico. Among patients with genotype 1 — the most common strain of the infection in the United States — 98 percent of the 126 previously untreated patients and 98 percent of 41 patients whose infections remained even after the triple therapy were considered cured, with no detectable virus in their blood three months after the treatment had stopped. Results were similar in study participants infected with genotypes 2 or 3, strains that are less common in the United States.

The study participants took a daily combination of 60 milligrams of daclatasvir and 400 milligrams of sofosbuvir, with or without ribavirin.

In December 2013, the U.S. Food and Drug Administration (FDA) approved sofosbuvir in combination with peginterferon and ribavirin for the treatment of genotype 1 infection and in combination with only ribavirin for genotype 2 and 3 infection. Daclatasvir has not yet been approved by the FDA.

Sulkowski says that if daclatasvir and other new drugs for hepatitis C win approval from the FDA, the dreaded weekly injections of peginterferon will be a thing of the past.

Sulkowski, a professor at the Johns Hopkins University School of Medicine, also says that the so-called "pill burden" of what had been standard therapy for genotype 1 could go down from some 18 pills per day and one injection per week to as few as one or two pills per day and no injections. Side effects from the new pill combination were generally mild, but included fatigue, headache and nausea, a safety profile that Sulkowski says compares favorably with that of the peginterferon-based therapy, which is tied to severe side effects which may include fatigue and depression.

The new study is one of the first to show that hepatitis C can be cured without the use of ribavirin, which is known to cause anemia.

The advent of simpler pill-only regimens, Sulkowski adds, should make it easier for those infected with hepatitis C to be cured, preventing the development of liver cancer and liver failure and obviating the need for liver transplant. Currently, he says, fewer than 5 percent of the estimated 3.2 million Americans with hepatitis C have been cured, according to the U.S. Centers for Disease Control and Prevention (CDC). Further, the CDC estimates that between 50 and 75 percent of people who live with chronic hepatitis C are unaware that they are infected.

Sulkowski says the arrival of simpler treatment regimens could not come soon enough. Many of the people diagnosed with the infection, mainly those born between 1945 and 1965, were infected during the 1970s and 1980s through injection drug use and tainted blood transfusions and are now suffering from cirrhosis and liver cancer tied to chronic infection.

This is why, he says, the CDC recommended hepatitis C screenings in 2012 for all baby boomers.

Sulkowski says that further research is being performed by Gilead Sciences of Foster City, Calif., on a regimen that combines sofosbuvir with another experimental drug it manufactures, called ledipasvir, into a single tablet which can be taken once a day. Ledipasvir is similar to daclatasvir, which is made by Bristol-
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Myers Squibb of Princeton, N.J., in that it inhibits replication of the hepatitis nonstructural protein NS5A. The combination of sofosbuvir and ledipasvir has not yet been approved by the FDA.

The newly published study, which took two years to complete, was funded by Gilead Sciences and Bristol-Myers Squibb. Sulkowski is a paid consultant to both Gilead Sciences and Bristol-Myers Squibb. The terms of his arrangements are managed by The Johns Hopkins University in accordance with its conflict of interest policies.

Besides Sulkowski, other study investigators involved in this study were Maribel Rodriguez-Torres, M.D., at the Fundacion de Investigacion in San Juan, Puerto Rico; K. Rajender Reddy, M.D., at the University of Pennsylvania; Tarek Hassanein, M.D., at Southern California Liver Center in Coronado, Calif.; Ira Jacobson, M.D., at Weil Cornell Medical College in New York; Eric Lawitz, M.D., at the University of Texas Southwestern Medical Center in San Antonio; Ann Lok, M.D., at the University of Michigan, Ann Arbor; Federico Hinestrosa, M.D., at Orlando Immunology Center in Florida; Paul Tuluvath, M.D., at Mercy Medical Center in Baltimore, Md.; Howard Schwartz, M.D., at Miami Research Associates in Florida; David Nelson, M.D., at the University of Florida; and Gregory Everson, M.D., at the University of Colorado Denver.

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Press release from Johns Hopkins University

FDA approves Complera for patients switching from a stable regimen

Gilead Sciences, Inc. recently announced that the U.S. Food and Drug Administration (FDA) has approved the single tablet HIV-1 regimen Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) for use in certain virologically-suppressed (HIV RNA <50 copies/mL) adult patients on a stable antiretroviral regimen in order to replace their current antiretroviral treatment regimen.

Complera was first approved in 2011 for patients new to therapy and is now one of the most widely-prescribed HIV regimens in the United States. Complera combines a complete course of three antiretroviral medications into a single, once-daily tablet. The product contains Gilead’s Truvada, which itself is a fixed-dose combination of two HIV medicines, and Janssen R&D Ireland’s rilpivirine (marketed as Edurant). Patients switching to Complera should have no history of virologic failure, have suppressed viral load for at least six months, be on their first or second antiretroviral regimen, and have no current or past history of resistance to Complera components.

The efficacy of Complera was established in patients who were virologically suppressed (HIV RNA <50 copies/mL) on a stable ritonavir-boosted protease inhibitor-containing regimen. This approval is supported by clinical data from the Phase 3 SPIRIT (Study 106) clinical trial. In this randomized, open-label study, virologically suppressed patients who were taking multi-tablet HIV therapy containing a ritonavir-boosted protease inhibitor (PI) either switched to Complera or remained on their PI-based regimen.

The study found that, after 48 weeks of treatment with Complera, 89 percent (n=283/317) of switch patients had viral load less than 50 copies/mL, compared to 90 percent (143/159) of patients who remained on a PI-regimen for 24 weeks.

Complera was well tolerated in SPIRIT and there were few treatment discontinuations due to adverse events. The most common side effects in previous clinical studies of Complera were headache, depressive disorders and insomnia (2 percent for all). No new adverse reactions were identified in SPIRIT, but the frequency of adverse reactions increased from 2 percent to 2.4 percent.

Press release from Gilead Sciences, Inc.
Low lymphocyte count a risk factor for infections for people taking HCV therapy

By Michael Carter

A low lymphocyte count is associated with an increased risk of infections during hepatitis C virus (HCV) treatment that includes pegylated interferon and ribavirin, according to the results of a large observational study published in the online edition of Clinical Infectious Diseases.

Moderate-to-severe infections occurred in approximately a fifth of study participants. Independent risk factors were female sex, a history of depression and nadir (lowest-ever) lymphocyte count.

“These findings have important implications for the management of patients during HCV treatment that includes PegIFN-alfa [pegylated interferon-alfa],” comment the authors. “Our data suggest that lymphocytopenia may be an important marker of increased risk of moderate, severe, or life-threatening infections.”

PegIFN-alfa and ribavirin are the backbone of HCV therapy. Known side-effects of interferon include cytopenias – a reduction in the number of blood cells. The incidence of severe neutropenia (a lack of a type of white blood cell) among patients taking PegIFN-alfa/ribavirin therapy ranges between 4 and 12%.

Approximately a quarter of people taking HCV therapy develop infections, but the relationship between cytopenia and the risk of infections has not been well researched.

Investigators from the IDEAL (Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy) study designed an observational study involving 3070 people. The incidence of mild, moderate, severe and life-threatening infections was monitored and their risk factors assessed.

The adult participants were all HCV-treatment naive at baseline (had not taken HCV treatment before) and had compensated liver disease. Blood chemistry was monitored every two to six weeks during the 48-week course of HCV therapy, which consisted of PegIFN-alfa-2a/b with weight-based ribavirin. Dose reductions were required when neutrophils fell to below 0.75x10^9/l and treatment was discontinued in instances of a decline in neutrophils below 0.5x10^9/l.

Infections developed in 36% of participants, and in 19% of individuals' infections were moderate, severe or life threatening.

Approximately a fifth (21%) of patients had at least one neutrophil count below 0.75x10^9/l, only 8% of individuals experienced a sustained fall in neutrophils below this level. Twelve patients (0.4%) had severe or life-threatening infections and moderate-to-severe neutropenia. Absolute lymphocyte count fell to below 0.5x10^9/l in 107 patients, including 34 patients who also had nadir neutrophil counts below 0.75x10^9/l.

Several risk factors were independently associated with an increased risk of infections of moderate or greater severity. These included female sex (AOR = 1.61; 95% CI, 1.33-1.97), a history of depression (AOR = 0.68; 95% CI, 0.55-0.83) and nadir on-treatment lymphocyte count (AOR = 0.48; 95% CI, 0.37-0.68); all p < 0.001. Nadir neutrophil count was not associated with risk of moderate, severe or life-threatening infections.

“We identified a strong relationship between treatment-induced lymphocytopenia and incident infection,” comment the investigators. “Our findings suggest that clinicians should monitor ALC [absolute lymphocyte count] (in addition to ANC [absolute neutrophil count]) carefully during treatment….another question worthy of study is whether increased monitoring of patients at higher risk of infection, such as those with cirrhosis, is warranted.”

The relationship between sex and the risk of infection was independent of lymphocyte count. Although acknowledging further research into this finding is warranted, the authors nevertheless recommend that “clinicians should be aware of the increased infection incidence in women treated with PegIFN/RBV”.

The investigators conclude that physicians should carefully monitor both lymphocyte and neutrophil counts in patients treated with PegIFN/ribavirin. Dose reductions should be considered for patients who experience a fall in lymphocyte count below 0.5x10^9/l.

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Long-term immune response to vaccines impaired in people with HIV

By Michael Carter

The long-term immune response to most vaccines is impaired in people with HIV, according to the results of a meta-analysis published in the online edition of Clinical Infectious Diseases. Comparison with vaccination outcomes in HIV-negative individuals showed that the effect of immunizations waned more rapidly in people with HIV.

“Our analyses showed a rapid decrease in seroprotection after immunization in HIV-infected patients,” comment the authors.

The study has important implications, showing that vaccine responses needed to be closely monitored in people living with HIV and revaccination provided when antibody levels are no longer protective. It’s already known that initial immune responses to most vaccines are impaired in people with HIV.

However, little is known about the persistence of vaccine-induced antibodies in the long-term. This is an important gap in knowledge. Recommendations about booster injections for people with HIV are currently based on data obtained from HIV-negative individuals.

A team of French investigators therefore performed a meta-analysis and systematic review of data from prospective studies reporting on the long-term persistence of antibody concentrations after vaccination with licensed products.

A total of 59 studies were reviewed and 19 were included in the meta-analysis. Results of the meta-analysis showed that less of half of people with HIV who had a primary response to hepatitis B vaccination still had protective immunity two years after immunization (28% in adults; 61% in children), and that only 17% were still protected after five years. Doubling the vaccine dose did not improve long-term responses.

A slight decrease over time in the protective immunity provided by hepatitis A vaccination was also observed. Pooled results showed that 92% of individuals were still protected two years after vaccination, and 82% after five years.

Meta-analysis of the measles vaccine was restricted to studies focusing on children who had acquired HIV vertically (through mother-to-baby transmission), immunized between the ages of 6 and 42 months with the MMR vaccine. Pooled results showed that 68% of initial responders still have protective antibodies after two years, falling to 40% after five years.

Protective levels of antibodies to tetanus were present in 74 and 43% of initial responders two and five years after immunization, respectively. Few studies reported on the long-term responses to vaccination against polio, pertussis and diphtheria. However, all showed that the duration of protection was shorter for children with HIV compared to HIV-negative children.

Analysis of long-term responses to immunization against Streptococcus pneumoniae included studies examining either the PCV or PPSV23 vaccines. After PPSV23 in adults, rates of decrease in antibody concentrations were either similar or more rapid than those observed in HIV-negative adults. After five years, antibody levels were no longer protective. This was more likely to be the case for people with a low CD4 cell count or detectable viral load at the time of vaccination. Children with HIV who initially responded to Streptococcus pneumoniae immunization had a significantly greater decline in antibody levels during follow-up compared to HIV-negative children.

Rates of long-term sero-protection among vertically infected children with an initial response to Haemophilus influenzae b varied between 16% and 78%.

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The advent of direct-acting antivirals has revolutionized hepatitis C treatment, but many prospective patients and providers are waiting for all-oral regimens that avoid interferon, which must be injected weekly and can cause debilitating side-effects.

"Recently approved medications and several others on the horizon promise to cure nearly all treated patients without the many side-effects that have plagued past treatment regimens," said AASLD panel co-chair Donald Jensen during a media teleconference introducing the website and guidelines.

The new guidelines were developed by a panel of 27 liver disease and infectious diseases specialists and a patient advocate. The evidence-based consensus recommendations reflect the latest data on screening, management and treatment of chronic hepatitis C.

The guidelines are intended for use by both hepatologists and infectious disease doctors who have traditionally treated people with hepatitis C, as well as by other types of providers who will be called on to treat the growing number of people seeking care due to expanded screening and availability of better treatments.

"We expect the guidelines to be used by practitioners well versed in nuances of antiviral therapy, but also by many who are inexperienced or even new to the field of hepatitis C," said IDSA panel co-chair David Thomas.

**Treatment recommendations**
The first iteration of the new guidelines covers testing, linkage to care and specific treatment recommendations. Panel members noted that the website includes off-label recommendations that go beyond FDA-approved indications. Furthermore, it provides recommendations for special patient populations — including people with HIV and hepatitis C co-infection, patients with kidney failure, people with decompensated liver cirrhosis and liver transplant recipients — that have not yet have been extensively studied.

"FDA only will approve drugs that have gone through rigorous testing," said IAS-USA panel co-chair Michael Saag. "We cannot run a phase 3 trial on every possible [drug] combination or every possible patient population."

**Recommendations for Initial therapy**
Recommendations for initial therapy for people with hepatitis C virus (HCV) who have decided to start treatment include the following:

For initial treatment of genotype 1 hepatitis C, the panel recommends the recently approved HCV polymerase inhibitor sofosbuvir (Sovaldi) plus weight-based ribavirin and pegylated interferon for 12 weeks, regardless of HCV subtype 1a or 1b.

An alternative is the HCV protease inhibitor simeprevir (Olysio) for 12 weeks plus pegylated interferon and ribavirin for 24 weeks for people with genotype 1b or those with 1a who do not carry the Q80K resistance mutation.

For people with genotype 1 who cannot take interferon, the panel recommends sofosbuvir plus simeprevir, with or without ribavirin, for 12 weeks. This off-label regimen has not been through phase 3 testing, but performed very well in the phase 2 COSMOS trial.

An alternative for this group is sofosbuvir plus ribavirin for 24 weeks, though the panel noted that it is not as effective as sofosbuvir plus simeprevir, especially for people with liver cirrhosis.

For people with easier-to-treat HCV genotype 2, the panel recommends first-line treatment using sofosbuvir plus weight-based ribavirin for 12 weeks.

For people with HCV genotype 3, the recommendation is sofosbuvir plus weight-based ribavirin for 24 weeks, with an alternative of sofosbuvir plus ribavirin plus pegylated interferon for 12 weeks.

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HCV drug development news

By Alan Franciscus, Editor-in-Chief
HCV Advocate

This article will focus on recent news about HCV drugs in clinical development to treat hepatitis C. It was a very busy month, with two studies published in the prestigious New England Journal of Medicine—AbbVie and Gilead/Bristol-Myers Squibb. Other news included the approval of Sovaldi in Europe and BMS’s European submission for approval of their HCV medication. In addition there were preliminary results from a couple of cross-company trials. I think, however, that the most fascinating news of the month is about a drug that may cure hepatitis C with just one infusion—at least that is what the study will eventually evaluate in people with HCV.

AbbVie

AbbVie’s HCV interferon-free combination therapy is currently in Phase 3 studies. The article that appeared in the New England Journal of Medicine gives the final results from their Phase 2b study.

Study Drugs:
ABT-450/r (protease inhibitor)boosted with ritonavir,
ABT-333 (polymerase inhibitor) or ABT-267 (NS5A inhibitor) or both,
Ribavirin (one arm did not contain ribavirin)

Treatment Duration:
8, 12, or 24 weeks.

Arms:
14 treatment arms—total of 571 patients

Patients:
Genotype 1, treatment naïve & treatment experienced—no patients had cirrhosis

SVR12/Cure rates:
88% among those who received the therapy for 8 weeks
95% among those who received the therapy for 12 weeks
83% to 100% among all the groups including treatment-naïve and treatment-experienced patients.

The most frequent adverse events (side effects) were fatigue, headache, nausea, and insomnia. The cure rates were similar among people who had positive and negative predictors of treatment response (HCV subtype 1a, race, HCV RNA, non-cc IL28B).

One percent (8 patients) discontinued treatment due to adverse events (side effects). ABT-450/r and ABT-267 were dosed once daily; ABT-333 and ribavirin were dosed twice daily.

Comments:
The high response rates and shorter treatment duration all point to a very effective therapy to treat hepatitis C. Although this was a Phase 2b study, the fact that this trial had a large patient population with similar cure rates among all groups is significant. In fact, the Phase 3 studies that have been released so far have reported similar cure rates.

Bristol-Myers Squibb & Gilead

The final results from a clinical trial of the combination of sofosbuvir and daclatasvir (with and without ribavirin) was also published in the New England Journal of Medicine.

Study Drugs:
Daclatasvir (NS5A inhibitor)
Sofosbuvir (polymerase inhibitor)
Ribavirin (included study arms with and without ribavirin)

Treatment Duration:
12 – 24 weeks (some patients received 1 week lead-in with sofosbuvir followed by 23 weeks with daclatasvir/sofosbuvir)

Arms:
10 groups – 211 patients

Patients
Genotype 2 = 26 patients
Genotype 3 = 18 patients
Genotype 1 (treatment naïve) = 126 patients
Genotype 1 (treatment experienced) = 41 patients—prior treatment experienced patients who were previously treated with HCV protease inhibitors (boceprevir or telaprevir)

SVR/Cure Rates
Genotype 1 treatment naïve = 98%
Genotype 1 treatment experienced = 98%
Genotype 2 treatment naïve = 92%
Genotype 3 treatment naïve = 89%

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The usual negative predictors of treatment response (genotype 1a, and 3, non-CC IL28B genotype, race) did not affect the cure rates. The cure rates were also similar between the groups that did and did not receive ribavirin. Both drugs are dosed once-daily.

Comments:
This study has been the focus of a lot of noise in 2013. While the study has a relatively small patient population the cure rates are very impressive. Below I have listed the recently announced Phase 3 studies of daclatasvir and sofosbuvir (with and without ribavirin) that BMS is sponsoring.

ALLY 1: daclatasvir and sofosbuvir with and without ribavirin for 12 weeks. The study has 4 arms that will include genotypes 1 through 6 to test the drugs in people with cirrhosis who may need a liver transplant.

ALLY 2: daclatasvir and sofosbuvir for 12 weeks to treat HCV in people who are coinfected with HIV—treatment naïve and treatment experienced. The trial will include genotypes 1 through 6.

ALLY 3: daclatasvir and sofosbuvir for 12 weeks to treat HCV genotype 3. The study will include treatment-naïve and treatment-experienced patients.

BMS & Vertex
The first data from a Phase 2a study of the combination of Vertex’s VX-135 (200 mg) plus daclatasvir for 12 weeks to treat HCV treatment-naïve patients were released. Eighty-three percent (83%—10 of 12 patients) achieved an SVR4.

The arm containing VX-135 (100 mg) plus daclatasvir produced SVR4 results of 73% (8 of 11 patients). Janssen & Idenix

The preliminary data (SVR4) from a small study of 150 mg simeprevir, 50 mg samatasvir (IDX719) and ribavirin were released. In this part of the study, HCV genotypes 1b and 4 (treatment-naïve, non-cirrhotic patients) were treated with the triple combination for 12 weeks. Eighty-five percent (85%—17 of 20 patients) achieved SVR4. Both drugs are dosed once-daily.

The combination was well-tolerated. The other arms contained the triple therapy but the dose of samatasvir was either 50, 100 or 150 mg—those results have not yet been released. Simeprevir and samatasvir are dosed once daily.

One-Shot Cure?
Probably the most fascinating news item that I have seen in quite a while was a recent news release about a new therapeutic technology that hopes to cure hepatitis C (and other diseases) with one shot! The technology is based on gene-silencing. The drug is named TT-034 and it is infused once. The first in-human trial of TT-034 has been cleared by the Food and Drug Administration (FDA) for human studies.

Here’s how it is supposed to work: The medicine is infused into the body — it will travel through the bloodstream to the liver where it will enter any hepatitis C virus. Once inside the virus TT-034 releases molecules that interfere with and stop the hepatitis C virus from replicating. Not only that, but the medicine will continue to replicate in the liver so that it can prevent any further HCV from replicating. Now, wouldn’t that be something!

The hope is that this type of therapy could be the key to curing many diseases including hepatitis B, HIV and many other potentially life-threatening diseases.

European Medicines Agency
On January 17, 2014 Gilead announced that Sovaldi combination therapy had been approved by the European Medicines Agency (EMA) to treat HCV genotype 1 through 6. The EMA also approved all-oral Sovaldi for HCV patients who can not take interferon and for those awaiting liver transplantation (to prevent HCV recurrence).

BMS recently submitted their application to the EMA for daclatasvir to treat HCV genotypes 1, 2, 3, and 4 in Europe. BMS commented that they expect the approval will enable daclatasvir to be prescribed with other HCV medications….which drug? Hint – Sovaldi (sofosbuvir).

Research Halted
Boehringer Ingelheim (BI) announced on January 17, 2013 that it had halted the clinical development of deleobuvir-containing therapies. The company commented that the combination of deleobuvir (with faldaprevir, ribavirin) was halted because the combina-
Study associates pro-inflammatory molecules with early death

A study led by researchers at Boston University School of Medicine (BUSM) provides new insight into the impact that pro-inflammatory molecules have on early death in HIV patients who abuse alcohol. The findings, published online in the journal AIDS, pinpoint the inflammatory markers most associated with early death and may help explain why some patients die earlier than others even when all of these patients are on antiretroviral therapy.

Daniel Fuster, MD, PhD, a researcher at the Clinical Addiction Research and Education (CARE) unit at BUSM, is the study’s lead author. Unique in its investigation of inflammatory markers in HIV and alcohol abuse, the study is the product of collaboration between Boston University School of Public Health, Boston Medical Center and the University of Pittsburgh Graduate School of Public Health.

Although breakthroughs have been accomplished in HIV antiretroviral therapy, some patients fare better than others. Factors influencing these differences have been identified, including co-infection with hepatitis viruses (especially hepatitis C), substance abuse (alcohol, as well as other drugs), noncompliance with antiviral drugs, CD4+ cell count and HIV viral load.

Additionally, researchers have previously identified pro-inflammatory molecules called cytokines that have been associated with elevated HIV viral loads and more advanced HIV disease. Independently, alcohol abuse and chronic hepatitis C infection have also been associated with higher levels of inflammation in the bodies of HIV infected persons. However, it was previously unknown if the elevated inflammatory state in these patients was due to their HIV or other independent risk factors.

Investigators recruited 400 HIV positive subjects who were known to abuse alcohol chronically. Half of these subjects also had chronic hepatitis C. They were followed for a three- to five-year period during which clinical information and laboratory samples were collected. Levels of seven well-known pro-inflammatory cytokine molecules were measured at baseline. From the beginning of the study in 2001 until data gathering was concluded in 2009, all patients were tracked in a national database to verify their survival status.

Based on this analysis, the researchers found that at the end of the study period, 85 out of the original 400 patients had died. Although these patients represent a population already at high risk of mortality from many problems (smoking, drug abuse, homelessness, etc.), most deaths in the study period were a result of either HIV or hepatitis C. Adjusting for known risk factors, such as age, smoking and hepatitis status, the researchers found that an increased burden of inflammation was strongly associated with increased mortality in alcohol-abusing HIV patients.

This association was found, regardless of whether or not patients were taking their antiretroviral drugs. One inflammatory molecule in particular, known as interleukin-6 (IL-6) was found to have the strongest association with mortality among patients in the study.

"Current antiretroviral drug regimens may be able to improve mortality in most patients, but are unable to decrease the potentially dangerous burden of a chronic inflammatory state in the body," said Fuster. "Additional research should explore how to better manage chronic inflammation in these patients."

This research was supported by the National Institute on Alcohol Abuse and Alcoholism (grant award numbers R01-AA13216 and K24-AA015674); the National Institute on Drug Abuse (grant award number R25DA13582), and the Spanish Ministries of Education (grant award number EDU/3495/2010), Science and Innovation (grant award numbers RD06/001/0021 and RD06/006/1014), and Health (grant award number EC11-042).

Press release from Boston University Medical Center

Save the Date

2nd Annual Hemophilia Walk
Saturday, October 25, 2014
Lincoln Memorial and Reflecting Pool

For more information, go to www.dchemophiliawalk.com
Vertex announces sustained viral response rate data from study

Vertex Pharmaceuticals Inc. recently announced the first data from the initial cohorts of an open-label Phase 2a study of VX-135, Vertex's nucleotide analogue hepatitis C virus (HCV) polymerase inhibitor, in combination with daclatasvir, Bristol-Myers Squibb's NS5A replication complex inhibitor. In an intent-to-treat analysis, the sustained viral response rate four weeks after the completion of treatment (SVR4) was 83 percent (10 of 12) in treatment-naive genotype 1 patients who received 200 mg of VX-135 in combination with daclatasvir. In this arm, one patient discontinued treatment after the first dose due to a serious adverse event of vomiting/nausea. The 11 other patients in this arm completed 12 weeks of treatment, and 91 percent (10 of 11) achieved SVR4. In the study, the majority of adverse events were mild.

The data is from the first two cohorts of an open-label Phase 2a study of VX-135 in combination with daclatasvir. The initial two cohorts of the study evaluated 100 mg and 200 mg once-daily doses of VX-135 in combination with daclatasvir once daily (60 mg) for 12 weeks of total treatment. Twenty-three people with chronic genotype 1 hepatitis C who were new to treatment (treatment-naive) and did not have liver cirrhosis were enrolled in these cohorts. More than 75 percent of all patients enrolled had genotype 1a HCV.

The majority of adverse events observed in the study were mild. The most common adverse events observed in greater than 10 percent of patients across the study were fatigue, headache and nausea. Safety and efficacy data for the two arms of the study are provided below:

200 mg of VX-135 in combination with daclatasvir (60 mg): In an intent-to-treat analysis, 58 percent (7 of 12) of patients had undetectable HCV RNA after 4 weeks of treatment and 83 percent (10 of 12) of patients had undetectable HCV RNA four weeks after the completion of treatment (SVR4). One patient in this arm experienced viral breakthrough while receiving the combination regimen and one patient relapsed during the follow-up period. 5

Vertex expects to submit these data for presentation at a medical meeting in 2014.

VX-135 is a uridine nucleotide analogue pro-drug designed to inhibit the replication of the hepatitis C virus by acting on the NS5B polymerase. Vertex gained worldwide rights to ALS-2200, known as VX-135 in Phase 2 studies, through an exclusive licensing agreement signed with Alios BioPharma, Inc. in June 2011.

Press release from Vertex Pharmaceuticals Inc.

Continued from page 11

ation showed a higher rate of premature discontinuation of treatment which suggested that the effectiveness is not comparable to other interferon-free therapies.

Important: BI is currently conducting STARTVerso trials (faldaprevir, pegylated interferon plus ribavirin) that are expected to be completed soon and the trial results will be submitted to the Food and Drug Administration (FDA) for marketing approval.

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Men’s Support Group

2014 Dinners will take place March 3, April 8, May 5, June 10, July 7, August 4, September 8, October 6, November 3 and December 1

All meetings will start at 6:30 p.m.

Meeting location will be determined on a month-to-month basis so check your email or www.HACACares.org

No social worker will be in attendance
RSVP to Brenda, 703-352-7641 or admin@hacacares.org
Continued from page 8

One study looked at responses to the varicella vaccine, showing that less than 50% of children still had detectable antibodies one year after immunization. Response to yellow fever vaccine was only examined in retrospective studies, their results showing that antibody levels fell more rapidly in people with HIV compared to HIV-negative individuals, with only 17 to 23% still having protective antibody levels ten years post-vaccination. A single study examined the long-term response to vaccination against Japanese encephalitis among children taking HIV therapy. Only a handful of initial responders had lost protective immunity after three years, suggesting the long-term effectiveness of the vaccination in this population.

“Duration of seroprotection...is shorter in HIV-infected patients than in otherwise healthy persons for most licensed vaccines,” comment the authors.

They believe their results have several implications:

**Hepatitis B:** Antibodies should be measured yearly in adults and every two to five years in children. Closer monitoring could be considered for people whose initial response to the vaccine is weak.

**Hepatitis A:** Individuals with an increased risk of this infection (men who have sex with men, individuals with chronic liver disease, travelers) should have antibody responses checked every five years.

**Tetanus:** A booster every ten years should be administered.

**Measles:** The initial should ideally be administered after children have started HIV therapy. If viral load is undetectable, two doses are recommended. Children who are vaccinated before they start antiretrovirals, or who have a detectable viral load, should receive a third dose two to five years after initial vaccination.

**Yellow fever:** Immunity wanes more rapidly in people with HIV. Antibody levels should be assessed in people at risk of this infection and revaccination is recommended for people who lack protective immunity.

**Streptococcus pneumoniae:** Data are too preliminary to inform optimal timing of booster injections for adults.

The investigators were concerned that the median number of participants per study was only 40. They comment: “Data on immunogenicity of vaccines in the immunocompromised host are scarce and the small samples in each category give little power for comparisons between age classes or vaccine schemes.”

The authors suggest that the clinical implications of their findings should be explored in larger prospective studies. They also believe their results have implications for future vaccine research: “The evaluation of new vaccines that specifically target persons with impaired immunity...should confront clinical effectiveness with precise evaluation of both humoral and cellular responses, in an attempt to establish reliable correlates of protection in these populations.”

**Reference**

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For people with HCV genotype 4 – which has not been as extensively studied – the panel chose sofosbuvir plus weight-based ribavirin and pegylated interferon for 12 weeks, or sofosbuvir plus ribavirin alone for 24 weeks for patients who cannot use interferon. An alternative is simeprevir for 12 weeks plus pegylated interferon/ribavirin for 24-48 weeks.

For people with HCV genotype 5 or 6 – about which even less is known – the recommendation is sofosbuvir plus weight-based ribavirin for 12 weeks, with an alternative of pegylated interferon/ribavirin for 48 weeks.

**Treatment recommendations for previous non-responders**
Recommendations for re-treating people who did not respond to prior interferon-based therapy include:

For re-treatment of people with HCV genotype 1, the panel recommends sofosbuvir plus simeprevir with or without weight-based ribavirin, for 12 weeks. Alternative regimens combine sofosbuvir or simeprevir with pegylated interferon and ribavirin for 24 to 48 weeks.
The panel recommends sofosbuvir plus weight-based ribavirin for 12 or 24 weeks for re-treatment of prior non-responders with genotype 2 or 3, respectively. Again, alternative regimens include pegylated interferon and ribavirin.

The recommended second-line treatment for HCV genotypes 4, 5, and 6 is sofosbuvir plus weight-based ribavirin and pegylated interferon for 12 weeks, with an alternative of 24 weeks of sofosbuvir plus ribavirin alone for those who cannot take interferon.

**Recommendations for people with HIV/HCV co-infection**

Recommendations for people with HIV/HCV co-infection include:

For co-infection with HCV genotype 1 – either treatment-naive or prior relapsers – the panel recommends sofosbuvir, weight-based ribavirin plus pegylated interferon for 12 weeks.

For people with HIV/HCV co-infection who are unwilling or unable to take interferon, alternatives include sofosbuvir plus ribavirin alone for 24 weeks. Another option is sofosbuvir plus simeprevir, with or without ribavirin, but simeprevir can interact with several HIV drugs.

The panel's recommendations for people with HIV/HCV co-infection with genotypes 2 or 3 are the same as for those with HCV alone, that is, sofosbuvir plus ribavirin for 12 or 24 weeks, respectively.

For almost all patients, the panel specifically recommends against the old standard of care, pegylated interferon plus ribavirin alone. They also advise against regimens containing the first-generation HCV protease inhibitors boceprevir (Virectelis) or telaprevir (Incivo), which can improve cure rates compared to interferon/ribavirin alone but come with added side-effects and potential for drug interactions.

**Future plans**

The HCVguidelines.org website does not yet include recommendations about one of the most vexing questions facing people with hepatitis C and their providers: who should start treatment and when? Given the difficulty and suboptimal cure rates of interferon-based therapy, traditionally treatment has only been recommended for people with hepatitis C who have progressive liver disease, as determined by liver biopsy or non-invasive methods such as FibroScan.

With the advent of more effective and better-tolerated direct-acting antivirals, many experts believe that more people are now eligible for treatment. But given the rapid advances in the field, it is often unclear whether to treat someone now with available drugs or to wait for something better.

Many patients have been "warehoused" for the past few years awaiting interferon-free therapy. The first such regimens are now available for people who are unable or unwilling to use interferon, but new and potentially better options are in the pipeline, including Gilead Science's sofosbuvir/ledipasvir coformulation, Bristol-Myers Squibb's daclatasvir (a candidate for combination with sofosbuvir), and AbbVie's '3D' combination. The panel is currently working on recommendations about which patients to treat and when, as well as guidelines for managing acute hepatitis C infection and monitoring during and after treatment.

One issue the panel did not address is the cost of treatment. "The guidelines are not designed to address cost, and we haven't really taken that into full consideration," said Jensen. "Our recommendations are based on what we think is best for a patient who needs treatment at this time." In countries with single-payer health systems like the United Kingdom, however, cost is one of the factors taken into account.

European advocates have expressed concern that patients may be required to start with less effective and poorly tolerated interferon-based regimens due to their lower cost.

"We're all really excited that for the first time we have curative therapies for hepatitis C which are much more effective than what we had before and much easier to tolerate," said Henry Masur of the US National Institutes of Health. "This is really a revolution, and it's very important that clinicians have access to guidance on how to use these drugs as new trials are quickly done and as new information becomes available."

References


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Hemophilia Association of the Capital Area
2014 Calendar of Events

March
3  Men’s Dinner, Location TBD – 6:30 pm
11 Infusion Class, Children’s National Medical Center HTC – 6:30 pm
13 KUWYH Dinner, Joint Health, Rock Bottom Restaurant, Arlington, VA – 6:30 pm. Program given in English. Spanish interpreter will be present
27 GMU Health and Fitness Expo
27-28 Region 3 HTC Annual Meeting, Alexandria, VA
27-29 HFA Symposium

April
5-6 Adult Retreat – Washington, DC (in conjunction with HFM and VHF)
7 Board Meeting, 7:00 pm – Location TBD
8 Men’s Dinner, Location TBD – 6:30 pm
12-13 Teen Retreat – Charlottesville, VA (in conjunction with HFM and VHF)
17 World Hemophilia Day
17 KUWYH Lunch, Transition Children to Independence, Washington, DC, Location/Time TBD
29-May 1 NHF Regional Leadership Seminar

May
1 KUWYH Dinner, Sports and Exercise, Maryland, Location/Time
5 Men’s Dinner, Location TBD – 6:30 pm
15 Deadline for Price Scholarship
17 Educational Seminar (w/out Annual Business Meeting) – Four Points Sheraton, Downtown, Washington, DC, 1 pm

June
TBD Deadline for Getting in the Game Applications
1 Pre-Camp Activity
2 19th Annual Golf Tournament – Old Hickory Golf Club
10 Men’s Dinner, Location TBD – 6:30 pm
13-19 Summer Camp at Hole in the Wall Gang Camp, Ashford, CT
16 Board Meeting, 7:00 pm – Location TBD
25 KUWYH Dinner, Persistent Pain, Virginia, Location/Time TBD

July
7 Men’s Dinner, Location TBD – 6:30 pm

All events are free to HACA members. To join or register for an event, contact us at 703-352-7641 or admin@hacacares.org