When liver disease hijacks the brain

By Lucinda K. Porter, RN
HCV Advocate

In 2010, Karen Hoyt noticed that her feet and abdomen were swollen. She had ridden her bike in 100-degree heat, and blamed these symptoms on the temperature. A friend insisted that Karen see a doctor. Upon examining her, the nurse practitioner sent Karen to the hospital. She would learn that she had cirrhosis caused by hepatitis C. Karen was in end-stage liver disease, and she was dying.

Karen didn’t believe any of it, and tried to check herself out of the hospital against medical advice. Karen is bright, but at that moment, her intelligence was useless; she was cognitively impaired and didn’t know it. Karen didn’t have the ability to comprehend her diagnosis because she had hepatic encephalopathy (HE), a brain disorder that develops when the liver is unable to remove toxins in the body. One toxin is ammonia, produced by the body when proteins are digested. If ammonia builds up in the bloodstream, it can damage the nervous system.

HE is a horrific complication of liver disease. Not only does it affect patients, it can be devastating for those caring for a loved one with HE. It is like watching your loved one become someone else, someone that you don’t know. This pain is captured in the movie, “He’s Back: Wrestling the Monster” at www.hesback.com.

About seven out of ten people with cirrhosis develop HE, although many cases are mild. Early HE diagnosis is critical, and may help reduce HE progression. People with chronic liver disease are at greater risk of developing a more chronic form of the disorder where symptoms get worse or continue to come back, known as “HE recurrence.”

HE may begin with subtle changes in behavior, mental state, and thinking ability. HE is graded on a scale of zero to four.

Grade 0 is hard to detect. In this stage, there are memory changes, impaired concentration, slight decrease in intellectual function, or loss of coordination.

Grade 1 includes a short attention span, sleep problems and mood changes such as depression or irritability.

Grade 2 is when forgetfulness is noticeable. Energy levels are low; speech may be slurred; doing simple mental tasks such as math or spelling may be difficult. Patients may have tremors, deterioration of handwriting and decreased small motor coordination. They may have shaking of the hands or “flapping” when the arms are held up front of the body with hands lifted like someone making a motion telling someone to “stop.”

Grade 3 is severe HE. Patients in this stage don’t know where they are, what the day is, or who the president is. They are confused and sleepy. Patients feel anxious and their behavior may be strange.

Grade 4: The last stage of HE is when the patient is comatose.

Don’t try to diagnose yourself. Most of us have days when we feel like we have
Co-infection can increase risk of osteoporosis, fractures

By Michael Carter

Co-infection with HIV and hepatitis C virus (HCV) is associated with increased risks of low bone mineral density (BMD) and fracture, investigators report in the online edition of AIDS. Results of 15 separate studies showed that people living with co-infection have a higher risk of osteoporosis than people with HIV-mono-infection, and that fracture incidence was higher among people with HIV-mono-infection and healthy controls. The authors believe their findings underline the importance of monitoring bone mineral density in all older people with co-infection.

“Our review found that HIV/HCV-co-infected individuals have a modestly increased risk of osteoporosis and fractures compared with HIV-mono-infected controls, and substantially higher risk than uninfected controls,” comment the researchers.

Chronic hepatitis C is associated with an increased risk of osteoporosis. HIV infection and antiretroviral therapy have also been associated with an increased risk of low bone mineral density and fractures. Large numbers of people are living with HIV and HCV co-infection. A team of US investigators therefore wanted to see if people with co-infection had an increased risk of osteoporosis and fractures compared to people with HIV-mono-infection and people with neither infection (healthy controls).

They therefore conducted a systematic review and meta-analysis of studies published or presented at major conferences before 2013 that compared these outcomes between people with co-infection, people with HIV-mono-infection and healthy controls.

A total of 15 studies were eligible for inclusion: nine provided data on osteoporosis and six reported on fracture risk. The studies were conducted in the US, Europe and Taiwan. Four studies included women only and one included only men. Sample size varied from 22 post-menopausal women to approximately 37,000 people receiving care in the US.

Prevalence of osteoporosis in people with co-infection ranged from 5-45%. The pooled estimate was 22%. Co-infection was associated with a significantly increased risk of low bone mineral density compared to HIV mono-infection (OR = 1.63; 95% CI, 1.27-2.11). The risk was little altered after the authors excluded the study with post-menopausal women (overall prevalence= 20%; OR = 1.61; 95% CI, 1.23-2.12).

Co-infection was also associated with an increased fracture incidence. The risk was significantly increased when people with co-infection and people with HIV-mono-infection were compared (IRR = 1.77; 95% CI, 1.44-2.18). People with co-infected also had a significantly higher incidence of fragility fractures compared to people with HIV-mono-infection (IRR = 1.70; 95% CI, 1.18-2.43). Moreover, fracture incidence was substantially higher among people with co-infection when compared to people in the control group (IRR = 2.95; 95% CI, 2.17-4.01).

Factors independently associated with an increased risk of osteoporosis were HIV/HCV co-infection, older age, lower BMI (body mass index), post-menopausal status and longer duration of therapy with an HIV protease inhibitor. Smoking, low physical activity and methadone use were identified as risk factors in some studies.

Risk factors for fracture included co-infection, older

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Snapshots of recent studies

By Lucinda K. Porter
HCV Advocate

**Article:** HCV Genotype 3 Is Associated with an Increased Risk of Cirrhosis and Hepatocellular Cancer in a National Sample of U.S. Veterans with HCV—Fasiha Kanwal, et al.

**Source:** Hepatology July 2014 Volume 60, Issue 1, pages 98–105

Hepatocellular carcinoma (HCC) is the most common cause of death in patients with hepatitis C virus (HCV)-induced cirrhosis. Compared to genotype 2, HCV genotype 1 is associated with a higher risk of developing HCC; genotype 1b may have a higher risk of HCC than genotype 1a. This study examined risk of cirrhosis and HCC in patients with genotype 3.

Collecting data from 2000 through 2009, Veteran Administration researchers adjusted for age, race, gender, HIV infection, alcohol use, body mass index, diabetes, and history of antiviral treatment. Of the 110,484 HCV-positive veterans, nearly 80% (88,348) had genotype 1, almost 12% (13,077) had genotype 2, 7.5% (8,337) had genotype 3, and less than 1% (1,082) had genotype 4 infection.

**The Bottom Line:** Compared to genotype 1 patients, those with HCV genotype 3 had a 31% higher risk of developing cirrhosis and an 80% increased risk for HCC. This risk was independent of age, diabetes, body mass index, or antiviral treatment.

**Editorial Comment:** This is particularly distressing because treatment for genotype 3 patients has not progressed as rapidly as treatment has for genotypes 1 and 2.

**Article:** Hepatitis C Virus Infection Increases Risk of Developing End-Stage Renal Disease Using Competing Risk Analysis—Jia-Jung Lee, et al.

**Source:** PLoS One June 27, 2014; 9(6): e100790

This prospective study conducted in Taiwan, enrolled 4,185 subjects with chronic kidney disease. The study group was 59% male, the mean age was 62 and it took place from 2002 through 2009. HCV prevalence was 7.6%, a prevalence that increased as chronic kidney disease stages increased. The prevalence of hepatitis B (HBV) was nearly identical (7.4%), but was not associated with trends in kidney disease stages.

There were 446 deaths and 1,205 patients advanced to end-stage renal disease.

**The Bottom Line:** Those with HCV, but not HBV, had higher risk of developing end-stage renal disease compared to those without HCV (52.6% vs. 38.4%).

**Editorial Comment:** The prevalence of kidney disease is increasing in the US. Patients with HCV, especially if they have cirrhosis, are at risk for chronic kidney disease. Kidney disease has vague symptoms in its early stages, symptoms much like HCV.

**Article:** Combination of Blood Tests for Significant Fibrosis and Cirrhosis Improves the Assessment Of Liver-Prognosis In Chronic Hepatitis C—J. Boursier, et al.

**Source:** Alimentary Pharmacology & Therapeutics July 2014 Volume 40, Issue 2, pages 178–188

Noninvasive tests that assess liver fibrosis are making their way into mainstream medical practice. How do they stack up? This study compared the accuracy of six blood fibrosis tests and liver biopsy to see how well they predicted liver-related events in chronic HCV. Additionally, the researchers evaluated whether a combination of blood fibrosis tests would improve the liver-prognosis assessment.

This 9.5-year French study enrolled 373 HCV patients; none had decompensated cirrhosis, other liver disease, or high alcohol use. In addition to undergoing a liver biopsy, patients had fibrosis blood tests (APRI, FIB4, Fibrotest, Hepascore, FibroMeter), and the CirrhoMeter blood test if they had cirrhosis.

**The Bottom Line:** The blood tests measuring fibrosis were as good as or better than liver biopsy when predicting liver disease prognosis. Combining FibroMeter and CirrhoMeter had the best results.

**Editorial Comment:** This month there were at least four published papers about non-invasive liver fibrosis tests (blood and Fibroscan). The evidence suggests that when used correctly, especially when combined with more than one test, noninvasive tests yield results that are comparable to liver biopsy. Noninvasive tests have clear advantages—for patients and their
Researchers discover how hepatitis C virus persists for years

Hepatitis C virus (HCV) lingers in the human body for years, slowly damaging the liver and leading to liver diseases such as hepatitis, cirrhosis and liver cancer, which is often fatal. Research conducted at the University of North Carolina at Chapel Hill has discovered a mechanism that facilitates the virus achieving this life-long persistence. Chronic HCV infection is the leading cause of liver cancer in the United States.

"Liver cancer is one of the most important causes of cancer mortality worldwide. It's also increasing in rapidly incidence within the United States, due largely to the spread of HCV among Americans in the 60s and 70s," said Stanley M. Lemon, MD, Professor of Medicine at the UNC School of Medicine and a member of the UNC Lineberger Comprehensive Cancer Center.

In a paper published online by Nature Medicine recently, a team led by Dr. Lemon and colleague Daisuke Yamane, DVM, PhD, found that HCV has a sensor function that allows it to be regulated by the oxidative damage to cell membranes that occurs as a byproduct of its replication and the body's response to it. This slows down virus growth when oxidative membrane damage becomes too high, but allows it to resume when the membrane damage is reduced. By auto-regulating its replication in this way, the virus maintains a low profile, helping it escape detection by the immune system.

"You might consider it like a thermostat," said Dr. Lemon, "one that regulates the growth of the virus like your thermostat regulates the temperature of your house."

The reason why HCV is able to achieve life-long persistence in most individuals who become infected has never been well explained. "What we have done in this paper is to show that the replication of a wide variety of hepatitis C virus strains is uniquely regulated by oxidative stress in the liver. This is an absolutely unique attribute of hepatitis virus that sets it apart from similar viruses," said Dr. Lemon.

Oxidative stress occurs when tissue injury generates free radicals, normal biological byproducts that can cause cellular damage when present in excess amounts. This promotes inflammation and progressive scarring within the liver, leading to further disease like cirrhosis and cancer. Lipid peroxidation occurs on membranes when there are excess free radicals, and that regulates the growth of hepatitis C vir-
Dolutegravir demonstrates good efficacy despite resistance

By Liz Highleyman
aidsmap

Antiretroviral regimens containing the recently approved HIV integrase inhibitor dolutegravir (Tivicay) demonstrated high rates of viral suppression even in treatment-experienced people who had virus with resistance to NRTIs. Among people starting treatment for the first time, no resistance was detected through 96 weeks, according to study findings presented at the 20th International AIDS Conference recently in Melbourne.

Modern antiretroviral treatment is highly effective and generally well-tolerated, but novel agents – especially in newer drug classes – can offer valuable options for people such as those with resistance to existing drugs and those who have difficulty tolerating specific side-effects.

Jim Demarest of ViiV Healthcare and colleagues performed a post-hoc combined analysis looking at virological outcomes among participants enrolled in phase 3 trials of dolutegravir-based regimens.

The SPRING-2, SINGLE and FLAMINGO studies looked at people who had not taken treatment before (treatment naive), while SAILING enrolled treatment-experienced people with resistance to at least two drug classes who had not yet used integrase inhibitors.

All the treatment-naive studies performed resistance testing at baseline and excluded people who were resistant to study drugs. In SAILING, resistance to two or more drug classes was an inclusion criterion, and baseline resistance testing was used to select an optimized background regimen. All studies called for additional resistance testing if participants experienced virological failure (either failure to achieve viral suppression or viral rebound while on treatment).

The first three trials found that dolutegravir plus two nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs) worked as well as or better than the older integrase inhibitor raltegravir (Isentress), the non-nucleoside reverse transcriptase inhibitor efavirenz (Sustiva) and the boosted protease inhibitor darunavir (Prezista), respectively.

In the treatment-naive trials, no study participants developed emergent resistance to either dolutegravir or the background drugs through 48 or 96 weeks of follow-up.

SAILING showed that dolutegravir bested raltegravir in treatment-experienced people. In this study, 71% of participants assigned to receive dolutegravir plus a background regimen achieved virological suppression (50 copies/ml) at 48 weeks, compared with 64% of those assigned to take raltegravir.

Among SAILING participants who experienced protocol-defined virological failure, there was significantly less emergent drug resistance in the dolutegravir arm than in the raltegravir arm. Integrase inhibitor resistance was detected in 1% and 5%, respectively, while resistance to background drugs was seen in 1% and 3%, respectively.

Response rates were similar for SAILING participants who either had never used boosted darunavir (67% in the dolutegravir arm vs 60% in the raltegravir arm) or had done so and had no primary protease inhibitor resistance mutations (69% vs 70%, respectively).

Among people taking darunavir who had primary protease mutations, however, dolutegravir performed significantly better (86% vs 67%). Among people who included any protease inhibitor in their regimen, half as many experienced treatment failure in the dolutegravir arm compared with the raltegravir arm (6% vs 12%).

Among the 32 SAILING participants who received dolutegravir with only two NRTIs (nucleoside reverse transcriptase inhibitors), none experienced protocol-defined virological failure, even if both of their background NRTIs were not fully active due to resistance. In contrast, 22% of participants assigned to take raltegravir plus two NRTIs did experience virological failure.

SAILING included 25 participants whose background regimen included lamivudine (Epivir) or emtricitabine (Emtriva, also in several co-formulations) and who had the M184V viral mutation, which confers resistance to these drugs. None of the participants in the dolutegravir arm experienced virological failure – even if their second NRTI also appeared to be compromised by thymidine-analog resistance mutations – compared with one-third of those taking raltegravir.

"Dolutegravir-based regimens showed substantial and durable antiviral activity" in integrase inhibitor-naive patients, the researchers concluded. "The resistance profile for dolutegravir will be defined further"
Sofosbuvir + ribavirin cures hepatitis C for more than 80% of people with HIV and HCV co-infection

By Liz Highleyman

An interferon-free regimen of sofosbuvir (Sovaldi) plus ribavirin for 24 weeks led to sustained hepatitis C virological response in 84 to 89% of HIV-positive people with chronic hepatitis C genotypes 1, 2, 3 or 4, according to results from the phase 3 PHOTON-2 study presented recently at the 20th International AIDS Conference (AIDS 2014) in Melbourne, Australia. Cure rates were lower, however, for genotype 1a patients with liver cirrhosis.

People with HIV and hepatitis C virus (HCV) co-infection experience more rapid liver disease progression than people with hepatitis C alone and do not respond as well to interferon-based therapy. Direct-acting antivirals that target different steps of the HCV lifecycle offer the prospect of shorter treatment, fewer side-effects and higher cure rates for people with HIV and HCV co-infection as well as for people with HCV mono-infection.

Jean-Michel Molina from University of Paris Diderot presented data from the phase 3 PHOTON-2 trial, which included 274 people with co-infection in Europe and Australia. Most participants (81%) were men and the mean age was 47 years. The most common HCV genotypes were 1 (41%) and 3 (39%), followed by 4 (11%) and 2 (9%). Most people with genotype 1 had harder-to-treat subtype 1a.

Most participants (80%) had not been treated previously for hepatitis C. Overall, 20% had cirrhosis (13% of previously untreated, rising to 45% of treatment-experienced). Nearly half had the favorable IL28B CC gene variant.

Almost all study participants were on stable suppressive antiretroviral therapy for HIV and the mean CD4 cell count was nearly 600 cells/mm3. The most commonly used antiretrovirals were efavirenz (Sustiva, also in the Atripla co-formulation) at 25%, raltegravir (Isentress) at 23%, ritonavir-boosted darunavir (Prezista) at 21% and boosted atazanavir (Reyataz) at 17%. All used an NRTI combination of tenofovir and emtricitabine (the drugs in Truvada). Early studies found no clinically relevant drug-drug interactions between sofosbuvir and these antiretrovirals, and sofosbuvir is already approved in Europe and the U.S. for coinfected patients.

All participants received Gilead Sciences' HCV polymerase inhibitor sofosbuvir (400mg once daily) plus ribavirin (weight-based 1000-1200 mg/day). A small number of previously untreated participants with HCV genotype 2 (19 people) were treated for 12 weeks, while all treatment-experienced people and everyone with harder-to-treat genotype 1 or 4 were treated for 24 weeks.

Sustained virological response rates at 12 weeks after completing treatment (SVR12) were 85% for people with genotype 1, 88% for those with genotype 2, 89% for genotype 3 and 84% for genotype 4. Relapse rates were 13%, 8%, 9% and 16%, respectively. One person with genotype 3 experienced viral breakthrough during treatment.

Among the participants with HCV genotype 1, response rates were higher for people who did not have liver cirrhosis (88% overall, 87% for subtype 1a and 100% for subtype 1b) compared to those with cirrhosis (65%, 62% and 75%, respectively). Presence of cirrhosis was the only significant risk factor for poorer response in a multivariate analysis.

For people with other genotypes, cirrhosis had less impact, although the effect was a bit larger for treatment-experienced compared to treatment-naive participants with genotypes 2 or 3.

Response rates did not differ significantly between HCV subtypes 1a and 1b, but the number with the latter type was small. Likewise, there were too few people not taking antiretroviral therapy to permit a separate analysis.

Looking at HIV-related outcomes, four people experienced intermittent low-level HIV viral load breakthrough, though none required modification of their antiretroviral regimen. Absolute CD4 cell counts increased temporarily during hepatitis C treatment, but CD4 percentages remained stable.

Sofosbuvir plus ribavirin was generally safe and well-
tolerated. Six people experienced serious adverse events and three stopped treatment early due to adverse events.

The most frequent side-effects among people treated for 24 weeks were fatigue (20%), insomnia (17%), headache (16%), nausea (15%) and diarrhoea (11%).

One in five developed grade 3-4 laboratory abnormalities, most commonly elevated bilirubin among people taking atazanavir. While 10% developed low haemoglobin levels – a known side-effect of ribavirin – only one person had severe anaemia.

"Sofosbuvir + ribavirin resulted in high SVR12 rates in HIV patients coinfected with HCV genotype 1, 2, 3 or 4," the PHOTON-2 researchers concluded. "Sofosbuvir was well tolerated, with a low rate of treatment discontinuations due to adverse events."

Results from the PHOTON-1 study were published this week in the Journal of the American Medical Association. This study tested the same regimens in people with HIV and HCV co-infection, but it was conducted in the US and had a different genotype distribution that allowed for other subgroups comparisons. Just over half had HCV genotype 1 (79% with 1a), while the remainder were roughly evenly split between genotype 2 and 3.

As previously reported at this year's Conference on Retroviruses and Opportunistic Infections (CROI), the overall SVR12 rate for people with genotype 1 was 76%. Among those with genotype 2, response rates were similar for treatment-naive people treated for 12 weeks and treatment-experienced people treated for 24 weeks (88% and 92%, respectively). Among those with genotype 3, however, previously untreated patients taking the shorter duration had a lower response rate (67% vs 94%).

The response rates in the PHOTON trials are not particularly impressive compared to the 90-100% SVR12 rates seen in several other recent interferon-free studies. Sofosbuvir works better when combined with other direct-acting antivirals such as the NSSA inhibitors ledipasvir or daclatasvir (Daklinza), which are expected to be approved soon. A disadvantage of ledipasvir is that it does not have potent activity against HCV genotypes 2 or 3.

Molina suggested that sofosbuvir plus ribavirin may be a good option for people who have HIV and HCV co-infection, with genotype 2 or 3 HCV, who do not have liver cirrhosis. "Ribavirin is generic," he noted, and this combination "might be attractive in places where you don't have access to all the new drugs."

At a separate session discussing the hepatitis C treatment revolution and how to make recent advances available worldwide, Andrew Hill of Liverpool University and others noted that pangenotypic drugs – those that work against multiple HCV genotypes – could potentially mean we will not need genotype testing, which would lower the overall cost of care.

References
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by use in clinical practice and additional clinical trials." Regulators in the US are currently evaluating a fixed-dose co-formulation containing dolutegravir plus abacavir/lamivudine (the drugs in Kivexa or Epzicom). If this is approved, it will be the first one-pill, once-daily regimen that does not contain tenofovir DF, which some people wish to avoid due to its risk of kidney and bone toxicity. The combination, due to be marketed as Triumeq in Europe, has already received scientific approval by the European Medicines Agency and is expected to receive marketing approval within the next few months.

Reference
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New drugs in the pipeline, and tips to manage side effects

By Alan Franciscus
HCV Advocate

This column is going to take a different path: I will report on the drugs in development and the most common side effects reported as well as offer some self-help tips to help manage the less severe ones.

BMS Approval in Japan
On July 7, 2014 the Japanese Ministry of Health, Labor and Welfare (MHLW) approved Daklinza (daclatasvir—HCV NS5A inhibitor) and Sunvepra (asunaprevir—HCV protease inhibitor) for the treatment of chronic hepatitis C genotype 1 for a treatment period of 24 weeks. According to a Bristol-Myers Squibb (BMS) company press release, of the HCV genotype 1b patients treated 84.7% were cured. The number of people in Japan with hepatitis C is estimated at 1.2 million, and approximately 70% have HCV genotype 1b. Among patients 65 years of age or older who were either interferon-ineligible or intolerant, 91.9% were cured. In the patients with compensated cirrhosis the cure rates were 90.9%. The treatment discontinuation rate due to adverse events was 5%. The rate of serious adverse events (SAEs) reported was 5.9%, and the press release stated that “few SAEs were experienced by more than one patient.”

Nasopharyngitis: The most common side effect (30.2%) reported in the study was nasopharyngitis (upper respiratory system inflammation, infection, the common cold).

Self-help tips: Standard care for the common cold – bed rest, over-the-counter cold remedies, and nasal sprays including saline.

AbbVie / Gilead
The Food and Drug Administration (FDA) is expected to approve Gilead’s sofosbuvir/ledipasvir by October 10, 2014, and AbbVie’s 3D combination by December 22, 2014. The new oral combination therapies have higher cure rates, lower side effects and shorter treatment durations than some of the current drug regimes. However, all drugs have side effects and this article will focus on the most frequent side effects reported in the Phase 3 clinical trials. For this article, I am going to combine the most frequent side effects reported for both drugs in the clinical trials. It is important to know, however, that in clinical trials every symptom is reported whether or not it is related to the study drug, so you could potentially have a symptom of hepatitis C during the study period that would be listed as a side effect of the study drug. Another issue is that many times the patient population of clinical studies is made up of patients who are typically ‘the easiest to treat.’ Therefore, many health issues and side effects may not emerge until the medications are taken by many more people with the condition who may have a wide range of other health issues that may affect the tolerability, adherence and side effects of the newly approved drugs. Another issue is that the side effects listed in the Phase 3 studies are not rated by severity so some of them might be mild and others might be severe. However, the number of people who discontinued treatment due to side effects in both Gilead’s and AbbVie’s Phase 3 clinical trials was less than 1% which would indicate that the majority of side effects were mild to moderate.

Below are some of the most frequent side effects that occurred and some common tips for managing them. If you do experience these side effects or others that become more than annoying they should be reported to a medical provider before they become worse.

Fatigue: The most common symptom of hepatitis C is fatigue and it is also the most common side effect of the new medications. Fatigue can range from feeling mildly tired to feeling totally exhausted. It can interfere with almost every area of life including work, family and social interactions and it can also lead to anxiety, depression and isolation.

Self-help tips: Be sure to get enough sleep and daily exercise. Take short naps (no more than 10 to 20 minutes and do not nap too close to bedtime). Make sure the fatigue is not caused by something else—talk with your medical provider. Ask for help! Get organized! Try deep breathing—watch your breathing. Many people who are tired and stressed hold their breath which can lead to more stress and fatigue.

Headache: The second most common side effect of the new medications is headache.

Self-help tips: Limit caffeine in coffee, sodas, teas, chocolate, and tobacco. Avoid loud noises, bright lights and strong odors. Cold compresses on the head may help. Use over-the-counter pain aids. If a headache is very painful or persists over time talk to a medical provider.

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Insomnia: This is a common symptom of hepatitis C that is also a common side effect of the new all-oral therapies. Insomnia can lead to fatigue, headaches and a whole host of other symptoms.

**Self-help tips:** Stay away from caffeine, as mentioned above, especially too close to bedtime. Avoid a partner who snores or makes a lot of noise when they sleep. The room should be dark, and not too cold or hot. Don’t eat too much food before bed but don’t go to bed hungry. Establish healthy and regular sleeping habits—going to bed the same time every night, developing a routine such as reading a non-stimulating book before bedtime, trying to turn off your mind before bedtime. If you find that you can’t sleep, get up and do something boring; then go back to bed. Chronic insomnia can be effectively treated with medications.

Nausea: Feeling sick to your stomach is a common symptom of hepatitis C as well as a side effect of the all-oral therapies.

**Self-help tips:** Eat some dry crackers; avoid food and odors that act as triggers; stay away from spicy, greasy, and deep-fried foods. Eat small frequent healthy meals instead of three large meals a day. Chew food slowly; try over-the-counter medications for nausea; try peppermint, chamomile, or ginger tea to help calm the stomach; chew or suck on ginger. Acupuncture or acupressure (also wristbands) may offer relief. The BRATT diet (bananas, rice, applesauce, toast and tea) is also recommended.

Asthenia (lack of muscle strength): This can go hand in hand with fatigue and can lead to balance issues and accidents that can be dangerous.

**Self-help tip:** Be careful when getting up from a sitting position and when walking. Talk to your medical provider if this issue becomes worse.

Diarrhea: Persistent diarrhea can be much more than annoying—it can lead to and exacerbate many of the symptoms above and can affect the absorption of medications and nutrients.

**Self-help tip:** Drink plenty of clear fluids (water, weak tea or broth); eat popsicles or gelatin, eat small frequent meals, keep track of bowel movements; eat banana and potatoes (high in potassium); stay away from high-fiber foods such as whole-grain breads and cereals, spicy, fried and greasy food, alcohol, caffeinated drinks and tobacco products. Try the BRATT diet (see above).

Rash/Pruritus (itching): The rash seen in the all-oral therapies is not as severe as the rashes seen in previous HCV drug combinations and was only reported in a minority of patients.

**Self-help tips:** There are many strategies to combat dry skin and rashes including, and most importantly, drinking clear fluids; avoid soap—especially scented soaps; apply moisturizer especially after a shower; avoid hot showers and baths; oatmeal baths and lotions can soothe the itching. Over-the-counter antihistamines can relieve the itching.

Irritability: Persistent irritability can be a sign of or a precursor to depression.

**Self-help tip:** Try deep breathing, meditation and prayer. If irritability worsens talk to a professional.

Cough: A cough can simply be from a dry throat or could possibly be a symptom of a cold or lung infection.

**Self-help tip:** Drink plenty of clear fluids as listed above; suck on cough drops; If the cough is persistent or if there is a fever—see a doctor.

Janssen (Olysio) / Gilead (Sovaldi)

Janssen submitted a supplemental new drug application (sNDA) to the Food and Drug Administration (FDA) in June. On July 15, 2014, Janssen announced that the FDA designated the sNDA a Priority Review.

The most common side effects of Sovaldi are discussed above. The most common side effect of Olysio is rash and photosensitivity. Rash is discussed above. Photosensitivity is discussed below.

Photosensitivity: This basically means that your skin is allergic to the sun. This is caused by many different drugs or substances that trigger a person’s immune system to react to the sun. The symptoms can be a mild rash to itchy red bumps and welts. It can last for minutes, hours or days. If the rash becomes serious it should be evaluated by a medical provider. There is no particular diagnostic test for photosensitivity — diagnosis is usually made by observing the skin rash. However, a physician may want to get at the cause and do certain other tests. But since the cause is known to be a reaction to Olysio it is unlikely that further testing will be done.

**Self-help tip:** Treatment consists of avoiding the sun, wearing clothing to prevent exposure to the sun and the use of corticosteroid ointments to relieve the pain and itching. In severe cases UV light therapy might offer some relief. After treatment the condition will resolve.

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A look at extrahepatic manifestations

By Alan Franciscus
HCV Advocate

In a recent Patients First column (www.hcvadvocate.org), I wrote about reporting symptoms to your medical provider and making sure that any symptoms are included in your medical records. I also touched briefly on extrahepatic manifestations (EH).

In this article, I would like to discuss some of the more serious extrahepatic manifestations in greater detail for a variety of reasons — the main reason is that many medical providers are unaware of these serious conditions: Diagnosing HCV-related extrahepatic manifestations is important so they can be treated and also because successfully treating these conditions will add to the body of evidence that HCV treatment is recommended and needed. The more serious extrahepatic manifestations I will discuss are cryoglobulinemia and conditions associated with cryoglobulinemia including glomerulonephritis (kidney disease) and vasculitis, as well as a certain type of cancer called non-Hodgkin Lymphoma (NHL).

Cryoglobulinemia that is associated with hepatitis C is called mixed cryoglobulinemia. Hepatitis C accounts for more than 90% of cases of mixed cryoglobulinemia and it is the most common disorder that is related to the hepatitis C virus. It is caused by abnormal proteins in the blood called cryoglobulins that clump together when the blood is chilled and then dissolve when warmed. The proteins can be deposited in the small and medium sized blood vessels which then restricts the flow of blood and can lead to further problems. To diagnose cryoglobulinemia a blood test is given to detect the proteins called cryoglobulins. Important note: the blood sample must be kept at room temperature and handled correctly. Fortunately, while the markers are common in people with HCV the symptoms and disorders are uncommon.

The symptoms can be mild, moderate or severe.

The symptoms can include:
- Red or purple blotching skin—especially on the lower extremities of the body
- Rashes, sores, and ulcers
- Joint pain and inflammation
- Mild to severe pain
- Generalized pain
- Lymph node enlargement
- Numbness and tingling in the hands, legs and feet due to decreased blood flow and/or inflammation of the peripheral nerves (peripheral neuropathy)
- Stomach pain
- Internal bleeding and blood clot formation

Glomerulonephritis is a condition affecting the kidneys. It simply means inflammation of the kidney. It can be caused by many factors including cryoglobulinemia. But it can also be caused by hepatitis C disease progression and from circulating HCV antibodies and viral particles which can damage small blood vessels in the kidney (Membranous nephropathy).

Vasculitis (also called essential cryoglobulinemia vasculitis) is an inflammation of blood and lymphatic vessels caused by cryoglobulins. Vasculitis is sometimes referred to as the ‘hurting disease’ because it is commonly associated with pain. Vasculitis can affect almost every organ of the body.

The most common symptoms and conditions of vasculitis include:
- Purplish red spots usually found on the legs
- Joint aches and swelling as well as arthritis
- Cough, shortness of breath and lung disease
- Kidney disease, loss of protein through the urine
- Low red and/or white blood cells
- Chronic sinus congestion and infection, hearing problems, and inflammation of the nasal passages
- Damage to the vessels of the eyes
- Headaches, difficulty with coordination
- Pain and numbness in the arms and legs (neuropathy)

Diagnosis of vasculitis is similar to the diagnosis of cryoglobulinemia—a blood test to check for cryoglobulins, check for underlying autoimmune disease, skin and tissue biopsy and arteriography (pictures of blood vessels).

Treatment of Cryoglobulinemia and Associated Diseases

HCV Therapy: The treatment consists of treating the...
underlying cause—hepatitis C, but the results vary by the type of HCV medications used and the types of disorders.

In two studies that treated vasculitis with pegylated interferon, ribavirin and either boceprevir or telaprevir, complete clinical response rates were achieved in 57% and 79% of the patients treated.

To date there have not been any published studies of the newer HCV inhibitor therapies to treat cryoglobulemia or the conditions associated with it, but they are now recommended since the treatment duration is shorter, the HCV cure rates are higher and side effects are less severe.

Treating hepatitis C is generally recommended as a first line of treatment for cryoglobulemia.

Plasmapheresis: This procedure removes blood from the body, chills it and filters and removes the cryoglobulins and returns the blood back to the body.

Rituximab: An immunosuppressant drug that has been found to be successful when used to treat cryoglobulinemia and some of the conditions associated with it. It is usually given if HCV treatment does not work, but has also been found useful when used in combination with HCV therapies.

Non-Hodgkin Lymphoma (NHL) is a form of cancer that starts in the lymphatic system. The lymphatic system is an important network of lymph vessels that carry a clear fluid called lymph, made up of a type of white cell that helps to fight infection.

Lymphoma occurs when white blood cells divide continuously without pause, which prevents the cells from maturing. This causes the overproduction of immature cells that crowd out the mature white cells, platelets and red blood cells.

NHL is uncommon in people with hepatitis C and when it does occur it is usually after many years of ongoing HCV infection.

The symptoms of NHL include:

- Pain, swelling, or a feeling of fullness in the abdomen

Diagnosis is usually made with a series of blood tests, physical tests, chest x-rays and possibly a biopsy to look at lymph tissue. In people with hepatitis C, the usual recommendation is to treat hepatitis C since it is believed that hepatitis C infection causes NHL.

Treatment of HCV-related NHL consists of closely monitoring NHL, but most likely the underlying cause—hepatitis C—will be treated. Hepatitis C treatment (especially successful treatment) has been found to lead to successful remission of NHL. This happens only in people with HCV-related NHL, which validates that hepatitis C causes NHL.

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age, smoking, white ethnicity, alcohol and substance abuse, diabetes and low BMI. Some studies also found that injecting drug use or opioid therapy, hormone replacement therapy or oral contraception, kidney function, menopause and peripheral neuropathy were also risk factors. In multivariate analysis, co-infection, older age, white ethnicity, alcohol and substance abuse, kidney function and diabetes all remained associated with a significant increase in the risk of fracture.

“This systematic review and meta-analysis suggests an increase in osteoporosis in HIV/HCV-co-infected individuals,” comment the authors. “HIV/HCV-co-infection is also associated with a pooled fracture IRR of 1.77 when compared with HIV mono-infection, with higher IRR values for traumatic fractures.”

They conclude their findings “confirm the importance of risk modification and DXA screening at age 50 for prevention of osteoporosis and fractures in HIV/HCV-co-infected individuals.”

Reference

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People with HIV in the normal weight range who gain a substantial amount of weight shortly after starting antiretroviral therapy (ART) may have an increased risk of cardiovascular disease and diabetes, according to findings from the D:A:D study presented recently at the 20th International AIDS Conference in Melbourne.

Several observational studies - including the large international Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study - have found that people with HIV have higher rates of cardiovascular disease and metabolic conditions such as diabetes. However, the relative contributions of HIV infection itself, resulting inflammatory and metabolic changes, antiretroviral toxicities, and other factors are not yet fully understood. Many people with HIV gain weight after starting ART, and this may have a detrimental effect on health.

Amit Achhra from the Kirby Institute in Sydney and colleagues looked at the relationship between short-term changes in body mass index (BMI) after treatment initiation and subsequent risk of cardiovascular disease and diabetes in the D:A:D cohort.

Out of nearly 50,000 participants in the full cohort, this analysis included 9321 people who were starting ART for the first time, had no prior history of cardiovascular disease before treatment initiation and had BMI data available from before and one year after initiation.

People who developed cardiovascular disease or diabetes within the first year were excluded.

About three-quarters of participants were men, the average age was approximately 40 years and about 5% had a family history of heart disease. Before starting ART 6% were underweight (BMI <18.5), 64% were normal weight (18.5-24.9), 23% were overweight (>25) and 6% were obese (>30). The median CD4 T-cell count was approximately 270 cells/mm3 in the latter three groups, but only 170 cells/mm3 in the underweight group, reflecting more advanced disease.

Overall, about one-third of participants were current smokers - although heavier people were less likely to smoke - and about 10% had hepatitis C virus coinfection. As expected, overweight and obese participants had higher blood pressure and were more likely to have pre-existing diabetes, rising from 1.6% among underweight people to 6.8% in the obese group.

The researchers looked at a composite cardiovascular disease endpoint that included myocardial infarctions or heart attacks, strokes, sudden cardiac death and related surgical procedure such as coronary artery bypass or angioplasty. Diabetes assessment was based on medical records or use of anti-diabetic drugs.

Overall, participants gained weight after starting ART, with a mean BMI change of 0.67 at one year. Weight gain was greatest among people who were underweight (BMI <18.5) when they started treatment, moderate among people who started out with normal weight (18.5-24.9) or overweight (>25) and relatively stable among people who were obese (>30) at ART initiation.

A total of 97 cardiovascular disease events occurred during nearly 44,000 person-years of follow-up, for a rate of 2.21 per 1000 person-years. Of these, 46 were heart attacks, 33 were strokes and 18 were invasive procedures.

The cardiovascular event rate (again, per 1000 person-years) rose with increasing body weight: 1.73 in the underweight group, 2.13 in the normal weight group, 2.41 in the overweight group and 2.78 in the obese group. After adjusting for demographics and other factors, a 1-unit gain in BMI was associated with an 18% increased risk of cardiovascular events in the normal weight group. However, people in the underweight, overweight and obese groups did not see a significant change in risk.

Turning to diabetes, a total of 125 new events occurred among the 9193 participants who did not have diabetes at study entry, a rate of 2.89 cases per 1000 person-years. As with cardiovascular disease, the likelihood of developing diabetes rose with body weight, though the risk increased more sharply: 2.04, 2.01, 4.05 and 9.97 events per 1000 person-years in the respective weight categories. After adjusting for other factors, a 1-unit gain in BMI was associated with about a 10% increased risk of diabetes across all categories.
Regimen cures most genotype 1 HCV in co-infected people

By Liz Highleyman aidsmap

An oral regimen of three direct-acting antivirals plus ribavirin taken for 12 weeks demonstrated a sustained virological response rate of 94% for people with both HIV and genotype 1 hepatitis C co-infection. They had undetectable HIV viral load on a stable antiretroviral regimen containing either atazanavir or raltegravir (45% and 55%, respectively), and the mean CD4 cell count was approximately 630 cells/mm3.

Participants in this open-label study were randomly assigned to take the 3D regimen plus ribavirin for either 12 or 24 weeks. The primary endpoint was sustained virological response, or undetectable HCV RNA at 12 weeks after completing treatment (SVR12). All participants in the 12-week arm and about two-thirds in the 24-week arm had reached this endpoint.

The SVR12 rate was 94% for participants in the 12-week arm. In the 24-week arm, the SVR4 rate—which is too soon to consider a cure—was 97%. Among the 20 people in this arm who had reached 12 weeks of post-treatment follow-up, the SVR12 rate was 95% and none had relapsed.

Two participants experienced virological failure—one relapse and one viral breakthrough while on treatment. Sulkowski noted that both were prior null responders with cirrhosis who had HCV subtype 1a and the least favourable IL28B TT gene variant. Both had resistance-associated viral variants at the time of treatment failure that were not present at baseline.

The 3D regimen plus ribavirin was generally safe and well-tolerated. None of the participants experienced serious adverse events or discontinued treatment early for this reason. The most common side-effects were fatigue (58% in the 12-week arm and 38% in the 24-week arm), insomnia (16% and 22%, respectively), nausea (16% and 19%) and headache (19% and 13%). Most adverse events were mild or moderate.

Looking at laboratory abnormalities, 35% in the 12-week arm and 19% in the 24-week arm experienced bilirubin elevations. Four people in the 12-week arm and three in the 24-week arm developed low hemoglobin, but no one progressed to severe anemia. Six people reduced their ribavirin dose due to anemia, but all went on to achieve SVR12.

Five people experienced episodes of low-level HIV viral load during treatment, but all regained undetectable HIV RNA while remaining on the same antiretroviral regimen. There were no notable changes in CD4 count.

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grade 2 HE. Low energy and forgetfulness happen to everyone, even those without liver disease. If you have cirrhosis and those around you suspect that you have HE, see your doctor.

Dehydration and electrolyte abnormalities may trigger HE. Karen’s bike ride in extreme heat explains why her symptoms showed up on that particular day. Other conditions that may lead to HE are metabolic abnormalities, infection, constipation, surgery, eating too much protein, kidney problems and insufficient levels of oxygen in the body.

A variety of medications are used to treat HE, the most common being lactulose. Lactulose is a laxative that absorbs ammonia from the blood and carries it out via the colon. Lactulose is effective in reducing HE symptoms, but it comes with a price: diarrhea, flatulence, bloating, and other gastric problems. Neomycin, rifaximin, metronidazole, zinc, and probiotics are also used to treat HE. An article published June 2014 in Clinical Gastroenterology and Hepatology found that three months of probiotic administration significantly reduced measurable signs of HE, and was effective in preventing HE in patients with cirrhosis. ("Probiotics Prevent Hepatic Encephalopathy in Patients with Cirrhosis," by Manish Kumar Lunia, et al.)

Patients with HE should consult with their medical providers before taking all medications. Drugs that suppress the central nervous system, such as sedatives and tranquilizers may worsen the symptoms. Alcohol and recreational drugs may also intensify HE. Drugs containing ammonium, including certain antacids, should be avoided.

Treating the underlying liver condition or liver transplantation may reverse HE or improve the symptoms. Since hepatitis C is a leading cause of end-stage liver disease, it makes sense that if hepatitis C is cured, patients will be spared the misery of HE. However, access to healthcare is still limited. I think about this every time I read another piece about the cost of the new hepatitis C drug, sofosbuvir. Some state Medicaid programs are unable to pay the high cost of treatment. Hepatitis C patients with HE are unable to advocate for themselves. It is up to us to fight for them.

“HE makes you feel very vulnerable. You can’t tell when you are in the middle of it. You must maintain relationships so people around you can tell if you are going off course. At the same time, HE hurts your social skills, so you are isolated and unable to com-
medical providers. It looks like we are moving out of the HCV dark ages.


**Source:** Clinical Infectious Diseases Advance Access first published online July 2, 2014

An HCV-antibody assay is the first test ordered to determine if a person may have HCV. A positive antibody result merely means that a person was exposed to HCV; it does not mean that HCV is present. A viral load (HCV RNA) is required for proper diagnosis. This study analyzed HCV RNA testing practices by collecting data from four major healthcare systems in the US. Of the 87,431 (9.2%) who had an HCV antibody test, 5,860 (6.7%) had a positive result.

Nearly 61% of those who were HCV antibody-positive had an HCV RNA test performed. Reasons for inadequate testing varied. Providers’ lack of knowledge regarding follow-up testing was cited, as was patients not returning for follow-up testing. Low income was associated with decreased chances of follow-up with viral load testing.

**The Bottom Line:** Less than two-thirds of those who tested positive for HCV antibody had the necessary follow-up HCV RNA testing for proper HCV diagnosis. The researchers recommended reflex testing, a system that automatically triggers an HCV RNA test after a positive HCV antibody result.

**Editorial Comment:** These findings are disturbing, not least of which is that a large percentage of patients who weren’t properly tested are walking around with insufficient information that could help them manage and perhaps cure HCV.

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Findings were similar in sensitivity analyses that excluding people with a history of injecting drug use and those with undetectable HIV viral load (<400 copies/ml) at one year after starting ART. Achhra noted that people who inject drugs IDU are at higher risk for heart problems not related to atherosclerosis.

"Short-term gain in BMI post ART initiation could be associated with the increased risk of cardiovascular disease, largely in those with normal/mid-levels of pre-ART BMI," the researchers concluded. "Gain in BMI also associated with risk of diabetes in all groups."

However, they added that there was "no appreciable change in risk of cardiovascular disease with gain in BMI in those with high pre-ART BMI."

As a limitation, they noted that BMI may not reflect abdominal or central obesity - which is most strongly related to metabolic abnormalities and heart disease - and the study did not have access to information about diet or exercise, which can affect risk independent of weight.

**Reference**


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Hemophilia Association of the Capital Area
2014 Calendar of Events

September
4  KUWYH Dinner, Transition Children to Independence, Green Turtle Restaurant, Fairfax, VA 6:30 pm. Pfizer presenting.
7  Women’s Support Group Meeting, home of Laura Shumway, Reston, VA - 3:00 pm
9  KUWYH Dinner, Setting Educational Expectations, Cuba Libre, Washington, DC. Biogen Idec presenting.
15 Board Meeting, Gadsby’s Tavern, 138 North Royal Street, Alexandria, VA – 7:00 pm.
18-20 NHF Annual Meeting, Washington, DC (HACA is host chapter)
20-22 NHF Insurance Meeting, Washington, DC
24  Infusion Class, Children’s National Health System, Washington, DC – 6:30 pm

October
2  KUWYH Lunch, Exploring Mental Health in Hemophilia Community, Buca di Bepo, Washington, DC, - 6:30 pm. Pfizer presenting.
6  Men’s Support Group and Dinner, Tutto Bene Restaurant, Arlington, Virginia – 6:30 pm
17-19 CSL Behring Getting in the Game, Phoenix, Arizona
25  National Hemophilia Walk, Lincoln Memorial, Washington, DC.

November
5  KUWYH Dinner, Navigating the Financial Aid and Scholarship Process, Joe’s Seafood, Prime Steak and Stone Crab Restaurant, Washington, DC. Biogen Idec presenting.
8  Women’s Day Out: Capitol Hill Food Tour, CSL Behring presenting.

December
1  Men’s Support Group and Dinner, Tutto Bene Restaurant, Arlington, Virginia – 6:30 pm
7  Holiday Event, A Christmas Carol at Ford’s Theatre, Washington, DC. Time TBD.

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